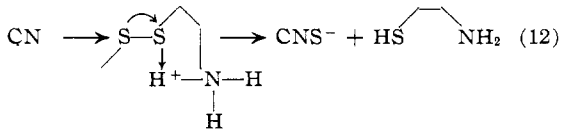
basis of such a model, the reaction (12) may be catalyzed by hydrogen ion, acting intramolecularly.



Hydrogen ion catalysis of disulfide exchange, a related reaction, has been demonstrated[22,23] to occur with several cystine derivatives, and thus intramolecular hydrogen ion catalysis of cyanide and sulfite displacement on sulfur may also be operative, and the relative values of the rate constants, 200:5.5:1, for the reaction of cyanide with cystine$^{\pm\pm}$, cystine$^{\pm-}$, and cystine^{--}, respectively, may be due to both electrostatic and intramolecular catalytic effects. If such intramolecular catalytic effects occur, it is also of interest to note that ions such as carbonate and phosphate may exert their inhibitory effects by interfering with such intramolecular hydrogen ion catalysis.

Table I also indicates the negligible rate of reaction of bisulfite ion with cystine$^{\pm\pm}$ and, presumably, also with cystine$^{\pm-}$ and cystine^{--}. The negligible activity of bisulfite ion as an S-nucleophile in this reaction may be correlated with the weakness of bisulfite ion as a base, pK_a 1.9 for the conjugate acid, since, in general, the greater the base strength the greater is the degree of S-nucleophilicity.[11]

Acknowledgment.—Support of this work by Grant G-24212 from the National Science Foundation is gratefully acknowledged.

(22) A. P. Ryle and F. Sanger, *Biochem. J.*, **60**, 535 (1955).
(23) R. E. Benesch and R. Benesch, *J. Am. Chem. Soc.*, **80**, 1666 (1958).

COMMUNICATIONS TO THE EDITOR

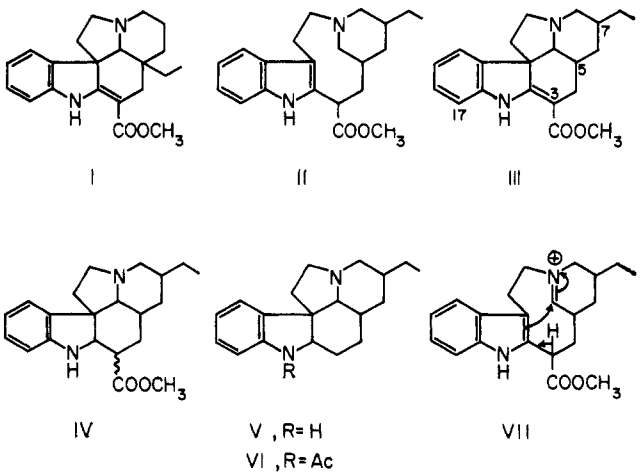
The Synthesis of a Vincadifformine-Type Skeleton *via* a Novel Transannular Cyclization Reaction

Sir:

The Aspidosperma alkaloids have received considerable attention for a long time and, particularly in recent years, a large number of these alkaloids have been isolated. One of the interesting variations of the Aspidosperma type skeleton is exemplified by the Vinca alkaloid, vincadifformine (I), recently elucidated largely by means of mass spectrometry.[1] This alkaloid and the structurally related alkaloids such as tabersonine,[2] minovincine,[3] minovincinine,[3] and vindolinine[4] are of considerable biogenetic interest since they may provide the connecting links between the aspidospermine- and akuammicine-type bases.[5] We now wish to present the first laboratory synthesis of a vincadifformine-type skeleton *via* a transannular cyclization reaction similar to the type proposed in Wenkert's biosynthetic hypothesis.[5]

In a previous communication[6] we were able to demonstrate the transannular cyclization of an ionic intermediate to an Aspidosperma skeleton and had suggested that an entry into the vincadifformine type of system could probably be realized by utilization of the appropriate carbomethoxydihydrocleavamine derivative. The results presented here provide experimental evidence in support of this claim.

Carbomethoxydihydrocleavamine (II),[7] on reaction with mercuric acetate in acetic acid at room temperature followed by reflux, provided a crude mixture which, after chromatographic separation, yielded a major product obtained as an amorphous powder and two other alkaloids in smaller amounts. These latter two substances are discussed in the accompanying communication[8] while evidence is presented here which establishes structure III for the amorphous product. This amorphous material possessed the molecular formula[9] $C_{21}H_{26}O_2N_2$, $[\alpha]^{26}D$ −503° (EtOH), and showed the following spectral properties. λ_{max}^{MeOH} 226, 298, and 326 mμ (log ϵ 4.07, 4.12, and 4.24); $\lambda_{max}^{CCl_4}$ 6.0 and 6.25 μ; n.m.r. signals[10]: 6.7–7.6 p.p.m., area = 4H; 8.95 p.p.m., area = 1H; 3.77 p.p.m., area = 3H, in good agreement with vincadifformine.[1] Chemical evidence in support of III was provided by zinc–sulfuric acid reduction[1,11] of the latter to yield two isomeric dihydro derivatives. The major product,[12] isolated as a white



(1) C. Djerassi, H. Budzikiewicz, J. M. Wilson, J. Gosset, J. Le Men, and M. M. Janot, *Tetrahedron Letters*, 235 (1962).
(2) M. Plat, J. Le Men, M. M. Janot, J. M. Wilson, H. Budzikiewicz, L. J. Durham, Y. Nakagawa, and C. Djerassi, *ibid.*, 271 (1962).
(3) M. Plat, J. Le Men, M. M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. soc. chem. France*, 2237 (1962).
(4) C. Djerassi, S. E. Flores, H. Budzikiewicz, J. M. Wilson, L. J. Durham, J. Le Men, M. M. Janot, M. Plat, M. Gorman, and N. Neuss, *Proc. Natl. Acad. Sci.*, **48**, 113 (1962).
(5) E. Wenkert, *J. Am. Chem. Soc.*, **84**, 98 (1962).
(6) J. P. Kutney and E. Piers, *ibid.*, **86**, 953 (1964).
(7) We are very grateful to Dr. M. Gorman and Dr. N. Neuss, Eli Lilly Laboratories, for providing the experimental procedure for preparing this compound prior to publication. This compound was first prepared by Professor G. Büchi, Massachusetts Institute of Technology.
(8) J. P. Kutney, R. T. Brown, and E. Piers, *J. Am. Chem. Soc.*, **86**, 2287 (1964).
(9) Satisfactory analyses were obtained for all substances reported.
(10) All n.m.r. spectra were measured in deuteriochloroform with tetramethylsilane as the internal standard using a Varian A60 spectrometer. All signals are reported as (c.p.s./60) units in p.p.m.
(11) P. N. Edwards and G. F. Smith, *J. Chem. Soc.*, 152 (1961).
(12) A more detailed description of the dihydro derivatives and the various interconversions will be presented in our full paper.

powder from ether, $C_{21}H_{28}O_2N_2$, mol. wt. 340 by mass spectrometry, exhibited spectral properties consistent with structure IV (λ_{max}^{MeOH} 244 and 299 mμ; 5.80 μ). Final confirmation of structure IV was obtained from the mass spectrum. The most intense peak in the mass spectrum occurred at m/e = 124 whereas the second most intense peak was present at m/e = 254 (M − 86) due to the loss of the elements of methyl acrylate. Indeed, comparison of the above spectrum with a mass spectrum of authentic dihydrovincadifformine,[1,13] kindly provided by Professor Djerassi, indicated that both spectra were *identical*.[14] Further chemical verification was provided by heating III with 2 *N* hydrochloric acid[1] to yield a gum which showed the expected spectral properties of an indolenine system[1,15] (λ_{max}^{MeOH} 221, 227 (inflection), 250 mμ (very broad), no infrared carbonyl absorption). This latter substance, on reduction with lithium aluminum hydride, afforded a crystalline product, m.p. 89–90° (from acetone), $[\alpha]^{26}D$ −60° ($CHCl_3$). The cyclic structure V was assigned to this product on the basis of the following evidence. $C_{19}H_{26}N_2$, mol. wt. 282 by mass spectrometry; λ_{max}^{MeOH} 243 and 295 mμ (log ϵ 3.81 and 3.45); n.m.r. signals 6.4–7.3 p.p.m., area = 4H; mass spectrum showed significant peaks at m/e = 282 (M^+), 281 (M − 1), 254 (M − 28), 190, 152, 144, 138, 130, and a very strong peak at 124. Indeed, the mass spectrum of V was identical with the mass spectrum of a previously established substance possessing the aspidosperma skeleton.[6,16] Finally, more evidence for the Aspidosperma system in V was obtained from the N-acetyl derivative VI, $C_{21}H_{28}N_2O$, m.p. 107.5–109° (from petroleum ether). The spectral properties were in excellent agreement with demethoxypalosine[17] (λ_{max}^{MeOH} 253, 279, and 289 mμ (log ϵ 4.13, 3.58, and 3.51); λ_{min} 226, 276, and 287 mμ (log ϵ 3.51, 3.56, and 3.45)); n.m.r. signals 7.15 p.p.m., broad, area = 3H; 8.13 p.p.m. (C-17–H). The spectral data were generally in very good agreement with our previous work.[6,18]

The stereochemistry of this transannular cyclization (see VII) is presently being considered by X-ray methods since a convenient correlation to a known alkaloid is not possible at this time. However, we do feel that the demonstration of this type of reaction will open interesting avenues to the synthesis of several alkaloid systems. For example, the obvious extension of this reaction to an alkaloid such as vincadine[19] should provide a direct route to vincadifformine (I) and its relatives.

(13) See also C. Djerassi, *Pure Appl. Chem.*, **6**, 575 (1963).

(14) This evidence indicates that the mass spectrometric method cannot distinguish in the region normally considered (above m/e = 120) between an Aspidosperma skeleton possessing an ethyl group at C-5 and one at C-7.

(15) K. Biemann, M. Spiteller-Friedmann, and G. Spiteller, *J. Am. Chem. Soc.*, **85**, 631 (1963).

(16) The peak at m/e = 190 which was also present in the previously reported spectrum[6] was disregarded since there was good reason at that time to believe that it was due to an impurity in the mass spectrometer. We have recently established that this peak is characteristic of this system and may represent an interesting variation in the fragmentation process normally postulated for the Aspidosperma alkaloids.

(17) B. Gilbert, J. A. Brissolese, J. M. Wilson, H. Budzikiewicz, L. J. Durham, and C. Djerassi, *Chem. Ind.* (London), 1949 (1962).

(18) Since it is known that the starting material, II, has a different stereochemistry at the asymmetric center bearing the ethyl group from that present in dihydrocleavamine, the compound assigned structure V will possess a different stereochemistry at least at this center from the previously described substance.[6]

(19) J. Mokry, I. Kompis, L. Dubravkova, and P. Sefcovic, *Tetrahedron Letters*, 1185 (1962).

It will be of considerable interest to observe whether alkaloids possessing the system III will be found in nature.

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The Synthesis of Iboga Alkaloids *via* a Novel Transannular Cyclization Reaction

Sir:

In connection with the chemistry of the known Vinca alkaloid catharanthine,[1] we were able to establish the structure of cleavamine (I),[2] one of the acid-rearrangement products of this Iboga-type alkaloid. Consideration of the mechanistic aspects of this rearrangement process led us in turn to consider some of the biosynthetic hypotheses which have been proposed for the Iboga alkaloids. Wenkert[3] introduced an attractive scheme wherein he visualized the cyclization of an ionic intermediate such as II to provide a pathway to the Iboga alkaloid system. It is immediately apparent that this latter intermediate possesses a cleavamine-like skeleton and it was, therefore, of considerable interest to evaluate the feasibility of such a cyclization process. We now wish to report the first synthesis of several Iboga alkaloids *via* a transannular cyclization of the type mentioned above.

Carbomethoxydihydrocleavamine (III)[4,5] on reaction with mercuric acetate would be expected to generate an intermediate with the iminium group ($>C{=}\overset{+}{N}<$) involving C-19 and/or C-5. The intermediate with the C-19 $=\overset{+}{N}<$ group could, by the appropriate transannular cyclization process, provide a vincadifformine-type system,[6] whereas the substance with the C-5 $=\overset{+}{N}<$ group could, by a different transannular cyclization scheme (see IV), provide entry into the Iboga alkaloid system. Indeed, we have now been able to show that both processes are feasible—the formation of the vincadifformine-type skeleton is presented in the accompanying communication[7] whereas the generation of the Iboga system is described here.

Carbomethoxydihydrocleavamine (III), on reaction with mercuric acetate in acetic acid at room temperature followed by reflux, provided a crude mixture which was then subjected to chromatography on alumina.

(1) N. Neuss and M. Gorman, *Tetrahedron Letters*, 206 (1961).

(2) J. P. Kutney, J. Trotter, T. Tabata, A. Kerigan, and N. Camerman, *Chem. Ind.* (London), 648 (1963).

(3) E. Wenkert, *J. Am. Chem. Soc.*, **84**, 98 (1962).

(4) We are very grateful to Dr. M. Gorman and Dr. N. Neuss, Eli Lilly laboratories, for providing the experimental procedure for preparing this compound prior to publication. This compound was first prepared by Professor G. Büchi, Massachusetts Institute of Technology.

(5) The numbering system used here is that normally used in the Iboga alkaloid series.

(6) C. Djerassi, H. Budzikiewicz, J. M. Wilson, J. Gosset, J. Le Men, and M. M. Janot, *Tetrahedron Letters*, 235 (1962).

(7) J. P. Kutney, R. T. Brown, and E. Piers, *J. Am. Chem. Soc.*, **86**, 2286 (1964).