A NEW METHOD FOR THE SYNTHESIS OF ESTERS OF β-THIOPHENECARBOXYLIC ACIDS

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A method for the synthesis of esters of β-thiophenecarboxylic acids and diethyl 3-methyl-2,4-thiophenedicarboxylate by the deamination of derivatives of 2-amino-3-ethoxycarbonylthiophene has been proposed. Ethyl tetrahydrothionaphthene-3-carboxylate has been converted by dehydrogenation on heating with sulfur into ethyl thionaphthene-3-carboxylic acid. The corresponding acids have been obtained by the hydrolysis of the esters. A number of dialkylaminoalkyl esters has been obtained from β-thiophenecarboxylic acids and 3-methyl-2,4-thiophenedicarboxylic acid via the acid chlorides.

β-Thiophenecarboxylic acids have been studied comparatively little [1]. They have been obtained by the oxidation of 3-alkylthiophenes [2, 3] and 3-thiophenealdehydes [4, 5], by the action of cyanides on 3-halogen derivatives of thiophene with the subsequent saponofication of the nitriles obtained [6, 7], and also via organomagnesium compounds of thiophene [8–12]. The low yields of β-thiophenecarboxylic acids in some cases [2, 3] and the difficulty in obtaining the initial thiophenes [1] limit the use of these methods.

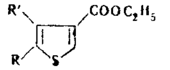
We have proposed a method for obtaining esters of β-thiophenecarboxylic and 2,4-thiophenedicarboxylic acids [13] by the deamination of derivatives of 2-amino-3-ethoxycarbonylthiophene which have recently become widely available [14–19]. The diazo compounds of 2-amino-3-ethoxycarbonylthiophenes are relatively unstable. When they are heated in alcohol with catalytic amounts of copper acetate, the elimination of the amino group takes place readily with the formation of esters of the corresponding acids. When the diazo compounds were decomposed in the presence of cuprous chloride by the Sandmeyer reaction, again only the deamination of the 2-amino-3-ethoxycarbonylthiophenes was found. Attempts to obtain thiophene analogs of salicylic acid by replacing the amino group in derivatives of 2-amino-3-ethoxycarbonylthiophene by a hydroxy group under the conditions described for anthranilic acid [20] proved unsuccessful. In this case, again, only the elimination of the amino group took place. Derivatives of 2-amino-3-ethoxycarbonylthiophene with position 5 free from substituents form nitroso compounds under diazotization conditions.

A number of esters of β-thiophenecarboxylic acids (III–VI) and diethyl 3-methyl-2,4-thiophenedicarboxylate (VII) have been obtained with yields of 25–60%.

Ethyl tetrahydrothionaphthene-3-carboxylate (VI) has been converted by dehydrogenation on heating with sulfur [21, 22] into ethyl dihydrothionaphthene-3-carboxylate (IX) and on further dehydrogenation into ethyl thionaphthene-3-carboxylate (X). Hydrolysis of the esters with ethanolic alkali has given the corresponding acids (XI–XVIII). The esters of 2-methyl-4-thiophenecarboxylic acid (III) and thionaphthene-3-carboxylic acid (X) have yielded the acids (XI and XVIII) which have been synthesized previously by other methods [8, 23, 24]. Consequently, the substances formed by the condensation of carbonyl compounds with cyanoacetic ester and sulfur are actually derivatives of 2-amino-3-ethoxycarbonylthiophene.

Table 1

Esters of Mono- and Dicarboxylic Acids of Substituted Thiophenes



Compound	R	R′	Bp, °C (pressure, mm)	n_D^{20}	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	S	C	H	S	
III	CH_3	H	74–75(2)	1.5186	$C_8H_{10}O_2S$	56.19 56.60	5.91 5.95	18.64 19.11	56.44	5.92	18.84	45.1
IV	C_2H_5	H	79–80(1)	1.5120	$C_9H_{12}O_2S$	58.17 58.32	6.43 6.20	17.07 17.15	58.66	6.56	17.40	42
V	CH_3	CH_3	100–100,5(4)	1.5209	$C_9H_{12}O_2S$	58.66 59.00	6.56 6.44	17.08 17.36	58.66	6.56	17.40	58.1; 31*
VI	R,R′ = $(CH_2)_4$		103–105(1)	1.5502	$C_{11}H_{14}O_2S$	62.87 62.90	6.44 6.35	15.32 15.36	62.82	6.71	15.55	50.9; 52*
VII	$COOC_2H_5$	CH_3	**	—	$C_{11}H_{14}O_4S$	54.75 54.93	5.77 5.93	12.94 13.11	54.53	5.82	13.23	60.6
VIII	$CH_2CH_2OCOCH_3$	CH_3	147–150(3)	1.5118	$C_{12}H_{16}O_4S$	55.82 56.20	5.90 6.10	12.24 12.43	56.23	6.29	12.51	24.5

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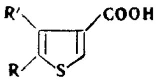
*Under the conditions of the Sandmeyer reaction.

**Mp 35-35.5° C (from methanol).

Table 2

Mono-and Dicarboxylic Acids of Substituted Thiophenes



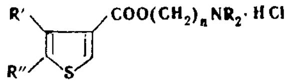
Compound	R	R'	T Mp, °C	Empirical formula	Found, %		Calculated, % %		Yield, %
					C	H	C	H	
XI	CH_3	H	130—131*	$C_6H_6O_2S$	50.60 50.70	4.35 4.16	50.68	4.25	94
XII	C_2H_5	H	66—67	$C_7H_8O_2S$	53.85 54.18	5.07 5.00	53.82	5.16	87.5
XIII	CH_3	CH_3	149—150	$C_7H_8O_2S$	53.75 53.94	5.41 5.40	53.82	5.16	89.3
XIV	R, R' = $(CH_2)_3$		166—167	$C_8H_8O_2S$	57.16 57.20	4.80 4.66	57.12	4.79	7.1**
XV	R, R' = $(CH_2)_4$		181—182	$C_9H_{10}O_2S$	59.38 59.47	5.31 5.57	59.31	5.53	92
XVI	COOH	CH_3	Above 250 (decomp)	$C_7H_6O_4S$	45.35 45.50	3.53 3.50	45.15	3.25	89

*According to the literature [8], mp 131-132°C.

**Yield shown for 2-amino-3-ethoxycarbonylcyclopenta[b]thiophene.

Table 3

Hydrochlorides of Dialkylaminoalkyl Esters of Mono- and Dicarboxylic Acids of Substituted Thiophenes



Compound	n	R	R'	R''	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
							C	H	N	C	H	N	
XIX	3	CH_3	CH_3	CH_3	168—169	$C_{12}H_{19}NO_2S \cdot HCl$	51.92 52.03	7.05 7.40	5.23 5.30	51.87	7.25	5.04	90.2
XX	2	C_2H_5	R',R'' = $(CH_2)_4$		172—174	$C_{15}H_{23}NO_2S \cdot HCl$	56.20 56.60	7.43 7.36	4.62 4.72	56.67	7.61	4.41	86
XXI	3	CH_3	R',R'' = $(CH_2)_4$		192—194	$C_{14}H_{21}NO_2S \cdot HCl$	55.53 55.73	7.20 7.13	4.42 4.60	55.33	7.30	4.61	92.3
XXII	2	C_2H_5	CH_3	$COO(CH_2)_2N(C_2H_5)_2 \cdot HCl$	208—209	$C_{19}H_{32}N_2O_4S \cdot 2HCl$	49.57 49.63	7.39 7.41	6.20	50.09	7.08	6.15	95
XXIII	3	CH_3	CH_3	$COO(CH_2)_3N(CH_3)_2 \cdot HCl$	214—216	$C_{17}H_{28}N_2O_4S \cdot 2HCl$	47.10 47.52	6.93 6.95	6.65 6.67	47.54	7.04	6.52	94

With the object of biological investigations, the 3-thiophenecarboxylic acids and 3-methyl-2, 4-thiophenedicarboxylic acid were converted via their chlorides into the dialkylaminoalkyl esters XIX–XXII. In a comparison of the IR spectra of 2-amino-3-ethoxycarbonylthiophenes and derivatives of β-thiophenecarboxylic acid, the bands characteristic for the NH group were found to have disappeared and a band connected with the vibrations of the α-CH group at 3120 cm^{-1} to have appeared [25, 26]. At the same time the frequency of the carbonyl absorption had increased by 60 cm^{-1} (from 1660 to 1720 cm^{-1}). The strongest of the absorption bands of thiophene had shifted from 785 to 740 cm^{-1}. The IR spectra of the dialkylaminoalkyl esters of the mono- and dicarboxylic acids of thiophene had a broad absorption band in the 2500–2600 cm^{-1} region.

In the UV spectra, on passing from 2-amino-3-ethoxycarbonylthiophenes to the esters of the thiophenecarboxylic acids there was a displacement of the absorption bands characteristic for the thiophene ring [1, 15, 17–19] in the short-wave direction. In place of the absorption bands with λ_{max} 230 nm (log ε 4.40–4.48) and λ_{max} 308 nm (log ε 3.70–3.98), bands with λ_{max} 205–210 nm (log ε 4.19) and λ_{max} in the 245 nm region with a somewhat lower intensity appeared.

EXPERIMENTAL

2-Amino-3-ethoxycarbonyl-5-methylthiophene (I). Ten milliliters of diethylamine was added to 26.3 g (0.45 mole) of propionaldehyde, 50.8 g (0.45 mole) of cyanoacetic ester, and 11.2 g (0.35 g-atom) of finely ground sulfur in 100 ml of ethanol, and the mixture was boiled in the water bath for 1 hr with stirring. The ethanol was distilled off and the substance was extracted with petroleum ether. The yield of I was 40 g (47.6%), mp 48°–48.5° C (from petroleum ether). According to the literature [19], mp 46° C.

2-Amino-3-ethoxycarbonyl-5-ethylthiophene (II). The experiment was carried out with 18 g (0.25 mole) of butyraldehyde, 28.2 g (0.25 mole) of cyanoacetic ester, 8 g (0.25 g-atom) of finely ground sulfur, and 6 ml of diethylamine in 50 ml of ethanol. The conditions were those of the preceding experiment. The reaction solution was cooled and the crystals were filtered off and washed with 60% methanol. The yield of II was 32.5 g (65.3%), mp 73°–73.5° C (from 60% methanol). According to the literature [19], mp 73° C.

Deamination of derivatives of 2-amino-3-ethoxycarbonylthiophene. 75 ml of concentrated hydrochloric acid was added to 0.1 mole of a 2-amino-3-ethoxycarbonylthiophene derivative in 90 ml of dioxane. With vigorous stirring and external cooling, a saturated aqueous solution of 13.8 g (0.2 mole) of sodium nitrite was added to the solution cooled to −10° C. The diazonium solution was left at −7° C for 20 min. Then it was added to a solution of 0.38 g of copper acetate in 200 ml of ethanol and the reaction mixture was kept at 70° C for 30 min, after which it was cooled and diluted with three volumes of water. The substance produced was extracted with ether. The solvent was evaporated off. The residue was distilled in vacuum. Data on the esters of β-thiophenecarboxylic acid (III–VI) and of 3-methyl-2, 4-thiophenedicarboxylic acid (VII) are given in Table 1.

Ethyl 2-ω-acetoxyethyl-3-methyl-4-thiophenecarboxylate (VIII). The diazotization of 11.2 g (0.04 mole) of 5-ω-acetoxyethyl-2-amino-3-ethoxycarbonyl-4-methylthiophene was carried out under the conditions of the preceding experiment. The diazonium solution was mixed with a solution of 0.12 g of copper acetate in 40 ml of ethanol and was kept at 70° C for 30 min. Then it was cooled and diluted with three volumes of water, and the substance was extracted with ether. The solvent was distilled off and the residue was boiled with 15 ml of acetic anhydride for 4 hr. The excess of anhydride was driven off and the VIII was distilled in vacuum. Data concerning VIII are given in Table 1.

Deamination of 2-amino-3-ethoxycarbonyl-4, 5-dimethylthiophene and 2-amino-3-ethoxycarbonyltetrahydrothionaphthene under the conditions of the Sandmeyer reaction. The experiment was carried out with 0.1 mole of substituted 2-amino-3-ethoxycarbonylthiophene and 8.3 g (0.12 mole) of sodium nitrite. The diazotization was carried out under the conditions of the preceding experiment. With vigorous stirring, the diazonium solution was added to a hot aqueous solution of 14 g of cuprous chloride and was kept in the boiling water bath for 1 hr. The reaction mixture was cooled, the substance was extracted with ether, the solvent was evaporated off, and the residue was distilled in vacuum. Data on V and VI are given in Table 1.

Ethyl dihydrothionaphthene-3-carboxylate (IX). A mixture of 11 g (0.053 mole) of VI and 3.2 g (0.106 g-atom) of finely ground sulfur was heated at 200°–210° C for 6 hr. The substance was distilled in vacuum. The yield of IX was 6.5 g (59.6%), bp 114°–115° C (1 mm); n_D^{20} 1.5763. Found, %: C 63.87; 63.95; H 5.63; 5.48; S 15.22; 15.48. Calculated for $C_{11}H_{12}O_2S$, %: C 63.46; H 5.81; S 15.40%.

Ethyl thionaphthene-3-carboxylate (X). A mixture of 6.5 g (0.031 mole) of IX and 1.3 g (0.04 g-atom) of finely ground sulfur was heated at 235°–245° C for 4 hr. The substance was distilled in vacuum. The yield of X was 4.5 g (70.3%), bp 118°–119° C (1 mm); n_D^{20} 1.6009. Found, %: C 63.80; 64.03; H 4.85; 4.82; S 15.38; 15.62. Calculated for $C_{11}H_{10}O_2S$, %: C 64.12; H 4.89; S 15.56.

Production of carboxylic (XI, XIII, XV) and dicarboxylic (XVI) acids of thiophene derivatives. A mixture of 0.015 mole of thiophenecarboxylic acid ester and a solution of 1.2 g (0.03 mole) of caustic soda in 15 ml of ethanol was boiled for 30 min. The reaction solution was diluted with three volumes of water and acidified with hydrochloric acid to Congo Red. The acid was filtered off, washed with water, and recrystallized from methanol. Data on the acids are given in Table 2.

Dihydrothionaphthene-3-carboxylic acid (XVII). Five grams (0.024 mole) of IX was hydrolyzed under the conditions of the preceding experiment. The yield of XVII was 3.6 g (83.7%), mp 152°–153° C (from methanol). Found, %: C 59.95; 60.19; H 4.50; 4.40. Calculated for $C_9H_8O_2S$, %: C 59.98; H 4.47.

Thionaphthene-3-carboxylic acid (XVIII). The hydrolysis of 2.2 g (0.01 mole) of X was carried out under the conditions of the preceding experiment. The yield of XVIII was 1.6 g (84.2%), mp 175°–176° C (from methanol). According to the literature [23, 24], mp 174°–175° C. Found, %: C 60.80; 61.03; H 3.06; 3.33. Calculated for $C_9H_6O_2S$, %: C 60.65; H 3.39. Amide, mp 197°–198° C (from methanol). According to the literature [24], mp 197°–198° C. Anilide, mp 171°–172° C (from benzene). According to the literature [24], mp 172°–173° C.

Cyclopenta[b]thiophene-4-carboxylic acid (XIV). Ten grams (0.05 mole) of 2-amino-3-ethoxycarbonylcyclopenta[b]thiophene was diazotized under the conditions described above. The diazonium solution was added to a solution of 0.15 g of copper acetate in 50 ml of ethanol. After the evolution of nitrogen had ceased, the reaction mixture was heated at 70° C for 30 min, cooled, and diluted with three volumes of water, and the substance was extracted with ether. The solvent was driven off and the residue was distilled in vacuum at 135°–140° C (5 mm). 1.2 g (0.006 mole) of the ester obtained was heated with ethanolic alkali (0.5 g of caustic soda in 7 ml of ethanol) for 30 min. Data on the acid XIV are given in Table 2.

Dialkylaminoalkyl esters of β-thiophenecarboxylic and 3-methyl-2, 4-thiophenedicarboxylic acids. A mixture of 0.02 mole of the thiophenecarboxylic acid and 12 ml (0.16 mole) of thionyl chloride was boiled for 45 min (or, in the case of 3-methyl-2, 4-thiophenedicarboxylic acid, 12 hr). The excess of thionyl chloride was distilled off in vacuum. The acid chloride formed was dissolved in 10 ml of benzene. The resulting solution was treated with 0.02 mole of dialkylaminoalkanol and the reaction solution was boiled in the water bath for 1 hr and was then cooled. The precipitate of dialkylaminoalkyl ester hydrochloride was separated off and recrystallized from acetone (XIX, XX) or methanol (XXI–XXIII). Data on the dialkylaminoalkyl esters XIX–XXIII are given in Table 3.

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