A Novel Synthesis of (±)-Tylophorine

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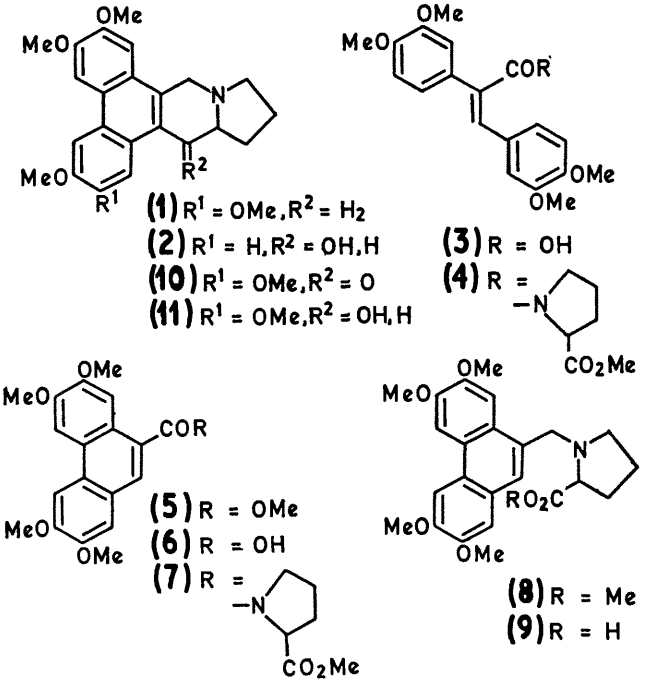
Summary (±)-Tylophorine was synthesised by a route involving as a key step the highly selective reduction of an amide to the corresponding amine in the presence of an ester function with triethyloxonium fluoroborate followed by sodium borohydride.

THE structure of tylophorine, the major alkaloid of *Tylophora asthmatica* has been shown to be (**1**),[1,2] confirmed by synthesis.[3] In the course of a study of the *Tylophora* bases we have devised a new synthesis of tylophorine which we report here.

3,4-Dimethoxy-α-(3,4-dimethoxyphenyl)cinnamic acid (**3**)[4] gave a methyl ester, m.p. 125—126°, λ_{max} (EtOH) 234, 293 (s), 327 nm (log ε 4·27, 4·12, 4·24), ν_{max} (Nujol) 1712 cm^{-1}. Photolysis (Hanovia UVS 500 A lamp) of a 6×10^{-2}M-solution of this ester with iodine (*ca.* 3 mole %) in cyclohexane gave, as the major product (31% yield after chromatography on silica), methyl 2,3,6,7-tetramethoxyphenanthrene-9-carboxylate (**5**),[1] m.p. 202—204°, λ_{max} (EtOH) 226, 264, 281, 290, 327 nm (log ε 4·02, 4·74, 4·44, 4·49, 4·05), τ ($CDCl_3$) 2·48 (1H, s), 2·81 (1H, s), 3·48 (1H, s), 3·54 (1H, s), 3·96 (1H, s), 6·98 (9H, s), 7·07 (6H, s). Whilst this photolytic ring closure does not proceed in outstanding yield it has the advantage over the comparable Pschorr reaction in a much improved yield over fewer steps. The carboxylic acid (**6**) identical with authentic 2,3,6,7-tetramethoxyphenanthrene-9-carboxylic acid[1] was obtained quantitatively by alkaline hydrolysis of the ester (**5**). Condensation of freshly prepared methyl prolinate[5] with the acid (**6**) using dicyclohexylcarbodi-imide in methylene chloride (3·5 hr. at room temperature) yielded 76% of the amide (**7**) m.p. 204—206°, ν_{max} ($CHCl_3$) 1740, 1630 cm^{-1}, after silica chromatography. This compound could be prepared more conveniently and in slightly better overall yield, under conditions similar to those used above, by reaction of the cinnamic acid (**3**) with methyl prolinate followed by photolytic cyclisation of the product (**4**).

Borch has shown that sodium borohydride reduction of the salts formed by *O*-alkylation of secondary and tertiary amides with triethyloxonium fluoroborate gives the corresponding amines.[6] As esters are reported to be unreactive towards the latter reagent[7] it seemed likely that the amide ester (**7**) would reduce to the amino-ester (**8**) under the conditions used by Borch. In the event, a 77% yield of the desired product (**8**) was obtained following silica chromatography, m.p. 159—162°, ν_{max} ($CHCl_3$) 1740 cm^{-1}, τ ($CDCl_3$) 1·8 (1H, s), 2·18 (2H, s), 2·52 (1H, s), 5·86 (9H, s), 5·96 (3H, s), 6·3 (3H, s), 6·2—8·5 (8H, unresolved), and 5·43 (1H, *J* 12 Hz, one of the new benzylic protons the other being partially obscured by the methoxyl protons. The low-field resonance of one of these protons is attributable to deshielding by the ester carbonyl).

Hydrolysis of (**8**) to the corresponding amino-acid was achieved under basic but not acidic conditions (yield 79%, m.p. 203—205°). Polyphosphoric acid cyclisation of this product (**9**) at 100° for 30 min. under nitrogen gave a very unstable product in approximately 40% yield (allowing for recovered amino-acid) which was presumably the ketone (**10**). It was not successfully characterized as such but could be reduced with sodium borohydride, however, to a stable alcohol (**11**) whose mass spectral fragmentation was strictly analogous to the highly characteristic pattern of the alkaloid tylophorinine (**2**) [*m/e* 409 (M^+), 340 ($M^+ - C_4H_7N$), 312 (340 — CO); *cf.* tylophorinine *m/e* 379 (M^+), 310 ($M - C_4H_7N$), 282 (310 — CO)]. The alcohol could not be hydrogenolysed (Pd–C/acetic acid/perchloric acid) to tylophorine. Of the conventional methods for direct complete reduction of the ketone only the Clemmensen reaction proved successful although proceeding in poor yield. (This step is not considered to be optimized. Nonetheless the overall yield for this synthesis is better than the previously reported synthesis by a factor of *ca.* 2). Tylophorine (**1**) thus obtained was identical with the natural alkaloid (t.l.c., i.r., u.v., and mass spectra) except in optical activity.



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