CXLVI.—*The Methylurethanes of α-3-Hydroxy-4-methoxyphenylethyldimethylamine and α-4-Hydroxy-3-methoxyphenylethyldimethylamine and their Miotic Activities.*

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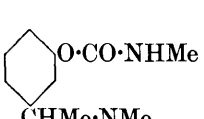
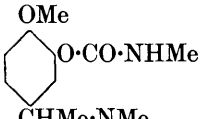
IN recent papers (*Biochem. J.*, 1926, **20**, 719; 1929, **23**, 17) we have shown that carbamic esters of aminophenols possess the general property of producing a constriction of the pupil when instilled into the eye. This miotic action was found to be most pronounced with urethanes derived from methylcarbamic acid, and, amongst the many compounds of this type which have been prepared and examined, the methylurethane of α-*m*-hydroxyphenylethyldimethylamine, $NHMe{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}CHMe{\cdot}NMe_2$, has been observed (J., 1929, 609) to possess a particularly marked miotic activity. On account of its intense miotic properties, which are, in fact, of the same order of magnitude as those of physostigmine, this substance has been named *miotine* (Proc. XIIIth Internat. Physiol. Congress, *Amer. J. Physiol.*, 1929, **90**, 528), and a more detailed study of its pharmacological properties, as well as those of a few similar urethanes, has shown (White and Stedman, *J. Pharm. Exp. Ther.*, 1931, **41**, 259) that urethanes of this type possess all the physiological activities of physostigmine. It is therefore clear that the relationship between chemical constitution and miotic action established in the papers referred to above is more extensive than has been previously claimed, and it can now be stated that phenyl esters of carbamic acid or of substituted carbamic acids, which contain a basic group, will, in general, resemble physostigmine in their physiological activities, *i.e.*, will stimulate the parasympathetic nervous system. The factors modifying their general physiological activities will doubtless be similar to those which have been found to modify their miotic activities.

In view of the intense physiological activity of miotine (I), which is considerably greater than that of its *o*- and *p*-isomerides, it was thought to be of interest to ascertain the manner in which its

activity would be influenced by the introduction of another substituent into the benzene ring. A quantity of *iso*vanillin was placed at our disposal by Dr. M. Guggenheim of Messrs. Hoffmann Laroche and Co., Basel, for this purpose, and we have therefore prepared the methylurethane of α-3-*hydroxy*-4-*methoxyphenylethyldimethylamine* (II). At the same time an isomeride (III) derived from



(I.)



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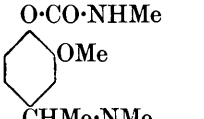

(III.)

vanillin has also been prepared. Identical reactions were employed for the preparation of the two substances. The phenolic hydroxyl group was first protected by benzoylation, and the benzoylvanillin converted into the corresponding benzoyloxymethoxyphenylmethylcarbinol, $BzO{\cdot}C_6H_3(MeO){\cdot}CHMe{\cdot}OH$, by means of magnesium methyl iodide. During this reaction there was a partial removal of the benzoyl group in the case of *iso*vanillin and probably also in that of vanillin. Conversion of the carbinol into its chloride was effected by interaction with thionyl chloride, and the *α-benzoyloxymethoxyphenylethyl chloride*, $BzO{\cdot}C_6H_3(MeO){\cdot}CHMeCl$, so obtained was treated with dimethylamine. During this treatment the benzoyl group was completely removed, for the product consisted of *α-hydroxymethoxyphenylethyldimethylamine*, $HO{\cdot}C_6H_3(MeO){\cdot}CHMe{\cdot}NMe_2$. This reacted directly with methylcarbimide to give the required urethane. Unfortunately neither urethane could be isolated in the free state in pure condition, although analytically pure salts were obtained.

Despite the somewhat unsatisfactory yields in some of the reactions, sufficient material was obtained to enable some pharmacological tests to be carried out; these were made, through the kindness of Dr. M. Guggenheim, by Dr. M. Reinert of Messrs. Hoffmann Laroche and Co., and have established quite definitely that compounds (II) and (III) possess miotic activities which are considerably smaller than that of miotine (I). It is also probable from the results that compound (III) is more active than the methylurethane of α-*p*-hydroxyphenylethyldimethylamine (the *p*-isomeride of miotine).

EXPERIMENTAL.

Benzoylation of iso*Vanillin.*—In carrying out the preparation of benzoyl*iso*vanillin from *iso*vanillin by the method of Pschorr and Stohrer (*Ber.*, 1902, **35**, 4398) it was found convenient to reduce the

quantity of sodium carbonate employed by one half and to isolate the benzoyl derivative by collecting the almost solid reaction product with the aid of a pump, washing it with water, and allowing it to dry in the air. It was then ground to a powder and extracted with hot alcohol to separate the benzoyl derivative from unchanged sodium carbonate; after addition of water to the hot filtrate, benzoyl*iso*vanillin crystallised, on cooling, in rosettes of prisms, m. p. 74°. Yield, 29·5 g. from 30 g. of *iso*vanillin.

*Action of Magnesium Methyl Iodide on Benzoyl*iso*vanillin.*—Many experiments were carried out under different conditions, but in no case was the reaction product homogeneous. This was doubtless due to the partial removal of the benzoyl group, for in different experiments 3-hydroxy-4-methoxyphenylmethylcarbinol and 3-benzoyloxy-4-methoxyphenylmethylcarbinol were isolated from the reaction product. Examples are therefore given of two such experiments from which the respective substances were isolated.

(1) A solution of benzoyl*iso*vanillin (25·6 g.) in warm ether (about 400 c.c.) was added to a solution of magnesium methyl iodide (2 mols.; 30 g. of methyl iodide, 5·1 g. of magnesium) in ether. The reaction product, a sticky yellow mass, was worked up in the usual manner, and the ethereal solution obtained was washed first with sodium hydroxide and then with water. Evaporation of the ether, after drying, gave 23 g. of an oil which would not crystallise. The above-mentioned alkaline extract, together with the washings, was acidified with hydrochloric acid and shaken with ether. There were thus obtained 5 g. of an oil which would not crystallise spontaneously It was therefore dissolved in hot benzene, and light petroleum added to the solution. A crystalline product, admixed with some oily material, slowly separated. The solvents were decanted and the oil was removed by pressing the residue on a porous plate. After two crystallisations from benzene there was thus obtained 0·95 g. of 3-*hydroxy*-4-*methoxyphenylmethylcarbinol*, large irregular plates with a faint pink colour; m. p. 94° (Found : C, 64·5, 64·7; H, 6·9, 7·1. $C_9H_{12}O_3$ requires C, 64·3; H, 7·1%). 3-Hydroxy-4-methoxyphenylmethylcarbinol gives with ferric chloride a deep blue coloration, changing first to green and finally to brown. Sodium carbonate transforms the blue colour to pink.

(2) In this case the magnesium methyl iodide (1 mol.) was added to a solution of benzoyl*iso*vanillin (25·5 g.) in warm ether (about 1 litre). The precipitate which formed was more granular than in the preceding example. When the product was worked up as before, a non-phenolic syrup (25 g.), which partly crystallised on standing in a vacuum desiccator, was obtained. This was treated with a small volume of ether, which dissolved the syrup. After

filtration solid material (1·3 g.) was obtained, which was recrystallised from alcohol; *3-benzoyloxy-4-methoxyphenylmethylcarbinol* then separated in flat hexagonal prisms, m. p. 138° (Found: C, 70·6; H, 5·2. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

α-3-*Hydroxy*-4-*methoxyphenylethyldimethylamine*.—Thionyl chloride was added slowly to the crude syrup obtained in an experiment similar to (2) above. A vigorous reaction took place with the formation of a homogeneous solution. After 30 minutes the excess of thionyl chloride was removed under diminished pressure, and the residue was dissolved in benzene and added to an excess of dimethylamine in the same solvent. On the following day, the solution was extracted with hydrochloric acid, and the acid extract was shaken with ether to remove traces of benzene, and again extracted with ether after being made alkaline with sodium carbonate. Evaporation of the ether, after drying over sodium sulphate, gave 9·4 g. of an oil. This was distilled under diminished pressure, and the fraction passing over at 165—170°/14 mm. collected separately. Partial crystallisation of this fraction took place slowly. It was drained on a porous plate and recrystallised from light petroleum, 4 g. of α-3-*hydroxy*-4-*methoxyphenylethyldimethylamine* being obtained in thick prisms, m. p. 99—100° (Found: N, 7·3. $C_{11}H_{17}O_2N$ requires N, 7·2%). The picrate crystallised from water and had m. p. 158°.

The same base was also obtained in poor yield by saturating a solution of the crude carbinol with hydrogen bromide, removing the excess of the latter, and pouring the product into an excess of dimethylamine in the manner described above. The use of hydrobromic acid, however, was less satisfactory than that of thionyl chloride owing to the formation of much tarry material.

Methylurethane of α-3-*Hydroxy*-4-*methoxyphenylethyldimethylamine*.—The free urethane has not been obtained in a pure state. Material from which salts can be prepared is best obtained by dissolving the phenolic base in excess of methylcarbimide and subsequently removing the excess of the latter reagent under diminished pressure. In this way a syrup is obtained which will not crystallise. When warmed with methyl iodide, however, it reacts to form a viscous oil, which dissolves in hot acetone; crystalline material separates from the latter on cooling. When crystallised by the addition of ether to its alcoholic solution, the *methiodide* of the *methylurethane* of α-3-*hydroxy*-4-*methoxyphenylethyldimethylamine* forms plates, m. p. 177° (efferv.) (Found: N, 7·2. $C_{14}H_{23}O_3N_2I$ requires N, 7·1%). The hydrochloride of the urethane is extremely hygroscopic. When an ethereal solution of the crude urethane is treated with alcoholic hydrogen chloride, this salt separates as an oil. By decanting the

solvents, repeatedly washing the residue with dry ether, and rubbing it with a glass rod, it can be made to crystallise, and can then be recrystallised by the careful addition of dry ether to its alcoholic solution. Filtration and all subsequent operations must, however, be carried out in a perfectly dry atmosphere.

4-*Benzoyloxy*-3-*methoxyphenylmethylcarbinol*.—This was prepared from benzoylvanillin by the method employed by Finnemore (J., 1908, **93**, 1520). The yield of pure carbinol (85%) mentioned by this author was, however, seldom attained. On one occasion, when magnesium methyl iodide was added to the ethereal solution of the benzoylvanillin, 23·2 g. of product, which crystallised spontaneously, were obtained from 25·6 g. of benzoylvanillin. In other experiments carried out under apparently identical conditions, or in which the benzoylvanillin was added to the Grignard reagent, spontaneous crystallisation did not occur and the method of Finnemore had to be resorted to in order to procure crystalline material; in such cases the yield of pure carbinol never exceeded 50% of the theoretical.

4-*Benzoyloxy*-3-*methoxyphenylethyl Chloride*.—Thionyl chloride (4 c.c.) was added slowly to the carbinol (10 g.). After completion of the reaction the liquid product solidified. The excess of thionyl chloride was removed under diminished pressure, and the solid washed with light petroleum on to a Buchner funnel. When recrystallised from ligroin, α-4-*benzoyloxy*-3-*methoxyphenylethyl chloride* formed rosettes of prisms, m. p. 98—99° (Found: Cl, 12·3. $C_{16}H_{15}O_3Cl$ requires Cl, 12·2%). Yield of pure substance, 8 g. This chloride is readily soluble in benzene but practically insoluble in cold light petroleum; it can, however, be recrystallised from the latter solvent.

α-4-*Hydroxy*-3-*methoxyphenylethyldimethylamine*.—To a solution of 8 g. of the above chloride in 100 c.c. of benzene, excess of dimethylamine in 250 c.c. of benzene was added. The base was isolated in the manner described for its isomeride; an oil (4 g.), which solidified after standing in a vacuum desiccator, was then obtained. When recrystallised from light petroleum, α-4-*hydroxy*-3-*methoxyphenylethyldimethylamine* formed thick prisms, m. p. 90—91° (Found: N, 7·2%).

Methylurethane of α-4-*Hydroxy*-3-*methoxyphenylethyldimethylamine*.—A fragment of sodium was added to a solution of the above phenolic base in benzene. When this had dissolved, slightly more than one equivalent of methylcarbimide was added. After 3 days a small amount of flocculent precipitate was removed by filtration and the solvents were evaporated under diminished pressure. The oily residue, which would not crystallise, was converted into its

hydrochloride by addition of alcoholic hydrogen chloride to its ethereal solution. An oily precipitate was obtained which became crystalline after repeated washing with dry ether. After being crystallised twice by addition of dry ether to its alcoholic solution, the *hydrochloride* of the *methylurethane* of α-4-*hydroxy*-3-*methoxyphenylethyldimethylamine* formed aggregates, m. p. about 145° (efferv.) (Found : Cl, 12·0; N, 9·7. $C_{13}H_{21}O_3N_2Cl$ requires Cl, 12·3; N, 9·7%).

Physiological Activity of Urethanes.—The hydrochlorides of the two urethanes and the methiodide of the one from *iso*vanillin have been examined pharmacologically by Dr. M. Reinert of Messrs. Hoffmann Laroche and Co. All three substances produced miosis when instilled into the eye of a cat and caused an increase in the tone of the isolated intestine of the rabbit. Since, however, their activities were considerably less than that of miotine, extensive experiments were not carried out; the report of the biological work will not, therefore, be quoted in detail.

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