760. *The Isolation of* (±)- *and* (+)-*Vincadifformine and of* (+)-1,2-*Dehydroaspidospermidine from* Rhazya stricta.

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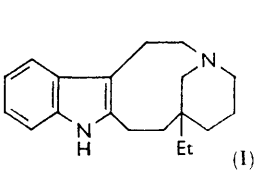
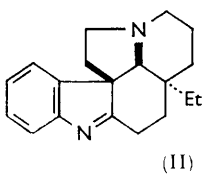
The isolation of the bases named in the title is described. (+)-1,2-Dehydroaspidospermidine (II) is reduced to (−)-quebrachamine (I) and to (+)-aspidospermidine (IV). The relative and absolute stereochemistries of the latter are the same as in (−)-aspidospermine.

The alkaloid content of the leaves and roots of *Rhazya stricta* was first investigated by Chatterjee *et al.*,[1] who reported the isolation of (−)-quebrachamine (0·06%) and of a base, $C_{21}H_{24}N_2O_3$ (0·015%), which they named rhazine and has since been shown to be akuammidine.[2] More recently, by vapour-phase chromatography combined with mass spectrometry, Biemann and his collaborators[3] detected quebrachamine, 1,2-dehydroaspidospermidine, aspidospermidine, eburnamonine, and eburnamenine in the less polar basic fraction.

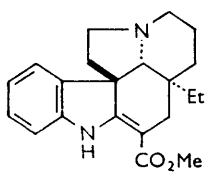
In our hands, chromatography of the petroleum-soluble leaf alkaloids has so far yielded three homogeneous bases: (−)-quebrachamine (I) in 0·045% yield, (+)-1,2-dehydroaspidospermidine (II) as a viscous colourless liquid (0·21%), and a mixture of (±)- and



(I)



(II)

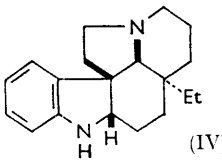


(III)

(+)-vincadifformine[4] (dihydrotabersonine[5]) (III) (0·006%) as a colourless resin, from which some of the racemate crystallised on seeding. Dr. Le Men has informed us that his school

[1] Chatterjee, Ghosal, Adityachaudhury, and Ghosal, *Chem. and Ind.*, 1961, 1034; Chatterjee, Ghosal, and Adityachaudhury, *ibid.*, 1962, 266.
[2] Silvers and Tulinsky, *Tetrahedron Letters*, 1962, 339.
[3] Schnoes, Burlingame, and Biemann, *Tetrahedron Letters*, 1962, 993.
[4] Djerassi, Budzikiewicz, Wilson, Gosset, Le Men, and Janot, *Tetrahedron Letters*, 1962, 235.
[5] Plat, Le Men, Janot, Wilson, Budzikiewicz, Durham, Nakagawa, and Djerassi, *Tetrahedron Letters*, 1962, 271.

has isolated a similar mixture of (±)- and (+)-vincadifformine from *Vinca difformis* and that he too has so far failed to crystallise the (+)-base.



(IV)

The most abundant alkaloid, (+)-1,2-dehydroaspidospermidine, has an ultraviolet spectrum corresponding to that expected of a 3*H*-indole, and the infrared spectrum likewise shows the characteristic Ph·N=C stretching frequency at 1579 cm.$^{-1}$. Lithium aluminium hydride in ether reduces it in good yield to (+)-aspidospermidine (IV) and sodium borohydride in methanol reduces it to a mixture of (+)-aspidospermidine and (−)-quebrachamine.

1,2-Dehydroaspidospermidine and aspidospermidine were first detected by Biemann *et al.*[6] in *Aspidosperma quebracho blanco* bark by their extraordinarily powerful combination of vapour-phase chromatography and mass spectrometry. They isolated enough dehydroaspidospermidine to convert it into aspidospermidine, but were unable to measure the specific rotations. Dr. Biemann has kindly shown the mass spectra of our specimens to be identical with his.

More recently Djerassi, Janot, and their colleagues[4] reported the structure of vincadifformine, a racemic alkaloid, to be (III), and found that (−)-6,7-dihydrotabersonine was (−)-vincadifformine.[5] Hydrolysis and decarboxylation of these two bases gave (±)- and (−)-dehydroaspidospermidine, respectively, reduction of which with sodium borohydride gave (±)- and (+)-quebrachamine, respectively.[4,5]

The proton resonance spectrum of (+)-aspidospermidine is almost identical with that of deacetylaspidospermine, except for the benzene proton region and the methoxyl peak in the latter. This supports very strongly the identity of the relative stereochemistries of these two molecules and allows us to suggest the relative stereochemistry shown in (IV) for (+)-aspidospermidine and in (II) for (+)-1,2-dehydroaspidospermidine. Further, the formation of (−)-quebrachamine from the latter base shows it, and therefore (+)-aspidospermidine, to have the same absolute stereochemistry as (−)-aspidospermine.[7]

Djerassi *et al.*,[5] on the basis of a shift to high field in the absorption in the methylene region of some products of reduction of vincadifformine and tabersonine by lithium aluminium hydride, suggest the modified, more strained stereochemistry for vincadifformine shown in structure (III). A similar phenomenon is observable in the proton resonance spectrum of 1,2-dehydroaspidospermidine (II), which we have shown by conversion into aspidospermidine (IV) to have the normal, less strained stereochemistry of aspidospermine: the integration between 9·2 and 9·8 τ corresponds to 5 protons, and the curve is quite different in appearance from that of the corresponding region for aspidospermidine and deacetylaspidospermine, which in each case contains only the 3 protons of the *C*-methyl group as a very distorted triplet.

(The structural formulæ in this paper do not represent the absolute configurations.)

Experimental

Isolation of (+)-1,2-Dehydroaspidospermidine and Vincadifformine.—Dried powdered leaves of *Rhazya stricta* (200 g.) were extracted (Soxhlet) for 12 hr. with ethyl acetate. The extract was shaken with dilute hydrochloric acid (3 × 100 c.c.), and the aqueous phase was washed with ethyl acetate, basified with sodium carbonate, and extracted with ethyl acetate (3 × 100 c.c.). The dried extracts yielded the total bases (11·2 g., 5·7%). A solution of these bases in ethyl acetate (10 c.c.) was added dropwise with stirring to benzene (200 c.c.). The precipitate was filtered off, and the filtrate concentrated to 20 c.c. and added dropwise with stirring to light petroleum (b. p. 60—80°; 500 c.c.). The solution was filtered, concentrated to about 10 c.c., and treated with light petroleum (b. p. 60—80°; 100 c.c.). The pale yellow solution was decanted from a small quantity of insoluble material and the solvent removed *in vacuo*, yielding a pale brownish-yellow gum (3·4 g.). This was chromatographed on alumina

[6] Biemann, Spiteller, and Spiteller-Friedmann, *Tetrahedron Letters*, 1961, 484.
[7] Biemann and Spiteller, *Tetrahedron Letters*, 1961, 299.

(grade H; 200 g.). Benzene eluted (−)-quebrachamine, m. p. and mixed m. p. 147—149°, $[\alpha]_D^{18}$ −108° in EtOH (0·090 g., 0·045%). This was followed by a mixture of (±)- and (+)-vincadifformine as a colourless syrup, $[\alpha]_D^{20}$ +402° (in EtOH) (0·012 g., 0·006%), the infrared spectrum of which was identical with that of authentic (±)-vincadifformine supplied by Dr. Le Men. The specific rotation of this mixture was low: (−)-vincadifformine has $[\alpha]_D$ −540° in EtOH.[5] Seeding of this fraction (62 mg.) with (±)-vincadifformine resulted in crystallisation: filtration and one washing with ethanol at 0° yielded (±)-vincadifformine, m. p. 120—126° (4 mg.), undepressed on admixture with authentic material. The specific rotation, $[\alpha]_D^{20}$ +34°, shows it to be contaminated with a small amount of the (+)-isomer.

Elution of the column was continued with ether, which yielded essentially pure 1,2-dehydroaspidospermidine (0·420 g., 0·21%). Short-path distillation at 0·01 mm. (bath-temp. 150°) yielded a colourless syrup which showed a great tendency to autoxidise (C, 81·35; H, 8·6. $C_{19}H_{24}N_2$ requires C, 81·4; H, 8·6%) and had $\lambda_{max.}$ 263, 222 mμ (ε 7050, 31,500 in EtOH, $\nu_{max.}$ 1579 $cm.^{-1}$ (C=N str) (liquid film), and $[\alpha]_D^{20}$ +243° (in EtOH).

Aspidospermidine.—A solution of 1,2-dehydroaspidospermidine (2·04 g.) in ether (80 c.c.) was added to one of lithium aluminium hydride (1 g.) in ether (100 c.c.), and the mixture was refluxed for 10 min. The basic ether-soluble product (1·90 g.) was crystallised three times from methanol, to give *aspidospermidine* as rectangular plates, m. p. 120—121° (1·24 g.) (C, 80·6; H, 9·35. $C_{19}H_{26}N_2$ requires C, 80·85; H, 9·2%), $\lambda_{max.}$ 297, 245 mμ (ε 2980, 6650), $[\alpha]_D^{20}$ +17° (in EtOH).

Reduction of (+)-1,2-Dehydroaspidospermidine by Potassium Borohydride.—A solution of 1,2-dehydroaspidospermidine (0·282 g.) in ethanol (50 c.c.) was treated with potassium borohydride (0·5 g.), and refluxed for 30 min. The ether-soluble basic product was chromatographed on alumina (grade H). Benzene eluted (−)-quebrachamine, m. p. and mixed m. p. 141—143°, $[\alpha]_D^{20}$ −108° (in EtOH) (0·210 g., 74%). The latter fractions were partially crystalline and showed an indoline type of ultraviolet absorption. Recrystallisation of the crystalline material from methanol yielded aspidospermidine, m. p. and mixed m. p. 118—120° (17 mg.).

We thank Dr. W. I. Taylor for a specimen of (−)-quebrachamine, Dr. J. Le Men for seed crystals and the infrared spectrum of (±)-vincadifformine, Dr. Z. U. Abideen for *Rhazya stricta* leaves, and the Pakistan C.S.I.R. for a grant (to M. A. W.).

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