"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Chem

10

Synthetic antispasmodics II. Benzhydryl β-(diethylamino)propionate and related compounds. Z. J. Vejdělek and M. Protiva (United Pharm. Works, Prague). *Collection Czech. Chem. Communt.* 15, 671-6(1950)(in English); cf. preceding abstr.—$Et_2NCH_2CH_2CO_2CHPh_2$ (I), an isomeride of trasentin (Meier, *C.A.* 31, 1009[4]; Miescher, *et al.*, *C.A.* 36, 2543[8]) is an *antispasmodic* of the papaverine type, inhibiting the $BaCl_2$ contractions of isolated intestine. I possesses 1% of the activity of atropine, and is 10% as effective as benadryl against histamine contractions. The I was tested as its HCl salt (II). I was prepd. as follows: (a) Hydrolyze $Et_2NCH_2CH_2CO_2Et$ (Fuson, *C.A.* 21, 2144) with alc. KOH, isolate the free acid, convert it to its Na salt by an equiv. amt. of NaOEt soln., evap. to dryness under reduced pressure, cover the residue with C_6H_6, treat with Ph_2CHBr, reflux 9 hrs. on the water bath, and treat the cooled mixt. with water and the required amt. of HCl; shaking seps. white needles of II, m. 171-2° (from EtOH). Treatment of II with Na_2CO_3 and subsequent extn. with Et_2O frees I, oil, b. 158-62°; *picrolonate*, lustrous yellow needles, m. 117° (from EtOH). (b) Treat 4.8 g. $CH_2CHCO_2CHPh_2$ (III) with 1 ml. Et_2NH (IV) with external cooling for 10 min., repeat with another ml. IV, let stand overnight, reflux the mixt. 6 hrs. at 140° on an oil bath, dil. the cold mixt. with C_6H_6, and filter off the solid; treatment of the filtrate with the required amt. of dil. HCl causes sepn. of II. After filtering off II as in (a) above, *N,N-diethylbenzhydrylamine* (V), m. 59° (from MeOH), was obtained as follows: Make the aq. layer alk. with NaOH, ext. with Et_2O, evap. off the Et_2O, and distill the residue under reduced pressure; at 0.5 mm. and 140° (bath), appears as oil crystg. to V; *picrate*, needles, m. 187.5° (from MeOH). *Dibenzhydrylamine* (VI), prepd. in 2.4 g. yield by heating 15.9 g. Ph_2CHNH_2 (VII) (Hauser, *et al.*, *C.A.* 43, 2081[a]) with 9 g. $BrCH_2CH_2CO_2Et$ in the autoclave 10 hrs. to 170-80°, extg. the cold reaction mixt. with 100 ml. of boiling EtOH, and cooling the ext., needles, m. 141-3°, (cor.) from EtOH. The filtrate was evapd. under reduced pressure, the residue decompd. with excess NH_3, extd. with Et_2O, the soln. dried over K_2CO_3, and the residue fractionated under reduced pressure (the 1st fraction is VII); trituration of the residue with EtOH yielded *N-benzhydryl-β-(benzhydrylamino)propionamide* (VIII), which after recrystn. from EtOH, m. 141-3° (cor.). Mixed samples greatly depressed the m. p. of VI.

Lawrence Rosen

1951

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Chem A

10

Synthesis of a new histamine analog, 2-(2-aminoethyl)-4,5-dihydroglyoxaline. J. O. Jilek and M. Protiva (United Pharm. Works, Prague). *Collection Czech. Chem. Commun.* 15, 669-70(1950)(in English).—2-(2-Aminoethyl)-4,5-dihydroglyoxaline (I) possesses no marked *histaminic or antihistaminic activity.* Since I contains the structural fragment —N:CX.NRR' (Ia) (M. Protiva, *Čas. opvis vědeckého Vědeckého* 62, 143(1949)) necessary for histaminic activity (X = Et, Pr, or iso-Pr, R and R' = H or Me), Ia is not a sufficient condition for histaminic activity. All reported m.ps. are cor. and analytical samples were dried 10 hrs. at 0.2 mm. over P_2O_5. *2-(2-Benzamidoethyl)-4,5-dihydroglyoxaline* (II) was prepd. by 2 methods: (1), $BzNHCH_2CH_2C(OEt):NH.HCl$ (III) (43 g.) in 250 ml. EtOH was refluxed (water bath) 6 hrs. with 10 g. $(CH_2NH_2)_2$ (IV), $(CH_2NH_2)_2.2HCl$ (V) filtered off, the filtrate concd. to 0.5 vol., the residue treated with picric acid (VI) (30 g.) in warm EtOH, and allowed to stand in the cold; the picrate (VII) of II, filtered off and recrystd. from 700 ml. EtOH and 400 ml. Me_2CO, m. 200-2.5°. VII (41 g.) was decompd. with 400 ml. 3 *N* HCl, the liberated VI taken up in $PhNO_2$ (VIII), the VI and VIII removed by extn. with Et_2O, the remaining acid soln. refluxed 4 hrs., the BzOH (IX) filtered off, the filtrate evapd. to dryness, and the residue crystd. from EtOH to yield a mixt. (X) of di-HCl salts of I and V. X could not be resolved by crystn. from 90% EtOH, therefore 6.5 g. was allowed to stand 4 days (occasional stirring) in 100 ml. NaOEt soln. (1.7 g. Na), the NaCl filtered off, the filtrate to dryness, evapd., and the residue distd. in a Hickman flask; the fraction $b_{0.1}$ 115-120° (crystd. in the receiver) was I, hygroscopic, m. 66-8° (deliquescent in air). *Derivs.* of I: *di-HCl salt*, m. 219-21° (from aq. EtOH); *dipicrate*, m. 193-5° (from water). Prepn. (2) (on a larger scale): III, EtOH, and IV were refluxed 1 hr. (water bath), the V filtered off, the filtrate concd. under addnl. 6 hrs., more V filtered off, the filtrate refluxed an reduced pressure (water bath), the residue taken up in 3 *N* HCl, the soln. refluxed 3 hrs., the IX filtered off, the filtrate evapd. to dryness under reduced pressure, the residue digested in hot EtOH, and the product which sepd. collected and dried; prepn. (2) now continued like (1). Another method of prepg. I by adding IV to *o-$C_6H_5CO_2NCH_2CH_2C(OEt):NH.HCl$* (XII) in EtOH and refluxing the mixt. yielded *1,2-diphthalimidoethane* (XIII). To prep. *N-(2-aminoethyl)-4,5-dihydro-2-glyoxalineacetamide* (XIII), 10.6 g. $EtO_2CCH_2C(OEt):NH.HCl$, 6.7 g. IV, and 60 ml. EtOH were refluxed 8 hrs. (water bath), and the mixt. allowed to stand 48 hrs.; the *di-HCl salt* (XIV) of XIII crystd., and addnl. XIV was obtained by addn. of 2 g. HCl in Et_2O to the mother liquor. XIV m. 193-4° (from EtOH). To prep. *4,5-dihydro-2-glyoxalineacetamide* (XV), 30 g. $H_2NCOCH_2C(OEt):NH.HCl$ (XVI), 18 g. IV, and 250 ml. EtOH were refluxed 4 hrs., to give, on cooling, 25 g. *HCl salt* (XVII) of

over
(continued)

1951

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Chem A

10

XV, needles, m. 218° (decompn., from 50% EtOH). A soln of 20 g. **XVII** in 250 ml. NaOEt (contg. 2.8 g. Na) was stirred 30 min., filtered the next day, and the filtrate evapd under reduced pressure, giving **XV**, prisms, m. 158-9° (from EtOH). **XV** is not stable and turns red-brown in air. Trituration with EtOH and filtration of the compact mass resulting from the treatment of 23 g. $NCCH_2CO_2Et$ with 6 g. **IV** yielded 18 g. *N,N'-bis(cyanoacetyl)ethylenediamine*, m. 192-3° (from EtOH). Recrystn. from PrOH (contg. charcoal) of the melt resulting from heating (200°, 3 hrs., oil bath) $NC(CH_2)_2CO_2Et$ and ethylenediamine *p*-toluenesulfonate gave an unidentified product, white needles, m. 241-2°. *o*-$C_6H_4(CO)_2NCH_2CH_2CN$ (17 g.) in 50 ml. dry $CHCl_3$ and 3 ml. EtOH was satd. with dry HCl at 0°, the mixt. allowed to stand 10 days, and the solvents distd. off; the crystals of **XII** soften 95-100° (slow heating), resolidify and finally m. 270°. An attempt to prep. *N*-substituted deriva. of **I** by the Mannich reaction between 1-benzylisidine and piperidine or Et_2NH (as HCl salts) and HCHO was unsuccessful. The *acid succinate* (**XVIII**) deriv. of *lysidine*, m. 182-3° (from EtOH). A suspension of **XVI** (15 g.) in 50 ml. EtOH was treated with 200 ml. 8% alc NH_3 (shaking, 30 min.), and the soln. concd. after several hrs., yielding 5.5 g. *o-(carbamylamidocarboxy)acetamidine HCl* (**XIX**), m. 176-7° (from aq. EtOH). The **XIX** prepd above differs in behavior upon heating from the **XIX** prepd by Pinner (*Ber.* 28, 1, 479(1895)). Lawrence Rosen

1951

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

17

Combination of anesthetics and antihistamines. J. Urban and M. Protiva. *Chem. Listy* 44, 22(1950).—Substitution derivs. of p-$H_2NC_6H_4CO_2CH_2CH_2NEt_2$ were prepd. and tested for antihistamine activity (approx. 1/2 of that of Benadryl). p-$PhCH_2NHC_6H_4CO_2CH_2CH_2NEt_2$ (I) was prepd. from 30 g. procaine in 80 ml. C_6H_6 by adding 31 g. Zn powder and a mixt. of 15.5 g. BzH and 30 g. AcOH over a period of 2 hrs. and refluxing 1 hr. after the addn. of 7.5 g. AcOH. Free I, $b_{0.2-0.3}$ 224–30°, $b_{0.1}$ 250–65° (decompn.) (92.5%), was liberated with 33% NaOH and purified as I-HCl, m. 143–8° (from EtOH-acetone). I *picrate*, m. 116–17.5° (from MeOH and acetone). p-$PhCH_2(Et_2NCH_2CH_2)NC_6H_4CO_2CH_2CH_2NEt_2$ (II) was prepd. by allowing to stand 12 hrs. and by refluxing 4 hrs. of 32.6 g. I, 13.5 g. $Et_2NCH_2CH_2Cl$ in 150 ml. C_6H_6, and 4.3 g. $NaNH_2$ (added in portions). The product was extd. with dil. HCl, and free II liberated with NH_3, extd. with Et_2O, and chromatographed. The 1st fraction formed a dihydrochloride, m. 200–2°. p-$PhCH_2(Me_2NCH_2CH_2)$-$NC_6H_4CO_2CH_2CH_2NEt_2$, $b_{0.2}$ 230–40°, was prepd. in a similar manner. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

10

Some substituted dithiocarbonates. M. Protiva. *Chem. Listy* 44, 22-3(1950).—*EtPr*, (60%), b. 210-13°, 30% 2-*ethoxyethyl*, b_{12} 132-42°, 80% *carbethoxymethyl*, b_{12} 163°, and 45% 2-*carbethoxyethyl ethylxanthate*, b_{12} 170°, were prepd. by refluxing $EtOCS_2K$ in EtOH with PrBr, $EtOCH_2CH_2Cl$, $ClCH_2CO_2Et$, and $BrCH_2CH_2CO_2Et$, resp. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

10

N-(2-Pyridyl)benzamide. M. Protiva, J. Urban, and J. O. Jilek. *Chem. Listy* 44, 40-1(1950).—2-(*Dibenzoylamino*)*pyridine*, m. 168-8.5°, was prepd. in 21% yield from 2-aminopyridine (I) by the Schotten-Baumann benzoylation. *N*-(2-*Pyridyl*)*benzamide*, m. 81-2°, was prepd. from I and BzCl in Et_2O or $CHCl_3$ soln. in 10% yield or by heating equiv. amts. of I and BzOH 15 min. at 210-40°.

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

1C

N-Substituted 4-amino-3,3-diphenyl-2-butanones. J. O. Jilek and M. Protiva. *Chem. Listy* 44, 49-51(1950).—*4-(1-Piperidyl)-* (I), *4-(4-morpholinyl)-* (II), and *4-dimethylamino-3,3-diphenyl-2-butanone* (III) were prepd. by the Mannich reaction from *Ph_2CHAc* (IV). To prep. IV, Ph_2CH_2Ac was brominated in ether to give 93% $Ph_2CHBrAc$, which gave 65% IV by heating with C_6H_6 and $AlCl_3$. Another method for prepg. IV was the reaction of $Ph_2CHCOCl$ with MeCdCl prepd. from MeMgBr and $CdCl_2$ (yield 59%). $C_5H_{10}N.HCl$ (3.3 g.), 5.7 g. IV, 1.2 g. $(CH_2O)_n$, and 4 drops concd. H_2SO_4 were refluxed on the steam bath 1 hr., 0.75 g. $(CH_2O)_n$ added, heating continued 2 hrs., and the mixt. poured into 100 ml. Me_2CO to give 2.85 g. I, m. 195-6°; an addnl. 1.8 g. was obtained from the mother liquors. The yield of I, m. 204-5° (from EtOH), $b_{0.5}$ 153-6° (decompn.), was 51%. II (45%), m. 192.5°, was prepd. analogously from morpholine-HCl. III (10%), m. 165-6° (from acetone), was prepd. from $Me_2NH.HCl$. A better yield (38%) was obtained when 7 g. IV, 4 g. $Me_2NH.HCl$, and 1.5 g. $(CH_2O)_n$ were refluxed 45 min. at 140° in 20 ml. iso-AmOH and the mixt. treated with an equal vol. of ether. The salt was purified as free III, liberated by NaOH.

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CH

2-Dimethylaminocyclohexanone. M. Protiva and M. Borovička. *Chem. Listy* **44**, 91(1950).—2-Chlorocyclohexanone (I) (132 g.) and 300 g. 25% Me_2NH in EtOH were heated 1 hr. at 100° and 8 hrs. at 140° in an autoclave. From the acidified reaction mixt., 42 g. I was recovered by extn. with ether. The crude product, obtained with alkali, yielded 34.5 g. 2-dimethylaminocyclohexanone, b_{20} 98-105°, b_{10} 104-8°. The free base is unstable. M. H.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

Ethyl γ-methylmercapto-α-(3-pyridylcarbonyl)butyrate. M. Protiva. *Chem. Listy* **44**, 91-2(1950).—Powd. Na (2.3g.) and 19.3 g. Et (3-pyridylcarbonyl)acetate in 100 ml. dioxane were treated with 11 g. $MeSCH_2CH_2Cl$ at 60°, the mixt. heated 3 hrs. at 50-60°, the NaCl was removed, the dioxane stripped off *in vacuo*, the residue dissolved in dil. HCl, filtered with Norit and made alk., and the oil extd. with $CHCl_3$ and distd. at 190-5° at 1 mm. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

10

N-(2-Anilinoethyl)nicotinamide. M. Protiva and J. Urban. *Chem. Listy* 44, 91-2(1950). -Nicotinic acid (6.5 g.) and 7 g. $PhNHCH_2CH_2NH_2$ were heated 15 min. at 200-30°, and the melt digested with satd. $NaHCO_3$ soln., washed with water, and crystd. from $CHCl_3$ to yield *N*-(2-anilinoethyl)nicotinamide, m. 141-3° (uncor.), sol. in hot water and MeOH. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

10

Derivatives of β-cyanopropionic acid. M. Protiva, V. Reficha, and J. O. Jilek. *Chem. Listy* 44, 231-2(1950).—KCN (105 g.) in 400 ml. 96% EtOH, at 50° was treated with 240 g. $EtO_2CCH_2CH_2Br$ in 150 ml. EtOH; after the spontaneous reaction subsided, the mixt. was refluxed 2.5 hrs., the NaBr filtered off, the EtOH evapd. *in vacuo*, the residue extd. with $CHCl_3$, the $CHCl_3$ stripped off, and the residue distd. at 110-1° at 15 mm. or 120-1° at 20 mm. to yield 112 g. (67%) *$EtO_2CCH_2CH_2CN$* (I). I (63.5 g.), 25 g. EtOH, and 400 ml. Et_2O satd. with dry HCl with cooling yielded 95 g. (91%) *$EtO_2CCH_2CH_2C(:NH)OEt$* (II); *HCl salt*, m. 102-5° (decompn.), after standing in the icebox. II (20.9 g.) in 50 ml. EtOH, allowed to stand with 150 ml. 6% NH_3 in EtOH 12 hrs. at room temp. and a few hrs. in the icebox, yielded 11 g. 2-imino-5-pyrrolidone (III), m. 190-5°, raised by a few crystns. from dil. EtOH to 227-30° (decompn.). III (2 g.) gave 0.8 g. succinimide by hydrolysis with 60 ml. water after refluxing 3 hrs. Hydrolysis of III by $Ba(OH)_2$ gave succinic acid. *N-Benzyl-β-carbethoxypropionamidine* (IV) (1.5 g.) was prepd. by treating 2 g. II, with 2 g. $PhCH_2NH_2$ in 10 ml. EtOH at room temp.; evapg. the solvent *in vacuo* and treating the residue with Me_2CO. IV is sol. in water and EtOH and insol. in Me_2CO. The *hydrazide*, m. 70°, of *$HO_2CCH_2CH_2CN$* was prepd. by refluxing 2.54 g. I and 1 g. $N_2H_4.H_2O$ 2 hrs. in 5 ml. EtOH; evapn. left a glassy material. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

10

Synthetic experiments in the pyrimidine series. V. Reficha and M. Protiva. *Chem. Listy* 44, 232-5(1950).—With the general objective of prepg. 5-(2-aminoethyl)-pyrimidine the following compds. were prepd.: *2-mercapto-4,6-dihydroxy-5-(2-carboxyethyl)pyrimidine* (I) from *tri-Et α-carboxyglutarate* (II), *2-amino-4-methyl-5-(2-carbethoxyethyl)-6-hydroxypyrimidine* (III) from *di-Et α-acetylglutarate* (IV), *2-amino-4-methyl-5-(2-carboxyethyl)-6-hydroxypyrimidine* (V) from III, *2-mercapto-4,6-dihydroxy-5-(2-dimethylaminoethyl)-pyrimidine* (VI) from *di-Et (2-diethylaminoethyl)malonate* (VII) and *(2-diethylaminoethyl)acetylacetone* (VIII). Na (11.5 g.) in 200 ml. EtOH was treated at 0° with 160 g. $CH_2(CO_2Et)_2$, heated 1 hr. at 60° with 90.5 g. $BrCH_2CH_2CO_2Et$, the mixt. refluxed 1 hr., the NaBr filtered off, EtOH stripped *in vacuo*, and the residue distd. to yield 75 g. (58%) II, b_{20} 160–175°, mostly b_{20} 169–72°. II (15.6 g.) and $CS(NH_2)_2$ were refluxed 20 hrs. in 90 ml. EtOH with 1.38 g. Na, the EtOH distd. off, the residue dild. with 80 ml. water, made alk. with 5 ml. 40% NaOH, and the soln. filtered and acidified with 15 ml. HCl to yield 5.9 g. (40%) I, m. 235–6°. IV (68%), b_{20} 153–7°, was prepd. by the method of Findlay and Dougherty (*C.A.* 44, 602*i*). IV (36 g.), 14 g. guanidine carbonate, and 150 ml. abs. EtOH, refluxed 10 hrs. and the ppt. (19.5 g., 53%) crystd. from EtOH yield III, m. 237–9° (decompn.). The *HCl salt*, m. 201–3° (from EtOH), of III was prepd. from 2.25 g. III and 20 ml. 10% HCl by boiling 20 min.; the product (1 g.) was sol. in water, less sol. in EtOH, and sparingly sol. in Me_2CO. V, m. above 270°, was prepd. from III by hydrolysis with water, 12% HCl, and $NaNO_2$, or by alk. hydrolysis with 10% NaOH. Na (4.6 g.), 150 ml. Et_2O, and 32 g. $CH_2(CO_2Et)_2$ were refluxed 3 hrs., 27 g. $Et_2N-CH_2CH_2Cl$ added, the refluxing continued 3 hrs., the ether distd. off, the mixt. refluxed 2 hrs. with 100 ml. C_6H_6, the salt removed, the C_6H_6 distd. off, and the residue distd. to yield 23 g. (45%) VII, b_{20} 148–54°, $b_{0.4}$ 115–16°. VII (7.8 g.) and $CS(NH_2)_2$ were refluxed 10 hrs. with 20 ml. EtOH contg. 0.69 g. Na, the EtOH distd. off, the mixt. treated with 20 ml. water, extd. with ether to remove unreacted VII, and the aq. layer neutralized with 60 ml. 0.5 *N* HCl; a small amt. of crystals, m. above 270°, insol. in water and EtOH, and sol. in dil. NaOH and HCl, sepd., $CH_2(CO_2Et)_2$ (16 g.), 2.3 g. Na, and 100 ml. abs. C_6H_6 were refluxed 5 hrs., then 1 hr. with 7.5 g. $ClCH_2CN$ in 50 ml. C_6H_6, 50 ml. water added to the mixt., the C_6H_6 layer sepd., dried, the solvent distd. off, and the residue distd. to yield 6 g. $NCCH_2CH(CO_2Et)_2$, $b_{0.4}$ 110–15°, $b_{0.4}$ 120–3°. VIII, $b_{0.4}$ 100–2°, was prepd. by refluxing 1 hr. a mixt. of 3.5 g. Na powder in 100 ml. C_6H_6 and 15.2 g. Ac_2CH_2, adding 20.5 g. $Et_2NCH_2CH_2Cl$, refluxing an addnl. 3 hrs., removing the salt, distg. off the C_6H_6 and fractionating the residue *in vacuo* (14 g.) at 140–50° (most part 145–8°) and 17 mm.

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

10

Antihistamine substances. XVIII. Derivatives of benzosuberan and some related compounds. M. Pestiva and M. Borovička (Czech. Chem. Works, Prague). *Collection Czech. Chem. Communs.* 16, 57-64(1951)(in English); cf. *C.A.* 46, 5006b.—Basic ethers of 5-phenyl-5-benzosuberol, 5-benzosuberol, 1-indanol and 1,2,3,4-tetrahydro-1-naphthol were prepd. and their antihistamine activities detd. The ethers were prepd. by heating the carbinol with $Me_2NCH_2CH_2Cl$ or $(CH_3)_2NCH_2CH_2Cl$ with $NaNH_2$ in C_6H_6. Derivs. of benzosuberan: *dl-5-phenyl-5-[2-dimethylaminoethoxy]*, *methiodide*, m. 195-6°; *dl-5-phenyl-5-[2-(1-piperidyl)ethoxy]*, not cryst.; *dl-5-(2-dimethylaminoethoxy)*, *methiodide*, m. 160-2°; *dl-5-[2-(1-piperidyl)ethoxy]*, $b_{0.2}$ 170-2°. Derivs. of indan: *dl-1-(2-dimethylaminoethoxy)*, *HCl salt*, m. 148.5-9.5°; *dl-1-[2-(1-piperidyl)ethoxy]*, b_0 155-60° (*picrate*, m. 119-20°). Derivs. of 1,2,3,4-tetrahydronaphthalene: *dl-1-(2-dimethylaminoethoxy)*, b_0 140-2° (*picrate*, m. 162-3°); *dl-[2-(1-piperidyl)ethoxy]*, b_0 177-9° (*methiodide*, m. 102-3°).

Alfred Hoffman

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

C a.
1951

Organic chemistry
10

Preparation of some primary alcohols from esters by means of lithium-aluminum hydride reduction. Miroslav Protiva (United Pharm. Works, Prague, Czech.). *Chem. Listy* **45**, 20-3(1951).—The following alcs. were prepd. from the corresponding esters by the $LiAlH_4$ reduction (yields in % in parentheses): Ph_2CHCH_2OH, m. 62.5-4°, b$_{10}$ 152° (98); $Ph_2CHCH_2CH_2OH$, b$_{10}$ 152-4° (83.8); Ph_2COHCH_2OH, m. 121° (86.4); *2-pyridylcarbinol*, b$_{10}$ 135-40°, (22) (*picrate*, m. 157-8°); *3-pyridylcarbinol*, b$_{10}$ 154-6°, b$_{10}$ 156-8° (49%); and *4-pyridylcarbinol*, b$_{10}$ 152-4° (53.2%) (*picrate*, m. 162°). M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

C.A.
1951

Organic Chemistry
10

Some additional basic benzhydryl ethers M. Protiva, M. Šustr, and M. Borovička (United Pharm. Works, Prague, Czech.). *Chem. Listy* 45, 33-4(1951). *$Ph_2CHO(CH_2)_2NH_2$*, prepd. from *Ph_2CHBr* (I) and *$HO(CH_2)_2NH_2$* in 65% yield, $b_{0.2}$ 152-9°, m. 69-72° (from ether); *HCl salt*, m. 165-6° (from Me_2CO). *$Ph_2CHO(CH_2)_2Cl$* (II) was prepd. by refluxing 25 g. I, 10.5 g. *$HO(CH_2)_2Cl$*, and 10.6 g. Na_2CO_3 8 hrs. at 120-30° with stirring; vacuum distn. after removal of the salt yielded 20.7 g. (84%) II, $b_{0.4}$ 149-50°. *$Ph_2CHO(CH_2)_2NHMe$* was prepd. by heating 10 g. II 12 hrs. at 140° with 75 ml. alc. $MeNH_2$ (contg. 24 g. $MeNH_2$) in an autoclave; stripping off the EtOH, adding 30 ml. H_2O, extg. the product with Et_2O, purifying by way of the HCl salt, and distg. at 137-9° and 0.25 mm. (13.7 g., 74%); *HCl salt*, m. 159-60° (from Me_2CO). *$Ph_2CHO(CH_2)_2NEt_2$* [37 g. (82.5%)] from 32.5 g. *Ph_2CHOH* and 19 g. *$Cl(CH_2)_2NMe_2$* in 150 ml. C_6H_6 refluxed 8 hrs. with 7.5 g. $NaNH_2$] b. 167-74°; *HCl salt*, m. 166-8° (from Me_2CO). *$HO(CH_2)_3NMe_2$* (III) [12 g. (80%)] from 14 g. $HO(CH_2)_3Cl$ and 100 ml. MeOH soln. of 22.5 g. Me_2NH heated 6 hrs. at 100° and 8 hrs. at 180° in an autoclave, the alc. stripped off, the residue acidified with HCl, extd. with Et_2O, the aq. layer alkalized, and the base extd. with Et_2O, b_{10} 129-30°. III (10 g.) and 10 g. Na_2CO_3, heated to 120°, 17 g. molten I added, the mixt. heated 5 hrs. at 110°, mixed with ether after cooling, and distd. to yield 15.8 g. (74%) *$Ph_2CHO(CH_2)_3NMe_2$*, $b_{0.5}$ 230-5°; *methiodide* m. 129-31° (from Me_2CO). *$Ph_2CHOCH_2CH(OH)CH_2NHCHPh_2$* was prepd. by heating 12 g. *$Ph_2CHOCH_2CH(OH)CH_2OH$* and 9 g. *Ph_2CHNH_2* 10 hrs. at 130-5° in an autoclave, stripping off the unreacted materials, dissolving the residue in Et_2O, and treating with alc. HCl to give (7.5 g.) HCl salt, m. 162.5-3.5°.

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

C. a
1951

Organic Chemistry
10

Diethyl ester of benzhydrylformylaminomalonic acid. Z. J. Vejdělek and M. Protiva (United Pharm. Works, Prague, Czech.). *Chem. Listy* **45**, 44-5(1951).—*HCONHCH(CO₂Et)₂* (I) (10.15 g.) and 1.15 g. Na dust in 45 ml. xylene were refluxed 10 hrs. with 12.35 g. *Ph₂CHBr* in 15 ml. xylene, and treated with water; *Ph₂CHCH(NHCHO)(CO₂Et)₂* (II) (3.7 g.) sepd. in crystals, m. 189.5° (from C_6H_6); an addnl. 0.88 g. was obtained by chromatography from the C_6H_6 extn. of the aq. layer, after stripping off the C_6H_6 and unreacted I. Yield 4.58 g. (43%). $(Ph_2CH)_2$ (0.9 g.) was isolated from the reaction mixt. M. H.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

C.A.

10

New synthesis of 2,5-xylenol. V. Řeřicha and M. Protiva (Pharm. Works, Prague, Czech.). *Chem. Listy* 45, 157-8(1951).—*m*-Cresol (I) was transformed to *6-diethylaminomethyl-m-cresol* (II) with Et_2NH and CH_2O. II was hydrogenated to *2,5-xylenol* (III), this transformed to *4-nitroso-2,5-xylenol* (IV), which was oxidized to *2,5-xyloquinone* (V), reduction of which gave *2,5-xylohydroquinone* (VI). I (54 g.) in 25 ml. MeOH was treated with 44 g. Et_2NH and 70 g. 33% aq. CH_2O (the temp. rose to 60-70°), the mixt. stirred 3 hrs., the org. layer sepd. and distd., yielding 65.2 g. (68%) II, $b_{0.5}$ 114-25°; *picrate*, m. 142.5-3°. II (62 g.) hydrogenated at 180-90° and an initial pressure of 150 atm. over 6 g. Raney Ni yielded 31 g. (80%) III, b. 200-10° (mostly 204-6°), m. 71-3°. III (12.2 g.) was nitrosated to give 10 g. IV, m. 162° (decompn). To crude IV from 31 g. III was added with cooling 80 g. $Na_2Cr_2O_7$ and 150 ml. H_2SO_4; after 2 days, steam distn. gave 19 g., V, m. 123-4° (from dil. EtOH). A lower yield of V was obtained by coupling III with diazotized sulfanilic acid, reducing the azo compd., and oxidizing the 4-amino-2,5-xylenol. V (17 g.) was reduced with 30 g. Zn in 100 ml. AcOH and 30 ml. water by boiling 15 min., yielding 12 g. VI, m. 212-15°.

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CA

10

Antihistamine compounds. XIX. Oxygen analog of antergan. V. Reficha and M. Protiva (Pharm. Works, Prague, Czech.). *Chem. Listy* 45, 158-9(1951).—As an O analog of antergan, *N-(2-methoxyethyl)-N-benzylaniline* (I), was prepd. by refluxing 18.3 g. $PhNHCH_2Ph$, 9.5 g. $MeOCH_2CH_2Cl$, and 4.3 g. $NaNH_2$ 10 hrs. in 100 ml C_6H_6; after decompn. of the mixt. with water, the C_6H_6 layer yielded 18 g. $b_{0.5}$ 135-55°, which, purified by acetylating the admixed $PhNHCH_2Ph$, gave pure I, $b_{0.5}$ 144-5°. **XX. Some new basic ethers.** M. Protiva and J. O. Jilek. *Ibid.* 159-60.—Ph_2COH and $Ph_2(PhCH_2)COH$ refluxed several hrs. with $C_5H_{10}NCH_2CH_2Cl$ (I) and $NaNH_2$ in C_6H_6, yield approx. 50% $Ph_2COCH_2CH_2NC_5H_{10}$, m. 88-90° [*methiodide*, m. 220.5° (from EtOH)], and $Ph_2(PhCH_2)COCH_2CH_2NC_5H_{10}$, $b_{0.3}$ 205-15° [*methiodide*, m. 209-10° (from EtOH)], resp. Similarly, *1-[2-(4-morpholinyl)ethoxy]-1-(3-pyridyl)-1-(p-tolyl)ethane* was obtained from 3-pyridyl(p-tolyl)methylcarbinol and 2-(4-morpholinyl)ethyl chloride by refluxing with $NaNH_2$ in C_6H_6, evapg. the solvent, and purifying the product by chromatography; *dipicrate*, m. 160-2° (from EtOH-Me_2CO). Ph_2CHSH, I, and $NaNH_2$ gave $Ph_2CHSCH_2CH_2NC_5H_{10}$, which was isolated as the *HCl salt*, m. 180-1° (from iso-PrOH). From the previously prepd. $Ph_2CHOCH_2CH_2NC_5H_{10}$, was obtained an acid succinate, m. 124° (EtOH-Me_2CO). Cf. *C.A.* 45, 95214.

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Report

3

Chem

antihistamines of the ether series. XXI. Sulfonium analogs of antihistamines. Miroslav Protiva and Otto Exner (Biochem. and Pharmaceutical Research Inst., Prague, Czech.). *Chem. Listy* 45, 305-8(1951); cf. *Collection Czech. Chem. Communs.* 16, 680-95(1951)(in English); cf. *C.A.* 46, 5000b; 47, 11194h.—2-Aryloxyethyl Me sulfides and benzhydryloxyethyl Me sulfides treated with MeI gave sulfonium salts effective as antihistamines. E.g., *o*-$PhCH_2C_6H_4OH$ (16.5 g.) and 9.9 g. $ClCH_2CH_2SMe$ refluxed 6 hrs. with 100 ml. EtOH contg. 2.07 Na, the NaCl filtered off and the filtrate concd. *in vacuo*, dild. with 50 ml. C_6H_6, washed twice with 20-ml. portions of H_2O and 10% NaOH, then with H_2O and distd., yielded 13.7 g. (59%) *o-$PhCH_2C_6H_4OCH_2CH_2SMe$*, b_4 184-5°, n_D^{20} 1.5882. The *methiodide* (I), m. 125°, (93.7%) was prepd. in Me_2CO soln. Similarly, the following $ROCH_2CH_2SMe$ (with R, % yield, b.p., and n_D^{20}, resp.) were prepd.: *2-isopropyl-5-methylphenyl* (II), 56.5, b_2 126-7°, 1.5332 (*methiodide*, 31%, m. 123°); *1-naphthyl*, 50.5, m. 23°, b_4 169°, 1.6232 (*methiodide*, 89.6%, m. 128°); and *2-naphthyl* (III), 70.6, m. 62° (*methiodide*, 96.8%, m. 127°). *$Ph_2CHOCH_2CH_2SMe$* (IV) was prepd. by heating 11 g. $HOCH_2CH_2SMe$, 11 g. anhyd. Na_2CO_3, and 24.7 g. Ph_2CHBr 4 hrs. at 130°, and dilg. the cooled mixt. with 50 ml. C_6H_6, washing with two 50-ml. portions of H_2O, drying, and distg. to yield 14.6 g. (56.5%) IV, b_5 168-70°, n_D^{20} 1.5753; *methiodide* (V) (92.5%), m. 98°. The following $R'C_6H_4CHPhOCH_2CH_2SMe$ (with R', % yield, b.p., and n_D^{20}, resp.) and the corresponding methiodides were prepd. similarly: *o-Me*, 58, b_2 176-9°, 1.5778 (*methiodide*, 63%, m. 111°); *m-Me*, 60.8, b_2 181-2°, 1.5748 (*methiodide*, 76%, m. 105°); and *p-Me*, 60.6, b_2 179-80°, 1.5730 [*methiodide* (VI), 80%, m. 109°]. The antihistamine effects of I, V, and VI are 1.2, 0.6, and 2.0, resp., compared with 1.0 for Benadryl. [*2-(2-Isopropyl-5-methylphenoxy)ethyl]dimethylsulfonium Me sulfate* (2.2 g.), m. 130° (from C_6H_6 with EtOH), was prepd. from 2.2 g. II, and 1.2 g. Me_2SO_4 in 10 ml. C_6H_6. [*2-(o-Benzylphenoxy)-ethyl]dimethylsulfonium picrate*, m. 116° (from H_2O), was prepd. from I. 2-(2-Naphthoxyethyl methyl sulfone (2.3 g., 91.3%), m. 180-1°, (from EtOH) was prepd. by boiling 2.2 g. III and 5 ml. 30% H_2O_2 in 10 ml. AcOH.

M. Hudlický

C.A. V-48
Jan 10, 1954
Organic Chemistry

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

Relation between chemical structure and physiological action. Cesk. farm. 1 no. 11-12:704-717 1952. (CLML 24:1)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

"Antihistaminic activity in homologous series."
Chemicke Zvesti, Bratislava, Vol 6, No 2, Feb 1952, p. 129

SO: Eastern European Accessions List, Vol 3, No 10, Oct 1954, Lib. of Congress

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Pharmaceuticals - II

OA

Methods of pharmaceutical chemistry. M. Protiva (Biochem. and Pharm. Research Inst., Prague, Czech.). *Chem. Listy* 46, 120-8(1952).—A review with 38 references. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

in 25 ml. EtOH, the mixt. [illegible] ml. H_2O, extd. with C_6H_6, and the ext. [illegible] yielded 4.5 g. $Ph_2CHSCH_2CH_2SMe$ (VI), $b_{0.5}$ 160-70° [illegible] Sulfonium salts (methiodides) were prepd. by allowing the sulfides to stand 2-4 days with excess MeI. II-MeI (79%) m. 128°, IV-MeI m. 117°, V-MeI (92%) m. 95°, and VI-MeI (75%) m. 114-15°. The antihistamine effect of the methiodides is very low. XXIV. α-Alkyl homologs of antihistamines of the *N*-benzylethylenediamine series. [illegible]

[illegible] $b_{0.5}$ 160-72° (*picrate*, m. 12[illegible] [illegible] and *Bu* [illegible] prepd. by an alternative method from [illegible] and $Ph_2CH(CHRPh)$ by refluxing with [illegible] Similarly, 27% 2-[(α-*methylbenzyl*)-[illegible]*pyridine*, $b_{0.5}$ 145-7° (*dipicrate*, [illegible] 2-[(α-*methylbenzyl*)(2-*diethylamino*-[illegible]

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

2/2

Otto Exner, Milos Borovička & Miroslav Protiva

ethyl)amino]pyridine, $b_{0.5}$ 157–63°, (*dipicrate*, m. 143–5°), were obtained from PhCHMeCl and II and III, resp. Acid succinates of VI and of 2-[(α-ethylbenzyl)(2-dimethylaminoethyl)amino]pyridine, $b_{0.4}$ 145–7°, were of the same and double the efficiency, resp., compared with benadryl. XXV. Three new basic benzhydryl ethers. Miroslav Protiva and Miloš Borovička. *Ibid.* 427–9.—(Ph_2CH-$OCH_2CH_2NMeCH_2)_2$ (I), 1-(2-benzhydryloxyethyl)-4-(2-(2-hydroxyethyl)piperazine (II), and 1-(2-benzhydryloxyethyl)-4-(2-chloroethyl)piperazine (III) were prepd. by the following series of reactions: $(CH_2NH_2)_2$ (120 g.) in 640 ml. anhyd. C_5H_5N and 740 g. p-$MeC_6H_4SO_2Cl$ heated 1 hr. at 80°, and poured into 400 ml. H_2O, 500 ml. concd. HCl, and 100 g. ice gave a quant. yield of cryst. (p-$MeC_6H_4SO_2NH$-$CH_2)_2$ (IV), m. 160–1° (from EtOH), also obtained, in 46% yield by refluxing 2 hrs. 34.2 g. p-$MeC_6H_4SO_2NH_2$, 11.2 g. KOH, 22 ml. H_2O, 18.8 g. $(CH_2Br)_2$, and 100 ml. EtOH. I (82 g.) with 79 g. MeI in a mixt. of 20.5 g. NaOH, 40 ml. H_2O, and 223 ml. EtOH gave 77 g. (87%) (p-MeC_6H_4-$SO_2NMeCH_2)_2$ (V), m. 167–8.5° (from Me_2CO), hydrolyzed with dil. H_2SO_4 at 155–65° to $MeNHCH_2(CH_2$-$NHMe)_2$ (VI), b. 110–14° (*HCl salt*, m. 236°). VI (33 g.) in 40 ml. H_2O, treated first with 60.4 g. $HOCH_2CH_2Cl$ and then with 33.7 g. NaOH in 120 ml. H_2O at 40°, 150 g. NaOH added, the mixt. extd. with $CHCl_3$, and the ext. distd. yielded 12 g. (18%) $(HOCH_2CH_2NMeCH_2)_2$ (VII), b_3 140–55°; *dipicrate*, m. 222–3° (from dil. Me_2CO). VII (11 g.) and 16 g. anhyd. Na_2CO_3 was treated during 30 min. with 32 g. Ph_2CHBr at 150°, refluxed 3 hrs., H_2O and C_6H_6 were added, and the crude I left after evapn. of the C_6H_6 layer was transformed to the *dipicrate*, m. 173–4°; *disuccinate*, m. 141–2.5° (from H_2O). II, m. 67–8° (from petr. ether), $b_{0.4}$ 214–17°, was similarly prepd. in 22% yield from Ph_2CHBr and 1,4-bis(2-hydroxyethyl)piperazine at 140–50°; *disuccinate*, m. 118–19° (from EtOH-Me_2CO). III and $SOCl_2$ in C_6H_6 gave 77% of III.2HCl, m. 185–7° (from EtOH). II *disuccinate* has a strong antihistamine effect.

M. Hudlický

7

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

Chemical Abst.
Vol. 48 No. 5
Mar. 10, 1954
Organic Chemistry

Antihistamine substances. XXVI. Some new heterocyclic derivatives of ethylenediamine. Miroslav Protiva, Jiří O. Jílek, Zdeněk J. Vejdělek, and Otto Exner (Pharm. Biochem. Research Inst., Prague, Czech.). *Chem. Listy* 46, 551–4(1952); cf. *C.A.* 47, 4300a; 48, 146c.—Alkylation of 4-phenyl-1,2,3,4-tetrahydroquinaldine (I), *acridan* (II), and *2-phenyl-3-methyl-4-azaindole* (III) with *N*-substituted aminoalkyl chlorides gave new heterocyclic derivs. of $(CH_2NH_2)_2$, of which only acridan derivs. showed antihistamine activity. 4-Phenylquinaldine (10 g.) reduced with 16.5 g. Na in 165 ml. boiling BuOH gave, through its HCl salt, m. 209–15°, 3.7 g. (37%) I, m. 65–7° (from EtOH). II, m. 168–70°, was prepd. in 71% yield by the reduction of 9-acridanone with Na in AmOH. For the prepn. of III, 3-nitro-2,6-lutidine, m. 37°, b. 220–30°, was hydrogenated over Raney Ni to give 70% 3-amino-2,6-lutidine, m. 123°, b. 228–35°; this treated with BzCl yielded 70% 3-benzamido-2,6-lutidine, m. 171°, which was cyclized to III, m. 280° (decompn.), with NaOEt in 71% yield. I, II, and III with $NaNH_2$ and (alkylamino)-alkyl chlorides gave the following *N*-derivs. of I (% yield and b.p.): I, $Me_2NCH_2CH_2$, 68, $b_{0.4}$ 150–60° (HCl salt, m. 215–17°); $Et_2NCH_2CH_2$, 38, $b_{0.4}$ 165–75° (HCl salt, m. 162.5°); (2-piperidinoethyl), 75, $b_{0.4}$ 180–200° (HCl salt, m. 239–40°); (2-morpholinoethyl), 27, b_1 180–200° (HCl salt, m. 225–7.5°). Derivs. of II: $Me_2NCH_2CH_2$ (IV), 45, b_1 198–200° (picrate, m. 165–6°); $Et_2NCH_2CH_2$, 53, b_1 220° (picrate, m. 269–71°); Me_2NCH_2CHMe (V), 61, b_1 183–4°; Et_2NCH_2CHMe, 35, $b_{0.4}$ 170–5° (picrate, m. 158°). Deriv. of III: $Me_2NCH_2CH_2$, 45, $b_{1.5}$ 200–4° ($2HCl.2H_2O$, m. 213–14°; dipicrate, m. 212°). The disuccinates of IV and V showed 7 times and 2.5 times the antihistamine activity of Benadryl. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROKIVA, MIROSLAV Czech CA: 47:11194

with JIRI PLIML and EDUARD KNOBLOCH

Pharm. Biochem. Research Inst., Prague, Czech.

"Antihistamine substances. XXVII. Stereoisomeric benzhydryl-2-(2,6-dimethylpiperidino)ethyl ethers."

Chem. Listy 46, 758-51 (1952); cf. ibid. 551; CA 47, 4300a, 7433e, 9928e.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M. Czech CA: 47:11182

with J. PLIML

Pharm. Biochem. Research Inst., Prague, Czech.

"Synthetic experiments in the histamine series. III. New methods of the reduction of 4(5)-cyanomethyl)imidazole to histamine."

Chem. Listy 46, 772-3 (1952); cf. CA 45, 8017d, 9534g.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

PROTIVA, M.; PLIML, J.

Antihistamine substances. XXVIII. Arsonium analogue of benadryl. p.773
(Chemicke Listy, Praha. Vol. 46, No. 12, Dec. 1952)

SO: Monthly List of East European Accessions, (EEAL), LC, Vol. 4, No. 6, June 1955, Uncl.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

(2)

Protiva, M., and Jilek, J. O.: Zaklady pracovni techniky v organickochemicke laboratori. Prague: SNTL. 1953. 120 pp. Kcs. 8.20. Reviewed in *Chem. Listy* 48, 324 (1954).

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

PROTIVA, M.; EXNER, O.; BOROVICKA, M.; PLIML, J.

Antihistamine substances. Part 22: synthetic antispasmodics. Part 4. Basic ethers derived from aliphatic carbinols and α-substituted benzyl alcohols [in English with summary in Russian]. Sbor.Chekh.khim.rab. 18 no.1:86-101 F '53. (MLRA 7:6)

1. Pharmaceutical and Biochemical Research Institute, Prague.
(Antihistamines) (Antispasmodics)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

JILEK, J.O.; BOROVICKA, M.; PROTIVA, M.

Synthetic antispasmodics. Part 5. Cyclic analogues of substances of the 3,3-diphenylpropylamine series [in English with summary in Russian]. Sbor.Chekh.khim.rab. 18 no.2:257-269 Ap '53. (MLRA 7:6)

1. Pharmaceutical and Biochemical Research Institute, Prague.
(Antispasmodics)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

HACH, V.; PROTIVA, M.

Local anesthetics. Part.1. The synthesis of some analogues of "xylocaine" [with summary in English]. Sbor.Chekh.khim.rab. 18 no.5:684-693 O '53. (MLRA 7:6)

1. Pharmaceutical and Biochemical Research Institute, Prague. (Xylocaine) (Anesthetics)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M., AND OTHERS

"Antihistamine Substances. XXIV. α-alkyl Homologues of Antihistamines of the N-benzylethylene-diamine Series. XXV. Three New Basic Benzhydryl Ethers", P. 724, (COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, Vol. 18, No. 5, October 1953, Praha, Czech.)

SO: Monthly List of East European Accessions (EEAI), LC, Vol. 4, No. 3, March 1955, Uncl.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.; PLIML, J.

Synthetic analogs of curare alkaloids. Part 1. Quaternary salts of polybasic aliphatic ethers an thioethers [in German with summary in Russian]. Sbor. Chekh.khim.rab. 18 no.6:836-841 D '53. (MLRA 7:6)

1. Nauchno-issledovatel'skiy institut farmatsii i biokhimii, Praga. (Ethers) (Curare)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA M.

VEJDELEK, Z.J.; TRCKA, V.; PROTIVA, M.

Pyridine derivatives of pharmacologic interest. Part 4. Some new esters and amides of nicotinic acid [abstract; in English]. Sbor.Chekh. khim.rab. 18 no.6:884 D '53. (MLRA 7:6)

1. Pharmaceutical and Biochemical Research Institute.
(Nicotinic acid)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA M.

Synthetic spasmolytics of the ester series. p.213
(Chemicke Listy. Vol. 47. no. 2, Feb. 1953) Czechoslovakia

SO: Monthly List of East European Accessions, Vol. 2, #8, Library of Congress, August 1953, Incl.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA M.

Parasympathomimetics. I. Synth etic spasmolytics. VII. Synthesis of a new sulphur analogue of acetylcholine and sulphonium salts of the "Tifene" type. p.219 (Chemicke Listy. Vol. 47, no. 2, Feb. 1953) Czechoslovakia

SO: Monthly List of East European Accessions, Vol. 2, #8, Library of Congress, August 1953, Incl.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV,

Ganglionic blocking agents. I. Sulfonium analogs of the lower methonium iodides. Miroslav Protiva, Jiří O. Jílek, and Otto Exner (Farm. biochem. výzkumný ústav, Prague, Czech.). *Chem. Listy* 47, 580-3(1953).—As S analogs of the lower methonium iodides were prepd. sulfonium salts from $MeS(CH_2)_nSMe$, from $(MeSCH_2CH_2)_2S$ (I), and from $MeSCH_2CH_2OCOC{:}CH.CH{:}CHN{:}CH$ (II).

MeSH [from 80 g. $MeSC(:NH)NH_2.H_2SO_4$] passed through a soln. of 4 g. Na in 150 ml. EtOH, the soln. treated with 15 g. $(CH_2Br)_2$, the boiling (from a spontaneous evolution of heat) continued 2 hrs., the mixt. filtered, the filtrate evapd., the residue dild. with 30 ml. Et_2O, washed with 30 ml. H_2O, the sepd. aq. layer extd. with 30 ml. Et_2O, and the ether exts. evapd., and distd. gave 6.3 g. (64%) $(CH_2SMe)_2$, b_{10-11} 78-80°; *monomethiodide*, m. 93-4° (from EtOH). Similarly were prepd., $MeS(CH_2)_3SMe$, b_{18} 92° (65%) [*dimethiodide*, m. 154° (decompn.) (from aq. EtOH)]; $MeS(CH_2)_4SMe$ [from $I(CH_2)_4I$], b_{28} 121-3° [*dimethiodide*, m. 156-7° (decompn.)]; $MeS(CH_2)_5SMe$, b_8 112-14° (*dimethiodide*, m. 176-8°). A mixt. of 18 g. $(CH_2SH)_2$, 3.83 g. Na, and 125 ml. EtOH refluxed 7 hrs. with 18.5 g. $MeSCH_2CH_2Cl$ filtered, the filtrate evapd. *in vacuo*, the residue dissolved in 100 ml. Et_2O, and the ether soln. washed with 50 ml. H_2O and distd. yielded 25.7 g. (85%) I, $b_{1.5}$ 107° (melting on heating with the hand); *dimethiodide*, m. 151° (decompn.) (from H_2O). II, *2MeI* m. 128° (decompn.) (from H_2O).

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVIM

Synthetic analogs of curare alkaloids. I. Quaternary salts derived from polybasic aliphatic ethers and thioethers. Miroslav Protiva and Jiří Pliml (Farm. biochem. výzkumný ústav, Prague, Czech.). *Chem. Listy* 47, 409–12 (1953).—Quaternary analogs of "decamethonium iodide" were prepd. from MeI and EtI, resp., and tertiary amines obtained by condensing glycols, $HO(CH_2)_nOH$, $MeN(CH_2CH_2OH)_2$, and $N(CH_2CH_2OH)_3$, with $Et_2NCH_2CH_2Cl$ (I) and by the reaction of $I(CH_2)_nI$ (II) with $Me_2NCH_2CH_2SH$ (III). To a stirred emulsion of 5.7 g. $(CH_2OH)_2$ in 50 ml. PhMe was added 12 g. 70% $NaNH_2$, the mixt. refluxed 2 hrs., treated with 26.6 g. I in 25 ml. PhMe, refluxing continued 1 hr., the mixt. dild. with 25 ml. H_2O, and the org. layer washed with 10 ml. H_2O, dried, and distd. *in vacuo* to yield 5.05 g. (21%) $(Et_2NCH_2CH_2OCH_2)_2$. The reverse procedure, condensing $Me_2NCH_2CH_2ONa$ with $(CH_2Br)_2$, was not successful. A soln. of 2.9 g. Na in 60 ml. EtOH treated with 13.2 g. III, b_{16} 126–32°, in 40 ml. EtOH and 19.5 g. II, the mixt. refluxed 3 hrs., the EtOH distd. off, the residue dild. with Et_2O, the NaI filtered off, the filtrate evapd., and the residue distd. gave 13.3 g. (80%) $[Me_2NCH_2CH_2SCH_2CH_2]_2$ (IV), $b_{1.4}$ 152–8°. Tertiary amines of the general formula $(Et_2NCH_2CH_2O)_2X$ [X, yield, b.p./mm., and m.p. of the corresponding ethiodide (all N atoms completed) given]: $(CH_2)_2$, 21, 164–6°/20, 157–9°; $(CH_2)_3$, 31, 120°/0.3, 124–6°; $(CH_2)_4$, 35, 130°/0.3, 185–6°; $(CH_2)_5$, 38, 134–6°/0.3, 129°; $(CH_2)_6$, 50, 152°/0.4, 104°; $(CH_2)_2NMe(CH_2)_2$, 58, 152°/0.5, 262°; $(CH_2)_2N[(CH_2)_2O(CH_2)_2NEt_2](CH_2)_2$, 38, 205°/0.3, 247°. *Methiodide* of IV m. 224°; *ethiodide* m. 197°. Also in *Collection Czechoslov. Chem. Communs.* 18, 836–41(1953)(in German). M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M. AND OTHERS

Protiva, M. and others "Synthetic spasmolytics. VIII Further derivatives of indan-i-carbolylic acid and 1, 2, 3, 4-tetrahydronaphthoic acid. p. 584 CASOPIS PRO PESTOVANI MATEMATIKY. CZECHOSLOVAK MATHEMATICAL JOURNAL. Vol. 47, no. 4, Apr. 1953, Praha, Czechoslovakia.

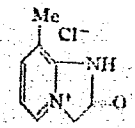
SO: Monthly List of East European Accessions, LC., Vol. 3, No. 1, Jan. 1954, Uncl.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Protiva, Miroslav

Local anesthetics. I. Synthesis of the analogs of Xylocaine. Vladimír Hach and Miroslav Protiva (Farm. biochem. výzkumný ústav, Prague, Czech.). *Chem. Listy* 47, 729-35(1953).—Analogs of *Xylocaine* were prepd by treating aromatic and heterocyclic amines with $ClCH_2COCl$ (I), and the $ClCH_2CO$ derivs with Et_2NH (II). To 80 g. *o*-$EtC_6H_4NH_2$ (b_{747} 210-15°, Ac deriv., m. 106-8°) in 310 ml. AcOH cooled to 5° was added 80 g. I and the mixt. poured into a soln. of 210 g. cryst. NaOAc in 600 ml. H_2O to give 101 g. (77%) *o*-$EtC_6H_4NHCOCH_2Cl$ (III), m. 93-5° (from dil. EtOH). The analogous reaction of 14.5 g. *o*-$PhC_6H_4NH_2$ (Ac deriv., m. 115°), 9 ml. I, 75 ml. AcOH, and 60 g. NaOAc in 480 ml. H_2O yielded 20 g. (95%) *o*-$PhC_6H_4NHCOCH_2Cl$ (IV), m. 95-7° (from EtOH). 2,3-Dihydroindole (3.6 g.) (b. 227-30°), 2.5 ml. I in 30 ml. Me_2CO, and 30 g. NaOAc in 150 ml. H_2O gave a quant. yield of *1-chloroacetyl-2,3-dihydroindole* (V), m. 134-5° (from EtOH). 1,2,3,4-Tetrahydroquinoline, b_{15} 120-3° (26 g.), 22 g. I in 120 ml. Me_2CO, and 60 g. NaOAc in 400 ml. H_2O yielded, almost quantitatively, oily *1-chloroacetyl-1,2,3,4-tetrahydroquinoline* (VI). A mixt. of 4 g. $(ClCH_2CO)_2O$ (m. 40°, b_{21} 126°) and 2 g. carbazole with 2 drops concd. H_2SO_4, heated 1 hr. at 100-120° and poured into H_2O, gave 1.5 g. (50%) *9-chloroacetylcarbazole* (VII), m. 100-2° (from EtOH). Refluxing 18 g. acridan, m. 168-70°, with 8 ml. I in 120 ml. PhMe and distg. off the PhMe *in vacuo* gave 16.5 g. (65%) *10-chloroacetylacridan* (VIII), m. 118-20° (from EtOH). To a cooled soln. of 4.8 g. 2-aminopyridine in 60 ml. C_6H_6 was added during 30 min. with cooling 6 g. I in 20 ml. C_6H_6, the C_6H_6 was decanted from the repd. *HCl salt* which crystd. after the addn. of EtOH, and this, when alkalinized with Na_2CO_3, gave 2.8 g. (33%) *2-(2-chloroacetamido)pyridine* (IX), m. 122-4° (from petr. ether). An analogous prepn. yielded 40% of the *HCl salt* of *2-(2-chloroacetamido)thiazole* (X), m. 162-4° (from EtOH-Et_2O). From the reaction of 40 g. 2-amino-3-picoline with 48 g. I was obtained 45 g. (probable) Xa, m. 265° (from EtOH-Et_2O). Refluxing the $ClCH_2CO$ derivs. 4-5 hrs. with 2.6



moles II in 500 ml. C_6H_6, filtering off the HCl salt of II, and distg. the filtrate *in vacuo* gave Et_2NCH_2CO compds., derived from III-X (the starting $ClCH_2CO$ derivs., b.ps. of the Et_2NCH_2CO compds., and m.ps. of their HCl salts and picrates given): III, $b_{0.5}$ 143-7°, 137-9°, —; IV, —, 206-8°, —; V, $b_{0.4}$ 140-5°, —, 200°; VI, $b_{1.3}$ 163°, —, 145-7°; VII, —, 217-18°, —; VIII, —, —, 175-7°; IX, $b_{1.5}$ 136°, (*di-HCl salt*) 191-2°, —; X, $b_{0.7}$ 158-62°, —, 176°. *2-(2-Diethylaminoacetamido)-3-picoline* $b_{2.5}$ 145-50°; 2,4-$Me_2C_6H_3NHCOCH_2NEt_2$ $b_{0.5}$ 142-6° (*HCl salt*, m. 110-12°). Compds. derived from IV and VII showed higher surface anesthesia than Xylocaine. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M., EXNER, O.

"Synthetic Spasmolytics. IX. Sulphonium Analogues of Artan" p. 736 (CHEMICKE LISTY, Vol. 47, no. 5, May 1953, Praha, Czechoslovakia).

SO: Monthly List of East European Accessions, LC, Vol. 2, No. 11, Nov. 1953, Uncl.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

CZECH

112

Synthetic experiments in the estrogenic hormone series. II. Synthesis of crystalline ethyl 2-methyl-2-carbethoxy-5-(4-methoxyphenyl)cyclohexan-1-one-6-acetate. Jiří O. Jílek, Vladislav Šimák, and Miroslav Protiva (Farm. biochem výzkumný ústav, Prague, Czech.). *Chem. Listy* 47, 874–80(1953); *Collection Czechoslov. Chem. Communs.* 19, 333–9 (1954)(in English); cf. *C.A.* 47, 8034c.—The Friedel-Crafts reaction of *Et 2-methyl-2-carbethoxy-5-cyclohexen-1-one-6-acetate* (I) with MeOPh gave *Et 2-methyl-2-carbethoxy-5-(p-methoxyphenyl)cyclohexan-1-one-6-acetate* (II) which was transformed to *2-methyl-5-(p-methoxyphenyl)-1-cyclohexanone-6-acetic acid* (III). 2-Carbethoxycyclohexanone (75 g.), 10 g. Na dust, and 250 ml. C_6H_6 refluxed 4 hrs., the mixt. treated with 75 g. $BrCH_2CO_2Et$, refluxed 5 hrs., decompd. with 200 ml. dil. HCl, and the C_6H_6 layer washed, dried, and distd. gave 84 g. (74%) Et *2-carbethoxycyclohexanone-2-acetate* (IV), b_3 156–68°; $ClCH_2CO_2Et$ gave only 60% yield. Similarly was prepd. the *di-Me ester* (42%), b_{1-3} 153–5°. IV (24 g.) refluxed 8 hrs. with 2.4 g. Na and 35 ml. EtOH gave, after acidification and extn. 13 g. (54%) *Et 2-carbethoxycyclohexanone-6-acetate* (V), $b_{0.6}$ 130–45°. V (13 g.) refluxed 7 hrs. with 70 ml. C_6H_6 and 1.2 g. Na dust, cooled, treated with 10 ml. MeI, let stand 2 hrs. at room temp., then refluxed 2 hrs., yielded 8.5 g. (63%) *Et 2-methyl-2-carbethoxycyclohexanone-6-acetate* (VI), $b_{0.2}$ 110–20°, also obtained (b_3 166–7°), without isolating V, by refluxing 20 g. IV 8 hrs. with 2 g. Na in 30 ml. EtOH. Bromination of VI in CCl_4 yielded 84% *Et 2-methyl-2-carbethoxy-6-bromocyclohexanone-6-acetate* (VII), $b_{1.1}$ 144–7°. Dehydrobromination of VII by refluxing with Me_3NPh or with collidine gave, resp., 78% and 85% I, $b_{0.4}$ 131–2°, $b_{1.1}$ 147–51°. I (20 g.) and 70 ml. PhOMe, treated at −5 to 0° with 30 g. $AlCl_3$, satd. with HCl and worked up yielded 16 g. recovered I and 5 g. (90%) II, $b_{0.3}$ 200–10°, m. 84° (from C_6H_{14}). Sapon. of 0.4 g. II by refluxing 2 hrs. with aq. NaOH gave 0.3 g. III, m. 138°. Sapon. of IV with NaOH in MeOH gave 60% *1,2,6-hexanetricarboxylic acid*, m. 86–7°, esterified with MeOH and HCl to 55% *tri-Me ester* (VIII), b_3 162–8°. Refluxing 4.9 g. VIII with 0.5 g. Na dust and 10 ml. C_6H_6 18 hrs. in a N atm., dilg. the mixt. with 10 ml. C_6H_6, and methylating in 5 hrs., with 10 ml. MeI gave 3 g. (65%) *Me 2-methyl-2-carbomethoxycyclohexanone-6-acetate*, $b_{0.4}$ 115–24°, which on bromination in CCl_4 yielded *Me 2-methyl-2-carbomethoxy-6-bromocyclohexanone-6-acetate*, m. 90–3°. III. **Synthesis of racemic 1-ethyl-2-methyl-9-methoxy-1,2,3,4-tetrahydro-2-phenanthrenecarboxylic acid.** Miroslav Protiva and Ludvík Novák. *Chem. Listy* 47, 881–4.—*Me 1-oxo-2-methyl-9-methoxy-1,2,3,4-tetrahydro-2-phenanthrenecarboxylate*, m. 136–7° (I), was obtained by the following series of reactions: 1-naphthol → $1\text{-}C_{10}H_7OMe$, b_{10} 140° (81%) → *4,1-MeO$C_{10}H_6COCH_2CH_2CO_2H$*, m. 172° (quant.), → *4,1-MeO$C_{10}H_6(CH_3)_2CO_2H$*, m. 120° (70%) → *1-oxo-9-methoxy-1,2,3,4-tetrahydrophenanthrene*, m. 98–100° (80%) → *Me 1-oxo-9-methoxy-1,2,3,4-tetrahydro-2-phenanthreneglyoxylate*, m. 123–4° (90–5%) → *Me 1-oxo-9-methoxy-1,2,3,4-tetrahydro-2-phenanthrenecarboxylate*, m. 118–21° (90%). I gave estrogenically inactive *1-ethyl-2-methyl-9-methoxy-1,2,3,4-tetrahydro-2-phenanthrene-*

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

2/2

Jiri O. Jilek

carboxylic acid (II). The Grignard reaction of 12 g. I in 100 ml. C_6H_6 with EtMgBr prepd. from 1.25 g. Mg and 5 ml. EtBr in 50 ml. Et_2O yielded 8.5 g. (65%) *Me 1-hydroxy-1-ethyl-2-methyl-9-methoxy-1,2,3,4-tetrahydro-2-phenanthrene-carboxylate*, m. 100° (from MeOH), dehydrated by boiling 1 hr. with $POCl_3$ in C_5H_5N, gave 72% Me *1-ethylidene-2-methyl-9-methoxy-1,2,3,4-tetrahydro-2-phenanthrenecarboxylate* (III), m. 117°, sapond. by evapg. with KOH in dil. EtOH at 140-70° to 80% free *acid* m. 223° (from Me_2CO), which, hydrogenated in dil. NaOH 4 hrs. at 50° and 80 atm. initial pressure over Raney Ni, gave after acidification, 85% II, m. 178° (from Me_2CO and MeOH). Refluxing 0.2 g. III 1 hr. with 1 g. Raney Ni in 20 ml. MeOH gave 0.17 g. (85%) *1-Et analog* of III, m. 147° (from MeOH). IV. Synthesis of 9a-methyl-1,2,3,4,4a,9a-hexahydro-9-fluorenone. *Ibid.* 885-8.—Cyclization of the chloride of *1-methyl-2-phenylcyclohexanecarboxylic acid* (I), prepd. by a series of reactions from Et 2-methylcyclohexanone-2-carboxylate (II), yielded *9a-methyl-1,2,3,4,4a,9a-hexahydro-9-fluorenone* (III). II, b_{15} 112°, (30.8 g.) in 30 ml. Et_2O boiled with PhMgBr (from 5.2 g. Mg and 31.4 g. PhBr in 30 ml. Et_2O) gave 67-74% *Et 1-methyl-2-phenyl-2-hydroxycyclohexane-1-carboxylate*, $b_{0.4}$ 120°, dehydrated with $POCl_3$ in C_5H_5N to 72% *Et 1-methyl-2-phenyl-2-cyclohexene-1-carboxylate*, $b_{0.4}$ 110° (IV). Sapon. of IV with KOH in dil. EtOH at 140-80° gave 80% free *acid* (V), m. 135° (from aq. MeOH-Me_2CO). Hydrogenation of IV in EtOH over Raney Ni at 60° and 100 atm. initial pressure gave 86% *Et ester of I*, b_{15} 145°, hydrolyzed to 94% I. I, obtained in almost quant. yield by the hydrogenation of V in aq. KOH 3 hrs. over Raney Ni at 80° and 133 atm. initial pressure, m. 93° (from petr. ether). Crude I (10 g.) in 100 ml. Et_2O treated 90 min. with 8.5 g. $SOCl_2$, the Et_2O evapd., the residue dild. with 100 ml. C_6H_6, the soln. cooled, shaken 3 min. with 8 ml. $SnCl_4$, decompd. with ice and 50 ml. HCl, and the org. layer evapd. gave 5.2 g. (67%) III, b_{15} 145-7°; *2,4-dinitrophenylhydrazone*, m. 123° (from EtOH). M. Hudlicky

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECH

Antihistamine substances. XXIX. Pyridine analogs of Benadryl. Miroslav Protiva and Otto Exner (Farm. biochem. výzkumný ústav, Prague, Czech.). *Chem. Listy* 47, 1038-40(1953); cf. *C.A.* 47, 111945.—Pyridine analogs of Benadryl were prepd. by the reaction of C_5H_5N and its homologs with $Ph_2CHOCH_2CH_2Cl$ or $Ph_2CHOCH_2CH_2I$ (I). The highest antihistamine activity, equal to 20% of that of Benadryl, was obtained from the deriv. of C_5H_5N. Ph_2CHBr (120 g.) and 100 g. ICH_2CH_2OH (b_{21} 80-81°), treated with 60 g. anhyd. Na_2CO_3 and heated 5 hrs. at 130°, gave 131 g. (80%) I, $b_{0.1-0.5}$ 153-8°, $b_{0.4}$ 157°. The compds. of the general formula $[Ph_2CHOCH_2CH_2N{:}CHCH{:}CH{:}CH{:}CH]^+I^-$ (II), where alkyls were substituted for the pyridine hydrogens, were prepd. by allowing I to stand with 20% excess of the pyridine base at room temp., or by heating the mixt. 20-30 hrs. at 100°. Alkyls position, temp., yield (%), and m.p. of II: —,—, 20°, 87, 165°; Me, 2, 20°, 29, 170°; Me, 3, 20°, 90, 112°; Me, 4, 20°, 81, 171°; di-Me, 2,4, 100°, 70, 120°; di-Me, 2,6, 100°, 36, 170°; tri-Me, 2,4,6, 100°, 44, 132°; benzo-, 2,3, 20°, 36, 180°. $Cl(Ph_2CHOCH_2CH_2)N{:}CH.CH{:}CH.CH{:}CH$, prepd. by heating C_5H_5N with $Ph_2CHOCH_2CH_2Cl$ 24 hrs. at 70-90° in 27% yield, m. 103°. **XXX. Synthetic spasmolytics. (II). Hydrazinium salts.** *Ibid.* 1481-5.—Highly active antihistaminics and spasmolytics were prepd. by the reaction of β-substituted ethyl chlorides with H_2NNMe_2. p-$MeC_6H_4CHPhCl$ (25 g.), 10 g. $ClCH_2CH_2OH$ (I), and 12 g. anhyd. Na_2CO_3 refluxed 5 hrs. at 120°, cooled, dild. with 20 ml. C_6H_6, filtered, and the soln. evapd. and distd. to yield 25.9 g. (86%) p-$MeC_6H_4CHPhOCH_2CH_2Cl$, $b_{0.7}$ 150-6°, $b_{0.8}$ 153°. Refluxing 19.7 g. $PhPrCHCOCl$ 8 hrs. with 8.4 g. I gave 20.4 g. (83%) $PhPrCHCOOCH_2CH_2Cl$, $b_{0.4}$ 117-19°. Similarly were obtained 88% $Ph_2CHCOOCH_2CH_2Cl$, $b_{0.5}$ 160°, and $C_6H_{11}PhCHCOOCH_2CH_2Cl$ (87%), b_1 151-2°, m. 37° (from aq. EtOH). $Me_2NNH_2.HCl$ (2.1 g.) mixed with 0.5 g. Na in 20 ml. EtOH gave Me_2NNH_2 which treated with 6.7 g. $Ph_2CHOCH_2CH_2I$ (II) overnight at room temp., yielded 4.1 g. (52%) $Ph_2CHOCH_2CH_2N(NH_2)Me_2I$, m. 159° (from EtOH). Substituted 1,1-dimethylhydrazinium chlorides were prepd. by treating, at room temp., 30% excess of Me_2NNH_2 with substituted ethyl chlorides (yields, m.ps.): $Ph_2CHOCH_2CH_2N(NH_2)Me_2Cl$, 99, 127°; p-$MeC_6H_4CHPhOCH_2CH_2N(NH_2)Me_2Cl$, 98, 132-3°; $PhPrCHCOOCH_2CH_2N(NH_2)Me_2Cl$, 88, 90°; $Ph_2CHCOOCH_2CH_2N(NH_2)Me_2Cl$, 73, 146°; $C_6H_{11}PhCHCOOCH_2CH_2N(NH_2)Me_2Cl$, 99, 127-8°. Refluxing 6.8 g. II with 1.5 g. $CS(NH_2)_2$ and 5 ml. EtOH 3 hrs., and pptg. with Et_2O yielded 7.8 g. (96%) $Ph_2CHOCH_2CH_2SC(:NH)NH_2I$, m. 142° (from EtOH-$Et_2O$). **XXXI. Contribution to the mechanism of the antihistamine activity. Simple benzylammonium and benzhydrylammonium salts.** Miroslav Protiva, Jiří O. Jílek, Otto Exner, Miloš Borovička, Jiří Plíml, Vladislav Šimák, and Zdeněk Šedivý. *Ibid.* 1621-32.—From the study of antihistamine substances it follows that the ac-

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

MIROSLAV PROTIVA

Hylty is due to the presence of arylmethyl groups which can be easily split off as cations. The onium group has only an auxiliary function, that of increasing the solubility of the compd. A chain of three atoms between the onium group and arylmethyl group seems to be essential. A series of slightly active arylmethylammonium compds. was prepd. A spontaneous reaction between 30 ml. 17% alc. Me_2NH and 12.5 g. Ph_2CHBr (I) gave Ph_2CHNMe_2, m. 70–1°, b_{11} 117–20°; *HCl salt*, m. 244–5° (from EtOH-Et_2O). I (46.5 g.) and 50 ml. C_5H_5N gave, after washing with EtOH and H_2O, 41.1 g. (87%) $Ph_2CHNC_5H_5$, m. 75°; *HCl salt*, m. 226°. Treating 55.6 g. I with 60 ml. C_5H_5N and washing the crystals with EtOH yielded 46.7 g. (63%) *N-benzhydrylpyridinium bromide*, m. 195–8°. *o-Methylbenzhydrylmethylamine* (from Me_2NH and *o*-methylbenzhydryl chloride), yield 69%, m. 44–5°, $b_{0.7}$ 105°; *HCl salt*, m. 256–8°. Similarly prepd. were the *m-methyl isomer*, 78%, m. 88–9°, (dil. EtOH), $b_{1.4}$ 110–12°, and the *p-methyl isomer*, 60%, $b_{0.4}$ 106–7°. Refluxing 67.5 g. Ph_2CHCN in 670 ml. C_6H_6 with 22 g. 70% $NaNH_2$ 2 hrs. and then refluxing the mixt. with 70 g. MeI 5 hrs. gave, after decompn. with 200 ml. H_2O, 62.7 g. (93%) Ph_2CMeCN, b_{18} 180–1°, b_{18} 178–85°, b_2 133–40°. This compd. yielded by boiling with 75% H_2SO_4 39% $Ph_2CMeCONH_2$, m. 102–3°, which gave by treatment with NaOBr (from 13.5 g. NaOH, 13.5 g. Br, and 70 ml. H_2O) 75% Ph_2CMeNH_2, b_{18} 166–75° (*HCl salt*, m. 235° (MeOH-AcOEt)), and *N,N'-bis(α-methylbenzhydryl)urea*, m. 189–90°; *p-PhOC₆H₄Bz*, $b_{0.4}$ 192–200°, gave the oxime, m. 143°, the hydrogenation of which over Raney Ni in EtOH at 100° and initial pressure 80 atm. yielded, after evapn. of the EtOH and treatment with an ether soln. of HCl, 80% *HCl salt* of *p-PhOC₆H₄CHPhNH₂*, m. 215° (from MeOH-AcOEt). Boiling 16.4 g. $PhNHCH_2CH_2NMe_2$, 160 ml. C_6H_6, 5.6 g. 70% $NaNH_2$, and 15.3 g. 1-chloroindan 6 hrs. gave 5.35 g. (20%) *N-phenyl-N-(1-indanyl)-N',N'-dimethylethylenediamine*, $b_{0.4}$ 155–7°. Adding at 130° 30.5 g. 1-chloroindan to 12.2 g. $HOCH_2CH_2NH_2$ and heating at 130–40° 1.5 hrs. gave, after treatment with NaOH and extn., 7.5 g. *N-(1-indanyl)ethanolamine*, $b_{0.4}$ 124–4.5°; *HCl salt*, m. 138–9°. $(PhCH_2)_2S$, m. 49°, was prepd. in 68% yield by refluxing 2 hrs. 24.8 g. $PhCH_2SH$ with 25.2 g. $PhCH_2Cl$ in 200 ml. EtOH in which 4.6 g. Na had been dissolved. Similar reaction in which I was substituted for $PhCH_2Cl$ gave 42% $PhCH_2SCHPh_2$, m. 71°. To a soln. of Ph_2CHSNa prepd. from 1.15 g. Na in 25 ml. EtOH and 10 g. Ph_2CHSH was added 13.6 g. I and the mixt. refluxed 5 hrs. to give 9.5 g. (50%) $(Ph_2CH)_2S$, $b_{0.4}$ 220–7°, m. 65–6.5° (from EtOH). Adda. of 10 ml. Et_2O to a soln. of 2.15 g. $(PhCH_2)_2S$, 4.6 g. HgI_2, and 4.3 g. $PhCH_2I$ in 10 ml. Me_2CO, pptd. 8.55 g. (96.5%) of a compd., m. 137°, which, after shaking in 100 ml. Me_2CO with 8 g. $AgNO_3$ 6 hrs., filtering, and pptg. the filtrate with H_2S, gave 1.5 g. $[(PhCH_2)_2S]_2HSO_4$, m. 172° (from EtOH). XXXII. Benzhydryl ethers of glycerol and β-benzhydryloxypropionic acid. Jiří O.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

313

MIROSLAV PROTIVA

ek and Miroslav Protiva. *Ibid.* 1811–13.—Benzhydryl derivs. prepd. by treating glycerol (I) with Ph_2CHBr (II) and $BrCH_2CH_2CO_2Et$ (III) with Ph_2CHONa (IV) were inactive as antihistamines. Heating 9.2 g. I, $b_{1.5}$ 130–5°, 12.3 g. II, 7 g. anhyd. Na_2CO_3, and 25 ml. xylene at 160–80°, distg. off the xylene, adding another 25 ml. xylene, and repeating 4 times gave, after diln. with 50 ml. H_2O and extn. with C_6H_6, 2.35 g. of the *dibenzhydryl ether*, $b_{0.4}$ 220–30°. When 10.6 g. Na_2CO_3 and 46 g. I were heated 4 hrs. at 140°, with 12.3 g. II, 5.1 g. of the *monobenzhydryl ether*, $b_{0.4}$ 160–70°, and 0.5 g. of the *tribenzhydryl ether*, m. 99–101° (from EtOH), were obtained. IV, prepd. from 1.5 g. Na dust and 12 g. Ph_2CHOH in 100 ml. C_6H_6, was refluxed 2 hrs. with 12 g. III to give 7.5 g. $Ph_2CHCH_2CH_2CO_2Et$, which, refluxed with KOH in MeOH and H_2O, gave 1.9 g. $Ph_2CHCH_2CH_2CO_2H$, m. 85° (from petr. ether-C_6H_6). XXXIII. New types of basic benzyl and benzhydryl ethers. *Ibid.* 1814–18.—$BzCH_2Cl$ was transformed in 56% yield to $BzCH_2NMe_2$, b_3 119–21° (*picrate*, m. 144°), which gave, by the reduction with $LiAlH_4$ in Et_2O, 83% $PhCH(OH)CH_2NMe_2$ (I), b_{11} 123–6°; *HCl salt*, m. 146–9°; *methiodide*, m. 225–6°. Refluxing 16.5 g. I, 16 g. anhyd. Na_2CO_3, and 30 ml. xylene at 160°, adding 12.5 g. $PhCH_2Cl$, and continuing the heating gave a mixt. consisting of $PhCH_2NMe_2$ (*HCl salt*, m. 175°), I, a compd. m. 67°, and BzMe (semicarbazone, m. 198–9°). Treating 13 g. I in 100 ml. C_6H_6 with 4.6 g. 70% $NaNH_2$ at room temp. and boiling the mixt. with 10 ml. $PhCH_2Cl$ in 10 ml. C_6H_6 5 hrs. yielded 2 g. $PhCH_2NMe_2$, 3.4 g. I, and 9.7 g. (48%) $PhCH(OCH_2Ph)CH_2NMe_2$, b_{12} 175–80°, $b_{1.4}$ 127–9° [*HCl salt*, m. 177° (from Me_2CO)]. To a mixt. prepd. from 5.8 g. 70% $NaNH_2$ in 50 ml. C_6H_6 and 10.9 g. 3-pyridylcarbinol (b_{12} 142–52°) in 10 ml. C_6H_6 was added 24.7 g. Ph_2CHBr in 25 ml. C_6H_6, and the mixt. refluxed 5 hrs. to give 0.9 g. $(Ph_2CH)_2$, m. 210–12°, and 5 g. (18%) crude *3-benzhydryloxymethylpyridine*; *picrate*, m. 160°. $Ph_2MeCOCH_2Br$ CH_2NMe_2 (II) (cf. *C.A.* 45, 577e) (2.14 g.) in 25 ml. EtOH and 1.7 g. 8-chlorotheophylline (m. 291°) mixed with 25 ml. Et_2O gave 3.3 g. of the *8-chlorotheophyllinate*, $C_{26}H_{32}ClN_6O_3$. (III), m. 160°. *Picrate* of II m. 127–8°. Ph(iso-Bu)CHOH (164 g.) and 107.5 g. $Et_2NCH_2CH_2Cl$ gave, by the $NaNH_2$ method, 156.3 g. (59%) Ph(iso-Bu)$CHOCH_2CH_2NEt_2$, $b_{1.4}$ 115–25°; *citrate*, m. 90° (from EtOH-Et_2O). Only compd. III showed antihistamine activity. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA MIROSLAV

1/2

Synthetic analogs of the curare alkaloids. II. Bis-(tertiary sulfonium salts) and sulfur analogs of succinylcholine. Miroslav Protiva, Jiří Pliml, and Pavla Finglová (Farm. biochem. výzkumný ústav, Prague, Czech.). *Chem. Listy* 47, 1197–1203(1953); cf. *C.A.* 49, 199*d*.—S analogs of *decamethonium iodide* and of succinylcholine were prepd. none of which showed practical curarelike activity. Refluxing 9.2 g. Na in 150 ml. EtOH with 22 g. *p*-HOC_6H_4OH in 75 ml. EtOH and with 50 g. $MeSCH_2CH_2Cl$ 6 hrs. gave 16.1 g. (on purification) *o*-$C_6H_4(OCH_2CH_2SMe)_2$, $b_{0.4-0.6}$ 155–90°, m. 47–8° (from EtOH); *MeI salt*, m. 133–4°. Similarly was prepd. *p*-$C_6H_4(OCH_2CH_2SMe)_2$ (40%), m. 41–2°; *di-MeI salt*, m. 155–6°. Refluxing 31 g. $MeSCH_2CH_2OH$ (I), 150 ml. C_6H_6, and 18 g. 70% $NaNH_2$ 1 hr., adding 35.3 g. $Br(CH_2)_3Br$ and refluxing the mixt. 7 hrs. gave 19.4 g. (50%) $MeS(CH_2)_3O(CH_2)_3O(CH_2)_3SMe$, $b_{0.4}$ 144°; *di-MeI salt*, noncryst. Refluxing 5 hrs. a mixt. prepd. from 4.6 g. Na, 250 ml. EtOH, 21.6 g. $MeSCH_2CH_2SH$ (II), and 18.8 g. $(BrCH_2)_2$ yielded after dissolving the NaBr in 1 l. H_2O, 22.5 g. (90%) $MeS(CH_2)_2S(CH_2)_2S(CH_2)_2SMe$, m. 64–5° (from AcOEt); *di-MeI salt*, m. 138°. Similarly were prepd. $MeS(CH_2)_2S(CH_2)_2SMe$ (85%), $b_{0.4}$ 167–9°; $MeS(CH_2)_2S(CH_2)_2S(CH_2)_2SMe$ (98%), m. 30°, and $MeS(CH_2)_2S(CH_2)_2S(CH_2)_2SMe$ (62%), $b_{0.4}$ 180–9°. *Dimethiodides* of the last 3 compds. were oily. Refluxing a mixt. of 4.6 g. Na, 250 ml. EtOH, 21.6 g. II, and 16.1 g. $HOCH_2CH_2Cl$, distg. off the EtOH, dilg. the residue with Et_2O, filtering off the NaCl and distg. the ext. gave 23.3 g. (76%) $MeS(CH_2)_2S(CH_2)_2OH$, b_{10} 160°. From the mixt. of 55.4 g. $Me_2NCH_2CH_2OH$ (b. 130–3°), 20 g. $(CH_2CO_2Et)_2$ (b_{11} 85°), and 0.15 g. Na was distd. EtOH at 70–80 mm. during 1 hr., and the residue fractionated to give 26 g. (97.5%) $[Me_2N(CH_2)_2OCOCH_2]_2$, $b_{0.2}$ 130°; *di-MeI salt*, m. 250–1°. Treating 10.5 g. $Me_2NCH_2CH_2SH$ in 100 ml. C_6H_6 at 10° with 7.75 g. $(CH_2COCl)_2$ (III) (b_{10-11} 94–6°) in 100 ml. C_6H_6 gave, after sepg. the NaCl and extg. the alkalinized soln. with C_6H_6, 7.4 g. (51%) $[Me_2N(CH_2)_2SCOCH_2]_2$, $b_{0.4}$ 166–7°; *di-MeI salt*, m. 107°. Refluxing 1 hr. 20.3 g. I in 100 ml. C_6H_6 with 15.5 g. III gave 21.7 g. (81.5%) $[MeS(CH_2)_2OCOCH_2]_2$, $b_{0.2}$ 159–61°; *dimethiodide*, m. 159°. Distg. off the EtOH from the mixt. of 4.6 g. Na, 60 ml. EtOH, and 21.6 g. II, and refluxing the residue with 125 ml. C_6H_6 and 15.5 g. III gave 15.2 g. (51%) $[MeS(CH_2)_2SCOCH_2]_2$, $b_{0.4}$ 198° (*dimethiodide*, oily). Treating 3.6 g. $(CH_2OH)_2$ in 10 ml. C_5H_5N with 16 g. $MeSCH_2CH_2COCl$ (IV) (b_{14} 70°), gave 11.3 g. (74%) $[MeS(CH_2)_2CO_2CH_2]_2$, $b_{0.15}$ 160°. Refluxing 1 hr. the mixt. of 4.45 g. $(CH_2SH)_2$ (b_{10} 76°), 13.1 g. IV, and 50 ml. C_6H_6, yielded 7.2 g. (51%) $[MeS(CH_2)_2COSCH_2]_2$, $b_{0.4}$ 205°. The methiodides were prepd. in Me_2CO, C_6H_6, EtOH, or without solvent, and were crystd. from EtOH or dil. EtOH. III. Pyridine derivatives of pharmacological interest. 9. Quaternary salts of glycol diesters of monocarboxylic acids of the pyridine and piperidine series. Jiří Pliml and Miroslav Protiva. *Ibid.* 1204–0; cf. *C.A.* 49, 337*d*.—Glycol esters of pyridinemonocarboxylic acid were prepd. and treated with MeI to give the corresponding dimethiodides. Picolinic chloride prepd. by refluxing 15 min. 14.6 g. picolinic acid in 1250 ml. C_6H_6 with 14 ml. $SOCl_2$, heated 2 hrs. with 8.5 g. $HO(CH_2)_2OH$ gave, after treatment with 6.8 g. $NaHCO_3$ in 120 ml. H_2O, 1.1 g. *tetramethylene dipicolinate*, m. 81–2° (from H_2O). Most part of the starting acid was recovered. Refluxing 37 g. nicotinic acid 2 hrs. with 180 ml. $SOCl_2$, evapg. the

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

2/2 MIROSLAV PROTIVA, et al

unchanged $SOCl_2$, washing the cryst. residue with C_6H_6, and refluxing with 6.2 g. $(CH_2OH)_2$ (I) in 100 ml. C_6H_6 gave, after alkalinization with $KHCO_3$, 22.3 g. (82%) *ethylene dinicotinate*, m. 126° (from EtOH); *di-MeI salt*, m. 208°. Similar treatment of 37 g. isonicotinic acid (the *HCl salt of the chloride* did not melt below 200°) with 6.2 g. I gave 19.9 g. (72%) *ethylene diisonicotinate*, m. 175° (from EtOH); *di-MeI salt* (II), m. 213° (decompn.). Hydrogenation of II in EtOH over PtO_2 gave 88% *di-HI salt*, m. 178°, of *ethylene bis(N-methylisopipecolinate)*, $b_{0.4}$ 176° (insol. in Et_2O); *bis(methiodide)*, m. 287-8°. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

Bijulolidyl. Z. J. Veldlík, B. Kakáč, and M. Protiva (Farm. biochem. výzkumný ústav, Prague, Czech.). Chem. Listy 47, 1676-9(1953).—Julolidine was prepd. from tetrahydroquinoline and $Br(CH_2)_3Br$ in 73% yield and characterized as the *styphnate*, m. 172° (decompn.) (from EtOH); *picrolonate*, m. 194° (from EtOH). *Julolidine* (2.88 g.) dissolved in 12.5 ml. HCl (1:1) was treated at −12° with 10 g. ice and 1.25 g. $NaNO_2$ in 5 ml. H_2O, the ppt. filtered after 2 hrs., dissolved in 10 ml. H_2O, the soln. alkalized with aq. Na_2CO_3 and extd. with Et_2O and C_6H_6. Evapn. of the solvents yielded 1.50 g. (27.7%) *bijulolidyl*, m. 205-6° (from EtOH); *di-HCl salt*, m. above 300°; *dipicrolonate*, m. 193-4° (from EtOH). M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

Synthetic experiments in the histamine series. IV. 4(5)-(2-benzylaminoethyl)imidazole. J. Plíml. and M. Protiva (Farm. biochem. výzkumný ústav, Prague, Czech.). Chem. Listy 47, 1874-5(1953); cf. C.A. 48, 12737g.—Reductive alkylation of histamine (I) (1.1 g.) with BzH (1.06 g.) in 15 ml. EtOH, over 0.2 g. PtO_2 in 10 ml. EtOH gave, on repeated hydrogenation, *N-benzylhistamine; dipicrate*, m. 191-2°; *di-HCl salt*, m. 220-2°. Similar alkylation with PhBz was unsuccessful. *N-Benzhydrylidenehistamine*, m. 142-3°, prepd. by condensing BzPh with I, did not undergo hydrogenation over PtO_2 at 20 or 60°, nor with Raney Ni at 170° and 130 atm. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Protiva, Miroslav

1/2

Syntheses in the estrogenic hormone group. V. Syntheses of 2-hydroxy-13-methyl-5,6,7,8,12,13-hexahydro-9-fluorenone and 13-methyl-5,6,7,8,12,13-hexahydro-1,2-benzo-9-fluorenone. Ludvík Novák and Miroslav Protiva (Výzkumný ústav farm. biochem., Praha). *Chem. Listy* 48, 70-6(1953); cf. *ibid.* 47, 885(1953).—To a Grignard reagent prepd. during 8 hrs. from 3.8 g. Mg and 27.3 g. p-BrC_6H_4OMe in 30 ml. Et_2O was added 27.7 g. Et 1-methyl-2-cyclohexanonecarboxylate (I), the mixt. refluxed 30 min., decompd. with dil. HCl, and extd. with Et_2O to give 20.5 g. (48%) *Et 1-methyl-2-(4-methoxyphenyl)-2-cyclohexanol-1-carboxylate* (II), $b_{0.4}$ 150-5°, and some (p-$MeOC_6H_4$)$_2$, m. 169°, $b_{0.4}$ 165°. Refluxing 30 min. 42 g. II, 420 ml. anhyd. C_5H_5N, and 42 ml. $POCl_3$, pouring the mixt. onto ice and HCl, and extg. with Et_2O gave 36 g. (94%) *Et 1-methyl-2-(4-methoxyphenyl)-2-cyclohexene-1-carboxylate* (III), $b_{0.4}$ 140-3°, $b_{1.4}$ 150°. Adding 3 g. III dissolved in 20 ml. EtOH to a soln. of 7 g. KOH in 5 ml. H_2O heated to 140°, evapg. the EtOH, raising the temp. to 180° and keeping it there for 15 min., dissolving the K salt in 300 ml. H_2O, extg. with Et_2O, acidifying the aq. layer with HCl, and extg. again with Et_2O yielded 2.5 g. (91%) *1-methyl-2-(4-methoxyphenyl)-2-cyclohexene-1-carboxylic acid* (IV), m. 75° (from petr. ether). Hydrogenation of 19.5 g. III in 20 ml. EtOH over $PdCl_2$ gave 19 g. (97%) *Et 1-methyl-2-(4-methoxyphenyl)-1-cyclohexanecarboxylate* (V), $b_{0.4}$ 122°. V was also obtained by the hydrogenation of III over Raney Ni at 70°, yield 95%, $b_{0.4}$ 120°. Hydrogenating 12.5 g. IV in a soln. of 4.3 g. KOH in 150 ml. H_2O 2 hrs. at 70° and 130 atm. over 1 g. Raney Ni gave 10 g. (90%) *1-methyl-2-(4-methoxyphenyl)-1-cyclohexanecarboxylic acid* (VI), m. 156° (from C_6H_6-petr. ether). The same product was obtained by alk. hydrolysis of V (93% yield). VI (7.4 g.), 4.8 g. $SOCl_2$, and 4 drops of C_5H_5N in 100 ml. Et_2O was allowed to stand at room temp. 1.5 hrs., the Et_2O was distd. off *in vacuo*, the residue mixed with 100 ml. C_6H_6, the C_6H_6 evapd. *in vacuo*, and the residue shaken 5 min. at room temp. with 2.7 ml. $SnCl_4$ to give 1 g. (15%) *2-methoxy-13-methyl-5,6,7,8,12,13-hexahydro-9-fluorenone* (*C.A.*, 2-methoxy-8a-methyl-4b,5,6,7,8,8a-hexahydro-9-fluorenone) (VII); *2,4-dinitrophenylhydrazone*, m. 167° (from EtOAc-EtOH). A better result was obtained by treating, at room temp., 7.4 g. VI with 7.5 g. PCl_5 in 100 ml. C_6H_6, stirring the mixt. with 6 ml. $SnCl_4$ 20 min. at room temp., decompg. with ice and 50 ml. HCl, and distg. *in vacuo* to give 5.6 g. (81%) VII, $b_{0.4}$ 124-5°. Heating 2.0 g. VII and 26 g. $C_5H_5N.HCl$ 3 hrs. at 170-80°, digesting the cold residue with 100 ml. dil. HCl, and extg. the oil with Et_2O gave 2.1 g. (89%) *2-hydroxy-13-methyl-5,6,7,8,12,13-hexahydro-9-fluorenone* (VIII), $b_{0.4}$ 155-60°, m. 108-9° (from Et_2O-petr. ether); *2,4-dinitrophenylhydrazone*, m. 191-5° (from C_6H_6-petr. ether). To a Grignard soln. prepd. from 7.4 g. Mg in 45 ml. Et_2O and 61.8 g. 2-bromo-

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

S/2 LUDVIK NOVAK & MIROSLAV PETRAK

naphthalene (obtained from 2-naphthylamine, m. 57°) in 90 ml. Et_2O was added 55.5 g. I in 60 ml. Et_2O, the mixt. refluxed 30 min., decompd. with dil. HCl, extd. and evapd. to give $C_{10}H_8$, m. 80°, *2-bromonaphthalene*, m. 57°, *2,2'-dinaphthyl*, m. 185°, and 55 g. (59%) *Et 1-methyl-2-(2-naphthyl)-2-cyclohexanol-1-carboxylate* (IX), $b_{0.4}$ 182–5°. Refluxing the mixt. of 54 g. IX with 54 ml. $POCl_3$ in 500 ml. C_6H_5N 3 hrs. gave 30 g. (73%) *Et 1-methyl-2-(2-naphthyl)-2-cyclohexene-1-carboxylate* (X), $b_{1.4}$ 170–5°. Hydrolysis of 5 g. X gave 4.1 g. (93%) *1-methyl-2-(2-naphthyl)-2-cyclohexene-1-carboxylic acid* (XI), m. 173.5° (from MeOH-Me_2CO). Hydrogenation of 13.5 g. X in 200 ml. EtOH over Pd on C gave 10.8 g. (80%) *Et 1-methyl-2-(2-naphthyl)cyclohexane-1-carboxylate* (XII), $b_{0.5}$ 165–70°. Alk. hydrolysis of XII gave 85% *1-methyl-2-(2-naphthyl)-cyclohexane-1-carboxylic acid* (XIII), m. 152° (from C_6H_6-petr. ether). Hydrogenation of 27.5 g. X in 150 ml. EtOH over 4 g. Raney Ni at 80° and 130 atm. gave, after 4 hrs., 27.5 g. *Et 1-methyl-2-(5,6,7,8-tetrahydro-2-naphthyl)cyclohexane-1-carboxylate* (XIV), $b_{0.1}$ 130°. Alk. hydrolysis of XIV gave *1-methyl-2-(5,6,7,8-tetrahydro-2-naphthyl)cyclohexane-1-carboxylic acid* (XV), m. 141° (from aq. EtOH or dil. AcOH). The same product was obtained by the hydrogenation of XI in alk. soln. over Raney Ni at 70° and 80 atm. XIII (5.4 g.), 50 ml. Et_2O, 3.2 ml. $SOCl_2$, and 4 drops dry C_5H_5N gave a chloride of XIII which treated with 1.8 ml. $SnCl_4$ yielded 4.3 g. (87%) *13-methyl-5,6,7,8,-12,13-hexahydro-1,2-benzo-9-fluorenone*, $b_{0.6}$ 145–60°; *2,4-dinitrophenylhydrazone*, m. 243–5°. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Prot. V.A., M.

1

Herout, V., Keil, B., Protiva, M., Hudlicky, M., Ernest, I., and Gut, J.: Laboratorní technika organické chemie. Prague: Nakl. CSAV. 1954. 756 pp. Kčs 86. Reviewed in *Chem. Listy* 49, 1415(1955).

CH

Chem) + Educ

Herout, V., Keil, B., Protiva, M., Hudlicky, M., Ernst, I., and Gut, J.: Organic Chemistry Laboratory Techniques. Publishing House CSAV. 1954. 756pp. Kcs. 86. Reviewed in Chem. Listy 49, 1415(1955).

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, Miroslav

Sulfonium analogues of physiologically effective ammonia salts. Cesk.farm. 3 no.4:138-145 Ap '54.

1. Z Vyzkumneho ustavu pro farmacii a biochemii v Praze.
(AMMONIA,
*sulfonium analogues of physiologically effective ammonia salts)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

Antihistamine substances. XXVII. Arsonium analog of Benadryl. M. Protiva and J. Pliml (Pharm. Biochem. Research Inst., Prague). *Collection Czechoslov. Chem. Commun.* 19, 132-3(1954)(in English).—See *C.A.* 47, 11104g. R. J. C.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

Synthetic experiments in the histamine series. III. New methods of the reduction of 4(5)-(cyanomethyl)imidazole to histamine. J. Pliml and M. Protiva (Pharm. Biochem. Research Inst., Prague). Collection Czechoslov. Chem. Communs. 19, 184-6(1954)(in English).—See C.A. 47, 111324. E. I. C.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

EXNER, O.; SIMAK, V.; JILEK, J.O.; PROTIVA, M.

Synthesis in the estrogene hormone group. Part 1. m-methoxyphenylacetylene [in English with summary in Russian]. Sbor.Chekh.khim.rab. 19 no.2:330-332 Ap '54. (MLRA 7:6)

1. Pharmaceutical and Biological Research Institute, Prague.
(Estrogens)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

JILEK, J.O.; SIMAK, V.; PROTIVA, M.

Synthesis in the estrogenic hormone group. Part 2. Synthesis of crystalline ethyl 2-methyl-2-carbethoxy-5-(4-methoxyphenyl) cyclohexan-1-one-6-acetate [in English with summary in Russian]. Sbor.Chekh.khim. rab. 19 no.2:333-339 Ap '54. (MLRA 7:6)

1. Pharmaceutical and Biochemical Research Institute, Prague.
(Estrogens)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

CZECH

Synthetic spasmolytics. VI. Sulfonium analogs of the ester type spasmolytics. Miroslav Protiva and Otto Exner (Pharm. Biochem. Research Inst., Prague). *Collection Czechoslov. Chem. Communs.* 19, 534-9(1954)(in English).—See *C.A.* 49, 1981*i*. E. J. C.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

CZECH

✓ Antihistamine substances. XXX. Synthetic Spasmolytics. (10). Hydrazinium salts. Miroslav Protiva and Otto Exner (Pharm. Biochem. Research Inst., Prague). *Collection Czechoslov. Chem. Communs.* 19, 531-5(1954)(in English).—See *C.A.* 49, 247*i*. E. J. C.

1

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA MIROSLAV

CZECH

Synthetic experiments in the estrogenic hormone series. III. Synthesis of racemic 1-ethyl-2-methyl-9-methoxy-1,2,-3,4-tetrahydro-2-phenanthrenecarboxylic acid. Miroslav Protiva and Ludvík Novák (Pharm. Biochem. Research Inst., Prague). *Collection Czechoslov. Chem. Communs.* 19, 536-40(1954)(in English). See *C.A.* 49, 197*f*. IV. Synthesis of 9a-methyl-1,2,3,4,4a,9a-hexahydro-9-fluorenone. Miroslav Protiva and Ludvík Novák (Pharm. and Biochem. Inst., Prague). *Ibid.* 541-4(in English).—See *C.A.* 49, 197*h*. B. J. C.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

11

CZECH

Antihistamine substances. XXXI. Contribution to the mechanism of the antihistamine activity. Simple benzylammonium and benzhydrylammonium salts. Miroslav Protiva, Jiří O. Jílek, Otto Exner, Miloš Borovička, Ilo Phul, Vladislav Šimák, and Zdeněk Šedivý (Pharm. Biochem. Research Inst., Prague). *Collection Czechoslov. Chem. Communs.* 19, 732-43(1951)(in English).—See *C.A.* 49, 218e. XXXV. Kinetics of the hydrolysis of antihistaminics of the benzhydryl type. Eduard Knobloch, František Mácha, Otto Exner, and Miroslav Protiva. *Ibid.* 976-81.—See *C.A.* 49, 2425e. E. J. C.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

CZECH

Syntheses in the estrogenic hormone group. V. Syntheses of 2-hydroxy-13-methyl-5,6,7,8,12,13-hexahydro-9-fluorenone and 13-methyl-5,6,7,8,12,13-hexahydro-1,2-benzo-9-fluorenone. Ludvík Novák and Miroslav Protiva. *Collection Czechoslov. Chem. Communs.* 19, 983-8(1951)(in English).—See *C.A.* 49, 1666a. E. J. C.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

Antihistamine substances. XXXIV. A new type of homologous arylmethyl antihistaminics. Otto Exner, Jiří Pliml, and Miroslav Protiva (Výzkumný ústav farm. biochem., Prague, Czech.). *Chem. Listy* 48, 65-9(1954); cf. *C.A.* 49, 2496.—Refluxing 7.9 g. Ph_2CHCH_2OH, 5.4 g. $Me_2NCH_2CH_2Cl$, and 3 g. 70% $NaNH_2$ 6 hrs. in 40 ml. C_6H_6 gave 7.8 g. (73%) $Ph_2CHCH_2OCH_2CH_2NMe_2$, b_1 143-4° (after purification). $PhCH:CHCO_2H$ (60 g.) in 760 ml. C_6H_6 treated 2 hrs. with 100 g. $AlCl_3$ and dry HCl gave, after decompn. with 600 ml. ice-H_2O and 500 ml. dil. HCl (1:1), 30 g. (55%) $Ph_2CHCH_2CO_2H$ (I), m. 150°. Reduction of 22.6 g. I with 4.8 g. $LiAlH_4$ in Et_2O yielded, after decompn. with 10% H_2SO_4, 17 g. (80%) $Ph_2CHCH_2CH_2OH$, $b_{2.5}$ 161-5°. This compd. was transformed in the usual way to $Ph_2CHCH_2CH_2OCH_2CH_2NMe_2$, b_1 153-4° (yield 78%); *HCl salt*, m. 132° (from Et_2O-Me_2CO). $Ph_2CHCOCl$ (29.2 g.) in 300 ml. Et_2O added to 21.6 g. C_6H_{11} in 300 ml. Et_2O gave overnight, 20.7 g. (58%) Ph_2CHCON-C_6H_{12} (II), m. 108-9°. Refluxing 12.8 g. II and 2 g. $LiAlH_4$ in 650 ml. Et_2O 24 hrs. (with stirring), decompg. the mixt. with 60 ml. H_2O and 100 ml. 3*N* H_2SO_4, alkalizing the aq. layers with 40% KOH, and extg. the bases with Et_2O yielded 7.2 g. (59%) $Ph_2CHCH_2NC_6H_{10}$, b_1 167-70°, $b_{0.4}$ 157-9°; *HCl salt*, m. 140°. $(PhCH_2)_2CO$, b_1 160°, was transformed to $(PhCH_2)_2C:NOH$, m. 122-3° which (28 g.) hydrogenated in 150 ml. EtOH over 6 g. Raney Ni 2 hrs. at 100° and 115 atm. initial pressure yielded 22.2 g. (85%) $(PhCH_2)_2CHNH_2$, m. 44-5°, $b_{0.5}$ 130-1°; *HCl salt*, m. 198-9°. None of the prepd. compds. was effective as antihistaminic.

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

1/2

Antihistamine substances. XXXV. Kinetics of the hydrolysis of antihistaminics of the benzhydryl type. Eduard Knobloch, František Mácha, Otto Exner, and Miroslav Protiva (Výzkumný ústav farm. biochem., Prague, Czech.). Chem. Listy 48, 226-31(1954); cf. C.A. 49, 1604d.—Kinetic measurements of the hydrolysis of antihistaminics of the benzhydryl type indicate the acid-catalyzed cryptobimolecular reaction. The generally accepted scheme of this reaction was checked by the primary salt effect. The effect of substituents in various positions of the diphenylmethane radical on the hydrolysis rate corresponds to the theoretical considerations. The rate of hydrolysis and antihistamine activity parallel each other though not without exceptions. XXXVI. Preparation of p-substituted analogs of Antistine. Jiří O. Jilek, Josef Pomykáček, and Miroslav Protiva (Výzkumný ústav farm. biochem., Prague, Czech.). Ibid. 232-4.—p-$MeC_6H_4CH:NPh$, m. 42-4°, $b_{0.4}$ 125-6° (50 g.) in 85 ml. MeOH hydrogenated over 10 g. Raney Ni at normal temp. and 100 atm. gave 51 g. (100%) p-$MeC_6H_4CH_2$-

(over)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

2/2

Eduard Knobloch

NHPh (I), m. 42–5°; *HCl salt*, m. 181° (from EtOH). Similarly was prepd. *p*-$MeOC_6H_4CH_2NHPh$ (II), m. 64–6° (from EtOH), from *p*-$MeOC_6H_4CH{:}NPh$, m. 60°. To prep. *p*-$ClC_6H_4CH_2NHPh$ (III), 232 g. $PhNH_2$ in 60 ml. H_2O and 66.2 g. $NaHCO_3$ were treated at 90–5° with 100 g. *p*-$ClC_6H_4CH_2Cl$, b_{15} 96°; distn. of the filtered crude product gave 51 g. (38%) III, $b_{0.5}$ 135–40°; *HCl salt*, m. 207°. 2-Chloromethylimidazoline-HCl (IV), m. 190–2°, and $PhCH_2NHPh$ gave 2-(*N-benzylanilinomethyl*)-2-*imidazoline* (Antistine), m. 121–3°; *HCl salt*, m. 233–4°; methanesulfonate, m. 168–9°. IV (17.2 g.), 50 g. I, and 75 ml. EtOH refluxed 8 hrs., the EtOH distd. off, the residue stirred with 90 ml. H_2O, mixed with 8.5 g. $NaHCO_3$ in 90 ml. H_2O at 50–60°, the mixt. extd. with PhMe, and the aq. phase allowed to cryst. in the icebox gave 16.3 g. (52%) *HCl salt* of 2-[*N*-(*p-methylbenzyl*)*anilinomethyl*]-2-*imidazoline*, m. 224° (from EtOH). Similarly were prepd., from II, 2-[*N*-(*p-methoxybenzyl*)*anilinomethyl*]-2-*imidazoline-HCl*, m. 209–12° (from EtOH-Me_2CO), and, from III, the 2-[*N*-(*p-chlorobenzyl*)*anilinomethyl*] *analog*, m. 232–3°. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.; JILEK, J.; POMYKACEK, J.

"Antihistamine Substances. XXXVI. Preparation of Some P-Substituted Analogues of Antistine", P. 232, (CHEMICKE LISTY, Vol. 48, No. 2, Feb. 1954, Praha, Czechoslovakia)

SO: Monthly List of East European Accessions, (EEAL), LC, Vol. 3, No. 12, Dec. 1954, Uncl.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

~~MIROSLAV, PROTIVA~~
PROTIVA, Miroslav

CZECH

CH

Antihistamine substances. XXXVII. Synthetic spasmolytics. XI. Phosphonium salts. Comparison of activities of various types of onium salts. Miroslav Protiva and Otto Exner (Výzkumný ústav farm. biochem., Prague). *Chem. Listy* 48, 1370-3(1954); *Collection Czechoslov. Chem. Commun.* 20, 210-13(1955)(in English); cf. *C.A.*, 49, 2471, 2125g.—Addition of $Ph_2CHOCH_2CH_2I$ (I) and $C_6H_{11}PhCHCO_2CH_2CH_2I$ (II) to Et_3P gave P analogs of Benadryl and Trasentine H. Refluxing 47.4 g. $C_6H_{11}PhCHCOCl$ (III) and 34.5 g. ICH_2CH_2OH in 140 ml. C_6H_6 3 hrs., washing the soln. with H_2O, 2% $Na_2S_2O_3$, and again H_2O, and evapg. the soln. yielded 73 g. II, m. 64° (from aq. EtOH), $b_{0.3}$ 158-61°. Heating 9.5 g. II, 0.5 ml. EtOH, and 3 g. Et_3P (b. 115-25°) 8 hrs. at 120° in a sealed tube under N gave 7.0 g. $C_6H_{11}PhCHCO_2CH_2CH_2PEt_3I$ (IV), m. 123-4° (from Me_2CO and Et_2O). Heating 4.7 g. Et_3P, 13.5 g. I, and 1 ml. EtOH under N in a sealed tube 5 hrs. at 100-20°, dissolving the oil in 10 ml. EtOH, and pptg. with Et_2O gave 3.53 g. $Ph_2CHOCH_2CH_2PEt_3I$, m. 120° (from EtOH), and $HOCH_2$-

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

MIROSLAV PROTIVA

CH_2PEt_2I, m. 207° (from EtOH). $Ph_2CHOCH_2CH_2NEt_2$, prepd. by alkalization of 8 g. HCl salt, was treated with 5 g. EtI to give 8.65 g. $Ph_2CHOCH_2CH_2NEt_2I$, m. 139° (from EtOH). Treating 5.9 g. III with 2.3 g. $HOCH_2CH_2NMe_2$ and 10 ml. C_6H_6 yielded 7.3 g. $C_6H_{11}PhCHCO_2CH_2CH_2NMe_2.HCl$, m. 109° (from Me_2CO-Et_2O). The free base (12.9 g.) liberated from the HCl salt was treated with 8 g. MeI to give 10 g. $C_6H_{11}PhCHCO_2CH_2CH_2NMe_2I$, m. 162° (from EtOH). Refluxing 3.7 g. II 5 hrs. with a soln. of MeSNa prepd. from 0.23 g. Na in 10 ml. MeOH and from MeSH, evapg. the MeOH, washing the residue with water, and extg. with C_6H_6 gave 1.9 g. $C_6H_{11}PhCHCO_2CH_2CH_2SMe$, b_1 150–60°. Mixing 1.8 g. of the sulfide with 2 ml. MeI gave 2.06 g. $C_6H_{11}PhCHCO_2CH_2CH_2SMe_2I$ (V), m. 101°. Spasmolytic action of IV and V is much higher than that of Trasentine H. XXXVIII. Hydrolysis of 2-(*N*-benzylanilinomethyl)imidazoline. J. O. Jilek and M. Protiva. *Chem. Listy* 48, 1584–5(1954).—Alk. hydrolysis of $PhCH_2NPhCH_2C{:}N.CH_2.CH_2.NH$ (I) by heating the HCl salt of I in aq. NaOH 5 hrs. at 90°, and treatment of the base with HCl in Et_2O gave *dihydrochloride hydrate* of $PhCH_2NPhCH_2CONHCH_2CH_2NH_2$ (II), m. 135–7° (decompn.) (from EtOH). Refluxing I 3 hrs. with H_2O gave an oil from which abs. alc. HCl pptd. anhyd. *mono-HCl salt* of II, m. 185–6°, whereas in the presence of H_2O was obtained *di-HCl salt hydrate*. Both salts give identical $HClO_4$ salt of II, m. 125–8°.

M. Hudlický

2/2

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECH

4

Ganglionic blocking agents. II. Bis-quaternary salts derived from 1,5-diamino-3-thiapentane. Miloš Borovička and Miroslav Protiva (Výzkumný ústav farm. biochem., Prague). ~~Chem. Listy~~ 48, 1374-7(1954); *Collection Czechoslov. Chem. Communs.* 20, 273-6(1955); cf. *C.A.* 49, 155c.—Condensation of *N*-disubstituted 2-aminoethylmercaptides with *N*-disubstituted 2-aminoethylchlorides, and the subsequent reaction of the products with MeI or EtI gave bis-quaternary salts derived from 1,5-diamino-3-thiapentane. The compounds resemble in ganglioplegic action their analog pentamethonium iodide. The mercaptans were prepd. by hydrolysis of the isothiuronium hydrochlorides. Isothiuronium hydrochlorides (yield in %, m.p.) and mercaptans (b.p.) are given: $Me_2NCH_2CH_2SC(:NH)NH_2HCl$, 70, 178-80°, $Me_2NCH_2CH_2SH$ (I), 124-7°; $Et_2NCH_2CH_2SC(:NH)NH_2.HCl$, 75, 192-3°, $Et_2NCH_2CH_2SH$ (II), b_{11} 65-6°; $C_5H_{10}NCH_2CH_2SC(:NH)NH_2.HCl$, 72, 220.5-2° (decompn.), $C_5H_{10}NCH_2CH_2SH$ (III), b_{11-12} 83-7°; $RCH_2CH_2SC(:NH)NH_2.HCl$ (R=morpholino), 65, 235-6° (decompn.), RCH_2CH_2SH (IV), b_{12} 96-7°. Yields of mercaptans were 30-40%. As a by-product, $(Et_2NCH_2CH_2)_2S$, b_{10} 141-3° was isolated. Adding 12 g. I to a soln. prepd. from 2.7 g. Na and 60 ml. EtOH, treating the mixt. after 30 min. with 12.3 g. $Me_2NCH_2CH_2Cl$ in 20 ml. EtOH, refluxing the mixt. 4 hrs., filtering off the salt, evapg. the filtrate, diig. the residue with 150 ml. Et_2O, washing with H_2O, drying, and evapg. the ext. yielded 12 g. (60%) $(Me_2NCH_2CH_2)_2S$, b_{10} 100°; *bismethiodide*, m. 291-2°; *bisethiodide*, m. 276-7°. Similarly were prepd., from the corresponding chlorides and mercaptides, $(Et_2NCH_2CH_2)_2S$ (from II in 76%), b_{10} 138-7°; *bismethiodide*, m. 260-69°; *bisethiodide*, 258-9°. $(C_5H_{10}NCH_2CH_2)_2S$ (from III in 53% yield), $b_{0.4}$ 130-2°; *bismethiodide*, m. 256-7°; *bisethiodide*, m. 244-5°; $(RCH_2CH_2)_2S$ (from IV in low yield), b_{10} 195-200°; *bismethiodide*, m. 245-6°.

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

4

CZECH

CH

Syntheses in estrogenic hormones group. VI. Derivatives of cyclohexanol-2,3-dicarboxylic acids. Otto Exner and Miroslav Protiva (Výzkumný ústav farm. biochem., Prague). *Chem. Listy* 48, 1060-48(1954); cf. C.A. 49, 6808g.—Starting with hydroxylated phthalic acids, the synthesis of *8-methyl-1,4-hydroxdanedione* and *1,4-hydrindanedione* was attempted. Low yields of the intermediates and nonduplicability of the hydrogenation of the aromatic derivs. to the alicyclic ones made the synthesis impracticable. *p*-Benzoquinone, KCN, and H_2SO_4 gave 75% 1,2,3,6-$(NC)_2C_6H_2(OH)_2$, hydrolyzed with 50% KOH to 70% 1,2,3,6-$(HO_2C)_2C_6H_2(OH)_2$, m. 213°, decompn. (from H_2O), which gave 60% 1,2,3,6-$(MeO_2C)_2C_6H_2(OH)_2$ (I), m. 140° (from H_2O). Acetylation of I with AcCl in C_5H_5N gave 47% 1,2,3,6-$(MeO_2C)_2C_6H_2(OAc)(OH)$ (II), m. 118° (from H_2O). Hydrogenation of II in EtOH over Raney Ni at 120 atm. and 180° (no reaction at 140°) gave, after 1 hr., 30% 2,3-$(MeO_2C)_2C_6H_7(OAc)$, b. 150°. Hydrogenation of 1.52 g. I in 30 ml. AcOH over PtO_2 (0.4 g.) gave, after 14 hrs., 2 g. 1,2,3,6-$(MeO_2C)C_6H_3(OAc)_3$, m. 165-70°. Hydrogenation of 22.6 g. I in 100 ml. MeOH over 3 g. Raney Ni at 100° and 130 atm. gave, after 2 hrs., 16.6 g. of a

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

4

OTTO FUHLER

stereoisomeric mixt. of 1,2,3,6-$(MeO_2C)_2C_6H_8(OH)_2$ (III), $b_{0.4}$ 162°. Treating 17.5 g. III in 60 ml. C_6H_6 with 7.2 g. C_5H_5N and at 40° with 6.2 g. AcCl gave 13.8 g. stereoisomeric mixt. of 1,2,3,6-$(MeO_2C)C_6H_8(OAc)(OH)$ (IV), $b_{0.4}$ 160-5°. Treating 13.6 g. IV in 100 ml. AcOH during 30 min. with 4.3 g. CrO_3 dissolved in 4 ml. H_2O and 20 ml. AcOH, stirring the mixt. with cooling one hr. longer, adding 5 ml. EtOH, evapg. the mixt. *in vacuo* at 45°, stirring the residue with 100 ml. H_2O, extg. the mixt. with C_6H_6, and distg. the ext. yielded 10.5 g. stereoisomeric mixt. of CO.CH(CO₂Me).CH(CO₂Me).CH(OAc).CH₂.CH₂ (V), $b_{0.4}$ 162-72°. Adding 10.5 g. V to 1.1 g. Na dust in 20 ml. C_6H_6, refluxing the mixt. 4 hrs., treating with 3.5 g. MeI, and refluxing 4 more hrs. gave 6.4 g. CO.CMe(CO₂Me).CH(CO₂Me).CH(OAc).CH₂.CH₂ (VI), $b_{0.4}$ 148-52°. Shaking 4.1 g. VI with a mixt. of 10 ml. $PhCH_2SH$, 1 g. anhyd. $ZnCl_2$, and 1 g. anhyd. Na_2SO_4 at 0°, letting stand 3 days, extg. with

2/3

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

OTTO EXTR

C_6H_6, and evapg. the solvent gave 5.6 g. crude mercaptole of VI. This (5 g.) was refluxed 5 hrs. with stirring with 15 ml. suspension of Raney Ni in 150 ml. EtOH, filtered and evapd. *in vacuo*. The residue dissolved in 10 ml. EtOH, refluxed with 20 ml. 20% KOH in EtOH 4 hrs., evapd. *in vacuo*, dissolved in 20 ml. H_2O, acidified with HCl, evapd. *in vacuo* to dryness, and extd. with Et_2O gave a glassy residue which was dissolved in 40 ml. MeOH, treated with dry HCl, evapd. and distd. to give 1.4 g. of a mixt. the chromatography of which over Al_2O_3 yielded 0.7 g. stereoisomeric mixt. of

$CH(CO_2Me)_2CH(OH)(CH_2)_3CMeCO_2Me$, $b_{0.4}$ 140° (bath temp.). 2,3-$(MeO_2C)C_6H_3NO_2$, m. 67-8°, hydrogenated in MeOH over Raney Ni at normal pressure gave 95% 2,3-$(MeO_2C)C_6H_3NH_2$ which was transformed via the diazonium salt in 70% yield to 2,3-$(MeO_2C)C_6H_3OH$ (VII), $b_{0.4}$ 125-30°, m. 68° (monohydrate). Anhyd. VII m. 54-5°. Sapon. of VII with KOH gave 95% diacid, m. 160° (from Et_2O-petr. ether). Hydrogenation of 21 g. VII in 100 ml. MeOH over Raney Ni at 160-80° and 120 atm. gave after

chromatography 20% $CH(CO_2Me)_2CH(OH)(CH_2)_3CHCO_2Me$ (VIII), $b_{0.4}$ 120-5°, and di-Me hexahydrophthalate. Oxidation of 5.5 g. VIII in 30 ml. AcOH with 2.3 g. CrO_3 in a mixt. of 3.6 ml. H_2O and 25 ml. AcOH at 18-20° gave, after

benzene extn., 3.3 g. (61%) $CH(CO_2Me)_2CO(CH_2)_3CHCO_2Me$, $b_{0.4}$ 105-110°. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

Hydroxyalkyl esters of nicotinic acid. Zdeněk J. Vejdělek and Miroslav Protiva. Czech. 84,183, May 1, 1955. Nicotinylchloride (I) and $HO(CH_2)_nOH$ (II) (where n is 2-6) give products showing high vasodilatory activity, low toxicity, and high soly. in water. I 14.1 g. in 20 ml. dry C_6H_6 is slowly added to a mixt. of 20 g. II (n = 2), 8 ml. dry pyridine (III), and 35 ml. C_6H_6, the mixt. dild. with water to sep. 4.6 g. ethylene glycol dinicotinate (m. 128°), the filtrate alkalized with K_2CO_3, and extd. with $CHCl_3$, and the product distd., yielding 57% $HOCH_2CH_2$ ester, b_3 142-4°, of nicotinic acid; picrate, m. 138° (from EtOH). I 14.1 g., 18 g. II (n = 3), and 8 ml. III in 55 ml. C_6H_6 yield 3.8 g. trimethylene glycol dinicotinate, m. 95°, and 4.42 g. $HO(CH_2)_3$ ester, $b_{0.7}$ 144°, of nicotinic acid (picrate, m. 106°). I 14 g. and 15.0 g. II (n = 5) in 8 ml. III and 30 ml. abs. ether yield 5.84 g. $HO(CH_2)_5$ ester, $b_{0.3}$ 160°, of nicotinic acid very sol. in ether; picrate, m. 106°. I 7.1 g. and 10 g. II (n = 6) in 4 ml. III and 30 ml. C_6H_6 yield 2.8 g. $HO(CH_2)_6$ ester, $b_{0.4}$ 178°, of nicotinic acid; picrate, m. 68°. L. J. U.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Protiva, Miroslav

Alkyl ethers with antihistaminic and antispasmodic properties. Miroslav Protiva. Czech. 84,863, Oct. 2, 1955. Physiologically active basic ethers PhCYZOCH$_2$CH$_2$NR$_2$ (I) (where R is alkyl, Z is H or alkyl, and Y is a heterocyclic residue) are prepd. by condensing compds. derived from substituted ethanolamines of the type OHCH$_2$CH$_2$NR$_2$ with PhCYZOH (II). The alcoholate prepd. by boiling 5 g. II [Y = Me, Z = 3-pyridyl (III)] (IV) with 1.0 g. NaNH$_2$ in benzene was refluxed 6 hrs. with 3.4 g. ClCH$_2$CH$_2$NEt$_2$, yielding 5.7 g. I (Y = Me, Z = III, R = Et), b$_{0.5}$ 160–72°; dipicrate, m. 135–7° (cor.) (from acetone-EtOH). IV (5.0 g.) and 2.7 g. ClCH$_2$CH$_2$NMe$_2$ yielded I (Y = Me, Z = III, R = Me); dipicrate, m. 172.5–4° (cor.) (from acetone-dioxane-EtOH). IV (5.0 g.) and 3.7 g. β-piperidinoethyl chloride yielded I (Y = Me, Z = III, NR$_2$ = piperidino); dipicrate, m. 152–4° (cor.) (from dioxane-acetone-EtOH). II (Y = H, Z = 2-furyl) (8.7 g.) and 5.3 g. ClCH$_2$CH$_2$NMe$_2$ yielded I (Y = H, Z = 2-furyl, R = Me), b$_{0.5}$ 116°, which gave unstable products with HCl and picric acid but cryst. addn. products with alkyl halides and esters of inorg. acids. Also prepd. were I (Y = Me, Z = III, NR$_2$ = morpholine) (dipicrate, m. 173–4°) and I (Y = Et, Z = III, R = Me) (dipicrate, m. 148–50°). Czech. 84,864. Direct condensation of tertiary 3-pyridylcarbinols with β-aminoethyl halides (without prepg. alco-

1/2

(over)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Alkyl ethers with antihistaminic...

holates) yields ether bases showing physiol. activity. A mixt. of 5 g. IV, 3.4 g. $ClCH_2CH_2NEt_2$, and 1.0 g. $NaNH_2$ in 10 ml. C_6H_6 was refluxed 6 hrs. and decompd. with water. The crude product was chromatographed on Al_2O_3 and eluted with C_6H_6, yielding I (Y = Me, Z = III, R = Et); dipicrate, m. 135–7° (from acetone-EtOH). Also prepd. were the following I (Y, Z, R, and m.p. of dipicrate given): Me, III, Me, 172.5–4° (from acetone-dioxane-EtOH); Me, III, NR_2 = piperidino, 152.4° (from dioxane-acetone-EtOH); Me, III, NR_2 = morpholino, 173–4° (from dioxane); and Et, III, Me, 148–50° (from PhAc-EtOH). 1-(β-dimethylaminoethoxy)-1-(p-tolyl)-1-(3-pyridyl)ethane dipicrate, m. 155–7° (from dioxane-acetone-EtOH), and 1-(β-dimethylaminoethoxy)-1-(1-naphthyl)-1-(3-pyridyl)ethane dipicrate, m. 200–2° (from PhAc-EtOH), were also prepd.

L. J. Urbanek

2/2

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Protiva, Miroslav

2

Compounds with antihistamine and antispasmic activity. Václav Rečicha and Miroslav Protiva. Czech. 84,865, Oct. 2, 1955. Condensation of 2-(*p*-methoxybenzylamino)pyridine (I) with 2-piperidino- or 2-morpholinoethyl halides yields products showing biol. activity, notably high antihistamine effects. I (16.7 g.) in 100 ml. dry C_6H_6 treated with 11.5 g. 2-piperidinoethyl chloride and 3.4 g. $NaNH_2$; the mixt. allowed to stand overnight, refluxed on a steam bath 6 hrs., dild. with water, extd. with Et_2O, and the ext. distd. yields *2-[p-methoxybenzyl(2-piperidinoethyl)amino]-pyridine*, b_1 220–8°; *monopicrate* (60%), m. 122–3.5° (from EtOH). Analogously was prepd. *2-[p-methoxybenzyl-(2-morpholinoethyl)amino]pyridine*, $b_{1.5}$ 230–40°; *monopicrate* (70%), m. 110°.

L. J. Urbánek

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

3

2

M. A YOUTZ
2 copies

Tertiary 3-pyridylcarbinols. Miroslav Protiva and Miloš Borovička. Czech. 85,411, Dec. 1, 1955. Tertiary 3-pyridylcarbinols are prepd. by treating arylmagnesium halides with 3-pyridyl alkyl ketones. A Grignard reagent prepd. from 2.4 g. Mg and 15 g. PhBr in 70 ml. Et_2O treated with cooling with 8.2 g. 3-acetylpyridine in 20 ml. Et_2O, the mixt. refluxed 30 min., and the product decompd. with ice and extd. with Et_2O yields *3-pyridylphenylmethylcarbinol*, $b_{0.6}$ 164–7°, m. 80.5–1.5°; *HCl salt*, m. 163–4°. Similarly prepd. were *3-pyridyl(p-tolyl)methylcarbinol*, m. ~108° [*HCl salt*, m. 160–2° (41%)]; *3-pyridylphenylethylcarbinol*, $b_{0.9}$ 171–7°, m. 104–6° [*HCl salt*, m. 126–7.5° (60%)]; and *3-pyridyl(1-naphthyl)methylcarbinol*, m. 183–70° (50%).

L. J. Urbánek

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, Miroslav

Syntheses in estrogenic hormones group. VI. Derivatives of cyclohexanol-2,3-dicarboxylic acids. Otto Exner and Miroslav Protiva. *Collection Czechoslov. Chem. Communs.* 20, 757-63(1955)(in English).—See *C.A.* 49, 11568e. E. J. C.

CH

1

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

MIRO
PROTIVA, MIROSLAV

V Syntheses in estrogenic hormone group. VII. Crystalline methyl-2-methyl-2-carbomethoxy-5-(*p*-methoxyphenyl)cyclohexanone-6-acetate and attempts to cyclize stereoisomeric 2-methyl-5-(*p*-methoxyphenyl)cyclohexanone-6-acetic acids. Jiří O. Jílek and Miroslav Protiva (Výzkumný ústav farm. biochem., Prague). *Chem. Listy* 49, 98–105 (1955); *Collection Czechoslov. Chem. Communs* 20, 765–76 (1955)(in German); cf. *C.A.* 49, 11568*e*.—Reësterification of 5 g. *Et 2-methyl-2-carbethoxy-5-(p-methoxyphenyl)cyclohexanone-6-acetate* (I), m. 84°, by refluxing 2 hrs. with 42.5 g. MeOH and 0.07 g. Na, decompg. the cooled mixt. with 750 ml. H_2O, extg. with Et_2O, evapg. the ext., and dissolving the residue (4.8 g.) in 20 ml. 80% aq. MeOH, and cooling yielded 4.2 g. *Me 2-methyl-2-carbomethoxy-5-(p-methoxyphenyl)cyclohexanone-6-acetate*, m. 97° (from 83% MeOH). Sapong. 35 g. liquid I (the mother liquor from the crystn. of I) (*C.A.* 49, 197*a*) by refluxing 10 hrs. with 28 g. NaOH in 250 ml. H_2O, dilg. the mixt. with 250 ml. H_2O, acidifying with HCl, filtering off the 6 g. of crystals (isomer IIa), m. 206–9° (from EtOH), and extg. the soln. with Et_2O gave 7 g. stereoisomer (IIb), m. 138° (from C_6H_6), of *2-methyl-5-(p-methoxyphenyl)cyclohexanone-6-acetic acid*. Adding 5 g. IIa to 25 g. polyphosphoric acid (160°), heating the mixt. 10 min. at 150°, cooling dilg. with 100 g. ice, and extg. with Et_2O gave 4 g. of a *lactone* (IIIa) of *3-methyl-6-(p-methoxyphenyl)-2-hydroxy-1-cyclohexene-1-acetic acid*, m. 91° (from 80% EtOH), which regenerated IIa on alk. hydrolysis. Similar treatment of 5 g. IIb by heating with 25 g. polyphosphoric acid 2 hrs. at 100° gave 4 g. crude and 2.2 g. pure stereoisomer (IIIb), $b_{0.4}$ 210–15°, alk. hydrolysis of which gave IIb. Catalytic hydrogenation of 2 g. IIIa in 40 ml. AcOH over Pd in the presence of 2 ml. 60% $HClO_4$ gave 0.6 g. of an isomer (IVaα) of a satd. *lactone of 3-methyl-6-(p-methoxyphenyl)-2-hydroxycyclohexaneacetic acid*, $b_{0.4}$ 185–90°, m. 93–4° (from 80% MeOH). Similar treatment of 2.2 g. IIIb in 50 ml. AcOH and 1.5 ml. $HClO_4$ in the presence of Pd catalyst (added twice during the hydrogenation) gave, after chromatography, 1.15 g. isomeric lactone (IVb), $b_{0.4}$ 195–200° (bath temp.). Reduction of 2 g. IIIa with 1.5 g. $LiAlH_4$ in 150 ml. Et_2O by refluxing 30 min. gave after chromatography 1.2 g. *3-methyl-5-(p-methoxyphenyl)-6-(2-hydroxyethyl)cyclohexanone*, $b_{0.4}$ 190–2°. IIa (0.8 g.) was transformed with 0.7 g. PCl_5 in 30 ml. C_6H_6 to its chloride which, treated with 1 ml. $SnCl_4$ 3 hrs. at 0°, gave, after decompn. with 15 ml. 3*N* HCl, 0.05 g. IIa and 0.10 g. of a *lactone* (Va) of (*3-methyl-6-(p-methoxyphenyl)-2-hydroxy*)-$\Delta^{1,\alpha}$-*cyclohexaneacetic acid*, $b_{0.4}$ 200–10°, m. 116–17° (from MeOH), sapon. of which gave IIa. Catalytic hydrogenation of 190 mg. Va in 10 ml. AcOH with Pd and 0.1 ml. $HClO_4$ gave 40 mg. of an isomer (IVaβ) of IVaα, m. 109–2° (from MeOH). Similar cyclization of 2 g. IIb yielded after ether extn. and chromatography 0.5 g. of a stereoisomeric lactone (Vb), $b_{0.3}$ 205–15°, m. 99–103° (from MeOH). Thermal cyclization of IIa by heating 0.4 g. IIa 10 min. at 240° gave, after distn. *in vacuo*, 250 mg. of a mixt. of IIIa and Va which regenerated IIa on alk. hydrolysis. Partial hydrolysis of the liquid portion of I (7.4 g.) in 20 ml. EtOH gave 4.4 g. fluxing 5 hrs. with 1.1 g. KOH in 100 ml. EtOH by re- *2-methyl-2-carbethoxy-5-(p-methoxyphenyl)cyclohexanone-6-acetic acid* (VI), which treated in 100 ml. C_6H_6 at 0° with 4 ml. 4 g. PCl_5, the crude chloride shaken 15 min. at 0° with 20 g. ice and 20 ml. $SnCl_4$, and the mixt. decompd. with HCl, gave, after chromatography, 1.2 g. (probably) *2-methyl-2-carbethoxy-7-(p-methoxyphenyl)-1,9-dioxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene*, $b_{0.4}$ 200–10°. To verify the formation of unsatd. lactones, 4.3 g. cyclohexanone-2-acetic acid, m. 72–4°, was added to 22 g. polyphosphoric acid at 150°, and the mixt. heated 10 min. at 150°, decomposed. with 100 g. ice, and extd. with ether to give 1.8 g. *lactone of 2-hydroxy-$\Delta^{1,\alpha}$-cyclohexaneacetic acid*, $b_{0.4}$ 102–5, m. 20–22°. In connection with the syntheses, a mixt. of 13.5 g. *Et 2-methyl-2-carbethoxycyclohexanone-6-acetic acid* (*loc. cit.*) and 8.35 g. $BrCH_2CO_2Et$ was heated with 3.26 g. Zn, 80 ml. C_6H_6, and 70 ml. PhMe 4 hrs. at

(over) 1

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Jiri O. Jilek

100°, decompd. with 50 ml. 10% AcOH, and the org. layer washed with 50 ml. 10% NH_3 soln. and distd. to give 10.0 g. of a mixt. of stereoisomeric *2-methyl-2-carbethoxy-1,6-bis-(carboethoxymethyl)cyclohexanols*, the dehydration of which (5 g.) by refluxing 3 hrs. with 50 ml. 85% HCO_2H gave 2 g. isomeric unsatd. esters, dl-Et *3-methyl-3-carbethoxy-1-cyclohexene-1,3-diacetate*, and *Et 2-methyl-2-carbethoxy-6-carbethoxymethyl-$\Delta^{1,6}$-cyclohexaneacetate*, $b_{0.4}$ 130–5°. Infrared spectra of IIIa, IVaα, and Va are given. M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.;EXNER, O.

Antihistamine substances. XXXVII. Synthetic antispasmodics. XI. Phosphonium salts; comparison of the activity of various types of onium salts. In English. p. 210

Vol. 20, no. 1, Feb. 1955
SBORNIK CHEKHOSLOVATSKIKH KHIMICHESKIKH RABOT
Praha, Czechoslovakia

So: Eastern European Accession Vol. 5 No. 4, April 1956

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26840.

Author : Protiva, Miroslav; Simák, Vladislav, Hach, Vladimir, Exner, Otto.

Inst :

Title : Local Anesthetics. III. Sulfonium Salts.

Orig Pub: Chem listy, 1955, 49, No. 2, 222 - 226.

Abstract: With a view to compare the local anesthetic activity of analogous nitrous and sulfurous compounds, the following substances were produced: of the novocaine type - 2-methylmercaptoethyl esters of n-amine (I), n-butoxybenzoic (II), n-metoxycinnamic (III) and n-metoxythiocinnamic (IV) acids; of the xylocaine type - N-(methylmercaptoacetyl)-2,4-xylidine (V),

Card 1/7

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26840.

N-(methylmercaptoacetyl)-2-methyl-5,6,7,8-tetrahydro-1-naphthylamine (VI); of the percaine type - 2-methylmercaptoethylamides of 2-chlorocinchonine acid (VII) and 2-butoxycinchonine acid (VIII), as well as iodomethylates of I to VIII. Iodomethylate of II has the same activity as novocaine, the activity of iodomethylate of III is 20% of that of novocaine. The analogy of the physiological activity of sulfonium and ammonium salts extends also on the local anesthetics. Iodomethylate of VIII has no local anesthetic action. The mixture of 8.25 g of ethyl esters of n-aminobenzoic acid, 16 g of 2-methylmercaptoethanol (IX) and 0.05 g of Na was slowly heated with distilling

Card 2/7

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26840.

125 - 126° (from alcohol). The alcohol solution was azeotropically distilled off with C_6H_6 in 3 hours' time from the mixture of C_2H_5ONa solution (of 3.4 g of Na and 75 ml of absolute alcohol) and 16.1 g of 2-methylmercaptoethylmercaptane, condensed down to 75 ml, 29 g of X was added, and 12 hours later the mixture was boiled 2 hours and decomposed with 75 ml of water, IV was separated by distillation of the organic layer, yield 50%, boiling point 182 - 190°/1 mm, melting point 45 - 56°; iodomethylate contains 2 mols of IV per 1 mol of CH_3I, melting point 110° (from alcohol). The solution of 15 g of methylmercatide of sodium (XI) and 30 g of N-chloracetyl-2,4-xylidine in 300 ml of alcohol

Card 4/7

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26840.

was boiled 2.5 hours, the filtrate was mixed with 150 ml of water and V was separated by distilling the ether layer, yield 65%, melting point 147-148° (from petroleum ether), iodomethylate, melting point 102-103° (from alc.-acetone). The mixture of 20 ml of alcohol solution of 3 g of IX and of the solution of 6.5 g of N-chloracetyl-2-methyl-5,6,7,8-tetrahydro-1-naphthylamine in 100 ml of hot alcohol was boiled 2.5 hours, filtered, alcohol was distilled off, the residue was mixed with 100 ml of water and 100 ml of C_6H_6, and VI was separated from the benzene layer, yield 59%, melting point 146-147° (from alcohol). The solution of 50 g of 2-methylmercaptoethylchloride in

Card 5/7

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26840.

500 ml of alcohol, saturated with NH_3 (gas) at -10°, was left staying at 0° for 6 days, alcohol was distilled off, the residue was decomposed by the solution of 40 g of NaOH, extracted with ether, and 2-methylmercapto-ethylamine was separated through chlorhydrate, yield 10%, boiling point 140-150°. The mixture of 3 g of 2-methylmercaptoethylamine, 7.8 g of chloranhydride of 2-chlorocinchonine acid and 50 ml of C_6H_6 was left staying at 20° for 1 hour, washed with soda solution, the soda solution was extracted with ether , and 4 g of VII, melting point 146-147° (from benzene-ether), was separated from the benzene and ether extracts. The mixture of sodium butylate (of 0.2 g of Na

Card 6/7

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26840.

and 35 ml of n-C_4H_9OH) and 3.6 g of VII was left at 20° for 2 hours and at 80° for 4 hours, boiled 3 hours, washed with water, the aqueous layer was extracted with ether and the combined butanol and ether extracts were distilled down, 2 g of VIII, melting point 107 to 108° (from 25%-ual alcohol) was obtained; iodomethylate, melting point 108-110° (from alcohol-ether). See RZhKhim, 1955, 21207 for report II.

Card 7/7

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26841.

Author : Hach, Vladimir, Horáková, Zdena, Protiva, Miroslav.

Inst :

Title : Local Anesthetics. IV. n-Aminobenzoates of 4-piperidinomethyl-1,2-benzocycloalkanoles-3.

Orig Pub: Chem. listy, 1955, 49, No. 2, 227 - 230.

Abstract: 2-piperidinomethylindanol (IV), 2-piperidinomethyltetralol (V) and 6-piperidinomethylbenzosuberol-5 (VI) were prepared by reduction of 2-piperidinomethylindanone (I), 2-piperidinomethyltetralone (II) and 6-piperidinomethylbenzosuberone-5 (III) with $LiAlH_4$. n-Nitrobenzoates of IV, V and VI (VIII, IX and X) were

Card 1/5

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26841.

obtained from IV to VI at a low yield by the interaction with n-nitrobenzoylchloride (VII). VIII to X produced corresponding n-aminobenzoates (XI, XII and XIII) by hydrogenation over PtO_2. IV, V and VI were obtained in the shape of one stereoisomer in all cases. In the duration of 20 min. 18 g of chlorohydrate of I was introduced into the suspension of 1.8 g of $LiAlH_4$ in 400 ml of absolute ether, the mixture was boiled 10 minutes, decomposed with 20 g of NaOH and 250 ml of water and extracted with ether; HCl (gas) was let through the dry distilled down ether extract and chlorohydrate of IV was received, yield 61%, melting point 202-203° (from alcohol). Similarly, V was received from

Card 2/5

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26841.

chlorohydrate of II and $LiAlH_4$, yield 47%, melting point 98-100° (from petroleum ether). When boiled with HBr (acid, 1 : 3), V splits producing piperidine bromohydrate, melting point 230-232° (from alcohol). Chlorohydrate of VI, melting point 205° (from alcohol-ether) was received from chlorohydrate of III similarly to IV, yield 74%. The mixture of the solution of IV (separated with soda from 5 g of chlorohydrate) in 75 ml of $CHCl_3$ and of the solution of 3 g of VII in 75 ml of $CHCl_3$ was distilled dry in air, chlorohydrate of VIII, melting point 164-165° (from alcohol-ether) was in the residue. Solution of 4 g of V and 3 g of VII in 25 ml of pyridine was heated (100°, 3 min.), 48 hours

Card 3/5

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

CZECHOSLOVAKIA/Organic Chemistry. Synthetic Organic Chemistry. E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26841.

later it was decomposed with the solution of $NaHCO_3$, the precipitate was suspended in ether and converted by HCl (gas) into chlorohydrate of IX, melting point 182-183° (from alcohol-ether). Chlorohydrate of X, melting point 206-207° (from alcohol-ether) was obtained from VI and VII. 3.1 g of chlorohydrate of VIII in 300 ml of alcohol was hydrogenated over 0.4 g of PtO_2, alcohol was distilled off, the base was separated by soda solution and extracted by ether, XI was obtained, yield 90%, melting point 140-141° (from alcohol-petroleum ether). XII was produced from IX in the same way, yield 75%, melting point 139-141° (from alcohol-petroleum ether), and XIII from X, yield 60%,

Card 4/5

E-2

Abs Jour: Ref Zhur - Khimiya, No. 8, 1957, 26841.

melting point 143-144° (from alcohol). The infiltrating anesthetic capacity of XI, XII and XIII is about 110% of that of nupercaine (XIV), the superficial anesthesia was tested by the introduction of 0.05 ml of 0.1%-ile solution of chlorohydrates of XI, XII and XIII into the eye of a guinea pig, XI possesses 110%, XII possesses 130% and XIII possesses 100% of the XIV activity. The toxity was tested by intravenous introduction of 0.02%-ile solution of the preparation to white mice weighing 16-20 g; LD50 is (in mg/kg): XI - 3, XII - 7, XIII and XIV - 6; XI, XII and XIII lower the blood pressure similarly to XIV.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-

Card 5/5

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

5

Synthetic spasmolytics. I. 2-(*m*-Hydroxydiphenylamino-methyl)imidazolines. M. Protiva and J. Kolinský (Výzkumný ústav farm. biochem. Prague). *Chem. Listy* 49, 272-4(1955).—Heating resorcinol with aromatic amines in the presence of their HCl salts at 165-70° gave 40% *3-hydroxydiphenylamine* (I), b_8 208°, m. 81-2°; 53% *3-hydroxy-2'-methyldiphenylamine* (II), b_1 187°, and 71% *3-hydroxy-3'-methyldiphenylamine* (III), $b_{0.7}$ 182°. Heating 14.9 g. I, 12.8 g. 2-chloromethylimidazoline-HCl (IV) and 90 ml. xylene with stirring 7 hrs. at 145-50°, boiling the mixt. shortly with 40 ml. H_2O, cooling to 60°, adding 20 ml. H_2O and 50 ml. AcOEt, boiling again, sepg. the aq. layer at 40°, and evapg. *in vacuo* to 30 ml. gave 8.6 g. of the *HCl salt of 2-(3-hydroxydiphenylaminomethyl)imidazoline* (V), m. 211° (from aq. EtOH). Similar treatment of 19.9 g. II, 17 g. IV, and 120 ml. xylene gave 7.6 g. *2-(3-hydroxy-2'-methyldiphenylaminomethyl)imidazoline-HCl* (VI), m. 240-1°. The same procedure with 19.9 g. III gave 10.9 g. of the *HCl salt of 2-(3-hydroxy-3'-methyldiphenylaminomethyl)imidazoline* (VII), m. 221-2°. *2-(3-Hydroxy-4'-methyldiphenylaminomethyl)imidazoline* m. 109°; *HCl salt*, m. 238-40°; *trichloroacetate*, m. 137.5° (decompn.); *$MeSO_4H$ salt*, m. 176°. The effect of VI is depressoric, that of VII is pressoric; V is indifferent. II. (1,4-Benzodioxan-2-ylmethyl)dimethylsulfonium iodide. M. Protiva and V. Šimák. *Ibid.* 374-5.—Refluxing 38 g. 2-chloromethyl-1,4-benzodioxan in 120 ml. EtOH 2.5 hrs. with 165 ml. of a soln. of 25 g. MeSNa 2.5 hrs., filtering off the salt, evapg. the filtrate, and shaking the residue with H_2O and Et_2O gave 34 g. (75%) *2-(methylthiomethyl)-1,4-benzodioxan*, $b_{1.6}$ 124-6°, $b_{0.11}$ 104-5°; *methiodide*, m. 111-13° (from Me_2CO). M. H.

CH

MST

(2)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

CZECH

Synthetic experiments in the histamine group. V. 4-Methylmercaptomethylimidazole. M. Protiva and J. O. Jilek (Výzkumný ústav farm. biochem., Prague). *Chem. Listy* 49, 372-4(1955); cf. C.A. 49, 1016e.—Treating MeSNa (from MeSH, 4.6 g. Na, and 100 ml. EtOH) with 14 g. 4-chloromethylimidazole-HCl (m. 144°), refluxing the mixt. 3 hrs., filtering off the salt, and distg. the filtrate *in vacuo* gave *4-methylmercaptomethylimidazole*, $b_{0.4}$ 180°; m. 86° (from Et_2O); *HCl salt* (I), m. 151° (from 5:1 Me_2CO-EtOH). I (0.2 g.), 2 ml. MeI, and 1 ml. MeOH refluxed 2 hrs. gave I.MeI, m. 205-7° (decompn.) (from MeOH).

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.; SIMAK, V.

Synthetic sympatholytics. II. 2-(1, 4-benzodioxanyl) methyl-dimethylsulfonium iodide. p. 374.
CHEMICKE LISTY Vol. 49, No. 3, Mar. 1955

SO: Monthly East European Accession (EEAL), LC, Vol. 9, Sept. 1955 Uncl.

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, M.

1/ Ganglionic blocking agents. IV. Pentamethylene-1,5-bis(*N*-methyl)pyrrolidinium salts. M. Borovička, Z. Šedivý, and M. Protiva (Výzkumný ústav farm. biochem., Prague). *Chem. Listy* 49, 777-8(1955); cf. *C.A.* 50, 1639*h*. —Treating *p*-$MeC_6H_4SO_2NHMe$ with BuBr according to Lukeš and Přeučil (*C.A.* 33, 983[4]) gave 81% *p*-$MeC_6H_4SO_2$-*NMeBu*, b_{15} 209-12°. This compd. was hydrolyzed to 50% MeNHBu, b. 88-90°, which was transformed to *N-methylpyrrolidine* (I), b. 78-80°, in 40-3% yields according to *C.A.* 40, 571[4]. I (100 g.), 135 g. $Br(CH_2)_5Br$, and 50 ml. Me_2CO mixed, cooled, and allowed to stand overnight, the solid product stirred with 100 ml. Et_2O, the quaternary salt filtered off with suction and washed with 250 ml. 1:1 Et_2O-iso-PrOH gave 200 g. *1,1'-pentamethylenebis(N-methylpyrrolidinium bromide* (II), extremely hygroscopic crystals; *dipicrate*, m. 274° (from PhAc-EtOH). II (105 g.) in 1500 ml. H_2O was decompd. with Ag_2O (from 500 g. $AgNO_3$), the filtrate mixed with 150 g. tartaric acid, the soln. evapd. *in vacuo*, and the residue crystd. from 400 ml. EtOH and 70 ml. H_2O to give 240 g. of the acid tartrate of II, m. 213-14° (decompn.). M. Hudlický

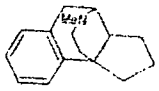
(2)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

Synthetic analgetics. I. Attempted syntheses of *N*-methyl-6-normorphinan. Miroslav Protiva, Vladimir Mychajlyszyn, and Jiří O. Jílek (Výzkumný ústav farm. biochem., Prague). *Chem. Listy* 49, 1045-52(1955).—Procedures described by Grewe and Mondon (*C.A.* 43, 4270*a*) and by Schnider and Hellerbach (*C.A.* 45, 2010*d*) were applied to a cyclopentane analog of *N*-methylmorphinan called throughout the paper *N*-methyl-6-normorphinan (I).



(I)

I would have resulted from cyclization of *1-methyl-2-benzyl-3,4-cyclopenteno-1,2,5,6-tetrahydropyridine* (II) with H_3PO_4, but prepn. of II from $PhCH_2MgCl$ and *3,4-cyclopentenopyridine methiodide* (III) was unsuccessful. An alternate method was based on the following series of reactions: cyclopentanone and $CH_2(CN)CO_2H$ gave *1-cyclopenten-1-ylacetonitrile* (IV), the reduction of which yielded *2-(1-cyclopenten-1-yl)ethylamine* (V). This compd. treated with $PhCH_2COCl$ gave *N-phenylacetyl-2-(1-cyclopenten-1-yl)ethylamine* (VI) which was transformed with P_2O_5 to *2-benzyl-3,4-cyclopenteno-5,6-dihydropyridine* (VII). Hydrogenation of the methiodide of VII yielded II but the attempt to cyclize II to I was unsuccessful. 2-Carbethoxycyclopentanone (VIII) (96 g.), 72 g. $NCCH_2CO_2Et$, and 15 ml. $C_5H_{11}N$ gave 82 g. *Et ester* of *2-carbethoxy-1-cyclopenten-1-ylcyanoacetic acid* (IX), b_{2-4} 145-8°. Substituting 66 g. $NCCH_2CO_2Me$ for the $NCCH_2CO_2Et$, heating the mixt. 4 hrs. at 100°, dilg. with 400 ml. Et_2O, washing 3 times with 100 ml. HCl (1:4), and distg. the ext. gave 57% of the *Me ester* of IX, b_{2-4} 128-32°. Refluxing Et (or Me) ester of IX 10 hrs. with concd. HCl yielded 46% (or 39%) *2-carboxy-1-cyclopenten-1-ylacetic acid* (X) m. 178-81° (from H_2O), and 30% (or 23%) *2,6-dihydroxy-3,4-cyclopentenopyridine* (XI), m. 263-4° (from 50% AcOH). Esterification of X with EtOH and PhMe gave 61% *mono-Et ester* of X, m. 96-7° (from H_2O). XI (24 g.) and $POCl_3$ (100 ml.) gave 20.5 g. *2,6-dichloro-3,4-cyclopentenopyridine* (XII), m. 34-5°, $b_{0.7}$ 102-5° (Prelog and Metzler, *C.A.* 41, 455*f*). Hydrogenating 29 g. XII in a soln. of 8 g. Na in 150 ml. EtOH over 35 g. Raney Ni 6 hrs. at 76-80° and 100 atm. gave 12.5 g. 3,4-cyclopentenopyridine (XIII), b_{10} 76-82°; III, m. 65-7° (from Me_2CO-Et_2O). Refluxing a mixt. of 50 g. $NCCH_2CO_2H$, 50 g. cyclopentanone, 50 ml. C_6H_6, and 2 g. NH_4OAc 7 hrs. at 150-60° with continual removal of H_2O gave after cooling 80 g. cyclopentylidenecyanoacetic acid, m. 125-8° (from H_2O). Distn. of this product *in vacuo* gave 75% IV, b_{10} 81°, b_{20} 85-8°, n_D^{20} 1.469, also obtained in 58% yield by refluxing 90 g. cyclopentanone, 90 g. $NCCH_2CO_2H$, 50 ml. C_6H_6, and 4 g. NH_4OAc at 150-65° 4 hrs. with continuous water removal, and by distg. the crude mixt. *in vacuo* at 20 mm. Adding during 2 hrs. 21.4 g. IV to a stirred mixt. of 10 g. $LiAlH_4$ in 400 ml. Et_2O cooled with ice and salt, keeping the mixt. 90 min. in the cooling bath, decompg. the mixt. with 40% NaOH, and extg. the aq. layer with Et_2O gave 7 g. V, b_{12} 60-3°; *HCl salt*, m. 105° (decompn.) (from Me_2CO); *picrate*, m. 145-6° (from

(over) (2)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

MIROSLAV PROTIVA

EtOH). Adding 10 g. IV in 20 g. BuOH and 200 ml. PhMe to a suspension of 9.2 g. Na dust in 130 ml. boiling PhMe, refluxing and stirring the mixt. 2.5 hrs., decomp. with 50 ml. H_2O, sep. the aq. layer, extg. the PhMe layer with a mixt. of 15 ml. HCl and 45 ml. H_2O, alkalizing the acidic ext. with 20% KOH, and extg. the base with ether gave 4 g. *2-cyclopentylethylamine*, b_{20} 55–70°; *HCl salt*, m. 197° (from EtOH-Me_2CO). Treating a mixt. of 15 g. $PhCH_2COCl$, 7 g. V, and 3.5 g. of the HCl salt of V in 50 ml. H_2O with 60 ml. 20% NaOH with stirring, filtering off the solid, and boiling it with 100 ml. H_2O gave 19 g. VI, m. 62° (from C_6H_6-petr. ether). Refluxing 11 g. VI, 30 ml. C_6H_6, and 30 g. P_2O_5 1 hr., decomp. the mixt. with ice, alkalizing the soln., extg. with Et_2O, and evap. the ext. gave 8 g. crude VII; *picrate*, m. 114–15° (from Me_2CO-EtOH). When the crude product was distd., $b_{0.5}$ 120–2°, the picrate of the same compn. m. 109° (from EtOH); *methiodide* (from the undistd. VII), m. 181° (from MeOH-Et_2O). Hydrogenation of the methiodide of VII (8.5 g.) in 100 ml. MeOH over 20 g. Raney Ni in the presence of 3 g. KOH at 110° and room temp. gave 3 g. II, $b_{0.5}$ 117–22°; *picrolonate*, m. 182–4° (from aq. EtOH). In another expt., or

by hydrogenation of the MeI salt of VII over Pt, a quaternary salt $C_{11}H_{23}NI$, m. 192° (from MeOH-Et_2O), was obtained. Hydrogenation of undistd. free base VII (3.3 g.) in 20 ml. MeOH over 1 g. Raney Ni at room temp. and atm. pressure 25 min., alkalization and ether extn. of the mixt. gave 2.4 g. *2-benzyl-3,4-cyclopentano-1,2,5,6-tetrahydropyridine*; *picrate*, m. 115° (from EtOH); *picrolonate*, m. 138–9° (from EtOH). Heating 0.5 g. II 72 hrs. at 150–60° with 10 ml. concd. H_3PO_4 gave 0.3 g. recovered II but no expected I.

M. Hudlický

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

PROTIVA, MIROSLAV

Synthetic analogs of the curare alkaloids. V. Bis(quaternary salts) derived from α,ω-diphenyl-α,ω-diaminoalkanes. Miroslav Protiva, Miloš Horovička, and Jiří Plíml (Výzkumný ústav farm. biochem., Prague). *Chem. Listy* 49, 1872-7(1955); cf. *C.A.* 49, 9665f.—The Friedel-Crafts synthesis from C_6H_6 and dicarboxylic chlorides gave α,ω-diketones, $Bz(CH_2)_nBz$ (I, $n = 2$), (II, $n = 4$), (III, $n = 6$), and (IV, $n = 8$), which were transformed to the corresponding *dioximes* (V, $n = 4$), (VI, $n = 6$), and (VII, $n = 8$), whose hydrogenation yielded *diamines* $PhCH(NH_2)(CH_2)_nCH(NH_2)Ph$ (VIII, $n = 4$), (IX, $n = 6$), and (X, $n = 8$). VIII and MeI gave a bis(quaternary methiodide). Since the same procedure failed for IX and X, another method was chosen for the prepn. of the quaternary methiodides: I, II, and IV were reduced with $LiAlH_4$ to diols, $PhCH(OH)(CH_2)_nCH(OH)Ph$ (XI, XII, and XIII for $n = 2$, 4, and 8), and these transformed with $SOCl_2$ to the corresponding chlorides, $PhCHCl(CH_2)_nCHClPh$ (XIV, XV, and XVI for $n = 2$, 4, and 8), which with Me_2NH yielded bis(dimethylamines), $PhCH(NMe_2)(CH_2)_nCH(NMe_2)Ph$ (XVII, XVIII, and XIX for $n = 2$, 4, and 8), metalated with MeI to bis(quaternary salts), $PhCH(NMe_3)(CH_2)_nCH(NMe_3)PhI_2$ which are either ineffective or less effective than the decamethonium bromide. I-IV [yields in %, m.p. (from EtOH)]: 55, 145-6°; 72, 106-7°; very good yield, 88°; 75%, 89-91°. V-VII were prepd. from II-IV with $NH_2OH.HCl$ and AcOK in aq. EtOH (yields in %, m.p.): 91, 222-3° (from AcOH); —, 105-6° (from dioxane); and 88%, 119-21° (from EtOH). Hydrogenation of V-VII

(over)

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"

"APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3

Synthetic Analogs

over Raney Ni in dioxane at 100° and 150 atm. initial pressure yielded 55% VIII, $b_{0.5}$ 180–2° [*di-HCl salt*, m. 330° (from EtOH-Et_2O)], 72% IX, $b_{0.5}$ 190–220° [*diformyl deriv.*, m. 188° (from EtOH)], and 49% X, $b_{0.5}$ 215–25° (decompn.) [*dipicrate*, m. 204–5° (from aq. EtOH); *diformyl deriv.*, m. 116° (from EtOH)], resp. Reduction of I, II, and IV with excess $LiAlH_4$ in Et_2O, respectively in Et_2O-C_6H_6 yielded 75% XI, m. 94–5° (from aq. EtOH), 87% XII, m. 152–3° (from MeOH), and 60% XIII, m. 70–1° (from C_6H_6-petr. ether), resp. The IR-sp. coincide with those of XI-XIII prepd. from I, II, and IV by the Meerwein-Ponndorf reduction. Refluxing XI-XIII 2 hrs. with $SOCl_2$ in C_6H_6 gave 93% purity cryst. XIV (XIVa), m. 103–4° (from EtOH), only XV, and oily XVI. Treating the dichlorides with a 30% soln. of Me_3NH in MeOH at room temp., heating the mixt. 1–5 hrs. at 100° in an autoclave, evapg. the solvent, alkalinizing the residue with NaOH, and extg. with Et_2O or C_6H_6 yielded: 40% XVII, $b_{0.4}$ 142–5° [*dimethiodide*, m. 219–20° (from EtOH-Et_2O)]; XIVa gave 39% XVII, $b_{0.4}$ 147–8° [*dimethiodide*, m. 177–8°]; 70% XVIII, $b_{0.4}$ 170–6° [*di-HCl salt*, m. 275–0° (from EtOH-Me_2CO); *dimethiodide*, m. 227–8° (from aq. EtOH), also prepd. by refluxing VIII with MeI, NaOH, and MeOH 4 hrs.]; and 51% XIX, $b_{0.4}$ 198–203°, $b_{0.4}$ 190° [*dimethiodide*, m. 182° (from EtOH)].

M. Hudlický

2/2

APPROVED FOR RELEASE: 09/19/2001 CIA-RDP86-00513R001343320011-3"