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STAT

USSR Work on Alkaloids and Local Anesthetics

(1) ANESTHETIZING DERIVATIVES OF CONVOLINE AND CONVOLAMINE

M. S. Rabinovich and R. A. Konovalova

(2) ALKALOIDS OF THE MAGNOLIA FUSCATA

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(3) LOCAL ANESTHETICS OF THE QUINOLINE-4-CARBOXYLIC ACID CLASS

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(4) STUDY OF THE MILK-LIKE JUICE OF THE SPURGE EUPHORBIA MICLANDULOSA BOISS - N. P. Kir'yalov

(5) ALKALOIDS OF THE SALSOLA RICHTERI. IV.

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ANESTHETIZING DERIVATIVES OF CONVOLVIN AND CONVOLAMIN

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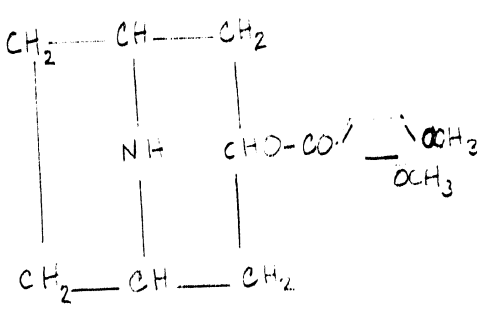
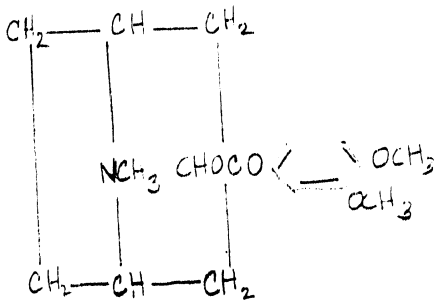
The alkaloids convolvin and convolamin were first extracted in 1933 by R. A. Konovalova and A. P. Orekhov from the plant Convolvulus subhirsutus Rgl. et Schmalh. (The alkaloid property of this plant was first established in 1931 by the head of the expedition of the Scientific Research Chemico-Pharmaceutic Institute, P. S. Massagetov.)

This was the first time an alkaloid was found in a plant of the Convulvaceae family. The same authors showed the structure of both alkaloids [2] which turned out to be ethers of nortropin and tropin respectively with veratric acid:



Convolvin



Convolamin

A pharmacological study of these alkaloids showed that they both possess a strong local anesthetic action, but have the defect

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that when used as anesthetics of the cornea and conjunctiva of the eye, they provoke a certain irritation and hyperemia.

The aim of the present work was to obtain a series of derivatives from the above mentioned alkaloids and to study the relation between their chemical structure and pharmacological properties, with the idea of obtaining a substance answering to all the requisites of a good anesthetic.

It seemed particularly interesting to obtain derivatives of nortropin and nortropidin, because this group of substances is almost unexplored because of the small availability of nortropin. As is known, the latter could be obtained up to date only by way of saponification of ~~nergeocyamin~~ [3], which can be found in insignificant quantities in certain plants of the Solanaceae family, or by way of demetylization of tropin, which gives very poor results. Thanks to the discovery of convolvin, nortropin has today become an easily accessible substance.

As a result of our work we have obtained 18 new substances differing from each other in the substituting radicals, or by certain changes in the ~~very~~ skeleton of the molecule.

The comparison of the pharmacological properties of our preparations permits certain preliminary conclusions to be made as to the connection between anesthetic action and chemical structure.

We started our work by ~~obtaining~~ preparing benzoyl-N-β-oxyethylnortropidine. This substance was first obtained by Braun [4] and described by him as strongly anesthetic and less toxic than cocaine, but unfortunately

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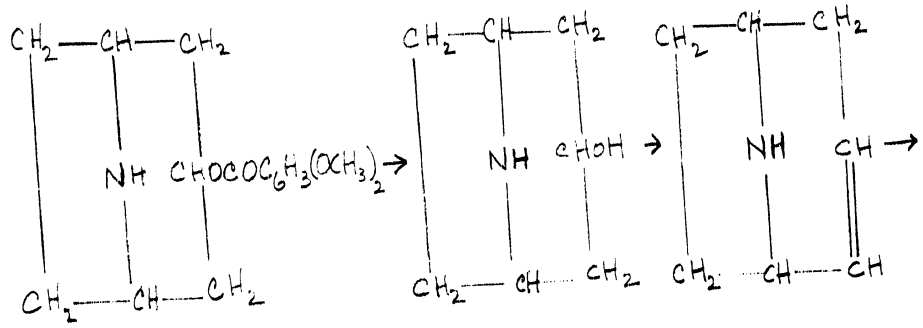
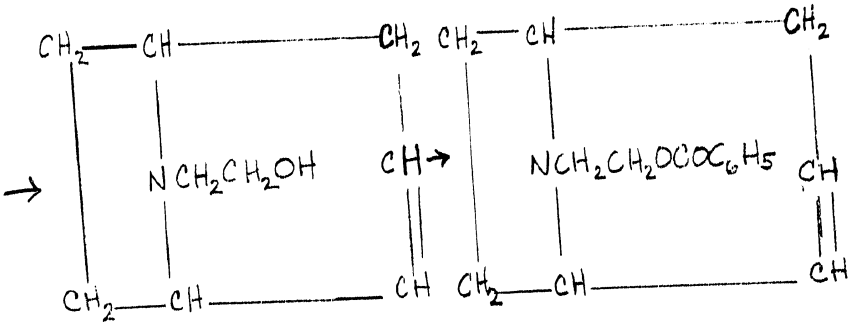
not very accessible because of the difficulty of obtaining nortropin.

The initial substance for the obtaining of benzoyl-N-β-oxyethylnortropidin was convolvin. The latter was saponified by action of alcoholic alkali and the nortropin thus obtained was subjected to dehydration with the help of strong sulphuric acid. The nortropidin obtained was heated with ethylene oxide and then was benzoylated under conditions precisely described by Braun [4].



Convolvin Nortropin Nortropidin



N-β-oxyethylnortropidin Benzoyl-N-β-oxyethylnortropidin

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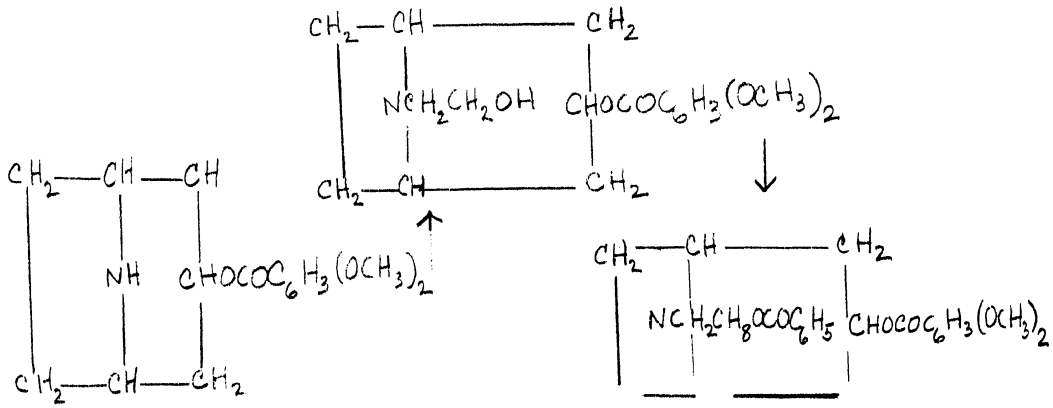
The substance obtained fully corresponds by its constants to benzoyl-N-β-oxyethylnortropidin as described by Braun.

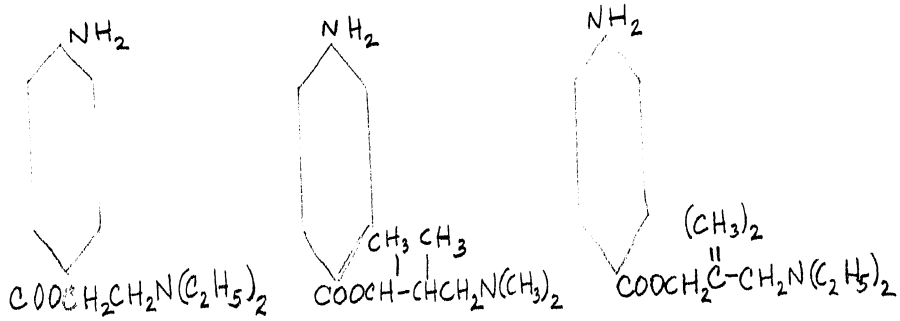
In analogy with this substance we also obtained a benzoyl-N-β-oxyethylic derivative of convolvin, for which purpose the latter was condensed with ethylene oxide and then was benzoylated:



Convolvin N-β-oxyethylconvolvin Benzoyl-N-β-oxyethylconvolvin

Benzoyl-N-β-oxyethylconvolvin is a well-crystallizing substance, giving crystallic hydrochloride and picrate.

Further it was interesting to study the analogous ethers of tropin, nortropin and N-β-oxyethylnortropin connection with the known and described anesthetizing substances [5] which are ethers of p-amino-benzoic acid, for instance:



Novocaine Tymacaine Larocaine

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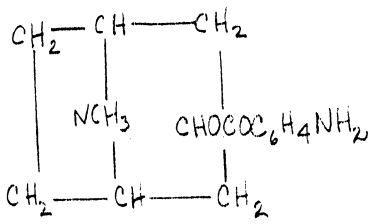
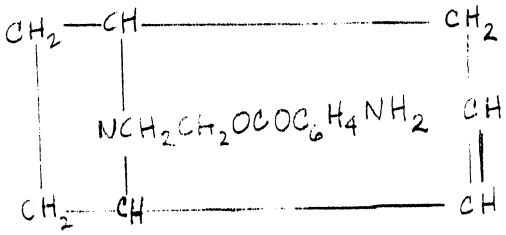
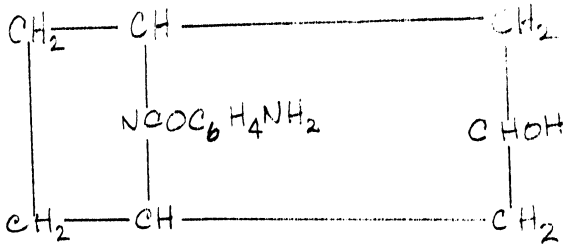
With this aim in mind we obtained: aminobenzoyltropin, aminobenzoyloxyethylnortropidin and aminobenzoylnortropin. The latter turned out to be a substance of very weak basic character, which shows that the aminobenzoylic radical is attached to the nitrogen atom:



p-aminobenzoyltropin



p-aminobenzoyl-N-β-oxyethylnortropin



p-aminobenzoylnortropin

All these substances were obtained through condensation of the corresponding amino alcohols: tropin, nortropin and N-β-oxyethyl-

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nortropidin with p-nitrobenzoyl chloride and which were then reduced to amino compounds.

Aminobenzoyltropin is a crystallic substance producing a crystallic hydrochloride, acetate, phenyl acetate, mono- and dipicrate.

Aminobenzoyl-N-β-oxyethylnortropidin crystallizes well and produces crystallic hydrochloride and picrate.

Aminobenzoylnortropin is hard to dissolve in acids and gives no sediment with silico-wolframic acid. Its salts with mineral acids are strongly hydrolyzed in aqueous solution, as a result of which the latter has an acid Congo reaction. For this reason this substance could not be studied pharmacologically.

Since it is known that the derivatives of pseudotropin, such as tropococaine and psicaine, are stronger anesthetics and less toxic [6], than the corresponding derivatives of tropin, it was interesting to obtain and study derivatives of pseudotropin.

We obtained pseudotropin from tropin under conditions precisely described by Willstatter and then we condensed it with nitrobenzoylchloride and reduced it precisely in the same way as in the case of aminobenzoyltropin.

Aminobenzoylpseudotropin is a crystallic substance. It forms a crystallic hydrochloride and phenyl acetate.

In order to clarify the influence of the acetyl radical on anesthetic action and toxicity of the substance we also obtained the acetyl derivative of aminobenzoyltropin:

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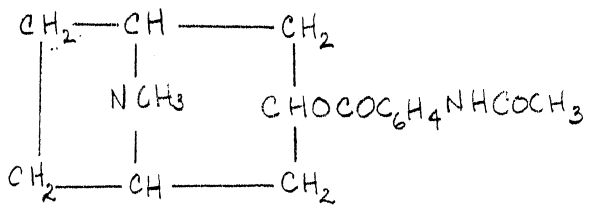
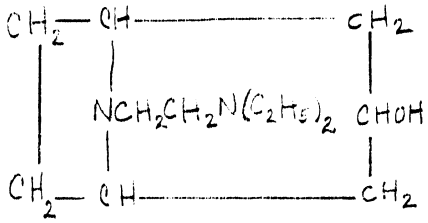
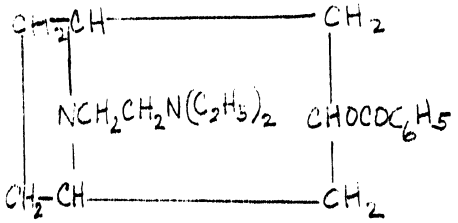


This substance was obtained through action of acetic anhydride on aminobenzoyltropin. It is a crystallic substance and produces crystallic hydrochloride and phenyl acetate.

In order to study the action of the diethylaminoethylic radical which is also often contained by anesthetic substances, we obtained the corresponding derivatives of nortropin, benzoyl-nortropin and nortropidin.



N-diethylaminoethylnortropin



Benzoyl-N-diethylaminoethylnortropin

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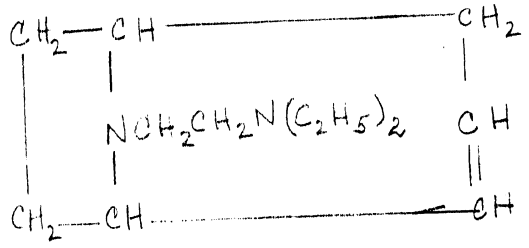

N-diethylaminoethylnortropidin

These bases were obtained through the action of diethylaminoethylchloride on the corresponding amino alcohols.

Diethylaminoethylnortropin is obtained in the shape of a crystallic substance yielding crystallic picrate and hydrochloride.

Benzoyl-N-diethylaminoethylnortropin is obtained in the shape of a crystallic hydrochloride.

Diethylaminoethylnortropidin is a liquid base which gives a crystallic picrate.

Further, from the works of Rider [8] we know that with the action of phenylisocyanide on the derivatives of piperidin containing hydroxyl radicals, one obtains substances possessing considerable local anesthetic properties. Starting from these data it was interesting to study the phenylurethanes of tropin and of oxyethylnortropidin:

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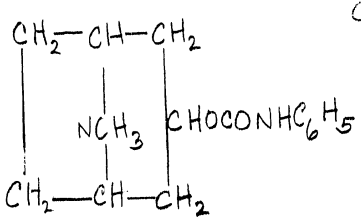
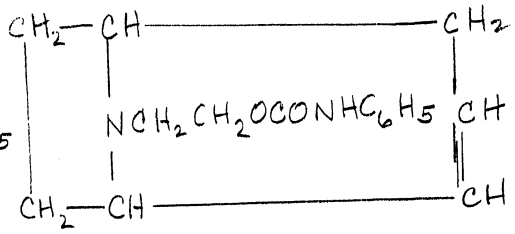


Phenylurethane of Tropin



Phenylurethane of N-B-oxyethylnortropidin

which were obtained through the action of an equimolecular quantity of phenylisocyanide on the corresponding amino alcohols. Both bases give crystallic hydrochlorides and phenyl acetates easily soluble in water.

The pharmacological study of our compounds showed that the phenyl acetates are more active than the hydrochloric salts of the corresponding bases, a fact that confirms the interesting results of Regnier's work [9] which proved with cocaine that the power of the anesthetic action of a substance depends not only upon [redacted] the character of the base, but also upon [redacted] the acid with which the given base is combined.

One must also note the fact that the molecule of the phenylacetic acid, introduced into tropin as an etherifying radical, did not manifest any positive action on the pharmacological properties of the tropin phenylacetic ether thus obtained.

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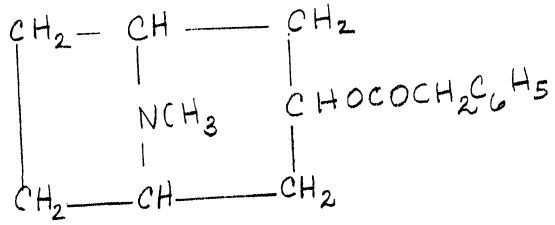
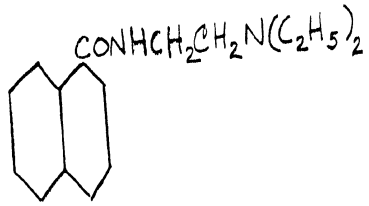


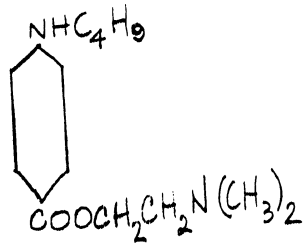
Phenylacetic Ether of Tropin

The latter was obtained by means of condensation of tropin with phenacetyl chloride (the acid chloride was obtained under the conditions described in the work by Anschutz [10]) and was in the shape of a well crystallizing hydrochloride.

Percaine and pantocaine, containing a butyl radical are among the most active local anesthetic substances obtained during the past years [5, 6, 11]:



Percaine



Pantocaine

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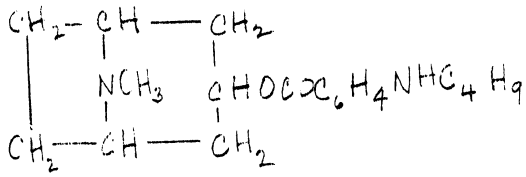
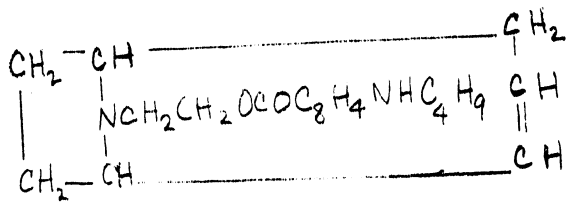
Having obtained, as we said earlier, a series of derivatives of p-aminobenzoic acid, it was entirely natural to obtain and study the corresponding derivatives of p-butylaminobenzoic acid.

We obtained butylaminobenzoyltropin, butylaminobenzoyl-pseudotropin and butylaminobenzoyl-N-β-oxyethylnortropidin:





Butylaminobenzoyltropin and pseudotropin

Butylaminobenzoyl-N-β-oxyethylnortropidin

All these bases were obtained by means of the action of butylaminobenzoyl chloride on the corresponding amino alcohols. They are all well crystallizing substances, producing hydrochlorides which are comparatively hard to dissolve in cold water.

The work to obtain new anesthetic substances, derivatives of tropin and nortropin which, after the discovery of the alkaloids convolvin and convolamin, have become very accessible substances, continues in various directions.

Here we give a table of the compared anesthetic actions of

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our compounds. From it we can make certain preliminary conclusions about the relation of pharmacological properties to the chemical structure of the substance.

The pharmacological study of our compounds, made by Doctor Ya. Kh. Holle in the pharmacological department of NIKhFI, produced the following data (Table 1):

[See next page for Table 1]

It can be seen from the table that convolvin (1), convolamin (2), benzoyloxyethylconvolvin (3) give a prolonged anesthesia, but all three preparations provoke hyperemia and epiphora. Among them convolvin is more toxic and N-β-oxyethylconvolvin is less toxic.

Benzoyloxyethylnortropidin (6) is much less toxic than cocaine, but is also weaker.

Aminobenzoyloxyethylnortropidin (7) acts in lesser concentration than benzoyloxyethylnortropidin, but is also more toxic than the latter.

Aminobenzoyltropin, in the form of hydrochloride (11), provokes an anesthesia 2 to 2.5 times more prolonged than cocaine, but is also about twice as toxic.

Aminobenzoyltropin, in the shape of phenylacetic salt (12), is as toxic as the hydrochloride, but produces an anesthesia which is 3 - 3.5 times more prolonged than that of cocaine.

Diethylaminoethylnortropin (4), with an open hydroxyl radical, provokes no anesthesia at all, while its benzoylic derivative (5)

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TABLE 1

Order No [1]	Name of Preparation [2]	Solution Concentration (%) [3]	Duration of Total Anesthesia in Minutes [4]	Lethal Dose in Mg per Kg of White Mouse Weight [5]
1	Convolvin (hydrochloride)	1	40 - 50	70 - 80
2	Convolamin (hydrochloride)	1	30 - 40	100 - 110
3	Benzoyloxyethylconvolvin (hydrochloride)	2	30 - 40	200 - 300
4	Diethylaminoethylnortropin (hydrochloride)	1 - 5	no anesthetic action	1000 - 1200
5	Benzoyldiethylaminoethylnortropin (hydrochloride)	2 - 3	30 - 40	450 - 600
6	Benzoyloxyethylnortropidin (hydrochloride)	5	10 - 12	500 - 600

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[1]	[2]	[3]	[4]	[5]
7	Aminobenzoyloxyethylnortropidin (hydrochloride)	3	10 - 15	300 - 400
8	Diethylaminoethylnortropidin (hydrochloride)	1 - 10	no anesthetic action	300 - 450
9	Phenylurethane of Oxyethylnortropidin (hydrochloride)	1	30 - 50	800 - 1000
10	Phenylurethane of oxyethylnortropidin (phenyl acetate)	0.5 - 1	50 - 80	800 - 1000
11	Aminobenzoyltropin (hydrochloride)	1	30 - 50	80 - 100
12	Aminobenzoyltropin (phenyl acetate)	0.5 - 1	20 - 70	80 - 100
13	Acetylaminobenzoyltropin (hydrochloride)	1	no anesthetic action	150 - 200
14	Acetylaminobenzoyltropin			

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[1]	[2]	[3]	[4]	[5]
	(phenyl acetate)	1	10 - 15	150 - 200
15	Aminotropococaine (phenyl acetate)	0.5 - 2	30 - 60	250 - 300
16	Phenylacetic Ether of Tropin (hydrochloride)	2 - 5	5 - 10	250 - 300
17	Phenylurethane of Tropin (hydrochloride)	5 - 6	25 - 30	800 - 1000
18	Butylaminobenzoyltropin (hydrochloride)	1:8000	30 - 40	20
19	Butylaminobenzoylpseudotropin (hydrochloride)	0.1	40 - 50	25
20	Butylaminobenzoyl Oxyethylnortropidin (hydrochloride)	0.25	30 - 40	50
21	Cocaine (hydrochloride)	1	15 - 20	150 - 200
22	Novocaine (hydrochloride)	4	doubtful	600 - 700

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provokes a very short anesthesia even though this preparation is three times less toxic than cocaine.

Diethylaminoethylnortropidin (18), provokes no anesthesia and has a toxicity two times less than cocaine.

Phenylurethane of tropin provokes anesthesia only in 5 - 6 percent solutions, but is less toxic even than novocaine.

Phenylurethane of oxyethylnortropidin as a hydrochloride (9) provokes a lengthy and fast appearing anesthesia and is distinguished by its extremely low toxicity.

Phenylurethane of oxyethylnortropidin as a phenylacetic salt (10) has an equally low toxicity and gives an even longer anesthesia.

Butylaminobenzoyltropin (18) is very toxic and is a very powerful anesthetic. Butylaminobenzoylpseudotropin (19) is slightly less toxic than (18). Butylaminobenzoyloxyethylnortropidin (20) has a less powerful action than the two preceding preparations, but is also less toxic.

Clinical tests of the substances described above (called convocains) showed that they may very well substitute cocaine in eye surgery.

EXPERIMENTAL PART

(1) Saponification of Convolvin

50 grams of convolvin, melting point 144 - 116 degrees centigrade, are added to a solution of 50 grams of KOH in 450

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milliliters of methyl alcohol and are boiled for three hours in a flask equipped with a reflux condenser over a water bath. Then the methyl alcohol is distilled in a vacuum until dry and to the residue, after cooling, one adds 10 percent HCl up to an acid Congo reaction. The veratric acid thus obtained is pumped off, washed several times in water, and the aqueous hydrochloric acid solution thus obtained is boiled down in a vacuum. The obtained concentrated solution of nortropin hydrochloride is saturated with a 40 percent solution of NaOH and is extracted with chloroform. The latter is boiled down to small volume and receives a gradual addition of an HCl alcoholic solution up to acid reaction, then receives absolute ether. The nortropin hydrochloride separated is pumped away and is washed with absolute ether. The yield is 23 - 25 grams, which represents 82 - 89 percent of theory.

The nortropin hydrochloride obtained is transformed into a base by dissolving it in water 1:1 and by adding to it 40 percent of NaOH. The base thus separated is recrystallized out of xylene 1:20, after which it is melted at 161 degrees.

(2) Saponification of Convolamin

20 grams of convolamin, melting point 115 - 116 degrees, is boiled for three hours with 100 milliliters of a 10 percent solution of KOH in methyl alcohol. Then the methyl alcohol is steamed away in a vacuum until dry and the residue is extracted with hot ether. After desiccation with potassium carbonate the ether is distilled and the remaining oil is distilled at 110 - 111 degrees (9 - 10 millimeters). With cooling the product swiftly crystallizes. The yield is 7.5 - 8 grams, representing 81 - 87 percent of the empirical [redacted] value.

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(3) Nortropidin

Add slowly 40 milliliters of H_2SO_4 (1.84) to 20 grams of nortropin hydrochloride. Heat the obtained solution over a water bath at 80 - 90 degrees centigrade for 4 - 5 hours. After cooling pour the solution over a small amount of ice, saturating it by means of violent cooling in the presence of a 40 percent solution of NaOH. Separate with ether. After drying with sodium sulphate, boil down the ether in a flask equipped with a dephlegmator. Distill the residue under normal pressure. Boiling point, 160 - 163 degrees. Yield, 6 grams, or 45 percent of theory.

(4) N-β-Oxyethylconvolvin

Dissolve 6 grams of convolvin in 10 milliliters of chloroform; add to the solution 1.8 grams of ethylene oxide and heat in a sealed tube at 60 degrees for 4 hours. Boil down the chloroform. Transform the oil-like residue into hydrochloride by adding alcoholic HCl. Melting point is 235 - 237 degrees.

Separate the base from the hydrochloride by adding ammonia. The oil comes to the surface first and crystallizes after a period of rest. Brilliant scales come out after recrystallization from water. Dry these at 60 - 70 degrees. Melting point 128 - 129 degrees. A sample mixed with convolvin has a melting point of 95 - 100 degrees.

6.054 grams of substance: 0.227 milliliters N_2(754 millimeters, 27 degrees)

5.311 grams of substance: 0.208 milliliters N_2(748.5 millimeters, 27.5 degrees)

Found percent: N 4.13; 4.27.

$C_{18}H_{25}NO_5$. Calculated percent: N 4.17

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Picrate

The mixing of alcoholic solutions of the base with picric acid produces an oil which after heating and trituration becomes a powder. Recrystallize from acetone, obtaining minute crystals. Melting point 212 - 214 degrees.

(5) Benzoil N-β-Oxyethylconvolvin

Dissolve 0.5 grams of crystallic base (melting point 128 - 129 degrees) in 5 milliliters of dry chloroform and add 0.2 milliliters of benzoyl chloride. Boil for one hour over water bath with reflux condenser.

After cooling add slowly absolute ether. A white crystallic powder is obtained. Yield, 0.6 grams.

Recrystallize from 15 milliliters of alcohol. Yield, 0.25 grams of well crystallized substance. Does not melt up to 250 degrees.

6.797 milligrams of substance: 2.163 milligrams AgCl

Found percent: Cl 7.87

$C_{25}H_{29}NO_6 \cdot HCl$. Calculated percent: Cl 7.46

Base

Dissolve one gram of hydrochloride in 10 - 15 milliliters of water and add ammonia to the solution obtained in the presence of ether. Separate the milky white solution obtained with ether, then dry the ether with heated potash and distill it. The residue is 0.8

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grams of oil which crystallizes during trituration with water. Recrystallize from water and dry at 60 - 70 degrees. The melting point is 131 - 133 degrees.

Picrate

Mix aqueous solutions of hydrochloride and picric acid. A cotton-like deposit is obtained. Transform it into a powder by heating. Pump the powder out, recrystallize it from a mixture of alcohol and acetone. The melting point is 214 - 216 degrees.

A sample mixed with N-B-oxyethylconvolvin picrate has a melting point of 195 - 198 degrees.

(6) Diethylaminoethylnortropin

Add 1.5 grams of diethylaminoethylchloride (boiling point 135.5 degrees at 12 millimeters) to a hot solution of 2 grams of nortropin in 65 milliliters of absolute toluene. The solution immediately becomes clouded and after further boiling a sediment is formed. Continue the heating for 4 hours, then after cooling pump off the sediment. This sediment consists of nortropin hydrochloride.

The toluene mother liquor is separated by 10 percent HCl. The latter is saturated with a 40 percent solution of NaOH and is separated with ether. After drying and distillation of the ether there remains a liquid base. Purify this through picrate. Obtain the latter by mixing an alcoholic solution of picric acid with a solution of the base in ethylacetic ether. The melting point of the picrate is 160 - 162 degrees. Separate the base from the latter by action of 20 percent HCl and by subsequent saturation of the acid

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solution with a 40 percent solution of NaOH and by separating with ether. After drying and distilling of the latter, there remains an oil which immediately crystallizes. Recrystallize it from petroleum ether. Melting point: 59 - 61 degrees.

2.615 milligrams of substance: 0.275 milliliters N_2 (744 millimeters, 14.5 degrees)

2.910 milligrams of substance: 0.307 milliliters N_2 (744 millimeters, 14.5 degrees)

Found percent: N 12.10; 12.13

$C_{13}H_{26}N_2O$. Calculated percent: N 12.3

Hydrochloride

Dissolve the base in absolute alcohol and add alcoholic HCl. After boiling down there remains a white powder. Recrystallize this from a mixture of absolute alcohol and acetone. Melting point 200 - 201 degrees.

(7) Benzoyldiethylaminoethylnortropin

Dissolve 0.5 grams of diethylaminoethylnortropin in 4 milliliters of absolute toluene. Add 0.25 grams of benzoylchloride and boil for about one hour with reflux condenser over a net. After cooling pump away the crystallic hydrochloride of the benzoyl derivative (0.5 grams). Obtain 0.2 grams more from the mother liquor by adding ether. Recrystallize 0.5 grams from one milliliter of absolute alcohol. The melting point is 228 - 229 degrees with decomposition.

5.085 milligrams of substance: 3.693 milligrams of AgCl

3.647 milligrams of substance: 2.627 milligrams of AgCl

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Found percent: Cl 17.96; 17.82

$C_{20}H_{30}N_2O_2(HCl)_2$. Calculated percent Cl 17.61

(8) Nitrobenzoylnortropin

Dissolve 4.5 grams of nortropin (melting point 160 - 161 degrees) in 60 milliliters of dry chloroform and to the boiling solution gradually add 7 grams of nitrobenzoylchloride in 10 milliliters of dry chloroform.

A crystallic sediment is formed at once. Continue the heating for approximately 6 hours over water bath with reflux condenser. After cooling pump off the sediment. The 3 grams of substance obtained are nortropin hydrochloride. Boil down the chloroform mother liquor and extract the dry residue with hot ether in order to dissolve the nitrobenzoylchloride which has not entered into the reaction. Recrystallize the remaining substance (4.2 grams) from a mixture of acetone and alcohol.

The minute cubic crystals have a melting point of 223 - 224 degrees. The nitrobenzoylnortropin obtained does not possess basic character and does not give a sediment with silico-wolframic acid.

2.755 milligrams of substance: 0.258 milliliters N_2(733.5 millimeters, 19 degrees)

3.338 milligrams of substance: 0.304 milliliters N_2(746.5 millimeters, 20 degrees)

Found percent: N 10.39; 10.25

$C_{14}H_{16}N_2O_4$. Calculated in percent: N 10.14

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(9) Aminobenzoylnortropin

Gradually add through a drop-funnel and with constant mixing at a temperature of 65 - 67 degrees, a solution of 1.5 grams of nitrobenzoylnortropin in 35 milliliters of alcohol to a mixture of 1 gram of iron filings and 3 milliliters of 7 percent acetic acid.

The reducing continues for 5 hours. Condense the mother liquor in a vacuum (after removing the iron). Dissolve the residue in 10 percent HCl. Filter [redacted] it off and saturate the solution with a 40 percent solution of NaOH in the presence of ethylacetic ether.

The base comes from the latter in the aspect of needle-like crystals in the amount of 0.7 grams.

Recrystallize from ethylacetic ether. The melting point is 201 - 202 degrees.

3.581 milligrams of substance: 0.339 milliliters of N_2(758 millimeters, 19 degrees)

3.924 milligrams of substance: 0.399 milliliters of N_2(755 millimeters, 18.5 degrees)

Found percent: N 11.52; 11.66

$C_{14}H_{18}N_2O_2$. Calculated percent: N 11.38.

Hydrochloride

Dissolve 0.4 grams of base in 5 - 6 milliliters of absolute alcohol. To this solution add alcoholic HCl up to an acid reaction. After boiling down there remains a white powder. Recrystallize this

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from alcohol. The melting point is 222 - 224 degrees with decomposition.

The aqueous solution of the hydrochloride has a strong Congo acid reaction.

(10) N-β-oxyethylnortropidin

Add 11.6 milliliters of a chloroform solution of ethylene oxide (containing 2.5 grams of ethylene oxide) to 5 grams of nortropidin. Heat the obtained mixture over water bath at 45 - 55 degrees during 5 hours. Distill the chloroform and sublimate the residue in a vacuum.

I fraction -- 0.7 grams up to 140 degrees (17 millimeters)

II fraction -- 4.3 grams at 140 - 141 degrees (17 millimeters)

Yield: 61.4 percent of [redacted] empirical value.

(11) Benzoyl N-β-oxyethylnortropidin

Add 3.5 milliliters of benzoylchloride to 4.3 grams of N-β-oxyethylic derivative of nortropidin dissolved in 45 milligrams of dry chloroform. Boil the mixture over a water bath during one hour and a half. After cooling add absolute ether. The crystallic hydrochloride is immediately separated. Pump off the latter, wash it with absolute ether and recrystallize it from 13 milliliters of a mixture of absolute alcohol and absolute ether (1:1). The melting point is 187 - 188 degrees.

The yield is 6.5 grams, which constitutes 79.2 percent of the [redacted] empirical value.

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(12) Nitrobenzoyl N-β-oxyethylnortropidin

Dissolve 4.2 grams of crystallic, freshly-distilled nitrobenzoylchloride (boiling point 161 - 162 degrees at 22 millimeters) in 10 milliliters of chloroform. To the solution obtained add 2.7 grams of N-β-oxyethylnortropidin dissolved in 5 milliliters of chloroform. During mixing of the solution there occurs a very strong heating and an immediate crystallization of the hydrochloride. Boil the reaction mixture for another hour and a half. Cool and add absolute ether. Pump off the hydrochloride, wash it with ether and recrystallize it from water (1:3). Melting point: 209 - 210 degrees. Yield: 2.8 grams, or 81.3 percent of theory.

4.487 milligrams of substance: 0.332 milliliters of N_2(756.5 millimeters, 21.5 degrees)

4.623 milligrams of substance: 0.333 milliliters of N_2(756.5 millimeters, 21 degrees)

Found percent: N 8.39; 8.20

$C_{16}H_{18}N_2O_4HCl$. Calculated percent: N 8.28.

0.2493 grams of substance: 7.2 milliliters 0.1 and $AgNO_3$ (Folgardt)

Found in percent: Cl 10.25

$C_{16}H_{18}N_2O_4 \cdot HCl$ Calculated in percent: Cl 10.48

Separation of Base

Dissolve 0.5 grams of hydrochloride (melting point 209 - 210 degrees) in 4.5 milliliters of water. In the presence of ether add ammonia to this solution. An oil will come to the surface which will crystallize during trituration. Long prisms. Melting point 60 - 62 degrees.

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3.167 milligrams of substance: 0.255 milliliters of N_2(745 millimeters, 17 degrees)

3.445 milligrams of substance: 0.275 milliliters of N_2(749.5 millimeters, 16 degrees)

Found percent: N 9.15; 9.17.

$C_{16}H_{18}N_2O_4$. Calculated percent: N 9.23

Picrate

Picrate is obtained by adding an aqueous solution of picric acid to an aqueous solution of hydrochloride. The powder obtained is recrystallized from acetone. Melting point: 225 - 226 degrees.

(13) Aminobenzoyl N-β-oxyethylnortropidin

Dissolve 4.3 grams of nitrobenzoyl N-β-oxyethylnortropidin hydrochloride in 15 - 20 milliliters of water. Add it through dripping funnel and constantly stir to a mixture of 2.9 grams of iron powder plus 7.5 milliliters of 7 percent acetic acid. Heat over water bath at 55 - 60 degrees. Heating and stirring should continue for five hours. After cooling pump off the iron and wash it with water. To the mother liquor add a saturated solution of potash and extract it with ether. Dry the latter with heated potash and boil down to 20 - 25 milliliters. Add petroleum ether to this concentrated solution, until slightly clouded. After rest a crystallic base will separate. Pump this off (2.1 grams). Its melting point is 96 - 96.5 degrees. Obtain 0.5 grams more from the ether mother liquor. The yield is 2.6 grams, or 66 percent of the [redacted] theoretical value.

3.957 milligrams of substance: 0.353 milliliters of N_2(753.5

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millimeters, 22 degrees)

3.260 milligrams of substance: 0.301 milliliters of N_2(746.5 millimeters, 23 degrees)

Found percent: N 10.04; 10.25

$C_{16}H_{20}N_2O_2$. Calculated percent: N 10.29.

Hydrochloride

Dissolve the crystallic base in absolute alcohol (1:4) and add alcoholic HCl up to an acid reaction. Pump off the resulting residue and recrystallize it from absolute alcohol (1:7). Melting point 206 - 207 degrees.

Picrate

Add alcoholic solution of picric acid to the base dissolved in alcohol. A powderlike sediment will result. After recrystallization in acetone, minute cubic crystals are obtained. Melting point 150 - 151 degrees.

(14) Diethylaminoethylnortropidin

Dissolve 0.9 grams of nortropidin in a few milliliters of toluene and add 0.85 grams of diethylaminoethylchloride. The transparent solution will cloud after a few minutes of boiling. A crystallic deposit of nortropidin hydrochloride (0.5 grams) is formed. Pump this off. Treat the toluene mother liquor with 10 percent HCl. Saturate the acid solution with alkali and potash and extract with ether. After drying and distilling of the latter, there remains a live oil (0.7 - 0.8 grams). Dissolve the base obtained in ethylacetic ether and make it over into picrate by

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adding alcoholic solution of picric acid. Thus 2.3 grams of picrate are obtained. Pump them off. The melting point is 173 - 175 degrees after recrystallization.

Out of the picrate, by action of 20 percent HCl and by subsequent saturation with alkali, obtain the base and extract it with ether. After drying and sublimation of the latter there remains 0.5 grams of light oil.

2.378 milligrams of substance: 0.276 milliliters of N_2(746 millimeters, 12.5 degrees)

2.887 milligrams of substance: 0.334 milliliters of N_2(752.5 millimeters, 13.5 degrees)

Found percent: N 13.48; 13.48

$C_{13}H_{24}N_2$. Calculated percent: N 13.46

(15) Phenylurethane N-β-oxyethylnortropidin

Dissolve 1.2 grams of oxyethylnortropidin in a few milliliters of absolute ether and add a solution of 0.9 grams of phenylisocyanate in a few milliliters of absolute ether. Boil the mixture for five hours until the odor of phenylisocyanate is gone.

After cooling add an alcoholic solution of HCl up to a weak litmus acid reaction.

Trituration will produce a minute crystallic deposit. Recrystallize this from absolute alcohol (1:7.5). Minute cubic crystals are obtained with a melting point of 182 - 183 degrees.

4.030 milligrams of substance: 1.911 milligrams of AgCl

4.872 milligrams of substance: 2.290 milligrams of AgCl

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Found percent: Cl 11.73; 11.63.

$C_{16}H_{20}N_2O_2HCl$. Calculated percent: Cl 11.5

Phenylacetic Acid Salt

Dissolve 0.5 grams of base in a few milliliters of absolute alcohol and to the solution obtained add 0.25 grams of phenylacetic acid in 2 - 3 milliliters of absolute alcohol. By rubbing with a glass rod one obtains a snow-white powder.

Recrystallize 0.5 grams from 10 milliliters of absolute ether plus 5 milliliters of ethylacetic ether. Crystallization will occur promptly with cooling. Melting point 113 - 114 degrees.

(16) Nitrobenzoyltropin

Dissolve 6.7 grams of crystallic tropin in 15 milliliters of absolute toluene and add 13 grams of freshly sublimated nitrobenzoylchloride dissolved in 20 milliliters of absolute toluene. Heat the obtained mixture for eight hours at 119 - 121 degrees in an oil bath. After cooling pump off the formed hydrochloride of nitrobenzoyltropin (13.5 grams) and dissolve it in 200 milliliters of water, then decompose it with ammonia in the presence of ether. After a few minutes, from the ammonia solution a base is separated in the shape of flaky crystals. Nine grams of base are obtained, which represents 65.7 percent. Recrystallize the substance from alcohol. Melting point, 135 - 136 degrees.

3.105 milligrams of substance: 0.253 milliliters of N_2(756 millimeters, 19 degrees)

3.293 milligrams of substance: 0.283 milliliters of N_2(755 millimeters,

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20.5 degrees)

Found percent: N 9.33; 9.47

$C_{15}H_{18}O_4N_2$. Calculated percent: N 9.65.

(17) Aminobenzoyltropin

Dissolve 6.6 grams of nitrobenzoyltropin in 10 milliliters of 20 percent acetic acid and slowly add the solution obtained, constantly stirring at 60 - 65 degrees, to a mixture of 4 grams of iron filings and 10 milliliters of 7 percent acetic acid. Continue the heating and stirring for 4 hours. After cooling pump off the iron and saturate the aqueous mother liquor with a concentrated solution of soda, then extract with ether. After drying and distilling the ether there remains a faintly yellow crystallic substance (5.8 grams). After recrystallization from a mixture of ether and ethylacetic ether, one obtains 5 grams of crystallic substance, which corresponds to 84.7 percent of theory. Melting point, 149 - 150 degrees.

2.736 milligrams of substance: 0.265 milliliters of N_2(735 millimeters, 19 degrees)

2.467 milligrams of substance: 0.236 milliliters of N (738 millimeters, 18 degrees)

Found percent: N 10.77; 10.73

$C_{15}H_{20}O_2N_2$. Calculated percent: N 10.76

Hydrochloride

Dissolve 2 grams of base in 6 milliliters of absolute alcohol and to this solution add alcoholic HCl up to a litmus acid reaction. Pump off the crystallic powder obtained (2.1 grams) and recrystallize

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it from alcohol (1:20). Does not melt up to 250 degrees.

4.000 milligrams of substance: 1.961 milligrams AgCl.

4.216 milligrams of substance: 2.073 milligrams AgCl.

Found percent: Cl 12.13; 12.16.

$C_{15}H_{20}O_2N_2$. Calculated percent: Cl 11.95

Monopicrate

With the mixing of an aqueous solution of hydrochloride acid with an aqueous solution of an equimolecular quantity of picric acid, a yellow minute crystallic sediment appears. After recrystallization from a mixture of alcohol and acetone the melting point is 230 degrees with decomposition.

Dipicrate

With the addition of a surplus of picric acid an orange picrate is obtained which, through recrystallization in the presence of picric acid remains orange. Melting point 173 - 175 degrees.

With recrystallization without picric acid it becomes lighter and is transformed into monopicrate with a melting point of 230 degrees.

The monopicrate, through recrystallization in the presence of picric acid becomes orange and is transformed into dipicrate with a melting point of 173 - 175 degrees.

Acetic Acid Salt

Mix a solution of base in absolute alcohol with a few drops

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of iced acetic acid. Trituration will produce a crystallic powder. Through recrystallization from ethylacetic ether (1:20), shiny flakes are obtained whose melting point is 171 - 172 degrees.

Phenylacetic Acid Salt

Add 0.36 grams of phenylacetic acid in 25 milliliters of absolute alcohol to 0.7 grams of base dissolved in 2 milliliters of absolute alcohol. Recrystallize the yellowish powder from acetone after boiling down in open air. Melting point, 143 - 145 degrees.

The sample mixed with the base melts at 100 - 109 degrees.

3.714 milligrams of substance: 0.235 milliliters of N_2(745 millimeters, 20.5 degrees)

4.132 milligrams of substance: 0.263 milliliters of N_2(755 millimeters, 20 degrees)

Found percent: N 7.09; 7.24.

$C_{23}H_{28}O_4N_2$. Calculated percent: N 7.07.

(18) Acetylaminobenzoyltropin

Add 4 milliliters of freshly distilled acetic anhydride to 1 gram of aminobenzoyltropin. Heat the obtained solution during 5 - 6 hours over a boiling water bath. After cooling add 4 - 5 milligrams of water to the solution, then add 25 percent ammonia. Pump off the base which has formed, dry it in a vacuum desiccator, after which recrystallize 0.5 grams of it from 2 milliliters of a mixture of ethylacetic and sulphuric ether (1:1). With cooling the base will crystallize in the shape of needles. After drying until constant weight the melting point will be 151 - 152 degrees.

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3.195 milligrams of substance: 0.248 milliliters of N_2(751 millimeters, 21 degrees)

3.619 milligrams of substance: 0.282 milliliters of N_2(748 millimeters, 23.5 degrees)

Found percent: N 8.77; 8.66

$C_{17}H_{22}O_3N_2$. Calculated percent: N 9.23.

Hydrochloride

Dissolve 0.5 grams of base in a few milliliters of absolute alcohol. Add an alcoholic solution of HCl up to an acid reaction. A white powder will immediately form. Recrystallize this from 36 percent alcohol (0.5 grams from 10 milliliters). During cooling the hydrochloride emerges in the shape of minute shiny cubic crystals. They do not melt up to 250 degrees.

Phenylacetic Acid Salt

Dissolve 0.5 grams of base in a few milliliters of absolute alcohol. Add to the mixture obtained 0.21 grams of phenylacetic acid dissolved in 1 milliliter of absolute alcohol. After removal of the alcohol in a vacuum desiccator there remains a light oil which crystallizes during trituration. Recrystallize 0.65 grams of this from 10 milliliters of ethylacetic ether. Small cubic crystals appear after cooling. Melting point 141 - 142 degrees.

The sample mixed with the phenylacetic salt of aminobenzoyltropin melts at 128 - 130 degrees.

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(19) Pseudotropin

Add 5 grams of crystallic tropin, dissolved in 5 grams of isoamyl alcohol, to a boiling solution of 10 grams of metallic natrium dissolved in 100 grams of isoamyl alcohol (boiling point 130 degrees). Boil the resulting solution for 2 hours, 15 minutes. Cool and shake strongly with 40 milliliters of water. Separate the water layer and process the alcohol layer several times with 10 percent HCl. Extract the aqueous alkaline solution with ether, and process the latter with 10 percent HCl.

Combine the acid solutions and saturate them with dry KOH. Then extract with ether. After drying and distillation of the latter down to a small volume, pseudotropin crystallizes. Pump this off and wash with absolute ether. The yield of pseudotropin is 2.5 grams. The melting point is 109 - 110 degrees.

(20) Nitrobenzoylpseudotropin

Dissolve 2 grams of pseudotropin in 10 milliliters of absolute toluene and gradually add 3.4 grams of nitrobenzoylchloride in 10 milliliters of absolute toluene. During the mixing of the solutions a warming up occurs and the reaction mixture changes into a dense crystallic mass.

Pump off the nitrobenzoylpseudotropin hydrochloride after 3-4 hours of heating in an oil bath at 130 - 140 degrees. Yield, 4.2 grams.

Separation of the Base

Dissolve 0.5 grams of hydrochloride in 15 milliliters of water and to the solution obtained, in the presence of ether, add ammonia.

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Then extract the formed base with 60 - 75 milliliters of ether. After condensation of the latter down to 4 - 5 milliliters, nitrobenzoylpseudotropin will crystallize in the shape of rectangular flakes. Melting point, 126 - 127 degrees.

3.036 milligrams of substance: 0.261 milliliters of N_2 (743.5 millimeters, 23 degrees)

3.893 milligrams of substance: 0.332 milliliters of N_2 (744 millimeters, 22.5 degrees)

Found percent: N 9.5; 9.46

$C_{15}H_{18}O_4N_2$. Calculated percent: N 9.65.

(21) Aminobenzoylpseudotropin

Dissolve 3.8 grams of nitrobenzoylpseudotropin in 50 milliliters of water with light warming. Pour the obtained solution through a dripping funnel and constantly mix into a mixture of 2 grams of iron plus 11 milliliters of 7 percent acetic acid at a temperature of 60 - 65 degrees. The reduction is continued for 5 hours. After cooling pump off the iron and add ammonia to the filtrate in the presence of ether. Extract the base with ether and after drying and distilling of the latter it will crystallize in the shape of colorless needles. Yield, 2.1 grams. Melting point, 163 - 165 degrees.

4.118 milligrams of substance: 0.396 milliliters N_2 (740 millimeters, 20.5 degrees)

3.715 milligrams of substance: 0.361 milliliters N_2 (727 millimeters, 23 degrees)

Found percent: N 10.7; 10.66

$C_{25}H_{20}O_2N_2$. Calculated percent: N 10.76.

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Phenylacetic Acid Salt

Dissolve 0.4 grams of base and 0.2 grams of phenylacetic acid in absolute alcohol. After removal of the alcohol there remains an oil which, under trituration crystallizes. Rub these crystals to a powder.

Recrystallize 0.5 grams of the salt from 4 milligrams of ethylacetic ether. Melting point, 116 - 117 degrees.

3.293 milligrams of substance: 0.202 milliliters N_2 (742 millimeters, 21.5 degrees)

3.394 milligrams of substance: 0.204 milliliters N_2 (744 millimeters, 21.5 degrees)

Found percent: N 6.81; 6.71

$C_{23}H_{28}O_4N_2$. Calculated percent: N 7.07

Hydrochloride

A minutely crystallized hydrochloride (0.3 grams) forms immediately upon addition of an alcoholic solution of HCl to an alcoholic solution of the base. Recrystallize it from 15 milliliters of 96 percent alcohol. It will form in the shape of minute silky needles. Does not melt up to 235 degrees.

6.095 milligrams of substance: 3.008 milligrams AgCl

6.315 milligrams of substance: 3.038 milligrams AgCl

Found percent: Cl 12.2; 11.91.

$C_{15}H_{20}O_2N_2 \cdot HCl$. Calculated percent: Cl 11.95

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(22) Phenylacetic Ether of Tropin

Chloride of Phenylacetic Acid

Dissolve 3 grams of phenylacetic acid in 15 milliliters of dry chloroform and to the cooled solution add 4 grams of PCl_5. The solution will heat strongly. Heat the reaction mixture on a water bath with a reflux condenser until no more HCl forms. After cooling remove the surplus of chloroform and of phosphorus oxychloride. Sublimate the residue and obtain a colorless live liquid. Boiling point, 78 - 80 degrees (3 - 5 millimeters).

Etherification of Tropin

Dissolve 1 gram of tropin in 15 milliliters of absolute toluene. Add 1.5 grams of freshly distilled chloride of phenylacetic acid. The solution will become hot and there will be a sediment. Heat the reaction mixture during 4 and a half hours in an oil bath at 120 - 125 degrees.

After cooling pump off the sediment and dissolve it in 4 - 5 milliliters of water. Wash the aqueous solution with ether and saturate it with potash, then extract with ether. After drying and distilling of the solvent, there remains a live oil.

Hydrochloride

Add an alcoholic solution of HCl to the liquid base. The hydrochloride will crystallize immediately. Recrystallize 0.5 grams from 5 milliliters of dry acetone. Melting point, 198 - 200 degrees.

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6.747 milligrams of substance: 0.284 milliliters N_2 (743.5 millimeters, 20 degrees)

6.618 milligrams of substance: 0.279 milliliters N_2 (732.5 millimeters, 19 degrees)

Found percent: N 4.72; 4.67.

$C_{16}H_{21}N.HCl$. Calculated percent: N 5.31

(23) Phenylurethane of Tropin

Dissolve 1 gram of tropin (boiling point 110 - 111 degrees at 9 - 10 millimeters) in 10 - 15 milliliters of absolute ether and add 0.85 grams of phenylisocyanate dissolved in 5 - 7 milliliters of absolute ether. Boil the mixture for 2 and a half to 3 hours until the odor of phenylisocyanate disappears. Pump off the crystallic substance which forms. 1.7 grams of colorless substance is obtained. Melting point, 167 - 168 degrees.

Recrystallize 1 gram from 3 milliliters of absolute alcohol. Minute cubic crystals are obtained. Melting point 170 - 171 degrees.

4.281 milligrams of substance: 0.387 milliliters N_2 (752 millimeters, 18.5 degrees)

3.302 milligrams of substance: 0.303 milliliters N_2 (752 millimeters, 18 degrees)

Found percent: N 10.31; 10.48.

$C_{15}H_{20}N_2O_2$. Calculated percent: N 10.77

Hydrochloride

Dissolve the base in absolute alcohol, add alcoholic HCl and pump off the white minutely crystallized precipitate. Wash it in

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absolute alcohol and recrystallize from the latter (1:10). Minute needles are obtained which do not melt at 270 degrees.

4.602 milligrams of substance: 2.296 milligrams AgCl

4.530 milligrams of substance: 2.078 milligrams AgCl

Found percent: Cl 12.34; 12.43

$C_{15}H_{20}N_2O_2 \cdot HCl$. Calculated percent: Cl 11.97.

(24) Butylaminobenzoyltropin

Chloride of the Butylaminobenzoic Acid

Gradually and with constant mixing and external ice refrigeration add 10 grams of butylaminobenzoic acid to 35 grams of thionyl chloride. Stir the reaction mixture for 2 hours, then add 70 milliliters of absolute ether. Pump off the precipitate of hydrochloride of the butylaminobenzoic acid chloride and wash it several times with absolute ether. After drying in a vacuum desiccator the melting point will be 103 - 104 degrees. Yield, 80 percent.

Condensing with Tropin

Add 10 grams of freshly prepared hydrochloride of the butylaminobenzoic acid chloride to a solution of 5 grams of tropin in 50 milliliters of absolute toluene. Heat the reaction mixture for 7 - 8 hours in an oil bath at the boiling temperature of toluene. Pour the toluene off the sediment and dissolve the latter in 30 - 40 milligrams of water. Wash the aqueous solution of hydrochloride thus obtained with ether and neutralize it with 25 percent ammonia. Pump off the base of butylaminobenzoyltropin which has formed in the amount of 10 grams, wash it with water and recrystallize it from 100 - 125

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milliliters of ether. Purify the base which has crystallized during cooling by sending it through some hydrochloride obtained by adding alcoholic hydrochloric acid to the alcoholic solution of the base. Recrystallize the obtained hydrochloride from water (6.5 grams from 13 milliliters), then transform back into base by trituration in mortar with 12.5 percent ammonia. Pump off the base and recrystallize it from ether (5 grams from 120 milliliters). Melt it at 89 - 90 degrees.

3.305 milligrams of substance: 0.268 milliliters N_2 (750 millimeters, 30 degrees)

3.330 milligrams of substance: 0.265 milliliters N_2 (751 millimeters, 28 degrees)

Found percent: N 8.78; 8.69.

$C_{19}H_{28}O_2N_2$. Calculated percent: N 8.86.

Hydrochloride

Dissolve 3.5 grams of crystallic base in several milliliters of alcohol and to the solution obtained add drop by drop an alcoholic solution of HCl up to a weak acid reaction. The hydrochloride will precipitate immediately in the shape of a white curdled sediment. Pump it off and wash it with a mixture of ether and alcohol. Three grams of hydrochloride are obtained. Recrystallize from 12 milliliters of water. The hydrochloride will crystallize promptly from the aqueous solution during cooling. Does not melt up to 270 degrees.

3.694 milligrams of substance: 1.482 milligrams AgCl

4.017 milligrams of substance: 1.616 milligrams AgCl

Found percent: Cl 9.92; 9.95

$C_{18}H_{28}O_2N_2.HCl$. Calculated percent: Cl 10.07

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(25) Butylaminobenzoylpseudotropin

Add 4 grams of hydrochloride of the butylaminobenzoic acid chloride to a solution of 2 grams of pseudotropin in 25 milliliters of absolute toluene. Heat the reaction mixture for 3 - 4 hours at 140 - 150 degrees. After cooling pour the toluene off the sediment which appears as a frozen glasslike mass. Treat the latter with 10 - 15 milliliters of water. Wash the acid aqueous solution obtained with ether then slowly add it to a 12.5 percent solution of ammonia (in the presence of ether). The base precipitating during this operation immediately transfers to the ether when shaken. Dry the ether solution with heated natrium sulphate and boil it down. The remaining base will crystallize immediately. The melting point is not sharp: 90 - 102 degrees. After recrystallization from ether and drying to constant weight the melting point will be 109 - 111 degrees.

4.139 milligrams of substance: 0.316 milliliters N_2 (759.5 millimeters, 19.5 degrees)

4.089 milligrams of substance: 0.310 milliliters N_2 (759.5 millimeters, 20 degrees)

Found percent: N 8.76; 8.68.

$C_{19}H_{28}O_2N_2$. Calculated percent: N 8.86.

Hydrochloride

Dissolve 1.3 grams of base (melting point 109 - 111 degrees) in a few milliliters of absolute alcohol. Add alcoholic solution of HCl to the solution thus obtained. Pump off the curdlike hydrochloride and recrystallize it from 12 milliliters of absolute alcohol.

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It will crystallize in the shape of needles. Does not melt up to 270 degrees.

(26) Butylaminobenzoyl-N-β-oxyethylnortropidin

Dissolve 3 grams of N-β-oxyethylnortropidin in 30 milliliters of dry chloroform, then slowly add 6 grams of hydrochloride of the butylaminobenzoic acid chloride. The latter will dissolve and the solution will be heated. After the chloride has dissolved boil the reaction mixture 3 more hours over a water bath. After that dilute the chloroform solution with ether and extract it with 50 - 60 milliliters of water. To the aqueous solution of the hydrochloride thus obtained, in the presence of ether, add 25 percent of NH_4OH. The precipitating base will dissolve in the ether. Extract the ammonia mother liquor two more times with ether, then dry the latter with heated sulphate and boil it down. The base which remains in the shape of oil crystallizes promptly. Recrystallize it from low-boiling petroleum ether (1:5). After cooling the butylamino-benzoyl-N-β-oxyethylnortropidin separates in the shape of greyish mother-of-pearl flakes. Melting point, 66 - 68 degrees.

3.493 milligrams of substance: 0.266 milliliters N_2 (753.5 millimeters, 17.5 degrees)

3.255 milligrams of substance: 0.248 milliliters N_2 (753 millimeters, 19.5 degrees)

Found percent: N 8.73; 8.68.

$C_{20}H_{28}O_2N_2$. Calculated percent: N 8.53.

Hydrochloride

Dissolve one gram of base in a few milliliters of absolute

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alcohol, add alcoholic HCl, pump off the hydrochloride which separates and wash it with a mixture of absolute ether and alcohol. Recrystallize 1.2 grams of hydrochloride from 6 milliliters of mixture of absolute alcohol and ether (1:1). After cooling there appears a crystallic substance with a boiling point of 149 - 151 degrees.

CONCLUSIONS

(1) A series of new derivatives of tropin, nortropin and nortropidin, endowed with local anesthetic action, has been obtained.

(2) On the basis of the pharmacological study of the substances obtained one can make preliminary conclusions as to the connection between the chemical structure and the pharmacological actions:

(a) The adding of radicals to the nitrogen atom in the convolvin molecule diminishes both the toxicity and the anesthetizing power.

(b) The introduction of an amino radical into the benzoyl group increases the anesthetizing action, but also heightens the toxicity.

(c) Acetylization of the amino radical leads to a drop in toxicity and in anesthetizing effect.

(d) Substances containing a free hydroxyl radical have extremely low toxicity, but do not possess anesthetizing power.

(e) Substances not containing ether radicals do not

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provoke anesthesia.

(f) The introduction into the molecule of a phenylurethane radical lowers the toxicity exceedingly.

(g) The introduction of a butylic group into the original [redacted] radical exceedingly heightens the anesthetizing power, but also considerably increases toxicity.

(h) The derivatives of the pseudotropin class are less toxic than the correspondent derivatives of the tropin class and do not give in to the latter in power of anesthetizing action.

(i) Salts formed with phenylacetic acid have a stronger anesthetizing action than the salts of the hydrochloric acid.

(j) The introduction into the molecule of a double bond cuts down both the toxicity and the anesthetizing power.

(3) These conclusions refer only to the narrowly defined group of tropin and nortropin derivatives and do not pretend to a wider meaning.

(4) Clinical tests of some of the substances described above (called convocaines), conducted in the eye clinics of the I Leningrad Medical Institute, the I Moscow Medical Institute and the Moscow Ophthalmic Hospital, have proven that these substances may well replace cocaine in ophthalmic practice [12].

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ALKALOIDS OF THE MAGNOLIA FUSCATA

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Hardly anything is known at the present time about the alkaloids of plants of the Magnoliaceae family.

True, there are in literature some purely qualitative indications of the presence of alkaloids in the Lyriodendron tulipefera and in the Magnolia Blumei. But not one single alkaloid was separated in its pure form. Within the borders of the USSR one finds but a small amount of plants of this family, growing on the Black Sea coast and on the southern coast of Crimea.

Studying leaves of the Magnolia fuscata, received by us from the VIR introductory nursery in Sukhuma, we discovered in them the presence of a considerable quantity (1 - 2 percent) of alkaloids. The amount of the latter is subject to strong oscillations according to the age of the leaves. So, for instance, large leaves gathered in August 1937 yielded 1.4 percent of the sum of the bases, while small leaves (gathered in July of the same year) yielded 2.1 percent.

The alkaloid mixture, separated by the usual methods, is an amorphous powder. The separation of pure, individual, crystallic bases met at first with considerable difficulties. However, by applying the right solvents (see experimental part) we were able to obtain two alkaloids in their crystallic state. These differ in

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all their properties from all those described up to date.

The first alkaloid, for which we suggest the name of "magnolin", is a crystallic substance with a melting point of 178 - 179 degrees and a specific rotation $|\alpha|_D$ = -9.60 degrees. It is hard to dissolve in the common organic solvents. The analysis of the base approximates the formula $C_{18}H_{21}NO_3$. The determination of the oxygen function showed the presence of one metoxyl and one hydroxyl radical of the phenol type, while the functions of the third atom of oxygen remain unknown up to date. The nitrogen atom is bonded with the methyl radical and apparently is tertiary. The formula of magnolin can therefore be developed into

$$C_{16}H_{14}O(N \cdot CH_3)\ (CH_3O)\ (OH)$$

The second alkaloid, for which we suggest the name of "magnolamin", is also a crystallic substance with a melting point of 117 - 119 degrees and a specific rotation $|\alpha|_D$ = + 111.6 degrees. It differs from magnolin by its vastly superior solubility in the common organic solvents.

The analysis of this base leads to the formula $C_{20}H_{23}NO_4$.

The determination of the oxygen functions shows the presence of one hydroxyl radical of the phenol type and of one metoxyl radical. The functions of the third and fourth atoms of oxygen have not been clarified todate. The nitrogen is bonded to the methyl radical and apparently has a tertiary character. The magnolamin formula can be developed into

$$C_{18}H_{16}O_2(N \cdot CH_3)\ (CH_3O)\ (OH).$$

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Since both alkaloids are characterized by difficult combustibility, we do not consider the formulas $C_{18}H_{21}NO_3$ and $C_{20}H_{23}NO_4$ as definitely established, but only as orientation formulas. It is possible to make these formulas precise after study and analysis of their derivatives and products of decomposition.

Besides these two crystallic alkaloids there remains a comparatively large number of amorphous bases, the study of which has not yet been completed. Our studies of the Magnolia fuscata alkaloids continues.

EXPERIMENTAL PART

Separation of the Alkaloids

We mixed 3 kilograms of dried and thinly triturated leaves of Magnolia fuscata (gathered in Sukhuma in August 1937) with 8 percent ammonia and percolated them with dichlorethane. We extracted the dichlorethane extract with 10 percent sulphuric acid. To the sulphuric solution we added 10 percent ammonia up to alkaline reaction. A yellow, powderlike residue precipitated. We pumped it off and washed it several times with water. The yield of the sum of alkaloids is 43 grams (1.4 percent). The yield varies somewhat depending on the age of the leaves.

Thus, 9 kilograms of small leaves, gathered on 14 July 1937, yielded after a similar processing 191.5 of the sum of bases (2.1 percent).

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Separation of the Alkaloids. Separation of Magnolin

We processed the sum of alkaloids obtained (43 grams) over a water bath with reflux condenser with 200 milliliters of benzene. We poured the hot solution away from the undissolved residue, and once more processed the latter with 200 milliliters of hot benzene. After repeating this operation several times, nothing more passes over to the benzene. The residue, unsoluble in benzol, is a dark brown hard mass (5.1 grams) which, after processing with 10 milliliters of alcohol, becomes a light yellow powder with a melting point of 172 - 175 degrees. After two crystallizations from alcohol, in which it is very hard to dissolve it, magnolin is obtained in the form of an almost colorless, minutely crystallized powder with a melting point of 178 - 179 degrees. Magnolin is soluble in 5 percent NaOH, is very hard to dissolve in alcohol, acetone and chloroform, almost insoluble in benzene, ether, petroleum ether and water. Because of its [redacted] solubility the specific rotation could be determined only in a pyridinic solution.

0.0781 grams dissolved in 15 milliliters of pyridine:

l = 2dm; α_D = -0.10 degrees

$[\ ]_D$ = - 9.60 degrees

2.913 milligrams of substance: 7.678 milligrams CO_2, 1.885 milligrams H_2O.

3.569 milligrams of substance: 9.438 milligrams CO_2, 2.280 milligrams H_2O.

3.435 milligrams of substance: 0.142 milliliters N (27 degrees, 755 millimeters).

5.285 milligrams of substance: 0.216 milliliters N (17 degrees, 755 millimeters).

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27.810 milligrams of substance: 5.58 milliliters 0.1 $Na_2S_2O_3(OCH_3)$.

15.477 milligrams of substance: 3.13 milliliters 0.1 $Na_2S_2O_3(OCH_3)$.

27.810 milligrams of substance: 2.96 milliliters 0.1 $Na_2S_2O_3(OCH_3)$.

9.88 milligrams of substance: 0.88 milliliters CH_4 (0 degrees, 760 millimeters).

11.10 milligrams of substance: 0.95 milliliters CH_4 (0 degrees, 760 millimeters).

Found percent: C 71.89 and 72.12; H 7.24 and 7.15

N 4.55 and 4.49; OCH_3 10.35 and 10.43

CH_3 (N) 5.14; OH 6.81 and 6.54

$C_{18}H_{21}NO_3$. Calculated percent: C 72.24; H 7.03;

N 4.68; OCH_3 10.36; CH_3 (N) 5.02; OH 5.68.

With the mineral acids HCl, HBr, and HJ, magnolin gives salts [redacted] soluble in water. These precipitate from the aqueous solution in the form of resinous masses. By drying in vacuum desiccators these salts are transformed into glasslike masses, easily soluble in alcohol and acetone. It has not been possible to obtain them in a crystallized form from the alcoholic and acetone solutions.

Magnolin picrate precipitates in the form of a yellow powder-like substance after addition of watery picric acid to an acetic acid solution of the base. It is difficult to dissolve in water, somewhat easier to dissolve in alcohol. After the second recrystallization from alcohol it comes out in the form of a fine yellow powder with a melting point of 160 - 162 degrees. (It melts with decomposition and liberation of gaseous bubbles. At 140 degrees it begins to contract and to darken.)

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Magnolin picrolonate precipitates in the form of a yellow powder from the acetic acid solution of the base after addition of an alcoholic solution of picrolonic acid. After double crystallization from alcohol, it precipitates in the form of a powderlike sediment. It does not melt clearly. At 160 degrees it begins to detach itself from the walls of the capillary and to darken. At 190 degrees it melts with separation of gaseous bubbles.

Processing of the Benzene Solution. Separation of Magnolamin

A light yellow powder (yield, 26 grams) precipitates from the hot benzene solutions poured together with the insoluble part (see above). This substance, which represents impure magnolamin, is crystallized 5 times from benzene.

After the first 4 crystallizations and after dissolving the base in benzene, there remains a small quantity of insoluble resinous substance, from which we pour off the benzene solution. During the fifth crystallization the substance dissolves completely. After cooling, magnolamin precipitates from benzene in the form of minute colorless needles. After drying in a vacuum desiccator until constant weight, it melts at 117 - 119 degrees (softens at 110 degrees).

Magnolamin is easy enough to dissolve in alcohol, hot benzene and chloroform, but is insoluble in water. It dissolves easily in 5 percent alkali.

0.1226 grams dissolved in 10 milliliters of alcohol:

$\alpha_D = +1.30$ degrees; $l = 1$ dm; $[\alpha]_D = +111.6$ degrees

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3.578 milligrams of substance: 9.233 milligrams CO_2 and 2.215 milligrams H_2O.

3.631 milligrams of substance: -9.389 milligrams CO_2 and 2.251 milligrams H_2O.

5.396 milligrams of substance: 0.207 milliliters N (22 degrees, 748 millimeters).

5.478 milligrams of substance: 0.213 milliliters N (19 degrees, 741 millimeters).

21.75 milligrams of substance: 4.38 milliliters 0.1 $Na_2S_2O_3$ (CH_3O).

22.67 milligrams of substance: 4.58 milliliters 0.1 $Na_2S_2O_3$ (Ch_3O).

12.88 milligrams of substance: 1.11 milliliters CH_4 (0 degrees, 760 millimeters).

14.02 milligrams of substance: 1.22 milliliters CH_4 (0 degrees, 760 millimeters).

Found percent: C 70.38 and 70.52; H 6.93 and 6.94; N 4.29 and 4.36; OCH_3 10.39 and 10.42; OH 6.58 and 6.64.

$C_{20}H_{23}NO_4$. Calculated percent: C 70.38; H 6.75; N 4.10; OCH_3 9.09; OH 4.98.

The magnolamin salts with mineral acids (HCl, HBr, HJ) are hard to dissolve in water and precipitate from the aqueous solution as viscous resinous masses. In a vacuum desiccator these salts harden into glasslike masses easily dissolved in alcohol and acetone.

Magnolamin picrate is obtained in the form of a yellow powder by adding aqueous picric acid to the acetic acid solution of the base. After double crystallization from alcohol it has a melting point of 142 - 145 degrees.

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Magnolamin picrolonate precipitates from the acetic acid solution of the base with addition of alcoholic picrolonic acid. It is a yellow powder. After double crystallization from alcohol it melts at 163 - 165 degrees (begins to soften at 153 degrees).

CONCLUSIONS

(1) From the leaves of Magnolia fuscata we separated two new alkaloids: magnolin $C_{18}H_{21}NO_3$ and magnolamin $C_{20}H_{23}NO_4$.

(2) The determination of the functional groups allows development of these formulas as follows: $C_{16}H_{14}O$ $(N.CH_3)$ (OCH_3) (OH) and $C_{18}H_{16}O_2$ $(N.CH_3)$ (OCH_3) (OH).

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LOCAL ANESTHETICS OF THE QUINOLIN-4-CARBOXYLIC ACID CLASS

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The derivatives of quinolin-4-carboxylic acid have long found application in medicine.

Thus, 2-phenylquinolin-4-carboxylic acid, under the name of "atophan", is used as antigout remedy. It turned out that many derivatives of ~~the~~ quinolin-4-carboxylic acid have ~~partially~~ in part anti-pyretic and ~~especially~~ particularly anesthetizing properties. The antipyretic qualities of these compounds, of atophan in particular, have been known for a long time, and atophan is often ~~referred to~~ included in the group of antipyretics. The anesthetizing properties of the derivatives of ~~the~~ quinolin-4-carboxylic acid have been discovered comparatively recently in connection with the synthesis of the so-called "percaine", hydrochloride of diethylethylenediamine-2-butoxy-quinolin-4-carboxylic acid [1].

At the present time much attention is given to the study of the anesthetizing properties of the derivatives, especially ~~ethers~~ esters, and amides of ~~the~~ quinoline-4-carboxylic acid. The center of this research is the relationship between the anesthetizing action and the chemical structure of these compounds.

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The research of chemists in recent times has shown that derivatives of the quinolin-4-carboxylic acid with radicals in positions 2 and 4 possess anesthetizing properties [2].

H. Wojahn's work [3] is dedicated to the study of the influence of the structure of side groups bonded to the carbon atom of the quinolinic nucleus in the position 2, in regards to the anesthetizing action. He established that the anesthetizing action of the whole compound increases with the increase of the number of carbon atoms of the alkoxy group radical. However, the power of the corresponding derivatives is maximal when the number of carbon atoms in the radical is equal to 4. Further increase of the number of carbon atoms leads to an increase of anesthetizing power, but also to a strong increase in toxicity. Thus, out of all the diethylaminoethylic ethers of the 2-alkoxyquinolin-4-carboxylic acid, the diethylaminoethylic ether of the 2-butoxyquinolin-4-carboxylic acid proved to be the best for its anesthetizing properties.

The present research aims to study the influence of the lateral chain, bonded to the carboxyl of the quinolin-4-carboxylic acid in the position 4, and at the same time to study the influence of the radicals in position 2; with this aim in mind the following derivatives of the quinolin-4-carboxylic acid were synthetized:

(1) Diethylaminoethylic ethers of the 2(phenyl, ethoxy, n.-propoxy, butoxy and isoamiloxy)-quinolin-4-carboxylic acids.

(2) Diethylaminopropyl ethers of the 2(phenyl, ethoxy, n.-propoxy, n.-butoxy)-quinolin-4-carboxylic acids.

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(3) α,α-dimethyl-diethylaminopropyl ethers of the 2(phenyl, ethoxy, propoxy, n.-butoxy)-quinolin-4-carboxylic acids.

(4) α,β-dimethyl-diethylaminopropyl ether of the 2-n.-butoxyquinolin-4-carboxylic acid.

The synthesis of the above acids consists of two basic stages: synthesis of the quinolin-4-carboxylic acids, and the synthesis of the ethers of these acids. From quinolin-4-carboxylic acids we obtained 2-phenylquinolin-4-carboxylic acid and 2-alkoxy (ethoxy, propoxy, butoxy, amiloxy)-quinolin-4-carboxylic acids. 2-phenyl-quinolin-4-carboxylic acid (atophan) was obtained by the method of Pfitzinger from isatan [4]. 2-alkoxyquinolin-4-carboxylic acids by a somewhat modified Camp's method.

As to the etherification of the quinolin-4-carboxylic acids, we conducted it exclusively by action of the chlorides of alkylamines on the sodium salts of the corresponding acids, for in the case of reaction between aminoalcohols and acid chlorides of the acids, the yield is lower and one must be on the constant lookout against saponification of the ethers, as indicated by H. Wojahn. With the methods applied in the current work, the yield of ethers reaches 80-90 percent of theory. It is interesting to point out that the advantages of the method described are also in accord with theory.

The attention of chemists has been long attracted by the behavior of certain acids, as for instance of the trinitrobenzoic acid, whose peculiarity is that it is very hard to etherize by means of alcohol and hydrogen chloride. And these ethers are very hard to saponify.

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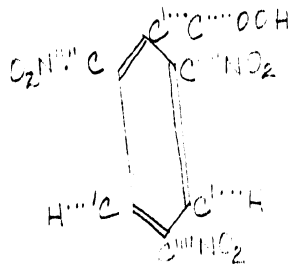
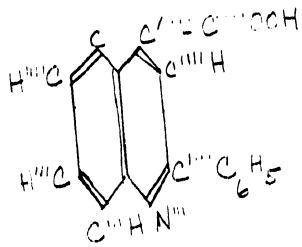
2-phenylquinolin-4-carboxylic acid behaves exactly in the same way as the trinitrobenzoic acid. Although literature indicates that its ethers are obtained by action of acid and alcohol, the yields with this method are almost nil, while on the contrary, by action of halogenoalkyls on the salts of phenylcinchoninic acid, almost quantitative yields are obtained. The behavior of these acids is fully justified from the point of view of the electronic theory in the Organic Chemistry of Professor A. M. Bergenheim.

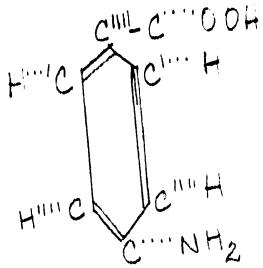
By comparing the electronic formulas of the following acids:



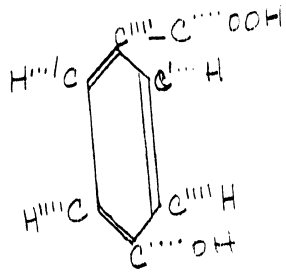
Trinitrobenzoic Acid



2-phenyl-quinolin-4-carboxylic acid



p-aminobenzoic Acid



O-oxybenzoic Acid

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it is easy to see that in quinolin-4-carboxylic acid the carbon atom of the carbonyl group C'''' is bonded to the carbon atom of the quinolinic nucleus C'''' similarly to the carbonic bond in the trinitrobenzoic acid, while in the p-oxybenzoic, p-aminobenzoic acids there occurs the bonding of the carbon atom C''''' of the nucleus with the carbon atom C'''' of the carboxylic radical. The acids in which the carbon atom of the carboxyl is bonded to the carbon atom of the nucleus, thus: C''''-C'''' must differ by their chemical properties from the acids where the carbon atom of the carboxyl is bonded to the carbon of the nucleus thus: C'''''-C''''. In the acids of the first type the hydrogen ion of the carboxylic radical must be more mobile than the hydrogen ion in the acids of the second type, that is, must dissociate more easily; and, vice versa, the OH radical of the carboxyl must be bonded to the carbon atom in a more solid manner. Probably the presence of a bond of the first type in the trinitrobenzoic acid changes the behavior of this acid and is the cause why the synthesis of the ethers of this acid out of its silver salts is so easy, and it also explains the bad saponification of the ethers of trinitrobenzoic and similar acids.

All the ethers of the quinolin-4-carboxylic acid indicated above turned out to be strong anesthetic agents when tested on the cornea of rabbit's eyes. The power of these ethers is caused by the structure of the radical of the 2-alkoxy-group, but mainly by the structure of the lateral chain bonded to the carbon atom of the carboxyl in the position 4. With the increase of the number of carbon atoms of this chain, the anesthetizing power of the compound also

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increases. Thus, the diethylaminopropyl ethers of the 2-alkoxyquinolin-4-carboxylic acids have a much stronger anesthetizing action than the diethylaminoethyl ethers of the corresponding 2-alkoxyquinolin-4-carboxylic acids. The diethylaminopropyl ether of the 2-butoxyquinolin-4-carboxylic acid provokes anesthesia equal in its completeness to that of cocaine, and surpassing cocaine in duration of action. The substitution in the lateral chain, position 4, of three atoms of carbon by five, leads to different results depending from the structure of this chain. In the compounds with the group

$$-\underset{\underset{CH_3}{|}}{CH}-\underset{\underset{CH_3}{|}}{CH}-CH_2N(C_2H_5)_2$$

the anesthetic action is considerably higher than in the diethylaminopropyl ethers of the corresponding quinolin-4-carboxylic acids. While in the compounds with the group

$$-H_2C-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_2N(C_2H_5)_2$$

the power of superficial anesthesia declines.

What concerns the toxicity of the derivatives of quinolin-4-carboxylic acid, one can affirm on the basis of initial studies that they are more toxic than novocaine, but less toxic than cocaine.

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The diethylaminobutyl ether of the 2-butoxylquinolin-4-carboxylic acid turned out to be the most toxic of all the ethers, yet its toxicity is less than that of cocaine. The toxicity of the α,β-dimethyl-γ-diethylaminopropyl ether of the 2-butoxylquinolin-4-carboxylic acid is less than that of the diethylaminopropyl ether of the same acid.

In the derivatives of the 2-phenylquinolin-4-carboxylic acid, the change of structure of the lateral chain has almost the same effect on the anesthetic action as in the 2-alkoxyderivatives of the quinolin-4-carboxylic acid.

Almost all the ethers act irritatingly on the tissues of the eye. The ethers having a five-member carbon group between the oxygen atom of the carboxyl and the nitrogen atom of the lateral chain, provoke the highest degree of irritation.

A more detailed description of research results will be published in the Pharmacological Journal. The study of the anesthetizing capacities of substances of the quinolin-4-carboxylic acid type was done at the Pharmacological Institute of the I Moscow Medical Institute by V. V. Nikolaev and M. A. Levchenko, to whom I bring my thanks.

EXPERIMENTAL PLANT

I. Synthesis of 2-alkoxyquinolin-4-carboxylic Acids

The 2-alkoxyquinolin-4-carboxylic acids were obtained by a somewhat modified method of Camp's [5].

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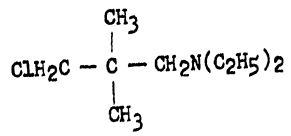
Introduce 5 grams of metallic sodium into 50 grams of alcohol (ethyl, propyl, butyl, amyl, etc). When the separation of hydrogen is over introduce 10 grams of 2-chloroquinolin-4-carboxylic acid into the obtained alcoholate. Heat the reaction mixture to the boiling point and boil, mixing well for half an hour. In the case of ethyl and propyl alcohol add to the cooled reaction mixture a triple quantity of water and 5 percent solution of hydrochloric acid up to an acid Congo reaction. The corresponding quinolin-4-carboxylic acids precipitate immediately. Filter them off and recrystallize from 50 percent alcohol. In the case of butyl and amyl alcohols, distill the excess alcohol in a vacuum, neutralize the remainder with a 5 percent solution of hydrochloric acid and extract the oil which appears with ether. Distill the ether under normal pressure and distill the alcohol (butyl, amyl) in a vacuum until the mass begins to harden. Recrystallize the acids from 50 percent alcohol. The melting point of 2-etoxyquinolin-4-carboxylic acid is 144-145 degrees; of 2-n.-propoxy 136-137 degrees; of 2-n.-butoxy 98 (111) degrees; of 2-isobutoxy 145-146 degrees; of 2-isoamylquinolin-4-carboxylic acid, 120-122 degrees.

II. Synthesis of α,α-dimethyl-β-diethylaminopropylchloride



The synthesis consists of the following three stages. The first two stages are obtained by the method of Mannich [6].

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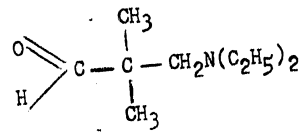
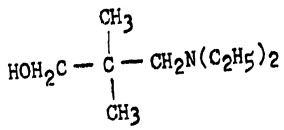
(1) Synthesis of α,α-dimethyl-β-diethylaminopro[redacted]panal



Heat during 3 and a half hours, mixing well, a mixture consisting of 37 grams of isobutyric aldehyde, 25 grams of ethyl alcohol, 38 grams of paraform and 45 grams of diethylamin hydrochloride. After cooling add a 40 percent solution of caustic soda up to a strongly alkaline reaction of the reaction mixture. An oil will come to the surface. Separate it from the water in a separating funnel, and extract the water layer with ether. Combine the ether extract with the oil, dry it with heated Na_2SO_4 and, having distilled the ether, fractionate. Gather the propanal at 173-179 degrees. The yield is 56 grams, or 70 percent of [redacted]

(2) Synthesis of α,α-dimethyl-β-diethylaminopropanol



Dissolve 25 grams of α,α-dimethyl-β-diethylaminopropanal in 200 grams of 50 percent acetic acid and to the solution add, in small doses and mixing well, 1 to 2 percent of sodium amalgam. The temperature dusting the reaction is 20-25 degrees. At the end of the

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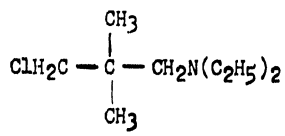
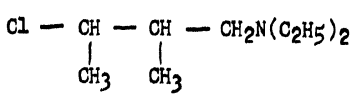
reaction add 50 percent solution of caustic potash and having separated it from the mercury, extract it with ether. Dry the ether extract. Distill the ether and fractionate in a vacuum. Gather the fractions boiling at 90-92 degrees (14 millimeters). Yield, 17.5 grams, or 70 percent of theory.

(3) Synthesis of α,α-dimethyl-β-diethylaminopropylchloride



Dissolve 12 grams of α,α-dimethyl-β-diethylaminopropanol in 24 grams of dry benzene and to this solution, mixing well and cooling, slowly add 10 grams of thionyl chloride. When all the thionyl chloride has been added, heat the mixture [redacted] for 5 hours [7]. The dark-red, dense liquid obtained must be treated in the cold with a saturated solution of potash and extracted with ether. Distill the ether and sublimate the chloride. Boiling point, 72 degrees (10 millimeters). Yield, 8 grams or 69 percent of [redacted] The [illegible]

III. Synthesis of α, β-dimethyl-γ-diethylaminopropylchloride



The works of Mannich [8] are [redacted] the basis of this synthesis. The synthesis consists of three stages.

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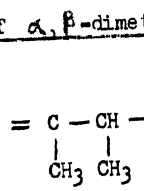
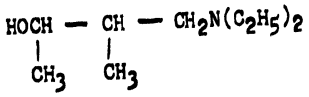
(1) Synthesis of α, β-dimethyl-γ-diethylaminopropylketone



Heat for 4.5 hours over a water bath a mixture of 25 grams of methylethylketone, 20 grams of diethylamin hydrochloride, 8 grams of paraform and 5 grams of alcohol. Thus the paraform dissolves entirely. Add a 40 percent solution of caustic soda to the cooled reaction mixture up to a strongly alkaline reaction. An oil will come to the surface. Separate it and distill it in a vacuum. The boiling point is 78-80 degrees (15 millimeters). Yield, 77 grams, or 70 percent of the [redacted] theoretical value.

(2) Synthesis of α, β-dimethyl-γ-diethylaminopropyl alcohol



Dissolve 20 grams of aminoketone in 160 grams of 50 percent acetic acid. To this solution add gradually 800 grams of 2 percent sodium amalgam. When all the amalgam has been added, neutralize the reaction mixture with a 50 percent solution of KOH, then extract with ether.

After distilling the ether, fractionate in a vacuum. Boiling point, 84 degrees (13 millimeters).

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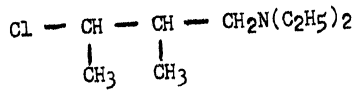
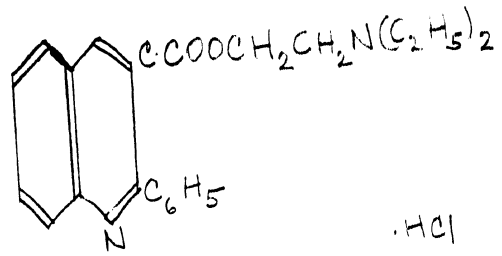
(3) Synthesis of α,β-dimethyl-γ-diethylaminopropylchloride



To the 24 grams of alcohol (see stage 2) dissolved in 48 grams of dry benzene, add, constantly mixing and with good refrigeration, 19.5 grams of thionylchloride. After all the thionylchloride has been added, heat the mixture for two hours in a water bath. Treat with potash and extract with ether. Boiling point of chloride 78-79 degrees (13 millimeters). Yield, 21.5 grams, or approximately 80 percent of [redacted] The [illegible]

IV. Synthesis of the diethylaminoethyl ethers of the 2-substituted quinolin-4-carboxylic acid

(1) Hydrochloride of the diethylaminoethyl ether of the 2-phenyl-quinolin-4-carboxylic acid



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Introduce 5 grams of 2-phenylquinolin-4-carboxylic acid obtained by Pfitzinger's method from isatin into a solution of alcoholate prepared from 0.47 grams of metallic sodium and 60 grams of ethyl alcohol. Distill the alcohol in a vacuum at 20-30 millimeters pressure and dry the remaining sodium salt of the phenylcinchonic acid in that same vacuum for two hours over a boiling bath. Suspend the obtained dry salt in 75 grams of dry xylene. Add 3.5 grams of hydrochloride of diethylaminoethylchloride and 1.5 grams of heated potash. Boil the reaction mixture for 10 hours. Filter away from NaCl, wash the filtrate with water, separate from the aqueous layer and process with 10 percent hydrochloric acid. Add potash to the solution up to alkaline reaction. The base of the diethylaminoethyl ether of the 2-phenylquinolin-4-carboxylic acid will come to the surface in the form of a yellow oil. Extract the oil with ether. Carefully add a calculated amount of 10 percent alcoholic solution of hydrogen chloride to the ether extract dried with Na_2SO_4. A white amorphous sediment precipitates. Recrystallize from alcohol. Melting point. Hard to dissolve in cold water, easy to dissolve in warm water and alcohol. Yield, 6.5 grams, or 84 percent of [redacted] Theoretical value.

Determination of Chlorine

0.1170 grams of substance: 3 milliliters 0.1 $AgNO_3$

Found %: Cl 9.08

Calculated %: Cl 9.2

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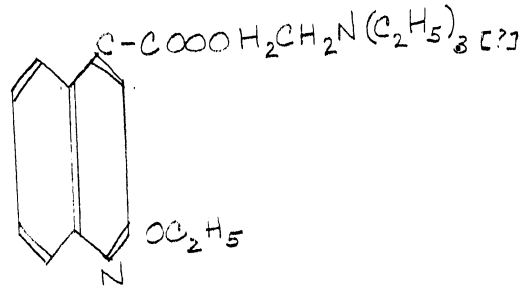
(2) Hydrochloride of the diethylaminoethyl ether of the 2-etoxyquinolin-4-carboxylic acid



HCl

Suspend 5 grams of the sodium salt of the 2-etoxyquinolin-4-carboxylic acid in 75 grams of xylene and add 4 grams of hydrochloride of diethylaminoethylchloride and 1.6 grams of heated potash. Heat the mixture for 10 hours and process as in the preceding experiment.

White amorphous powder with a melting point 170-170.5 degrees. Soluble in water, alcohol; insoluble in ether. Yield, 6.4 grams, or 80 percent of [redacted] Theoretical Value.

Determination of Nitrogen. (To determine the nitrogen we used the table in Hans Meyer's book, 127 (1935)).

0.1213 grams of substance: 8.5 milliliters N
(20.5 degrees; 753.5)
Found %: N 7.87
Calculated %: N 7.94.

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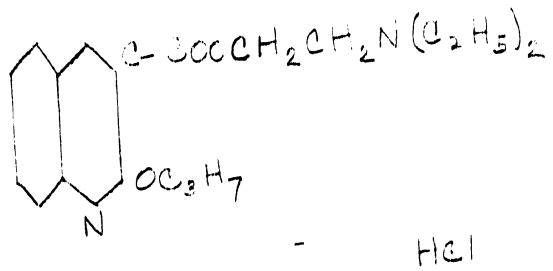
Determination of Chlorine

0.1971 grams of substance: 5.6 milliliters 0.1 $AgNO_3$.

Found %: Cl 10.25.

Calculated %: Cl 10.06.

(3) Hydrochloride of the diethylaminoethyl ether of the 2-n.-propoxyquinolin-4-carboxylic acid



Suspend 5 grams of the sodium salt of the 2-n.-propoxyquinolin-4-carboxylic acid in 75 grams of xylene and add 5 grams of hydrochloride of diethylaminoethylchloride and 2 grams of heated potash. Boil the mixture for 10 hours. Further processing as in the preceding experiments. Yield, 87 percent.

White crystals, easy to dissolve in water, alcohol. Melting point 169.5-170.5 degrees.

Determination of Chlorine

0.1522 grams of substance: 4.2 milliliters 0.1 $AgNO_3$

Found %: Cl 9.78.

Calculated %: Cl 9.72.

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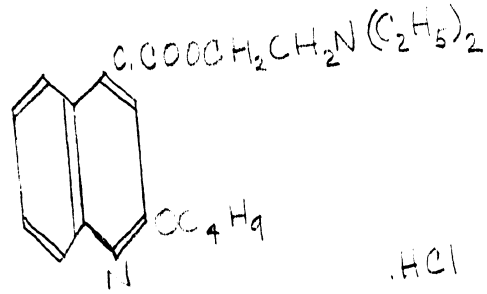
Determination of Nitrogen

0.1245 grams of substance: 8.4 milliliters N (18 degrees, 755 millimeters)

Found %: N 7.7

Calculated %: N 7.63.

(4) Hydrochloride of the diethylaminoethyl ether of the 2-butoxy-quinolin-4-carboxylic acid



Suspend 5 grams of the sodium salt of 2-n.-butoxyquinolin-4-carboxylic acid, 4 grams of hydrochloride of diethylaminoethylchoride and 1.5 grams of potash in 75 grams of dry xylene. Heating and processing as in the preceding experiments.

White crystals, easy to dissolve in water, alcohol. Melting point 149 degrees. Yield, 75 percent of theory (5.7 grams).

Determination of Chlorine

0.1066 grams of substance: 2.8 milliliters 0.1 $AgNO_3$

Found %: Cl 9.31

Calculated %: Cl 9.32

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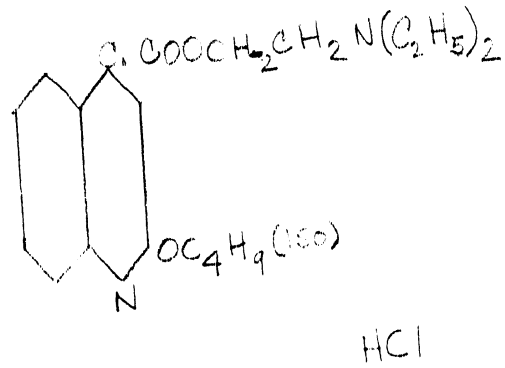
(5) Hydrochloride of the diethylaminoethyl ether of the 2-isobutoxyquinolin-4-carboxylic acid



Same quantities and same method as in experiment No 4. Melting point 152-153 degrees. Easily soluble in water.

Determination of Chlorine

0.1179 grams of substance: 3.1 milliliters 0.1 $AgNO_3$

Found %: Cl 9.32

Calculated %: Cl 9.32

Determination of Nitrogen

0.1097 grams of substance: 7.6 milliliters N(23 degrees, 750 millimeters)

Found %: N 7.57

Calculated %: N 7.36

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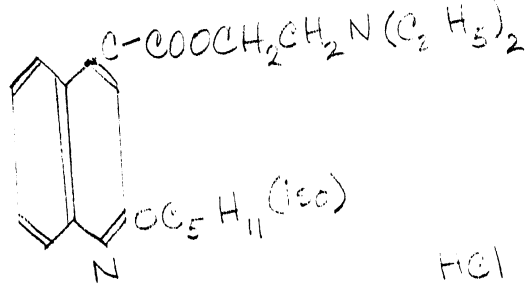
(6) Hydrochloride of the diethylaminoethyl ether of the 2-isoamyloxyquinolin-4-carboxylic acid



Suspend 5 grams of sodium salt of the 2-isoamyloxyquinolinic acid, 3.8 grams of hydrochloride of diethylaminoethyl chloride and 1.4 grams of heated potash in 75 grams of xylene. Heating and processing as in preceding experiments. White crystals with melting point at 160-161 degrees. Well soluble in water and alcohol.

Determination of Chlorine

0.1373 grams of substance: 3.5 milliliters 0.1 $AgNO_3$

Found %: Cl 9.04

Calculated %: Cl 8.97.

V. Synthesis of the diethylaminopropyl ethers of the 2-substituted quinolin-4-carboxylic acid

(1) Hydrochloride of the diethylaminopropyl ether of the 2-phenyl-quinolin-4-carboxylic acid [9]

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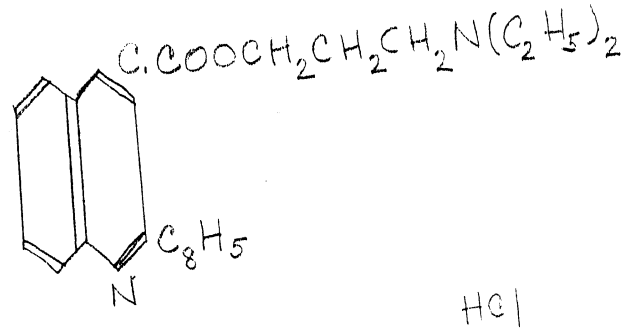

Suspend 5 grams of sodium salt of the 2-phenylquinolin-4-carboxylic acid and 4 grams of diethylaminopropylchloride (boiling point 170-171 degrees) in 75 grams of xylene. Heating and processing as in preceding experiments. Yield, 80 percent.

White crystals. Melting point 178-179 degrees. Hard to dissolve in cold water, well soluble in warm water and alcohol.

Determination of Nitrogen

0.1025 grams of substance: 6.6 milliliters N (21 degrees 754 millimeters)

Found %: N 7.23

Calculated %: N 7.28.

Determination of Chlorine

0.1120 grams of substance: 2.8 milliliters 0.1 $AgNO_3$

Found %: Cl 8.86

Calculated %: Cl 8.88.

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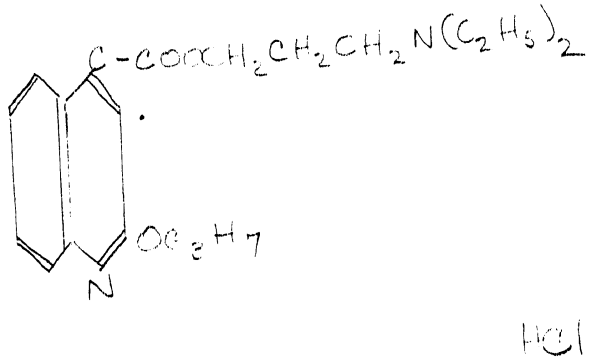
(2) Hydrochloride of the diethylaminopropyl ether of the 2-etoxyquinolin-4-carboxylic acid



Suspend 5 grams of sodium salt of the 2-etoxyquinolin-4-carboxylic acid, and 4.5 grams of diethylaminopropylchloride in 75 grams of xylene. Heating and processing as in the previous experiments. An oil which crystallizes only after three days is separated with the action of the hydrogen chloride alcoholic solution on the ether solution of the base. Spreads strongly when exposed to air. Becomes a hard substance after permanence in a P_2O_5 essicator. Besides the hydrochloride, a citrate (melting at 99 - 100 degrees) was also obtained.

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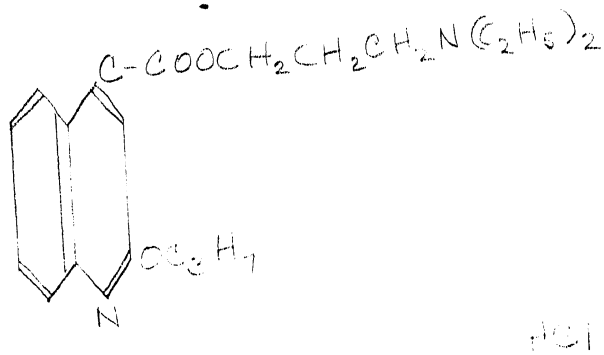
(3) Hydrochloride of the Diethylaminopropyl Ether of the 2-n.-propoxy-quinolin-4-carboxylic acid



Suspend 5 grams of sodium salt of the 2-n.-propoxyquinolin-4-carboxylic acid and 5 grams of diethylaminopropylchloride in 75 grams of xylene. Heating and processing as in preceding experiments.

White crystals with a melting point of 136 degrees. Well soluble in water, alcohol; insoluble in ether.

Determination of Chlorine

0.1019 grams of substance: 2.7 milliliters 0.1 $AgNO_3$

Found percent: Cl 9.38

Calculated percent: Cl 9.32

Determination of Nitrogen

0.1133 grams of substance: 7.6 milliliters N (18 degrees, 747 millimeters)

Found percent: N 7.57

Calculated percent: N 7.36.

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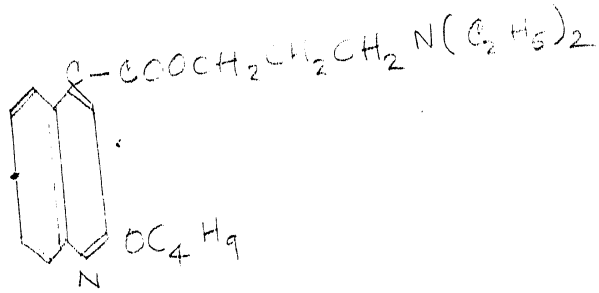
(4) Hydrochloride of the Diethylaminopropyl Ether of the 2-n.-butoxy-quinolin-4-carboxylic Acid



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Suspend 5 grams of sodium salt of the 2-n.-butoxyquinolin-4-carboxylic acid and 3.5 grams of diethylaminopropylchloride in 75 grams of xylene. Heating and processing as in preceding experiments. The hydrochloride is very hard to crystallize and an amorphous mass is obtained. The base is a light yellow oil distilled in a vacuum (2.5 millimeters) at 207 - 211 degrees.

Determination of Nitrogen in the Base

0.1437 grams of substance: 10.4 milliliters N (757.8 millimeters, 22 degrees)

Found percent: N 8.13

Calculated percent: N 7.82

Determination of Chlorine in the Hydrochloride

0.1284 grams of substance: 5.7 milliliters 0.1 $AgNO_3$

Found percent: Cl 16.5

Calculated percent: Cl 16.4

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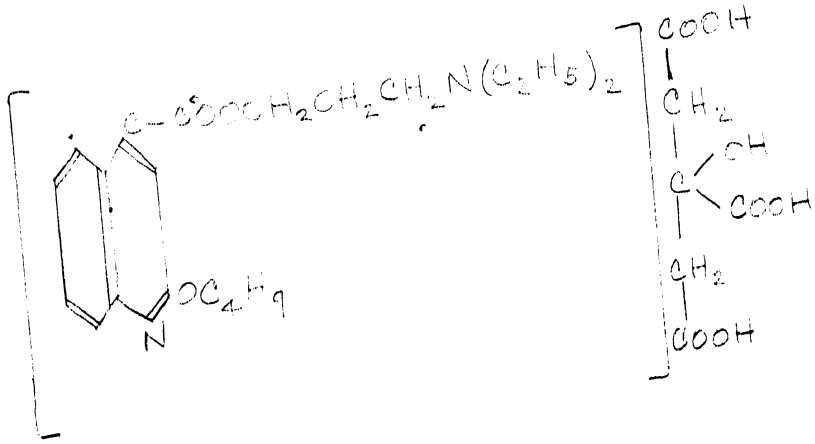
Since the hydrochloride is very hard to crystallize we obtained the citrate of the diethylaminopropyl ether of the 2-butoxyquinolin-4-carboxylic acid



Melting point 115 - 116 degrees.

Determination of Nitrogen in the Citrate

0.0948 grams of substance: 4.5 milliliters N (757 millimeters, 24 degrees).

Found percent: N 5.27

Calculated percent: N 5.09

VI. Synthesis of α, α-dimethyl-β-diethylaminopropyl Ethers of the 2-substituted quinolin-4-carboxylic Acid

(1) Hydrochloride of the α, α-dimethyl-β-diethylaminopropyl Ether of the 2-phenylquinolin-4-carboxylic Acid

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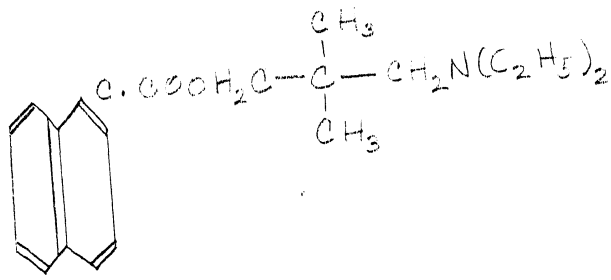

HCl

Heat 5 grams of sodium salt of the 2-phenylquinolin-4-carboxylic acid and 4.5 grams of , -dimethyl-β-diethylamino-propylchloride with 75 grams of xylene. Processing as in the preceding experiments. Yield, 85 percent.

White crystals with a melting point of 176 - 177 degrees. Well soluble in water, alcohol. Base: transparent pale creamy crystals which yellow with time. Melting point 44 - 46 degrees.

Determination of Chlorine

0.1127 grams of substance: 2.5 milliliters 0.1 $AgNO_3$

Found percent: Cl 7.85

Calculated percent: Cl 8.3

Determination of Nitrogen in the Base

0.1134 grams of substance: 7.5 milliliters N (21.5 degrees, 758 millimeters)

Found percent: N 7.45

Calculated percent: N 7.18

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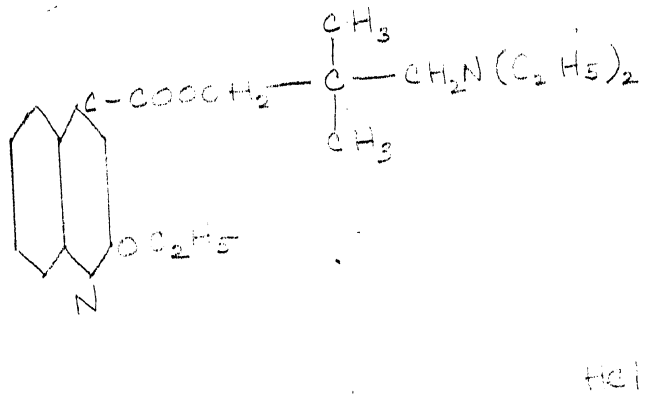
(2) Hydrochloride of the α, α-dimethyl-β-diethylamino-propyl Ether of the 2-etoxyquinolin-4-carboxylic Acid



Heat 5 grams of sodium salt of the 2-etoxyquinolin-4-carboxylic acid and 4 grams of , -dimethyl-β-diethylaminopropyl-chloride with 75 grams of xylene. Processing as in the preceding experiments. The hydrochloride precipitates as a mass, but crystallizes after a two-day rest. Melting point 115 - 116 degrees.

White, greenish crystals, well soluble in water, alcohol.

Determination of Chlorine

0.0962 grams of substance: 2.5 milliliters 0.1 $AgNO_3$

Found percent: Cl 9.21

Calculated percent: Cl 8.98

Determination of Nitrogen

0.0989 grams of substance: 6.6 milliliters N (748 millimeters, 22 degrees)

Found percent: N 7.41

Calculated percent: N 7.12

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Base: a light yellow oil boiling at 207 degrees (3 millimeters)

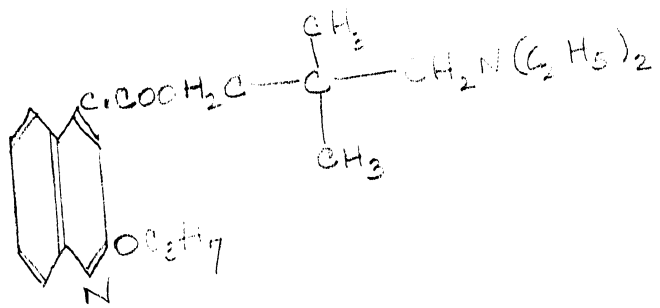
Determination of Nitrogen in the Base

0.1079 grams of substance: 7.5 milliliters N (756.6 millimeters, 23 degrees)

Found percent: N 7.85

Calculated percent: N 7.8

(3) Hydrochloride , -dimethyl-β-diethylaminopropyl ether of the 2-n.-propoxyquinolin-4-carboxylic acid



Suspend 3 grams of sodium salt of the 2-n.-propoxyquinolin-4-carboxylic acid and 2.5 grams of , -dimethyl-β-diethylamino-propyl-chloride in 45 grams of dry xylene. Heating and processing as in preceding experiments.

White crystals well soluble in water, alcohol. Melting point, 123 - 124 degrees.

Determination of Nitrogen

0.1061 grams of substance: 6.8 milliliters N (746

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millimeters, 24 degrees)

Found percent: N 7 percent

Calculated percent: N 6.85

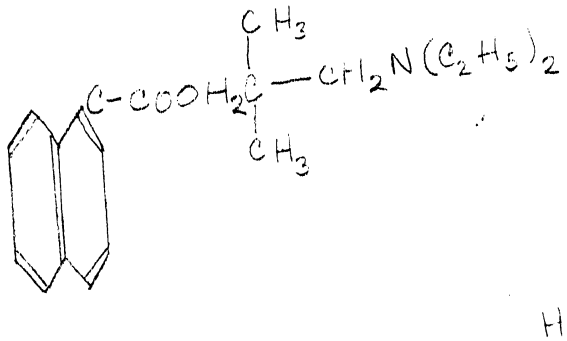
Determination of Chlorine

0.0983 grams of substance: 2.4 milliliters 0.1 $AgNO_3$

Found percent: Cl 8.65

Calculated percent: Cl 8.67

(4) Hydrochloride of the [illegible], [illegible]-dimethyl-β-diethylamino-propyl ether of the 2-n.-butoxy-quinolin-4-carboxylic acid



Suspend 5 grams of sodium salt of the 2-butoxyquinolin-4-carboxylic acid and 4.2 grams of [illegible], [illegible]-dimethyl-β-diethylamino-propyl-chloride in 75 grams of xylene. Heating and processing as in preceding experiments.

White crystals with a melting point of 137 - 138 degrees. Well soluble in water.

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Determination of Chlorine

0.1093 grams of substance: 2.5 milliliters 0.1 $AgNO_3$

Found percent: Cl 8.1

Calculated percent: Cl 8.39

Determination of Nitrogen

0.1003 grams of substance: 6.3 milliliters N (748 millimeters, 23.5 degrees)

Found percent: N 6.92

Calculated percent: N 6.62

From the hydrochloride we separated the base, a light yellow oil boiling at 207 - 210 degrees (3 millimeters).

Determination of Nitrogen in the Base

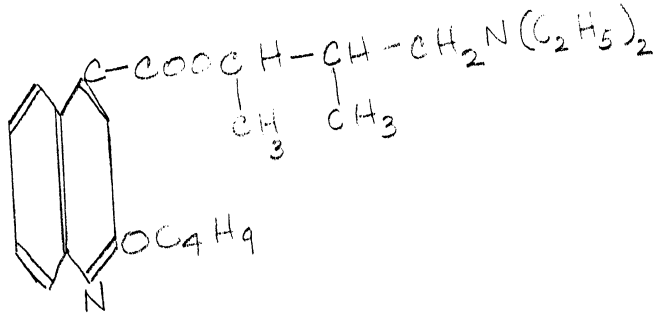
0.1079 grams of substance: 7.2 milliliters N (23 degrees, 756.6 millimeters)

Found percent: N 7.45

Calculated percent: N 7.25.

VII. α-β-dimethyl-γ-diethylaminopropyl Ethers of the 2-substituted quinolin-4-carboxylic acids

(1) α-β-dimethyl-γ-diethylaminopropyl ether of the 2-butoxy-quinolin-4-carboxylic acid



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Suspend 5 grams of sodium salt of the 2-butoxyquinolin-4-carboxylic acid and 4.2 grams of B-dimethyl- -diethylamino-propylchloride in 75 grams of xylene. Heating and processing as in preceding experiments. Distill the ether and fractionate the base in a vacuum. Base: yellow oil, boiling at 214 - 217 degrees 93 millimeters).

Determination of Nitrogen

0.1457 grams of substance: 9.5 milliliters N (758.8 millimeters, 23 degrees).

Found percent: N 7.30

Calculated percent: N 7.25

Acetate: White crystals, well soluble in water. Melting point 78 - 79 degrees

I bring earnest thanks to Professor A. M. Berkenheim for his advice and cooperation in the present work.

The present work is subsidized by GUUZ HKTP, to which I express thanks for the help given me in the conducting of this research.

CONCLUSIONS

(1) By action of the alkylamin chlorides on the sodium salts of the quinolin-4-carboxylic acids in the medium of an organic solvent (xylene), it is easy to obtain the corresponding ethers of these acids.

(2) The ethers of the derivatives of the quinolin-4-carboxylic

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acids possess a strong anesthetic action; the defect of many of these anesthetics is their way of irritating the tissues of the eye of rabbits.

LITERATURE

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STUDY OF THE MILK-LIKE JUICE OF THE SPURGE EUPHORBIA BIGLANDULOSA BOISS

II. STRUCTURE OF BIGLANDULINIC ACID

N. P. Kir'yalov

Chemical Laboratory of the Vegetal Raw Material Department of the Academy of Sciences Botanical Institute USSR

In the first report [1] I showed some properties of biglandulinic acid which are [redacted] not yet described in literature and which were [redacted] found and separated by me from the milk-like juice of the Spurge Euphorbia Biglandulosa Boiss.

Now I have enough material to be able to make conclusions as to the structure of the acid.

Biglandulinic acid has an empirical composition $C_9H_{10}O_6$; out of the six oxygen atoms present, four are in the form of two carboxylic radicals, while the other two are locked in a lactone ring. Biglandulinic acid possesses one double bond, since its reduction leads to dihydrobiglandulinic acid $C_9H_{12}O_6$, which with heating easily loses one molecule of CO_2 with the formation of a saturated lactonic acid $C_8H_{12}O_4$, with a melting point of 129-131 degrees [1], which in the following text I will permit myself to call dinic acid. It is unknown in literature. If we acidify the dinic acid with permanganate in an alkaline solution, we obtain with the theoretic yield a tribasic

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acid $C_8H_{12}O_6$, with a melting point 143-145, which turns out to be identical with α,α-dimethyltricarballylic acid.

Both in the diglandulinic and the dinic acids the lactone group are in a γ-position, because I have established the exceptional stability of the lactone ring in relation to neutral aqueous solutions and even to cold and weak aqueous alkali. The oxy acids, obtained after opening of the lactone rings of the biglandulinic of dinic acids by heating with weak aqueous alkali, are very unstable and, with slight heating and in an acid medium, change wholly back to the original lacto-acids.

Biglandulinic and dinic acids do not change from heating with H_2SO_4 and HCl.

As I have said before [1], Biglandulinic acid is optically passive: the supposition that it might represent a racemic compound was not confirmed. After several crystallizations of the brucinic salt of the biglandulinic acid, the resulting brucinic salt had the very same melting point 185-187 degrees (with decomposition).

The starting point for the solving of the problem of biglandulinic acid structure was the fact that the unstable dihydrobiglandulinic acid sheds one molecule of CO_2 and becomes dinic acid. By acidification of the latter with permanganate we obtain α,α-dimethyltricarballylic acid. Thus the structure of dinic acid can be presented as follows (I, or II, or III formulas).

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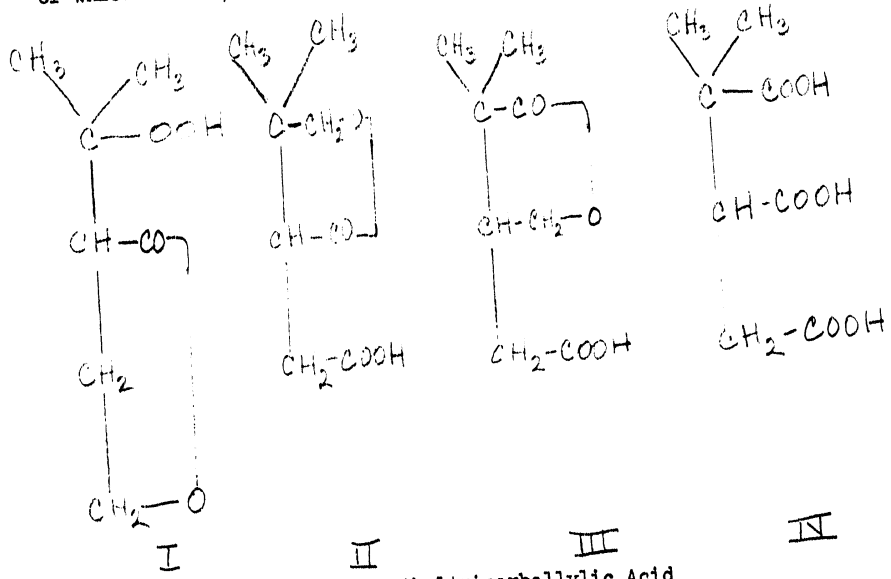
All three offered structure formulas of dinic acid (I, II, III) may with acidification give α,α-dimethyltricarballylic acid (IV).

On the basis of the indicated possible formulas (I, II, III) for dinic acid one must surmise that with its acidification with permanganate in an alkaline medium, first its lactone ring opens and the salt of the oxydibasic acid is formed, and then the free primary alcoholic radical is acidified into a carboxyl, as a result of which the α,α-dimethyltricarballylic acid is formed.



I II III IV

α,α-Dimethyltricarballylic Acid

Diglandulinic acid differs from dinic acid only by the fact that the former contains one double bond (which is absent in dinic acid) and two carboxyls (dinic acid has one, while only the hydrogen remains of the second). The carbon skeleton is the same in both

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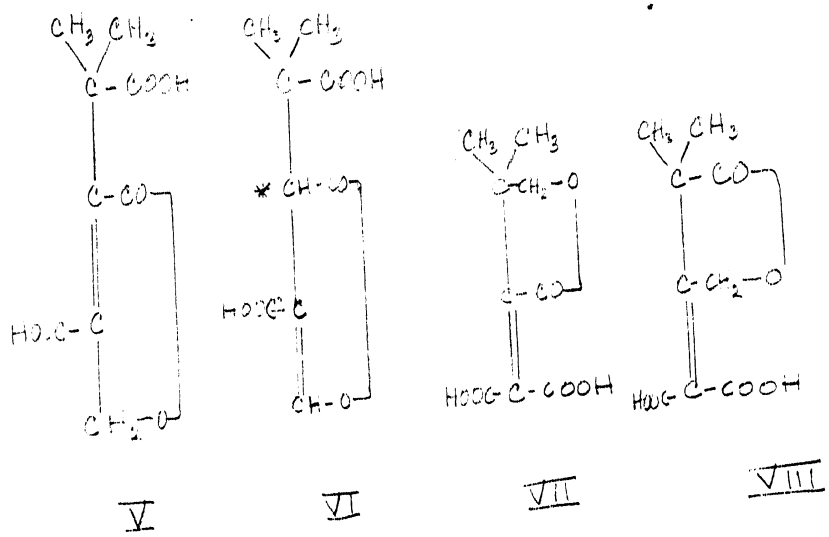
acids. Because of all this, issuing from the three possible formulas for dinic acid, all sorts of variations for the structure of biglandulinic acid were contrived and put into the formulas (V), (VI), (VII), (VIII).



V VI VII VIII

The following determines which of the four formulas (V), (VI), (VII), (VIII) for biglandulinic acid is the [redacted] founded.

Formulas (VII) and (VIII) admit two carboxyl radicals with one carbon atom. In this case it would be natural to expect shedding during heating of the biglandulinic acid of one molecule CO_2. This is not confirmed experimentally. Through heating, biglandulinic acid separates water and becomes anhydride with a melting point 210-212 degrees and with the same number of carbon atoms [1]. Thus the

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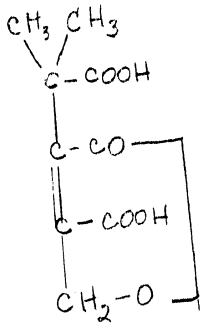
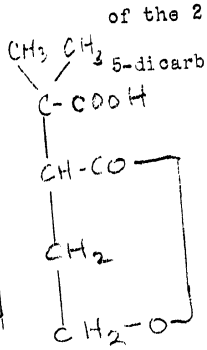
formulas (VII) and (VIII) are discarded. Of the remaining two biglandulinic acid formulas (VI) and (V) with a double bond in the lactone ring we must consider formula (V) as the most likely, because formula (VI) presupposed the presence of an asymmetrical atom of carbon (marked in the formula (VI) by the sign *) in the γ-position of the carbonic chain. Because of this biglandulinic acid should be an optically active compound. In reality, as was established experimentally, biglandulinic acid is optically passive and is not a racemate. Consequently it does not contain an asymmetric atom, which condition is satisfied by formula (V). Thus, biglandulinic acid is apparantly an λ-lactone of the 2-methylpenten-3-01-5-tricarboxylic 2,3,4-acid. The free acid of this lactone is not known and apparently does not exist.

Corresponding[redacted] to the structure of biglandulinic acid we can accept formula (1) for dinic acid. Then dinic acid will become a γ-lactone of the 2-methylpenthanol-5-dicarboxyl 2,3-acid. The oxy acid of this lactone is unstable in its free state.

Biglandulinic acid, or γ-lactone of the 2-methyl-3-01-5-tricarboxylic 2,3,4 acid



Dinic acid, or γ-lactone of the 2 methyl-penthanol-5-dicarboxylic 2,3-acid



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A final proof of the structural formulas for biglandulinic and dinic acids can be produced by synthesis.

It is still unknown what role is played by biglandulinic acid in the biosynthetic activity of the plant. But we can surmise that biglandulinic acid has a function in the producing of resins by the plant. Because of a series of properties these resins are important for the varnish and paint industry. Certain data on the question touched will be communicated later.

EXPERIMENTAL PART

Relationship of Biglandulinic Acid to H_2SO_4, HCl and Alkali

A prolonged (1-2 hours) heating of biglandulinic acid with 50 percent H_2SO_4 or strong HCl over a boiling water bath does not produce any changes and the acid is again separated unchanged (melting point around 170 degrees; a mixed sample does not produce depression during melting; and finally, it is easy to obtain the characteristic colored reaction with $FeCL_3$, which disappears with addition of H_2SO_4). A precisely neutralized and cold 1 percent aqueous solution of biglandulinic acid preserved with neutral reaction for 5 days. The same solution reacted with weak alkali. The reaction was slow in cold temperature and much faster with heating.

0.5123 grams of biglandulinic acid required during cold titration 0.5 n. KOH -- 9.6 milliliters.

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After boiling for 30 minutes with an excess 0.5 n. KOH and back -- titration with 0.5 n. sulphuric acid on alkali entered in the reaction, 0.5123 grams of biglandulinic acid required 0.5 n. KOH -- 14.3 milliliters.

Consequently, because of heating with excess of weak alkali, the weighing of diglandulinic acid required an additional 0.5 n. KOH -- 4.7 milliliters.

0.5 n. KOH -- 4.78 milliliters were calculated for one lactone group for $C_9H_{10}O_6$. With additional acidification the diglandulinic acid separates unchanged (melting point around 170 degrees, colored reaction with $FeCL_3$).

Thus biglandulinic acid contains one lactone group which is situated, according to the properties of the acid, in a γ-position.

Effect of Heating with H_2SO_4, HCl and Alkali on Dinic Acid

A prolonged heating (2-3 hours) of dinic acid with concentrated hydrochloric or 50 percent sulphuric acids over a boiling water bath does not produce any noticeable changes. The original, unchanged acid separates (melting point 129-131 degrees).

If we neutralize dinic acid under refrigeration and then leave a 2-3 percent solution of the salt to stand for 5 days, in spite of the prolonged action of the neutral aqueous solution, the lactone radical is not saponified, and the solution maintains its neutral reaction. If we boil a neutral aqueous solution for 2

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hours, there also is no saponification. Only in an alkaline solution, slowly under refrigeration and faster with heating, does a saponification of the lactone radical occur. With acidification the salt formed of the oxydibasic acid easily reverts to the original dinic acid. This shows that the lactone ring in dinic acid is in the γ-position.

Melting with Alkali. To melt, mix 4.5 grams of dinic acid with a saturated aqueous solution of KOH (27 grams of KOH in 40 milliliters of water) in a porcelain cup, and heat the mixture to 150-180 degrees during 15-20 minutes. Cool the melted mass and extract the salts with ethyl alcohol. Distill the alcohol and carefully (avoiding heating) acidify the residue dissolved in a small quantity of water with diluted sulphuric acid. Extract the separated substance with ether, carefully boil down the ether and the residue will be a substance with an indistinct melting point of 180-188 degrees. During recrystallization from water or heating the substance changes and melts at 130-132 degrees. Yield, 3.9 grams of pure substance.

During The study of the substance with a 130-132 degrees melting point, the following results were obtained:

0.1162; 0.1388 grams of substance required under refrigeration 0.5 n. KOH 1.47, 1.62 milliliters.

During heating with an excess 0.5 n. KOH during 30 minutes, the substance required an additional 0.5 n. KOH 1.51, 1.59 milliliters.

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After acidification the original substance with a melting point of 129-131 degrees separates. It is obvious that the substance was a lactone-acid.

Element Analysis

0.1170; 0.1036 grams of substance: 0.2396, 0.2118 grams CO_2; 0.0751, 0.0646 grams H_2O.

Found %: C 55.85; 55.75; H 7.13; 6.93.

$C_8H_{12}O$. Calculated %: C 55.81; H 7.00.

The substance obtained, mixed with the original dinic acid, gives no depression during melting. Thus we may consider as established that the obtained substance is the original dinic acid which remained unchanged under the action of alkali.

The unstable substance with a melting point of 180-188 degrees is apparently a oxydibasic acid which easily sheds water and changes into dinic acid (after the substance with its original 180-188 degrees melting point had stayed in an essicator with sulphuric acid for a few days, it lowered its melting point to 129-132 degrees, that is, probably shed water and was transformed into dinic acid).

Oxidation of Dinic Acid

2 grams of dinic acid were dissolved in 75 milligrams of hot water. The solution was alkalinized up to a clearly alkaline reaction during boiling for 15-20 minutes. A 4 percent solution of permanganate (3 grams of $KMnO_4$ in 75 millimeters of water) was added

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little by little to the alkaline solution. The mixture was heated over a boiling water bath for [redacted] 1 and a half-two hours. Then the excess of permanganate was removed with a few drops of methyl alcohol, the manganese peroxide was filtered away and the liquid boiled down to a small volume. The rest of the liquid was acidified with diluted sulphuric acid and the acid solution extracted with ethyl ether. The ether extracts were dried with heated Glauber salt, the ether was distilled. At the bottom of the flask there remained a very thick colorless liquid gradually congealing into a snow-white mass (with the aid of quick friction with a glass rod). During congealment the liquid adheres very strongly to the glass. Yield, 2.3 grams. The substance obtained is easily soluble in ether, alcohol, ethylacetic ether and water. It is insoluble in petroleum ether and chloroform. The substance had acid properties, did not contain a lactone radical, gave no reaction with $FeCl_3$. A copper salt, of a pale blue color, is obtained by adding a solution of $CuSO_4$ to a neutral aqueous solution of the acid. The salt is comparatively easily soluble in cold water and is insoluble in boiling water. The acid crystallizes from a mixture of ether and ligroin in the form of thin short needles. Melting point 143-145 degrees.

The supposition that the substance is a tribasic acid was confirmed by the results of titration and burning of the silver salt. Titration: 0.1262; 0.0998 grams of substance required

18.25; 14.27 milliliters, 0.1 n. KOH

$C_5H_9(COOH)_3$. Calculated 18.56; 14.68 milliliters 0.1 n. KOH

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The silver salt, obtained by the usual method and dried to constant weight in a vacuum essicator, showed during burning a percentage of Ag close enough for a tribasic acid.

Analysis of the Silver Salt:

0.1294; 0.1046 grams of substance: 0.0794; 0.0640 grams of Ag.

Found %: Ag 61.36; 61.08.

$C_5H_9(COOAg)_3$. Calculated %: Ag 61.71.

The somewhat lower percentage of Ag found in comparison with that calculated is common for polybasic acids.

Element Analysis:

0.1386; 0.1208 grams of substance: 0.2392; 0.2074 grams CO_2; 0.0724; 0.0638 grams H_2O.

Found %: C 47.06; 46.82; H 5.80; 5.86.

$C_8H_{12}O_6$. Calculated %: C 47.06; H 5.88.

The tribasic acid obtained loses one molecule of water during heating at 210 degrees at 210 millimeters of pressure and changes into an anhydro-acid with a melting point 143-146 degrees (from ethylacetic ether). During heating with water the anhydro-acid returns to the original acid.

Analysis of the Anhydro-Acid:

0.1104 grams of substance: 0.2079 grams CO_2; 0.0552 grams H_2O.

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Found %: C 51.35; H 5.55.

$C_8H_{10}O_5$. Calculated %: C 51.61; H 5.38.

In accord with these data the obtained tribasic acid can be identified as α,α-dimethyltricarballylic, for which Tiemann and Semmler [2], and also Bayer [3] indicate analogous composition and properties.

Obtaining the Brucinic Salt of the Biglandulinic Acid

Two grams of brucine in 100 milliliters of alcohol were added to 2 grams of biglandulinic acid in alcoholic solution (10 percent solution). A voluminous sediment of the acid salt of brucine precipitated immediately. The salt is hard to dissolve in cold alcohol, but dissolves well in hot alcohol and water. The acid salt, recrystallized 3 times from alcohol, had a melting point of 185-187 degrees (with decomposition). Fractionated crystallization from an alcohol-aqueous solution gave a substance with the same melting point of 185-187 degrees in all its fractions.

Evidently the acid salt of brucine was one individual substance, while the biglandulinic acid was a non-racemic compound.

CONCLUSIONS

(1) The structure of biglandulinic acid separated from the milk-like juice of the Spurge Euphorbia biglandulosa Boiss has been established. Biglandulinic acid is a γ-lactone of the 2-methylpenten-3-ol-5-tricarboxyl 2,3,4-acid (V).

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(2) Dihydrobiglandulinic acid $C_9H_{12}O_6$, easily loses one molecule of CO_2 during heating and is changed into a lactone-acid $C_8H_{12}O_4$. The name of dinic acid has been suggested for the compound obtained, which has not yet been described in literature.

By its structure dinic acid is a γ-lactone of the 2-methylpenthanol-5-dicarboxyl 2,3-acid (I).

LITERATURE

(1) Kir'yalov N. P. ZhOKh, 8, 740 (1938).

(2) Tiemann and Semmler. Ber., 28, 1349 (1895).

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ALKALOIDS OF THE SALSOLA RICHTERI. IV

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In our preceding work on the alkaloids of the Salsola Richteri we described a new alkaloid l-salsolidin and showed that it has the structure of 1-methyl-6,7-dimethoxytetrahydroisoquinoline [1].

Soon after that there appeared the work by E. Späth and Dengel [2], in which they describe the synthesis of salsolidin and its splitting into optically active antipodes. It turned out that certain properties of the synthetic salsolidin differ from our data. Thus, for optically active salsolidin, Späth and Dengel find a melting point of 47.5-48.5 degrees, while we found that this substance crystallizes from water with two molecules of H_2O and melts at 60-61 degrees. After drying in a vacuum it loses the crystallization water and melts at 71-73 degrees. Further Späth and Dengel point out that the specific rotation of salsolidin found by them ($/\alpha/_D$ = + 59.7 degrees) is higher than the quantity indicated by us (+52.9 and -53.1 degrees). A still bigger disparity is noted in the properties of racemic salsolidin for which Späth and Dengel find a melting point of 53-53.5 degrees, while we indicate a melting point of 117-119 degrees.

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One must note that the working method of Späth and Dengel somewhat differs from ours. While we purified salsolidin by crystallization from water, they apply distillation in a vacuum.

The presence of these disparities induced us to conduct an experimental checking.

It turned out that, in full accord with our previous data, l-salsolidin, crystallized from water and containing two molecules of H_2O, melts at 60-61 degrees and during drying changes into an anhydrous form which melts at 71-73 degrees. Although this substance had already been analyzed by us, we nevertheless made a controlling analysis, the results of which exactly correspond to the formula $C_{12}H_{17}NO_2$.

Subjecting this l-salsol[redacted]idin (melting point 71-73 degrees) to distillation in a vacuum, we found that it distills in shape of a thick oil which crystallizes with cooling and melts, in accord with the observations of Späth and Dengel, at 41-45 degrees.

The somewhat lowered and less abrupt melting point found by us is explained by the fact that Späth and Dengel determined the melting point in a vacuum-capillary, while we determine it by the usual way, in an open capillary. If we subject the distilled product with a melting point of 41-45 degrees to crystallization from hot water, then we again obtain the hydrate form with a melting point of 60-61 degrees which, with drying changes into the anhydrous form with a melting point of 71-73 degrees. Exactly similar

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phenomena are observed in the case of d-salsolidin: after distillation in a vacuum one obtains a substance with a melting point 41-45 degrees, changing after cyrstallization from water into a hydrate form with a melting point of 60-61 degrees, which after drying in a vacuum gives a form with a melting point of 71-73 degrees.

Thus an experimental check showed that our observations are as accurate as those by Späth and Dengel. This check bared an interesting and unforeseen fact: both optically active forms of salsolidin can exist in two interchangeable forms with melting points of 47-48 degrees and 71-73 degrees. After distillation in a vacuum one obtains the low melting form which, after recrystallization from water, changes into the high melting form. Both forms give identical salts and in solution have the selfsame specific rotation which leads us to believe that we are confronted by two polymorphous, interchangeable forms. (The divergence between the specific rotation shown in our article and the data of Späth and Dengel is explained by the fact that our figures ($[\alpha]_D$ = -52.9 degrees and +53.5 degrees) refer to the hydrate form $C_{12}H_{17}NO_2 \cdot 2H_2O$. Calculating from the anhydrous base we find for $[\alpha]_D$ the value -62.1 degrees and +62.8 degrees. The control determinations, done with the anhydrous form $C_{12}H_{17}NO_2$, gave us $[\alpha]_D$ = 63.6 degrees and +62.8 degrees.

As to the racemic salsolidin, for which we indicate a melting point of 117-119 degrees, it is necessary to introduce a correction of our data. Our check showed that this substance (obtained by

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methylization of the racemic salsolidin) and of which at the time we had not made a full analysis, is in reality not a free base, but a carbonate $(C_{12}H_{17}NO_2)_2CO_2$. In contradistinction to the optically active salsolidin, fully stable in contact with the atmosphere, the racemate easily attracts the carbon dioxide from the air, giving the above mentioned carbonate [redacted] a melting point of 117-119 degrees. This interesting difference in the ease of absorbing carbon dioxide, observed between the optically active forms and the racemate, is particularly obvious in the following experiment. Upon sending a current of carbon dioxide through an ether solution of racemic salsolidin there immediately forms a sediment of crystallic carbonate, insoluble in ether. If we send CO_2 under the same conditions through a solution of optically active salsolidin, the solution remains transparent for a long time and only after lengthy treatment with CO_2 does an insoluble carbonate $(C_{12}H_{17}NO_2)_2H_2CO_3$ form. This has a melting point of 80-81 degrees. Because of this ease of CO_2 absorption, upon separation of the racemic salsolidin by the usual way, instead of the base one obtains its carbonate, which fact explains the high melting point indicated by us. Upon distillation of the carbonate in a vacuum it decomposes and gives the crystallic base with a melting point of 47-50 degrees (in an open capillary). In this case we were not able to note the existence of two isomorphous forms.

In our preceding article [1], we pointed out that while salsolin is found in the plant as a mixture of racemate and the dextrorotatory form, salsolidin is found exclusively in its

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optically active (levorotatory) form. This observation is true only for certain samples of Salsola, gathered at a certain time. Studying the samples gathered in 1936-1937 we discovered in the mother liquors remaining after the separation of salsolin and ℓ-salsolidin, also some racemic salsolidin. This substance was obtained in the form of its carbonate $(C_{12}H_{17}NO_2)_2CO_2$ with a melting point of 117-119 degrees and was separated into optically active antipodes which have properties exactly corresponding To [redacted] the properties of the optically active forms of salsolidin described above.

The third alkaloid, salsamin, which we previously separated from the last mother liquors, also apparently is not always present in the plant. It was impossible to discover it in the samples gathered in 1936 and 1937.

Thus the composition of the alkaloid mixture coming out of the Salsola Richteri is subjected to rather significant variations which depend from the moment of the gathering and perhaps also from the place where the plant had grown and from climatic conditions of the given year.

EXPERIMENTAL PART

ℓ-Salsolidin

Dissolve the salsolidin hydrochloride (melting point 233-235 degrees) obtained by the method prescribed before, in water and alkalinize it with ammonia. The base precipitates in the shape of

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small colorless scales melting at 60-61 degrees. After drying in a vacuum the melting point is 71-73 degrees.

0.2310 grams of anhydrous base in 10 milliliters of alcohol ℓ= 0.95 dm; α_D = -1.5 degrees; $[\alpha]_D$ = -63.6 degrees.

2.815 milligrams of substance: 7.133 milligrams CO_2; 2.131 milligrams H_2O.

2.900 milligrams of substance: 7.370 milligrams CO_2; 2.161 milligrams H_2O.

4.528 milligrams of substance: 0.265 milliliters N_2 (21.5 degrees, 752 mm)

3.478 milligrams of substance: 0.206 milliliters N_2 (21 degrees, 753 mm)

Found %: C 69.49, 69.31; H 8.47, 8.34; N 6.59; N 670.

$C_{12}H_{17}NO_2$. Calculated %: C 69.56; H 8.21; N 6.75.

Distill in a vacuum the pure base obtained in such a way (melting point 71-73 degrees). At 3-4 millimeters of pressure and at 140-150 degrees it distills in the form of a thick oil that crystallizes with cooling. Melting point 41-45 degrees (in an open capillary). Upon recrystallization of this substance from water, minute colorless scales with a melting point of 60-61 degrees are obtained. Upon drying in a vacuum they lose two molecules of H_2O and then melt at 71-73 degrees. The low and the high melting forms give the same hydrochloride with a melting point of 233-235 degrees and $[\alpha]_D$ = -26.5 degrees. Upon sending a current of CO_2 through an ether solution of anhydrous ℓ-salsolidin the solution remains transparent for a long time and only after a lengthy contact with

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CO_2 does a colorless powderlike residue of carbonate appear. This is insoluble in ether, soluble in water and alcohol. Melting point 80-81 degrees with separation of gas bubbles.

3.105 milligrams of substance: 7.170 milligrams CO_2; 2.163 milligrams H_2O.

14.757 milligrams of substance: 34.000 milligrams CO_2; 10.320 milligrams H_2O.

4.860 milligrams of substance: 0.251 milliliters N_2 (19 degrees, 742 millimeters)

3.656 milligrams of substance: 0.191 milliliters N_2 (20.5 degrees 742 millimeters)

Found %: C 62.98, 62.84; H 7.80, 7.83; N 5.80, 5.86.

$(C_{12}H_{17}NO_2).H_2CO_3$. Calculated %: C 63.02; H 7.56; N 5.88.

SEPARATION OF THE RACEMIC SALSOLIDIN FROM ACETONE MOTHER LIQUORS OBTAINED DURING PURIFICATION OF ℓ - SALSOLIDIN HYDROCHLORIDE

We moistened 70 kilograms of green parts of Salsola Richteri (gathered in 1936-1937) with ammonia and extracted with dichlorethane. The sum of alkaloids separated by the method described earlier gave upon processing with acetone 76 grams of salsolidin.

After distillation of the solvent and processing with 10 percent hydrochloric acid, we obtained the ℓ-salsolidin hydrochloride from the acetone solution. We purified it by repeated extraction with hot acetone. The yield was 60 grams of ℓ-salsolidin hydrochloride. We boiled down to dryness the aqueous and acetone mother

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liquors obtained during the separation and purification of ℓ-salsolidin hydrochloride.

The residue, which was in the form of a thick, dark brown mass, was dissolved in an amount of water five times greater with the precipitation of a viscous dark brown resin. The solution was filtered away from the resin, was washed with chloroform until the latter ceased to be colored, and was processed with activated coals. The filtrate, obtained after purification with coal, was saturated with potash and extracted with ether. The residue after distillation of the ether was a thick, dark yellow oil (24 grams) which in time partially crystallized. The powderlike precipitate was filtered away and was washed with ether. Yield 5.2 grams. Melting point 115-117 degrees.

3.125 milligrams of substance: 7.557 milligrams CO_2; 2.107 milligrams H_2O.

2.783 milligrams of substance: 6.742 milligrams CO_2; 1.910 milligrams H_2O.

3.248 milligrams of substance: 0.178 milliliters N_2 (20 degrees, 742 millimeters)

4.714 milligrams of substance: 0.258 milliliters N_2 (17.5 degrees, 742 millimeters)

Found %: C 65.95, 66.07; H 7.54, 7.68; N 6.12, 6.19.

$(C_{12}H_{17}NO_2)_2CO_2$. Calculated %: C 65.50; H 7.42; N 6.11.

The substance thus obtained (melting point 115-117 degrees) was subjected to distillation in a vacuum. At 3-4 millimeters of

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pressure it distills at 140-150 degrees and upon cooling immediately hardens into a crystallic mass with a melting point of 47-50 degrees (in an open capillary).

In contact with air it quickly changes into a crystallic powder insoluble in ether and melting at 117-119 degrees. Upon processing of this substance with alcoholic hydrochloric acid one observes bubbles of CO_2 and one obtains a crystallic hydrochloride which after cyrstallization from absolute alcohol, melts at 194-195 degrees.

A sample mixed with the hydrochloride of racemic salsolidin obtained by methylization of r-salsolin, gives no depression.

SEPARATION OF d-α-SALSOLIDIN INTO OPTICALLY ACTIVE COMPONENTS

Process 3.5 grams of d-α-salsolidin (melting point 117-119 degrees) with a solution of an equimolecular amount of d-tartaric acid. Recrystallize three times the tartrate precipitate from water and decompose it with ammonia. The base precipitates in the form of minute colorless scales, melting point 60-61 degrees. After drying in a vacuum the melting point is 71-73 degrees, $[\alpha]_D$ = -63 degrees. After distillation in a vacuum (140-150 degrees at 3-4 millimeters) one obtains a form melting at 41-45 degrees.

After separation of the ℓ-salsolidin tartrate, saturate the mother liquor with potash and extract with ether. To the obtained base, after distillation of the ether, add 10 percent hydrochloric acid. Pump off the crystallic precipitate of hydrochloride and boil

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5 times with acetone, until its melting point reaches 226-228 degrees. Recrystallize the hydrochloride twice from water. Melting point 233-235.

0.350 grams of substance in 10 milliliters of alcohol: ℓ equals 0.95 dm; α_D = +1.0 degrees; $[\alpha]_D$ = +26.6 degrees.

Upon decomposition of the hydrochloride with ammonia the base comes out in the shape of minute scales with a melting point of 60-61 degrees. After drying in a vacuum the melting point is 71-73 degrees.

0.2336 grams of substance in 10 milliliters of alcohol: ℓ equals 0.95 dm; α_D = +1.4 degrees; $[\alpha]_D$ = +62.8 degrees.

Upon mixing of equal weights of the hydrochlorides of the d- and ℓ-salsolidin (melting point 233-235 degrees) and recrystallization from absolute hot alcohol, one obtains a d-ℓ-hydrochloride melting at 194-195 degrees.

CONCLUSIONS

(1) Optically active salsolidin can exist in two interchangeable forms. Upon distillation in a vacuum one obtains the low melting form (41-45 degrees) which upon crystallization from water and drying changes into the high melting form (71-73 degrees).

(2) Racemic salsolidin was also isolated from the mother liquors obtained after purification of ℓ-salsolidin. Both alkaloids

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(salsolin and salsolidin) consequently find themselves in the plant as a mixture of the optically active and the racemic forms.

(3) The substance earlier described by us as racemic salsolidin (melting point 117-119 degrees) turned out to be in reality the carbonate of that base $(C_{12}H_{17}NO_2)_2CO_2$.

(4) The ease with which CO_2 combines with the racemic salsolidin is considerably higher than in the case of its optically active forms.

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