430. *Diospyrol, a Constituent of* Diospyros mollis.

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The principal constituent of the fruit of *Diospyros mollis* is a 2 : 2′-dinaphthyl, closely related to gossypol.

The crude extract of the fruit of the shrub, *Diospyros mollis*, which is used in Far Eastern countries as an anthelmintic, has been examined and the principal component appears to be a readily oxidisable, new, tetrahydric phenol, diospyrol, $C_{22}H_{18}O_4$, which is devoid of methoxyl groups, contains two *C*-methyl groups, and gives a tetra-acetate. On methylation diospyrol furnishes tetra-*O*-methyldiospyrol, the general properties and infrared spectrum of which confirm the absence of additional hydroxyl or carbonyl functions. Oxidation of tetra-*O*-methyldiospyrol gives a di-*p*-quinone, di-*O*-methyldiospyroquinone, $C_{22}H_{12}O_4(OMe)_2$, which is converted by reductive acetylation into tetra-*O*-acetyl-di-*O*-methyldiospyroquinol, $C_{22}H_{12}(OAc)_4(OMe)_2$. These results, in conjunction with the spectral data, indicate a dinaphthyl type of structure for diospyrol. From an inspection of the ultraviolet absorption spectra of diospyrol and its derivatives (Table 1) together with those of various 2 : 2′-dinaphthyls (Table 2) and of deoxygossypol derivatives,[1,2] it seems reasonably certain that diospyrol contains a 2 : 2′-dinaphthyl

[1] Shirley and Sheehan, *J. Amer. Chem. Soc.*, 1955, **77**, 4606.
[2] Shirley and Dean, *ibid.*, p. 6077.

chromophore. Furthermore, a comparison of the ultraviolet absorption spectra of tetra-*O*-methyldiospyrol, 1 : 1′-dimethoxy-2 : 2′-dinaphthyl, and 4 : 8 : 4′ : 8′-tetramethoxy-3 : 3′-dimethyl-2 : 2′-dinaphthyl indicates the possible presence of a 1 : 1′-dihydroxy-2 : 2′-dinaphthyl nucleus in diospyrol.

TABLE 1. *Absorption spectra of diospyrol derivatives.*[a]

Substance	$\lambda_{max.}$ (mμ)	log ε	$\lambda_{min.}$ (mμ)	log ε
Tetra-*O*-methyldiospyrol	225	4·64	228	4·63
	242	4·88		
	ca. 256 [b]	*ca.* 4·71	281	4·09
	300—340 [c]	*ca.* 4·2		
Tetra-*O*-acetyldiospyrol	221	4·76	225	4·74
	237	4·99		
	250 [b]	4·81		
	ca. 290 [b]	*ca.* 4·1		
Tetra-*O*-acetyldi-*O*-methyldiospyroquinol	218	4·73	229	4·63
	239	4·82	248	4·66
	261	4·79		
	ca. 300 [b]	*ca.* 4·15		
Di-*O*-methyldiospyroquinone [d]	—	—	238	4·43
	256	4·52		
	375	3·94	311	3·46

[a] Results were obtained in 95% ethanol on a Unicam Model S.P. 500 Quartz Spectrophotometer. [b] Shoulder. [c] Ill-defined fine structure. [d] In dioxan.

TABLE 2. *Absorption spectra of some dinaphthyls.*[a]

Substance	$\lambda_{max.}$ (mμ)	log ε	$\lambda_{min.}$ (mμ)	log ε
2 : 2′-Dimethoxy-1 : 1′-dinaphthyl [e]	230	4·95	254	3·62
	282	3·91	291	3·86
	294	3·87	314	3·49
	326	3·68	330	3·67
	340	3·76		
1 : 1′-Dimethoxy-2 : 2′-dinaphthyl	218	4·74	227	4·64
	236	4·72	243	3·68
	257	4·81		
	ca. 292 [b]	*ca.* 4·14		
4 : 8 : 4′ : 8′-Tetramethoxy-3 : 3′-dimethyl-2 : 2′-dinaphthyl	224	4·84	230	4·83
	243	4·95	283	4·11
	289	4·14	294	4·14
	301	4·17	312	4·04
	315	4·06	326	3·80
	330	3·89		
1 : 4 : 1′ : 4′-Tetra-acetoxy-2 : 2′-dinaphthyl [g]	217	4·75	225	4·67
	235	4·82		
	ca. 247 [b]	*ca.* 4·77		
	ca. 286 [b,c]	*ca.* 4·18		
2 : 2′-Di-1 : 4-Naphthaquinone [d,h]	246	4·49	226	4·33
	266	4·45	260	4·43
	337	3·79	315	3·74
	428	2·87	396	2·75

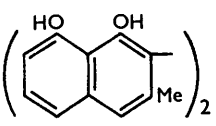
[a–d] See Table 1. [e] Ostermayer and Rosenhek, *Ber.*, 1884, **17**, 2453. [f] Clemo, Cockburn, and Spence, *J.*, 1931, 1265. [g] Rosenhauer, Braun, Pummerer, and Riegelbauer, *Ber.*, 1937, **70**, 2281. [h] Ullmann, *Helv. Chim. Acta*, 1926, **9**, 442.

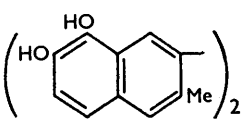
This concept is compatible with the fact that the strongest band in the ultraviolet spectra of the diospyrol derivatives (λ 237—242 mμ; log ε *ca.* 4·9) and of 1 : 1′-disubstituted 2 : 2′-dinaphthyls (λ 235—243 mμ; log ε *ca.* 4·8) is at a shorter wavelength than that of 2 : 2′-dinaphthyl (λ 245 mμ; log ε 5·0). The hypsochromic shift is due to hindered rotation, attributable to substituents in the 1- and/or 3-position, preventing a completely planar structure.[3,4] Current theories of plant product biogenesis,[5] in conjunction with

[3] Friedel, Orchin, and Reggel, *J. Amer. Chem. Soc.*, 1948, **70**, 199.
[4] Edwards and Cashaw, *ibid.*, 1954, **76**, 6141.
[5] Birch and Donovan, *Chem. and Ind.*, 1954, **32**, 1047.

the isolation [6,7,8,9] of plumbagin (VII) from various species of *Diospyros* and of the phenol (VIII) from *D. hebecarpa* [6] and other general considerations, provide collateral biogenetic evidence in support of the proposed symmetrical structure for diospyrol, for the location of hydroxyl groups in the 1 : 1′-positions, and for the 3 : 3′-methyl groups, which from the spectral data for gossypol, should produce no further hypsochromic effects on the spectrum. These desiderata, in conjunction with the green ferric reaction of diospyrol, indicate a structure (I), although alternative formulations, *e.g.*, (II), cannot be excluded.

Confirmation of structure (I) for diospyrol was sought by an unequivocal synthesis of 4 : 8 : 4′ : 8′-tetramethoxy-3 : 3′-dimethyl-2 : 2-dinaphthyl (VI), an isomer of tetra-*O*-methyldiospyrol, which it was hoped would afford di-*O*-methyldiospyroquinone (III) on


(I)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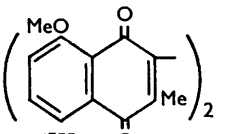
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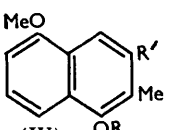
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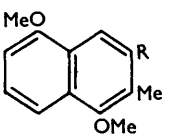
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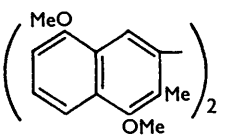
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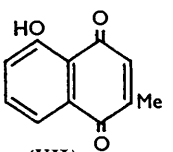
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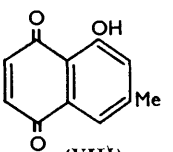
(VIII)

oxidation. The Stobbe condensation of *o*-methoxybenzaldehyde with ethyl methylsuccinate followed by cyclisation [10] of the product gave the acetoxynaphthoate (IV; R = Ac, R′ = CO_2Et), which was then converted by the stages (IV; R = H, R′ = CO_2H), (IV; R = Me, R′ = CO_2Me), (IV; R = Me, R′ = $CO{\cdot}NH{\cdot}NH_2$), (V; R = NH_2), and (V; R = I) into the desired 2 : 2′-dinaphthyl (VI), according to standard methods. Unfortunately, repeated attempts to obtain a crystalline quinone from (VI) with chromic oxide, hydrogen peroxide, lead tetra-acetate, or periodic acid were unsuccessful.

Experimental

Tetra-O-*methyldiospyrol*.—When the dried, crushed, ripe fruit of *Diospyros mollis* (10 kg.) was extracted continuously with ether, the crude phenol (70—90 g.) gradually separated from the ethereal solution as a grey powder, which gave an intense green ferric reaction in alcohol and was extremely sensitive to aerial oxidation, especially in solution. Repeated crystallisation of the product from methanol (charcoal) furnished *diospyrol* in needles, m. p. 251—257° (decomp.), which darkened rapidly in air and had an intense green ferric reaction in alcohol (Found : C, 76·8; H, 5·4; *C*-Me, 8·7. $C_{20}H_{12}O_4Me_2$ requires C, 76·3; H, 5·2; *C*-Me, 8·0%). Material sufficiently pure for methylation and acetylation was obtained when a slurry of the crude phenol (1 part) in methanol (5 parts) was rapidly heated to the b. p. and filtered and the residue washed with hot methanol (5 parts). A mixture of this product (8 g.), potassium carbonate (25 g.), methyl sulphate (16 g.), and acetone (200 ml.) was heated under reflux in nitrogen for 10 hr. A solution of the methylation product in benzene was treated with charcoal and filtered and the yellow fluorescent filtrate chromatographed on aluminium oxide. Purification of the eluate from benzene gave *tetra*-O-*methyldiospyrol* (3·1 g.) in tablets, m. p. 232°, unchanged by sublimation at 250°/0·01 mm. [Found : C, 77·4, 77·7; H, 6·7, 6·9; OMe, 30·3, 30·2; *C*-Me, 6·5, 6·5%; *M* (ebullioscopic in benzene) 397, 412. $C_{20}H_8Me_2(OMe)_4$ requires C, 77·6; H, 6·5; OMe, 30·9; *C*-Me, 7·5%; *M*, 402]. This ether was sparingly soluble in the usual organic solvents and devoid of a ferric reaction in alcohol.

[6] Cooke and Dowd, *Austral. J. Sci. Res.*, 1952, **5**, *A*, 760.
[7] Meijer, *Rec. Trav. chim.*, 1947, **66**, 193.
[8] Paris and Moyse-Mignon, *Compt. rend.*, 1949, **228**, 2063.
[9] Paris and Prista, *Ann. Pharm. franç.*, 1954, **12**, 375.
[10] Borsche, *Annalen*, 1936, **526**, 1.

Tetra-O-*acetyldiospyrol*.—A solution of partially purified diospyrol (5 g.) in acetic anhydride (50 ml.), containing sodium acetate (8 g.), was refluxed for 1 hr. and then poured on ice. Next day the precipitate was purified from methanol, chromatographed on aluminium oxide from a solution in benzene, and then sublimed at 240°/0·01 mm., giving *tetra*-O-*acetyldiospyrol* (1·7 g.) which separated from benzene–ethanol in prisms, m. p. 233°, devoid of a ferric reaction; with tetra-*O*-methyldiospyrol it melted at *ca.* 208—225° (Found: C, 69·8, 70·4; H, 5·2, 5·1. $C_{30}H_{26}O_8$ requires C, 70·0; H, 5·1%).

Tetrabromotetra-O-*methyldiospyrol*.—Prepared by adding an excess of bromine in chloroform to a solution of tetra-*O*-methyldiospyrol (250 mg.) in chloroform, *tetrabromotetra*-O-*methyldiospyrol* (85 mg.) separated from benzene in needles, m. p. 310° (Found: C, 43·1; H, 2·9; Br, 48·2. $C_{26}H_{22}O_4Br_4$ requires C, 43·5; H, 3·1; Br, 44·4%).

Di-O-*methyldiospyroquinone*.—Hydrogen peroxide (12 ml.; 100-vol.) was added during 15 min. to a boiling solution of tetra-*O*-methyldiospyrol (2 g.) in acetic acid (80 ml.), followed by water (80 ml.), and the solution boiled for a further 15 min., a crystalline product separating. Purification of this from acetic acid and then toluene gave *di*-O-*methyldiospyroquinone* (0·27 g.) in dark red prisms, m. p. 250° (decomp.) [Found: C, 71·7, 71·6; H, 4·7, 4·7; OMe, 14·9; *C*-Me, 6·7, 7·0. $C_{20}H_6O_4Me_2(OMe)_2$ requires C, 71·6; H, 4·5; OMe, 15·5; *C*-Me, 7·5%].

Reductive acetylation of this quinone (170 mg.) in boiling acetic anhydride (10 ml.), containing sodium acetate (0·2 g.) and zinc dust (0·1 g.), for ½ hr. gave *tetra*-O-*acetyldi*-O-*methyldiospyroquinol* (120 mg.) which separated from methanol in almost colourless prisms, m. p. 242° [Found: C, 66·7; H, 5·3; OMe, 10·9%; *M* (*X*-ray crystallographic), 562. $C_{30}H_{24}O_8(OMe)_2$ requires C, 66·9; H, 5·3; OMe, 10·8%; *M*, 575].

4 : 8 : 4′ : 8′-*Tetramethoxy*-3 : 3′-*dimethyl*-2 : 2′-*dinaphthyl*.—To a well-stirred mixture of sodium hydride (25 g.) and benzene (500 ml.) in nitrogen, ethanol (5 ml.) was added, followed dropwise by a solution of *o*-methoxybenzaldehyde (57 g.) in ethyl methylsuccinate (200 ml.), at a rate sufficient to maintain a steady evolution of hydrogen and a temperature of 40°. The mixture was then stirred for 1 hr. and acetic acid (100 ml.) was cautiously added, followed by water (200 ml.). An ethereal solution of the product was repeatedly washed with an excess of 2N-aqueous sodium carbonate, and the combined washings were acidified and extracted with ether. Evaporation of the dried extracts gave ethyl hydrogen β-2-methoxybenzylidene-α-methylsuccinate (77 g.) as an oil which was cyclised with boiling acetic anhydride (140 ml.) and sodium acetate (21 g.) during 5 hr. The mixture was poured on ice and next day the dark oil which had separated was repeatedly extracted with boiling light petroleum (b. p. 60—80°). The residue left on evaporation of the combined extracts was purified from ethanol (100 ml.), giving *ethyl* 4-*acetoxy*-8-*methoxy*-3-*methyl*-2-*naphthoate* which formed needles (17 g.), m. p. 112°, from methanol or light petroleum (b. p. 60—80°) (Found: C, 67·6; H, 6·1. $C_{17}H_{18}O_5$ requires C 67·5; H, 6·0%). Hydrolysis of this ester (16 g.) with boiling 10% aqueous–alcoholic sodium hydroxide for 5 hr. gave 4-*hydroxy*-8-*methoxy*-3-*methyl*-2-*naphthoic acid* (12 g.) which separated from acetic acid in needles, m. p. 244° (Found: C, 67·1; H, 5·3; OMe, 13·4. $C_{12}H_9O_3{\cdot}OMe$ requires C, 67·2; H, 5·2; OMe, 13·4%).

Methylation of this phenolic acid (13 g.) in boiling acetone (200 ml.) with methyl iodide (20 ml.) and potassium carbonate (10 g.) for 9 hr. furnished *methyl* 4 : 8-*dimethoxy*-3-*methyl*-2-*naphthoate* (12 g.), forming yellow prisms, m. p. 110°, from light petroleum (b. p. 60—80°) [Found: C, 68·9; H, 6·4; OMe, 35·7. $C_{13}H_7O(OMe)_3$ requires C, 69·2; H, 6·2; OMe, 35·8%]. A solution of this ester (1 g.) in ethanol (10 ml.), containing hydrazine hydrate (2 ml.), was refluxed for 7 hr. and evaporated to a small volume. The resulting *hydrazide* was recrystallised from ethanol, forming needles, m. p. 211° (Found: C, 64·2; H, 5·8; N, 10·8. $C_{14}H_{16}O_3N_2$ requires C, 64·6; H, 6·2; N, 10·8%).

A solution of this hydrazide (11·2 g.) in hot alcohol (500 ml.) was cooled until crystallisation began, and then treated with ethanolic hydrogen chloride (16 ml., containing 2·3 g. of hydrogen chloride) followed by ethyl nitrite (4 g.) in alcohol (10 ml.). The mixture was kept for 15 hr. at 0°, 1 hr. at room temperature, and 1 hr. at 100°, the greater part of the solvent was then distilled off, and the residue mixed with 20% methanolic potassium hydroxide (250 ml.), boiled for ½ hr., cooled, and extracted with benzene. The benzene extract was washed with warm 2N-hydrochloric acid, and the amine precipitated from the acidic extract with ammonia (*d* 0·88) at 0°. Purification from light petroleum (b. p. 60—80°) followed by vacuum-sublimation gave 4 : 8-*dimethoxy*-3-*methyl*-2-*naphthylamine* in needles (5·7 g.), m. p. 90° (Found: C, 71·9; H, 6·6. $C_{13}H_{13}O_2N$ requires C, 71·9; H, 7·0%).

A solution of this amine (5·3 g.) in water (70 ml.) and concentrated sulphuric acid (10·5 ml.) was diazotised at 0° with sodium nitrite (2 g.) in water (20 ml.), and 1½ hr. later the mixture was treated with potassium iodide (11 g.) in water (10 ml.), kept for 1½ hr., and heated on the steam-bath for 30 min. The product, isolated with light petroleum (b. p. 60—80°) and purified by chromatography on aluminium oxide followed by crystallisation from aqueous alcohol, gave *3-iodo-1 : 5-dimethoxy-2-methylnaphthalene* in needles (7·6 g.), m. p. 98° (Found : C, 47·8; H, 4·0. $C_{13}H_{13}O_2I$ requires C, 47·6; H, 4·0%).

A mixture of the iodonaphthalene (7·5 g.), copper bronze (5 g.), and a crystal of iodine was heated at 210° for 5 hr., and the cooled, crushed product exhaustively extracted with light petroleum (b. p. 60—80°). The extract was chromatographed on aluminium oxide from benzene to give *4 : 8 : 4′ : 8′-tetramethoxy-3 : 3′-dimethyl-2 : 2′-dinaphthyl* which separated from methanol in prisms (2·1 g.), m. p. 176° [Found : C, 77·6; H, 6·8; OMe, 31·2. $C_{22}H_{14}(OMe)_4$ requires C, 77·6; H, 6·5; OMe, 30·8%].

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