Table III. Results of the Thermal Isomerization of Ib and Ic

From	Yields, %,[a] of— IIb	IIc	IIIb + IIIc	IIb:IIc	
Ib	66	12	15	85	15
Ic	11	52	7	17	83

[a] Yields were determined by vpc (20% DC-11 on Chromosorb W at 140°) and uv spectroscopy.

Table IV. Chemical Shifts (τ, 60 MHz in $CDCl_3$) of Protons in IIa, IIb, and IIc

	H_2	H_3	$H_{8,9}$	H_1	H_4	H_{7a}	H_{7b}
IIa	3.80	4.17	4.17	6.10	7.10	6.80	7.43
IIb	3.85	4.20	4.20	6.10	7.10	7.37	7.37
IIc	3.80	4.27	4.03	5.73	7.13	6.80	7.40

of IIa, IIb, and IIc are shown in Table IV.[15] Under these thermal conditions, no interconversion between the products IIb and IIc and IIIb and IIIc was observed. This fact along with the findings shown in Table III clarify that the thermal isomerization of the 5-methylenebicyclo[4.2.0]octa-2,7-diene system I leading to the tricyclo[4.3.0.0^{4,6}]nona-2,8-diene system II takes place with *moderate stereospecificity*.

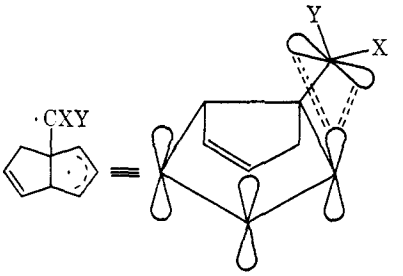
These results would be accommodated by considering the rearrangement of I to II to be mainly a concerted process, but not a stepwise radical process as suggested by the Syntex group.[16] However, the reaction path *via* a short-lived diradical intermediate VII which is formed from I by a one-step process could not be ruled out. Such an intermediate (VII) would be expected to cyclize with the observed stereochemistry because the orbital at the C_2 position is closer to one lobe of the side-chain p orbital.[17] On the other hand, in the concerted mechanism, two orbital symmetry allowed paths are possible. The first is a one-step concerted reaction, *i.e.*, a [$_\pi 2_a + {}_\sigma 2_s$] process as shown in VIII. The second is a two-step reaction composed of each concerted process, *i.e.*, conrotatory ring opening followed by internal Diels–Alder reaction of an intermediate such as *cis,trans,cis*-triene (IX) having an exocyclic double bond.[18] Although the Diels–Alder reaction is noted as a [$_\pi 4_a + {}_\pi 2_a$] process, the bond formation between the C_1 and C_5 positions seems quite feasible because the distance between them is less than 2.3 Å. This two-step concerted mechanism is similar to an alternative one proposed by Baldwin and Kaplan[3] for the thermal antara–antara Cope rearrangement of bicyclo[3.2.0]hepta-2,6-dienes and bicyclo[4.2.0]octa-2,7-dienes. Thus, a real reaction mechanism for the rearrangement of I to II is still ambiguous at present and further discussion from the viewpoint of a kinetic study will be reported in the near future.[13]

(15) Some of the coupling constants in compounds IIa and IIb could not be determined due to overlap of some signals (*cf.* Table II). However, those in IIc could be measured as follows: $J_{1,2} = 2.2$, $J_{1,3} = 2.0$, $J_{1,4} = 2.0$, $J_{1,7a} = J_{1,7b} = 2.1$, $J_{1,8} = 2.0$, $J_{1,9} = 1.3$, $J_{2,3} = 5.5$, $J_{3,4} = 2.0$, and $J_{8,9} \simeq 6$ Hz.

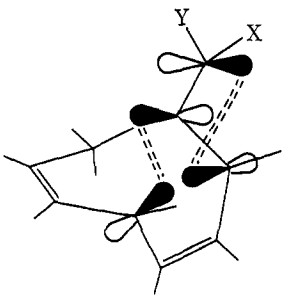
(16) P. H. Nelson, J. W. Murphy, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, 90, 5572 (1968).

(17) This mechanism was proposed by a referee, whom the authors would like to thank for his suggestion.

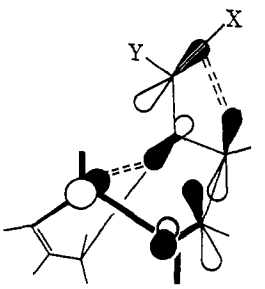
(18) Although there are two conrotatory processes for the ring opening of I, the other one leads to the formation of *trans,cis,cis*-triene, in which the distance between C_1 and C_5 positions is *ca.* 3.8 Å.



VII



VIII



IX

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Structure and Absolute Configuration of (+)-Coronaridine Hydrobromide. A Comment on the Absolute Configuration of the Iboga Alkaloids

Sir:

The Iboga alkaloids have attracted the interest of numerous groups over the years. The elegant investigations of the Ciba group[1,2] culminated in a structure proposal for this family and this was subsequently confirmed by the X-ray analysis of ibogaine hydrobromide.[3] This latter determination provided only relative configuration and thereby the absolute configuration remained on a tentative basis. During more recent investigations in one of our laboratories[4-13] it was possible to interrelate various nine-membered derivatives of the cleavamine series (I) with the rigid pentacyclic members, dihydrocatharanthine (III) and coronaridine (VII), according to the sequences I → II → III and I →

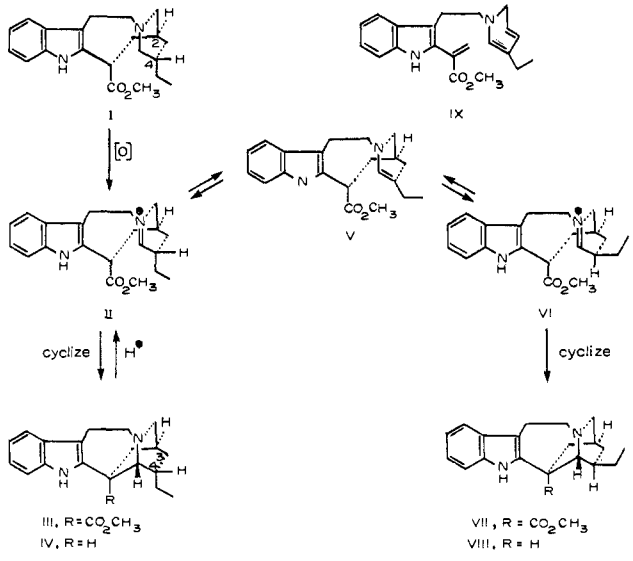
(1) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Amer. Chem. Soc.*, 80, 126 (1958).
(2) For a summary, see W. I. Taylor, *Alkaloids*, 11, 79 (1968).
(3) G. Arai, J. Coppola, and G. A. Jeffery, *Acta Crystallogr.*, 13, 553 (1960).
(4) J. P. Kutney, J. Trotter, T. Tabata, A. Kerigan, and N. Camerman, *Chem. Ind. (London)*, 648 (1963).
(5) N. Camerman and J. Trotter, *Acta Crystallogr.*, 17, 384 (1964).
(6) J. P. Kutney and E. Piers, *J. Amer. Chem. Soc.*, 86, 953 (1964).
(7) J. P. Kutney, R. T. Brown, and E. Piers, *ibid.*, 86, 2287 (1964).
(8) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, 43, 1545 (1965).
(9) A. Camerman, N. Camerman, J. P. Kutney, E. Piers, and J. Trotter, *Tetrahedron Lett.*, 637 (1965).
(10) A. Camerman, N. Camerman, and J. Trotter, *Acta Crystallogr.*, 19, 314 (1965).
(11) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, 44, 637 (1966).
(12) J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, and V. R. Nelson, *J. Amer. Chem. Soc.*, 92, 1704 (1970).
(13) J. P. Kutney, R. T. Brown, E. Piers, and J. R. Hadfield, *ibid.*, 92, 1708 (1970).

Table I. ORD Data for Various Natural[a] and Synthetic[b] Iboga Alkaloids[e]

Alkaloid	λ, nm 350	325	300	275	260	250
(+)-Catharanthine-HCl[a]	1819[c]	3035	7,892	6,070	−11,537	−13,962
(+)-Dihydrocatharanthine (A)[b]	1316	3075	12,304	−14,502	−30,327	−21,976
(+)-Dihydrocatharanthine (B)[b]	1098	2197	6,371	−5,932	−12,307	−8,790
(+)-Dihydrocatharanthine (C)[b]		1463	4,944	−7,323	−13,185	−9,520
(+)-Coronaridine[a] (A)	1219	1463	5,859	−6,348	−11,232	−6,103
(+)-Coronaridine (B)[b]	1537	1976	5,932	−2,415	−10,328	−4,612
(+)-Coronaridine (C)[b]	1316	2636	7,031	−5,711	−7,909	−5,711
(−)-Coronaridine[a,c]			−8,150 (304)		+15,400 (265)	
(+)-Ibogamine[b,c]			+1,200 (298)		−6,600 (270)	−1,800 (257)
(−)-Ibogamine[c,d]			−1,460 (298)		+2,080 (270)	+2,500 (257)

[a] Natural compounds. [b] All synthetic compounds were prepared in our laboratories according to the procedures already mentioned. [c] These compounds were measured at Yale at the wavelengths indicated. All other values were determined in Vancouver. [d] Sample obtained from Dr. N. Farnsworth. [e] Values given at the various wavelengths are presented in terms of [Φ].

II → VII, respectively. Based on all of these findings we were able to propose[11,13] the absolute configuration for the above-mentioned alkaloids as well as for ibogamine (VIII), the latter being obtained by the Lilly group[14] from dihydrocatharanthine. There has been a recent revival of interest in this area in view of the recent publication by a Czech group[15] and the considerable interest in the biosynthesis of the Iboga family.[16,17] In the latter studies it appears essential to postulate the intermediacy of a dehydrosecodine derivative (for example, IX), lacking any asymmetric centers, as a biointermediate in the later stages of the biosynthetic pathway. This enzymic conversion places particular importance on an unambiguous assignment to the absolute configuration of this family of alkaloids. We wish to report our most recent findings which, in the first instance, establish the correctness of our previous postulates[11,13] and finally establish beyond doubt the overall situation of the absolute configuration in this family of alkaloids.



A specific isomer, 18β-carbomethoxy-4β-dihydrocleavamine (I), prepared in the previously described manner[12] was subjected to the mercuric acetate oxidation and transannular cyclization procedure.[13] The isolated products, dihydrocatharanthine (III, sample C in Table I) and coronaridine (VII, sample C in Table I) were then compared with authentic samples in the usual manner (tlc, nmr, uv, ORD, and CD). The ORD values for the various alkaloids are presented in Table I. Dihydrocatharanthine (III, sample A in Table I) was obtained *via* catalytic reduction[14] of natural catharanthine isolated from *Vinca rosea L.* and kindly provided by the Lilly Laboratories. Another sample of III (sample B in Table I) was obtained for comparison from the reaction of the hydrogenated material (sample A) with glacial acetic acid (19-hr reflux).[14] Two samples of coronaridine were available for comparison with the compound obtained from cyclization of I. The first of these (sample A in Table I) represents the *same* material employed earlier in our comparisons[7,11,13] some years ago and is also the *same* alkaloid subjected to X-ray analysis mentioned below.[18] The second sample of coronaridine (sample B in Table I) was obtained from dihydrocatharanthine employing the glacial acetic acid procedure mentioned above.[14] The sample of (−)-coronaridine was obtained from *Vinca rosea* during studies at Yale.

An analysis of the results presented in Table I reveals the following facts. Natural catharanthine as well as its dihydro derivative (III, sample A) both possess a positive Cotton effect. Synthetic III obtained in the transannular cyclization process, *i.e.*, I → II → III, shows a similar curve and is clearly identical with sample A. Synthetic coronaridine obtained in the cyclization sequence, *i.e.*, I → II → V → VI → VII, *also* shows a positive Cotton effect and is clearly identical with the authentic coronaridine (sample A) used in the previous[7,11,13] and present comparisons. Finally, synthetic VII obtained by the acetic acid method developed by the Lilly group,[14] *i.e.*, III → II → V → VI → VII, is identical in every respect with the other two samples (A and C) of coronaridine. In summation, the transannular cyclization of I yields (+)-dihydrocatharan-

(14) M. Gorman, N. Neuss, and N. J. Cone, *J. Amer. Chem. Soc.*, 87, 93 (1965).

(15) K. Blaha, Z. Koblicova, and J. Trojanek, *Tetrahedron Lett.*, 2763 (1972).

(16) For a review and collection of references, see A. I. Scott, *Accounts Chem. Res.*, 3, 151 (1970).

(17) For a review and collection of references, see J. P. Kutney, J. F. Beck, C. Ehret, G. A. Poulton, R. S. Sood, and N. D. Westcott, *Bioorg. Chem.*, 1, 194 (1971); J. P. Kutney, *J. Heterocycl. Chem.*, 9, Suppl. Issue, S-1 (1972).

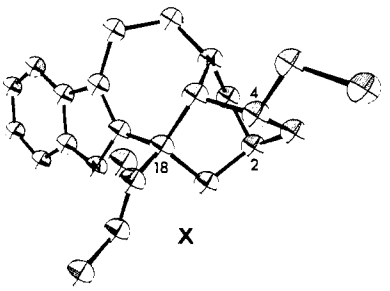
(18) This sample was kindly provided by the Lilly Laboratories where investigations on a variety of plant species which contain this alkaloid were conducted; M. Gorman, N. Neuss, N. J. Cone, and J. A. Deyrup, *J. Amer. Chem. Soc.*, 82, 1142 (1960). The sample is a natural alkaloid although recent correspondence and discussions with Drs. G. Svoboda and M. Gorman have failed to provide accurate information as to the specific plant species from which it was obtained. Other pure samples for the various comparisons and the X-ray work mentioned here could not be obtained.

thine and (+)-coronaridine possessing the absolute configuration portrayed in III and VII, respectively, and in agreement with the previous proposal.[11,13] On this basis, ibogamine (now indicated as (+)-ibogamine in Table I) and epiibogamine obtained from dihydrocatharanthine[14] *must* also belong to this stereochemical series and possess the structures VIII and IV, respectively.

To eliminate any doubt as to the correctness of the above assignments, (+)-coronaridine (sample A) was converted by the British Columbia group to the crystalline hydrobromide salt, mp 225–226° dec, and submitted to X-ray analysis.

The hydrobromide crystallizes in the monoclinic space group $P2_1(C_2^2)$ with one molecule per asymmetric unit and $a = 14.16$ (1), $b = 9.667$ (7), $c = 7.421$ (5) Å, and $\beta = 80.31$ (4)°. A right-handed coordinate system was maintained throughout the analysis. The intensities of all reflections in the hkl, $\bar{h}kl$, $hk\bar{l}$, and $\bar{h}k\bar{l}$ octants with $\theta \leq 60°$ were measured using Cu Kα X-rays (1.5418 Å). After Lorentz polarization and background corrections a total of 2830, out of the measured 3230, were judged to be observed ($F_o \geq 3\sigma(F_o)$).

The structure was phased by the heavy atom procedure.[19] All 25 nonhydrogen atoms were located in the first two electron density syntheses and the 26 hydrogens appeared in a subsequent difference synthesis. Full-matrix least-squares refinements with anisotropic temperature factors for the heavy atoms and isotropic hydrogens reduced the conventional crystallographic discrepancy index to 0.047. The mirror image of the original structure could only be refined to a discrepancy index of 0.050. This statistically significant difference means that the correct absolute configuration was chosen at the outset.[20] Structure X depicts a computer-generated perspective drawing of the correct



X

absolute configuration of coronaridine. All bond distances and angles agree well with generally accepted values.[21]

It is now established that there are *two* stereochemical series possible within the Iboga alkaloid family although the results presented here are conclusive for only the alkaloids mentioned. Thus, the alkaloid (+)-catharanthine and the compounds, (+)-coronaridine and (+)-ibogamine, which have been interrelated with it during the various investigations in the Lilly and our laboratories, comprise members of one series while (−)-coronaridine and (−)-ibogamine studied by Blaha and coworkers[15] represent members possessing antipodal stereochemistry. We hasten to add that our previous and present results must not be taken as indicative of the absolute configuration of *all* the Iboga alkaloids which have been reported. Some of the confusion which has arisen in the literature has resulted from the assumption that our previous interrelationships, within a few members of the Iboga family, necessarily imply a distinct absolute configuration in other members which possess varying functionality particularly in the "nontryptophan" portion of the alkaloid system. We do not feel that a rotation value at one wavelength (usually 589 nm) is a conclusive criterion and even in the more preferable approach involving ORD and CD studies[15] caution must be exercised since the influence of substituents on the Cotton effect, for example, is not known accurately.

Finally, we would like to indicate that in the course of studies at Yale on the biosynthesis of Iboga alkaloids in *V. rosea* it was observed[22] that no measurable bioconversion of (+)-catharanthine to (−)-coronaridine took place, although both alkaloids were present at late and early stages of germination, respectively (with the chirality indicated), and *both* were efficiently biosynthesized from a common precursor, geissoschizine.

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(19) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT and FRIEDEL," U. S. Atomic Energy Commission Report IS-2625, Iowa State University–Institute for Atomic Research, Ames, Iowa, 1971; W. R. Busing, K. O., Martin and H. A. Levy, "A Fortran Crystallographic Least Squares Program," U. S. Atomic Energy Commission Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations," U. S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.

(20) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(21) O. Kennard and D. G. Watson, "Molecular Structures and Dimensions," Crystallographic Data Centre, Cambridge, England, 1970.

(22) Unpublished work by J. Michael, P. Reichardt, and J. G. Sweeny. Specific incorporations of ^{3}H-labeled catharanthine into coronaridine in *V. rosea* of less than 0.002% were obtained.

(23) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee, 1972–1977; Fellow of the Alfred P. Sloan Foundation 1973–1975.

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Stereoselective Chemical Reduction of 5,10-Methenyltetrahydrofolate

Sir:

We wish to report the stereoselective synthesis of diastereoisomeric 5,10-methylenetetrahydrofolate with deuterium substitution at the bridging carbon atom.