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DEMETHYLPROTOEMETINOLS FROM ALANGIUM LAMARCKII[1]

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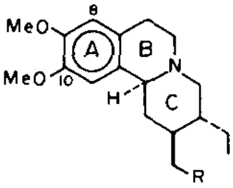
Abstract —Structures of two new isomeric alkaloids isolated from the seeds of *Alangium lamarckii* have been established as 10-demethylprotoemetinol (**10**) and 9-demethylprotoemetinol (**11**).

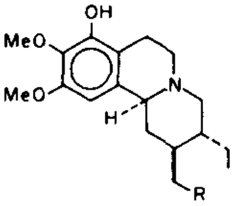
A. lamarckii Thw. (*Alangiaceae*), like *Cephaelis ipecacuanha* Rich. (*Rubiaceae*), is a rich source[2] of 9,10-dimethoxybenzo[*a*]quinolizine alkaloids like cephaeline (**1**). It is, however, known to elaborate not only compounds with different substitution patterns in the aromatic ring A but also some novel structural types. Thus, alangicine (**2**)[3,4,5] with an additional phenolic group at C-8, 9-demethylpsychotrine (**3**)[3,6,7], 9- or 10-demethylcephaeline (**4**)[8,9] as well as benzoquinolizine-β-carboline hybrid structures, *viz.* tubulosine (**5**)[10] and related bases including 10-demethyltubulosine (**6**)[11,12] and pyridobenzoquinolizines like alamarine[13] have been isolated from *A. lamarckii* besides some simple alkaloids[14]. Interestingly enough, protoemetine (**7**)[15], the postulated biogenetic intermediate of the 9,10-dimethoxybenzo[*a*]quinolizine alkaloids has not so far been encountered in this plant. Nevertheless, protoemetinol (**8**)[15] has been detected in the leaves[16] and root-bark[17] while the corresponding 8-hydroxy compound, ankorine (**9**)[16,18] has been isolated from the leaves[19] of *A. lamarckii*.

We now report both the 9- and 10-demethylprotoemetinols (**11** and **10**) from the seeds of *A. lamarckii* leading to the isolation of all the protoemetinols corresponding to the four substitution patterns in ring A found in the benzoquinolizine alkaloids of this plant.

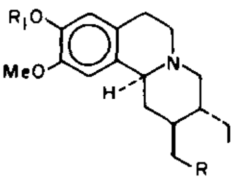
The total alkaloids obtained from the methanol extract of defatted seeds were dissolved in chloroform and extracted with buffer of pH 6.4. After removal of tubulosine, cephaeline and isocephaeline, the buffer soluble part yielded an amorphous base apparently homogeneous by tlc. The ir, uv and the mass spectra of the sample indicated it to be a demethylprotoemetinol. However, four aromatic singlets in the nmr spectrum indicated it to be an almost 1:1 mixture of two isomers.



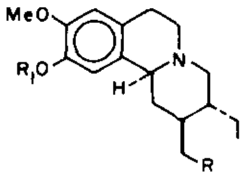
1 R = X
5 R = Z
7 R = CHO
8 R = CH_2OH



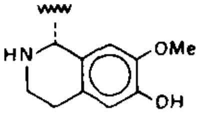
2 R = Y
9 R = CH_2OH



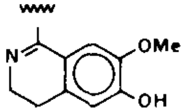
3 R = Y, R_1 = H
11 R = CH_2OH, R_1 = H
13 R = CH_2OAc, R_1 = Ac



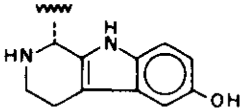
4 R = X, R_1 = H
6 R = Z, R_1 = H
10 R = CH_2OH, R_1 = H
12 R = CH_2OAc, R_1 = Ac



X



Y

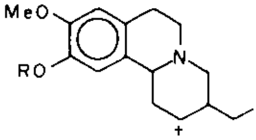


Z

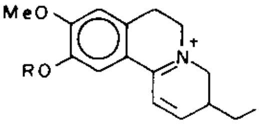
Acetylation of the sample indeed furnished a mixture of two acetates which were separated by preparative tlc to yield one of the acetates (12) as an oil, $[\alpha]_D$-15.8° ($CHCl_3$); ir ($CHCl_3$): ν_{max} 2810, 2760 (Bohlmann bands), 1755(ArOAc), 1730 (R-OAc) cm^{-1}; uv (EtOH): λ_{max} (log ε), 204 (3.72), 221sh (3.74), 286 (3.04) nm; nmr ($CDCl_3$): δ 0.90t ($C\underline{H}_3$-CH_2-), 2.06 ($ROCOC\underline{H}_3$), 2.30 ($ArOCOC\underline{H}_3$), 3.79 ($ArOC\underline{H}_3$), 4.16brt (-$C\underline{H}_2$-OAc), 6.64s and 6.84s (Ar-$\underline{H}$); ms: m/z (rel.int.) 389 (M^+, 78), 388 (M-1, 100), 346 (M-CH_3CO, 32), 330 (M-CH_3COO, 17), 302 (a, 12), 300 (b, 34), 274 (c, 76), 258 (d, 10), 233 (e, 69) and 177 (f, 77). Hydrolysis of the acetate yielded the phenol 10 as an amorphous powder, $[\alpha]_D$-11.9° ($CHCl_3$); uv (EtOH): λ_{max} (log ε), 227 (4.01) and 286 (3.77) nm; uv (EtOH-0.1NNaOH): λ_{max} (log ε), 212 (4.63), 247 (3.90) and 303 (3.79) nm; ms m/z (rel. intensity) 305 (M^+, 51), 304 (M-1, 80), 260 (g, 28), 258 (d, 17), 232 (h, 100), 191 (i, 93) and 177 (f, 98).

All the above data, particularly the characteristic mass spectral fragmentation pattern[2], led to the alternative structure 10 or 11 for the alkaloid. Though isomeric 6-hydroxy-7-methoxy- and 7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinolines are difficult to distinguish by spectroscopic methods, the corresponding 3,4-dihydroisoquinolines can be differentiated by the strong uv absorption of the 6-hydroxy compounds at around 400 nm in neutral medium[20]. Accordingly, the phenol 10 was subjected to mercuric acetate oxidation. The uv spectrum of the product at pH 7 with absorption maxima at 302 and 350 nm was consistent with a 7-hydroxy- rather than a 6-hydroxy-3,4-dihydroisoquinoline chromophore. The alkaloid could, therefore, be inferred to be (-)-10-demethylprotoemetinol (10), confirmed by comparison of the diacetate with synthetic (±)-12 (ir and nmr) and (-)-12 (sign of optical rotation)[21].

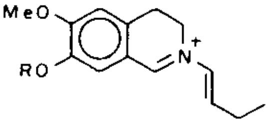
The unstable nature and poor yield of the second acetate precluded its complete characterisation. However, the mass spectrum of a freshly purified sample, $[\alpha]_D$ -24.3^{o} ($CHCl_3$), was almost identical with that of 12. Comparison of the nmr spectrum of 12 with that of the mixture of acetates allowed the assignment of structure 13 to the second acetate, corroborated by evidences as in the sequel.



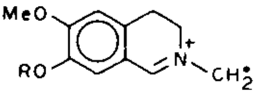
a *m/z* 302 (R=Ac)
g *m/z* 260 (R=H)



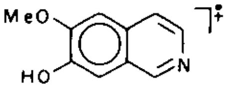
b *m/z* 300 (R=Ac)
d *m/z* 258 (R=H)



c *m/z* 274 (R=Ac)
h *m/z* 232 (R=H)



e *m/z* 233 (R=Ac)
i *m/z* 191 (R=H)



f *m/z* 177

Methylation of the original mixture of the two phenols with diazomethane yielded protoemetinol (8) as the sole product. The mercuric acetate oxidation product of the same mixture showed an uv absorption band at 392 nm at pH 7 indicating the presence of a 6-hydroxy-3,4-dihydroisoquinoline chromophore. The second phenolic alkaloid, therefore, could be reasonably inferred to be 9-demethylprotoemetinol (11). Though the total synthesis of (-)-9-demethylprotoemetinol has recently been accomplished[21], a direct comparison was not possible due to paucity of the natural product.

REFERENCES

1. Part 70 in the series, 'Studies on Indian Medicinal Plants', for Part 69 see B. Achari, S. Chakrabarty, S. Bandyopadhyay, and S. C. Pakrashi, *Heterocycles*, 1982, **19**, 1203.
2. H. Budzikiewicz, S. C. Pakrashi, and H. Vorbrueggen, *Tetrahedron*, 1964, **20**, 399.
3. S. C. Pakrashi and E. Ali, *Tetrahedron Letters*, 1967, 2143.
4. T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, *Tetrahedron Letters*, 1967, 2553.
5. T. Fujii, S. Yoshifujii, S. Minami, S. C. Pakrashi, and E. Ali, *Heterocycles* 1977, **8**, 175.
6. T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, *Heterocycles*, 1979, **12**, 1463.
7. T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, *Tetrahedron Letters*, 1979, 4955.
8. S. C. Pakrashi and B. Achari, *Experientia*, 1970, **26**, 933.
9. T. Fujii and M. Ohba, *Heterocycles*, 1982, **19**, 857.
10. P. Brauchli, V. Deulofeu, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, 1964, **86**, 1895.
11. A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Letters*, 1966, 1081.
12. T. Fujii, M. Ohba, A. Popelak, S. C. Pakrashi, and E. Ali, *Heterocycles*, 1980, **14**, 971.
13. S. C. Pakrashi, B. Achari, E. Ali, P. P. Ghosh Dastidar, and R. R. Sinha, *Tetrahedron Letters*, 1980, **21**, 2667.
14. B. Achari, E. Ali, P. P. Ghosh Dastidar, R. R. Sinha and S. C. Pakrashi, *Planta Medica*, *Suppl.*, 1980, 5.
15. A. R. Battersby, G. C. Davidson, and B. J. T. Harper, *J. Chem. Soc.*, 1959, 1744.
16. A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, *Tetrahedron Letters*, 1966, 4965.
17. J. D. Albright, J. C. Van Meter, and L. Goldman, *Lloydia*, 1965, **28**, 212.
18. T. Fujii and S. Yoshifuji, *J. Org. Chem.*, 1980, **45**, 1889 and refs. cited.
19. B. Dasgupta, *J. Pharm. Sci.*, 1965, **54**, 481.
20. G. Johnson, *Acta Chem. Scand.*, 1966, **22**, 2755.
21. T. Fujii, M. Ohba, H. Suzuki, S. C. Pakrashi, and E. Ali, *Heterocycles*, following paper.

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