1-Methyl 2,3-Dibutyl Hemimellitate. A Novel Component of *Viburnum prunifolium*[1]

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During investigations on the antispasmodic components of *Viburnum prunifolium*[2] it was necessary to fractionate large quantities of bark extract. Subsequently, 1-methyl 2,3-dibutyl hemimellitate was isolated from aqueous extracts of stem bark and identified. It is believed to be the first naturally occurring hemimellitic acid derivative. Of the three benzenetricarboxylic acids, only trimesic acid, benzene-1,3,5-tricarboxylic acid, has been previously reported as a natural product.[3]

The ester was obtained from aqueous bark extract by counter extraction, subsequent sequential column chromatography, and vacuum distillation. The mass spectrum showed a molecular ion at *m/e* 336 and an empirical formula of $C_{18}H_{24}O_6$. Additionally, the spectrum showed peaks at *m/e* 281 ($M - C_4H_7$) and *m/e* 263 ($M - OC_4H_9$), both being characteristic of *n*-butyl esters. Peaks also occurred at *m/e* 207 ($M - OC_4H_9$, and $-C_4H_8$) and at *m/e* 205 ($M - OC_4H_9$ and $M - C_2H_2O_2$), the former being consistent with a butyl ester and the latter strongly suggesting a methyl ester function. Fragments with lesser interpretative importance occurred at *m/e* 235, 163, and 149.

On running a thin film ir spectrum, the ester was found to have characteristic frequencies at 3060, 1600, 1580, 740, and 705 cm^{-1} and a pronounced shoulder at 780 cm^{-1}. These were suggestive of a conjugated aromatic compound with a possible 1,2,3 substitution pattern.[4] In the carbonyl region a principle band was at 1735 cm^{-1}; it had satellite bands at 1760 and 1720 cm^{-1} indicating three types of ester carbonyl functions. There were bands at 1275 and 1125 cm^{-1} which have been described as characteristic of aromatic acid esters.[5] Additionally, there was a frequency at 1205 cm^{-1} associated with aroyl methyl esters.[6] As expected, frequencies indicative of methyl and methylene groups were found at 2950, 2860, 1460, 1395, 2840, and 1490 cm^{-1}, respectively, but there were no bands indicative of alkyl branching.

On the basis of $C_{18}H_{24}O_6$ as its empirical formula the nmr spectrum of the compound showed resonance frequencies centered at δ 7.68 (3 H), 4.74 (3 H), 4.25 (4 H), 1.58 (8 H), 1.07 (3 H), and 0.97 (3 H). The 11-line complex multiplet from δ 7.45 to 7.95 clearly suggested the aromatic system to be an ABC type.[7] The band at δ 4.74 was assigned to ester O–Me on the basis of ir spectral evidence although anomalously far downfield; *e.g.*, trimethyl hemimellitate has O–Me at δ 3.92 and 4.02. Close examination of the ester $O-CH_2$ bands centered at δ 4.25 showed superposition of two triplets, δ 4.27 (J = 6 cps) and 4.20 (J = 6 cps) indicating two ester functions with CH_2 adjacent to the $O-CH_2$ groups. The CH_2 resonance frequencies centered at δ 1.58 were so complicated that no coupling patterns were discernible; however, they were typical for unbranched alkyl groups. Two alkyl chain Me groups were indicated by the broad singlet at δ 1.07 and the doublet at 0.97.

A synthesis of the evidence pointed to either 2-methyl 1,3-dibutyl hemimellitate or 1-methyl 2,3-dibutyl hemimellitate. On this basis it was decided to gather chemical evidence on the nature of the material. Attempts at controlled acidic and basic hydrolysis were inconclusive due to the ease with which partial hydrolysis products underwent decarboxylation to yield dibutyl phthalate and methyl butyl phthalate. The selective synthesis of either empirical isomer using standard approaches[8] was equally unprofitable. Ultimately, both compounds were obtained by acid-catalyzed transesterification of tributyl hemimellitate with methanol; the transesterification products were separated by preparative glpc. With the exception of its nmr spectrum the synthetic isomeric ester had properties very similar to the compound isolated from the plant extract. The nmr spectrum showed Me (δ 9.97), CH_2 (1.07), and ester $O-CH_2$ (4.32, J = 6 cps; 4.40, J = 6 cps) resonance frequencies similar to those of the isolated material. Outstanding differences were seen in the remaining regions of the spectrum. The aromatic protons occurred as broad singlets at δ 8.25 (1 H), 8.15 (1 H), and an incipient quartet ranging from 7.67 to 7.40 (1 H). These resonance frequencies, even though the singlet splitting was indistinct, provided reasonable evidence for an A_2B system. Such a condition would only arise if the concerned structure were 2-methyl 1,3-dibutyl hemimellitate. The ABC system found in the compound isolated from *V. prunifolium* extract would only occur in the 1-methyl isomer. On this basis and the facile conversion of tributyl hemimellitate into the desired compound, the compound is identified as 1-methyl 2,3-dibutyl hemimellitate. Synthetic 1-methyl 2,3-dibutyl hemimellitate is identical in all respects with the natural product. On investigation of the ester for antispasmodic properties no activity was noted.

Experimental Section

Analysis by Midwest Microlab Inc., Indianapolis, Ind. Ir spectra were run using a Perkin-Elmer Model 237 grating type, double beam spectrophotometer. Nmr spectra (CCl_4 *vs.* TMS) were run using a Varian Model A-60A spectrometer. The alu-

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(1) Presented at the 5th International Symposium on the Chemistry of Natural Products, London, 1968.

(2)(a) C. H. Jarboe, C. M. Schmidt, J. A. Nicholson, and K. A. Zirvi, *Nature*, **212**, 837 (1966); (b) C. H. Jarboe, K. A. Zirvi, J. A. Nicholson, and C. M. Schmidt, *J. Med. Chem.*, **10**, 488 (1967).

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(5) K. Nakanishi, "Infrared Absorption Spectroscopy, Practical," Holden-Day, Inc., San Francisco, Calif., 1962, p 44.

(6) C. H. Jarboe and K. A. Zirvi, unpublished results.

(7) R. H. Bible, "Interpretation of Nmr Spectra—An Empirical Approach," Plenum Press, New York, N. Y., 1965, p 77.

(8) E. Wenkert, D. B. R. Johnston, and K. G. Dave, *J. Org. Chem.*, **29**, 2534 (1964).

mina used in chromatography was Woelm, neutral, Brockmann activity grade 1, except as noted; silica gel used in chromatography was Merck "H."

Isolation of 1-Methyl 2,3-Dibutyl Hemimellitate.—Dried and granulated *Viburnum prunifolium* stem bark (50 kg) was extracted with distilled water in an Eppenbach stirrer. The aqueous filtrate was extracted with CH_2Cl_2 to yield 61.5 g (0.12%) of aromatic viscous oil. This product was processed in 2.5-g fractions. They were dissolved in 100 ml of MeOH, cooled to 5°, and centrifuged for 15 min to precipitate the waxes. The MeOH was filtered and evaporated to yield 2 g of oil which was chromatographed sequentially. The column materials, quantities, and eluting solvent mixtures were as follows: alumina, 5 g, $CHCl_3$; silicic acid, 5 g, $CHCl_3$; Florisil®, 5 g, ethyl ether; Woelm alumina (cationotropic, activity grade I), 5 g, ethyl ether; silica gel (Merck, "H"), 5 g, petroleum ether (bp 30–60°). Purity of material processed in this fashion was established by tlc on silica gel "H" using petroleum ether–ethyl ether (85:15), R_f 0.39. Vacuum distillation of the total product gave 7 g (0.01%) of 1-methyl 2,3-dibutyl hemimellitate: bp 150–152°; $n^{20}{}_{\mathrm{D}}$ 1.4959.

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.68; H, 6.80.

Transesterification of Tributyl Hemimellitate and Trimethyl Hemimellitate.—The hemimellitate ester (100 mg) was mixed with 5 cc of the appropriate alcohol containing 0.1 cc of concentrated H_2SO_4. The solution was heated on a water bath for 12 hr, the solvent evaporated at room temperature, and the crude product washed with water to remove the catalyst. After drying, the product was submitted to preparative glpc using an Autoprep Model 700 instrument with stream splitting and H_2 flame detection. Operating parameters were injector at 250°, column at 230°, and collector at 250°. The copper column was 5 ft × 0.25 in. of 60–80 mesh nonacid-washed Chromosorb W with 15% SE-30; N_2 delivery was at 12 psi. In each case the product mixture contained all possible products of transesterification and all related phthalates. Retention times of the methyl dibutyl hemimellitates relative to dimethyl phthalate were: 2-methyl 1,3-dibutyl hemimellitate, 7.87; and 1-methyl 2,3-dibutyl hemimellitate, 8.75.

Registry No.—1-Methyl 2,3-dibutyl hemimellitate, 21615-80-5.

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Calophyllum Products. V. A New 4-Phenylcoumarin from *Calophyllum australianum* FvM Vesq.[1]

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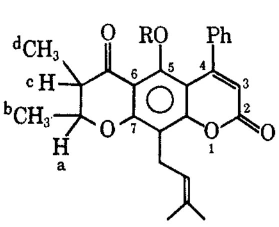
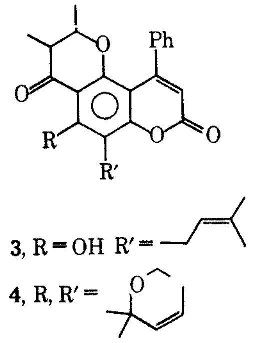
In the course of our studies of the resins of the Guttiferae, we have isolated in small yield a new 4-phenylcoumarin (1), $C_{25}H_{24}O_5$, from the dried bark of *Calophyllum australianum.* The nmr spectrum of 1 shows characteristic signals which may be assigned to a *trans*-2,3-dimethylchromanone ring,[1a] an isopentenyl chain,[1a] a chelated hydroxyl,[1a] and a monosubstituted phenyl group.[2,3] A 1 H singlet at τ 4.03 is consistent with the C-3 proton of a 4-substituted coumarin, and the frequent occurrence of such compounds among the products of *Calophyllum* and related genera supports this assignment.[2–6] The coumarin and *o*-hydroxychromanone systems produce the expected carbonyl bands at 5.82 and 6.08 μ. Oxygenation of the coumarin system is expected by analogy to occur at C-5 and C-7, and is confirmed by comparison of the uv spectrum of 1 (Table I) to those of a number of other 6-acyl-4-phenyl-5,7-dioxycoumarins.[7]



1, R = H
2, R = Me



3, R = OH R′ =
4, R, R′ =

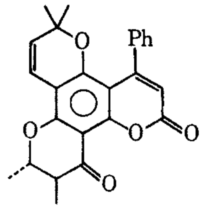


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TABLE I

	$\lambda_{\max}^{\mathrm{EtOH}}$, nm ($\epsilon$)	
1	286 (26,100)	337 (8820)
Mammea A/AB[a]	283 (29,500)	333 (10,200)
Mammeisin[b]	281 (27,500)	338 (10,000)

[a] Reference 2. [b] Reference 6.

The presence of a chelated hydroxyl rules out 8-acyl structures and limits the possibilities to 1 and 3. Nigam, Mitra, *et al.*,[4] have pointed out that in 4-phenylcoumarins bearing a 2,3-dimethylchromanone ring bridging C-5 and C-6, the nmr signals of the chromanone substituents show marked shifts from their normal values[1a,3–5] as a result of proximity to the phenyl ring. As is seen from Table II, our product does not show these shifts and may consequently be assigned structure 1.

TABLE II

	a (1 H)	b (3 H)	c (1 H)	d (3 H)
Tomentolide A (4)[a]	τ 6.22	9.29	7.82	9.00
Inophyllolide (5)[b]	5.68	8.42	7.54	8.79
1	5.75	8.45	7.4	8.80

[a] Reference 4. [b] Reference 3.

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(7) Structure **1** shows numbering based on a coumarin system.