[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, ROYAL INSTITUTE OF SCIENCE]

Derivatives of Salicylic Acid. VI. Reaction of Thionyl Chloride on Esters of Hydroxybenzoic Acids in the Presence of Finely Divided Copper. Part I. Synthesis and Constitution of Bis-(3-carboxy-4-hydroxyphenyl) Thio-ether and its Related Compounds

BY N. W. HIRWE, G. V. JADHAV AND Y. M. CHAKRADEO

The varied use of thionyl chloride in organic synthesis is well known.[1] Sulfides and sulfoxides particularly have been obtained by various investigators, with or without the use of catalysts.[2] The sulfide, as also the sulfoxide, of salicylic acid is unknown and is expected to possess important therapeutic properties. The present work aimed at its preparation.

It was found that thionyl chloride along with salicylic acid gave rise to various anhydro compounds, while with methyl salicylate the $COOCH_3$ group totally inhibited the reaction. However, with copper as a catalyst thionyl chloride and methyl salicylate yielded a compound from which the required bis-(3-carboxy-4-hydroxyphenyl) thio-ether could be obtained.

The mechanism of the reaction is expressed by the equations

$$4SOCl_2 + 3Cu \longrightarrow 3CuCl_2 + 2SO_2 + S_2Cl_2 \quad (1)^3$$

$$2C_6H_4(OH)COOCH_3 + S_2Cl_2 \xrightarrow{Cu} (C_6H_3(OH)COOCH_3)_2S + 2HCl + S \quad (2)$$

$$2CuCl_2 + SO_2 \longrightarrow Cu_2Cl_2 + SO_2Cl_2 \quad (3)$$

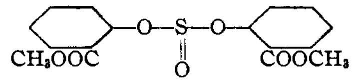
$$2SOCl_2 + Cu_2Cl_2 \longrightarrow CuCl_2 + SO_2 + SCl_2 \quad (4)$$

$$2C_6H_4(OH)COOCH_3 + SCl_2 \xrightarrow{Cu} (C_6H_3(OH)COOCH_3)_2S + 2HCl \quad (5)$$

This mechanism expressing the continuous nature of the reaction is supported by the following observations. (1) The reaction product contains free sulfur, the quantity of which depends on the amount of copper used (see Equations 1 and 2). (2) The quantity of the sulfide exceeds that calculated on copper, indicating catalytic progress of the reaction. (3) Since the reaction also could be effected with cuprous chloride and hydrated copper chloride, but not with anhydrous copper chloride, until sulfur dioxide is passed into the reaction mixture or a trace of water added, suggests that the mutual transformation of cuprous and cupric chloride by thionyl chloride and sulfur dioxide is responsible for the progress (see Equations 3 and 4), when sulfur dichloride gives more of the required sulfide (see Equation 5). (4) With methyl salicylate and sulfur monochloride, with a trace of copper, the sulfide mixed with free sulfur is obtained, while with sulfur dichloride it is obtained pure.

The chart of formulas shows the structure of the reaction product and of seven other substances.

Since phenol reacts with thionyl chloride in the presence of pyridine to form a sulfurous acid ester,[4] the structure



instead of I comes up for consideration. However, the formation of acetyl and benzoyl derivatives establishes the phenolic character. The conversion of II through III to V establishes the linkage of the sulfur atom. The II to V relationship proves that, of the equivalent 3 and 5 positions in I, one of these positions is unoccupied and becomes substituted in bromination of III, and nitration is accompanied by replacement of sulfur by a nitro group on each of the two ring nuclei V. The II–VII relationship points to the symmetrical linking of two salicylic acid nuclei on the sulfur atom. Finally, with concentrated nitric acid, both II and VII are converted to picric acid, VIII.

Experimental

Bis-(3-carbomethoxy-4-hydroxyphenyl) Thio-ether.—Method I. Methyl salicylate (30 g.) and thionyl chloride (50 g.) were mixed and copper dust (20 g.) was added gradually, when heat and dense fumes of sulfur dioxide and hydrogen chloride were evolved. The reaction mixture was left overnight at room temperature and then heated on the water-bath for about half an hour. It was now treated with hot chloroform and filtered from residual copper. The solution on evaporation gave a pasty solid which was washed with petroleum ether. To free the substance from sulfur, it was crystallized repeatedly from acetic acid as colorless needles of m. p. 147–148°. It is insoluble in water, petroleum ether and carbon tetrachloride, and soluble in chloroform, benzene, acetic acid,

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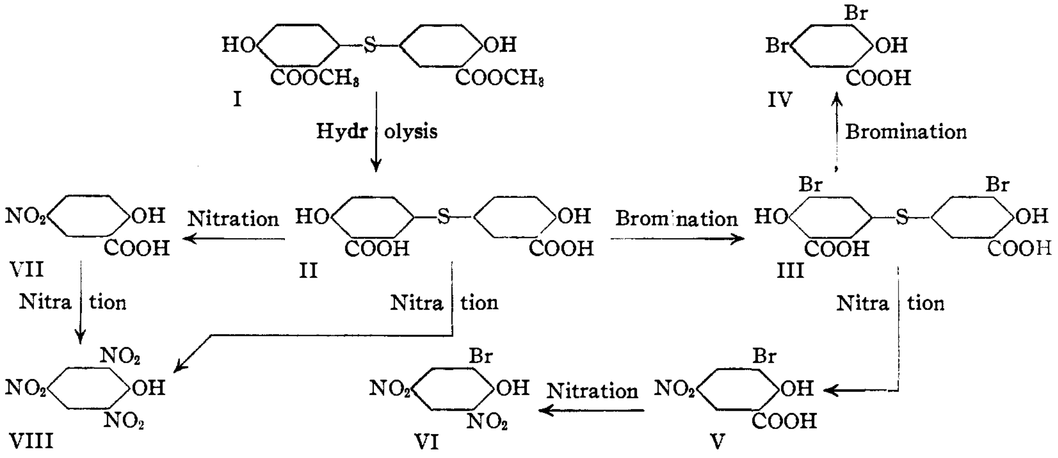
(1) Silberrad, *J. Soc. Chem. Ind.*, **45**, 36–38, 55–57 (1926).

(2) Tassinari, *Gazz. chim. ital.*, **20**, 362 (1890); Michaelis and Loth, *Ber.*, **27**, 2540 (1894); Smiles and Bain, *J. Chem. Soc.*, **97**, 2249 (1910); Naik and collaborators, *J. Ind. Chem. Soc.*, **7**, 137 (1930); **9**, 127, 471 (1932).

(3) Mellor, "Inorganic Chemistry," Vol. X, p. 662, on reactions of thionyl chloride on bivalent metals.

(4) Richter, *Ber.*, **49**, 2339 (1916).



ethyl alcohol, carbon disulfide, pyridine and acetone. It gives a bluish-violet coloration with ferric chloride. Calcd. for $C_{16}H_{14}O_6S$: equiv., 167.0; S, 9.6. Found: equiv., 167.6; S, 9.48.

I also is obtained by mixing methyl salicylate and sulfur monochloride (Method II) or sulfur dichloride (Method III) in molecular proportions and adding traces of copper. The crude product in Method II is accompanied by free sulfur, while it is almost pure in Method III.

Bis-(3-carboxy-4-hydroxyphenyl) Thio-ether.—The ester (10 g.) was hydrolyzed with caustic soda (100 cc., 10%). On acidification a solid was obtained which was recrystallized from acetic acid as colorless plates of m. p. 269–270°. It is insoluble in water and petroleum ether, difficultly soluble in chloroform and benzene, and easily soluble in acetone, ethyl alcohol and glacial acetic acid. It gives a bluish-violet coloration with ferric chloride.

Anal. Calcd. for $C_{14}H_{10}O_6S$: equiv., 153.0; S, 10.46. Found: equiv., 152.9; S, 10.30. Sodium salt, crystallized from dilute alcohol. Calcd. for $C_{14}H_8O_6SNa_2 \cdot H_2O$: Na, 12.5; H_2O, 4.9. Found: Na, 12.62; H_2O, 4.56. Potassium salt, crystallized from hot water. Calcd. for $C_{14}H_8O_6SK_2 \cdot 2H_2O$: K, 18.7; H_2O, 8.6. Found: K, 18.58; H_2O, 8.43. Calcium salt, crystallized from hot water. Calcd. for $C_{14}H_8O_6SCa \cdot 4H_2O$: Ca, 9.6; H_2O, 17.3. Found: Ca, 9.43; H_2O, 17.4. Barium salt, crystallized from hot water. Calcd. for $C_{14}H_8O_6SBa \cdot 4H_2O$: Ba, 26.7; H_2O, 14.00. Found: Ba, 26.63; H_2O, 13.86.

Action of Nitric Acid on Bis-(3-carboxy-4-hydroxyphenyl) Thio-ether.—(a) When the thio-ether was kept with dilute nitric acid, 10%, at 0° for about a month, or (b) 2 g. was warmed with dilute nitric acid (100 cc. of 6.5%) until a clear solution was obtained, it gave 5-nitrosalicylic acid, which crystallized from boiling water with m. p. 228°. This agrees with the values given by others,[5] and was confirmed by a mixed melting point. (c) With warm concentrated nitric acid there was obtained picric acid with m. p. 123°.

Action of Bromine on Bis-(3-carboxy-4-hydroxyphenyl) Thio-ether. (A) **Bis-(3-carboxy-4-hydroxy-5-bromophenyl) Thio-ether.**—Bis-(3-carboxy-4-hydroxyphenyl) thio-ether (10 g.) was suspended in boiling glacial acetic acid (500 cc.). To this an acetic acid (20 cc.) solution of bromine (12 g.) was added during three hours, when the solid had dissolved completely. On cooling crystals were obtained which were recrystallized from acetic acid to colorless needles of m. p. 274–275° with effervescence. It is insoluble in water, benzene and petroleum ether, and soluble in ethyl alcohol and acetone. Calcd. for $C_{14}H_8O_6SBr_2$: Br, 34.48; S, 6.89. Found: Br, 34.63; S, 6.89.

(B) By refluxing the same ether with bromine on a water-bath there resulted 3,5-dibromosalicylic acid, m. p. 224–225°.[6] Calcd. for $C_7H_4O_3Br_2$: Br, 54.0. Found: Br, 55.83.

Action of Nitric Acid on Bis-(3-carboxy-4-hydroxy-5-bromophenyl) Thio-ether.—(A) 3-Bromo-5-nitrosalicylic acid, m. p. 222–223°,[7] was obtained when the ether (1.5 g.) was warmed with dilute nitric acid (100 cc., 13%). Calcd. for $C_7H_4O_5NBr$: N, 5.34; Br, 30.53. Found: N, 5.27; Br, 30.27. (B) The same (1.3 g.) when warmed as before with nitric acid (50 cc., 32.5%) gave 2-bromo-4,6-dinitrophenol, m. p. 118°.[8] Calcd. for $C_6H_3O_5N_2Br$: N, 10.64; Br, 30.42. Found: N, 10.39; Br, 30.26. (C) With concentrated nitric acid it gave picric acid, m. p. 123°.

Bis-(3-carbomethoxy-4-acetoxyphenyl) Thio-ether.—This was obtained by warming bis-(3-carbomethoxy-4-hydroxyphenyl) thio-ether (3 g.) with acetic anhydride (15 g.) with a few drops of sulfuric acid; it recrystallized from alcohol in colorless needles of m. p. 94°, insoluble in water, benzene, petroleum ether, and soluble in acetic acid, chloroform and alcohol. Calcd. for $C_{20}H_{18}O_8S$: S, 7.6. Found: S, 7.78.

Bis-(3-carbomethoxy-4-benzoyloxyphenyl) thio-ether was obtained with benzoyl chloride in pyridine and crystallized from alcohol in flat needles of m. p. 117°. Calcd. for $C_{30}H_{22}O_8S$: S, 5.9. Found: S, 6.2.

Bis-(3-carbomethoxy-4-hydroxy-5-bromophenyl) Thio-ether.—An acetic acid solution of bromine (5 g.) was added gradually to a boiling solution of bis-(3-carbomethoxy-4-hydroxyphenyl) thio-ether (3 g.) in glacial

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(5) Hübner, *Ann.*, **198**, 258 (1879); Deninger, *J. prakt. Chem.*, **42**, 1142 (1890); Meldola, Foster and Brightmann, *J. Chem. Soc.*, **111**, 536 (1917); Meldrum and Hirwe, *J. Ind. Chem. Soc.*, **5**, 95 (1928).

(6) Rollwage, *Ber.*, **10**, 1707 (1877), and Lellmann and Grothmann, *ibid.*, **17**, 2728 (1884), give m. p. 223°.

(7) Lallmann and Grothmann, *ibid.*, **17**, 2724 (1884).

(8) Körner, *Jahresber. Chem.*, 337 (1875).

acetic acid (200 cc.). On dilution a solid resulted which is insoluble in water, benzene, petroleum ether, and soluble in acetic acid, acetone and alcohol; it recrystallized from glacial acetic acid in colorless needles of m. p. 133°. Calcd. for $C_{16}H_{12}O_6Br_2S$: Br, 32.5; S, 6.5. Found: Br, 32.31; S, 6.31.

Bis-(3-carbamido-4-hydroxyphenyl) thio-ether was obtained by shaking bis-(3-carbomethoxy-4-hydroxyphenyl) thio-ether with strong ammonia for eight hours. The resulting solid was crystallized from boiling glacial acetic acid, m. p. 272–273° with decomposition. It is insoluble in most of the common organic solvents. Calcd. for $C_{14}H_{12}O_4N_2S$: S, 10.53; N, 9.21. Found: S, 10.46; N, 8.98.

Bis-(3-carboxy-4-acetoxyphenyl) Thio-ether.—Bis-(3-carboxy-4-hydroxyphenyl) thio-ether (2 g.) was acetylated in the same way as its methyl ester. It was crystallized from alcohol in colorless needles of m. p. 164°. Calcd. for $C_{18}H_{14}O_8S$: S, 8.2. Found: S, 8.3.

Bis-(3-carboxy-4-benzoyloxyphenyl) thio-ether was obtained by treating the thio-ether in caustic soda solution (10%, 25 cc.) with benzoyl chloride. It was crystallized from alcohol as colorless needles of m. p. 129°. It is soluble in glacial acetic acid, acetone and ethyl and methyl alcohols; it is insoluble in water, benzene and petroleum ether, and soluble with difficulty in chloroform. Calcd. for $C_{28}H_{18}O_8S$: S, 6.22. Found: S, 6.23.

Bis-(3-carboxy-4-methoxyphenyl) thio-ether was obtained by refluxing the alkaline mixture of the thio-ether (3 g.) and dimethyl sulfate (4 g.) for about three hours. The pasty solid obtained was triturated several times with ice-cold water and then crystallized from alcohol in colorless needles of m. p. 157°. It is insoluble in water, benzene, petroleum ether, and soluble in chloroform, glacial acetic acid, acetone and ethyl alcohol. Calcd. for $C_{16}H_{14}O_6S$: S, 9.58. Found: S, 9.4.

Bis-(3-carbethoxy-4-hydroxyphenyl) thio-ether was prepared in two ways: (1) by esterification of bis-(3-carboxy-4-hydroxyphenyl) thio-ether by the usual method; (2) by the action of thionyl chloride on ethyl salicylate in the presence of finely divided copper, in exactly the same way as its methyl isomer, m. p. 110°. It resembles the methyl isomer in solubility and gives a bluish-violet color with ferric chloride solution. Calcd. for $C_{18}H_{18}O_6S$: S, 8.84. Found: S, 8.9.

Bis-(3-carbethoxy-4-acetoxyphenyl) Thio-ether.—This was prepared and crystallized in the same way as its methyl isomer, m. p. 92°. Calcd. for $C_{22}H_{22}O_8S$: S, 7.2. Found: S, 7.05.

Bis-(3-carbophenoxy-4-hydroxyphenyl) Thio-ether.—Salol (15 g.), thionyl chloride (25 g.) and copper dust were used and the experiment was finished in the same way as in the case of the methyl and ethyl esters. The solid crystallizes from acetone with m. p. 158°. It is soluble in chloroform, acetone, acetic acid, benzene, methyl and ethyl alcohols, and insoluble in water and sparingly soluble in petroleum ether. It gives a bluish-violet coloration with ferric chloride solution and is hydrolyzed to the corresponding acid. Calcd. for $C_{26}H_{18}O_6S$: S, 6.98. Found: S, 6.87.

Bis-(3-carbophenoxy-4-acetoxyphenyl) thio-ether was prepared in the same way as its methyl and ethyl isomers, and crystallized from acetic acid, m. p. 144°. Calcd. for $C_{30}H_{22}O_8S$: S, 5.9. Found: S, 5.73.

Summary

Phenols are easily condensed with thionyl chloride, but such is not the case with hydroxy aromatic acids. The presence of a carboxylic group (a) introduces the possibility of formation of different anhydro compounds, and also (b) inhibits the progress of the reaction. The former difficulty was overcome by using methyl salicylate instead of salicylic acid, and the latter by the use of finely divided copper.

The progress of the reaction is divided into two stages: (1) copper and thionyl chloride producing sulfur monochloride, sulfur dioxide and copper chloride; (2) sulfur dioxide converting copper chloride into cuprous chloride to give sulfur dichloride by its action on thionyl chloride in addition to sulfur dioxide and copper chloride; (3) sulfur monochloride and sulfur dichloride react with the ester in the presence of copper or cuprous chloride to give the thio-ether.

It has been shown that the condensation takes place in the para position to the OH group.

Various derivatives and salts are described.

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