[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

1-PHENYL-2-(N-METHYL-N-BENZYLAMINO)ETHANOL AND RELATED COMPOUNDS

WALTER BECK,[1, 2] IRVING ALLAN KAYE,[3] IRVING C. KOGON,[1] HOWARD C. KLEIN,[1] AND WILLIAM J. BURLANT

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Since N-methyl-N-benzyl-2-phenethylamine (1) and related compounds (2–4) have been reported to possess valuable pharmacological properties, it seemed worthwhile to prepare analogous compounds of general formula, Z-CHX-CH_2-$N(CH_3)CH_2Y$ (I), where Z is phenyl or 2-thienyl, X is hydrogen, hydroxyl, chlorine or alkoxyl, and Y is phenyl, substituted phenyl or 2-furyl.

The preparation of the 1-phenyl-2-(N-methyl-N-substituted benzylamino) ethanols and 1-phenyl-2-(N-methyl-N-2-furfurylamino)ethanol, from styrene oxide and the appropriate secondary amines, was an adaptation of the method of Noller and Kneeland (5). The thiophene aminoalcohols (I, Z is 2-thienyl, X is hydroxyl) were not prepared by the same method because of the unavailability of 2-vinylthiophene oxide. These compounds were obtained by the Meerwein-Pondorf-Verley reduction of the aminoketones, which were formed by condensing the secondary amines with α-bromo-2-acetothienone. Good yields were obtained by both methods, although the second was the more involved. None of the thienyl- and only three of the phenyl-aminoethanols could be converted to crystalline chloride hydrochloride salts (I, Z is phenyl, X is chlorine) with thionyl chloride. The methyl and ethyl ethers of the 1-phenyl-2-(N-methyl-N-substitutedamino)ethanols were obtained readily by condensing an alkyl ether of 2-bromo-1-phenylethanol with an amine. The unstable ethers of the thiophene aminoalcohols could not be prepared by this procedure but were formed, though in poor yields, by the reaction of α-thienylmagnesium bromide with the requisite aminoacetal. N-Methyl-N-3-methoxybenzylhomoveratrylamine was made by the methylation of N-3-methoxybenzylhomoveratrylamine, obtained by catalytic reduction of the Schiff base, with formaldehyde and formic acid (6).

These reactions are illustrated by the equations appearing on the following pages.

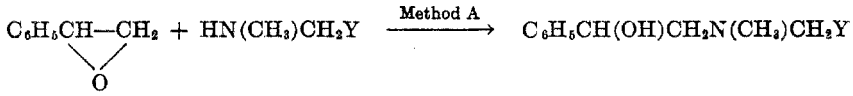
The hydrochlorides of 1-phenyl-2-(N-methyl-N-4-methoxybenzylamino)ethanol, N-methyl-N-3-methoxybenzylhomoveratrylamine, and N-3-methoxybenzylhomoveratrylamine as well as 1-phenyl-2-(N-methyl-N-2,3-dimethoxybenzylamino)ethanol, 1-phenyl-2-(N-methyl-N-4-dimethylaminobenzylamino)ethanol, and 1-phenyl-2-(N-methyl-N-2-furfurylamino)ethanol were inactive in retarding the growth of Sarcoma 180.[4] Further pharmacological testing is in progress, results of which will be reported elsewhere.

[1] From theses submitted to the Graduate Faculty of Brooklyn College by Walter Beck, June 1949; Irving C. Kogon, January 1951; and Howard C. Klein, January 1949, in partial fulfillment of the requirements for the Masters of Arts degree.

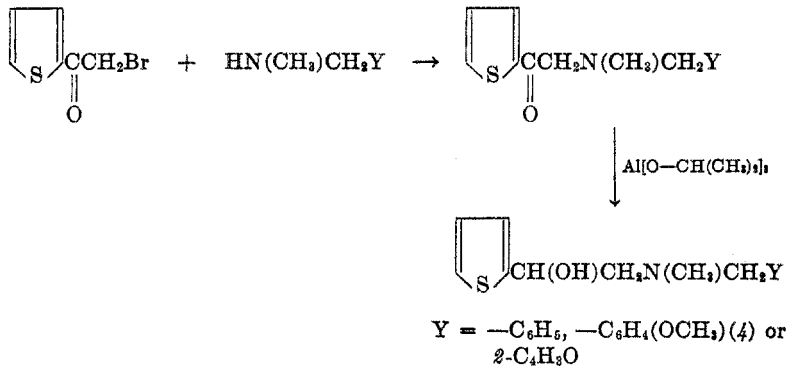
[2] Present address: Blackman Brands, Inc., Long Island City 1, N. Y.

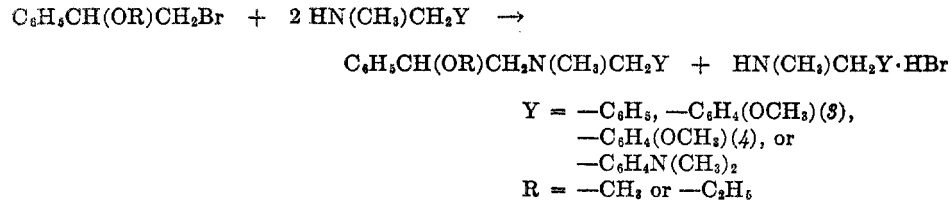
[3] Inquiries should be addressed to this author.

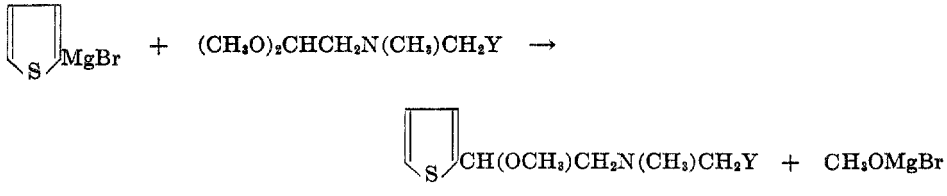
[4] These tests were conducted under the supervision of Dr. C. Chester Stock at the Sloan-Kettering Institute for Cancer Research.

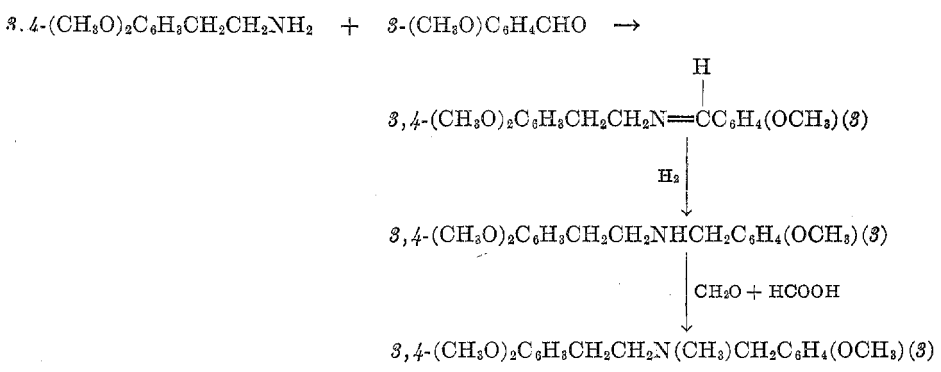

Method A
Y = C6H5, —C6H4(OCH3)(3)
—C6H4(OCH3)(4),
—C6H3(OCH3)2(2,3),
—C6H3(OCH3)2(3,4),
—C6H3(O2CH2)(3,4),
—C6H4N(CH3)2(4), or 2-C4H3O
SOCl2
C6H5CHClCH2N(CH3)CH2Y·HCl
Y = —C6H5, —C6H4(OCH3)(3) or
—C6H3(O2CH2)(3,4)

Method B


HN(CH3)CH2Y
Al[O—CH(CH3)2]3
Y = —C6H5, —C6H4(OCH3)(4) or
2-C4H3O


C6H5CH(OR)CH2Br + 2 HN(CH3)CH2Y →
HN(CH3)CH2Y·HBr
Y = —C6H5, —C6H4(OCH3)(3),
—C6H4(OCH3)(4), or
—C6H4N(CH3)2
R = —CH3 or —C2H5


MgBr
(CH3O)2CHCH2N(CH3)CH2Y →
CH3OMgBr
Y = —C6H5 or —C6H4(OCH3)(4)



EXPERIMENTAL

All melting points are corrected, boiling points are not.

Schiff bases related to N-methylbenzalimine. These compounds were prepared by the method of Cromwell, Babson, and Harris (7). N-Methylbenzalimine (7), b.p. 183–185° was obtained in 96% yield; N-methyl-3-methoxybenzalimine (8), b.p. 106.5–108° (11 mm.), in 92% yield; N-methyl-4-methoxybenzalimine (9), b.p. 125° (18 mm.), in 73% yield; N-methyl-2,3-dimethoxybenzalimine (8), m.p. 38.5°, in 82% yield; N-methyl-3,4-dimethoxybenzalimine (8), b.p. 143–150° (11 mm.), in 70% yield; and N-methylfurfuralimine (10), b.p. 55–60° (17 mm.), in 82% yield.

Reduction of the Schiff bases. With the exception of N-methylfurfuralimine, the above imines were reduced in 150–200 g. quantities without solvent in the presence of 4–9 g. of 10% palladium-charcoal catalyst at 30–60 lbs. pressure. The hydrogen uptake was very rapid. N-Methylbenzylamine (7), b.p. 88–90° (31 mm.) was obtained in 86% yield; N-methyl-3-methoxybenzylamine (11), b.p. 130–133° (28 mm.), in 91% yield; N-methyl-4-methoxybenzylamine (9), b.p. 92–96° (4 mm.), in 56% yield; N-methyl-2,3-dimethoxybenzylamine (12), b.p. 143–144° (19 mm.), in 96% yield; and N-methyl-3,4-dimethoxybenzylamine (13), b.p. 141–143° (11 mm.), in 23% yield.

Secondary amines by the catalytic hydrogenation of a mixture of the amine and aldehyde. The aldehyde (0.4 mole) dissolved in about 150 ml. of a concentrated absolute ethanolic solution of methylamine, was reduced at an initial pressure of 50 lbs. in the presence of 5 g. of 10% palladium-charcoal. Over 90% of the theoretical amount of hydrogen was absorbed in 30 minutes. After removal of the catalyst and solvent, the residue was dissolved in 25 ml. of 6 *N* hydrochloric acid. The acid solution of the amine was extracted with benzene and then made strongly alkaline. The product was extracted with benzene and obtained by distillation, after removal of the solvent. In this manner there was obtained a 68% yield of N-methyl-3,4-methylenedioxybenzylamine (5), b.p. 123–124° (14 mm.). A similar method of preparation for this and related compounds has been described recently in Organic Syntheses (12).

N-Methyl-2-furfurylamine, b.p. 80–85° (24 mm.), was prepared in 35% yield by this method and in only 12% yield by the method of Schwabbauer (10) wherein the Schiff base was reduced with sodium and alcohol. The product darkens on standing.

N-Methyl-4-dimethylaminobenzylamine, b.p. 123–124° (14 mm.) was obtained in 59% yield.

Anal. Calc'd for $C_{10}H_{16}N_2$: C, 73.10; H, 9.83.

Found: C, 72.73; H, 10.33.

1-Phenyl-2-(N-methyl-N-substitutedbenzylamino)ethanols and 1-phenyl-2-(N-methyl-N-2-furfurylamino)ethanol. (Method A). A mixture consisting of 0.24 mole of styrene oxide,[5]

[5] A sample of this compound was generously donated by: (a) the Dow Chemical Company; (b) the Socony-Vacuum Oil Company, Inc.; (c) the General Aniline and Film Corp.; and (d) the Monsanto Chemical Company.

TABLE I

1-PHENYL[OR 1-(2-THIENYL)]-2-(N-METHYL-N-SUBSTITUTEDAMINO)ETHANOLS, $ZCH(OH)CH_2N(CH_3)CH_2Y$

Z	Y	B.P., °C.	MM.	METHOD	YIELD, %	METHIODIDE,[k] M.P., °C.	FORMULA	ANALYSES			
								Calc'd		Found	
								C	H	C	H
Phenyl	C_6H_5	107–108	0.06	A	83	192.5–194[a, b]	$C_{16}H_{19}NO$	79.63	7.94	79.35	7.79
Phenyl	$C_6H_4(OCH_3)(3)$	123	.05	A	91	139–140[c]	$C_{17}H_{21}NO_2 \cdot CH_3I$		30.71[d]		30.50[d]
Phenyl	$C_6H_4(OCH_3)(4)$	133	.05	A	85	191–192[a, b, e]	$C_{17}H_{21}NO_2$	75.25	7.80	74.64	7.86
							$C_{17}H_{21}NO_2 \cdot CH_3I$		30.71[d]		30.78[d]
Phenyl	$C_6H_4N(CH_3)_2(4)$	127	.05	A	54	208–210[f]	$C_{18}H_{24}N_2O$	76.02	8.51	76.04	8.65
							$C_{18}H_{24}N_2O \cdot 2CH_3I$		44.69[d]		44.25[d]
Phenyl	$C_6H_3(OCH_3)_2(2, 3)$	140	.05	A	89	168–169[f]	$C_{18}H_{23}NO_3$	71.73	7.69	71.75	7.86
Phenyl	$C_6H_3(OCH_3)_2(3, 4)$	155	.06	A	62	[g]	$C_{18}H_{23}NO_3$	71.73	7.69	71.60	7.65
Phenyl	$C_6H_3(O_2CH_2)(3, 4)$	141–142	.05	A	75	201.5–202.5[a]	$C_{17}H_{19}NO_3 \cdot CH_3I$		29.71[d]		29.42[d]
Phenyl	$C_4H_3O(2)$[h]	96	.05	A	76	173–174 d.[f]	$C_{14}H_{17}NO_2$		6.06[i]		6.08[i]
2-Thienyl	C_6H_5	149–150	1	B	70[j]	206–207[a]	$C_{14}H_{17}NOS$		5.66[i]		5.35[i]
							$C_{14}H_{17}NOS \cdot CH_3I$		32.61[d]		32.90[d]
2-Thienyl	$C_6H_4(OCH_3)(4)$	184–185	1	B	71[j]	191.5–193[a]	$C_{15}H_{19}NO_2S$		5.04[i]		5.00[i]
							$C_{15}N_{19}NO_2S \cdot CH_3I$		30.27[d]		30.55[d]
2-Thienyl	$C_4H_3O(2)$[h]	152–153	1	B	51[j]	144.5–146.5[f]	$C_{12}H_{15}NO_2S$		5.90[i]		5.71[i]
							$C_{12}H_{15}NO_2S \cdot CH_3I$		33.46[d]		33.58[d]

[a] Recrystallized from methanol. [b] These two methiodides, when admixed, melted at 183.5–186.5°. [c] The gummy methiodide was crystallized once from water and then recrystallized from propanol-2. [d] Iodine (ionizable). [e] The hydrochloride, prepared in ether and recrystallized from propanol-2–ether, melted at 141–141.5°. [f] Recrystallized from propanol-2. [g] The methiodide was obtained as a gum. Even after crystallization from hot water and three recrystallizations from propanol-2, it melted over a broad range, *ca.* 116–140°. [h] 2-Furyl. [i] Nitrogen. [j] This is an over-all yield from 2-acetothienone. [k] Methiodides were prepared because of the difficulty in obtaining crystalline salts.

0.30 mole of the secondary amine, and 50 ml. of water was emulsified by shaking for a few minutes and left at room temperature for at least three days with occasional shaking. The supernatant aqueous layer was decanted and the residue distilled *in vacuo*.

Methiodides were prepared by refluxing a solution of one gram of the aminoalcohol and one ml. of methyl iodide in 10 ml. of acetone. After standing overnight at 5°, the solution was seeded with crystals prepared from a small aliquot of the solution. The crystalline salt was then recrystallized from an appropriate solvent. In some instances where tars were formed, crystallization could be effected conveniently from hot water.

Results are summarized in Table I.

1-Phenyl-2-(N-methyl-N-benzylamino)ethyl chloride hydrochloride. A solution of 1 ml. of purified thionyl chloride in 5 ml. of dry benzene was added to 1 g. of the aminoalcohol dissolved in 10 ml. of benzene. The reaction temperature was maintained at 10° during the addition. After refluxing for 16 hours, the benzene and excess thionyl chloride were removed *in vacuo*. A little benzene was added and then removed *in vacuo*. This was repeated several times so as to eliminate traces of thionyl chloride whose presence tended to hinder crystallization. The viscous residue was dissolved in 35 ml. of propanol-2 and the solution decolorized with charcoal. Isopropyl ether was then added to incipient cloudiness and the solution set aside at 5° for a week. The tan solid which precipitated was recrystallized in a similar manner from the same mixture of solvents; charcoal was used again to effect further decolorization. The white product now melted at 157–159°. Two more recrystallizations from propanol-2-isopropyl ether raised the melting point to 159–160°.

Anal. Calc'd for $C_{18}H_{18}ClN \cdot HCl$: Cl, 23.90. Found: Cl, 23.39.

Attempts to prepare this product under a variety of conditions other than those described were unsuccessful. For example, a shortened period of reflux or a longer reaction period at room temperature yielded hygroscopic solids which could not be crystallized. Even under these optimum conditions, only two other aminoalcohols of this series could be converted into crystalline chloride hydrochlorides. The others failed to crystallize.

1-Phenyl-2-(N-methyl-N-3-methoxybenzylamino)ethyl chloride hydrochloride. Prepared by the above procedure, the compound melted at 139–140° after one recrystallization from propanol-2-isopropyl ether.

Anal. Calc'd for $C_{17}H_{20}ClNO \cdot HCl$: Cl, 21.80. Found: Cl, 21.62.

1-Phenyl-2-(N-methyl-N-piperonylamino)ethyl chloride hydrochloride. The product precipitated as a gummy solid during the reflux period. It was separated and washed well with isopropyl ether, followed by hot propanol-2, m.p. 176–178°. Recrystallized from a mixture of methanol and isopropyl ether the melting point rose to 178–179°. Further recrystallization from the same solvent mixture did not change the melting point.

Anal. Calc'd for $C_{17}H_{18}ClNO_2 \cdot HCl$: Cl, 20.82. Found: Cl, 20.82.

α-Bromo-2-acetothienone (14). On long standing at room temperature the distilled product underwent decomposition forming a black solid. Since an ether solution, kept in a refrigerator, remained unchanged for months and since the aminoketones could be prepared from the crude bromoketone in ether at low temperatures, the compound was not isolated but was used in solution without purification.

The theoretical amount of bromine (239.7 g., 1.5 moles), was added over a period of one-half hour at 10° to a stirred solution of 189.3 g. (1.5 moles) of 2-acetothienone (15)[5b] in one liter of anhydrous ether. Stirring was continued for one-half hour after the addition, the temperature of the solution being maintained at 10–20°. After being concentrated *in vacuo* to a volume of *ca.* 400 ml. so as to remove most of the dissolved hydrogen bromide, the solution was washed well with saturated aqueous sodium chloride until neutral to litmus, dried over potassium carbonate, and diluted with dry ether to a final volume of 500 ml. Each 100 ml. of this solution was equivalent to 0.3 mole of starting 2-acetothienone.

1-(2-Thienyl)-2-(N-methyl-N-substitutedamino)ethanols. (*Method B*). The α-bromo-2-acetothienone solution (100 ml.) was added over a period of one-half hour to a stirred solution of 0.55 mole of the secondary amine in 150 ml. of ether. After two days at 5° the excess starting amine (as hydrobromide) was removed and washed well with ether. To the filtrate,

after it had been concentrated to 100–200 ml., was added sufficient propanol-2 (previously dried over calcium hydride) to make a volume of about 400 ml. The solution was distilled, keeping its volume constant during the distillation by the dropwise addition of propanol-2, through a short Vigreux column till the vapor temperature reached 82°. Then 61.3 g. (0.3 mole) of aluminum isopropoxide dissolved in an equal weight of toluene was added. Slow distillation was continued until acetone could no longer be detected in the distillate (16); the volume was again kept constant during the distillation. The solution was then poured into 400 ml. of 10% aqueous sodium hydroxide and the organic layer separated. The aqueous layer was extracted three times with ether and the ether extracts, combined with the organic layer, were washed with water and dried over potassium carbonate. After removal of the solvents, the product was obtained by a reduced pressure distillation. Results are summarized in Table I.

Dimethyl acetal of N-methyl-N-4-methoxybenzylaminoacetaldehyde. A mixture of 302.4 g. (2.0 moles) of N-methyl-4-methoxybenzylamine and 124.5 g. (1.0 mole) of chloroacetaldehyde dimethyl acetal[56] was heated in an oil-bath until the internal temperature reached 175°. Heating was discontinued and the reaction mixture cooled to moderate the exothermic reaction. The mixture was then heated at a bath temperature of 170–180° for 7 hours. Ether was added to the cooled reaction mixture and the precipitated N-methyl-N-4-methoxybenzylamine hydrochloride separated and washed well with ether. The salt weighed 195.7 g., representing a conversion of 77.2%. After removal of the ether, the residue was distilled *in vacuo*. The product, weighing 160.7 g. (67%), b.p. 143–147° (5 mm.), was redistilled. The fraction collected at 144–146° (6 mm.), weighing 149.0 g. (62%), was a pale yellow liquid.

Anal. Calc'd for $C_{13}H_{21}NO_3$: N, 5.85. Found: N, 5.78.

Methyl ether of 1-(2-thienyl)-2-(N-methyl-N-4-methoxybenzylamino)ethanol. To an ethereal solution of the Grignard reagent, prepared from 19.4 g. (0.8 mole) of magnesium and 130.4 g. (0.8 mole) of 2-bromothiophene, was added 96.0 g. (0.4 mole) of the dimethyl acetal of N-methyl-N-4-methoxybenzylaminoacetaldehyde. The solution was heated with stirring while most of the ether was removed by distillation. Then 300 ml. of xylene (technical grade, b.p. 135–140°, dried over calcium hydride) was added and the distillation continued until the temperature of the reaction-mixture reached 135–140°; it was then refluxed with stirring for four hours. A white precipitate appeared during this reflux period. Hydrolysis was effected with 120 ml. of saturated aqueous ammonium chloride. The magnesium salts were removed and washed well with xylene. After removal of the solvent, the residue was distilled *in vacuo*. The fraction distilling at 118–123° (0.3 mm.) weighed 8.7 g. (7.9%). Since the product was air-sensitive, it was titrated shortly after distillation by the method of Fritz (17).

Anal. Calc'd for $C_{16}H_{21}NO_2S$: Neut. equiv., 291.4. Found: Neut. equiv., 291.4.

Methyl ether of 1-(2-thienyl)-2-(N-methyl-N-benzylamino)ethanol. Prepared by the same procedure from 83.6 g. (0.4 mole) of the dimethyl acetal of N-methyl-N-benzylaminoacetaldehyde (18), 10.0 g. (9.6%) of product, b.p. 175–180° (7 mm.) was obtained.

Anal. Calc'd for $C_{15}H_{19}NOS$: Neut. equiv., 261.4. Found: Neut. equiv., 257.7.

Methyl ether of 1-phenyl-2-(N-methyl-N-benzylamino)ethanol. A solution of 32.2 g. (0.15 mole) of the methyl ether of 2-bromo-1-phenylethanol (19) and 36.4 g. (0.3 mole) of N-methylbenzylamine in 100 ml. of dry toluene was refluxed for 40 hours. After cooling, the mixture was filtered and the N-methylbenzylamine hydrobromide washed with ether. The solvents were removed from the filtrate and the residue distilled *in vacuo*. The product, collected at 170–178° (22 mm.), weighed 34.4 g. (91%). Prepared by the method used in the preparation of the thiophene ethers, the yield was 30%. The *hydrochloride*, recrystallized from methyl ethyl ketone, melted at 160–161°.

Anal. Calc'd for $C_{17}H_{21}NO \cdot HCl$: N, 4.80; Cl, 12.16.
Found: N 4.87; Cl, 12.15.

The *methiodide*, recrystallized from acetone, melted at 147.5–148.5°.

Ethyl ether of 1-phenyl-2-(N-methyl-N-3-methoxybenzylamino)ethanol. A solution of 11.5 g. (0.05 mole) of the ethyl ether of 2-bromo-1-phenylethanol (20) and 15.1 g. (0.1 mole) of

N-methyl-3-methoxybenzylamine in 80 ml. of dry toluene was refluxed for 72 hours. Since the N-methyl-3-methoxybenzylamine hydrochloride separated as an oil, the previous procedure had to be modified. After cooling to room temperature, 100 ml. of water was added. The aqueous layer was separated and extracted 4 times with ether. The ether extracts were combined with the toluene layer and dried over potassium carbonate. The product, obtained after removal of the solvents, weighed 12.7 g. (42%), b.p. 126–130° (1 mm.). The *methiodide*, recrystallized from acetone, melted at 149–150°.

Anal. Calc'd for $C_{19}H_{25}NO_2 \cdot CH_3I$: N, 3.17; I, 28.77.

Found: N, 2.98; I, 29.10.

Ethyl ether of 1-phenyl-2-(N-methyl-N-4-methoxybenzylamino)ethanol. A mixture of 45.3 g. (0.3 mole) of N-methyl-4-methoxybenzylamine and 34.4 g. (0.15 mole) of the ethyl ether of 2-bromo-1-phenylethanol was heated in an oil-bath to an internal temperature of 160°. Heating was discontinued until the vigorous exothermic reaction had abated somewhat. The mixture was then heated at a bath temperature of 170–180° for 24 hours. When cool, ether was added. The excess starting amine (as hydrobromide) was separated and washed well with ether. The ether was removed from the filtrate and the residue distilled to give a limpid yellow liquid, weighing 32.2 g. (72%); b.p. 164–168° (2 mm.). The *methiodide* melted at 157–157.5° after recrystallization from propanol-2.

Anal. Calc'd for $C_{19}H_{25}NO_2 \cdot CH_3I$: N, 3.17; I, 28.77.

Found: N, 3.11; I, 28.79.

Ethyl ether of 1-phenyl-2-(N-methyl-N-4-dimethylaminobenzylamino)ethanol. A mixture of 32.8 g. (0.2 mole) of N-methyl-4-dimethylaminobenzylamine and 22.9 g. (0.1 mole) of the ethyl ether of 2-bromo-1-phenylethanol was heated in an oil-bath to an internal temperature of 170°. At this point an exothermic reaction occurred and the temperature rose to 212°. The mixture was then heated for 24 hours at a bath temperature of 170°. When cool, 25 ml. of water was added. The aqueous layer was separated and extracted with ether several times. The ether extracts, combined with the organic layer, were dried over potassium carbonate. The ether was removed and the product obtained by distillation *in vacuo*. The amber liquid, distilling at 150–155° (1.5 mm.), weighed 14.9 g. (48%).

The *methiodide* melted at 200–201° after four recrystallizations from methanol.

Anal. Calc'd for $C_{20}H_{28}N_2O \cdot 2CH_3I$: N, 4.78; I, 43.57.

Found: N, 4.65; I, 43.97.

Repetition of this preparation, but refluxing in toluene for 72 hours, gave only a 17% yield of product.

3-Methoxybenzyl-β-3,4-dimethoxyphenethylamine hydrochloride. To a mixture of 10.0 g. (0.056 mole) of β-3,4-dimethoxyphenethylamine[5d] and 8.5 g. (0.063 mole) of 3-methoxybenzaldehyde, which had been left at room temperature for 24 hours (and which had become turbid during this period), was added 100 ml. of benzene. The water in the reaction mixture was removed by azeotropic distillation. After all the benzene had been removed, the residue was dissolved in 100 ml. of anhydrous ethanol and reduced at an initial pressure of 58 lbs. in the presence of 1 g. of 10% palladium-charcoal. After removal of the catalyst, the filtrate was concentrated *in vacuo* to about 40 ml. An excess of alcoholic hydrogen chloride was added and on cooling a tan solid precipitated. After the addition of ether, the solid was recrystallized from propanol-2. The salt melted at 138–139° and weighed 17.1 g. (91%). Recrystallized three more times from the same solvent, the melting point rose to 144.5–145.5°.

Anal. Calc'd for $C_{18}H_{23}NO_3 \cdot HCl$: C, 63.98; H, 7.16.

Found: C, 63.67; H, 7.20.

N-Methyl-3-methoxybenzyl-β-3,4-dimethoxyphenethylamine hydrochloride.[6] This product

[6] The referee has pointed out that the analysis of this product does not distinguish between the structure assigned to it, and 2-(3-methoxybenzyl)-6,7-dimethoxytetrahydroisoquinoline. Derivatives of homoveratrylamine are easily cyclized to 6,7-dimethoxytetrahydroisoquinolines under the usual Clarke-Eschweiler conditions [*cf.* Buck and Baltzly, *J. Am. Chem. Soc.*, **64**, 2263 (1942)].

was obtained as an oil by the Eschweiler-Clarke procedure (6) from 3-methoxybenzyl-β-3,4-dimethoxyphenethylamine and a mixture of formaldehyde and formic acid. It was converted to its hydrochloride in ether and recrystallized from propanol-2; yield, 73%; m.p. 167–168°. Further crystallization did not change the melting point.

Anal. Calc'd for $C_{19}H_{25}NO_3 \cdot HCl$: C, 64.86; H, 7.45.
Found: C, 64.94; H, 7.36.

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SUMMARY

The preparation of 1-phenyl-2-(N-methyl-N-benzylamino)ethanol, and analogous compounds wherein the phenyl group is replaced by 2-thienyl or methoxylated phenyl, the alcohol group by hydrogen, chlorine, methoxyl or ethoxyl, and the benzyl by a substituted benzyl or 2-furfuryl, is described.

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REFERENCES

(1) MOISSET DE ESPANES AND WEKSLER, *Proc. Soc. Exptl. Biol. Med.*, **63**, 195 (1946).
(2) ALLES AND ELLIS, *J. Pharmacol. Exptl. Therap.*, **94**, 416 (1948).
(3) BUCK, SUTER, AND SURREY, U. S. Patent 2,527,527 (October 31, 1950).
(4) HEINZELMANN, U. S. Patent 2,525,674 (October 10, 1950).
(5) NOLLER AND KNEELAND, *J. Am. Chem. Soc.*, **68**, 201 (1946).
(6) CLARKE, GILLESPIE, AND WEISSHAUS, *J. Am. Chem. Soc.*, **55**, 4571 (1933).
(7) CROMWELL, BABSON, AND HARRIS, *J. Am. Chem. Soc.*, **65**, 313 (1943).
(8) MOFFETT AND HOEHN, *J. Am. Chem. Soc.*, **69**, 1792 (1947).
(9) CROMWELL AND HOEKSEMA, *J. Am. Chem. Soc.*, **67**, 1658 (1945).
(10) SCHWABBAUER, *Ber.*, **35**, 411 (1902).
(11) BALTZLY AND BUCK, *J. Am. Chem. Soc.*, **65**, 1984 (1943).
(12) COPE, *Org. Syntheses*, **30**, 59 (1950).
(13) TIFFENEAU, *Bull. soc. chim.*, (4) **9**, 930 (1911).
(14) KITCHEN AND SANDIN, *J. Am. Chem. Soc.*, **67**, 1645 (1945).
(15) HARTOUGH AND KOSAK, *J. Am. Chem. Soc.*, **68**, 2640 (1946).
(16) ADAMS, *Org. Reactions*, **2**, 204 (1944).
(17) FRITZ, *Anal. Chem.*, **22**, 1028 (1950).
(18) KAYE AND MINSKY, *J. Am. Chem. Soc.*, **71**, 2272 (1949).
(19) LAUER AND SPIELMAN, *J. Am. Chem. Soc.*, **55**, 4923 (1933).
(20) LAUER AND SPIELMAN, *J. Am. Chem. Soc.*, **53**, 1533 (1931).