[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Cyclic Sulfides. III. The Reaction of Some Ethylene Sulfides with Triphenylphosphine and with Triethyl Phosphite

ROBERT EARL DAVIS[1,2]

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The products of the reaction of two ethylene sulfides with triphenylphosphine and with triethyl phosphite in ether have been examined. The most favored reaction is the elimination of the sulfur atom of the three membered ring and formation of the olefin, the sulfur being donated to the $P^{(III)}$ compound forming the thiono $P^{(V)}$ derivative.

Various ethylene sulfides were reported to react with triphenyl- and triethyl-phosphine to give the corresponding phosphine sulfide and with triethyl phosphite to produce the thionophosphate;[3] however, the remainder of the ethylene sulfide ring was not determined. The other products of this reaction are the subject of this report. Triphenylphosphine appears to be a mild and selective reagent for degradation of various types of sulfur compounds.

EXPERIMENTAL[4]

The preparation and purification of the ethylene sulfides have been reported previously.[1]

Cyclohexene sulfide with triphenyl phosphine. Freshly distilled cyclohexene sulfide (5.493 g., 0.0481 mole) was dissolved in 10 ml. of anhydrous ether and cooled in an ice bath. Triphenylphosphine (12.613 g., 0.0481 mole) was dissolved in ether and the solution quantitatively added to the sulfide solution (total volume 80 ml.). The flask was tightly stoppered and placed in a water bath at 25.0° in the dark. The solution soon became turbid and platelets separated. After three days at 25.0° the mixture was filtered giving 10.15 g. of white platelets, m.p. 159–161°, recrystallized from alcohol, m.p. 160.5–161°. The infrared spectrum, melting point and mixed melting point with an authentic sample identified the material as triphenylphosphine sulfide.[5]

The ether liquor was quantitatively transferred onto a vacuum line with the aid of a known amount of ether. The solution was frozen and then the volatile components removed and condensed in traps. The residue amounted to 3.402 g., m.p. 145–159°. Infrared analysis demonstrated the presence of some unreacted triphenyl phosphine (2 ± 1% based on the over-all reaction) and some of the polymer of cyclohexene sulfide (1 ± 0.5%). The remainder was the phosphine sulfide, from alcohol, m.p. 160–161°. The total amount of phosphine sulfide accounted for was 96 ± 2%.

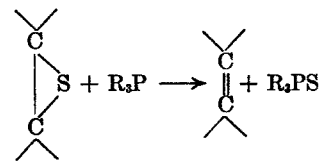
The volatile components collected in the traps were analyzed by infrared spectra and vapor-phase chromatography, which demonstrated the presence of 3.90 g., 95%, of cyclohexene, b.p. 83°, n_D^{25} 1.4441, identical with an authentic sample. Ultraviolet spectra[1] disclosed 0.5% of unreacted cyclohexene sulfide.

Cyclohexene sulfide with triethyl phosphite. Cyclohexene sulfide (3.99 g., 0.035 mole) and triethyl phosphite (5.81 g.) were reacted together in 50 ml. of anhydrous ether at 25° for three days. The turbid reaction mixture was fractionally distilled. The solvent was removed at 35–36°; cyclohexene was recovered at 83°, 2.63 g., 91%; traces of triethyl phosphite, b.p. 155° were obtained. The remainder was distilled in vacuum and triethyl thionophosphate obtained, b.p. 102–103° at 20 mm., 6.01 g., 87%. The products were identified by comparison of the physical properties and infrared spectra with authentic samples. The pot residue and chaser contained at least 5% of the polymer of cyclohexene sulfide.

Propylene sulfide with triphenyl phosphine. Propylene sulfide (2.84 g.) was dissolved in 25 ml. of anhydrous ether and quantitatively added to an ether solution of triphenyl phosphine (10.00 g. in 100 ml. ether) at room temperature. The flask was connected to an ice condenser, an ice trap, and then to a Dry Ice–acetone trap. As the reaction progressed some propylene (b.p., −48°) collected in the Dry Ice trap. The infrared spectrum was identical with an authentic sample. From the ether solution triphenylphosphine sulfide (10.5 g., 94%, m.p. 160–162°) was isolated.

DISCUSSION

The most favored reaction between ethylene sulfides and triphenylphosphine or triethyl phosphite is the removal of the sulfur atom forming the corresponding olefin and the thion phosphorus-V derivative.



The amount of polymer formation seems to be slight if the solvent is anhydrous and has low ability to solvate ions. Reactions of the ethylene sulfides in alcoholic solvents[3] sometimes lead to more polymer formation; possibly the solvent lyate ion contributes to this reaction. Polymer formation increases with increasing temperature.[3]

Other examples are available of the ability of many trivalent phosphorus compounds to remove sulfur from various sulfur compounds. Alkane thiols are desulfurized with triethyl phosphite under irradiation to form the thionophosphate and the alkane.[6,7] Certain reactive disulfides as tetramethylthiuram disulfide and aroyl disulfides readily donate

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(2) National Science Foundation predoctoral fellow, 1955–1957.

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one sulfide sulfur to triphenylphosphine forming the phosphine sulfide.[8,9] Other disulfides are reactive under conditions of photolysis or free radicals.[7]

Recently Scott[10] has observed the reaction of triethyl phosphite with epoxides forming the corresponding olefin and triethyl phosphate. The reaction conditions were much more severe (three hours at 150–175°) than those needed for the sulfur compounds (one to three days at 25°). Scott suggested a mechanism involving ring opening by the phosphite at the carbon atom and then formation of a four membered 1-oxa-2-phosphacyclobutane ring which then decomposes to the phosphate and the olefin. Wittig[11] studied the reaction of triphenylphosphine with epoxides at 160–180°. A four center transition state was postulated and the relationship to the Wittig reaction is obvious. Discussions concerning the reaction mechanism are speculative.

Phosphines and phosphites appear to be well suited as reagents in the structure determination of various sulfur compounds. The conditions are mild; polysulfides, disulfides, thiiranes, thiols, and other functional groups can be easily degraded. Investigation of other functional groups containing sulfur is continuing with phosphorus-III compounds.

CAMBRIDGE 38, MASS.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN]

Carbonic Anhydrase Inhibitors. I. Benzothiazole Derivatives

JEROME KORMAN

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A number of aryl-substituted benzothiazole-2-sulfonamides have been prepared, all of which are potent carbonic anhydrase inhibitors. One of these, the 6-ethoxybenzothiazole-2-sulfonamide, produces a clinically useful diuresis.

Carbonic anhydrase inhibitors have become important drugs for the treatment of conditions which are evidenced by edema.[1] The more important substances are diuretics, which produce a beneficial loss of sodium and water with concurrent body weight loss, and are characterized by a sulfonamide group in which the sulfonamide nitrogen is unsubstituted.[2] Research in this field was prompted by the experiments of Schwartz[3] with sulfanilamide in cases of congestive heart failure. Although diuresis occurred, low potency and the recognized toxic effects of sulfanilamide rendered it valueless for this purpose.

In the search for a more active replacement, Roblin and Clapp[4] prepared a large number of heterocyclic sulfonamides, many of which were indeed powerful carbonic anhydrase inhibitors. Among these, benzothiazole-2-sulfonamide, which appeared to be one of the most potent enzyme inhibitors, was subsequently reported[5] to be devoid of diuretic activity, a fact which was confirmed in these laboratories. This apparent anomaly can be reasonably explained on the basis of insolubility or an unfavorable rate of metabolism. Since diuretic activity in these compounds had been attributed to carbonic anhydrase inhibition,[3] it seemed of interest to prepare a series of substituted benzothiazole-2-sulfonamides and determine, firstly, the effect of the substituent and its position on carbonic anhydrase activity and, secondly, what effects, if any, these substituents might have upon such factors as solubility and metabolism.

Prior to the report of Roblin and Clapp, very few heterocyclic sulfonamides had been prepared. Chlorosulfonation, which works admirably with aromatic compounds to produce a sulfonyl chloride, fails generally with heterocyclic systems. Although a few such reactions have been reported,[6,7] the yields are poor, and the usual product is one in which nuclear chlorination has taken place. Similarly the reaction involving conversion of the salt of a sulfonic acid into the acid chloride results either in chlorination or replacement of the sulfonic acid

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