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Studies on Sulfenamides. IV.[1] Oxidation of 4′-, 3′-, and 2′-Substituted 2-Nitrobenzenesulfenanilides with Lead Dioxide

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The oxidation of 4′-, 3′-, and 2′-substituted 2-nitrobenzenesulfenanilides (4′-Br (**3e**), 4′-CO_2Et (**3f**), 4′-COMe (**3g**), 4′-OEt (**3h**), 4′-NO_2 (**3i**), 4′-SO_2NH_2 (**3j**), 3′-Me (**4b**), 2′-OMe (**5a**), 2′-Me (**5b**)) with lead dioxide was carried out in acetonitrile containing 1% CF_3COOH and 1% $(CF_3CO)_2O$. The oxidation of **3e**, **3f**, **3g**, **3h**, **3i**, and **4b** gave the corresponding 2,7-disubstituted phenazines (**2e**—**i** and **2b**), whereas that of **3j**, **5a**, and **5b** did not. N-(2-Nitrophenylthio)acetamide (**6**) was obtained on the oxidation of **3e**—**j**, **4b**, **5a**, and **5b**. 2,2′-Dinitrodiphenyl disulfide (**7**) was obtained from **3f**, **3g**, **3h**, **3j**, and **5a**. The oxidation of **5b** gave a small amount of N-(2-nitrophenylthio)-2′-methyl-*p*-benzoquinoneimine (**8b**), whereas that of **5a** gave a mixture of N-(2-nitrophenylthio)-2′-methoxy-, *p*- and *o*-benzoquinoneimines (**8a** and **8a′**).

Keywords——2-nitrobenzenesulfenanilides; oxidation of benzenesulfenanilides; oxidation with lead dioxide; synthesis of 2,7-disubstituted phenazines; N-(2-nitrophenylthio)acetamide; N-(2-nitrophenylthio)benzoquinoneimine; nitrenium ion; sulfenylium ion

In the previous paper[3] we reported the results of the oxidation of benzenesulfenanilides (4′-OMe (**1a**), 4′-Me (**1b**), 4′-Cl (**1c**), 4′-H (**1d**)) and 2-nitrobenzenesulfenanilides (4′-OMe (**3a**), 4′-Me (**3b**), 4′-Cl (**3c**), 4′-H (**3d**)) with lead dioxide. The oxidation of **1a** and **1b** in benzene gave the corresponding 2,7-disubstituted phenazines, whereas that of **1c**, **1d**, and **3a**—**d** did not. The oxidation of **3a**—**d** in acetonitrile containing 1% CF_3COOH and 1% $(CF_3CO)_2O$ gave the corresponding 2,7-disubstituted phenazines (**2**) and N-(2-nitrophenylthio)acetamide.

In order to develop a new method for the synthesis of **2**, we have now studied the oxidation of 4′-, 3′-, and 2′-substituted 2-nitrobenzenesulfenanilides (4′-Br (**3e**), 4′-CO_2Et (**3f**), 4′-COMe (**3g**), 4′-OEt (**3h**), 4′-NO_2 (**3i**), 4′-SO_2NH_2 (**3j**), 3′-Me (**4b**), 2′-OMe (**5a**), 2′-Me (**5b**)) in acetonitrile containing 1% CF_3COOH and 1% $(CF_3CO)_2O$.

Results

The results of the oxidation of **3e**—**j**, **4b**, **5a**, and **5b** are summarized in Table I. Physical and spectroscopic data for the products obtained are summarized in Table II. The oxidation of **3e**, **3f**, **3g**, **3h**, **3i**, and **4b** gave the corresponding 2,7-disubstituted phenazines (X=Br (**2e**), CO_2Et (**2f**), COMe (**2g**), OEt (**2h**), NO_2 (**2i**), Me (**2b**)), whereas that of **3j**, **5a**, and **5b** did not. The yield of **2** was highest for the oxidation of **3h** and lowest for that of **4b**. N-(2-Nitrophenylthio)acetamide (**6**) was obtained on the oxidation of **3e**—**j**, **4b**, **5a**, and **5b**. 2,2′-Dinitrodiphenyl disulfide (**7**) was obtained from **3f**, **3g**, **3h**, **3j**, and **5a**, and *p*-nitroaniline from **3i**.

Orange-yellow crystals obtained on the oxidation of **5b** were identified as N-(2-nitrophenylthio)-2′-methyl-*p*-benzoquinoneimine (**8b**) by elemental analysis, and from the ultraviolet (UV), visible (VIS), infrared (IR), nuclear magnetic resonance (NMR), and mass (MS) spectra. On the other hand, the NMR spectrum of the orange-yellow crystals obtained on

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[1] Part III: H. Sayo, K. Mori, and T. Michida, *Chem. Pharm. Bull.* (Tokyo), **27**, 2093 (1979).

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[3] H. Sayo, K. Mori, and T. Michida, *Chem. Pharm. Bull.* (Tokyo), **27**, 351 (1979).

Table I. Results of Oxidation of 2′-, 3′- and 4′-Substituted 2-Nitrobenzenesulfenanilides with PbO_2 in Acetonitrile containing 1% CF_3COOH and 1% $(CF_3CO)_2O$ at 40°

Compound No.	Conc. (mg/ml)	Products identified	Yields mg	Yields %
3e	195/60	2,7-Dibromophenazine	24.7	24.3
		N-(2-Nitrophenylthio)acetamide	20.4	16.2
3f	190/60	2,7-Diethoxycarbonylphenazine	29.7	30.7
		N-(2-Nitrophenylthio)acetamide	39.1	30.9
		2,2′-Dinitrodiphenyldisulfide	4.2	4.6
3g	174/60	2,7-Diacetylphenazine	12.9	16.2
		N-(2-Nitrophenylthio)acetamide	41.8	32.7
		2,2′-Dinitrodiphenyldisulfide	5.2	5.6
3h	195/60	2,7-Diethoxyphenazine	26.7	33.8
		N-(2-Nitrophenylthio)acetamide	15.9	11.1
		2,2′-Dinitrodiphenyldisulfide	5.1	4.9
3i	174/60	2,7-Dinitrophenazine	9.5	11.8
		N-(2-Nitrophenylthio)acetamide	17.9	14.1
		p-Nitroaniline	14.9	18.1
3j	196/60	N-(2-Nitrophenylthio)acetamide	19.8	15.5
		2,2′-Dinitrodiphenyldisulfide	1.7	1.8
4b	152/60	2,7-Dimethylphenazine	2.4	3.0
		N-(2-Nitrophenylthio)-3′-methylbenzoquinoneimines	5.6	3.5
		N-(2-Nitrophenylthio)acetamide	17.3	16.5
5a	166/60	N-(2-Nitrophenylthio)-2′-methoxybenzoquinoneimines	1.4	0.8
		N-(2-Nitrophenylthio)acetamide	16.6	13.0
		2,2′-Dinitrodiphenyldisulfide	11.9	12.9
5b	149/60	N-(2-Nitrophenylthio)-2′-methyl-*p*-benzoquinoneimine	3.4	2.2
		N-(2-Nitrophenylthio)acetamide	18.6	15.3

$$\underset{\mathbf{3}}{\text{X-C}_6\text{H}_4\text{NHSR}} \xrightarrow{-e} \underset{\text{A}}{\text{X-C}_6\text{H}_4\dot{\text{N}}\text{H}^+\text{-SR}} \xrightarrow{-e} \underset{\text{B}}{\text{X-C}_6\text{H}_4\dot{\text{N}}\text{H}^+\text{-}\dot{\text{S}}^+\text{R}}$$

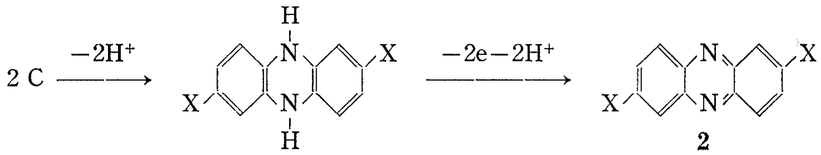
$$\text{A} \longrightarrow \underset{\text{C}}{\text{X-C}_6\text{H}_4\text{NH}^+} + \text{RS}\cdot$$

$$2\,\text{RS}\cdot \longrightarrow \underset{\mathbf{7}}{\text{BSSR}}$$

$$\text{B} \longrightarrow \text{C} + \text{RS}^+$$

$$\text{RS}^+ + \text{CH}_3\text{CN} \longrightarrow \text{RSN}^+\!\equiv\!\text{CCH}_3 \xrightarrow{+\text{H}_2\text{O}} \underset{\mathbf{6}}{\text{RSNHCOCH}_3}$$

$$\text{C} + \text{solvent} \longrightarrow \text{X-C}_6\text{H}_4\text{NH}_2 \xrightarrow{-ne} \text{unidentified products}$$



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R=2-nitrophenyl

Chart 1

TABLE II. Physical and Spectroscopic Data for the Products obtained on Oxidation of **3e**—**i**, **4b**, **5a**, and **5b**

Compound No.	mp (°C)		Analysis (%)		UV $\lambda_{\max}^{\mathrm{CH_3CN}}$ nm (log ε)	NMR ($CDCl_3$) δ(ppm), J(Hz)	IR $\nu_{\max}^{\mathrm{KBr}}$, cm^{-1}	MS *m/e*
			Calcd.	Found				
2e	251 (dec.)	C	42.64	42.74	260(5.20)	7.8—8.15 (4H, m)		340/338/336 (M^+)
(X=Br)	(lit.,[a] 251—252)	H	1.79	1.80	365(4.17)	8.44 (2H, d, J=2)		259/257 (M^+-Br)
		N	8.29	8.48	378(4.19)			178 (M^+-2Br)
2f	202.5 (dec.)	C	66.66	66.33	266(5.10)	1.49 (6H, t, J=7, CH_3)	1715(C=O)	324 (M^+)
(X=CO_2Et)		H	4.97	4.96	366(4.17)	4.53 (4H, q, J=7, CH_2)	1250(C-O)	279 (M^+-OEt)
		N	8.64	8.58		8.2—8.5 (4H, m)	1170(C-O)	251 (M^+-CO_2Et)
						8.99 (2H, broad s)		
2g	255—257 (dec.)	C	72.72	72.64	273(5.08)	2.83 (6H, s, CH_3)	1665(C=O)	264 (M^+)
(X=COMe)		H	4.58	4.57	366(4.16)	8.2—8.5 (4H, m)		249 (M^+-Me)
		N	10.60	10.47		8.83 (2H, broad s)		
2h	216—218 (dec.)	C	71.62	71.59	264(4.97)	1.52 (6H, t, J=7, CH_3)	1210(C-O-C)	268 (M^+)
(X=OEt)		H	6.01	6.02	346(3.87)	4.24 (4H, q, J=7, CH_2)	1005(C-O-C)	240 ($M^+-C_2H_4$)
		N	10.44	10.21	408(4.00)	7.25—7.55 (4H, m)		212 ($M^+-2C_2H_4$)
					427(4.03)	7.99 (2H, d, J=9)		
2i	231—234 (dec.)	C	53.34	53.03	227(4.45)	8.45—8.8 (4H, m)	1555(NO_2)	270 (M^+)
(X=NO_2)		H	2.24	2.23	283(4.73)	9.27 (2H, d, J=3)	1345(NO_2)	224 (M^+-NO_2)
		N	20.74	20.51	365(4.20)			178 (M^+-2NO_2)
8a+**8a′**	226—228 (dec.)	C	53.79	53.43	248(4.08)	3.91 (s), 4.02 (s)	1330(NO_2)	290 (M^+)
		H	3.47	3.32	418(4.36)	5.80—6.0 (1H, m)	1510(NO_2)	
		N	9.65	9.47		6.35—6.65 (1H, m)	1640(C=O)	
						7.0—7.6 (2H, m)		
						7.6—7.9 (1H, m)		
						8.2—8.6 (1H, m)		
8b	200.5—203 (dec.)	C	56.93	56.93	254(4.24)	2.33 (3H, d, J=1)	1330(NO_2)	274(M^+)
		H	3.67	3.54	430(4.39)	6.4—6.7 (2H, m)	1510(NO_2)	
		N	10.21	10.13		7.3—7.9 (3H, m)	1640(C=O)	
						8.36 (1H, dd, J=1.5 and 8)		
						8.50 (1H, dd, J=1.5 and 8)		
9b+**9b′**	203—204 (dec.)	C	56.93	56.77	251(4.13)	2.07 (d, J=1.5)	1330(NO_2)	274 (M^+)
		H	3.67	3.52	434(4.37)	2.14 (d, J=1.5)	1500(NO_2)	
		N	10.21	10.07		6.5—6.7 (1H, m)	1630(C=O)	
						7.0—7.25 (1H, m)		
						7.3—7.65 (2H, m)		
						7.65—7.9 (1H, m)		
						8.36 (1H, dd, J=1.5 and 8)		
						8.56 (1H, dd, J=1.5 and 8)		

[a] D.L. Vivian, *J. Org. Chem.*, **21**, 824 (1956).

the oxidation of **5a** showed two singlet peaks at $\delta=3.91$ and 4.02[4] which were assigned to two kinds of methoxy groups. The crystals were concluded to be a mixture of N-(2-nitrophenylthio)-2′-methoxy-*p*-benzoquinoneimine (**8a**) and N-(2-nitrophenylthio)-2′-methoxy-*o*-benzoquinoneimine (**8a′**) on the basis of elemental analysis, and UV, VIS, IR, NMR, and MS spectra. The mixture could not be resolved by thin-layer chromatography (TLC). The oxidation of **4b** gave similar orange-yellow crystals, which were concluded to be a mixture of N-(2-nitrophenylthio)-3′-methyl-*p*-benzoquinoneimine (**9b**) and N-(2-nitrophenylthio)-3′-methyl-1: 6-benzoquinoneimine (**9b′**).

Discussion

The following schemes are suggested for the oxidation of **3e**—**j**. **3** is oxidized to B in two one-electron transfer steps. A part of A undergoes homolytic cleavage of the S–N bond to form a nitrenium ion (C) and 2-nitrophenylthinyl radical, and the latter dimerizes into **7**. Most of A is oxidized further to B, and the S–N bond in B is immediately cleaved to form C and a sulfenylium ion. Nucleophilic attack of acetonitrile on the sulfenylium ion followed by hydrolysis gives **6**. A part of C abstracts hydrogen atoms from the solvent to form a substituted aniline, which, except in the case of *p*-nitroaniline, is oxidized further to unidentified compounds. The relatively high yield of *p*-nitroaniline obtained on the oxidation of **3i** can be explained in terms of low reactivity of *p*-nitroaniline toward oxidants. The rest of C dimerizes into a 2,7-disubstituted 5,10-dihydrophenazine, which is oxidized further to **2**. However, it is not clear why the oxidation of **3j** did not give **2**.

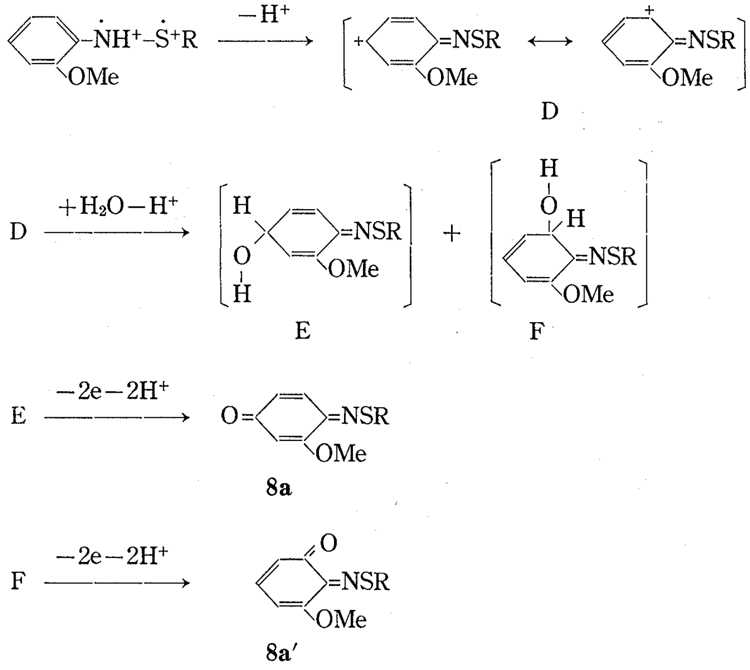

Chart 2

As for the oxidation of **5a**, in addition to Chart 1, the following schemes are suggested. Steric hindrance caused by the 2′-substituent inhibits the dimerization of C, and hence 1,6-dimethoxyphenazine is not obtained. A part of B is immediately deprotonated to form D. Nucleophilic attack of water[5] on D followed by deprotonation gives E and F, which are

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4) Tetramethylsilane was used as an internal standard.

5) The purified acetonitrile contained 5—10 mM water.[3]

oxidized further to **8a** and **8a′**. However, it is not clear why the oxidation of **5b** gave only one isomer of the quinoneimine.

The oxidation of **4b** can be interpreted as intermediate between that of **3b** and that of **5b**. That is, the extent of steric hindrance caused by the 3′-methyl group is not great enough to inhibit the dimerization of C, and hence a small amount of 2,7-dimethylphenazine is obtained. In addition, the quinoneimines are obtained in the same way as **8a** and **8a′**.

Experimental

Materials——2-Nitrobenzenesulfenanilides were prepared from 2-nitrobenzenesulfenyl chloride and the corresponding anilines by a known method:[6] substituent, mp, solvent of recrystallization were as follows; 4′-Br, 152—152.5°, 95% EtOH (lit.,[6] 146—146.5°); 4′-CO_2Et, 159—160°, 95% EtOH (lit.,[7] 157—158°); 4′-COMe, 203—204°, 95% EtOH; 4′-OEt, 89°, 95% EtOH (lit.,[7] 89—90°); 4′-NO_2, *ca.* 180° (dec.), acetone (lit.,[8] *ca.* 160°); 4′-SO_2NH_2, 199—200°, 60% EtOH (lit.,[7] 203—204°); 3′-Me, 109.5—110°, 95% EtOH (lit.,[6] 106.5—107°); 2′-OMe, 118.5—119°, 95% EtOH; 2′-Me, 123—124°, 95% EtOH (lit.,[9] 119.5—120°). Each compound gave the expected analysis results. Acetonitrile was purified as described previously.[10] Lead dioxide, trifluoroacetic acid, and trifluoroacetic anhydride were reagent chemicals and were used without further purification.

Apparatus——UV, IR, and NMR spectra were obtained as described previously.[11] Mass spectra were obtained on a Hitachi M-60 spectrometer at an ionizing voltage of 20 eV.

Isolation of Products——Typical examples of the procedure are given below. a) Compound **3f** (190 mg, 0.60 mmol) was dissolved in acetonitrile containing 1% CF_3COOH and 1% $(CF_3CO)_2O$ (60 ml) and treated with PbO_2 (0.15 g) at 40°. The mixture was stirred with a magnetic stirrer. After 10 min, another portion of PbO_2 (0.15 g) was added to the solution. After a further 30 min, solid Na_2CO_3 (0.5 g) was added to the reaction mixture. The mixture was filtered and the filtrate was cooled. Yellow needles separated out; these were filtered off, recrystallized from benzene and identified as **2f** (29.7 mg) by elemental analysis, and from the UV, IR, NMR, and MS spectra (Table II). The filtrate from the separation of **2f** was evaporated to dryness, and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was subjected to preparative thin-layer chromatography on alumina with $CHCl_3$–benzene (1: 2) as the developing solvent. Four bands were obtained, and each band was scraped off and extracted with $CHCl_3$. **7** (4.2 mg) and **6** (39.1 mg) were obtained from the top and the second (from bottom) bands, respectively. The compounds from the lowest and the third band could not be identified.

b) **3i** (174 mg, 0.60 mmol) was treated with PbO_2 in the manner described above. Solid Na_2CO_3 (0.5 g) was added to the reaction mixture. The mixture was filtered off, the filtrate was evaporated to dryness, and the residue was extracted with ethyl acetate. The ethyl acetate solution was subjected to preparative thin-layer chromatography on alumina with $CHCl_3$–benzene (1:1) as the developing solvent. *p*-Nitroaniline (14.9 mg) and **6** (17.9 mg) were obtained from the top and the middle bands. The residue after extraction with ethyl acetate was dissolved in $CHCl_3$ and treated with active carbon. Removal of the $CHCl_3$ gave yellow crystals, which were recrystallized from benzene and identified as **2i** (9.5 mg).

c) **5a** (166 mg, 0.60 mmol) was treated with PbO_2, and the reaction mixture was worked up according to procedure b. **7** (11.9 mg), a mixture of **8a** and **8a′** (1.4 mg), and **6** (16.6 mg) were obtained from the top, the middle, and the bottom bands, respectively.

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