Chemistry of Heterocyclic Compounds, Vol. 33, No. 7, 1997

SYNTHESIS AND PROPERTIES OF ESTERS OF BENZOTHIAZOLYLAMINO(IMINO)PROPIONIC ACIDS

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Reaction of 2-alkylaminothiazoles with methyl acrylate leads predominantly to the formation of N-alkyl-N-(β-methoxycarbonylethyl)-2-aminobenzothiazoles on boiling or to 2-(alkylimino)-3-(β-methoxycarbonylethyl)-benzothiazolines at room temperature. A complex mixture of products was obtained from unsubstituted 2-aminobenzothiazole and methyl acrylate, of which the main was 2-oxo-3,4-dihydro-2H-pyrimido[2,1-b]benzothiazole. Complete or partial destruction of the benzothiazolines occurred on heating to 140°C.

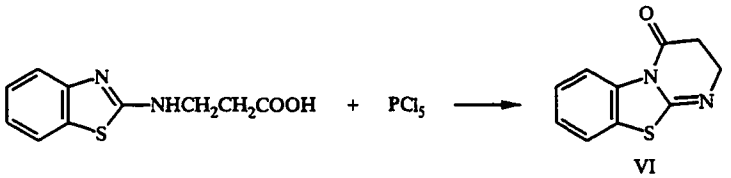
The reaction of 2-aminobenzothiazole (Ia) and its derivatives (Ib, c) with methyl acrylate has been investigated in the present work as a continuation of the study of ambifunctional heterocyclic amines in nucleophilic substitution and addition reactions [1].

The reactions of unsaturated acid esters with compound (Ia) have been described using esters of β-aminocrotonic [2], ethoxymethylenemalonic [3, 4], 2-aminofumaric [5], and ethoxyacrylic acids [6] as examples. In all cases, reaction was observed at the ester group, the double bond was not affected. Nucleophilic addition of 2-aminobenzothiazoles to propiolic acid ester [6-9] and to acetylenedicarboxylic acid ester [5, 9, 10] has been effected. The formation of 2-oxopyrimidobenzothiazoles in these reactions indicated that addition to the C≡C bond occurs with the participation of the endocyclic nitrogen atom of the heterosystem. Reactions of 2-(R-amino)benzothiazoles with unsaturated acid esters have not been studied up to the present time.

On boiling amines (Ib, c) in methyl acrylate solution, N-alkyl-N-(β-methoxycarbonylethyl)-2-aminobenzothiazoles (IIIb, c) were isolated in place of the expected 2-(alkylamino)-3-(β-methoxycarbonylethyl)benzothiazolines (IIb, c). In the case of the unsubstituted amine (Ia) 2-oxo-3,4-dihydro-2H-pyrimido[2,1-*b*]benzothiazole (IV) was isolated under these conditions in addition to compound (IIIa). The cyclization product (IV) is probably formed from the intermediate iminoester (IIa). Carrying out the latter reaction at 50-55°C enabled the isolation of the aminoester (IIIa) in addition to the cyclic product (IV).

An alternate synthesis of compound (IV) was effected by the cyclization of 3-(β-carboxyethyl)-2-iminobenzothiazoline (Va) by the action of thionyl chloride. For comparison, 4-oxo-2,3-dihydro-4H-pyrimido[2,1-*b*]benzothiazole (VI) was synthesized by treating 2-(β-carboxyethylamino)benzothiazole with phosphorus pentachloride.

Supposing that the amino compounds (IIIb, c) are formed as a result of imine–amine isomerization, as took place with carboxyethyl derivatives of aminobenzothiazoles [11], we reacted amines (Ia-c) with methyl acrylate at room temperature. Significant quantities of imino products (IIa-d) [amine (Ia) forms products of mono and bis addition] and also dihydro-2H-pyrimidobenzothiazole (IV) were detected in the reaction mixtures in addition to the amino isomers (IIIa-c). The esters (IIb-d) were isolated from the mixtures and were also obtained by alternate syntheses, viz. the esterification of the appropriate acids (Vb-d) with dimethyl sulfate.



VI

Institute of Plant Chemistry, Uzbek Academy of Sciences, Tashkent 700170. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 981-987, July, 1997. Original article submitted March 19, 1996; revision submitted November 22, 1996.

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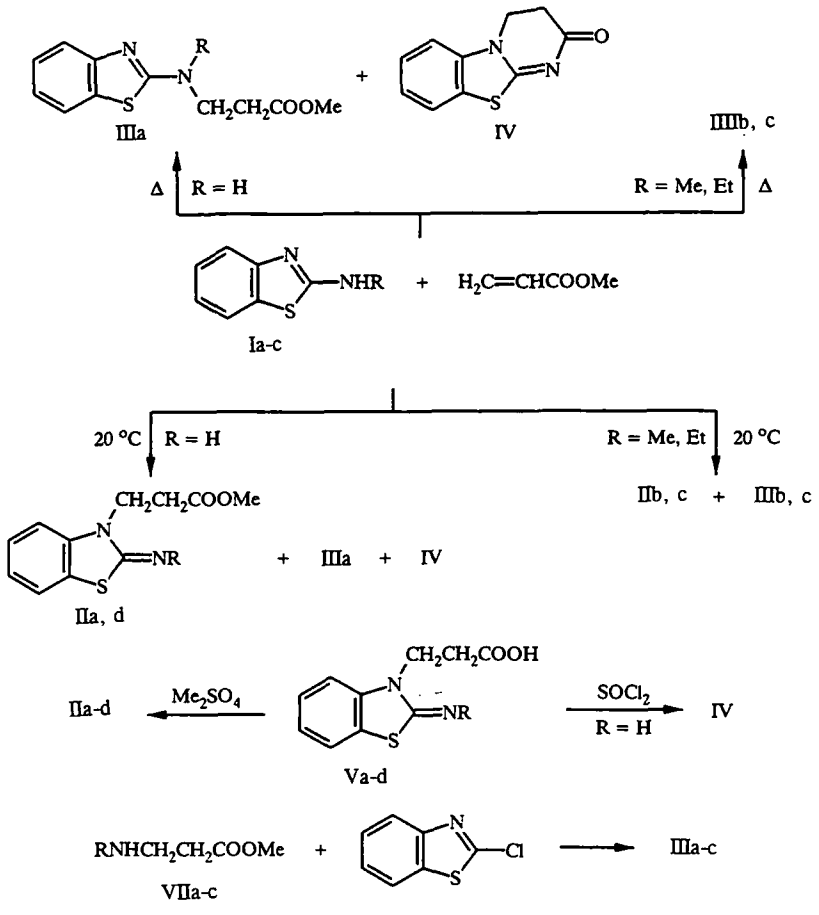


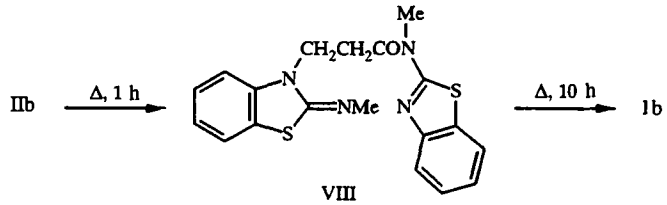
a R = H, b R = Me, c R = Et, d R = CH_2CH_2COOMe

We did not succeed in isolating ester (IIa) in a pure state since an equimolar mixture of esters (IIa) and (IIb) (from PMR data) was formed on esterifying acid (Va). The corresponding acid was obtained on attempting to purify (IIa) by column chromatography, as in the case of compounds (IIb-d).

The amino esters (IIIa-c) were not saponified on the chromatographic column. They were also obtained by an alternate synthesis by the alkylation of methyl esters of β-alkylaminopropionic acids (VIIa-c) with 2-chlorobenzothiazole.

The thermal stability of compound (IIb) was studied to check the concept of isomerization of imino esters (II) into amino esters (III). The formation of amide (VIII) was recorded after boiling (IIb) for 1 h in xylene, but after 10 h complete destruction of (IIb) into amine (Ib) had occurred.

The formation of amide (VIII) is probably the result of alkylation by ester (IIb) of amine (Ib) formed by the partial decomposition of (IIb). Although the imino ester (IIb) is thermally unstable, no isomerization of it into amino ester (IIIb) was observed. Probably the exclusive or prevalent formation of amino esters (IIIb, c) on boiling thiazoles (Ib, c) in methyl acrylate is explained by a combination of two factors. These are the dual reactivity of amines (Ib, c) and the thermolability of their imino isomers (IIb, c), the decomposition of which to amines (Ib, c) leads to the gradual accumulation of compounds (IIIb, c) which are completely stable under the reaction conditions.



The use of high-performance liquid chromatography (HPLC) enabled the dynamics of the accumulation of imino and amino products to be traced in the reaction mixture. It is evident from Table 1 that as the reaction time of amines (Ib, c) with

TABLE 1. Results of the Reaction of Compounds (Ib, c) with Methyl Acrylate at 20-25°C (HPLC data)

Initial amine	Reaction time, days	Content of compound in reaction mixture, %		
		I	II	III
Ib	6	96	3	1
	30	20	57	23
	50	8	62	30
	0,42*	16	—	84
Ic	30	26	56	18
	35	14	64	22
	0,75*	12	28	60

*Reaction was carried out by boiling the reactants.

methyl acrylate increases, the overall yield of esters (IIb, c) and (IIIb, c) grows but the ratios (IIb):(IIIb) and (IIc):(IIIc) are reduced.

The structures of the compounds obtained were confirmed by physicochemical methods (Table 2). There were intense absorption bands in the IR spectra of esters (II) and (III) for the stretching vibrations of the exocyclic (1640-1650 cm^{-1}) and endocyclic (1551-1580 cm^{-1}) C=N bonds. The ester carbonyl group was represented as an intense absorption band at 1734-1750 cm^{-1}. The differences in the IR spectra of the 2-oxo- and 4-oxopyrimidobenzothiazoles (IV) and (VI) are caused by the presence or absence of conjugation of the C=N and C=O bonds.

Peaks were observed in the mass spectra of compounds (II) and (III) for the molecular ions. These were maximal for the amino derivatives (III) but were far less intense in the case of the imino derivatives (II), which confirms our data on the different thermostabilities of these compounds. In the PMR spectra of these substances there was a characteristic two-proton triplet for the CH_2 group at 3.40-3.85 if this group was linked to a nitrogen atom of the side chain, or at 4.01-4.45 ppm if it was bound to a ring nitrogen atom. A bathochromic shift on going from the imino esters (II) to their amino isomers (III) was characteristic of the long-wave absorption maxima in the UV spectrum.

We have effected for the first time the addition of 2-aminobenzothiazoles to an unsaturated acid ester and have shown that under conditions of kinetic control the reaction is effected mainly at the endocyclic nitrogen atom of the heterosystem.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in KBr disks, and the UV spectra on a Hitachi EPS-3T spectrophotometer in ethanol. The PMR spectra of solutions of compound (IV) in trifluoroacetic acid and of the remaining compounds in deuterochloroform were recorded on a Tesla BS-567 (100 MHz) instrument at 20-25°C, the internal standard was HMDS. The mass spectra were obtained on an MX-1310 instrument, the temperature of the direct insertion probe was 100-130°C, ionizing voltage was 50 eV, and the reference substance was perfluorokerosene. The mass spectrum of ester (IIa) was recorded under conditions of low temperature evaporation of a test sample of the reaction mixture obtained by the reaction of amine (Ia) with methyl acrylate at 20°C. The HPLC analyses were carried out on a Millichrome 1 instrument on a steel column (64 × 2 mm) packed with Silasorb 600 sorbent of particle size 5 μm. A mixture of hexane–chloroform–isopropanol (80:15:5 by vol.) was used as mobile phase, elution rate was 100 μl/min, and UV detection at 250 nm was used. The separation and purification of substances was carried out on chromatographic columns of silica gel L 100/160. A check on the progress of reactions and the homogeneity of substances was effected by TLC on Silufol UV-254 plates in the systems: a) benzene–chloroform–acetone (1:1:1), b) benzene–acetone (4:1), c) ethanol–water (2:1). Melting points were determined on a Boetius microscope stage. Freshly distilled methyl acrylate stabilized with hydroquinone was used in the experiments. The initial amine (Ia) was a commercial product. The other compounds used were synthesized by known procedures: (Ib) [12], (Ic) [13], (Va, d) [14], (Vb, c) [15], (VIIa) [16], (VIIb) [17], (VIIc) [18], 2-chlorobenzothiazole [19], and 2-(β-carboxyethyl)-aminobenzothiazole [20].

TABLE 2. Spectral Characteristics of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm	Mass spectrum, m/z (I_{rel}, %)		PMR spectrum, δ, ppm				
	C=N	C=O		M^+	remaining ions	CH_2N t	CH_2CO t	MeO s	H_{arom}, m	other protons
IIb	1650	1740	222,5, 263, 302	250(35)	219(8), 191(32), 177(6), 164(100), 150(14), 136(51), 135(29)	4,15	2,67	3,57	6,80...7,50 (4H)	2,99 (3H, s, NMe)
IIc	1640	1750	224, 263,5, 306	264(45)	249(36), 233(8), 205(29), 192(14), 178(100), 177(31), 163(52), 150(74), 136(49), 135(25)	4,12	2,67	3,52	6,75...7,70 (4H)	1,19 (3H, t, $CH_2\underline{CH_3}$); 3,15 (2H, q, $\underline{CH_2}CH_3$)
IId	1640	1750	222,5, 263, 303	322(48)	291(25), 263(62), 249(100), 236(80), 189(13), 173(63), 163(77), 150(46), 136(28), 135(21)	4,15, 3,40	2,70, 2,60	3,58	6,82...7,55 (4H)	—
IIIa	1580	1748	224, 267,5, 297 (sh)	236(100)	205(21), 177(90), 163(81), 150(71), 136(28), 135(27)	3,76	2,75	3,70	7,0...7,75 (4H)	—
IIIb	1558	1734	227, 270, 298 (sh)	250(100)	219(17), 191(61), 177(100), 164(83), 163(39), 150(16), 136(74), 135(26)	3,85	2,70	3,65	7,0...7,75 (4H)	3,12 (3H, s, NMe)
IIIc	1551	1740	227,275, 299 (sh)	264(99)	249(4), 233(16), 205(31), 191(57), 178(35), 177(59), 163(100), 150(15), 136(21), 135(11)	3,80	2,74	3,60	7,0...7,75 (4H)	1,20 (3H, t, $CH_2\underline{CH_3}$); 3,42 (2H, q, $\underline{CH_2}CH_3$)
IV	1535	1660	217,3, 232 (sh), 255 (sh), 273 (sh), 282,5 (sh), 310	204(42)	176(100), 148(37), 134(4)	4,45	3,00	—	7,25...7,70 (4H)	—
VI	1648	1725	—	204(100)	177(23), 162(68), 150(18), 149(25), 135(49)	3,75	2,62	—	6,80...7,80 (4H)	—
VIII	1555	1680	224, 277, 289 (sh), 300,5	382(4)	219(47), 218(48), 189(51), 177(41), 164(100), 136(90), 135(76)	4,01	3,12	—	6,90...7,85 (8H)	3,20 (3H, s, NMe); 3,75 (3H, s, NMe)

2-Imino-3-(β-methoxycarbonylethyl)benzothiazoline (IIa). Dimethyl sulfate (0.73 g, 5.8 mmole) was added dropwise with stirring to a suspension of acid (Va) (1.2 g, 5.5 mmole) and calcined potassium carbonate (0.8 g, 6.9 mmole) in dry acetone (10 ml) and the mixture boiled for 5 h. The cooled reaction mixture was filtered, the filtrate evaporated, and the residue extracted with ether (3 × 5 ml). The extract was evaporated and the residue extracted with hot hexane (2 × 5 ml). After evaporating the hexane, an oily product (0.38 g) was obtained which was a mixture (1:1) of esters (IIa) and (IIb) according to HPLC and PMR spectrum. The yield of compound (IIa) was 15% and of (IIb) 14%. Ester (IIa) PMR spectrum: 2.72 (2H, t, CH_2CO); 3.60 (3H, s, OMe); 4.25 (2H, t, CH_2N); 6.80-7.50 ppm (4H, m, H_{arom}). Mass spectrum, m/z (I, %): M^+ 236 (19), 205 (4), 177 (21), 163 (33), 150 (100), 135 (10). The spectral characteristics of ester (IIb) are given in Table 2. On attempting to separate the mixture of esters (IIa) and (IIb) on a chromatographic column (eluents hexane, benzene, ethanol) acid (Va) (0.13 g) was obtained of mp 148-150°C, R_f 0.54 (c) and acid (Vb) (0.11 g) of mp 156-157°C, R_f 0.41 (c). Melting points of samples of compounds (Va) and (Vb) mixed with specimens synthesized previously gave no depression.

2-Methylamino-3-(β-methoxycarbonylethyl)benzothiazoline (IIb). Dimethyl sulfate (2.93 g, 23 mmole) was added dropwise with stirring to a suspension of acid (Vb) (5.4 g, 23 mmole) and calcined potassium carbonate (3.15 g, 23 mmole) in dry acetone (50 ml), and the mixture boiled for 5 h. After cooling, the inorganic solid was filtered off, the filtrate evaporated, and the residue extracted with boiling hexane. Ester (IIb) (4.5 g, 79%) was obtained, having mp 31-33°C (from hexane) and R_f 0.73 (a). Found, %: C 57.39; H 5.55; N 11.25. $C_{12}H_{14}O_2S$. Calculated, %: C 57.58; H 5.64; N 11.19.

Compounds (IIc) and (IId) were obtained analogously from acids (Vc) and (Vd) respectively.

2-Ethylamino-3-(β-methoxycarbonylethyl)benzothiazoline (IIc). Yield 54%. Oil, Rf 0.72 (a). Found, %: C 59.21; H 6.27; N 10.50. $C_{13}H_{16}N_2O_2S$. Calculated, %: C 59.07; H 6.10; N 10.60.

2-(β-Methoxycarbonylethylamino)-3-(β-methoxycarbonylethyl)benzothiazoline (IId). Yield 80%. Mp 48.5-49°C (from hexane), R_f 0.82 (a). Found, %: C 56.13; H 5.41; N 8.61. $C_{15}H_{18}N_2O_4S$. Calculated, %: C 55.95; H 5.63; N 8.70.

N-(β-Methoxycarbonylethyl)-2-aminobenzothiazole (IIIa). A mixture of 2-chlorobenzothiazole (0.85 g, 5 mmole) and ester (VIIa) (1.01 g, 10 mmole) was stirred in an oil bath at 125-130°C for 2 h. The reaction mixture was cooled, washed with water, dried, and the oil rubbed with hexane. Amino ester (IIIa) (0.3 g, 25%) was obtained having mp 87-88°C (from hexane). R_f 0.42 (a). Found, %: C 56.05; H 5.37; N 11.67. $C_{11}H_{12}O_2S$. Calculated, %: C 55.91; H 5.56; N 11.86.

Compound (IIIb) and (IIIc) were obtained analogously from amines (VIIb) and (VIIc) respectively.

N-Methyl-N-(β-methoxycarbonylethyl)-2-aminobenzothiazole. Yield 35%. Mp 85-86°C (from hexane), R_f 0.80 (a).

N-Ethyl-N-(β-methoxycarbonylethyl)-2-aminobenzothiazole (IIIc) was purified by column chromatography. Yield 31%. Oil, R_f 0.82 (a). Found, %: C 58.89; H 5.99; N 10.57. $C_{13}H_{16}N_2O_2S$. Calculated, %: C 59.07; H 6.10; N 10.60.

2-Oxo-3,4-dihydro-2H-pyrimido[2,1-*b*]benzothiazole (IV). Thionyl chloride (0.6 g, 5 mmole) was added to ethanol (5 ml) cooled to −10°C and then acid (Va) (0.62 g, 2.8 mmole) was added in portions. The reaction mixture was stirred for 1 h at room temperature, then evaporated in the air. The residue was dissolved in water, the solution neutralized with ammonia, the product filtered off, and washed with water. Compound (IV) (0.45 g, 79%) was obtained, having mp 212-213°C (from acetone−hexane, 1:1) [22], R_f 0.08 (b).

Reaction of 2-(R-Amino)benzothiazoles with Methyl Acrylate on Heating. A. Amine (Ia) (1.5 g, 10 mmole) in methyl acrylate (10 ml) was stirred at 50-55°C (water bath) for 50 h. The reaction mixture was evaporated, the residue washed with acetone (3 ml), and product (IV) (0.41 g, 20%) obtained. Ester (IIIa) (0.25 g, 11%) was isolated from the filtrate by column chromatography.

B. Amine (Ia-c) (10 mmole) was boiled in methyl acrylate for 10 h and the reaction mixture then evaporated. In the case of amine (Ia) the residue after evaporation was washed with hot benzene, and product (IV) isolated in 23% yield. In the case of (Ib, c) the residue was extracted with hot hexane, and esters (IIIb, c) respectively were obtained after evaporating the extract. Product (IIIb) was purified by recrystallization, yield was 56%. Product (IIIc) was purified by column crystallization, yield was 42%.

Compounds (IIIa-c) and (IV) were identical with known samples described above in R_f, HPLC retention time, and IR spectra, and by the absence of a depression of mp in a mixing test in the case of compounds (IIIa, b) and (IV).

Reaction of 2-(R-amino)benzothiazoles with Methyl Acrylate at Room Temperature. The amine (Ia-c) (5 mmole) was stirred in methyl acrylate (3 ml) for 5 h and left for 6-50 days (Table 1), shaking periodically. In the case of amine (Ia) the reaction mixture was filtered after 35 days, the residue washed with ether and with methanol, and compound (IV) obtained in 19% yield. The washings from the residue were combined with the filtrate, evaporated, and the residue (1) obtained was analyzed by TLC and HPLC. According to HPLC, amine (Ia) (12%), ester (IIa) (45%), ester (IId) (30%), and compound (IV) (13%) were present. Residue (1) was treated with cold pentane, the extract evaporated, and the resulting residue (2) treated

once again as residue (1). On mass spectrometric analysis of the total residue (3) at various temperature regimes the mass spectra of compounds (IIa) and (IId) were obtained. Attempts to isolate the latter from residue (3) by column chromatography using sequential elution with hexane, benzene, and ethanol gave acid (Va) of mp 149-150°C and R_f 0.54 (c), and acid (Vd) of mp 164-165°C and R_f 0.69 (c). Acids (Va) and (Vd) gave no depression of mp with samples synthesized previously [14].

In the case of amine (Ib) the reaction mixture was evaporated after 50 days, and the residue (HPLC data see Table 1) washed with a hexane–methanol (10:1) mixture. The yield of ester (IIIb) was 22%. The mother liquor was evaporated, the residue triturated with hexane at −78°C, and then recrystallized from hexane. The yield of ester (IIb) was 43%.

The reaction mixture obtained from amine (Ic) and methyl acrylate was evaporated after 35 days (Table 1). Ester (IIc) was isolated in 25% yield by multiple precipitation of the residue from hexane at −78°C. Ester (IIIc) (yield 16%) and amine (Ic) (yield 10%) were isolated from the filtrate by column chromatography (eluent was hexane).

Products (IIb, c), (IIIb, c), and (IV) were identical with known samples described above in R_f, HPLC retention time, and IR spectra, and also by the absence of a depression of mp in a mixing test in the case of compounds (IIb), (IIIb), and (IV).

4-Oxo-2,3-dihydro-4H-pyrimido[2,1-*b*]benzothiazole (VI). Phosphorus pentachloride (0.15 g, 7.2 mmole) was added to a suspension of 2-(β-carboxyethylamino)benzothiazole (0.05 g, 2.3 mmole) in dry chloroform (3 ml). The reaction mixture was stirred for 2 h, the solid filtered off, dissolved in water, and the solution neutralized with aqueous ammonia. Compound (VI) (0.03 g, 67%) was obtained having mp 84-86°C (from aqueous ethanol) and R_f 0.62 (b). Found, %: C 58.71; H 3.89; N 13.80. $C_{10}H_8N_2OS$. Calculated, %: C 58.81; H 3.95; N 13.72.

N-Methyl-N-(2-benzothiazolyl)-β-(2-methylimino-3-benzothiazolinyl)propionamide (VIII). A mixture of ester (IIb) (0.8 g, 3.2 mmole) and m-xylene (10 ml) was boiled for 2 h. The reaction mixture was evaporated, washed with ethanol (2 ml), and amide (VIII) (0.15 g, 25%) obtained having mp 210-212°C (from benzene), R_f 0.79 (a). Found, %: C 59.41; H 4.50; N 17.44. $C_{19}H_{18}N_4OS_2$. Calculated, %: C 59.66; H 4.74; N 14.65.

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