Tetrahedron Letters No.11, pp. 637-642, 1965. Pergamon Press Ltd.
Printed in Great Britain.

# STEREOCHEMICAL STUDIES IN THE TRANSANNULAR CYCLIZATION SERIES. CONVERSION OF QUEBRACHAMINE TO ASPIDOSPERMIDINE AND THE ABSOLUTE CONFIGURATION OF 7-ETHYL-5-DESETHYLASPIDOSPERMIDINE

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(Received 18 January 1965)

In some of our recent work in the transannular cyclization series we were able to demonstrate that the cyclization of the appropriate iminium derivative of dihydrocleavamine can lead to alkaloids of the Aspidosperma, Iboga and Vinca types (1, 2, 3). It was not possible at that time to determine the stereochemistry of this conversion in the Aspidosperma series since direct correlation to the natural alkaloids could not be made. The stereochemical question is of utmost importance particularly since this reaction is of potential interest in the laboratory synthesis of various classes of alkaloids and it has been postulated as a possible biosynthetic pathway to Aspidosperma and Iboga bases (4). We wish to present some very recent results which provide conclusive chemical and X-ray evidence to show that this transannular cyclization process is completely stereospecific. Indeed the stereochemical course of the reaction is determined by the configuration at C-5 (see I and V)** and therefore by the appropriate choice of starting material it is possible to synthesize the two stereochemical series which are known to exist in the Aspidosperma alkaloids.

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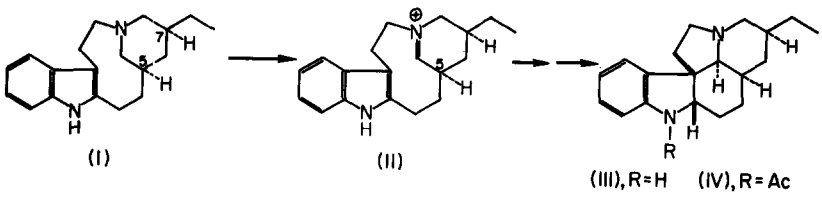
** The numbering system employed here is the one normally used for the Aspidosperma alkaloids.

The solution to the stereochemical aspects of this cyclization reaction was obtained from chemical and from X-ray studies. First of all it was of interest to consider the stereochemistry of the cyclization product (III) previously obtained (1) from the iminium derivative, II, prepared from dihydrocleavamine (I).*** In this instance the allylic nature of the hydrogen atom at C-5 might permit a possible alteration in configuration at this center prior to cyclization. Since the absolute configuration of this position in I is known from our previous X-ray work on cleavamine (5), the X-ray method was the obvious approach to the solution of this problem. Consequently the N-acetate derivative, IV, was converted to its $N_b$-methiodide, m.p. 281-282° (dec) and subjected to X-ray analysis.




It was found that the crystals of this derivative are orthorhombic, $\underline{a}$ = 9.32, $\underline{b}$ = 11.28, $\underline{c}$ = 19.70 Å, $\underline{Z}$ = 4 and the space group is $\underline{P2_12_12_1}$. The intensities of about 1350 reflexions were measured with a scintillation counter and Mo$\underline{K}\alpha$ radiation, and the structure was determined by heavy-atom

*** The stereochemistry at C-7 in I, which is obtained from the catalytic reduction of cleavamine, is now known from the X-ray work in our laboratory.

Patterson and Fourier methods. The positional and anisotropic thermal parameters were refined by least squares with the final discrepancy factor being 0.066. Finally the absolute configuration was determined by the anomalous dispersion method (6), using CuK$\alpha$ radiation. There are many large, and easily detectable, differences between $F(hkl)$ and $F(\overline{hkl})$, and these unambiguously indicated the absolute configuration. The results of the X-ray analysis show that the compound under investigation was $N_a$-acetyl-7-ethyl-5-desethylaspidospermidine $N_b$-methiodide thereby confirming the previously postulated structure (1) and establishing the absolute configuration of the cyclization product as shown in III. This product can now be termed as 7-ethyl-5-desethylaspidospermidine. Some additional details of the structure of the $N_a$-acetyl $N_b$-methiodide are illustrated in Fig. 1: the N-Me group is $\alpha$; the non-planarity of each five-membered ring, the chair conformation of ring C, and the boat conformation of ring D are evident.

The structure and relative configuration of the Aspidosperma skeleton was first established conclusively by Mills and Nyburg in their X-ray analysis of (-)-aspidospermine $N_b$-methiodide (7). Our own work provides the first instance in which the X-ray method has been used to determine the absolute configuration of an Aspidosperma system.

It was now clear that the above cyclization reaction proceeds in such a manner as to retain the absolute configuration at C-5.

On the other hand the obvious extension of the transannular cyclization reaction to the quebrachamine series, as previously mentioned (1), should provide an entry into the natural Aspidosperma alkaloids and thereby conclusive chemical evidence for the stereochemistry of this reaction. For this purpose, (-)-quebrachamine (V)**** was reacted with mercuric acetate

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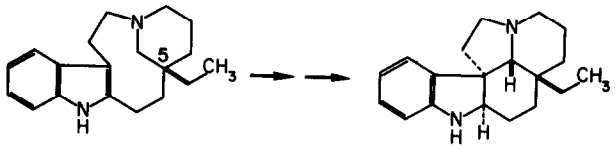
**** We are very grateful to Dr. George F. Smith, Manchester University, for providing us with this sample.

in glacial acetic acid at room temperature (36 hrs, in a nitrogen atmosphere)



(V) (VI)

followed by reflux (6 hrs) to provide a crude mixture ($\lambda_{max}^{MeOH}$ 223, 273, 280, 290 mμ ; $\lambda_{min}$ 255 mμ ) which was not purified further but immediately reduced with lithium aluminum hydride. The latter mixture on purification by preparative thin-layer chromatography (silica gel $GF_{254}$, ethyl acetate-ethanol (10:7)) followed by recrystallization from acetone provided an analytically pure product (25% overall yield from quebrachamine), m. p. 119.5 - 121°, $[\alpha]_D^{23}$ + 21° (EtOH). This material was shown to be identical in every respect with (+)-aspidospermidine (VI).***** The absolute configuration of this latter alkaloid has been suggested by Schmid (8) to be as shown in VI.

The above results establish that this cyclization reaction is stereospecific and its stereochemical course is completely determined by the asymmetry at C-5. It is attractive that one is able to generate from an intermediate possessing only one asymmetric center, both stereochemical

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

series known in the natural Aspidosperma alkaloids. For example, it is now obvious that (+)-quebrachamine, the known optical antipode of V (9) would yield (-)-aspidospermidine, the optical antipode of VI.

We wish to mention that very recently Schmid and coworkers have obtained (+)-1,2-dehydroaspidospermidine from (-)-quebrachamine in a closely related reaction (10).

Although the significance of this reaction in Nature still remains an open question, its potential for laboratory syntheses of a considerable variety of indole and dihydroindole alkaloids is now clear. We hope to present some results in this direction in the near future.

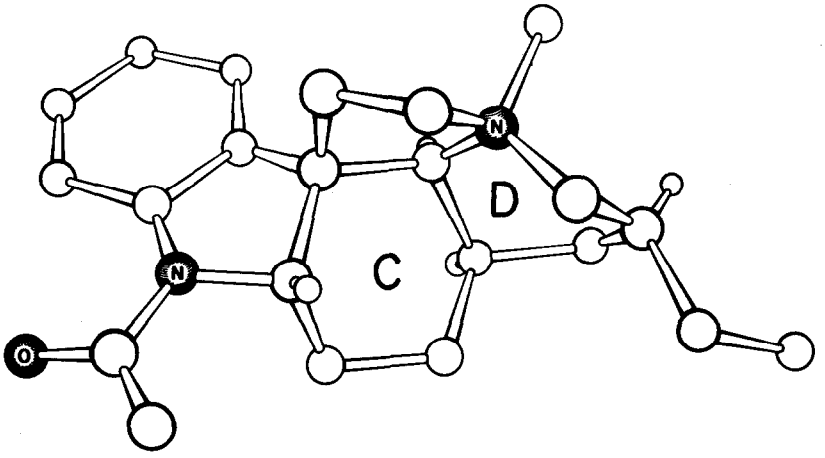


FIG. I

Acknowledgements. We gratefully acknowledge the financial support from the National Cancer Institute of Canada and the National Research Council of Canada. Two of us (A.C. and N.C.) are also indebted to the Council for Research Studentships. We also wish to thank the Staff of the U. B. C. Computing Center for assistance.

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