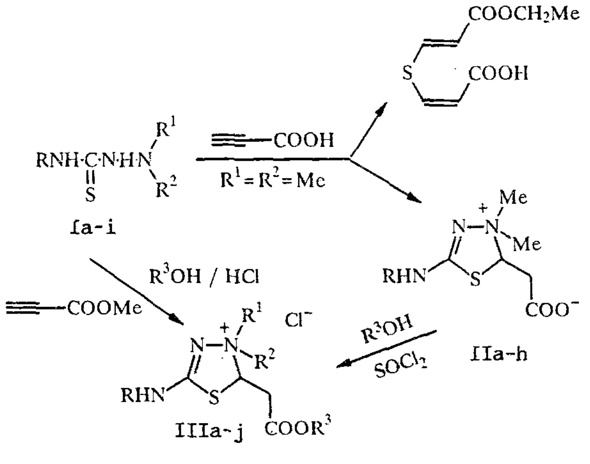
REACTIONS OF 1,1—DIALKYLTHIOSEMICARBAZIDES WITH PROPIOLIC ACID AND ITS ESTERS

V. Ya. Kauss, A. F. Mishnev, and I. Ya. Kalvin'sh

The betaines 2—amino—4,4—dimethyl—Δ^2*—1,3,4—thiadiazolin—4—io—5—acetates are formed in the reaction of 1,1—dimethylthiosemicarbazides with propiolic acid. 2—Amino—4,4—disubstituted—5—carboalkoxy-methyl—*Δ^2*—1,3,4—thiadiazolinium chlorides, the structure of which has been confirmed by X—ray crystallography, are formed by the reaction of 1,1—disubstituted thiosemicarbazides lower alkyl propiolates in the presence of hydrochloric acid.*

We previously reported the reaction of substituted thiosemicarbazides with acetylenedicarboxylic acid and its dimethyl ester [1]. It was shown that condensation of the α—carboxyl group with the amino group at $N_{(4)}$ of the thiosemicarbazide occurred after nucleophilic *trans*—addition of the sulfur atom of the thiosemicarbazide residue to the triple bond. 1,1—Disubstituted thiosemicarbazides react differently with propiolic acid under analogous conditions to give 2—amino—Δ^2—1,3,4—thiadiazolin—4—io—5—acetates (IIa—g) as a result of β,β—diaddition of the S and $N_{(1)}$ atoms of the thiosemicarbazides to propiolic acid. The betaines IIa—h were obtained by heating equimolar amounts of the reagents in ethanol, acetone, toluene, water, or acetic acid. Propiolic acid esters do not react with 1,1—disubstituted thiosemicarbazides in aprotic solvents. The corresponding semicarbazides and a mixture of isomeric β,β′—thiodiacrylic acid esters were obtained only when the reaction mixture was boiled for along time [3]. The betaines IIa—h were always obtained when this reaction was carried out in water, ethanol—water, or acetic acid (8 h, 40 h, and 2 h respectively).



I,II a R = H, b R=Me, c R = $CH_2CH=CH_2$, d R= n—Bu, f R = adamantyl, h R = naphthyl; I, IIa—h $R^1 = R^2$ = Me; Ig and i R = Ph, Ig $R^1 = R^2$ = Me, Ii R^1 = Me, $R^2 = CH_2Ph$; IIIa, b, c, g R = Me, IIId R = $CH_2CH=CH_2$, IIIe—h, j R = Ph, i R = n—Bu; IIIa—d, g, i $R^1 = R^2$ = Me, f, j R^1 = Me, $R^2 = CH_2Ph$. h $R^1 = R^2$ = Et; IIIa, d—f R^3 = Me, g—j R^3 = Me, b and h R^3 = Et.

Latvian Institute of Organic Chemistry, Riga, Latvia LV—1006. Translated from Khimiya Geterotsiklicheskikh Soedenenii, No. 12, pp. 1674-1679, 1992. Original article submitted October 12, 1992.

0009-3122/92/2812-1439$12.50

TABLE 1. Physicochemical Characteristics of Compounds IIa–h and IIIa–j

Compound	Molecular formula	Mp, °C *	IR spectra, ν, cm^{-1}	Yield, %
IIa	$C_6H_{11}N_3O_2S$	240...242	3230, 1658, 1610, 1570	66
IIb	$C_7H_{13}N_3O_2S$	196...198	3205, 1612, 1590, 1570	91
IIc	$C_9H_{15}N_3O_2S$	149...151	3195, 1605, 1570	68
IId	$C_{10}H_{19}N_3O_2S$	176...168	3230, 1687, 1583	56
IIe	$C_{11}H_{15}N_3O_2S$	233...235	3200, 1640, 1610, 1595	94
IIf	$C_{16}H_{25}N_3O_2S$	231...233	3215, 1605, 1590, 1565	62
IIg	$C_{16}H_{17}N_3O_2S$	183...185	3440, 1610, 1592, 1550	36
IIIa	$C_8H_{16}N_3O_2SCl$	223...225	3195, 3110, 1738, 1593	79
IIIb	$C_9H_{18}N_3O_2SCl$	204...206	3165, 3100, 1737, 1589	80
IIIc	$C_{10}H_{20}N_3O_2SCl$	183...185	3158, 3108, 1740, 1596	72
IIId	$C_{10}H_{18}N_3O_2SCl$	174...176		50
IIIe	$C_{13}H_{18}N_3O_2SCl$	219...221	3245, 3190, 1732, 1623	83
IIIf	$C_{19}H_{22}N_3O_2SCl$	224...226	3238, 3182, 1733, 1623	79
IIIg	$C_{16}H_{24}N_3O_2SCl$	226...229	3238, 3178, 1732, 1620	70
IIh	$C_7H_{14}N_3O_2SCl$	239...241		83
IIIi	$C_{10}H_{20}N_3O_2SCl$	191...193	3410, 3140, 1718, 1583	74
IIIj	$C_{18}H_{20}N_3O_2SCl$	174...176	3230, 3180, 1734, 1613	65

---

*All compounds melted with decomposition.

TABLE 2. ^{1}N NMR Spectra of Betaines IIa–h in D_2O

Compound	Chemical shift, δ, ppm					Coupling constant, Hz		
	RNH	$N(CH_3)_2$	H_A	H_B	H_X	J_{AB}	J_{AX}	J_{BX}
IIa	—	3,29; 3,50	2,93	3,27	5,70	14,0	10,5	4,0
IIb	2,84	3,29; 3,50	2,90	3,24	5,66	15,5	10,5	4,0
IIa*	3,6...3,9 (NCH_2); 5,0...5,4 ($=CH_2$); 5,6...6,1 ($=CH$)	3,10; 3,41	2,48	2,93	5,58	15,0	11,5	4,0
IId	0,8 (CH_3); 1,05...1,7 (CH_2CH_2); 3,20 (CH_2N)	3,27; 3,46	2,85	3,20	5,60	15,5	10,5	4,0
IIe	7,0...7,6 (C_6H_5)	3,36; 3,56	2,97	3,29	5,70	15,0	10,5	4,5
IIf	1,65...1,7 (6H)	3,26; 3,46	2,86	3,18	5,58	15,0	10,5	4,0
IIh	7,3...8,0 (7H)	3,12; 3,32	2,84	3,18	5,58	15,5	10,5	4,0

---

*Spectrum recorded in DMSO–d_6.

Results have been reported [2] on the addition of 1,1–dimethylhydrazine in different directions to propiolic acid and methyl propiolate in aprotic solvents. The interaction of 1,1–dimethylhydrazine with methyl propiolate depends on the protropic character of the solvent. As with addition of the fully substituted nitrogen atom of the hydrazine unit of thiosemicarbazide, addition to the multiple bond is possible only after protonation.

The reaction of 1–substituted thiosemicarbazides with activated acetylenes has been used previously for the synthesis of Δ^2–1,3,4–thiadiazolines [4]. However we were able to obtain betaines of the 2–amino–1,3,4–thiadiazolinecarboxylic acid series for the first time by using propiolic acid as the acetylenic component. The betaine structure was confirmed by NMR and IR spectra (Table 1). The C–O stretching frequency in the 1610–1580 cm^{-1} region shows the presence of a COO^- group in IIa–h, while the magnetic nonequivalence of the N–methyl groups is explained by the inclusion of the dimethylamino group in the ring. Their relatively large weak–field shift (3.3 and 3.5 ppm) in the PMR spectra indicates a positive charge and consequently the quaternized nitrogen atom (Table 2). Coupling of the protons of the substituents R with the NH proton confirm the presence of an exocyclic R–NH amino group. The appearance of an ABX system in the PMR spectra of compounds IIa–h may allow conclusions to be drawn about the possibility of α,β or β,β addition but it does not exclude the alternative five–

TABLE 3. ^{1}H NMR Spectra of Thiadiazolin–4–ium Chlorides in DMSO–d_6

Compound	Chemical shift, δ, ppm						Coupling constant Hz		
	RNH	R^3	R^1R^2N	H_A	H_B	H_X	J_{AB}	J_{AX}	J_{BX}
IIIa*	2,87	3,77	3,36; 3,56	3,30	3,64	5,91	16,0	10,0	4,0
IIIb	3,19 (CH_3); 8,62 (NH)	1,21; 4,13	3,22; 3,49	3,24	3,71	5,87	16,0	11,0	4,0
IIIc	2,73; 8,85	0,91; 1,60; 4,04	3,22; 3,55	3,11	3,73	5,88	16,0	11,0	4,0
IIId*	3,6...3,8; 5,0...5,3; 5,6...6,1	3,69	3,24; 3,51	3,14	3,52	5,90	17,0	11,0	4,0
IIIe**	7,0...7,55	3,79	3,45; 3,65	3,30	3,68	5,95	17,0	11,0	4,0
IIIf*	6,9...7,75 ($2C_6H5$); 11,15	—	3,10; 5,20 (CH_2)	3,37	3,90	5,85	17,0	11,0	3,0
IIIh*	6,9...7,6; 11,1 (NH)	1,00; 4,11	1,30; 3,77	***	***	5,86	***	11,0	4,0
IIIg*	2,87	—	3,38; 3,56	3,23	3,54	5,82	17,0	10,0	4,0
IIIi	0,89; 1,1...1,75; 3,08; 8,45 (NH)	—	3,22; 3,47	3,12	3,62	5,80	15,5	11,0	4,0
IIIj	6,9...7,7; 11,6 (NH)	—	3,13; 5,01 (CH_2)	3,26	3,82	5,84	17,0	11,0	3,0

---

* In D_2O

** In CD_3OD

and six–membered ring structures. The ^{13}C NMR spectrum of compound IIb also fails to provide a clear solution to the problem since it is difficult to explain the coupling (^{13}C—^{1}H) for the carboxylate carbon ($J_{C,H}$ 1.6 and 7.0 Hz) without information on the geometry of the molecule. These values could correspond to either geminal or vicinal ^{13}C—^{1}H coupling constants. An X-ray crystallographic analysis was carried out on compound IIIe, prepared by esterification of betaine IIb, to determine the structure of the products from the reaction of 1,1–dimethylthiosemicarbazides with propiolic acid. The 1,3,4–thiadiazoline structure was established for the first time (Fig.1). All the atoms of this molecule lie approximately in the same plane. This allows delocalization of the π–electron system in the $N_{(3)}$—$C_{(2)}$—$N_{(13)}$—Ph as indicated by the shortening of the $N_{(13)}$—$C_{(14)}$ (1.405 Å) and $C_{(2)}$—$N_{(13)}$ (1.349 Å) single bonds and the lengthening of the $C_{(2)}$—$N_{(3)}$ (1.311 Å) double bond by comparison of standard values [5]. In their turn, the $N_{(3)}$—$N_{(4)}$ (1.461 Å) and $N_{(4)}$—$C_{(5)}$ (1.523 Å) bonds are lengthened which is explained by the pyramidal nature of the positively charge $N_{(4)}$ atom and by the inductive effect of the methyl groups. The conformation of the five–membered ring is characterized by the torsion angles cited in Fig.1, the smallest of which is $S_{(1)}$—$C_{(2)}$—$N_{(3)}$—$N_{(4)}$ = −6.8°. Atom $C_{(5)}$ deviates from the mean squared plane through $S_{(1)}$, $C_{(2)}$, $N_{(3)}$, $N_{(4)}$ (maximum deviation 0.03 Å) by 0.42 Å. The $S_{(1)}$...$O_{(8)}$ distance (3.142 Å) is equal to the sum of the van der Waal's radii [6]. Packing of the models in the crystal is stabilized by $N_{(13)}$—H...Cl hydrogen bonds of length 3.120 Å (H...Cl = 2.25 Å).

Splitting of the C—S in the intermediate isothiosemicarbazides is a side process to the addition of thiosemicarbazides to propiolic acid. Therefore (*E,Z*)—β,β′—thiodiacrylic acid monoethyl ester is formed if the reaction is carried out in ethanol.

It should be noted that only a single isomer, with the ethyl acrylate unit in the *E*—configuration, was isolated in every case. This was confirmed by ^{13}C NMR spectroscopy with partial decoupling of the protons. The coupling constant of the carboxyl carbon to the β—proton was $^3J_{C,H}$ = 12.5 Hz, which shows that the carboxyl group is *trans* to the β—proton of the acrylate group.

The corresponding 5—carboalkoxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chlorides IIIa—j were obtained by the addition of 1,1—disubstituted thiosemicarbazides to propiolates in the presence of hydrochloric acid in lower alcohols. The side reaction of C—S bond scission in the isothiosemicarbazide residue was not observed. It may therefore be assumed that the first step in these conditions is the addition of protonated $N_{(1)}$ of the thiosemicarbazide to the triple bond. This is similar to the reaction of 1,1—dimethylhydrazine to activated acetylenes and ethylenes in acid media.

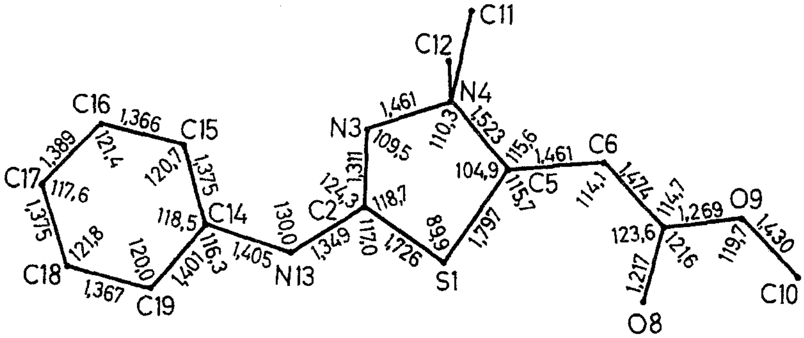


Fig. 1. Bond lengths and angles in compound IIIe

TABLE 4. Atomic Coordinates

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
S1	0.5129(1)	0.0528(1)	0.3527(1)	C11	0.7011(4)	0.0265(4)	0.0972(4)
C2	0.6802(3)	0.0666(4)	0.3551(3)	C12	0.6800(4)	-0.1687(3)	0.2387(4)
N3	0.7465(6)	0.0211(3)	0.2779(4)	N13	0.7337(3)	0.1266(2)	0.4362(3)
N4	0.6592(4)	-0.0464(4)	0.2097(3)	C14	0.8652(4)	0.1482(4)	0.4616(4)
C5	0.5193(4)	-0.0058(4)	0.2211(4)	C15	0.9691(4)	0.1146(4)	0.4019(5)
C6	0.4189(3)	-0.0899(4)	0.1941(3)	C16	1.0936(4)	0.1406(5)	0.4333(4)
C7	0.2859(5)	-0.0429(5)	0.1891(4)	C17	1.1193(3)	0.2061(4)	0.5232(5)
O8	0.2600(6)	0.0563(3)	0.2087(4)	C18	1.0150(4)	0.2394(4)	0.5827(4)
O9	0.1988(3)	-0.1134(2)	0.1592(3)	C19	0.8898(5)	0.2120(4)	0.5539(4)
C10	0.0658(4)	-0.0777(3)	0.1522(4)	Cl	0.5166(1)	0.2648(2)	0.5494(1)

Esters IIIa—h were also obtained from the corresponding betaines IIb—e by reaction with thionyl chloride in lower alcohols. However the attempted synthesis of betaines from ester chlorides IIIa—h was not successful. Treatment of compound IIIa with the anion exchanger IRA—401 gave only 1,1,4—trimethylsemicarbazide in place of the betaine IIb, which indicates the instability of betaines of type II in basic media.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker WH—90 (90 MHz) spectrometer in $CDCl_3$, DMSO—d_6, or D_2O with TMS or DSS as internal standard. ^{13}C NMR spectra were recorded with a Bruker WH—90 (22.62 MHz) spectrometer in DMSO—d_6. IR spectra of Nujol mulls were obtained with a Perkin Elmer 580 B machine. The course of reactions and the purity of products were monitored by TLC on Silufol UV—254 strips with 1:2 ethyl acetate—hexane or 8:6:1 chloroform—methanol—water mixtures as eluents.

Characteristics of the compounds synthesized are give in the tables.

Elemental analysis results agreed with calculated values.

Thiosemicarbazide starting materials were synthesized by a standard method from hydrazines and the corresponding isothiocyanates [7, 8]. 1,1—Dimethylthiosemicarbazide was obtained by hydrolysis of the corresponding 4—benzoylthiosemicarbazide in hydrochloric acid. 1,1—Diethyl— and 1—methyl—1—benzylhydrazines were obtained from the corresponding amines by nitrosation followed by reduction of the nitroso group with zinc in hydrochloric acid. The physicochemical characteristics of the thiosemicarbazide starting materials agreed with literature data [6].

X—ray crystallographic analysis. Monoclinic monocrystals: $a = 10.272(2)$, $b = 11.698(3)$, $c = 12.599(2)$ Å, $\beta = 91.06(2)°$, $V = 1513.6(4)$ Å^3, $d_{calc} = 1.39$ g/cm^3. sp.gr. $P2_1/c$, $Z = 4$.

The intensities of 1856 independent reflections were measured with a Syntex $P2_1$ automatic diffractometer (CuK_α radiation, graphite monochromator) with $\theta/2\theta$ scanning to $2\theta_{max} = 120°$. 1647 Reflections with $I > 2\sigma$ were used in the calculations. The structure was solved by the MULTAN program in the XTL system and refined in the full matrix least squares approximation to $R = 0.065$. Atomic coordinates are given in Table 4.

2-Amino-4,4-dimethyl-Δ^2-1,3,4-thiadiazolin-4-io-5-acetate(IIa). Propiolic acid (0.77 g, 11 mmol) was added to a solution of 1,1—dimethylthiosemicarbazide (1.19 g, 10 mmol) in ethanol (20 ml) and the mixture was boiled for 2.5 h with TLC monitoring and cooled. The precipitate was filtered off, washed with chloroform, and recrystallized from ethanol to give colorless crystals of IIa (1.24 g, 66%), m.p. 240—242°C (dec). The filtrate was evaporated and the residue extracted with chloroform. The chloroform was evaporated, the residue was treated with isopropanol and the colorless crystals were filtered off to give the monoethyl ester of β,β'—(*E,Z*)—thiodiacrylic acid (0.10 g), m.p.189—191°C. PMR spectrum (in DMSO—d_6): 1.22 (3H, t, CH_3), 4.15 (2H, q, CH_2O), 6.00 and 7.00 (1H, d, $J = 9.5$ Hz, *cis*—CH=CH), 6.20 and 8.00 (1H, d, $J = 15.5$ Hz, *trans*—CH=CH), 12.5 ppm (1H, br s, COOH). ^{13}C NMR spectrum (in DMSO—D_6): 15.12 (CH_3), 61.04 (CH_2), 117.39 and 118,39 (α—C), 145.00 and 147.90 (β—C), 165.22 ($COOCH_2$), 167.94 ppm (COOH).

2—Methylamino—4,4—dimethyl—Δ^2—1,3,4—thiadiazolin—4—io—5—acetate (IIb) was obtained analogously from 1,1,4—trimethylthiosemicarbazide (Ib). ^{13}C NMR spectrum (in DMSO—d_6): 174.5 (COO^-), 166.4 (C=N), 81.5 ($C_{(5)}$), 56.0 and 50.2 ($N(CH_3)_2$), 38.0 (CH_2), 31.6 ppm (NCH_3).

2—Allylamino—4,4—dimethyl—Δ^2—1,3,4—thiadiazolin—4—io—5—acetate (IIc) was prepared from Ic, **2—*n*-butyl—4,4—dimethyl—Δ^2—1,3,4—thiadiazolin—4—io—5—acetate (IId)** from Id in acetone, **2—phenyl—4,4—dimethyl—Δ^2—1,3,4—thiadiazolin—4—io—5—acetate (IIe)** from Ie, **2—adamantyl—4,4—dimethyl—Δ^2—1,3,4—thiadiazolin—4—io—5—acetate (IIf)** from If, and **2—(α—naphthyl)—4,4—dimethyl—Δ^2—1,3,4—thiadiazolin—4—io—5—acetate (IIg)** from Ig in acetone.

2—Methylamino—4,4—dimethyl—5—carbomethoxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIIa). Betaine Ib (1.0 g, 5 mmol) was suspended in methanol (25 ml), the mixture was cooled to 0°C and thionyl chloride (1.2 g) was added dropwise over 30 min. The mixture was stirred for a further 6 h at 20°C. The product was filtered off and washed with cold methanol to give the chloride IIIa (1.0 g 79%).

2—Methylamino—4,4—dimethyl—5—carboethoxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIIb) was obtained analogously from betaine Ib and ethanol, **2—methylamino—4,4—dimethyl—5—carbopropoxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIIc)** was obtained from Ib and isopropanol, **2—allylamino—4,4—dimethyl—5—carbomethoxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIId)** was obtained from Ic and methanol, **2—phenylamino—4,4—dimethyl—5—carbomethoxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIIe)** was obtained from Id and methanol.

2—Phenylamino—4,4—dimethyl—5—carboethoxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIIh). 1,1,—Diethyl—4—phenylthiosemicarbazide (2.23 g, 10 mmol) was dissolved in a mixture of ethanol (30 ml) and concentrated hydrochloric acid (2 ml). Methyl propiolate (0.93 g, 11 mmol) was added with stirring and the mixture was boiled for 8 h. The solvent was evaporated and the residue recrystallized from ethanol to give IIIa (2.5 g, 70%).

2—Phenylamino—4—benzyl—4—methyl—5—carbomethoxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIIf) was prepared analogously from 1—benzyl—1—methyl—4—thiosemicarbazide and methyl propiolate in methanol. The chlorides IIIa, d, and e were obtained analogously.

2—Methylamino—4,4—dimethyl—5—carboxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIIg) was prepared analogously 1,1,4—trimethylthiosemicarbazide and ethyl propiolate in methanol over 2 h.

2—Butylamino—4,4—dimethyl—5—carbomethoxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIIi) was prepared under conditions analogous to IIIg from 1,1—dimethyl—4—butylthiosemicarbazide.

2—Phenylamino—4—benzyl—4—methyl—5—carboxymethyl—Δ^2—1,3,4—thiadiazolin—4—ium chloride (IIIj) was prepared under conditions analogous to IIIi from 1—benzyl—1—methyl—4—phenylthiosemicarbazide.

Reaction of 5—carbomethoxymethyl—Δ^2—1,3,4—thiadiazalon—4—ium chloride (IIIa) with a strongly basic ion—exchange resin. Chloride IIIa (2.53 g, 10 mmol) was dissolved in water (20 ml) and passed through a column of IRA—401 (OH^- form) ion—exchange resin with water as eluent. The water was evaporated and the residue recrystallized from ethanol to give colourless crystals of 1,1,4—trimethylsemicarbazide (1.0 g), m.p. 119°C. ^1H NMR spectrum (DMSO—d_6): 2.37 (6H, s, $N(CH_3)_2$), 2.55 (3H, d, $NHCH_3$), 6.31 (1H, br q, $NHCH_3$), 6.86 ppm (1H, s, NH). The physicochemical properties agreed with literature values [7].

REFERENCES

1. V. Ya. Kauss, É. É. Liepin'sh, I. Ya. Kalvin'sh, and É. Lukevits. Khim. Geterotsikl. Soedin., No.1, 120 (1990).

2. L. K. Dalton, S. Demerac, and B. C. Elmes. Austral. J. Chem., **33**, No. 6, 1365 (1980).
3. J. Lown and J. C. N. Ma. Canad. J. Chem., **45**, No. 9, 953 (1967).
4. F. S. Nakhmanovich, E. S. Domnina, N. D. Abramova, Z. V. Stepanova, T. E. Glotova, and L. V. Andriyankova. Abstr. IVth All—Union Conference on the Chemistry of Nitrogen Containing Heterocyclic Compounds [in Russian]. Novosibirsk (1987), p.122.
5. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, and A. Orper. J. Chem. Soc. Perkin 2, No. 1, 1 (1987).
6. Yu. V. Zefirov and P. M. Zorkii, Zh. Strukt. Khim., **17**, No. 6, 994 (1976).
7. K. A. Jensen, U. Anthoni, B. Kagi, Ch. Larsen, and C. Pedersen. Acta. Chem. Scand., **22**, No. 1, 1 (1968).
8. J. E. Oliver and J. B. Stokes. J. Med. Chem., **13**, No. 4, 779 (1970).