Synthesis of Protostephanine by a Route Related to the Biosynthetic Pathway

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Protostephanine from *Stephania japonica* Miers has the novel structure[1] (X) which has been confirmed by synthesis.[2] We aimed to synthesise protostephanine from a 1-benzylisoquinoline, along the lines of Barton's suggestion[3] for the biosynthetic pathway. This involves the dienone (III) which could arise from (I) by phenolic oxidation and subsequent *O*-methylation. The corresponding dienol may then undergo rearrangement as (IV) → (VI) → (VII) with a final reductive step to generate protostephanine (X).

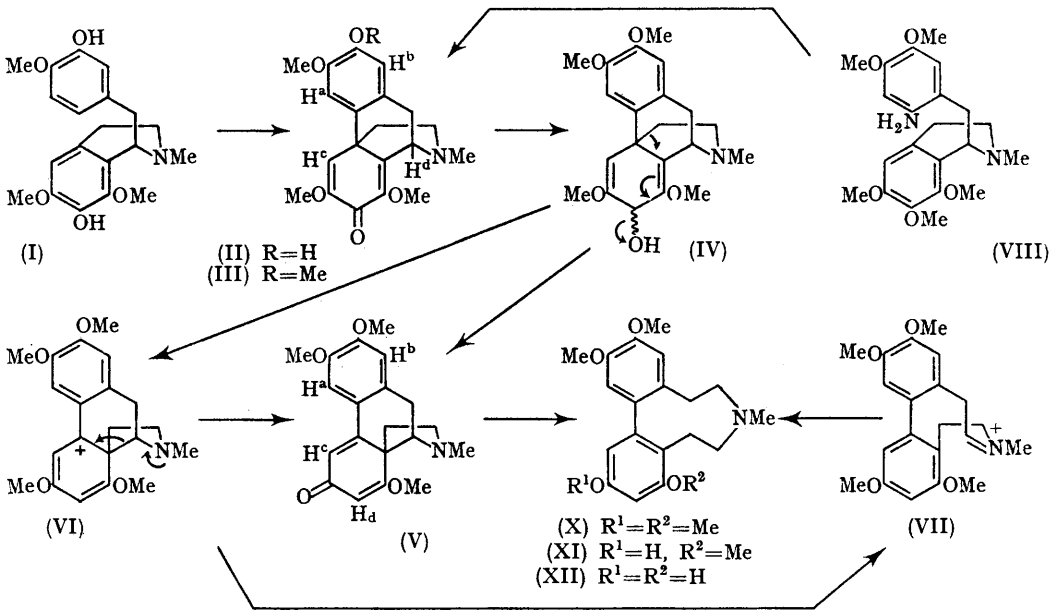
Ferricyanide oxidation of the diphenol† (I), prepared by standard methods, afforded many products, from which the dienone (II) was isolated (1·7% yield) together with isoboldine [(IX), 2% yield]. Formation of the latter involves elimination of one methoxy-group, probably as formaldehyde, and precedents are known.[4] *O*-Methylation of (II) gave the ether (III) though this was prepared more readily from the amine (VIII). Thus, diazotisation followed by Pschorr cyclisation[5] afforded the dienone (III), named protostephanone, in 25% yield, M^+ 371, ν_{max} 1663 and 1628 cm.$^{-1}$, τ 3·20 (s, 1H^a), 3·35 (s, 1H^b), 3·63 (s, 1H^c), 5·60 (dd, 1H^d), 6·12 and 6·18 (s, 6H each, 4OMe), and 7·50 (s, 3H, NMe). Reduction of (III) with borohydride yielded the epimeric dienols (IV) quantitatively; these were separable (M^+ 373 for both) but were used in admixture for rearrangement catalysed by sulphuric acid. The product (80%) was a dienone (M^+ 341) to which structure (V) is assigned by chemical evidence adduced below and because of its spectroscopic properties, λ_{max} 352 mμ; ν_{max} 1647, 1611, and 1591 cm.$^{-1}$, τ 3·0 (s, 1H^a), 3·22 (s, 1H^b), 3·72 (d, 1H^c, J 2 c./sec.), 4·39 (d, 1H$_D$, J 2 c./sec.), 6·06 (s, 6H, 2OMe), 6·14 (s, 3H, OMe), and 7·46 (s, 3H, NMe). When the above preparation of (V) was repeated with use of borodeuteride in the reductive step, the product (M^+ 342) showed no n.m.r. signal corresponding to H^d and the signal arising from H^c was a singlet.

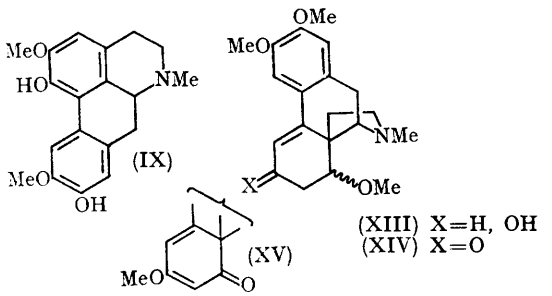
Borohydride reduction of (V) afforded the epimeric enols [(XIII), M^+ 345] which were oxidised by chromic acid to an enone (M^+ 343) with spectroscopic properties in agreement only with structure (XIV). This evidence eliminates the arrangement (XV), which otherwise is a possible alternative to structure (V).

When the dienone (V) was heated with magnesium iodide[6] and the products were reduced with

† This base has also been prepared in work at Imperial College by Dr. A. Wiechers.

lithium aluminium hydride, two phenols [(XI), M^+ 343), the major component, and [(XII), M^+ 329] were obtained in a combined yield of 46%. Both phenols, by *O*-methylation with diazomethane, yielded protostephanine (X), identical with the natural product.





This synthesis brings about the desired conversion of a 1-benzylisoquinoline into protostephanine and reproduces *in vitro* the late stages of the biosynthetic pathway.‡ Tracer experiments covering all stages in the sequence are in progress with *Stephania japonica* plants.

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‡ Unpublished work by Dr. P. Hackett has established the incorporation of dienone (II) into protostephanine in *S. japonica* plants (2·9% incorp.).

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