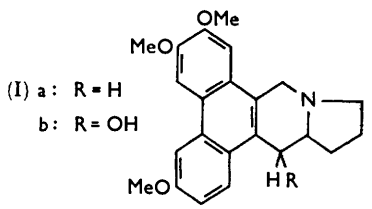
256. *Synthesis of* 9,11,12,13,13a,14-*Hexahydro*-2,3,6-*trimethoxydibenzo*[f,h]*pyrrolo*[1,2-b]*isoquinoline.*

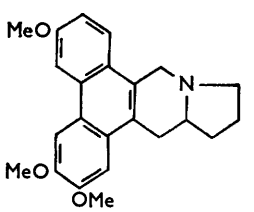
By T. R. Govindachari, I. S. Ragade, and N. Viswanathan.

The synthesis of 9,11,12,13,13a,14-hexahydro-2,3,6-trimethoxydibenzo-[*f*,*h*]pyrrolo[1,2-*b*]isoquinoline, one of the two possible structures assigned earlier to deoxytylophorinine, is reported.

Degradative experiments[1] have led to the alternative structures (Ia) and (II) for deoxytylophorinine, the deoxy-base from tylophorinine (Ib) which is a minor alkaloid of *Tylophora asthmatica*. The synthesis of compound (Ia) and its identity with deoxytylophorinine were also reported therein. The synthesis of compound (II) from the hitherto unknown 3,6,7-trimethoxyphenanthrene-9-carboxylic acid (VIIa) is reported in the present paper.



(I) a: R = H
b: R = OH

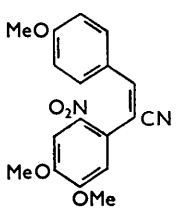


(II)

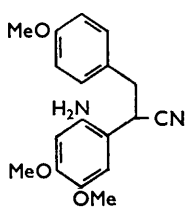
p-Anisaldehyde with 4,5-dimethoxy-2-nitrobenzyl cyanide in the presence of piperidine yielded α-(4,5-dimethoxy-2-nitrophenyl)-4-methoxycinnamonitrile (III). Catalytic reduction of this in the presence of palladised charcoal gave, as the main product, the amine (IV): a neutral by-product was identified as 5,6-dimethoxy-3-4′-methoxybenzylindole (V) by its ultraviolet absorption spectrum and positive Ehrlich reaction. The formation of indoles in the reduction of analogous nitro-nitriles has been observed by Plieninger and Nógrádi[2] and by Walker.[3] The amino-nitrile (IV) gave, by Pschorr ring closure, 9-cyano-9,10-dihydro-3,6,7-trimethoxyphenanthrene (VI). Hydrolysis of this nitrile by prolonged heating with alkali was accompanied by dehydrogenation, for the acid

[1] Govindachari, Pai, Ragade, Rajappa, and Viswanathan, *Tetrahedron*, 1961, **14**, 288.
[2] Plieninger and Nógrádi, *Chem. Ber.*, 1955, **88**, 1961.
[3] Walker, *J. Amer. Chem. Soc.*, 1956, **77**, 3844.

obtained yielded a methyl ester having ultraviolet and infrared spectra characteristic of phenanthrene esters. That dehydrogenation had not occurred under the conditions of the Pschorr ring closure was shown by the fact that the Pschorr product gave correct analyses for the dihydro-nitrile (VI) and had an ultraviolet spectrum different from that of 9-cyano-2,3,6-trimethoxyphenanthrene.



(III)



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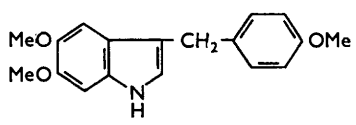
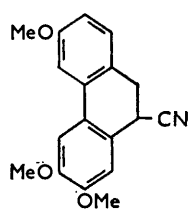
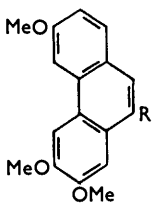


(V)



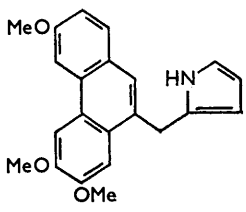
(VI)

In analogy with earlier work,[1] the methyl ester (VIIb) was reduced by lithium aluminium hydride to the alcohol (VIIc) which was converted into the chloride (VIId) by thionyl chloride. With pyrrylmagnesium bromide this gave the pyrrole (VIII) which was catalytically reduced to the pyrrolidine (IX). *N*-Formylation followed by cyclisation

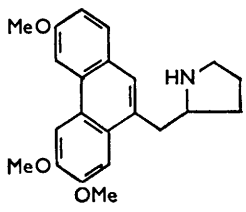


a: R = CO_2H
b: R = CO_2Me
c: R = CH_2·OH
d: R = CH_2Cl

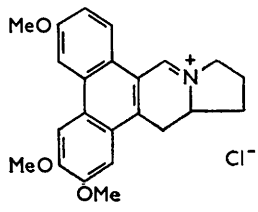
(VII)



(VIII)



(IX)



(X)

with phosphorus oxychloride afforded the quaternary compound (X), which was reduced by sodium borohydride to the desired base (II). Its infrared spectrum showed differences from that of deoxytylophorinine (I) in the fingerprint region and in the Hofmann degradation it yielded a different methine.

Experimental

Ultraviolet absorption spectra were determined for 95% ethanol solutions on a Beckman model DU spectrophotometer. Microanalyses were carried out by Mr. S. Selvavinayakam. Light petroleum had b. p. 40—60°.

α-(4,5-*Dimethoxy*-2-*nitrophenyl*)-4-*methoxycinnamonitrile*.—4,5-Dimethoxy-2-nitrobenzyl cyanide [3] (15·3 g.) and *p*-anisaldehyde (10·2 g.) were refluxed in ethanol (250 ml.) containing piperidine (9 ml.) for 30 min., then cooled, kept at 30° for 48 hr., and filtered. The residue was washed with boiling ethanol (100 ml.). Crystallisation from acetic acid gave the *cinnamonitrile* (20·5 g.) as yellow needles, m. p. 201° (Found: C, 63·3; H, 4·7. $C_{18}H_{16}N_2O_5$ requires C, 63·5; H, 4·7%).

2-*Amino*-4,5-*dimethoxy*-α-(4-*methoxybenzylbenzyl*) *Cyanide*.—The above nitrile (3 g.) in ethyl acetate (150 ml.) was shaken with hydrogen at a pressure of 40 lb./in.^{2} in the presence of 7% palladised charcoal (1·5 g.) at 70° for 2½ hr., then cooled, filtered, and evaporated. Triturating the residue with a little methanol gave pale yellow crystals (1·6 g.). Two crystallisations from methanol gave the *aminobenzyl cyanide*, m. p. 130° (Found: C, 68·8; H, 6·5. $C_{18}H_{20}N_2O_3$ requires C, 69·2; H, 6·4%).

From a number of batches of reduction was isolated in small quantity 5,6-*dimethoxy*-3-4′-*methoxybenzylindole*. Separation from the amino-compound was effected by utilising its sparing solubility in methanol. Crystallisation from chloroform–methanol gave the indole as needles, m. p. 158—159° (Found: C, 72·7; H, 6·3. $C_{18}H_{19}NO_3$ requires C, 72·7; H, 6·4%), $\lambda_{max.}$ 226, 284, 297 mμ (log ε 4·60, 3·91, 3·95), $\nu_{max.}$ (in $CHCl_3$) 2·82 and 6·1 μ.

9-*Cyano*-9,10-*dihydro*-3,6,7-*trimethoxyphenanthrene*.—A solution of the aminobenzyl cyanide (5 g.) in acetone (200 ml.) was treated at −2° dropwise, with stirring, with 4N-sulphuric acid (25 ml.) and after 5 min. cooled to −8°. Butyl nitrite (2·3 ml.) was added. After 1 hour's stirring at −8°, copper bronze (3 g.) was added. Stirring was continued for a further 3 hr. and the mixture then allowed to reach room temperature, left overnight, and filtered. The residue was washed with hot acetone. The residue obtained on removal of acetone was taken up in chloroform, washed with sodium hydrogen carbonate solution, then with water, dried (Na_2SO_4), and recovered. This residue was extracted with hot benzene (150 ml.) and the benzene solution evaporated. The product (3 g.), on chromatography in benzene over alumina, gave the *phenanthrene*, m. p. 179—180° (from ethyl acetate–methanol) (Found: C, 72·9; H, 5·8. $C_{18}H_{17}NO_3$ requires C, 73·2; H, 5·8%).

Methyl 3,6,7-*Trimethoxyphenanthrene*-9-*carboxylate*.—The preceding nitrile (8 g.) was heated with potassium hydroxide (20 g.) in water (16 ml.) and 2-ethoxyethanol (65 ml.) for 18 hr. at 130°. The acid obtained (7 g.) was, without purification, converted into the methyl ester by refluxing it with methanol (230 ml.) and concentrated sulphuric acid (6 ml.) on a steam-bath for 6 hr. The crude ester (5·2 g.) was passed through alumina with chloroform as eluent. Crystallisation from methanol gave the *ester* (3·5 g.) as plates, m. p. 155° (Found: C, 69·5; H, 5·8. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%), $\lambda_{max.}$ 225, 265, 285, 325 mμ (log ε 4·12, 4·56, 4·45, 3·90), $\nu_{max.}$ (in $CHCl_3$) 5·84 (aromatic ester). It was also obtained as a *form*, m. p. 138° (from methanol) (Found: C, 69·4; H, 5·5%). A solution of this in methanol when seeded with the ester, m. p. 155°, gave crystals of m. p. 155°. The ultraviolet and infrared ($CHCl_3$) spectra of the two samples were identical. Alkaline hydrolysis of both samples gave 3,6,7-*trimethoxyphenanthrene*-9-*carboxylic acid*, m. p. 215° (from methanol) (Found: C, 69·2; H, 4·8. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

9-*Hydroxymethyl*-3,6,7-*trimethoxyphenanthrene*.—Methyl 3,6,7-trimethoxyphenanthrene-9-carboxylate (2 g.) in dry tetrahydrofuran (50 ml.) was added with stirring to a suspension of lithium aluminium hydride (1·2 g.) in tetrahydrofuran (25 ml.). After 4 hours' stirring, the mixture was decomposed with moist ether and water. The ether–tetrahydrofuran mixture was decanted, dried, and distilled. Crystallisation of the residue from ethanol gave the *hydroxymethylphenanthrene* (1·5 g.), m. p. 157—158° (Found: C, 72·1; H, 5·8. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%).

9-*Chloromethyl*-3,6,7-*trimethoxyphenanthrene*.—A solution of the alcohol (1·5 g.), thionyl chloride (1·4 ml.), and pyridine (0·5 ml.) in chloroform (70 ml.) was refluxed for 1½ hr., cooled, and poured into ice-cold water. After 30 min. the chloroform layer was separated, washed with sodium hydrogen carbonate solution, then with water, and dried. The solution was concentrated to a small volume and an excess of light petroleum added. Recrystallisation of the precipitate from benzene–light petroleum yielded the *chloromethylphenanthrene* (1·2 g.) as needles, m. p. 163—164° (Found: C, 68·7; H, 5·9. $C_{18}H_{17}ClO_3$ requires C, 68·3; H, 5·4%).

2-(3,6,7-*Trimethoxy*-9-*phenanthrylmethyl*)*pyrrole*.—The chloromethylphenanthrene (1·5 g.) in tetrahydrofuran was added to pyrrylmagnesium bromide in ether (from 0·75 g. of magnesium, 2·4 ml. of ethyl bromide, and 1·93 ml. of pyrrole) under nitrogen with stirring and cooling in ice. Stirring was continued for a few more hours during which the mixture was allowed to rise to room temperature. Next morning ether was added and the oily complex decomposed with saturated ammonium chloride solution. The organic layer was separated, washed with water, dried, and distilled. Chromatography of the residue over alumina in chloroform yielded the *pyrrole* (0·98 g.), cubes (from chloroform–benzene), m. p. 147—148° (Found: C, 75·7; H, 6·1. $C_{22}H_{21}NO_3$ requires C, 76·1; H, 6·0%).

2-(3,6,7-*Trimethoxy*-9-*phenanthrylmethyl*)*pyrrolidine*.—The above pyrrole (0·35 g.) in acetic acid (25 ml.) was shaken with hydrogen at a pressure of 50 lb./in.^{2} in the presence of Adams catalyst (0·25 g.) for 20 hr. The solution was filtered and the solvent evaporated *in vacuo*. The residue was extracted repeatedly with hot dilute hydrochloric acid. The acid extracts were combined, washed with ether, and basified. Extraction with chloroform and chromatography of the product in chloroform over alumina gave the pyrrolidine (0·19 g.) as a gum.

The *picrate* crystallised from acetic acid in orange-red needles, m. p. 229° (Found: C, 58·2; H, 4·9. $C_{28}H_{28}N_4O_{10}$ requires C, 57·9; H, 4·8%).

9,11,12,13,13a,14-*Hexahydro*-2,3,6-*trimethoxydibenzo*[f,h]*pyrrolo*[1,2-b]*isoquinoline*.—The foregoing pyrrolidine (0·37 g.) was heated at 180° for 1½ hr. with 98% formic acid (2 ml.). The mixture was cooled, taken up in chloroform, washed with sodium hydrogen carbonate solution, water, dilute hydrochloric acid, and again with water, dried, concentrated to a small volume, and chromatographed in chloroform over alumina. The *N*-formylpyrrolidine (0·33 g.) obtained did not crystallise. It was refluxed with phosphorus oxychloride (4 ml.) and toluene (9 ml.) for 1½ hr. An excess of light petroleum was added and the precipitated quaternary chloride washed repeatedly with light petroleum and reduced with sodium borohydride (0·4 g.) in methanol (15 ml.). The methanol was removed *in vacuo* and the residue extracted with chloroform. Chromatography of the product in chloroform over alumina gave the pentacyclic *base* (0·12 g.), m. p. 213—215° (from chloroform–methanol) (Found: C, 76·0; H, 7·2. $C_{23}H_{25}NO_3$ requires C, 76·0; H, 6·9%), $\lambda_{max.}$ 260, 287, 343 mμ (log ε 4·87, 4·63, 3·16).

This base (20 mg.) in chloroform (5 ml.) was refluxed with excess of methyl iodide for 2 hr. and left overnight. The solvent and excess of methyl iodide were distilled off. The residual methiodide was shaken in water (10 ml.) with silver oxide (from 0·5 g. of silver nitrate) for 5 hr. The mixture was filtered and the filtrate evaporated at 50° *in vacuo*. The residue was heated at 100°/0·1 mm. for 30 min. The product was extracted with hot benzene and the soluble portion crystallised twice from benzene–light petroleum, to yield the *methine* (5 mg.), m. p. 169—170°, depressed to 155—160° on admixture with a sample of the methine, m. p. 171·5°, obtained by Hofmann degradation of natural deoxytylophorinine (Found: C, 76·2; H, 7·2. $C_{24}H_{27}NO_3$ requires C, 76·4; H, 7·2%), $\lambda_{max.}$ 260, 285, 340 mμ (log ε 4·76, 4·51, 3·12).

We thank the Government of India for a Research Training Scholarship (to I. S. R.) and the Council of Scientific and Industrial Research for a Senior Research Fellowship (to N. V.).

Department of Chemistry, Presidency College, Madras-5. [*Received, October 9th*, 1961.]