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Naphthoquinone Derivatives from the Ebenaceae. III.[1] Shinanolone from *Diospyros japonica* SIEB.

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Three naphthoquinones, isodiospyrin (I), bisisodiospyrin (II), and 7-methyljuglone (IV), a new tetralone derivative named shinanolone (III) and four triterpenes, taraxerol, lupeol, betulin, and betulinic acid, were isolated from the roots of *Diospyros japonica.* The structure of shinanolone was elucidated to be 4,8-dihydroxy-6-methyl-1-tetralone and the application of the dibenzoate chirality rule was attempted for the compound.

Diospyros japonica SIEB. (Japanese name, shinanogaki) (Ebenaceae) is a shrub growing in southern part of this country. In the course of our studies on naphthoquinone derivatives widely distributed in the Ebenaceae,[1,3,4] chloroform extract of the dried roots of *D. japonica* was examined by the same method as in the previous paper.[1] As the result two naphthoquinones, isodiospyrin (I) and bisisodiospyrin (II), were isolated and identified with those obtained from *D. lotus* L.[1] and *D. morrisiana* HANCE[1] besides four triterpenoids, taraxerol, lupeol, betulin, and betulinic acid. As the new natural products a tetralone derivative (III), named shinanolone after the structure and the Japanese name of the plant, and a red pigment of mp 220—225°, $C_{18}H_{15}O_3N$, were isolated but, due to the scarcity of the sample the latter has not been characterized further. From methanol extract of the same source 7-methyljuglone (IV) was isolated and identified.

Shinanolone (III), mp 110—111°, $[\alpha]_D^{21}$ -22.8 ($CHCl_3$), has a molecular formula $C_{11}H_{12}O_3$ (M^+ 192.078 *m/e*, Calcd. 192.079). The ultraviolet (UV) spectrum of (III), λ_{max}^{EtOH} mμ (log ε): 218 (4.24), 268 (4.08), 333 (3.54) (Fig. 1), suggested an acetophenone chromophore in the molecule.[5] The infrared (IR) absorptions ($\nu_{C=O}$ 1635, the dibenzoate, $\nu_{C=O}$ 1690 cm^{-1}) and the nuclear magnetic resonance (NMR) spectrum (δ_{CDCl_3} 12.15) indicated the presence of a hydrogen bond between the carbonyl group and a hydroxyl group. Besides the phenolic hydroxyl group the presence of a secondary alcoholic group was shown by IR (ν_{O-H} 3260 cm^{-1}), NMR (δ_{CDCl_3} 4.87 (1H, dd, $J=5$, 6.5 Hz) and the formation of monoacetate (IR 1754, 1230 cm^{-1}, NMR δ_{CDCl_3} 6.09 (1H, t, $J=5$ Hz)) and dibenzoate (M^+ 400.133 *m/e*, Calcd. for $C_{25}H_{20}O_5$, 400.131, IR 1745, 1720 cm^{-1}, NMR δ_{CDCl_3} 6.30 (1H, t, $J=4.5$ Hz)). The NMR spectrum also indicated the presence of an aromatic methyl group (δ_{CDCl_3} 2.36) and two *m*-coupled aromatic protons (δ_{CDCl_3} 6.75, 6.88 (each 1H, $w_{1/2}$ 3Hz)). Thus the compound (III) contains 6-substituted 2-hydroxy-4-methylacetophenone unit and, since the presence of two methylene groups was also shown by the NMR (δ_{CDCl_3} 2.0—2.4 (2H, m), 2.4—3.3 (2H, m)), the compound must be expressed by the formula (A). The spin-decoupling experiments of (III) (Fig. 2) indicated that the carbinyl proton (δ_{CDCl_3} 4.87) is coupled with the higher methylene (δ_{CDCl_3}

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1) Part II: K. Yoshihira, M. Tezuka, and S. Natori, *Chem. Pharm. Bull.* (Tokyo), **19**, 2308 (1970).

2) Location: *Kamiyoga-1-chome, Setagaya-ku, Tokyo.*

3) K. Yoshihira, S. Natori, and P. Kanchanapee, *Tetrahedron Letters*, **1967**, 4857; K. Yoshihira, M. Tezuka, and S. Natori, *Tetrahedron Letters*, **1970**, 7; K. Yoshihira, M. Tezuka, C. Takahashi, and S. Natori, *Chem. Pharm. Bull.* (Tokyo), **19**, 851 (1971).

4) K. Yoshihira, M. Tezuka, P. Kanchanapee, and S. Natori, *Chem. Pharm. Bull.* (Tokyo), **19**, 2271 (1971).

5) A.I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, Oxford, 1964, p. 100. The calculated value of the E.T. Band for the structure (III) according to Scott's rule is λ 266 mμ.

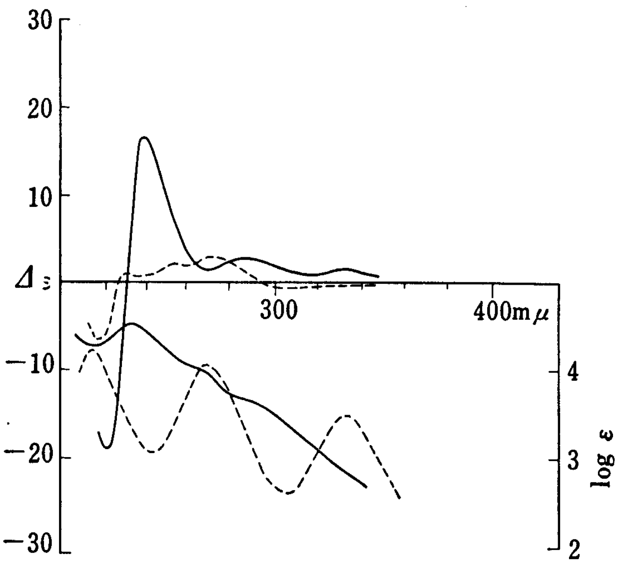

Fig. 1. UV and CD Curves of Shinanolone (III) and the Dibenzoate (in MeOH)

———: dibenzoate of shinanolone
-------: shinanolone (III)

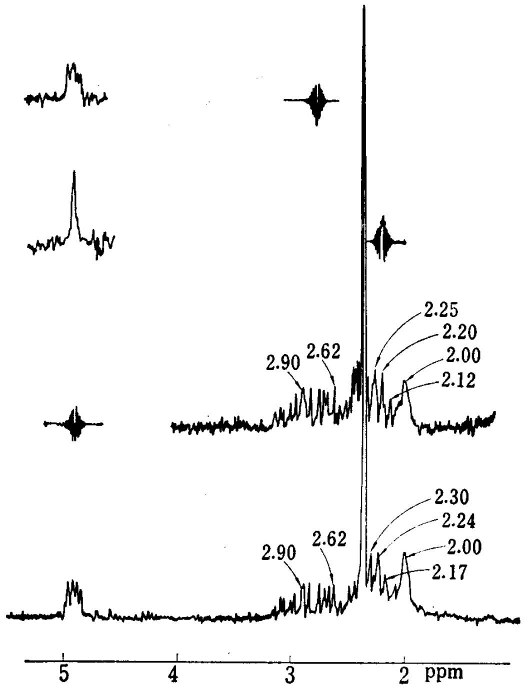

Fig. 2. Spin-decoupling Experiment of Shinanolone (III) (in $CDCl_3$ at 100MHz)

2.0—2.4) but not with the lower methylene (δ_{CDCl_3} 2.4—3.3). Thus the compound (III) must be either 2,8-dihydroxy-6-methyl-1-tetralone or 4,8-dihydroxy-6-methyl-1-tetralone.

The oxidation of (III) with 2,3-dichloro-5,6-dicyanobenzoquinone in benzene or manganese dioxide in benzene⁶⁾ afforded 7-methyljuglone (IV). On the contrary the reduction of (IV) with lithium aluminum hydride⁷⁾ afforded the racemate of (III) as the main reaction product and the identity was confirmed by thin-layer chromatography (TLC) and IR. The selective reduction of one of the carbonyls in (IV) is assumed to be due to the presence of a hydroxyl group forming a hydrogen bond. Thus the structure of shinanolone was proved to be 4,8-dihydroxy-6-methyl-1-tetralone (III).

The conformational dissymmetry rule is not safely applied to the phenyalkylcarbinols when the most bulky substituent is at the same time the highly polarizable phenyl group, since preference of polarizability consideration or steric consideration gives the opposite conclusion.⁸⁾ The direct application of octant rule is also impossible. Recent proposal of "the dibenzoate rule" has been extended to "the aromatic chirality method" and the application to several cases has been reported.⁹⁾ In order to apply the method without any doubt the removal of the carbonyl group in (III) was attempted in vain and the further trial was abandoned due to the scarcity of the sample. However, the dibenzoate of (III), $C_{25}H_{20}O_5$, showed strong Cotton effects, $\Delta\varepsilon_{241}+16$, $\Delta\varepsilon_{224}-19$ (in MeOH) (Fig. 1), quite similar to those shown by two interacting benzoates. If so, the first positive effect indicates that the dibenzoate has a positive chirality (right-handed screw) (Fig. 3) and the absolute configuration at C-4 in the tetralone is assigned to *R* (the hydroxyl is β in the formula (III)).

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6) K. Suzuki, T. Sassa, H. Tanaka, H. Aoki, and M. Namiki, *Agric. Biol. Chem.*, **32**, 1471 (1968).
7) E. Boyland and D. Manson, *J. Chem. Soc.*, **1950**, 1837.
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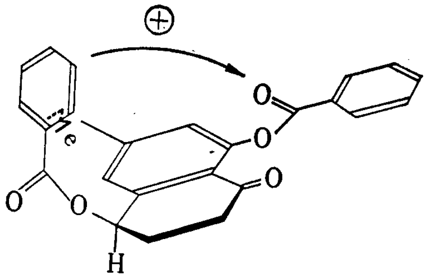

Fig. 3. The Positive Chirality of the Dibenzoate of III

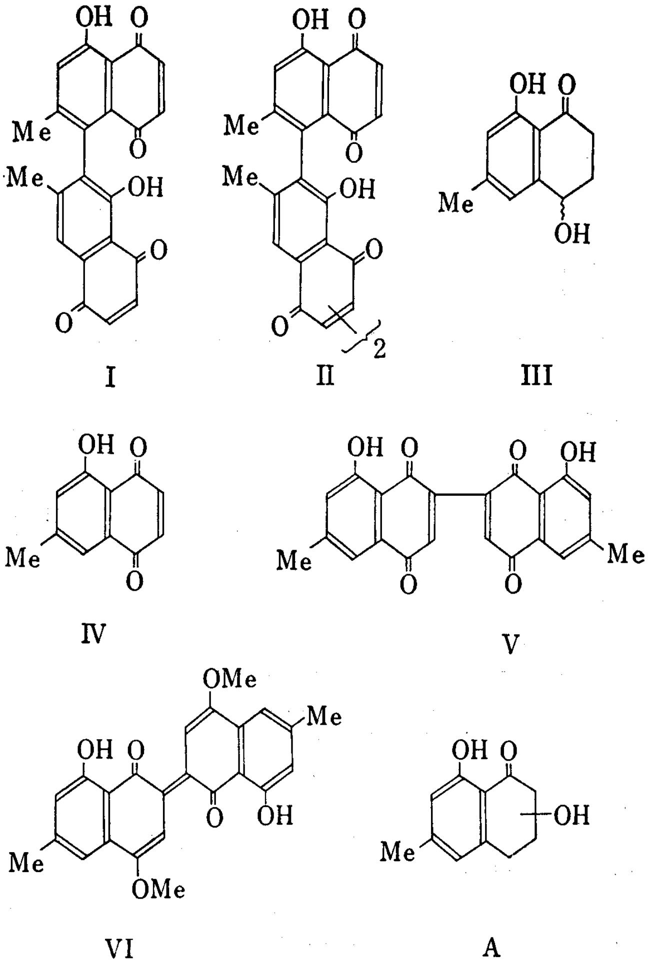

Chart 1

Shinanolone (III) was later isolated from *D. kaki* Thunb. var. *sylvestris* Makino (Japanese name, yamagaki) along with I, IV, mamegakinone (V), and the 2,2′-binaphthyl-1,1′-quinone[10] (VI), and the isomer of III named isoshinanolone was also isolated from *D. maritima* Blume (Japanese name, kurobo) along with plumbagin, elliptionone and maritinone.[11] Although the biogenetical situation of shinanolone (III) among naphthol and naphthoquinone derivatives widely distributed in the Ebenaceae is not clear at the moment, the presence of the 6-methyl-4,8-dihydroxy-1-tetralone (III) in the plants together with 6-methyl-8-hydroxyl-1,4-naphthoquinones (I, II, IV—VI) may suggest some biogenetical significance.

Experimental[12]

Extraction of the Roots of *D. japonica*——The dried and milled roots (3.5 kg) of *D. japonica* collected at Kiyosumi, Chiba Prefecture, October 1969, and Tanegashima, Kagoshima Prefecture, May 1969, were extracted with boling $CDCl_3$ for 8 hr. The extract (45 g) was chromatographed on a column of silica gel using benzene containing increasing amount of EtOAc as the developer. Each fraction was examined by thin-layer chromatography (TLC) and, if necessary, the column and preparative layer chromatographies were repeated. The following compounds were separated in the order of elution and identified with authentic samples respectively by TLC, IR, and mixed fusions. In the case of the triterpenoids, their acetates were also prepared and identified.[13]

(i) Taraxerol, mp 287° (from hexane), 20 mg. (ii) Lupeol, mp 190—193° (from hexane), 400 mg. (iii) The red needles of mp 220—225° (from hexane), 6 mg. M^+ 293.104 *m/e* (Calcd. for $C_{18}H_{15}O_3N$, 293.105). UV λ_{max}^{EtOH} mμ (log ε): 275 (4.36), 416 (3.80), *ca.* 500 (sh. 3.56). IR ν_{max}^{KBr} cm^{-1}: 3480 (br.), 3300, 1630, 1580 (s), 1518, 1500, 1388, 1320, 1275, 1225, 850. NMR δ (in $CDCl_3$): 1.62 (2H, s), 2.40 (3H, s), 2.48 (3H, s), 6.30 (1H, s), 7.02 (1H, m), *ca.* 7.25 (4H, s), 7.55 (2H, m), 11.65 (1H, s). (iv) Isodiospyrin (I), mp 234—236° (from benzene), 250 mg. (v) β-Sitosterol, mp 132° (from hexane), 30 mg. (vi) A mixture of fatty acids. (vii) Betulin, mp

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10) O.C. Musgrave and D. Skoyles, *Chem. Commun.*, **1970**, 1461.

11) M. Kuroyanagi, M. Tezuka, K. Yoshihira, and S. Natori, *Abstracts Papers*, The 91st Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, April 1971, p. 774.

12) The melting points were determined in a Yanagimoto melting point apparatus and not corrected. For column chromatography silica gel (Mallinckrodt) was used and for thin-layer chromatography Silica gel G was used unless otherwise specified.

13) The detailed physical data of the known compounds are shown in the previous papers.[1,4]

250—251° (from MeOH), 50 mg. (viii) Shinanolone (III), mp 110—111° (from hexane), 200 mg (*vide infra*). (ix) Bisisodiospyrin (II), mp>310° (from $CHCl_3$), 400 mg. (x) Betulinic acid, mp>310° (from MeOH), 1.2 g.

The same material (100 g) was extracted with methanol and the extract was treated by the same method. 7-Methyljuglone (IV), mp 112° (from hexane), 13 mg, and isodiospyrin (I), 14 mg, were isolated and identified.

Shinanolone (III)——Mp 110—111° from hexane. $[\alpha]_D^{21}$ $-22.8°$ ($c=0.806$, $CHCl_3$). Mass Spectrum *m/e*: 192.078 (M^+, $C_{11}H_{12}O_3$ (Calcd. 192.079)), 177.054 (M^+-CH_3, $C_{10}H_9O_3$ (Calcd. 177.055)), 174.071 (M^+-H_2O, $C_{11}H_{10}O_2$ (Calcd. 174.068)), 164.083 (M^+-CO, $C_{10}H_{12}O_2$ (Calcd. 164.084)), 135.045 (M^+-C_3H_5O, $C_8H_7O_2$ (Calcd. 135.045)). UV λ_{max}^{EtOH} mμ (log ε): 218 (4.24), 268 (4.08) 333 (3.54) (Fig. 1). IR ν_{max}^{KBr} cm^{-1}: 3260, 3160, 2920, 1635 (s), 1336, 1260, 1195, 845, 820. NMR δ (in $CDCl_3$): 2.36 (3H, s), 2.0—2.4 (2H, m), 2.4—3.3 (2H, m), 4.87 (1H, dd, $J=5$, 6.5 Hz), 6.75 and 6.88 (each 1H, $w\frac{1}{2}$ 3 Hz), 12.15 (1H, s). Circular dichroism (CD) (Fig. 1).

Shinanolone 4-Acetate——Shinanolone (III) (14 mg) was acetylated by Ac_2O and pyridine and the product was repeatedly purified by TLC, monitered by a UV lump (365 mμ), to give a colorless viscous oil (12 mg) showing a single spot, UV λ_{max}^{EtOH} mμ (log ε): 220 (4.31), 267 (4.12), 333 (3.69). IR ν_{max}^{KBr} cm^{-1}: 1754, 1645, 1230, 1030. NMR δ(in $CDCl_3$): 2.15 (3H, s), 2.39 (3H, s), 2.2—2.5 (2H, m), 2.7—3.4 (2H, m), 6.09 (1H, t, $J=5$ Hz), 6.81 (2H, br. s), 12.18 (1H, s).

Sinanolone 4,8-Dibenzoate——To a solution of shinanolone (40 mg) in pyridine (0.2 ml) was added benzoyl chloride (0.1 g) and the mixture was warmed on a water bath for 3 min. After standing overnight at room temperature the reaction mixture was treated as usual and the product was purified by preparative layer chromatography on Silica gel HF_{254} to give a colorless viscous oil (65 mg), UV λ_{max}^{MeOH} mμ (log ε): 233 (4.53) (Fig. 1). IR ν_{max}^{KBr} cm^{-1}: 1745, 1720, 1960. NMR δ (in $CDCl_3$): 2.44 (3H, s), 2.2—3.2 (4H, m), 6.30 (1H, t, $J=4.5$ Hz), 6.98 (1H, $w\frac{1}{2}$ 3 Hz), 7.23 (1H, $w\frac{1}{2}$ 3 Hz), 7.3—7.5 (6H, m), 7.9—8.2 (4H, m), Mass Spectrum *m/e*: 400.133 (M^+, $C_{25}H_{20}O_5$ (Calcd. 400.131)), 296.104 ($C_{18}H_{16}O_4$ (Calcd. 296.105)), 295.097 ($C_{18}H_{15}O_4$ (Calcd. 295.097)), 279.101 ($C_{18}H_{15}O_3$ (Calcd. 279.102)), 278.095 ($C_{18}H_{14}O_3$ (Calcd. 278.094)). CD (Fig. 1).

The Oxidation of Shinanolone (III) to 7-Methyljuglone (IV)——(i) A mixture of shinanolone (III) (6 mg), MnO_2 (50 mg), and benzene (5 ml) was refluxed for 7 hr. The reaction mixture was purified by preparative layer chromatography and the zone corresponding to 7-methyljuglone (IV) was collected and extracted. Recrystallization from hexane gave orange needles of mp 105° (1 mg) and identified with 7-methyljuglone (IV).

(ii) The mixture of shinanolone (III) (25 mg) in benzene (6 ml) and 2,3-dichloro-5,6-dicyanobenzoquinone (40 mg) was refluxed for 8 hr. The reaction mixture was evaporated to *ca.* 2 ml and purified by preparative TLC to give orange crystals (2 mg), which was identified with 7-methyljuglone (IV) by TLC and IR.

Lithium Aluminum Hydride Reduction of 7-Methyljuglone (IV) to Shinanolone (III)——$LiAlH_4$ (80 mg) in ether (anhyd., 10 ml) was added to 7-methyljuglone (IV) (30 mg) in ether (anhyd., 10 ml) and the reaction mixture was stirred for 8 hr. After the addition of water the reaction product was extracted with ether and the solvent was evaporated. The residue was applied on silica gel plate, the developed zone corresponding to shinanolone (III) was collected and the purification was repeated to give colorless needles (from benzene–hexane) (1.5 mg) of mp 70—73°. The comparison with the *laevo*-rotatory natural product was carried out by TLC and IR.

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