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STRUCTURE AND SYNTHESIS OF ATALAPHYLLINE AND RELATED ALKALOIDS

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Abstract—The structure of atalaphylline, (**1**; 1,3,5-trihydroxy-4-(γ,γ-dimethylallyl)acridone an alkaloid of *Atalantia monophylla*, was confirmed by oxidative degradation and by total synthesis. The synthesis involved the preparation of 1,3,5-trihydroxy-9-acridone followed by direct prenylation to give atalaphylline and a monoprenylated product.

INTRODUCTION

Atalantia monophylla Correâ (Rutaceae) is a shrub with brown bark and thorny branches growing wild in the mountainous regions of India, Sri Lanka and Burma. From the petrol extract of its root bark, several acridone alkaloids [1–7] have been isolated and characterized. The structures of atalaphylline and *N*-methylatalaphylline were reported by Govindachari *et al.* [1]. In this report we discuss the oxidative degradation of atalaphylline and its synthesis.

RESULTS AND DISCUSSION

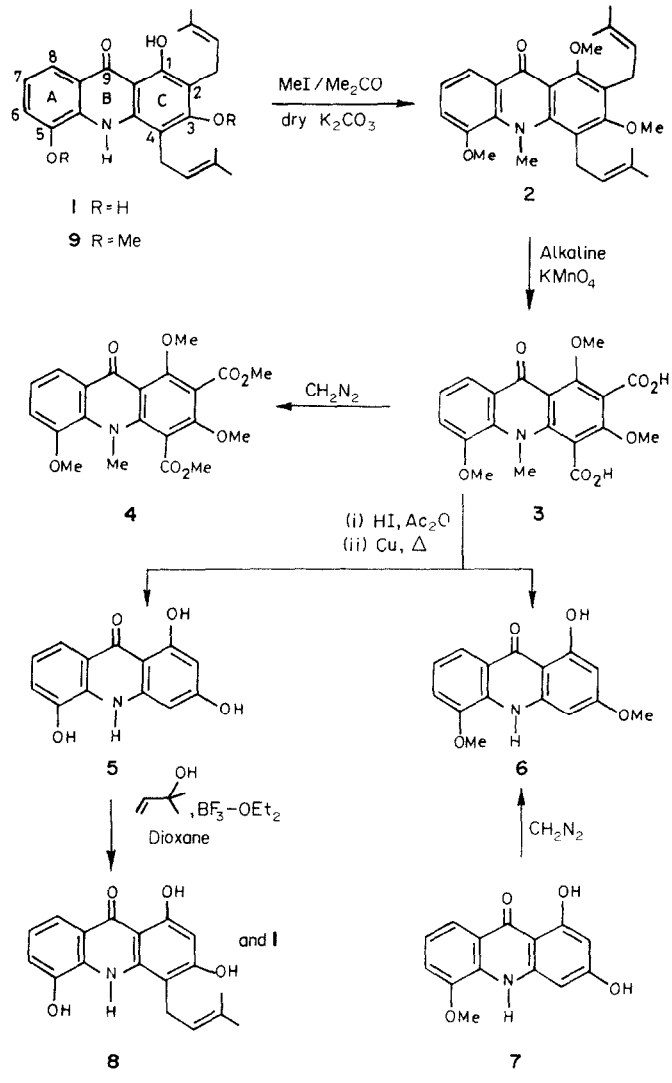
Compound **1** was methylated with methyl iodide and anhydrous potassium carbonate in dry acetone. The methylated product (**2**) was oxidized with alkaline potassium permanganate to an acid (**3**) which was converted to its methyl ester (**4**). Compound **4**, $C_{21}H_{21}NO_8$, showed the characteristics of an ester in its IR spectrum 1730 (>C=O of ester), 1650 (>C=O of acridone ring) and 1290 cm^{-1} (C–O–Me). The NMR spectrum indicated the presence of two carbomethoxy groups at δ 3.70 (6H) and three methoxy groups at δ 3.92 (3H) and 4.00 (6H). The NMe protons appeared at δ 3.84 (3H).

The acid (**3**) on demethylation followed by decarboxylation gave a mixture which on chromatography gave two pure products (**5**) and (**6**).

Compound **5**, mp 319–320° (d), $C_{13}H_9NO_4$ (M^+ 243), gave a positive ferric chloride test indicating the presence of a phenolic hydroxyl group. The UV spectrum showed the characteristic absorptions of 9-acridones. The IR spectrum showed bands assignable to nonbonded and bonded hydroxyl (3500, 3350 cm^{-1}), >NH (3275 cm^{-1}) and carbonyl of the acridone (1640 cm^{-1}). The NMR spectrum indicated the presence of two hydroxyl groups at δ 14.39 (strongly deshielded OH-1 by O-9) and 11.11 (OH-5 in the vicinity of acridone >NH), δ 8.28 (NH). These signals were exchangeable with D_2O. The aromatic region of the spectrum (integrating for 4H) showed the presence of an ABX system [8]: C-8 proton at δ 7.66 (*dd*, $J = 7.5$ and 2.5 Hz), C-6 and C-7 at δ 7.10 (*m*). The other proton in this region which was exchangeable with D_2O was assigned to a hydroxyl group probably at C-3. The signals at δ 6.73 (1H, *s*) and 6.05 (1H, *s*) were expected to be in ring C only. As these are singlets, they cannot be *ortho* to each other. These two signals were absent in the NMR spectrum of atalaphylline (**1**) and in **4** and were generated after decarboxylation of the acid (**3**).

Compound **5** was synthesized for the first time in an excellent yield by condensing 3-hydroxyanthranilic acid with phloroglucinol in butanol–benzene (2:1) in the presence of anhydrous zinc chloride under reflux. Hence, the NMR signals at δ 6.73 and 6.05 could be assigned to C-4 and C-2 protons. This also proved that the two prenyl groups present in atalaphylline could be at C-4 and C-2. This synthesis also supports the placement of the third hydroxyl group at C-3.

Compound **6** was found to be identical with the product obtained on diazomethane treatment of compound **5**, mp 215–218°, $C_{15}H_{13}NO_4$ (M^+ 271), showing IR bands at 1250 and 1065 cm^{-1} (=C–O–C) and NMR signals at δ 4.09 (3H, *s*) and 3.93 (3H, *s*) for two methoxyl groups. This compound also responded to the ferric chloride test indicating the presence of a phenolic hydroxyl group suggesting the methylation of OH-3 and OH-5 groups. The hydroxyl group at C-1 could not be methylated under such conditions because of strong hydrogen bonding with the C-9 carbonyl group. Compound **6** was found to be identical with a sample obtained by diazomethane treatment of 1,3 - dihydroxy - 5 - methoxyacridone [9] (**7**, M^+ 257).



Thus, from the structure of the degradation products, it could be concluded that the hydroxyl groups in atalaphylline are at positions C-1, C-3 and C-5 and the prenyl groups at C-2 and C-4.

Atalaphylline was synthesized from trihydroxy-acridone (**5**) by treatment [10] with 2 - methyl - 3 - butene - 2 - ol in dioxane in the presence of BF_3-etherate to give **1**, mp 242–245°, $C_{23}H_{25}NO_4$ (M^+ 379) and **8**. Compound **1** was found to be identical with atalaphylline in all respects.

Compound **8**, mp 248–249° (d), $C_{18}H_{17}NO_4$ (M^+ 311) had the characteristic UV and IR absorptions of a hydroxy acridone. The NMR spectrum showed the presence of a γ,γ-dimethylallyl group, δ 1.76 (3H, *s*, signal for the other methyl of the gem-dimethyl overlapping with the solvent impurity of D_3CCOCD_3); benzylic methylene at δ 3.62 (2H, *d*, $J = 7$ Hz) and vinylic at δ 5.20 (1H, *t*, $J = 7$ Hz). It also had signals for a chelated hydroxyl at δ 14.08, a phenolic hydroxyl at δ 9.60, >NH at δ 9.00, and another hydroxyl in the region δ 7.00–7.30 in addition to the expected ABX system for C-6, C-7 and C-8 protons. Furthermore, the spectrum showed a signal at δ 6.24 (1H, *s*) which could be that of the C-2 proton if the prenyl group is placed at C-4 or vice-versa. From the study of NMR spectra of several synthetic and natural acridone derivatives [7], it was found that the C-2 proton resonated between δ 6.00 and 6.20 whereas the C-4 proton resonated between δ 6.40 and 6.70. Therefore, the signal at δ 6.24 could be due to the C-2 proton. Hence **8** could be named as 1,3,5 - trihydroxy - 4 - (γ,γ - dimethylallyl)acridin - 9 - one.

Atalaphylline-3,5-dimethyl ether (**9**), which was isolated [6] from *A. manophylla*, was prepared from atalaphylline by treatment with diazomethane.

EXPERIMENTAL

Mps are uncorr. NMR spectra were recorded at 100 MHz using TMS as int. standard.

N-Methyl-tri-O-methylatalaphylline (**2**). A soln of atalaphylline (**1**) (100 mg) in dry Me_2CO was refluxed with MeI (10 ml) and dry K_2CO_3 (5 g) for 96 hr (TLC monitoring). The reaction mixture, after work-up, was chromatographed on Si gel. Elution with petrol (bp 60–80°)–EtOAc (9:1) yielded **2** (27 mg) as a pale yellow gum.

1,3,5 - *Trimethoxy* - 10 - *methylacridone* - 2,4 - *dicarboxylic acid* (**3**). A soln of *N* - methyl - tri - *O* - methylatalaphylline (**2**) (2 g) in Me_2CO (200 ml) was refluxed with a mixture of NaOH (5 g) and $KMnO_4$ (excess) for 48 hr. The mixture was cooled, filtered and the solvent removed under vacuum. The gum so obtained was extracted with $CHCl_3$ to remove unreacted material. It was then acidified with HCl, extracted with $CHCl_3$ and the solvent removed to obtain crude **3** (750 mg).

1,3,5 - *Trimethoxy* - 10 - *methylacridone* - 2,4 - *dimethylcarboxylate* (**4**). An Et_2O soln of 1,3,5 - trimethoxy - 10 - methylacridone - 2,4 - dicarboxylic acid (**3**, 750 mg) was treated with an excess of CH_2N_2–Et_2O. After usual work-up, a product was obtained which was chromatographed on Si gel, and elution with C_6H_6–EtOAc (3:2) gave **4** (100 mg) as a gum. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1650, 1600, 1590, 1290, 1170 and 1050. (Found: C, 60.48; H, 5.04. $C_{21}H_{21}NO_8$ requires: C, 60.72; H, 5.06%.) NMR ($CDCl_3$): δ 7.30 (3H, *s*), 4.00 (6H, *s*), 3.92 (3H, *s*), 3.84 (3H, *s*) and 3.70 (6H, *s*).

1,3,5 - *Trihydroxyacridone* (**5**). 1,3,5 - Trimethoxy - 10 - methyl - 2,4 - dicarboxylic acid (**3**, 500 mg) in HI (10 ml) and Ac_2O (10 ml) was boiled for 30 min. Usual work-up afforded a crude product (200 mg) which gave a positive $FeCl_3$ test. This product was then heated with a Cu catalyst (50 mg) at 250° for 30 min. Et_2O extraction of the resultant tar gave a yellow gum which was chromatographed on Si gel. Fractions collected with C_6H_6–EtOAc (1:1) afforded **5** (80 mg), mp 319–320° (d). UV λ_{max}^{MeOH} nm: 205, 228, 255, 269, 278, 299, 315 and 380 (log ϵ 4.09, 3.92, 4.47, 4.17, 4.16, 3.94, 3.81 and 3.46). IR ν_{max}^{Nujol} cm^{-1}: 3500, 3350, 3275, 1640, 1600, 1365, 1150, 1100 and 800. (Found: C, 64.43; H, 3.95. $C_{13}H_9NO_4$ requires: C, 64.20; H, 3.70%.) NMR (DMSO-d_6): δ 14.39 (1H, *s*), 11.11 (1H, *s*), 8.28 (1H, *s*), 7.66 (1H, *dd*, $J = 7.5$ and 2.5 Hz), 7.00–7.20 (3H, *m*), 6.73 (1H, *s*) and 6.05 (1H, *s*). MS *m/z* (rel. int.): 243 $[M]^+$ (100), 242 (13), 214 (21), 176 (36), 163 (46), 156 (16), 154 (15), 102 (45) and 77 (25).

1-*Hydroxy*-3,5-*dimethoxyacridone* (**6**). Fractions collected with petrol–EtOAc (17:3) from the above column afforded crystalline **6**, mp 215–218° as the major component. UV λ_{max}^{MeOH} nm: 204, 229, 256, 268, 277, 298, 312 and 388 (log ϵ 3.91, 3.44, 4.01, 3.79, 3.81, 3.46, 3.33 and 3.09). IR ν_{max}^{Nujol} cm^{-1}: 3370, 1665, 1610, 1575, 1250, 1150 and 800. (Found: C, 66.30; H, 4.70. $C_{15}H_{13}NO_4$ requires: C, 66.41; H, 4.79%.) NMR ($CDCl_3$): δ 8.26 (1H, *s*), 7.94 (1H, *dd*, $J = 7.5$ and 2.5 Hz), 7.14–7.30 (2H, *m*), 6.30 (1H, *s*), 6.26 (1H, *s*), 4.09 (3H, *s*) and 3.93 (3H, *s*). MS *m/z* (rel. int.): 271 $[M]^+$ (100), 256 (28), 242 (7), 228 (3), 213 (5), 200 (4), 185 (8), 157 (2) and 135 (3).

1,3,5-*Trihydroxyacridone* (**5**) was prepared by condensing phloroglucinol with 3-hydroxyanthranilic acid according to the method described in ref. [11].

3-*Hydroxyanthranilic acid* was prepared from 3-aminobenzoic acid following the procedure of ref. [12].

1,3 - *Dihydroxy* - 5 - *methoxyacridone* (**7**) was prepared from 3-methoxyanthranilic acid and phloroglucinol according to the method of ref. [9].

Atalaphylline (**1**). To a stirred soln of 1,3,5-trihydroxyacridone (**5**, 500 mg) in dioxane (100 ml) was gradually added 2 - methyl - 3 - butene - 2 - ol (1.25 ml) in dioxane (50 ml) and then BF_3-etherate (10 drops). The reaction mixture was stirred for 90 hr. It was then diluted with H_2O (200 ml), extracted with EtOAc, dried and the solvent removed to give a gum. The gum was chromatographed on Si gel (40 g) and 50 ml fractions were collected; the separation was monitored by TLC. Fractions collected with C_6H_6 afforded atalaphylline **1** (30 mg), mp 242–245° (hexane–EtOAc). (Found: C, 72.82; H, 6.50. $C_{23}H_{25}NO_4$ requires: C, 72.82; H, 6.59%.)

Chromatography of the mixture gave **1** and 1,3,5 - trihydroxy - 4 - (γ,γ - dimethylallyl)acridone (**8**) in pure crystalline form. TLC of the mixture showed the presence of some other minor products which could not be obtained in a pure state.

1,3,5 - *Trihydroxy* - 4 - (γ,γ - *dimethylallyl*)*acridone* (**8**). Fractions collected with petrol–EtOAc (9:1) from the above column afforded crystalline **8** (30 mg), mp 248–249° (d). UV λ_{max}^{MeOH} nm: 206, 230, 254, 280, 304, 330 and 396 (log ϵ 4.17, 4.09 4.59, 4.33, 4.13, 3.72 and 3.71). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1640, 1615, 1500 and 800. (Found: C, 69.34; H, 5.35. $C_{18}H_{17}NO_4$ requires: C, 69.45; H, 5.46%.) NMR (D_3CCOCD_3): δ 14.08 (1H, *s*) 9.60 (1H, unresolved), 9.00 (1H, *br s*), 7.77 (1H, *dd*, $J = 7.5$ and 2.5 Hz), 7.00–7.30 (3H, *m*), 6.24 (1H, *s*), 5.20 (1H, *t*, $J = 7$ Hz), 3.62 (2H, *d*, $J = 7$ Hz) and 1.76 (3H, *s*). MS *m/z* (rel. int.): 311 $[M]^+$ (73), 296 (16), 294 (15), 268 (19), 256 (51), 255 (40), 243 (100), 227 (10), 190 (6), 170 (6), 147 (8), 121 (9) and 107 (11).

Atalaphylline - 3,5 - *dimethyl ether* (**9**). A soln of **1** (25 mg) in MeOH (5 ml) was treated with excess CH_2N_2–Et_2O in the cold and left overnight at room temp. Evaporation of the solvent followed by crystallization from petrol–Et_2O gave **9** (20 mg) as yellow needles, mp 145–147°. UV λ_{max}^{MeOH} nm: 215, 262, 280, 310, 323 and 405 (log ϵ 4.10, 4.58, 4.42, 3.94, 3.99 and 3.43). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1640, 1605, 1590, 1570, 1375, 1325, 1270, 1245, 1225, 1195, 1170, 1120, 1080, 1030, 975, 955, 895, 850 and 725. (Found: C, 73.90; H, 7.46. $C_{25}H_{29}NO_4$ requires: C, 73.71; H, 7.13%.) NMR ($CDCl_3$): δ 14.20 (1H, *s*), 8.78 (1H, *br s*), 7.75 (1H, *dd*, $J = 7.5$ and 3 Hz), 7.20–6.80 (2H, *m*), 5.14 (2H, *br*), 3.93 (3H, *s*), 3.80 (3H, *s*), 3.40 (4H, *br*), 1.92 (3H, *s*), 1.76 (6H, *s*) and 1.64 (3H, *s*). MS *m/z* (rel. int.): 407 $[M]^+$ (78), 392 (25), 364 (84), 352 (100), 336 (51), 308 (62), 296 (29) and 282 (70).

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