339. iso*Thebaine: The Synthesis of* 2 : 3 : 6-*Trimethoxyaporphine.*

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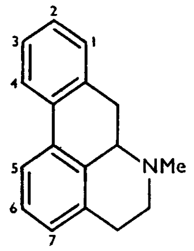
2 : 3 : 6-Trimethoxyaporphine has been synthesised by a combination of the Bischler–Napieralsky *iso*quinoline, and the Pschorr phenanthrene synthesis, and been found to differ from *iso*thebaine methyl ether.

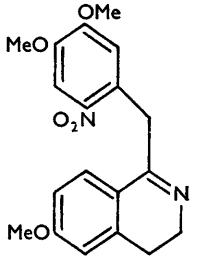
The alkaloid *iso*thebaine, which occurs in the roots of *Papaver orientale* after ripening and withering of the aerial parts,[1] was considered to be 4-hydroxy-3 : 5-dimethoxyaporphine [aporphine has the structure (I)] by Klee,[2] who degraded the methyl ether to 3 : 4 : 5-trimethoxyphenanthrene, a result subsequently confirmed by Schlittler and Müller.[3] This identity of the end-product of degradation with 3 : 4 : 5-trimethoxyphenanthrene has however been challenged by Kiselev and Konovalova[4] who for this reason rejected the structure suggested by Klee.

On biogenetic grounds Bentley and Cardwell[5] suggested that the alkaloid could be 2(or 4)-hydroxy-3 : 6(or 5)-dimethoxyaporphine. Of the possibilities embodied in this suggestion one is the structure suggested by Klee; and the 4-hydroxy-3 : 6-dimethoxy- and the 2-hydroxy-3 : 6-dimethoxy-structure can be eliminated as *iso*thebaine methyl ether is not identical with morphothebaine dimethyl ether or with 2 : 3 : 6-trimethoxyaporphine, which was synthesised as described below. In view of these results, and of the fact that *iso*thebaine cannot be 5-hydroxy-3 : 6-dimethoxyaporphine since its methyl ether is not identical with *N*-methyltuduranine methyl ether, Kiselev and Konovalova's disagreement with the experimental work of Klee and of Schlittler and Müller can be discounted.

(I)



(II)



2 : 3 : 6-Trimethoxyaporphine was synthesised in the following way. 4 : 5-Dimethoxy-2-nitrophenylacetyl chloride was condensed with 2-*m*-methoxyphenylethylamine, and the resulting amide dehydrated with phosphorus pentachloride to 1-(4 : 5-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro-6-methoxy*iso*quinoline (II), the methiodide of which with zinc and

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[1] Gadamer, *Arch. Pharm.*, 1911, **249**, 39.

[2] Klee, *Arch. Pharm.*, 1914, **252**, 211.

[3] Schlittler and Müller, *Helv. Chim. Acta*, 1948, **31**, 1119.

[4] Kiselev and Konovalova, *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19**, 148.

[5] Bentley and Cardwell, *J.*, 1955, 3252.

hydrochloric acid gave 1-(2-amino-4 : 5-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline. This base on diazotisation and treatment with zinc dust underwent Pschorr phenanthrene ring closure, yielding 2 : 3 : 6-trimethoxyaporphine. This base could not be induced to form a crystalline hydrogen (—)-tartrate as does *iso*thebaine methyl ether, and the ultraviolet spectrum of the synthetic base showed significant differences from that of *iso*thebaine; the two bases are clearly not identical.

EXPERIMENTAL

N-(4 : *5-Dimethoxy-2-nitrophenylacetyl*)-2-m-*methoxyphenylethylamine*.—Phosphorus pentachloride (25 g.) was slowly added to a suspension of 4 : 5-dimethoxy-2-nitrophenylacetic acid (13·1 g.) in cold, dry chloroform (80 ml.), and when the reaction was complete the resulting solution of the acid chloride was added slowly, with vigorous stirring, to a mixture of 2-*m*-methoxyphenylethylamine (12 g.), chloroform (50 ml.) and 0·70N-aqueous sodium hydroxide (600 ml.), with ice-cooling. After 20 min. the chloroform layer was separated, the aqueous layer was extracted once with chloroform, and the combined chloroform solutions were washed with dilute acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). On evaporation of the chloroform a viscous oil was obtained and this was crystallised from methanol (yield 17·5 g.). The *amide* was obtained as yellow prisms, m. p. 156°, on recrystallisation from ethanol (Found : C, 60·7; H, 5·9; N, 7·3. $C_{19}H_{22}O_6N_2$ requires C, 60·9; H, 5·9; N, 7·5%).

1-(4 : *5-Dimethoxy-2-nitrobenzyl*)-3 : *4-dihydro-6-methoxy*iso*quinoline* (II).—A solution of the foregoing amide (10 g.) and phosphorus pentachloride (12 g.) in chloroform (80 ml.) was set aside at 15° for 3 days. The solvent was removed *in vacuo*, the residue dissolved in boiling water, and the solution filtered. The sparingly soluble salt that separated when the solution was cooled was collected, dissolved in hot water, and decomposed with aqueous ammonia. The liberated base was collected and recrystallised from methanol, 1-(4 : *5-dimethoxy-2-nitrobenzyl*)-3 : *4-dihydro-6-methoxy*iso*quinoline* (7·5 g.) being obtained as colourless prisms, m. p. 172° (Found: C, 64·1; H, 5·7; N, 7·8. $C_{19}H_{20}O_5N_2$ requires C, 64·0; H, 5·6; N, 7·9%). The *methiodide*, prepared by refluxing the base with excess of methyl iodide for 30 min., was obtained from ethanol as yellow prisms, m. p. 182 (Found: C, 48·1; H, 4·5; N, 5·6; I, 25·3. $C_{19}H_{20}O_5N_2,CH_3I$ requires C, 48·1; H, 4·6; N, 5·6; I, 25·5%).

1-(*2-Amino-4* : *5-dimethoxybenzyl*)-1 : 2 : 3 : *4-tetrahydro-6-methoxy-2-methyl*iso*quinoline*.—Zinc dust (25 g.) was slowly added to a stirred suspension of the nitrobenzyl*iso*quinoline methiodide (3·5 g.) in concentrated hydrochloric acid (80 ml.) and water (35 ml.) at 80—90°. The filtered solution was subsequently made alkaline with ammonia, and the liberated base extracted with ether. The ether extracts furnished a viscous oil, and the amino-compound was characterised as the *dihydrochloride*, colourless prisms, m. p. 240° (from ethanol) (Found: C, 57·6; H, 7·0; N, 6·8; Cl, 17·1. $C_{20}H_{26}O_3N_2,2HCl$ requires C, 57·7; H, 6·8; N, 6·8; Cl, 17·1%).

(±)-2 : 3 : *6-Trimethoxyaporphine*.—1-(2-Amino-4 : 5-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline dihydrochloride (1·94 g.) in methanol (10 ml.) and 2N-sulphuric acid (10 ml.) was diazotised with aqueous sodium nitrite. The mixture was kept for 2 hr. at 10—15°, and then boiled under reflux for 1 hr., with the addition of concentrated hydrochloric acid (3 ml.) and zinc dust (5 g.). The filtered solution was made strongly alkaline with aqueous sodium hydroxide, and the precipitate extracted with ether. The ether extract yielded (±)-2 : 3 : *6-trimethoxyaporphine* as an uncrystallisable oil. The *perchlorate* formed almost colourless prisms, m. p. 213°, from 50% ethanol (Found: C, 56·4; H, 5·2; N, 3·4; Cl, 8·2. $C_{20}H_{23}O_3N,HClO_4$ requires C, 56·6; H, 5·7; N, 3·3; Cl, 8·4%). The *methiodide* was obtained as almost colourless prisms, m. p. 207°, from aqueous ethanol (Found: C, 54·2; H, 5·2; N, 3·3; I, 27·5. $C_{20}H_{23}O_3N,CH_3I$ requires C, 54·0; H, 5·4; N, 3·0; I, 27·3%).

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