

**Synthesis of 4:6-dimethoxy-2-[beta]-methylaminoethylbenzaldehyde /
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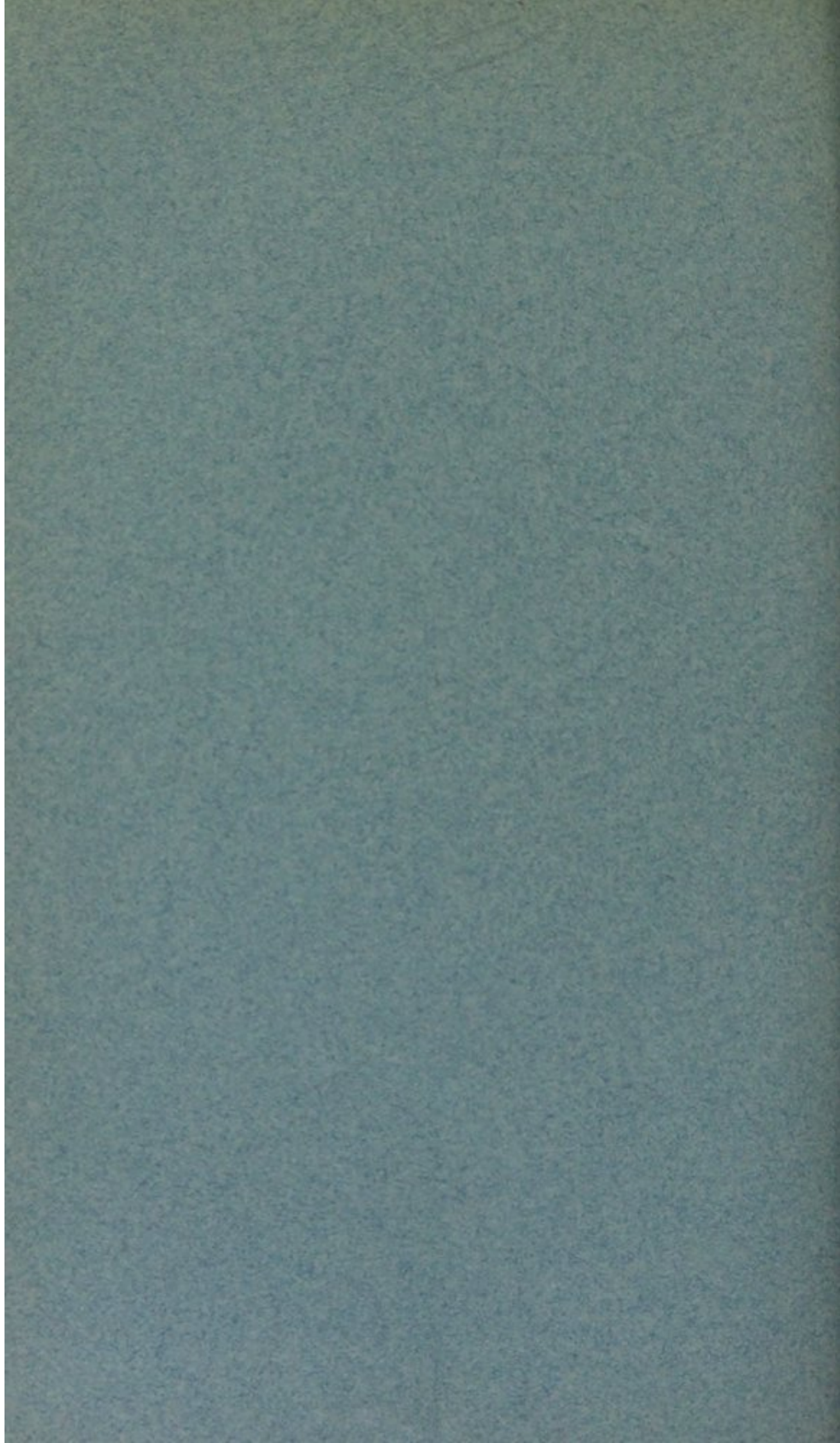
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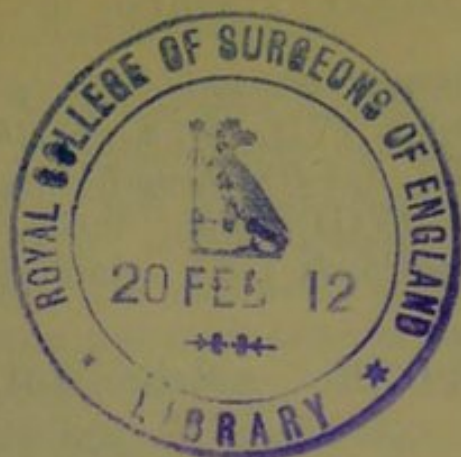
SYNTHESIS
OF
4:6-DIMETHOXY-
2- β -METHYLAMINOETHYLBENZALDEHYDE

BY
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(From the Transactions of the Chemical Society, Vol. 99, 1911)



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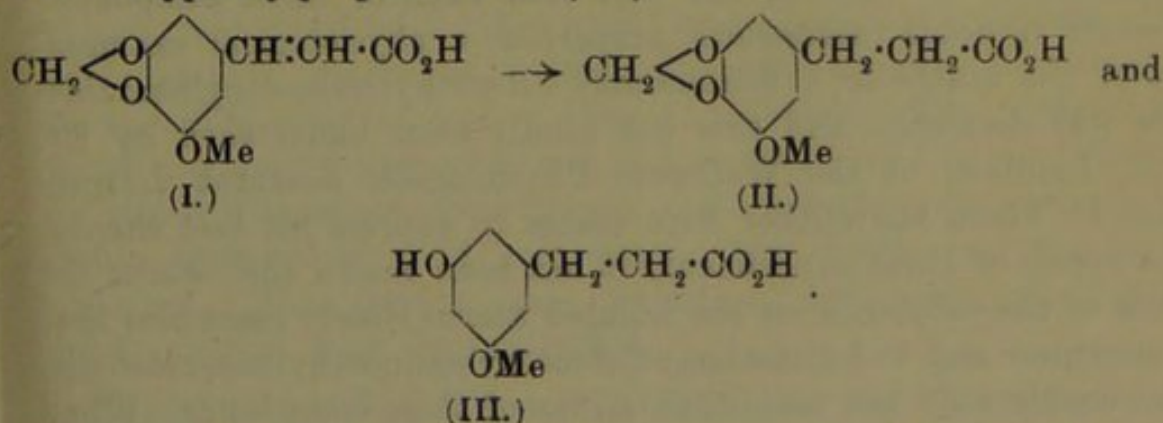




CXLV.—*Synthesis of 4:6-Dimethoxy-2-β-methyl-aminoethylbenzaldehyde.*

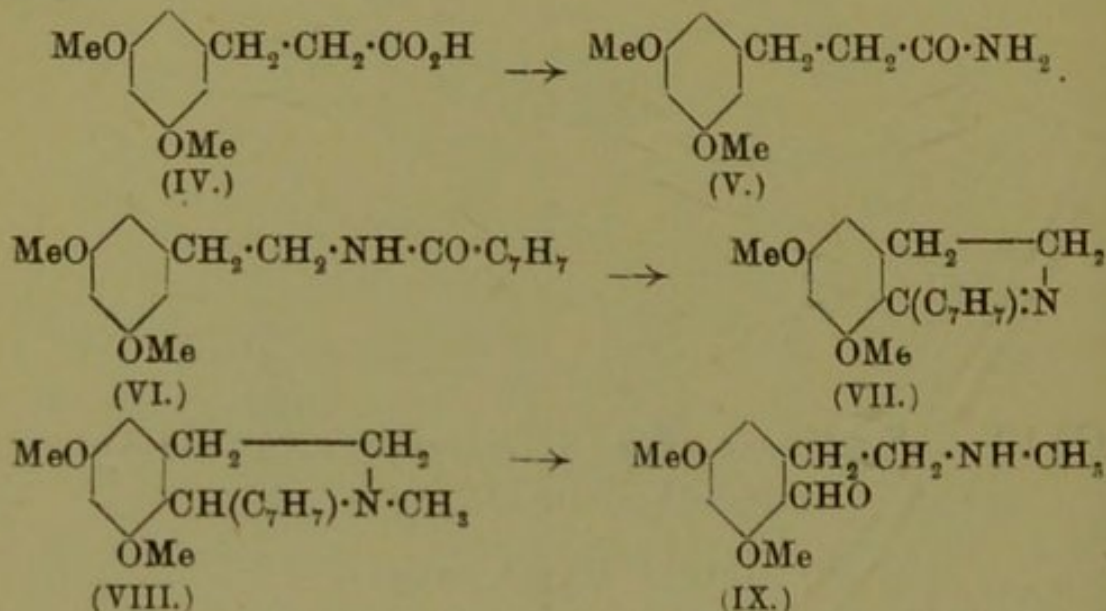
By ARTHUR HENRY SALWAY.

IN a previous communication (Trans., 1910, **97**, 2413) it was shown that 3-methoxy-4:5-methylenedioxybenzoic acid (I) is converted by the action of sodium amalgam into a mixture of β-3-methoxy-4:5-methylenedioxyphenylpropionic acid (II) and β-5-hydroxy-3-methoxyphenylpropionic acid (III):



This reduction was originally conducted with the object of preparing β-3-methoxy-4:5-methylenedioxyphenylpropionic acid (II), from which the synthesis of cotarnine was accomplished by a series of reactions already described (Trans., 1910, **97**, 1208). It now seemed desirable to subject the second reduction product, β-5-hydroxy-3-methoxyphenylpropionic acid (III), to a similar series of reactions, since the final product thus obtained would be closely allied to cotarnine, and therefore likely to possess valuable therapeutic properties. Accordingly, β-5-hydroxy-3-methoxyphenylpropionic acid (III) was first methylated, and the resulting β-3:5-dimethoxyphenylpropionic acid (IV) transformed successively into

β -3:5-dimethoxyphenylpropionamide (V), phenylacetyl- β -3:5-dimethoxyphenylethylamide (VI), 6:8-dimethoxy-1-benzyl-3:4-dihydroisoquinoline (VII), 6:8-dimethoxy-1-benzyl-2-methyl-1:2:3:4-tetrahydroisoquinoline (VIII), and, finally, 4:6-dimethoxy-2- β -methylaminoethylbenzaldehyde (IX), according to the following scheme:



4:6-Dimethoxy-2- β -methylaminoethylbenzaldehyde (IX) is closely allied to cotarnine and hydrastinine, and is also isomeric with 4:5-dimethoxy-2- β -methylaminoethylbenzaldehyde, recently obtained by Pyman (Trans., 1909, 95, 1266) by the oxidation of the alkaloid laudanosine. In view of the fact that each of these compounds possesses valuable therapeutic properties, a physiological examination of the synthetic 4:6-dimethoxy-2- β -methylaminoethylbenzaldehyde was desirable, and this has kindly been undertaken by Dr. P. P. Laidlaw, of the Wellcome Physiological Research Laboratories, to whom the author here wishes to express his best thanks. As a result of these experiments it has been shown that whilst the action of the substance on the isolated uterus closely resembles that of cotarnine and 4:5-dimethoxy-2- β -methylaminoethylbenzaldehyde, it is considerably less toxic than either of these compounds. When injected into the blood-stream of a cat it produces a rise in blood pressure, accompanied by a slowing of the heart-beat, in this respect having a closer resemblance to 4:5-dimethoxy-2- β -methylaminoethylbenzaldehyde than to cotarnine.

EXPERIMENTAL.

β -3:5-Dimethoxyphenylpropionamide (V, above).

This compound was prepared from β -3:5-dimethoxyphenylpropionic acid (Trans., 1910, 97, 2417) by the successive action of phosphorus pentachloride and ammonia, the method employed being

the same as that already described in connexion with the preparation of β -3-methoxy-4:5-methylenedioxyphenylpropionamide (Trans., 1910, 97, 1211). The crude acid amide was extracted with chloroform, and the chloroform solution washed with water, dried, and the solvent removed. The oily product thus obtained in almost quantitative yield soon solidified, and was purified by recrystallisation from benzene and petroleum:

0.0978 gave 0.2256 CO_2 and 0.0632 H_2O . $\text{C}=62.9$; $\text{H}=7.2$.

$\text{C}_{11}\text{H}_{15}\text{O}_3\text{N}$ requires $\text{C}=63.2$; $\text{H}=7.2$ per cent.

β -3:5-Dimethoxyphenylpropionamide is readily soluble in benzene, chloroform, or alcohol, but insoluble in light petroleum. It crystallises from a mixture of benzene and petroleum in colourless needles, melting at $80-81^\circ$. The fused substance, after resolidification, melts at 86° .

Phenylacetyl- β -3:5-dimethoxyphenylethylamide (VI, p. 1321).

The above-described acid amide was finely powdered, and shaken continuously with a slight excess of sodium hypochlorite (compare Trans., 1910, 97, 1212) until the whole had passed into solution. The liquid was then heated to 100° for a short time, and, after cooling, thoroughly extracted with ether. The ethereal solution, which contained the β -3:5-dimethoxyphenylethylamine formed in the reaction, was agitated with small portions of dilute hydrochloric acid until no further quantity of base was extracted. The acid extracts were then united, and shaken with an excess of phenylacetyl chloride in the presence of alkali. The crude phenylacetyl derivative thus obtained did not solidify; it was therefore extracted with ether, the ethereal solution washed successively with dilute hydrochloric acid and water, then dried, and the solvent removed. The residue soon solidified, and was purified by crystallisation from dilute alcohol:

0.1104 gave 0.2918 CO_2 and 0.0701 H_2O . $\text{C}=72.1$; $\text{H}=7.1$.

$\text{C}_{18}\text{H}_{21}\text{O}_3\text{N}$ requires $\text{C}=72.2$; $\text{H}=7.0$ per cent.

Phenylacetyl- β -3:5-dimethoxyphenylethylamide crystallises from dilute alcohol in colourless, prismatic needles, melting at 73° . It is readily soluble in the usual organic solvents, except light petroleum.

In one experiment for the preparation of the above compound a considerable excess of sodium hypochlorite was used, which caused the reaction to take an abnormal course, as indicated by the formation of a phenylacetyl derivative, melting at 106° , instead of 73° . This product was found to contain chlorine, and gave, on analysis, the following result:

0.1050 gave 0.2498 CO_2 and 0.0575 H_2O . $\text{C}=64.8$; $\text{H}=6.1$.

0.2331 „ 0.0990 AgCl . $\text{Cl}=10.5$.

$\text{C}_{18}\text{H}_{20}\text{O}_3\text{NCl}$ requires $\text{C}=64.8$; $\text{H}=6.0$; $\text{Cl}=10.6$ per cent.

The chlorinated base corresponding with this phenylacetyl compound yielded a hydrochloride, which crystallised in radiating clusters of colourless needles, melting at 188° :

0.1096 gave 0.1930 CO_2 and 0.0618 H_2O . $\text{C}=48.0$; $\text{H}=6.3$.

0.1510 „ 0.0858 AgCl . Cl (as hydrochloride) = 14.1.

$\text{C}_{10}\text{H}_{14}\text{O}_2\text{NCl}\cdot\text{HCl}$ requires $\text{C}=47.6$; $\text{H}=6.0$;

Cl (as hydrochloride) = 14.1 per cent.

It is thus evident that in the above experiment one atom of hydrogen had been substituted for one atom of chlorine, and since the chlorinated compound yielded, on oxidation, a monochloro-dimethoxybenzoic acid (m. p. $181-182^\circ$) of the formula $\text{C}_9\text{H}_9\text{O}_4\text{Cl}$ (neutralisation value: Found: 254.6. Calc., 259.1), it follows that the chlorine must be present in the nucleus. The above compound, melting at 188° , is therefore the *hydrochloride of β -2(4)-chloro-3:5-dimethoxyphenylethylamine*.

6:8-Dimethoxy-1-benzyl-3:4-dihydroisoquinoline (VII, p. 1321).

A quantity (10 grams) of phenylacetyl- β -3:5-dimethoxyphenylethylamide was dissolved in xylene, the solution heated to boiling, and phosphoric oxide added in small quantities, with agitation, until a small portion of the xylene solution gave no precipitate of unchanged substance with light petroleum. The solvent was then decanted from the yellow mass of phosphorus compound, and the latter decomposed by warming with an excess of dilute hydrochloric acid. The acid liquid was filtered to remove a little resinous matter, then rendered alkaline, and extracted with ether. After washing with water, the ethereal solution was shaken with small portions of dilute hydrochloric acid until no further basic matter was removed. The extracts were then united, and concentrated to a small volume, when an almost colourless, crystalline hydrochloride was deposited, which was collected and purified by recrystallisation from a mixture of alcohol and ethyl acetate. The yield of pure substance amounted to 8 grams:

1.6464 lost, at 110° , 0.1678 H_2O . $\text{H}_2\text{O}=10.2$.

$\text{C}_{18}\text{H}_{20}\text{O}_2\text{NCl}\cdot 2\text{H}_2\text{O}$ requires $\text{H}_2\text{O}=10.2$ per cent.

0.1060 * gave 0.2652 CO_2 and 0.0643 H_2O . $\text{C}=68.2$; $\text{H}=6.7$.

0.4730 * „ 0.2140 AgCl . $\text{Cl}=11.2$.

$\text{C}_{18}\text{H}_{20}\text{O}_2\text{NCl}$ requires $\text{C}=68.0$; $\text{H}=6.3$; $\text{Cl}=11.2$ per cent.

6:8-Dimethoxy-1-benzyl-3:4-dihydroisoquinoline hydrochloride is

* Anhydrous substance.

only moderately soluble in cold water, but readily so in hot, and crystallises from the latter in almost colourless, rhombohedral prisms, which contain two molecules of water of crystallisation, and melt and decompose at 181° . It is best crystallised from a mixture of alcohol and ethyl acetate, when it is obtained in stout, colourless prisms. The free base, 6:8-dimethoxy-1-benzyl-3:4-dihydroisoquinoline, when prepared from the pure hydrochloride by addition of alkali, was obtained as a viscid oil, which did not solidify at the ordinary temperature. It yields a *picrate*, which is only moderately soluble in hot water, but readily so in alcohol, from which it crystallises in small, yellow prisms, melting at 184° .

6:8-Dimethoxy-1-benzyl-2-methyl-1:2:3:4-tetrahydroisoquinoline
(VIII, p. 1321).

This compound was prepared by the conversion of 6:8-dimethoxy-1-benzyl-3:4-dihydroisoquinoline into its methochloride, and subsequent reduction with tin and hydrochloric acid, the method employed being identical with that previously described in the preparation of benzylhydrocotarnine from 8-methoxy-6:7-methylenedioxy-1-benzyl-3:4-dihydroisoquinoline (Trans., 1910, **97**, 1215). The crude product of the reaction was a brown oil, which slowly solidified. It was purified by recrystallisation from light petroleum, from which it separated in stout, colourless, prismatic needles:

0.0927 gave 0.2620 CO_2 and 0.0660 H_2O . $\text{C}=77.1$; $\text{H}=7.9$.

$\text{C}_{19}\text{H}_{23}\text{O}_2\text{N}$ requires $\text{C}=76.8$; $\text{H}=7.7$ per cent.

6:8-Dimethoxy-1-benzyl-2-methyl-1:2:3:4-tetrahydroisoquinoline is a crystalline, colourless solid, melting at 52° , and is readily soluble in organic solvents. It yields a *picrate*, which is only moderately soluble in hot water, but readily so in alcohol, and crystallises from the latter in small, feathery needles, melting and decomposing at 195° .

4:6-Dimethoxy-2- β -methylaminoethylbenzaldehyde (IX, p. 1321).

Five grams of 6:8-dimethoxy-1-benzyl-2-methyl-1:2:3:4-tetrahydroisoquinoline, dissolved in dilute sulphuric acid (15 per cent.), were oxidised by heating on the water-bath for about an hour with 4 grams of pyrolusite. An excess of sodium carbonate was then added, and the precipitated manganese carbonate removed by filtration. The filtrate contained, in suspension, some benzaldehyde formed during the oxidation, and was therefore extracted with ether, after which it was rendered strongly alkaline with aqueous sodium hydroxide, and the liberated base dissolved in benzene. The benzene extract was washed with a little water, and then shaken

with successive small portions of dilute hydrobromic acid until no further quantity of base was removed by this treatment. The aqueous solution of hydrobromide thus obtained was concentrated to dryness on the water-bath, and the solid residue purified by crystallisation from a mixture of alcohol and ethyl acetate:

0.2516 (air-dried) lost 0.0148 H_2O at 100° . $\text{H}_2\text{O}=5.9$.

$\text{C}_{12}\text{H}_{16}\text{O}_2\text{NBr}, \text{H}_2\text{O}$ requires $\text{H}_2\text{O}=5.9$ per cent.

0.1154 * gave 0.2138 CO_2 and 0.0608 H_2O . $\text{C}=50.5$; $\text{H}=5.9$.

0.2219 * „ 0.1444 AgBr . $\text{Br}=27.7$.

$\text{C}_{12}\text{H}_{16}\text{O}_2\text{NBr}$ requires $\text{C}=50.3$; $\text{H}=5.6$; $\text{Br}=28.0$ per cent.

4:6-Dimethoxy-2- β -methylaminoethylbenzaldehyde hydrobromide is readily soluble in alcohol or water, giving deep yellow solutions. It crystallises from a mixture of alcohol and ethyl acetate in pale yellow needles, which contain one molecule of water of crystallisation. The hydrated salt, when heated rapidly, melts at 100° , whilst the anhydrous substance melts without decomposition at 164° . The hydrochloride, owing to its hygroscopic nature, is more difficult to crystallise than the hydrobromide. It separates, however, from absolute alcohol and ethyl acetate in almost colourless, well-formed needles, which contain two molecules of water of crystallisation:

0.2437 (air-dried) lost 0.0304 H_2O at 90° . $\text{H}_2\text{O}=12.5$.

$\text{C}_{12}\text{H}_{16}\text{O}_2\text{NCl}, 2\text{H}_2\text{O}$ requires $\text{H}_2\text{O}=13.0$ per cent.

The hydrated hydrochloride melts in its water of crystallisation at 95° . The free base, 4:6-dimethoxy-2- β -methylaminoethylbenzaldehyde, was obtained only in the form of a gummy solid on the addition of an excess of sodium hydroxide to a concentrated aqueous solution of the hydrobromide. It is freely soluble in water, but is reprecipitated on the addition of a concentrated aqueous solution of sodium hydroxide. It yields a *picrate*, which is readily soluble in hot water, and crystallises from this solvent in glistening, yellow needles, melting at $155-156^\circ$. The *aurichloride* crystallises from hot alcohol in golden-yellow leaflets, which melt at $131-132^\circ$:

0.0938 gave 0.0339 Au . $\text{Au}=36.1$.

$\text{C}_{12}\text{H}_{16}\text{O}_2\text{N}, \text{AuCl}_4$ requires $\text{Au}=36.1$ per cent.

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* Anhydrous substance.