[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

A THIOPHENE ISOSTER OF CHLORAMPHENICOL IN THE ERYTHRO SERIES[1]

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It has become evident that structural modifications of chloramphenicol involving the *p*-nitro substituted benzene ring still retain some antibiotic activity (1, 2). However, much more demanding structural requirements must be met by the 2-acylamidopropanediol side chain or complete loss of activity results (3, 4).

An obvious move in a structure-activity study is the replacement of the *p*-nitrobenzene ring by a nitro-substituted heterocyclic ring. The problems involved in the synthesis of the furan analog have been discussed by Hayes and Gever (5). A thiophene analog of chloramphenicol has been recorded by Carrara and Weitnauer (6). We wish to report some work carried out in 1949 on the same subject which supplements that of Carrara and Weitnauer. Approaching the synthesis somewhat differently, 2-dichloroacetamido-1-[2-(5-nitrothienyl)]-1,3-propanediol was obtained in both of its possible stereoisomeric DL modifications (Ia and Ib). One of these modifications was crystalline (m.p. 165°) and had no antibiotic activity whereas the other as obtained by our method could not be induced to crystallize. It showed roughly one-fifth the antibiotic activity of DL-chloramphenicol. The compound of Carrara and Weitnauer, whose biological activity was not reported, melted at 133°. Our results indicate that their compound may be assigned the *threo*-configuration and our crystalline compound (Ia), the *erythro*-configuration. This parallels the situation in the chloramphenicol series where only one of the two DL-pairs has antibiotic activity.

Our synthesis in general followed the one described by Long and Troutman (7) and started with aminomethyl 2-thienyl ketone hydrochloride (II). In our hands the preparation of II *via* bromination of methyl 2-thienyl ketone, reaction with hexamethylenetetramine, and decomposition with hydrochloric acid gave better yields than a previously reported method by Barger and Easson (8) which involves reduction of the nitrosoketone. II was dichloroacetylated (III), reacted with formaldehyde (IV), and reduced with sodium borohydride to the alcohol (V). From the reduction mixture, the *erythro* racemate (Va), crystallized while from the mother liquors there was obtained an approximately equal amount of non-crystalline *threo*-alcohol (Vb). However, the sodium borohydride reduction of the benzamide corresponding to III to the alcohol, 2-benzamide-1-(2-thienyl)-1-ethanol, where the complication of a second asymetric carbon atom

[1] Since the receipt of proof of this manuscript, a paper on the same subject by Hermann and Kreuchunas has appeared [*J. Am. Chem. Soc.*, **74**, 5168 (1952)]. Our paper however presents additional information. The duplicated portions corroborate each other.

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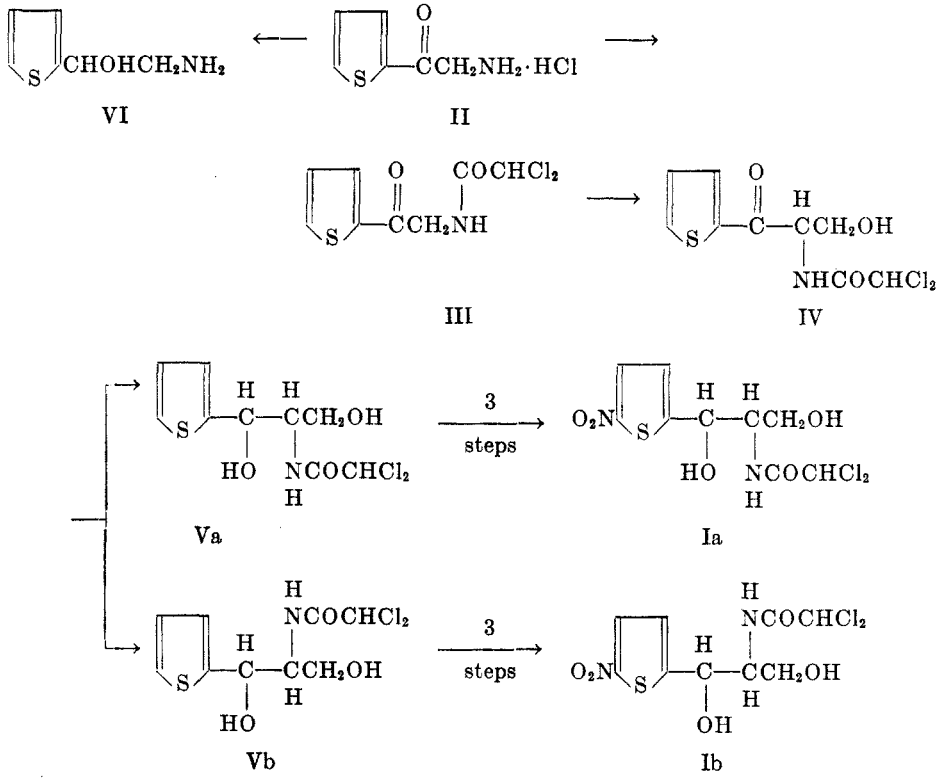
is not present, could be carried out in excellent yield to a single crystalline compound.



It may be mentioned in passing that II was successfully reduced with sodium borohydride to 2-amino-1-(2-thienyl)-1-ethanol (VI), a thiophene isoster of the ephedrine type pressor amine,[3] whereas this reduction by the usual means then available was tried by Barger and Easson (8) without success.

Va and Vb were acetylated, nitrated by nitric acid-acetic anhydride, and deacetylated with two molar equivalents of base to yield the desired thiophene analogs of chloramphenicol, Ia and Ib. The series of products from Va to Ia were all crystalline while none of the corresponding diastereoisomers in the series Vb–Ib could be obtained crystalline. Attempts to purify Ib and obtain it in a crystalline form, which included chromatography, were unsuccessful. The resulting preparation of Ib was characterized by its absorption spectrum which is similar to that of its crystalline isomer Ia (Fig. 1) with a minimum in the

[3] The pressor activity of VI (the DL base) is about 60% that of L-ephedrine hydrochloride in dogs. From the published data [Crimson and Tainter, *J. Pharmacol. Exptl. Therap.*, **66**, 146 (1939)] on the comparative activities of 2-amino-1-phenyl-1-ethanol and ephedrine it can be estimated that the former and its thiophene isoster (VI) have about equal pressor activity. This is reminiscent of the report by Barger and Easson (8) that β-2-thienylethylamine and β-phenylethylamine are indistinguishable in pressor activity.

neighborhood of 240–245 mμ and a maximum at 326 mμ. The deviations are due to minor impurities which are also indicated by paper chromatography. Using the technique applied to chloramphenicol by Smith and Worrel (9), the R_f

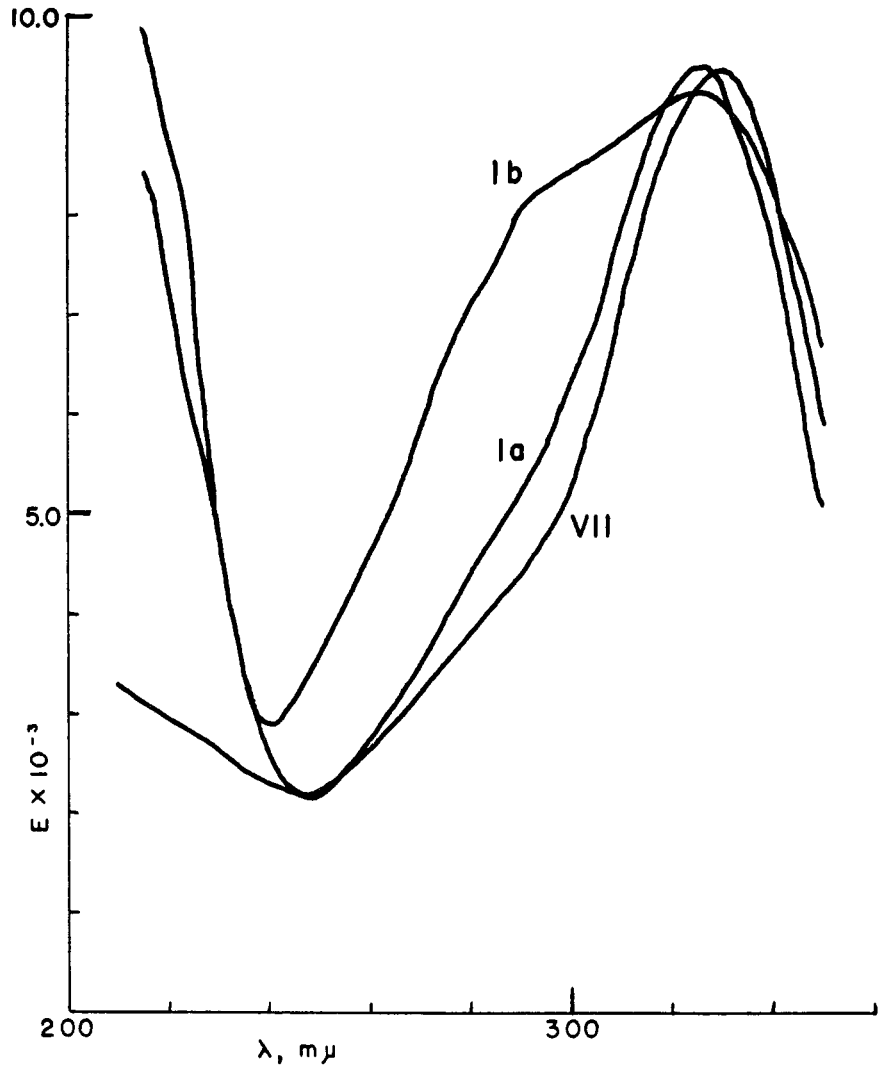


FIGURE 1. ULTRAVIOLET SPECTRA OF 2-DICHLOROACETAMIDO-1-[2-(5-NITROTHIENYL]-1,3-PROPANEDIOL, *erythro* SERIES (Ia); 2-DICHLOROACETAMIDO-1-[2-(5-NITROTHIENYL)]-1,3-PROPANEDIOL, *threo* SERIES (Ib); AND 2-METHYL-5-NITROTHIOPHENE (VII)

values of Ia and Ib were identical with orange spots appearing at a value of 0.83. In addition two minor spots (an orange spot at 0.40 and a yellow spot at 0.27) were noted in the two different preparations of Ib examined.

Ib exhibited the following fractional activities of DL-chloramphenicol: one-

fifth that of DL-chloramphenicol against *S. paradysenteriae*, *Staph. aureus*, and *S. schottmülleri*; one-tenth against *K. pneumoniae*; and one-twentieth against

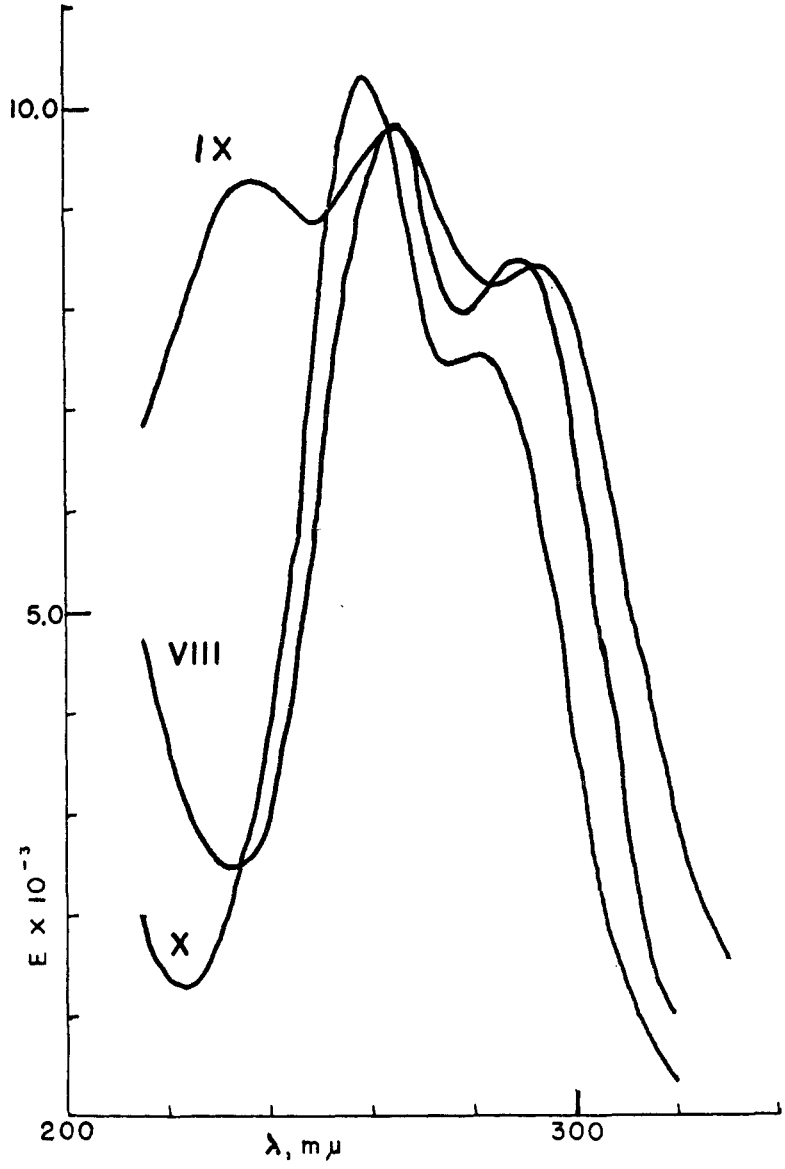


FIGURE 2. ULTRAVIOLET SPECTRA OF 2-DICHLOROACETAMIDO-1-(2-THIENYL)-1-PROPEN-2-ONE (IX), 3-ACETOXY-2-DICHLOROACETAMIDO-1-(2-THIENYL)-1-PROPANONE (VIII), AND METHYL 2-THIENYL KETONE (X)

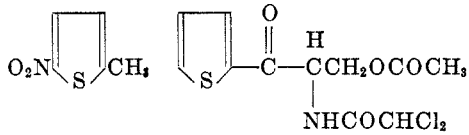
Str. pyogenes and *D. pneumoniae*. It should be borne in mind that these activities are minimum values since they were not determined with crystalline Ib.

The nitro group in I (a and b) is assigned to the 5-position on the basis of

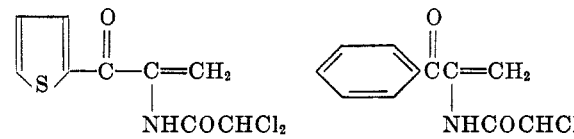
indirect evidence. The nitration of 2-methylthiophene under essentially the same conditions used to nitrate the diacetate of V has been reported by Rinkes (10) to yield 2-methyl-5-nitrothiophene (VII) as the only isolable product. We have repeated this work and Fig. 1 indicates the almost complete identity of the ultraviolet absorption spectra of Ia and VII. The spectra of 2-methyl-3-nitro- and 2-methyl-4-nitro-thiophene from analogy with corresponding compounds in the benzene series (11) would be expected to differ significantly from VII.

In an effort to obtain a crystalline reduction product of IVc in the *threo*- rather than the *erythro*-series, 3-acetoxy-2-dichloroacetamido-1-(2-thienyl)-1-propanone (VIII) was reduced by sodium borohydride to the mixture of alcohols. Only one of these crystallized. By conversion to the diacetate, this crystalline reduction product was shown to also belong to the *erythro*-series. It is interesting to note that attempted acetylation of IV with acetic anhydride-pyridine instead brought about dehydration to the propenone (IX). The presence of the new double bond in IX is indicated by the new ultraviolet absorption band appearing at 237 mμ as compared to the substituted propanone (VIII) and to methyl- 2-thienyl ketone (X) (Fig. 2). VIII was, however, successfully obtained by the sulfuric acid-catalyzed acetylation of IV.

An analogous dehydration by acetic anhydride-pyridine of the keto alcohol also occurred in the benzene series whereas acetylation in the absence of pyridine yielded the expected O-acetate. Thus, 2-dichloroacetamido-3-hydroxy-1-phenyl-1-propanone (XI) was dehydrated to 2-dichloroacetamido-1-phenyl-1-propene-2-one (XII). XII, as expected from its α,β-unsaturated ketone nature, showed moderate antibiotic activity (12). It was bacteriostatic at a dilution of 1:100,000 against *Staph. aureus* and *B. subtilis* and at a dilution of 1:1000 against *E. coli* and *Ps. aeruginosa*.



VII VIII



IX XII

The bacterial assays were kindly carried out under the supervision of Dr. R. L. Mayer and Dr. P. Eisman of the Microbiological Division of these laboratories. Dr. A. Plummer of the Macrobiological Division has determined the pressor activity of VI. We wish to express thanks to Mr. L. Dorfman for the microanalytical data and to Dr. J. L. Marsh for advice regarding nomenclature. We are

indebted to the Socony-Vacuum Oil Co., Inc., Chemical Division, for a gift of 2-methylthiophene and methyl 2-thienyl ketone.

EXPERIMENTAL[4]

Aminoethyl 2-thienyl ketone hydrochloride (II). A solution of 82 ml. of bromine in 50 ml. of chloroform was added with stirring to 200 g. of methyl 2-thienyl ketone in 1 liter of chloroform. The solution was warmed at the beginning until the first portions of bromine were decolorized. The mixture was then cooled to 20° and further bromination readily proceeded and was finished in one-half hour. A stream of air was run through the reaction to remove the hydrogen bromide. The chloroform solution was washed with aqueous bicarbonate, dried over sodium sulfate, and stirred with 230 g. of hexamethylenetetramine for six hours with warming in the steam-bath during the first half hour of the experiment. The quaternary salt was filtered and stirred overnight with a mixture of 340 ml. of concentrated hydrochloric acid and 700 ml. of ethanol. The reaction mixture was cooled during the first half-hour in an ice-bath. The amine hydrochloride was filtered and washed twice by stirring into a paste with a small amount of ice-water. The salt is rather soluble in water. Recrystallization from 3 *N* hydrochloric acid gave a substance melting at 220–222° (dec.), yield 200 g. Barger and Easson (8) report the melting point as 215–218°.

2-Thienyl thioureidomethyl ketone. Reaction of II with thiocyanate gave 2-thienyl thioureidomethyl ketone as an easily prepared derivative. It is interesting to note that the usual spontaneous dehydration of the keto thiourea to a 2-mercaptoimidazole does not occur.

One gram of II was warmed with 0.5 g. of potassium thiocyanate in 5 ml. of 1 *N* HCl. The thiourea readily separated and was recrystallized from water, m.p. 140–142°. Above its melting point resolidification occurred with melting again at 270°. This is undoubtedly the 2-mercaptoimidazole formed above the melting point of the ketothiourea.

Anal. Calc'd for $C_7H_8N_2OS_2$: C, 41.98; H, 4.02; N, 13.99.
Found: C, 41.96; H, 3.90; N, 13.72.

Dichloroacetamidomethyl 2-thienyl ketone (III). Compound II (37 g.) was suspended in 200 g. of ice and 100 ml. of dichloroacetyl chloride and 250 g. of sodium acetate in 500 ml. of water were added dropwise from two separatory-funnels at the rate of one drop of the former to five drops of the latter. Cooling with an external ice-salt bath was necessary to keep the temperature below 5°. After one hour the crude amide was filtered and recrystallized from ethanol-water, m.p. 135–136°, yield 18 g.

2-Dichloroacetamido-3-hydroxy-1-(2-thienyl)-1-propanone (IV). A mixture of 15 g. of III, 1.8 g. of paraformaldehyde, and 0.5 g. of sodium carbonate in 90 ml. of methanol was shaken for 2 hours. The solution was poured into 200 ml. of water and concentrated to a small volume *in vacuo* when the product began to crystallize. It was recrystallized from ethanol-water; m.p. 118–120°, yield 10 g.

Anal. Calc'd for $C_9H_9Cl_2NO_3S$: N, 4.96; Cl, 25.13.
Found: N, 5.12; Cl, 24.94.

2-Dichloroacetamido-1-(2-thienyl)-1,3-propanediol, erythro series (Va). To a solution of 3 g. of IV in 30 ml. of methanol was added 0.5 g. of sodium borohydride. After refluxing for 15 minutes, the mixture was made just acid and concentrated to dryness *in vacuo*. The semicrystalline residue was dissolved in ethyl acetate, washed with water, and concentrated to dryness. Recrystallization from ethanol and concentration of the mother liquors gave several crystalline crops, m.p. 152–153°, total yield 0.8 g.

Anal. Calc'd for $C_9H_{11}Cl_2NO_3S$: N, 4.93; Cl, 24.95.
Found: N, 5.02; Cl, 24.74.

Acetylation with acetic anhydride-pyridine gave the *diacetate*, m.p. 95–96°.

Anal. Calc'd for $C_{13}H_{15}Cl_2NO_5S$: N, 3.80; Cl, 19.26.
Found: N, 3.91; Cl, 19.13.

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[4] All melting points are uncorrected. Ultraviolet absorption spectra were determined in 95% ethanol.

2-Dichloroacetamido-1-[2-(5-nitrothienyl)]-1,3-propanediol diacetate, erythro series. The diacetate of Va (0.5 g.) was dissolved in 1.5 ml. of acetic anhydride and added dropwise to a solution of 1 ml. of fuming nitric acid in 4 ml. of acetic anhydride at −30°. The mixture was allowed to warm up to 0° and then poured into chipped ice. The crystalline product was filtered and recrystallized from ethanol, m.p. 127–128°, yield 0.5 g.

Anal. Calc'd for $C_{13}H_{14}Cl_2N_2O_7S$: N, 6.78; Cl, 17.16.

Found: N, 6.89; Cl, 17.32.

2-Dichloroacetamido-1-[2-(5-nitrothienyl)]-1,3-propanediol, erythro series (Ia). The nitration product (0.5 g.) was dissolved in 10 ml. of methanol and treated with 3 ml. of 1 *N* sodium hydroxide. After 12 hours at room temperature, hydrochloric acid was added to neutrality and the mixture was evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate and extracted with dilute sodium hydroxide, washed with water, and dried over sodium sulfate. The resinous residue remaining after removal of the ethyl acetate crystallized on rubbing with ethanol, yield 80 mg. Recrystallization from water or from ethyl acetate-petroleum ether gave needles melting at 165° with a transition point at about 110°.

Anal. Calc'd for $C_9H_{10}Cl_2N_2O_5S$: C, 32.83; H, 3.06; N, 8.51; Cl, 21.54.

Found: C, 32.67; H, 3.30; N, 8.47; Cl, 21.27.

2-Dichloroacetamido-1-[2-(5-nitrothienyl)]-1,3-propanediol, threo series (Ib). The syrup from the mother liquors of Va (0.5 g.) was carried through the same sequence of reactions as described in the *erythro* series to yield 0.25 g. of a syrupy final product (Ib). Crystallization at this or any of the intermediate stages could not be effected. None of several fractions obtained by chromatography of larger quantities on alumina from ether and developing with 10% ethanol in ether could be crystallized.

Benzamidomethyl 2-thienyl ketone. The crude aminoketone hydrochloride (120 g.) (II) was suspended in 1 kg. of chipped ice and stirred with 50 ml. of benzoyl chloride while a cold solution of 200 g. of potassium hydroxide in 500 ml. of water was added over a period of one-half hour. The reaction mixture was kept at 5° by external cooling. After stirring for one hour, the benzoate was filtered, washed well with water, and recrystallized from ethanol, m.p. 139–142°, yield 95 g.

Anal. Calc'd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71.

Found: C, 63.93; H, 4.55; N, 5.67.

2-Benzamido-1-(2-thienyl)-1-ethanol. Benzamidomethyl 2-thienyl ketone (2 g.) in 20 ml. of boiling methanol was treated with 0.35 g. of sodium borohydride. After 5 minutes, 3 ml. of 5.9 *N* sodium hydroxide was added and refluxing was continued 10 minutes to hydrolyze any borate esters. Concentrated hydrochloric acid was added until neutrality and the solution concentrated *in vacuo* to a small volume. The needles separating were recrystallized from ethanol, m.p. 121–122°, yield 1.7 g.

Anal. Calc'd for $C_{13}H_{13}NO_2S$: N, 5.67. Found: N, 5.55.

2-Amino-1-(2-thienyl)-1-ethanol (VI). One gram of sodium borohydride was added with rapid mixing to a solution of 5 g. of II in 50 ml. of water at room temperature. After one-half hour the mixture was made slightly acid with hydrochloric acid and concentrated to a volume of 5 ml. This solution was saturated with potassium carbonate and extracted three times with ethyl acetate. The extract was concentrated to dryness and the residue was recrystallized three times from benzene, m.p. 81–83°, yield 1.6 g.

Anal. Calc'd for C_6H_9NOS: N, 9.78. Found: N, 9.64.

3-Acetoxy-2-dichloroacetamido-1-(2-thienyl)-1-propanone (VIII). To one gram of IV suspended in 2 ml. of acetic anhydride was added a drop of sulfuric acid. Solution occurred immediately with spontaneous warming. After 15 minutes water was added and 0.8 g. of the acetate obtained on recrystallization from methanol, m.p. 135–136°.

Anal. Calc'd for $C_{11}H_{11}Cl_2NO_4S$: N, 4.32. Found: N, 4.48.

2-Dichloroacetamido-1-(2-thienyl)-1,3-propanediol-3-acetate, erythro series. Compound VIII (0.65 g.) was reduced with 0.06 g. of sodium borohydride in methanol. The syrup obtained after working up the reaction in the usual way partly crystallized after several months in the refrigerator. After recrystallization from ethanol-water, the melting point was 110–112°.

Anal. Calc'd for $C_{11}H_{13}Cl_2NO_4S$: C, 40.50; H, 4.02.
Found: C, 40.57; H, 4.02.

Acetylation with acetic anhydride-pyridine gave a compound of melting point 95–96°, identical to Va diacetate.

2-Dichloroacetamido-1-(2-thienyl)-1-propen-2-one (IX). Compound IV (0.5 g.) was allowed to stand at room temperature for 24 hours in solution with 0.2 ml. of acetic anhydride and 3 ml. of pyridine. Water was added and the oily residue partly crystallized when taken up in a small volume of ethanol. Recrystallization from ethanol gave a substance melting at 108–109°.

Anal. Calc'd for $C_9H_7Cl_2NO_2S$: C, 40.93; H, 2.67; N, 5.30.
Found: C, 41.07; H, 2.72; N, 5.41.

2-Dichloroacetamido-3-hydroxy-1-phenyl-1-propanone (XV). Treatment of aminomethyl 2-phenyl ketone hydrochloride with dichloroacetyl chloride as described above for the thiophene compound, yielded dichloroacetamidomethyl 2-phenyl ketone. m.p. 125–126°.

Anal. Calc'd for $C_{10}H_9Cl_2NO_2$: N, 5.69. Found: N, 5.80.

A mixture of 5.5 g. of this compound, 0.8 g. of paraformaldehyde, and 0.1 g. of sodium carbonate was shaken overnight in 30 ml. of methanol. The crude hydroxyketone which was precipitated with water was recrystallized from ethyl acetate-petroleum ether, m.p. 136–137°.

Anal. Calc'd for $C_{11}H_{11}Cl_2NO_3$: C, 47.84; H, 4.02; N, 5.07.
Found: C, 47.88; H, 3.96; N, 5.13.

The *3-acetate of XI* was obtained by refluxing 1 g. of XI with 10 ml. of acetyl chloride for 30 minutes, removing the excess by distillation *in vacuo*, and recrystallization of the residue from ethyl acetate and from ethanol, m.p. 133–134°.

Anal. Calc'd for $C_{13}H_{13}Cl_2NO_4$: C, 49.07; H, 4.12; Cl, 22.29.
Found: C, 49.34; H, 4.15; Cl, 22.12.

2-Dichloroacetamido-1-phenyl-1-propen-2-one (XII). Dehydration of XI was accomplished with acetic anhydride and pyridine as described above under IX. The product was recrystallized three times from ethyl acetate-petroleum ether to give a product melting sharply at 115–116°.

Anal. Calc'd for $C_{11}H_9Cl_2NO_2$: C, 51.18; H, 3.51; Cl, 27.48.
Found: C, 51.11; H, 3.67; Cl, 27.38.

SUMMARY

The synthesis of a thiophene analog of chloramphenicol, 2-dichloroacetamido-1-[2-(5-nitrothienyl)]-1,3-propanediol, is described. Aminomethyl 2-thienyl ketone hydrochloride was dichloroacetylated, reacted with formaldehyde, and the resulting ketone reduced with sodium borohydride to a mixture of the two possible racemic alcohols. The crystalline alcohol, after protective acetylation, was nitrated to yield the antibiotically inactive *erythro* thiophene analog of chloramphenicol. Similarly, the non-crystalline alcohol gave a mixture containing the non-crystalline *threo* analog which showed about one-fifth the antibiotic activity of chloramphenicol. A thiophene analog of the ephedrine type, 2-amino-1-(2-thienyl)-1-ethanol, having high pressor activity has been prepared.

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