Oxidation of 2,6-Piperazinediones

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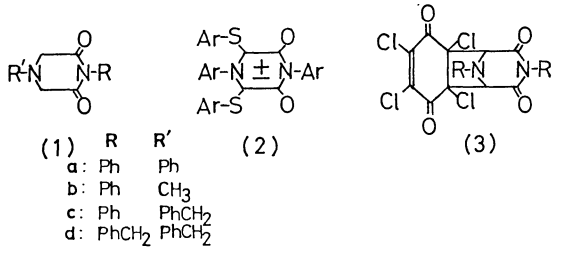
1,4-Disubstituted 2,6-piperazinediones (**1**) are susceptible to oxidation at the methylene group in the piperazine ring, giving piperazinetetrone (**4**) on being treated with selenium dioxide in boiling dioxane. Treatment of 1,4-diphenyl-2,6-piperazinedione (**1a**) with either nitrobenzene or tosyl chloride and triethylamine in benzene gives cyclic dimer (**9**) of dehydrogenated **1a**. Cycloadduct (**10**) is obtained in the presecne of *N*-phenylmaleimide. It seems that both **9** and **10** are formed *via* labile mesoionic intermediate (**8**). Piperazinedione (**1a**) reacted with tosyl chloride, pyridine, and benzoyl chloride to give mesoionic compound (**11**) having 3-benzoyl and 5-(*p*-tolylthio) groups.

Only a few papers have appeared on the oxidation of 2,6-piperazinedione derivatives. Oxidation of piperazinediones by chromium trioxide[1] or nitric acid[2] was reported to afford piperazinetetrones. Honzl *et al.*[3] reported that the reaction of 1,4-disubstituted 2,6-piperazinedione (**1**) with phosphorus pentachloride followed by hydrolysis afforded a piperazinetetrone, while the reaction of 1,4-disubstituted 2,6-piperazinedione with arenesulfonyl chloride in pyridine yielded six-membered mesoionic compound (**2**) by dehydrogenation and substitution at positions 3 and 5. The reaction of 1,4-disubstituted 2,6-piperazinedione with chloranil afforded cycloadducts (**3**) formed by the addition of chloranil to the dehydrogenated 2,6-piperazinedione at positions 3 and 5.[4]



The peculiar behavior of 2,6-piperazinedione to form a mesoionic intermediate is similar to that of hydrogenated benzenoid aromatics which show a tendency to form aromatic systems by dehydrogenation. These results prompted us to examine the behavior of 2,6-piperazinedione towards various oxidizing reagents. The positions susceptible to oxidation are apparently 3 and 5, the anticipated reactions being the formation of piperazinetetrone (**4**) and a mesoionic intermediate (**8**). The final products of the latter reaction depend on the stability of the mesoionic intermediate and the nature of the oxidizing reagents employed. In the case the intermediate is labile, isolation of its substituted derivative, dimerization product or cycloadduct with a trapping reagent may be anticipated. The present paper deals with the reaction of 1,4-disubstituted 2,6-piperazinediones with several oxidizing reagents other than those so far reported.

Results and Discussion

Oxidation with Selenium Dioxide. Selenium dioxide is usually used for the oxidation of an active methylene or methyl group to a carbonyl group and sometimes

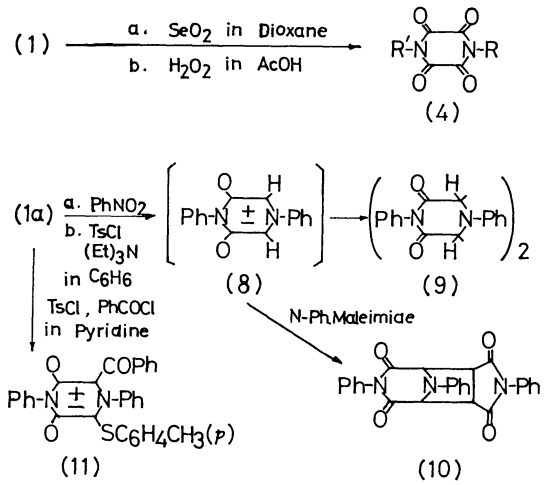


Fig. 1. Reaction scheme of 1,4-disubstituted 2,6-piperazinediones.

for the dehydrogenation of dihydroaromatics to aromatic compounds. We have found that the oxidation of 1,4-disubstituted 2,6-piperazinediones (**1**) with selenium dioxide in dioxane afforded the corresponding piperazinetetrones, (**4a**—**d**) no formation of mesoionic intermediate being observed. The yields, melting points, and IR absorptions of the products are summarized in Table 1.

When some acid anhydrides are used as the cyclization reagent in the synthesis of five-membered mesoionic heterocycles, the products isolated are frequently their stable derivatives formed by acylation of the cyclization products.[5] An attempt to isolate the labile intermediate in the form of its acetyl derivatives by using acetic anhydride instead of dioxane was unsuccessful.

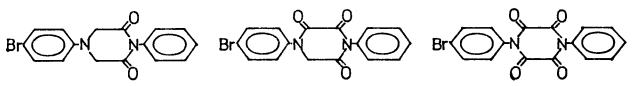
In view of the current mechanism of the selenium dioxide oxidation,[6] the selective oxidation of ring methylene group to carbonyl group can be ascribed to the initial enolization which facilitates the attack of selenium dioxide. When 1,4-diphenyl- or 1-phenyl-4-benzyl-2,6-piperazinedione was oxidized with selenium dioxide in dioxane, a samll amount of the corresponding *N*,*N*′-disubstituted oxamide was isolated along with the tetrone. That these oxamides are formed by hydrolysis of the tetrones was confirmed by a separate experiment wherein the hydrolysis of 1,4-diphenylpiperazinetetrone in boiling dioxane containing a small amount of water in the presence of selenium dioxide

Table 1. Products from the oxidation of 1,4-disubstituted 2,6-piperazinedione with selenium dioxide

	Product R	R′	Mp (°C) (Recryst. solv.)	IR (cm^{-1})			Yield (%)	By-product (Yield %)
4a	Ph	Ph	290—295 (DMF-EtOH)	1770 1689	1710 1680	1696	34	$(PhNHCO)_2$ (6%)
4b	Ph	CH_3	314—316 (DMF-EtOH)	1767 1704	1744 1688	1712	65	
4c	Ph	$PhCH_2$	268—271 (Acetone-Et_2O)	1770 1688	1713	1704	46	$PhNHCOCONHCH_2Ph$ (3%)
4d	$PhCH_2$	$PhCH_2$	263—265 (CH_2CN)	1760 1686	1705	1696	99	

afforded *N*,*N*′-diphenyloxamide. The formation of the tetrone derivatives was also observed when 1,4-diphenyl-2,6-piperazinedione was oxidized with hydrogen peroxide in acetic acid.

Reaction with Bromine. Investigation of the behavior of 2,6-piperazinediones towards bromine seems to be of interest in view of the validity of bromine both as an oxidizing and brominating reagent and the polyfunctional structure of 1,4-disubstituted 2,6-piperazinedione. Among the reactions of bromine we have carried out, only one reaction gave an isolable product: the reaction of 1,4-diphenyl-2,6-piperazinedione (**1a**) with an equimolar of bromine in acetic acid at room temperature occurred immediately affording 4-(*p*-bromophenyl)-1-phenyl-2,6-piperazinedione hydrobromide which was readily hydrolyzed by water to give the free base (**5**). This shows that the *p*-position of the 4-phenyl substituent is activated by the amino nitrogen towards electrophilic substitution. Further reaction of the free base with bromine in chloroform immediately gave a precipitation, but work up of the precipitate gave mostly the starting material. From the mother liquor of the reaction, trione (**6**) was isolated in poor yield which was characterized by elemental and spectral analyses. When **5** was reacted with bromine in nitrobenzene at 100 °C, tetrone (**7**) was isolated along with the trione in a poor yield.



(5) (6) (7)

Oxidation with Nitrobenzene. A well-known reaction in which nitrobenzene plays a role of dehydrogenation to form an aromatic system is the Skraup synthesis of quinoline. The fact that 2,6-piperazinediones are readily dehydrogenated to an aromatic system led us to investigate the reaction of 2,6-piperazinediones with nitrobenzene, the formation of mesoionic intermediates being expected.

When **1a** was heated in nitrobenzene under reflux, a product isolated in poor yield was considered to be a dimer of mesoionic intermediate (**8**) on the basis of elemental and spectral analyses. The formation of this dimer (**9**) was not observed at 170—175 °C and decomposition of **1a** predominated at 210 °C. It was found that the addition of acetic anhydride to the reaction mixture loweres the reaction temperature, improving the yield of the dimer to 23%. However, the role of acetic anhydride in this reaction remains unsettled. The formation of the dimer may be ascribed to the dimerization of the 1,3-dipolar mesoionic intermediate (**8**). The proposed intermediate could successfully trapped by addition of *N*-phenylmaleimide to the reaction mixture and a cycloadduct (**10**) was obtained. **10** was isolated by the reaction of **1a** with chloranil in the presence of *N*-phenylmaleimide.[4]

Reaction of 2,6-Piperazinedione with Tosyl Chloride. Honzl *et al.* obtained mesoionic compounds (**2**) by the reaction of 2,6-piperazinedione with tosyl chloride in pyridine, though the mechanism of this reaction remains unsolved. We tried to improve the yield of the mesoionic product following their procedure[3] by varying the reaction time, reaction temperature, molar ratio of the reactants and using pyridine homologues as the solvent instead of pyridine. However, no improvement was achieved. The reaction of 2,6-piperazinedione with tosyl chloride in benzene in the presence of triethylamine gave the same dimer (**9**) as that obtained by oxidation of 2,6-piperazinedione with nitrobenzene. When the reaction was carried out in the presence of *N*-phenylmaleimide, the cycloadduct (**10**) was obtained. We then performed the reaction of 2,6-piperazinedione with tosyl chloride in pyridine in the presence of benzoyl chloride anticipating the formation of a mesoionic compound having benzoyl groups instead of *p*-tolylthio groups of compound **2**. The reaction gave mesoionic compound (**11**) with a 3-benzoyl-5-(*p*-tolylthio) substituent in 14% yield along with a small quantity of **2**, no 3,5-dibenzoyl derivative being isolated. Compound **11** could be formed neither from **1a** nor **2** by heating with benzoyl chloride in pyridine. This indicates that **11** was formed not *via* **2**, but presumably by benzoylation of mesoionic intermediate having one *p*-tolylthio group.

Experimental

All the melting points are uncorrected. The IR spectra were recorded on a JASCO IRA-2 spectrometer and NMR spectra on a JEOL H-100 spectrometer.

Materials. Commercial seleium dioxide, chloroform, nitrobenzene, triethylamine, benzoyl chloride, pyridine, and *N*-phenylmaleimide were used without further purification. Dioxane was distilled and tosyl chloride was recrystallized from benzene.

General Procedure for Oxidation with Selenium Dioxide. Selenium dioxide (10 mmol) was added to a solution of 1,4-disubstituted 2,6-piperazinedione (5 mmol) in dioxane (20 ml), and the resulting mixture was refluxed for 6 h. After being cooled, solid products were collected by filtration and subjected to continuous extraction with acetone in a Soxhlet apparatus. The extract was evaporated to dryness under reduced pressure and the residue was recrystallized from the solvents given in Table 1.

*1-Methyl-4-phenylpiperazinetetrone (**4b**).* Colorless silky crystals, mp 314—316 °C. Found: C, 56.86; H, 3.38; N, 12.21%. Calcd for $C_{11}H_8N_2O_4$: C, 56.89; H, 3.48: N, 12.07%.

*1-Benzyl-4-phenylpiperazinetetrone (**4c**).* Colorless silky crystals, mp 268—271 °C. Found: C, 66.30; H, 3.96; N, 8.93%. Calcd for $C_{17}H_{12}N_2O_4$: C, 66.22; H, 3.93; N, 9.09 %.

*1,4-Dibenzylpiperazinetetrone (**4d**).* Colorless needles, mp 263—265 °C. Found: C, 67.19; H, 4.38; N, 8.79%. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.39; N, 8.69%.

*4,9,11,12-Tetraphenyl-4,9,11,12-tetraazatricyclo[5.3.1.1^{2,6}]dodecane-3,5,8,10-tetrone (**9**).* *Method A*: A mixture of **1a** (3 g, 11.3 mmol), acetic anhydride (2.3 g, 22.6 mmol), and nitrobenzene (30 ml) was heated at 170—175 °C for 5 h. The mixture was concentrated under reduced pressure and cooled, and the resulting brown solid was filtered and washed with ethanol. Recrystallization of the solid from DMSO gave 0.8 g (27%) of **9**. Colorless needles, mp 420—423 °C. Found: C, 72.35; H, 4.60; N, 10.58%. Calcd for $C_{32}H_{24}N_4O_4$: C, 72.71; H, 4.58; N, 10.60%. IR (KBr): 1730, 1690 cm^{-1}. MS: *m/e* 528 (M$^+$).

Method B: Triethylamine (3 g, 30 mmol) was added to a solution of **1a** (4 g, 15 mmol) and tosyl chloride (5.7 g, 30 mmol) in benzene (55 ml), and the resulting mixture was refluxed for 27 h. The solvent was evaporated under reduced pressure to give an oil which gradually crystallized by addition of a small amount of benzene under cooling. The crystals were filtered and washed with water to give 0.4 g (10%) of crude **9**.

*4,9,11-Triphenyl-4,9,11-triazatricyclo[5.3.1.0^{2,6}]undecane-3,5,8,-10-tetrone (**10**).* *Method A*: A mixture of **1a** (1 g. 3.3 mmol), *N*-phenylmaleimide (0.65 g, 3.8 mmol), and nitrobenzene (15 ml) was refluxed for 8 h. After cooling, crystals were filtered and washed with diethyl ether. Recrystallization of the product from acetonitrile gave 0.2 g (12%) of **10** as colorless needles, mp 326—327 °C. IR (KBr): 1742, 1708, 1684 cm^{-1}. The product was identified as **10** by comparison of its IR spectrum and mixed melting point measurement with the authentic sample synthesized by the method using chloranil.[4]

Method B: Triethylamine (0.8 g, 8 mmol) was added to a solution of **1a** (1 g, 3.8 mmol), *N*-phenylmaleimide (0.65 g, 3.8 mmol), and tosyl chloride (1,5 g. 7.9 mmol) in benzene (10 ml), and the mixture was refluxed for 20 h. White crystals formed gradually during the course of heating were filtered and washed with water. The crude product was recrystallized from acetonitrile.

*Anhydro-3-benzoyl-2,6-dihydroxy-1,4-diphenyl-5-(p-tolylthio)-pyrazinium dihydroxide (**11**).* A solution of benzoyl chloride (3.2 g, 22.6 mmol) in pyridine (15 ml) was added dropwise to a solution of **1a** (3 g, 11.3 mmol) and tosyl chloride (4.3 g, 22.6 mmol) in pyridine (40 ml) under reflux over a period of 1 h. The resulting mixture was refluxed for 19 h. After cooling, the reaction mixture was poured into ice-water and the resulting dark brown solid was chromatographed on silica gel using chloroform as an eluent. The 4th fraction gave 0.73 g (13.8%) of **11** as yellow needles, mp *ca.* 240 °C. This was recrystallized from 1-propanol to give yellow needles, mp 244—245 °C. Found: C, 73.13; H, 4.58; N, 5.54%. Calcd for $C_{30}H_{22}N_2O_3S$: C, 73.45; H, 4.52; N, 5.71%. IR (KBr): 1675, 1650, 1620 cm^{-1}. NMR (τ): 2.4—3.0 (m, 19, Ar-H), 7.75 (s, 3, CH_3). MS: *m/e* 490 (M$^+$).

Mesoionic 1,4-diphenyl-3,5-di(*p*-tolylthio) derivative (**2**) was isolated from the 3rd fraction of chromatography described above as yellow needles, mp 239—241 °C.

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