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

PART I. POSITION ISOMERISM IN RELATION TO THE MIOTIC ACTIVITY OF SOME SYNTHETIC URETHANES.

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PHYSOSTIGMINE occurs in the ripe seed of *Physostigma venenosum*, Balfour. It is employed therapeutically in virtue of its power, when applied locally to the eye, of producing miosis and simultaneously causing a reduction in intra-ocular pressure. Its general pharmacological action is to stimulate the peripheral nerve-endings of the parasympathetic system, its action in this respect being antagonistic to that of atropine. The particular grouping responsible for this specific action of physostigmine has hitherto escaped recognition, partly, no doubt, owing to the incomplete knowledge which, until recently, has existed regarding the structure of this alkaloid. It has been known since the work of Salway [1912] and Straus [1913, 1914], who revised the views of earlier workers, and of Polonovsky and Nitzberg [1916], who effected the partial synthesis of physostigmine by allowing eseroline and methyl isocyanate to interact under appropriate conditions; that physostigmine is the methyl carbamido-derivative of a phenolic compound, eseroline, which is produced when the alkaloid is hydrolysed. During an investigation of the constitution of physostigmine the author [1924] succeeded in synthesising the ethyl ether of a substance, physostigmol, which had previously been obtained by Straus by the dry distillation of eseroline methiodide. Physostigmol was thus shown to have the structure I, a result which, combined with the results of other workers mentioned above, indicated that grouping II was present in the physostigmine molecule. Subsequently the work was extended by Stedman and Barger [1925] who showed that the structure of physostigmine could be

represented by formula III. In view of the fact that eseroline does not possess the pharmacological properties of physostigmine, the synthesis of physostigmol and the demonstration that grouping II was present in the alkaloid led to the suggestion that the physiological properties of physostigmine depended upon the fact that the alkaloid was a phenyl ester of methylcarbamic acid (*i.e.* a urethane), and experiments were at once undertaken to determine whether similar esters of simpler phenols would possess the same properties.

The number of phenols from which urethanes of the required type could be prepared is, of course, extremely large and it was decided, in the first instance, to confine the work to those of a simple nature, bearing in mind the necessity for the introduction of a basic group in order to permit the formation of soluble salts. The simplest phenols fulfilling this last condition are the aminophenols. In view, however, of the fact that the method contemplated for the preparation of the urethanes consisted in allowing the phenol to interact with methyl isocyanate and that the latter substance also reacts with amino-groups with the formation of substituted urea derivatives, the use of the aminophenols would lead to the formation of unnecessarily complicated molecules in which the urea grouping might conceivably mask the properties of the urethane grouping and, in any case, would cause the compounds to be of such a feebly basic nature that their salts would undergo hydrolytic dissociation with the production of strongly acid solutions and possibly the precipitation of the base. While this difficulty might be overcome by modifying the method of preparation, it appeared preferable to eliminate entirely the possibility of such a complication by methylation of the amino-group. The urethanes described in the experimental portion are therefore mainly derivatives of the three isomeric dimethylaminophenols. Variations have been made in the urethane grouping itself in order to determine what influence this had on the physiological properties. A few preliminary experiments with other phenols have also been carried out. The results of these together with a description of some compounds prepared incidentally in the course of this work are included in the experimental portion.

EXPERIMENTAL.

Preparation of o-, m- and p-dimethylaminophenol. Of the three isomerides, only the *meta*-compound, which is an intermediate in the preparation of dye-stuffs, can be obtained commercially; this source of the phenol was utilised during the later stages of this investigation, but in the first experiments it

was prepared by a method similar to that employed in the case of the *ortho*- and *para*-isomerides and described below. *o*-Dimethylaminophenol was prepared by Griess [1880] by the distillation of the corresponding methochloride under normal pressure, and the *para*-compound by Pechmann [1899] by similar means, using, however, the quaternary iodide and carrying out the distillation under diminished pressure. The latter method was adopted in the case of all isomerides. For the preparation of the quaternary iodides it was found convenient to modify the methods of Griess and Pechmann. The dimethylaminophenol was dissolved in methyl alcohol, an equal weight of finely powdered, anhydrous sodium carbonate and slightly more than three molecules of methyl iodide added, and the mixture refluxed for about 10 hours, small additional quantities of methyl iodide being occasionally added to compensate for that carried out of the condenser by the carbon dioxide liberated in the reaction. In the case of the *meta*- and *para*-isomerides, 40 cc. of methyl alcohol were employed for 10 g. of aminophenol. When the reaction was complete the mixture was cooled and the methiodide filtered and recrystallised from methyl alcohol. In this way 10 g. of aminophenol yielded 20 g. of pure methiodide. For the preparation of the *ortho*-compound 50 cc. of methyl alcohol were used for 10 g. of aminophenol. The methiodide did not, in this case, separate from the reaction mixture but was precipitated by addition of dry ether (yield: 17 g. from 10 g. of aminophenol). It is suitable in this form for distillation, but may, if desired, be purified by recrystallisation from water.

Owing to the ease with which the dimethylaminophenols undergo oxidation with the formation of coloured products, these substances were only prepared in small quantities as required for immediate use. The quaternary iodide was distilled under diminished pressure, the distillate taken up in ether, filtered from any methiodide which had been formed by recombination, and the ether evaporated.

URETHANES DERIVED FROM *p*-DIMETHYLAMINOPHENOL.

p-Dimethylaminophenyl ester of methylcarbamic acid. 1.4 g. of *p*-dimethylaminophenol were dissolved in dry ether (5 cc.), an excess of methyl isocyanate was added, and the mixture left overnight. The urethane, which had meanwhile separated in crystalline form, was then filtered and washed with ether (yield 1.3 g.). When recrystallised from alcohol it forms lustrous plates which melt at 131°.

The *hydrochloride* was obtained by dissolving 0.7 g. of the base in an alcoholic solution of hydrochloric acid. It rapidly commenced to separate in crystalline form, and, after addition of ether, was filtered (yield 0.8 g.). When recrystallised from a mixture of acetone and alcohol, it forms prisms which melt at 157°.

Analysis. 0.2016 g. gave 0.1228 g. AgCl.

Cl found, 15.1 %; calc., 15.4 %.

The *methiodide* separates when a solution of the urethane in methyl iodide is allowed to stand for some hours. A further quantity is precipitated on the addition of ether. It can be recrystallised from alcohol, when it forms plates which melt at 170° with effervescence.

The *picrate* is only sparingly soluble in alcohol. When recrystallised from aqueous alcohol, it forms long prisms which melt at about 179° with decomposition.

p-Dimethylaminophenyl ester of ethylcarbamic acid. This substance was originally prepared without difficulty by a method similar to that described above for the lower homologue, when 1.9 g. of the urethane were obtained from 1.6 g. of the phenol. In subsequent experiments, however, addition of ethyl isocyanate to an ethereal solution of *p*-dimethylaminophenol caused the formation of a brown substance which rendered purification of the urethane difficult. Whether this was due to the presence of impurities in either the phenol or the ethyl isocyanate, or whether some other factor was responsible, is not at present known. It is probable that impurities were present in the isocyanate, for while the same difficulties were encountered in the preparation of other *N*-ethyl urethanes, this was not the case with the corresponding *N*-methyl urethanes. Although the formation of the brown impurities could not be entirely prevented, the following example indicates how the pure urethane may be obtained. The *p*-dimethylaminophenol prepared from 5 g. of the methiodide was dissolved in ethyl isocyanate. By the next day the mixture had solidified. It was ground up with a little ether, filtered, and washed with small quantities of ether (yield, 1.7 g.). The product so obtained was slightly brown and was purified by dissolving in benzene, adding light petroleum until the coloured impurities were precipitated, and decanting the clear supernatant liquid. The process was repeated on the brown residue and the solutions united and diluted with light petroleum. On standing the urethane separated in crystalline form. It can be recrystallised from benzene or alcohol and forms plates which melt at 123° .

The *hydrochloride*, prepared by treating the base with an alcoholic solution of hydrochloric acid and adding ether, crystallises from acetone in lustrous plates which melt at 77° .

Analysis. 0.2186 g., when dried *in vacuo*, lost 0.0148 g.

0.2038 g. (dried *in vacuo*) gave 0.1183 g. AgCl.

H₂O found, 7.3 %; calc. for 1H₂O, 6.9 %.

Cl found, 14.4 %; calc., 14.5 %.

The *methiodide* may be prepared as in the case of the lower homologue. It may be recrystallised from a mixture of acetone and alcohol and melts at 160° with effervescence.

The *picrate*, when recrystallised from alcohol, sinters at 145° and melts at 158° .

p-Dimethylaminophenyl ester of phenylcarbamic acid. A solution of 1.5 g. of *p*-dimethylaminophenol in 15 cc. of ether was treated with 1.7 cc. of phenyl

isocyanate. After standing overnight the urethane which had separated was filtered and washed with ether (yield 1.9 g.). When recrystallised from alcohol it forms stout prisms which melt at 163°.

The *hydrochloride* is obtained by treating an alcoholic solution of the base with a solution of hydrochloric acid in alcohol and precipitating with ether. Recrystallised from a mixture of alcohol and ether, it forms tabular prisms which melt at 182° with effervescence.

Analysis. 0.2117 g. gave 0.1026 g. AgCl.

Cl found, 12.0 %; calc., 12.0 %.

The *methiodide* was prepared by treating 0.2 g. of the base with excess of methyl iodide and sufficient methyl alcohol to produce a clear solution. On standing, the methiodide separated. After the addition of ether it was filtered (yield 0.28 g.) and recrystallised from a mixture of methyl and ethyl alcohols when it formed plates which melted at 169°.

The *picrate* is sparingly soluble in ethyl alcohol. When recrystallised from this solvent it forms tabular prisms which melt at 177° with decomposition.

Attempted preparation of the p-dimethylaminophenyl ester of carbamic acid. It was thought that it would be possible to obtain this substance by passing an excess of phosgene gas through a solution of the aminophenol in an inert solvent, separating the chlorocarbonic ester of the phenol (which, it was anticipated, would be formed) from the other products, and treating this with dry ammonia. This method did, in fact, succeed in the case of the *meta*-isomeride, but with the *para*- and *ortho*-compounds only the diphenyl carbonates could be isolated from the products of the reactions. The conditions were varied by dropping an ethereal solution of the phenol into liquid phosgene cooled in a freezing mixture, but with no better results. Only the former experiment need, therefore, be described.

A stream of phosgene gas was passed through a solution of 3 g. of *p*-dimethylaminophenol in 30 cc. of ether for about half an hour. The sticky precipitate which at first formed slowly became granular, a process which was hastened by rubbing it with a glass rod. Some liquid phosgene was then added and the flask corked and left for 2 days. After this time the solution was filtered, the solid being stored in a desiccator while the filtrate was evaporated under diminished pressure. The residue from the filtrate, which should have contained the chlorocarbonic ester, was so small that it was not examined further. The solid which had meanwhile been stored in a desiccator was suspended in dry ether and a current of ammonia gas passed through the suspension. This liberated the base which dissolved in the ether. The ethereal solution was then filtered to remove the ammonium chloride which had been formed, and the ether evaporated. An oil which soon crystallised was thus obtained. This consisted of unchanged dimethylaminophenol together with some tetramethyl-*p*-diaminodiphenyl carbonate. The latter was isolated by crystallising the mixture from aqueous alcohol (yield 0.8 g.). When recrystallised from alcohol, *tetramethyl-p-diaminodiphenyl carbonate* forms flat prisms which melt at 157°.

The *hydrochloride*, when recrystallised from methyl alcohol, forms radiating aggregates which melt at 222° with effervescence.

Analysis. 0.1952 g. gave 0.1505 g. AgCl.

Cl found, 19.07 %; calc., 19.04 %.

The required chlorocarbonic ester could probably be prepared by the action of phosgene on the sodium salt of the phenol, but the author has not yet had an opportunity of testing this method.

URETHANES DERIVED FROM *m*-DIMETHYLAMINOPHENOL.

m-Dimethylaminophenyl ester of methylcarbamic acid. The dimethylaminophenol from 5 g. of the methiodide was dissolved in methyl isocyanate and the solution allowed to stand for some hours. Addition of light petroleum precipitated the urethane as an oil which soon crystallised. This was filtered and washed with light petroleum (yield 2.5 g.). It was recrystallised from aqueous alcohol when it formed tablets which melted at 85–86°.

The *hydrochloride* was prepared by dissolving 0.6 g. of the base in alcoholic hydrochloric acid. The salt separated after a short time (yield 0.6 g.). When recrystallised from a mixture of alcohol and acetone it forms prisms which sinter at 164° and melt at 170° with effervescence.

Analysis. 0.2089 g. gave 0.1293 g. AgCl.

Cl found, 15.3 %; calc., 15.4 %.

The *methiodide* can be recrystallised from a mixture of acetone and alcohol when it forms long prisms which melt at 165° with effervescence.

The *picrate*, when recrystallised from aqueous alcohol, forms stout rhombohedral prisms which darken at about 172° and melt at 177° with decomposition.

m-Dimethylaminophenyl ester of ethylcarbamic acid. 2 g. of *m*-dimethylaminophenol were treated with excess of ethyl isocyanate. The liquid immediately became brown and the phenol slowly dissolved. After standing for 2 days, light petroleum was added to the solution. This precipitated a brown oil. The colourless supernatant liquid was decanted and the residual oil treated with benzene and light petroleum in the manner described in connection with the corresponding *para*-compound. From the united solution so obtained, the urethane separated as a white crystalline solid. This was recrystallised twice from aqueous alcohol, when it formed colourless prisms which melted at 99–100°. The final yield obtained was 0.8 g. The considerable losses which occurred were due to the difficulty of separating the coloured by-products. The hydrochloride can be crystallised from alcohol and ether, but is hygroscopic.

The *methiodide* separates from a solution of the base in methyl iodide when this is allowed to stand for 2 days. When recrystallised from alcohol it forms prisms which melt at 152° with effervescence.

Analysis. 0.1179 g. gave 0.0788 g. AgI.

I found, 36.12 %; calc., 36.29 %.

The *picrate* is fairly soluble in alcohol but separates from this solvent on the addition of light petroleum in the form of long prisms which melt at 95°.

m-Dimethylaminophenyl ester of phenylcarbamic acid. 1.5 g. of *m*-dimethylaminophenol were dissolved in 10 cc. of benzene and treated with 1.7 cc. of phenyl isocyanate. The urethane separated on standing. It was filtered, washed with light petroleum (yield 2 g.) and recrystallised from alcohol when it formed prisms which melted at 159°.

The *hydrochloride*, when precipitated by the addition of ether to its alcoholic solution, forms clusters of radiating needles which melt at 180° with effervescence.

The *methiodide* is prepared by treating the base with excess of methyl iodide, and adding sufficient methyl alcohol to cause it to dissolve. After standing for a day the addition of ether precipitates the methiodide. When recrystallised from a mixture of acetone and alcohol it forms flat prisms which melt at 160° with effervescence.

Analysis. 0.1577 g. gave 0.0927 g. AgI.

I found, 31.8 %; calc., 31.9 %.

m-Dimethylaminophenyl ester of carbamic acid. A brisk stream of phosgene gas was passed through a solution of 4 g. of *m*-dimethylaminophenol in 30 cc. of ether for about 30 minutes. The sticky precipitate which formed at the commencement of this process was caused to assume a granular state by rubbing with a glass rod. Some liquid phosgene was then added to the mixture, after which the flask was corked and stored until the following day. The solution was then filtered, the solid being stored in a desiccator while the filtrate was evaporated under diminished pressure. The solid residue from the filtrate was suspended in dry ether and a stream of dry ammonia passed through the suspension for about half an hour. It was then filtered and the filtrate evaporated to dryness. This yielded a small quantity of crystalline material which was, however, too small for further investigation. The solid was then treated with water, which removed the ammonium chloride and any urea which may have been present, and crystallised from aqueous alcohol (yield 0.7 g.). This proved to be the required urethane. When recrystallised from alcohol it forms plates which melt at 137°. The solid which had meanwhile been stored in a desiccator yielded 2.5 g. of unchanged dimethylaminophenol.

The *hydrochloride* of the urethane is sparingly soluble in ethyl alcohol and can be conveniently crystallised from a mixture of ethyl and methyl alcohols, when it forms prisms which melt at 174° with effervescence.

Analysis. 0.1884 g. gave 0.1249 g. AgCl.

Cl found, 16.4 %; calc., 16.4 %.

URETHANES DERIVED FROM *o*-DIMETHYLAMINOPHENOL.

o-Dimethylaminophenyl ester of methylcarbamic acid. An ethereal solution of the *o*-dimethylaminophenol obtained from 5 g. of the corresponding methiodide was treated with excess of methyl isocyanate. After standing for some hours light petroleum was added, which precipitated the urethane. This was filtered and washed with light petroleum (yield 2.5 g.). When re-

crystallised from aqueous alcohol, it forms stout prisms which melt at 76° . The *hydrochloride* is an oil which will not crystallise.

The *methiodide* separates from a solution of the base in methyl iodide when allowed to stand for 2 days (0.2 g. base gave 0.35 g. methiodide). When recrystallised by addition of ether to its solution in acetone, it sinters at $78-80^{\circ}$ and then melts with effervescence.

Analysis. 0.1161 g. gave 0.0807 g. AgI.

I found, 37.6 %; calc., 37.8 %.

The *picrate* crystallises from alcohol in the form of prisms which melt at 152° with effervescence.

o-Dimethylaminophenyl ester of ethylcarbamic acid. The *o*-dimethylaminophenol obtained from 5 g. of the corresponding methiodide was dissolved in ethyl isocyanate and allowed to stand for a day. Addition of light petroleum then precipitated a yellow oil. The yellow impurity was removed by treating the oil with benzene and light petroleum in the manner described above in connection with the isomeric *N*-ethyl urethanes. In this way the urethane was obtained in the form of colourless crystals. It was recrystallised by addition of light petroleum to its solution in benzene, when it separated slowly in the form of large prisms which melted at 61° . The *hydrochloride*, as in the case of other urethanes derived from *o*-dimethylaminophenol, could not be crystallised.

The *methiodide* separates as an oil from a solution of the base in methyl iodide. When the oil is washed with ether and allowed to stand it slowly solidifies (0.2 g. base gave 0.29 g. methiodide). It can be crystallised by slow addition of ether to its alcoholic solution. It melts at 119° with effervescence.

Analysis. 0.1206 g. gave 0.0805 g. AgI.

I found, 36.1 %; calc., 36.3 %.

The *picrate* crystallises from alcohol in the form of prisms which melt at 124° .

o-Dimethylaminophenyl ester of phenylcarbamic acid. 1.6 g. of *o*-dimethylaminophenol were dissolved in 10 cc. of benzene and 1.7 cc. of phenyl isocyanate added. The urethane crystallised from the solution on standing (yield 2.3 g.). When recrystallised from alcohol it forms long prisms which melt at 144° .

Attempted preparation of the o-dimethylaminophenyl ester of carbamic acid. A solution of 3 g. of *o*-dimethylaminophenol in 30 cc. of ether was treated with phosgene in the manner described for the corresponding experiments with the *para*- and *meta*-isomerides, and the product worked up in the same way. The ethereal solution left only negligible amounts of crystalline products. The solid, on the other hand, yielded a mixture of unchanged phenol and tetramethyl-*o*-diaminodiphenyl carbonate, from which the latter was isolated by crystallisation from aqueous alcohol (yield 1 g.). When recrystallised from aqueous alcohol tetramethyl-*o*-diaminodiphenyl carbonate forms prisms with pyramid ends which melt at 72° . The *hydrochloride* could not be obtained in crystalline form.

The *methiodide* crystallises from a solution of the base in methyl iodide when this is allowed to stand for a week (0.2 g. base yielded 0.27 g. *methiodide*). When recrystallised from alcohol and ether, it forms flat prisms which melt at 183° with effervescence.

Analysis. 0.1015 g. gave 0.0800 g. AgI.

I found, 42.6 %; calc., 43.5 %.

URETHANES DERIVED FROM HORDENINE.

Methylcarbamido-derivative of hordenine. Owing to the very limited amount of hordenine available it was not possible to repeat the following experiment, which, although resulting in the preparation of the hydrochloride of the urethane in the pure state, was unsatisfactory in that the urethane itself was not isolated in a pure condition.

1 g. of hordenine was dissolved in 50 cc. of ether, treated with 1 cc. of methyl isocyanate and left for 3 days. Experiments with a test portion then showed that the hordenine was largely unchanged. The solvent was therefore evaporated and the residual oil dissolved in methyl isocyanate. After standing for a day the excess methyl isocyanate was evaporated under diminished pressure, the residual oil dissolved in benzene, and the urethane precipitated by addition of light petroleum. The oily precipitate quickly solidified and was then filtered. Unsuccessful attempts were made to crystallise it from various solvents, during which process the substance became brown in colour. It was therefore dissolved in ether and treated with alcoholic hydrochloric acid. The precipitate which formed was filtered and recrystallised from a mixture of alcohol and acetone. When obtained in this way, the *hydrochloride* of the *methylcarbamido-derivative* of hordenine forms lustrous plates which melt at 161°.

Analysis. 0.2195 g. gave 0.1218 g. AgCl.

Cl found, 13.73 %; calc., 13.73 %.

A small amount of what was probably the free base was obtained from the benzene light petroleum filtrate in the form of clusters of needles which melted at about 65°.

Phenylcarbamido-derivative of hordenine. 0.5 g. of hordenine was dissolved in phenyl isocyanate. After a short time solid began to separate. Light petroleum was then added, which caused a further precipitate to form, and the mixture filtered. The solid was crystallised by dissolving it in about 10 cc. of benzene and adding light petroleum. When crystallised in this way the *phenylcarbamido-derivative* of hordenine forms long prisms which melt at 119°.

The *hydrochloride* can be recrystallised from alcohol, when it forms plates which melt at 194° with effervescence.

Analysis. 0.1801 g. gave 0.0804 g. AgCl.

Cl found, 11.04 %; calc., 11.08 %.

URETHANES DERIVED FROM 8-HYDROXYQUINOLINE.

Methylcarbamido-derivative of 8-hydroxyquinoline. 1 g. of 8-hydroxyquinoline was treated with a solution of methyl isocyanate in benzene. It slowly dissolved, and, on standing, the urethane separated from the solution. Light petroleum was added to complete the precipitation, when the solid was filtered and washed with dry ether (yield 1.35 g.). When recrystallised from alcohol the methylcarbamido-derivative of 8-hydroxyquinoline forms rectangular tablets which sinter at 152° and melt at 161°.

The *hydrochloride* quickly separated when 0.7 g. of the base was dissolved in alcoholic hydrochloric acid (yield 0.8 g.). When recrystallised from a mixture of alcohol and acetone it forms prisms which melt at 168° with effervescence.

Analysis. 0.1777 g. gave 0.1050 g. AgCl.

Cl found, 14.62 %; calc., 14.88 %.

Ethylcarbamido-derivative of 8-hydroxyquinoline. 1 g. of 8-hydroxyquinoline was dissolved in ethyl isocyanate. The urethane quickly separated in crystalline form. The excess of ethyl isocyanate was then evaporated under diminished pressure, light petroleum added to the residue and the suspension filtered and washed with the same solvent (yield 1.4 g.). When recrystallised from alcohol, the ethylcarbamido-derivative of 8-hydroxyquinoline forms rhombohedral plates which melt at 150° with effervescence.

The *hydrochloride* crystallises from acetone in the form of prisms which melt at 84°.

Analysis. 0.2118 g. gave 0.1184 g. AgCl.

Cl found, 13.83 %; calc., 14.06 %.

MIOTIC ACTION OF SYNTHETIC URETHANES.

It will be observed that the urethanes described in the preceding section of the experimental portion fall into the following three groups with respect to the position of the basic nitrogen atom: (1) those derived from the isomeric dimethylaminophenols and hence containing the dimethylamino-group attached directly to the benzene ring; (2) those prepared from hordenine with the basic group in a side chain; and (3) those containing a quinoline grouping in which the basic nitrogen atom forms part of a heterocyclic ring. Corresponding with these differences in the nature of the basic groups differences in the basic properties of the urethanes would be expected, and it has, in fact, been found that the hydrochlorides of the first group are, in general, hydrolysed by water to a sufficient extent to yield solutions with an acid reaction but, with the exception of the *N*-phenylurethanes, insufficient to cause the precipitation of the base. It was the discovery that the salts of these urethanes undergo appreciable hydrolysis that led, in the first instance, to the preparation of the urethanes of group two, which, as was anticipated, proved to be stronger bases and hence yielded hydrochlorides which dissolved in water without

appreciable hydrolysis. The urethanes of group three, on the other hand, possess such feeble basic properties that their hydrochlorides are hydrolysed by water to such an extent that the free base is partially precipitated. Since solutions of these quinoline urethanes could therefore only be obtained in the presence of excess of acid they were not considered suitable for pharmacological tests. Experimental work on the physiological activity has, therefore, been confined to the urethanes of the dimethylaminophenol and hordenine series. In both series the hydrochlorides have been employed for this purpose, whilst in the dimethylaminophenol series the methiodides have also been examined. The latter salts were tested partly because, being derived from the strong quaternary ammonium bases, they gave neutral solutions in water, and partly because it was of interest to determine whether the physiological properties of the urethanes underwent any change when the tertiary basic group was converted into a quaternary ammonium group.

A detailed study of the pharmacological properties of these compounds has not, at the present stage of the work, been attempted. On the contrary, they have been examined only with respect to their ability to cause a contraction of the iris when applied to the eye. For this purpose, 5 % solutions of the salts in Ringer's fluid were usually employed. In the cases, however, of the hydrochlorides of the *o*-dimethylaminophenyl esters of methyl- and ethylcarbamic acids and of the *m*-dimethylaminophenyl ester of ethylcarbamic acid, which do not yield solid hydrochlorides, the bases were dissolved in the theoretical amount of 0.115 *N* hydrochloric acid, giving approximately 2 % solutions; while with the methiodide of the *m*-dimethylaminophenyl ester of phenylcarbamic acid and the hydrochloride of the phenylcarbamidoderivative of hordenine, which are only sparingly soluble in Ringer, saturated solutions in this solvent were used. In each case, one drop of the solution so prepared was introduced from a pipette into one eye of a cat. With those compounds which exhibited miotic activity, the pupil commenced to contract in from 10–30 minutes. This effect slowly increased, reached a maximum in about an hour, and persisted to a greater or smaller degree over a period of about 4 hours. The results obtained with the various substances tested are tabulated below:

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

The application of the substances with miotic activity to the eye of a cat did not usually produce any effect beyond their action on the iris. Occasionally, however, they also produced salivation. This can no doubt be attributed to the action of the drugs on the salivary glands after passage through the lachrymal duct. Nevertheless, this effect was not a constant one but apparently depended upon the individual cat employed, for a substance which produced salivation in one experiment frequently failed to do so in another although its action on the iris was unchanged.

On the other hand, those urethanes which were devoid of miotic activity were found to have an irritant action on the eye, the irritation being accompanied by intense salivation and lacrimation. This was particularly the case with the derivatives of *o*-dimethylaminophenol. In these cases the salivation can probably be attributed to the irritant action of the drugs rather than to a physostigmine-like action.

The miotic action of physostigmine can be readily demonstrated with a 1 % solution of a salt of this base. It will be observed that the solutions of the synthetic urethanes employed in these experiments were considerably more concentrated. An experiment was therefore carried out with a 1 % solution of the hydrochloride of the *m*-dimethylaminophenyl ester of methyl-carbamic acid. Miosis was produced in almost undiminished intensity.

DISCUSSION.

A consideration of the possibility, opened by the results recorded above, of the employment of synthetic urethanes in therapeutics must be reserved, and the discussion confined to an analysis of the results with regard to their bearing on the problem of the relationship between chemical constitution and physiological action. In this connection it must be borne in mind that the synthetic compounds have been examined pharmacologically only with respect to one particular property, namely, their action on the iris. While it is probable that the general action on the organism of those urethanes which show miotic activity qualitatively resembles that of physostigmine, at any rate, as regards its selective action on the parasympathetic nervous system, experimental proof that such is the case is at present lacking. Any reference which may be made below to the identity between the physiological properties of the synthetic and natural urethanes must therefore be understood in this limited sense.

In order to facilitate discussion the structural formulae (IV-VII) of the synthetic urethanes, excluding those not tested, are shown below:

In each formula R represents a methyl or phenyl group. In IV, V and VI it may also represent an ethyl group and in V a hydrogen atom.

When R is a methyl group, all the compounds resemble physostigmine in physiological properties, and a comparison of the formulae shows that their structures possess two features in common with the alkaloid: they are all substituted phenyl esters of methylcarbamic acid, and they all contain a basic group. It is evident that it is the aromatic urethane grouping which confers miotic properties on these compounds. Whether the basic group is essential for activity is not at present known. Nevertheless, it is certain that the intensity of the activity varies with the position of this group, and it is therefore probable that it not only serves the function of permitting soluble salts to be prepared but also modifies the properties of the urethane grouping in a manner essential to its activity.

That the urethane grouping is itself susceptible to certain changes without completely losing its power of conferring miotic properties on these compounds is also clear from these experiments. Thus, the *m*-dimethylaminophenyl ester of carbamic acid ($R = H$ in V) and the *o*-dimethylaminophenyl ester of ethylcarbamic acid ($R = C_2H_5$ in VI) both produce a contraction of the pupil. Nevertheless, the general effect of such substitutions is to diminish the activity of the compounds. While, from the nature of the tests employed, it would not be legitimate to make this statement on the grounds that the activities of the two compounds mentioned were actually observed to be less than those of the corresponding methyl urethanes, its validity is evident from the fact that the *p*- and *m*-dimethylaminophenyl esters of ethylcarbamic acid ($R = C_2H_5$ in IV and V) were completely inactive under the same experimental conditions. The effect of the phenyl group is difficult to determine owing either to the extent to which salts of the *N*-phenylurethanes are hydrolysed or to their slight solubility in water. No activity has been observed with those compounds tested, but the possibility that some *N*-phenylurethanes may possess activity cannot be definitely excluded. Of the synthetic urethanes examined, those which, like physostigmine, are derivatives of methylcarbamic acid thus appear to be the most active miotics.

The influence of the basic group must now be considered in greater detail. That this may be attached directly to the benzene ring, or present in a side chain or a heterocyclic ring, as in physostigmine, is obvious from the experiments described above. Beyond this general result, however, a comparison of different types of compounds of different molecular composition can give little information concerning the influence of the basic group. It is difficult to decide, in such cases, what portion of any observed differences in activity is attributable to differences in the position of the basic group and what is to be ascribed to other differences in structure. This difficulty disappears when isomeric compounds of the same type are compared; it is, indeed, largely for this reason that the work here recorded deals mainly with such isomerides. The results obtained with the isomeric dimethylaminophenyl esters of methylcarbamic acid do not, however, yield very much information on this point. No striking difference was observed between the activities of these isomerides,

although the impression was gained that the *p*-compound is somewhat less active than either the *o*- or *m*-compound. The results with the corresponding esters of ethylcarbamic acid are much more definite. Of these, both the *p*- and *m*-compounds, in contrast to the *o*-compound, are completely inactive. Combining the results obtained with the two series of isomerides the author feels justified in concluding that the dimethylamino-group modifies the activity of the urethane grouping in such a way that the activities of the isomerides are in the order $o > m, p$. In any case, it is evident that the basic group exerts a distinct influence on the urethane grouping and that this influence varies according to its position relative to the latter.

When the tertiary basic group is converted into a quaternary ammonium group, a remarkable change, which is in the same direction in both series of isomerides considered in the preceding paragraph, is produced in the activities of these compounds. In the *N*-methylurethane series, the activity of the *m*-isomeride is unmistakably increased, whilst that of the *o*- and *p*-compounds is apparently abolished. Similarly, in the *N*-ethylurethane series the *p*-compound remains inactive, the *o*- loses its activity, whilst the *m*-isomeride, although previously inactive, now manifests distinct activity. The effect of transforming the tertiary basic group into a quaternary ammonium group is thus to diminish the activity of the urethane grouping when the basic group is in the *o*- or *p*-position to the latter, and to intensify this activity when it is in the *m*-position.

VIII

IX

The contrast between the physiological properties of the *o*- and *p*- isomerides, on the one hand, and the *m*- on the other, immediately recalls the differences which are observed between the reactivities of the position isomerides of certain di-derivatives of benzene. In attempting to interpret this resemblance it is convenient to employ the notation of the polarity theory. According to the latter the electronegative dimethylamino-group in dimethylaminophenol would induce the polarities indicated in formula VIII, which may be regarded as representing either of the isomerides. The effect of the positive quaternary ammonium group is similarly indicated in formula IX. Of the three dimethylaminophenols the phenolic group of the *o*- and *p*-compounds should thus be less strongly acidic than that of the *m*-isomeride, whilst the reverse should be the case with the corresponding quaternary salts. Now, except in so far as it has been impossible to differentiate with certainty between the activities of the urethanes derived from *m*- and *p*-dimethylaminophenol, it is, in each series of isomerides, precisely with those urethanes

derived from phenols which, on the polarity theory, are least acidic that the miotic properties are the most pronounced. It should be pointed out that the polarities indicated in formula VIII can only be assigned to the free bases and that, in dealing with salts, it would be necessary to reverse them. Since, however, all the salts of the corresponding urethanes undergo appreciable hydrolysis in aqueous solution, it may be assumed that they react in the organism in the form of the free base.

The fact that the chemical properties, as predicted by the polarity theory, of the phenols from which the urethanes are derived can be correlated with the physiological properties of the latter, indicates that chemical reactivity is one of the factors responsible for their activity. The precise nature of this chemical reactivity has not yet been determined with certainty. Nevertheless, it should be pointed out that the miotics described above are readily susceptible to hydrolysis. This can be shown by boiling an aqueous solution of one of the methiodides. Hydrolysis takes place with such rapidity that the odour of the isocyanate is almost instantaneously detectable. Since the ease with which hydrolysis would take place would undoubtedly vary with the degree to which the phenolic moiety of the molecule possessed acidic properties, it appears reasonable to assume that the physiological properties are dependent on, and vary in some way with, the rate at which the urethanes are hydrolysed. It is conceivable that one of the products of hydrolysis, liberated after adsorption of the urethane by the nerve or nerve ending, might be responsible for the activity of these compounds. Relatively difficultly hydrolysable urethanes would then be inactive on account of the slowness of the formation of the active substances, whilst those which were hydrolysed with extreme ease would be decomposed into surface inactive constituents before reaching the site of their activity.

It is possible that the suggestions made above are applicable to other substances (*e.g.* the tropeines and cocaines) containing easily hydrolysable groups. Such a mechanism would explain the differences in the activities of the enantiomorphic hyoscyamines, if it be assumed that hydrolysis takes place under the influence of enzymes.

SUMMARY.

1. The miotic action of physostigmine (eserine) has been shown to be mainly due to the urethane grouping which is present in the molecule.
2. A number of urethanes, the properties and methods of preparation of which are described, have been synthesised and, where possible, tested for miotic activity.
3. The active urethanes include the isomeric dimethylaminophenyl esters of methylcarbamic acid, the *m*-dimethylaminophenyl ester of carbamic acid, the *o*-dimethylaminophenyl ester of ethylcarbamic acid, and the methylcarbamido-derivative of hordenine. The *m*- and *p*-dimethylaminophenyl esters

of ethylcarbamic acid are inactive, as also are those esters of phenylcarbamic acid which were tested.

4. The basic group modifies the action of the urethane grouping and is probably essential to its activity.

5. Conversion of the tertiary basic group present in the urethanes derived from the isomeric dimethylaminophenols into a quaternary ammonium group exerts a profound influence on the activity of these compounds. The activities of the *m*-compounds are intensified, whilst those of the *o*- and *p*-compounds are abolished.

6. In each series of isomeric urethanes, those compounds derived from phenols which, according to the polarity theory, should be the most acidic are the least active.

7. This correspondence between the alternation in physiological and chemical properties suggests that chemical factors, as distinguished from physical properties, are at least partly responsible for the activity of the compounds.

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