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Bifunctional Amines and Ammonium Compounds
II. Bis-β-dialkylaminoethyl Ethers and their Quaternary Ammonium Halides

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The present paper describes the preparation of bis-β-trialkylammonium-ethyl ether halides (I) by various routes. These compounds were evaluated with respect to their action on the transmission in autonomic ganglia.

$$X^-R_1R_2R_3\overset{+}{N}CH_2CH_2OCH_2CH_2\overset{+}{N}R_1'R_2'R_3'X^-$$

I

The finding that succinylcholine (II), which can be considered as a 'twin'-molecule of acetylcholine linked through the acetyl groups had curarizing properties comparable to these of decamethonium compounds (III)[1,2] has provided a great stimulus to the search for new curarimimetic agents among the 'twin' or 'bolaform' molecules [3,4,5].

$$X^-(CH_3)_3\overset{+}{N}CH_2CH_2OCOCH_2CH_2COOCH_2CH_2\overset{+}{N}(CH_3)X^-$$

II

$$X^-(CH_3)_3\overset{+}{N}CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2\overset{+}{N}(CH_2)_3X^-$$

III

$$X^-(CH_3)_3\overset{+}{N}CH_2CH_2CH_2CH_2CH_2\overset{+}{N}(CH_3)_3X^-$$

IV

This work has shown that, in general, introduction of one or more, 'hetero' atoms in the alkylene chain between the two charged nitrogen atoms does not greatly influence the biological activity of the molecule.

Although the similarity between the action of succinylcholine and decamethonium is doubtless very superficial the same line of reasoning would lead one to believe that, since bis-trimethylammoniumpentane halides (IV) and certain bis-trialkylammoniumhexane halides (hexamethonium halides) are ganglion blocking agents, the bis-trialkylammonium-oxa-pentane halides (I), which can be considered as 'twin' molecules of choline and its homologues should also possess ganglionic blocking activity. Although this view is not easy to reconcile with the observation by Dale [6] that bis-trimethylammoniumethyl ether had weak muscarinic properties (of the same order of magnitude as the activity of choline), it was substantiated through the present work, a prerequisite for appearance of ganglion blocking activity being that one of the methyl substituents on each nitrogen be exchanged for a higher alkyl group *e.g.* ethyl.

This is in line with newer results from this laboratory [7] showing bis-trialkylammonium-thia-pentane halides with at least one ethyl group on each nitrogen to be more potent ganglionic blocking agents than bis-trimethylammonium-thia-pentane halides, which were recently reported by Bergel [8] to possess such activity. A similar relation exists for the bis-trialkylammoniumhexane halides themselves [9] and for the bis-trialkylammonium-aza-pentane halides [10].

The preparation of bis-ammoniumethyl ethers was attempted first by the classical route [11] from bis-β-haloethyl ether and tertiary amine. This method leaves little choice in the combination of N-alkyl groups and it soon became apparent that the method also had other shortcomings. The most serious of these was the necessity of using bis-iodoether if yields of a higher order were required. The use of the more readily accessible β-chloroether, due to the more strenous reaction conditions, consistently resulted in low yield of the desired quaternary compound and a high proportion of by-products, presumably due to ring closure. An exception to this was the preparation of bis-pyridiniumethyl ether chloride, where no alkyl split with subsequent ring closure can take place.

It was later found that bis-ammonium ethers could be prepared conveniently by alkylation of the bis-tertiary amines (V) obtained by a Williamson condensation of a β-dialkylaminoethyl chloride with the sodium alkoxide of a β-dialkylaminoethanol in an inert medium. This method makes possible a much greater variety in the combination of N-alkyls, including 'hybrid' ethers, *i.e.* ethers containing different groupings in the two ends of the molecule.

$$(R_1)_2NCH_2CH_2OCH_2CH_2N(R_2)_2$$

V

Table 1.

$$X^-R_3(R_1)_2\overset{+}{N}CH_2CH_2OCH_2CH_2\overset{+}{N}(R_2)_2R_3X^-$$

Code no.	R_1	R_2	R_3	X	M.p. °C	Recryst. from [a]	Yield, % [b]	Emp. formula	Anal. calc.	%X^- found
As-3553	CH_3	CH_3	CH_3	J	305	—	88	$C_{10}H_{26}ON_2J_2$	57.10	56.85
As-3558	CH_3	CH_3	CH_3	CH_3SO_4 [c, d]	199	A	46	$C_{12}H_{32}O_9N_2S_2$		
As-3554	CH_3	CH_3	C_2H_5	Br	277	—	69	$C_{12}H_{30}ON_2Br_2$	42.30	42.31
As-3501	CH_3	CH_3	n-C_3H_7	Br	189	A-Ac(1:5)	64	$C_{14}H_{34}ON_2Br_2$	39.35	39.12
As-3502	CH_3	CH_3	n-C_4H_9	Br	222	A-Ac(1:5)	79	$C_{16}H_{38}ON_2Br_2$	36.80	36.94
As-3504	CH_3	CH_3	C_3H_5	Br	179	A-Ac(2:1)	41	$C_{14}H_{30}ON_2Br_2$	39.75	39.55
As-3508	CH_3	CH_3	CH_2Ph	Cl [d]	194	A-Ac(1:3)	42	$C_{22}H_{34}ON_2Cl_2$	17.15	17.18
As-3509	CH_3	CH_3	CH_2COOEt	Cl [d]	169	A-Ac(1:5)	78	$C_{16}H_{34}O_3N_2Cl$	17.48	17.34
As-3659	C_2H_5	C_2H_5	CH_3	J	259	—	96	$C_{14}H_{34}ON_2J$	50.75	50.19
As-3689	C_2H_5	C_2H_5	C_2H_5	Br	235	A	41	$C_{16}H_{38}ON_2Br_2$	36.80	37.01
As-4179	C_2H_5	CH_3	CH_3	J	262	M-A(1:1)	58	$C_{12}H_{30}ON_2J_2$	53.75	53.83
As-4178	C_2H_5	CH_3	C_2H_5	Br	261	—	68	$C_{14}H_{34}ON_2Br_2$	39.25	39.18
As-3594	pyridinium			Cl	156	—	62	$C_{14}H_{18}ON_2Cl_2$	23.60	23.04

[a] A:ethanol; Ac:acetone; M:methanol.
[b] after recrystallization.
[c] % N calc. 6.79; % N found 6.84.
[d] hygroscopic.

Thus from the three possible ethers having two ethyl groups or two methyl groups on nitrogen *viz.* bis-β-dimethylaminoethyl ether (V) ($R_1 = R_2 = CH_3$), bis-β-diethylaminoethyl ether (V, $R_1 = R_2 = C_2H_5$), and bis-(β-dimethyl-β'-diethyl)aminoethyl ether (V, $R_1 = CH_3$; $R_2 = C_2H_5$) six different ammonium compounds having only ethyl and methyl substituents on nitrogen together with a number of compounds with other alkyl substituents on nitrogen have been prepared. These ammonium compounds are summarized in Table 1.

The extension of the method to the preparation of ethers in which the nitrogen is part of a heterocyclic ring system and to the preparation of ethers containing other alkylene groups than ethylene will be the subject of subsequent papers.

The quaternary bis-ammonium halides (I) were examined for ganglionic blocking activity on the cervical ganglion of the cat (nictitating membrane contraction).

Some preliminary data are shown in Table 2.

A more detailed report on the pharmacology of these compounds will appear elsewhere.

Table 2.

Compound	G.B.A. [a]	LD_{50} [c] mg/kg
Hexamethonium bromide [b]	100	38
As 3553	7	1450
As 3554	40	215
As 4178	140	46

a) Expressed in per cent of hexamethonium bromide activity.

b) In doses of 0.25 — 1.00 mg/kg i.v.

c) Mice, intraperitoneal route.

EXPERIMENTAL *

Bis-β-chloroethyl ether. The only quality of bis-(β-chlorethyl) ether available at the outset of this work contained rather large amounts of halogenated impurities, which could only be removed by laborious methods. Accordingly a laboratory method for preparation of the bis-chloroether was developed using bis-β-hydroxyethyl ether (diethylene glycol, Mo & Domsjö) as starting material. Diethylene glycol, 106 g (1 mole) was dissolved in 212 g of pyridine (2.66 mole). To this was added 238 g (2 moles) of thionyl chloride under stirring during two hours. After one night at room temperature, the mixture was refluxed for one hour, cooled, and poured into 2 l of a 5 % solution of sodium hydroxide in water. This mixture was extracted with ten portions of 300 ml ether, the ether extract washed with approximately 100 ml of 4 *N* sulfuric acid, then twice with 500 ml of water, and dried over calcium chloride. The ether was removed and the residue distilled at reduced pressure. Yield: 88 g (62 %). B.p. 65° C at 15—16 mm Hg. Redistillation at atmospheric pressure gives a b.p. 176—177° (Literature [12] 177—178°).

$C_4H_8Cl_2O$ (M : 143) Calc. Cl 49.6 Found Cl 50.06 (Stepanow)

Bis-β-iodoethyl ether. Prepared form 29.7 g (0.1 mole) of mercuric sulfate and an excess of ethylene by the method of Sand [13] as modified by Schoeller [14]. Yield 23 g (74 %) of crude product.

Condensations with bis- chloroethyl ether, bis-(β-pyridinumethyl) ether dichloride. (As-3594). Dry pyridine, 16 g (appr. 0.2 mole) was mixed with 14.2 g of β-dichloroethyl ether (0.1 mole) and heated under reflux for twenty minutes (*cf.*[15]). After cooling down to room temperature the mixture separates into two layers of which the lower crystallizes on standing. The reaction mixture is dissolved in absolute ethanol which, upon evaporation, leaves only crystals. These are recrystallized twice from ethanol-acetone (1 : 2). M.p. 155—7° C, Yield 18.5 g (62 %) (see Table 1). Similar attempts of preparing bistrialkylammoniumethyl ethers by heating equimolar amounts of the reagents in a solvent (*i. e.* ethanol or isopropanol) to 100° C in sealed tubes for periods of time varying from two to twenty four hours afforded in every case a very small amount of crystalline material. The main products were liquid and distillable, but no further attempt of elucidating their structure was made.

* All melting and boiling points are uncorrected. The nitrogen and halogen values are macro determinations by Mrs. E. Ifversen and Mrs. G. Speggers of this laboratory. Carbon and hydrogen values are micro determinations by Mr. A. Grossmann, University of Copenhagen.

Bis-(β-trimethylammonium)-ethyl ether diiodide (As-3553). Prepared according to Ewins [11] from 15.6 g (0.05 mole) of bis-β-iodoethyl ether and 100 ml of ethanol containing approximately 10 g of trimethylamine. Yield 6.5 g (32 %) of plates, m.p. 301° (from ethanol), (Lit. [11] 275°). No depression of m.p. when mixed with a specimen prepared by the other method.

Bis-β-dimethylaminoethyl ether ($V, R_1=R_2=CH_3$). An alkoxide is prepared from 89.1 g of β-dimethylaminoethanol (1 mole) dissolved in 300 ml of dry toluene by addition of 23 g of clean sodium metal. The alkoxide soon begins to separate. It is necessary to heat under reflux for approximately 8 hours to ensure complete reaction. Any unreacted sodium is removed before proceeding. In the meantime a solution of β-dimethylaminoethyl chloride in toluene is prepared by hydrolyzing 144.1 g of the hydrochloride of β-dimethylaminoethyl chloride (1 mole) with a solution of 60 g sodium hydroxide in 150 ml of water, extracting the free chloroamine three times with 300 ml of toluene, and drying the combined toluene extracts with 150 g of potassium carbonate. This solution is filtered and added to the alkoxide suspension. Heating is continued for another 8 hours, when the salt formed in the reaction is removed by filtration, air-dried, and weighed for control. The filtrate is distilled through a 60 cm Widmer column for removal of toluene. The residue is distilled *in vacuo* which gives 105 g (66 %) of the desired ether, b.p. 79—83° C at 12—16 mm Hg. Redistillation to prepare a sample for analysis affords 83 g (52 %) of a middle fraction, colorless oil which darkens on standing, b.p. 79—81° C at 15 mm Hg. n_D^{25} 1.4290.

$C_8H_{20}N_2O$ (160)	Calc.	C 60.00	H 12.55	N 17.48
	Found	» 59.62	» 12.45	» 16.89

The hydrochloride was prepared by passing a stream of dry hydrogen chloride through the reaction mixture in toluene. The brown mass formed was crystallized from benzene-ethanol (1 : 1), m.p. 163°.

$C_8H_{22}N_2OCl_2$ (233.2) Calc. Cl 30.4, found 30.4. Picrate, m.p. 140°

Bis-β-diethylaminoethyl ether (V, $R_1=R_2=C_2H_5$). Prepared exactly like the bis-dimethyl ether from 117.2 g of diethylaminoethanol (1 mole), 23 g of sodium, and 172.1 g of diethylaminoethyl chloride, HCl. Heating period 12 h. Yield 132 g (60 %) of colorless oil, b.p. 121—23° C at 15 mm Hg. n_D^{23} 1.4389.

$C_{12}H_{28}N_2O$ (216.4)	Calc.	C 66.60	H 13.06	N 12.95
	Found	» 66.55	» 12.91	» 12.77

Hydrochloride, m.p. 214°

$C_{12}H_{30}N_2OCl_2$ (289.3) Calc. Cl 24.5, found Cl 24.82. Picrate, m.p. 130° (recryst. lowers m. p.).

Ethyl-β-diethylaminoethyl ether. Condensation was also carried out in ethanol as a solvent. The major part of the reaction product in this case destilled at 55—60° C at 15 to 16 mm Hg, indicating that in alcohol sodium ethoxide reacts in preference to the amino-alkoxide.

Bis-(β-dimethyl-β'-diethyl)-aminoethyl ether (V,$R_1=CH_3$, $R_2=C_2H_5$). Prepared exactly as above from 117.2 g of diethylaminoethanol, 23 g of sodium, and 144.1 g of dimethylaminoethyl chloride, HCl. Heating period 18 h. Yield 83 g (44 %) of colorless oil, b.p. 103° C at 15 mm. n_D^{25} 1.4337.

$C_{10}H_{24}N_2O$ (188.3)	Calc.	C 63.8	H 12.8	N 14.90
	Found	» 64.06	» 12.69	» 14.85

Hydrochloride, m.p. 180°.

$C_{10}H_{26}N_2OCl_2$ (261.2) Calc. Cl 27.15, found Cl 27.44. Picrate, m.p. 106°.

Bis-(β-trialkylammoniumethyl ether halides. (Table 1.) The quaternary compounds were prepared by mixing the amine, the appropriate alkyl halide (or dimethyl sulfate) in a slight excess, and the tenfold volume of dry acetone. If no precipitate had formed after one night the mixture was heated for 6 h., if necessary in a sealed tube. The precipitate was then removed by filtration and recrystallized. The quaternary derivatives were formed very readily from the bis-dimethylaminoethyl ether, the methoiodide, methosulfate and allobromide in a violent reaction, while the mixed ether reacted less readily and the bis-diethylether showed little tendency to react. The physical constants of these derivatives are summarized in Table 1.

SUMMARY

A convenient synthesis (Williamson condensation) for the preparation of bis-β-dialkylaminoethyl ethers is described.

The preparation of thirteen bis-β-trialkylammoniumethyl ether salts is described.

These compunds have a paralyzing action on the transmission in autonomic ganglia. The 'asymmetric' members shows the higher order of activity.

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