[Chem. Pharm. Bull. 16(2) 202—210 (1968)]

UDC 547.567.3.07 : 547.56.04

Reaction of Phenol Derivatives with Sulfoxides. III.[1] Synthesis and Characterization of 2-Alkylthio- and 2-Arylthio-5-hydroxy-*p*-benzoquinones[2]

Shigeo Ukai and Kazuo Hirose

Gifu College of Pharmacy[3]

(Received December 13, 1966)

2-Arylthio- or 2-alkylthio-5-hydroxy-*p*-benzoquinones (XV—XXI) were easily synthesized by the oxidation of 4-arylthio- or 4-alkylthioresorcinols (VIII—XIV) with potassium nitrosodisulfonate. VIII—XIV were prepared from the sulfonium perchlorates (I—VII) synthesized by the reaction of resorcinol with sulfoxides. The structure of these hydroxybenzoquinones (XV—XXI) was elucidated.

Further, the Thiele addition of acetic anhydride to 2-arylthio- or 2-alkylthio-*p*-benzoquinones was examined. Only in the case of the arylthio compounds, the Thiele reaction progressed smoothly to afford arylthiohydroxhydroquinone triacetates (XXX—XXXII). The position of the acetoxyl group in these compounds XXX—XXXII was determined.

A number of studies have been made on the synthesis and biological activities of monohydroxy derivatives of benzoquinone.[4–8]

However, no report is found on the monohydroxy derivatives containing an alkylthio or arylthio group as a substituent in the ring of benzoquinone.

Up to the present, the most common synthetic method for monohydroxybenzoquinones has been the procedure of Thiele[4] as shown in Chart 1.

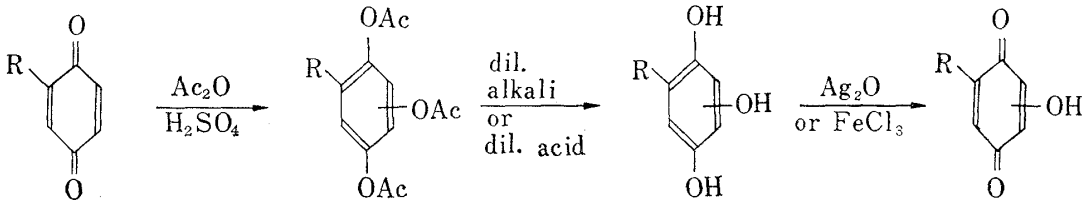


Chart 1

This method is not satisfactory for the preparation of monohydroxybenzoquinones because the position of the introduced acetoxyl group is uncertain. The hydrolysis of the hydroxyhydroquinone triacetates in nitrogen stream and the oxidation of hydrolyzates are also cumbersome.

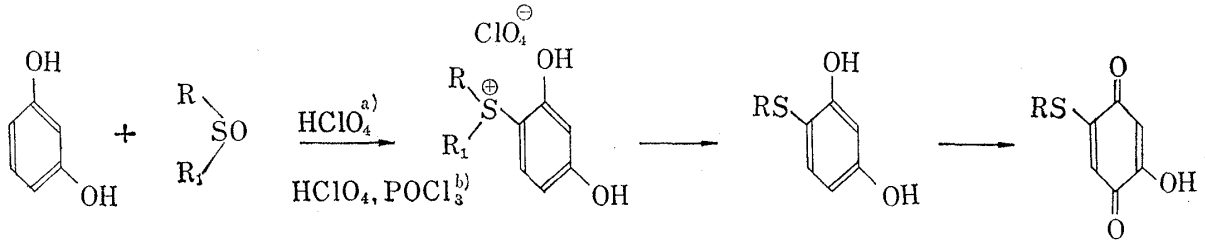
The previous work[9] in this series has shown that 4-arylthio or 4-methylthioresorcinols (VIII, IX, XI) were easily obtained from the sulfonium perchlorates (I, II, IV) prepared

1) Part II: *Chem. Pharm. Bull.* (Tokyo), **16**, 195 (1968).
2) Presented at the meeting of the Tokai-Blanch of the Pharmaceutical Society of Japan, Gifu, June 24, 1967.
3) Location: *492—36, Mitahora, Gifu.*
4) J. Thiele and E. Winter, *Ann.*, **311**, 341 (1900).
5) W.M. McLamore, *J. Am. Chem. Soc.*, **73**, 2225 (1951).
6) K. Hirose, *Gifu-yakka-daigaku Kiyo*, **11**, 65, 73, 78 (1961).
7) W.K. Anslow and H. Raistrick, *Biochem. J.*, **32**, 687 (1938).
8) H. Ozawa, S. Natori, and K. Momose, *Chem. Pharm. Bull.* (Tokyo), **13**, 1029 (1965).
9) K. Hirose and S. Ukai, *Yakugaku Zasshi*, **86**, 187 (1966).

by the reaction of resorcinol with methyl aryl sulfoxides (aryl=C_6H_5, C_6H_4-CH_3(p)) in 70% perchloric acid or with dimethyl sulfoxide in a mixture (1:0.8) of 70% perchloric acid and phosphoryl chloride.

The present paper deals with the formation of 2-arylthio- or 2-alkylthio-5-hydroxy-*p*-benzoquinones (XV—XXI) by the oxidation with potassium nitrosodisulfonate of 4-arylthio- or 4-alkylthio-resorcinols (VIII—XIV) prepared through the reaction mentioned above, as shown in Chart 2, and with the characterization of these hydroxybenzoquinones (XV—XXI). Further, the Thiele addition of acetic anhydride to 2-arylthio- or 2-alkylthio-*p*-benzoquinones was examined.

Only in the case of the arylthio compounds, the Thiele reaction proceeded with facility to afford arylthiohydroxyhydroquinone triacetates (XXX—XXXII). The position of the newly introduced acetoxyl group during the reaction was determined (see below).



R_1=CH_3, R=C_6H_5,[a] p-$CH_3C_6H_4$,[a] p-ClC_6H_4;[a] (I—III)
R_1, R=CH_3,[b] C_2H_5,[b] n-C_3H_7,[b] n-C_4H_9;[b] (IV—VII)
a) Method A *b*) Method B

(VIII—X)
(XI—XIV)

(XV—XVII)
(XVIII—XXI)

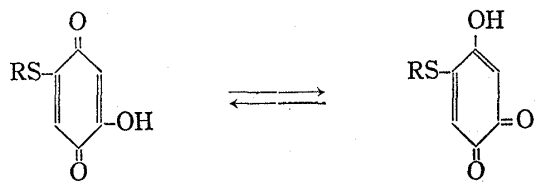
Chart 2

According to the procedure described earlier,[9] the condensation of resorcinol with methyl *p*-chlorophenyl sulfoxide in 70% perchloric acid or with dialkyl sulfoxides (alkyl=C_2H_5, n-C_3H_7, n-C_4H_9) in a mixture of 70% perchloric acid and phosphoryl chloride progressed smoothly to give 2,4-dihydroxyphenyl-*p*-chlorophenylmethylsulfonium perchlorate (III) or 2,4-dihydroxyphenyldialkylsulfonium perchlorates (V—VII) in good yields. The sulfonium perchlorates were viscous oils and were identified by conversion to their corresponding picrates.

Sulfonium perchlorate (III) was heated in a saturated aqueous solution of potassium chloride for 4—5 hours to afford 4-*p*-chlorophenylthioresorcinol (X) in a good yield. In the same way as 2,5-dihydroxyphenyldialkylsulfonium perchlorates,[10] sulfonium perchlorates (V—VII) were refluxed in an excess of pyridine for 4—5 hours, to give 4-alkylthioresorcinols (XII—XIV) in 63—68% yield.

4-Arylthio- or 4-alkylthio-resorcinols (VIII—XIV) were oxidized with potassium nitrosodisulfonate in aqueous methanol under ice-cooling to afford 2-arylthio- or 2-alkylthio-5-hydroxy-*p*-benzoquinones (XV—XXI) in 49—61% yield.

These hydroxybenzoquinones (XV—XXI) are presumably the *p*-quinonoid form according to the Teuber's report[11]: the phenols without any substituents except the hydroxy group in a *para*-position of a phenolic hydroxy group give *p*-quinones by oxidation with potassium nitrosodisulfonate. However, the presence of two tautomers shown by the following formulae



R=alkyl or aryl

10) S. Ukai and K. Hirose, *Chem. Pharm. Bull.* (Tokyo), **16**, 199 (1968).
11) H.J. Teuber and W. Rau, *Ber.*, **86**, 1036 (1953).

is expected because 2-hydroxy-3-methylthiophenazine (XXVIII) was obtained when 2-methylthio-5-hydroxy-*p*-benzoquinone (XVIII) was treated with *o*-phenylenediamine in acetic acid.

The tautomers are probably in equilibrium in the solution. For its characterization, methylation of XVIII was carried out as follows.

The compound (XVIII) was treated (a) with dimethyl sulfate and potassium carbonate in acetone, (b) with methyl iodide and silver oxide in acetone, (c) with a small amount of hydrochloric acid or boron trifluoride–ether solution in methanol, or (d) with diazomethane in ether.

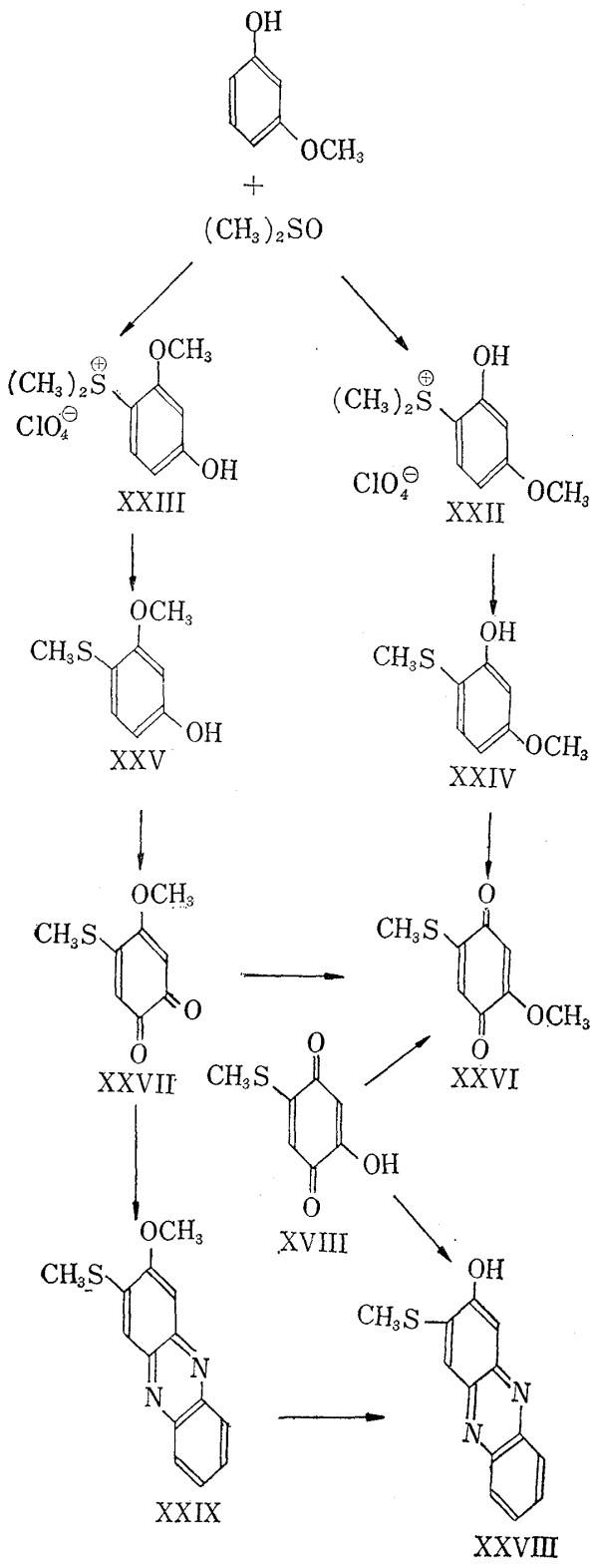


Chart 3

Only one methylated product (XXVI) was obtained in a poor (a, b), good (c), or quantitative yield (d). No other product was found except the starting material. The structure of XXVI was confirmed by the following procedure (Chart 3).

In the presence of perchloric acid and phosphoryl chloride, resorcinol monomethyl ether condensed with dimethyl sulfoxide to afford a mixture of 2-hydroxy-4-methoxyphenyldimethylsulfonium perchlorate (XXII) and 2-methoxy-4-hydroxyphenyldimethylsulfonium perchlorate (XXIII). The mixture was separated into its components by fractional recrystallizations from methanol to give colorless rhombs (XXII), mp 154°, in 34% yield, and colorless needles (XXIII), mp 204—205°, in 57% yield. These sulfonium salts (XXII and XXIII) gave by boiling in a hot saturated potassium chloride solution 1-hydroxy-2-methylthio-5-methoxybenzene (XXIV) as a colorless oil, bp 82—83° (0.15 mmHg), and 1-hydroxy-3-methoxy-4-methylthiobenzene (XXV) as colorless needles, mp 97.8°, respectively. XXIV was soluble in petroleum ether, but XXV was insoluble in the solvent. Therefore, the mixture of XXIV and XXV obtained from the mixture of sulfonium salts (XXII and XXIII) could be separated into its components by treatment with petroleum ether.

These compounds (XXIV and XXV) were oxidized with potassium nitrosodisulfonate in aqueous methanol under ice-cooling to afford 2-methylthio-5-methoxy-*p*-benzoquinone (XXVI) as orange needles, mp 256—257° (decomp.), which gave blue

color in the Craven's test, and 4–methylthio–5–methoxy–*o*–benzoquinone (XXVII) as red–orange leaves, mp 197—198°, which gave purple red color in the Craven's test, respectively. The compound (XXVII) was proved to be in the *o*–quinonoid form, because it gave 2–methoxy–3–methylthiophenazine (XXIX) by the reaction with *o*–phenylenediamine in acetic acid. The *o*–quinone (XXVII) was readily converted into 2–methylthio–5–methoxy–*p*–benzoquinone (XXVI) when it was allowed to stand in methanol containing a small amount of hydrochloric acid. Such a result is similar to the Fieser's observation[12] that 4–methoxy–1,2–naphthoquinone was converted into 2–methoxy–1,4–naphthoquinone by the treatment with boiling methanol containing hydrochloric acid.

Accordingly, it is concluded that XXVI is in *p*–quinonoid form and XXVII is in *o*–quinonoid form.

The compound obtained by methylation of XVIII was proved to be identical with 2–methylthio–5–methoxy–*p*–benzoquinone (XXVI) by the mixed melting point test and the comparison of their infrared spectra.

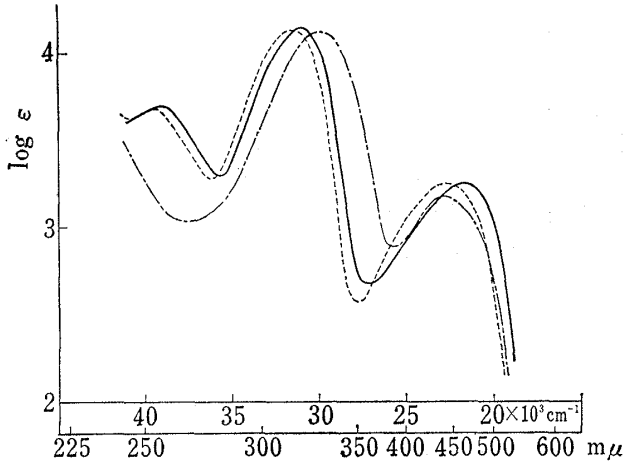


Fig. 1. Ultraviolet Absorption Spectra of XVIII, XXVI, XXVII in $CHCl_3$

------- XXVI
——— XVIII
– – – – – XXVII

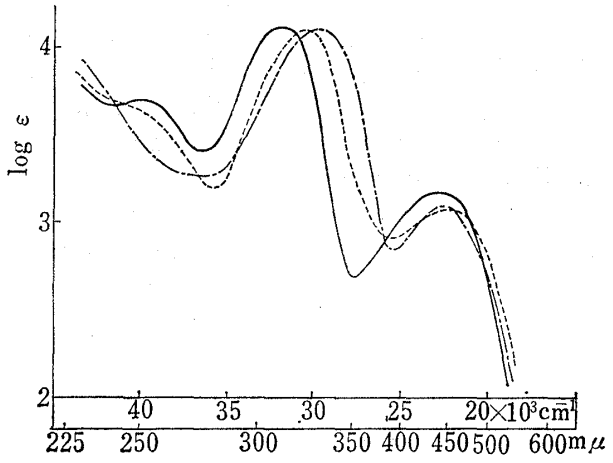


Fig. 2. Ultraviolet Absorption Spectra of XVIII, XXVI, XXVII in MeOH

——— XXVI
------- XVIII
– – – – – XXVII

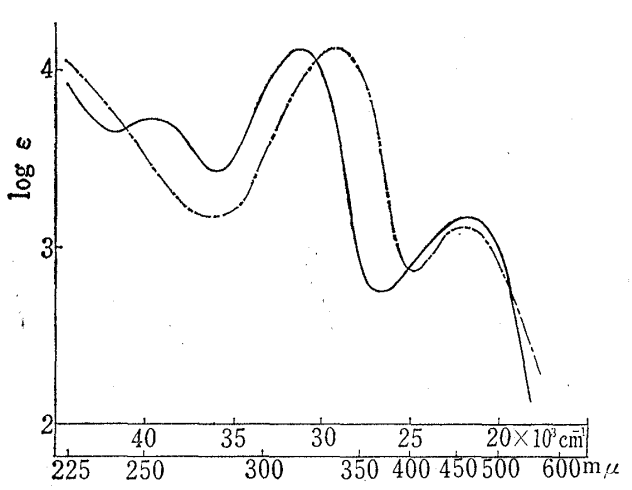


Fig. 3. Ultraviolet Absorption Spectra of XXVI, XXVII in 20—30% Methanolic Aqueous Solution

——— XXVI
•—•—•— XXVII

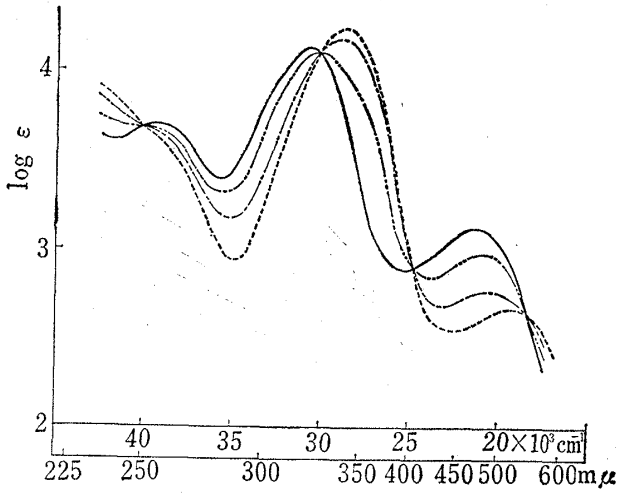


Fig. 4. Ultraviolet Absorption Spectra of XVIII in pH 1,6–9,0

——— pH 1,6—3,2
—•—•— pH 4,4
—••—•• pH 3,6
------ pH 5,6—9,0

12) L.F. Fieser, *J. Am. Chem. Soc.*, **48**, 2922 (1926).

Thus, in all these cases, methylation of 2-methylthio-5-hydroxy-*p*-benzoquinone (XVIII) gave only one *p*-quinonoid compound (XXVI).

Ultraviolet absorption spectrum of XVIII in chloroform is similar to that of XXVI, but quite different from that of XXVII (Fig. 1).

The spectra of XXVI and XXVII in methanol are similar to their spectra in chloroform; the spectrum of XVIII in methanol is somewhat different from that in chloroform, and has a shoulder at 250—255 mμ and a maximum at 328 mμ (Fig. 2). The spectral evidences indicate that XVIII exists mostly in the *p*-quinonoid form in chloroform, and as a tautomeric mixture in methanol. In ultraviolet spectra of XVIII in media of various pH (pH 1.6—9.0), as shown in Fig. 4, the spectrum exhibited two maxima (255 and 325 mμ) in a strongly acid medium (pH 1.6—3.2). The maxima are similar to those (253 and 322 mμ) of XXVI in 20—30% methanolic aqueous solution (Fig. 3). But the spectrum changed markedly in pH 3.6—5.6. With the increase of pH value, the maximum (pH 1.6—3.2) at 255 mμ gradually weakened and that (pH 1.6—3.2) at 325 mμ shifted, with increasing intensity, to a longer wave length (349 mμ): absorption maximum in the visible region shifted, with decreasing intensity, to a longer wave length (510 mμ). The spectrum (pH 5.6—9.0) was different from that of XXVII in 20—30% methanolic aqueous solution.

The presence of the isosbestic points in the spectra indicates the occurrence of one dissociation step in the pH range and, in fact, the pH titration proved that XVIII has only one dissociation step in pH 2.28—12.50 and is an acid substance (pK_a=3.5).

These results suggest that XVIII is in the *p*-quinonoid form at pH 1.6—3.2 and, with the increase of pH value, gradually converts into an anion, *i.e.*, a resonance hybrid of the limit formulae as shown in Chart 4, and exists as the anion at pH 5.6—9.0.

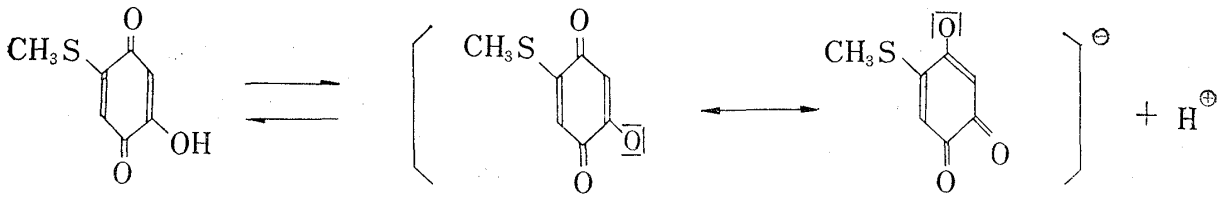


Chart 4

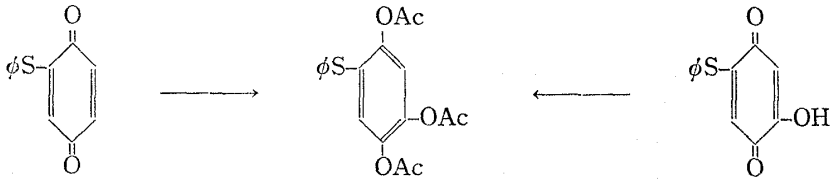
These hydroxybenzoquinones (XV—XXI) gave deep green color in the $FeCl_3 \cdot K_3Fe(CN)_6$ test[13] and red color in an alkaline solution. The infrared spectra of XV to XXI in chloroform solution exhibited two absoption bands at 3350—3380 cm^{-1} and 3625—3650 cm^{-1} for hydroxy group, and an absorption band at 1645—1650 cm^{-1} for carbonyl group. But in Nujol, the stretching absorption of hydroxy group of these compounds appeared at 3350—3380 cm^{-1}, and the absorption at 3625—3650 cm^{-1} disappeared. The ultraviolet spectra of XV to XXI exhibited maxima at 254—258 and 315—323 mμ, and their spectra in the visible region showed a maximum at 462—470 mμ, as indicated in Table IV. The pK_a value of XV—XXI measured by spectrophotometry[14] were 3.5—3.65, as shown in Table IV.

Thus, the result described above indicates that compounds XV to XXI are mostly in the *p*-quinonoid form.

In our initial study, we examined the Thiele addition of acetic anhydride to 2-arylthio-*p*-benzoquinones[10] (aryl=C_6H_5, C_6H_4-CH_3(*p*), C_6H_4-Cl(*p*)) and 2-alkylthio-*p*-benzoquinones[10] (alkyl=CH_3, C_2H_5, C_3H_7, C_4H_9) using 70% perchloric acid, sulfuric acid, or boron trifluoride as an acid-catalyst. The arylthio compounds underwent the Thiele reaction smoothly, and arylthiohydroxyhydroquinone triacetates (XXX—XXXII) could be isolated easily in good yields. But the alkylthio compounds did not undergo the Thiele reaction. In this

13) G.M. Barton, *Nature*, **170**, 249 (1952).
14) K. Nakanishi, *Yukikagaku-no-Shinpo*, **12**, 19 (1957).

case, the expected triacetates could not be found, and only the starting material or a resinous product was found. Hydrolysis of these triacetates (XXX—XXXII), before oxidation of the hydrolyzates to arylthiohydroxybenzoquinones, was not successful. These triacetates (XXX—XXXII) were proved to be identical with 2-arylthio-1,4,5-triacetoxybenzenes (XXX—XXXII), which were synthesized by the reduction of 2-arylthio-5-hydroxy-*p*-benzoquinones (XV—XVII) with zinc powder in acetic anhydride, by the mixed melting point test.



XXX—XXXII XV—XVII

$\phi = C_6H_5$, C_6H_4-CH_3(*p*), C_6H_4-Cl(*p*)

Chart 5

Accordingly, it is obvious that the position of the newly introduced acetoxyl group in 2-arylthio-*p*-benzoquinones by the Thiele reaction is *para* to the arylthio group.

Experimental[15-17]

2,4-Dihydroxyphenyl-*p*-chlorophenylmethylsulfonium Perchlorate (III)——Resorcinol (3.3 g, 0.03 mole) and methyl *p*-chlorophenyl sulfoxide (4.8 g, 0.03 mole) were treated in 70% $HClO_4$ (30 ml) according to the method A described in the previous paper.[9,10] By this method, III was obtained as a viscous oil. The picrate of III was recrystallized from EtOH (Table I).

2,4-Dihydroxyphenyldialkylsulfonium Perchlorates (V—VII)——Resorcinol (3.3 g, 0.03 mole) and dialkyl sulfoxide (0.03 mole) were treated in a mixture of 70% $HClO_4$ (10 ml) and $POCl_3$ (8 ml) according to the method B described in the previous paper.[6,7] By this method, V—VII were obtained as viscous oils. The picrates of V—VII were recrystallized from EtOH (Table I).

4-*p*-Chlorophenylthioresorcinol (X)——III (0.02 mole) was refluxed in a hot saturated aqueous solution of KCl (100 ml) for 4—5 hr to liberate an oily substance. After cooling, the oily substance was extracted with ether, and the organic layer was dried over anhyd. $CaCl_2$, and evaporated. The residue was recrystallized from the mixture of ligroin and toluene (Table II).

4-Alkylthioresorcinols (XII—XIV)——Sulfonium perchlorates (V—VII) (0.02 mole) in pyridine (40 ml) were treated in the same manner as described in the previous paper.[10] The compounds (XII—XIV) were purified by distillation under reduced pressure (Table II).

2-Arylthio- or 2-Alkylthio-5-hydroxy-*p*-benzoquinones (XV—XXI)——An ice-cooled solution of 2-arylthio- or 2-alkylthio-resorcinol (VIII—XIV) (0.005 mole) in MeOH (200 ml) was added at one time to the suspension of $NO(SO_3K)_2$ (2.68 g, 0.01 mole) in ice-water (120 ml).

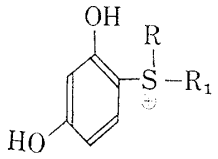
The mixture was vigorously shaked. The characteristic violet color of $NO(SO_3K)_2$ turned to orange, immediately. Then the mixture began to liberate an orange-brown precipitate. After cooling in an ice-bath for 1 hr, the precipitate was collected, dried, and recrystallized from benzene (Table III).

2-Arylthio-1,4,5-triacetoxybenzenes (XXX—XXXII)——Reductive acetylation of XV—XVII: Zinc powder (2.5 g) was added to a solution of 2-arylthio-5-hydroxy-*p*-benzoquinone (0.005 mole) in Ac_2O (25 ml). The mixture was refluxed for 1 hr until its orange color almost faded. And then zinc powder (0.5 g) was added again, and the refluxing was continued until the solution became colorless.

After cooling, zinc was filtered, and the filtrate was poured into ice-water to separate a crystalline solid, which was collected and dried. Recrystallization from EtOH afforded XXX—XXXII, accordingly. XXX (1.7 g), colorless needles, mp 122—123°, *Anal.* Calcd. for $C_{18}H_{16}O_6S$: C, 59.99; H, 4.48. Found: C, 60.08; H, 4.45. XXI (1.8 g), colorless crystals, mp 100—101°, *Anal.* Calcd. for $C_{19}H_{18}O_6S$: C, 60.95; H, 4.85. Found: C, 60.97; H, 4.71. XXXII (1.8 g), colorless prisms, mp 129—129.5°, *Anal.* Calcd. for $C_{18}H_{15}O_6SCl$: C, 54.76; H, 3.83. Found: C, 54.92; H, 3.92.

15) The operations with $HClO_4$ were performed in a draftchamber.
16) Melting and boiling points are uncorrected.
17) Ultraviolet absorption spectra were taken with a Hitachi EPS-2U automatic recording spectrophotometer. Infrared spectra were taken with a Hitachi EPI-S_2.

Table I.

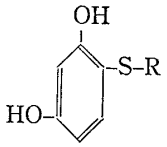


Compd. No.	R_1	R	Salt	mp (°C)	Yield[a] (%)	Appearance
Ⅲ	CH_3	*p*-ClC_6H_4	picrate	190—192	91	pale yellow prisms
Ⅴ	C_2H_5	C_2H_5	picrate	173—174	80	pale yellow crystals
Ⅵ	*n*-C_3H_7	*n*-C_3H_7	picrate	186—189	81	pale yellow crystals
Ⅶ	*n*-C_4H_9	*n*-C_4H_9	picrate	170—171	85	pale yellow needles

Compd. No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Ⅲ	$C_{19}H_{14}O_9N_3SCl$	46.02	2.85	8.48	46.17	2.83	8.51
Ⅴ	$C_{16}H_{17}O_9N_3S$	44.96	4.01	9.83	44.71	4.00	9.78
Ⅵ	$C_{18}H_{21}O_9N_3S$	47.47	4.65	9.23	47.70	4.65	9.55
Ⅶ	$C_{20}H_{25}O_9N_3S$	49.68	5.21	8.69	49.86	5.21	8.98

a) Yields of sulfonium perchlorates.

Table Ⅱ.

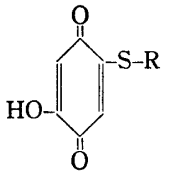


Compd. No.	R	mp (°C) (bp (°C/mm Hg))	Yield (%)	Appearance	Formula	Analysis (%) Calcd. C	H	Found C	H
X	*p*-ClC_6H_4	102—103	73	white needles	$C_{12}H_9O_2SCl$	57.03	3.59	56.98	3.62
Ⅻ	C_2H_5	(148—152/5)	63	colorless oil	$C_8H_{10}O_2S$	56.45	5.92	56.61	6.07
XIII	*n*-C_3H_7	(128—132/2)	68	colorless oil	$C_9H_{12}O_2S$	58.67	6.56	58.74	6.67
XIV	*n*-C_4H_9	(155—158/4)	65	colorless oil	$C_{10}H_{14}O_2S$	60.58	7.12	60.71	7.25

Thiele reaction of 2-arylthio-*p*-benzoquinone[10] (aryl= C_6H_5, C_6H_4-CH_3 (*p*), C_6H_4-Cl (*p*)): To a solution of 2-arylthio-*p*-benzoquinone (0.05 mole) in Ac_2O (10 ml) were added 2—3 drops of 70% $HClO_4$ or concd. H_2SO_4 with stirring. The color of the orange mixture immediately changed pale brown. The mixture was allowed to stand at room temperature for 2 hr, and poured into ice-water to separate a crystalline solid, which was collected and dried. Recrystallization from EtOH afforded colorless needles (XXX), mp 123°, or colorless crystals (XXXI), mp 100°, or colorless crystals (XXXII), mp 129—130°, respectively. These compounds were identified as XXX—XXXII, respectively, by the mixing melting point test with those samples prepared by the above reductive acetylation.

2-Hydroxy-4-methoxyphenyldimethylsulfonium Perchlorate (XXII) and 2-Methoxy-4-hydroxyphenyldimethylsulfonium Perchlorate (XXIII)——Resorcinol monomethyl ether (12.4 g), dimethyl sulfoxide (7.8 g), 70% $HClO_4$ (20 ml), and $POCl_3$ (8 ml) were treated in the same manner as described for V—VII. The reaction mixture was allowed to stand overnight and poured on ice to afford a crystalline solid, which was collected and dried. Fractional recrystallization of the solid from EtOH afforded XXII as white crystals. Recrystallization from EtOH gave colorless rhombs (8.8 g, 31%), mp 154°. *Anal.* Calcd. for $C_9H_{14}O_6SCl$: C, 37.97; H, 4.60. Found: C, 38.35; H, 4.67. The above filtrate was evaporated under reduced pressure. The

Table III.



Compd. No.	R	mp (°C) (decomp.)	Yield (%)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
XV	C_6H_5	146	61	red orange needles	$C_{12}H_8O_3S$	62.06	3.47	62.06	3.33
XVI	p-$CH_3C_6H_4$	137—138	55	red brown needles	$C_{13}H_{10}O_3S$	63.40	4.09	63.43	3.93
XVII	p-ClC_6H_4	156—157	49	red orange needles	$C_{12}H_7O_3SCl$	54.04	2.65	54.32	2.71
XVIII	CH_3	149—151	58	deep red needles	$C_7H_6O_3S$	49.40	3.55	49.45	3.58
XIX	C_2H_5	124	49	red needles	$C_8H_8O_3S$	52.16	4.38	52.33	4.35
XX	n-C_3H_7	133	50	red brown needles	$C_9H_{10}O_3S$	54.53	5.09	54.80	5.05
XXI	n-C_4H_9	140—142	53	deep red needles	$C_{10}H_{12}O_3S$	56.58	5.70	56.47	5.65

Table IV. Infrared Absorption Spectra, Ultraviolet Absroption Maxima and pK_a Values of 2-Arylthio- or 2-Alkylthio-5-Hydroxy-p-Benzoquinones (XV—XXI)

	XV	XVI	XVII	XVIII	XIX	XX	XXI
IR $\nu_{max}^{CHCl_3}$ cm^{-1}	3650	3640	3630	3625	3650	3650	3650
	3380	3375	3375	3350	3375	3360	3350
	1650	1645	1650	1645	1645	1645	1645
UV $\lambda_{max}^{CHCl_3}$ mμ (log ε)	254(3.75)	254(3.71)	257(3.71)	255(3.68)	257(3.63)	258(3.65)	258(3.65)
	320(4.04)	314(4.07)	316(4.03)	321(4.11)	322(4.08)	323(4.08)	323(4.08)
	466(3.25)	470(3.28)	462(3.20)	462(3.24)	464(3.25)	466(3.28)	467(3.29)
a)	3.58	3.53	3.61	3.58	3.59	3.65	3.60
pK_a b)				3.5			
(mμ) c)	(253, 326)	(252, 327)	(255, 323)	(251, 330)	(253, 330)	(253, 331)	(252, 331)

a) Spectrophotometry in buffer solution (6×10^{-5} M) at 25°
b) Potentiometry in 20% v/v EtOH–H_2O at 25°
c) Isosbestic points in UV.

residue was recrystallized from BuOH to afford XXIII (15.4 g, 54%), as colorless needles, mp 204—205°. *Anal.* Calcd. for $C_9H_{14}O_6SCl$: C, 37.97; H, 4.60. Found: C, 37.94; H, 4.51.

1-Hydroxy-2-methylthio-5-methoxybenzene (XXIV) and 1-Hydroxy-3-methoxy-4-methylthiobenzene (XXV)——A mixture of XXII or XXIII (0.02 mole) in a hot saturated KCl solution (60 ml) was refluxed for 4—5 hrs.

In the case of XXII, an oily substance was separated from the reaction mixture after cooling, and was extracted with ether. The organic layer was dried over anhyd. Na_2SO_4 and evaporated to give an oily residue. Distillation of this residue afforded XXIV (1.8 g) as a colorless oil, bp 82—84° (0.15 mm Hg). *Anal.* Calcd. for $C_8H_{10}O_2S$: C, 56.44; H, 5.92. Found: C, 56.24; H, 6.05. In the case of XXIII, a crystalline solid was separated from the reaction mixture, washed with water, and dried.

Recrystallization from EtOH afforded XXV (1.5 g) as colorless needles, mp 97.8°. *Anal.* Calcd. for $C_8H_{10}O_2S$: C, 56.44; H, 5.92. Found: C, 56.57; H. 6.02.

Isolation of XXIV and XXV from the mixture of XXII and XXIII: A mixture (14.3 g, 0.05 mole) of XXII and XXIII in a hot saturated KCl solution (100 ml) was refluxed for 5 hr. When cooled, an oily substance was separated from the reaction mixture, and extracted with AcOEt. The organic layer was dried over anhyd. $MgSO_4$, and was evaporated. Extraction of the residue with hot petroleum ether remained insoluble crystalline residue, which was recrystallized from toluene and petroleum ligroin to afford XXV (3.3 g) as colorless needles, mp 97.5°. The extracted solution with petroleum ether was evaporated to give an oily residue. Distillation afforded XXIV (2.0 g) as a colorless oil, bp 82—84° (0.15 mm Hg).

2-Methoxy-5-methylthio-p-benzoquinone (XXVI)——a) Oxidation of 1-Hydroxy-3-methoxy-5-methylthiobenzene (XXIV): XXIV (0.85 g), $NO(SO_3K)_2$ (2.68 g), ice-water (120 ml) and MeOH (100 ml) were treated in the same manner as described for XV—XXI.

Recrystallization from BuOH afforded XXVI (0.7 g) as orange needles, mp 256—257°. *Anal.* Calcd. for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 52.14; H, 4.60. UV $\lambda_{max}^{CHCl_3}$ mμ (log ε): 252 (3.66), 316 (4.13), 444 (3.24). IR ν_{max}^{Nujol} cm^{-1}: 1615, 1630, 1650.

Conversion to 2-Methoxy-5-methylthio-*p*-benzoquinone (XXVI) from 4-Methoxy-5-methylthio-*o*-benzoquinone (XXVII): To a solution of XXVII (0.5 g) in MeOH (50 ml) was added concd. HCl (1 ml). The mixture was allowed to stand at room temperature, gradually to liberate orange flakes. After 5 hr, the crystals were collected, and the filtrate was evaporated under reduced pressure to obtain a crystalline residue. The crystals and crystalline residue were combined. Recrystallization from BuOH afforded orange needles (0.4 g), mp 256—257°. The compound was identified with XXVI prepared by oxidation of XXIV, by the mixing melting point test and by the IR comparison.

Methylation of 2-Methylthio-5-hydroxy-*p*-benzoquinone (XVIII): a) To a solution of XVIII (0.17 g) in acetone (50 ml) were added K_2CO_3 (1.7 g) and $(CH_3)_2SO_4$ (3.0 g). The mixture was refluxed for 2 hr. After cooling, the precipitate containing potassium salt of XVIII was filtered off. The filtrate was evaporated to obtain a crystalline residue, which was washed with water and dried. Crystallization from BuOH afforded orange needles (0.02 g).

b) To a solution of XVIII (0.17 g) in acetone (50 ml) were added Ag_2O (0.3 g) and CH_3I (1.5 ml). The mixture was refluxed for 8 hr. A precipitate was filtered off, and the filtrate was evaporated to obtain a crystalline residue, which was washed with 2% Na_2CO_3 and with water, and then dried. Crystallization from BuOH afforded orange needles (0.01 g).

c) To a solution of XVIII (0.17 g) in MeOH (30 ml) was added concd. HCl (1 ml) or BF_3–ether (1 ml). The mixture was refluxed for 3 hr gradually to separate a little orange flake, and then poured into ice–water to precipitate a crystalline substance which was collected and dried. Recrystallization from BuOH afforded orange needles (0.12 g).

d) A solution of XVIII (0.17 g) in ether (50 ml) was added with cooling and stirring, to 0.5% CH_2N_2–ether (50 ml). Immediately an orange, crystalline precipitate appeared with the evolution of N_2.

The reaction mixture was allowed to stand below 5° for 5 hr, and further at room temperature for 6 hr. The orange, crystalline precipitate was collected, and the filtrate was evaporated under reduced pressure to obtain a crystalline residue. The crystals and crystalline residue were combined. Recrystallization from BuOH afforded orange needles (0.18 g). These orange needles obtained by methods a)—d) were identified with the sample (XXVI) prepared by the oxidation of XXIV by the mixing melting point test and the IR comparison.

4-Methoxy-5-methylthio-*o*-benzoquinone (XXVII)——1–Hydroxy–3–methoxy–4–methylthiobenzene (XXV) (0.85 g), $NO(SO_3K)_2$ (2.68 g), ice–water (120 ml) and MeOH (100 ml) were treated in the same manner as described for XV—XXI. Crystallization from benzene afforded reddish orange needles (0.65 g), mp 196—198°. *Anal.* Calcd. for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 52.44; H, 4.67. UV $\lambda_{max}^{CHCl_3}$ mμ (log ε): 336 (4.11), 443 (3.17). IR ν_{max}^{Nujol} cm^{-1}: 1645, 1660.

2-Hydroxy-3-methylthiophenazine (XXVIII)——To a solution of *o*–phenylenediamine (0.1 g) in AcOH (5 ml) was added a solution of XVIII (0.1 g) in AcOH (5 ml). The mixture was kept at 50° for 1 hr to isolate a yellowish brown precipitate. When cooled, the precipitate was collected. Recrystallization from AcOH afforded XXVIII (0.19 g) as pale yellow needles, mp 275° (decomp.). *Anal.* Calcd. for $C_{13}H_{10}ON_2S$: C, 64.44; H, 4.16. Found: C, 64.66; H, 4.32.

2-Methoxy-3-methylthiophenazine (XXIX)——XXVII (0.18 g), *o*–phenylenediamine (0.1 g) and AcOH (10 ml) were treated in the same manner as described for XXVIII. The green–brown precipitate obtained above was dissolved in benzene. Insoluble residue was filtered off, and the filtrate was evaporated to give a yellow residue. Crystallization from dil. EtOH afforded XXIX (0.1 g) as pale yellow silky needles, mp 164.5°. *Anal.* Calcd. for $C_{14}H_{12}ON_2S$: C, 65.60; H, 4.72. Found: C, 65.32; H, 4.98.

Methylation of XXVIII: To a solution of XXVIII (0.1 g) in 5% KOH–MeOH (5 ml) was added CH_3I (0.6 g). The mixture was refluxed for 3 hr, then poured into ice–water to separate an orange precipitate, which was collected and washed with water. Recrystallization from dil. EtOH afforded pale yellow silky needles (0.07 g). The compound was identified with the sample prepared by the method described above, by the mixing melting point test.

Acknowledgement The authors express their deep gratitude to Prof. M. Akagi, University of Hokkaido, for his valuable advice, and to Prof. T. Shimano, President of this College, for his kind encouragement during the course of this work. They are indebted to all the staff of the instrument room of this College for elemental analysis.