92. α- and β-Hydroxylaudanosines. Part II. The Products of Exhaustive Methylation.

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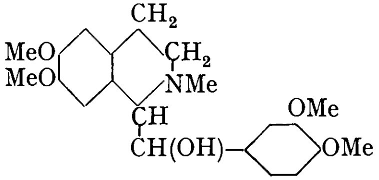
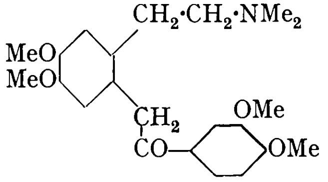
The recently described α- and β-hydroxylaudanosines (I) (King, L'Ecuyer, and Pyman, J., 1936, 731) not only have significance in regard to the oxidation of laudanosine but, as derivatives of this alkaloid, also possess an interest which justifies a more detailed investigation of their reactions, and a beginning has been made with the exhaustive methylation of the isomerides.

(I.)



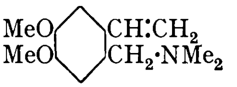


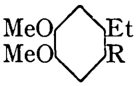
(II.)

The decomposition products of 1-benzyltetrahydro*iso*quinolinium hydroxides may in theory be two-fold, depending on which of the C–N links in the heterocyclic ring is severed, but the analogies provided by the first stages in the Hofmann degradation of laudanosine (Decker and Galatty, *Ber.*, 1909, **42**, 1179), of narcotine (Roser, *Annalen*, 1888, **247**, 169), and of hydrastine (Freund, *ibid.*, 1892, **271**, 350) suggest that ring-opening in the hydroxylaudanosines is more likely to be restricted to that position which will result in the production—through its enolic form—of the keto-base (II). Actually, an unusual reaction was found to occur.

The effect of aqueous sodium hydroxide and of silver oxide, under various conditions, on the *methiodides* and *methochlorides* of both α- and β-hydroxylaudanosines was to give a relatively volatile oil from which the *methiodide* and the *picrate* of a base, $C_{13}H_{19}O_2N$, were obtainable. When this base was extracted from the product by means of acid, the residue was veratraldehyde (recognised by derivatives which included the 2 : 4-*dinitrophenylhydrazone*), and it became apparent that the compound $C_{13}H_{19}O_2N$ was 4 : 5-*dimethoxy-2-vinylbenzyldimethylamine* (III). The novelty of the decomposition of the hydroxylaudanosine methohydroxides in comparison with others of similar constitution suggests that the initial phase in the degradation is the detachment of the veratryl nucleus; no alternative to the formation of the vinyl base (III) would then be possible.

(III.)





(IV.)

In conformity with its unsaturated character, the amine polymerised on attempted distillation, and absorbed two atoms of hydrogen when catalytically reduced, giving 4 : 5-*dimethoxy-2-ethylbenzyldimethylamine* (IV, R = $CH_2{\cdot}NMe_2$). This was a liquid which was identified by its *picrate, methiodide,* and *methochloride,* the last being identical with the catalytic reduction product of 4 : 5-*dimethoxy-2-vinylbenzyltrimethylammonium chloride.*

Since Hofmann's method of exhaustive methylation is not applicable to amines such as (III), the second phase in the degradation was attempted by the Emde process, for which purpose the methochloride of the reduced base (IV, R = $CH_2{\cdot}NMe_2$) was used.

The oil remaining when the evolution of trimethylamine had ceased was 4-*methyl*-5-*ethylveratrole* (IV, R = Me), and on demethylation this gave the solid 4-methyl-5-ethylcatechol, which, being difficult to purify, was characterised by its crystalline *di*-p-*nitrobenzoate*.

The constitution of the ultimate degradation product was proved by a synthesis from 4-methylveratrole, conveniently prepared from veratraldehyde by the Clemmensen reduction process. The introduction of an acetyl group gave 4 : 5-dimethoxy-2-methylacetophenone (Harding and Weizmann, J., 1910, **97**, 1127), and a further application of the Clemmensen method of reduction completed the synthesis. The product was afterwards demethylated and compared with the material originating from the hydroxylaudanosines by means of the di-*p*-nitrobenzoate.

An attempted preparation of the amine (IV, R = $CH_2{\cdot}NMe_2$) had to be abandoned because a necessary intermediate reaction—the introduction of an acetyl group into veratryl acetate—could not be accomplished.

A synthesis of 4 : 5-dimethoxy-2-ethylbenzyltrimethylammonium iodide was, however, effected. Nitration of 4-ethylveratrole in acetic acid solution gave 5-*nitro*-4-*ethylveratrole* (IV, R = NO_2), which was converted by reduction, either with tin and hydrochloric acid, or, better, by the catalytic method, into the crystalline 5-amino-4-ethylveratrole (IV, R = NH_2), characterised by an *acetyl* derivative. Diazotisation and the action of cuprous cyanide gave the related *cyano*-compound (IV, R = CN), which the action of sodium and alcohol reduced to 4 : 5-dimethoxy-2-ethylbenzylamine (IV, R = $CH_2{\cdot}NH_2$), characterised as its *picrolonate*. Methylation with excess of methyl iodide produced the crystalline methiodide of 4 : 5-dimethoxy-2-ethylbenzyldimethylamine, which was readily identified with the corresponding salt of degradative origin.

In an attempt to obtain the free amine (IV, R = $CH_2{\cdot}NMe_2$) from the related methochloride, the dry salt was heated under reduced pressure, for under these conditions benzyltrimethylammonium chloride, for example, yields benzyldimethylamine and methyl chloride together with benzyl chloride and trimethylamine (Collie and Schryver, J., 1890, **57**, 778). The solid distillate, however, consisted entirely of 4 : 5-*dimethoxy*-2-*ethylbenzyl chloride* (IV, R = CH_2Cl), which was subsequently prepared in one operation from 4-ethylveratrole, formaldehyde, and hydrochloric acid. It proved an ideal intermediate for the synthesis of the desired *amine* (IV, R = $CH_2{\cdot}NMe_2$), which was formed in good yield on heating the chloride with methyl-alcoholic dimethylamine.

EXPERIMENTAL.

α- and β-Hydroxylaudanosine Methiodides and Methochlorides.—When heated with methyl iodide under reflux on a steam-bath for 2 hours, α-hydroxylaudanosine (7 g.), m. p. 138°, gave a *methiodide* which, after evaporation of the surplus reagent and crystallisation from alcohol, formed stout colourless prisms (10 g.), m. p. 168° (efferv.) (Found: C, 51·3; H, 6·1; I, 24·6. $C_{21}H_{27}O_5N,CH_3I$ requires C, 51·3; H, 5·8; I, 24·7%). The salt (8 g.) was digested with freshly prepared silver chloride (8 g.) and water (100 c.c.) on a steam-bath for ½ hour, and the resulting solution filtered from silver compounds and evaporated under diminished pressure. On crystallisation of the residue from alcohol, *α-hydroxylaudanosine methochloride* was obtained in colourless prisms, m. p. 165—166° (efferv.) (Found: Cl, 8·1. $C_{21}H_{27}O_5N,CH_3Cl$ requires Cl, 8·3%).

The formation of *β-hydroxylaudanosine methiodide* from the base of m. p. 108—109° (40 g.) began exothermally, and after brief heating under reflux the excess of methyl iodide was evaporated and the product triturated with cold methyl alcohol. Crystallisation from water afforded stellate clusters of large colourless prisms, m. p. 223—225° (Found: I, 24·8%). By the action of silver chloride there was obtained the *methochloride* (37 g.), which separated from alcohol in aggregates of opaque white prisms, m. p. 217—218° (efferv.) (Found: Cl, 8·2%).

Degradation of Hydroxylaudanosine Metho-salts.—(a) *With sodium hydroxide.* In the earlier experiments a solution of the methiodide (10 g.) in water (20 c.c.) was heated with aqueous sodium hydroxide (50 c.c. of 30%) in an oil-bath. The pale yellow oil liberated during 2 hours' boiling was removed in chloroform, and the solution dried with sodium sulphate and evaporated. On distillation, almost the entire product passed over as a colourless liquid (6—6·5 g.), b. p. 128°/2 mm. (Found: C, 68·0, 68·4; H, 8·4, 8·5; N, 5·2%). With alcoholic picric acid it yielded a *picrate*, which crystallised from alcohol in shining yellow thin prisms, m. p. 158—

159°, and was subsequently identified as that of 4 : 5-dimethoxy-2-vinylbenzyldimethylamine (III) (Found : C, 51·1; H, 5·1; N, 12·6; OMe, 14·1. $C_{13}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 50·7; H, 5·2; N, 12·5; OMe, 14·0%). The *methiodide* of the base (III), which resulted from the vigorous reaction of the oil with excess of methyl iodide, separated from alcohol in stellate clusters of colourless prisms, m. p. 197—198° (Found : C, 46·5; H, 6·0; N, 4·3; OMe, 17·3. $C_{13}H_{19}O_2N,CH_3I$ requires C, 46·3; H, 6·3; N, 3·9; OMe, 17·1%).

On further investigation it was shown that, although no degradation occurred unless the sodium hydroxide solutions were boiled for a time, relatively low concentrations (*e.g.*, 1·2 mols. of 2%) were effective. Nevertheless, the distilled chloroform extracts, whether from α- or β-hydroxylaudanosine methiodide or methochloride, were invariably alike, each yielding the identical picrate, m. p. 158—159°, and methiodide, m. p. 197—198°. The extracted alkaline solutions on acidification gave small amounts of white precipitate, which after crystallisation from water had m. p. 181° alone or mixed with veratric acid.

(b) *With silver oxide.* A solution of α-hydroxylaudanosine methiodide (10 g.) in water (75 c.c.) was shaken in the cold with freshly prepared silver oxide (5 g.). Silver iodide was formed, and after a few minutes the liquid was filtered and boiled for ½ hour. The solution remained clear, and was accordingly evaporated under reduced pressure at 50°, a white solid being obtained, m. p. (rapidly heated) *ca.* 115° (efferv.). It showed an alkaline reaction, and was presumably the methohydroxide. When heated under diminished pressure at 75—85°, it decomposed, evolving water and leaving an oil, b. p. 128°/2 mm., which gave the already known picrate, m. p. 158—159°, and methiodide, m. p. 197—198°.

This oil was likewise obtained from the other hydroxylaudanosine metho-salts, and in order to separate its constituents, the product from β-hydroxylaudanosine methochloride (37 g.), after being washed with aqueous sodium hydroxide to remove traces of veratric acid, was distilled, and the distillate (28 g.) shaken with excess of dilute hydrochloric acid. The insoluble portion was removed by chloroform, and on distillation gave a product (12 g.), b. p. 148°/11 mm., which solidified and had m. p. 44—45° alone or mixed with veratraldehyde. Its identity was further established by the preparation of the phenylhydrazone, m. p. 120° (121°; Juliusberg, *Ber.*, 1907, **40**, 119), semicarbazone, m. p. 181° (177°; Béhal and Tiffeneau, *Bull. Soc. chim.*, 1908, **3**, 309), and 2 : 4-*dinitrophenylhydrazone*, which crystallised from acetic acid in short orange needles, m. p. 253—255° (Found : N, 16·4. $C_{15}H_{14}O_6N_4$ requires N, 16·1%).

The acid-soluble portion was liberated from the hydrochloric acid layer by neutralisation with alkali. It was a colourless oil (*ca.* 15 g.), of which specimens gave virtually quantitative yields of the picrate, m. p. 158—159°, and the methiodide, m. p. 197—198°. An attempted distillation in a high vacuum caused formation of a non-volatile resinous polymer which was acid-soluble but gave no crystalline derivatives.

4 : 5-*Dimethoxy*-2-*ethylbenzyldimethylamine* (IV, $R = CH_2{\cdot}NMe_2$).—A solution of the foregoing unsaturated base (3·4 g.) in alcohol (30 c.c.) was acidified with concentrated hydrochloric acid (2 c.c.) and catalytically reduced by using palladium chloride (0·4 g.). Approximately the theoretical quantity of hydrogen (350 c.c.) was quickly absorbed, and after filtration the solution was evaporated to obtain the hydrochloride of the amine (IV, $R = CH_2{\cdot}NMe_2$), which was an uncrystallisable gum and was therefore dissolved in water and decomposed by sodium carbonate. The precipitated 4 : 5-*dimethoxy*-2-*ethylbenzyldimethylamine* was removed by chloroform, and the solution dried with sodium sulphate and distilled; the base, a colourless oil of faint fish-like odour, had b. p. 108°/0·06 mm. (Found : C, 69·7; H, 9·3; N, 6·1. $C_{13}H_{21}O_2N$ requires C, 70·0; H, 9·4; N, 6·3%). Mixture of equivalents of the amine and picric acid in alcoholic solution produced the *picrate*, long yellow needles, m. p. 110—111° (Found : N, 12·6. $C_{13}H_{21}O_2N,C_6H_3O_7N_3$ requires N, 12·4%).

4 : 5-*Dimethoxy*-2-*ethylbenzyltrimethylammonium Chloride.*—(a) When methyl iodide (2 c.c.) was added to the pure base (IV, $R = CH_2{\cdot}NMe_2$) (2 g.), a vigorous reaction ensued, giving the *methiodide* (3 g.) which formed clusters of colourless needles, m. p. 209° (Found : I, 34·9. $C_{13}H_{21}O_2N,CH_3I$ requires I, 34·8%), from alcohol. A solution of the salt (2 g.) in water (45 c.c.), digested with silver chloride, gave on evaporation the *trimethylammonium chloride* as a white solid. Crystallised from alcohol, it formed long hexagonal prisms, m. p. 150—151°, of the *monohydrate* (Found : loss on drying at 115°, 6·0. $C_{13}H_{21}O_2N,CH_3Cl,H_2O$ requires H_2O, 6·2%. Found in dried material : Cl, 12·7. $C_{13}H_{21}O_2N,CH_3Cl$ requires Cl, 13·0%).

(b) From the methiodide of the unsaturated base (III) by the action of silver chloride the corresponding *methochloride* was obtained. It was very soluble in alcohol, but slowly crystallised from methyl ethyl ketone in colourless microcrystals, m. p. 218° (efferv.) (Found : Cl, 13·0. $C_{13}H_{19}O_2N,CH_3Cl$ requires Cl, 13·1%). A solution of the chloride (10 g.) in alcohol (100 c.c.)

was reduced by hydrogen in presence of platinum oxide catalyst (0·4 g.). The reaction ceased in 2 hours after approximately the required amount of hydrogen (825 c.c.) had been absorbed, and when filtered and evaporated, the solution yielded the methochloride of the amine (IV, $R = CH_2{\cdot}NMe_2$), m. p. 150—151° alone or mixed with a specimen obtained as in (a).

Degradation of 4 : 5-*Dimethoxy*-2-*ethylbenzyltrimethylammonium Chloride by Emde's Method.*—A solution of the chloride (4 g.) in water (50 c.c.) was heated on a steam-bath and, with carbon dioxide passing through the liquid, sodium amalgam (14 g.) was added during 6 hours. After acidification with hydrochloric acid, the oily upper layer which had appeared was dissolved in benzene, which was then dried and distilled. 4-*Methyl*-5-*ethylveratrole* (IV, R = Me) (1·8 g.) was thus obtained as a colourless oil of distinctive odour, b. p. 105°/5 mm. (Found : C, 73·5; H, 8·9. $C_{11}H_{10}O_2$ requires C, 73·3; H, 8·9%). The oil (1·7 g.) and hydriodic acid (25 c.c., b. p. 126°) were heated in a carbon dioxide atmosphere under reflux at 140° for 1 hour. The solution was cooled, diluted with water, and shaken with chloroform; this extracted 4-methyl-5-ethylcatechol, a somewhat hygroscopic solid which was difficult to purify. When it was dissolved in pyridine and treated with *p*-nitrobenzoyl chloride (2 mols.), a vigorous reaction occurred which was completed by heating on a steam-bath for ½ hour. After the addition of water, the pale yellow solid was washed with acid, then alkali, and finally water, and crystallised from alcohol or a little ethyl acetate diluted with alcohol. 4-*Methyl*-5-*ethylcatechol di*-p-*nitrobenzoate* then formed colourless needles, m. p. 124—125° (Found : C, 61·4; H, 4·2. $C_{23}H_{18}O_6N_2$ requires C, 61·3; H, 4·0%).

3 : 4-*Dimethoxytoluene.*—Veratraldehyde (100 g.), prepared as by Barger and Silberschmidt (J., 1928, 2924), was heated for 15 hours with concentrated hydrochloric acid (1000 c.c.) boiling under reflux with amalgamated zinc (500 g.). After dilution with water, the reaction mixture was steam-distilled, and the distillate extracted with chloroform. The chloroform layer, dried and distilled, gave 3 : 4-dimethoxytoluene (29 g.), b. p. 110°/18 mm. (Found : C, 71·2; H, 7·9. Calc. for $C_9H_{12}O_2$: C, 71·1; H, 7·9%).

4-*Methyl*-5-*ethylveratrole* (IV, R = Me).—4 : 5-Dimethoxy-2-methylacetophenone (20 g.), prepared from 3 : 4-dimethoxytoluene by the method of Harding and Weizmann (*loc. cit.*), and amalgamated zinc (100 g.) were heated with concentrated hydrochloric acid (200 c.c.) boiling under reflux. After 15 hours, more acid (100 c.c.) was added, the heating being continued for a further 5 hours; the liquid was then diluted and steam-distilled. The chloroform-soluble product, 4-methyl-5-ethylveratrole, was an oil (14 g., yield 78%), b. p. 105°/5 mm. (Found : C, 73·2; H, 8·8%). Its identity with the Emde degradation product was proved by demethylation to the catechol compound, which was converted into the di-*p*-nitrobenzoate as already described, the synthetical material having m. p. 124—125° alone or mixed with a specimen originating from the hydroxylaudanosines.

Veratryl Alcohol, and Experiments with Veratryl Acetate.—A solution of veratraldehyde (25 g.) in methyl alcohol (150 c.c.) was reduced by hydrogen under pressure (maximum 2—3 atm.) with platinum oxide (0·7 g.) as catalyst. The absorption of gas (*ca.* 3,700 c.c.; 1 mol.) was rapid, and after 10 minutes all reaction ceased. The solution was then filtered (small quantities of platinum promote condensation to tetramethoxydihydroanthracene during distillation) and evaporated, and the alcohol distilled : yield, above 95% of b. p. 165°/11 mm. (compare the use of platinum-black by Vavon, *Compt. rend.*, 1912, **154**, 360; and by Carrara and Cohn, *Gazzetta*, 1926, **56**, 144) (Found : C, 64·5; H, 7·2. Calc. for $C_9H_{13}O_3$: C, 64·3; H, 7·1%).

A strongly cooled solution of the alcohol (5 g.) in pyridine (18 c.c.) was treated with acetyl chloride (2·5 g., 1·1 mols.), and after 1 hour at the ordinary temperature was poured into dilute hydrochloric acid. The brownish oil extracted by ether gave on distillation veratryl acetate, b. p. 134°/0·08 mm. A further preparation of 41 g., b. p. 168°/14 mm., was obtained by refluxing the alcohol (36 g.) with excess of acetic anhydride (cf. Vavon, *loc. cit.*; Tiffeneau and Fuhrer, *Bull. Soc. chim.*, 1914, **15**, 171) (Found : C, 62·4; H, 6·9. Calc. for $C_{11}H_{14}O_4$: C, 62·2; H, 6·7%).

The action of powdered aluminium chloride (60 g.) added in portions at intervals of 10 minutes to the acetate (30 g.) and acetyl chloride (13 g.) in carbon disulphide (1500 c.c.) occurred smoothly at room temperature, and was completed after 24 hours on a hot water-bath. The solvent was then decanted, and the product submitted to steam-distillation. The light brown solid residue could not be crystallised, and an attempted reduction by the Clemmensen process left it largely unchanged, although a small amount of a compound which crystallised from alcohol in colourless needles, m. p. 215°, was isolated (Found : C, 69·9; H, 6·8%).

5-*Nitro*-4-*ethylveratrole.*—4-Ethylveratrole (25 g.) (Barger and Silberschmidt, *loc. cit.*) was added dropwise to a solution of nitric acid (15 c.c.) in water (15 c.c.) maintained at 0°. The solution darkened and became viscous, and on removing it from the freezing mixture heat was evolved. After 2 hours, the product was heated on a water-bath at 60° for 40 minutes and then poured into water. The heavy oil solidified and was collected and dried. 5-*Nitro*-4-*ethylveratrole* distilled at 177°/12 mm. and crystallised from light petroleum in clusters of long yellow prisms, m. p. 54—54·5° (Found: C, 57·1; H, 6·1. $C_{10}H_{13}O_4N$ requires C, 56·9; H, 6·1%). In later experiments a solution of 4-ethylveratrole (25 g.) in acetic acid (25 c.c.) was added to cooled nitric acid (15 c.c.); yield 25 g., b. p. 138°/0·02 mm.

5-*Amino*-4-*ethylveratrole*.—Tin-foil (25 g.) was added in portions to a suspension of 5-nitro-4-ethylveratrole (10 g.) in concentrated hydrochloric acid (110 c.c.), and when the reaction had slackened the mixture was heated on a steam-bath for ½ hour. Water was added, and the tin precipitated by hydrogen sulphide. The amine being easily soluble in water, the filtered solution was concentrated under diminished pressure to *ca.* 100 c.c., saturated with ammonium sulphate, and basified with ammonia. The purple oil was removed by several extractions with ether, and gave 5-amino-4-ethylveratrole (3 g.) as a pale yellow liquid, b. p. 154°/3 mm., crystallising in prisms, m. p. 63°, which slowly darkened. It was characterised by the *acetyl* derivative, which crystallised from water in colourless prisms, m. p. 147° (Found: N, 6·4. $C_{12}H_{17}O_3N$ requires N, 6·3%).

The nitro-compound (20 g.) was more conveniently reduced by dissolving it in alcohol (250 c.c.) and shaking the solution with hydrogen (maximum pressure, 2—3 atm.) in contact with palladised strontium carbonate (7 g. of 5%). The theoretical amount of hydrogen (6·3 l.) was absorbed in 1½ hours, and the filtered solution was then evaporated and the residue distilled; yield of pure amine, 16 g.

5-*Cyano*-4-*ethylveratrole*.—Cuprous chloride, prepared by reducing a solution of copper sulphate (27·5 g.) and sodium chloride (9·8 g.) in hot water (90 c.c.) with aqueous sodium sulphite [from sodium bisulphite (7·6 g.) and sodium hydroxide (5·6 g.) in water (40 c.c.)], was suspended in water (50 c.c.) and treated with a solution of sodium cyanide (15 g.) in 25 c.c. of water. 5-Amino-4-ethylveratrole (16 g.), dissolved in concentrated hydrochloric acid (20 c.c.) and water (75 c.c.), was cooled in a freezing-mixture and diazotised with a solution of sodium nitrite (6·6 g.) in water (20 c.c.). The diazo-solution was neutralised with a little solid sodium carbonate, and the cuprous cyanide, cooled by crushed ice and mixed with benzene (50 c.c.), was introduced in small quantities below 0°. Vigorous stirring was continued for 5 hours at room temperature, and the mixture was then heated for ½ hour at 50°. The benzene layer was thoroughly washed (acid; alkali; water), dried, and evaporated, leaving 5-*cyano*-4-*ethylveratrole*, which showed signs of decomposition when heated under 15 mm., but distilled at 126—127°/0·05 mm. as a straw-coloured liquid (11 g.). It solidified on cooling, having m. p. 56—58°, and crystallised from light petroleum in colourless elongated prisms, m. p. 60° (Found: C, 69·1; H, 6·8; N, 7·5. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%).

4 : 5-*Dimethoxy*-2-*ethylbenzylamine*.—To a solution of the cyanide (5 g.) in alcohol (90 c.c.) boiling under reflux on a steam-bath, sodium (8 g.) was added in portions of *ca.* 1 g. during 1½ hours. When all the sodium had dissolved, water (50 c.c.) was added, and the alcohol was evaporated on a steam-bath with the assistance of a stream of air. The product was extracted with ether, and the basic constituent removed from the extract by shaking with dilute hydrochloric acid, leaving in the ether a neutral oil, b. p. 51°/1 mm. (Found: C, 77·3; H, 9·9%). The acid solution was basified, and the precipitated 4 : 5-dimethoxy-2-ethylbenzylamine isolated and distilled. It was a colourless liquid, b. p. 102—103°/1 mm., and with alcoholic picrolonic acid gave a sparingly soluble *picrolonate*, crystallising in rosettes of pale yellow needles, m. p. *ca.* 235° (decomp.) (Found: N, 15·6. $C_{11}H_{17}O_2N,C_{10}H_8O_5N_4$ requires N, 15·3%).

The amine was methylated by boiling for several hours with a large excess of methyl iodide. The product, which was isolated by evaporation to dryness, was dissolved in a little alcohol, and after 2 days a crystalline deposit of 4 : 5-dimethoxy-2-ethylbenzyltrimethylammonium iodide had formed, m. p. 208° alone or mixed with the salt from the hydroxylaudanosines.

4 : 5-*Dimethoxy*-2-*ethylbenzyl Chloride*.—When heated in a high vacuum, 4 : 5-dimethoxy-2-ethylbenzyltrimethylammonium chloride gave a distillate, b. p. 128°/1 mm., consisting of 4 : 5-*dimethoxy*-2-*ethylbenzyl chloride* (IV, R = CH_2Cl), which crystallised on cooling and had m. p. 40° (Found: C, 62·0; H, 7·0; Cl, 16·2. $C_{11}H_{15}O_2Cl$ requires C, 61·6; H, 7·0; Cl, 16·3%). It was also obtained when aqueous formaldehyde (15 c.c.; 40%) containing 4-ethylveratrole (5 g.) was boiled with concentrated hydrochloric acid under reflux for ½ hour. The oily portion darkened and became more viscous, and on cooling was extracted by ether and fractionally distilled. The first fraction (2·3 g.), b. p. 129°/1 mm., formed colourless crystals (Found:

C, 61·2; H, 7·0%), m. p. 40° alone and when mixed with the degradation product of the quaternary chloride (IV, R = $CH_2\cdot NMe_3Cl$).

4 : 5-*Dimethoxy-2-ethylbenzyldimethylamine*.—On adding the foregoing chloride (1·8 g.) to a solution of dimethylamine (3 g.) in methyl alcohol (7 c.c.), heat was evolved, but the mixture was heated in a sealed tube at 120° before attempting to isolate the product. The alcohol was evaporated, the residue acidified with hydrochloric acid, and non-basic material removed by ether. An excess of sodium hydroxide added to the acid layer liberated the tertiary *amine* (IV, R = $CH_2\cdot NMe_2$) as a colourless liquid, b. p. 108°/0·06 mm. (Found: N, 6·4. $C_{13}H_{21}O_2N$ requires N, 6·3%). The picrate, m. p. 110—111°, and the methiodide, m. p. 209°, were identified with specimens obtained in the course of the degradation experiments.

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