ALANCINE, A NEW BENZOQUINOLIZIDINE ALKALOID FROM ALANGIUM LAMARCKII

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Abstract — The new benzoquinolizidine alkaloid alancine (1) has been isolated from the stem bark of Alangium lamarckii Thw. (Alangiaceae) and characterized by spectral evidence and preparation from ankorine (2).

Alangium lamarckii Thw. (Alangiaceae) is a deciduous tree or small shrub indigenous to the forests of India and Burma.[1] Extracts of the root bark of this plant have been used medicinally as an anthelmintic, purgative, emetic and febrifuge as well as in the treatment of leprosy and other skin diseases.[1] The genus Alangium is a rich source of alkaloids of numerous classes, including benzoquinolizidines, benzopyridoquinolizidines, benzoquinolizidine-isoquinoline dimers, benzoquinolizidine-β-carboline dimers as well as the pyridine bases venoterpine and anabasine, the tetrahydroisoquinoline salsoline, the amino alcohol N-benzoylphenylalaninol and the tetrahydroprotoberberine bharatamine.[2]

Extraction of the defatted stem bark (15 kg) with ethanol and systematic partitioning in the usual fashion[3] afforded a nonquaternary and a quaternary alkaloid fraction, the latter of which was precipitated as a Mayer's complex and passed through a column of anion exchange resin (Cl).[3] The eluted quaternary and/or water soluble alkaloids were chromatographed over silicic acid in chloroform and elution with chloroform-methanol (9:1) afforded alancine (1) (8 mg), mp 229-230°C; $[\alpha]_D^{25}$ -40° (c 0.1, MeOH); uv, λ_{max}^{MeOH} nm (log ε) 230 (sh) (3.56), 273 (2.86) and 282 (2.84) with a bathochromic shift in alkali to 282 nm and 293 (sh); ir, ν_{max}^{KBr} cm^{-1} 3325 (br), 2720, 1725, 1615, 1590, 1515, 1465, 1440, 1420, 1410, 1395, 1370, 1340, 1330, 1295, 1245, 1205, 1180, 1168, 1160, 1125, 1110, 1055, 1045, 1015, 997, 982, 970, 935, 875, 860 and 808.

The salient features of the ^{1}H-nmr spectrum (90 MHz, CD_3OD, TMS, δ in ppm) included the presence of one C-methyl group at 0.97 (3H, t, J=6 Hz, $CH_2\underline{CH}_3$), two methoxy groups at 3.77 (3H, s) and 3.82 (3H, s) and one aromatic proton at 6.41 (1H, s). The ms exhibited the M^+ at m/z 349 (40%) for $C_{19}H_{27}O_5N$ with other significant fragment ions at m/z 348 (75%), 334 (18), 332 (28), 320 (5), 290 (16), 262 (56), 221 (72), 207 (8), 192 (82) and 55 (100). Alancine was soluble in polar solvents including water and methanol but insoluble in less polar solvents such as acetone, chloroform and benzene. It displayed tlc behavior consistent with a quaternary base but on treatment with methyl iodide formed a compound whose R_f was lower than that of alancine itself, suggesting that alancine was a water-soluble alkaloid. A consideration of the solubility, tlc behavior and spectral data (particularly the ms with its retro-Diels-Alder fragment ion at m/z 262[4,5] plus the ir spectrum with its carbonyl function[6] at 1725 cm^{-1}) suggested that alancine was an ankorine (2) analog containing two methoxy groups and one phenolic hydroxy group in ring A and a carboxylic acid function in ring C.

Treatment of alancine (5 mg) with diazomethane afforded O-methylalancine methyl ester (3) whose ^{1}H-nmr spectrum (90 MHz, $CDCl_3$, TMS, δ in ppm) indicated the presence of one C-methyl group at 1.21 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), one aliphatic methyl ester group at 3.70 (3H, s)[7], three aromatic methoxy groups at 3.83 (3H, s) and 3.84 (6H, s) and one aromatic proton at 6.47 (1H, s). The ms showed M^+ at m/z 377 (8%)(28 mass units higher than alancine) for $C_{21}H_{31}O_5N$ and other significant fragment ions at m/z 362 (4%), 346 (6), 304 (2), 276 (12), 235 (20), 221 (25), 206 (22) and 55 (100). Oxidation of ankorine (2) (10 mg) in DMSO and H_3PO_4 with DCC[8] at 50°C for 8h followed by work-up and then stirring with Ag_2O[9] in MeOH for 8h afforded, after purification via preparative tlc, a white residue (2 mg), mp 225°C, $[\alpha]_D^{28}$ -49° (c 0.12, MeOH), identical to alancine (mp, specific rotation, uv, ms, tlc, co-tlc).

A comparison of the ^{13}C-nmr spectra (22.5 MHz) of alancine (1) (CD_3OD) and ankorine (2) ($CDCl_3$)[10] showed great similarity despite solvent differences (chemical shifts for ankorine (2) are given first and those for alancine (1)[11] are given second): C-1[a] (37.5) (37.2), C-2 (36.7) (35.9), C-3 (42.2) (39.4), C-4 (62.5) (61.2), C-6 (60.6) (59.3), C-7[b] (24.4) (21.9), C-7a (116.2) (113.2), C-8 (148.6) (149.1), C-9[c] (136.0) (137.2), C-10 (152.3) (153.7), C-11 (101.4) (101.4), C-11a[c] (134.5) (128.7), C-11b (64.2) (63.7), $\underline{CH}_2CH_3$[b] (24.2) (23.6), $CH_2\underline{CH}_3$ (11.3) (10.5), $\underline{CH}_3O$ at C-9 (56.5) (56.6), CH_3O at C-10 (53.1) (52.2), $\underline{CH}_2CH_2OH$[a] (38.7) (---), $CH_2\underline{CH}_2OH$ (61.1) (---),

$\underline{CH_2}COOH^a$ (---) (38.1). Finally, a comparison of the cd curves of ankorine (2) ($[\alpha]_D^{26}$ -62° ($CHCl_3$))[4] and alancine (1) ($[\alpha]_D^{25}$ -40° (c 0.1, MeOH)) in MeOH suggests that they possess the same stereochemistry with both alkaloids exhibiting a single, well-defined negative Cotton effect curve (ankorine (2) $[\theta]_{281}$ -153 and alancine (1) $[\theta]_{282}$ -674).

To our knowledge, the isolation of alancine from A. lamarckii constitutes the first report of a benzoquinolizidine alkaloid containing a carboxylic acid moiety. Since ankorine (2) has been previously isolated from A. lamarckii,[4,12] it is not unreasonable to expect that alancine (1) may be an oxidative metabolite of ankorine (2) arising via the action of dehydrogenase or oxidase enzymes plus suitable coenzymes.

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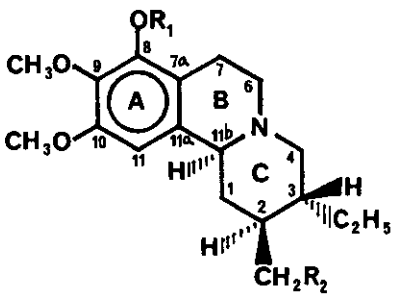
a,b,c These assignments may be reversed



1 R_1=H, R_2=COOH

2 R_1=H, R_2=CH_2OH

3 R_1=CH_3, R_2=$COOCH_3$

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REFERENCES

1. R. N. Chopra, I. C. Chopra, K. L. Handa and L. D. Kapur, 'Indigenous Drugs of India', 2nd ed. , U. N. Dhur and Sons Pvt. Ltd., Calcutta, 1958, p. 270.
2. A. Brossi, 'The Alkaloids, Vol. XXII', Academic Press, New York, 1983, pp. 1-50 and S. K. Chattopadhyay, Ph.D. Dissertation, University of Pittsburgh, 1983, pp. 86-96 plus references therein.
3. F. K. Duah, P. D. Owusu, J. E. Knapp, D. J. Slatkin and P. L. Schiff, Jr., Planta Med., 1981, 42, 275.
4. A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant and S. S. Salgar, Tetrahedron Lett., 1966, 4965.
5. C. Szántay, E. Szentirmay and L. Szabó, Tetrahedron Lett., 1974, 3725.
6. K. Nakanishi, 'Infrared Absorption Spectroscopy', Holden-Day, Inc., San Francisco, 1962, pp. 42-48.
7. C. J. Pouchert and J. R. Campbell, 'The Aldrich Library of NMR Spectra', Vol III, Aldrich Chemical Company, Milwaukee, Wisconsin, 1974, pp. 19-36.
8. K. E. Pfitzner and J. Moffatt, J. Am. Chem. Soc., 1963, 85, 3027.
9. L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis', John Wiley and Sons, Inc., New York, 1967, p. 1012.
10. T. Fujii, Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa, Japan - personal communication.
11. Signals assigned by comparison with the spectrum of ankorine (ref. 10).
12. B. Dasgupta, J. Pharm. Sci., 1965, 54, 481.

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