THIENOPYRYLIUM SALTS

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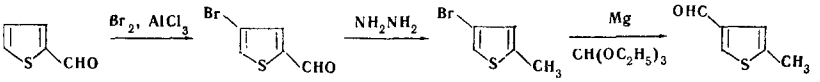
The catalytic acylation and subsequent heterocyclization of α- and β-acetonyl derivatives of thiophene were studied. Mechanisms for the synthesis of thienopyrylium salts, the reaction of which with ammonia leads to the difficult-to-obtain thienopyridines, are proposed.

The simplest and most convenient method for the synthesis of cycloalkeno- and 2-benzopyrylium salts is catalytic acylation of cyclohexenylacetone, cyclohexenylacetophenone, and other cycloalkenylketones as well as methoxy-substituted arylacetones [1-6].

As an extension of these investigations we studied the acylation of acetonyl derivatives of thiophene, which should have led to the synthesis of thienopyrylium salts which have not yet been reported.

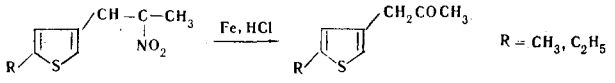
It is well known that thiophene is readily electrophilically substituted at the α-position. We therefore primarily studied the acylation of β-acetonyl derivatives of thiophene.* The starting acetonylthiophenes were obtained from the corresponding aldehydes. 2-Methyl-4-formylthiophene was synthesized via the scheme



The starting 2-ethyl-4-formylthiophene was similarly synthesized.

1-(2'-Methyl-4'-thienyl)- and 1-(2'-ethyl-4'-thienyl)-2-nitropropylenes were obtained from 2-methyl- and 2-ethyl-4-formylthiophenes. The condensation of aldehydes with nitroalkanes is usually carried out in the presence of bases [7-9], but we used a recently described method [10], according to which the nitroolefins are readily and rapidly obtained from Schiff bases and nitroalkanes in glacial acetic acid.

The previously unreported 2-methyl- and 2-ethyl-4-acetonylthiophenes were obtained in yields of 20-65% by reduction of thienylnitropropylenes with iron in an acidic medium [11].



The acylation of 2-methyl- and 2-ethyl-4-acetonylthiophenes with aliphatic acid anhydrides in the presence of equimolecular amounts of 70% perchloric acid leads to the formation of 2-acyl-3-acetonylthiophene derivatives, which are cyclized under the reaction conditions to form thieno[2,3-c]pyrylium perchlorates. The reaction proceeds at room temperature, and the pyrylium salts, which are crystalline substances, are easily isolated from the reaction mixture in 53-85% yields.

*We have previously reported [5] the synthesis of thieno[2,3-c]pyrylium perchlorate by acylation of 2-methyl-4-acetonylthiophene.

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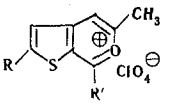
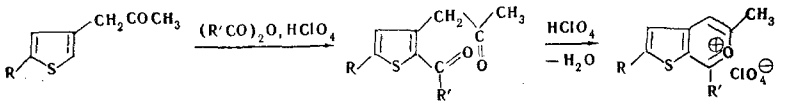
TABLE 1. Thieno[2,3-c]pyrylium Perchlorates

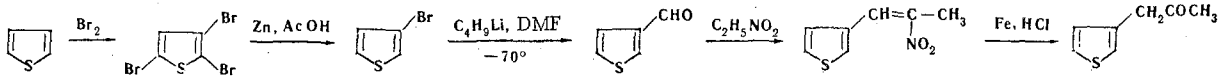


R	R′	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	Cl	S	C	H	Cl	S	
H	CH_3	162—164	$C_9H_9ClO_5$	40,54	3,77	13,09	11,84	40,83	3,43	13,40	12,11	70,0
H	C_2H_5	68—69	$C_{10}H_{11}ClO_5$	43,37	4,13	12,90	11,75	43,09	3,98	12,72	11,51	66,5
H	C_3H_7	117—118	$C_{11}H_{13}ClO_5$	45,10	4,77	12,08	10,72	45,13	4,48	12,11	10,95	71,7
CH_3	CH_3	160—161	$C_{10}H_{11}ClO_5$	43,20	3,68	12,61	11,40	43,09	3,98	12,72	11,51	80,7
CH_3	C_2H_5	130—131	$C_{11}H_{13}ClO_5$	45,38	4,04	11,90	10,77	45,13	4,48	12,11	10,95	78,2
C_2H_5	CH_3	166—168	$C_{11}H_{13}ClO_5$	45,02	4,14	11,79	10,69	45,13	4,48	12,11	10,95	61,6
C_2H_5	C_2H_5	123—124	$C_{12}H_{15}ClO_5$	47,06	4,80	11,03	10,20	46,98	4,93	11,56	10,45	52,6

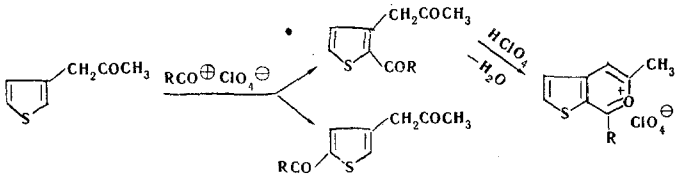


Thus, we obtained the previously unreported 2,5,7-trialkylthieno[2,3-c]pyrylium perchlorates, the constants and yields of which are presented in Table 1.

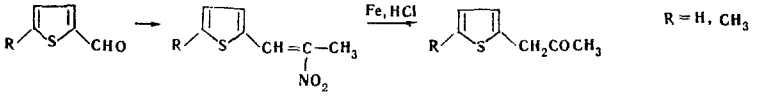
In order to clarify the necessity for the presence of an alkyl substituent in the α position of the thiophene ring to prevent side reactions, we studied the acylation of 3-acetonylthiophene, which was obtained from thiophene via the scheme



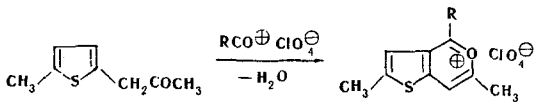
This accomplished the synthesis of 5,7-dialkylthieno[2,3-c]pyrylium perchlorates in yields up to 72%. This fact indicates that the acyl cation attacks 3-acetonylthiophene primarily at the 2-position. The 2-acyl-3-acetonylthiophenes thereby formed are subsequently cyclized to the thieno[2,3-c]pyrylium salts.



In order to obtain thieno[3,2-c]pyrylium salts, we studied the acylation of 2-acetonyl derivatives of thiophene. The starting compounds were synthesized from 2-formylthiophene and 5-methyl-2-formylthiophene via the scheme



Acylation of 5-methyl-2-acetonylthiophene with carboxylic acid anhydrides in the presence of 70% perchloric acid leads to the formation of 2,4,6-trialkylthieno[3,2-c]pyrylium salts in yields up to 22%.



Thus, 2,4,6-trimethyl- and 2,6-dimethyl-4-propylthieno[3,2-c]pyrylium perchlorates were obtained by using acetic and butyric anhydrides. The low yield of the thieno[3,2-c]pyrylium salts attests to the occurrence of side acylation at the neighboring β-position.

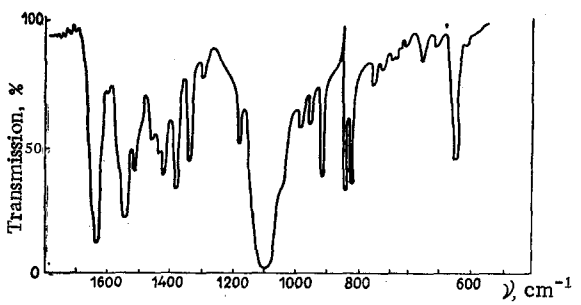


Fig. 1. IR spectrum of 5,7-dimethylthieno[2, 3-c]pyrylium perchlorate (UR-20 spectrometer, KBr pellet).

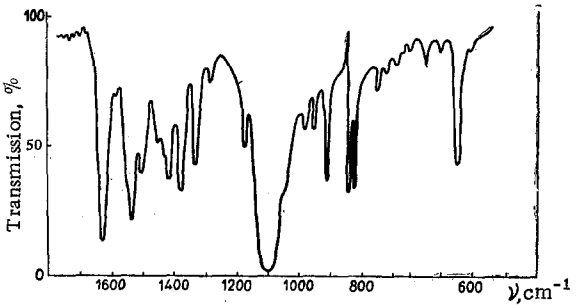


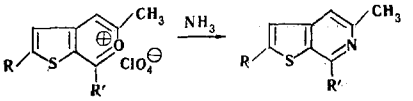
Fig. 2. IR spectrum of 2,4,6-trimethylthieno-[3,2-c]pyrylium perchlorate (UR-20 spectrometer, KBr pellet).

The acetylation of 2-acetonylthiophene did not give thieno[3,2-c]pyrylium salts as a consequence of primary acylation of the starting ketone at the most reactive α-position of the thiophene ring, and subsequent polycondensation of the 2-acetyl-5-acetonylthiophene was thus obtained.

The structures of the thienopyrylium salts were confirmed by a study of their IR absorption spectra. The strong band at 1610-1640 cm^{-1} belongs to the symmetrical valence vibrations of the pyrylium cation (8a in the Wilson classification [12]) and serves as a reliable indication of the presence of the latter in molecules of the investigated compounds, since it is not, as a rule, overlapped by other bands. This band is found at 1633-1638 cm^{-1} in the spectra of thieno[2,3-c]pyrylium perchlorates (Fig. 1) and is shifted to the low-frequency region (1623-1625 cm^{-1}) in the spectra of thieno[3,2-c]pyrylium salts (Fig. 2). A group of bands of the valence vibrations of the pyrylium and thiophene rings is found at 1400-1600 cm^{-1}. The band in the 1040 cm^{-1} region ($\nu_{C=C}$ of the thiophene ring [13]) is manifested as an inflection as a consequence of merging with the broad absorption band of the ClO_4^- anion. The band at 690-750 cm^{-1}, characteristic for thiophene [13], is shifted to higher frequencies (820-860 cm^{-1}) and is split. This sort of shift can be explained by the electron-accepting effect of the pyrylium cation on the thiophene ring in thieno[2,3-c]- and thieno[3,2-c]pyrylium salts. The two intense bands at 1100 cm^{-1} (broad) and 625 cm^{-1} belong to the vibrations of the ClO_4^- anion.

Since thieno[2,3-c]- and thieno[3,2-c]pyridines have received little study and are difficult-to-obtain compounds, it seemed of interest to us to study the possibility of transformation of the pyrylium salts which we synthesized to compounds of this class.

We showed that thieno[2,3-c]pyrylium salts, like alkyl-substituted pyrylium salts, form thieno[2,3-c]-pyridine derivatives in 76-80% yields by saturating alcohol suspensions of them with ammonia.



The pyridine bases obtained are vacuum-distillable liquids. They readily form picrates and quaternary salts as well as hydrochlorides by the action of concentrated hydrochloric acid in acetone.

We isolated two of these thienopyridines (R = H, R' = CH_3 and R = R' = CH_3) in pure form, while the remaining were identified as the picrates.

Thieno[3,2-c]pyrylium salts react with ammonia similarly to give thieno[3,2-c]pyridines.

Our proposed convenient method for the synthesis of alkyl-substituted thieno[2,3-c]- and thieno[3,2-c]-pyridines differs favorably from the well-known Bischler–Napieralski and Pictet–Gams methods for their preparation in that, in addition to increasing the yields of products, it makes it possible to vary the alkyl substituents in the pyridine and thiophene rings.

EXPERIMENTAL

4-Bromo-2-formylthiophene. This was obtained by bromination of 2-formylthiophene in the presence of excess aluminum chloride [14]. Kishner reduction of the product gives 2-methyl-4-bromothiophene.

2-Methyl-4-formylthiophene. Ethyl orthoformate (60 ml) was added to a Grignard reagent prepared from 9 g (0.38 mole) of magnesium, 32.6 g (0.184 mole) of 4-bromo-2-methylthiophene, and 20 g (0.184 mole) of ethyl bromide in 200 ml of absolute ether; and the reaction mixture was refluxed for 6 h. The ether was then removed by distillation, and the residue was heated on a boiling-water bath for 30 min and poured into water. The organic layer was extracted with ether, the ether was distilled from the extract, and the residual oil was mixed with 40 ml of 15% sulfuric acid. This mixture was distilled and 200 ml of distillate was collected. This distillate was extracted with ether, and the ether solution was dried with calcium chloride. The ether and propionaldehyde were removed by distillation on a water bath, and the residue was vacuum distilled to give 5 g (21%) of 2-methyl-4-formylthiophene with bp 70-78° (5 mm) [bp 91-100° (13 mm) [14]].

2-Methyl-4-thienalpropylamine. n-Propylamine (10 ml) and 10 ml of dry toluene were added to 10.1 g (0.008 mole) of 2-methyl-4-formylthiophene, and the mixture was allowed to stand overnight at room temperature. The toluene and evolved water were distilled under a vacuum produced by a water aspirator, and the residue was vacuum distilled to give 13 g (97%) of 2-methyl-4-thienalpropylamine with bp 95-98° (5 mm). Found %: N 8.18. $C_9H_{13}NS$. Calculated %: N 8.37.

1-(2'-Methyl-4'-thienyl)-2-nitropropylene. Nitroethane [5.3 g (0.07 mole)] was added to 12 g (0.07 mole) of 2-methyl-4-thienalpropylamine in 15 ml of glacial acetic acid. The resulting mixture was heated on a boiling-water bath for 30 min. Cooling of this mixture gave a yellow precipitate which was filtered, washed on the filter with acetic acid, and dried to give 8.5 g of product. An additional 4.3 g of compound was obtained from the filtrate by the addition of water to it. The overall yield of product was 11.8 g (90%) with mp 57-59° (yellow needles from alcohol). Found %: N 7.51. $C_8H_9NO_2S$. Calculated %: N 7.65.

2-Methyl-4-acetonylthiophene. This was obtained in 65% yield by reduction of 1-(2'-methyl-4'-thienyl)-2-nitropropylene according to the method in [11] and had bp 113° (12 mm). Found %: C 62.21; H 6.40; S 20.67. $C_8H_{10}OS$. Calculated %: C 62.30; H 6.54; S 20.79.

4-Bromo-2-ethylthiophene. This was obtained by bromination of 2-acetothienone in the presence of aluminum chloride and Kishner reduction [15] of the resulting 4-bromo-2-acetothienone.

2-Ethyl-4-formylthiophene. This was similarly obtained in 13% yield and had bp 218-220°. The 2,4-dinitrophenylhydrazone had mp 200-201°. Found %: N 17.34. $C_{13}H_{12}N_4O_4S$. Calculated %: N 17.50.

1-(2'-Ethyl-4'-thienyl)-2-nitropropylene. This was obtained in the same way as 1-(2'-methyl-4'-thienyl)-2-nitropropylene and was an oily liquid. This product was used without purification for reduction to 2-ethyl-4-acetonylthiophene.

2-Ethyl-4-acetonylthiophene. This was obtained in 20% yield and had bp 120-130° (6 mm). Found %: C 63.90; H 6.85; S 18.70. $C_6H_{12}OS$. Calculated %: C 64.24; H 7.19; S 19.05.

2,3,5-Tribromothiophene. This was obtained by the bromination of thiophene [16].

3-Bromothiophene. This was obtained by reduction of 2,3,5-tribromothiophene with zinc in acetic acid [17].

3-Thienalbenzylamine. Ether solutions of butyllithium (from 2.2 g of lithium) and 16.3 g of 3-bromothiophene in 30 ml of ether cooled to −70° were mixed under nitrogen. After 5 min the resulting solution of 3-thienyllithium was added to a stirred mixture of 10 ml of diethylformamide and 40 ml of ether. Stirring was continued for another 2 h, and the reaction mixture was allowed to stand overnight. It was then poured over ice, the ether layer was separated, and the aqueous layer was extracted with ether. The residue after removal of the solvent was vacuum distilled. The distillate was then distilled at atmospheric pressure, and the fraction boiling at 175-205° was collected. This fraction was mixed with 5 ml of benzylamine in 20 ml of benzene, the benzene was removed by distillation, and 3-bromothiophene and excess benzylamine were removed from the residue by heating it in vacuo on a boiling-water bath. The residual oily product began to crystallize on cooling to give 6.97 g (35%) of 3-thienalbenzylamine with mp 42° (colorless needles from hexane). Found %: N 7.04. $C_{12}H_{11}NS$. Calculated %: N 6.96.

1-(3'-Thienyl)-2-nitropropylene. This was obtained in 79% yield from 3-thienalbenzylamine and nitroethane and had mp 71-72° (mp 72.5-73.5° [11]).

3-Acetonylthiophene. This was obtained by reduction of 1-(3'-thienyl)-2-nitropropylene [11].

5-Methyl-2-formylthiophene. Phosphorus oxychloride (50 ml) was added dropwise with cooling and stirring to a solution of 48.2 g (0.5 mole) of 2-methylthiophene and 43.8 g of dimethylformamide in 50 ml of absolute benzene. The reaction mixture was then heated with stirring on a water bath for 2 h, poured over 300 g of crushed ice, and the resulting mixture was neutralized with sodium carbonate. The benzene layer was separated, and the aqueous layer was extracted with benzene. The solvent was removed by distillation, and the residue was distilled to give 55.3 g (87.5%) of 5-methyl-2-formylthiophene with bp 202-205° [bp 84-85° (3.5 mm) [18]].

5-Methyl-2-thienalbenzylamine. This was obtained in 92% yield from 5-methyl-2-formylthiophene and benzylamine and had mp 68° (from petroleum ether). Found %: N 6.37. $C_{13}H_{13}NS$. Calculated %: N 6.51.

1-(5'-Methyl-2'-thienyl)-2-nitropropylene. This was obtained in 90% yield from 5-methyl-2-thienalbenzylamine according to the method in [10] and had mp 117° (from alcohol). Found %: N 7.83. $C_8H_9NO_2$. Calculated %: N 7.65.

5-Methyl-2-acetonylthiophene. This was obtained in 50% yield by reduction of 1-(5'-methyl-2'-thienyl)-2-nitropropylene by the above method [11] and had bp 98-100° (10 mm). Found %: C 62.11; H 6.40; S 20.67. $C_8H_{10}OS$. Calculated %: C 62.30; H 6.54; S 20.79.

2,5,7-Trimethylthieno[2,3-c]pyrylium Perchlorate. An ice-cooled mixture of 5 ml of acetic anhydride and 0.8 ml of 70% perchloric acid was added dropwise to 1.54 g (0.01 mole) of 2-methyl-4-acetonylthiophene in 5 ml of glacial acetic acid with constant stirring. Slight warming of the reaction mixture was observed in the process, and the mixture was allowed to stand at room temperature for 10 min. After this an orange precipitate formed. Ether (15 ml) was added to the mixture, and the precipitate was filtered, washed on the filter with ether, and dried to give 2.26 g (80.7%) of the pyrylium salt with mp 160-161° (pale-yellow needles from alcohol). The constants, yields, and analytical data for the thieno[2,3-c]pyrylium salts similarly obtained are presented in Table 1.

2,4,6-Trimethylthieno[3,2-c]pyrylium Perchlorate. A total of 5.6 ml of 70% perchloric acid was added slowly with stirring to a mixture of 11 g (0.07 mole) of 5-methyl-2-acetonylthiophene and 35 ml of acetic anhydride. After 2 h the reaction mixture was diluted with 200 ml of ether, which resulted in the liberation of the pyrylium salt as a heavy, viscous liquid. The ether solution was carefully decanted, and the residue was treated with 20 ml of isopropyl alcohol. The pyrylium salt began to crystallize after some time; it was filtered, washed on the filter with isopropyl alcohol and ether, and dried to give 3.9 g (20%) of the pyrylium salt with mp 163-164° (from chloroform). Found %: C 43.30; H 3.69; Cl 12.81; S 11.32. $C_{10}H_{11}ClO_5S$. Calculated %: C 43.09; H 3.98; Cl 12.72; S 11.51.

2,6-Dimethyl-4-propylthieno[3,2-c]pyrylium Perchlorate. This was similarly obtained in 22% yield using butyric anhydride and had mp 144-146° (from chloroform). Found %: C 47.07; H 4.77; Cl 11.38; S 10.26. $C_{12}H_{15}ClO_5S$. Calculated %: C 46.98; H 4.93; Cl 11.56; S 10.45.

2,5,7-Trimethylthieno[2,3-c]pyridine. Gaseous ammonia was passed in the course of 5-10 min into a mixture of 2.8 g (0.01 mole) of 2,5,7-trimethylthieno[2,3-c]pyrylium perchlorate and 10 ml of alcohol. The reaction mixture was then poured into 100 ml of cold water, the organic layer was extracted with ether, and the ether solution was washed with water and dried over potassium hydroxide. After removal of the ether the residue was vacuum distilled to give 1.4 g (80%) of thienopyridine with bp 126-129° (8 mm). The picrate had mp 176-178° (from alcohol). Found %: N 14.00. $C_{16}H_{14}N_4O_7S$. Calculated %: N 13.79.

2,5-Dimethyl-7-ethylthieno[2,3-c]pyridine. This was similarly obtained. The picrate had mp 190-191° (yellow needles from alcohol). Found %: N 13.55. $C_{17}H_{16}N_4O_7S$. Calculated %: N 13.33.

5,7-Dimethylthieno[2,3-c]pyridine. This was obtained in 76% yield from 5,7-dimethylthieno[2,3-c]-pyrylium perchlorate and had bp 116-118° (3 mm). The picrate had mp 189° (needles from alcohol). Found %: N 14.13. $C_{15}H_{12}N_4O_7S$. Calculated %: N 14.28. The hydrochloride had mp 313-315° (from aqueous acetone). Found %: N 6.89. $C_9H_{10}ClNS$. Calculated %: N 7.01. The methiodide had mp 255-257°. Found %: N 4.30. $C_{10}H_{12}INS$. Calculated %: N 4.59.

5-Methyl-7-ethylthieno[2,3-c]pyridine. This compound was similarly obtained. The picrate had mp 202-204° (yellow needles from alcohol). Found %: N 13.65. $C_{16}H_{14}N_4O_7S$. Calculated %: N 13.79.

5-Methyl-7-propylthieno[2,3-c]pyridine. The picrate had mp 148-149° (yellow needles from alcohol). Found %: N 13.19. $C_{17}H_{16}N_4O_7S$. Calculated %: N 13.33.

2,4,6-Trimethylthieno[3,2-c]pyridine. This was obtained in 60% yield by the action of ammonia on 2,4,6-trimethylthieno[3,2-c]pyrylium perchlorate. The picrate had mp 151-153° (from alcohol). Found %: N 14.00. $C_{17}H_{14}N_4O_7S$. Calculated %: N 13.79. The hydrochloride had mp 145-147° (from aqueous acetone). Found %: N 6.27. $C_{10}H_{12}ClNS$. Calculated %: N 6.55.

2,6-Dimethyl-4-propylthieno[3,2-c]pyridine. The picrate had mp 144-145° (from alcohol). Found %: N 12.47. $C_{19}H_{18}N_4O_7S$. Calculated %: N 12.56.

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