[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

THIOPHANE-2,5-DICARBOXYLIC ACID AND RELATED COMPOUNDS[1]

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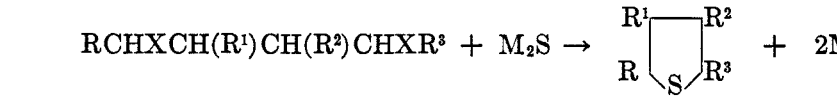
The disclosure in 1942 of the structure of biotin (1) aroused interest in the comparatively unexplored field of thiophane chemistry. One method of preparation of thiophane compounds has been the reaction between substituted 1,4-dihalobutanes and an alkali metal sulfide in aqueous or alcoholic solution.



Thiophane (2, 3, 4), methylthiophanes (4), 2,5- and 3,4-di-*n*-propylthiophanes (5), 3,4-dihydroxythiophane (6), and thiophane-2,5-dicarboxylic acid (7) have been prepared by this method. Recently, Kilmer and McKennis (8) used a variation of the above reaction in the preparation of 3,4-diaminothiophane by treatment of 2,3-diaminobutane-1,4-disulfuric acid with sodium sulfide.

The authors have extended the cyclization reaction to *meso*-ethyl 2,5-dibromoadipate (9) and have prepared *cis*-2,5-dicarbethoxythiophane (10) in good yield. The cyclization was found to be sensitive to different conditions and media. If the amount of sodium sulfide was in great excess or if the reaction was carried out at elevated temperatures, the secondary reaction of hydrolysis was greatly promoted. The most suitable diluent for cyclization was ethanol, and indeed other common organic solvents were found to be unsatisfactory. When small amounts of potassium iodide were tried as catalyst, the yield of the thiophane ester was increased.

Cis-2,5-dicarbethoxythiophane was found to be unexpectedly sensitive to reagents. In hot concentrated caustic solution, there is apparently some cleavage of the sulfide linkage, and the yield of thiophane-2,5-*cis*-dicarboxylic acid by saponification is unsatisfactory. However, in acid solution, the hydrolysis proceeded smoothly and with good yield. The dibasic acid had similar properties to the thiophane-2,5-*cis*-dicarboxylic acid described by Fredga (7) and Brown and Kilmer (10). It has been proved beyond doubt (7) that the carboxyl groups had a *cis* structure. The *cis* diacid formed an anhydride when its salt was treated with thionyl chloride.

By treatment of *cis*-2,5-dicarbethoxythiophane with aqueous ammonia after the following equilibrium had been established by means of sodium methylate in

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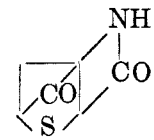
methanol solution, according to the procedure of Sessions (11), 2,5-dicarbamylthiophane was obtained.

$$RCO_2C_2H_5 + CH_3OH \rightleftarrows RCO_2CH_3 + C_2H_5OH$$

In view of the work by Baker, Brown, and associates (12, 13), a *trans* structure may be assigned to the diamide because of the inversion of a *cis* to a *trans* form due to the sodium methylate.

The *trans*-amide underwent dehydration in the presence of phosphorus pentachloride to form the corresponding *trans*-nitrile. However, when *trans*-2,5-dicarbamylthiophane was treated with phosphorus oxychloride, a cyclic imide (I) was obtained.



(I)

A *cis* structure is assigned to the imide in view of a similar transformation noted by Baker and co-workers (14), in which a *trans*-amide, 2-(δ-carboxybutyl)-4-carbanilidothiophane-3-*trans*-carboxylic acid, was converted to a *cis*-imide, namely, 2-(δ-carboxybutyl) thiophane-3,4-*cis*-dicarboxanil.

The *cis*-imide was found to be similar to phthalimide in its reactions with alkyl halides. For example, an excellent yield of N-(*n*)-amylthiophane-2,5-dicarboxylic acid imide was obtained when the sodium salt of the imide was treated with *n*-amyl bromide.

When 2,5-dicarbamylthiophane was submitted to the Hofmann rearrangement in the presence of sodium hypobromite, there was complete sulfide cleavage and destruction of the thiophane nucleus. This is in agreement with the observations of Brown and Kilmer (10) who attempted the synthesis of 2,5-diaminothiophane by the hydrolysis of a 2,5-bis-(carbethoxyamino)thiophane. These investigators noted a similar cleavage and commented on the instability of compounds of the general type: $RSCH(NH_2)R^1$.

Cis-2,5-dicarbethoxythiophane was transesterified with 2-diethylaminoethanol and 3-diethylaminopropanol to yield the corresponding bis-alkamine esters. In view of the fact that the transesterification was carried out in the presence of a sodium alcoholate, the products are equilibrium *trans-cis* mixtures.

EXPERIMENTAL

Cis-2,5-dicarbethoxythiophane (10). A mixture of 36 g. (0.1 mole) of *meso*-ethyl 2,5-dibromoadipate (9), 200 cc. of 95% ethyl alcohol, 30 g. (0.125 mole) of sodium sulfide (nonahydrate), and 2 g. of potassium iodide was stirred at room temperature for six hours. The alcohol was removed *in vacuo* and the residue, acidified with sulfuric acid, was extracted with ether. The ether extracts were washed with sodium thiosulfate solution and with water. The oil obtained, after removal of the ether, distilled at 100° at 0.3 mm. and weighed 16.5 g. (71%); n_D^{25} 1.4808.

Anal. Calc'd for $C_{10}H_{16}O_4S$: S, 13.79. Found: S, 13.56.

Trans-2,5-dicarbamylthiophane. To 30 cc. of methanol containing a small piece of dissolved sodium was added 23.2 g. (0.1 mole) of *cis*-2,5-dicarbethoxythiophane and the mixture was allowed to come to equilibrium in a stoppered flask at room temperature for eighteen hours. At the end of this time, 125 cc. of concentrated aqueous ammonia (sp. g., 0.9) was added and after the mixture was thoroughly agitated, it was placed in the cold for one week. The white solid which had precipitated was collected, washed with ether and dried. The yield was 12.8 g., m.p. 179–181°. The concentrated filtrate furnished 2.5 g. more, raising the total yield to 15.3 g. (88%).

Anal. Calc'd for $C_6H_{10}N_2O_2S$: N, 16.08. Found: N, 15.92.

Thiophane-2,5-cis-dicarboxylic acid (7, 10). A mixture of 23.2 g. (0.1 mole) of *cis*-2,5-dicarbethoxythiophane, 140 cc. of water, 20 cc. of concentrated sulfuric acid, and 70 cc. of glacial acid was heated under reflux for twelve hours. The solution was concentrated *in vacuo* and the white solid which precipitated was collected, washed with ether, and dried. The yield was 13.5 g. (76.7%); m.p. 135–136°. Fredga (7) reported a melting point of 144–145°.

Anal. Calc'd for $C_6H_8O_4S$: S, 18.19. Found: S, 18.30.

The anhydride of thiophane-2,5-dicarboxylic acid. Seven and two-tenths grams (0.035 mole) of the sodium salt of thiophane-2,5-*cis*-dicarboxylic acid, prepared by the addition of sodium ethylate to an alcohol solution of the dibasic acid, was added to a mixture of 2.14 g. (0.018 mole) of thionyl chloride and 55 cc. of acetic anhydride in a round-bottom flask equipped with a condenser, fitted with a calcium chloride tube, and a mechanical stirrer. The mixture was heated on a water-bath at 70° for two hours. A small amount of solid matter was filtered off and the filtrate was evaporated under diminished pressure. The darkly colored residue was taken up in hot nitromethane, treated with Norit, and filtered. The concentrated filtrate yielded 1.25 g. (22.6%) of transparent rods and plates, m.p. 141–142°.

Anal. Calc'd for $C_6H_6O_3S$: C, 45.55; H, 3.82; S, 20.26.
Found: C, 45.55; H, 4.03; S, 20.00.

The imide of thiophane-2,5-cis-dicarboxylic acid. In a small distilling-flask connected to a receiver was placed 8.7 g. (0.05 mole) of *trans*-2,5-dicarbamylthiophane and 20 cc. (0.217 mole) of phosphorus oxychloride. The mixture was heated on a steam-bath for one and one-half hours and the excess phosphorus oxychloride was then removed under diminished pressure. Water was added to the chilled residue, and when all evidence of an oil had disappeared, the solid imide was filtered and washed with water. The yield was 6.4 g. (81.6%); m.p. 145–146°.

Anal. Calc'd for $C_6H_7NO_2S$: N, 8.91; S, 20.39.
Found: N, 8.95; S, 20.36.

N-(n)-Amylthiophane-2,5-dicarboxylic acid imide. In a three-necked flask, equipped with a mechanical stirrer, a condenser protected with a calcium chloride tube, and a dropping-funnel, were placed 10.24 g. (0.32 mole) of dry methanol and 0.92 g. (0.04 g. atom) of sodium. When the sodium had dissolved, 6.28 g. (0.04 mole) of thiophane-2,5-dicarboxylic acid imide was introduced, and while the solution was chilled in an ice-bath, 11.6 g. (0.77 mole) of freshly distilled *n*-amyl bromide was added dropwise. The solution was allowed to come to room temperature slowly and then heated for one hour at 60° and for four hours at 80–90°. The solution then gave a negative test with moist red litmus paper. The solvent was distilled *in vacuo*, and the residue was dissolved in ether. The filtered ether solution was evaporated to a syrup, which was crystallized from 10% aqueous ethanol. The crystallizate weighed 7.4 g. (81%); m.p. 52°. After two recrystallizations from dilute ethanol the m.p. was 68°, unchanged by further crystallization.

Anal. Calc'd for $C_{11}H_{17}NO_2S$: N, 6.16. Found: N, 6.09.

Trans-2,5-dicyanothiophane. An intimate mixture of 8.7 g. (0.05 mole) of *trans*-2,5-dicarbamylthiophane and 24.4 g. (0.117 mole) of phosphorus pentachloride was placed in a distilling-flask which was attached to a condenser. The reactants were heated at 115–120° for one and one-half hours, and at the end of this time, the darkly colored residue was ex-

tracted several times with ether. The united ether extracts were washed with sodium bicarbonate and with water. The dried ether solution was distilled, first at atmospheric pressure, and finally *in vacuo*. A fraction of b.p. 124°/1 mm. crystallized in the form of fine, colorless needles; weight, 0.80 g. (11.6%); m.p. 87° after recrystallization from dilute alcohol.

Anal. Calc'd for $C_6H_8N_2S$: N, 20.29. Found: N, 20.46.

The sulfone of cis-2,5-dicarbethoxythiophane. A mixture of 5.8 g. (0.025 mole) of *cis*-2,5-dicarbethoxythiophane, 25 cc. of glacial acetic acid, and 15 cc. of 30% hydrogen peroxide were placed in a small stoppered flask and allowed to stand at room temperature for eight days. The solvent was then removed under diminished pressure and the oil that remained was distilled, b.p. 155°/1 mm.; n_D^{25} 1.4790. The distillate crystallized in the form of colorless flaky plates, m.p. 40°; yield, 2.7 g. (41%).

Anal. Calc'd for $C_{10}H_{16}O_6S$: S, 12.13. Found: S, 12.00.

2,5-bis-(3-Diethylaminocarbopropoxy)thiophane. Eighty-five and fifteen one-hundredths grams (0.65 mole) of 3-diethylaminopropanol, containing a small amount of dissolved sodium, was added to 11.6 g. (0.05 mole) of *cis*-2,5-dicarbethoxythiophane, and the mixture was heated at 165–170° for seven hours. At the end of this time, the excess 3-diethylaminopropanol was removed under diminished pressure, and the residue was extracted with several portions of ether. The united extracts were shaken with saturated sodium chloride solution, dried with calcium chloride, and evaporated. The residual oil was resubmitted to transesterification in the manner just described. Repetition of the isolation procedure gave a colorless distillate; b.p. 195–197°/1 mm.; weight 3.0 g. (15%); n_D^{25} 1.4840.

Anal. Calc'd for $C_{20}H_{38}N_2O_4S$: N, 6.95. Found: N, 6.65.

2,5-bis-(2-Diethylaminocarbethoxy)thiophane. This ester was prepared in a manner similar to that described for 2,5-bis-(3-diethylaminocarbopropoxy)thiophane. From 76 g. of 2-diethylaminoethanol and 11.6 g. (0.05 mole) of *cis*-2,5-dicarbethoxythiophane was obtained 5.0 g. (26.7%) of product; b.p. 177–179°/0.75 mm.; n_D^{25} 1.4858.

Anal. Calc'd for $C_{18}H_{34}N_2O_4S$: N, 7.48. Found: N, 7.33.

SUMMARY

The condensation of *cis*-ethyl 2,5-dibromoadipate with sodium sulfide to yield *cis*-2,5-dicarbethoxythiophane has been studied.

The products obtained by treatment of *cis*-2,5-dicarbethoxythiophane and related compounds with a variety of reagents are reported.

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REFERENCES

(1) DUVIGNEAUD, *Science*, **96**, 455 (1942).
(2) VON BRAUN AND TRUMPLER, *Ber.*, **43**, 545 (1910).
(3) BOST AND CONN, *Oil Gas J.*, **32**, (3) 17 (1933).
(4) GRISCHKEVITSCH-TROCHIMOVSKI, *Chem. Zent.*, (1923) I, 1502.
(5) MARVEL AND WILLIAMS, *J. Am. Chem. Soc.*, **61**, 2714 (1939).
(6) KILMER, ARMSTRONG, BROWN, AND DUVIGNEAUD, *J. Biol. Chem.*, **145**, 459 (1942).
(7) FREDGA, *J. prakt. Chem.*, **150**, 124 (1938).
(8) KILMER AND MCKENNIS, *J. Biol. Chem.*, **152**, 103 (1944).
(9) INGOLD, *J. Chem. Soc.*, 955 (1921).
(10) BROWN AND KILMER, *J. Am. Chem. Soc.*, **65**, 1674 (1943).
(11) SESSIONS, *J. Chem. Ed.*, **19**, 130 (1942).
(12) BAKER, QUERRY, SAFIR, AND BERNSTEIN, *J. Org. Chem.*, **12**, 138 (1947).
(13) BROWN, BAKER, BERNSTEIN, AND SAFIR, *J. Org. Chem.*, **12**, 155 (1947).
(14) BAKER, QUERRY, MCEWEN, BERNSTEIN, SAFIR, DORFMAN, AND SUBBAROW, *J. Org. Chem.*, **12**, 186 (1947).