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ANTHOCEPHALUS ALKALOIDS: ISODIHYDROCADAMBINE.

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A recent communication[1] described the isolation and structure determination of cadambine and 3α-dihydrocadambine (2) from Anthocephalus cadamba. We now report a third glycosidic indole alkaloid - isodihydrocadambine - for which we propose the structure 3a containing a novel N-4 — C-19 bond.

After gel permeation, ion exchange and partition chromatography of a methanolic extract, isodihydrocadambine was isolated as the acetate derivative $[\alpha]^{25}_{D}$ -66° (MeOH), for which a molecular formula of $C_{37}H_{44}N_2O_{15}$ was established by mass measurement. The molecular ion of the corresponding propionate derivative differed by 70 m.u., indicating five acylable groups; none involved nitrogen since all were deacylated by brief treatment with sodium methoxide, and the basic function must therefore be a tertiary amine. Mild catalytic hydrogenation had no effect, so no readily reducible double bonds were present.

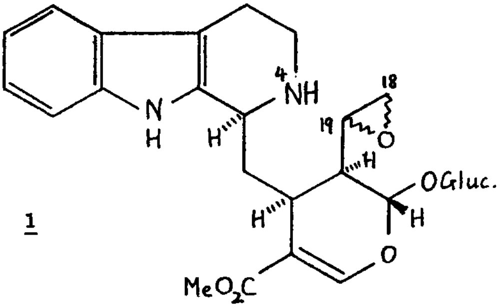
The UV spectrum was consistent with the presence of indole and methyl β-alkoxyacrylate chromophores, which were confirmed by signals in the NMR spectrum at τ 2.25 (s, $>$NH), 2.4-3.2 (m, 4 aromatic H) 2.61 (s, H-17) and 6.42 (s, $-CO_2CH_3$) and in the IR at 3485 ($>$NH) 1710 and 1645 ($-O-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$) cm^{-1}. Extension of the structure to a tetrahydro-β-carboline was possible from mass measurement of the typical ions at m/e 184, 170, 169 and 156[2], and also by oxidation to a 3,4-dihydro-β-carbolinium chromophore (λ_{max} 372 nm) with mercuric acetate.

A further characteristic[3] mass spectral series at m/e 381 (M-331) 365 (M-347), 331, 169 and 109 indicated a hexoside tetraacetate, which also had NMR signals at τ 4.7 - 5.3 (H-1', 2', 3', 4'), 5.82 (H_2-6') 6.4 (H-5') and 7.91 - 8.02 (4Ac). Deacetylation and cleavage with β-D-glucosidase established the identity of the sugar. Unlike the glucoside, on addition of alkali the UV spectrum of the aglucone underwent a rapid, large increase in absorption at ca. 275 nm attributable to ionization of a β-hydroxyacrylate chromophore. Since the mass spectrum indicated that the sugar was not attached as an enol ether the newly liberated hydroxyl group must form part of a labile hemi-acetal system: $MeO_2C-\overset{|}{C}=\overset{|}{C}-\underset{|}{\overset{|}{C}}-OH$.

The partial structure so far apparent was reminiscent of dihydrocadambine and derived from very similar spectral and chemical data. However, one striking difference was an intense ion at m/e 683 ($C_{34}H_{39}N_2O_{13}$) in the mass spectrum of isodihydrocadambine acetate which had no counterpart in the other. This was attributed to a loss of a $-CH_2OAc$ group so facile as to be consistent only with the cleavage of a C - C bond α to N-4 where the resulting ion was stabilised by the lone pair. A close analogy was provided by adirubine triacetate (4)[4] whose base peak was formed by loss of $-CH_2OAc$ from C-5 which was likewise α to nitrogen. However, in the present case substitution at C-5 was excluded by the occurrence of the β-carbolinium fragments at m/e 184, 170, 169 rather than 182, 169, 168[2], and the dehydrogenation by mercuric acetate eliminated C-3 as a likely site. The $-CH_2OAc$ must therefore have been part of the third alkyl group of the tertiary amine outside ring C. Assuming a reasonable biogenesis from secologanin the structure 3b for the acetate was consistent with the above data. Furthermore, it readily explained the base peak at m/e 335 ($C_{20}H_{19}N_2O_3$) as due to 6 formed by a favourable retro-Michael elimination from the immonium ion 5 - a process supported by metastable ions at 616.6 and 164.3.

A detailed examination of the NMR spectrum with the aid of decoupling allowed most of the hydrogens to be assigned in accordance with structure 3b and also provided stereochemical information. Thus H-21 (τ 4.16) had a trans-diaxial interaction (9.5 Hz) with H-20 (τ 7.84), which had a coupling (~ 5Hz, cis) with H-15 and also with H-19 (τ 7.04) although in the latter case the constant did not reveal the stereochemistry; in turn H-19 was coupled to the C-18 methylene group found as an AB pair at τ 5.5. Another ABX set of signals at τ 6.30 and 8.2 - 8.6 was attributed to H-3 and the C-14 methylene group respectively. By analogy with standard tetra- and pentacyclic indole alkaloids the chemical shift of H-3 suggested a 3α configuration (cis to H-15), which was supported by trans-quinolizidine IR bands in the 2700 - 2860 cm^{-1} region. Finally in the CD spectrum a strong positive Cotton effect between 300 and 260 nm established the absolute configuration at C-3 as α[5].

Hence isodihydrocadambine corresponds to 3a containing a N-4 — C-19 bond which is almost unique — the only other example being perakine (7), a probable artefact of vomeniline (8)[6]. It is presumably formed from an 18,19-epoxystrictosidine (1) by nucleophilic attack of N-4 on C-19 rather than C-18 as with dihydrocadambine (2). Whether isodihydrocadambine comes from the 19S epoxide like dihydrocadambine or is derived from the 19R remains an open question.



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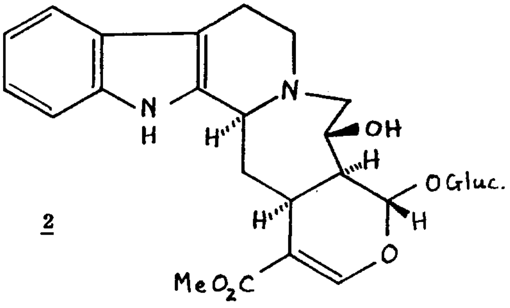

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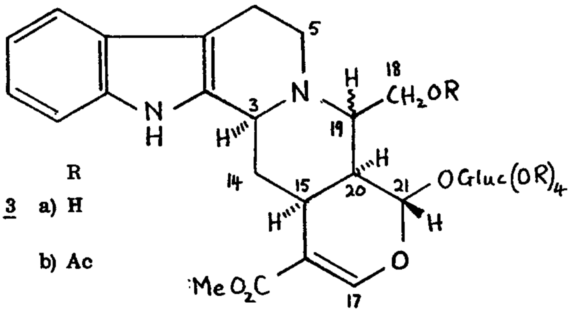
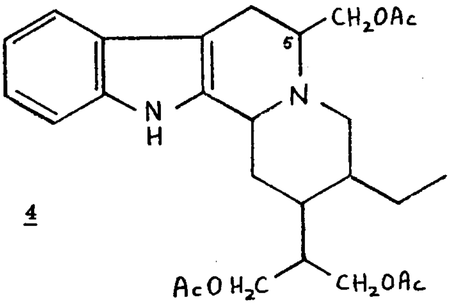


R

3 a) H

b) Ac



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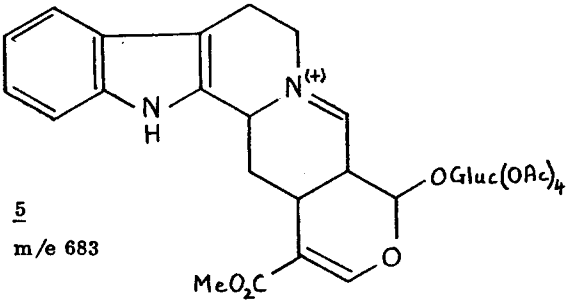

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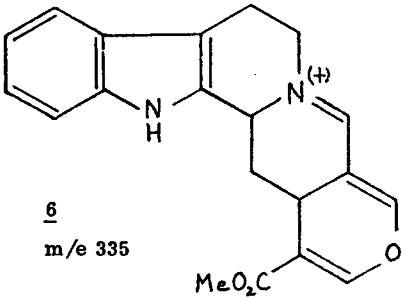
m/e 683



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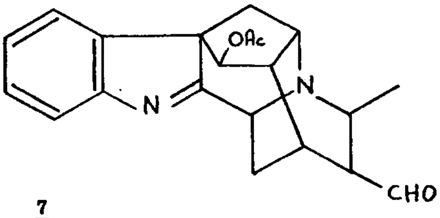
m/e 335



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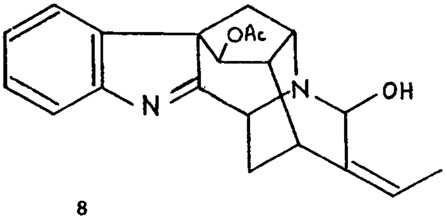

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