LXXXVIII.—*The Methylurethanes of the Isomeric α-Hydroxyphenylethyldimethylamines and their Miotic Activity.*

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In investigations carried out by one of the authors during the past three years a new relationship between chemical constitution and physiological action has been discovered. It has been shown (*Biochem. J.*, 1926, **20**, 719; 1929, in the press) that certain urethanes possess in common, and to a more or less pronounced degree, the property of producing miosis when instilled into the eye. The effect of variations in the structure of the constituent portions of the molecule has not yet been completely determined, but it has been shown to be highly probable that miotic activity is only associated with urethanes which are phenyl, as distinguished from alkyl, esters of carbamic acids; that, of the substituted carbamic acids examined, the esters of methylcarbamic acid are, other conditions being the same, the most active miotics; and that the presence of a basic group in the molecule is essential for the activity of the urethanes.

The substances hitherto examined include two series of isomeric methylurethanes, namely, the dimethylaminophenyl esters of methylcarbamic acid, $NHMe{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}NMe_2$, and the methylurethanes of the hydroxybenzyldimethylamines,

$$NHMe{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}CH_2{\cdot}NMe_2.$$

None of the compounds of these series contains an asymmetric carbon atom, and, in view of the known difference in activity of the enantiomorphs of certain physiologically active substances, experiments have been carried out with the object of introducing such asymmetry into the latter of the above series of isomerides. For this purpose, the methylurethanes of the isomeric α-hydroxyphenylethyldimethylamines have been prepared, this particular series being chosen because the introduction of an asymmetric carbon atom is effected with the minimal structural alterations necessary for this purpose. Unfortunately, despite numerous attempts, the authors have not yet succeeded in obtaining these urethanes in optically active forms. Work in this direction is still proceeding. In the meantime, the results obtained with the racemic bases are here recorded.

The preparation of the three isomeric urethanes was carried out in the following manner. The methoxybenzaldehydes were converted into the methoxyphenylmethylcarbinols by Grignard's reaction. By treatment with hydrobromic acid the carbinols yielded the corresponding bromides, which reacted with dimethylamine to give the α-methoxyphenylethyldimethylamines. These were demethylated with hydrobromic acid, and the phenols thus obtained converted into the methylurethanes, $NHMe{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}CHMe{\cdot}NMe_2$, by interaction with methylcarbimide under appropriate conditions. The details of these reactions are described below and only the last stage need be commented upon here. Whereas α-*m*-hydroxyphenylethyldimethylamine reacts smoothly with an excess or the calculated quantity of methylcarbimide, with or without the use of an inert solvent, to yield the methylurethane, such is not the case with the *o*- and *p*-isomerides. If solutions of these substances in benzene are treated with an excess of methylcarbimide there results as product an oil from which no crystalline derivative can be prepared and which is clearly not homogeneous. By restricting the amount of methylcarbimide to one molecular proportion and carrying out the reaction in ethereal solution in the presence of a trace of the sodium salt of the phenol, formed by addition of a fragment of metallic sodium to the ethereal solution of the phenol, it has been possible to isolate the *o*-isomeride in a pure state. Identical conditions cannot, unfortunately, be employed for the preparation of the *p*-isomeride owing to the insolubility of the phenol in ether. If, in this case, benzene is employed as solvent in place of ether, the conditions being otherwise the same as those used for the *o*-isomeride, an oil is obtained which, although it is clearly not completely homogeneous, nevertheless yields a considerable proportion of the hydrochloride of the required urethane. Attempts to recover this urethane in a pure state from its hydrochloride, employing extremely mild conditions for the purpose, have failed. This failure may be connected with the instability of the urethanes. Instances are cited in the experimental section of decompositions which have occurred on the application of heat during the course of the preparation of the urethanes, and it has, in fact, been found advisable to carry out all stages of the preparation as far as possible at room temperature. Nevertheless, once the urethanes or their salts have been obtained in a solid state, they appear, as far as observation extends, to be quite stable in this condition at normal room temperature.

It was anticipated that the relative strengths as miotics of the hydrochlorides and methiodides of the methylurethanes of the isomeric α-hydroxyphenylethyldimethylamines would correspond to those of the similar salts of the methylurethanes of the isomeric hydroxybenzyldimethylamines. This, however, has not proved to be the case. In the latter series (benzyl series) the activities of the hydrochlorides were in the order $o > p > m$; in the former (α-phenylethyl series) the order has been found to be $m > o, p$; and, just as in the benzyl series the *o*-compound was much more active than either the *p*- or the *m*-isomeride, so in the α-phenylethyl series the *m*-compound has proved to be much more active than the *o*- and *p*-, the latter two isomerides being, in fact, only feebly active. In both series conversion of the tertiary bases into quaternary ammonium salts increased the miotic activity of the *o*- and diminished that of the *m*- and *p*-isomerides, the methiodides of the *p*-compounds being, indeed, inactive in the dilutions employed.

From the many examples which have now been brought forward, it is clear that the physiological properties of urethanes of the type discussed are due to the phenylcarbamate structure common to them all. The basic group, the presence of which is necessary on other grounds, is also probably essential to the activity of the compounds. In any case, variation in the nature of this group, such as the conversion of the tertiary base into a quaternary ammonium salt, or even a change in its position relative to the urethane grouping, is seen to exert a profound influence on the activity of the compounds. It is not proposed, however, to discuss the problem of the origin of these influences until further work on the pharmacological action of these compounds, which has now been commenced, is completed.

EXPERIMENTAL.

m-*Methoxyphenylmethylcarbinol.*—A solution of 60 g. of *m*-methoxybenzaldehyde in an equal volume of dry ether was added slowly to a solution of magnesium methyl iodide, prepared from 12 g. of magnesium and 68 g. of methyl iodide, in 500 c.c. of dry ether. The solution was then boiled under reflux for 30 minutes. On cooling, white crystals of the addition compound separated. The product was decomposed with hydrochloric acid and ice, and the ethereal solution separated and dried over calcium chloride. Evaporation of the ether yielded a straw-coloured liquid which was distilled under diminished pressure, *m*-methoxyphenylmethylcarbinol being obtained in practically theoretical yield as a colourless viscous liquid, b. p. 133°/14·5 mm.

α-m-*Methoxyphenylethyldimethylamine.*—A solution of the carbinol from the above experiment in 300 c.c. of benzene was saturated with dry hydrogen bromide. After the water formed in the reaction had been separated from the brown solution, the benzene and hydrogen bromide were removed by distillation under diminished pressure at a bath temperature not exceeding 35°. The crude α-*m*-methoxyphenylethyl bromide was dissolved in an equal volume of benzene, and the solution added slowly with gentle shaking to a solution of 50 g. of anhydrous dimethylamine in 250 c.c. of benzene cooled in a freezing mixture. After standing over-night, the solution was filtered from the dimethylamine hydrobromide which had separated, and extracted with hydrochloric acid. The acid extract was shaken with a small volume of ether to remove traces of benzene, and the base precipitated with sodium hydroxide and extracted with ether. After drying over sodium sulphate, the ether was removed and the residue distilled under diminished pressure.

α-*m*-Methoxyphenylethyldimethylamine is a colourless liquid, b. p. 118—119°/17 mm. (yield, 50 g.).

The hydrochloride is very soluble in alcohol, but is precipitated from the solution, by the slow addition of ether, in colourless prisms, m. p. 105° after softening at 101°.

The *methiodide* crystallises in flat, pale cream prisms, m. p. 142°, from alcohol, in which it is very soluble, on the addition of ether (Found : I, 39·4. $C_{12}H_{20}ONI$ requires I, 39·6%).

α-m-*Hydroxyphenylethyldimethylamine.*—A solution of the corresponding methoxy-compound (50 g.) in 200 c.c. of constant-boiling hydrobromic acid was boiled under reflux for 5 hours. After removal of the hydrobromic acid by distillation under diminished pressure, the residual syrup was dissolved in water, the solution made alkaline with sodium carbonate, and the precipitated oil extracted with ether. From the dried extract, an oil was obtained which rapidly crystallised (yield, 45 g.). When recrystallised by the slow addition of light petroleum to its solution in benzene, α-*m*-hydroxyphenylethyldimethylamine forms prisms, m. p. 87—88°. In the preparation of this phenol it is essential, if considerable losses are to be avoided, to boil the methoxy-compound with hydrobromic acid for a sufficient length of time to hydrolyse the methoxy-group completely, since a separation of the methoxy-compound from the phenol cannot be effected quantitatively by the customary methods. For instance, in an early experiment, an aqueous solution of the hydrobromide, prepared as described above, was made strongly alkaline with sodium hydroxide and then extracted with ether with a view to removing any unchanged methoxy-compound which might be present. On evaporation of the ether, however, the residual oil crystallised and proved to be the required phenol, identical with a larger fraction obtained by extracting the mother-liquor, made alkaline with sodium carbonate. The acidic properties of this phenol are apparently so weak that its sodium salt is hydrolysed even in strongly alkaline solutions.

The *hydrochloride* crystallises from alcohol in colourless prisms, m. p. 197—198° (Found: Cl, 17·5. $C_{10}H_{15}ON,HCl$ requires Cl, 17·6%). The methiodide separates as micro-crystals, m. p. 160° after softening at 145°, from alcohol–ether.

α-o-*Methoxyphenylethyldimethylamine.*—*o*-Methoxyphenylmethylcarbinol was prepared from *o*-methoxybenzaldehyde (Baeyer and Villiger, *Ber.*, 1902, **35**, 3013) and magnesium methyl iodide. It was obtained as a thick oil, b. p. 128°/17 mm. (compare Pschorr and Einbeck, *Ber.*, 1905, **38**, 2077). This was treated successively with hydrobromic acid and dimethylamine under the same conditions as the *m*-isomeride. α-*o*-Methoxyphenylethyldimethylamine was thus obtained as a liquid, with a faint greenish-yellow colour, which, in two different experiments, had b. p. 105—107°/12 mm. and 108·5°/13·5 mm.

The hydrochloride was obtained as an oil which could not be crystallised. The *methiodide* separated from alcohol–ether in cream-coloured prisms, m. p. 136—137° (Found: I, 39·7. $C_{12}H_{20}ONI$ requires I, 39·6%).

α-o-*Hydroxyphenylethyldimethylamine.* — Hydrolysis of the methoxy-compound was effected as in the case of the *m*-isomeride. Conversion into the phenol was never, however, complete. It was therefore necessary to extract the product successively from solutions made alkaline with sodium hydroxide and with sodium carbonate. The extract from the former solution was a mixture of unchanged methoxy-compound and phenol, and that from the latter was practically pure phenol. On prolonged boiling with hydrobromic acid, considerable decomposition occurred in which dimethylamine was removed from the phenolic base. α-*o*-Hydroxyphenylethyldimethylamine is a colourless oil, b. p. 112—114°/14 mm.

The *hydrochloride*, m. p. 136—137°, crystallises on the slow addition of ether to its solution in alcohol (Found: Cl, 17·5. $C_{10}H_{15}ON,HCl$ requires Cl, 17·6%). An aqueous solution of this salt of the phenol gives an intense violet coloration with ferric chloride.

The reaction with methyl iodide yielded a sticky product from which, by crystallisation from alcohol, tetramethylammonium iodide was isolated. The methiodide is evidently unstable and decomposes with the elimination of the basic group.

p-*Methoxyphenylmethylcarbinol.*—This was prepared from anisaldehyde by the method employed for the *o*- and *m*-isomerides.

In the decomposition of the addition compound with magnesium methyl iodide care must be taken to prevent the solution from becoming acid, otherwise dehydration occurs with the formation of the corresponding styrene or its polymerisation products. For instance, in one experiment in which the carbinol was extracted from acid solution, an attempt was made to distil the product under diminished pressure. The boiling point rose slowly and continuously and the distillate became extremely viscid on standing. In a second similar experiment dehydration and polymerisation occurred even without distillation. In view of these results no further attempt has been made to distil this carbinol, but the crude product obtained by extracting the alkaline solution with ether has been employed for the following experiments without further purification.

α-*p*-Methoxyphenylethyldimethylamine, a colourless liquid, b. p. 118°/14 mm., was prepared from the carbinol by the procedure adopted in the case of its isomerides (yield, 55·5 g. from 60 g. of anisaldehyde).

The *hydrochloride* crystallises from alcohol–ether in small prisms, m. p. 213° (Found : Cl, 16·2. $C_{11}H_{17}ON,HCl$ requires Cl, 16·5%). The methiodide is readily soluble in alcohol, but separates from alcohol–ether in plates, m. p. 128—130°.

Di-[α-p-*methoxyphenylethyl*]*dimethylammonium Bromide*.—When 57 g. of anhydrous dimethylamine were added to a benzene solution of crude α-*p*-methoxyphenylethyl bromide, prepared from 60 g. of anisaldehyde, a vigorous reaction took place and a considerable amount of solid slowly separated. This was filtered off, treated with water to remove the dimethylamine hydrochloride, and crystallised from alcohol, *di*-[α-p-*methoxyphenylethyl*]*dimethylammonium bromide* being obtained in thick plates, m. p. 109° (Found : loss on drying, 4·7. $C_{20}H_{28}O_2NBr,H_2O$ requires H_2O, 4·4%. Found in material dried in a vacuum : Br, 21·1. $C_{20}H_{28}O_2NBr$ requires Br, 20·3%). A further quantity separated as an oil ,which slowly solidified, when the aqueous mother-liquor was made strongly alkaline with sodium hydroxide. The benzene mother-liquor was worked up for α-*p*-methoxyphenylethyldimethylamine in the usual manner (yield, only 25 g.). The above quaternary bromide was not formed when the α-methoxyphenylethyl bromide was slowly added to a cooled solution of the dimethylamine in benzene in the manner described in the preceding experiments.

α-p-*Hydroxyphenylethyldimethylamine*.—The product of the hydrolysis of the methoxy-compound with hydrobromic acid was obtained as a thick purple oil, from which the hydrobromide of the phenolic base partly crystallised on cooling. The phenol liberated from this in the manner described for its isomerides was contaminated with a brown impurity which could not be completely removed by repeated crystallisations. The semi-crystalline mass was therefore ground with cold acetone, in which the hydrobromide is practically insoluble, and the residue washed thoroughly with acetone; an almost colourless, crystalline powder (64 g. from 55·5 g. of methoxy-base) was thus obtained. After recrystallisation from alcohol this was decomposed with sodium carbonate, and the phenolic base extracted with ether. α-*p*-Hydroxyphenylethyldimethylamine crystallises from benzene–light petroleum and has m. p. about 115° (not sharp).

The hydrobromide crystallises from alcohol, in which it is sparingly soluble, in long prisms, m. p. 178°. It is readily soluble in water and sparingly soluble in hot acetone. The *hydrochloride* crystallises from alcohol in rosettes of needles, m. p. 183° (Found: Cl, 17·7; N, 7·0. $C_{10}H_{15}ON,HCl$ requires Cl, 17·6; N, 6·9%). In aqueous solution it gives an intense violet coloration with ferric chloride. The methiodide could not be prepared. It apparently decomposes in a manner similar to its *o*-isomeride.

Methylurethane of α-m-*Hydroxyphenylethyldimethylamine.*—A solution of 4 g. of the phenol in 10 c.c. of benzene was treated with 2·1 c.c. (about 2 mols.) of methylcarbimide. On the following day the solvents were evaporated under diminished pressure, the residue was dissolved in ether, and the supersaturated solution of the urethane thus obtained rapidly filtered from a small quantity of brown material. The urethane partly crystallised from the filtrate and a further quantity was obtained on concentration of the ethereal solution (total yield, 3·6 g.). The *methylurethane* of α-*m*-hydroxyphenylethyldimethylamine is moderately easily soluble in benzene, although it can be crystallised from this solvent, and insoluble in light petroleum. It is best crystallised from ether, from which it separates as tablets with triangular ends, m. p. 86° (Found : N, 13·0. $C_{12}H_{18}O_2N_2$ requires N, 12·6%).

The hydrochloride was prepared from the base and hydrogen chloride in cold alcohol, and separated on the addition of dry ether. It is very soluble in alcohol, insoluble in acetone, and separates from alcohol–ether in rosettes of prisms which melt incompletely and with effervescence at 169°. In the preparation of this hydrochloride it appears essential to use cold reagents. On one occasion the solid base was warmed with alcoholic hydrogen chloride on the water-bath to hasten solution : addition of ether precipitated an oil which would not crystallise. It is probable that warming caused partial hydrolysis of the urethane group with the consequent formation of a mixture of products.

When methyl iodide is added to a solution of the base in acetone, the *methiodide* separates slowly as an oil which slowly crystallises—a process which is accelerated by seeding. When ether is added to an alcoholic solution of the methiodide, this again separates as an oil which only crystallises after some hours. It then has m. p. about 130° (effervescence and after previous sintering) and is quite pure (Found : I, 34·8. $C_{13}H_{21}O_2N_2I$ requires I, 34·9%).

Methylurethane of α-o-*Hydroxyphenylethyldimethylamine.*—After a number of experiments carried out in benzene solution, from which no homogeneous product could be isolated, this urethane was finally obtained under the following conditions. A trace of metallic sodium was added to a solution of 1 g. of the phenol in 5 c.c. of ether. The sodium dissolved with the evolution of hydrogen. Methylcarbimide (0·48 c.c.; 1 mol.) was then added, and the mixture allowed to stand. After 2 days, large crystals of the urethane separated. The supernatant liquid was decanted and the crystals were washed with a small volume of ether, dissolved in warm benzene, and filtered from a small quantity of flocculent material; the urethane then separated in prisms, m. p. 90°. Addition of light petroleum to the benzene solution caused the separation of a further quantity of the urethane. The ethereal mother-liquor from the above preparation was evaporated under diminished pressure at room temperature; the oily residue slowly crystallised. The crystals were dissolved in a small volume of ether, but on evaporation of the latter on a water-bath the residue failed to crystallise, apparently owing to partial decomposition of the urethane during the evaporation.

The hydrochloride separates in crystalline form from alcohol–ether, but is so extremely hygroscopic that it is transformed into a pasty mass during the short time necessary for filtration. The *methiodide* separates from a solution of the base and methyl iodide in acetone on the addition of ether. When recrystallised from acetone, it forms prisms, m. p. 148° (efferv.) (Found : I, 34·3. $C_{13}H_{21}O_2N_2I$ requires I, 34·9%).

Methylurethane of α-p-*Hydroxyphenylethyldimethylamine.*—Attempts to prepare this urethane in the free state have not been successful. Of six experiments carried out under various conditions, the following gave the best result. A trace of sodium was added to a solution of 2 g. of the phenol in 15 c.c. of benzene. When this had dissolved, 1 c.c. of methylcarbimide was added, the solution being kept cool in ice. After 2 days, a small quantity of amorphous material was removed by filtration and the solvents were evaporated under diminished pressure at low temperature. The oily residue, which showed no signs of crystallising even after some days, was dissolved in ether and treated with alcoholic hydrogen chloride; the *hydrochloride* of the required urethane then separated as a sticky mass which became solid on the addition of further alcohol and rubbing (yield, 1·4 g.). It was recrystallised from alcohol and had m. p. 203° after previously sintering (Found: N, 10·9. $C_{12}H_{18}O_2N_2$,HCl requires N, 10·8%). In an attempt to recover the urethane a suspension of the hydrochloride (0·5 g.) in ether was treated with 40 c.c. of *N*/10-sodium carbonate, and the base extracted with ether. Evaporation of the dried ethereal extract at low temperature left a thick oil which would not crystallise. Its solution in acetone was therefore treated with methyl iodide; the *methiodide* separated as an oil which subsequently crystallised. Recrystallised from alcohol, it formed plates, m. p. 173° (efferv.) (Found: I, 35·2. $C_{13}H_{21}O_2N_2I$ requires I, 34·9%).

Miotic Action of Urethanes.—The three urethanes have been tested for miotic activity in the form both of their hydrochlorides and methiodides by instillation into cats' eyes. For this purpose 1·5% solutions of the substances in physiological saline have, in general, been employed. In the case of the hydrochloride of the methylurethane of α-*o*-hydroxyphenylethyldimethylamine, which is extremely hygroscopic, the free urethane was dissolved in the calculated quantity of 0·153*N*-hydrochloric acid and then diluted to 1·5% with physiological saline. With the exception of the methiodide of the methylurethane of α-*p*-hydroxyphenylethyldimethylamine, which had no action at this dilution, a contraction of the pupil resulted in each case, the extent of the miosis differing with the various substances employed. The estimated order of activity is: *m*-HCl>*o*-MeI>*p*-HCl, *o*-HCl, *m*-MeI>*p*-MeI. This order can, of course, only be regarded as a provisional one until the activities on other organs have been compared. Nevertheless it should be pointed out that the observed activities of *p*-HCl, *o*-HCl, and *m*-MeI were, in the dilutions employed, quite small, those of the *m*-HCl and *o*-MeI being very much greater. In the case of the *m*-HCl the action was extremely intense and persisted for a period exceeding 18 hours. It is probable that the miotic activity of this substance approaches, if not equals, that of physostigmine.

The expenses of this investigation, which has been carried out during the tenure by one of us of a Carnegie Teaching Fellowship, have been partly met by grants from the Moray Research Fund of this University.

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[*Received, December* 13*th*, 1928.]