261. *Molecular Dissymmetry and Physiological Activity.*

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In connexion with an investigation on the subject of the title (see *Chem. and Ind.*, 1932, **51**, 910), it became necessary to prepare a number of *methylurethanes* of the general formula *m*-$NHMe\cdot CO\cdot O\cdot C_6H_4\cdot CHR\cdot NMe_2$, as well as the *urethane* *m*-$NHMe\cdot CO\cdot O\cdot C_6H_4\cdot CMe_2\cdot NMe_2$. The preparation and properties of these and related compounds are now described. The results obtained in the more biological experiments, together with a discussion of the theoretical aspect of the subject, will be published elsewhere.

With the exception of the methylurethane of α-*m*-hydroxyphenyl*iso*propyldimethylamine, the above compounds were prepared from *m*-methoxybenzaldehyde. By interaction with the appropriate alkyl-(or aryl-)magnesium halide, this yielded the carbinol *m*-$MeO\cdot C_6H_4\cdot CHR\cdot OH$, from which the bromide *m*-$MeO\cdot C_6H_4\cdot CHRBr$ was obtained by the action of hydrogen bromide in a suitable solvent. On treatment with dimethylamine the bromide was converted into the amine *m*-$MeO\cdot C_6H_4\cdot CHR\cdot NMe_2$, from which the urethane was obtained by demethylation and direct interaction of the resulting phenol with methylcarbimide. The excepted methylurethane (above) was obtained from the carbinol *m*-$MeO\cdot C_6H_4\cdot CMe_2\cdot OH$ by a similar series of reactions.

EXPERIMENTAL.

Preparation of m-*Methoxybenzaldehyde*.—This was effected by methylating technical *m*-hydroxybenzaldehyde with sodium hydroxide and methyl sulphate according to the procedure of Chakravarti, Haworth, and Perkin (J., 1927, 2269). When, however, this preparation was used in certain of the reactions described below, products were obtained the formation of which could only be explained on the assumption that the methoxybenzaldehyde contained appreciable quantities of methoxybenzyl alcohol, no doubt produced by a Cannizzaro reaction during the methylation process. In order to prevent the formation of this alcohol, the addition of the reagents was so regulated that the solution was never allowed to become alkaline, as occurred in the original process. Nevertheless, the formation of a small quantity of this alcohol could never be wholly suppressed, nor could it be entirely eliminated from the product by careful fractionation.

m-*Methoxyphenylethylcarbinol*.—To the ethylmagnesium iodide prepared from 12 g. of magnesium, 75 g. of ethyl iodide, and 250 c.c. of ether, were added 60 g. of *m*-methoxybenzaldehyde. After about an hour, the product was poured on ice and acidified with 50 c.c. of concentrated hydrochloric acid. The ethereal layer was separated, dried over potassium carbonate, the solvent evaporated, and the residue distilled under diminished pressure; 62 g. of m-*methoxyphenylethylcarbinol* were obtained as a colourless oil, b. p. 135—138°/11 mm. (Found: C, 71·6; H, 8·3. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%).

α-m-*Methoxyphenyl*-n-*propyldimethylamine*.—The above carbinol (62 g.) was dissolved in about 250 c.c. of benzene, and the solution saturated with dry hydrogen bromide. The water liberated was removed with calcium bromide, and the dark solution evaporated to a small bulk under diminished pressure and at low temperature (35°) in order to remove the bulk of the hydrogen bromide. The residual oil containing the crude *m*-methoxyphenylethyl bromide was dissolved in 150 c.c. of cooled benzene, and then added to a solution of 33 g. of anhydrous dimethylamine in 150 c.c. of ice-cold benzene. The separation of dimethylamine hydrobromide soon started, and continued for a few days. When this process appeared to be complete, the solid was filtered off, and the filtrate extracted with dilute hydrochloric acid (from 50 c.c. of acid, *d* 1·19). The extract was washed with ether, made alkaline with sodium hydroxide, and the resulting oil shaken out with ether. After drying over potassium carbonate, the ether was removed, and the residual oil distilled under diminished pressure. The main fraction (40 g.) consisted of α-m-*methoxyphenyl*-n-*propyldimethylamine*, a colourless oil, b. p. 119°/11 mm. (Found: C, 74·3; H, 9·9. $C_{12}H_{19}ON$ requires C, 74·6; H, 9·9%). A small quantity of a lower-boiling fraction was also collected. This had been obtained in larger amounts in some earlier experiments, and was identified as *m*-methoxybenzyldimethylamine by conversion into its hydrochloride, m. p. 173° both alone and after admixture with an authentic specimen. Its formation can no doubt be attributed to the presence of some methoxybenzyl alcohol in the aldehyde used in these experiments (see above).

The *hydrochloride* of α-*m*-methoxyphenyl-*n*-propyldimethylamine crystallises from methyl ethyl ketone in clusters of small needles, m. p. 149° (Found : Cl, 15·6. $C_{12}H_{19}ON,HCl$ requires Cl, 15·5%); it is somewhat deliquescent. The *methiodide* separates slowly from a solution of the base in acetone to which methyl iodide has been added; it crystallises from acetone in plates, m. p. 187° (Found : I, 38·1. $C_{12}H_{19}ON,CH_3I$ requires I, 37·9%). The picrate crystallises from alcohol or aqueous alcohol in stout yellow prisms, m. p. 117°.

α-m-*Hydroxyphenyl*-n-*propyldimethylamine*.—The above methoxy-base (20 g.) was boiled under reflux with constant-boiling hydrobromic acid (80 c.c.) for 5—6 hours. The acid was removed by distillation under diminished pressure, and the residual syrup dissolved in water. Addition to this of a saturated solution of sodium carbonate precipitated the phenolic base as an oil, which was extracted with ether. The brown oil which remained after evaporation of the ether solidified on standing. It was purified by distillation under diminished pressure, 149—150°/8 mm. On recrystallisation from ligroin, α-m-*hydroxyphenyl*-n-*propyldimethylamine* forms flat prisms, m. p. 103° (Found : C, 73·8; H, 9·4. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6%).

The *hydrochloride* crystallises from acetone in prisms, m. p. 163° (Found : Cl, 16·3. $C_{11}H_{17}ON,HCl$ requires Cl, 16·4%); the *methiodide* from acetone in flat prisms, m. p. 150° (Found : I, 39·3. $C_{11}H_{17}ON,CH_3I$ requires I, 39·6%); and the picrate from aqueous alcohol in long yellow prisms, m. p. 141°.

Methylurethane of α-m-*Hydroxyphenyl*-n-*propyldimethylamine*.—The interaction between the foregoing base and methylcarbimide was very slow in benzene or ethereal solution. The phenolic base (4 g.) was therefore dissolved directly in excess (3 c.c.) of freshly-prepared methylcarbimide, the mixture being cooled in ice. After standing over-night, the excess methyl carbimide was removed under diminished pressure without the application of heat. The residual syrup was stirred with a relatively large volume of dry ether, but a considerable amount failed to dissolve. The solution was therefore decanted through a filter, and the clear filtrate treated with alcoholic hydrogen chloride, avoiding excess. This caused the hydrochloride to separate as an oil. The solvents were decanted, and the oil washed with dry ether and dissolved in warm acetone. Crystalline material (3·5 g.) slowly separated from this solution. The *hydrochloride* of the *methylurethane* of α-m-*hydroxyphenyl*-n-*propyldimethylamine* crystallises from acetone in triangular pyramids, m. p. 153° (Found : Cl, 13·0. $C_{13}H_{20}O_2N_2,HCl$ requires Cl, 13·0%).

The *methiodide*, similarly prepared with methyl iodide in place of alcoholic hydrogen chloride, crystallises from alcohol–ether or from acetone in stout prisms, m. p. 111° (efferv.) (Found, in air-dried material : I, 31·9, 32·1; loss on drying in vacuum at 70—80°, 4·5. $C_{13}H_{20}O_2N_2,CH_3I,H_2O$ requires I, 32·0; H_2O, 4·5%. Found, in material dried in vacuum : I, 33·7. $C_{13}H_{20}O_2N_2,CH_3I$ requires I, 33·5%).

All attempts to prepare the free urethane in a crystalline condition, either directly from the reaction product or after recovery from the pure hydrochloride, failed. The salts described above were, moreover, not obtained originally without considerable difficulty. This was due to the presence of the above-mentioned oil in the reaction product, which could not be completely removed with ether unless a large volume of this solvent was employed. Subsequent examination of this oil, the origin of which is discussed below (p. 1096), showed that it was soluble in water and was, in fact, salt-like. Its aqueous solution was therefore treated with sodium carbonate, which caused precipitation of an oil. This was extracted with ether, but failed to crystallise on evaporation of the dried extract. It readily formed, however, a hydrochloride which proved to be identical with that of the urethane described above. The recovery of this material rendered the yield of the urethane practically theoretical.

Preparation of m-*Methoxyphenyldimethylcarbinol*.—Béhal and Tiffeneau (*Bull. Soc. chim.*, 1908, **3**, 316) state that this carbinol can be prepared by the action of 2 mols. of methylmagnesium iodide on ethyl *m*-methoxybenzoate, and it was eventually obtained by this method in the present investigation. Attempts were first made to prepare it, however, by the interaction of methylmagnesium iodide and *m*-methoxyacetophenone. *m*-Methoxyphenylmethylcarbinol, prepared according to Stedman and Stedman (J., 1929, 609) except that no acid was employed in decomposing the product of the Grignard reaction, was oxidised by Klages and Eppelsheim's method (*Ber.*, 1903, **36**, 3584) to *m*-methoxyacetophenone. The latter (81 g.) was run into a solution of methylmagnesium iodide (15 g. Mg; 85 g. MeI) in 500 c.c. of ether, and the Grignard compound decomposed with ice without the use of acid. The ethereal layer was syphoned from the product, dried over potassium carbonate, and the residue obtained by evaporation of the ether distilled under diminished pressure, 70 g. of a colourless oil, b. p. 102—105°/13 mm., being obtained. From its odour, this was evidently not the required carbinol;

moreover, it decolorised a cold solution of potassium permanganate, and absorbed bromine immediately. It thus clearly consisted of slightly impure *m*-methoxy*iso*propenylbenzene, which, according to Béhal and Tiffeneau (*loc. cit.*), is obtained if 3 mols. of methylmagnesium iodide are used in their method.

In view of this result, the carbinol was prepared from ethyl *m*-methoxybenzoate. *m*-Methoxybenzoic acid was obtained by the slow addition of the corresponding aldehyde to a slight excess of aqueous potassium permanganate, and the excess of the latter finally destroyed by warming the solution with a little methyl alcohol. The solution was filtered, acidified with hydrochloric acid, and the acid which separated was filtered off and recrystallised from water; m. p. 106·5°. (The m. p.'s given in the literature range from 104·5° to 110°; these preparations were, however, made by methods different from the above.) It was then esterified with ethyl alcohol in the presence of sulphuric acid, and the ethyl *m*-methoxybenzoate (40 g.) converted into *m*-methoxyphenyldimethylcarbinol, b. p. 130°/13 mm. (yield 31 g.), by interaction with methylmagnesium iodide according to the usual procedure but avoiding the use of acid.

α-m-*Methoxyphenyl*iso*propyldimethylamine.*—This was first prepared by the successive action of hydrogen bromide and dimethylamine (40 g.) on *m*-methoxy*iso*propenylbenzene (70 g.) under the conditions described above (p. 1094), 3 days being allowed for the interaction between the bromide and the dimethylamine. On working up the product, only 10 g. of α-m-*methoxyphenyl*iso*propyldimethylamine*, b. p. 125—127°/13 mm., were obtained. The hydrochloride, m. p. 96°, crystallises from acetone; the *methiodide*, octagonal tablets which decompose without melting at about 180° (Found : I, 37·8. $C_{12}H_{19}ON,CH_3I$ requires I, 37·9%) from acetone; and the picrate, yellow hexagonal plates, m. p. 138°, from alcohol.

The same base was similarly prepared from *m*-methoxyphenyldimethylcarbinol. From 31 g. of the carbinol and 22 g. of dimethylamine only 5 g. were obtained. In order to discover the cause of the poor yield, the benzene solution from which the base had been extracted was dried over potassium carbonate and the benzene removed by distillation. The residue was distilled under diminished pressure, and 17 g. of a colourless oil, b. p. 102°/13 mm., were obtained. This was evidently pure *m*-methoxy*iso*propenylbenzene for which von Auwers (*Annalen*, 1917, **413**, 309) gives b. p. 99°/12 mm. It is clear that dimethylamine removes hydrogen bromide from the greater portion of the α-*m*-methoxyphenyl*iso*propyl bromide with the formation of a styrene.

α-m-*Hydroxyphenyl*iso*propyldimethylamine*, obtained by demethylation of the above methoxy-base with hydrobromic acid, crystallises from benzene in flat prisms, m. p. 129° (Found : N, 7·8, 7·7. $C_{11}H_{17}ON$ requires N, 7·8%). The *methiodide* crystallises from alcohol–ether in prisms, m. p. 151° (Found : I, 39·7. $C_{11}H_{17}ON,CH_3I$ requires I, 39·6%), and the *hydrochloride* from alcohol in long needles, m. p. 213° (Found : Cl, 16·6. $C_{11}H_{17}ON,HCl$ requires Cl, 16·5%).

Methylurethane of α-m-*Hydroxyphenyl*iso*propyldimethylamine.*—The above phenolic base (1 g.) was treated with methylcarbimide (1·5 c.c.), in which it slowly dissolved with some evolution of heat. By the next day a mass of crystals had separated. After removal of the excess methylcarbimide, the crude urethane was treated with ether, in which the crystals dissolved; the solution was decanted from the sticky residue (A, see below), and the solvent evaporated. The crystalline product was dissolved in hot light petroleum, the solution cooled rapidly, and filtered from a little oil which separated. The *methylurethane* of α-m-*hydroxyphenyl*iso*propyldimethylamine* crystallised from the filtrate in hexagonal plates, m. p. 96° (Found : C, 65·8, 65·6; H, 8·5, 8·4; N, 11·5. $C_{13}H_{20}O_2N_2$ requires C, 66·1; H, 8·5; N, 11·9%). The *hydrochloride* crystallises from methyl alcohol in prisms, m. p. 234° (efferv.) (Found : Cl, 13·1. $C_{13}H_{20}O_2N_2,HCl$ requires Cl, 13·0%), and the *methiodide* from alcohol–ether in clusters of needles, which melt at 160° on rapid heating, but immediately resolidify (Found : I, 33·7. $C_{13}H_{20}O_2N_2,CH_3I$ requires I, 33·5%).

The residue (A) crystallised from acetone, and on recrystallisation by addition of ether to its alcoholic solution, it formed hexagonal plates, m. p. 143°. Like the substance obtained during the preparation of the isomeric urethane, it was salt-like in nature, and on treatment with sodium carbonate yielded the pure urethane. It contained sulphur, but although possessing the appearance of a pure *substance* gave analytical results (Found : C, 48·1; H, 6·7; N, 10·9, 11·0; S, 8·5, 8·3%) from which no satisfactory formula could be deduced. It is clear, however, that the sulphur must have originated from an impurity present in the methylcarbimide, which was prepared from methyl sulphate and potassium cyanate. One would presume, further, that the impurity was acidic were it not for the fact that the formation of this compound could not be suppressed even when the methylcarbimide was redistilled from quick-lime.

Except where details are given, the following compounds were prepared by methods similar to those described above.

α-m-*Methoxyphenyl*-n-*butyldimethylamine* (36 g. from 66 g. of the corresponding carbinol), b. p. 129—130°/11·5 mm. (Found : C, 75·0; H, 10·2. $C_{13}H_{21}ON$ requires C, 75·4; H, 10·2%). The hydrochloride crystallises in fine needles from methyl ethyl ketone but is very deliquescent. The *methiodide* crystallises from acetone in triangular platelets, m. p. 119·5° (Found : I, 36·3. $C_{13}H_{21}ON,CH_3I$ requires I, 36·4%). The picrate forms yellow needles from alcohol, m. p. 99—100°.

α-m-*Hydroxyphenyl*-n-*butyldimethylamine*, slender prisms, m. p. 107°, from ether or ligroin (Found : C, 74·9; H, 9·9. $C_{12}H_{19}ON$ requires C, 74·6; H, 9·9%). It was purified by distillation under diminished pressure, and then had b. p. 170°/12 mm.; yield 93%. The *hydrochloride* crystallises from methyl ethyl ketone in tablets, m. p. 86° (Found, in air-dried material : Cl, 14·4, 14·5; loss in weight when dried in a vacuum at 60°, 7·2. $C_{12}H_{19}ON,HCl,H_2O$ requires Cl, 14·3; H_2O, 7·3%); the *methiodide* crystallises from acetone in thick hexagonal tablets, m. p. 191—192° (rapid heating) (Found : I, 37·7. $C_{12}H_{19}ON,CH_3I$ requires I, 37·9); and the picrate separates from alcohol as yellow rhombs, m. p. 154°.

Phenylurethane of α-m-*hydroxyphenyl*-n-*butyldimethylamine*. The phenolic base (4 g.) and phenylcarbimide (2·5 g.) were dissolved in benzene (20 c.c.). After 2 days, a crystalline deposit (probably diphenylurea) was removed by filtration, and light petroleum added to the filtrate, causing crystalline material (5·7 g.) to separate. When recrystallised from ligroin, this *phenylurethane* forms stout prisms, m. p. 96° (Found : C, 73·2; H, 7·7. $C_{19}H_{24}O_2N_2$ requires C, 73·1; H, 7·8%). The *hydrochloride* crystallises from acetone containing a little alcohol in small rectangular tablets, m. p. 201° (efferv.; rapid heating) (Found : Cl, 10·2. $C_{19}H_{24}O_2N_2,HCl$ requires Cl, 10·2%). The methiodide crystallises from acetone–ether in prisms, m. p. 146°.

Methylurethane of α-m-*hydroxyphenyl*-n-*butyldimethylamine*.—The free urethane could not be obtained crystalline, but the *hydrochloride* crystallised from acetone in prisms, m. p. 143° (Found : Cl, 12·4. $C_{14}H_{22}O_2N_2,HCl$ requires Cl, 12·3%), and the *methiodide* from the same solvent in slender flat prisms, m. p. about 176° (efferv.) (Found : I, 32·6, 32·2. $C_{14}H_{22}O_2N_2,CH_3I$ requires I, 32·4%).

m-*Methoxyphenyl*-n-*butylcarbinol*, b. p. 130—133°/3 mm.; yield 88% (Found : C, 73·6; H, 9·2. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·4%).

α-m-*Methoxyphenyl*-n-*amyldimethylamine*, b. p. 146—148°/13 mm. (Found : C, 75·6; H, 10·5. $C_{14}H_{23}ON$ requires C, 76·0; H, 10·5%); yield 50%. The *hydrochloride* crystallises from ethyl acetate or acetone in flat prisms, m. p. 130·5° (Found : Cl, 13·9. $C_{14}H_{23}ON,HCl$ requires Cl, 13·8%). The picrate, m. p. 91°, forms flat yellow prisms from alcohol. The methiodide could not be crystallised.

α-m-*Hydroxyphenyl*-n-*amyldimethylamine*, b. p. 173°/10 mm., pyramid-shaped crystals, m. p. 91° from ligroin or ether (Found : C, 75·3; H, 10·1. $C_{13}H_{21}ON$ requires C, 75·4; H, 10·2%); yield 87%. The hydrochloride could not be crystallised. The *methiodide* crystallised from acetone–ether in hexagonal plates, m. p. 141° (Found : I, 36·5. $C_{13}H_{21}ON,CH_3I$ requires I, 36·4%). The picrate, m. p. 126°, separates from alcohol in yellow rhombs. Neither the methylurethane nor its salts could be obtained crystalline, but the *phenylurethane* crystallises from ligroin in stout prisms, m. p. 103° (Found : C, 73·9; H, 8·1. $C_{20}H_{26}O_2N_2$ requires C, 73·6; H, 8·0%). The *hydrochloride*, m. p. 166°, crystallises in long prisms from acetone containing a little alcohol (Found : Cl, 9·9. $C_{20}H_{26}O_2N_2,HCl$ requires Cl, 9·8%).

m-*Methoxydiphenylmethyldimethylamine*, a thick colourless oil, b. p. 179°/12 mm. (Found : C, 79·5; H, 8·1. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9%); *hydrochloride*, rectangular prisms, m. p. 182° (Found : Cl, 12·8. $C_{16}H_{19}ON,HCl$ requires Cl, 12·8%), from acetone.

m-*Hydroxydiphenylmethyldimethylamine*, b. p. 205—207°/10 mm., crystallises from ligroin in tablets, m. p. 94°. The *hydrobromide* separates from the reaction mixture, in the demethylation process, as a crystalline mass. It was recrystallised from water and from acetone–ether (Found, in air-dried material : Br, 24·8; loss in weight on drying in a vacuum at 100°, 5·5. $C_{15}H_{17}ON,HBr,H_2O$ requires Br, 24·5; H_2O, 5·5%. Found, in dried material : Br, 26·1. $C_{15}H_{17}ON,HBr$ requires Br, 26·0%). The picrate forms yellow prisms, m. p. 129°, from alcohol. The *phenylurethane* crystallises from ligroin in needles, m. p. 119° (Found : C, 76·3; H, 6·4. $C_{22}H_{22}O_2N_2$ requires C, 76·3; H, 6·4%), and the methiodide of the latter from acetone in pyramids, m. p. 186° (efferv.; rapid heating).

Methylurethane of m-*Hydroxydiphenyldimethylamine*.—After removal of the excess methylcarbimide from the product of its interaction with the phenolic base, the residual syrup was stirred with ether, and the solution decanted from some insoluble material. The *methylurethane* was obtained as an oil on evaporation of the ether. It separated from benzene–light petroleum in square crystals, m. p. 80° (Found: N, 9·75, 9·8. $C_{17}H_{20}O_2N_2$ requires N, 9·9%). The *hydrochloride* crystallises from alcohol–ether in prisms, m. p. 204° (efferv.) (Found: Cl, 11·2. $C_{17}H_{20}O_2N_2,HCl$ requires Cl, 11·1%); the *methiodide* from alcohol–ether in rectangular prisms which decompose above 140° without melting (Found: I, 29·95. $C_{17}H_{20}O_2N_2,CH_3I$ requires I, 29·8%), and the *picrate* from acetone in yellow double pyramids, m. p. 182° (Found: N, 13·4. $C_{17}H_{20}O_2N_2,C_6H_3O_7N_3$ requires N, 13·7%). The last salt was prepared before the urethane had been obtained crystalline, and the base could be recovered from it without decomposition by shaking it with ammonia and ether.

The material, insoluble in ether, which was formed in the preparation of this urethane crystallised from alcohol–ether and had m. p. 124° (efferv.). Like the similar material obtained in the preparation of the other methylurethanes, it yielded the required methylurethane on treatment with sodium carbonate. Analyses (Found: C, 54·7; H, 6·6; N, 8·7, 8·65; S, 6·8%) could not, however, be interpreted.

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