

Similarly, after a mixture of 0.1 g. of the hydrochloride of XV, 10 ml. of 50% alcohol, 1 g. of sodium hydroxide and 3 ml. of chloroform was refluxed for three hours, 70% of the original hydrochloride could be recovered.

Summary

The preparations, properties and inter-relationships

of some tri-, tetra- and pentasubstituted pyridine derivatives are described.

4-Deshydroxymethylpyridoxin has been prepared and is shown to be singularly unreactive toward substitution in the 4-position.

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[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA, CITRUS EXPERIMENT STATION]

Mechanisms of Insecticidal Action. I. Dithienyltrichloroethanes

BY ROBERT L. METCALF AND FRANCIS A. GUNTHER

The pharmacological effects of the replacement of phenyl groups by thienyl groups in biologically active molecules have been studied by numerous investigators.¹ As might be predicted from certain similarities in the physical properties of thiophene and benzene, and the close approximation in molecular size of the two groups,² thienyl isomers have, in some cases, inhibited normal biological processes and in others have retained at least a portion of the activity of the parent compound.

It was therefore of interest in connection with our studies of the mode of action of DDT to prepare certain dithienyltrichloroethanes and to compare their insecticidal activities with those of the corresponding DDT derivatives. Insecticidal evaluations were performed with two laboratory test insects, the greenhouse thrips, *Heliothrips haemorrhoidalis* (Bouché), and the fly, *Drosophila melanogaster* Meig.

Results and Discussion

Dithienyltrichloroethane has been described by Peter³ and by Prill, *et al.*,⁴ who found it insecticidally inactive against the housefly.

Because of the possible significance of alkaline dehydrohalogenation in the mode of toxic action of compounds of the DDT type,⁵ the molar per cent. dehydrohalogenation of the compounds described in this paper was measured by the method of Müller.⁵

As is indicated in Table I, none of the thienyltrichloroethanes showed any appreciable insecticidal activity to the two test insects. Supplementary tests with compounds II, IV and VI applied externally to the german cockroach, *Blattella germanica* (L.), and in the food of the confused flour beetle, *Tribolium confusum* Duv., also failed to give any appreciable indication of insecticidal activity, but compound II appeared to be slightly

toxic to the honey bee *Apis mellifera* L. The data obtained on molar per cent. dehydrohalogenation agree well with that of Müller⁵ for compounds I, III, V and VII. The corresponding thienyl isomers are fully as responsive to alkaline dehydrohalogenation, and it therefore seems improbable that failure of this mechanism is responsible for the non-activity of compounds II, IV, VI, VIII and IX. It was hoped that the properties of compounds VIII and IX would yield information as to whether 2-substituted-thienyl- or 3-substituted-thienyl-trichloroethane was more similar spatially to *p,p'*-DDT and its analogs: but the results were inconclusive.

TABLE I

AROMATIC AND PSEUDOAROMATIC DISUBSTITUTED TRICHLOROETHANES

Compound	R =	M. p., °C.	(R) ₂ CHCCl ₂		Approximate relative toxicity ^a at LD ₅₀ to <i>D. m.</i> and <i>H. r.</i>
			Mole % HCl released in 1 N KOH		
I	<i>p</i> -ClC ₆ H ₄ —	109–110	1.06	1	1
II	5-ClC ₄ H ₂ S—	65–66	0.99	>1000	100
III	<i>p</i> -BrC ₆ H ₄ —	136–137	1.10	1000	5
IV	5-BrC ₄ H ₂ S—	94.0–94.7	1.07	>1000	>100
V	C ₆ H ₅ —	64–65	0.54	1000	100
VI	C ₆ H ₅ S—2—	78.4–79.2	1.08	>1000	100
VII	<i>p</i> -CH ₃ C ₆ H ₄ —	86–87	0.22	10	3
VIII	5-CH ₃ C ₄ H ₂ S—	70–71	1.06	>1000	>100
IX	4-CH ₃ C ₄ H ₂ S—	124–125	0.59	>1000	>100

^a Figures represent the relative amounts of materials necessary to give equivalent mortalities when *p,p'*-DDT = 1.

The failure of compounds II, IV, VIII and IX to give the indophenol reaction indicates that either the 2-5 or the 2-3 positions are blocked in all these compounds.⁶ Steric considerations, however, make it seem probable that the 2,5 positions are the ones actually filled. That the condensation takes place in the 2-position was indicated by the alkaline dehydrohalogenation of the parent compound 2,2-bis-(thienyl-2)-1,1,1-trichloroethane (VI) to the corresponding ethylene, followed by oxidation to the known ketone 2,2'-

(6) Steinkopf, "Die Chemie des Thiophens." Theodor Steinkopf Dresden, 1941, pp. 125–126.

(1) Dunn and Dittmer, *THIS JOURNAL*, **68**, 2561 (1946).
 (2) Schomaker and Pauling, *ibid.*, **61**, 1769 (1939).
 (3) Peter, *Ber.*, **17**, 1341 (1884).
 (4) Prill, Synerholm and Hartzell, *Contrib. Boyce Thompson Inst.*, **14**, 341 (1946).
 (5) Martin and Wain, *Ann. Repts. Long Ashton Res. Sta.*, 121 (1944); Busvine, *Nature*, **156**, 169 (1945); Busvine, *J. Soc. Chem. Ind.*, **65**, 356 (1946); Domenjoz, *Helv. Chim. Acta*, **29**, 1317 (1946); Müller, *ibid.*, **29**, 1560 (1946).

dithienyl ketone, m. p. 87–88°. The ketones corresponding to compounds II, IV, VIII and IX have not previously been prepared, and proofs of their structures will be reported subsequently together with the syntheses of the ketones involved.

Experimental

Bioassay.—One milliliter of a standard acetone solution of the compound was pipetted onto an 11-cm. Whatman No. 1 filter paper and allowed to dry. The paper was then rolled, placed in a shell vial, approximately 25 *Drosophila* added, and the vial capped with cotton soaked in sugar solution. After twenty-four hours the dead flies were counted. Each test was replicated at least eight times and each material was tested at several levels.

Medium-sized mature Valencia oranges were immersed in a standard acetone solution of the compound for one second. After drying, the fruit was placed in a 250-ml. beaker, approximately 25 adult greenhouse thrips were brushed on, and the beaker was capped with cloth. Replications and mortality counts were made as above.

Alkaline Dehydrohalogenation.—Exactly 0.002 mole of the compound was dissolved in 100 ml. of 95% ethyl alcohol, 5 ml. of standard *N* alcoholic potassium hydroxide was added and the mixture was allowed to stand for sixteen hours at 27°. The unneutralized base was then titrated with standard hydrochloric acid to the phenolphthalein end-point.

2-Chlorothiophene.—The procedure of Thöl and Eberhard⁷ was followed. Fractionation of the reaction product at atmospheric pressure yielded 47.8 g. (40% of the theoretical, based upon sulfuryl chloride) of crude 2-chlorothiophene, b. p. 126–130°, n_D^{20} 1.543, n_D^{25} 1.550, with the chloromercury derivative melting at 219.5–220.5° after one recrystallization from ethanol (2-chloromercury-5-chlorothiophene).

An attempted preparation of 2-chlorothiophene by the general procedure used by Blicke and Burckhalter⁸ for the synthesis of 2-bromothiophene yielded only 2,2'-dichlorodithienyl as compact prisms, m. p. 109–110°, and whose identity was demonstrated by means of a mixed m. p. with an authentic specimen prepared from thiophene, sulfuryl chloride and aluminum chloride.

2,2-bis(2-Chlorothiényl)-1,1,1-trichloroethane.—In a 2-liter three-necked flask fitted with an efficient mercury-sealed stirrer, a dropping funnel, and a condenser there were placed 32 g. of 2-chlorothiophene, 11.5 g. of benzene, 20 g. of freshly distilled chloral and 200 ml. of glacial acetic acid. The flask was immersed in an ice-bath, and a cold mixture of 200 ml. of glacial acetic acid and 250 ml. of concentrated sulfuric acid was added with stirring over a three-hour period, followed by 250 ml. of concentrated sulfuric acid over another three-hour period. Stirring was continued for four hours longer, until the indophenin test was negative. The resulting cream-colored emulsion was poured onto 1 kg. of crushed ice, then placed in the refrigerator for three days, to yield 17 g. of gray nodular crystals. Treatment with Nuchar 3X and repeated recrystallizations from ethanol afforded 16 g. (32% of the theoretical, based upon chlorothiophene) of small, colorless rhombs, m. p. 65–66°. The indophenin reaction was negative.

Anal. Calcd. for $C_{10}H_5Cl_5S_2$: C, 32.75; H, 1.36; Cl, 48.40. Found: C, 32.95; H, 1.51; Cl, 49.53.

2,2-bis(2-Bromothiényl)-1,1,1-trichloroethane.—When 44 g. of 2-bromothiophene, 11.5 g. of benzene and 20 g. of freshly distilled chloral were treated as in the above preparation of the 2-chlorothiophene derivative, there was secured a total of 35.2 g. (57% of the theoretical, based upon bromothiophene) of needles from ethanol, m. p. 94.0–94.7°. The indophenin reaction was negative.

Anal. Calcd. for $C_{10}H_5Br_2Cl_3S_2$: C, 26.37; H, 1.11; total halogen, 58.44. Found: C, 26.41; H, 1.23; total halogen, 57.27.

(7) Thöl and Eberhard, *Ber.*, **26**, 2947 (1893).

(8) Blicke and Burckhalter, *This Journal*, **64**, 477 (1942).

2,2-bis-(Thienyl-2)-1,1,1-trichloroethane.—When 23 g. of thiophene, 11.5 g. of benzene and 20 g. of freshly distilled chloral were treated as in the above preparation of the 2-chlorothiophene derivative, there was secured a total of 23.4 g. (58% of the theoretical, based upon thiophene) of tiny, colorless platelets from ethanol, m. p. 78.4–79.2°. The compound gave a red-violet indophenin reaction after standing fifteen minutes.

Anal. Calcd. for $C_{10}H_7Cl_3S_2$: C, 40.34; H, 2.37; Cl, 35.73. Found: C, 40.63; H, 2.52; Cl, 36.40.

2,2-bis-(2-Methylthienyl)-1,1,1-trichloroethane.—When 26.5 g. of 2-methylthiophene (n_D^{24} 1.5172), 11.5 g. of benzene, and 20 g. of freshly distilled chloral were treated as in the above preparation of the 2-chlorothiophene derivative, there was secured a total of 19 g. (43% of the theoretical, based upon methylthiophene) of colorless granules from ethanol, m. p. 70–71°. The indophenin reaction was negative.

Anal. Calcd. for $C_{12}H_{11}Cl_3S_2$: C, 44.23; H, 3.41; Cl, 32.69. Found: C, 44.21; H, 3.47; Cl, 32.50.

2,2-bis-(3-Methylthienyl)-1,1,1-trichloroethane.—When 26.5 g. of 3-methylthiophene (n_D^{24} 1.5181), 11.5 g. of benzene and 20 g. of freshly distilled chloral were treated as in the above preparation of the 2-chlorothiophene derivative, there was secured a total of 13.2 g. (30% of the theoretical, based upon methylthiophene) of colorless needles from ethanol, m. p. 124–125°. A mixed melting point with the preceding 2-methylthiophene derivative exhibited depression. The indophenin reaction was negative.

Anal. Calcd. for $C_{12}H_{11}Cl_3S_2$: C, 44.23; H, 3.41; Cl, 32.69. Found: C, 44.06; H, 3.45; Cl, 32.70.

2,2-bis-(4-Chlorophenyl)-1,1,1-trichloroethane,⁹ **2,2-bis-(4-bromophenyl)-1,1,1-trichloroethane**,⁹ **2,2-bis-(4-methylphenyl)-1,1,1-trichloroethane**¹⁰ and **2,2-bis-(phenyl)-1,1,1-trichloroethane**¹¹ were prepared by the condensation of chloral with the appropriate benzene derivatives in the classical manner.

Degradation of 2,2-bis-(Thienyl-2)-1,1,1-trichloroethane.—From 5 g. of the thienyl compound, when refluxed one hour with 5 g. of potassium hydroxide in 75 ml. of ethanol, there was obtained nearly 4 g. of a non-crystallizable, viscous, yellow oil and 1.22 g. (98 per cent of the theoretical) of potassium chloride. Treatment of this oil with chromic anhydride in refluxing glacial acetic acid for four hours afforded 1 g. of yellow granules of 2,2'-dithienylketone, m. p. 79–82°. Recrystallization from ethanol raised the m. p. to 87–87.5°; 2,4-dinitrophenylhydrazone, m. p. 222–223°; phenylhydrazone, m. p. 134–135°. Admixture of these three compounds with authentic specimens¹² did not depress their melting points.

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Summary

Five dithienyltrichloroethanes, four of them previously unreported, have been synthesized. Their molar per cent. dehydrohalogenation and quantitative insecticidal action have been meas-

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

(10) Fischer, *ibid.*, 1191 (1874).

(11) Baeyer, *ibid.*, **5**, 1098 (1872).

(12) Preparations to be reported elsewhere.

ured and compared with the corresponding diphenyltrichloroethanes. None of the dithienyltrichloroethanes showed any contact insecticidal action to the insects investigated comparable to the action of DDT and its derivatives.¹³ The thi-

(13) These compounds showed no appreciable fungicidal action

enyltrichloroethanes, however, dehydrohalogenated in alkaline solution fully as readily as did the corresponding DDT derivatives.

against species of *Phytophthora*, *Dothiorella*, and *Macrosporium* in tests by Dr. George Zentmeyer, of this station.

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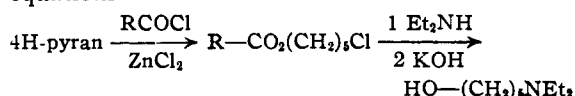
[CONTRIBUTION FROM THE BOYCE THOMPSON INSTITUTE FOR PLANT RESEARCH, INC.]

The Cleavage of Tetrahydropyran by Acid Chlorides in the Presence of Zinc Chloride. The Preparation of 5-Diethylaminopentanol-1

BY MARTIN E. SYNERHOLM

It is known that aliphatic ethers and ethylene oxide are cleaved by acid iodides¹ and by acid chlorides in the presence of zinc chloride.² The application of this reaction to the fission of other cyclic ethers has received very little attention. Paul³ in 1939 concluded that tetrahydrofuran and tetrahydropyran rings could be cleaved by acetic anhydride only in the presence of zinc chloride and at 190° or higher. Wilson⁴ described what he considered to be the best conditions for preparing 5-bromo-*n*-amyl acetate. His procedure consisted of allowing a mixture of tetrahydropyran and an acetic anhydride solution of hydrogen bromide to react over a period of six days. He did not report his yield, but stated that his product contained about 2.5 moles per cent. of pentamethylene dibromide.

The application of this reaction using tetrahydropyran and acid chlorides in the presence of zinc chloride is described here. An example of its usefulness in organic synthesis is illustrated in the preparation of 5-diethylaminopentanol-1. This preparation is shown in the following sequence of equations



The paucity of references to 5-chloropentanol-1 or its derivatives is undoubtedly due, at least in part, to the fact that this material is not stable but reverts easily, with loss of hydrogen chloride, to tetrahydropyran. The acetate has been reported by Bennett and Heathcoat,⁵ who prepared it in 41% yield by the action at 100° for eight days of acetyl chloride on pentamethylene glycol. This acetate has now been prepared in 85% yield by warming acetyl chloride and tetrahydropyran in the presence of zinc chloride. Benzoyl chloride reacts in an analogous fashion to give a comparable yield of the benzoate. Zinc chloride is necessary in the reaction; without it the starting

materials are recovered unchanged. The product, on warming with diethylamine for twenty-four hours, gave the expected benzoate^{5a} of 5-diethylaminopentanol-1 in 38% yield. Increasing the time of heating to seven days raised the yield to 77%. The benzoate was then saponified with a 68% recovery of 5-diethylaminopentanol-1. This amino alcohol was described in 1933 by Magidson and Strukow,⁶ who prepared it in 26% yield by the Bouveault and Blanc reduction of ethyl δ -diethylaminovalerate.

Experimental

Benzoate of 5-Chloropentanol-1.—A mixture of 38 g. (0.27 mole) of redistilled benzoyl chloride, 30 g. (0.35 mole) of tetrahydropyran (dried over sodium hydroxide flakes and distilled) and 5 g. of freshly fused and coarsely ground zinc chloride was heated one hour on the steam-bath, cooled, diluted with 75 ml. of benzene and shaken, first with 50 ml. of cold water until the brown color had changed to yellow (about one minute), then with 50 ml. of a cold saturated solution of sodium bicarbonate until carbon dioxide was no longer evolved. The benzene layer, dried over anhydrous sodium sulfate, after fractionation boiled at 141–143° (2 mm.). The weight was 52 g. (yield 85%, based on the benzoyl chloride); n_D^{20} 1.5169; d_4^{20} 1.109; M_D calcd. 60.5; found 61.5.

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_2\text{Cl}$: Cl, 15.63. Found: Cl (Parr bomb), 15.52.

Acetate of 5-Chloropentanol-1.—The acetate was prepared in 85% yield from acetyl chloride (25 g.), tetrahydropyran (30 g.) and zinc chloride (5 g.) under the conditions used in the preparation of the benzoate. The product boiled at 113–115° (34 mm.) or at 104° (18 mm.). This material is reported⁵ to boil at 103° (18 mm.).

Benzoate of 5-Diethylaminopentanol-1.—A mixture of 100 g. (0.44 mole) of the benzoate of 5-chloropentanol-1 and 150 ml. of diethylamine (Sharples, dried over potassium hydroxide sticks and distilled) was heated in a pressure bottle at 75° for seven days, cooled, diluted with 100 ml. of benzene and evaporated *in vacuo* on a water-bath. The cooled mixture was diluted with 200 ml. of water and acidified with dilute hydrochloric acid (congo red), was extracted twice with 50-ml. portions of benzene. The combined benzene layers, after removal of the solvent, were found to contain about 15 g. of acid-insoluble material, of which about 5 g. consisted of unchanged 5-chloroamyl benzoate. The aqueous layer was neutralized carefully (in the presence of ice) with potassium carbonate, finally saturated with this reagent, and was extracted twice with 100-ml. portions of benzene. The combined

(5a) New compound.

(6) Magidson and Strukow, *Arch. Pharm.*, **271**, 569 (1933).

(1) Gustus and Stevens, *THIS JOURNAL*, **55**, 378 (1933).

(2) Norris and Rigby, *ibid.*, **54**, 2088 (1932).

(3) Raymond Paul, *Compt. rend.*, **206**, 587 (1939).

(4) Christopher L. Wilson, *J. Chem. Soc.*, 48 (1945).

(5) Bennett and Heathcoat, *ibid.*, 268 (1929).