NEW METHOD FOR THE SYNTHESIS OF MACROCYCLIC COMPOUNDS

XII.* STUDY OF THE INTRAMOLECULAR ACYLATION OF ω-(5-METHYL-2-THIENYL)ALKANOYL CHLORIDES

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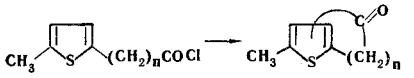
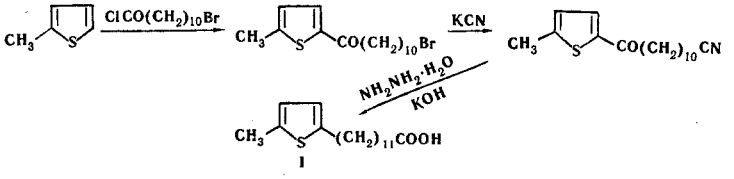
A mixture of isomers corresponding to closing of the ring at the 3 and 4 positions of the thiophene ring is formed during intramolecular acylation of 12-(5-methyl-2-thienyl)-lauryl chloride in a homogeneous medium; the reaction proceeds primarily to favor the formation of the isomer with the larger ring (80%). A method for the synthesis of macrocyclic α-alkylcycloalkanones by reductive desulfurization of the corresponding bicyclic ketones, which contain thiophene rings, was developed.

We have previously examined intramolecular acylation as a method for the synthesis of compounds of various types based on thiophene (see, e.g., [1, 2]). It was of interest to investigate a similar process in a number of thiophene homologs since, in this case, alkyl-substituted cycloketones should be formed, and alkyl-substituted cycloaliphatic ketones with a large number of links might be obtained by the reductive desulfurization of them. The latter compounds are interesting because they include muscone (β-methylcyclopentadecanone) – a natural compound with a most intense odor of musk. One of the representatives of this class, γ-isopropylcyclotetradecanone, was synthesized by us [3] by isopropylation of (10)-α-cyclothienone with subsequent reductive desulfurization. At the present time, in connection with the development of methods for obtaining α- and β-methylthiophenes from the corresponding diene hydrocarbons and hydrogen sulfide [4, 5], compounds of this type are becoming completely accessible for the realization of a simpler scheme for obtaining alkylcyclothienones starting, e.g., from α-methylthiophene:



In itself, the presence of alkyl substituents in the 2 and 5 positions of the thiophene ring in this case makes electrophilic attack at the 3 and 4 positions almost equally probable during intramolecular acylation, and the prevailing direction of the process should apparently be determined only by steric factors. As an example, we used 12-(5-methyl-2-thienyl)lauric acid (I), which was synthesized via a previously developed method [6] with small changes:



I

*See Izv. Akad. Nauk SSSR, Ser. Khim., 2228 (1970) for Communication XI.

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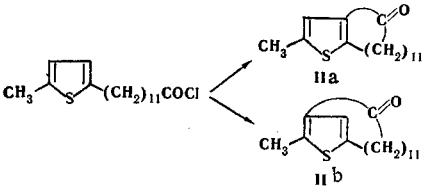
In view of the fact that several difficulties (which will be reported separately) were encountered during cyclization in the presence of silica gel, we selected a method involving cyclization in a homogeneous medium using excess aluminum chloride etherate [7]. It turned out that a mixture of two compounds is actually formed in the cases investigated. From elementary analysis and determination of the molecular weight by precision ebullioscopy, the product obtained corresponded to the structure of a macrocyclic compound but, according to thin-layer chromatography, contained two substances with quite different R_f values, which made it possible to hope that they could be successfully separated by preparative chromatography. In fact, two isomeric ketones were isolated by chromatographic separation of the cyclization product of the acid chloride of I on a column filled with activity II aluminum oxide. We subsequently used their p-nitrophenylhydrazones to separate these compounds since the losses during chromatography of the ketones themselves are extremely significant. One should note here that the ketones obtained form two series of p-nitrophenylhydrazones, apparently the syn and anti configurations. Two spots, corresponding to mixtures of the red and yellow isomers, are observed during thin-layer chromatography of the mixture of p-nitrophenylhydrazones. The pairs of p-nitrophenylhydrazones isolated from the corresponding zones can be readily separated into individual compounds as a consequence of the significant difference in their solubilities in hexane. It turned out that the p-nitrophenylhydrazones of one of the ketones are labile and are readily converted from one modification to the other (as shown by thin-layer chromatography). The p-nitrophenylhydrazones of the other ketone are stable compounds; they do not change on repeated chromatography and give a melting-point depression when they are mixed. A similar phenomenon was previously observed for the p-nitrophenylhydrazones of benzosuberone [8]. Individual ketones were isolated from their p-nitrophenylhydrazones by the method in [9]. On the basis of the results obtained, it can be assumed that two isomeric cyclothienones are formed during the cyclization of the acid chloride of I.



Compound IIa, α'-methyl[12,α,β]cyclothien-1-one, is a crystalline substance, while IIb, α'-methyl-[12,α,β']cyclo-thien-1-one, is an uncrystallized heavy oil. * Attempts to separate these compounds with gas-liquid chromatography were unsuccessful. The structures that we assigned to IIa and IIb are confirmed by their PMR spectra.

The PMR spectrum of crystalline isomer IIa (Fig. 1) contains a quadruplet at 6.79 ppm (J = 1.2 Hz), which should be assigned to the proton of the thiophene ring, a doublet at 2.35 ppm (J = 1.2 Hz) from the protons of the CH_3 group, a triplet at 3.07 ppm, a multiplet at 2.55 ppm, and a multiplet from the methylene protons from 0.45-1.88 ppm. The relative integral intensities are, respectively, 1: 3: 2: 2: 18. The spin–spin coupling constant of 1.2 Hz between the CH_3 group and the proton of the thiophene ring indicates that the observed constant is J_{CH_3-4H}, i.e., that the ring is closed precisely at the 3 position of the thiophene ring. The triplet at 3.07 ppm should be assigned to the protons of the CH_2 group linked to the carbonyl group, while the multiplet at 2.55 ppm should be ascribed to the protons of the CH_2 group linked to the double bond, in which the protons are apparently nonequivalent. This assignment was made on the basis of an analysis of the spectra of ethyl-substituted thiophenes [11] in which the signal from the protons of the CH_2 group has a shift of no more than 2.70 ppm. The strong-field multiplet with an intensity of 18 is assigned to the protons of the nine CH_2 groups of the polymethylene chain.

The spectrum of liquid isomer IIb (Fig. 2) contains a broad triplet at 6.82 ppm, a broad singlet at 2.55 ppm from the protons of the CH_3 group, which overlap with the multiplet, and a strong-field multiplet with an integral intensity ratio of 1 : 7 : 18, respectively. The width of the signal from the CH_3 protons indicates that they interact with the proton in the 3 position with $J_{CH_3-3H} \leq 0.6$ Hz; however, the triplet

*See [10] for the nomenclature of macrocyclic compounds including a thiophene ring. This case is not completely encompassed by the nomenclature principle expounded there. We therefore consider it useful to add to it the following: if a substituent is attached to a carbon atom of the thiophene ring which does not enter into the numbering of the carbon skeleton of the macrocycle, its position is then designated by a Greek letter corresponding to the position of the thiophene ring to which it is attached.

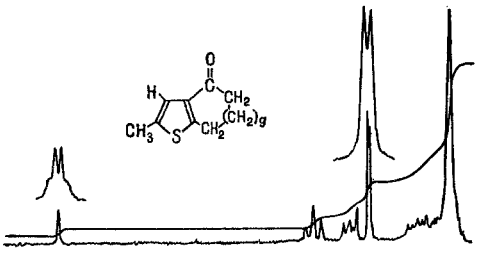


Fig. 1. PMR spectrum of α'-methyl[12,α,β]-cyclothien-1-one (IIa).

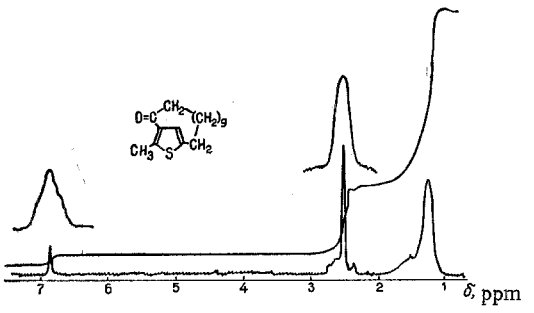
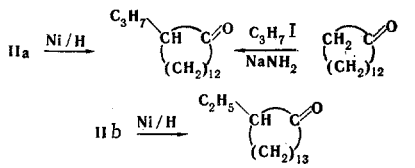


Fig. 2. PMR spectrum of α'-methyl[12,α,β]-cyclothien-1-one (IIb).

structure of the signal at 6.88 ppm indicates that there is also an allyl spin–spin coupling constant for interaction of the proton in the 3 position of the thiophene ring with the protons of the CH_2 group attached to the 2 position of the thiophene ring. The literature data on the PMR spectra of a number of thiophene derivatives [11, 12] indicate that the allyl constants $J_{2CH_3,3H}$, $J_{3CH_3,2H}$, $J_{4CH_3,5H}$, and $J_{5CH_3,4H}$ are no less than 0.9 Hz (0.9-1.25) and that the majority of them are greater than 1 Hz. In addition, the spin–spin coupling constants through three C–C bonds, i.e., $J_{2CH_3,4H}$, $J_{3CH_3,5H}$, $J_{4CH_3,2H}$, and $J_{5CH_3,3H}$, are no more than 0.5 Hz (0.2-0.5 Hz). Thus, from an analysis of the literature data and the spectra of the investigated isomers one can conclude that the crystalline isomer has the IIa structure and the liquid isomer has the IIb structure. A peculiarity of the PMR spectra of isomers IIa and IIb is the substantial difference in the chemical shifts of the protons of the methylene groups at the ends of the polymethylene chain in both isomers. This is especially true for the signal (triplet) from the protons of the CH_2 group adjacent to the carbonyl group: in the spectrum of isomer IIb this signal is shifted by 0.5 ppm to stronger field as compared with isomer IIa. As a result, the signals from the protons of the indicated CH_2 groups and the signal from the protons of the CH_3 group are superimposed in the spectrum of isomer IIb. This change in chemical shifts is probably associated with a different orientation of the carbonyl group in the isomers.

The results obtained were used for the quantitative analysis of a mixture of isomers IIa and IIb. The analysis was based on a determination of the areas of the proton signals of the thiophene ring, which differ by 0.09 ppm. It was found that the mixture contains about 20% of ketone IIa, which has a smaller ring.

Additional confirmation of the structure of ketones IIa and IIb was obtained during an investigation of their desulfurization. Reductive desulfurization of ketones IIa and IIb proceeds without complications under the conditions previously used by us and leads to the formation of α-propylcyclotetradecanone (from IIa) (which has the odor of musk), and α-ethylcyclopentadecanone (from IIb). The structure of the α-propyltetradecanone obtained by desulfurization of ketone IIa was proved by the synthesis of this compound by an independent route – direct alkylation of cyclotetradecanone with propyl iodide in the presence of sodium amide [13].



This preparation did not depress the melting point of a sample obtained by desulfurization of ketone IIa. Their semicarbazones were also identical. The PMR spectrum of the synthesized α-propylcyclotetradecanone confirms the absence of an oxygen-alkylated product.

EXPERIMENTAL

The PMR spectra were obtained with Varian PC-60 and DA-60 spectrometers with an operating frequency of 60 MHz. Hexamethyldisiloxane was used as the internal standard. The preparations were dissolved in CCl_4, and the solutions were degassed in vacuo. Gas-liquid chromatography was carried out with an LKhM-7A chromatograph.

ω-Bromoundecanoyl Chloride. A mixture of 10 g (0.038 mole) of ω-bromoundecanoic acid and 13 ml [21.5 g (0.18 mole)] of $SOCl_2$ was stirred for 1.5 h at room temperature and then refluxed for 1 h. Distillation in vacuo yielded 8.1 g (76%) of acid chloride with bp 116° (0.27 mm). Found %: C 47.1; H 7.1. $C_{11}H_{20}BrClO_2$. Calculated %: C 46.6; H 7.1. The methyl ester had bp 106° (0.04 mm) and n_D^{20} 1.4650. Found %: C 51.8; H 8.2; Br 28.3. $C_{12}H_{23}BrO_2$. Calculated %: C 51.6; H 8.3; Br 28.6.

5-Methyl-2-thienyl 10-Bromodecyl Ketone. Stannic chloride [59.5 g (0.228 mole)] was added dropwise at 5° to a solution of 22.4 g (0.228 mole) of 2-methylthiophene and 64.7 g (0.228 mole) of ω-bromodecanoyl chloride in 220 ml of absolute benzene, after which the mixture was stirred for 1 h at room temperature. The reaction mixture was then treated at 10° with 7% hydrochloric acid. The benzene layer was washed with water and $NaHCO_3$ solution, the solvent was removed, and the residue was recrystallized from hexane to give 67.7 g (86%) of ketone with mp 60-61°. Found %: C 56.0; H 7.3; S 9.3; Br 23.3. $C_{16}H_{25}BrOS$. Calculated %: C 55.6; H 7.3; S 9.3; Br 23.1.

5-Methyl-2-thienyl 10-Cyanodecyl Ketone. Potassium cyanide [16.5 g (0.24 mole)] (based on 100% purity) was added to a mixture of 55 g (0.16 mole) of 5-methyl-2-thienyl 10-bromodecyl ketone and 2.75 g of KI in 600 ml of 90% alcohol and the mixture was refluxed for 6 h, after which another 8.3 g (0.13 mole) of KCN was added, and the mixture was refluxed for another 14 h. The solvent was almost completely removed, and the residue was extracted with 200 ml of benzene and 200 ml of water. The benzene solution was washed with water, dried with $MgSO_4$, and the solvent was removed. After recrystallization from alcohol, 32.5 g (70%) of nitrile with mp 70.5-72° was obtained. Found %: C 70.1; H 8.5; S 11.0; N 4.5. $C_{17}H_{25}NOS$. Calculated %: C 70.1; H 8.6; S 11.0; N 4.8.

The yield was somewhat poorer when the reaction was carried out in methanol; in 80% methyl cellosolve the yield of nitrile fell sharply, and a considerable amount (up to 40%) of 5-methyl-2-thienyl 10-hydroxydecyl ketone with mp 56-57° (from benzene–hexane) was formed. Found %: C 68.0; H 9.3; S 11.1. $C_{16}H_{26}O_2S$. Calculated %: C 68.0; H 9.2; S 11.3.

12-(5-Methyl-2-thienyl)lauric Acid. Powdered KOH [31 g (0.55 mole)] was added to a solution of 45 g (0.15 mole) of 5-methyl-2-thienyl 10-cyanodecyl ketone and 30 ml (0.60 mole) of hydrazine hydrate in 275 ml of diethylene glycol, and the resulting mixture was heated for 3 h at 136°. Some of the water and excess hydrazine hydrate were distilled off up to a mass temperature of 215°, and the mixture was heated at this temperature for 5 h. The mixture was cooled, diluted with 2 volumes of water, acidified, and extracted with ether; the extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was recrystallized from aqueous acetone to give 35 g (76%) of acid with mp 69-71°. Found %: C 69.0; H 9.3; S 11.0. $C_{17}H_{28}O_2S$. Calculated %: C 68.8; H 9.5; S 10.8. The ethyl ester had bp 182-183° (0.27 mm) and n_D^{20} 1.4882. Found %: C 70.3; H 9.7; S 9.7. $C_{19}H_{32}O_2S$. Calculated %: C 70.3; H 9.9; S 9.9. The anilide had mp 91-93°. Found %: N 3.8. $C_{23}H_{33}NOS$. Calculated %: N 3.8.

Cyclization of 12-(5-Methyl-2-thienyl)lauric Acid. A solution of 5 g (0.017 mole) of 12-(5-methyl-2-thienyl)dodecanoic acid in 25 ml of absolute ether was treated with excess (5 ml) thionyl chloride. After stirring for 1 h at room temperature and refluxing for another 1 h, the solvent and excess thionyl chloride were distilled off without access to air moisture. The residue was dissolved in 40 ml of anhydrous chloroform and added by means of an injector-dosing apparatus at 3.5 ml/h through a high-dilution nozzle [10] to a stirred, vigorously boiling mixture of 90 g of aluminum chloride etherate and 520 ml of anhydrous chloroform. Addition was complete in 13 h, after which the mixture was refluxed for another 2 h, cooled to below 15°, and 300 ml of dilute (1 : 10) hydrochloric acid was gradually added to it. The chloroform solution was washed with water, evaporated, and the residue was treated with hexane to remove high-molecular-weight products. The hexane solution was treated with 25 ml of a saturated $Ba(OH)_2$ solution to remove acidic substances, and the hexane was evaporated. The residue was treated with alcohol (three 25-ml aliquots), and the insoluble compounds were removed. The solution was evaporated, and the product obtained was sublimed under high vacuum (10^{-3}–10^{-5} mm) at a bath temperature of 60-80° to give 55% of a mixture of ketones IIa and IIb containing 18-23% of IIa (PMR data). This mixture (2.72 g) was separated by chromatography on 112 g of activity II aluminum oxide (column height 20 cm, eluent 4% ether in hexane); 0.2 g of IIa, 0.32 g of a mixture of IIa and IIb, and 0.86 g of IIb were obtained; the losses from irreversible adsorption were 50%. Thin-layer chromatography (TLC) on Al_2O_3 (activity III, benzene eluent) showed R_f 0.64 for IIa and R_f 0.52 for IIb. Treatment of the mixture of IIa and IIb with p-nitrophenylhydrazine in alcohol converted it to a mixture of p-nitrophenylhydrazones, which was subjected to chromatographic separation on activity II Al_2O_3 (benzene eluent). The eluent fractions, which contained the isomeric p-nitrophenyl-

hydrazones of IIa and IIb of yellow and red color, were evaporated separately. The residues were treated with hexane. The hexane-insoluble p-nitrophenylhydrazone of IIb was recrystallized from alcohol. The hexane solutions containing the p-nitrophenylhydrazone of IIa, somewhat contaminated with the p-nitrophenylhydrazone of IIb, were treated repeatedly with hexane. The p-nitrophenylhydrazone of IIb (yellow isomer) had mp 178-179° and R_f 0.47 (TLC on activity III Al_2O_3, benzene eluent). Found %: C 66.4; H 7.4; S 8.2; N 10.0. $C_{23}H_{31}N_3O_2S$. Calculated %: C 66.8; H 7.6; S 7.7; N 10.2. The red isomer had mp 176-178.5° and R_f 0.20 (TLC). Found %: C 66.3; H 7.5; S 7.8; N 10.4.

The p-nitrophenylhydrazone of IIa was an uncrystallizable, vitreous mass with a softening point of 50-70° and consisted of two isomers which interconvert during chromatography on Al_2O_3. Found %: C 66.7; H 7.6; S 7.3. $C_{23}H_{31}N_3O_2S$. Calculated %: C 66.8; H 7.6; S 7.7. Compound IIb was isolated from the p-nitrophenylhydrazones by the method described in [9]. Copper carbonate (10 g) was added gradually to 4 g of the p-nitrophenylhydrazone in 20 ml of 80% formic acid, another 80 ml of formic acid was added, and the mixture was refluxed for 4 h. After cooling, the mixture was filtered and the residue was washed with alcohol and benzene. The filtrate was evaporated in vacuo, and the residue was dissolved in hexane. The solution was washed with a $NaHCO_3$ solution, dilute (1:10) hydrochloric acid, and water. The solution was dried over $MgSO_4$, evaporated, and passed through a column with a fivefold quantity of Al_2O_3. The product was sublimed at 10^{-3}-10^{-5} mm and a bath temperature of 60-80°. The yield of pure IIb was almost quantitative. Ketone IIb was a viscous liquid with n_D^{20} 1.5468. Found %: C 73.6; H 9.2; S 11.1. $C_{17}H_{26}OS$. Calculated %: C 73.3; H 9.4; S 11.5. Mol. wt. (ebullioscopic, in benzene): found 283.9; calculated 282.4.

Compound IIa was similarly isolated and was then additionally purified by chromatography on Al_2O_3. Ketone IIa had mp 48°. Found %: C 73.2; H 9.4; S 11.2. $C_{17}H_{26}OS$. Calculated %: C 73.3; H 9.4; S 11.5. Mol. wt. (ebullioscopic, in benzene): found 278.0; calculated 282.4.

α-Propylcyclotetradecanone. Compound IIa (0.37 g) was refluxed in 25 ml of alcohol and 7 ml of acetone with 12 g of Raney nickel until the mixture gave a negative test for sulfur (31 h). The nickel was filtered and thoroughly washed with alcohol, and the washes were combined with the filtrate and evaporated to give α-propylcyclotetradecanone with mp 29-32°. Found %: C 81.1; H 12.7. $C_{17}H_{32}O$. Calculated %: C 80.8; H 12.8. The semicarbazone had mp 176-177° (from alcohol). Mixed samples of the ketones and their semicarbazones with samples obtained by independent paths (see below) did not give melting-point depressions.

α-Ethylcyclopentadecanone. This was obtained by reductive desulfurization of IIb in the same way as was used to obtain α-propylcyclotetradecanone; sublimation at 60-80° and 10^{-3}-10^{-5} mm gave a viscous liquid with n_D^{20} 1.4784 and d_4^{20} 0.9165. Found %: C 80.9; H 12.7; MR_D 78.03. $C_{17}H_{32}O$. Calculated %: C 80.8; H 12.8; MR_D 78.52. The semicarbazone had mp 135-140° (from alcohol). Found %: C 69.9; H 11.2. $C_{18}H_{35}N_3O$. Calculated %: C 70.00; H 11.4.

Alkylation of Cyclotetradecanone. Sodium [0.33 g (0.0122 g-atom)] was dissolved in anhydrous liquid ammonia in the presence of catalytic amounts of $Fe(NO_3)_3$; 2 g (0.0095 mole) of cyclotetradecanone and 30 ml of absolute ether were added to the resulting mixture. The mixture was refluxed for 3 h, 16 g of $n\text{-}C_3H_7I$ was added, and the mixture was refluxed for 8 h. The ether was removed, and the mixture was refluxed for another 18 h (mass temperature 100°) and diluted with water. After the usual treatment and hydrolysis in 10 ml of dioxane and 15 ml of 2% H_2SO_4, 1.05 g (44%) of α-propylcyclotetradecanone with mp 30.5-31.5° (from hexane) was obtained. Found %: C 80.8; H 12.8. $C_{17}H_{32}O$. Calculated %: C 80.8; H 12.8. The semicarbazone had mp 174-175°. Found %: C 69.9; H 11.5. $C_{18}H_{32}N_3O$. Calculated %: C 69.9; H 11.4.

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