FUNCTIONAL DERIVATIVES OF THIOPHENE

IV.* NEW METHOD FOR THE SYNTHESIS OF 4H-THIENO[2,3-b][1,4]BENZOTHIAZINES

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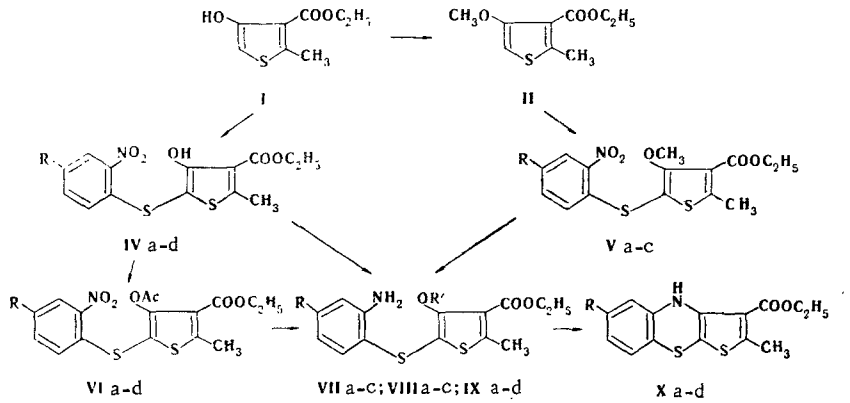
A preparative method for the synthesis of thienobenzothiazines – phenothiazine analogs – was worked out on the basis of 2-methyl-3-carbethoxythiophene derivatives and nitroarenesulfenyl chlorides.

Some thiophene analogs of phenothiazine – thienobenzothiazines [4, 5] – are of interest in connection with the search for medicinal preparations. However, the starting compounds for their synthesis are relatively difficult to obtain.

We propose a fundamentally new method for the synthesis of a number of 4H-thieno[2,3-b][1,4]benzothiazines from the accessible 2-methyl-3-carbethoxythiophene derivatives (I [6], II) and 2-nitroarenesulfenyl chlorides (IIIa-d) via the scheme



a R=H, b R=Cl, c R=Br, d R=$COOC_2H_5$; VII R′=H, VIII R′=CH_3, IX R′=$COCH_3$

We have found that nitroarylthiothiophenes (IVa-d, Va-c) are formed in 80-98% yield in the reaction of I-II with arenesulfenyl chlorides (IIIa-d). Derivatives VIa-d are obtained by acylation of IVa-d. Reduction of nitro compounds IVa-c, Va-c, and VIa-d with iron in aqueous dioxane in the presence of catalytic amounts of hydrochloric acid leads to aminoarylthiothiophenes (VIIa-c, VIIIa-c, and IXa-d), the yields of which depend on the character of the substituent in the 4 position of the thiophene ring. Partial resinification is observed in the reduction of IVa-c, while aminoarylthiothiophenes VIIIa-c and IXa-d are obtained in high yields.

The cyclization of VIIa-c and VIIIa-c to 4H-thieno[2,3-b][1,4] benzothiazine derivatives (Xa-c) proceeds on heating in the presence of catalytic amounts of iodine and without solvents. In this case, VIIIa-c

*See [1-3] for communications I-III.

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TABLE 1. Nitroarylthiothiophenes

Compound	R′	R′	mp, °C	Empirical formula	Found, %					Calc., %					Yield, %
					C	H	Cl (Br)	N	S	C	H	Cl (Br)	N	S	
IVa	H	H	141,5—143	$C_{14}H_{13}NO_5S_2$	49,4	3,9	—	4,1	18,8	49,5	3,9	—	4,1	18,6	96,0
IVb	Cl	H	155,5—156	$C_{14}H_{12}ClNO_5S_2$	45,0	3,2	9,6	3,6	17,0	45,0	3,2	9,5	3,7	17,1	95,0
IVc	Br	H	151,5—152	$C_{14}H_{12}BrNO_5S_2$	40,2	2,9	19,3	3,3	15,3	40,2	2,9	19,1	3,3	15,3	98,0
IVd	$COOC_2H_5$	H	128,5—129,5	$C_{17}H_{17}NO_7S_2$	—	—	—	3,5	15,5	—	—	—	3,4	15,6	85,5
Va	H	CH_3	86—87	$C_{15}H_{15}NO_5S_2$	50,9	4,3	—	4,0	17,9	51,0	4,3	—	4,0	18,1	85,0
Vb	Cl	CH_3	99—100	$C_{15}H_{14}ClNO_5S_2$	46,4	3,6	9,1	3,5	16,6	46,4	3,6	9,1	3,6	16,5	80,0
Vc	Br	CH_3	129—131	$C_{15}H_{14}BrNO_5S_2$	41,5	3,5	18,6	3,2	14,8	41,7	3,3	18,5	3,2	14,8	81,0
VIa	H	$COCH_3$	128,5—129	$C_{16}H_{15}NO_6S_2$	50,3	4,0	—	3,7	17,1	50,4	4,0	—	3,7	16,8	91,0
VIb	Cl	$COCH_3$	124—125	$C_{16}H_{14}ClNO_6S_2$	46,3	3,3	15,7	3,5	15,7	46,2	3,4	8,5	3,4	15,4	92,5
VIc	Br	$COCH_3$	129—129,5	$C_{16}H_{14}BrNO_6S_2$	41,5	3,2	17,4	2,9	13,9	41,7	3,1	17,4	3,0	13,9	95,0
VId	$COOC_2H_5$	$COCH_3$	97—98	$C_{19}H_{19}NO_8S_2$	50,5	4,2	—	—	14,1	50,3	4,2	—	—	14,1	94,0

TABLE 2. Aminoarylthiothiophenes

Compound	R	R′	mp, °C	Empirical formula	Found, %					Calc., %					Yield, %
					C	H	Cl (Br)	N	S	C	H	Cl (Br)	N	S	
VIIa	H	H	59—60	$C_{14}H_{15}NO_3S_2$	54,5	4,9	—	4,3	20,6	54,3	4,9	—	4,5	20,7	45,0
VIIb	Cl	H	102—103	$C_{14}H_{14}ClNO_3S_2$	48,6	4,2	10,3	4,1	18,8	48,9	4,1	10,3	4,1	18,7	51,0
VIIc	Br	H	96—97	$C_{14}H_{14}BrNO_3S_2$	43,5	3,6	20,8	3,6	16,5	43,3	3,6	20,6	3,6	16,5	56,0
VIIIa*	H	CH_3	148—150	$C_{15}H_{17}NO_3S_2 \cdot HCl$	50,2	5,0	9,5	3,9	17,9	50,0	5,0	9,8	3,9	17,8	83,0
VIIIb	Cl	CH_3	61,5—62,5	$C_{15}H_{16}ClNO_3S_2$	50,4	4,5	10,1	4,1	18,1	50,3	4,5	9,9	3,9	17,9	75,0
VIIIc	Br	CH_3	74—75	$C_{15}H_{16}BrNO_3S_2$	44,6	3,9	19,9	3,5	16,2	44,8	4,0	19,7	3,5	15,9	80,0
IXa†	H	$COCH_3$	120—121	$C_{18}H_{19}NO_5S_2$	54,6	4,7	—	3,5	16,3	54,6	4,9	—	3,6	16,3	90,0
IXb	Cl	$COCH_3$	94—95	$C_{16}H_{16}ClNO_4S_2$	50,0	4,1	9,1	3,8	16,6	49,8	4,2	9,2	3,6	16,6	95,5
IXc	Br	$COCH_3$	102—103	$C_{16}H_{16}BrNO_4S_2$	44,7	3,7	18,7	3,3	14,9	44,7	3,8	18,6	3,3	14,9	95,0
IXd	$COOC_2H_5$	$COCH_3$	103,5—104,5	$C_{19}H_{21}NO_6S_2$	54,2	5,1	—	—	15,0	53,9	5,0	—	—	15,1	95,0

* The substance was isolated as the hydrochloride.

† The liquid substance was characterized as the aminoacetyl derivative.

TABLE 3. 4H-Thieno[2,3-b][1,4]benzothiazines

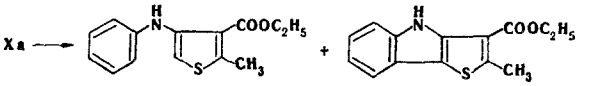
Compound	R	mp, °C	Empirical formula	Found, %					Calc., %					Yield, %		
				C	H	Cl (Br)	N	S	C	H	Cl (Br)	N	S	A	B	C
Xa	H	76,5—77,5	$C_{14}H_{13}NO_2S_2$	58,0	4,6	—	4,7	22,0	57,7	4,5	—	4,8	22,0	68,5	37,0	55,0*
Xb	Cl	92,5—93,5	$C_{14}H_{12}ClNO_2S_2$	51,8	3,6	10,9	4,5	19,6	51,6	3,7	10,9	4,3	19,7	63,0	36,4	61,0
Xc	Br	103,5—104,5	$C_{14}H_{12}BrNO_2S_2$	45,5	3,3	21,6	3,8	17,4	45,4	3,3	21,6	3,8	17,3	70,0	35,6	61,0
Xd	$COOC_2H_5$	94—95	$C_{17}H_{17}NO_4S_2$	56,1	4,7	—	—	17,6	56,2	4,7	—	—	17,6	—	—	65,0

* The yield given is based on VIIa.

are cyclized under more severe conditions, and Xa-c are therefore obtained in lower yields. The cyclization of acetoxy derivatives IXa-d to thienobenzothiazines Xa-d proceeds in dioxane in the presence of concentrated hydrochloric acid. The synthesis of thienobenzothiazines Xa-d through acetoxy derivatives is the most successful variant (the overall yield of Xa-d by this method is 48-54%, based on I).

The entry of the arenesulfenyl group into the α position of the thiophene ring of I and II is proved by the absence in the PMR spectrum of IV and V of a single signal at 6.1 ppm, which corresponds to the α proton of thiophene. The IR spectra of aminoarylthiothiophenes VII-IX do not contain the absorption bands at 1300-1350 and 1500-1550 cm^{-1} that are characteristic for the nitro group, and two bands of the stretching vibrations of a primary amino group appear at 3300-3500 cm^{-1}. Absorption is observed at 3340-3360 cm^{-1} (imino group) in the IR spectra of Xa-d. There are three absorption bands with λ_{max} (log ε) 220 (4.51), 260 (4.36), and 340 (3.59) nm in the UV spectra of Xa-d; this is in agreement with the literature data for other thienobenzothiazine derivatives [5].

The Smiles rearrangement [7] and, consequently, the formation of one of two isomeric compounds – 4H-thieno[2,3-b][1,4]benzothiazine or 4H-thieno[3,2-b][1,4]benzothiazine or a mixture of them – is possible in the cyclization of VIIa-c, VIIIa-c, and IXa-d.



XI XII

An investigation of the mixture obtained as a result of cyclization of VIIa by means of gas–liquid chromatography (GLC) demonstrated that in this case only one substance, which is a thienobenzothiazine, is formed. The structure of this compound, the individuality of which was confirmed by GLC and thin-layer chromatography (TLC) data, was proved by desulfuration of the thiazine ring of Xa with a Raney nickel catalyst. 3-Phenylamino-4-carbethoxy-5-methylthiophene (XI) and 2-methyl-3-carbethoxy[3,2-b]indole (XII) were isolated by chromatography of the desulfuration products with a column filled with aluminum oxide. Compounds XI and XII were identified by means of their IR and UV spectra and also by the absence of a melting-point depression of mixtures with samples obtained by other methods [1, 6]. According to the GLC data, the percentages of XI and XII in the reaction mixture are, respectively, 43.5 and 5.67%.

Thus Smiles rearrangement is not observed in the cyclization of VIIa.

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions were obtained with a Hitachi EPS-3 spectrophotometer. The PMR spectrum of a deuterochloroform solution was recorded with a JEOL JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard. The GLC was carried out with an IGS-810 chromatograph with a flame-ionization detector, a 200- by 0.3-cm partition column, a stationary phase consisting of 1% (by weight) of neopentylglycol sebacate, and a solid support of Chromosorb W (0.2-0.31-mm fraction). The temperatures of the column and input unit were 195 and 230°, respectively. The retention times of the compounds were as follows: Xa 13.5 min, XI 9.25 min, XII 3.5 min.

The o-nitrobenzenesulfenyl chlorides (IIIc, d) were obtained by the method described for other arenesulfenyl chlorides [8].

2-Nitro-4-bromophenylsulfenyl Chloride (IIIc). This compound had mp 103.5-104° (from CCl_4). Found: C 26.7; H 1.3; Cl+Br 43.0; N 5.2; S 11.6%. $C_6H_3BrClNO_2S$. Calculated: C 26.8; H 1.1; Cl+Br 42.9; N 5.2; S 11.9%.

Bis(2-nitro-4-carbethoxyphenyl) Disulfide. This compound had mp 163.5-164.5° (from alcohol). Found: S 14.2%. $C_{18}H_{16}N_2O_8S_2$. Calculated: S 14.1%.

2-Nitro-4-carbethoxyphenylsulfenyl Chloride (IIId). This compound had mp 77-78° (from CCl_4). Found: C 41.2; H 3.1; Cl 13.5; S 12.2%. $C_9H_8ClNO_4S$. Calculated: C 41.2; H 3.3; Cl 13.5; S 12.5%.

2-Methyl-3-carbethoxy-4-methoxythiophene (II). A solution of 19 g (0.1 mole) of I in a mixture of 100 ml of dioxane and 25 ml of acetone was cooled to 5°, after which 200 ml of 2 N sodium hydroxide and 19 ml (0.2 mole) of dimethyl sulfate were added successively with stirring in such a way that the temperature of the mixture did not rise above 10°. The mixture was then stirred at room temperature for 1 h and poured into cold water. The resulting dark oil was extracted with ether, and the ether solution was washed with water until it was neutral. It was then dried with magnesium sulfate, the solvent was removed by distillation, and the residue was vacuum-distilled to give 12 g (56%) of II with bp 121-122° (3 mm) and n_D^{20} 1.5257. Found: C 54.3; H 6.1; S 15.9%. $C_9H_{12}O_3S$. Calculated: C 54.0; H 6.0; S 16.0%.

2-Methyl-3-carbethoxy-4-hydroxy-5-(2'-nitroarylthio)thiophenes (IVa-d). A mixture of 0.11 mole of I, 0.11 mole of IIIa-d, and 40 ml of dry dioxane was refluxed with stirring for 15 min, after which it was cooled. The crystals were removed by filtration, washed with methanol, and dried. Data on the nitroarylthiothiophenes (IVa-d) are presented in Table 1.

2-Methyl-3-carbethoxy-4-methoxy-5-(2'-nitroarylthio)thiophenes (Va-c). A mixture of 0.01 mole of II and 0.01 mole of IIIa-c was heated at 85-90° for 15 min, after which it was cooled, and the resulting crystalline mass was recrystallized from methanol. Data on Va-c are presented in Table 1.

2-Methyl-3-carbethoxy-4-acetoxy-5-(2'-nitroarylthio)thiophenes (VIa-d). A mixture of 0.15 mole of IVa-d and 0.001 g of p-toluenesulfonic acid and 200 ml of acetic anhydride was refluxed for 1 h, after which it was cooled and poured over ice. The precipitate was removed by filtration, washed with water, and dried. Data on VIa-d are presented in Table 1.

2-Methyl-3-carbethoxy-4-hydroxy(methoxy)-5-(2'-aminoarylthio)thiophenes (VIIa-c, VIIIa-c). A 0.36 g-atom sample of iron filings* was added to a solution of 0.06 mole of IVa-c or Va-c in 600 ml of 65% aqueous dioxane, after which the mixture was heated with vigorous stirring on a water bath; at 70-80°, a solution of 1.2 ml of concentrated hydrochloric acid in 24 ml of water was added slowly dropwise to the mixture, and the resulting mixture was heated at 100° for 6 h. The resulting precipitate was removed by filtration and washed with hot dioxane. The dioxane was removed from the filtrate by vacuum distillation, and the residue was extracted with ether. The ether solution was washed with water and dried with magnesium sulfate. The solvent was then removed by distillation, and the residue was dissolved in the minimum amount of absolute ether and acidified with an ether solution of hydrogen chloride. The precipitated hydrochloride was separated and washed with absolute ether. To obtain the base, an aqueous solution of the hydrochloride was treated with 10% ammonium hydroxide and extracted with ether. The extract was washed with water and dried with magnesium sulfate. The solvent was removed by distillation, and the residue was crystallized from methanol. Data on VIIa-c and VIIIa-c are presented in Table 2.

2-Methyl-3-carbethoxy-4-acetoxy-5-(2'-aminoarylthio)thiophenes (IXa-d). As in the preceding experiment, 0.12 mole of VIa-d was reduced with 0.72 g-atom of iron filings in 700 ml of 65% aqueous dioxane and 3 ml of concentrated hydrochloric acid in 57 ml of water. The resulting precipitate was separated, and the filtrate was poured over ice. The precipitate was separated, washed with water, and dried. Data on IXa-d are presented in Table 2.

4H-Thieno[2,3-b][1,4]benzothiazines (Xa-d). A. A 0.07-mole sample of VIIa-c was heated at 110-115° for 15 min in the presence of 0.02 g of iodine. The resulting precipitate was separated and recrystallized from methanol. Data on Xa-c are presented in Table 3.

B. A mixture of 0.03 mole of VIIIa-c and 0.01 g of iodine was heated at 150-160° for 15 min, and the resulting crystalline mass was treated with ether. The ether solution was washed with water and

* Iron filings with particles smaller than 0.25 mm were used for the experiment.

dried, and the ether was removed by distillation. The residue was recrystallized from methanol. The resulting Xa-c did not depress the melting points of samples obtained by method A.

C. A mixture of 0.01 mole of IXa-d, 200 ml of dioxane, and 40 ml of concentrated hydrochloric acid was refluxed for 40 min, after which it was cooled and poured over ice. The precipitate was separated, washed with water, dried, and crystallized from alcohol. The resulting Xa-c did not depress the melting points of samples obtained by methods A and B.

Desulfuration of Xa. A mixture of 5.8 g (0.02 mole) of Xa and 36 g of Raney nickel paste in 70 ml of absolute alcohol was refluxed with stirring for 1.5 h. The nickel was then removed by filtration and washed with alcohol, and the filtrate was evaporated. The residue was chromatographed on 120 g of activity-II Al_2O_3 with petroleum ether as the eluent (10-ml fractions were collected). The first 15 fractions yielded 1.6 g (31.4%) of XI with mp 55-56° (from methanol) (mp 54-55° [1]). No melting-point depression was observed for a mixture of XI with a sample of 3-phenylamino-4-carbethoxy-5-methylthiophene obtained by the method in [1]. Found: C 64.3; H 5.9; N 5.3; S 12.2%. $C_{14}H_{15}NO_2S$. Calculated: C 64.3; H 5.8; N 5.4; S 12.3%.

Further elution with petroleum ether—benzene (10:1) gave 0.26 g (5%) of XII with mp 172-173° (from acetone) (mp 171-172° [6]). No melting-point depression was observed for a mixture of XII with a sample of 2-methyl-3-carbethoxy[3,2-b]indole obtained by the method in [6].

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