Synthesis of the Tetrahydroisoquinoline Alkaloids (±)-Tepenine, Tehaunine, and (±)-*O*-Methylgigantine and Revised Structure of Gigantine

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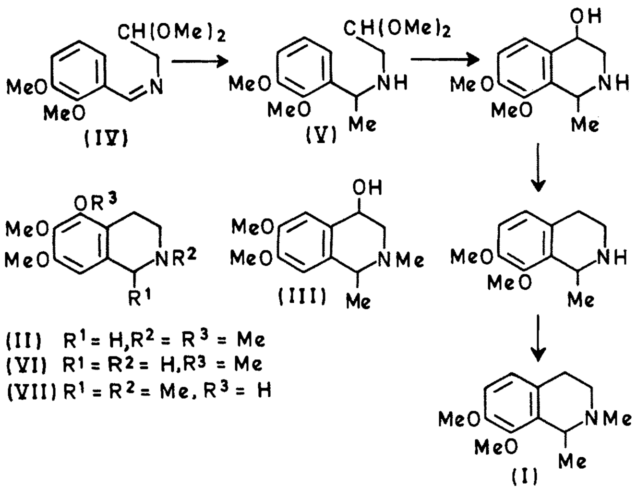
Summary The tetrahydroisoquinoline alkaloids tepenine, tehaunine, and gigantine (as its methyl ether) have been synthesized; a revised structure of gigantine is offered.

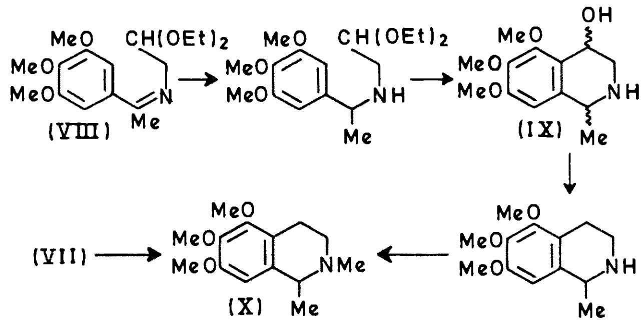
THE naturally occurring 7,8-dioxygenated (*a*) and 5,6,7-trioxygenated (*b*) tetrahydroisoquinoline alkaloids are by far less commonly encountered than the corresponding 6,7- and 6,7,8-polyoxygenated analogues. To our knowledge, only two natural products of type *a* are known thus far: petaline[1] and tepenine (I).[2] The tetrahydroisoquinolines of type *b* are extremely rare in the Cactaceae family and perhaps hitherto represented solely by tehaunine (II)[2], although there are some examples of 1-benzyltetrahydroisoquinolines with the 5,6,7-trioxygenated pattern in other plant families.[3] Gigantine, reported by Hodgkins *et al.*[4] as a hallucinogenic constituent of the cactus *Carnegia gigantea*, was originally assigned structure (III) which was later questioned[5] and recently rejected[6] on the basis of its non-identity with both *cis*- and *trans*-isomers of (III) obtained synthetically by Brossi and his co-workers.[6]

Isolation of tepenine (I) and tehaunine (II) from the cactus *Pachycereus tehauntepecanus* and their structure elucidation were recently accomplished by Weisenborn and his co-workers.[2] Our synthesis of (I) was based on the reaction of 2,3-dimethoxybenzaldehyde with aminoacetaldehyde dimethyl acetal, according to Bobbitt's modification[7] of the Pomeranz–Fritsch isoquinoline synthesis, leading to the Schiff base (IV) which was treated with methyl Grignard reagent to give the benzylamine derivative (V). Cyclization of the latter using hydrochloric acid, followed by hydrogenolysis and *N*-methylation with formaldehyde–$NaBH_4$, afforded racemic tepenine (I)[8] in *ca.* 24% overall yield.

Tehaunine (II)[8] was synthesized by *N*-methylation of the base (VI), previously reported by Bobbitt *et al.*,[7] by a sequence similar to that outlined above (overall yield 35·8%). The synthesis of (I) and (II) provides additional support to the suggested[2] structures of these unusual alkaloids.

In a re-investigation of the structure of gigantine, it was observed that the alkaloid gave a positive Gibb's test, characteristic of phenols having the *para*-position unsubstituted, which was not compatible with the structure (III) originally put forward by Hodgkins *et al.*[5] However, the 100 MHz n.m.r. spectrum favoured structure (VII), since addition of strong alkali produced the characteristic[9] upfield shift (0·41 p.p.m.) of the signal at δ 6·29 (s, 1H) assignable to aromatic proton *para* to the phenolic hydroxy-group. Moreover, the C-1 methyl signal at δ 1·35 (d, *J* 6·5 Hz) was not affected by this base treatment, which is in accord with structure (VII) but in contrast to the behaviour of the isomeric pellotine, anhalonidine, and other 1-methyl-8-hydroxy-analogues, all of which exhibit an upfield shift (*ca.* 0·30 p.p.m.) of the methyl signals. Further support for the revised structure (VII) of gigantine was obtained by synthesis of its methyl ether. Treatment of 3,4,5-trimethoxyacetophenone with aminoacetaldehyde diethyl acetal, followed by reduction of the resulting Schiff base (VIII) and its cyclization in hydrochloric acid solution, gave an isomeric mixture of (IX) which was subjected to hydrogenolysis and *N*-methylation to afford (X) (overall yield 29·8%) found to be identical with the *O*-methyl derivative of gigantine.[8] This alkaloid appears to be the second example of the tetrahydroisoquinolines of type *b*.





It would seem attractive to envisage alkaloids (I), (II), and (VII) as resulting biogenetically from appropriately substituted phenethylamines. Alkaloid (I) would, however, result from an unusual cyclization involving the *ortho*-position (relative to the C-3 oxygen function in a dopamine type of precursor) rather than the *para*-position which gives several common 6,7-dioxygenated tetrahydroisoquinolines. The biogenesis of these alkaloids is currently under investigation.

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7 J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, 1965, **30**, 2247.

8 The i.r., n.m.r., and mass spectra of all the synthetic compounds were consistent with the structures shown. The i.r. spectrum of the synthetic (±)-tepenine (I) was identical with that of the natural product. Synthetic and natural tehaunine (II) were identical by their i.r., n.m.r., and mass spectra, and by undepressed mixed m.p. Similarly, the i.r., n.m.r., and mass spectra of the synthetic (±)-*O*-methylgigantine (X) and the *O*-methyl ether of natural gigantine were identical.

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