Studies on Sulfamides. II.  
Oxidation of 2- and 4'-Substituted 
Benzenesulfanilamides with Lead Dioxide

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2- and 4'-Substituted benzensulfanilamidyl radicals were generated by the oxidations of benzencesulfanilamides (4'-OMe (1a), 4'-Me (1b), 4'-Cl (1c), 4'-H (1d)) and 2-nitrobenzencesulfanilamides (4'-OMe (3a), 4'-Me (3b), 4'-Cl (3c), 4'-H (3d)) with lead dioxide, and their electron spin resonance (ESR) and visible spectra were investigated. The radicals generated from 1a, 1b, 3a, and 3b in benzene were fairly stable and gave well-resolved ESR spectra, whereas those from 1c, 1d, 3c, and 3d were less stable and decomposed thoroughly in an hour. The oxidations of 1a and 1b in benzene gave the corresponding 2,7-disubstituted phenazines as the final products, whereas those of 1c, 1d, 3a—3d did not. The oxidations of 3a—3d in acetonitrile containing 1% CF₃COOH and 1% (CF₃CO)₂O gave the corresponding phenazines and N-(2-nitrophenylthio)acetamide (6). The formation of 6 was interpreted in terms of acetylimidation of the sulfonylum ion.

Keywords—benzenesulfanilamides; oxidation of benzenesulfanilamides; oxidation with lead dioxide; electron spin resonance; benzenesulfanilamidyl radicals; nitrene; nitrenium ion; synthesis of phenazines; 2-nitrobenzensulfanilamium ion; acetylimidation

In the previous paper we reported the results on the controlled potential electrolyses of benzenesulfanilamides (4'-OMe (1a), 4'-Me (1b), 4'-Cl (1c), 4'-H (1d)) in acetonitrile. Electrolyses of 1a—c gave 2,7-dimethoxyphenazine (2a), 2,7-dimethylphenazine (2b), and 2,7-dichlorophenazine (2c), respectively, whereas that of 1d did not. Intermediacy of nitrenes was suggested for the formation of the phenazines.

In order to elucidate the mechanism of the formation of the phenazines more clearly, we have now studied the oxidations of benzenesulfanilamides (1a—d) and 2-nitrobenzenesulfanilamides (4'-OMe (3a), 4'-Me (3b), 4'-Cl (3c), 4'-H (3d)) with lead dioxide both in benzene and acetonitrile. Oxidation of Benzenesulfanilamides have been attempted with various oxidizing agents. However, phenazines were not identified as the products except for the reaction of NN-bis-β-methoxyphenylbenzenesulfanamide in liquid sulfur dioxide, in which 5,10-dihydro-2,7-dimethoxy-5,10-bis-β-methoxyphenylphenazine was obtained in yield of 1%.

Results

Electron Spin Resonance (ESR) Studies

A benzene solution of 1 and 3 was degassed by three freeze-and-thaw cycles and then treated with PbO₂. ESR spectrum of the mixture was recorded. The radicals generated from 1a, 1b, 3a, and 3b had half-lives of several hours, whereas those from 1c, 1d, 3c, and 3d decomposed thoroughly in an hour. The coupling constants are summarized in Table 1.

2) Location: Ikawa-dani-cho, Tarumi-ku, Kobe 673, Japan.
TABLE I. ESR Spectral Data of 2- and 4'-Substituted Benzenesulfanilidyl Radicals in Benzene

<table>
<thead>
<tr>
<th>Radical</th>
<th>Coupling constants (G)</th>
<th>g-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4'-X</td>
<td>A_N A_2-H A_3,5-H A_4-H A_4'-H A_4'-H A_4'-x</td>
<td></td>
</tr>
<tr>
<td>OCH_3</td>
<td>NO_2 9.30 — 0.21 0.68 0.68 4.00 1.06 0.68 2.0050</td>
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</tr>
<tr>
<td>OCH_3</td>
<td>H 9.50 0.60 0.20 0.625 0.60 3.85 1.10 0.65 2.0055</td>
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<tr>
<td>CH_3</td>
<td>NO_2 9.42 — 0.22 0.68 0.68 3.98 1.24 5.20 2.0050</td>
<td></td>
</tr>
<tr>
<td>CH_3</td>
<td>H 9.50 0.725 0.225 0.75 0.725 3.75 1.20 4.70 2.0059</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>NO_2 9.38 — 0.26 0.72 0.72 3.90 1.36 0.52 2.0057</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>H 9.40 0.775 0.30 0.80 0.775 3.65 1.27 0.325 2.0062</td>
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</tr>
<tr>
<td>H</td>
<td>NO_2 9.48 — 0.24 0.78 0.78 3.90 1.32 4.48 2.0049</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H 9.45 0.775 0.275 0.80 0.775 3.70 1.25 4.20 2.0061</td>
<td></td>
</tr>
</tbody>
</table>

^a) No splittings have been observed from 2-nitro nitrogen.

Together with g-values. The values of A_H in the aniline part are larger than those in the phenylthionyl part. The unpaired electron is, therefore, distributed mainly on the aniline part. The coupling constants of 2-nitrobenzenesulfanilidyl radicals are nearly equal to those of the corresponding benzenesulfanilidyl radicals. The g-values of the former radicals are somewhat smaller than those of the latter. No splittings have been observed from 2-nitro nitrogen. The small splittings observed from 4'-chlorine atoms are in disagreement with the reported results. Such a small splitting of chlorine atom was reported on the radical cation of 1,3-benzodioxoles.

The benzenesulfanilidyl radicals and 2-nitrobenzenesulfanilidyl radicals were also generated in acetonitrile, and their ESR spectra were recorded. The radicals generated from 1a, 1b, 3a, and 3b showed poorly resolved spectra, and had half-lives of several minutes, whereas those from 1c, 1d, 3c, and 3d had half-lives of less than a minute and did not give distinct spectra. The radicals generated from 3a and 3b in acetonitrile containing 1% trifluoroacetic acid and 1% trifluoroacetic anhydride were unstable and decomposed thoroughly in a minute.

Spectrophotometric Studies

A benzene solution of 1a (1 mm, 10 ml) was deoxygenated by passage of nitrogen through the solution and then PbO_2 (25 mg) was added. The reaction mixture was stirred with a magnetic stirrer, and 0.5 ml portions of the reaction mixture were taken out at regular time intervals, filtered, and diluted 50 times with benzene. At first a visible spectrum of the filtrate showed a λ_max at 593 nm, which is responsible for the blue color. The absorbance at 593 nm decreased gradually during the course of the reaction with a half-life (t_1/2) of ca. 90 min, while new λ_max's appeared at 405 and 427 nm and their absorbances increased with the reaction time. The λ_max's at 405 and 427 nm indicated the presence of 2a. The oxidations of 1b and 1c in benzene also gave blue solutions, λ_max 594 (t_1/2= ca. 30 min) and 606 nm (t_1/2= ca. 2 min), respectively. On the other hand, a green color observed on the oxidation of 1d was so transient that the λ_max could not be determined. After a day the reaction mixture of 1b showed a new λ_max at 364 nm, which indicated the presence of 2b. On the other hand, the reaction mixtures of 1c and 1d showed new λ_max's at 458 and 454 nm, respectively, which did not correspond to those of the corresponding phenazines. Acetonitrile solutions of 1a—d were also treated with PbO_2. The reaction mixtures of 1a and 1b showed λ_max's which corresponded to those of the phenazines, respectively, whereas those of 1c and 1d did not.

Benzene solutions of 3a—d were treated with PbO₂ in a similar manner as above, but the visible spectra of the reaction mixtures gave no indication of the presence of the corresponding phenazines even after a day. Acetonitrile solutions of 3a—d were also treated with PbO₂, but the visible spectra of the reaction mixtures did not show λ_{max}’s which corresponded to those of the phenazines. Since the anodic oxidations of 3a—c in acetonitrile, in which the anolyte becomes acidic with a progress of electrolysis, gave 2a—c,⁷ the effect of an acid on the oxidation was investigated. Acetonitrile containing 1% trifluoroacetic acid and 1% trifluoroacetic anhydride was used as solvent. The latter was added to the solution in order to reduce the water content in the solution. Although 1 decomposed immediately in the solution, 3 did not decompose in the solution within 6 hours. The ultraviolet (UV) and visible (VIS) spectra of the reaction mixtures of 3a—c in the solution indicated the presence of the corresponding phenazines, whereas that of 3d did not.

**Products Studies**

The results of the oxidations of 1 and 3 are summarized in Table II. Although the oxidations of 1a and 1b gave the corresponding phenazines as the final products, those of 1c and

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Conc. (mg/ml)</th>
<th>Solvent</th>
<th>PbO₂ g</th>
<th>Temp °C</th>
<th>Time hr</th>
<th>Products identified</th>
<th>Yield mg</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>116/50</td>
<td>C₆H₄</td>
<td>0.53</td>
<td>30</td>
<td>2</td>
<td>2,7-Dimethoxyphenazine</td>
<td>33.1</td>
<td>54.0</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Diphenyl disulfide</td>
<td>36.9</td>
<td>67.3</td>
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<tr>
<td>1b</td>
<td>160/74</td>
<td>C₆H₄</td>
<td>1.28</td>
<td>35</td>
<td>22</td>
<td>2,7-Dimethylphenazine</td>
<td>26.7</td>
<td>33.9</td>
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<td></td>
<td></td>
<td></td>
<td>Diphenyl disulfide</td>
<td>46.4</td>
<td>57.3</td>
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<tr>
<td>1c</td>
<td>25/10</td>
<td>C₆H₄</td>
<td>0.05</td>
<td>40</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1d</td>
<td>20/10</td>
<td>C₆H₄</td>
<td>0.05</td>
<td>40</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1a+1b</td>
<td>(187+172)/160</td>
<td>CH₃CN</td>
<td>1.00</td>
<td>40</td>
<td>15</td>
<td>2,7-Dimethoxyphenazine</td>
<td>19.7</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2,7-Dimethylphenazine</td>
<td>4.6</td>
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<tr>
<td>3a</td>
<td>140/50</td>
<td>b</td>
<td>0.25</td>
<td>40</td>
<td>0.67</td>
<td>2,7-Dimethoxyphenazine</td>
<td>27.3</td>
<td>44.3</td>
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<td></td>
<td></td>
<td>2,7-Dimethylphenazine</td>
<td>19.9</td>
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<tr>
<td>3b</td>
<td>157/60</td>
<td>b</td>
<td>0.31</td>
<td>40</td>
<td>0.67</td>
<td>N-(2-Nitrophenylthio)acetamide</td>
<td>15.6</td>
<td>21.1</td>
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<td>2,2’-Dinitrodiphenyl disulfide</td>
<td>14.0</td>
<td>19.9</td>
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<tr>
<td>3c</td>
<td>171/60</td>
<td>b</td>
<td>0.31</td>
<td>40</td>
<td>0.67</td>
<td>N-(2-Nitrophenylthio)acetamide</td>
<td>16.4</td>
<td>22.1</td>
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<td>2,2’-Dinitrodiphenyl disulfide</td>
<td>5.5</td>
<td>7.1</td>
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<tr>
<td>3d</td>
<td>247/100</td>
<td>b</td>
<td>0.61</td>
<td>40</td>
<td>0.67</td>
<td>2,7-Dichlorophenazine</td>
<td>31.1</td>
<td>40.7</td>
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<td></td>
<td></td>
<td></td>
<td>N-(2-Nitrophenylthio)acetamide</td>
<td>37.7</td>
<td>52.9</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2,2’-Dinitrodiphenyl disulfide</td>
<td>21.9</td>
<td>10.3</td>
</tr>
</tbody>
</table>

a) Products were not identified.
b) CH₃CN containing 1% CF₃COOH and 1% (CF₃CO)₂O.

1d did not. The rate of formation of 2b from 1b was much slower than that of 2a from 1a. The oxidations of 1a and 1b in acetonitrile also gave the corresponding phenazines as the final products, and the rate of formation of 2a and 2b was faster in acetonitrile than in benzene. Thus the oxidation of an equimolar mixture of 1a and 1b was carried out in acetonitrile.

The oxidation of 3 was carried out in acetonitrile containing 1% trifluoroacetic acid and 1% trifluoroacetic anhydride, because the formation of the phenazines was negligible in benzene and in acetonitrile. The yield of 2,2’-dinitrodiphenyl disulfide was much lower than

that of diphenyl disulfide, whereas N-(2-nitrophenylthio)acetamide was obtained from the oxidation of 3.

**Discussion**

The following schemes are suggested for the oxidations of 1a and 1b (Chart 1). The formation of 2,7-disubstituted phenazines through intermediacy of nitrenes was reported on

\[
\begin{align*}
\text{A} & \quad \xrightarrow{\text{e}^-} \quad \text{A}^+ \quad \xrightarrow{\text{H}^+} \quad \text{A}^+ \\
\text{2C} & \quad \xrightarrow{2\text{e}^-} \quad \text{2B} \\
\text{B} & \quad \xrightarrow{\text{ne}} \quad \text{unidentified products}
\end{align*}
\]

Chart 1

the pyrolysis of p-methoxyphenylazide in cumene and on the rearrangement of azobenzenes to phenazines. Since the observation of crossover products was claimed to favor the nitrene pathway in the latter reaction, the formation of 2-methoxy-7-methylphenazine on the oxidation of an equimolar mixture of 1a and 1b is considered to give an evidence, although not conclusive, for the nitrene pathway.

As to the oxidation of 3 in acetonitrile, the effect of an acid has to be considered. The nitrogen atom of A3 is considered to be less basic than that of A1 because of electronegativity of 2-nitro group, and hence in the absence of CF₃COOH A3 is immediately deprotonated and oxidized further to unidentified products. ESR experiments showed that B3 is unstable in the presence of PbO₂. In the presence of CF₃COOH, a part of A3 undergoes homolytic cleavage of the S–N bond, and most of A3 are oxidized further to D without deprotonation,

\[
\begin{align*}
\text{A3} & \quad \xrightarrow{\text{e}^-} \quad \text{A}^+ \\
\text{D} & \quad \xrightarrow{2\text{e}^-} \quad \text{C} + \text{R}^+
\end{align*}
\]

Chart 2

and the S–N bond in D is immediately cleaved to form C and the sulfenylammonium ion. Nucleophilic attack of acetonitrile on the sulphenylammonium ion followed by hydrolysis yield 6 (Chart 2).

The sulphenylammonium ion has been suggested as a possible reaction intermediate in various electrophilic reactions.9 Detailed kinetic analyses failed, however, to support such a mechanism. The strong evidence supporting the existence of sulphenylammonium ions so far available is the ionic behavior of sulphenyl chloride–Lewis acids adducts and results from conductivity, spectroscopic, and cryoscopic studies of 2,4-dinitrobenzenesulphenyl chloride in sulfuric acid solutions.10 However, the recent study on the nuclear magnetic resonance (NMR) and conductimetric behavior of methane- and ethane-sulphenyl chloride in liquid sulfur dioxide gave no indication of the presence of sulphenylammonium ion.11 Our result on the formation of N-(2-nitrophenylthio)acetamide can be considered to be a conclusive evidence for the intermediacy of sulphenylammonium ion. Nucleophilic attack of acetonitrile on carbonium ions was reported by Eberon and Nyberg for the anodic oxidations of pivalic acid and polymethylbenzenes in acetonitrile.12a

The relationship between the stability of the sulphenanilidyl radicals and the formation of the phenazines is not clear at present. As to the oxidation of 3 the phenazines are formed most efficiently in acetonitrile containing 1% CF₃COOH and 1% (CF₃CO)₂O, in which the 2,4-dinitrobenzenesulphenanilidyl radicals are most unstable. On the other hand, the oxidation of 3d, which gives the most unstable radical, yields only a negligible amount of phenazine. Detailed studies are required on this.

Experimental

Materials—Benzenesulphenanilides were prepared as described previously. 2-Nitrobenzenesulphenanilides were prepared from 2-nitrobenzenesulphenyl chloride and the corresponding anilines by a known method. Acetonitrile was purified as described previously. The purified acetonitrile contained 5–10 mm of water as determined by the method of Hogan et al. Lead dioxide, trifluoroacetic acid, and trifluoroacetic anhydride were reagent grade chemicals and were used without further purification.

Apparatus—ESR spectra were recorded on a JES-FE 1X spectrometer, equipped with 100 kHz field modulation, at room temperature. Computer simulation of the spectrum was carried out using a JEOL EC-100 computer system. UV, IR, and NMR spectra were obtained as described previously.14

Isolation of Products—Typical examples of the procedure are given below.

a) In a flask 1a (116 mg) was dissolved in benzene (50 ml), and PbO₂ (530 mg) was added to the solution. The flask was placed in a thermostatic bath (30°) and the mixture was stirred with a magnetic stirrer. After 2 hr the reaction mixture was filtered and the filtrate was extracted with HCl solution (10%). When the HCl solution was made slightly alkaline with NH₄OH solution, yellow crystals separated out, which were collected and subjected to column chromatography on neutral alumina with benzene as eluant. The yellow crystals (30.8 mg, mp 249–250) obtained from the first eluent were identified as 2a from its UV, visible, IR, and NMR spectra in comparison with those of an authentic sample. The benzene layer which had been extracted with HCl solution was subjected to column chromatography on alumina with CCl₄ as eluant. The white crystals obtained from the first fraction were identified as diphenyl disulphide (4) (36.9 mg, mp 61–62°). After 4 was eluted completely, the eluant was changed to CHCl₃. The yellow crystals obtained from the effluent were identified as 2a (2.3 mg).

b) 1a (187 mg) and 1b (172 mg) were dissolved in acetonitrile (160 ml) and treated with PbO₂ (997 mg) at 40°. After 15 hr the mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in benzene and the benzene solution was extracted with HCl solution

When the HCl solution was made slightly alkaline with 20% NaOH, a yellow precipitate separated out, which was collected and subjected to column chromatography on alumina with CCl₄ as eluant. The yellow crystals obtained from the effluent were subjected to preparative thin-layer chromatography on alumina with benzene as the developing solvent. Three yellow bands were obtained, and each band was scraped off and extracted with CHCl₃. From the top band 2b (6.4 mg, mp 162.5—163°) was obtained. Yellow crystals obtained from the middle band was recrystallized from n-hexane (15.3 mg, mp 167.5—168.5°) and identified as 2-methoxy-7-methylphenazine by elemental analysis, UV, and NMR spectra. _Anal._ Calcd. for C₁₄H₁₃N₂O: C, 74.98; H, 5.40; N, 12.49. Found: C, 74.72; H, 5.43; N, 12.58. UV λ_{max} nm (e): 258 (97000), 352 (8380), 392 (8400), 410 (7420). NMR (CDCl₃) δ (ppm): 2.63 (3H, s, CH₃), 4.02 (5H, s, OCH₃), 7.35—7.75 (3H, m, aromatic protons), 7.9—8.15 (3H, m, aromatic protons). From the lowest band 2a (19.7 mg) was obtained.

3a (140 mg) was dissolved in acetonitrile containing 1% CF₃COOH and 1% (CF₃CO)₂O (50 ml) and treated with PbO₂ (250 mg) at 40°. After 40 min solid Na₂CO₃ (100 mg) was added to the reaction mixture. The mixture was filtered and the filtrate was evaporated to dryness. The residue was subjected to preparative thin-layer chromatography on alumina with CHCl₃—benzene (1:2) as the developing solvent. Three bands were obtained, and each band was scraped off and extracted with CHCl₃. 2,2'-Dinitrodiphenyl disulphide (14.0 mg) and 2a (27.3 mg) were obtained from the top and the middle bands, respectively. From the lowest band yellow crystals (15.7 mg, mp 179—180°) were obtained and identified as N-(o-nitrophenylthio)acetamide (6) by elemental analysis, IR, NMR and Mass spectra. _Anal._ Calcd. for C₄H₆N₂O₂S: C, 45.25; H, 3.79; N, 13.20; S, 15.11. Found: C, 44.70; H, 3.79; N, 13.21; S, 14.98. IR ν_{max} cm⁻¹: 3200 (NH), 1660 and 1560 (CO, amide), 1560 and 1335 (NO₂), 1300 and 1240 (S-N). NMR (CDCl₃) δ: 2.16 (3H, s, CH₃), 7.3—7.5 (2H, m, aromatic protons), 7.65—7.9 (1H, m, aromatic proton), 8.25—8.45 (1H, m, aromatic proton), 9.68 (1H, s, NH). Mass Spectrum m/e: 212 (M⁺). 6 was synthesized separately from 2-nitrobenzenesulfonyl chloride and acetamide, which was identical with 6 obtained from the oxidation of 3.

15) Tetramethylsilane was used as the internal standard.