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NEW ALKALOIDS FROM ALANGIUM LAMARCKII THW.

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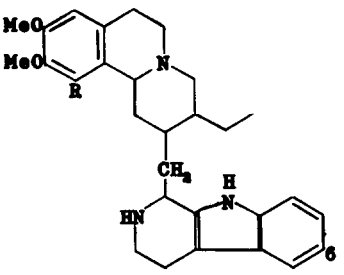
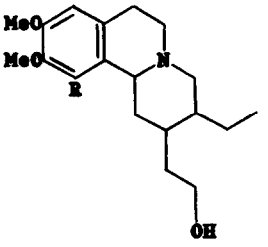
Our earlier work (1,2) on the alkaloids of Alangium lamarckii Thw. (fam. Alangiaceae), has been extended by examining the leaves of this plant and bases of previously unknown structure have been isolated in addition to the known (2) deoxytubulosine (I, R=H).

The first new alkaloid, alangimarckine, $C_{29}H_{37}N_3O_3$ (mol. wt. 475 by mass spectrum), has m.p. 184-6°, $[\alpha]_D^{25}$ -67.7° (pyridine). Its ultraviolet spectrum corresponds to the sum of isolated indole and di-, or tri-alkoxybenzene chromophores. Absorptions due to one OH group (3508 cm.$^{-1}$) and one NH group (3460 cm.$^{-1}$) appear in the infrared spectrum and these functions were confirmed by the infrared spectrum of N,O-diacetylalangimarckine (M^+, 559, mass spectrum), which shows absorptions at 1755 cm.$^{-1}$ (ArOAc) and 1630 cm.$^{-1}$ ($\rangle$NAc). The 100 Mc. n.m.r. spectrum of alangimarckine proves the presence of one C-methyl group (triplet, 9.16 τ) forming part of an ethyl residue, two O-methyl groups (singlets, 6.24 τ and

6.30 τ), one aromatic proton (singlet, 3.73 τ) and a complex of signals in the range 2.5 - 3.1 τ corresponding to four aromatic protons. A broad signal at 5.84 τ (1 H) is assigned to $-CH_2.\underline{CH}(Ar).NH-$ since it was shown by spin-decoupling to arise by interaction with a methylene group at 8.06 τ (see also below). Little change occurred in the position of these various signals when N,O-diacetylalangimarckine was examined save that the signal from the one aromatic proton moved downfield to 3.17 τ and the 5.84 τ signal was also shifted to 4.09 τ; singlets appeared at 7.83 (3 H) and 7.76 (3 H) corresponding to the N-, and O-acetyl groups.



(I)



(II)

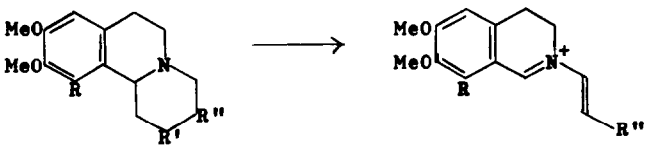
The structure of alangimarckine was revealed by its mass spectrum which is closely similar to those of tubulosine (I, R=H with OH at position 6) (3,4) and deoxytubulosine (I, R=H) (2). Those peaks in the spectra of the last two alkaloids derived from the benzoquinolizidine portion of their molecules are displaced to higher m/e values by 16 units in the spectrum of alangimarckine. Further, the base

peak at m/e 171 establishes the presence of an unsubstituted tetrahydro-β-carboline system. It follows that the phenolic hydroxyl group must be placed in the benzoquinolizidine moiety and bearing in mind the high field position of the n.m.r. signal from the one aromatic proton (3.73 τ) and the proven orientation for ankorine which accompanies it (see later), the structure (I, R=OH) can be assigned to alangimarckine. It is probable that the absolute stereochemistry of alangimarckine is identical with that of deoxytubulosine (2) and tubulosine (4) but lack of material has so far precluded the desired chemical correlation.

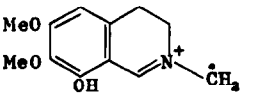
A second alkaloid, $C_{19}H_{23}NO_4$ (mol. wt. 335 by mass spectrum) has m.p. 174-6°, $[\alpha]_D^{28}$ -62° ($CHCl_3$), and is thus shown to be identical with ankorine, previously isolated from A. lamarckii Thw. (5). The structure (II, R=OH) has been deduced for this base which shows ultraviolet absorption corresponding to a tri-oxygenated aromatic ring (272 mμ, log ε 2.96 in EtOH); its phenolic nature was shown by the spectral change in alkali (to 287 mμ, log ε 3.43 in 0.1 N-NaOH). The infrared spectrum supports the presence of a phenolic hydroxyl group (3518 $cm.^{-1}$) and indicates a bonded hydroxyl group (3250 $cm.^{-1}$). Treatment of ankorine with diazomethane yields a monomethyl ether (M^+, 349) and acetylation of the alkaloid affords a diacetyl derivative (M^+, 419). The latter product shows absorptions in the infrared spectrum at 1758 $cm.^{-1}$ (ArOAc) and 1725 $cm.^{-1}$ (OAc).

Signals appear in the 100 Mc. n.m.r. spectrum of ankorine due to a C-methyl (3H, triplet, 9.12 τ) present in

an ethyl group, two O-methyl groups (6.22 τ and 6.24 τ) and a singlet (1H, 3.76 τ) corresponding to an aromatic proton. The position of the last signal agrees with a proton at position 5 of a 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6) and the shift of this signal to 3.36 τ in the spectrum of O,O-diacetylankorine supports (7) the orientation shown at (II, R=OH). In addition to signals corresponding to the O-acetyl residues, the spectrum also displayed a multiplet (2H) at 5.85 τ arising from the $-CH_2$.OAc system in place of a multiplet at 6.33 τ in the case of ankorine, due to $-CH_2$.OH. These results establish the primary nature of the alcoholic group.



(III) (IV)



(V)

The mass spectrum of ankorine (II, R=OH) was closely similar to that of dihydroprotoemetine (II, R=H) (8) save that the important peaks corresponding to fragments containing the isoquinoline residue (see later) were displaced to higher m/e values by 16 units; this mass spectrometric shift (9) provides powerful evidence that ankorine is the phenolic relative of dihydroprotoemetine. Many benzoquinolizidines of known constitution (III) have been examined in the mass spectrometer and an important fragmentation (10) leads to the ion (IV). A strong peak appears in the spectrum of ankorine at m/e 262 corresponding to (IV, R=OH, R'' =Et) and this was replaced in the spectra of O-methylankorine and O,O-diacetylankorine by peaks respectively at m/e 276 and 304. The base peak in the spectrum of ankorine is at M^+-1 (loss of H α to nitrogen) and further important fragments appear at m/e 320, 318, 221, 207 and 192; the last three can be assigned, respectively to the radical ion (V) and to the corresponding ions lacking CH_2 and CH_2 plus CH_2. Confirmation of this assignment was obtained from the mass spectra of O-methyl-, and O-ethylankorine when the corresponding sets of three fragments appeared respectively at m/e 235, 221, 206 and at 249, 235, 220.

Ferricyanide oxidation of O-ethylankorine afforded 3-ethoxy-4,5-dimethoxyphthalic acid, isolated as the N-methylimide and identified by full spectroscopic study, m.p. and mixed m.p. 92° with authentic material (11). The structure (II, R=OH) can thus be assigned to ankorine with the absolute stereochemistry yet to be determined.

The third base closely followed deoxytubulosine (I, R=H) through all our fractionation steps and was not obtained totally free from the indolic base. The mass spectrum of the best preparation was identical with that of dihydroprotoemetine,(II, R=H; Found: M^+, 319.2138, $C_{19}H_{29}NO_3$ requires 319.2147). The identity was confirmed by comparing the Alangium alkaloid with authentic dihydroprotoemetine (8) (II, R=H) by thin-layer chromatography on silica gel and alumina in a range of solvents (12). The presence of dihydroprotoemetine in a specimen of slightly impure cephaeline from A. lamarckii Thw. was recently detected mass spectrometrically but the substance was not isolated (13).

The occurrence in A. lamarckii Thw. of dihydroprotoemetine with tubulosine (I, R=H with OH at position 6) and deoxytubulosine (I, R=H) (cf. 14) is of considerable biosynthetic interest and this holds also for ankorine (II, R=OH) and alangimarckine (I, R=OH). Tracer experiments with A. lamarckii Thw. plants are in progress.

References

1. R.S. Kapil, D.S. Bhakuni, N. Anand and M.L. Dhar, J. Sci. Ind. Res., India, 20B, 136 (1961).
2. A.R. Battersby, J.R. Merchant, E.A. Ruveda and S.S. Salgar, Chem. Comm., 315 (1965).
3. P. Brauchli, V. Deulofeu, H. Budzikiewicz and C. Djerassi, J. Amer. Chem. Soc., 86, 1895 (1964).

4. H. Monteiro, H. Budzikiewicz, C. Djerassi, R.R. Arndt and W.H. Baarschers, Chem. Comm., 317 (1965); H.T. Openshaw and N. Whittaker, Chem. Comm., 131 (1966).

5. B. Dasgupta, J. Pharm. Sci., 54, 481 (1965).

6. D.H.R. Barton, R. James, G.W. Kirby, D.W. Turner and D.A. Widdowson, Chem. Comm., 294 (1966); T. Kametani, K. Ohkubo and I. Noguchi, J. Chem. Soc. C, 715 (1966).

7. R.J. Highet and P.F. Highet, J. Org. Chem., 30, 902 (1965).

8. A.R. Battersby and B.J.T. Harper, J. Chem. Soc., 1748 (1959).

9. K. Biemann, Tetrahedron Letters, No. 15, 9 (1960).

10. We are grateful to Professor K.L. Rinehart for helpful discussion on this point.

11. R.H.F. Manske and H.L. Holmes, J. Amer.Chem. Soc., 67, 95 (1945). We thank Dr. R.H.F. Manske for providing the comparison sample.

12. Dr. R.R. Arndt has kindly informed us that dihydroprotoemetine has been detected in a South African plant in his Laboratory.

13. J.D. Albright, J.C. Van Meter and L. Goldman, Lloydia, 28, 212 (1965).

14. A. Popelak, E. Haack and H. Spingler, Tetrahedron Letters, 1081 (1966).