[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTH TEXAS STATE COLLEGE]

Thiophene Analogs of DDT

BY PRICE TRUITT, MARJORIE MATTISON[1] AND EUGENE RICHARDSON[1]

Since thiophene very often yields compounds that are analogous to benzene derivatives in general physiological properties,[2] it was decided to prepare a number of compounds derived from thiophene and halogenated thiophenes that would be analogous to DDT, 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)-ethane.[3]

1,1,1-Trichloro-2,2-bis-(thienyl)-ethane had been previously prepared by the action of phosphorus pentoxide on a mixture of thiophene and chloral, and in a similar fashion 1,1,1-tribromo-2,2-bis-(thienyl)-ethane has been prepared from bromal and thiophene with sulfuric acid as a condensing agent.[4] However, it seemed desirable to again prepare these compounds and test their insecticidal properties along with the new compounds.

In our hands, the use of sulfuric acid with thiophene and substituted thiophene without a diluent gave very little of the desired product and a large amount of orange-colored material which was soluble in alkali.

The use of phosphorus pentoxide was very unsatisfactory since the material became very lumpy and difficult to stir. However, when acetic acid was used as a diluent with sulfuric acid,[5] the amount of sulfonation was materially reduced, and the desired products obtained. None of the above methods was satisfactory for the preparation of 1,1,1-tribromo-2,2-bis-(thienyl)-ethane.

Experimental

Thiophene used in this work was obtained from Socony-Vacuum and was used without further purification.

2-Chlorothiophene.—This compound was prepared by the action of sulfuryl chloride on thiophene in ether with aluminum chloride as a catalyst according to the directions of Thol and Eberhard.[6] 200 g. of thiophene gave 145 g. of 2-chlorothiophene, b. p. 127–128°, $n^{20}D$ 1.5510.

2-Bromothiophene.—This compound was donated by Michigan Chemical Corporation, St. Louis, Michigan, and was used without further purification.

2-Iodothiophene.—This compound was prepared according to the procedure given in "Organic Syntheses."[7]

2-Methylthiophene.—This compound was donated by Socony-Vacuum and was used without further purification.

Chloral.—This compound was donated by Westvaco Chlorine Products Company, New York, N. Y.

1,1,1-Trichloro-2,2-bis-(chlorothienyl)-ethane.—To a well-stirred mixture of 34.0 g. (0.29 mole) chlorothiophene and 14.7 g. (0.1 mole) of chloral in 150 ml. of glacial acetic acid, 67 g. of concentrated sulfuric acid were added dropwise over a period of one hour. The temperature was kept below 5° during addition, and the reaction mixture was stirred in an ice-bath for several hours. The reaction mixture was neutralized with 10% potassium hydroxide solution, and the crystals which separated were filtered. The product was recrystallized from 95% ethanol, and when pure melted at 63.7–63.8°.

Anal. Calcd. for $C_{10}H_5S_2Cl_5$: Cl, 48.38. Found: Cl, 48.21.

1,1-Dichloro-2,2-bis-(chlorothienyl)-ethylene.—A solution of 6.73 g. of 1,1,1-trichloro-2,2-bis-(chlorothienyl)-ethane and 3.2 g. of potassium hydroxide in 100 ml. of ethanol was refluxed for two hours. Some of the alcohol was removed *in vacuo*, and the remainder of the alcoholic solution was poured over ice. The oil which separated was extracted with ether. The ethereal solution was dried over sodium sulfate. The ether was removed under reduced pressure, and the residue was distilled *in vacuo*. The product boiled at 208–210° (6 mm.), $n^{21}D$ 1.6833.

Anal. Calcd. for $C_{10}H_4S_2Cl_4$: Cl, 42.97. Found: Cl, 42.64.

1,1,1-Trichloro-2,2-bis-(bromothienyl)-ethane.—To a well-stirred mixture of 24 g. (0.15 mole) of bromothiophene and 8.85 g. (0.06 mole) of chloral in 150 ml. of glacial acetic acid, 54 g. of fuming sulfuric acid were added dropwise over a period of two hours. The temperature was kept below 15° during addition, but the reaction was heated to 55° after addition was complete and was stirred for twenty-four hours. The product mixture was poured into ice-water, and the organic fraction which separated as an oil was extracted with ether. The ether solution was washed with water, bicarbonate solution, and dried over anhydrous calcium chloride. The ether was evaporated, and the crude crystalline product obtained. The product was recrystallized from a mixture of petroleum ether and *n*-hexane, and when pure melted at 93.7°.

Anal. Calcd. for $C_{10}H_5S_2Cl_3Br_2$: Cl, 23.35; Br, 35.09; Found: Cl, 23.32; Br, 35.03.

1,1,1-Trichloro-2,2-bis-(iodothienyl)-ethane.—To a well-stirred mixture of 63.8 g. (0.31 mole) iodothiophene and 19.1 g. (0.13 mole) of chloral in 50 ml. of glacial acetic acid, 100 g. of concentrated sulfuric acid was added dropwise over a period of two hours. The temperature was kept below 20° during addition, and the reaction mixture was stirred in an ice-bath for two hours and at room temperature for twenty-four hours. The product mixture was poured into ice-water, and the organic fraction, a black oily mass, was extracted with ether. The ether solution was washed with water, bicarbonate solution, and dried over sodium sulfate. The ether was evaporated, and petroleum ether was added to the residue. The mixture was cooled overnight, and the brown crystals which separated were filtered and washed with *n*-hexane. The crude product was recrystallized from *n*-hexane and when pure melted at 94.8–95.1°.

Anal. Calcd. for $C_{10}H_5S_2Cl_3I_2$: Cl, 19.36; I, 46.20. Found: Cl, 19.36; I, 46.27.

1,1,1-Trichloro-2,2-bis-(methylthienyl)-ethane.—To a well-stirred mixture of 75 g. (0.75 mole) of 2-methylthiophene and 49.5 g. (0.30 mole) of chloral hydrate in 100 ml. of glacial acetic acid, 184 g. of concentrated sulfuric acid were added dropwise with stirring while the temperature was kept at 15°. The reaction mixture was stirred at room temperature for twenty-four hours. The product mixture was poured into ice water, and the aqueous layer decanted. The crystalline product was dissolved in ether. The ether solution was washed with water, bicarbonate solution, and dried over anhydrous calcium chloride. The ether was evaporated, and the product recrystallized from an alcohol–acetone mixture. When pure it melted at 72.2°.

(1) The work described in this paper was carried out under a grant from the Graduate School, North Texas State College, Denton, Texas.

(2) Steinkopf and Ohse, *Ann.*, **437**, 14 (1933).

(3) Zeidler, *Ber.*, **7**, 1180 (1874).

(4) Peter, *ibid.*, **17**, 1345 (1884).

(5) Cristol and Haller, THIS JOURNAL, **68**, 140 (1946).

(6) Thol and Eberhard, *Ber.*, **26**, 2947 (1893).

(7) Blatt, "Organic Syntheses," Coll. Vol. II, p. 357.

Anal. Calcd. for $C_{12}H_{11}S_2Cl_3$: Cl, 32.70. Found: Cl, 32.26.

Discussion of Results

1,1,1-Trichloro-2,2-bis-(thienyl)-ethane was previously reported melting at 76.0°. Using the same procedure in preparation of this compound, we obtained a compound, when pure, melting at 78.4°.[8] However, analysis of this product proves it to be the desired product.

Attempts to determine the structure of 1,1,1-trichloro-2,2-bis-(chlorothienyl)-ethane were carried out by the method of Cristol and Haller.[9]

This method failed to give the product anticipated. Treatment of 1,1-dichloro-2,2-bis-(chlorothienyl)-ethylene with chromic oxide in boiling glacial acetic acid gave a yellow oil which failed to crystallize. Since the bis-chlorothienyl ketone was expected to be a solid, it was concluded the susceptibility of the thiophene nucleus to oxidation led to decomposition.

When the olefin was refluxed with alkaline and neutral potassium permanganate, the original product was recovered. Hydrolysis of the olefin with barium hydroxide[10] in ethylene glycol gave a neutral oil and a trace of acidic material. The yield of neutral product was insufficient for characterization, but a qualitative test showed the presence of sulfur and a trace of halogen. A halogen analysis indicated approximately 1.0% chlorine. Evidently the chlorine in the thiophene nucleus was removed by barium hydroxide as well as that attached to the ethylenic chain. No definite structure has been assigned to these compounds, but on the basis of analysis and the known high reactivity of the 2,5-positions of thiophene, it is suspected that the thiophene nucleus is joined at the 5-position.

Laboratory tests of the insecticidal properties indicate that 1,1,1-trichloro-2,2-bis-(chlorothienyl)-ethane is the most effective compound against cockroaches; however, the derivatives of 2-bromothiophene and 2-iodothiophene show some activity. The derivative of 2-methylthiophene shows no insecticidal activities. 1-Trichloro-2,2-bis-(chlorothienyl)-ethane seems to be as active as DDT against cockroaches.

(8) Peter, ref. 4, p. 1345.

(9) Cristol and Haller, ref. 5, p. 140.

(10) Cristol, Soloway and Haller, THIS JOURNAL, **69**, 510 (1947).

Summary

A series of thiophene analogs of DDT have been prepared. The ones not previously reported are: 1-trichloro-2,2-bis-(chlorothienyl)-ethane, 1-dichloro-2,2-bis-(chlorothienyl)-ethylene, 1-trichloro-2,2-bis-(bromothienyl)-ethane, 1-trichloro-2,2-bis-(iodothienyl)-ethane, 1-trichloro-2,2-bis-(methylthienyl)-ethane.

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Biophysical Studies of Blood Plasma Proteins. VII. Separation of γ-Globulin from the Sera of Various Animals[1]

BY J. CHARLES NICHOL AND H. F. DEUTSCH

The separation of the components of biological tissues and fluids by ethanol fractionation as carried out by Cohn, *et al.*,[2] is directed to the isolation and recovery of all recognizable entities of the system in question. Often, however, in the interests of expediting the recovery or of increasing the yield of a given component it may be desirable to separate such an entity with immediate (but not necessarily eventual) disregard for other constituents. The antibodies of various animal species immunized to different antigens are known to possess the gross physical-chemical characteristics of the γ-globulins and to separate from solution with them. The scientific and technical importance of these antibody-rich fractions is the incentive which has led us to the development of a simple and effective procedure for removal of the normal γ-globulins from the sera of human beings and of the goat, dog, rabbit, rat, chicken and guinea pig.

It is found that in the individual species the chemical treatment may vary somewhat, but in all cases there is an initial and important step in which the antibody-rich γ-globulins are precipitated from a diluted serum which may be followed by a purification treatment to remove certain small amounts of contaminant β-globulins. In this way the γ-globulins are obtained in relatively pure form. The methods used involve variations in ethanol and salt concentrations and *p*H such as were used previously in studies on human γ-globulin.[3,4,5]

The general scheme, based in part upon our previous work,[3,4] consists in diluting one volume of serum with three volumes of water, adjusting the

(1) This work was supported in part by grants from Eli Lilly and Company, the Wisconsin Alumni Research Foundation, and the U. S. Public Health Service.

(2) (a) E. J. Cohn, J. A. Luetscher, Jr., J. L. Oncley, S. H. Armstrong, Jr., and B. D. Davis, THIS JOURNAL, **62**, 3396 (1940); (b) E. J. Cohn, L. E. Strong, W. L. Hughes, D. J. Mulford, J. N. Ashworth, M. Melin and H. L. Taylor, *ibid.*, **68**, 459 (1946).

(3) H. F. Deutsch, L. J. Gosting, R. A. Alberty and J. W. Williams, *J. Biol. Chem.*, **164**, 109 (1946).

(4) H. F. Deutsch, R. A. Alberty and L. J. Gosting, *ibid.*, **165**, 21 (1946).

(5) J. L. Oncley, M. Melin, D. A. Richert, J. W. Cameron and P. M. Gross, Jr., in press.