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SYNTHESIS OF DIHYDROANGUSTINE

R.T. Brown and A.A. Charalambides
Department of Chemistry, The University, Manchester M13 9PL,
and H.T. Cheung
Department of Pharmacy, University of Sydney, Sydney, Australia.

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The isolation of the indoloquinolizidine alkaloids angustine, angustoline and angustidine from Strychnos angustiflora Benth. has been recently reported and their structures assigned on the basis of spectral data[1]. Since pyridine alkaloids such as gentianine are known to arise from iridoid precursors[2] it seemed likely that angustine (and its congeners) could similarly be derived from secologanin and tryptamine via vincoside lactam or strictosidine lactam. In order to substantiate this and also provide a formal chemical proof of structure we undertook the partial synthesis of 18,19-dihydroangustine (1), previously prepared by catalytic hydrogenation of angustine.

Vincoside lactam[3,4] tetraacetate in methanol was hydrogenated over Adams catalyst, and subsequent Zemplen deacetylation afforded 18,19-dihydrovincoside lactam (2a) $[\alpha]_D^{25}$ - 77° (MeOH) λ_{max}^{MeOH} (log ε): 227 (4.45), 273 (3.91), 281 (3.85), 290 (3.81) nm. Cleavage of the sugar with β-glucosidase in pH 5 buffer gave the aglycone (2b), characterised by a large intensification at ca. 280 nm in its U.V. absorption on addition of alkali. On standing for 48 hrs. with concentrated ammonia the aglycone was converted to a product whose U.V. spectrum [λ_{max}^{MeOH} (log ε): 226 (4.31), 285 (4.17), 290 (4.16) nm] was quite different, and had a characteristic shift in acid solution [λ_{max}^{MeOH/H^+} (log ε): 225 (4.31), 284 (4.03) inf., 292 (4.06) inf., 306 (4.11) nm]. From I.R. and N.M.R. spectra it corresponded to the carbinolamine (3) but could not be identified further since it was so unstable that a molecular ion could not be detected in the mass spectrum.

Treatment of (3) with sulphur in refluxing xylene achieved dehydration and oxidation to a compound $C_{20}H_{19}ON_3$. Since the N.M.R. spectrum in TFA had two one-proton singlets at τ 0.55 and 1.45 corresponding to the two α positions of a pyridine, and the U.V. spectrum was virtually the sum of indole and nicotinamide chromophores, the product was readily assigned the structure of tetrahydroangustine (4). Finally, when (4) was allowed to stand in TFA overnight it was oxidised further to dihydroangustine (1) m.p. 289-294°; λ_{max}^{MeOH} (log ε): 221 (4.44), 252 (4.15), 290 (3.90), 300 (3.81), 375 (4.46), 395 (4.48) nm;

λ_{max}^{MeOH/H^+} (log ε): 220 (4.53), 248 (4.16), 260 (4.19), 289 (3.96) inf., 299 (3.91) inf., 326 (4.01), 439 (4.68) nm. This was identical in all respects to the compound derived from angustine and thus confirmed the structure previously proposed.

On standing in TFA for several days exposed to air the carbinolamine (3) also was slowly converted into dihydroangustine which suggests that angustine and its congeners could be artefacts of vincoside lactam aglycone.

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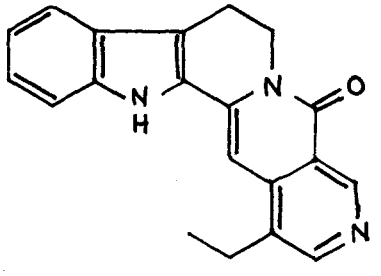

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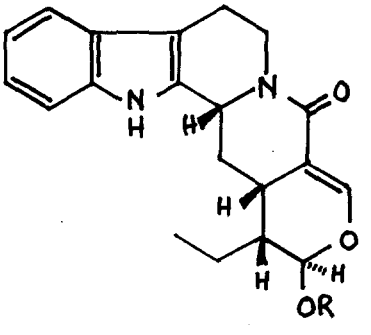
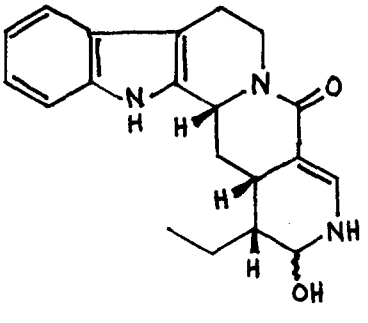


2 a) R = Gluc.
b) R = H



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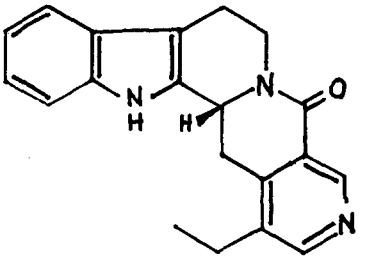

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