Tetrahedron Letters, No.11, pp. 1387-1392, 1968. Pergamon Press. Printed in Great Britain.

THE STRUCTURES OF ARDISIAQUINONES A, B AND C, BIS(BENZOQUINONYL)-OLEFINE DERIVATIVES FROM *ARDISIA SIEBOLDII* MIQUEL.

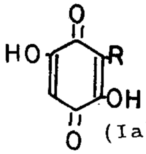
H. Ogawa, S. Sakaki, K. Yoshihira and S. Natori
National Institute of Hygienic Sciences,
Tamagawayoga, Setagaya-ku, Tokyo, Japan

(Received in Japan 6 November 1967)

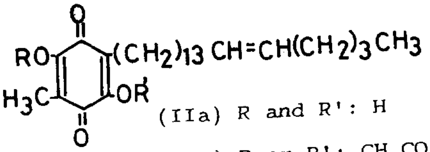
RECENT discovery of the biological importance of benzoquinone derivatives(1) urged us to work on the biochemical examinations of hydroxybenzoquinone derivatives(2) and on the screening of the distribution of these compounds among Myrsinaceae plants.(3) As the results embelin (Ia), rapanone (Ib), maesaquinone (IIa), acetylmaesaquinone (IIb), and new compounds, namely 2-hydroxy-5-methoxy-3-pentadecenyl(tridecenyl, tridecyl)-benzoquinone (III) and novel bis(benzoquinonyl)-olefines designated ardisiaquinones A, B and C (IV, V and VI), have been isolated.(3)

Ardisiaquinones were isolated from the root bark of *Ardisia sieboldii* Miquel. (Japanese name: Mokutachibana) in the respective yields of 0.02, 0.02 and 0.0005 % by benzene extraction and separation by column chromatography on acid-washed silica-gel, along with a triterpene 'ilexol' (probably a mixture of bauerenol and baueradienol(4)) and the mixture of Ia and Ib (yield, 0.3 %).(3) Ardisiaquinones showed the following properties:

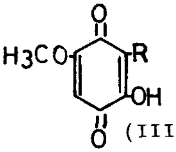
Ardisiaquinone A (IV), m.p. 154°, $C_{30}H_{40}O_8$, M^+ 528, yellow crystals; UV λ_{max}^{EtOH} 289, 425 mμ (log ε 4.60, 2.83); IR (KBr) 3320, 1655(sh), 1633(m), 1598(s) cm^{-1}; NMR($CDCl_3$) τ 2.7(2H), 4.16(2H, s), 4.67(2H, br.t, J=6 cps), 6.13(6H, s), 7.4-7.8(4H), 7.9-8.1(4H), 8.4-8.8(ca. 20 H).



(Ia) R: $C_{11}H_{23}$
(Ib) R: $C_{13}H_{27}$



(IIa) R and R': H
(IIb) R or R': CH_3CO, R' or R: H



(III) R: $C_{15}H_{29}$ ($C_{13}H_{25}$, $C_{13}H_{27}$)

Ardisiaquinone B (V), m.p. 119°, $C_{30}H_{40}O_8$, M^+ 528, orange red crystals; UVλ_{max}^{EtOH} 291, 428 mμ (logε4.56, 2.82): IR (KBr) 3300, 1605(s) cm^{-1}; NMR ($CDCl_3$) τ 2.42(3H), 4.14(1H, s), 4.67(2H, br.t, J=6 cps), 6.13(3H, s), 7.5-7.8(4H), 7.8-8.2(4H), 8.07(3H, s), 8.5-8.8(ca. 20 H).

Ardisiaquinone C (VI), m.p. 69-70°, $C_{32}H_{42}O_9$, M^+ 570, yellow crystals; UV λ_{max}^{EtOH} 281, 420 mμ (logε4.41, 2.81); IR (KBr) 3328, 1774(s), 1635(m), 1603(s) cm^{-1}; NMR($CDCl_3$) τ 2.79(2H), 4.26(1H, s), 4.72(2H, br.t, J=5 cps), 6.24(3H, s), 7.71(3H, s), 7.5-7.8(4H), 7.8-8.2(4H), 8.06(3H, s), 8.3-8.9 (ca. 20 H).

The spectral data and color reactions suggested that they are benzoquinone derivatives.

Ardisiaquinones gave following derivatives: Catalytic hydrogenation followed by airing afforded the respective dihydro derivatives (VII - IX) showing nearly the same spectral properties as IV - VI. Treatment of IV and V with sodium hydroxide solution for a short time afforded the respective demethylated compounds (X and XI). The same treatment of VI was accompanied by deacetylation to afford the same demethylated product (XI). Acetylation of IV and VII gave diacetates (XII and XIV), while V and VIII gave triacetates (XIII and XV), the number of the phenolic acetyl groups being proved by IR and NMR spectra. Acetylation of IX gave the compound identical with XV; thus ardisiaquinone C (VI) must be monoacetate of ardisiaquinone B (V).

Formation of these derivatives and their spectral data, especially NMR spectra, disclosed the following functional groups in the quinones:

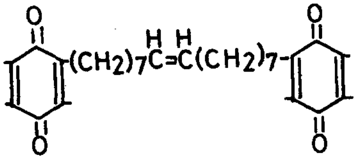
IV: 2 x CH_3O, 2 x OH, 2 x H (the two identically situated on the quinone rings), and an aliphatic chain($C_{16}H_{30}$) with one double bond.

V: 1 x CH_3O, 3 x OH, 1 x CH_3, 1 x H(on the quinone rings), and the $C_{16}H_{30}$ chain.

VI; Same as V except 1 x CH_3COO instead of 1 x OH.

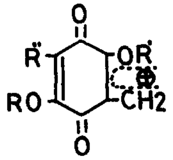
The nature of the aliphatic chain has been revealed by alkaline hydrogen peroxide oxidation. The oxidation of the dihydro derivatives (VII and VIII) afforded the same octadecane-1,18-dioic acid(identified by a mixed fusion, IR and v.p.c. of the methyl ester). The oxidation of IV and V afforded an identical unsaturated acid, though it was impossible to obtain a sample showing sharp m.p. The ozonolysis of the acid followed by silver oxide oxidation gave azelaic acid as a sole product and identified (m.p., IR and v.p.c. of the methyl ester). The comparison of the unsaturated acid by IR and v.p.c. of the methyl ester with cis-octadec-9-ene-1,18-dioic acid(5) prepared from octadec-9-yne-1,18-dioic acid(5) clearly showed that the acid must be the cis-isomer. Thus the chain was proved to be cis-hexadec-8-ene.

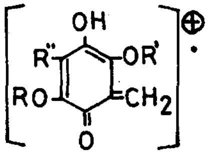
From the molecular formulae, the functional groups and the aliphatic chain thus revealed, the remaining $C_{12}O_4$ was supposed to be two benzoquinone nuclei. The molecular extinction of the UV spectra of IV and V are about twice of those of 2,5-dihydroxy(methoxyhydroxy)-3-alkylbenzoquinones.(6) Thus the quinones A, B and C must be expressed by the partial formulae (XVI).

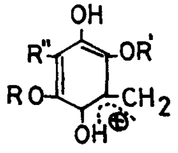

(XVI)

(IV)	(V)	(VI)
$-OCH_3$	$-OCH_3$	$-OCH_3$
$-OCH_3$	$-OH$	$-OCOCH_3$
$-OH$	$-OH$	$-OH$
$-OH$	$-OH$	$-OH$
$-H$	$-CH_3$	$-CH_3$
$-H$	$-H$	$-H$

There have been several reports concerning the mass spectra of benzoquinone derivatives(7) and dihydroxy(methoxy)alkylbenzoquinones show prominent peaks corresponding to benzylium ion (a), a+1 (b), a+2*(c), M^+-28 (M^+-CO), M^+ and M^++2.* In IV, V, VII and VIII the peaks a, b and c appear at 167, 168 and 169 m/e, while in XI at 153, 154, 155, 167, 168 and 169 m/e, indicating the presence of one each of hydroxyl and methoxyl groups in the both rings in IV and one of them in V, while two hydroxyls and one C-methyl group in the other ring of V. The application of the empirical rule for the determination of the relative positions of hydroxyl groups in dihydroxyalkylbenzoquinones by


a


b


c

---

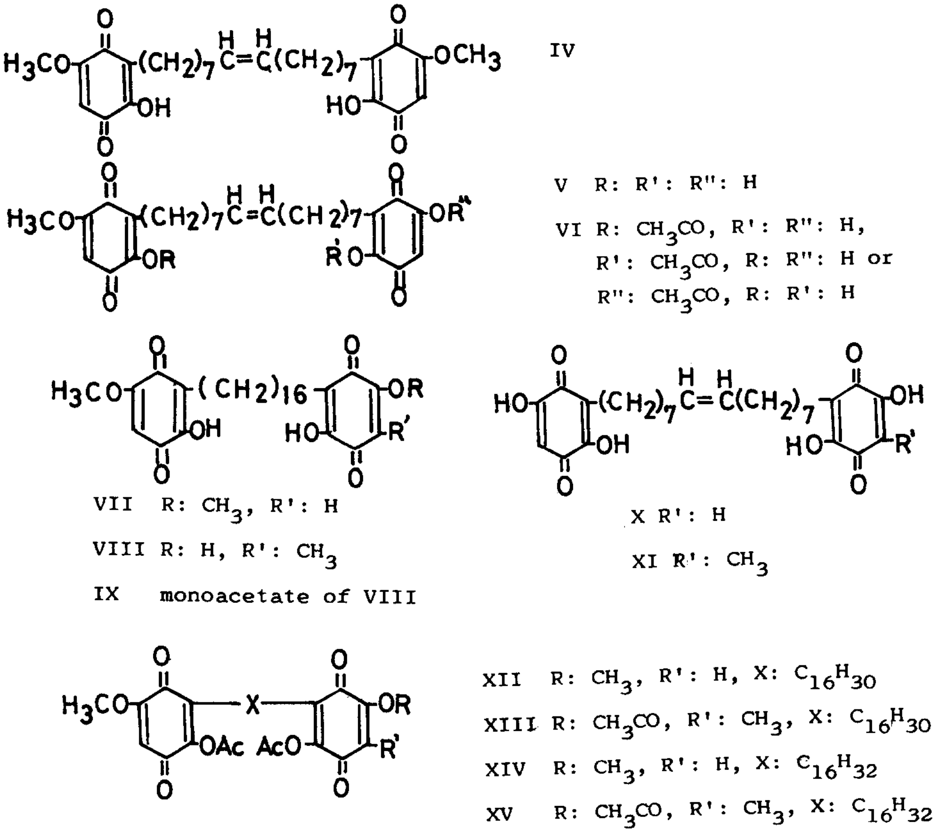
* For the formation of the corresponding hydroquinone in ionization chamber by water and the fragments thereof, see Ref. (7).

UV and IR absorptions(6) has been made as follows: The UV absorptions of IV, V and the derivatives appear in longer wave length than those of 2,3-dihydroxy compounds and agree well with those of 2,5- and 2,6-dihydroxy derivatives, while ν_{O-H}^{KBr} (3300 cm^{-1}) and $\nu_{C=O}^{KBr}$ (1605 cm^{-1}(s), unsplitted) of X and XI demonstrated the 2,5-dihydroxy substitution. Finally the relative position of the hydroxyl group and the methoxyl group has been learned from NMR spectra: Shielding values reported for aromatic compounds(8) and the accumulated data for naphthoquinone derivatives(9) indicate that the proton adjacent to hydroxyl and methoxyl groups appear in higher field than those adjacent to acetoxyl and alkyl groups. Actually examinations of the reported values and the data obtained for the compounds of known structures indicated the former appear in 4.0-4.7 τ, while the latter in 3.4-3.7 τ. The ring protons in IV and V (4.16, 4.17 τ) remain in the nearly the same field (4.25, 4.23 τ) by acetylation (XII and XIII), clearly demonstrating that the positions are occupied by methoxyl groups. Thus the structures of ardisiaquinones A, B and C must be expressed by the formulae IV, V and VI (Chart 1).

In order to exclude the ambiguity existed in the application of the empirical rule for the determination of the substitution pattern(6) in the case of dimeric compounds such as IV and V, synthetic confirmation of the structures has been carried as shown in Chart 2. 1,16-bis(2,5-Bismethylamino-p-benzoquinon-3-yl)-hexadecane (XVII), m.p. 218-221°, thus prepared was proved to be identical with the compound derived from dihydroardisiaquinone A (VII).

The structures are assumed to be unique, since the compounds are presumably polyketide compounds derived from <u>cis</u>-octadec-9-ene-1,18-dioic acid.

Acknowledgement ------- The authors are grateful to Mr. M. Taki and Mr. M. Satake (the collection and identification of the plant materials), Drs. T. Miki, H. Mima, T. Oba and Miss R. Koyama (spectral determinations), Professor W. J. Gensler and Dr. A. Tanaka (fatty acids samples) and to Dr. S. Yoshikawa (the supply of tapsic acid).



IV

V R: R': R'': H

VI R: CH_3CO, R': R'': H,
R': CH_3CO, R: R'': H or
R'': CH_3CO, R: R': H

VII R: CH_3, R': H

VIII R: H, R': CH_3

IX monoacetate of VIII

X R': H

XI R': CH_3

XII R: CH_3, R': H, X: $C_{16}H_{30}$

XIII R: CH_3CO, R': CH_3, X: $C_{16}H_{30}$

XIV R: CH_3, R': H, X: $C_{16}H_{32}$

XV R: CH_3CO, R': CH_3, X: $C_{16}H_{32}$

CHART 1

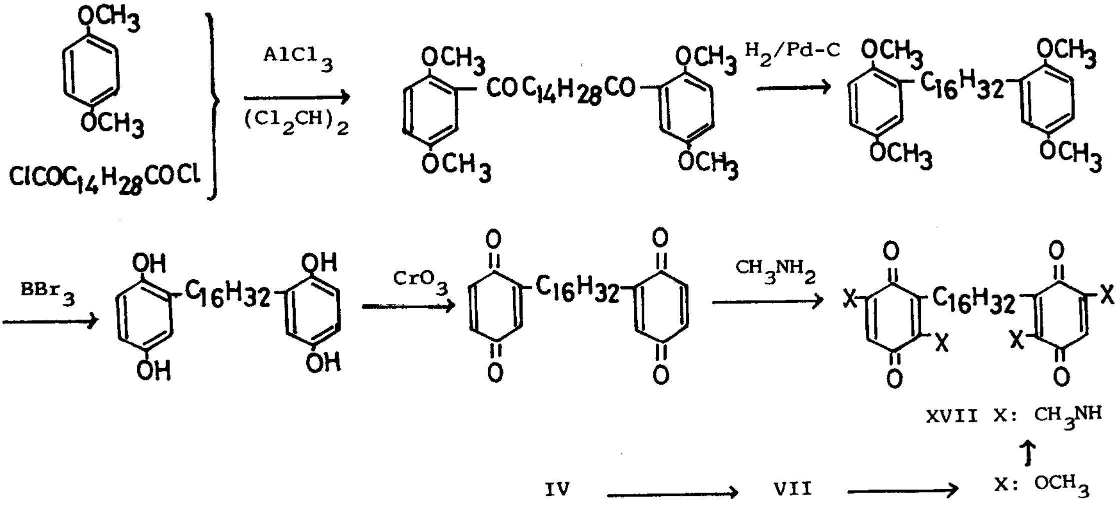


CHART 2

References

1. R. A. Morton, ed., 'Biochemistry of Quinones', Academic Press, N. Y. (1965).
2. H. Ozawa, K. Momose, S. Natori, H. Ogawa and K. Yamaguchi, Biochem. Biophys. Acta 86, 397 (1964); H. Ozawa, S. Natori and K. Momose, Chem. Pharm. Bull. (Japan) 13, 1029 (1965), 15, 1095 (1967); H. Ozawa, K. Momose, M. Machida, S. Natori and K. Yoshihira, ibid. to be published.
3. H. Ogawa and S. Natori, Phytochem. in the press.
4. F. N. Lahey and M. V. Leeding, Proc. Chem. Soc. 1958, 342.
5. G. Dupont, R. Dulou and J. Cohen, Bull. Soc. Chim. France, 1956, 819; L. Ruzicka, Pl. A. Plattner and W. Widmer, Helv. Chim. Acta 25, 1086 (1942); W. J. Gensler and H. N. Schlein, J. Am. Chem. Soc. 77, 4846 (1955).
6. B. W. Bycraft and J. C. Roberts, J. Org. Chem. 28, 1429 (1963); S. Natori, H. Ogawa and H. Nishikawa, Chem. Pharm. Bull. (Japan) 12, 236 (1964); H. Ogawa and S. Natori, ibid. 13, 511 (1965); H. Nakata, K. Sasaki, I. Morimoto and Y. Hirata, Tetrahedron 20, 2319 (1964); K. Yoshihira and S. Natori, Chem. Pharm. Bull. (Japan) 14, 1052 (1966).
7. B. C. Das, M. Lounasmaa, C. Tendille and E. Lederer, Biochem. Biophys. Res. Comm. 21, 318 (1965); R. T. Aplin and W. T. Pike, Chem. & Ind. 1966, 2009; P. Friis, G. D. Daves and K. Folkers, J. Am. Chem. Soc. 88, 4754 (1966); R. F. Muraca, J. S. Whittick, G. D. Daves, P. Friis and K. Folkers, J. Am. Chem. Soc. 89, 1505 (1967); H. Morimoto, T. Shima, I. Imada, M. Sasaki and A. Ouchida, Ann. 702, 137 (1967).
8. J. A. Ballantine and C. T. Pillinger, Tetrahedron 23, 1961 (1967) and the references cited therein.
9. R. E. Moore and P. J. Scheuer, J. Org. Chem. 31, 2372 (1966).