# The Reaction of Chlorourea with Tertiary Phosphite Esters and Triphenylphosphine

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The preparation of alkyl esters of ureidophosphoric acid from chlorourea and tertiary phosphites is reported. A mechanism for the reaction is proposed and physical properties of the products are presented. Chlorourea and triphenylphosphine give ureidotriphenylphosphonium chloride, $H_2NCOHP(C_6H_5)_3Cl$, in a similar reaction.

The chemistry of chlorourea reported in the literature is restricted predominantly to aqueous or alcoholic systems. In these cases chlorourea acts simply as a mild chlorinating or oxidizing agent.[1] However, by using aprotic solvents, different and new reactions of chlorourea have been observed. As an example, the reaction with tertiary phosphite esters and triphenylphosphine is described.[2]

The reaction of tertiary phosphites with various alkyl and acyl halides, accompanied by loss of alkyl halide and formation of a phosphonate (eq. 1) has been observed with a large number of halides such as ethyl iodide,[3,4] bromomalonamide,[5] chloroformates,[6] acetyl chloride, benzoyl chloride,[7] and carbamoyl chlorides.[8] Halides involving halogen bonded to elements other than carbon are also known to give the same reaction; these are sulfenyl chlorides[9] and halosuccinimide.[10] We have now found that chlorourea represents another example of an N–Cl compound following the above pattern in its reaction with tertiary phosphite esters.

$$RX + P(OR')_3 \longrightarrow RPO(OR')_2 + R'X \qquad (1)$$

## Results and Discussion

**A. Reaction with Phosphite Esters.**—Chlorourea and tertiary alkyl phosphites produce in a strongly exothermic reaction esters of ureidophosphoric acid and the corresponding alkyl halide (eq. 2). The reaction proceeds instantaneously at temperatures as low as −40°. On standing, the products usually precipitate from the reaction mixture as white crystalline materials in good-to-moderate yields. The general nature of the reaction was verified by preparing the methyl, ethyl, isopropyl, and *n*-butyl derivatives (Table I). All compounds are stable crystalline solids and can be recrystallized from aqueous alcohol. They are highly resistant to acid or base hydrolysis. The samples were recovered unchanged after refluxing in both 2 *N* mineral acid and alkali hydroxide.

$$ClNHCONH_2 + P(OR)_3 \longrightarrow H_2NCONHPO(OR)_2 + RCl \qquad (2)$$

TABLE I
ESTERS OF UREIDOPHOSPHORIC ACID

| Ester | Yield, % | M.p., °C. |
|---|---|---|
| Methyl | 50 | 184–186 |
| Ethyl | 42 | 208–209 |
| Isopropyl | 44 | 196–197 |
| *n*-Butyl | 48 | 175–176 |

The composition and structure of the compounds were established as $H_2NCONHPO(OR)_2$ by elemental analysis and infrared absorption (Table II). The spectra show essentially the patterns of urea and the phosphite ester, with minor shifts. Generally, the NH stretch is found at 2.9–3.0, the C=O stretch at 5.9–6.0, NH deformation at 6.2, P → O at 8.1–8.2, and POC at 9.8–10.0 μ.

TABLE II
INFRARED SPECTRA OF $H_2NCONHPO(OR)_2$ DERIVATIVES

| R | | | |
|---|---|---|---|
| $CH_3$, μ | $C_2H_5$, μ | iso-$C_3H_7$, μ | *n*-$C_4H_7$, μ |
| 2.98 (m) | 2.95 (s) | 2.94 (s) | 2.96 (s) |
| 3.11 (w) | 3.11 (s) | 3.12 (m) | 3.12 (m) |
| 3.25 (w) | 3.24 (w) | 3.34 (m) | 3.38 (s) |
| 3.38 (w) | 3.35 (w) | 3.41 (w) | 3.48 (m) |
| 3.54 (w) | 3.52 (w) | 5.96 (s) | 5.97 (s) |
| 6.10 (s) | 5.98 (s) | 6.08 (w) | 6.16 (m) |
| 6.68 (s) | 6.16 (m) | 6.18 (w) | 6.65 (s) |
| 7.41 (w) | 6.68 (s) | 6.70 (s) | 7.24 (w) |
| 8.10 (s) | 7.25 (w) | 7.24 (w) | 7.42 (w) |
| 8.45 (w) | 7.41 (w) | 8.14 (s) | 8.18 (s) |
| 9.46 (s) | 8.10 (s) | 8.51 (w) | 8.94 (w) |
| 9.71 (s) | 8.60 (w) | 8.80 (w) | 9.75 (s) |
| 11.02 (w) | 8.95 (w) | 9.05 (w) | 10.03 (m) |
| 11.99 (m) | 9.76 (s) | 10.00 (s) | 10.48 (w) |
| 12.40 (s) | 10.20 (w) | 11.20 (w) | 11.05 (w) |
| | 10.38 (w) | 13.00 (w) | 12.65 (w) |
| | 12.80 (m) | | 13.70 (w) |

The evolved halocarbons were swept from the reaction system by a stream of dry nitrogen, trapped in a cold bath and identified by boiling point and infrared pattern.

The identity of the products as esters of ureidophosphoric acid was confirmed by the alternate synthetic routes in eq. 3 and 4.

$$H_2NCONHNa + ClPO(OR)_2 \longrightarrow H_2NCONHPO(OR)_2 + NaCl \qquad (3)$$

$$H_2NCONHCl + NaOP(OR)_2 \longrightarrow H_2NCONHPO(OR)_2 + NaCl \qquad (4)$$

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(1) A. A. Petrov, *Dokl. Akad. Nauk SSSR*, **78**, 63 (1951).

(2) The corresponding arsenic and antimony compounds were found to react with chlorourea in a similar way. The results will be reported at a later date.

(3) A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.*, **38**, 687 (1906).

(4) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 121–123.

(5) T. Mukaiyama, T. Hata, and K. Tasaka, *J. Org. Chem.*, **28**, 481 (1963).

(6) A. E. Arbuzov and A. A. Dunin, *J. Russ. Phys. Chem. Soc.*, **46**, 295 (1914); *Chem. Abstr.*, **8**, 2551 (1914).

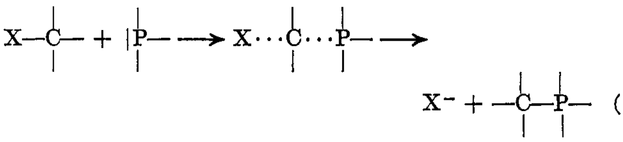
(7) M. I. Kabachnik and P. A. Rossiskaya, *Bull. Acad. Sci. USSR., Classe sci. chim.*, 364 (1945); *Chem. Abstr.*, **40**, 4688 (1946).

(8) B. A. Arbuzov and Rizpolozhenskii, *Izv. Akad. Nauk USSR, Otd. Khim. Nauk*, 847, 854 (1952); *Chem. Abstr.*, **47**, 10, 457, 9903 (1953).

(9) D. C. Morrison, *J. Am. Chem. Soc.*, **77**, 181 (1955).

(10) A. K. Tsolis and E. McEwen, *Tetrahedron Letters*, 3217 (1964).

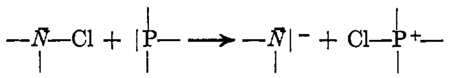
The mechanism of the over-all reaction (which is shown in eq. 2) appears to be of a rather complex nature involving at least two steps. Owing to their strongly nucleophilic character, tertiary phosphites react with alkyl halide by an SN2 mechanism. The initial attack of the phosphite is on the carbon atom, displacing the halogen (eq. 5). However, in



$$\mathrm{X{-}C{-}} + \mathrm{|P{-}} \longrightarrow \mathrm{X\cdots C\cdots P{-}} \longrightarrow \mathrm{X^-} + \mathrm{{-}C{-}P{-}} \qquad (5)$$

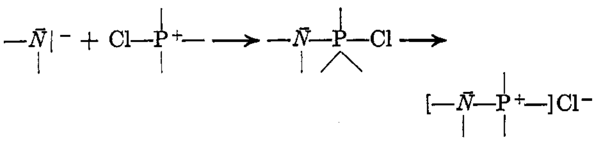
the case of N-halo compounds such as chlorourea the polarization, giving the halogen atom a partial positive charge, makes a nucleophilic attack on the halogen more likely. The center of the SN2 reaction is thus shifted from the nitrogen to the halogen.

As a consequence, an ion pair with a halogenphosphonium cation and a nitrogen anion is initially formed (eq. 6). This assumption is supported by the fact



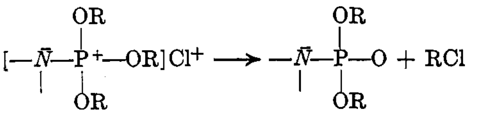
$$\mathrm{{-}\bar{N}{-}Cl} + \mathrm{|P{-}} \longrightarrow \mathrm{{-}\bar{N}|^-} + \mathrm{Cl{-}P^+{-}} \qquad (6)$$

that in solvolytic solvents only the solvolysis products of the ion pair are observed. Evidence for the probability of such an ion-pair formation was presented by Haszeldine[11] for the carbon analog. The ion pair can lead *via* reactive intermediates to the same phosphonium halide (eq. 7) as direct SN2 substitution of



$$\mathrm{{-}\bar{N}|^-} + \mathrm{Cl{-}P^+{-}} \longrightarrow \mathrm{{-}\bar{N}{-}P{-}Cl} \longrightarrow [\mathrm{{-}\bar{N}{-}P^+{-}}]\mathrm{Cl^-} \qquad (7)$$

the halogen by primary attack of the phosphite on the nitrogen atom. Nucleophilic attack by the halide ion on the alkyl carbon would give the observed products (eq. 8). The formation of ureidophosphoric acid



$$[\mathrm{{-}\bar{N}{-}\overset{OR}{\underset{OR}{P}}{}^+{-}OR}]\mathrm{Cl^+} \longrightarrow \mathrm{{-}\bar{N}{-}\overset{OR}{\underset{OR}{P}}{-}O} + \mathrm{RCl} \qquad (8)$$

esters from chlorourea and tertiary phosphite represents essentially a Michaelis–Arbuzov reaction with an N-halo compound, thereby demonstrating the generality and wide scope of this reaction.

Esters of ureidophosphoric acid can be prepared, in addition to the methods outlined in eq. 3 and 4, by ammonolysis of isocyanatophosphate esters.[12] However, the preparation from chlorourea and phosphite as described here represents by far the most convenient and shortest route using readily available and inexpensive starting materials. Furthermore, chlorourea can be prepared by chlorination of a urea suspension in acetonitrile. This solution can be used directly for the reaction with the phosphorus compounds, thereby eliminating the isolation and storage problem of chlorourea.

**B. Reaction with Tertiary Phosphines.**—Substituted phosphines such as triphenyl phosphine react with chlorourea in the same manner as tertiary phosphites; a white crystalline material starts to precipitate from the solution as the exothermic reaction is completed. Elemental analysis and infrared absorption of the product suggest the quasi-phosphonium salt[13] shown in eq. 9. The infrared absorption pattern of

$$\mathrm{ClNHCONH_2 + P(C_6H_5)_3 \longrightarrow [H_2NCONHP^+(C_6H_5)_3]Cl^-} \qquad (9)$$

the compound is similar to that of urea and triphenylphosphine except for a minor shift of the carbonyl band to 5.89 $\mu$ as compared to 5.99 $\mu$ in urea. The compound hydrolyzes readily in warm water to give urea, hydrogen chloride, and triphenylphosphine oxide.

The mechanism of the reaction should follow the pattern as outlined for chlorourea and tertiary phosphites (eq. 6 and 7). However, the reaction stops at the phosphonium halide due to the stability of the latter.

## Experimental

**Materials.**—All reagents (Eastman) were redistilled before use. Acetonitrile and tetrahydrofuran were predried over potassium hydroxide and distilled over calcium hydride.

**Infrared Spectra.**—The infrared spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer using the KBr pressed-plate technique.

**The Preparation of $\mathrm{H_2NCONHPO(OCH_3)_2}$.**—The compound can be prepared from chlorourea[14] or, more simply, as described here, from urea and chlorine forming chlorourea directly in the reaction solution. If a 100% excess of urea is employed, the unreacted urea serves as a buffer for the liberated hydrogen chloride thereby stabilizing the chlorourea–acetonitrile system. The subsequent reaction with the phosphite ester can be followed by titration of the oxidizer content (N–Cl). A sample, drawn from the reaction mixture, is added to acid aqueous potassium iodide, and titrated with thiosulfate.

A suspension of 0.6 mole (36 g.) of pulverized urea in 450 ml. of acetonitrile is cooled to 0° and chlorinated while stirring rapidly. Moisture is excluded by an atmosphere of dry nitrogen; gas introduction is discontinued as soon as 0.3 mole (21.3 g.) of chlorine has been absorbed. The resulting clear, colorless solution is stirred for an additional 30 min. If a yellow solution is obtained it should be discarded. Trimethylphosphite, diluted by an equal volume of acetonitrile, is added dropwise while maintaining the temperature at 10–15° by external cooling. The addition of phosphite is terminated as soon as an HI test fails to produce iodine. Normally, 35 to 38 g. of trimethylphosphite is required. The reaction mixture is allowed to stand for 5–6 hr. at 0°. The precipitate is separated by filtration, washed with cold acetonitrile, and dried *in vacuo*. Recrystallization from five parts of hot water or acetonitrile produces 25 g. of fine white needles melting at 186–187°.

*Anal.* Calcd. for $\mathrm{C_3H_9N_2O_4P}$: C, 21.44; H, 5.39; N, 16.69. Found: C, 21.65; H, 5.42; N, 16.65.

**The Preparation of $\mathrm{H_2NCONHPO(OC_2H_5)_2}$.**—A solution of 0.3 mole chlorourea in acetonitrile is prepared as described in the preceding experiment. Approximately 0.3 mole (50 g.) of triethylphosphite is diluted with 50 ml. of acetonitrile and dropped into the stirred chlorourea solution at 10–15° until a negative HI test is obtained. The product precipitates on standing at 0° for several hours. Filtration and recrystallization from 12 parts of hot water produces 26 g. of fine needles melting at 208–209°.

*Anal.* Calcd. for $\mathrm{C_5H_{13}N_2O_4P}$: C, 30.62; H, 6.68; N, 14.28. Found: C, 31.20; H, 6.69; N, 14.15.

**The Preparation of $\mathrm{H_2NCONHPO(OC_3H_7)_2}$.**—Acetonitrile solutions of 0.3 mole of chlorourea and 0.3 mole of triisopropylphosphite are reacted in a manner similar to the preceding examples. The precipitate is recrystallized from 15 parts of ethanol yielding 30 g. of long white needles melting at 196–197°.

*Anal.* Calcd. for $\mathrm{C_7H_{17}N_2O_4P}$: C, 37.50; H, 7.64; N, 12.49. Found: C, 37.97; H, 7.63; N, 12.10.

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[11] R. N. Haszeldine and B. O. West, *J. Chem. Soc.*, 3631 (1956).

[12] G. I. Kerkach and L. I. Samarai, *Zh. Obshch. Khim.*, **33**, 1587 (1963).

[13] H. Hoffman and H. J. Diehr, *Angew. Chem. Intern. Ed. Engl.*, **3**, 737 (1964).

[14] A. Behal and A. Detreuf, *Compt. Rend.*, **153**, 682 (1911).

**The Preparation of $H_2NCONHPO(OC_4H_9)_2$.**—Analogous treatment of 0.3 mole of chlorourea and 0.3 mole of tri-*n*-butylphosphite produced after recrystallization from 30 parts of ethanol 36 g. of long white needles, melting at 175–176°.

*Anal.* Calcd. for $C_9H_{21}N_2O_4P$: C, 42.85; H, 8.39; N, 11.10. Found: C, 43.08; H, 8.40; N, 10.92.

**The Preparation of $H_2NCONHP(C_6H_5)_3$ Cl.**—A solution of 0.1 mole (26.2 g.) of triphenylphosphine in 150 ml. of acetonitrile (or tetrahydrofuran) is dropped into a stirred solution of 0.1 mole (9.4 g.) of chlorourea in 150 ml. of acetonitrile. The temperature of the reaction mixture is maintained at 10–15° by external cooling. After completion of addition the temperature is lowered to 0° for 5 hr. The precipitate is collected, washed with cold acetonitrile, and dried under vacuum. The filtrate is combined with the wash liquor, concentrated under vacuum to 50-ml. volume, and diluted with 100 ml. of acetone. After standing for 24 hr., the insoluble portion is separated by filtration, washed with cold acetonitrile, and added to the first crop. Recrystallization from absolute ethanol yields 15 g. of compact crystals melting at 194–195°.

*Anal.* Calcd. for $C_{19}H_{18}ClN_2OP$: C, 63.96; H, 5.08; Cl, 9.93; N, 7.85. Found: C, 63.78; H, 5.08; Cl, 9.36; N, 7.55.

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# Sulfostyril (2,1-Benzothiazine 2,2-Dioxide). I. Preparation and Reactions of 3,4-Dihydrosulfostyril

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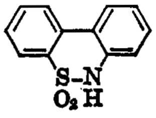
3,4-Dihydrosulfostyril was synthesized as a potential intermediate to the hitherto unknown parent aromatic sultam, sulfostyril (5). The reactions and properties of dihydrosulfostyril are described. N-Bromosuccinimide in dimethylformamide proved to be a very convenient nuclear-brominating agent.

The preparation and properties of aliphatic sultams have been investigated well[1,2]; however, there has been little reported on aromatic sultams. At the time this work was initiated, the only aromatic sultams known were the completely aromatic derivatives [diphenylenesultam (1)[1] and 1,8-naphthosultam (2)[1]] and the sulfonyl analog of isooxindole (3).[1,3] After the present work had been completed, the preparation of 4, the sulfonyl analog of oxindole, was reported.[4]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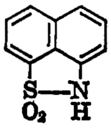
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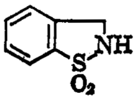
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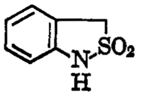
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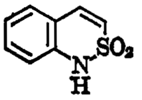
We were interested in preparing the remaining member of the aromatic sultam series, sulfostyril (5),[5] in order to compare the physical and chemical properties of it and its derivatives with those of carbostyril (6).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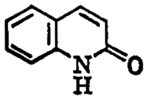
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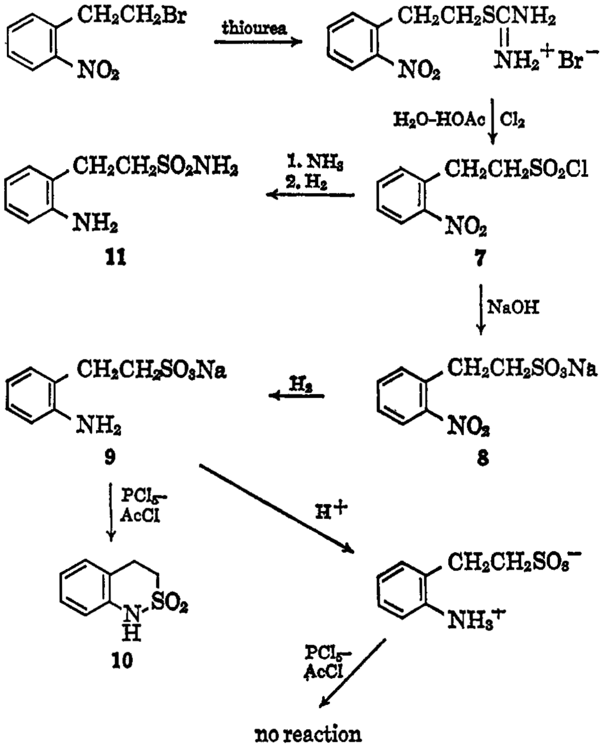
In this paper, we describe the synthesis of dihydrosulfostyril (10), originally intended to serve (*via* dehydrogenation) as the immediate precursor of 5.

CHART I



The synthesis of dihydrosulfostyril (10) is outlined in Chart I. 2-Nitrophenethyl bromide was converted in two steps to the sulfonyl chloride, 7. Alkaline hydrolysis gave the sodium sulfonate 8[6] which was readily catalytically reduced to the amine 9. Acidification of an aqueous solution of 9 gave the very insoluble zwitterion. This zwitterion could not be converted to the desired sultam by heating (it decomposed), and was recovered unchanged from treatment with phosphorus pentachloride, phosphorus oxychloride, acetyl chloride, or mixtures of these reagents. However, trituration

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[1] A. Mustafa, *Chem. Rev.*, **54**, 206 (1954), and A. Mustafa, "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press Inc., New York, N. Y., 1960, p. 183.

[2] W. F. Erman and H. C. Kretschmar, *J. Org. Chem.*, **26**, 4841 (1961), and references cited therein.

[3] Compound **3** has been called "benzyl sultam," but this ambiguous name should be avoided since it could also refer to compound **4**.

[4] J. F. Bunnett, T. Kato, R. R. Flynn, and J. A. Skorcz, *J. Org. Chem.*, **28**, 1 (1963).

[5] Compound **5** can be systematically named as 2,1-benzothiazine 2,2-dioxide or, less satisfactorily, as *o*-aminostyrene-β-sulfonic acid sultam; for convenience, we prefer the name "sulfostyril," by analogy with the name "carbostyril" used for compound **6**.

[6] Compound **8** was also prepared in one step by the reaction of *o*-nitrophenethyl bromide with sodium sulfite; however, the yield of **8** by this route was very low.