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CONDENSED PYRIDINE BASES. A NEW APPROACH TO THE SYNTHESIS OF 3-PHENACYLBENZO[*b*]THIOPHENES AND 3-PHENACYL-5-ETHYLTHIENO[2,3-*b*]THIOPHENE. SYNTHESIS OF NEW DERIVATIVES OF BENZOTHIENO[2,3-*c*]PYRYLIUM AND THIENO[2′,3′:5,4]THIENO[2,3-*c*]PYRYLIUM AND PYRIDINE BASES

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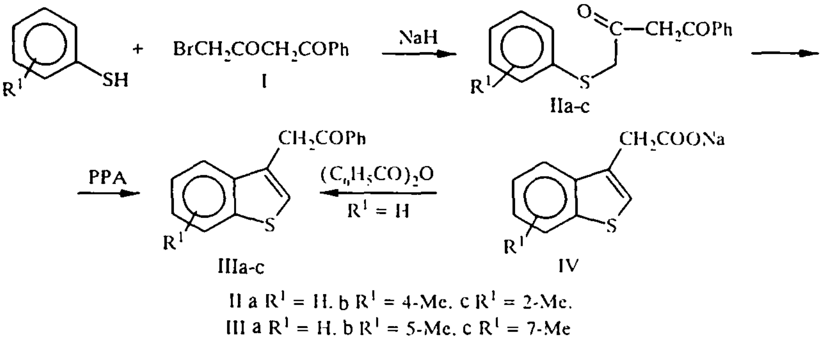
A new method is proposed for the production of substituted 3-phenacylbenzo[b]thiophenes by the intramolecular cyclization of 1-phenyl-4-phenylthio-1,3-butanediones in polyphosphoric acid. The analogous cyclization of 1-phenyl-4-(5-ethyl-2-thienylthio)-1,3-butanedione leads to 3-phenacyl-5-ethylthieno[2,3-b]thiophene. The acylation of substituted 3-phenacylbenzo[b]thiophenes and 3-phenacyl-5-ethylthieno[2,3-b]thiophene by the anhydrides of aliphatic acids in the presence of perchloric acid leads to 1-alkyl-3-phenylbenzothieno[2,3-c]pyrylium perchlorates and 2-ethyl-5-phenyl-7-methylthieno[2′,3′:5,4]thieno[2,3-c]pyrylium perchlorate. The action of ammonium acetate on the obtained salts gives the corresponding pyridine bases.

One of the promising directions in the chemistry of pyrylium salts is the synthesis of new biologically active compounds based on them. Thus, we earlier realized the synthesis of 1,3-dialkylbenzo[b]thieno[2,3-c]pyrylium salts and from them 1,3-dialkylbenzo[b]thieno[2,3-c]pyridines, among which compounds having neuroleptic activity were found [1]. Acid-catalyzed heterocyclization, involving the acylation of 3-acetonylbenzo[b]thiophene by aliphatic acid anhydrides in the presence of perchloric acid, was used for the synthesis of the pyrylium salts [2]. The present communication is a continuation of researches into acid-catalyzed heterocyclization in the benzo[b]thiophene and thieno[2,3-b]thiophene series [3, 4]. The subjects of heterocyclization were 3-phenacylbenzo[b]thiophenes and 3-phenacyl-5-ethylthieno[2,3-b]thiophene. The latter have not been described in the literature. The synthesis of the phenacyl derivatives of aromatic and heteroaromatic systems usually starts from the corresponding aryl(heteryl)acetic acids [5-6]. In view of the poor accessibility of the initial benzo[b]thiophene-3-acetic acids, obtained by the method in [7, 8], this method seemed to us unattractive. A synthetic approach analogous to the synthesis of 3-phenacylbenzo[b]furans [9] and involving the intramolecular cyclization of 1-phenyl-4-phenylthio-1,3-butanediones (IIa-c) in polyphosphoric acid was used for the synthesis of the 3-phenacylbenzo[b]thiophenes. The initial 1-phenyl-4-phenylthio-1,3-butanediones (IIa-c) were obtained by the reaction of sodium thiophenolates with 1-phenyl-4-bromo-1,3-butanedione (I).



II a R^1 = H, b R^1 = 4-Me, c R^1 = 2-Me,
III a R^1 = H, b R^1 = 5-Me, c R^1 = 7-Me

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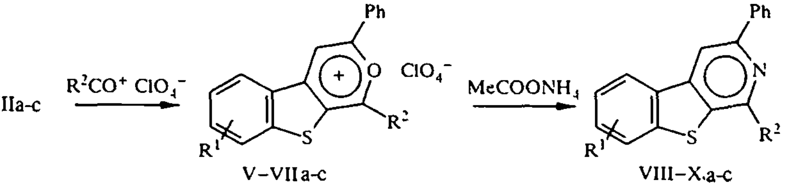
TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, % C	H	Cl	S	mp, °C	Yield, %
Va	$C_{18}H_{13}ClO_5S$	57.7 57,4	3.8 3,5	9.2 9,4	8.2 8,5	270...271	93
Vb	$C_{19}H_{15}ClO_5S$	58.1 58,4	3.9 3,8	9.4 9,1	8.4 8,2	255...256	91
Vc	$C_{20}H_{17}ClO_5S$	59.6 59,3	4.0 4,2	8.5 8,8	8.1 7,9	233...234	90
VIa	$C_{19}H_{15}ClO_5S$	58.6 58,4	3.6 3,8	9.0 9,1	8.5 8,2	265...266	92
VIb	$C_{20}H_{17}ClO_5S$	59.1 59,3	4.0 4,2	8.6 8,8	7.8 7,9	249...251	91
VIc	$C_{21}H_{19}ClO_5S$	60.4 60,2	4.2 4,5	8.7 8,5	7.5 7,7	244...245	91
VIIa	$C_{19}H_{15}ClO_5S$	58.5 58,4	3.6 3,8	9.3 9,1	8.0 8,2	275...276	94
VIIb	$C_{20}H_{17}ClO_5S$	59.0 59,3	4.0 4,2	8.7 8,8	7.7 7,9	258...259	91
VIIc	$C_{21}H_{19}ClO_5S$	60.4 60,2	4.7 4,5	8.4 8,5	7.6 7,7	256...257	90

An attempt to obtain the diketones (IIa-c) by the Claisen reaction from (phenylthio)acetic esters and acetophenone, similar to the production of 1-phenyl-4-phenoxy-1,3-butane diones [9], was unsuccessful, since in this case hydrolysis of the esters occurred. According to the IR and PMR spectra, the diketones (IIa-c) are present in the enolic form. The IR spectra contain a group of absorption bands of the C=C and C=O bonds in the enolic form in the region of 1610-1655 cm^{-1}. In the PMR spectra there is a signal for the proton at the double bond in the region of 5.5 ppm and for the OH group of the enolic form in the region of 14.3 ppm.

The cyclization of 1-phenyl-4-phenylthio-1,3-butanediones (IIa-c) to the substituted 3-phenacylbenzo[b]thiophenes (IIIa-c) takes place on heating in polyphosphoric acid. The yields of the ketones amount to 60%. An alternative synthesis of 3-phenacylbenzo[b]thiophene (IIIa) was realized by heating sodium benzo[b]thiophene-3-acetate with benzoic anhydride. The compound (IIIa) obtained by the different methods was identical.



V, VIII R^1 = H, VI, IX R^1 = 6-Me, VII, X R^1 = 8-Me.
a R^2 = Me, b R^2 = Et, c R^2 = C_3H_7

The acylation of the ketones (IIIa-c) by aliphatic acid anhydrides in the presence of perchloric acid leads to the 1-alkyl-3-phenylbenzothieno[2,3-c]pyrylium perchlorates (V-VIIa-c), which were isolated with yields close to quantitative (Table 1).

In the IR spectra of the salts (V-VIIa-c) there are absorption bands in the regions of 1610 and 1530 cm^{-1}, corresponding to the stretching vibrations of the pyrylium ring.

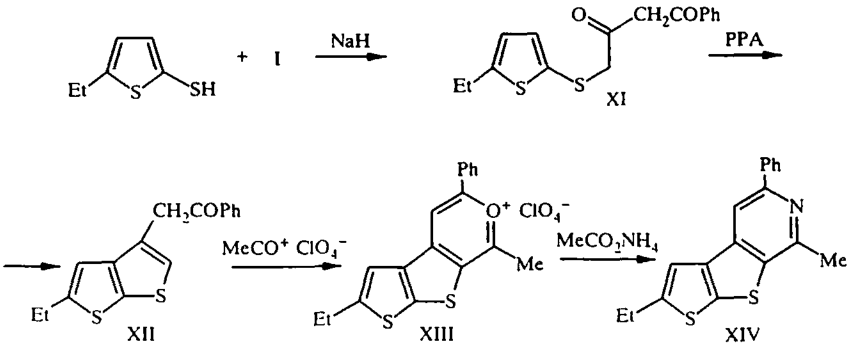


TABLE 2. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % Calculated, %				mp, °C	Yield, %
		C	H	N	S		
VIIIa	$C_{18}H_{13}NS$	78.4 78,6	4.9 4,7	5.0 5,1	11.5 11,6	74...76	89
VIIIb	$C_{19}H_{15}NS$	78.8 78,9	5.0 5,2	4.6 4,8	11.4 11,1	97...98	88
VIIIc	$C_{20}H_{17}NS$	79.5 79,2	5.8 5,6	4.7 4,6	10.4 10,6	71...73	90
IXa	$C_{19}H_{15}NS$	78.7 78,9	5.3 5,2	5.0 4,8	11.0 11,1	94...95	91
IXb	$C_{20}H_{17}NS$	79.4 79,2	5,8 5,6	4.4 4,6	10.5 10,6	66...68	90
IXc	$C_{21}H_{19}NS$	79.4 79,5	6.2 6,0	4.5 4,4	10.3 10,1	59...60	87
Xa	$C_{19}H_{15}NS$	78.7 78,9	5.0 5,2	4.7 4,8	11.4 11,1	103...104	89
Xb	$C_{20}H_{17}NS$	79.3 79,2	5.5 5,6	4.6 4,6	10.3 10,6	128...129	87
Xc	$C_{21}H_{19}NS$	79.3 79,5	6.2 6,0	4.6 4,4	10.3 10,1	104...105	88
XIV	$C_{18}H_{15}NS_2$	69.5 69,9	4.7 4,9	4,8 4,5	20.5 20,7	69...70	84

It seemed of interest to use the developed method for the synthesis of 3-phenacylthieno[2,3-b]thiophene. The reaction of 2-mercapto-5-ethylthiophene with the bromo diketone (I) gave 1-phenyl-4-(5-ethyl-2-thienylthio)-1,3-butanedione (XI), the cyclization of which in polyphosphoric acid gave 3-phenacyl-5-ethylthieno[2,3-b]thiophene (XII). Acylation with acetic anhydride took place at the free α position of the thiophene ring, giving the pyrylium perchlorate (XIII). The 1-alkyl-3-phenylbenzothieno[2,3-c]pyridines (VIII-Xa-c) and 2-ethyl-5-phenyl-7-methylthieno[2′,3′:5,4]thieno[2,3-c]pyridine were obtained by heating the respective pyrylium salts with ammonium acetate in acetic acid (Table 2).

EXPERIMENTAL

The IR spectra were recorded in Vaseline oil on a UR-20 spectrometer. The PMR spectra were recorded on a Tesla BS-267 instrument at 60 MHz with TMS as internal standard. The spectra of the pyrylium salts were recorded in trifluoroacetic acid, and those of the pyridine bases in carbon tetrachloride.

1-Phenyl-4-bromo-1,3-butanedione (I). To a solution of 16.2 g (0.1 mole) of benzoylacetone in 150 ml of dry ether with cooling in iced water we added 16 g (0.1 mole) of bromine. The solution was stirred for 2 h and left at room temperature for 24 h. The product was poured onto ice, and the ether solution was separated, washed with 5% sodium bicarbonate solution and with water, and dried with sodium sulfate. The ether was removed, and the residue was crystallized from hexane. The yield was 20 g (83%); mp 32°C. PMR spectrum, C_7F_8 (δ, ppm): 3.43 (2H, s, CH_2); 5.87 (1H, s, $-C=$); 6.80-7.20 (5H, m, H_{arom}); 14.3 (1H, s, $HO-C=C$). Found %: C 50.1; H 3.5; Br 33.5. $C_{10}H_9BrO_2$. Calculated %: C 49.8; H 3.7; Br 33.2.

1-Phenyl-4-phenylthio-1,3-butanedione (IIa). To 2.4 g (0.1 mole) of sodium hydride in 100 ml of dry THF we added dropwise a solution of 11.0 g (0.1 mole) of thiophene in 30 ml of THF. To the obtained suspension of sodium thiophenolate we added 24.1 g (0.1 mole) of 1-phenyl-4-bromo-1,3-butanedione. The mixture was stirred at room temperature for 30 min and at 60°C for 1 h. The tetrahydrofuran was distilled at reduced pressure. To the residue we added 100 ml of water, and we filtered off the crystals. The yield was 19.2 g (71%); mp 49-51°C (from hexane). IR spectrum, cm^{-1}: 1650-1610 ($C=C$ and $C=O$), 1570, 1300, 1270, 1080. PMR spectrum, C_5D_5N (δ, ppm): 3.90 (2H, s, CH_2); 6.60 (1H, s, $-CH=$); 7.00-7.70 (10H, m, H_{arom}). Found %: C 71.3; H 5.0; S 12.0. $C_{16}H_{14}O_2S$. Calculated %: C 71.1; H 5.2; S 11.9.

1-Phenyl-4-(p-tolylthio)-1,3-butanedione (IIb). The compound was obtained by a method similar to the production of compound (IIa), using p-thiocresol as starting compound. The yield was 73%; mp 41-42°C (from hexane). Found %: C 71.5; H 5.8; S 11.5. $C_{17}H_{16}O_2S$. Calculated %: C 71.8; H 5.6; S 11.3.

TABLE 3. Spectral Characteristics of the Compounds (Va-Xa, XIII, XIV)

Compound	PMR spectrum, δ, ppm
Va	3,30 (3H, s, 1-CH_3); 7,60...8,67 (9H, m, H_{arom}); 8,87 (1H, s, 4-H)
VIa	2,53 (3H, s, 6-CH_3); 3,29 (3H, s, 1-CH_3); 7,60...8,60 (8H, m, H_{arom}); 8,77 (1H, s, 4-H)
VIIa	2,67 (3H, s, 8-CH_3); 3,30 (3H, s, 1-CH_3); 7,81...8,78 (8H, m, H_{arom}); 8,90 (1H, s, 4-H)
VIIIa	2,71 (3H, s, 1-CH_3); 7,21...8,15 (10H, m, H_{arom})
IXa	2,51 (3H, s, 6-CH_3); 2,71 (3H, s, 1-CH_3); 7,21...8,10 (9H, m, H_{arom})
Xa	2,57 (3H, s, 8-CH_3); 2,70 (3H, s, 1-CH_3); 7,20...8,10 (9H, m, H_{arom})
XIII	1,50 (3H, t, 2-$CH_2\underline{CH_3}$); 3,00 (2H, q, 2-$\underline{CH_2}CH_3$); 3,17 (3H, s, 7-CH_3); 7,50 (1H, s, 3-H); 7,60...8,60 (6H, m, H_{arom})
XIV	1,38 (3H, t, 2-$CH_2\underline{CH_3}$); 2,64 (3H, s, 7-CH_3); 2,90 (2H, q, 2-$\underline{CH_2}CH_3$); 7,10 (1H, s, 3-H); 7,20...8,10 (6H, m, H_{arom})

1-Phenyl-4-(o-tolylthio)-1,3-butanedione (IIc). The compound was obtained by a method similar to the production of compound (IIa), using o-thiocresol as starting compound. The yield was 70%; mp 35-36°C (from hexane). PMR spectrum, C_7F_8 (δ, ppm): 1.90 (3H, s, CH_3); 3.30 (2H, s, CH_2); 5.50 (1H, s, $-CH=$); 6.90-7.70 (9H, m, H_{arom}); 14.2 (1H, s, $HO-C=C$). Found %: C 71.5; H 5.7; S 11.5. $C_{17}H_{16}O_2S$. Calculated %: C 71.8; H 5.6; S 11.3.

3-Phenacylbenzo[b]thiophene (IIIa). A. To 200 g of polyphosphoric acid with vigorous stirring we added 27 g (0.1 mole) of the diketone (IIa). The obtained mixture was kept at 75-80°C for 2.5 h. The mixture was cooled and poured onto 0.5 kg of ice. The product was extracted with benzene, and the benzene extract was washed with 100 ml of a 3% solution of sodium hydroxide and dried with sodium sulfate. The benzene was distilled, and the residue was crystallized from hexane. The yield was 15 g (60%); mp 110-112°C. IR spectrum, cm^{-1}: 1675 (C=O), 1585, 1330, 1210, 980, 775. Found %: C 76.4; H 5.1; S 12.4. $C_{16}H_{12}OS$. Calculated %: C 76.2; H 4.8; S 12.7.

B. Sodium benzo[b]thiophene-3-acetate (0.1 mole) was heated with a twofold excess of benzoic anhydride (0.2 mole) at 180°C and kept at this temperature for 1 h. The mixture was cooled, and 100 ml of a 20% solution of sodium hydroxide was added. After the benzoic acid had dissolved the substance was extracted with benzene, and the benzene layer was washed with water and dried with sodium sulfate. The benzene was removed, and the residue was crystallized from hexane. The yield was 60%. The IR spectrum of the product was identical with the spectrum of compound (IIIa), obtained by cyclization of the diketone (IIa) by method A. A mixed melting test did not give a melting point depression.

5-Methyl-3-phenacylbenzo[b]thiophene (IIIb). The compound was obtained by a similar method by the cyclization of compound (IIb). The yield was 63%; mp 57-59°C. IR spectrum, cm^{-1}: 1680 (C=O). Found %: C 76.4; H 5.0; S 12.1. $C_{17}H_{14}OS$. Calculated %: C 76.7; H 5.3; S 12.0.

7-Methyl-3-phenacylbenzo[b]thiophene (IIIc). The compound was obtained by a similar method by the cyclization of the diketone (IIc). The yield was 63%; mp 101-102°C. IR spectrum, cm^{-1}: 1680 (C=O). Found %: C 76.5; H 5.2; S 12.3. $C_{17}H_{14}OS$. Calculated %: C 76.7; H 5.3; S 12.0.

General Procedure for the Preparation of 1-Alkyl-3-phenylbenzothieno[2,3-c]pyrylium Perchlorates (V-VIIa-c) and the Perchlorate (XIII). To a solution of 0.01 mole of the ketone (IIIa-c) in 7 ml of the respective anhydride at room temperature and with stirring we added 1 ml of 70% perchloric acid. The reaction mixture heated, and after some time it solidified. After 30 min, 20 ml of ether was added to the reaction mixture. The precipitate was filtered off, washed with alcohol and with ether, and dried. The product was crystallized from acetic acid (Table 1).

General Procedure for the Preparation of 1-Alkyl-3-phenylbenzothieno[2,3-c]pyridines (VIII-Xa-c) and the Pyridine (XIV). A mixture of 0.01 mole of the compound (V-VIIa-c, XIII), 10 g of ammonium acetate, and 80 ml of glacial acetic acid was boiled for 3 h. The solution was evaporated to half and poured into 100 ml of cold water. The precipitate was filtered off and crystallized from hexane (Table 2).

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