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Translation

PESTICIDE CHEMISTRY AND PRODUCTION PROCESSES

By

N.N. Mel'nikov

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PESTICIDE CHEMISTRY AND PRODUCTION PROCESSES

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[Excerpts from book "Pesticide Chemistry and Production Processes" by N.N. Mel'nikov, Izdatel'stvo "Khimiya", 768 pages]

CONTENTS

ANNOTATION

This book is a scientific monograph describing the chemistry of all classes of compounds used as pesticides, and the production processes for some products. Toxicity data for mammals and fish are presented for most products.

The book is intended for a broad range of chemists and process engineers as well as workers in agriculture, agrochemists, biologists and physicians. It may be used as a training aid by students at chemical and agricultural VUZ's.

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FOREWORD

Chemicals used to protect plants from pests, diseases and weeds and chemicals used to protect animals from ectoparasites have acquired very great significance in agriculture and associated areas. The scale of their production and application is constantly growing, and the volume of scientific research being carried out in this area, so important to the national economy, is increasing. Suffice it to say that more than 10,000 scientific communications and patents associated with pesticide research are published each year. This is fully understandable, since the various chemicals used in agriculture are capable of preserving at least a third of the total yield, and of reducing the labor of caring for the crops.

Pesticides are being studied by scientists with the most diverse specialties, to include chemists (synthetic chemists, process engineers, analytical chemists, physical chemists), biochemists, entomologists, plant and animal physiologists, phytopathologists, veterinarians, toxicologists, agronomists, physicians, agricultural machinery specialists and many others. Despite the fact that the requirements on modern preparations are continually growing, new pesticides are appearing each year. Their number has already exceeded 1,000, and the number of forms of their use in different countries now totals more than 100,000. In this connection generalization of the accumulated material is highly significant to persons of the most diverse specialties. Systematic presentation of this is especially important to students and graduate students specializing in biologically active compounds, as well as to specialists entering research in this area for the first time.

The author has attempted to generalize and describe, in the shortest possible way, the principal classes of compounds and particular substances used and studied as pesticides. In contrast to other handbooks on this problem, the contents of the book are arranged not in relation to applications but in relation to different classes of chemical compounds, which can produce a fuller impression of the pesticidal activity of particular classes of compounds. This approach received a favorable evaluation from the scientific public as is evident from translation and publication of the author's book "Khimiya pestitsidov" [Pesticide Chemistry] in English.

To prepare this book, the author made use of the vast monographic and patent literature. The book includes some information on production processes associated with pesticides and intermediate products used in their production, this material coming mainly from patent and periodical literature. The author believes that production flowcharts presented here would satisfy the qualified engineer; if necessary, information of greater detail may be found in the cited original works.

This was all the more desirable because detailed description of certain processes would have unjustifiably increased the book's volume or made it necessary to abbreviate other sections.

Being a researcher more interested in some problems and less in others, the author was unable to avoid certian nonuniformities in presentation of the material, something that was inevitable in most cases. The author attempted to describe the most important preparations to the fullest extent possible, but because of the book's limited volume the properties of many drugs are summarized in tables, without a complete description.

The author hopes that the book will help readers acquaint themselves with the latest advances in pesticides, and that it will promote their more correct use in agriculture and other areas.

Because certain mistakes may have been made in this book, all notices of omissions and errors will be received with deep gratefulness.

I wish to express my sincere gratefulness to Candidate of Chemical Sciences I. L. Vladimirova for her great help in drawing up the manuscript. I also wish to express sincere gratefulness to Dr Henry Martin for providing some of the materials.

N. Mel'nikov

INTRODUCTION

More than 500 different species of animals were known in ancient Greece, about 2,000 years ago. Today the number of known species of animals and microorganisms exceeds 2 million. The Soviet entomologist N. N. Bogdanov-Kot'kov estimates that there are more than 68,000 different insects that can do harm to man, domesticated animals, plants and various materials. The number of various harmful microorganisms and plants is no less. It has been established with some precision that pests and diseases rob agriculture of not less than a third of its yield, and significantly more when they are not subjected to systematic control. Thus for example in the absence of systematic control of the diseases and pests of agricultural crops, in the best case we would be able to harvest not more than 37 percent of the normal yield of potatoes, not more than 22 percent of the yield of cabbage, 10 percent of the apple yield, 9 percent of the peach yield and so on.

There are many examples in world practice of massive annihilation of various crops by plant diseases and pests. Owing to massive infection of potatoes by phytophthora in Ireland in 1845-1851, a large part of the yield perished, resulting in the starvation and death of about a million persons. In 1930 up to 30 percent of the USA's wheat harvest perished due to stem rust, and in 1954 about 3 million tons of wheat in western Canada were killed by stem rust (1).

Plant pests and pathogens have representatives among various living organisms, to include insects, ticks, mollusks, nematodes (round worms), fungi, bacteria, viruses, parasitic plants and so on. A large number of phytopathogenic microorganisms and insects infect potatoes, corn, grains, legumes, fruits, vegetables, cotton and flax. Rodents are responsible for enormous losses in agriculture. One gray rat and its progeny can destroy foodstuffs worth a total of not less than 400 rubles in the course of 1 year.

Data on worldwide losses of various agricultural crops to pests, plant diseases and weeds are shown below (2,3):

Crop	Harvested Yield, Million Tons/Year	Losses, Million Tons/Year
Grains (wheat, rice, corn, millet, buckwheat, barley, rye, etc.)	960-1,000	500-510
Sugar beets	211	69.0

Sugar cane	483.4	566.8
Potatoes	270.8	129.1
Grapes	50.7	26.6
Cotton (fiber)	11.06	5.69
Soy	31.98	13.07
Fruits	66.6	21.4
Vegetables	201.7	78.2

Insect pests and microorganisms do significant harm, destroying wood, paper, articles made from cotton, wool and silk, natural and synthetic rubber, plastic, leather, and so on. Nonmetallic materials undergo especially rapid destruction in a moist, warm climate. Thus in the tropics cotton and wool textiles and wood break down in 1 or 2 months. Even optical glass can undergo spoilage in the tropics (4).

Harmful insects, pests and other parasites are also a great danger to animal husbandry, since many of them are not only infectious disease vectors, but they also damage the animal's hide and serve as an irritant to the animal, reducing the milk yield and weight gain. Losses caused by just a single parasite in the USSR, the cattle fly, are estimated at 500 million rubles per year.

It would be difficult to overstate the harm done to human health by various insect pests and ticks, which carry infectious diseases, especially if we recall that not so long ago more than 100 million persons on the globe were infected by malaria, and in some regions of our planet this disease is still taking millions of lives each year. Encephalitis, typhus, recurrent fever, sleeping sickness, elephantiasis and many other diseases carried by various insects and arachnids offer a serious hazard to man (5). This hazard is aggravated by the swiftness with which insects reproduce. Thus a housefly, which can undergo seven generations in a season, may produce a progeny of $3.5 \cdot 10^{12}$ individuals, while the apple aphid, with a reproductive capacity of 20 generations per season, can produce 35^{20} individuals. It is only the high mortality of these insects that keeps them from accumulating in nature to their maximum potential (6).

Losses suffered by agriculture due to weeds are no less great. They remove moisture and nutrients from soil and crops, they shade crops and hinder their normal growth, they contaminate harvested grain with seeds poisonous to man and animals and so on. In some cases a harvest may be lost entirely. In the course of a single season, a kilogram of weeds (corrected for dry matter) consume from 250 to 1,000 liters of water. Withdrawal of nutrients from soil is shown in Table 1, given average infestation of crops by weeds (130-150 plants per square meter) (7,8).

Given a worldwide yield totaling about $140 billion per year, losses due to pests, diseases and weeds are estimated at $75 billion per year (2).

The chemical method is one of the most convenient for controlling harmful organisms. Chemicals used to annihilate certain species of harmful organisms are called pesticides.

Table 1. Withdrawal of Nutrients by Different Weeds

Plant	Nutrient Consumption, kg/ha			
	Nitrogen	P_2O_5	K_2O	Total (Corrected for Technical Fertilizers)
Thistle (field sow-thistle)	138.1	31.0	116.9	739
Common centaurea	65.4	24.0	98.2	460
Joint weed	84.8	47.2	70.4	589
Fireweed	72.4	25.8	91.9	479
Coltsfoot	74.0	27.2	234.8	724
Sowthistle	67.0	28.7	159.7	600
Quick-grass	48.6	31.5	68.5	406
Common cyperus	210.8	67.4	270.4	1,392

Pesticides are divided into the following basic groups depending on the targets of their application.

Acaricides--to control ticks.

Algicides--to kill algae and other aquatic vegetation.

Antiseptics--to protect nonmetallic materials from destruction by microorganisms.

Arboricides--to kill undesirable woody plants and shrubs.

Bactericides--to control bacteria and bacterial diseases of plants.

Herbicides--to control weeds.

Zoocides--to control rodents. This group is often referred to as rodenticides in the foreign literature.

Insecticides--to control insect pests. Certain groups of insecticides have been given more specific names; for example aphicides are preparations used to control aphids.

Limacides or molluscosides--to control various mollusks, including gastropods.

Nematocides--to control round worms (nematodes).

Fungicides--to control plant diseases and various fungi.

Also categorized as pesticides are chemical plant growth stimulators and inhibitors, leaf removing preparations (defoliants) and plant drying preparations (dessicants) used to permit mechanization of the laborious operations of harvesting cotton, soy, potatoes and many other crops, and preparations that repel (repellents), attract (attractants) and sterilize insects (sexual sterilizers).

Herbicides, insecticides and fungicides have found the widest use in agriculture and other sectors.

Insecticides are divided into the following basic subgroups depending on the way they penetrate into the organism: contact insecticides, which kill insects on contacting any part of the body; intestinal insecticides which penetrate into the insect body through feeding organs and which kill it as a result of entry of poison into the intestine; systemic insecticides, which are capable of moving through the plant vascular system and poisoning insects using such plants as food; fumigants, which penetrate into the insect body through respiratory organs. It should be noted that most of the drugs used today may penetrate into the insect body by different pathways. In this connection certain drugs are placed in particular subgroups on the basis of the principal pathway of their penetration into the insect body. Thus for example, lindane has contact, intestinal and fumigant action, but it is usually classified as a contact drug.

Some insecticides block up the insect's respiratory tract, causing the insect to die by asphyxiation. Such preparations include mineral oils, silica gels (in finely dispersed state) and some others.

Fungicides are usually divided into two basic subgroups: Fungicides used to control diseases of vegetating plants, and seed disinfectants, which are used on seeds prior to planting to protect sprouts from various diseases. In turn, fungicides used on green plants are divided into drugs having preventive action, used to protect plants from various infections, and preparations having exterminant (therapeutic) action, used to treat plants. As with the insecticides, the fungicides include drugs having contact and systemic action, though the latter group of substances is extremely small in number. Antiseptics used on nonmetallic materials and bactericides are often classified as fungicides. In many cases the same substances used for plant protection are also used as antiseptics and bactericides. It should be noted that many fungicides have weak bactericidal activity (9-12).

Herbicides are divided into two basic subgroups depending on the nature of their action upon the plant: general, acting upon all species of plants, and selective, dangerous only to certain plant species and safe in relation to other plants. This division is arbitrary because depending on the concentrations used and the consumption rate per unit of treated area, the same substances may act as both general and selective herbicides (13).

All herbicides are divided into three subgroups depending on the outward signs of their action upon plants and the application methods: contact herbicides, systemic herbicides and herbicides acting upon the root system of plants or germinating seeds.

Contact herbicides include substances which injure plant leaves and stems when the latter come in direct contact with the drug. This disturbs the plant's normal vital activities, and it dies. It should be considered, however, that such herbicides affect only those portions of the plant upon which the preparation settles; moreover in some cases we observe growth of new shoots and further development of an injured plant. The reason for this is that substances within this group are incapable of moving through the plant's vascular system.

Systemic herbicides include substances capable of moving through the vascular system of plants. Such herbicides, on coming in contact with plant leaves and roots, spread quickly throughout the entire plant, causing it to die. Systemic preparations are especially valuable in the control of weeds with large root systems and perennial weeds.

The third subgroup consists of herbicides introduced into soil to destroy the seeds, germinating seeds and roots of weeds.

Defoliants and dessicants are close in the nature of their action to contact herbicides; in many cases contact herbicides are used as defoliants and dessicants, if they are safe to the seeds of the crop being processed.

In most cases arboricides and algicides are classified as herbicides as well.

Plant growth regulators also enjoy some use both to stimulate the growth and raise the yield of various crops and to inhibit sprouting of various roots and tubers stored for a long period of time.

Economic Effectiveness of Pesticide Use

As was noted earlier, the losses suffered by the national economy due to various pests are very high, and pesticide use can sharply reduce the harm done. Outlays in agriculture on pesticides within a single season (including outlays on their application) are compensated several times over. The effectiveness of pesticides in relation to different crops is especially evident from a comparison of the data shown in Table 2.

Table 2. Yield Increments of Different Agricultural Crops Resulting From Plant Pest Control in the USA in 1953 (Based on a Selective Poll of Farmers and Entomologists)

Crop	Yield Losses, %		Yield Increase As a Result of Chemical Treatment by __ Times
	Without Chemical Treatment	With Chemical Treatment	
Beans	66	13	2.6
Grapes	77	11	4.8
Cherries	78	8.5	4
Strawberries	34	13.5	1.3
Grains	13.5	12	1.1
Cabbage	82	12	4.9
Potatoes	72	15	3
Onions	64	9	2.5
Tomatoes	32	15	1.7
Apples and pears	93	15	12

The effectiveness with which pesticides are used for public health needs can be judged from this example (14): Before modern insecticides came into use in Ceylon, more than 2 million cases of malaria were recorded each year; by 1964, owing to systematic use of DDT to control malaria mosquitoes, the number of illnesses decreased to 13, while after the use of DDT was halted in 1968, more than 1 million persons fell ill.

The high economic effectiveness of pesticides in agriculture and other sectors is promoting rapid development of this sector of chemical industry, in which case we observe not only growth in production of certain forms of pesticides but also constant change and improvement of their assortment. Table 3 shows the figures for production and sales of new organic pesticides in the USA from 1947 to 1969.

Table 3. Pesticide Production and Sales in the USA From 1947 to 1969 (Wholesale Prices)

(1) Годы	(2) Произведено		(3) Продано		Годы	Произведено		Продано	
	(4) тыс. т	(5) млн. долл.	тыс. т	млн. долл.		тыс. т	млн. долл.	тыс. т	млн. долл.
1947	56,4	—	—	—	1964	355,4	481,9	314,3	427,1
1952	139,6	—	—	—	1965	398,4	582,9	356,8	497,0
1957	232,2	—	—	—	1966	459,9	727,7	373,3	583,8
1961	317,1	—	—	—	1967	476,5	914,0	407,4	787,0
1962	331,3	427,4	287,8	346,3	1968	540,7	—	434,4	900,0
1963	346,6	456,0	295,8	369,1	1969	501,2	—	421,8	1015

Key:
1. Year
2. Produced
3. Sold
4. Thousands of tons
5. Millions of dollars

It is suggested (16,17) that further growth of pesticide production in the USA will have the following proportions:

	1975	1980
Pesticides (million $)	2,000	2,800
Fertilizers (million $)	3,250	4,750
Ratio of pesticide cost to fertilizer cost, %	61.5	58.9

In 1969 the cost of pesticides was 34 percent of the cost of fertilizers in the FRG, and it was about 40 percent in Japan.

World pesticide production was estimated in 1972 at 11 billion West German marks (18,19). It is believed that by 1975 it will reach 16 billion West German marks, and 24 billion marks by 1980 (18).

In the USSR, pesticide production totaled 103,200 tons in 1965, 163,800 tons in 1970 and 173,000 tons in 1972. It is to be raised in 1975 to 256,600 tons (corrected for the active ingredient) (20).

The world assortment of pesticides now numbers more than 100,000 names made from more than 900 chemicals belonging to the most diverse classes of organic and inorganic compounds.

In the last 5 years production of chemical plant protection and weed control resources in the Soviet Union grew by more than three times, and it will be raised to 455,000 tons per year by the end of the current five-year plan in compliance with a decision of the July 1970 Plenum of the CPSU Central Committee (20). The assortment of drugs will increase significantly as well.

General Requirements on Pesticides

A large number of different chemical compounds exhibiting high physiological activity in relation to many harmful organisms are known. If pesticides are to be used successfully in agriculture, industry and public health, in addition to high biocidal action against various pests, the preparations must be reasonably safe to man, domesticated animals and useful plants, insects and microorganisms.

The quantities of pesticide residues on plants must not present a hazard to animals and man. This is so important that many of the world's countries have set norms for the concentration of pesticides in various foodstuffs used by man and domesticated animals. Special laboratories have been created in the Soviet Union to monitor the quality of agricultural products and their pesticide concentrations, as well as possible accumulation of pesticides in the environment (in soil, water and so on). In some countries the quantities of pesticide residues in foodstuffs are not regulated, but legislation establishes the minimum time prior to harvesting that plants can be treated with pesticides, and the expenditure norms for preparations used to treat plants. The plant treatment schedule is established in such a way that by harvest time, any preparations used would be completely or almost completely broken down (21,22). Discussing the dangers of pesticides to man and animals, we should also note, as a mandatory condition, absence of blastomogenic action (23,24).

There are different methods for estimating the toxicity of chemicals to mammals. In the GDR and FRG, for example, all drugs that are acutely toxic to animals are divided into three groups (where the LD_{50}* refers not to the active ingredient but to the finished preparation) (25):

1. Preparations with an LD_{50} up to 100 mg/kg.
2. Preparations with an LD_{50} of 100-300 mg/kg.
3. Preparations with an LD_{50} above 300 mg/kg.

The first group of pesticides includes strong-acting substances released to users by special permission; the second group contains substances of average toxicity; substances in the third group are mildly toxic.

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*LD_{50}--average dose of a preparation, mg per kg live weight, causing 50 percent mortality of experimental animals.

In the USSR, strongly acting preparations are those with an LD_{50} up to 50 mg/kg; highly toxic substances have an LD_{50} of 50-200 mg/kg, substances with moderate toxicity have an LD_{50} of 200-1,000 mg/kg, and mildly toxic preparations have an LD_{50} above 1,000 mg/kg.

It should be noted, however, that this division is to a certain extent arbitrary, since the toxicity of pesticides to man and animals depends not only on the absolute value of the preparation's lethal doses but also on a number of other conditions. When determining the toxicity of a preparation, we must keep in mind its chronic toxicity, the possibility of its accumulation in the human and animal body, the reversibility and irreversibility of toxic effects, the pathways by which it enters the organism and a number of other factors. We should also consider the toxicity of compounds produced when a preparation is metabolized* in plant and animals cells. The last property is important also because the metabolic products of some pesticides are more toxic than the initial compounds. In this connection to correctly determine the possible danger of a pesticide, we would need to not only determine its LD_{50} but also study its metabolism.

Before determining what sensible use of a pesticide would be, it would be very important for us to first evaluate the possible pathways by which it can penetrate into the human body. Substances in the first group, which have the capacity to penetrate through human skin (resorption) and through the respiratory tract, are especially hazardous. In this connection when we study the toxicity of preparations on experimental animals, we determine the LD_{50} not only when the preparation is introduced by way of the mouth but also when it is applied to the skin, when its vapors are inhaled, and when it enters the body by other means.

To correctly determine the danger of a certain preparation to human health, we must study the mechanism of its action and establish the basic ways in which the preparation interacts with the most important enzymatic systems of man and animals. Such data also have great significance to creating preparations with selective toxicity--that is, ones that are toxic to some species of organisms and safe to others.

One of the most important problems associated with pesticide use in agriculture is that of possible remote consequences resulting from systematic intake with food by man and animals in residual quantities (26-29). In this connection the quantities of pesticide residues in foodstuffs of plant and animal origin are subjected to standardization (28,29). Most countries have set extremely low norms for pesticide concentration--close to zero (within the sensitivity limits of modern analytical methods)--for many products which enjoy the greatest demand and which appear in man's daily ration (flour, meat, milk, butter and so on) (30), while for seasonally consumed products (fruits, vegetables, berries and so on) the norms are slightly higher.

The norms for the quantities of pesticide residues adopted by the USSR, USA and FRG for the second group of products named above are presented below:

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*Metabolism--transformation of chemical compounds in various biological objects and substrates.

	Norm for Quantities of Pesticide Residues in Vegetables and Fruits, mg/kg		
Pesticide	USSR	USA	FRG
DDT	0.5	3.5	1
HCH	0.5-1	10	2
Heptachlor	0	0-0.1	0
Carbofos	3.0	8	0.5-3
Metaphos	0	1	0.5
Chlorophos	2	-	-
Carbaryl	0.3	7	3

For this reason production of persistent drugs has recently been declining while production of drugs with low persistence, ones which decompose completely within the course of a single season and which do not remain in the yield, is rising.

Pesticides used to protect plants from pests must be completely safe to plants, while preparations used against animal parasites must be safe to animals. Moreover pesticides must not worsen the yield quality.

The time a given preparation remains within the environment is usually called its persistence. The persistence of a preparation depends both on the physical and on the chemical properties of substances (volatility, resistance to hydrolysis, resistance to the action of soil microorganisms, to oxidation by atmospheric oxygen and to the action of sunlight, and so on).

Among the physical properties of pesticides, volatility is the most significant: The lower the volatility, the longer a pesticide may persist in the environment. As a certain approximation, volatility characterizes the evaporativity of a substance at a given temperature, which may be calculated by the formula:

$$V = \frac{Mp_T \cdot 1{,}000}{760 B_T},$$

where V--volatility (evaporativity) of the substance at a given temperature, gm/m^3; M--molecular weight; p_T--pressure of saturated steam at this temperature, mm Hg; B_T--volume of a gram-molecule at the same temperature, liters.

The size of V characterizes the volatility of the substance in a motionless atmosphere. It is rather difficult to calculate volatility in dynamic conditions, since not only the temperature and rate of movement of air but also the heat capacity of the substance and of all materials coming in contact with it, the surface form of the preparation and so on must be taken into account. For practical purposes most preparations are sprayed as solutions, emulsions or suspensions. Preparations are used not in their pure form but in a complex mixture, and therefore there are certain difficulties in calculating the evaporativity of their droplets.

Evaporation of the droplets of a pure substance in a motionless atmosphere has been studied relatively well, and it may be calculated by Langmuir's formula:

$$-\frac{dm}{dk} = 4\pi r D \frac{Mp_{sat}}{RT}$$

where dm/dt--droplet evaporation rate (decrease in droplet mass per second), gm/sec; r--droplet radius, cm; D--coefficient of diffusion, cm^2/sec; p_{sat}--saturation pressure of evaporating substance, mm Hg; R--gas constant; T--temperature, °K; M--substance's molecular weight.

Using this equation we can derive a formula by which to calculate the time of complete evaporation of a droplet of the substance, k (sec):

$$k = \frac{DRT}{2dMp_{sat}} r^2$$

where d--the substance's density, gm/cm^3.

It should be noted that the rate of evaporation of droplets in moving air is considerably greater.

Different persistence requirements are imposed on a preparation depending on its purpose. However, in all cases decomposition of the preparation on plants by harvest time is mandatory. The persistence of preparations introduced into soil must be the highest possible, but it should not exceed one season for herbicides and two seasons for drugs used to control pests inhabiting the soil. In this case the preparation must not be absorbed by plants and accumulated in fruits or other plant parts used by man or domesticated animals as food. If plants are treated not long before harvest time, such preparations must be distinguished by low persistence, and they must decompose completely prior to harvest time.

Pesticides are usually divided into the following six groups depending on the rate of their decomposition in soil (31):

1. Pesticides with a decomposition period longer than 18 months (organochloride insecticides, compounds containing arsenic and selenium).
2. Pesticides with a decomposition period of about 18 montns (some triazine herbicides, piloram, some arylurea derivatives).
3. Pesticides with a decomposition period of about 12 months (benzoic acid halide derivatives, and some acid amides).
4. Pesticides with a decomposition period of up to 6 months (acid nitriles, some aryloxyalkane carboxylic acid derivatives, treflan and its analogues, etc.).
5. Pesticides with a decomposition period up to 3 months (arylcarbamic acid derivatives).
6. Pesticides with a decomposition period less than 3 months (organophosphorus pesticides).

The rates of decomposition of some organophosphorus insecticides in soil are shown in Table 4 (15).

We can see from these data that even a persistent organophosphorus insecticide such as dursban undergoes 82 percent decomposition in soil within a month, owing to which its accumulation in sizeable quantities is practically impossible.

Table 4. Decomposition Rates of Some Organophosphorus Insecticides in Soil

Preparation	Experiment Duration, Days	Degree of Insecticide Decomposition in Soil, %		
		Sterilized	Irradiated by UV Light	Normal
Carbofos	1	7	90	97
Ciodrin	1	4	34	87
DDVP	1	17	88	99
Mevinphos	1	1	38	95
Metaphos	7	20	26	95
Supracide	7	17	20	50
Thiophos	14	17	16	35
Phosphamide	14	18	20	77
Tsinofos	28	17	24	71
Dursban	28	33	38	82

Toxicity of pesticides to fish and plankton is also an important question. We do not as yet have sufficiently complete information on toxicity to fish; according to the available data, even the chemical compounds of the same class exhibit extremely diverse toxicity. The toxicities of some pesticides to fish exposed to them for 24 hours are shown below:

Pesticide	AC_{50}*, $\times10^{-9}$	
	For Rainbow Trout	For Blue Carp
Endrin	0.7	0.8
Endosulfan	1.8	2.7
Toxaphene	7.6	7.2
DDT	8	7
Methoxychlor	20	31
Lindane	30	61
Pyrethrin (extract)	56	78
Carbofos	100	120
Captan	250	-
Neopinamin	180	-
Diazinon	380	54
DDVP	500	1,000
Phosalone	1,200	-
Phthalophos	5,300	-
Metaphos	7,000	8,500
Abat	8,200	-
Chlorophos	27,500	5,600

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*AC_{50}--average concentration of a substance causing 50 percent mortality of experimental organisms.

As a rule organochloride pesticides are the most toxic to fish, while organic phosphorus compounds and carbamates are significantly less toxic. Organochloride pesticides can accumulate in fish fat in rather sizeable quantities, and they can enter the bodies of man and wild animals and birds through the digestive tract. In some cases organochloride insecticides are used to kill trash fish in various water basins. However, subsequent decontamination of such water basins proceeds rather slowly.

Pesticides must be explosion-proof, noncombustible (they must have a high ignition point), they must be easy to handle, and they should not attack ordinary metallic and nonmetallic materials used in packaging and apparatus.

In addition to the requirements listed above, those associated with economics have great significance as well: for example, presence of the raw material base, availability and cheapness of raw materials and production methods, low preparation consumption norms per unit of treated surface, low cost and so on.

Besides general requirements, there are also particular ones imposed on individual groups of preparations, for example fumigants, household preparations for parasite control, herbicides, seed disinfectants and fungicides. These requirements will be examined below.

Most Important Methods of Pesticide Application

Depending on the form of the preparation, different methods are used to process plants, animals and materials.

Dusting, spraying and introducing preparations into soil in granulated form have the broadest acceptance in agriculture. Treatment by liquid preparations is displacing dusting more and more.

With ordinary spraying of plants, liquid consumption is from 200 to 2,000 liters per hectare, it is from 5 to 50 liters for low volume spraying, and 1-10 liters per hectare for ultralow volume spraying. Low volume spraying means a dramatic rise in labor productivity, owing to which a tendency for making broader use of this method can be observed.

Ultralow volume spraying usually requires substances with extremely low volatility, which makes it possible to control droplet size and obtain good results at minimum preparation consumption (32,33).

The optimum diameter of droplets to be sprayed from an airplane may be calculated by the following formula, the results of which are highly probable:

$$D = \frac{hv}{v_c}$$

where h--height of droplet fall, meters; v--wind velocity, m/sec, v_c--rate of droplet fall due to gravity, m/sec.

The probability W that droplets of the substance would settle on the surface being processed may be determined by the formula:

$$W = \frac{dvD^2}{18\eta h}$$

where d--substance density, gm/cm^3; v--rate of air movement, m/sec; D--droplet diameter, mm; η--air viscosity, Pa•sec; h--height of droplet fall, meters.

Animal parasites are controlled by pressurized spraying, by bathing, and more rarely by dusting with solid preparations. Systemic preparations are added to feed.

When pesticides are used as antiseptics on nonmetallic materials, the latter are saturated with solutions, suspensions or emulsions of the pesticides, or pesticides mixed with paint are applied to them.

Poison bait consisting of pesticide and food are broadly employed in rodent control. The bait method is also used to control some insect pests, but due to its laboriousness, it is being supplanted more and more by improved methods. The bait method using attractants is recommended as a means for forecasting development of certain species of insect pests and maintaining a record of their distribution. Attractants may possibly be used in the future for local destruction of pests.

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CHAPTER 1

FORMS OF PESTICIDE USE

The success of using pesticides to control harmful insects, ticks, microorganisms and weeds depends to a great extent on the form of the preparation and on the conditions under which the chemical compound comes in contact with plant pests, plant pathogens, pests that attack stored foodstuffs and destroy nonmetallic materials, and undesirable plants. Because chemical compounds and the objects to which they are applied are so diverse, a large number of forms of preparations must be created. Depending on the physicochemical properties of the preparation's active ingredient, its purpose and the means of its use, we select that form of its application which is most effective and economical in the given concrete conditions.

The form of application we select goes a long way to define the process by which the preparation is made.

In the world today, there are more than 100,000 different forms of application of pesticides made from 950 different chemical compounds. The USA uses more than 2,500 preparations based just on organochloride insecticides alone (1,2).

The most important forms of preparations are as follows.

1. Powders (dusts)--for dusting and powdering.
2. Granulated (grainy) preparations--for plant processing and introduction into soil.
3. Microcapsulated preparations--for introduction into soil and plant processing.
4. Solutions in water and in organic solvents (including for ultralow volume plant spraying).
5. Wettable powders used in the form of water suspensions for spraying.
6. Emulsion concentrates that form sprayable emulsions when diluted with water.
7. Aerosols and fumigants.
8. Other forms of use--antiseptic and insecticidal soaps, paints, varnishes, ointments, pastes, waxes, insecticide crayons, insecticidal and bactericidal paper, various baits and so on. However, these forms of preparations enjoy more-limited use, and they are produced in relatively small amounts. The only exception is poison baits, which are the principal form of preparations used in rodent control.

Powders (Dusts)

Insecticidal, fungicidal and herbicidal dusts and combined powders are mechanical mixtures of a pesticide and an inert filler ground to a particle size of 3-30 μ. As the mixture is ground up, the pesticide particles are spread among the filler particles, which they coat. In this connection grinding the pesticide together with the filler produces a more effective preparation than separate grinding and subsequent mixing of the ingredients. The more finely the active ingredient of a sprayed powdered preparation is ground, the more effective is the preparation. This is explained by the fact that preparations that are more finely ground cling to plants and insects better, and they cover them more uniformly. (The usual dosage of dusts is 10 to 40 kg per hectare. A rather fine grind would be required for uniform distribution of a preparation over such a surface area.)

Pesticides can be turned into powdered state more or less easily depending on their properties. Substances with a well formed crystal structure that is sufficiently brittle and not very elastic are ground down the most easily. As an example pure DDT with a melting point not less than 106°C grinds down easily. But technical-grade DDT containing oily impurities is harder to grind; as it is ground, it cakes, forming large clumps that stick to the walls of the mill. Solid organic pesticides are usually ground in the presence of an inert filler. The filler prevents caking of the preparation during both grinding and storage. The quantity of filler depends on its sorption capacity. Thus for example when technical-grade DDT is ground in the presence of silica gel (with a bulk density of 0.14 gm/cm^3), 5-10 percent filler would be enough, while when ordinary kaolin is used, not less than 25 percent would be required. Caking usually occurs when a preparation is ground in a ball mill. This apparently is connected with the increase in temperature inside the mill resulting from collisions of the balls, which causes partial melting of the substance being ground. In this connection adding a larger quantity of filler and performing the process at the lowest possible temperature would be desirable when grinding pesticides with a low melting point.

Most organic preparations to be made into dusts are usually ground in ball mills equipped for air-jet separation. Sometimes grinding is performed in two stages: First concentrated powder is prepared (in crusher-roll mills, in a ball mill or in another type of machine). Then the necessary quantity of filler is added, and the mixture is ground further in a ball mill. The best dusts are obtained with air-jet mills, but this significantly increases the cost of the product owing to high consumption of electric power.

It has now been demonstrated that grinding a low melting point organic pesticide together with a mineral filler in a ball mill produces dust differing little from a preparation obtained by saturating filler with pesticide dissolved in a volatile organic solvent, followed by distillation of the solvent, since during the grinding process the filler is coated by a thin layer of pesticide.

Interest has been shown in obtaining dust by mixing melted pesticide with ground filler. Several modifications are known of this method of obtaining, in dust form, low melting point pesticide having high plasticity. As an example dusts are easily obtained in this way from a melted mixture of DDT and technical-grade γ-hexachlorocyclohexane, from a solution of DDT in mineral oil and so on. In some cases adding melted preparation to filler heated to 30-40°C is recommended as a way to delay crystallization of the pesticide (3-7). There are also other methods of making dusts from melted pesticide. For example, melted pesticide can be sprayed in a chamber similar to the sort used for spray drying. Filler is introduced into such a chamber in suspended state. Pesticide droplets stick to the filler particles and settle to the floor of the chamber. The process may be adjusted in such a way that a completely uniform dust is obtained. Dusts can also be obtained by precipitating pesticide vapor on filler; however, this method could hardly be thought of as economically advantageous.

Dusts are made from liquid organic substances by mixing filler with the pesticide. When the pesticide concentration in the dust is very low, mixing is performed in several stages (usually in two).

Figure 1 shows the general flow of dust production.

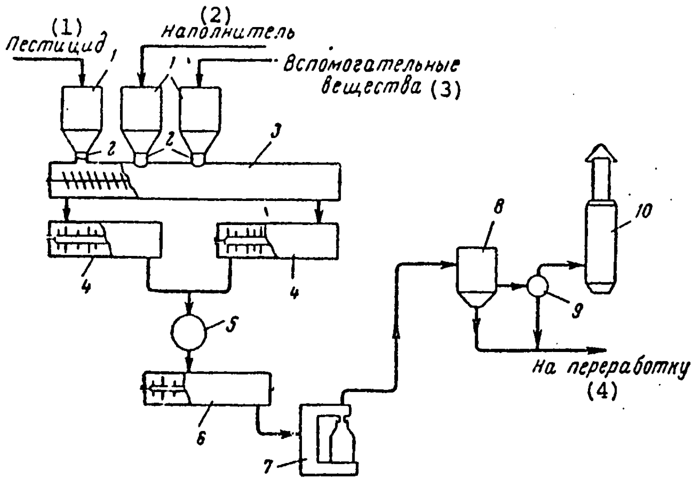

Figure 1. Basic Diagram of Pesticide Dust Production: 1--raw material hoppers; 2--metering units; 3--worm conveyer; 4,6--mixing units; 5--mill; 7--packaging units; 8--dust trap; 9--dust extractor; 10--filters trapping residual dust

Key:
1. Pesticide
2. Filler
3. Auxiliary substances
4. To processing

If the pesticide is a liquid, it is sprayed into the mixing unit through special nozzles. In this case it is better to use pulverized filler, which would exclude the grinding stage and restrict the mixing process to just two stages.

The concentration of active ingredient in dust depends on the effectiveness of the pesticide. DDT dusts usually contain 5-10 percent technical-grade preparation, thiophos contains 1 percent and growth regulators contain 0.05-0.1 percent.

Hydrophobic minerals such as talcum and pyrophyllite are usually used as fillers in production of pesticide dusts; chalk, gypsum, kaolin, diatomaceous earth, tripolite and silica gel are used more rarely. The choice of filler must account not only for its physical but also its chemical properties, since some fillers may catalyze decomposition of pesticides or have an effect on their photochemical stability. Thus for example, alkaline fillers are not recommended for making dusts out of esters, hydrocarbon halide derivatives and so on. Esters may also be hydrolyzed in the presence of acid substances. Introduction of special additives blocking the harmful effects of the filler is recommended when using such fillers. In some cases it would be suitable to use mixtures of several fillers. Use of hydrophilic minerals such as kaolin, clay and bentonite in the presence of high moisture is not recommended, since dusts made with such fillers start caking readily after even slight wetting.

To make dusts cling better to plants, hydrophobic substances may be added to them--calcium stearate, mineral oils and so on. The stickiness of powdered preparations and their ability to cling to plants determines the preparation's time of action in many cases. These characteristics depend not only on the shape of the dust particles (this has great significance, of course) but also on the chemical composition of the active ingredient and the special additives in the dust. The choice of recipes for a given preparation must account for not only the method of its application but also the crops for which it is intended.

Wettable Powders

Wettable powders is a name usually given to powdered preparations which form rather stable suspensions when diluted with water. In most cases more interest is shown in pesticide suspensions than in dusts. Spraying plants and other surfaces with various preparations is almost always more effective than dusting (given equal pesticide consumption). Dusting is totally inappropriate in buildings to control mosquitoes, flies and gnats, and for disinfection.

Suspensions are especially convenient when dusts cling poorly to the surface being worked, fruits for example, and when emulsions are readily absorbed, owing to which significant quantities of toxic residues remain on the fruit. Suspended particles cling well to surfaces, and they do not penetrate, which means that they could be washed off easily when necessary.

The following requirements are imposed on wettable powdered pesticides.

1. Resistance to aging and absence of caking.
2. Quick formation of a suspension and slow settling of solid particles.
3. Good wettability of sprayed objects and easy spreading over their surface.
4. Retention on surfaces for a more or less long period of time.

One of the main conditions ensuring effectiveness of suspensions used to control plant pests and diseases and weeds is small particle size of the preparation's active ingredient. Good wettable powders usually contain not less than 80 percent particles up to 3 μ in size.

Wettable powders can be divided into three groups: preparations with a high active ingredient concentration (from 60 to 90 percent), with a moderate concentration (from 30 to 60 percent) and with a low concentration (up to 30 percent). The last are usually made from liquid or waxy substances, because the preparation readily cakes when the concentration of such substances in wettable powder is high.

Usually the composition of wettable powder includes, in addition to the active ingredient, a filler and a dispersant. Special stickers are also sometimes added to preparations in order to raise their adherence to plants or other surfaces (5-8, 24).

Wettable powders usually have the following composition (percent):

Pesticide . . .	10-90
Dispersant . . .	2-10
Filler	Up to 100

When preparations are made with a high active ingredient concentration, in almost all cases the substances used are sufficiently pure, they contain no oily impurities, and the filler's bulk density is low and its sorption capacity is relatively high. In particular, special grades of silica gel with a bulk density not greater than 0.15 gm/cm^3 are recommended. Some other hydrophilic fillers can also be used: Aluminum hydroxide, synthetic calcium silicate and so on. Wettable powders can also be made without a filler, if the preparation's active ingredient has a sufficiently high melting point and if it grinds easily.

Various detergents are used to make wettable powders, including alkali metal sulfonates (sodium oxydibutyldiphenyl sulfonate, sodium alkybenzene sulfonate, particularly sodium dodecylbenzene sulfonate, sodium alkanesulfonate and so on), alkylaryl esters of polyethylene glycol and polypropylene glycol (substances such as OP-7 and OP-10) and so on. These substances are used to obtain wettable powders and pastes both independently and in combination with other products, for example with sulfite-liquor waste.

Sodium salts of aromatic sulfonic acids and ligninosulfonic acids are used as auxiliary substances. Compounds usually used as film forming agents include carboxymethyl cellulose, methyl cellulose, unsaturated alcohol polymers, gelatin, animal glues, caseinates, resinates and so on.

Highly concentrated wettable powders are obtained by grinding a mixture of pesticide, filler and other ingredients in a colloid mill. Grinding in air-jet mills of various designs produces good results. Grinding in ball mills produces coarser powders; in this case grinding the pesticide together with the filler in the presence of water produces satisfactory results. Next the paste is dried and ground a second time.

The process for obtaining wettable powders from crystalline pesticide is diagrammed in Figure 2.

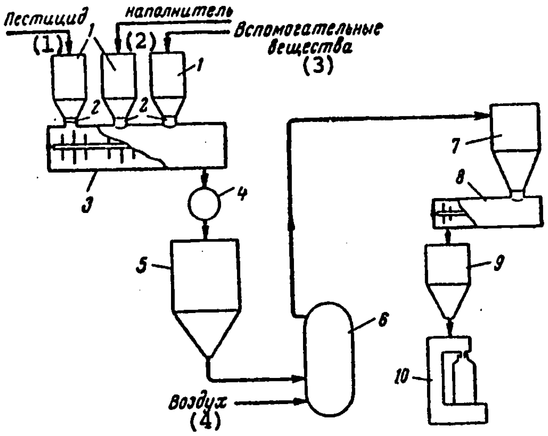

Figure 2. Basic Diagram of Wettable Powder Production: *1*--raw material hoppers; *2*--metering units; *3*--mixing units; *4*--initial grinding mill; *5*,*7*--ground preparation collecting hoppers; *6*--air-jet mill; *8*--mixing unit bringing preparation to required concentration; *9*--finished product collecting hopper; *10*--packaging unit

Key:

1. Pesticide
2. Filler
3. Auxiliary substances
4. Air

Pesticides obtained by precipitation out of aqueous solutions may be used to make wettable powders without grinding. In this case all of the substances used to make the wettable powder are added to precipitated and washed pesticides, and then dried in a spray dryer. This method can be used to make wettable powders out of pesticides such as copper oxychloride, ziram, curpous oxide and so on (25). However, additional grinding is sometimes required. In addition to technical-grade pesticides the ingredients of such wettable powders usually include 2-3 percent OP-7 auxiliary substance, 2-3 percent sulfite-liquor waste and up to 5 percent carboxymethyl cellulose. Wettable powders with an active ingredient concentration of 70-80 percent have enjoyed the broadest use.

The ingredients of some wettable powders are shown in Table 5.

Table 5. Ingredients of Some Wettable Pesticide Powders (%)

	Initial Pesticide			
Ingredients	Simazine	Phthalophos	Diuron	Sevin
Pesticide	50-80	30	80	80
Kaolin	45-46	55-60	15-17	15-17
Aerosil	-	5-12	-	-
Sulfite-liquor waste or sulfonate	1.5-2.5	1-2	1.5-2	1.5-2
OP-7	1-2	2-4	1-1.5	1.5-2.5
Chalk	16-17	-	-	-

Pastes, which contain a small quantity of organic solvent and water in addition to auxiliary substances, have properties close to those of wettable powders. However, it is less convenient to use pastes because their composition may change during storage owing to evaporation of some of the water or organic solvent. Stable pastes are obtained by adding high molecular weight, water-soluble protective colloids having a viscosity not less than 10 mPa•sec (10 centipoise) in a 10 percent solution at 25°C. Methyl- and carboxymethyl cellulose are the most easily available substances with this viscosity. Polyethylene glycol alkylarylates with a molecular weight of 400-600 are used as surfactants. Pastes may be obtained by emulsifying the ingredients in a liquid colloid mill at high temperature.

Wettable powders have been proposed having complex action, containing several pesticides of different purposes. Use of such preparations in agriculture saves a certain amount of labor in plant processing.

Emulsion Concentrates

One of the convenient forms of use of different pesticides is emulsion concentrates which, when diluted with water, form stable emulsions. In some cases this form of pesticide preparations has advantages over suspensions, since many liquid pesticides can be used to prepare such concentrates without the need for solvents and fillers. Given equal concentrations of the active ingredient, emulsions are more effective as a rule than suspensions. In this respect they are similar to pesticide solutions in organic solvents, but solvent consumption is many times lower.

Two types of pesticide emulsion concentrates are known.

1. Emulsion concentrates obtained by dispersing, in water using a colloid mill, pesticide dissolved in solvent immiscible with water. These concentrates would better be called concentrated emulsions. Highly dispersed concentrated emulsions that are stable when stored can be obtained by mechanical dispersion. Emulsions of this type are used in agriculture, but they can only be made from pesticides resistant to water. This method is used to obtain oil emulsions of DDT, hexachlorocyclohexane, anthracene oil and some other preparations. Concentrated emulsions are stabilized by the addition of sulfite-liquor waste.

Concentrated pesticide emulsions are obtained by mixing an aqueous solution of sulfite-liquor waste with pesticide dissolved in oil or another organic solvent (the density of the pesticide in the organic solvent must be close to unity in order to obtain sufficiently stable concentrated emulsions). The resulting coarse dispersion is fed into a mechanical homogenizer.

Homogenized concentrated emulsions can withstand low temperatures and prolonged storage without significant changes. Sometimes they thicken when stored, but mixing returns them to their normal state.

2. Pesticide emulsion concentrates (so-called miscible oils) usually contain a sizeable quantity of pesticide. Mixing them with water produces stable emulsions. Concentrates of this type consist of pesticide, organic solvent and emulsifier. Use of solvent with liquid pesticides is not mandatory, though organic solvents often make it possible to reduce the concentration of emulsifiers in the concentrate.

Solvents may include hydrocarbons and their halide derivatives, esters, various petroleum products, Creolin, coal oils and many other compounds. Emulsifiers include calcium sulfonates, polyethylene and polypropylene glycol esters, higher fatty acid monoesters of sorbitol and mannitol, various soaps, naphthenic acid salts and so on. Especially good results are obtained with mixtures of two or more emulsifiers, one of which is a polyethylene glycol ester and the other is calcium alkylaryl sulfonate or ammonium or alkylsulfate obtained from higher alcohols.

Emulsion concentrate is obtained by dissolving the pesticide in the selected solvent and then mixing it with the emulsifier while heating to 40-80°C. After it is cooled the concentrate must be a homogenous mass without a precipitate. The concentrate is filtered to remove mechanical impurities. A general diagram of the process by which pesticide emulsion concentrates are acquired is shown in Figure 3.

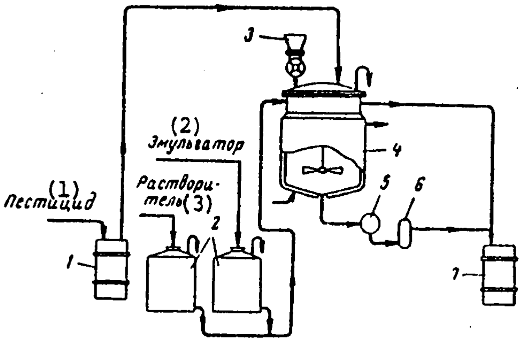

Figure 3. Basic Diagram of Pesticide Emulsion Concentrate Production: *1,2*--liquid pesticide, solvent, emulsifier and auxiliary substance storage containers; *3*--metering unit for solid ingredients; *4*--machine units in which emulsion concentrates are obtained; *5,6*--filters; *7*--finished product collector

Key:

1. Pesticide	3. Solvent
2. Emulsifier	

Concentrates with not very high a viscosity may be conveniently used in agriculture, but viscous concentrates would be safer in the case of highly toxic organophosphorus compounds, since they are absorbed slowly if they settle on the skin, and they may be easily washed off with water.

Disinfectants and insect exterminating preparations are used in the form of emulsion concentrates. Disinfectant soaps containing antiseptics and insecticides are emulsion concentrates, as are various antiseptic pastes used to protect wood and other non-metallic materials.

So-called "reversible emulsions" obtained by diluting appropriate concentrates with water are broadly employed. Enough water is added to obtain a product with a consistency of a water-oil emulsion. These concentrates are used in low volume spraying, since presence of an oil film prevents droplet evaporation.

Special additives, for example butylamine stearate ("lovo" preparation) are introduced to reduce evaporation of droplets sprayed from an aircraft or by other means.

Aerosols

One of the new forms of pesticide use in public health and agriculture is aerosols. Much attention is being devoted to developing this application method.

Three basic ways of obtaining insecticidal and fungicidal aerosols are known.

1. The burning of various compounds containing insecticides, fungicides or bactericides that are volatilized to form smoke or mist toxic to insects, fungi and bacteria. Pesticides may also be vaporized by special heating instruments, electric lamps for example.

2. The spraying of pesticides dissolved in volatile solvents which, when they evaporate in air, leave the pesticide in the form of a fine dispersion.

3. Mechanical atomization of pesticide solutions with special spraying units. Sometimes this method is combined with the second. Heated solutions of pesticides in organic solvents, mainly petroleum products, are sprayed. When the compound is sprayed, some of the solvent evaporates, which reduces droplet size to that close to aerosols. This method is known as low-volume finely dispersed spraying.

The simplest method of obtaining pesticide aerosols is to burn special smoke bombs, paper and other flammable porous materials saturated with insecticides, fungicides and bactericides. The ingredients of combustible smoking compounds include, in addition the pesticide, a combustible substance, filler and oxidizer. Nitrates, nitrites, chlorates, chromates, bichromates, persulfates and their mixtures are used as oxidizers. Fillers promoting controlled burning include kaolin, diatomaceous earth and so on. The necessary temperature is maintained by adding wood chips, wood pulp production wastes, coal, bitumen and various tars.

The ingredients of some insecticidal smoke mixtures are presented below (percent):

1.		2.		3.	
Potassium chlorate	23-26	Potassium chlorate	19	Potassium chlorate	25.8
Crude anthracene	9-12	Urotropin	8	Urea	7.3
Ammonium chloride	9-12	Diatomite	9	Thiourea	12
Dicyanodiamide	4-6	Hexachlorocyclohexane	64	DDT	54.9
Hexachlorocyclohexane	50-52				

When such compounds are burned, more than 80 percent of the insecticide is volatilized without decomposition, and only 10-17 percent transforms into products that are nontoxic to insects.

Insecticidal paper which forms smoke toxic to insects when burned is obtained by saturating unsized paper with insecticide solution. The paper is first saturated with an aqueous solution of sodium or potassium nitrite and dried.

Insecticidal smoke bombs are effective against blood-sucking dipterans and pests found in storage facilities. They are also used in hothouses. Special tetraethyl dithiopyrophosphate cartridges are recommended in the last case. It should be noted, however, that because these compounds are highly toxic to man, their use as mists may be a serious hazard.

Use of smokes and mists obtained by burning smoke bombs does not produce a very good protective effect against plant pests in the field.

Aerosols obtained by dispersing insecticide solutions in volatile solvents are usually recommended for control of flies and other flying insects in enclosed spaces. Such solutions are placed in metallic aerosol tanks supplied with a spraying device. Pressure is created in the tank with carbon dioxide or a low boiling point solvent (Freon, methylchloride and so on). This pressure promotes good atomization of the preparation. After the solution is sprayed in air and the solvent evaporates, the pesticide remains in the atmosphere in finely dispersed state. Pesticide particle size is related to the size of solution droplets, and it may vary within broad limits depending on tank pressure and the design of the spraying device.

Table 6 shows the compositions of different aerosol mixtures.

Table 6. Compositions of Aerosol Mixtures*

	Composition, Parts By Weight				
Ingredients	I	II	III	IV	V
Main insecticide	3	0.5	5	6.3	4
Supplementary insecticide	2	1	-	4.4	-
Freon-12	85	83.5	-	83.75	88
Acetone	-	-	35	4.4	-
Cyclohexanone	5	5	5	-	-
Methylchloride	-	-	50	-	-
Kerosene	-	5	-	-	4
Petrolatum oil	-	-	-	1.1	-
Machine oil	5	-	5	0.05	-
Synergist	-	5	-	-	-
Insecticide stabilizer	-	-	-	-	0.5
Other auxiliary substances	-	-	-	-	3.5

*Pressure is created with carbon dioxide.

Aerosols obtained by these methods are usually used to control insects or microorganisms that are very sensitive to insecticides; they are not used against plant pests.

Aerosols made by mechanically dispersing pesticide solutions in organic solvents are used in agriculture. Low volume spraying of finely dispersed aerosols is effective both in greenhouses and in large forests and fields; preparation consumption is low with such spraying. Good results are achieved when granaries are treated by this method (26).

Petroleum products with a relatively high boiling point serve as the solvents in low volume finely dispersed spraying. Pesticide solubility is increased by adding intermediate solvents (xylol, polymethyl naphthalene and so on). Many sprayer units are designed to use exhausts from internal combustion engines to mechanically disperse pesticide solutions. It should be kept in mind that some pesticide could be lost with this dispersal method owing to its partial thermal breakdown. When this method is used to obtain aerosols, the temperature requirements must be complied with strictly in order to avoid the pesticide's breakdown.

Other Forms of Pesticide Use

The brief description of the most important forms of pesticide use presented here does not exhaust all of the avenues of employing and making different forms of preparations. Thus for example, packaging is treated with insecticides (lindane, pyrethrins, etc.) to control storage facility pests. Grain in such packaging suffers practically no damage from storehouse pests.

The most toxic systemic insecticides are introduced into soil in gelatin capsules, which precludes contact of workers with the toxic preparation. In the soil, the gelatin gradually breaks down, and the insecticide is released into soil water and absorbed by plant roots.

The poison bait method is extensively employed to control rodents, and fumigants are often employed to destroy pests attacking stored foodstuffs.

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CHAPTER 2

HYDROCARBONS

To date, many hydrocarbons have been studied for their pesticide activity. However, only a few of them are used to control harmful organisms.

Research has been conducted on the insecticidal properties of aliphatic hydrocarbons from methane to hexacosane, including isomeric hydrocarbons, olefins and acetylenes. It has been established that the insecticidal and acaricidal activity of hydrocarbons grows as their molecular weight increases, and that it achieves a maximum with paraffins and isoparaffins with a molecular weight of 320-350, after which it remains constant for the compounds studied thus far. A similar dependence is also observed with unsaturated and alicyclic compounds, with alicyclic hydrocarbons exhibiting weaker insecticide properties than unsaturated hydrocarbons. The insecticidal activity of unsaturated hydrocarbons grows as we proceed from olefins to acetylenes and dienes. Branched-chain paraffins are more active than similar hydrocarbons with normal structure (1,2).

The fungicidal and herbicidal activity of paraffin hydrocarbons is insignificant. Activity rises somewhat as we progress to unsaturated compounds. Ethylene has strong defoliant action, and it hastens ripening of tomatoes and some other crops. Plants placed in a chamber containing traces of ethylene (up to 1 percent) quickly lose their leaves. The defoliant action of ethylene and acetylene homologues is significantly weaker.

The pesticidal properties of aromatic hydrocarbons have been studied in somewhat greater detail. Some of them are used in agriculture and industry, for example benzene, toluol, xylols, ethylbenzene, trimethylbenzene, isopropylbenzene, isopropyltoluene, *sec-* and *tert-*butylbenzene, pentamethyl- and hexamethylbenzene, dihydronaphthalene, tetralene, naphthalene, methyl- and polymethylnaphthalenes, diphenyl, diphenylmethane, toluylene, fluorene, acenaphthalene, anthracene, dihydroanthracene, phenathrene, chrysene, retene, terphenyl and some other polycyclic hydrocarbons. The biocidal activity of aromatic hydrocarbons is higher than compounds in the aliphatic and alicyclic series, but in comparison with pesticides used today, their physiological activity is low. Xylols, naphthalene homologues, tetralene and other liquid aromatic hydrocarbons are used as solvents for chlorene- and phosphorus-containing insecticides and some herbicides. Among individual hydrocarbons, only naphthalene and diphenyl enjoy limited applications. Naphthalene is used in small quantities both to control moths and as a grain fumigant, but it is being supplanted more and more by other more effective preparations.

Diphenyl, which has a melting point of 70.5°C and density d_4^{25} 1.156, is practically insoluble in water and readily soluble in most organic solvents. The vapor pressure of diphenyl varies with temperature as follows:

Temperature, °C	70.6	117	187	229.4	254.9
Pressure, mm Hg	1	10	100	400	760

The LD_{50} of diphenyl in relation to rats is 3,280 mg/kg. Prolonged inhalation of vapor containing 0.005 mg diphenyl per liter of air is hazardous to man.

One of the most important methods of obtaining diphenyl is pyrolysis of benzene. It is isolated as a byproduct of various processes.

Diphenyl can inhibit fungal growth, which is why paper in which citrus fruits are wrapped is saturated with it. It is recommended that paper be treated with a melted mixture of diphenyl and paraffin (1:1) at a rate of 30 gm diphenyl per 1 kg paper, and 100 gm diphenyl per 1 kg cardboard (3).

The concentration of diphenyl in fruits has been standardized in a number of countries; it must not exceed 100 mg/kg.

Petroleum Oils

Petroleum oils are the longest-known pesticides. They have been used against plant pests and weeds many decades. According to available information crude oil was first used to control plant pests in 1778, and kerosene has been used to control orange scale insects since 1865. Despite such a long history of use of petroleum hydrocarbons in agriculture, research is still continuing in this area.

Petroleum products are used as pesticides in agriculture in the following basic directions:

1. For summer spraying of fruit trees (summer oils).

2. To control wintering pests of fruit trees and ornamental plants (winter oils).

3. As solvents for various insecticidal, fungicidal and herbicidal emulsion concentrates and solutions intended for low volume fine spraying.

4. As solvents for insecticides and antiseptics to control insect pests in the home and to protect nonmetallic materials.

5. To control weeds occurring with umbeliferous and some other agricultural plants.

The principal requirements imposed on oils used to control plant pests are as follows: high toxicity to plant pests, harmless to processed plants, low toxicity to man and animals, availability and cheapness.

Petroleum products used to make pesticidal preparations employed in greenhouses and especially in animal buildings must not have an unpleasant odor, and they must not contain substances toxic to man and animals. Preparations used in residential buildings are usually made from the kerosene fractions of petroleum from which sulfur compounds and aromatic and unsaturated hydrocarbons have been removed. In some cases pesticide preparations are made from purified low boiling point petroleum fractions and turpentine.

As was indicated above, one of the important conditions imposed on petroleum products used to control plant pests or weeds is selectivity and harmlessness to useful plants. It has been established that in relation to most plant species, the phytocidal activity of mineral oils depends both on the physical properties of the oil and on its composition and the structure of the hydrocarbons it contains. Aromatic and unsaturated hydrocarbons which form acids that are highly toxic to plants when oxidized by atmospheric oxygen make up the most phytocidal fraction of mineral oils. Paraffins and naphthenes are oxidized slowly by atmospheric oxygen, and therefore their phytocidal activity is low (4).

Petroleum products can display their herbicidal action only when they contain a high concentration of aromatic compounds. In this case substances toxic to plants are produced as a result of conjugate oxidation of aromatic hydrocarbons and compounds of other classes. It has been demonstrated that the rate of oxidation of different aromatic compounds by atmospheric oxygen is directly correlated with the light absorption spectrums of these compounds. Those substances which have their absorption maximum within the visible or near-ultraviolet portions of the spectrum undergo oxidation the fastest. Phytocidal products are also obtained when hydrocarbons interact with ozone, which is always present in the atmosphere in small quantities.

Petroleum products containing more than 10 percent aromatic and unsaturated hydrocarbons can be used as herbicides, and oils from which aromatic and unsaturated compounds have been removed can be used to control plant pests.

Petroleum products with a high concentration of aromatic hydrocarbons can be used successfully as general herbicides.

In this case the concentration of aromatic hydrocarbons with a boiling point of 150-300°C must be not less than 70 percent. Petroleum products containing about 20 percent aromatic hydrocarbons are used to control weeds occurring with umbeliferous plants at consumption norms from 325 to 890 liters/ha.

Oils used in summer spraying of green plants must not contain significant quantities of aromatic hydrocarbons (the unsulfurizing residue in summer oils must be not less than 95 percent). Engler viscosity should be within 1.5-1.8°. Oil having greater viscosity is dangerous to plants because it can cause burns. When even relatively safe oils settle on plant leaves, they are quickly absorbed, and if their viscosity is high they may clog vessels, impairing the plant's vital activities.

Because acids also have phytocidal action, the acidity of summer oil must be not more than 0.1 mg KOH per 100 gm oil. The emulsifier employed and various additives have an effect on the phytocidal properties of oils (2,4-8).

Preparation 30 containing the following ingredients (percent) is used as a summer plant spray to control San Jose scale and other similar pests (6).

Paraffin distillate from select Surakhany petroleum	40
Transformer oil	40
Sulfite-liquor waste	2
OP-7	0.5
Water	17.5

A basic flowchart for production of preparation 30 is shown in Figure 4.

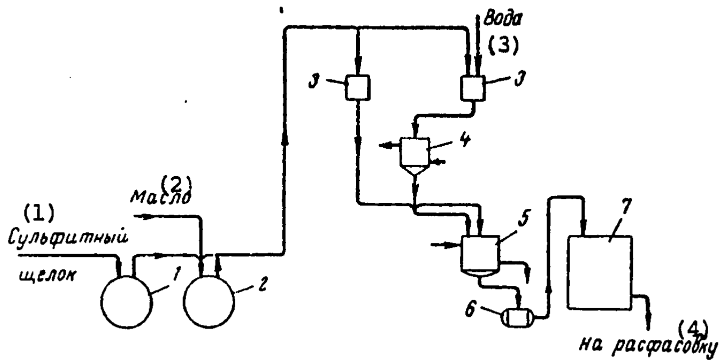


Figure 4. Basic Flowchart for Making Preparation 30: *1*,*2*--raw material storage containers; *3*--gaging tank; *4*--oil heater; *5*--emulsion making apparatus; *6*--colloid mill; *7*--finished product collector

Key:

1. Sulfite liquor
2. Oil
3. Water
4. To packaging

Preparation 30A is made with paraffin distillate obtained from Archedinsk petroleum, while preparation 30M is made with paraffin distillate from Martyshinsk petroleum.

Looser requirements are imposed on the phytocidal action of oils sprayed on defoliated plants and in early spring. There is information, however, that systematic spraying of fruit trees with various oils reduces their frost resistance, especially if the plants are processed in late fall.

Plants can be sprayed before budding by very phytotoxic oils, such as green oil, which is a residue of petroleum cracking. It contains a significant quantity of unsaturated and aromatic compounds. This oil is toxic to most plant pests and storehouse pests. Fruit and ornamental trees and shrubs are sprayed with green oil emulsion to control scale insects, armored scale, psylla, aphids, ticks, and some other pests.

The way in which oils act upon plant pests and their eggs is not entirely clear at the moment; however, it is hypothesized that gas exchange is disturbed (access to oxygen is hindered), the water balance of the insect and its eggs is disturbed, outer coverings are disturbed (to include shells, which is especially important to eggs), oils penetrate into the insect body or the egg and impair enzymatic processes, protoplasm undergoes coagulation, and tissue structure is disturbed.

Disturbance of gas exchange is apparently the most important factor. This is confirmed by the high activity of oils having a large concentration of paraffins and isoparaffins, which are resistant to oxidation and which consequently form a persistent coat that prevents metabolism within the egg or in the insect body.

The requirements imposed on petroleum products used as pesticide solvents are the same as those on oils used on their own, but in this case phytocidal activity has somewhat different significance, since oils used jointly with insecticides and fungicides are consumed in significantly smaller concentrations. In this connection even some aromatic compounds can be used as pesticide solvents.

It would be interesting to note that when unsaturated compounds are present in oils, the activity of halide insecticides and some organic fungicides decreases. This is connected with partial destruction of fungicides when they undergo conjugate oxidation by atmospheric oxygen. Halide insecticides enter into a telomerization reaction with unsaturated compounds as well as with hydrocarbons contained in turpentine.

Some petroleum products possess noticeable fungicidal action. This has been noted particularly for petrolatum, which has been proposed for lumber protection and as an ingredient of fungicidal pastes.

CHAPTER 4

HALIDE DERIVATIVES OF ALICYCLIC HYDROCARBONS

General Description of Pesticide Properties

A large number of halide derivatives of alicyclic hydrocarbons have been found to have practical significance as pesticides. Some of them are now produced on a large industrial scale. In terms of the amount produced, certain representatives of this series have conceded only to DDT.

The dependence of insecticidal and fungicidal activity on composition and structure observed for mono- and dihalide derivatives of alicyclic hydrocarbons is the same as for aliphatic hydrocarbon derivatives. As a rule bromide derivatives are more active than the corresponding chloride derivatives. Growth in the number of halogen atoms per molecule somewhat increases the compound's activity, but only to a certain limit.

Systematic study of the insecticidal properties of large numbers of different halide derivatives of alicyclic hydrocarbons showed that compounds with a molecular weight below 480 and a melting point below 200°C have insecticidal properties (1). Compounds with higher molecular weight and lower solubility in lipoids are practically inactive as contact insecticides, which is apparently connected with their low permeability through outer coverings and negligible rate of diffusion and movement through insect tissues.

A large number of valuable insectofungicides have been discovered among halide derivatives of alicyclic hydrocarbons with molecular weight below 480.

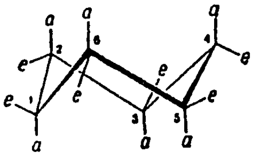
Hexachlorocyclohexane is a monocyclic derivative that has enjoyed broad use. Halide derivatives of polycyclic hydrocarbons are represented by chlorindanol, heptachlor, aldrin, isodrin, dihydroheptachlor, and dieldrin and endrin.

Some Representatives

Hexachlorocyclohexane (HCH) and Its Analogues (2)

1,2,3,4,5,6-Hexachlorocyclohexane is an important active insecticide. Of the eight known stereoisomers of hexachlorocyclohexane, only the γ-isomer is an active insecticide.

Chlorine atoms in the molecules of isomeric hexachlorocyclohexanes have the following orientation:



isomer		isomer	
α	aaeeee	ε	aeeaee
β	eeeeee	ζ	aaeaee
γ	aaaeee	η	aeaaee
δ	aeeeee	ϑ	aeaeee

The melting points of the isomers of hexachlorocyclohexane and some related compounds are presented below:

Compound	Melting Point, °C
α-Hexachlorocyclohexane	157.5-158.5
β-Hexachlorocyclohexane	309
γ-Hexachlorocyclohexane	112.8
δ-Hexachlorocyclohexane	138-139
ε-Hexachlorocyclohexane	218.5-219.3
ζ-Hexachlorocyclohexane	88-89
η-Hexachlorocyclohexane	89.8-90.5
ϑ-Hexachlorocyclohexane	124-125
α-1,1,2,4,4,5-Hexachlorocyclohexane	145
β-1,2,4,5-Tetrachlorocyclohexane	228
β-1,2,4,5-Tetrabromocyclohexane	218
β-1,2-Dibromo-4,5-dichlorocyclohexane	240
α-Hexabromocyclohexane	221
β-Hexabromocyclohexane	253
γ-Hexabromocyclohexane	160
β-1,2-Dibromo-3,4,5,6-tetrachlorocyclohexane	282
1,2,3,4-Tetrabromo-5,6-dichlorocyclohexane	203
1,2,4,5-Tetrabromo-I,4-dichlorocyclohexane	200
α-Heptachlorocyclohexane	147

It should be noted that with the exception of the γ-isomer of hexachlorocyclohexane, the compounds presented above exhibit practically no toxicity toward most insects and fungi. Only δ-hexachlorocyclohexane has noticeable fungicidal action. Table 9 shows the relative insecticidal activity of different hexachlorocyclohexane isomers in relation to different insect species; in this table, the insecticidal activity of the γ-isomer is given a value of 1. This table also shows the toxicity of hexachlorocyclohexane isomers to albino rats.

Table 9. Comparative Toxicity of Hexachlorocyclohexane Isomers

Species	Hexachlorocyclohexane Isomers					
	α	β	γ	δ	ε	ζ
Granary weevil	1/900	1/5 000	1	1/5 500	—	—
Malaria mosquito	1/250	1/10 000	1	1/250	—	—
Housefly	1/10 000	—	1	1/1 300	1/10 000	—
Leaf beetle	1/520	1/220	1	1/55	—	1/410
Confused flour beetle	1/2 800	—	1	1/7,3	1/53	—
Thrips	1/1 000	1/10 000	1	1/10 000	—	1/10 000
Rats (LD_{50}, mg/kg)	500	6 000	125	1 000	1000	—

As we can see from Table 9, γ-hexachlorocyclohexane is superior to all other isomers in insecticidal activity. It would be interesting to note that the mixture of 1,2,3,4,5,6-hexachloro-1-methylcyclohexanes obtained by photochemical chlorination of toluol also exhibits high insecticidal properties in relation to a number of insects.

Hexachlorocyclohexane isomers differ in their solubility in organic solvents. They dissolve rather poorly in paraffins and cycloalkanes, better in unsaturated hydrocarbons, and even better in aromatic hydrocarbons. Their solubility in chloride derivatives of aromatic and aliphatic hydrocarbons is higher than in hydrocarbons. Hexachlorocyclohexanes are readily soluble in some alcohols, ketones, esters and ethers. The solubility of some isomers of hexachlorocyclohexane in water and in organic solvents is shown in Table 10.

Table 10. Solubility of Hexachlorocyclohexane Isomers

Solvent	Solubility, gm per 100 gm Solution			
	α	β	γ	δ
Acetone	13,9	7,9	43,5	71,1
Benzene	9,9	1,12	28,9	41,1
Water	$1 \cdot 10^{-4}$	$0{,}5 \cdot 10^{-4}$	$1 \cdot 10^{-4}$	—
Dichloroethane	7,9	0,6	28,9	27,3
Iso-octane	12,7	6,9	35,7	58,5
Isopropanol	0,6	0,4	2,8	18,0
Xylol	8,5	3,3	24,7	42,1
Methanol	2,3	1,6	7,4	27,3
Chloroform	6,3	0,3	24,0	13,7
Ethanol	1,8	1,1	6,4	24,2

Isomers are separated and pure γ-hexachlorocyclohexane is isolated by capitalizing on the different solubilities of these isomers in organic solvents. Methanol or acetone is usually used for this purpose. These chemicals are capable of extracting the γ-isomer from the reagent mixture.

The γ-isomer of hexachlorocyclohexane is volatile (vapor pressure at 20°C is $9.4 \cdot 10^{-6}$ mm Hg); polychlorodiphenyls, polychloronaphthalenes and some other substances are often added to it to prolong its active life.

The maximum permissible concentration of hexachlorocyclohexanes in air is 0.1 mg/m^3, while that of pure γ-isomer is 0.05 mg/m^3.

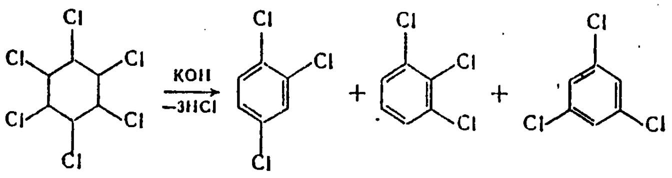
Hexachlorocyclohexane differs relatively little in chemical properties from other halide derivatives of hydrocarbons in which halogen atoms are attached to neighboring carbon atoms.

Hexachlorocyclohexane reacts slowly with water at room temperature; a noticeable quantity of hydrogen chloride is liberated only when it is heated to 100°C. Thus when hexachlorocyclohexane is exposed to steam for 1 hour at about 102°C, about 0.13 percent of hydrogen chloride contained in the α-isomer is liberated. Heating of α-hexachlorocyclohexane in the presence of water at 200°C in sealed tubes produces 1,2,4-trichlorobenzene and its hydrolysis products. The reaction is accelerated by light and in the presence of alkali:

$$C_6H_6Cl_6 \xrightarrow[-HCl]{} C_6H_5Cl_5 \xrightarrow[-HCl]{} C_6H_4Cl_4 \xrightarrow[-HCl]{} C_6H_3Cl_3$$

Pentachlorocyclohexane and tetrachlorocyclohexadiene impurities impart a typical unpleasant odor to hexachlorocyclohexane. Very pure hexachlorocyclohexane has no odor, and it is only when it is stored in the presence of light and moisture or alkali that it acquires an unpleasant odor.

When hexachlorocyclohexane interacts with caustic alkali in alcohol solution and when heated in aqueous solutions, it transforms into trichlorobenzene:



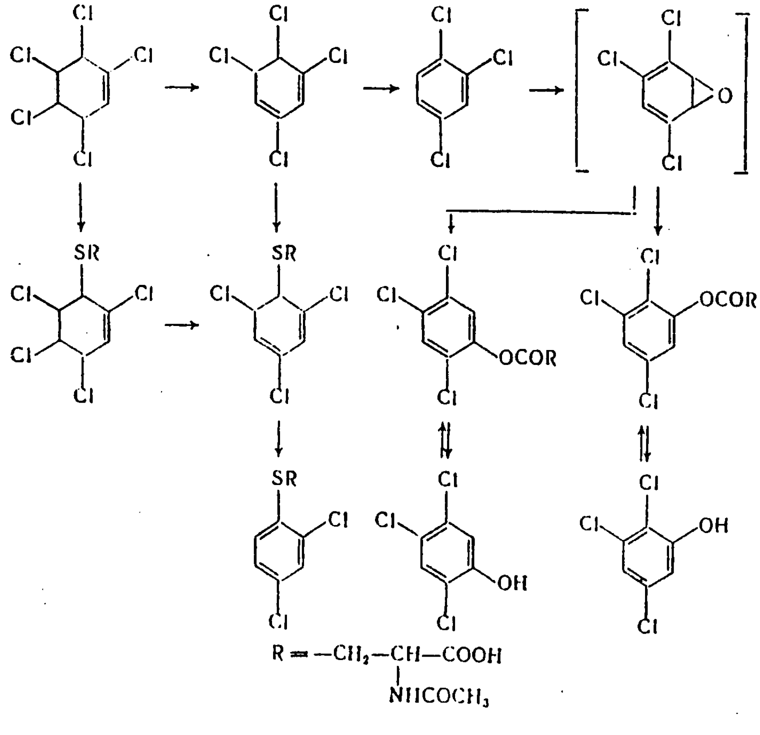
The principal reaction product is 1,2,4-trichlorobenzene (a 75-95 percent yield). Other products are 1,2,3-trichlorobenzene (3-20 percent) and 1,3,5-trichlorobenzene (0-17.6 percent). The kinetic method of quantitative determination of the γ-isomer in a mixture is based on the differences in the reaction rates between caustic alkali and the isomers of hexachlorocyclohexane.

HCl is also split off when this compound interacts with lime, ammonium and organic amines. Decomposition of hexachlorocyclohexane to form trichlorobenzene and hydrogen chloride proceeds at higher temperature (250-350°C) in the presence of substances capable of initiating such decomposition (chlorine, iron, aluminum, their salts, etc.). When chlorine is used as the initiator, part of the trichlorobenzene is chlorinated, and in addition to trichlorobenzene, we get its chlorination products. In the presence of excess chlorine, good yields of hexachlorobenzene may be obtained. This reaction is used on an industrial scale to obtain tri-, tetra- and hexachlorobenzene from nontoxic hexachlorocyclohexane isomers.

Hexachlorocyclohexanes undergo isomerization when heated to 170°C. In the presence of iron chloride the reaction proceeds to not more than 50 percent completion; the relative quantity of γ-isomer formed did not exceed 4.4 percent in any of the experiments run. When exposed to zinc dust in an acid medium, hexachlorocyclohexane transforms into benzene; this reaction is used for its quantitative determination. Hexachlorocyclohexane reacts slowly with chlorine; its chlorination to undecachlorocyclohexane has been reported. It also reacts with sulfides and thiocyanates of alkali metals and some other substances.

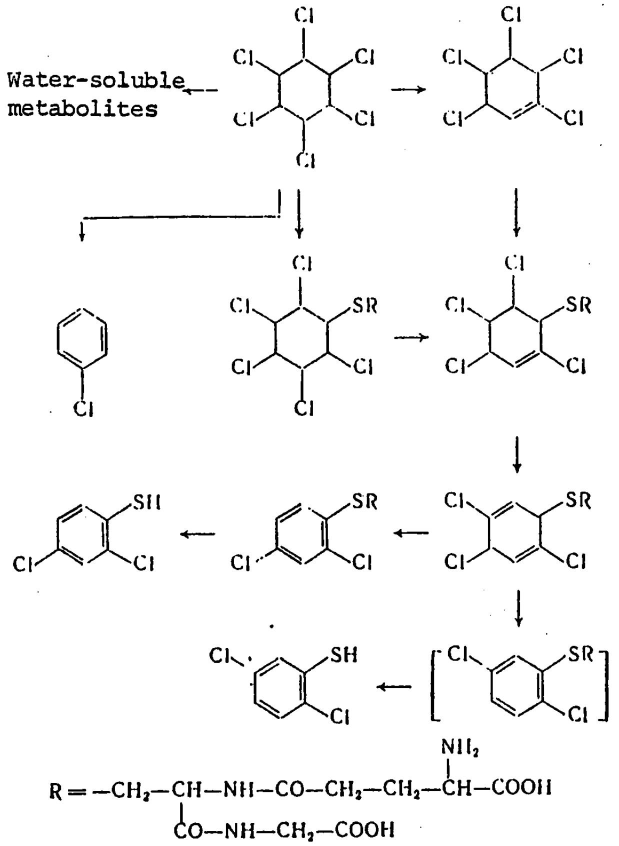
Metabolism of γ-hexachlorocyclohexane in the bodies of homeothermic animals, insects and plants, and in soil has been studied (3-5). The first metabolite of hexachlorocyclohexane is always pentachlorocyclohexane. The next stage of metabolism proceeds differently in the bodies of homeothermic animals and insects.

A general flowchart for metabolism of γ-$C_6H_6Cl_6$ in rats is shown below:



The formed thiophenols and phenols are released from the body as compounds of glycuronic and sulfuric acids.

Metabolism of γ-hexachlorocyclohexane in insects proceeds as follows:



Hexachlorocyclohexane is obtained by chlorination of benzene (industrial method) and by chlorination of cyclohexane and cyclohexene:

$$C_6H_6 + 3Cl_2 \longrightarrow C_6H_6Cl_6$$
$$C_6H_{12} + 6Cl_2 \longrightarrow C_6H_6Cl_6 + 6HCl$$
$$C_6H_{10} + 5Cl_2 \longrightarrow C_6H_6Cl_6 + 4HCl$$

Photochemical chlorination of benzene has become the most widespread method in industry. Chlorination proceeds in excess benzene or in a solution of other organic solvents, usually methylene chloride. Good results are produced by chlorination in aliphatic nitriles (5a). Chlorination of benzene produces a mixtures of the following composition (percent):

α-Isomers	53-70
β-Isomers	3-14
γ-Isomers	11-18
δ-Isomers	6-10
Other isomers	3-5
Heptachlorocyclohexane	3-4
Octachlorocyclohexane	0.5-1
Oily substances (of undetermined composition)	0.5-3

The optimum conditions for obtaining hexachlorocyclohexane having the largest possible concentration of γ-isomer are as follows:

1. Low chlorination temperature (from -20 to -30°C). Conducting the process in organic solvents is recommended because benzene crystallizes below +6°C. When chlorination is performed in excess benzene, keeping the temperature below 24°C is recommended. Chlorination at a lower temperature would significantly reduce the reaction rate and consequently decrease the productivity of the apparatus. The dependence of the yield of γ-isomer on chlorination temperature (6) is shown in Figure 5.

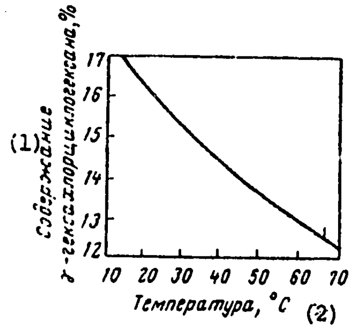


Figure 5. Dependence of γ-Hexachlorocyclohexane Concentration in Technical-Grade Product on Benzene Chlorination Temperature

Key:
1. Concentration of γ-hexachlorocyclohexane, %
2. Temperature, °C

2. A high concentration of chlorine in the reaction medium.

3. A low concentration of chlorination products in the final reaction solution (12-15 percent).

The purity of the initial product has great significance because impurities such as atmospheric oxygen and the compounds of iron and some other substances have a negative influence on the process. Iron impurities not only retard the principal process but also promote formation of reaction byproducts--the products of substitution of hydrogen in the benzene molecule by chlorine (6-11).

Following chlorination, the reaction product may be isolated from the reaction solution by many methods: by distillation of the solvent (or excess benzene) with live steam in a vacuum, at atmospheric pressure, by partial distillation of the solvent (or excess benzene) or by separation of part of the product by filtration, followed by subsequent distillation of the remaining solvent which live steam. For practical purposes in the last case only α- and β-isomers are separated in the first filtration step, and the technical-grade product obtained following distillation of the remaining solvent contains 30-40 percent γ-isomer. After drying, this product may be used to produce lindane (see below).

A flowchart for production of technical-grade hexachlorocyclohexane using the method described above is shown in Figure 6.

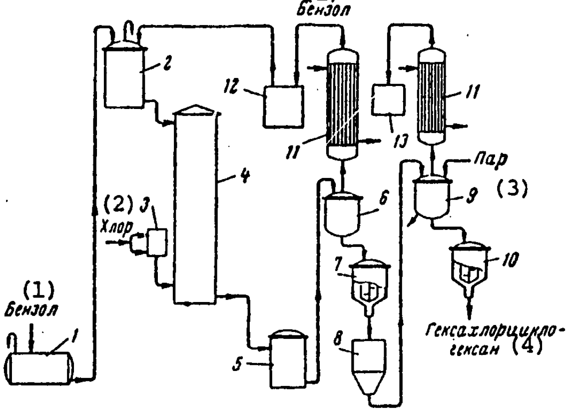


Figure 6. Flowchart for Production of Hexachlorocyclohexane: *1*--benzene storage container; *2*--pressure tank; *3*--chlorine filter; *4*--chlorinator; *5*--hexachlorocyclohexane solution collector; *6*--benzene partial distillation vat; *7,10*--crystallizers; *8*--centrifuge; *9*--vat for distillation of benzene with steam; *11*--heat exchangers; *12*--returned benzene collector; *13*--wet benzene collector

Key:

1. Benzene	3. Steam
2. Chlorine	4. Hexachlorocyclohexane

Technical-grade hexachlorocyclohexane is also obtained on an industrial scale by chlorination of benzene in the presence of aqueous solutions of caustic alkalis or lime at about 0°C. The ingredients usually added to the apparatus include benzene, ice and alkali solution, to which liquid chlorine is fed. During the reaction the temperature increases somewhat, sometimes reaching 30°C. This process is more difficult to regulate than the one described above. The technical-grade product obtained by this method contains up to 18 percent γ-hexachlorocyclohexane (2).

γ-Hexachlorocyclohexane can be obtained from technical-grade product by extraction with the appropriate solvent. The crude product is treated with a calculated quantity of methanol (or another suitable solvent), undissolved α- and β-isomers are filtered out, and the filtrate is allowed to cool. This produces technical-grade γ-isomer which, following separation from the mother liquor and drying, contains more than 90 percent target substance. To obtain lindane, the preparation is recrystallized, or α-isomer is separated from it by extraction. Thus the yield of lindane may be more than 80 percent (12,18).

Not only the temperature and the ratio of ingredients but also the crystal size of the technical-grade product and many other factors have an influence on extraction. γ-Hexachlorocyclohexane is extracted best of all by multiple use of mother liquor obtained following isolation of γ-isomer (12).

Hexachlorocyclohexane is used to control various harmful insects--plant pests and animal parasites. However, its use in animal husbandry is being reduced owing to the possibility of its accumulation in animal tissues and its entry into milk and meat.

Hexachlorocyclohexane is used in various forms: dusts, wettable powders, emulsion concentrates, smoke bombs and so on.

Hexachlorocyclohexane is used to control plant pests mainly in the form of 99.5-100 percent γ-isomer (lindane). A preparation containing not less than 90 percent γ-hexachlorocyclohexane is often used as an additive to seed treaters. Technical-grade product containing 10-14 percent γ-isomer is rarely used today.

Also of practical interest are other isomers of hexachlorocyclohexane, so-called non-toxic isomers which may be used to produce valuable preparations for agriculture and industry. Some of these products are shown in Table 11.

Acquisition of these substances from hexachlorocyclohexane isomers is shown in the diagram on p 51 (19-22).

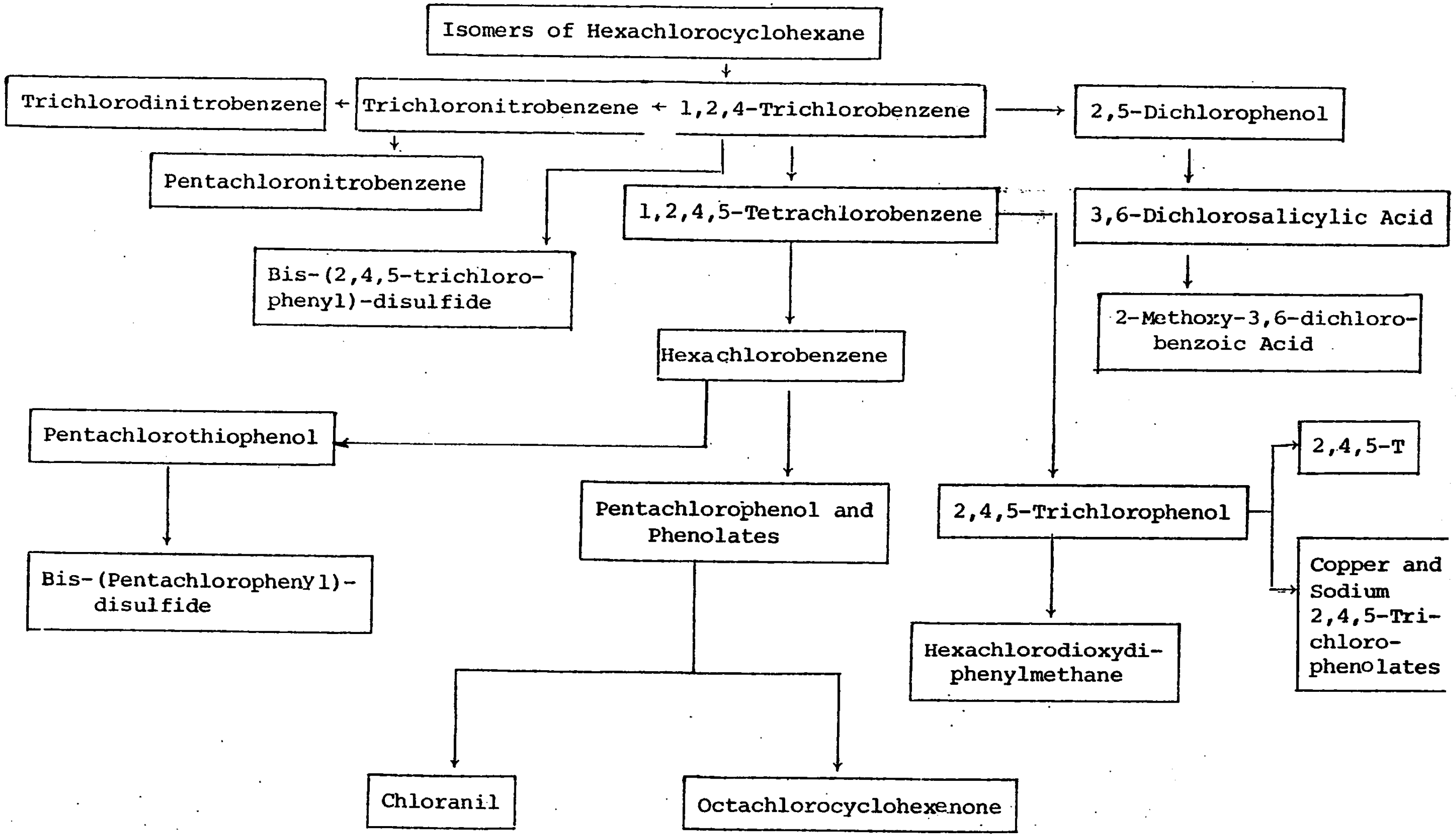
Technical-grade hexachlorocyclohexane and lindane are ingredients of complex-action seed treaters. Seed treaters are known to be combined with γ-hexachlorocyclohexane and ethylmercuric chloride (mercuran), hexachlorobenzene (hexagamma), and copper tetramethylthiuram disulfide and trichlorophenylate (fentiuram) and many other fungicides. Usually such seed treaters contain, in addition to fungicide and filler, from 10 to 50 percent γ-hexachlorocyclohexane.

δ-Hexachlorocyclohexane has also been suggested as an ingredient of seed treaters, since it improves the fungicidal properties of some preparations, which makes it possible to reduce the concentration of the active ingredients of the principal fungicide, and of γ-isomer.

Lindane is used together with DDT against the Colorado beetle and other pests. Such a combined preparation has doubtless advantages, for example in the control of synanthropic insects. In the latter case methoxychlor is also added to the mixture.

Table 11. Substances Obtained From Isomers of Hexachlorocyclohexane

Compound	Use
Trichlorobenzene	Solvent, transformer fluid, intermediate product for organic synthesis
1,2,4,5-Tetrachlorobenzene	Herbicide, intermediate product for organic synthesis
Hexachlorobenzene	Seed treater, intermediate product for organic synthesis
2,3,5,6-Tetrachloronitrobenzene	Potato sprouting inhibitor
Pentachloronitrobenzene	Soil fungicide, seed treater
Trichlorodinitrobenzene	Selective fungicide
2,5-Dichlorophenol	Intermediate product for organic synthesis
2,4,5-Trichlorophenol	Antiseptic, intermediate product for organic synthesis
Sodium 2,4,5-trichlorophenolate	Antiseptic
Copper 2,4,5-trichlorophenolate	Cotton seed treater, antiseptic for nonmetallic materials
Pentachlorophenol	Antiseptic, dessicant, herbicide
Sodium pentachlorophenolate	Antiseptic, dessicant, herbicide
2,4,5-Trichlorothiophenol	Intermediate product in (renatsit) acquisition
Pentachlorothiophenol	Intermediate product for (renatsit) acquisition
Tetrachlorobenzoquinone	Seed treater, intermediate product for organic synthesis
2,4,5-Trichlorophenoxyacetic acid and its derivatives	Herbicides
2-Methoxy-3,6-dichlorobenzoic acid	Herbicide
2-Methoxytrichlorobenzoic acid	Herbicide
Hexachlorodioxydiphenylmethane	Antiseptic
Hexachlorocyclohexanone	Herbicide


Isomers of Hexachlorocyclohexane
Trichlorodinitrobenzene
Trichloronitrobenzene
1,2,4-Trichlorobenzene
2,5-Dichlorophenol
Pentachloronitrobenzene
1,2,4,5-Tetrachlorobenzene
3,6-Dichlorosalicylic Acid
Bis-(2,4,5-trichloro-phenyl)-disulfide
2-Methoxy-3,6-dichloro-benzoic Acid
Hexachlorobenzene
Pentachlorothiophenol
2,4,5-T
Pentachlorophenol and Phenolates
2,4,5-Trichlorophenol
Copper and Sodium 2,4,5-Tri-chloro-phenolates
Bis-(Pentachlorophenyl)-disulfide
Hexachlorodioxydi-phenylmethane
Chloranil
Octachlorocyclohexenone

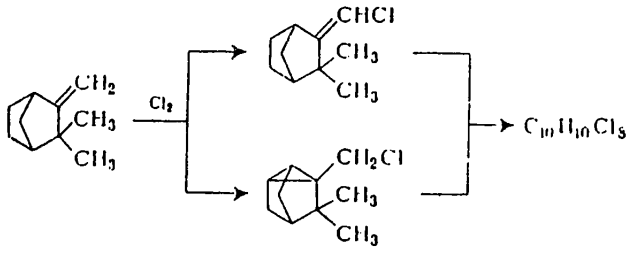
Polychloroterpenes

Polychloroterpenes were first used in the Soviet Union to control some animal parasites. A preparation made from the chlorination products of the pinene fraction of galipot turpentine with a bound chlorine concentration of up to 55 percent has been used as an insecticide. However, this preparation cannot be used to control plant pests due to its high phytocidal action, which is apparently associated with liberation of hydrogen chloride in response to the action of light and water. A somewhat less phytocidal product of pinene chlorination containing up to 66-68 percent chlorine goes under the names of strobane and chloropinane, but this preparation's insecticidal action is inferior to that of other known chlorinated terpenes.

Research has been conducted on the chlorination products of many terpenes, to include pinene, camphene, dipentene, fenchene, phellandrene, carene, thujone and others, but only a few of them are of practical interest. 2,6,7-Trichlorocamphane has noticeable insecticidal action, but it is also phytocidal.

Toxaphene (polychlorocamphene, khlorfen): Of terpene chlorination products, polychlorocamphene ($C_{10}H_{10}Cl_8$), obtained by chlorination of camphene to a chlorine concentration of 67-69 percent, is the best known.

Toxaphene is a complex mixture of polychlorocamphenes and polychlorocamphanes of various structure; certain quantities of chlorination products of tricyclene and related compounds may be present as well:



Toxaphene is a white waxy substance with a melting point of 65-90°C and density d_{20}^{20} 1.6. It is practically insoluble in water, but it is readily soluble in many organic solvents. Its LD_{50} in rats is 60 mg/kg.

In the presence of toxic alkalis part of the chlorine splits off easily in the form of hydrogen chloride. When a hexane solution of toxaphene is heated in the presence of pyridine and KOH in methanol, it is turned. Some other chlorinated terpenes produce a similar reaction.

To obtain toxaphene and its analogues by camphene chlorination, the reaction mixture is usually illuminated by various light sources. Chlorination may be performed in the presence of free radical initiators, for example azo-bis-isobutyronitrile (23). Camphene chlorination proceeds very swiftly at first, with large amounts of heat liberated, but then the rate of chlorination decreases sharply, and the reaction must be continued at higher temperature. However, considering the relatively low thermal stability of the chlorination product, the reaction temperature must not be too high. To reduce the viscosity of the reaction medium, chlorination is very often performed in carbon tetrachloride, which is distilled away following chlorination (24-26). Figure 7 shows a flowchart for photochemical production of polychlorocamphene.

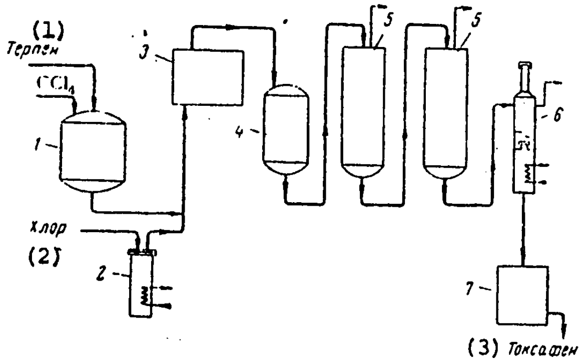


Figure 7. Basic Flowchart for Toxaphene Production: *1*--terpene solution preparation apparatus; *2*--chlorine evaporator; *3*--photochemical chlorination reactor; *4*--final chlorinator; *5,6*--solvent distillation columns; *7*--finished product collector

Key:
1. Terpene
2. Chlorine
3. Toxaphene

It should be noted that toxaphene slowly liberates hydrogen chloride during storage. A small quantity of glycerin epichlorohydrin is added to stabilize it and to bind hydrogen chloride.

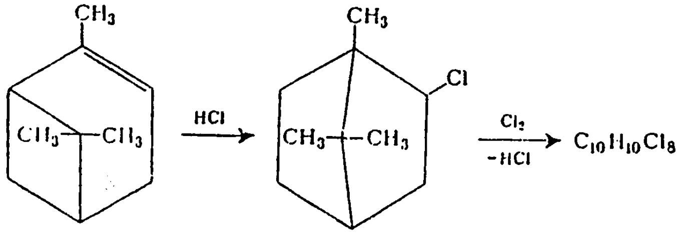
Camphene would best be chlorinated in glass apparatus, since metallic apparatus is easily corroded. Moreover the metal salts that are formed (especially of iron) catalyze toxaphene's breakdown. When glass chlorinators are used, the light source may be located outside the apparatus. Daylight lamps are used most often as the light source, though mercury lamps may also be used.

Toxaphene is used in the form of dust and suspensions, or in the form of emulsions and solutions for low volume spraying and ultralow volume spraying.

One of the positive properties of toxaphene is its low toxicity to bees. The maximum quantities of toxaphene allowed on fruits to be used as food are 7 mg/kg in the USA and 0.4 mg/kg in the FRG.

Toxaphene produces satisfactory results in rodent control. For this purpose it may be used in the form of dietary bait and as an oil mixture. In the latter case the preparation is applied to burrow entrances.

Polychloropinene (khlorten): Polychloropinene is obtained by photochemical or initiated chlorination of bornyl chloride to 64-67 percent chlorine. The pinene fraction of galipot turpentine is usually used for production purposes; turpentine is hydrochlorinated by the action of hydrogen chloride, and the resulting bornyl chloride is chlorinated by chlorine (23,26-28). Bornyl chloride is chlorinated in all the same conditions as camphene chlorination:



Polychloropinene is a viscous colorless oil having a consistency reminiscent of honey; d_{20}^{20} 1.5-1.6. It is practically insoluble in water, and it is freely soluble in organic solvents. It is similar in chemical properties to toxaphene. The LD_{50} is 350-525 mg/kg. The maximum permissible concentration in air is 0.2 mg/m^3.

Polychloropinene's phytocidal action is superior to that of toxaphene. In contrast to toxaphene, it is toxic to bees. Polychloropinene is used in the USSR for beet pest control in the form of emulsions or oil solutions intended for low volume spraying. The consumption norm is 1-2 kg/ha.

Polychloropinene is close to strobane in toxicity to fish. The AC_{50} to blue carp is 15 parts per billion with an exposure time of 24 hours (29).

Strobane (chloropinane): Strobane is obtained by chlorination of pinene to not less than 66 percent chlorine. It is a dense viscous mass with d_{20}^{20} 1.6 and n_D^{20} 1.5790, and its vapor pressure at 20°C is $3 \cdot 10^{-7}$ mm Hg. It is practically insoluble in water, and it is freely soluble in organic solvents, for example in ethanol (12-14 percent). Its LD_{50} in albino rats is 250 mg/kg.

Its insecticidal activity is about 1.5 times weaker than toxaphene.

Strobane is obtained similarly as polychloropinene, by chlorination of turpentine in the presence of light (30) or in the presence of catalysts--PCl_5 for example (31). According to patent data (30) the first step in obtaining strobane involves hydrochlorination of pinene with the purpose of transforming it into bornyl chloride. To remove hydrogen chloride, the chlorination product is washed with diluted soda solution and water. Chlorination is performed at 50-150°C (30).

Because strobane may liberate hydrogen chloride during lengthy storage, it is stabilized by the addition of pinene (up to 2 percent), which binds hydrogen chloride, transforming into bornyl chloride.

Practically all of the polychloroterpenes described above have a certain amount of acaricidal action and exhibit extremely low activity as fungicides and bactericides.

Owing to high toxicity to fish, polychloropinene and its analogues have enjoyed some use in the destruction of trash fish in small water basins, but because of their long active life and relatively slow breakdown, they should be used in this way with caution.

The preparation polidofen (32), which contains DDT (20 percent), polychlorocamphene (40 percent), the nonphytocidal fraction of diesel fuel from petroleum from the Archedinsk deposit, petroleum solvent and OP-7 emulsifier, has been suggested as an insecticide to control cotton pests.

Because of low cost and ease of production, polychloroterpenes have enjoyed rather widespread use in agriculture, but owing to the common shortcomings typical of all stable organic compounds of chlorine, the use of these preparations is tending to decline. But the scale of their use is still rather great.

CHAPTER 10

ALIPHATIC CARBOXYLIC ACIDS AND THEIR DERIVATIVES

Saturated aliphatic monobasic and dibasic carboxylic acids have relatively low pesticidal activity, and they have not enjoyed practical application.

The insecticidal activity of acids and their salts in relation to the leguminous aphis increases as molecular weight increases, and it achieves its maximum with lauric acid, after which it decreases.

Calcium propionate $(CH_3CH_2COO)_2Ca$, used in baking and cheese-making industry to improve the storage qualities of baked goods and cheese, possesses fungistatic and bacteriostatic properties. Propionic acid has enjoyed some use as a preservative. Dithiodiundecanic acid has been proposed as a herbicide (6).

Unsaturated aliphatic acids possess significantly greater biological activity. They have been found to have the properties of attractants, fungicides, herbicides and plant growth regulators (1-5). Sorbic (*trans*,*trans*-hexadien-2,4-oic) acid has enjoyed broad use as a feed preservative in animal husbandry, and as a preservative in cosmetics and various other products.

Sorbic acid is a white crystalline substance with a melting point of 134.5°C and a boiling point of 228°C at 760 mm Hg (partial decomposition occurs). Its solubility in 100 gm water is 0.16 gm at 20°C, 0.6 gm at 50°C and 3.6 gm at 100°C; its solubility in 100 gm absolute ethanol is 14.5 gm. Its LD_{50} in rats is 7,360 mg/kg (7).

Sorbic acid is obtained by condensation of crotonic aldehyde with ketene in the presence of boron trifluoride (the industrial method) or with malonate:

$$CH_3{-}CH{=}CH{-}CHO + CH_2{=}C{=}O \xrightarrow{BF_3} CH_3{-}CH{=}CH{-}CH{=}CH{-}COOH$$

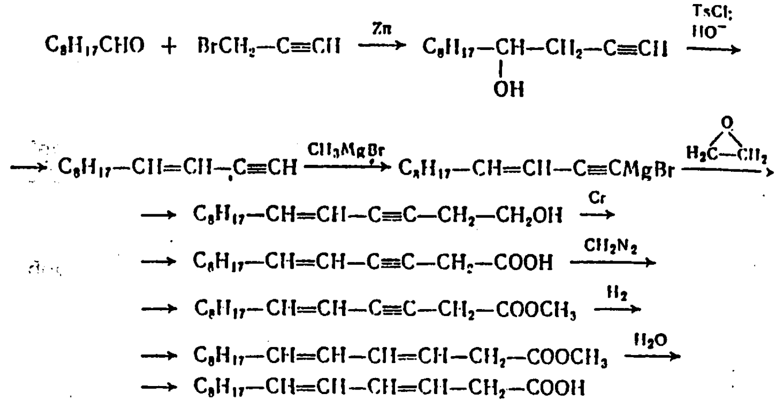
$$CH_3{-}CH{=}CH{-}CHO + CH_2(COOC_2H_5)_2 \longrightarrow$$

$$\longrightarrow CH_3{-}CH{=}CH{-}CH{=}C(COOC_2H_5)_2 \longrightarrow$$

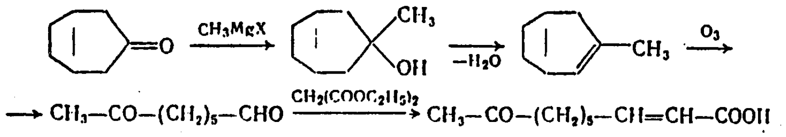
$$\longrightarrow CH_3{-}CH{=}CH{-}CH{=}C(COOH)_2 \longrightarrow CH_3{-}CH{=}CH{-}CH{=}CH{-}COOH$$

Undecylenic acid (boiling point 275°C at 760 mm Hg, melting point 24.5°C) and some of its derivatives have herbicidal action, but they have not yet enjoyed practical application.

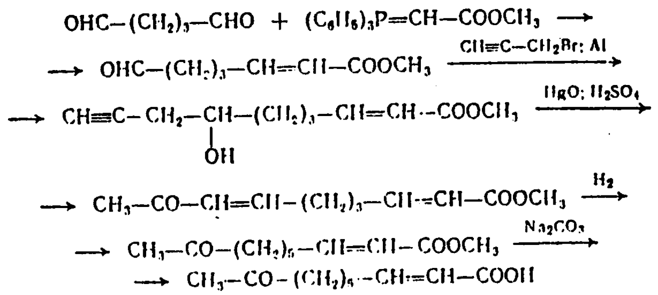
cis,trans-Tetradecadien-3,5-oic acid (1,2,4), which is synthesized as follows (2), is an attractant of the leather beetle:



Honeybee attractant released together with secretions from the uterus is an unsaturated keto acid (1,2,3). It has been determined to be *trans*-9-ketodecen-2-oic acid, and it may be obtained from cycloheptanone (2,8,9):

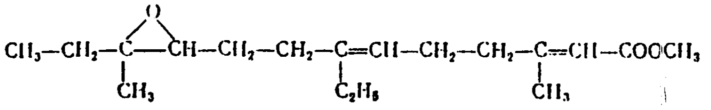


and from glutaric aldehyde (2,10,11):



The second method is rather simple, and it may be used to make sizeable quantities of the preparation. The greatest difficulties lie in isolating the pure *trans*-isomer.

Among the natural substituted unsaturated acids, we should mention an insect juvenile hormone--the methyl ester of *trans,trans*-3,11-dimethyl-7-ethyl-10,11-epoxytridecadien-2,6-oic acid (I) (12-15):



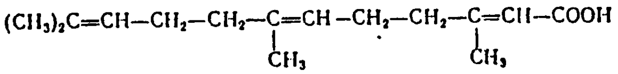
I

presence of which in the necessary quantities promotes normal development of insects; in excess quantities it disturbs metamorphosis and subsequently causes the death of the insect. Hormone preparations of this sort have been proposed to control plant pests (12-19).

A relatively simple way for synthesizing juvenile hormone and similar compounds has been developed (15); however, only very pure compounds, ones which do not contain isomeric impurities, have high activity, and their purification presents significant difficulties.

It has been established that the hormonal activity of substances such as juvenile hormone may be amplified by the addition of synthetic synergists (17).

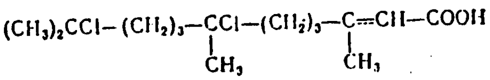
The properties of juvenile hormone are possessed by some derivatives of farnesilic (3,7,11-trimethyldodecatrien-2,6-10-oic) acid (II) (16,18,19):



$$(CH_3)_2C{=}CH{-}CH_2{-}CH_2{-}\underset{CH_3}{C}{=}CH{-}CH_2{-}CH_2{-}\underset{CH_3}{C}{=}CH{-}COOH$$

II

Esters of 7,11-dichloro-3,7,11-trimethyldodecen-2-oic acid have high activity in particular (18,19). 7,11-Dichloro-3,7,11-trimethyldodecen-2-oic acid (melting point 92-93°C) (III) forms in sizeable quantities when farnesilic acid solutions in methanol are saturated with gaseous hydrogen chloride:

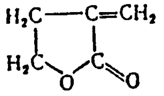


$$(CH_3)_2CCl{-}(CH_2)_3{-}\underset{CH_3}{C}Cl{-}(CH_2)_3{-}\underset{CH_3}{C}{=}CH{-}COOH$$

III

Its methyl ester apparently possess the greatest activity. The farnesilic acid required for its synthesis may be obtained by oxidation of farnesol (3,7,11-trimethyldodecatrien-2-6,10-ol-1, which enjoys a certain amount of use in perfume industry.

Two preparations have been released as experimental pesticides (19a): entakon (TsR-515)--the isopropylate of 11-methoxy-3,7,11-trimethyldodecadien-2-4-oic acid (LD_{50} 10,000 mg/kg), and entokon (TsR-512)--the ethylate of 3,7,11-trimethyldodecadien-2,4--oic acid (LD_{50} 34,000 mg/kg). 2-Methylene butyrolactone is a factor in the natural resistance of poppies and some other plants to *Fusarium oxysporium* (20):



The pesticidal activity of acids grows dramatically when hydrogen atoms in the alkyl radical are substituted by halogens. Thus compounds as simple as acetic monohalide possess significant pesticidal activity, and some of them are used in agriculture and public health.

The pesticide activity of carboxylates is higher as rule than the activity of free acids and their salts. Amides of various aliphatic acids and their halide derivatives are the most active. Amides exhibit moderate insecticidal and acaricidal activity, but they are rather strong fungicides and herbicides. More than 20 aliphatic acid amides have achieved practical use in the control of plant weeds and for other purposes. Acid nitriles and thio derivatives as well as derivatives of dibasic aliphatic acids also possess pesticidal properties.

The toxicity of fluoroalkylcarboxylic acids to homeothermic animals depends on the number of CH_2 groups separating fluorine from the carbon atom of the carboxyl group. The toxicity of some fluoroalkylcarboxylates (in propylene glycol) to animals is given below:

	LD_{50} mg/kg
FCH_2COOCH_3	15
$F(CH_2)_2COOC_2H_5$	200
$F(CH_2)_4COOC_2H_5$	160
$F(CH_2)_5COOC_2H_5$	4
$F(CH_2)_7COOC_2H_5$	9
$F(CH_2)_9COOC_2H_5$	10
$F(CH_2)_{10}COOC_2H_5$	100
$F(CH_2)_{11}COOC_2H_5$	20

Compounds with an odd number of CH_2 groups are more toxic. This is explained by the fact that compounds with an even number of CH_2 groups are oxidized to form fluoroformic acid, and subsequently carbonic acid, while acids with an uneven number of CH_2 groups produce extremely toxic fluoroacetic acid:

$$FCH_2{-}CH_2{-}CH_2{-}COOH \longrightarrow$$

$$\longrightarrow FCH_2{-}CH{=}CH{-}COOH \xrightarrow[-CO_2;\ -H_2O]{[O]} FCH_2{-}COOH$$

The toxicity of fluoroacetic acid is associated with a number of metabolic processes, the most important one of which is formation of fluorocitric acid (21).

Salts and some amides of fluoroacetic acid are used as extremely toxic zoocides. Fluoroacetic acid amides may be used as systemic insecticides to control sucking plant pests (22-32) and as herbicides (33).

Fluoroacetic acid is obtained by reacting monochloroacetates with potassium fluoride at 200-220°C under pressure:

$$ClCH_2{-}COOCH_3 \xrightarrow[-KCl]{+KF} FCH_2{-}COOCH_3 \xrightarrow[-CH_3OH]{+H_2O} FCH_2{-}COOH$$

and by causing a reaction between carbon monoxide, formaldehyde and hydrogen chloride under pressure:

$$HF + CO + CH_2O \longrightarrow FCH_2{-}COOH$$

Fluoroacetic acid may also be obtained by oxidation of 2-fluoroethanol and a number of other compounds (34,35).

Amides and analides of fluoroacetic acid can be produced in sizeable quantities by reacting fluoroacetyl chloride, fluoroacetan hydride or fluoroacetic acid with the appropriate amines (26,28,32,36,37):

$$RNH_2 + FCH_2COOH \xrightarrow[-H_2O]{} FCH_2CONHR$$

or by reacting the appropriate amides of monochloro- or monobromoacetic acids with potassium fluoride (29,32):

$$XCH_2CONHR \xrightarrow[-KX]{+KF} FCH_2CONHR$$

Sodium and barium fluoroacetates--white crystalline substances that are freely soluble in water--have enjoyed practical use in rodent control. These salts are used as aqueous solutions or in dietary bait. Their LD_{50} is 0.22-4 mg/kg. Due to the very high toxicity of these preparations, only specially trained people are allowed to work with them.

The amide and anilide of fluoroacetic acid (melting points 108°C and 75-76°C respectively) have also been proposed as zoocides. They are less toxic to vertebrates and safer to use. The toxicity of fluoroacetamide to homeothermic animals (LD_{50}) is 4-5 mg/kg, while the toxicity of fluoroacetanilide is 10-12 mg/kg.

N-Methyl-N-(naphthyl-1)-fluoroacetamide (MNFA), obtained by any of the methods described above (32), has enjoyed some use as a systemic insecticide. It is a white crystalline substance with a melting point of 87-88°C. It is poorly soluble in water and freely soluble in organic solvents. It may be used to control plant pests as a wettable powder or an emulsion concentrate. Its LD_{50} is 25 mg/kg in rats and 158 mg/kg in mice.

A very large number of various fluoroacetanilides and fluoroacetamides have been studied (22-32,36,38), but they have not as yet enjoyed practical application.

Fluoroacetates and halide phenolates have insecticidal properties (39), while polyfluoropropionic acid analides possess fungicidal and herbicidal properties (40).

Sodium 2,2,3,3-tetrafluoropropionate--a white, extremely hygroscopic substance with a melting point of 152°C--has recently enjoyed application as a herbicide to control annual and perennial monocotyledonous weeds. It is practically insoluble in hydrophobic organic solvents. Its solubility in water at 20°C is about 3,000 gm/liter

(41-44). Its LD_{50} in rats is about 10 gm/kg. Its AC_{50} in fish is about 100 mg/liter. It is extremely stable when stored, and it is highly resistant to various external factors.

It is used for weed control in the form of an aqueous solution containing 900 gm/liter active ingredient, in the form of granules with 6 percent active ingredient (Orga-3045 and Orga-3045-granulyat) and in the form of a granulated preparation combined with diuron (6 and 3 percent), simazine (6 and 2 percent) and amitrole 44. The preparation's consumption norm is 3-6 kg/ha (active ingredient).

The most convenient way to obtain 2,2,3,3-tetrafluoropropionic acid is to react perfluoroethylene with sodium cyanide in the presence of water in acetonitrile or dimethylformamide, followed by hydrolysis of the formed nitrile by sulfuric acid (45,46):

$$C_2F_4 + NaCN \xrightarrow[-NaOH]{+H_2O} CHF_2-CF_2-CN \xrightarrow[-NH_4HSO_4]{+2H_2O;\ +H_2SO_4} CHF_2-CF_2-COOH$$

The first reaction proceeds at low pressure and a temperature up to 80°C, while the second proceeds at 70-80°C. This acid may also be obtained by oxidation of fluoroolefins (34).

The pesticidal properties of chloroalkane carboxylic acids have been studied to the greatest detail in recent years. Derivatives of chloroalkane carboxylic acids have achieved the greatest significance as herbicides. In particular, herbicidal properties are possessed by mono- di- and trichloroacetic acids, di-, tri-, tetra- and tetrachloropropionic acids, mono-, di- and trichlorobutyric and isobutyric acids and many others. The biological activity of halogenated acids is significantly influenced by the position of the halogen in relation to the carbonyl group. α-Halogenated acids possess the greatest activity. Bromo- and iodo- acids have been studied less, but active fungicides and herbicides have been found among them (47,48).

Monochloroacetic acid: This acid has a melting point of 63°C, it is freely soluble in water and in many organic solvents, and it causes burns on plants.

Monochloroacetic acid is now obtained by chlorination of acetic acid in the presence of catalysts (iodine, sulfur, phosphorus chlorides and their combinations):

$$CH_3COOH + Cl_2 \xrightarrow[-HCl]{} ClCH_2COOH$$

as well as by hydration of trichloroethylene followed by hydrolysis of the resulting alcohol:

$$CHCl{=}CCl_2 + H_2SO_4 \longrightarrow ClCH_2-CCl_2-OSO_3H \xrightarrow[-H_2SO_4]{+H_2O}$$

$$\longrightarrow ClCH_2-CCl_2OH \xrightarrow[-HCl]{} ClCH_2-COCl \xrightarrow[-HCl]{+H_2O} ClCH_2-COOH$$

The first method is used in various modifications in the industry of many countries. Acetic acid is chlorinated at high temperature in the presence of catalysts. Recently sulfur or phosphorus has been used most often as the catalyst, in an amount equivalent to 3 percent of the mass of acetic acid to be chlorinated (49). Chlorination of acetic acid produces a small quantity of dichloro- and trichloroacetic acids as by-products. By chlorination in harsher conditions this mixture is transformed into trichloroacetic acid and is then used to produce herbicidal preparations (50). Acetic acid may be chlorinated in the presence of acetic anhydride (0.07 percent of the mass of monochloroacetic acid obtained) (51). A basic flowchart for production of monochloroacetic acid using this method is shown in Figure 8 (51).

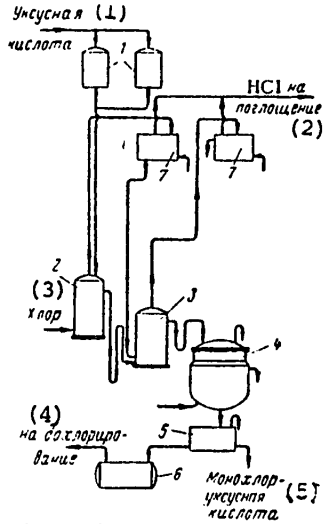


Figure 8. Basic Flowchart for Production of Monochloroacetic Acid by a Continuous Method: *1*--gaging tanks; *2*,*3*--chlorinators; *4*--crystallizer; *5*--centrifuge; *6*--mother liquor collector; *7*--heat exchangers

Key:

1. Acetic acid
2. Absorption
3. Chlorine
4. Final chlorination
5. Monochloroacetic acid

Pure monochloroacetic acid is usually isolated by crystallization from the reaction mixture (or from the distilled reaction mixture); upon cooling, the bulk of the monochloroacetic acid contained in this mixture precipitates out, and the mixture of high-chlorine products and unreacted acetic acid remains in liquid form, and is separated by centrifugation.

Monochloroacetic acid is used in agriculture in the form of its sodium salt, obtained by the acid's neutralization by soda or by sodium hydroxide at low temperature, since at high temperature sodium monochloroacetate transforms readily into glycolic acid. Sodium monochloroacetate is used as a herbicide and a defoliant at a consumption norm of 5-20 kg/ha.

Monochloroacetic acid and its sodium salt are used to produce important herbicides such as 2,4-D, 2M-4C, 2,4,5-T and others.

Use of monochloroacetic acid esters and amides as herbicides and fungicides has also been proposed.

Trichloroacetic acid: Melting point 57.3°C, boiling point 195°C at 760 mm Hg.

Trichloroacetic acid is obtained by direct catalytic chlorination of acetic, monochloroacetic and dichloroacetic acids and their mixtures, or by oxidation of the chloral form of nitric acid:

$$CH_3COOH \xrightarrow{Cl_2} CCl_3COOH \xleftarrow{[O]} CCl_3CHO$$

The latter method is somewhat simpler, and it produces a good yield of trichloroacetic acid. Salts of this acid can be obtained by neutralizing it with the appropriate basis at the lowest possible temperature, since higher temperature would cause the acid's decomposition:

$$CCl_3COOH \longrightarrow CHCl_3 + CO_2$$

Trichloroacetic acid is used in agriculture to control monocotyledonous weeds. It is used almost exclusively in the form of salts of alkali metals or amines.

Alkali metal trichloroacetates are used mainly to control monocotyledonous weeds in sugar beets, alfalfa, sugar cane and other crops, in which case the consumption norms of the preparation are relatively high (12-60 kg/ha). The preparations are applied prior to sprouting or prior to planting, since crops can be injured when the consumption norms are so high.

The preparations are practically nontoxic to homeothermic animals. The LD_{50} of sodium trichloroacetate is 3,300-5,000 mg/kg.

The glycolic ester of trichloroacetic acid (glitak) has enjoyed some use as a herbicide (19a).

α,α-Dichloropropionic acid: Boiling point 193-197°C at 760 mm Hg. LD_{50} 6,000-8,000 mg/kg.

α,α-Dichloropropionic acid is obtained by chlorination of propionic acid at high temperature (the reaction proceeds better in light) in the presence of catalysts:

$$CH_3-CH_2-COOH \xrightarrow[-2HCl]{+2Cl_2} CH_3-CCl_2-COOH$$

The technical-grade preparation contains an insignificant quantity of α,β-dichloro- and α-chloropropionic acids.

α,α-Dichloropropionic acid is used to control monocotyledonous weeds in the form of a water-soluble sodium salt.

Sodium α,α-dichloropropionate (dalapon): Melting point 174-176°C (some decomposition occurs). It is produced in the form of an 87-95 percent preparation.

To obtain the sodium salt, concentrated acid is processed with 40 percent sodium hydroxide solution in a chilled environment; the crystallized salt is filtered out and dried, and the mother liquor is used as a solvent to obtain new portions of salt. A sufficiently pure salt is obtained in this way with minimum losses. When the preparation is neutralized in diluted solutions followed by evaporative concentration, a significant proportion of the preparation decomposes, and a highly contaminated product results.

Dalapon is capable of moving through the plant vascular system, owing to which it is highly active against many monocotyledonous plants in relation to which other herbicides exhibit low activity. The consumption norm is 12-40 kg/ha.

Alkali metal dichloropropionates react with water to form herbicidally inactive pyruvic acid; therefore storage of their aqueous solutions for a long period of time is not recommended.

Because the simplest halogenated alkane carboxylic acids are used extensively in agriculture, the metabolism of chloroacetic acids and of dichloropropionic acid in soil, plants, animals and microorganisms has been studied in rather great detail (61). Decomposition of these compounds in soil may be represented by the following general formulas:

$$CH_2Cl{-}COOH \xrightarrow[-HCl]{+H_2O} CH_2OH{-}COOH \xrightarrow[-H_2O]{+O_2} HOOC{-}COOH$$

$$CHCl_2{-}COOH \xrightarrow[-2HCl]{+H_2O} OHC{-}COOH \xrightarrow{+O_2} HOOC{-}COOH$$

$$CCl_3{-}COOH \xrightarrow[-3HCl]{+2H_2O} HOOC{-}COOH$$

$$CH_3{-}CCl_2{-}COOH \xrightarrow[-2HCl]{+H_2O} CH_3{-}CO{-}COOH$$

Oxalic acid formed upon hydrolysis and oxidation of haloacetic acids transforms, upon further oxidation, into carbonic acid, while pyruvic acid obtained from dalapon may be included in Krebs' cycle to form amino acids and proteins.

2,4,5-Trichlorophenoxyethyl dichloropropionate (erbon): Melting point 49-50°C; boiling point 161-164°C at 4 mm Hg; LD_{50} 700-1,100 mg/kg. Used as a general herbicide at a consumption norm of 14-20 kg/ha.

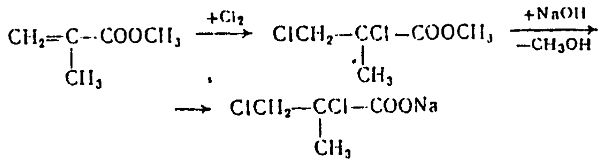
In addition to dalapon, the sodium salt of α,α,β-trichloropropionic acid is used in agriculture. At a consumption norm of 4-12 kg/ha this salt produces satisfactory results in the control of monocotyledonous annual weeds.

Trichloropropionic acid (melting point 65-66°) is obtained by chlorination of acrylonitrile followed by saponification of trichloropropionitrile in 50 percent sulfuric acid:

$$CH_2{=}CHCN \xrightarrow[-HCl]{+2Cl_2} ClCH_2{-}CCl_2{-}CN \xrightarrow[-NH_4HSO_4]{+2H_2O;\ +H_2SO_4} ClCH_2{-}CCl_2{-}COOH$$

The sodium salt of trichloropropionic acid is obtained in conditions similar to those of obtaining dalapon.

The sodium salt of dichloroisobutyric acid has been suggested as a plant sterilizer (it elicits male sterility). Melting point 170-175°C (some decomposition occurs). The boiling point for the free acid is 130-134°C at 35 mm Hg. Its LD_{50} in rats is about 8,000 mg/kg. It is synthesized as follows:

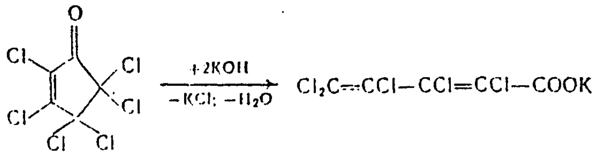


$$CH_2{=}C(CH_3){-}COOCH_3 \xrightarrow{+Cl_2} ClCH_2{-}CCl(CH_3){-}COOCH_3 \xrightarrow[-CH_3OH]{+NaOH} ClCH_2{-}CCl(CH_3){-}COONa$$

Dichloroisobutyrates have been proposed for use as herbicides (52).

The sodium salt of α,α-dichlorobutyric acid (DBA) is a white crystalline substance. It is freely soluble in water and almost insoluble in hydrophobic organic solvents. It is used in the form of an aqueous solution. It may be obtained by chlorination of butyric acid followed by neutralization with sodium hydroxide. Its LD_{50} is more than 2,000 mg/kg. It is used as a general herbicide at a consumption norm of 10-30 kg/ha.

2,3,4,5,5-Pentachloropentadienic acid: Melting point 124-125°C. It is obtained when potassium hydroxide reacts with hexachlorocyclopentanone:



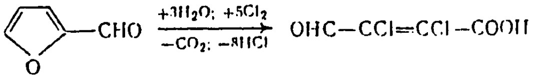
Pentachloropentadienic acid has been proposed as a dessicant and herbicide, but it is still in the research stage.

The sodium salt of *cis*-β-chloroacrylic acid (PREP-defoliant) has a melting point of 162°C, and its solubility in water is 40 percent. It is moderately toxic to animals, and its LD_{50} in rats is 320 mg/kg. Its toxicity to the goldfish is 5,000 mg/liter at an exposure time of 48 hours.

At consumption norms from 2 to 5 kg/ha it quite satisfactorily removes leaves from cotton plants.

Derivatives of dichloro- and trichloroacrylic acids and their homologues have also been proposed as herbicides and fungicides (53-58). Defoliant and dessicant properties are possessed by 2,3,5,5,5-pentachloro-4-ketopenten-2-oic acid, which is a satisfactory cotton dessicant at a consumption norm of 2-8 kg/ha (59), and it causes leaf drop within 6-14 days.

Mucochloric acid is an important intermediate product in the synthesis of a number of pyridazone derivatives with herbicidal action. This acid may be obtained by chlorination of furfural in a hydrochloric acid medium:



and by oxidative chlorination of butynediol:

$$HOCH_2-C\equiv C-CH_2OH \xrightarrow[-6HCl]{+4Cl_2;\ +H_2O} OHC-CCl=CCl-COOH$$

Depending on the conditions of the process, the yield of mucochloric acid is 50-90 percent of theoretical (60). Because of the high aggressiveness of the reaction medium, great difficulties are encountered in selecting the chlorination equipment and in waste treatment.

Mucochloric acid is rather highly poisonous, and when it settles on exposed skin it causes severe irritation. Blisters recalling those produced by thermal burns appear. Mucochloric acid and some of its simplest derivatives have fungicidal action, but owing to their high phytotoxicity their use in this direction is impossible at the moment.

CHAPTER 12

AROMATIC CARBOXYLIC ACIDS AND THEIR DERIVATIVES

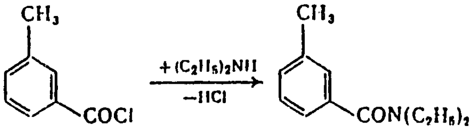
Benzoic Acid Derivatives

N,N-diethyl-*m*-toluamide (DETA)--colorless liquid; boiling point 111°C at 1 mm Hg; d_4^{20} 1.0095, n_D^{20} 1.5206. Practically insoluble in water, freely soluble in most organic solvents, in ethyl and isopropyl alcohols, in propylene glycol and cottonseed oil, in halogen derivatives of aliphatic and aromatic hydrocarbons and in aromatic hydrocarbons. Its LD_{50} in rats is 2,000 mg/kg.

The technical-grade preparation contains not less than 95 percent total isomers of N,N-diethyltoluamide, in which case the concentration of N,N-diethyl-*m*-toluamide must be not less than 70 percent.

When applied to the skin, DETA repels blood-sucking insects for 8-10 hours, in contrast to dimethylphthalate, which provides absolute protection from mosquito bites to the skin for only 1.5-2 hours.

Diethyl-*m*-toluamide is obtained by reacting *m*-toluyl chloride with diethylamide in the presence of caustic alkalis or excess amine, or by reacting *m*-toluylic acid with diethylamine at high temperature in the presence of catalysts:



The apparent simplicity of the second method is enticing, but conversion does not exceed 70 percent, and in just 10-20 hours the catalyst loses its activity and conversion declines to 30 percent.

A flowchart for production of DETA using the first method is shown in Figure 9 (27-30).

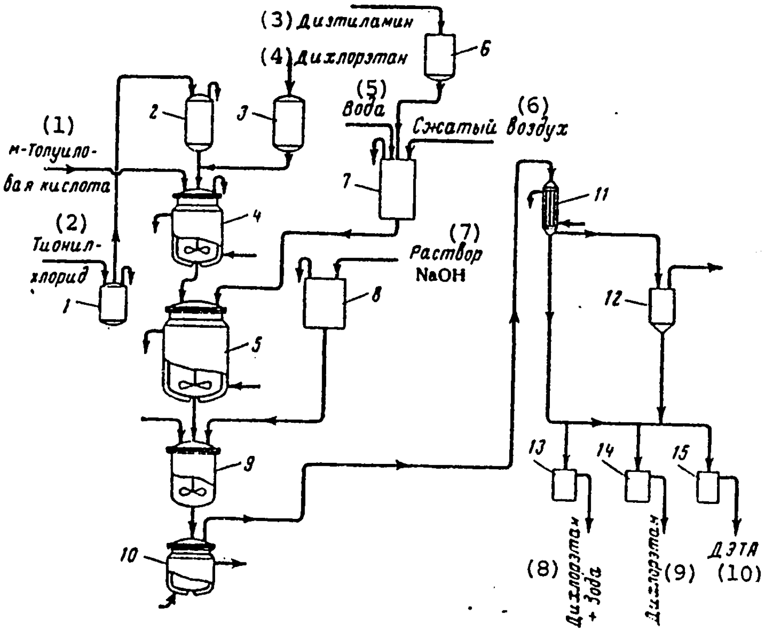


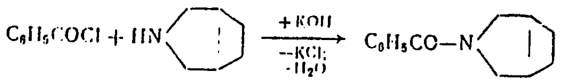
Figure 9. Basic Flowchart for Production of the Diethylamide of *m*-Toluylic Acid (DETA): *1*--thionyl chloride storage tank; *2*--receiver; *3*--dichloroethane gaging tank; *4*--reactor for *m*-toluyl chloride synthesis; *5*--reactor for DETA synthesis; *6,7,8*--gaging tanks for diethylamine, water and aqueous alkali solution; *9*--neutralizer; *10*--reaction mixture distillation vat; *11*--heat exchanger; *12*--spray trap; *13,14*--dichloroethane-water and dichloroethane fraction collectors; *15*--finished product collector

Key:

1. *m*-Toluylic acid	6. Compressed air
2. Thionyl chloride	7. Solution
3. Diethylamine	8. Dichloroethane + water
4. Dichloroethane	9. Dichloroethane
5. Water	10. DETA

A good yield of *m*-toluylic acid is obtained by oxidation of *m*-xylol by atmospheric oxygen at high temperature and slight pressure in the presence of catalysts, usually cobalt salts and organic acids. This reaction also produces a certain quantity of isophthalic acid. The mixture is separated by fractional precipitation out of aqueous alkali salt solutions by mineral acids, or by extraction of *m*-toluylic acid by organic solvents, in which isophthalic acid is poorly soluble.

Strong repellent properties are also inherent to hexamethylene benzamide, which is synthesized by reacting benzoyl chloride with hexamethylenamine in the presence of alkali:

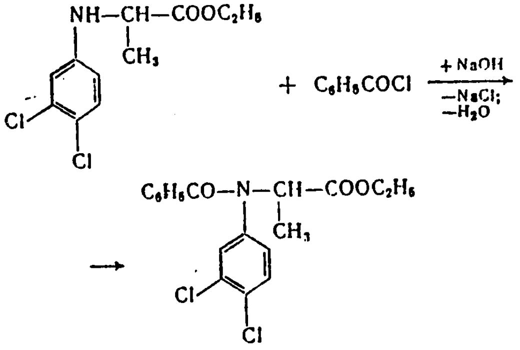


This preparation is used in the USSR under the name of benzimin. It is an ingredient of "Tayga" repellent cream. Benzimin does not cause irritation of the skin, its toxicity to man is low, and it remains active for a long period of time.

This preparation was first proposed by A. N. Kost, and it is now regularly used to protect man and animals from blood-sucking insects.

The ethyl ester of N-benzoyl-N-(3,4-dichlorophenyl)-alanine (sufiks, VL-17731) (131) is a white crystalline substance with a melting point of 70-71°C. It is practically insoluble in water and freely soluble in organic solvents: 45 percent in carbon tetrachloride at 20°C, 70 percent in acetone, 20 percent in methanol and about 10 percent in ethanol (weight by volume). Its LD_{50} in rats is 1,550 mg/kg, it is 715 mg/kg in mice, and it is about 1,000 mg/kg in domesticated birds. It is moderately toxic to fish.

It may be obtained by benzoylation of the ethyl ester of N-(3,4-dichlorophenyl)-alanine by benzoyl chloride in the presence of hydrogen chloride acceptors:



The preparation is a selective herbicide used to control wild oats in wheat fields. It produces satisfactory results at consumption norms up to 1 kg/ha, and it is safe to wheat. Barley is more sensitive to the preparation. It is used in the crop's tillering phase.

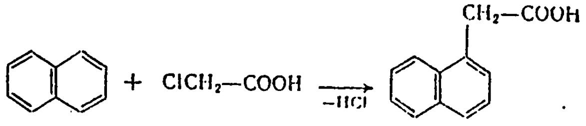
The preparation is marketed as a 40 percent wettable powder and as solutions in mineral oils. The ratio of preparation to mineral oil is 1 to 12-14 kg. The total liquid volume (including water for spraying under various conditions) is from 66 to 500 liters/ha.

Arylalkane Carboxylic Acids and Their Derivatives

α-Naphthylacetic acid is a white crystalline substance with a melting point of 131-132°C. Its solubility in 100 ml water at 25°C is 41-42 mg, and it is practically nontoxic to mammals. The acid amide melts at 183°C.

The most important methods of obtaining α-naphthylacetic acid are as follows:

1. Condensation of monochloroacetic acid with excess naphthaline at 200-220°C in the presence of a catalyst:



This reaction proceeds for 15-20 hours. The α-naphthylacetic acid yield is about 70 percent. A certain quantity of naphthylenediacetic acid is formed as a byproduct. It is easily separated owing to its better solubility in water. It may also be separated by distillation of methylates in a vacuum. This method is used for industrial production of α-naphthylacetic acid (see Figure 10).

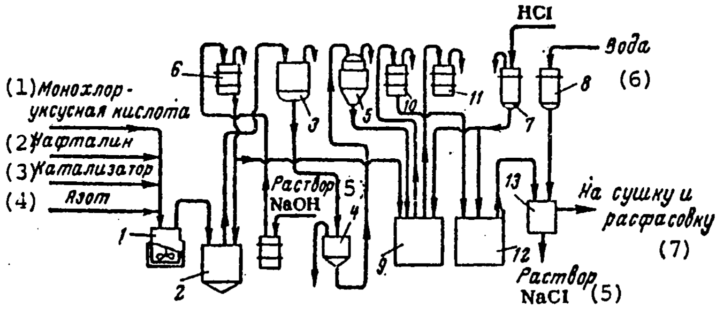
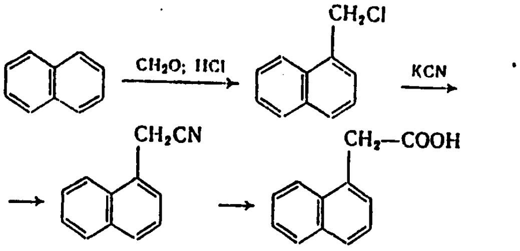


Figure 10. Basic Flowchart for Production of α-Naphthylacetic Acid: *1*--reactor; *2*--reactor-extractor; *3*--extract settling tank; *4*--Nutsch filter; *5*--extract gaging tank; *6,7,8*--gaging tanks for NaOH, HCl and water; *9*--neutralizer; *10*--salt solution collector; *11*--resin collector; *12*--α-naphthylacetic acid precipitation apparatus; *13*--vacuum filter

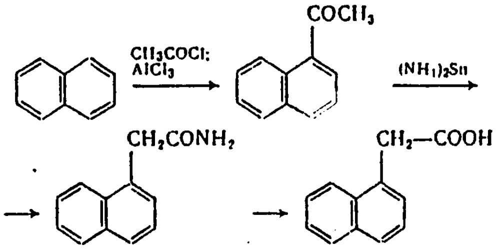
Key:
1. Monochloroacetic acid
2. Naphthaline
3. Catalyst
4. Nitrogen
5. Solution
6. Water
7. To drying and packaging

2. Hydrolysis of naphthylacetonitrile. The latter is synthesized by reacting chloromethylnaphthaline with hydrocyanic acid salts:



This method is more complex, but it produces a good yield of pure preparation.

3. Synthesis out of α-naphthylmethylketone using Willgerodt's reaction produces α-naphthylacetic acid with a high degree of purity:



The intermediate product in this reaction is α-naphthylacetamide, which may be used without further processing as a plant growth regulator. The α-naphthylmethylketone required for this synthesis is produced by the Fridel-Crafts reaction from naphthylene and acetylchloride in dichloroethane at 34°C. The yield is 94 percent. When the reaction conditions are kept optimum, the technical-grade separation contains not more than 3 percent 2-isomer impurities (234).

Esterification of α-naphthylacetic acid by methanol in the presence of sulfuric acid forms a quantitative yield of methyl-α-naphthylacetate (boiling point 122-122.5°C at 1 mm Hg). A quantitative yield of the ester is achieved only when the reaction is performed at room temperature; its yield decreases dramatically when heated. This ester is used as a 3.5 percent dust in clay (preparation M-1) to retard sprouting in long-term storage; the consumption norm is 100 gm per ton of potatoes.

α-Naphthylacetic acid and its amide are also used to thin out apple blossoms and to delay blossoming with the purpose of protecting the blossoms from freezing, and in some other cases.

The metabolism of α-naphthylacetic acid, its amide and its methyl ester has been studied. It has been established that the acid decomposes into oxymethylnaphthaline, α-naphthoic acid and phthalic acid. α-Naphthylacetic acid undergoes analogous decomposition when its aqueous solutions are illuminated by sunlight or ultraviolet light (235).

CHAPTER 13

ARYLOXYALKANE CARBOXYLIC ACIDS AND THEIR DERIVATIVES

General Description of Pesticide Properties

The aryloxyalkane carboxylic acids and their derivatives that have been studied possess weak insecticidal properties, but many compounds of this group are herbicides, fungicides and plant growth regulators. Aryloxyalkane carboxylic acids have greatest significance as herbicides and plant growth regulators. In terms of the scale of their production and use, aryloxyalkane carboxylic acids have the lead among preparations of other classes; production of this important group of herbicides is exhibiting a tendency for growth.

The physiological activity of many aryloxyalkane carboxylic acids has been studied, and the general dependencies between variations in activity and structure have been established, though the mechanism of their action upon plants is not yet sufficiently clear (1,102).

The physiological activity of phenoxyacetic acid increases when halogen atoms are introduced into its molecule. Fluorine and chlorine have the greatest influence, while that of bromine and iodine is less significant; moreover the activity of the compound is also affected by the position of the halogen. 4-Halophenoxyacetic acids exhibit the highest activity. Isomeric dichlorophenoxyacetic acids fall into the following order in relation to their physiological activity:

2,4- > 2,5- > 3,4- > 3,5- > 2,6-

The herbicidal activity of 2,5-dichloro- and 3,4-dichlorophenoxyacetic acids is so great that they have been proposed for agricultural use together with 2,4-dichlorophenoxyacetic acid. One favorable property of 3,4-dichlorophenoxyacetic acid is its greater selectivity of action in comparison with the preparation 2,4-D: It is less harmful to cotton, alfalfa, potatoes and sugar beets, but it is highly toxic to sunflower and many dicotyledonous weeds.

Among isomeric trichlorophenoxyacetic acids, 2,4,5-trichlorophenoxyacetic acid possesses the greatest activity; it is close to 2,4-D in the strength of its herbicidal action. Isomeric trichlorophenoxyacetic acids fall into the following order in terms of their activity:

2,4,5- > 2,3,4- > 3,4,5- > 2,3,5- > 2,4,6- > 2,3,6-

Among tetrachlorophenoxyacetic acids, only 2,3,4,5-tetrachlorophenoxyacetic acid displays noticeable physiological activity in relation to plants, while 2,3,4,6- and 2,3,5,6-tetrachlorophenoxyacetic acids are inactive. Pentachlorophenoxyacetic acid is inactive as a plant growth regulator, but it is a systemic fungicide (2).

2,4,6-Trichloro- and 2,4,6-tribromophenoxyacetic acids are inactive as herbicides, and according to some data they are even antagonists to preparation 2,4-D, but 2,4-dichloro-6-fluoro- and 2,4-dibromo-6-fluorophenoxyacetic acids are similar to this preparation in their activity. 2,4,6-trifluorophenoxyacetic acid, many mixed polyhalofluorophenoxyacetic acids and their derivatives exhibit relatively high herbicidal activity.

Introduction of an aliphatic hydrocarbon radical into the benzene ring of the phenoxyacetic acid molecule raises the compound's activity insignificantly. In this case the activity of 2-alkyl-, 4-alkyl, 2-halogen-4-alkyl- and 4-halogen-2-alkylphenoxyacetic acids decreases as the alkyl radical increases. A similar pattern is observed when an aromatic radical is introduced into the phenoxyacetic acid molecule. When the benzene ring of alkyl- and arylphenoxyacetic acids is halogenated, their activity rises.

4-Halogen-2-alkylphenoxyacetic acids are somewhat more active than 2-halogen-4-alkylphenoxyacetic acids. Isomeric halomethylphenoxyacetic acids differ especially strongly in their activity. When a second halogen atom is introduced into the alkylphenoxyacetic acid molecule, the compound's activity declines in most cases. The same is observed with the addition of a third halogen atom. An exception is 2,4-dichloro--5-methylphenoxyacetic acid, which exhibits rather strong herbicidal action. This acid is a structural analogue of 2,4,5-trichlorophenoxyacetic acid.

Introduction of a fluoromethyl group into the phenoxyacetic acid molecule does not affect its activity as a plant growth stimulator, but it sharply reduces the compound's herbicidal activity. Thus for example, 4-chloro-2-chloromethylphenoxyacetic acid is of no practical interest as a herbicide, while 4-chloro-2-methylphenoxyacetic acid (preparation 2M-4C) is broadly employed in agriculture to control dicotyledonous weeds (3,4).

Chloromethylphenoxyalkane carboxylic acids exhibit the properties of systemic fungicides (5,6). A similar pattern is observed when a thiocyanomethyl group is introduced (7), but such derivatives are somewhat more phytotoxic.

Acetylphenoxyacetic acids are inactive, apparently due to presence of a carbonyl group in their molecule and the consequent possibility of forming additional hydrogen bonds. The activity of phenylenediacetic acids and carboxyphenoxyacetic acids is probably low for the same reason.

Among aryloxyacetic acids containing an alkoxy group in their aromatic ring, compounds with the alkoxy group in position 3 are most active, while 2-isomers are the least active. By increasing the number of carbon atoms in the alkoxy residue, we can raise activity, but only to a certain limit (C_3), after which it falls abruptly. This is possibly connected with the substance's lower rate of diffusion in plant cells. Halogenated alkoxyphenoxyacetic acids are less active than acids not containing halogen. Thus 2-chloro-4-methoxyphenoxyacetic acid is close in its ability to stimulate root formation in bean plant cuttings to that of γ-(indolyl-3)-butyric acid.

4,5-Dichloro-2-methoxyphenoxyacetic acid and its derivatives exhibit noticeable fungicidal activity (8).

A mixture of aryloxyacetic acids obtained from phenols with a boiling point of 180-200°C, obtained from dry wood distillation, has been proposed for weed control. This mixture contains up to 40 percent chloroguaiacoloacetic acids (a mixture of isomers) and about 25 percent 2,4-dichloro- and 4-chloro-2-methylphenoxyacetic acids.

Nitro-, amino-, acylamino-, alkylamino- and sulfo- derivatives of phenoxyacetic acids have low physiological activity. Even 2-nitro-4-chlorophenoxyacetic acid and its analogues exhibit low activity. However, sulfamidophenoxyacetic acids exhibit fungicidal properties (9,10).

Introduction of halogen into the methylene group of 2,4-dichlorophenoxyacetic acid reduces the compounds's physiological activity. Thus 2,4-dichlorophenoxyfluoroacetic acid is less active than 2,4-dichlorophenoxyacetic acid, in which case the (+)-form of 2,4-dichlorophenoxychloroacetic acid is a stronger growth stimulator in relation to pea epicotyl cuttings than the (-)-form and the racemic mixture, and it is more active as a herbicide. The activity of 2,4-dichlorophenoxydifluoroacetic acid is lower than that of monofluoro- derivatives.

Substitution of hydrogen in the methylene group by a hydrocarbon radical decreases the compound's activity as a rule; in this case the more carbon atoms there are in the hydrocarbon radical, the more activity declines. The (+)-forms of stereoisomeric compounds are more active than racemates, while the (-)-forms exhibit low activity, or they are antagonists to plant growth stimulators.

Aryloxyacetylchlorides and aryloxyacetic acid anhydrides do not differ from the acid forms in their activity, since upon hydrolysis they transform into the corresponding acids.

Hydroxamic acids are herbicides and rather strong fungicides (11,12). Esters formed from hydroxamic acids have strong herbicidal action (12-16). The activity of amides, anilides and other similar derivatives is similar in most cases to the activity of the corresponding acids.

A very large number of N-substituted amides of aryloxyalkane carboxylic acids (17-33) of both the aliphatic (19,21,24-26,29,31-34) and aromatic (20,22,23,25,30,35,36) series containing the most diverse substituents in the hydrocarbon ring at the nitrogen atom--thiocyanate (19), amino (21), alkylthio (24,28), carbonyl (22,32), trifluoromethyl (20,23,30), thiophosphoryl (33) and other groups--have now been synthesized and studied.

Aryloxyacetylamino acids exhibit high activity that depends not only on the structure of the aryloxyacetic acid but also on the configuration of the initial amino acid. This may be connected with the capability of various plant enzymes for breaking aryloxyacetylamino acids down into the corresponding aryloxyacetic acids.

Aryloxyacetylates are stronger herbicides than the free acids and their salts. This is usually explained by the higher rate of their penetration through the leaf cuticle. However, this cannot satisfactorily explain the fact that a significantly lower dose of the ester is required to achieve the same effect as the salt (a two- to three-fold difference) (37). The herbicidal activity of the esters of high molecular weight alcohols is lower than that of esters of low molecular weight alcohols, which is connected in all probability with their lower solubility in lipoids and waxes and their lower rate of diffusion in plants.

The activity of the salts of aryloxyacetic acids formed from various organic bases is 1.2-1.7 times greater than the activity of the salts of these acids made with alkali metals. It may be possible that the herbicidal action of amine salts increases owing to change in the surface tension of their aqueous solutions. Other factors responsible for the higher activity of these salts have not yet been established.

In certain cases aryloxyacetic acids dissolved in organic solvents exhibit higher herbicidal activity than do their salts and even their esters.

When hydroxyl oxygen in the carboxyl group of aryloxyacetic acids is substituted by sulfur, significant changes do not occur in the compound's physiological activity, while substitution of the ester oxygen by sulfur or by other diatomic groups reduces the compound's activity.

A large number of aryloxyalkanethiocarboxylates have been synthesized. Some of them may be of interest as herbicides and dessicants (38-41). Esters made with substituted benzyl alcohols (42), with heterocyclic oxygen-containing (43,46), phosphorus-containing (44) and nitrogen-containing compounds (45,46) and with dithiophosphoric acid derivatives (47) also exhibit herbicidal properties. Arylthio- and arylsulfonylalkane carboxylic acids and their derivatives exhibit fungicidal and bactericidal action (48).

Naphthoxyacetic acids are significantly inferior to phenoxyacetic acids in their activity. Of the naphthoxyacetic acids, β-naphthoxyacetic acid is the most active. Introduction of halogens and other substituents into the naphthaline ring reduces the compound's activity. However, the esters and amides of these acids as well as the appropriate derivatives of α- and β-phenoxypropionic acids (34,35,49,50) are of certain practical interest because they are effective against a number of weeds resistant to other preparations made from this group of compounds.

Fluorenyloxy- and acenaphthenyloxyacetic acids and analogous derivatives of other polycyclic hydrocarbons are weak herbicides, and they offer no practical interest.

Aryloxyalkane carboxylic acids [$ArO(CH_2)_nCOOH$] with an odd number of methylene groups has herbicidal activity in relation to many dicotyledonous plants, while acids containing an even number of methylene groups do not display herbicidal action. The explanation for this is that most plants (except the legumes) subject aryloxyalkane carboxylic acids to β-oxidation, as a result of which the former group of compounds is transformed into the appropriate aryloxyacetic acids while the latter group is transformed into inactive phenols:

$$ArO(CH_2)_3COOH \xrightarrow[-2CO_2;\ -2H_2O]{+6O} ArOCH_2COOH$$

$$ArO(CH_2)_4COOH \xrightarrow[-2CO_2;\ -2H_2O]{+6O} ArOCOOH \xrightarrow[-CO_2]{} ArOH$$

In leguminous plants, β-oxidation of γ-(aryloxy)-butyric acids to the corresponding aryloxyacetic acids does not occur, and therefore γ-(aryloxy)-butyric acids can be used successfully to control dicotyledonous weeds in fields of leguminous crops.

As the number of methylene groups in acids with an odd number of methylene groups increases, their herbicidal activity decreases.

Nitriles of aryloxyalkane carboxylic acids display the same form of activity that acids do (51,52). Thus the nitriles of fluoro- and fluorochlorophenoxyalkane carboxylic acids are strong herbicides (51), and the nitrile of pentachlorophenoxyacetic acid (melting point 158-160°C) is a strong fungicide (52).

Aryloxyacetic Acids

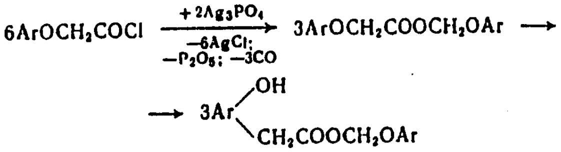
Aryloxyacetic acids and their various derivatives are used as herbicides to control dicotyledonous weeds in cereal grain plantations and brush and tree seedlings on meadows, to destroy undesirable trees when cleaning terrain for construction of hydroelectric power plants and so on.

Compounds in widespread use include 2,4-dichlorophenoxyacetic acid (2,4-D), 4-chloro--2-methylphenoxyacetic acid (2M-4C), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and their derivatives. 3,4-Dichlorophenoxyacetic acid, 2,4-dichloro-5-methylphenoxyacetic acid, 4-chlorophenoxyacetic acid and other compounds are presently undergoing industrial experimentation. 2-Naphthoxyacetic acid is a plant growth regulator. It is used in some countries in small amounts to obtain seedless tomatoes.

All aryloxyacetic acids are weak acids. Their dissociation constants are within $5.2 \cdot 10^{-4}$-$25 \cdot 10^{-4}$.

Aryloxyacetic acids are similar in chemical properties to other carboxylic acids. They typically form acid chlorides and anhydrides, amides, esters and many other derivatives.

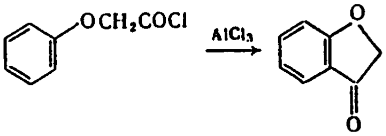
When aryloxyacetylchlorides react with silver phosphate, the aromatic ring undergoes alkylation:



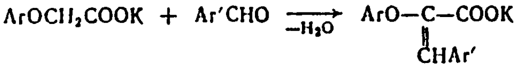
Silver salts of aryloxyacetic acids react with bromine in approximately similar fashion:

$$2ArOCH_2COOAg \xrightarrow[-2AgBr;\ -CO_2]{+Br_2} ArOCH_2COOCH_2OAr$$

When aluminum chloride reacts with aryloxyacetylchlorides, ring formation occurs and the corresponding coumaranone derivatives are obtained:



When aryloxyacetic acids are mixed with aldehydes Perkin's reaction occurs, with the corresponding derivatives of cinnamic acid forming:



$$ArOCH_2COOK + Ar'CHO \xrightarrow[-H_2O]{} ArO-\underset{\underset{CHAr'}{\|}}{C}-COOK$$

When aryloxyacetic acids are mixed with concentrated nitric acid, mono- or dinitroaryloxyacetic acids form depending on the nitration conditions and the structure of the initial acid.

When aryloxyacetic acids are subjected to halogenation, the corresponding halogen derivatives are formed, some of which are obtained rather pure and in good amounts. This reaction is often used for industrial synthesis of 2,4-D, 2M-4C and 4-fluorophenoxyacetic acid. Chlorination and bromination proceed the most easily, while iodination is significantly more difficult. Some aryloxyacetic acids are not iodinated by free iodine.

Hydrolysis of the simple ester bond proceeds relatively easily when aryloxyacetic acids are heated together with acid halides. The reaction proceeds quickly with hydrogen iodide and significantly more slowly with hydrogen chloride. The more acid the phenol obtained upon hydrolysis, the faster this reaction proceeds.

Esters are obtained in good amounts when aryloxyacetic acids interact with alcohols in the presence of catalytic quantities of sulfuric acid or other similar compounds. The reaction between aryloxyacetic acid salts and dimethylsulfate (53) or between the acids themselves and tetramethylammonium hydroxide (55) is used to synthesize methyl ethers of these acids, which are used in chromatographic analysis.

Several general methods of obtaining aryloxyacetic acids are known.

1. Oxidation of aryloxyethanols by various oxidants or oxygen in the presence of catalysts:

$$ArO-CH_2-CH_2OH \xrightarrow[-H_2O]{+2O} ArO-CH_2-COOH$$

This reaction produces a very small yield of aryloxyacetic acid. When oxidation occurs in the presence of platinum catalysts, the yield is higher but the productivity of the catalyst is low.

2. Oxidation of unsaturated phenol esters, for example arylallyl esters, 1-aryloxy--2-chlorobutene-2 and others:

$$\mathrm{ArO{-}CH_2{-}CH{=}CH_2 \xrightarrow[-CO_2;\ -H_2O]{+5O} ArO{-}CH_2{-}COOH}$$

3. Synthesis of aryloxyacetic acids by way of arylchloromethyl ethers, obtained by chlorination of the corresponding anisoles in the presence of phosphorus pentachloride:

$$\mathrm{ArOCH_3 \xrightarrow[-HCl]{+Cl_2} ArOCH_2Cl \xrightarrow[-NaCl]{+NaCN} ArOCH_2CN \xrightarrow[-NH_3]{+H_2O} ArOCH_2COOH}$$

This is the way 2,4-dichlorophenoxyacetic acid is synthesized from anisoles with a 60 percent yield.

4. One of the most widespread methods of obtaining aryloxyacetic acids is to react alkali metal phenolates with the salts of monochloroacetic acid:

$$\mathrm{ArONa \xrightarrow[-NaCl]{+ClCH_2COONa} ArOCH_2COONa \xrightarrow[-NaCl]{+HCl} ArOCH_2COOH}$$

This reaction may be performed both in aqueous solution and in organic solvents using excess phenolate, or in the presence of table salt with the purpose of reducing hydrolysis of sodium monochloroacetate, and so on. When carried out without pressure, the optimum temperature for the process is 105-107°C.

5. Aryloxyacetic acids may also be obtained by way of the esters or amides of haloacetic acids:

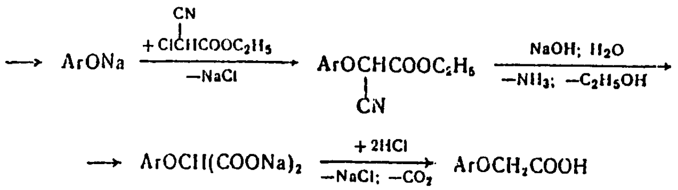
$$\mathrm{ArONa \xrightarrow[-NaX]{+XCH_2COOR} ArOCH_2COOR \xrightarrow[-ROH]{+NaOH}}$$

$$\mathrm{\longrightarrow ArOCH_2COONa \xrightarrow[-NaCl]{+HCl} ArOCH_2COOH}$$

$$\mathrm{ArONa \xrightarrow[-NaCl]{+ClCH_2CONH_2} ArOCH_2CONH_2 \xrightarrow[-NH_4HSO_4]{H_2O;\ H_2SO_4} ArOCH_2COOH}$$

The latter method is only of preparatory significance in the synthesis of aryloxyacetic acids in the laboratory.

6. Aryloxyacetic acids may be obtained by reacting phenolates with chlorocyanacetates, but this method is only of theoretical significance:



$$\longrightarrow \mathrm{ArONa} \xrightarrow[-\mathrm{NaCl}]{+\mathrm{Cl}\overset{\mathrm{CN}}{\mathrm{C}}\mathrm{HCOOC_2H_5}} \mathrm{ArO}\underset{\mathrm{CN}}{\mathrm{C}}\mathrm{HCOOC_2H_5} \xrightarrow[-\mathrm{NH_3};\ -\mathrm{C_2H_5OH}]{\mathrm{NaOH};\ \mathrm{H_2O}}$$

$$\longrightarrow \mathrm{ArOCH(COONa)_2} \xrightarrow[-\mathrm{NaCl};\ -\mathrm{CO_2}]{+2\mathrm{HCl}} \mathrm{ArOCH_2COOH}$$

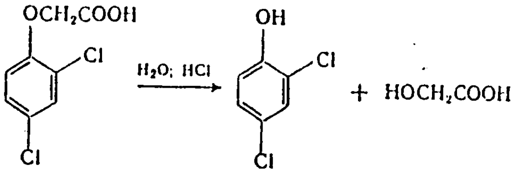
2,4-Dichlorophenoxyacetic acid (2,4-D) is a white crystalline substance with a melting point of 141°C and a boiling point of 160°C at 0.4 mm Hg. The pure acid is practically odorless. Not more than 0.3 percent dichlorophenol is permitted in technical-grade preparation. Its solubility in water at 20°C is 540 mg/liter; solubility in 100 gm solvent is, at 25°C, 130 gm for ethanol, 243 gm for ester, 0.67 gm for toluol and 0.1 gm for *n*-heptane. It is readily soluble in benzene, carbon tetrachloride, acetone and tetra- and pentachloroethanes. The dissociation constant is $23 \cdot 10^{-4}$.

2,4-Dichlorophenoxyacetic acid is stable when stored as solutions in various solvents, and when stored in crystalline state; it may decompose to a slight extent when exposed to ultraviolet light. It forms stable salts with inorganic and organic bases. The properties of some salts of 2,4-dichlorophenoxyacetic acid are shown below:

Salt	Melting Point, °C	Solubility in 100 gm Water, gm (at Indicated Temperature, °C)
Ammonium	-	1.2 (31.5)
Sodium (monohydrate)	216-218	27.5 (0)
		33.5 (20)
		50.6 (30)
		74.6 (45)
Potassium	-	7 (20)
Calcium	-	0.025 (20)
Magnesium	-	0.17 (20)
Methylamine	157-159	450 (20)
n-Butylamine	93-94.5	1.8 (30.5)
Allylamine	106-107	1.2 (31.5)
Benzylamine	138-319	1.6 (31.5)
Monoethanolamine	145-147	>50% (20)
Dimethylamine	85-87	Good (20)
Diethylamine	129-131	>50% (20)
Di-*n*-butylamine	107-109	1.2 (31.5)
Diallylamine	-	710 (32)
Diethanolamine	94-94.5	480 (30)
Triethylamine	-	340 (20)
Triethanolamine	-	440 (32)
Morpholine	136-138	220 (30)
Piperidine	131-132	230 (31)

The salts of bivalent metals are poorly soluble in water, which is why a precipitate may form when 2,4-dichlorophenoxyacetic acid is dissolved in hard water. To avoid this, complexones (Trilon B) are added to technical-grade 2,4-D preparations.

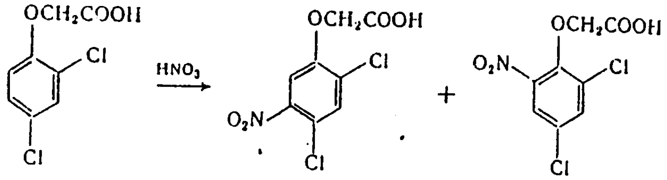
With lengthy boiling of 2,4-dichlorophenoxyacetic acid together with hydrobromic or hydrochloric acids, it may decompose:



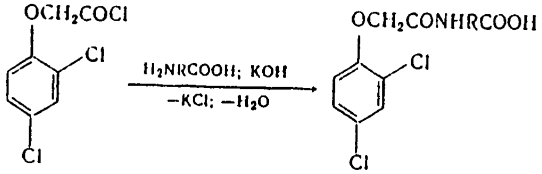
Chlorination with gaseous chlorine forms 2,4,6-trichlorophenoxyacetic acid, but at 200-205°C breakdown products have been discovered: 2,4-dichlorophenol, bis-(2,4,-dichlorophenoxy)-methane and others.

Chlorination of the ethyl ester of 2,4-dichlorophenoxyacetic acid at 195-210°C without a catalyst produces 2,4-dichlorophenoxychloro- and 2,4-dichlorophenoxydichloroacetate, dichloroacetate and 2,4-dichlorophenylchloromethylate.

The principal product of this acid's nitration by nitric acid or a nitrating mixture is 2,4-dichloro-4-nitrophenoxyacetic acid with a slight amount of 2,4-dichloro-6-nitrophenoxyacetic acid impurity:



A large number of amides having high herbicidal activity have been obtained by reacting 2,4-dichlorophenoxyacetylchloride with amino acids:

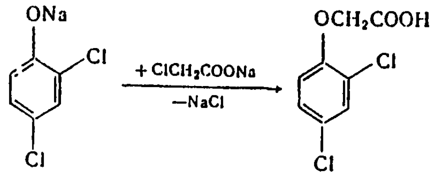


Some species of microorganisms oxidize 2,4-dichlorophenoxyacetic acid into 4-chloropyrocatechin (by way of the oxy derivative and 2,4-dichlorophenol). 2,4-Dichlorophenoxyacetic acid has antiseptic properties; this is especially true of its phenol esters.

2,4-D is moderately toxic to mammals. When introduced orally into experimental animals, the LD_{50} is 375-1,000 mg/kg; the maximum safe dose in monkeys is 214 mg/kg. It is presumed that the lethal dose of 2,4-D in man is about 15 gm. The norm set in the USA for 2,4-D traces in foodstuffs is 5 mg/kg.

A large number of methods of obtaining 2,4-D are known, but only two have practical significance to industrial production.

1. Condensation of the salts of monochloroacetic acid with 2,4-dichlorophenolates of alkali metals or ammonium, in water or in a water-free medium (55-59):



To decrease hydrolysis of monochloroacetic acid, the reaction may be performed with excess 2,4-dichlorophenolate, which is removed after oxidation of the reaction medium by distillation with live steam. The yield from 2 moles of sodium 2,4-dichlorophenolate and 1 mole of sodium monochloroacetate attains 94 percent of theoretical, while without excess phenolate the yield under similar conditions does not exceed 83 percent. 2,4-Dichlorophenol distilled away with steam may be later returned to the process. Adding sodium chloride has been suggested as a way to suppress hydrolysis in the reaction mixture.

It should be noted that the purest possible 2,4-dichlorophenol would best be used to produce 2,4-D; this would mean lower waste of expensive monochloroacetate in the formation of byproducts.

Additionally, the 2,4-D obtained from pure 2,4-dichlorophenol is higher in quality.

The technical-grade preparation almost always contains a small quantity of 2,4-dichlorophenol, and owing to this it has an unpleasant odor.

2,4-Dichlorophenol is obtained by direct chlorination of phenol by chlorine, followed by purification of the chlorination products by rectification. Performing chlorination at a temperature somewhat above the melting point of phenol is usually recommended. Chlorination at higher temperatures produces a large quantity of 2,6-dichlorophenol as a byproduct. Very pure (98 percent) 2,4-dichlorophenol may be obtained by chlorination of phenol in liquid sulfur anhydride at a temperature not exceeding the boiling point of sulfur anhydride, which hinders formation of the 2,6-isomer and practically excludes the possibility of obtaining 2,4,6-trichlorophenol. Sufficiently pure 2,4-dichlorophenol is also obtained when phenol is chlorinated in nitromethane (the phenol concentration should be about 25 percent, the temperature is 40°C) (61-63).

2,4-Dichlorophenol may be purified by extraction of the 2,6-isomer with alkali (60), since the latter's acidity is higher.

2,4-Dichlorophenol may also be obtained by alkaline hydrolysis of a mixture of isomeric forms of trichlorobenzene (from nontoxic isomers of hexachlorocyclohexane), but the resulting product is a mixture of isomeric dichlorophenols, in which the concentration of the needed isomer does not exceed 25 percent.

2,4- and 2,5-isomers of dichlorophenol may be separated by sulfation with sulfuric acid at 50-100°C: The 2,5-isomer is separated in the form of sulfonic acid, since it is sulfated more easily than the 2,4-isomer (64). Separation may also be achieved by precipitation of the binary compound of 2,5-dichlorophenol and urea out of their solutions in organic solvents (65).

The basic flowchart for production of 2,4-dichlorophenoxyacetic acid by this method (1) is shown in Figure 11.

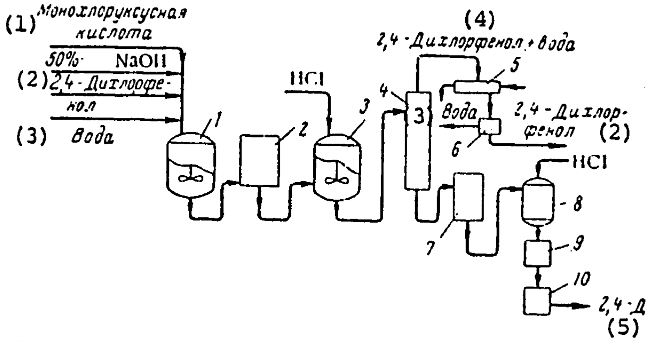


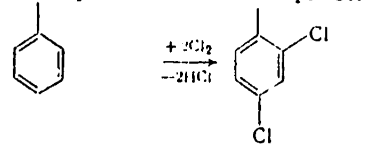
Figure 11. Basic Flowchart for Production of Preparation 2,4-D: *1*--reactor for synthesis of the sodium salt of 2,4-D; *2*--intermediate storage; *3*--apparatus for removal of excess 2,4-dichlorophenol; *4*--2,4-dichlorophenol distillation unit; *5*--heat exchanger; *6*--settling tank; *7*--collecting tank for 2,4-D sodium salt solution; *8*--2,4-D isolating apparatus; *9*--centrifuge; *10*--dessicator

Key:

1. Monochloroacetic acid
2. 2,4-Dichlorophenol
3. Water
4. 2,4-Dichlorophenol + water
5. 2,4-D

2. Chlorination of phenoxyacetic acid or its esters. Chlorine, sodium hypochlorite, a mixture of sodium chlorate and hydrochloric acid, sulfuryl chloride and chloramines can be used as chlorinating agents.

Phenoxyacetic acid is chlorinated with chlorine both in an aqueous medium and in organic solvents and in melt (66,67):

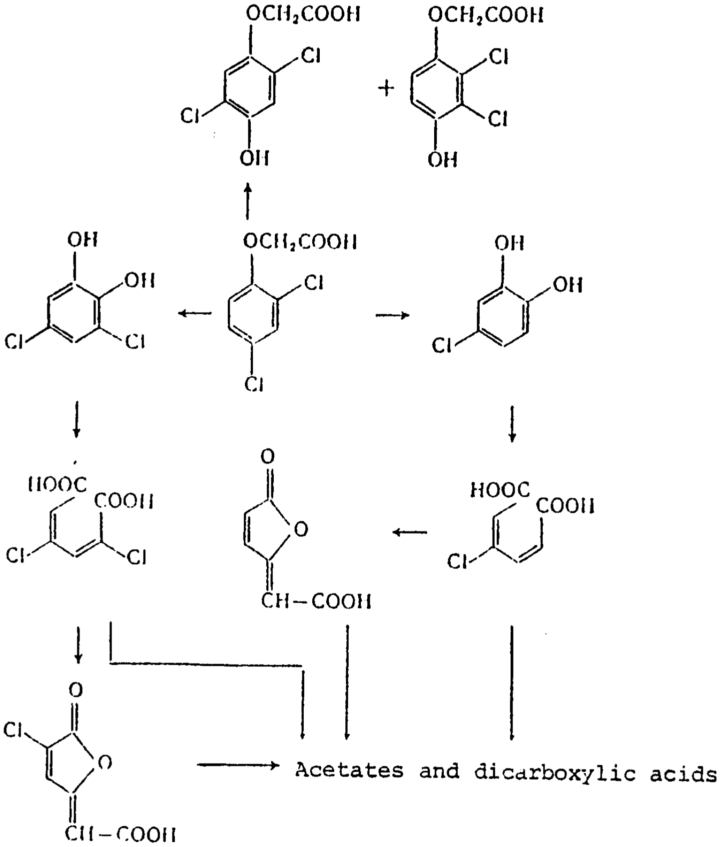


The product obtained by this method does not contain 2,4-dichlorophenol. The impurities it contains include 4- and 2-chlorophenoxyacetic acids, 2,4,6-trichlorophenoxyacetic acid and 2,4,6-trichlorophenol. The 2,4-D yield, when calculated in relation to total chlorophenoxyacetic acids, is more than 90 percent, but this method produces a product of lower quality than that obtained from purified 2,4-dichlorophenol.

Phenoxyacetic acid necessary for production of 2,4-D by the chlorination method is formed by reacting sodium phenylate with sodium monochloroacetate at high temperature, the yield being 80-90 percent:

$$C_6H_5ONa + ClCH_2COONa \xrightarrow[-NaCl]{} C_6H_6OCH_2COONa \xrightarrow[-NaCl]{+HCl} \longrightarrow C_6H_5OCH_2COOH$$

The metabolism of 2,4-dichlorophenoxyacetic acid in various environmental objects has been studied (68-80). It has been established that the first stage of metabolism in plants is hydroxylation (71,79,80), which proceeds to form 2,3- and 2,5-dichloro-4-oxyphenoxyacetic acids. Under the influence of soil microorganisms, not only does the ring undergo hydroxylation, but also the ester bond breaks down and the aromatic system is destroyed (70,71,74). It should be noted that when 2,4-D is applied repeatedly to soil, its decomposition accelerates. Decomposition of 2,4-dichlorophenoxyacetic acid may be represented in general form as follows:

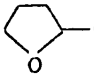


Esters of 2,4-dichlorophenoxyacetic acid: The effectiveness of esters derived from 2,4-dichlorophenoxyacetic acid against various weeds is significantly higher than the effectiveness of its salts and of its various other derivatives. Destruction of an equal amount of dicotyledonous weeds by esters requires consumption norms that are two to three times lower than the consumption norms for the sodium salt (as corrected for the acid). In a number of cases esters act upon weeds against which salts are not very effective.

2,4-Dichlorophenoxyacetates are enjoying increasingly broader use in agriculture. They now represent more than 50 percent of the total production of all other derivatives of this acid.

Lower alkyl esters of 2,4-dichlorophenoxyacetic acid (ethyl, isopropyl, butyl and so on) have relatively high volatility, and their vapors may injure crops sensitive to this acid located on plots neighboring those being processed. As molecular weight increases, the volatility of the esters decreases. Thus the vapor pressure of isooctyl ester is almost 17 times lower than the vapor pressure of butyl ester. However, high molecular weight esters such as, for example, cetyl ester, are less effective, apparently due to their poor solubility in plant juices and their slow movement through the plant vascular system.

The properties of some esters of 2,4-dichlorophenoxyacetic acid ($Cl_2C_6H_3OCH_2COOR$) are shown below:

R	Melting Point, °C	Boiling Point, °C (at Indicated Pressure, mm Hg)
CH_3	43	119 (1,0)
C_2H_5	15,2—15,4	149—150 (1,0)
$(CH_3)_2CH$	24	183 (18,0)
$CH_3(CH_2)_2CH_2$	9	146—147 (1,0)
$(CH_3)_2CHCH_2$	17	133—134 (1,0)
$CH_3(CH_2)_3CH_2$	15	160 (2,0)
$(CH_3)_2CHCH_2CH_2$	—	136—138 (1,0)
$CH_3(CH_2)_3CH(C_2H_5)CH_2$	12	173—174 (0,5)
$CH_3(CH_2)_6CH_2$	—	173—174 (1,0)
$CH_3(CH_2)_7CH_2$	43	—
$CH_3CCl{=}CHCH_2$	33—34	186—188 (1,0)
2,4-$Cl_2C_6H_3OCH_2CH_2$	88	Does not sublimate
—CH_2	—	197—198 (2,0)

Of the large number of esters of this acid that have been studied, the ethyl, isopropyl, butyl, amyl, heptyl, octyl and isooctyl, chlorocrotyl, polypropylene and polyethylene glycol, and other esters have enjoyed practical use.

2,4-Dichlorophenoxyacetates are produced industrially by esterification of the acid by appropriate alcohols, or by chlorination of phenoxyacetates. Esterification is usually performed in the presence of acid catalysts, in which case water is distilled away in the form of an azeotropic mixture with an organic solvent.

The basic flowchart for production of 2,4-dichlorophenoxyacetates by esterification of the acid by alcohol followed by azeotropic distillation of water is shown in Figure 12.

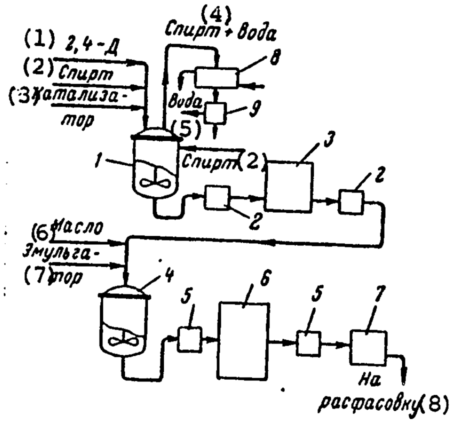


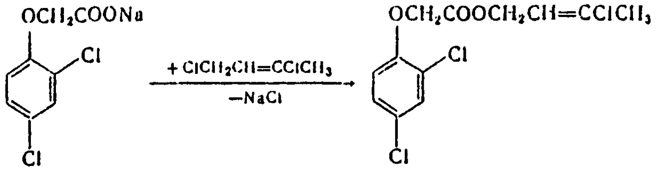
Figure 12. Basic Flowchart for Production of Esters of 2,4-Dichlorophenoxyacetic Acid: *1*--ester synthesis reactor; *2,3*--filters; *4*--ester collector; *5*--apparatus for acquisition of ester emulsion concentrate; *6*--intermediate storage; *7*--finished product collector; *8*--heat exchanger; *9*--water removal apparatus;

Key:

1. 2,4-D
2. Alcohol
3. Catalyst
4. Alcohol + water
5. Water
6. Oil
7. Emulsifier
8. To packaging

2,4-Dichlorophenoxyacetates may be obtained by chlorination of phenoxyacetates in the presence of catalysts. The esters obtained in this way contain 96-97 percent of the required isomer (60).

The 3-chlorocrotyl ester of 2,4-dichlorophenoxyacetic acid (crotyline) is obtained by reacting dichlorobutene with the sodium salt of this acid:



In addition to those described above, a large number of other esters have been synthesized and described (81-85): benzyl (85), chloro- and trichloroallyl (82) and others (81,84). Dibutylstannous-2,4-dichlorophenoxyacetate has been suggested as a nonvolatile preparation (83).

The methyl ester of 2,4-dichlorophenoxyacetic acid may be used to obtain the amine salts of this acid:

$$Cl_2C_6H_3OCH_2COOCH_3 \xrightarrow[-CH_3OH]{+(CH_3)_2NH;\ +H_2O} Cl_2C_6H_3OCH_2COOH \cdot HN(CH_3)_2$$

Thus sufficiently pure preparations not containing free dichlorophenols may be obtained by a relatively simple method while producing a minimum quantity of effluents.

Among the derivatives of 2,4-dichlorophenoxyacetic acid that are moderately toxic to fish, mention should be made of *o*-chloroanilide (LD_{50} 2,560 mg/kg, AK_{50} in fish 1.1 mg/liter).

The amide form of 2,4-dichlorophenoxythioacetic acid (Bay-50870) is an experimental herbicide. It is being studied on cereal grain fields at consumption norms of 1-3 kg/ha. The preparation is mildly toxic to animals (LD_{50} 2,500 mg/kg).

4-Chloro-2-methylphenoxyacetic acid (2M-4C) is a white crystalline substance with a melting point of 120-120.2°C. The acid's solubility is 0.063 gm in 100 ml water at 20°C. It is readily soluble in alcohol, ether, carbon tetrachloride, dichloroethane, benzene, chlorobenzene and other organic solvents. Its dissociation constant is $5.4 \cdot 10^{-4}$.

The solubility of some salts of 4-chloro-2-methylphenoxyacetic acid in water at 20°C (percent) is shown below:

Ammonium	32.0	Magnesium	7.6
Potassium	48.0	Diethylamine	58.0
Sodium	25.0	Diethanolamine	58.0
Calcium	0.55	Triethanolamine	28.0

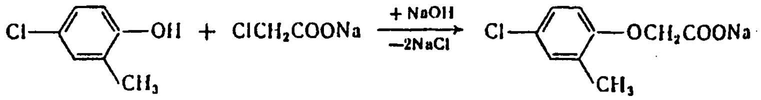
Pure 4-chloro-2-methylphenoxyacetic acid has practically no odor, while the technical-grade preparation usually has the unpleasant odor of chlorocresol.

2M-4C Is stable when stored both as solutions and in crystalline state. Its toxicity to mammals is close to that of 2,4-D, and its LD_{50} is 590-1,000 mg/kg. Technical-grade preparation containing related compounds is somewhat more toxic than pure acid. Thus dekoteks has an LD_{50} of about 540 mg/kg in white mice. The toxicity of 2M-4C to fish is 200 mg/liter (AC_{50}).

4-Chloro-2-methylphenoxyacetic acid is fully analogous in its chemical properties to 2,4-dichlorophenoxyacetic acid.

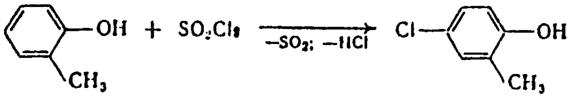
4-Chloro-2-methylphenoxyacetic acid may be obtained industrially by two pathways: condensation of 4-chloro-2-methylphenol with monochloroacetates, and chlorination by 2-methyl-phenoxyacetic acid.

Performing the reaction between 4-chloro-2-methylphenol and monochloroacetates is recommended in an alkaline medium (with a pH of about 10) while keeping the reaction mixture at 103-105°C:



Both pure 4-chloro-2-methylphenol and technical-grade product containing 6-chloro- and 4,6-dichloro-2-methylphenol impurities may be used in the reaction. In the latter case, however, the resulting preparation is highly contaminated, and it requires special purification.

4-Chloro-2-methylphenol is obtained by chlorination of *o*-cresol by chlorine, by alkali metal hypochlorites or by sulfuryl chloride. The purest 4-chloro-2-methylphenol forms when *o*-cresol is chlorinated by sulfuryl chloride:

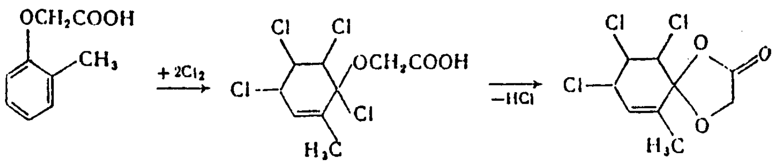


When *o*-cresol is chlorinated by chlorine and by other chlorinating agents, the resulting mixture contains 65-70 percent 4-chloro-2-methylphenol and 6-chloro- and 4,6-dichloro-2-methylphenol. To isolate pure 4-chloro-2-methylphenol, the technical-grade product is subjected to rectification.

6-Chloro-2-methylphenol is used to produce antiseptic for nonmetallic materials, and to synthesize polyethylene glycol esters which, when mixed with 4-chloro-2-methylphenoxyacetates, are used as herbicides to control weeds on grain fields resistant to 2M-4C.

The second method of obtaining 2M-4C is of great interest: chlorination of 2-methylphenoxyacetic acid by chlorine or hypochlorite. This process is usually conducted in dry organic solvents, with and without catalysts. Chlorination is easier in water-free solvents, since corrosion of the apparatus decreases dramatically and the resulting preparation contains almost no impurities. Halogen derivatives of aliphatic hydrocarbons and esters, and their mixtures have been proposed as solvents. The basic flowchart for production of 2M-4C is shown in Figure 13.

In addition to the principal product and a small quantity of 6-chloro-2-methylphenoxyacetic acid, the acetal ester of 4,5,6-trichloro-2-methylcyclohexene-2-one and glycolic acid forms (melting point 137°C):



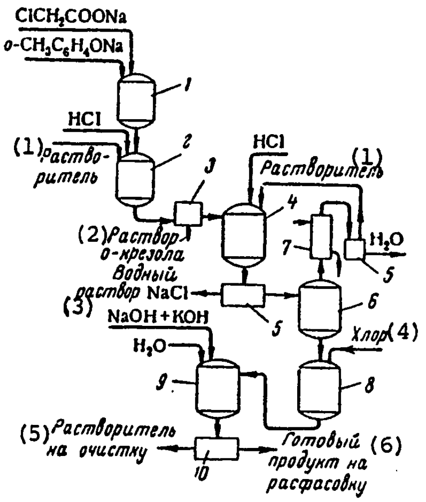
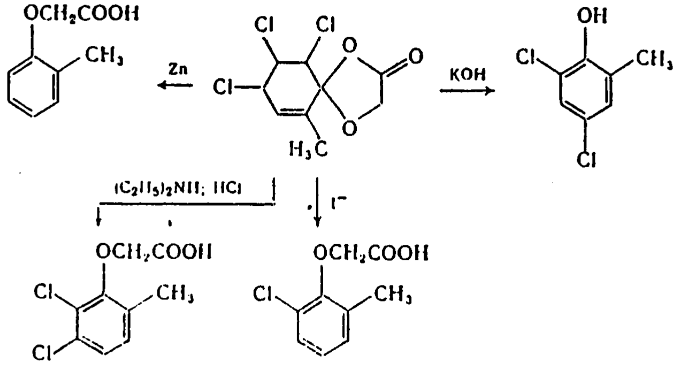


Figure 13. Basic Flowchart for Production of 2M-4C: *1*--reactor for synthesis of the sodium salt of 2-methylphenoxyacetic acid; *2*--apparatus for isolation and extraction of *o*-cresol; *3*--apparatus for separation of *o*-cresol; *4*--apparatus for isolation and extraction of 2-methylphenoxyacetic acid; *5,10*--apparatus for separation of water and solvent; *6*--apparatus for dessication of 2-methylphenoxyacetic acid solution; *7*--heat exchanger; *8*--chlorinator; *9*--apparatus for extraction of 2M-4C

Key:

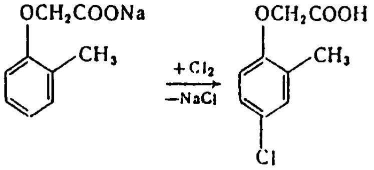
1. Solvent
2. *o*-Cresol solution
3. Aqueous NaCl solution
4. Chlorine
5. Solvent to be purified
6. Finished product to be packaged

Some transformations of this compound are shown below:



2M-4C may be isolated by two methods depending on the solvent employed. 2M-4C is extracted from hydrophobic solvents by caustic alkali; the solvent is then purified and returned to the process, while the aqueous solution of alkali salts of 2M-4C, following appropriate purification, is sold as a commercial product, or evaporated to a dry state or, finally, oxidized by mineral acids to release free acid which is subsequently processed into the required form. When chlorination is performed in hydrophobic solvents the latter are distilled in a vacuum, and following appropriate purification the acid is used to make commercial forms.

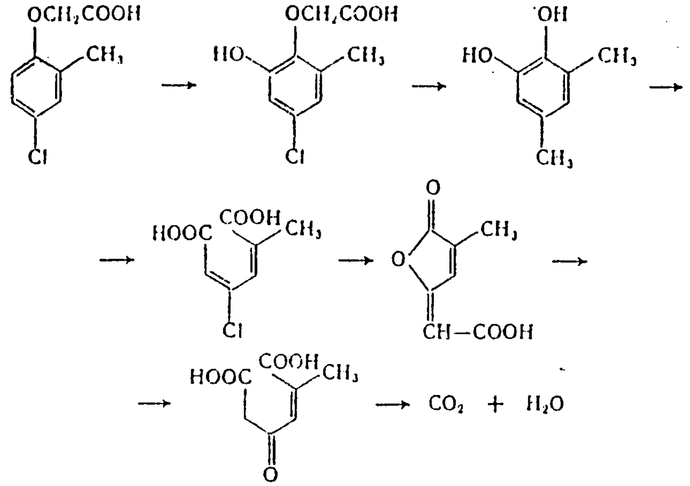
2-Methylphenoxyacetic acid can also be chlorinated in aqueous solution or in melt. 2-Methylphenoxyacetic acid salt is usually chlorinated in aqueous solution:



4-Chloro-2-methylphenoxyacetic acid is close in herbicidal activity to 2,4-dichlorophenoxyacetic acid, but it is less harmless to a number of crops, for which reason it has enjoyed broad application. This herbicide is especially convenient against weeds in flax plantations and some other crops.

Esters of 4-chloro-2-methylphenoxyacetic acid are more effective herbicides than its salts, for which reason a significant quantity of this herbicide is produced in the form of esters with various alcohols, obtained by methods similar to those used to acquire esters of 2,4-dichlorophenoxyacetic acid.

4-Chloro-2-methylphenoxyacetic acid is somewhat more stable in soil than is preparation 2,4-D; however, soil microorganisms are able to completely decompose it as well (71). This decomposition may be diagrammed as follows:



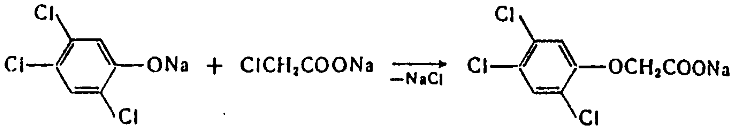
2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) is a white crystalline substance with a melting point of 158-159°C. Its solubility in water at 20°C is 0.189 gm/liter. It is freely soluble in alcohol, ether, chloroform and benzene, and it is moderately soluble in toluol and paraffin hydrocarbons. Its LD_{50} in rats is 500 mg/kg.

Despite the fact that in relation to its acute oral toxicity 2,4,5-T is classified as a moderately toxic preparation, its use has recently been severely limited. The reason for this is that small quantities of 2,3,7,8-tetrachlorodibenzodioxine have been detected in the technical-grade product. Even in minimum doses, this compound has a teratogenic effect on both animals and man (86-88).

The properties of some salts of 2,4,5-trichlorophenoxyacetic acid are presented below:

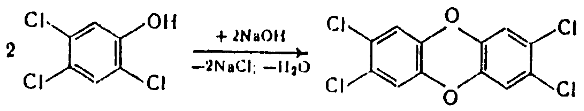
Salt	Melting Point, °C	Solubility in 100 gm Water at 20°C, gm
Sodium	-	3.5
Trimethylamine	-	330.0
Triethylamine	104-106	400.0
Monoethanolamine	179-181	>50.0
Diethanolamine	157-159	>50.0

The principal method used to synthesize 2,4,5-trichlorophenoxyacetic acid is to heat concentrated aqueous solutions of 2,4,5-trichlorophenylates and monochloroacetates of alkali metals at pH 10-12 and a temperature of 103-107°C.



This process may be performed in butanol, but this method is less convenient since greater difficulties are encountered in removing, from the 2,4,5-trichlorophenoxyacetic acid, trichlorophenol that had not reacted with monochloroacetate.

When sodium hydroxide reacts with 2,4,5-trichlorophenol small quantities of tetrachlorodibenzodioxine form as a byproduct. Not only does this compound exhibit teratogenic action, but it also severely irritates the skin. This was a cause of occupational illnesses among workers (87). Formation of tetrachlorodibenzodioxine proceeds as follows:



Impurities are removed from 2,4,5-trichlorophenoxyacetic acid by crystallizing its salts (89).

2,4,5-Trichlorophenoxyacetates are obtained by esterification of the acid by the appropriate alcohols and distillation of water in the form of an azeotropic mixture with organic solvents (90,92). The melting and boiling points of some esters of this acid are shown below:

Ester	Melting Point, °C	Boiling Point, °C (at Indicated Pressure, mm Hg)
Ethyl	66-67.5	-
Isopropyl	46	-
n-Butyl	29	-
Amyl	15	-
n-Hexyl	26	-
n-Octyl	-	187-189 (0.3)
n-Nonil	43	-
2-Methoxyethyl	-	145-150 (1.0)
2-Methoxypropyl	-	148-152 (1.0)
Phenyl	116-117	-
Pentachlorophenyl	269-270	-

2,4,5-Trichlorophenoxyacetates are used as herbicides against undesirable woody plants when clearing pastures, and against trees on land to be flooded in connection with construction of hydroelectric power plants.

The sodium salt of 2,4,5-trifluorophenoxyacetic acid is used as a plant growth stimulator (to obtain parthenocarpic tomatoes).

In addition to the aryloxyacetic acids described above, a large number of other compounds of this class have been synthesized and studied, and are now attracting a certain amount of practical attention as well. The melting points of some of these compounds are shown below:

Acid	Melting Point, °C
4-Chlorophenoxyacetic acid	159-160
4-Fluorophenoxyacetic acid	117
2,5-Dichlorophenoxyacetic acid	157
3,4-Dichlorophenoxyacetic acid	156
2,3,4-Trichlorophenoxyacetic acid	141
2,4-Dichloro-5-methylphenoxyacetic acid	143
2-Naphthoxyacetic acid	155-156

Aryloxypropionic Acids

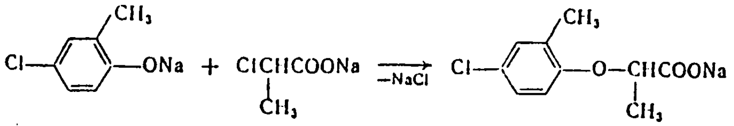
As was indicated above, β-aryloxypropionic acids do not possess pesticidal properties, and in this connection there is no interest in using them in agriculture. α-Aryloxypropionic acids are active herbicides and plant growth regulators.

α-(4-Chloro-2-methylphenoxy)-propionic acid (2M-4CP) is a white crystalline substance with a melting point of 94-95°C. Its solubility in 100 ml water at 20°C is 0.06 gm. The solubilities of salts in water at 20° are: 32 percent (corrected for acid) for the potassium salt and 58 gm in 100 ml for the diethanolamine salt; solubilities in 100 ml water at 0°C are: 26 gm for the sodium salt, 0.45 gm for the calcium salt and 4.5 gm for the magnesium salt. The free acid and its salts are stable when stored.

The active form of the acid is the (+)-form. Its LD_{50} in mice is 650 mg/kg.

2M-4CP is used against weeds in the form of salts of alkali metals or amine salts (ethanolamines, diethylamine) at consumption norms of 2-2.5 kg/ha. It is one of the new herbicides used against bedstraw and common chickweed on grain fields.

α-(4-Chloro-2-methylphenoxy)-propionic acid is synthesized by condensation of the salts of α-chloropropionic acid and 4-chloro-2-methylphenol (93-95):



and by chlorination of 2-methylphenoxypropionic acid by chlorine (96,97). The process would best be performed in water-free hydrophobic organic solvents, similar to that used to make preparation 2M-4C. The acid can be extracted from organic solvents with an aqueous solution of alkali or a lower amine. In the latter case we obtain a commercial product having the form of an aqueous solution of amine salts with a minimum phenol concentration (98).

α-(2,4-Dichlorophenoxy)-propionic acid (2,4-DP, dikhlorprop) is a white crystalline substance with a melting point of 117-118°C. Its solubility in 100 ml water at 20°C is 0.35 gm. The solubility of the sodium salt is 66 percent, that of the potassium salt is 90 gm in 100 gm water, and the solubility of the diethanolamine salt is 74 gm in 100 gm water. Its LD_{50} in rats is 800 mg/kg.

α-(2,4-Dichlorophenoxy)-propionic acid is obtained by chlorination of phenoxypropionic acid or by reacting 2,4-dichlorophenol with monochloropropionic acid. It is used in the form of salts or esters of various alcohols. It is close in biological activity to preparation 2M-4CP, differing somewhat from the latter only in its range of action on weeds.

α-(2,4,5-Trichlorophenoxy)-propionic acid (2,4,5-TP) is a white crystalline substance with a melting point of 179-181°C. Its solubility in 100 ml water at 25°C is 0.014 gm, and its salts with alkali metals and amines exhibit much better solubility. Its LD_{50} is 650 mg/kg.

The herbicidal activity of 2,4,5-TP is close to that of 2,4,5-T, but it is safer to cotton, which permits its use against woody vegetation and brush in cotton growing regions. When pears are sprayed in fall, the yield in the following year increases somewhat.

α-(2,4,5-Trichlorophenoxy)-propionic acid is obtained by reacting sodium 2,4,5-trichlorophenylate with sodium α-monochloropropionate in an aqueous medium.

Other α-(aryloxy)-propionic acids have been synthesized and studied as well: α-(3-chloro-2-methylphenoxy)-propionic (melting point 131-132°C), α-(4-chloro-2,3--dimethylphenoxy)-propionic (melting point 136.5-137.5°C) etc. Some of them have been found to be rather active selective herbicides, but they have not as yet enjoyed practical use in agriculture.

In addition to derivatives of phenoxyacetic and phenoxypropionic acids, derivatives of β-naphthoxyacetic and α-naphthoxypropionic acids have recently found some uses. Salts of β-naphthoxyacetic acid are used to obtain parthenocarpic tomatoes, while its methylester is used as a herbicide.

The methylester of β-naphthoxyacetic acid is a white crystalline substance with a melting point of 75°C. It is practically insoluble in water, and it is soluble in most organic solvents. Its LD_{50} to rats is 2,800 mg/kg.

It is obtained by esterification of the acid with methanol, similarly as in obtaining 2,4-dichlorophenoxyacetates. It is produced in the form of a wettable powder. When used at consumption norms on the order of 3 kg/ha, it exhibits good results against field camomile and (romashka nepakhuchaya) [unscented daisy?].

1-(2',4'-Dichlorophenoxyacetyl)-2,5-dimethylpyrazole (tomakon) is a white crystalline substance with a melting point of 136°C. Its LD_{50} in mice is about 1,100 mg/kg. It is used as a tomato growth regulator in the form of a 0.15 percent aqueous dispersion.

Also described as an experimental herbicide is the diethylamide of α-naphthoxypropionic acid (LD_{50} 5,000 mg/kg), recommended against weeds such as quick-grass and some others (50).

CHAPTER 18

MERCAPTANS, SULFIDES AND THEIR DERIVATIVES

Perchloromethylmercaptan and Its Derivatives

Owing to its high toxicity to man and animals and its strong corrosive action, perchloromethylmercaptan is not used in agriculture. It is the principal raw material for synthesis of various trichloromethylthioimides and trichloromethylthioamides possessing fungicidal properties.

Perchloromethylmercaptan is a red oily liquid with a boiling point of 148°C at 760 mm Hg (partial decomposition occurs) and 73°C at 50 mm Hg; d_4^{20} 1.6947. It is so toxic to mammals that it was proposed as a toxic agent in World War I, but for practical purposes it was almost never used for this purpose.

Metals and other reducing agents transform perchloromethylmercaptan into thiophosgene:

$$CCl_3SCl \longrightarrow CSCl_2$$

Oxidants oxidize it to trichloromethane sulfochloride:

$$CCl_3SCl + 2O \longrightarrow CCl_3SO_2Cl$$

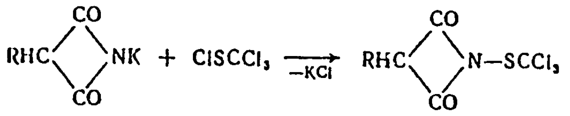
Alkali hydrolize perchloromethylmercaptan to form salt mixtures, slowly when cold and quickly when heated.

Perchloromethylmercaptan reacts relatively easily with unsaturated compounds to produce trichloromethylchloroalkyl sulfides:

$$RCH{=}CH_2 + CCl_3SCl \longrightarrow RCHCl{-}CH_2{-}S{-}CCl_3 \xrightarrow[-HCl]{} RCH{=}CHSCCl_3$$

As a rule these sulfides are strong fungicides, and they kill many species of phytopathogenic microorganisms, but the majority of them are also dangerous to agricultural plants, since they cause severe burns on leaves.

Perchloromethylmercaptan may be used as a donor of a trichloromethylmercaptan group to the molecules of organic compounds, for example:



Perchloromethylmercaptan is obtained by the following basic methods.

1. Chlorination of carbon disulfide in the presence of iodine:

$$2CS_2 + 5Cl_2 \xrightarrow{I_2} 2CCl_3SCl + S_2Cl_2$$

The byproduct of this reaction is sulfur chloride, the separation of which presents certain difficulties. The simplest laboratory method of purifying perchloromethylmercaptan is to distill it with live steam. In this case sulfur chloride is broken down completely by water, but the perchloromethylmercaptan yield decreases to 10-15 percent owing to its hydrolysis by water. However, this method of purifying perchloromethylmercaptan is difficult in industrial conditions owing to the high corrosiveness of the medium. The second (industrial) method of removing sulfur chloride from perchloromethylmercaptan is to rectify it in a vacuum, but in this case the purified preparation contains up to 3 percent sulfur chloride, and repeat rectification means significant losses of the product.

Purifying perchloromethylmercaptan by processing it with sulfuric acid at a temperature not higher than 10°C has been proposed. In this case the sulfur chloride transforms into water-soluble tetrathionic acid:

$$S_2Cl_2 + 2H_2SO_3 \longrightarrow H_2S_4O_6 + 2HCl$$

the calcium salt of which is used to control true powdery mildews.

The shortcoming of this purification method is the possibility of side reactions when the temperature is higher and when the time of contact of perchloromethylmercaptan with aqueous sulfuric acid solution is longer. At temperatures above 35°C perchloromethylmercaptan is reduced by sulfuric acid to thiophosgene (melting point 78°C), which is highly voltaile and more toxic than perchloromethylmercaptan:

$$CCl_3SCl + H_2SO_3 + H_2O \longrightarrow CSCl_2 + 2HCl + H_2SO_4$$

Separation of sulfur chloride from perchloromethylmercaptan may be performed in a continuous process (24), as shown in Figure 14.

2. Chlorination of carbon disulfide in the presence of a small quantity of water at low temperature (25,26):

$$CS_2 + 5Cl_2 + 4H_2O \longrightarrow CCl_3SCl + H_2SO_4 + 6HCl$$

This process can also be performed in the presence of diluted mineral acids (27). Chlorination would best be performed at the lowest possible temperature (not above

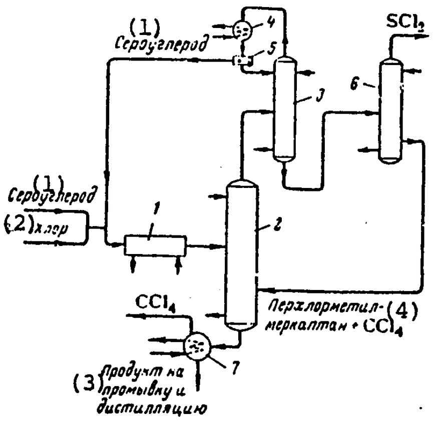


Figure 14. Basic Flowchart for Continuous Production of Perchloromethylmercaptan: *1*--carbon disulfide chlorination reactor; *2*--chlorination product distillation column; *3*--carbon disulfide distillation column; *4*--condenser; *5*--carbon disulfide separating unit; *6*--perchloromethylmercaptan, carbon tetrachloride and sulfur chloride distillation column; *7*--carbon tetrachloride residue distillation unit

Key:
1. Carbon disulfide
2. Chlorine
3. Product to be washed and distilled
4. Perchloromethylmercaptan + CCl_4

10°C) while agitating well in glass or (igurit) apparatus. In this case the productivity of the apparatus is 30-35 kg/hr perchloromethylmercaptan in a 100 liter reaction volume; the yield is up to 85 percent, and purity is 95 percent (27).

3. Chlorination of methylmercaptan and dimethyldisulfide:

$$(CH_3S)_2 + 7Cl_2 \longrightarrow \\ \longrightarrow 2CCl_3SCl + 6HCl$$

This method produces a good yield of sufficiently high quality perchloromethylmercaptan.

In addition to sulfur chloride, technical-grade perchloromethylmercaptan also contains some carbon tetrachloride formed due to further chlorination of perchloromethylmercaptan by chlorine.

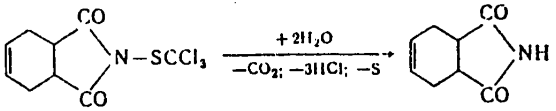
Perchloromethylmercaptan may be used to obtain chlorofluromethylsulfinyl chlorides--intermediate products in the synthesis of a number of fungicides (28-32):

$$CCl_3SCl + HF \xrightarrow[-HCl]{} CFCl_2SCl$$
$$CCl_3SCl + 2HF \xrightarrow[-2HCl]{} CF_2ClSCl$$

A very large number of derivatives of trihalomethylsulfenic acid have now been described in the literature, but the sulfenylamides of various carboxylic and sulfonic acids are the main ones to have achieved practical application, though there are indications that heterocyclic sulfenamides do have high fungicidal activity (33).

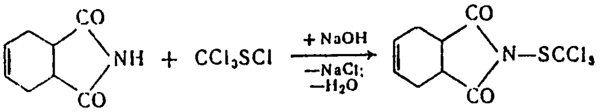
N-Trichloromethylmercapto-1,2,3,6-tetrahydrophthalimide (captan) is a white almost odorless crystalline substance with a melting point of 172°C. The technical-grade product is yellow or gray, and it has the typical odor of perchloromethylmercaptan and thiophosgene, with a melting point of 164°C. It is practically insoluble in water, and it is poorly soluble in most organic solvents. Its LD_{50} in rats is 9,000 mg/kg. No abnormal deviations were noted in the course of a year and more when the preparation was introduced into animal feed. It may cause slight irritation when coming in regular contact with the skin.

Captan undergoes hydrolysis when wet:



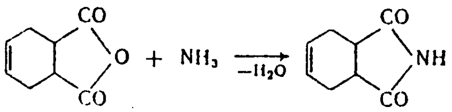
This reaction proceeds especially quickly in the presence of alkali and at high temperature. In this connection captan is incompatible with all other alkaline preparations.

Captan is obtained by reacting tetrahydrophthalimide with perchloromethylmercaptan in an aqueous alkaline medium, while agitating well at the lowest possible temperature, to avoid hydrolysis of both captan and perchloromethylmercaptan:

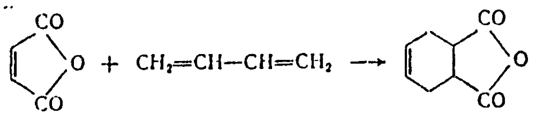


When the conditions of the process are complied with strictly, the captan yield reaches 90 percent.

Tetrahydrophthalimide is obtained from ammonium and tetrahydrophthalic anhydride at temperatures above 200°C:



Tetrahydrophthalic anhydride is formed with a practical quantitative yield upon condensation of divinyl with maleic anhydride, at 100-160°C. This process may be performed very easily under industrial conditions as a continuous process:



The flowchart for captan production is shown in Figure 15 (34).

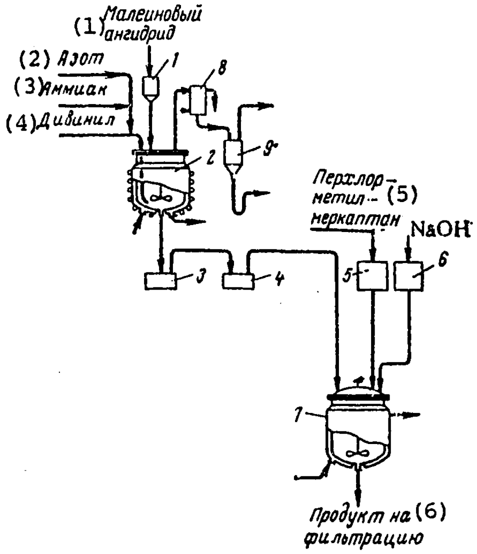


Figure 15. Basic Flowchart for Captan Acquisition: *1*--maleic anhydride hopper; *2*--reactor for synthesis of tetrahydrophthalimide; *3*--crystallizer; *4*--tetrahydrophthalimide mill; *5*,*6*--metering tanks for perchloromethylmercaptan and alkali; *7*--reactor for captan synthesis; *8*--heat exchanger; *9*--condensate collector

Key:

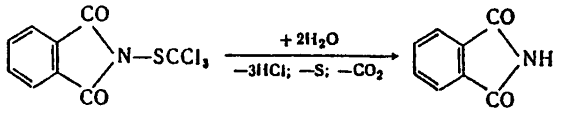
1. Maleic anhydride
2. Nitrogen
3. Ammonium
4. Divinyl
5. Perchloromethylmercaptan
6. Product to be filtered

Captan is produced in the form of 50 percent wettable powder and 75 percent preparation as a seed disinfectant; it is used for plant protection at a concentration of 0.3-0.5 percent.

Captan is used as a broad-profile protective fungicide to control various diseases of agricultural plants, including as a disinfectant of the seeds of a number of crops. When grapes are processed with captan, the latter has an unfavorable effect on alcohol fermentation during wine production, since it inhibits development of yeast fungi.

N-Trichloromethylmercaptophthalimide (ftalan, phaltan) is a white crystalline substance with a melting point of 177°C. It is insoluble in water, and it is poorly soluble in ordinary organic solvents. Ftalan is mildly toxic to mammals, and its LD_{50} in rats is more than 10,000 mg/kg.

It is slowly hydrolyzed by water, especially in an alkaline medium. In this connection the preparation must be carefully dried during its production, and dry fillers must be used. Presence of 1 percent water in the preparation may hydrolyze about 10 percent of the ftalan:



Hydrolysis liberates a large quantity of hydrogen chloride and therefore, as is equally true with captan, ftalan cannot be packaged in paper containers, since the latter break down very quickly.

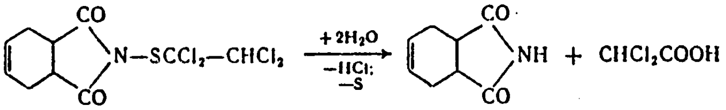
It is produced in the form of 50 percent wettable powder, and the concentration of the active ingredients of the applied product is 0.2-0.3 percent.

Ftalan is obtained similarly as with captan, by reacting perchloromethylmercaptan with phthalimide in the presence of sodium hydroxide in an aqueous medium. When sufficiently pure perchloromethylmercaptan is used, the ftalan yield is about 90 percent of theoretical. The main impurity in the technical-grade product is the initial phthalimide that did not react or that formed as a result of hydrolysis; a slight quantity of sulfur is present as well.

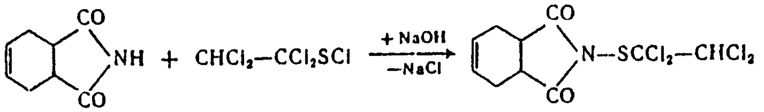
Phthalimide and its analogues are formed with a practical quantitative yield when phthalic anhydride is heated in the presence of urea to 130-140°C (35).

N-(1',1',2',2'-Tetrachloroethylmercapto)-1,2,3,6-tetrahydrophthalimide (captafol, difolatan, foltsid) is a white crystalline substance with a melting point of 162°C; it is practically insoluble in water and poorly soluble in most ordinary organic solvents, though it is somewhat more soluble than captan. Its LD_{50} in rats is more than 6,000 mg/kg.

The preparation is more resistant to hydrolysis than captan and ftalan, and it is hydrolyzed slowly by water and faster by caustic alkali:



Difolatan is obtained by reacting tetrahydrophthalimide with tetrachloroethylsulfinyl chloride in the presence of sodium hydroxide:



Tetrachloroethylsulfinyl chloride is synthesized out of sulfur chloride and trichloroethylene, followed by chlorination of the resulting bis-(tetrachloroethyl)-disulfide (36):

$$CHCl{=}CCl_2 + S_2Cl_2 \longrightarrow (CHCl_2{-}CCl_2)_2S_2 \xrightarrow{+Cl_2} 2CHCl_2CCl_2SCl$$

It is less difficult to obtain this product than perchloromethylmercaptan, and there are grounds for suggesting that N-(1′,1′,2′,2′-tetrachloroethyl)-1,2,3,6-tetrahydrophthalimide is a serious competitor of captan.

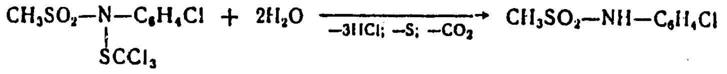
Difolatan is produced in the form of a 50 percent wettable powder, and it is used similarly as captan and ftalan. The main crops for which this preparation is recommended are potatoes and grapes.

A large number of other similar compounds have been synthesized as well, but they have not yet found applications in agriculture.

N-Trichloromethylsulfamides of aliphatic sulfonic acids are close in fungicidal activity to captan, while the corresponding amides of aromatic sulfonic acids are significantly less active. Introduction of a trichloromethylmercapto group does not always raise the activity of sulfonic acid amides. Thus N-(trichloromethyl-mercapto-N-(4-chlorophenyl)-methanesulfamide is a strong fungicide while N-(trichloromethylmercapto)-N-(4-thiocyanatophenyl)-methanesulfamide is not very active.

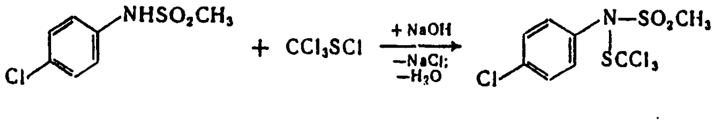
N-(Trichloromethylmercapto)-N-(4-chlorophenyl)-methanesulfamide (mesul'fan, an analogue of captan No 6) is a white crystalline substance with a melting point of 113-114°C. It is insoluble in water and moderately soluble in organic solvents. Its LD_{50} in rats and mice is more than 5,000 mg/kg (37).

It recalls captan in its chemical properties: It is unstable in an alkaline medium and it is hydrolyzed by water:



$$CH_3SO_2{-}\underset{\displaystyle SCCl_3}{\underset{|}{N}}{-}C_6H_4Cl + 2H_2O \xrightarrow[-3HCl;\ -S;\ -CO_2]{} CH_3SO_2{-}NH{-}C_6H_4Cl$$

Mesul'fan is produced at a good yield by reacting perchloromethylmercaptan with 4-chlorophenylmethanesulfamides in the presence of sodium hydroxide:



Mesul'fan is produced in the form of 50 percent wettable powder; it is less active than captan.

N-Trichloromethylsulfamide homologues of methanesulfonic acid are somewhat less active, with the exception of ethanesulfonic acid derivatives, which are equivalent to the corresponding derivatives of methanesulfonic acid. Introduction of chlorine into the methyl radical of methanesulfonic acid does not raise the compound's activity.

Research has also been conducted on a large number of aliphatic and aromatic trichloromethylthiosulfonates. Many of them have strong fungicidal action, but all compounds of this type are phytotoxic, owing to which they are not used in agriculture.

Trichloromethylthiosulfonates are obtained with a good yield by reacting the sodium salts of sulfinic acids with perchloromethylmercaptan:

$$RSO_2Na + CCl_3SCl \xrightarrow[-NaCl]{} RSO_2SCCl_3$$

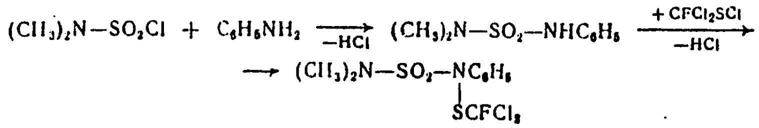
The fungicidal activity of compounds containing a trichloromethylmercapto group is connected, in the opinion of many researchers, with the high reactivity of this group. Interacting with different sulfhydryl groups in the fungal cell, it disturbs vitally important biochemical processes in microorganisms.

Research has been conducted on, in addition to derivatives of sulfonic acids, the N-alkylmercapto derivatives of sulfuric acid amides, of which the preparation eparen (dikhlorfluanid) has enjoyed practical application (28-32).

N-N-dimethyl-N'-dichlorofluoromethylmercapto-N'-phenylsulfamide (eparen, dikhlorfluanid) is a crystalline substance with a melting point of 105.5-105.6°C. Its vapor pressure is $1 \cdot 10^{-6}$ mm Hg at 20°C and $4 \cdot 10^{-5}$ mm Hg at 45°C. It is practically insoluble in water. Its solubility (gm per 100 ml solvent) is 1.5 in methanol and 7.0 in xylol. Its LD_{50} in rats is 500-1,000 mg/kg with different methods of administration.

In its chemical properties it recalls the corresponding derivatives of perchloromethylmercaptan, but it is somewhat more stable.

Eparen may be obtained as follows:



$$(CH_3)_2N{-}SO_2Cl + C_6H_5NH_2 \xrightarrow[-HCl]{} (CH_3)_2N{-}SO_2{-}NHC_6H_5 \xrightarrow[-HCl]{+CFCl_2SCl} (CH_3)_2N{-}SO_2{-}\underset{\substack{| \\ SCFCl_2}}{NC_6H_5}$$

The acid chloride of sulfuric acid dimethylamide may be obtained by reacting dimethylamine with sulfuryl chloride or by reacting dimethylchloramine with sulfur dioxide:

$$(CH_3)_2NH \xrightarrow[-HCl]{+SO_2Cl_2} (CH_3)_2N{-}SO_2Cl \xleftarrow{+SO_2} (CH_3)_2NCl$$

Eparen is produced in the form of 50 percent wettable powder to be used as a 0.075-0.1 percent aqueous suspension and as a 7.5 percent dusting powder. Eparen has a good effect against apple scab, gray mold on strawberries and stone fruit crops, and other plant diseases.

N,N′-Dimethyl-N′-dichlorofluoromethylmercapto-N′-*p*-tolylsulfamide (eparen M) has a melting point of 95-95°C, and its vapor pressure at 20°C is 10^{-5} mm Hg. Its solubility in water at 20°C is 4 gm/liter. It is freely soluble in most organic solvents (41,42). Its LD_{50} in rats is 1,000 mg/kg.

The N,N-dialkyl-N′-tetrachlorofluoroethylmercapto-N′-phenylamides of sulfuric acid (38) and of organic sulfonic acids (39) also have fungicidal properties.

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CHAPTER 25

ORGANIC PHOSPHORUS COMPOUNDS

General Description of Pesticide Properties

One of the most important classes of modern pesticides is the organic compounds of phosphorus, more than 100 of which are used in agriculture. Among the organic phosphorus compounds, substances have been found with different pesticidal properties, to include insecticides, acaricides, nematocides, herbicides, defoliants and fungicides.

Organic phosphorus compounds are used especially broadly to control plant pests and the ecto- and, in part, endoparasites of domesticated animals.

The scale of application of organic phosphorus compounds as pesticides is close to the scale of use of organic chlorine compounds in agriculture.

World production of the most important preparations in this class, intended for control of weeds and plant pests and diseases, has now exceeded 150,000 tons per year, and the number of preparations now in use is nearing 150. Such swift growth in the production and application of organophosphorus pesticides is connected with a number of their positive properties, the most important ones of which are:

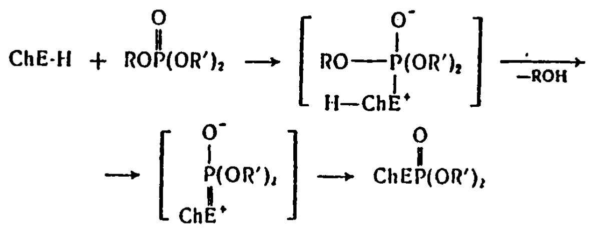
1. High insecticidal and acaricidal activity and broad spectrum of action against plant pests.
2. The possibility of having compounds with the most diverse persistence, the decomposition of which in different living organisms proceeds with formation of compounds that are practically nontoxic to man and animals.
3. Relatively fast metabolism in the vertebrate body and absence of a capability for deposition in the body, as well as relatively low product toxicity or its complete absence.
4. Systemic or deep action of a number of preparations.
5. Low consumption of preparations per unit of worked surface and fast action against plant pests and animal parasites.
6. Fast decomposition in soil and moderate toxicity to fish.

One negative property of many organophosphorus compounds is their relatively acute toxicity to vertebrates, which requires compliance with the appropriate precautionary measures when using them. A large number of organophosphorus compounds that are moderately or mildly toxic to mammals have also been synthesized in recent years. Such compounds are fully safe to use in agriculture.

Research on the mechanism of action of organophosphorus compounds upon mammals and insects showed that in the animal body, they phosphorylate vitally important esterases, inhibiting their normal functions. It is believed that the action of these compounds is based mainly on inhibition of cholinesterase, the physiological functions of which are very important in the animal body. Cholinesterase hydrolyzes acetylcholine:

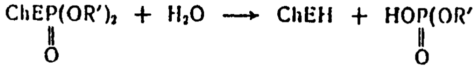
$$(\mathrm{CH_3})_3\overset{+}{\mathrm{N}}\mathrm{CH_2CH_2OCOCH_3} \xrightarrow{\mathrm{ChE{\cdot}H}} (\mathrm{CH_3})_3\overset{+}{\mathrm{N}}\mathrm{CH_2CH_2OH} + \mathrm{CH_3COOH}$$

The mechanism by which cholinesterase is inhibited by organophosphorus compounds may be diagrammed as follows (1-4,549):



$$\mathrm{ChE{\cdot}H} + \mathrm{RO}\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{(OR')_2} \longrightarrow \left[\begin{array}{c} \mathrm{O^-} \\ | \\ \mathrm{RO{-\!\!-}P(OR')_2} \\ | \\ \mathrm{H{-}ChE^+} \end{array}\right] \xrightarrow[-\mathrm{ROH}]{} \left[\begin{array}{c} \mathrm{O^-} \\ | \\ \mathrm{P(OR')_2} \\ \| \\ \mathrm{ChE^+} \end{array}\right] \longrightarrow \mathrm{ChE}\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{(OR')_2}$$

At first, esterase apparently forms a complex with the organophosphorus compound. This complex then breaks down to produce an esterase phosphorylation product and the corresponding oxy compound. Phosphorylated esterase may be gradually hydrolyzed by water, which restores its esterase activity. The rate of dephosphorylation is so low for some substances that it does not have practical significance. Thus for example, dephosphorylation of cholinesterase inhibited by tetraethylpyrophosphate proceeds very slowly in water, and in 28 days only 50 percent of the initial activity is restored:

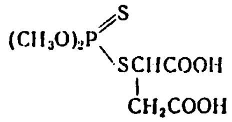


$$\mathrm{ChE}\underset{\mathrm{O}}{\underset{\|}{\mathrm{P}}}\mathrm{(OR')_2} + \mathrm{H_2O} \longrightarrow \mathrm{ChEH} + \mathrm{HO}\underset{\mathrm{O}}{\underset{\|}{\mathrm{P}}}\mathrm{(OR')_2}$$

The activity of organophosphorus compounds depends strongly on the structure of the ester groups in the molecule of the phosphoric acid ester; nor is the structure of each of the radicals immaterial. Thus for example, O,O-diisopropyl-O-4-nitrophenylthiophosphate is almost 100 times less active against bee cholinesterase than O,O-diethyl-O-4-nitrophenylthiophosphate.

For maximum effect, the organophosphorus molecule must have a "lock and key" fit with the active centers of the esterase (5).

It is entirely obvious that the activity of the same compound would differ in relation to cholinesterase from different species of animals and insects. This is connected with the difference in the structure of cholinesterase from different organisms (1,4) and with differences in the metabolic pathways of organophosphorus compounds in the insect and animal body (2). Thus for example, carbofos undergoes the usual transformations in the housefly body, while in the rat body it transforms into mildly toxic malathionic acid:



while pyrophosphoric acid octamethyltetramide transforms in the animal body into a product that is more toxic than the initial compound.

To correctly understand the reasons why specific organophosphorus compounds are toxic to particular species of animals, we need to know not only the general mechanism of their action but also their metabolism within the given animal species.

Very often the activity of a compound in relation to cholinesterase is associated with the organophosphorus compound's rate of hydrolysis, which is not always valid: Activity also depends on the steric features of molecular structure.

In addition to hydrolysis and the structural features of organophosphorus molecules, the rate of dealkylation of phosphoric acid esters also has a great influence on their toxicity (6). Phosphate dealkylation is apparently the principal reaction in the animal body competing with phosphorylation of cholinesterase. That methylphosphates are less toxic to mammals than homologous esters can be explained by dealkylation of phosphoric esters. In this case esters are decomposed by dealkylation before they reach their place of action, as was first asserted by the author back in 1961. This point of view has now achieved substantial confirmation (7).

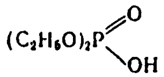
Various phosphorus compounds are used as pesticides, to include derivatives of phosphorous and thiophosphorous acids, thio- and dithiophosphoric acids, and phosphonic and thiophosphonic acids.

In contrast to the situation with most other classes of compounds, the nomenclature of organophosphorus compounds has not been adequately worked out yet, and different countries use their own naming systems. In most cases organophosphorus compounds are interpreted as derivatives of the appropriate acids and hydrogen phosphide--phosphine.

Derivatives of phosphorous acid have "ite" endings while derivatives of phosphoric acid have "ate" endings. For example the diethyl ester of phosphorous acid (I) is called diethylphosphite, while the diethyl ester of phosphoric acid (II) is called diethylphosphate:

$(C_2H_5O)_2PHO$

I

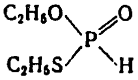


II

When a sulfur atom is present in the molecule, the compound is named as follows: Depending on the position of the sulfur atom, the diethyl ester of thiophosphorous acid is called O,O-diethylthiophosphite (III) or O,S-diethylthiophosphite (IV):

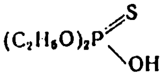
$(C_2H_5O)_2PHS$

III

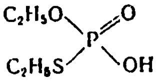


IV

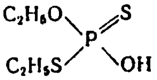
The derivatives of thiophosphoric acids are named analogously, as can be seen from the following examples:



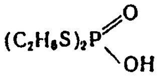
O,O-Diethylthiophosphate



O,S-Diethylthiophosphate

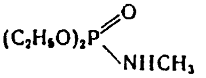


O,S-Diethyldithiophosphate

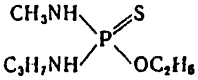


S,S-Diethyldithiophosphate

Amides of the acids of phosphorus are named according to the same system. Thus compound V would be named O,O-diethyl-N-methylamidophosphate, while compound VI would be named O-ethyl-N-methyl-N'-propyldiamidothiophosphate:



V



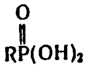
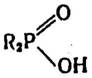
VI

The names of complete amides of phosphorous acid are sometimes derived from hydrogen phosphide as well. In this case compound VII may be called hexamethyltriaminophosphine:

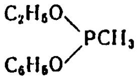
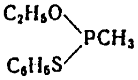
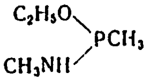
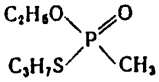
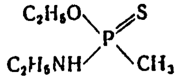
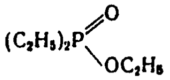
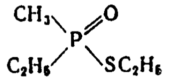
$[(CH_3)_2N]_3P$

VII

Acids of phosphorus having a C-P bond are named as follows:

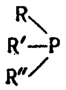
 $RP(OH)HO$	Alkylphosphonous
R_2PHO	Dialkylphosphinous
 $RP(=O)(OH)_2$	Alkylphosphonic
	Dialkylphosphinic

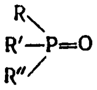
The nomenclature of the derivatives of these acids may be explained by the following examples:

	O-Ethyl-O-phenylmethylphosphonite
	O-Ethyl-S-phenylmethylthiophosphonite
	O-Ethyl-N-methylamidomethylphosphonite
	O-Ethyl-S-propylmethylthiophosphonate
	O-Ethyl-N-ethylamidomethylthiophosphonate
	O-Ethyldiethylphosphinate
	S-Ethylethylmethylthiophosphinate

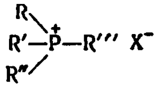
The names of alkyl- and arylphosphinous acid chlorides may be derived from phosphine; for example CH_3PCl_2 (VIII) is called methyldichlorophosphine.

Compounds with the general formula IX below are called phosphines while compounds with the general formula X are called phosphinoxides:


IX


X

The salts of tetrasubstituted phosphonium (XI)



XI

are named similarly as the corresponding ammonium derivatives.

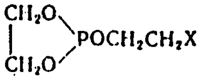
Phosphorous Acid Derivatives

Research on the pesticidal properties of a large number of phosphorous acid derivatives established that many compounds in this series have weak insecticidal and acaricidal activity, but some derivatives of phosphorous and thiophosphorous acids have high herbicidal activity.

The herbicidal activity of esters of phosphorous acid increases as the number of carbon atoms in the aliphatic ester radicals grows. Complete esters formed from phosphorous acid and haloaryloxyethanols display the greatest activity; one such compound used in agriculture is falone.

Tributyltrithiophosphite has enjoyed rather broad use under the names merfos and foleks as a defoliant of cotton and some other crops (9). The compound is also active when combined with the most diverse compounds including tertiary amines (10). Other active defoliants are dibutyldithiochlorophosphite (11) and triarylphosphites (12).

Cyclic pyrocatechol chlorophosphites (13) and diallylphosphite (14) exhibit fungicidal action. Cyclic phosphite (XII) has been proposed as an insect sterilizer (15). Phosphites are broadly employed as intermediate products in the synthesis of a large number of pesticides.



XII (X = Cl, Br, F, I)

The most important methods of obtaining dialkylphosphites are as follows (16).

1. Interaction of phosphorus trichloride and alcohols:

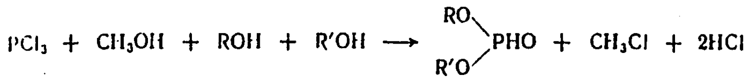
$$PCl_3 + 3ROH \longrightarrow (RO)_2PHO + RCl + 2HCl$$

2. Partial hydrolysis of trialkylphosphites or dialkychlorophosphites:

$$(RO)_3P + H_2O \longrightarrow (RO)_2PHO + ROH$$

3. Dialkylphosphites can also be obtained by oxidation of white phosphorus in the appropriate alcohol (17). The yield of diethylphosphite in this case is about 43 percent.

Of these methods, the first has the greatest practical significance. It is used extensively in industry. The reaction is usually performed in an inert organic solvent at low temperature (18). A convenient solvent for acquisition of dimethylchlorophosphite would be methylchloride, which acts here as a coolant as well, since the reaction is usually performed at its boiling point (-24°C). This method can also be used to obtain dialkyphosphites with mixed radicals (19) and alkylarylphosphites (20,21), using a mixture of two alcohols and methanol in a reaction with PCl_3:



$$PCl_3 + CH_3OH + ROH + R'OH \longrightarrow \begin{matrix} RO \\ R'O \end{matrix}\!\!>PHO + CH_3Cl + 2HCl$$

Byproducts appearing in small quantities in the reaction between phosphorus trichloride and alcohols include monoalkylphosphite and phosphorous acid, formed as a result of the reaction between dialkyphosphite and hydrogen chloride.

Dialkyphosphites can be produced from PCl_3 and alcohols by both cyclic and continuous processes (18).

Lower dialkylphosphites may be purified by distillation in a vacuum using a continuous-action film evaporator at a residual pressure of 1-5 mm Hg.

Trialkyphosphites may be industrially obtained by reacting phosphorus trichloride and alcohols in the presence of hydrogen chloride acceptors (22-24) (ammonium, ammoniate (23) and tertiary amines (24)) and by an ester interchange reaction performed with triarylphosphites and alcohols (25). The latter reaction proceeds in the presence of alkaline catalysts at high temperature.

Figure 16 shows the basic flowchart for production of trimethylphosphite out of methanol and triphenylphosphite (25).

The purity of trimethylphosphite obtained by this method is 98 percent, and its yield is 80-85 percent. This yield is achieved after several recyclings of triphenylphosphite.

Another interesting method of obtaining trialkyphosphites is to react alcohols with triaminophosphines:

$$3ROH + (R'_2N)_3P \longrightarrow (RO)_3P + 3R'_2NH$$

The oldest method is to react phosphorus trichloride with sodium or magnesium alcoholates, but the trialkylphosphite yields do not exceed 61 percent of theoretical.

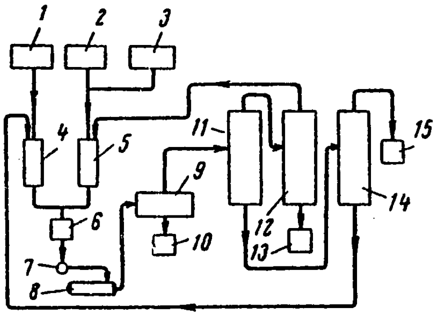


Figure 16. Basic Flowchart for Production of Trimethylphosphite Out of Methanol and Triphenylphosphite: *1*--triphenylphosphite container; *2*--methanol container; *3*--catalyst (sodium methylate) container; *4,5*--metering units; *6*--reactor-mixer; *7*--pump; *8*--tunnel reactor; *9*--evaporator; *10*--vat residue collector; *11*--column for separation of methanol and trimethylphosphite from phenol and triphenylphosphite; *12*--column for separation of methanol and trimethylphosphite; *13*--trimethylphosphite collector; *14*--column for separation of phenol and triphenylphosphite; *15*--phenol collector

Dialkylthiophosphites may be obtained by reacting hydrogen sulfide with trialkylphosphites in the presence of organic bases (26), and trialkyltrithiophosphites can be obtained from mercaptans and trialkyphosphites in the presence of zinc or cadmium acetates (27). However, the best industrial method of obtaining trialkytrithiophosphites is to react phosphorus trichloride with mercaptans. In this reaction, equimolar quantities of these substances are heated. This is the way the preparation merfos is obtained industrially:

$$PCl_3 + 3C_4H_9SH \longrightarrow (C_4H_9S)_3P + 3HCl$$

Tris-(2,4-dichlorophenoxyethyl)-phosphite (falone) is a thick oily liquid with a mild odor, it does not sublimate without decomposing in a low vacuum, it is practically insoluble in water, and it is freely soluble in organic solvents.

Its LD_{50} in rats is 850 mg/kg.

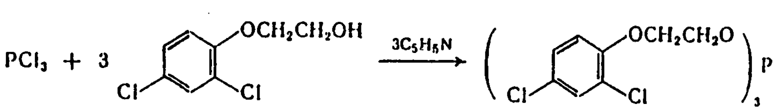
Oxidation of the preparation produces the appropriate phosphate:

$$(2,4\text{-}Cl_2C_6H_3OCH_2CH_2O)_3P \xrightarrow{[O]} (2,4\text{-}Cl_2C_6H_3OCH_2CH_2O)_3PO$$

When it interacts with water, falone first transforms into the corresponding dialkylphosphite which, on being hydrolyzed and oxidized, produces 2,4-dichlorophenoxyethanol and phosphoric acid.

The action of falone in soil is apparently based on its transformation into 2,4-D. Falone is recommended against weeds in corn, potatoes, strawberries and some other crops at consumption norms from 4 to 8 kg/ha. Aqueous emulsions of the preparation are usually used to process soil.

Falone is obtained by reacting phosphorus trichloride with 2,4-dichlorophenoxyethanol in the presence of pyridine, dimethylaniline or other tertiary amines:



Following separation of pyridine hydrochloride, the reaction product is used without further purification to make emulsion concentrate.

Di-(2,4-dichlorophenoxyethyl)-phosphite also has herbicidal properties, but its activity is inferior to that of falone.

Tributyltrithiophosphite (merfos, foleks) is a light oily liquid with a boiling point of 150-152°C at 2 mm Hg. It is almost insoluble in water, and it is freely soluble in organic solvents.

Its LD_{50} in rats is 350 mg/kg.

The preparation is used to defoliate cotton in the form of aqueous emulsions at consumption norms of 1-2 kg/ha. In terms of the speed of its action and the resulting effect, merfos is one of the best defoliants.

Merfos is slowly oxidized by atmospheric oxygen to tributyltrithiophosphate; this reaction goes faster in the presence of heat, and it may be used as an intermediate step in acquisition of tributyltrithiophosphate and in production of S,S,S-tributyltrithiophosphate in industry. Tributyltrithiophosphate enjoys extensive use as a defoliant of cotton and other crops. It is marketed as butifos and DEF. It is an oily liquid with an unpleasant odor; its boiling point is 150°C at 0.3 mm Hg; its LD_{50} in experimental animals is 170-250 mg/kg.

Impurities contained in the technical-grade preparation include a small quantity (up to 10 percent) of tributyltrithiophosphite and dibutyldisulfide. It is used as oil solutions or emulsion concentrates at consumption norms of 1-1.5 kg/ha.

Some homologues of merfos and butifos have been proposed as defoliants, but they have not as yet enjoyed practical application.

Because merfos and butifos are readily oxidized by various oxidants, they may be neutralized by oxidizing and chlorinating them with calcium and alkali metal hypochlorites. However, it should be kept in mind that in a number of cases hypochlorites react with these defoliants very violently, with ignition occurring.

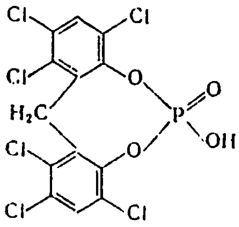
Phosphoric Acid Derivatives

As we proceed from phosphites to phosphates, the insecticidal and acaricidal activity of the compound rises. Mixed esters of phosphoric acid, where one of the ester radicals is acidic, are especially active. The higher the dissociation constant of such an alcohol or phenol (or acid), the more toxic the compound is to insects and animals. Thus for example, in the series 0,0-diethyl-0-4-chlorophenylphosphate, 0,0-diethyl-0-2,4-dichlorophenylphosphate and 0,0-diethyl-0-2,4,5-trichlorophenylphosphate, the last ester exhibits the greatest insecticidal activity (the dissociation constants of 4-chlorophenol, 2,4-dichlorophenol and 2,4,5-trichlorophenol are $4.1 \cdot 10^{-10}$, $3.1 \cdot 10^{-8}$ and $4.26 \cdot 10^{-8}$). Dialkylfluorophosphates as well as fluorophosphoric acid amides are highly toxic. However, when the length of alkyl radicals in phosphoric acid esters and amides is increased, toxicity to animals decreases. Maximum toxicity for many mixed esters of phosphoric acid is achieved with diethyl derivatives, but exceptions are observed as well. As a rule dimethylphosphates are significantly less toxic, apparently due to their high alkylating capacity in relation to various nitrogen and sulfur compounds present in biological substrates, and their high rate of hydrolysis.

Not only the nature of the substituent in the aromatic radical but also its position has a great influence on the toxicity of mixed phosphate to insects and ticks. Insecticidal properties are increased the most when nitro- and methylmercapto groups are introduced into the aromatic radical. In general the activity of arylphosphate with substituents at position 4 is higher than that of arylphosphates with the substituents at positions 2 and 3.

Systematic study of the biological activity of different mixed aliphatic-aromatic phosphates showed that some of them may be of practical interest as insecticides (28-30), fungicides (31) and herbicides (33). In particular, herbicidal action is exhibited by tris-(butyoxyethyl)-phosphate (34).

High biological activity is exhibited by some phosphates obtained from oximes of benzaldehyde and acetophenone derivatives (35) containing different substituents in the aromatic ring. Cyclic ester XIII, obtained from phosphorus chloroxide and hexachlorophene, has herbicidal action (36):

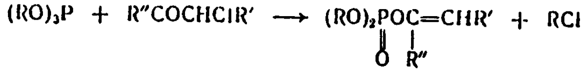


XIII

Mixed esters and esteramides of phosphoric acid possessing various heterocyclic radicals have significant insecticidal and acaricidal activity (37-40,42-45), while benzofurazan derivatives have nematocidal action (41). Dialkylhalopyridyl phosphates are good insecticides with moderate toxicity to homeothermic animals. An example is preparation dauks-217 (0,0-dimethyl-0-(3,5,6-trichloropyridyl)-phosphate). Its LD_{50} in rats is 869 mg/kg (42,43).

Among mixed esters of phosphoric acid, various enol phosphates have been subjected to the deepest study in recent years; many of them have achieved extensive practical application in agriculture and in the control of synanthropic insects. Table 44 shows some phosphoric acid esters that have achieved some sort of application in agriculture.

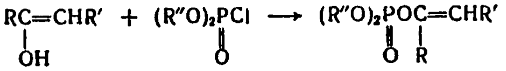
As we can see from Table 44 vinylphosphates containing various substituents in the vinyl group have enjoyed the widest use. Perkov's reaction (47) is a general method of obtaining 0,0-dialkyl-0-vinylphosphate--interaction of α-halocarbonyl compounds with trialkylphosphites:



$$(RO)_3P + R''COCHClR' \longrightarrow (RO)_2\underset{O}{\overset{}{P}}O\underset{R''}{C}{=}CHR' + RCl$$

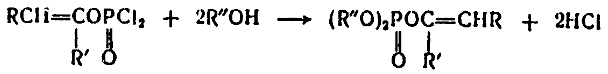
This reaction proceeds easily with both aliphatic and aromatic carboxylic acid aldehydes, ketones, esters and amides.

0,0-Dialkyl-0-vinylphosphates may also be obtained by reacting dialkylchlorophosphates with the appropriate enols in the presence of hydrogen chloride acceptors (4). Both inorganic and organic bases may be used as hydrogen chloride acceptors.



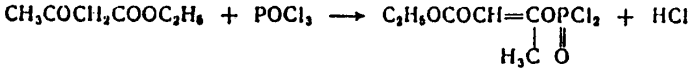
$$R\underset{OH}{C}{=}CHR' + (R''O)_2\underset{O}{P}Cl \longrightarrow (R''O)_2\underset{O}{P}O\underset{R}{C}{=}CHR'$$

Acquisition of dialkylvinylphosphates by reacting vinylphosphoric acid chlorides with the appropriate alcohols in the presence of hydrogen chloride acceptors has been described in patents (49):



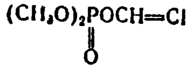
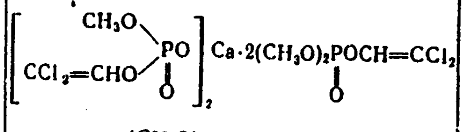
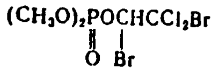
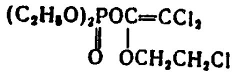
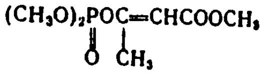
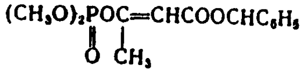
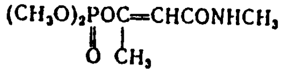
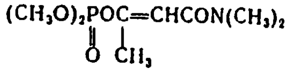
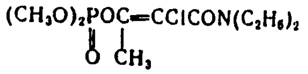
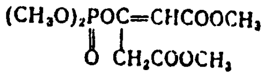
$$RCH{=}\underset{R'}{C}O\underset{O}{P}Cl_2 + 2R''OH \longrightarrow (R''O)_2\underset{O}{P}O\underset{R'}{C}{=}CHR + 2HCl$$

The vinyldichlorophosphates required for this reaction are obtained from phosphorus chloroxide and enols, for example acetoacetate:



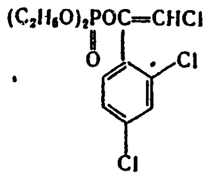
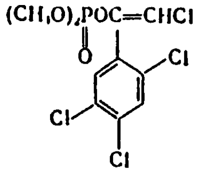
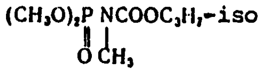
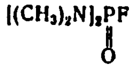
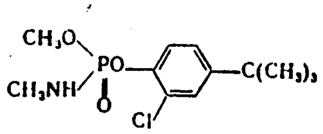
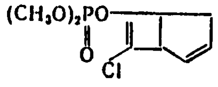
$$CH_3COCH_2COOC_2H_5 + POCl_3 \longrightarrow C_2H_5OCOCH{=}\underset{H_3C}{C}O\underset{O}{P}Cl_2 + HCl$$

Table 44. Phosphoric Acid Esters

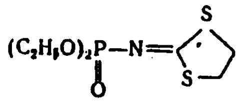
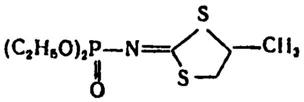
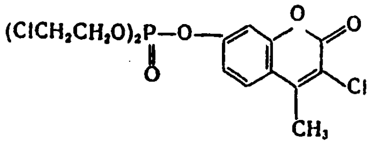
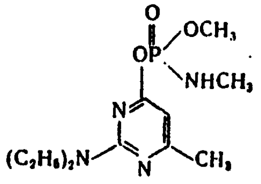
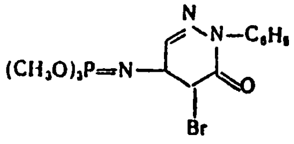
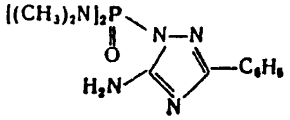
Chemical Name	Formula	Synonyms
O,O-Dimethyl-O-(2,2-dichlorovinyl-phosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}OCH{=}Cl$	Dichlorophos, DDVP, nuvan, vapona, nogos
	 $\left[\begin{matrix}CH_3O\\CCl_2{=}CHO\end{matrix}\underset{\overset{\|}{O}}{P}O\right]_2Ca\cdot 2(CH_3O)_2\underset{\overset{\|}{O}}{P}OCH{=}CCl_2$	Nestan
O,O-Dimethyl-O-(1,2-dibromo-2,2-dichloroethyl)-phosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}O\underset{\overset{\|}{Br}}{C}HCCl_2Br$	Naled, dibrom, nikabrom
O,O-Diethyl-O-(2,2-dichloro-1-β-chloroethoxyvinyl)-phosphate	 $(C_2H_5O)_2\underset{\overset{\|}{O}}{P}O\underset{\overset{\|}{OCH_2CH_2Cl}}{C}{=}CCl_2$	Fosfinon
O,O-Dimethyl-O-(1-methyl-2-carbomethoxyvinyl)-phosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}O\underset{\overset{\|}{CH_3}}{C}{=}CHCOOCH_3$	Mevinphos, phosdrin
O,O-Dimethyl-O-[1-methyl-2-(carboxy-α-phenylethyl)-vinyl]-phosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}O\underset{\overset{\|}{CH_3}}{C}{=}CHCOOCHC_6H_5$	Ciodrin
O,O-Dimethyl-O-[1-methyl-2-(methylcarbamoyl)-vinyl]-phosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}O\underset{\overset{\|}{CH_3}}{C}{=}CHCONHCH_3$	Azodrin, nuvacron
O,O-Dimethyl-O-[1-methyl-2-(dimethylcarbamoyl)-vinyl]-phosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}O\underset{\overset{\|}{CH_3}}{C}{=}CHCON(CH_3)_2$	Bidrin, carbicron, ektafos
O,O-Dimethyl-O-[1-methyl-2-chloro-2-(diethylcarbamoyl)-vinyl]-phosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}O\underset{\overset{\|}{CH_3}}{C}{=}CClCON(C_2H_5)_2$	Phosphamidon, dimecron, dovip
O,O-Dimethyl-O-(1-carbomethoxymethyl-2-carbomethoxyvinyl)-phosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}O\underset{\overset{\|}{CH_2COOCH_3}}{C}{=}CHCOOCH_3$	Bamil

That Have Attained Use as Pesticides

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility in Water, mg/liter	LD$_{50}$ in Rats (Orally) mg/kg / LD$_{50}$ in Rabbits (Subcutaneously), mg/kg	Use. Forms of Application and Consumption Norms
74 (1)	—	10 000	$\frac{80}{107}$	Contact insecticide. Aerosol preparations, granules, e.c. [emulsion concentrates]; 0.2-1 kg/ha
	63—66	40 000	$\frac{330}{3400}$	Contact and intestinal insecticide. Controls ectoparasites and synanthropic insects.
110 (0,25)	26,5—27,5	Insoluble	$\frac{430}{1100}$	Insecticide, weak fungicide. E.c. Used in greenhouses.
124 (4)	—	Poor	$\frac{6,8}{9,7}$	Insecticide with broad range of action.
76 (0,2)	−56	Good	$\frac{6—7}{33,8}$	Insecticide with short active period. 50% e.c.
135 (0,03)	—	1200	$\frac{125}{385}$	Insecticide to control ectoparasites in animal husbandry. E.c.
—	53—55 25—30 (Technical grade)	Good	$\frac{21}{354}$	Insecticide and acaricide with broad spectrum of action. Controls cotton pests. 20 and 60% water-soluble e.c.; 0.25-0.5 kg/ha.
90—95 (0,001)	—	Good	$\frac{22}{225}$	Insecticide and acaricide with broad spectrum of action. Water-soluble concentrate; 0.25-0.5 kg/ha
115 (0,2)	—	Mixes	$\frac{18—27}{530}$	Insecticide with broad spectrum of action. Various forms; 0.2-1 kg/ha.
155—164 (2)	—	—	32	Insecticide, 25% w.p. [wettable powder]

Chemical Name	Formula	Synonyms
O,O-Diethyl-O-[2-chloro-1-(2′,4′-dichlorophenyl)-vinyl]-phosphate		Birlane, supona, sapekron, chlorfenvinphos
O,O-Dimethyl-O-[2-chloro-1-(2′,4′,5′-trichlorophenyl)-vinyl]-phosphate		Gardona, tetrachlorvinphos, rabon
O,O-Dimethyl-(N-isopropoxycarbamoyl)-phosphate	 $(CH_3O)_2\underset{\substack{\| \\ O}}{P}NHCOOC_3H_7\text{-iso}$	Avenin
O,O-Dimethyl-(N-isopropoxy-N-methylcarbamoyl)-phosphate	 $(CH_3O)_2\underset{\substack{\| \\ O}}{P}\underset{\substack{| \\ CH_3}}{N}COOC_3H_7\text{-iso}$	Dimufos
Bis-(dimethylamido)-fluorophosphate	 $[(CH_3)_2N]_2\underset{\substack{\| \\ O}}{P}F$	Dimefox, pestox, khanan, terrasytam
O-Methyl-O-(2-chloro-4-*tert*-butylphenyl)-methylamidophosphate		Ruelene
O,O-Dimethyl-O-(6-chloro-bicyclo[3,2,0]heptadien-1,5-yl-5)-phosphate		HOE-2982

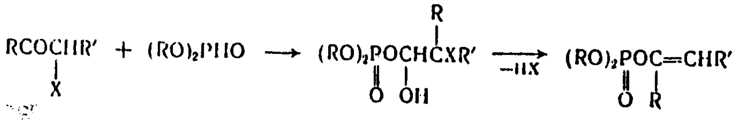
Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility-Water, mg/liter	$\frac{\text{LD}_{50}\text{ in Rats (Orally) mg/kg}}{\text{LD}_{50}\text{ in Rabbits (Subcutaneously), mg/kg}}$	Use. Forms of Application and Consumption Norms
110 (0,001)	—	145	$\frac{24-39}{180-400}$	Insecticide controlling soil-inhabiting pests. e.c., granules; 0.5-1 kg/ha
—	97—98	11	$\frac{1500-5000}{6000}$	Insecticide with broad spectrum of action. 24% e.c., w.p., granules; 0.5-1.5 kg/ha
—	—	Poor	5000	Systemic insecticide controlling beet pests. Seed disinfectant
114—115 (3)	—	Poor	950	Systemic insecticde against various insects. E.c.
125 (2)	—	Good	$\frac{1-1,5}{5}$	Systemic insecticide for soil application. In gelatinous capsules and in other forms.
117—118 0,01	62—62,5	0,5%	660—1000	Insecticides controlling animal ectoparasites.
—	Liquid	Poor	98—117	Systemic insecticide with short-term action. Controls vegetable pests.

Chemical Name	Formula	Synonyms
O,O-Diethyl-N-(1,3-dithiolanimido)-phosphate		Tsiolan, ditiolen, iminofosfat
O,O-Diethyl-N-(5-methyl-1,3-dithiolanimido)-phosphate		Dithiolane
O,O-Bis-(β-chloroethyl)-O-(3-chloro-4-methylcoumarinyl-7)-phosphate		Haloxon
O-Methyl-N-methylamidO-O-(2-diethylamino-6-methylpyrimidinyl-4)-phosphate		San-52 135-03
5-(Trimethyoxyphosphazo)-4-bromo-2-phenylpyridazinone-3		SGA-18796
(5-Amino-3-phenyl-1H-1,2,4-triazolyl-1)-bis-(dimethylamido)-phosphate		Triamfos, vepsin

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, "C	Solubility Water, mg/liter	LD_{50} in Rats (Orally) mg/kg / LD_{50} in Rabbits Subcutaneously), mg/kg	Use. Forms of Application and Consumption Norms
115—118 $(1 \cdot 10^{-4})$	37—45	Poor	$\frac{8,9}{17}$	Insecticide with broad spectrum of action controlling cotton pests. E.c., granules; 0.5-1 kg/ha.
—	120	Poor	12	Insecticide with broad spectrum of action controlling cotton pests. 25% e.c., 10% granules.
—	92	Poor	900	Antihelminthic
—	93,5—94,5	—	790—1590	Insecticide and acaricide. Working concentrations 0.025-0.2%.
—	98—99	210	—	Herbicide controlling weeds in sugar beets.
—	166—170	250	$\frac{23—27}{1500}$	Fungicide against powdery mildews. 25% w.p., 10% e.c.

The reaction proceeds at low temperature in the presence of tertiary amines, and the obtained product is placed into reaction with alcohols without separation.

Vinylphosphates can also be obtained starting with dialkylphosphites and halocarbonyl compounds in the presence of bases (50). In this case the reaction proceeds in two stages: In the first stage dialkylphosphite is joined to the halocarbonyl compound to form phosphonate, and in the second, hydrogen halide is split off to form dialkylvinylphosphate:

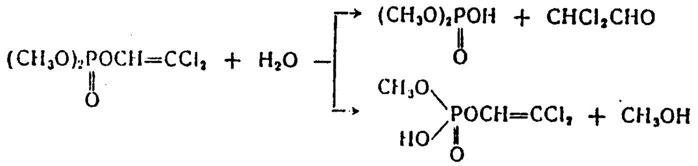


$$RCO\underset{X}{\underset{|}{C}}HR' + (RO)_2PHO \longrightarrow (RO)_2\underset{O}{\underset{\|}{P}}O\underset{OH}{\underset{|}{C}}H\overset{R}{\overset{|}{C}}XR' \xrightarrow[-HX]{} (RO)_2\underset{O}{\underset{\|}{P}}O\underset{R}{\underset{|}{C}}=CHR'$$

Among the pesticides shown in Table 44, dichlorophos, phosphamidon, bidrin, gardona and ruelene have enjoyed the widest use. Their properties will be described in greater detail below.

O,O-Dimethyl-O-(2,2-dichlorovinyl)-phosphate (dichlorophos) is a colorless liquid with a boiling point of 35°C at 0.05 mm Hg, 53°C at 0.2 mm Hg and 74°C at 1 mm Hg. Vapor pressure at 20°C is $1.2 \cdot 10^{-2}$, at 30°C it is $3.0 \cdot 10^{-2}$ and at 40°C it is $7.0 \cdot 10^{-2}$ mm Hg; volatility is 145 mg/m^3 at 20°C, 350 mg/m^3 at 30°C and 800 mg/m^3 at 40°C; d_4^{20} 1.420, n_D^{20} 1.4541 (see also Table 44). It is readily soluble in most organic solvents. At 20°C, 50 percent of dichlorophos hydrolyzes in 61.5 days, while at 70°C 50 percent hydrolyzes in 25 minutes. Hydrolysis proceeds faster in acid or alkaline media.

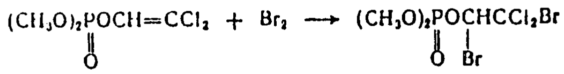
Hydrolysis proceeds as follows:



$$(CH_3O)_2\underset{O}{\underset{\|}{P}}OCH=CCl_2 + H_2O \longrightarrow \begin{cases} (CH_3O)_2\underset{O}{\underset{\|}{P}}OH + CHCl_2CHO \\ \begin{matrix} CH_3O \\ HO \end{matrix}\!\!>\!\underset{O}{\underset{\|}{P}}OCH=CCl_2 + CH_3OH \end{cases}$$

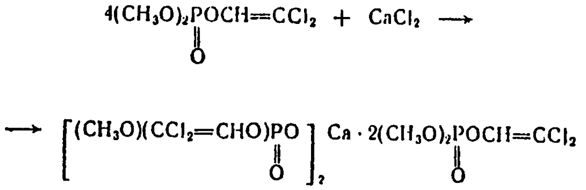
Next the acid ester is hydrolyzed to phosphoric acid. A similar reaction also proceeds in various plant and animal organisms (55).

Dichlorophos easily binds with bromine at its double bond to form another insecticide--dibrom:



$$(CH_3O)_2\underset{O}{\underset{\|}{P}}OCH=CCl_2 + Br_2 \longrightarrow (CH_3O)_2\underset{O}{\underset{\|}{P}}O\underset{Br}{\underset{|}{C}}HCCl_2Br$$

When heated with calcium and dialkylphosphoric acid salts, dichlorophos forms binary compounds (56) having insecticidal properties (57,59). Insecticidal compounds are also obtained by heating dichlorophos together with calcium chloride:

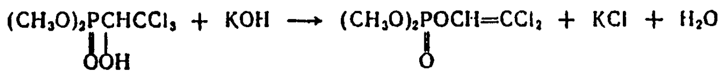


$$4(\mathrm{CH_3O})_2\underset{\overset{\|}{\mathrm{O}}}{\mathrm{P}}\mathrm{OCH{=}CCl_2} + \mathrm{CaCl_2} \longrightarrow$$

$$\longrightarrow \left[(\mathrm{CH_3O})(\mathrm{CCl_2{=}CHO})\underset{\overset{\|}{\mathrm{O}}}{\mathrm{P}}\mathrm{O}\right]_2 \mathrm{Ca}\cdot 2(\mathrm{CH_3O})_2\underset{\overset{\|}{\mathrm{O}}}{\mathrm{P}}\mathrm{OCH{=}CCl_2}$$

Two methods of obtaining dichlorophos are described in the literature.

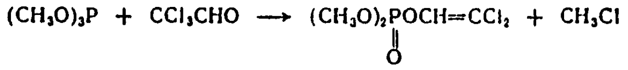
1. Splitting off hydrogen chloride from chlorofos in aqueous solution by the action of alkali (51,53):



$$(\mathrm{CH_3O})_2\underset{\overset{\|}{\mathrm{O}}}{\mathrm{P}}\underset{\overset{|}{\mathrm{OH}}}{\mathrm{CH}}\mathrm{CCl_3} + \mathrm{KOH} \longrightarrow (\mathrm{CH_3O})_2\underset{\overset{\|}{\mathrm{O}}}{\mathrm{P}}\mathrm{OCH{=}CCl_2} + \mathrm{KCl} + \mathrm{H_2O}$$

It is best to perform the reaction in a biphasal system (water and an immiscible organic solvent) in such a way that dichlorophos would be continually removed as it is formed; in this case the dichlorophos yield may reach 80-85 percent of theoretical. Following distillation in a vacuum, the concentration of the target substance reaches 93-97 percent, depending on the purity of the initial chlorofos.

2. The second method is based on reacting chloral with trimethylphosphite (52):



$$(\mathrm{CH_3O})_3\mathrm{P} + \mathrm{CCl_3CHO} \longrightarrow (\mathrm{CH_3O})_2\underset{\overset{\|}{\mathrm{O}}}{\mathrm{P}}\mathrm{OCH{=}CCl_2} + \mathrm{CH_3Cl}$$

When the reaction is performed in a low vacuum and a temperature of about 40°C, the dichlorophos yield exceeds 99 percent.

The maximum permissible concentration of dichlorophos in air has been set at 0.2 mg/m^3 (54).

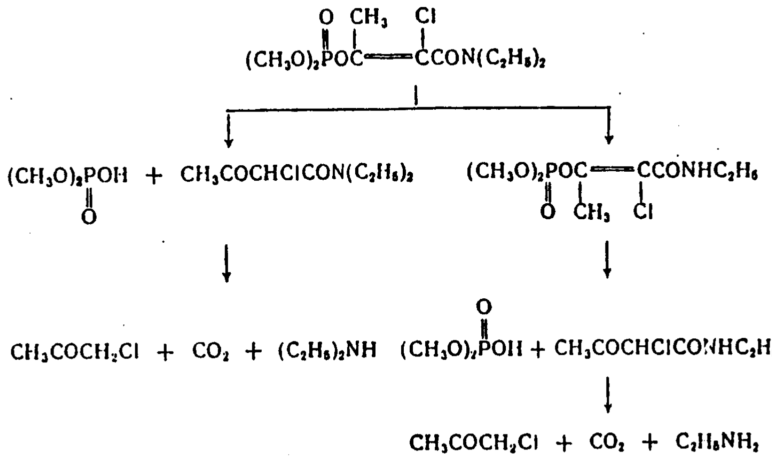
When traces of moisture are present in stored dichlorophos, the latter decomposes to release acid products that catalyze the further decomposition of the preparation. In order to stabilize the technical-grade product, small quantities of epichlorohydrin (2-4 percent) are added to it to bind the acid substances and improve the storage conditions. It would be best to store the preparation in glass or metallic enameled containers.

Symmetrical homologues of dichlorophos are significantly less toxic to insects. The following have recently been proposed as insecticides: O,O-dimethyl-O-(2-chloro-2--fluorovinyl)-phosphate (60), O-methyl-O-butyl-O-(2,2-dichlorovinyl)-phosphate (61), O-(2'-bromoethyl)-O-alkyl-O-2,2-dichlorovinyl)-phosphate (62) and some others (63).

O,O-Dimethyl-O-[1-methyl-2-chloro-2-(N,N-diethylcarbamoyl)-vinyl]-phosphate (phosphamidon) is a colorless liquid freely soluble in water, alcohol and acetone, and poorly soluble in saturated hydrocarbons; its boiling point is 70°C at 0.01 mm Hg, its vapor pressure at 20°C is $2.5 \cdot 10^{-5}$ mm Hg, and its volatility is 0.41 mg/m^3 (see also Table 44).

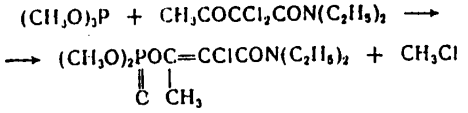
Phosphamidon is resistant to neutral and weakly acid aqueous solutions, while it undergoes hydrolysis quickly in an alkaline medium.

In plants, phosphamidon breaks down as follows (64):



Despite the relatively high toxicity of phosphamidon to animals, it is used as a systemic insecticide to control sucking pests of cotton and other crops. It is also effective against some gnawing pests (for example the Colorado beetle).

The best way to obtain phosphamidon is to react trimethylphosphite with dichloroacetoacetic acid diethylamide:



$$(CH_3O)_3P + CH_3COCCl_2CON(C_2H_5)_2 \longrightarrow$$
$$\longrightarrow (CH_3O)_2\underset{\substack{\| \\ C}}{P}O\underset{\substack{| \\ CH_3}}{C}=CClCON(C_2H_5)_2 + CH_3Cl$$

The reaction proceeds readily when an equimolar quantity of trimethylphosphite is added to boiling dichloroacetoacetic acid diethylamide solution in chlorobenzene. With this method the phosphamidon yield attains 83 percent.

Dichloroacetoacetic acid diethylamide required for synthesis of phosphamidon is obtained with a yield of more than 90 percent of theoretical by chlorination of diethylacetoacetamide by sulfuryl chloride (65):

$$CH_3COCH_2CON(C_2H_5)_2 + 2SO_2Cl_2 \longrightarrow$$
$$\longrightarrow CH_3COCCl_2CON(C_2H_5)_2 + 2HCl + 2SO_2$$

Chlorination may also be performed by chlorine in the presence of urea in a water or water-alcohol medium (66).

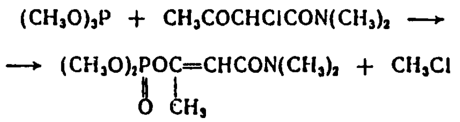
O,O-Dimethyl-O-[1-methyl-2-(N,N-dimethylcarbamoyl)-vinyl]-phosphate (bidrin) is an active systemic insecticide. It is a liquid that mixes with water at all dilution ratios; d_{15}^{15} 1.22 (see also Table 44).

At pH 9 and at 37°C, 50 percent of the preparation hydrolyzes in 50 days, while at pH 1 the same amount hydrolyzes in 100 days.

Bidrin is recommended against various plant pests at consumption norms from 0.25 to 1 kg/ha, and against some gnawing plant pests.

The metabolism of this compound in plant and animal organisms proceeds similarly as with metabolism of phosphamidon (67,68).

Bidrin is synthesized by Perkov's reaction out of monochloroacetoacetic acid dimethylamide and trimethylphosphite:



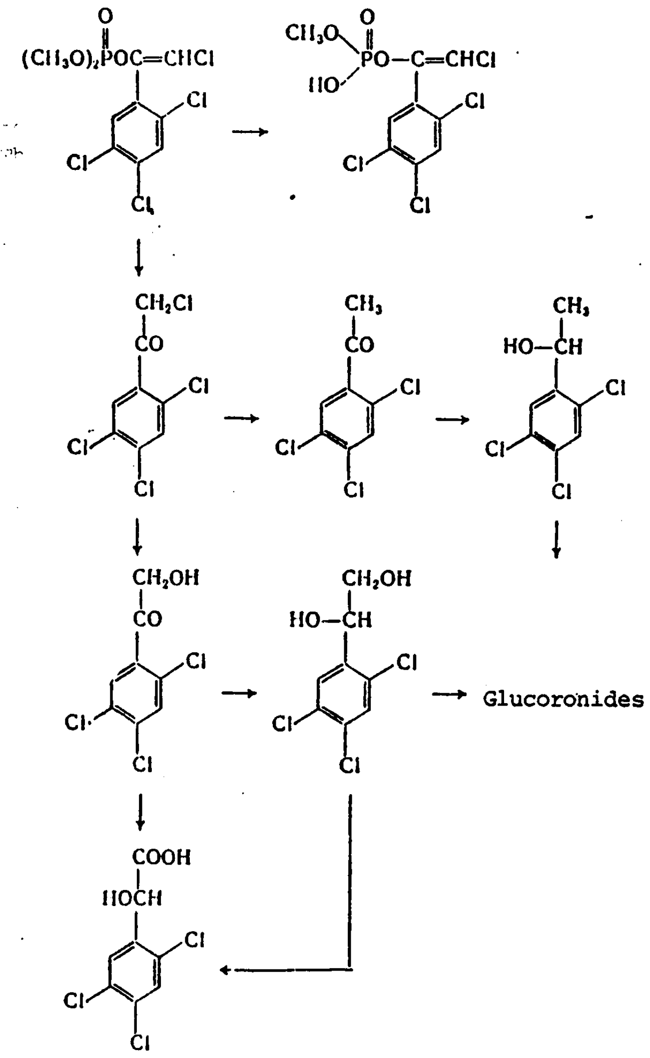
$$(CH_3O)_3P + CH_3COCHClCON(CH_3)_2 \longrightarrow$$
$$\longrightarrow (CH_3O)_2\underset{\underset{O}{\|}}{P}O\underset{\underset{CH_3}{|}}{C}{=}CHCON(CH_3)_2 + CH_3Cl$$

The closest analogue, azodrin, is obtained in similar fashion (69). Its chemical properties are similar to those of bidrin.

A large number of analogues and homologues of bidrin and azodrin have been synthesized (70-75), containing, in the vinyl group, not only a carbamoyl (70,73) but also carboalkoxy and carboaryloxy groups (71,72,74,75).

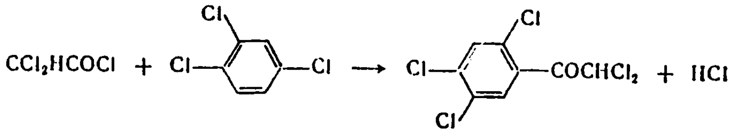
O,O-Dimethyl-O-[2-chloro-1-(2',4',5'-trichlorophenyl)-vinyl]-phosphate (gardona) is a promising insecticide against many insects. It is active against a large number of gnawing plant pests, and its toxicity to homeothermic animals is low (76-78).

The *trans*-isomer (in which the positions of the chlorine atom and the trichlorophenyl group are switched), which is a crystalline substance with a melting point of 97-98°C (see also Table 44), is used against plant pests and animal ectoparasites. The compound is freely soluble in organic solvents; its vapor pressure at 20°C is $4.2 \cdot 10^{-5}$ mm Hg. In acid and neutral media gardona hydrolyzes slowly--at 50°C and pH 7 its half-life is 1,300 hours, and at pH 10.5 it is 80 hours. It is used in various forms. The metabolism of gardona in different species of organisms may be diagrammed as follows (76,77,79):

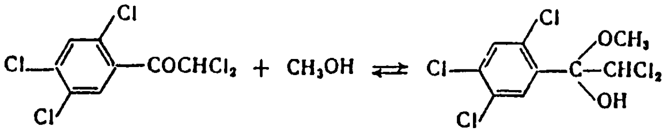


Gardona may be obtained by any of the methods described above for obtaining enol phosphates, to include the reaction between pentachloroacetophenone and trimethylphosphite (47,76,80-83,86), between pentachloroacetophenone and dimethylphosphite in the presence of bases (84), and between tetrachloroacetophenone and dimethylchlorophosphate in the presence of bases (48,85).

The pentachloroacetophenone required for synthesis of gardona is synthesized by the Friedel-Crafts reaction out of 1,2,4-trichlorobenzene and dichloroacetyl chloride in the presence of anhydrous aluminum chloride (80,81,83,87):

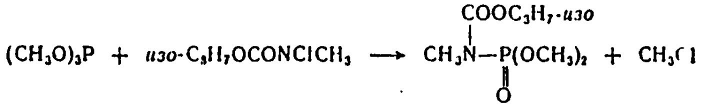


This reaction produces a mixture of isomers containing about 80 percent 2,4,5-isomer, 10 percent 2,3,6-isomer and 10 percent other isomers. The mixture is separated by isolating the needed isomer in the form of a methylketal (80,87), which at low temperature crystallizes readily out of pentane (melting point 110-111°C). Ketone is regenerated from monoketal by simple heating in a vacuum (87):



A large number of other enol phosphates containing aromatic radicals in the vinyl group have been synthesized and proposed for use as insecticides, but they have not as yet achieved practical application (88,89).

Dimufos is an interesting new low-toxicity insecticide that can be obtained with a good yield from trimethylphosphite and N-methyl-N-chloroisopropylcarbamate (90):

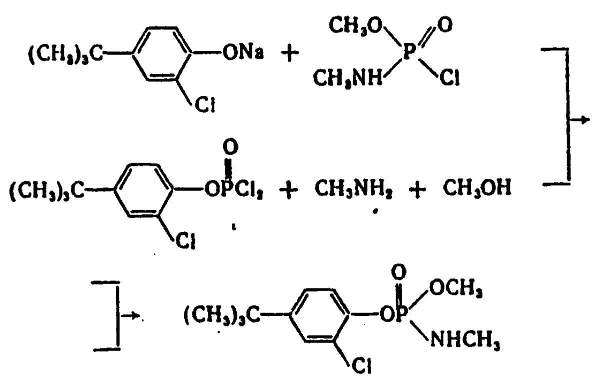


$$(CH_3O)_3P + изо\text{-}C_3H_7OCONClCH_3 \longrightarrow CH_3\overset{COOC_3H_7\text{-}изо}{\overset{|}{N}}-\underset{\overset{\|}{O}}{P}(OCH_3)_2 + CH_3Cl$$

This preparation is proving to be successful in tests against beet pests and other plant pests (91).

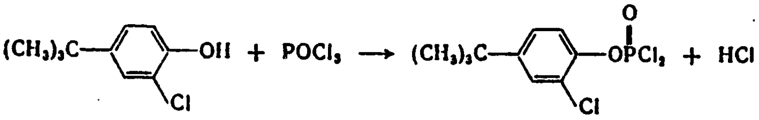
O-Methyl-O-(2-chloro-4-*tert*-butylphenyl)-N-methylamidophosphate (ruelene) (see also Table 44) is used against tapeworms in domesticated animals and gadflies as a feed additive. The consumption norms for different animals vary within 37-150 mg of the preparation per kg live weight. Good results can also be achieved against gadflies by spraying animals with 0.25-0.37 percent solutions. The preparation does not accumulate in the animal's organs, and it decomposes quickly.

Ruelene may be obtained by reacting 2-chloro-4-*tert*-butylphenol with O-methyl-N-methylamidochlorophosphate in the presence of bases, or by reacting 2-chloro-4-*tert*-butylphenyldichlorophosphate with methanol and methylamine:



The second reaction is usually performed in hydrophobic organic solvent, using anhydrous methylamine.

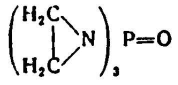
The 2-chloro-4-*tert*-butylphenyldichlorophosphate needed for the reaction is formed with a yield of up to 80 percent by reacting 2-chloro-4-*tert*-butylphenol with excess phosphorus chloroxide in the presence of calcium chloride or anhydrous magnesium chloride:



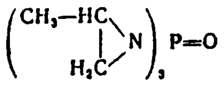
This reaction proceeds with prolonged boiling.

2-Chloro-4-*tert*-butylphenol may be obtained at a satisfactory yield by chlorinating *tert*-butylphenol or condensing isobutylene with *o*-chlorophenol in the presence of various catalysts. The product usually marketed is 92 percent pure.

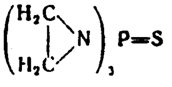
In addition to the use of phosphoric acid derivatives as insecticides and acaricides, use of some amides of phosphoric acid has been proposed for sexual sterilization of insects. The deepest research has been conducted on derivatives of ethylenimine, such as tris-(ethylenimido)-phosphate (TEPA, aphoxide), its methyl homologue (metepa, metafoksid), (tris-ethylenimido)-thiophosphate (thio-TEPA), its methyl homologue (metiotefa), hexa-(ethylenimido)-cyclotriphosphazine (apholate) and hexamethyltriamidophosphate (HMPA):



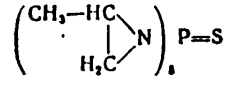
TEPA



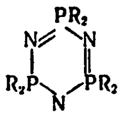
metepa



thio-TEPA



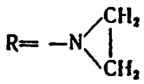
metiotepa



apholate

$[(CH_3)_2N]_3P{=}O$

HMPA



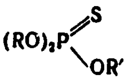
When these compounds are fed to insects, they do not produce normal progeny. These compounds should be used to control only those species of insects which produce large populations within a single season.

These compounds are toxic and dangerous to vertebrate animals and man, for which reason their use is very limited for the moment, and they have essentially not gone beyond the stage of production experiments.

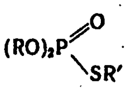
Thiophosphoric Acid Derivatives

Substitution of one of the oxygen atoms by sulfur in phosphoric acid derivatives causes a significant decrease in the compound's toxicity to mammals without significantly changing its insecticidal and acaricidal activity, though there are exceptions to this general rule. In this connection derivatives of thiophosphoric acid are broadly employed in agriculture to control plant pests.

As we know, thiophosphoric acid derivatives may have a thion (I) or thiol structure (II):



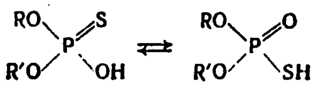
I



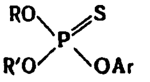
II

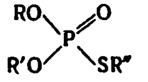
Thiol derivatives of thiophosphoric acid are more toxic to mammals.

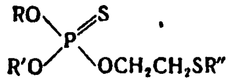
Thion derivatives regroup into thiol isomers when heated or when brought in contact with certain reagents. This reaction is known in the literature as Pishchemuka regrouping. Depending on the conditions and the reagents employed, the simplest derivatives of thiophosphoric acid (salts for example) are capable of forming either thiol or thion isomers, due to the dual reaction capacity of thiophosphoric acid derivatives stemming from tautomeric transformations:

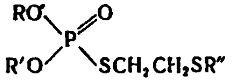


It is mainly the mixed esters of thiophosphoric acid with the general formulas III-VII that are used as pesticides. Here, R and R'--lower aliphatic radical, Ar--aromatic or heterocyclic radicals containing different substituents in the aromatic or heterocyclic ring, and R"--aliphatic, aromatic or heterocyclic radical:


III


IV


V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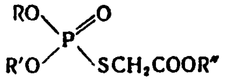
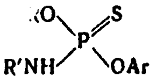
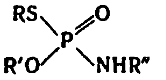
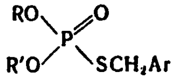

VII


VIII


IX


X

Mixed esteramides of thiophosphoric acid (VIII and IX) are also used as pesticides, but these groups contain fewer representatives. Mixed esters of thiophosphoric acid with general formula X have recently come into use against plant diseases.

A large number of compounds containing the most varied substituents in the aromatic radical, to include one halogen atom in the *ortho*, *metha* and *para* positions, two halogen atoms in different positions and three halogen atoms, have been described among mixed esters of thiophosphoric acid with general formula III. Among the trihaloaryl-O,O-dialkylthiophosphates, those offering the greatest interest include 2,5-dichloro-4-bromophenyl- (94), 2,4-dibromo-5-chlorophenyl- (92,93), 2,5-dichloro-4-iodophenyl- (95-97) and haloalkylphenyl-O,O-dialkylthiophosphates (98). Esters have also been described containing, in the aromatic radical, nitro (99-105), cyan (106), acyl (107-111), dialkylaminomethyl (112), carbalkoxyl (113), thiocarbamido (114), carbamoylamido (115), trifluoromethyl (116), alkylsulfide (117-123), sulfamide (124-127) and sulfon groups (128-130). In addition mixed esters of thiophosphoric acid made from bis-phenols containing a sulfide and a disulfide group have been described (131-135). The following generalizations may be made about this series.

1. The strongest insecticides and acaricides are mixed esters of thiophosphoric acid in which R and R' are lower aliphatic radicals with the number of carbon atoms totaling not more than four; in this case compounds containing two ethyl radicals or one methyl and one ethyl radical exhibit maximum activity. O,O-dimethyl-O-aryl esters of thiophosphoric acid are minimally toxic to mammals.

2. Mixed aliphatic-aromatic esters of thiophosphoric acid not containing functional groups in the aromatic radical exhibit low insecticidal activity.

3. Among substituted O,O-dialkyl-O-aryl esters of thiophosphoric acid, esters containing a nitro group at position 4 in the aromatic ring have maximum insecticidal activity. Esters containing a cyan, sulfide, sulfoxide or a sulfon group at position 4 exhibit rather high activity. However, most insecticidal compounds of this series are also relatively highly toxic to mammals. Compounds with other substituents are less effective. The corresponding 2- and 3-substituted compounds have weaker insecticidal action.

4. Introduction of a second substituent in the aromatic radical somewhat reduces the compound's toxicity to mammals without significantly reducing its insecticidal activity. In this case the position of the substituents has a great influence. Thus introduction of an alkyl group or a halogen atom at position 3 of an initial 4-nitro- or 4-methylthiophenol decreases toxicity to vertebrates and does not reduce the insecticidal activity of the compound, while introduction of these substituents at position 2 reduces the biological activity of the preparations in all respects.

Compounds also exhibit satisfactory insecticidal activity when they contain substituents in positions 2, 4, 5: for example O,O-dimethyl-O-(2,4,5-trichlorophenyl)--thiophosphate and O,O-dimethyl-O-(2,5-dichloro-4-bromophenyl)-thiophosphate, the toxicity of these compounds to mammals being negligible.

5. Presence of more than three substituents in the aromatic radical reduces the compound's insecticidal activity; sometimes the preparation's nature of action changes as well. Thus O,O-dialkyl-O-2,3,4,5,6-pentachlorophenyl)-thiophosphates exhibit fungicidal activity, though not strongly enough for practical use.

7. As we proceed from compounds with the general formula III to compounds with formula VIII, in many cases the insecticidal activity persists (136-139), but this group's fungicidal activity is significantly higher, and some alkylamido-O-alkyl-O--(2-nitroaryl)-thiophosphates have been proposed for practical use as herbicides (140,141). Haloarylamidothiophosphates, the preparation tsitron being an example, have herbicidal properties.

8. O,O-dialkyl-S-arylthiophosphates in many cases have not only insecticidal but also fungicidal action (142-144). However, their toxicity to homeothermic animals is higher than that of the corresponding thionphosphates.

9. O,O-dialkyl-O-arylcyanoxime thiophosphates (145-148) have high insecticidal activity. The new insecticide foksim (145) is an example of such compounds. Some compounds of this type also have fungicidal action (148).

Some phosphorylated (at the N) N-methyl-O-arylcarbamates also have selective toxicity (149).

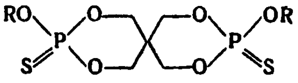
10. O,O-dialkyl-S-benzylthiophosphates, both simple and containing various substituents in the aromatic radical, have high fungicidal activity (150-162). Similar properties are also possessed by O-alkylalkylamido-S-benzothiophosphates and their homologues (152,155,156) and O,O-dialkyl-S-arylthioalkylthiophosphates (160).

11. O-Alkyl-O-aryl-N-alkylamidothiophosphates (163) have noticeable fungicidal activity.

12. The pesticidal activity of diaryl-O-alkylthiophosphates and triarylthiophosphates is significantly lower than that of O-O-dialkyl-O-aryl-thiophosphate, though there are indications in the literature that triarylthiophosphates do have pesticidal activity (164). Some alkyldiarylthiophosphates have been proposed as zoocides (165).

13. Cyclic thiophosphates obtained from salicyl alcohol (166-170) and pyrocatechol derivatives (171) are also active insecticides.

14. There are indications that compounds with general formula XI have nematocidal action (172):



XI

15. It would be interesting to note that O-alkyl-S-alkyl-O-arylthiophosphates exhibit high insecticidal activity but are rather toxic to homeothermic animals (173-175).

16. In most cases substitution of an aromatic radical by a heterocyclic radical also produces active insecticides, examples of which would be diazinon, dursban, tsinofox, azuntol, sayfos and others. Mixed esters and esteramides containing the most diverse heterocyclic radicals have been studied, to include mixed esters of thiophosphoric acid and derivatives of thiophene (176), pyridine (177-183), quinoline (184), imidazole (185), benzimidazole (186,187), thiazole (188), pyridazinone (189-191), oxycoumarin (192-193), triazole (194-196), pyrimidine (197-207), benzoxazine (208,213), benzotriazine (214-216), benzofurazan (217,218), 1,3,4-thiadiazole (219), benzothiadiazole (220), dithiane (221,222), quinoxaline (223-228) and others (229,230). Most nitrogenous heterocyclic compounds have not only insecticidal but also fungicidal action, though just a few substances in this class have achieved practical use as fungicides thus far.

17. Among the homologues of the O,O-dialkyl-O-arylthiophosphates, methyl esters have the least toxicity in relation to homeothermic animals, owing to their high alkylating capacity, as a consequence of which they break down faster in the bodies of homeothermic animals. This is true for practically all series of mixed esters of the acids of phosphorus; in this case mixed esters of dithiophosphoric acid have a higher alkylating capacity, and owing to this they are even less toxic to homeothermic animals. Thiol isomers have a lower alkylating capacity, and are more toxic.

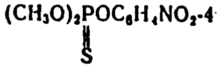
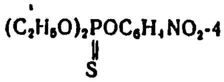
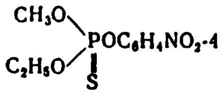
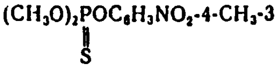
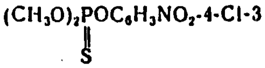
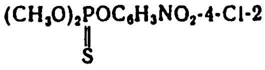
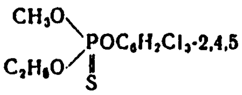
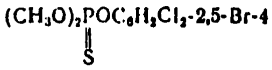
Some preparations in this class which have achieved practical use are given in Table 45.

The following general dependencies between activity and structure are observed for compounds with general formulas V and VI:

1. When the total number of carbon atoms in R and R' is more than four, the compound's insecticidal activity decreases.

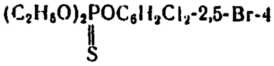
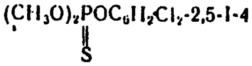
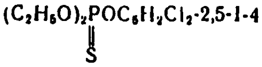
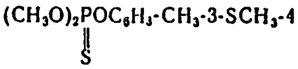
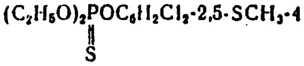
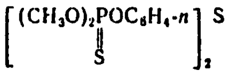
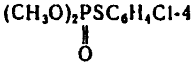
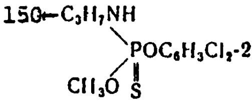
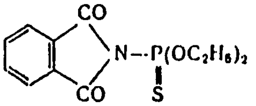
2. When the number of methylene groups between phosphorus and sulfur atoms is more than four, the compound's activity declines sharply. Maximum activity is seen in compounds containing one or two methylene groups.

Table 45. Aryl and Heterocyclic Derivatives

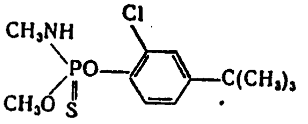
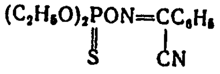
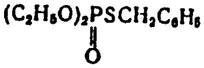
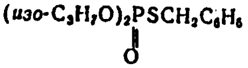
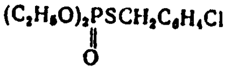
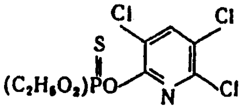
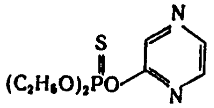
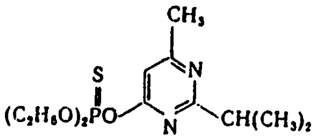
Chemical Name	Formula	Synonyms
O,O-Dimethyl-O-(4-nitrophenyl)-thiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}OC_6H_4NO_2\text{-}4$	Metaphos, methylparathion, metacide, folidol, vofatoks
O-O-Diethyl-O-(4-nitrophenyl)-thiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\|}}{P}OC_6H_4NO_2\text{-}4$	Thiophos, parathion, E-605
O-Methyl-O-ethyl-O-(4-nitrophenyl)-thiophosphate	 $\begin{matrix}CH_3O\diagdown\\ C_2H_5O\diagup\end{matrix}\underset{\underset{S}{\|}}{P}OC_6H_4NO_2\text{-}4$	Thiophos ME, methylethylthiophos, methylethylparathion
O,O-dimethyl-O-(4-nitro-3-methylphenyl)-thiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}OC_6H_3NO_2\text{-}4\text{-}CH_3\text{-}3$	Metilintrofos, sumition, metation, fenitrotion
O,O-Dimethyl-O-(4-nitro-3-chlorophenyl)-thiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}OC_6H_3NO_2\text{-}4\text{-}Cl\text{-}3$	Chlorthion
O,O-Dimethyl-O-(4-nitro-2-chlorophenyl)-thiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}OC_6H_3NO_2\text{-}4\text{-}Cl\text{-}2$	Dicapthion, isochlorthion
O,O-Diethyl-O-(2,4-dichlorophenyl)-thiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\|}}{P}OC_6H_3Cl_2\text{-}2,4$	VTs-13, dikhlorfention
O,O-Dimethyl-O-(2,4,5-trichlorophenyl)-thiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}OC_6H_2Cl_3\text{-}2,4,5$	Ronnel, trolene, korlan, nankor, trikhlormetafos, etrolene, Dow ET-14, Dow ET-57
O-Methyl-O-ethyl-O-2,4,5-trichlorophenyl)-thiophosphate	 $\begin{matrix}CH_3O\diagdown\\ C_2H_5O\diagup\end{matrix}\underset{\underset{S}{\|}}{P}OC_6H_2Cl_3\text{-}2,4,5$	Trikhlormetafos-3
O,O-Dimethyl-O-(2,5-dichloro-4-bromophenyl)-thiosphosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}OC_6H_2Cl_2\text{-}2,5\text{-}Br\text{-}4$	Bromofos, neksion

of Thiophosphoric Acid Used as Pesticides

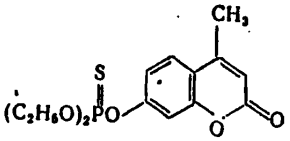
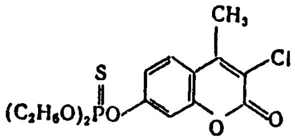
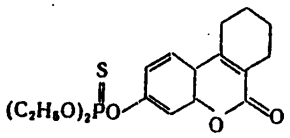
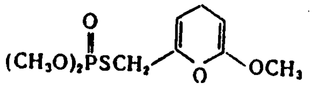
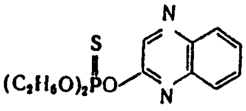
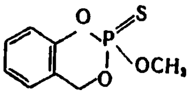
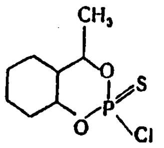
Boiling Point, °C (At Indicated Pressure), mm/Hg	Melting Point, °C	Solubility Water, mg/liter	LD_{50} in Rats (Orally) mg/kg / LD_{50} in Rabbits (Cutaneously), mg/kg	Use. Forms of Application and Consumption Norms
109 (0,05)	35—36	55	25—50 / 200—300	Contact insecticide with broad spectrum of action. E.c., w.p., dusts; 0.2-1 kg/ha.
113 (0,05)	6,1	24	6—12 / 40—50	Contact insecticide with broad spectrum of action. E.c., w.p., dusts, granules; 0.2-1 kg/ha.
116 (0,12)	—	40	6—8 / 40—100	Contact insecticide with broad spectrum of action. E.c.; 0.2-1 kg/ha.
95 (0,01)	—	30	242—433 / 3000	Contact insecticide with broad spectrum of action. E.c. Intended for ultralow volume spraying; 0.2-1 kg/ha.
136 (0,2)	21	40	880—980 / 1500	Contact insecticide. E.c., dusts, w.p.
—	52—53	35	330—400 / 900	Insecticide.
108 (0,01)	—	245	270 / 6 000	Nematocide. 75% E.c.
97 (0,01)	41	44	400—3000 / 1600—2000	Insecticide controlling animal ectoparasites.
127 (0,15)	—	40	320—800	Contact insecticide controlling plant pests and animal ectoparasites. E.c.
140—142 (0,01)	54	40	2000—4000 / 3200	Contact insecticide with broad spectrum of action. E.c., w.p., granules.

Chemical Name	Formula	Synonyms
O,O-Diethyl-O-(2,5-dichloro-4-bromophenyl)-thiophosphate	 $(C_2H_5O)_2\underset{\substack{\|\\S}}{P}OC_6H_2Cl_2\text{-}2,5\text{-}Br\text{-}4$	Bromofos-etil, neksagan
O,O-Dimethyl-O-(2,5-dichloro-4-iodophenyl)-thiophosphate	 $(CH_3O)_2\underset{\substack{\|\\S}}{P}OC_6H_2Cl_2\text{-}2,5\text{-}I\text{-}4$	Iodfenfos, iodofos, nuvanol-N
O,O-Diethyl-O-(2,5-dichloro-4-iodophenyl)-thiophosphate	 $(C_2H_5O)_2\underset{\substack{\|\\S}}{P}OC_6H_2Cl_2\text{-}2,5\text{-}I\text{-}4$	Ts-8874
O,O-Dimethyl-O-(4-cyanophenol)-thiophosphate	 $(CH_3O)_2\underset{\substack{\|\\S}}{P}OC_6H_4CN\text{-}4$	Cyanox
O,O-Dimethyl-O-(3-methyl-4-methylmercaptophenyl)-thiophosphate	 $(CH_3O)_2\underset{\substack{\|\\S}}{P}OC_6H_3\text{-}CH_3\text{-}3\text{-}SCH_3\text{-}4$	Lebaycid, baytex, fenthion, sul'fidofos
O,O-Diethyl-O-(2,5-dichloro-4-methylmercaptophenyl)-thiophosphate	 $(C_2H_5O)_2\underset{\substack{\|\\S}}{P}OC_6H_2Cl_2\text{-}2,5\text{-}SCH_3\text{-}4$	S-2957
O,O-Diethyl-O-(4-methylsulfinylphenyl)-thiophosphate	 $(C_2H_5O)_2\underset{\substack{\|\\S}}{P}OC_6H_4\underset{\substack{\|\\O}}{S}CH_3\text{-}4$	Fensulfothion
Bis-[O,O-dimethylthiophosphoryl-O-phenyl-4-)-sulfide	 $\left[(CH_3O)_2\underset{\substack{\|\\S}}{P}OC_6H_4\text{-}n\right]_2S$	Abat, difos
O,O-Dimethyl-S-(4-chlorophenyl)-thiosphosphate	 $(CH_3O)_2\underset{\substack{\|\\O}}{P}SC_6H_4Cl\text{-}4$	Funtion
O-Methyl-N-isopropylamido-O-(2,4-dichlorophenyl)-thiophosphate	 $iso\text{-}C_3H_7NH,\ CH_3O\ \underset{\substack{\|\\S}}{P}OC_6H_3Cl_2\text{-}2,4$	Tsitron
O,O-Diethyl-N-phthalimidothiophosphate		Dowco-199

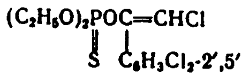
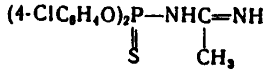
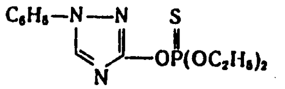
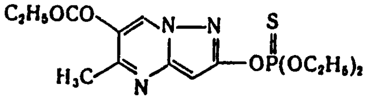
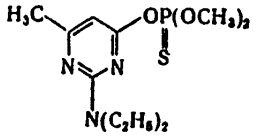
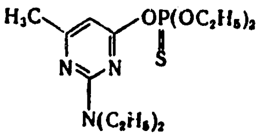
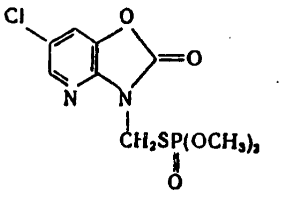
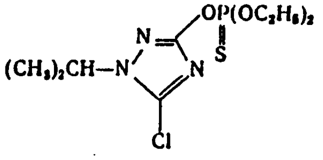
Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility Water, mg/liter	LD50 in Rats (Orally) mg/kg / LD50 in Rabbits Cutaneously), mg/kg	Use. Forms of Application and Consumption Norms
122—123 (0,003)	—	2	270 / 1366	Contact insecticide with broad spectrum of action.
—	74	2	2100	Insecticide with broad spectrum of action. W.p., e.c.
—	47—48	—	140	Contact insecticide. 30% e.c.; 2-4 kg/ha.
—	14—15	—	995	Contact insecticide. 50% e.c.; 0.5-1 kg/ha.
109 (0,01)	—	54	241—316 / 341	Contact insecticide controlling plant pests and animal parasites.
—	Liquid	—	13	Insecticide with broad spectrum of action. 50% e.c.
138—141 (0,01)	—	1540	2,2—10,5 / 3,5	Nematocide. 10% granules.
—	30—30,5	—	2000—2300 / 970—1900	Insecticide controlling mosquitoes.
101—106 (0,006)	—	Insoluble	125	Insecticide controlling soil pests. 50% e.c., 2% dust.
—	51,4	5	270	Herbicide. Used to control undesirable vegetation among ornamental plants; 10-20 kg/ha
—	83—84	—	500	Fungicide.

Chemical Name	Formula	Synonyms
O-Methyl-N-methylamido-O-(2-chloro-4-*tert*-butylphenyl)-thiophosphate		Dowco-109, narlen
O,O-Diethylphosphoryl-O-(α-cyanobenzaldoxime)	 $(C_2H_5O)_2\underset{\underset{S}{\parallel}}{P}ON{=}\underset{\underset{CN}{\vert}}{C}C_6H_5$	Foksim, valekson
O,O-Diethyl-S-benzylthiophosphate	 $(C_2H_5O)_2\underset{\underset{O}{\parallel}}{P}SCH_2C_6H_5$	Ketatsin
O,O-Diisopropyl-S-benzylthiophosphate	 $(\text{изо-}C_3H_7O)_2\underset{\underset{O}{\parallel}}{P}SCH_2C_6H_5$	Ketatsin-P
O,O-Diethyl-S-(4-chlorobenzyl)-thiophosphate	 $(C_2H_5O)_2\underset{\underset{O}{\parallel}}{P}SCH_2C_6H_4Cl$	Danifos
O,O-Diethyl-O-(3,5,6-trichloropyridyl)-thiophosphate		Dursban
O,O-Diethyl-O-pyridazinyl-2)-thiophosphate		Zinophos, thionazin
O,O-Diethyl-O-(2-isopropyl-4-methylpyrimidyl-6)-thiophosphate		Diazinon, basudin, ekzodin

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility Water, mg/liter	LD$_{50}$ in Rats (Orally) mg/kg LD$_{50}$ in Rabbits Cutaneously), mg/kg	Use. Forms of Application and Consumption Norms
103—115 (0,01)	—	7	700—800	Antihelminthic.
102 (0,01)	3—4	7	2000	Insecticide with broad spectrum of action, including against soil pests. 50% e.c., 40% w.p., 5% granules.
120 (0,05)	—	50 000	320	Fungicide controlling (pirikulyariya) in rice.
126 (0,04)	—	50 000	620	Fungicide controlling (pirikulyariya) in rice. 17% granules, 68% e.c., 2% dust.
—	—	40	17	Insecticide and fungicide. 50% e.c.
—	41,5—43	2	135—163 1000—2000	Insecticide with broad spectrum of action. Various forms; 0.5-1 kg/ha.
80 (0,001)	—1,7	1140	12	Nematocide. E.c., 10% granules.
125 (1)	—	40	120—220 450—900	Insecticide with broad spectrum of action. Various forms; 0.3-1 kg/ha.

Chemical Name	Formula	Synonyms
O,O-Diethyl-O-(4-methylcoumarinyl-7)-thiophosphate		Potasan, E-838
O,O-Diethyl-O-(3-chloro-4-methylcoumarinyl-7)-thiophosphate		Asuntol, resitox, muscatox, co-ral, coumafos
O,O-Diethyl-O-(3,4-cyclohexanocoumarinyl-7)-thiophosphate		Dithion
O,O-Dimethyl-S-(5-methoxypyranyl-2-methyl)-thiophosphate		Endotion, fosfopiran, eksotion
O,O-Diethyl-O-(quinoxalyl-2)-thiophosphate		Bayrusil (dietilkhinaldin)
4,5-Benzo-2-methoxy-1,3,2-dioxaphosphorinanthion-2		Salition
4,5-Cyclohexano-6-methyl-2-chloro-1,3,2-dioxaphosphorinanthion-2		UK-8305

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility Water, mg/liter	LD_{50} in Rats (Orally) mg/kg / LD_{50} in Rabbits Cutaneously), mg/kg	Use. Forms of Application and Consumption Norms
—	38	Poor	19—42 / 300	Selective insecticide controlling Colorado beetle.
—	95	1,5	100	Insecticide and antihelminthic. Use in animal husbandry.
—	88—89		150	Insecticide for animal husbandry.
—	90—91	20	30—50 / 400—1000	Systemic insecticide. 25% w.p.
—	35—36	20	66	Insecticide with broad spectrum of action. 25% e.c., 5% granules.
—	54—55	—	91	Insecticide. W.p., e.c.
78 (0,2)	—	—	120	Insecticide.

Chemical Name	Formula	Synonyms
O,O-Diethyl-O-[1-(2′,5′-dichlorophenyl)-2-chlorovinyl]-thiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\|}}{P}O\underset{\underset{C_6H_3Cl_2\text{-}2',5'}{\mid}}{C}{=}CHCl$	Acton
O,O-Bis-(4-chlorophenyl)-N-acetimidinylthiophosphate	 $(4\text{-}ClC_6H_4O)_2\underset{\underset{S}{\|}}{P}\text{—}NH\underset{\underset{CH_3}{\mid}}{C}{=}NH$	–
O,O-Diethyl-O-(1-phenyl-1,2,4-triazolyl-3)-thiophosphate		Khostation, fentriazofos
O,O-Diethyl-O-(5-methyl-4-carbethoxypyridopyrazolyl-9)-thiophosphate		Afugan, pirazofos, kuramil
O,O-Dimethyl-O-(2-diethylamino-6-methylpyrmidinyl-4)-thiophosphate		Pirimifos-metil, aktelli
O,O-Diethyl-O-(2-diethylamino-6-methylpyrimidyl-4) thiophosphate		Pirimifos-etil, primitsid
S-(6-Chloroxazolopyridinon-2-yl-3-methyl)-O,O-dimethylthiophosphate		SGA-18809
O-(5-Chloro-1-isopropyl-1,2,4-triazolyl-3)-O,O-diethylthiophosphate		SGA-12223

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point °C	Solubility Water, mg/liter	LD_{50} in Rats (Orally) mg/kg LD_{50} in Rabbits Cutaneously), mg/kg	Use. Forms of Application and Consumption Norms
145 (0,005)	26	—	146	Insecticide and acaricide. E.c.
—	104—106	—	3,7—7,5	Zoocide. Used in baits.
—	Decomposes when sublimated	—	82	Insecticide, acaricide, nematocide. E.c.
—	—	50—51	140—632	Fungicide. E.c.
—	Liquid	—	2050	Insecticide and acaricide. E.c.
—	Liquid	—	138—192	Insecticide and acaricide. E.c.
—	89	1100	1750	Insecticide with broad spectrum of action. Various forms.
—	Liquid	—	60	Insecticide with broad spectrum of action, including against soil pests.

3. Oxidation of sulfur in a carbon radical to a sulfoxide group or formation of a sulfonium compound increases the compound's toxicity, especially in the latter case.

4. Introduction of different substituents into R″ also sometimes produces active compounds (231,232).

5. Practically all preparations with structure V and VI have systemic action, with the contact action of thion isomers being somewhat weaker than that of thiol isomers.

6. Substitution of sulfur by nitrogen results in compounds toxic to both insects and ticks on one hand and mammals on the other.

7. Increasing the number of carbon atoms in R″ to more than three reduces the compound's insecticidal activity.

8. Compounds in which R″ is represented by aromatic radicals exhibit lower insecticidal activity than do compounds of the aliphatic series.

9. Introduction of hydrocarbon radicals into an ethylene radical also produces active compounds (233).

10. Substitution of sulfide sulfur by oxygen as a rule raises the compound's phytocidal activity, especially if an aromatic residue is bound to the oxygen (234-236).

11. O,S-dialkylamidothiophosphates (237-242) also have high insecticidal activity; however, these compounds are rather highly toxic to homeothermic animals. When the amide group is acylated by carboxylic acids the compound's toxicity to animals decreases significantly (242). Acylated dialkylhydrazidothiophosphates also have pesticidal activity (243).

12. Diamidoalkylthiophosphates, triamidothiophosphates and mixed alkyldiamidothiophosphates have a broad spectrum of pesticidal activity. Fungicides (163), nematocides (244), sexual sterilizers (245) and herbicides (246) have been found among these groups of compounds.

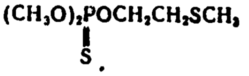
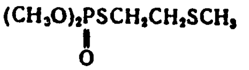
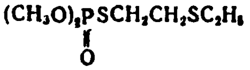
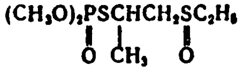
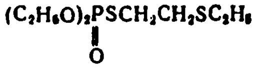
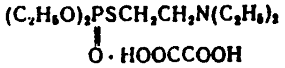
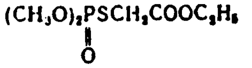
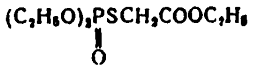
O,O-Dialkyl-S-thiocyanatomethylthiophosphates are also active pesticides (247).

13. O,O-Dialkyl-S-vinylthiophosphates and O,O-dialkyl-S-vinylthiophosphates with various substituents in the vinyl radical are also active insecticides (248-253).

14. Mixed esters of thiophosphoric acid containing a carbalkoxyl and a carbamoyl group in one of the hydrocarbon radicals have high insecticidal activity as well (254-255). It should be noted, however, that the toxicity of this type of compounds is higher in most cases than that of the corresponding dithiophosphates.

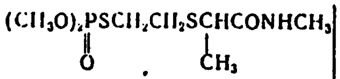
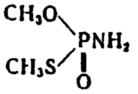
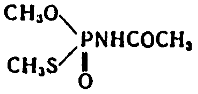
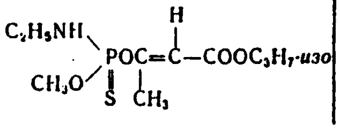
Compounds which have come into practical use are shown in Table 46.

Table 46. Aliphatic Derivatives of

Chemical Name	Formula	Synonyms
O,O-Dimethyl-O-(2-methylmercaptoethyl)-thiophosphate O,O-Dimethyl-S-(2-methylmercaptoethyl)-thiophosphate	 $(CH_3O)_2\underset{\overset{\|}{S}}{P}OCH_2CH_2SCH_3$  $(CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2CH_2SCH_3$	Tinoks (mixture of both compounds, 30-40:60-70 respectively)
O,O-Dimethyl-O-(2-ethylmercaptoethyl)-thiophosphate O,O-Dimethyl-S-(2-ethylmercaptoethyl)-thiophosphate	 $(CH_3O)_2\underset{\overset{\|}{S}}{P}OCH_2CH_2SC_2H_5$  $(CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2CH_2SC_2H_5$	Methyl-mercaptophos, methyl-demeton, methyl-systox (mixture of both compounds, 70:30 respectively)
O,O-Dimethyl-S-(2-ethylmercaptoethyl)-thiophosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2CH_2SC_2H_5$	Meta-systox I, demeton-S-methyl
O,O-Dimethyl-S-(2-ethylsulfinylethyl)-thiophosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2CH_2\underset{\overset{\|}{O}}{S}C_2H_5$	Meta-systox R, demeton-O-methylsulfoxide
O,O-Dimethyl-S-(2-ethylsulfonylethyl)-thiophosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2CH_2SO_2C_2H_5$	Demeton-S-methylsulfone
O,O-Dimethyl-S-(1-ethylsulfinylpropyl-2)-thiophosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}S\underset{\overset{\|}{CH_3}}{CH}CH_2\underset{\overset{\|}{O}}{S}C_2H_5$	Meta-systox S
O,O-Diethyl-O-(2-ethylmercaptoethyl)-thiophosphate O,O-Diethyl-S-(2-ethylmercaptoethyl)-thiophosphate	 $(C_2H_5O)_2\underset{\overset{\|}{S}}{P}OCH_2CH_2SC_2H_5$  $(C_2H_5O)_2\underset{\overset{\|}{O}}{P}SCH_2CH_2SC_2H_5$	Demeton, systox, mercaptophos (mixture of both compounds, 70:30 respectively)
O,O-Diethyl-S-(2-diethylaminoethyl)-thiophosphate•oxalate	 $(C_2H_5O)_2\underset{\overset{\|}{O}\cdot HOOCCOOH}{P}SCH_2CH_2N(C_2H_5)_2$	Amiton, tetram, inferno, metramac
O,O-Dimethyl-S-(carbethoxymethyl)-thiophosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2COOC_2H_5$	Metilatsetofos
O,O-Diethyl-S-(carbethoxymethyl)-thiophosphate	 $(C_2H_5O)_2\underset{\overset{\|}{O}}{P}SCH_2COOC_2H_5$	Atsetofos
O,O-Dimethyl-S-(N-methylcarbamoylmethyl)-thiophosphate	 $(CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2CONHCH_3$	Ometoat, folimat

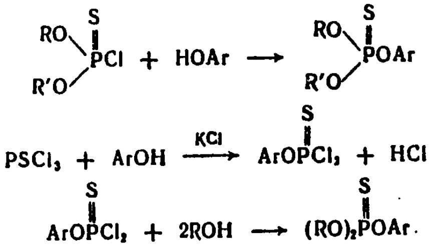
Thiophosphoric Acid Used as Pesticides

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility- Water, mg/liter	LD$_{50}$ in Rats (Orally) mg/kg LD$_{50}$ in Rabbits Subcutaneously), mg/kg	Use. Forms of Application and Consumption Norms
115 (2)	—	500	50	Systemic insecticide and acaricide. E.c.; 0.5-1 kg/ha.
109 (2)	—	2000	40	
93 (0.5)	—	330	140	Systemic insecticide and acaricide. 30-50% e.c.; 0.5-1 kg/ha.
102 (0,4)	—	3300	40—60 80—100 (для смеси)	
—	—	—	—	Systemic insecticide and acaricide. E.c.; 0.5-1 kg/ha.
106 (0,01)	—	Mixes	65—75	Systemic insecticide and acaricide. 25-50% e.c.; 0.5-1 kg/ha.
—	50	3300	40	Systemic insecticide and acaricide. Used in mixture with azinphos-methyl. E.c., w.p.
115 (0,02)	—	Good	105	Systemic insecticide and acaricide. 50% e.c.; 0.5-1 kg/ha.
106 (0,4)	—	60	7—10	Systemic insecticide and acaricide. 30-50% e.c.; 0.3-1 kg/ha.
100 (0,25)	—	2000		
—	100—101	Good	3—7	Systemic insecticide and acaricide.
116 (0,35)	—	Good	1000	Contact insecticide. E.c., dust.
120 (0,15)	—	Good	300—700	Contact insecticide. E.c., dust.
Decomposes when distilled	—	Good	$\frac{50}{700}$	Systemic acaricide and insecticide. 50% e.c.; up to 1 kg/ha.

Chemical Name	Formula	Synonyms
O,O-Dimethyl-S-[2-(N-methylcarbamoylethylmercapto)-ethyl]-thiophosphate	 $(CH_3O)_2\underset{\underset{O}{\Vert}}{P}SCH_2CH_2S\underset{\underset{CH_3}{\vert}}{C}HCONHCH_3$	Vamidotion, kil'val', trutsidor
O-Methyl-S-Methylamidothiophosphate		Tamaron, monitor
O,S-Dimethyl-N-acetylamidothiophosphate		Ortho-12420
N-Ethylamido-O-methyl-O-[1-methyl-2-(carbisopropoxy)-vinyl]-thiophosphate		San. 52-139

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility—Water, mg/liter	LD$_{50}$ in Rats (Orally) mg/kg / LD$_{50}$ in Rabbits (Subcutaneously), mg/kg	Use. Forms of Application and Consumption Norms
—	46—48	Good	$\frac{64-105}{1140}$	Systemic insecticide and acaricide. 40% e.c.; 0.3-1 kg/ha.
—	44,5	Good	$\frac{30}{118}$	Systemic acaricide and insecticide. E.c., granules.
—	80	Good	$\frac{866-945}{2000}$	Insecticide. 75% w.p.
87—89 (0,005)	—	0,5%	$\frac{110-120}{1250}$	Insecticide. 25% e.c., 10% granules.

The following reactions are the principal methods of obtaining thiophosphates III and V:



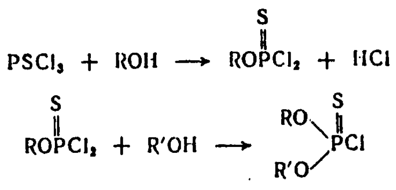
The first of these reactions proceeds readily when both organic and inorganic bases are used as hydrogen chloride acceptors. The best organic bases to use are tertiary amines, for example triethylamine or pyridine. The reaction proceeds with high yields in the presence of caustic alkali or alkali metal carbonates. The best results are obtained with potash, especially when the process is carried out in a solution of aliphatic ketones (acetone, methylethylketone). The reaction may also be carried out in the presence of catalytic quantities of tertiary amine, followed by saturation of the reaction medium with sodium or magnesium chloride (256).

Good yields of mixed esters of thiophosphoric acid may be obtained by performing the reaction in an aqueous medium in the presence of surfactants and in organic solvents. When the process is performed in organic solvents, the resulting preparations are purer as a rule, but the process is more complex because the solvent must be distilled away in a rather high vacuum, and film-type continuous-action evaporators must be used. The reason for this is that many mixed esters of thiophosphoric acid can decompose when heated at 80-140°C for a long period of time; moreover such decomposition may proceed spontaneously with an explosion occurring. Mixed esters of thiophosphoric acid containing a nitro group in the aromatic radical decompose especially readily. However, when sufficiently pure phenols and dialkylchlorothiophosphates are used in an aqueous medium, mixed thiophosphates can be obtained with good yields and with a target substance concentration greater than 90 percent. The process would best be carried out at 50-100°C, and with rather intensive mixing to maintain a constant pH in the medium. An aqueous solution of alkali metal phenolate is placed in a reactor containing an effective agitator, and after the solution is raised to the required optimum temperature, dialkylchlorothiophosphate is added gradually. Because dialkylchlorothiophosphate undergoes partial hydrolysis, the medium's pH changes rather quickly; alkali is added to the reaction mixture to keep the pH constant. The optimum pH varies for different phenols.

After the reaction ends, the oily layer is separated away and washed with an aqueous alkali solution (to remove phenol that had not entered into the reaction). After it is dried, it is used to make the required form of the preparation.

One of the most important conditions of storing mixed esters of thiophosphoric acid is absence of moisture, inasmuch as the compound may undergo hydrolysis, and when metallic containers are used colloids may form, resulting in gelatinization of the preparation which makes it difficult to use. Nor must the preparation contain significant quantities of trialkylthiophosphates, especially trimethylthiophosphates.

The dialkylchlorothiophosphates required for the synthetic processes described above are obtained at good yields as follows:

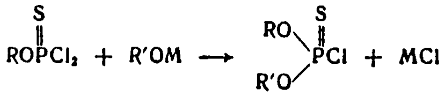


$$PSCl_3 + ROH \longrightarrow RO\overset{S}{\overset{\|}{P}}Cl_2 + HCl$$

$$RO\overset{S}{\overset{\|}{P}}Cl_2 + R'OH \longrightarrow \begin{matrix} RO \\ R'O \end{matrix}\!>\!\overset{S}{\overset{\|}{P}}Cl$$

The reaction between $PSCl_3$ and alcohols proceeds readily in response to slight heating, and the alkyldichlorothiophosphate yield is not less than 90 percent of theoretical. Alkyldichlorothiophosphates are allowed to react with alcohols at temperatures from -5 to 0°C while stirring vigorously. Both tertiary amines and caustic alkali can be used to bind hydrogen chloride, and when dimethylchlorothiophosphate is the target substance, 40 percent aqueous sodium hydroxide solution can be used. Mixed dialkylchlorothiophosphates in which a methyl group is one of the ester radicals form with a yield close to 90 percent.

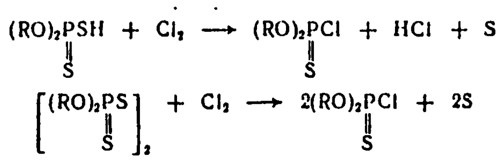
High yields of dialkylchlorothiophosphates are also obtained by reacting alkyldichlorothiophosphates with sodium or magnesium alcoholates:



$$RO\overset{S}{\overset{\|}{P}}Cl_2 + R'OM \longrightarrow \begin{matrix} RO \\ R'O \end{matrix}\!>\!\overset{S}{\overset{\|}{P}}Cl + MCl$$

The optimum temperature for a reaction with sodium alcoholate is from -10 to -15°C. At higher temperatures the yield decreases and a significant quantity of trialkylthiophosphates forms. Synthesis of dialkylchlorothiophosphates from magnesium alcoholates is relatively simple, and it proceeds at higher temperature.

A good method of obtaining dialkylchlorothiophosphates is chlorination of dialkyldithiophosphoric acids (257) or bis-(dialkylthiophosphone)-disulfides:



$$(RO)_2\underset{S}{\underset{\|}{P}}SH + Cl_2 \longrightarrow (RO)_2\underset{S}{\underset{\|}{P}}Cl + HCl + S$$

$$\left[(RO)_2\underset{S}{\underset{\|}{P}}S\right]_2 + Cl_2 \longrightarrow 2(RO)_2\underset{S}{\underset{\|}{P}}Cl + 2S$$

In the presence of excess chlorine, sulfur chloride is obtained as a byproduct.

Chlorination may be carried out not only with chlorine but also with various chlorinating agents, to include phosphorus pentachloride, sulfur chloride and dichloride, sulfuryl chloride and other similar compounds. The reaction is carried out at lower temperatures, both with and without various organic solvents. It would be convenient to perform the reaction with chlorine, and then remove sulfur chloride by treating the product with H_2S. In this case sulfur chloride transforms into elemental sulfur, which is easily separated from dialkylchlorothiophosphate by simple filtration. The yield of dialkylchlorothiophosphate in this method is about 90 percent; the concentration of the target product is more than 90 percent (269).

This is a convenient method for obtaining dialkylchlorothiophosphates with identical hydrocarbon radicals; if dialkylchlorothiophosphates with different radicals are required, it would be better to use the reaction with $PSCl_3$, described above. In turn, $PSCl_3$ can be obtained industrially at a quantitative yield by passing PCl_3 vapor through melted sulfur to which alkali metal polysulfides are added as catalysts (258).

A flowchart for production of $PSCl_3$ is shown in Figure 17 (258).

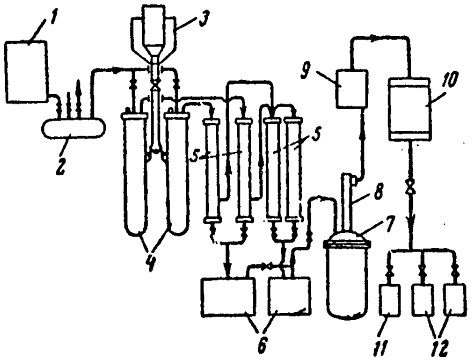
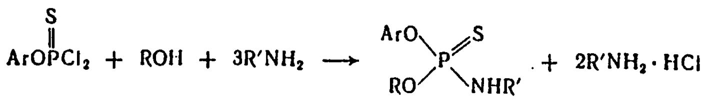


Figure 17. Flowchart for Production of Phosphorus Thiotrichloride: *1*--PCl_3 gaging tank; *2*--PCl_3 evaporator; *3*--sulfur gaging tank; *4*--reaction columns; *5*--air coolers; *6*--condensate collectors; *7*--distillation vat; *8*--rectification column; *9*--fractionating column; *10*--cooler; *11*--PCl_3-$PSCl_3$ mixture receiver; *12*--$PSCl_3$ receivers

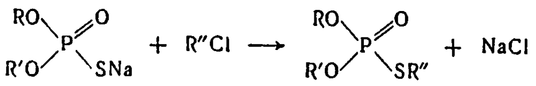
Aryldichlorothiophosphates are formed with prolonged heating (not less than 10 hours) at 110-115°C together with the appropriate phenol and excess $PSCl_3$, in the presence of small quantities of potassium chloride or anhydrous magnesium chloride. After the reaction ends, excess $PSCl_3$ is distilled away in a water bath in a vacuum, and the aryldichlorothiophosphate is subjected to further processing (260).

To obtain dialkylarylthiophosphates, aryldichlorothiophosphate is reacted with the alcoholates of the appropriate alcohols. Alcohol can also be used in the presence of a hydrogen chloride acceptor, but in this case the yield of dialkylarylthiophosphates is lower.

O-Aryl-O-alkyl-N-alkylamidothiophosphates are synthesized by reacting amines with aryldichlorothiophosphates in the appropriate alcohol:



Thiolphosphates IV, VI and VII are usually obtained by reacting dialkylthiophosphoric acid salts with halogen derivatives:



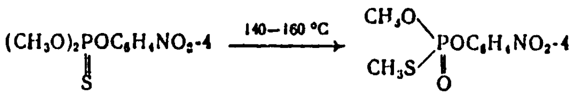
This reaction proceeds readily with most dialkylthiophosphates, with dimethylthiophosphate being an exception. Methylation proceeds in reactions of the latter, and a significant quantity of trimethylthiolphosphate is formed as a byproduct (261).

Some of the most important derivatives of thiophosphoric acid are described in greater detail below.

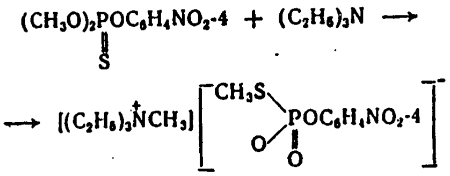
O,O-Dimethyl-O-(4-nitrophenyl)-thiophosphate (metaphos) is a white crystalline substance; its vapor pressure at 20°C is $0.97\cdot10^{-5}$ mm Hg; its volatility is 0.14 mg/m^3; d_4^{20} 1.358; n_D^{35} 1.5515. It is poorly soluble in paraffin hydrocarbons and readily soluble in aromatic hydrocarbons and in most organic solvents (see also Table 45).

The rate of hydrolysis of metaphos is significantly higher than that of thiophos; At 20°C and pH 1-5, 50 percent of the preparation hydrolyzes in 175 days, while at 70°C it takes 11 hours. The rate of hydrolysis in an alkaline medium is even greater.

Relatively speaking, metaphos is thermally unstable, and when heated to 140-160°C it transforms almost completely into the corresponding thiol isomer; sometimes an explosion occurs, and a porous mass containing a large quantity of carbon forms:



This reaction also proceeds when an alcohol solution of metaphos is heated for a long period of time at 100°C. The products of thermal decomposition of metaphos have also found to include trimethylsulfonium salts, obtained as a result of methylation of dimethylsulfide; the latter possibly forms from O-methyl-S-methyl-O,4--nitrophenylthiophosphate. Metaphos is a strong alkylating agent and is capable of methylating sulfides, amines, phosphines, thiourea, and many other compounds:



$$(CH_3O)_2\underset{\overset{\|}{S}}{P}OC_6H_4NO_2\text{-}4 + (C_2H_5)_3N \longrightarrow$$

$$\longrightarrow [(C_2H_5)_3\overset{+}{N}CH_3]\left[\begin{array}{c} CH_3S \\ O \end{array}\!\!>\!\underset{\overset{\|}{O}}{P}OC_6H_4NO_2\text{-}4\right]^-$$

The high methylating capability of metaphos is possibly a cause of its lower toxicity to mammals, since part of the preparation is broken down by demethylation prior to reaching the reactive centers of cholinesterase (261).

In all other chemical properties metaphos is similar to thiophos.

The toxicity of metaphos to homeotherms is significantly lower (LD_{50} 25-50 mg/kg); in comparison with thiophos it does not penetrate through skin as easily, which makes work with it less difficult. The maximum permissible concentration of metaphos in air is 0.1 mg/m^3.

Metaphos is marketed as emulsions, wettable powders and dusts. When selecting fillers for dusts and wettable powders, it should be kept in mind that even weakly alkaline fillers are ill-suited, since metaphos (and thiophos as well) breaks down relatively quickly in these filters and loses its insecticidal properties.

The preparation is used against a broad range of plant pests, similarly as with thiophos. Because it is less toxic to mammals, metaphos is gradually supplanting thiophos. World production of metaphos is higher than thiophos production, and it is exhibiting a tendency toward further growth.

Metaphos may be synthesized by all of the methods described above for obtaining mixed aliphatic-aromatic esters of thiophosphoric acid. The most important industrial method of obtaining metaphos is to react dimethylchlorothiophosphate with *p*-nitrophenol in the presence of hydrogen chloride acceptors or with sodium *p*-nitrophenylate; the reaction is performed in water in the presence of emulsifiers (for example ammonium naphthenate or amines) and in organic solvents. Chlorobenzene, xylol or aliphatic ketones (acetone and methylethylketone) are used most often.

When the reaction is carried out in organic solvents, the solvent must subsequently be distilled away, which must be done at the lowest possible temperature in continuous-action film evaporators. Otherwise the metaphos may break down, sometimes even with an explosion.

Preparation containing up to 96-98 percent O,O-dimethyl-O-(4-nitrophenyl)-thiophosphate is obtained by reacting dimethylchlorothiophosphate with *p*-nitrophenol in the presence of anhydrous potash in acetone, using sufficiently pure initial products. For convenience of handling and transportation, this product is diluted with 10-15 percent xylol.

When the reaction is performed in an aqueous medium, the resulting preparation contains 85-90 percent target substance. With different methods, the metaphos yields vary within 75-90 percent of theoretical.

Impurities in the technical-grade preparation include small quantities of *p*-nitrophenol, O-methyl-O,O-bis-(4-nitrophenyl)-thiophosphate and trimethylthiophosphate. In addition preparations obtained in organic solvents also contain O,S-dimethyl-O--(4-nitrophenyl)-thiophosphate as an impurity.

The insecticidal properties of all metaphos isomers have been studied, to include the (+) and (-) forms of O,S-dimethyl-O-(4-nitrophenyl)-thiophosphates, of which the left isomer has been found to be more toxic to animals (LD_{50} in rats is 25 mg/kg, while the toxicity of the right isomer is 135 mg/kg). Of the three thiophosphates with sulfur in different positions, the most toxic is O,O-dimethyl-S-(4-nitrophenyl)--thiophosphate (the LD_{50} in mice is 7.5 mg/kg).

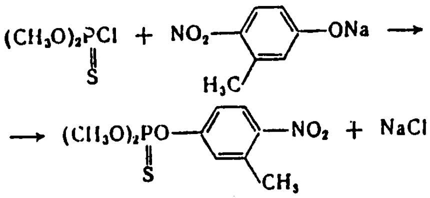
O,O-Dimethyl-O-(4-nitro-3-methylphenyl)-thiophosphate (metilnitrofos) is a light-colored liquid with unpleasant odor; its vapor pressure at 20° is $6.0 \cdot 10^{-6}$ mm Hg; its volatility is 0.09 mg/m^3; its viscosity at 30°C is 20.8 centipoise; d_4^{20} 1.308; n_D^{20} 1.5505. It is freely soluble in most organic solvents, it mixes in all ratios with methyl and ethyl alcohols, alkylacetates (262,263), ketones and aromatic hydrocarbons. Its solubility is about 4 percent in kerosene and about 7 percent in petroleum ether (see also Table 45).

Its LD_{50} in various experimental animals is within 142-1,000 mg/kg. Its nature of action upon animals is similar to that of metaphos.

Metilnitrofos is practially indistinguishable from metaphos in its chemical properties, but its rate of hydrolysis by water and alkalis is somewhat lower. Thus it takes 5 minutes for 50 percent of metaphos to be hydrolyzed in 0.1 N sodium hydroxide solution at 30°C, while metilnitrofos takes 12 minutes.

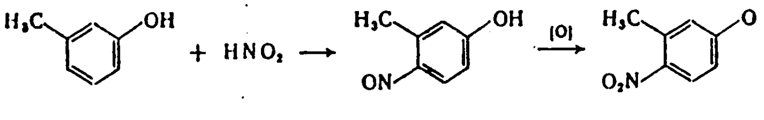
This preparation's thermal stability is also not very high, and when heated above 100°C it undergoes Pishchemuka isomerization and may explode as it decomposes. In this connection overheating of the preparation should be avoided, both during its production and during storage. The preparation must be stored in enamel, aluminum or glass containers. Iron promotes this preparation's decomposition, as is true with most other organophosphorus compounds.

O,O-Dimethyl-O-(4-nitro-3-methylphenyl)-thiophosphate is obtained by condensation of dimethylchlorothiophosphate with sodium 4-nitro-3-methylphenolate in an aqueous medium, or with nitrocresol itself in the presence of anhydrous potash in acetone or methylethylketone:



It is very difficult to synthesize 4-nitro-3-methylphenol, since as with direct nitration of *m*-cresol, a mixture of 4-nitro- and 6-nitro-isomers containing not more than 60 percent of the needed product forms.

Sufficiently pure 4-nitro-3-methylphenol can be isolated either by nitration of esters of *m*-cresol and carboxylic acids or by oxidation of the appropriate nitrosophenol (272):

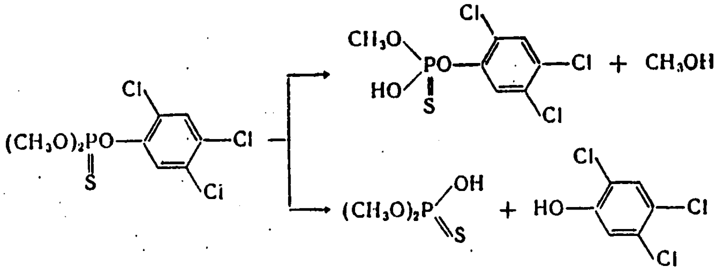


However, up to 30 percent of valuable *m*-cresol is lost in both methods of obtaining 4-nitro-3-methylphenol.

Systematic investigation of the insecticidal properties of mixtures of various compounds showed that O,O-dimethyl-O-(6-nitro-3-methylphenyl)-thiophosphate is an active synergist in relation to many organophosphorus insecticides--thiophos, metaphos, thiophos-ME and O,O-dimethyl-O-(4-nitro-3-methylphenyl)-thiophosphate. When mixed at a 1:1 ratio with O,O-dimethyl-O-(6-nitro-3-methylphenyl)-thiophosphate, each of these organophosphorus compounds is active at the same concentrations as the pure compound on its own. A mixture of O,O-dimethyl-O-(4-nitro-3-methylphenyl)-thiophosphate and 6-nitro isomer, which is obtained by reacting dimethylchlorothiophosphate with isomeric nitrocresols--products of direct nitration of *m*-cresol by nitric acid--has been proposed for use in agriculture. In terms of its insecticidal and acaricidal activity this mixture is practically indistinguishable from pure O,O-dimethyl-O-(4-nitro-3-methylphenyl)-thiophosphate. This preparation is called metilnitrofos in the USSR (264,265).

Metilnitrofos and its analogues are marketed in the form of a 50 percent emulsion concentrate and as a preparation for ultralow volume spraying.

O,O-Dimethyl-O-(2,4,5-trichlorophenyl)-thiophosphate (ronnel, trikhlormetafos) is a white crystalline substance; d_4^{20} 1.4850; vapor pressure at 25°C is $0.8 \cdot 10^{-3}$ mm Hg. It is readily soluble in most organic solvents (see also Table 45). Trikhlormetafos is stable at temperatures up to 80°C. In weakly alkaline medium it hydrolyzes to form predominantly O-methyl-O-(2,4,5-trichlorophenyl)-thiophosphoric acid, while in a highly alkaline medium it forms predominantly O,O-dimethylthiophosphoric acid:



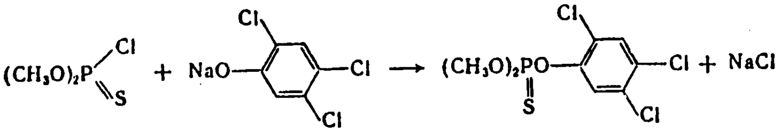
In the bodies of cows and rats about half of the administered preparation is eliminated with urine as O-methyl-O-(2,4,5-trichlorophenyl)-thiophosphoric acid, while in the bodies of insects it breaks down predominantly into dimethylthiophosphoric acid and 2,4,5-trichlorophenol.

Trikhlormetafos is characterized as mildly toxic to homeothermic animals, and it is used against ectoparasites of farm animals, both as topical emulsions and as feed additives.

The LD_{50} in animals is within 400-3,000 mg/kg.

Several methods of obtaining trikhlormetafos have been described, the most important ones of which are:

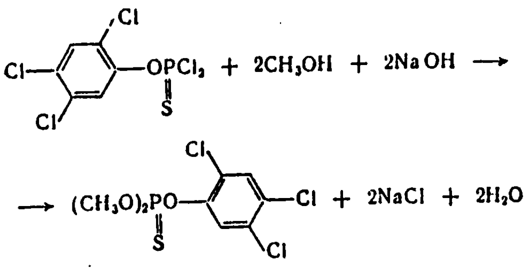
1. Reacting sodium 2,4,5-trichlorophenolate with dimethylchlorothiophosphate in an aqueous medium in the presence of emulsifiers:



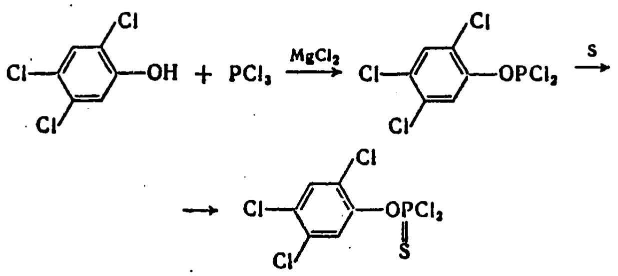
In this reaction the yield of trikhlormetafos is 85-90 percent of theoretical; it contains a certain quantity of 2,4,5-trichlorophenol as an impurity; the latter can be washed away with a small quantity of sodium hydroxide.

2. Reacting dimethylchlorothiophosphate with 2,4,5-trichlorophenol in methylethylketone in the presence of finely pulverized potash, the yield being up to 80 percent.

3. Methanolizing O-(2,4,5-trichlorophenyl)-dichlorothiophosphate in the presence of sodium hydroxide:



The O-(2,4,5-trichlorophenyl)-dichlorothiophosphate needed for this synthesis is obtained in the following reaction:



O-(2,4,5-trichlorophenyl)-dichlorophosphite is formed with a yield of about 90 percent when 2,4,5-trichlorophenol is heated for a long period of time with phosphorus trichloride (in great excess) in the presence of a catalytic quantity of anhydrous magnesium chloride. Sulfur is attached without isolating O-(2,4,5-trichlorphenyl)-dichlorophosphite in pure form, and it is only after the second reaction that the phosphorus trichloride is distilled away. The removed phosphorus trichloride is returned to the acquisition process of O-(2,4,5-trichlorophenyl)-dichlorophosphite

Volatile impurities can be removed from trikhlormetafos by distillation with live steam (266,267).

The preparation is marketed in the USA with two degrees of purity: Ninety eight-ninety nine percent main ingredient, and about 95 percent main ingredient.

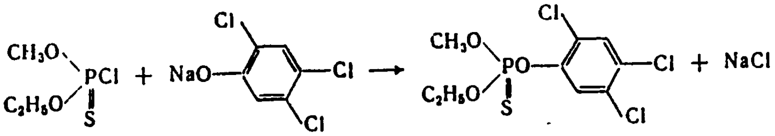
O-Methyl-O-ethyl-O-(2,4,5-trichlorophenyl)-thiophosphate (trikhlormetafos-3) is the closest homologue of trikhlormetafos, and it was first synthesized and proposed for agricultural use in the Soviet Union. It is a colorless oily liquid having a vapor pressure at 20°C of about $0.6 \cdot 10^{-3}$ mm Hg; its volatility is about 8 mg/m^3; d_4^{20} 1.4345; n_4^{20} 1.5520 (see also Table 45). It is freely soluble in most organic solvents, and its solubility in water is 40 mg/liter.

Its LD_{50} in various experimental animals is 330-800 mg/kg.

Trikhlormetafos-3 is used against insects and flies serving as a public health nuisance. It is applied topically and administered gastrically at consumption norms on the order of 35-40 mg/kg animal live weight to control the cattle fly. At such doses the preparation is eliminated relatively quickly from the animal body, and it does not remain in milk and meat. It is also recommended against plant pests, and it is effective against many sucking insects and ticks at a 0.1 percent concentration. At these concentrations it does not injure plants (in contrast to ronnel, which is highly phytocidal).

It is marketed in the form of 30 and 50 percent emulsion concentrates containing emulsifiers in addition to the active ingredient.

The main method of obtaining trikhlormetafos-3 is to react O-methyl-O-ethylchlorothiophosphate with sodium 2,4,5-trichlorophenylate in an aqueous medium in the presence of emulsifiers (the yield is 85 percent):



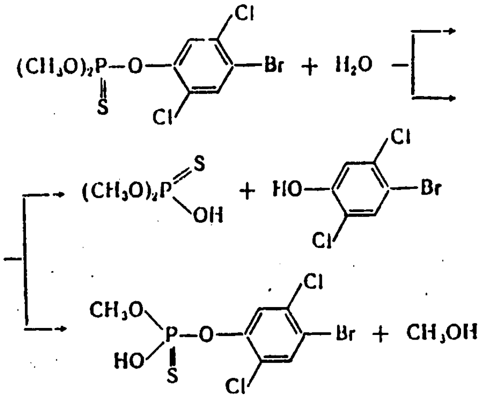
The impurities in trikhlormetafos-3 include small quantities of 2,4,5-trichlorophenol, dimethylethylthiophosphate and some other compounds. The purity of the initial substances, and primarily of methylethylchlorothiophosphate and 2,4,5-trichlorophenol, has great significance to the quality of the preparation obtained. The former must not contain diethylchlorothiophosphate impurities while the latter must not contain dichlorophenols and isomeric trichlorophenols. Phenols can be removed from trikhlormetafos-3 by washing it with aqueous alkali solutions, while trimethylthiophosphate and other volatile impurities can be removed by distillation with live steam (266).

Trikhlormetafos-3 is similar in chemical properties to ronnel, but it differs from the latter in being more resistant to hydrolysis and reacting more slowly with amines. Hydrolysis of trikhlormetafos proceed similarly as with hydrolysis of ronnel.

O,O-Diethyl-O-(2,4,5-trichlorophenyl)-thiophosphate is significantly more toxic to mammals than ronnel and trikhlormetafos-3.

O,O-Dimethyl-O-(2,5-dichloro-4-bromophenyl)-thiophosphate (bromofos) is a white crystalline substance; its vapor pressure at 20°C is $1.3 \cdot 10^{-4}$ mm Hg; its solubility in organic solvents at 20°C is (in gm per 100 gm): 109 in acetone, 21 in diesel fuel, 8 in isopropyl alcohol, 10 in methanol, 120 in methylethylketone, 90 in xylol, 98 in chlorobenzene and 112 in methylene chloride (see also Table 45).

In an alkaline medium bromofos hydrolyzes similarly as with ronnel to form O,O-dimethylthiophosphoric acid, 2,5-dichloro-4-bromophenol, O-methyl-O-(2,5-dichloro-4-bromophenyl)-thiophosphoric acid and methanol.



At 22°C and pH 13, 50 percent of the preparation hydrolyzes in 3.5 hours. On plants, bromofos decomposes practically completely in 13-20 days, depending on the plant species. Bromofos is a mildly toxic preparation: Its LD_{50} to various animal species is within 2,000-4,000 mg/kg.

Bromofos may be synthesized by all of the methods described for ronnel. The greatest difficulty lies in making 2,5-dichloro-4-bromophenol which apparently would best be obtained by bromination of 2,5-dichlorophenol. In turn, 2,5-dichlorophenol can be formed by saponification of 1,2,4-trichlorobenzene by sodium hydroxide in methanol at 160-190°C under pressure. In this case a mixture of 2,4- and 2,5-dichlorophenols is produced, which is then separated by fractional precipitation out of alkaline solutions, since the two compounds have different dissociation constants, or they may be separated by complexing with urea (270,271).

Bromofos has been proposed for use against the most diverse species of insect pests, to include flies and other insects causing a public health nuisance. It is used as 20 and 25 percent emulsion concentrates, as 5 percent granulated preparations and as aerosols.

The nearest homologue of bromofos is bromofos-etil, [O,O-diethyl-O-(2,5-dichloro-4--bromophenyl)-thiophosphate], which is an oily liquid; its vapor pressure at 30°C is $4.2 \cdot 10^{-5}$ mm Hg (see also Table 45).

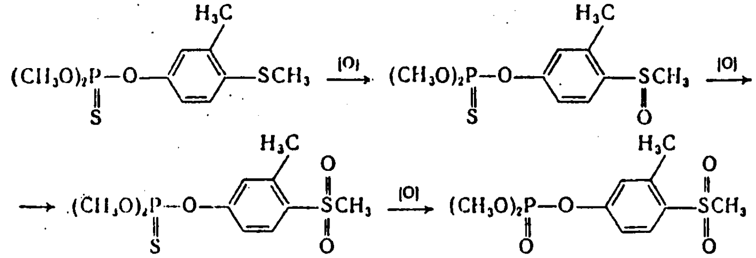
Its LD_{50} in rats is 238 mg/kg.

Bromofos-etil is close to bromofos in its insecticidal activity. The preparation iodfenfos (iodofos), or O,O-dimethyl-O-(2,5-dichloro-4-iodophenyl)-thiophosphate, which has been recommended in animal husbandry to control a number of flying insects (see Table 71) [table not reproduced], has a wide spectrum of action and a long time of action.

O,O-Dimethyl-O-(4-methylmercapto-3-methylphenyl)-thiophosphate (lebaycid) is a colorless oil; its vapor pressure at 20°C is $3 \cdot 10^{-5}$ mm Hg. Its volatility is 0.46 mg/m^3. It is freely soluble in most organic solvents, including alcohols, ethers, esters and halogen derivatives of aromatic and aliphatic hydrocarbons, and it is poorly soluble in petroleum ether (see also Table 45).

Its LD_{50} in rats is 215-245 mg/kg.

Lebaycid is more resistant to hydrolysis and heating than metaphos. At 80°C 50 percent of the preparation hydrolyzes in an acid medium in 36 hours, and in an alkaline medium in 95 minutes. When it reacts with oxidizers, lebaycid oxidizes first to sulfoxide and then to sulfone:



Then oxidizers split off the thion sulfur from sulfone, which transforms into the appropriate phosphate.

In natural conditions lebaycid is stable, and it may persist for a long period of time.

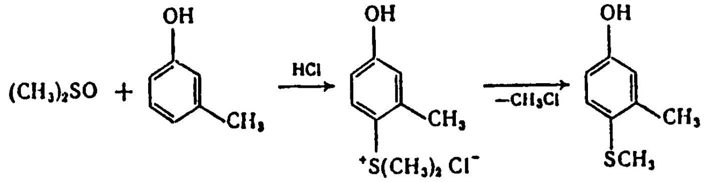
In terms of its toxicity to insects, lebaycid is similar to chlorofos, but its selectivity is lower, since its toxicity to mammals is higher.

In animals and on plants, lebaycid oxidizes to sulfone, which then hydrolyzes and breaks down into products harmless to animals.

It is marketed in the form of a 50 percent emulsion concentrate, a 25 percent wettable powder and a 3 percent dust.

Lebaycid is obtained with a 90 percent yield (of theoretical) by reacting 4-methylmercapto-3-methylphenol with dimethylchlorothiophosphate in methylethylketone at 60°C in the presence of finely pulverized potash.

The 4-methylmercapto-3-methylphenol required for this purpose is synthesized out of dimethylsulfoxide and *m*-cresol (268):



4-Methylmercapto-3-methylphenol can also be obtained by reacting dimethyldisulfide and sulfuryl chloride with *m*-cresol.

A large number of analogues and homologues of lebaycid have been synthesized and studied, but most compounds are more toxic to animals than lebaycid. In particular both O,O-dimethyl-O-(4-methylmercaptophenyl)-thiophosphate and its oxygen analogue are more toxic. When a methyl group or a halogen atom is introduced in many mixed thiophosphates at the meta-position in relation to the ester group, toxicity to vertebrates decreases while comparatively little change occurs in insecticidal properties (see metilnitrofos, chlorthion, ronnel, trikhlormetafos-3, bromofos).

In addition to mixed esters of thiophosphoric acid containing aromatic radicals, mixed thiophosphates in the heterocyclic series have enjoyed some use as insecticides and acaricides. Certain representatives of this series are effective, and they are used on a broad scale.

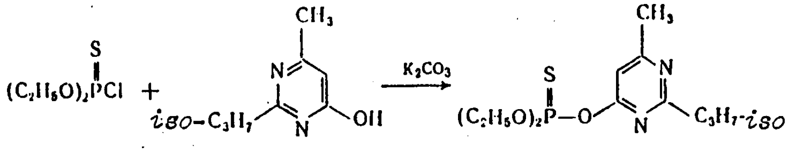
O,O-Diethyl-O-(2-isopropyl-4-methylpyrimidyl-6)-thiophosphate (diazinon) is a colorless oil with a boiling point of 89°C at 0.1 mm Hg; its vapor pressure at 20°C is $8.4 \cdot 10^{-5}$ mm Hg; its volatility is 1.39 mg/m^3; d_4^{20} 1.115. It is readily soluble in most organic solvents (see also Table 45).

Its LD_{50} in various experimental animals is 76-320 mg/kg.

In terms of its hydrolytic stability diazinon is inferior to thiophos. In an acid medium it hydrolyzes 12 times more quickly than thiophos, while in an alkaline medium hydrolysis proceeds at practically the same rate. In excess water the main hydrolysis products of diazinon are diethylthiophosphoric acid and 2-isopropyl-4-methyl-6-oxypyrimidine, but when water is lacking in an acid medium, a small quantity of tetraethyldithio- and tetraethylthiopyrophosphates forms.

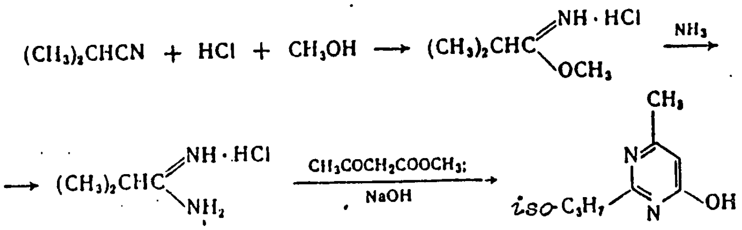
Diazinon is marketed as emulsion concentrates, wettable powders, dusts and granulated preparations, and it is used against various plant pests and animal parasites. Despite its relatively high toxicity to mammals, diazinon is believed to be a safe preparation in most countries, and it is usually classified as a group III toxic compound.

Diazinon is obtained with an 85 percent yield (of theoretical) by reacting 2-isopropyl-4-methyl-6-oxypyrimidine with diethylchlorothiophosphate in the presence of potash:



The reaction proceeds well in dimethylformamide solution at 50-60°C.

2-Isopropyl-4-methyl-6-oxypyrimidine may be synthesized with satisfactory yields by the following pathway:



O,O-Diethyl-O-(3,5,6-trichloropyridyl)-thiophosphate (dursban) is a white crystalline substance; its vapor pressure at 25°C is $1.9 \cdot 10^{-5}$ mm Hg. It is readily soluble in most organic solvents (see also Table 45).

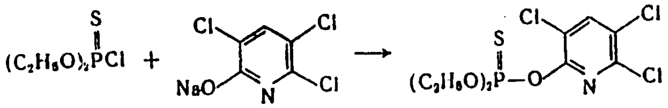
Its LD_{50} in rats is 150 mg/kg, and in guinea pigs it is 500 mg/kg.

In acid and alkaline media the preparation is slowly hydrolyzed by water to form diethylthiophosphoric and ethylthiophosphoric acid and trichloroxypyridine. When oxidized, it may transform into the corresponding phosphate.

Dursban is an active insecticide used against sucking and gnawing insect pests as well as against household parasites. The preparation's active life on various surfaces is 6-11 weeks, but its life on plant leaves is shorter, apparently due to its fast hydrolysis by enzymes, though on cereal grain plants the preparation's life is several weeks. Dursban is especially effective against mosquito larvae. When applied to marshes at a consumption norm of 0.5 kg/ha, it caused 100 percent death of mosquitoes in 2 months.

There are indications that dursban is effective against soil-inhabiting plant pests.

Dursban is synthesized by reacting the sodium salt of diethylchlorothiophosphate in dimethylformamide:



In this reaction the yield of the preparation is 80-85 percent. In turn, 3,5,6-trichloro-2-oxypyridine is formed by saponification of 2,3,5,6-tetrachloropyridine by sodium hydroxide at high temperature.

O,O-Diethyl-O-(3-chloro-4-methylcoumarinyl-7)-thiophosphate (asuntol) is a white crystalline substance; d_4^{20} 1.474 (see also Table 45).

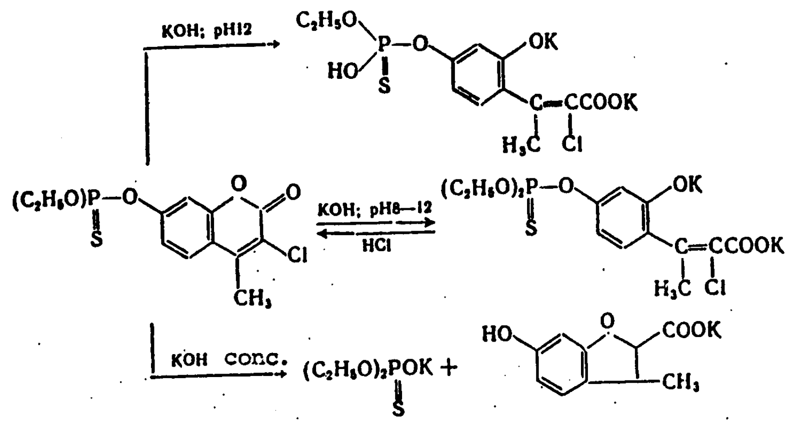
Asuntol is poorly soluble in most organic solvents, and it is rather soluble in the lower carboxylic acid esters and ketones.

Its LD_{50} in different experimental animals is 55-200 mg/kg.

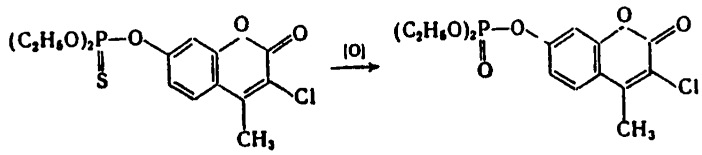
Asuntol is resistant to hydrolysis in alkaline and acid media, and it withstands boiling in 8 percent soda solution for 2 hours.

It interacts with diluted and concentrated alkali in different ways. Dilute potassium hydroxide breaks open the pyran ring. Following subsequent oxidation the ring once again closes, and the initial product returns to its initial form. However, when it is subjected to the prolonged action of dilute alkali, the ring opens and the ethoxy group partially splits off; this process is irreversible.

Asuntol breaks down when heated in concentrated alkali:

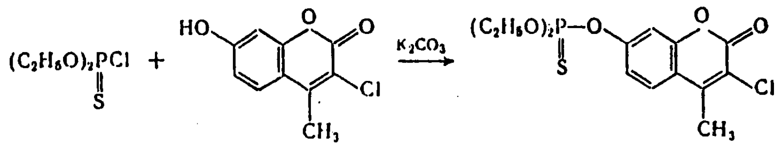


When oxidized by nitric acid or other oxidants, asuntol forms O,O-diethyl-O-(3-chloro-4-methylcoumarinyl-7-)-phosphate, known in the literature as coroxon:



Asuntol is a valuable insecticide against ectoparasites of domesticated animals. In the animal body it breaks down quickly, transforming into diethyl- and ethylthiophosphoric and -phosphoric acids, as well as H_3PO_4. Owing to its low toxicity to fish, asuntol is also of interest as a resource against mosquito larvae.

It is obtained with a yield of more than 90 percent by reacting diethylchlorothiophosphate with 3-chloro-7-oxy-4-methylcoumarin in the presence of potash:

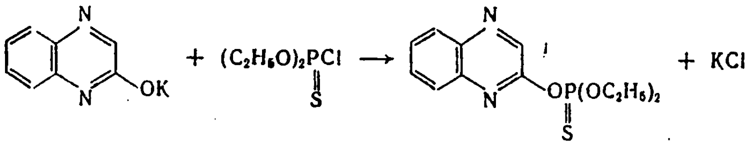


O,O-Diethyl-O-(quinoxalyl-2)-thiophosphate (bayrusil) is a white crystalline substance; d_4^{20} 1.230. It is readily soluble in most organic solvents (see also Table 45). It decomposes when heated to 120°C.

Its LD_{50} in rats is 66 mg/kg; its LD_{50} in the goldfish and carp with an exposure time of 96 hours is 1-10 mg/liter.

It is used as 25 percent emulsion concentrate and 5 percent granules to control plant sucking pests.

Bayrusil is obtained by condensation of diethylchlorophosphate with alkaline derivatives of 2-oxyquinoxaline (225,273):

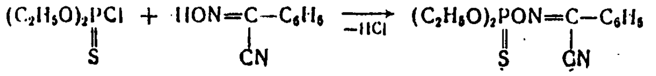


The methyl homologue of bayrusil, which is a white crystalline substance with a melting point of 51°C, is obtained similarly. This preparation is known as metilkhinalfos. Its LD_{50} is 900 mg/kg (orally) and 2,500 mg/kg (cutaneously). It is undergoing testing as a contact insecticide with a rather broad spectrum of action. Its relatively low thermal stability is a shortcoming. Thus a 30°C it may decompose down to 10 percent within 1 week, obviously due to its high alkylating capacity. Preparations containing substituents in the aromatic ring are more stable (224).

O,O-diethylthiophosphoryl-O-(α-cyanobenzaldoxime) (foksim) is an insecticide with a broad spectrum of action against sucking and gnawing plant pests (see Table 45).

It is marketed under the name of baytion as an agent against storehouse pests. It is suitable against pests inhabiting the soil; in this case it is used in the form of granules embedded in soil. Foksim is photochemically unstable, owing to which its life is relatively short when sprayed on plants. It is hydrolyzed by water and alkali.

Foksim is obtained by reacting diethylchlorothiophosphate with the oxime form of α-benzoylcyanide in the presence of hydrogen chloride acceptors (146,147):



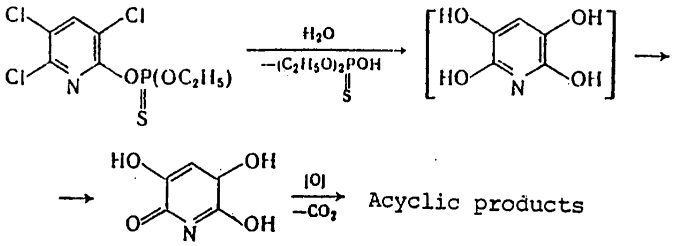
$$(C_2H_5O)_2\underset{\underset{S}{\|}}{P}Cl + HON{=}\underset{\underset{CN}{|}}{C}{-}C_6H_5 \xrightarrow[-HCl]{} (C_2H_6O)_2\underset{\underset{S}{\|}}{P}ON{=}\underset{\underset{CN}{|}}{C}{-}C_6H_5$$

Foksim is a promising substitute for some organochloride preparations, and in this respect it deserves the most meticulous study upon various objects.

Because dialkylarylthiophosphates are extensively used against various harmful insects and ticks, the metabolism of most thiophosphates in various species of living organisms and in the environment has been studied (274,275). Compounds that have been studied include abat (274,276), bromofos (277,278), dazonit (279), diazinon (274,280-283), dursban (274,284-287), chlorthion, coumaphos, thiophos, metaphos, trikhlormetafos, zinophos, lebaycid, tsitron, VTs-12, metilnitrofos etc. (274).

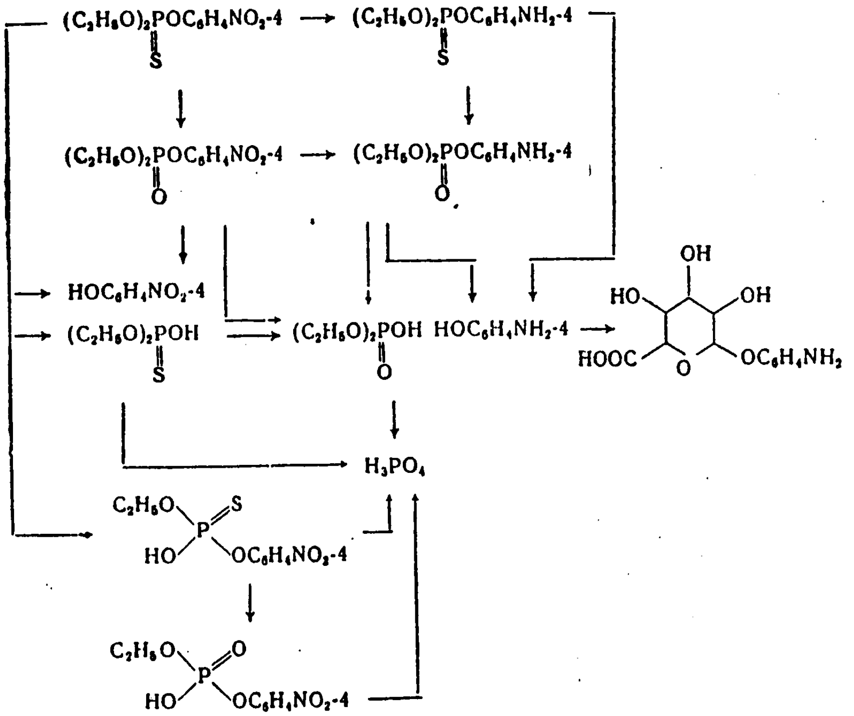
Investigation of the metabolism of a large number of mixed esters of thiophosphoric acid in various media showed that the metabolism of these compounds proceeds in two basic directions: hydrolysis and oxidation. Depending on the structure and reactivity of the initial substance, either hydrolysis or oxidation occurs first, but in some cases these processes occur simultaneously (275). Hydrolysis may occur at the P-OAr bond (or at the oxygen atom bound to the heterocycle) or at the P-OAlk bond; as a rule the rate of hydrolysis is somewhat higher in the first case than in the second; however, in some cases these reactions proceed concurrently, though at different rates. Oxidation occurs first at the thion sulfur. If sulfide sulfur is present in the ester molecule, sulfoxides and sulfones form, after which the molecule undergoes destruction. Aromatic and heterocyclic residues may enter into a reaction with carbohydrates to form the appropriate glucuronates.

However, in many cases the organophosphorus compound may decompose all the way down to the simplest products. This is what happens, for example, in photochemical decomposition of one of the most persistent organophosphorus insecticides--dursban (287). This decomposition occurs as follows:



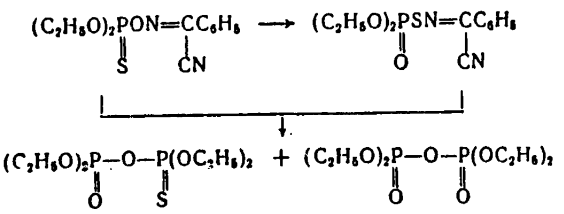
It would be interesting to note that hydrolysis of organophosphorus compounds is accelerated in the presence of copper salts (289).

The metabolism of thiophos may be diagrammed as follows:



The metabolism of other thiophosphates proceeds in similar fashion.

Investigation of the metabolism of foksim showed that isomerization is the first event to occur in response to light; this is followed by decomposition resulting in tetraethylpyrophosphate and tetraethylthiopyrophosphate (288):

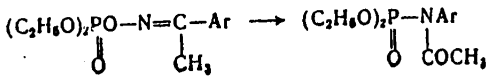


$$(C_2H_5O)_2\underset{\underset{S}{\|}}{P}ON{=}\underset{\underset{CN}{|}}{C}C_6H_5 \rightarrow (C_2H_5O)_2\underset{\underset{O}{\|}}{P}SN{=}\underset{\underset{CN}{|}}{C}C_6H_5$$

$$\downarrow$$

$$(C_2H_5O)_2\underset{\underset{O}{\|}}{P}-O-\underset{\underset{S}{\|}}{P}(OC_2H_5)_2 + (C_2H_5O)_2\underset{\underset{O}{\|}}{P}-O-\underset{\underset{O}{\|}}{P}(OC_2H_5)_2$$

Fukuto et al. (288a) observed interesting thermal regrouping of oxime phosphates:



$$(C_2H_5O)_2\underset{\underset{O}{\|}}{P}O-N=\underset{\underset{CH_3}{|}}{C}-Ar \rightarrow (C_2H_5O)_2\underset{\underset{O}{\|}}{P}-\underset{\underset{COCH_3}{|}}{N}Ar$$

Mixed aliphatic esters of thiophosphoric acid are of significant interest as systemic insecticides, among which mercaptophos, methyl-mercaptophos and its sulfoxide and sulfone, and vamidotion have enjoyed rather broad application. Due to the high toxicity of mercaptophos to animals, its use has recently decreased significantly, while the other preparations are enjoying rather broad use.

Methyl-mercaptophos is a methyl homologue of mercaptophos. Technical-grade methyl-mercaptophos is a mixture of the thiol (30 percent) and thion (70 percent) isomers of O,O-dimethyl-2-ethylmercaptoethylthiophosphate.

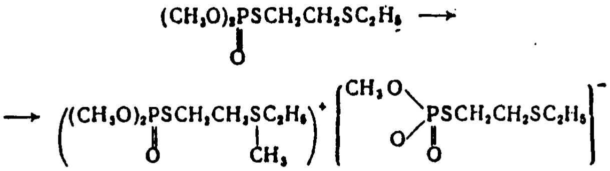
The thion isomer of methyl-mercaptophos is a liquid with a characteristic unpleasant odor; its vapor pressure at 20° is $1.85 \cdot 10^{-5}$ mm Hg; its volatility is 23.3 mg/m^3; d_4^{20} 1.1904. It is freely soluble in most organic solvents (see also Table 46).

The thiol isomer of methyl-mercaptophos is a liquid; its vapor pressure at 20°C is $3.6 \cdot 10^{-4}$ mm Hg; its volatility is 4.5 mg/m^3; d_4^{20} 1.207. It is freely soluble in organic solvents (see also Table 46).

The chemical stability of methyl-mercaptophos is lower than that of mercaptophos. Thus for example methyl-mercaptophos is saponified at pH 3 and 70°C in 4.9 hours, while mercaptophos takes 10 hours; the difference is even more significant in an alkaline medium.

Regrouping of the thion isomer into the thiol isomer also proceeds faster. While it takes 91 days for the thion isomer of mercaptophos to transform at 40°C into a mixture containing 90 percent thion and 10 percent thiol isomer, the thion isomer of methyl-mercaptophos undergoes 10 percent isomerization under the same conditions in 8 days.

In the presence of traces of water, methyl-mercaptophos may enter into an intermolecular methylation reaction:



$$(CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2CH_2SC_2H_5 \longrightarrow$$

$$\longrightarrow \left((CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2CH_2\underset{\overset{|}{CH_3}}{S}C_2H_5\right)^+ \left[\begin{array}{l} CH_3O\diagdown \\ \qquad\quad \underset{\overset{\|}{O}}{P}SCH_2CH_2SC_2H_5 \\ \quad O\diagup \end{array}\right]^-$$

which in a number of cases is a reason for the product's spoilage during long-term storage. Metallic iron and some of its compounds have a negative influence on the stability of methyl-mercaptophos, for which reason storage of this preparation in iron containers is not recommended. It would be best of all to store methyl-mercaptophos in enameled containers or in containers made from pure aluminum.

Methyl-mercaptophos is less toxic than mercaptophos. The LD_{50} of the technical-grade preparation is within 80-100 mg/kg. The LD_{50} of the thion isomer is 180 mg/kg, while that of thiol isomer is 40 mg/kg. The maximum permissible concentration in air is 0.1 mg/m^3.

The metabolism of methyl-mercaptophos in plants and insects proceeds similarly as with mercaptophos, except that when methyl-mercaptophos enters into plants, it quickly undergoes isomerization into the thiol isomer, which then undergoes metabolism similarly as with mercaptophos. The oxidation products of the thion isomer of methyl-mercaptophos have not been observed, but they have been obtained synthetically.

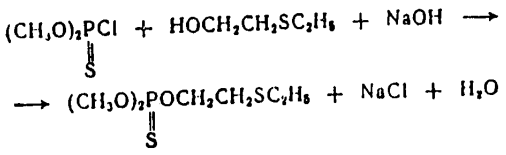
Transformation and decomposition of methyl-mercaptophos proceeds relatively quickly in plants, owing to which its life as an insecticide does not usually exceed 3 weeks.

The oxidation products of methyl-mercaptophos and their toxicity to rats are shown below:

Compound	Boiling Point, °C (mm Hg)	LD_{50} mg/kg
$(CH_3O)_2\underset{\underset{S}{\|}}{P}OCH_2CH_2SOC_2H_5$ . . .	95—96 (0,01)	600
$(CH_3O)_2\underset{\underset{S}{\|}}{P}OCH_2CH_2SO_2C_2H_5$ . . .	101 (0,01)	500
$(CH_3O)_2\underset{\underset{O}{\|}}{P}SCH_2CH_2SOC_2H_5$ . . .	105 (0,01)	40
$(CH_3O)_2\underset{\underset{O}{\|}}{P}SCH_2CH_2SO_2C_2H_5$ . . .	115 (0,01) Melting Point 52°C	40

Methyl-mercaptophos is used as aqueous emulsions, and it is marketed in the form of concentrates containing 30 and 50 percent isomer mixtures. A synergist of methyl-mercaptophos has been found in the USSR. It reduces the consumption norm for the preparation by 20-40 percent and reduces its toxicity by almost three times. This preparation is known as sinerfos.

Methyl-mercaptophos is obtained by reacting β-oxydiethylsulfide and dimethylchlorothiophosphate in the presence of hydrogen chloride acceptors (followed by isomerization of part of the product into the thiol isomer):



$$(CH_3O)_2\underset{\underset{S}{\|}}{P}Cl + HOCH_2CH_2SC_2H_5 + NaOH \longrightarrow$$

$$\longrightarrow (CH_3O)_2\underset{\underset{S}{\|}}{P}OCH_2CH_2SC_2H_5 + NaCl + H_2O$$

Impurities in the technical-grade preparation include a small quantity of trimethylthiophosphate, β-oxydiethylsulfide and some other thiophosphates. However, the total concentration of thiol and thion isomers is usually not less than 90 percent.

Tinoks: A preparation marketed in the GDR under the name of tinoks is close in properties to methyl-mercaptophos. The technical-grade preparation is a mixture of the thiol (60-70 percent) and thion (30-40 percent) isomers of O,O-dimethyl-O--(2-methylmercaptoethyl)-thiophosphate.

The thion isomer is a liquid; its vapor pressure at 20°C is $28.4 \cdot 10^{-4}$ mm Hg; its volatility is about 35 mg/m^3; d_4^{20} 1.154. It is freely soluble in most organic solvents (see also Table 46).

Its LD_{50} in rats is more than mg/kg.

The thiol isomer is a liquid; it is freely soluble in most organic solvents (see also Table 46).

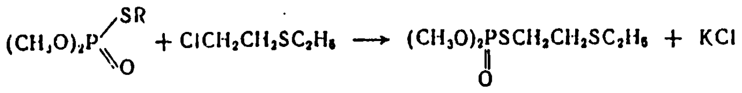
Its LD_{50} in rats is about 40 mg/kg.

Tinoks is similar to methyl-mercaptophos in its chemical properties, insecticidal activity and life. It is marketed in the form of a 50 percent emulsion concentrate.

The methods by which tinoks is obtained are fully similar to those of obtaining mercaptophos and methyl-mercaptophos.

O,O-Dimethyl-S-(2-ethylmercaptoethyl)-thiophosphate (meta-systox I) is a systemic and contact fast-acting preparation. It is a thiol isomer of methyl-mercaptophos. Without repeating the description of its properties, we will simply note that it is marketed as a 50 percent emulsion concentrate.

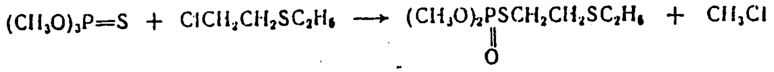
The best method of synthesizing meta-systox I is to react 2-chlorodiethylsulfide with salts of dimethylthiolphosphoric acid:



$$(CH_3O)_2P\genfrac{}{}{0pt}{}{\diagup SR}{\diagdown\!\!\diagdown O} + ClCH_2CH_2SC_2H_5 \longrightarrow (CH_3O)_2\underset{\underset{O}{\|}}{P}SCH_2CH_2SC_2H_5 + KCl$$

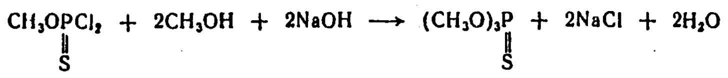
The yield of the thiol isomer of methyl-mercaptophos with this method is not less than 85-90 percent. The reaction may be performed both in an aqueous medium and in organic solvents.

O,O-Dimethyl-S-ethylmercaptoethylthiophosphate is also formed by reacting trimethylthiophosphate with 2-chlorodiethylsulfide while heating to a temperature somewhat above 100°C:



$$(CH_3O)_3P{=}S + ClCH_2CH_2SC_2H_5 \longrightarrow (CH_3O)_2\underset{\underset{O}{\|}}{P}SCH_2CH_2SC_2H_5 + CH_3Cl$$

Trimethylthiophosphate can be synthesized with very good yields out of methyldichlorothiophosphate and methanol in the presence of sodium hydroxide:



$$CH_3O\underset{\underset{S}{\|}}{P}Cl_2 + 2CH_3OH + 2NaOH \longrightarrow (CH_3O)_3\underset{\underset{S}{\|}}{P} + 2NaCl + 2H_2O$$

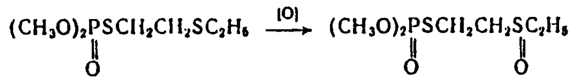
O,O-Dimethyl-S-(2-ethylsulfinylethyl)-thiophosphate (meta-systox R) is a yellow liquid with a mild odor; its volatility at 20°C is 0.09 mg/m^3. Meta-systox R is freely soluble in water and poorly soluble in aliphatic hydrocarbons. It is freely soluble in methylene chloride and in halogen derivatives of aromatic hydrocarbons (see also Table 46).

In an acid medium it is more resistant to hydrolysis than methyl-mercaptophos, but in an alkaline medium it hydrolyzes faster than the latter.

Meta-systox R is close in its insecticidal activity to methyl-mercaptophos, and it has a less pleasant odor. It is marketed in the form of a 25 percent concentrate, and it is used with an active ingredient concentration of 0.025 percent. The maximum permissible quantity of residues in the USA is 0.75 mg/kg.

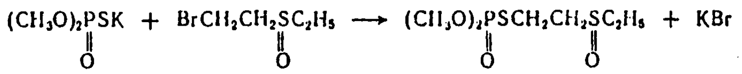
Its LD_{50} in rats is 65-75 mg/kg.

Meta-systox R is obtained either by oxidation of the thiol isomer of methyl-mercaptophos by different oxidants (hydrogen peroxide, hypochlorites, bromine etc.)



$$(CH_3O)_2\underset{\underset{O}{\|}}{P}SCH_2CH_2SC_2H_5 \xrightarrow{[O]} (CH_3O)_2\underset{\underset{O}{\|}}{P}SCH_2CH_2\underset{\underset{O}{\|}}{S}C_2H_5$$

or by reacting the salts of dimethylthiolphosphoric acid with 2-(ethylsulfinyl)-ethylbromide



$$(CH_3O)_2\underset{\underset{O}{\|}}{P}SK + BrCH_2CH_2\underset{\underset{O}{\|}}{S}C_2H_5 \longrightarrow (CH_3O)_2\underset{\underset{O}{\|}}{P}SCH_2CH_2\underset{\underset{O}{\|}}{S}C_2H_5 + KBr$$

O,O-Dimethyl-S-[2-(N-methylcarbamoylethylmercapto)-ethyl]-thiophosphate (vamidotion) is a white crystalline substance with a melting point of 46-48°C; the melting point of the technical-grade preparation is 33-38°C. It is freely soluble in water (4 kg/liter), in acetone, methylethylketone, ethyl acetate and acetonitrile, and it is poorly soluble in hexane, cyclohexane and other paraffin and cycloparaffin hydrocarbons; its solubility in xylol is 125 gm/liter (see also Table 46).

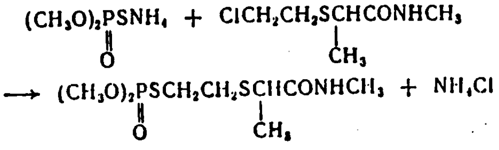
Vamidotion is somewhat more resistant to hydrolysis than methyl-mercaptophos and mercaptophos. Oxidants transform it first into sulfoxide and then into sulfone (290).

The first metabolic product of vamidotion in plants is sulfoxide. Simultaneously with oxidation in plants, the preparation undergoes hydrolysis to form dimethylphosphoric and phosphoric acid.

The LD_{50} of vamidotion is (mg/kg): 64-100 in rats, 43-68 in mice and 85 in guinea pigs.

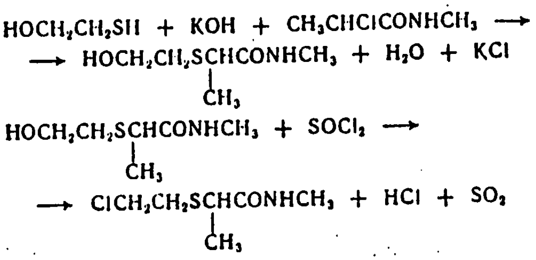
The insecticidal activity of vamidotion is close to that of methyl-mercaptophos, but it is significantly superior to the latter in the time of its action.

Vamidotion is obtained by reacting ammonium or alkali metal dimethylthiophosphate with α-(2-haloethylmercapto)-propiomethylamide:



$$(CH_3O)_2\underset{\underset{O}{\|}}{P}SNH_4 + ClCH_2CH_2S\underset{\underset{CH_3}{|}}{CH}CONHCH_3 \longrightarrow (CH_3O)_2\underset{\underset{O}{\|}}{P}SCH_2CH_2S\underset{\underset{CH_3}{|}}{CH}CONHCH_3 + NH_4Cl$$

The greatest difficulties are encountered in obtaining α-(2-haloethylmercapto)--propiomethylamide, which is synthesized as follows:



$$HOCH_2CH_2SH + KOH + CH_3CHClCONHCH_3 \longrightarrow HOCH_2CH_2S\underset{\underset{CH_3}{|}}{CH}CONHCH_3 + H_2O + KCl$$

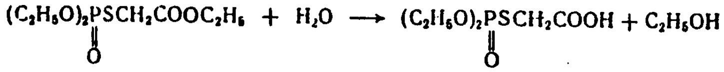
$$HOCH_2CH_2S\underset{\underset{CH_3}{|}}{CH}CONHCH_3 + SOCl_2 \longrightarrow ClCH_2CH_2S\underset{\underset{CH_3}{|}}{CH}CONHCH_3 + HCl + SO_2$$

Other ways of synthesizing this compound are possible as well.

Compounds containing an ester group in one of the ester radicals have also been suggested as insecticides. The preparations atsetofos and metilatsetofos are examples of such compounds.

O,O-diethyl-S-(carbethoxymethyl)-thiophosphate (atsetofos) is a colorless liquid with a specific unpleasant odor; its boiling point is 120°C at 0.15 mm Hg; its vapor pressure at 20°C is about $7.5 \cdot 10^{-4}$ mm Hg; d_4^{20} 1.1840. It is freely soluble in water and in most organic solvents (see also Table 46).

When the compound reacts with water in acid and alkaline media, it undergoes hydrolysis, with ester groups splitting off. Decomposition of this type of compound proceeds differently in homeothermic animals and insects, owing to which it is less toxic to mammals while exhibiting high insecticidal activity. According to O'Brien's data, hydrolysis of the compound in homeothermic animals proceeds as



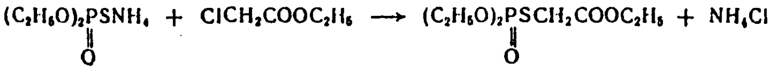
$$(C_2H_5O)_2\underset{\underset{O}{\|}}{P}SCH_2COOC_2H_5 + H_2O \longrightarrow (C_2H_5O)_2\underset{\underset{O}{\|}}{P}SCH_2COOH + C_2H_5OH$$

while in insects an acetic acid residue is split off and vitally important enzymes are inhibited.

The compound's LD_{50} in various animals is 300-700 mg/kg.

Atsetofos is a contact insecticide, but its activity is close to that of chlorophos.

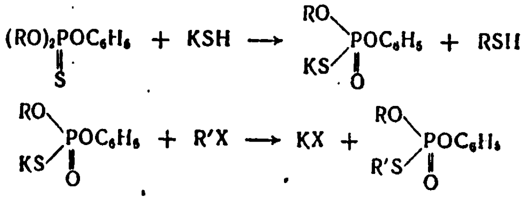
It is obtained by reacting ethyl monochloroacetate with the ammonium salt of diethylthiophosphoric acid in a suitable organic solvent (benzene for example):



$$(C_2H_5O)_2\underset{\underset{O}{\|}}{P}SNH_4 + ClCH_2COOC_2H_5 \longrightarrow (C_2H_5O)_2\underset{\underset{O}{\|}}{P}SCH_2COOC_2H_5 + NH_4Cl$$

The yield of the target product in this reaction is close to 90 percent.

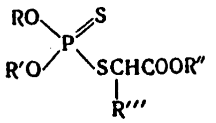
As was noted earlier, mixed esters of thiophosphoric acid containing one aromatic and two different aliphatic radicals have recently been proposed as active insecticides and nematocides. An interesting method of obtaining these compounds is to react O-aryl-O,O-dialkylthioposphates with alkali metal hydrosulfide and alkylhalide (173):



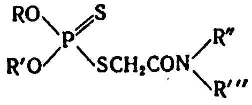
Dithiophosphoric Acid Derivatives

Besides thiophosphoric acid derivatives, dithiophosphoric and trithiophosphoric acid derivatives also enjoy extensive use as pesticides. Among derivatives of dithiophosphoric acid, preparations used to control plant pests have the greatest significance, and it is only recently that fungicides and herbicides have been found among them.

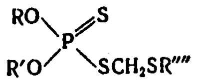
The general formulas of known pesticidal derivatives of dithiophosphoric acid are shown below:



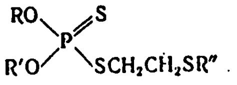
XII



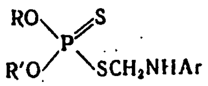
XIII



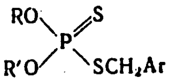
XIV



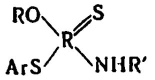
XV



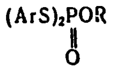
XVI



XVII



XVIII



$(ArS)_2P(=O)OR$

XIX

where R, R' and R''--lower aliphatic radicals, R'''--hydrogen or some radical , Ar--aromatic or heterocyclic radical, R''''--aliphatic or aromatic radical.

As we proceed from derivatives of thiophosphoric acid to the corresponding derivatives of dithiophosphoric acid, in most cases the toxicity of the compound decreases and its chemical stability increases. Owing to this its life in the field grows somewhat. Moreover the range of action of the preparations changes as well. Many dithiophosphoric acid derivatives, especially those containing heterocyclic radicals, exhibit high activity not only against sucking plant pests but also against gnawing insects.

The following laws governing the dependence between biological activity and structure can be stated for the series of compounds with general formula XII:

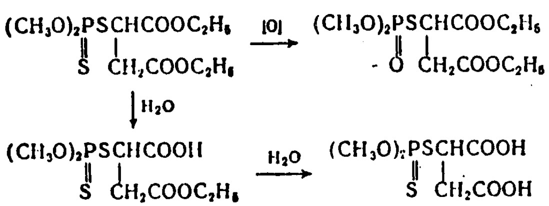
1. All dithiophosphoric acid derivatives with this structure are less toxic to vertebrates than are the corresponding derivatives of thiophosphoric and phosphoric acids.

2. Mixed esters in which R and R' are methyl radicals are least toxic to vertebrates. An increase in the number of carbon atoms in these radicals increases the toxicity of the compounds to vertebrates without increasing their insecticidal activity.

Change in R''' has a less significant influence on the toxicity of mixed dithiophosphates to vertebrates, but it has a significant effect on insecticidal and acaricidal properties. Compounds in which R''' is an aromatic residue exhibit the highest activity.

Introduction of a carbalkoxyl group into R''' greatly reduces the compound's toxicity to vertebrates and has almost no effect on insecticidal and acaricidal properties. This is valid for aliphatic derivatives, but not aromatic derivatives.

The great difference in the toxicity of this group of mixed esters of dithiophosphoric acid to insects and vertebrates can be explained by differences in the pathways by which the preparations are metabolized in animals. Thus for example, in the insect body carbofos transforms into a more-toxic ester of thiophosphoric acid--0,0-dimethyl-S-(1,2-dicarbethoxyethyl)-thiophosphate, while in homeothermic animals the ester residue undergoes saponification (at the carboxyl group) to produce a compound that is practically nontoxic to animals (2,291):



Compounds with general formula XIII usually have not only contact but also systemic insecticidal action.

Compounds with general formula XIII in which $R = R' = CH_3$ exhibit high insecticidal activity and moderate toxicity to mammals. Substitution of just one methyl group by an ethyl or other group containing a large number of carbon atoms sharply increases the compound's toxicity to mammals without significantly changing its insecticidal activity. Thus for example, the LD_{50} of 0,0-dimethyl-S-(N-methylcarbamoylmethyl)-dithiophosphate in rats is 250 mg/kg, while that of 0-methyl-0-ethyl-S-(N--methylcarbamoylmethyl)-dithiophosphate is 12 mg/kg.

Substitution of the methyl radical in the amide group by an ethyl radical does not significantly change the compound's toxicity to homeothermic animals, but enlarging the number of carbon atoms in the hydrocarbon radical at the nitrogen atom reduces the compound's insecticidal activity. Substitution of the second hydrogen atom at the nitrogen atom by hydrocarbon radicals also reduces the preparation's insecticidal activity. When this hydrogen atom is substituted by a carbalkoxyl or formyl residue, the compound's activity against insects does not decrease, but its toxicity to mammals grows significantly. However, there are exceptions to this general rule (297,298).

Addition of a carboxyl or a carbamoyl group to the hydrocarbon radical at the nitrogen atom produces acaricides and insecticides with highly selective action that are moderately toxic to homeothermic animals (292,293). Compounds obtained by joining dialkyldithiophosphoric acids to esters of cysteine (296) and acylated unsaturated amino acids also possess insecticidal properties.

Insecticidal properties also persist when halogen atoms (299), alkyl- and acylamino groups (300), cyano (301,302) and phenyl and carbalkoxy groups (303) are added to the hydrocarbon residue at the nitrogen atom. Substitution of hydrogen at the nitrogen atom by alkylsulfonyl and arylsulfonyl groups (304), sulfonylamido and acylamido groups (305), alkylamino and dialkylamino groups (306-308) and alkyl- and alkoxy groups (309,310) produces substances with sufficiently high acaricidal and insecticidal activity. In the last case, however, phytocidal activity rises somewhat. Phytocidal activity increases especially strongly when one of the alkoxyls at the phosphorus atom is substituted by an aryloxy residue (311). The resulting mixed dithiophosphates have herbicidal action. When an amide group is substituted by a nitrogenous heterocyclic residue, herbicides form as well (312,313).

Mixed esters of ethylene glycol also have insecticidal action (314). O-Alkyl-N-alkyl-(dialkyl)amido-S-N-methylcarbamoylmethyldithiophosphates have not only insecticidal and acaricidal action but also fungicidal properties (315-317).

Compounds with general formula XIII enjoy rather broad use in agriculture as insecticides and acaricides.

Compounds with general formulas XIV and XV possess strong systemic acaricidal and insecticidal action. The basic principles concerning the dependence of insecticidal and acaricidal activity on the structure of these two groups of compounds may be stated as follows:

1. For compounds with general formula XIV, increasing the number of carbon atoms to more than two in all hydrocarbon radicals reduces toxicity to animals and to plant pests. The most toxic compound is the ester in which $R = R' = R'''' = C_2H_5$. Substitution of R'''' by an aromatic radical somewhat decreases toxicity to mammals while maintaining acaricidal and insecticidal properties.

2. Of compounds with general formula XV, those with $R = R' = CH_3$ are the least toxic to mammals. Substitution of one methyl radical by an ethyl or higher hydrocarbon residue sharply increases toxicity and somewhat intensifies insecticidal properties. When the total number of carbon atoms in the R and R′ radicals increases over four, compounds with relatively low insecticidal activity form.

3. When various functional groups are introduced at R″, compounds with high insecticidal and acaricidal activity form (318-321,324). Mixed esters of dithiophosphoric acid containing a carbalkoxyl or carbamide group at the methylene bridge have the highest activity (318-321).

4. The appropriate sulfoxides and sulfones have high insecticidal and acaricidal activity as well (322,323).

5. Compounds in which R″ is a dialkyldithiophosphoric residue also have acaricidal and insecticidal properties (327-329).

6. Substitution of sulfide sulfur by oxygen bound to an aryl group leads in most cases to higher phytocidal activity (330,331). Some compounds of this type have been proposed as herbicides.

7. As we proceed from derivatives of dithiophosphoric acid to derivatives of tri- and tetrathiophosphoric acids, the insecticidal and acaricidal properties diminish while fungicidal and phytocidal activity increases (316,317,332,333).

8. When the carbon residue at the sulfide sulfur is substituted by a carbamic or dialkyldithiocarbamic acid residue, the resulting substances have fungicidal properties (334).

9. When the sulfide sulfur is substituted by an acylamino or an alkylamino group, the resulting substances have varying pesticidal activity (335-347). Mixed dithiophosphates with carboxylic acid residues at the nitrogen atom have insecticidal and acaricidal properties (335-339); alkylamino derivatives also have similar properties (347). If the acyl group is a residue of an aliphatic sulfonic acid residue (340-342), the substance has insecticidal and acaricidal properties. But when an aromatic sulfonic acid residue is introduced, phytocidal activity rises and the substances exhibit herbicidal action. There are indications that O,O-dialkyl-S-hydrazomethyldithiophosphates have not only insecticidal but also nematocidal action (348).

Mixed dithiophosphates containing halogen atoms at one of their aliphatic radicals, for example O,O-dialkyl-S-(1,2,2-trihaloethyldithio)-phosphates and their homologues, are active insecticides (350,353-359). O-Alkyl-S-alkyl-S-aryldithiophosphates are active insecticides and fungicides (349,351,352,360-363), while O,O-dialkyl-S-alkenyldithiophosphates obtained by attaching dialkyldithiophosphoric acids to butadiene and allenes have nematocidal properties (355).

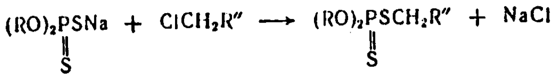
Many amido esters of dithiophosphoric acid have fungicidal properties (163). Active fungicides exhibiting highly selective action include O,O-dialkyl-S-benzyldithiophosphates and especially O-alkyl-S-alkyl-S-benzyldithiophosphates (364-372)--both unsubstituted and containing various substituents in the benzyl radical (367-372), and diamido-S-benzyldithiophosphates (373). O-Alkyl-S,S-diaryldithiophosphates, meanwhile, have fungicidal action (374-378). O-Alkyl-S,S-dialkyldithiophosphates are rather active nematocides (379).

Though a very large number of various derivatives of dithiophosphoric acid with heterocyclic substituents have now been described in the literature, it is still impossible to deduce any sort of laws governing the dependence of the pesticidal activity of the compounds on their structure.

Dithiophosphoric acid derivatives that have achieved practical use against various harmful organisms are shown in Table 47.

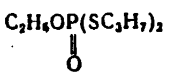
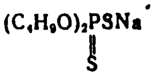
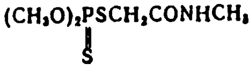
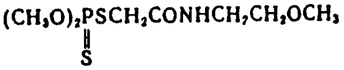
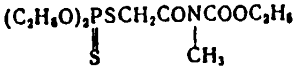
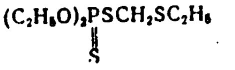
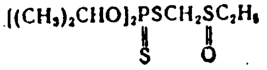
The principal methods of obtaining mixed esters of dithiophosphoric acid are as follows:

1. Reacting dialkyldithiophosphoric acid salts with the appropriate halogen derivatives:



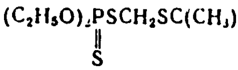
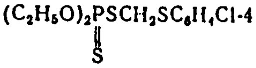
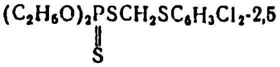
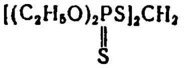
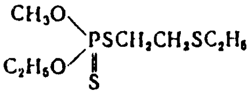
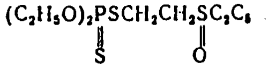
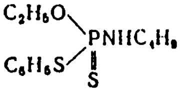
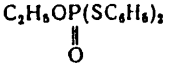
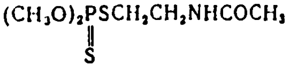
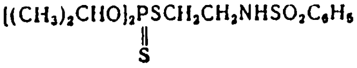
$$(RO)_2\underset{\overset{\|}{S}}{P}SNa + ClCH_2R'' \longrightarrow (RO)_2\underset{\overset{\|}{S}}{P}SCH_2R'' + NaCl$$

Table 47. Dithiophosphoric Acid

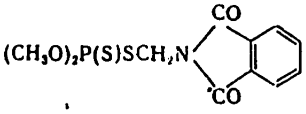
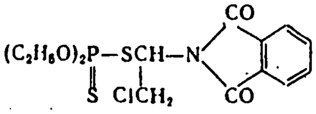
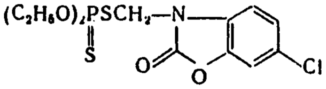
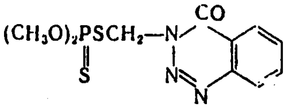
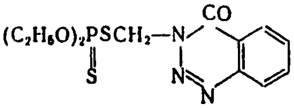
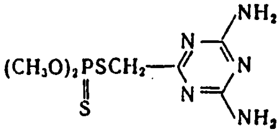
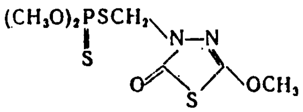
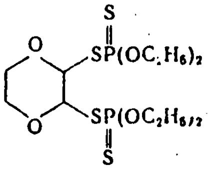
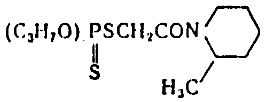
Chemical Name	Formula	Synonyms
O-Ethyl-S-S-dipropyldithiophosphate	 $C_2H_5O\underset{\underset{O}{\|}}{P}(SC_3H_7)_2$	Mokap
Sodium O,O-dibutyldithiophosphate	 $(C_4H_9O)_2\underset{\underset{S}{\|}}{P}SNa$	Defoleks
O,O-Dimethyl-S-(1,2-dicarbethoxyethyl)-dithiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}S\underset{\underset{CH_2COOC_2H_5}{\vert}}{C}HCOOC_2H_5$	Carbofos, melathion, phosphothion
O,O-Dimethyl-S-(N-methylcarbamoylmethyl)-dithiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}SCH_2CONHCH_3$	Phosphamide, dimethoate, rogor, Bi-58, fostion MM, roxion, perfekthion
O,O-Dimethyl-S-(N-ethylcarbamoylmethyl)-dithiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}SCH_2CONHC_2H_5$	Fitios, B/77
O,O-Diethyl-S-(N-isopropylcarbamoylmethyl)-dithiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\|}}{P}SCH_2CONHCH(CH_3)_2$	Protoat, fak-20
O,O-Dimethyl-S [N-β-methoxyethyl)-carbamoylmethyl]-dithiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}SCH_2CONHCH_2CH_2OCH_3$	Tiokron, amidotion
O,O-Dimethyl-S-(morpholidocarbomethyl)-dithiophosphate		Morfotion, ekatin-F, ekatin-M
O,O-Dimethyl-S-(N-methyl-N-formylcarbamoylmethyl)-dithiophosphate	 $(CH_3O)_2\underset{\underset{S}{\|}}{P}SCH_2CO\underset{\underset{CH_3}{\vert}}{N}CHO$	Formothion, anthio
O,O-Diethyl-S-(N-methyl-N-carbethoxycarbamoylmethyl)-dithiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\|}}{P}SCH_2CO\underset{\underset{CH_3}{\vert}}{N}COOC_2H_5$	Mekarbam, murfotoks
O,O-Diethyl-S-ethylmercaptomethyldithiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\|}}{P}SCH_2SC_2H_5$	Thimet, phorate
O,O-Diisopropyl-S-ethylsulfinylmethyldithiophosphate	 $[(CH_3)_2CHO]_2\underset{\underset{S}{\|}}{P}SCH_2\underset{\underset{O}{\|}}{S}C_2H_5$	Afidan

Derivatives Used as Pesticides

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point °C	Solubility Water, mg/liter	$\frac{\text{LD}_{50} \text{ in Rats (Orally) mg/kg}}{\text{LD}_{50} \text{ in Rabbits [Cutaneously), mg/kg}}$	Use. Forms of Application and Consumption Norms
86—91 (0,2)	—	Poor	61,5	Nematocide and soil insecticide. E.c., granules.
—	—	Good	1000	Defoliant, dessicant. 40% aqueous solution; 10-15 kg/ha.
120 (0,2)	2,8—3,7	145	$\frac{1375}{4100}$	Insecticide and acaricide with broad spectrum of action. E.c., 90% preparation for ultralow volume spraying; 1 kg/ha.
107 (0,05)	51—52	3900	$\frac{250}{600}$	Insecticide and acaricide with broad spectrum of action, has systemic action, e.c.; 0.3-1 kg/ha.
—	67—68	8500	350	Analogous with phosphamide.
135 (0,01)	28,5	2500	$\frac{8,9}{650}$	Insecticide and acaricide with systemic action. E.c., w.p; 0.3-1 kg/ha.
—	46	2%	600—660	Insecticide and acaricide with systemic action. E.c.; 0.5-1 kg/ha.
—	63—64	0,5%	190	Contact and systemic insecticide and acaricide. E.c.; 0.5-1 kg/ha.
—	25—26	0,1%	$\frac{375}{400-1600}$	Insecticide and acaricide with systemic action. E.c.; 0.5-1 kg/ha.
144 (0,02)	9	1000	36—39	Insecticide and acaricide. 40% e.c.; 0.1-0.2 kg/ha.
100 (0,4)	—	50	1,1—2,3	Systemic insecticide for soil introduction. 25% e.c., powder made with activated charcoal.
Liquid	—	1700	84	Insecticide against soil pests. 5% granules.

Chemical Name	Formula	Synonyms
O,O-Diethyl-S-(*tert*-butylmercaptomethyl)-dithiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\Vert}}{P}SCH_2SC(CH_3)_3$	AC-92100
O,O-Dimethyl-S-(4-chlorophenylmercaptomethyl)-dithiophosphate	 $(CH_3O)_2\underset{\underset{S}{\Vert}}{P}SCH_2SC_6H_4Cl\text{-}4$	Metiltrition
O,O-Diethyl-S-(4-chlorophenylmercaptomethyl)-dithiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\Vert}}{P}SCH_2SC_6H_4Cl\text{-}4$	Trithion, carbophenothion
O,O-Diethyl-S-(2,5-dichlorophenylmercaptomethyl)-dithiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\Vert}}{P}SCH_2SC_6H_3Cl_2\text{-}2,5$	Fenkapton
Methylene-bis-S,S-[O,O-diethyldithiophosphate]	 $[(C_2H_5O)_2\underset{\underset{S}{\Vert}}{P}S]_2CH_2$	Ethion, nialate, diethion, metion, etikon
O,O-Dimethyl-S-(2-ethylmercaptoethyl)-dithiophosphate	 $(CH_3O)_2\underset{\underset{S}{\Vert}}{P}SCH_2CH_2SC_2H_5$	Tiometon, ekatin, intration, M-81, ekavit
O,O-Diethyl-S-(2-ethylmercaptoethyl)-dithiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\Vert}}{P}SCH_2CH_2SC_2H_5$	Di-syston, disulfoton, M-74
O-Methyl-O-ethyl-S-(2-ethylmercaptoethyl)-dithiophosphate	 $\begin{matrix}CH_3O\diagdown \\ C_2H_5O\diagup\end{matrix}\underset{\underset{S}{\Vert}}{P}SCH_2CH_2SC_2H_5$	Teration
O,O-Diethyl-S-(2-ethylsulfinylethyl)-dithiophosphate	 $(C_2H_5O)_2\underset{\underset{S}{\Vert}}{P}SCH_2CH_2\underset{\underset{O}{\Vert}}{S}C_2C_6$	Di-syston-S, di-syston sulfoxide
O,O-Dimethyl-S-(α-carbethoxybenzyl)-dithiophosphate	 $(CH_3O)_2\underset{\underset{S}{\Vert}}{P}S\underset{\underset{C_6H_5}{\vert}}{C}HCOOC_2H_5$	Tsidial, paption, elsan, fentoat
O-Ethyl-N-butylamido-S-phenyldithiophosphate	 $\begin{matrix}C_2H_5O\diagdown \\ C_6H_5S\diagup\end{matrix}\underset{\underset{S}{\Vert}}{P}NHC_4H_9$	Fosbutil
O-Ethyl-S,S-diphenyldithiophosphate	 $C_2H_5O\underset{\underset{O}{\Vert}}{P}(SC_6H_5)_2$	Khinozan, edifenfos
O,O-Dimethyl-S-(2-acetamidoethyl)-dithiophosphate	 $(CH_3O)_2\underset{\underset{S}{\Vert}}{P}SCH_2CH_2NHCOCH_3$	Aminfos
O,O-Diisopropyl-S-(2-benzosulfamidoethyl)-dithiophosphate	 $[(CH_3)_2CHO]_2\underset{\underset{S}{\Vert}}{P}SCH_2CH_2NHSO_2C_6H_5$	Bensulid, betazan, prefar

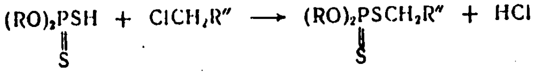
Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility Water, mg/liter	$\frac{LD_{50} \text{ in Rats (Orally) mg/kg}}{LD_{50} \text{ in Rabbits (Cutaneously), mg/kg}}$	Use. Forms of Application and Consumption Norms
69 (0,01)	—	1200	$\frac{1,6}{1-2}$	Insecticide controlling soil pests. 5% granules.
125 (0,01)	—	1	180	Contact insecticide and acaricide. E.c., 25% w.p.
130 (1)	—	2	10—30	Contact insecticide and acaricide. E.c., 25% w.p.; 0.5-1 kg/ha.
120 (0,001)	—	Insoluble	200—260	Acaracide. E.c., 20% w.p.; 0.25-1 kg/ha.
164—165 (0,3)	—	2	55	Acaracide and insecticide. E.c., w.p.; 0.5-1 kg/ha.
104 (0,3)	—	200	85	Systemic acaricide and insecticide. 50% e.c., granules made with activated charcoal.
128 (1)	—	25	$\frac{2,6-12,5}{41}$	Systemic insecticide and acaricide. E.c., granules; 0.2-1 kg/ha.
—	—	30	1,2—22,3	Systemic acaricide and insecticide controlling mites on hops. Preparation is introduced into soil.
Decomposes	—	100	$\frac{3,6}{90}$	Systemic insecticide and acaricide. E.c., granules; 0.5-1 kg/ha.
70—80 ($2{,}5 \cdot 10^{-5}$)	17,5	11	200—300	Insecticide with broad spectrum of action. E.c., granules.
150—151 (0,3)	—	200	300	Fungicide. E.c. 1-2 kg/ha.
154 (0,01)	—	Insoluble	150—340	Fungicide controlling (pirikulyariya) in rice. E.c.; 1-3 kg/ha.
—	22—23	Poor	405	Systemic insecticide and acaricide. 40% e.c.; 0.5-1 kg/ha.
Liquid	—	25	1900	Herbicide controlling annual weeds. E.c., granules; 6-15 kg/ha.

Chemical Name	Formula	Synonyms
O,O-Dimethyl-S-phthalimidomethyldithiophosphate		Phthalophos, imidan
O,O-Diethyl-S-(2-chloro-1-phthalimidoethyl)-dithiophosphate		Dialifor, torak
O,O-Diethyl-S-(6-chlorobenzoxazolinon-2-yl-3-methyl)-dithiophosphate		Phosalone, zolone, rubitoks, benzofosfat
O,O-Dimethyl-S-(3,4-dihydro-4-oxo-5,6-benzo-1,2,3-triazinyl-3-methyl)-dithiophosphate		Gusathion, guthion, azinphos-methyl
O,O-Diethyl-S-(3,4-dihydro-4-oxo-5,6-benzo-1,2,3,-triazinyl-3-methyl)-dithiophosphate		Azinfos, guzation-Kh, gution-K
O,O-Dimethyl-S-4,6-diamino-1,3,5-triazinyl-2-methyl)-dithiophosphate		Menazon, sayfos, saphizon, azidition
O,O-Dimethyl-S-(2-methoxy-1,3,4-thiadiazolon-5-yl-4-methyl)-dithiophosphate		Methidathion, ultracid, supracide
2,3-Bis-O,O-diethyldithiophosphoryl)-dioxane-1,4		Delnav, sikaden, rufos, kvimafos, dioxathion, navadel
O,O-Di-(*n*-propyl)-S-(2-methylpiperidyl-1-carbomethyl)-dithiophosphate		S-19490

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility Water, mg/liter	$\frac{LD_{50}\text{ in Rats (Orally) mg/kg}}{LD_{50}\text{ in Rabbits (Cutaneous), mg/kg}}$	Use. Forms of Application and Consumption Norms
—	72–73	25	$\frac{40\text{–}200}{3100}$	Insecticide with broad spectrum of action. E.c., w.p.; 0.5-1 kg/ha.
—	61–62	1	$\frac{43\text{–}71}{146}$	Insecticide and acaricide with broad spectrum of action. 46% e.c.; 0.5-1 kg/ha.
—	47–48	10	$\frac{135}{390}$	Insecticide with broad spectrum of action. E.c., w.p.; 0.5-1 kg/ha.
—	73–74	30	$\frac{11\text{–}20}{88\text{–}200}$	Insecticide and acaricide with broad spectrum of action. E.c., w.p.; 0.1-0.5 kg/ha.
111 (0,001)	53	—	$\frac{12{,}5\text{–}17{,}5}{250\text{ (in 2 hr)}}$	Broad-spectrum insecticide and acaricide. E.c., w.p.; 0.1-0.5 kg/ha.
—	160–162	0,1%	900	Insecticide with systemic action against aphids. W.p., granules; 0.5-1 kg/ha.
—	39–40	0,1%	$\frac{25\text{–}48}{150}$	Insecticide and acaricide with broad spectrum of action. 40% e.c.; 0.5-1 kg/ha.
Liquid (*cis* isomer)	80–81 (*trans* isomer)	Insoluble	23–43	Contact insecticide and acaricide. E.c., w.p.; up to 1 kg/ha.
—	—	50	410	Selective herbicide controlling weeds growing with rice.

This reaction produces a good yield of O,O-dialkyl-S-benzyldithiophosphates (364-372, 380), dioxydihydrothienylmethyl-O,O-dialkyldithiophosphates (381), O,O-dialkyl-S-thienylsulfonyldithiophosphates (382), O,O-dialkyl-S-phthalimidoalkyldithiophosphates (383-386), O,O-dialkyl-S-benzoxazolinyl-2-methyldithiophosphates (388-392), O,O-dialkyl-S-pyridylalkyldithiophosphates (387), O,O-dialkyl-S-benzoxazolinyl-2-chloroethyldithiophosphates (393), O,O-dialkyl-S-(2-oxopyridyl-1-methyl)-dithiophosphates (394), O,O-dialkyl-S-carbamidomethyldithiophosphates (395-399), O,O-dialkyl-S-(1,2-oxazolyl-2-methyl)-dithiophosphates (400), O,O-dialkyl-S-oxadiazolylmethyldithiophosphates (401,402), O,O-dialkyl-S-thiadiazolyl-3-methyldithiophosphates (403), O,O-dialkyl-S-triazinyldithiophosphates, O,O-dialkyl-S-triazinylmethyldithiophosphates (405) and a number of other heterocyclic compounds (406-414).

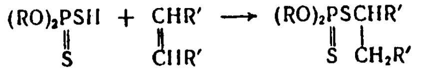
In some cases not only salts but also free acids can be used. In this case the process is slower, and it requires a higher temperature:



$$(RO)_2\underset{\underset{S}{\|}}{P}SH + ClCH_2R'' \longrightarrow (RO)_2\underset{\underset{S}{\|}}{P}SCH_2R'' + HCl$$

The reaction with salts is usually performed in an aqueous medium or in organic solvents, while the reaction with acids is performed without solvents.

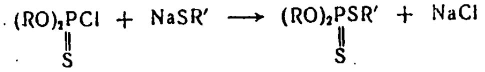
2. Attachment of dialkyldithiophosphoric acids to unsaturated compounds:



$$(RO)_2\underset{\underset{S}{\|}}{P}SH + \underset{\underset{CHR'}{\|}}{CHR'} \longrightarrow (RO)_2\underset{\underset{S}{\|}}{P}S\underset{\underset{CH_2R'}{|}}{C}HR'$$

This reaction can be used to obtain mixed dithiophosphates of the most diverse types (294,295,352,355,357,415-419), to include those containing heterocyclic radicals (419). The reaction is usually performed without solvent or in an apolar solvent. Sometimes excess reagent, to which dialkyldithiophosphoric acids join, is used as the solvent.

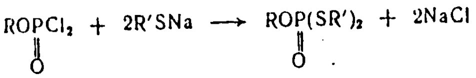
3. Interaction between dialkylchlorothiophosphates and the appropriate thiols:



$$(RO)_2\underset{\underset{S}{\|}}{P}Cl + NaSR' \longrightarrow (RO)_2\underset{\underset{S}{\|}}{P}SR' + NaCl$$

This reaction proceeds readily in the presence of hydrogen chloride acceptors. Both caustic alkali and various organic bases can be used for this purpose.

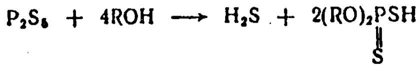
4. Interaction between alkylphosphoric acid dichlorides and mercaptans in the presence of hydrogen chloride acceptors (374-375):



$$RO\underset{\underset{O}{\|}}{P}Cl_2 + 2R'SNa \longrightarrow RO\underset{\underset{O}{\|}}{P}(SR')_2 + 2NaCl$$

The reaction between diphenyldisulfide and metallic sodium in the presence of alkyldichlorophosphate may be used to obtain O-alkyl-S,S-diphenyldithiophosphates.

The dialkyldithiophosphoric acids required for synthesis of mixed dithiophosphates can be obtained with a good yield by reacting phosphorus pentasulfide with alcohols:



$$P_2S_5 + 4ROH \longrightarrow H_2S + 2(RO)_2\underset{\overset{\|}{S}}{P}SH$$

Trialkyldithiophosphate is formed in small quantities as a byproduct.

The purity of the initial phosphorus pentasulfide is highly significant to synthesis of dialkyldithiophosphoric acids, since impurities increase the amount of byproducts, removal of which presents significant difficulties. Usually, phosphorus pentasulfide is obtained directly by reacting equimolar quantities of sulfur and yellow phosphorus at high temperature. When sufficiently pure initial substances are used, technical-grade phosphorus pentasulfide does not require further purification. When P_2S_5 must be purified, it is either crystallized out of carbon disulfide or it is subjected to vacuum distillation.

The basic flowchart for producing dialkyldithiophosphoric acids out of phosphorus pentasulfide and alcohol is shown in Figure 18 (420).

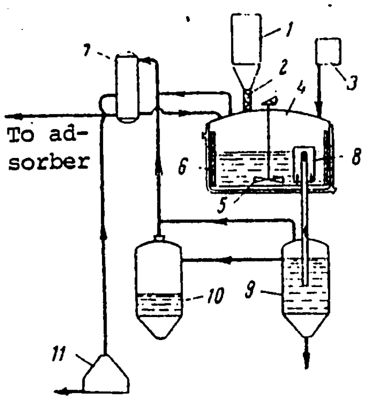
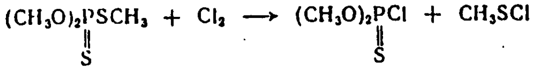


Figure 18. Basic Flowchart for Dialkyldithiophosphoric Acid Production: *1*--P_2S_5 hopper; *2*--worm feeder; *3*--alcohol gaging tank; *4*--reactor; *5*--agitator; *6*--blade for additional mixing; *7*--gas cooler; *8*--valve; *9*--separator; *10*--receiver; *11*--finished product collector

Most dialkyldithiophosphates obtained by this method are sufficiently pure; however, owing to its high alkylating capacity dimethyldithiophosphoric acid contains rather sizeable quantities of trimethyldithiophosphate. Trimethyldithiophosphate may be separated away either by distillation with live steam or by conversion of dimethyldithiophosphoric acid into a sodium or other salt, followed by separation of trimethyldithiophosphate by extraction with hydrophobic organic solvents (toluol, xylol etc.). Free acid is separated by the action of table salt upon concentrated sulfuric acid (421). This purification method can produce 95-100 percent dimethyldithiophosphoric acid.

The resulting trimethyldithiophosphate may be used to make dimethylchlorothiophosphate:



$$(CH_3O)_2\underset{\overset{\|}{S}}{P}SCH_3 + Cl_2 \longrightarrow (CH_3O)_2\underset{\overset{\|}{S}}{P}Cl + CH_3SCl$$

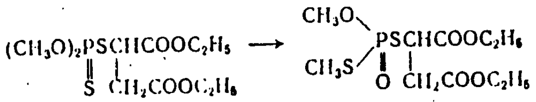
Dimethylchlorothiophosphate contains, as an impurity, a certain quantity of isomeric O-methyl-S-methylchlorothiophosphate.

The most important representatives of these types of compounds are presented below.

O,O-Dimethyl-S-(1,2-dicarbethoxyethyl)-dithiophosphate (carbofos, malathion) is a colorless liquid; d_4^{25} 1.23, n_D^{25} 1.4985; vapor pressure at 20°C is $1.25 \cdot 10^{-4}$ mm Hg; volatility is 2.26 mg/m^3. Carbofos is freely soluble in most organic solvents, with the exception of saturated hydrocarbons (see also Table 47).

The LD$_{50}$ in various experimental animals is 500-1,500 mg/kg. The maximum permissible concentration is air is 0.5 mg/m^3.

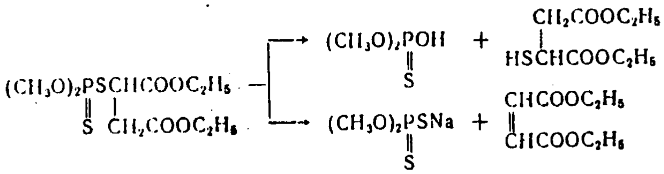
When heated for a long period of time at 150°C carbofos undergoes isomerization, transforming into the appropriate thiol isomer:



$$(CH_3O)_2\underset{\overset{\|}{S}}{P}S\underset{\overset{|}{CH_2COOC_2H_5}}{CH}COOC_2H_5 \longrightarrow \begin{matrix} CH_3O \\ CH_3S \end{matrix}\!\!>\!\underset{\overset{\|}{O}}{P}S\underset{\overset{|}{CH_2COOC_2H_5}}{CH}COOC_2H_5$$

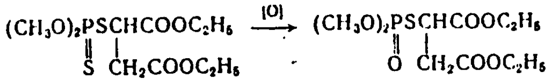
At higher temperature this reaction proceeds violently, and a significant part of the product breaks down, sometimes even with an explosion. When impurities such as trimethyldithiophosphate, dimethyldithiophosphoric acid and some others are present in the preparation, intense decomposition of carbofos may occur even at lower temperature.

Hydrolysis of carbofos in acid and alkali media proceeds in different ways. While in an acid medium the main hydrolysis products are dimethyldithiophosphoric acid and mercaptosuccinate, in alkaline medium dimethyldithiophosphoric acid salts and a fumaric acid ester form:



The reaction is used for quantitative polarographic determination of carbofos.

When carbofos is oxidized by nitric acid or other strong oxidants, the thionic sulfur atom splits off, and the corresponding thiolphosphoric ester forms:



$$(CH_3O)_2\underset{\underset{S}{\|}}{P}S\underset{\underset{CH_2COOC_2H_5}{|}}{C}HCOOC_2H_5 \xrightarrow{[O]} (CH_3O)_2\underset{\underset{O}{\|}}{P}S\underset{\underset{CH_2COOC_2H_5}{|}}{C}HCOOC_2H_5$$

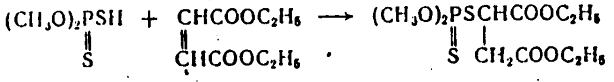
When allowed to remain in prolonged contact with iron or materials containing iron, carbofos breaks down and loses its insecticidal properties completely. In this connection it cannot be stored in iron containers. It is preserved best in glass containers.

The preparation is marketed as an emulsion concentrate containing 30-60 percent active ingredient, an emulsifier and a solvent. Xylol is used as the solvent.

The preparation is made for ultralow volume spraying as a 90-96 percent concentrate containing only an insignificant quantity of additives.

Carbofos can also be used in the form of dusts or suspensions obtained from wettable powder. Usually carbofos is used in agriculture at a 0.2-0.25 percent concentration (active ingredient). Residual quantities of carbofos have been established in the USSR at not more than 8 mg/kg.

The main method of obtaining carbofos is to attach dimethyldithiophosphoric acid to maleic acid ester. The reaction proceeds very readily in the presence of basic catalysts, both in various organic solvents and without them:



$$(CH_3O)_2\underset{\underset{S}{\|}}{P}SH + \underset{\underset{CHCOOC_2H_5}{\|}}{C}HCOOC_2H_5 \longrightarrow (CH_3O)_2\underset{\underset{S}{\|}}{P}S\underset{\underset{CH_2COOC_2H_5}{|}}{C}HCOOC_2H_5$$

This reaction may be combined with that of obtaining dimethyldithiophosphoric acid from methanol and phosphorus pentasulfide. This process is performed in a diethylmaleate medium. However sometimes the reaction (in the combined method) proceeds so violently that the product undergoes spontaneous decomposition.

Technical-grade carbofos obtained by this method contains small quantities of trimethyldithiophosphate, diethylmaleate and solvent. Xylol is usually used as the solvent for carbofos synthesis. The carbofos yield with this reaction is more than 80 percent of theoretical, but when condensation is combined with acquisition of dimethyldithiophosphoric acid, the yield is somewhat lower.

The basic flowchart of obtaining carbofos by this method is shown in Figure 19.

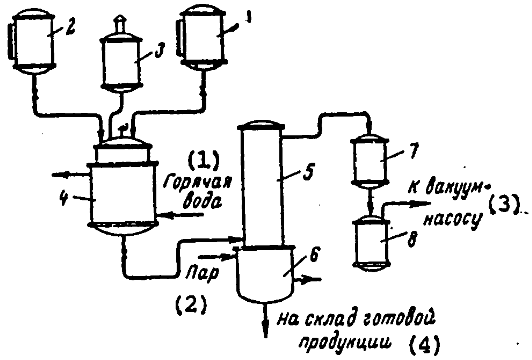
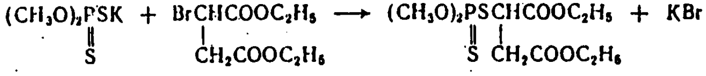


Figure 19. Basic Flowchart for Production of Carbofos: *1*--gaging tank for dimethyldithiophosphoric acid; *2*--gaging tank for diethylmaleate; *3*--cooler; *4*--reactor; *5*--methanol distillation column; *6*--heating zone; *7*--cooler; *8*--methanol collector

Key:

1. Hot water
2. Steam
3. To vacuum pump
4. To finished product storage

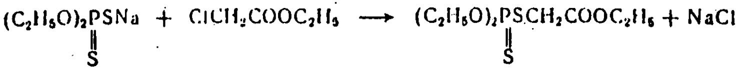
Carbofos can also be obtained by prolonged boiling of a solution of sodium or potassium salts of dimethyldithiophosphoric acid and diethylsuccinate in alcohol or another polar solvent, but this method is more complex, and it is rarely used in practice:



$$(CH_3O)_2\underset{\substack{\| \\ S}}{P}SK + Br\underset{\substack{| \\ CH_2COOC_2H_6}}{C}HCOOC_2H_5 \longrightarrow (CH_3O)_2\underset{\substack{\| \\ S}}{P}S\underset{\substack{| \\ CH_2COOC_2H_6}}{C}HCOOC_2H_5 + KBr$$

Volatile impurities, including trimethyldithiophosphates, can be removed from carbofos by distillation with live steam (422), while excess dimethyldithiophosphoric acid can be removed by washing with alkalis (423) or with sodium sulfide solution (424). Unreacted diethylmaleate is hydrolyzed (423). The unpleasant odor is removed by oxidizing the preparation with oxygen in the presence of heavy metals (425), or cumyl hydroxide is added (426-428). It should be noted that when carbofos is allowed to stand for a long period of time, the unpleasant odor returns.

A large number of analogues and homologues of carbofos have been synthesized and studied, but most of them are highly toxic to animals, owing to which they have not enjoyed much use. O,O-Diethyl-S-(carbethoxymethyl)-dithiophosphate known in the literature as atsetion (boiling point 92°C at 0.01 mm Hg; d_4^{30} 1.176; LD_{50} in rats 1,050-1,100 mg/kg), is of interest as a resource against flies. It is synthesized by reacting ethylmonochloroacetate with sodium diethyldithiophosphate in an aqueous medium while heating for a short period of time:



$$(C_2H_5O)_2\underset{\substack{\| \\ S}}{P}SNa + ClCH_2COOC_2H_5 \longrightarrow (C_2H_5O)_2\underset{\substack{\| \\ S}}{P}SCH_2COOC_2H_6 + NaCl$$

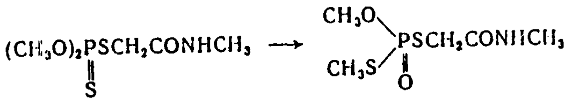
Although it is not in use, this preparation is of connsiderable theoretical interest, since its low toxicity to animals was predicted on the basis of research on the metabolism of organic phosphorus compounds.

When the ester group in the acetic acid residue of atsetion and its homologues is substituted by an amide group, the compound's insecticidal activity rises dramatically; concurrently its toxicity to mammals increases as well. However, the increase in toxicity to mammals is less significant, owing to which many such amides are of significant practical interest, and some of them are used in agriculture. Today seven preparations in this group of substances are in use, and a number of compounds are presently being studied.

O,O-Dimethyl-S-(N-methylcarbamoylmethyl)-dithiophosphate (phosphamide) is a snow-white crystalline substance; vapor pressure at 20°C is $8.5 \cdot 10^{-6}$ mm Hg; volatility is 0.107 mg/m^3. It is freely soluble in water and in most organic solvents, but it is poorly soluble in paraffin hydrocarbons (see also Table 47).

The LD_{50} of pure preparation in rats is 250-265 mg/kg. Technical-grade preparation is more toxic (LD_{50} 150-160 mg/kg) due to presence of impurities, the most important of which is O,O-dimethyl-S,N-methylcarbamoylmethyl)-thiophosphate (LD_{50} in rats 55 mg/kg).

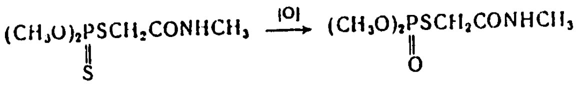
Phosphamide is thermally unstable, and it decomposes when heated, primarily undergoing Pishchemuka isomerization:



$$(CH_3O)_2\underset{\overset{\|}{S}}{P}SCH_2CONHCH_3 \longrightarrow \begin{matrix}CH_3O\\ CH_3S\end{matrix}\!\!>\!\underset{\overset{\|}{O}}{P}SCH_2CONHCH_3$$

The resulting O,S-dimethyl-S-(N-methylcarbamoylmethyl)-dithiophosphate is more toxic to mammals than the initial phosphamide (LD_{50} in rats 100 mg/kg).

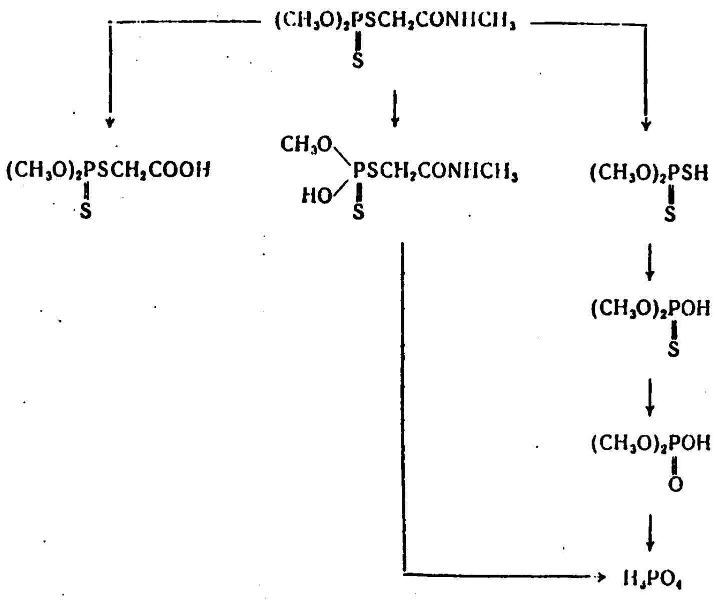
When oxidized by various oxidants or atmospheric oxygen (oxidation by atmospheric oxygen proceeds especially readily on the green leaves of plants), phosphamide transforms into O,O-dimethyl-S-(N-methylcarbamoylmethyl)-thiophosphate:



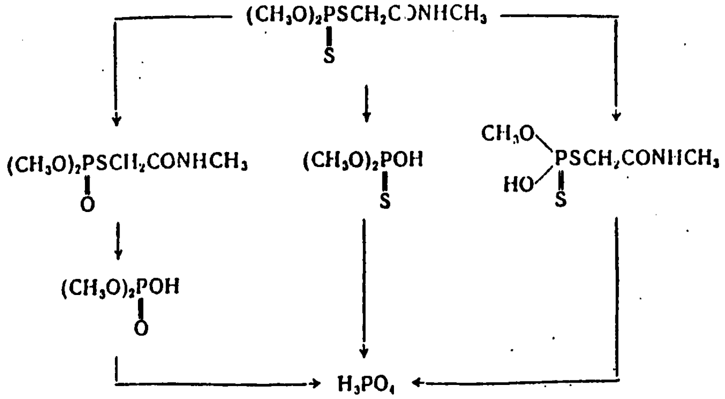
$$(CH_3O)_2\underset{\overset{\|}{S}}{P}SCH_2CONHCH_3 \xrightarrow{[O]} (CH_3O)_2\underset{\overset{\|}{O}}{P}SCH_2CONHCH_3$$

Hydrolysis of phosphamide proceeds most freely in an alkaline medium; in an acid medium it is more stable (at 70°C 50 percent of phosphamide undergoes saponification in 0.8 hours at pH 9 and in 21 hours at pH 2).

Metabolism of phosphamide apparently differs in plants and animals. The following flowchart may be suggested for metabolism in rats and cows on the basis of the products excreted:



The following flowchart may be suggested for plants:



Depending on the consumption norm, the preparation usually breaks down in a plant within 15-20 days. Of course this also depends on the nature of the plant and on the meteorological conditions.

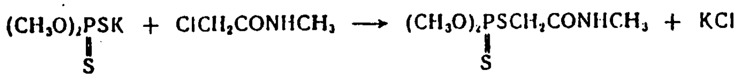
Phosphamide is relatively unstable when stored, and it quickly decomposes, especially at higher temperature. Impurities in phosphamide catalyze its decomposition. Preparation containing traces of organic bases decomposes at a high rate; decomposition of phosphamide in the presence of bases is accompanied by alkylation. Solutions of phosphamide in organic solvents are more stable.

Phosphamide reacts with phenols and alkylphenols to produce molecular compounds that have been proposed for use as insecticides (429-431).

Usually phosphamide is marketed as a 40 percent emulsion concentrate containing, in addition to the active ingredient, an emulsifier and organic solvent. It is used against herbivorous mites, aphids and other sucking plant pests at preparation consumption norms of 700-1,000 gm/ha (active ingredient). At higher concentrations phosphamide is phytocidal.

The preparation's time of action is about 15 days. In many countries its life expectancy is set at 10-15 days.

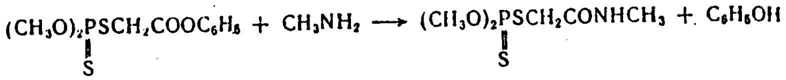
Phosphamide may be obtained by two methods: First, by reacting dimethyldithiophosphoric acid salts with N-methylchloroacetamide:



$$(CH_3O)_2\underset{\underset{S}{\|}}{P}SK + ClCH_2CONHCH_3 \longrightarrow (CH_3O)_2\underset{\underset{S}{\|}}{P}SCH_2CONHCH_3 + KCl$$

This reaction is usually performed in a medium consisting of water and some organic solvents. The product yield is 80-95 percent; the purity of the initial substances has great significance.

Second, phosphamide may be obtained by reacting O,O-dimethyl-S-(carboxymethyl)- or S-(carbalkoxymethyl)-dithiophosphate with hydrated methylamine at low temperature (432):



$$(CH_3O)_2\underset{\underset{S}{\|}}{P}SCH_2COOC_6H_5 + CH_3NH_2 \longrightarrow (CH_3O)_2\underset{\underset{S}{\|}}{P}SCH_2CONHCH_3 + C_6H_5OH$$

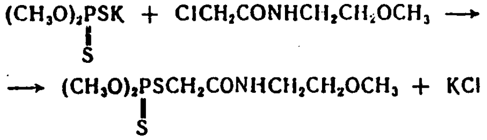
Both the phenyl and the ethyl esters are used. The phosphamide yield is more than 90 percent of theoretical; however, the phosphamide obtained by this method is less stable. Stabilization of the preparation requires very careful removal of all impurities, and primarily excess methylamine, traces of which promote decomposition of phosphamide.

As with most other organophosphorus compounds, storage of phosphamide in iron containers is not recommended. Even stainless steel promotes faster decomposition of stored preparation.

O,O-Dimethyl-S-[N-(β-methoxyethyl)-carbamoylmethyl]-dithiophosphate (tiokron) is crystalline when pure, with a melting point of 46°C. Technical-grade product is a liquid with unpleasant odor that cannot be distilled in a high vacuum. It is moderately soluble in water, and more so in alcohols and esters, while it is poorly soluble in aliphatic hydrocarbons (see also Table 47).

The LD_{50} in rats is 600-660 mg/kg.

Tiokron is similar in chemical properties to phosphamide. Tiokron is synthesized by reacting alkali metal or ammonium dimethyldithiophosphates with monochloroacetic acid methoxyethylamide:



$$(CH_3O)_2\underset{\substack{\|\\S}}{P}SK + ClCH_2CONHCH_2CH_2OCH_3 \longrightarrow$$
$$\longrightarrow (CH_3O)_2\underset{\substack{\|\\S}}{P}SCH_2CONHCH_2CH_2OCH_3 + KCl$$

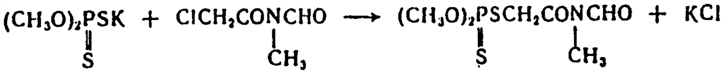
Tiokron is a good contact acaricide and insecticide, having systemic action for 15-20 days. It is marketed in the form of an emulsion concentrate. At the moment the scale of this preparation's use is not great, but it is doubtlessly interesting due to its low toxicity to animals and man. The metabolism of this preparation in plants is apparently similar to metabolism of phosphamide.

O,O-Dimethyl-S-(N-methyl-N-formylcarbamoylmethyl)-dithiophosphate (formothion) is poorly soluble in water and readily soluble in organic solvents; d_4^{26} 1.361 (see also Table 47).

Its LD_{50} in rats is 330 mg/kg.

It is similar in chemical properties to phosphamide, but it is more stable when stored and heated. One of the principal metabolic products in the animal organism is O,O-dimethyl-S-(carboxymethyl)-dithiophosphate, which is subsequently hydrolyzed to dimethylthiophosphoric and phosphoric acids.

Formothion is obtained by reacting dimethyldithiophosphoric acid salts with N-formyl-N-methylchloroacetamide:



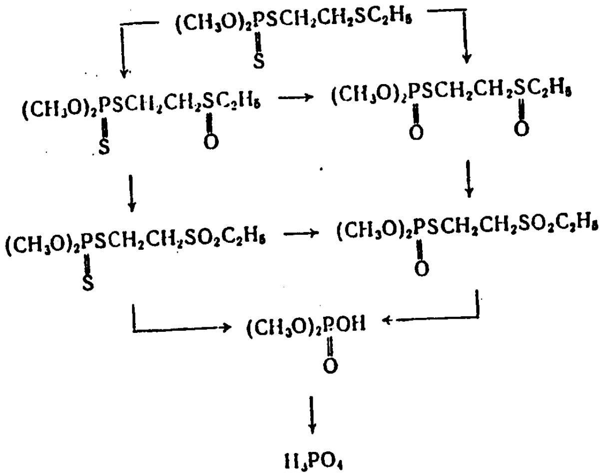
$$(CH_3O)_2\underset{\substack{\|\\S}}{P}SK + ClCH_2CO\underset{\substack{|\\CH_3}}{N}CHO \longrightarrow (CH_3O)_2\underset{\substack{\|\\S}}{P}SCH_2CO\underset{\substack{|\\CH_3}}{N}CHO + KCl$$

It is marketed in the form of a 25 percent emulsion concentrate, and it is used against various sucking and some gnawing plant pests at consumption norms of 0.5-1 kg/ha.

O,O-Dimethyl-S-(2-ethylmercaptoethyl)-dithiophosphate (tiometon, preparation M-81) is a colorless oil with a strong and unpleasant odor; vapor pressure at 20°C is $3 \cdot 10^{-4}$ mm Hg; volatility is 4.0 mg/m^3; d_4^{20} 1.209. It is readily soluble in most organic solvents, with the exception of aliphatic and some alicyclic hydrocarbons (see also Table 47).

At normal temperature M-81 is stable, but it may decompose when heated. The first stage of thermal transformation is Pishchemuka regrouping. It is hydrolyzed with water similarly as with methyl-mercaptophos.

Metabolism of M-81 in plants is diagrammed below:

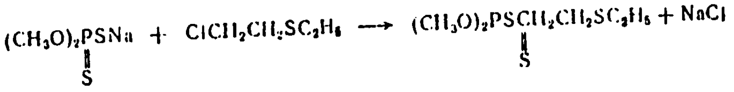


Its LD_{50} in various animals is 70-120 mg/kg. The maximum permissible concentration in air is 0.1 mg/m^3.

M-81 is a good systemic insecticide with approximately the same time of action as methyl-mercaptophos, but its initial contact insecticidal activity is somewhat weaker. It is believed that its contact insecticidal properties manifest themselves following transformation of part of the product into the thiol isomer of methyl-mercaptophos or its metabolites.

Preparation M-81 is produced in the form of emulsion concentrates containing from 20 to 50 percent active ingredients, and in the form of granulated preparation.

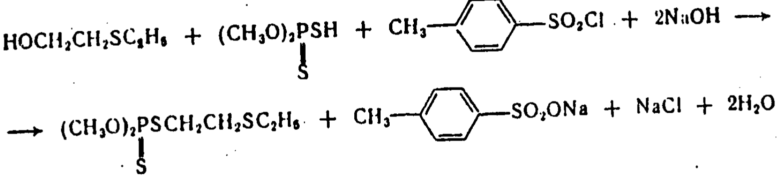
The principal method of obtaining M-81 with a yield of about 90 percent of theoretical is to react dimethyldithiophosphoric acid salts with 2-chlorodiethylsulfide:



$$(CH_3O)_2\underset{\overset{\|}{S}}{P}SNa + ClCH_2CH_2SC_2H_5 \longrightarrow (CH_3O)_2\underset{\overset{\|}{S}}{P}SCH_2CH_2SC_2H_5 + NaCl$$

The process is performed both in an aqueous medium with vigorous agitation and in organic solvents.

M-81 can also be synthesized by reacting 2-oxydiethylsulfide with dimethyldithiophosphoric acid in the presence of sodium hydroxide and *p*-toluol sulfochloride:



However, in this case the yield does not exceed 75-78 percent. It is believed that the 2-oxydiethylsulfide ester of *p*-toluol sulfonic acid is formed as an intermediate product in this process, but it has not yet been isolated in the course of the reaction.

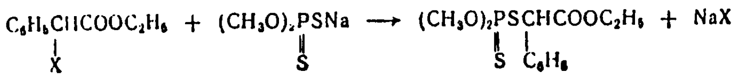
O,O-Dimethyl-S-(α-carbethoxybenzyl)-dithiophosphate (tsidial) is an oily liquid with a characteristic unpleasant odor that decomposes when distilled in a vacuum. It is freely soluble in most organic solvents and poorly soluble in water; d_4^{20} 1.226. Its ignition point is 168-172°C.

Tsidial is thermally unstable, and when heated to 120°C for 110 hours it undergoes almost 50 percent decomposition. At 50°C it withstands 30-day heating without noticeable decomposition (see also Table 47).

Tsidial may manifest insecticidal action for 15-25 days. It is an insecticide with a broad spectrum of action, and it is used against herbiverous mites and sucking insects, as well as against leaf-miners. Tsidial also produces good results against the codling moth.

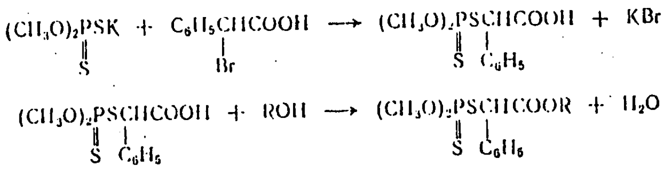
Tsidial is classified as a moderately toxic preparation to mammals: Its LD_{50} in rats is 250-300 mg/kg.

Tsidial is obtained by reacting alkali metal dimethyldithiophosphates with halophenylacetic acid esters (434,435).



$$C_6H_5\underset{X}{C}HCOOC_2H_5 + (CH_3O)_2\underset{S}{\overset{\|}{P}}SNa \longrightarrow (CH_3O)_2\underset{S}{\overset{\|}{P}}S\underset{C_6H_5}{C}HCOOC_2H_5 + NaX$$

This group of compounds may also be obtained with halophenylacetic acid. Subsequent esterification of the obtained product by alcohol would be required (436-438):



$$(CH_3O)_2\underset{S}{P}SK + C_6H_5\underset{Br}{C}HCOOH \longrightarrow (CH_3O)_2\underset{S}{P}S\underset{C_6H_5}{C}HCOOH + KBr$$

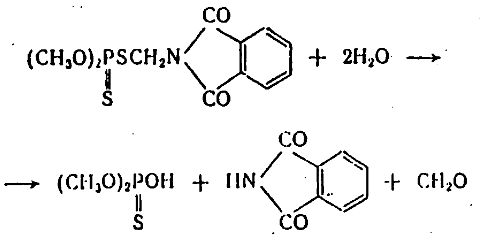
$$(CH_3O)_2\underset{S}{P}S\underset{C_6H_5}{C}HCOOH + ROH \longrightarrow (CH_3O)_2\underset{S}{P}S\underset{C_6H_5}{C}HCOOR + H_2O$$

The reaction is performed in an organic solvent medium at 70-90°C. Esterification may be performed without isolation of the intermediate product. This produces a preparation that does not contain impurities which would raise its toxicity.

O,O-Dimethyl-S-(N-phthalamidomethyl)-dithiophosphate (phthalophos) is a white crystalline substance with a melting point of 72-72.7°C. It is readily soluble in acetone, methylethylketone, cyclohexanone, methylene chloride, xylol and other organic solvents; aliphatic hydrocarbons, in which the preparation is poorly soluble, are an exception (see also Table 47).

Its LD_{50} in experimental animals is 400-200 mg/kg.

In an acid medium phthalophos is resistant to hydrolysis, and at pH 4.5 it hydrolyzes to 50 percent in 15 days in an aqueous solution, while it takes 12 hours at pH 7 and 4 hours at pH 8.3. The end products of hydrolysis are phthalimide, dimethylthiophosphoric acid and formaldehyde:

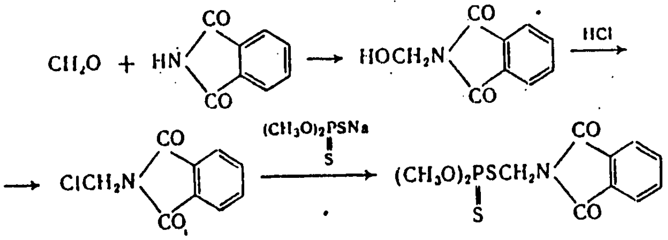


However, these products are subsequently capable of undergoing hydrolysis to phosphoric and phthalic acids.

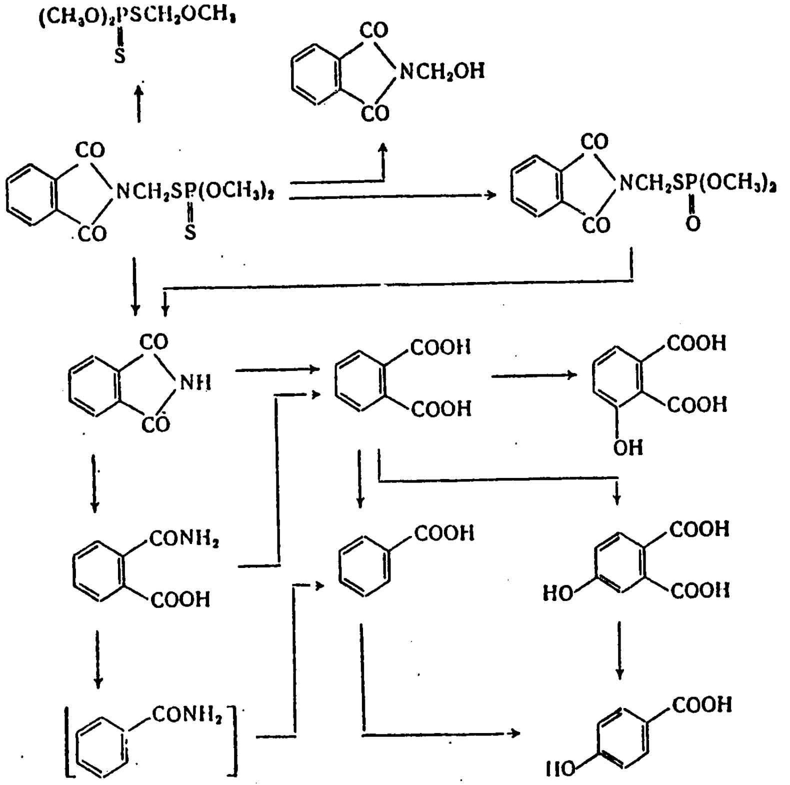
Oxidants also break down the preparation, with oxidation occurring primarily at the sulfur atom.

Phthalophos is marketed in the form of a 20 percent emulsion concentrate, a 50 percent wettable powder and a 10 percent granulated preparation. It is recommended against various pests of cotton, fruits and other crops. Its use against the codling moth instead of DDT is of interest, since it is broken down relatively easily, and it does not leave toxic residues on fruits.

Phthalophos may be obtained as follows (386) (all stages of the process proceed with good yield):



Metabolism of phthalophos in different objects may be generally diagrammed as follows (274):



O,O-Diethyl-S-(6-chlorobenzoxazolinon-2-yl-3-methyl)-dithiophosphate (phosalone) is a white crystalline substance with the odor of garlic. Phosalone is poorly soluble in water and freely soluble in many organic solvents (see also Table 47).

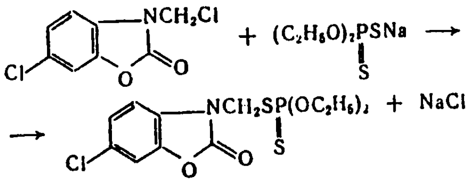
Its LD_{50} in rats is 135 mg/kg, and in mice it is 180 mg/kg.

In an acid medium phosalone is relatively stable, while hydrolysis proceeds rather quickly in an alkaline medium. The principal hydrolysis products are 6-chlorobenzoxazolone, diethylthiophosphoric acid and formaldehyde.

When phosalone reacts with oxidants, first the thion sulfur breaks off and the preparation transforms into O,O-diethyl-S-(6-chlorobenzoxazolon-2-yl-3-methyl)-thiophosphate, which is relatively unstable and breaks down quickly. It is believed that this compound is the first metabolite of phosalone in plants.

Phosalone is recommended against pests of various crops, and it is a highly promising substitute of DDT and other persistent organochloride insecticides. It is also used as a seed disinfectant with the purpose of protecting plant sprouts against damage by harmful insects and mites.

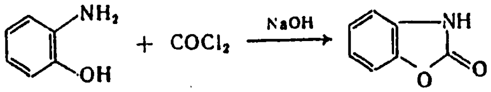
Phosalone is obtained by condensation of sodium or ammonium diethyldithiophosphate with 6-chloro-3-chloromethylbenzoxazolone:



The 3-chloromethyl-6-chlorobenzoxazolone required for synthesis of phosalone is produced with a good yield by the action of formalin and hydrochloric acid upon 6-chlorobenzoxazolone (392). The reaction may also be performed in one stage without isolation of 3-oxymethyl-6-chlorobenzoxazolone. In turn, 6-chlorobenzoxazolone is obtained with a good yield by direct chlorination of benzoxazolone by chlorine in tetrachloroethane or tetrachloroethylene (433). Because benzoxazolone and its di- and trichloro derivatives are readily soluble in tetrachloroethane, the purity of 6-chlorobenzoxazolone obtained by direct chlorination of benzoxazolone in tetrachloroethane is high, and following separation from the solvent, it may be used without further purification to make phosalone.

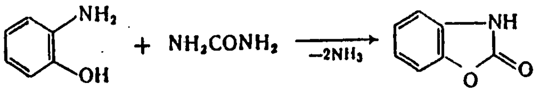
Two methods have been described in the literature for acquiring benzoxazolone:

1. Condensation of *o*-aminophenol with phosgene:



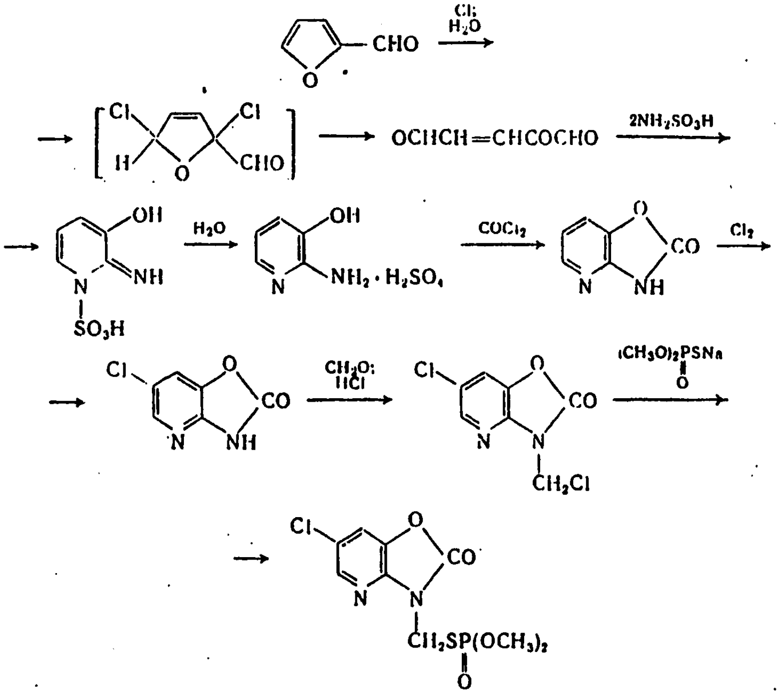
which proceeds in an aqueous medium in the presence of sodium hydroxide as a hydrogen chloride acceptor.

2. Condensation of *o*-aminophenol with urea:



This reaction proceeds at high temperature, and it is usually performed in some sort of organic solvent. It may also be performed without the solvent, by simple heating of the melted components. The reaction time is about 6 hours. Benzoxazolone may be purified by distillation in a vacuum. In the author's opinion the second method of obtaining benzoxazolone is more convenient and economical, since cheap, available urea is used in place of expensive, toxic phosgene.

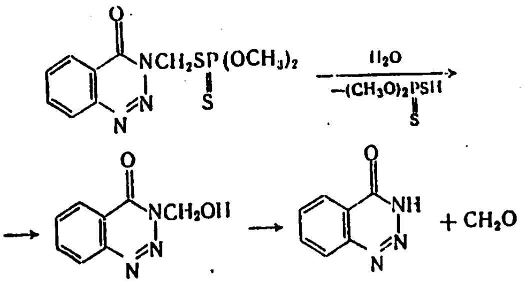
The nearest analogue of phosalone is preparation SGA-18809 (see Table 45), which is obtained as follows:



O,O-Dimethyl-S-(3,4-dihydro-4-oxo-5,6-benzo-1,2,3-triazinyl-3-methyl)-dithiophosphate (gusathion) is a white crystalline substance with a melting point of 73-74°C; vapor pressure at 20°C is $2.2 \cdot 10^{-7}$ mm Hg; volatility is 0.004 mg/m^3. When heated in a high vacuum it decomposes to release gaseous products (see also Table 47).

Gusathion is classified as a substance highly toxic to mammals. Its LD_{50} in mice is 15-17 mg/kg.

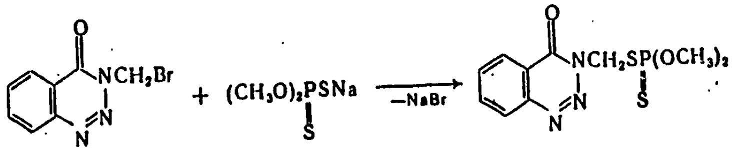
Gusathion is stable in chemical respects, and it may persist at room temperature in the absence of moisture for an unlimited time. In aqueous solution at pH 5 and 70°, gusathion saponifies to 50 percent at 8.9 hours, while at 20°C it takes 240 days. In an alkaline medium gusathion decomposes several times faster. When subjected to careful hydrolysis in an acid medium, gusathion produces 3,4-dihydro-4-oxo-1,2,3-benzotriazine, while in an alkaline medium it produces its oxymethyl derivative:



Oxidants cause substitution of thion sulfur by oxygen to form P-O-gusathion.

Gusathion is recommended against various plant pests. It produces good results on cotton, fruits and many other crops. It is marketed in the form of emulsion concentrates and wettable powders intended for spraying as water suspensions.

Gusathion is obtained by reacting N-halomethyl derivatives of benzohydrotriazinone with salts of dimethyldithiophosphoric acid:



When the bromomethyl derivative is used, gusathion is formed with a practical quantitative yield.

The 4-oxo-3,4-dihydro-1,2,3-benzotriazine needed for synthesis of gusathion may be obtained from anthranylic acid amide and sodium nitrite in an acid medium.

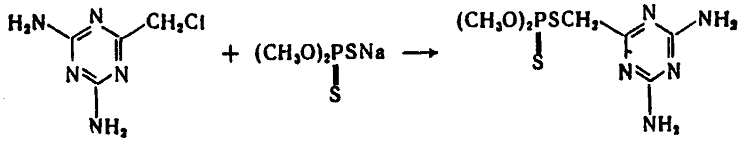
O,O-Dimethyl-S-(4,6-diamino-1,3,5-triazinyl-2-methyl)-dithiophosphate (menazon) is a white crystalline substance with a melting point of 160-162°C. It is poorly soluble in most organic solvents (see also Table 47). Menazon is a systemic insecticide with low toxicity to mammals.

Its LD_{50} is 900 mg/kg.

It is capable of penetrating into plants through the root system and imparting insecticidal properties to them for a long period of time. It is similar in chemical properties to other dithiophosphates of this type.

Menazon is marketed in the form of 70 percent wettable powder and as granules to be introduced into soil. Especially good results have been enjoyed with this preparation against vectors of viruses causing potato diseases.

Menazon is obtained by reacting alkali metal or ammonium dimethyldithiophosphates with 4,6-diamino-2-chloromethyl-1,3,5-triazine:



In a number of countries the norm for residual quantities of the pesticide has been set at 0.1 mg/kg.

Pyrophosphoric Acid Derivatives

Produced in Germany in 1943, tetraethylpyrophosphate was the first organophosphorus insecticide, known under the names of bladan and TEPP. After information on the insecticidal properties of tetraethylpyrophosphate and related compounds was published, systematic research on the pesticidal properties of organic compounds of phosphorus began. A number of compounds were found among the studied derivatives of pyrophosphoric acid; some of them are still significant today.

The following laws were established for the dependence between insecticidal activity and structure of pyrophosphates.

The insecticidal activity of tetraalkylpyrophosphates decreases as the ester radical grows in size. The most active compound is tetraethylpyrophosphate, while the activity of tetramethylpyrophosphate is somewhat lower.

Tetraalkylmonothiopyrophosphates exhibit greater insecticidal activity than tetraalkylpyrophosphates, but their toxicity to mammals is concurrently higher. Addition of a second sulfur atom at the phosphorus atom reduces the compound's toxicity to mammals without noticeably decreasing its insecticidal activity.

Addition of a third sulfur atom to the phosphorus atom reduces the compound's insecticidal activity. Thus for example, O,O,O,O-tetraalkyldithiopyrophosphates have greater insecticidal activity than do O,O,O,O-tetraalkyltrithiopyrophosphates with the same hydrocarbon radicals.

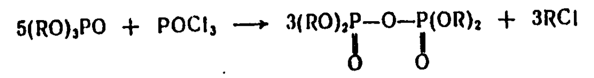
Tetraalkydithiopyrophosphates containing different hydrocarbon radicals exhibit almost the same insecticidal activity as do the corresponding symmetrical tetraalkyldithiopyrophosphates with the same molecular weight.

All pyrophosphates have strong contact insecticidal action, and have practically no systemic insecticidal action due to their low hydrolytic stability and fast decomposition on plants to form nontoxic products. Systemic activity appears as we proceed from pyrophosphoric acid esters to amides. Contact insecticidal activity decreases in this case. Pyrophosphoric acid octamethyltetramide has been proposed as a systemic insecticide. It does not have contact insecticidal activity, which is why it is used to protect mulberry trees from sucking pests.

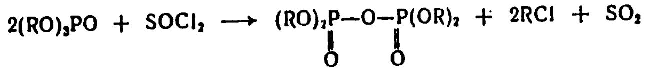
Many general methods of obtaining esters and amides of pyrophosphoric, thio-, dithio- and trithiopyrophosphoric acids have been described in the literature. We will note only the most important methods, those having significance to production of this type of compounds.

The principal methods of synthesizing tetraalkylpyrophosphates are:

1. Reacting trialkylphosphates with phosphorus chloroxide or other acid chlorides:

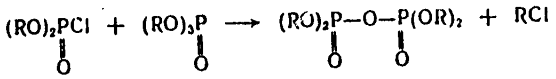


$$5(RO)_3PO + POCl_3 \longrightarrow 3(RO)_2\underset{\underset{O}{\|}}{P}-O-\underset{\underset{O}{\|}}{P}(OR)_2 + 3RCl$$



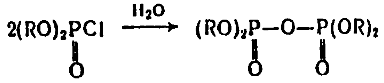
$$2(RO)_3PO + SOCl_2 \longrightarrow (RO)_2\underset{\underset{O}{\|}}{P}-O-\underset{\underset{O}{\|}}{P}(OR)_2 + 2RCl + SO_2$$

This reaction proceeds at relatively low temperature, and tetraalkylpyrophosphates form with a satisfactory yield; however, the technical-grade product is somewhat contaminated by other derivatives of phosphoric acid. Dialkylchlorophosphate can also be used as an acid halide:



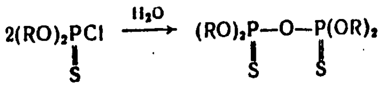
$$(RO)_2\underset{\underset{O}{\|}}{P}Cl + (RO)_3\underset{\underset{O}{\|}}{P} \longrightarrow (RO)_2\underset{\underset{O}{\|}}{P}-O-\underset{\underset{O}{\|}}{P}(OR)_2 + RCl$$

2. Reacting dialkylchlorophosphates with water in the presence of bases:



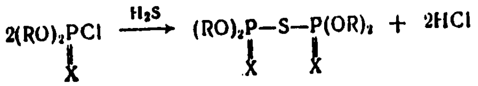
$$2(RO)_2\underset{\underset{O}{\|}}{P}Cl \xrightarrow{H_2O} (RO)_2\underset{\underset{O}{\|}}{P}-O-\underset{\underset{O}{\|}}{P}(OR)_2$$

Both organic tertiary amines and alkali metal carbonates can be used as the bases. This reaction produces the purest preparations with a good yield. This method is also suitable for synthesis of symmetrical tetraalkyldithiopyrophosphates out of dialkylchlorothiophosphates:



$$2(RO)_2\underset{\underset{S}{\|}}{P}Cl \xrightarrow{H_2O} (RO)_2\underset{\underset{S}{\|}}{P}-O-\underset{\underset{S}{\|}}{P}(OR)_2$$

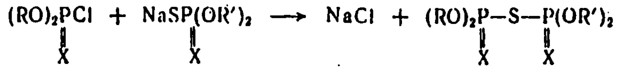
When water is substituted by hydrogen sulfide, good yields of tetraalkylthio- and tetralkyltrithiopyrophosphates can be obtained:



$$2(RO)_2\underset{\underset{X}{\|}}{P}Cl \xrightarrow{H_2S} (RO)_2\underset{\underset{X}{\|}}{P}-S-\underset{\underset{X}{\|}}{P}(OR)_2 + 2HCl$$

X = O or S

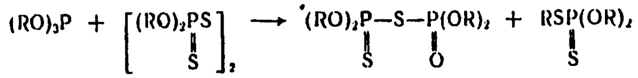
Asymmetrical tetraalkylpyrophosphates form when dialkylphosphoric acids salts react with the corresponding dialkychlorophosphates:



$$(RO)_2\underset{\substack{\|\\X}}{P}Cl + NaS\underset{\substack{\|\\X}}{P}(OR')_2 \longrightarrow NaCl + (RO)_2\underset{\substack{\|\\X}}{P}{-}S{-}\underset{\substack{\|\\X}}{P}(OR')_2$$

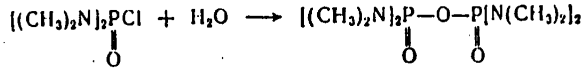
This is a convenient method of obtaining thio-, dithio- and trithiopyrophosphates.

Asymmetrical tetraalkyldithiopyrophosphates are synthesized with a good yield by the following reaction:



$$(RO)_3P + \left[(RO)_2\underset{\substack{\|\\S}}{P}S\right]_2 \longrightarrow (RO)_2\underset{\substack{\|\\S}}{P}{-}S{-}\underset{\substack{\|\\O}}{P}(OR)_2 + RS\underset{\substack{\|\\S}}{P}(OR)_2$$

Pyrophosphoric acid octamethyltetramide and its analogues are produced industrially by reacting tetramethyldiaminochlorophosphate with water the presence of organic or inorganic bases:

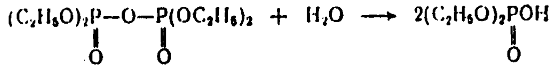


$$[(CH_3)_2N]_2\underset{\substack{\|\\O}}{P}Cl + H_2O \longrightarrow [(CH_3)_2N]_2\underset{\substack{\|\\O}}{P}{-}O{-}\underset{\substack{\|\\O}}{P}[N(CH_3)_2]_2$$

Tetraethylpyrophosphate (TEPP) is a colorless liquid with an unpleasant specific odor; its boiling point is 82°C at 0.05 mm Hg; d_4^{20} 1.185; vapor pressure at 20°C is $1.55 \cdot 10^{-4}$ mm Hg; volatility is 2.5 mg/m^3. It mixes with water in all ratios, it is relatively soluble in alcohol, acetone, aromatic hydrocarbons and carbon tetrachloride, and it is poorly soluble in petroleum ether and ligroin.

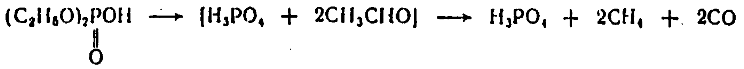
When heated to 170°C, TEPP decomposes to release ethylene; at 208-215°C decomposition proceeds very swiftly.

TEPP is quickly hydrolyzed by water, even at room temperature, to form diethylphosphoric acid, which is atoxic to both insects and animals:



$$(C_2H_5O)_2\underset{\substack{\|\\O}}{P}{-}O{-}\underset{\substack{\|\\O}}{P}(OC_2H_5)_2 + H_2O \longrightarrow 2(C_2H_5O)_2\underset{\substack{\|\\O}}{P}OH$$

Diethylphosphoric acid is decomposed practically completely by sunlight into phosphoric acid, methane and carbon dioxide. Formation of the last two products proceeds by way of acetaldehyde:



$$(C_2H_5O)_2\underset{\substack{\|\\O}}{P}OH \longrightarrow [H_3PO_4 + 2CH_3CHO] \longrightarrow H_3PO_4 + 2CH_4 + 2CO$$

TEPP reacts readily with alcohols and amines, producing trialkylphosphate and diethylphosphoric acid in the first case and diethylphosphoric acid amide and salt in the second. It enters into an interesting reaction with anhydrous hydrogen fluoride and potassium bifluoride, in which diethylfluorophosphate, which is toxic to mammals, forms.

TEPP is characterized as being toxic to animals and man, for which reason it must be handled with great caution. Its LD_{50} in rats is 1.2 mg/kg. The insecticidal activity of TEPP is close to three times weaker than that of thiophos, owing to which its use is continually decreasing.

It is used in the form of aqueous solutions (0.2 percent) to control herbivorous mites and aphids.

TEPP is synthesized by one of the general methods described above.

Tetraethyldithiopyrophosphate (pirofos, sul'fotep, bladafum) is a colorless liquid with a boiling point of 92°C at 1 mm Hg; at 20°C its vapor pressure is $1.7 \cdot 10^{-4}$ mm Hg. Volatility is 9 mg/m^3; solubility in water is 25 mg/liter. It is readily soluble in most organic solvents except aliphatic hydrocarbons.

Its LD_{50} in rats is about 5 mg/kg.

Pirofos is close to thiophos in insecticidal activity. It is used in the FRG in small quantities as a fumigant to control aphids in hothouses. Pirofos is effective against mollusks and soft scales. It is obtained by one of the general methods described above.

A large number of homologues and analogues of pirofos have been synthesized.

The LD_{50} of tetraethylmonothiopyrophosphate is 0.5 mg/kg.

Tetra-*n*-propyldithiopyrophosphate (NPD) is a liquid with a boiling point of 104°C at 0.01 mm Hg. It is practically insoluble in water, readily soluble in most organic solvents and poorly soluble in petroleum ether and ligroin.

Its LD_{50} in rats is 100 mg/kg.

NPD has moderate contact insecticidal activity, and it is marketed in the form of a 35 percent wettable powder and an 85 percent emulsion concentrate. It has been released as an experimental preparation in the USA.

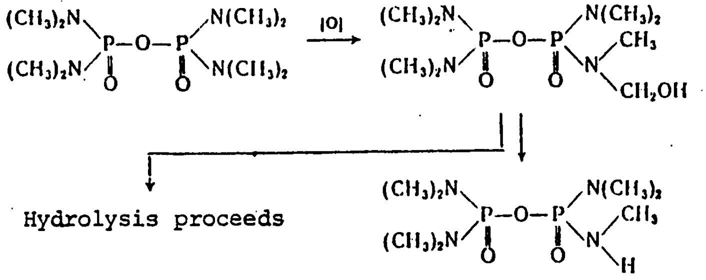
As with pirofos, it is resistant to hydrolysis, and its chemical reactions recall those of other pyrophosphates.

Pyrophosphoric acid octamethyltetramide (octamethyl, OMPA, pestox-III, schradan, sytam) is a colorless liquid with a boiling point of 126°C at 1 mm Hg; vapor pressure at 20°C is $6.5 \cdot 10^{-4}$ mm Hg; volatility is 9.5 mg/m^3. It crystallizes when cooled, with a melting point of about 20°C. Octamethyl mixes with water in all ratios. It is readily soluble in alcohols, ketones and halogen hydrocarbon derivatives, and it is poorly soluble in petroleum ether, kerosene and ligroin.

The aqueous solution of pure preparation is neutral, and it may be stored indefinitely without changing. In an acid medium octamethyl quickly decomposes, while in an alkaline medium it is more stable. Thus for example, 50 percent of the preparation hydrolyzes in neutral aqueous solution in 100 years, while it takes 200 minutes in 1 N HCl solution and 70 days in 1 N sodium hydroxide solution.

Its LD_{50} in rats is about 9 mg/kg. The maximal permissible concentration in air is 0.02 mg/m^3.

Octamethyl has almost no contact insecticidal activity, acting only as a systemic insecticide by way of the plant. The reason for this is that it transforms into a more-toxic metabolite in plants and in the animal body. Metabolism of octamethyl in plants and in animals may be diagrammed as follows:

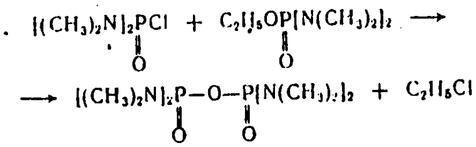


Octamethyl can be oxidized by potassium permanganate or other oxidants.

Octamethyl is chlorinated to form, in the first stage of the process, the corresponding chloromethyl derivative. A total of four chlorine atoms can be introduced.

Octamethyl is used on a minor scale as a long-acting systemic insecticide. It is used in the USSR to control sucking pests of the mulberry tree, since it is harmless to silkworms that feed on the leaves of the mulberry tree.

The principal industrial method of producing octamethyl is to react tetramethyldiamidochlorophosphates with water in the presence of tertiary amines, for example pyridine or, still better, tetraethylamine. Good yields are also obtained by reacting tetramethyldiamidochlorophosphate with potash. Octamethyl can also be synthesized by reacting tetramethyldiamidoethylthiophosphate with tetramethyldiamidochlorophosphate at 140°C:



$$[(CH_3)_2N]_2\underset{\underset{O}{\|}}{P}Cl + C_2H_5O\underset{\underset{O}{\|}}{P}[N(CH_3)_2]_2 \longrightarrow$$
$$\longrightarrow [(CH_3)_2N]_2\underset{\underset{O}{\|}}{P}-O-\underset{\underset{O}{\|}}{P}[N(CH_3)_2]_2 + C_2H_5Cl$$

Phosphonic Acid Derivatives

Active insecticides, acaricides, fungicides and herbicides have been found among the large number of alkyl- and arylphosphonic, alkylthio-, arylthio- and dithiophosphonic, and dialkyl- and diarylphosphonic acid derivatives, but only a few compounds have found practical applications in agriculture. Most organophosphorus derivatives of this type are still in the research stage.

The toxicity of mixed esters of methyl- and ethylthiophosphonic acids to homeothermic animals is higher in most cases than that of analogous mixed esters of phosphoric acid (2), though there are exceptions as well. Toxicity decreases as the size of the hydrocarbon radical bound to phosphorus increases. The toxicity of alkylphosphonic acids is relatively low, and it depends to a great extent on which radicals are bound to phosphorus. The corresponding derivatives of thio- and dithiophosphonic acids exhibit extremely variable toxicity to mammals, which depends to a great extent on the structure of ester radicals (293,439-441).

Mixed esters of thio- and dithioalkylphosphonic acids have insecticidal and acaricidal action in most cases (442-455); they are active against soil-inhabiting pests as well (453). Many amido esters of alkylphosphonic and thiophosphonic acids also have insecticidal and acaricidal properties (456-458). Epoxypropylphosphonic acid derivatives have bactericidal action (460). It would be interesting to note that substitution of one of the ester radicals by a benzyl group causes fungicidal properties to arise in alkylthio- and alkyldithiophosphonates. Benzylthiophosphonates also have similar properties (461,462).

Many mixed esters of alkylthio- and alkyldithiophosphonic acids containing different functional groups in both the ester radicals and the radical bound to phosphorus have insecticidal and acaricidal properties (443,465-469,471). Insecticidal properties have also been noted in methylphosphonate and methylthiophosphonate hydrazides (470).

Substitution of hydrogen in the hydrocarbon radical at the phosphorus atom of alkylphosphonic acid derivatives by a halogen atom reduces toxicity to vertebrates. Thus for example, mixed esters and ester amides of chloromethyl-, chloromethylthio- and chloromethyldithiophosphonic acids exhibit lower toxicity than the corresponding derivatives of methyl-, methylthio- and methyldithiophosphonic acids (443,463,464).

Ester amides of chloromethylthiophosphonic acid have herbicidal action, and they are recommended for use on rice and vegetables to control millet-like weeds (464). It would be interesting to note that accumulation of halogen atoms in the methyl group reduces the compound's herbicidal activity. Complete chloromethylthiophosphonic acid amides are even less active, while the corresponding derivatives of chloromethylphosphonic acid are still less active (463,464).

2-Chloroethylphosphonic acid is an interesting plant growth regulator (472-476). It hastens maturation of fruits, and it causes leaf fall in a number of crops. The action of 2-chloroethylphosphonic acid and its acid esters is based on their decomposition and liberation of ethylene.

Allyldithiophosphonates have nematocidal action (477,478). Alkoxyvinyldithiophosphonates (479) and dialkoxythiophosphonacetates (480) have similar properties. Alkoxyvinyl-, alkylsulfonyl- and alkylsulfinyldithiophosphates have herbicidal action (481-486). Aminomethylphosphonates have herbicidal action as well (487).

Addition of a hydroxyl radical at the carbon atom bound to phosphorus as a rule reduces toxicity of esters and other derivatives of alkylphosphonic acids to mammals, though there are exceptions to this general dependence.

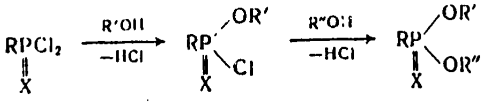
Enlargement of the hydrocarbon radical bound to phosphorus reduces the toxicity and insecticidal activity of the compound. For example the LD_{50} in rats (mg/kg) is 2.5 for O-ethyl-O-(4-nitrophenyl)-methylthiophosphonate, 25 for O-ethyl-O-(4-nitrophenyl)-isopropylthiophosphonate and 250 for O-ethyl-O-(4-nitrophenyl)-*n*-hexylthiophosphonate. Toxicity to mammals changes depending on the structure of ester radicals in the same order as for esters of phosphoric and thiophosphoric acid. Thus O-alkyl-O-(4-nitrophenyl) esters of alkylphosphonic acids are more toxic than the O-alkyl-O-(2,4,5-trichlorophenyl) esters of these acids.

As we proceed from alkylphosphonic, alkylthiophosphonic and alkyldithiophosphonic acids to the derivatives of arylphosphonic, arylthiophosphonic and aryldithiophosphonic acids, toxicity to vertebrates decreases significantly, while in most cases the pesticidal properties persist. This is valid primarily in relation to mixed esters of arylphosphonic acids, which are less toxic than the corresponding esters of alkylphosphonic acids.

Many phosphonic and thiophosphonic acids containing thiofuran (490,491), furan (494), piperidine (489) and other heterocyclic residues are also active insecticides, acaricides and bactericides.

Some compounds of these series which have enjoyed some practical use are shown in Table 48.

The usual method of obtaining mixed esters of alkylphosphonic, alkylthiophosphonic and alkyldithiophosphonic acids is to react the appropriate acid chlorides with alcohols, phenols and mercaptans in the presence of hydrogen chloride acceptors (496-507):



Tertiary amines, alkali and alkali-earth metal carbonates, caustic alkalis and other inorganic and organic bases may be used as hydrogen chloride acceptors. Metallic copper is often used in the reaction as a catalyst (496).

Similarly as with mixed esters of thiophosphoric acid, mixed esters of alkylthiophosphonic acid are obtained in acetone or methylethylketone in the presence of potash or soda by prolonged boiling of the reaction mixture. The reaction with mercaptans is also performed in the presence of hydrogen chloride acceptors (507, 508), which are usually tertiary amines.

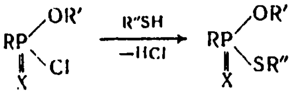
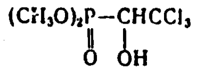
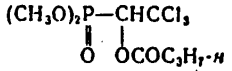
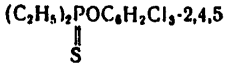
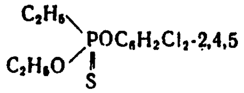
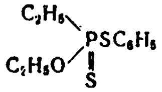
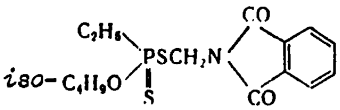
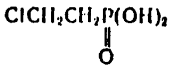
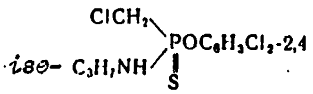
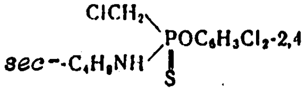
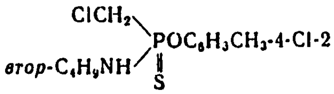
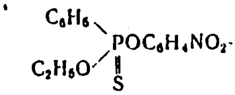
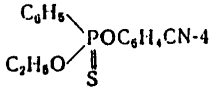
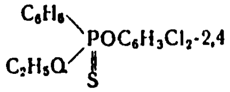
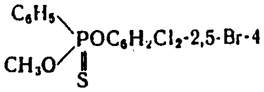
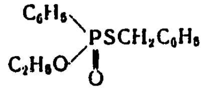
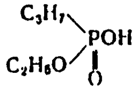
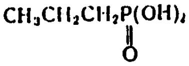
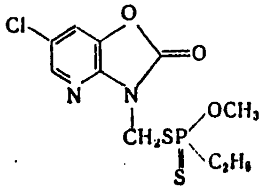


Table 48. Derivatives of Alkyl- and Aryl-

Chemical Name	Formula	Synonyms
O,O-Dimethyl-(1-oxy-2,2,2-trichloroethyl)-phosphonate	 $(CH_3O)_2P(=O)-CH(OH)CCl_3$	Chlorofos, trichlorfon, dipterex, dylox, Bayer L-13/59, meguvan, tugon
O,O-Dimethyl-1-butyroxy-2,2,2-trichloroethylphosphonate	 $(CH_3O)_2P(=O)-CH(OCOC_3H_7\text{-}n)CCl_3$	Butonate
O-(2,4,5-trichlorophenyl)-diethylthiophosphinate	 $(C_2H_5)_2P(=S)OC_6H_2Cl_3\text{-}2,4,5$	Agvitor
O-Ethyl-O-(2,5-dichloro-4-iodophenyl)-ethylphosphonate		Ts-18244
O-Ethyl-O-(2,4,5-trichlorophenyl)-ethylthiophosphonate		Trikhloronat
O-Ethyl-S-phenylethyldithiophosphonate		Difonat
O-Isobutyl-S-phthalimidomethylethyldithiophosphonate		Kh-4543
2-Chloroethylphosphonic acid	 $ClCH_2CH_2P(=O)(OH)_2$	Ethrel, etefon
O-(2,4-dichlorophenyl)-N-(isopropylamido)-chloromethylthiophosphonate		Izofos-2
O-(2,4-dichlorophenyl)-N-(*sec*-butylamido)-chloromethylthiophosphonate		Izofos-1

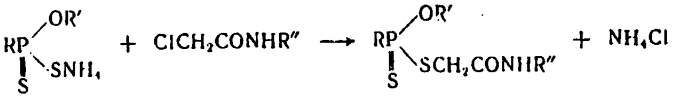
phosphonic Acids Used as Pesticides

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility Water, mg/liter	LD_{50} in Rats (Orally) mg/kg / LD_{50} in Rabbits (Cutaneously), mg/kg	Use. Forms of Application and Consumption Norms
100 (0,1)	73—74 (83—84)	12300	$\frac{560}{2000}$	Insecticide with broad spectrum of action, used in agriculture, animal husbandry and public health. Aqueous solutions, w.p., solutions for ultralow volume spraying. E.c. In agriculture, 0.5-2 kg/ha.
112—114 (0,03)	—	Moderate	700	Contact insecticide for animal husbandry. E.c.
—	—	Insoluble	17	Insecticide controlling soil-inhabiting pests.
—	60—67	0,2	40	Insecticide controlling soil-inhabiting pests. 40% e.c., 5% granules.
108 (0,01)	—	50	$\frac{16-37,5}{341}$	Insecticide controlling onion fly, cabbage maggot and carrot rust-fly. 50% e.c., 2.5-7.5% granules.
130 (0,1)	—	20	$\frac{16,5}{147}$	Insecticide controlling soil-inhabiting pests. E.c., granules.
127—128 $(1 \cdot 10^{-6})$	58—60	12	$\frac{75}{121}$	Insecticide with broad spectrum of action. E.c., w.p.
—	74—75	Good	$\frac{4220}{5300}$	Plant growth regulator. In plants, releases ethylene as the active agent. 24% aqueous solution.
141—142 (0,5)	—	2,44	$\frac{315}{1200-1300}$	Herbicide controlling millet-like weeds in rice and vegetable crops. E.c.; 4-8 kg/ha.
134—135 (0,13)	—	—	425	Herbicide controlling millet-like weeds in rice. E.c.; 4-6 kg/ha.

Chemical Name	Formula	Synonyms
O-(2-Chloro-4-methylphenyl)-N-(*sec*-butylamido)-chloromethylthiophosphonate		Izofos-3
O-Ethyl-O-(4-nitrophenyl)-phenylthiophosphonate		EPN
O-Ethyl-O-(4-cyanophenyl)-phenylthiophosphonate		Surecide
O-Ethyl-O-(2,4-dichlorophenyl)-phenylthiophosphonate		Ts-Seven
O-Methyl-O-(2,5-dichloro-4-bromophenyl)-phenylthiophosphonate		V-506
O-Ethyl-S-benzylphenylthiophosphonate		Inezin
N-Phosphonomethylglycine	 $(HO)_2\underset{\overset{\|}{O}}{P}CH_2NHCH_2COOH$	NOM-113
O-Ethylpropylphosphonic acid		NIA-10637
Propylphosphonic acid	 $CH_3CH_2CH_2\underset{\overset{\|}{O}}{P}(OH)_2$	NIA-10656
S-(6-Chloroxazolopyridinon-2-yl-3-methyl)-O-methylethyldithiophosphonate		SGA-16088

Boiling Point, °C (At Indicated Pressure), mm Hg	Melting Point, °C	Solubility Water, mg/liter	LD50 in Rats (Orally) mg/kg LD50 in Rabbits (Cutaneously), mg/kg	Use. Forms of Application and Consumption Norms
147—148 (0,1)	—	—	510	Herbicide controlling millet-like weeds in rice and vegetables. E.c.; 3-5 kg/ha.
—	36	Insoluble	8—36 45	Acaricide and insecticide. 25% w.p.; up to 1 kg/ha.
—	83	"	43,7 (in mice)	Insecticide and acaricide with broad spectrum of action. 28.5% e.c.
Liquid, does not distill	—	"	274	Insecticide controlling soil-inhabiting pests. 3% dust; 1-3 kg/ha.
—	42	8	28	Insecticide with broad spectrum of action. E.c.; 1-2 kg/ha.
—	Liquid	7	750	Fungicide controlling (pirikulyariya) in rice.
—	—	Freely soluble	Mildly toxic	Herbicide used at consumption norms of 0.5-1 kg/ha as amine salts. Used against perennials, including wheat-grass.
—	Liquid, does not distill	Good	2300	Plant growth regulator.
—	Liquid	Good	3723	Plant growth regulator.
—	55—57	—	470	Contact and intestinal insecticide. Also effective against miners.

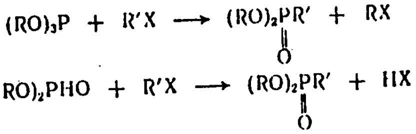
Mixed esters of alkylthio- and alkyldithiophosphonic acids can be obtained from salts and halogen derivatives (293,509). This reaction proceeds especially readily with thiophosphonic acid salts and halobenzyls (509), and especially the salts of alkyldithiophosphonic acid and various derivatives of monochloroacetic acid (293):



A similar reaction can be used to obtain ester amides of alkylphosphonic and alkylthiophosphonic acids (510).

The alkylphosphonic, alkylthiophosphonic and alkyldithiophosphonic acids required for the synthetic processes can be obtained by various methods (22).

Arbuzov's reaction and the Mikhaelis-Bekker reaction are among the most general methods of forming a C-P bond (511,512):



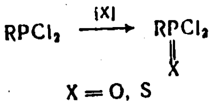
$$(RO)_3P + R'X \longrightarrow (RO)_2\underset{\underset{O}{\|}}{P}R' + RX$$

$$(RO)_2PHO + R'X \longrightarrow (RO)_2\underset{\underset{O}{\|}}{P}R' + HX$$

Both of these reactions are ideal methods of obtaining various esters of alkylphosphonic acids. Subsequent transformation of alkylphosphonates into mixed esters or into other derivatives presents certain difficulties due to the large number of stages in the process, for which reasons a number of other methods of obtaining aliphatic compounds with a C-P bond have been developed. Among such methods, we should first mention the reaction between red phosphorus and alkylhalides in the presence of powdered copper, which proceeds at 300-360° in a flow-through system and produces satisfactory yields of alkyldichlorophosphines (22):

$$RCl + P \longrightarrow RPCl_2 + R_2PCl$$

which can be used to easily obtain alkylphosphonic and alkylthiophosphonic acid chlorides:



$$RPCl_2 \xrightarrow{[X]} R\underset{\underset{X}{\|}}{P}Cl_2$$

$X = O, S$

Of even greater interest is the reaction between alkylhalides and yellow phosphorus in phosphorus trichloride, which proceeds at about 200°C under pressure (513):

$$RCl + PCl_3 + P \longrightarrow RPCl_2$$

A similar reaction may be used to obtain phenylene-bis-dihalophosphines (514), which are also intermediate products used in pesticide synthesis (515,516).

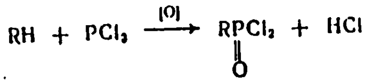
Alkyldichlorophosphines may also be obtained by reacting phosphorus trichloride with trialkylaluminum:

$$PCl_3 + AlR_3 \longrightarrow RPCl_2 + AlCl_3$$

The reaction should be performed in the presence of a large excess of phosphorus trichloride, since otherwise the products would be dialkylchlorophosphines and trialkylphosphines.

This reaction may be of significant practical interest, considering the large amounts of trialkylaluminum produced.

Alkylphosphonic acid chlorides may be obtained with a good yield by chlorophosphinating hydrocarbons (517):



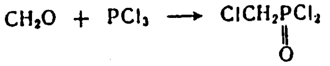
$$RH + PCl_3 \xrightarrow{[O]} R\underset{\overset{\|}{O}}{P}Cl_2 + HCl$$

Alkylphosphonic acid chlorides may also be transformed into alkylthiophosphonic acid chlorides by the action of phosphorus pentasulfide:

$$R\underset{\overset{\|}{O}}{P}Cl_2 + P_2S_5 \longrightarrow R\underset{\overset{\|}{S}}{P}Cl_2 + P_2O_5$$

Alkyldichlorophosphines are also obtained by reacting organic compounds of lead, mercury, magnesium and other metals with phosphorus trichloride, but these reactions cannot be used for industrial production.

Many other particular methods of obtaining various alkylphosphonic acids are known. Thus for example, when phosphorus trichloride is heated in an autoclave with paraform under pressure, a good yield of chloromethylphosphonic acid is obtained:



$$CH_2O + PCl_3 \longrightarrow ClCH_2\underset{\overset{\|}{O}}{P}Cl_2$$

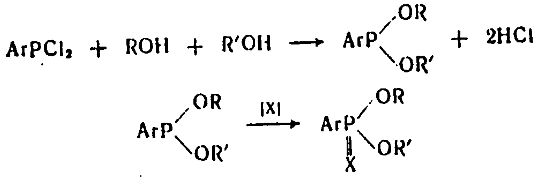
while dialkyloxymethylphosphonate, which has insecticidal properties, is formed out of orthoformate and PCl_3 in the presence of anhydrous zinc chloride (518). Methylthiophosphonic acid chloranhydride is obtained as a mixture with dimethylthiophosphinic acid chloride by heating dimethyldisulfide with phosphorus chloride to 300-400°C (519). A number of other methods of obtaining alkylphosphonic and alkylthiophosphonic acid chlorides have been described (22).

Various benzylphosphonic and benzothiophosphonic acids, the esters of which are fully analogous with alkylphosphonic acid derivatives, are obtained similarly as alkylphosphonic acids (520-523). Most such derivatives have fungicidal properties.

Esters and other derivatives of arylphosphonic and arylthiophosphonic acids are also obtained by reacting actid chlorides of the corresponding acids with alcohols, phenols or mercaptans in the presence of hydrogen chloride acceptors (524-536). The reaction proceeds in conditions similar to those described above for aliphatic compounds. The arylphosphonic and arylthiophosphonic acid chlorides required for this purpose are obtained as follows.

A reaction is performed between hydrocarbons and phosphorus trichloride at high temperature to obtain aryldichlorophosphines, which are then transformed by conventional methods into arylphosphonic or arylthiophosphonic acid chlorides (22). Aryldichlorophosphines are also obtained with satisfactory yields by reacting aromatic hydrocarbons or their derivatives with phosphorus trichloride in the presence of Lewis acids.

Mixed esters and ester amides of arylphosphonic and arylthiophosphonic acids are obtained with good yields by oxidation or by attachment of sulfur to the appropriate esters or ester amides of arylphosphonous acid; the latter are formed by reacting alcohols, phenols and mercaptans with aryldichlorophosphines in the presence of hydrogen chloride acceptors:



$X = O, S$

Compounds with the formula

$$R_3P{=}N{-}\overset{}{\underset{\overset{\|}{X}}{P}}R'_2,$$

obtained from the amides of phosphonic acids and their derivatives, have been proposed as defoliants (537).

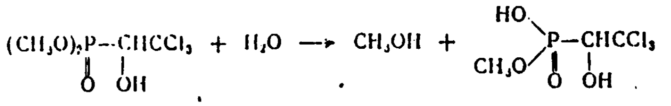
Because a number of derivatives of phosphonic acids are enjoying extensive application, the metabolism of some preparations in various biological media has been studied, to include chlorofos (274,538,539), difonat (540,541), VTsS-506 (542) and other preparations of this type. It should be noted that the P-C bond is rather strong, and that during metabolism it is broken apart rather slowly; compounds having substituents such as halogen, hydroxyl and so on at the α-carbon atom are an exception. Such compounds break down rather quickly to form, in the end, phosphoric acid, which is assimilated completely by plants. The most important representatives of this type of compounds are presented below.

O,O-Dimethyl-(1-oxy-2,2,2-trichloroethyl)-phosphonate (chlorofos) is a white crystalline powder; its solubility (gm/100 gm) is 12.3 in water, 15.2 in benzene and 75 in chloroform. It is poorly soluble in paraffin hydrocarbons. Determination of the molecular weight of chlorofos showed that it is a dimeric compound. The vapor pressure of chlorofos at 20°C is $7.8\cdot10^{-6}$ mm Hg. Its volatility is 0.11 mg/m^3 (see also Table 48).

Chlorofos is classified as a moderately toxic compound. Its LD_{50} in rats is 560 mg/kg. The maximum permissible concentration in air is 0.5 mg/m^3.

The preparation is broadly employed against various plant pests (sucking and gnawing), to include eurygaster, codling moth, corn borer, various species of flies and the cattle fly. The cattle fly is controlled by a special form of the preparation containing chlorofos solution mixed with mineral oil and isopropyl or butyl alcohol. This solution penetrates quickly through the animal's skin, which permits dramatic reduction of the dose of the preparation used to process the animals.

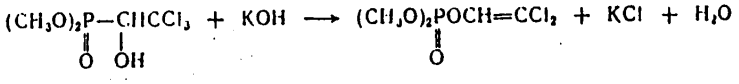
Chlorofos is stable in an acid medium and undergoes fast hydrolysis in an alkaline medium; hydrolysis proceeds along two pathways. In an acid medium the first product of hydrolysis is O-methyl-(1-oxy-2,2,2-trichloroethyl)-phosphonic acid, which hydrolyzes further to phosphoric acid:



$$(CH_3O)_2\underset{\overset{\|}{O}}{P}-\underset{\overset{|}{OH}}{C}HCCl_3 + H_2O \longrightarrow CH_3OH + \overset{HO}{\underset{CH_3O}{\quad}}\!\!>\!\underset{\overset{\|}{O}}{P}-\underset{\overset{|}{OH}}{C}HCCl_3$$

Chlorofos decomposes especially quickly when exposed to light in dilute solutions.

In an alkaline medium chlorofos undergoes dehydrochlorination and concurrent regrouping. The principal reaction product is O,O-dimethyl-O-(2,2-dichlorovinyl)-phosphate (DDVP):



$$(CH_3O)_2\underset{\overset{\|}{O}}{P}-\underset{\overset{|}{OH}}{C}HCCl_3 + KOH \longrightarrow (CH_3O)_2\underset{\overset{\|}{O}}{P}OCH{=}CCl_2 + KCl + H_2O$$

Dichloroacetaldehyde, dimethylphosphoric acid and some other compounds are formed as products in side reactions (for example as a result of hydrolysis of DDVP).

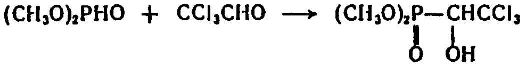
Chlorofos is a good methylating agent, and for example it can react with potassium iodide to form methyliodide.

When aqueous solutions of chlorofos are stored for a long period of time, the preparation undergoes partial hydrolysis, owing to which the solution becomes acidic due to presence of phosphoric, dimethylphosphoric and hydrochloric acids. Storage of chlorofos in unlined iron containers is not recommended.

Reducing agents also decompose chlorofos.

Two methods can be used to obtain it on an industrial scale:

1. Condensation of dimethylphosphite with chloral:



$$(CH_3O)_2PHO + CCl_3CHO \longrightarrow (CH_3O)_2\underset{O}{\underset{\|}{P}}-\underset{OH}{\underset{|}{C}}HCCl_3$$

The reaction proceeds at room temperature, and heat is liberated. Chlorofos may be obtained with a practical quantitative yield.

The purity of the initial dimethylphosphite has great significance in this method. The purer the dimethylphosphite is, the greater is the yield and the better is the quality of the chlorofos. It is best to use distilled dimethylphosphite. It can be distilled in a film evaporator at 5-8 mm Hg. Such dimethylphosphite usually contains 93-96 percent principal substance, and when it is used, 93-95 percent chlorofos forms, with a small quantity of acidic impurities. When technical-grade undistilled dimethylphosphite is used, the concentration of the principal substance in the resulting chlorofos is 87-88 percent. It contains a rather large amount of acidic impurities, as well as O-methyl-2,2,2-trichloro-1-oxyethylphosphonic acid and the reaction product of chloral and phosphoric acid.

The dimethylphosphite required for synthesis of chlorofos is obtained by reacting phosphorus trichloride with methanol:

$$PCl_3 + 3CH_3OH \longrightarrow (CH_3O)_2PHO + 2HCl + CH_3Cl$$

Usually the process is performed in an organic solvent at low temperature. Methylchloride is a convenient solvent. It boils at -24°C, and as it evaporates it cools the reaction mixture while simultaneously removing the hydrogen chloride formed. Dimethylphosphite is usually obtained in a continuous process. After the reaction ends, the solvent is distilled away, and the light fractions are evaporated in a column. Dimethylphosphite is purified by distilling it in a film evaporator at a temperature on the order of 120°C at 5-8 mm Hg. The dimethylphosphite yield in this method exceeds 90 percent, if we count phosphorus trichloride.

Obtaining dimethylphosphite in the presence of water has been proposed as a way of avoiding formation of methylchloride (549):

$$PCl_3 + 2CH_3OH + H_2O \longrightarrow (CH_3O)_2PHO + 3HCl$$

However, no information on industrial use of this method has been published.

Monomethylphosphite and phosphoric acid are formed in small quantities as byproducts of the dimethylphosphite acquisition process:

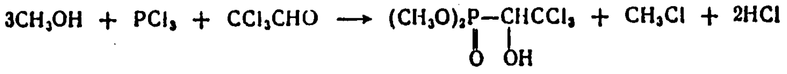
$$(CH_3O)_2PHO + HCl \longrightarrow CH_3OP(OH)_2 + CH_3Cl$$
$$(CH_3O)_2PHO + 2HCl \longrightarrow H_3PO_3 + 2CH_3Cl$$

At high temperature phosphoric acid is capable of undergoing disproportionation, releasing phosphine:

$$4H_3PO_3 \longrightarrow 3H_3PO_4 + PH_3$$

When the process of obtaining dimethylphosphite is performed incorrectly, liberation of phosphine may be a cause of spontaneous combustion.

2. In the second method the reaction of forming dimethylphosphite and its reaction with chloral are combined into a single stage. The process is performed in organic solvent, with the heat being extracted:



$$3CH_3OH + PCl_3 + CCl_3CHO \longrightarrow (CH_3O)_2\underset{O}{\underset{\|}{P}}-\underset{OH}{\underset{|}{C}}HCCl_3 + CH_3Cl + 2HCl$$

The chlorofos yield in this combined method is more than 80-85 percent.

Chlorofos is purified by recrystallizing it out of water or organic solvent. The mother liquor from chlorofos recrystallization is usually used to produce DDVP, which is enjoying increasingly greater application in agriculture and at home.

There are many modifications of the second method of obtaining chlorofos; Various solvents can be used (carbon tetrachloride, methylchloride, chlorobenzene etc.); the process can be performed in a broad interval of temperatures. Chlorofos may be obtained by both the first and the second method in periodic and continuous processes (543,544).

Chlorofos obtained by the methods described above can be purified by washing away the acidic impurities in chloroform solution; when the latter is evaporated away, the resulting chlorofos contains more than 90 percent principal ingredient and a minimum quantity of impurities. Wettable powders are easily produced from such chlorofos. Surfactants and solid carriers performing the role of crystallization centers are added to technical-grade chlorofos to hasten its crystallization (545).

A large number of analogues and homologues of chlorofos has been synthesized, but their insecticidal properties are significantly weaker than those of chlorofos. Thus for example, O,O-diethyl-(1-oxy-2,2,2-trichloroethyl)-phosphonate is almost 15 times less active against flies than chlorofos, and it is more toxic to homeothermic animals. Among the derivatives of chlorofos, some of its esters with various acids have attracted interest in their use as insecticides.

Mention should also be made of O,O-dimethyl-(2,3,6-trichloro-α-oxybenzyl)-phosphonate, obtained by condensation of dimethylphosphite with 2,3,6-trichlorobenzaldehyde, which exhibits herbicidal action (546).

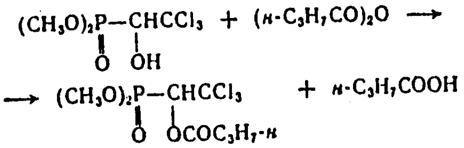
O,O-Dimethyl-(1-butyroxy-2,2,2-trichloroethyl)-phosphonate (butonate) is a colorless liquid with almost no odor; d_4^{20} 1.3998; n_D^{0} 1.4740. Butonate is moderately soluble in water and freely soluble in most organic solvents (see also Table 48).

Its LD_{50} in rats is 700 mg/kg.

Butonate has strong contact action, and it is used mainly against ectoparasites in domesticated animals. It is marketed as an emulsion concentrate.

The preparation is more resistant to hydrolysis than chlorofos. Its hydrolysis proceeds quickly in an alkaline medium. The end products of hydrolysis are phosphoric, hydrochloric and butyric acids.

Butonate is obtained by reacting chlorofos with the anhydride or acid chloride of butyric acid:



$$(CH_3O)_2\underset{\overset{\|}{O}}{P}-\underset{\overset{|}{OH}}{C}HCCl_3 + (n\text{-}C_3H_7CO)_2O \longrightarrow$$

$$\longrightarrow (CH_3O)_2\underset{\overset{\|}{O}}{P}-\underset{\overset{|}{OCOC_3H_7\text{-}n}}{C}HCCl_3 + n\text{-}C_3H_7COOH$$

Phosphonium Salts

Besides phosphoric acid esters and amides, some salts of substituted phosphonium, which have varied pesticidal activity, have been studied as pesticides. One of the first to be used against moths was 3,4-dichlorobenzyltriphenylphosphonium chloride, which was an ingredient of eylan, with which furs and wool were impregnated to prevent destruction by moths. Tetraalkylphosphonium salts have almost the same bactericidal and fungicidal action as do ammonium salts with identical hydrocarbon radicals (547).

The preparation fosfon-D--tributyl-2,4-trichlorobenzylphosphoniumchloride enjoyed some

Systematic study of the biological activity of phosphonium salts established that the activity of a compound depends not only on the structure of the cation but also on the structure of the anion. Substances have been found among phosphonium salts that exhibit not only microbiological and insecticidal activity but also herbicidal properties (548). However, they have not as yet found practical applications.

Some practical applications as a fungicide have been found for the binary salt of triphenyldecylphosphonium bromide and triphenylol chloride (melting point 114°C, LD_{50} 700-1,010 mg/kg), which has been suggested as an agent against phytophthora and cercosporosis as a 50 percent wettable powder.

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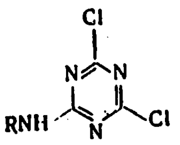
CHAPTER 29

HETEROCYCLIC COMPOUNDS WITH THREE AND MORE HETEROCYCLIC ATOMS PER RING

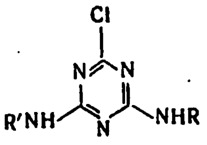
Derivatives of Six-Membered Heterocycles

s-Triazine Derivatives

Despite the fact that research on the pesticidal properties of *s*-triazine derivatives began relatively recently, there have been significant successes in this area, and a large number of preparations have found practical applications in agriculture and industry. Triazines of the following types (XII-XVIII) are used as pesticides (61):



XII



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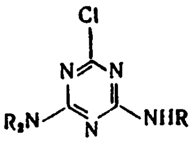

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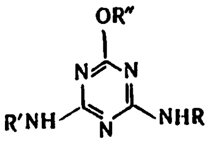
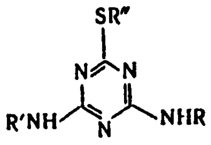
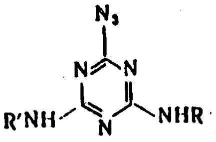


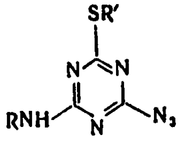
XV



XVI



XVII



XVIII

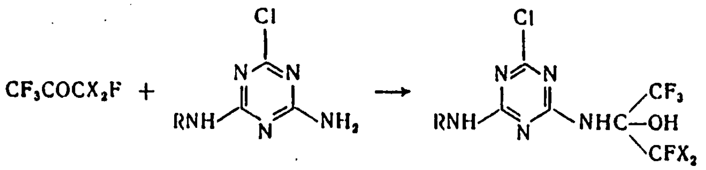
Compounds with general formula XII containing an aliphatic radical at the noncyclic nitrogen atom are inadequately stable, and they do not enjoy practical use, though they do have herbicidal properties. When this aliphatic radical is replaced by an aromatic radical the phytocidal properties decrease, and the compound's fungicidal activity rises. The most active compound used against plant diseases is 2,4-dichloro-6-(2′-chlorophenylamino)-*s*-triazine (diren). Its isomers with halogen in other positions are less active.

Compounds with general formula XIII exhibit high herbicidal activity in the event that the hydrocarbon radicals at the noncyclic nitrogen atom contain not more than four carbon atoms. When the length of the carbon chain of the radicals at the nitrogen atom increases ($>C_4$), the compound's herbicidal activity decreases. A similar law is observed with the series of compounds with general formula XIV.

When a halogen atom is substituted by a hydroxyl group the compound loses its herbicidal properties completely, while substitution by an alkoxyl group (compounds with formula XV) or an alkylmercapto group (compounds with formula XVI), the compound's selectivity changes while herbicidal properties are retained. Compounds of this series exhibit optimum activity when the alkoxyl or alkylmercapto group contains one carbon atom, though there are indications in the literature that compounds containing a carbomethylmercapto group (62,63) and some other groups (64) do have herbicidal properties as well. Substitution of the halogen atom by a 2-chlorallylmercapto (65,66), benzylmercapto (61) or benzyloxy group (68) causes fungicidal properties to appear.

2-Fluoro, 2-azido (70-73), 2-cyano (75-77), 2-dialkylaminooxy (78) and 2-dialkylaminomercapto (79) 4-alkylamino-6-alkylamino-*s*-triazines also have herbicidal properties. Herbicidal properties are possessed by 2-azido-4-methylmercapto-6-alkylamino-*s*-triazines (69,74) and trialkoxy-*s*-triazines (80) as well.

Herbicidal properties are exhibited by diamino-*s*-triazines containing hydrocarbon radicals at the noncyclic nitrogen of the most diverse structure, to include secondary (61,82) and tertiary (61,83,84) alkyl groups, unsaturated groupings (85-89) such as allyl (87), acetylene hydrocarbon residues (86,89) and polyfluoroalkyl groups (90,91) obtained in the reaction between 2-chloro-4-alkylamino-6-aminotriazine and polyfluorochloracetones:



X = Cl, Br, F, SCN

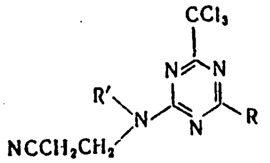
A large number of 2-chloro-4-amino-6-cyclopropyl-*s*-triazines and their 2-methoxy- and 2-methylmercapto- analogues (92-100) as well as 2-chloro-, 2-methoxy and 2-methylmercapto-4-alkylamino-6-alkoxyalkyl-*s*-triazines (101-104) and -6-alkylmercaptoalkyltriazines (105) have been patented for use as herbicides. *s*-Triazines containing heterocyclic radicals at the nitrogen atom have also been described (106,107).

2-Chloro-, 2-methoxy- and 2-methylmercapto-4-alkylamino-6-(N-alkyl-N-acylamino)-*s*-triazines (109-112), containing (as the acyl group) carboxylic and sulfonic acid residues as well as residues of various derivatives of the acids of phosphorus, have been patented as herbicides.

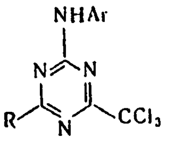
A large number of *s*-triazines containing a nitrile group in the hydrocarbon radical at the noncyclic nitrogen atom have been described (113-118); some compounds of this class have enjoyed practical use (an example is the herbicide bladeks (121)). In addition 2-chloro-4-hydrazino-6-alkylamino-*s*-triazines have been described in the literature (119,120), but they have not yet achieved practical use.

Substitution of one of the hydrocarbon radicals at the noncyclic nitrogen atom in diamino-*s*-triazines by an alkoxyl group reduces the compound's stability and decreases its life, which may be of great practical interest in relation to some compounds (81). Introduction of imine nitrogen into the hydrocarbon radical at the noncyclic nitrogen atom of 2-chloro-, 2-methoxy- or 2-methylmercapto-4-alkylamino-6-alkylamino-*s*-triazines produces herbicidal compounds (108).

Compounds with general formula XIX have also been proposed as herbicides (122-124); compounds with general formula XX possess fungicidal properties (125-127).



XIX



XX

R and R' = Alk

Fungicides have been found among the N-oxyamino derivatives of aminotriazines also (128).

In addition insecticides (129) and insect sterilizers (130,131) have been found among derivatives of *s*-triazine.

2,4-Dimethoxy-6-pentachlorophenylmercapto-*s*-triazine (melting point 162°C) has herbicidal action (132).

Derivatives of *s*-triazine that have come into use as pesticides are shown in Table 49.

2-Chloro-4,6-bis-(alkylamino)-*s*-triazines may exist in three tautomeric forms; however, in most cases the equilibrium is shifted in the direction of the amine form XIII (133):

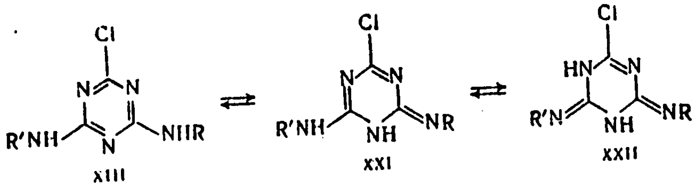
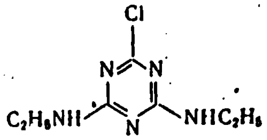
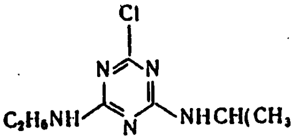
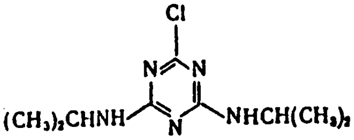
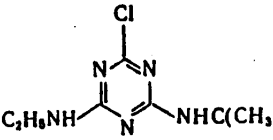
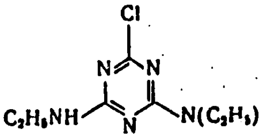
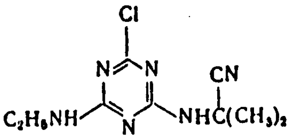
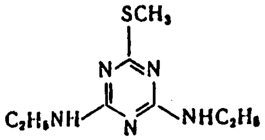
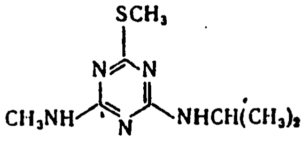
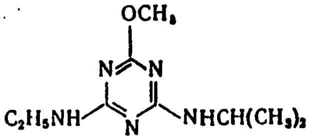
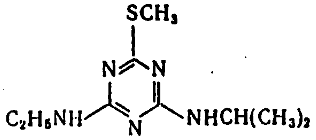
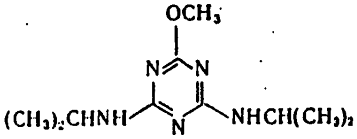
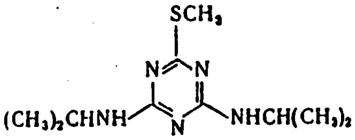
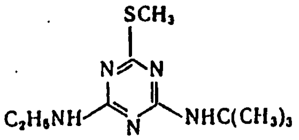
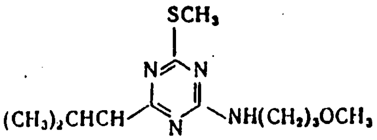


Table 49. Derviatives of

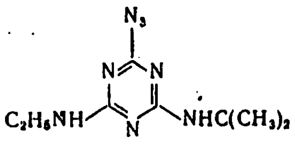
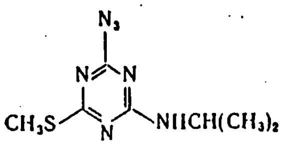
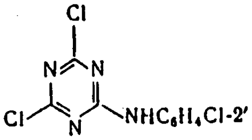
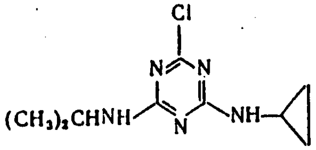
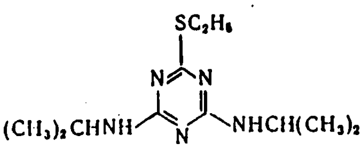
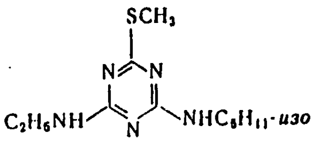
Chemical Name	Formula	Synonyms
2-Chloro-4,6-bis-(ethylamino)- -*s*-triazine		Simazine, primatol-S, gesatop, G-27692
2-Chloro-4-ethylamino-6-isopropylamino-*s*-triazine		Atrazine, primatol-A, izaprim, aatrex, G-30027
2-Chloro-4,6-bis-(isopropylamino)-*s*-triazine		Propazin, gesamil, milogard, primatol-P, G-30028
2-Chloro-4-ethylamino-6- -*tert*-butylamino-*s*-triazine		Primatol-M, GS-13529
2-Chloro-4-ethylamino-6-diethylamino-*s*-triazine		Gesafloc, trietazine, G-27901
2-Chloro-4-ethylamino-6-(2'- -cyanopropyl-2'-amino)- -*s*-triazine		Bladeks, tsianazin, VL-19805, SD-15418
2-Methylmercapto-4,6-bis- -(ethylamino)-*s*-triazine		Gi-bon, G-32911

s-Triazines Used as Pesticides

Melting Point, °C	Solubility in Water, mg//liter	Vapor Pressure, mm Hg	LD_{50} in Rats (Orally) mg/kg	Use. Forms of Application and Consumption Norms
225—227	5	$6{,}1 \cdot 10^{-9}$	5000	Herbicide controlling weeds in corn. 50,80% w.p.; 0.2-3 kg/ha. A total herbicide at 5-20 kg/ha. Also used mixed with other herbicides.
173—175	33	$3 \cdot 10^{-7}$	3080	Herbicide controlling weeds in corn, sorghum, sugar cane etc. 50,80% w.p.; 0.75-3 kg/ha.
212—214	8,6	$2{,}9 \cdot 10^{-8}$	5000	Herbicide controlling weeds in sorghum and carrots. 50 and 80% w.p.; 0.5-2 kg/ha.
177—179	8,5	$1{,}12 \cdot 10^{-6}$	2160	Total herbicide; additionally used to control weeds in vegetables, corn, potatoes. 50% w.p.; 1-3 kg/ha.
102—104	20	—	1750	Herbicide controlling weeds in potatoes and chrysanthemums. W.p.; 1-2 kg/ha.
167,5—169	171 (25 °C)	$1{,}6 \cdot 10^{-9}$	149—334	Herbicide controlling weeds in corn, potatoes, soy. W.p.; 0.5-3 kg/ha.
81—82,5	450	$7{,}1 \cdot 10^{-7}$	535	Herbicide controlling weeds in rice; 0.5-1 kg/ha. AC_{50} in fish, about 26 mg/liter.

Chemical Name	Formula	Synonyms
2-Methylmercapto-4-methylamino-6-isopropylamino-*s*-triazine		Semeron, desmetrin, G-34360
2-Methoxy-4-ethylamino-6-isopropylamino-*s*-triazine		Atraton, gezatamin, G-32293
2-Methylmercapto-4-ethylamino-6-isopropylamino-*s*-triazine		Ametryne, gezapaks, G-34162
2-Methoxy-4,6-bis-(isopropylamino)-*s*-triazine		Prometon, primatol-O, primatol, G-31435
2-Methylmercapto-4,6-bis-(isopropylamino)-*s*-triazine		Prometryne, gezapaks, caparol, G-34161
2-Methylmercapto-4-ethylamino-6-*tert*-butylamino-*s*-triazine		Terbutrin, igran, preban, GS-14260
2-Methylmercapto-4-isopropylamino-6-(3′-methoxypropylamino)-*s*-triazine		Metoprotrin, metotrin, gezaran, G-36393

Melting Point, °C	Solubility in Water, mg/ /liter	Vapor Pressure mm Hg	LD_{50} in Rats (Orally) mg/kg	Use. Forms of Application and Consumption Norms
84—86	580	$1{,}0 \cdot 10^{-6}$	650	Herbicide controlling weeds in cabbage. W.p.; 0.5-1.5 kg/ha.
94—96	1654	$2{,}9 \cdot 10^{-6}$	1465	Herbicide controlling weeds in coffee, pineapple and sugar cane. W.p.; 1-2 kg/ha. Total herbicide at 5-10 kg/ha.
84—86	193	$8{,}4 \cdot 10^{-7}$	1110	Herbicide controlling weeds in sugar cane, carrots, pineapple. 50% w.p., 25% e.c.; 1-5 kg/ha.
91—92	750	$2{,}3 \cdot 10^{-6}$	2980	Herbicide controlling weeds in sugar cane. W.p.; 1-1.5 kg/ha.
118—120	48	$10 \cdot 10^{-6}$	3750	Herbicide controlling weeds in cotton, carrots, rice, vegetables. W.p.; 0.5-2.5 kg/ha. AC_{50} in fish, above 23.6 mg/liter.
104—105	58	$9{,}6 \cdot 10^{-7}$	2400	Herbicide controlling weeds in cereal grain crops. W.p.; 1-2 kg/ha.
68—70	320	—	5000	Herbicide controlling weeds in cereal grains and corn. W.p.; 0.5-2 kg/ha.

Chemical Name	Formula	Synonyms
2-Azido-4-ethylamino-6-*tert*-butylamino-*s*-triazine		VL-9385
2-Azido-4-methylmercapto-6-isopropylamino-*s*-triazine		Aziprotrin, mezoranil, brasoran, Ts-7019
2,4-Dichloro-6-(2′-chloro-phenylamino)-*s*-triazine		Diren
2-Chloro-4-isopropylamino-6-cyclopropylamino-*s*-triazine		Utfoks, prefok, tsiprazin
2-Ethylmercapto-4,6-bis-(isopropylamino)-*s*-triazine		Sankap, kotofor
2-Methylmercapto-4-ethyl-amino-6-*sec*-isoamylamino-*s*-triazine		S-18898

Melting Point, °C	Solubility in Water, mg//liter	Vapor Pressure, mm Hg	LD_{50} in Rats (Orally) mg/kg	Use. Forms of Application and Consumption Norms
101—104	72	$7{,}4 \cdot 10^{-7}$	460	Herbicide controlling monocotyledonous annual weeds in cereal grain. W.p.; 1-3 kg/ha.
91—93	75	—	5833	Herbicide controlling weeds in cabbage. W.p.; 1.25-3 kg/ha.
155—157	—	—	2710	Fungicide controlling potato and tomato diseases. 50% w.p.
Liquid	—	—	410—1200	Selective herbicide. E.c.; 0.6-2 kg/ha.
104—106	16	—	5000	Selective herbicide. W.p.; 1-2 kg/ha.
151—153 (0,05)	50	—	5000	Selective herbicide. Used mixed with S-19490 in rice crops.

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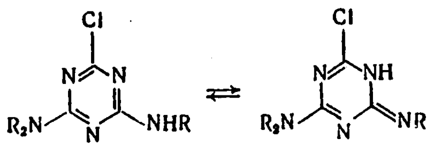
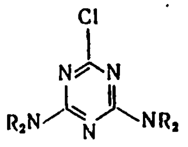
Only two tautomeric forms XXIII and XXIV are possible for 2-chloro-4-dialkylamino-6-alkylamino-*s*-triazines, while only one amine form XXV is possible for 2-chloro-4,6-bis-(dialkylamino)-*s*-triazines:



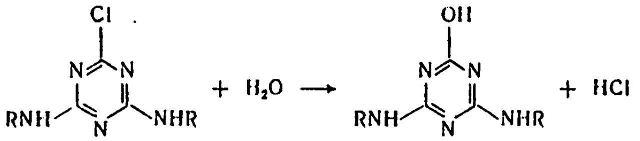
XXIII XXIV



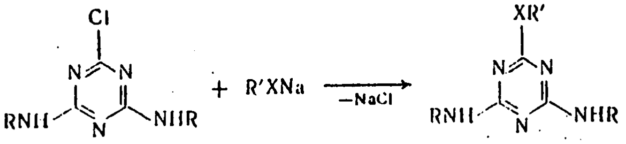
XXV

These groups of compounds also differ in physical properties. 2-Chloro-4,6-bis-(alkylamino)-*s*-triazines are predominantly solid crystalline substances with high melting points and poorly soluble in water and in organic solvents, while 2-chloro-4,-4,6-bis-(dialkylamino)-*s*-triazines have a low melting point and are soluble in many organic solvents.

2-Chloro-4,6-bis-(alkylamino)-*s*-triazines are stable when stored at room temperature, and they can be stored practically indefinitely without change. When heated with water, especially in the presence of organic or inorganic bases, they hydrolyze to inactive oxy compounds:



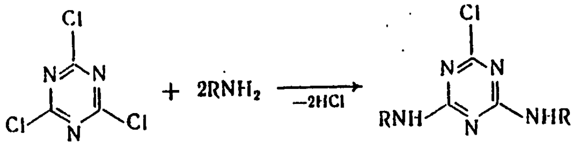
The halogen atom may also be substituted by other groups; thus when these compounds react with metal alcoholates, the appropriate 2-alkoxy-4,6-bis-(alkylamino)-*s*-triazines form, and when they react with mercaptamides, 2-alkylthio-4,6-bis-(alkyamino)-*s*-triazines form:



$X = O, S$

Both of the groups of compounds formed as a result are valuable herbicides.

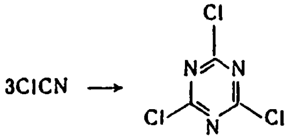
2-Chloro-4,6-bis-(alkylamino)-*s*-triazines are obtained with good yields by reacting cyanurochloride with amines. If both amine groups contain identical hydrocarbon radicals, the reaction is performed in a single stage:



But when the radicals in the amino groups are different, a two-stage process would be suitable. In the first stage one of the amine molecules is made to react, forming 2,4-dichloro-6-alkylamino-*s*-triazines; one molecule of the secondary amine is then attached to the latter. Both inorganic and organic bases or excess amine can be used as the hydrogen chloride acceptor.

This reaction is at the basis of industrial acquisition of 2-chloro-4,6-bis-(alkylamino)-*s*-triazines (134-137). In this case if the target compound is symmetrical 2-chloro-4,6-bis-(alkylamino)-*s*-triazine, the reaction may be performed in a single stage, using sodium hydroxide or some other inorganic base, including ammonium, as the hydrogen chloride acceptor (136).

The cyanurochloride required for synthesis of substituted triazines is obtained by polymerization of cyanogen chloride:



The reaction is performed in the presence of activated charcoal at 350-400°C, or in a liquid phase under pressure in various organic solvents using, as the catalyst, anhydrous aluminum chloride, boron fluoride, hydrogen chloride and so on. The basic flowchart for production of cyanurochloride is shown in Figure 20 (138).

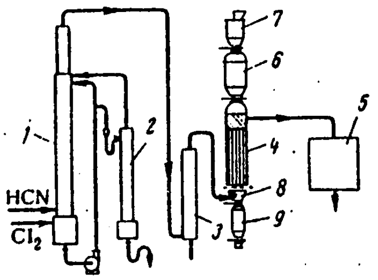
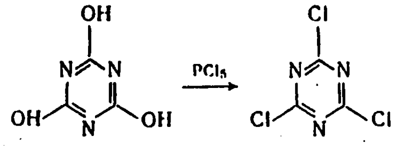


Figure 20. Basic Flowchart for Production of Cyanurochloride: *1*--column for acquisition of cyanogen chloride; *2*--column for regeneration of HCN; *3*--cyanogen chloride drying column; *4*--reactor for acquisition of cyanurochloride; *5*--cyanurochloride collector; *6*,*7*,*8*,*9*--devices allowing for catalyst (activated charcoal) replacement

Cyanurochloride may also be obtained by the action of phosphorus pentachloride on cyanuric acid (the yield is 55-59 percent, while when cyanogen chloride is subjected to polymerization, the cyanurochloride yield is more than 90 percent of theoretical):



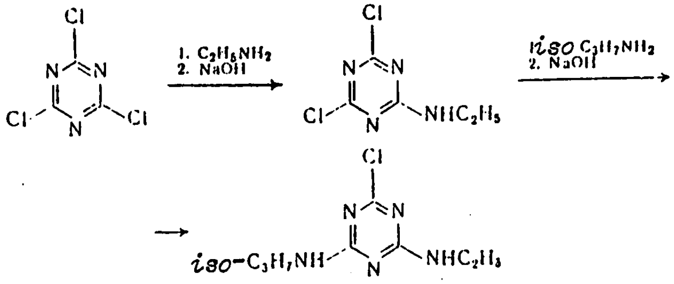
When methylrhodanide is chlorinated, the cyanurochloride yield is 85 percent, but it is difficult to remove other chlorination products from the target compound.

Pure cyanurochloride is a white crystalline substance with a melting point of 146-147° 146-147°C, it is practically insoluble in water, and it is freely soluble in most organic solvents. It is readily hydrolyzed by water, transforming into cyanuric acid. Hydrolysis proceeds especially quickly at high temperature and in the presence of bases. This must be considered when using cyanurochloride to synthesize substituted triazines in an aqueous medium. In the presence of bases, cyanurochloride reacts with many compounds containing active hydrogen.

Gaseous cyanurochloride formed out of cyanogen chloride upon trimerization in charcoal catalyst may be used to obtain symmetrical chlorotriazines; cyanurochloride is passed through an aqueous solution of amine and sodium hydroxide (134).

The formed chloroaminotriazine is filtered, washed with water and dried. This method can be used to obtain simazine (Figure 21) and propazin. Other triazines obtained by this method are low in quality because they contain a large quantity of related compounds. This process can also be employed to obtain symmetrical fluorotriazines, using four moles of amine to every mole of cyanurochloride (134). In this case the process is carried out without adding sodium hydroxide, and the amine is regenerated in the next stage.

Acquisition of asymmetrical triazines may be demonstrated with the example of atrazine:



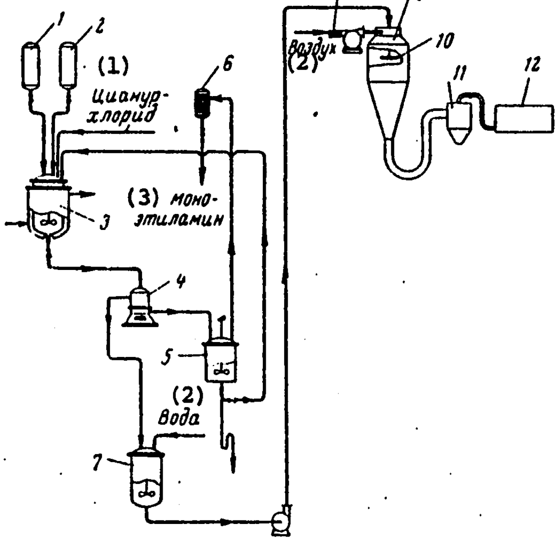


Figure 21. Flowchart for Production of Simazine Out of Gaseous Cyanurochloride: *1*--ethylamine gaging tank; *2*--sodium hydroxide solution gaging tank; *3*--reactor; *4*--centrifuge; *5*--vat for distillation of ethylamine from mother liquor; *6*--cooler; *7*--container for acquisition of simazine pulp; *8*--calorifier; *9*--spray dryer; *10*--spray disk; *11*--cyclone; *12*--dust filter

Key:
1. Cyanurochloride
2. Air
3. Monoethylamine

These reactions are easily performed even in the same apparatus, since the second reaction proceeds at a higher temperature than the first.

It has been suggested that in some cases the reaction of obtaining asymmetrical chloroaminotriazine should be carried out in a mixture of water and an organic solvent that is immiscible with water. In this case the 2,4-dichloro-6-alkylaminotriazine formed in the first stage moves into the organic solvent, which reduces the possibility of its hydrolysis by water and its interaction with the second amine molecule. Chlorobenzene, dichloroethane and a number of others have been recommended as organic solvents. The reaction with the second amine as a rule results in a product poorly soluble in organic solvents and readily filtered out. A flowchart for acquisition of atrazine is shown in Figure 22.

It should be noted that owing to high persistence, production of symmetrical fluorothiazines such as simazine and propazin is continually decreasing. These compounds are being substituted by less-persistent preparations--primarily various 2-methylmercapto-4,6-bis-alkylamino-*s*-triazines as well as the corresponding azides. The latter can be obtained either by an exchange reaction between the appropriate chloride derivatives and sodium azide (139)

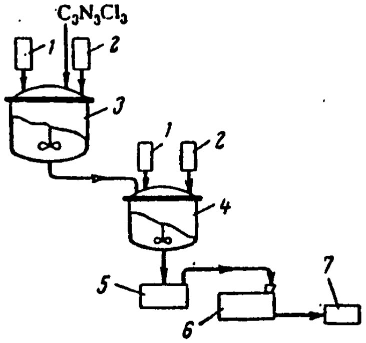
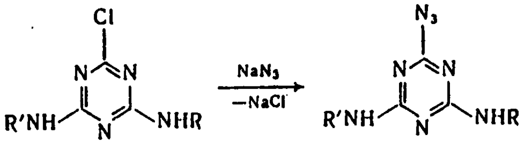
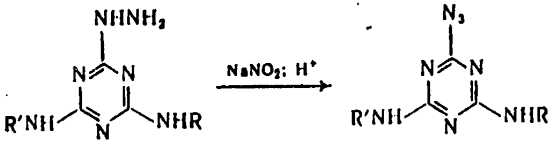


Figure 22. Flowchart for Acquisition of Triazine: *1*--amine gaging tanks; *2*--sodium hydroxide gaging tanks; *3*--reactor for obtaining 2,4-dichloro-6-ethylamino-*s*-triazines; *4*--reactor for atrazine acquisition; *5*--filter; *6*--dryer; *7*--atrazine collector

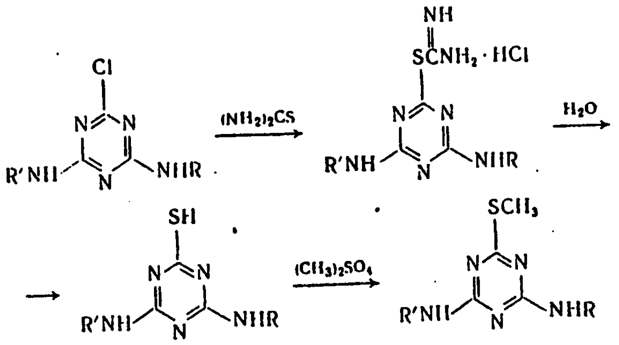


or by reacting the appropriate hydrazides with nitrous acid at 0-5°C (140):



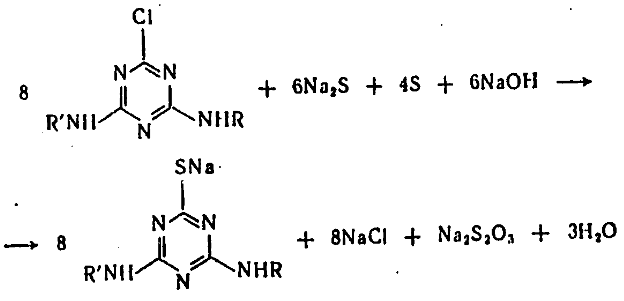
2-Methylmercapto-4,6-bis-(alkylamino)-*s*-triazines may be obtained, as was indicated earlier, by reacting methylmercaptide with 2-chloro-4,6-bis-(alkylamino)-*s*-triazines (141). This reaction proceeds both in an aqueous medium and in organic solvents. According to the patent literature, when isopropyl or *sec*-butyl alcohol is used as the solvent, the yield of the end product may climb as high as 98 percent. The reaction proceeds at 70-75°C (141,142).

In another interesting method, 2-methylmercapto-4,6-bis-(alkylamino)-*s*-triazines are obtained as follows (143):



The merit of this method is that it does not require acquisition of methylmercaptan. However, the process consists of many stages, and it requires the use of toxic dimethylsulfate and rather expensive thiourea.

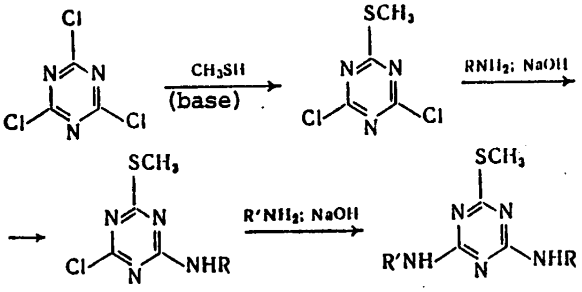
A simpler method of obtaining 2-methylmercapto-4,6-bis-(alkylamino)-*s*-triazines is to react 2-chloro-4,6-bis-(alkylamino)-*s*-triazines with a mixture of sodium sulfide and sodium polysulfide:



The reaction proceeds relatively easily in an aqueous solution at high temperature. The resulting sodium salt of 2-mercapto-4,6-bis-(alkylamino)-*s*-triazine is easily transformed, without separation, into 2-methylmercapto-4,6-bis-(alkyalmino)-*s*-triazine in response to the action of dimethylsulfate. The yield of the sought triazine exceeds 90 percent of theoretical.

However, intermediate 2-mercapto-4,6-bis-(alkylamino)-*s*-triazine can also be obtained by oxidation with mineral acids; in this case the final 2-methylmercapto product is completely free of initial chlorotriazine impurities. This method requires simple apparatus, and it provides a sufficiently pure 2-methylmercapto compound (148).

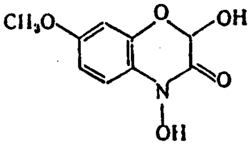
Moreover 2-methylmercapto-4,6-bis-(alkylamino)-*s*-triazine can also be obtained by the following pathway (144-147):



The process may be carried out in both an aqueous medium and in a mixture of water and an immiscible organic solvent; either alkali or organic bases can be used as the hydrogen chloride acceptor. There are indications that the entire series of the transformations described here may be carried out within a single reactor, in which individual stages of the reaction are performed in succession (146).

As was noted earlier, 2-alkoxy-4,6-bis-(alkylamino)-*s*-triazines may be obtained by the action of alkali metal alcoholates upon the appropriate chlorotriazines. The reaction proceeds most readily in organic solvents at high temperature.

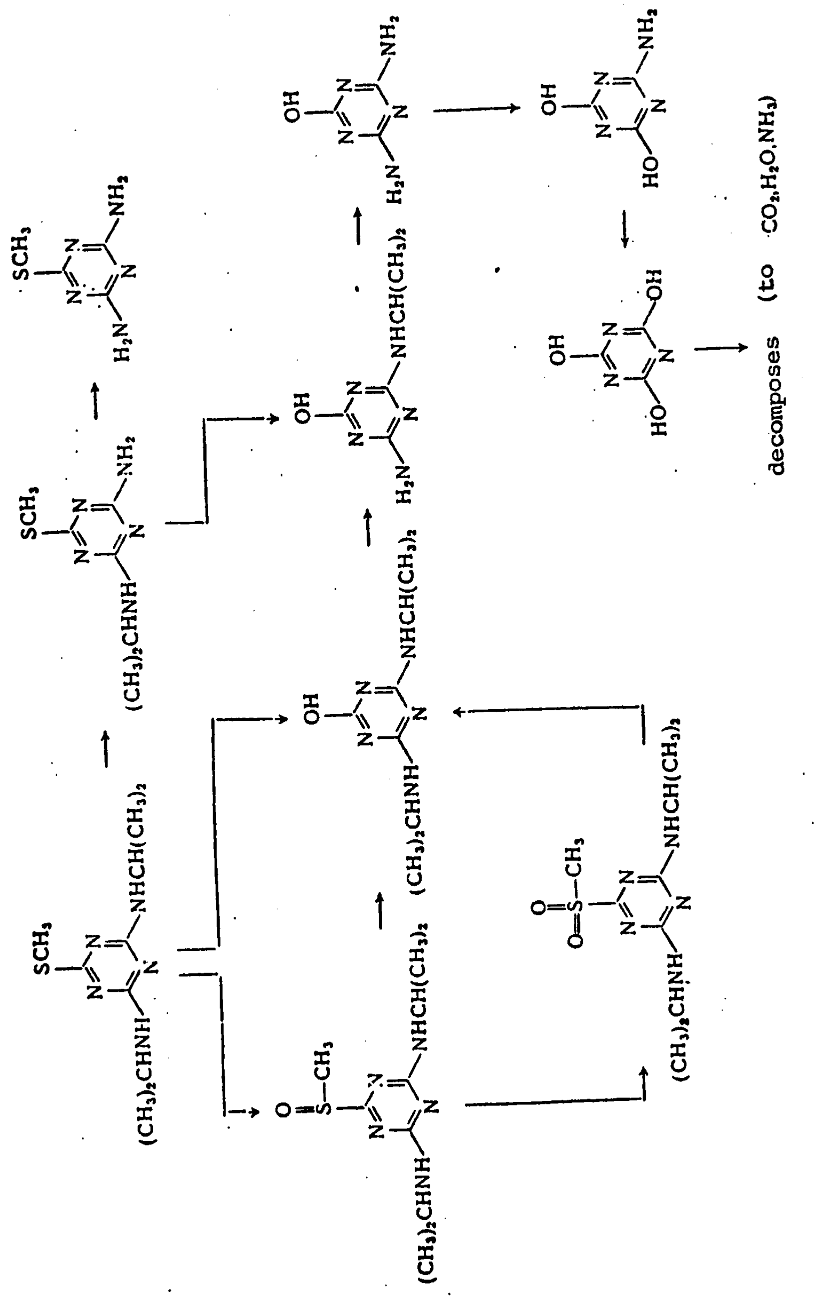
Most substituted *s*-triazines are sufficiently stable at room temperature, but when heated to 240-250°C, they undergo dealkylation to form olefins (149). It has been established that the principal pathways of metabolic transformation of triazines are: hydrolysis (in which halogen atoms and alkoxyl and methylmercapto groups are split off), dealkylation at the noncyclic nitrogen atom, and splitting of the triazine ring; these reactions proceed at different rates in different media. It is believed that hydrolysis is catalyzed in plants resistant to chlorotriazines by 2,4-dioxy-7-methoxybenzo-1,4-oxazinone-3 (151,156).

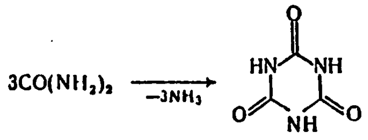


The metabolism of prometryne is an example of this (see diagram on p 252).

In addition to the *s*-triazines described above, a large number of other compounds of this series with pesticidal properties have been synthesized, particularly 2-chloro-4-dialkylamino-6-dialkylthioamido-*s*-triazines, which have fungicidal properties (157).

Among the hydrated derivatives of *s*-triazine, mention should be made of the derivatives of tetrahydro-*s*-triazine (158,159) and 1-aryl-4,6-diisopropyl-3,5-dimethyl-hexahydro-*s*-triazine (160), which have herbicidal properties, and a number of other derivatives of hexahydro-*s*-triazine possessing insecticidal and fungicidal properties (161), though they have not as yet achieved practical applications in this direction. Various products of cyanuric acid that are easily obtained by thermal cyclization of urea should be included among the derivatives of hexahydro-*s*-triazine:

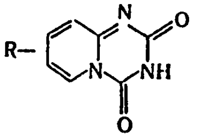

SCH₃
(CH₃)₂CHNH
NHCH(CH₃)₂
NH₂
H₂N
OH
HO
O=S—CH₃
decomposes (to CO₂,H₂O,NH₃)



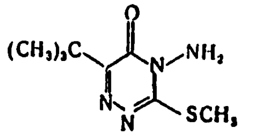
The simplest derivatives of cyanuric acid are binary compounds of copper salts, which have a chelate structure and which possess fungicidal properties (162). Fungicidal and bactericidal properties are exhibited by chloro- and dichlorocyanuric acids and their alkali metal salts (163) as well as by trichlorocyanuric acid, which is easily obtained by chlorination of cyanuric acid in aqueous alkali solution (164). Depending on the chlorination conditions and the number of chlorine atoms, all three derivatives of cyanuric acid may be obtained.

The sodium salt of dichlorocyanuric acid has enjoyed the broadest use as a bleach, an antiseptic and a disinfecting preparation. It has almost no odor at all, it is readily soluble in water, and it contains a significant quantity of active chlorine.

Herbicidal action is also exhibited by benzotetrahydro- and benzohexahydro- derivatives of *s*-triazine with general formula XXVI (165-167).



XXVI



XXVII

A compound with formula XXVII--4-amino-3-methylmercapto-6-*tert*-butyl-1,2,4-triazinone-5 (metributin)--has recently achieved practical use of a herbicide. It consists of colorless crystals with a melting point of 118-125.5°C.

Its solublility in water at 20°C is 1.2 gm/liter, and it is freely soluble in organic solvents (168,169).

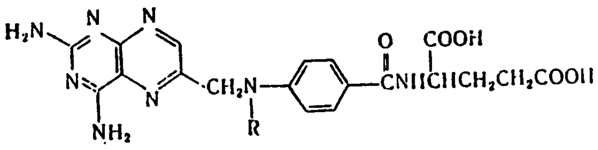
Its LD_{50} in rats is 2,200 mg/kg; its AC_{50} in fish is about 10 mg/liter.

Metributin is produced in the form of 70 percent wettable powder. It is used against di- and monocotyledonous weeds in soy, potatoes and other crops (168-171).

Other benzotriazines (172,173), benzotetrazines (174) and seven-membered heterocycles with three nitrogen atoms (175) have also been proposed as pesticides.

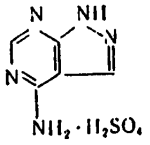
Derivatives of Other Heterocycles

In addition to the derivatives of the heterocycles described above, a number of heterocyclic compounds are presently being studied in production conditions as sexual sterilizers of insects. Compounds with sterilizing action include some derivatives of folic acid XXVIII:

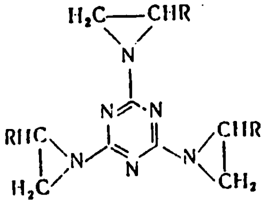


XXVIII

As is true with 5-fluorouracil and 5-fluorouracil-6-carboxylic acid (see Chapter 28), the action of these compounds is apparently based on substitution of metabolites. Sterilizing action is also exhibited by 4-amino-1′H-pyrazolopyrimidine (sulfate) (XXIX), tris-ethylenimino-*s*-triazines and tris-methylethylamino-*s*-triazines (XXX) (R = H or CH_3):

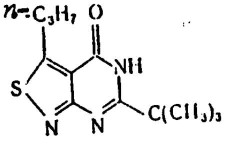


XXIX

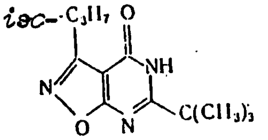


XXX

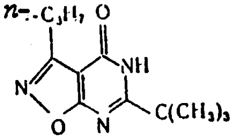
Preparations NIA-19873 (XXXI) (LD_{50} 10,200 mg/kg), NIA-21844 (XXXII) (LD_{50} 15,400 mg/kg), NIA-21861 (XXXIII) (LD_{50} 6,800 mg/kg) and NIA-23486 (XXXIV) (LD_{50} 6,834 kg/ha) have been released in the USA as experimental herbicides (176).



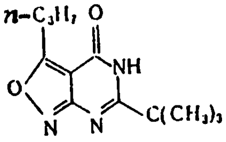
XXXI



XXXII



XXXIII



XXXIV

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