Transformations of 4,5,6,7-tetrahydrothieno[3,2-*c*]- and 1,2,3,4-tetrahydrobenzothieno[2,3-*c*]pyridines in reactions with alkynes activated by electron-withdrawing substituents

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The transformations of tetrahydrothieno[3,2-*c*]- and tetrahydrobenzothieno[2,3-*c*]pyridines in the reactions with acetylenedicarboxylic ester, alkyl propiolates, and acetylacetylene in alcohols were studied. Tetrahydrobenzothieno[3,2-*d*]azocines and 2-methoxyethyl-3-vinylaminoethylbenzothiophenes were synthesized.

Key words: tandem transformations, thienopyridines, benzothienopyridines, benzothienoazocines, activated alkynes.

An interest in the development of procedures for the synthesis of benzomorphanes and their heterocyclic analogs is associated with the presence of the azocine fragment in natural alkaloids.[1] It is also known[2] that bicyclic azocines, *viz.*, benzomorphanes, have analgesic activity. Heterofused azocines remain virtually unknown.

Procedures for the synthesis of thienoazocines described in the literature are few in number and are based on either the cleavage of dithienomorphanes and thienobenzomorphanes[3,4] or the Beckmann rearrangement of benzothienocycloheptanone oximes.[5,6] Recently, we have demonstrated[7,8] that tetrahydropyrrolo[3,2-*c*]pyridines and their benzo analogs, *viz.*, tetrahydro-β- and γ-carbolines, can be transformed into tetrahydropyrrolo[2,3-*d*]azocines and tetrahydroazocino[5,4-*b*]- and -[4,5-*b*]indoles under the action of activated alkynes. Studies of the characteristic features of these transformations resulted in the development of an original procedure for the synthesis of the above-mentioned fused azocines.

We expected that tetrahydrothieno[3,2-*c*]- and tetrahydrobenzothieno[2,3-*c*]pyridines, which are analogs of tetrahydropyrrolopyridines and carbolines, would be transformed into thieno[2,3-*d*]azocines and benzothieno[3,2-*d*]azocines, respectively, under the same reaction conditions.

5-(*o*-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]-pyridine (**1**) and its 2-formyl derivative **2**, as well as 1,2,3-trimethyl- and 1,2,3,5,8-pentamethyl-1,2,3,4-tetrahydrobenzo[*b*]thieno[2,3-*c*]pyridines (**3** and **4**, respectively), were studied in the reactions with dimethyl acetylenedicarboxylate (DMAD), ethyl- and methyl propiolates, acetylacetylene, and propiolaldehyde.

Unlike tetrahydropyrrolo[3,2-*c*]pyridines, thienopyridine **1** reacts with DMAD in methanol only upon prolonged reflux. The expected 3-methoxymethylthiophene **5** was isolated from the resulting multicomponent mixture in 17% yield. The formation of the latter proceeds through the zwitterion **A**. The nucleophilic assistance of methanol through the formation of the transition state **B** facilitates the C(4)—N bond cleavage (Scheme 1).

The reaction of thienopyridine **1** with DMAD in boiling propan-2-ol afforded *N*-(dimethoxycarbonylvinyl)tetrahydrothieno[3,2-*c*]pyridine **6** and a small amount of 3-hydroxymethylthiophene **7**. This reaction pathway is, apparently, attributed to steric hindrance to the formation of the transition state **B** with propan-2-ol, resulting in debenzylation of the zwitterionic intermediate. Thiophene **7** is formed as a result of cleavage of the tetrahydropyridine fragment due to the presence of a water impurity in propan-2-ol and elimination of the benzyl fragment. The ability of thiophene to stabilize electron-deficient centers is much lower than that of pyrrole,[9] which is responsible for low activity of thienopyridine **1** in the reaction with DMAD.

2-Formyltetrahydrothienopyridine **2** reacts with DMAD in methanol and with ethyl propiolate in ethanol already at room temperature for 6 and 4 days, respectively, to form multicomponent mixtures.

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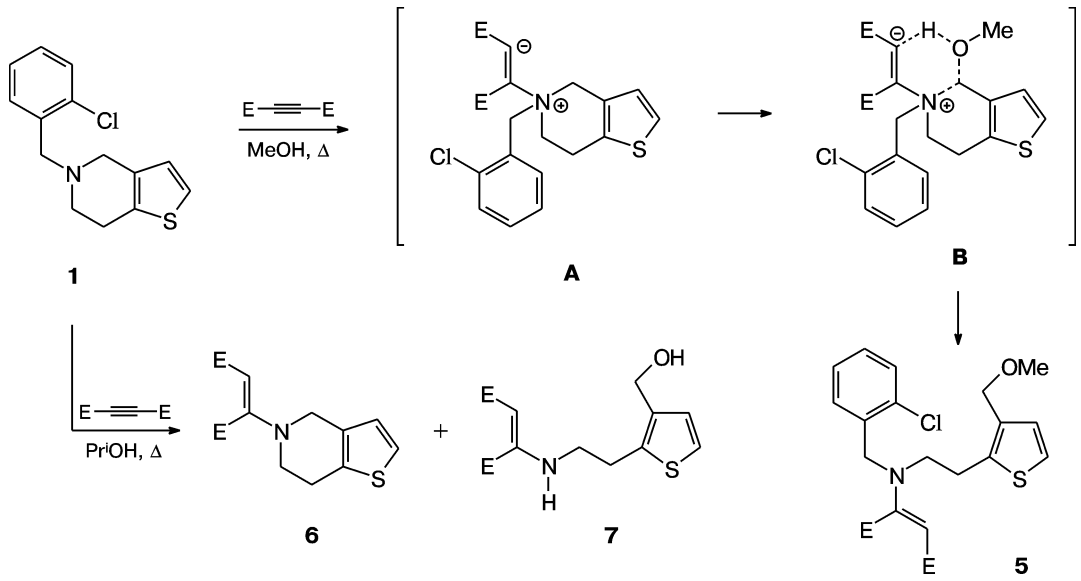
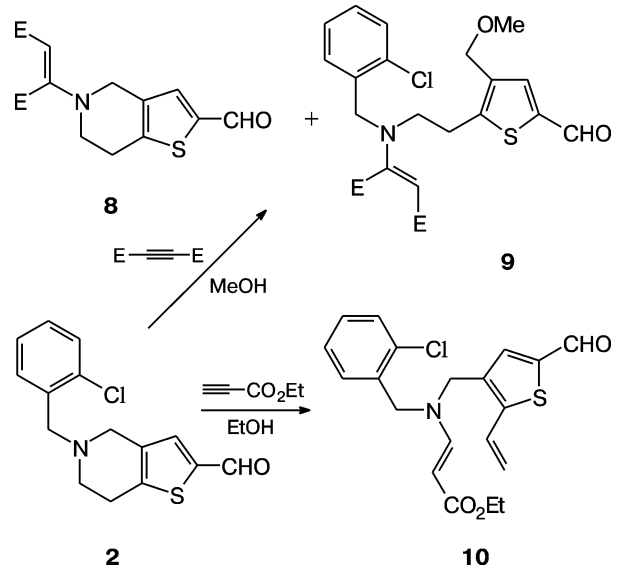
Scheme 1



E = CO_2Me

The reaction of formylthienopyridine **2** with DMAD afforded the debenzylation product (*N*-dimethoxycarbonylvinyl-2-formylthienopyridine **8**) and the cleavage product of the tetrahydropyridine ring (2-formyl-3-methoxymethylthiophene **9**) in equal amounts (27 and 28%, respectively), whereas the reaction with ethyl propiolate gave only 5-formyl-2-vinylthiophene **10**, which is formed as a result of the Hofmann cleavage of the tetrahydropyridine ring (Scheme 2).

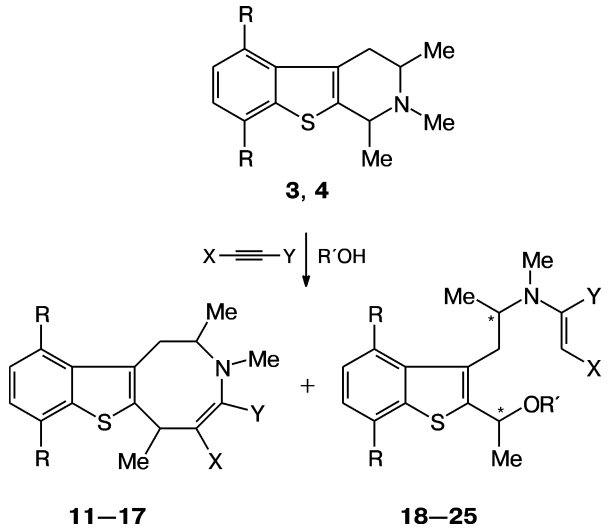
Scheme 2



E = CO_2Me

The reactions of tetrahydropyridines **3** and **4** with DMAD, methyl propiolate, ethyl propiolate, and acetyl-

Scheme 3



R = H (**3**), Me (**4**)

Compound	R	X	Y	Compound	R	R′	X	Y
11	H	CO_2Me	CO_2Me	**18**	H	Me	CO_2Me	CO_2Me
12	H	CO_2Me	H	**19**	H	Me	CO_2Me	H
13	H	COMe	H	**20**	H	Me	COMe	H
14	Me	CO_2Me	CO_2Me	**21**	Me	Me	CO_2Me	CO_2Me
15	Me	CO_2Et	H	**22**	Me	Et	CO_2Et	H
16	Me	CO_2Me	H	**23**	Me	Me	CO_2Me	H
17	Me	COMe	H	**24**	Me	Me	COMe	H
				25	Me	Me	CHO	H

acetylene in methanol proceed at room temperature and are completed in one day. In all cases, tetrahydrobenzothieno[3,2-*d*]azocines **11—17** and 2-methoxyethyl-3-(vinylaminopropyl)benzothiophenes **18—25** were isolated from the reaction mixtures in 2—9 and 22—50% yields, respectively, after chromatographic separation (Scheme 3, Table 1). The latter products, except for compound **22**, were obtained as mixtures of diastereomers (^{1}H NMR spectroscopic data).

The reactions of compounds **3** and **4** with propiolaldehyde[10] proceed with difficulty and are not brought to completion even in the presence of a 10-fold excess of alkyne. In the case of benzothienopyridine **4**, only 2-methoxyethylthiophene **25** was isolated from the reaction mixture in 47% yield.

It is known[11] that the reactions of tetrahydro-β-carbolines, which are analogs of tetrahydrothienopyridines **3** and **4**, with methyl and ethyl propiolates in acetonitrile produce exclusively azocino[5,4-*b*]indoles in 35—70% yields. The reactions of benzothienopyridines **3** and **4** with methyl propiolate and acetylacetylene at room temperature give mixtures, from which 5-methoxycarbonyl-substituted benzothienoazocines **12** and **16** and 5-acetyl derivative **17** were isolated chromatographically in 4—6% yields.

Attempts to perform cyclization of 2-methoxyethyl-substituted benzothiophenes **18—25** (by analogy with methoxymethyl-substituted indoles[7]) under the action of Lewis acids ($AlCl_3$, $ZnCl_2$, $TiCl_4$, or $Et_2O \cdot BF_3$) to prepare the corresponding benzothieno[3,2-*d*]azocines failed.

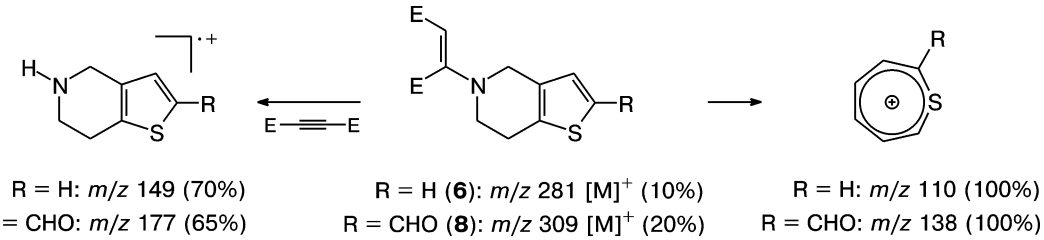
The structures of the resulting compounds were established by IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and X-ray diffraction. The

Table 1. Yields, physicochemical characteristics, mass spectrometric data, and elemental analysis data for benzothienoazocines **11—17** and 2-alkoxyethylbenzothiophenes **18—25**

Compound	Yield (%)	M.p.* /°C	MS, *m/z* ([M]$^+$)	Found / Calculated (%)			Molecular formula
				C	H	N	
11	4.5	Oil	374**	64.58	6.00	3.40	$C_{20}H_{23}NO_4S$
				64.32	6.21	3.75	
12	5.5	132—134	315	68.32	7.01	4.35	$C_{18}H_{21}NO_2S$
				68.54	6.71	4.44	
13	2	120—122	299	72.53	6.84	4.52	$C_{18}H_{21}NOS$
				72.20	7.07	4.68	
14	9	Oil	402**	66.03	6.52	3.46	$C_{22}H_{27}NO_4S$
				65.81	6.78	3.49	
15	4	110—111	357	70.31	7.42	4.01	$C_{21}H_{27}NO_2S$
				70.55	7.61	3.92	
16	4	196—198	343	70.23	7.00	4.15	$C_{20}H_{25}NO_2S$
				69.93	7.34	4.08	
17	6	234—236	327	73.58	7.29	4.24	$C_{20}H_{25}NOS$
				73.35	7.69	4.28	
18	50	80—82	405	62.38	6.80	3.30	$C_{21}H_{27}NO_5S$
				62.20	6.71	3.45	
19	25.5	Oil	348**	66.02	6.95	4.20	$C_{19}H_{25}NO_3S$
				65.68	7.29	4.03	
20	29	Oil	332**	68.42	7.68	4.42	$C_{19}H_{25}NO_2S$
				68.85	7.60	4.23	
21	35	114—116	433	63.58	7.43	3.42	$C_{23}H_{31}NO_5S$
				63.72	7.21	3.23	
22	22	Oil	404**	68.70	8.45	3.59	$C_{23}H_{33}NO_3S$
				68.45	8.24	3.47	
23	39	82—84	375	66.95	7.56	3.82	$C_{21}H_{29}NO_3S$
				67.17	7.78	3.73	
24	33	Oil	360**	70.01	8.39	4.12	$C_{21}H_{29}NO_2S$
				70.15	8.13	3.90	
25	47	98	345	69.90	7.98	4.18	$C_{20}H_{27}NO_2S$
				69.53	7.88	4.05	

* Hexane—AcOEt as the solvent.
** $[M + H]^+$ (LC-MS data).

Scheme 4



molecular structure of benzothienoazocine **16** is shown in Fig. 1.

The azocine ring adopts a boat conformation. The C(7), C(13), C(10), and C(11) atoms lie in one plane, whereas the N(1), C(8), C(9), and C(12) atoms are located above this plane at distances of 0.41, 0.49, 1.49, and 0.51 Å, respectively. The methyl groups at the C(9) and C(12) atoms are in *syn* orientations with respect to the eight-membered ring.

The IR spectra of compounds **11—24** show stretching bands of the corresponding functional groups. For example, these vibrations in the spectra of tetrahydrothieno[3,2-*d*]azocines **11** and **14** and alkoxyethylbenzothiophenes **18** and **21** are observed as two bands of the ester groups at 1730—1736 and 1680—1686 cm^{-1}, whereas the corresponding vibrations in the spectra of derivatives **12**, **15**, **16**, **19**, **22**, and **23** appear as one band at 1682—1665 cm^{-1}. The absorption band at 1624—1687 cm^{-1} belongs to the COMe group (compounds **13**, **17**, **20**, and **24**); the band at 1650 cm^{-1}, to the aldehyde group (methoxyethylbenzothiophene **25**). In the spectra of compounds **11—24**, the stretching vibrations of the double bond of the enamine fragment (—CH=CH—NMe) appear at 1563—1630 cm^{-1}.

The mass spectra of all compounds have molecular ion peaks corresponding to their molecular formulas. The major fragmentation pathways of the [M]$^+$ ions of *N*-dimethoxycarbonyl-substituted compounds **6** and **8** are associated with elimination of the DMAD molecule and retrodiene decomposition (Scheme 4).

The major fragmentation pathway of alkoxyethyl-substituted benzothiophenes **18—25** involves elimination through β-cleavage of the Me—CH=N$^+$(Me)—C(Y)=CH(X) fragment, whose peak has the maximum intensity. The main fragmentation channel for the [M]$^+$ ions of benzothienoazocines **11—17** is associated with the cleavage of the tetrahydroazocine moiety, resulting in the fragment ions with the highest intensity at *m/z* 174 (for azocines **11—13**) and 202 (for azocines **14—17**). These compounds have, apparently, the benzothiepinium structure (Scheme 5).

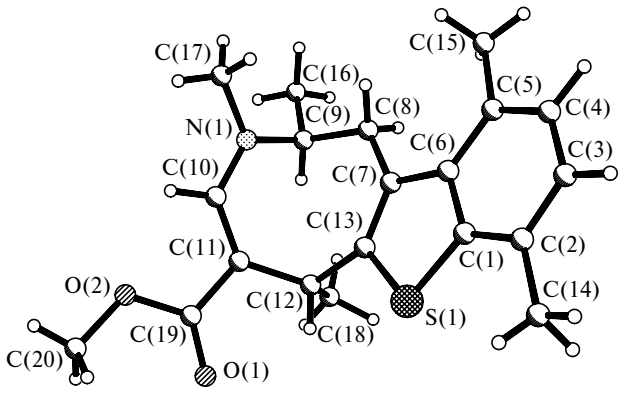
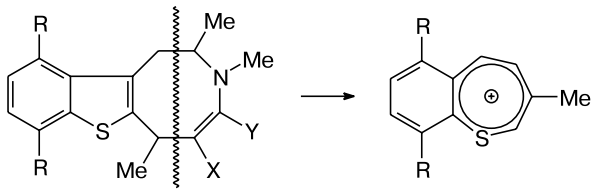


Fig. 1. Molecular structure of benzothienoazocine **16**.

Scheme 5



The ^{1}H NMR spectra of benzothienoazocines **11—17** and substituted benzothiophenes **18—25** show signals for all protons of the molecules with the corresponding chemical shifts and spin-spin coupling constants (Tables 2 and 3). The ^{1}H NMR spectra of azocines **12**, **13**, and **15—17** have a singlet for the H(4) proton at δ 7.40—7.56. The ^{1}H NMR spectra of diastereomers **18** and **21** are characterized by two singlets for the vinyl proton (δ 4.62, 4.64 and δ 4.57, 4.59, respectively); the spectra of mixtures of diastereomers of **19**, **20**, and **22—24**, by two doublets for the vinyl protons of each diastereomer at δ 7.37—7.58 and 4.55—5.06. In the spectrum of compound **25**, these signals appear as doublets at δ 6.78 and 6.94 and a multiplet at δ 5.14. The spin-spin coupling constants (12.1—12.9 Hz) are indicative of the *trans* configuration of the enamine fragment.

To summarize, we demonstrated that the transformations of fused tetrahydrothieno(benzothieno)pyridines in the reactions with activated alkynes start with the addition of the amine nitrogen atom at the triple bond and are

Table 2. ^{1}H NMR spectra of benzothienoazocines **11—17**

Compound	δ (*J*/Hz)									
	C(1)H$_2$ (dd)	H(2) (m)	H(6) (q)	C(2)Me (d)	C(6)Me (d)	NMe (s)	C(4)Y (s)	C(5)X	C(8)R, C(11)R	H(9), H(10)
11	2.94 (*J* = 16.8, *J* = 4.8); 3.20 (*J* = 16.8, *J* = 12.7)	4.35	4.76 (*J* = 7.2)	1.45 (*J* = 6.4)	1.60 (*J* = 7.2)	2.41	3.73 (OMe)	3.75 (s, OMe)	7.76, 7.63 (both d, *J* = 7.7)	7.35, 7.29 (both t, *J* = 7.7)
12	2.93 (*J* = 16.9, *J* = 3.2); 3.20 (*J* = 16.9, *J* = 12.7)	4.59	4.79 (*J* = 7.3)	1.44 (*J* = 6.6)	1.64 (*J* = 7.3)	2.79	7.55	3.72 (s, OMe)	7.73, 7.59 (both d, *J* = 7.5)	7.35, 7.29 (both t, *J* = 7.5)
13	2.98 (*J* = 17.0, *J* = 3.1); 3.29 (*J* = 17.0, *J* = 12.8)	4.69	5.03 (*J* = 7.1)	1.50 (*J* = 6.7)	1.65 (*J* = 7.1)	2.26	7.40	2.81 (s, Me)	7.61, 7.74 (both d, *J* = 7.9)	7.28—7.37 (m)
14	3.16 (*J* = 16.9, *J* = 4.7); 3.70 (*J* = 16.9, *J* = 12.7)	4.32	4.81 (*J* = 7.2)	1.42 (*J* = 6.4)	1.60 (*J* = 7.2)	2.70	3.72 (OMe)	3.76 (s, OMe)	2.44, 2.47 (both s, Me)	7.00, 6.95 (both d, *J* = 7.3)
15	3.20 (*J* = 16.9, *J* = 2.9); 3.65 (*J* = 16.9, *J* = 12.7)	4.54	4.85 (*J* = 7.2)	1.38 (*J* = 6.6)	1.65 (*J* = 7.2)	2.42	7.56	1.29 (t, Me, *J* = 7.1); 4.18 (q, CH$_2$, *J* = 7.1)	2.79, 2.76 (both s, Me)	6.98, 6.19 (both d, *J* = 7.3)
16	3.18 (*J* = 16.9, *J* = 2.9); 3.65 (*J* = 16.9, *J* = 12.7)	4.58	4.83 (*J* = 7.2)	1.39 (*J* = 6.6)	1.63 (*J* = 7.2)	2.42	7.55	3.72 (s, OMe)	2.79, 2.76 (both s, Me)	6.98, 6.92 (both d, *J* = 7.3)
17	3.21 (*J* = 16.7, *J* = 2.9); 3.69 (*J* = 16.7, *J* = 12.9)	4.62	5.05 (*J* = 7.3)	1.43 (*J* = 6.5)	1.62 (*J* = 7.3)	2.24	7.40	2.81 (s, Me)	2.85, 2.77 (both s, Me)	6.92, 6.97 (both d, *J* = 7.2)

common for such heterocyclic systems. The predominance of a particular transformation pathway is, apparently, determined by the electronic properties of the heterocyclic fragment.

Experimental

The IR spectra were recorded on an Infralum FT-801 Fourier-transform spectrometer in KBr pellets (for crystalline compounds) or in films (for oils). The mass spectra were obtained on Finnigan MAT 95XL and Hewlett—Packard MS-5988 mass spectrometers using a direct inlet system; the ionizing voltage was 70 eV. The ESI mass spectra were measured on an Agilent 1100 series LC/MSD Trap System VL mass spectrometer. The ^{1}H NMR spectra were recorded on a Varian Unity 400 instrument (400 MHz) in $CDCl_3$ with Me_4Si as the internal standard. The TLC analysis was performed on Silufol UV-254 plates (visualization with iodine vapor). Column chromatography was carried out on aluminum oxide (Brockmann activity 2; 60 mesh, Fluka) using an AcOEt—hexane mixture, (1 : 10)—(1 : 50), as the eluent.

The yields, physicochemical characteristics, elemental analysis data, and spectroscopic characteristics of the compounds are given in Tables 1—4.

5-(*o*-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**1**) was isolated from the pharmaceutical Ticlid by the alkaline treatment followed by extraction with diethyl ether. Compounds **3** and **4** were provided by the L. M. Litvinenko Institute of Physicoorganic and Coal Chemistry of the National Academy of Sciences of Ukraine. The synthesis of these compounds will be described elsewhere.*

5-(*o*-Chlorobenzyl)-2-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (2). Freshly distilled phosphorus oxychloride (2.9 g, 19 mmol) was added dropwise to anhydrous DMF (5 mL, 64 mmol) cooled to −5 °C. After 50 min, the reaction mixture was warmed to 20 °C, and a solution of thienopyridine **1** (0.5 g, 1.9 mmol) in anhydrous DMF (7 mL) was added. The reaction was performed at ~20 °C for 7 h and at 60—65 °C for 9 h. The course of the reaction was monitored by TLC. The reaction mixture was made alkaline (pH 10) with a 20% NaOH solution and extracted with diethyl ether (3×40 mL). The extract was dried with magnesium sulfate. Then diethyl ether was distilled off, and the residue was chromatographed. Formylthienopyridine **2** was obtained in a yield of 0.18 g (31%). Found (%): N, 4.83. $C_{15}H_{14}ClNOS$. Calculated (%): N, 4.80. IR, ν/cm^{-1}: 1700 (CHO). ^{1}H NMR, δ: 2.89 (t, 2 H, C(6)H$_2$, *J* = 5.3 Hz); 2.97 (t, 2 H, C(7)H$_2$, *J* = 5.3 Hz); 3.65 (s, 2 H, C(4)H$_2$); 4.40 (s, 2 H, C$\underline{H}_2$Ar); 7.19—7.29 (m, 2 H, H arom.); 7.38 (dd, 1 H, H arom., *J* = 7.6 Hz, *J* = 1.5 Hz); 7.39 (s, 1 H, H(3)); 7.50 (dd, 1 H, H arom., *J* = 7.3 Hz, *J* = 2.0 Hz); 9.79 (s, 1 H, CHO). MS, *m/z*: 291 [M]$^+$ (for ^{35}Cl).

Reaction of 5-(*o*-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (1) with DMAD. A mixture of thienopyridine **1** (0.3 g, 1.1 mmol) and DMAD (0.19 g, 1.34 mmol) in anhydrous MeOH or Pr^{i}OH (10 mL) was refluxed for 4 days. The course of the reaction was monitored by TLC. The solvent was distilled off

* S. V. Tolkunov, M. A. Kryuchkov, O. V. Shishkin, and R. I. Zubatyuk, *J. Heterocycl. Chem.*, 2007, in press.

Table 3. ^{1}H NMR spectra of 2-alkoxyethylbenzothiophenes **18—25**

Compound	δ (*J*/Hz)													*Z**
	C(2)R			C(3)R							C(4)R	C(7)R	H(5), H(6)	
	1′-Me	H(1′)	OR′	C(1′)H$_2$	2′-Me	H(2′)	NMe	C(4′)Y	C(5′)X	H(5′)				
18′	1.57 (d, *J* = 6.4)	4.72 (m)	3.26 (s, Me)	3.03 (m)	1.16 (d, *J* = 6.6)	3.82 (m)	2.83 (s)	3.61 (s, OMe)	3.61 (s, OMe)	4.64 (s)	7.64 (d, *J* = 7.9)	7.83 (d, *J* = 7.8)	7.31—7.40 (m)	1.86 : 1
18″	1.54 (d, *J* = 6.4)	4.72 (m)	3.27 (s, Me)	3.03 (m)	1.24 (d, *J* = 6.7)	3.82 (m)	2.80 (s)	3.62 (s, OMe)	3.62 (s, OMe)	4.62 (s)	7.60 (d, *J* = 7.6)	7.83 (d, *J* = 7.8)	7.31—7.40 (m)	
19′	1.54 (d, *J* = 6.4)	4.72 (m)	3.27 (s, Me)	3.02 (m)	1.24 (d, *J* = 7.1)	3.72 (m)	2.70 (s)	7.50 (d, *J* = 12.8)	3.65 (s, Me)	4.55 (d, *J* = 12.8)	7.61 (d, *J* = 7.8)	7.83 (d, *J* = 7.8)	7.34—7.39 (m)	1.22 : 1
19″	1.57 (d, *J* = 6.4)	4.72 (m)	3.29 (s, Me)	3.02 (m)	1.30 (d, *J* = 6.4)	3.72 (m)	2.72 (s)	7.58 (d, *J* = 12.8)	3.66 (s, Me)	4.57 (d, *J* = 12.8)	7.61 (d, *J* = 7.8)	7.83 (d, *J* = 7.8)	7.34—7.39 (m)	
20′	1.54 (d, *J* = 6.4)	4.73 (m)	3.28 (s, Me)	3.04 (m)	1.28 (d, *J* = 6.6)	3.80 (m)	2.74 (s)	7.46 (d, *J* = 12.7)	2.01 (s, Me)	5.04 (d, *J* = 12.7)	7.61 (d, *J* = 7.6)	7.61 (d, *J* = 7.6)	7.32—7.40 (m)	1 : 1
20″	1.57 (d, *J* = 6.4)	4.73 (m)	3.29 (s, Me)	3.04 (m)	1.33 (d, *J* = 6.6)	3.80 (m)	2.76 (s)	7.54 (d, *J* = 12.7)	2.04 (s, Me)	5.06 (d, *J* = 12.7)	7.83 (d, *J* = 7.9)	7.83 (d, *J* = 7.9)	7.32—7.40 (m)	
21′	1.53 (d, *J* = 6.4)	4.64 (m)	3.23 (br.s, Me)	3.09 (m)	1.24 (d, *J* = 6.9)	3.72 (m)	2.83 (s)	3.57 (s, OMe)	3.31 (s, OMe)	4.59 (s)	2.49 (br.s, Me)	2.66 (s, Me)	6.97—7.03 (m)	1.5 : 1
21″	1.55 (d, *J* = 6.4)	4.64 (m)	3.23 (br.s, Me)	3.09 (m)	1.30 (d, *J* = 6.7)	3.72 (m)	2.79 (s)	3.57 (s, OMe)	3.31 (s, OMe)	4.57 (s)	2.49 (br.s, Me)	2.79 (s, Me)	6.97—7.03 (m)	
22	1.24 (d, *J* = 6.5)	4.78 (q, *J* = 6.3)	1.28 (m, Me); 3.42 (m, C$\underline{H}_2$Me)	3.17 (m)	1.20 (d, *J* = 6.3)	3.58 (m)	2.49 (s)	7.49 (d, *J* = 12.9)	1.34 (t, Me, *J* = 7.4); 4.11 (q, C$\underline{H}_2$Me, *J* = 7.4)	4.59 (d, *J* = 12.9)	2.68 (s)	2.68 (s)	7.00, 7.04 (both d, *J* = 7.7)	—**
23′	1.32 (d, *J* = 6.7)	4.70 (m)	3.28 (s, Me)	3.17 (m)	1.52 (d, *J* = 6.2)	3.60 (m)	2.50 (s)	7.43 (d, *J* = 12.9)	3.64 (s, OMe)	4.55 (d, *J* = 12.9)	2.70 (br.s)	2.70 (br.s)	7.00 (d, *J* = 7.3)	6.7 : 1
23″	1.25 (d, *J* = 6.7)	4.70 (m)	3.29 (s, Me)	3.17 (m)	1.56 (d, *J* = 6.4)	3.60 (m)	2.50 (s)	7.34 (d, *J* = 12.9)	3.65 (s, OMe)	4.57 (d, *J* = 12.8)	2.70 (br.s)	2.70 (br.s)	7.05 (d, *J* = 7.3)	
24′	1.54 (m)	4.67 (m)	3.27 (s, Me)	3.17 (m)	1.27 (d, *J* = 6.3)	3.64 (m)	2.48 (br.s)	7.37 (d, *J* = 12.3)	2.01 (s, Me)	5.04 (m)	2.68 (br.s)	2.68 (br.s)	7.01 (d, *J* = 7.3)	1.5 : 1
24″	1.54 (m)	4.67 (m)	3.30 (s, Me)	3.17 (m)	1.33 (d, *J* = 6.5)	3.64 (m)	2.48 (br.s)	7.49 (d, *J* = 12.1)	2.01 (s, Me)	5.04 (m)	2.68 (br.s)	2.68 (br.s)	7.05 (d, *J* = 7.5)	
25′	1.54 (d, *J* = 6.2)	4.63 (m)	3.29 (s, Me)	3.18 (m)	1.35 (d, *J* = 6.7)	3.69 (m)	2.50 (s)	6.94 (m)	8.96 (s, CHO)	5.14 (m)	2.69 (br.s)	2.78 (br.s)	7.05 (m)	1.5 : 1
25″	1.55 (d, *J* = 6.4)	4.63 (m)	3.26 (s, Me)	3.18 (m)	1.40 (d, *J* = 6.8)	3.69 (m)	2.50 (s)	6.78 (m)	8.91 (s, CHO)	5.14 (m)	2.69 (br.s)	2.78 (br.s)	7.05 (m)	

* The ratio between the major (singly primed) and minor (doubly primed) diastereomers.
** One diastereomer.

in vacuo, and the residue was chromatographed. The reaction in methanol produced **dimethyl (*E*)-2-[*N*-(*o*-chlorobenzyl)-2-(3-methoxymethylthiophen-2-yl)ethyl]aminobut-2-ene-1,4-dioate (5).** The reaction in propan-2-ol afforded **dimethyl (*E*)-2-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-yl)but-2-ene-1,4-dioate (6)** and **dimethyl (*E*)-2-[2-(3-hydroxymethylthiophen-2-yl)ethyl]aminobut-2-ene-1,4-dioate (7)**.

Compound **5**. The yield was 0.08 g (16.6%), yellow oil. Found (%): N, 3.22. $C_{21}H_{24}ClNO_5S$. Calculated (%): N, 3.20. MS (LC-MS), *m/z*: 438 $[M + H]^+$ (for ^{35}Cl).

Compound **6**. The yield was 0.06 g (18%), yellow oil. Found (%): N, 4.93. $C_{13}H_{15}NO_4S$. Calculated (%): N, 4.98. ^{1}H NMR, δ: 2.92 (t, 2 H, C(6)H$_2$, *J* = 5.6 Hz); 3.50 (t, 2 H, C(7)H$_2$, *J* = 5.6 Hz); 3.65 and 3.95 (both s, 3 H each, MeO); 4.25 (s, 2 H, C(4)H$_2$); 4.85 (s, 1 H, CH=); 6.75 (d, H(3), *J* = 5.2 Hz); 7.15 (d, 1 H, H(2), *J* = 5.2 Hz). MS, *m/z*: 281 $[M]^+$ (for ^{35}Cl).

Compound **7**. The yield was 0.02 г (6%), yellow oil. Found (%): N, 4.63. $C_{13}H_{17}NO_5S$. Calculated (%): N, 4.68. ^{1}H NMR, δ: 2.90 and 3.50 (both t, 2 H each, CH$_2$, *J* = 5.3 Hz); 3.60 and 4.00 (both s, 3 H each, MeO); 4.25 (s, 2 H, C$\underline{H}_2$OH); 4.83 (s, 1 H, CH=); 6.78 (d, 1 H, H(4)); 7.14 (d, 1 H, H(5)). MS, *m/z*: 299 $[M]^+$ (for ^{35}Cl).

Reaction of 5-(*o*-chlorobenzyl)-2-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (2) with DMAD and ethyl propiolate. Acetylenedicarboxylic ester (0.1 g, 0.7 mmol) or ethyl propiolate (0.68 g, 0.7 mmol) was added to a solution of formylthienopyridine **2** (0.17 g, 0.58 mmol) in anhydrous MeOH or EtOH

Table 4. ^{13}C NMR of compounds **16**, **18—20**, **24**, and **25** (in $CDCl_3$)

Compound	δ
16	19.5, 19.7, 23.0, 24.9, 34.2, 34.4, 51.2, 54.2, 96.8, 98.5, 114.8, 123.7, 127.8, 129.1, 130.1, 138.4, 140.1, 140.9, 154.0, 170.2
18	18.1 (18.2), 23.8 (23.9), 30.6 (30.5), 31.3, 50.7, 52.7 (52.5), 56.3, 56.7 (56.4), 73.0 (73.1), 84.5 (84.5), 121.3 (121.2), 122.7 (122.8), 124.1, 124.4, 128.1, 138.8 (138.9), 139.5, 145.1 (145.0), 154.6, 165.8 (165.9), 167.9
19	11.1 (13.9), 22.6 (23.6), 28.6 (30.4), 38.7, 50.5, 56.4, 68.1, 73.0, 84.7, 121.1, 122.9, 124.4 (124.1), 128.5, 128.7 (130.8), 132.4, 138.9, 139.4, 144.9 (150.4), 167.7 (169.8)
20	19.3, 23.5, 23.6, 29.5 (29.4), 32.7 (32.6), 56.3 (56.5), 61.8 (61.7), 73.1 (73.0), 97.0, 121.1, 122.8 (122.7), 124.0, 124.4 (124.3), 128.2 (128.0), 138.8 (138.7), 139.2 (139.1), 144.7 (144.9), 150.0 (149.9), 195.2
24	18.9, 19.9, 21.4 (21.5), 23.6 (23.3), 28.2 (28.1), 29.6, 34.0 (33.7), 56.2 (56.6), 63.4, 72.9 (73.3), 97.5, 124.5 (124.3), 128.1, 129.6 (129.8), 130.1 (130.4), 137.1, 139.9 (138.8), 144.2, 145.0, 150.2, 195.2
25	10.9, 14.1, 23.0, 28.9, 33.4, 38.7, 63.5, 68.1, 73.5, 102.0, 124.6, 128.1, 128.1, 129.3, 132.5, 137.0, 140.1, 144.2, 145.3, 189.4

Note. The chemical shifts for the minor isomer are given in parentheses; in other cases, the signals of diastereomers are identical.

(10 mL), respectively. The reaction mixture was stirred at ~20 °C for 4—7 days. The course of the reaction was monitored by TLC. The solvent was evaporated *in vacuo*, and the residue was chromatographed. The reaction with DMAD produced **dimethyl (*E*)-2-(2-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-yl)but-2-ene-1,4-dioate (8)** and **dimethyl (*E*)-2-{*N*-*o*-chlorobenzyl-2-[(5-formyl-3-methoxymethylthiophen-2-yl)ethyl]amino}but-2-ene-1,4-dioate (9)**. The reaction with ethyl propiolate afforded **ethyl (*E*)-3-[*N*-*o*-chlorobenzyl-2-(5-formyl-2-vinylthiophen-3-ylmethyl)amino]acrylate (10)**.

Compound **8**. The yield was 0.06 g (27%), yellow oil. Found (%): N, 4.58. $C_{14}H_{15}NO_5S$. Calculated (%): N, 4.53. ^1H NMR, δ: 2.99 and 3.50 (both t, 2 H each, CH_2, J = 5.6 Hz); 3.65 and 3.96 (both s, 3 H each, MeO); 4.27 (s, 2 H, CH_2); 4.86 (s, 1 H, CH=); 7.42 (s, 1 H, H(3)); 9.83 (s, 1 H, CHO). MS (LC-MS), m/z: 310 $[M + H]^+$.

Compound **9**. The yield was 0.91 g (28%), yellow oil. Found (%): N, 2.93. $C_{22}H_{24}ClNO_6S$. Calculated (%): N, 3.01. ^1H NMR, δ: 3.15 (t, 2 H, CH_2, J = 5.3 Hz); 3.35 (s, 3 H, MeO); 3.55 (t, 2 H, CH_2, J = 5.3 Hz); 3.61 and 3.95 (both s, 3 H each, MeO); 4.35 (s, 2 H, CH_2OMe); 4.40 (s, 2 H, CH_2Ar); 4.85 (s, 1 H, CH=); 7.10—7.50 (m, 4 H, H arom.); 7.61 (s, 1 H, H(4)); 9.80 (s, 1 H, CHO). MS (LC-MS), m/z: 466 $[M + H]^+$ (for ^{35}Cl).

Compound **10**. The yield was 0.43 g (16%), yellow oil. Found (%): N, 3.63. $C_{20}H_{20}ClNO_3S$. Calculated (%): N, 3.59. ^1H NMR, δ: 1.26 (t, 3 H, CH_3CH_2, J = 5.8 Hz); 3.69 (s, 2 H, CH_2); 4.20 (q, 2 H, CH_2CH_3, J = 5.8 Hz); 4.32 (s, 2 H, CH_2Ar); 4.75 (d, 1 H, CH=, J = 13.1 Hz); 5.39 (d, 1 H, CH_2=, J = 10.7 Hz); 5.76 (d, 1 H, CH_2=, J = 17.1 Hz); 6.65 (dd, 1 H, CH=, J = 10.1 Hz, J = 17.1 Hz); 7.40 (s, 1 H, H(4)); 7.75 (d, 1 H, CH=, J = 13.1 Hz); 9.78 (s, 1 H, CHO). MS, m/z: 389 $[M]^+$ (for ^{35}Cl).

Reactions of tetrahydrobenzothieno[2,3-*c*]pyridines 3 and 4 with activated alkynes (general procedure). Activated alkyne (1 mmol, 0.14 g of DMAD, 0.084 g of methyl propiolate, 0.068 g of acetylacetylene, or 0.054 g of propiolaldehyde) was added to a solution of compound **3** (0.2 g, 0.84 mmol) or compound **4** (0.22g, 0.84 mmol) in anhydrous MeOH (5 mL). The reaction with ethyl propiolate was carried out in anhydrous EtOH. The reaction mixture was stirred for 20—24 h. The course of the reaction was monitored by TLC. Methanol (ethanol) was evaporated *in vacuo*, and the residue was chromatographed. Benzothienoazocines **11—17** and 2-alkoxyethylbenzothiophenes **18—25** were successively eluted. The yields, physicochemical constants, and elemental analysis data for compounds **11—25** are given in Table 1; the ^1H NMR spectroscopic data for benzothienoazocines **11—17**, in Table 2; the ^1H NMR spectroscopic data for benzothiophenes **18—25**, in Table 3; the ^{13}C NMR spectroscopic data for compounds **16**, **18—20**, **24**, and **25**, in Table 4.

X-ray diffraction study of compound 16. X-ray diffraction data were collected on an Enraf—Nonius CAD-4 diffractometer (Mo-Kα radiation, β filter, ω/2θ-scanning technique, $1.68° < \theta < 25.23°$) from a crystal of compound **16** of dimensions 0.56×0.21×0.20 mm. The crystals are monoclinic: a = 6.1639(1) Å, b = 18.704(4) Å, c = 15.867(3) Å, β = 93.31(3)°, V = 1826.0(6) Å^3, space group $P2(1)/c$, Z = 4, d_{calc} = 1.249 g cm^{-3}, μ = 0.189 mm^{-1}, T = 293 K. The intensities of 3286 independent reflections were measured. The structure was solved by direct methods using the SHELXS-97 program package[12] and refined anisotropically by the full-matrix least-squares method using the SHELXL-97 program package.[13] The final structure refinement was carried out based on all F^2 to $wR_2 = 0.0920$, $R_1 = 0.0339$, $S = 0.873$.

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