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ANTHOCEPHALUS ALKALOIDS: CADAMBINE AND 3α-DIHYDROCADAMBINE.

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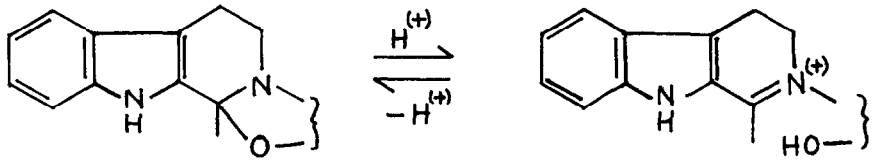
Investigation of the polar constituents of Anthocephalus cadamba by gel-permeation and ion-exchange chromatography has led to the isolation of two related indole alkaloid glycosides- cadambine, $C_{27}H_{32}N_2O_{10}$, m.p. 207-211° $[\alpha]_D^{25}$ -71°, and 3α-dihydrocadambine, $C_{27}H_{34}N_2O_{10}$, $[\alpha]_D^{25}$ -40°. We propose the novel structures 1 (R = H) and 2a (R = R' = H) respectively on the basis of chemical and spectroscopic evidence of which only the salient features are outlined below[1].

Cadambine had four acylable sites, as shown by formation of acetate, m.p. 149-151° $[\alpha]_D^{25}$ - 93° and propionate derivatives differing by 56 m.u. None of these involved nitrogen since Zemplen O-deacetylation followed by propionylation gave only the tetrapropionate derivative, and consequently the basic nitrogen function must be tertiary.

In neutral and basic solution the UV spectrum was the sum of indole and β-alkoxy-acrylate chromophores, but stepwise addition of acetic acid caused the progressive appearance of a 3,4-dihydro-β-carbolinium absorption at 360 nm. This process was immediately reversed on basification, which suggested an



equilibrium of the form shown above. Accordingly, reduction of cadambine tetra-acetate with $NaBH_4$ in acetic acid afforded two dihydrocadambine tetra-acetates, the major product (2b, R = H, R' = Ac) having a 3β and the minor (2a, R = H, R' = Ac) having a 3α configuration, as judged from their CD spectra[2]. Both now contained a new secondary hydroxyl group since acetylation caused one proton at τ 5.8 in the n.m.r. spectra to shift downfield by ca. 1.1 p.p.m. in both cases. Subsequently, 3α-dihydrocadambine penta-acetate (2a, R = R' = Ac), m.p. 197-199° $[\alpha]_D^{25}$ - 135° was found to be identical with the acetate derivative of the second alkaloid isolated from A. cadamba and hence linked the two structure determinations.

Confirmation of the basic tetrahydro-β-carboline structure of cadambine tetra-acetate was provided by mass spectral ions at m/e 184, 170, 169, and 156, four aromatic protons between τ 2.4 and 3.1 and an indolic NH at τ 0.4 in the n.m.r. spectrum. A methyl β-alkoxyacrylate chromophore was consistent with i.r. bands at 1710 and 1630 cm^{-1}, a methoxyl spike at τ 6.39 and a vinyl hydrogen singlet at τ 2.55. Characteristic ions at m/e 381 (M-331), 365 (M-347), 331, 169, 109 and n.m.r. signals at τ 5.44(H_a-6'), 5.81(H_b-6'), 6.26(H-5'), 4.7 - 5.0(H-1',2',3',4') and 7.97 - 8.03 (4Ac) indicated a glucoside tetra-acetate. Subsequent cleavage of cadambine with β-D-glucosidase confirmed the nature of the sugar moiety.

At this stage the above data coupled with general biogenetic reasoning suggested for cadambine the gross structure 1 (R = H) which also readily explained intense ions at m/e 321, 225, and 139 in the mass spectra of its acyl derivatives. (See Scheme).

Detailed examination of n.m.r. spectra with double irradiation and benzene shifts enabled the most important protons to be assigned accordingly, and, furthermore, coupling constants provided information about the relative stereochemistry. For instance, in cadambine tetra-acetate H-21(τ 4.35) had a trans-diaxial coupling (9.5 Hz) with H-20(τ 8.36), which had a substantial cis-interaction (6 Hz) with H-15(τ ~6.8) and a small one (~ 2 Hz) with H-19(τ 5.22); in turn H-19 was strongly coupled (7 Hz) to the cis H-18_b (τ 7.09) but only weakly (< 1 Hz) to H-18_a (τ 6.55). Similar analyses for 3α-dihydrocadambine and its derivatives confirmed that it had structure 2a.

Finally, the CD spectrum of cadambine exhibited a strong negative Cotton effect between 250 and 300 nm indicating an α orientation of the alkyl residue at C-3(S). It followed from the rigidity of the bridged structure that the absolute configuration was then as indicated in 1, which was, moreover, in agreement with its derivation from secologanin.

Cadambine and dihydrocadambine are thus analogues of rubenine[3] with the unusual N-4 — C-18 bond in a seven-membered ring. Presumably 3α-dihydrocadambine is derived from 18,19S-epoxystrictosidine and then undergoes further oxidation to cadambine.

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References.

1. Formulae for all molecules and ions were determined by mass measurement; rotations were measured in methanol.

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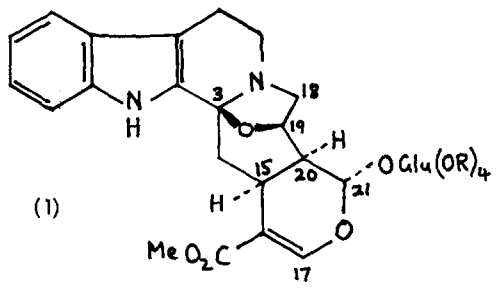

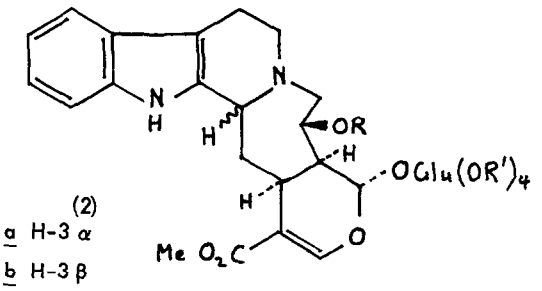

Scheme.