SYNTHESIS AND RING-CHAIN TAUTOMERISM OF SUBSTITUTED 4-HYDROXY-HEXAHYDROPYRIMIDINE-2-THIONES

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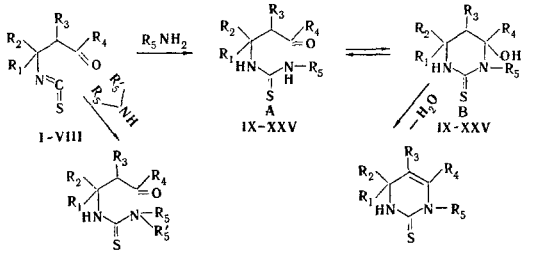
The synthesis of a number of substituted 4-hydroxyhexahydropyrimidine-2-thiones has been effected. The prototropic ring-chain tautomerism of compounds of this type in chloroform solution has been investigated by IR spectroscopy. The dependence of the relative stability of the cyclic tautomeric forms on the structures of the compounds studied has been elucidated.

In preceding communications [1, 2] we have described the reaction of some β-isothiocyanatoketones with ammonia and primary and secondary amines. In view of the fact that the 4-hydroxyhexahydropyrimidine-2-thiones so formed were found to possess the capacity for prototropic ring-chain tautomerism [2], it appeared necessary to study this phenomenon in more detail in order to determine the laws connecting the structure of the compounds synthesized with their capacity for tautomeric conversions.

This paper describes the synthesis and a study of the structure of the products of the reaction of the β-isothiocyanatoaldehydes I–III and some of the previously-described β-isothiocyanatoketones IV–VIII with various primary amines.



I–VIII IX–XXV IX–XXV XXVI–XXIX XXX–XXXI

I $R_1 = R_2 = R_3 = R_4 = H$; II $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$; III $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$; IV $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$; V $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$; VI $R_1 = R_3 = H$, $R_2 = R_4 = CH_3$; VII $R_1 = R_3 = R_4 = CH_3$, $R_2 = H$; VIII $R_1 = R_2 = R_4 = CH_3$, $R_3 = H$; XXVI $R_1 = R_2 = H$, $R_3 = R_4 = R_5 = R_5' = CH_3$; XXVII $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$, $R_5 + R_5' = (CH_2)_5$; XXVIII $R_1 = R_3 = H$, $R_2 = R_4 = CH_3$, $R_5 + R_5' = (CH_2)_5$; XXIX $R_1 = R_3 = H$, $R_2 = R_4 = R_5 = CH_3$, $R_5' = C_6H_5$

The synthesis of the β-isothiocyanatoaldehydes I–III was effected by the addition of thiocyanic acid at the moment of its liberation to acrolein, methacrolein, and crotonaldehyde.

The addition of primary amines to the β-isothiocyanatocarbonyl compounds I–VIII in the absence of mineral acids takes place in a similar manner to that described before [1], leading to the crystalline substituted 4-hydroxyhexahydropyrimidine-2-thiones (XI–XXV), the conditions of the synthesis and the properties of which are given in the table.

In addition to these compounds a number of N-oxoalkyl-N', N'-disubstituted thioureas, XXVI–XXIX, were synthesized from the β-isothiocyanatoketones IV–VI and secondary amines (dimethylamine, piperidine, methylaniline). For comparison with the compounds IX–XXV investigated, the previously-known [3] 3, 4, 6, 6-tetramethyl-1, 2, 3, 6-tetrahydropyrimidine-2-thione (XXX) and 3-ethyl-4, 6, 6-trimethyl-1, 2, 3, 6-tetrahydropyrimidine-2-thione (XXXI) were obtained from the β-isothiocyanatoketone VIII.

In order to elucidate the structure of the compounds XIX–XXXI synthesized, we studied their IR absorption spectra. The presence in the IR spectra of all three classes of compounds of the absorption band of a thioamide group at 1520–1560 cm^{-1} (amide II) and 3200–3400 cm^{-1} (NH) and the absence of absorption in the frequency ranges 2500–2600 cm^{-1} (SH group) and 1600–1650 cm^{-1} (C=N group) shows the thione structure of these compounds.

A consideration of the IR spectra of compounds IX–XXV (typical spectra are given in Fig. 1) shows that in the crystalline state they all possess the cyclic structure B, which is evident from the absence of absorption bands of carbonyl groups in the 1680–1730 cm^{-1} region. The bands at 3200–3500 cm^{-1} characterize intermolecular hydrogen bonds of the types

$$-OH\cdots N\lessgtr,\quad -OH\cdots O\lessgtr,\quad =NH\cdots N\lessgtr.$$

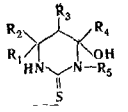
In view of the A ⇄ B ring-chain tautomerism that we have observed [2], we have made a detailed study of the behavior in solutions of both the newly-synthesized compounds IX–XXV and also their homologs described in the preceding paper [1].

In the 1700–1720 cm^{-1} region of the IR spectra of solutions of the majority of the compounds studied, taken in chloroform or CCl_4 at concentration c of $3–5 \cdot 10^{-3}$ M, soon after dissolution the absorption band of a C=O group appears the intensity of which rises with time, reaching a constant value after a certain interval. This phenomenon is connected with the passage of the cyclic forms B into the acyclic tautomers having the structures of substituted N-oxoalkyl-N'-alkyl(aryl)thioureas A. The increase in the intensity of the C=O band corresponds to an increase in the content of the acyclic form A in the tautomeric system, and the cessation of the growth of the intensity of this band shows the achievement of the A ⇄ B tautomeric equilibrium. Depending on the structure of the compound, the equilibrium in chloroform is established in 6–15 hr.

Fig. 2 gives typical IR spectra of solutions of IX–XXV taken 2–3 days after the dissolution of the samples.

The mutual reversibility of the tautomeric transitions A ⇄ B is shown by the disappearance from the

Substituted 4-Hydroxyhexahydropyrimidine-2-thiones



Compound	R_1	R_2	R_3	R_4	R_5	Reaction time, hr	Reaction temperature, °C	Reaction medium	Mp, °C	Solvent for crystallization	Empirical formula	Found, %				Calculated, %				Yield, %
												C	H	N	S	C	H	N	S	
IX	CH_3	H	H	H	CH_3	2	20	Water	143—144	Acetone	$C_6H_{12}N_2OS$	45.03	7.67	17.50	—	44.98	7.56	17.49	—	38.0
X	H	H	H	H	n-C_3H_7	2	20	Water	93.5—95	Chloroform	$C_7H_{14}N_2OS$	48.24	8.02	—	18.21	48.25	8.11	—	18.37	44.5
XI	CH_3	CH_3	H	CH_3	CH_3	4	10	Water	158—159	Ethanol	$C_8H_{16}N_2OS$	—	—	—	17.31	—	—	—	17.00	89.2
XII	CH_3	CH_3	H	CH_3	C_2H_5	3	10	Water	138—139	Water	$C_9H_{18}N_2OS$	53.13	9.30	—	16.34	53.43	8.99	—	15.82	71.4
XIII	CH_3	CH_3	H	CH_3	n-C_3H_7	3	10	Water	135—136	Acetone	$C_{10}H_{20}N_2OS$	55.66	8.98	13.00	15.02	55.52	9.34	12.94	14.79	74.2
XIV	CH_3	H	H	CH_3	CH_3	2	55	Water	116.5—117.5	Ethanol	$C_7H_{14}N_2OS$	—	—	15.90	18.36	—	—	16.08	18.37	80.0
XV	CH_3	H	H	CH_3	C_2H_5	2	35	Water	114—115.5	Acetone	$C_8H_{16}N_2OS$	50.82	8.22	14.30	—	51.02	8.52	14.88		57.6
XVI	CH_3	H	H	CH_3	n-C_3H_7	2	35	Water	93—94	Water	$C_9H_{18}N_2OS$	53.42	9.02	13.90	—	53.43	8.99	13.85	—	68.2
XVII	CH_3	H	H	CH_3	C_6H_5	3	70	Chloroform	135—136	Methanol	$C_{12}H_{16}N_2OS$	60.61	6.85	11.70	—	60.97	6.84	11.85	—	67.1
XVIII	CH_3	H	CH_3	CH_3	C_2H_5	2	35	Water	148—149	Water	$C_9H_{18}N_2OS$	53.44	8.94	—	16.25	53.43	8.99	—	15.82	69.8
XIX	CH_3	H	CH_3	CH_3	n-C_3H_7	3	30	Benzene	135—136.5	Ethyl acetate	$C_{10}H_{20}N_2OS$	55.43	9.46	—	14.76	55.52	9.34	—	14.79	87.6
XX	CH_3	H	CH_3	CH_3	iso-C_4H_9	24	20	Ether	118—119	Acetone	$C_{11}H_{22}N_2OS$	57.45	9.34	11.7	—	57.34	9.46	12.16	—	76.1
XXI	CH_3	H	CH_3	CH_3	C_6H_5	48	20	Water	126—128	Methanol	$C_{13}H_{18}N_2OS$	62.08	7.42	—	12.63	62.36	7.26	—	12.77	65.0
XXII	CH_3	H	CH_3	CH_3	$C_6H_5CH_2$	24	20	Water	104—105	Ethanol	$C_{14}H_{20}N_2OS$	63.60	7.70	—	12.39	63.60	7.64	—	12.11	59.2
XXIII	CH_3	H	CH_3	CH_3	p-$C_6H_4NO_2$	72	20	Water	176—177	Methanol	$C_{13}H_{17}N_3O_3S$	—	—	—	10.93	—	—	—	10.83	53.3
XXIV	CH_3	H	CH_3	CH_3	p-$C_6H_4OCH_3$	30	20	Water	116—117	Ethanol	$C_{14}H_{20}N_2O_2S$	59.20	7.23	—	11.57	59.96	7.20	—	11.41	48.2
XXV	H	H	H	CH_3	C_2H_5	2	50	Water	99—100	Water	$C_7H_{14}N_2OS$	48.27	8.11	—	18.68	48.25	18.11	—	8.37	76.3

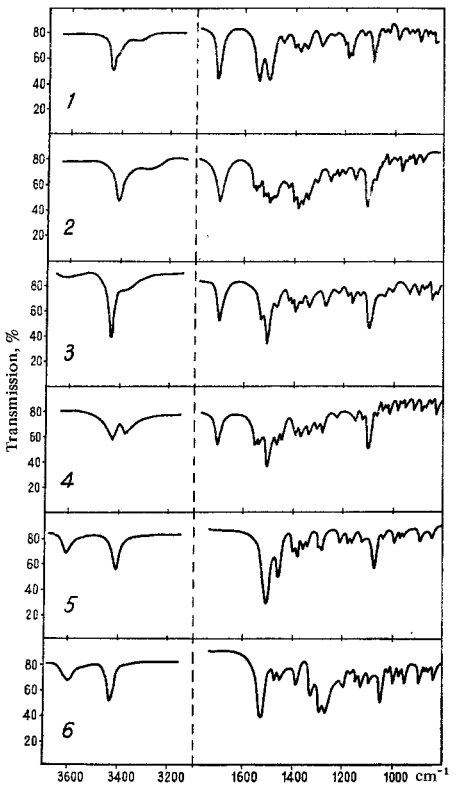


Fig. 1. IR spectra: 1) XXV; 2) XIV; 3) XX; 4) XII; 5) X; 6) 4-hydroxy-3,4,5-trimethylhexahydropyrimidine-2-thione.

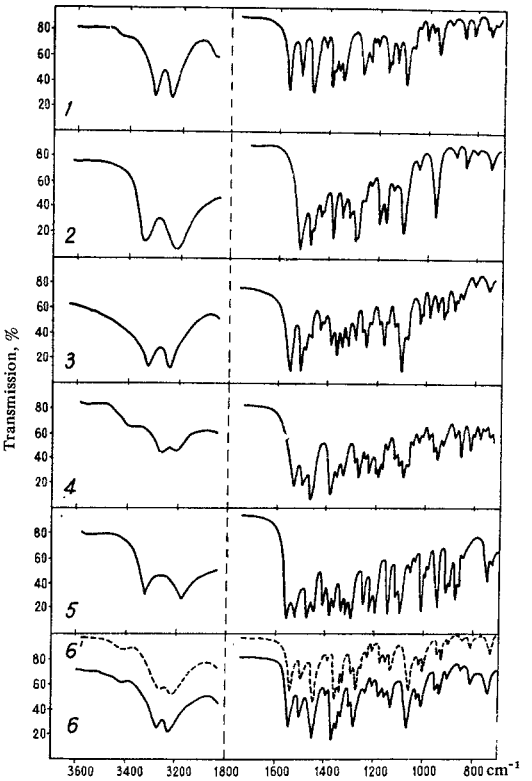


Fig. 2. IR Spectra: 1) XXV; 2) XIV; 3) XVIII; 4) XX; 5) XII; 6) IX. Solvent: chloroform, c 0.001 M d 0.998 mm.

spectrum of a crystalline sample of 4-hydroxy-3, 4, 5-trimethylhexahydropyrimidine-2-thione (**XXXII**) [1], obtained after the elimination of the solvent, of the C=O band observed in a solution of this compound. The IR spectra of the initial **XXXII** after dissolution and that obtained after the elimination of the chloroform proved to be completely identical (curves 6 and 6', Fig. 1).

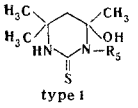
In order to elucidate the correlation between the structures of **IX–XXV** and of their homologs [1] and the position of the tautomeric equilibrium, using IR spectroscopy we have made an approximate evaluation of the content of the tautomers A in the equilibrium systems A ⇄ B. As the working parameter for determining the content of tautomeric forms, we selected the area of the absorption bands of the carbonyl group in the 1705–1715 cm^{-1} region, which is proportional to the integral intensity [4]. Compounds of authentic acyclic structure—N-oxoalkyl-N', N'-disubstituted thioureas **XXVI–XXIX**—were used as reference materials.

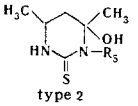
From measurements of the areas of the C=O absorption bands recorded for several concentrations of different reference samples we constructed a calibration graph in the coordinates concentration versus area of the absorption band of the C=O group. The fact that the maximum of the absorption band and its area are independent of the substituents at N' and in the oxoalkyl part of the molecule was shown by the correspondence of the frequencies and areas of the bands recorded for model compounds differing in the number and position of the substituents in the molecule (at equal concentrations). The amount of acyclic tautomer A in the equilibrium systems A ⇄ B was determined from the calibration graph on the assumption that the area of the absorption band in the C=O group of the model compounds corresponded to the area of the same band for the completely open form of a tautomeric compound (at the same concentrations).

In spite of the approximate evaluations of the contents of the tautomers, we succeeded in deducing some laws connecting the structures of the substances studied with the positions of the tautomeric equilibrium.

It follows from the results obtained that the stability of the cyclic forms B in solutions is determined by the following structural factors: a) by the substituents on the $C_{(5)}$ and $C_{(6)}$ carbon atoms (in the α and β positions with respect to the hydroxyl group); b) by the substituent at $C_{(4)}$ participating directly in the tautomeric triad; and c) by the substituent attached to the $N_{(3)}$ nitrogen atom responsible for the tautomerism.

Depending on the number and positions of the CH groups on the $C_{(5)}$ and $C_{(6)}$ atoms, the cyclic forms B can be subdivided into five types and arranged in the following sequence characterizing the relative stability of the rings:


type 1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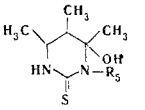
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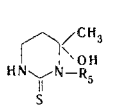
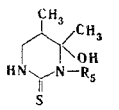

type 4


type 5

The greatest tendency to transition into the acyclic tautomeric form is shown by the compounds of type 5 [1] with a methyl substituent in the α-position with respect to the hydroxyl group. In solutions of compounds of type 5 in chloroform, the opening of the ring B begins only a few minutes after dissolution, and after 6–8 hr the A ⇄ B equilibrium with 85–95% of the acyclic form A in the tautomeric system has become established.

An increase in the electron-donating properties and effective volume of the substituent R_5 attached to the $N_{(3)}$ nitrogen of the tautomeric triad is accompanied by an increase in the rate of opening of the cyclic forms B and by an increase in the content of the linear form A (85% for $R_5 = CH_3$, 90% for $R_5 = C_2H_5$, and 95% for $R_5 = C_3H_7$).

The opposite behavior is exhibited by compounds of structural type 1 with gem-dimethyl groups in the β position with respect to the $C_{(4)}$=OH group. A study of the IR spectra of solutions has shown that compounds **XI–XIII** retain their cyclic structure in chloroform for 48 hr (curve 5 of Fig. 2). In addition to this, in the spectra of **XI–XIII** absorption bands at 1685 cm^{-1} (C=C) characteristic for the products of their dehydration (**XXX–XXXI**) appear after 3 days or more and increase in intensity with time. The IR spectrum of a crystalline sample obtained after the elimination of the solvent 20 days after the dissolution of **XII** is a proof of the dehydration of compounds **XI–XIII** taking place in chloroform solution, this spectrum proving to be identical with that of **XXXI**, which has a known structure [3]. Thus, the presence of gem-dimethyl substituents in the β-position with respect to the hydroxyl group inhibits the transition of the cyclic forms B into the tautomers A but favors the spontaneous dehydration of B.

Chloroform solutions of compounds **XIV–XVI** of type 2 show the simultaneous occurrence of both processes, as is confirmed by the presence in the IR spectra of solutions of bands at 1710 cm^{-1} (C=O) and 1685 cm^{-1} (C=C). This fact does not permit any kind of reliable evaluation of the content of the tautomers in equilibrium systems of compounds of type 2.

At the same time, the spectra of solutions of compounds **XVIII–XX** and **XXV**, of types 3 and 4, have only symmetrical bands at 1710–1712 cm^{-1}, which shows the predominance of the ring-opening process.

In these compounds, the tautomeric equilibrium is established more slowly than in the corresponding homologs of type 5 (after 12–15 days) and the content of the acyclic tautomer A in the equilibrium mixture does not exceed 75%; the passage from **XVIII** to **XIX** and **XX** is accompanied by an increase in the content of the tautomer A in the system (52, 57, and 75%, respectively).

The replacement of a CH_3 group on the $C_{(4)}$ atom by hydrogen markedly increases the stability of the

cyclic forms **B**: in chloroform, no ring opening was found 20 days after the dissolution of **IX** and **X** (curve 6 of Fig. 2).

EXPERIMENTAL

The IR spectra were taken on a UR-10 (Zeiss) double-beam spectrophotometer using LiF prisms in the 3700–2000 cm^{-1} region and an NaCl prism in the 1800–700 cm^{-1} region.

The IR spectra of crystalline samples of the compounds were taken in the form of mulls in paraffin oil and the spectra of solutions in dismountable liquid cells with layer thicknesses of from 0.998 to 4.036 mm.

3-Isothiocyanatopropanal (I). In an atmosphere of nitrogen at 0–3° C with vigorous stirring, a solution of 16.1 g (0.21 mole) of ammonium thiocyanate in 15 ml of water and a 50% solution of 10.6 g (0.15 mole) of H_2SO_4 were added simultaneously to 12 g (0.215 mole) of acrolein, after which the mixture was stirred at 20° C for 1 hr. The oily product forming the upper layer was extracted with ether and the ethereal extracts were washed with 5% potassium carbonate solution and then with water to neutrality. Then they were dried with magnesium sulfate, the ether was driven off, and the residue was distilled in vacuum, giving 5.5 g (52.5%) of **I**. Colorless liquid with a sharp smell, rapidly oxidizing on storage, with bp 95–98° C (10 mm), d_4^{20} 1.1983; n_D^{20} 1.5498. Found, %: C 41.61; H 4.44. MR_D 30.54. Calcalculated for C_4H_5NOS, %: C 41.75; H 4.40. MR_D 30.53.

3-Isothiocyanatobutanal (II). Similarly, 10.6 g (0.152 mole) of crotonaldehyde, 17.3 g (0.152 mole) of 50% aqueous ammonium thiocyanate, and 7.45 g (0.076 mole) of 50% H_2SO_4 gave 11.7 g (68%) of **II** with bp 87–90° C (10 mm); d_4^{20} 1.1032; n_D^{20} 1.5533. Found, %: C 46.56; H 5.76. MR_D 35.33. Calculated for C_5H_7NOS, %: C 46.50; H 5.47. MR_D 35.20.

3-Isothiocyanato-2-methylpropanal (III). Similarly, 16.4 g (0.23 mole) of methacrolein, 22 g (0.29 mole) of 50% aqueous ammonium thiocyanate, and 14.4 g (0.15 mole) of 50% H_2SO_4 gave 9 g (30.2%) of **III** with bp 95–97° C (10 mm), d_4^{20} 1.1360; n_D^{20} 1.5276. Found, %: N 10.45; MR_D 34.95. Calculated for C_5H_7NOS, %: N 10.83; MR_D 35.20.

3-Ethyl-4-hydroxy-4, 6, 6-trimethylhexahydropyrimidine-2-thione (XII). With vigorous stirring at 5–8° C, 4.5 g (0.077 mole) of n-propylamine was added to 10 g (0.064 mole) of **VIII** in 20 ml of water. The reaction mixture was stirred at 10–13° C for 3 hr.

The white crystals that separated out were filtered off, washed with water, and dried to give 10.2 g of **XII** in the form of white acicular crystals moderately soluble in water, ethanol, and acetone.

4-Hydroxy-4, 5, 6-trimethyl-3-phenylhexahydropyrimidine-2-thione (XXI). A solution of 3.6 g (0.038 mole) of aniline in 5 ml of ether was added dropwise at 10–12° C to a solution of 6 g (0.038 mole) of **VII** in 15 ml of dry ether. The solution was kept at 18–20° C for 48 hr. The white crystals that had deposited were filtered off and dried to give 6.16 g of **XXI** in the form of white crystals soluble in ethanol and chloroform and insoluble in water.

Compounds **IX–XI, XIII–XX,** and **XXII–XXV** (table) were obtained similarly.

N, N-Dimethyl-N'-(2-methyl-3-oxobutyl)thiourea (XXVI). At 8–10° C, 6 g (0.04 mole) of **V** in 20 ml of dry ether was mixed with a 25% ethereal solution of 2.7 g (0.06 mole) of dimethylamine. The solution was left at 18–20° C for 72 hr. The oil that had separated out was removed from the ethereal solution and the ether was driven off, giving 3.66 g of crystals, while trituartion of the oil in petroleum ether yielded an additional 1.56 g of crystals. The total yield was 5.16 g (62.9%) of snow-white acicular crystals of **XXVI** with mp 36–37° C (from petroleum ether) soluble in ethanol, acetone, and chloroform. R_f 0.34 (Al_2O_3 of activity II, benzene–ether, 2:1). Found, %: N 14.6; S 17.11. Calculated for $C_8H_{16}N_2OS$, %: N 14.89, S 17.00.

N-(3-Oxobutyl)-N'-pentamethylenethiourea (XXVII). At 15° C, a solution of 11.2 g (0.132 mole) of piperidine in 20 ml of ether was added to a solution of 17 g (0.132 mole) of **IV** in 30 ml of dry ether. The reaction mixture was heated to the boil for 3 hr 30 min. On cooling, the lower oily layer rapidly crystallized. After drying, 22.1 g (75.6%) of **XXVII** with mp 96–97.5° C (from petroleum ether) was obtained in the form of white acicular crystals soluble in ethanol, chloroform, and acetone. Found, %: C 56.32; H 8.51; N 14.90. Calculated for $C_{10}H_{18}N_2OS$, %: C 56.04; H 8.48; N 14.93.

N-(2-Oxopent-4-yl)-N'-pentamethylenethiourea (XXVIII). Similarly, 11.3 g (0.079 mole) of **VI** and 7.4 g (0.08 mole) of piperidine in 25 ml of dry ether gave 12.5 g (72.6%) of **XXVIII** with mp 67–68° C (from petroleum ether). Found, %: C 57.88; H 9.18; N 11.90. Calculated for $C_{11}H_{20}N_2OS$, %: C 57.85; H 8.84; N 12.27.

N-Methyl-N'-(2-oxopent-4-yl)-N-phenylthiourea (XXIX). Similarly, 13.7 g (0.095 mole) of **VI** and 10.3 g (0.095 mole) of methylaniline in 40 ml of ether gave 11.5 g (48.2%) of **XXIX** with mp 108–109.5° C (from ethanol). R_f 0.44 (Al_2O_3 of activity grade **II**, benzene–ether, 3:1). Found, %: N 11.20; S 12.92. Calculated for $C_{13}H_{18}N_2OS$, %: N 11.19; S 12.78.

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