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STRUCTURE OF APETALIC ACID*

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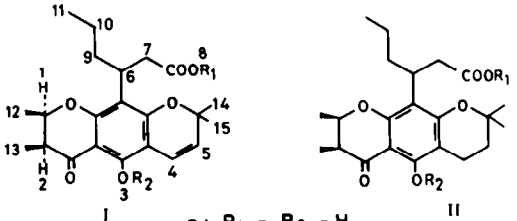
Abstract—Structure Ia assigned earlier to apetalic acid has been confirmed by the synthesis of the degradation product VIb.

IN A preliminary communication[1] we reported the isolation of an acid named apetalic acid from the bark of *Calophyllum apetalum* Willd. (Family: Guttiferae). On the basis of its spectral properties and comparison with blancoic acid[2] (IV), structure Ia was advanced for apetalic acid, dihydroapetalic acid being IIa and the bis-2,4-dinitrophenylhydrazone from methyl apetalate being III.

Treatment of apetalic acid with anhydrous aluminium chloride in benzene gives "lactone A", m.p. 113–114°, which was assigned structure V. Treatment of the acid with hydriodic acid gives the stereoisomeric "lactone B" (VIa), m.p. 130°. Both isomers have mol wt 304 (by mass spectrum) and on methylation with methyl iodide and potassium carbonate lead to the same methyl ether (VIb), lactone A epimerizing under the methylation conditions to give the more stable isomer with H_1 and H_2 *trans*. Double resonance studies on the NMR spectra of lactones "A" and "B" show that the coupling J_{H_1,H_2} is 3·2 c/s in lactone A (*cis*) and 11·3 c/s in "lactone B" (*trans*).



I II

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

Structure VIb assigned to the methyl ether obtained from lactones A and B has been confirmed by its synthesis. 2,6-Dihydroxy-4-methoxybutyrophenone,[3] obtained by partial methylation of phlorobutyrophenone with diazomethane was reacted with carbomethoxymethylene-triphenyl-phosphorane[4] to yield 5-hydroxy-7-methoxy-4-n-propylcoumarin (VII). This could also be obtained in poor yield by partial methylation of 5,7-dihydroxy-4-n-propylcoumarin[5] with diazomethane. Reduction of the coumarin (VII) with sodium amalgam in ethanol yielded a 1:1 mixture of the dihydrocoumarin (VIII) (mol wt by mass spectrum 236) and the dimer (IX; mol wt by mass

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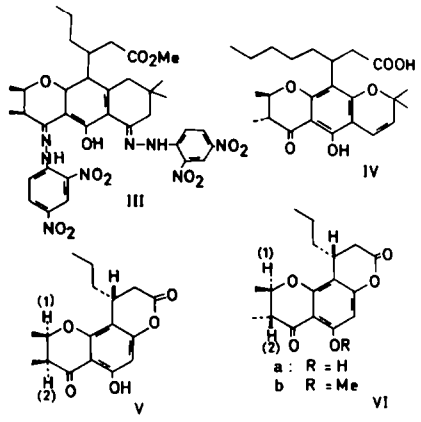
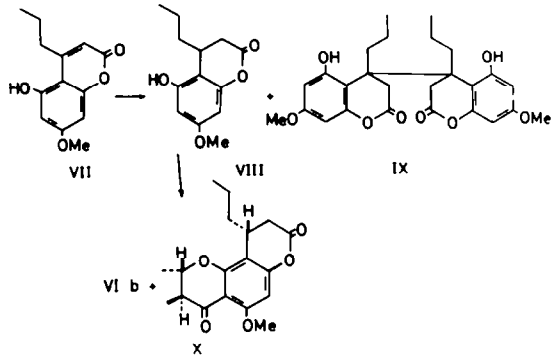
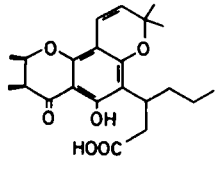


spectrum 570). The NMR spectrum of the dimer as well as the presence of a very strong peak at *m/e* 235 in its mass spectrum support a symmetric structure.



Treatment of the dihydrocoumarin (VIII) with tigloyl chloride in presence of polyphosphoric acid gave a 4:1 mixture of the diastereoisomers (VIb and X). Repeated crystallization gave the major product, m.p. 213–214°. This was identical (TLC, UV, NMR spectra) with the methyl ether obtained from lactones A and B and hence represents the racemic form of the degradation product. The minor isomer could not be obtained pure. The preponderance of one of the diastereoisomers in the formation of the chromanone ring is obviously due to the steric effect of the propyl group and the major isomer is hence assigned the relative stereochemistry shown in VIb. Attempts to prepare VIb by Fries rearrangement of the tiglate ester of VIII were fruitless.

The synthesis of the lactone (VIb) confirms the structure Ia assigned to apetalic



XI

acid. The alternate structure XI for the acid is untenable since attempts to lactonize it with acid catalysts or dicyclohexyl-carbodiimide were unsuccessful. The shifts in the positions of the chromene protons in the NMR spectrum of O-acetyl methyl apetalate as compared with methyl apetalate are in agreement with the observations of Arnone *et al.*[6] on dimethylchromenes having an OH in the *peri* position.

	δ (ppm)	
	H-4	H-5
Methyl apetalate (Ib)	6·58	5·4
O-Acetyl methyl apetalate (Id)	6·3	5·5

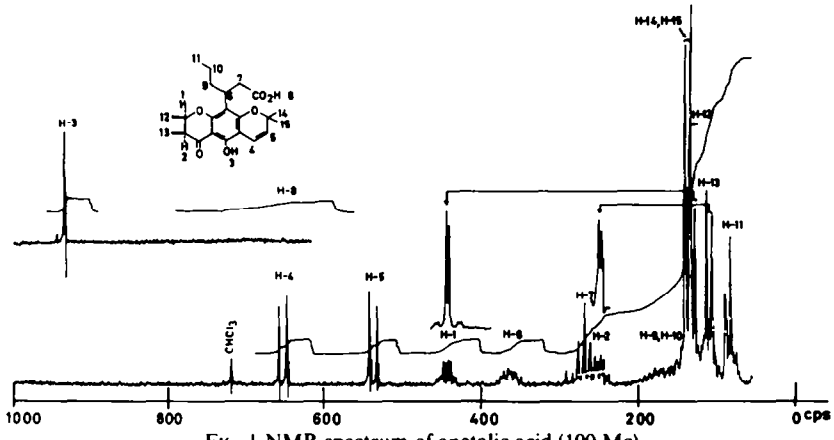


FIG. 1 NMR spectrum of apetalic acid (100 Mc).

EXPERIMENTAL

M.ps are uncorrected. UV spectra were measured in EtOH soln with a Beckman DB spectrophotometer. IR spectra were recorded on a Perkin–Elmer Model 421 instrument. Optical rotations were determined in 2–3% soln in $CHCl_3$ at 25°.

Isolation of apetalic acid (Ia). The bark (7·5 kg) of *Calophyllum apetalum* Willd. collected in Goa was ground and extracted thrice with hexane. The combined extracts were evaporated to about 800 ml and set aside in an ice chest for a week. The yellow crystals that separated were filtered off, washed with hexane and recrystallized from ether–hexane to yield *apetalic acid* (85 g), lemon yellow cubes, m.p. 117°, $[\alpha]_D$ +28·4°, λ_{max} 227, 268, 276, 301, 315, 368 mμ (log ε 3·99, 4·49, 4·53, 4·00, 4·03, 3·37) shifted to 398 mμ (log ε 3·73) on addition of NaOH, ν_{max} (CH_2Cl_2) 3500, 1700, 1645, 1620, 1575 cm^{-1} (Found: C, 68·1; H, 7·5. $C_{22}H_{28}O_6$ requires: C, 68·0; H, 7·3%); mass spectrum: *m/e* 388, 373, 345, 329, 313, 301, 285, 271, 257. The acid gives a dark green colour with $FeCl_3$.

Chromatography over silica gel of the mother liquor from the isolation yielded friedelin, m.p. 263°, identical with an authentic sample.

Methyl apetalate (Ib). A soln of apetalic acid (3 g) in MeOH (30 ml) was treated with excess ethereal diazomethane. After 24 hr the solvents were evaporated and the oily residue chromatographed over silica gel in benzene to yield the *methyl ester*, yellow viscous liquid, b.p. 180–190°/0·3 mm, $[\alpha]_D$ +30·4° λ_{max} 228, 267, 276, 301, 315, 368 mμ (log ε 3·83, 4·34, 4·39, 3·84, 3·88, 3·21), shifted to 397 mμ (log ε 3·54) on addition of NaOH, ν_{max}(CH_2Cl_2) 3620, 1730, 1640, 1620, 1575 cm^{-1} (Found: C, 68·7; H, 7·6. $C_{23}H_{30}O_6$ requires: C, 68·6; H, 7·5%).

Dihydroapetalic acid (IIa). A soln of apetalic acid (0·5 g) in EtOH (30 ml) was reduced with H_2 (at 1 atm. pr.) over 10% Pd-C catalyst (0·1 g). The soln was filtered from the catalyst and evaporated *in vacuo* to yield the dihydro-acid as a yellow gum, λ_{max} 217, 300, 348 mμ (log ε 4·34, 4·27, 3·49), λ_{sh} 232 mμ (log ε 4·17).

Methyl dihydroapetalate (IIb). A soln of methyl apetalate (0·6 g) in MeOH (30 ml) was reduced with H_2 (at 1 atm. pr.) over 10% Pd-C catalyst (0·2 g) to yield the *dihydro-ester*, yellow glassy liquid, b.p. 180°/0·5 mm, λ_{max} 215, 298, 344 mμ (log ε 4·33, 4·22, 3·46), λ_{sh} 232 mμ (log ε 4·13), shifted to λ_{max} 376 mμ (log ε 3·65) on addition of NaOH (Found: C, 68·3; H, 8·0. $C_{23}H_{32}O_6$ requires: C, 68·3; H, 8·0%).

Methyl O-methylapetalate (Ic). A soln of methyl apetalate (1·2 g) in anhyd. acetone (50 ml) was refluxed for 48 hr with Me_2SO_4 (5 ml) and anhyd K_2CO_3 (6 g). The soln was filtered, the solvent evaporated and the residue treated with ammonia to decompose excess Me_2SO_4. Extraction of the product with ether gave the *methyl ether* as a liquid, b.p. 180–190°/0·4 mm, ν_{max} (CH_2Cl_2) 1735, 1675, 1645, 1590 cm^{-1} (Found: C, 69·5; H, 7·8. $C_{24}H_{32}O_6$ requires: C, 69·2; H, 7·7%).

O-*Acetyl methyl apetalate* (Id). Methyl apetalate (2 g) was heated at 80° for 10 hr with pyridine (3 ml) and Ac_2O (10 ml). The soln was poured on water and extracted with CH_2Cl_2 to yield the *acetate* (1 g), purified by chromatography over silica gel in C_6H_6–$CHCl_3$ (1:1), ν_{max} (CH_2Cl_2) 1770, 1730, 1670, 1640, 1600 cm^{-1}. (Found: C, 67·1; H, 7·4. $C_{25}H_{32}O_7$ requires: C, 67·6; H, 7·3%).

Bis-2,4-*dinitrophenylhydrazone* (III) *from methyl apetalate*. A soln of methyl apetalate (0·5 g) in EtOH (30 ml) was refluxed with 2,4-dinitrophenylhydrazine (0·5 g) and a few drops of conc HCl for 4 hr. The solvent was removed *in vacuo*, the residue taken up in benzene and chromatographed over silica gel. Elution with benzene gave the *bis*-2,4-*dinitrophenylhydrazone* (0·3 g), dark red needles (from CH_2Cl_2–hexane), m.p. 235° (dec), λ_{max} 382 mμ (log ε 4·70), ν_{max} (KBr) 1740, 1620, 1590 cm^{-1} (Found: C, 53·9; H, 5·0. $C_{35}H_{38}O_{13}N_8$ requires: C, 54·0; H, 4·9%).

Alkaline degradation of apetalic acid. A soln of apetalic acid (1 g) in 7% NaOH aq (45 ml) was heated to boiling, N_2 gas being bubbled into the soln, with a condenser set for downward distillation. The outlet tube was dipped into a soln of 2,4-dinitrophenylhydrazine (100 mg) in EtOH containing a few drops of conc. HCl. The DNP solution was kept at 50° for ½ hr and left overnight at room temp. The soln was evaporated *in vacuo*, the residue taken up in benzene and filtered through a short column of silica gel. The product was examined by TLC (silica gel; benzene–hexane–ether mixtures) and paper chromatography (cyclohexane–MeOH–AcOH–water, 60:12:1:2) and found to consist of the 2,4-dinitro-phenylhydrazones of acetone and acetaldehyde.

"*Lactone A*" (V). A soln of apetalic acid (2 g) in dry benzene (100 ml) was treated with powdered anhyd $AlCl_3$ (3 g). The mixture was refluxed with stirring for 2 hr, cooled and decomposed with ice and HCl. The benzene soln was washed with $NaHCO_3$ aq and water, dried (Na_2SO_4) and evaporated. The residue was chromatographed over silica gel in hexane. Elution with hexane gave only oily products. Subsequent elution with benzene yielded "lactone A" (0·27 g), prisms (from ether–hexane), m.p. 113–114°, $[\alpha]_D$ −40·5°, λ_{max} 214, 284, 344 mμ (log ε 4·49, 4·32, 3·58), λ_{sh} 229 mμ (log ε 4·30), shifted to λ_{max} 254, 339 mμ (log ε 3·91, 4·56) on addition of NaOH, ν_{max} (KBr) 1785, 1655, 1650, 1625 cm^{-1}. (Found: C, 67·4; H, 6·9. $C_{17}H_{20}O_5$ requires: C, 67·1; H, 6·6%); mass spectrum: *m/e* 304, 261, 205. The compound gave a purple colour with $FeCl_3$.

"*Lactone B*" (VIa). Apetalic acid (2 g) was refluxed for 4 hr with HI (57%; 10 ml) and red P (0·1 g), the mixture cooled and poured on ice. Extraction with ether gave a reddish gum which was chromatographed over silica gel. Elution with benzene gave "*lactone B*" (0·1 g), needles (from hexane), m.p. 130°, $[\alpha]_D$ +20·4°, λ_{max} 215, 284, 344 mμ (log ε 4·41, 4·23, 3·50), λ_{sh} 229 mμ (log ε 4·21), shifted to λ_{max} 252, 340 mμ (log ε 3·99, 4·47) on addition of NaOH, ν_{max} (KBr) 1778, 1655, 1650, 1625 cm^{-1}. (Found: C, 67·3; H, 7·0. $C_{17}H_{20}O_5$ requires: C, 67·1; H, 6·6%); mass spectrum: *m/e* 304, 261, 205. The IR spectra of lactones "A" and "B" showed differences in the fingerprint region. Their mixed m.p. was depressed to 90–95°.

Methylation of lactones "A" and "B" to (VIb). (a) A soln of "lactone A" (0·6 g) in acetone (40 ml) was refluxed for 16 hr with MeI (5 ml) and anhyd K_2CO_3 (4 g). The soln was filtered, evaporated and the residue crystallized from etherhexane to yield the *methyl ether* (VIb; 0·2 g), needles, m.p. 170°, $[\alpha]_D$ +45·5°, λ_{max} 277, 324 mμ (log ε 4·15, 3·58), λ_{sh} 226 mμ (log ε 4·29), ν^{max} (KBr) 1775, 1680 cm^{-1} (Found: C, 67·8; H, 7·1. $C_{18}H_{22}O_5$ requires: C, 67·9; H, 7·0%).

(b) "Lactone B" (0·2 g) on methylation as above yielded the *methyl ether* (VIb), identical (TLC, mixed m.p., UV and IR spectra) with the above sample.

Synthesis of the lactone (VIb)

1. 2,6-*Dihydroxy-4-methoxy-butyrophenone*. Phlorobutyrophenone[7] (13 g) was treated with ethereal diazomethane (from 50 g of nitrosomethylurea). After 12 hr the product was chromatographed over silica gel in benzene to yield the 4-methyl ether (3·2 g), m.p. 125–127° (lit.[3] m.p. 127–128°).

2. 4-*n*-*Propyl*-5-*hydroxy*-7-*methoxycoumarin* (VII) (a). A soln of 2,6-dihydroxy-4-methoxybutyrophenone

(0·4 g) in anhyd xylene (20 ml) was refluxed for 12 hr with carbomethoxymethylene-triphenylphosphorane[4] (1 g), cooled and extracted with NaOH aq. The alkaline soln was acidified with HCl and extracted with ether to yield the *coumarin* (VII; 0·1 g), m.p. 167–169° (from ether–hexane), λ_{max} 252, 259, 322 mμ (log ε 3·87, 3·90, 4·17), ν_{max} (KBr) 1670, 1605 cm^{-1}. (Found: C, 66·9; H, 6·0. $C_{13}H_{14}O_4$ requires: C, 66·7; H, 6·0%).

(b) 5,7-Dihydroxy-4-n-propylcoumarin[5] (10 g) was treated with ethereal diazomethane (from 35 g of nitrosomethylurea) and the product chromatographed over silica gel in benzene to yield the *coumarin* (VII; 0·3 g), m.p. 168–170°, identical (TLC. mixed m.p., UV and IR spectra) with the above sample.

3. *Reduction of 5-hydroxy-7-methoxy-4-n-propylcoumarin.* A soln of VII (2·7 g) in EtOH (100 ml) was warmed to 60° and treated with 3% NaHg (160 g) during 1 hr with periodic addition of aqueous AcOH to keep the pH neutral. After 1 hr more at 60°, the solvent was removed *in vacuo* and the residue acidified with dil. HCl. The solid that separated was filtered and recrystallized from EtOAc–hexane to yield the *dimer* (IX; 1·2 g), m.p. 267–269°, λ_{max} 280 mμ (log ε 3·93), ν_{max} (KBr) 1730, 1625, 1590 cm^{-1}. (Found: C, 66·2; H, 6·7. $C_{26}H_{30}O_8$ requires: C, 66·4; H, 6·4%); mass spectrum: *m/e* 470, 235, 206, 193. The filtrate from the dimer was extracted with $CHCl_3$ and the product chromatographed over silica gel in C_6H_6–$CHCl_3$ (1:1) to yield the *dihydrocoumarin* (VIII; 1·1 g), m.p. 112–113° (from CH_2Cl_2–hexane), λ_{max} 280 mμ (log ε 3·20), ν_{max} (KBr) 1735, 1635, 1605 cm^{-1}. (Found: C, 66·0; H, 7·0. $C_{13}H_{16}O_4$ requires: C, 66·1; H, 6·8%); mass spectrum: *m/e* 236, 193, 149.

4. *Lactone* (VIB). The above dihydrocoumarin (VIII; 0·3 g) was heated at 80° with stirring for 2 hr with tigloyl chloride (0·19 g) and polyphosphoric acid (0·5 g). The soln was cooled, poured on ice and extracted with $CHCl_3$. Chromatography of the product over silica gel in $CHCl_3$ yielded a solid (0·15 g), m.p. 195–200°. NMR examination showed it to consist of a mixture of isomers in the appropriate ratio of 4:1. Repeated crystallization from MeOH yielded *lactone* (VIb; 90 mg), m.p. 213–214°, identical (TLC, UV IR spectra in CH_2Cl_2, and NMR spectra) with the degradation product obtained by methylation of lactones "A" and "B". (Found: C, 67·8: H, 6·9. $C_{18}H_{22}O_5$ requires: C, 67·9; H, 7·0%). The minor isomer could not be obtained pure.

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