SYNTHESES BASED ON ALDEHYDES OF THE THIOPHENE SERIES

COMMUNICATION 1. SYNTHESIS OF SOME ALIPHATIC AMINO HYDROXY ACIDS FROM THIOPHENE DERIVATIVES

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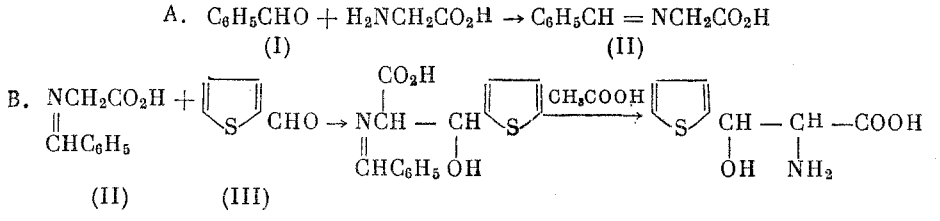
Aliphatic amino acids substituted by a hydroxy group in the β-position are protein fragments [1, 2], and some containing the hydroxy group in the γ-position have recently been isolated from various plants [3, 4]. Methods of preparing these compounds and their reactions have been treated in a number of reviews [1-6]. The most accessible are the lower α-amino β-hydroxy acids, for which a relatively large number of methods are known for their synthesis in high yields. However, these methods are not always suitable for the preparation of α-amino β-hydroxy acids with a longer carbon chain, not only because of the poor accessibility of the starting substances, but often because the yields at the separate stages of the process are not altogether satisfactory. The accessibility of α-amino acids containing a hydroxy group in other than the β-position is still less.

Only a few of the higher amino hydroxy acids have been described. In 1930 papers by Keimatsu and coworkers [7] appeared which described the synthesis of 2-amino-4-hydroxyheptanoic acid from 2-furanacrylic acid. Reduction of the latter gave a lactone, which by the action of bromine and then ammonia was converted into 2-amino-4-hydroxyheptanoic acid. The formation of a mixture of amino hydroxy acids by the action of ammonia on epoxystearic acid is described in a patent [8]. Much greater success was attained in syntheses of higher α-amino β-hydroxy acids, both with normal and with branched carbon chains. Hellman and Piechota [9] described the preparation of α-amino β-hydroxy acids through the stage of the aldol condensation of acetylmalonic monoesters with aliphatic aldehydes in presence of triethylamine. However, this method gives good results only with the lower aldehydes. With the lengthening of the carbon chain the yield of the desired product rapidly diminishes, being, e.g., only 0.5% in the case of octanal.

In 1962 Mix [10] successfully applied the method [11] of condensing copper salts of glycine with aliphatic aldehydes in a strongly alkaline medium for the synthesis of higher amino hydroxy acids. Under these conditions the yields of amino hydroxy acids were fairly high. This paper describes also the separation of the diastereoisomers of the α-amino β-hydroxy carboxylic acids obtained with the aid of internal-complex copper compounds. A separate paper is devoted to 2-amino-3-hydroxyheptanoic acid [12].

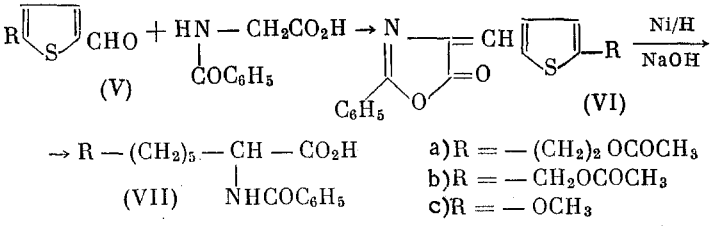
Continuing our study of the reductive desulfurization of thiophene compounds, we decided to verify the possibility of its use for one particular type of terfunctional compound—the higher aliphatic amino hydroxy acids. By this method various higher amino acids, amino dicarboxylic acid, etc., have been prepared in recent years [13-15]. In the present work we have shown, on the basis of a few simple examples, that the method of the reductive desulfurization of thiophene compounds can be applied for the synthesis of both the known 2-amino-3-hydroxyheptanoic acid and also the higher α-amino ω-hydroxy carboxylic acids.



Scheme 1

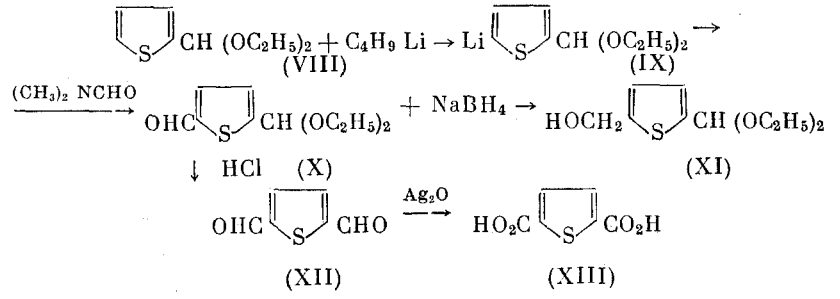
By the action of Raney nickel on 2-thiopheneserine in presence of ammonia or aliphatic amines in an aqueous medium 2-amino-3-hydroxyheptanoic acid is formed. We obtained the best yield (20%) by carrying out the reaction in presence of diethylamine. The original 2-thiopheneserine was synthesized by a known method [16]—the condensation of glycine with two molecules of an aldehyde. By carrying out stages A and B (Scheme 1) separately, we were able to replace one half of the 2-thiophenecarboxaldehyde (III) by the more readily available benzaldehyde (I).

To purify the reductive-desulfurization product, which contained a certain amount of nickel, we treated the solution obtained with dimethylglyoxime [17]. The method that we used for the preparation of α-benzamido ω-hydroxy carboxylic acids is illustrated in the following scheme.



Scheme 2

The 5-(2-acetoxyethyl)-2-thiophenecarboxaldehyde (Va) was synthesized by the method described by Ibragimova [18], and the 5-methoxy-2-thiophenecarboxaldehyde required (Vc) was prepared by Sise's method [19]. 2-Thiophenecarboxaldehyde containing a hydroxymethyl group in the 5-position (Vb, R = $-CH_2OCOCH_3$) was prepared by us for the first time. Our method consisted essentially in the metalation of 2-thiophenecarboxaldehyde diethyl acetal (VIII) with butyllithium (Scheme 3), the replacement of lithium in (IX) by an aldehyde group with the aid of dimethylformamide, and the reduction of the free aldehyde group of 2,5-thiophenedicarboxaldehyde mono[diethyl acetal] (X) with sodium borohydride to the hydroxymethyl group of the desired compound (XI).



Scheme 3

2,5-Thiophenedicarboxaldehyde mono[diethyl acetal] (X), which was obtained in 70% yield [based on the amount of the acetal (VIII) that reacted], is of interest as an intermediate product for many syntheses. The fact that one of the aldehyde groups of this compound is blocked makes it possible to prepare monoderivatives of 2,5-thiophenedicarboxaldehyde in the pure state or to change one of the aldehyde functions in a required direction. By taking advantage of these circumstances we prepared 5-(hydroxymethyl)-2-thiophenecarboxaldehyde diethyl acetal (XI). When we attempted to vacuum-distill this, alcohol was eliminated and we obtained a transparent mass, probably a polyacetal formed as a result of the displacement of ethoxy groups by its own hydroxymethyl groups. This polymer dissolves when heated in organic solvents and reacts like the monomer with formation of a normal semicarbazone, oxazolinone, etc. As will be seen from Scheme 2, the 2-thiophenecarboxaldehydes containing a hydroxyalkyl or methoxy group in the 5-position were condensed with hippuric acid to give the oxazolinones (VI). By the reductive desulfurization of the latter under conditions similar to those described previously [19] we obtained good yields of the benzamido acids (VIIa) and (VIIc), but we were unable to eliminate sulfur completely from the oxazolinone (VIb) even after extremely long boiling (80 h) with Raney nickel. It is still not clear to us why this is so. 2,5-Thiophenedicarboxaldehyde mono[diethyl acetal] (X) can readily be converted into the previously unde-

scribed 2,5-thiophenedicarboxaldehyde (XII) by the action of dilute hydrochloric acid. The structure of (XII) was proved by its oxidation to 2,5-thiophenedicarboxylic acid (XIII).

EXPERIMENTAL

2-Thiopheneserine. A solution of 16.8 g of potassium hydroxide in 80 ml of absolute alcohol was added with stirring to a mixture of 15.9 g of benzaldehyde and 11.2 g of glycine in 40 ml of abolute alcohol. The mixture was kept for 40 min at 40° and then cooled to 3°; 17.2 g of 2-thiophenecarboxaldehyde was added at such a rate that the temperature did not rise above 5°. The mixture, which contained a mass of crystals, was left overnight. The reaction product was filtered off, washed on the filter with alcohol, and dissolved in 50 ml of 20% acetic acid. 50 ml of alcohol was added to the solution obtained, and the mixture was left overnight in a refrigerator. The precipitate formed was filtered off, washed with alcohol, and dried. We obtained 12.72 g [48%, based on (III)] of 2-thiopheneserine (IV). After one crystallization from 50% alcohol the substance melted at 185-187° (decomp.). The literature [16] gives m.p. 194-195°. By repeated crystallization from the same solvent the melting point was raised and attained 199°. A mixture of the product with 2-thiopheneserine prepared by a known method [16] melted without depression.

2-Amino-3-hydroxyheptanoic Acid. A mixture of 9.3 g of 2-thiopheneserine (IV), 40 g of Raney nickel, 150 ml of water, and 10 ml of diethylamine was stirred at 70° until a test on the solution for sulfur was negative (ten hours). The precipitate was then filtered off and washed with hot water, and the filtrate was vacuum-evaporated. The residue was dissolved in boiling water, and the solution was filtered and treated with excess of dimethylglyoxime. The precipitate formed was separated, and the filtrate was extracted with ether. The aqueous solution was evaporated down to 20-30 ml. On cooling 1.62 g (20%) of 2-amino-3-hydroxyheptanoic acid came down; m.p. 222°, unchanged after repeated crystallization from water. The literature gives m.p. 223° [9], 224° [10]. Found: C 51.91; 52.12; H 9.22; 9.22; N 8.91; 8.77%. $C_7H_{15}NO_3$. Calculated: C 52.18; H 9.37; N 8.69%.

4-[5-(2-Acetoxyethyl)-2-thenylidene)-2-phenyl-2-oxazolin-5-one (VIa). 8.0 g of 5-(2-acetoxyethyl)-2-thiophenecarboxaldehyde (Va) was mixed with 18.3 g of acetic anhydride and a ground mixture of 8.16 g of freshly fused sodium acetate and 10.4 g of hippuric acid. The mixture was heated for two hours on a steam bath. When cool, the product was ground and mixed with 30 ml of alcohol. The paste was pressed off on the filter and washed with 50 ml of alcohol. The residue was boiled for 20 min with 500 ml of water, separated, and dried. We obtained 11.50 g (70%) of an orange powder, m.p. 116°. On recrystallization from a mixture of benzene and heptane orange crystals were formed, m.p. 116-116.5°. Found: C 62.99; 63.12; H 4.54; 4.03; S 9.50; 9.53%. $C_{18}H_{15}NO_4S$. Calculated: C 63.34; H 4.40; S 9.20%.

2-Benzamido-9-hydroxynonanoic Acid (VIIa). 5.0 g of 4-[5-(2-acetoxyethyl)-2-thenylidene)-2-phenyl-2-oxazolin-5-one (VIa) was suspended in 100 ml of 50% methanol, and 10 ml of 15% sodium hydroxide solution was added gradually to the mixture. The resulting alkaline solution was heated with stirring for two hours at 70° 30 g of Raney nickel was then added, and stirring was continued at 70° until a test for sulfur was negative (three hours). The precipitate was then separated and washed with water, and the filtrate was vacuum-evaporated. The residue (4.8 g) was dissolved in 50 ml of hot water, the solution was filtered, and 3 ml of 15% sodium hydroxide solution was added. The solution was boiled for one hour and then acidified to Congo Red. The oil that was precipitated crystallized on standing. The crystals were filtered off and dried. We obtained 3.27 g (70%) of (VIIa), m.p. 110-111°, raised by crystallization from a mixture of ethyl acetate and ether to 112-112.5°. Found: C 65.44; 65.68; H 7.91; 8.06; N 4.85; 4.69%. $C_{16}H_{23}NO_4$. Calculated: C 65.49; H 7.94; N 4.77%.

4-(5-Methoxy-2-thenylidene)-2-phenyl-2-oxazolin-5-one (VIc). A mixture of 2.53 g of 5-methoxy-2-thiophenecarboxaldehyde (Vc) [19], 3.22 g of hippuric acid, 2.44 g of freshly fused sodium acetate, and 5 g of acetic anhydride was treated as indicated for the preparation of (VIa). We obtained 2.76 g (43%) of the oxazolinone (VIc), m.p. 165-166°, raised to 168-168.5° by recrystallization from a mixture of benzene and heptane. Found: C 63.48; 63.58; H 3.87; 3.84; N 4.76; 4.72; S 11.65; 11.41%. $C_{15}H_{11}NO_3S$. Calculated: C 63.16; H 3.89; N 4.91; S 11.25%.

2-Benzamido-7-methoxyheptanoic Acid (VIIc). By the reaction of 6.4 g of 4-(5-methoxy-2-thenylidene)-2-phenyl-2-oxazolin-5-one (VIc) with 40 g of Raney nickel in presence of 0.34 g of KOH in 120 ml of methanol for eight hours at 65-70° with subsequent treatment as described in the experiment on the preparation of 2-benzamido-9-hydroxynonanoic acid (VIIa), we obtained 5.40 g (86%) of a white product of m.p. 80-82°, raised to 86-87° by recrystallization from ether and hexane. Found: C 64.66; 64.56; H 7.34; 7.43; N 5.22; 5.08%. $C_{15}H_{21}NO_4$. Calculated: C 64.49; H 7.58; N 5.01%.

2,5-Thiophenedicarboxaladehyde Mono[Diethyl Acetal] (X). An ethereal solution of 6.4 g of butyllithium was added gradually in an atmosphere of nitrogen at −30 to −20° to a solution of 16.8 g of 2-thiophenecarboxaldehyde diethyl acetal [20] in 100 ml of dry ether. When the addition was complete thecooling mixture was removed and the mixture was kept for 2.5 h at room temperature. The dark-colored solution formed was added in an atmosphere of nitrogen at −20 to −10° to a solution of 14 ml of dimethylformamide in 80 ml of dry ether. The cooling bath was then removed, and the mixture was left for one hour at 20° and then boiled for 30 min in a water bath. Water was added to the mixture formed, and the ether layer was washed with water three times and dried over potassium carbonate. Distillation gave 11.3 g of 2,5-thiophenedicarboxaldehyde mono[diethyl acetal]; b.p. 152-154° (11 mm); n_D^{20} 1.5211. The oxime of 2,5-thiophenedicarboxaldehyde mono[diethyl acetal] melted at 95-96° (from chloroform+heptane). Found: N 6.39; 6.21%. $C_{10}H_{15}NO_3S$. Calculated: N 6.11%.

5-(Hydroxymethyl)-2-thiophenecarboxaldehyde (XI). 2.2 g of sodium borohydride was added gradually over a period of 40 min to a stirred solution of 10.7 g of 2,5-thiophenedicarboxaldehyde mono[diethyl acetal] (X) in 70 ml of absolute methanol. After two hours the mixture was poured into four times its volume of water. The oil that separated was extracted with ether, and the ether layer was washed with water and dried with potassium carbonate. Ether was driven off, and there remained 10.5 g of pale-yellow liquid, n_D^{20} 1.5075. On vacuum distillation partial elimination of alcohol occurred, and the product was converted into a transparent glassy polymer, which was soluble in acetic anhydride and in hot alcohol. The semicarbazone of 5-(hydroxymethyl)-2-thiophenecarboxaldehyde had m.p. 203-204°. Found: N 21.09; 20.88%. $C_7H_9N_3O_2S$. Calculated: N 21.11%.

4-[5-(Acetoxymethyl)-2-thenylidene)-2-oxazoline-5-one (VIb). By heating a solution of 7.26 g of the polymer formed from 5-(hydroxymethyl)-2-thiophenecarboxaldehyde in 15 ml of acetic anhydride with a mixture of 7.16 g of hippuric acid and 5.40 g of freshly fused sodium acetate for two hours in a water bath and giving the further treatment described for the preparation of (VIa), we obtained 4.05 g (42%) of 4-[5-(acetoxymethyl)-2-thenylidene)-2-oxazolin-5-one. In the course of the formation of the oxazolinone the acetylation of the original hydroxy aldehyde occurred. After recrystallization from alcohol we obtained yellow crystals, m.p. 145°. Found: C 62.18; 62.38; H 4.22; 4.20; S 9.61; 9.60%. $C_{17}H_{13}NO_4S$. Calculated: C 62.37; H 4.00; S 9.80%.

2.5-Thiophenedicarboxaldehyde (XII). 4 ml of 3% hydrochloric acid was added to 2.0 g of 2,5-thiophenedicarboxaldehyde mono[diethyl acetal] in 10 ml of alcohol, and the solution was heated to the boil. When cool, the mixture was poured into water, and the precipitate was filtered off and dried. We obtained 1.17 g (90%) of 2,5-thiophenedicarboxaldehyde in the form of white plates, which turned yellow in air. After recrystallization from dilute alcohol they had m.p. 114-114.5°. Found: C 51.36; 51.58; H 2.38; 2.92; S 22.85; 22.91%. $C_6H_4O_2S$. Calculated: C 51.42; H 2.85; S. 22.91%.

On oxidation of 1.40 g of 2,5-thiophenedicarboxaldehyde with silver oxide (from 6.8 g of $AgNO_3$ and 3.2 g of NaOH) [21] we obtained 1.47 g of 2,5-thiophenedicarboxylic acid (XIII), the dimethyl ester of which had m.p. 147-148.5°. The literature [22] gives m.p. 148.5-149.5°. A mixture of this ester with a known sample melted without depression.

SUMMARY

1. The reductive desulfurization of thiophene compounds can be applied for the preparation of the higher amino hydroxy acids.

2. Some substituted oxazolinones containing the thiophene nucleus were prepared and converted by reductive desulfurization into N-acyl derivatives of amino hydroxy acids.

3. A method was developed for the preparation of 2,5-thiophenedicarboxaldehyde and its monoacetal.

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