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STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XIV. A PARTIAL SYNTHESIS OF THE THIOPHENE ANALOG OF CHLORAMPHENICOL[1, 2]

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After the isolation and successful synthesis of chloramphenicol (1–4), interest has been manifested in the preparation of various analogs. Variation of the position of the nitro group (5, 6) as well as its actual replacement by other substituents (7–9) has been carried out in an effort to ascertain the particular structural features responsible for its pharmacological activity. Recently, studies (10, 11) have been reported on the effect produced by the replacement of the benzene ring by another ring system. Since the presence of a thiophene ring in certain pharmacologically effective compounds has been known to influence their toxicity (12), while still maintaining a high degree of activity, it seemed of interest to prepare the thiophene analog of chloramphenicol. In this communication some of our preliminary findings are presented.

Although the method of synthesis of chloramphenicol consisting in the utilization of *p*-nitroacetophenone as the starting material was quite successful (4), attempts at the preparation of the thiophene analog by employing a similar procedure were limited by the fact that 5-nitro-2-acetothienone could not be readily obtained in any appreciable quantity. Nitration of 2-acetothienone yields the 5-nitro- and 4-nitro-isomers (13). Subsequent separation of their oximes as reported by Rinkes (14) failed to give the 5-isomer in any desirable amount. This is believed to be due to the *meta*-directing influence of an acetyl group. Although 5-nitro-2-acetothienone may be prepared by a sequence of reactions (15–17) involving the formation of 5-nitro-2-thiophenecarboxylic acid, the steps involved are too numerous to be practicable.

In order to alleviate this difficulty, the preparation of DL-*threo*-1-(2-thienyl)-2-acetamido-1,3 propanediol (IX) was carried out since it was thought that the triacetyl derivative could be nitrated in the 5-position. Hydrolysis of the latter would yield the aminodiol which could be converted into the thiophene analog of chloramphenicol by dichloroacetylation. Two different approaches were utilized as shown in Chart I.

In the first case, isonitroso-2-acetothienone (VI) was prepared according to the procedure of Barger and Easson (18), and reduced with stannous chloride and hydrochloric acid to give a tin complex (VII), the acetylation of which

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[1] Chloramphenicol is the generic name for the compound D-(*levo*)-*threo*-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol.

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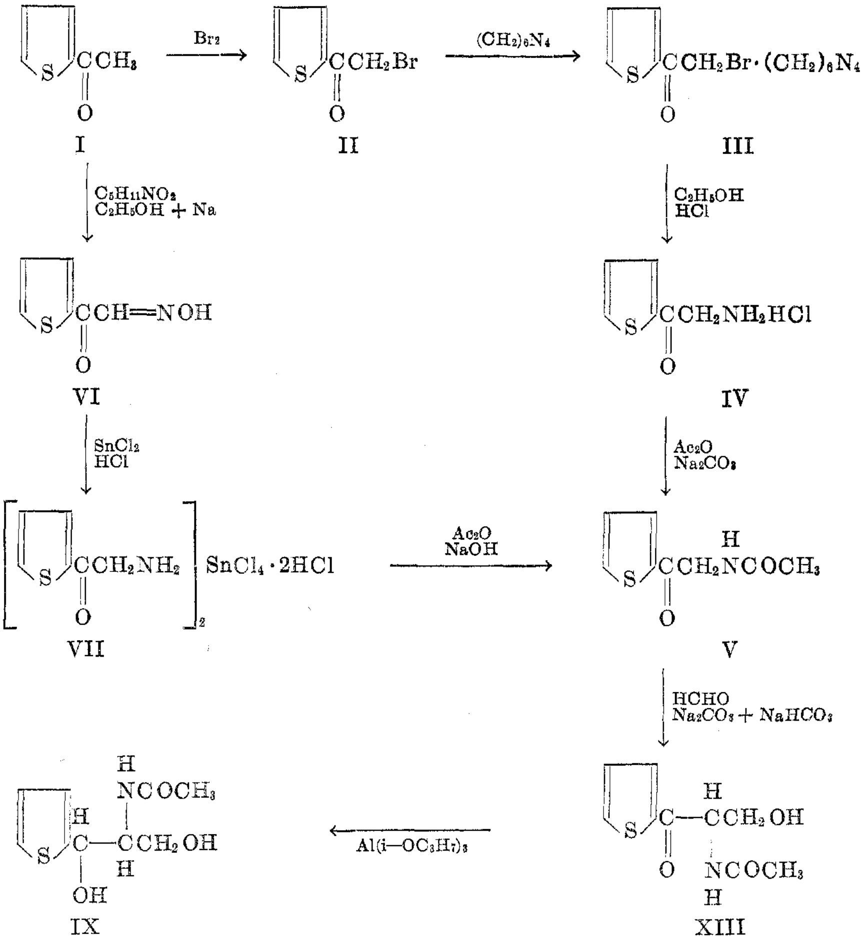
yielded α-acetamido-2-acetothienone (V). However the yield based on the amount of 2-acetothienone used amounted to only 8%.

Consequently an alternate procedure was employed. It consisted in the bromination of 2-acetothienone (19) followed by the direct formation of the hexamethylenetetramine salt (III) without isolation of the bromo-2-acetothienone

CHART I



(II). Hydrolysis of the salt with alcoholic hydrochloric acid gave the crude amine hydrochloride (IV) which was acetylated without further purification. The resulting α-acetamido-2-acetothienone (V) was obtained in 38% yield and was found to be identical with a sample prepared by the first procedure.

The monohydroxymethylation of V in the presence of sodium bicarbonate to form α-acetamido-β-hydroxy-2-propiothienone (VIII) proceeded satisfactorily; however subsequent reduction with aluminum isopropoxide gave poor yields of DL-*threo*-1-(2-thienyl)-2-acetamido-1,3 propanediol (IX). Variations in experimental conditions failed to affect the yield appreciably.

Although the reduction of certain ketones with aluminum isopropoxide generally results in the formation of two isomers, it does not necessarily produce them in equal amounts (4). Fractional crystallization of 1-(2-thienyl)-2-acetamido-1,3-propanediol from ethyl acetate gave only one isomer which, in accord with previous findings (6–8), we have tentatively assigned as the DL-*threo*-racemate.

EXPERIMENTAL[4]

Hexamethylenetetramine salt of bromomethyl 2-thienyl ketone (III). A solution of 126 g. (1 mole) of 2-acetothienone in 900 ml. of dry carbon tetrachloride was brominated according to Ref. 19. The volatiles were removed by distillation under slightly reduced pressure until about 300 ml. of solution remained. Then 1200 ml. of chloroform or chlorobenzene and 120 g. (1 mole) of powdered hexamethylenetetramine was added in one portion at room temperature with efficient stirring. The mixture became thick and the temperature increased to about 42°. After an additional three hours of stirring, the temperature was decreased to room temperature and the product was filtered and washed with dry acetone. After drying in air 266 g. (77%) of the crude product was obtained. For analysis a sample was recrystallized from water, m.p. 148–149°.

Anal. Calc'd for $C_{12}H_{17}BrN_4OS$: N, 16.23. Found: N, 15.93.

α-Acetamido-2-acetothienone (V). The hexamethylenetetramine salt of bromomethyl 2-thienyl ketone (69 g., 0.2 mole) was added to 175 ml. of ethanol and 85 ml. of concentrated hydrochloric acid with stirring. After ten minutes a clear solution was obtained followed by the separation of crystals. Stirring was continued for four hours and the mixture allowed to stand overnight. After filtration the mother liquor was concentrated *in vacuo*. The additional crystals so obtained were added to the main product which consisted of crude α-amino-2-acetothienone hydrochloride (IV) and ammonium chloride.

The solid was dissolved in 150 ml. of water and 150 g. of chipped ice was added. With stirring and cooling to 0°, 40 ml. of acetic anhydride was added followed by the gradual addition of 40–50 g. of sodium carbonate. The temperature of the mixture was kept below 5° by the addition of ice from time to time. When the evolution of carbon dioxide had ceased, an additional 5 ml. of acetic anhydride was added and the stirring continued for 15 minutes. After filtering and washing with cold water the product was dried; 18.2 g. (50%) of α-acetamido-2-acetothienone was obtained. The product could be distilled, b.p. 191°/3 mm. It can be recrystallized from either ethyl acetate or benzene, m.p. 120–123°.

Anal. Calc'd for $C_8H_9NO_2S$: C, 52.45; H, 4.91; N, 7.65.
Found: C, 52.75; H, 4.70; N, 7.39.

Isonitroso-2-acetothienone (VI) was obtained in accord with the procedure reported in Ref. 18.

Reduction of isonitroso-2-acetothienone (VII). Isonitroso-2-acetothienone (9.3 g., 0.06 mole) was reduced with stannous chloride according to the procedure employed to reduce α-nitroacetophenone (3). A tin complex was obtained in a yield of 15–17 g. (81–89%), m.p. 260–262°.

α-Acetamido-2-acetothienone (V). The above tin complex salt was acetylated with acetic anhydride and sodium hydroxide (6) in 60% yield, m.p. 120–122°. A mixed melting point with a sample prepared from the other procedure gave no depression.

α-Acetamido-β-hydroxy-2-propiothienone (VIII). A mixture of 12 g. (0.07 mole) of α-acetamido-2-acetothienone, 5 ml. of methanol, and 6 ml. of 36–38% aqueous formaldehyde was

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[4] The 2-acetothienone used in this research was obtained through the courtesy of Dr. N. B. Sommer of the Jefferson Chemical Co.

heated with stirring to 35°. A solution of 0.6 g. of sodium bicarbonate and 0.2 g. of sodium carbonate in 10 ml. of water was then added. After five minutes a clear solution was obtained, and after an additional 15–20 minutes a cake had formed. Fifteen minutes later the mixture was cooled to 5°, filtered, and washed with a small portion of ice-cold water. After drying, 10.7 g. (80%) of crystals were obtained. Recrystallization from ethyl acetate (charcoal) gave crystals, m.p. 112–113°.

Anal. Calc'd for $C_9H_{11}NO_3S$; N, 6.57. Found: N, 6.75.

DL-*threo-1-(2-thienyl)-2-acetamido-1,3-propanediol* (IX). To a hot solution of 100 ml. of isopropyl alcohol containing 30.4 g. (0.1 mole) of aluminum isopropoxide was added 8 g. (0.04 mole) of α-acetamido-β-hydroxy-2-propiothienone. After a few minutes a reddish-brown solution was formed. Acetone was distilled off through a Hahn condenser over a period of six hours, after which time the acetone test was negative. A total of 70 ml. of isopropyl alcohol was removed by distillation. The residue was allowed to cool just below reflux temperature and 25 ml. of water was added. The mixture was refluxed for 15 minutes and then filtered through a layer of Super-Cel. The filter-cake was extracted twice by refluxing with 50 ml. of 80% isopropyl alcohol. The first filtrate and last two extracts were combined and concentrated in *vacuo*. The residue was dissolved in a small quantity of ethyl acetate and cooled to 0°. The crystalline material which separated was filtered and washed with cold ethyl acetate. Recrystallization from the same solvent and drying yielded 2.2–2.4 g. (26–29%) of crystals, m.p. 142–142.5°.

Anal. Calc'd for $C_9H_{13}NO_3S$: C, 50.23; H, 6.04.
Found: C, 49.95; H, 5.72.

SUMMARY

The synthesis of DL-threo-1-(2-thienyl)-2-acetoamido-1,3-propanediol, an important intermediate in the preparation of the thiophene analog of chloramphenicol, has been presented.

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