

Alkaloids from *Mitragyna javanica*, Koord. and Valetton and *Mitragyna hirsuta*, Havil

SIR,—We have isolated a number of alkaloids from ethyl acetate extracts of the leaves of *Mitragyna javanica*, Koord. and Valetton and *Mitragyna hirsuta*, Havil. The chemical constitution of two and possibly three new alkaloids is now presented (Table 1).

The extracts of *Mitragyna javanica* yielded ajmalicine, mitraphylline, isomitraphylline, Pa 7 [which may be identical with vineridine (Kasymov, Yuldashev & Yunusov, 1965a,b)] and mitrajavine, together with a yellow alkaloid, m.p. 238–240°.*

The extracts of *Mitragyna hirsuta* yielded mitraphylline, isomitraphylline, rhynchophylline, isorhynchophylline and hirsutine.

Mitraphylline, isomitraphylline, rhynchophylline, isorhynchophylline and ajmalicine were identified by comparison of the m.p., mixed m.p., $[\alpha]_D$, Rf values (thin layer chromatography), ultraviolet and infrared spectra of the isolated and authentic samples of these alkaloids.

The data obtained indicate that Pa 7 is an oxindole alkaloid of a methoxy-mitraphylline type (I; R = OMe). The nmr spectrum of Pa 7 (Table 2) shows a splitting pattern of the aromatic protons (ca. 3.4 τ , 2H; ca. 2.9 τ , 1H) which is similar in chemical shift and integral to the aromatic splitting pattern (ca. 3.4 τ , 2H; ca. 2.8 τ , 1H) seen in the nmr spectrum of 6-methoxy-*N*-methyl oxindole but not in the nmr spectra of the 4,5 or 7-methoxy analogues. This indicates that the aromatic methoxy group of Pa 7 is in the 11 position of I. The 5–10 τ region of the nmr spectrum of Pa 7 differs from the corresponding region of specio-phylline (Beckett, Shellard, Phillipson & Lee, 1965) but shows similarities to that of mitraphylline and isomitraphylline, suggesting that the C/D/E ring junctions are the same in Pa 7, mitraphylline and isomitraphylline.

Since the isolation and characterisation of Pa 7, Kasymov & others (1965a,b) have reported the constitution of vineridine and vinerine as being of the 11-methoxy-mitraphylline type. The m.p. of Pa 7 is similar to that of vineridine (179–180°) and although the reported optical rotations differ, vineridine +22.7° (c, 2.32, pyridine), it is possible that these two alkaloids are identical.†

The alkaloids mitrajavine and hirsutine were shown to be indoles by colour tests, and by ultraviolet, infrared and nmr spectra. The physical data, along with elemental analysis and equivalent weight determinations indicate the structure of mitrajavine to be that of a methoxy-ajmalicine type (II; R = OMe) with a molecule of water of hydration indicated by a two-proton singlet in the nmr spectrum at about 7.2 τ which disappears upon deuteration. The closed E ring is indicated by the presence of a three-proton doublet for the C19-Me (9.10 τ)‡ and the C19-H one-proton multiplet at about 5.6 τ . A *cis* C₃H orientation is indicated by the absence of any *trans* CH bands (below 2800 cm⁻¹, KCl disc) in the infrared spectrum (Wenkert & Roychaudhuri, 1956; Bohlmann, 1957; Rosen, 1961) and the presence of a one-proton multiplet in the nmr spectrum at 5.55 τ (Wenkert, Wickberg & Leicht, 1961a,b; Uskokovic, Bruderer, Planta, Williams & Brossi, 1964). The aromatic splitting pattern of mitrajavine (3.47 τ , 1H; 2.91 τ , 2H) is similar to that of mitragynine (Beckett,

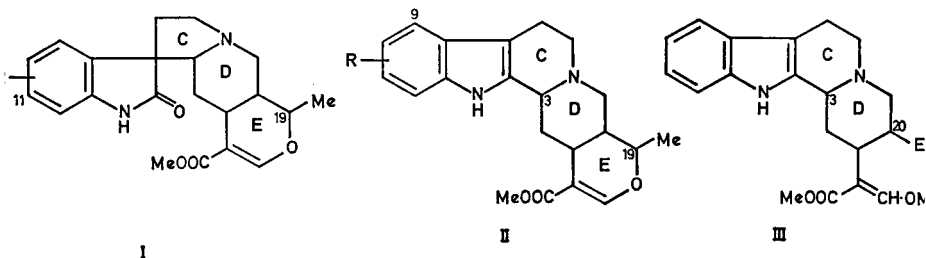
* Found: C, 73.3; H, 4.7; N, 10.7; OMe, 0%; *M*, 313 (by mass spectroscopy); λ_{\max} (abs. ethanol) 256, $\log \epsilon = 4.24$; 285, $\log \epsilon = 4.03$; 294, $\log \epsilon = 4.10$; 305, $\log \epsilon = 4.15$; 380, $\log \epsilon = 4.51$; 398, $\log \epsilon = 4.62$. ν (KCl), 3450, 3280, 1642, 1605 cm⁻¹, base HClO₄, m.p., 254°. Found: C, 55.4; H, 4.1; N, 9.7%.

† Work is in progress to determine the identity or non-identity of the two alkaloids.

‡ This upfield position suggests that the methyl group is shielded by the indole ring.

Shellard & Tackie, 1965) (3.52 τ , 1H; 3.08 τ , 2H) showing that the aromatic methoxy group (6.10 τ) is in the 9 position of II. This evidence indicates that mitrajavine is a 9-OMe compound of the ajmalicine type (II, R = 9-OMe) with the C₃H *cis* to the nitrogen lone pair.

The physical data, along with elemental analysis and equivalent weight determinations indicate the structure of hirsutine to be of the corynanthei dine-type (III). The methyl of the ethyl group is indicated by the three-proton triplet at 9.21 τ in the nmr spectrum. The ester and methoxy groups appear at 6.29 and

TABLE 1. PROPERTIES AND SPECTRAL DATA OF SOME *Mitragyna* ALKALOIDS

Analyses	C	H	N	OMe	Equiv. wt.
Structure I (R = OMe) requires for C ₂₂ H ₂₆ N ₂ O ₅ ..	66.3	6.5	7.0	15.5	398
Pa 7 found ..	66.0	6.45	7.45	11.5§	404†
Structure II (R = OMe) requires for C ₂₂ H ₂₆ N ₂ O ₄ ·H ₂ O ..	66.0	7.0	7.0	15.5	400
Mitrajavine found ..	65.7	6.9	7.1	15.4	385†
Structure III requires for C ₂₂ H ₂₈ N ₂ O ₅ ..	71.7	7.6	7.6	16.85	368
Hirsutine found ..	70.4	8.3	7.7	17.8	370†

	Pa 7 I R = 11-OMe	Mitrajavine II R = 9-OMe	Hirsutine III
Melting point (Recryst. from dry ether)	180°	117°	101°
$\alpha_D^{23} \pm 0.5^\circ$ (CHCl ₃)	+77.4° (c, 0.195)	-37.6° (c, 0.26)	+68.6° (c, 0.32)
Approx. Rf* (a) alumina/CHCl ₃ (b) silica gel/ether	0.50 0.10	0.80 0.05	0.70 0.0
Ultraviolet spectra (abs. ethanol)	λ m μ log ϵ 220 4.97 240 4.76 282 4.15 291 4.11	λ m μ log ϵ 227 4.47 265 3.89 292 3.73	λ m μ log ϵ 226 4.64 282 3.84 290 3.79
Infrared spectra (Nujol) cm ⁻¹			
Ester	3500	3500	3400
C = O	1700	1685	1695
C = C	1620	1615	1620
Oxindole	1705	—	—
C/D <i>trans</i> bands (KCl)	—	Nc bands between 2800 and 2500 cm ⁻¹	
Derivative m.p. (from abs. ethanol)	methyl iodide 205°	hydrobromide 230°	methyl iodide 254°
Analyses of derivatives	C ₂₂ H ₂₆ N ₂ O ₅ ·CH ₂ I Req. Found C 51.1 51.6% H 5.4 5.8 N 5.2 5.3	C ₂₂ H ₂₆ N ₂ O ₄ ·HBr·2H ₂ O Req. Found C 52.6 51.5% H 6.2 6.1 N 5.6 5.4	C ₂₂ H ₂₈ N ₂ O ₅ ·CH ₂ I Req. Found C 53.9 53.4% H 6.1 6.1 N 5.5 5.0

* Thin layer chromatography. Reference values: Mitraphylline, (a) 0.17, (b) 0.03. Ajmalicine, (a) 0.83, (b) 0.45. Corynantheidine, (a) 0.83, (b) 0.72.

† Titration in non aqueous media.

§ The presence of two methoxy groups is indicated in the nmr spectrum (Table 2).

TABLE 2. NMR SPECTRA OF SOME *Mitragyna* ALKALOIDS IN CDCl_3 , 60 MC (τ values, ppm from tetramethylsilane)

Protons	Pa 7 I	Mitrajavine II	Hirsutine-III
$\begin{array}{c} \text{---C---Me} \\ \diagup \quad \diagdown \\ 19 \quad \text{R} \\ \diagdown \quad \diagup \\ \text{---O---} \end{array}$ $\begin{array}{c} \text{---CO---OMe} \\ \diagup \quad \diagdown \\ \text{---O---} \end{array}$ $\begin{array}{c} \text{---OMe} \\ \diagup \quad \diagdown \\ \text{Ar---O---} \end{array}$ $\begin{array}{c} \text{---C---H} \\ \diagup \quad \diagdown \\ 19 \quad \text{H} \\ \diagdown \quad \diagup \\ \text{---O---} \end{array}$ C_6H <i>cis</i> aromatic olefinic H -N-	--- 8.88 doublet (J = 6.5 cps) --- 6.41 singlet --- 6.18 singlet ca. 5.6 multiplet --- ca. 3.4 (2H) ca. 2.9 (1H) multiplets 2.53 singlet 1.20* singlet	--- 9.10 doublet (J = 6.5 cps) --- 6.29 singlet --- 6.10 singlet ca. 5.6 multiplet --- 5.55 multiplet 3.47 (1H) 2.91 (2H) multiplets 2.42 singlet 1.30* singlet	9.21 triplet --- 6.29 singlet 6.22 singlet --- 5.5 multiplet ca. 2.7 (4H) multiplet 2.65 singlet 1.82* singlet

* Disappears on deuteration.

6.22 τ . A *cis* C_3H is demonstrated by the absence of *trans* CH bands (below 2800 cm^{-1} , KCl disc) in the infrared spectrum and a one-proton *cis* C_3H multiplet in the nmr spectrum at 5.55 τ . The absence of an aromatic methoxy group is shown by the lack of an aromatic three-proton singlet at about 6.15 τ and the presence of four aromatic protons (unsplit signal at about 2.7 τ). This evidence suggests that hirsutine is an alkaloid of the corynantheidine-type with the C_3H *cis* to the nitrogen lone pair.

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