for 24 hr. The slightly tan solution was evaporated to dryness and the crystalline residue was redissolved in hot absolute ethanol. The solution was diluted with one-fourth volume of benzene and allowed to crystallize at 4°. After three recrystallizations, 1.70 g of colorless, rhombohedral crystals of **6** was obtained (44% yield): R_f = 0.54, mp 139°, $[\alpha]^{25}D$ −59° (*c* 0.5, water).

Anal. Calcd for $C_7H_{15}NO_4$: C, 47.44; H, 8.53; N, 7.91. Found: C, 47.41; H, 8.69; N, 7.75.

Gentosamine Hydrochloride (3-Methylamino-3-deoxy-D-xylose Hydrochloride) (7). A solution of 0.530 g of **6** in 20 ml of 1.5 *M* hydrochloric acid was heated on a steam bath for 20 hr. The cooled stirred solution was adjusted to pH 5 by the portionwise addition of Dowex 1-X8 (carbonate form), and the resin is filtered off and washed with water. Filtrate and washings were concentrated and crystallization was allowed to proceed from methanol–ethanol–acetone mixture at 4°. One recrystallization from the same solvent system gave 0.304 g of gentosamine hydrochloride (51% yield), mp 173° dec, $[\alpha]^{25}D$ −4° (extrapolated to 0 time), with a constant rotation, $[\alpha]^{25}D$ +28°, after 40 min. *Anal.* Calcd for $C_6H_{14}NO_4Cl$: C, 36.10; H, 7.07; N, 7.02. Found: C, 36.46; H, 7.25; N, 6.91.

Methyl N-Acetyl-β-gentosaminide. [Methyl 3-(N-Methylacetamido)-3-deoxy-β-D-xylopyranoside] (9). A solution of 0.100 g of **6** in 1 ml of methanol and 0.15 ml of acetic anhydride was allowed to react at room temperature for 24 hr. Methanol was evaporated under reduced pressure and the syrup was diluted with 1 ml of absolute ethanol. The solution was kept at 4° for 24 hr after addition of 1.5 ml of ether. The resulting needles were recrystallized once from the same solvent mixture affording 85 mg of **9** as long needles (69% yield), mp 183°, $[\alpha]^{25}D$ −59.5 (*c* 0.8, water). *Anal.* Calcd for $C_9H_{15}NO_5$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.27; H, 7.89; N, 6.23.

Acknowledgment. We acknowledge in part the support of the National Institute of Allergy and Infectious Diseases under Public Health Service Grant No. AI-06182.

Total Synthesis of Indole and Dihydroindole Alkaloids. I.[1] Introduction and the Transannular Cyclization Approach

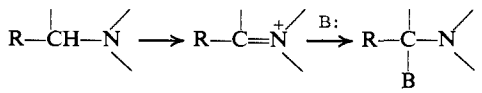
James P. Kutney, Edward Piers, and Richard T. Brown

Contribution from the Department of Chemistry, University of British Columbia, Vancouver 8, Canada. *Received April 7, 1969*

Abstract: An introduction to the transannular cyclization reaction and its application to indole and dihydroindole alkaloid syntheses is presented. The first successful laboratory realization of this process has been accomplished by converting 4β-dihydrocleavamine (I) into 7β-ethyl-5-desethylaspidospermidine (V). The partial synthesis of (+)-aspidospermidine (X) from (−)-quebrachamine (IX) illustrates an extension of this approach to the natural Aspidosperma series. The stereochemistry of this reaction has been established by X-ray analysis on the N_b-methiodide of the N_a-acetyl derivative VI. This study made available the first compound bearing the Aspidosperma skeleton for which an absolute configuration was available. Its importance in connection with the determination of absolute configuration in the natural Aspidosperma series is noted.

The vast domain of indole and dihydroindole alkaloids offers a formidable challenge to the synthetic chemist. Coupled with the recent interests in alkaloid biosynthesis, there is considerable stimulus for developing chemical reactions which not only provide laboratory syntheses of these natural products, but which may have some parallel in the natural pathways inherent in the living plant system. Clearly, reactions which are fundamentally simple, but general in their application to the elaboration of these alkaloid systems, would be highly desirable. We chose to study such a process, and the results presented in this and the succeeding publications have been obtained from such an investigation.

The reaction selected for this work is, in its simplest terms, straightforward and well known. It involves the creation of an electrophilic center (iminium salt) in



the original amine, as indicated, followed by reaction of the latter intermediate with a nucleophile (B:) to yield the desired product. The intervention of imines as possible intermediates in alkaloid biosynthesis has long been recognized,[2] and this functional group has also played a major role as an intermediate in some elegant alkaloid syntheses, particularly in the pyrrolidine, piperidine, and quinolizidine series.[2,3]

We felt that this reaction could be of general application to the indole and dihydroindole group where tremendous structural variety is available, particularly from the recent investigations in the Vinca, Iboga, and Aspidosperma families. Indeed, postulates on the possible biosynthetic pathways of these alkaloids have invoked these imine intermediates[4] and their use in the synthesis of some indole alkaloids had already been demonstrated.[5] Similarly, mechanistic interpretations on the interesting acid-catalyzed rearrangements of the alkaloid catharanthine have employed such intermediates although no direct experimental evidence was available for such postulates.[6,7]

(1) For a preliminary report on this work, see J. P. Kutney and E. Piers, *J. Amer. Chem. Soc.*, 86, 953 (1964); A. Camerman, N. Camerman, J. P. Kutney, E. Piers, and J. Trotter, *Tetrahedron Lett.*, 637 (1965).

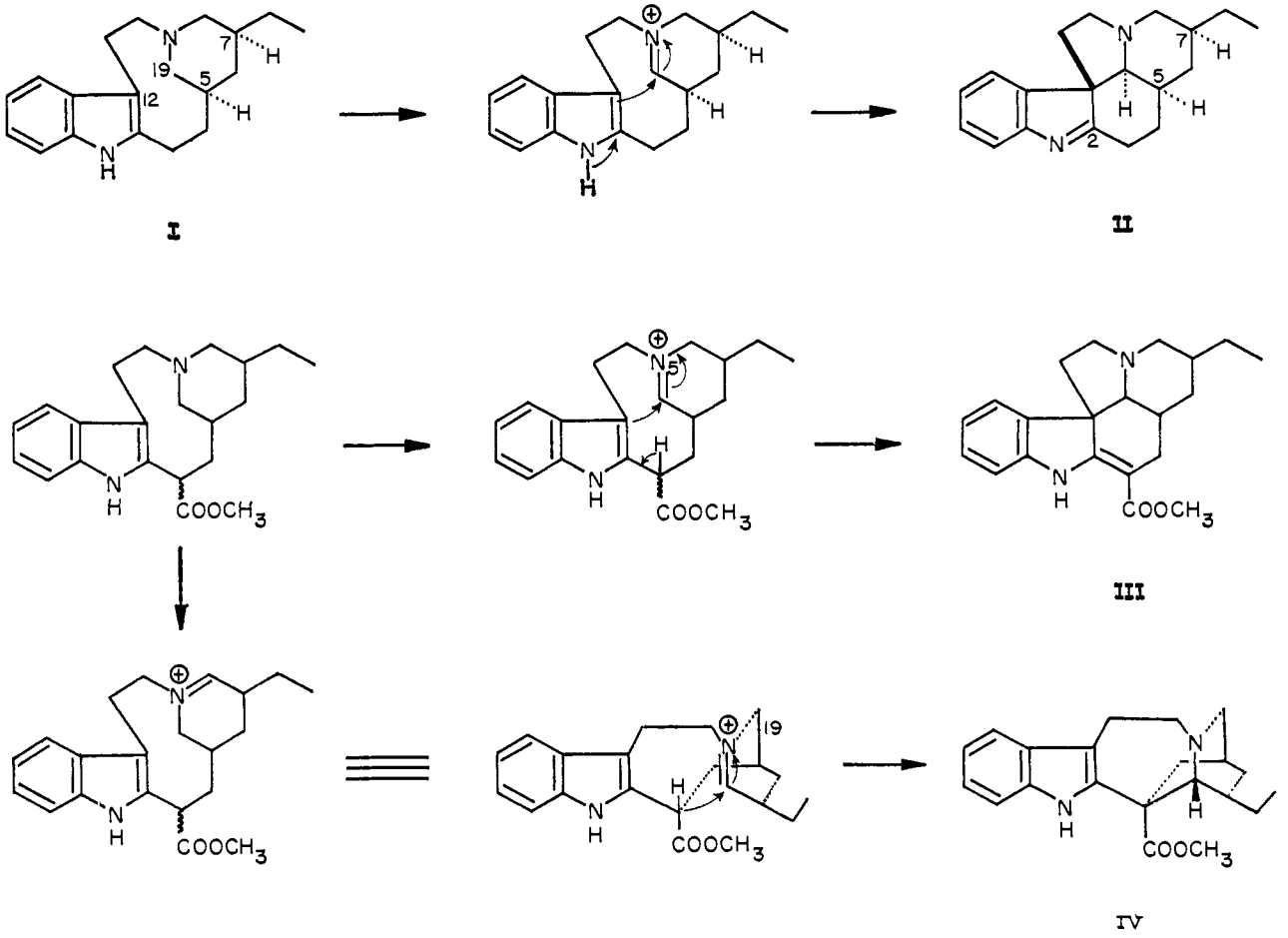
(2) K. Mothes and H. R. Schütte, *Angew. Chem. Intern. Ed. Engl.*, 2, 341 (1963), and references cited therein.

(3) E. E. van Tamelen, *Progr. Chem. Org. Nat. Prod.*, **19**, 243 (1961).

(4) E. Wenkert, *J. Amer. Chem. Soc.*, **84**, 98 (1962), and references cited therein.

(5) E. Wenkert and B. Wickberg, *ibid.*, **84**, 4914 (1962).

Scheme I

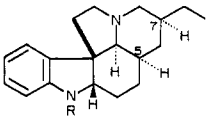


Our initial considerations were then directed at the possible elaboration of the typical skeletal systems present in the Aspidosperma (II), Vinca (III), and Iboga (IV) alkaloids, as schematically presented above (Scheme I).

As indicated in Scheme I, the iminium intermediates generated from the nine-membered ring compounds of the cleavamine series[6,7] could be envisaged to convert to the respective cyclic products *via* a transannular cyclization reaction in which the nucleophile is either the π-electron system of the indole chromophore or an activated carbon atom at an appropriate site in the molecule.

Although the transannular cyclization of dihydrocleavamine (I) to the corresponding cyclic product (II) does not lead to a naturally occurring alkaloid, its ready availability from catharanthine[6,7] made it an attractive model for this study. Furthermore, its close structural relationship to the known alkaloid, quebrachamine,[8] would allow extension of these results to the natural Aspidosperma series.

4β-Dihydrocleavamine (I),[9] when allowed to react with an excess of mercuric acetate at room temperature, was readily oxidized, as evidenced by the precipitation of mercurous acetate (81% by weight in 24 hr). The known instability of the indolenine system which would be present in the desired product (II) encouraged us to immediately subject this reaction product to reduction with lithium aluminum hydride. Chromatographic purification of the latter product afforded a crystalline compound, $C_{19}H_{26}N_2$, mp 128–129°, in an overall 29% yield. The evidence obtained for this substance was consistent with the rigid Aspidosperma system presented in V (no stereochemistry implied at this point).



V, R = H
VI, R = Ac

Of particular value in establishing the cyclic structure V was the mass spectrum (Figure 1). The characteristic fragmentation exhibited by Aspidosperma alkaloids was well established from the previous work of Biemann[10] and Djerassi,[11] and it was clear that a similar fragmen-

(6) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, **43**, 1545 (1965).

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

(8) K. Biemann and G. Spiteller, *ibid.*, **84**, 4578 (1962), and references cited therein.

(9) The ethyl group at C_4 in this compound (Iboga alkaloid numbering) has been established to be in the β orientation. A more detailed discussion will be presented in the latter portion of this paper although some mention of this fact has already appeared in a previous publication.[6] The numbering system and nomenclature used in this publication are those normally employed in the Aspidosperma series. For the sake of clarity and convenient comparisons with previous publications, the more recent proposals for numbering and nomenclature of indole alkaloids (J. Le Men and W. I. Taylor, *Experientia*, **21**, 508 (1965); J. Trojanek and K. Blaka, *Lloydia*, **29**, 149 (1966)) have not been adopted in this or succeeding papers.

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

(11) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry. Alkaloids," Vol. 1, Holden-Day, Inc., San Francisco, Calif., 1964.

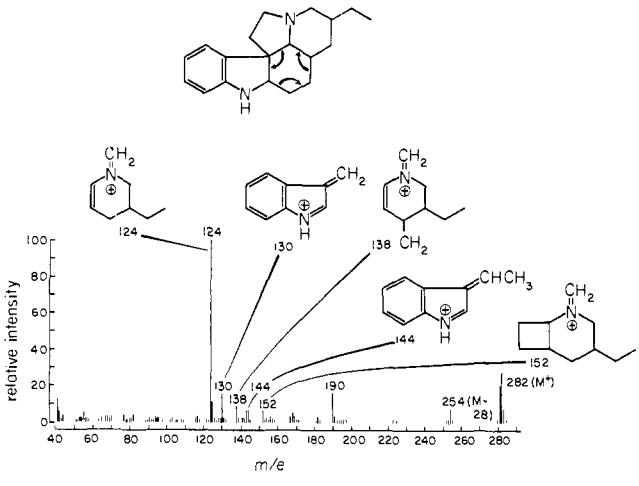
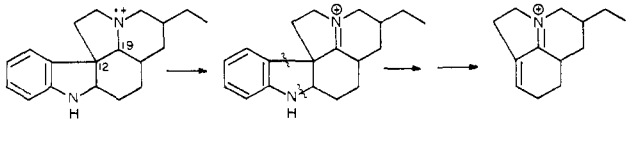


Figure 1. Mass spectrum of 7β-ethyl-5-desethylaspidospermidine.

tation pathway should persist in the above molecule, since the displacement of the C_5 ethyl group present in the natural series to C_7 in the present instance should not bring about a significant variation. Indeed, Figure 1 illustrates the typical loss of ethylene (M − 28) and the other characteristic fragments normally encountered in the mass spectra of Aspidosperma alkaloids. On the other hand, some interesting differences suggesting an alternative fragmentation process are also apparent.

One of the significant differences which is noteworthy is the presence of a strong M − 1 peak which is considerably more intense than normally encountered in the spectra of the Aspidosperma series. Djerassi has shown[12] that the loss of the C_{19} hydrogen atom is responsible for the M − 1 peak, and it is clear that such a loss must occur to a significant extent in our case. The appearance of a strong peak at *m/e* 190 represents the other significant difference which should receive mention. We feel that both of these features can be rationalized by proposing an alternative fragmentation scheme, as shown below.

Loss of the C_{19} hydrogen atom provides the ion VII, which can fragment as indicated to yield the relatively stable ion VIII. Further support for this postulate will be provided in a subsequent paper in which again a



strong M − 1 peak is accompanied by a fragment appearing at *m/e* 190. The latter species does not seem to be present in instances where the loss of the C_{19} hydrogen atom does not appear significant. Djerassi has observed a strong M − 1 peak in the spectrum of an isomeric deacylcylindrocarpine derivative and suggests that the loss of the C_{19} hydrogen atom may be assisted by a *trans*-electron pair on N_b.[12]

The usefulness of nuclear magnetic resonance spectroscopy in the structural elucidation of Aspidosperma alkaloids is also well established,[13] and its application in this work was invaluable. The nmr spectrum of V showed a typical complex pattern of lines in the aromatic region,[13] and when coupled with nmr data obtained on the N_a-acetyl derivative, VI, provided direct evidence for the dihydroindole system present in V.

Obviously, the potential of the above approach is markedly dependent on the stereochemical course of this reaction, and to this end, a detailed investigation of the stereochemistry of the product V was warranted.

Previous work from our laboratory[14,15] had provided conclusive evidence for the structure and *absolute* configuration of cleavamine. On this basis, the stereochemistry of the same asymmetric center (C_5) in dihydrocleavamine was also established as shown in I.

Consideration of the cyclization process with the aid of molecular models revealed that the necessary "folding" of the molecule to bring the potential reacting centers (C_{12} and C_{19}) into reasonable proximity for bond formation should result in the stereochemistry shown in II.[16] The subsequent hydride reduction of the indolenine system could theoretically proceed from either the α or β face of the molecule, although the tremendous rigidity inherent in the cyclic Aspidosperma skeleton predicted a definite preference for β reduction. Indeed, models indicated that the 2α-H orientation in the aspidospermidine system is extremely unfavorable, if not impossible.

The solution to the stereochemical aspects of this cyclization reaction was clearly available only from X-ray studies. For this purpose, the N_a-acetyl derivative of the cyclization product was converted to its N_b-methiodide, and the latter subjected to X-ray analysis. Since a detailed discussion of this investigation has been presented elsewhere,[17] it is merely necessary to indicate that these results showed that the compound under investigation was N_a-acetyl-7β-ethyl-5-desethylaspidospermidine (VI), thereby confirming the previously postulated structure[1] and establishing the *absolute* configuration as shown in V. This latter product can now be termed as 7β-ethyl-5-desethylaspidospermidine (V).

Several important features available from the above results are worthy of mention. First of all, the absolute configuration at C_5 in V is the *same* as in dihydrocleavamine (I). Second, the above X-ray study provided the first instance in which the absolute configuration of an Aspidosperma system was established.[18] Therefore, the N_a-acetyl derivative, VI, could now serve as the parent system for the determination of the absolute configuration in this large family of alkaloids. Indeed, this compound has been utilized in such an investigation[19] and the correctness of the resulting stereochemical assignments has been recently established by X-ray analysis.[20]

(12) K. S. Brown, H. Budzikiewicz, and C. Djerassi, *Tetrahedron Lett.*, 1731 (1963).

(13) See, for example, C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, J. N. Shoolery, and L. F. Johnson, *Experientia*, **16**, 532 (1960).

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

(15) N. Camerman and J. Trotter, *Acta Crystallogr.*, **17**, 384 (1964).

(16) See also, E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, **87**, 1580 (1965).

(17) A. Camerman, N. Camerman, and J. Trotter, *Acta Crystallogr.*, **19**, 314 (1965).

(18) For relative configuration by X-ray, see J. F. D. Mills and S. C. Nyburg, *J. Chem. Soc.*, 1458 (1960).

(19) W. Klyne, R. J. Swan, B. W. Bycroft, and H. Schmid, *Helv. Chim. Acta*, **49**, 833 (1966), and references cited therein.

(20) B. M. Craven, B. Gilbert, and L. A. Paes Leme, *Chem. Commun.*, 955 (1968). We are grateful to Dr. B. M. Craven for informing us of his results prior to publication.

As already mentioned previously, the extension of the transannular cyclization reaction to the natural Aspidosperma series is obvious and was now considered. When (−)-quebrachamine (IX)[21] was treated with mercuric acetate and the resultant product reduced with lithium aluminum hydride, (+)-aspidospermidine (X), mp 119.5–121°, $[\alpha]^{23}D$ +21°, was obtained. The synthetic compound was shown to be identical in every respect with the natural Aspidosperma alkaloid (X).[22]

IX X

We wish to mention that in a related reaction, Schmid and coworkers have obtained (+)-1,2-dehydroaspidospermidine from (−)-quebrachamine.[23]

Finally, it is seen that any totally synthetic pathway leading to either the cleavamine or quebrachamine systems must focus attention on only *one* asymmetric center, namely C_5, since the latter determines the total stereochemistry of the cyclization product.

Experimental Section

General.[24] Melting points (Kofler block) and boiling points are uncorrected. Ultraviolet spectra were measured in methanol solution (unless otherwise indicated) on either a Cary Model 11 or a Cary Model 14 spectrophotometer. Infrared spectra were recorded on Perkin-Elmer Infracord Model 137 and Perkin-Elmer Model 21 spectrophotometers. Nuclear magnetic resonance (nmr) spectra were taken in deuteriochloroform solution at 60 MHz (unless otherwise indicated) on either a Varian A60 spectrometer or on a JEOLCO C-60-H spectrometer. Line positions are given in the Tiers τ scale, with tetramethylsilane as an internal standard; the multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. Mass spectra were recorded on an Atlas CH-4 mass spectrometer and high-resolution molecular weight determinations were determined on a AEI, type MS-9, mass spectrometer.

Unless otherwise stated, silica gel G and Woelm neutral TLC alumina were used for thin layer chromatography (tlc); the type of absorbent used and the solvent system employed for development are given in parentheses. The alumina used for column chromatography was, unless otherwise indicated, Shawinigan reagent, deactivated with 10% aqueous acetic acid (3 ml/100 g of alumina). Microanalyses were performed by Dr. A. Bernhardt and associates, Mulheim (Ruhr), Germany, and by Mrs. C. Jenkins and Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver, Canada.

7β-Ethyl-5-desethylaspidospermidine (V). A solution of 4β-dihydrocleavamine (I, 2.5 g, 8.9 mmol) and mercuric acetate (5.9 g, 18.5 mmol) in glacial acetic acid (80 ml) was stirred, under an atmosphere of nitrogen, at room temperature. Precipitation of mercurous acetate began almost immediately. After 24 hr reaction time, the reaction mixture was filtered, producing 3.75 g (81%) of mercurous acetate. The filtrate was diluted with glacial acetic acid (30 ml) and the resulting solution was refluxed, with stirring under nitrogen, for 6 hr. The cooled reaction mixture was filtered and the acetic acid was removed under reduced pressure, leaving a dark oil as residue. This material (containing II as one of the components), which showed λ_{max} 222, 278 (very broad), 288 (shoulder) mμ, was not purified, but immediately subjected to lithium aluminum hydride reduction.

The above material was taken up in dry tetrahydrofuran (50 ml), and the resulting solution was added slowly to a stirred mixture of lithium aluminum hydride (5 g) and dry tetrahydrofuran (200 ml). After refluxing for 6 hr, the reaction mixture was cooled to −10° (ice–salt bath), and the excess hydride was destroyed by careful addition of ice-cold water. The resulting mixture was diluted with chloroform (100 ml) and then filtered. The inorganic salts were washed thoroughly with further volumes of chloroform. The combined filtrate and washings were washed once with water, dried (anhydrous potassium carbonate), and evaporated under reduced pressure. The gummy brown residue was subjected to chromatography on alumina (150 g). Elution with 1:1 benzene–petroleum ether (bp 30–60°) (1400 ml) afforded a mixture (600 mg) consisting nearly entirely of 4α- and 4β-dihydrocleavamine. Further elution with 1:1 benzene–petroleum ether (1000 ml), 3:2 benzene–petroleum ether (400 ml), and 2:1 benzene–petroleum ether (600 ml) gave 790 mg of crystalline material. Recrystallization from acetone afforded V as colorless plates (750 mg, 29%), mp 128–129°; $[\alpha]^{23}D$ −105° ($CDCl_3$); λ_{max} 242, 294 mμ (log ε 3.78, 3.42, respectively); λ_{min} 223, 269 mμ (log ε 3.52, 2.99, respectively); ν_{max}^{KBr} 3360 (NH), 1605 (aromatic C=C) cm^{-1}; nmr τ 2.7–3.6 (diffuse, 2 H, aromatic), 6.4–7.2 diffuse, 4 H), and 9.1 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.44; H, 9.16; N, 10.29.

N_a-Acetyl-7β-ethyl-5-desethylaspidospermidine (VI). To a solution of 7β-ethyl-5-desethylaspidospermidine (105 mg, 0.27 mmol) in dry pyridine (1 ml) was added acetic anhydride (2 ml). The resulting solution was heated on a steam bath for 1.5 hr. The cooled solution was poured into ice-cold dilute ammonium hydroxide and the resulting mixture was extracted thrice with ether. The combined ether extracts were washed twice with water, dried (anhydrous magnesium sulfate), and evaporated under reduced pressure. The gummy residue crystallized immediately upon addition of petroleum ether (bp 60–80°). Recrystallization from petroleum ether afforded 112 mg (93%) of colorless needles, mp 99–100°; λ_{max}^{KBr} 1654 ($NC(=O)CH_3$), 1600 (aromatic C=C) cm^{-1}; nmr τ 1.85 (unresolved multiplet, 1H, C_{17}-H), 5.98 (quartet), 6.70-7.10 (diffuse, 2 H, "aspidospermine fingerprint"), 7.75 (singlet, 3 H, $NC(=O)CH_3$), and 9.07 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{28}N_2O$: C, 77.73; H, 8.70; N, 8.63; O, 4.93. Found: C, 77.38; H, 8.67; N, 8.87; O, 5.20.

N_a-Acetyl-7β-ethyl-5-desethylaspidospermidine N_b-Methiodide. N_a-Acetyl-7β-ethyl-5-desethylaspidospermidine (VI) (100 mg) was dissolved in a mixture of freshly distilled methyl iodide (2 ml) and methanol (2 ml). The resulting solution was allowed to stand at room temperature for 5 days. Removal of the solvent and excess reagent under reduced pressure afforded a gummy solid which proved very difficult to crystallize. After many attempts, it was finally crystallized from a mixture of methanol and acetone, producing pale yellow clusters. The latter, after repeated recrystallization from anhydrous ethanol, gave pale yellow blocks, mp 281–282° dec.

Anal. Calcd for $C_{22}H_{31}N_2OI$: C, 56.65; H, 6.70; N, 6.01; O, 3.43. Found: C, 56.68; H, 6.67; N, 6.16; O, 3.47.

(+)-Aspidospermidine (X). A solution of (−)-quebrachamine (IX, 800 mg, 2.84 mmol) and mercuric acetate (2.00 g, 6.28 mmol) in glacial acetic acid (30 ml) was stirred at room temperature, under an atmosphere of nitrogen, for 36 hr. Filtration of the reaction mixture produced 730 mg (50%) of mercurous acetate. The filtrate was refluxed under nitrogen for 6 hr. After filtration of the cooled reaction mixture, the acetic acid was removed under reduced pressure, affording a dark gum as residue. The latter showed λ_{max} 223, 273, 280, 290 mμ; λ_{min} 255, 288 mμ. The crude residue was taken up in dry tetrahydrofuran (15 ml) and the resulting solution was added slowly to a stirred mixture of lithium aluminum hydride (2 g) in tetrahydrofuran (45 ml). The mixture was refluxed with stirring for 5 hr, cooled to −10° (ice–salt bath), and the excess hydride destroyed by careful addition of ice-cold water. After sufficient water had been added, the mixture was diluted with methylene chloride (40 ml) and filtered. The inorganic salts were washed thoroughly with methylene chloride. The combined filtrate and washings were washed twice with water, dried (anhydrous potassium carbonate), and evaporated under reduced pressure, producing a crude brown solid as residue. A tlc analysis (silica gel, 2:1 ethyl acetate–ethanol) of this product showed, in addition to a number of minor components, one major component with an R_f value identical with that of authentic (+)-aspidospermidine. Since column chromatography of the mixture failed to effect adequate separation of the components, the mixture was subjected to purifi-

(21) We are grateful to Dr. George F. Smith, Manchester University, for providing us with a small sample of this compound.

(22) We are very grateful to Professor H. Schmid, Zurich, for providing us with an authentic sample of this alkaloid.

(23) B. W. Bycroft, D. Schumann, M. B. Patel, and H. Schmid, *Helv. Chim. Acta*, **47**, 1147 (1964).

(24) This general section is common to this and succeeding papers in this series and will not be repeated. Any deviations from the general information given will be indicated in the pertinent sections of the publications.

cation by preparative tlc. Silica gel GF_{254} plates (20 × 60 cm, 0.5 mm thick) were used, with ethyl acetate–ethanol (10:7) being employed as developing solvent. Approximately 150 mg of the crude mixture was applied per plate, and the (+)-aspidospermidine band of each plate was eluted with warm methanol. Evaporation of the combined eluants produced 200 mg of crystalline material. Recrystallization from acetone afforded 180 mg (22.5%) of colorless needles, which were identified as pure (+)-aspidospermidine (X) by comparison with an authentic sample: mp 119.5–121°, lit.[23] mp 119–120°, mmp 119–120.5°; $[\alpha]^{23}D$ +21° (*c* 0.99, ethanol), lit.[23] $[\alpha]^{23}D$ +24 ± 5° (*c* 0.39, ethanol); identical R_f value on tlc (silica gel, 2:1 ethyl acetate–ethanol); identical infrared spectra (KBr disks); λ_{max} 242.5, 296 mμ (log ε 3.79, 3.44, respectively); λ_{min} 225, 270 mμ (log ε 3.55, 2.97, respectively); nmr τ 2.70–3.55 (diffuse, 4 H, aromatic), 6.25–7.25 (diffuse, 4 H), 9.39 (triplet, 3 H, CH_2CH_3).

Acknowledgment. We gratefully acknowledge financial support from the National Research Council of Canada and the National Cancer Institute of Canada. One of us (R. T. B.) is indebted to the Canadian Commonwealth Scholarship and Fellowship Committee for a scholarship during this study. We express our sincere thanks to Drs. M. Gorman and N. Nuess, Eli Lilly and Company, for generous supplies of catharanthine hydrochloride.

Total Synthesis of Indole and Dihydroindole Alkaloids. II.[1] The Partial Synthesis of Some Nine-Membered Ring Intermediates from Catharanthine

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Contribution from the Department of Chemistry, University of British Columbia, Vancouver 8, Canada. *Received April 7, 1969*

Abstract: An investigation of the reaction of catharanthine with zinc in glacial acetic acid is presented. Four isomeric carbomethoxydihydrocleavamine derivatives have been isolated and fully characterized. It is also shown that heating catharanthine in a mixture of acetic acid and sodium borohydride provides a very convenient method for the preparation of the previously unknown 18β-carbomethoxycleavamine. These compounds provide the desired intermediates for the synthesis of various Iboga alkaloids.

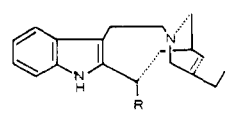
The potential interest of the cleavamine and quebrachamine ring systems in the laboratory synthesis of dihydroindole alkaloids has already been demonstrated.[1] Further investigations of this approach required the availability of various cleavamine derivatives, and, therefore, their preparation came under study in our laboratory.

Cleavamine (I) was initially obtained by the Lilly group in their investigations on Vinca alkaloids,[2,3] while a further study in our laboratory on the acid-catalyzed reactions of catharanthine allowed the isolation of two dihydrocleavamine derivatives in addition to cleavamine.[4] None of the products possessing the cleavamine skeleton still retained the ester function and were, therefore, of little interest to our immediate requirement.

The reaction of catharanthine with zinc in acetic acid on the other hand was shown to yield a carbomethoxydihydrocleavamine,[3,5] and it became of immediate importance to our investigations. It was necessary for us to study this reaction in more detail in the hope that other carbomethoxydihydrocleavamine or carbomethoxycleavamine derivatives could be isolated.

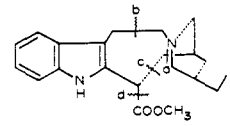
In our hands, catharanthine, on reaction with zinc dust in refluxing glacial acetic acid, provided a complex mixture from which four compounds (representing approximately 40% of the crude reaction mixture) could be isolated and characterized. The major component (isomer C),[6] mp 172°, was identical with the previously reported carbomethoxydihydrocleavamine[3,5,7] while the other three compounds required characterization.

Isomer A, mp 144–147°, appeared to be another carbomethoxydihydrocleavamine derivative when elemental analysis and mass spectrometry established the molecular formula, $C_{21}H_{28}N_2O_2$. The molecular ion (*m/e* 340) was accompanied by fragments which were immediately reminiscent of the quebrachamine and cleavamine fragmentation process[3] (Figure 1). Thus, the fragment at *m/e* 215 may arise from cleavage at a and b as shown in II, while loss of the ester group (d) from the latter would generate the species at *m/e* 156.



I, R = H

IX, R = $COOCH_3$



II

(1) Part I. J. P. Kutney, E. Piers, and R. T. Brown, *J. Amer. Chem. Soc.*, 92, 1700 (1970).

(2) N. Neuss, M. Gorman, H. E. Boaz, and N. J. Cone, *ibid.*, 84, 1509 (1962).

(3) M. Gorman, N. Neuss, and N. J. Cone, *ibid.*, 87, 93 (1965).

(4) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, 43, 1545 (1965).

(5) N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Buchi, and R. E. Manning, *J. Amer. Chem. Soc.*, 86, 1440 (1964).

(6) For the sake of clarity, the compounds are designated A, B, C, D in order of increasing polarity on a silica gel chromatoplate.

(7) We are very grateful to Dr. M. Gorman, Lilly Research Laboratories, for an authentic sample of this compound.