OXIDATIONS WITH POTASSIUM NITROSODISULFONATE (FREMY'S RADICAL). THE TEUBER REACTION

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Contents

I. Introduction

A. SCOPE

One of the major trends in modern organic synthesis is the development of very selective reagents. In the area of oxidation reactions of organic compounds the number of such selective oxidizing agents is still fairly small. One of the few of these agents is potassium nitrosodisulfonate or Fremy's radical (**1**). This salt selectively oxidizes phenols to the corresponding quinones. Aromatic amines also are oxidized by **1**; however, the product formed depends on the structure of the starting amine. Aniline and other primary aromatic amines undergo an oxidative condensation; secondary aromatic amines react with **1** to yield quinone imines which are hydrolyzed to quinones. Fairly detailed studies have been reported on the mechanism of the Teuber reaction involving phenols. However, mechanistic studies of oxidations of other substrates with **1** have not been as extensive. As a consequence, this review will summarize the oxidation reactions of **1** and, where necessary, provide mechanistic interpretations for numerous reactions, which are consistent with the experimental results.

B. FREMY'S RADICAL

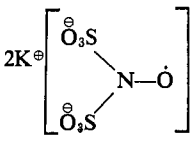
1. Historical

Fremy[1] was the first to prepare potassium nitrosodisulfonate (**1**). Raschig,[2] who showed by an electrochemical method that **1** occurs in solution as a dibasic anion, also summarized earlier reports on **1**.[3,4]

1 was compared with dinitrogen tetroxide by Hantzsch and Semple.[5] These authors concluded that solutions of **1**, which are purple in color, contain monomeric nitrosodisulfonate ions; the yellow solid of **1**, however, is made up of dimeric species. More recently their findings were confirmed by a magnetochemical study.[6] The radical nature of the solution species has been confirmed by esr studies.[7-14] Also its radiation chemistry has been recently studied.[15] **1** has been reported to undergo explosive decomposition when being prepared. Its controlled decomposition in solution has been studied.[16,17] The first oxidation of an organic compound by **1** was achieved by Raschig[2] who converted aniline into nitrosobenzene. In a series of papers beginning in 1951, Teuber[18] and his coworkers developed oxidation and dehydrogenation methods using **1** as the active reagent. Short reviews of methods using **1** as an oxidizing agent have appeared.[19]

2. Physical and Spectral Properties

1, which in solution is represented by the structure



was found to exist in the solid state in two distinct crystalline modifications. One form is monoclinic and is dimeric. The other is a triclinic form and is monomeric.[20,21] The triclinic,

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** Environmental Health Trainee, 1968–1970.

(1) E. Fremy, *Ann. Chim. Phys.*, 15, 408 (1845).

(2) F. Raschig, "Schwefel- and Stickstoff-Studien," Verlag Chemie, Leipzig–Berlin, 1924.

(3) A. Claus, *Ber.*, 4, 508 (1871); *Justus Liebigs Ann. Chem.*, 158, 205 (1871).

(4) T. Haga, *J. Chem. Soc.*, 85, 78 (1904).

(5) A. Hantzsch and W. Semple, *Chem. Ber.*, 28, 2744 (1895).

(6) R. W. Asmussen, *Z. Anorg. Chem.*, 212, 317 (1933).

(7) G. E. Pake, J. Townsend, and S. I. Weissman, *Phys. Rev.*, 85, 682 (1952).

(8) J. P. Lloyd and G. E. Pake, *ibid.*, 94, 579 (1954).

(9) S. T. Weissman and T. R. Tuttle, *J. Phys. Chem.*, 61, 28 (1957).

(10) Y. H. Tchao and J. Herve, *C. R. Acad. Sci.*, 248, 3696 (1959).

(11) Y. H. Tchao and J. Herve, *ibid.*, 249, 53 (1959).

(12) W. Müller-Warmuth and P. Parikh, *Z. Naturforsch.*, 15, 86 (1960).

(13) J. J. Windle and A. K. Weiseman, *J. Chem. Phys.*, 39, 1139 (1963).

(14) Z. Luz, B. L. Silver, and C. Eden, *ibid.*, 44, 4421 (1966).

(15) N. T. Rakintzis and G. Stein, *J. Phys. Chem.*, 70, 727 (1966).

(16) J. H. Murib and D. M. Ritter, *J. Amer. Chem. Soc.*, 74, 3394 (1952).

(17) J. C. M. Li and D. M. Ritter, *ibid.*, 75, 5823, 5831 (1953).

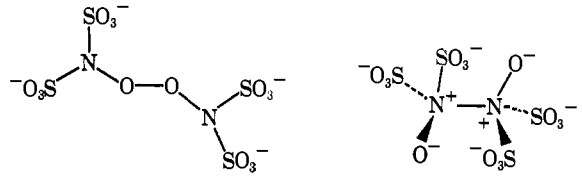
(18) H.-J. Teuber and G. Jellineck, *Naturwissenschaften*, 38, 259 (1951).

(19) (a) L. F. Fieser and M. Fieser, "Reagents for Organic Chemistry," Wiley, New York, N. Y., 1968: Vol. 1, p 940; Vol. 2, p 347; (b) H. Musso, *Angew. Chem. Int. Ed. Engl.*, 2, 723 (1963).

(20) W. Moser and R. A. Howie, *J. Chem. Soc. A*, 3039 (1968).

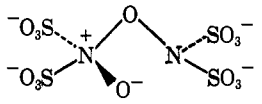
(21) R. A. Howie, L. S. D. Glasser, and W. Moser, *ibid.*, *A*, 3043 (1968).

orange-brown form of **1** shows in its esr spectrum a broad band at 9.3 × 10^5 cps, at a field strength of 3303 G. The yellow-orange monoclinic form does not show an absorption throughout the sweep of the esr spectrometer.[21] For the dimer of **1**, three possible structures based on ir spectra are considered.[22] According to Moser,[20,21] structure A seems to



A

B



C

best accommodate the ir and X-ray data. Of structures B and C, the latter one also was considered as a possibility based on ir evidence.[23] These were rejected by Moser based on a reinterpretation of the ir data and on an X-ray analysis of the two forms of **1**.

3. Chemical Properties

Because of its radical character, **1** is a rather unstable compound. It oxidizes organic compounds, especially phenols, very easily and it is generally very sensitive toward reduction. As a solid, it is reported to be rather unstable.[1,2,4,6,16,17,22-26] In fact, it sometimes undergoes spontaneous decomposition which occasionally results in a violent explosion. Impurities are usually assumed to be the cause for the lack of stability of **1**. Chloride ion or manganese dioxide[25] was thought to be responsible for this instability.[27] However, recent convincing evidence has appeared[20] and shows that the cause for the spontaneous decomposition and general unstable behavior of **1** is due to the presence of nitrite ion. Acidic solutions of **1** are most unstable. The decomposition of **1** is dependent on the hydrogen ion concentration.[2] In addition, nitrous acid propagates decomposition by a chain reaction. Also alkaline solutions with pH values above 10 initiate a rather complicated decomposition process of **1** to yield eventually hydroxylamine trisulfonate.[17]

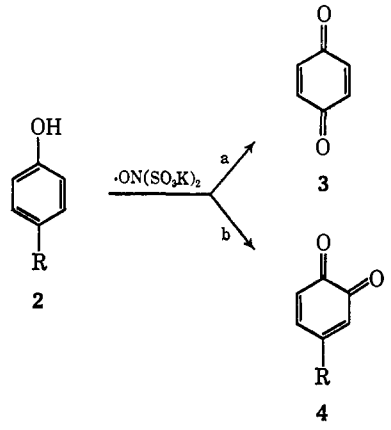
II. Oxidations with Fremy's Radical

A. AROMATIC HYDROXY COMPOUNDS

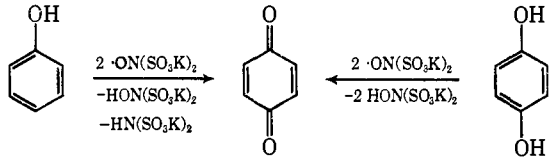
1. Phenols

The oxidation of phenols with **1** represents an excellent synthetic method for the preparation of either *o*- or *p*-benzoquinones, under very mild conditions and usually in good yield.[27-33] The presence (or absence) of substituents on the aromatic ring, para to the hydroxyl group, appears to control which kind of benzoquinone will be formed.

When the position para to the hydroxyl group in **2** is unsubstituted (R = H), *p*-benzoquinones (**3**) are formed (pathway a). If the position para to the hydroxyl group is substituted (R = OR, alkyl), oxidation leads to the formation of *o*-benzoquinones (**4**) (pathway b). One exception has been reported, namely when R = Cl. In this case, the oxidation proceeds, *via* pathway a, to form *p*-benzoquinones with the loss of chlorine.[30,34]



The mechanism of Fremy's radical oxidations has been extensively studied and has been fairly well established in the case of phenols. The overall stoichiometry of the oxidation of phenols has been shown[27] to involve the reaction of 1 equiv of phenol with 2 equiv of **1** to give 1 equiv of benzoquinone, 1 equiv of dipotassium hydroxyimidodisulfate, and 1 equiv of dipotassium imidobissulfate. The oxidation of hydroquinones also results in the formation of benzoquinones,[27] but the stoichiometry is different. For example,[27] 1 equiv of hydroquinone reacts with 2 equiv of **1** to give 1 equiv of benzoquinone and 2 equiv of hydroxyimidodisulfate.

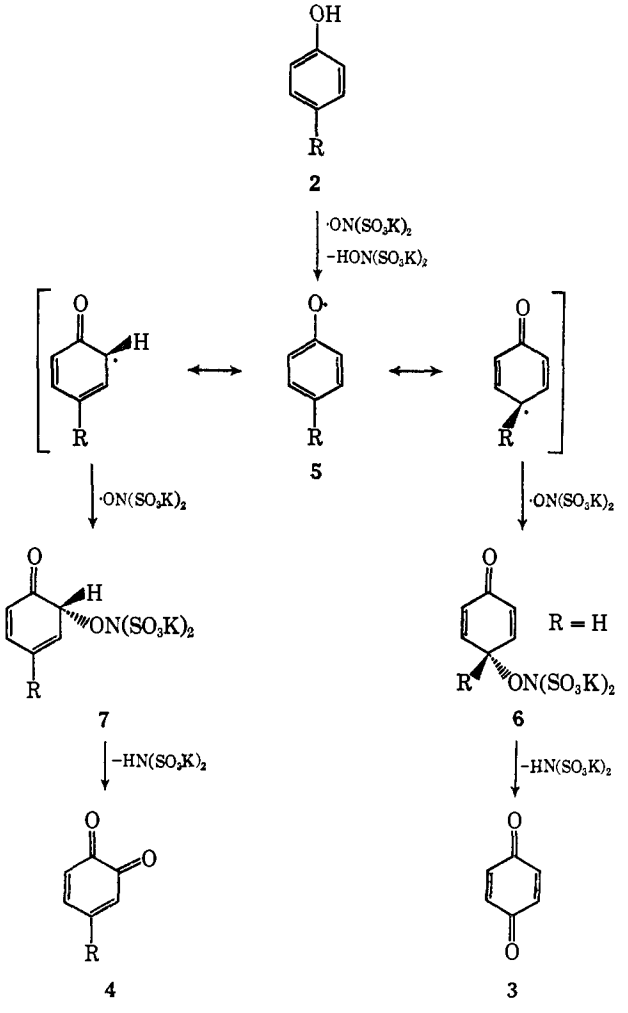


A general mechanistic interpretation, consistent with the observed stoichiometry, has been suggested[27] for Fremy's radical oxidation of phenols and is depicted in Scheme I.

Hydrogen abstraction from **2** by **1** results in the formation of dipotassium hydroxyimidobissulfate and the resonance-stabilized phenoxy radical **5**. This can then react with a second equivalent of **1** to give either of the cyclohexadienone intermediates **6** or **7**, depending on the nature of R, followed by loss of the elements of dipotassium imidobissulfate to give the benzoquinones **3** or **4**.

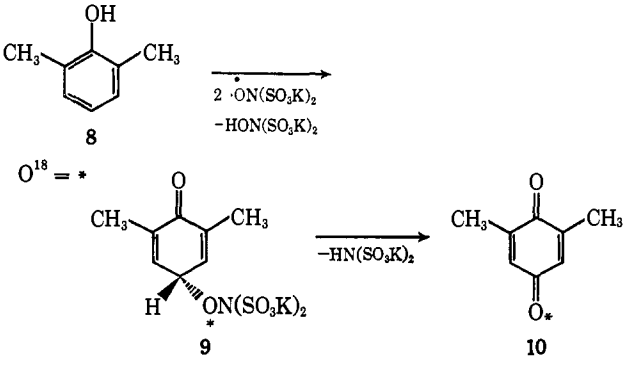
(22) S. Yamada and R. Tsuchida, *Bull. Chem. Soc. Jap.*, 32, 721 (1959).
(23) W. P. Griffith, J. Lewis, and G. Wilkinson, *J. Inorg. Nucl. Chem.*, 7, 38 (1958).
(24) H.-J. Teuber and G. Jellinek, *Ber.*, 85, 92 (1952).
(25) R. P. Singh, *Can. J. Chem.*, 44, 1994 (1966).
(26) C. Salt and M. L. Tomlinson, *Chem. Ind. (London)*, 549 (1961).
(27) H.-J. Teuber and W. Rau, *Chem. Ber.*, 86, 1036 (1953).
(28) H.-J. Teuber and G. Staiger, *ibid.*, 88, 802 (1955).
(29) L. Horner, G.-G. Schmelzer, and B. Thompson, *ibid.*, 93, 1774 (1960).
(30) H.-J. Teuber and O. Glosauer, *ibid.*, 98, 2643 (1965).
(31) E. A. Obolrikova, O. I. Volkova, L. P. Davydova, and G. A. Samokhvalov, *Izobret. Prom. Obstraztsy, Tovarnye Zanki*, 44 (13), 33 (1967); USSR Patent 197,598 (1967); *Chem. Abstr.*, 69, 35749 (1968).
(32) A. V. El'tsov, *J. Org. Chem. USSR*, 33, 1952 (1963).
(33) H.-W. Wanzlick and U. Jahnke, *Chem. Ber.*, 101, 3744 (1968).
(34) H.-J. Teuber, *Angew. Chem.*, 70, 607 (1958).

Scheme I



The intermediacy of cyclohexadienones in Fremy's radical oxidations has been suggested,[35,36] and if this were the case, the new oxygen atom which is incorporated into the quinone moiety should be derived from **1** and not from the solvent. This has been confirmed using ^{18}O-labeled **1**.[37] 2,6-Dimethylphenol (**8**) was oxidized with ^{18}O-labeled **1** (Scheme II). It

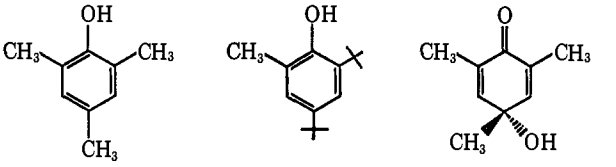
Scheme II



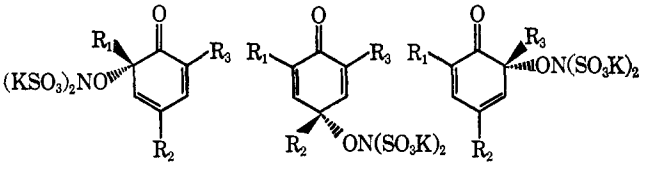
(35) H.-J. Teuber and G. Thaler, *Chem. Ber.*, **92**, 667 (1959).
(36) H.-J. Teuber and H. Gotz, *ibid.*, **89**, 2654 (1956).
(37) H.-J. Teuber, *Angew. Chem., Int. Ed. Engl.*, **4**, 871 (1965).

was observed that 97% of the ^{18}O was incorporated as the new oxygen of the 2,6-dimethyl-1,4-benzoquinone (**10**). Essentially no oxygen was incorporated from the solvent (*e.g.*, ether, alcohol, or acetone) nor was there any exchange of the oxygen with the solvent.

Further support for the intermediacy of cyclohexadienones in Fremy's radical oxidations was obtained from a study[38] of the oxidation of 2,4,6-trialkylphenols. Oxidation of mesitol (**11**) or 4,6-di-*tert*-butyl-2-methylphenol (**12**) with **1** gave colorless solutions whose spectra[38] were found to be very similar to that of 2,4,6-trimethyl-*p*-benzoquinols (**13**,

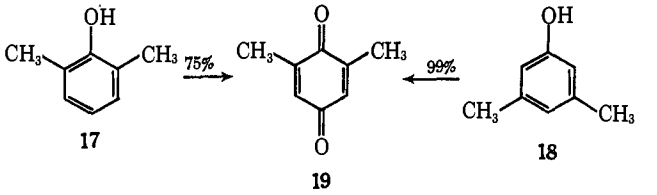


2,5-cyclohexadienone derivative) but differed from that of *o*-benzoquinols (2,4-cyclohexadienone derivatives).[39] Of the products that could be formed, **14–16**, only **15** should be



a, $R_1 = R_2 = R_3 = CH_3$
b, $R_1 = CH_3$; $R_2 = R_3 =$ *tert*-butyl

colorless, whereas **14** and **16** would be yellow like other 2,4-cyclohexadienone derivatives.[39] This indicates that the principal species in solution are the 2,5-dyclohexadienones, although the presence of small amounts of the 2,4-cyclohexadienone isomer could not be excluded. Tables I and II summarize the *o*- and *p*-benzoquinones which have been prepared by Fremy's radical oxidations. It can be seen from Table I that certain phenols, when oxidized by **1**, give rise to the same *p*-benzoquinone. However, the yields of the quinones, from the respective phenols, are significantly different. For example, both **17** and **18** are oxidized to **19**. The formation of **19** from **17** proceeds in 99% yield and from **18** in 75% yield. Two factors appear to affect the extent of product for-

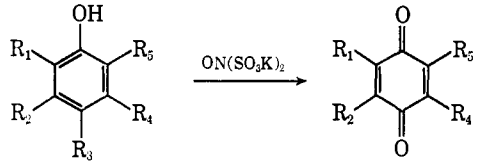


mation: (1) electronic stabilization of the incipient phenoxy radical; and (2) steric requirements connected with the formation of the cyclohexadienone intermediates corresponding to **6** and **7**.

(38) (a) R. Magnusson, *Acta Chem. Scand.*, 18, 759 (1964); (b) *ibid.*, 20, 2211 (1966).
(39) A discussion of the spectroscopic properties of 2,4- and 2,5-cyclohexadienones has appeared: A. J. Waring in "Advances in Alicyclic Chemistry," Vol. 1, H. Hart and G. J. Karabatsos, Ed., Academic Press, Inc., New York, N. Y., 1966, pp 184–193.

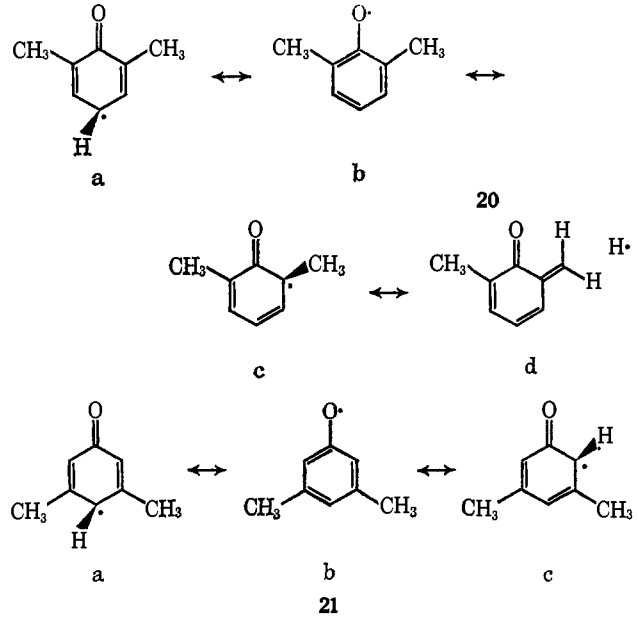
Table I

Oxidation of Phenols with Fremy's Radical and the Formation of *p*-Benzoquinones



R_1	R_2	R_3	R_4	R_5	Mol formula	% yield	Ref
H	H	H	H	H	$C_8H_4O_2$	81	27
CH_3	H	H	H	H	$C_7H_6O_2$	82	27
H	CH_3	H	H	H	$C_7H_6O_2$	63	27
OCH_3	H	H	H	H	$C_7H_6O_3$	90	27
H	OCH_3	H	H	H	$C_7H_6O_3$	56	27
CH_3	CH_3	H	H	H	$C_8H_8O_2$	75	27
CH_3	H	H	H	CH_3	$C_8H_8O_2$	99	27
H	CH_3	H	CH_3	H	$C_8H_8O_2$	75	27
CH_3	H	H	CH_3	H	$C_8H_8O_2$	87.5	27
H	CH_3	Cl	CH_3	H	$C_8H_8O_2$	85–87	30, 34
OCH_3	H	H	H	OCH_3	$C_8H_8O_4$	98.5	27
H	OCH_3	H	OCH_3	H	$C_8H_8O_4$	76	27
OCH_3	H	H	OCH_3	H	$C_8H_8O_4$	99	27
CH_3	CH_3	H	CH_3	H	$C_9H_{10}O_2$	88	27
CH_3	H	H	H	C_2H_5	$C_9H_{10}O_2$	35	27
CH_3	H	H	OCH_3	OCH_3	$C_9H_{10}O_4$	..	31
CH_3	CH_3	H	CH_3	CH_3	$C_{10}H_{12}O_2$	87	27
CH_3	H	H	$CH(CH_3)_2$	H	$C_{10}H_{12}O_2$	98	27
$CH(CH_3)_2$	H	H	CH_3	H	$C_{10}H_{12}O_2$	73	27
C_6H_5	H	H	H	H	$C_{12}H_8O_2$	85	27
C_6H_5	H	H	H	C_6H_5	$C_{18}H_{12}O_2$	89	30

In connection with the first of these factors, radical **20** tends to be more stable than radical **21** because delocalization of the odd electron in **20** can occur adjacent to the methyl groups, as in **20c**, thus making additional stabilization through inductive and/or hyperconjugative involvement of the methyl groups in **20d** possible. In the related structure **21**,



the radical cannot be stabilized through such an involvement by the methyl groups.

Alternatively, formation of the cyclohexadienone intermediate, previously described, from **20a** is sterically more favorable than from **21a**. Consequently, there may be a significant difference in the yield of the *p*-quinone, depending on which phenol is oxidized. Which effect, the electronic stabilization of the radical or the steric effect on the formation of the cyclohexadienone intermediate, is more important in Fremy's radical oxidations has not been quantitatively assessed.

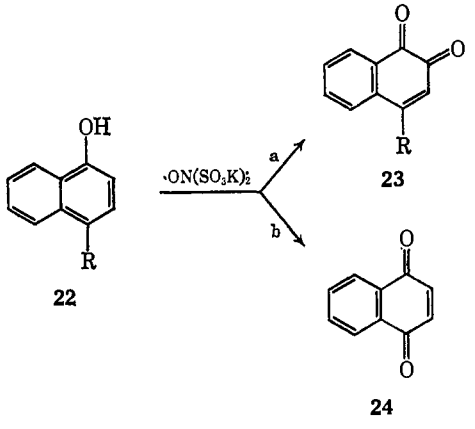
2. Condensed Phenols

Numerous examples of Fremy's radical oxidations of condensed phenols have been reported.[40-48] Most of these studies, however, have dealt with oxidation of α- and β-naphthols.[40,43,44,46]

a. α-Naphthols

α-Naphthols (**22**) are oxidized by **1** to yield either *o*- or *p*-naphthoquinones (**23** and **24**), respectively. In some examples, both **23** and **24** are formed. As in the case of phenols, the formation of **23** and **24** strongly depends on the nature of substituent R at position 4, para to the hydroxyl group.

Oxidation of **22** in which position 4 is unsubstituted (R = H) generally leads to the formation of **24** (path b). 1,2-Naphthoquinones (**23**) will be formed if (a) an alkyl group or aryl group occupies position 4 or (b) a hydroxy group occupies position 2 (path a). When a hydroxy group occupies

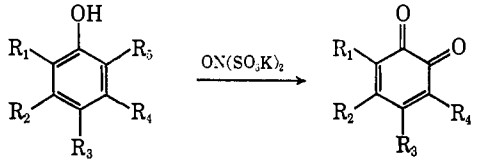


position 5 of α-naphthol, approximately equal amounts of *o*- and *p*-naphthoquinones are formed.[40] This is probably a result of the severe peri interaction[49] between the hydroxy group in the 5 position and the incoming **1** yielding **25**. The steric requirements leading to **26** are considerably less than that for **25**, and thus a substantial amount of the *o*-naphthoquinone is formed.

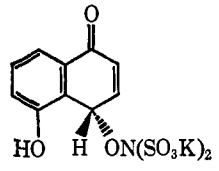
(40) H.-J. Teuber and N. Götz, *Chem. Ber.*, 87, 1236 (1954).
(41) H.-J. Teuber and H. Linder, *ibid.*, 92, 921 (1959).
(42) H.-J. Teuber and H. Linder, *ibid.*, 92, 927 (1959).
(43) H.-J. Teuber and G. Steinmetz, *Angew. Chem.*, 76, 612 (1964); *Angew. Chem. Int. Ed. Engl.*, (1964).
(44) H.-J. Teuber and G. Steinmetz, *Chem. Ber.*, 98, 666 (1965).
(45) H.-J. Teuber and H. Linder, *ibid.*, 92, 932 (1959).
(46) H. Cassebaum, *ibid.*, 90, 2876 (1957).
(47) O. Dann and H. G. Heller, *ibid.*, 93, 2829 (1960).
(48) H.-J. Teuber, *ibid.*, 86, 1495 (1953).
(49) For a discussion of peri interaction in naphthalene derivatives, see V. Balasubramaniyan, *Chem. Rev.*, 66, 567 (1966).

Table II

Oxidation of Phenols with Fremy's Radical and the Formation of *o*-Benzoquinones



R_1	R_2	R_3	R_4	R_5	*Mol formula*	*% yield*	*Re*
H	H	CH_3	H	H	$C_7H_6O_2$	71	28
H	H	OCH_3	H	H	$C_7H_6O_3$	87	28
H	H	$-CH_2-CH_2-$		H	$C_8H_6O_2$	11–12	29
H	H	CH_3	CH_3	H	$C_8H_8O_2$	80–85	28
CH_3	H	CH_3	H	H	$C_8H_8O_2$	75	28
OCH_3	H	CH_3	H	H	$C_8H_8O_3$	68	28
H	CH_3	CH_3	CH_3	H	$C_9H_{10}O_2$	91.5	28
CH_3	H	CH_3	CH_3	H	$C_9H_{10}O_2$	80	28
OCH_3	H	C_2H_5	H	H	$C_9H_{10}O_3$	81	28
OCH_3	H	$CH_2CH=CH_2$	H	H	$C_{10}H_{10}O_3$	70	28
H	H	$C(CH_3)_3$	H	H	$C_{10}H_{12}O_2$	80.5	28
H	CH_3	$C(CH_3)_2$	H	H	$C_{10}H_{12}O_2$	77	28
H	H	$OCH_2C_6H_5$	H	H	$C_{13}H_{10}O_3$	72	28
H	H	$CH_2C(CH_3)_2$ | $(CH_3)_3CCH_2$	H	H	$C_{15}H_{22}O_2$	72	28
CH_3	H	$C(CH_3)_3$	H	$C(CH_3)_3$	$C_{15}H_{22}O_2$	65	38
CH_2COCH_3	H	$C(CH_3)_3$	H	$C(CH_3)_3$	$C_{17}H_{24}O_3$	70	38
$CH_2CHOHCH_3$	H	$C(CH_3)_3$	H	$C(CH_3)_3$	$C_{17}H_{26}O_3$	60	38
$C(CH_3)_3$	H	CH_3	H	$C(CH_3)_3$	$C_{15}H_{22}O_2$	20	38
H	$-O-CH_2CH_2-O-$		H	H	$C_8H_6O_4$	90	32
H	OCH_3	OCH_3	H	H	$C_8H_8O_4$	86	32
H	$-O-CH_2-O-$		H	H	$C_7H_5O_4$	—	32



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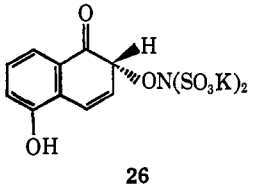
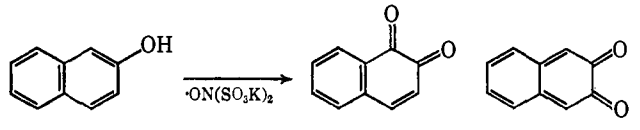


26

In general, whenever a choice between the formation of the two types of naphthoquinones exists in Fremy's radical oxidations, the *p*-naphthoquinone is usually formed. Table III summarizes the oxidation studies of α-naphthols with **1**.

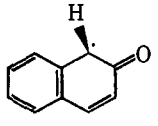
b. β-Naphthols

β-Naphthols are generally oxidized to give *o*-naphthoquinones. For example, **27** is oxidized exclusively to **28**. No **29** is ever formed. **30** and **31** are the radical intermediates which would



27 28 29

lead to **28** and **29**, respectively; radical **30** is more stable than radical **31**, which would lead to **29**, since, in radical **31**,



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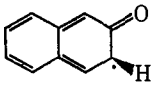
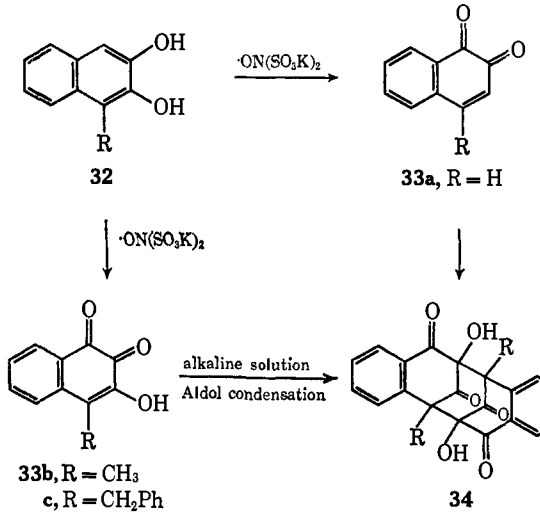


31

the benzenoid character of the condensed ring system has been disrupted. In the case of **30**, however, the benzenoid character of one ring is still maintained. Table IV summarizes the β-naphthols which have been oxidized to *o*-naphthoquinones.

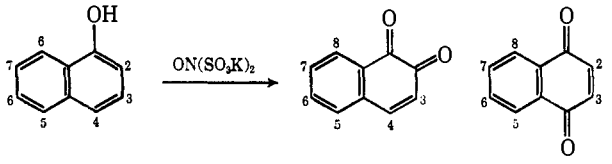
β-Naphthols, when oxidized with **1**, can also lead to dimeric products.[43,44] This is generally a function of the pH of the solution in which the oxidation is carried out and is also a function of the structure of the *o*-naphthoquinone. For example, **32** (R = H) is oxidized under neutral conditions to give



predominantly the dimer **34**. Only a small amount of **33a** (R = H) (see Table IV), the initial oxidation product, is

Table III

Oxidation of α-Naphthols with Fremy's Radical

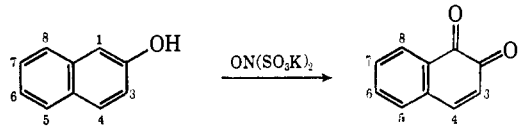


Position of substituent							% yield of quinone			
2	3	4	5	6	7	8	Ortho[b]	Para	Mol formula	Ref
H	H	H	H	H	H	H	..	91	$C_{10}H_6O_2$	40
OH	H	H	H	H	H	H	95	..	$C_{10}H_6O_2$	40
H	H	OH	H	H	H	H	..	95	$C_{10}H_6O_2$	40
H	OH	H	H	H	H	H	..	81	$C_{10}H_6O_2$	40
H	H	H	OH	H	H	H	51	49	$C_{10}H_6O_2$	40
H	H	H	H	OH	H	H	..	91	$C_{10}H_6O_2$	40
H	H	H	H	H	OH	H	..	92	$C_{10}H_6O_2$	40
H	H	H	H	H	H	OH	..	81	$C_{10}H_6O_2$	40
H	H	OCH_3	H	H	H	H	97	..	$C_{11}H_8O_2$	40
OH	OCH_3	H	H	H	H	H	99	..	$C_{11}H_8O_2$	40
H	OH	CH_3	H	H	H	H		6	$C_{11}H_8O_2$	44
H	H	*p*-$MeOC_6H_4$	H	H	OCH_3	H	*	..	$C_{18}H_{14}O_4$[a]	46
H	H	*o*-$MeOC_6H_4$	OMe	H	H	H	*	..	$C_{18}H_{14}O_4$[a]	46
H	H	α-$C_{10}H_7$[c]	H	H	H	H	*	..	$C_{20}H_{12}O_2$[a]	46

[a] Yields were not quoted in the case of these examples. [b] An asterisk indicates the kind of quinone formed. [c] α-Naphthyl.

Table IV

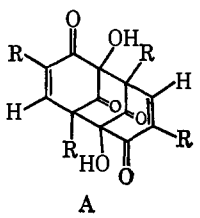
Oxidation of β-Naphthols



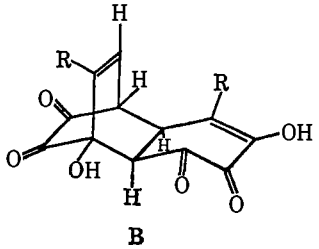
Position of substituent							% yield	Mol formula	Ref
1	3	4	5	6	7	8			
H	H	H	H	H	H	H	91	$C_{10}H_8O_2$	40
H	H	H	H	OH	H	H	92	$C_{10}H_8O_3$	40
H	H	H	H	H	OH	H	>80	$C_{10}H_8O_3$	40
H	OH	H	H	H	H	H	8.5	$C_{10}H_8O_3$	44
H	OCH_3	H	H	H	H	H	99	$C_{11}H_8O_3$	40
H	OH	CH_3	H	H	H	H	66	$C_{11}H_8O_3$	44
H	OH	CH_2Ph	H	H	H	H	62	$C_{17}H_{12}O_3$	44

isolated. When **32** (R = $-CH_3$, $-CH_2Ph$) is oxidized in a slightly alkaline solution, **33b** and **33c** are the predominant products (Table IV) and the dimer **34** is formed to a lesser extent.[50]

(50) The oxidation of certain phenols was also thought to lead to dimers having the structure A. These were subsequently shown to have the structure B. The formation of B was shown to arise from a Diels–Alder dimerization, the *o*-quinone functioning both as a diene and dienophile.



A

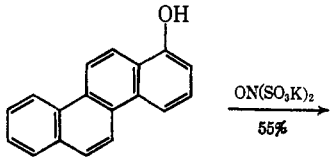


B

R = H, Et, *tert*-Bu

c. Miscellaneous Condensed Phenols

Fremy's radical has been employed in the synthesis of some polycondensed quinones. Chrysenequinone (1,4) (**36**) and dinaphthoanthraquinone (**38**) have been prepared by using **1**[41] for the oxidation of **35**.



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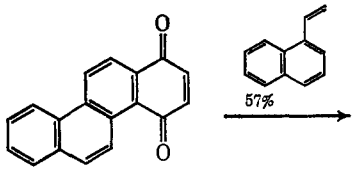

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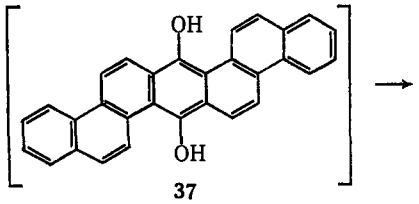

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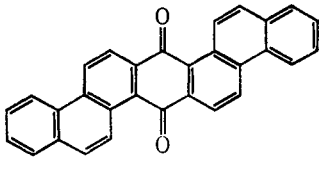
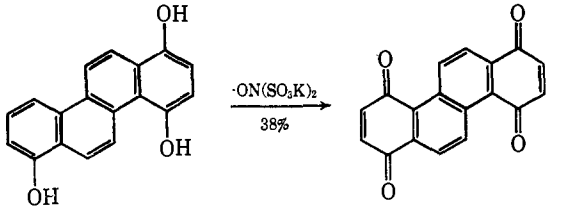


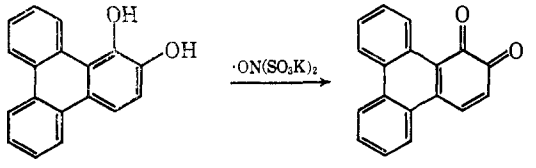
38

Chrysenediquinone (1,4:7,10) (**40**) has been prepared[42] in a low-yield synthetic sequence which employs **1** in the final step of the sequence in which **39** is oxidized to **40**.



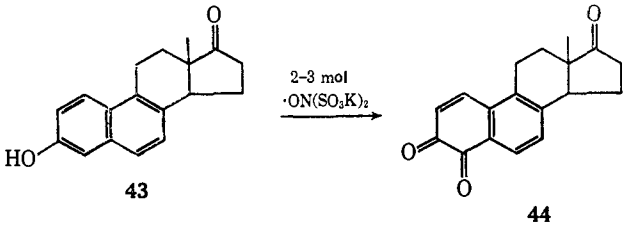
39 **40**

1,2-Dehydroxytriphenylene (**41**) is oxidized[45] to triphenylenequinone (**42**). Also, equilenequinone (**44**) has been pre-



41 **42**

pared[48] in 75% yield from oxidation of equilene (**43**) using **1**.

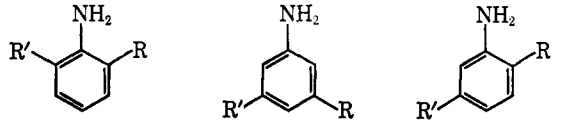


43 **44**

B. AROMATIC AMINES

1. Aniline and Substituted Anilines

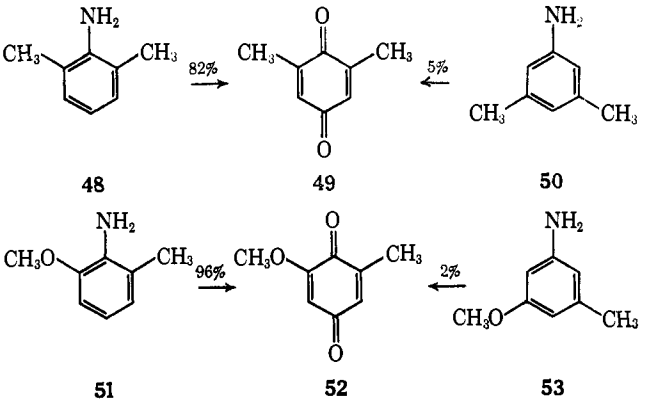
Aniline and substituted anilines react with 2 equiv of potassium nitrosodisulfonate to give *p*-benzoquinones in good yields. The oxidation of disubstituted anilines **45–47** has been examined.[51] When different disubstituted anilines,



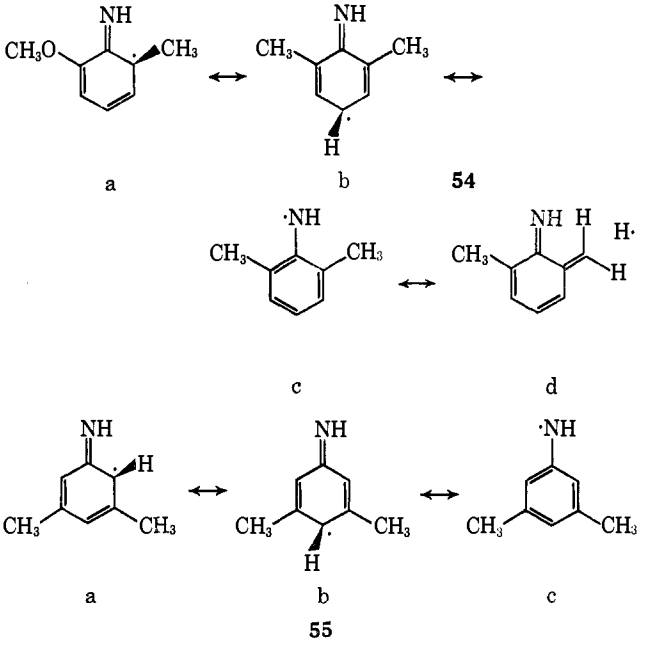
45 **46** **47**

e.g., **45** and **46**, react with **1** to give the same *p*-benzoquinone, it is observed that anilines of type **45** lead to higher yields of quinone than anilines of type **46**. This same effect was also observed for phenols but, in the case of anilines, it appeared to be more pronounced. For example, the processes **48** → **49** and **51** → **52** proceed in higher yield than the processes **50** → **49** and **53** → **52**.

Several reasons might be envisaged as possible explanations for this effect.[28] Introduction of the oxygen para to the amino group in 2,6-disubstituted anilines proceeds *via* a less sterically hindered transition state than in the case of the meta-disubstituted anilines. Alternatively, side reaction of the original amino group with the quinone oxygen may be a process which is sterically hindered when the amino group is flanked by two ortho substituents. Finally, stability of the



incipient radical intermediate will have a controlling effect on quinone formation. For example, radicals of the type **54** are more stable than **55**, presumably owing to added stabilization from hyperconjugative interaction involving the methyl group as shown in **54d**.



Disubstituted anilines of type **47** also yield *p*-quinones.[51] The yields in the case of **56** and **57** are excellent. When the ethoxy group is replaced by a methoxy group, a decrease in yield is observed. When two methoxy groups are the substituents, an excellent yield of the corresponding *p*-quinone (**63**) is obtained.

Trisubstituted anilines also yield *p*-quinones in fair to excellent yields. Examples have been reported[51] where cleavage of methyl and methoxy groups occurs. Cleavage of a methyl group has been found to be more facile than cleavage of a methoxy group, although both processes occur fairly readily (**64, 65** → **49**). The *p*-quinones obtained in the oxidation of di- and trisubstituted anilines are summarized in Table V.

A systematic study of the mechanism of oxidation of anilines has not been reported. However, a mechanistic interpretation, consistent with the observed stoichiometry, is shown in Scheme III.

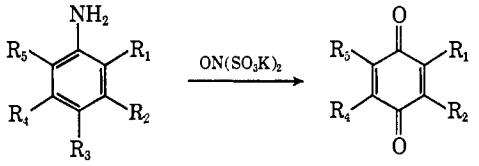
Isolation of quinone imines[52] from these oxidations is consistent with the intermediacy of **68**, which is subsequently

(51) H.-J. Teuber and M. Hasselbach, *Chem. Ber.*, 92, 674 (1959).

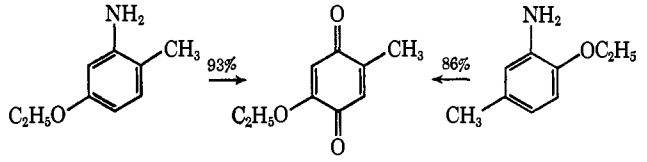
(52) L. Horner and K. Sturm, *ibid.*, 88, 329 (1955).

Table V

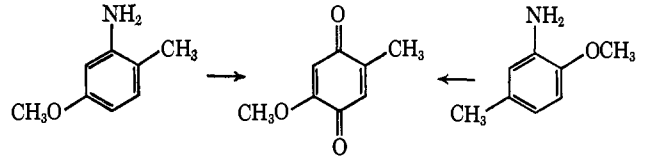
Oxidation of Primary Aromatic Amines with Fremy's Radical and the Formation of *p*-Benzoquinones



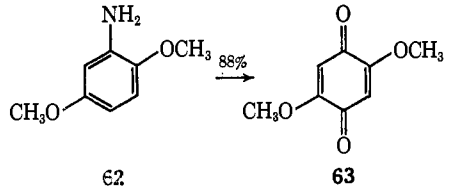
R_1	R_2	R_3	R_4	R_5	% yield	Mol formula	Ref
CH_3	H	H	H	CH_3	82	$C_8H_8O_2$	51
CH_3	H	H	CH_3	H	1	$C_8H_8O_2$	51
H	CH_3	H	CH_3	H	5	$C_8H_8O_2$	51
CH_3	H	OCH_3	H	CH_3	75	$C_8H_8O_2$	51
CH_3	H	CH_3	H	CH_3	95	$C_8H_8O_2$	51
CH_3	H	H	H	OCH_3	96	$C_8H_8O_3$	51
H	CH_3	H	OCH_3	H	2	$C_8H_8O_3$	51
CH_3	H	H	OCH_3	H	37	$C_8H_8O_3$	51
OCH_3	H	H	CH_3	H	76	$C_8H_8O_3$	51
CH_3	H	CH_3	H	OCH_3	49	$C_8H_8O_3$	51
OCH_3	H	H	OCH_3	H	88	$C_8H_8O_4$	51
CH_3	H	H	OC_2H_5	H	93	$C_9H_{10}O_3$	51
OC_2H_5	H	H	CH_3	H	86	$C_9H_{10}O_3$	51
CH_3	OCH_3	H	CH_3	H	8	$C_9H_{10}O_3$	51
CH_3	OCH_3	H	H	OCH_3	85	$C_9H_{10}O_4$	51
OCH_3	OCH_3	H	H	OCH_3	87	$C_9H_{10}O_5$	51



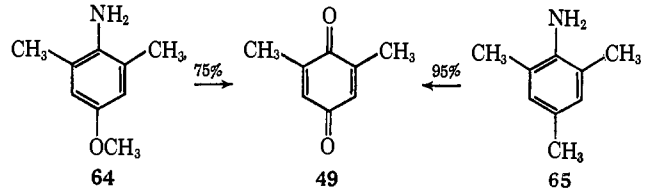
56 58 57



59 61 60



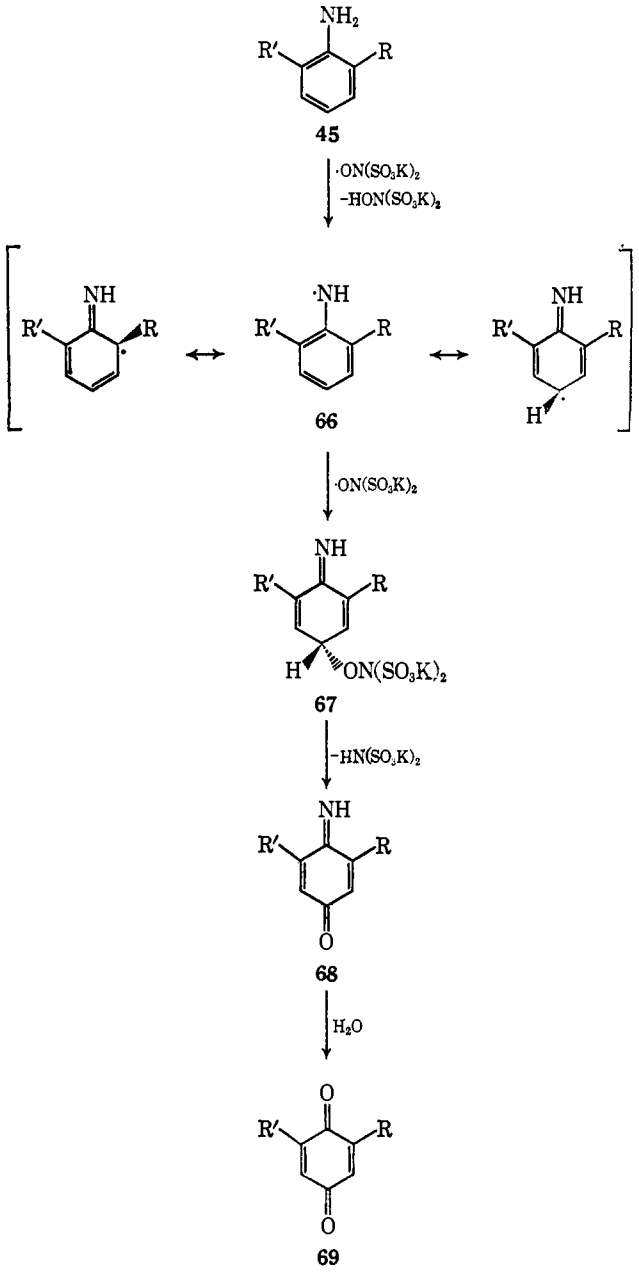
62 63



64 49 65

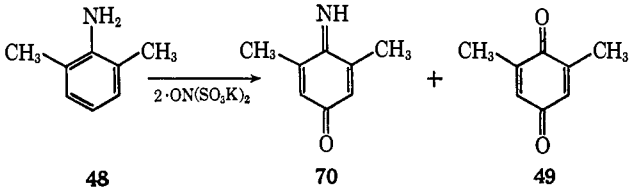
hydrolyzed in the aqueous media in which the reaction is carried out. With the use of labeled **1** and 2,6-dimethylaniline (**48**) it should be relatively easy to test the above mechanism in a manner previously described for phenols.[58]

Scheme III



45 66 67 68 69

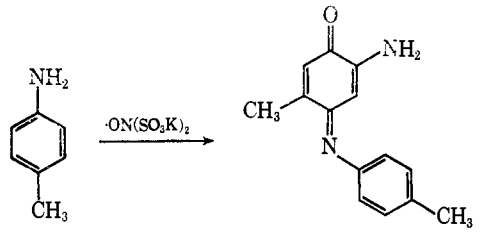
Quinone imines have been isolated in the reaction of primary aromatic amines with 2 mol of **1**.[52]



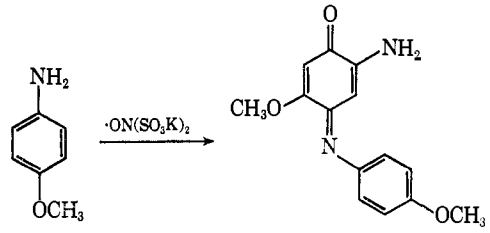
48 70 49

If the position *para* to the amino group is occupied by an alkyl or alkoxy group, substituted quinone anils are frequently formed.[52-54]

(53) H.-J. Teuber and G. Jellinck, *Chem. Ber.*, 87, 1841 (1964).
(54) A. G. Holmes-Seidle and B. C. Saunders, *Chem. Ind. (London)*, 164 (1959).

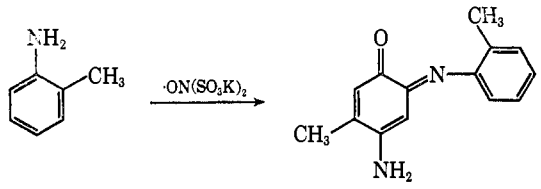


71 72

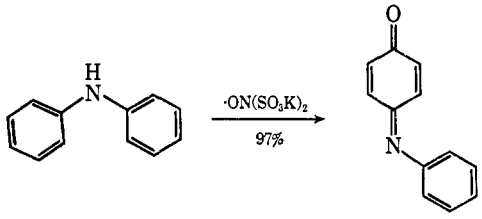


73 74

It was found that optimum anil formation depends on the presence of a para substituent in the amine.[55] Treatment of *o*-toluidine with **1** gave a poor yield of 5-amino-4-methyl-*o*-benzoquinone 1-(2-methylanil) (**76**). Quinone anils which



75 76

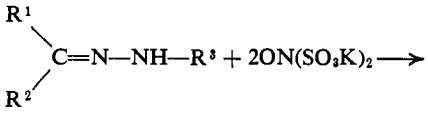


77 78

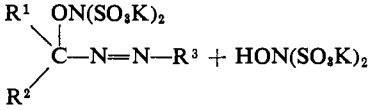
have been obtained by oxidation of aromatic amine with **1** are summarized in Table VI.

2. Phenylhydrazones

Phenylhydrazones (**79**, R^1 = H, alkyl, aryl; R^2 = alkyl, aryl; R^3 = aryl) have been reported[56] to react with **1** yielding



79



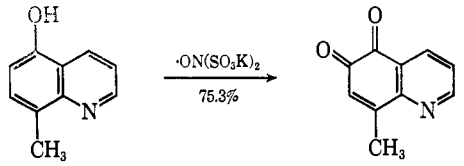
80

azo compounds **80**. In this manner the phenylhydrazones of furfural, cinnamaldehyde, salicylaldehyde, *o*-chlorobenzaldehyde, *o*-, *m*-, and *p*-nitrobenzaldehyde, acetone, benzophenone, acetophenone, isobutyraldehyde, cyclohexanone, and cyclopentanone were oxidized by **1**. The substituent in the hydrazone group can also be varied (2,3-, 2,4-, or 2,5-$(CH_3)_2C_6H_3$, *o*-ClC_6H_4, *p*-$NO_2C_6H_4$, or *p*-$CH_3C_6H_4$). It was found that an *o*-nitrophenyl, 2,4-dinitrophenyl, or benzenesulfonyl substituent in the hydrazone group prevents the reaction as does replacement of the hydrogen attached to nitrogen. Semicarbazones also do not react with **1**.

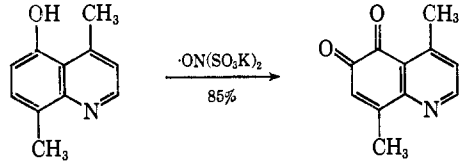
3. Condensed Heterocyclic Systems

a. Quinolines

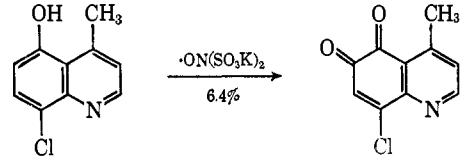
5-Hydroxyquinolines have been oxidized by **1** to the corresponding 5,6-quinones.[57] The presence of *o*-quinone structure



81 82

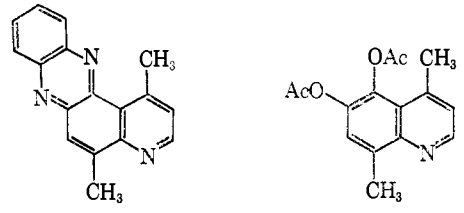


83 84



85 86

was demonstrated by treatment with *o*-phenylenediamine to form pyridophenazines of type **87**, and by reduction–acetylation to form diacetates of type **88**.

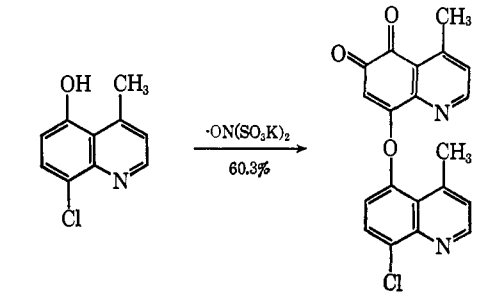


87 88

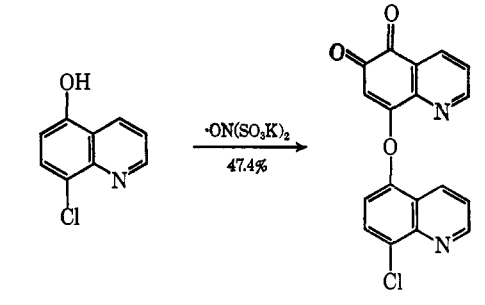
When the oxidation was performed under more acidic conditions (pH 4.5–4.7), dimer formation was observed to occur with chlorinated quinolines (**85, 90**). Mechanistically, dimer formation is postulated to occur in these cases by initial formation of the normal *o*-quinone, followed by a reaction involving addition of a second molecule of the hydroxyquinoline **85** to the *o*-quinone with subsequent elimination of chloride ion.

Hydroxyquinolines, having a free 8 position, have been oxidized by **1** to 7,8-dioxoquinolines (**93** and **95**).[58]

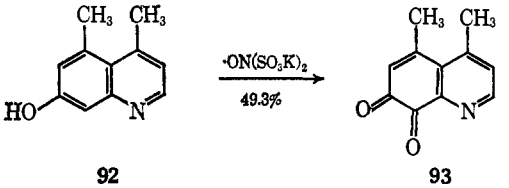
(55) H.-J. Teuber and G. Staiger, *Chem. Ber.*, 87, 1251 (1954).
(56) H.-J. Teuber and K. H. Dietz, *Angew. Chem., Int. Ed. Engl.*, 5, 1049 (1966).
(57) H.-J. Teuber and S. Benz, *Chem. Ber.*, 100, 2918 (1967).
(58) H.-J. Teuber and S. Benz, *ibid.*, 100, 2077 (1967).



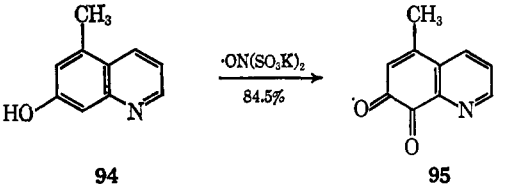
85 89



90 91



92 93



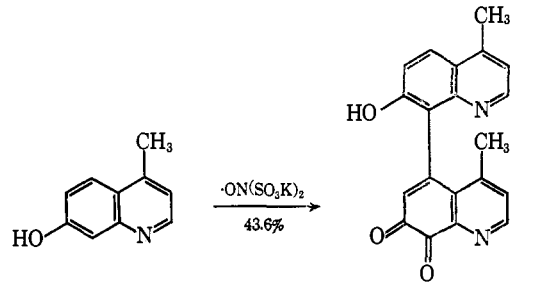
94 95

In acidic solution, quinolines, with a free 5 position, add to the starting phenol to give the nucleus–nucleus linked quinones **97, 99,** and **101** instead of the ether-linked dimers as was observed with the 5-hydroxyquinolines **85** and **90**. Under neutral conditions, oxidation gave quinones with an ether linkage (**102** and **103**).[56,57]

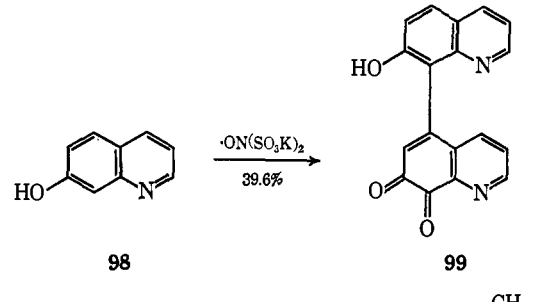
There has been no report of the oxidation of a hydroxyquinoline where the hydroxy group was a substituent of the same ring containing the heteroatom. Potentially, oxidation of this type of hydroxyquinoline could give rise to compounds of types **104** and **105**. Type **105** quinones might be obtainable only from 4-substituted 3-hydroxyquinolines. The oxidation to **105** of hydroxyquinolines possibly might be complicated by the occurrence of the well-known 9-hydroxyquinoline–γ-carbostyril tautomerism.

b. Indoles

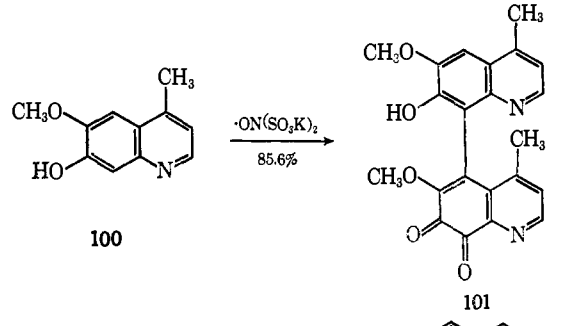
i. Ring Closures. Indole ring closures have been observed[59] in the oxidation of monohydroxyphenethylamine derivatives with **1**. When the oxidation was carried out under neutral conditions (pH 7), the corresponding 4,5-indolequinone was obtained.



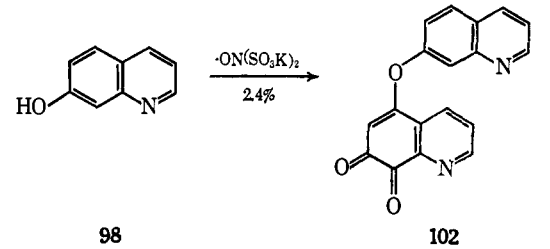
96 97



98 99



100 101



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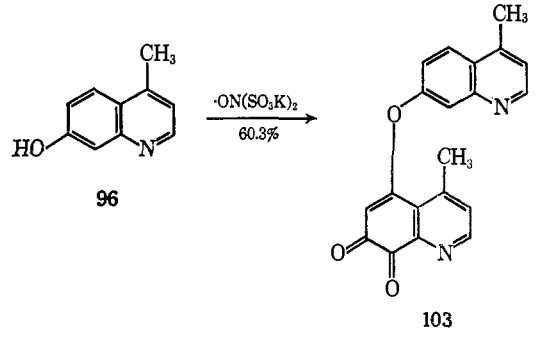
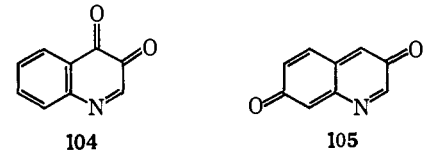


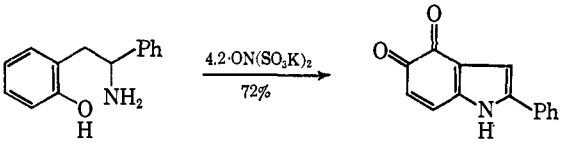
96 103



104 105

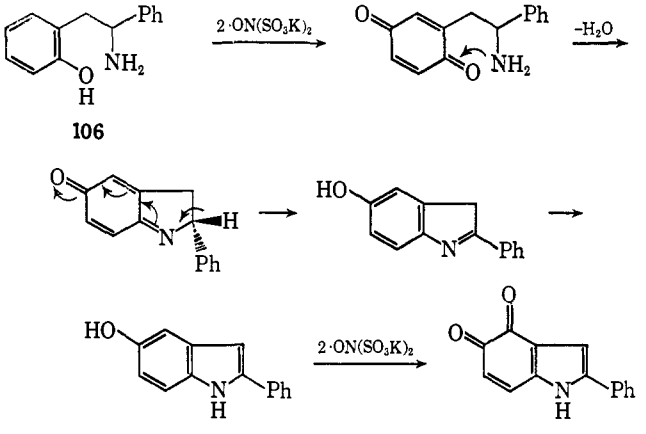
A possible mechanism for the formation of **107** from **106**, consistent with the observed stoichiometry, involves initial oxidation of **106** to the *p*-quinone, condensation, and two

(59) H.-J. Teuber and O. Glosauer, *Chem. Ber.*, 98, 2648 (1965).



106 107

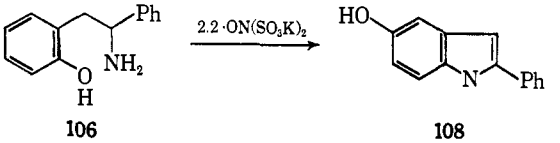
prototropic shifts yielding **108**, followed by normal oxidation with **1** to give **107**.



106

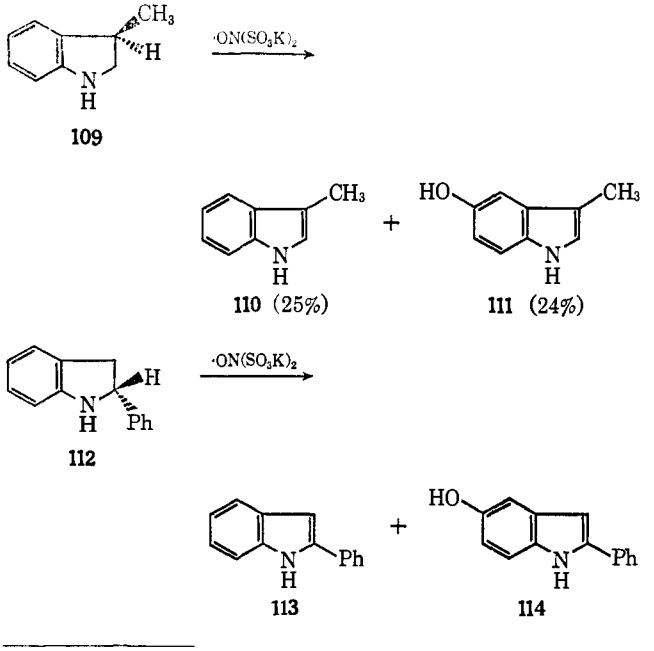
108 107

Oxidation of the same substrate under acidic conditions yielded the corresponding 5-hydroxyindole **108**, which seems to confirm this mechanism.



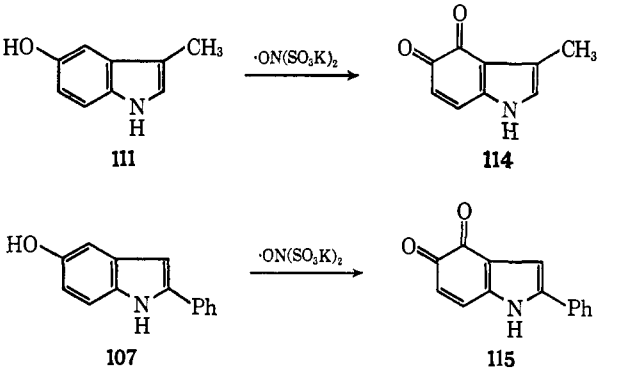
106 108

ii. Dehydrogenation of Indole Derivatives. Dihydroindoles have been successfully dehydrogenated when treated with **1** to give the corresponding indoles. In the two examples reported,[60] the 5-hydroxyindole analog was also isolated. This is a result of further oxidation of the indole, which is initially formed.

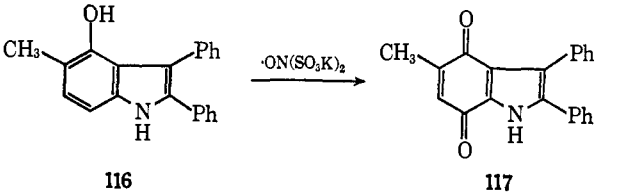


(60) H.-J. Teuber and G. Staiger, *Chem. Ber.*, 89, 489 (1956).

iii. Quinone Formation. Indole quinones have been obtained in excellent yields by oxidation with **1** of the corresponding 5-hydroxyindoles.[60] In the two examples reported, the 4,5-quinone was obtained from the corresponding 5-hydroxyindoles.

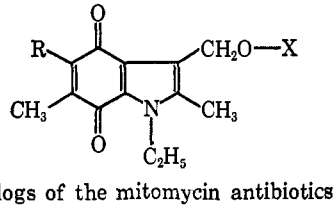


One example of the oxidation of a 4-hydroxyindole, with an occupied 5 position, has been reported.[61] The yield of the 4,7-quinone, which was obtained, was not indicated.



116 117

Recently, the synthesis of analogs of the mitomycin antibiotics, having the indole quinone nucleus present, has been reported.[62-68]

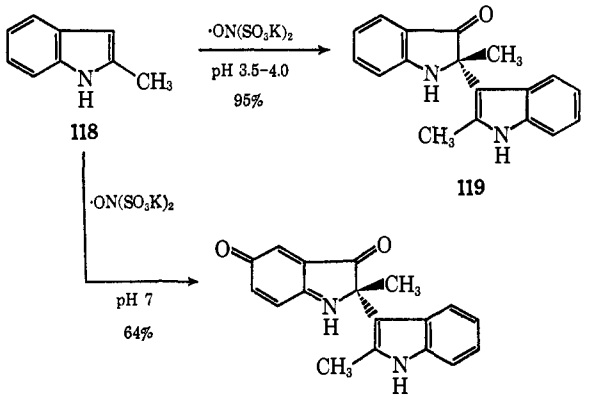


analogs of the mitomycin antibiotics
R = H, CH_3, OCH_3; X = H, $CONHCH_3$

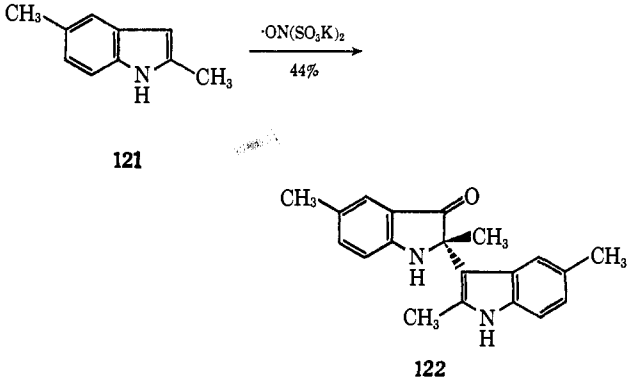
The quinones analogous to **114**, **115**, and **117** were synthesized from the 4- or 5-hydroxyindole by reactions with **1**.

iv. Indoxyl Derivatives. Treatment of 2-methylindole (**118**) with **1** at pH 3.5–4.0 yielded the indoxyl **119** in excellent yield.[69] Under neutral conditions (pH 7), **118** was oxidized to **120** on treatment with **1**.

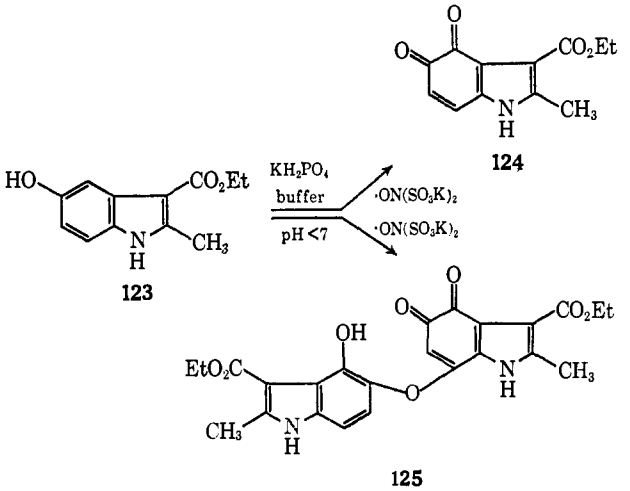
(61) H.-J. Teuber and G. Staiger, *ibid.*, 92, 2385 (1959).
(62) W. A. Remers, P. M. James, and M. J. Weiss, *J. Org. Chem.*, 28, 1169 (1963).
(63) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Amer. Chem. Soc.*, 86, 3877 (1964).
(64) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *ibid.*, 86, 3879 (1964).
(65) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Org. Chem.*, 30, 2897 (1965).
(66) W. A. Remers, R. H. Roth, and M. J. Weiss, *ibid.*, 30, 4381 (1965).
(67) W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, 88, 804 (1966).
(68) P. H. Roth, W. A. Remers, and M. J. Weiss, *J. Org. Chem.*, 31, 1012 (1966).
(69) H.-J. Teuber and G. Staiger, *Chem. Ber.*, 88, 1066 (1955).



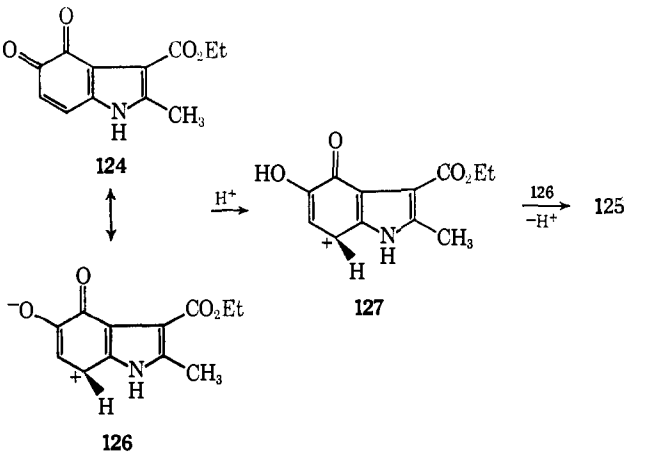
Reaction of 2,5-dimethylindole (**121**) with **1** in a buffered solution yielded 2,5-dimethyl-2-(2,5-dimethyl-3-indolyl)indoxyl (**122**).



v. Carbethoxy Indoloquinones. 3-Carbethoxy-5-hydroxyindoles are converted by **1** to the corresponding indole-4,5-quinones in excellent yields.[70] When the oxidation was carried out in a buffered (KH_2PO_4) mixture of acetone–acetic acid, **123** yielded **124**. When **123** was oxidized under more acidic conditions, the dimeric species **125** was isolated. A possible mechanism for formation of the dimeric species was suggested.

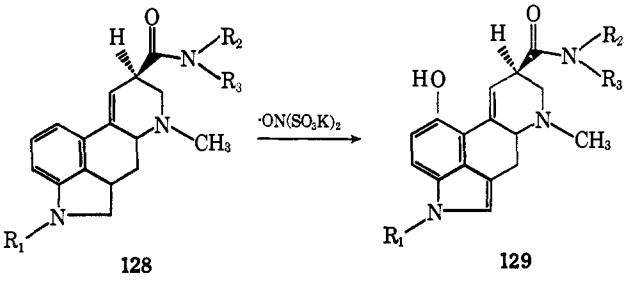


Under strongly acidic conditions, the following process is considered to take place.

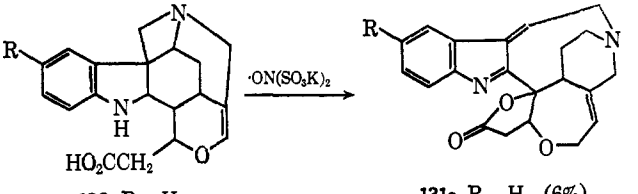


The 3-carbethoxy-4,5-indolequinones which have been synthesized are summarized in Table VII.

vi. Lysergic Acid Derivatives. The dehydrogenation–hydroxylation of 2,3-dihydrolysergic acid amides (**128**) to 12-hydroxylysergic acid moieties (**129**) has been effected using **1**. Table VIII summarized the type **128** compounds which have been oxidized.



vii. Isostrychnic Acid. Oxidation of isostrychnic acid (**130**) with **1** gave rise to the *lactone base* **131a** as well as the hydroxylated lactone base **131b**.[72]



c. Carbazole

Hexahydrocarbazole derivatives also have been dehydrogenated to the tetrahydrocarbazole derivative in fair yields by **1**.[55,60] As indicated below, on one of the examples, quinone formation was reported (**134**),[61] while in another case hydroxylation to **137** was observed to take place.[55]

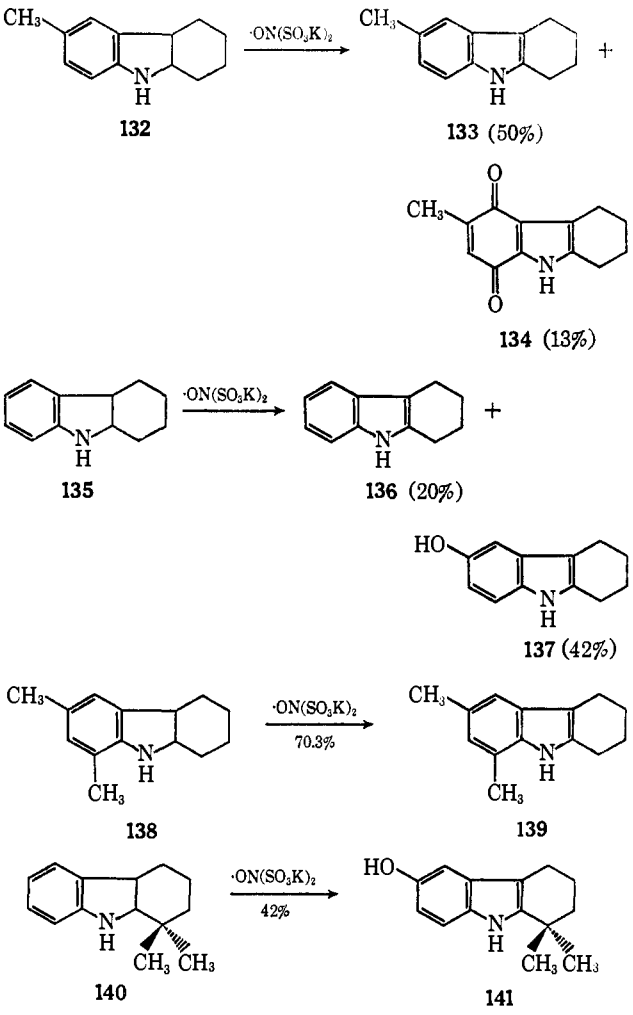
In one example,[55] it was reported that the dehydrogenated–hydroxylated compound was the only material isolated and identified (**141**).

Oxidation of **142** yielded the tetrahydrohydroxylated compound **143** as well as a small amount of the quinone **144**.[60] The yield of **144** could be increased to 63% by oxidation of **142** in the presence of potassium hydrogen phthalate buffer.[55]

(70) H.-J. Teuber and G. Thaler, *Chem. Ber.*, **91**, 2253 (1958).

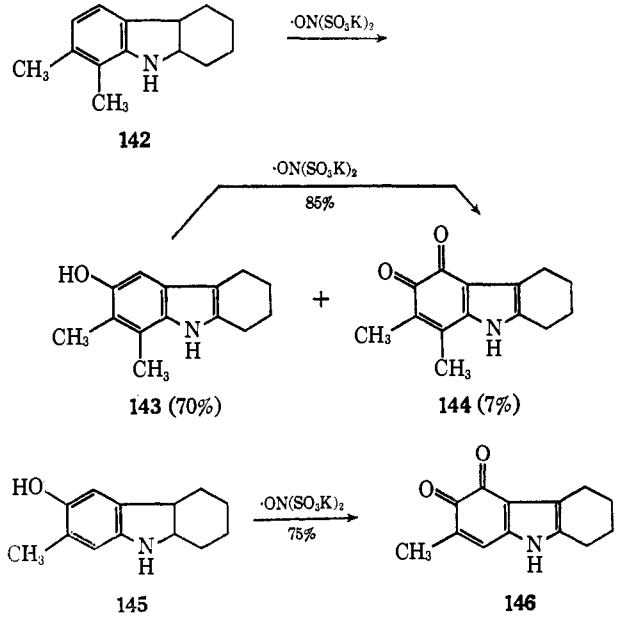
(71) P. A. Stadler, A. J. Frey, F. Troxler, and A. Hofmann, *Helv. Chem. Acta*, **47**, 756 (1964).

(72) H.-J. Teuber and E. Fahrbach, *Chem. Ber.*, **91**, 713 (1968).

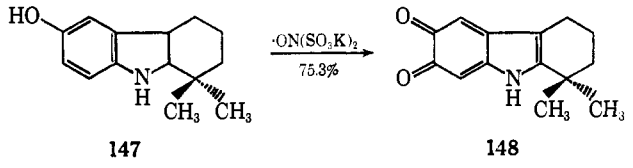


An excellent yield of **144** was obtained on oxidation of **143** by **1**.[56]

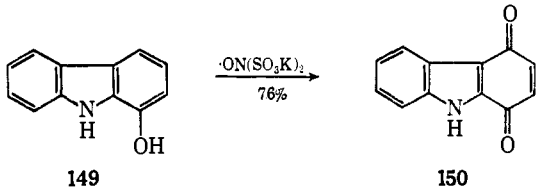
In a similar fashion, oxidation of **145** gave a good yield of 5,6-quinone **146**.[55]



Oxidation of the hydroxylated tetrahydrocarbazole derivative **147** yielded the 6,7-quinone **148** in good yield.[60]



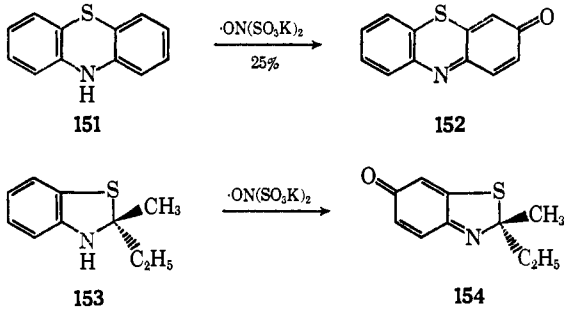
Oxidation of 1-hydroxycarbazole (**149**) yielded 1,4-carbazolequinone (**150**).[55]



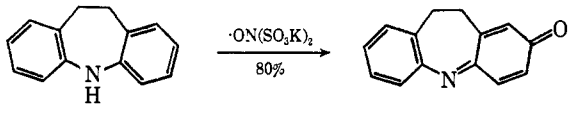
d. Heterocyclic Iminoquinones

A variety of heterocyclic iminoquinones have been obtained on treatment of the corresponding heterocyclic amine with **1**.

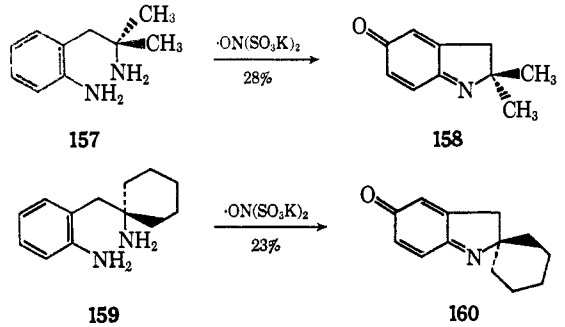
Phenothiazine (**151**) has been oxidized to phenothiazone (**152**), and a benzothiazoline (**153**) has been oxidized[73a] to the corresponding benzothiazolone (**154**).



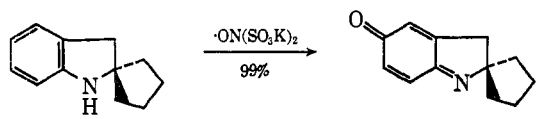
o,o'-Iminobibenzyl (**155**) has been oxidized[73b] by **1** in excellent yield to the corresponding *p*-iminoquinone **156**.



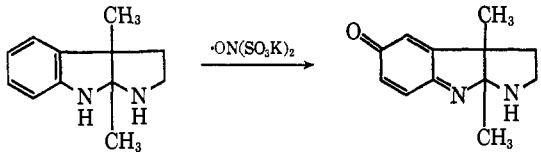
Suitably substituted analogs of *o*-aminophenethylamine were oxidized by **1** with cyclization to the indoline *p*-quinone imides.[74] Since the α position is blocked by two methyl groups or is spiranoid, rearrangement to the corresponding 5-hydroxyindoles does not take place. Two other indoline *p*-quinone imide types were obtained in excellent yields by oxidizing the corresponding indoline derivative.



(73) (a) H.-J. Teuber and H. Waider, *Chem. Ber.*, 91, 2341 (1958); (b) H.-J. Teuber and W. Schmidtke, *ibid.*, 93, 1257 (1960).
(74) H.-J. Teuber and O. Glosauer, *ibid.*, 98, 2939 (1965).



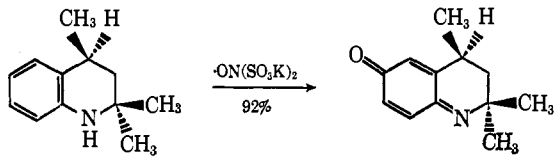
161 162



163 164

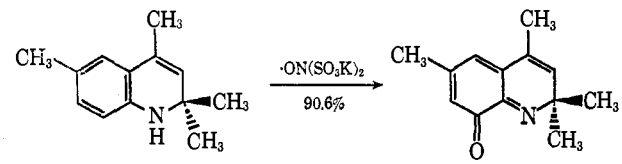
A variety of substituted 1,2-dihydroquinolines, unsubstituted in the 6 position, have been oxidized to corresponding 6-quinolones[74] in good to excellent yields. These compounds are listed in Table IX.

A 1,2,3,4-tetrahydroquinoline has also been oxidized to the corresponding quinolone.[74]

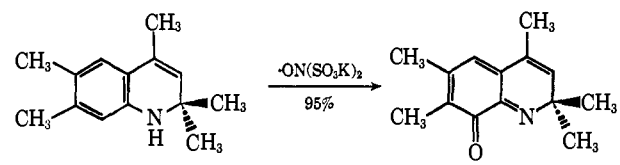


165 166

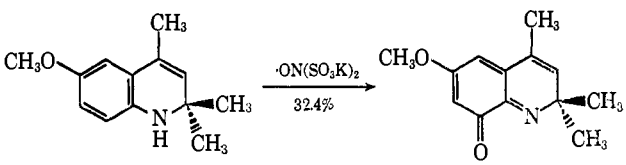
When the 6 position is substituted in a 1,2-dihydroquinoline, oxidation to the corresponding 8-quinolone is observed. Three examples have been reported.[74]



167 168



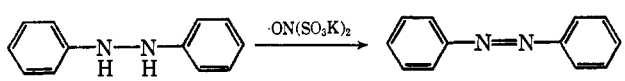
169 170



171 172

C. MISCELLANEOUS REACTIONS OF FREMY'S RADICAL

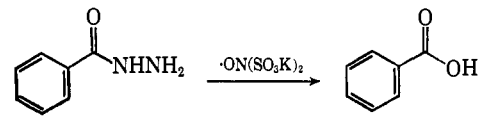
Hydrazobenzene (**173**) is dehydrogenated by **1** to give a 73% yield of azobenzene **174**.[75]



173 174

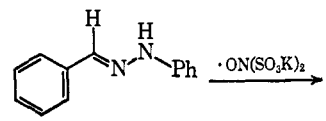
Treatment of benzyhydrazide with **1** yields benzoic acid.[68]

(75) H.-J. Teuber and G. Jellinck, *Chem. Ber.*, 85, 95 (1952).

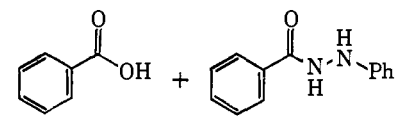


175 176

Two products were isolated in the reaction of **1** with the phenylhydrazone of benzaldehyde.[75]



177



176 (7%) 178 (15.5%)

The overall course of the reaction of hydroxylamine with **1** was determined to be the following.[76]

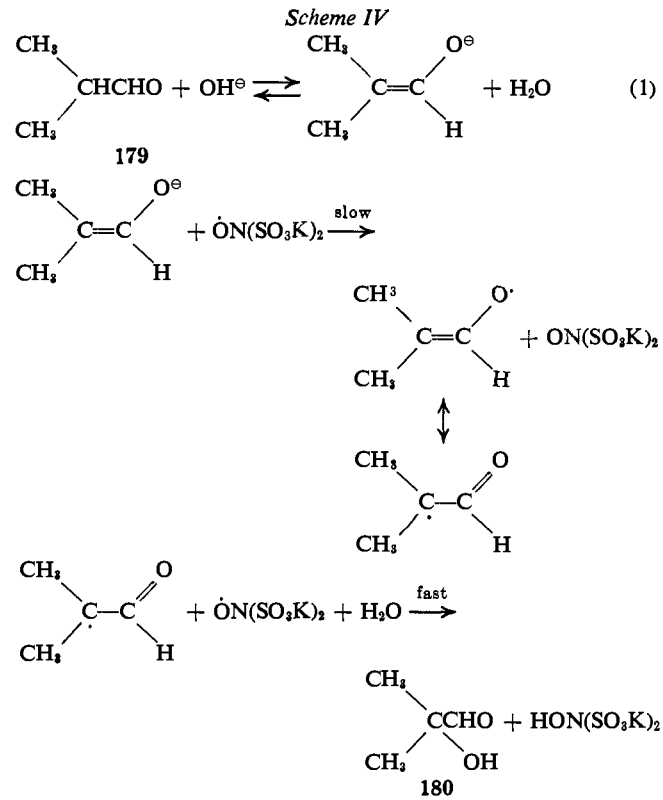
$$2NH_2OH + 4(KSO_3)_2NO \longrightarrow N_2O + 4(KSO_3)_2NOH + H_2O$$

Nitrogen is formed on treatment of hydrazine with **1** according to the following stoichiometric equation.[77]

$$4ON(SO_3K)_2 + N_2H_4 \longrightarrow 4HON(SO_3K)_2 + N_2$$

Certain active methylene compounds have been oxidized with **1**. Isobutyraldehyde (**179**) is oxidized under alkaline conditions to give α-hydroxyisobutyraldehyde (**180**).[78] The mechanism, shown in Scheme IV, involves oxidation of the enolate anion of isobutyraldehyde.

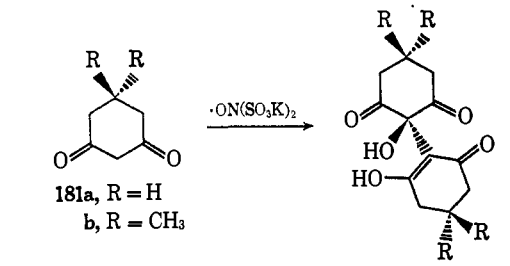
Scheme IV



(1)

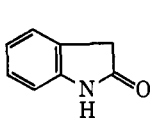
(76) H. Gahlen and G. Dase, *Z. Anorg. Allgem. Chem.*, 275, 327 (1954).
(77) H. Gehlen, E. Elchlepp, and J. Armak, *ibid.*, 274, 293 (1953).
(78) G. D. Allen and W. A. Waters, *J. Chem. Soc.*, 1132 (1956).

Dihydroresorcinol (**181a**) and dimedone (**181b**) are oxidized with **1** to give the dimers **182**.[79] Oxindole (**183**) is oxidized to **184**, which gives isoindigo on dehydration. 4,6-Dimethyl-

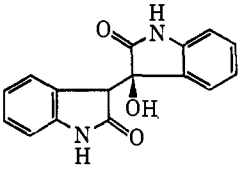


181a, R = H
b, R = CH_3

182a, R = H
b, R = CH_3



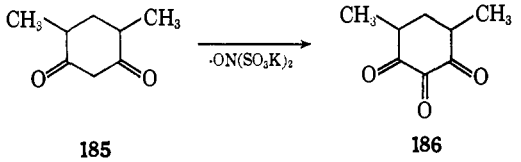
183



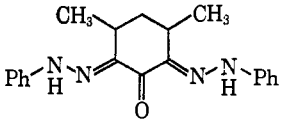
184

1,3-cyclohexanedione (**185**) is oxidized by **1** to give **186** which is isolated as the bisphenylhydrazone **187**.

The aldol condensation between **185** and **186** to give the dimer analogous to **183** does not occur.



185 **186**



187

Finally, benzaldehyde has been oxidized to *o*-hydroxybenzophenone in 72% yield.[80]

D. PREPARATION OF FREMY'S RADICAL

Though **1** is commercially available, it still seems to be not only advantageous but advisable to prepare it freshly before use. Practically all procedures for preparing **1** involve an oxidation of hydroxylaminedisulfonate, $HON(SO_3K)_2$, in alkaline solutions. This compound is easily prepared by the reaction between bisulfite and nitrite ions.

$$NaNO_2 + 2NaHSO_3 \longrightarrow HON(SO_3Na)_2 + NaOH$$

Fremy[1] used PbO_2 as an oxidizing agent. Raschig[2] reported the use of MnO_4^-. Other reagents such as ozone also were used to bring about oxidation of the hydroxylaminedisulfonate.

Raschig[2] gives a summary of all the early preparations of **1**, whereas Moser and Howie[20] list the more recent developments concerning the preparation of **1**. These authors also provide a procedure which seems to be the most satisfactory one introduced so far and which is given below.

1. Preparation of Fremy's Salt

Sodium nitrite (5 *M*, 100 ml) is placed in a 1-l. beaker and cooled in an ice bath. Chopped ice (200 g) is added and the solution stirred steadily during the addition of fresh sodium bisulfite solution (100 ml, 35% w/v), followed by glacial acetic acid (20 ml). Reaction is complete in 2–3 min, as shown by the momentary darkening in color of the reaction mixture and by its failure to decolorize iodine solution. After addition of concentrated ammonia solution (25 ml, sp gr 0.88), the mixture is again cooled in an ice bath, and fresh ice added whenever necessary to keep some present in the reaction mixture throughout the next stage. Ice-cold 0.2 *M* potassium permanganate (400 ml) is now added dropwise with continued stirring, during *ca.* 1 hr.

The precipitated manganese dioxide is removed by gravity filtration (Whatman No. 5, 24 cm), using two or more funnels in parallel to reduce the time required. The filtrate is allowed to come to room temperature as filtration proceeds, but any unfiltered suspension is kept in an ice bath.

A portion of the filtrate (10–15 ml) is treated with an equal volume of saturated potassium chloride solution to precipitate some Fremy's salt for seeding the main batch. The bulk of the filtrate is stirred steadily, while saturated potassium chloride solution (250 ml) is added dropwise over a period of about 45 min. Small portions of the previously prepared suspension are added from time to time during this period until the solid persists in the bulk solution. Precipitation is completed by stirring the bulk solution cooled in ice for a further 45 min.

The orange solid is collected on a Büchner funnel but is not sucked dry. It is washed with ammoniacal saturated potassium chloride solution (containing *ca.* 5% v/v 0.88 ammonium hydroxide), twice with ammoniacal methanol (containing *ca.* 5% v/v 0.88 ammonium hydroxide), and finally with acetone. Only after the whole washing process is all the liquid sucked away, but even then air is not drawn through. The solid is spread on a watch glass and the acetone allowed to evaporate for 10–15 min. Finally, the orange crystals are stored in a desiccator over calcium oxide, in the presence of ammonium carbonate in a separate dish to provide an ammoniacal atmosphere. Under these conditions even this relatively crude material is stable for several months (crude yield, based on bisulfite, 81–82%).

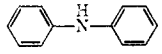
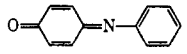
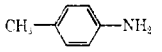
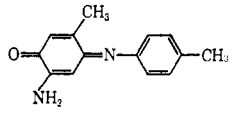
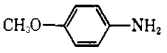
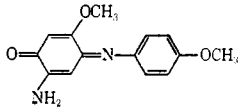
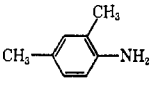
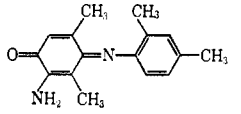
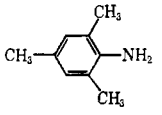
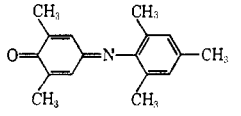
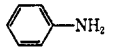
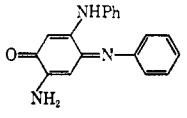
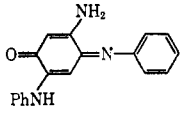
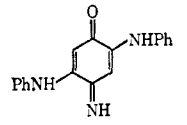
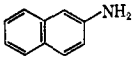
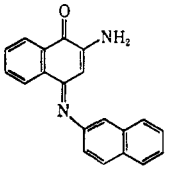
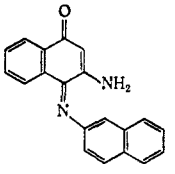
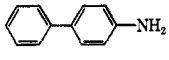
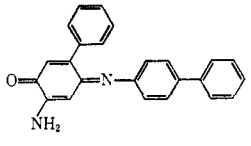
2. Recrystallization of Fremy's Salt

For bulk recrystallization, Fremy's salt is suspended in a solution, 2 *M* in potassium of whichever potassium salt is selected. Solution is completed by heating, if necessary up to 50°, when the solubility is of the order of 3 g per 100 ml of solution. The resulting solution is filtered and cooled overnight and crystallization completed by cooling in ice for 2 hr. The filtered solid is washed with methanol (twice) and acetone (twice), dried in air, and stored in a dry ammoniacal atmosphere as before. By carrying out the recrystallization in about six 10-g batches, using the same liquor throughout, it is possible to attain a yield of 62–65%, relative to the original bisulfite, of analytically pure product. The product can contain both crystalline modifications of Fremy's salt.

(79) H.-J. Teuber, *Angew. Chem.*, 81, 190 (1969); *Angew. Chem., Int. Ed. Engl.*, 8, 218 (1969).
(80) H. Akashio and R. Oda, *J. Chem. Soc. Jap., Ind. Chem. Sect.*, 57, 944 (1954); *Chem. Abstr.*, 50, 900*a* (1956).

Table VI

Oxidation of Aromatic Amines with Fremy's Radical and the Formation of Quinone Anils

Aromatic amine	*Oxidation product*	*% yield*	*Mol formula*	*Ref*
		97	$C_{12}H_9NO$	55
		86–95	$C_{14}H_{14}N_2O$	52 53
		85	$C_{14}H_{14}N_2O_3$	53
		44	$C_{16}H_{18}N_2O$	52
		42	$C_{17}H_{19}NO$	54
	 or  + 	34 49	$C_{18}H_{15}N_3$ $C_{18}H_{15}N_3$	53 53
	 or 	86	$C_{20}H_{14}N_2O$	53
		90	$C_{24}H_{15}N_2O$	53

E. ADDENDUM

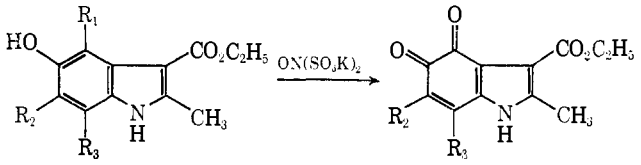
Fremy's radical (**1**) has been used as a selective oxidizing agent in the syntheses of polycyclic quinones.[81] In general, the Diels–Alder adduct of 1,4-benzoquinone or 1,4-naphthoquinone and substituted 1,3-cyclohexadienes is dehydrogenated by **1** to the corresponding polycyclic quinone in good yield. This reaction represents a very selective oxidation since attempts to bring about the same transformation utilizing 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) were unsuccessful. Table X summarizes the examples of this oxidation which have been studied.

An electrolytic method for the generation of **1** has been

(81) V. H. Powell, *Tetrahedron Lett.*, 3463 (1970).

Table VII

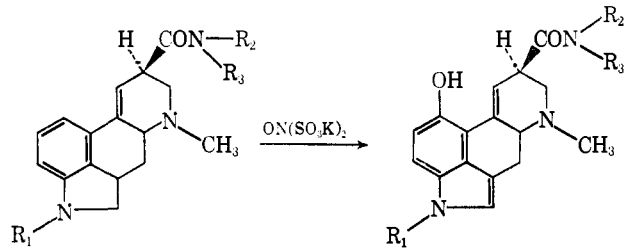
Oxidation of 3-Carbethoxy-5-hydroxyindoles with Fremy's Radical. Formation of 3-Carbethoxy-4,5-indolequinones



R_1	R_2	R_3	% yield	*Mol formula*	*Ref*
OH	H	Cl	100	$C_{12}H_{10}ClNO_4$	70
H	H	H	85	$C_{12}H_{11}NO_4$	70
OH	CH_3	Cl	100	$C_{13}H_{12}ClO_4$	70
H	CH_3	H	92	$C_{13}H_{13}NO_4$	70
H	CH_3	CH_3	90	$C_{14}H_{15}NO_4$	70

Table VIII

Dehydrogenation–Hydroxylation to Lysergic Acid Derivatives with Fremy's Radical[a]



R_1	R_2	R_3	*Mol formula*	*Ref*
H	CH_3CHCH_2OH	H	$C_{19}H_{23}N_3O_3$	71
H	C_2H_5	H	$C_{20}H_{25}N_3O_2$	71
H	$C_2H_5CHCH_2OH$	H	$C_{20}H_{25}N_3O_3$	71
CH_3	$C_2H_5CHCH_2OH$	H	$C_{21}H_{27}N_3O_3$	71

[a] No yields were reported.

Table IX

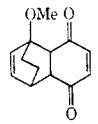
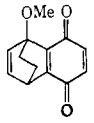
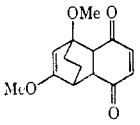
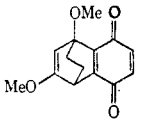
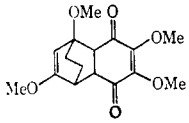
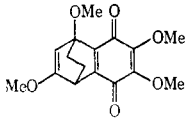
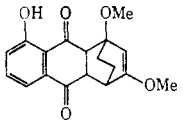
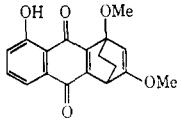
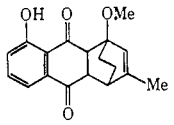
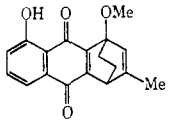
Oxidation of 1,2-Dihydroquinolines with Fremy's Radical. Formation of 1,2-Dihydro-6-quinolones

R_1	R_2	R_3	R_4	% yield	*Mol formula*	*Ref*
H	H	H	H	75	$C_{12}H_{15}NO$	74
H	H	H	H	68.5	$C_{13}H_{17}NO$	74
Cl	OH	CH_3	CH_3	86.3	$C_{14}H_{18}ClNO$	74
H	H	CH_3	CH_3	88	$C_{14}H_{19}NO$	74

described.[82] Thus, alkaline solutions of potassium hydroxylaminedisulfonate are electrolyzed at a platinum, nickel, or carbon anode in a divided cell to produce **1** in quantitative yield. Nitrite ion, which is an impurity of hydroxylaminedisulfonate prepared by conventional methods and a cause of instability of **1**, is simultaneously oxidized to nitrate ion.

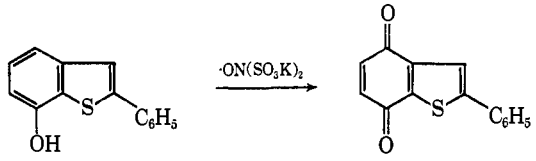
(82) W. R. T. Cottrell and J. Farrar, *J. Chem. Soc. A*, 1418 (1970).

Table X

Diels–Alder adduct	*Oxidation product*	% yield[a]
		95
		80
		85
		80
		90

[a] % Yield by weight of crystalline material recovered.

Recently a series of papers dealing with the orientational and steric effects in the oxidation of heterocyclic phenols has appeared.[83,84] Indoles, benzothiophenes, benzofurans, and related systems having a hydroxy group in the 7 position and substituents in the 2 and/or 3 positions have been oxidized by **1**. For example, **188**, which has a phenyl ring in the 2 position, is oxidized to give only the *p*-quinone **189**. If the



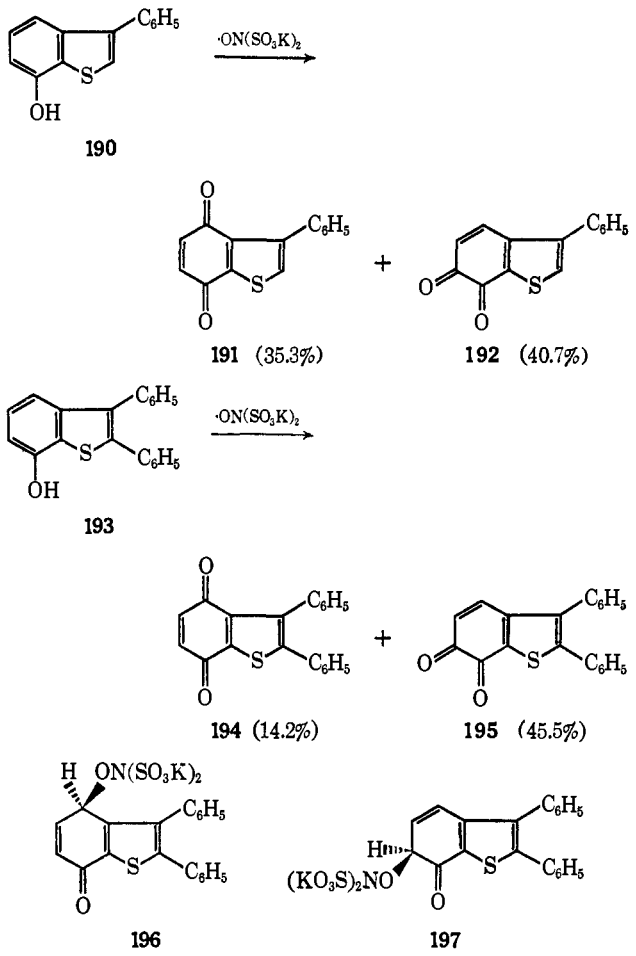
188 **189** (31.5%)

phenyl substituent is in the 3 position, as in **190**, the major product is now the *o*-quinone **192**. If phenyl substituents are in both the 2 and 3 positions, as in **193**, the yield of the *p*-quinone **194** has now significantly decreased.

These observations are explained by considering the oxidation intermediates **196** and **197** which ultimately lead to the formation of quinones **194** and **195**, respectively. Intermediate **196** is more sterically hindered than intermediate **197** and thus the reaction proceeds to give predominately the *o*-quinone **195** and a lesser amount of the *p*-quinone **194**. These examples represent additional evidence for the pronounced steric effects associated with Fremy's radical oxidations which have

(83) H. Ishii, T. Hanaoka, Sugano, and M. Ikeda, *Yakugaku Zasshi*, **90**, 1290 (1970), and references cited therein.

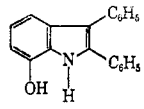
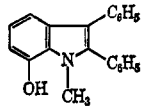
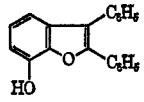
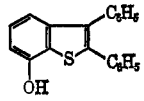
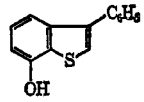
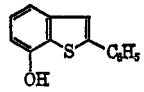
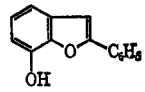
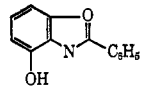
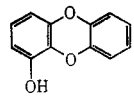
(84) H. Ishii, M. Konno, M. Wakabayashi, F. Kuriyagawa, and M. Ikeda, *ibid.*, **90**, 1298 (1970).



been previously observed in the oxidation of phenols and naphthols. Table XI summarizes some of the ring systems which have been oxidized. Examination of the yields of the *o*- and *p*-quinones vividly demonstrates the trend in the observed steric effects which manifest themselves in the oxidation of these systems.

Table XI

Oxidation of Some Heterocyclic Phenols with Fremy's Radical

Heterocyclic phenols	*p-Quinone, %*	*o-Quinone, %*
	20	61
	0	38.5
	40	>40
	14.2	45.5
	35.3	40.7
	31.5	0
	37	0
	~30	0
	45.3	0

F. SUMMARY

Fremy's radical has been shown to be an excellent and very specific oxidizing agent which brings about conversion of phenols to quinones. Secondary aromatic amines can be oxidized by **1** to quinones. In these cases, the original oxidation product is a quinone imine or an acid which is subsequently hydrolyzed to the corresponding quinone under the reaction conditions. Simple heterocyclic phenols such as hydroxyquinolines are also oxidized by **1**, in a very specific manner, to quinones. However, it seems that with more complex molecules such as indoles and carbazoles, oxidation by **1** becomes less specific. Besides formation of quinones, dehydration and coupling reactions frequently occur. In many cases, the formation of these products represents the main pathway of the reaction of **1** with such compounds. An explanation for the loss of specificity of oxidations involving **1** and more complex molecules might be found in small differences of the stabilities of the incipient radicals which can be formed upon attack by **1** and thus open up more pathways for the ensuing reactions.