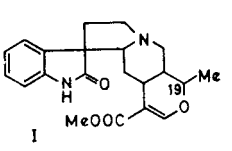
Letters to the Editor

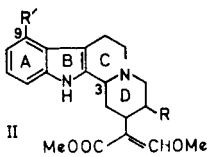
Alkaloids from *Mitragyna speciosa* (Korth.)

SIR,—We have isolated from a methanolic extract of the leaves of *Mitragyna speciosa* Korth. a number of alkaloids, three of which have not been previously described (Table 1). The picrates prepared from the ether-extracted crude

TABLE 1. PROPERTIES AND SPECTRAL DATA OF SOME MITRAGYNA ALKALOIDS



I



II

Analyses	C	H	N	OMe	Equiv. wt.
Structure I requires for $C_{21}H_{24}N_2O_4$	68·5	6·5	7·6	8·4	368
Speciophylline found	67·9	6·8	7·5	8·7	373†
Structure IIa requires for $C_{23}H_{30}N_2O_4$	69·3	7·6	7·0	23·4	398
Speciogynine found	68·9	7·8	7·0	23·2	400†
Structure IIb requires for $C_{23}H_{28}N_2O_4$	69·7	7·1	7·0	23·5	396
Paynantheine found	69·2	7·5	7·2	22·5	407†

	Speciophylline I	Speciogynine IIa R′=OMe, R=CH_2Me	Paynantheine IIb R′=OMe, R=CH=CH_2
Melting-point (Recryst. from . . .)	183° (dry ether)	214° (dry ether)	98° softens
$[\alpha]_{23\pm0.5°}^{D}$ ($CHCl_3$)	+91·3° (*c*, 0·21)	+28·4° (*c*, 0·26)	−28·9° (*c*, 0·27)
Approx. hRf* (a) alumina/$CHCl_3$	12	78	80
(b) silica gel/ether	3	40	52
Ultraviolet spectra (Abs. ethanol)	λ mμ log ε 224 (min) 3·98 224 4·14 283 3·34	λ mμ log ε 227 4·66 274s 3·92 284s 3·84 293 3·84	λ mμ log ε 227 4·63 272s 3·95 283s 3·86 292 3·84
Infrared spectra cm^{-1} (KCl) –N–H	3220	3372	3390
C/D Trans bands	—	2750, 2808, 2850	2755, 2800, 2853
–CH	*ca.* 2950	2950	2938
Ester/oxindole C=O	1713, 1685	1684	1706
C=C	1623	1614	1625, 1640
Picrate m.p. (From abs. ethanol)	215°	224°	202°
Picrate analyses	$C_{21}H_{24}N_2O_4$. $C_6H_3O_7N_3$ Req. Found C 54·3 54·3% H 4·5 4·9 N 11·7 11·85	$C_{23}H_{30}N_2O_4$. $C_6H_3O_7N_3$ Req. Found C 55·5 55·9% H 5·3 5·4 N 11·2 11·3	$C_{23}H_{28}N_2O_4$. $C_6H_3O_7N_3$ Req. Found C 55·7 55·3% H 5·0 5·15 N 11·2 10·4

* Thin-layer chromatography. Reference values: Mitraphylline (I), (a) 19, (b) 5; Mitragynine (II, R′ = OMe, R = CH_2Me), (a) 85, (b) 71.
† Titration in non-aqueous media.

bases yielded mitragynine (Beckett, Shellard & Tackie, 1965) and subsequently corynantheidine, isomitraphylline and a second isomer of mitraphylline which we have named *speciophylline* (I). The picrate mother liquors yielded ajmalicine, an isomer of mitragynine named *speciogynine* (IIa), a 9-methoxy derivative of corynantheine-like structure named *paynantheine* (IIb) and unidentified alkaloids. The ether-insoluble bases yielded mainly mitraphylline.

Mitraphylline, isomitraphylline, ajmalicine and corynantheidine were identified by comparison of the m.p., mixed m.p., $[\alpha]_D$,hRf values (thin-layer chromatography), ultraviolet, infrared and nmr spectra, with authentic samples of these alkaloids.

The data obtained indicate that speciophylline is an oxindole alkaloid of general structure similar to that of mitraphylline (I). The nmr spectrum of speciophylline (Table 2) shows that the ester methoxy group of the compound

TABLE 2. NMR SPECTRA OF SOME MITRAGYNA ALKALOIDS IN $CDCl_3$ 60 MC
(τ values from tetramethylsilane)

Protons	Speciophylline I	Speciogynine IIa	Paynantheine IIb
–C–Me	—	9·08 triplet	—
19 Me / –O R	8·74 doublet (J = 6·5 cps)	—	—
–CO–OMe	6·62 singlet	6·36 singlet	6·28 singlet
–OMe	—	6·27 singlet	6·23 singlet
C_6H·OMe	—	6·12 singlet	6·11 singlet
19 R / –O H	5·79 multiplet	—	—
–CH = CH_2	—	—	5·2–4·2 multiplets
aromatic	3·15–2·77 (4H) multiplet	3·54 (1H) 3·08 (2H) multiplets	3·50 (1H) 3·03 (2H) multiplets
olefinic	2·59 singlet	2·63 singlet	2·61 singlet
–N– H	0·50* singlet	2·00* singlet	2·07* singlet

* disappears upon deuteration.

(6·62τ) is shifted upfield compared with mitraphylline (6·40τ) and isomitraphylline (6·42τ). This is due to the position of the methoxyl group above the oxindole ring.

The alkaloids speciogynine and paynantheine were shown to be indoles by colour tests, ultraviolet, infrared and nmr data. These physical data, along with elemental analysis and equivalent weight determinations, indicate the structure of speciogynine to be generally similar to that of mitragynine (II; R′ = OMe, R = CH_2Me). A methoxy group in the 9-position of both speciogynine and paynantheine is suggested by the similarity of the splitting pattern of the aromatic protons for all these alkaloids [cf. mitragynine 3·52τ (1H), 3·08τ (2H)] and the three-proton aromatic methoxy singlet at about 6·1τ [mitragynine 6·14 τ] in the nmr spectrum (Table 2).

Infrared and nmr spectra of speciogynine and paynantheine indicate a trans C_3H junction for these alkaloids since bands are present between 2700–2800 cm^{-1} in the infrared spectrum (Wenkert & Roychaudhuri, 1956; Bohlmann, 1957; Rosen, 1961) and no C_3H multiplet in the nmr is present above 6·0τ (Wenkert, Wickbert & Leicht, 1961a,b; Uskokovic, Bruderer, von Planta, Williams & Brossi, 1964). The nmr spectrum of paynantheine is different from those of mitragynine and mitraciliatine in having no three-proton triplet for the C–CH_3 in the 9·1τ region. However, paynantheine has multiplets integrating for three protons in the olefinic region 5·2–4·2τ corresponding in chemical shift, multiplicity and integral with the vinyl signals of corynantheine (II; R′ = H, R = CH = CH_2). Paynantheine is therefore a 9-methoxy derivative of corynantheine-type structure and the first compound of this type to be reported.

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The inhibition of adrenergic α-receptors and tryptamine receptors by macusine B

SIR,—Macusine B, an alkaloid isolated from *Strychnos toxifera*, blocks α-adrenergic receptors, stimulates β-adrenergic receptors and competitively inhibits tryptamine receptors in the guinea-pig isolated ileum (Leonard, 1965). A quantitative comparison has now been made with other compounds known to inhibit these receptors.

The antagonism of 5-hydroxytryptamine (5-HT) by macusine B was measured on the guinea-pig isolated ileum and the rat isolated uterus preparations. These tissues were suspended in an organ bath of Tyrode and De Jalon solutions respectively, as described previously (Leonard, 1965), and the pA_2 and pA_{10} values measured (Schild, 1947). The inhibition of adrenergic receptors was assessed using the guinea-pig isolated vas deferens preparation (Leach, 1956), and on the rabbit aortic strip preparation of Furchgott & Bhadrakom (1953). A modified aorta strip was prepared. A 3 cm length of aorta was first slit longitudinally, placed on a filter paper moistened with Krebs solution and then cut from each side in the horizontal plane so that the cuts alternated but did not extend to the mid-line. By leaving an uncut portion 1 mm wide down the midline and alternating the horizontal cuts by about 1 mm, a robust strip was achieved.

The aorta was then suspended in an organ bath of Krebs solution and attached to a frontal writing lever, backweighted by a load of 0·5 g, giving a × 10 magnification. Aorta prepared in this way gave regular responses to adrenaline ($2–4 \times 10^{-7}$M) for at least 12 hr.

In all experiments the pA values were measured on tissues from at least two animals and the pA_2 and pA_{10} values were measured separately on different pieces of tissue from the same animal. The pA_2 and pA_{10} values for macusine B on all the tissues were in the range 5·02–6·87 and 4·01–5·77 respectively; there was a slight increase in the value (0·08–0·65 pA units) when the contact time of the antagonist was increased from 2 to 10 min (Table 1). Schild (1957) calculated the pA_2–pA_{10} value for a first order competitive antagonist to be 0·95.