

TABLE III (Continued)

No. of base (Table I)	Salt	Yield, % <sup>a</sup>	M.p., °C. <sup>b</sup>	Crystallizing solvent	Empirical formula	Halogen, %	
						Calcd.	Found
19	CH <sub>3</sub> Br	75	181-183	Benzene	C <sub>19</sub> H <sub>38</sub> BrNO <sub>2</sub> <sup>o</sup>	Br, 20.47	Br, 19.98
20	HCl	65	120-132	EtOAc	C <sub>22</sub> H <sub>32</sub> ClNO <sub>2</sub>	Cl, 9.35	Cl, 9.29
21	HCl	56	153-154	EtOAc	C <sub>19</sub> H <sub>36</sub> ClNO <sub>2</sub>	Cl, 10.23	Cl, 10.25
22	HCl	81	148.5-150	MeEtCO + EtOAc	C <sub>23</sub> H <sub>34</sub> ClNO <sub>2</sub>	Cl, 9.05	Cl, 8.89
22	CH <sub>3</sub> Br	52	164-166	Benzene	C <sub>24</sub> H <sub>36</sub> BrNO <sub>2</sub> <sup>p</sup>	Br, 17.74	Br, 17.99
23	HCl	73	153-156.5	Me- <i>i</i> -BuCO	C <sub>22</sub> H <sub>32</sub> ClNO <sub>2</sub>	Cl, 9.38	Cl, 9.32
25	HCl	83	108-112	EtOAc	C <sub>22</sub> H <sub>32</sub> ClNO <sub>2</sub>	Cl, 9.38	Cl, 9.48
26	HCl	41	95-97.5	EtOAc + Et <sub>2</sub> O	C <sub>19</sub> H <sub>36</sub> ClNO <sub>2</sub>	Cl, 10.02	Cl, 10.19
27	HCl	75	138-140	EtOAc	C <sub>23</sub> H <sub>34</sub> ClNO <sub>2</sub>	Cl, 9.05	Cl, 8.92
28	HCl	91	137-138	EtOAc	C <sub>22</sub> H <sub>36</sub> ClNO <sub>2</sub>	Cl, 9.28	Cl, 9.25
29	HCl	86	140-141	EtOAc	C <sub>22</sub> H <sub>32</sub> ClNO <sub>2</sub>	Cl, 9.38	Cl, 9.34
30	HCl	89	145.5-146.5	MeEtCO + EtOAc	C <sub>19</sub> H <sub>36</sub> ClNO <sub>2</sub>	Cl, 10.02	Cl, 10.10
31	HCl	76	146.5-149	MeEtCO	C <sub>22</sub> H <sub>32</sub> ClNO <sub>2</sub>	Cl, 9.38	Cl, 9.38
32	HCl	81	120-125	EtOAc	C <sub>21</sub> H <sub>30</sub> ClNO <sub>2</sub>	Cl, 9.74	Cl, 9.70
33	HCl	62	138-144	MeEtCO	C <sub>21</sub> H <sub>32</sub> ClNO <sub>2</sub>	Cl, 9.69	Cl, 9.56
34	HCl	81	96.5-98.5	EtOAc + Et <sub>2</sub> O	C <sub>18</sub> H <sub>34</sub> ClNO <sub>2</sub>	Cl, 10.68	Cl, 10.59
35	HCl	73	165-167	Me <sub>2</sub> CO	C <sub>22</sub> H <sub>32</sub> ClNO <sub>2</sub>	Cl, 9.35	Cl, 9.37
36	HCl	21	148-150	EtOAc	C <sub>19</sub> H <sub>36</sub> ClNO <sub>2</sub>	Cl, 10.23	Cl, 10.23
37	HCl	55	109-112	Tetrahydrofuran + C <sub>6</sub> H <sub>14</sub>	C <sub>20</sub> H <sub>38</sub> ClNO <sub>2</sub> <sup>q</sup>	Cl, 9.85	Cl, 9.75

<sup>a</sup> 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. <sup>b</sup> Melting points are uncorrected. <sup>c</sup> See footnote *b* Table II. <sup>d</sup> Calcd.: C, 62.55; H, 7.64; N, 3.32. Found: C, 62.42; H, 7.87; N, 3.58. <sup>e</sup> Calcd.: C, 61.76; H, 7.40; N, 3.43. Found: C, 61.47; H, 7.66; N, 3.44. <sup>f</sup> Calcd.: C, 62.55; H, 7.64; N, 3.32. Found: C, 61.83; H, 7.17; N, 3.32. <sup>g</sup> Calcd.: C, 57.44; H, 9.11; N, 3.72. Found: C, 56.96; H, 9.09; N, 3.67. <sup>h</sup> Calcd.: C, 62.55; H, 7.64; N, 3.32. Found: C, 62.74; H, 7.70; N, 3.51. <sup>i</sup> Calcd.: C, 63.29; H, 7.85; N, 3.21. Found: C, 63.47; H, 8.00; N, 3.40. <sup>j</sup> Calcd.: C, 62.25; H, 8.07; N, 3.30. Found: C, 62.17; H, 7.87; N, 3.44. <sup>k</sup> Calcd.: C, 58.15; H, 9.76; N, 3.57. Found: C, 57.99; H, 9.59; N, 3.51. <sup>l</sup> This compound was prepared by the low pressure hydrogenation of free base No. 14 (Table II) with PtO<sub>2</sub> catalyst. The reduced free base was not isolated but was converted to its hydrochloride. <sup>m</sup> Calcd.: C, 63.29; H, 7.85; N, 3.21. Found: C, 63.35; H, 7.69; N, 2.99. <sup>n</sup> Calcd.: C, 62.55; H, 7.64; N, 3.32. Found: C, 62.07; H, 7.57; N, 3.34. <sup>o</sup> Calcd.: C, 58.43; H, 9.30; N, 3.59. Found: C, 58.39; H, 9.51; N, 3.75. <sup>p</sup> Calcd.: C, 63.99; H, 8.06; N, 3.11. Found: C, 64.17; H, 7.84; N, 3.32. <sup>q</sup> 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  $\alpha$ -substituted mandelic acids has been prepared. Also disubstituted acetic acid esters have been made from hexamethylenaminoethanol 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.<sup>1</sup> However their toxicity is usually high. The report by Blicke and Tsao<sup>2</sup> of a remarkably active series of esters of thienylglycolic acids kindled renewed interest in basic esters of  $\alpha$ -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<sup>3</sup> 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  $\alpha$ -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.<sup>3</sup> The salts of these basic

(1) K. Fromherz, *Arch. expil. Path. Pharmacol.*, **178**, 86 (1933).

(2) F. F. Blicke and M. U. Tsao, *THIS JOURNAL*, **66**, 1645 (1944).

(3) R. B. Moffett, J. L. White, R. D. Aspergren and F. E. Visscher, *ibid.*, **77** 1562 (1955), and preceding papers.

TABLE I  
 PHARMACOLOGICAL ACTIVITIES

No. of base	Formula of base	Salt	Toxicity LD <sub>50</sub> , (mg./kg.) <sup>a</sup>	Antispasmodic activity, (At. I.) <sup>b</sup>	Antisecretory activity, ED <sub>50</sub> (mg./kg.) <sup>c</sup>
1	C <sub>6</sub> H <sub>5</sub> CH(OH)COOCH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	..	<0.01	....
2	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C(OH)COOCH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	100 36 <sup>d</sup>	0.12 0.2	.... >1.0
3	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C(OH)COOCH <sub>2</sub> CH <sub>2</sub> NC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	167	0.17	>3.0
4	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> C(C <sub>6</sub> H <sub>5</sub> )(OH)COOCH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	64 <sup>d</sup>	0.5	>3.0
5	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> C(C <sub>6</sub> H <sub>5</sub> )(OH)COOCH <sub>2</sub> CH <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	64 <sup>d</sup>	1.0	2.0
6	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> C(C <sub>6</sub> H <sub>5</sub> )(OH)COOCH <sub>2</sub> CH <sub>2</sub> NC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	233	0.14	4.0
7	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHC(C <sub>6</sub> H <sub>5</sub> )(OH)COOCH <sub>2</sub> CH <sub>2</sub> NC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	112 <sup>d</sup>	1.0	0.5
7	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHC(C <sub>6</sub> H <sub>5</sub> )(OH)COOCH <sub>2</sub> CH <sub>2</sub> NC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub> Br	65 21 <sup>d</sup>	0.75	0.2
8	CH <sub>2</sub> C(C <sub>6</sub> H <sub>5</sub> )(OH)COOCH <sub>2</sub> CH <sub>2</sub> N(CH <sub>3</sub> )(C <sub>6</sub> H <sub>5</sub> )	CH <sub>3</sub> Br	167	2.0 <sup>e</sup>	1.0
9	C <sub>6</sub> H <sub>5</sub> CH(CH <sub>2</sub> OH)COOCH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	Citrate	..	0.01	>5.0
10	C <sub>6</sub> H <sub>5</sub> CH(CH <sub>2</sub> OH)COOCH <sub>2</sub> CH <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	650 150 <sup>d</sup>	0.2	2.0
11	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	650	<0.01	....
12	CH=CHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl/	200	0.2	2.0
12	CH=CHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub> Br	65	0.3 <sup>e</sup>	1.5
13	CH=CHCH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH <sub>3</sub>	HCl	200	....	....
13	CH=CHCH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH <sub>3</sub>	CH <sub>3</sub> Br	65	0.5 <sup>e</sup>	1.0
14	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> NC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )CH <sub>2</sub> CHCH <sub>3</sub>	HCl	167	....	>5.0
15	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	100	0.07	....
16	CH=CHCH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	200	0.07	....
17	CH=CHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	HCl	300	0.1	....
18	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> N(CH <sub>3</sub> )CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub> Br	65	3.5	0.15
19	CH=CHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )COOCH <sub>2</sub> CH <sub>2</sub> N[CH(CH <sub>3</sub> ) <sub>2</sub> ]	CH <sub>3</sub> Br	65	1.0 <sup>e</sup>	1.0

<sup>a</sup> Unless otherwise indicated the compounds were administered to mice intraperitoneally. The values are approximations with an accuracy of about +100% to -50%. <sup>b</sup> Unless otherwise indicated the antispasmodic activity was determined on isolated rabbit intestine by the method of Magnus [*Arch. ges. Physiol. (Pflügers)*, 102, 123 (1904); *ibid.*, 103, 515 (1904)]. The results are expressed as the ratio of the activity of the compound to that of atropine sulfate (Atropine Index). <sup>c</sup> 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%. <sup>d</sup> Intravenous in mice. <sup>e</sup> This activity was determined in Thiry-Vella dogs [O. H. Plant, *J. Pharmacol. Exptl. Therap.*, 16, 311 (1921)]. This atropine index is not strictly comparable with that determined by the method of Magnus. <sup>f</sup> See footnote p, Table II.

esters were in general, less active antispasmodic and antisecretory agents (Table I) than the previously reported pyrrolidyl analogs. The physical properties of the bases and salts are given in Table II. A few other miscellaneous esters are also included in the tables. One of these (No. 18) is the methyl bromide salt of a base previously reported.<sup>4</sup> It has exceptionally high antispasmodic and antisecretory activity. The esters of the disubstituted acetic acids were prepared in the usual way<sup>3</sup> through the acid chlorides. The preparations of the intermediate acids and amino alcohols if not previously reported are given in the experimental section. Since acid chlorides cannot readily be made from hydroxy acids most of the esters of these acids were prepared by heating a mixture of the acid and the aminoethyl chloride hydrochloride with an excess of potassium carbonate. The free basic esters were not isolated but were converted to hydrochlorides. An example is given in the Experimental section.

The methyl bromide quaternary salts were prepared by liberating the free base from the purified

hydrochloride and then treating with methyl bromide.<sup>3</sup>

Most of the compounds reported here can exist in several stereoisomeric forms. However, for the most part, no attempt was made to separate or resolve them (see footnote p of Table II).

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### Experimental

2-(2,2-Dimethyl-1-pyrrolidyl)-ethyl Chloride Hydrochloride.—Hydrogen chloride gas was passed into a cooled solution of 85.9 g. (0.6 mole) of 2-(2,2-dimethyl-1-pyrrolidyl)-ethanol<sup>6</sup> in 250 ml. of dry benzene until the solution was strongly acid. Then 118.9 g. (1.0 mole) of thionyl chloride was slowly added. The mixture was heated on a steam-bath for one hour and allowed to stand overnight. The white crystalline precipitate was collected, washed with benzene and ether and dried. The remainder of the product was precipitated by the addition of ether to the filtrate. The combined yield was nearly quantitative,

(4) R. B. Moffett, J. H. Hunter and E. H. Woodruff, *J. Org. Chem.*, 15, 1013 (1950).

(5) R. B. Moffett and J. L. White, *ibid.*, 17, 407 (1952).

TABLE II  
 PHYSICAL PROPERTIES

No. of base from Table I	Salt	Yield, % <sup>a</sup>	M.p., °C. <sup>b</sup>	Crystallizing solvent	Empirical formula	Halogen, %		Nitrogen, %	
						Calcd.	Found <sup>c</sup>	Calcd.	Found <sup>c</sup>
1	HCl <sup>d</sup>	35 <sup>e</sup>	144-144.5	<i>i</i> -PrOH	C <sub>14</sub> H <sub>20</sub> ClNO <sub>3</sub> <sup>f</sup>	Cl, 12.41	Cl, 12.30	4.90	4.95
2	HCl <sup>d</sup>	28 <sup>e</sup>	173-173.5	<i>i</i> -PrOH + MeEtCO	C <sub>20</sub> H <sub>24</sub> ClNO <sub>3</sub> <sup>g</sup>	Cl, 9.80	Cl, 9.71	3.87	4.11
3	HCl <sup>h</sup>	70	143-145	MeEtCO + EtOAc	C <sub>22</sub> H <sub>28</sub> ClNO <sub>3</sub>	Cl, 9.09	Cl, 9.01	3.59	3.79
4	HCl <sup>d</sup>	60	161-161.5	MeEtCO	C <sub>19</sub> H <sub>30</sub> ClNO <sub>3</sub>	Cl, 9.97	Cl, 9.54	..	..
5	HCl <sup>h</sup>	61	140-141	EtOAc + Et <sub>2</sub> O	C <sub>20</sub> H <sub>32</sub> ClNO <sub>3</sub>	Cl, 9.59	Cl, 9.58	..	..
5	CH <sub>3</sub> Br	70	148-151	Benzene	C <sub>21</sub> H <sub>34</sub> BrNO <sub>3</sub> <sup>i</sup>	Br, 18.65	Br, 18.32	3.27	3.14
6	HCl	81	113.5-116	EtOAc + Heptane	C <sub>21</sub> H <sub>34</sub> ClNO <sub>3</sub>	Cl, 9.23	Cl, 9.39	3.65	3.91
7	HCl <sup>j</sup>	60	162-163.5	MeEtCO	C <sub>21</sub> H <sub>32</sub> ClNO <sub>3</sub>	Cl, 9.29	Cl, 9.17	3.67	3.83
7	CH <sub>3</sub> Br	60	192-194	<i>i</i> -PrOH + MeEtCO	C <sub>22</sub> H <sub>34</sub> BrNO <sub>3</sub>	Br, 18.13	Br, 18.16	..	..
8	CH <sub>3</sub> Br <sup>k</sup>	..	195-197	EtOH	C <sub>19</sub> H <sub>24</sub> BrNO <sub>3</sub> <sup>l</sup>	Br, 20.27	Br, 20.05	3.55	3.60
9	Citrate <sup>d</sup>	..	..... <sup>m</sup>	EtOH	C <sub>21</sub> H <sub>29</sub> NO <sub>10</sub>	.....	.....	3.08	3.12
10	HCl <sup>h</sup>	27	139-141	MeOH + MeEtCO	C <sub>16</sub> H <sub>24</sub> ClNO <sub>3</sub>	Cl, 11.30	Cl, 11.40	4.46	4.65
11	HCl <sup>n</sup>	80 <sup>p</sup>	130.5-132	EtOAc	C <sub>18</sub> H <sub>34</sub> ClNO <sub>2</sub>	Cl, 10.68	Cl, 10.66	..	..
12	HCl <sup>n</sup>	98 <sup>p</sup>	142.5-143.5 <sup>p</sup>	Acetone	C <sub>22</sub> H <sub>32</sub> ClNO <sub>2</sub>	Cl, 9.41	Cl, 9.40	..	..
12	CH <sub>3</sub> Br	92 <sup>q</sup>	140-143	EtOH + MeEtCO	C <sub>23</sub> H <sub>34</sub> BrNO <sub>2</sub> <sup>r</sup>	Br, 18.31	Br, 18.38	3.21	3.21
13	HCl <sup>e</sup>	.. <sup>t</sup>	120-122	MeEtCO	C <sub>22</sub> H <sub>32</sub> ClNO <sub>2</sub> <sup>u</sup>	Cl, 9.38	Cl, 9.15	3.71	3.98
13	CH <sub>3</sub> Br	..	135-137	Benzene	C <sub>23</sub> H <sub>34</sub> BrNO <sub>2</sub> <sup>v</sup>	Br, 18.31	Br, 18.30	3.21	3.57
14	HCl	..	124-134	<i>i</i> -PrOH + MeEtCO	C <sub>21</sub> H <sub>40</sub> ClNO <sub>2</sub>	Cl, 9.24	Cl, 9.51	..	..
15	HCl	71 <sup>w</sup>	156-158	MeEtCO + EtOAc	C <sub>18</sub> H <sub>34</sub> ClNO <sub>2</sub>	Cl, 10.68	Cl, 10.94	..	..
16	HCl	76 <sup>x</sup>	110-118	EtOAc	C <sub>21</sub> H <sub>30</sub> ClNO <sub>2</sub>	Cl, 9.74	Cl, 9.80	..	..
17	HCl	75 <sup>y</sup>	143.5-144.5	MeEtCO	C <sub>22</sub> H <sub>32</sub> ClNO <sub>2</sub>	Cl, 9.38	Cl, 9.35	..	..
18	CH <sub>3</sub> Br	63 <sup>z</sup>	197-199	EtOH + Et <sub>2</sub> O	C <sub>20</sub> H <sub>32</sub> BrNO <sub>2</sub> <sup>aa</sup>	Br, 20.06	Br, 20.15	3.52	3.43
19	CH <sub>3</sub> Br	32 <sup>bb</sup>	177-179	EtOH + Et <sub>2</sub> O	C <sub>23</sub> H <sub>36</sub> BrNO <sub>2</sub> <sup>cc</sup>	Br, 18.23	Br, 17.91	3.20	3.34

<sup>a</sup> In cases where the free basic esters were isolated the yields of the hydrochlorides are based on the distilled free bases. When the bases were not isolated the yields are based on the acid from which the esters were prepared. The yields of the methyl bromide salts are based on the purified hydrochlorides. <sup>b</sup> Melting points are uncorrected. <sup>c</sup> Analyses are by Mr. William A. Struck and staff of our analytical chemistry laboratory. <sup>d</sup> The intermediate 2-(1-pyrrolidyl)-ethyl chloride and hydrochloride has been reported [J. B. Wright, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, 70, 3098 (1948)]. <sup>e</sup> This compound was prepared by Dr. James H. Hunter in these laboratories by the reaction of the appropriate acid with 2-(1-pyrrolidyl)-ethyl chloride (footnote *d*) by the method of R. R. Burtner and J. W. Cusic, THIS JOURNAL, 65, 262 (1943). <sup>f</sup> Calcd.: C, 58.84; H, 7.04. Found: C, 58.85; H, 6.98. <sup>g</sup> Calcd.: C, 66.38; H, 6.68. Found: C, 66.40; H, 6.77. <sup>h</sup> The intermediate 2-(2-methyl-1-pyrrolidyl)-ethyl chloride hydrochloride has been reported [H. G. Kolloff, J. H. Hunter, E. H. Woodruff and R. B. Moffett, THIS JOURNAL, 71, 3988 (1949)]. <sup>i</sup> Calcd.: C, 58.87; H, 8.00. Found: C, 58.77; H, 8.14. <sup>j</sup> The intermediate  $\alpha$ -cyclopentylmandelic acid has been reported [J. H. Biel, H. L. Friedman, H. A. Leiser and E. P. Sprengeler, THIS JOURNAL, 74, 1485 (1952)]. <sup>k</sup> The corresponding hydrochloride (Labotropin) was obtained from the Fallex Products Co. <sup>l</sup> Calcd.: C, 57.87; H, 6.38. Found: C, 57.82; H, 6.27. <sup>m</sup> The hydrochloride failed to crystallize. It was converted to the acid citrate which crystallized from ethanol. The product however was a very hygroscopic solvate without definite melting point. Drying in a vacuum desiccator removed the solvent and gave a glass with the correct analysis. <sup>n</sup> The requisite 2-(2-methyl-1-piperidyl)-ethanol has been reported [R. O. Clinton, V. J. Salvador and S. C. Laskowski, THIS JOURNAL, 71, 3366 (1949)]. <sup>o</sup> The intermediate free base was isolated in 89% yield, b.p. 131° (0.7 mm.), *n*<sub>D</sub><sup>20</sup> 1.4733. Anal. Calcd. for C<sub>18</sub>H<sub>33</sub>NO<sub>2</sub>: N, 4.71. Found: N, 4.69. <sup>p</sup> The intermediate free base was isolated in 93% yield, b.p. 164° (0.07 mm.), *n*<sub>D</sub><sup>20</sup> 1.5274. Anal. Calcd. for C<sub>22</sub>H<sub>31</sub>NO<sub>2</sub>: N, 4.13. Found: N, 4.13. This was converted to the hydrochloride (m.p. about 132°) in 98% yield. By fractional crystallization from acetone and ethyl acetate two diastereoisomers were isolated. The " $\alpha$ " isomer had the m.p. given, the " $\beta$ " isomer m.p. 131-132.5°. The analysis given in the table is for the mixture of isomers. The " $\alpha$ " isomer, found Cl, 9.41. The " $\beta$ " isomer, found Cl, 9.26. Both had approximately the same antispasmodic and antisecretory activity. <sup>q</sup> This is the total yield of the methyl bromide salt prepared from a mixture of the stereoisomers (footnote *p*). <sup>r</sup> Calcd.: C, 63.29; H, 7.89. Found: C, 63.04; H, 8.01. <sup>s</sup> The requisite 2-(2,6-dimethyl-1-piperidyl)-ethanol has been reported [R. O. Clinton, V. J. Salvador, S. C. Laskowski and J. S. Buck, THIS JOURNAL, 72, 1331 (1950)]. <sup>t</sup> The intermediate free base was isolated in 71% yield, b.p. 163° (0.1 mm.), *n*<sub>D</sub><sup>20</sup> 1.5202. <sup>u</sup> Calcd.: C, 69.91; H, 8.54. Found: C, 69.96; H, 8.36. <sup>v</sup> Calcd.: C, 63.29; H, 7.85. Found: C, 63.35; H, 7.65. <sup>w</sup> The intermediate free base was isolated in 85% yield, b.p. 125° (0.08 mm.), *n*<sub>D</sub><sup>20</sup> 1.4763. Anal. Calcd. for C<sub>18</sub>H<sub>33</sub>NO<sub>2</sub>: N, 4.74. Found: N, 4.79. <sup>x</sup> The intermediate free base was isolated in 89% yield, b.p. 135° (0.02 mm.), *n*<sub>D</sub><sup>20</sup> 1.5259. Anal. Calcd. for C<sub>21</sub>H<sub>29</sub>NO<sub>2</sub>: N, 4.28. Found: N, 4.46. <sup>y</sup> The intermediate free base was isolated in 84% yield, b.p. 148° (0.012 mm.). Anal. Calcd. for C<sub>22</sub>H<sub>31</sub>NO<sub>2</sub>: N, 4.10. Found: N, 4.33. <sup>z</sup> Prepared from the previously reported<sup>4</sup> hydrochloride. <sup>aa</sup> Calcd.: C, 60.29; H, 8.10. Found: C, 60.44; H, 7.99. <sup>bb</sup> The intermediate free base was prepared from phenyl- $\Delta^2$ -cyclohexenyl-acetyl chloride and  $\beta$ -diisopropylaminoethanol in 77.5% yield, b.p. 136° (0.03 mm.), *n*<sub>D</sub><sup>20</sup> 1.5104. Anal. Calcd. for C<sub>22</sub>H<sub>33</sub>NO<sub>2</sub>: C, 76.92; H, 9.68; N, 4.11. Found: C, 76.99; H, 9.62; N, 4.21. The yield of the methyl bromide salt was based on the distilled free base. <sup>cc</sup> Calcd.: C, 63.00; H, 8.27. Found: C, 62.92; H, 8.07.

m.p. 201-202°. A sample recrystallized from isopropyl alcohol gave the same melting point.

Anal. Calcd. for C<sub>8</sub>H<sub>17</sub>Cl<sub>2</sub>N: N, 7.07; Cl, 35.79. Found: N, 6.98; Cl, 35.84.

**$\alpha$ -Isoamylmandelic Acid.**—Isoamylmagnesium bromide was prepared from 34 g. (1.4 moles) of magnesium turnings and 211 g. (1.4 moles) of isoamyl bromide in 500 ml. of dry tetrahydrofuran. This solution was slowly siphoned into a solution of 97.6 g. (0.65 mole) of benzoylformic acid in 200 ml. of dry tetrahydrofuran contained in a 2-l. flask, fitted with a stirrer and reflux condenser, and cooled in an ice-

bath. When the addition of the Grignard reagent was complete the mixture was stirred at room temperature for one hour. At this point a test for Grignard reagent with Michler's ketone was negative. The mixture was poured into ice-water, acidified with hydrochloric acid, and extracted with ether. The ether solution was extracted with aqueous sodium carbonate. This basic solution was treated with decolorizing charcoal, filtered and acidified. The product was crystallized from hexane, and then from ethanol-water giving 28 g. (19.4%) of  $\alpha$ -isoamylmandelic acid, m.p. 125.5-126.5°.

*Anal.* Calcd. for  $C_{13}H_{18}O_3$ : C, 70.22; H, 8.16; neut. equiv., 222.3. Found: C, 70.29; H, 7.86; neut. equiv., 224.3.

**2-(2,2-Dimethyl-1-pyrrolidyl)-ethyl  $\alpha$ -Isoamylmandelate Hydrochloride.**—A mixture of 8.0 g. (0.036 mole) of  $\alpha$ -isoamylmandelic acid, 7.15 g. (0.036 mole) of 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl chloride hydrochloride, 21 g. (0.15 mole) of anhydrous potassium carbonate, and 100 ml. of methyl isobutyl ketone<sup>6</sup> was heated under reflux for eight hours. Water was added and the solution was extracted with ether. The ether solution was dried over anhydrous potassium carbonate and filtered. Hydrogen chloride gas was passed in until the solution tested strongly acid. The hydrochloride separated as an oil which crystallized on standing. It was recrystallized from a mixture of ethyl acetate and ether giving 11.2 g. (81%) of product, m.p. 109–115°. A second recrystallization from ethyl acetate

(6) In one run acetone was used as a solvent but no appreciable reaction occurred in 20 hours. In the preparation of the other  $\alpha$ -hydroxy acid esters (Table II) acetone or methyl ethyl ketone were satisfactory.

and Skellysolve C raised the melting point to 113.5–116°. **2-(2,2,4,6-Tetramethyl-1-piperidyl)-ethanol.**—A mixture of 141.2 g. (1 mole) of 2,2,4,6-tetramethylpiperidine (obtained from Shell Development Co.) and 80.5 g. (1 mole) of ethylene chlorohydrin was slowly heated until the temperature reached 155°. After cooling an excess of 50% sodium hydroxide solution was added and the mixture was extracted repeatedly with ether. The ether solution was dried over potassium carbonate. After removing the solvent the product was distilled, b.p. 120° (12 mm.),  $n_D^{25}$  1.4761. The yield was 62.2 g. (34%).

*Anal.* Calcd. for  $C_{11}H_{23}NO$ : N, 8.10. Found: N, 8.04, 8.23.

**2-(Hexamethyleneimino)-ethanol.**—This was prepared by a procedure similar to that described above using 49.6 g. (0.5 mole) of hexamethyleneimine and 40.3 g. (0.5 mole) of ethylene chlorohydrin. The product was distilled, b.p. 103° (15 mm.),  $n_D^{25}$  1.4826.

*Anal.* Calcd. for  $C_6H_{11}NO$ : C, 67.10; H, 11.97; N, 9.78. Found: C, 67.52; H, 11.89; N, 9.91.

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[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

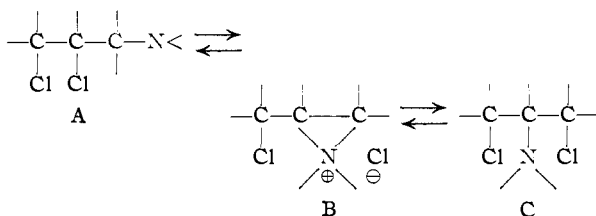
## $\beta,\gamma$ -Dihalopropylamines. I. 1-Amino-2,3-dichloropropanes and 1,4-Diamino-2,3-dichlorobutanes

BY NORMAN H. CROMWELL AND ALFRED HASSNER

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The hydrochlorides of 1-piperidino, 1-dimethylamino and 1-dibenzylamino-2,3-dichloropropane have been prepared by chlorine addition to the corresponding allylamine hydrochlorides. Compared with 2-piperidino-1,3-dichloropropane hydrochloride, the 1-piperidino-2,3-dichloropropane hydrochloride is thermally more stable. These compounds react slowly with piperidine to produce triaminopropanes. The dihydrochlorides of 1,4-dipiperidino, 1,4-bis-dimethylamino and 1,4-dimorpholino-2,3-dichlorobutane have been prepared by chlorine addition to the corresponding 1,4-diaminobutene dihydrochlorides. These compounds have been synthesized for pharmacological testing as anti-tumor agents, etc.

As a part of a general program concerned with the syntheses of potential anti-cancer agents it seemed of interest to obtain for pharmacological testing a series of compounds having the functional group arrangement represented by the general formulas A and/or C.<sup>1</sup>



The relationship of the structural arrangements of A and C to that present in the nitrogen mustards is apparent.

Compounds A and C might be expected to be converted to the same potentially pharmacologically important<sup>2,3</sup> intermediate quaternary ethylen-

(1) The ability of various  $\beta$ -haloethylamines to rearrange to quaternary ethylene immonium ions and subsequently to an isomeric  $\beta$ -haloethylamine has been adequately demonstrated in the literature; see for example: (a) N. H. Cromwell and D. J. Cram, *THIS JOURNAL*, **65**, 301 (1943); (b) N. H. Cromwell and I. H. Witt, *ibid.*, **65**, 308 (1943); (c) N. H. Cromwell, *et al.*, *ibid.*, **75**, 5384 (1953); (d) E. M. Schultz, C. M. Robb and J. M. Sprague, *ibid.*, **69**, 188 (1947); (e) J. F. Kerwin, *et al.*, *ibid.*, **69**, 2961 (1947); (f) P. D. Bartlett, S. D. Ross and C. G. Swain, *ibid.*, **69**, 2971 (1947); (g) S. D. Ross, *ibid.*, **69**, 2982 (1947); (h) C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946).

(2) The vesicant properties of tris-( $\beta$ -chloroethyl)-amine and methylbis-( $\beta$ -chloroethyl)-amine are well known, see: (a) K. Ward, *THIS JOURNAL*, **57**, 914 (1935); (b) O. Risleb, *Ber.*, **74**, 1433 (1941);

immonium chloride (B) in neutral or basic media.

A possible method of synthesis for compounds of structures A and C involves reaction of the corresponding aminodiols with thionyl chloride. Previous communications from this Laboratory have reported the development of methods of synthesis

of aminodiols,  $-C(OH)C(OH)CN<$ , which might serve as precursors for  $\beta,\gamma$ -dichloroamines of type A.<sup>4</sup>

Many investigators<sup>1d-f,5</sup> have reported the successful conversion of  $\beta$ -aminoalcohols with thionyl chloride to  $\beta$ -chloroamines. Others<sup>6</sup> have apparently experienced difficulties in attempting

to convert aminodiols,  $-C(OH)C(N<)C-OH$ , to

(c) Jensen and Lundquist, *Dansk. Tidsskr. Farm.*, **15**, 201 (1941). These compounds have been called "nitrogen mustards" because of their relationship structurally and biologically with mustard gas.

(3) Various biological investigations have suggested possible therapeutic applications for such substances, see: (a) A. Gilman and F. S. Philips, *Science*, **103**, 409 (1946); (b) E. Boyland, *Brit. J. Pharmacol.*, **1**, 247 (1946).

(4) (a) N. H. Cromwell and F. W. Starks, *THIS JOURNAL*, **72**, 4108 (1950); (b) N. H. Cromwell and N. G. Barker, *ibid.*, **72**, 4110 (1950); (c) N. G. Barker and N. H. Cromwell, *ibid.*, **73**, 1051 (1951); (d) K. C. Tsou and N. H. Cromwell, *J. Org. Chem.*, **15**, 1293 (1950).

(5) (a) N. H. Cromwell and W. E. Fitzgibbons, *THIS JOURNAL*, **70**, 387 (1948); (b) P. Ofner, *J. Chem. Soc.*, 1800 (1951).

(6) E. R. H. Jones and W. Wilson, *J. Chem. Soc.*, 547 (1949), obtained only the cyclic sulfite from 2-amino-2-methyl-1,3-propanediol, but prepared the desired 2-dimethylamino-2-methyl-1,3-dichloropropane hydrochloride from 2-dimethylamino-2-methyl-1,3-propanediol and thionyl chloride in chloroform solution.