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4,4-DIALKYL-SUBSTITUTED N-METHYLMORPHOLINIUM 3,5-DICYANO-6-OXO-1,4,5,6-TETRAHYDROPYRIDINE-2-THIOLATES AND SOME OF THEIR PROPERTIES

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4,4-Dialkyl-substituted N-methylmorpholinium 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates were synthesized by the condensation of 2-alkyl-2-cyanoethyl crotonates with cyanothioacetamide and N-methylmorpholine. They were used for the production of substituted 2-alkylthio-1,4,5,6-tetrahydropyridines, 2-acetylthio-1,4,5,6,-tetrahydropyridine, 6-hydrazino-1,4,5,6-tetrahydropyridine, and 2,3,4,5,6,7-hexahydrothiazolo[3,2-a]pyridine. The structure of 6-bromo-3-bromomethyl-6,8-dicyano-7,7-dimethyl-2,3,4,5,6,7-hexahydrothiazolo[3,2-a]pyridine was proved by X-ray crystallographic analysis.

Keywords: 4,4-dialkyl-substituted 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates, alkylation, acylation, bromination, condensation, nucleophilic substitution, X-ray crystallographic analysis, cyclization.

Derivatives of 4,4-disubstituted tetrahydropyridones are promising from the standpoint of the search for new pharmacological products [1-3]. Methods for the synthesis of these compounds involve the condensation of aliphatic ketones with cyanoacetamides [4] or of cinnamoyl chlorides with substituted 3-aminoacrylonitrile [5]. Recently we proposed a new method for the synthesis of such structures, consisting of the reaction of substituted ethyl crotonates **1** with cyanothioacetamide **2** and N-methylmorpholine [6].

In the course of this reaction, which takes place by a mechanism of the Michael addition type with the formation of the adduct **3**, 4,4-disubstituted N-methylmorpholinium 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates of type **4** were synthesized.

In the present work we obtained the familiar thiolate **4a** [6] and also the new thiolate **4b** and studied some of their properties. It was found that the condensation of compounds **1** and **2** takes place nonstereoselectively, as shown by the data from spectral investigations. Thus, the ^{1}H NMR spectrum of compound **4b** shows splitting of the equal-intensity signals for the protons at positions 4 and 5 (Table 1). By alkylation of the salts **4a**,**b** with halides **5a-d** it is possible to obtain organic sulfides **6a-d**, while acylation of the salt **4a** with acetic anhydride gives thioester **7**. Here the ^{1}H NMR spectrum of compound **6b** also contains split equal-intensity signals for the protons of the 4-Me group and 5-H (Table 1). Thus, the 1:1 ratio of the stereoisomers of compound **4b** remains unchanged in its alkylation products. These data make it possible to state that the salt **4b** exists as a mixture of equal amounts of stereoisomers with the *syn*-periplanar (*sp*) and *anti*-periplanar (*ap*) arrangement of the substituents in the tetrahydropyridine ring:

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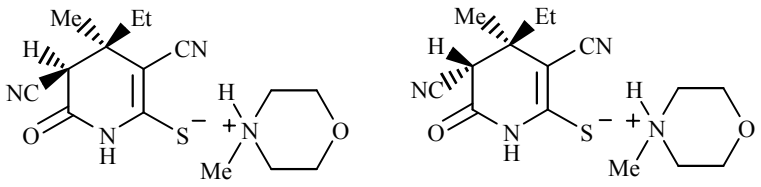
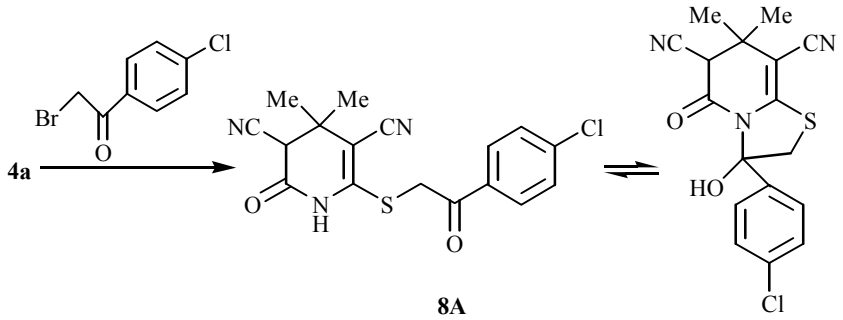


(*sp*)-isomer **4b** (*ap*)-isomer **4b**

During alkylation of thiolate **4a** with 4-chlorophenacyl bromide substituted tetrahydropyridine **8** is formed. In solution in DMSO-d_6 it exists as a mixture of equal amounts of the isomers **8A** and **8B**, as shown by the data from the ^{1}H NMR spectrum (Table 1):

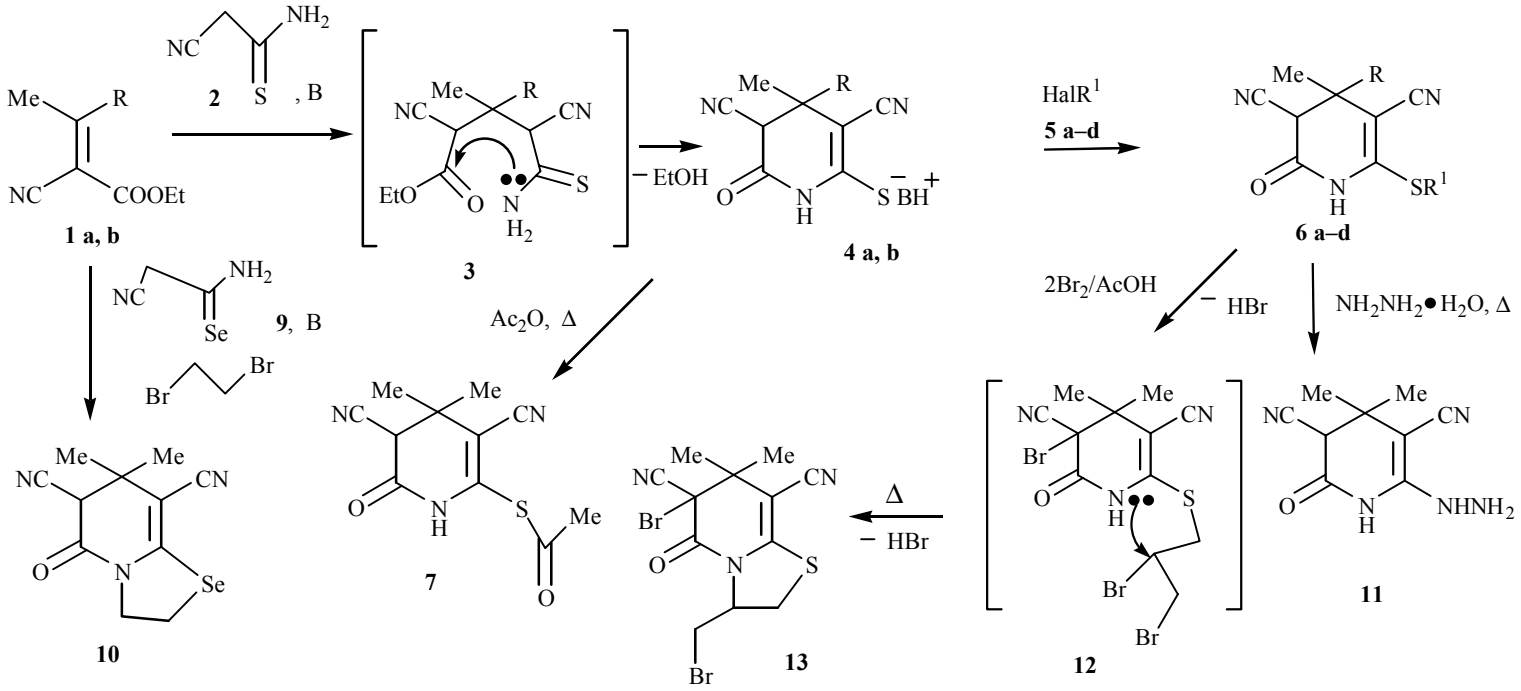


8A **8B**

It is not possible to obtain the selenium analogs of salts **4** by the above-mentioned path on account of the predominance of various side processes in this reaction and, in particular, the smooth dimerization of cyanoselenoacetamide (**9**) [7]. At the same time the use of 1,2-dibromoethane in reaction with substituted ethyl crotonate **1a** and amide **9** led to the formation of 6,8-dicyano-7,7-dimethyl-6-oxo-2,3,4,5,6,7-hexahydroselenazolo[3,2-*a*]pyridine (**10**) with a yield of 68%.

Substituted tetrahydropyridones **6** contain alkylthio groups fairly active toward nucleophilic reagents. Thus, substituted 6-hydrazinotetrahydropyridine **11** is formed when compound **6a** is boiled with hydrazine hydrate. The bromination of 2-alkylthio-substituted tetrahydropyridine **6d** with a twofold excess of bromine, the mechanism of which has not yet been established, takes place in solution in boiling acetic acid with the probable formation of compound **12**, which then undergoes cyclization by an intramolecular alkylation path to substituted 2,3,4,5,6,7-hexahydrothiazolo[3,2-*a*]pyridine **13**. Features of the molecular and crystal structure of compound **13** were investigated by X-ray crystallographic analysis (Fig. 1 and Table 2).

The central bicyclic system of compound **13** is essentially nonplanar; the declinations of the atoms from the mean-square plane amount to 0.401 Å. Here both the six-membered ring N(1)C(1-5) and the five-membered ring S(1)N(1)C(5)C(10)C(11) are appreciably nonplanar. In the first the N(1)C(1)C(4)C(5) group is planar within 0.053 Å, whereas the C(2) and C(3) atoms project from this plane by -0.310 and 0.385 Å respectively. According to the modified Cremer–Pople parameter [8] the conformation of the heterocycle N(1)C(1-5) can be described as a *half-boat* (S = 0.42, θ = 48.2°, ψ = 27.6°). The five-membered ring has an *envelope* conformation; the S(1)N(1)C(5)C(10) atoms are coplanar within 0.059 Å, the S(1)C(10)C(11) "corner" forms a dihedral angle of 151.9° with this plane, and the substituent CH_2Br occupies the axial position. [The C(11)–C(12) bond is directed at an angle of 75.5° in relation to the S(1)N(1)C(5)C(10) plane.] The N(1) atom has a plane-trigonal configuration for the valence bonds. (The sum of the bond angles at this atom amounts to 360.0°.) The n(N(1))–π(C(1)=O(1)) and n(N(1))–π(C(4)=C(5)) conjugation leads to substantial shortening of the N(1)–C(1) bond to 1.358(13) Å and N(1)–C(5) to 1.397(12) Å compared with the standard values of 1.43-1.45 Å for an ordinary N(sp^2)–C(sp^2) bond [9, 10]. The S(1)–C(5) 1.745(11) and S(1)–C(11) 1.819(10) Å bond lengths are normal [11].



1, **4 a** R = Me, **b** R = Et; **5 a** Hal = I, R^1 = Me; **b** Hal = Br, R^1 = $CH_2CH{=}CH_2$; **c** Hal = Cl, R^1 = $CH_2CMe{=}CH_2$; **d** Hal = I, R^1 = Et; **6 a** R = Me, R^1 = Et; **b** R = Et, R^1 = Me; **c** R = Me, R^1 = $CH_2CMe{=}CH_2$; **d** R = Me, R^1 = $CH_2CH{=}CH_2$; **B** = N-methylmorpholine

TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
4b	$C_{15}H_{22}N_4O_2S$	55.71 / 55.87	6.63 / 6.88	17.49 / 17.38	171-173*[2]	83
6a	$C_{11}H_{13}N_3OS$	55.92 / 56.14	5.40 / 5.57	18.03 / 17.86	154-155	72
6b	$C_{11}H_{13}N_3OS$	55.94 / 56.14	5.35 / 5.57	18.05 / 17.86	151-153	79
6c	$C_{13}H_{15}N_3O_2S$	59.68 / 59.76	5.58 / 5.79	16.19 / 16.08	193	74
7	$C_{11}H_{11}N_3OS$	52.83 / 53.00	4.21 / 4.45	16.97 / 16.86	179-181	67
8	$C_{17}H_{14}ClN_3O_2S$	56.66 / 56.75	3.80 / 3.92	11.77 / 11.68	172-174	88
10	$C_{11}H_{11}N_3OSe$	46.95 / 47.15	4.13 / 3.96	14.81 / 15.00	186-188	68
11	$C_9H_{11}N_5O$	52.51 / 52.67	5.23 / 5.40	34.29 / 34.13	223-225	83
13	$C_{12}H_{11}Br_2N_3OS$	35.41 / 35.58	2.85 / 2.74	10.14 / 10.37	193-195	86

* Solvents for crystallization: butanol (compound **6a**), acetic acid (compounds **6b**,**c**-**8**, **10**, **13**), and ethanol (compound **11**).
*[2] The compound was not crystallized.

TABLE 2. The Spectral Characteristics of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1} *		^{1}H NMR spectrum(DMSO-d_6), δ, ppm (*J*, Hz)
	C=O, N–H	C≡N	
4b	1710, 3360	2190, 2265	9.32 (1H, br. s, NH); 4.20 and 4.10 (1H, two s, 3-H); 7.84 (4H, m, CH_2OCH_2); 3.25 (4H, m, CH_2NCH_2); 2.81 (3H, s, NCH_3); 1.44 (2H, m, CH_2); 1.25 and 1.03 (3H, two s, 4-CH_3); 0.82 (3H, m, $CH_2\underline{CH_3}$)
6a	1714, 3217	2209, 2260	11.22 (1H, br. s, NH); 4.75 (1H, s, 3-H); 3.02 (2H, m, CH_2); 1.33 (3H, s, CH_3); 1.25 (3H, t, *J* = 7.7, $CH_2\underline{CH_3}$); 1.12 (3H, s, CH_3)
6b	1692, 3200	2204, 2255	11.13 (1H, br. s, NH); 4.84 and 4.73 (1H, two s, 3-H); 2.50 (3H, s, SCH_3); 1.52 (2H, m, CH_2); 1.32 and 1.14 (3H, two s, CH_3); 0.95 (3H, q, *J* = 7.4, CH_3)
6c	1700, 3260	2209, 2254	11.22 (1H, br. s, NH); 4.93 and 4.82 (1H and 1H, two d, 2*J* = 2.1, CH_2=); 4.51 (1H, s, 3-H); 3.72 (2H, s, SCH_2); 1.84 (3H, s, CH_3); 1.35 and 1.13 (3H and 3H, two s, $2CH_3$)
7	1740, 3180	2190, 2245	11.22 (1H, br. s, NH); 4.71 (1H, s, 3-H); 2.54 (3H, s, $COCH_3$); 1.42 (3H, s, CH_3); 1.13 (3H, s, CH_3)
8	1705, 1722, 3450	2188, 2258	11.15 (1H, br. s, NH); 3.52 (1H, br. s, OH); 7.40-8.12 (4H, m, H_{arom}); 4.92 and 4.51 (1H, two s, 3-H); 4.84 (2H, c, CH_2 isomer **A**); 4.70 (2H, c, CH_2 isomer **B**); 1.12-1.43 (6H, m, $2CH_3$)
10	1699	2192, 2255	4.53 (2H, m, 3-H and NCH_2); 4.12 (2H, m, NCH_2); 3.42 (2H, m, $SeCH_2$); 1.43 (3H, s, CH_3); 1.22 (3H, s, CH_3)
11	1700, 3344, 3420	2205, 2250	10.81 (1H, br. s, NH); 10.62 (1H, br. s, NH); 4.93 (2H, br. s, NH_2); 4.22 (1H, s, 3-H); 1.41 (3H, s, CH_3); 1.25 (3H, s, CH_3)
13	1695	2205, 2250	4.12-4.28 (3H, m, $BrCH_2CH$); 3.89 (1H, m, SCH); 3.20 (1H, m, SCH); 1.53 and 1.43 (3H, two s, $2CH_3$)

* The IR spectra were obtained in vaseline oil.

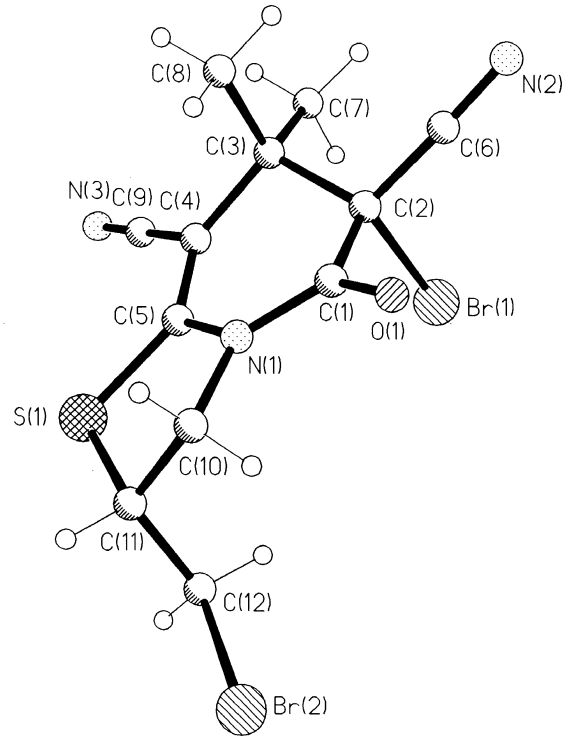


Fig. 1. The general appearance of the molecule of **13** with the numbering of the non-hydrogen atoms.

In the crystal the molecules of compound **13** (Fig. 2) are linked by van der Waals forces.

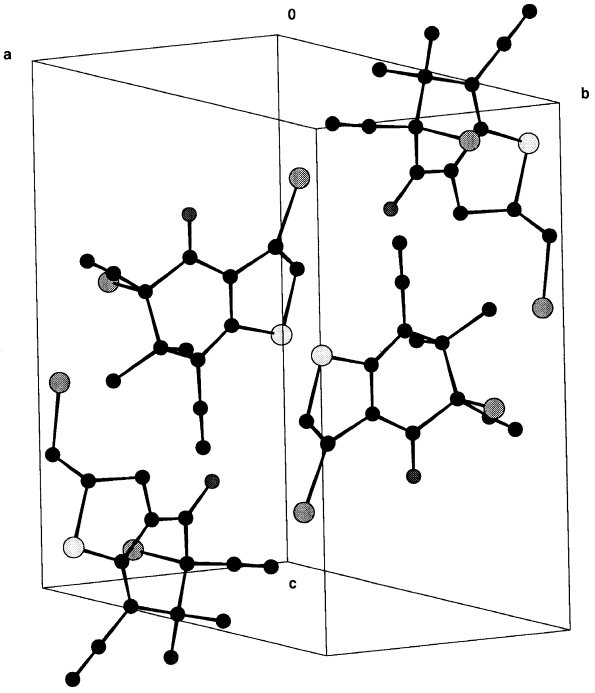


Fig. 2. The crystal packing of compound **13**.

TABLE 3. The Principal Bond Lengths (*d*) and Bond Angles (ω) in the Molecule of Compound **13**

Bond	*d*, Å	Angle	ω, deg
Br(1)–C(2)	1.978(10)	C(5)–S(1)–C(11)	92.9(5)
Br(2)–C(12)	1.949(10)	C(1)–N(1)–C(5)	122.5(8)
S(1)–C(5)	1.745(11)	C(1)–N(1)–C(10)	123.3(8)
S(1)–C(11)	1.819(10)	C(5)–N(1)–C(10)	114.2(8)
O(1)–C(1)	1.226(12)	O(1)–C(1)–N(1)	122.2(9)
N(1)–C(1)	1.358(13)	O(1)–C(1)–C(2)	121.7(9)
N(1)–C(5)	1.397(12)	N(1)–C(1)–C(2)	116.0(9)
N(1)–C(10)	1.476(12)	C(1)–C(2)–C(3)	112.8(9)
N(2)–C(6)	1.153(14)	C(2)–C(3)–C(4)	106.2(8)
N(3)–C(9)	1.132(13)	C(3)–C(4)–C(5)	120.3(9)
C(1)–C(2)	1.51(2)	C(4)–C(5)–N(1)	121.9(9)
C(2)–C(3)	1.572(14)	C(4)–C(5)–S(1)	127.0(8)
C(3)–C(4)	1.51(2)	N(1)–C(5)–S(1)	111.1(7)
C(4)–C(5)	1.346(13)	S(1)–C(11)–C(10)	105.6(7)
C(10)–C(11)	1.51(2)	N(1)–C(10)–C(11)	107.1(8)

TABLE 4. The Atomic Coordinates ($\times 10^4$) and the Equivalent Isotropic Temperature Parameters U_{eq} ($Å^2 \times 10^3$) in the Structure of Compound **13**

Atom	*x*	*y*	*z*	U_{eq}
Br(1)	9556(1)	2158(1)	3939(1)	62(1)
Br(2)	7048(1)	6818(1)	1487(1)	60(1)
S(1)	7257(4)	6255(3)	4531(2)	53(1)
O(1)	6255(8)	2191(7)	2812(5)	49(2)
N(1)	6685(9)	3975(9)	3745(5)	39(2)
N(2)	7180(13)	-646(11)	4018(7)	74(3)
N(3)	8979(12)	4886(11)	6769(7)	74(3)
C(1)	6804(11)	2671(11)	3543(7)	38(2)
C(2)	7720(11)	1857(10)	4253(7)	39(3)
C(3)	7636(10)	2291(11)	5267(7)	47(3)
C(4)	7838(11)	3772(9)	5298(6)	37(3)
C(5)	7308(10)	4528(10)	4576(6)	38(3)
C(6)	7409(12)	472(12)	4099(8)	51(3)
C(7)	8771(12)	1576(12)	5936(8)	57(3)
C(8)	6199(11)	1940(10)	5424(8)	57(3)
C(9)	8481(12)	4388(11)	6111(7)	44(3)
C(11)	6595(11)	6271(10)	3307(6)	38(3)
C(10)	5926(12)	4935(11)	3101(7)	51(3)
C(12)	7721(11)	6525(11)	2788(7)	47(3)

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded on an IK-29 instrument. The ^{1}H NMR spectra of compounds **4b**, **6a**,**b**, **7**, **8**, and **11** were recorded on a Bruker WP-100 SY instrument (100 MHz), the spectrum of compound **6c** was recorded on a Bruker AM-300 instrument (300 MHz), and the spectra of compounds **10** and **13** were recorded on a Bruker WM-250 instrument (250 MHz) with TMS as internal standard. The mass spectrum of compound **13** was recorded on a Kratos MS-890 instrument (70 eV). The

melting points were determined on a Kofler bench. The reactions were monitored by TLC (Silufol UV-254, 3:5 acetone–hexane, development with iodine vapor). The characteristics of compounds **4b**, **6a-c**, **7**, **10**, **11**, and **13** are given in Tables 1 and 2.

X-ray Crystallographic Analysis of Single Crystal of Compound 13 ($C_{12}H_{11}Br_2N_3OS$). The investigation was carried out at room temperature on an Enraf-Nonius CAD-4 automatic four-circle diffractometer (λMo$K\alpha$ radiation, graphite monochromator, ratio of scan rates ω/2θ 1.2, θ_{max} 24°, segment of sphere $0 \le h \le 11$, $0 \le k \le 11$, $-16 \le l \le 16$). In all 2439 reflections, of which 2239 were independent, were collected (R factor 0.030). The crystals of compound **13** are monoclinic, a = 9.940(2), b = 10.092(2), c = 14.741(3) Å; β = 99.29(3)°; V = 1459.3(5) Å^3; Z = 4; d_{calc} = 1.84 g/cm^3; μ = 5.69 mm^{-1}; F(000) 792; space group $P2_1/c$ (No. 14). The structure was interpreted by the direct method and refined in full-matrix anisotropic approximation using SHELXS and SHELXL93 software [12, 13]. In the refinement we used 2007 reflections with $I > 2\sigma(I)$ (172 refined parameters, number of reflections per parameter 11.7, weighting scheme $\omega = 1/[\sigma^2(F_o^2) + (0.1157P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$. A correction was included for anomalous scattering; corrections were not made for absorption. All the hydrogen atoms were revealed objectively and were included in the refinement with fixed thermal and positional parameters. The final divergence factors were $R1(F)$ 0.075 and $R_w(F^2)$ 0.176, GOOF 1.063. The residual electron density from the Fourier difference series after the last refinement cycle was 0.87 and -1.18 e/Å^3. The atomic coordinates are given in Table 4.

N-Methylmorpholinium 3,5-Dicyano-4,4-dimethyl-6-oxo-1,2,3,4-tetrahydropyridine-2-thiolate (4a) and N-Methylmorpholinium 3,5-Dicyano-4-ethyl-4-methyl-6-oxo-1,2,3,4-tetrahydropyridine-2-thiolate (4b). The compounds were obtained by the method in [6]. The characteristics of salt **4a** were given in [6].

3,5-Dicyano-6-ethylthio-4,4-dimethyl-1,2,3,4-tetrahydropyridin-2-one (6a), 3,5-Dicyano-4-ethyl-4-methyl-6-methylthio-1,2,3,4-tetrahydropyridin-2-one (6b), 3,5-Dicyano-6-methallylthio-4,4-dimethyl-1,4,5,6-tetrahydropyridin-2-one (6c), 6-Allylthio-3,5-dicyano-4,4-dimethyl-1,2,3,4-tetrahydropyridin-2-one (6d), and 6-(4-Chlorobenzoylmethylthio)-3,5-dicyano-4,4-dimethyl-1,2,3,4-tetrahydropyridin-2-one (8). The compounds were obtained by the method in [6]. The characteristics of compound **6d** were given in [6].

6-Acetylthio-3,5-dicyano-4,4-dimethyl-1,2,3,4-tetrahydropyridin-2-one (7). Solution of the salt **4a** (3.1 g, 10 mmol) in acetic anhydride (15 ml) was boiled for 4 h and was then kept at room temperature for 48 h. The white crystalline precipitate was filtered off and washed with ethanol and hexane. Compound **7** was obtained.

6,8-Dicyano-7,7-dimethyl-2,3,4,5,6,7-hexahydroselenazolo[3,2-*a*]pyridin-5-one (10). To solution of ethyl acrylate **1a** (1.5 g, 10 mmol) in absolute ethanol (15 ml) at 20°C in atmosphere of argon we added with stirring cyanoselenoacetamide **9** (1.5 g, 10 mmol) and N-methylmorpholine (1.7 ml, 15 mmol). The reaction mixture was then kept in a covered vessel at room temperature for 48 h, 1,2-dibromoethane (0.9 ml, 10 mmol) was added, and the mixture was kept for a further 24 h. The precipitate was filtered off and washed with ethanol and with hexane. Compound **10** was obtained.

3,5-Dicyano-2-hydrazino-4,4-dimethyl-1,2,3,4-tetrahydropyridin-5-one (11). Mixture of compound **6** (2.4 g, 10 mmol) and hydrazine hydrate (1 ml, 10 mmol) in ethanol (20 ml) was boiled for 40 min and was then kept at 20°C for 3 h. The precipitate was filtered off and washed with ethanol and with hexane. Compound **11** was obtained.

6-Bromo-3-bromomethyl-6,8-dicyano-7,7-dimethyl-2,3,4,5,6,7-hexahydrothiazolo[3,2-*a*]pyridin-5-one (13). To solution of compound **6d** (2.5 g, 10 mmol) in boiling glacial acetic acid (15 ml) with exposure to a lamp (500 W) we added dropwise (each time after decolorization of the reaction mixture) bromine (1 ml, 20 mmol). The mixture was kept at room temperature for 2 days and was then diluted with water (2 ml). The white precipitate was filtered off and washed with ethanol and with hexane. Compound **13** was obtained. Mass spectrum, *m/z* (I_{rel}, %): 405 $[M]^+$ (18), 390 (13), 324 (41), 309 (59), 179 (78), 108 (46), 73 (60), 39 (100).

REFERENCES

1. G. Culliamet, *J. Pharm. Belg.*, **49**, 216 (1994).
2. S. Pavlov, M. Bogavac, and Z. Arsenijevic, *Pharmazie*, **45**, 286 (1990).
3. V. V. Kuznetsov, *Khim.-Farm. Zh.*, No. 7, 61 (1991).
4. *German Patent Appl.* P 3844355 (1990); *Ref. Zh. Khim.*, 10N108P (1991).
5. A. K. D. Chowdhury, M. Sarkar, S. R. Chowdhury, and K. K. Mahalanabis, *Synth. Commun.*, **26**, 4233 (1996).
6. V. D. Dyachenko, A. A. Nikishin, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 996 (1997).
7. V. D. Dyachenko, Yu. A. Sharanin, V. P. Litvinov, V. N. Nesterov, V. E. Shklover, Yu. T. Struchkov, V. K. Promonenkov, and A. V. Turov, *Zh. Obshch. Khim.*, **61**, 747 (1991).
8. N. S. Zefirov and V. A. Palyulin, *Dokl. Akad. Nauk*, **252**, 111 (1980).
9. R. W. Alder, N. C. Goode, T. J. King, J. M. Mellor, and B. W. Miller, *J. Chem. Soc., Chem. Commun.*, No. 5, 173 (1976).
10. M. Burke-Laing and M. Laing, *Acta Crystallogr.*, **B32**, 3216 (1976).
11. V. A. Naumov and O. N. Kataeva, *Molecular Structure of Organic Compounds of Oxygen and Sulfur* [in Russian], Nauka, Moscow (1990), p. 192.
12. G. M. Sheldrick, *SHELXS-86. Program for the Solution of Crystal Structures*, Univ. of Göttingen, Göttingen, Germany (1986).
13. G. M. Sheldrick, *SHELXL-93. Program for the Refinement of Crystal Structures*, Univ. of Göttingen, Göttingen, Germany (1993).