Total Synthesis of the Isoquinoline Alkaloid (±)-Xylopinine by Thermolysis

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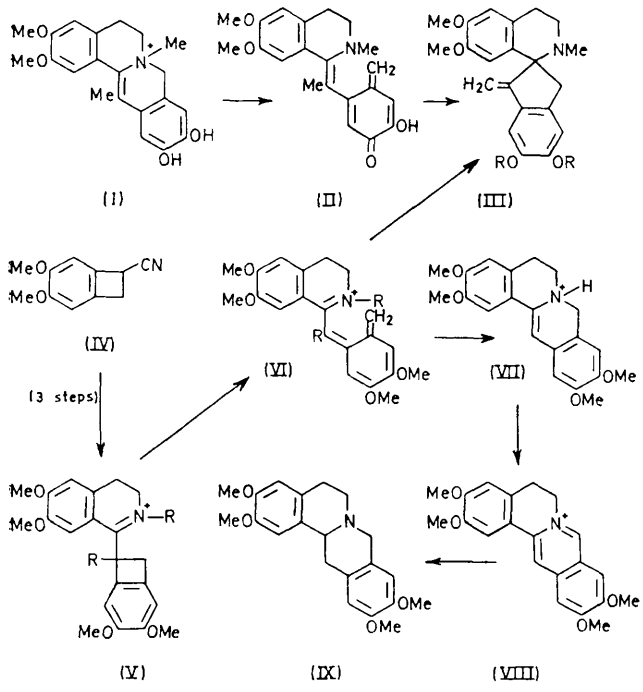
Summary (±)-Xylopinine (IX) was synthesised from 1-benzocyclobutenylisoquinoline (V) in good yield by thermolysis.

IT has been shown by Shamma and Jones that the quinoid compound (II) derived from basic treatment of the dihydroprotoberberinium metho-salt (I) rearranges to the spirobenzylisoquinoline (III; R = H) in good yield.

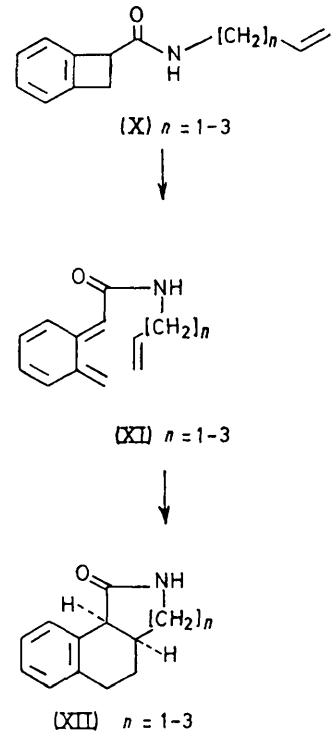
We were interested to discover if the same type of rearrangement could occur with the *o*-quinodimethane (VI), which has the same kind of electronic environment as the quinoid compound (II),[1] to give the dihydroprotoberberine (VII) [starting from (V; R = H)] and the spirobenzylisoquinoline (III; R = Me) [starting from (V; R = Me)].



SCHEME 1

To test this, the benzocyclobutenylisoquinoline hydrochloride (V; R = H), m.p. 189—190°,† was synthesised in good yield from the known cyanobenzocyclobutene (IV)[2] *via* a three-step operation. It was expected that this compound would undergo cleavage to the *o*-quinodimethane intermediate (VI; R = H) on heating, as Oppolzer has demonstrated that the benzocyclobutenes (X) give the corresponding tricyclic compounds (XII) *via* *o*-quinodimethane intermediates (XI) on thermolysis.[3]

Thus, the hydrochloride (V; R = H) was heated at 155° for 20 min in bromobenzene under nitrogen. Removal of the solvent by filtration left the crude protoberberine (VIII)



SCHEME 2

chloride in 90% yield as yellow crystals, purified as the chloride, m.p. 212—215°.† (VIII) may be formed from the expected dihydroprotoberberine (VII) by thermal dehydrogenation. Hydrogenation of (VIII) on platinum oxide in methanol afforded the known (±)-xylopinine (IX) hydrochloride, m.p. 213—214°,[4] in 90% yield, which was confirmed by comparison of its i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectra and t.l.c. behaviour ($CHCl_3$–MeOH ≡ 20:1) with those of natural xylopinine. The free base of (V; R = H) gave neither the dihydroprotoberberine (VII, free base) nor the protoberberine (VIII), on thermolysis, but an unidentified compound instead.

The rearrangement of the benzocyclobutenylisoquinoline (V; R = Me) to the spirobenzylisoquinoline (III; R = Me) is under investigation.

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† Characterised by n.m.r. and m.s. measurements.

[1] M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 4009; M. Shamma and C. D. Jones, *ibid.*, 1970, **92**, 4943.
[2] I. L. Klundt, *Chem. Rev.*, 1970, **70**, 471.
[3] W. Oppolzer, *J. Amer. Chem. Soc.*, 1971, **93**, 3833, 3834, 3836.
[4] T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Hirokawa Inc., Tokyo, 1968, pp. 118, 246.