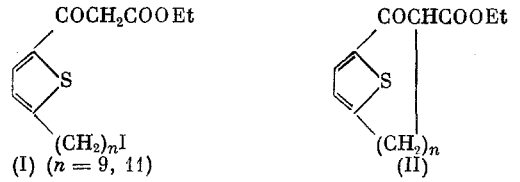
THIENYL-2-ACETIC ACID AS A SYNTHETIC AGENT FOR THE PREPARATION OF MACROCYCLIC COMPOUNDS CONTAINING A THIOPHENE RING

S. Z. Taits and V. N. Bulgakova

UDC 542.954.1:66.095.253:547.732

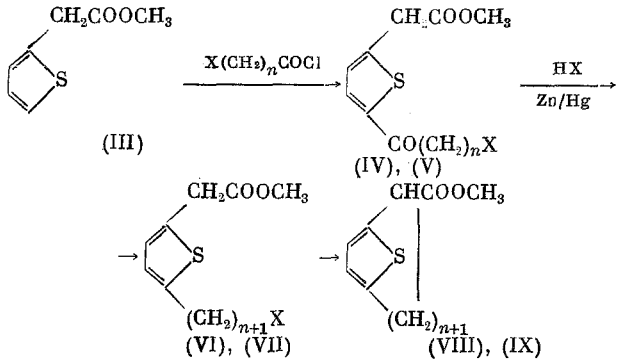
In previous work [1, 2], we used the intramolecular alkylation of 2-(ω-haloalkyl)-5-carboethoxyacetylthiophenes (I) at high dilution in the presence of anhydrous K_2CO_3 (≤200 mesh) in methyl ethyl ketone (MEK) to prepare carboethoxycyclothienones (II) in yields up to 70%



It was of interest to carry out this intramolecular alkylation using other thiophene derivatives, including thienylacetic acid which is an available industrial compound [3].

There is no information in the literature on the alkylation of thienyl-2-acetic acid and its ring derivatives at the α-carbon. However, thienyl-3-acetate esters are known to undergo alkylation at the α-carbon by means of alkyl bromides in the presence of NaH in DMF to yield monoalkyl derivatives [4]. Similar behavior is found for ethyl (3-nitro-2-thienyl)pyruvate [5] and the alkylation in this case proceeds not only by the action of metallic sodium but also in the presence of Na_2CO_3 and Li_2CO_3. In the case of the closest carbocyclic analog of thienyl-2-acetic acid, namely, phenylacetic acid, the acid itself, its esters and amides are alkylated in liquid ammonia in the presence of alkali metal amides with the formation of mono-α-alkyl derivatives. Phenylacetonitrile is alkylated in the presence of NaH or $NaNH_2$ with the formation of mono-α-alkyl derivatives with a higher yield than that obtained for the acid itself [8]. It is interesting to note that phenylacetonitrile is alkylated by alkyl chlorides in the presence of NaOH in DMF to form α,α-dialkyl derivatives [9].

Hence, we may propose that the intramolecular alkylation of 5-(ω-haloalkyl)thienyl-2-acetic acids proceeds by the scheme given below. We should note that the synthesis of the starting compounds in this case is simpler than our previously reported method for the preparation of (II) [1]



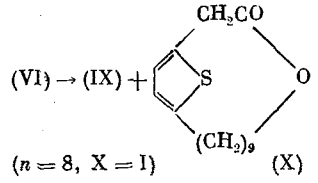
n = 8, X = Cl, Br (IV); n = 10, X = Br (V); n = 8, X = Br, I (VI); n = 10, X = Br (VII); n = 10 (VIII); n = 8 (IX).

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow.
Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 1, pp. 218-225, January, 1984. Original article submitted April 12, 1983.

0568-5230/84/3301-0195$08.50

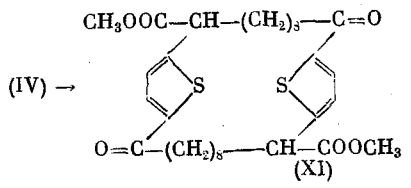
Macrocyclic compounds (VIII) and (IX) contain a thienyl-2-acetic acid fragment and hold interest for the synthesis of semisynthetic antibiotics.

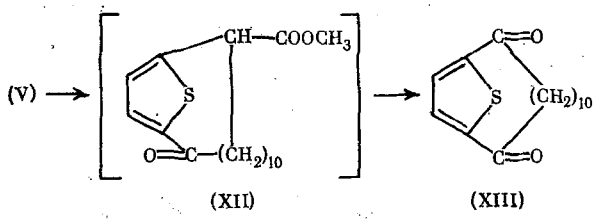
The acylation of (III) with the formation of (IV) and (V) and their Clemmensen reduction proceed with relatively high yields although the intramolecular alkylation of 5-(ω-haloalkyl)-2-carbomethoxymethylthiophenes (VI) and (VII) under our conditions (120°C, anhydrous K_2CO_3 in DMF–MEK, high dilution) does not proceed by a single pathway. Thus, the intramolecular alkylation of 2-(9-iodononyl)-5-carbomethoxymethylthiophene ((VI), n = 8, X = I) gives a mixture of products containing 32% 1-carbomethoxy-[10]-α-cyclothiene (IX) and 6% of the macrocyclic lactone, 3-oxa-[12]-α-cyclothien-2-one (X) (approximately the same results were obtained for the cyclization of (VI) with n = 8 and X = Br).



The cyclization of 2-(11-bromoundecyl)-5-carbomethoxymethylthiophene under the same conditions gives only one product, 1-carbomethoxy-[12]-α-cyclothiene (VIII) in 34% yield. Thus, the extension of the chain undergoing cyclization by two units eliminates O-alkylation which gives lactones such as (X).

It was of interest to study the intramolecular alkylation of ω-haloalkyl (5-carbomethoxymethyl-2-thienyl) ketones (IV) and (V) since these compounds should form the corresponding carbanions since (IV) and (V) may be considered as vinylogs of 2-(ω-haloalkyl)-5-carboethoxyacetylthiophenes (I). Indeed, the course of the reaction is significantly altered in the case of intramolecular alkylation of compounds such as (IV) and (V) which have a carbonyl group at C-5 which is conjugated to the thiophene ring

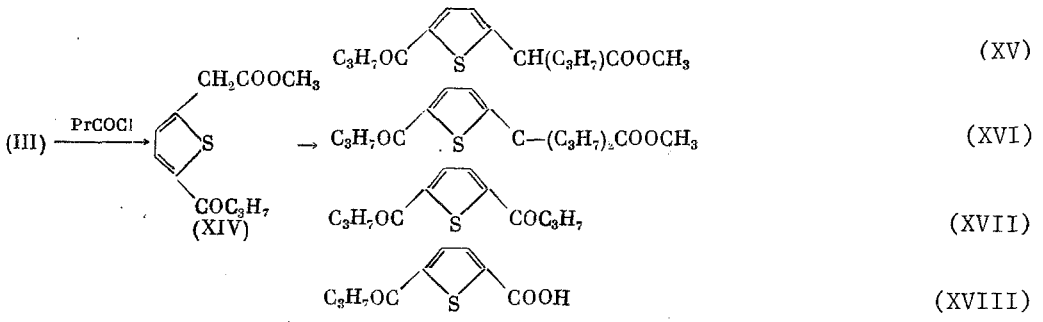




Thus, 2-(9-bromononanoyl)-5-carbomethoxymethylthiophene (IV) gives 10,24-bis(carbomethoxy)-[10,10]-α-cyclothiene-1,15-dione (XI) in 30% yield. The formation of the dimerization product (XI) maybe attributed to the presence of the carbonyl function at C-5 of starting (IV), which should be in the plane of the thiophene ring, enhancing the "rigid group" which hinders intramolecular alkylation to form a 14-membered ring. The correctness of this hypothesis was supported by the finding that the intramolecular alkylation of (VI) which does not contain a carbonyl group conjugated to the thiophene ring yields product (IX) also having a 14-membered ring, which should have been formed upon the intramolecular alkylation of (IV). When 2-(11-bromoundecanoyl)-5-carbomethoxymethylthiophene (V) is used as the starting compound in the cyclization [12]-α-cyclothiene-1,12-dione (XII) was unexpectedly formed from the reaction mixture in 14% yield instead of the expected 12-carbomethoxy-[12]-α-cyclothien-2-one (XII). The composition and structure of (XIII) were shown by elemental analysis and mass spectroscopy. The coincidence of the chemical shifts for $H_{\beta'}$ and H_{β} of the thiophene ring in the PMR spectrum and the nature of the ^{13}C NMR spectrum also indicate molecular symmetry. The presence of two C=O groups conjugated to the ring was shown by the IR band at 1675 cm^{-1}. The IR spectrum of 2,5-diacetylthiophene obtained according to our previ-

our procedure [10] also had this characteristic band. The formation of macrocyclic diketone (XIII) presumably occurs as a result of the oxidative decarboxylation of intermediate (XII). Indeed, running the intramolecular alkylation reaction in an argon atmosphere reduces the yield of (XIII) to 7% although we were unable to isolate intermediate (XII) in this case as well.

The formation of diketones such as (XIII) is quite interesting since the preparation of dicarbonyl derivatives of aromatic compounds is a difficult problem. Thus, we attempted to determine whether these transformations are characteristic only for compounds with macrocyclic structure or are possible for other 5-alkyl-substituted thienylacetic acids. For this purpose, we investigated the alkylation of 2-butanoyl-5-carbomethoxymethylthiophene (XIV) by propyl bromide under conditions analogous to those used for intramolecular alkylation



We found that the use of one mole of propyl bromide per mole (XIV) gave, in addition to 2-butanoyl-5-(1-carbomethoxy-1-butyl)thiophene (XV) (21% yield), 2,5-bis(butanoyl)thiophene (XVII) in 18.5% yield with the concurrent formation of 2-butanoylthiophene-5-carboxylic acid (XVIII) in 25% yield. An increase in the amount of propyl bromide to two moles per mole (XIV) gave 2-butanoyl-5-(4-carbomethoxy-4-heptyl)thiophene (XVI) in 56% yield. The alkylation of ketone (XIV) by propyl bromide in MEK in the absence of DMF gave the monoalkylation product (XV) in 67% yield relative to (XIV) consumed. In order to prove that diketone (XVII) may be obtained through the intermediate formation of (XV), the latter was subjected to the action of the air. Air treatment of an ethanolic solution of (XV) in an alkaline medium yields (XVII). The formation of (XVIII) may be attributed to the capacity of (XIV) to undergo oxidation in alkaline medium in the presence of an oxidizing agent, which is the air in this case. A similar process was observed previously [11] in the treatment of methyl 5-acetylthienyl-2-acetate by atmospheric oxygen, which gives a 64.7% yield of 5-acetylthiophene-2-carboxylic acid. However, this is apparently the first report of the oxidative decarboxylation of such systems with the formation of diketones.

Thus, the formation of thiophene diketones from 2-acyl-5-carbomethoxymethylthiophenes is a general reaction which proceeds by the oxidation of mono-α-alkyl-substituted 2-acylthienyl-3-acetic acids.

EXPERIMENTAL

The PMR spectra were taken on a Tesla BS-497 spectrometer at 100 MHz and on a Varian DA-60-IL spectrometer using CCl_4 and $CHCl_3$ as solvents and TMS or HMDS as internal standard. The IR spectra were obtained on a UR-20 spectrometer in KBr pellets and in CCl_4 and $CHCl_3$ solution. The UV spectra were taken on a Specord UV-VIS spectrometer in ethanol. The ^{13}C NMR spectra were taken on a Bruker WP-60 spectrometer at 15.08 MHZ in $CDCl_3$. Alumina with grade II activity was used for the column chromatography, while Silufol UV-254 plates were used for the thin-layer chromatogaphy. The mass spectra were taken on a Varian MAT CH-6 spectrometer at 60 eV ionizing voltage and 50-200°C ionizing chamber temperature.

Methyl Thienylacetate (III). A mixture of 142 g (1 mole) thienylacetic acid and 2.2 g (0.01 mole) toluenesulfonic acid in 433 ml methanol was heated at reflux for 7 h with stirring. Then, methanol was evaporated and water was added to the residue, which was then extracted with benzene. The extract was washed with water, aqueous $NaHCO_3$, and again with water, dried over $MgSO_4$, and evaporated. The residue was distilled to yield 125 g (80%) (III) with bp 71-71.5°C (0.15 mm), n_D^{20} 1.5206.

TABLE 1. Methyl 5-(ω-Haloalkanoyl)- and 5-(ω-Haloalkyl)thienyl-2-acetates (IV)-(VII)

Compound	mp, °C	Yield, %	Found / Calculated %				Chemical formula
			C	H	halogen	S	
(IV)	44–45 (hexane)	80	58,15 58,07	7,09 7,01	10,87 10,71	9,74 9,68	$C_{16}H_{23}O_3ClS$
(IV)	36,5–38 (hexane)	60,4	50,65 51,19	6,32 6,20	21,38 21,39	8,58 8,54	$C_{16}H_{23}O_3BrS$
(V)	54–55 (Ethyl acetate)	75	53,62 53,59	6,77 6,75	19,58 19,81	7,85 7,95	$C_{18}H_{27}O_3BrS$
(VI) *	172 (0,3) 1,5071	56,8	60,35 60,64	8,14 7,95	11,32 11,19	10,23 10,12	$C_{16}H_{25}O_2ClS$
(VI) *	170–174 (0,1)	54,5	52,78 53,18	6,97 6,97	22,13 22,12	8,8 8,87	$C_{16}H_{25}O_2BrS$
(VI) *	207 (0,3)	80	47,31 47,06	6,30 6,17	30,97 31,08	7,83 7,85	$C_{16}H_{25}O_2IS$
(VII) *	208 (0,4) 1,5148	54	55,51 55,52	7,64 7,51	20,33 20,52	8,16 8,23	$C_{18}H_{29}O_2BrS$

*Bp, °C (p, mm Hg) and n_D^{20} given for (VI) and (VII).

Acylation of Methyl Thienylacetate Using Acid Chlorides of Haloalkanoic Acids. A solution of 24.7 ml $SnCl_4$ in 20 ml benzene was added to a solution of 21.6 g (0.14 mole) (III) and 0.22 mole acid chloride of a chloroalkanoic or bromoalkanoic acid in 405 ml benzene at from −3° to 0°C and then warmed to ~20°C. The mixture was recooled to −5°C and 370 ml 1:10 HCl was added. The organic layer was separated and washed with water, saturated aqueous $NaHCO_3$, and again with water and dried over $MgSO_4$. The benzene was evaporated and the residue was recrystallized to give methyl haloalkanoyl-2-thienylacetates. Bromopelargonic acid was obtained by a standard procedure [12]. The data for (IV) and (V) are given in Table 1.

Methyl ω-Haloalkyl-2-thienylacetates (VI) and (VII). A mixture of 0.09 mole methyl ω-haloalkanoyl-2-thienylacetate, zinc amalgam obtained from 98 g zinc treated with a solution of 9.1 g mercuric chloride in 34 ml HCl and 78.3 ml water, 152 ml methanol, 98 ml HCl, and 39 ml water was heated at reflux with rapid stirring for 1 h. The zinc was filtered off and washed with ether. The aqueous layer was separated and extracted with ether. The extract was washed with water, aq. $NaHCO_3$, dried over $MgSO_4$ and evaporated. The residue was distilled to yield methyl ω-haloalkyl-2-thienylacetates. The data for (VI) and (VII) are given in Table 1.

Methyl 5-(9-Iodononyl)-2-thienylacetate ((VI), X = I). A mixture of 12.59 g (0.04 mole) ((VI), X = Cl) and 17 g (0.11 mole) NaI in 112 ml MEK was heated at reflux with stirring for 20 h. The salt precipitate was filtered off and the filtrate was evaporated. A sample of water was added to the residue and it was extracted with ether.

The extract was washed with aq. $Na_2S_2O_3$ and water, dried over $MgSO_4$ and evaporated. The products of MEK condensation were distilled off the residue in vacuum to give 13.26 g (80%) ((VI), X = I).

Cyclization of Methyl 5-(ω-Haloalkyl)-2-thienylacetates and Methyl 5-(ω-Haloalkanoyl)-2-thienylacetates. A solution of 0.025 mole of the compound to be cyclized in 200 ml MEK was added with rapid stirring over 25 h to a mixture of 300 g dry K_2CO_3 ground to <200 mesh, 1250 ml DMF and 500 ml MEK at 120°C. After the addition was completed, the mixture was heated at reflux for 6 h and then the K_2CO_3 was filtered off and thoroughly washed with solvent. The filtrate was evaporated and the residue was treated with water and extracted with ether or chloroform. The extract was washed with water and 5% $Na_2S_2O_3$, dried over $MgSO_4$ and evaporated. The MEK condensation products were distilled off in vacuum (<1 mm) and the reaction products were purified by crystallization or molecular distillation. The yields and physical constants of the compounds obtained are given in Table 2.

2-Butanoyl-5-carbomethoxymethylthiophene (XIV). The acylation of 23.1 g (0.15 mole) ester (III) using 21.3 g (0.2 mole) butanoyl chloride was carried out analogously to the method described above to give 24.5 g (72%) (XIV).

TABLE 2. Characteristics of Compounds Obtained by the Intramolecular Alkylation of 2-Butanoyl-5-carbomethoxymethylthiophene and Its Derivatives

Compound	mp, °C or bp, °C (mm Hg)	(PMR spectra (δ, ppm)	Found / Calculated, %				Chemical formula	Yield, %
			C	H	S	M[a]		
(IX)[b]	Oil, R_f=0,55	CCl_4, 0,92–1,78 m (14H, CH_2), 2,68–2,8 m (2H, CH_2Th[c]), 3,6 s (2H, CH_2CO); 4,0 t (2H, CH_2O, J=7), 6,4 d (1H, Th$_{\beta'}$), 6,7 d (1H, Th$_\beta$)	68,20 / 68,53	8,78 / 8,63	11,37 / 11,43	270 / 280,4	$C_{16}H_{24}O_2S$	32
(X)[b]	Oil, R_f=0,7	CCl_4, 0,9–2 m (16H, CH_2), 2,76 t (2H, ThCH_2, J=7) 3,46–2,7 m (4H, CHCO and OCH_3), 6,58 d (1H, Th$_{\beta'}$, 6,75 d (1H, Th$_\beta$)	67,61 / 67,62	8,41 / 8,32	12,16 / 12,04	266 / 266,4	$C_{15}H_{22}O_2S$	6
(VII)	210 (0,4)	CCl_4, 0,92–1,78 m (18H, CH_2), 2,6–2,8 m (2H, CH_2Th), 3,6 s (2H, CH_2CO), 4,0 t (2H, CH_2O, J=7), 6,4 d (1H, Th$_{\beta'}$ 6,7 d (1H, Th$_\beta$)	70,23 / 70,08	9,13 / 9,15	10,68 / 10,39	308 / 308,4	$C_{18}H_{28}O_2S$	34
(XI)	135–137 (heptane)	$CHCl_3$, 1–2,06 m (28H, CH_2); 2,6–2,8 m (4H, CH_2CO), 3,6–3,8 m (8H, CH and OCH_3), 6,9 d (2H, Th$_{\beta'}$), 7,46 d (2H, Th$_\beta$)	65,43 / 65,27	7,26 / 7,53	10,43 / 10,89	588 / 588,8	$C_{32}H_{44}O_6S_2$	30
(XIII)[d]	77,5–78,5 (ether)	CCl_4, 0,8–1,36 m (12H, CH_2), 1,7–1,9 m (4H, CH_2), 2,78 t (4H, $COCH_2$), 7,74 s (2H, Th$_{\beta'}$ and Th$_\beta$)	69,25 / 69,02	7,90 / 7,96	11,61 / 11,52	278 / 278,4	$C_{16}H_{22}O_2S$	14[e]
(XIV)	162,5 (2,2) n_D^{25} 1,5333 R_f=0,3	CCl_4, 0,84–1,0 m (3H, CH_3, J=7), 1,16–1,38 m (2H, CH_2, J=7), 2,62 t (2H, CH_2CO, J=7), 3,6 s (3H, OCH_3), 3,7 s (2H, CH_2O), 6,8 d (1H, Th$_{\beta'}$, 7,4 d (1H, Th$_\beta$)	58,48 / 58,38	6,26 / 6,24	14,02 / 14,17	226 / 226,3	$C_{11}H_{14}O_3S$	72

TABLE 2 (Continued)

Compound	mp, °C or bp, °C (mm Hg)	PMR spectra (δ, ppm)	Found / Calculated %				Chemical formula	Yield, %
			C	H	S	M[a]		
(XV)	121 (0,3) R_f=0,53	$CHCl_3$, 0,84–1,6 m (6H, CH_3), 1,1–2,2m (6H, CH_2), 2,7 t (2H, CH_2CO, J=7), 3,6 s (3H, OCH_3), 3,5–3,8 m (1H, CH), 6,8 d (1H, Th_β'), 7,4 d (1H, Th_β)	63,10 / 62,65	7,65 / 7,51	11,74 / 11,95	268 / 268,4	$C_{14}H_{20}O_3S$	67[f]
(XVI)	188 (1,7) n_D^{20} 1,5183	CCl_4, 0,84–1,0m (9H, CH_3), 1,1–1,2 m (10H, CH_2), 2,75 t (2H, CH_2CO, J=7), 3,6s (3H, OCH_3), 6,8d (1H, Th_β'), 7,4 d (1H, Th_β)	65,60 / 65,76	8,41 / 8,44	10,97 / 10,32	310 / 310,4	$C_{17}H_{26}O_3S$	56,4
(XVII)	117–118 (ether) R_f=0,6	$CHCl_3$, 0,76–1,08 t (6H, CH_3), 1,6–1,93 m (4H, CH_2), 2,8t (4H, $COCH_2$), 7,64 s (2H, Th_β' and Th_β)	64,33 / 64,25	7,15 / 7,19	13,87 / 14,29	224 / 224,3	$C_{12}H_{16}O_2S$	18,5
(XVIII)	164–165 (benzene)		54,39 / 54,53	4,94 / 5,08	16,07 / 16,17	198 / 198,2	$C_9H_{10}O_3S$	25

[a]Molecular ion mass. [b]Products (X) and (IX) were purified by sublimation at 110°C (0.03 mm). [c]Thiophene ring. [d]^{13}C NMR (δ, ppm) for (XIII): C_α (146.55), C_β (131.68), C^1 (194.65), C^2 (39.2), C^3 (27.3), C^4 (26.95), C^5 (26.65), C^6 (26.23); UV spectrum (λ_{max}, nm (log ε)): 290 (4.03), 265 (3.98), 208(3.46). [e]The yield of (XIII) was 7% in the cyclization in an argon atmosphere. [f]Yield of (XV) relative to the amount of (XIV) consumed.

TABLE 3. Conditions and Products of the Alkylation of (XIV) by Propyl Bromide

Solvent	(XIV), moles	T, °C	Reaction products (yield, %)
182 ml DMF 38 ml MEK	0,035	117	(XV), 22 (XVII), 10
250 ml MEK	0,035	79	(XV), 67
104 ml DMF 22 ml MEK	0,02 *	117	(XVII), 18,5 (XVIII), 25

*Air was bubbled through the reaction mixture.

Reaction of Methyl 5-Butanoyl-2-thienylacetate (XIV) with an Equimolar Amount of Propyl Bromide in the Presence of K_2CO_3. Equimolar amounts of propyl bromide and (XIV) were added to a mixture of 114 g K_2CO_3 in solvent and then heated at reflux with stirring for 4 h. After treatment of the reaction mixture as in the case of the intramolecular alkylation described above, 2-butanoyl-5-(1-carbomethoxy-1-butyl)thiophene (XV), 2,5-bis(butanoyl)thiophene (XVII), and 2-butanoylthiophene-5-carboxylic acid (XVIII) were isolated. Product (XV) was isolated chromatographically on a column with 30-mm diameter packed with 310 ml alumina using 4:1 hexane–ethyl acetate as eluant. The physical constants and yields of the compounds obtained are given in Table 2, while the alkylation conditions are given in Table 3.

2-Butanoyl-5-(4-carbomethoxy-4-heptyl)thiophene (XVI). The alkylation of (XIV) was carried out under the conditions described above using 2 moles of propyl bromide per mole (XIV) to yield 5.23 g (56.4%) (XVI).

Reaction of 2-Butanoyl-5-(1-carbomethoxy-1-butyl)thiophene with Air in Ethanolic Alkali. A sample of 52 ml 50% ethanolic alkali was added to 0.69 g (0.02 mole) (XV) in 81 ml ethanol. The mixture turned yellow. Air was introduced until the color disappeared (40 min) and the mixture was stirred for an additional 40 min The formation of (XVII) was indicated by thin-layer chromatography on a Silufol UV-254 plate using 4:1 hexane–ethyl acetate as eluant.

CONCLUSIONS

1. The intramolecular alkylation of 5-(ω-haloalkyl)-2-carboalkoxymethylthiophenes yields esters of macrocyclic carboxylic acids containing the thiophene ring.

2. The cyclization of 5-(ω-haloacyl)-2-(carboalkoxymethyl)thiophenes gives macrocyclic diketones containing a thiophene ring bearing carbonyl groups at C-1 and C-6.

3. 2,5-Diacylthiophenes are formed in the alkylation of 5-acyl-2-carbomethoxymethylthiophenes by alkyl halides in the presence of air.

LITERATURE CITED

1. S. Z. Taits, Ya. L. Gol'dfarb, and V. N. Bulgakova, Izv. Akad. Nauk SSSR, Ser. Khim., 1299 (1963).
2. S. Z. Taits, É. A. Kransyanskaya, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 762 (1968).
3. E. H. Flynn, Belgian Patent No. 618,663; Chem. Abstr., 59, 5176c (1963).
4. M. M. Chandavoine and M. Chignal, US Patent No. 4,186,137; Chem. Abstr., 93, 8006 (1980).
5. A. Scott, B. Hoogenboom, and H. Snyder, J. Org. Chem., 29, 2165 (1964).
6. S. Work, D. Bryant, and C. Hauser, J. Org. Chem., 29, 722 (1964).
7. W. Kenyon, R. Meyer, and C. Hauser, J. Org. Chem., 28, 3108 (1963).
8. H. Normant and T. Cewigny, Bull. Soc. Chim. France, 1881 (1965).
9. L. Taranko and R. Perry, J. Org. Chem., 34, 226 (1969).
10. Ya. L. Gol'dfarb, A. P. Yakubov, and L. I. Belen'kii, Dokl. Akad. Nauk SSSR, 185, 91 (1969).
11. T. Hibino, Japanese Patent No. 7,814,264; Chem. Abstr., 90, 168440 (1979).
12. Organic Syntheses [Russian translation], No. 4, Inostr. Lit., Moscow (1953), p. 312.