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A CONVENIENT METHOD FOR THE PREPARATION OF THIOLS SUSCEPTIBLE TO OXIDATION. THE EFFECT OF NITROGEN ON THE SUSCEPTIBILITY TO OXIDATION-REDUCTION IN SULFUR OF BIVALENT SULFUR COMPOUNDS.

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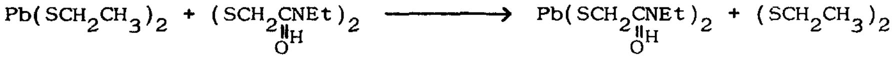
It is known that bivalent organic sulfur compounds possess the facile properties to form the stable metal complexes with Hg^{2+}, Cu^{2+}, or Pb^{2+} and to participate in oxidation-reduction with electron transfer in the sulfur atom. These properties are ascribed to the use of d_{π} orbitals to form multiple bonds and to both their low ionization potentials and high electron affinities. Recently, studies on new synthetic reactions utilizing these important features of bivalent organic sulfur compounds have been investigated in our laboratory. In the previous paper,2) the oxidizing power of the disulfides determined by reactions of lead thiolates with disulfides was shown to increase in the following order : diphenyl disulfide < dibenzoyl disulfide < bis(thiobenzoyl) disulfide < bis(diethylthiocarbamoyl) disulfide(1). This sequence depends primarily upon the stabilities of the corresponding thiolate anions of disulfides. In the present paper, the effect of the nitrogen atom on the oxidizing power of various disulfides was studied in detail with the assumption that the oxidizing power of 1 would essentially be attributed to its diethylamino group.

When lead ethanethiolate3) was allowed to react with 2,2'-dithiobis (N-ethylacetamide)(2) in chloroform at room temperature, the reaction was completed within ten minutes to give lead N-ethylcarbamoylmethanethiolate(3) and diethyl disulfide in 97 and 67% yields, respectively. Similarly, by treating lead ethanethiolate with 2,2'-dithiodianiline at room temperature, lead *o*-aminobenzenethiolate(98%)



$$Pb(SCH_2CH_3)_2 + (SCH_2\underset{\underset{O}{\|}}{C}\underset{H}{N}Et)_2 \longrightarrow Pb(SCH_2\underset{\underset{O}{\|}}{C}\underset{H}{N}Et)_2 + (SCH_2CH_3)_2$$

2 **3**

and diethyl disulfide(53%) were obtained. The results of reduction of various disulfides with lead thiolates are shown in Table I. In the case of the reaction of L-cystine with lead ethanethiolate in aqueous alkaline solution at room temperature, optically active L-cysteine hydrochloride hydrate was obtained in good yield. This type of oxidation-reduction reaction could therefore be simply generalized as follows :

Table I

Reduction of Disulfides with Lead Thiolates

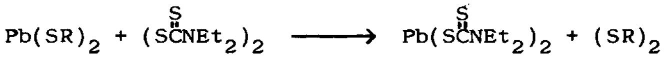
$$Pb(SR)_2 + (SR')_2 \longrightarrow Pb(SR')_2 + (SR)_2$$

		Reaction		Yield, %	
R	R'	Temp., °C	Time, min.	$Pb(SR')_2$	$(SR)_2$
Et	$CH_2CONHEt$	25	10	97	67
Ph	$CH_2CONHEt$	25	60	98	98
Et	C_6H_4-NH_2-o	25	20	98	53
Ph	C_6H_4-NH_2-o	65	20	99	94

$$Pb(S-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-)_2 + \begin{matrix} S-C-C-N- \\ | \\ S-C-C-N- \end{matrix} \longrightarrow Pb\left(\begin{matrix} \swarrow N-\overset{|}{C}- \\ \searrow S-\underset{|}{C}- \end{matrix}\right)_2 + (S-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-)_2$$

In addition, it was established that treatment of **2** with lead carbethoxymethanethiolate in chloroform at room temperature for ten minutes resulted in the formation of **3** and 2,2'-dithiodiacetic acid diethyl ester in almost quantitative yields. These results clearly indicate that the introduction of an amino group into the β-carbon greatly increases the oxidizing power of disulfides.

However, it was confirmed by the following reaction that these disulfides with an amino group have weak oxidizing power in comparison with **1** (see Table II).

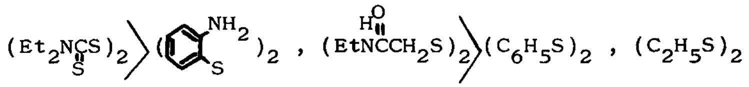


$$Pb(SR)_2 + \underset{\underline{\mathbf{1}}}{(S\overset{S}{\overset{\|}{C}}NEt_2)_2} \longrightarrow Pb(S\overset{S}{\overset{\|}{C}}NEt_2)_2 + (SR)_2$$

Table II

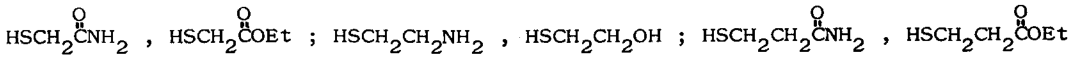
R	Yield, % Pb($S_2CNEt_2)_2$	$(SR)_2$
CH_2CH_3	97	66
CH_2CO_2Et	97	84
$CH_2CONHEt$	97	96
C_6H_4-NH_2-o	98	97
CH_2CH_2OH	98	91
CH_2CH_2NHAc	98	96

The above results afford the new order of oxidizing power of disulfides as shown below :



It is well known that thiols become more susceptible to oxidation as their acidities increase. The pKa values[4)] of ethanethiol, 2-aminoethanethiol, benzenethiol, and o-aminobenzenethiol are reported to be 10.50, 8.35, 7.78, and 6.59, respectively, indicating that the introduction of an amino group into the β-carbon of thiols largely increases their acidities.

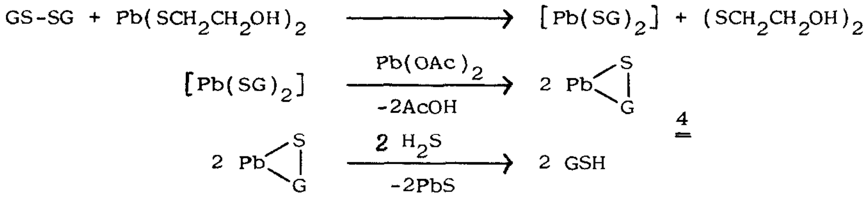
Further, it can be said that thiols with an amino group are generally susceptible to oxidation in comparison with the oxygen analogues in the following pairs of thiols :



$$HSCH_2\overset{O}{\overset{\|}{C}}NH_2\ ,\ HSCH_2\overset{O}{\overset{\|}{C}}OEt\ ;\ HSCH_2CH_2NH_2\ ,\ HSCH_2CH_2OH\ ;\ HSCH_2CH_2\overset{O}{\overset{\|}{C}}NH_2\ ,\ HSCH_2CH_2\overset{O}{\overset{\|}{C}}OEt$$

In summary, it was concluded that the introduction of an amino group into the β-carbon of disulfides and into that of thiols increases the oxidizing power of disulfides and *vice versa* increases the reducing power of thiols. This conclusion suggests that the nitrogen atom would facilitate oxidation-reduction with electron transfer in the sulfur atom of bivalent sulfur compounds.

Next, the conclusion led to the successful synthesis of thiols susceptible to oxidation from the corresponding disulfides by the reaction with lead thiolates. When oxidized glutathione(GSSG) was allowed to react with lead 2-hydroxyethanethiolate in the presence of 1 equiv of lead acetate at room temperature under nitrogen atmosphere in water overnight with stirring, lead complex(**4**)5) was obtained. Lead acetate was used in order to remove 1 equiv of reduced glutathione(GSH), γ-L-glutamyl-L-cysteinyl-glycine, from the reaction mixture as the water-insoluble lead complex **4**. This complex was then treated with hydrogen sulfide to give optically active GSH (mp 190-192°, $[\alpha]_D^{20}$ -20.1 (C 2.0, H_2O)) in 81% yield.



In addition, it was found that the complex **4** resulted by treating GSSG with 2 equiv of 2-hydroxyethanethiol and 2 equiv of lead acetate under the same conditions. Treatment of **4** with hydrogen sulfide gave optically active GSH in 87% yield.

REFERENCES

1) Sankyo Chemical Industry Co., Ltd., Ofuna, Kamakura, Japan.

2) T. Mukaiyama and T. Endo, *Bull. Chem. Soc. Japan*, **40**, 2388 (1967).

3) All compounds gave satisfactory elemental analytical values.

4) J. P. Danehy and C. J. Noel, *J. Am. Chem. Soc.*, **82**, 2511 (1960).

5) Elemental analysis showed that the molar ratio of Pb and GSH in **4** was 1 : 1, but the detailed structure of **4** remains unknown. For the structure of the lead complex of cysteine, see H. Bauer and K. Burschkies, *Chem. Ber.*, **66**, 1041 (1933).