Tetrahedron, 1960, Vol. 9, pp. 53 to 57. Pergamon Press Ltd. Printed in Northern Ireland

CHEMICAL EXAMINATION OF *TYLOPHORA ASTHMATICA*—III

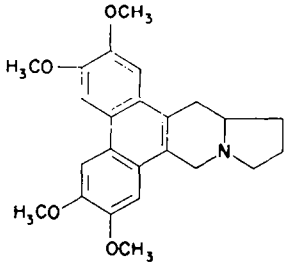
THE COMPLETE STRUCTURE OF TYLOPHORINE

T. R. GOVINDACHARI, M. V. LAKSHMIKANTHAM, B. R. PAI and S. RAJAPPA
Department of Chemistry, Presidency College, Madras

(*Received* 2 *October* 1959)

Abstract—2,3,6,7-Tetramethoxyphenanthrene-9,10-dicarboxylimide has been synthesized and proved to be identical with the oxidation product of tylophorine isomethohydroxide, confirming the previous formulation of tylophorine as 2,3,6,7-tetramethoxyphenanthro (9,10,6′,7′)-indolizidine. Some further interesting degradation reactions on tylophorine have been carried out.

THE alkaloid tylophorine[2] had been assigned structure I on the basis of degradation evidence presented in a previous communication.[1] Although one point of fusion of the heterobicyclic system was conclusively shown to be the 9- position of the phenanthrene ring, the location of the second point of fusion as the 10- position was based on biogenetic considerations and the incompatibility of the degradation results with fusion at the 8,9- position.



I

Definite evidence is now presented, which proves that the fusion of the indolizidine ring is indeed at the 9,10- position as in structure I.

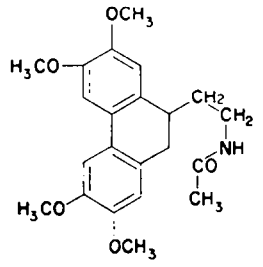
On submitting tylophorine to zinc dust distillation, a compound, m.p. 135–137°, was obtained. This had absorption maxima in the ultra-violet identical with that of 9,10-dimethylphenanthrene and its melting point was not depressed on admixture with the latter (m.p. 144°).

Oxidation of isodihydrohomotylophorinemethine[1] had yielded a dicarboxylic acid considered to be 2,3,6,7-tetramethoxyphenanthrene-9,10-dicarboxylic acid. Attempts to confirm this structure by preparing this compound by oxidation of the methyl groups in 2,3,6,7-tetramethoxy-9,10-dimethylphenanthrene, obtained by the Clemmensen reduction[3] of 2,2′-diacetyl-4,5,4′,5′-tetramethoxydiphenyl, were all unsuccessful.

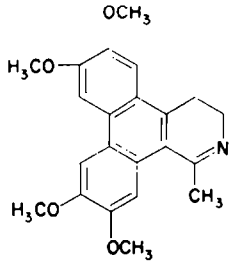
It had been reported[1] that oxidation of tylophorine isomethohydroxide yielded

[1] Part II, T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan and B. R. Pai, *Tetrahedron* **4**, 311 (1958).
[2] T. R. Govindachari, B. R. Pai and K. Nagarajan, *J. Chem. Soc.* 2801 (1954).
[3] D. M. Hall, J. E. Ladbury, M. S. Lesslie and E. E. Turner, *J. Chem. Soc.* 3475 (1956).

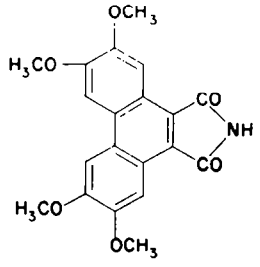
an imide considered to be 2,3,6,7-tetramethoxy-9,10-dicarboxylimide. This has now been confirmed by the following synthesis, which therefore provides conclusive proof about the positions of fusion of the indolizidine system to the phenanthrene ring. Condensation of 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde[1] with nitromethane yielded the corresponding 9-2′-nitrovinylphenanthrene, which was reduced by lithium aluminium hydride to 2,3,6,7-tetramethoxy-9-2′-aminoethylphenanthrene, characterized as the acetyl derivative II. Cyclization with phosphorus oxychloride gave the



II



III



IV

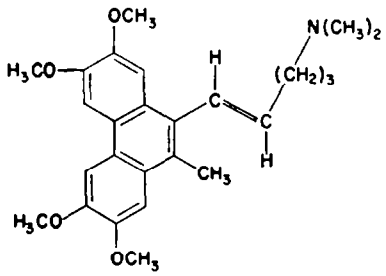
dihydroisoquinoline (III), whose methiodide on oxidation with aqueous potassium permanganate yielded 2,3,6,7-tetramethoxyphenanthrene-9,10-dicarboxylimide (IV), identical in all respects (mixed m.p. infra-red and ultra-violet absorption spectra) with the oxidation product from tylophorine.

A study of the Hofmann and Emde degradations applied to tylophorine has brought to light certain interesting features. It is found that Emde degradation of tylophorine methiodide yields a product identical with that obtained from tylophorine isomethiodide.[1] Evidently, conversion to the *iso* compound precedes bond cleavage.[4] When tylophorinemethine[1] is submitted to an Emde degradation, a compound $C_{26}H_{33}O_4N$, m.p. 155–156°, is obtained, isomeric and not identical with isodihydrohomotylophorinemethine,[1] m.p. 142°, reported earlier. Apparently, in the present case, during the Emde degradation, reductive cleavage of a —C—N— bond has occurred, but not reduction of the double bond present in the methine.

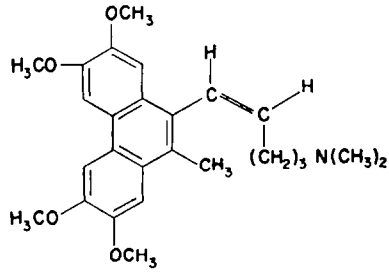
The compounds m.p. 155–156° and m.p. 142° have almost identical infra-red spectra, except that the latter has a strong band at 10·23 μ absent in the former, and in the common product, tetrahydrohomotylophorinemethine, m.p. 138–140°, obtained by catalytic reduction of either compound. It is evident that the two compounds are geometrical isomers, the compound m.p. 142°, being the *trans* (V) and the compound m.p. 155–156° being the cis (VI) isomers.

When tylophorine methiodide is subjected to Hofmann degradation, the double bond formed in the elimination reaction is likely to have the less strained *cis*- configuration, since it would have to form part of a nine-membered ring (VII).[5] When isodihydrohomotylophorine methiodide (VIII) is subjected to a Hofmann degradation, no such restriction is present and the more stable *trans*- isomer results, as borne out by the infra-red spectrum showing a strong band at 10·23 μ, characteristic of a *trans*- disubstituted ethylenic linkage.[6]

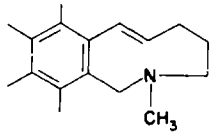
[4] E. Gellert, *Aust. J. Chem.* **9**, 489 (1956).
[5] A *trans* double bond in a 9-membered ring is known to be strained. A. T. Blomquist, L. H. Liu and J. C. Bohrer, *J. Amer. Chem. Soc.* **74**, 3643 (1952).
[6] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* p. 31. Methuen, London (1954).



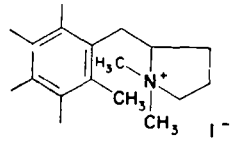
V



VI



VII



VIII

EXPERIMENTAL

Zinc dust distillation of tylophorine

Tylophorine (50 mg) was intimately mixed with zinc dust (B.D.H. Analar grade; 5 g) and heated in a Pyrex tube at 450–500° in a current of dry, oxygen-free nitrogen for 45 min. The tube was then cooled, the zinc tapped off, and the distillate washed into a flask with ether and alcohol. Twenty such batches were run and the collected distillate sublimed at 160–180°/2 × 10^{-3} mm. The sublimate was crystallized twice from alcohol to give a product (<1 mg), m.p. 135–137° after slight sintering at 130°. The m.p. was unaffected on admixture with authentic 9,10-dimethylphenanthrene[8] (m.p. 144°). Both the compounds had λ_{max} 255, 300, 335, 352 mμ (there being insufficient material for determination of ε_{max}).

2,3,6,7-*Tetramethoxy*-9,10-*dimethylphenanthrene*

(a) 2,2′-*Diacetyl*-4,5,4′,5′-*tetramethoxydiphenyl.* 6-Aminoacetoveratrone[7] (5 g) dissolved in dil HCl (40 ml; 4N) was diazotized at 0° with aqueous sodium nitrite solution (1·8 g in 5 ml), added dropwise with stirring. Ice-cold hydroxylamine solution (from 2·2 g hydroxylamine hydrochloride in 6 ml water and 5·1 ml 4N NaOH) was added with stirring to the cuprammonium solution obtained by treatment of aqueous copper sulphate solution (7·5 g in 25 ml) with liquid ammonia (10·2 ml) at 0°. To this reducing solution was added the diazo solution dropwise with stirring at 10° and left at 30° till the evolution of nitrogen ceased. The solid was filtered, washed with water, dried and then recrystallized from ethanol containing acetic acid to give 2,2′-*diacetyl*-4,5,4′,5′-*tetramethoxydiphenyl* (3 g), m.p. 212°. (Found: C, 67·2; H, 6·3. $C_{20}H_{22}O_6$ requires: C, 67·0; H, 6·1%.).

(b) 2,3,6,7-*Tetramethoxy*-9,10-*dimethylphenanthrene.* A mixture of the foregoing diketone (4 g), amalgamated zinc (40 g), ethanol (100 ml) and conc HCl (50 ml) was refluxed for 4 hr. The organic matter was extracted with chloroform, washed with water, dried (Na_2SO_4) and distilled. The residue was recrystallized from alcohol to give the pure *dimethylphenanthrene* (1·2 g), m.p. 225°; λ_{max} 255, 290, 340, 355 mμ (log ε 4·80, 4·54, 3·06, 2·64) (Found: C, 73·3; H, 6·8. $C_{20}H_{22}O_4$ requires: C, 73·6; H, 6·7%).

2,3,6,7-*Tetramethoxyphenanthrene*-9,10-*dicarboxylimide*

(a) 2,3,6,7-*Tetramethoxy*-9-2′-*nitrovinylphenanthrene.* A mixture of 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde[1] (1·5 g) nitromethane (8 ml), ammonium acetate (1·5 g) and glacial acetic acid (10 ml) was refluxed for 2 hr and poured into water. The solid was filtered, washed and dried. Recrystallization from acetic acid gave the pure *nitrostyrene* (1·2 g), m.p. 250° (decomp) (Found: C, 64·7; H, 5·4. $C_{20}H_{19}O_6N$ requires: C, 65·0; H, 5·2%).

[7] J. C. E. Simpson, C. M. Atkinson, K. Schofield, and O. Stephenson, *J. Chem. Soc.* 646 (1945).

(b) 2,3,6,7-*Tetramethoxy*-9-2'-*acetamidoethylphenanthrene*. The foregoing nitrostyrene (1·4 g) was added gradually with stirring to a suspension of lithium aluminium hydride (1·5 g) in dry tetrahydrofuran (150 ml) at 30°. After several hours, the mixture was decomposed by the addition of moist ether (150 ml) followed by water. The solvent mixture was separated, dried and the solvents removed to give the crude basic material (1·4 g). This could not be purified and was acetylated by refluxing with acetic anhydride (5 ml) and fused sodium acetate (0·5 g) for 1 hr. The acetyl derivative was extracted with chloroform, dried and distilled. The residue (1·6 g) on recrystallization from alcohol gave the *acetyl derivative* (0·8 g), m.p. 190° (Found: C, 66·9, 67·1, 67·4; H, 6·8, 7·0, 6·8. $C_{22}H_{25}O_5N \cdot \frac{1}{2}H_2O$ requires: C, 67·4; H, 6·6%).

(c) *The Dihydroisoquinoline* (III). The acetyl derivative (0·4 g) was refluxed with phosphorus oxychloride (6 ml) for 1 hr, and then poured on crushed ice. After removal of the non-basic material by extraction with benzene, the solution was cooled, basified with ammonia and extracted with chloroform. The chloroform extract was washed with water and dried over anhydrous potassium carbonate. Removal of the solvent gave the free base (0·25 g) which was chromagraphed in benzene solution on alumina, the base being eluted with benzene containing alcohol (1%). The solid obtained on evaporation of the eluate was recrystallized from methanol to give the *dihydroisoquinoline*, m.p. 180° (Found: C, 71·9; H, 6·5. $C_{22}H_{23}O_4N$ requires: C, 72·3; H, 6·3%). The *picrate* made by mixing alcoholic solutions of the base and picric acid, was recrystallized from acetic acid and had m.p. 245° (decomp) (Found: C, 56·9; H, 4·6. $C_{28}H_{26}O_{11}N_4$ requires: C, 56·6; H, 4·4%).

(d) 2,3,6,7-*Tetramethoxyphenanthrene*-9,10-*dicarboxylimide*. The foregoing dihydroisoquinoline was converted to the methiodide by refluxing with methyl iodide in chloroform solution. The methiodide (0·25 g) in water (70 ml) was treated at 30° with aqueous potassium permanganate solution (0·5 g in 70 ml) added dropwise with stirring. The mixture was left overnight, then treated with excess sulphurous acid and exhaustively extracted with chloroform. The combined chloroform extracts were washed with water and dried over anhydrous magnesium sulphate. The solvent was removed and the residue filtered in fresh chloroform solution through a short column of alumina. The solid obtained by evaporation of the eluate was recrystallized from pyridine to give the *imide*, m.p. 355° (decomp) with shrinking above 330°, identical (m.p. and Infra-red) with that obtained by the oxidation of tylophorine isomethohydroxide[1] (Found: C, 65·2; H, 4·5. Calc. for $C_{20}H_{17}O_6N$: C, 65·4; H, 4·6%).

Emde degradation of tylophorine.

Tylophorine methiodide (0·25 g) was refluxed with silver chloride (from 1 g silver nitrate) in water (10 ml) and alcohol (10 ml) for 5 hr, and left overnight. The mixture was filtered, and the alcohol distilled off. The aqueous solution of the methochloride was treated with sodium amalgam (5%; 25 g) at 100° and left overnight. The solid which had separated was extracted with benzene, dried and distilled. The residual solid (75 mg) was crystallized from benzene–petroleum ether (b.p. 40–60°) to give the Emde base, m.p. and mixed m.p. with isodihydrohomotylophorine[1], 200–202°, $[\alpha]_D^{30}$ +0°.

Emde degradation of tylophorinemethine

Tylophorinemethine methiodide[2] (0·9 g) was converted to the methochloride by refluxing with silver chloride (from 3 g silver nitrate) in water (20 ml) and alcohol (20 ml) for 4 hr, filtering and evaporating the alcohol. The aqueous solution of the methochloride (100 ml) was treated with sodium amalgam (5%; 100 g) at 100° over 3 hr. Heating was continued for 3 more hr and left overnight at 30°. After decanting from the mercury, the mixture was repeatedly extracted with ether, the ether solution dried and distilled, leaving behind a white solid (0·4 g), m.p. 155–156° (from ether), not identical with isodihydrohomotylophorinemethine[1] (m.p. 142°) (Found: C, 73·8; H, 7·9. $C_{26}H_{33}O_4N$ requires: C, 73·8; H, 7·8%). λ_{max} 258, 288, 340, 355 mμ (log ε 4·84, 4·66, 3·19, 2·89).

Catalytic reduction of the Hofmann-Emde base

The above base (100 mg) in water (10 ml) containing 4 N HCl (2 ml) was hydrogenated at 50 lbs/in^2 in presence of Adams catalyst (50 mg) for 3 hr. The solution was then filtered, basified with ammonia and extracted with ether. The residue (100 mg) after evaporation of the ether was recrystallized from dry ether to give *tetrahydrohomotylophorinemethine*, m.p. 138–140°. On admixture with the starting

material, (m.p. 155–156°), it melted at 134–135°; on admixture with isodihydrohomotylophorinemethine (m.p. 142°) it had m.p. 130–134°. (Found: C, 73·2; H, 8·1. $C_{26}H_{35}O_4N$ requires: C,73·4; H, 8·2%). λ_{max} 255, 290, 340, 355 mμ (log ε 4·73, 4·48, 3·03, 2·55).

Catalytic reduction of isodihydrohomotylophorinemethine

Isodihydrohomotylophorinemethine (100 mg) was reduced as before, to give a product (100 mg), identical with tetrahydrohomotylophorinemethine (m.p., mixed m.p. and infra-red) (Found: C, 73·6; H, 8·3%).

Acknowledgement—We are grateful to Dr. K. Nagarajan for many valuable discussions, to Prof. C. L. Stevens for some of the infra-red spectra, and to Mr. S. Selvavinayakam for the microanalyses. We thank the Government of India for the award of a National Research Fellowship (to M. V. L.) and the Council of Scientific and Industrial Research for a Senior Research Fellowship (to S. R.) and a maintenance grant.