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STRUCTURE OF TYLOPHORINE

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The isolation of tylophorine, $C_{24}H_{27}O_4N$, the major alkaloid of *Tylophora asthmatica*, and its Hofmann degradation were reported earlier.¹ It is now shown that tylophorine most probably has structure (I).

Mild oxidation of tylophorine methohydroxide gave two products, $C_{20}H_{16}O_7$, m.p. 315-325° (decomp.) and $C_{20}H_{17}O_6N$, m.p. 355° (decomp.), considered to be 2:3:6:7-tetramethoxy-9:10-phenanthrenedicarboxylic anhydride and its imide respectively (good analyses have been obtained for all compounds reported in this communication). The former yielded by the action of ethereal diazomethane, the dimethyl ester, $C_{22}H_{22}O_8$, m.p. 246-247°, which was also obtained from tylophorinemethine¹ by oxidation with alkaline hydrogen peroxide followed by esterification of the acidic product. Vigorous oxidation of tylophorine methiodide gave *m*-hemipinic acid, identified as the *N*-ethylimide, m.p. 230-231°.

Treatment of tylophorine with cyanogen bromide gave in good yield a bromocyanamide, m.p. 163°, which reacted readily with diethylamine to give a compound, m.p. 157°, indicating that the C-N bond cleaved forming a C=C-CH₂-N< system, possibly a benzylamino group. Attempted reduction of the bromocyanamide with sodium borohydride led only to replacement of the bromine by a hydroxyl group to give a hydroxy cyanamide, m.p. 195-198°, which regenerated tylophorine on hydrolysis. The presence of a 1:5- or 1:6-aminoalcohol system in the hydroxycyanamide could thus be inferred. An attempted reduction of tylophorinemethine, $[\alpha]_D^{20} \pm 0^\circ$ led to the formation of tylophorine isomethohydroxide, indicating that the methine had an eight-, nine- or ten-membered ring containing the nitrogen atom and that tylophorine had the nitrogen common to two rings which are five- or six-membered. Tylophorine itself is recovered unchanged under a variety of hydrogenation conditions.

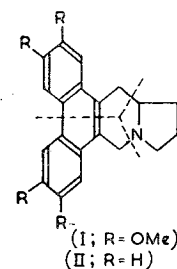
Tylophorine methiodide was converted to the isomethiodide by hot alkali (*cf.* Gellert and Riggs;² Gellert³). Emde degradation of the derived isomethochloride gave isodihydrohomotylophorine, $C_{25}H_{31}O_4N$, m.p. 200-202°, $[\alpha]_D^{20} \pm 0^\circ$ which was dehydrogenated to a non-basic compound, $C_{25}H_{27}O_4N$, m.p. 235°, which showed positive pine splinter and Ehrlich tests and which regenerated the Emde base on hydrogenation. One of the nitrogen-carrying rings must therefore be five-membered.

Hofmann degradation of the Emde base gave a basic methine, $C_{26}H_{33}O_4N$, m.p. 142°, confirming that tylophorine has a nitrogen atom common to two rings.

Oxidation of isodihydrohomotylophorinemethine and separation of the product after esterification gave two compounds, $C_{22}H_{22}O_8$, m.p. 246-247°, and $C_{21}H_{22}O_6$, m.p. 185-186°. The former was identical with the dimethyl ester obtained by oxidation of tylophorine methohydroxide or tylophorinemethine. The latter was hydrolyzed to an acid, m.p. 225-227°, which yielded on decarboxylation 2:3:6:7-tetramethoxy-9-methylphenanthrene, m.p. 188-189°. This was identical with a specimen synthesized from 2:3:6:7-tetramethoxyphenanthrene-9-carboxylic acid through the 9-aldehyde by the method of Buchanan *et al.*⁴

The degradative results outlined so far are best explained by structure (I) for tylophorine.

Alternative formulae involving attachment of the heterobicyclic system at the 9:8-position are not ruled out but attachment at the 9:10-position as in formula (I) would imply derivation of the alkaloid from two dihydroxyphenylalanine units and ornithine, on the basis of analogy with Sir Robert Robinson's dissection of cryptopleurine, into two phenylalanine residues and a lysine moiety.⁵



The parent compound (II) has been synthesized from phenanthrene-9-aldehyde. Condensation with 8-nitrobutyl benzoate and lithium aluminium hydride reduction gave 4-amino-5-(9-phenanthryl)pentanol. Its *N*-formyl derivative was cyclized with phosphoryl chloride to give a compound which on hydrogenation yielded phenanthro(9:10:6':7')indolizidine (II). The synthesis of tylophorine by an analogous procedure is in progress. Full details of this work will be published elsewhere.

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