Laboratory Model for the Biosynthesis of Vallesamine, Apparicine, and Related Alkaloids

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Summary The alkaloid vallesamine has been prepared by partial synthesis from stemmadenine using a modified Polonovsky reaction in a sequence which provides a biogenetic model for this class of alkaloid.

AN interesting series of indole alkaloids which lacks one of the original carbon atoms (C-2) of tryptophan[1] exemplified by vallesamine (**9**) and apparicine (**4**) has recently been the subject of experimental[2,3] and theoretical[4,5] study. The intriguing suggestion by Potier and Janot[4] that such alkaloids, together with the uleine and ellipticine families, might be formed by intervention of the biochemical fragmentation of the *N*-oxides (**2**) or (**3**) merits particular attention in view of the *in vitro* chemistry of tryptamine *N*-oxides.[6]

The biosynthetic studies of Kutney,[2] however, showed clearly that in the bioconversion of secodine (**5**) into

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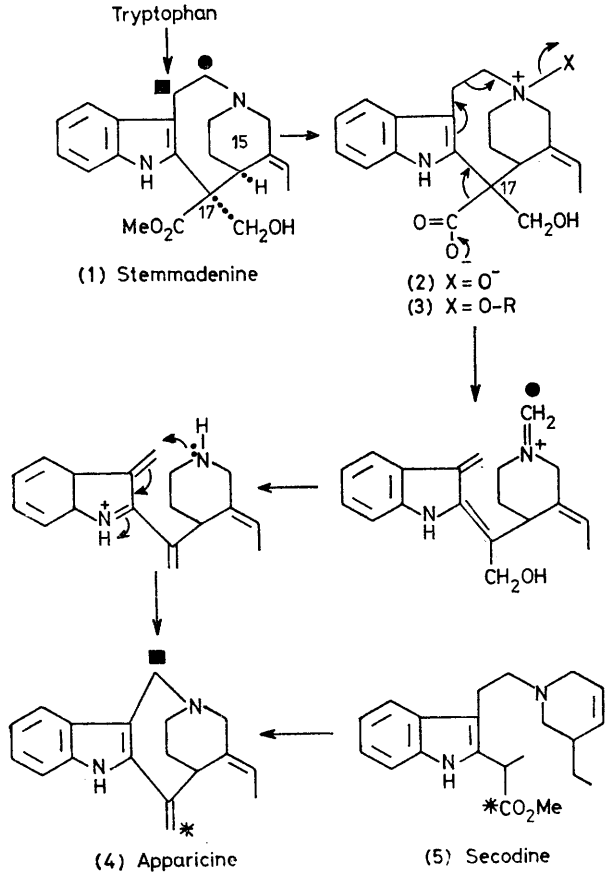
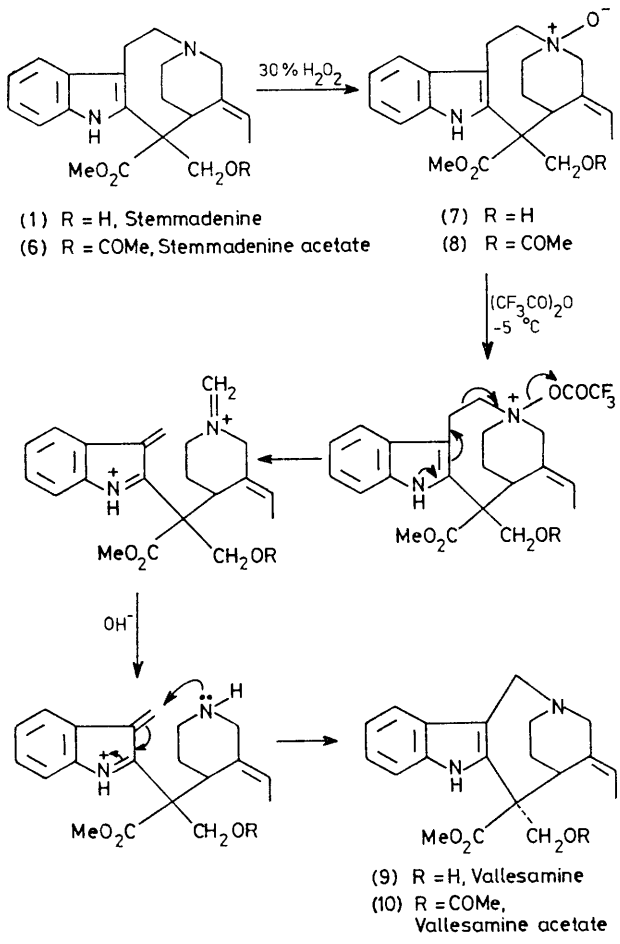
apparicine (**4**) no loss of carbon (*) of the methoxycarbonyl group at C-17 occurs, requiring modification of the earlier mechanism[4,5] (Scheme 1). At the same time, stemmadenine (**1**) and tryptophan were incorporated into apparicine with



SCHEME 1

retention of C-3 of tryptophan. However, the inherent reactivity of *N*-oxide systems does not require synchronous participation of either decarboxylation or deformylation processes at C-17 and this point is now illustrated in a simple transformation of stemmadenine (**1**) and its acetate (**6**) to the prototype of the 'nor' alkaloids, vallesamine (**9**) and its acetate (**10**), which is also a natural product.

Treatment of (**1**) and (**6**) with 30% H_2O_2 furnished the corresponding *N*-oxides (**7**) and (**8**) in high yield. Decomposition of (**7**) and (**8**) in trifluoracetic anhydride (−5 °C) followed by mild hydrolysis (NaOH) and acidification gave vallesamine (**9**) and vallesamine acetate (**10**) in 25 and 12% yields, respectively. The structures of these materials were confirmed by m.p., n.m.r., t.l.c., high resolution mass, i.r., and u.v. spectral comparison with the authentic alkaloids. Furthermore, the c.d. spectra for natural and synthetic (**9**) were identical showing that the stereochemistry at C-15 and C-17 corresponds in stemmadenine and apparicine. A



SCHEME 2

mechanism for this transformation is shown in Scheme 2, which involves the operation of a modified Polonovsky reaction on the trifluoroacetate of stemmadenine *N*-oxide (**7**), the liberation of formaldehyde during workup, and the reclosure of the system to vallesamine (**9**). We suggest that the biochemical implications of this work are that (a) *N*-oxides may be the true precursors of the 'nor' series, (b) several of the 'nor' alkaloids may be 'natural artefacts', and (c) the simple modification (Scheme 2) of Potier's hypothesis,[4] in which decarboxylation is not required in the fragmentation reaction, now accommodates all the tracer experiments. The intervention of secodine (**5**) in the biochemical pathway still presents a mechanistic problem.[2]

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