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ALKALOIDS OF *ATALANTIA MONOPHYLLA* CORREA*

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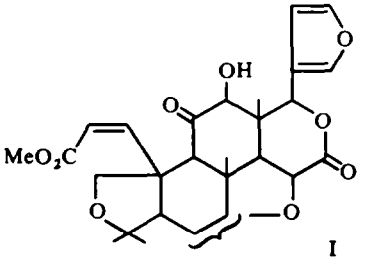
Abstract—Atalaphylline and N-methylatalaphylline, two new acridone alkaloids isolated from *Atalantia monophylla*, have been shown to have structures (IVa) and (IVb) respectively.

ATALANTIA MONOPHYLLA Correa[1] (Family: *Rutaceae*) is a wild thorny tree which has been claimed as useful in the treatment of snake-bite and rheumatism. Recently, Thakar and Sabata[2] reported the isolation from its root bark of a new tetranortriterpenoid, atalantin, to which they assigned structure (I). These authors had



I

used for their isolation plant material collected in Orissa. From the root bark of the plant collected in Madras we have not been able obtain any atalantin. We have, however, isolated from this material two new acridone alkaloids and we wish to present here the isolation and structure determination of these.

Extraction of the defatted plant material with acetone yielded a brownish solid which was taken up in hot benzene. Chromatography of the benzene-soluble material over silica gel yielded two new acridone alkaloids. The major one (yield 0·017%) was named atalaphylline (IVa) and the minor alkaloid (yield 0·002%) has been found to be N-methylatalaphylline (IVb).

Atalaphylline, m.p. 246°, $C_{23}H_{25}NO_4$ (M^+ at m/e 379) shows ultraviolet and infrared absorption spectra (see *Experimental*) characteristic of 9-acridones[3-6]. The presence of a phenolic hydroxyl group is indicated by the brownish green ferric reaction of the alkaloid as well as by the presence of infrared absorption at 3200 cm^{-1}. The sharp band at 3370 cm^{-1} in the infrared spectrum is ascribed to the acridone NH.

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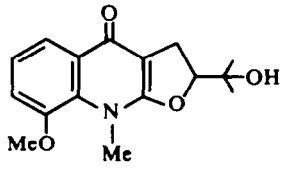
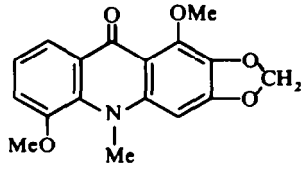
The NMR spectrum of atalaphylline shows the absence of methoxyl, methylenedioxy and methylimino groups. The presence of two prenyl units is indicated by the signals at δ 1·70, 1·77, 1·80, 1·97 (slightly split singlets, 3 protons each), δ 3·53 (broad, 4 protons) and δ 5·22 ppm (broad, 2 protons). Two low-field protons at δ 10·28 and 8·95 ppm, which are washed out by D_2O, are assigned to a hydroxyl and an NH. The aromatic region of the spectrum indicated the presence of three protons of an ABX system. The quartet at δ 7·72 ppm (J = 7 and 2·5 c/s) must belong to H_8, deshielded by the neighbouring 9-carbonyl group. The multiplet at δ 6·85–7·2 ppm arises from H_6 and H_7. This region of the spectrum shows a striking similarity to that of lunacrine (II) and tecleanthine (III)[7] which have a similar ABX system.



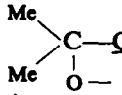
II



III

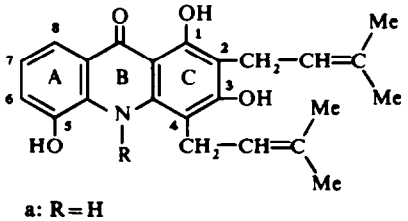
The mass spectrum of atalaphylline shows strong peaks at m/e 324 (M-55) and m/e 268 (324–56) due to cleavage of the two prenyl groups. The presence of these groups was confirmed by catalytic hydrogenation to give tetrahydroatalaphylline, m.p. 255–258° (d), $C_{23}H_{29}NO_4$ (M^+ at m/e 383), whose mass spectrum shows significant peaks at m/e 326 (M-57) and m/e 270 (326–56). Its NMR spectrum shows the four secondary C-methyls at δ 0·93–1·08 ppm.

Methylation of atalaphylline with diazomethane yielded a dimethyl ether, m.p. 145–147°, which still contained a phenolic hydroxyl as shown by its dark green ferric reaction. Methylation with methyl iodide and potassium carbonate under forcing conditions effected methylation of the inert hydroxyl as well as the NH to yield the N-methyl-tri-O-methyl ether whose NMR spectrum showed peaks at δ 3·47 (1 NMe), 3·8 (1 OMe) and 3·92 (2 OMe) ppm. It was evident from this that atalaphylline has three hydroxyls of which one is inert, being *peri* to the carbonyl group.

Treatment of atalaphylline with formic acid resulted in the cyclization of both prenyl groups with adjacent hydroxyls to give bicyloatalaphylline, m.p. 251–253° (d), $C_{23}H_{25}NO_4$ (M^+ at m/e 379). Its NMR spectrum showed peaks at δ 2·7 (4H, broad), 1·9 (4H, broad), 1·43 (6H, s) and 1·39 (6H, s) ppm, in agreement with the presence of two dimethylchroman rings in the molecule. Of the two hydroxyls which have participated in the cyclization, one had to be the unreactive C_1–hydroxyl since the hydroxyl still present in bicycloatalaphylline could be methylated with diazomethane to yield O-methyl-bicycloatalaphylline, m.p. 225–227°. The NMR spectrum of the latter ($CDCl_3$, 100 Mc) showed the presence of four C-Me groups at δ 1·37 (6H, s) and 1·47 (6H, s), two pairs of triplets at δ 1·90 (4H, ), a triplet at δ 2·65 (4H, Ar—$\underline{CH}_2$—), one methoxyl at δ 3·93 (3H, s), two aromatic protons at δ 6·80–7·10 (multiplet) and the low-field aromatic C_8-proton as a quartet at 7·95 ppm. The signal due to NH was found buried at δ 7·95 ppm. Addition of D_2O washed out

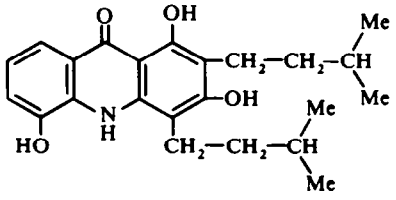
the NH signal leaving H_8 as a quartet with J = 7·5 and 1·8 c/s. The complex AB part (δ 6·80–7·10 ppm) of the ABX system was reduced to a clear AB pattern on irradiation of the H_8 signal. This was in complete agreement with the location of the methoxyl, and hence of one hydroxyl in atalaphylline at C_5 in ring A of the molecule.

The above evidence shows that atalaphylline has a hydroxyl group at C_5 with no other substituent in ring A. Ring C has to have a hydroxyl at C_1 and a prenyl group at C_2. The second hydroxyl and prenyl groups can be located at C_3 and C_4 or *vice versa*. In conformity with their postulated biogenetic origin from phloroglucinol and a 2-aminobenzaldehyde unit, all known acridone alkaloids are oxygenated at C_1 and C_3.[8] This consideration favours the location of the third hydroxyl at C_3 leading to structure (IVa) for atalaphylline. Tetrahydroatalaphylline would then have structure (V), atalaphylline dimethyl ether (VIa), N-methyl-tri-O-methylatalaphylline (VIb), bicycloatalaphylline (VIIa) and O-methylbicycloatalaphylline (VIIb).

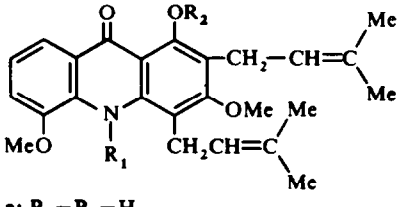


a: R = H
b: R = Me

IV

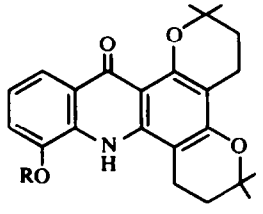


V



a: $R_1 = R_2 = H$
b: $R_1 = R_2 = Me$
c: $R_1 = Me; R_2 = H$

VI



a: R = H
b: R = Me

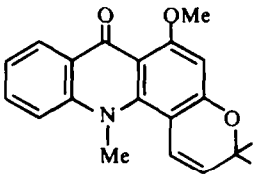
VII

The minor alkaloid from *Atlantia monophylla* has m.p. 192–193° and ultraviolet and infrared absorption spectra similar to atalaphylline. The alkaloid, $C_{24}H_{27}NO_4$ (M^+ at m/e 393), in its NMR spectrum, shows the presence of three aromatic hydrogens of the ABX type as in atalaphylline, one methylimino group at δ3·6(s) and two prenyl groups at δ5·32 (2H, broad), 3·51 (4H, broad), 1·82 (6H,s), 1·78 (3H,s) and 1·75 (3H,s) ppm. The mass spectrum of the alkaloid showed strong peaks at m/e 338 (M-55) and m/e 282 (338–56). Methylation with diazomethane yielded a dimethyl ether (VIc) whose NMR spectrum showed the C_1-OH at δ14·2, two methoxyls at δ3·93 and 3·8 and the methylimino group at δ3·55 ppm. Further methylation of the dimethyl ether with methyl iodide and potassium carbonate yielded the trimethyl ether (VIb) obtained earlier from atalaphylline. This establishes the structure of the minor alkaloid as N-methyl-atalaphylline (IVb).

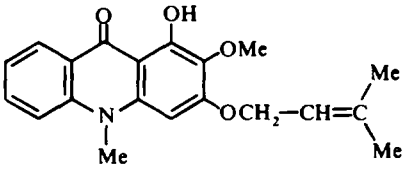
Till recently, no naturally occurring acridone oxygenated in ring A had been

isolated. Teclearthine (III),[7] from *Teclea natalensis*, marked the first instance of such a compound. Atalaphylline and N-methylatalaphylline are the only other alkaloids possessing this feature.

These two alkaloids have close structural similarities to the anti-tumour alkaloid acronycine (VIII) and its congeners, noracronycine, des-N-methyl-acronycine and des-methylnoracronycine.[9-14] The only other prenylacridone, evoprenine (IX),[15] has an O-prenyl group.



VIII



IX

EXPERIMENTAL

M.ps. are uncorrected. Infrared spectra were recorded in Nujol on a Perkin-Elmer Infracord. NMR spectra were determined at 60 Mc in $CDCl_3$, a few drops of CD_3SOCD_3 being added where necessary.

Isolation. The powdered root bark (3kg) of *Atalantia monophylla* collected from the Rajbhavan forests, Madras, was defatted with light petroleum and then extracted with acetone. Evaporation of the acetone extract gave a brownish solid which was repeatedly extracted with hot benzene. Removal of benzene gave the crude alkaloid mixture (32g) as a brownish yellow solid. TLC examination showed this to consist mainly of two compounds in addition to much polar material. The mixture (6g) was chromatographed over silica gel (350g). The column was eluted with a mixture of C_6H_6:EtOAc:MeOH (40:10:1). Fractions of 25 ml were collected and monitored by TLC. Fractions 4–8 yielded N-methylatalaphylline (60 mg) and fractions 12–22 gave atalaphylline (520 mg). The later fractions yielded only gums.

N-Methylatalaphylline. This compound crystallized from C_6H_6—EtOAc as yellow needles, m.p. 192–193°. λ_{max}^{EtOH} 260 (sh), 273, 336, 415 mμ (log ε 4·36, 4·48, 4·06, 3·65), ν_{max} 3500, 1620, 1580, 1540, 1510 cm^{-1} (Found: C, 73·84; H, 7·09; N, 3·51. $C_{24}H_{27}NO_4$ requires C, 73·26; H, 6·92; N, 3·56%). NMR: δ7·82 (1H, q, J = 6·5, 2·5 c/s), 7·05–7·35 (3H, m, 2 Ar—H, 1 NH), 5·32 (2H, br), 3·63 (3H, s, NMe), 3·51 (4H, br), 1·82 (6H, s, 2C—CH_3), 1·78 (3H, s, C—CH_3) and 1·75 (3H, s, C—CH_3) ppm. Mass spectrum: m/e 393 (M^+, 100%), 378 (18%), 350 (38%), 338 (50%), 322 (80%), 294 (37%) 282 (46%), 280 (20%), 268 (20%).

Atalaphylline. This crystallized from C_6H_6—EtOAc as yellow needles, m.p. 246°, λ_{max}^{EtOH} 255, 265, 284, 312, 402 mμ (log ε 4·53, 4·54, 4·48, 4·20, 3·75), ν_{max} 3370, 3200 (br), 1650, 1620, 1610, 1560 cm^{-1}. (Found: C, 72·82; H, 6·50; N, 4·26. $C_{23}H_{25}NO_4$ requires C, 72·80; H, 6·64; N, 3·69%). NMR: δ 10·28, 8·95 (NH, OH), 7·72 (1H, q, J = 7, 2·5 c/s), 6·85–7·2 (2H, m), 5·22 (2H, br), 3·53 (4H, br), 1·97 (3H, s, C—CH_3), 1·80 (3H, s, C—CH_3), 1·77 (3H, s, C—CH_3) and 1·70 (3H, s, C—CH_3) ppm. Mass spectrum: m/e 379 (M^+, 80%), 364 (10%), 336 (65%), 324 (70%) 308 (30%), 280 (82%), 268 (100%), 257 (22%).

Tetrahydroatalaphylline (V). A solution of atalaphylline (0·4 g) in EtOH (30 ml) was shaken with H_2 (1 atm) in the presence of PtO_2 (0·1 g). The soln was filtered, evaporated and the residue crystallized from ether–hexane as yellow needles (150 mg), m.p. 255–258° (d), λ_{max}^{EtOH} 252, 265, 284, 305, 402 mμ (log ε 4·68, 4·65, 4·64, 4·33, 3·76). ν_{max} 3580, 3420, 1635, 1610, 1590 cm^{-1}. (Found: C, 72·17; H, 7·69. $C_{23}H_{29}NO_4$ requires C, 72·03; H, 7·62%). NMR: δ 8·71 (NH), 7·8 (1H, q, J = 7, 2 c/s), 7·0–7·2 (2H, m), 2·75 (4H, br), 1·5 (4H, br), 0·93–1·08 (12 H, 4 $\diagdown$CH—$\underline{CH_3}$). Mass spectrum: m/e 383 (M^+), 340, 326, 270.

Atalaphylline dimethyl ether (VIa). (1) *with diazomethane:* A soln of atalaphylline (0·1 g) in MeOH (5 ml) was treated with excess ethereal CH_2N_2 and left overnight at room temp. Evaporation and

crystallization of the residue from ether–hexane gave yellow needles of VIa (60 mg), m.p. 145–147°, insoluble in aq NaOH. The compound gave a dark green colour with $FeCl_3$ in MeOH soln and has λ_{max}^{EtOH} 260, 278 (sh), 310, 321, 402 mμ (log ε 4·63, 4.43, 4·04, 4·07, 3·77), ν_{max} 3360, 1640, 1620, 1590, 1570 cm^{-1}. (Found: C, 73.87; H, 7·17. $C_{25}H_{29}NO_4$ requires C, 73·68; H, 7·17%). NMR: δ 8·7 (NH), 7·75 (1H, q), 6·85–7·0 (2H, m), 5·2 (2H, br), 3·92 (3H, s, 1 OMe), 3·8 (3H, s, 1 OMe), 3·48 (4H, br), 1·7–1·95 (12H, 4 C—CH_3). (2) *with* Me_2SO_4: Atalaphylline (0·1 g) in acetone (20 ml) was refluxed with Me_2SO_4 (1 ml) and anhyd. K_2CO_3 (3 g) for 12 h, filtered and evaporated. The residue crystallized from ether-hexane to yield the dimethyl ether, m.p. and mixed m.p. with the above sample, 145–147°. The two samples were also identical by TLC and IR spectra.

Bicycloatalaphylline (VIIa). Atalaphylline (0·3 g) was heated at 80–100° for 4 h with formic acid (98%; 5 ml) and then left at room temp overnight. Water was added and the soln extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with $NaHCO_3$ aq, H_2O, dried (Na_2SO_4) and evaporated. The residue was chromatographed over silica gel (10 g) in C_6H_6; EtOAc: MeOH (40:10:1). Fractions of 10 ml were collected; 1–4 contained traces of recovered atalaphylline; 6 and 7 gave VIIa (150 mg), yellow crystals (from CH_2Cl_2–hexane), m.p. 251–253° (d), which gave a brown colour with $FeCl_3$. It had λ_{max}^{EtOH} 260, 300, 381 mμ (log ε 4·64, 4·20, 3·79), ν_{max} 3420, 1630, 1610, 1590, 1560, 1520 cm^{-1}. (Found: C, 72·57; H, 6·87. $C_{23}H_{25}NO_4$ requires C, 72·80; H, 6·64%). NMR: δ 7·8 (1H, q), 6·9–7·15 (2H, m), 2·7 (4H, br), 1·9 (4H, br), 1·43 (6H, s, 2, C—CH_3), 1·39 (6H, s, 2 C—CH_3). Mass spectrum: m/e 379 (M^+, 100%), 323 (95%), 308 (30%), 280 (45%), 268 (50%), 267 (50%).

O-Methylbicycloatalaphylline (VIIb). A soln. of VIIa (0·4 g) in MeOH (10 ml) was treated with excess CH_2N_2. The product was chromatographed over silica gel (20 g) and the column eluted with C_6H_6:EtOAc:MeOH (40:10:1). Fractions of 20 ml were collected. The material from fractions 4–10 crystallized from CH_2Cl_2–hexane as cream-coloured needles (150 mg), m.p. 225–227°, which gave no colour with $FeCl_3$. It had λ_{max}^{EtOH} 259, 277, 299, 376 mμ (log ε 4·62, 4.52, 4·25, 3·65), ν_{max} 3460, 1640, 1620, 1605, 1530 cm^{-1} (Found: C, 73·55; H, 6·97. $C_{24}H_{27}NO_4$ requires C, 73.26; H, 6·92%). NMR ($CDCl_3$, 100 MC): δ 7·95 (2H, NH and C_8–H, q, J = 7·5, 1·8 c/s), 6·8–7·1 (2H, m), 3·93 (3H, s, OMe), 2·65 (4H, t), 1·9 (4H, t), 1·47 (6H, s, 2 C—CH_3), 1·37 (6H, s, 2 C—CH_3) ppm. Mass spectrum: m/e 393 (M^+), 350, 338, 282.

N-Methyl-tri-O-methylatalaphylline (VIb). Atalaphylline (0·5 g) in acetone (50 ml) was refluxed with MeI (20 ml) and anhyd K_2CO_3 (10 g) for 72 h. The soln was filtered, evaporated and the product chromatographed over silica gel (10 g) in C_6H_6:$CHCl_3$ (1:1) to yield VIb as an uncrystallizable gum, homogenous by TLC in several different solvent systems. It had $\nu_{max}^{CH_2Cl_2}$ 1640, 1600, 1575, 1555, 1545 cm^{-1}. NMR: δ 7·85 (1H, q), 7–7·2 (2H, m), 5·3 (2H, br), 3·92 (6H, s, 2 OMe), 3·8 (3H, s, 1 OMe), 3·47 (3H, s, 1NMe) ppm.

Methylation of N-methylatalaphylline. (1) *dimethyl ether* (VIc): A soln of VIb (0·2 g) in MeOH (20 ml) was treated with excess CH_2N_2 and the product chromatographed over silica gel in C_6H_6: EtOAc (4:1) to yield VIc as a yellow gum, homogenous by TLC. It has $\nu_{max}^{CH_2Cl_2}$ 1610, 1580, 1550 cm^{-1}. NMR: δ 14·2 (s, OH), 7·85 (1H, q), 7·05–7·3 (2H, m), 5·3 (2H, br), 3·93 (3H, s, OMe), 3·8 (3H, s, OMe), 3·55 (3H, s, NMe), 1·78 (6H, s, 2 C—CH_3), 1·68 (6H, s, 2 C—CH_3) ppm. (2) *trimethyl ether* (VIb): The above dimethyl ether (150 mg) was refluxed in acetone (20 ml) with MeI (10 ml) and anhyd K_2CO_3 (5 g) for 48 h, filtered, evaporated and chromatographed over silica gel to yield the trimethyl ether, identical (TLC, IR) with the trimethyl ether obtained from atalaphylline.

Acknowledgement—We are grateful to Dr. H. Fuhrer for running the 100 Mc NMR spectrum of O-methylbicycloatalaphylline, Dr. H. Hürzeler for the mass spectra and Dr. S. Selvavinayakam for the analytical data. We are thankful to Professor B. G. L. Swamy and Dr. E. Govindarajulu for the identification and to the chief Conservator of Forests, Guindy Park, for collection of the plant. The awards of a Senior Fellowship (to P.S.S.) and a Junior Research Fellowship (to V.N.R.) by the C.S.I.R., New Delhi, are gratefully acknowledged. We thank Dr. K. Nagarajan for his interest in the work.

REFERENCES

[1] *The Wealth of India, Raw Materials*, Vol. I, p. 134, Council of Scientific and Industrial Research, New Delhi (1948)

[2] M. R. Thakar and B. K. Sabata, *Ind. J. Chem.*, **7**, 870 (1969)

[3] R. D. Brown and F. N. Lahey, *Austral. J. Sci. Res.* **A3**, 593 (1950)

[4] H. Brockmann, H. Muxfeldt and G. Haese, *Chem. Ber.* **89**, 2174 (1956)
[5] A. W. Sangster and K. L. Stuart, *Chem. Rev.* **65**, 69 (1965)
[6] L. E. Orgel, *The Chemistry of Heterocyclic Compounds, Acridines* (Edited by A. Weissberger), p. 289, Interscience, London (1956)
[7] K. H. Pogel and W. G. Wright, *J. Chem. Soc.* (*C*), 2327 (1969)
[8] G. K. Hughes and E. Ritchie, *Austral. J. Sci. Res.* **A4**, 423 (1951)
[9] P. L. Macdonald and A. V. Robertson, *Austral. J. Chem.* **19**, 275 (1966)
[10] T. R. Govindachari, B. R.Pai and P. S. Subramaniam, *Tetrahedron* **22**, 3245 (1966)
[11] G. H. Svoboda, G. A. Poore, P. J. Simpson and G. B. Boder, *J. Pharm. Sci.* **55**, 758 (1966)
[12] G. H. Svoboda, *Lloydia* **29**, 206 (1966)
[13] G. H. Svoboda and R. W. Kattau, *Lloydia* **30**, 364 (1967)
[14] J. R. Beck, R. Kwook, R. N. Booher, A. C. Brown, L. E. Patterson, P. Pranc, B. Rockey and A. Pohland, *J. Am. Chem. Soc.* **90**, 4706 (1968)
[15] J. A. Diment, E. Ritchie and W. C. Taylor, *Austral. J. Chem.* **20**, 1719 (1967).