46. *Investigations on the Influence of Chemical Constitution upon Toxicity. Part III. Compounds related to "Miotine."*

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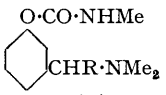
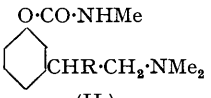
In Parts I and II it was observed that metho-salts of the "doryl" and "prostigmine" types were usually more toxic than the salts of the corresponding tertiary bases, and that in the limited number of cases examined the ratio of toxicity by subcutaneous injection to that by oral injection was usually about 30 in the metho-salts as compared with a value of 4 with the salts of tertiary bases. In addition, it was found that the action of salts of tertiary bases was usually more prolonged than that of the corresponding quaternary salts, and these differences may be ascribed to the slower excretion of the tertiary bases.

An examination has been made of the urethanes of hydroxyphenylalkylamines of types



(I.)



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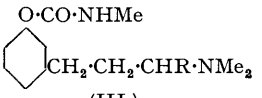

(III.)

(I), (II), and (III), together with their *o*- and *p*-analogues, and nuclear-alkylated homologues; the results are recorded in Table I.

Table I.

L.D.$_{50}$ *for Methiodides and Hydrochlorides of* N-*Methylurethanes of Hydroxybenzyldimethylamines and Homologues.*

Name.	L.D.$_{50}$ (mg./kg.). Methiodide.	Hydrochloride.
(*a*) 2-Hydroxybenzyldimethylamine	7·2	—
Dimethyl-α-(2-hydroxyphenyl)-*n*-propylamine	10·0	40
2-Hydroxy-3-methylbenzyldimethylamine	—	300
2-Hydroxy-5-methylbenzyldimethylamine	75	120
2-Hydroxy-4-methylbenzyldimethylamine	—	145
Dimethyl-α-(4-hydroxy-*m*-tolyl)ethylamine	12	47
(*b*) 4-Hydroxybenzyldimethylamine	—	60
Dimethyl-α-(4-hydroxyphenyl)ethylamine	—	25
Dimethyl-α-(4-hydroxyphenyl)-*n*-propylamine	250—450	—
Dimethyl-β-(4-hydroxyphenyl)ethylamine	—	10
Dimethyl-γ-(4-hydroxyphenyl)-*n*-propylamine	50	5—7·5
Dimethyl-γ-(4-hydroxyphenyl)-α-methyl-*n*-propylamine	40	100 (unstable in water)
(*c*) 3-Hydroxybenzyldimethylamine	7	10
Dimethyl-α-(3-hydroxyphenyl)ethylamine	—	0·8 6·0 (oral)
Dimethyl-α-(3-hydroxyphenyl)-*n*-propylamine	4·5	2·8
Dimethyl-β-(3-hydroxyphenyl)ethylamine	7·5	3·0
Dimethyl-β-(3-hydroxyphenyl)-*n*-propylamine	0·6	0·4
Dimethyl-γ-(3-hydroxyphenyl)-α-methyl-*n*-propylamine	16	9
1-Dimethylamino-7-hydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene	20	Hydrobromide 4

The toxicities of the *N*-methylurethane of three phenolic derivatives are recorded in Table II, and the following main points emerge from the tables.

(1) In general the toxicities of hydrochlorides are not particularly high, the L.D.$_{50}$ values usually lying between 10 and 60, but two compounds are highly toxic; "miotine" (I, R = Me), previously prepared by Stedman and his co-workers (*J.*, 1929, 609; 1931, 1126; 1932, 2513;

TABLE II.

L.D.$_{50}$ *for Methiodides and Hydrochlorides of* N-*Methylurethanes of Some Hydroxytetrahydro-*iso*quinolines.*

Name.	L.D.$_{50}$ (mg./kg.). Methiodide.	Hydrochloride.
6-Hydroxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline	100	35
5 : 6-Dihydroxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline	60	20
6 : 7-Dihydroxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline	800	400—800

1933, 1094; *Biochem. J.*, 1929, **23**, 17; 1933, **27**, 1257; *J. Pharm. Exp. Ther.*, 1931, **41**, 259; 1937, **60**, 198; see also Part II of this series for other references), and the N-*methylurethane* of *dimethyl*-β-(3-*hydroxyphenyl*)-n-*propylamine hydrochloride* (II; R = Me) have L.D.$_{50}$ values of 0·8 and 0·4 respectively.

(2) The methiodides are far less toxic as a rule than those of the prostigmine series with the exception of the methiodide of (II; R = Me) with L.D.$_{50}$ 0·6.

(3) A *m*-orientation of the hydroxy-group with respect to the side chain favours high toxicity.

(4) In contrast to the results in the prostigmine series, the hydrochlorides of tertiary bases of types (I, (II), and (III) are frequently more toxic than the corresponding metho-salts. The alkaloid arecoline shows a similar behaviour, the hydrobromide and methiodide having L.D.$_{50}$ values of 19 and 30, respectively.

(5) Nuclear alkylation of 2-hydroxybenzyldimethylamine and its homologues is not attended by a marked increase in toxicity. Orientation difficulties were encountered during attempts to prepare alkylated 3- and 4-hydroxybenzyldimethylamines, but the properties of the *N*-methylurethane of 1-dimethylamino-7-hydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene (Table I, *c*) and the *iso*quinolines shown in Table II indicate that nuclear alkylation may lead to a reduction in toxicity in these substances.

(6) On the other hand, alkylation of the side chain leads to a substantial increase in toxicity.

New tests indicate that miotine is somewhat less toxic than was reported previously by White and Stedman (*J. Pharm. Exp. Ther.*, 1931, **41**, 259). There is very little species variation; oral toxicity is high (L.D.$_{50}$, 6), and symptoms are consistent with an accumulation of acetylcholine, due to the anti-choline esterase activity of miotine, and deaths are probably due to cessation of respiration.

2-Hydroxybenzyldimethylamine and its nuclear-methylated homologues were prepared by the Mannich reaction from phenol and the cresols (Décombe, *Compt. rend.*, 1933, **196**, 866). The Mannich reaction was also employed in the conversion of 5-ethoxyindole (Hoshino and Kotake, *Annalen*, 1935, **516**, 76) into *5-ethoxy-3-dimethylaminomethylindole*. This compound had L.D.$_{50}$, 150 mg./kg., but attempts to convert it into 5-hydroxy-3-dimethylaminomethylindole were unsuccessful.

The following series of reactions were employed extensively in the preparation of *o*-, *m*-, and *p*-ethers of type (IV).

$$MeO{\cdot}C_6H_4{\cdot}COR \longrightarrow \text{Oxime} \xrightarrow{H_2} MeO{\cdot}C_6H_4{\cdot}CHR{\cdot}NH_2 \xrightarrow[HCO_2H]{CH_2O \text{ and}} MeO{\cdot}C_6H_4{\cdot}CHR{\cdot}NMe_2 \quad \text{(IV.)}$$

In the *o*-series, the reactions were used in cases where R = Me and Et, and in the *m*- and *p*-series compounds where R = H, Me, and Et were prepared. Miotine (I; R = Me) was obtained in good yield from 3-methoxyacetophenone, and the conversions of 2-methoxy-5-methylacetophenone and 7-methoxy-1-tetralone into *dimethyl*-α-(4-*hydroxy*-m-*tolyl*)*ethylamine* and 1-*dimethylamino*-7-*hydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene* respectively were effected.

Dimethyl-β-(4-hydroxyphenyl)ethylamine was prepared from β-(4-methoxyphenyl)ethylamine by methylation with formaldehyde and formic acid and subsequent demethylation. During attempted methylations of β-(3-methoxyphenyl)ethylamine and β-(3 : 4-dimethoxyphenyl)ethylamine by a similar procedure it was found, not unexpectedly, that ring closures occurred to 6-methoxy- and 6 : 7-dimethoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline, respectively. In order to obtain the dimethyl-β-phenylethylamine bases it was therefore necessary to methylate β-(3-methoxyphenyl)ethylamine with methyl iodide and sodium carbonate; the resulting quaternary ammonium iodide, which did not decompose smoothly on heating, was converted into the corresponding chloride, and the latter on heating gave dimethyl-β-(3-methoxyphenyl)ethylamine. γ-(4-Methoxyphenyl)propylamine, obtained from γ-(4-methoxyphenyl)butyramide, was methylated by formaldehyde to dimethyl-γ-4-methoxy-

TABLE III.

Methoxyphenyl tertiary amines.

Name.	B. p.	Derivative.	Formula.	Found, %.	Required, %.
Dimethyl-α-(2-methoxyphenyl)-*n*-propylamine	124°/16 mm.	Picrate; prisms, m. p. 146°	$C_{18}H_{24}O_8N_4$	C, 51·5; H, 5·2	C, 51·2; H, 5·2
Dimethyl-β-(3-methoxyphenyl)ethylamine	121°/13 mm.	Picrate; needles, m. p. 162° Hydrochloride; m. p. 133° Methiodide; m. p. 182°	$C_{17}H_{20}O_8N_4$	C, 49·9; H, 5·0	C, 50·0; H, 4·9
Dimethyl-β-(3-methoxyphenyl)-*n*-propylamine	136°/16 mm.	Methiodide; prisms, m. p. 168°	$C_{13}H_{22}ONI$	C, 46·6; H, 7·0	C, 46·6; H, 6·6
		Picrate; prisms, m. p. 141°	$C_{18}H_{22}O_8N_4$	C, 51·3; H, 5·2	C, 51·2; H, 5·2
Dimethyl-γ-(4-methoxyphenyl)-α-methyl-*n*-propylamine	155°/14 mm.	Hydrochloride; plates, m. p. 166° Picrate; m. p. 129°	$C_{13}H_{22}ONCl$	Cl, 14·9	Cl, 14·6
Dimethyl-γ-(3-methoxyphenyl)-α-methyl-*n*-propylamine	155°/15 mm.				
Dimethyl-α-(4-methoxy-*m*-tolyl)ethylamine	117°/14 mm.	Picrate; prisms, m. p. 144°			
1-Dimethylamino-7-methoxytetralin	152°/17 mm.	Methiodide; needles, m. p. 141°	$C_{14}H_{22}ONI$	I, 36·0	I, 36·6
6-Methoxy-2-methyltetrahydro*iso*quinoline	138°/13 mm.	Picrate, m. p. 125°	$C_{17}H_{18}O_8N_4$	C, 50·3; H, 4·7	C, 50·2; H, 4·4
		Methiodide, m. p. 174°	$C_{12}H_{18}ONI$	I, 39·3	I, 39·8
		Hydrochloride, m. p. 172° (See i)			
5 : 6-Dimethoxy-2-methyltetrahydro*iso*quinoline	167°/13 mm.	Picrate; prisms, m. p. 133° (See ii)	$C_{18}H_{20}O_9N_4$	C, 49·5; H, 4·6	C, 49·6; H, 4·6
6 : 7-Dimethoxy-2-methyltetrahydro*iso*quinoline	M. p. 78° See (iii)	Picrate; prisms, m. p. 159°	$C_{18}H_{20}O_9N_4$	C, 49·6; H, 4·3	C, 49·6; H, 4·6

(i) Buck, *J. Amer. Chem. Soc.*, 1934, **56**, 1769, gives hydrochloride, m. p. 170°.
(ii) Haworth, *J.*, 1927, 2283, gives picrate, m. p. 164°.
(iii) Pyman, *J.*, 1909, **95**, 1266, gives m. p. 83—84°.

TABLE IV.

Phenolic tertiary bases.

Name.	B. p., etc.	Derivative.	Formula.	Found, %.	Required, %.
Dimethyl-α-(2-hydroxyphenyl)-*n*-propylamine	130°/15 mm.				
Dimethyl-α-(4-hydroxyphenyl)-*n*-propylamine	M. p. 108°		$C_{11}H_{17}ON$	C, 73·3; H, 9·3	C, 73·7; H, 9·4
		Picrate; prisms, m. p. 155°	$C_{17}H_{20}O_8N_4$	C, 50·1; H, 4·9	C, 50·0; H, 4·9
		Hydrochloride, m. p. 170°	$C_{11}H_{18}ONCl$	Cl, 16·0	Cl, 16·5
Dimethyl-β-(4-hydroxyphenyl)ethylamine	M. p. 118° See (i)	Hydriodide, m. p. 148°		—	—
Dimethyl-β-(3-hydroxyphenyl)ethylamine	M. p. 98° See (ii)	Picrate, m. p. 140°	$C_{16}H_{18}O_8N_4$	C, 48·5; H, 4·4	C, 48·7; H, 4·8
		Hydrochloride, m. p. 162°			
Dimethyl-β-(3-hydroxyphenyl)-*n*-propylamine	175°/11 mm.	Picrate, m. p. 179°	$C_{17}H_{20}O_8N_4$	C, 50·1; H, 5·1	C, 50·0; H, 4·9
		Methiodide, m. p. 168°	$C_{12}H_{20}ONI$	C, 44·7; H, 6·3	C, 44·9; H, 6·2
Dimethyl-γ-(4-hydroxyphenyl)-α-methyl-*n*-propylamine	Needles, m. p. 64°	Hydrochloride; polyhedra, m. p. 153°	$C_{12}H_{20}ONCl$	Cl, 10·8	Cl, 11·1
Dimethyl-γ-(3-hydroxyphenyl)-α-methyl-*n*-propylamine	Prisms, m. p. 83°		$C_{12}H_{19}ON$	C, 74·5; H, 9·5	C, 74·6; H, 9·7
		Hydrochloride; rods, m. p. 115°	$C_{12}H_{20}ONCl$	Cl, 15·1	Cl, 15·5
Dimethyl-α-(4-hydroxy-*m*-tolyl)ethylamine	112°/13 mm.	Hydrochloride; needles, m. p. 62°	$C_{11}H_{18}ONCl$	Cl, 16·8	Cl, 16·5
		Methiodide; needles, m. p. 250°			
1-Dimethylamino-7-hydroxytetralin	160°/15 mm.	Methiodide; plates, m. p. 150°	$C_{13}H_{20}ONI$	I, 37·6	I, 38·1
5 : 6-Dihydroxy-2-methyltetrahydro*iso*quinoline	M. p. 203°	Hydrobromide, m. p. 236°	$C_{10}H_{14}O_2NBr$	C, 46·3; H, 5·3	C, 46·1; H, 5·4
		Picrate, m. p. 190°	$C_{16}H_{16}O_9N_4$	C, 47·2; H, 4·1	C, 47·1; H, 3·9
6 : 7-Dihydroxy-2-methyltetrahydro*iso*quinoline	Prisms, m. p. 221°	See (iii)			
		Hydrobromide; m. p. 248°	$C_{10}H_{14}O_2NBr$	C, 45·8; H, 5·2	C, 46·1; H, 5·4

(i) Barger, *J.*, 1909, **95**, 2196, gives m. p. 118°.
(ii) D.R.-P. 233,069 gives m. p. 103°.
(iii) Pyman, *J.*, 1910, **97**, 264, gives m. p. 222°.

TABLE V.

N-Methylurethanes and derivatives.

N-Methylurethane of—	M. p.	Derivative.	Formula.	Found, %.	Required, %.
Dimethyl-α-(2-hydroxyphenyl)-*n*-propylamine		Methiodide, m. p. 194°	$C_{14}H_{23}O_2N_2I$	I, 32·7	I, 33·6
Dimethyl-α-(4-hydroxyphenyl)-*n*-propylamine		Methiodide, m. p. 170°	$C_{14}H_{23}O_2N_2I$	I, 32·7	I, 33·6
β-(3-Hydroxyphenyl)ethylamine		Hydrochloride, m. p. 162°	$C_{12}H_{19}O_2N_2Cl$	Cl, 13·5	Cl, 13·7
		Methiodide, m. p. 183°	$C_{13}H_{21}O_2N_2I$	I, 34·1	I, 34·9
Dimethyl-β-(3-hydroxyphenyl)-*n*-propylamine		Hydrochloride, m. p. 213°	$C_{13}H_{21}O_2N_2Cl$	Cl, 12·8	Cl, 13·0
		Methiodide, hygroscopic needles	$C_{14}H_{23}O_2N_2I$	I, 32·4	I, 33·6
Dimethyl-γ-(4-hydroxyphenyl)-*n*-propylamine		Hydrochloride; prisms, m. p. 159°	$C_{13}H_{21}O_2N_2Cl$	Cl, 12·9	Cl, 13·0
		Methiodide; prisms, m. p. 133°	$C_{14}H_{23}O_2N_2I$	I, 33·5	I, 33·6
Dimethyl-γ-(4-hydroxyphenyl)-α-methyl-*n*-propylamine		Hydrochloride; rods, m. p. 110°	$C_{14}H_{23}O_2N_2Cl$	Cl, 12·3	Cl, 12·4
		Methiodide; prisms, m. p. 129°	$C_{15}H_{25}O_2N_2I$	I, 31·7	I, 32·2
Dimethyl-γ-(3-hydroxyphenyl)-α-methyl-*n*-propylamine		Hydrochloride; needles, m. p. 130°	$C_{14}H_{23}O_2N_2Cl$	Cl, 12·7	Cl, 12·4
		Methiodide; needles, m. p. 102°	$C_{15}H_{25}O_2N_2I$	I, 31·9	I, 32·2
2-Hydroxy-5-methylbenzyldimethylamine		Hydrochloride, very hygroscopic		—	—
		Methiodide; needles, m. p. 125°	$C_{13}H_{21}O_2N_2I$	I, 35·5	I, 34·9
Dimethyl-α-(4-hydroxy-*m*-tolyl)ethylamine		Hydrochloride; needles, m. p. 150°	$C_{13}H_{21}O_2N_2Cl$	Cl, 12·7	Cl, 13·0
		Methiodide; polyhedra, m. p. 182°	$C_{14}H_{23}O_2N_2I$	I, 33·8	I, 33·6
1-Methylamino-7-hydroxytetralin	Needles, m. p. 129° from ligroin		$C_{14}H_{20}O_2N_2$	C, 67·9; H, 8·0	C, 67·7; H, 8·1
		Hydrobromide; hygroscopic prisms	$C_{14}H_{21}O_2N_2Br$	Br, 22·5	Br, 24·3
		Methiodide; prisms, m. p. 152°	$C_{15}H_{23}O_2N_2I$	I, 31·7	I, 32·5
6-Hydroxy-2-methyltetrahydro*iso*quinoline	Needles, m. p. 121°				
		Hydrochloride; needles, m. p. 165°	$C_{12}H_{17}O_2N_2Cl$	Cl, 13·8	Cl, 13·7
		Methiodide; needles, m. p. 187°	$C_{13}H_{19}O_2N_2I$	I, 34·5	I, 35·1
5 : 6-Dihydroxy-2-methyltetrahydro*iso*quinoline	Prisms, m. p. 165°		$C_{14}H_{19}O_4N_3$	C, 56·9; H, 6·4	C, 57·3; H, 6·5
		Hydrochloride, hygroscopic	$C_{14}H_{20}O_4N_3Cl$	Cl, 10·2	Cl, 10·8
		Methiodide, hygroscopic	$C_{14}H_{19}O_4N_3$	C, 57·2; H, 6·5	C, 57·3; H, 6·5
6 : 7-Dihydroxy-2-methyltetrahydro*iso*quinoline	Prisms, m. p. 163°				
		Hydrochloride, hygroscopic			
		Methiodide; needles, m. p. 185°	$C_{15}H_{12}O_4N_3I$	I, 28·9	I, 29·2

phenylpropylamine, and the isomeric dimethyl-β-(3-methoxyphenyl)propylamine was prepared from 3-methoxyacetophenone by the following series of reactions :

$$MeO\cdot C_6H_4\cdot CO\cdot CH_3 \xrightarrow[\text{and Zn}]{[\ CH_2Br\cdot CO_2Et} MeO\cdot C_6H_4\cdot CMe{:}CH\cdot CO_2H \xrightarrow[\text{(iv) MeI and } Na_2CO_3,\ \text{(v) AgCl, (vi) Heat}]{\text{(i) } H_2,\ \text{(ii) Amide, (iii) NaOCl,}} MeO\cdot C_6H_4\cdot CHMe\cdot CH_2\cdot NMe_2$$

Dimethyl-γ-(3- and 4-methoxyphenyl)-α-methylpropylamines were obtained from the methoxybenzaldehydes by the following route :

$$MeO\cdot C_6H_4\cdot CHO \longrightarrow MeO\cdot C_6H_4\cdot CH{:}CH\cdot COMe \xrightarrow[\text{(iv) } CH_2O \text{ and } H\cdot CO_2H]{\text{(i) } H_2,\ \text{(ii) Oxime, (iii) reduction,}} MeO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CHMe\cdot NMe_2$$

The methoxy-compounds were demethylated with hydrobromic acid, and the phenol converted into the *N*-methylurethane as described in earlier Parts of the series. Excess of methyl *iso*cyanate should be avoided in the case of 2-hydroxybenzyldimethylamine otherwise a diurethane containing the O·CO·NMe·CO·NHMe group is produced.

Experimental.

5-Ethoxy-3-dimethylaminomethylindole.—5-Ethoxyindole (2·5 g.), dimethylamine hydrochloride (2·3 g.), and sodium acetate (1 g.) were dissolved in a mixture of acetic acid (3·5 g.) and 40% formaldehyde (1 c.c.). The brown solution gradually deposited a white solid, and after 18 hours the *indole*, precipitated by the addition of potassium hydroxide, was collected (2·3 g.) and crystallised from aqueous acetone; colourless needles, m. p. 146° (Found : C, 71·7; H, 8·1. $C_{13}H_{18}ON_2$ requires C, 71·6; H, 8·3%), were obtained. The *hydrochloride* separated from alcohol-ether in colourless prisms, m. p. 150° (Found : Cl, 13·9. $C_{13}H_{19}ON_2Cl$ requires Cl, 14·0%).

The aldehydes and ketones were prepared by methods described in the literature. 3-Methoxybenzylacetone, which is new, was prepared by catalytic reduction of 3-methoxybenzylideneacetone; it was an oil, b. p. 164—166°/10 mm., giving a *semicarbazone*, which separated from alcohol in needles, m. p. 125° (Found : C, 61·5; H, 7·2. $C_{12}H_{17}O_2N_3$ requires C, 61·4; H, 7·2%).

The oximes were prepared by standard methods. The following crystalline oximes are new : *2-Methoxypropiophenone oxime*, prisms, m. p. 87° from methyl alcohol (Found : C, 67·0; H, 6·9. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·2%); *4-methoxybenzylacetoxime*, long needles, m. p. 76° (Found : N, 8·0. $C_{10}H_{13}O_2N$ requires N, 7·8%) from alcohol; *7-methoxy-1-tetralone oxime*, stout prisms, m. p. 87° from ligroin (Found : C, 69·3; H, 7·1. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8%).

Of the acid amides, *β-3-methoxyphenylbutyramide*, m. p. 72° (Found : C, 68·0; H, 7·8. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%), was new. The primary amines were frequently methylated to the tertiary bases without further purification, but in a few cases new primary amines were characterised. The following were obtained by reduction of the corresponding oxime with 4% sodium amalgam : α-(2-Methoxyphenyl)propylamine, an oil, b. p. 128°/18 mm., yielding a *picrate*, which separated from alcohol in yellow prisms, m. p. 160° (Found : C, 48·3; H, 4·4. $C_{16}H_{18}O_8N_4$ requires C, 48·7; H, 4·6%). α-(4-Methoxy-*m*-tolylethylamine, an oil, b. p. 120°/14 mm., gave a *picrate*, yellow rhombs from alcohol, m. p. 197° (Found : C, 48·5; H, 4·5). 1-Amino-7-methoxytetralin, b. p. 162—165°/16 mm., gave a *hydrochloride* which separated from alcohol in hexagonal plates, m. p. 233° (Found : Cl, 17·1. $C_{11}H_{16}ONCl$ requires Cl, 16·7%). γ-(4-Methoxyphenyl)-α-methyl-*n*-propylamine, b. p. 165°/16 mm., gave a picrate, m. p. 129°, and a *hydrochloride*, plates, m. p. 129° (Found : Cl, 16·0. $C_{11}H_{18}ONCl$ requires Cl, 16·5%). γ-(3-Methoxyphenyl)-α-methyl-*n*-propylamine, b. p. 148°/11 mm., gave a *picrate*, m. p. 154° (Found : C, 50·4; H, 5·0. $C_{17}H_{20}O_8N_4$ requires C, 50·0; H, 4·9%). The last two bases were prepared by the action of sodium hypochlorite on the corresponding acid amides.

Conversion of Primary into Tertiary Amines.—The primary amine (1 mol.) was mixed with 90% formic acid (5 mols.) and 35—40% aqueous formaldehyde (2·2 mols.) and refluxed for 1 hour after the evolution of carbon dioxide had ceased (usually 2—3 hours in all). The mixture was made acid to Congo-red by addition of dilute hydrochloric acid, neutral substances were removed in ether, and the tertiary base was liberated with sodium hydroxide and isolated with ether. New methoxy tertiary bases are described in Table III.

Demethylation to phenolic tertiary amines was effected by 5—6 hours' boiling with constant-boiling hydrobromic acid (5 vols.); most of the acid was removed under reduced pressure, just sufficient solid potassium hydroxide added to give a solution alkaline to phenolphthalein, and the phenol isolated with ether. New phenolic tertiary *amines* and the *urethanes*, prepared by the methods described in Part II, and the *methiodides* and *hydrochlorides* are described in Tables IV and V respectively.

Our thanks are due to Dr. D. Woodcock for preparation of the *N*-methylurethane of 2-hydroxybenzyldimethylamine, and to the Director General of Scientific Research (Defence) for permission to publish the results.

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