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THE STRUCTURE OF DIOSPYROL, THE PRINCIPLE FROM THE FRUIT OF DIOSPYROS MOLLIS[*1]

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THE extracts of the fresh fruits of Diospyros mollis Griff.(Ebenaceae) are widely used in Thailand as an anthelmintic and a readily oxidizable phenolic constituent(1,2) named diospyrol (I) is assumed to be the active principle. The chemical studies on the constituent was first carried out by Loder et al.(1) and tetrahydroxydimethyl-2,2'-binaphthyl nature of the compound was revealed by their study. Although the structure (Ia) was proposed as a most probable structure,(1) the positions of the substituents and the linkage have not been proved conclusively.

As a part of our joint studies on the medicinal resources in Thailand we have reexamined the phenolic substance.[*3] Methylation of I with dimethyl sulfate afforded dimethyl ether (III), m.p. 183-184°, λ_{max}^{EtOH} mμ (log ε) 224, 243, 258, 315, 327, 340 (4.52, 4.54, 4.46, 3.96, 3.97, 4.01), besides the tetramethyl ether(1)(II). III was the main product when I was methylated with diazomethane. Further methylation of III with dimethyl sulfate gave

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[*3] Prepared by the reported method.(3) Since the authentic specimens of the British workers(1) have not been available(Professor W. B. Whalley, private communication), the direct comparison of our specimens with theirs has not been carried out. However all the properties of I, II, IV and V showed good agreement with the reported values except the m.p. of V.

CHART 1

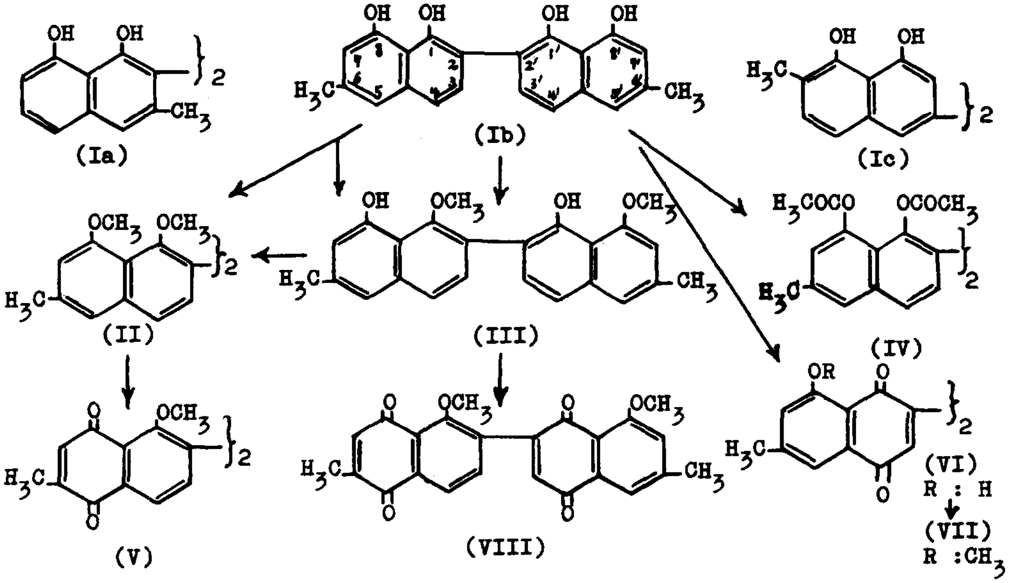

TABLE 1 NMR Spectra of Diospyrol Derivatives

(δ values in ppm from the internal standard TMS)

compound	solvent	1- and 1'-OH, OMe or OAc	3- and 3'-H	4- and 4'-H	5- and 5'-H	6- and 6'-CH_3	7- and 7'-H	8- and 8'-OH, OMe or OAc
II	$CDCl_3$+ CF_3COOH	3.58	7.36 (d, J= 8 cps)	7.54	7.24 (br)	2.45	6.72 (br)	3.89
III	$CDCl_3$	3.49	7.22 (d, J= 8 cps)	7.34	7.05 (br)	2.43 *	6.68 (br)	9.71
		9.60	7.36 (d, J= 9 cps)	7.43	7.28 (br)	2.39 *	6.58 (br)	3.97
IV	$CDCl_3$	1.96	7.33 (d, J= 8 cps)	7.71	7.57	2.50 (d, J= 1.5 cps)	6.98	2.34
V	$CDCl_3$+ CF_3COOH	3.58	7.62 (d, J= 10 cps)	7.94	= 0	2.16 (d) (J= 1.5 cps)	6.74 (q)	= 0
VI	$CDCl_3$+ CF_3COOH	= 0	7.05	= 0	7.54 (br)	2.48	7.18 (br)	---
VII	$CDCl_3$	= 0	6.87	= 0	7.56 (br)	2.49	7.05 (br)	3.94
VIII	$CDCl_3$+ CF_3COOH	3.79	7.72 (d, J= 8 cps)	8.09	= 0	2.25 (d) (J= 1.5 cps) *	6.98 (q)	= 0
		= 0	7.10	= 0	7.73 (br)	2.57	7.29 (br)	3.99

* confirmed by the spin-decoupling.

II. The tetraacetate (IV) and di-O-methyldiospyroquinone (V), m.p. 275° (lit.(1) m.p. 250°(dec.)), were prepared according to the literature.(1) The oxidation of I with Fremy's salt afforded a hydroxynaphtho-1,4-quinone derivative (VI), m.p. 253°, $\lambda_{max}^{dioxane}$ mμ (log ε) 253, 275, 434 (4.34, 4.28, 3.96), ν(KBr) 1652, 1625 cm^{-1}, and no hydroxyl absorption. The methylation of VI with methyl iodide and silver oxide in pure chloroform(4) afforded the dimethyl ether (VII), m.p. > 250°, $\lambda_{max}^{CHCl_3}$ mμ (log ε) 253, ca. 414 (4.32, 3.70), ν(KBr) 1655 cm^{-1}, which is very sensitive for daylight and acid.(4,5) The oxidation of III with Fremy's salt gave a methoxynaphtho-1,4-quinone derivative (VIII), m.p. 269°(under sublimation), $\lambda_{max}^{dioxane}$ mμ (log ε) 252, 380 (4.37, 3.79), ν(KBr) 1655 cm^{-1}.

As was discussed by Loder et al.(1) UV absorptions of I-IV and V-VIII clearly suggested that they are naphthalene and naphtho-1,4-quinone derivatives respectively. The molecular formula of I was further confirmed by analyses and mass spectra (M^+ of II, m/e 402). Symmetrical disposition of the substituents on the binaphthyl nucleus was revealed by NMR spectra (Table 1) and mass spectra (doubly charged ions less than m/e 201.5($(M + 1)^{++}$) in II). Since the ν_{OH} absorption was not observed in the IR spectrum of VI, the hydroxyl groups in I must be 1,5- or 1,8-positions. The formation of dimethyl ether (III) from I and the presence of hydrogen bonds between the methoxyl groups and the hydroxyl groups in III ($\nu_{OH}(CCl_4)$ 3420 cm^{-1}(br)(unaffected by dilution)(6,7) and δ 9.71, 9.60 ppm (in $CDCl_3$)(7)) clearly demonstrated 1,8-dihydroxynaphthalene structure for I. In the NMR spectra of II, III and IV pairs of ortho-coupled protons and meta-coupled protons are observed. In V the former pair has been retained, while in VI and VII the latter pair exists. These observations suggest the positions of the methyl group and the binaphthyl linkage at 2- and 6- or 4- and 6-positions. The formation of the isomeric naphtho-1,4-quinones (V and VII) and the δ values of the lower half in the ortho-coupled protons leave the structure Ib and Ic as the possible structures of diospyrol (I). The presence of the vinylic coupling of the methyl protons and the adjacent ring proton(8) in V and VIII suggests 6-methyl-2-naphthyl structure for these compounds. Thus diospyrol must be expressed by the formula (Ib).

The correlation of the derivatives is shown in Chart 1 and all the spectral and analytical data show good accord with these formulations. UV absorptions and the high chemical shifts of methoxyl and acetoxyl methyls at 1 and 1' positions indicate non-coplanarity of the both naphthyl nuclei.

Further chemical works are now in progress.

The phenolic constituents so far elucidated from Ebenaceae extractives(1,7,9) are assumed to be derived from a precursor equivalent to 1,8-dihydroxy-3-methylnaphthalene. Diospyrol is also assumed to be formed by the oxidative coupling of the naphthalene. The same sort of binaphthyl derivatives related to 1,8-dihydroxynaphthalene(10) and 1,8-dihydroxy-2-acetyl-3-methylnaphthalene(4) have also been known.

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