zations from Skellysolve A, melted at 57–58°, 0.70 g. (70%). The melting point reported by Ochiai and Yanai[1] was 57–58°.

Reduction of Dimethylstyrylpyrimidine.—A solution of 3.0 g. (0.012 mole) of the dimethylstyrylpyrimidine hydrochloride and 200 ml. of ethanol was catalytically reduced with 47 lb./sq. in. of hydrogen using a 5% palladium-on-carbon catalyst. The solution was then filtered and the solvent removed *in vacuo*. The dimethyl-β-(phenylethyl)-pyrimidine hydrochloride, after three recrystallizations from methanol–ethyl acetate solutions, melted at 185–186°, 1.9 g. (63%). A mixed melting point with the 2,6-dimethyl-4-(β-phenylethyl)-pyrimidine hydrochloride prepared from 2,6-dimethyl-4-pyrimidylmethyllithium and benzyl bromide melted at 185–186°—no depression of melting point.

4-Acetonyl-2,6-dimethylpyrimidine Oxime.—This compound was prepared using a procedure similar to that of Bachmann and Boatner.[9] In a 300-ml. flask fitted with a reflux condenser were placed 12.1 g. (0.074 mole) of 4-acetonyl-2,6-dimethylpyrimidine, 12.1 g. (0.174 mole) of hydroxylamine hydrochloride, 50 ml. of dry pyridine and 50 ml. of absolute ethanol. This mixture was refluxed for three hours, then the solvents removed *in vacuo* and the residue dissolved in a solution of nine parts of acetone and one part of ethanol. This solution was then treated with anhydrous hydrogen chloride which precipitated the insoluble 4-acetonyl-2,6-dimethylpyrimidine oxime dihydrochloride. The product, after three recrystallizations from methanol–ethyl acetate solutions, melted at 172–173°, 9.0 g. (47%).

Anal. Calcd. for $C_9H_{13}N_3O\cdot 2HCl$: C, 42.87; H, 5.96; N, 16.67; Cl, 28.12. Found: C, 42.75; H, 5.70; N, 16.27; Cl, 27.69.

2,6-Dimethyl-4-phenacylpyrimidine Oxime.—This compound was prepared using the same procedure of Bachmann and Boatner.[9] The mixture of 22.5 g. (0.32 mole) of 2,6-dimethyl-4-phenacylpyrimidine, 22.5 g. (0.68 mole) of hydroxylamine hydrochloride, 110 ml. of dry pyridine and 110 ml. of absolute ethanol gave the desired 2,6-dimethyl-4-phenacylpyrimidine oxime which was isolated as the hydrochloride salt. Its melting point, after recrystallization from methanol–ethyl acetate, was 222–223°, 15.0 g. (54%).

Anal. Calcd. for $C_{14}H_{15}N_3O\cdot HCl$: C, 60.54; H, 5.81; N, 15.12; Cl, 12.75. Found: C, 60.81; H, 5.97; N, 15.03; Cl, 12.46.

4-(β-Aminopropyl)-2,6-dimethylpyrimidine.—A mixture of 5.7 g. (0.042 mole) of 4-acetonyl-2,6-dimethylpyrimidine oxime dihydrochloride, 200 ml. of absolute ethanol and 2.0 g. of Raney nickel was reduced under 50 lb. of hydrogen for 36 hours. The solution was filtered and the solvent removed *in vacuo* to give a solid residue. This residue was dissolved in water, washed with ether and then made alkaline with 50% sodium hydroxide to yield a light yellow oil which was taken up in ether, dried over anhydrous magnesium sulfate and then treated with maleic acid to form the maleate salt. The 4-(β-aminopropyl)-2,6-dimethylpyrimidine maleate, recrystallized from methanol–ethyl acetate, melted at 130–131°, 2.0 g. (18%).

Anal. Calcd. for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.45; H, 7.13; N, 14.83.

4-(β-Aminophenylethyl)-2,6-dimethylpyrimidine.—Using the identical procedure that was used to prepare the 4-(β-aminopropyl) derivative, 3.15 g. (0.0114 mole) of 2,6-dimethyl-4-phenacylpyrimidine oxime hydrochloride was reduced to yield the desired 4-(β-aminophenylethyl)-2,6-dimethylpyrimidine which was isolated as the maleate salt also. After two recrystallizations from methanol–ethyl acetate, the product melted at 170–171° dec., 1.0 g. (25%).

Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.17; N, 12.24. Found: C, 63.14; H, 5.79; N, 12.20.

PHILADELPHIA, PENNSYLVANIA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. VI. Pyrrolidylalkyl Esters and their Quaternary Salts[1]

BY ROBERT BRUCE MOFFETT, JOHN L. WHITE, BROOKE D. ASPERGREN AND FRANK E. VISSCHER

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Twenty-five new hydrochlorides and fourteen new quaternary salts of pyrrolidyl and substituted pyrrolidylalkyl esters were prepared. Their antispasmodic activities are reported, and some of the quaternary salts are among the most active known. A number also were tested for gastric antisecretory activity and four were found to be exceptionally active.

The high antispasmodic activity of some of the esters of methyl substituted pyrrolidylethanol, reported in paper V[2] of this series, prompted us to expand this series. Thus a number of new esters of 2-(2,2-dimethyl-1-pyrrolidyl)-ethanol, and one ester of 2-(2,2-dimethyl-1-pyrrolidyl)-propanol were prepared. In addition a series of pyrrolidylethyl esters substituted with three methyl groups, with an ethyl group, and with both methyl and ethyl groups were made.

The hydrochlorides of these basic esters were tested for antispasmodic activity (Table I). In all cases they were less potent than some of the compounds previously reported.[2]

In recent years a number of quaternary salts of anticholinergic compounds have been successfully introduced for the treatment of peptic ulcer and other ailments of the gastro-intestinal tract. It has long been known that quaternization of this type of compound generally increases its antispasmodic activity but this is usually offset by increase in toxicity. We have prepared quaternary salts of a number of the pyrrolidylalkyl esters herein or previously reported. In most cases no increase in antispasmodic therapeutic ratio was noted. However, with the most active compounds (*e.g.*, methyl bromide salts of nos. 17 and 18, Table I) a considerable increase in therapeutic ratio was observed.

Since the secretion of acid gastric juice is believed to have a deleterious effect on peptic ulcers it is desirable to test anticholinergic compounds for their antisecretory activity. Some of the compounds included in this study were so tested, and four of them (the quaternary salts of nos. 1, 4, 17 and 18, Table I) had an exceptionally high order of activity. In general it seems that the quaternary salts give a much more favorable antisecretory therapeutic ratio than the hydrochlorides.

The free basic esters (Table II) and their hydrochlorides (Table III) were prepared by methods

(1) Reported in part before the Division of Medicinal Chemistry, A.C.S. at Los Angeles, California, March, 1953, Abstracts, p. 8L.

(2) R. B. Moffett and J. H. Hunter, THIS JOURNAL, **74**, 1710 (1952).

TABLE I

PHARMACOLOGICAL ACTIVITIES

No. of base	Formula of base	Salt	Toxicity LD_{50} (mg./kg.)[a]	Antispasmodic activity (At. I.)[b]	Antisecretory activity ED_{50} (mg./kg.)[c]
1	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NCH_2CH_2CH_2CH_2$	$(CH_3)_2CHBr$	65	0.3[d]	0.1
2	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH(CH_3)NCH_2CH_2CH_2CH_2$	CH_3Br	53	1.5	1.0
3	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NCH(CH_3)CH_2CH_2CH_2$	CH_3Br	65	2.5	0.4
4	$CH_2CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NCH(CH_3)CH_2CH_2CH_2$	CH_3Br	65	1.0	0.1
5	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2CH_2NCH(CH_3)CH_2CH_2CH_2$	CH_3Br	65	0.5	>1.0
6	$CH{=}CHCH_2CH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	CH_3Br	65	1.5	0.5
7	$CH_2CH_2CH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	CH_3Br	65	1.0[d]	1.0
8	$CH_3CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	CH_3Cl	74.[e]	0.8	0.3
8	$CH_2CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	CH_3Br	8.2[e]	0.9	0.5
9	$CH_3(CH_2)_4CH(CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	HCl	200	0.1	....
10	$CH_3(CH_2)_3CH[CH(CH_3)_2]COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	HCl	200	0.5	....
11	$CH_3CH(CH_3)CH_2CH_2CH(CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	HCl	233	0.08	....
12	$CH_3CH(CH_3)CH_2CH_2CH(CH_2CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	HCl	....	0.5	....
12	$CH_3CH(CH_3)CH_2CH_2CH(CH_2CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	CH_3Br	100	1.0	1.0
13	$[CH_3(CH_2)_4]_2CHCOOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	HCl	200	0.05	....
14	$C_6H_5CH_2CH_2CH(CH_2CH{=}CH_2)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	HCl	200	0.02	....
15	$C_6H_5CH_2CH_2CH(CH_2CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CH_2$	HCl	200	0.05	....
16	$CH_3CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH(CH_3)NC(CH_3)_2CH_2CH_2CH_2$	HCl	200	0.15	>5.0
17	$CH{=}CHCH_2CH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NCH(CH_3)CH_2CH_2CHCH_3$	CH_3Br	65	4.0	0.1
18	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NCH(CH_3)CH_2CH_2CHCH_3$	CH_3Br	65	3.0	0.1
19	$CH_3CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NCH(CH_3)CH_2CH_2CHCH_3$	CH_3Br	65	0.1[d]	0.5
20	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NC(CH_3)_2CH(CH_3)CH_2CH_3$	HCl	....	0.1	....
21	$CH_2CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH(CH_3)CH_2CH_3$	HCl	....	0.05	....
22	$CH{=}CHCH_2CH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NC(CH_3)_2CH_2CH(CH_3)CH_2$	HCl	....	0.07	....
22	$CH{=}CHCH_2CH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NC(CH_3)_2CH_2CH(CH_3)CH_2$	CH_3Br	65	0.3[d]	>2.0
23	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NC(CH_3)_2CH_2CH(CH_3)CH_2$	HCl	167	0.04	....
24	$CH_2CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH_2CH(CH_3)CH_2$	Base[f]	....	0.03	....
25	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CHCH_3$	HCl	146	0.4	....
26	$CH_3CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NC(CH_3)_2CH_2CH_2CHCH_3$	HCl	....	0.07	....
27	$CH{=}CHCH_2CH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NCH(CH_3)CH_2C(CH_3)_2CH_2$	HCl	233	0.01	....
28	$CH{=}CHCH_2CH_2CH_2CHCH(CHCH_2CH_2CH{=}CH)COOCH_2$-$CH_2NCH(CH_3)CH_2C(CH_3)_2CH_2$	HCl	....	0.01	....
29	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NCH(CH_3)CH_2C(CH_3)_2CH_2$	HCl	....	0.05	....
30	$CH_2CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NCH(CH_3)CH_2C(CH_3)_2CH_2$	HCl	....	<0.01	....
31	$CH{=}CHCH_2CH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NCH(CH_2CH_3)CH_2CH_2CH_2$	HCl	....	0.07	....
32	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NCH(CH_2CH_3)CH_2CH_2CH_2$	HCl	....	0.08	....
33	$CH_2CH_2CH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NCH(CH_2CH_3)CH_2CH_2CH_2$	HCl	....	0.03	....
34	$CH_2CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NCH(CH_2CH_3)CH_2CH_2CH_2$	HCl	....	0.07	....
35	$CH{=}CHCH_2CH_2CHCH(C_6H_5)COOCH_2CH_2NC(CH_3)(CH_2CH_3)CH_2CH_2CH_2$	HCl	....	0.01	....
36	$CH_2CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NC(CH_3)(CH_2CH_3)CH_2CH_2CH_2$	HCl	....	0.07	....
37	$CH_2CH_2CH_2CH_2CHCH(CH_2CH_2CH_3)COOCH_2CH_2NCH(CH_3)CH(CH_2CH_3)CH(CH_3)CH_3$	HCl	100	0.01	....
38	Atropine	$1/2H_2SO_4$	150	1.00	0.07

[a] Unless otherwise indicated the compounds were administered to mice intraperitoneally. The values are approximations with an accuracy of about +100% to −50%. [b] Unless otherwise indicated the antispasmodic activity was determined by the method of Magnus [*Arch. ges. Physiol.* (*Pflugers*), **102**, 123 (1904); *ibid.*, **103**, 515 (1904)] on isolated rabbit intestine stimulated with acetylcholine chloride. The results are expressed as the Atropine Index (At. I., the ratio of the activity of the compound to that of atropine sulfate). [c] The gastric antisecretory activity was determined after intravenous dosage in pyrolic ligation rats [F. E. Visscher, P. H. Seay, A. P. Tazelaar, Jr., W. Veldkamp and M. J. VanderBrook, *J. Pharmacol. Exptl. Therap.*, **110**, 118 (1954)]. It is expressed as the effective dose necessary to reduce gastric secretion by approximately 50%. [d] This antispasmodic activity was determined on Thiry-vella dogs (O. H. Plant, *J. Pharmacol. Exptl. Therap.*, **16**, 311 (1921)). The results are expressed as At. I., but this atropine index is not strictly comparable with that obtained by the Magnus technique. [e] Intravenous in mice. [f] Tested as a solution of the free base in dilute hydrochloric acid. The hydrochloride was not obtained crystalline.

TABLE II

NEW FREE BASES

No. of base (Table I)	Yield, %[a]	B.p. °C.	Mm.	$n^{25}D$	Empirical formula	Nitrogen, % Calcd.	Found[b]
9	71[c]	80	0.05	1.4510	$C_{17}H_{33}NO_2$	4.94	5.07
10	37[c]	77	.01	1.4513	$C_{17}H_{33}NO_2$	4.94	4.80
11	50[c]	80	.03	1.4500	$C_{17}H_{33}NO_2$	4.94	4.95
12	60[c]	88	.01	1.4510	$C_{18}H_{35}NO_2$	4.71	4.86
13	70[c]	102	.01	1.4532	$C_{20}H_{39}NO_2$	4.31	4.43
14	87[c]	120	.02	1.5020	$C_{21}H_{31}NO_2$	4.25	4.24
16	68	118	.07	1.4688	$C_{19}H_{35}NO_2$	4.53	4.49
20	75	142	.05	1.5160	$C_{22}H_{31}NO_2$	4.22	4.36
21	33	104	.06	1.4690	$C_{19}H_{35}NO_2$	4.52	4.60
22	76	150	.045	1.5170	$C_{23}H_{33}NO_2$	3.94	4.15
23	88	132	.02	1.5117	$C_{22}H_{31}NO_2$	4.10	4.24
24	73	96	.01	1.4650	$C_{19}H_{35}NO_2$	4.53	4.70
25	79	136	.04	1.5138	$C_{22}H_{31}NO_2$	4.10	4.43
26	86	107	.03	1.4660	$C_{19}H_{35}NO_2$	4.53	4.63
27	90	136	.01	1.5131	$C_{23}H_{33}NO_2$	3.94	3.99
28	61	128	.015	1.4932	$C_{22}H_{35}NO_2$	4.05	4.06
29	85	130	.02	1.5079	$C_{22}H_{31}NO_2$	4.10	4.14
30	80	99	.015	1.4610	$C_{19}H_{35}NO_2$	4.53	4.62
31	87	147	.02	1.5227	$C_{22}H_{31}NO_2$	4.10	4.09
32	72	132	.03	1.5179	$C_{21}H_{29}NO_2$	4.28	4.28
33	85	126	.015	1.5110	$C_{21}H_{31}NO_2$	4.25	4.23
34	61	104	.02	1.4685	$C_{18}H_{33}NO_2$	4.74	4.71
35	50	143	.03	1.5069	$C_{22}H_{31}NO_2$	4.22	4.50
36	35	110	.06	1.4675	$C_{19}H_{35}NO_2$	4.52	4.92
37	54	129	.01	1.4608	$C_{20}H_{37}NO_2$	4.33	4.29

[a] Unless indicated the yields of distilled free basic ester are based on the corresponding acid chloride. [b] Analyses by Mr. William Struck and staff of our Analytical Chemistry Laboratory. [c] Yield based on starting acid. The acid chloride was not isolated.

pyrrolidyl alcohols were described[4] in earlier communications. The quaternary salts (Table III) were made by the action of the appropriate alkyl halide on the free base. As would be expected considerable variation was encountered in the ease of reaction of various alkyl halides. Methyl bromide proved to be one of the most satisfactory. If an inert solvent is used no pressure equipment is necessary. The higher homologs sometimes react with difficulty and we have succeeded in adding isopropyl bromide only to the least hindered amines and then in poor yield.

All the compounds reported here may exist in more than one stereoisomeric form; however, no attempt has been made to separate or resolve the isomers.

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Experimental

General Preparation of Methyl Bromide Quaternary Salts.—The pure hydrochloride was converted to the free base by treating with an excess of aqueous sodium carbonate solution and extracting several times with benzene. The benzene solution was washed with water and dried by distilling part of the benzene under reduced pressure. The benzene solution, in a round-bottomed flask, was cooled to near its freezing point. A large excess of cold methyl bromide was added and the stopper was clamped in place. After standing at room temperature for several days the methyl bromide salt was collected on a filter and dried. In many cases no further purification was necessary. In such cases the crystallizing solvent in Table III is given as

TABLE III

NEW SALTS

No. of base (Table I)	Salt	Yield, %[a]	M.p., °C.[b]	Crystallizing solvent	Empirical formula	Halogen, % Calcd.	Found[c]
1	$(CH_3)_2CHBr$	<36	131–134	EtOAc	$C_{22}H_{32}BrNO_2$[d]	Br, 18.92	Br, 18.67
2	CH_3Br	62	117–119	Benzene	$C_{21}H_{30}BrNO_2$[e]	Br, 19.57	Br, 19.37
3	CH_3Br	36	150–155	EtOH + Et_2O	$C_{22}H_{32}BrNO_2$[f]	Br, 18.92	Br, 19.01
4	CH_3Br	58	153–156	EtOH + Et_2O	$C_{18}H_{34}BrNO_2$[g]	Br, 21.23	Br, 21.20
5	CH_3Br	76	162–165	Benzene	$C_{22}H_{32}BrNO_2$[h]	Br, 18.92	Br, 18.96
6	CH_3Br	78	175–178	Benzene	$C_{23}H_{34}BrNO_2$[i]	Br, 18.31	Br, 18.43
7	CH_3Br	60	184–186	EtOH + MeEtCO	$C_{22}H_{34}BrNO_2$[j]	Br, 18.83	Br, 19.52
8	CH_3Cl	22	180.5–181.5	EtOAc	$C_{19}H_{36}ClNO_2$	Cl, 10.28	Cl, 10.00
8	CH_3Br	85	206–209	MeEtCO	$C_{19}H_{36}BrNO_2$	Br, 20.51	Br, 20.63
9	HCl	77	92.5–95	EtOAc + Et_2O	$C_{17}H_{34}ClNO_2$	Cl, 11.12	Cl, 11.23
10	HCl	84	112–113	EtOAc + C_6H_{14}	$C_{17}H_{34}ClNO_2$	Cl, 11.12	Cl, 10.94
11	HCl	80	121.5–122.5	EtOAc + C_6H_{14}	$C_{17}H_{34}ClNO_2$	Cl, 11.12	Cl, 11.10
12	HCl	89	115–117	EtOAc + Et_2O	$C_{18}H_{36}ClNO_2$	Cl, 10.62	Cl, 10.65
12	CH_3Br	77	197–198	Benzene	$C_{19}H_{38}BrNO_2$[k]	Br, 20.36	Br, 20.43
13	HCl	70	129–131.5	EtOH + C_6H_{14}	$C_{20}H_{40}ClNO_2$	Cl, 9.80	Cl, 9.75
14	HCl	58	72–76	EtOAc + Et_2O	$C_{21}H_{32}ClNO_2$	Cl, 9.69	Cl, 9.70
15	HCl	83[l]	85.5–88	EtOAc + Et_2O	$C_{21}H_{34}ClNO_2$	Cl, 9.64	Cl, 9.59
16	HCl	75	108.5–110	EtOAc + C_6H_{14}	$C_{19}H_{36}ClNO_2$	Cl, 10.25	Cl, 10.24
17	CH_3Br	91	177–180	Benzene	$C_{23}H_{34}BrNO_2$[m]	Br, 18.31	Br, 18.50
18	CH_3Br	65	130–133	EtOH + MeEtCO	$C_{22}H_{32}BrNO_2$[n]	Br, 18.92	Br, 18.92

previously described.[2,3] The requisite substituted benzene. When the salt required purification it was crystallized from the solvent indicated in Table III.

2-(1-Pyrrolidyl)-ethyl Phenyl-Δ^2-cyclopentenylacetate Isopropyl Bromide.—A solution of 30 g. (0.1 mole) of free basic

(3) R. B. Moffett, J. H. Hunter and E. H. Woodruff, *J. Org. Chem.*, **15**, 1013 (1950); H. G. Kolloff, J. H. Hunter and R. B. Moffett, THIS JOURNAL, **72**, 1650 (1950); H. G. Kolloff, J. H. Hunter, E. H. Woodruff and R. B. Moffett, *ibid.*, **71**, 3988 (1949); *ibid.*, **70**, 3862 (1948).

(4) R. B. Moffett, *J. Org. Chem.*, **14**, 862 (1949); R. B. Moffett and J. L. White, *ibid.*, **17**, 407 (1952).

TABLE III (*Continued*)

No. of base (Table I)	Salt	Yield, %[a]	M.p., °C.[b]	Crystallizing solvent	Empirical formula	Halogen, % Calcd.	Found
19	CH_3Br	75	181–183	Benzene	$C_{19}H_{36}BrNO_2$[o]	Br, 20.47	Br, 19.98
20	HCl	65	120–132	EtOAc	$C_{22}H_{32}ClNO_2$	Cl, 9.35	Cl, 9.29
21	HCl	56	153–154	EtOAc	$C_{19}H_{36}ClNO_2$	Cl, 10.23	Cl, 10.25
22	HCl	81	148.5–150	MeEtCO + EtOAc	$C_{23}H_{34}ClNO_2$	Cl, 9.05	Cl, 8.89
22	CH_3Br	52	164–166	Benzene	$C_{24}H_{36}BrNO_2$[p]	Br, 17.74	Br, 17.99
23	HCl	73	153–156.5	Me-*i*-BuCO	$C_{22}H_{32}ClNO_2$	Cl, 9.38	Cl, 9.32
25	HCl	83	108–112	EtOAc	$C_{22}H_{32}ClNO_2$	Cl, 9.38	Cl, 9.48
26	HCl	41	95–97.5	EtOAc + Et_2O	$C_{19}H_{36}ClNO_2$	Cl, 10.02	Cl, 10.19
27	HCl	75	138–140	EtOAc	$C_{23}H_{34}ClNO_2$	Cl, 9.05	Cl, 8.92
28	HCl	91	137–138	EtOAc	$C_{22}H_{36}ClNO_2$	Cl, 9.28	Cl, 9.25
29	HCl	86	140–141	EtOAc	$C_{22}H_{32}ClNO_2$	Cl, 9.38	Cl, 9.34
30	HCl	89	145.5–146.5	MeEtCO + EtOAc	$C_{19}H_{36}ClNO_2$	Cl, 10.02	Cl, 10.10
31	HCl	76	146.5–149	MeEtCO	$C_{22}H_{32}ClNO_2$	Cl, 9.38	Cl, 9.38
32	HCl	81	120–125	EtOAc	$C_{21}H_{30}ClNO_2$	Cl, 9.74	Cl, 9.70
33	HCl	62	138–144	MeEtCO	$C_{21}H_{32}ClNO_2$	Cl, 9.69	Cl, 9.56
34	HCl	81	96.5–98.5	EtOAc + Et_2O	$C_{18}H_{34}ClNO_2$	Cl, 10.68	Cl, 10.59
35	HCl	73	165–167	Me_2CO	$C_{22}H_{32}ClNO_2$	Cl, 9.35	Cl, 9.37
36	HCl	21	148–150	EtOAc	$C_{19}H_{36}ClNO_2$	Cl, 10.23	Cl, 10.23
37	HCl	55	109–112	Tetrahydrofuran + C_6H_{14}	$C_{20}H_{38}ClNO_2$[q]	Cl, 9.85	Cl, 9.75

[a] The yields of the hydrochlorides are based on the distilled free bases (Table II). The yields of the quaternary salts are based on the pure hydrochlorides. [b] Melting points are uncorrected. [c] See footnote *b* Table II. [d] Calcd.: C, 62.55; H, 7.64; N, 3.32. Found: C, 62.42; H, 7.87; N, 3.58. [e] Calcd.: C, 61.76; H, 7.40; N, 3.43. Found: C, 61.47; H, 7.66; N, 3.44. [f] Calcd.: C, 62.55; H, 7.64; N, 3.32. Found: C, 61.83; H, 7.17; N, 3.32. [g] Calcd.: C, 57.44; H, 9.11; N, 3.72. Found: C, 56.96; H, 9.09; N, 3.67. [h] Calcd.: C, 62.55; H, 7.64; N, 3.32. Found: C, 62.74; H, 7.70; N, 3.51. [i] Calcd.: C, 63.29; H, 7.85; N, 3.21. Found: C, 63.47; H, 8.00; N, 3.40. [j] Calcd.: C, 62.25; H, 8.07; N, 3.30. Found: C, 62.17; H, 7.87; N, 3.44. [k] Calcd.: C, 58.15; H, 9.76; N, 3.57. Found: C, 57.99; H, 9.59; N, 3.51. [l] This compound was prepared by the low pressure hydrogenation of free base No. 14 (Table II) with PtO_2 catalyst. The reduced free base was not isolated but was converted to its hydrochloride. [m] Calcd.: C, 63.29; H, 7.85; N, 3.21. Found: C, 63.35; H, 7.69; N, 2.99. [n] Calcd.: C, 62.55; H, 7.64; N, 3.32. Found: C, 62.07; H, 7.57; N, 3.34. [o] Calcd.: C, 58.43; H, 9.30; N, 3.59. Found: C, 58.39; H, 9.51; N, 3.75. [p] Calcd.: C, 63.99; H, 8.06; N, 3.11. Found: C, 64.17; H, 7.84; N, 3.32. [q] Calcd.: N, 3.89. Found: N, 3.91.

ester in 94 ml. (1.0 mole) of isopropyl bromide was heated in a bomb at 100° for 24 hours. Addition of ether to the reaction mixture caused the separation of 15 g. (36%) of crude quaternary salt. This was recrystallized from ethyl acetate giving a product with the properties of the first compound in Table III.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. VII. Aminoethyl Esters of Substituted Glycolic and Acetic Acids

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A series of tertiary aminoethyl esters of α-substituted mandelic acids has been prepared. Also disubstituted acetic acid esters have been made from hexamethyleneaminoethanol and from several methyl substituted piperidinoethanols. Most of these compounds were less active as antispasmodic or gastric antisecretory agents than those previously reported, but a few have interesting biological properties.

For many years it has been known that aminoalkyl esters of benzilic acid are very active antispasmodics.[1] However their toxicity is usually high. The report by Blicke and Tsao[2] of a remarkably active series of esters of thienylglycolic acids kindled renewed interest in basic esters of α-hydroxy acids and a number have been reported recently. Since we have found that pyrrolidyl, and methyl substituted pyrrolidyl, ethyl esters of disubstituted acetic acids are good antispasmodic and gastric antisecretory agents[3] it seemed desirable to prepare some substituted glycolic esters of some of these amino alcohols. These basic esters were obtained as hydrochlorides and a few were also converted to their methyl bromide salts. They are listed with some of their pharmacological properties in Table I and their physical properties are given in Table II. One of these esters, 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl α-cyclopentylmandelate methyl bromide (U-0371) (No. 7 methyl bromide in Table I), had sufficiently interesting properties to warrant clinical study.

Our study of antispasmodic esters has been extended by the preparation of a number of methyl substituted piperidyl, and hexamethyleniminoethyl esters. The disubstituted acetic acids used to make these esters were those previously found to give good antispasmodics.[3] The salts of these basic

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