The Reaction of Ketene Diethyl Acetal with Cyanuric Chloride

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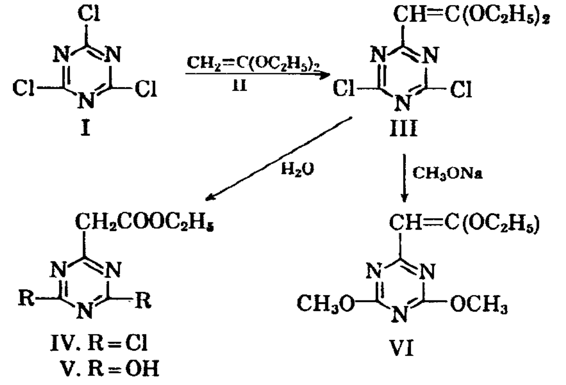
The preparation of acyl ketene acetals by the reaction of aromatic and aliphatic acyl chlorides with ketene acetals has been the subject of several papers.[1-3] As in many of its properties cyanuric chloride (I) resembles acyl halides, the objective of the present investigation was to explore whether the chlorine atoms of compound I were sufficiently active to undergo reaction with dialkyl ketene acetals.

Compound I reacted readily with ketene diethyl acetal (II) in ethereal solution to form a well crystallized yellow compound, the diethyl acetal of 2,4-dichloro-*s*-triazinyl-6-ketene (III). The chlorine atoms in 2- and 4-positions were not affected by excess II and prolonged refluxing. Compound III is stable for longer periods of time only when kept under complete exclusion of atmospheric moisture. Upon standing in the air, it liquefied within a few hours to form a yellow colored oil. While the infrared spectrum of compound III showed all the features to be expected for its structure, the spectrum of the oil was different inasmuch as upon prolonged exposure to air the unsaturation gradually disappeared and the intensity of absorption for carbonyl increased. From this observation it is concluded that compound III, when exposed to moisture, is converted into ethyl 2,4-dichloro-*s*-triazinyl-6-acetate (IV), although compound IV could not be isolated in its pure form because the remaining chlorine atoms undergo partial hydrolysis even under these mild conditions. When compound III was heated briefly with aqueous ethanol, the yellow color of the solution faded and compound III was quantitatively converted into ethyl 2,4-dihydroxy-*s*-triazinyl-6-acetate (V).

Substitution of the chlorine atoms in 2- and 4-positions of compound III without affecting the ketene diethyl acetal group was accomplished with sodium methoxide in refluxing methanolic solution. The diethylacetal of 2,4-dimethoxy-*s*-triazinyl-6-ketene (VI), thus obtained, showed a pronounced gelatinizing effect on benzene.



Reaction could not be achieved when compound I was treated with ketene instead of the diethyl acetal. Relevant experiments, carried out in cold or refluxing cyclohexane with a large excess of ketene and in the presence of aluminum chloride, resulted in the nearly quantitative recovery of compound I.

EXPERIMENTAL[4]

Diethyl acetal of 2,4-dichloro-s-triazinyl-6-ketene (III). Ketene diethyl acetal[5] (II, 35 g., slightly above 0.3 mole) was added to a solution of cyanuric chloride (I, 6.15 g., 0.033 mole) in 300 ml. of anhydrous ether. The colorless reaction mixture became intensively yellow colored after a few moments, indicating that reaction occurred at room temperature. To complete the reaction, the mixture was refluxed for 6 hr. Evaporation of the ether *in vacuo* resulted in a yellow colored oil, which was recrystallized from petroleum ether (b.p. 90–97°) to give 7.05 g. (81%) of compound III, yellow colored crystals, m.p. 64–66°. Further recrystallization did not result in an increase of the melting point.

Anal. Calcd. for $C_9H_{11}N_3Cl_2O_2$: C, 40.92; H, 4.20; N, 15.91; Cl, 26.85. Found: C, 40.20; H, 4.24; N, 15.93; Cl, 26.64.

The structure of this compound was supported by an infrared spectrum which showed the features to be expected for unsaturation (6.25 μ), the *s*-triazine structure (6.56 μ)[6] as well as for the ethyl group (C—H stretching 3.35 μ, 3.45 μ; C—H deformation 6.9 μ, 7.1 μ, 7.25μ, 7.35 μ) and the C-Cl group (12.45 μ) besides weak absorption for carbonyl (5.75 μ).

Upon standing in the air, the yellow colored crystals turned into a yellow colored oil which showed a different infrared spectrum inasmuch as the absorption for C—Cl (12.45 μ) and for unsaturation (6.25 μ) disappeared and the carbonyl intensity of absorption (5.75 μ) increased.

Ethyl 2,4-dihydroxy-s-triazinyl-6-acetate (V). A sample of the diethylacetal of 2,4-dichloro-*s*-triazinyl-6-ketene (III) was refluxed with a small amount of aqueous ethanol. After a few seconds, the yellow colored solution became colorless Cooling of the solution at 0° for 24 hr. resulted in the precipitation of colorless needles which were found to be compound V. This compound, recrystallized several times from water, melted over a wide temperature range; it started to soften at 156°. but had not completely liquefied at 200°.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.21; H, 4.56; N, 21.10. Found: C, 42.33; H, 4.69; N, 20.51.

In another experiment, compound III was refluxed with aqueous ethanol as described above. The reaction mixture was then allowed to stand at −15° for 2 weeks. The white solid which had precipitated was filtered and again proved to

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(1) S. M. McElvain and H. F. McShane, Jr., *J. Am. Chem. Soc.*, **74**, 2662 (1952).

(2) S. M. McElvain and G. R. McKay, Jr., *J. Am. Chem. Soc.*, **78**, 6068 (1952).

(3) H. D. Stachel, *Ber.*, **93**, 756 (1960).

(4) All melting points were determined with the Fisher-Johns apparatus. Infrared spectra were obtained using a Perkin-Elmer Model 21 instrument. Analyses by Central Analytical Department, Olin Mathieson Chemical Corp., New Haven, Conn.

(5) P. R. Johnson, H. B. Barnes, and S. M. McElvain, *J. Am. Chem. Soc.*, **62**, 964 (1940).

(6) H. A. Schroeder, *J. Am. Chem. Soc.*, **81**, 5658 (1959).

have the composition of compound V, but did not melt at 330°.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.21; H, 4.56; N, 21.10. Found: C, 41.68; H, 5.00; N, 20.96.

Diethyl acetal of 2,4-dimethoxy-s-triazinyl-6-ketene (VI). Diethyl acetal of 2,4-dichloro-*s*-triazinyl-6-ketene (III, 2.64 g., 0.01 mole) was added to the solution of sodium (0.46 g., 0.02 mole) in 25 ml. of methanol. The reaction mixture was refluxed for 5 min. After standing at room temperature overnight, the sodium chloride formed was filtered off and the methanol removed *in vacuo* to give a yellow colored oil. Treatment of the oil with hot benzene resulted in the precipitation of a further small amount of sodium chloride which was removed by filtration. Upon cooling of the filtrate to room temperature, it formed a very stiff gel. After standing for 2 days, the gel was subjected to a vacuum of 3 mm. The gel did not break upon this procedure, but had to be heated to remove the solvent which occurred between 60–75° (3 mm.). Attempted distillation of the remaining oil was unsuccessful. Distillation did not occur applying a vacuum of 0.7 mm. and heating the bath to 160°. At this temperature, the content of the distillation flask solidified. The solid formed was treated with 15 ml. of cold petroleum ether (b.p. 90–97°) to give a yellow powder which was filtered. The powder was extracted with 15 ml. of hot petroleum ether (b.p. 90–97°). From this extract yellow needles precipitated which, after two further recrystallizations from the petroleum ether, melted at 78–80° and were found to be compound VI.

Anal. Calcd. for $C_{11}H_{17}N_3O_4$: C, 51.75; H, 6.71; N, 16.47. Found: C, 51.61; H, 6.76; N, 17.20.

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Production of Pyrophosphate from *S-n*-Butylphosphorothioate[1,2]

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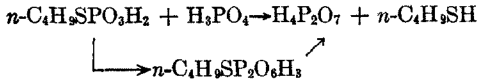
Esters of thiols (such as coenzyme A) and phosphoric acid have been suggested as intermediates in biological phosphate transfers[3]; and *S-n*-butylphosphorothioate accomplishes the nonenzymic phosphorylation of alcohols and even acetic acid,[4] the latter yielding acetyl phosphate.

In view of these findings, it was of interest to determine if *S-n*-butylphosphorothioate could transfer phosphate to phosphoric acid to yield pyrophosphate.

We wish to report that pyrophosphate is produced when disodium *S-n*-butylphosphorothioate is treated with phosphoric acid, either in the presence or absence of iodine. The best yields of pyrophosphate (determined roughly by comparisons of paper chromatograms of known amounts of pyrophosphate with paper chromatograms of the reaction products) appeared to be obtained when the reaction was run in dioxane in the presence of iodine. Wieland and Lambert have shown that iodine had a beneficial effect on the phosphorylation of alcohols.[4] As iodine reacts immediately and quantitatively with *S-n*-butylphosphorothioate, the increased yields in the presence of iodine may be caused partly by facilitation of the dehydration of phosphoric acid by the hydriodic acid produced.

The pyrophosphate may be formed either by a direct phosphorylation of phosphoric acid or by the reaction of two moles of ester to give a thiopyrophosphate ester which is hydrolyzed to the products.



$$n\text{-}C_4H_9SPO_3H_2 + H_3PO_4 \rightarrow H_4P_2O_7 + n\text{-}C_4H_9SH$$
$$\rightarrow n\text{-}C_4H_9SP_2O_6H_3 \nearrow$$

Pyrophosphate was reported as an impurity in the preparation of *S-n*-propylphosphorothioate.[3a] It was not clear whether the pyrophosphate was formed during the reaction of the thiol with phosphorous oxychloride or afterwards from the thioester itself.[5] It is known that phosphorus oxychloride and phosphoric acid yield pyrophosphoric acid.[6]

Occasionally, paper chromatography of acidified aqueous solutions of barium or disodium *S-n*-butylphosphorothioate showed evidence of pyrophosphate. Because the salts initially were pure, it is probable that pyrophosphate formation proceeded as indicated in the equations above.

Precise quantitative data on yields are lacking, but visual estimates of the yields from a comparison of the size and intensity of the spots of known and unknown quantities of pyrophosphate were between 40 and 70%.

EXPERIMENTAL

Barium and disodium S-n-butylphosphorothioate. The barium salt (as its alcoholate) was prepared by the method of Wieland and Lambert[4] with modifications.[7] The sodium salt was prepared by trituration of the barium salt with sodium sulfate.[7]

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(1) Taken from the B.S. thesis of Virginia Opshelor, University of Pennsylvania, 1958.

(2) We gratefully acknowledge the support of the National Institutes of Health (Grant A-1023) for part of this work.

(3)(a) E. O'F. Walsh, *Nature*, **169**, 546 (1952); (b) G. Feuer and M. Wollemann, *Acta Physiol. Acad. Sci. Hung.*, **7**, 343 (1955); *Chem. Abstr.*, **50**, 1097 (1956); M. Wollemann, *Acta Physiol. Acad. Sci. Hung.*, **10**, 171 (1956); *Chem. Abstr.*, **51**, 6730 (1957); T. Stadtman, P. Elliott, and L. Tiemann, *J. Biol. Chem.*, **231**, 961 (1958).

(4) T. Wieland and R. Lambert, *Chem. Ber.*, **89**, 2476 (1956).

(5) In a private communication, Dr. E. O'F. Walsh was of the opinion that the pyrophosphate impurity was formed in a reaction of phosphoric acid with *S-n*-propylphosphorothioate.

(6) A. Geuther, *J. prakt. Chem.*, **116**, 359 (1873).

(7) O. B. Ramsay, Ph.D. thesis, University of Pennsylvania, February 1960.

(8) Analysis by Galbraith Laboratories, Knoxville, Tenn.