Interconversion of *Corynanthe*, *Aspidosperma*, and *Iboga* Alkaloids. A Model for Indole Alkaloid Biosynthesis

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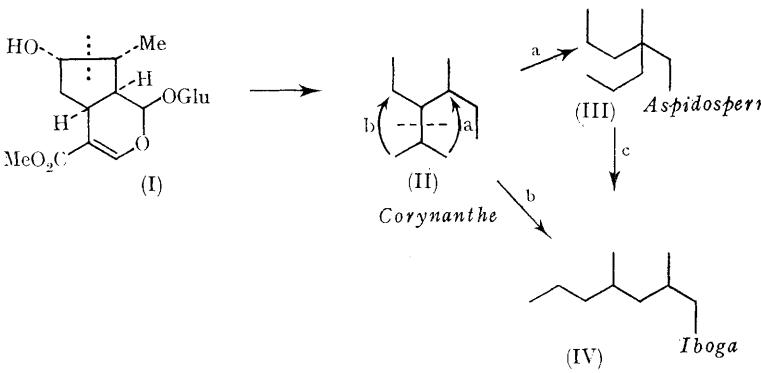
THE monoterpenoids geraniol[1] and loganin[2] (I) have recently been proved to be intermediates for the non-tryptophan derived segment of the three main classes of indole alkaloid, oxidative cleavage of loganin(I) providing a satisfactory rationale for genesis of the *Corynanthe* skeleton (II).[3] The nature of the rearrangements which give rise to the *Aspidosperma* (III) and *Iboga* (IV) patterns



(summarised in IIa, b) has received speculative comment[4,5] but experimental analogy for these processes is lacking. In particular the chemistry of 1,5-dicarbonyl systems was used to provide an ingenious rationale for the process (II) → (III) (path *a*) + (IV) (path *b*). We now illustrate a different, but equally attractive, mechanism of extended Mannich chemistry† which requires a specific oxidation level of the alkaloidal system. When this requirement is met, convenient and mild procedures for the conversion (II) → (III) (path *a*) → (IV) (path *c*) emerge.

For example we have found that ready isomerisation of the *Aspidosperma* alkaloid (−)-tabersonine (V)[6] to the *Iboga* alkaloid (±)-catharanthine‡ (VI) occurs in refluxing acetic acid solution. Since these conditions convert (+)-catharanthine into pseudocatharanthine (VII),[7] the yield of (±)-catharanthine (12%) isolated (after 16 hr.) may not be optimal, the remainder of the mixture consisting of pseudocatharanthine (28%) and unchanged tabersonine.

As a second example, the functionality and oxidation level of (+)-stemmadenine[8] (VIII) was chosen to illustrate the complete sequence (II) → (III) → (IV). After 34 hr. at reflux temperature in acetic acid, stemmadenine is converted into a separable mixture of (±)-tabersonine‡ (V) (12%), (±)-catharanthine‡ (VI) (9%), pseudocatharanthine (VII) (16%), and unchanged (VIII). In both the above examples the reactive racemic intermediate (IX) formed by the appropriate reverse Mannich reaction† provides an attractive rationale for the observed products and may be reached from stemmadenine by (i) isomerisation of the double bond to the 20,21-position to allow the bond cleavage implicit in the rearrangement and (ii) dehydration of the primary alcoholic function.

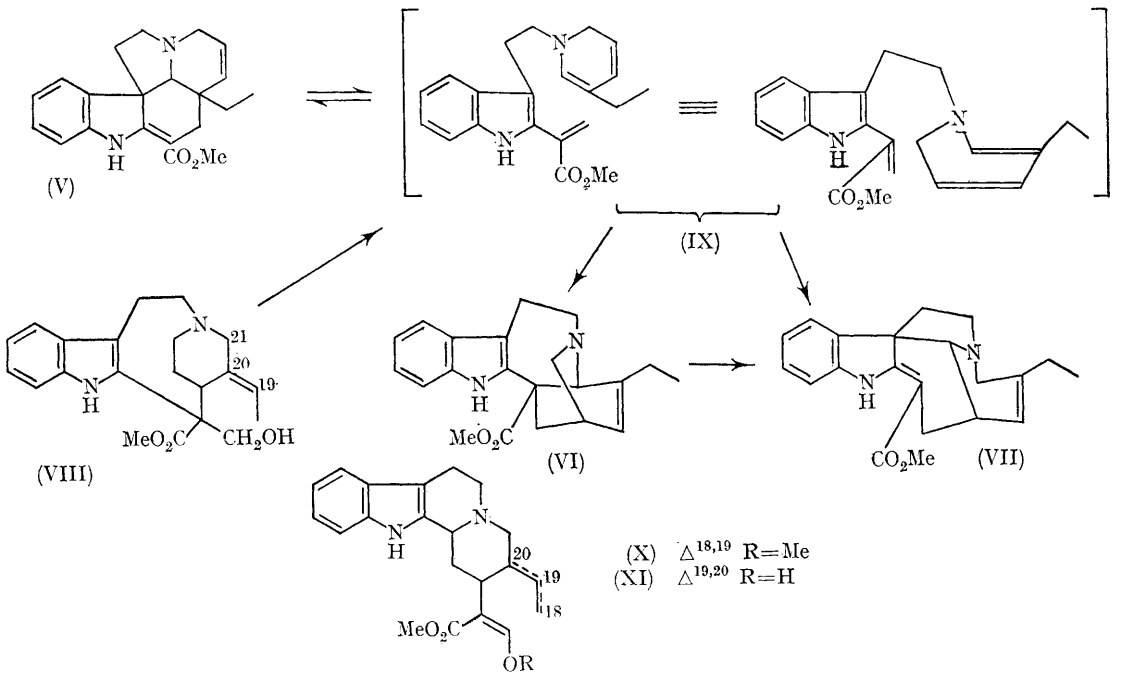
A survey of the functionality and oxidation level of the majority of indole alkaloids suggests that this theoretical model of biosynthesis imposes remarkably specific requirements for each type of precursor. Consequences of the theory include the following predictions:

(i) Stemmadenine is a key biosynthetic intermediate for *Aspidosperma* and *Iboga* alkaloids;

(ii) With the assumption that stemmadenine is

† As an alternative it should be noted that electrocyclic mechanisms for the formation and reactions of (IX) can be formulated. These proposals were first made at the Natural Products Symposium, Kingston, Jamaica, January 1968.

‡ Identical in every respect (except optical activity) with the natural alkaloid.



formed from corynantheine (X) and/or geissoschizine (XI) by mechanistically plausible pathways, the biosynthesis of the *Strychnos* family will also require stemmadenine as a specific intermediate;[9]

(iii) Tabersonine is a precursor for the more complex *Aspidosperma* alkaloids and for the *Iboga* series.

Preliminary evidence‡ from the sequential isolation and biological conversions of corynantheine aldehyde, (X; R = H), stemmadenine, tabersonine, and catharanthine in one species (*Vinca rosea*) support the sequence suggested by the above analogies *viz.* (II) → (III) → (IV). Moreover utilisation of these transformations in planning total stereospecific synthesis of complex indole alkaloids is receiving attention.

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‡ *Cf.* A. A. Qureshi and A. I. Scott, accompanying Communications.

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[8] A. Sandoval, F. Walls, J. N. Shoolery, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Tetrahedron Letters*, 1962, 409. These authors noted the correspondence of the structure of stemmadenine with the *skeleton* of a 1,5-dicarbonyl intermediate in Wenkert's hypothesis (ref. 5).

[9] *Cf.* the *in vitro* conversion of stemmadenine into condylocarpine (ref. 8) and the co-occurrence (F. Walls, O. Collera, and A. Sandoval, *Tetrahedron*, 1958, **2**, 173; D. Stauffacher, *Helv. Chim. Acta*, 1961, **44**, 2006; O. Collera, F. Walls, A. Sandoval, F. Garcia, J. Herran, and M. C. Perezamador, *Bol. Inst. Quim. Univ. nac. auton. Mexico*, 1962, **14**, 3) of stemmadenine, norfluorocurarine, and voacangine. For another viewpoint of *Strychnos* biogenesis see ref. 5.