Biogenetically Patterned Stereoselective Total Synthesis of the Indole Alkaloid Roxburghine D

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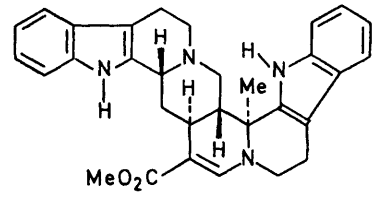
Summary Condensation of tryptamine with an indoloquinolizidine precursor gives a keto-amide which cyclises stereoselectively to yield the octacyclic ring structure of the Roxburghines.

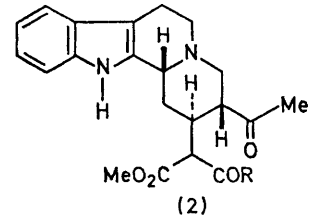
ROXBURGHINE D is the main alkaloid of a group of five, isolated from the leaves and stems of *Uncaria Gambier* Roxb. by Merlini and his co-workers.[1] The biogenetically interesting structure and configuration (**1**) was elucidated mainly by n.m.r. spectra, using extensive decoupling experiments, by mass spectroscopy, and finally by biogenetic considerations.[1] As roxburghine D obviously is derived from two tryptophane units and one loganin-derived C_{10}-unit Merlini proposed that an oxo-derivative of Geissoschizine (**2a**) was the biogenetic precursor which by condensation with another tryptamine unit and subsequent cyclisation is transformed into this new octacyclic indole alkaloid.

Cyclisations of this type have been reported already and have been shown to proceed stereoselectively.[2] As cyclisation products proved to be identical with products of attack of Grignard reagents on the corresponding imonium salt, a *trans*-quinolizidine junction with an α-axial methyl group as shown for Roxburghine D (**1**) is indicated for this cyclisation.

Addition of methyl t-butyl malonate to the unsaturated ketone (**3**)[3] gave (**2b**) as the single product under thermodynamic control.[3] After cleavage with trifluoroacetic acid

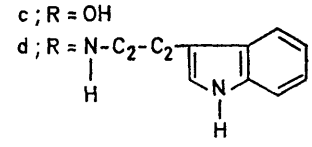


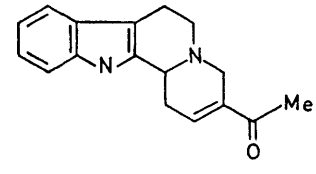
(1)



(2)

a ; R = H
b ; R = $OCMe_3$
c ; R = OH
d ; R = N-C_2-C_2

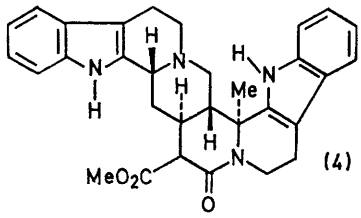




(3)

at room temperature, acid (**2c**) was smoothly transformed into the amide (**2d**) by treatment with tryptamine and dicyclohexylcarbodi-imide.

Treatment of this compound with acid yielded lactam (**4**)† stereoselectively.



(4)

Partial reduction of (**4**) with di-isobutyl aluminium hydride in glyme at −70° yielded roxburghine D together with a second product whose structure is not yet known. The synthetic material was identical (u.v. and i.r. spectra, t.l.c.) with a natural sample, supporting the configurational assignment and the proposed biogenetic scheme for the roxburghines.[1]

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† All compounds were characterised by i.r., u.v., n.m.r., and mass spectra, and gave satisfactory C, H, and N analyses.

[1] L. Merlini, R. Mondelli, G. Nasini, and M. Hesse, *Tetrahedron*, 1970, **26**, 2259.
[2] E. Winterfeldt, *Chem. Ber.*, 1964, **97**, 2463.
[3] E. Winterfeldt, H. Radunz, and T. Korth, *Chem. Ber.*, 1968, **101**, 3172.