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10-HYDROXY- AND 10-METHOXYAPPARICINE: TWO NEW ALKALOIDS FROM OCHROSIA OPPOSITIFOLIA

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From the leaves of Ochrosia oppositifolia we have isolated two new alkaloids which correspond to the 10-hydroxy (2) and 10-methoxy (3) derivatives of apparicine (1). Furthermore an E configuration of the ethylidene group has been established for all three alkaloids and hence resolved the remaining unknown structural feature of apparicine.[1]

A methanolic extract of freshly gathered leaves (35 g) was evaporated in vacuo, the residue taken up in 2% tartaric acid, defatted with petrol and the basic material (0.2 g) isolated with chloroform after neutralisation. Preparative TLC afforded the known isoreserpiline[2] (90 mg) and another alkaloid (20 mg) which was recrystallised from acetone, m.p. 199 - 202° $[\alpha]_D^{25}$ - 129° ($CHCl_3$). Accurate mass measurement (M^+ 294.173) gave a molecular formula of $C_{19}H_{22}N_2O$, and the IR spectrum indicated an NH or OH and a lack of carbonyl groups. A UV maximum at 314 nm (log ε 4.92) could not be ascribed to any known chromophore but was reminiscent of the 2-vinylindole system of apparicine. Comparison of the mass spectrum with that of apparicine revealed further similarities with a constant difference of 30 m.u. (CH_2O) for major ions at m/e 294, 279, 265, 252, 238 in the former and at m/e 264, 249, 235, 222, 208 in the latter. Again the 90 MHz NMR spectrum was very similar except for the presence of a methoxyl singlet at τ 6.15 and three rather than four aromatic protons. Finally a complete analysis of the 300 MHz spectrum (see Table) allowed assignment of every proton in accordance with either a 10- or 11-methoxyapparicine structure.[‡]

In order to distinguish between these two alternatives the methoxyapparicine was hydrogenated over Adams's catalyst to reduce the 16,17-vinyl group and obtain a known methoxyindole chromophore. In the event the major product was a hexahydro derivative $C_{19}H_{28}N_2O$ (M^+ 300.220) rather than that expected for saturation of two double bonds. Uptake of two more hydrogens was attributable to hydrogenolysis of the indolylic C-6—N-4 bond to give the cleaved structure 4, and this was confirmed when N-acetylation to 5 showed that N-4 was secondary rather than tertiary. Both compounds had UV maxima at 231 and 283 nm identical with those of 5-methoxy-2,3-dimethylindole[3] thus placing the methoxy group at C-10.

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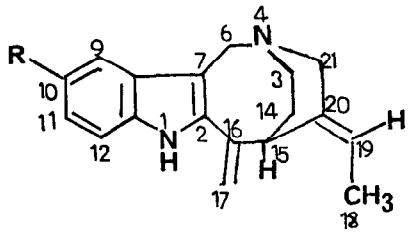
‡ The standard biogenetic numbering scheme for monoterpenoid indole alkaloids has been used with allowance for loss of C-5.

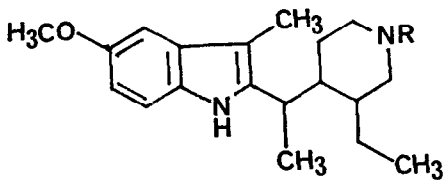
TABLE

300 MHz NMR Spectrum of 10-Methoxyapparicine in $CDCl_3$

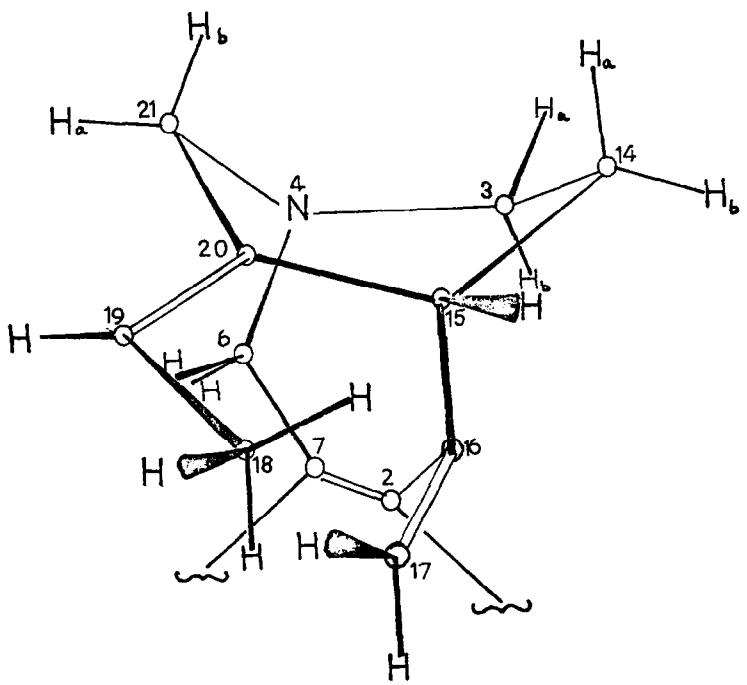
Proton	τ (ppm)	Multiplicity	J (Hz) / Coupling proton
H-1	2.15	s	
H-3a	6.56	m	13/H-3b; 8/H-14a; 1.5/H-14b
H-3b	6.92	m	13/H-3a; 11/H-14a; 6.5/H-14b
H-6a	5.52	d	17/H-6b
H-6b	5.75	d	17/H-6a
H-9	3.17	bs	~1/H-11
H-11	3.13	dd	9/H-12; ~1/H-9
H-12	2.78	d	9/H-11
H-14a	7.83	m	14/H-14b; 8/H-3a; 11/H-3b; 5/H-15
H-14b	8.10	m	14/H-14a; 6.5/H-3b; 1.5/H-3a; ~ 1/H-15; < 1/H-21a
H-15	6.08	bs	<1/H-17; ~1/H-19; 5/H-14a; ~1/H-14b
H-17a	4.60	bs	<1/H-17b
H-17b	4.74	bs	<1/H-17a
H_3-18	8.54	dd	6/H-19; 1.5/H-21a
H-19	4.72	bq	6/H_3-18; ~1/H-15
H-21b	6.78	bd	16/H-21a
H-21a	6.16	d	16/H-21b; 1.5/H_3-18; <1/H-14b
OMe	6.15	s	



	R
1	H
2	OH
3	OCH_3



	R
4	H
5	Ac



Figure

From the TLC separation of the extract was obtained a second amorphous alkaloid $[\alpha]_D^{25}$ - 90° ($CHCl_3$) M^+ 280 which analysed for $C_{18}H_{20}N_2O$. Its UV maximum at 310 nm (log ε 4.84) was similar to that of 10-methoxyapparicine but differed by shifting on addition of alkali, indicating the presence of a phenolic hydroxyl rather than a methyl ether. A series of ions in the mass spectrum lower by 14 m.u. (CH_2) than methoxyapparicine, and the NMR spectrum also substantiated the relationship. Finally, when treatment with diazomethane afforded 10-methoxyapparicine, the structure was confirmed as 10-hydroxyapparicine (2).

One structural feature in apparicine remaining unknown after the original work[1] was the geometry of the 19,20 double bond. Examination of Dreiding models indicated that the 18-Me could be close to H-15 in the E configuration or to H-21 in the Z configuration. When the methyl NMR signal was irradiated an NOE enhancement of 10% was observed for the H-15 absorption. Although the same phenomenon could not be observed for 10-methoxyapparicine due to overlap of the methoxyl and H-15 peaks, 10-hydroxyapparicine gave an identical NOE. Hence all three alkaloids have the E configuration of the ethylidene group, as indeed have the few other examples in monoterpenoid indole alkaloids where it has been established.

Apparicine is one of the rare examples of Strychnos type alkaloids in which both enantiomers occur naturally, i.e. H-15 can have been epimerised, but the absolute configuration of neither is known as yet. Similar Cotton effects in the CD spectra show that (-)-10-methoxyapparicine (Θ_{314} - 5.4 x 10^3 deg cm^2 $decimol^{-1}$) in all probability belongs to the same enantiomeric series as (-)-apparicine (Θ_{303} - 4.3 x 10^3). From a comparison of the NMR coupling constants with values estimated from dihedral angles in Dreiding models we conclude that in (-)-apparicine and its derivatives the piperidine ring adopts the slightly twisted boat conformation shown in the Figure. In particular the angles subtended by H-15 of ca. 70° with H-14b and ca. 50° with H-14a are in agreement with J values of ~1 and 5 Hz respectively; furthermore there is an observable coupling between H-14b and H-21a, presumably due to a long range 1,5 in-plane interaction. Additional evidence in favour of this conformation has been obtained from an analysis of the complete sets of T_1 measurements for apparicine and 10-methoxyapparicine.[4]

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