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THE STRUCTURE AND STEREOCHEMISTRY OF MICRANTHINE

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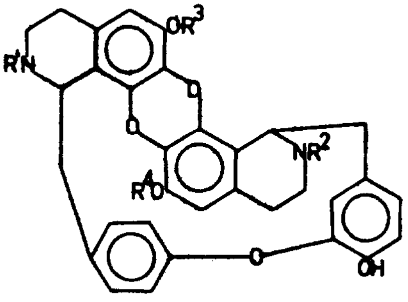
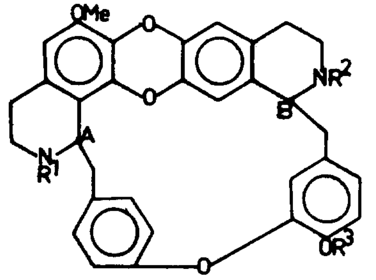
Micranthine was first isolated as a minor alkaloid from bark of Daphnandra micrantha Benth. (Monimiaceae) by Pyman,[1] who ascribed the formula $C_{36}H_{32}O_6N_2$ to it and found it gave a blue colour with a mixture of nitric and sulphuric acids. This colour test was interpreted by Bick and Todd[2] as due to the presence of a dibenzodioxin system,[3] and from analyses and degradative studies they proposed a structure of type (I) for micranthine, but were unable to decide between several possible structural isomers.

From D. micrantha bark collected in Whian Whian State Forest, New South Wales, we have isolated a sample of micranthine identical (m.p. and mixed m.p., m.s., i.r., and t.l.c.) with the original material described by Pyman.[1] The p.m.r. spectrum showed the presence of one methoxyl and one N-methyl group and ten aromatic protons, and the molecular ion in the mass spectrum appeared at m/e 548. These data are at variance with a structure of type (I) and point rather to an isotrilobine-type structure with one phenolic group instead of the two adduced previously. O,N-Dimethylmicranthine, m.p. 210-214°, in fact agrees closely in mass and i.r. spectra with isotrilobine, m.p. 213-215° (II),[3,4] and the p.m.r. spectra of the two are superimposable, but differ considerably from those of the synthetic isomers (IV) and (V).[5] The specific rotation of O,N-dimethylmicranthine ($[\alpha]_D^{20}$ -241°) is, however, of opposite sign to that of (II), and the two bases are evidently enantiomers, but should give the same product on Hofmann degradation: both indeed give a methine base, $[\alpha]_D$ ±0, with the same reported melting point of 115°.[2,4]

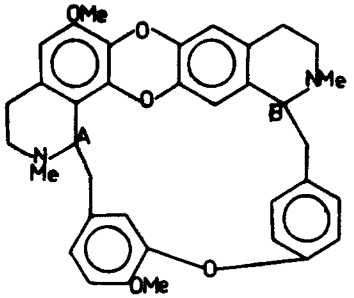
The structure of isotrilobine (II) has been rigorously established by degradation[4,6] and by synthesis,[7] and the absolute configurations of the two asymmetric centres have been shown to be S S.[5] The R R enantiomer, (III), has also been prepared as its picrate,[8] m.p. 188-189°, $[\alpha]_D$ -226°. Although we have not been able to make a direct comparison between the two, we consider O,N-dimethylmicranthine (picrate: m.p. 189-190°, $[\alpha]_D$ -218°) to be identical with (III).



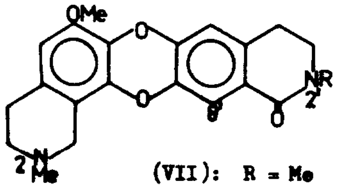
(I): $R^1 = H$, $R^2 = Me$ or *vice versa*
$R^3 = H$, $R^4 = Me$ or *vice versa*



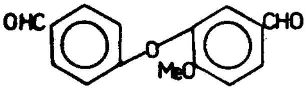
(II): $R^1 = R^2 = R^3 = Me$; $A = B = $ *S*
(III): $R^1 = R^2 = R^3 = Me$; $A = B = $ *R*
(IX): $R^1 = Me$, $R^2 = R^3 = H$; $A = B = $ *R*



(IV): $A = $ *R*, $B = $ *S*
(V): $A = $ *S*, $B = $ *S*



(VII): R = Me
(VIII): $R = CD_3$



(VI)

The phenolic hydroxyl group in micranthine had been located previously in a benzyl residue by ethylation and degradation,[2] and this position has been confirmed by the strong doubly- and singly-charged ions, formed by double benzylic fission, which appear in the mass spectrum of micranthine at m/e 168 and m/e 335 respectively, the latter involving loss of hydrogen as well.[9] The locations of the secondary amino and methylimino groups remained to be fixed; accordingly, a preliminary oxidative photolysis[10] was carried out on O,N-dimethylmicranthine (III), from which the dialdehyde (VI)[11] was obtained together with a lactam carbinolamine intermediate, which was reduced with sodium borohydride[10] to the corresponding aminolactam. The spectroscopic properties and reactions of the latter, including the high-resolution m.s., were in complete accord with structure (VII), and in particular the p.m.r. spectrum showed a low-field aromatic singlet at τ 2.42, assigned to the $C^{8'}$ – H which lies in the deshielding zone of the amide carbonyl; the protons of the 2'-N-CH_3 group likewise resonate at considerably lower field (τ 6.86) than those of the corresponding 2-N-methyl (τ 7.52). When O-methyl-N-trideuteriomethylmicranthine, formed by N- alkylating[12] O-methylmicranthine with formaldehyde-d_2[13] and sodium borodeuteride, was degraded by the same method, the aminolactam produced had a p.m.r. spectrum which differed from that of (VII) only in having the τ 6.86 peak reduced to about half intensity, corresponding to a 50% incorporation of deuterium into the 2'-methylimino group. The structure of the deuteriated compound must thus be (VIII), and micranthine is represented by (IX).

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