MINOR ALKALOIDS OF *MEDICOSMA CUNNINGHAMII* HOOK. f.*

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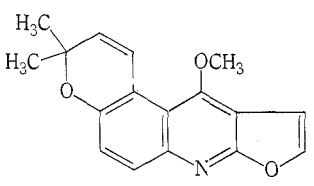
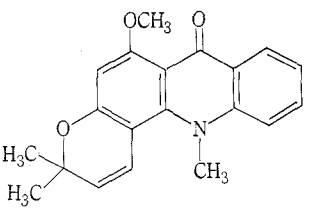
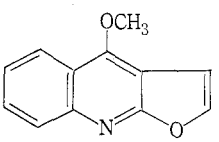
An interest in medicosmine (I) as an analogue of acronycine (II), recently found to have high inhibitory activity against a broad spectrum of test tumours,[1] has led us to reinvestigate the alkaloids of *Medicosma cunninghamii* Hook. f., of which medicosmine is the main alkaloidal constituent.[2] Three other bases were isolated in very small amounts and two have been identified as dictamnine (III) and pteleine (IV).



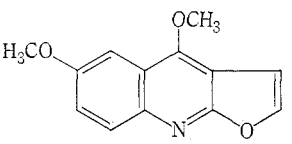
(I)



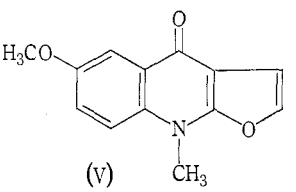
(II)



(III)



(IV)



(V)

The presence of a molecular ion peak at *m/e* 199 in the mass spectrum and the n.m.r. spectrum which was typical of a 4-methoxyfuroquinoline[3] (signal from C4 methoxyl group at δ 4·32, Hα and Hβ furan ring protons at δ 7·53 and δ 6·45 with J 3·0 c/s, and signals from other aromatic protons) indicated that one of the minor alkaloids was dictamnine, and this identification was confirmed by direct comparison with authentic dictamnine.

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[1] Svoboda, G. H., Poore, G. A., Simpson, P. J., and Boder, G. B., *J. pharm. Sci.*, 1966, **55**, 758.

[2] Lamberton, J. A., and Price, J. R., *Aust. J. Chem.*, 1953, **6**, 173.

[3] Robertson, A. V., *Aust. J. Chem.*, 1963, **16**, 451.

Another of the newly isolated bases, m.p. 136–138°, M^+ at *m/e* 229, was also readily characterized as a 4-methoxyfuroquinoline by its n.m.r. spectrum, which showed signals from two methoxyl groups at δ 4·53 (C4 methoxyl) and δ 4·02, from Hα and Hβ furan ring protons at δ 7·65 and δ 7·09 (*J* 2·8 c/s), and from three aromatic protons of which one at δ 8·05 exhibited only an *ortho* coupling (*J* 9·0 c/s). The spectroscopic evidence indicated that the alkaloid was a dimethoxyfuroquinoline with one methoxyl group at C4 and the other at C6 or C7, and it seemed probable that the alkaloid was identical with pteleine (IV), an alkaloid from *Ptelea trifoliata*,[4] which has been reported to have essentially the same melting point (137–139°). As no reference sample of pteleine was available for comparison, the alkaloid was converted by heating with methyl iodide into isopteleine (V), which was shown to be identical with a sample of (V) prepared from normedicosmine by alkaline degradation and subsequent methylation of the product.[2]

The third minor base, which was obtained as a yellow-fluorescing substance, m.p. 136–137°, was not available in sufficient quantity for characterization. The mass spectrum showed an apparent molecular ion peak at *m/e* 261 which is difficult to reconcile with a simple relationship to either medicosmine or dictamnine. In the n.m.r. spectrum (C.A.T. averaged) there was a strong singlet signal at δ 1·5 which may indicate the presence of a dimethylpyran ring as in medicosmine, but a possible *N*-methyl signal at δ 2·8 and the absence of any methoxyl group signal indicated that the alkaloid is probably unlike the other *Medicosma* alkaloids.

Experimental

Extraction of Medicosmine

Three extraction procedures were investigated. (i) The method of Lamberton and Price,[2] involving extraction with methanol, removal of solvent, addition of water and Na_2CO_3, extraction with ether, extraction from the ether solution with 10% HCl, and recovery by dilution with water and extraction into chloroform, gave medicosmine in 0·4% yield, but was considered unsuitable for use on a large scale. (ii) Direct extraction of the bark with ether in a Soxhlet extractor, precipitation of the alkaloids as hydrochlorides with gaseous hydrogen chloride, and chromatography of the crude alkaloids on alumina afforded medicosmine in 0·03% yield; this method was the most convenient procedure on a laboratory scale, but it was not employed on a large scale because of the fire hazard. (iii) The bark (53 lb) was extracted with methanol, the extract concentrated to the point of complete removal of methanol, water added, and the mixture left for 48 hr. The aqueous layer was decanted from a thick tar which precipitated and the tar dissolved in ether (7·8 l.). The ether solution was saturated with hydrogen chloride, left for 2 hr, the precipitate (c. 110 g) taken up in chloroform and chromatographed on deactivated alumina. Medicosmine (15 g, 0·06%) was obtained by elution with benzene.

Minor Alkaloids and Lupeol

Extraction of bark (12 lb) by procedure (ii) led to precipitated alkaloid hydrochlorides and a supernatant ether solution. The latter, chromatographed on alumina, gave lupeol, m.p. 213°, which was identified by a mixed melting point determination and by comparison of the i.r. and n.m.r. spectra with those of authentic lupeol. The alkaloid hydrochlorides were dissolved in chloroform, washed with a saturated solution of NaCl, and chromatographed on alumina with benzene as eluent. Fractions 6–8 contained lupeol (108 mg), fractions 16–19 contained medicosmine (1·6 g), m.p. 135–136°, and the minor alkaloids dictamnine and pteleine, fractions 20–23 contained mostly pteleine with some medicosmine, and succeeding fractions contained pteleine with lesser amounts

[4] Frolova, V. I., Kuzovkov, A. D., and Kibalchich, P. N., *Zh. obshch. Khim.*, 1964, **34**, 3499.

of two other alkaloids. After crystallization of medicosmine from fractions 16–19, dictamnine was isolated from the mother liquors by preparative t.l.c. on plates of Kieselgel G developed with ethyl acetate–benzene (1 : 3). From methylene chloride–light petroleum it formed colourless crystals (2·5 mg) which melted at 132·5–133° and showed no m.p. depression on mixing with authentic dictamnine.

Pteleine (3·5 mg) was isolated by preparative t.l.c. from fractions 20–23. It was obtained as crystals, m.p. 136–138°, from chloroform–light petroleum, and gave a picrate, m.p. 197–198°. Heating with methyl iodide gave isopteleine, m.p. 212–213°, which was identified by a mixed melting point determination and comparison of its i.r. spectrum with that of authentic isopteleine.[2]

Thin-layer chromatography of fractions 29–33 yielded a third minor base which gave crystals, m.p. 136–137°, from chloroform–light petroleum, and showed a yellow fluorescence in ultraviolet light. Only methyl signals were clearly resolved in the n.m.r. spectrum of this base and insufficient material was available for further characterization.

Acknowledgment

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