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SOME NEW MITRAGYNA-TYPE INDOLES AND OXINDOLES; THE INFLUENCE OF STEREOCHEMISTRY ON MASS SPECTRA

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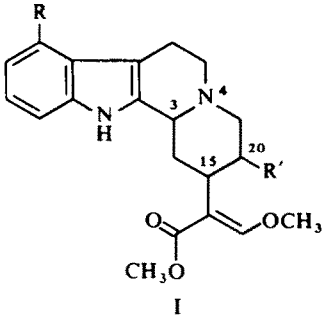
Abstract—The indole alkaloids corynantheidine and paynantheine have been epimerized to two new compounds and corynantheidine and mitragynine have been transformed to the corresponding oxindoles. The stereochemistry of the new compounds is deduced from physical data. Mass spectral fragmentation of the *mitragyna* indole and oxindole alkaloids is discussed with reference to their stereochemistry.

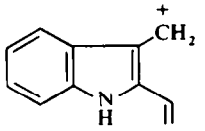
RECENT reports that mass spectrometry may reflect stereochemical characteristics as well as structural information prompted an examination of indole alkaloids of type I whose stereochemistry is now well defined.[1] In the unsubstituted series (I; R = H, R′ = Et) the isomer of *epiallo* configuration has not yet been isolated from natural sources and was prepared from the naturally occurring *allo* isomer, corynantheidine. On treatment with mercuric acetate in acetic acid, corynantheidine yielded the 3,4-dehydro acetate which on reduction with zinc and acetic acid gave a mixture containing the less stable $C_3\beta$—H epimer now named isocorynantheidine.[2] This compound showed the predicted physical characteristics of the *epiallo* configuration[1] (Exptl.).



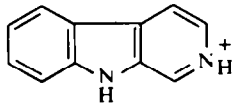
I

configuration	C_3H	$C_{15}H$	$C_{20}H$
normal	α	α	β
pseudo	β	α	β
allo	α	α	α
epiallo	β	α	α

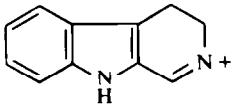
The main features in mass spectra are fragments *m/e* 156 (a), 169 (b), 170 (c), 184 (d), 225 (e), 239 (f), and a strong M-1 ion characteristic of tetrahydro β-carboline compounds[3] (Fig. 1). All these peaks are shifted by 30 mass units in the 9-methoxy alkaloids (I; R = OMe, R′ = Et; Fig. 2) and accurate mass measurements confirm the assignments in accordance with ajmalicine:[3]



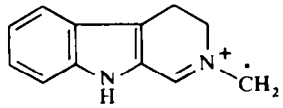
a: *m/e* 156(186)*



b *m/e* 169(199)



c: *m/e* 170(200)



d: *m/e* 184(214)

* Numbers in brackets refer to the 9-OCH_3 substituted compounds.

Fragments a, b and c (R = H) appear to have stereochemical importance being significantly less intense in corynantheidine and isocorynantheidine where the C_{20}-Et substituent is axial. This effect is not observed with 9-OMe series (Fig. 2) and cannot be used as a reliable guide to the C_{20} stereochemistry. However, the fragments *m/e* 225 (255) and *m/e* 239 (269) do provide a correlation in both series; a C_{20}-Et *axial* substituents (*allo* and *epiallo*) leads to a more intense 239 (269) ion whereas a C_{20} *equatorial* substituent (*normal* and *pseudo*) exhibits a more abundant 225 (255) ion (Fig. 3). The C_{20}-vinyl analogues (I; R = OMe, R′ = $CH{=}CH_2$) paynantheine (*normal*) and the isomer now prepared, 3-isopaynantheine (*pseudo*), gave ions at *m/e* 253 and 267 rather than *m/e* 255 and 269 indicating that the C_{20}-vinyl group has not been lost from the parent molecule. Further the ions 253 and 267 had equal relative intensities instead of the predominance of the 253 ion over the 267 ion expected of *normal* and *pseudo* compounds. Thus the type of substituents at C_{20} as well as its configuration influences the intensities of these fragments.

Accurate mass measurements carried out on the spectrum of mitragynine (I; R = OMe, R′ = Et; *allo*) gave the constitution of *m/e* 255 as $C_{16}H_{19}N_2O$ and *m/e* 269 as $C_{17}H_{21}N_2O$. It seems likely that both these ions arise from a common intermediate and a possible pathway is shown in Scheme I. Hydrogen transfer from C_{21} to C_{15} provides an intermediate which can fragment further to give *m/e* 255 and 269. Stereo models suggest that *normal* and *pseudo* compounds would produce a *trans* double bond whereas *allo* and *epiallo* compounds would provide a *cis* double bond in the intermediate and this factor would account for the observed relative intensities of the fragments **e** and **f**.

Further the M-CH_3 fragment could be used to differentiate between *normal* and *pseudo*, and *allo* and *epiallo*; it is more intense in the *pseudo* and *epiallo* compounds. Mass spectrometry, then, does in this series provide a means of distinguishing stereoisomers.

Oxindole analogues

The stereochemistry of the closely related rhynchophylline-type oxindoles II could also have mass spectral significance. The asymmetric centre at C_7 provides A and B oxindoles and the centres at C_3 and C_{20} *normal*, *pseudo*, *allo* and *epiallo* configurations, though conformational analysis suggests the *pseudo* pair are too unstable to exist.[4]

Naturally occurring corynoxine (*allo* A, II; R = H), not available to us, was prepared by oxidation of the corresponding *allo* indole alkaloid, corynantheidine

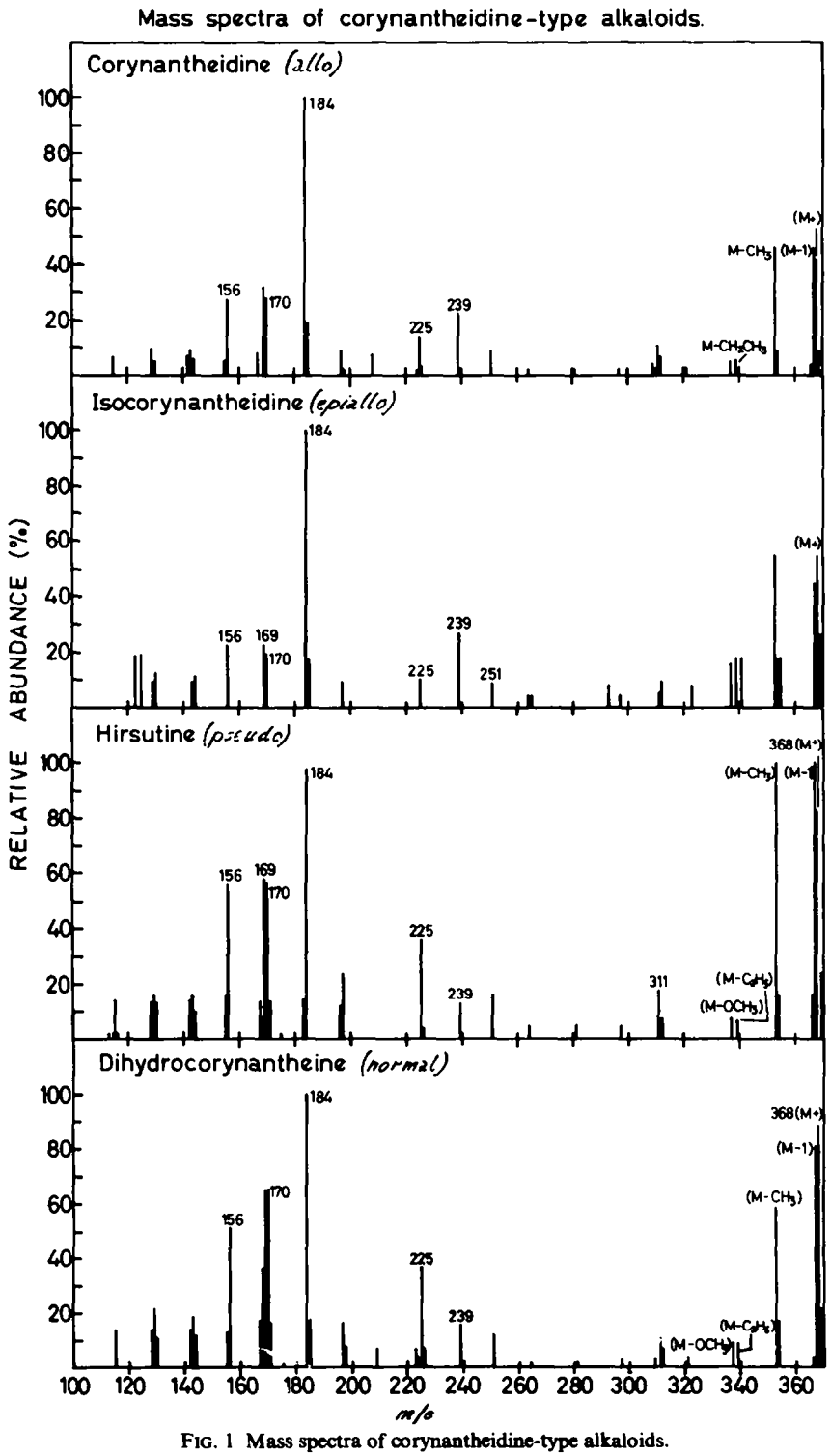


FIG. 1 Mass spectra of corynantheidine-type alkaloids.

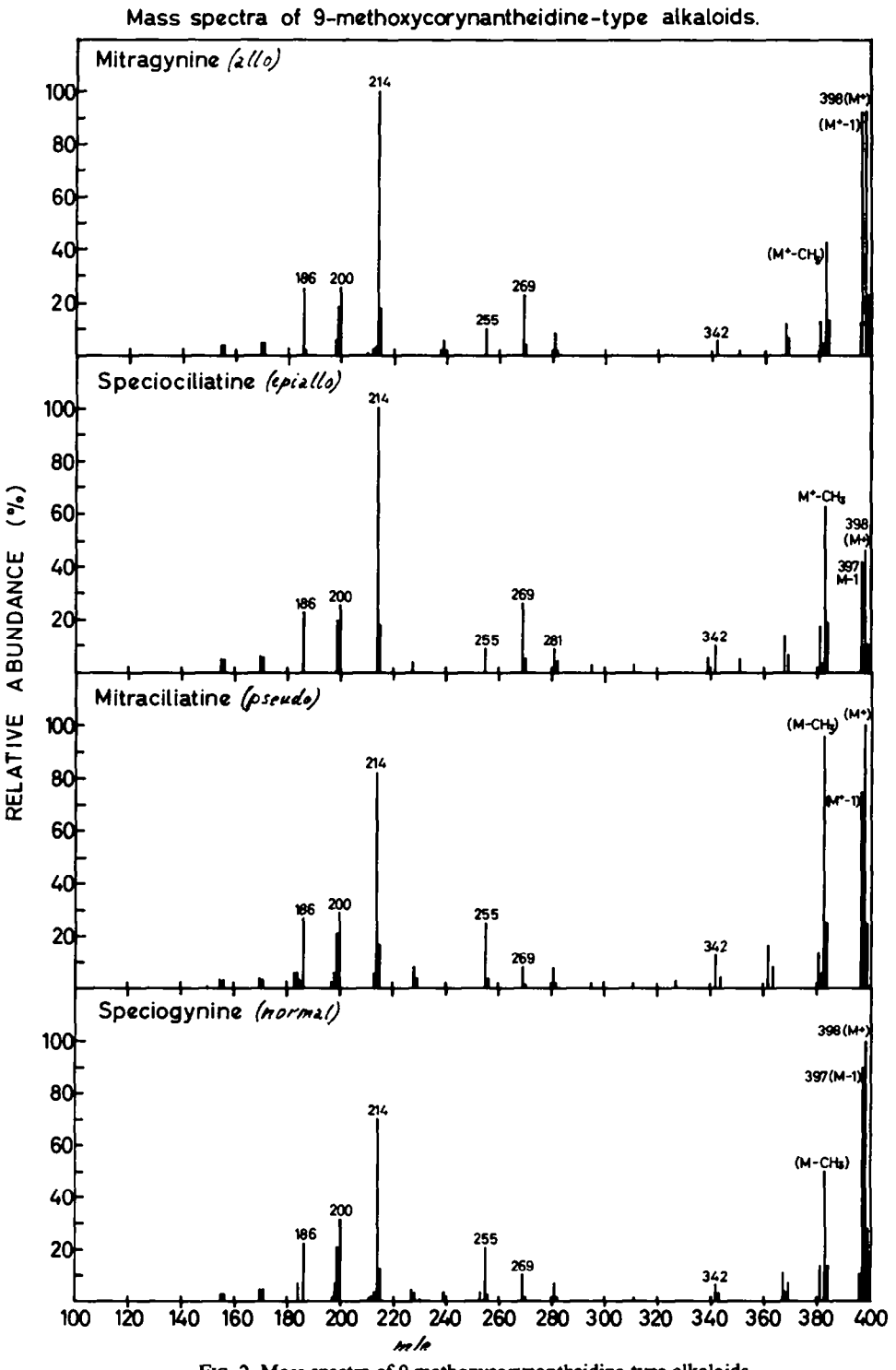


FIG. 2 Mass spectra of 9-methoxycorynantheidine-type alkaloids.

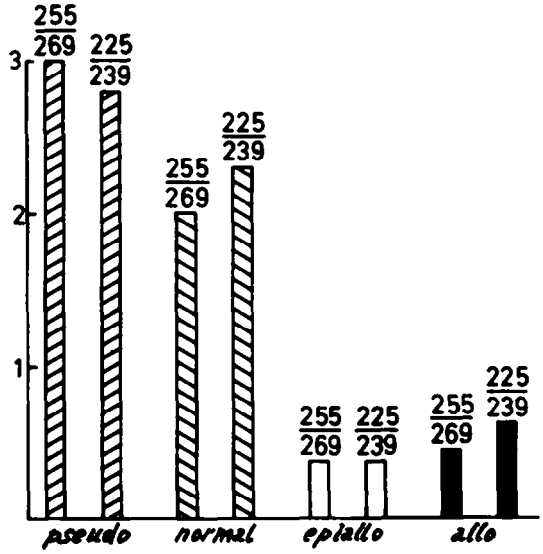
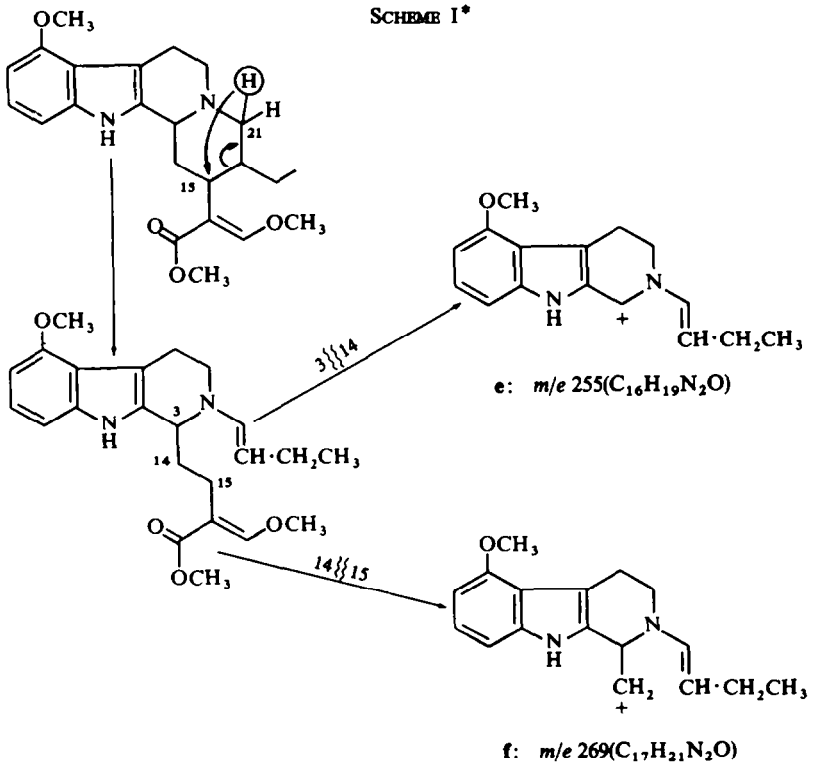


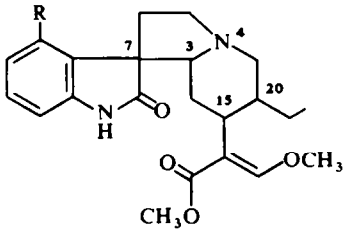
FIG. 3 The influence of configuration on the ratio *m/e* 255 to *m/e* 269 for 9-methoxycorynantheidine-type alkaloids, and *m/e* 225 to *m/e* 239 for the non-methoxycorynantheidine-type alkaloids.

SCHEME I*



* The authors thank Dr B. J. Milland, School of Pharmacy, University of London, Brunswick Square, London, W.C.1 for this scheme.

(I; R = H, R′ = Et) using t-butyl hypochlorite.[5] The unstable α- and β-chloro-indolinenes were separated*; both yielded oxindoles on treatment with a trace of acetic acid whereas only the α-chloro indolinene gave an oxindole on treatment with methanolic sodium hydroxide followed by dilute acid.[5] Acetic acid isomerization



II

provided the C_7 epimer corynoxine-B (*allo* B). In the 9-OMe series (II; R = Me) the known *allo* indole, mitragynine (I; R = OMe, R′ = Et), was oxidized with t-butyl hypochlorite and isomerization of the reaction products with glacial acetic acid gave a new oxindole *mitragynine oxindole-B*. NMR examination (100 mc) revealed a symmetrical C_{18}-Me triplet (0·86 δ) indicating an *axial* C_{20}-Et group, that is an *allo* or *epiallo* configuration; using glacial acetic acid as solvent the 3-proton singlet of the aromatic OMe group appeared at 3·88 δ compared with a value of 3·83 δ using deuterochloroform. This suggests a B stereochemistry at C_7 since one would expect the compound of A stereochemistry (Fig. 4) to experience a downfield shift in glacial acetic acid of some 0·2 ppm due to the proximity of the OMe group to the protonated nitrogen, as has been observed for the *normal*-A oxindole rhynchociline (II; R = Me).[4] Further the CD curve of mitragynine oxindole-B showed maxima 280 mμ (negative), 255 mμ (positive), identical to the known *normal-B* alkaloids ciliaphylline (II; R = OMe) and isorotundifoline (II; R = OH). On this basis the B stereochemistry at C_7 is assigned to *mitragynine oxindole-B*. Isomerization of this compound in pyridine gave a mixture of mitragynine oxindole-B (70%) and one other basic compound (30%) as revealed by TLC. Isomerization is believed to proceed via a ring opened intermediate[5] (Fig. 4) and could result theoretically in four compounds *allo-A*, *allo-B*, *epiallo-A*, and *epiallo-B* by epimerization of both C_7 and C_3. Since conformational analysis indicates that the *epiallo* configurations would be much less stable than the *allo* configurations the new compound can be tentatively assigned *allo-A* stereochemistry. Some confirmation comes from the CD curve of this compound which shows maxima 285 mμ (positive), 255 mμ (negative) identical to rhynchociline (II; R = OMe) and rotundifoline (II; R = OH), compounds of known *normal-A* stereochemistry.

The main mass spectral fragments of the above oxindoles arise from cleavages seen in Scheme II.[7]

* Designated as α or β by comparing their CD trace with known 7α-acetoxy yohimbine and the 7-chloroyohimbines.[6]

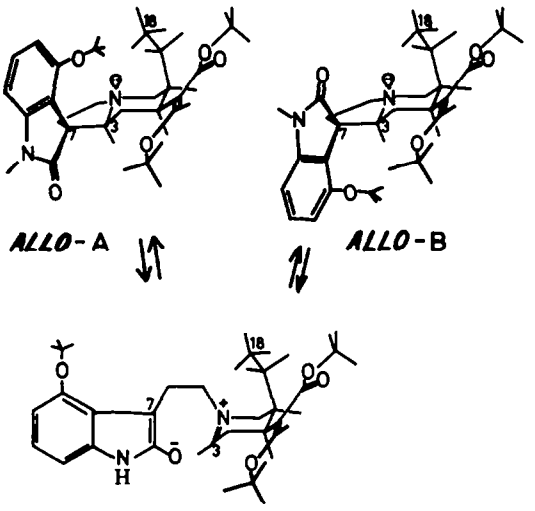
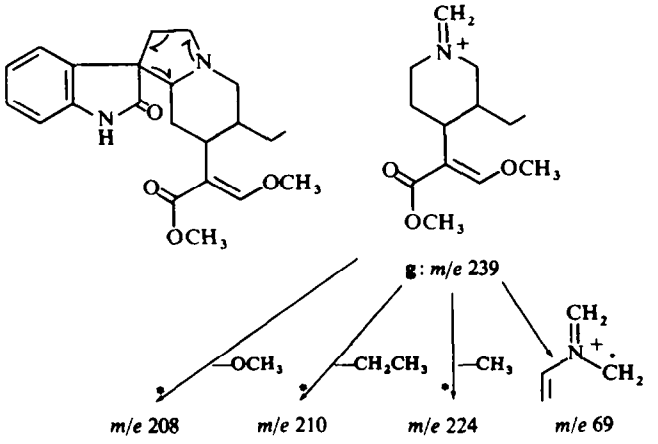


FIG. 4

The abundance of the *m/e* 239 fragment seems to be independant of the stereochemistry at C_7, but this effect may be due to thermal isomerization which has been shown to be extremely rapid at the high temperatures of the inlet. Suitable deuterated compounds were not available but evidence that the Et group lost from **g** does originate as the C_{20}-Et comes from the spectrum of specionoxeine, a 9-OMe C_{20} vinyl analogue of II. This compound gives a fragment corresponding to at *m/e* 237 which loses the elements of Me to give 222 and OMe to give 206 but not Et to give 208. Nevertheless

SCHEME II



* Mestable ion observed.

the relative abundance of *m/e* 210 involving the loss of the C_{20}-Et from **g** does not reflect stereochemical differences at C_{20} in *normal* and *allo* oxindoles, and neither do the intensities of the other major peaks in the spectrum (Table 1).

TABLE 1. RELATIVE ABUNDANCES OF THE MAJOR MASS SPECTRAL FRAGMENTS OF SOME OXINDOLE ALKALOIDS

Compound, II		Relative abundance %					
		M	239	224	210	208	69
Normal A							
Isorhynchophylline	R = H	100	54	26	18	17	63
Rotundifoline	R = OH	100	100	40	24	29	67
Rhynchociline	R = OCH_3	80	100	35	25	30	75
Normal B							
Rhynchophylline	R = H	100	82	27	15	16	70
Isorotundifoline	R = OH	65	75	30	20	24	100
Ciliaphylline	R = OCH_3	78	100	40	22	23	50
Allo A							
Corynoxine	R = H	75	46	20	11	15	100
Allo B							
Corynoxine B	R = H	100	71	33	20	26	68
Mitragynine oxindole B	R = OCH_3	100	100	36	20	32	47

EXPERIMENTAL

Mass spectra were determined on a AEI MS 902 high resolution mass spectrometer at 70 eV; inlet temps: 250°-indoles, 270°-oxindoles.

Isocorynantheidine

A mixture of corynantheidine (1·08 g) in glacial AcOH (30 ml) containing mercuric acetate (2·3 g) was heated at 60° for 24 hr. The soln was filtered and 3 ml water and Zn dust (4 g) added. After stirring for 16 hr at room temp, the soln was filtered, neutralized with dil NH_4OH and extracted with $CHCl_3$ (2 × 25 ml) which on evaporation gave 1·22 g oily residue. TLC (alumina—$CHCl_3$) showed two compounds corynantheidine (R_f 0·94) and a new compound (R_f 0·76). Repeated chromatography on alumina (Spence H) eluting with light petroleum-ether mixtures yielded a small quantity (60 mg) of the new compound now named *isocorynantheidine*. It could not be crystallized and rapidly turned yellow in air. ν_{max}^{KCl}: 3420, 1703, 1645, 1630, 1250, 1120, 745, 780 cm^{-1}; λ_{max}^{dioxan}: 230 (4·53), 285 (3·83), 292 (3·76) mμ; $NMR_{60\ mc}^{CDCl_3}$: 0·88 (3H tr), 3·67 (3H s), 3·74 (3H s), 4·18 (1H m), 7·15 (4H m), 7·39 (1H s), 7·82 (NH) δ; CD^{dioxan}: 298 mμ ($\Delta\varepsilon$ −1·9).

Isopaynantheine

A mixture of speciogynine I (R = OMe R′ = Et, *normal*) and paynantheine I (R = OMe R′ = CH = CH_2 *normal*) dissolved in glacial AcOH (50 ml) containing mercuric acetate (3 gm) was heated at 60°–65° for 48 hr. The soln was filtered, 5 ml water added, and stirred with Zn dust (4·6 gm) for 16 hr at room temp. Neutralization with dil ammonia and extraction with $CHCl_3$ yielded on evaporation 1·95 gm brown solid which on extensive TLC examination were shown to contain paynantheine, speciogynine, mitraciliatine (I, R = OMe, R′ = Et, *pseudo*) and a fourth component of very similar chromatographic properties to mitraciliatine. Repeated column chromatography on alumina (Spence H) and eluting with dry ether yielded a small sample of the new compound, running slightly ahead of mitraciliatine, now named *isopaynantheine* m.p. 142° from ether–light petroleum; *m/e*: 396, 395, 381, 267, 253, 214, 200, 199, 186; ν_{max}^{KCl}: 3370, 1690,

1625, 1247, 1100, 910, 710, 730, 719 cm^{-1}; λ_{max}^{dioxan}: 228 (4·46), 270 sh(3·73), 285 sh(3·67), 291 (3·61) mμ; $NMR_{60\,mc}^{CDCl_3}$: 3·65 (3H s), 3·72 (3H s), 3·88 (3H s) 4·40 (1H m), 4·6–5·0 (3H), 7·22 (1H), 7·90 (NH) δ; CD^{dioxan}: 265 mμ (Δε −5·1).

7-chloro corynantheine

A mixture of corynantheidine (500 mg) and Et_3N (0·25 ml) in CH_2Cl_2 (20 ml), cooled to −5° in an ice-salt bath under N_2 and protected from light, was treated dropwise with a soln of t-butyl hypochlorite (1·3 ml, freshly distilled) in CH_2Cl_2 (10 ml). After the addition, the mixture was allowed to stand at room temp for 30 min and then concentrated to small volume. Preparative TLC (silica–benzene:EtOAc 7/2) and extraction with ether gave 7-α-chlorocorynantheidine (R_f 0·5) and 7-β-chloro corynantheidine (R_f 0·25), both very unstable amorphous solids. 7-α-chloro: CD; 260 (positive), 280 sh (positive) mμ; 7-β chloro: CD; 258 mμ (negative), 315 mμ (weak positive).

7-αacetoxy yohimbine

This compound was prepared by the method of Finch,[6] m.p. 120° (lit. 121°); CD 245 mμ (positive, 290 mμ (positive).

Corynoxine and corynoxine B.

Corynantheidine (500 mg) was reacted with t-butyl hypochlorite as described above. After concentrating to small volume, the mixture was taken up in MeOH (10 ml) containing 1% aqueous AcOH (2 ml) and refluxed for 1 hr. Glacial AcOH (5 ml) was added and refluxing continued for further 12 hr. Solvents were distilled *in vacuo* and the residue was extracted with CH_2Cl_2 and absorbed onto 0·5 gm of silica. The silica was placed on the top of a column of dry silica-gel (Mallinckrodt AR 100, deactivated with 3% water) packed in a nylon tube, and developed with EtOAc. The column was cut up and extracted with MeOH to furnish corynoxine B, m.p. 171–172° from ether, *pKa* 7·51. (Spectral properties previously published[4].)

A sample of corynoxine B was reflux in pyridine for 48 hr. After removal of the solvent under reduced pressure, dry column chromatography (silica-gel + 3% water, EtOAc) afforded corynoxine m.p. 166–168° from light ether–light petroleum p*Ka* 6·46.

Mitragynine oxindoles.

Mitragynine (400 mg) was oxidized with t-butyl hypochlorite and treated with AcOH as described above. Separation on dry column of silca-gel using EtOAc as developer furnished mitragynine oxindole B m.p. 239° (dec); λ_{max}^{MeOH}: 242 mμ (4·06), 219 mμ (4·47); $NMR_{100\,mc}^{CDCl_3}$: 0·86 (3H tr), 3·52 (3H s), 3·56 (3H s), 3·79 (3H s), 7·22 (1H s) δ; CD^{MeOH}: 280 mμ (Δε − 2·3), 255 mμ (Δε + 3·4), > 240 mμ (tends negative).

A sample of mitragynine oxindole-B was refluxed in pyridine 48 hr. After removal of the solvent under reduced preparative TLC (Silica–$CHCl_3$:Acetone 5/4) yielded mitragynine oxindole-A (amorph); λ_{max}^{MeOH}: 243 mμ (4·06), 219 mμ (4·46); CD^{MeOH}: 285 mμ (Δε +1·5), 255 mμ (Δε −2·6), >245 mμ (tends negative), TLC (a) Silica—$CHCl_3$:Acetone (5:4); (b) Alumina—$CHCl_3$. Mitragynine oxindole—A R_f 0·30 (a), 0·15 (b); Mitragynine oxindole-B R_f 0·17 (a), 0·20 (b).

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