Neumarine, a Bis-isococlaurine Alkaloid

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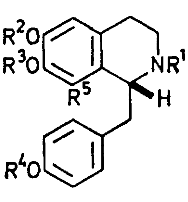
Summary Nemuarine, obtained from a New Caledonian monimiaceous plant, has structure (VI) and is the first example of a 5-6′ linked bisbenzylisoquinoline alkaloid, presumably derived from two isococlaurine units.

The monimiaceous plant *Nemuaron vieillardii* Baill., endemic in New Caledonia, has been found to contain an alkaloid m.p. 220—221°, $[\alpha]_D^{20}$ − 42·7° ($CHCl_3$), for which the formula $C_{37}N_{40}N_2O_6$ has been established by microanalysis and mass spectrometry. This base, which we have called nemuarine, is the major alkaloid of the leaves, but it also occurs in small amounts in the bark; both contain a number of other alkaloids which will be reported on elsewhere. The formula and spectroscopic data of nemuarine pointed to its being a bisbenzylisoquinoline alkaloid of a head-to-head, tail-to-tail type, with three methoxy- and two methylimino-groups, and a phenolic hydroxy-group which can be methylated with diazomethane. The mass spectrum of neumarine in particular shows intense doubly and singly charged ions at $(M-212)/2$ and $M - 213$, respectively, corresponding to a double benzylic cleavage and loss of a diphenyl ether fragment, plus an extra hydrogen atom in the latter case;[1,2] these ions show also that the phenolic hydroxy-group is present in a benzyl residue. This location is confirmed by the mass spectrum of *O*-methylnemuarine in which the expected mass shifts of the corresponding ions are observed.

The methoxy- and methylimino-protons for the abovementioned types of bisbenzylisoquinolines resonate at characteristic chemical shifts[2,3] depending upon the particular structure and stereochemistry. The corresponding proton singlets for *O*-methylnemuarine [τ 7·43 (6H), 7·11 (3H), 6·35 (3H), 6·24 (3H), 6·16 (3H)] form a pattern distinctly different from those of previously known types, and in particular, one of the methoxy-groups appears to be shielded to an unprecedented degree: this implies that *O*-methylnemuarine belongs to a structural type not previously encountered. On reduction with sodium in liquid ammonia,[4] it gave a phenolic and a non-phenolic product, which proved identical with (—)-*N*-methylisococlaurine (I) and (—)-*O*-methylarmepavine (II), respectively. When *O*-methylnemuarine was first deuteriated[5] under acid conditions, the Birch reduction gave (I) and a non-phenolic product with an n.m.r. spectrum almost the same as that of (II) except that the high-field aromatic singlet at τ 4·02 had virtually disappeared. This signal is produced by the shielded C-8 proton of armepavine,[6] so that the non-phenolic product must be represented by (III), and in the original *O*-methylnemuarine, the armepavine unit must be linked at C-5 to the isococlaurine unit; *O*-methyl nemuarine and nemuarine thus have structures (V) and (VI), respectively, and nemuarine is the first example of an alkaloid with a 5–6′ ether link between the isoquinoline residues. The largest group of bisbenzylisoquinolines, considered to be formed by a phenol oxidation process from two coclaurine (IV) units,[7] are linked 8–7′, while smaller groups linked 5–7′ or 8–6′ are presumably derived from one coclaurine and one isococlaurine unit.[2] In line with this the biosynthesis of nemuarine would appear to involve two isococlaurine units.

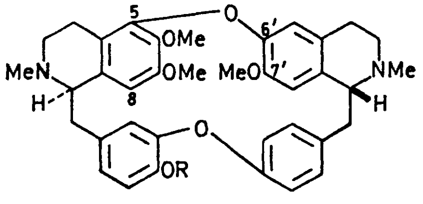


(I) $R^1 = R^3 = Me$, $R^2 = R^4 = R^5 = H$

(II) $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = H$

(III) $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = D$

(IV) $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$



(V) R = Me

(VI) R = H (Nemuarine)

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[1] M. Tomita, T. Kikuchi, K. Fujitani, A. Kato, H. Furukawa, Y. Aoyagi, M. Kitano, and T. Ibuka, *Tetrahedron Letters*, 1966, 875; D. C. DeJongh, S. R. Shrader, and M. R. Cava, *J. Amer. Chem. Soc.*, 1966, **88**, 1052; J. Baldas, Q. N. Porter, I. R. C. Bick, and M. J. Vernengo, *Tetrahedron Letters*, 1966, 2059; J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, *J.C.S. Perkin I*, 1972, 592; J. Baldas, I. R. C. Bick, M. R. Falco, J. X. de Vries, and Q. N. Porter, *ibid.*, p. 598.

[2] J. Baldas, Q. N. Porter, I. R. C. Bick, G. K. Douglas, M. R. Falco, J. X. de Vries, and S. Yu. Yunusov, *Tetrahedron Letters*, 1968, 6315.

[3] I. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Vernengo, *J. Chem. Soc.*, 1961, 1896; M. R. Falco, J. X. de Vries, A. G. de Brovetto, Z. Macció, S. Rebuffo, and I. R. C. Bick, *Tetrahedron Letters*, 1968, 1953; E. Fujita, T. Tomimatsu, and Y. Kitamura, *Bull. Inst. Chem. Res., Kyoto Univ.*, 1964, **42**, 235.

[4] M. Tomita, E. Fujita, and F. Murai, *J. Pharm. Soc. Japan*, 1951, **71**, 226, 1035.

[5] M. R. Falco, J. X. de Vries, Z. Macció, and I. R. C. Bick, *Chem. Comm.*, 1971, 1056; Y. Inubushi, T. Kikuchi, T. Ibuka, and I. Saji, *Tetrahedron Letters*, 1972, 423.

[6] M. Tomita, T. Shingu, K. Fujitani, and H. Furukawa, *Chem. and Pharm. Bull.* (*Japan*), 1964, **13**, 921.

[7] D. H. R. Barton and T. Cohen, 'Festshrift Arthur Stoll,' Birkhäuser, Basel, 1957, p. 117; D. H. R. Barton, G. W. Kirby, and A. Wiechers, *Chem. Comm.*, 1966, 266.