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THE STRUCTURE OF ISOMITRAJAVINE

E. J. SHELLARD and K. SARPONG

Pharmacognosy Research Laboratories, Department of Pharmacy, Chelsea College, University of London, Manresa Road, London, S.W.3.

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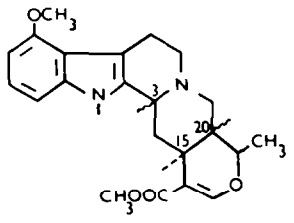
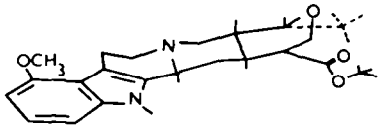
Abstract—The *pseudo* indole alkaloid, mitrajavine has been epimerised to a new compound named isomitrajavine (*normal*), the structure of which is discussed. The mass spectra of mitrajavine, isomitrajavine and some other closed E ring alkaloids are considered in relation to their open E ring analogues.

MITRAJAVINE, a closed E ring *pseudo* indole alkaloid (I, C3-Hβ, C20-Hβ) isolated from the leaves of *Mitragyna javanica* Koord and Valeton,[1] has been epimerised to a new compound named isomitrajavine by oxidation with mercuric acetate followed by reduction of the 3,4-dihydroacetate with zinc and hydrochloric acid.[2, 3] Structure II is proposed for isomitrajavine (*normal* configuration).



I.



II.

The UV spectrum of isomitrajavine (λ_{max} 227 nm, log ε = 4·59; 292 nm log ε = 3·87); λ_{min} 288 nm, log ε = 380) is similar to that of mitrajavine.

The IR spectrum (KCl disc) shows bands at 3530, 1670 and 1615 cm^{-1} indicating an imino, a carbonyl and a double bond respectively. Bohlmann bands are present at 2832, 2802 and 2762 cm^{-1} in addition to the major CH absorption band at 2940 cm^{-1} and suggest that at least two hydrogens are *trans* diaxial to the N_4 lone pair.[2, 4] Hence the compound must differ from mitrajavine at C3 and must have a C3Hα configuration since mitrajavine has a C3Hβ configuration.

The NMR spectrum shows a three-proton doublet at 1·16 ppm indicating a CH_3 group adjacent to —CH group and proving that the E ring is closed as in mitrajavine. It has been shown that ajmalicine (*normal*) and 3-isoajmalicine (*pseudo*) both with

trans D/E ring junction give the C19-CH_3 doublet at 1·16 ppm and 1·19 ppm respectively,[5] while C19-CH_3 the *cis* D/E compounds tetrahydroalstonine (*allo*) and rauniticine (*epiallo*), show this doublet at lower field, 1·38 ppm and 1·42 ppm.[6] Isomitrajavine shows the C19-CH_3 doublet at 1·16 ppm and has therefore a *trans* D/E ring junction and would be of the *normal* configuration, the corresponding *pseudo* isomer, mitrajavine showing the doublet at 0·89 ppm. The C19-H signal occurs at 4·5 ppm and indicates no change in its β-orientation.[5, 6]

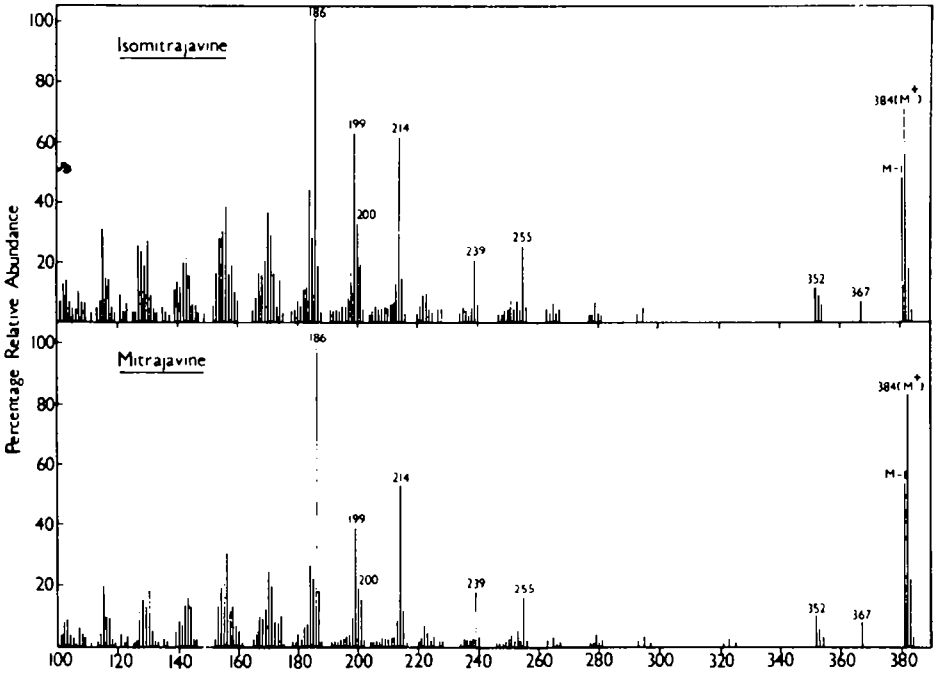


FIG 1. Mass spectra of isomitravine and mitrajavine.

A one-proton singlet for the olefinic proton is shown at 7·58 ppm, and the imino proton at 8·05 ppm. Two three-proton singlets at 3·77 ppm and 3·81 ppm indicate the presence of two MeOH groups. The aromatic region integrates for only three protons, suggesting that isomitrajavine has one substituent in the aromatic nucleus. The splitting pattern of the aromatic protons (1H, 6·50 ppm; 2H, 6·80–7·20 ppm) is similar to that of mitragynine[7] which possesses a C9-OMe.

The mass spectrum of isomitrajavine (M^+ 382) (Fig. 1) shows prominent peaks at *m/e* 186, 199, 200 and 214 confirming the presence of the tetrahydro β-carboline skeleton with MeO substituent.[8, 9] Peaks at *m/e* 156, 169, 170, 239, 255, 352 (M-30, OCH_3), 367 (M-15, CH_3) are also noted.

A strong M-1 peak (*m/e* 381) is indicative of the yohimbine–heteroyohimbine-type alkaloids. The mass spectrum of isomitrajavine is very similar to that of ajmalicine[8] except for a shift of 30 mass units in the peaks belonging to the indole or the tetrahydro β-carboline unit, and hence indicates close similarity in the structure of the two alkaloids. A comparison of the mass spectrum of isomitrajavine with that of mitra-

javine (C3-Hβ) also shows striking similarity both exhibiting their base peaks at *m/e* 186. Some of the noteworthy differences are summarized in Table 1. Since the

TABLE 1.

m/e	% age relative abundance	
	Mitrajavine	Isomitrajavine
199	40	61·8
200	20·3	32·4
214	54	61
255	17	25

production of these peaks are related to the rupture of the C3-C14 double bond,[8] it is likely that the differences in the relative intensities of the peaks in the two isomers differing only in their C3-H orientation is a reflection of the stereochemistry at the C3 centre.

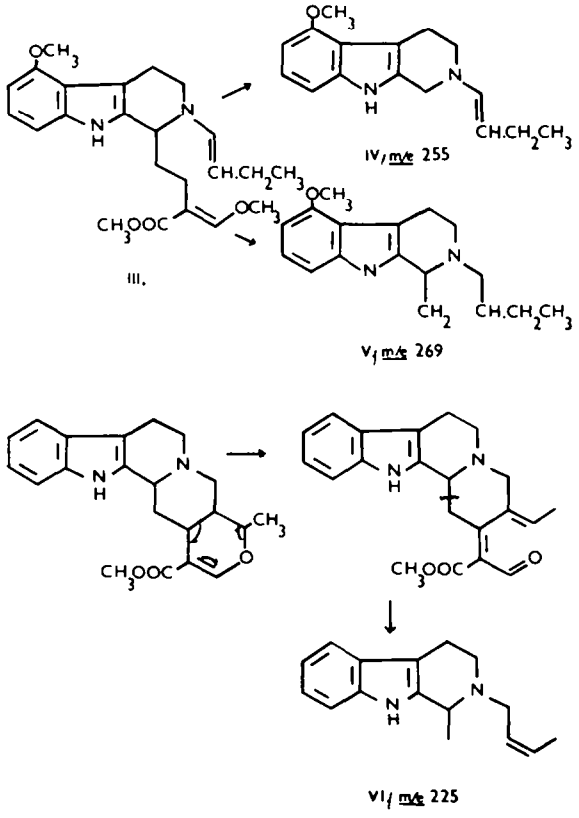


FIG 2.

As a result of studying the mass spectra of the E *seco* heteroyohimbine alkaloids it is suggested that the intermediate (III) formed by hydrogen transfer from C21 to C15

can fragment to give species (IV) at *m/e* 255 and 269.[10] A peak at *m/e* 255 is present in the mass spectra of mitrajavine and isomitrajavine but not that at *m/e* 269. The mass spectra of ajmalicine and related alkaloids show a peak at *m/e* 225[10] which has been assigned structure (VI), the corresponding peak for the mitrajavines occurring at *m/e* 255. Since this species is formed by a different mechanism from that proposed for the open E ring analogues,[10] it is likely that the peaks represent different species. The *m/e* 269 peak in the E *seco* compounds is not present in the mitrajavines and this could be used to differentiate between the E *seco* and E closed heteroyohimbine alkaloids. The peak at 239 is also significant since it corresponds to a peak at 209 in tetrahydroalstonine and ajmalicine but which is not present or is insignificant in the E *seco* series of alkaloids. This could be a further pointer towards distinguishing E *seco* from E closed heteroyohimbine alkaloids. (Fig. 2.)

EXPERIMENTAL

M.p. (uncorrected); Towson and Mercer m.p. apparatus; U.V. spectrum: Unicam S.P. 800 Spectrophotometer; IR spectrum; Unicam S.P. 100 (0·5% KCl disc); NMR spectrum: Varian A-60 using 10% W/V $CDCl_3$ solutions (TMS internal ref.): Mass spectra: A.E.I., M.S.902 high resolution mass spectrometer at 70 eV, inlet temperature 240°C. TLC was undertaken on several systems including (a) Alumina (Merck)/chloroform, (b) Silica gel G(Merck)/ether and (c) Silica gel G(Merck)/chloroform–acetone: 5:4.

Mitrajavine (500 mg) was dissolved in glacial AcOH (20 ml) containing mercuric acetate (1·8 g) and heated at 60–65°C for 36 hr. The precipitated mercurous acetate was filtered off, H_2S passed into the filtrate to remove excess mercuric ion and filtered. A portion of the filtrate was made alkaline with NH_3, extracted with $CHCl_3$ and examined by TLC. There was only one spot which remained on the starting line. Zinc dust (4 g) and H_2O (5 ml) were then added to the filtrate and stirred continuously for 48 hr at room temperature. After filtration, the filtrate was made alkaline with NH_3 and extracted with $CHCl_3$ (3 × 10 ml). The $CHCl_3$ extracts were washed, dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. TLC examination of the residue indicated the presence of two spots one corresponding to mitrajavine.

The residue (360 mg) was dissolved in $CHCl_3$ (2 ml) and streaked on to silica gel plates (1 mm thick, 40 cm × 20 cm) which were run in $CHCl_3$ acetone: (5:4). The appropriate zones were scraped off and extracted with $CHCl_3$–MeOH 1:1 (2 × 25 ml). The extracts were concentrated to dryness and redissolved in $CHCl_3$ (5 ml). Evaporation to dryness yielded mitrajavine (210 mg) and a new compound (65 mg) which crystallized from MeOH (fine colourless needles) and was subsequently characterized and named isomitrajavine.

Characterization of Isomitrajavine. The compound prepared from mitrajavine and named isomitrajavine was obtained as fine needles from MeOH, m.p. 194–195°. It is soluble in $CHCl_3$, MeOH and ether.

hRf values (a) 82–85, (b) 60–65), (c) 62–66. Details of the UV absorption spectrum, IR absorption spectrum, NMR spectrum and mass spectrum are given in the discussion.

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