Evidence from Synthesis and Isolation Concerning the Rearrangement Process in Indole Alkaloid Biosynthesis

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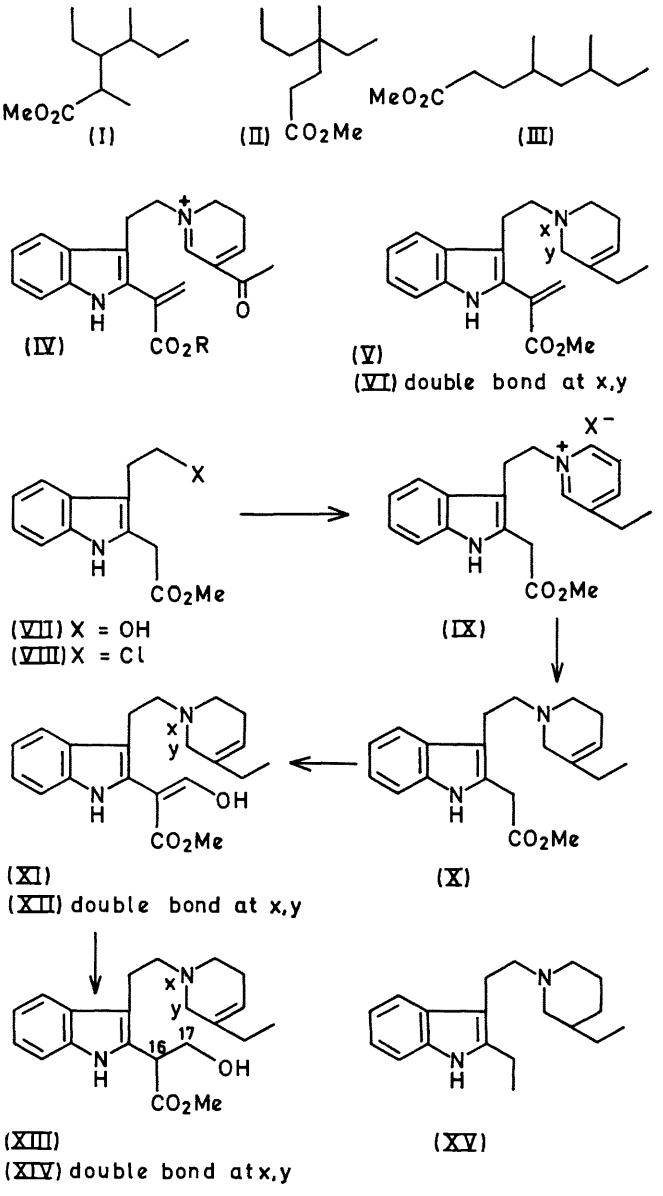
Summary The base (XIII) is synthesised and is shown to be present in *Rhazya orientalis* plants.

THE process whereby the unrearranged non-tryptamine unit of the *Corynanthe–Strychnos* alkaloids (I) is converted into the rearranged *Aspidosperma* (II) and *Iboga* (III) units has recently been studied intensively[1–4] both *in vitro* and *in vivo*. Wenkert's speculations[5] on the mechanism of rearrangement invoked the acrylic acid derivative (IV) and its dihydro-derivative as intermediates, whilst Qureshi and Scott's results led them to suggest[1] a different mechanism, making use of the acrylic ester (VI) and the corresponding enamine. Further, it seemed possible at the outset of our synthetic work that the enol (XII) might be formed *in vivo*.[6]

It is evident that compounds (V), (VI), (XII), and (XIV) are all derivable, in principle, from (XI) and (XIII) so these two were selected as the initial targets. The diazoketone derived from indole-2-carboxylic acid was photolysed in methanol to form methyl 2-indolylacetate.[7] Treatment of this ester with ethylene oxide and stannic chloride[8] gave the alcohol (VII) which was converted into the chloride (VIII) with methanolic hydrogen chloride. This sequence conveniently yields small quantities of (VIII) but Wenkert's route,[9] published during our work, is preferable for larger amounts. 3-Ethylpyridine reacted with (VIII) to form the salt (IX) shown to be identical with the degradation product from akuammicine.[10] Borohydride reduction of the pyridinium system (IX) gave the tetrahydropyridine‡ (X), m.p. 81—82°. This was formylated with trityl sodium and methyl formate[11] and the crystalline enol (XI), m.p. 100—101°, was reduced with sodium borohydride under strict control to yield the alcohol (XIII), m.p. 150—151°. Normal borohydride reduction of (XI) afforded the diol (XIII, CH_2OH in place of CO_2Me).

[O-*methyl*-^{3}H]Loganin was administered to *Rhazya orientalis* shoots and after 1—3 days, the shoots were worked for alkaloids with the addition of synthetic (XIII) as carrier. The constant specific activity found for the rigorously purified alcohol (XIII) corresponded to 0·013% incorporation from loganin. This activity was unchanged by repetitive conversion of (XIII) into its crystalline picrate, recovery of the base and further recrystallisation. It is thereby proved that the alcohol (XIII) is a natural product present in *Rhazya orientalis* probably arising from a biosynthetic intermediate blocked by reduction (*e.g.* XII) or by hydration and reduction (*e.g.* VI). The alcohol (XIII) is named 16,17-dihydrosecodin-17-ol on the basis of secodine for the ester[12] (V). These results give further support to the suggested cleavage process for the biosynthesis of indole alkaloids in the *Aspidosperma* and *Iboga* families. The relationship of (XIII) to the alkaloid[13] (XV) and to the dimeric secamines[14] should be noted.[12]



When the foregoing experiment was repeated with shoots

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‡ Full spectroscopic and analytical data in agreement with the assigned structures were obtained for all new compounds.

of *Vinca rosea*, radioactive (XIII) was again isolated but of very low specific activity.

Further work based upon (XIII) and its derivatives is in progress both *in vivo* and *in vitro*

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