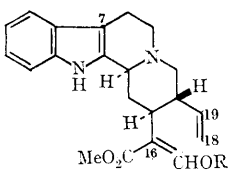
Biogenetic-type Synthesis of *Iboga* Alkaloids: (±)-Catharanthine

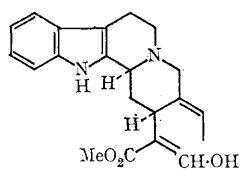
By A. A. QURESHI and A. I. SCOTT*

(*The Chemical Laboratory, University of Sussex, Brighton* BN1 9QJ)

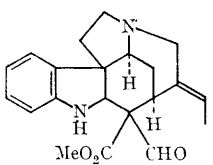
THE possible role of members of the *Corynanthe* family as intermediates in the biosynthesis of *Aspidosperma* and *Iboga* alkaloids has been invoked[1] in a scheme involving as a first step one electron oxidative coupling between C-7 and C-16 in (I). Several alternative processes can be considered where either corynantheine aldehyde (I) or geissoschizine (II) can readily serve as



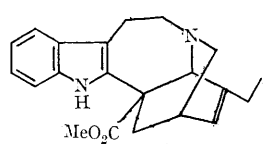
(I) R=H
(Ia) R=Me
(Ib) R=H ($\Delta^{18,19}$ reduced)



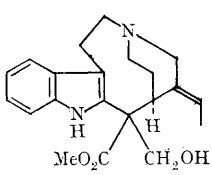
(II)



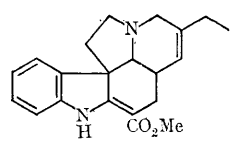
(III)



(IV)



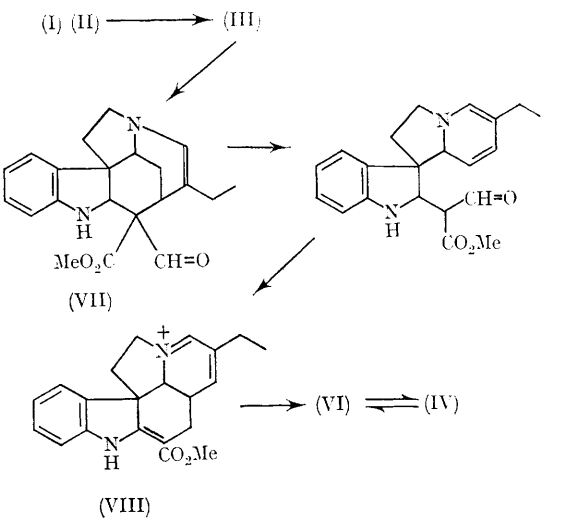
(V)



(VI)

progenitors of the *Strychnos* skeleton [exemplified by (III)] and thence the *Iboga* alkaloids [*e.g.* catharanthine (IV)] and the *Aspidosperma* series *via* the *Corynanthe-Strychnos* "hybrid" stemmadenine[2] (V). We now illustrate an *in vitro* relationship between the *Corynanthe* series and the *Iboga* alkaloids by a direct conversion of the aldehydes (I) and (II) into (±)-catharanthine (IV). When a solution of (I) or (II) in glacial acetic acid is refluxed under nitrogen for 72 hours, t.l.c. and spectroscopic analysis of the reaction mixture indicates the presence of pseudocatharanthine[3] (VI) (15%) and catharanthine (5%). Under these conditions (VI) has been found to be in equilibrium with (IV) so that the conversion of (I) and (II) into catharanthine is of considerable synthetic utility. The synthetic racemic catharanthine isolated by preparative t.l.c. had solution and mass spectral characteristics identical with those of the natural alkaloid.

Several mechanistic variants for this reaction can be suggested, but the observation that under



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certain conditions the isolated pseudocatharanthine (VI) retains some optical activity is indicative of the process outlined above. The suggested intermediates[4] include the *Strychnos* prototype[1] (III) whose double-bond isomer (VII) can undergo reverse and forward Mannich reactions and dehydration to generate (VIII). The required reduction of this penultimate immonium species has ample precedent in the reductive disproportionation of catharanthine (IV) in refluxing acetic acid to a mixture of pseudocatharanthine (VI) and its dihydro-derivative.[3]

The essential requirements for this reaction include both the β-dicarbonyl system and the correct oxidation level of the two-carbon side chain, since corynantheine (Ia) and the dihydro-aldehyde (Ib) fail to rearrange under these conditions.

The relevance of this simple procedure, which constitutes the total synthesis of (±)-catharanthine,[5] to the biosynthesis of *Vinca rosea* alkaloids is under experimental test. In this connection it is interesting to note that corynantheine and its relatives belong to the same stereochemical series as stemmadenine,[2] strychnine, and catharanthine, whilst tabersonine and vindoline, representative of the *Aspidosperma* alkaloids of *V. rosea*, belong to the antipodal series, requiring a non-asymmetric intermediate as suggested in the accompanying communications.

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[1] E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, 1965, **87**, 1580.
[2] A. A. Qureshi and A. I. Scott, accompanying Communications.
[3] M. Gorman, N. Neuss and N. J. Cone, *J. Amer. Chem. Soc.*, 1965, **87**, 93.
[4] Precedent for this type of rearrangement can be found, for example, in the work of J. Harley-Mason and W. R. Waterfield, *Tetrahedron*, 1963, **19**, 65; and A. J. Gaskell and J. A. Joule, *ibid.*, 1967, **23**, 4053.
[5] For the total synthesis of corynantheine and the aldehyde (I), see E. E. van Tamelen and I. G. Wright, *Tetrahedron Letters*, 1964, 295.