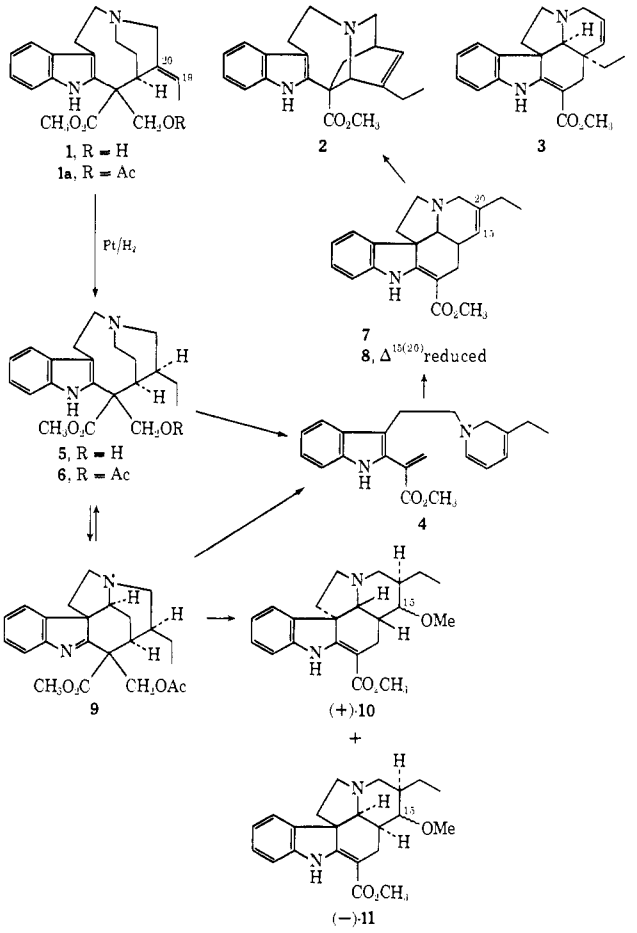
## Regio- and Stereospecific Models for the Biosynthesis of the Indole Alkaloids. The *Corynanthe/Strychnos–Iboga* Relationship

*Sir:*

In a previous communication[1] we reported the conversion of the *Corynanthe/Strychnos* alkaloid stemmadenine (**1**) to a mixture of (±)-catharanthine (**2**) (*Iboga*) and (±)-tabersonine (**3**) (*Aspidosperma*) and in rationalizing the mechanism invoked intermediacy of the acrylic ester, dehydrosecodine (**4**). This experiment, performed on milligram quantities of a rare alkaloid, was apparently crucially sensitive[2] to external temperature and/or surface effects but nevertheless provided a far-reaching concept for subsequent biochemical experiments[3] and total[4] and partial[2,5] synthesis. Moreover, the occurrence of a new class of alkaloids based on the structure **4** has since been demonstrated.[6] While recognizing the significance of this experiment Smith, *et al.*,[7] have reported that the reaction of stemmadenine in acetic acid produces only the *O*-acetate **1a**. With a fresh source of **1** in hand we have now reexamined the essential factors for the success of our earlier experiment. These appear to include (a) concentration, (b) temperature, (c) the presence of silica or alundum boiling grains (0.2–1.5 mm mesh), (d) oxidative and reductive processes mediated by hydrogen transfer to and from immonium and dihydropyridine species,[8] and (e) aerial oxidation.

A control experiment designed to take account of these factors (including total evaporation of solvent which had been observed in several 1–2-ml runs under the original conditions) consisted of heating 19,20-dihydrostemmadenine acetate[9] (**6**) on a silica surface[10] at 150° for 45 min in air. Separation of the reaction mixture using tlc systems previously reported[11] afforded (±)-pseudocatharanthine (**7**) (1%) and its dihydro derivative **8** (0.5%). No tabersonine (**3**) could be detected under these conditions. In order to assess the effect of oxidation to the pentacyclic *Strychnos* framework, dihydropreakuammicine acetate (**9**) (a known[5] autoxidation product of **6**) was prepared by regioselective oxidation ($Pt/O_2$–EtOAc)[12] of the acetate **6**. Thermolysis of **9** (silica gel, 150°, 20 min) gave (±)-pseudocatharanthine (**7**) in yields consistently higher (2–5%) than in the direct reaction of **6**.



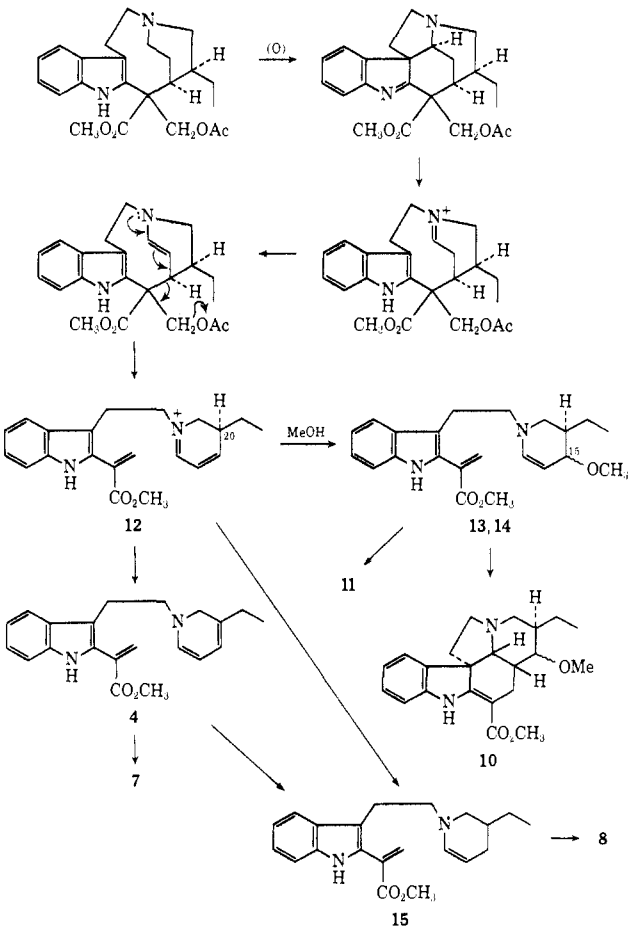

A remarkably facile entry to the pseudocatharanthine system was discovered when **9** was treated with methanol at 80° (15 min) or at room temperature for 4 hr. The products of this reaction were the dextrorotatory 15-methoxypseudocatharanthine (**10**) together with a levorotatory diastereomer **11** in the ratio 9:1. The formation of optically active rearrangement products (combined yield, 3.5%) under very mild conditions provides considerable insight into the mechanism and stereochemical control of the cyclization process. We consider that the immonium acrylic ester **12** (Scheme I) formed either by thermolysis or methanolysis of **9**, which still retains a center of chirality at $C_{20}$, is trapped as the addends **13** and **14** and that the $C_{15}$ and $C_{20}$ stereocenters then control cyclization to (+)-(**10**) and (−)-(**11**) which show typical[13] Cotton effects associated with the absolute stereochemistry depicted. The relative configurations at $C_{15}$ in **10** and **11** remain to be determined.

In the case of the thermal reaction we suggest that the chiral species **12** loses the $C_{20}$ proton to generate achiral dehydrosecodine A (**4**) which, without detectable conversion to the isomeric diene[14] associated with the *Aspidosperma* series, undergoes both ionic cycliza-

(1) A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 947 (1968).
(2) A. I. Scott and P. C. Cherry, *J. Amer. Chem. Soc.*, **91**, 5872 (1969).
(3) Reviews: A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970); J. P. Kutney, J. F. Beck, C. Ehret, G. Poulton, R. S. Sood, and N. D. Westcott, *Bioorg. Chem.*, **1**, 194 (1971).
(4) F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3492 (1970).
(5) A. I. Scott and C. C. Wei, unpublished work in this laboratory.
(6) G. D. Cordell, G. F. Smith, and G. N. Smith, *Chem. Commun.*, 189 (1970).
(7) R. T. Brown, J. S. Hill, G. F. Smith, K. S. J. Stapleford, J. Poisson, M. Muquet, and N. Kunesch, *ibid.*, 1475 (1969).
(8) *E.g.*, M. Gorman, N. Neuss, and N. J. Cone, *J. Amer. Chem. Soc.*, **87**, 93 (1965).
(9) Prepared by catalytic ($Pt/H_2$) reduction of stemmadenine and acetylation ($Ac_2O$–pyridine) of 19,20-dihydrostemmadenine (**5**). Compound 6 exhibited the expected nmr spectrum with signals ($CDCl_3$) at δ 1.04 (t, 3 H, $CH_2CH_3$), 2.0 (s, 3 H, $OC(=O)CH_3$), 3.96 (s, 3 H, $C(=O)OCH_3$), 4.84 (s, 2 H, $CH_2O$), 7.2–7.8 (m, 4 H, aromatics), 9.80 (s, 1 H, >NH); mass spectrum *m/e* 398 (30%), 339 (75%), 268 (60%), 124 (100%).
(10) For convenience silica gel plates (G-254) were used both analytically and preparatively, and the substrate applied in methanol solution. The conversion 6 → 7 was confirmed independently (tlc analysis) by Dr. M. Uskokovic (Hoffmann-La Roche, Inc.) whom we thank for this experiment.
(11) Details of the tlc systems developed by Dr. A. A. Qureshi in these laboratories are given by R. T. Brown, J. S. Hill, G. F. Smith, and K. S. J. Stapleford, *Tetrahedron*, **27**, 5217 (1971).
(12) D. Schumann and H. Schmid, *Helv. Chim. Acta*, **66**, 1966 (1963).
(13) W. Klyne, R. J. Swan, B. W. Bycroft, D. Schumann, and H. Schmid, *ibid.*, **48**, 443 (1965).
(14) A. I. Scott and C C. Wei, *J. Amer. Chem. Soc.*, **94**, 8264 (1972).

tion to pseudocatharanthine (**7**) and hydrogen transfer to **12**. The intermediate **15** from the latter reaction then cyclizes to dihydropseudocatharanthine (**8**).[15]

**Scheme I**



We would like to suggest that these experiments demonstrate not only the separation of an "*Iboga* synthetase" model from earlier, less specific reaction conditions but augur well for the synthesis of indole alkaloids based on the emerging chemistry of dihydropyridine acrylic esters, since in spite of the present low yields, transformations involving stereocontrol from one family to another are now possible.[16]

**Acknowledgment.** This work was supported by grants from the National Institutes of Health and the National Science Foundation.

(15) It is interesting to note that the (±)-dihydropseudocatharanthine (**8**) from this reaction is capable of formation in optically active form, but in conformity with earlier experience the product can easily racemize. The milder conditions (MeOH; 25–80°) used in the formation of **10** and **11**, however, allow considerable retention (70–80%) of optical purity.

(16) In this and the subsequent two communications all of the reaction products were identified by spectroscopic and tlc comparison with authentic samples of the natural alkaloids, with the exception of compounds **10** and **11** which were assigned these structures on the basis of mass spectral, uv, and ORD data.[5] Thus, **10** and **11** had $\lambda_{max}^{MeOH}$ 226, 298, and 328 nm; *m/e* 368 ($M^+$, 40%), 337 ($M^+ - OCH_3$, 19%), and 154 (100%); **10** showed $(\Phi)_{345\ nm}$ +25,000 and **11** had $(\Phi)_{345\ nm}$ −28,000.

**A. I. Scott,* C. C. Wei**

*Sterling Chemistry Laboratory, Yale University*
*New Haven, Connecticut 06520*

*Received August 3, 1972*

## Regio- and Stereospecific Models for the Biosynthesis of the Indole Alkaloids. The *Corynanthe–Aspidosperma* Relationship

*Sir:*

In the previous communication[1] we described the regio- and stereospecific conversion of stemmadenine acetate (**1**) to the *Iboga* alkaloids *via* dehydrosecodine A (**2**). In order to define the mechanism and conditions whereby a mixture of *Aspidosperma* and *Iboga* types were formed in acetic acid at high temperatures[2] we have developed a technique for the specific generation of the isomeric intermediate *chano* structure, dehydrosecodine B (**3**) in the expectation that the cyclization reaction of **3** would lead to a preponderance of the *Aspidosperma* type of alkaloid exemplified by vincadifformine (**4**) and tabersonine (**5**). The experimental design was guided by the reactions which have already been noted[2] in acetic acid at high temperature, *viz.* acetylation and disproportionative oxidation and reduction.[3] In the event, the reaction proceeded with complete regio- and stereospecific control (see Scheme I).

Thus the simple isomerization mechanism (Scheme II) suggested earlier for the conversion of stemmadenine to both *Iboga* and *Aspidosperma* alkaloids can be separated from the accompanying *redox* mechanism as follows. Stemmadenine *O*-acetate (**1**) (as the hydrochloride salt) was heated at 150° on a silica gel surface[1] for 25 min. Preparative tlc of the reaction mixture afforded some unchanged starting material together with a small but reproducible yield (0.15–0.2%) of (±)-vincadifformine (**4**) identical[4] with the natural, racemic alkaloid. No trace of tabersonine (**5**) could be detected in this reaction. We suggest that direct isomerization of **1** to the isostemmadenine acetate (**6**) takes place. This is followed by the reverse Mannich reaction shown in Scheme II which generates dehydrosecodine B (**3**). The latter in turn is reduced by hydride to secodine B (**7**) whereupon cyclization of this tetrahydropyridine acrylic ester completes the regio- and stereospecific production of (±)-vincadifformine from a *Corynanthe* alkaloid.

An alternative method of generating the dehydrosecodine B system embodies the observations that stemmadenine acetate (**1**) is quite sensitive to aerial oxidation in acetic acid solution and that catalytic reduction of **1** ($Pt/H_2$) gave a 75% yield of tetrahydrosecodine[4] (**8**). This type of reaction which proceeded without deliberate control in earlier experiments[2] can be sequentially studied by platinum-catalyzed oxidation of **1** regiospecifically to precondylocarpine acetate[5]

(1) A. I. Scott and C. C. Wei, *J. Amer. Chem. Soc.*, **94**, 8263 (1972).
(2) A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 947 (1968).
(3) M. Gorman, N. Neuss, and N. J. Cone, *J. Amer. Chem. Soc.*, **87**, 93 (1965).
(4) (±)-Vincadifformine and (±)-tabersonine were identified by procedures referred to in ref 1, footnotes 11 and 16, and their racemic nature confirmed $[\alpha]_{300-600\ nm}$ 0°. Tetrahydrosecodine (**8**) was obtained as the racemic version $[\alpha]_{300-600\ nm}$ 0° with tlc and spectroscopic data identical with natural material (G. A. Cordell, G. F. Smith, and G. N. Smith, *Chem. Commun.*, 189 (1970)): mass spectrum *m/e* 342 (10%), 126 (100%); $\lambda_{max}^{MeOH}$ 226, 278 (sh), 286, 292 nm; nmr δ($CDCl_3$) 0.9 (t, 3 H, $CH_2CH_3$), 1.55 (d, 3 H, $CH_3CHCO_2Me$), 3.64 (s, 3 H, $COOCH_3$), 4.1 (q, 1 H, $CH_3CHCO_2CH_3$), 7.0–7.5 (4 H, m, Ar H), 8.4 (s, 1 H, >NH).
(5) Precondylocarpine acetate: $\lambda_{max}^{MeOH}$ 221, 273, 282 (sh), 291 (sh) nm; *m/e* 394 (50%), 335 (98%), 321 (100%), 278 (88%), 275 (90%); nmr δ ($CDCl_3$) 1.55 (d, 3 H, C=$CHCH_3$), 3.60 (s, 3 H, $COOCH_3$), 5.2 (q, 1 H, =$CHCH_3$), 6.8–7.2 (m, 4 H, Ar H).