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The Synthesis of Methylthio- and Bis(methylthio)phenazine Derivatives

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Synopsis. A number of methylthio- and bis(methylthio)phenazine derivatives have been prepared by the reactions of various halogenophenazines and their *N*-oxides with sodium methyl sulfide.

Phenazine derivatives have received much attention because of their potential biological activities.[1] In previous paper,[2-4] the syntheses of piperidino-, morpholino-, and carboxymethylthiophenazines were reported. This note will describe the preparation of methylthiophenazines. Kidani *et al.*[5] reported that 1- and 2-methylthiophenazine were prepared from 1- and 2-phenazine isothiouronium chloride respectively. Recently 1-methylthiophenazine 5-oxide was derived from *N*-acyl-2′-methylthio-2-nitrodiphenylamine by a photochemical reaction.[6] In the present work, methylthio- and bis(methylthio)phenazines were prepared by nucleophilic displacement on the corresponding halogenophenazine derivatives.

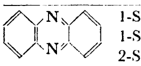
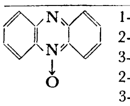
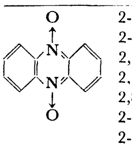
The reactions of monohalogenophenazines, their *N*-oxides, and *N,N′*-dioxides with an equimolecular quantity of sodium methyl sulfide gave the corresponding methylthiophenazine derivatives in good yields. The reactions of dihalogenophenazines, their *N*-oxides, and *N,N′*-dioxides with a two-molar quantity of the sulfide gave the corresponding bis (methylthio)phenazine derivatives. In these reactions, the *N*-oxides, and *N,N′*-dioxides underwent a partial elimination of the oxide group to form the desired methylthiophenazines and their *N*-oxides respectively. In the presence of an excess of the reagent, the replacement reaction of the halogenophenazine *N*-oxide or *N,N′*-dioxide is accompanied by the removal of the oxide group to give the methylthio compound, as was found during substitution with sodium mercaptoacetate.[4,7] The results of the deoxygenation reactions observed during the nucleophilic displacement of halogen atoms of the monohalogenophenazine *N*-oxides are summarized in Table 1. By these replacement reactions, all the isomers of methylthio- and bis(methylthio)phenazine could be prepared from the corresponding halogenophenazine derivatives.

TABLE 1. REACTION OF HALOGENOPHENAZINE *N*-OXIDES WITH METHANETHIOL

Halogeno-phenazine 5-oxide	(Product Yield,[a] %)		
	Methylthio-phenazine	Its oxide	Its dioxide
1-Cl	4	87	
	98		
2-Cl	18	79	
	98		
2-Br	8	90	
	99		
3-Cl	2	95	
	98		
3-Br	1	97	
	98		
2-Cl[b]	2	8	76
	81	1	
2-Br[b]	1	3	87
2-Cl, 7-OMe	16	74	
	63		

a) The numerical data in the upper column are the yield when the reactions are run in the equimolecular quantity of the thiol, and those in the lower column are the yield when the reactions are run in five molar quantity of the reagent.
b) This compound is 5,10-dioxide.

TABLE 2. SYNTHESES AND PROPERTIES OF METHYLTHIO- AND BIS(METHYLTHIO)PHENAZINE DERIVATIVES

Compound		Mp (°C)	Synth. method	Reaction time (hr)	Yield (%)
Ring	Substituent				
	1-SMe	173—174[a]	A, F	10, 0.1	98, 86
	1-SMe, 6-OMe	227—228	A	10	79
	2-SMe	159—160[b]	A, B, F	5, 4, 0.1	98, 79, 96
	2-SMe, 7-OMe	211—212	A, F	6, 0.2	63, 85
	2-SMe, 9-OMe	132—133	A	10	81
	2-SMe, 9-Me	132—133	A	8	90
	1,2-Bis(SMe)	161—162	C, F	10, 0.2	92, 97
	1,3-Bis(SMe)	185—186	C, F	10, 0.2	85, 88
	1,4-Bis(SMe)	264—265	C	8	92
	1,6-Bis(SMe)	270—271	C	10	93
	1,7-Bis(SMe)	184—185	B	10	83
	1,8-Bis(SMe)	190—191	C, F	10, 0.2	92, 90
	1,9-Bis(SMe)	225—226	C	10	88
	2,3-Bis(SMe)	123—125	C	10	90
	2,7-Bis(SMe)	217—218	C	10	91
	2,8-Bis(SMe)	200—201	C	10	91
	1-SO_2Me	230—231	D, F	3, 0.2	85, 87
	2-SO_2Me	223—224	D, F	2.5, 0.3	85, 98
	2-SO_2Me, 7-OMe	220—222	D, F	2, 0.2	70, 83
	1-SMe	208—209(dec)[c]	B	7	87
	2-SMe	147—148	B	4	90
	3-SMe	171—172	B	4	97
	2-SMe, 7-OMe	187—188	B	6	74
	3-SMe, 8-OMe	195—196	B	4	3
	1,2-Bis(SMe)	181—182	B	8	57
	1,3-Bis(SMe)	223—224(dec)	B	7.5	71
	1,7-Bis(SMe)	234—235(dec)	B	10	15
	1,8-Bis(SMe)	200—201	B	8	66
	1,9-Bis(SMe)	242—243(dec)	B	8	50
	2,3-Bis(SMe)	209—210	B	8	37
	2,7-Bis(SMe)	210—211	B	8	37
	2,8-Bis(SMe)	213—214(dec)	B	8	51
	1-SO_2Me	241—242(dec)	E, D	18, 3	86, 68
	2-SO_2Me	207—208	D	3	91
	3-SO_2Me	187—188	D	3	90
	2-SO_2Me, 7-OMe	217—218(dec)	D	2	64
	2-SMe	187—188(dec)	B	4	87
	2-SMe, 7-OMe	218—219(dec)	B	4	86
	2,3-Bis(SMe)	225—226(dec)	B	8	30
	2,7-Bis(SMe)	222—223(dec)	B	7	32
	2,8-Bis(SMe)	228—229(dec)	B	8	33
	2-SO_2Me	202—203(dec)	E, D	18, 5	84, 78
	2-SO_2Me, 7-OMe	205—206(dec)	E, D	18, 2	90, 83

a) Reported mp: 172—173°C.[5] b) Reported mp: 159.5—160°C.[5] c) Reported mp: 213°C.[6]

The results of the series of reactions show that the halogen atoms of the mono- and dihalogenophenazines are easily displaced with the methyl sulfide, in contrast to the cases of the alcoholysis[8] and the hydrolysis,[8,9] as can be expected in view of the high nucleophilicity of the sulfide.[10] These substitutions are especially useful for the identification of the halogenophenazine derivatives.

The methylthiophenazine *N*-oxides and *N,N'*-dioxides were deoxygenated more effectively by treatment with zinc powder in acetic acid to give the methylthiophenazines, from which the sulfones were then prepared by oxidation with a limited amount of hydrogen peroxide in acetic acid. The oxidation of these compounds with an excess of hydrogen peroxide afforded the methylsulfonylphenazine *N*-oxide or *N,N'*-dioxide, which was subsequently converted into the methylsulfonylphenazine by reduction with zinc powder in acetic acid.

The syntheses and properties of the methylthio- and bis(methylthio)phenazine derivatives thus obtained are listed in Table 2.

Experimental

All the melting points are uncorrected.

Starting Materials. The following compounds were prepared by the methods given in the literature: phenazine (1-chloro-,[8] 1-chloro-6-methoxy-,[11] 2-bromo-,[12] 2-chloro-,[8] 2-chloro-7-methoxy-,[13] 2-chloro-9-methoxy-,[11] 2-chloro-9-methyl-,[14] 1,2-dichloro-,[15] 1,3-dichloro-,[15] 1,4-dichloro-,[15] 1,6-dichloro-,[16] 1,8-dichloro-,[17] 1,9-dichloro-,[17] 2,3-dichloro-,[15] 2,7-dibromo-,[18] 2,7-dichloro-,[9] and 2,8-dichloro-[15]), phenazine 5-oxide (1-chloro-,[8] 2-bromo-,[12] 2-chloro-,[8] 2-chloro-7-methoxy,[8] 3-bromo-,[12] 3-chloro-,[8] 1,2-dichloro-,[15] 1,3-dichloro-,[15] 1,7-dichloro-,[17] 1,8-dichloro-,[17] 1,9-dichloro-,[17] 2,3-dichloro-,[17] 2,7-dibromo-,[18] 2,7-dichloro-,[8] and 2,8-dichloro-[15]), and phenazine 5,10-dioxide (2-bromo-,[19] 2-chloro-,[9] 2-chloro-7-methoxy-,[19] 2,3-dichloro-,[17] 2,7-dichloro-,[8,9] and 2,8-dichloro-[17]).

Syntheses of Methylthio- and Bis(methylthio)phenazine Derivatives. These compounds were prepared by the six general methods (A, B, C, D, E, and F). The mthods, the reaction times, the yields, and the melting points, for each compound are summarized in Table 2. All the products had satisfactory elemental analyses (C, H, and N).

Method A. To a hot solution of the halogenophenazine derivative (10 mmol) in ethanol (80—500 ml), a 20% aqueous solution of sodium methyl sulfide (50 mmol) was added. After refluxing, the hot mixture was diluted with water. The crystals thereby separated were chromatographed over alumina, using benzene as the solvent, and then recrystallized from an appropriate solvent.

Method B. This method is the same as Method A except that the theoretical quantity of the sulfide is used.

Method C. This method is the same as those above except that a ten molar quantity of the sulfide is used.

Method D. A solution of methylthiophenazine (5 mmol) in a 30% aqueous solution (2 ml) of hydrogen peroxide and acetic acid (50 ml) was warmed at 55 °C and then poured into water. To the aqueous solution, sodium bicarbonate (15 g) was added. The crystals thus separated were recrystallized from an appropriate solvent.

Method E. To a solution of methylthio- or methylsulfonylphenazine (5 mmol) in acetic acid (100—200 ml) and acetic anhydride (10 ml), a 30% aqueous solution (20 ml) of hydrogen peroxide was added. The mixture was warmed at 55 °C and then poured into water (1—1.5 l). The crystals thus separated were recrystallized from an appropriate solvent.

Method F. Into a solution of the pheanzine *N*-oxide (2 mmol) in acetic acid (20—50 ml), zinc powder (1—1.5 g) was stirred in small portions. The mixture was then heated on a water bath and filtered while hot. After the ordinary treatment, the recrystallization of the product from an appropriate solvent afforded the phenazine.

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