7.3–7.9. This difference is presumably due to the fact that the nondelocalized O-protonated species is a contributor to the structure of **6**. The fact that the electronic spectrum of **5** is similar to that of **6** [λ_{max} (CF_3COOH) 375 (ϵ 66,700), 518 (15,200), 569 nm (25,700)], but bathochromically shifted by ~12 nm, is probably due to the same cause.

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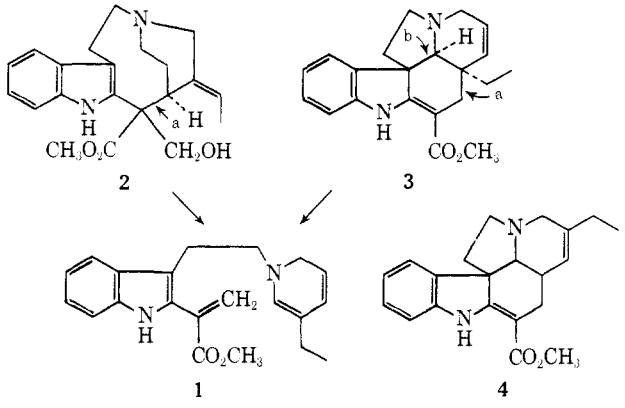
Regio- and Stereospecific Models for the Biosynthesis of the Indole Alkaloids. Prologue and Commentary

Sir:

In 1968 we proposed[1] a theoretical model for the enzymatic interconversions linking the *Corynanthe*, *Strychnos*, *Aspidosperma*, and *Iboga* alkaloids. Since the original disclosure of this hypothesis a large body of biochemical and structural evidence has accumulated[2] which supports in every detail the utilization of a dihydropyridine acrylic ester (**1**) as a highly reactive, pivotal biointermediate. This structure has since been named dehydrosecodine[3] and forms the nucleus of a new class of *chano* alkaloids corresponding formally



to the cleavage of the bonds marked a and b in stemmadenine (**2**) and tabersonine (**3**). The extended Mannich chemistry implicit in the formation and reactions of **1** not only bridges the major structural types of indole alkaloid but has also been employed in an elegant synthesis of *Aspidosperma* alkaloids.[4]

However, a discordant note in the proper and logical development of this field was sounded in 1969 by Smith, *et al.*,[5] who reported their inability to generate **1** from either **2** or **3** in hot acetic acid solution according to the general directions outlined[1b] in our preliminary note. In spite of extensive private communication in which the critical factors necessary for the success of these capricious but nevertheless authentic conversions were detailed to the best of our ability, the Anglo-French group elected to question the validity of our experiments. Thus there has arisen in the secondary literature[6] an erroneous impression that these transformations, which are of vital importance for the development of mechanistic models for the biosynthesis of indole alkaloids, cannot be effected. Due to the scarcity of the substrates **2** and **3** it has, until recently, been impossible for us to comment further except to note[7] that high external temperatures were efficacious. It should probably be pointed out that the manipulation of microgram quantities in biomimetic experiments is an art which, in our experience, has oft-times required *several hundred trials before declaring a negative result.*

The situation has now been resolved as a result of a series of expeditions to the tropical jungle in the state of Veracruz, Mexico, whereby a good source (*Stemmadenia Donnell-Smithii*) of stemmadenine (**2**) has become available after a 3-year interim. In the accompanying three communications we report on the complete vindication and extension of our original observations together with suggestions for the lack of corroboration elsewhere.[5,8]

Finally we are compelled to comment on what can only be described as an unfortunate breach of both the letter and spirit of scientific inquiry on the part of Smith, *et al.* For example Smith, *et al.*, state[5,8] that the reference compound used in all of their work to assay the extent of the conversions **2** or **3** → **1** is an amorphous levorotatory ($[\alpha]_D$ −60°) preparation to which they allude as pseudocatharanthine (**4**). In our hands (and in agreement with previous literature[9]) **4** is a crystalline racemic base ($[\alpha]_{300-600\ nm}$ 0°) and all of the products resulting from **1** are of course optically inactive. As will be seen from the accompanying communications, knowledge of the optical purity of the various preparations is a vital probe for the mechanisms in operation. Indeed, one of the most severe criticisms of our earlier work by Smith, *et al.*, concerned interconversion experiments with "pseudocatharanthine" ($[\alpha]_D$ −60°) to give[5] "catharanthine [(−) or (±)]. It is obvious from these statements that Smith, *et al.*, were utilizing mixtures of uncertain optical purity, thus formally vitiating many conclusions that can be drawn about their work. We would submit that in spite of the lack of explicit detail (occasioned by the then current scarcity of **2** and **3**) contained in our preliminary communication[1b] progress in this area of bioorganic chemistry has been unnecessarily hindered by the incontinent publication of these negative results.

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