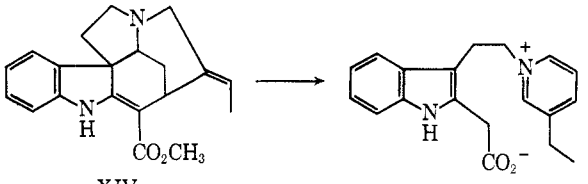
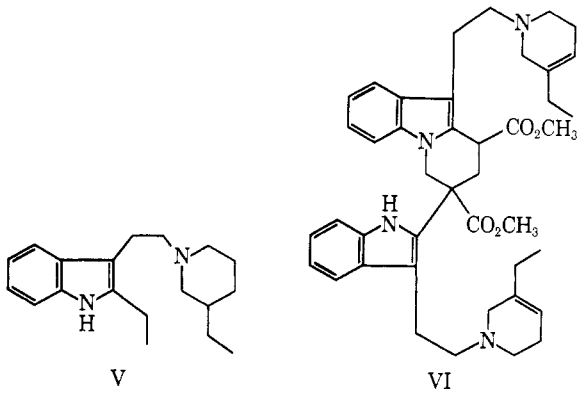
arrangement and hydrogen transfer from the dihydropyridine to the acrylic ester function yielding the hemiketal X with loss of 3-ethylpyridine as indicated. Elimination of methanol and further rearrangement then give the carbazole VIII. In support of the latter process 1-methyl-2-methoxycarbazole (IX) could be detected and characterized as a minor product of the reaction.



XIV XIII



V VI

More direct evidence for the formation of I was obtained by the capture in 50% yield of the racemic salt XI when catharanthine was heated in methanol at 140° for 2 hr. The pyridinium salt had λ_{max} (EtOH) 219, 269, 283 (sh), 291 nm; $[\alpha]_{300-600}$ 0° (EtOH); nmr[8] (D_2O) τ 1.7–3.3, 8 H, m (Ar–H); 5.30 and 6.66, 4 H, 2t ($-CH_2CH_2-$); 6.12, 1 H, q, J = 7.5 Hz ($CH(CH_3)CO_2CH_3$); 6.33, 3 H, s (CO_2CH_3); 7.55, 2 H, q, J = 7.5 Hz (CH_2CH_3); 8.62, 3 H, d, J = 7.5 Hz ($CH(CH_3)CO_2CH_3$); 9.18, 3 H, t, J = 7.5 Hz (CH_2CH_3).

In contrast to the intramolecular formation of the carbazole from the dihydropyridineacrylic ester I in the aprotic solvent xylene, the availability of solvent protons in the latter case appears to divert the collapse of this intermediate in methanol *via* an ionic mechanism to the pyridinium salt XI.[9] This salt is stable in methanol at 175° but on pyrolysis at this temperature affords the carbazole VIII, presumably *via* elimination of ethylpyridine and cyclization of the resulting vinyl ester XII. The generation of I in methanol solution could also be rationalized by an ionic mechanism[4] which recalls the formation of the betaine XIII from akuammicine (XIV).[10] Since the species I and XI could be reached *in vivo* from stemmadenine,[4] tabersonine (II), and catharanthine (III), it will be of interest to test these three alkaloids as biochemical precursors for V and VI and also to consider the system I $\rightleftarrows$ XI as a labile but isolable biosynthetic intermediate for the *Aspidosperma* and *Iboga* alkaloids. These experiments also provide a mechanistic rationale for the previous *in vitro* transformations[4] which have been found to be particularly sensitive to the temperature employed in the reaction[7] and where merging electrocyclic and ionic mechanisms may be operating.

(9) When the reaction is carried out in CH_3OD solution, the nmr spectrum of the salt no longer shows a signal at τ 6.12 ($CD(CH_3)CO_2CH_3$) and the doublet at τ 8.62 ($CH(CH_3)CO_2CH_3$) is replaced by a singlet (3 H). These observations are in accord with the mechanism I → XI.

(10) P. N. Edwards and G. F. Smith, *J. Chem. Soc.*, 1458 (1961).

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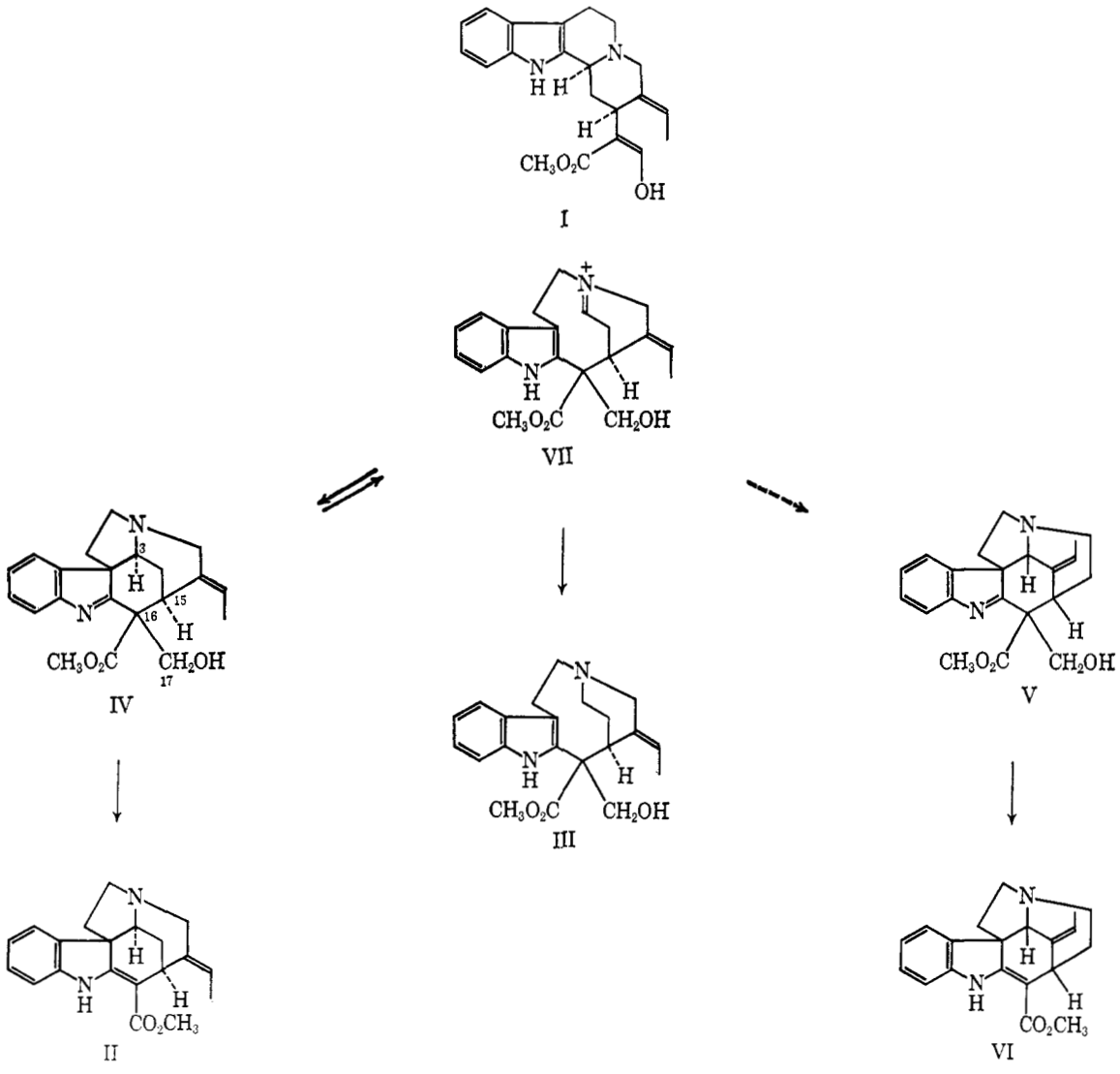
Biogenesis of *Strychnos*, *Aspidosperma*, and *Iboga* Alkaloids. The Structure and Reactions of Preakuammicine

Sir:

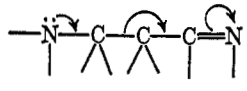
In the course of biosynthetic and biogenetic investigation of the indole alkaloid family, models have been devised[1-3] to simulate the *Corynanthe* → *Strychnos* → *Aspidosperma* → *Iboga* transformations. However the information revealed by these and related feeding experiments[4,5] still leaves unanswered both the nature of the intermediates between geissoschizine (I) (*Corynanthe*), akuammicine (II) (*Strychnos*), and stemmadenine (III) ("*Corynanthe–Strychnos*") and the mechanisms connecting them. It has been suggested[6] that a key member of this family situated at the main branching point of the pathway would be a prototype (IV) of the *Strychnos* alkaloids *retaining all ten of the original geraniol* carbon atoms which could suffer irreversible loss of a single carbon function to the "C_9" alkaloids, *e.g.*, akuammicine (II) and strychnine, or by a series of rearrangements generate the *Aspidosperma* and *Iboga* alkaloids. Such a model was demonstrated in the laboratory and detailed suggestions made implicating stemmadenine (III) as a key intermediate for this latter process.[3] We now describe the isolation and properties of a new alkaloid, *preakuammicine*, for which the long sought structure IV is proposed and which, from its position in the *Vinca* sequence, meets at least one of the criteria as an intermediate. Furthermore the chemistry of IV provides *in vitro* analogy for its presumptive role as a true biointermediate.

Careful separation by repeated tlc of the alkaloidal fraction of 42–48-hr-old seedlings of *Vinca rosea* afforded material with homogeneous tlc behavior (R_f 0.41 in 20% $CHCl_3$–MeOH; silica gel G). The amorphous alkaloid preakuammicine, $C_{21}H_{24}N_2O_3$ (IV), obtained in this way was characterized as an indolenine: λ_{max}^{EtOH} 262 nm (ϵ 6000), changing on storage at 20° to λ_{max} 292, 325 nm (chromophore II); nmr ($CDCl_3$) τ 2.2–3.0 m (Ar–H); 4.7 q ($CH_3CH=$); 6.05 s (CH_2OH); 6.15 s (CO_2CH_3); 8.45 d ($CH_3CH=$); mass spectrum (rela-

(1) A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 945 (1968).
(2) A. A. Qureshi and A. I. Scott, *ibid.*, 947 (1968).
(3) A. I. Scott, *Chimia*, **22**, 310 (1968).
(4) A. I. Scott, 2nd Symposium on Natural Products, Mona, Jamaica, Jan 1968.
(5) A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 948 (1968).
(6) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.* **87**, 1580 (1965); *cf.* A. R. Battersby, *Pure Appl. Chem.*, **14**, 117 (1967); *Chimia*, **22**, 313 (1968).



tive intensity) M^+ 352.1757 (2) (calcd for $C_{21}H_{24}N_2O_3$: 352.1787), 322.1683 (100) (calcd for $C_{20}H_{22}N_2O_2$: 322.1682), 263.1560 (25) (calcd for $C_{18}H_{19}N_2$: 263.1549). The mass and infrared spectra of IV were very similar to those reported for the isomeric precondylocarpine[7] (V). In particular the mass spectra of both IV and V show base peaks corresponding to the loss of the C_{17} carbon as formaldehyde to give the $C_{20}H_{22}N_2O_2^+$ species associated with akuammicine (II) and condylocarpine (VI). Treatment of preakuammicine with base (NaOMe in MeOH, 60°, 15 min) afforded an almost quantitative yield of akuammicine (II) identified by uv, mass spectral, tlc, and ord comparison. This deformylation reaction which finds analogy in the conversion of V to condylocarpine (VI)[7] thus secures the stereochemistry of IV at positions 3 and 15 as well as simulating the "$C_{10} \rightarrow C_9$" stage of the biogenesis of the *Strychnos* alkaloids. In a second model experiment sodium borohydride reduction of IV afforded a separable mixture of akuammicine (II) and stemmadenine (III). The formation of the latter authenticated intermediate of *Aspidosperma* biosynthesis[3] can be rationalized by the well-known[8] collapse of the

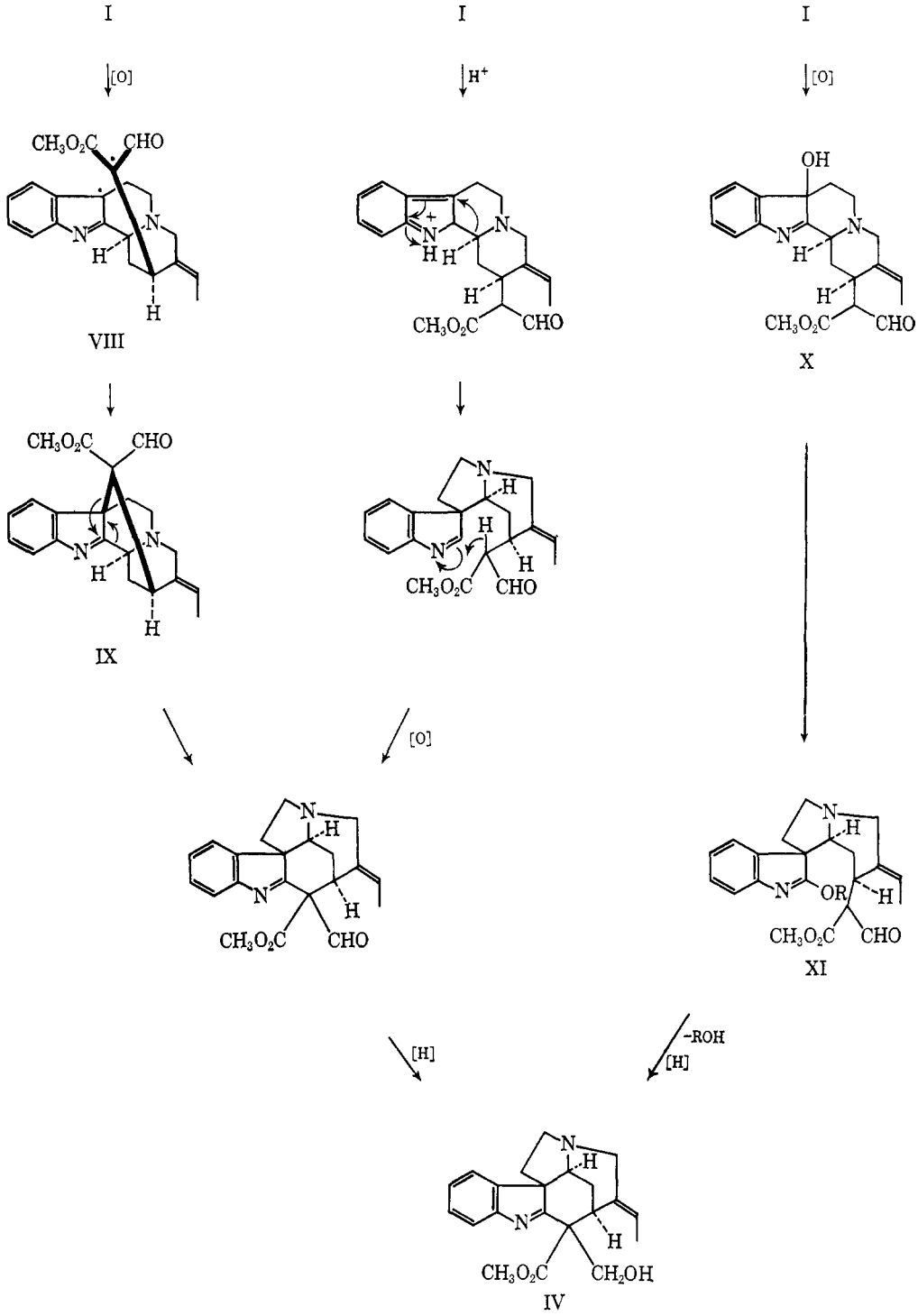


system to generate the secoimmonium salt VII. Hydride reduction then affords III which contains the complete carbon skeleton of IV and two of the original stereochemical centers. This experiment provides a satisfactory analogy for the biochemical reduction of IV to III and also for the biochemical interconversion of IV and V *via* VII, thus leading to a predicted connection between the *Strychnos* and *Condylocarpine* series. Apart from allocation of the stereochemistry at C_{16} (which is also unknown in stemmadenine), structure IV follows for preakuammicine. The lability of solutions of IV indicates that this alkaloid has so far defied isolation because of its ready transformation to akuammicine at extremes of pH. From its reactivity and sequence position there seems little doubt that IV and/or the corresponding aldehyde (IV, CH_2OH = CHO)[9]

(7) A. Walser and C. Djerassi, *Helv. Chim. Acta*, **48**, 391 (1965). We thank Dr. Carl Djerassi for kindly providing us with detailed spectral data for V.

(8) For a review with many examples see B. Gilbert, *Alkaloids*, **8**, 335 (1965).

(9) Preliminary experiments indicate that this aldehyde is also present in immature *V. rosea* and that IV occurs in the mature plant.



will play a key role in the intermediary metabolism of *V. rosea* and other species.

Finally the mechanism of biogenesis of IV from geissoschizine (I) must be considered. Wenkert[6] has suggested that coupling of the radical VIII derived from geissoschizine (I) leads to the well-known *akuamma* skeleton IX, rearrangement of IX to IV completing the process. We have previously provided analogy[2] for a protonation–rearrangement mechanism which with subsequent dehydrogenation connects I and IV. We wish to suggest a third possibility which on the basis of recent model experiments[10] seems to offer an equally attractive rationale and which involves initial oxidation of I to the β-hydroxyindolenine X followed by formation of the oxindole XI (R = H) which as the imino ether XI (R = alkyl or phosphate) is well placed to undergo condensation[11] to IV.

Experimental test of these possibilities is in progress.

Acknowledgment. Generous support of this work by National Institutes of Health Grant CA-11095 is acknowledged. We thank Dr. W. J. McMurray for the computerized high-resolution mass spectral data.

(10) Unpublished work by Dr. C. R. Bennett.

(11) *Cf.* T. Oishi, M. Nagai, and Y. Ban, *Tetrahedron Letters*, 491 (1968).

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