45. *Investigations on the Influence of Chemical Constitution upon Toxicity. Part II. Compounds related to "Prostigmine."*

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The effect of the structure on the toxicity of the phenyltrimethylammonium iodides has been examined. The parent compound has L.D.$_{50}$ 85 mg./kg. on subcutaneous injection into mice, and the influence of simple nuclear substituents is shown in Table I, from which it is seen that the nitro-, amino-, acetamido-, methyl, aldehyde, ureido-, alcoholic, or phenolic groups, introduced into the *m*- or *p*-positions with respect to the $-NMe_3I$ group, have but minor effects on the toxicity.

In view of the lactonic structure of the powerful cardiac poisons, a quaternary salt of a basic lactone was worthy of investigation. The activity of the methiodides of 4-methyl-7-dimethylamino- and -7-diethylamino-coumarin proved to be low with L.D.$_{50}$ values of 143 and 194, respectively, and the low toxicities of all these compounds confirm a conclusion mentioned in Part I that there is apparently no simple substituent which can replace the $-O{\cdot}CO{\cdot}NHR$ group and yet preserve the high activity associated with the urethanes of quaternary ammonium salts.

Table I.

L.D.$_{50}$ for phenyltrimethylammonium salts.

	L.D.$_{50}$ (mg./kg.).*
Phenyltrimethylammonium iodide	85
m-Tolyltrimethylammonium iodide	125
p-Tolyltrimethylammonium iodide	180
3-Hydroxyphenyltrimethylammonium iodide	100
4-Hydroxyphenyltrimethylammonium iodide	73
3-Aminophenyltrimethylammonium iodide	186
4-Aminophenyltrimethylammonium iodide	231
3-Acetamidophenyltrimethylammonium iodide	323
4-Acetamidophenyltrimethylammonium iodide	241
3-Nitrophenyltrimethylammonium iodide	109
3-Formylphenyltrimethylammonium iodide	79
4-Formylphenyltrimethylammonium iodide	111
4-Hydroxymethylphenyltrimethylammonium iodide	139
3-Ureidophenyltrimethylammonium iodide	375
4-Ureidophenyltrimethylammonium iodide	130
3-Hydroxypyridine methiodide	1350

* These refer to subcutaneous injections into mice unless otherwise stated.

Stedman and his co-workers (*Biochem. J.*, 1926, **20**, 719; 1927, **21**, 1902; 1931, **25**, 1147; 1932, **26**, 1214; *Proc. Roy. Soc.*, 1936, *B*, **121**, 142) found that the *N*-methylurethanes of the quaternary salts of 3-dialkylaminophenols showed pharmacological properties similar to the alkaloid physostigmine. During a further investigation of these and similar compounds,

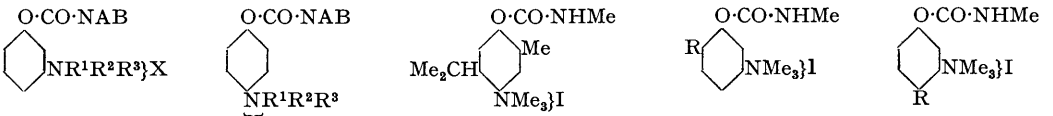
Aeschlimann and Reinert (*J. Pharm. Exp. Ther.*, 1931, **43**, 413) found that certain salts, *e.g.*, the metho-salts of the *N*-methyl- and *N*-benzyl-urethanes of 3-dimethylaminophenol with L.D.$_{80}$ of 0·1 mg./kg. on intravenous injection into mice are more toxic than physostigmine (L.D.$_{80}$, 0·5 mg./kg.). It was also shown that 3-dimethylaminophenol derivatives were more active than the 4-isomerides (Type II), and in this series, unlike the doryl class, the *N*-methylurethanes were more toxic than either *N*-dimethylurethanes or urethanes.

Since Aeschlimann and Reinert's data for the pharmacological activity of these urethanes relate to their toxicity on intravenous injection or orally, a number of these substances have been prepared, and Table II shows the L.D.$_{50}$ values obtained by subcutaneous injection. Attention was not confined entirely, however, to urethanes with *m*-orientation, and *o*-compounds were found to have greatly reduced toxicity: the L.D.$_{50}$ values for the *N*-methylurethanes of the three isomeric dimethylaminophenol methiodides were *m*-, 0·44; *p*-, 50; *o*-, 430.

TABLE II.

	L.D.$_{50}$ (mg./kg.).
Methiodide of urethane of 3-dimethylaminophenol	37
Methiodide of *N*-methylurethane of 3-dimethylaminophenol	0·44
	0·26 (rabbits)
Methochloride of *N*-methylurethane of 3-dimethylaminophenol	0·27
Ethiodide of *N*-methylurethane of 3-dimethylaminophenol	0·38
	0·13 (rabbits)
Methiodide of *N*-methylurethane of 3-diethylaminophenol	0·29
	0·15 (rabbits)
	0·17 (cats)
Methiodide of *N*-benzylurethane of 3-dimethylaminophenol	0·35
	0·20 (rabbits)
Methiodide of *N*-4-methoxybenzylurethane of 3-dimethylaminophenol	0·24
Methiodide of *N*-methylurethane of 2-dimethylaminophenol	430
Methiodide of *N*-methylurethane of 4-dimethylaminophenol	50

A new impetus to the investigation of nuclear substituents was given by the work of Stevens and Beutel (*J. Amer. Chem. Soc.*, 1941, **63**, 308), who showed that the introduction of nuclear alkyl groups, particularly *iso*propyl groups, may increase by a 100- or 1000-fold the toxicity of the *N*-methylurethanes of 4-dimethylaminophenols. For instance, the *N*-methylurethanes of 6-dimethylamino-4-*iso*propyl-*m*-cresol methiodide and the *N*-methylurethane of 5-dimethylamino-4-*iso*propyl-*o*-cresol methiodide (III) have L.D.$_{50}$ in mice of 0·22 and 1·09 mg./kg., respectively. The presence of alkyl group in the *N*-methylurethane of the isomeric 2-dimethylaminophenol methiodide, with an L.D.$_{50}$ of 430, was also accompanied with a marked increase in toxicity: the *N*-methylurethane of 3-dimethylamino-*p*-cresol methiodide has L.D.$_{50}$ of 2·0 mg./kg. In order to examine the effect of introducing alkyl groups into the quaternary salts of the methylurethanes of 3-dimethylaminophenols, which are themselves about 100 times more active than the *p*-isomerides, methods were



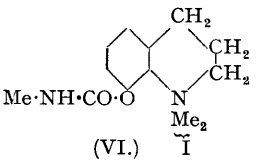
(I.) (II.) (III.) (IV.) (V.)

devised for the preparation of nuclear alkylated derivatives of types (IV) and (V), where R = methyl, ethyl, *iso*propyl or *cyclo*hexyl, and of polyalkylated compounds such as the methiodides of the *N*-methylurethane of 6-dimethylamino-*m*-4-xylenol and -4-*iso*propyl-*o*-cresol. The toxicities of these substances, along with our findings with the *N*-methylurethane of 5-dimethylamino-4-*iso*propyl-*o*-cresol methiodide (III) are summarised in Table III, from which the following points emerge: (i) Although the presence of methyl groups increases the toxicity in the 3-dimethylaminophenol series, the increase is fourfold as contrasted with the 10^2 to 10^3 increase observed in the 4-dimethylaminophenol series. (ii) The toxicities of the methiodides of the *N*-methylurethanes of nuclear-alkylated aminophenols reach a limiting value of 0·1 mg./kg. (iii) The maximum activity is obtained with one or more methyl substituents; ethyl, *iso*propyl, and *cyclo*hexyl groups reduce the toxicity, although the toxicities may remain high in the presence of these groups provided that methyl groups be also present. (iv) The position of the methyl group is of secondary importance, but the position of the *iso*propyl group has an enormous influence on toxicity. (v) Ethylation instead of methylation of the amino-groups is of secondary importance.

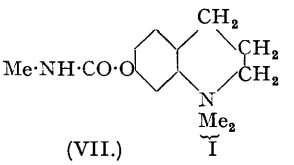
TABLE III.

Methiodide of *N*-methylurethane of—	L.D.$_{50}$ (mg./kg.).
4-Dimethylamino-*o*-cresol	0·11
3-Dimethylamino-6-ethylphenol	0·75
3-Dimethylamino-6-*iso*propylphenol	125
3-Dimethylamino-6-*cyclo*hexylphenol	175
4-Diethylamino-*o*-cresol	0·2
2-Dimethylamino-*p*-cresol	0·16
3-Dimethylamino-4-ethylphenol	0·4
3-Dimethylamino-4-*iso*propylphenol	1·0
5-Dimethylamino-*m*-cresol	0·17
5-Dimethylamino-4-*iso*propyl-*o*-cresol	0·11
6-Dimethylamino-*m*-4-xylenol	0·1
6-Dimethylamino-4-*iso*propylo-cresol	0·1
8-Hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline	45
8-Hydroxyquinoline	31
7-Hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline	0·33
N-Methyl-*N*-β-diethylaminoethyl-4-aminophenol	100
2 : 4-Tetramethyldiaminophenol	7
2 : 5-Tetramethyldiaminophenol	500—1000
6-Chloro-3-dimethylaminophenol	4

Simulation of the essential features of the *N*-methylurethane of nuclear alkylated dimethylaminophenol methiodides is obtained in the *N*-methylurethanes of 8- and 7-hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline methiodide (VI) and (VII); (VI) has a low order of toxicity (L.D.$_{50}$, 45) but (VII), with L.D.$_{50}$, 0·33 mg./kg., is among the most toxic compounds encountered during this work. The influence of the *m*-orientation of the methylurethane and basic group is again very apparent.



(VI.)



(VII.)

The effect on toxicity of chlorine as a substituent was investigated in the case of the *N*-methylurethane of 6-chloro-3-dimethylaminophenol methiodide, and the pharmacological activity was relatively low (L.D.$_{50}$, 4). Toxicity was not increased by the introduction of a second quaternary ammonium group, and the *N*-methylurethanes of 2 : 4- and 2 : 5-tetramethyldiaminophenol dimethiodides had L.D.$_{50}$ values of 7 and 500—1000, respectively; a disparity of this magnitude in the activity of two such closely related compounds is probably not real, and may be attributable to loss of methyl *iso*cyanate during the pharmacological tests.

During the toxicity tests on rabbits, Dr. Kilby observed that symptoms developed within 5—10 minutes of injection and consisted of very excessive salivation, defaecation, twitching of the voluntary muscles, muscular weakness, and slow respiration and heart rate, accompanied in most cases by anoxæmic convulsions. With fatal doses, death occurred within 10—30 minutes, and was probably due to cessation of respiration, although in a few cases it might have been due to excessive secretion of mucous in the trachea and bronchii. Post-mortem examination revealed that the liver, kidneys, and lungs were congested with petichial hæmorrhages in some rabbits. In the trachea and bronchii the mucosa were also congested and occasionally excessive amounts of mucosa were found. Intravenous injection of the *N*-methylurethane of 3-dimethylaminophenol methiodide into cats produced similar symptoms, and death was again attributed to paralysis of the respiratory centre.

Although many of the *N*-methylurethane methiodides are extremely toxic it was found, in general, that the effects of sublethal doses were transitory and complete recovery of rabbits occurred within one hour. This is probably due to rapid excretion. Aeschlimann and Reinert (*loc. cit.*) found that quaternary ammonium salts were far less toxic when administered orally than intravenously, and attributed this partly to hydrolysis *in vivo*, but more particularly to rapid elimination from the blood while absorption is still in progress. On the basis of these observations a high ratio of the oral to the subcutaneous lethal dose was also anticipated and it was found that the L.D.$_{50}$ values for oral administration of the *N*-methylurethanes of the methiodides of 3-dimethylaminophenol, 3-diethylaminophenol, and 4-dimethylamino-*o*-cresol

were respectively 16, 52, and 27 times as large as the corresponding values for subcutaneous injection.

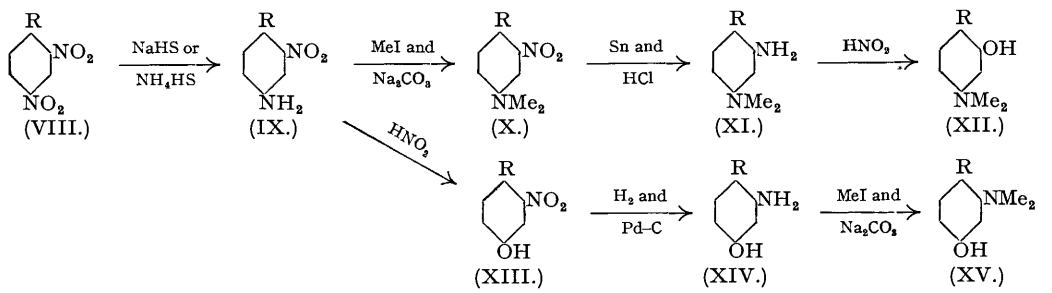
It has been shown that the hydrochlorides of the *N*-methylurethanes of 3-dimethylaminophenol, and the nuclear alkylated and chlorinated homologues did not possess marked toxicity: the L.D.$_{50}$ values were 10—100 times higher than those of the corresponding quaternary salts. On the other hand in the limited number of cases examined, the ratio of the

TABLE IV.

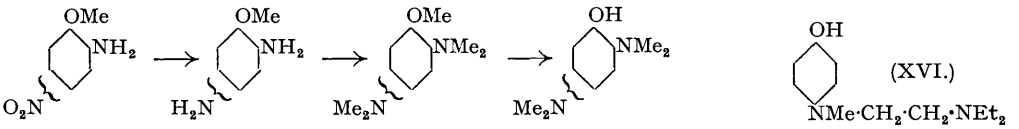
N-Methylurethane of—	L.D.$_{50}$ (mg./kg.). Subcut.	Oral.
Hydrochloride of 3-dimethylaminophenol	25	100
Hydrochloride of 2-dimethylamino-*p*-cresol	10—15	60
Hydrochloride of 3-dimethylamino-4-*iso*propylphenol	70	—
Hydrochloride of 6-dimethylamino-*o*-4-xylenol	10	50
Hydrochloride of 7-hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline	30	—
Hydriodide of 8-hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline	5000	—
Hydrochloride of 8-hydroxyquinoline	500	—
Hydrochloride of 2 : 4-tetramethyldiaminophenol	60	—
Hydrochloride of 2 : 5-tetramethyldiaminophenol	50—75	—
Hydrochloride of 6-chloro-3-dimethylaminophenol	45	—
Dihydrobromide of *N*-methyl-*N*-β-diethylaminoethyl-4-aminophenol	16	—
Dihydrochloride of 2-hydroxy-4-dimethylaminobenzyldimethylamine	500—2500	—

oral to the subcutaneous lethal dose was approximately 4, and this suggested that hydrochlorides of tertiary bases might be excreted more slowly and therefore have more prolonged effects than quaternary ammonium salts. This aspect of the work is developed in Part III.

A few aminophenols were commercial products, but many were prepared by the following series of reaction which was also employed in the preparation of isomers and related compounds:



Phenols containing two nuclear basic centres such as 2 : 4- and 2 : 5-tetramethyldiaminophenols were prepared from 4- and 5-nitro-1-methoxyaniline by the following changes:



The phenol (XVI), containing one nuclear and one extranuclear basic centre, was also prepared from metol and 2-diethylaminoethyl chloride.

8-Hydroxy-1-methyltetrahydroquinoline was prepared from 8-hydroxyquinoline as described by Fischer (*Ber.*, 1881, **14**, 1368; 1883, **16**, 714), and the isomeric 7-hydroxy-compound was obtained by *N*-methylation of 7-hydroxytetrahydroquinoline (von Braun, *Ber.*, 1914, **47**, 2198).

EXPERIMENTAL.

The substituted phenyltrimethylammonium iodides were prepared by existing methods. The following are new:

4-*Ureidophenyltrimethylammonium iodide*, prepared by the action of methyl iodide on a cold acetone solution of 4-ureidophenyldimethylamine (Buck, *J. Amer. Chem. Soc.*, 1936, **58**, 2060), was obtained as needles, m. p. 229° (Found: I, 39·5. $C_{10}H_{16}ON_2I$ requires I, 39·5%), from alcohol.

3-*Ureidophenyldimethylamine*, prepared from potassium cyanate and *m*-aminodimethylaniline hydrochloride, crystallised from alcohol in needles, m. p. 124° (Found: C, 60·8; H, 7·5. $C_9H_{13}ON_3$ requires C, 60·3; H, 7·3%). The *methiodide* crystallised from alcohol in needles, m. p. 199° (Found: N, 12·6; I, 38·8. $C_{10}H_{16}ON_2I$ requires N, 13·1; I, 39·6%).

7-Dimethylamino-4-methylcoumarin (Pechmann and Schaal, *Ber.*, 1899, **32**, 3690) was converted into its methiodide, which separated from ethyl alcohol in lemon-yellow needles, m. p. 188—189°. The corresponding 8-*dimethylamino*-4-*methylcoumarin*, prepared from 3-diethylaminophenol and ethyl acetoacetate, was obtained from ligroin as stout prisms, m. p. 71—72° (Found : C, 73·1; H, 7·6. $C_{14}H_{17}O_2N$ requires C, 72·6; H, 7·4%), yielding a *methiodide*, pale yellow rhombs, m. p. 177°, from water (Found : I, 33·5. $C_{15}H_{20}O_2NI$ requires I, 34·0%.).

Preparation of Dinitro-compounds (VIII) *and* m-*Nitroaniline Derivatives* (IX).—The hydrocarbons employed were obtained as follows : *m*-xylene and *p*-cymene were commercial products, ethylbenzene was obtained from acetophenone, *iso*propylbenzene was prepared from benzene, *iso*propyl bromide and aluminium chloride, and *cyclo*hexylbenzene from benzene, *cyclo*hexyl chloride, and aluminium chloride. These hydrocarbons were dinitrated as described by Ruggli, Zimmermann, and Thouvay (*Helv. Chim. Acta*, 1931, **14**, 1252), Wheeler and Harris (*J. Amer. Chem. Soc.*, 1927, **49**, 495), Weisweiller (*Monatsh.*, 1904, **21**, 39), Bogert and Stirling (*J. Org. Chem.*, 1939, **4**, 24) and Mayer and Turner (*J.*, 1929, 500), respectively. Reduction to the nitroanilines (IX) was carried out with sodium hydrogen sulphide or ammonia and hydrogen sulphide in the usual way; the bases were freed from sulphur-containing by-products by solution in 2N-hydrochloric acid.

2-*Nitro*-4-*amino*iso*propylbenzene*, obtained in 55% yield, had b. p. 135—140°/0·4 mm. and separated from ether–ligroin in yellow plates, m. p. 51—52° (Found: C, 60·0; H, 6·7. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·7%).

N-*Alkylation to Compounds of Type* (X).—The nitroaniline (1 mol.) was refluxed for 18 hours with methyl iodide (4·5 mols.) and anhydrous sodium carbonate (3·5 mols.) in methyl alcohol (5—10 mols.). In some cases alkylation resulted in the formation of tertiary bases, but in others, quaternary salts were obtained which either crystallised from the hot, filtered, alcoholic solution or were precipitated by addition of ether. It was usual to evaporate the methylation mixture to dryness, decompose the residual quaternary ammonium salt by heating at 180—200°, and distil the teriary amine at 0·5 mm. The distillate was finally warmed with acetic anhydride (1 part) for ½ hour on the water-bath, the excess anhydride removed, the residue treated with dilute hydrochloride acid, and non-basic inpurities removed in ether, and the tertiary base was recovered by addition of ammonia, isolated with ether, and purified by distillation at 0·5 mm. and finally by crystallisation

The new *compounds* described in Table V were frequently characterised as methiodides.

Reduction to Compounds of Type (XI).—The nitrodialkylaniline (X) was reduced with tin (2·5 mols.) and concentrated hydrochloric acid (7 mols.), and the amine, isolated with ether, was distilled at 0·5 mm. and frequently characterised as the acetyl derivative. New *bases* are described in Table VI. Nitro-anisidines were reduced catalytically (palladium and hydrogen) to the corresponding diaminoanisoles.

Conversion into Compounds of Type (XII).—A concentrated solution of sodium nitrite (1·1 mol.) was added to a solution of the 3-aminodialkylaniline in 2N-sulphuric acid (15—16 vols.) at −5°. The diazo-solution was poured into a suspension of copper bronze (1 g. per 5 g. of base) in boiling 2N-sulphuric acid (15—16 vols.), and after 10 minutes the cooled, filtered solution was treated with excess of sodium bicarbonate and the 3-dialkylaminophenol was isolated with ether, distilled at 0·5 mm., and crystallised from ligroin. New *compounds* are described in Table VII.

Conversion of Nitroanilines (IX) *into Nitrophenols* (XIII).—The diazotisation was carried out as described above with the exception that a temperature of 10—15° was employed. The diazo-solution was poured into a boiling solution of hydrated copper sulphate (12 parts) in 2N-sulphuric acid (12 vols.). Of the new compounds of type (XIII), 3-nitro-4-ethylphenol was obtained as an oil, b. p. 142—144°/1·3 mm., and 3-*nitro*-4-iso*propylphenol*, b. p. 138—142°/1 mm., separated from ligroin in yellow prisms, m. p. 56—58° (Found : C, 59·5; H, 6·4. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1%).

Reduction of Nitrophenols (XIII) *to Aminophenols* (XIV).—This was effected in methyl alcohol with hydrogen in the presence of 15% palladium–charcoal. 3-Amino-4-ethylphenol was not isolated in pure condition, 3-*amino*-4-iso*propylphenol* crystallised from water in colourless prisms, m. p. 102—103° (Found : C, 70·8; H, 8·8. $C_9H_{13}ON$ requires C, 71·5; H, 8·6%).

Methylation to Aminophenols (XV).—This process was carried out as described in *N*-alkylation to compounds of type (V). The distillate was extracted with 20% sodium hydroxide, and the insoluble anisole derivative removed in ether. The alkaline extracts were acidified and then neutralised with sodium bicarbonate, and the phenol was isolated with ether and distilled. An additional yield was obtained by hydrolysis of the dimethylaminoanisole with hydriodic acid (5 vols., *d* 1·7).

This method was used for the preparation of 5-dimethylamino-4-*iso*propyl-*o*-cresol, m. p. 94° [hydrochloride, prisms, m. p. 215°; *acetyl* derivative, prisms, m. p. 58—60°, from ether (Found : Ac, 18·4. $C_{14}H_{21}O_2N$ requires Ac, 18·3%); *methiodide*, prisms from alcohol, m. p. 230° (Found : I, 38·4. $C_{13}H_{22}ONI$ requires I, 37·9%)], and for 7-*hydroxy*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydroquinoline*, obtained from 7-amino-1-benzoyltetrahydroquinoline (von Braun, *Ber.*, 1914, **47**, 498), as an oil, b. p. 150°/0·8 mm., which crystallised from ether–ligroin in colourless rhombs, m. p. 73—74° (Found : C, 73·3; H, 7·6. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0%).

Preparation of Urethanes and their Salts.—Methyl *iso*cyanate was prepared by Slotta's method (*Ber.*, 1925, **58**, 1320; 1927, **60**, 298). Benzyl *iso*cyanate, prepared by the action of carbonyl chloride on a toluene solution (200 c.c.) of benzylamine (6 g.) at 110—120°, was obtained as a viscous liquid, b. p. 86—88°/12 mm. (Eng. Pat. 462,182 gives b. p. 82—84°/10 mm.). 4-*Methoxybenzyl* iso*cyanate*, b. p. 102—104°/1 mm., was prepared similarly (Found : N, 8·8. $C_9H_9O_2N$ requires N, 8·6%).

The dialkylaminophenol (1 mol.) and methyl *iso*cyanate (5 mols., or alternatively 1·5—2 mols. in 3 vols. of ether or benzene) were mixed with ice-cooling, and after 24 hours the solvent and excess of *iso*cyanate were removed under reduced pressure and the residue was triturated with ether. With 5-dimethylaminocarvacrol it was necessary to avoid an excess of methyl *iso*cyanate, otherwise compounds containing the diurethane group, –O·CO·NMe·CO·NHMe, were produced. The urethanes were usually purified by crystallisation from ligroin or methyl alcohol, and in some cases distillation at 0·1 mm. could be effected without decomposition.

The hydrochlorides were prepared by the action of dry hydrogen chloride in ethereal solution, and

TABLE V.

Nitrodialkylanilines.

Compound.	M. p. or b. p.	Base.	Found, %.	Required, %.	Derivative.	Formula.	Found, %.	Required, %.
2-Nitro-4-dimethylamino-1-ethylbenzene	Yellow oil, b. p. 145°/1 mm.		—	—	Methiodide; yellow plates, m. p. 180°	$C_{11}H_{17}O_2N_2I$	I, 38·5	I, 37·8
2-Nitro-4-dimethylamino-1-*iso*propylbenzene	Yellow oil, b. p. 135°/1 mm.		—	—	Methiodide; hexagonal plates, m. p. 195°	$C_{12}H_{19}O_2N_2I$	I, 36·5	I, 36·3
2-Nitro-4-dimethylamino-1-*cyclo*hexylbenzene	Yellow prisms, m. p. 55° from ligroin	$C_{14}H_{20}O_2N_2$	C, 67·6; H, 8·6	C, 67·7; H, 8·1	Methiodide; prisms, m. p. 185°	$C_{15}H_{23}O_2N_2I$	I, 33·3	I, 32·6
2-Nitro-4-diethylaminotoluene	Yellow oil, b. p. 145°/15 mm.		—	—			—	—
3-Nitro-5-dimethylaminotoluene	Red plates, m. p. 51° from ligroin	See (i)	—	—	Methiodide; plates, m. p. 178°	$C_{10}H_{15}O_2N_2I$	I, 39·0	I, 39·4
4-Nitro-6-dimethylamino-*m*-xylene	Yellow oil, b. p. 118°/0·8 mm.	See (ii)	—	—	Methiodide; needles, m. p. 162°	$C_{11}H_{17}O_2N_2I$	I, 37·3	I, 37·8
2-Nitro-6-dimethylamino-4-*iso*propyltoluene	Yellow oil, b. p. 117°/0·4 mm.		—	—			—	—
4-Chloro-3-nitrodimethylaniline	Prisms, m. p. 79° from alcohol	$C_8H_9O_2N_2Cl$ See (iii)	C, 48·6; H, 4·7	C, 47·9; H, 4·5	Methiodide; prisms, m. p. 176°	$C_9H_{12}O_2N_2ClI$	I, 36·9	I, 37·1

(i) Haibach, *J. pr. Chem.*, 1902, **65**, 246. (ii) Morgan and Micklethwait, *J.*, 1907, **41**, 365. (iii) Clemo and Smith, *J.*, 1928, 2420.

TABLE VI.

Aminodialkylamines.

Compound.	B. p.	Base.	Found, %.	Required, %.	Acetyl derivative.	Formula.	Found, %.	Required, %.
2-Amino-4-dimethylamino-1-ethylbenzene	125°/1·2 mm.		—	—	Prisms, m. p. 126°	$C_{12}H_{18}ON_2$	C, 69·7; H, 9·0	C, 69·9; H, 8·7
2-Amino-4-dimethylamino-1-*iso*propylbenzene	125°/0·8 mm.		—	—	Prisms, m. p. 118°	$C_{13}H_{20}ON_2$	C, 70·4; H, 9·0	C, 70·9; H, 9·1
2-Amino-4-dimethylamino-1-*cyclo*hexylbenzene	(M. p. 65°, from ligroin)	$C_{14}H_{22}N_2$	C, 77·0; H, 10·3	C, 77·0; H, 10·0			—	—
2-Amino-4-diethylaminotoluene	130°/1·5 mm.		—	—	Needles, m. p. 82°	$C_{13}H_{20}ON_2$	N, 13·0	N, 12·7
3-Amino-5-dimethylaminotoluene	118°/0·5 mm.		—	—	Needles, m. p. 141°	$C_{11}H_{16}ON_2$	N, 14·4	N, 14·6
4-Amino-6-dimethylamino-*m*-xylene	108°/0·4 mm.		—	—	Needles, m. p. 138°	$C_{12}H_{18}ON_2$	N, 13·8	N, 13·6
2-Amino-6-dimethylamino-4-*iso*propyltoluene	110°/0·4 mm.	$C_{12}H_{20}N_2$	N, 14·8	N, 14·5			—	—

TABLE VII.

Dialkylaminophenols.

Compound.	M. p. etc.	Base.	Found, %.	Required, %.	Derivative.	Formula.	Found, %.	Required, %.
4-Dimethylamino-*o*-cresol	Prisms, 99°	$C_9H_{13}ON$	C, 71·5; H, 8·8	C, 71·5; H, 8·7	Methiodide; m. p. 169°	$C_{10}H_{16}ONI$	I, 42·1	I, 43·0
5-Dimethylamino-2-ethylphenol	Prisms, 90°	$C_{10}H_{15}ON$	C, 72·4; H, 9·3	C, 72·7; H, 9·1	Methiodide; plates, m. p. 182°	$C_{11}H_{18}ONI$	I, 41·0	I, 41·4
5-Dimethylamino-2-*iso*propylphenol	Plates, 120°	$C_{11}H_{17}ON$	C, 73·7; H, 9·5	C, 73·7; H, 9·5	Methiodide; prisms, m. p. 178°	$C_{12}H_{20}ONI$	I, 38·7	I, 39·5
5-Dimethylamino-2-*cyclo*hexylphenol	Prisms, 120°	$C_{14}H_{21}ON$	C, 76·5; H, 9·6	C, 76·7; H, 9·6			—	—
4-Diethylamino-*o*-cresol	Prisms, 46—47°	$C_{11}H_{17}ON$	C, 74·3; H, 9·8	C, 73·7; H, 9·5	Methiodide; prisms, m. p. 173°	$C_{12}H_{20}ONI$	I, 40·0	I, 39·5
2-Dimethylamino-*p*-cresol	Prisms, 72°	$C_9H_{13}ON$ See (i)	C, 71·0; H, 8·7	C, 71·5; H, 8·7	Methiodide; plates, m. p. 170°	$C_{10}H_{16}ONI$	I, 42·2	I, 43·0
3-Dimethylamino-4-ethylphenol	(Oil, b. p. 110°/0·5 mm.).		—	—	Methiodide; prisms, m. p. 171°	$C_{11}H_{18}ONI$	I, 40·6	I, 41·4
3-Dimethylamino-4-*iso*propylphenol	Prisms, 67°	$C_{11}H_{17}ON$	C, 73·9; H, 9·9	C, 73·7; H, 9·5	Methiodide; prisms, m. p. 191°		—	—
5-Dimethylamino-*m*-cresol	Needles, 62°	$C_9H_{13}ON$	C, 71·8; H, 9·0	C, 71·5; H, 8·7	Acetyl; plates, m. p. 140°	$C_{11}H_{16}ON_2$	N, 14·4	N, 14·6
6-Dimethylamino-*m*-4-xylenol	Rhombs, 88°	$C_{10}H_{15}ON$	C, 72·4; H, 9·1	C, 72·7; H, 9·1			—	—
6-Dimethylamino-4-*iso*propyl-*o*-cresol	Prisms, 81°	$C_{12}H_{19}ON$	C, 74·5; H, 9·9	C, 74·6; H, 9·8	Methiodide; prisms, m. p. 169°	$C_{13}H_{22}ONI$	I, 37·6	I, 37·9
5-Dimethylamino-4-*iso*propyl-*o*-cresol	Prisms, 94°	See (ii)	—	—	Methiodide; prisms, m. p. 230°	$C_{13}H_{22}ONI$	I, 38·2	I, 37·9
1-Dimethylamino-2-hydroxynaphthalene	Prisms, 54°	$C_{12}H_{13}ON$	C, 77·1; H, 7·2	C, 77·0; H, 7·0			—	—
3-Hydroxypyridine			See (iii)	—	Methiodide; needles, m. p. 110°	C_6H_8ONI	I, 52·9	I, 53·5
7-Hydroxy-1-methyltetrahydroquinoline	Rhombs, 73—74°	$C_{10}H_{13}ON$	C, 73·2; H, 7·5	C, 73·6; H, 8·0				
2 : 4-Tetramethyldiaminophenol	60—62°		—	—	Dimethiodide; plates, m. p. 205°	$C_{12}H_{22}ON_2I_2$	I, 53·8	I, 54·7
2 : 5-Tetramethyldiaminophenol	84—87°		—	—	Dihydrochloride	$C_{10}H_{18}ON_2Cl_2$	Cl, 27·6	Cl, 28·0
2-Chloro-5-dimethylaminophenol	Prisms, 105°	$C_8H_{10}ONCl$	C, 56·3; H, 6·1	C, 56·1; H 5·9			—	—
4-Amino-*N*-methyl-*N*-2′-diethylaminoethylphenol	(B. p. 180°/0·5 mm.)	See (iv)		—	Dihydrochloride, m. p. 222°	$C_{13}H_{24}ON_2Cl_2$	Cl, 23·9	Cl, 24·0
				—	Dimethiodide; needles, m. p. 161°	$C_{15}H_{28}ON_2I_2$	I, 49·9	I, 50·2
4-Dimethylamino-2-hydroxybenzyldimethylamine			—	—	Dihydrochloride, m. p. 165°	$C_{11}H_{20}ON_2Cl_2$	Cl, 25·8	Cl, 26·4

(i) Mohlau, Klimmer, and Kahl, *Z. Farben u. Textilchemie*, 1902, I, 321, give m.p. 46°.
(ii) Stevens and Beutel, *J. Amer. Chem. Soc.*, 1941, **63**, 318.
(iii) Machik, *Monatsh.*, 1938, **72**, 77.
(iv) Austrian Patent, 8712/1927.

TABLE VIII.

Urethanes.

Urethane.	M. p., etc.	Formula.	Found, %.	Required, %.	Derivative.	Formula.	Found, %.	Required, %.
N-Methylurethane of 2-dimethylaminophenol	77°. See (i)		—	—	Methiodide; m. p. 137—138°	$C_{11}H_{17}O_2N_2I$	I, 36·8	I, 37·8
N-Methylurethane of 4-dimethylaminophenol	133°. See (i)		—	—	Methiodide; m. p. 176—178°	$C_{11}H_{17}O_2N_2I$	I, 38·1	I, 37·8
Urethane of 3-dimethylaminophenol	132°. See (i)		—	—	Methiodide; m. p. 175—178°	$C_{10}H_{15}O_2N_2I$	I, 39·0	I, 39·4
N-Methylurethane of 3-dimethylaminophenol	86—89°. See (i)		—	—	Methiodide; m. p. 175°	$C_{11}H_{17}O_2N_2I$	I, 38·2	I, 37·8
					Hydrochloride; m. p. 171—172°. See (ii)			
					Ethiodide; m. p. 160°	$C_{12}H_{19}O_2N_2I$	I, 36·3	I, 36·3
N-Methylurethane of 3-diethylaminophenol	85—86°	$C_{12}H_{18}O_2N_2$	C, 65·1; H, 8·2	C, 64·9; H, 8·1	Methiodide; m. p. 140—143°. See (ii)	$C_{13}H_{21}O_2N_2I$	I, 35·0	I, 34·9
N-Benzylurethane of 3-dimethylaminophenol	See (ii)		—		Methiodide; m. p. 160°	$C_{17}H_{21}O_2N_2I$	I, 31·0	I, 30·8
N-Benzylurethane of 3-diethylaminophenol	87°	$C_{18}H_{22}O_2N_2$	C, 72·8; H, 7·5	C, 72·5; H, 7·4	Methiodide, dec. by water		—	—
N-4-Methoxybenzylurethane of 3-dimethylaminophenol	(Oil)		—	—	Methiodide; m. p. 158°	$C_{18}H_{23}O_3N_2I$	I, 29·0	I, 29·4
N-Methylurethane of 4-dimethylamino-*o*-cresol	Rhombs, m. p. 93°	$C_{11}H_{16}O_2N_2$	C, 64·0; H, 7·7	C, 63·4; H, 7·8	Methiodide; needles, m. p. 188°	$C_{12}H_{19}O_2N_2I$	I, 35·8	I, 36·0
N-Methylurethane of 5-dimethylamino-2-ethylphenol	Prisms, m. p. 97°	$C_{12}H_{18}O_2N_2$	C, 65·1; H, 8·4	C, 64·8; H, 8·1	Methiodide; prisms, m. p. 162°	$C_{13}H_{21}O_2N_2I$	I, 34·9	I, 34·8
N-Methylurethane of 5-dimethylamino-2-*iso*propylphenol	Prisms, m. p. 116°	$C_{13}H_{20}O_2N_2$	C, 66·0; H, 8·6	C, 66·1; H, 8·5	Methiodide; prisms, m. p. 179°	$C_{14}H_{23}O_2N_2I$	I, 33·1	I, 33·6
N-Methylurethane of 2-dimethylamino-3-*cyclo*hexylphenol	Prisms, m. p. 132°	$C_{16}H_{24}O_2N_2$	C, 68·9; H, 9·0	C, 69·5; H, 8·7	Methiodide; prisms, m. p. 184°	$C_{17}H_{27}O_2N_2I$	I, 31·6	I, 31·0
N-Methylurethane of 4-diethylamino-*o*-cresol	M. p. 80—82°	$C_{13}H_{20}O_2N_2$	C, 65·7; H, 8·4	C, 66·0; H, 8·5	Methiodide; m. p. 157°	$C_{14}H_{23}O_2N_2I$	I, 34·1	I, 33·6
N-Methylurethane of 2-dimethylamino-*p*-cresol	Plates, m. p. 89°	$C_{11}H_{16}O_2N_2$	C, 63·8; H, 8·0	C, 63·4; H, 7·8	Methiodide; prisms, m. p. 154°	$C_{12}H_{19}O_2N_2Cl$	I, 35·7	I, 36·0
					Hydrochloride; cubes, m. p. 156°	$C_{11}H_{17}O_2N_2Cl$	Cl, 13·8	Cl, 14·5
N-Methylurethane of 3-dimethylamino 4-ethylphenol	Prisms, m. p. 104°	$C_{12}H_{18}O_2N_2$	C, 65·2; H, 8·4; N, 12·3	C, 64·8; H, 8·1; N, 12·6	Methiodide; plates, m. p. 157°	$C_{13}H_{21}O_2N_2I$	I, 34·8	I, 34·8
N-Methylurethane of 3-dimethylamino-4-*iso*propylphenol	Prisms, m. p. 110°	$C_{13}H_{20}O_2N_2$	C, 66·2; H, 8·5; N, 11·7	C, 66·0; H, 8·5; N, 11·9	Methiodide; prisms, m. p. 167°	$C_{14}H_{23}O_2N_2I$	I, 33·4	I, 33·6
					Hydrochloride; needles, m. p. 187°	$C_{13}H_{21}O_2N_2Cl$	Cl, 13·1	Cl, 13·0
N-Methylurethane of 5-dimethylamino-*m*-cresol	Plates, m. p. 76°	$C_{11}H_{16}O_2N_2$	C, 64·7; H, 8·3	C, 63·4; H, 7·8	Methiodide; plates, m. p. 185°	$C_{12}H_{19}O_2N_2I$	I, 35·3	I, 36·0

Urethane.	M. p., etc.	Formula.	Found, %.	Required, %.	Derivative.	Formula.	Found, %.	Required, %.
N-Methylurethane of 6-dimethylamino-*m*-4-xylenol	Prisms, m. p. 95°	$C_{12}H_{18}O_2N_2$	C, 65·0; H, 8·4	C, 64·8; H, 8·1	Methiodide; plates, m. p. 162°	$C_{13}H_{21}O_2N_2I$	I, 34·6	I, 34·8
					Hydrochloride; rhombs, m. p. 181°	$C_{12}H_{19}O_2N_2Cl$	Cl, 13·4	Cl, 13·7
N-Methylurethane of 6-dimethylamino-4-*iso*propyl-*o*-cresol	Prisms, m. p. 80°	$C_{14}H_{22}O_2N_2$	C, 66·7 H, 8·8	C, 67·2; H, 8·8	Methiodide; rhombs, m. p. 175°	$C_{15}H_{25}O_2N_2I$	I, 32·6	I, 32·4
N-Methylurethane of 5-dimethylamino-4-*iso*propyl-*o*-cresol	Needles, m. p. 68°	$C_{14}H_{22}O_2N_2$	C, 67·4; H, 8·9; N, 11·3	C, 67·2; H, 8·8; N, 11·2	Methiodide; plates, m. p. 163°	See (iii)	—	—
N-Methylurethane of 1-dimethylamino-2-naphthol	M. p. 90°	$C_{14}H_{16}O_2N_2$	C, 69·3; H, 6·7	C, 68·8; H, 6·1	Does not form a methiodide.			
N-Phenylurethane of 3-hydroxypyridine	Plates, m. p. 132°	$C_{12}H_{10}O_2N_2$	C, 67·6; H, 5·3	C, 67·3; H, 4·7	Methiodide; m. p. 131°; dec. by water	$C_{13}H_{13}O_2N_2I$	I, 35·2	I, 35·6
N-Methylurethane of 8-hydroxy-1-methyltetrahydroquinoline	Prisms, m. p. 98°	$C_{12}H_{16}O_2N_2$	C, 64·5; H, 7·3	C, 65·4; H, 7·3	Methiodide; prisms, m. p. 215°	$C_{13}H_{19}O_2N_2I$	I, 35·0	I, 35·1
				—	Hydriodide; prisms, m. p. 160°	$C_{12}H_{17}O_2N_2I$	I, 35·7	I, 36·5
N-Methylurethane of 7-hydroxy-1-methyltetrahydroquinoline			—	—	Methiodide; prisms, m. p. 166°	$C_{13}H_{19}O_2N_2I$	I, 34·6	I, 35·1
					Hydrochloride; m. p. 160°	$C_{12}H_{17}O_2N_2Cl$	Cl, 13·6	Cl, 13·8
N-Methylurethane of 8-hydroxyquinoline	M. p. 178°. See (i)		—	—	Methiodide; prisms, m. p. 162°	$C_{12}H_{13}O_2N_2I$	I, 37·1	I, 36·9
				—	Hydrochloride; plates, m. p. 155°	$C_{11}H_{11}O_2N_2Cl$	Cl, 14·3	Cl, 14·8
N-Methylurethane of 2 : 4-tetramethyldiaminophenol	Cubes, m. p. 89°		—	—	Dimethiodide; prisms, m. p. 197°	$C_{14}H_{25}O_2N_3I_2$	I, 45·2	I, 48·6
				—	Dihydrochloride; prisms, m. p. 173°	$C_{12}H_{21}O_2N_3Cl_2$	Cl, 22·4	Cl, 22·9
N-Methylurethane of 2 : 5-tetramethyldiaminophenol	Rhombs, m. p. 94°	$C_{12}H_{19}O_2N_2$	C, 61·3; H, 8·5	C, 60·7; H, 8·1	Dimethiodide; prisms, m. p. 215°	$C_{14}H_{25}O_2N_3I_2$	I, 48·5	I, 48·6
					Dihydrochloride; prisms, m. p. 158°	$C_{12}H_{21}O_2N_3Cl_2$	Cl, 22·5	Cl, 22·9
N-Methylurethane of 2-chloro-5-dimethylaminophenol	Prisms, m. p. 92°		—	—	Methiodide; prisms, m. p. 159°	$C_{11}H_{16}O_2N_2ClI$	I, 34·6	I, 34·3
					Hydrochloride; prisms.	$C_{10}H_{14}O_2N_2Cl_2$	Cl, 13·0	Cl, 13·4
N-Methylurethane of 4-amino-*N*-β-diethylaminoethylphenol			—	—	Methiodide; plates, m. p. 158°	$C_{16}H_{28}O_2N_3I$	I, 29·6; N, 10·5	I, 30·1; N, 10·0
					Dihydrobromide; m. p. 164°	$C_{15}H_{27}O_2N_3Br_2$	I, 29·6; N, 9·5	Br, 36·2; N, 9·5
N-Methylurethane of 4-dimethylaminobenzyl alcohol	M. p. 68—72°		—	—	Methiodide; m. p. 199°	$C_{12}H_{19}O_2N_2I$	I, 36·0	I, 35·3

(i) Stedman, *Biochem. J.*, 1926, **20**, 728. (ii) Aeschlimann and Reinert, *loc. cit.* (iii) Stevens and Beutel, *loc. cit.*

the methiodides were obtained by the action of either (*a*) methyl iodide in cold acetone solution or (*b*) excess of methyl iodide in a sealed tube at 100°.

The urethanes and their derivatives are included in Table VIII.

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