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AUTONOMIC BLOCKING AGENTS. I. BRANCHED ALIPHATIC QUATERNARY AMMONIUM AND ANALOGOUS CYCLIC AMMONIUM SALTS

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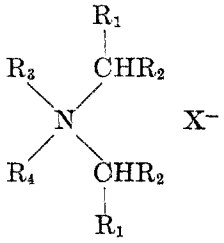
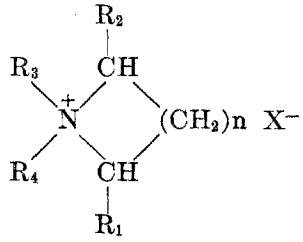
As a part of a rather extensive study of ganglion blocking agents begun in these laboratories several years ago a large number of quaternary ammonium salts was synthesized which included branched aliphatic quaternary and analogous cyclic ammonium salts and many ester derivatives of the corresponding alkanolammonium salts.[1] The objective was to find substances with improved ganglion blocking properties and if possible substances possessing oral activity. The literature reports many substances with greater blocking power than the tetraethylammonium salts currently used but, therapeutically, none have proved significantly better (1). Among the most promising of the newer agents are the polymethylene-*bis*-quaternary ammonium salts of Chou and de Elio (2) and of Barlow and Ing (3). Hexamethionium, hexamethylene-*bis*-trimethylammonium bromide, has been reported to possess some oral activity (4). Results of pharmacological tests on some of the first compounds prepared in this laboratory indicated that the introduction of one or two secondary alkyl groups in a simple quaternary salt enhanced its ganglion blocking power. The synthetic work was accordingly expanded on this basis as exemplified by formulas (A), (B), and (C).



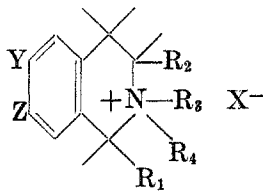
A

R_1 = H, methyl, and ethyl
R_2 = methyl, ethyl, propyl, and butyl
R_3, R_4 = methyl, ethyl, and hydroxyethyl



B

R_1, R_2 = H, methyl, and phenyl
R_3, R_4 = methyl, ethyl, propyl, benzyl, *p*-cymyl, hydroxyethyl and acetoxyethyl
n = 2 or 3



C

R_1 = H, methyl, heptyl, and benzyl
R_2 = H and methyl
R_3, R_4 = methyl and ethyl
Y, Z = H, hydroxy, and methoxy

Compounds 7 and 9 of Table II, diisobutyl and diisoamyl derivatives respectively, although exceptions to the general formula (A), are included in this table

[1] A report on the ester group of this series was presented before the Medicinal Division of the American Chemical Society, April, 1950, Philadelphia, Pennsylvania.

to show the effect of moving the site of branching away from the nitrogen atom. The lupetidinium salts of Table III are derivatives of a pure stereoisomeric form of b.p. 126°. Two stereoisomeric 2,6-lupetidines have been described by Wolffenstein (5) but their identity was not determined by him. Mannich (6) obtained the N-methyl derivative of the *cis* (*meso*) form (methiodide, m.p. 275°) by reduction of the corresponding 4-piperidinol derivative. The N-methyl methiodide of the lupetidine of b.p. 126° melts at 302°. This evidence, however, is too scant to justify any conclusions as to the stereochemical structure of the lupetidine at hand.

TABLE I

TERTIARY AMINES

NO.	NAME OF AMINE	FORMULA	B.P., °C.	n_D^{25}	NITROGEN	
					Calc'd	Found
1	Ethylisopropylmethyl[a]	$C_6H_{15}N$	90	1.3998	13.85	13.93,13.94
2	Ethyldiisopropyl[b]	$C_8H_{19}N$	126.5	1.4121	10.84	10.65,10.7
3	Diisobutylmethyl[c]	$C_9H_{21}N$	143	1.4070	9.78	9.65, 9.61
4	Methyldi-(1-methylpropyl)[c]	$C_9H_{21}N$	159	1.4220	9.78	9.72, 9.79
5	*Diisoamylmethyl*[c]	$C_{11}H_{25}N$	83–84[h]	1.4212	8.18	8.17, 8.15
6	Methyldi-(1-methylbutyl)[d]	$C_{11}H_{25}N$	196	1.4300	8.18	8.09, 8.10
7	Di-(1-ethylpropyl)methyl[e]	$C_{11}H_{25}N$	198	1.4300	8.18	8.13, 8.12
8	Diisopropylmethyl[f]	$C_7H_{17}N$	111	1.4100	12.16	12.09,12.14
9	Diethylisopropyl[g]	$C_7H_{17}N$	107.5	1.4047	12.16	12.11,12.13

[a] Ethylisopropylamine was prepared from acetone and ethylamine or acetaldehyde and isopropylamine by hydrogenation in methanol (Adams' catalyst). These condary base was methylated with formaldehyde-formic acid. [b] Prepared by reacting diisopropylamine with ethyl iodide in butanone. The yield was about 50%. [c] By N-methylation with formaldehyde-formic acid. [d] Prepared from 2-pentanone by hydrogenation in the presence of ammonia and subsequent methylation by formaldehyde and formic acid. [e] Prepared from 3-pentanone as described in note (*d*). [f] Previously recorded by Klages, Nober, and Bock, *Ann.*, **547**, 39 (1941), b.p. 109–112°. [g] Previously recorded by Caspe, *J. Am. Chem. Soc.*, **54**, 4457 (1932) who cites b.p. 108°. [h] Boiling point at 21 mm. pressure.

The 1,3-dimethyltetrahydroisoquinoline, of which two racemic forms are possible, yielded, by recrystallization of its hydrochloride from methanol, one pure form which melted at 287°. The remainder of the hydrochloride which melted rather sharply at 254° was evidently a mixture since it yielded a very small quantity of a second isomer of m.p. 294°. A mixture of the two hydrochlorides of m.p. 287 and 294° melted at 254°. Compound 3 of Table IV was prepared from the hydrochloride of m.p. 287°.

The 1-methyltetrahydro- and 1,3-dimethyltetrahydro-isoquinolines were obtained from the corresponding dihydroisoquinolines which were synthesized by the method of Späth (7). Späth's method, which consists in the cyclodehydration of acylphenylethylamines by phosphorus pentoxide at 200°, produces good results when the acyl group is larger than acetyl or when the acyl derivatives are benzoyl or phenylacetyl. Cyclodehydration of N-acetylphenylethylamines by

TABLE II

QUATERNARY AMMONIUM SALTS[a] (A)

NO.	AMMONIUM ION	ANION	M.P., °C. (Corr.)	REACTION		FORMULA	NITROGEN		HALOGEN		ACTIVITY,[b] $(Et)_4\overset{+}{N}Br^-$ = 1
				Temp., °C.	Time, (Hrs.)		Calc'd	Found	Calc'd	Found	
1	Diethylisopropylmethyl	Br	277	70	60	$C_8H_{20}BrN$	6.67	6.62	38.03	37.72	0.84
2	Triethylisopropyl	Br	264	70	60	$C_9H_{22}BrN$	6.25	6.17	35.65	36.17	2.58
3	Dimethyldiisopropyl	Cl	261	95	3	$C_8H_{20}ClN$	8.45	8.43	21.40	21.41	1.9
4	Diisopropylethylmethyl	Br	247	70	60	$C_9H_{22}BrN$	6.25	6.24	35.65	35.6	5.9
5	Diethyldiisopropyl	Cl	299	125	8	$C_{10}H_{24}ClN$	7.23	7.21	18.30	18.33	12.1
6	Di-*sec*-butylethylmethyl	I	199	80	20	$C_{11}H_{26}IN$	4.68	4.69	42.41	42.3	6.4
7	Diisobutylethylmethyl	I	162	80	20	$C_{11}H_{26}IN$	4.68	4.63	42.41	42.38	1.1
8	Bis(1-methylbutyl)ethylmethyl	I	117–118			$C_{13}H_{30}IN$	4.28	4.25	38.78	38.91	3.2
9	Diisoamylethylmethyl	Br	126–128	125	9	$C_{13}H_{30}BrN$	5.00	4.98	28.51	28.46	0.36
10	Bis(1-ethylpropyl)dimethyl	I	114	80	5	$C_{12}H_{28}IN$	4.47	4.42	40.51	40.17	3.0
11	(2-Hydroxyethyl)isopropyldimethyl	Br	274	70	24	$C_7H_{18}BrNO$	6.60	6.51	37.67	37.72	0.22
12	(2-Hydroxyethyl)isopropylethylmethyl	Br	262	70	24	$C_8H_{20}BrNO$	6.19	6.13	35.34	35.44	0.3
13	(2-Hydroxyethyl)diisopropylmethyl	Br	234	70	24	$C_9H_{22}BrNO$	5.83	5.72	33.27	33.15	0.85
14	(2-Hydroxyethyl)diisopropylethyl	Cl	206	80	60	$C_{10}H_{24}ClNO$	6.68	6.62	16.91	16.70	2.8

[a] Quaternization was carried out in butanone in all cases except one. In this case (compound number 6) the solvent was nitromethane. Columns 5 and 6 give the temperature and time of the reaction. The alkyl halides employed were as follows: For numbers 1, 2, 4, and 9, ethyl bromide; for numbers 5, 6, 7, and 14, ethyl iodide; for numbers 11, 12, and 13, methyl bromide; and for number 3, methyl chloride. The chlorides, numbers 5 and 14 were obtained by the action of silver chloride on the corresponding iodides. [b] Sympathetic ganglion blockade (nictitating membrane of the cat). The results are expressed as molar potency: $\frac{\text{mol. wt. of compound}}{\text{mol. wt. of } (Et)_4\overset{+}{N}Br^-} \times$ gram potency. Gram potencies are based on relative doses producing 50% relaxation of the nictitating membrane (10).

TABLE III

PYRROLIDINIUM AND PIPERIDINIUM SALTS[a] (B)

NO.	R_1	R_2	R_3	R_4	ANION	M.P., °C.	FORMULA	HALOGEN		ACTIVITY[b] $(C_2H_5)_4\overset{+}{N}Br^- = 1$
								Calc'd	Found	
1	CH_3	CH_3	CH_3	CH_3	Cl	287	$C_9H_{20}ClN$	19.95	19.92,19.94	2.0
2	CH_3	CH_3	CH_3	C_2H_5	Br	280	$C_{10}H_{22}BrN$	33.83	33.77,33.72	3.2
3	CH_3	CH_3	CH_3	n-C_3H_7	I	238	$C_{11}H_{24}IN$	42.70	42.60,42.65	3.3
4	CH_3	CH_3	C_2H_5	C_2H_5	Br	268	$C_{11}H_{24}BrN$	31.94	31.99,32.00	9.5
5	CH_3	CH_3	C_2H_5	Benzyl	Br	216	$C_{16}H_{26}BrN$	25.59	25.36,25.39	2.4
6	CH_3	CH_3	C_2H_5	p-Cymyl	Br	115	$C_{19}H_{32}BrN$	22.55	23.57,23.65	2.6
7	CH_3	CH_3	CH_3	$HOCH_2CH_2$	Br	260	$C_{10}H_{22}BrNO$	31.69	31.5, 31.5	2.4
8	CH_3	CH_3	C_2H_5	$HOCH_2CH_2$	Br	246	$C_{11}H_{24}BrNO$	30.02	30.1	0.85
9	CH_3	CH_3	CH_3	$CH_3COOCH_2CH_2$	Br	120–125	$C_{12}H_{24}BrNO$	27.16	26.90,26.90	1.89
10	C_6H_5	H	CH_3	CH_3	I	180	$C_{13}H_{20}IN$	40.01	40.05,39.93	1.3
11	CH_3	CH_3	C_2H_5	C_2H_5	Br	275	$C_{10}H_{22}BrN$	33.84	33.67	6.4
12	CH_3	CH_3	CH_3	$HOCH_2CH_2$	Br	298	$C_9H_{20}BrNO$	33.55	33.72	0.36
13	CH_3	CH_3	C_2H_5	$HOCH_2CH_2$	Br	272	$C_{10}H_{22}BrNO$	31.69	31.88	.75
14	H	C_6H_5	C_2H_5	C_2H_5	Br	190	$C_{14}H_{22}BrN$	28.12	28.00	.9
15	H	C_6H_5	CH_3	CH_3	I	130	$C_{12}H_{18}IN$	41.75	41.8	1.1

[a] Compounds 1 to 10, n = 3; 11 to 15, n = 2.

[b] Pharmacological results expressed as molar potency, see note ([b]) Table II.

TABLE IV

ISOQUINOLINIUM SALTS (C)

NO.	R_1	R_2	R_3	R_4	Y	Z	X^-	M.P., °C.	FORMULA	HALOGE		ACTIVITY,[a] $(C_2H_5)_4N^+$-Br^- = 1
										Calc'd	Found	
1	H	CH_3	C_2H_5	C_2H_5	H	H	Br	186	$C_{14}H_{22}BrN$	28.12	28.18	0.56
2	CH_3	H	C_2H_5	C_2H_5	H	H	Br	168	$C_{14}H_{22}BrN$	28.12	28.11	.65
3	CH_3	CH_3	CH_3	C_2H_5	H	H	Cl	190–215	$C_{14}H_{22}ClN$	14.79	14.66	.95
4	Benzyl	H	CH_3	CH_3	CH_3O	CH_3O	Cl	211	$C_{20}H_{26}ClNO_2$	10.19	10.18	4.0
5	Benzyl	H	CH_3	CH_3	HO	HO	Cl	207	$C_{18}H_{22}ClNO_2$	11.09	10.95	9.6
6	Benzyl	H	CH_3	C_2H_5	HO	HO	Cl	183	$C_{19}H_{24}ClNO_2$	10.62	10.5	7.8
7	Benzyl	H	C_2H_5	C_2H_5	HO	HO	Cl	175	$C_{20}H_{26}ClNO_2$	10.19	10.15	4.6
8	*n*-Heptyl	H	CH_3	CH_3	HO	HO	Cl	138	$C_{18}H_{30}ClNO_2$	10.81	10.92	3.8
9	4-Hydroxybenzyl	H	CH_3	CH_3	HO	HO	Cl	214	$C_{18}H_{22}ClNO_3$	10.56	10.59	1.6

[a] See note (b) Table II.

this method, however, leads to very poor yields of the 1-methyl-3,4-dihydroisoquinolines. This may be due to a more sensitive methyleneamine form which can readily lead to by-products. It was observed that chloroacetylphenylethylamines could be dehydrated by this method to give 1-chloromethyldihydroisoquinolines in yields comparable to those obtained by cyclodehydration of higher aliphatic acid amides or phenylacetamides. Moreover, the 1-chloromethyldihydroisoquinolines were dehalogenated by the reducing agent, zinc and hydrochloric acid, used for conversion to the tetrahydroisoquinolines and thus gave an improved and convenient synthesis of the 1-methyltetrahydroisoquinoline derivatives. The 6,7-dimethoxytetrahydroisoquinolines were prepared by cyclodehydration of N-acyl-(3,4-dimethoxyphenyl)ethylamines with phosphorus oxychloride in toluene as described by Buck and Perkin (8).

Pharmacology. The relatively high activity observed in the diisopropyl- and di-*sec*-butyl-ammonium salts was maintained in the analogous 2,6-lupetidinium[2] and 2,5-dimethylpyrrolidinium salts but was lower in the isoquinolinium salts (9). The 6,7-dihydroxyisoquinolinium salts which were prepared to test the influence of hydroxyl groups on oral activity were not improved with respect to oral activity but the presence of hydroxyl groups resulted in increased activity. In this series the 2,2-dimethyl derivatives were more active than the corresponding diethyl derivatives. The most active member of this group, compound 5, Table IV, was tested for curariform action and found to be devoid of such action except at high dosage levels.

The pharmacology of this series of compounds will be published by the Division of Biological Research of these laboratories.

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EXPERIMENTAL

1-Ethyl-2,6-lupetidine. Hydrogenation of 2,6-lutidine by the method of Adkins (11) gave 2,6-lupetidine which was purified by recrystallization of its hydrochloride from acetone. A yield of 83%, melting at 287°, was obtained. This method of purification was employed by Wolffenstein (5) for the separation of the two stereoisomers. The lupetidine obtained from the hydrochloride of melting point 287° distilled constantly at 126°. The N-ethyl derivative was produced by the action of ethyl sulfate and sodium hydroxide in aqueous medium. The N-ethyl derivative, b.p. 166°, was obtained in a yield of 77%.

1-Methyl-2,6-lupetidine. The lupetidine of boiling point 126° on methylation by the Eschweiler-Clarke method (12) gave the N-methyl derivative, b.p. 145°, in a yield of 90%.

1-Propyl-2,6-lupetidine. The action of *n*-propyl iodide on lupetidine gave the N-propyl derivative, b.p. 104°/65 mm.

2,6-Lupetidineëthanol. Lupetidine reacted with ethylene oxide according to the method of Burnett (13) and gave the hydroxyethyl derivative, b.p. 65°/0.3 mm., n_D^{25} 14818, in a yield of 80%.

[2] The pharmacology of 1,1-diethyl-2,6-lupetidinium bromide has been published by Cook, Hambourger, and Bianchi, *J. Pharmacol. Exptl. Therap.*, **99**, 435 (1950). Clinical data on this substance have been published by Longino, Chittum, and Grimson, *Proc. Soc. Exptl. Biol. Med.*, **70**, 467 (1949).

Anal. Calc'd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91.

Found: C, 68.59; H, 11.94; N, 9.0.

1-(2-Acetoxyethyl)-1-methyl-2,6-lupetidinium bromide. The action of acetic anhydride in acetic acid on 1-(2-hydroxyethyl)-1-methyl-2,6-lupetidium bromide produced the O-acetyl derivative.

Anal. Calc'd for $C_{12}H_{24}BrNO$: CH_3CO, 14.63. Found: CH_3CO, 14.32.

1-Ethyl-2,5-dimethylpyrrolidine. Acetonylacetone, 112 g., and 350 ml. of 33% aqueous ethylamine were heated under reflux for 2 hours. The pyrrole, which separated as a top layer, was dried over potassium carbonate and filtered through decolorizing carbon. This crude pyrrole was hydrogenated in 50-g. portions using 1.5 g. of platinum oxide and 250 ml. of acetic acid for each 50-g. portion. The hydrogenation, carried out at 45 lbs. pressure (25°), was complete in 3 hours. After adding one mole of concentrated hydrochloric acid to the acetic acid filtrate the acetic acid was distilled under diminished pressure. The free base was generated from the residue of hydrochloride and purified by distillation. A yield of 85 g., b.p. 130–131.5°, was obtained.

2,5-Dimethylpyrrolidineëthanol. 2,5-Dimethylpyrroleëthanol was prepared from acetonylacetone and ethanolamine in a yield of 74% by the procedure described above for 1-ethyl-2,5-dimethylpyrrole (the reaction temperature was kept within the range 100–110°). The pyrrole was purified by distillation, b.p. 137°/18 mm.

The hydrogenation of 0.4 mole (1 g. of platinum oxide, 250 ml. of acetic acid, 58–30 lbs. pressure, 25°) was complete in 3 hours. The 2,5-dimethylpyrrolidineëthanol,[3] 185 g., b.p. 86–91°/18 mm., was fractionated through a 30″ column packed with glass helices. The fraction, b.p. 86–89°/18 mm., n_D^{25} 1.4628, (146 g.), was converted to the hydrochloride (m.p. 165–168°) and purified by recrystallization from butanone, m.p. 168–169°.

Anal. Calc'd for $C_8H_{18}ClNO$: Cl, 19.73; N, 7.80.

Found: Cl, 19.44; N, 7.67.

The *picrate* melts at 107–108°.

1,1-Diethyl-2-phenylpyrrolidinium bromide. 2-Phenyl-2-pyrroline, b.p. 110°/1 mm., was prepared in a yield of 61% by the method of Craig (14). Hydrogenation to the corresponding pyrrolidine, b.p. 90–92°/1 mm. was effected over a promoted Raney nickel catalyst (15). N-Ethylation of the 2-phenylpyrrolidine was accomplished by the action of one-half mole of ethyl bromide in butanone solution. The addition of ethyl bromide to the 1-ethyl-2-phenylpyrrolidine was effected by heating to 100° for 14 hours in butanone solution. A yield of 40% was obtained.

1,1-Dimethyl-2-phenylpyrrolidinium iodide. 1-Methyl-2-phenylpyrrolidine was produced through methylation of 2-phenylpyrrolidine by the method of Eschweiler and Clarke (12). Quaternization with methyl iodide was effected in anhydrous ether.

2-Phenyl-1,1-dimethylpiperidinium iodide. 2-Phenylpyridine was prepared according to the method of Evans and Allen (16). The hydrochloride of 2-phenylpyridine was hydrogenated in ethanol. The hydrochloride (0.1 mole) over 0.5 g. of platinum oxide at 56–22 lbs. hydrogen pressure, 25°, absorbed 3 moles of hydrogen in one hour. The 2-phenylpiperidine was methylated with formaldehyde and formic acid (12) and the resulting N-methyl derivative was converted to its methiodide with methyl iodide in methanol.

1-Methyl-2,2-diethyl-1,2,3,4-tetrahydroisoquinolinium bromide. N-Chloroacetylphenethylamine (25 g.) dehydrated by phosphorus pentoxide in tetralin according to the method of Späth (7) gave 69% of 1-chloromethyl-3,4-dihydroisoquinoline (17) which was isolated as the hydrochloride. Reduction of 6 g. of the hydrochloride by zinc and dilute hydrochloric acid for 3 hours at reflux temperature gave 5.5 g. of 1-methyltetrahydroisoquinoline hydrochloride of m.p. 173°.

The reduction was also accomplished by hydrogenation over Raney nickel. The hydrochloride (10 g.), 4 g. of sodium hydroxide in 10 ml. of water, 200 ml. of ethanol, and 3–5 g.

[3] Previously recorded by Reid, Wright, Kolloff, and Hunter, (b.p. 113–114°/62 mm., picrate, m.p. 104–105°), *J. Am. Chem. Soc.*, **70**, 3100 (1948).

of Raney nickel were subjected to hydrogen at 45 lbs. pressure at 25°. One molar equivalent of hydrogen was absorbed in 5 minutes and a second mole in 3 hours. The product was isolated as the hydrochloride, 10 g., m.p. 173°. The base boils at 119°/19 mm. The pure hydrochloride melts at 178°.

Anal. Calc'd for $C_{10}H_{14}ClN$: Cl^-, 19.31. Found: Cl^-, 19.35.

The N-ethyl-derivative, b.p. 94°/1 mm., was produced in 50% yield by the action of ethyl bromide in butanone. The addition of ethyl bromide to the N-ethyl derivative was carried out in butanone yielding 90% of 1-methyl-2,2-diethyl-1,2,3,4-tetrahydroisoquinolinium bromide.

3-Methyl-2,2-diethyl-1,2,3,4-tetrahydroisoquinolinium bromide. Hydrogenation of 3-methylisoquinoline over a copper-chromium oxide catalyst (37KAF) (18) at 2000 lbs. pressure and 150° gave 3-methyltetrahydroisoquinoline, b.p. 121–123°/18 mm., n_D^{24} 1.5494. The N-ethyl-derivative was produced in a yield of 50% in the manner described for the 1-methyl-2-ethyltetrahydroisoquinoline. The hydrochloride of 3-methyl-2-ethyltetrahydroisoquinoline melts at 215°.

Anal. Calc'd for $C_{12}H_{18}ClN$: Cl^-, 16.75. Found: Cl^-, 16.71.

The addition of ethyl bromide to the 3-methyl-2-ethyltetrahydroisoquinoline was accomplished in butanone at 100° for 2 hours. The yield of the ethobromide was 60%.

1,2,3-Trimethyl-2-ethyl-1,2,3,4-tetrahydroisoquinolinium chloride. The cyclodehydration of N-chloroacetyl-(1-methyl-2-phenyl)ethylamine, 83 g., to the 1-chloromethyl-3-methyl-3,4-dihydroisoquinoline was accomplished by heating with 300 g. of phosphorus pentoxide in 1500 ml. of tetralin at 200° for 90 minutes. The dihydroisoquinoline derivative was isolated as the hydrochloride and reduced with zinc and hydrochloric acid as described for the reduction of 1-chloromethyltetrahydroisoquinoline. The yield of crude 1,3-dimethyltetrahydroisoquinoline hydrochloride melting at 240–245° was 52 g. (67%). By recrystallization from methanol 20 g. of a pure hydrochloride, needles, m.p. 287°, was obtained.

Anal. Calc'd. for $C_{11}H_{16}ClN$: Cl^-, 17.94. Found: Cl^-, 18.08.

After concentration of the filtrate another crystalline form, prisms, m.p. 254°, separated. By recrystallization of this product from water about one gram more of the hydrochloride of m.p. 287° separated after which a hydrochloride of m.p. 294° separated.

Anal. Calc'd for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16; N, 7.09; Cl^-, 17.94.
Found: C, 66.86; H, 8.03; N, 7.08; Cl^-, 17.89.

A mixture of the hydrochlorides of m.p. 287° and 294° melts at 254°.

On concentration of the aqueous filtrate the hydrochloride which separated melted at 254°. Recrystallization from water or methanol produced no further change in this substance.

Anal. Found: Cl^-, 17.88.

The free base from the 1,3-dimethyltetrahydroisoquinoline hydrochloride of m.p. 287° by methylation with formaldehyde and formic acid gave 18 g. of the N-methyl derivative which distilled at 80°/2 mm. The 1,2,3-trimethyltetrahydroisoquinoline was converted to the ethiodide by the action of ethyl iodide in butanone at reflux temperature for 90 minutes. The chloride was obtained from the iodide by the action of silver chloride and purified by recrystallization from propanol-2 and ether. A yield of 21 g. was obtained.

1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. 2-(3,4-Dimethoxyphenyl)ethyl-α-toluamide, m.p. 111°, was prepared in 95% yield by heating together equimolar quantities of α-toluic acid and 3,4-dimethoxyphenylethylamine for one hour at 180–200°.

Anal. Calc'd for $C_{18}H_{21}NO_3$: N, 4.68; CH_3O, 20.73.
Found: N, 4.63; CH_3O, 20.57.

Cyclodehydration of the amide to produce 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline was accomplished by the action of phosphorus oxychloride in toluene as described by Buck and Perkin (8) for the synthesis of an analogous isoquinoline derivative. The product, isolated as the hydrochloride, m.p. 175°, was obtained in 94% yield. Its methobromide melts at 165–175°.

The hydrochloride was reduced by zinc and hydrochloric acid to give an 85% yield of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride of m.p. 215°.

1-Benzyl-2,2-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride. 1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline on refluxing with excess methyl iodide in methanol with a sodium acetate buffer gave 82% of 1-benzyl-2,2-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium iodide of m.p. 216°. The corresponding chloride was obtained by the action of silver chloride.

1-Benzyl-2,2-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolinium chloride. 1-Benzyl-2,2-dimethyl-6,7-dimethoxytetrahydroisoquinolinium chloride, 3.5 g., was heated under reflux with 25 ml. of 48% hydrobromic acid for one hour. The hydrobromic acid was distilled and the residue was refluxed one hour longer with 25 ml. more of 48% hydrobromic acid. The mixture was dissolved in water and the iodide precipitated by the addition of potassium iodide. The iodide, m.p. 211°, (3.5 g.) was purified by recrystallization from water (yield 2.75 g., m.p. 225°) and converted to the chloride by the action of silver chloride in a yield of 80%.

1-Benzyl-2-methyl-2-ethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolinium chloride. 1-Benzyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was converted to the ethobromide by the action of ethyl bromide in butanone and demethylated by refluxing in 48% hydrobromic acid as previously described for the 2,2-dimethyltetrahydroisoquinolinium derivative. The intermediate iodide, m.p. 205°, was converted to the chloride by the action of silver chloride.

1-Benzyl-2,2-diethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolinium chloride. 1-Benzyl-2-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, obtained by the action of ethyl sulfate on the corresponding tetrahydroisoquinoline, was further ethylated by the action of ethyl bromide in butanone. The demethylation by hydrobromic acid and preparation of the chloride by the action of silver chloride proceeded as in previous cases.

1-Heptyl-2,2-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolinium chloride. This substance was prepared from caprylic acid and 2-(3,4-dimethoxyphenyl)ethylamine by the sequence of reactions previously described for the analogous 1-benzyltetrahydroisoquinolinium salts. The over-all yield was 59%.

1-(4-Hydroxybenzyl)-2,2-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolinium chloride. This substance was prepared from 4-methoxy-α-toluic acid and 2-(3,4-dimethoxyphenyl)ethylamine in the same way as was the unsubstituted benzyl derivative.

SUMMARY

Several aliphatic quaternary ammonium salts containing one to two secondary alkyl groups and comparable quaternary derivatives of piperidine, pyrrolidine, and tetrahydroisoquinoline have been synthesized and evaluated for autonomic ganglion blocking action.

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