NEUROMUSCULAR BLOCKING AGENTS

‡Part VII. Linear Polyonium Ethers

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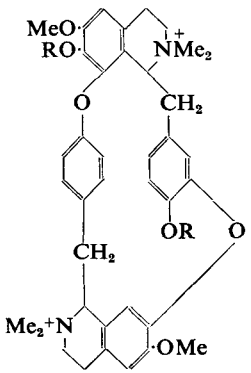
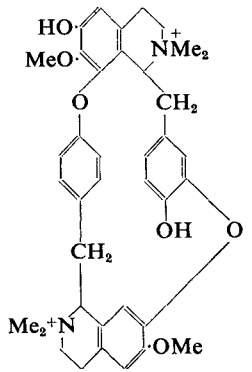
The tris-onium ethers (XIII, A and B) and the tetra-onium ethers (XV A, B and C), together with the corresponding polymethylene tris-onium (XIV A and B) and polymethylene tetra-onium compounds (XVI, A, B and C), have been synthesised. Replacement of a methylene group in the inter-onium polymethylene chain by an ether link almost always lowers muscle relaxant potency.

Before the introduction of muscle relaxants, ether was often the volatile anaesthetic of choice, since it is safe and gives good muscle relaxation. Ether not only possesses muscle-relaxant properties of its own[1–9], but it has also been shown to potentiate the actions of tubocurarine, gallamine and other non-depolarising relaxants. Many natural and synthetic non-depolarising muscle relaxants including tubocurarine, gallamine laudexium, prodeconium and oxydipentonium are themselves ethers, and, their potency is often dependent on the nature and position of the ether links[10]. Thus tubocurarine dimethylether (I, R = Me) is more potent than tubocurarine, (I, R = H)[10,11], though higher alkyl ethers of tubocurarine are less potent than the parent compound. The isomeric (+)-chondocurarine (II), which differs from (+)-tubocurarine solely in the position of the methoxyl and hydroxyl substituents, is approximately 2·9 times more potent than the latter in the rabbit[10]. Collier and



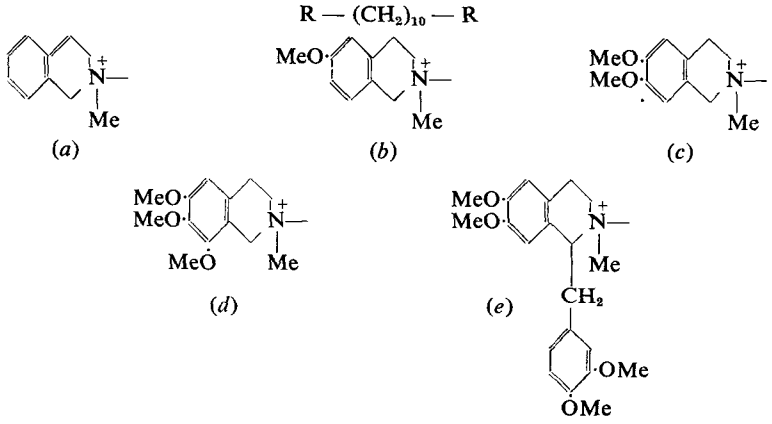
(I)



(II)

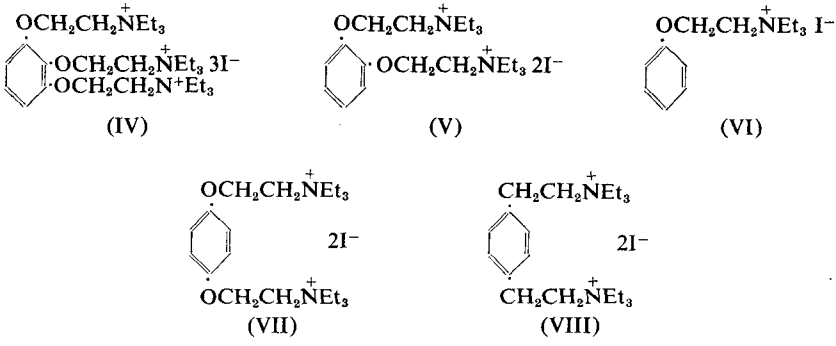
‡Part VI, see Reference 26.

others[12,13] have shown similarly in a series of methylene bis-tetrahydroisoquinolinium (III*a*-III*d*) and related compounds that activity increases with aromatic methoxyl substitution. Laudexium (III*e*)[12–14] is one of the most potent curarising agents in this series.



(III)

Bovet and others have synthesised and tested a large number of muscle relaxants containing ether links, including a series of ethers of choline and homologous amino-alcohols with mono- di- or tri-hydric phenols. Comparison of gallamine (IV), the most important compound of this group, with compounds 2559F (V) and 3697RP (VI) shows that potency increases as the number of β-(triethylammonium)-ethoxy groups increases[15]. Bovet and his colleagues[16] have shown, however, that compounds (VII) and (VIII) which are analogous, though not strictly comparable, are equipotent in the rabbit, and this suggests that potency is more a function of the number of ethonium groups rather than of the number of ether links.



(IV) (V) (VI)

(VII) (VIII)

Aliphatic ethers with curarising activity are also known. In 1953 Levis and her colleagues[17,18] investigated a group of compounds which resembled the methonium compounds of Barlow and Ing[19] and Paton and Zaimis,[20] but containing one, two, or three ether oxygens in the interonium

chain. The compounds (IX, $n = 4$ or 5) were less potent than decamethonium, whilst a second or third oxygen in compounds (X) and (XI) progressively lowered potency. The view has been put forward by Girod and Häfliger[21] that the curarising potency in aliphatic compounds with two or more ether oxygens is related primarily to the number of methylene groups separating the ether oxygens, and their observations on the series of compounds (XII) suggest that this may be so. Thus activity

$$\left[Me_3\overset{+}{N}\cdot(CH_2)\cdot_n O\cdot(CH_2)\cdot_n\overset{+}{N}Me_3\right]2I^- \quad \left[Me_3\overset{+}{N}\cdot(CH_2)_2\cdot O\cdot(CH_2)\cdot_2\overset{+}{N}Me_3\right]2I^-$$

(IX) (X)

$$\left[Me_3\overset{+}{N}\cdot(CH_2)_2\cdot O\cdot(CH_2)_3\cdot O\cdot(CH_2)_2\cdot O\cdot(CH_2)\cdot_2\overset{+}{N}Me_3\right]2I^-$$

(XI)

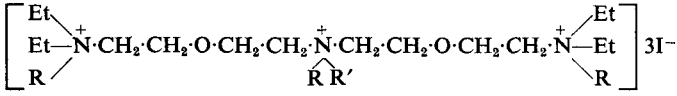
$$\left[R_3\overset{+}{N}\cdot(CH_2)_m\cdot O\cdot(CH_2)_n\cdot O\cdot(CH_2)_m\cdot\overset{+}{N}R_3\right]2I^-$$

(XII)

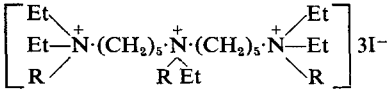
falls progressively in the three compounds (XII) where R = Et, $n = 10$, $m = 2$; R = Et, $n = 8$, $m = 3$; and R = Et, $n = 6$, $m = 4$. This, however, leaves undetermined the question of the relative importance of inter-oxygen or oxygen-nitrogen distances, since further comparisons are between compounds of varying inter-onium spacing. Nor is this point clarified by the work of Hazard and Cheymol[29] and of Vanecek and Protiva[23] on similar compounds. The difficulties of assessing clearly the influence of ether oxygen upon curarising activity in aliphatic compounds are accentuated by the fact that different workers have used different preparations and species and that results for comparable non-ethers are not always available.

Chemical

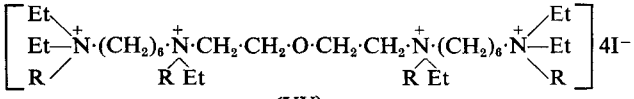
The preparation of the tris-onium compounds (XIII, R′ = Et, R = Me and Et) and of the tetra-onium compounds (XV, R = Me and Et) incorporating the diethyl ether link is now described. The related polymethylene compounds (XIV, R = Me, Et and Pr) and (XVI, R = Me, Et and Pr) have also been prepared for comparison with the ether-linked derivatives.



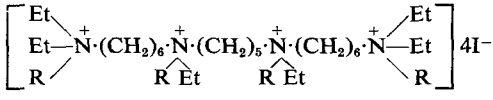
(XIII)



(XIV)



(XV)



(XVI)

The closely related compound (XIII, R = Et, R′ = Me) prepared by Protiva and Pliml[25] was obtained by condensation of diethylaminoethyl chloride with *N*-methyldiethanolamine in the presence of sodamide, and quaternisation of the resulting bis(2-diethylaminoethoxyethyl) methylamine. Although the latter was obtained in 57 per cent yield, the ready availability of diglycollic acid led to the choice of the following methods based on those used in our earlier work[25,26], for the preparation of bis(2-diethylaminoethoxyethyl) ethylamine.

Diglycollic anhydride prepared by dehydration of diglycollic acid with acetic anhydride[27], was treated with methanol to yield methyl hydrogen diglycollate[28], and the latter converted via the acid chloride to methyl *NN*-diethyldiglycollate (XVII). Reduction of the latter with lithium aluminium hydride gave an excellent yield of diethylaminoethoxyethanol (XVIII) which, however, was converted via diethylaminoethoxyethyl bromide hydrobromide into *N*(2-diethylaminoethoxyethyl)ethylamine (XIX) only in rather poor yield. Bromination of diethylaminoethoxy-

$Et_2N{\cdot}CO{\cdot}CH_2O{\cdot}CH_2COO{\cdot}Me$ (XVII)

$Et_2N{\cdot}(CH_2)_2{\cdot}O{\cdot}(CH_2)_2{\cdot}OH$ (XVIII)

$Et_2N{\cdot}(CH_2)_2{\cdot}O(CH_2)_2{\cdot}NH\ Et$ (XIX)

ethanol with thionyl bromide[29] under much milder conditions than with hydrobromic acid failed to improve the yield of the base (XIX), the low yield probably being due to the preferential cyclisation of 2-diethylaminoethoxyethyl bromide in the presence of ethylamine.

NN-Diethyldiglycollamic acid (XXIII) required for the condensation with *N*(2-diethylaminoethoxyethyl) ethylamine, was prepared by hydrolysis of methyl *NN*-diethyldiglycollamate with ethanolic potassium hydroxide. The product, obtained after evaporation of the ethanol, acidification extraction and distillation, had a high equivalent weight, and could not be separated into its components by fractionation or by chromatography on a charcoal-cellulose column. Normal two-phase extraction procedures were also incapable of effecting a separation of acidic and neutral fractions of the product, due to their high water-solubility. A satisfactory separation was, however, effected by dissolving in dry ether, and precipitating acid material with dry ammonia gas. Evaporation of the ether gave a neutral oil which was identified as *NNN′N′*-tetra-ethyldiglycolldiamide (XX). The precipitated ammonium salts were only partially soluble in ethanol, the insoluble material being identified as ammonium diglycollate (XXI). Precipitation of the ethanol-soluble salt with ether gave ammonium *NN*-diethyldiglycollamate (XXII). Purification of the latter, however, proved difficult, owing to its partial

dissociation in the hot ethanol used for recrystallisation, which resulted in loss of ammonia and consequent contamination of the salt by traces of

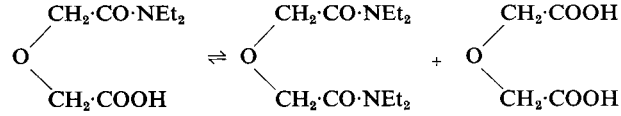
$Et_2N{\cdot}CO{\cdot}CH_2O{\cdot}CH_2{\cdot}CO{\cdot}NEt_2$ (XX)

$NH_4{\cdot}O{\cdot}CO{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}NH_4$ (XXI)

$Et_2N{\cdot}CO{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}COO{\cdot}NH_4$ (XXII)

the more-soluble parent acid. Decomposition of the almost pure ammonium *NN*-diethyldiglycollamate with dilute hydrochloric acid, yielded the required *NN*-diethyldiglycollamic acid (XXIII).

At this stage no satisfactory explanation could be advanced for the formation of *NNN'N'*-tetraethyldiglycolldiamide (XX) and diglycollic acid as by-products in the preparation of *NN*-diethyldiglycollamic acid by hydrolysis of pure methyl *NN*-diethyldiglycollamate. Attention was therefore turned to the preparation of *NN*-diethyldiglycollamic acid by an alternative route, the reaction of diglycollic anhydride with diethylamine. Direct condensation under reflux in the absence of solvent followed by distillation gave an impure product, which, when dissolved in ether and treated with ammonia as described above, gave the same three products obtained in the first method. Similar results were also obtained when the distillation step was omitted, suggesting that *NNN'N'*-tetraethyldiglycolldiamide and diglycollic acid are formed as by-products of the condensation reaction, though this was shown subsequently not to be the case. Thus condensation of diglycollic anhydride with diethylamine under much milder conditions, using benzene as solvent and isolation of the product, without prior distillation, by precipitation of the ammonium salt, gave the required *NN*-diethyldiglycollamic acid, and only trace amounts of diglycollic acid and its bis-diethylamide. That these by-products are formed in all the above reactions by the following disproportionation at elevated temperatures was demonstrated by distilling *NN*-diethyldiglycollamic acid under vacuum, and examining the distillate by the ammonium salt separation technique. All three products were found to be present, *NNN'N'*-tetraethyldiglycolldiamide being formed to the extent of approximately 20 per cent. The separation method is not suitable for a more

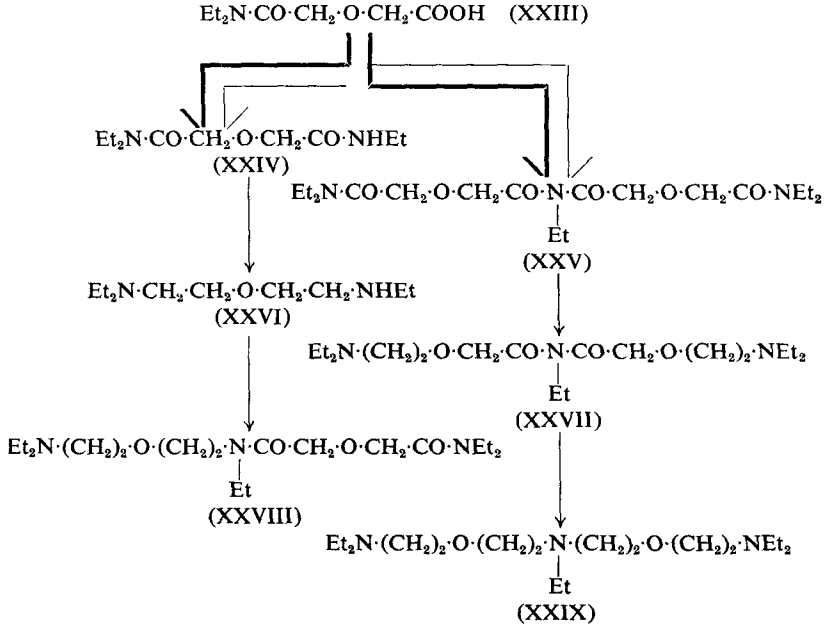


detailed study of the disproportionation owing to the partial dissociation of both ammonium diglycollate and ammonium *NN*-diethyldiglycollamate.

Analogous disproportionations, described by Fourneaux and Sabetay[30,31], have been used for the preparation of the monoesters of succinic, glutaric, adipic, azelaic, sebacic and similar dibasic acids. The acids when heated for several hours with the corresponding di-ester reach an equilibrium with the monoester, which is present to the extent of 20 to 30 per cent. The position of the equilibrium, which can also be reached from the monoester, appears to vary with the nature of the acid,

the time of heating and the temperature. So far as we are aware such acidolysis type reactions have not been reported previously in the preparation of the half amides of dibasic acids, and were not observed in the preparation either of *NN*-diethylglutaramic acid (present work) or of *NN*-diethyladipamic and *NN*-di-n-propyladipamic acids[25]. Anschutz and Jaeger[28], however, have reported the formation of dimethyl diglycollate as a by-product in the preparation of methyl hydrogen diglycollate from diglycollic anhydride and methanol, which suggests that such disproportionations are facilitated by the ether link in the diglycollic acid series. The significantly lower dissociation constants of diglycollic acid (pK_1 2·96, pK_2 4·43) compared with glutaric acid (pK_1 4·32, pK_2 5·54) suggest that the mechanism may perhaps be ionic as in the Cannizzaro and related reactions.

NN-Diethyldiglycollamic acid (XXIII) was used to prepare *N*-(2-diethylaminoethoxyethyl) ethylamine in improved yield as outlined below. Conversion to the acid chloride and reaction with excess ethylamine gave *NNN'*-triethyldiglycolldiamide (XXIV) together with some bis-(*NN*-diethyldiglycollamoyl) ethylamine (XXV). Reaction of the acid



chloride with ethylamine in the presence of triethylamine, on the other hand, gave mainly the base (XXV). The two amides were not readily separated by fractional distillation, but reduction of the mixture with lithium aluminium hydride yielded the required *N*-(2-diethylaminoethoxyethyl) ethylamine (XXVI), which was readily separated by fractionation from the accompanying *NN*-bis(2-diethylaminoethoxyacetyl) ethylamine (XXVII). Condensation of the base (XXVI) with *NN*-diethyldiglycollamoyl chloride, gave *NNN'*-triethyl-*N'*-(2-diethylaminoethoxyethyl)

diglycolldiamide (XXVIII), which on reduction with lithium aluminium hydride yielded *NN*-bis-(2-diethylaminoethoxyethyl) ethylamine (XXIX). Quaternisation of the latter with methyl and ethyl iodides gave the required tris-onium compounds (XIII, R′ = Et, R = Me and Et).

The resistance of the imide link in *NN*-bis(2-diethylaminoethoxyacetyl)-ethylamine (XXVII) to reduction by lithium aluminium hydride is typical of such compounds. Phthalimide is reduced, in unstated yield, only after 28 hours refluxing with the reagent in ether[32]. Prolonged reduction of the imide (XXVII) with lithium aluminium hydride, similarly gave *NN*-bis-(2-diethylaminoethoxyethyl) ethylamine (XXIX) in 35 per cent yield.

The polymethylene tris-onium compounds (XIV, R = Me and Et) were obtained by quaternisation of *NN*-bis-(5-diethylaminopentyl)ethylamine, which was prepared from ethyl hydrogen glutarate by methods already described for the preparation of *NN*-bis-(6-diethylaminohexyl)ethyl-amine[25].

1,19-Bis-diethylamino-7,13-diethyl-7,13-diazanonadecane and 1,19-bis-diethylamino-7,13-diethyl-7,13-diaza-10-oxanonadecane, intermediates in the preparation of the tetra-onium compounds (XVI, R = Me and Et) and (XV, R = Me and Et), were obtained from glutaric and diglycollic acids respectively, and 6-diethylaminohexyl-ethylamine by methods already described[26].

Experimental

Ethyl NN-*diethylglutaramate* was prepared from ethyl hydrogen glutarate (93·5 g.) by the method described for the preparation of ethyl *NN*-diethyladipamate.[25] *Ethyl* NN-*diethylglutaramate* was obtained as a yellow oil (114·2 g., 91 per cent), b.p. 120–124°/0·3 mm., n_D^{25} 1·4520. Found: N, 6·2 per cent. $C_{11}H_{21}NO_3$ requires N, 6·5 per cent.

5-*Hydroxpentyldiethylamine* was prepared by lithium aluminium hydride reduction of ethyl *NN*-diethylglutaramate (89 g.) and was obtained as a colourless oil (60·1 g., 91·3 per cent)[24], b.p. 90°/0·55 mm. n_D^{21} 1·4528.

5-*Diethylaminopentylethylamine* was prepared from 5-hydroxypentyl-diethylamine by the method described for the preparation of 6-diethyl-aminohexylethylamine[25]. The *product* was obtained as a colourless oil (6·8 g., 12 per cent), b.p. 68–70°/0·25 mm., $n_D^{24·5}$ 1·4428.

NN-*Diethylglutaramic acid* was prepared from ethyl *NN*-diethyl-glutaramate (24·5 g.) by the method described for the preparation of *NN*-diethyladipamic acid[25]. NN-*Diethylglutaramic acid* was obtained as a yellow viscous oil (11·3 g., 54 per cent), b.p. 173–175°/0·45 mm., n_D^{24} 1·4747. Found: N, 7·5 per cent. $C_9H_7NO_3$ requires N, 7·5 per cent.

Bis-5-*diethylaminopentylethylamine* was prepared from *NN*-diethyl-glutaramic acid (4·8 g.) and excess 5-diethylpentylethylamine (6·7 g.) by the method described for the preparation of bis-6-diethylaminohexyl-ethylamine[25].

Bis-5-*diethylaminopentylethylamine* was obtained as a yellow oil (2·4 g., 33 per cent), b.p. 147–150°/0·25 mm., n_D^{23} 1.4585. Found: N, 12·8 per cent. $C_{20}H_{45}N_3$ requires N, 12·8 per cent.

Diglycollic anhydride was prepared from diglycollic acid (269 g.) by refluxing with acetic anhydride (525 g.) for 4 hours. Acetic acid was removed by distillation, and the product refluxed with acetic anhydride (242 g.) for a further 2 hours. Removal of excess acetic anhydride and distillation gave the product as a colourless crystalline solid (220 g., 94·4 per cent), b.p. 130–131°/20 mm., m.p. 97°. Hurd and Glass[27] gave b.p. 130°/20 mm.

Methyl hydrogen diglycollate. Diglycollic anhydride (186 g.) was refluxed with methanol (65 ml.) for 2 hours, and the product fractionated to yield methyl hydrogen diglycollate (175·6 g., 74 per cent), b.p. 176°/14 mm., n_D^{23} 1.4450. Anschutz and Jaeger[28] gave b.p. 173–174°/12 mm.

Methyl NN-*diethyldiglycollamate.* Methyl hydrogen diglycollate (175·6 g.) in thionyl chloride (150 ml.) was heated to reflux for 1½ hours, and the excess reagent removed under reduced pressure. The acid chloride without further purification, in ether (300 ml.) was added (45 minutes) to a stirred solution of diethylamine (280 ml.) in ether (1 l.). The diethylamine hydrochloride was removed by filtration, the filtrate dried (Na_2SO_4), the solvent distilled, and the product fractionated to yield *methyl* NN-*diethyldiglycollamate* as a pale yellow oil (200 g., 83 per cent), b.p. 128–130°/0·55 mm., $n_D^{23·5}$ 1·4583. Found: N, 6·8. $C_9H_{17}NO_4$ requires N, 6·9 per cent.

NN-*Diethyldiglycollamic acid.* (*a*) Methyl *NN*-diethyldiglycollamate (198·2 g.) was refluxed for 30 minutes with ethanolic potassium hydroxide (1,889 ml.; 1·033 0·5N). After neutralisation of the excess alkali with dilute hydrochloric acid (100 ml.; 1·084 0·5N), the bulk of the ethanol was removed by distillation, the solution acidified with dilute hydrochloric acid (172 ml.; 5N) and concentrated under reduced pressure. The solution was extracted with benzene, the solution dried (Na_2SO_4), the solvent evaporated and the product distilled to yield a yellow oil (156 g.), b.p. 180–187°/0·3 mm., n_D^{18} 1·4759, containing some solid material. Found: equiv. 237·8 ($C_8H_{15}NO_4$ requires, equiv. 189·2). The crude product (54 g.) was dissolved in ether (1 l.) and dry ammonia gas bubbled through the solution for 20 minutes, to yield a precipitate of mixed ammonium salts (37·2 g.). Evaporation of the filtrate and distillation of the product yielded NNN'N'-*tetraethyldiglycolldiamide* as a pale yellow oil (21·5 g.) b.p. 159–160°/0·08 mm., n_D^{20} 1·4777. Found: N, 11·6 per cent. $C_{12}H_{24}N_2O_3$ requires N, 11·5 per cent.

The mixed ammonium salts were refluxed gently with ethanol (300 ml.), and the solution cooled, and filtered to yield the insoluble crude *ammonium diglycollate*, m.p. 225–226° (decomp.). Concentration of the ethanolic solution and addition of ether gave a colourless crystalline precipitate of *ammonium* NN-*diethyldiglycollamate* (29·5 g.), m.p. 125°–126°. Found: N, 13·8. $C_8H_{18}NO_4$ requires N, 13·6 per cent.

Ammonium *NN*-diethyldiglycollamate (29 g.) was acidified with dilute hydrochloric acid (142 ml.; 0·9945N), and the solution extracted with benzene to yield NN-*diethyldiglycollamic acid* as a yellow viscous oil (20·5 g.), n_D^{24} 1·4743, which slowly crystallised on standing to yield an almost colourless solid m.p. 68°. Found: N, 7·3; equiv. 188·9. $C_8H_{15}NO_4$

requires N, 7·4 per cent; equiv. 189·2. S-*Benzylthiuronium salt*, m.p. 150–151°. Found: N, 11·65. $C_{16}H_{25}N_4O_2S$ requires N, 11·8 per cent.

(*b*) Diethylamine (25 ml.) was slowly added to diglycollic anhydride (25 g.) and the mixture permitted to reflux, without the external application of heat, until the anhydride had completely dissolved (45 minutes). The mixture was refluxed for a further 30 minutes, and excess diethylamine then removed by evaporation under reduced pressure. The crude product was dissolved in ether (250 ml.) and dry ammonia gas bubbled through the solution for 60 minutes, to yield a precipitate of mixed ammonium salts. Evaporation of the filtrate yielded a neutral oil (11·7 g.), which on distillation gave *NNN'N'*-tetraethyldiglycolldiamide b.p. 160°/0·08 mm. $n_D^{17·5}$ 1·4792. Found: N, 11·4. Calc. for $C_{12}H_{24}N_2O_3$, N, 11·5 per cent.

The mixed ammonium salts were gently heated with dry ethanol (50 ml.), and the solution cooled and filtered to yield ammonium diglycollate (6·9 g.) m.p. 225–226° (decomp.). Concentration of the ethanolic solution and addition of ether gave a precipitate of ammonium *NN*-diethyldiglycollamate (15·1 g.), m.p. 125°. Evaporation of the mother liquors yielded an acid oil (12·1 g.), being a mixture of ammonium *NN*-diethyldiglycollamate and *NN*-diethyldiglycollamic acid. *NN*-Diethyldiglycollamic acid (9·3 g.) was obtained by decomposition of the ammonium *NN*-diethyldiglycollamate by the method described above.

(*c*) Diethylamine (150 ml.) in dry benzene (300 ml.) was run into an ice-cold solution of diglycollic anhydride (70 g.) in dry benzene (250 ml.), the mixture slowly heated and refluxed for 3 hours. Evaporation of the solvent and excess diethylamine under reduced pressure gave an oil, which was dissolved in dry benzene (400 ml.). Dry hydrogen chloride was passed into the solution until a precipitate of diethylamine hydrochloride was obtained (ca. 20 min.). The precipitate was removed by filtration, and the filtrate treated for a further 5 minutes with dry hydrogen chloride. Excess HCl was removed by passing a stream of air through the solution heated to about 30°, solvent lost by evaporation being made up by further additions (3 × 150 ml.) from time to time. The solution was cooled in ice and salt, filtered from diethylamine hydrochloride, dried (Na_2SO_4), and evaporated to yield a golden brown viscous oil, which formed a brownish-white solid (93·5 g., 82 per cent) on standing. The solid was gently melted and triturated with dry ether (100 ml.) to yield *NN*-diethyldiglycollamic acid as a fine white solid, which was filtered and dried over P_2O_5 *in vacuo*. The product which was not completely pure, had equiv. 204·6, and was used in the next stage. An analytical sample was obtained by dissolving the acid (1 g.) in distilled water (20 ml.) and passed through a column of Zeocarb 225 (column dimensions 12 in. × 1¼ in., 120 g.) in its H^+ form. Evaporation of the eluate (800 ml.), yielded a clear oil which readily crystallised on cooling to yield *NN*-diethyldiglycollamic acid monohydrate, m.p. 68–69°. Found: N, 6·5; equiv. 206·1. $C_8H_{15}NO_4.H_2O$ requires N, 6·76; equiv. 207·2. Over P_2O_5 the monohydrate becomes oily, but recrystallises on exposure to air.

Disproportionation of NN-*diethyldiglycollamic acid.* *NN*-Diethyldiglycollamic acid (11 g.), 95–98 per cent pure, obtained from previous

experiments by the ammonium salt precipitation was distilled, to yield a homogeneous distillate (9·65 g.) b.p. 160–162°/0·06 mm, n_D^{22} 1·4757, equiv. 221·6. The products separated by precipitation from ether with ammonium as described above yielded *NNN'N'*-tetraethyldiglycolldiamide (1·90 g.), ammonium diglycollate (0·940 g.) and *NN*-diethyldiglycollamic acid (3·8 g.) equiv. 194 (required 189·2). A further yield of crude *NN*-diethyldiglycollamic acid (1·075 g.) was also obtained.

2-*Diethylaminoethoxyethanol.* Methyl *NN*-diethylglycollamate (76·6 g.) was reduced with lithium aluminium hydride as described for the preparation of 6-hydroxydiethylamine[33] to yield 2-diethylaminoethoxyethanol (53 g., 88 per cent) as a colourless oil, b.p. 79°/0·5 mm., n_D^{22} 1·4475. Found: N, 8·9; equiv. 160·1. Calc. for $C_8H_{19}NO_2$, N, 8·7 per cent; equiv. 161·2. Horne and Schriner[34] gave b.p. 92–95°/7 mm.

N-(2-*Diethylaminoethoxyethyl*)*ethylamine.* (*a*) *N*-(2-Diethylaminoethoxyethyl)ethylamine was prepared from 2-diethylaminoethoxyethanol (12·7 g.) by the method described for the preparation of 6-*n*-propylhexyldi-*n*-propylamine[25]. The *product* was obtained as a colourless oil (3·2 g., 21·6 per cent), b.p. 74°/0·45 mm., $n_D^{19·5}$ 1·4455.

(*b*) 2-Diethylaminoethoxyethanol (39·1 g.) in benzene (200 ml.) was stirred while a solution of thionyl bromide[29] (50·6 g.) in benzene (50 ml.) was added (40 min.). Evaporation of the reaction mixture under reduced pressure yielded a dark brown viscous liquid, which failed to crystallise. The liquid was dissolved in ethanol (100 ml.), and added (10 min.) to a refluxing solution of ethylamine (100 ml.) in ethanol (100 ml.), and the mixture refluxed for 1 hour. Evaporation of the liquid, basifying and extraction with ether yielded N-(2-*diethylaminoethoxyethyl*)*ethylamine* as a colourless oil (2·6 g., 5·8 per cent), b.p. 76°/0·5 mm., n_D^{21} 1·4470.

(*c*) *NN*-diethyldiglycollamic acid (38·3 g.) in benzene (20 ml.) was refluxed with thionyl chloride (20 ml.) for 15 minutes, and evaporated under reduced pressure. The acid chloride in benzene (120 ml.) was added slowly (25 min.) to a stirred solution of ethylamine (120 ml.) in benzene (500 m.). After evaporation to dryness under reduced pressure it was extracted with ether, filtered (to remove ethylamine hydrochloride) and dried (Na_2SO_4). On removal of solvent the product was distilled at 100–166°/0·45 mm. (35 g.). Lithium aluminium hydride reduction of the mixed amides and fractionation of the product yielded crude N-(2-*diethylaminoethoxyethyl*)-*ethylamine* b.p 78–82°/0·4 mm. (9·59 g., 25·2 per cent) n_D^{21} 1·4470. Continued fractionation yielded NN-*bis*-(2-*diethylaminoethoxyacetyl*)-*ethylamine*, b.p. 105/0·35 mm. (9·4 g.), $n_D^{25·5}$ 1·4713. Found equiv. (titration) 180·2. $C_{18}H_{37}N_3O_4$ requires equiv. 179·8.

NN-*Bis*-(2-*diethylaminoethoxyethyl*)*ethylamine.* (*a*) *NN*-Bis-(2-diethylaminoethoxyethyl)ethylamine was prepared from *NN*-diethyldiglycollamic acid (4·6 g.) and *N*-(2-diethylaminoethoxyethyl)ethylamine (4·6 g.) by the method described for the preparation of bis-(6-di-*n*-propylaminohexyl)-n-propylamine[25], and was obtained as a pale yellow *oil* (1·5 g., 19 per cent), b.p. 140–142°/0·3 mm., $n_D^{22·5}$ 1·4567. Found: N, 12·5. $C_{18}H_{41}N_3O_2$ requires N, 12·7 per cent.

(*b*) *NN*-Bis-(2-diethylaminoethoxyacetyl)ethylamine (14·3 g.) in ether (20 ml) was added (10 min.) to a stirred refluxing solution of lithium aluminium hydride (3 g.) in ether (200 ml). After refluxing for 14 hours and standing for 32 hours at room temperature the mixture was worked up and extracted in the usual manner to yield an oil, b.p. 80–130° (bath)/0·75 mm. (9·5 g.). Further extractions with benzene and ether yielded only a few more drops of oil. Fractionation of the product yielded (1) NN-*Bis*-(2-*diethylaminoethoxyethyl*)*ethylamine* as a pale yellow oil, b.p. 84–90°/0·75 mm. (5 g.), n_D^{21} 1·4645. Found equiv. (titration) 114·0. $C_{18}H_{41}N_3O_2$ requires equiv. 110·5. (2) Unchanged *NN*-bis-(2-diethylaminoethoxyacetyl)ethylamine b.p. 101–105°/0·7 mm. (3·2 g.), n_D^{21} 1·4660. Found equiv. (titration) 205·6. $C_{18}H_{37}N_3O_4$ requires equiv. 179·8.

NNN-*Tris-onium Compounds* were prepared from either *bis*-(5-diethylaminopentyl)ethylamine or *NN*-bis-(2-diethylaminoethoxyethyl)ethylamine by refluxing with the appropriate alkyl halide in ethanol, evaporation of the solvent and crystallisattion. Reflux time, crystallisation solvent and yields are indicated for each compound in that order, in parenthesis.

6,6-*Diethyl*-6-*azoniaundecylenebis*-(*triethylammonium*)*tri-iodide* (45 min., ethanol-ether; 36 per cent), m.p. 273–274°. Found: N, 5·1; I, 47·9. $C_{26}H_{60}I_3N_3$ requires N, 5·3; I, 47·9 per cent.

6-*Ethyl*-6-*methyl*-6-*azoniaundecylenebis*-(*diethylmethylammonium*) *tri-iodide* (10 min.; ethanol-methanol; 64 per cent), m.p. 266°. Found: N, 5·4; I, 50·6. $C_{23}H_{54}I_3N_3$ requires N, 5·6; I, 50·5 per cent.

6-*Ethyl*-6-n-*propyl*-6-*azoniaundecylenebis*-(*diethyl*-n-*propylammonium*) *tri-iodide* (60 min.; acetone-ethanol-ether; 17 per cent), m.p. 221–222°. Found: N, 5·0; I, 45·1. $C_{29}H_{66}I_4N_4$ requires N, 5·0; I, 45·45 per cent.

6,6-*Diethyl*-3,9-*dioxa*-6-*azoniaundecylenebis*(*triethylammonium*) *tri-iodide* (30 min.; ethanol-methanol; 32 per cent), m.p. 255°. Found: N, 5·3; I, 47·2. $C_{24}H_{56}I_3N_3O_2$ requires N, 5·3; I, 47·6 per cent.

6-*Ethyl*-6-*methyl*-3,9-*dioxa*-6-*diazoniaundecylenebis* (*diethylmethylammonium*) *tri-iodide* (15 min.; methanol; 71 per cent), m.p. 262–263°. Found: N, 5·6; I, 50·1. $C_{21}H_{50}I_3N_3O_2$ requires N, 5·5; I, 50·3 per cent.

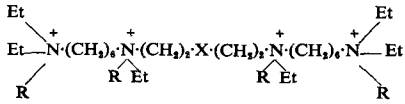
1,19-*Bis*-(*diethylamino*)-7,13-*diethyl*-7,13-*diazanonadecane* was prepared from glutaric acid (2·7 g.) and excess 6-diethylaminohexylethylamine (16·7 g.) by the method described for the preparation of 1,20-bisdiethylamino-7,14-diethyl-7,14-diazaeicosane[26]. 1,19-*Bis*-(*diethylamino*)-7,13-*diazanonadecane* was obtained as a pale yellow oil (4·5 g., 43·4 per cent), b.p. 250–255° (bath 0·55 mm.). Found: N, 11·8; equiv. 116·4. $C_{29}H_{64}N_4$ requires N, 11·9 per cent; equiv. 117·2.

1,19-*Bis*-(*diethylamino*)-7,13-*diethyl*-7,13-*diaza*-10-*oxanonadecane* was prepared from diglycollic acid (3·3 g.) and excess 6-diethylaminohexylethylamine (19·9 g.) by the method described for the preparation of 1,20-bis-(diethylamino)-7,14-diethyl-7,14-diazaeicosane[26]. 1,19-*Bis*-(*diethylamino*)-7,13-*diethyl*-7,13-*diaza*-10-*oxanonadecane* was obtained as a pale yellow oil (4·7 g., 40·6 per cent), b.p. 240–250° (bath)/0·3 mm., n_D^{20} 1·4639. Found: N, 11·9; equiv. 119·4. $C_{28}H_{62}N_4O$ requires N, 11·9 per cent; equiv. 117·7.

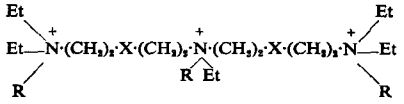
NNNN-*Tetra-onium compounds* were prepared from either 1,19-bis-(diethylamino)-7,13-diethyl-7,13-diazanonadecane or 1,19-bis-(diethylamino)-7,13-diethyl-7,13-diaza-10-oxanonadecane by refluxing with the appropriate alkyl halide in ethanol, evaporation of the solvent and crystallisation. Reflux time, crystallisation solvent and yields are indicated for each compound in that order, in parenthesis.

TABLE I

RELATIVE MOLAR POTENCIES OF XIII A AND B; XIV A, B AND C; XV A, B AND C AND XVI A, B AND C



Compound	R	X	Relative molar potencies				
			Cat	Rabbit	Chick	Mouse	Frog
XV A	Et	O	278	108	139	165	375
XVI A	Et	CH_2	417	125	230	174	208
XV B	Me	O	87	66	110	132	77
XVI B	Me	CH_2	110	82	158	165	26
XV C	Pr	O	234	96	242	146	63
XVI C	Pr	CH_2	263	110	242	151	72



XIII A	Et	O	5	5	No paralysis with 5 mg./kg.	*	*
XIV A	Et	CH_2	50	*	101	22	*
XIII B	Me	O	No paralysis with 2 mg./kg.	*	16	No paralysis with 20 mg./kg.	*
XIV B	Me	CH_2	6	*	52	11	*
XIV C	Pr	CH_2	2	*	88	13	*

* Insufficient material.

7,7,13,13-*Tetra-ethyl*-7,13-*diazonianonadecylenebis*-(*triethylammonium*) *tetra-iodide* (25 min.; ethanol; 98 per cent), m.p. 264°. Found: N, 5·0; I, 46·2. $C_{37}H_{84}I_4N_4$ requires N, 5·1; I, 46·4 per cent.

7,13-*Diethyl*-7,13-*dimethyl*-7,13-*diazonianonadecylenebis*-(*diethylmethyl ammonium*) *tetra-iodide* (10 min.; ethanol-methanol; 98 per cent), m.p. 236–237°. Found: N, 5·3; I, 48·8. $C_{33}H_{76}I_4N_4$ requires N, 5·4; I 48·95 per cent.

7,13-*Diethyl*-7,13-*di-n-propyl*-7,13-*diazonianonadecylenebis*-(*diethyl-n-propylammonium*) *tetra-iodide* (50 min.; acetone-ethanol-ether; 24 per cent), m.p. 175–176°. Found: N, 4·9; I, 43·6. $C_{41}H_{92}I_4N_4$ requires N, 4·9; I, 44·2 per cent.

7,7,13,13-*Tetraethyl*-7,13-*diazonia*-10-*oxanonadecylenebis*-(*triethylammonium*) *tetra-iodide* (25 min.; ethanol; 54 per cent), m.p. 236°. Found: N, 5·2; I, 46·4. $C_{36}H_{82}I_4N_4O$ requires N, 5·1; I, 46·3 per cent.

7,13-*Diethyl*-7,13-*dimethyl*-7,13-*diazonia*-10-*oxanonadecylenebis*-(*diethyl methylammonium*) *tetra-iodide* (10 min.; ethanol-ether; 72·5 per cent), m.p. 210–211°. Found: N, 5·4; I, 48·5. $C_{32}H_{74}I_4N_4O$ requires N, 5·4; I, 49·0 per cent.

Pharmacological Methods and Results

The experimental methods and the materials have been described elsewhere[26,43,44]. The results are shown in Table I, which sets out the comparative molar potencies. All the compounds showed muscle-relaxant properties of the tubocurarine type without depolarising activity. The tetra-onium compounds (XV A, B and C) which contained only one ether link were much more potent than the tris-onium derivatives (XIII A and B) which contained two such linkages. The former were usually more potent than tubocurarine itself.

The results show therefore that the non-ether compounds were more potent than the analogous ethers and that introduction of a second ether link further lowered potency. The tetra-onium compounds showed no ganglion-blocking activity when tested on the nictitating membrane of the cat or the guinea pig ileum; the tris-onium derivatives when tested on these preparations showed some ganglion-blocking activity but less than that of tubocurarine. Thus there was no significant fall in blood pressure when muscle-relaxant doses were given by intravenous injection into pentobarbitone-anaesthetised cats.

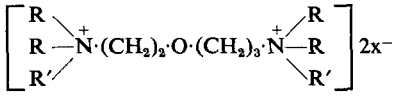
Discussion

The results show that replacement of a methylene group ($-CH_2-$) of the interonium-polymethylene chain by an ether link lowers neuromuscular-blocking potency in almost every compound. If it can be assumed that in our compounds repulsion of like charges on the onium nitrogen results in the chains being maximally extended then replacement of a $-\overset{|}{C}-\overset{|}{C}-\overset{|}{C}-$ link by a $-\overset{|}{C}-O-\overset{|}{C}-$ link reduces chain length by 0·12Å. This change seems inadequate to explain the fall in potency observed.

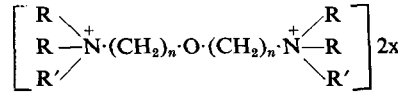
Other factors to be considered include solubility changes, which may modify tissue distribution, and the possibility of increased bonding at "sites of loss". Actual solubilities have not been recorded, but our experience of diglycollic acid derivatives and related substances, leads us to believe that the water-solubility of poly-onium compounds will be enhanced by the presence of the ether link. In view of the already high water-solubility of the corresponding polymethylene compounds it seems unlikely that this factor is significant in itself, though it could alter the balance of tissue distribution. The possibility that ether-linked compounds suffer increased binding at sites of loss may be determined by the study of absorption, distribution and excretion in the intact animal,

though this seems unlikely in view of the extreme range of ganglion-blocking potency shown by the closely related onium-ethers (XXX) and (XXXI) discussed below[35–38]. The study of such physical properties as solubility, distribution and adsorption characteristics in corresponding ether and polymethylene compounds should, however, throw light on this point.

If it is assumed, in the absence of direct evidence to the contrary, that structural differences between ether-linked and polymethylene-linked polyonium compounds are unimportant for concentration at the site of action, then questions of drug-receptor binding and intrinsic activity[39,40] are relevant. In this connection the ideas of Fakstorp and Pedersen[37] seem worthy of further consideration. Thus it was suggested that in a series of bis-choline ethers, which they examined for ganglion-blocking activity, proximity of the ether oxygen to the quaternary nitrogen might cause an electron drift from the oxygen which would then assume a partial positive charge. This concept was used to explain the more stable attachment to the negatively charged "berth" of the esteratic site in the conventional receptor model[41] in the compounds (XXX, when R = R′ = Me; R = Me, R′ = Et; and R = Et, R′ = Me) which are more active than hexamethonium.



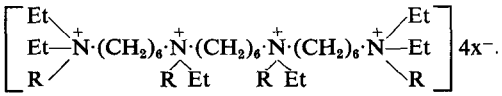
(XXX)



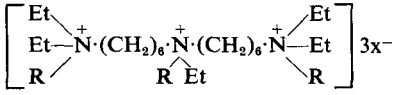
(XXXI)

This electron drift, however, is only likely to be significant where at the most one or two carbon atoms separate the –O– and $-\overset{+}{N}<$ links, and will tend to be nullified when the ether link is situated symmetrically with respect to the two onium groups. It might be argued, therefore, that the enhanced availability of electrons contributes to the fall in potency seen in the analogous compounds of structure (XXXI, where $n = 2$ and 3), but it must be emphasised that unequivocal conclusions are not possible because changes of inter-onium distance are also involved. This criticism, however, does not apply to the comparison of our own ether-linked compounds with the corresponding polymethylene derivatives, and the observed reduction in potency could be due to an anti-bonding effect arising from the availability of electrons on the symmetrically linked ether oxygen.

The tetra-onium compounds (XVI A, B and C) are more potent than the analogous trihexatetrazonium compounds (XXXII, R = Et, Me and n-Pr)[26,42], but the tris-onium compounds (XIV, R = Me and Et) are less potent than the analogous compounds (XXXIII, R = Me and Et)[25].



(XXXII)



(XXXIII)

In all four series of compounds [(XIII), (XIV), (XV) and (XVI)] examined, subsitution of any one *N*-ethyl by an *N*-methyl or *N*-propyl substituent reduces activity. This strengthens the view that optimum receptor fit at the anionic site is to be obtained with polyonium compounds when all groups on the onium atom are ethyl[25,26].

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