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

SYNTHESIS OF TYLOPHORINE[2]

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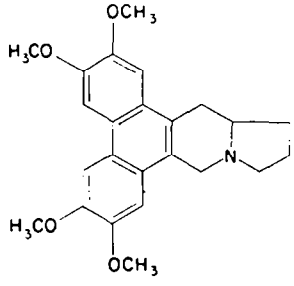
Abstract—Structure (I) assigned to tylophorine has been confirmed by a total synthesis.

TYLOPHORINE, the major alkaloid from *Tylophora asthmatica* Wight et Arn (Asclepiadaceae) has been shown to be 2,3,6,7-tetramethoxyphenanthro(9,10:6′,7′)indolizidine (I) on the basis of degradation studies.[1,3]



I

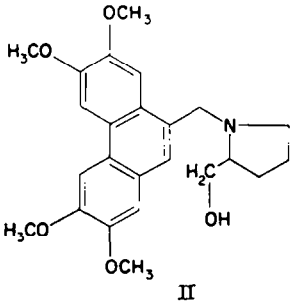
It was considered of interest to establish this structure by synthesis. The synthesis of the parent system, phenanthro(9,10:6′,7′)indolizidine, was reported in an earlier paper.[3] However, this method could not be applied to the synthesis of tylophorine itself, since the condensation of 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde with δ-nitrobutyl benzoate yielded a complex mixture of as yet unidentified products, but not the desired nitropentene.

A second approach was based on the lines of Marchini and Belleau's synthesis[4] of cryptopleurine. Here again no basic product could be obtained from the condensation of 2,3,6,7-tetramethoxy-9-chloromethyl-phenanthrene with proline ester, self condensation of the latter apparently proceeding much faster than reaction with the halide. The halide condensed in good yield with prolinol to yield N-(2,3,6,7-tetramethoxyphenanthrylmethyl)prolinol (II) which could not however be cyclized to tylophorine under a variety of conditions attempted.

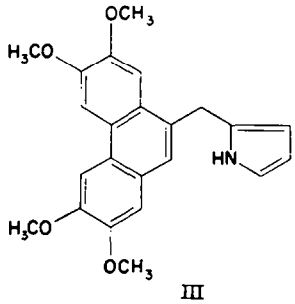
Finally, a successful synthesis of tylophorine was effected on the following lines: Treatment of pyrrylmagnesium bromide with 2,3,6,7-tetramethoxy-9-chloromethylphenanthrene yielded 2-(2,3,6,7-tetramethoxy-9-phenanthrylmethyl)pyrrole (III). This

[1] Part III, T. R. Govindachari, M. V. Lakshmikantham, B. R. Pai and S. Rajappa, *Tetrahedron* **9**, 53 (1960).
[2] A part of this work has been published in the form of a brief note: T. R. Govindachari, M. V. Lakshmikantham and S. Rajadurai, *Chem. & Ind.* 664 (1960).
[3] T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan and B. R. Pai, *Tetrahedron* **4**, 311 (1958).
[4] P. Marchini and B. Belleau, *Canad. J. Chem.* **36**, 581 (1958).

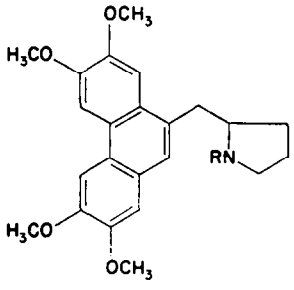
was reduced in acetic acid solution in the presence of Adams catalyst to the corresponding pyrrolidine (IV). The N-formyl derivative of this base (IVa) underwent smooth cyclization to the quaternary salt (V) on heating with phosphorus oxychloride in toluene. The last compound was reduced without further purification in good yield to (±)2,3,6,7-tetramethoxyphenanthro(9,10:6′,7′)indolizidine (I). After purification by chromatography and crystallization from chloroform–ethanol, the product melted at 289° (decomp) when introduced in a bath preheated to 250° as did (−)tylophorine and a mixture melted with decomposition at 282°.



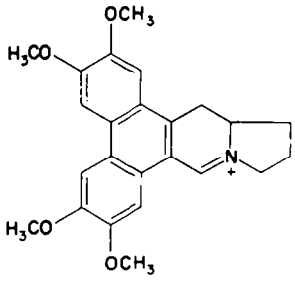
II



III



IV : R = H
IVa : R = CHO



V

The infra-red spectra of the synthetic (±) and natural (−) tylophorine were identical in chloroform soluton. The synthetic compound was further resolved through (+) camphorsulphonic acid into (−)tylophorine, m.p. 292°, $[\alpha]_D^{30}$ −11·5° and (+)tylophorine, m.p. 292°, $[\alpha]_D^{30}$ +12·25°. The (−)tylophorine was identical in every respect with natural tylophorine. The structure assigned to tylophorine has, therefore, been fully confirmed by the synthesis reported here.

EXPERIMENTAL

2,3,6,7-*Tetramethoxy-9-hydroxymethylphenanthrene.* Methyl 2,3,6,7-tetramethoxyphenanthrene. 9-carboxylate[3] (6 g) was added portionwise with stirring to a slurry of lithium aluminium hydride (2 g) in dry tetrahydrofuran (100 ml). Stirring was continued for 2 hr more. The complex was decomposed as usual and the organic layer separated and dried (Na_2SO_4). The solvent was distilled off and the residue, dissolved in chloroform, was passed through a column of alumina and then recrystallized from benzene to give the *alcohol* (4 g), m.p. 185° (Found: C, 69·8; H, 6·3. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·1%).

2,3,6,7-*Tetramethoxy-9-chloromethylphenanthrene.* The foregoing carbinol (1·4 g) dissolved in dry chloroform (50 ml) containing dry pyridine (1 ml) was treated with thionyl chloride (2 ml) in chloroform (10 ml) at 5°. The mixture was then gently warmed on a water bath for 1 hr and poured

into crushed ice. The chloroform layer was washed well with water, dil Na_2CO_3 solution and again with water and dried (Na_2SO_4). The solvent was removed and the residue recrystallized from benzene–petroleum ether (b.p. 40–60°) to give the *chloride* (1·2 g), m.p. 192° (Found: C, 66·0; H, 5·5. $C_{19}H_{19}O_4Cl$ requires: C, 65·8; H, 5·5%).

N-(2,3,6,7-*Tetramethoxyphenanthrylmethyl*)*prolinol* (II). The chloride (0·2 g) and prolinol[5] (0·3 g) were dissolved in dry toluene and refluxed with stirring for 20 hr. The toluene solution was then repeatedly extracted with dil HCl. The combined acid extract was shaken once with ether and then cooled and basified with liquor ammonia. The liberated base was thoroughly extracted with chloroform. The chloroform layer was washed well with water and dried (Na_2SO_4). The residue obtained after removal of the solvent was recrystallized from benzene to give the substituted *prolinol* (0·2 g), m.p. 220° (Found: C, 69·9; H, 6·8. $C_{24}H_{29}O_5N$ requires: C, 70·1; H, 7·1%).

2-(2,3,6,7-*Tetramethoxy*-9-*phenanthrylmethyl*)*pyrrole* (III). To a mixture of magnesium (1·2 g) in dry ether (50 ml) was added dropwise a solution of ethyl bromide (5·5 g) in dry ether (30 ml). After stirring for 1 hr, the reaction vessel was cooled in ice and freshly distilled pyrrole (3·4 g) in dry ether (10 ml) was added dropwise and the stirring continued for 30 min more.

The above pyrrylmagnesium bromide was added dropwise to a solution of 2,3,6,7-tetramethoxy-9-chloromethylphenanthrene (2·5 g) in dry tetrahydrofuran (40 ml) with stirring. The stirring was continued for 3 hr and the complex was then decomposed with ice and a saturated solution of ammonium chloride. After decomposition, the whole was extracted with chloroform and the extract washed and dried (Na_2SO_4). The solvent was removed and the gummy residue passed through a column of acid-washed alumina in chloroform solution. The chloroform solution was evaporated and the residue recrystallized from benzene–petroleum ether (b.p. 40–60°) to give the *pyrrole* (1·8 g), m.p. 212° (Found: C, 73·1; H, 6·3. $C_{23}H_{23}O_4N$ requires: C, 72·8; H, 6·5%).

2-(2,3,6,7-*Tetramethoxy*-9-*phenanthrylmethyl*)*pyrrolidine* (IV). The foregoing pyrrole (0·2 g) in acetic acid (30 ml) containing Adams catalyst (0·15 g) was shaken with hydrogen at a press of 60 lbs/in^2 for 12 hr, with the addition of fresh catalyst (0·05 g) at the end of 4 hr. The solution was filtered and evaporated to dryness *in vacuo*. The residue was taken up in H_2SO_4 (2 N; 20 ml) and the acid extract shaken with ether. The acid layer was cooled and made alkaline with aqueous NaOH and the base extracted with chloroform. The solvent was removed and the gummy residue (0·08 g) recrystallized from benzene–petroleum ether (b.p. 40–60°) to give the *pyrrolidine*, m.p. 152° (Found: C, 72·1; H, 7·0. $C_{23}H_{27}O_4N$ requires: C, 72·4; H, 7·1%).

N-*Formyl derivative of* IV (IVa). The above pyrrolidine (0·3 g) was treated with formic acid (98%; 1·5 ml) and heated gradually to 180° and then maintained at 180° for 1 hr. The residue was cooled and taken up in chloroform, washed with dil $NaHCO_3$ solution and then with water and dried (Na_2SO_4). The residue after removal of the solvent was crystallized from dry ether to give the N-*formyl derivative* (0·2 g), m.p. 140° (Found: C, 70·6; H, 6·6. $C_{24}H_{27}O_5N$ requires: C, 70·4; H, 6·6%).

(±)*Tylophorine* (I). The above formyl derivative (0·2 g) was refluxed in dry toluene (6 ml) with phosphorus oxychloride (0·5 ml) for 1 hr. It was then diluted with a large volume of pet ether (b.p. 40–60°) and the precipitated quaternary compound (V) was repeatedly washed with pet ether. The crude compound was dissolved in methanol (15 ml) and treated with sodium borohydride (0·2 g) and left overnight. The solvent was then removed *in vacuo* and the residue was decomposed with water and extracted with chloroform. The residue obtained after removal of the solvent was passed through a column of alumina in chloroform solution. It was then recrystallized from chloroform–ethanol to give (±)*tylophorine* (0·05 g), m.p. 292°. The infra-red spectra of the synthetic and natural tylophorine were identical in chloroform solution (Found: C, 73·0; H, 7·1. $C_{24}H_{27}O_4N$ requires: C, 73·3; H, 7·0%).

Resolution of (±)*tylophorine*. (±)Tylophorine (0·15 g) in chloroform (5 ml) was added to a solution of (+)camphorsulphonic acid (0·09 g) in chloroform (5 ml) and the mixture was evaporated to dryness. The residue was recrystallized from methanol (2·5 ml). The crystalline mass (50 mg), m.p. 295° was filtered and washed with a little methanol. It was found to be the 1-base-d-salt having the rotation $[\alpha]_D^{30}$ +20° (*c*, 1·5; in $CHCl_3$). The filtrate was evaporated to dryness and the residue crystallized from chloroform–acetone to give the d-base-d-salt (40 mg), m.p. 285–287°, $[\alpha]_D^{30}$ +24·1° (*c*, 1·2; in $CHCl_3$). The base liberated from the 1-base-d-salt had m.p. 292°(decomp), $[\alpha]_D^{30}$ −11·5°

[5] P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta* **31**, 1617 (1948).

c, 0·866; in $CHCl_3$). The base liberated from the d-base-d-salt had m.p. 292° (decomp), $[\alpha]_D^{30}$ +12·25° (*c*, 0·733; in $CHCl_3$).

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