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CHEMICAL EXAMINATION OF *TYLOPHORA ASTHMATICA*—V[1]

STRUCTURE OF TYLOPHORININE[2]

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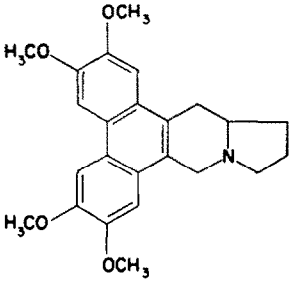
Abstract—Tylophorinine, the minor alkaloid of *Tylophora asthmatica*, has been oxidized to yield 2,3,6-trimethoxyphenanthrene-9,10-dicarboxylic acid. A synthesis of the corresponding imide has been achieved. Desoxytylophorinine, obtained by hydrogenolysis of the alkaloid, has been synthesized. These results in conjunction with other degradation experiments have enabled the assignment of the structure XIV to tylophorinine.

THE isolation of the alkaloids of *Tylophora asthmatica* has been described previously.[3] The major alkaloid, tylophorine, has been shown to have structure I by degradation[4]



I

as well as by synthesis.[1] The present paper deals with the elucidation of the structure of the minor alkaloid, tylophorinine.

Tylophorinine is a powerfully vesicant compound, occurring to the extent of less than 0·001 per cent in the dried plant. Initial attempts to prepare the alkaloid in a pure form were not wholly successful, tylophorine being the usual contaminant. However, a preliminary chromatography of the base over alumina without undue exposure to light, followed by conversion to the hydrochloride and repeated crystallization of the latter gave a pure material. Although the base liberated from the hydrochloride could be crystallized from chloroform, satisfactory analyses on the base could not be obtained, there being evidently some decomposition, as indicated by

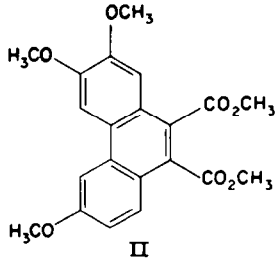
[1] Part IV: *Tetrahedron* **14**, 284 (1961).
[2] Parts of this work have been published in the form of brief notes: [a] T. R. Govindachari, B. R. Pai, S. Rajappa and N. Viswanathan, *Chem. & Ind.* 950 (1959); [b] T. R. Govindachari, B. R. Pai, I. S. Ragade, S. Rajappa and N. Viswanathan, *Ibid.* 966 (1960).
[3] T. R. Govindachari, B. R. Pai and K. Nagarajan, *J. Chem. Soc.* 2801 (1954).
[4] T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan and B. R. Pai, *Tetrahedron* **4**, 311 (1958); T. R. Govindachari, M. V. Lakshmikantham, B. R. Pai and S. Rajappa, *Ibid.* **9**, 53 (1960).

the deepening colour of the compound. On the basis of analyses of the hydrochloride, the formula of the base had to be revised from $C_{23}H_{27}O_4N$[3] to $C_{23}H_{25}O_4N$. Zeisel determination showed the presence of three methoxyls in the molecule. The ultraviolet absorption spectrum of tylophorinine (λ_{max} 258, 287, 340 mμ; log ε 4·61, 4·34, 2·91) was very similar to that of cryptopleurine[5] indicating that it was probably a 2,3,6-trimethoxyphenanthrene derivative.

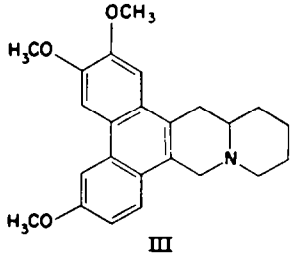
The fourth oxygen atom in the alkaloid was evidently present as an aliphatic hydroxyl group. The infra-red spectrum (nujol) of the base showed a band at 3·1 μ. Acetylation of tylophorinine yielded an acetate, $C_{25}H_{27}O_5N$, with infra-red absorption bands ($CHCl_3$) at 5·8 and 8·0 μ (—OCOMe). The U.V. spectrum of the base was unaffected by the addition of alkali, showing that the hydroxyl group was not phenolic.

Tylophorinine did not have an N-Me group and had no easily reducible unsaturation, but yielded a crystalline methiodide. Evidently tylophorinine is a tertiary base with nitrogen common to two rings as in tylophorine. With the intention of carrying out a series of reactions parallel to the successful degradation sequence in tylophorine, the alkaloid was subjected to both Hofmann and Emde reactions. However, the Hofmann degradation, carried out either by the pyrolysis of the methohydroxide, or by refluxing the methiodide with potassium t-butoxide in t-butanol, gave only a very meagre yield of a compound, whose analytical values were only in moderate agreement with the formula $C_{24}H_{27}O_4N$. Similarly the Emde degradation too gave a very small quantity of a base which was found to decompose spontaneously on keeping. Thus the extremely low yield in these degradation reactions precluded the possibility of the derivation of any useful information regarding the structure of the parent alkaloid.

Direct oxidation studies were however, more useful in the structural elucidation. Vigorous oxidation of tylophorinine methiodide gave *m*-hemipinic acid as the only isolable product. Mild oxidation of the methiodide yielded an imide, $C_{19}H_{15}O_5N$, and an acid which was converted to an anhydride (I.R. bands at 5·45 and 5·62 μ) under crystallization conditions. Methylation of the acid with diazomethane yielded a diester, $C_{21}H_{20}O_7$, m.p. 160–162°, identical with dimethyl 2,3,6-trimethoxyphenanthrene-9,10-dicarboxylate (II) obtained similarly from the methiodide of cryptopleurine (III).* Since the structure of cryptopleurine itself has been rigorously established by X-ray crystallographic analysis[6] as well as by synthesis[7] the part structure (IV) for tylophorinine follows:



II



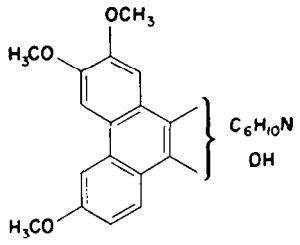
III

* We are extremely grateful to Dr. E. Gellert for a very generous gift of cryptopleurine.

[5] E. Gellert and N. V. Riggs, *Austral. J. Chem.* **7**, 113 (1954).

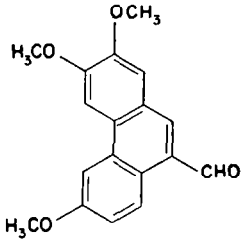
[6] J. Fridrichsons and A. Mathieson, *Nature, Lond.* **173**, 732 (1954).

[7] C. K. Bradsher and H. Berger, *J. Amer. Chem. Soc.* **80**, 930 (1958); P. Marchini and B. Belleau, *Canad. J. Chem.* **36**, 581 (1958).



IV

Simultaneously we had also undertaken the synthesis of the imide, $C_{19}H_{15}O_5N$, obtained in the oxidation of tylophorinine methiodide. 2,3,6-Trimethoxyphenanthrene-9-aldehyde (V), obtained by standard methods[8] from the corresponding acid[7] was converted to the amine (VI) through the nitrostyrene. Acetylation followed by cyclization yielded the dihydroisoquinoline (VII), whose methiodide, on oxidation,



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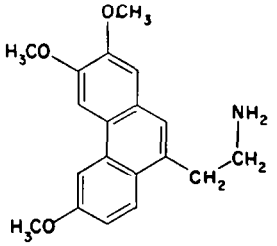
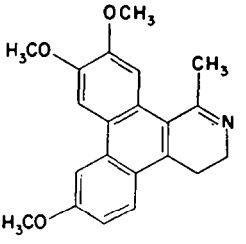
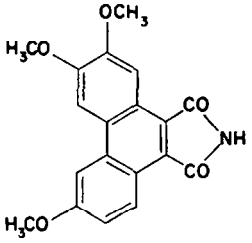


VI



VII



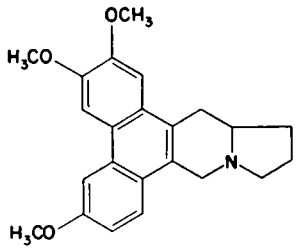
VIII

yielded 2,3,6-trimethoxyphenanthrene-9,10-dicarboxylimide (VIII), identical with the degradation product (infra-red).

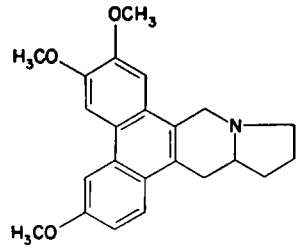
On the assumption that the heterocyclic portion of the molecule was similar to that in tylophorine, the location of the hydroxyl group was next investigated. Potentiometric titration of both tylophorinine hydrochloride as well as tylophorinine methiodide indicated that the base was not a carbinolamine. Catalytic hydrogenation of tylophorinine in acetic acid in the presence of palladium on charcoal and perchloric acid yielded desoxytylophorinine, $C_{23}H_{25}O_3N$, m.p. 252–254°, indicating the presence of a benzyl alcohol system in tylophorinine.

If tylophorinine were to contain a phenanthroindolizidine system as in tylophorine the desoxy derivative can have either of the two structures IX and X. The synthesis of

[8] J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.* 584 (1936).

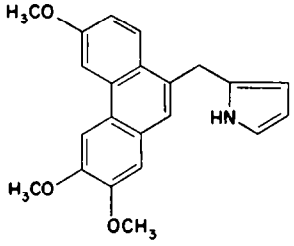


IX

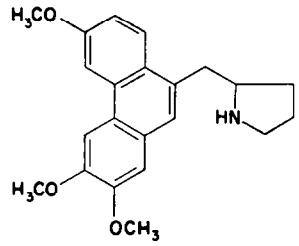


X

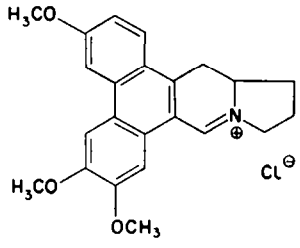
a structure corresponding to X was achieved as follows: Condensation of 2,3,6-trimethoxy-9-phenanthrylmethyl chloride[7] with pyrryl magnesium bromide gave 2-(2,3,6-trimethoxy-9-phenanthrylmethyl)pyrrole (XI), which was catalytically reduced to the pyrrolidine (XII). N-Formylation followed by cyclization gave the quaternary compound (XIII), which was reduced by sodium borohydride to 2,3,6-trimethoxy-phenanthro(9,10:7′,6′)indolizidine (X). The infra-red spectra of the synthetic compound and of desoxytylophorinine in chloroform solution were identical. The



XI



XII



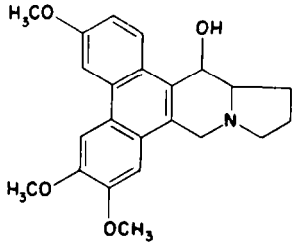
XIII

two compounds, on being subjected to the Hofmann degradation, gave in good yield the same methine, $C_{24}H_{27}O_3N$, m.p. 171·5° (identical m.p., mixed m.p., ultra-violet and infra-red spectra).

Since desoxytylophorinine is thus proved to be X, tylophorinine itself should be represented by XIV.

EXPERIMENTAL

Melting points are uncorrected. Ultra-violet absorption spectra were measured with a Beckmann Model DU Spectrophotometer. Infra-red spectra were measured by Mr. S. Selvavinayakam using a Perkin-Elmer Infracord Spectrophotometer.



XIV

Purification of tylophorinine

The crude alkaloidal material obtained by extraction of *Tylophora asthmatica*[3] was chromatographed in chloroform solution over alumina. The earlier fractions gave predominantly tylophorine. The later fractions had m.p. 235–245°. More of this material was obtained by elution of the column with chloroform containing 1% ethanol. This was rechromatographed in chloroform over alumina to get crude tylophorinine, m.p. 240–246°. The base was dissolved in chloroform, saturated with dry hydrogen chloride gas and the hydrochloride precipitated with dry ether. Three crystallizations of the product from ethanol gave pure *tylophorinine hydrochloride*, m.p. 257° (decomp); R_f 0·59 (n-butanol–water–acetic acid, 20:19:1) (Found: C, 66·6, 66·2; H, 6·2, 7·0; N, 3·3; OMe, 23·6, 20·6. $C_{25}H_{25}O_4N$. HCl requires: C, 66·4; H, 6·3; N, 3·4; 3 OMe, 22·4%). The base regenerated from the pure hydrochloride had m.p. 248–249° after crystallization from chloroform but satisfactory analyses could not be obtained for this due to decomposition. This base had λ_{max} 258, 287, 340 mμ (log ε 4·61, 4·34, 2·91). The yield of pure tylophorinine was about 0·001% based on the plant material used.

O-Acetyltylophorinine

Tylophorinine (100 mg) was heated on a water bath for 2 hr with acetic anhydride (2 ml) and a few drops of pyridine. The solution was cooled, diluted with water, basified with ammonia and extracted with ether. The residue from the ether layer after two crystallizations from benzene–pet ether (b.p. 40–60°) gave colourless needles of the *acetyl derivative* (30 mg), m.p. 222–223° (decomp) (Found: C, 71.0; H, 6·7. $C_{25}H_{27}O_5N$ requires: C, 71·3; H, 6·4%).

Tylophorinine methiodide

A solution of tylophorinine (0·5 g) in dry chloroform (100 ml) was refluxed for 3 hr on a water bath with methyl iodide (5 ml) and then left overnight. The solution was concentrated and the precipitated methiodide (0·6 g) was filtered off and washed with a little chloroform. It had m.p. 243–245° (decomp) but decomposed on crystallization from aqueous ethanol to give material, m.p. 240° (decomp), shrinking from 210°.

Oxidation of tylophorinine methiodide

(a) *Vigorous oxidation with potassium permanganate.* Tylophorinine methiodide (0·5 g) in water (150 ml) was treated with aqueous potassium permanganate (3%; 125 ml) with stirring at 30° and then at 100° till a faint pink colour persisted. The mixture was filtered and the manganese dioxide residue washed thoroughly with hot water. The filtrate was evaporated to dryness, acidified with dil H_2SO_4 and extracted continuously with ether for 12 hr. The extract was dried (Na_2SO_4) and evaporated. The residue was sublimed *in vacuo* (0·02 mm) at 170–200°. The sublimate was dissolved in ethanol (5 ml) and treated with ethylamine (1·5 ml). The solution was evaporated and the residue treated again with ethanolic ethylamine. The solvents were evaporated and the residue heated at 180° for 5 min and sublimed *in vacuo* at 150–160°. The sublimate (20 mg) on crystallization from ethanol had m.p. 190–215°. Chromatography in benzene over alumina followed by crystallization from ethanol gave N-ethyl-*m*-hemipinimide (5 mg) as colourless needles, m.p. and mixed m.p. 230–231°. Its ultraviolet and infra-red absorption spectra were also identical with those of the synthetic specimen.

The mother liquors from the above crystallization gave only a small amount of intractable product.

(b) *Mild oxidation with potassium permanganate.* A solution of tylophorinine methiodide (0·5 g) in pyridine (10 ml) and water (10 ml) was treated with stirring over a period of 3 hr with aqueous potassium permanganate (N/10; 220 ml), first at 30° and then at 40–45°. The manganese dioxide residue was filtered off, washed with water, dried and extracted in a Soxhlet with chloroform for 5 hr. The fluorescent chloroform solution was evaporated and the residue crystallized twice from pyridine to give yellow needles of 2,3,6-*trimethoxyphenanthrene*-9,10-*dicarboxylimide* (20 mg), m.p. 297°, identical in all respects with a synthetic sample (see below). (Found: C, 67·2; H, 5·0; $C_{19}H_{15}O_5N$ requires; C, 67·7; H, 4·5%). λ_{max} 260, 285, 315, 405 mμ (log ε 4·37, 4·11, 3·89 and 3·65).

The aqueous alkaline filtrate from the oxidation was evaporated *in vacuo* to 5 ml and acidified with conc HCl. The precipitated acid (0·25 g) was filtered, washed with water and dried. On recrystallization from acetic acid, yellow needles (80 mg) of the anhydride, m.p. 240–250° (decomp) were obtained. The anhydride (30 mg) was suspended in methanol and treated with ethereal diazomethane (from 3 g of nitrosomethylurea). After 24 hr the solvents were evaporated and the residue crystallized twice from methanol to give pale yellow needles of *dimethyl* 2,3,6-*trimethoxyphenanthrene*-9,10-*dicarboxylate* (12 mg), m.p. 160–162°. (Found: C, 65·5; H, 5·7; OMe, 40·7. $C_{21}H_{20}O_7$ requires C, 65·6; H, 5·2; 5 OMe, 40·4%). λ_{max} 265, 285, 330 mμ (log ε 4·58, 4·44 and 3·98). It was identical (mixed m.p., ultra-violet and infra-red spectra) with a sample made similarly by oxidation of cryptopleurine methiodide. 0·5 g of the methiodide gave, after oxidation and esterification, 20 mg of the diester. The ester was purified easily by chromatography in benzene over alumina. (Found: C, 65·6; H, 5·3%).

Synthesis of 2,3,6-*trimethoxyphenanthrene*-9,10-*dicarboxylimide*

(a) 2,3,6-*Trimethoxyphenanthrene*-9-*carboxylic acid hydrazide.* Ethyl 2,3,6-trimethoxyphenanthrene-9-carboxylate[7] (5 g) in amyl alcohol (50 ml) was refluxed for 4 hr with hydrazine hydrate (98%; 14 ml). The hydrazide separated on cooling. Ethanol (100 ml) was added and the mixture filtered warm. Crystallization from a large excess of ethanol gave needles of the *hydrazide* (5 g), m.p. 236° (decomp). (Found: C, 66·8; H, 5·7. $C_{18}H_{18}N_2O_4$ requires: C, 66·3; H, 5·5%).

(b) N-*Benzenesulphonyl*-2,3,6-*trimethoxyphenanthrene*-9-*carboxylic acid hydrazide.* Benzenesulphonyl chloride (7 g) was added dropwise with stirring to a suspension of the hydrazide (5 g) (previously dried at 110° for 5 hr *in vacuo*) in dry pyridine (150 ml) at 0°. The mixture was left overnight and then poured into ice and hydrochloric acid. The precipitated solid was collected and crystallized from ethanol to give the *benzenesulphonyl derivative* (5 g), m.p. 240° (decomp) (Found: C, 61·7; H, 5·1. $C_{24}H_{22}N_2SO_6$ requires: C, 61·8; H, 4·7%).

(c) 2,3,6-*Trimethoxyphenanthrene*-9-*aldehyde.* The above sulphonyl derivative (1 g), powdered and dried at 140° for several hours *in vacuo*, was treated in ethylene glycol suspension (10 ml) at 160°, with stirring, with anhydrous sodium carbonate (1 g). After 80 sec warm water was added. The mixture was cooled and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4) and evaporated and the residue crystallized from acetic acid giving the aldehyde (0·3 g) as pale yellow needles, m.p. 161° (Found: C, 73·2; H, 5·6. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

(d) 2,3,6-*Trimethoxy*-9-2′-*nitrovinylphenanthrene.* The aldehyde (1 g) in acetic acid (5 ml) was refluxed with nitromethane (2 ml) and ammonium acetate (0·5 g) for 2 hr. The contents were cooled and poured on ice. The gum that separated was washed with water and crystallized from acetic acid to give the *nitrovinylphenanthrene* (0·5 g) as orange plates, m.p. 192° (decomp) (Found: C, 67·4; H, 4·7. $C_{19}H_{17}O_5N$ requires: C, 67·2; H, 5·0%).

(e) 2,3,6-*Trimethoxy*-9-2′-*aminoethylphenanthrene.* The nitrovinylphenanthrene (0·7 g) in dry tetrahydrofuran (25 ml) was added to a well-stirred solution of lithium aluminium hydride (0·7 g) in tetrahydrofuran (30 ml). The mixture was stirred for 3 hr, left overnight and then decomposed as usual with ether and water. The ether–tetrahydrofuran extract was evaporated, the residue taken up in ether and extracted with dil HCl. The acid extract was basified and the base extracted with benzene. The benzene extract was washed with water, dried (Na_2SO_4) and the solvent removed to give the base as an uncrystallizable gum. The *picrate* crystallized from acetic acid as red needles, m.p. 235° (decomp) (Found: C, 55·5; H, 4·6. $C_{25}H_{24}O_{10}N_4$ requires: C, 55·5; H, 4·4%).

(f) 2,3,6-*Trimethoxy*-9-2′-*acetamidoethylphenanthrene.* The crude base obtained from 0·7 g of the nitrovinylphenanthrene was heated on a steam bath for 3 hr with acetic anhydride (2 ml) and

pyridine (1 ml). The contents were cooled, poured on ice and left aside for 1 hr. The solid that separated was filtered, washed with water and crystallized from ethyl acetate–ethanol to give the *acetamide* (0·3 g), m.p. 215° (Found: C, 71·7; H, 6·4. $C_{21}H_{23}O_4N$ requires: C, 71·4; H, 6·5%).

(g) *The dihydroisoquinoline* (VII). The acetamide (0·3 g) was heated on a steam bath with phosphorous oxychloride (7 ml) for 3 hr. The contents were cooled, poured into ice with shaking and left aside to decompose excess phosphorous oxychloride. More water was added and the contents warmed to dissolve the amine hydrochloride completely. The solution was extracted twice with benzene to remove any unreacted amide, basified and the liberated base extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4) and distilled. The residue obtained as an oil on removing the chloroform was without purification converted into the *methiodide* which crystallized from methanol as yellow needles, m.p. 239° (Found: C, 55·3; H, 5·0. $C_{22}H_{24}O_3NI$ requires: C, 55·4; H, 5·0%).

(h) 2,3,6-*Trimethoxyphenanthrene*-9,10-*dicarboxylimide*. The above methiodide (320 mg) in pyridine (2 ml) and water (25 ml) was treated dropwise with stirring with aqueous potassium permanganate solution (2%; 65 ml). Sulphur dioxide was passed into the contents to dissolve the manganese dioxide. The solution was extracted with chloroform, the chloroform solution washed with alkali, then with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed in chloroform over alumina. The imide, m.p. 296–297°, crystallized from pyridine–ethanol, was identical with the sample obtained by oxidation of tylophorinine methiodide (mixed m.p., ultra-violet and infra-red absorption spectra).

Hofmann degradation of tylophorinine

(a) *With silver oxide*. Tylophorinine methiodide (0·4 g) in water (50 ml) was shaken for 4 hr with freshly precipitated silver oxide (from 5 g silver nitrate). The solution was filtered, evaporated to dryness *in vacuo* and the residue heated at 0·5 mm for 30 min on a steam bath. The product was extracted with benzene and chromatographed in benzene solution over alumina. Elution with benzene containing 0·5% ethanol gave *tylophorinine methine* (20 mg), needles from benzene–pet ether (b.p. 40–60°), m.p. 196–197° (Found: C, 72·7; H, 6·4. $C_{24}H_{27}O_4N$ requires: C, 73·3; H, 6·9%). λ_{max} 260, 285, 315, 345, 360 mμ (log ε 4·73, 4·58, 4·05, 3·18 and 2·66).

(b) *With potassium t-butoxide*. Tylophorinine methiodide (0·2 g) was added to a solution of potassium (100 mg) in dry t-butanol (30 ml) and refluxed in an atmosphere of nitrogen for 14 hr on a water bath. The solvent was evaporated *in vacuo*, the residue diluted with water and extracted with chloroform. The chloroform solution was dried and the solvent removed. The residue, on purification, gave tylophorinine methine (25 mg), m.p. and mixed m.p. 196–197°.

Emde degradation of tylophorinine

Tylophorinine methiodide (0·2 g) was refluxed with silver chloride (from 1 g of silver nitrate) in water (10 ml) and ethanol (10 ml) for 5 hr and left overnight. The mixture was filtered and the filtrate boiled to remove the alcohol. To the hot aqueous solution was added sodium amalgam (5%; 25 g) over a period of 3 hr. The solution was further heated on a steam bath for 5 hr and left overnight. The product was extracted with benzene, the benzene solution dried (Na_2SO_4) and distilled. The residue was chromatographed in benzene over alumina. The first 20 ml of the eluate gave a small amount of gummy material. The subsequent 50 ml gave the *Emde base* (20 mg), needles from benzene–pet ether (b.p. 40–60°), m.p. 161–162° (Found: C, 73·4; H, 7·7. $C_{24}H_{29}O_4N$ requires: C, 72·9; H, 7·3%). λ_{max} 260, 285, 345, 360 mμ (log ε 4·40, 4·31, 2·90 and 2·57).

Desoxytylophorinine

Tylophorinine (0·2 g) in acetic acid (20 ml) containing perchloric acid (70%; 0·2 ml) was shaken with palladized charcoal (5%; 0·2 g) in presence of hydrogen at 23 lbs/in^2 at 55–60° for 1 hr. The solution was filtered from the catalyst and the solvent removed *in vacuo*. The product was basified with ammonia and extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and distilled and the residue chromatographed in chloroform over alumina. The product was crystallized twice from chloroform–methanol to give *desoxytylophorinine* (100 mg), m.p. 252–254° (decomp), $[\alpha]_D^{28}$ −3·7° (in $CHCl_3$) (Found: C, 76·1; H, 7·1. $C_{23}H_{25}O_3N$ requires: C, 76·0; H, 6·9%). λ_{max} 255, 290, 340 mμ (log ε 4·55, 4·31 and 3·25).

Hofmann degradation of desoxytylophorinine

Desoxytylophorinine (100 mg) in chloroform (20 ml) was refluxed with excess methyl iodide for 2 hr and left overnight. The solvent and excess of methyl iodide were distilled off, the residue triturated with water and the solid methiodide filtered. The methiodide in water (15 ml) was shaken with silver oxide (from 1 g of silver nitrate) for 4 hr. The mixture was filtered and the filtrate evaporated at 50° *in vacuo*. The residue was heated at 100° at 0·5 mm for 1 hr. The product was extracted with hot benzene and the material obtained crystallized twice from benzene–pet ether (b.p. 40–60°) to yield *desoxytylophorinine methine* (25 mg), m.p. 171·5° (Found: C, 76·0; H, 7·0. $C_{24}H_{27}O_3N$ requires: C, 76·4; H, 7·2%). λ_{max} 260, 285, 340 mμ (log ε 4·86, 4·59 and 3·32).

Synthesis of desoxytylophorinine

(a) 2-(2,3,6-*Trimethoxy*-9-*phenanthrylmethyl*)*pyrrole*. To ethylmagnesium bromide (prepared from 0·9 g magnesium) in dry ether (30 ml) was added, under nitrogen and with stirring, freshly distilled pyrrole (2·5 g). The contents were stirred for 5–10 min after the addition was completed. The homogeneous complex formed was taken in a dropping funnel and added dropwise to a well-stirred solution of 2,3,6-trimethoxy-9-phenanthrylmethyl chloride[7] (2 g) in tetrahydrofuran (25 ml) cooled in ice. After stirring for 3 hr in an atmosphere of nitrogen, the reaction mixture was decomposed with saturated ammonium chloride solution. Sufficient chloroform was added and the layers separated. The chloroform extract was washed with water, dried (Na_2SO_4) and the solvent evaporated. The residue was extracted with boiling benzene and the benzene soluble material chromatographed in chloroform over acid-washed alumina. The product crystallized from benzene–pet ether (b.p. 40–60°) to give 2-(2,3,6-*trimethoxy*-9-*phenanthrylmethyl*)*pyrrole* (0·9 g), m.p. 203° (Found: C, 75·8; H, 6·2. $C_{22}H_{21}O_3N$ requires: C, 76·0; H, 6·0%).

(b) 2-(2,3,6-*Trimethoxy*-9-*phenanthrylmethyl*)*pyrrolidine*. The above pyrrole (0·6 g) in acetic acid (30 ml) was reduced with Adams catalyst (0·15 g) at a hydrogen pressure of 50 lbs/in^2. After shaking for 3 hr more of the catalyst (0·1 g) was added. After shaking overnight, the solution was filtered from the catalyst and the solvent removed *in vacuo*. The residue was extracted thrice with 4 N H_2SO_4. The acid extract was extracted once with ether and then basified with sodium hydroxide. The white precipitate that separated was extracted with chloroform, the chloroform layer washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed in chloroform over alumina. Crystallization of the product from benzene–pet ether (b.p. 40–60°) gave the *pyrrolidine* (0·23 g), as plates, m.p. 140° (Found: C, 75·3; H, 7·1. $C_{22}H_{25}O_3N$ requires: C, 75·2; H. 7·1%).

(c) 2,3,6-*Trimethoxyphenanthro*(9,10:7′,6′)*indolizidine* (± -*desoxytylophorinine*). A mixture of the above pyrrolidine (0·225 g) and formic acid (98%; 1·5 ml) was heated gradually to 180° and maintained at that temp for 90 min. The cooled reaction product was taken up in chloroform, washed successively with $NaHCO_3$ solution, dil HCl and water. The dried (Na_2SO_4) extract was concentrated to a small bulk and chromatographed over alumina in chloroform. The formyl derivative thus obtained (140 mg) could not be crystallized. It was cyclized as such by refluxing with phosphorus oxychloride (3 ml) and toluene (6 ml) for 90 min. Sufficient pet ether (b.p. 40–60°) was added to the cooled contents to precipitate the chloride and the supernatant liquid was decanted off. The oily chloride was washed repeatedly with pet ether (b.p. 40–60°), dried *in vacuo* and reduced with sodium borohydride (0·3 g) in methanol (10 ml). The methanol was removed *in vacuo*, the residue taken up in chloroform, washed with water, dried (Na_2SO_4), concentrated to a small bulk and chromatographed over alumina in chloroform. Crystallization of the product from chloroform–methanol yielded 2,3,6-*trimethoxyphenanthro*(9,10:7′,6′)*indolizidine* (70 mg), as needles, m.p. 213–214° (Found: C, 75·8; H, 6·9. $C_{23}H_{25}O_3N$ requires: C, 76·0; H, 6·9%).

(d) *Hofmann degradation of* 2,3,6-*trimethoxyphenanthro*(9,10:7′,6′)-*indolizidine*. The above base (60 mg) was converted into the methiodide and subjected to the Hofmann degradation as in the case of natural desoxytylophorinine to yield the *methine* (30 mg), needles from benzene–pet ether (b.p. 40–60°), m.p. 171·5°, undepressed by admixture with a sample of natural desoxytylophorinine methine. Their ultra-violet as well as infra-red absorption spectra were identical. (Found: C, 76·7; H, 7·4. $C_{24}H_{27}O_3N$ requires: C, 76·4; H, 7·2%).

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