Biomimetic Synthesis of the Bis-indole Alkaloid Macralstonine

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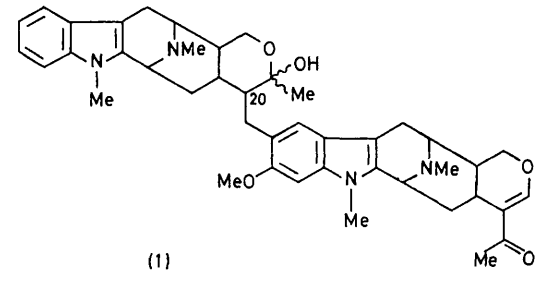
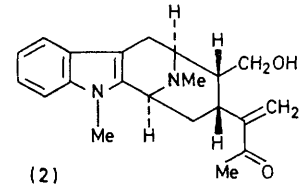
Summary Macralstonine (**1**) has been synthesized from macroline (**2**) and alstophylline (**3**) in dilute aqueous HCl, following a likely biogenetic route.

THE powerfully hypotensive[1] *Alstonia* bis-indole alkaloid[2] macralstonine, a constituent of *A. macrophylla*[3] and *A. muelleriana*,[4] was assigned the unique structure (**1**)[3] (without stereochemistry) from chemical and spectral data. Schmid and his co-workers have envisaged its possible biogenesis[5] from macroline (**2**)[6] and alstophylline (**3**).[7] Extending our recent biomimetic syntheses of villalstonine[8,10] and alstonisidine,[9,10] we now report a biomimetic synthesis of macralstonine.

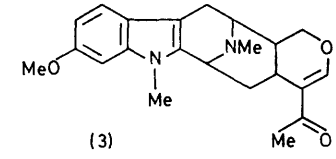
Alstophylline (**3**) was stirred with excess of macroline (**2**) in 0·2N-aqueous HCl at 20° for 120 h. Preparative layer chromatography of the isolated bases (SiO_2 gel) gave, in 40% yield, an amorphous solid indistinguishable from pure macralstonine on t.l.c. (3 systems), and with a virtually identical i.r. spectrum. The 100 MHz n.m.r. spectra of the synthetic and natural alkaloids were superimposable except that in the former the OMe group gave two signals of equal intensity (δ 3·84 and 3·90 p.p.m.: natural alkaloid, 3·90 p.p.m.), one NMe signal was similarly doubled, (δ 3·57 and 3·55 p.p.m.), the δ 2·38 p.p.m. N^b–Me signal in the natural base was also divided (δ2·38 and 2·42 p.p.m.), and the other N^b–Me signal (δ 2·26 p.p.m.) was slightly broadened.



(1)



(2)



(3)

Acetylation of the synthetic material (Ac_2O; pyridine; 40°) gave one product indistinguishable from *O*-acetylmacralstonine prepared from the natural base in t.l.c., i.r., and also the n.m.r. spectrum, the divided signals having coalesced to singlets identical with those in natural material, and with those previously reported.[3] The synthesis probably initially gives a mixture of C-20 epimers, and the acetylation step seems to involve conversion of the C-20-*epi*-macralstonine into *O*-acetylmacralstonine. Further work to establish the details of this process is under way.

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