44. *Investigations on the Influence of Chemical Constitution upon Toxicity. Part I. Compounds related to "Doryl."*

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Little information is available regarding the influence of chemical constitution upon toxicity. The quaternary ammonium salt group was selected for preliminary investigation partly on account of the solubility of these compounds in water, and partly in view of the physiological activity of various derivatives of choline. The high toxicity of the urethane of trimethyl-2-hydroxyethylammonium chloride ("Doryl") was confirmed but a wide range of homologues and analogues described in Part I was found to exhibit lower toxicity.

This work led to an investigation, described in Part II, of aromatic compounds of the type of the methosulphate ("Prostigmine") of the *N*-methylurethane of 3-dimethylaminophenol, previously examined by Aeschlimann and Reinert, and among this group minor alterations in structure often produced major changes in toxicity. Although some of these compounds were much more lethal on subcutaneous injection than the well-known poisons brucine, curare, nicotine, and aconitine, yet others were relatively harmless.

Part III contains an account of an examination of tertiary bases of the type of the *N*-methylurethane of dimethyl-2-(3-hydroxyphenyl)ethylamine ("Miotine"). These substances were, in general, less toxic than members of the "prostigmine" group though their action was more prolonged, probably on account of their slower excretion.

The investigations have been made possible by the ready collaboration of Professor J. H. Burn, F.R.S., who carried out the pharmacological tests on "doryl" and its analogues, Dr. and Mrs. Kilby, who performed similar tests on compounds of the "prostigmine" and "miotine" types, and Professor J. R. Gaddum, F.R.S.

Compounds Structurally Related to "Doryl".—Following the discovery by Hunt and Taveau (*Brit. Med. J.*, 1906, **2**, 1788; Hygienic Lab. Bull., 1911, **73**) and by Dale (*J. Pharm. Exp.*

Ther., 1914, **6**, 147) of the powerful parasympathetic action of acetylcholine, a large number of choline derivatives were prepared. Subsequent investigation of the pharmacological potency of some of these compounds showed that, whereas the activity of acetylcholine is largely reduced because of its rapid hydrolysis by the blood esterases to choline, other more stable choline derivatives, although less intense, are more prolonged in action. For example, of five choline compounds examined by Molitor (*ibid.*, 1936, **58**, 337) the urethane of trimethyl-2-hydroxyethylammonium chloride (Doryl) (I; $R^1 = R^2 = H$, $n = 2$) is not only the most active parasympathetically but also the most toxic. The $L.D._{50}$ values in mg./kg. for acetylcholine and doryl reported by Molitor are given in Table I.

TABLE I.

	Intravenous.		Subcutaneous.		Oral.	
Compound.	Mice.	Rats.	Mice.	Rats.	Mice.	Rats.
Acetylcholine chloride	20	22	170	250	3000	2500
Doryl	0·3	0·1	3	4	15	40

The early pharmacological work of Hunt, Dale, Renshaw, and others (see Molitor, *loc. cit.*, for bibliography) showed that physiological activity is affected by (*a*) modification in the alkyl groups of the quaternary ammonium centre and (*b*) alteration in the number of methylene groups separating the cation and the alcoholic group, but when the present work was started there was no evidence concerning doryl analogues in which the amide hydrogen atoms were replaced by alkyl groups.

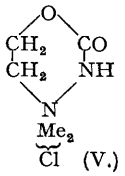
$Me_3\tilde{N}\cdot[CH_2]_n\cdot O\cdot CO\cdot NR^1R^2$ $\overset{\sim}{Cl}$ (I.) $\quad Me_2N\cdot CH_2\cdot CH_2\cdot O\cdot CS\cdot NHMe$ (II.) $\quad Me_2N\cdot CH_2\cdot CH_2\cdot O\cdot SO_2Me$ (III.)

Molitor's value for the toxicity of doryl has been confirmed, and Professor J. H. Burn has shown that doryl and its *N*-methyl derivatives (I; $R^1 = Me$, $R^2 = H$, $n = 2$) show species variation. Preliminary tests showed that doryl had an $L.D._{50}$ of 3 mg./kg. for mice, which was reduced to 0·25 mg./kg. for larger animals such as cats and dogs, and death followed from asphyxia due to blockage of the bronchial airway with mucous. It was observed that doryl has a constrictor action on the pupil of a cat but this property was not found with the homologues. The $L.D._{50}$ values in mg./kg. for an extended range of doryl analogues on subcutaneous injection in mice are reported in the last column of Table IV, and it is clear that replacement of one or both of the amide hydrogen atoms by alkyl groups, and increase in the number of methylene groups, diminish toxicity. The data in Table IV show some alternation in toxicity with increasing chain length, but higher homologues are definitely less toxic than lower members.

The *hydrochloride* and *methiodide* of the N-*methylthiourethane* of β-*dimethylaminoethanol* (II) and the *hydrochloride* of *methyl* 2-*dimethylaminoethanesulphonate* (III) proved to have low toxicities, but as the sulphur analogues of acetylcholine and doryl were rather inaccessible further work in this direction was discontinued.

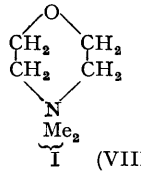
Replacement of the amide group in compounds of the doryl type by hydrazide or ether radicals resulted in substances of low toxicity. Girard-T (IV), the cyclic structure (V), obtained from *as*-dimethylhydrazine and 2-chloroethyl chloroformate, the vinyl ether (VI) of choline

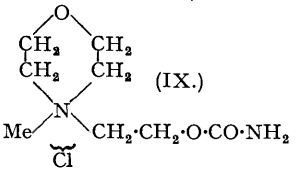
$Me_3\tilde{N}\cdot CH_2\cdot CO\cdot NH\cdot NH_2$ $\overset{\sim}{Cl}$ (IV.)


(V.)

$Me_3\tilde{N}\cdot CH_2\cdot CH_2\cdot O\cdot CH{:}CH_2$ $\tilde{I}$ (VI.)

$Me_3\tilde{N}\cdot CH_2\cdot CH{-}CH_2$ $\tilde{I}$ (VII.)


(VIII.)


(IX.)

$Me_2\overset{\sim}{NH}\cdot CH_2\cdot CH_2\cdot O\cdot CO\cdot NH_2$ $\overset{\sim}{Cl}$ (X.)

$Cl\cdot[CH_2]_n\cdot O\cdot COCl$ (XI.)

$Cl\cdot[CH_2]_n\cdot O\cdot CO\cdot NR^1R^2$ (XII.)

iodide, and the cyclic ethers (VII), (VIII), and (IX) have toxicities of a low order, and from a miscellaneous group of compounds which have been synthesised only choline nitrate, isolated

as a crystalline perchlorate, has any appreciable toxicity. Furthermore, as the hydrochloride of the urethane of 2-dimethylaminoethanol (X) is inactive, it is concluded that high toxicity in the doryl series depends upon the presence of both urethane and quaternary ammonium groupings.

2-Chloroethyl chloroformate (XI; $n = 2$), readily obtained from carbonyl chloride and ethylene chlorohydrin (Nemirowsky, *J. pr. Chem.*, 1885, **31**, 174; Schotte, Priewe, and Roeschiesen, *Z. physiol. Chem.*, 1928, **174**, 142; Swiss Patent, 154,952), was converted by cold ammonium hydroxide into 2-chloroethyl carbamate (XII; $R^1 = R^2 = H$; $n = 2$), and by reaction with a variety of primary and secondary amines a wide variety of compounds of type (XII; $R^1 = H$ or alkyl; $R^2 =$ alkyl; $n = 2$) was prepared. 2-Chloroethyl carbamate (XII; $R^1 = R^2 = H$; $n = 2$), when heated with trimethylamine at 120—130°, gave doryl (I; $R^1 = R^2 = H$; $n = 2$) in 80% yield, but during the preparation of analogues, difficulties, arising from two causes, were sometimes encountered. Some of the quaternary chlorides were hygroscopic, purification was difficult, and conversion into the corresponding iodide by treatment with alcoholic sodium iodide was desirable. In other cases the quaternary salts were contaminated with trimethylamine hydrochloride [see Schotte *et al.* (*loc. cit.*) and Pierce (*J. Amer. Chem. Soc.*, 1928, **50**, 242)] and tedious fractional crystallisations of the corresponding iodides were often necessary.

The method employed in the synthesis of doryl has also been applied to the preparation of homologues. The glycols, prepared by Bouveault–Blanc reduction of the diethyl esters of the appropriate dibasic acids, were converted into the corresponding chlorohydrins by the action of thionyl chloride and pyridine. Treated with carbonyl chloride, the chlorohydrins gave the ω-chloroalkyl chloroformate (XI) which in turn gave the ω-chlorocarbamates (XII), and these yielded doryl homologues (I) with trimethylamine.

The reactions of 2-chloroethyl and 3-chloropropyl carbamates with triethyl-, tri-*n*-propyl-, and tri-*n*-amyl-amines were examined at temperatures varying from 15° and 180°, both in the absence and in the presence of such solvents as ether, benzene, and benzyl alcohol, but the only recognisable products were the hydrochlorides of the original tertiary amines. Substitution of the iodo- for the chloro-carbamates was sometimes useful; 2-iodoethyl carbamate reacted normally with triethylamine to give the quaternary iodide, but 2-iodoethyl *N*-phenylcarbamate yielded 3-phenyloxazolid-2-one and triethylamine hydriodide.

The syntheses of a miscellaneous group of compounds related to choline and doryl are reported in the experimental section.

Experimental.

(i) *Preparation of Chloroalkyl Chloroformates* (XI).—The preparation of 2-chloroethyl chloroformate (XI; $n = 2$) is typical. Ethylene chlorohydrin (12 g.) and carbonyl chloride (13 c.c.) were kept in a sealed tube at 15° for 70 hours. Distillation yielded 2-chloroethyl chloroformate, b. p. 152°. New compounds of this class are described in Table II.

Table II.

Chloroalkyl chloroformates.

Chloroformate.	Formula XI:	B. p.	Formula.	Found: Cl, %.	Required: Cl, %.
4-Chlorobutyl	$n = 4$	89°/10 mm.	$C_5H_8O_2Cl_2$	41·4	41·5
5-Chloropentyl	$n = 5$	125—130/15 mm.	$C_6H_{10}O_2Cl_2$	38·0	38·4
6-Chlorohexyl	$n = 6$	120/12 mm.	$C_7H_{12}O_2Cl_2$	—	—
8-Chloro-octyl	$n = 8$	130/12 mm.	$C_9H_{16}O_2Cl_2$	—	—
9-Chlorononyl	$n = 9$	137/15 mm.	$C_{10}H_{18}O_2Cl_2$	—	—
10-Chlorodecyl	$n = 10$	170/12 mm.	$C_{11}H_{20}O_2Cl_2$	29·8	30·6

(ii) *Preparation of Chloroalkyl Carbamates* (XII).—(*a*) *2-Chloroethyl carbamate* (XII; $R^1 = R^2 = H$; $n = 2$). Ammonium hydroxide (15 c.c., 15%) was gradually added with shaking and cooling to 2-chloroethyl chloroformate (XI; $n = 2$) (6·5 g.). The product was extracted with ether, dried, and most of the solvent removed. Light petroleum (b. p. 40—60°) was added until crystallisation commenced, and after 12 hours the carbamate (XII; $n = 2$) (4·6 g.), m. p. 76°, was collected.

(*b*) In other cases the following method was used. The primary or secondary amine (2·1 mols.) in benzene (5 vols.) was added with cooling and shaking to the chloroformate (1 mol.) in benzene (5 vols.). After one hour the amine hydrochloride was collected and washed with benzene, and the combined filtrate and washings were washed with dilute hydrochloric acid, dried, and the solvent removed, and the product purified either by crystallisation or by distillation under reduced pressure.

(*c*) In preparing compounds such as 2-iodoethyl carbamate, the chloro-compound and sodium iodide were refluxed in alcoholic solution for 12 hours. The sodium chloride was removed, the filtrate concentrated, and the product, isolated with ether, was purified by crystallisation from benzene.

New compounds of type (XII) are included in Table III.

TABLE III.

Chloro- and iodo-carbamates.

Carbamate.	Formula, XII :	M. p. or b. p.	Formula.	Found, %.	Required, %.
2-Iodopropyl	I for Cl; $R^1 = R^2 = H$; $n = 3$	Plates, m. p. 74—76°		—	—
2-Chloroethyl *N*-propyl-	$R^1 = C_3H_7$; $R^2 = H$; $n = 2$	B. p. 138°/ 10 mm.	$C_6H_{12}O_2NCl$	Cl, 21·4	Cl, 21·4
2-Chloroethyl *N*-allyl-	$R^1 = C_3H_5$; $R^2 = H$; $n = 2$	B. p. 130°/ 10 mm.		—	—
2-Chloroethyl *N*-benzyl-	$R^1 = C_7H_7$; $R^2 = H$; $n = 2$	Needles, m. p. 48°	$C_{10}H_{12}O_2NCl$	Cl, 16·4	Cl, 16·6
2-Iodoethyl *N*-benzyl	As above with I for Cl	Plates, m. p. 92°	$C_{10}H_{12}O_2NI$	I, 41·5	I, 41·6
2-Chloroethyl *N*-dimethyl-	$R^1 = R^2 = CH_3$; $n = 2$	B. p. 92°/ 16 mm.	$C_4H_{10}O_2NCl$	Cl, 22·7	Cl, 23·4
2-Chloroethyl *N*-diethyl	$R^1 = R^2 = C_2H_5$; $n = 2$	B. p. 100°/ 13 mm.	$C_6H_{14}O_2NCl$	Cl, 20·1	Cl, 19·8
2-Chloroethyl *N*-dipropyl	$R^1 = R^2 = C_3H_7$; $n = 2$	B. p. 135°/ 20 mm.		—	—
Piperidinium *N*-2-chloroethyl	$R^1R^2 = C_5H_{10}$; $n = 2$	B. p. 135°/ 17 mm.		—	—
2-Chloroethyl *N*-dibenzyl	$R^1 = R^2 = C_7H_7$; $n = 2$	Needles, m. p. 64°	$C_{17}H_{18}O_2NCl$	Cl, 11·1	Cl, 11·7
3-Chloropropyl	$R^1 = R^2 = H$; $n = 3$	Prisms, m. p. 58°	$C_4H_8O_2NCl$	Cl, 25·5	Cl, 26·0
4-Chlorobutyl	$R^1 = R^2 = H$; $n = 4$	Plates, m. p. 74°	$C_5H_{10}O_2NCl$	Cl, 21·4	Cl, 20·8
5-Chloropentyl	$R^1 = R^2 = H$; $n = 5$	Plates, m. p. 78°	$C_6H_{12}O_2NCl$	N, 7·8	N, 8·4
6-Chlorohexyl	$R^1 = R^2 = H$; $n = 6$	Plates, m. p. 70°	$C_7H_{14}O_2NCl$	N, 7·5	N, 7·7
8-Chloro-octyl	$R^1 = R^2 = H$; $n = 8$	Plates, m. p. 83°		—	—
9-Chlorononyl	$R^1 = R^2 = H$; $n = 9$	Plates, m. p. 77°	$C_{10}H_{20}O_2NCl$	N, 6·4	N, 6·3
10-Chlorodecyl	$R^1 = R^2 = H$; $n = 10$	Prisms, m. p. 84°	$C_{11}H_{22}O_2NCl$	Cl, 14·7	Cl, 15·1

(iii) *Preparation of Quaternary Ammonium Salts.*—(a) *Doryl* (I; $R^1 = R^2 = H$; $n = 2$). Trimethylamine (10 c.c.) and 2-chloroethyl carbamate (6 g.) were heated in a sealed tube at 110—120° for 16 hours. The crystalline contents were triturated with ether, and the product (8·3 g.) collected and crystallised from alcohol–ether.

The above method was generally applicable, but careful temperature control was often necessary, and anhydrous solvents should be used for crystallisation purposes. Conversion of chlorides into quaternary iodides was effected by treatment with cold absolute alcohol (*ca.* 5 vols.) containing sodium iodide (1·5 mols.); after one hour the sodium chloride was collected, the filtrate evaporated, and the quaternary iodide, separated from excess sodium iodide by solution in chloroform, was crystallised from alcohol or alcohol–ether.

Trimethyl-2 : 3-epoxypropylammonium chloride and *iodide* (VII) and the *urethane* of N-2-*hydroxyethylmorpholine methochloride* (IX) were prepared by similar methods.

(b) The following quaternary salts were prepared by special methods.

(i) *Urethane of triethyl-2-hydroxyethylammonium iodide.* Ethylene chlorohydrin (1·1 g.) and triethylamine (1·6 g.) were heated at 100° for 4 days and the 2-hydroxyethylammonium chloride (1 g.), after crystallisation from alcohol–ether, was shaken with carbonyl chloride (3 c.c.) in chloroform solution (3 c.c.) for 24 hours. The product was evaporated, treated with 12% ammonium hydroxide (20 c.c.) and again evaporated, and the residue extracted with absolute alcohol. The extract was refluxed with excess of sodium iodide for 10 minutes, and after removal of sodium chloride, the quaternary iodide (0·65 g.), precipitated by addition of ether, was crystallised from alcohol.

(ii) N-*Phenylurethane of triethyl-2-hydroxyethylammonium iodide.* Phenyl *iso*cyanate (1 g.) was cautiously added to 2-diethylaminoethanol (1 g.); after 10 minutes the product was heated with benzene (3 c.c.) and ethyl iodide (1·5 c.c.) in a sealed tube at 100° for 2 hours, and the ethiodide crystallised from alcohol.

(iii) 2-*Keto*-4 : 4-*dimethyl*-2 : 3 : 5 : 6-*tetrahydro*-1 : 3 : 4-*oxadiazinium chloride* (V). *as*-Dimethylhydrazine (3·5 g.) and 2-chloroethyl chloroformate (4 g.) in benzene (50 c.c.) were allowed to react in the cold for 15 minutes. The dimethylhydrazine hydrochloride was collected, the benzene removed, and the residue heated in a sealed tube for 5 hours at 110—120°.

(iv) *Ureidotrimethylammonium iodide*, $NH_2{\cdot}CO{\cdot}NH{\cdot}NMe_3\}I$. An aqueous solution of *as*-dimethylhydrazine hydrochloride (1 mol.) and potassium cyanate (2 mols.) was evaporated, and the residue extracted several times with alcohol. The *dimethylaminourea*, after crystallisation from benzene, was converted into the *methiodide* by heating with methyl iodide in a sealed tube.

Urethane of 2-dimethylaminoethanol. Dimethylamine (3 c.c.) and 2-chloroethyl carbamate (4 g.) were heated at 95° for 20 hours, and after acidification with dilute hydrochloric acid the unchanged

TABLE IV.

Homologues and analogues of "Doryl".

Compound.	In (I):	Constant.	Formula.	Found, %.	Required, %.	L.D.$_{50}$ (mg./kg.).
Urethane of trimethyl-2-hydroxyethylammonium chloride ("Doryl")	$R^1 = R^2 = H$; $n = 2$	Prisms, m. p. 207°	See (i)	—	—	3
Urethane of trimethyl-2-hydroxyethylammonium iodide	As above, with I for Cl	Prisms, m. p. 193°	See (ii)	—	—	4·5
N-Methylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = CH_3$; $R^2 = H$; $n = 2$	Needles, m. p. 173°	See (ii) and (iii)	—	—	15
N-Ethylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = C_2H_5$; $R^2 = H$; $n = 2$	M. p. 196—200°	See (iii)	—	—	60
N-Propylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = C_3H_7$; $R^2 = H$; $n = 2$	M. p. 203—207°	$C_9H_{21}O_2N_2Cl$	Cl, 15·8	Cl, 15·8	15
N-Allylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = C_3H_5$; $R^2 = H$; $n = 2$	M. p. 167—173°	$C_9H_{19}O_2N_2Cl$	Cl, 15·9	Cl, 16·0	37·5
N-Phenylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = C_6H_5$; $R^2 = H$; $n = 2$	Needles, m. p. 192°	$C_{12}H_{19}O_2N_2Cl$	Cl, 13·3	Cl, 13·7	37·5
N-Benzylurethane of trimethyl-2-hydroxyethylammonium iodide	$R^1 = C_7H_7$; $R^2 = H$; $n = 2$	Powder, m. p. 96°	$C_{13}H_{21}O_2N_2I$	I, 34·6	I, 34·9	62·5
N-Dimethylurethane of trimethyl-2-hydroxyethylammonium iodide	$R^1 = R^2 = CH_3$; $n = 2$	Plates, m. p. 202°	$C_8H_{19}O_2N_2I$	I, 42·0	I, 42·0	20
N-Diethylurethane of trimethyl-2-hydroxyethylammonium iodide	$R^1 = R^2 = C_2H_5$; $n = 2$	Powder, m. p. 114°	$C_{14}H_{23}O_2N_2I$	I, 38·8	I, 38·5	42·5
N-Dipropylurethane of trimethyl 2 hydroxyethylammonium chloride	$R^1 = R^2 = C_3H_7$; $n = 2$	Powder, m. p. 99°	$C_{16}H_{27}O_2N_2Cl$	Cl, 14·1	Cl, 13·3	75
Piperidylcarbamate of trimethyl-2-hydroxyethylammonium iodide	$R^1R^2 = C_5H_{10}$; $n = 2$	Plates, m. p. 178°	$C_{11}H_{23}O_2N_2I$	I, 37·2	I, 37·1	18·5
N-Dibenzylurethane of trimethyl-2-hydroxyethylammonium iodide	$R^1 = R^2 = C_7H_7$; $n = 2$	Needles, m. p. 119—121°	$C_{20}H_{27}O_2N_2I$	I, 28·0	I, 28·0	75
Urethane of trimethyl-3-hydroxypropylammonium chloride	$R^1 = R^2 = H$; $n = 3$	Prisms, m. p. 207—209°	$C_7H_{17}O_2N_2Cl$	Cl, 17·6	Cl, 18·0	37·5
Urethane of trimethyl-4-hydroxybutylammonium chloride	$R^1 = R^2 = H$; $n = 4$	Prisms, m. p. 212—213°	$C_8H_{19}O_2N_2Cl$	Cl, 16·8	Cl, 16·8	12·5
Urethane of trimethyl-5-hydroxypentylammonium chloride	$R^1 = R^2 = H$; $n = 5$	Prisms, m. p. 195—197°	$C_9H_{21}O_2N_2Cl$	Cl, 16·1	Cl, 15·8	22
Urethane of trimethyl-6-hydroxyhexylammonium chloride	$R^1 = R^2 = H$; $n = 6$	Prisms, m. p. 211—212°	$C_{10}H_{23}O_2N_2Cl$	Cl, 15·2	Cl, 14·9	100

Compound.	In (I):	Constant.	Formula.	Found, %.	Required, %.	L.D.$_{50}$ (mg./kg.).
Urethane of trimethyl-8-hydroxyoctylammonium chloride	$R^1 = R^2 = H$; $n = 8$	Plates, m. p. 205°	$C_{12}H_{27}O_2N_2Cl$	Cl, 13·5	Cl, 13·6	200
Urethane of trimethyl-9-hydroxynonylammonium chloride	$R^1 = R^2 = H$; $n = 9$	Plates, m. p. 199°	$C_{13}H_{29}O_2N_2Cl$	Cl, 12·9	Cl, 12·7	185
Urethane of trimethyl-10-hydroxydecylammonium chloride	$R^1 = R^2 = H$; $n = 10$	Prisms, m. p. 202°	$C_{14}H_{31}O_2N_2Cl$	Cl, 12·3	Cl, 12·1	75
Urethane of triethyl-2-hydroxyethylammonium iodide	$Et_3\overset{\frown}{N}\cdot CH_2\cdot CH_2\cdot O\cdot CO\cdot NH_2$ $\overset{\smile}{I}$	Prisms, m. p. 205°	$C_9H_{21}O_2N_2I$	I, 39·8	I, 40·2	395
N-Phenylurethane of triethyl-2-hydroxyethylammonium iodide	$Et_3\overset{\frown}{N}\cdot CH_2\cdot CH_2\cdot O\cdot CO\cdot NHPh$ $\overset{\smile}{I}$	Prisms, m. p. 128°	$C_{15}H_{25}O_2N_2I$	I, 32·6	I, 32·4	450
2-Keto-4 : 4-dimethyl-2 : 3 : 5 : 6-tetrahydro-1 : 3 : 4-oxadiazinium chloride	(V)	Plates, m. p. 184°	$C_5H_{11}O_2N_2Cl$	Cl, 21·4	Cl, 21·3	194
Urethane of *N*-2-hydroxyethylmorpholine methochloride	(IX)	Plates, m. p. 138°	$C_8H_{17}O_3N_2Cl$	Cl, 15·6	Cl, 15·8	194
N-Methylmorpholine methiodide	(VIII)	Needles, m. p. 235°	See (iv)	—	—	83
Vinyl ether of trimethyl-2-hydroxyethylammonium iodide	(VI)	Prisms, m. p. 177°	See (iv)	—	—	33
Trimethyl-2 : 3-epoxypropylammonium iodide	(VII)	Needles, m. p. 175°	See (v)	—	—	126
Trimethyl-2 : 3-epoxypropylammonium chloride	(VII) with Cl for I	Needles, m. p. 130—135°	See (v)	—	—	90
Choline nitrate perchlorate		M. p. 182—183°	See (vi)	—	—	30
Urethane of 2-dimethylaminoethanol hydrochloride	(X)	Plates, m. p. 144—147°	$C_5H_{13}O_2N_2Cl$	C, 35·4; H, 8·0; Cl, 20·6	C, 35·6; H, 7·8; Cl, 21·1	1000—2000
N-Methylthiourethane of trimethyl-2-hydroxyethylammonium iodide	Methiodide of (II)	Leaves, m. p. 237° (decomp.)	$C_7H_{17}ON_2SI,H_2O$	I, 39·6	I, 39·4	40
Hydrochloride of *N*-methylthiourethane of 2-dimethylaminoethanol	Hydrochloride of (II)	Polyhedra, m. p. 97°	$C_6H_{15}ON_2SCl$	Cl, 17·5	Cl, 17·9	100
Hydrochloride of methyl 2-dimethylaminoethanesulphonate	Hydrochloride of (III)	M. p. 97°	$C_5H_{14}O_3NSCl,H_2O$	Cl, 16·0; S, 14·7	Cl, 16·0; S, 14·3	100

(i) Swiss Patent, 154,952.
(ii) D.R.-P. 539,329.
(iii) Sprinson, *J. Amer. Chem. Soc.*, 1941, **63**, 2251 (published after completion of this work).
(iv) Knorr, *Annalen*, 1898, **301**, 8; *Ber.*, 1899, **32**, 738.
(v) Schmidt and Hartmann, *Annalen*, 1904, **337**, 116.
(vi) Hofmann and Hobald, *Ber.*, 1911, **44**, 1767.

carbamate was taken up in ether. The aqueous layer was made faintly alkaline to thymolphthalein and extracted with ether in a continuous extractor. Evaporation yielded crude 2-dimethylaminoethyl carbamate (1 g.) as an oil, which was converted into the *hydrochloride* by treatment with ethereal hydrogen chloride.

Salts of the N-*methylthiourethane of* 2-*dimethylaminoethanol* (II). Methyl *iso*thiocyanate (2·2 g.) and 2-dimethylaminoethanol (2·7 g.) were heated for 18 hours in a sealed tube at 110°. The product was extracted with acetone, and after removal of the solvent, the residue was heated at 100°/12 mm. for 15 minutes and then stirred with ether (10 c.c.) and the ether extract was decanted from a gum. The hydrochloride, prepared from a portion of the extract, was obtained as an oil which gradually solidified and was crystallised from alcohol–ether.

Methyl 2-*dimethylaminoethanesulphonate* (III). Methanesulphonyl chloride (2·6 g.) (Johnson, *J. Amer. Chem. Soc.*, 1939, **61**, 176) in ether (5 c.c.) was added dropwise to 2-dimethylaminoethanol (2 g.). The product was converted into *hydrochloride* in alcoholic solution, and the salt crystallised from alcohol–ether.

The properties of these salts and their $L.D._{50}$ values (in mg./kg.) for subcutaneous injection into mice are included in Table IV.

Our thanks are due to R. E. Davies, M.Sc., and A. R. Pinder, B.Sc., who prepared the sulphur-containing compounds (II) and (III) and the ethers (VI, (VIII), and (IX), respectively, and to the Director General of Scientific Research (Defence) for permission to publish the results.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, June 6th,* 1946.]