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KASHMIRINE, A NEW STEROIDAL ALKALOID FROM FRITILLARIA ROYLEI, HOOK (LILIACEAE)

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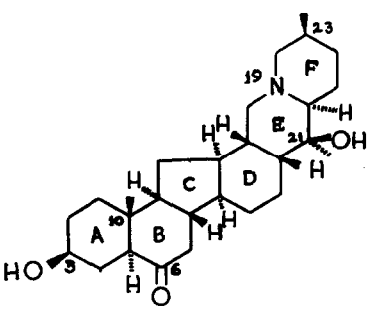
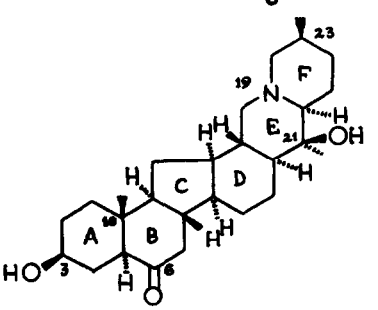
The basic fractions of the alcoholic extract of the bulbs of Fritillaria roylei, Hook afforded a C-nor D-homo steroidal alkaloid, kashmirine (I) $C_{27}H_{43}O_3N$ (M^+ 429.32429), m.p. 262-65° $[\alpha]_D$ -40.4° ($CHCl_3$). The IR spectrum shows diagnostic peaks at 3485 cm^{-1} (hydroxyl) and 1690 cm^{-1} (six-membered ketone) with a weak but distinct absorption at 2760 cm^{-1} (trans-quinolisidine system). Kashmirine is a dihydroxy base, one of the hydroxyls being tertiary and the other secondary - as evidenced from its acetylation, Jones oxidation experiments and also from the PMR spectra of the compound and its acetyl derivative.

The PMR spectrum of (I) (values in δ) reveals the presence of two tertiary methyls appearing as 3H-singlets at 0.74, 1.05 and one secondary methyl group (doublet at 1.07, J=7.0 Hz). The upfield signal at 0.74 is assigned to the methyl group situated at A/B ring juncture experiencing a diamagnetic shielding caused by the C_6-carbonyl group. This angular methyl shows downfield shifts both in the oxidation product (at 0.95) and in the reduction product (at 1.00) of kashmirine. This behaviour is typical of steroids bearing oxygen functionalities at the C_3 and C_6 positions[1]. Kashmirine and its oxidation product furnished the same triol when reduced with $NaBH_4$. Mass fragmentation pattern indicates that (I) is a C-nor D-homo-steroidal alkaloid having the verticinone (II) skeleton[2], the characteristic ion fragments being discernible at m/e 429 (M^+), 414 (M-15), 412 (M-17), 386 (M-43), 112 (base peak).

(II), $C_{27}H_{43}O_3N$ (M^+ 429), m.p. 212° was previously isolated from the same plant[3] and its structure and stereochemistry have been established by X-ray crystallography[4]. Correlation studies revealed that kashmirine and verticinone have the same gross structure but differ in steric configuration. The nature of their CD curves is similar, the essential difference being observed in the magnitude of their respective molecular ellipticity values at different wavelengths. This observation settles the placement of the ketocarbonyl at C_6 in (I)[5].



(I)



(II)

The structure of kashmirine has been established by X-ray analysis. A crystal (0.1x0.1x0.2 mm) was chosen and intensities were collected on an automatic four circle diffractometer Phillips PW 1100, with Cu-K_α radiation selected by a graphite monochromator. 1199 reflections above background (2σ) were measured. The system is monoclinic, space group $P2_1$ with a= 6.611, b= 12.388, c= 14.515 Å, β = 90.8° and Z= 2. The structure was solved by application of the phase function[6] and symbolic addition[7]. The different combinations of the numerical values of symbols were used in the tangent refinement procedure[8]. Two distorted rings appear on the E map corresponding to the second maximum of the phase function. The rest of the molecule was obtained by a recycling procedure. Full matrix least squares refinement with anisotropic thermal parameters led to a final conventional R of 6.7% (all non-methyl hydrogen atoms were located on a difference synthesis but their positions not refined). The molecule is illustrated in Fig.I.

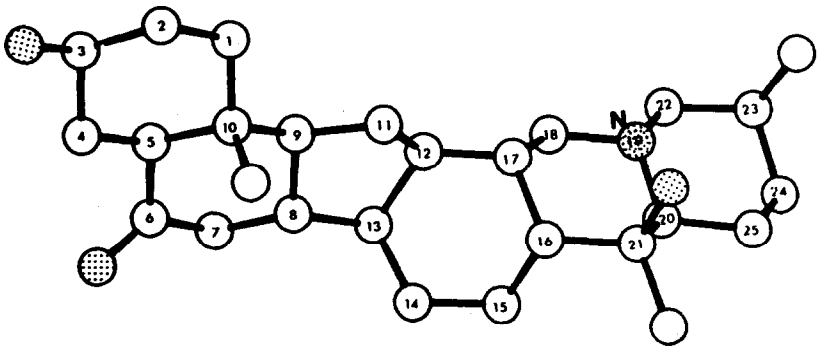


Fig.I

The skeleton is the same as verticinone. The stereochemistry of the ring juncture is: A/B trans, B/C trans, C/D cis, D/E cis and E/F trans. The configurations at the other chiral centres have been settled as C_3-OH equatorial, C_{10}-Me axial, C_{21}-OH axial, C_{23}-Me axial, lone pair on nitrogen axial and all these groups are in the β-orientation. Obviously kashmirine differs from verticinone in the stereochemistry of the D/E ring juncture. This steric feature is hitherto unknown in C-nor D-homo steroidal alkaloids. Examination of a Dreiding model of (I) shows that the rings A, B, E and F are in the chair conformation. The five-membered ring C turns to an envelope with ring D as a half-chair. The model also reveals that the skeleton is twisted strongly at the C-ring level so that axial C_{21}-OH and C_{23}-Me appear in the direction opposite to C_{10}-Me.

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