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Reaction of Phenol Derivatives with Sulfoxides. II.[1] A New Method of Synthesis of Monothio Derivatives of *p*-Benzoquinone[2]

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A new synthetic method of 2-arylthio- or 2-alkylthio-*p*-benzoquinones (XV—XXI) was established through the application of the reaction of hydroquinone with sulfoxides. The reaction of hydroquinone with methyl aryl sulfoxides in the presence of perchloric acid, or with dialkyl sulfoxides in the presence of both perchloric acid and phosphoryl chloride, progressed easily to afford 2,5-dihydroxyphenylarylmethylsulfonium perchlorates (I—III) or 2,5-dihydroxyphenyldialkylsulfonium perchlorates (IV—VII).

The treatment of these sulfonium perchlorates (I—VII) with potassium chloride or pyridine gave 2-arylthio- or 2-alkylthio-1,4-dihydroxybenzenes (VIII—XIV) and alkyl chlorides or N-alkylpyridinium perchlorates, respectively.

Thus it was shown that Hofmann's degradation did not take place in this case. Compounds VIII to XIV were easily oxidized by ferric chloride to 2-arylthio- or 2-alkylthio-*p*-benzoquinones (XV—XXI).

Alkylthio- and arylthio-*p*-benzoquinones have been prepared by the reaction of *p*-benzoquinone with thiols,[4-7] as shown in Chart 1.

In these cases, however, monosubstituted hydroquinones formed by the addition of thiols to the quinone are oxidized with the excess quinone to give monosubstituted *p*-benzoquinones and hydroquinone.

This monosubstituted quinones react further with excess thiols to give disubstituted hydroquinones, which in turn afford disubstituted *p*-benzoquinones. Thus, the repetition of addition and subsequent oxidation gives a mixture of mono-, di-, tri-, and tetrathio-*p*-benzoquinones. It is very difficult or impossible to isolate pure monothio derivatives from the reaction mixture, so the method is not practical for the synthesis of monosubstituted benzoquinones.

1) Part I: K. Hirose and S. Ukai, *Yakugaku Zasshi*, **86**, 187 (1966).
2) A part of this work was reported at the 9th Annual Tokai Local Meeting of the Pharmaceutical Society of Japan at Nagoya, October 12, 1960.
3) Location : *492—36, Mitahora, Gifu*.
4) J.M. Snell and A. Weissberger, *J. Am. Chem. Soc.*, **61**, 450 (1939).
5) O. Dimroth, L. Kraff, and K. Aichinger, *Ann.*, **545**, 124 (1940).
6) M. Schubert, *J. Am. Chem. Soc.*, **69**, 712 (1940).
7) A. Blackhall and R.H. Thomson, *J. Chem. Soc.*, **1953**, 1138.

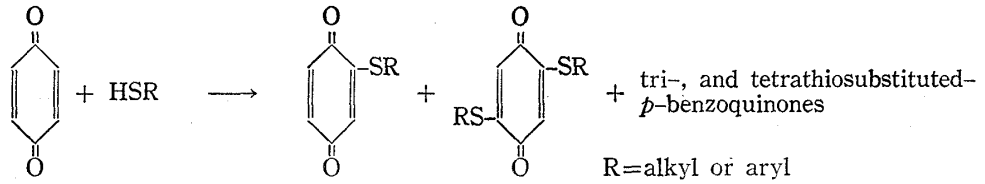


Chart 1

To avoid the formation of by-products, a synthetic method was proposed by Alcalay.[8] This method requires several steps and cumbersome operations, as given in Chart 2. Furthermore, this method is applicable only to the synthesis of monoalkylthio-*p*-benzoquinones and not to the synthesis of monoarylthio derivatives.

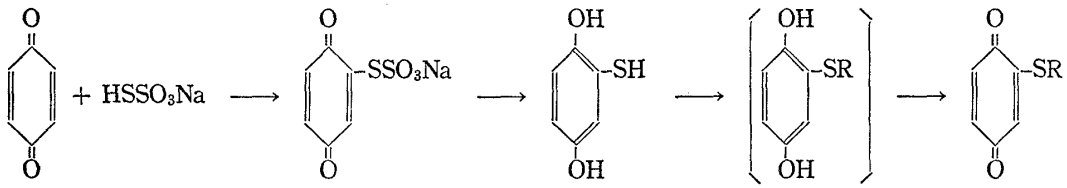
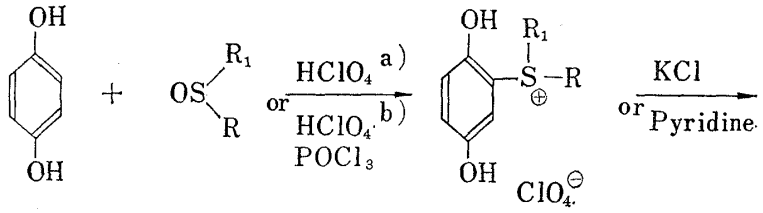


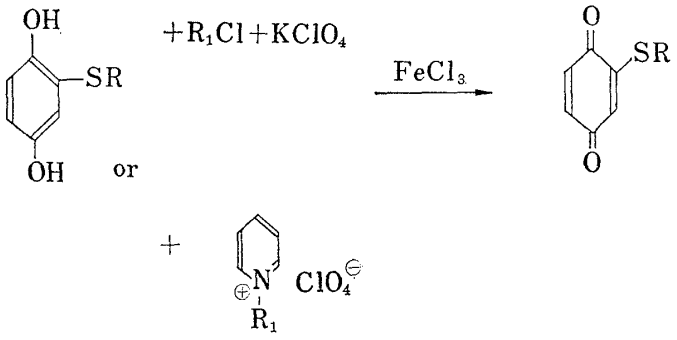
Chart 2

It was reported in our previous paper[9] that the reaction of phenols with methyl aryl sulfoxides in perchloric acid, or with dimethyl sulfoxide in a mixture of perchloric acid and phosphoryl chloride, progressed smoothly to give hydroxydiarylmethyl or hydroxyaryldimethylsulfonium perchlorates. These perchlorates were treated with potassium chloride to afford the corresponding hydroxydiaryl or hydroxyaryl methyl sulfides. This kind of reaction took place equally in the cases of methyl ethers of phenols. The present paper deals with the reaction of hydroquinone with methyl aryl or dialkyl sulfoxides, and with a



$R_1=CH_3$ $R=C_6H_5$,[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) (XV—XVII)
(XI—XIV) (XVIII—XXI)

Chart 3

8) W. Alcalay, *Helv. Chim. Acta*, **30**, 578 (1947).
9) K. Hirose and S. Ukai, *Yakugaku Zasshi*, **86**, 187 (1966).

new synthetic method of 2-arylthio- or 2-alkylthio-*p*-benzoquinones through the application of the reaction, as shown in Chart 3.

The results indicate that this new method is superior to those outlined in Chart 1 and 2.

According to the procedure[9] described previously, the condensation of hydroquinone with methyl aryl sulfoxides (aryl=C_6H_5, C_6H_4-CH_3 (*p*), C_6H_4-Cl(*p*)) in 70% perchloric acid gave 2,5-dihydroxyphenylarylmethylsulfonium perchlorates (I—III) in 90—93% yield.

It was attempted to condense hydroquinone with dialkyl sulfoxides (alkyl=CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9), but the result was unsuccessful leaving most of the hydroquinone, and the expected sulfonium compounds could not be obtained. However, when a mixture (1: 0.8) of 70% perchloric acid and phosphoryl chloride was used as a condensing agent, the reaction progressed smoothly to give 2,5-dihydroxyphenyldialkylsulfonium perchlorates (IV—VII) in 87—91% yield.

Of these sulfonium perchlorates (I—VII), compounds (II, III, V—VII) were viscous oils and were identified by converting them to the corresponding picrates. When the perchlorates (I—VII) were heated in aqueous saturated potassium chloride solution for 4—5 hours, 2-arylthio-1,4-dihydroxybenzenes (VIII—X) were obtained, respectively, from I—III in 69—74% yield, and 2-alkylthio-1,4-dihydroxybenzenes (XI—XIV) were obtained, respectively, from IV—VII in 45—54% yield.

Especially, the treatment of sulfonium perchlorates (VI, VII) with potassium chloride gave propyl chloride, bp 45—47°, and butyl chloride, bp 76—78°, respectively, in addition to XIII and XIV.

These alkyl chlorides were identified by conversion to the known S-alkylisothiuronium picrates.[10]

The formation of the alkyl chlorides by the treatment of VI and VII suggested the possibility that the reaction of other sulfonium perchlorates (I—V) with potassium chloride also gives alkyl chloride in addition to the compounds, VIII to XII. A similar reaction was already reported by Krollpfeiffer[11] that methylthiodiarylmethylsulfonium salts gave corresponding sulfides and methyl chloride when the sulfonium salts were treated with potassium chloride.

During our experiments on the decomposition of sulfonium salts in order to get the sulfides (VIII—XIV) in better yields from the sulfonium perchlorates (I—VII), the perchlorates (I—VII) were submitted to heating in an excess of pyridine for several hours.

According to this method, IV—VII gave 2-alkylthio-1,4-dihydroxybenzenes (XI—XIV) in improved yields, and also I—III afforded 2-arylthio-1,4-dihydroxybenzenes (VIII—X) in good yields.

Moreover, the treatment of sulfonium perchlorates (IV—VII) with pyridine gave following N-alkylpyridinium perchlorates: N-methyl, colorless prisms, mp 135°; N-ethyl, colorless prisms, mp 75°; N-propyl, and N-butyl, sirupy substances. In the case of sulfonium perchlorates (I—III), N-methylpyridinium perchlorate[12] was equally formed in a good yield. These N-alkylpyridinium perchlorates (alkyl=CH_3, C_2H_5, *n*-C_3H_7) were identified by conversion to their picrates and confirmed by mixed melting point determinations with the authentic samples.[13,14] However, N-butylpyridinium picrate, never found in literature, did not solidify, and it was confirmed by conversion to the meconate which was white needles, mp 167° (decomp.). Thus, the present experiments indicate that the treatment of sulfonium

10) O. Neunhoeffer, "Analytische Trennung und Identifizierung organischer Substanzen," p. 69, 1960, Walter de Gryter & Co.; E.L. Brown and N. Campbell, *J. Chem. Soc.*, **1937**, 1699.
11) F. Krollpfeiffer and W. Hahn, *Ber.*, **86**, 1049 (1953).
12) F.M. Kosower and P.E. Klinedinst, *J. Am. Chem. Soc.*, **78**, 3493 (1956).
13) F. Krollpfeiffer and E. Brown, *Ber.*, **69**, 2523 (1936).
14) E.L. Colichman, W.R. Vanderzanden, and S.K. Liu, *J. Am. Chem. Soc.*, **74**, 1953 (1952).

perchlorates (I—VII) with pyridine causes the migration of an alkyl group from the sulfonium salts to pyridine giving corresponding sulfides (VIII—XIV).

Accordingly, it is quite reasonable that, in the treatment of sulfonium perchlorates (I—VII) with potassium chloride or pyridine, Hofmann degradation does not take place, contrary to the observation reported recently by Franzen, *et al.*[15]

The 2-arylthio-1,4-dihydroxybenzenes (VIII—X) were easily oxidized with ferric chloride in ethanol to afford 2-arylthio-*p*-benzoquinones (XV—XVII) in 67—72% yields. Similarly the 2-alkylthio-1,4-dihydroxybenzenes (XI—XIV) were easily oxidized with ferric chloride in hot water to give 2-alkylthio-*p*-benzoquinones (XVIII—XXI) in 69—74% yields.

When only these quinones (XV—XXI) are required, it is better to use VIII—XIV without purification for the oxidation, because the yeilds are improved.

2-alkylthio-*p*-benzoquinones (XVIII—XXI) were also formed by the application of the Alcalay's method. According to this method, the mixture, prepared by the reaction between 2,5-dihydroxythiophenol and alkyl halogenides in a sealed tube, is subjected to oxidation without any further treatment. This mixture contains each of 2-alkylthio-1,4-dihydroxybenzenes. However, the yields were poor in the cases of compound XX and XXI, and unknown by-products were formed.

These quinones (XV—XXI) showed deep blue-green color in the Craven's test, and exhibited two infrared absorption bands of carbonyl group at 1645—1658 and 1668—1677 cm^{-1}. Their ultraviolet spectra exhibited an absorption maximum at 256—260 mμ, and the spectra in the visible region showed an absorption maximum at 428—440 mμ, as shown in Table III.

These results indicate that the synthetic route shown in Chart 3 is satisfactory as a new method for synthesizing 2-arylthio- or 2-alkylthio-*p*-benzoquinones (XV—XXI).

Experimental[16-19]

2,5-Dihydroxyphenylarylmethylsulfonium Perchlorates (I—III)——Method A[9]: Powdered hydroquinone (3.3 g, 0.03 mole) was added with stirring to 70% $HClO_4$ (30 ml) in an ice-bath. To the resulting suspension was gradually added methyl aryl sulfoxide (0.03 mole) in small portions, with stirring below 5°. The reaction mixture was stirred for 1 hr after completion of the addition and stirred further for 2—3 hr at 15—20°. The mixture became clear, and began to isolate a fine crystalline or an oily substance after a while. The mixture was allowed to stand overnight at room temperature, and was poured on ice to give crystals (I) or a viscous oil (II, III). The crystals of I were filtered ,dried on a clay plate, washed with ether, and dissolved in hot BuOH. The solution afforded crystals (I) by the addition of dry ether. The oil of II or III was separated by decantation, and then dissolved in AcOEt. The organic layer was washed with 50% $MgSO_4$ solution, and dried over anhyd. $MgSO_4$. Then it afforded a viscous oil (II, III) by the addition of dry ether. The picrates of II and III were recrystallized from EtOH (Table I).

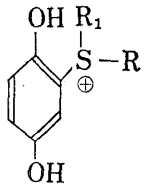
2,5-Dihydroxyphenyldialkylsulfonium Perchlorates (IV—VII)——Method B[9]: To a mixture of 70% $HClO_4$ (20 ml) and $POCl_3$ (16 ml) was added with stirring powdered hydroquinone (4.4 g, 0.04 mole) in an ice-bath. Dialkyl sulfoxide (0.04 mole) was gradually added to the resulting suspension in samll portion with stirring below 5°.

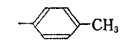
The mixture was stirred for 1 hr after completion of the addition, stirred further for 2—3 hr at 15—20°, and allowed to stand overnight at room temperature. The resulting reaction mixture was clear.

But in the case of IV, the mixture began to isolate a crystalline substance after a while. In the case of V—VII, the mixture was poured on ice to separate an oily substance which was salted out with $MgSO_4$ and extracted with EtOAc. The organic layer was washed with 50% $MgSO_4$ and dried over anhyd. $MgSO_4$. The solution was concentrated under reduced pressure. A viscous oil (V—VII) was separated on addition of dry ether. The picrates of V—VII were recrystallized from EtOH (Table I). The mixture, containing a

15) V. Franzen and C. Merz, *Ber.*, **93**, 2819 (1960); V. Franzen and H.J. Schmidt, *ibid.*, **94**, 2937 (1961); V. Franzen, H.I. Joschek, and C. Mertz, *Ann.*, **654**, 82 (1962).
16) The operations with $HClO_4$ were performed in a draftchamber.
17) Commercial 70% $HClO_4$ was used.
18) Melting and boiling points are uncorrected.
19) 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 (%)	Appearance
I	CH_3		perchlorate	146—147	91	white granules
II	CH_3		picrate	161—163	93[a]	yellow prisms
III	CH_3		picrate	152—154	90[a]	yellow prisms
IV	CH_3	CH_3	perchlorate	189—191	91	colorless needles
V	C_2H_5	C_2H_5	picrate	138—140	82[a]	pale yellow prisms
VI	n-C_3H_7	n-C_3H_7	picrate	165—166	79[a]	pale yellow needles
VII	n-C_4H_9	n-C_4H_9	picrate	159—161	86[a]	yellow prisms
	n-C_4H_9	n-C_4H_9	chloride[b]	157—158	86[a]	colorless prisms

Compd. No.	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	$C_{13}H_{13}O_6SCl$	46.92	3.94		47.06	4.10	
II	$C_{20}H_{17}O_9N_3S$	50.53	3.60	8.84	50.74	3.61	9.00
III	$C_{19}H_{14}O_9N_3SCl$	46.02	2.85	8.48	46.08	3.00	8.63
IV	$C_8H_{11}O_6SCl$	35.50	4.10		35.27	4.08	
V	$C_{16}H_{17}O_9N_3S$	44.96	4.01	9.83	45.15	4.10	9.74
VI	$C_{18}H_{21}O_9N_3S$	47.47	4.65	9.23	47.26	4.61	9.07
VII	$C_{20}H_{25}O_9N_3S$	49.68	5.21	8.69	49.64	5.33	9.00
	$C_{14}H_{23}O_2SCl$	57.81	7.97		58.08	8.05	

a) Yields of sulfonium perchlorates
b) The sulfonium chloride was prepared by treatment with conc. hydrochloric acid of sulfonium perchlorate (VII), it was recrystallized from butanol.

small amount of crystalline substance in the case of IV, was cooled with a freezing mixture (ice, NaCl) to separate crystals. The crystals were collected on a glass filter, dried on a clay plate, washed with ether, and recrystallized from BuOH (Table I).

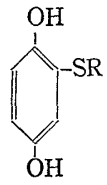
2-Arylthio- and 2-Alkylthio-1,4-dihydroxybenzenes (VIII—XIV)——a) Treatment with KCl: 2,5-Dihydroxyphenylarylmethylsulfonium perchlorate (I—III) or 2,5-dihydroxyphenyldialkylsulfonium perchlorate (IV—VII) (0.03 mole) was refluxed in a hot saturated KCl solution (100 ml) for 4—5 hr until an oil was separated. After cooling, a solid or oil was extracted with ether, and the organic layer was dried over anhyd. $CaCl_2$, and evaporated. The residue was purified by recrystallization from a suitable solvent, or by distillation under a reduced pressure (Table II). In the case of VI and VII, the mixture was distilled to separate an oil and water, after the treatment with KCl and addition of water (100 ml). The oil was distilled to afford propyl chloride (0.3 g), bp 45—47°, or butyl chloride (0.35 g), bp 76—78°.

This propyl chloride or butyl chloride was derived to S-propylisothiuronium picrate or S-butylisothiuronium picrate by the usual method.[10]

The identity with an authentic sample[10] was confirmed by the mixed melting point test.

b) Treatment with pyridine: A solution of sulfonium perchlorate (I—VII) (0.02 mole) dissolved in pyridine (40 ml) was refluxed for 4—5 hr. The mixture was evaporated under reduced pressure, and the residue was extracted with ether by refluxing. The separated organic layer was washed with 5% HCl and with a saturated NaCl solution, dried over anhyd. $CaCl_2$, and evaporated. The residue was purified according to the method described in (a) (Table II). In the case of I—V, the residue not extracted with ether was recrystallized from EtOH–acetone to afford N-methylpyridinium perchlorate,[12] mp 135° (*Anal.* Calcd. for $C_6H_8O_4NCl$: C, 37.23; H, 4.17. Found: C, 37.50; H, 4.33) from I—IV, and to afford N-ethylpyridinium perchlorate, mp 75° (*Anal.* Calcd. for $C_7H_{10}O_4NCl$: C, 40.50; H, 4.85. Found: C, 40.55; H, 4.72) from V.

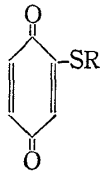
TABLE II.

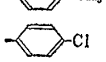
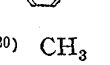


Compd. No.	R	mp (°C) (bp (°C/mm Hg))	Yield (%) a)	Yield (%) b)	Appearance	Recrystallization solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
VIII[5]		89—91	74	72	white prisms	benzene	$C_{12}H_{10}O_2S$	66.03	4.62	66.15	4.69
IX		100—103	72	73	colorless needles	benzene–ligroin	$C_{13}H_{12}O_2S$	67.21	5.21	67.48	5.31
X		124—125	69	70	white needles	benzene	$C_{12}H_9O_2SCl$	57.03	3.59	57.18	3.46
XI[20]	CH_3	82—83	54	68	colorless needles	benzene–ligroin	$C_7H_8O_2S$	53.82	5.16	53.90	5.11
XII	C_2H_5	(124—128 /0.5)	47	64	colorless oil		$C_8H_{10}O_2S$	56.45	5.92	56.52	6.01
XIII	C_3H_7	71—73	51	69	colorless prisms	benzene	$C_9H_{12}O_2S$	58.67	6.57	58.59	6.33
XIV	C_4H_9	37—38	45	65	colorless needles	benzene–ligroin	$C_{10}H_{14}O_2S$	60.57	7.12	60.64	7.32

a) Treatment with potassium chloride b) Treatment with pyridine

TABLE III.



Compd. No.	R	mp (°C)	Yield (%)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H	IR $\nu_{C=O}^{CCl_4}$ cm^{-1}	UV $\lambda_{max}^{CHCl_3}$ mμ (log ε)
XV[4,5]		112—114	69	orange–red leaves	$C_{12}H_8O_2S$	66.65	3.73	66.47	3.97	1650 1672	258 (4.08) 434 (3.44)
XVI		107—109	72	red orange prisms	$C_{13}H_{10}O_2S$	67.80	4.38	67.99	4.55	1647 1668	258 (4.05) 437 (3.45)
XVII		111—113	67	orange–brown needles	$C_{12}H_7O_2SCl$	57.49	2.81	57.48	2.71	1658 1677	260 (4.14) 428 (3.48)
XVIII[8,20]	CH_3	148—149	74	yellow–brown needles	$C_7H_6O_2S$	54.53	3.92	54.72	3.98	1648 1670	256 (4.14) 435 (3.59)
XIX[8]	C_2H_5	97—98	70	orange yellow flakes	$C_8H_8O_2S$	57.12	4.79	57.35	4.80	1650 1670	256 (4.11) 437 (3.59)
XX[8]	C_3H_7	90—90.5	69	orange yellow flakes	$C_9H_{10}O_2S$	59.31	5.53	59.22	5.75	1648 1670	257 (4.10) 440 (3.57)
XXI[8]	C_4H_9	87.5	71	orange yellow plates	$C_{10}H_{12}O_2S$	61.20	6.16	61.36	6.05	1645 1668	258 (4.05) 440 (3.52)

In the case of VI, the sirupy residue not extracted with ether, N-propylpyridinium perchlorate, and N-alkylpyridinium perchlorate (alkyl=CH_3, C_2H_5) were converted to their picrates. The identity with an authentic sample[13,14] was confirmed by the mixed melting point test. Also, in the case of VII the sirupy residue not extracted with ether was treated with equivalent amount of meconic acid in EtOH to afford N-butylpyridinium meconate, mp 167° (decomp.) (*Anal.* Calcd. for $C_{16}H_{18}NO_7$: C, 57.14; H, 5.39; N, 4.17. Found: C, 57.13; H, 5.43; N, 4.38).

2-Arylthio-*p*-benzoquinones (XV—XVII)——To a solution of VIII—X (0.02 mole) in EtOH (10 ml), 50% ethanolic solution of $FeCl_3$ (20 ml) was added, and the mixture was shaken vigorously, whereupon it immediately colored deep brown–red. After standing for 1 hr, the mixture gave a red orange precipitate by addition of H_2O (10 ml). The precipitate was collected and recrystallized from EtOH (Table III).

2-Alkylthio-*p*-benzoquinones (XVIII—XXI)——To a solution of XI—XIV (0.02 mole) in hot H_2O (300 ml), 70% aqueous $FeCl_3$ solution (25 ml) was added. When the mixture was shaken vigorously, an orange brown precipitate formed immediately. After cooling, the precipitate was collected and recrystallized from EtOH (Table III). In the case of XI, the filtrate was extracted with benzene. The organic layer was evaporated, and the residue was combined with the above precipitate.

Acknowledgement The authors express their deep gratitude to Prof.M. Akagi, University of Hokkaido, for his valuble 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.

20) T. Zincke and J. Müller, *Ber.*, **46**, 1777 (1913).