[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE PITTSBURGH PLATE GLASS CO., COLUMBIA CHEMICAL DIVISION]

A Study of the Reaction of Phenol with Thionyl Chloride

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Studies on the reactions of phenol with thionyl chloride are greatly complicated by the existence of readily-occurring nuclear substitution reactions.[1,2,3,4,5,6] These probably account for the fact that the preparation of diphenyl sulfite by the direct reaction of phenol with thionyl chloride in the absence of hydrogen chloride acceptors had not been reported prior to this time, and that the successful preparation of phenyl chlorosulfinate has been accomplished[7] only recently.

In a previous paper[8] on the reaction of thionyl chloride with alcohols, we described a novel method of operation which appeared to greatly reduce the complicating side reactions resulting from the action of hydrogen chloride on the newly-formed sulfite ester. In that method the reactions were carried out in the presence of a large amount of a refluxing solvent in which the reactants and products were soluble. but in which the hydrogen chloride was insoluble. We have now applied this technique to the phenol–thionyl chloride reaction to determine if the complex reactions previously reported[1-6] could be eliminated. Preliminary experiments showed that diphenyl sulfite and phenyl chlorosulfinate underwent a fairly rapid decomposition in the presence of hydrogen chloride, thereby emphasizing the need for removing this material from the zone of reaction as rapidly as possible. Utilizing the refluxing solvent technique to expel the hydrogen chloride, we then investigated the reaction of phenol with thionyl chloride at temperatures of 10° to 180°, and at molar ratios of 2:1 to 1:4, while observing the effect of temperature and the ratio of reactants on the yields and types of products obtained.

Experimental

Preparation of Materials.—The thionyl chloride used was a purified grade manufactured by this Division. The phenol was Merck reagent grade.

For the preliminary studies the diphenyl sulfite was prepared by the method of Gerrard.[9] On distillation through a 1.5 × 20-cm. Vigreux column, the sulfite was collected at 141–144° (2 mm.), m. p. 13–16°.

The phenyl chlorosulfinate was prepared as follows: Molten phenol (1.0 mole) was added to refluxing thionyl chloride (4.0 moles) in one hour with stirring after which the mixture was refluxed one hour longer. Fractionated through a 1.7 × 20-cm. Fenske column, the phenyl chlorosulfinate, 125 g. (71% yield) distilled at 92–98° (10 mm.). The stability tests in the following section were made with a redistilled product boiling at 95° (10 mm.), m. p. −16° to −13°.

Anal. Calcd. for $C_6H_5SO_2Cl$: S, 18.1; Cl, 20.1. Found: S, 18.8; Cl, 20.6.

Stability of Diphenyl Sulfite and Phenyl Chlorosulfinate to Hydrogen Chloride.—Hydrogen chloride (0.25 mole) was passed into freshly distilled diphenyl sulfite (93 g.; 0.4 mole) over a six-hour period at 70°. A gain in weight of 7.5 g. resulted. Distillation yielded (a) 16.7 g. (0.178 mole) of phenol, b. p. 83–84° (20 mm.), m. p. 40°, which was further identified by its benzoate, m. p. 69°; (b) 51 g. (0.218 mole) of diphenyl sulfite, b. p. 143–157° (3 mm.); (c) 14.5 g. of a viscous residue containing 18.5% sulfur and 1.7% chlorine. The yield of phenol, based on the diphenyl sulfite not recovered, was 98%, assuming that one mole of phenol was formed per mole of sulfite decomposed.

Hydrogen chloride (0.30 mole) was likewise passed into freshly distilled phenyl chlorosulfinate (106 g., 0.60 mole) over a six-hour period at 70° while collecting all volatile products in a Dry Ice trap. A gain in weight of 1 g. occurred. Distillation at 10 mm. yielded (a) a Dry Ice trap fraction of 5.2 g., (b) 79 g. (0.448 mole) of phenyl chlorosulfinate b. p. 92–93.5°, (c) 10 g. (0.04 mole) of diphenyl sulfite, b. p. 152–158°.

Anal. Calcd. for $(C_6H_5)_2SO_3$: S, 13.65. Found: S, 13.9; Cl, 0.9.

Redistillation of (a) at atmospheric pressure gave 4.7 g. (0.04 mole) of thionyl chloride, b. p. 75–76°.

Anal. Calcd. for $SOCl_2$: S, 26.9; Cl, 59.6. Found: S, 26.8; Cl, 58.6.

The yield of thionyl chloride and diphenyl sulfite was 53% each, based on the phenyl chlorosulfinate not recovered.

When phenyl chlorosulfinate (160 g.) was heated for six hours at 70° in the absence of hydrogen chloride and then redistilled, 97% (155 g.) was recovered. Treatment of diphenyl sulfite in a similar manner resulted in a recovery of 96% of the original material.

Reaction of Phenol with Thionyl Chloride in Refluxing Solvents.—The apparatus and the techniques used were the same as had been described previously,[8] except that the phenol was generally maintained slightly above its melting point while being added to the refluxing solvent. The solvents used, and their boiling points, were: ethyl chloride (12°), methylene chloride (42°), carbon tetrachloride (76°), thionyl chloride (78°), chlorobenzene (130°), and *o*-dichlorobenzene (180°). The addition of the phenol and thionyl chloride was made in *one* to *two* hours (with one exception), after which the refluxing was continued for *one* to *three* hours more. In the experiment with ethyl chloride as solvent a forty-eight hour reflux period was used. The yields of diphenyl sulfite and phenyl chlorosulfinate were determined by distillation and redistillation of the product at the reduced pressures already mentioned, through a 1.5 × 15-cm. Vigreux column. The yields were based on the weights of starting materials and on the reactant present in deficiency. A black tarry residue remained from every distillation. The results are summarized in Table I.

In the experiments at 12° and 42°, *p*-chlorophenol was isolated during the distillation of the products. This material had b. p. 107–110° (20 mm.); m. p. 20–25°, n^{20}_{D} 1.5655.

Anal. Calcd. for C_6H_5OCl: Cl, 27.6. Found: Cl, 27.4; S, 0.2. As further identification, the *p*-chlorophenol was converted to *p*-chlorophenyl benzoate, m. p. 87°.

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(1) Tassinari, *Gazz. chim. ital.*, **20**, 326 (1890).

(2) Voswinckel, *Pharm. Zeit.*, **40**, 241 (1895).

(3) Carré and Libermann, *Compt. rend.*, **196**, 275 (1933).

(4) Carré and Libermann, *Bull. soc. chim.*, (4) **53**, 1051 (1933).

(5) Courtot and Tung, *ibid.*, **200**, 1541 (1935).

(6) Lüttringhaus, *Ber.*, **72**, 887 (1939).

(7) Gerrard, *J. Chem. Soc.*, 99 (1939).

(8) Bissinger and Kung, THIS JOURNAL, **69**, 2158 (1947).

(9) Gerrard, *J. Chem. Soc.*, 224 (1940).

TABLE I

REACTION OF PHENOL WITH THIONYL CHLORIDE IN REFLUXING SOLVENTS

Reaction temp., °C.	Reactants, moles		Yields, %		Wt. of tarry residue, g.
	Phenol	$SOCl_2$	$(C_6H_5)_2SO_3$	C_6H_5OSOCl	
12	2	1	0	0	90[a,b]
42	2	1	0	0	87[c]
42	1	2	28	43	25
76	2	1	73	0	18[d]
76	2	1	17	0	88[e]
76	1	1	33	19	36
76	1	2	0	35	55
78	1	4	0	71	28
78	1	4	0	83	18[f]
78	2	8	3	81	14[f]
130	2	1	61	0	34[g]
130	2	1	87	0	9[f,h]
130	1	1	56	35	8
130	1	2	44	43	5
180	2	1	0	0	107[i]
180	1	2	32	47	4

[a] Unreacted phenol (48%) was isolated along with 0.104 mole of *p*-chlorophenol. [b] This residue contained 5.4% chlorine and 16.6% sulfur. [c] Fifty-one per cent. of the phenol was recovered and 0.04 mole of *p*-chlorophenol appeared on distillation. [d] One hundred ml. of carbon tetrachloride was placed in the flask while the other 400 ml. was used to prepare equivolume solutions of the phenol and $SOCl_2$, which were then added dropwise. The addition time was extended to seven hours. [e] Phenol (36%) was recovered. [f] The phenol was dissolved in chlorobenzene (100 ml. per mole of phenol) to facilitate addition. [g] Phenol (15%) was recovered. [h] In this experiment the rate of reflux was much higher than in the preceding experiment. [i] On attempted distillation only acidic gases were evolved.

Discussion of Results

In general, the reaction of thionyl chloride with phenol, even in the presence of a refluxing solvent, was observed to be far more sensitive to slight variations in the operating conditions than had been noted in the reaction of thionyl chloride with aliphatic alcohols. For example, very vigorous stirring and strong refluxing of the solvent was found conducive to definitely improved yields in the phenol reaction; in the aliphatic series these factors were not particularly important. There are indications, also, that the time of addition of the phenol and the thionyl chloride to the refluxing solvent may bear very significantly on the results. In the studies reported here, the effect of this variable was investigated in only one experiment, as will be discussed later in the paper. It should be clearly recognized, therefore, that our results were obtained under specific reaction conditions, and any marked deviation from these conditions may lead to considerable differences in yields.

The preparation of diphenyl sulfite by the direct reaction of phenol and thionyl chloride in the absence of hydrogen chloride acceptors has been accomplished for the first time through the use of the refluxing solvent technique. The data of Table I illustrate that at a 2:1 molar ratio of phenol to thionyl chloride the maximum yield (87%) of diphenyl sulfite was obtained at a reaction temperature of 130° with chlorobenzene as the refluxing solvent. It is not fully understood why this maximum yield appeared at such a high temperature. In contrast to the other experiments, it will be noted that in most cases at 130° essentially no tarry residues were obtained. Assuming that these resinous bodies were formed through a reaction of thionyl chloride with the benzenoid ring, it might be concluded that at 130° the esterification reaction becomes very much faster than the coupling reaction, thereby resulting in the predominant formation of diphenyl sulfite.

The fact that no diphenyl sulfite could be isolated from the experiments at 12° and 42° with a 2:1 molar ratio of phenol to thionyl chloride is in accord with the results of earlier workers.[1–6] It is apparent that under these conditions the refluxing solvent method did not eliminate the formation of undesirable by-products, represented by the tarry residues obtained on distillation. The high yield (73%) of diphenyl sulfite obtained at 76° with carbon tetrachloride as solvent was only obtained when a seven-hour addition time for the reactants was used. When the addition time was the usual one-to-two hour period, the yield of diphenyl sulfite was only 17%. These results afford strong evidence that even relatively minor variations in the reaction conditions may materially affect the yield figures.

The refluxing solvent technique, using a 300% excess of thionyl chloride at 78° as the sole refluxing solvent, furnished a very simple means of preparing phenyl chlorosulfinate. The discrepancy between the yields of 71% and 83%, as reported in Table I, can probably be attributed to the less vigorous stirring and the decreased rate of reflux used in the former case.

In all preparations of phenyl chlorosulfinate with thionyl chloride as the sole refluxing solvent, it was found that not more than 3% of diphenyl sulfite was obtained, providing vigorous stirring[10] was employed. The low yield of diphenyl sulfite indicates that in the absence of hydrogen chloride acceptors, the reaction of phenol with phenyl chlorosulfinate at 78° may be a much slower reaction than the corresponding reaction of alkanols with alkyl chlorosulfinates at this temperature. For example, when *n*-propyl alcohol was added to a 500% excess of refluxing thionyl chloride in a four-hour reaction period with vigorous stirring, a 30% yield[8] of *n*-propyl sulfite was obtained, along with the expected chlorosulfinate.

Although phenyl chlorosulfinate can be distilled at 90–100° without decomposition, it was found to be unstable on prolonged standing at room tem-

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(10) This is only true under conditions of strong agitation. In one experiment, phenol (2 moles) was added to refluxing thionyl chloride (8 moles), without stirring, over a two-hour period, followed by one additional hour of reflux. No phenyl chlorosulfinate was obtained, but a 41% yield of diphenyl sulfite was produced, along with a residue of 60 g.

perature. A purified sample, stored for about eleven months on the desk top in a glass-stoppered bottle, decomposed violently, rupturing the bottle and evolving heat.[11]

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Summary

1. The thermal stability of phenyl chlorosulfinate, although poor, was about equal to that of *n*-propyl chlorosulfinate and much greater than that of isopropyl chlorosulfinate.

2. Diphenyl sulfite reacted with hydrogen chloride producing phenol and a tarry residue; the other expected cleavage product, chlorobenzene, was not found. Phenyl chlorosulfinate, unlike the unreactive alkyl chlorosulfinates, underwent a disproportionation reaction in the presence of hydrogen chloride to form thionyl chloride and diphenyl sulfite.

3. The refluxing solvent technique afforded an excellent means of preparing phenyl chlorosulfinate and diphenyl sulfite in yields of 83% and 87%, respectively. This was the first successful preparation of the latter by the direct reaction of phenol with thionyl chloride without hydrogen chloride acceptors.

4. The variables of temperature and ratio of reactants have been studied in the reaction of phenol with thionyl chloride in a refluxing solvent. *Under the conditions used*, the lower reaction temperatures seemed to favor undesirable side-reactions; at a 2:1 molar ratio of phenol to thionyl chloride the best yield of diphenyl sulfite occurred at 130°, whereas with excess thionyl chloride the best yield of phenyl chlorosulfinate was obtained in refluxing thionyl chloride at 78°.

5. The reaction of phenol with thionyl chloride in a refluxing solvent is apparently very sensitive to relatively minor changes in the reaction conditions, such as stirring for example, and with such modifications quite different results from those reported here may be obtained. Such sensitivity was not apparent in the aliphatic series.

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[11] Carré and Libermann, *Compt. rend.*, **195**, 799 (1932), reported that the decomposition of phenyl chlorosulfinate was instantaneous at room temperature. The presence of impurities in their material may have been responsible for this reduced stability.

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Preparation of Spermine Tetrahydrochloride[1] (1,12-Diamino-4,9-diazadodecane Tetrahydrochloride)

BY HARRY P. SCHULTZ[2]

The reported synthesis of spermine[3,4] appeared impractical for the preparation of the quantity of material required in the antimalarial program. Therefore, a synthesis of spermine tetrahydrochloride was developed, which consisted of the hydrogenation of succinonitrile to putrescine (I); the dicyanoethylation of putrescine to N,N′-bis-(2-cyanoethyl)-putrescine (II); followed by hydrogenation of II to spermine (III). The tetramine was then converted to the tetrahydrochloride.

$H_2N(CH_2)_4NH_2$ I

$NC(CH_2)_2NH(CH_2)_4NH(CH_2)_2CN$ II

$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$ III

The hydrogenation of succinonitrile was carried out at 140° in liquid ammonia over Raney nickel. Even under these conditions, which are usually quite unfavorable to formation of secondary amines, the yield of pyrrolidine was more than twice as large as that of the desired primary amine. The dicyanoethylation reaction proceeded well in water, alcohol, or ether. The yield of II was almost quantitative, judged by the amount of the dihydrochloride that was isolated in some experiments. The preferred procedure was to carry out the cyanoethylation in ether solution and, without isolating II, add liquid ammonia and hydrogenate over Raney nickel at 140° to III. The tetramine (III) was then distilled and isolated and purified as the tetrahydrochloride. The over-all yield of the tetrahydrochloride, starting with putrescine, was 51% of the theoretical.

Experimental

Putrescine.—A steel reaction vessel having a void of 1300 ml. was charged with 200 g. (2.5 moles) of succinonitrile,[5] 9 g. of W-2 Raney nickel,[6] and 350 ml. of liquid ammonia. The contents of the bomb was reduced for two and one-half hours at 140° under a hydrogen pressure of 1700 p. s. i. The catalyst-free reaction mixture was distilled to give 79.7 g. (45% yield) of crude pyrrolidine that boiled at 87–88° (740 mm.), and 43 g. (20% yield) of putrescine, b. p. 60–65° (16 mm.); m. p. 27–28°. Ladenburg[7] reported a m. p. of 23–24° for putrescine, while Ciamician and Zanetti[8] gave m. p. 27–28°.

N,N′-bis-(2-Cyanoethyl)-putrescine.—Acrylonitrile from the Rohm and Haas Company (35.0 g., 0.66 mole)

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[3] Rosenheim, *Biochem. J.*, **18**, 1253 (1924).

[4] Dudley, Rosenheim and Starling, *ibid.*, **20**, 1082 (1926).

[5] Succinonitrile from du Pont Electrochemical Division was used without further purification.

[6] Mozingo, "Organic Syntheses," Vol. XXI, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 15.

[7] Ladenburg, *Ber.*, **19**, 781 (1886).

[8] Ciamician and Zanetti, *ibid.*, **22**, 1970 (1889).