Synthesis of 10-*Hydroxy*-4 : 5 : 6-*trimethoxyaporphine.*

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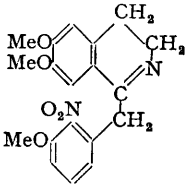
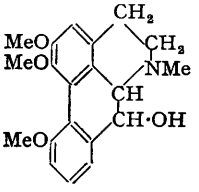
The synthesis of 10-hydroxy-4 : 5 : 6-trimethoxyaporphine is reported.

The principal alkaloid from *Artabotrys suaveolens*, Bl., was originally considered to be 10-hydroxy-4 : 5 : 6-trimethoxyaporphine (II) (Barger and Sargent, *J.*, 1939, 991). The synthesis of a compound having this structure was effected by the following procedure. Oxidation of 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline (I) (Govindachari and Pai, *J. Org. Chem.*, 1953, **18**, 1352) with potassium dichromate yielded 6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline, which was then reduced to 1-(α-hydroxy-3-methoxy-2-nitrobenzyl)-6 : 7-dimethoxy*iso*quinoline by aluminium *iso*propoxide in toluene or by sodium borohydride in cold methanol. The methiodide of the

(I)





(II)

last base was reduced in methanol in the presence of Adams catalyst to 1-(2-amino-α-hydroxy-3-methoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl-*iso*quinoline. When the synthesis had been brought to this stage, a publication by Schlittler and Huber (*Helv. Chim. Acta*, 1952, **35**, 111) appeared proving that the so-called " artabotrine " was identical with *iso*corydine. Nevertheless, the last step in the synthesis was completed in view of Schlittler and Lindenmann's finding (*ibid.*, 1949, **32**, 1880) that oxoaporphines were formed in much better yield than the corresponding aporphines in the Pschorr reaction and it was of interest to know whether this would be true of 10-hydroxy-aporphines also. However, 10-hydroxy-4 : 5 : 6-trimethoxyaporphine (II) was formed in less than 1% yield, whereas 4 : 5 : 6-trimethoxyaporphine itself has been obtained (Govindachari and Pai, *loc. cit.*) in about 10% yield.

Experimental

Ultra-violet absorption spectra were measured for absolute ethanol solutions with a Beckman Model DUV Spectrophotometer. Some analyses are by Mr. S. Selvavinayagam.

6 : 7-*Dimethoxy*-1-(3-*methoxy*-2-*nitrobenzoyl*)iso*quinoline*.—To a solution of 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline (Govindachari and Pai, *loc. cit.*) (5 g.) in 70% acetic acid (40 ml.) was added finely powdered potassium dichromate (10 g.), and the mixture refluxed for 2 hr. The mixture was then cooled and filtered. The residue was washed with dilute acetic acid and then with water (filtrate A). Crystallisation of the residue from alcohol yielded the benzoyl*iso*quinoline as pale yellow needles (3·03 g.), m. p. 212° (decomp.), $\lambda_{max.}$ 232 (log ε 4·70) and 350 mμ (log ε 3·93) (Found : C, 61·5; H, 4·4; N, 7·5. $C_{19}H_{16}O_6N_2$ requires C, 61·9; H, 4·3; N, 7·6%).

The filtrate A was diluted with a large volume of water and extracted with chloroform. The residue obtained from the dried chloroform extract was crystallised from water and then from alcohol, yielding a *substance* as bright yellow needles (0·10 g.), m. p. 245—247°, which was not further characterised (Found : C, 57·0; H, 4·1; N, 6·7. $C_{19}H_{16}O_8N_2$ requires C, 57·0; H, 4·0; N, 7·0%).

1-(α-*Hydroxy*-3-*methoxy*-2-*nitrobenzyl*)-6 : 7-*dimethoxy*iso*quinoline*.—(a) *Reduction by aluminium* iso*propoxide*. A solution of the foregoing 1-benzoyl*iso*quinoline (1 g.) in dry thiophen-free toluene (20 ml.) was refluxed with aluminium *iso*propoxide (2·3 g.) for 4 hr. The mixture was distilled with addition of dry *iso*propyl alcohol (75 ml.) in three equal portions, till the distillate was free from acetone and then cooled. The aluminium complex was decomposed by 4N-sulphuric

acid (25 ml.), and the toluene layer separated. The acid layer was rendered strongly alkaline with sodium hydroxide solution and extracted with benzene. The dried benzene extract, after removal of solvent, yielded the *alcohol* (0·86 g.) which after crystallisation from alcohol melted at 180° (decomp.), $\lambda_{max.}$ 242 (log ε 4·78), 315 (log ε 3·73), and 325 mμ (log ε 3·80) (Found : C, 61·6; H, 4·9; N, 7·3. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9; N, 7·6%).

The *acetate*, prepared by acetic anhydride in pyridine, crystallised from alcohol as colourless needles, m. p. 197° (Found : C, 61·1; H, 4·8; N, 7·2. $C_{21}H_{20}O_7N_2$ requires C, 61·1; H, 4·9; N, 6·8%). The *methiodide*, prepared at 100°, crystallised from methanol as pale yellow needles, m. p. 207° (decomp.) (Found : C, 46·9; H, 4·5; N, 5·6; I, 24·6. $C_{20}H_{21}O_6N_2I$ requires C, 46·9; H, 4·1; N, 5·5; I, 24·8%).

(b) *Reduction by sodium borohydride*. The 1-benzoyl*iso*quinoline (5 g.) was suspended in acetone-free methyl alcohol (50 ml.), and sodium borohydride (2·5 g.) was added. The mixture was shaken frequently and the temperature was kept below 30°. The benzoyl*iso*quinoline gradually disappeared and a fluffy material separated. Water (100 ml.) was added and the precipitate was collected, washed free from alkali, and dried *in vacuo*. The hydroxy-base so obtained (4·75 g.) melted at 180° (decomp.).

1-(2-*Amino*-α-*hydroxy*-3-*methoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*isoquinoline.—A suspension of the methiodide of the foregoing hydroxy-base (2·5 g.) in methyl alcohol (150 ml.) was shaken with hydrogen at 60 lb. per sq. in. after addition of Adams catalyst (0·18 g.), till absorption of hydrogen ceased. The solution was filtered from the catalyst and the filtrate rendered acidic and evaporated to dryness *in vacuo*. The residue was dissolved in water and extracted with benzene to remove non-basic matter. The aqueous solution was then made alkaline after good cooling, and extracted with ether. Purification was effected by one more passage through acid. The base was then converted into the dihydrochloride by passing dry hydrogen chloride through its ether solution. Crystallisation of the crude *dihydrochloride* (1·54 g.) from absolute alcohol yielded the pure salt, m. p. 208° (decomp.) (Found : C, 55·3; H, 6·7; N, 6·6; Cl, 16·5. $C_{20}H_{28}O_4N_2Cl_2$ requires C, 55·7; H, 6·5; N, 6·5; Cl, 16·5%).

10-*Hydroxy*-4 : 5 : 6-*trimethoxyaporphine*.—A solution of the foregoing dihydrochloride (2·0 g.) in methyl alcohol (15 ml.) and 2N-sulphuric acid (20 ml.) was cooled to 0° and treated with sodium nitrite (0·31 g.) in water (20 ml.) at <3°. After 1 hr. at 0°, the slight excess of sodium nitrite was decomposed by sulphamic acid. Freshly prepared copper powder (2 g.) was added to the solution which was allowed to come to room temperature and then heated on water-bath till evolution of nitrogen ceased. Zinc dust (1 g.) and 10N-hydrochloric acid (2 ml.) were then added and the mixture was heated on a water-bath for a further hour. The colourless solution was filtered from the zinc residue. The filtrate was cooled, rendered alkaline, and extracted with ether. The ether extract was stripped of basic material by shaking it with N-hydrochloric acid. The acid extract was made almost neutral by addition of sodium hydrogen carbonate and then saturated with potassium iodide. A brownish gum separated, from which the clear supernatant liquid was decanted.

The gum was extracted repeatedly with boiling water. The aqueous extract was decolorised by norite, cooled, rendered alkaline, and extracted with ether. The dried ether extract yielded on removal of solvent an oil (0·2 g.) which was repeatedly extracted with boiling light petroleum (b. p. 40—60°). The combined extracts were concentrated to 100 ml. The amorphous material which separated on cooling was removed by filtration. Further concentration to 10 ml. yielded a crystalline solid. Recrystallisation from benzene–light petroleum gave 10-*hydroxy*-4 : 5 : 6-*trimethoxyaporphine* (0·01 g.), m. p. 180°, $\lambda_{max.}$ 273 (log ε 4·10) and 300 mμ (log ε 4·01) (Found : C, 70·9; H, 7·2. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·8%).

The supernatant liquid decanted from the gummy hydriodide was rendered alkaline and extracted with ether. The dried ether extract on removal of solvent yielded 0·33 g. of a waxy *substance*, which gave colourless needles (0·18 g.), m. p. 138—139°, after crystallisation from alcohol (Found : C, 63·9; H, 7·3; N, 7·7. $C_{20}H_{26}O_5N_2$ requires C, 64·2; H, 7·0; N, 7·5%). This product could not be further characterised.

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