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HYDROXYSKYTANTHINES I AND II

TWO MINOR ALKALOIDS OF *SKYTANTHUS ACUTUS* MEYEN

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Abstract—Hydroxyskytanthines—I and —II, two minor alkaloids from the leaves of *Skytanthus acutus* Meyen are represented respectively by VI and VII.

A PREVIOUS paper[1] has described the isolation of the minor alkaloid D, $C_{11}H_{21}NO$, m.p. 93°, from the leaf alkaloids of *Skytanthus acutus*. Subsequently one of two alternative structures I or II was assigned to alkaloid D on the basis of its dehydration to the naturally occurring[2] dehydroskytanthine III or IV, which on hydrogenation afforded δ-skytanthine V.[3]

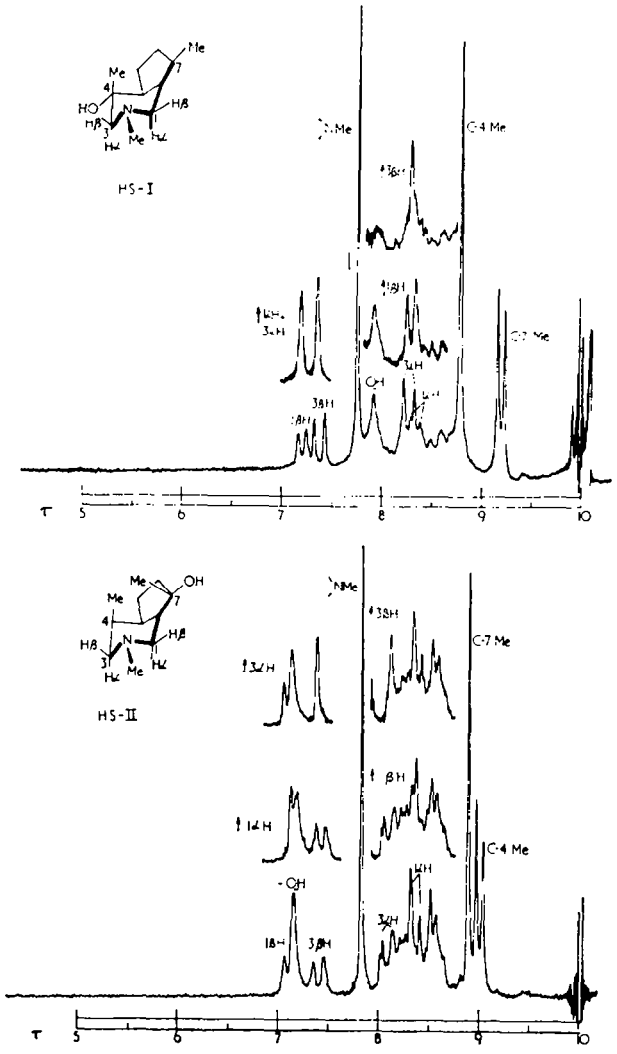
We have re-isolated alkaloid D, m.p. 94–95°, $[\alpha]_D$ +38·5° (cyclohexane), +35·8° (methanol), which we re-name hydroxyskytanthine—I [HS—I] and in addition have obtained in very small yield (0·001%) the isomeric hydroxyskytanthine—II [HS—II] m.p. 119–120°, $[\alpha]_D$ −38·5° (methanol) and assign to them respectively the structures VI and VII for the following reasons.

Like HS—I,[2] HS—II shows in its NMR spectrum evidence for the groupings $>NCH_3$ (3H singlet, τ 7·82), $>C(CH_3)OH$ (3H singlet, τ 8·88) and $>CH{\cdot}CH_3$ (3H doublet, J = 6 c/s, τ 9·00) (Figs 1 and 2). On the reasonable assumption that HS—II is also a hydroxyskytanthine (the similarity of its NMR spectrum to that of HS—I makes this very probable) its gross structure must be represented by VI or VII, HS—I then being VII or VI.

The structural and stereochemical deductions that follow are based largely on a detailed study of the regions in the NMR spectra of HS—I and HS—II ascribable to the four protons situated on carbon atoms 1 and 3 α to nitrogen (Figs 1 and 2). Thus the two equatorial β protons appear in both compounds as doublets in regions 0·8–1·3 τ downfield from their axial twins, as is the case with N-methylpiperidine.[4] In HS—II both low field doublets are further coupled with vicinal protons, whereas in HS—I only one doublet is so coupled. It follows that the tertiary OH is at C-4 in HS—I and therefore at C-7 in HS—II.

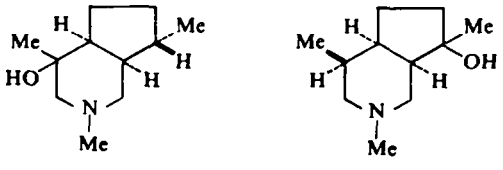
These conclusions are borne out by the mass spectra of the two substances. Thus the two most intense peaks in both at *m/e* 58 (100% HS—I and HS—II) and 44

[1] H. H. Appel and B Müller, *Scientia* (*Chile*) 1961, **115**, 3 (1961).
[2] C. G. Casinovi, F. Delle Monache, G. Grandolini, G. B. Marini-Bettolo and H. H. Appel, *Chem. & Ind.* 984 (1963).
[3] E. J. Eisenbraun, A. Bright and H. H. Appel, *Chem. & Ind.* 1242 (1962).
[4] J. B. Lambert and R. G. Keske, *J. Am. Chem. Soc.* **88**, 622 (1966).



FIGS. 1 and 2

(24% HS—I; 53% HS—II) are attributable[5] respectively to the ions VIII and IX. Peaks at *m/e* 84 (8%) and 110 (7%) attributable to ions X and XI on the other hand appear only in the spectrum of HS—II, in accordance with the assigned structures.



I II

[5] H. Budzikiewicz, C. Djerassi and D. H. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry* Vol. 1: *Alkaloids*, pp. 225–226. Holden-Day.

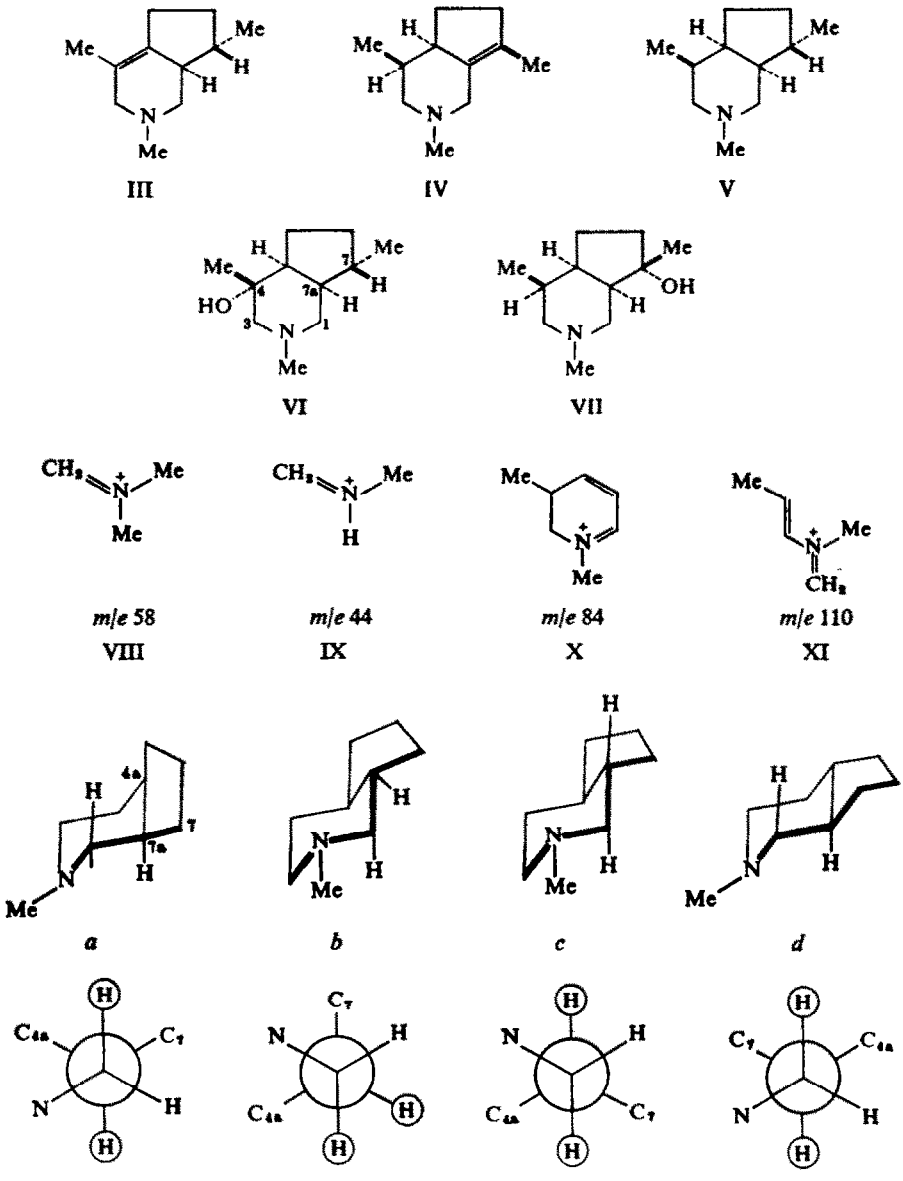


FIG. 3

Stereochemistry. Of the four possible configurations, a, b, c and d (Fig. 3)† in one antipodal series (that related to δ-skytanthine is here shown), *b* is unique in not having a pair of *trans*-axial hydrogens attached to carbon atoms 1 and 7a. In this case alone the doublet (large geminal coupling) arising from the C-1 axial proton will have a relatively minor additional coupling with the vicinal proton at C-7a. Double irradiation shows that this is the case with both HS—I and HS—II (Figs. 1 and 2).

† The large chemical shift previously mentioned between the axial and equatorial protons α to nitrogen [$\delta_{ae}(\alpha)$] in both hydroxyskytanthines shows that the N-methyl group must be equatorial.[4]

It therefore follows that both HS—I and HS—II must be *cis*-fused and exist in conformation *b*.

Based on conformation *b*, the OH groups in both HS—I and HS—II must be α-oriented, since the IR solution spectra show no evidence of intramolecular hydrogen bonding. Thus $\nu_{max}^{CCl_4}$ for HS—I is 3608, 3595(s) (two-OH conformations?) and for HS—II 3605 cm^{-1}. 3-Hydroxypiperidine[6] which approximates to HS—I with a C-4 β OH, has $\Delta\nu$ 89 cm^{-1}. If HS—II has a C-7 β OH, the shortest —OH . . . N distance (from Fieser models) is approx. 1·5 Å and again an intramolecular hydrogen bond would be expected.

The dehydroskytanthine (picrate m.p. 127°) obtained both naturally[2] and as a dehydration product of HS—I must be formulated as III.

EXPERIMENTAL

NMR spectra were obtained by Mr. J. Gall on the Varian HA 100 spectrometer, using approx. 0·2M solns in $CDCl_3$ with TMS as internal standard. IR spectra were taken by Mrs. F. Lawrie on the Unicam SP 100 spectrophotometer.

*Isolation of hydroxyskytanthines—*I *and* II. The extract from the leaves of *Skytanthus acutus* was prepared as previously described,[1] and the greater part of the skytanthines separated by steam distillation. Chf extraction of the remaining soln gave a mixture of bases (yield 0·1 %) which was chromatographed on alumina, affording successively hydroxyskytanthines—I and II. Hydroxyskytanthine—I (Alkaloid D; 0·005%), purified by sublimination, had m.p. (from cyclohexane) 94–95°, $[\alpha]_D^{19}$ +38·5° (*c*, 1·50 in cyclohexane), +35·8° (*c*, 1·80 in MeOH). It had NMR signals at τ 9·20 (3H doublet, C-7 Me), 8·77 (3H singlet, C-4 Me), 7·75 (3H singlet, N–Me), 8·32 (1H, doublet, J = 9 c/s C–1 α H) 8·25 (1H, doublet J = 12 c/s C–3 α H), 7·36 (1H, doublet, J = 12 c/s C–3 β H), 7·20 (2H doublet, J = 9 c/s C–1 β H).

Hydroxyskytanthine—II (0·001%), purified by sublimination had m.p. (from cyclohexane) 119–120°, $[\alpha]_D^{19}$ −38·5° (*c*, 1·00 in MeOH). The mixed m.p. with HS—I shows a strong depression. It had NMR signals at τ 9·00 (3H doublet, C-4 Me), 8·89 (3H singlet, C-7 Me), 7·83 (3H singlet, N–Me), 8·37 (1H doublet, J = 9 c/s C–1 α H), 8·09 (1H doublet, J = 11 c/s C–3 α H), 7·42 (1H doublet J = 11 c/s C–3 β H), 7·12 (1H doublet, J = 9 c/s C–1 β H).

TLC on Kieselgel G prepared with 0·1N NaOH, using MeOH–chf (1:1) gave for HS—I R_f 0·56–0·59, for HS—II R_f 0·30–0·33.

[6] J. Sicher and M. Tichy, *Coll. Czech. Chem. Comm.* 23, 2081 (1958).