SYNTHESIS OF SOME MONOTHIENYLALKYL ESTERS OF ALIPHATIC DICARBOXYLIC ACIDS

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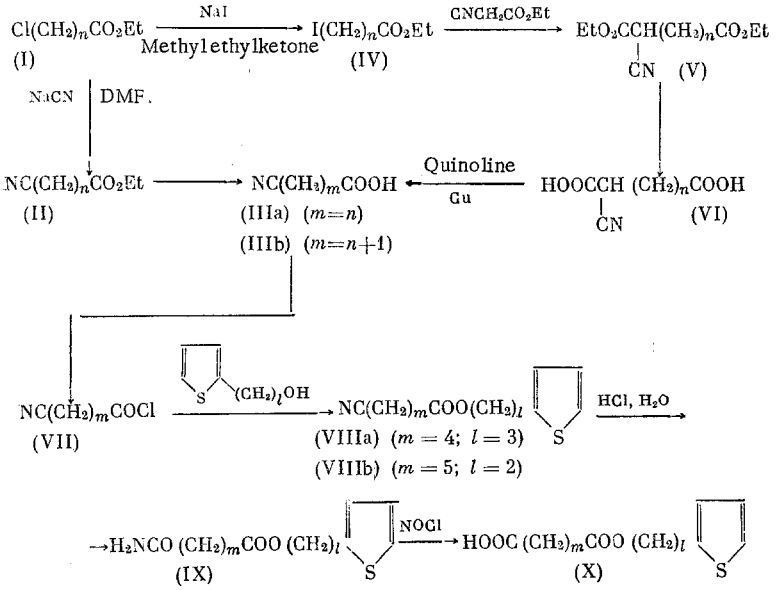
An important intermediate step in the synthesis of keto lactones using compounds of the thiophene series [1] is the preparation of the monothienylalkyl esters of dicarboxylic acids. For reasons that ensue from the chemical nature of the alcohol and acid fragments of these compounds, not one of the methods existing up to now for the synthesis of the monoesters of dicarboxylic acids can be applied for their preparation. The acidophobicity of the thienylalkanols does not permit the use of the widespread method of the "disproportionation" of diesters under the influence of catalysts with an acid character [2], while the method using the cyclic anhydrides of aliphatic dicarboxylic acids is practically limited to the anhydrides of glutaric and succinic acids. The selective alkaline hydrolysis of the diesters of dicarboxylic acids, which leads to the formation of monoesters, is applicable only for the lower alkyl esters of malonic acid [3] and sebacic acid [4], and for certain α-substituted C_6—C_9 dicarboxylic acids [5]. All of these circumstances caused us to develop another general scheme for the synthesis of the monothienylalkyl esters, with an elimination of the steps that could have a negative effect on the acidophobic compounds that are used in the synthesis



The esters of ω-haloalkanoic acids (I) served as the starting compounds for the synthesis, a number of which (with an odd number of carbon atoms) are readily available due to the commercial utilization of the reaction for the telomerization of ethylene with CCl_4. The selection of the first step (cyanation or condensation with cyanoacetic ester) is determined by the number of carbon atoms (even or odd) in the acid fragment of the half-ester of the dicarboxylic acid that is the desired compound. The cyanation of the (I) esters with NaCN in DMF gave us the esters of ω-cyanoalkanoic acids (II), the alkaline hydrolysis of which

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led to the ω-cyanoalkanoic acids (IIIa) with an even number of C atoms. In order to obtain the ω-cyanoalkanoic acids with an odd number of C atoms (IIIb) the (I) esters were converted to the alkyl esters of ω-iodoalkanoic acids (IV) by exchange with NaI; the condensation of the (IV) esters with cyanoacetic ester gave the diesters of α-cyanodicarboxylic acids (V), the hydrolysis of which led to the corresponding α-cyanodicarboxylic acids (VI). The ω-cyanoalkanoic acids (IIIb) were formed as a result of the decarboxylation of the α-cyanodicarboxylic acids (VI) in quinoline in the presence of copper bronze. Reaction of the acid chlorides (VII) of the obtained ω-cyanoalkanoic acids (III) with the appropriate thienylalkanols gave the thienylalkyl esters of the ω-cyanoalkanoic acids (VIII).

2-(2-Thienyl)ethyl alcohol was obtained as described in [6]. 3-(2-Thienyl)propyl alcohol was synthesized by the reduction of thienylacrylic acid with aluminum lithium hydride in ether [7] or in THF (50-55% yields); the reduction of the esters of thienylacrylic acid proceeds more smoothly (in up to 80% yield). When compared with other thienylalkyl alcohols [8], 3-(2-thienyl)propyl alcohol is apparently less stable and undergoes noticeable decomposition during storage and distillation.

Hydrolysis of the nitrile group of the nitrilo ester (VIII) under mild conditions with an equimolar amount of water gave the amido esters (IX). It should be mentioned that we were unable to synthesize the amido esters (IX) by the transesterification of the ethyl esters of amic acids with thienylalkanols, while attempts to obtain the acid chlorides of amic acids for the subsequent acylation of thienylalkanols with them led to acid chlorides (VII). The needed monoesters (X) are formed by the treatment of amido esters (IX) with nitrosyl chloride at 0-10°C in $CHCl_3$. The use of isoamyl nitrite, N_2O_4, N_2O_3 and $N_2O_3 \cdot BF_3$ as deamidation agents led to the formation of tars. When reacted with NH_3, the acid chlorides of the monoesters (X) gave amides that are identical with the (IX) amides. All of the steps were checked in advance on the examples of the preparation of the monoethyl and monooctyl esters of adipic acid. It should be mentioned that in the case of the readily available dicarboxylic acids the acid chlorides (VII) can be obtained by the scheme:

$$HOOC(CH_2)_nCOOH \rightarrow HOOC(CH_2)_nCOOEt \rightarrow ClCO(CH_2)_nCOOEt \rightarrow$$
$$\rightarrow H_2NCO(CH_2)_nCOOEt \rightarrow H_2NCO(CH_2)_nCOOH \rightarrow NC(CH_2)_nCOCl \rightarrow NC(CH_2)_nCOOC_8H_{17}$$
(VII)

This scheme was checked on the example of adipic acid.

EXPERIMENTAL METHOD

Compounds (I) and (II) and 3-(2-thienyl)propyl alcohol were analyzed by GLC on an LKhM-7A chromatograph, using a 2 m × 4 mm stainless steel column that was filled with poly(propylene glycol) (10%) deposited on Chromosorb W, at 198-200°, while (IV), (V) and (VIIIa, b) were analyzed on a 0.5 m × 4 mm column that was filled with poly(ethylene glycol adipate) (15%) deposited on Chromosorb P, respectively at 142, 168 and 221°; helium was the carrier gas, the flow rate was 43 ml/min, and a katharometer served as the detector. The neutralization equivalent was determined on a Radiometer automatic titrimeter; the NMR spectra were taken on a Varian DA 60-IL instrument using HMDS as the internal standard.

Ethyl Ester of δ-Cyanovaleric Acid (II). With stirring, to a refluxing solution of 89 g of NaCN in 350 ml of DMF was added in drops 200 g of the ethyl ester of δ-chlorovaleric acid (I) in 2.5 h, after which the mixture was heated for 1 h, filtered, the precipitate was washed with a little DMF and absolute alcohol, the solvent was removed, and the residue was treated with 0.5 liter of water and extracted with ether. The extract was dried over $MgSO_4$, and the solvent was distilled off. Vacuum-distillation of the residue gave 143.4 g (76.2%) of nitrilo ester (II); bp 68-70° (0.45 mm); n_D^{20} 1.4328 [9].

Ethyl Ester of δ-Iodovaleric acid (IV). Ester (IV) was obtained by the reaction of ester (I) with NaI as described in [10]; yield 98.7%; bp 77° (1 mm); n_D^{20} 1.4960.

Diethyl Ester of α-Cyanopimelic Acid (V). Ester (V) was obtained by the condensation of ester (IV) with cyanoacetic ester; yield 30.5%; bp 126-130° (0.35 mm) [11].

δ-Cyanovaleric Acid (IIIa). To a solution of 79 g of nitrilo ester (II) in 80 ml of MeOH at 0-4° was added in drops an equimolar amount of 20% aqueous NaOH solution in 2 h. The mixture was allowed to stand overnight at 20°. Then the MeOH was removed, and the residue was extracted with ether, acidified to pH 3.5, and extracted with $CHCl_3$ (5 × 25 ml). The solvent was distilled off, and the residue was vacuum-distilled to give 53.8 g (83.2%) of acid (IIIa); bp 133° (0.85 mm); n_D^{20} 1.4482 [12].

α-Cyanopimelic Acid (VI). Acid (VI) was obtained by the hydrolysis of diester (V) (2 moles of alkali per mole of diester); yield 64.4%; mp 114.5-115.5°. Found: C 51.74; H 5.83; N 7.62%. $C_8H_{11}O_4N$. Calculated: C 51.88; H 5.99; N 7.56%.

ε-Cyanocaproic Acid (IIIb). A mixture of 109 g of α-cyanopimelic acid (VI) and 1 g of copper bronze was heated at 165-172° for 1 h. At the end of gas evolution the mixture was heated for 10 min at 180-185°. The mixture was cooled and poured into 300 ml of water. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (4 × 75 ml). The combined extracts and organic layer were dried over $MgSO_4$, and then the solvent was removed. Vacuum-distillation gave 47.5 g (57.2%) of acid (IIIb); bp 154° (2 mm) [13].

Acid Chlorides of δ-Cyanovaleric and ε-Cyanocaproic Acids (VIIa, b). The acid chlorides were obtained by treating the acids (IIIa, b) with a 20% excess of $SOCl_2$. Compound (VIIa) was obtained in 83% yield, bp 111-114° (4 mm), and (VIIb) was obtained in 76% yield, bp 122-125° (3.5 mm); n_D^{20} 1.4570.

3-(2-Thienyl)propyl Alcohol. A. To a suspension of 19.6 g of $LiAlH_4$ in 250 ml of THF was added in drops a solution of 40 g of thienylacrylic acid in 80 ml of THF in 1.5 h, and then the mixture was stirred at 20° for 2 h. The reaction mass was decomposed with dilute H_2SO_4 solution, the organic layer was separated, and the aqueous layer was extracted with ether. The extracts and organic layer were dried, and the solvent was removed. Vacuum-distillation gave 20.54 g (55.5%) of 3-(2-thienyl)propyl alcohol.

B. To 16.0 g of $LiAlH_4$ in 150 ml of ether was added 43.4 g of ethyl thienylacrylate [14] in 30 min, after which the mixture was heated for another 1.5 h. After the usual workup we obtained 31.9 g (79.5%) of 3-(2-thienyl)propyl alcohol; bp 96° (1 mm); n_D^{20} 1.5410 [7]. NMR spectrum (CCl_4, δ in ppm from TMS): 1.81 (quintet 2H, J ≈ 7 Hz, CH_2); 2.82 (triplet, 2H, J ≈ 7.5 Hz, Th*CH_2); 3.52 (triplet, 2H, J ≈ 6.5 Hz, CH_2O); 4.31 (singlet, 1H, OH); 6.6-7.0 (multiplet, 3H, Th); cf. different assignment of signals in [7].

3-(2-Thienyl)propyl Ester of δ-Cyanovaleric Acid (VIIIa). To a solution of 23.5 g of the thienylpropanol and 18.4 g of Et_3N in 50 ml of absolute ether at 0° was added in drops a solution of 28.86 g of acid chloride (VIIa) in 30 ml of absolute ether in 3 h. The mixture was stirred for 1 h, filtered, the precipitate was washed with ether, and the solution was washed with saturated $NaHCO_3$ solution, then with water, and dried. The solvent was removed and the residue was vacuum-distilled to give 34.5 g (84.2%) of nitrilo ester (VIIIa); bp 161-162° (0.11 mm). Found: C 62.08; H 6.86; S 12.82%. $C_{13}H_{17}O_2NS$. Calculated: C 62.12; H 6.82; S 12.76%. The 2-(2-thienyl)ethyl ester of ε-cyanocaproic acid (VIIIb) was obtained in a similar manner from acid chloride (VIIb) and 2-(2-thienyl)ethyl alcohol in 86.4% yield; bp 170-171° (0.2 mm). Found: C 62.46; H 6.99; N 5.71%. $C_{13}H_{17}O_2NS$. Calculated: C 62.12; H 6.82; N 5.97%.

3-(2-Thienyl)propyl Ester of Adipamic Acid (IXa). A stream of dry HCl was passed into a mixture of 34.86 g of nitrilo ester (VIIIa), 80 ml of absolute ether, and 2.5 ml of water at 0°. After 2 h the mixture became homogeneous, and it was allowed to stand overnight at 4°. The ether was removed in vacuo at ~20°, and the residue was stirred with saturated $NaHCO_3$ solution for 4 h. The precipitate was filtered, while the aqueous solution was extracted with ethyl acetate (4 × 50 ml). The precipitate was dissolved in ethyl acetate, the solution was combined with the extracts, dried over $MgSO_4$, the solvent was removed, and the precipitate was again dissolved in ethyl acetate and reprecipitated with hexene. We isolated 25.65 g (68.6%) of amido ester (IXa), mp 54.5-55°. Found: C 58.11; H 6.90; S 12.10%. $C_{13}H_{19}O_3NS$. Calculated: C 57.97; H 7.11; S 11.90%. The 2-(2-thienyl)ethyl ester of pimelamic acid (IXb) was obtained in a similar manner; yield 92%; mp 73-75°. Found: C 57.39; H 6.90%. $C_{13}H_{19}O_3NS$. Calculated: C 57.97; H 7.11%.

Mono-3-(2-thienyl)propyl Ester of Adipic Acid (Xa). With stirring, to a solution of 7.39 g of amido ester (IXa) in 20 ml of absolute $CHCl_3$, cooled to 5°, was added in drops a solution of 2.3 g of nitrosyl chloride in 20 ml of $CHCl_3$. The mixture was stirred at 5-10° for 2 h, and then the temperature was raised to 20°. The excess nitrosyl chloride and solvent were removed in vacuo, the residue was dissolved in saturated $NaHCO_3$ solution, extracted with ether, and the aqueous solution was acidified with HCl (1 : 1) to pH 3, and again extracted with ether. The last extracts were dried, the ether was removed, while the residue was chromatographed on a column containing silica gel (I activity), using a 1 : 10 ether—hexane mixture as the eluant. The eluates that contained the pure monoester (Xa) (TLC, 11 : 8 ether—hexane mixture, R_f 0.61) were combined, the solvent was removed, and the residue was dried in a vacuum-desiccator over P_2O_5. The yield of (Xa) was 55.9%; neutralization equivalent: found 267.4; calculated 270.3. The mono-(2-thienyl)ethyl ester of pimelic acid (Xb) was obtained in a similar manner; yield 45.8%; neutralization equivalent: found 276.1; calculated 270.3.

*Th = thienyl.

Ethyl Ester of Adipamic Acid. To a solution of 15 ml of liquid NH_3 in 200 ml of absolute ether at −60° was added 50 g of the acid chloride of the monoethyl ester of adipic acid. The mixture was kept at −33° for 30 min, and then the temperature was raised to ~20°. The solvent was removed, while the residue was treated with benzene in a Soxhlet extractor for 4 h. We isolated 43.81 g (97.5%) of the ethyl ester of adipamic acid; mp 75-76°.

Adipamic Acid. To a solution of 25 g of the ethyl ester of adipamic acid in 200 ml of water at 0° was added in drops a solution of 5.83 g of NaOH in 30 ml of water in 2 h. Then the temperature was raised to ~20°. The solution was extracted with ethyl acetate, and the aqueous solution was acidified to pH 3 and kept in the refrigerator. The precipitate was filtered. We isolated 17.47 g (86.4%) of adipamic acid; mp 160-162°.

Octyl Ester of δ-Cyanovaleric Acid. A mixture of 2.5 g of adipamic acid and 6 ml of $SOCl_2$ was heated, the excess $SOCl_2$ was removed in vacuo, and the residue was dissolved in absolute ether. The obtained solution was added in drops to a mixture of 2.5 g of 1-octanol and 2.77 ml of pyridine in 20 ml of absolute ether. The reaction mass was kept in the refrigerator for 1.5 h and then treated with 50 ml of water. The organic layer was separated, washed in succession with dilute HCl solution, $NaHCO_3$ solution, and water, and dried over $MgSO_4$. The solvent was removed and the residue was vacuum-distilled to give 2.94 g (67%) of the octyl ester of δ-cyanovaleric acid; bp 165-167° (4 mm). Found: C 69.96; H 10.42%. $C_{14}H_{25}O_2N$. Calculated: C 70.24; H 10.52%.

CONCLUSIONS

1. A new method was developed for the synthesis of the half-esters of dicarboxylic acids.

2. Some members of the acid esters of acidophobic alcohols were synthesized, and specifically the mono-3-(2-thienyl)propyl ester of adipic acid and the mono-2-(2-thienyl)ethyl ester of pimelic acid.

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