NITRATION OF THIOPHENE ANALOGS
OF DDT

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THESIS

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CHAPTER I

INTRODUCTION

Previous workers,\(^1\) noting the structural analogy of the insecticide, bis-(4-chlorophenyl)-sulfone (I), and the antitubercular drug, bis-(4-aminophenyl)-sulfone (II), as pointed out by Laüger, Martin, and Müller,\(^2\) considered the possibility that an amino analog of DDT, 1,1,1-trichloro-2,2-bis-(4-aminophenyl)-ethane (III), would possess increased antitubercular activity since DDT, 1,1,1-trichloro-2,2-bis-(4-chlorophenyl)-ethane (IV), has an increased insecticidal action over the sulfone. It has been reported that in vitro test on the activity of 1,1,1-trichloro-2,2-bis-(4-aminophenyl)-ethane

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showed complete inhibition of growth of *Mycobacterium tuberculosis* at dilutions of 1/100,000 and some inhibition at dilutions of 1/1,000,000.³

Since thiophene very often yields compounds that are analogous to benzene derivatives in general physiological properties,⁴ it was decided to attempt to prepare the nitro and amino derivatives of 1,1,1-trichloro-2,2-bis-(2-thienyl)-ethane⁵ (V) as well as the nitro and amino derivatives of 2,2,3-trichloro-1,1-bis-(2-thienyl)-butane (VI).⁶ The latter derivatives were chosen since the DDT

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⁵ Peter, *Ber.*, 17, 1341 (1884).

analog, 2,2,3-trichloro-1,1-bis-(4-chlorophenyl)-butane has insecticidal activity near that of DDT.\textsuperscript{7}

In the nitration of the 1,1,1-trichloro-2,2-bis-(2-thienyl)-ethane a novel dehydrohalogenation took place giving the product, 1,1-dichloro-2,2-bis-(5-nitro-2-thienyl)-ethene. No other dehydrohalogenation in a reaction of this type has been reported in the literature, however, it has been reported that aryl substituted trichloroethanes loose hydrogen chloride very readily with alkali.\textsuperscript{8} The compound, 1,1,1-trichloro-2,2-bis-(4-aminophenyl)-ethane, is unstable, undergoing self-dehydrohalogenation.\textsuperscript{9}

\textsuperscript{7} G. Grisaud, Swiss, 241,599, Aug. 1, 1946.
\textsuperscript{9} Ibid.
All attempts to reduce the nitro derivatives to the corresponding amine gave a purple solid which could be neither purified nor identified.\textsuperscript{10}

The nitration of the 2,2,3-trichloro-1,1-bis-(2-thienyl)-butane yielded a small amount of material melting at 170°-173°. Repeated experiments yielded an oil which could never be crystallized.

In the proof of the structure of 1,1-dichloro-2,2-bis-(5-nitro-2-thienyl)-ethene, oxidation gave a dinitrodithienyl ketone. The position of the nitro group was assumed to be 5 because of the high reactivity of the 2 and 5 positions of thiophene. The infrared spectrum of the compound was studied to substantiate the structure given.

\textsuperscript{10} B. E. Bryant, Unpublished notes, Dept. of Chemistry, North Texas State College, 1950.
A 1-liter, three-neck, reaction flask was equipped with mechanical stirrer, reflux condenser and dropping funnel. This flask was charged with 66.4 g. of chloral hydrate and 160 ml. of 18 N sulfuric acid was added at 10°. To this well stirred solution, 67.2 g. of thiophene was added very rapidly. Then 200 ml. of conc. sulfuric acid was added dropwise over a period of 2 hours. The temperature was kept at 13° during the addition of the sulfuric acid. This mixture was stirred for 7 additional hours at 20°. At the end of this time, the reaction was poured into a 1000-ml. beaker of crushed ice. The yellow precipitate was filtered and washed with water, 5% sodium bicarbonate, and again with water. The yellow solid was charcoaled and recrystallized from methanol. A good yield of white needles was obtained, m.p. 79°.¹

(1) Peter, Ber., 17, 1341 (1884).
1,1-Dichloro-2,2-bis-(5-nitro-2-thienyl)-ethene

A cold solution of 4.2 ml. of fuming nitric acid (d. 1.5) in 25 ml. of acetic anhydride was added over a 30 minute period to 12 g. of 1,1,1-trichloro-2,2-bis(2-thienyl)-ethane in 50 ml. of acetic anhydride. The temperature of the well stirred solution was kept at -3° to 3° during the addition of the nitric acid solution and for one additional hour. At the end of this time the temperature was allowed to rise to room temperature. The resulting mixture was poured over crushed ice and left in the icebox overnight. The solid was charcoaled and recrystallized from a methyl cellosolve and water solution. The resultant yellow crystals melted at 127°.

Anal. Calcd. for C_{10}H_{4}Cl_{2}S_{2}N_{2}O_{4}: Cl, 20.23; S, 18.23; N, 7.98. Found: Cl, 20.1; S, 18.4; N, 8.03.
A 500-ml., three-neck flask was equipped with stirrer, condenser and dropping funnel. This flask was charged with 70.2 g. of butyl chloral and 160 ml. of 18 N sulfuric acid was added at 10°. To this well stirred mixture, 67.2 g. of thiophene was added over a period of about 1 hour. The reaction mixture was allowed to stir for 3 additional hours while the temperature was held at 10°. The reaction was then poured over crushed ice and allowed to set overnight. A green oil was formed which was charcoaled and crystallized from methanol. Recrystallization from methanol gave white needles, m.p. 89°.²

Nitration of 2,2,3-Trichloro-1,1-bis-(2-thienyl)-butane

A solution of 1.9 ml. fuming nitric acid (d. 1.5) in 15 ml. of acetic anhydride was added dropwise over a period of 15 minutes to 6.5 g. of 2,2,3-trichloro-1,1-bis-(2-thienyl)-butane in 20 ml. of acetic anhydride. The temperature of the well stirred mixture was kept at 25°-35° during the addition of the nitric acid solution and for a 30 minute period following the addition of 1.5 ml. of conc. sulfuric acid. At the end of this time the reaction was poured over 100 ml. of crushed ice and allowed to stand in the icebox overnight. The resulting product was recrystallized from methyl cellosolve and a small amount of product was obtained which melted at 170°-173°.

A solution of 5 g. of 1,1-dichloro-2,2-bis-(5-nitro-2-thienyl)ethene in 100 ml. acetic anhydride, 50 ml. acetic acid, and 1 ml. sulfuric acid was stirred vigorously while 10 g. of chromic anhydride was added over a period of one hour. The reaction was allowed to proceed for three additional hours at 80°-90°. The reaction was poured over crushed ice and the mixture filtered to give a solid product that was recrystallized from methanol, m.p. 150°-150.5°.  

Anal. Calcd. for $C_9H_4S_2N_2O_5$: $N$, 9.85. Found: $N$, 10.25
CHAPTER III

DISCUSSION

Nitration of 1,1,1-trichloro-2,2-bis-(2-thienyl)-ethane would normally be expected to give 1,1,1-trichloro-2,2-bis-(5-nitro-2-thienyl)-ethane. However, the chlorine, sulfur, and nitrogen analysis of the nitration product indicated that the molecule must have lost hydrogen chloride. The only feasible place to lose this hydrogen chloride would be in the alkane to give the olefin, 1,1-dichloro-2,2-bis-(5-nitro-2-thienyl)-ethene.

A test was made to see if bromine would be added to the double bond, but there was no evidence of such an addition. This would be expected since the large thiophenyl groups attached to the ethene would sterically hinder any addition to the double bond.

Infrared spectra were run from 3.0 to 13.0 microns on the 1,1,1-trichloro-2,2-bis-(2-thienyl)-ethane and its nitration product. This was done by placing a mineral oil paste of the sample between two sodium chloride disks. The spectra were run using only air as a blank, since no other cells were available. This should not induce very much error since sodium chloride absorbs very little in the region studied and mineral oil should absorb very little other than at 3.25 and 7.0 microns. Absorption bands were correlated with
the structure of the molecules with the aid of a chart, Spectra-Structure Correlations, by N. B. Colthrup of Stamford Research Labs, American Cyanamid Co.

A study of Figure 1, which is transmittancy of 1,1,1-trichloro-2,2-bis-(2-thienyl)-ethane plotted against wavelength, shows absorption at 9.6 and 10.2 microns due to the aromatic character of the thiophene rings and strong absorption at 11.7 and 12.4 microns which would probably represent the alkane and 

$\text{Cl}_3$ groups respectively. The absorption at 7.0 microns is naturally due to the mineral oil.
Figure 2, the transmittancy of 1,1-dichloro-2,2-bis-(5-nitro-2-thienyl)-ethene, is interesting, having absorption at 7.6 microns which can be attributed to the nitro group on the thiophene ring, absorption at 9.8, 10.7, 12.0, and 12.8 microns, characteristic for olefins, and absorption at 12.3 microns which is indicative of a C-Cl₂ group.

The transmittancy of the dinitrodiethenyl ketone received from the oxidation of the 1,1-dichloro-2,2-bis-(5-nitro-2-thienyl)-ethene is shown in Figure 3. The absorption at 7.5 microns can be attributed to the nitro on the thiophene while
absorption at 7.9 microns is due to a ketone. Conspicuous by their absence are the strong absorption bands due to alkane, olefin, C-Cl₃, and C-Cl₂ groups. This would indicate that this compound would be bis-(5-nitro-2-thienyl) ketone.

Nitration of the 2,2,3-trichloro-1,1-bis-(2-thienyl)-butane gave a product that gave a nitrogen analysis near that which would be expected for the nitrated dehydrohalogenated product. Even though the nitrogen analysis was not as close as it should have been, it did indicate that dehydrohalogenation did take place. Since additional samples of the compound were not isolated no further proof of the structure was made.
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Patents


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