650. α-*Methylbenzylamines. Part I.* 3-cyclo*Hexyloxy*-4-*methoxy*-α-*methylbenzylamines.*

By A. McCoubrey.

Attempts to prepare aryl ethers of 3-aminoethyl*cyclo*hexanols have been unsuccessful. Suitable 1 : 3-disubstituted *cyclo*hexane derivatives reverted to *cyclo*hexenes under alkaline or dehydrating conditions. A series of 3-*cyclo*hexyloxy-4-methoxy-α-methybenzylamines has been prepared by standard methods from *iso*acetovanillone.

Until recently there were two molecular models available for a study of the relation between chemical structure and biological activity in the analgesic field (excluding antipyretic analgesics), *viz.*, ethanol and the morphine bases. The contrast between the simple structure of ethanol and the complexity of morphine is striking, and, though there is little evidence to suggest that these two substances exert their analgesic activity by similar modes of action in the body, both are analgesic and euphoriant and cause habituation, indicating some common degree of biological involvement. Many drugs which exert effects in the nervous system, of which analgesics form one aspect, are notable for their simple molecular organisation and, with the above two considerations in mind, a search for a relatively simple molecule imbued with analgesic properties of opiate character seemed a feasible project. When this work was initiated pethidine was undergoing clinical trial and the subsequent work of recent years has made it apparent that almost any dissection of the morphine molecule, provided that the product bears the basic nitrogen atom, will have some degree of analgesic activity (cf. Bergel and Morrison, *Quart. Reviews*, 1948, **2**, 349), though advances in this field have to a large extent depended on the recent development of relatively satisfactory methods for detection of weak analgesic activity in small laboratory animals.

The report of the Committee on Drug Addiction of the U.S. National Research Council (Public Health Suppl., 1938, No. 138) provided the background for basic concepts, and the synthesis of aryl ethers of 3-aminoethyl*cyclo*hexanol was attempted.

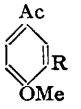
Interaction of *m*-methoxyphenylmagnesium bromide and *n*-butyl diethylaminomethyl ether (Robinson and Robinson, *J.*, 1923, **123**, 534) gave *NN*-diethyl-*m*-methoxybenzylamine, also obtained (less satisfactorily) by bromination of methyl *m*-tolyl ether with *N*-bromosuccinimide followed by reaction with diethylamine. Demethylation gave *NN*-diethyl-*m*-hydroxybenzylamine, but debenzylation occurred on catalytic hydrogenation and no nuclear reduction products were isolated.

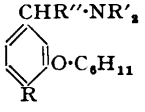
The addition of nitromethane to *cyclo*hex-2-enone gave a nitromethyl*cyclo*hexanone in moderate yield, whereas nitroethane under similar conditions gave a better yield of 3-1′-nitroethyl*cyclo*hexanone. A Nef reaction (*Annalen*, 1894, **280**, 263) then gave 3-acetyl*cyclo*hexanone, the structure of which was demonstrated by dehydrogenation to give *m*-hydroxyacetophenone. Reduction by aluminium *iso*propoxide gave 3-1′-nitroethyl*cyclo*hexanol, whence a Nef reaction led to 3-acetyl*cyclo*hexanol, the phenylurethane of which could be separated into two isomers by fractional crystallisation. 3-Acetyl*cyclo*hexanol was readily converted into the corresponding bromide or iodide but the alkaline conditions of etherification led to loss of hydrogen halide to give 3(?)-acetyl*cyclo*hexene. 3-Acetyl*cyclo*hexanol also gave acetyl*cyclo*hexene in contact with hot acid solutions.

In a third approach dihydroresorcinol was converted into 3-chloro*cyclo*hex-2-enone whence reaction with phenol, catechol, or guaiacol gave the 1-aryloxy*cyclo*hex-2-enones. These substances did not exhibit the typical ketone reactions. The 1 : 2-unsaturation conferred lability on the ether link and attempts to reduce the unsaturated ketone group by various methods gave rise mainly to the products of reductive cleavage; 3-phenoxy*cyclo*hex-2-enone was more labile than the *o*-methoxyphenyl analogue, so that 3-phenoxy*cyclo*hexanol was only obtainable in very poor yield by rapid reduction with sodium and hot alcohol. Catalytic hydrogenation over palladised charcoal, which caused complete cleavage of 3-phenoxy*cyclo*hexenone, slowly reduced the *o*-methoxyphenoxy-compound to (presumably) 3-*o*-methoxyphenoxy*cyclo*hexanone. Completion of the hydrogenation over platinum black gave a moderate yield of 3-*o*-methoxyphenoxy*cyclo*hexanol together with some *cyclo*hexanol and guaiacol. 3-*o*-Methoxyphenoxy*cyclo*hexanol and phosphorus tribromide gave an unstable bromide and attempts to prepare the Grignard reagent of this substance failed. This alcohol

readily gave a phenylurethane; phenyl *iso*cyanate and 3-phenoxy*cyclo*hexanol gave an unsaturated substance and carbanilide.

Attention was next turned to analogous α-methylbenzylamines. *NN*-Diethyl-3-hydroxy-4-methoxybenzylamine could only be obtained in prohibitive yield. *NN*-Diethyl-4-methoxy-3-nitrobenzylamine, readily obtained from 4-methoxy-3-nitrobenzyl chloride and diethylamine, was easily reduced to the amine (contrast the difficult reduction of 4-methoxy-3-nitrobenzyl alcohol; Fishman, *J. Amer. Chem. Soc.*, 1920, **42**, 2298), and the derived diazonium salt readily decomposed on warming (cf. Fishman, *loc. cit.*) but gave *NN*-diethyl-3-hydroxy-4-methoxybenzylamine in very poor yield. The diazonium group could however be replaced by bromine by the usual Sandmeyer procedure (cf. Fishman, *loc. cit.*) (the corresponding iodo-derivative could not be so prepared), but the product did not react at elevated temperatures with sodium or potassium *cyclo*hexyl oxide.

(I) 



(II)

Products of the desired structure were eventually obtained from *iso*acetovanillone (I; R = OH). Reduction of its oxime gave (±)-3-hydroxy-4-methoxy-α-methylbenzylamine, which was quite stable in contrast to the isomeric 4-hydroxy-3-methoxy-compound (Moore, *J.*, 1911, **99**, 418). Etherification of the amine with *cyclo*hexyl bromide and alkali did not proceed to a useful extent; nor did that of *iso*acetovanillone with *cyclo*hexanol and zinc chloride in presence of hydrochloric acid (*Chem. Abs.*, 1940, **34**, 1445), probably owing to formation of pyrylium salts by the acetyl group; however, it was effected by very slow addition of methanolic sodium or potassium hydroxide to a refluxing alcoholic solution of the ketone containing excess of *cyclo*hexyl bromide (Klarmann, Gatyas, and Shternov, *J. Amer. Chem. Soc.*, 1931, **53**, 3404)—*cyclo*hexyl chloride failed to react under similar conditions. At the best, *ca.* 40% of the ether was formed; it is probable that the reaction is progressively hindered by the accumulation of the products. 3-*cyclo*Hexyloxy-4-methoxyacetophenone oxime was readily reduced by sodium amalgam to the amine (II; R = OMe; R' = H; R'' = Me); *N*-derivatives of this amine were obtained by reduction of (I; R = *cyclo*hexyloxy) to the carbinol, conversion into the bromide, and reaction of this with the appropriate amine in benzene. Reduction of the carbonyl group of (I; R = *cyclo*hexyloxy) by sodium in ethanol, or by aluminium *iso*propoxide in xylene, gave a large proportion of low-boiling material, and catalytic methods gave a similar result if the solvent was either methanol or acetic acid. In ethyl acetate however, although the rate of absorption of hydrogen was greatly retarded, very little low-boiling material was produced. At the same time susceptibility to poisoning of the catalyst was markedly increased and samples of the ketone which could not be hydrogenated in ethyl acetate readily absorbed hydrogen in methanol or acetic acid. The alcohol, characterised as the phenylurethane, reacted with phosphorus tribromide to give an unstable bromide which slowly lost hydrogen bromide at room temperature but, when immediately treated with the appropriate amine in benzene, gave the *NN*-di-methyl, -ethyl, -*n*-propyl, and -*n*-butyl and the tetrahydro*iso*quinoline derivatives.

Experimental.

NN-*Diethyl*-m-*methoxybenzylamine*.—(*a*) The Grignard reagent from *m*-bromoanisole (20 g.) and magnesium (2·7 g.) in ether (50 c.c.) was added during 1 hour to *n*-butyl diethylaminomethyl ether (Robinson and Robinson, *loc. cit.*) (22 g.) in ether (50 c.c.). After 12 hours ammonium chloride solution was added and the product extracted with ether. Distillation of the dried ethereal extract gave an oil (10·2 g.), b. p. 132—135°/18 mm., which was converted into the hydrochloride. NN-*Diethyl*-m-*methoxybenzylamine hydrochloride* crystallised from alcohol in needles, m. p. 152° (Found: N, 5·9. $C_{12}H_{19}ON,HCl$ requires N, 6·1%). The *picrolonate* crystallised from alcohol in yellow prisms, m. p. 139° (Found: C, 57·5; H, 6·2; N, 14·6. $C_{12}H_{19}ON,C_{10}H_8O_5N_4,\frac{1}{2}C_2H_6O$ requires C, 57·5; H, 6·3; N, 14·6%).

(*b*) Methyl *m*-tolyl ether (24·5 g.), *N*-bromosuccinimide (36 g.), and benzoyl peroxide (0·3 g.) were heated under reflux in carbon tetrachloride (140 c.c.) for 4 hours. Succinimide was filtered off and the carbon tetrachloride distilled off. The residue, in benzene (100 c.c.), was treated with diethylamine (30 c.c.). After 12 hours diethylamine hydrobromide (7·6 g.) was filtered off and the filtrate extracted with 5N-hydrochloric acid. The acid extract was basified with sodium hydroxide and extracted with ether, and the extract dried (K_2CO_3) and distilled, to give the amine (7·5 g., 19%), b. p. 116—120°/6 mm. The acid-insoluble material remaining in the benzene was distilled, to give methyl *m*-tolyl ether (2·0 g.), b. p. 75—82°/16 mm., and a bromo-compound (18·7 g.), b. p. 110—115°/16 mm., shown to be 4-bromo-

3-methylanisole since carboxylation of the derived Grignard reagent gave 4-methoxy-2-methylbenzoic acid, m. p. 177° (Found : C, 65·3; H, 6·3. Calc. for $C_9H_{10}O_3$: C, 65·1; H, 6·0%) (cf. Darzens and Levy, *Compt. rend.*, 1931, **193**, 292).

NN-*Diethyl*-m-*hydroxybenzylamine*.—The foregoing amine (18·6 g.) and hydrobromic acid (48%; 60 c.c.) were refluxed for 4 hours. The bulk of the acid was distilled off under reduced pressure, and the base liberated by aqueous ammonia and extracted with ether, dried (K_2CO_3), and distilled. An oil (15·7 g.), b. p. 112—113°/0·3 mm., was collected which slowly solidified when kept at 0° to a white mass, m. p. 44—45°. The *hydrochloride* crystallised from alcohol–ether in white crystals, m. p. 123° (Found : N, 6·7. $C_{11}H_{17}ON$,HCl requires N, 6·5%). The *picrolonate* crystallised from alcohol in orange prisms, m. p. 191—192° (Found : N, 15·7. $C_{11}H_{17}ON$,$C_{10}H_8O_5N_4$ requires N, 15·8%). The base on hydrogenation in alcohol at 80°/80 atmospheres in presence of Raney nickel absorbed one molecular proportion of hydrogen. Diethylamine and *m*-cresol were isolated in 80% yield.

3-*Nitromethyl*cyclo*hexanone*.—To a stirred solution of nitromethane (9·4 g.) in methanol (20 c.c.) at 40° were added, at equivalent rates, a solution of sodium (3·75 g.) in methanol (50 c.c.) and of *cyclo*hex-2-enone (12 g.) (Whitmore and Pedlow, *J. Amer. Chem. Soc.*, 1941, **63**, 758) in methanol (10 c.c.). The mixture was stirred for 30 minutes, then cooled in ice water while acetic acid (50%; 25 c.c.) was added. Methanol was distilled off, the residue diluted with water and extracted with ether, and the extract washed with 2N-sodium carbonate, then with water, dried (K_2CO_3), and distilled. A viscous oil (10·4 g.), b. p. 100—102°/0·1 mm., was collected. The *semicarbazone* crystallised from alcohol in prisms, m. p. 167° (Found : C, 44·9; H, 6·9; N, 25·9. $C_8H_{14}O_3N_4$ requires C, 44·9; H, 6·6; N, 26·2%).

3-1′-*Nitroethyl*cyclo*hexanone*.—Prepared, as described for the previous compound, from nitroethane (46·4 g.) and *cyclo*hex-2-enone (48·5 g.), this was a viscous oil (65·5 g.), b. p. 101—102°/0·01 mm. The *semicarbazone* crystallised from alcohol in prisms, m. p. 179° (Found : N, 24·3. $C_9H_{16}O_3N_4$ requires N, 24·6%).

3-*Acetyl*cyclo*hexanone*.—3-1′-Nitroethyl*cyclo*hexanone (5·9 g.), dissolved in a solution of sodium hydroxide (1·6 g.) in water (30 c.c.), was added dropwise to sulphuric acid (30%; 35 c.c.) with stirring at 0°. Stirring was continued for 30 minutes while the solution attained room temperature. The solution was warmed slowly to 55°, saturated with ammonium sulphate, and extracted with ether (8 × 25 c.c.), and the extract dried (K_2CO_3) and distilled. An oil (3·15 g.), b. p. 140—145° (bath-temp.)/15 mm., was collected which solidified. 3-*Acetyl*cyclo*hexanone* crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 39° (Found : C, 68·4; H, 8·6. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%). The *dioxime* crystallised from alcohol in prisms, m. p. 158° (Found : C, 56·4; H, 8·0; N, 16·1. $C_8H_{14}O_2N_2$ requires C, 56·5; H, 8·2; N, 16·5%).

Dehydrogenation. The ketone (3·15 g.) was heated with palladium black (0·2 g.) at 220—240° for 6 hours. Extraction with 2N-sodium hydroxide gave an alkali-soluble substance, b. p. 150—180° (bath-temp.)/16 mm., which, crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 90—93° (0·1 g.). The semicarbazone crystallised from alcohol in prisms, m. p. 194—195° alone or mixed with *m*-hydroxyacetophenone semicarbazone. Unchanged 3-acetyl*cyclo*hexanone (0·85 g.) was recovered.

3-1′-*Nitroethyl*cyclo*hexanol*.—3-1′-Nitroethyl*cyclo*hexanone (66·5 g.) was heated under reflux with aluminium *iso*propoxide (130 g.) in dry toluene (500 c.c.). Acetone ceased to be detectable in the refluxing toluene after 6 hours. The solution was then poured into 2N-hydrochloric acid, and the toluene layer separated, dried (K_2CO_3), and distilled. A viscous oil (46·3 g.), b. p. 108—115°/0·1 mm., was collected. The *phenylurethane*, on fractional crystallisation from benzene–light petroleum (b. p. 80—100°), gave two isomers, m. p. 115° (Found : N, 9·6. $C_{15}H_{20}O_4N_2$ requires N, 9·6%) and m. p. 86—87° (Found : N, 9·8%).

3-*Acetyl*cyclo*hexanol*.—3-1′-Nitroethyl*cyclo*hexanol (46·3 g.), by the method described for 3-acetyl-*cyclo*hexanone, gave 3-acetyl*cyclo*hexanol (30·4 g.), b. p. 134—138°/13 mm. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in yellow needles, m. p. 165° (Found : C, 52·0; H, 5·9; N, 17·3. $C_{14}H_{18}O_5N_4$ requires C, 52·2; H, 5·6; N, 17·4%). The *phenylurethane* crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 91° (Found : N, 5·4. $C_{15}H_{19}O_3N$ requires N, 5·4%).

3-*Acetyl*cyclo*hexyl Bromide*.—3-Acetyl*cyclo*hexanol (1 g.) in hydrobromic acid (48%; 10 c.c.) was set aside at room temperature for 4 days. A heavy red oil slowly separated. The mixture was diluted with ice-water and extracted with ether, and the extract washed with sodium hydrogen carbonate solution, then with water, dried ($CaCl_2$), and distilled. An oil (1·05 g.), b. p. 130—135° (bath-temp.)/12 mm., was collected. The 2 : 4-dinitrophenylhydrazone was very soluble in all solvents except light petroleum and crystallised very slowly. The *semicarbazone* crystallised from alcohol in prisms, m. p. 180° (Found : N, 15·4; Br, 30·5. $C_9H_{16}ON_3Br$ requires N, 16·0; Br, 30·5%).

3-*Acetyl*cyclo*hexyl Iodide*.—Prepared as the bromide from 3-acetyl*cyclo*hexanol (10 g.) and hydriodic acid (100 c.c.), this was an oil (13·6 g.), b. p. 72—76°/0·03 mm. (decomp.), which gave a *semicarbazone*, prisms (from alcohol), m. p. 160° (Found : N, 14·1; I, 40·7. $C_9H_{16}ON_3I$ requires N, 13·6; I, 41·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in orange plates, m. p. 138—139° (Found : N, 13·0; I, 29·3. $C_{14}H_{17}O_4N_4I$ requires N, 13·0; I, 29·4%). Attempts to condense these halides with phenol or guaiacol in presence of alkalis led to tars and small yields of an oil with a powerful, pleasant odour, b. p. 95—100° (bath-temp.)/15 mm., which gave a 2 : 4-*dinitrophenylhydrazone*, brilliant red needles (from ethyl acetate), m. p. 203° (Found : C, 55·2; H, 5·4; N, 18·6. $C_{14}H_{16}O_4N_4$ requires C, 55·3; H, 5·2; N, 18·4%). The *semicarbazone* crystallised in plates (from alcohol), m. p. 206° (Found : N, 23·0. $C_9H_{15}ON_3$ requires N, 23·2%). The analyses are consistent with those required of 3-acetyl-*cyclo*hexene.

Dihydroresorcinol Mono-(o-methoxyphenyl) Ether.—3-Chlorocyclohex-2-enone (12 g.) (Crossley and Haas *J.*, 1903, **83**, 494) and guaiacol (12 g.) in acetone were refluxed with anhydrous potassium carbonate (15 g.) overnight, then filtered, and distilled. An oil, b. p. 210—230°/15 mm., which rapidly crystallised, was collected. The *ether* crystallised from benzene–light petroleum (b. p. 60—80°) in large prisms (14·1 g.), m. p. 97° (Found: C, 71·6; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·4%).

Dihydroresorcinol Monophenyl Ether.—When prepared similarly from 3-chlorocyclohex-2-enone (22·6 g.) and phenol (16 g.), this *ether* formed an oil (28·9 g.), b. p. 194—196°/18 mm., which slowly solidified and crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 39° (Found: C, 76·9; H, 6·8. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

Dihydroresorcinol o-Hydroxyphenyl Ether.—When prepared from 3-chlorocyclohex-2-enone (9·7 g.) and catechol (9·0 g.), the *o-hydroxyphenyl ether* (10·1 g.) had b. p. 170—185° (bath-temp.)/11 mm., rapidly solidified, and crystallised from benzene in pearly plates, m. p. 89—94° (decomp.) (Found: C, 70·4. H, 6·0. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

3-o-*Methoxyphenoxy*cyclo*hexanol.*—Dihydroresorcinol *o*-methoxyphenyl ether (twice distilled and twice crystallised) (7·5 g.) was shaken in ethyl acetate (100 c.c.) with hydrogen at room temperature and atmospheric pressure in presence of palladised charcoal (30%; 1 g.). 1100 C.c. of hydrogen were absorbed during 11 hours, whereafter the catalyst was changed to platinum oxide (0·3 g.). A further 780 c.c. of hydrogen were then absorbed during 8 hours. The solution was filtered and washed with 2N-sodium hydroxide to remove guaiacol. The ethyl acetate layer was dried and distilled. A viscous oil (5·5 g.), b. p. 189—198°/15 mm., was collected. The *phenylurethane* crystallised in needles (from alcohol), m. p. 121—122° (Found: C, 70·6; H, 6·4; N, 4·1. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·7; N, 4·1%).

Reduction of Dihydroresorcinol Monophenyl Ether.—Reduction of this ether over palladised charcoal (30%) terminated with absorption of two molar proportions of hydrogen. The products were *cyclo*hexanone (identified as the semicarbazone, m. p. 166—167°) and phenol (identified as tribromophenol, m. p. 90—92°). The ether (14·6 g.) in alcohol (600 c.c.) was treated with sodium (20 g.) without cooling. The mixture was acidified at 5° with acetic acid and extracted with ether. The extract was dried (K_2CO_3) and distilled. A low-boiling fraction containing phenol and *cyclo*hexanol was rejected and the fraction (3·25 g.), b. p. 130—135° (bath-temp.)/20 mm., was collected. In attempts to prepare the phenylurethane, carbanilide (m. p. 238°) was isolated.

NN-*Diethyl*-4-*hydroxy*-3-*nitrobenzylamine.*—Diethylamine (24 g.) in dry benzene (40 c.c.) was added during 0·5 hour to a refluxing solution of 4-hydroxy-3-nitrobenzyl chloride (27·5 g.) (Fishman, *J. Amer. Chem. Soc.*, 1920, **42**, 2288) in benzene (40 c.c.), and refluxing was continued for 1 hour. The base was taken up in 2N-hydrochloric acid, precipitated by addition of potassium carbonate, and extracted with chloroform, dried (Na_2SO_4) and freed from solvent. The residue was dissolved in dry ether, and the *hydrochloride* (17·5 g.) precipitated by gaseous hydrogen chloride. It crystallised from alcohol in yellow prisms (15·8 g.), m. p. 185° (Found: N, 10·9. $C_{11}H_{16}O_3N_2$,HCl requires N, 10·8%). The *base* crystallised from alcohol in yellow prisms, m. p. 109° (Found: N, 12·5. $C_{11}H_{16}O_3N_2$ requires N, 12·5%). 4-*Acetoxy*-NN-*diethyl*-3-*nitrobenzylamine hydrochloride* crystallised from alcohol in white needles, m. p. 191° (Found: N, 9·3. $C_{13}H_{18}O_4N_2$,HCl requires N, 9·3%).

NN-*Diethyl*-4-*methoxy*-3-*nitrobenzylamine.*—(*a*) *NN*-Diethyl-4-hydroxy-3-nitrobenzylamine (2·4 g.) and trimethylphenylammonium hydroxide [from the toluene-*p*-sulphonate (3·3 g.) (Rodionov, *Bull. Soc. chim.*, 1926, **39**, 305)] in methanol (15 c.c.) were heated at 150° for 3 hours. The mixture was acidified with acetic acid and steam-distilled and the residue basified with 2N-sodium hydroxide. Ether extracted a small amount of oil which gave a hydrochloride, crystallising from alcohol–ether in small prisms, m. p. 216°, identical (mixed m. p.) with the product described below.

(*b*) 4-Methoxy-3-nitrobenzyl chloride (69·5 g.) (Jacobs and Heidelberger, *J. Biol. Chem.*, 1915, **20**, 676) and diethylamine (51 g.) were refluxed in absolute alcohol (500 c.c.) for 1 hour. The product was isolated in the same manner as *NN*-diethyl-4-hydroxy-3-nitrobenzylamine. The *hydrochloride* (58·3 g., 62%) crystallised from alcohol in needles, m. p. 218° Found: N, 10·2. $C_{12}H_{18}O_3N_2$,HCl requires N, 10·2%).

3-*Amino*-NN-*diethyl*-4-*methoxybenzylamine.*—Tin (32 g.) was added to a cold solution of *NN*-diethyl-4-methoxy-3-nitrobenzylamine hydrochloride (58·3 g.) in hydrochloric acid (*d* 1·16; 200 c.c.). The mixture became hot and a white solid separated which redissolved during 1 hour's heating on the steam-bath. The filtered solution was basified with 40% aqueous sodium hydroxide, and the precipitated oil was taken up in ether, dried (K_2CO_3), and distilled. The distillate (37 g.), b. p. 171—174°/16 mm., was converted into the *dihydrochloride*, m. p. 207° (from alcohol) (Found: N, 9·6. $C_{12}H_{20}ON_2$,2HCl requires N, 10·0%).

NN-*Diethyl*-3-*hydroxy*-4-*methoxybenzylamine.*—3-Amino-4-methoxybenzyldiethylamine (4 g.) in sulphuric acid (50%; 10 c.c.) was diazotised at 0° by sodium nitrite solution (10%; 17·5 c.c.), and the solution added dropwise to a boiling (105°) solution of copper sulphate (35 g.) in water (35 c.c.). Boiling was continued for 3 minutes after the completed addition. The cooled solution was filtered, basified with aqueous ammonia, and extracted with chloroform, and the extract dried (K_2CO_3) and distilled. The distillate, b. p. 160° (bath-temp.)/13 mm., crystallised from light petroleum (b. p. 60—80°), giving the *hydroxy-amine* as prisms (0·3 g., 7%), m. p. 76° (Found: C, 68·6; H, 9·0; N, 6·9. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·1; N, 6·7%). In a similar experiment, which could not be repeated, the yield was 0·9 g. (22%). Other methods gave negative results.

3-*Bromo*-NN-*diethyl*-4-*methoxybenzylamine.*—The diazonium solution from 3-amino-*NN*-diethyl-4-methoxybenzylamine (18·5 g.) in hydrobromic acid (24%; 50 c.c.) was added to a freshly prepared cuprous bromide mixture prepared from copper sulphate (6 g.) at 0°. The mixture was warmed slowly to 80°,

then basified with aqueous ammonia, and the solution extracted with chloroform. The extract was dried (K_2CO_3) and distilled, to give a pale yellow oil (9·6 g.), b. p. 170—175°(bath temp.)/15 mm. The *hydrochloride* crystallised from alcohol–ether in hard prisms, m. p. 195° (Found: N, 4·7; Cl, 11·6. $C_{12}H_{18}ONBr,HCl$ requires N, 4·5; Cl, 11·5%).

(±)-3-*Hydroxy*-4-*methoxy*-α-*methylbenzylamine*.—*iso*Acetovanillone oxime (3 g.) (Schneider and Kraft, *Ber.*, 1922, **55**, 1896) in aqueous methanol (50%; 70 c.c.) was reduced by addition of sodium amalgam (3%; 100 g.) in small portions. The mixture was kept faintly acid by addition of acetic acid (50%). The solution was decanted from mercury, 5N-hydrochloric acid (5 c.c.) added, and unchanged oxime shaken out with ether. The product was precipitated by potassium carbonate and extracted with ether, the extract dried (K_2CO_3), and the ether distilled off. The residue, on crystallisation from benzene (charcoal), gave (±)-3-*hydroxy*-4-*methoxy*-α-*methylbenzylamine* as prisms (1·9 g.), m. p. 148° (Found: N, 8·3. $C_9H_{13}O_2N$ requires N, 8·4%).

3-cyclo*Hexyloxy*-4-*methoxyacetophenone*.—*iso*Acetovanillone (90 g.) (Coulthard, Marshall, and Pyman, *J.*, 1930, 290) and *cyclo*hexyl bromide (600 g., 6 mols.) were heated under reflux in alcohol (2 l.) while a solution of sodium hydroxide (146 g.) in methanol (600 c.c.) was added during 80 hours. Refluxing was continued for 8 hours more. The mixture was cooled to 0°, filtered from sodium bromide, and evaporated to small bulk. The residue was treated with 2N-sodium hydroxide, and the insoluble oil extracted with ether, dried (K_2CO_3), and distilled. A viscous oil (56·8 g.), b. p. 195—200°/10 mm., was collected which soon solidified. 3-cyclo*Hexyloxy*-4-*methoxyacetophenone* (53·5 g.) crystallised from 70% alcohol in large prisms, m. p. 61° (Found: C, 72·6; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%). Unchanged *iso*acetovanillone (30·5 g.) was recovered. The 2:4-*dinitrophenylhydrazone* crystallised from acetic acid in red needles, m. p. 191° (Found: N, 13·3. $C_{21}H_{24}O_6N_4$ requires N, 13·1%). The *oxime* crystallised from alcohol in needles, m. p. 99° (Found: N, 5·4. $C_{15}H_{21}O_3N$ requires N, 5·3%).

(±)-3-cyclo*Hexyloxy*-4-*methoxy*-α-*methylbenzylamine*.—3-*cyclo*Hexyloxy-4-methoxyacetophenone oxime (6·7 g.) was reduced as described for (±)-3-hydroxy-4-methoxy-α-methylbenzylamine. The base was an oil, b. p. 210—215°/13 mm., which solidified when kept below 10° but melted at 15—20°. The *hydrochloride* (5·2 g.) crystallised from alcohol–ether in needles, m. p. 213° (Found: N, 4·9; Cl, 12·3. $C_{15}H_{23}O_2N,HCl$ requires N, 4·9; Cl, 12·4%).

(±)-3-cyclo*Hexyloxy*-4-*methoxy*-α-*methylbenzyl Alcohol*.—3-*cyclo*Hexyloxy-4-methoxyacetophenone (16·0 g.) in ethyl acetate (50 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of platinum oxide (0·2 g.). Further additions of catalyst were required at 14% and 54% reduction, and reduction was terminated after 35 hours at 85% of the theoretical absorption of hydrogen. The solution was filtered and distilled. A thick colourless oil (13 g.), b. p. 210—220°/17 mm., was collected. The *phenylurethane* crystallised from light petroleum in needles, m. p. 163° (decomp.) (Found: C, 71·8; H, 7·4; N, 3·9. $C_{22}H_{27}O_4N$ requires C, 71·5; H, 7·3; N, 3·8%).

(±)-NN-*Dialkyl*-3-cyclo*hexyloxy*-4-*methoxy*-α-*methylbenzylamines*.—3-*cyclo*Hexyloxy-4-methoxy-α-methylbenzyl alcohol was converted into the bromide by addition of phosphorus tribromide (0·33 mol.) at <10° to its solution in dry benzene. After 1 hour at room temperature the mixture was treated with ice, and the benzene layer separated, washed with sodium hydrogen carbonate solution, and dried (Na_2SO_4). The appropriate dialkylamine was added and the mixture set aside overnight, then refluxed for 1 hour. Dialkylamine hydrobromide was filtered off, the benzene layer evaporated, and the residue dissolved in ether. Amines were extracted by repeated shaking with small quantities of 10% hydrochloric acid, and the base regenerated with ammonia, taken up in ether, dried, and distilled. The hydrochlorides were crystallised from alcohol–ether. The *products* are recorded in the table.

(±)-NN-*Dialkyl*-3-cyclo*hexyloxy*-4-*methoxy*-α-*methylbenzylamines*.

NR_2	B. p. of base (bath-temp.)	Hydrochloride, m. p.	Formula	Found, % C	Found, % H	Found, % N	Required, % C	Required, % H	Required, % N
NMe_2	145—150°/0·5 mm.	191°	$C_{17}H_{27}O_2N,HCl$	65·0	8·7	4·6	65·1	8·9	4·5
NEt_2	135—145°/0·03 mm.	110	$C_{19}H_{31}O_2N,HCl$	66·1	9·2	4·0	66·8	9·4	4·1
NPr^n_2	150—160°/0·1 mm.	135	$C_{21}H_{35}O_2N,HCl$	68·0	9·6	4·2	68·2	9·7	3·8
NBu^n_2	160—165°/0·5 mm.	133	$C_{23}H_{39}O_2N,HCl$	—	—	3·7 †	—	—	3·5
Tiq *	180—190°/0·05 mm.	179	$C_{24}H_{31}O_2N,HCl$	71·8	8·1	3·5	71·7	8·0	3·5

* Tetrahydro*iso*quinolino. † Found: Cl, 9·2. Required: Cl, 8·9%.

The author thanks the Directors of Messrs. May & Baker Ltd. for the generous facilities which made this work possible, Mr. S. Bance, B.Sc., for the semimicro-analyses, and Professor W. H. Linnell, D.Sc., F.R.I.C., for encouragement and advice.

Department of Biochemistry, Institute of Psychiatry, Denmark Hill, London, S.E.5.

[*Received, July 4th*, 1951.]