evaporation of the ether. By procedures previously described, *viz.*, co-chromatography with added methyl gallate and gallic acid, the identity of (a) and (b) as methyl gallate and gallic acid, respectively, was established.

Hydrolysis with Aqueous Sodium Bisulfite.—A solution of tannin B (1.0 g.) and sodium bisulfite (2.0 g.) in water (20 cc.) was heated under reflux for 6 hr., cooled and filtered from a yellow crystalline sodium salt (0.34 g.). The filtrate was extracted with ether, acidified and re-extracted with ether. Two-dimensional paper chromatograms showed the presence of pyrogallol and methyl gallate in the first ether extract and gallic acid in the second ether extract. The crystalline sodium salt, suspended in warm water and treated with hydrochloric acid, gave ellagic acid, m.p. >360°, λ_{max} 366, 256 mμ in ethanol.

Tannin A.—Paper chromatograms showed the presence of the same phenolic constituents in both tannin A and B, although in different relative amounts. Tannin A gave a positive Molisch carbohydrate test and appeared to contain free carbohydrate.

Acknowledgment.—The author wishes to thank L. M. White for performing the elementary analyses.

PASADENA, CALIF.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

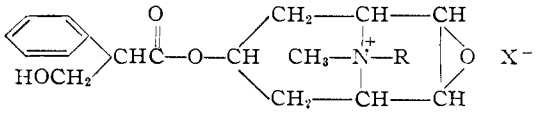
Antispasmodics. VIII. Scopolamine Derivatives

BY ROBERT BRUCE MOFFETT AND BROOKE D. ASPERGREN

RECEIVED FEBRUARY 2, 1956

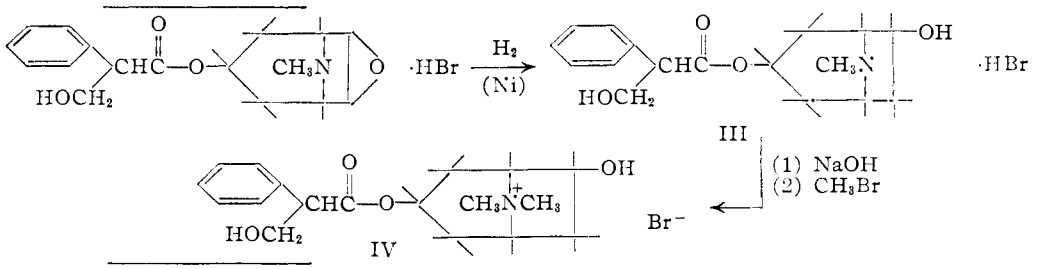
A variety of derivatives of scopolamine have been prepared and tested for their antispasmodic and gastric antisecretory activities. These include several quaternary salts (analogs of Pamine Bromide[1,2]) and a number of O-acyl esters of scopolamine and their salts. Aposcopolamine, desoxyscopolamine, 6-hydroxytropine tropate and an ester of scopoline together with their methobromides were also made and tested. Of the above, O-acetylscopolamine methobromide appears to be the most active anticholinergic, but several other O-acyl scopolamines show interesting properties. Most of these compounds are new but a few that have been previously reported are here more completely characterized.

The excellent properties of Pamine Bromide[1] as a visceral antispasmodic and gastric antisecretory agent[3] have prompted us to prepare a number of other derivatives of scopolamine. Besides the methyl bromide several other quaternary salts (I) were prepared. Some of these have been previously reported[4,5] but for the most part without analytical data.

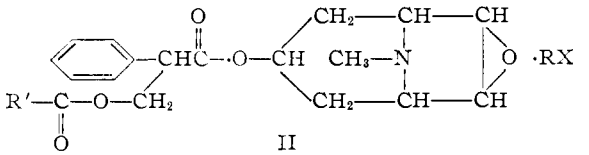


I

Pamine Bromide[1] was also prepared from radioactive (C^{14}) methyl bromide. This was used by Dr. William L. Miller[6] in studies of the metabolic disposition and excretion of Pamine in dogs.



O-Acetylscopolamine and its hydrobromide (II, R′ = CH_3, RX = HBr) were reported many years ago.[2,7] Recently an Australian patent specification[8] described this hydrobromide, giving considerably different properties from the older literature



II

but without analytical data. We have repeated the preparation and our results confirm the Australian work except that our melting point was nine degrees higher. The methyl bromide quaternary salt (II, R′ = CH_4, RX = CH_3Br) was also prepared and found to have excellent anticholinergic properties (Table I). Its clinical investigation is under way. Besides the acetate, a number of other O-esters of scopolamine salts (II) were prepared. These esters were made by the action of a large excess of the acid anhydride or the acid chloride and pyridine on scopolamine hydrobromide. In the case of the phenylurethan, scopolamine base was treated with phenyl isocyanate.

The epoxide ring of scopolamine hydrobromide has been hydrogenated by Fodor and Kovacs,[9] but they hydrolyzed the product to *dl-trans*-6-hydroxy-

(1) The Upjohn Company brand of Scopolamine Methyl Bromide (I, R = CH_3, X = Br).

(2) O. Hesse, *J. prakt. Chem.*, [ii] **64**, 353 (1901).

(3) F. E. Visscher, P. H. Seay, A. P. Tazelaar, Jr., W. Veldkamp and M. J. VanderBrook, *J. Pharmacol. Exp. Therap.*, **110**, 188 (1954); J. B. Kirsner and W. L. Palmer, *J. Am. Med. Assoc.*, **151**, 798 (1953); J. B. Kirsner, E. Levin, and W. L. Palmer, *Gastroenterology*, **26**, 852 (1954).

(4) E. Schmidt, *Arch. Pharm.*, **232**, 409 (1894).

(5) H. Wick, *Arch. exper. Path. Pharmacol.*, **213**, 485 (1951).

(6) W. L. Miller, J. J. Kruke and M. J. VanderBrook, to be published elsewhere.

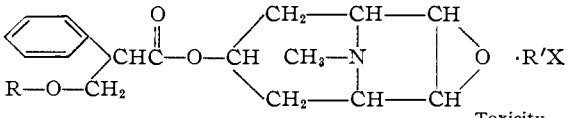
(7) E. Schmidt, *Arch. Pharm.*, **230**, 207 (1892).

(8) Australian Spec. 12181 (1952).

(9) G. Fodor and O. Kovacs, *J. Chem. Soc.*, 2341 (1953).

TABLE I

PHARMACOLOGICAL ACTIVITIES

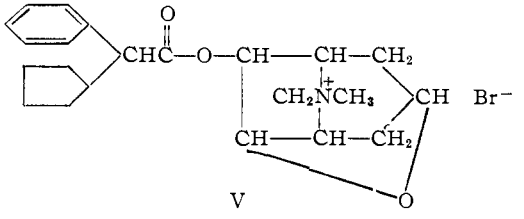


No.	R	R'X	Toxicity LD_{50}[a] (At.I.)[b]	Antispasmodic activity (At.I.)[b]	Antisecretory activity ED_{50}[c]
1	H	CH_3Br[1,2]	150	6.0	0.003
2	H	CH_3CH_2Br[4]	200	3.0	.02
3	H	$CH_2{=}CHCH_2Cl$[d]	83	1.0	.6
4	H	$CH_3(CH_2)_3I$[d]	200	0.2	.05
5	H	$HOCH_2CH_2Br$[5]	233	2.0	.5
6	H	$C_6H_5CH_2Cl$[d]	233	0.5	.5–5.0
7	H	$Br(CH_2)_6Br$[e]	5.3	0.2	.2
8	H	→O·HBr[f]	>1000	2.0	.02
9	CH_3CO	HBr[8]	533	2.0	
10	CH_3CO	CH_3Br	167	6.0	.004
11	CH_3CO	→O[g]	650	<0.1	>1.0
12	$(CH_3)_3CCO$	HCl	767	4.0	
13	$(CH_3)_3CCO$	CH_3Br	77	2.0	0.005
14	$(CH_3CH_2)_2CHCO$	HBr			
15	$(CH_3CH_2)_2CHCO$	CH_3Br			
16	$(CH_3)_2CHCH(CH_2CH_3)CO$	HBr	838	<1.0	
17	$(CH_3)_2CHCH(CH_2CH_3)CO$	CH_3Br	65	0.2	.05
18	$(CH_2)_4CHCH_2CH_2CO$	CH_3Br	167	0.3	.007
19	$CH_3CH_2OCH(CH_3)CO$	CH_3Br	200	2.0	.008
20	C_6H_5NHCO	HCl	233	0.2	
21	C_6H_5NHCO	CH_3Br	200	0.2	.05
22	Aposcopolamine (VI)	HNO_3[16]	650	<0.1	>2.0
23	Aposcopolamine	CH_3Br[h]	23	0.5	≫1.0
24	Desoxyscopolamine (VII)	Free base[17,i]	1000	0.1	>1.0
25	Desoxyscopolamine	CH_3Br[j]	30	1.0	
26	6-Hydroxytropine tropate	CH_3Br (IV)	167	3.0	0.05
27	Scopoline phenylcyclopentylacetate	CH_3Br (V)	65	0.1	Inactive

[a] The compounds were administered to mice intraperitoneally. The values are approximations with an accuracy of about +100 to −50%. They are expressed in mg./kg. [b] The antispasmodic activity was determined in Thiry-Vella dogs [O. H. Plant, *J. Pharmacol. Exp. Therap.*, 16, 311 (121)]. The results are expressed as the ratio of the activity of the compound to that of atropine sulfate (Atropine Index). [c] The gastric antisecretory activity was determined in pyloric ligation rats [F. E. Visscher, P. H. Seay, A. P. Tazelaar, Jr., W. Veldkamp and M. J. VanderBrook, *J. Pharmacol. Exp. Therap.*, 110, 188 (1954)]. It is expressed as the effective dose necessary to reduce the gastric secretion by approximately 50%. [d] The corresponding bromide has been reported by H. Wick.[5] [e] N,N-Hexamethylene bis-scopolammonium dibromide. [f] Scopolamine N-oxide hydrobromide. This was obtained as the monohydrate. It has been reported previously as the anhydrous salt [M. Polonovski and M. Polonovski, *Bull. soc. chim.*, [IV] **39**, 1147 (1926)]. [g] Scopolamine, acetate (ester) N-oxide. [h] The corresponding methiodide has been reported.[16] [i] The free base was dissolved in dilute hydrochloric acid for testing. [j] The corresponding methiodide has been reported.[17]

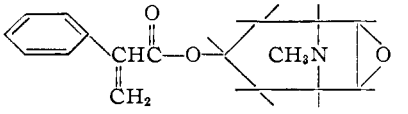
tropine without isolation of the intermediate tropic acid ester. In the present work the mixture of stereoisomeric 6-hydroxytropine tropate hydrobromide (III) was converted to the free base and then to the methobromide (IV) (Table I, No. 26).

Scopoline, the rearranged hydrolysis product of scopolamine, was esterified with phenylcyclopentylacetyl chloride and the resulting ester converted to its methyl bromide salt V. It had very little anticholinergic activity (Table I, No. 27).

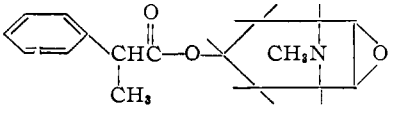


V

Besides the new derivatives of scopolamine, a few known compounds including aposcopolamine (VI) and desoxyscopolamine (VII) have been included in Table I since their anticholinergic activity has not been reported previously.



VI



VII

Acknowledgments.—The authors wish to express their appreciation to Dr. Richard V. Heinzelman for guidance in this work. The biological activities were obtained by Dr. Milton J. VanderBrook, Dr. Frank E. Visscher, Mr. A. P. Tazelaar, Jr., Dr.

TABLE II

SCOPOLAMINE QUATERNARY SALTS

No. table I	Yield, %	M.p., °C.[10]	$[\alpha]^{22}D^{a,10}$	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found[10]	Hydrogen Calcd.	Hydrogen Found[10]	Halogen Calcd.	Halogen Found[10]
1	94	218–220	−24°	$C_{15}H_{24}BrNO_4$	54.28	54.36	6.07	6.07	Br, 20.07	Br, 20.10
2	38	190–192	−23°	$C_{19}H_{26}BrNO_4$	55.34	55.59	6.36	6.35	Br, 19.43	Br, 19.61
3	38	154–156[b]	−21°	$C_{26}H_{26}ClNO_4$	63.23	63.44	6.90	7.02	Cl, 9.35	Cl, 9.28
4	37	132–135[c]	−18°	$C_{21}H_{30}INO_4$	51.75	51.77	6.20	6.01	I, 26.04	I, 25.83
5	62	186.5–188.5	−21°	$C_{19}H_{26}BrNO_5$	53.27	53.42	6.12	6.21	Br, 18.68	Br, 18.51
6	36	156–158	−22°	$C_{24}H_{28}ClNO_4$	67.04	67.01	6.56	6.69	Cl, 8.25	Cl, 8.00
7	10	214–215[d]	−16°	$C_{40}H_{54}Br_2N_2O_8$	56.47	56.46	6.39	6.71	Br, 18.79	Br, 18.36

[a] About 1–2% concentration in water. [b] Recrystallized from isopropyl alcohol. [c] Recrystallized from ethanol–ether. *Anal.* Calcd.: N, 2.87. Found: N, 2.63. [d] The reaction mixture was heated under reflux for 48 hr. The product was recrystallized from ethanol–ether.

Patrick H. Seay, Mr. William Veldkamp, Mr. Orlo F. Swoap and associates of the Department of Pharmacology to whom the authors wish to express their thanks.

Experimental[10]

Quaternary Salts of Scopolamine (No. 1–7).—To a solution of 43.8 g. (0.1 mole) of scopolamine hydrobromide trihydrate (U. S. P.) in 130 ml. of ice-water was added a cold solution of 12.7 g. (0.12 mole) of sodium carbonate in 150 ml. of water. The mixture was extracted with 200 ml. of benzene in three portions. The benzene solution was washed with water and then with saturated salt solution. A portion of the benzene solution was distilled at room temperature under reduced pressure to remove traces of water. If a solvent other than benzene was to be used for the quaternization all the benzene was removed under reduced pressure leaving the free base as a gummy solid.

The quaternary salts listed in Table II were prepared by adding a considerable excess of the requisite alkyl halide to the benzene solution of scopolamine base. In the case of the reaction with methyl bromide, an excellent yield was obtained by allowing the solution to stand at room temperature for 2 days, in a flask with the stopper clamped in. The product separated in crystalline form giving material of high purity, which, if desired, may be recrystallized from ethanol. Other alkyl halides reacted much less readily. In some cases it was necessary to allow the mixture to stand for 2 weeks or to heat the solution for an hour or more under reflux. Unless otherwise indicated, the salts were recrystallized from ethanol. With all radicals except methyl, two geometric isomers are possible. This may account for the low yields after recrystallization and in some cases discrepancies of the melting points with those reported in the literature. The properties of these salts are listed in Table II.

Radioactive Scopolamine Methobromide.—One millicurie of C^{14} methyl bromide (specific activity of 1.0 mc./m*M*) was received[11] in a sealed ampule with an inner break seal. The ampule was attached with a rubber connection to one arm of a T-tube containing a small magnet with which to break the seal. The second arm of the T-tube was attached to a vacuum pump through a stopcock. The third arm was attached by a ground glass joint to a 25-ml. flask. In the flask was placed a solution of 0.5 g. of scopolamine base (see above) in 4.0 ml. of methyl ethyl ketone. The flask was cooled in a Dry Ice–acetone bath and evacuated to 0.1 mm. The stopcock was closed and the seal was broken by a striking with the small magnet controlled by another magnet outside the tube. The ampule was then heated for 30 minutes in a boiling water-bath while the flask was cooled in the Dry Ice–acetone bath. While still very cold the flask was removed, stoppered and clamped. It was allowed to warm to room temperature and stand for 3 days. The nicely crystalline product was collected on a filter, washed with methyl ethyl ketone and absolute ether and dried at 100° (0.1 mm.). The yield was 0.372 g. (90.5%) of Pamine Bromide[1] with a specific activity of about 4×10^6 counts per min. per mg.

(10) Unless otherwise mentioned, melting points were taken in capillary tubes and are uncorrected. Analyses and optical rotations are by Mr. William A. Struck and staff of our analytical chemistry laboratory.

(11) The radioactive methyl bromide was obtained from Tracerlabs, Boston, Mass.

Scopolamine N-Oxide Hydrobromide Monohydrate (No. 8).—Scopolamine base from 43.0 g. (0.1 mole) of scopolamine hydrobromide trihydrate was dissolved in 265 ml. of 95% ethanol and treated with 20 ml. of 30% hydrogen peroxide solution. After standing at room temperature for 4 days a small amount of platinum black was added and the mixture was thoroughly shaken for 4 hr. to decompose the excess hydrogen peroxide. The solution was filtered and acidified with 12 ml. of 48% aqueous hydrobromic acid. On standing in the refrigerator crystals separated, weight 17.4 g., m.p. 133–134° dec. An additional yield was obtained by concentration of the filtrate. Recrystallization from water raised the melting point to 138–139° dec.; $[\alpha]^{23}D$ −24° (1% in H_2O). This compound was found to be the monohydrate by the Karl Fischer water determination and elementary analysis. The Karl Fischer water determination has been found to run high on some amine oxides due to reaction between the oxide and the reagent. Scopolamine N-oxide may exist in two geometric isomers. It is not known which the present compound represents or whether it is a mixture of both.

Anal. Calcd. for $C_{17}H_{22}BrNO_5 \cdot H_2O$: C, 48.81; H, 5.78; Br, 19.11; N, 3.35; H_2O, 4.31. Found: C, 49.13; H, 5.42; Br, 18.98; N, 3.35; H_2O, 4.71.

O-Acetylscopolamine Hydrobromide[8] (No. 9).—A mixture of 50 g. of *l*-scopolamine hydrobromide trihydrate and 200 ml. of acetic anhydride was heated on a steam-bath with stirring for 1.5 hr. The starting material all dissolved during the heating and the product started to crystallize. After cooling, the crystals were collected, washed with acetic acid and ether and dried giving 47.9 g. (98%) of material, $[\alpha]^{23}D$ −26° (1.4% in H_2O), m.p. 197–199° (reported[8] m.p. 189.5–190°). A mixed melting point with anhydrous scopolamine hydrobromide (m.p. 199–201°) gave a large depression (mixed m.p. 175–180°).

Anal. Calcd. for $C_{19}H_{24}BrNO_5$: C, 53.53; H, 5.67; Br, 18.75. Found: C, 53.66; H, 5.68; Br, 18.37.

A run on a 1-kg. scale gave similar results.

O-Acetylscopolamine Methobromide (No. 10).—A mixture of 966 g. (2.77 moles) of the above hydrobromide with ice-water was made basic (*p*H about 9) with ice-cold sodium hydroxide and sodium carbonate and extracted twice with ether. The aqueous solution was made strongly basic with sodium hydroxide and again extracted with ether. The ether solutions were washed twice with water, then with saturated sodium chloride solution and dried over sodium sulfate. Distillation of the ether under reduced pressure below 35° gave the free base as an oil.

This oil was dissolved in 3 l. of methyl ethyl ketone, cooled to 0° and 736 g. (7.75 moles) of cold methyl bromide was added. After standing at room temperature for 3 days the crystalline product was collected, washed with methyl ethyl ketone, then with absolute ether and dried in a vacuum oven at 75° for 4 hr. The yield was 946 g. (94.6%); in a capillary tube it sintered at about 150°, resolidified and remelted at 183–190° with decomposition. On a Fisher–Johns block it sintered at 162°, resolidified and remelted at 197–200° with decomposition. A sample recrystallized from isopropyl alcohol gave silky needles having a similar decomposition point; $[\alpha]^{23}D$ −24° (0.873% in H_2O).

Anal. Calcd. for $C_{20}H_{26}BrNO_5$: C, 54.53; H, 5.95; Br, 18.15. Found: C, 54.63; H, 5.67; Br, 18.19.

O-Acetylscopolamine N-Oxide (No. 11).—O-Acetylscopolamine base, prepared as above from 42.6 g. (0.1 mole) of

O-acetylscopolamine hydrobromide was dissolved in 300 ml. of 95% ethanol and 20 ml. of 30% hydrogen peroxide was destroyed by adding an aqueous slurry of 0.2 g. of platinum-on-charcoal. The mixture was shaken for 1.5 hours, filtered and distilled to dryness below 60° under reduced pressure. The gummy residue crystallized on standing and was recrystallized from acetone giving 8.24 g. (17.8%) of white crystals, m.p. 145–146°; $[\alpha]^{23}D$ +2° (0.63% in 95% ethanol).

Anal. Calcd. for $C_{19}H_{23}NO_5$: C, 63.10; H, 6.41; N, 3.88. Found: C, 63.43; H, 6.52; N, 4.13.

O-Trimethylacetylscopolamine.—To a suspension of 38.43 g. (0.1 mole) of anhydrous scopolamine hydrobromide in 100 ml. of dry pyridine was added 18.1 g. (0.15 mole) of trimethylacetyl chloride. The mixture became warm, the solid dissolved giving a yellow solution. After about 1 hr. crystals started to separate. The mixture was allowed to stand at room temperature for 4 days and was then dissolved in ice-water, treated with 200 ml. of 10% sodium carbonate and extracted twice with ether. To the aqueous solution was added 20 ml. of 50% sodium hydroxide, and it was extracted twice again with ether. The extracts were washed with water and saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed under reduced pressure giving 43.3 g. of crude crystalline free base.

A sample of 17.6 g. of this was recrystallized from hexane giving 12 g. of nearly white crystals, m.p. 92–93°, $[\alpha]^{23}D$ −27° (0.517% in 95% ethanol). An additional yield of 2 g. was obtained from the filtrate; total yield 14 g. (equivalent to 98%).

Anal. Calcd. for $C_{22}H_{29}NO_5$: C, 68.19; H, 7.54; N, 3.62. Found: C, 68.28; H, 7.24; N, 3.69.

Hydrochloride (**No. 12**).—A solution of 6.5 g. (0.0174 mole) of the above free base in 35 ml. of ethanol was acidified with concentrated hydrochloric acid. Absolute ether was added to turbidity and on standing the hydrochloride separated, giving 6.84 g. (95%) of crystalline product, m.p. 217–218°. A sample recrystallized from absolute ethanol had the same melting point, $[\alpha]^{23}D$ −20° (1.15% in H_2O).

Anal. Calcd. for $C_{22}H_{30}ClNO_5$: C, 62.33; H, 7.13; Cl, 8.36. Found: C, 62.37; H, 7.16; Cl, 8.33.

Methobromide (**No. 13**).—To a cold solution of 25.7 g. of the crude free base in 65 ml. of methyl ethyl ketone was added about 20 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 3 days. The resulting crystalline solid was collected and recrystallized from a mixture of methanol and ethanol giving 24.05 g. (85.6% based on the scopolamine hydrobromide), m.p. 207–209° dec., $[\alpha]^{23}D$ −18° (1.082% in H_2O).

Anal. Calcd. for $C_{23}H_{32}BrNO_5$: C, 57.26; H, 6.69; Br, 16.57. Found: C, 57.26; H, 6.48; Br, 16.71.

O-(α-Ethylbutyryl)-scopolamine Hydrobromide (**No. 14**).—To a suspension of 46.0 g. (0.12 mole) of anhydrous scopolamine hydrobromide in 120 ml. of dry pyridine was added 24.5 g. (0.18 mole) of α-ethylbutyryl chloride.[12] The mixture became warm and the solid dissolved giving a red solution. After standing at room temperature for 2 days, most of the solvent was removed by distillation under reduced pressure below 40°. The residue was treated with ice-water and 300 ml. of 10% aqueous sodium carbonate solution and was extracted twice with ether. The aqueous solution was then made strongly basic with sodium hydroxide solution and again extracted with ether. The ether extracts were washed with water, saturated sodium chloride solution and dried over sodium sulfate. Distillation of the ether under reduced pressure left 58.8 g. of crude free base as a brown oil.

An ethanolic solution of 38 g. of this base was acidified with hydrobromic acid and distilled nearly to dryness under reduced pressure below 40°. By fractional crystallization from acetone, isopropyl alcohol plus ether and then again from acetone, the product was separated from the less soluble pyridine hydrobromide. The O-(α-ethylbutyryl)-scopolamine hydrobromide tended to separate as a gelatinous solid, but it was finally crystallized from warm acetone solution by slow cooling with constant shaking. It was collected on a filter and dried in a vacuum desiccator giving 4.7 g. of white solid, m.p. 171–173.5°, $[\alpha]^{23}D$ −19° (1% in H_2O).

(12) M. Freund and P. Herrmann, *Ber.*, **23**, 189 (1890).

Anal. Calcd. for $C_{23}H_{32}BrNO_5$: C, 57.02; H, 6.66; Br, 16.50. Found: C, 56.64; H, 6.79; Br, 16.55.

Methobromide (**No. 15**).—To a cold solution of 20.0 g. of the crude free base in 50 ml. of methyl ethyl ketone was added 20 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 40 hr. The resulting precipitate was collected and recrystallized from 200 ml. of absolute ethanol giving 18.3 g. (90.4% over-all yield) of white crystals, m.p. 177–179°, $[\alpha]^{23}D$ −19° (1% in H_2O).

Anal. Calcd. for $C_{24}H_{34}BrNO_5$: C, 58.06; H, 6.90; Br, 16.10. Found: C, 58.00; H, 6.25; Br, 15.97.

O-(2-Ethyl-3-methylbutyryl)-scopolamine Hydrobromide (**No. 16**).—To a suspension of 19.22 g. (0.05 mole) of anhydrous scopolamine hydrobromide in 50 ml. of dry pyridine was added 10.2 g. (0.0687 mole) of 2-ethyl-3-methylbutyryl chloride.[13] The mixture became warm and red colored and the solid dissolved. After standing at room temperature for 2 days, the mixture was worked up as described above giving 25 g. of dark brown oily free base.

To a solution of 10 g. of this crude free base in 20 ml. of absolute ethanol was added a slight excess of 48% aqueous hydrogen bromide. The solution was diluted with ether and the crude hydrobromide separated as a yellow solid; weight 10.65 g., m.p. 158–163°. This was recrystallized from about 40 ml. of isopropyl alcohol (with Darco), giving 8.57 g. (86.1% over-all yield) of nearly white crystals, m.p. 179–181°. A second recrystallization from about 100 ml. of methyl ethyl ketone gave 7.59 g. of white crystals, m.p. 182–183°, $[\alpha]D$ −19° (1.101% in H_2O).

Anal. Calcd. for $C_{24}H_{34}BrNO_5$: C, 58.06; H, 6.90; Br, 16.10. Found: C, 58.31; H, 7.18; Br, 15.83.

Methobromide (**No. 17**).—To a cold solution of 15 g. of the above crude free base in 35 ml. of methyl ethyl ketone was added 18 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 3 days. The resulting crystals were collected, washed with methyl ethyl ketone and ether and dried giving 17.55 g. of tan colored crystals, m.p. 168–171° dec. This was recrystallized from about 100 ml. of absolute ethanol giving 13.66 g. (89.1% over-all yield) of white crystals, m.p. 182.5–184° dec.; $[\alpha]D$ −17° (0.994% in H_2O).

Anal. Calcd. for $C_{25}H_{36}BrNO_5$: C, 58.82; H, 7.11; Br, 15.66. Found: C, 58.85; H, 6.83; Br, 15.63.

O-(β-Cyclopentylpropionyl)-scopolamine Methobromide (**No. 18**).—To a suspension of 38.43 g. (0.1 mole) of anhydrous scopolamine hydrobromide in 100 ml. of dry pyridine was added 24.05 g. (0.15 mole) of β-cyclopentylpropionyl chloride.[14] The solid soon dissolved giving a red solution. After standing at room temperature for 4 days, the solution was worked up as described above giving 43.3 g. of brown oil.

To a cold solution of 25 g. of this crude free base in 75 ml. of methyl ethyl ketone was added 20 g. of cold methyl bromide. The flask was stoppered and clamped and allowed to stand at room temperature for 2 days. A gelatinous solid separated. To this was added 300 ml. of dioxane and after shaking, warming and standing, the solid was collected. The crude gummy solid was dissolved in a mixture of ethanol and methyl ethyl ketone and concentrated under reduced pressure until a solid started to separate. After cooling in the refrigerator the solid was collected giving 15.8 g. of light tan material, m.p. 164–166°. This was crystallized from 200 ml. of isopropyl alcohol giving 13.4 g. (45% over-all yield) of nearly white crystals, m.p. 163–164°, resolidifying and remelting at 170–173°; $[\alpha]^{23}D$ −23° (1.021% in H_2O).

Anal. Calcd. for $C_{26}H_{36}BrNO_5$: C, 59.77; H, 6.95; Br, 15.30. Found: C, 59.95; H, 6.98; Br, 15.26.

O-(α-Ethoxypropionyl)-scopolamine Methobromide (**No. 19**).—To a suspension of 38.43 g. (0.1 mole) of anhydrous scopolamine hydrobromide in 100 ml. of dry pyridine was added 20.5 g. (0.15 mole) of α-ethoxypropionyl chloride.[15] The mixture became warm, dark, and the solid soon dis-

(13) Prepared by Dr. George Slomp in these laboratories by the action of thionyl chloride on 2-ethyl-3-methylbutyric acid [A. W. Crossley and H. R. LeSueur, *J. Chem. Soc.*, **77**, 83 (1900)]. To be published elsewhere.

(14) J. W. Barrett, A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 1065 (1935).

(15) A. Demolis and G. A. R. Kon, *J. Chem. Soc.*, 2283 (1932).

solved. After standing at room temperature for 16 hr., the solution was worked up as described above giving 42.1 g. of brown oil.

To a cold solution of 20 g. of this crude free base in 50 ml. of methyl ethyl ketone was added about 10 g. of methyl bromide. The flask was stoppered and clamped and allowed to stand at room temperature for 3 days. The resulting tan solid was collected on a filter, washed with methyl ethyl ketone and crystallized from a mixture of isopropyl and ethyl alcohols; yield 18.54 g. (78.2%), m.p. 163–164°, resolidifying and remelting at 170–171°. This was recrystallized from absolute ethanol and dried at 100° (0.1 mm.) for 4.5 hours giving 16.7 g. of white crystals, m.p. 167–168° resolidifying and remelting at 172–173°, $[\alpha]^{23}D$ (1.061% in H_2O).

Anal. Calcd. for $C_{23}H_{32}BrNO_6$: C, 55.42; H, 6.47; Br, 16.04. Found: C, 55.68; H, 6.37; Br, 16.15.

Phenylurethan of Scopolamine Hydrochloride (No. 20).—A dry solution of scopolamine base in 200 ml. of benzene was prepared as described above under quaternary salts of scopolamine. To this was added 24 g. (0.2 mole) of phenyl isocyanate. The solution became warm and was cooled to room temperature and allowed to stand for 19 hr. Then 25 ml. of absolute ethanol was added and after standing for 4 hours, 16 ml. of 6.65 *N* ethanolic hydrogen chloride was added. The addition of a little absolute ether caused crystallization on standing. The product was collected giving 45.5 g. (99%) of white crystals, m.p. 187–192° dec. This was recrystallized again from absolute ethanol; m.p. 196.5–198° dec.

Anal. Calcd. for $C_{24}H_{27}ClN_2O_5$: C, 62.81; H, 5.93; N, 6.10; Cl, 7.73. Found: C, 63.00; H, 6.05; N, 6.16; Cl, 7.72.

Methobromide (No. 21).—To a cold aqueous solution of 27.5 g. (0.06 mole) of this hydrochloride was added 110 ml. of 10% sodium carbonate and the mixture was extracted twice with ether. Then 20 ml. of 20% sodium hydroxide was added to the aqueous solution, and it was again extracted twice with ether. The ether solutions were washed with water, saturated salt solution and dried over sodium sulfate. The ether was removed by distillation and the residual gummy free base was dissolved in 50 ml. of methyl ethyl ketone. The solution was cooled, 35 g. of cold methyl bromide was added and the flask was stoppered and clamped. After standing at room temperature for 2 days the crystalline product was collected; weight 30.62 g. (98.7%), m.p. 200.5–201.5° dec., $[\alpha]^{23}D$ −18° (0.531% in H_2O). Recrystallization from 400 ml. of 95% ethanol did not raise the melting point.

Anal. Calcd. for $C_{25}H_{29}BrN_2O_5$: C, 58.03; H, 5.65; Br, 15.45. Found: C, 57.87; H, 5.70; Br, 15.39.

Scopolamine Perchlorate.—To a slightly warm concentrated aqueous solution of scopolamine hydrobromide was added a slight excess of perchloric acid. Crystals soon separated and after cooling were collected and recrystallized from water giving prisms, m.p. 213–216°.

Anal. Calcd. for $C_{17}H_{22}ClNO_8$: C, 50.56; H, 5.49; N, 3.47. Found: C, 50.61; H, 5.47; N, 3.22.

Aposcopolamine.[16]—To 43.8 g. (0.1 mole) of scopolamine hydrobromide trihydrate was added 100 ml. of thionyl chloride. Gas was evolved and the solution became warm. The orange-yellow solution was allowed to stand for 1.5 hr. and then heated at 45–60° for 1 hr. It was then distilled to dryness under reduced pressure below 50°. Benzene was added and removed under reduced pressure. The resulting glassy mass was dissolved in ice-water, extracted twice with ether and made basic with sodium carbonate. The mixture was repeatedly extracted with ether and the ether solutions were washed with ice-water, then with saturated salt solution. On standing overnight some gummy oil had separated. The mixture was distilled on a steam-bath at atmospheric pressure until the ether was off and then heated for 30 minutes longer. The residue was dissolved in water, a few drops of hydrogen chloride were added and it was extracted with ether. The aqueous solution was made basic with cold sodium carbonate solution and extracted three times with ether (total volume about 800 ml.). The ether solution was washed with water, then with saturated salt solution and dried over sodium sulfate. The ether was removed and the residue was crystallized from 175 ml. of hexane giving 28.29 g. (99%) of white crystalline product, m.p. 95–98.5°.

Methobromide (No. 23).—A solution of 7.13 g. (0.025 mole) of aposcopolamine in 50 ml. of benzene was cooled to near the freezing point and an excess of cold methyl bromide was added. The flask was stoppered, clamped and allowed to stand at room temperature for 2 days. The crystalline precipitate was then collected, dried and recrystallized from absolute ethanol giving 2.63 g. of white crystals, m.p. 215–219°.

Anal. Calcd. for $C_{18}H_{22}BrNO_4$: C, 56.85; H, 5.83; Br, 21.02. Found: C, 57.44, 56.90; H, 5.66, 5.79; Br, 21.23.

Desoxyscopolamine[17] **(No. 24).**—A solution of 14.3 g. (0.05 mole) of aposcopolamine in 50 ml. of glacial acetic acid was hydrogenated with 0.2 g. of PtO_2 at 30 pounds pressure and room temperature. The theoretical amount of hydrogen was absorbed in about 30 minutes. After filtering, the solution was distilled nearly to dryness under reduced pressure below 60°. The oily residue was dissolved in water, cooled and made basic with cold sodium hydroxide solution. The free base was extracted with ether, washed with water, then with salt solution and dried over sodium sulfate. On removal of the ether, the free base crystallized, m.p. 73–76°. This was recrystallized from hexane, giving 8.36 g. of white crystals, m.p. 78–80°. By concentrating the filtrate and cooling an additional 3.94 g. was obtained, m.p. 73–77°; total yield 12.30 g. (85.7%).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.98; H, 7.48; N, 4.96.

Methobromide (No. 25).—To a cold filtered solution of 6.18 g. (0.0215 mole) of desoxyscopolamine in 50 ml. of benzene was added 10 ml. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 3 days. The resulting crystalline precipitate was collected, washed with benzene and absolute ether and dried; weight 6.45 g. (78.4%), m.p. 210–216°. This was recrystallized twice from isopropyl alcohol giving white crystals, m.p. 213–214° dec.

Anal. Calcd. for $C_{18}H_{24}BrNO_3$: C, 56.55; H, 6.33; Br, 20.91; N, 3.66. Found: C, 56.78; H, 6.32; Br, 20.60; N, 3.82.

6-Hydroxytropine Tropate.—A solution of 43.83 g. (0.1 mole) of scopolamine hydrobromide trihydrate in 200 ml. of water was hydrogenated at 60 pounds and 70° with 50 g. of wet Raney nickel catalyst. After about 3 hours the theoretical amount of hydrogen had been absorbed and the uptake stopped. The solution was filtered and distilled to dryness below 60° under reduced pressure giving a colorless glassy residue. The infrared spectrum on this crude hydrobromide indicated the expected groups. An aqueous solution of 15 g. of this crude hydrobromide was treated with 50 ml. of 10% sodium carbonate and extracted twice with methylene chloride. The extract was washed with saturated salt solution and dried over sodium sulfate. The solvent was removed below 45° under reduced pressure giving a gum. This crystallized from methyl ethyl ketone on standing in the refrigerator giving 3.34 g., m.p. 86–91°. A second recrystallization raised the melting point to 92–95.5° (with some sintering below the m.p.). All fractions may be mixtures of stereoisomers.

Methobromide (No. 26).—Free base was liberated from the crude hydrobromide as described above and dissolved in 100 ml. of methyl ethyl ketone. After cooling, about 13 g. of cold methyl bromide was added. The flask was stoppered, clamped and allowed to stand at room temperature for 2 days. The resulting solid was collected and dried; weight 22.6 g., m.p. 154–160°, $[\alpha]^{23}D$ −19° (0.85% in H_2O).

Anal. Calcd. for $C_{18}H_{26}BrNO_4$: Br, 19.97. Found: Br, 20.04.

β,6-Diacetate of 6-Hydroxytropine Tropate Hydrobromide.—To crude 6-hydroxytropine tropate hydrobromide,

(16) H. King, *J. Chem. Soc.*, **115**, 974 (1919); R. Willstätter and E. Hug, *Z. physiol. Chem.*, **79**, 146 (1912); German Patent, 247,819 (1911), *Chem. Zentr.*, **83, II**, 211 (1912).

(17) K. Hess and O. Wohl [*Ber.*, **55**, 1979 (1922)] report this compound, m.p. 69°.

prepared as above, was added 250 ml. of acetic anhydride. The mixture was heated, with stirring, on a steam-bath for 1.25 hours and allowed to stand at room temperature overnight. The solution was filtered and concentrated to small volumes below 60° under reduced pressure. The addition of absolute ether precipitated a gum. On long standing the gum crystallized poorly. Acetone was added and after standing in the refrigerator 13.3 g. of a white solid was obtained; m.p. 135–142°. This was dissolved in hot methyl ethyl ketone, filtered after a small amount of the first precipitate had separated and cooled. A yield of 6.53 g. of white solid, m.p. 143–146°, was obtained; $[\alpha]^{23}D$ −8° (2% in H_2O).

Anal. Calcd. for $C_{21}H_{28}BrNO_8$: C, 53.63; H, 6.00; Br, 17.00. Found: C, 53.36; H, 6.11; Br, 17.19.

Scopoline Phenylcyclopentylacetate.—A mixture of 7.0 g. (0.032 mole) of scopoline nitrate and a solution of 4 g. of sodium hydroxide in 5 ml. of water was extracted with 50 ml. of benzene. The benzene solution of the scopoline free base was dried over potassium carbonate and distilled to about 12 ml. Then 10 ml. of dry pyridine and 7.85 g. (0.035 mole) of phenylcyclopentylacetyl chloride[18] were added. After standing overnight at room temperature dilute sodium hydroxide solution was added. The benzene layer was washed with water and dried over sodium sulfate. The solvent was removed and the product was distilled under reduced pressure giving 4.4 g. (40%) of oily free base, b.p. 189° (0.03 mm.), $n^{23}D$ 1.5372.

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.86; H, 7.97; N, 4.10. Found: C, 74.35; H, 8.06; N, 3.77.

Methobromide (No. 27).—To a cold solution of 2.0 g. (0.006 mole) of this free base in 50 ml. of benzene was added a large excess of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature overnight. The white crystalline product was collected and dried; yield 2.2 g. (85%), m.p. 210–212°.

Anal. Calcd. for $C_{22}H_{30}BrNO_3$: C, 60.55; H, 6.93; Br, 18.31; N, 3.21. Found: C, 60.99; H, 7.12; Br, 18.00; N, 3.05.

(18) H. G. Kolloff, J. H. Hunter and R. B. Moffett, THIS JOURNAL, **72**, 1650 (1950).

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS AND COMPANY]

Synthetic Amebicides. I. Heterocyclic 2,2-Dichloro-N-(2-hydroxyethyl)-N-substituted Acetamides[1]

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Various heterocyclic 2,2-dichloro-N-(2-hydroxyethyl)-N-substituted acetamides containing the 2-, 3- and 4-pyridyl, 4-quinolyl, 7-chloro-4-quinolyl, 6-methoxy-2-methyl-4-quinolyl, 6-chloro-2-methoxy-9-acridinyl and 7-benz[c]acridinyl nuclei have been prepared by dichloroacetylation of the corresponding heterocyclic N-(2-hydroxyethyl)-amines. When tested against *Endamoeba histolytica in vitro* and against experimentally induced intestinal amebiasis in rats, several of these compounds were found to possess high activity.

Recently, several publications have appeared in the literature regarding the antiamebic activity of haloacetamides,[2–5] with particular reference to 2,2-dichloro-N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-acetamide (I) and related compounds. Further, biological studies conducted in these laboratories indicate that antiamebic activity among haloacetamide derivatives is not confined to compounds of general type I, but is widespread among diverse chemical types.[6] Although compound I possesses good activity against spontaneous *Endamoeba criceti* infections in hamsters[2,5] and against experimentally induced *Endamoeba histolytica* infections in rats,[7] it is ineffective against *E. histolytica*-induced amebic hepatitis in hamsters and against amebic dysentery in dogs.[7] In view of the observed activity of amodiaquin (Camoquin[8]) (IIa), chloroquine (IIb) and quinacrine (III) against experimental amebic hepatitis[9] and against hepatic amebiasis in man, it was of interest to prepare certain related dihaloacetamide derivatives (Vb, VIa and VII) containing the 7-chloro-4-quinolyl and 6-chloro-2-methoxy-9-acridinyl nuclei. This work was also extended to include other quinoline derivatives (Va and VIb), as well as certain pyridine (IVa through c) and benz[c]acridine (VIIIa and b) analogs.

2,2-Dichloro-N-(7-chloro-4-quinolylmethyl)-N-(2-hydroxyethyl)-acetamide (Vb) was prepared by acylation of 2-(7-chloro-4-quinolylmethylamino)-ethanol[10] with dichloroacetyl chloride in dimethylformamide; the related 2,2-dichloro-N-(2-hydroxyethyl)-N-(4-quinolylmethyl)-acetamide (Va) and 2,2-dichloro-N-(2-hydroxyethyl)-N-(3- and 4-pyridylmethyl)-acetamides (IVb and c) (Table II) were synthesized by treating the appropriate 2-(pyridyl or quinolylmethylamino)-ethanol (Table I) with methyl dichloroacetate in ethylene dichloride. Although compounds Va and IVb and c were isolated by the latter procedure as glistening colorless crystals, the product believed to be the dichloroacetamide (IVa) derived from 2-(2-pyridylmethylamino)-ethanol could be obtained only as an amber-colored gum. Numerous attempts to crystallize IVa from a variety of organic solvents failed to yield a solid product, as did several variations in reaction conditions. However, the crude gum showed a characteristic amide absorption in the infrared at 6.00 μ, indicating that the desired dichloroacetamide probably had been formed.

The intermediate 2-(pyridyl or quinolylmethyl-

(1) Presented before the Division of Medicinal Chemistry at the 129th National A.C.S. Meeting, April, 1956, in Dallas, Texas.

(2) A. R. Surrey, THIS JOURNAL, **76**, 2214 (1954).

(3) A. R. Surrey and M. K. Rukwid, *ibid.*, **77**, 3798 (1955).

(4) A. R. Surrey, G. Y. Lesher and S. O. Winthrop, *ibid.*, **77**, 5406 (1955).

(5) E. W. Dennis and D. A. Berberian, *Antibiotics and Chemotherapy*, **4**, 554 (1954).

(6) P. E. Thompson and E. F. Elslager, unpublished results.

(7) P. E. Thompson, unpublished results.

(8) Parke, Davis and Company trade name for 4-(7-chloro-4-quinolylamino)-α-diethylamino-o-cresol, dihydrochloride.

(9) For a description of test methods, see P. E. Thompson and J. W. Reinertson, *Am. J. Trop. Med.*, **31**, 707 (1951).

(10) K. N. Campbell, A. H. Sommers, J. F. Kerwin and B. K. Campbell, THIS JOURNAL, **68**, 1851 (1946).