Total Synthesis of *Hunteria* and *Aspidosperma* Alkaloids from a Common Intermediate

By J. E. D. BARTON and JOHN HARLEY-MASON
(*University Chemical Laboratory, Cambridge*)

ATTENTION has previously[1] been drawn to the fact that the "non-tryptophan" moieties of the *Hunteria* and *Aspidosperma* alkaloids are identical, though the mode of linkage in the two groups is very different. We have now constructed an equivalent (II) of such a "non-tryptophan" moiety and have used it to devise an extremely simple synthesis of both groups of alkaloids. Alkylation of the pyrrolidine enamine of methyl 4-formylhexanoate[2] (I) with allyl bromide gave methyl 4-ethyl-4-formylhept-6-enoate (II), b.p. 92—96°/0·2 mm., which with tryptamine readily gave the tetracyclic lactam (III) (75%), m.p. 220—221° [ν_{max} 3280 (NH), 1640 (C=C), and 1615 cm.$^{-1}$ (C=O)]. With osmium tetroxide (III) gave the diol (IV), m.p. 245—246° [ν_{max} 3400, 3280, and 3120 (OH and NH), and 1615 cm.$^{-1}$ (C=O)], which with sodium metaperiodate gave (±)-eburnamine *N*(*b*)-lactam (Va), m.p. 210—211° [ν_{max} 3275 (OH) and 1620 cm.$^{-1}$ (C=O)], spontaneous ring closure of the intermediate aldehyde having occurred. Lithium aluminium hydride reduction of (Va) yielded (±)-eburnamine,[3] (Vb). The mass spectrum of (Vb) was identical with that of eburnamenine,[4,5] due to the rapid dehydration prior to ionisation of eburnamine.

On the other hand, treatment of (III) with boron trifluoride–etherate at 100—110° gave an isomeric material (60%), m.p. 155—156° [ν_{max} 1665 (C=O), 1607 (aromatic), and 1578 cm.$^{-1}$ (C=N], whose ultraviolet spectrum (λ_{max} 217 and 265 mμ; ϵ_{max} 23,200 and 5180) was characteristic of an indolenine. The n.m.r. spectrum of this compound showed no olefinic protons, and that it was the pentacyclic indolenine-lactam (VI) was shown as follows. Lithium aluminium hydride reduction gave a product (glass), sublimed at 100°/10^{-2} mm., [ν_{max} 3370 (NH) and 1605 cm.$^{-1}$ (aromatic); λ_{max} 245 and 297 mμ, ϵ_{max} 6800 and 2990 (an indoline] whose mass spectrum had the following major features: *m/e* 296 (molecular ion) (33%), 281 (1·5%), 267 (3%), 254 (10%), 166 (4%), 144 (5%), 130 (4%,) and 124 (100%; base peak), which are characteristic of the aspidospermine skeleton,[6] and the product was therefore (±)-3-methylaspidospermidine (vincadifformane) (VIIa). This has been reported[7] as one of the reduction products of minovincinine tosylate, and the quoted mass spectrum agrees with that above.

Catalytic hydrogenation of (VI) over platinum in 30% acetic acid, when 1 mole of hydrogen was taken up, gave (±)-3-methyl-8-oxo-aspidospermidine (VIIb), m.p. 187—188° [ν_{max} 3300 (NH) and 1615 cm.$^{-1}$ (C=O); λ_{max} 247 and 298 mμ, ϵ_{max} 6700 and 3070]. Reduction of (VI) with potassium borohydride also gave (VIIb).

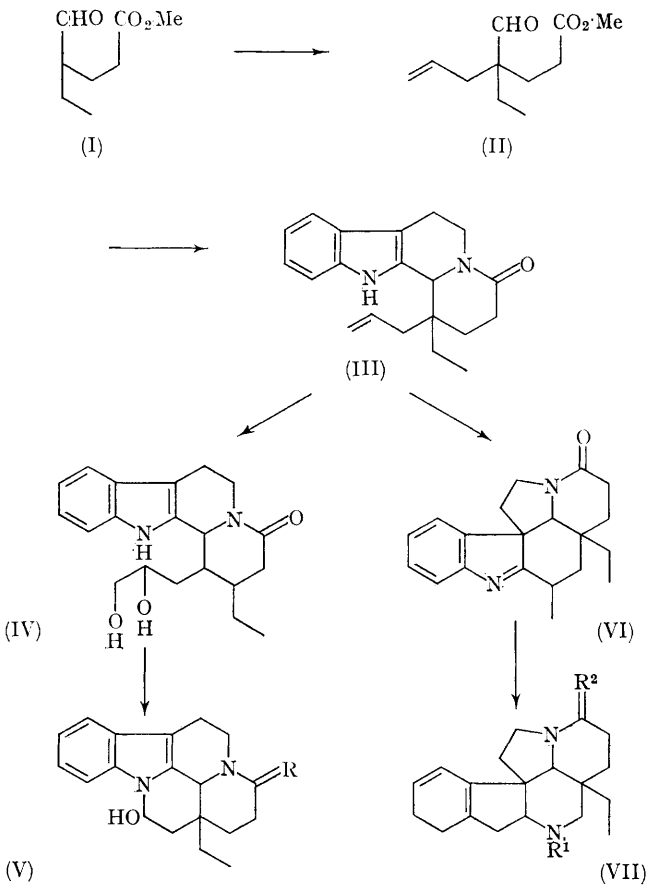
Acetylation of (VIIa), followed by sublimation at 120°/10^{-2} mm. gave (±)-1-acetyl-3-methylaspidospermidine (VIIc) [λ_{max} 253 and 282 mμ, ϵ_{max} 13,200 and 3780] as a glass, characterised as its methiodide, m.p. 262—264°, methopicrate, m.p. 239—240° (decomp.), picrate, m.p. 235—236°

[1] E. Schlittler and W. I. Taylor, *Experientia*, 1960, **16**, 244.
[2] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 1963, **85**, 207.
[3] M. F. Bartlett and W. I. Taylor, *J. Amer. Chem. Soc.*, 1960, **82**, 5941.
[4] M. Plat, D. D. Manh, J. Le Men, M-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. chim. France*, 1962, 1082.
[5] H. K. Schnoes, A. L. Burlingame, and K. Biemann, *Tetrahedron Letters*, 1962, 993.
[6] K. Biemann, M. Spiteller-Friedmann, and G. Spiteller, *J. Amer. Chem. Soc.*, 1963, **85**, 631.
[7] M. Plat, J. Le Men, M-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. chim. France*, 1962, 2237.

(decomp.), and perchlorate, m.p. 286—287° (decomp.).

The n.m.r. spectra of (VIIa) and (VIIc) had the aspidospermine "fingerprint" pattern in the region of τ 6·7—7·1 as described by Djerassi *et al.*[8] The n.m.r. spectrum of (VIIc) also showed the characteristic simplification[9] of the aromatic region associated with the change from (VIIa) to (VIIc).

It would be expected that two stereoisomeric forms of the tetracyclic lactam (III) would be obtained.[10] However, our product appeared to be entirely homogeneous (paper and thin-layer chromatography) and, moreover, the lithium aluminium hydride reduction product [(III): $>CH_2$ for $>C=O$] gave only one peak on gas chromatography. What is more remarkable, we were unable to obtain any evidence of inhomogeneity of the rearrangement product (VI) or of its reduction products (VIIa, b, c), so that the change (III) → (VI) appears to be entirely stereospecific. It is hoped to establish the actual stereochemistry of the methiodide of (VIIc) by *X*-ray analysis.



(*Received, March* 31*st*, 1965.)

[8] C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, J. N. Shoolery, and L. F. Johnson, *Experientia*, 1960, **16**, 532.

[9] *Cf.* M. E. Kuehne, *J. Amer. Chem. Soc.*, 1964, **86**, 2946.