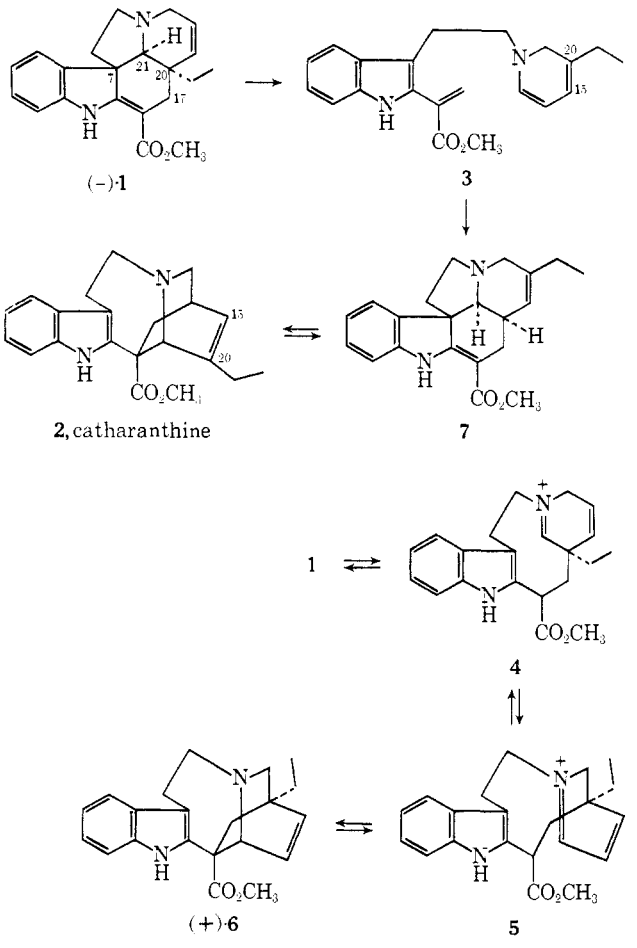
Regio- and Stereospecific Models for the Biosynthesis of the Indole Alkaloids. The *Aspidosperma–Iboga* Relationship

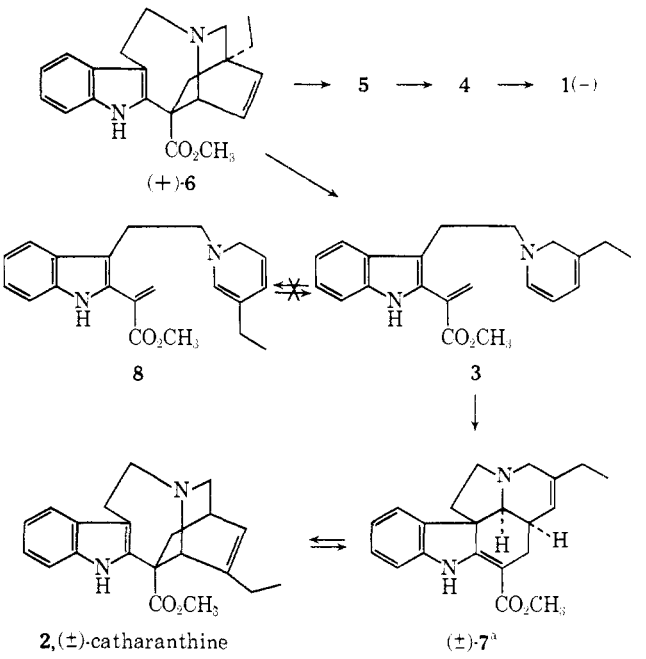
Sir:

In 1968 we reported on the *in vivo*[1] and *in vitro*[2] transformations of the *Aspidosperma* alkaloid tabersonine (**1**) to the *Iboga* alkaloid catharanthine (**2**) and proposed an intermediate **3** in this reaction which has since been found in a variety of stabilized versions.[3] In 1969[4] Smith, *et al.*, reported that, in their view, this reaction, which involves rupture of both the 7–21 and 17–20 bonds of **1**, proceeds only as far as cleavage of the 7–21 bond. The resultant immonium species **4** then rearranges to **5** and cyclizes to allocatharanthine (**6**), an optically active isomer of catharanthine (**2**) and pseudocatharanthine (**7**), the latter two *Iboga* structures being interconvertible. We have emphasized for some time[5] that both ionic and thermal requirements must be met in carrying out the full transformation which by passing through **3** affords the racemic products described earlier. In order to reconfirm and simplify the experiment, the ionic and thermal components have been separated as follows.



(−)-Tabersonine (**1**) was heated in acetic acid for 15 hr (external bath temperature, 140°). The resultant mixture was separated and (+)-allocatharanthine[4] (**6**) (11%) isolated. A solution of **6** was applied to a silica gel tlc plate, the solvent removed, and the plate heated at 150° for 30 min. Elution and chromatography on $AgNO_3$-impregnated silica gel plates[6] afforded two major products. These were (±)-pseudocatharanthine (**7**) (4%) identical with authentic material[7] and *optically pure* (−)-tabersonine (**1**) (4%). The absence of any racemization of tabersonine indicates the operation of the pathway **6** → **5** → **4** → **1** (Scheme I). Thus, not only is the *Aspidosperma* framework

Scheme I



[a] The (−) form is illustrated.

stable toward direct electrocyclic reaction, but in confirmation of the complete specificity noted in the previous communication for the reaction of dehydrosecodines A and B, *only the racemic product* **7** of cyclization of dehydrosecodine A (**3**) is observed, there being no evidence for equilibration with the B isomer **8** which would have yielded (±)-tabersonine. The bioconversion of (−)-tabersonine (**1**) to catharanthine (**2**) in *Vinca rosea* has been demonstrated[1] but recent feeding experiments reveal that [Ar^{3}H]-labeled **2** does not serve as a precursor for the alkaloid coronaridine (15,20-dihydrocatharanthine) in this plant,[8] In order to explain this puzzling result we propose that dehydrosecodine A (as the immonium salt) can undergo 1,4 reduction to secodine A which then cyclizes to coronaridine[9] *without* involving catharanthine (**2**) as an intermediate.

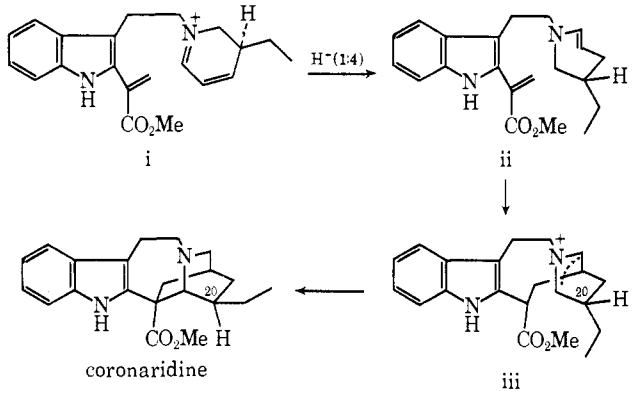
In summary, the reactions described in this and the foregoing communications support in every respect the

(1) A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 948 (1968). This experiment was independently confirmed by J. P. Kutney, C. Ehret, V. R. Nelson, and D. C. Wigfield, *J. Amer. Chem. Soc.*, **90**, 5929 (1968).
(2) A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 947 (1968).
(3) See, for example, G. A. Cordell, G. F. Smith, and G. N. Smith, *ibid.*, 189 (1970).
(4) R. T. Brown, J. S. Hill, G. F. Smith, K. S. J. Stapleford, J. Poisson, M. Muquet, and N. Kunesch, *ibid.*, 1475 (1969). Identical uv, nmr, chiroptical, and tlc data were obtained for our preparation of this compound.
(5) A. I. Scott and P. C. Cherry, *J. Amer. Chem. Soc.*, **91**, 5872 (1969).
(6) See A. I. Scott and C. C. Wei, *ibid.*, **94**, 8263 (1972), ref 11.
(7) M. Gorman, N. Neuss, and N. J. Cone, *ibid.*, **87**, 93 (1965).
(8) Unpublished experiments by Drs. J. G. Sweeney, P. B. Reichardt, and J. Michael.
(9) This process can be envisioned to occur by the mechanisms illustrated below. There is ample analogy for the inversion of the stereochemistry at C_{20} in iii *via* the appropriate enamine. Thus coronaridine and its 20-epimer are interconvertible in hot acetic acid. The implications of the process ii → iii in absolute stereochemical terms have very recently[10] assumed added significance in view of the revision of *Iboga*

stereospecific cyclization mechanism involving dehydrosecodine A and B for the *Iboga* and *Aspidosperma* alkaloids, respectively,[11] and further, their regiospecific elaboration from stemmadenine *via* suitably modified versions of the *prestrychnos* and *precondylocarpine* systems. Further biochemical and synthetic aspects of these fascinating rearrangements are now receiving intensive study.

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

alkaloid stereochemistry. These aspects will be discussed in our full paper.



(10) K. Bláha, Z. Koblicová, and J. Trojánek, *Tetrahedron Lett.*, 2763 (1972).

(11) The actual *biochemical* relationship could correspond to the *reverse* of the chemical reactivity by operation of the appropriate ionic mechanisms under enzyme control. Thus the processes involving species A (**3**) and B (**8**) as specific precursors for *Aspidosperma* and *Iboga* alkaloids *in vivo* remain to be defined.

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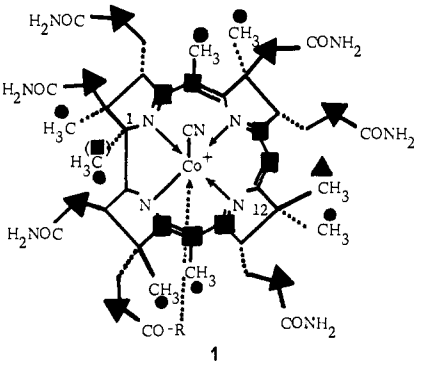
Biosynthesis of Corrinoids. Concerning the Origin of the Methyl Groups in Vitamin B_{12}

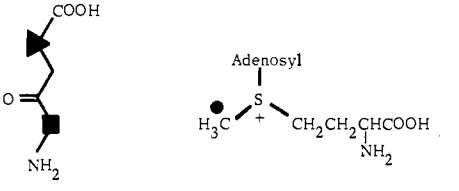
Sir:

As a result of the pioneering experiments of Shemin,[1] it has been established that the nucleus of vitamin B_{12} (**1**) is formed by the succinate–glycine pathway *via* δ-aminolevulinic acid (**2**, ALA) and thence by way of porphobilinogen (**3**, PBG) to the corrins, whose structures are reminiscent of uroporphyrinogen III (**4**, urogen III) in that the sequence of acetate and propionate functionality is "reversed" in ring D.[2] Of the eight methyl groups attached to the periphery of **1** it was suggested[3] that those at C-1 and C-12 stem from C-5 and C-2 of ALA, respectively, the latter by a well-documented[4] decarboxylation of acetate attached to the urogen system, while the derivation of the former (C-1) methyl group could be envisioned either as a reduction of a CH_2 bridge of urogen III[4,5] or as a result of direct cyclization of a linear tetrapyrrole,[2a] the six remaining methyl groups arising from methionine.[3] Support for these ideas came from Kuhn–Roth oxidation of corrinoids labeled with [5-^{14}C]- and [2,3-^{14}C]-ALA and [$^{14}CH_3$]methionine. As pointed out by Shemin[3] the yield of acetic acid from C-1 was low (10% of theoretical) and the severity of the problem of degradation of the vitamin has so far precluded rigorous definition of the preliminary results. We have now reexamined the problem using ^{13}C Fourier transform nmr and report on the fate of [2-^{13}C]- and [5-^{13}C]-labeled ALA and of [$^{13}CH_3$]methionine in *Propionibacterium shermanii*.

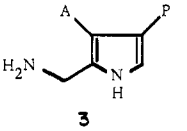


1

R = aminoisopropyl alcohol phosphate–ribose–DMBI–Co

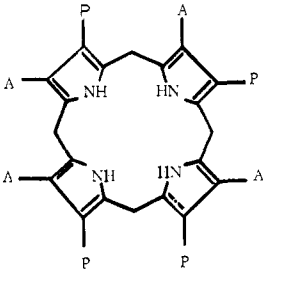


2 *S*-adenosylmethionine



3

A = —CH_2COOH
P = —CH_2CH_2COOH



4

Administration of [2-^{13}C]-ALA[6] to *P. shermanii* afforded a sample of vitamin B_{12} in which eight high-field signals in the CH_2 and CH_3 region were enriched as shown in the proton noise-decoupled ^{13}C FT nmr spectrum (Figure 1a). Assignments of the eight ^{13}C resonances were made to the seven CH_2CONH_2 methylenes and one of the geminal dimethyl groups of ring C in full accord with earlier ^{14}C studies. It is evident, however, that the methyl signal appears at lower field

(1) D. Shemin and R. C. Bray, *Ann. N.Y. Acad. Sci.*, **112**, 615 (1964); D. Shemin and G. Kikuchi, *ibid.*, **75**, 122 (1958).

(2) (a) J. H. Mathewson and A. H. Corwin, *J. Amer. Chem. Soc.*, **83**, 135 (1961); (b) D. Mauzerall, *ibid.*, **82**, 2601 (1960); (c) L. Bogorad, *Ann. N. Y. Acad. Sci.*, **104**, 676 (1963).

(3) R. C. Bray and D. Shemin, *Biochim. Biophys. Acta*, **30**, 647 (1958); R. C. Bray and D. Shemin, *J. Biol. Chem.*, **238**, 1501 (1963).

(4) B. F. Burnham in "Metabolic Pathways," 3rd ed, Vol. III, D. M. Greenburg, Ed., Academic Press, New York, N. Y., 1969, Chapter 18.

(5) A. I. Scott, C. A. Townsend, K. Okada, and M. Kajiwara, *Trans. N. Y. Acad. Sci.*, in press.

(6) [2-^{13}C]-ALA (60% enriched) was prepared by adaptation of the method of L. Pichat, J. Loheac, M. Herbert, and G. Chatelain, *Bull. Soc. Chim. Fr.*, **10**, 3271 (1966).