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Hydroxybenzoquinones from Myrsinaceae Plants. IV.[1] Further Confirmation of the Structures of Ardisiaquinones and Some Observations on Alkylaminobenzoquinone Derivatives

KUNITOSHI YOSHIHIRA, SETSUKO SAKAKI, HIDEKO OGAWA
and SHINSAKU NATORI

National Institute of Hygienic Sciences[2]

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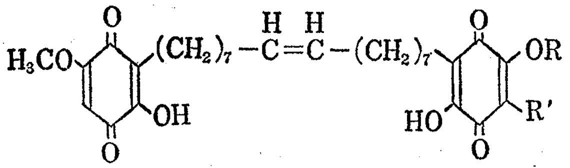
1,16-bis(2,5-Dimethylamino-*p*-benzoquinon-3-yl)hexadecane (II) was synthesized and proved to be identical with the tetrakis(methylamino) derivative prepared from dihydroardisiaquinone A (IX). The positions of methoxyl groups in ardisiaquinones (Ia—Ic) were confirmed by the examination of the nuclear Overhauser effect. Dealkylation was accompanied in alkylamination of VI and toluquinone. Some observations on nuclear magnetic resonance spectra of alkylaminobenzoquinone derivatives were also reported.

The proposed structures of ardisiaquinones A, B and C (Ia, Ib and Ic) from the root bark of *Ardisia sieboldii* MIQ. were chiefly based on the spectral observations of the derivatives and the results of the oxidation reactions.[1] Although the empirical rule for the determination of the substitution pattern by spectral methods was firmly established for monomeric alkylhydroxybenzoquinone derivatives,[1] there remained slight ambiguity in the application of the rule for the dimeric compounds such as Ia—Ic in which the interaction between the two quinone rings in a molecule might influence on the spectral data especially on electronic spectra. The ambiguity has now been removed by an unequivocal synthesis of 1,16-bis(2,5-dimethylamino-*p*-benzoquinon-3-yl)hexadecane (II) and the identification with the compound derived from ardisiaquinone A (Ia).



Ia : R=CH$_3$, R'=H
Ib : R=H, R'=CH$_3$
Ic : monoacetate of Ib

The synthesis of II has been carried out as follows: The Friedel–Crafts reaction of *p*-dimethoxybenzene and the dichloride of thapsic acid gave 1,14-bis(2,5-dimethoxybenzoyl)-tetradecane (III). The Clemmensen reduction of III did not give satisfactory results in obtaining a pure reduction product, but the catalytic reduction[3] gave 1,16-bis(2,5-dimethoxyphenyl)hexadecane (IV) in a good yield. Demethylation of IV with hydriodic acid[3] or with pyridine hydrochloride afforded resinous products. The reaction has gone smoothly by the use of boron tribromide[4] to afford 1,16-bis(2,5-dihydroxyphenyl)hexadecane (V), the hydroquinone being sensitive for air, heating and sun–light and changing into dark colored substances. The hydroquinone (V) was oxidized by chromium trioxide to the corresponding bisbenzoquinone (VI), which is also unstable. Methylamination of the quinone (VI) in

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[1] Part III: H. Ogawa and S. Natori, *Chem. Pharm. Bull.* (Tokyo), **16**, 1709 (1968); the preliminary communication, *Tetrahedron Letters*, **1968**, 1387.
[2] Location: *Kamiyoga-1-chome, Setagaya-ku, Tokyo.*
[3] K. Kakemi, T. Arita, R. Hori, T. Kiyotaki and H. Takenaka, *Yakugaku Zasshi*, **86**, 778 (1966); K. Kakemi, T. Arita, R. Hori and H. Takenaka, *ibid.*, **86**, 785, 791 (1966).
[4] F.L. Benton and T.E. Dillon, *J. Am. Chem. Soc.*, **64**, 1128 (1942).

chloroform–ethanol gave the objective 1,16-bis(2,5-dimethylamino-*p*-benzoquinon-3-yl)hexadecane (II), mp 219—221°, accompanied with 2,5-dimethylamino-*p*-benzoquinone[5] (VII) produced by dealkylation in the course of the reaction.

As encountered in the preparation of IV, V and VI and in attempts to hydrolyse II to demethyldihydroardisiaquinone A[1] (VIII) the dimeric compounds show different properties from the corresponding monomeric compounds.[6] The homologs of V were already synthesized as promissing antioxidants by Kakemi, *et al.*[3]

Dihydroardisiaquinone A (IX)[1] was derived to the dimethyl ether (X). The reaction of X with methylamine easily formed the corresponding tetrakis(methylamino) derivative, mp 218—221°, which was proved to be identical with II in every respects. Thus the structure of ardisiaquinone A (Ia) except the relative positions of the hydroxyl and the methoxyl groups have unequivocally been established.

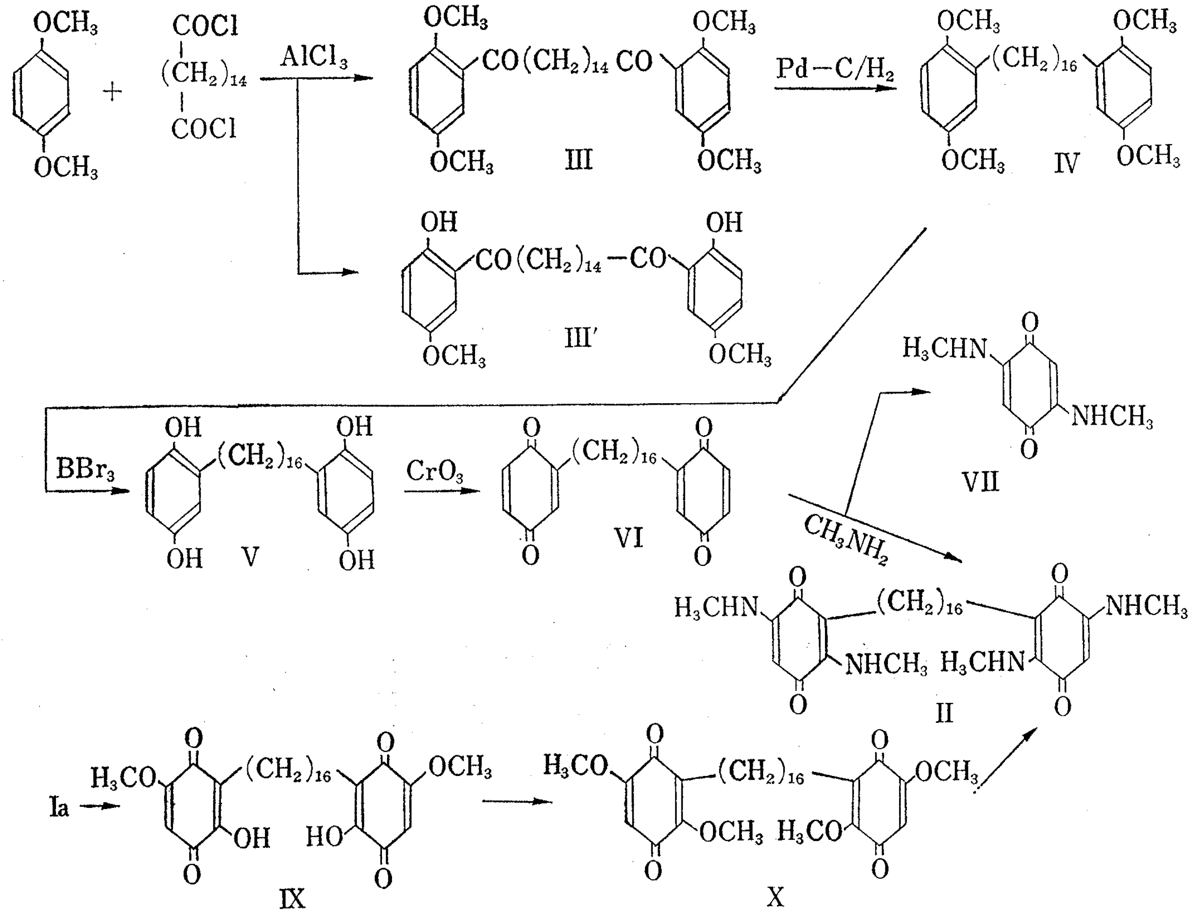

Chart 1

The relative positions of methoxyl and hydroxyl groups in ardisiaquinones were determined chiefly by the examination of the chemical shifts of quinonoid ring protons, which should be influenced by acetylation if there exist adjacent hydroxyl groups.[1] This point has now been further confirmed by the observations of the nuclear Overhauser effect (NOE)[7] between the methoxyl methyl protons and the ring protons in ardisiaquinones A and B (Ia and Ib). The irradiation at the methoxyl methyl protons at 3.86 ppm for Ia and Ib caused signi-

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[5] R.N. Harger, *J. Am. Chem. Soc.*, **46**, 2540 (1924).

[6] K. Yoshihira and S. Natori, *Chem. Pharm. Bull.* (Tokyo), **14**, 1052 (1966); H. Ozawa, K. Momose, M. Machida, S. Natori and K. Yoshihira, *ibid.*, **16**, 853 (1968).

[7] S. Winstein, P. Carter, F.A.L. Anet and A.J.R. Bourn, *J. Am. Chem. Soc.*, **87**, 5247 (1965); M.C. Woods, I. Miura, Y. Nakadaira, A. Terahara, M. Maruyama and K. Nakanishi, *Tetrahedron Letters*, **1967**, 321.

ficant increases of the heights and the integrated intensities of the quinonoid ring protons at 5.82 ppm for Ia and 5.83 ppm for Ib respectively (14% for Ia and 13% for Ib) (Fig. 1). Thus the methoxyl groups in ardisiaquinones must be adjacent to the ring protons.

In the course of catalytic hydrogenation of ardisiaquinones (Ia, Ib and Ic) to their corresponding dihydro derivatives the color of the solution changes from yellow into violet–red and finally to colorless.[1] The violet–red color suggests the formation of charge–transfer complex between the quinones and the hydroquinones.[8] This has now been confirmed by the observation of charge–transfer bands in the UV spectra of the partially hydrogenated solution of ardisiaquinone B (Ib) and 1,16-di-*p*-benzoquinonylhexadecane (VI) (Table I). Since the hydroquinones are sensitive for aerial oxidation quantitative treatment has not been carried out and the distinction between inter– and intra–molecular formation of the complex has been unsuccessful.[8]

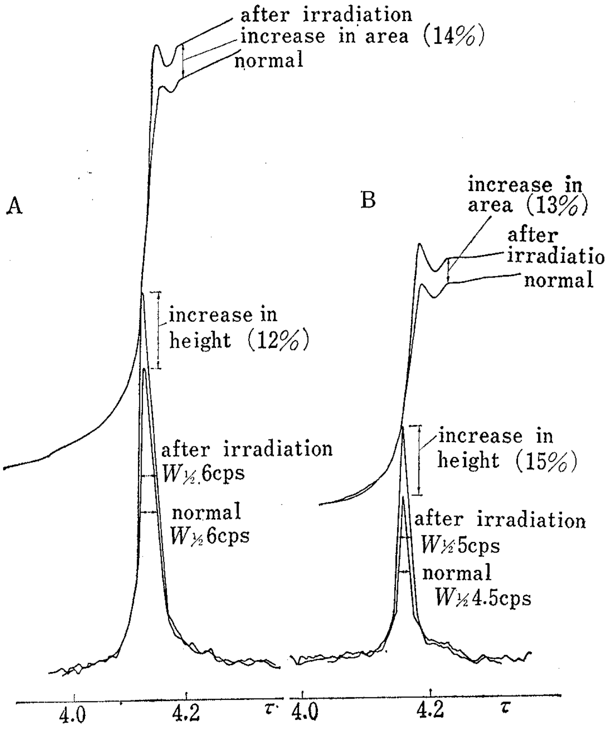

Fig. 1. The Nuclear Overhauser Effects observed in the Ring Protons of Ardisiaquinone A and B after Irradiating the Methoxyl Methyl Protons (on a Varian HA-100, 100 Mc, in $CDCl_3$ Solution)

Table I. UV Absorptions and Charge–Transfer Bands of Benzoquinones and the Hydroquinones

	λ_{max} (mμ)	Charge–transfer band	(mμ)	Solvent
p–Benzoquinone	247, 432	quinhydrone	365	tetrahydrofuran
Hydroquinone	298			
Ardisiaquinone B (Ib)	294, 430	the partially hydrogenated mixture from Ib	372	EtOH
1,16–Di–*p*–benzoquinonylhexadecane (VI)	252, 430	the partially hydrogenated mixture from VI (V+VI)	345	90% HOAc
1,16-Bis(2,5-dihydroxyphenyl)-hexadecane (V)	292			

As the model reaction for alkylamination of the bisbenzoquinone (VI) to the tetrakis-(methylamino) derivative (II), which was accompanied by the dealkylation to form 2,5-dimethylaminobenzoquinone (VII), the reaction of *p*-benzoquinone, toluquinone and rapanone dimethyl ether with methylamine, dimethylamine and isopropylamine has been carried out. Alkylamino derivatives thus prepared are listed in Table II. The demethylation has observed in the reactions of toluquinone with methylamine and isopropylamine giving the compounds identified with VII and XVI respectively as the by–products. The reaction of the amines with rapanone dimethyl ether did not accompany the dealkylation. The formation of VII from 2-methoxytoluquinone by demethylation has been reported.[9]

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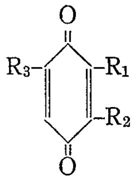
[8] R.E. Moser and H.G. Cassidy, *J. Org. Chem.*, **30**, 2602; 3336 (1966).
[9] W.K. Anslow and H. Raistrick, *J. Chem. Soc.*, **1939**, 1446.

Table II. Properties of Alkylaminobenzoquinone Derivatives



	R_1	R_2	R_3	mp (recrystallized from)	Formula	Anal. N%	
						Calcd.	Found
VII	H	$NHCH_3$	$NHCH_3$	250° (H_2O)b)			
XI	CH_3	$NHCH_3$	$NHCH_3$	233° (EtOH)d)			
XII	$C_{13}H_{27}$	$NHCH_3$	$NHCH_3$	167° (EtOH)f)	$C_{21}H_{36}O_2N_2$	8.04	8.30
XIII	H	$N(CH_3)_2$	$N(CH_3)_2$	175° (AcOEt)g)			
XIV	CH_3	OH	$N(CH_3)_2$	195° (EtOH)h)	$C_9H_{11}O_3N$i)	7.73	7.46
XV	$C_{13}H_{27}$	OCH_3	$N(CH_3)_2$	60.5° (EtOH)f,k)	$C_{22}H_{37}O_3N$	3.85	4.02
XVI	H	$NHCH(CH_3)_2$	$NHCH(CH_3)_2$	238° (under sublimation) (EtOH)	$C_{12}H_{18}O_2N_2$	12.60	12.84
XVII	CH_3	$NHCH(CH_3)_2$	$NHCH(CH_3)_2$	125° (EtOH)m)	$C_{13}H_{20}O_2N_2$	11.86	12.50
XVIII	$C_{13}H_{27}$	$NHCH(CH_3)_2$	$NHCH(CH_3)_2$	78° (EtOH)	$C_{25}H_{44}O_2N_2$	6.92	7.00

	IR (cm^{-1}) (Nujol)		NMR (τ)a) N-methyl or N-methin proton	
	$\nu_{NH(OH)}$	$\nu_{C=O(C=C, C=N)}$	in $CDCl_3$	in $CDCl_3 + CF_3COOH$
VII	3310 (3333)	1641, 1555 (1660, 1638, 1585)c)	7.11 (6H, d, $J=5$ cps)	6.88 (6H, s)
XI	3285	1638, 1590	6.76 (3H, d, $J=6$ cps), 7.14 (3H, d, $J=6$ cps)e)	6.47 (3H, s), 6.76 (3H, s)
XII	3180	1648, 1608	6.80 (3H, d, $J=6$ cps), 7.13 (3H, d, $J=6$ cps)	6.58 (3H, s), 6.80 (3H, s)
XIII	—— (——)	1626, 1550 (1625, 1545)c)	6.81 (12H, s)	6.63 (12H, s)
XIV	3270	1647, 1610	6.77 (6H, s)j)	6.34 (6H, s)
XV	(——)	(1652, 1610, 1570)l)	6.93 (6H, s)	6.46 (6H, s)
XVI	3270 (——)	1640, 1570 (1638, 1578)c)	6.38 (2H, octet, $J=7$ cps)	5.7—6.2 (2H, br)
XVII	3270	1643, 1595	5.77 (1H, m), 6.44 (1H, octet, $J=6$ cps)	5.55 (1H, m), 6.10 (1H, m)
XVIII	3280	1640, 1585	5.6—6.3 (1H, br), 6.44 (1H, m)	5.3—6.5 (2H, br)

a) Determined by a JNM C-60H Spectrometer (60 Mc) using TMS as the internal standard.

b) lit.[5] mp 270°

c) in $CHCl_3$ solution using a Koken DS-301 Spectrophotometer

d) lit. (F. Fichter, *Ann.*, **361**, 400 (1908)), mp 235°
As the by-product VII was obtained by demethylation.

e) Irradiation at the ring methyl protons (τ, 7.88) sharpens the lower N-methyl signal (no increase of the integrated intensity) but not the higher N-methyl peaks. Irradiation at the higher N-methyl protons increases the intensity of the ring proton (τ. 4.78) about 12%, while irradiation at the lower N-methyl protons does not influence the intensity of the ring proton. Thus it can be concluded that the lower signal is assigned for that adjacent to the ring-methyl, while the higher signal for that adjacent to the ring proton.

f) H. Ogugura and K. Furuhata, Abstracts of Papers, Annual Meeting of Pharmaceutical Society of Japan, Sendai, 1966, p. 141

g) lit.[5] mp 171°

h) The expected bis (dimethylamino) compound was not obtained. The structure (XIV) has been assigned from the analytical and spectral data.

i) *Anal.* Calcd. C, 59.66; H, 6.12; mol. wt., 181.2. Found: C, 60.02; H, 5.95; mol. wt. (osmometry), 185.6

j) other signals: 4.51 (1H, s, ring-H), 8.12 (3H, s, ring-methyl)

k) Bis (dimethylamino) compound has not been obtained. The structure (XV) assigned[f] has been supported by the analytical and spectral data.

l) in KBr disc using a Koken DS-301 Spectrophotometer

m) As the by-product XVI was obtained by demethylation.

Since two each of the four N-methyl groups in II are identically situated, two N-methyl signals have been expected in the NMR spectrum. However four signals are observed in $CDCl_3$ solution at room temperature while in $CDCl_3$-CF_3COOH two peaks are observed (Fig. 2a). In the same way each of the N–methyl groups in methylamino derivatives (VII, XI, XII) shows doublet peaks in $CDCl_3$ which change into a singlet by the addition of CF_3COOH (Fig. 2b and 2c). In the isopropylamino derivatives (XVI, XVII and XVIII) each N-methine

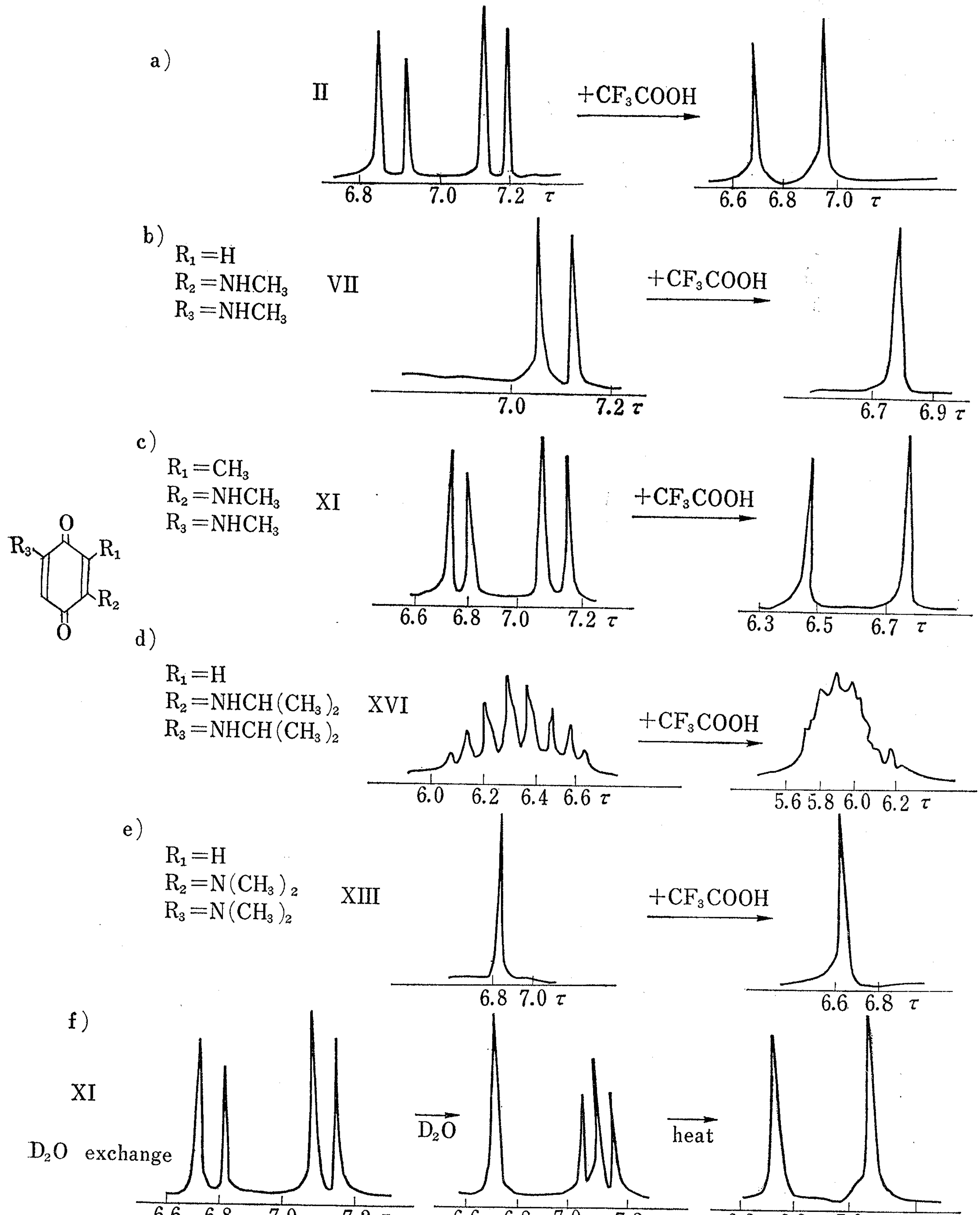
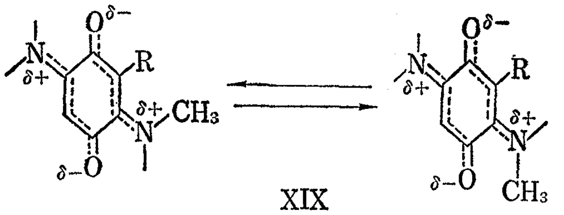


Fig. 2. NMR Spectra of N-Methyl or N-Methine Protons of Alkylaminobenzoquinone Derivatives (60 Mc, in $CDCl_3$ Solution)

proton appears in a complicated signal which is assigned as octet in the case of XVI (Fig. 2d). Recently the existence of aminobenzoquinones in a conjugated system (XIX) has been reported,[10] while magnetic non-equivalence of the groups bonded to a nitrogen atom suffering from the restricted rotation about C–N bond in a conjugated system such as amides and carbamates is a well known fact.[11] However the two N-methyl groups in dimethylamino derivatives (XIII, XIV and XV) appear in a singlet peak showing absence of the hindered rotation of the C–N bond at the condition employed (Fig. 2e). Furthermore the addition of D_2O to the $CDCl_3$ solution of XI collapsed the pair of doublets into two singlet peaks (Fig. 2f). Thus the splitting observed in the secondary amines has been proved to be spin-coupling by the proton in weakly basic NH group exchanging very slowly in the condition employed (Table II).


XIX

From these observations some problems arisen from the chemistry of ardisiaquinones have been solved and the structures become beyond any doubt. Biochemical examinations,[6,12] antitumor tests as the related compounds to mitomycins[13] and examinations as antioxidants[4,14] of these derivatives are now in progress.

Experimental[15]

1,14-Bis(2,5-dimethoxybenzoyl)tetradecane (III)——To *p*-dimethoxybenzene (2.5 mole) in tetrachlorethane $AlCl_3$ (2.5 mole) was added and then gradually the acid chloride (1 mole) prepared from thapsic acid and thionyl chloride. After heating at 100° for 7 hr the reaction mixture was decomposed with cold HCl, steam-distilled to remove the solvent and then extracted with ether. The extract was washed with $NaHCO_3$ and the residue from ethereal layer was chromatographed through a column of alumina (Brockmann, neutral). The fraction obtained by the elution with benzene-EtOAc (9:1) was recrystallized from EtOH to yellow needles of mp 78°, IR cm^{-1}: no OH absorption, $\nu_{C=O}$1674. Yield, 61%. *Anal.* Calcd. for $C_{32}H_{46}O_6$: C, 72.97; H. 8.80. Found: C, 73.21; H, 8.65.

1,14-Bis(2-hydroxy-5-methoxybenzoyl)tetradecane (III′)——The same reaction by the use of 8 mole of $AlCl_3$ afforded the partially demethylated compound (III′) as the main product. Colorless needles of mp 157° from EtOH, IR cm^{-1}: ν_{OH}3320, $\nu_{C=O}$1655, 1630. *Anal.* Calcd. for $C_{30}H_{42}O_6$: C, 72.26; H, 8.49. Found: C, 72.10; H, 8.17.

1,16-Bis(2,5-dimethoxyphenyl)hexadecane (IV)——i) The Clemmensen reduction of III or the partially demethylated compounds (III′) gave dark resinous products.

ii) The ketone (III) (5.0 g) in HOAc (50 ml) was hydrogenated in the presence of Pd-carbon (5%, 1.0g) under slight warming by an IR lump. The absorption of hydrogen ceased within 6 hr. After working up as usual the product was recrystallized from EtOH to colorless plates (3.4 g) of mp 56°. *Anal.* Calcd. for $C_{32}H_{50}O_4$: C, 77.06; H, 10.11. Found: C, 77.48; H, 10.10.

1,16-Bis(2,5-dihydroxyphenyl)hexadecane (V)——i) Demethylation with 47% HBr in HOAc, HBr in HOAc or pyridine hydrochloride afforded resinous products and the isolation of V was unsuccessful.

ii) Boron tribromide (12 g) was added to IV (5 g) under cooling and the reaction mixture was heated 80° for 40 min. After decomposition with conc. HCl and extraction with ether the extract was evaporated at a room temperature and the residue was recrystallized from toluene to colorless needles (4.2 g) of mp 131—133°; IR cm^{-1}: ν_{OH}3220; UV $\lambda_{max}^{ethanol}$ mμ (log ε): 295 (3.82). *Anal.* Calcd. for $C_{28}H_{42}O_4$: C, 75.97; H, 9.56. Found: C, 75.52; H, 9.30.

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[10] S. Dähne and D. Leupold, *Angew. Chem.*, **78**, 1029 (1966); W. Schäfer and H. Schlude, *Tetrahedron Letters*, **1967**, 4307.

[11] J.F.K. Wilshire, *Tetrahedron Letters*, **1968**, 475; T.M. Valega, *J. Org. Chem.*, **31**, 1150 (1967) and the references cited therein.

[12] H. Ozawa, *et al.*, *Biochem. Biophys. Acta*, **86**, 395 (1964); *Chem. Pharm. Bull.*, (Tokyo), **13**, 1029 (1965); **15**, 1095, 1841 (1967).

[13] J.S. Webb, *et al.*, *J. Am. Chem. Soc.*, **84**, 3185, 3186 (1962); A. Tulinsky, *ibid.*, **84**, 3188 (1962).

[14] M. Harada, *Yukagaku*, **17**, 558 (1968).

[15] Melting points were determined in a Yanagimoto melting point apparatus and not corrected. IR spectra were determined in Nujol mull on a Koken IRS Infrared Spectrophotometer unless otherwise specified. UV spectra were determined by a Hitachi Automatic Recording Spectrophotometer EPS-3T.

1,16-Di-*p*-benzoquinonylhexadecane (VI)——V (1.0 g) was dissolved in HOAc (25 ml), chromium trioxide (0.59 g) was added, and the mixture was heated on a water bath for 30 min. After cooling the deposited pale yellow crystals (0.8 g) were collected, washed and dried, mp 130—132°. IR cm^{-1}: $\nu_{C=O}$1661; UV $\lambda_{max}^{chloroform}$ (log ε): 252 (4.94). The attempts to purify the quinone have been unsuccessful, since the quinone is unstable for heating and sun-light. *Anal.* Calcd. for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 75.64; H, 8.57.

1,16-Bis(2,5-dimethylamino-*p*-benzoquinon-3-yl)hexadecane (II)—— The quinone (VI) (100 mg) in chloroform (30 ml) was mixed with an excess amount of methylamine saturated in EtOH (20 ml) and heated on a water bath for 5 min. After keeping at a room temperature for 4—5 days the deposited crystals were separated. The mother liquor was concentrated and the residue was chromatographed on a column of silica-gel (Mallinckrodt). The elution with benzene-EtOAc (20:3) afforded two bands, the lower of which gave the same compound with the deposited crystals. The combined crystals were recrystallized from chloroform to violet crystals (3 mg) of mp 219—220°. IR cm^{-1}: $\nu_{NH(OH)}$3280, $\nu_{C=O}(C=C,C=N)$ 1587. UV $\lambda_{max}^{chloroform}$ mμ (log ε): 337, 348 (4.61, 4.64). NMR ($CDCl_3$) τ: 3.0—3.8 (4H, NH), 4.85 (2H, s, ring H), 6.85 (6H, d, $J=5$ cps, NCH_3), 7.18 (6H, d, $J=6$ cps, NCH_3), 7.8—8.5 (4H, benzylic methylene), *ca.* 8.7 (28H, methylene). *Anal.* Calcd. for $C_{32}H_{50}O_4N_4$: C, 69.28; H, 9.09; N, 10.10. Found: C, 69.10; H, 9.15; N, 9.09.

The second band gave red crystals (10 mg) of mp 245° from chloroform and was identified with 2,5-dimethylamino-*p*-benzoquinone[5] (VII) by a mixed fusion, IR and thin-layer chromatography.

Dihydroardisiaquinone A Dimethyl Ether (X)——Dihydroardisiaquinone A (IX)[1] (100 mg) was methylated with dimethyl sulfate and K_2CO_3 in acetone by the conventional method. The reaction product was purified by chromatography on a column of silica-gel and recrystallized from MeOH to yellow needles of mp 91.5° (20 mg). IR cm^{-1}: 1652 (sh), 1632, 1590. *Anal.* Calcd. for $C_{32}H_{44}O_8$: C, 69.04; H, 7.97. Found: C, 69.13; H, 8.23.

Methylamination of X——X (15 mg) in chloroform (5 ml) was mixed with an excess amount of methylamine in EtOH (5 ml). After standing overnight the solvents were evaporated and the residue was recrystallized from $CHCl_3$ to violet crystals of mp 218—221° (5 mg). The mixed fusion with the synthetic sample of II did not show depression of mp. Thin-layer chromatography, UV and IR spectra were also identical.

Preparation of Alkylaminobenzoquinone Derivatives (VII, XI—XVIII)——*p*-Benzoquinone, toluquinone or rapanone dimethyl ether was dissolved in EtOH (hexane-EtOH in the case of *p*-benzoquinone), an excess amount of methylamine, dimethylamine or isopropylamine dissolved in EtOH was added, and the mixture was warmed on a water bath for 1 min. After keeping at a room temperature for a while deposited crystals were separated and purified through a column of silica-gel (Mallinckrodt) using benzene-EtOAc as the elution solvent. The product thus formed with their spectral data are shown in Table II.

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