BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48 (1), 363—364 (1975)

The Bromination of 1- and 2-Methylthiophenazine Derivatives

Masao TADA

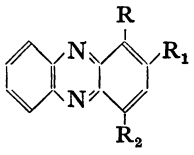
The Research Institute for Tuberculosis, Leprosy and Cancer, Tohoku University, Hirosemachi, Sendai 980

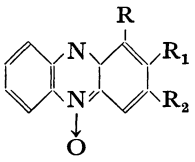
(Received August 7, 1974)

Synopsis. The bromination of 1-methylthiophenazine has been investigated and found to occur in Position 4. 2-Methylthiophenazine and its 5-oxide have been found to be brominated in Position 1. The bromination of these compounds in acetic acid gave both a ring-substituted product and its oxidised product.

In a previous paper,[1] it was reported that the methylthio- and bis(methylthio)phenazine derivatives were readily synthesized by the reactions of halogenophenazine derivatives with methyl mercaptan. In connection with the synthetic study of methylthiophenazine derivatives with potential biological activities, this paper will describe the brominations of 1- and 2-methylthiophenazine derivatives, by which it becomes feasible to prepare bis(methylthio)phenazines as a second route of synthesizing them.

The bromination of 1- (**1**) and 2-methylthiophenazine (**2**) was carried out using bromine in chloroform, to give two bromo compounds, **3** and **4** respectively. When the bromination of **1** was carried out using bromine in acetic acid, both the ring-substituted product, **3**, and its oxidised product, **5**, were produced. Compound **2** was treated with bromine under similar conditions to form **4** and its oxidised product, **6**, in good yields. Compounds **5** and **6** were also obtained by the controlled oxidation of **3** and **4** respectively with potassium bromate. It has been reported that the bromination of alkyl aryl sulfides in acetic acid gives ring-substituted products,[2] while the chlorination in acetic acid gives oxidised products.[3] It may be anticipated that **1** and **2** will prove susceptible to electrophilic attack in the 4- and 1-positions respectively. This results from the localizing of a negative charge at C_4 in **1** and at C_1 in **2**.[2,4] The positions of the bromine atoms in **3** and **4** were confirmed by the substitution reactions of **3** and **4** with methyl mercaptan.





1: R=SCH_3; R_1=R_2=H
2: R=R_2=H; R_1=SCH_3
3: R=SCH_3; R_1=H; R_2=Br
4: R=Br; R_1=SCH_3; R_2=H
5: R=$SOCH_3$; R_1=H; R_2=Br
6: R=Br; R_1=$SOCH_3$; R_2=H
7: R=R_2=SCH_3; R_1=H
8: R=R_1=SCH_3; R_2=H
9: R=SCH_3; R_1=R_2=H
10: R=R_1=H; R_2=SCH_3
11: R=$SOCH_3$; R_1=R_2=H
12: R=R_1=H; R_2=$SOCH_3$
13: R=R_2=H; R_1=SCH_3
14: R=Br; R_1=SCH_3; R_2=H
15: R=SO_2CH_3; R_1=H; R_2=Br
16: R=Br; R_1=SO_2CH_3; R_2=H
17: R=Br; R_1=SO_2CH_3; R_2=H

The reactions of **3** and **4** with the reagent afforded 1,4- (**7**) and 1,2-bis(methylthio)phenazine (**8**) respectively, which had both been derived from 1,4- and 1,2-dichlorophenazine.[1] It was thus confirmed that the oxidised products, **5** and **6**, are 1-bromo-4-methylsulfinyl- and 1-bromo-2-methylsulfinylphenazine respectively.

The bromination of 1- (**9**) and 3-methylthiophenazine-5-oxide (**10**) gave 1- (**11**) and 3-methylsulfinylphenazine-5-oxide (**12**) respectively, and no ring-substituted product was obtained in either case. 2-Methylthiophenazine-5-oxide (**13**) was treated with bromine under similar conditions to yield 1-bromo-2-methylthiophenazine-5-oxide (**14**), which was then converted into **4** by the reduction. The replacement reaction of **14** with an excess of methyl mercaptan afforded **8**, accompanied by the removal of the oxide group in *N*-oxide.

The oxidation of the methylthio compound (**3**) and its sulfoxide (**5**) with an excess of hydrogen peroxide in acetic acid gave sulfone (**15**). The treatment of **4** with a limited amount of hydrogen peroxide in acetic acid produced 1-bromo-2-methylsulfonylphenazine (**16**), which was also obtained from sulfoxide **6**. The oxidations of **4**, **6**, **14**, and **16** all afforded the same compound, 1-bromo-2-methylsulfonylphenazine-5-oxide (**17**).

Experimental

The melting points, the appearances, the solvents of recrystallization, and the results of elemental analyses are all listed in Table 1.

The Bromination of 1. *In Chloroform*: Into a solution of **1** (2.26 g, 10 mmol) in chloroform (30 ml), a solution of bromine (1.9 g, 12 mmol) in chloroform (10 ml) was stirred, drop by drop. The solution was stirred for a further 6 hr and then allowed to stand overnight at room temperature. The reaction mixture was evaporated under reduced pressure to dryness. The residue was suspended in diluted ammonia water, washed with water, dried, and chromatographed over alumina, using benzene as the solvent. From the effluent, **3** (1.12 g, 37%) was obtained.

In Acetic Acid: Into a solution of **1** (2.26 g, 10 mmol) in acetic acid (200 ml), a solution of bromine (1.9 g, 12 mmol) in acetic acid (10 ml) was stirred, drop by drop. The solution was then stirred for a further 3 hr and allowed to stand overnight. The mixture was then poured into water to yield crystals, which were subsequently dissolved in benzene. The benzene solution was then passed through a column of alumina and eluted with benzene. From the first effluent, **3** (0.87 g, 29%) was obtained. When the column was then further eluted with chloroform, **5** (0.84 g, 26%) was obtained.

The Bromination of 2. *In Chloroform*: **2** (2.26 g, 10 mmol) and bromine (1.9 g, 1.2 mmol) were treated as in the Procedure used in the preparation of **3** to afford **4** (2.36 g, 77%).

Table 1. Properties of phenazine derivatives

Compound	Mp (°C)[a]	Appearance[b]	Recrystal. from	Molecular formula	Analytical data					
					Found			Calcd		
					C	H	N	C	H	N(%)
3	197—198	Orange g	C_6H_6	$C_{13}H_9BrN_2S$	50.91	2.77	9.27	51.16	2.97	9.18
4	170—171	Bright yellow n	C_6H_6	$C_{13}H_9BrN_2S$	51.29	2.84	9.16	51.16	2.97	9.18
5	279—280	Yellow g	$CHCl_3$	$C_{13}H_9BrN_2OS$	48.75	2.69	8.86	48.61	2.82	8.72
6	225—226	Pale yellow g	C_6H_6	$C_{13}H_9BrN_2OS$	48.55	2.70	8.77	48.61	2.82	8.72
11	212—214[c]	Red-orange g	$CHCl_3$–EtOH	$C_{13}H_{10}N_2O_2S$	60.43	3.71	10.62	60.45	3.90	10.85
12	193—194	Yellow n	C_6H_6–EtOH	$C_{13}H_{10}N_2O_2S$	60.51	3.76	10.69	60.45	3.90	10.85
14	229—230[c]	Orange n	$CHCl_3$	$C_{13}H_9BrN_2OS$	48.89	2.72	8.94	48.62	2.82	8.72
15	297—298	Yellow p	$CHCl_3$–C_6H_6	$C_{13}H_9BrN_2O_2S$	46.46	2.65	8.46	46.31	2.69	8.31
16	226—227	Pale yellow n	$CHCl_3$	$C_{13}H_9BrN_2O_2S$	46.56	2.75	8.49	46.31	2.69	8.31
17	232—233[c]	Yellow n	$CHCl_3$	$C_{13}H_9BrN_2O_3S$	44.34	2.56	8.15	44.21	2.57	7.93

a) All the melting points are uncorrected. b) Granules, needles, and prisms are abbreviated as g, n, and p, respectively.
c) Decomposition point.

In Acetic Acid: **2** (2.26 g) was treated in the way described in the bromination of **1** to give both **4** (1.52 g, 50%) and **6** (1.02 g, 32%).

1-Bromo-4-methylsulfinylphenazine (5). Into a solution of **3** (305 mg) in acetic acid (50 ml), potassium bromate (56 mg) was stirred in small portions. The mixture was then warmed at 40 °C for 4 hr and allowed to stand overnight at room temperature. After the dilution of the water, sodium bicarbonate (10 g) was added to the reaction mixture. The crystals which separated were collected and washed with water to give **5** (310 mg, 97%).

1-Bromo-2-methylsulfinylphenazine (6). **4** (305 mg) was treated as in the above experiment to afford **6** (290 mg, 90%).

1,4-Bis(methylthio)phenazine (7). A mixture of **3** (305 mg) and a 20% aqueous solution (1.5 ml) of sodium methyl mercaptide in ethanol (150 ml) was refluxed for 6 hr and then diluted with water (100 ml). The crystals therby formed were collected and washed with water to yield **7** (230 mg, 85%), which showed no depression of melting point on admixture with an authentic specimen[1] of **7**.

1,2-Bis(methylthio)phenazine (8). *From 4*: **4** (915 mg) was treated as in the case of **7** to afford **8** (730 mg, 89%).

From 14: **14** (320 mg) was treated as in the case of **7** to give **8** (216 mg, 80%).

1-Methylsulfinylphenazine-5-oxide (11). Into a solution of **9** (1.41 g) in chloroform (50 ml), a solution of bromine (0.8 g) in chloroform (10 ml) was stirred, drop by drop. The mixture was then treated as in the Procedure used in the preparation of **3** to give **11** (530 mg, 41%). **9** (550 mg, 39%) was also recovered.

3-Methylsulfinylphenazine-5-oxide (12). **10** (1.41 g) was treated as in the above experiment to yield **12** (800 mg, 62%). **10** (260 mg, 18%) was also recovered.

1-Bromo-2-methylthiophenazine-5-oxide (14). **13** (1.41 g) was treated as in the case of **11** to give **14** (1.15 g, 72%).

A solution of **14** (160 mg) in dimethylaniline (4 ml) and acetic anhydride (10 ml) was refluxed for 4 hr and then evaporated to dryness under reduced pressure. The residue was chromatographed over alumina, using benzene as the solvent. From the effluent, **4** (110 mg, 72%) was obtained.

1-Bromo-4-methylsulfonylphenazine (15). *From 3*: To a solution of **3** (100 mg) in acetic acid (50 ml), a 30% aqueous solution (2 ml) of hydrogen peroxide was added. The mixture was warmed at 55 °C for 2 hr and then poured into water to give **15** (105 mg, 95%).

From 5: **5** (100 mg) was treated as in the case described above to afford **15** (85 mg, 81%).

1-Bromo-2-methylsulfonylphenazine (16). *From 4*: To a solution of **4** (610 mg) in acetic acid (35 ml), a 30% aqueous solution (3 ml) of hydrogen peroxide was added. The mixture was treated as in the procedure used in the preparation of **15** to give **16** (640 mg, 95%).

From 6: **6** (100 mg) and a 30% hydrogen peroxide aqueous solution (0.5 ml) were treated in the way described above to yield **16** (80 mg, 86%).

1-Bromo-2-methylsulfonylphenazine-5-oxide (17). *From 4*: To a solution of **4** (610 mg) in acetic acid (80 ml) and acetic anhydride (2 ml), a 30% aqueous solution (5 ml) of hydrogen peroxide was added. The mixture was warmed at 55 °C for 20 hr and then treated as in the above experiment to give **17** (630 mg, 89%).

From 6: **6** (320 mg) was treated as in the case described above to give **17** (317 mg, 90%).

From 14: *14* (100 mg) was treated as in the procedure in the preparation of **15** to yield **18** (95 mg, 86%).

From 16: *16* (220 mg) was treated as in the case of the From **4** above to give **17** (200 mg, 86%).

The author is grateful to Professor Yusaku Ikegami of Tohoku University for his encouragement and to Miss Mieko Sasaki to her experimental cooperation.

References

1) M. Tada, This Bulletin, **47**, 1803 (1974).
2) S. Clemanti and P. Linda, *Tetrahedron*, **26**, 2869 (1970).
3) H. M. Gilow, R. B. Camp, and E. C. Clifton, *J. Org. Chem.*, **33**, 230 (1968).
4) A. R. Forrester and J. L. Wardell, "Rodd's Chemistry of Carbon Compounds," 2nd ed., Vol. III, Part A, ed. by S. Coffey, Elsevier Publishing Co., Amsterdam (1971), p. 431.