The Synthesis of Some N-*Substituted* 2-(3 : 4-*Dihydroxyphenyl*)*ethylamines.*

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N-2-(3 : 4-Dihydroxyphenyl)ethyl-3 : 4-methylenedioxybenzylamine (I) has been synthesised with *O*-benzyl ethers as intermediates. *N*-(3 : 4-Dihydroxybenzyl)-2-(3 : 4-dihydroxyphenyl)ethylmethylamine (VII) has been prepared *via* its tetramethyl ether. In experiments relating to the synthesis of this tetramethyl ether, quaternary salts of Schiff's bases have been shown to undergo *N*-demethylation on catalytic reduction or treatment with lithium aluminium hydride.

N-SUBSTITUTED 2-(3 : 4-dihydroxyphenyl)ethylamines (3 : 4-dihydroxyphenethylamines) were required for oxidation experiments, and this paper describes their preparation. The routes employed were determined by the nature of the substituents in the aromatic rings.

N-2-(3 : 4-Dihydroxyphenyl)ethyl-3 : 4-methylenedioxybenzylamine (I) and the *N*-(3 : 4-dihydroxybenzyl) analogue were prepared by Buck (*J. Amer. Chem. Soc.*, 1931, **53**, 2192) by demethylation of the corresponding methyl ethers. While this method was satisfactory for the latter substance, it proved unsuitable for obtaining the former in any reasonable quantity. This is not surprising since Späth and Quietensky (*Ber.*, 1927, **60**, 1882) found that when a methylenedioxy-group and vicinal methoxy-groups were present together, the former was hydrolysed preferentially.

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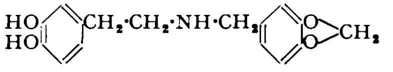
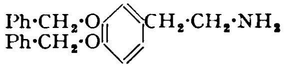
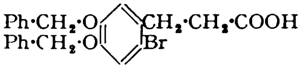
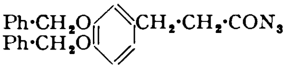



(II)

(III)


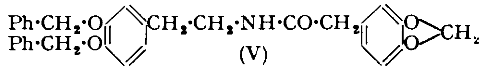

(IV)

Since *O*-benzyl groups can readily be removed by hydrogenolysis, which leaves methylenedioxy-groups intact, we turned to the preparation of the dibenzyl ether of (I), with 2-(3 : 4-dibenzyloxyphenyl)ethylamine (II) as a preliminary.

β-(3 : 4-Dibenzyloxyphenyl)propionic acid was prepared from the dihydroxy-acid, and its amide was subjected to the Hofmann reaction, first, with sodium hypochlorite, which was without effect, and then in methanolic sodium methoxide with bromine. The latter procedure gave a monobromo-derivative of the amide, which was hydrolysed to the corresponding bromo-acid (probably III) and ammonia.

Methyl β-(3 : 4-dibenzyloxyphenyl)propionate was converted, *via* the hydrazide, into the azide (IV) (cf. Schöpf, Perrey, and Jächk, *Annalen*, 1932, **497**, 52). This decomposed smoothly in benzene to give 2-(3 : 4-dibenzyloxyphenyl)ethyl *iso*cyanate, which was subsequently hydrolysed, under acid and alkaline conditions, though the amine (II) was not obtained in either case. Acid hydrolysis removed also the benzyl groups, and alkaline conditions afforded the symmetrical urea.

Schöpf *et al.* (*loc. cit.*) obtained a high yield of the amide (V) from 2-(3 : 4-dibenzyloxyphenyl)ethyl *iso*cyanate and 3 : 4-methylenedioxyphenylacetic acid. When, in the present work, 3 : 4-methylenedioxybenzoic acid was used the expected amide was also obtained, though the yield was so low (production of the urea and acid anhydride) that the route was not pursued further. The unwanted products may arise by disproportionation of the intermediate mixed anhydride (VI) at both of the positions indicated, followed by recombination of the appropriate fragments.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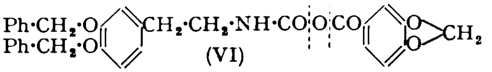
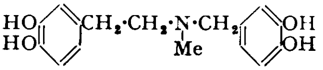
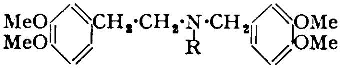

(VI)

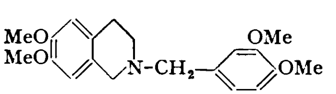
2-(3 : 4-Dibenzyloxyphenyl)ethylamine (II) was eventually obtained as its *N*-methoxycarbonyl derivative by decomposing the azide (IV) in boiling benzene containing methanol. The hydrolysis of the methoxycarbonyl compound with aqueous alcoholic alkali, to give 2-(3 : 4-dibenzyloxyphenyl)ethylamine (II), was unexpectedly easy. The amine (II) condensed readily with piperonaldehyde when heated, to give a Schiff's base, which was reduced catalytically to the dibenzyl ether of (I), in presence of a Raney nickel catalyst of only moderate activity. *O*-Debenzylation was accomplished by catalytically reducing the base hydrochloride in methanol at a palladium–barium sulphate catalyst. The product, *N*-2-(3 : 4-dihydroxyphenyl)ethyl-3 : 4-methylenedioxybenzylamine (I), was obtained in fine colourless needles (from propan-2-ol), m. p. 222°. Buck (*loc. cit.*) describes his product as a buff powder, m. p. 219°.

N-(3 : 4-Dihydroxybenzyl)-2-(3 : 4-dihydroxyphenyl)ethylmethylamine (VII) was obtained by demethylating its tetramethyl ether. During the preparation of this ether (VIII; R = Me) a number of unusual results were encountered.

Heating the secondary amine (VIII; R = H) with formaldehyde and formic acid gave a substance containing two hydrogen atoms less than the expected methylamine (VIII; R = Me). *O*-Demethylation furnished a substance which contained no *N*-methyl group and was again two hydrogen atoms short of the expected methylamine. The original product was then shown to be identical with 2-(3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy*iso*quinoline (IX) obtained by the action of hydrochloric acid on the intermediate hydroxymethylamine.

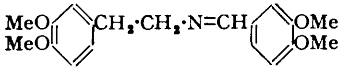
(VII)


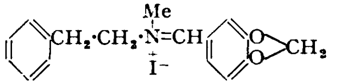

(VIII)


(IX)

Reduction of the quaternary methochloride of a 3 : 4-dihydro*iso*quinoline gave the corresponding tetrahydro-*N*-methyl*iso*quinoline (Späth and Hromatka, *Ber.*, 1929, **62**, 325). Likewise, the reduction of a quaternary salt of the Schiff's base 3 : 4-dimethoxybenzylidene-2-(3 : 4-dimethoxyphenyl)ethylamine (X) might be expected to give the required *N*-methylamine (VIII; R = Me) provided that hydrolytic conditions are avoided, as in catalytic reductions. In practice, the quaternary salt of the Schiff's base (X) dissolved in organic solvents only after addition of an appreciable amount of water, so reduction of the azomethine group was usually forestalled by its hydrolysis, which gave 2-(3 : 4-dimethoxyphenyl)ethylmethylamine. When aqueous dioxan was used as the solvent, the amount of water present was a minimum (1—2%), and reduction of the azomethine group ensued, though the result was unexpected. Not only was the double bond reduced, but the *N*-methyl group was eliminated, giving the secondary amine *N*-(3 : 4-dimethoxybenzyl)-2-(3 : 4-dimethoxyphenyl)ethylamine (VIII; R = H) obtained by reducing the Schiff's base (X). As far as the author is aware this is the only example known of the catalytic hydrogenolysis of an *N*-methyl group.

(X)





(XI)

A similar result was obtained when the closely related compound (XI) was treated with lithium aluminium hydride. When the dry solid methiodide (XI) was added to an ethereal solution of lithium aluminium hydride, a considerable evolution of gas accompanied dissolution of the yellow solid. From the resultant colourless solution the secondary amine *N*-(3 : 4-methylenedioxybenzyl)-2-phenylethylamine was isolated as the sole product. The reaction probably involves the initial elimination of the methyl group of the quaternary salt by a hydride ion, and in accordance with this view is the conversion of strychnine methosulphate into strychnidine with lithium aluminium hydride (Kenner and Murray, *J.*, 1949, S 178). This was considered to be an elimination reaction in which the methyl group, being more susceptible to S_N2 reactions than higher alkyl groups, was eliminated by a hydride ion (*idem, loc. cit.*). Both reactions may thus be formulated :

$$\equiv N^{+}—Me + H^{-} \longrightarrow \equiv N + CH_4$$

In the present case this would give a Schiff's base, which would be further reduced to a secondary amine. The use of the milder sodium borohydride in methanol (cf. Witkop and Patrick, *J. Amer. Chem. Soc.*, 1953, **75**, 4474) gave mixtures which were not further investigated.

N-(3 : 4-Dimethoxybenzyl)-2-(3 : 4-dimethoxyphenyl)ethylmethylamine (VIII; R = Me) was obtained when 2-(3 : 4-dimethoxyphenyl)ethylmethylamine was condensed with 3 : 4-dimethoxybenzyl chloride in ethanol. It was more satisfactorily prepared by catalytic reductive alkylation of *N*-(3 : 4-dimethoxybenzyl)-2-(3 : 4-dimethoxyphenyl)ethylamine (VIII; R = H). This elegant procedure was used by Tarbell and Craig (*J. Amer. Chem. Soc.*, 1948, **70**, 2783) to convert tetrahydropapaverine into laudanosine. The secondary amine (VIII; R = H) was treated with formaldehyde in ethanol, and the resulting hydroxymethylamine was hydrogenated at 3—4 atm. to the tertiary methylamine (VIII; R = Me) in 80% yield.

When heated with concentrated hydrochloric acid at 160—170°, the tertiary amine (VIII; R = Me) was smoothly demethylated to *N*-(3 : 4-dihydroxybenzyl)-2-(3 : 4-dihydroxyphenyl)ethylmethylamine (VII).

EXPERIMENTAL

2-(3 : 4-Dimethoxyphenyl)ethylamine was prepared by the hydrogenation of 3 : 4-dimethoxybenzyl cyanide in saturated alcoholic ammonia (Bide and Wilkinson, *Chem. and Ind.*, 1945, **64**, 84).

N-2-(3 : *4-Dimethoxyphenyl)ethyl-*3 : *4-methylenedioxybenzylamine.*—*N*-3 : 4-Methylenedioxybenzylidene-2-(3 : 4-dimethoxyphenyl)ethylamine (Buck, *loc. cit.*) (2·5 g.) was hydrogenated in dioxan (15 c.c.) at atmospheric pressure in presence of a fair quantity of Raney nickel. When reduction was complete (*ca.* 4 hr.), the liquid was filtered, the solvent was removed, and the residual amine was dissolved in dry ether. Treatment of the ethereal solution with dry hydrogen chloride precipitated the hydrochloride, needles, m. p. 200° (from dilute hydrochloric acid or ethanol) (Found : C, 61·6; H, 6·5; Cl, 10·0. Calc. for $C_{18}H_{22}O_4NCl$: C, 61·5; H, 6·3; Cl, 10·1%). Buck (*loc. cit.*) gives m. p. 219°. The *picrate* crystallised from aqueous ethanol in golden needles, m. p. 158° (Found : C, 52·9; H, 4·6; N, 10·2. $C_{24}H_{24}O_{11}N_4$ requires C, 52·9; H, 4·4; N, 10·3%).

β-(3 : *4-Dibenzyloxyphenyl)propionic Acid.*—β-(3 : 4-Dihydroxyphenyl)propionic acid (36 g.)

(Schöpf, Perrey, Jächk, *Annalen*, 1932, **497**, 52), benzyl chloride (68·5 g.), and anhydrous potassium carbonate (82 g.) in absolute methanol (450 c.c.) were heated under reflux for 6 hr. The resulting benzyl ester was hydrolysed by heating it with potassium hydroxide (25 g.) in water (40 c.c.) for 4 hr. Most of the methanol was then removed, and water (1·2 l.) was added, giving a homogeneous solution which was extracted with ether and treated with charcoal. Acidifying the cooled solution gave the *acid* which crystallised from a small quantity of methanol in needles, m. p. 116—117° (52 g.). A second crystallisation afforded a specimen, m. p. 118° (Found : C, 76·3; H, 6·0. $C_{23}H_{22}O_4$ requires C, 76·2; H, 6·1%).

β-(3 : 4-*Dibenzyloxyphenyl*)*propionamide*.—β-(3 : 4-Dibenzyloxyphenyl)propionic acid (1 g.), thionyl chloride (1 c.c.), and chloroform (5 c.c.) were heated under reflux for 1 hr. Volatile material was removed under reduced pressure, and the residue was dissolved in a few c.c. of dioxan and poured into ice-cold concentrated ammonia. The precipitated *amide* crystallised from methanol in needles, m. p. 126° (Found : C, 76·2; H, 6·3; N, 4·1. $C_{23}H_{23}O_3N$ requires C, 76·2; H, 6·4; N, 3·9%).

Hofmann Reaction on β-(3 : 4-*Dibenzyloxyphenyl*)*propionamide*.—The amide (1·8 g.) and sodium methoxide (0·5 g.) were dissolved in warm methanol (30 c.c.). When bromine (0·3 c.c.) was added to the cooled solution its colour was immediately discharged. After being heated under reflux for 30 min., the solution was poured into water, giving a copious precipitate of an *amide*, which crystallised from methanol in small needles, m. p. 141—141·5° (Found : C, 62·4; H, 4·5; Br, 18·1. $C_{23}H_{22}O_3NBr$ requires C, 62·7; H, 5·0; Br, 18·2%).

This compound is polymorphic for on remelting it has m. p. 152—153°, undepressed on admixture with a specimen of the monobromide obtained as feathery needles, m. p. 153°, from benzene (Found : C, 63·0; H, 4·6; N, 3·4; Br, 18·3. $C_{23}H_{22}O_3NBr$ requires N, 3·2%).

When the amide was heated with aqueous-alcoholic alkali, ammonia was evolved. After 8 hr., the product was poured into water, and acidified. An oil, which soon solidified, was collected, dried, and taken up in hot benzene–light petroleum, which, on cooling, deposited the *acid* in needles, m. p. 116° (Found : C, 62·4; H, 4·9; Br, 18·2. $C_{23}H_{21}O_4Br$ requires C, 62·6; H, 4·8; Br, 18·1%).

β-(3 : 4-*Dibenzyloxyphenyl*)*propionhydrazide*.—β-(3 : 4-Dibenzyloxyphenyl)propionic acid (10 g.) was esterified in dioxan (30 c.c.) with ethereal diazomethane. Evaporation *in vacuo* left a gum which was heated with 90% hydrazine hydrate (10 c.c.) and pentyl alcohol (5 c.c.) under reflux for 5 hr., then allowed to cool. Overnight the solution deposited the hydrazide in colourless needles (8·3 g.), m. p. 138—139°.

β-(3 : 4-*Dibenzyloxyphenyl*)*propionazide and Its Rearrangement*.—(*a*) β-(3 : 4-Dibenzyloxyphenyl)propionhydrazide was converted into the azide by the method of Schöpf, Perrey, and Jächk (*loc. cit.*). The benzene solution of the azide, so obtained, was heated under reflux for 2 hr. By this time the evolution of nitrogen had ceased, and the benzene was removed by distillation. The residual *iso*cyanate was then heated under reflux for 4 hr. with aqueous-alcoholic alkali. On cooling and dilution with water, there was obtained a semi-solid product, which, after decantation of the alkali and washing with water, was obtained crystalline by trituration with ethanol. Recrystallisation from benzene or alcohol afforded the NN′-*di*-[2-(3 : 4-*dibenzyloxyphenyl*)*ethyl*]*urea* in needles, m. p. 168° (Found : C, 78·2; H, 6·5; N, 3·9. $C_{45}H_{44}O_5N_2$ requires C, 78·0; H, 6·4; N, 4·0%).

(*b*) A rigorously dried solution of the azide in benzene was heated under reflux for 2 hr., and a solution of 3 : 4-methylenedioxybenzoic acid in dioxan–benzene (dried azeotropically) was added. On cooling, the solution deposited crystals of the urea, m. p. and mixed m. p. 166—167°. Evaporation of the filtrate produced a precipitate of N-2-(3 : 4-*dibenzyloxyphenyl*)-*ethyl*-3 : 4-*methylenedioxybenzamide*, which crystallised from ethanol in needles, m. p. 136—137° (Found : C, 74·5; H, 5·7; N, 3·0. $C_{30}H_{27}O_5N$ requires C, 74·8; H, 5·6; N, 2·9%). Further evaporation of the solution produced a residue of 3 : 4-*methylenedioxybenzoic anhydride*, which crystallised from ethanol-benzene in needles, m. p. 147° (Found : C, 61·3; H, 3·2. $C_{16}H_{10}O_7$ requires C, 61·3; H, 3·2%).

(*c*) A rigorously dried solution of the azide in benzene (from 5·6 g. of hydrazide) was heated under reflux with methanol (50 c.c.) for 4 hr. After removal of the solvent, *methyl* N-2-(3 : 4-*dibenzyloxyphenyl*)*ethylcarbamate* remained as a solid, which crystallised from light petroleum containing a little benzene in needles (4·2 g., 75%), m. p. 78° (Found : C, 73·6; H, 6·5; N, 3·75. $C_{24}H_{25}O_4N$ requires C, 73·7; H, 6·4; N, 3·6%).

2-(3 : 4-*Dibenzyloxyphenyl*)*ethylamine* (II).—The foregoing ester (2 g.) was heated under reflux with aqueous-alcoholic potassium hydroxide for 8 hr. The cooled solution was diluted with water and the precipitated amine extracted with ether. When hydrogen chloride was passed into the dried ethereal solution, 2-(3 : *4-dibenzyloxyphenyl)ethylamine hydrochloride* was obtained as plates, m. p. 133° (1·5 g., 80%), which recrystallised from ethyl acetate containing a little ethanol (m. p. unchanged) (Found : C, 71·5; H, 6·8; N, 4·0; Cl, 9·5. $C_{22}H_{23}O_2N,HCl$ requires C, 71·6; H, 6·5; N, 3·8; Cl, 9·5%).

2-(3 : *4-Dibenzyloxyphenyl)*-N-3 : *4-Methylenedioxybenzylidene-ethylamine.*—2-(3 : 4-Dibenzyloxyphenyl)ethylamine hydrochloride (1·2 g.) was suspended in water (10 c.c.), and just sufficient glacial acetic acid was added to render solution complete. Excess of alkali was then added and the precipitated amine extracted with chloroform (2 × 10 c.c.). The combined extracts were dried and the solvent was removed. Piperonaldehyde (0·5 g.) was added to the residual oil, and the mixture was heated at 100°/50 mm. for 30 min. By this time the water was removed, and the product was taken up in a large volume of hot ethanol, which, on cooling, deposited the *Schiff's base* (1·0 g.), needles, m. p. 77—78° (Found : C, 77·3; H, 6·1; N, 3·1. $C_{30}H_{27}O_4N$ requires C, 77·4; H, 5·8; N, 3·0%).

N-2-(3 : *4-Dibenzyloxyphenyl)ethyl*-3 : *4-methylenedioxybenzylamine.*—A solution of *N*-3 : 4-methylenedioxybenzylidene-2-(3 : 4-dibenzyloxyphenyl)ethylamine (2·0 g.) in dioxan (10 c.c.) was hydrogenated at atmospheric pressure with a Raney nickel catalyst of only moderate activity. After 1·5 hr., hydrogen uptake (1 mol.) was complete and the rate of adsorption had noticeably slackened. After filtration, the solution was evaporated, and water was added to the residue. The amine was extracted with ether and converted into its *hydrochloride* by hydrogen chloride. The salt crystallised from aqueous alcohol in needles (1·5 g.), m. p. 194° (Found : C, 71·5; H, 6·1; N, 2·7; Cl, 7·0. $C_{20}H_{29}O_4N,HCl$ requires C, 71·8; H, 6·0; N, 2·8; Cl, 7·0%).

N-2-(3 : *4-Dihydroxyphenyl)ethyl*-3 : *4-methylenedioxybenzylamine.*—The foregoing hydrochloride (1·0 g.) in absolute methanol (100 c.c.) was hydrogenated at atmospheric pressure with a 5% palladium–barium sulphate catalyst (0·5 g.). When hydrogen uptake was complete (2 mols.) the catalyst was removed by centrifugation, thus avoiding prolonged exposure of the product to air. The solvent was then removed *in vacuo*, leaving a residue which was crystallised from propan-2-ol. *N*-2-(3 : 4-Dihydroxyphenyl)ethyl-3 : 4-methylenedioxybenzylamine hydrochloride was thus obtained as needles, m. p. 222° (Found : C, 59·3; H, 5·8; N, 4·4; Cl, 10·6. Calc. for $C_{16}H_{17}O_4N,HCl$: C, 59·4; H, 5·6; N, 4·3; Cl, 10·8%).

2-(3 : *4-Dimethoxybenzyl)*-1 : 2 : 3 : *4-tetrahydro*-6 : *7-dimethoxy*iso*quinoline* (X).—A mixture of *N*-(3 : 4-dimethoxybenzyl)-2-(3 : 4-dimethoxyphenyl)ethylamine (5·0 g.), formic acid (3·8 c.c.), and 40% formaldehyde (1·8 c.c.) was heated on a steam-bath for 5 hr. On cooling, the mixture was rendered alkaline with 15% potassium hydroxide solution, giving a gum from which the aqueous layer was decanted. After being washed with water, the gum gave a white solid (2·5 g.) on trituration with ether. Extraction of the aqueous layer with chloroform gave a further quantity of base (0·5 g.). Two recrystallisations from ethanol afforded the iso*quinoline* in needles, m. p. 99° (Found : C, 69·7; H, 7·3. $C_{20}H_{25}O_4N$ requires C, 70·0; H, 7·3%).

The *methiodide* crystallised from aqueous methanol in needles, m. p. 222° (Found : I, 24·9. $C_{21}H_{28}O_4NI,MeOH$ requires I, 24·6%), and the *picrate* from aqueous methanol in needles, m. p. 172° (Found : C, 54·2; H, 4·9; N, 9·6. $C_{26}H_{28}O_{11}N_4$ requires C, 54·5; H, 4·9; N, 9·8%).

2-(3 : *4-Dihydroxybenzyl)*-1 : 2 : 3 : *4-tetrahydro*-6 : *7-dihydroxy*iso*quinoline.*—A solution of the amine (IX) (1·0 g.) in colourless hydriodic acid (10 c.c.) was heated at 125° under carbon dioxide. After 30 min. the evolution of methyl iodide had ceased, and the solution was then evaporated to dryness. The residue was dissolved in water (15 c.c.), and the solution was neutralised with ammonia. The precipitated base was collected and rapidly transferred to water (10 c.c.), sufficient dilute hydrochloric acid being added to effect dissolution. Treatment of the decolorised solution with concentrated hydrochloric acid (1 c.c.) precipitated N-(3 : *4-dihydroxybenzyl)*-1 : 2 : 3 : *4-tetrahydro*-6 : *7-dihydroxy*iso*quinoline hydrochloride*, which crystallised from dilute hydrochloric acid in needles, m. p. 228° (Found, after drying *in vacuo* at room temperature : C, 56·2; H, 5·5. $C_{16}H_{18}O_4NCl,H_2O$ requires C, 56·3; H, 5·8%).

Cyclisation of N-(3 : *4-Dimethoxybenzyl)*-N-2-(3 : *4-dimethoxyphenyl)ethyl*-N-*hydroxymethylamine.*—The named compound was prepared by heating *N*-(3 : 4-dimethoxybenzyl)-2-(3 : 4-dimethoxyphenyl)ethylamine (1 g.) and 40% formaldehyde (0·4 c.c.) on a steam-bath for 30 min. Water and excess of formaldehyde were then removed *in vacuo*, and 20% hydrochloric acid (4 c.c.) was added. After 1 hour's heating at 100° the solution was evaporated to dryness, giving a residue of 2-(3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy*iso*quinoline hydrochloride, whose picrate and methiodide had m. p. and mixed m. p. 171—172° and 221—222°, respectively.

N-(3 : *4-Dimethoxybenzyl)*-2-(3 : *4-dimethoxyphenyl)ethyldimethylammonium Iodide.*—*N*-(3 : 4-Dimethoxybenzyl)-2-(3 : 4-dimethoxyphenyl)ethylamine (1·8 g.) and methyl iodide (2·0 c.c.) in acetone (15 c.c.) were heated under reflux for 12 hr. Addition of water to the cooled solution produced a precipitate of the *methiodide*, which crystallised from methanol in needles, m. p. 184° (Found : C, 52·0; H, 6·5. $C_{21}H_{30}O_4NI$ requires C, 51·8; H, 6·2%).

Quaternary Salts of 3 : 4-*Dimethoxybenzylidene*-2-(3 : 4-*dimethoxyphenyl*)*ethylamine* (X) *and their Catalytic Reduction*.—(*a*) A solution of the Schiff's base (2·0 g.) and acid-free methyl sulphate (0·8 g.) in dry benzene (20 c.c.) was heated for 15 min. at 100°. On cooling, the solution deposited a gum which solidified when triturated with ethanol. After two recrystallisations from ethanol, the *methosulphate* was obtained as stout needles, m. p. 170—171° (Found : C, 55·2; H, 6·6. $C_{21}H_{29}O_8NS$ requires C, 55·4; H, 6·4%).

A solution of the methosulphate (1·0 g.) in ethanol (50 c.c.) and water (10 c.c.) was hydrogenated at atmospheric pressure in presence of Adams catalyst (50 mg.) (2 hr.). The basic material was isolated in the usual manner, giving 2-(3 : 4-dimethoxyphenyl)ethylmethylamine. Its picrate and its hydriodide had m. p. and mixed m. p. 162—163° and 131° respectively.

(*b*) The methiodide of the Schiff's base (X) was prepared by the method of Späth and Hromatka (*Ber.*, 1929, **62**, 325). A solution of this salt (0·5 g.) in dioxan (60 c.c.) was hydrogenated at atmospheric pressure with Adams catalyst (50 mg.). By the time hydrogen uptake (32 c.c.) was complete (4 hr.), a crystalline precipitate had formed. After the addition of water (5 c.c.) to dissolve the precipitate, the solution was filtered and evaporated to dryness. By crystallising the residue from water, N-(3 : 4-*dimethoxybenzyl*)-2-(3 : 4-*dimethoxyphenyl*)-*ethylamine hydriodide* was obtained in needles, m. p. 206° (Found : C, 49·3; H, 5·8. $C_{19}H_{26}O_4NI$ requires C, 49·7; H, 5·7%). The N-*nitroso-compound* crystallised from ethanol in needles, m. p. 109—110° (Found : N, 7·7. $C_{19}H_{24}O_5N_2$ requires N, 7·8%).

The hydriodide and *N*-nitroso-compound were also prepared from the amine obtained by reducing the Schiff's base 3 : 4-dimethoxybenzylidene-2-(3 : 4-dimethoxyphenyl)ethylamine and had m. p. and mixed m. p. 206° and 109—110° respectively.

Reduction of N-3 : 4-*Methylenedioxybenzylidene*-2-*phenylethylmethylammonium Iodide with Lithium Aluminium Hydride*.—The methiodide was prepared essentially by the method of Robinson and Hamilton (*J.*, 1916, 1033). The reaction can be expedited by heating the components in a sealed tube at 100° for 1 hr. The crystalline methiodide so obtained, m. p. 85—87°, was used without further purification since, on crystallisation from ethanol, it undergoes some decomposition. It (2 g.) was added portionwise to an excess of lithium aluminium hydride in ether (5·6 c.c., diluted to 25 c.c.—1 c.c. of original solution was equivalent to 80 c.c. of hydrogen). The solid dissolved rapidly with much effervescence, giving a colourless solution. After decomposition of the mixture with dilute sulphuric acid, the organic layer was removed, and the aqueous layer was basified and extracted with ether. Dry hydrogen chloride was passed into the dried ethereal extract, affording a precipitate of N-(3 : 4-*methylenedioxybenzyl*)-2-*phenylethylamine hydrochloride* (1·0 g., 67%). It crystallised from dilute hydrochloric acid in needles, m. p. 250° undepressed on admixture with an authentic specimen (Found : C, 65·7; H, 6·5; Cl, 12·1. $C_{16}H_{17}O_2N,HCl$ requires C, 66·0; H, 6·2; Cl, 12·0%).

The ethereal solution, obtained when the reaction mixture was decomposed with dilute acid, yielded a small amount of non-ketonic material which was not investigated further.

When the reaction mixture was decomposed with alkali, instead of acid, basic material was removed from the ether with dilute acid. Treatment of the acid extract with sodium nitrite afforded the *nitrosamine*, which was extracted with ether. Evaporation of the ethereal extract gave a gum, which solidified on trituration with ethanol. N-(3 : 4-*Methylenedioxybenzyl*)-N-*nitroso*-2-*phenylethylamine* crystallised from aqueous alcohol in fine colourless needles, m. p. 84° undepressed on admixture with an authentic specimen (Found : N, 9·7. $C_{16}H_{16}O_3N_2$ requires N, 9·9%).

Authentic specimens of the above hydrochloride and nitrosamine were prepared from the amine obtained by the catalytic reduction of 3 : 4-methylenedioxybenzylidene-2-phenylethylamine in dioxan with Raney nickel as catalyst.

Condensation of 2-(3 : 4-*Dimethoxyphenyl*)*ethylmethylamine with* 3 : 4-*Dimethoxybenzyl Chloride*.—2-(3 : 4-Dimethoxyphenyl)ethylmethylamine was prepared by decomposing the methiodide of the Schiff's base from 2-(3 : 4-dimethoxyphenyl)ethylamine and piperonaldehyde with water at 80°.

A solution of 2-(3 : 4-dimethoxyphenyl)ethylmethylamine (6·5 g.) and 3 : 4-dimethoxybenzyl chloride (5·1 g.) in absolute alcohol (20 c.c.) was set aside for 3 days. The dense crystalline precipitate which had formed was removed, washed with a little ethanol, dissolved in very dilute hydrochloric acid, and freed from secondary amine hydrochloride by treatment with sodium nitrite. After ether-extraction, the aqueous solution was basified and again extracted with ether. The last ethereal extract was dried and treated with dry hydrogen chloride, giving a precipitate of N-(3 : *4-dimethoxybenzyl*)-2-(3 : 4*-dimethoxyphenyl*)*ethylmethylamine hydrochloride* (3·2 g.), needles, m. p. 200° (from alcohol) (Found : C, 62·8; H, 7·4. $C_{20}H_{27}O_4N,HCl$ requires C, 63·0; H, 7·3%). The corresponding *hydriodide*, prepared by treating the hydrochloride with sodium iodide in water, crystallised from water in needles, m. p. 187—188° (Found : C, 51·0; H, 5·9. $C_{20}H_{28}O_4NI$ requires C, 50·7; H, 5·9%).

Reductive Alkylation of N-(3 : *4-Dimethoxybenzyl*)-2-(3 : *4-dimethoxyphenyl*)*ethylamine*.—A solution of this amine (2 g.) and 40% formaldehyde (0·5 c.c.) in absolute ethanol (50 c.c.) was heated under reflux for 30 min. When the solution was cold, the hydroxymethyl compound was hydrogenated at 4 atm. at a Raney nickel catalyst (3 hr.). The solution was filtered and evaporated. The residual oil was freed from secondary amine with nitrous acid and converted into its hydrochloride (1·8 g., 80%), m. p. 200° alone and mixed with *N*-(3 : 4-dimethoxybenzyl)-2-(3 : 4-dimethoxyphenyl)ethylmethylamine hydrochloride obtained previously. The *methiodide* crystallised from methanol in needles, m. p. 184° (Found : C, 52·0; H, 6·5. $C_{21}H_{30}O_4NI$ requires C, 51·8; H, 6·2%).

N-(3 : *4-Dihydroxybenzyl*)-2-(3 : *4-dihydroxyphenyl*)*ethylmethylamine*.—*N*-(3 : 4-Dimethoxybenzyl)-2-(3 : 4-dimethoxyphenyl)ethylmethylamine hydrochloride (2·5 g.) in concentrated hydrochloric acid (20 c.c.) was heated under carbon dioxide at 160—170° for 2 hr. The resultant colourless solution was evaporated to dryness *in vacuo*, leaving an almost colourless crystalline solid (Found : OMe, 0). This could not be recrystallised, nor could the hydriodide, both compounds being too deliquescent. The picrate was an amorphous solid.

To prove that the compound had undergone no further structural change during demethylation, it was dissolved in 33% potassium hydroxide and treated with methyl sulphate. Potassium iodide was then added, giving a precipitate of the methiodide, which after crystallisation from methanol had m. p. 184° alone and mixed with *N*-(3 : 4-dimethoxybenzyl)-2-(3 : 4-dimethoxyphenyl)ethylmethylamine methiodide.

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