worked up to give 0.69 g of a crude mixture of **16** and **1**. This was hydrolyzed by refluxing for 2 h with a solution of 0.5 g of KOH in CH_3OH (10 mL). Methanol was removed and the residue was diluted with H_2O. The clear alkaline solution was acidified and worked up to furnish 0.575 g of the crude diol **1**. It was crystallized from ether–petroleum ether to afford 0.51 g (76%) of **1**: mp 206–207 °C; IR 3350 cm^{-1} (broad OH); NMR ($CDCl_3$) δ 0.74 (3 H, CCH_3), 6.65 and 7.02 (2 H, ArH); MS *m/e* 298 (M^+, 99%). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.50; H, 8.76.

A bis-*p*-bromobenzoate was obtained by treatment of **1** with *p*-bromobenzoyl chloride and pyridine at room temperature. Selective hydrolysis[12] of the phenolic ester with sodium carbonate solution at room temperature provided compound **18**, mp 258–260 °C. Anal. Calcd for $C_{27}H_{29}O_3Br$: C, 67.4; H, 6.1; Br, 16.6. Found: C, 67.14; H, 6.08; Br, Br, 16.61.

4,6β-Ethanoestradiol 3-Methyl Ether (17). To a solution of **1** (0.075 g) in methanol (2 mL) and 1 N KOH (5 mL), dimethyl sulfate (0.7 mL) was added dropwise. The mixture was stirred for 4 h at room temperature and left overnight. The separated solid was collected by filtration and dried to yield 0.0555 g (69.4%) of the methylated product **17**. Recrystallization from methanol–chloroform–ether yielded a semisolid: NMR ($CDCl_3$) δ 0.70 (3 H, CCH_3), 3.84 (3 H, OCH_3), 6.83 and 7.05 (2 H, ArH); MS *m/e* 312 (M^+). Anal. Calcd for $C_{21}H_{28}O_2 \cdot 2CH_3OH$: C, 73.37; H, 9.64. Found: C, 73.46; H, 9.34.

4,6β-Ethanoestrone (2). Jones reagent[15] (0.15 mL) was added to a solution of 4,6β-ethanoestradiol **1** (0.08 g) in acetone (20 mL) cooled to 5 °C and the mixture was stirred for 10 min. The reaction mixture was diluted with water and extracted with ether to afford the ketone **2** (0.06 g, 75%) which on recrystallization from ether–petroleum ether gave needles: mp 220–222 °C; IR 3370 (phenolic OH), 1730 cm^{-1} (five-member C=O); MS *m/e* 296 (M^+). Anal. Calcd for $C_{20}H_{24}O_2 \cdot \frac{1}{2}H_2O$: C, 78.65; H, 7.89. Found: C, 78.47; H. 7.60.

17α-Ethynyl-4,6β-ethanoestradiol (3). Acetylene gas was bubbled into a solution of compound **2** (0.175 g) in dimethyl sulfoxide (6 mL) under N_2 for 10 min. Lithium acetylide–ethylenediamine complex[10,11] (0.3 g) was then added and the acetylene was continued for another 3 h. After the reaction mixture had stood overnight at room temperature, it was decomposed with a saturated solution of ammonium chloride. The reaction mixture was extracted with ethyl acetate. The solid left after removal of the solvent was purified by preparative thin layer chromatography (silica gel, $CH_3OH/CHCl_3$, 20:80) to give 0.13 g (68.4%) of **3**. Recrystallization from a mixture of chloroform, ether, and petroleum ether afforded a material: mp 162–164 °C; IR 3400 and 3325 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, CH_3), 2.63 (1 H, $-C\equiv CH$), 6.7 and 6.88 (2 H, ArH); MS *m/e* 322 (M^+). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.74; H, 8.12.

Acknowledgment. The authors would like to express their sincere thanks to Professor J. C. Sheehan and Drs. R. K. Razdan, H. C. Dalzell, and H. G. Pars for valuable suggestions throughout the period of this research. This work was supported by a contract from NICHD, NIH, Bethesda, Md. (NO1-HD-3-2733). The x-ray work was supported in part by Grant CA 10906, awarded by the National Cancer Institute, DHEW. We gratefully acknowledge the help of Dr. C. W. Weeks during x-ray crystallographic studies and Dr. C. Costello of The Massachusetts Institute of Technology for recording the mass spectra. Our thanks are also due to Schering AG., Berlin; Syntex S. A., Palo Alto, Calif.; and G. D. Searle, Chicago, Ill., for generous supplies of estrone.

Registry No.—**1**, 62842-06-2; **1** bis-*p*-bromobenzoate, 62842-07-3; **2**, 62842-08-4; **3**, 62842-09-5; **5**, 3434-45-5; **6**, 20823-31-8; **7**, 62842-10-8; **8**, 62842-11-9; **9**, 62842-12-0; **10**, 62842-13-1; **11**, 62842-14-2; **12**, 62842-15-3; **13**, 62842-16-4; **13** acid chloride, 62842-17-5; **14**, 62842-18-6; **15**, 62842-19-7; **16**, 62842-20-0; **17**, 62842-21-1; **18**, 62230-95-9; 3,17β-dihydroxy-6-oxo-1,3,5(10)estratriene, 571-92-6;17β-hydroxy-3-methoxy-6-oxo-1,3,5(10)-estratriene, 50731-96-9.

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Notes

A Convenient Synthesis of (Chloromethyl)thio Aromatics and (Chloromethyl)thio Heteroaromatics

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Received January 24, 1977

(Chloromethyl)thio aromatics, and methods for their preparation, have been previously described in the literature. German Patent 845 511 describes the preparation of (chloromethyl)thio aromatics by treating 1 mol of aromatic thiol with at least 1 mol of formaldehyde in the presence of hydrogen chloride:

$$ArSH + CH_2{=}O \xrightarrow[HCl]{} ArSCH_2Cl \quad (1)$$

Dolman et al.[1] described the reaction of 1 mol of an aromatic thiol with 1 mol of formaldehyde in the presence of a catalytic amount of sodium methoxide to give the corresponding (hydroxymethyl)thio aromatic which was subsequently treated with 1.1 mol of thionyl chloride to afford the corresponding (chloromethyl)thio aromatic:

$$ArSH + CH_2{=}O \xrightarrow[NaOCH_3]{} ArSCH_2OH \xrightarrow{SOCl_2} ArSCH_2Cl \quad (2)$$

Senning and Lawesson[2] described the preparation of 1-[(chloromethyl)thio]-2,3,4,5,6-pentachlorobenzene by the chlorination of 1-(methylthio)-2,3,4,5,6-pentachlorobenzene with chlorine in refluxing carbon tetrachloride.

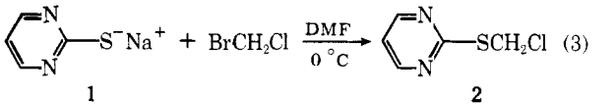
More recently, several examples of the preparation of (chloromethyl)thio heteroaromatics from the corresponding thiol and bromochloromethane have been described. In 1967, Pashkurov and Reznik[3] reported that the reaction of the so-

Table I. (Chloromethyl)thio Aromatics and (Chloromethyl)thio Heteroaromatics

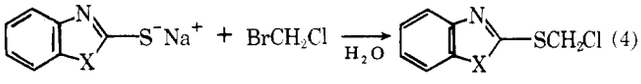
Thiol[h]	Product[i]	Yield, %[a]	Mp or bp (mm), °C	Mol of thiol	Mol of BrC-H_2Cl	Mol of BTEAB	Temp, °C	Reaction time, h
Benzenethiol	1-[(Chloromethyl)thio]benzene	57	83 (1.5)	0.50	11.53	0.0036	16–50	2.5
4-(1,1-Dimethylethyl)benzenethiol	1-[(Chloromethyl)thio]-4-(1,1-dimethylethyl)benzene	60	100–106 (3.0)	0.10	4.61	0.00055	*b*	*b*
2,4,6-Tribromobenzenethiol	1-[(Chloromethyl)thio]-2,4,6-tribromobenzene	91[f]	71–72	0.025	2.31	0.0011	*b*	*b*
2,3,5,6-Tetrafluorobenzenethiol	1-[(Chloromethyl)thio]-2,3,5,6-tetrafluorobenzene	84	65–66 (1.0)	0.055	3.85	0.0011	25–38	1.25[c]
2,3,5,6-Tetrachlorobenzenethiol	1-[(Chloromethyl)thio]-2,3,5,6-tetrachlorobenzene	82	81–82	0.025	3.07	0.0011	25–55	1.5
N,N-Diethyl-2-mercapto-3,4,5-trichlorobenzenesulfonamide	2-[(Chloromethyl)thio]-*N,N*-diethyl-3,4,5-trichlorobenzenesulfonamide	83	82–83	0.025	2.31	0.0015	26–30	2.33[d]
2,3,4,5,6-Pentachlorobenzenethiol	1-[(Chloromethyl)thio]-2,3,4,5,6-pentachlorobenzene	46	121–122	0.025	2.31	0.0015	26–31	2.25[d]
2,4′,6-Trichloro-4-mercaptobiphenyl	4-[(Chloromethyl)thio]-2,4′,6-trichlorobiphenyl	95	100–101	0.01	1.5	0.00055	25–27	1.25[e]
2-Mercaptoquinoline	2-[(Chloromethyl)thio]quinoline	43	51–53	0.33	7.69	0.0018	22–56	2.0
2-Mercaptobenzoxazole	2-[(Chloromethyl)thio]benzoxazole	80	53–54	0.05	3.07	0.00077	25–50	1.5
2-Mercaptobenzothiazole	2-[(Chloromethyl)thio]benzothiazole	58	43–44	0.50	15.38	0.0029	25–60	2.0
5-Chloro-2-mercaptobenzothiazole	5-Chloro-2-[(chloromethyl)thio]benzothiazole	97[g]	86–87	0.05	4.61	0.00099	30–50	3.0
6-Ethoxy-2-mercaptobenzothiazole	2-[(Chloromethyl)thio]-6-ethoxybenzothiazole	93	112–113	0.50	15.38	0.0037	*b*	*b*
2-Mercaptopyrimidine	2-[(Chloromethyl)thio]pyrimidine	58	46	0.20	3.07	0.0018	24–58	2.0

[a] Isolated yield employing 85% potassium hydroxide unless otherwise specified. [b] See Experimental Section. [c] Subsequently heated at 60 °C for 1.5 h. [d] Subsequently heated at reflux for 0.5 h. [e] Subsequently heated at 45 °C for 1.5 h. [f] A 78% yield was obtained when lithium hydroxide monohydrate was used. [g] Sodium hydroxide was used. [h] Registry no. are respectively 108-98-5, 2396-68-1, 24207-66-7, 769-40-4, 4707-16-8, 62669-51-6, 133-49-3, 62601-11-0, 2637-37-8, 2382-96-9, 149-30-4, 5331-91-9, 120-53-6, 1450-85-7. [i] Registry no. are respectively 7205-91-6, 62601-12-1, 62601-13-2, 62601-14-3, 62601-15-4, 62601-16-5, 62601-17-6, 62601-18-7, 62601-19-8, 37118-31-3, 28908-00-1, 62601-20-1, 62601-21-2, 19834-93-6.

dium salt of 2-pyrimidinethiol (**1**) with bromochloromethane at 0 °C in dry dimethylformamide gave 2-[(chloromethyl)thio]pyrimidine (**2**) in 35% yield (eq 3). In 1972, Pera and Raths[4] reported the preparation of 2-[(chloromethyl)thio]benzoxazoles, 2-[(chloromethyl)thio]benzothiazoles, and 2-[(chloromethyl)thio]benzimidazoles by the reaction of the sodium salt of the corresponding thiol with bromochloromethane in an aqueous system in the presence of a nonionic surfactant (eq 4).



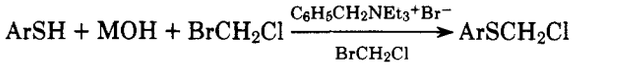
1 **2** (3)



(4)

X = NH, O, S

We have developed an improved procedure in which (chloromethyl)thio aromatics and (chloromethyl)thio heteroaromatics were prepared by the reaction of the corresponding thiol with 1 equiv of an alkali metal hydroxide (lithium, sodium, or potassium hydroxide) in bromochloromethane (using bromochloromethane as both reactant and solvent) in the presence of a catalytic amount (0.5–10 mol %) of benzyltriethylammonium bromide (BTEAB) (eq 5).[5] The procedure involved no aqueous phase, and was very simple to operate. A slurry of the finely powdered alkali metal hydroxide in bromochloromethane was prepared; the thiol was then added followed by the benzyltriethylammonium bromide. A mild exotherm was observed immediately upon adding the catalyst, and the reaction mixture was generally allowed to stir until it returned to room temperature)in some instances a 0.5-h reflux period was employed). The reaction mixture was then filtered to remove the alkali metal bromide which had precipitated. The filtrate was then dried, and the excess bromochloromethane removed in vacuo leaving the (chloromethyl)thio compound which was purified by recrystallization or distillation (several representative preparations are given in the Experimental Section). A variety of aromatic and heteroaromatic thiols have been employed in this reaction, and the results are summarized in Table I.

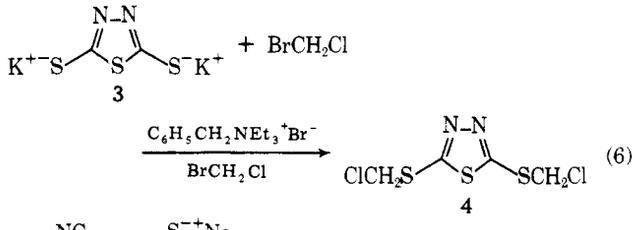


+ H_2O + MBr (5)

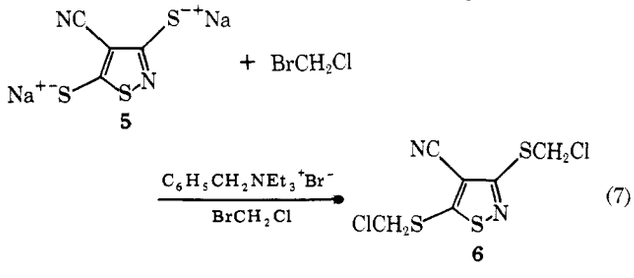
Ar = aromatic or heteroaromatic

M = Li, Na, or K

The reaction can also be carried out with a preformed alkali metal salt of an aromatic thiol. Thus, the dipotassium salt of 2,5-dimercapto-1,3,4-thiadiazole (**3**) afforded 2,5-bis[(chloromethyl)thio]-1,3,4-thiadiazole (**4**, eq 6) in 71% yield, and the



(6)



(7)

disodium salt of 4-cyano-3,5-(dimercapto)isothiazole (**5**) gave 4-cyano-3,5-bis[(chloromethyl)thio]isothiazole (**6**) in 60% yield (eq 7).

Experimental Section[6]

1-[(Chloromethyl)thio]-4-(1,1-dimethylethyl)benzene. To a slurry of 6.50 g (0.10 mol) of finely powdered 85% potassium hydroxide in 300 mL of bromochloromethane were added 12.5 g (0.10 mol) of 4-(1,1-dimethylethyl)benzenethiol. To this mixture, 0.125 g (0.00055 mol) of benzyltriethylammonium bromide was added, and the reaction mixture was stirred at 25–30 °C for 0.5 h. The reaction mixture was amber in color, and a pale yellow solid had precipitated. The reaction mixture was filtered, and the bromochloromethane removed in vacuo leaving a light amber oil. The oil was dissolved in 100 mL of ether, and the resulting solution filtered through anhydrous magnesium sulfate. The ether was removed in vacuo from the filtrate leaving 16.5 g of nearly colorless oil. The oil was distilled under reduced pressure to give 12.30 g (60% yield) of the title compound as a colorless liquid, bp 100–106 °C (3 mm).

1-[(Chloromethyl)thio]-2,4,6-tribromobenzene. To a slurry of 1.63 g (0.025 mol) of finely powdered 85% potassium hydroxide in 150 mL of bromochloromethane was added 8.70 g (0.025 mol) of 2,4,6-tribromobenzenethiol. To this mixture, 0.30 g of benzyltriethylammonium bromide was added, and the temperature rose from 26 to 28 °C in several minutes. The reaction mixture was stirred for 2 h and then filtered to remove the sodium bromide which separated. The bromochloromethane was removed in vacuo from the filtrate leaving a light, red-brown oil. The oil was treated with 75 mL of ether dissolving most of the material and leaving a small amount of red-brown oil. The ether solution was dried over anhydrous magnesium sulfate and filtered. The ether was diluted with an equivalent amount of hexane, and the resulting solution concentrated in vacuo to give 4.20 g of the title compound, mp 71–72 °C. Further concentration gave an additional 4.80 g, mp 71–72 °C (total yield 91%).

2-[(Chloromethyl)thio]-6-ethoxybenzothiazole. To a well-stirred slurry of 105.7 g (0.50 mol) of 6-ethoxy-2-mercaptobenzothiazole in 1 L of bromochloromethane were added 32.5 g (0.50 mol) of finely powdered 85% potassium hydroxide and 1.0 g of benzyltriethylammonium bromide. The temperature of the reaction mixture slowly rose from 23 to 38 °C over a period of 1.75 h. The stirring was continued for an additional 1 h, during which the temperature slowly fell to 32 °C. The precipitated potassium bromide was filtered off, and the organic filtrate washed with 500 mL of water. The organic layer was dried over anhydrous calcium chloride, and the bromochloromethane removed in vacuo leaving a damp powder. The powder was slurried with anhydrous diethyl ether to give an insoluble white powder which was filtered and dried to give 102 g of the title compound, mp 112–113 °C. A 24-g second crop was obtained from the ether filtrate (total yield 93%). A sample of this material was recrystallized from chloroform to give white plates, mp 112–113 °C.

2,5-Bis[(chloromethyl)thio]-1,3,4-thiadiazole (4). A slurry of 100 g (0.44 mol) of the dipotassium salt of 2,5-dimercapto-1,3,4-thiadiazole (**3**) in 850 mL of bromochloromethane containing 2 g of benzyltriethylammonium bromide was stirred for 6 h at 35–55 °C. The potassium bromide formed was filtered off and dissolved in water leaving 0.5 g of polymeric material. Acidification of the aqueous filtrate precipitated 2,5-dimercapto-1,3,4-thiadiazole equivalent to 17 g of the starting salt indicating 83% conversion. The bromochloromethane was removed in vacuo from the organic filtrate leaving a thick liquid which was extracted with 1 L of anhydrous ether. The ether was removed in vacuo leaving 71.0 g (78% yield) of the title compound as a white solid, mp 60–61 °C. Recrystallization from ether gave crystals with mp 64–65 °C.

Anal. Calcd for $C_4H_4Cl_2N_2S_3$: C, 19.40; H, 1.63; Cl, 28.70; N, 11.34; S, 39.90. Found: C, 19.90; H, 1.72; Cl, 28.50; N, 11.63; S, 39.20.

3,5-Bis[(chloromethyl)thio]-4-cyanoisothiazole (6). In a 500-mL flask equipped with a reflux condenser, a mechanical stirrer, and a thermometer were placed 10.90 g (0.05 mol) of the disodium salt of 4-cyano-3,5-dimercaptoisothiazole (**5**) and 300 mL of bromochloromethane. To this slurry, 0.44 g of benzyltriethylammonium bromide was added, and the reaction mixture was heated at 24–55 °C for 5 h. The reaction mixture was filtered to remove the sodium bromide produced, and the bromochloromethane was removed in vacuo from the filtrate leaving a tan solid. The solid was extracted with hot ether, and the ether solution was concentrated in vacuo to give 6.00 g of the title compound as a light yellow powder, mp 92–93 °C. Further concentration gave an additional 2.10 g, mp 88–89 °C (total yield, 60%).

Anal. Calcd for $C_6H_4Cl_2N_2S_3$: C, 26.57; H, 1.48; N, 10.33; S, 35.47. Found: C, 26.80; H, 1.73; N, 10.46; S, 36.18.

Registry No.—3 2K, 4628-94-8; **4**, 62601-22-3; **5** 2Na, 2076-67-7; **6**, 62653-99-0; bromochloromethane, 74-97-5.

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(6) All melting points and boiling points are uncorrected. All new compounds gave satisfactory elemental analyses and displayed infrared and NMR spectra which were in agreement with the assigned structures.

Electronic Effects in Multicenter Rearrangements of Compounds with Nitrogen–Nitrogen Bonds

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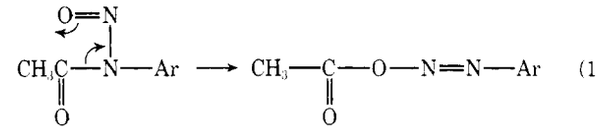
Huisgen and co-workers[1] and Hey and co-workers[2] have shown that the rates of rearrangements of *N*-nitroso amides **1** (eq 1) are but slightly influenced by either electron-withdrawing or electron-donating substituents.



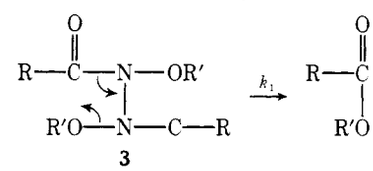
1 **2** (1)

A plot of rate data reported by these authors against Hammett σ^+ [4] constants shows some scattering of points but the best straight line has a slope of zero. Likewise we have measured the rates of rearrangement of *N*-nitroso-*N*-cyclohexylbenzamides, and found little effect from placing either electron-donating or electron-withdrawing substituents on the aromatic ring. These data have been interpreted as being consistent with a multicenter process[1,2] rather than an ionic process. In a multicenter process involving simultaneous bond breaking and bond formation, the influence of electron-donating and electron-withdrawing substituents would be conflicting.

We wanted to see if electronic effects on the decomposition of **3** by a multicenter process would likewise be confusing.

Previous work[3] has shown that the spontaneous reaction of **3a** in refluxing methanol or benzyl alcohol at room temperature occurred by a concerted process, while reaction in refluxing benzyl alcohol or with added acid occurred with the generation of a free acylium ion.

Scheme I



3

3a, R = CH_3; R′ = NC_3H_7
b, R = XC_6H_4; R′ = $C_6H_5CH_2$
c, R = CH_3; R′ = $XC_6H_4CH_2$