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The Nucleophilic Substitution Reaction of 1-Halogeno-2-methylsulfonylphenazine 5-Oxides

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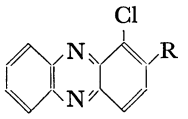
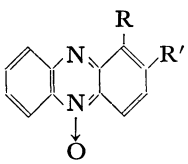
Synopsis. The halogen atom in 1-halogeno-2-methylsulfonylphenazine 5-oxide is reactive toward the anionoid reagents through the activating effects of both the sulfone group and the *N*-oxide group. By the nucleophilic substitutions, some 1-substituted 2-methylsulfonylphenazine derivatives have been prepared in high yields.

In a previous paper,[1] it has been shown that direct comparison of the reactivities of the halogen atoms in 1- and 2-halogenophenazines and their *N*-oxides has confirmed the activating effect of the *N*-oxide group. The halogen-activating effects from the presence of oxide groups have been shown in other compounds.[2] Heppolette *et al.*[3] reported that the halogen displacement in 2-halogenonitrobenzene could be strongly promoted by the introduction of a sulfone group in the 4-position. The author's interest in the activating effects of both a sulfone group and a *N*-oxide group has led to the suggestion that a halogen atom of 1-halogeno-2-methylsulfonylphenazine 5-oxide will be reactive toward anionoid reagents. As part of the synthetic study of phenazines with potential biological activities, this note will describe the preparation and the reaction of 1-halogeno-2-methylsulfonylphenazine 5-oxides.



1: R=Cl
3: R=SCH_3
5: R=SO_2CH_3



2: R=R′=Cl
4: R=Cl; R′=SCH_3
6: R=Cl; R′=SO_2CH_3
7: R=  ; R′=SO_2CH_3
8: R=Br; R′=SO_2CH_3
9: R=  ; R′=SO_2CH_3
10: R=Cl; R′=H
11: R=OH; R′=SO_2CH_3
12: R=OC_2H_5; R′=SO_2CH_3
13: R=$CH(CO_2C_2H_5)_2$; R′=SO_2CH_3
14: R=$CHCNCO_2C_2H_5$; R′=SO_2CH_3

The reaction of 1,2-dichlorophenazine (**1**)[4] and its 5-oxide (**2**)[4] with an equimolecular quantity of sodium methanethiolate gave the corresponding methylthiophenazines, **3** and **4**. Compound **4** was deoxygenated by the treatment with zinc dust in acetic acid to give **3**, from which sulfone (**5**) was then prepared by the oxidation with a limited amount of hydrogen peroxide in acetic acid. The further oxidation of **5** with an excess of hydrogen peroxide afforded 1-chloro-2-methylsulfonylphenazine 5-oxide (**6**), which was also derived from **4** by the oxidation. The position of the chlorine atom in **6** was confirmed by the following piperidination. The refluxing of **6** with piperidine in ethanol for 2 h afforded 2-methylsulfonyl-1-piperidinophenazine 5-oxide (**7**), which was also derived from 1-bromo-2-methylsulfonylphenazine 5-oxide (**8**).[5]

The heating of **6** or **8** with morpholine in ethanol for 2 h gave 2-methylsulfonyl-1-morpholinophenazine 5-oxide (**9**), whereas **5** was unreactive toward morpholine under similar conditions. The reactivity to the amine of either **6** or **8** is in contrast with that of 1-chlorophenazine 5-oxide (**10**).[6] The treatment of **8** with aqueous ethanolic alkali for 1.5 h afforded both 1-ethoxy- (**11**) and 1-hydroxy-2-methylsulfonylphenazine 5-oxides (**12**). The former was also obtained by the reaction of **6** or **8** with sodium ethoxide in ethanol, and the latter was also derived from **6** or **8** by the treatment with aqueous alkali. The reaction of **8** with active methylene compounds, such as diethyl malonate and ethyl cyanoacetate, gave the corresponding products, **13** and **14**.

The results of these substitutions of 1-halogeno-2-methylsulfonylphenazine 5-oxide show that the displacement of a halogen group in Position 1 can be strongly promoted by the presence of a methylsulfonyl group in Position 2.

Experimental

The melting points, the appearances, the solvents of recrystallization, and the results of elemental analyses are all listed in Table 1. The infrared spectra were taken with a Hitachi Model EPI-S_2 spectrophotometer.

1-Chloro-2-methylthiophenazine (3). *From 1*: To a hot solution of **1** (2.5 g) in ethanol (0.5 l), a 20% aqueous solution of sodium methanethiolate (3 ml) was added. The mixture was refluxed for 10 h and diluted with water. The crystals thereby separated were chromatographed over alumina, using chloroform as the solvent, to give **3** (960 mg, 37%).

From 4: To a solution of **4** (150 mg) in acetic acid (30 ml), zinc dust (0.5 g) was added in small portions. The mixture was then warmed on a water bath for 5 min and filtered while hot. The filtrate was diluted with water to afford **3** (135 mg, 92%).

1-Chloro-2-methylthiophenazine 5-Oxide (4). To a hot solution of **2** (5.3 g) in ethanol (0.8 l), a 20% aqueous solution of sodium methanethiolate (6 ml) was added. The solution was refluxed for 5 h and diluted with water. The crystals which separated were chromatographed over alumina using chloroform as the solvent. From the effluent, **4** (3.54 g, 64%), **3** (550 mg, 11%), and 1,2-bis(methylthio)phenazine 5-oxide[7] (120 mg, 2%) were obtained.

1-Chloro-2-methylsulfonylphenazine (5). A solution of **3** (260 mg) in acetic acid (10 ml) and a 30% aqueous solution of hydrogen peroxide (2 ml) was warmed at 55 °C for 3 h to give **5** (270 mg, 93%).

1-Chloro-2-methylsulfonylphenazine 5-Oxide (6). *From 3*: To a solution of **3** (520 mg) in acetic acid (20 ml) and

Table 1. Properties of 1,2-disubstituted phenazine derivatives

Compound	Mp (°C)[a]	Appearance[b]	Recrystal. from	Molecular formula	Found (%)			Calcd (%)		
					C	H	N	C	H	N
3	179—180	Yellow n	C_6H_6–EtOH	$C_{13}H_9ClN_2S$	60.13	3.40	10.78	59.88	3.48	10.74
4	234—235 (dec)	Dull orange n	$CHCl_3$	$C_{13}H_9ClN_2OS$	56.50	3.08	9.87	56.42	3.28	10.12
5	202—203	Yellow n	DMF–EtOH	$C_{13}H_9ClN_2O_2S$	53.36	3.10	9.50	53.34	3.10	9.57
6	226—227 (dec)	Brown-yellow l	DMF	$C_{13}H_9ClN_2O_3S$	50.84	2.86	9.19	50.57	2.94	9.07
7	197—198 (dec)	Red-brown n	EtOH	$C_{18}H_{19}N_3O_3S$	60.37	5.30	11.70	60.49	5.36	11.76
9	212—213 (dec)	Red-orange n	C_6H_6–EtOH	$C_{17}H_{17}N_3O_4S$	57.07	4.74	11.59	56.81	4.77	11.69
11	236—237 (dec)	Brassy n	EtOH	$C_{13}H_{10}N_2O_4S$	53.75	3.35	9.79	53.79	3.47	9.65
12	182—183	Yellow n	EtOH	$C_{15}H_{14}N_2O_4S$			8.81			8.80
13	178—179 (dec)	Yellow n	EtOH	$C_{20}H_{20}N_2O_7S$	55.82	4.92	6.57	55.55	4.66	6.48
14	196—198 (dec)	Orange-yellow n	EtOH–$CHCl_3$	$C_{18}H_{15}N_3O_5S$	55.90	3.71	10.62	56.10	3.92	10.90

a) All the melting points are uncorrected. b) Needles and leaflets are abbreviated as n and l, respectively.

acetic anhydride (1 ml), a 30% aqueous solution of hydrogen peroxide (3 ml) was added. The mixture was warmed at 55 °C for 15 h to give **6** (600 mg, 97%).

From 4: **4** (550 mg) and a 30% aqueous solution of hydrogen peroxide (3 ml) were treated, following the procedure used in the preparation of **5**, to afford **6** (600 mg, 97%).

From 5: **5** (580 mg) was treated as in the case of the "From **3**" above to give **6** (590 mg, 95%).

2-Methylsulfonyl-1-piperidinophenazine 5-Oxide (7). From 6: A mixture of **6** (310 mg) and piperidine (0.5 ml) in ethanol (50 ml) was refluxed for 2 h and then diluted with water to give **7** (320 mg, 90%).

From 8: **8** (350 mg) was treated as in the case described above to give **7** (330 mg, 92%).

2-Methylsulfonyl-1-morpholinophenazine 5-Oxide (9). A mixture of **6** (310 mg) and morpholine (0.5 ml) in ethanol (50 ml) was refluxed for 2 h to afford **9** (300 mg, 84%). **8** (350 mg) was treated in a similar way to give **9** (310 mg, 86%).

1-Hydroxy-2-methylsulfonylphenazine 5-Oxide (11). A suspension of **8** (350 mg) in a 5% aqueous solution of potassium hydroxide (20 ml) was refluxed for 2 h, filtered, and acidified with diluted acetic acid to give **11** (250 mg, 86%). **6** (310 mg) was treated in a similar way to give **11** (240 mg, 83%). IR (KBr): 3120 cm^{-1}.

1-Ethoxy-2-methylsulfonylphenazine 5-Oxide (12). To a solution of **8** (350 mg) in absolute ethanol (50 ml), sodium (100 mg) was added. The resulting mixture was refluxed for 2 h to give **12** (285 mg, 90%). **6** was treated in a similar way to give **11** (85%).

To a suspension of **8** (530 mg) in ethanol (30 ml), a 10% aqueous solution of potassium hydroxide (10 ml) was added. The mixture was refluxed for 1.5 h and diluted with water. The resulting crystals gave **12** (250 mg, 52%); from the filtrate, **11** (180 mg, 41%) was obtained.

1-[Bis(ethoxycarbonyl)methyl]-2-methylsulfonylphenazine 5-Oxide (13). To a sodium ethoxide solution prepared from sodium (92 mg) and absolute ethanol (40 ml), diethyl malonate (640 mg) was added. **8** (706 mg) was then added to the mixture and the resulting mixture was refluxed for 1 h to give **13** (660 mg, 76%). IR (KBr): 1762 and 1724 cm^{-1}.

1-(1-Cyano-1-ethoxycarbonylmethyl)-2-methylsulfonylphenazine 5-Oxide (14). A mixture of **8** (706 mg) and ethyl cyanoacetate (432 mg) was treated, following procedure used in the preparation of **13**, to afford **14** (690 mg, 90%). IR (KBr): 2250 and 1751 cm^{-1}.

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