III. STUDIES ON THE RELATIONSHIP BETWEEN CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION.

PART II. THE MIOTIC ACTIVITY OF URETHANES DERIVED FROM THE ISOMERIC HYDROXY- BENZYL-DIMETHYLAMINES.

By EDGAR STEDMAN.

From the Department of Medical Chemistry, University of Edinburgh.

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IN Part I of this series, the author [1926] synthesised, and tested for miotic activity, a number of substituted phenyl esters of substituted carbamic acids, thereby demonstrating that miotic activity was frequently associated with urethanes of this type. While certain variations could be made in the urethane grouping without necessarily destroying the activity of the compounds, greatest activity was observed with those urethanes which were esters of methylcarbamic acid. It was further found that both the nature and position of the basic group, which was present in all the compounds examined, could be varied without in all cases destroying the physiological properties of the urethane grouping. Nevertheless, an examination of the isomeric dimethylaminophenyl esters of methyl- and ethyl-carbamic acids showed that the power of these compounds to produce a contraction of the pupil varied according to the relative positions of the basic and urethane groupings, and, further, that conversion of the tertiary basic group into a quaternary ammonium grouping exerted a great influence on this power, in some cases increasing, and in others diminishing, the miotic activity. By application of the polarity theory the deduction was made that, for each series of isomeric urethanes examined, greatest activity was exhibited by those urethanes derived from the phenols with the smallest acidic properties, and the same conclusion can be reached by application of the more modern electronic theories.

In view of these results it appeared of interest to examine a new series of isomeric urethanes. The urethanes derived from the isomeric hydroxybenzyl-dimethylamines have therefore been prepared and tested for miotic activity. This particular series was chosen for two reasons. Firstly, it was desired to obtain substances the salts of which would not undergo appreciable hydrolytic dissociation in solution, as was the case when the basic group was attached directly to the benzene ring, since these would be more suitable for complete

pharmacological investigation. Secondly, it was hoped to gain further information regarding the relation between the miotic activity of the urethane and the acidic strength of the phenol from which it was derived.

The methods employed for the preparation of these compounds are described below and only one point requires comment. Whereas the dimethylaminophenols react smoothly with methyl *isocyanate* to give the urethanes described in Part I, the reaction in the case of the hydroxybenzyl dimethylamines is much more complicated. Using the conditions previously employed, the products from the *ortho*- and *para*-compounds appear to consist of a mixture of substances from which the required urethane can only be isolated with difficulty, if at all. By suitably modifying the conditions these difficulties have been overcome and, by strictly adhering to the conditions described in the experimental portion, the *N*-methylurethanes have been obtained in practically quantitative yield. In the case of the *N*-ethylurethanes, however, the difficulties have not been completely surmounted and these have only been isolated in the form of their salts.

Of the urethanes of this series which it has been possible to test, miotic activity has been confined to those which are esters of methylcarbamic acid; no activity has been observed with *N*-ethyl- or *N*-phenyl-urethanes. This corresponds with the results described in Part I, from which it was concluded that greatest activity was associated with esters of methylcarbamic acid. In conformity with the previous results, it has further been found that the activities of the three isomeric *N*-methylurethanes vary in intensity, the estimated order of the activities of the hydrochlorides being *ortho*- > *para*- > *meta*-. Not only does this order correspond with that of the lower homologues, but the difference between the activities of the *ortho*- and *para*-compounds has again proved to be much greater than that between the *para*- and *meta*-. Conversion of the tertiary basic group into the quaternary ammonium group intensifies the activity of the *ortho*-, diminishes that of the *meta*-, and abolishes that of the *para*-compound. This accords with the behaviour of the urethanes from the dimethylaminophenols in so far as the activities of the salts of the tertiary bases are different from those of the quaternary salts, but not as regards the direction in which the change occurs with the different isomerides. The author had hoped that it would have been possible to deduce the relative acidic strengths of the phenolic groups in the isomeric hydroxybenzyl dimethylamines (and in their quaternary ammonium salts) from electronic theories, but unfortunately it appears impossible to do so in the present state of the development of these theories. Hence, while it is not improbable that the urethanes of these series which are the most active miotics are again those derived from the least acidic phenols, a discussion of this point must be deferred until it has been possible to measure directly the acidic strengths in question.

In Part I it was tacitly assumed that the miotic activity of the active urethanes was associated with the fact that they were phenyl, as distinguished

from alkyl, esters of carbamic acids, but no proof was advanced that similar activity might not be exhibited by urethanes derived from alcohols, provided these contained a basic group. The methylurethanes of two amino-alcohols, namely, dimethylaminoethyl alcohol and tropine, have accordingly been prepared. As anticipated, neither possessed miotic properties. Owing to the failure to obtain the hydrochloride of the first-named urethane in a crystalline condition the substance was tested in the form of its methiodide, which was therefore the methylurethane of choline iodide. It is interesting to note that the methylurethane of tropine exhibited neither miotic nor mydriatic properties. That it is not a mydriatic corresponds, of course, with the fact that the tropine is esterified with an aliphatic acid.

EXPERIMENTAL.

Urethanes derived from m-hydroxybenzyl dimethylamine.

Methylurethane of m-hydroxybenzyl dimethylamine. Finely powdered *m*-hydroxybenzyl dimethylamine (1 g.), prepared according to the author's method [1927], was treated with excess of methyl isocyanate. The phenol dissolved slowly with slight evolution of heat. The mixture was cooled in ice and, after 24 hours, light petroleum added. This caused the precipitation of only a small amount of oil. Hence all solvents were removed by distillation under diminished pressure, when the oily residue slowly crystallised. It was recrystallised by addition of light petroleum to its solution in benzene, when it formed thick plates which melted at 86°.

The *hydrochloride* separated from a solution of the base in alcoholic hydrochloric acid. Recrystallised from alcohol, it formed radiating clusters of prisms which melted at 175° with effervescence.

Analysis. 0.2448 g. gave 0.1423 g. AgCl.
9.06 mg. contained 1.05 mg. N (micro-Kjeldahl).
Cl found, 14.4 %; calc., 14.5 %.
N found, 11.6 %; calc., 11.5 %.

The *methiodide* was prepared by treating the base with excess methyl iodide and sufficient methyl alcohol to cause the solid to dissolve. After standing overnight the methiodide was precipitated by addition of dry ether. When recrystallised from alcohol it formed aggregates which melted at 162°.

Ethylurethane of m-hydroxybenzyl dimethylamine. The finely powdered phenol was dissolved in ethyl isocyanate and allowed to stand for 24 hours. Evaporation of the excess of ethyl isocyanate under diminished pressure left an oil which could not be induced to crystallise. It was therefore divided into two portions, one of which was dissolved in alcoholic hydrochloric acid. After a short time the *hydrochloride* separated. It was recrystallised from alcohol when it formed rectangular tablets which melted at 156°.

Analysis. 0.2033 g. gave 0.1140 g. AgCl.
Cl found, 13.9 %; calc., 13.7 %.

The second portion of the crude base was dissolved in acetone and the solution treated with methyl iodide. The *methiodide* separated on standing. When recrystallised from alcohol it formed clusters of irregular plates which melted at 155–156° with effervescence.

Analysis. 0.1452 g. gave 0.0926 g. AgI.
I found, 34.5 %; calc., 34.9 %.

The results of a number of experiments made under varying conditions were practically identical with that of the above example. In no case was the base obtained in a solid condition, although the yield of salt was practically theoretical. Thus, in one experiment, 0.5 g. of *m*-hydroxybenzyltrimethylamine yielded 1.1 g. of the methiodide of the ethylurethane.

Phenylurethane of m-hydroxybenzyltrimethylamine. One molecular proportion (0.36 cc.) of phenyl isocyanate was added to a cooled solution of 0.5 g. of the phenol in 5 cc. of benzene and the mixture left overnight in the refrigerator. The solution was then filtered to remove a small quantity of non-basic material which had separated. Evaporation of the solvents under diminished pressure yielded an oil which rapidly crystallised. When recrystallised from benzene, in which it is fairly soluble, it formed prisms which melted at 93°.

The *hydrochloride* separated when the base was dissolved in alcoholic hydrochloric acid. Recrystallised from alcohol it formed short prisms which melted at 175°.

Analysis. 0.2580 g. gave 0.1185 g. AgCl.
9.88 mg. contained 0.89 mg. N (micro-Kjeldahl).
Cl found, 11.4 %; calc., 11.6 %.
N found, 9.0 %; calc., 9.1 %.

Urethanes derived from p-hydroxybenzyltrimethylamine.

Methylurethane of p-hydroxybenzyltrimethylamine. One molecular proportion (0.24 cc.) of methyl isocyanate was added to a cooled solution of 0.5 g. of the phenol in 5 cc. of benzene, causing the immediate formation of a slight precipitate. After standing overnight, light petroleum was added and a small amount of hygroscopic precipitate removed by filtration. The solvents were then evaporated at low temperature, when the residual oil crystallised. It was recrystallised by addition of light petroleum to a concentrated solution in benzene, when it formed a felted mass of fine crystals which melted at about 72°.

The *hydrochloride* separated when the base was dissolved in alcoholic hydrochloric acid. When recrystallised from alcohol it formed prisms with pyramid ends which melted at about 180° with effervescence.

Analysis. 0.2455 g. gave 0.1423 g. AgCl.
Cl found, 14.3 %; calc., 14.5 %.

The *methiodide* was prepared by addition of methyl iodide to a solution of the urethane in acetone. When recrystallised from alcohol it formed lustrous plates which melted at 188° with decomposition.

The *methochloride* was prepared by shaking for one hour a solution of the methiodide in methyl alcohol with a suspension of freshly precipitated silver chloride in methyl alcohol. The suspension was then filtered and the filtrate evaporated, when the residue, which consisted of the methochloride, crystallised. It was recrystallised from alcohol by the addition of dry ether, when it formed clusters of radiating needles which melted at about 110° with effervescence.

Analysis. 0.1575 g. gave 0.0855 g. AgCl.
Cl found, 13.4 %; calc., 13.7 %.

Ethylurethane of p-hydroxybenzyl dimethylamine. The phenol (1 g.) was dissolved in dry acetone (10 cc.), and the cooled solution treated with one molecular proportion (0.6 cc.) of ethyl isocyanate. The solvents were evaporated on the following day, when the oily residue partly crystallised. It was found impossible, however, to separate the crystals. The product was therefore dissolved in alcoholic hydrochloric acid. On addition of dry ether to this solution the *hydrochloride* separated as an oil which, after repeatedly washing with dry ether, mixtures of ether and acetone, and mixtures of ether and alcohol, finally crystallised. For complete purification it was necessary to recrystallise it three times by addition of ether to its alcoholic solution, when it formed rosettes of plates which melted at 165° with effervescence.

Analysis. 0.2105 g. gave 0.1148 g. AgCl.
Cl found, 13.5 %; calc., 13.7 %.

The same hydrochloride was obtained from the product of the action of an excess of ethyl isocyanate on the phenol.

The *methiodide* was prepared by the addition of methyl iodide to a solution of the crude urethane in methyl alcohol, from which it was precipitated by the addition of dry ether. When recrystallised from alcohol it formed irregular plates which melted at 186° .

Analysis. 0.1787 g. gave 0.1170 g. AgI.
I found, 35.4 %; calc., 34.9 %.

Phenylurethane of p-hydroxybenzyl dimethylamine. One molecular proportion (0.36 cc.) of phenyl isocyanate was added to a cooled solution of 0.5 g. of the phenol in 5 cc. of benzene. The urethane quickly separated as an amorphous precipitate. This was filtered and crystallised from alcohol, when it formed thick prisms which melted at 126° .

The *hydrochloride* crystallised from alcohol in rosettes of needles which melted at 182° .

Analysis. 0.2455 g. gave 0.1132 g. AgCl.
12.72 and 14.19 mg. contained respectively 1.13
and 1.30 mg. N (micro-Kjeldahl).
Cl found, 11.4 %; calc., 11.6 %.
N found, 8.9 and 9.1 %; calc., 9.1 %.

Urethanes derived from o-hydroxybenzyl dimethylamine.

Methylurethane of o-hydroxybenzyl dimethylamine. The phenol (0.5 g.) was dissolved in 5 cc. of ether and a trace of metallic sodium added. This dissolved with the evolution of hydrogen. The solution was then cooled and one

molecular proportion (0.24 cc.) of methyl isocyanate added. After some hours, a small quantity of flocculent material which had separated was removed by filtration and the filtrate evaporated at low temperature, when the residue crystallised. When recrystallised by addition of light petroleum to its solution in benzene it formed flat prisms which melted at 76°.

The *hydrochloride* was hygroscopic and could not be obtained crystalline.

The *methiodide* slowly separated from a solution of the base in acetone to which an excess of methyl iodide had been added. When recrystallised from alcohol it formed small prisms which melted at 175° with decomposition.

Analysis. 0.1565 g. gave 0.1045 g. AgI.
I found, 36.1 %; calc., 36.3 %.

Ethylurethane of o-hydroxybenzylidimethylamine. A number of experiments were carried out under different conditions, but in no case was it possible to isolate the urethane in a pure state. In the following experiment, however, a small quantity was obtained in the form of its methiodide. Attempts which have since been made to prepare larger quantities of this methiodide have unfortunately not been successful, although the experiments have been carried out under conditions as nearly identical as possible.

The phenol (0.5 g.) was dissolved in 5 cc. of dry ether and a trace of metallic sodium added. This dissolved with the evolution of hydrogen, when one molecular proportion (0.3 cc.) of ethyl isocyanate was added. After standing overnight the solution was filtered from a small quantity of insoluble material and the filtrate evaporated. An oil was thus obtained which showed no signs of crystallising. It was therefore dissolved in acetone and excess of methyl iodide added. Addition of ether then precipitated an oily methiodide which, after standing till the next day, crystallised. It was filtered and the sticky substance thus obtained recrystallised from acetone, when it formed prisms which melted at 149° with effervescence.

Analysis. 16.16 and 14.49 mg. contained respectively 1.21
and 1.14 mg. N (micro-Kjeldahl).
N found, 7.5 and 7.8 %; calc., 7.7 %.

Phenylurethane of o-hydroxybenzylidimethylamine. A solution of 0.5 g. of the phenol in 5 cc. of benzene was treated with one molecular proportion (0.36 cc.) of phenyl isocyanate. Some crystalline material separated slowly. This was filtered and washed with light petroleum (yield 0.48 g.). It was then warmed with a small volume of benzene, filtered from some insoluble crystals of a non-basic substance, concentrated, and placed in the refrigerator. A small quantity of the required urethane separated in the form of plates which melted at about 90°.

Analysis. 11.89 mg. contained 1.23 mg. N (micro-Kjeldahl).
N found, 10.4 %; calc., 10.4 %.

This urethane is apparently so unstable that considerable losses occur during recrystallisation.

The *methiodide* was prepared by warming the urethane with methyl iodide, dissolving the oil so produced in methyl alcohol, and then adding acetone and

dry ether, when the methiodide separated as a white solid. It was recrystallised by the slow addition of dry ether to its solution in acetone containing the minimum amount of methyl alcohol, when it formed rosettes of flat prisms which melted at 171°.

Urethanes derived from amino-alcohols.

Methylurethane of choline iodide. 1 g. of hydroxyethyltrimethylamine, cooled in a freezing mixture, was treated with excess of methyl isocyanate. After standing overnight, benzene and light petroleum were added, the mixture stirred, and the supernatant liquid decanted from a small amount of insoluble oil which was not further examined. The solvents were then evaporated, when a colourless liquid was obtained which would neither crystallise nor yield a solid hydrochloride. It was therefore dissolved in methyl iodide. A somewhat vigorous reaction took place and the methiodide separated in crystalline form. After addition of acetone, the crystals were filtered off and recrystallised from alcohol when they formed lustrous plates which melted at 174°.

Analysis. 0.1144 g. gave 0.0923 g. AgI.
I found, 43.6 %; calc., 44.1 %.

Methylurethane of tropine. The tropine, prepared from atropine, was dissolved in methyl isocyanate and allowed to stand for some hours. The excess of methyl isocyanate was then removed under diminished pressure and the residue crystallised from benzene, in which it is fairly soluble, when it formed rectangular plates which melted at about 126°.

The *hydrochloride* was precipitated as a sticky solid by addition of ether to a solution of the base in alcoholic hydrochloric acid. It was crystallised from a mixture of dry ether and alcohol, when it melted at 263° with decomposition.

Miotic activity of urethanes.

The tests for miotic activity were carried out on cats as described in Part I. In general, 2 % solutions of the urethane in Ringer's solution were employed. In the case of the methylurethane of *o*-hydroxybenzyltrimethylamine, the hydrochloride of which has not been obtained in crystalline form, the base was dissolved in the calculated quantity of hydrochloric acid. The results obtained are given in the following table in which the estimated relative intensities of the activities of the active urethanes are indicated.

Substance	Miotic activity
<i>m</i> -NH (CH ₃).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ , HCl ...	... ++
<i>m</i> -NH (CH ₃).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ I ...	... +
<i>m</i> -NH (C ₆ H ₅).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ , HCl ...	... -
<i>m</i> -NH (C ₆ H ₅).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ I ...	... -
<i>m</i> -NH (C ₆ H ₅).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ , HCl ...	... -
<i>p</i> -NH (CH ₃).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ , HCl ...	... +++
<i>p</i> -NH (CH ₃).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ I ...	... -
<i>p</i> -NH (C ₆ H ₅).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ , HCl ...	... -
<i>o</i> -NH (CH ₃).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ , HCl ...	... ++++
<i>o</i> -NH (CH ₃).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ I ...	... ++++
<i>o</i> -NH (C ₆ H ₅).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ I ...	... -
NH (CH ₃).CO.O.C ₆ H ₄ .CH ₂ .N (CH ₃) ₃ I ...	... -

SUMMARY.

1. The methyl-, ethyl- and phenyl-urethanes of the isomeric hydroxybenzyl-dimethylamines, and the methylurethanes of choline iodide and tropine have been prepared and, where possible, tested for mitotic activity.

2. Mitotic activity was confined to the methylurethanes of the isomeric hydroxybenzyl-dimethylamines, the urethanes of choline iodide and tropine being inactive in 2 % solutions. This confirms the view that activity is associated with the fact that the mitotics are substituted phenyl, as distinguished from alkyl, esters of carbamic acids.

3. The activities of the methylurethanes of the isomeric hydroxybenzyl-dimethylamines are estimated to be in the order *ortho*- > *para*- > *meta*-. Conversion of the tertiary basic group into the quaternary ammonium group increased the activity of the *ortho*-compound, diminished that of the *meta*-, and abolished that of the *para*-.

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