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SYNTHESIS, STRUCTURE, AND ELECTROCHEMICAL CHARACTERISTICS OF 4-ARYL-2-CARBAMOYLMETHYLTHIO-5-ETHOXYCARBONYL-1,4-DIHYDROPYRIDINE-3-CARBOXYLIC ACID NITRILES*

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We have obtained 4-aryl-2-carbamoylmethylthio-5-ethoxycarbonyl-1,4-dihydropyridine-3-carboxylic acid nitriles by S-alkylation of the corresponding 2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxylic acid nitrile by iodoacetamide or one-pot multicomponent synthesis methods: condensation of 2-arylidene-acetoacetic acid ethyl ester, 2-cyanothioacetamide, piperidine, and iodoacetamide; acetoacetic acid ethyl ester, 3-aryl-2-cyanothioacrylamide, piperidine, and iodoacetamide; acetoacetic acid ethyl ester, an aromatic aldehyde, 2-cyanothioacetamide, piperidine, and iodoacetamide. We have carried out a comparative analysis of the capability of 2-alkylthio-4-aryl-5-ethoxycarbonyl-1,4-dihydropyridine-3-carboxylic acid nitriles for electrochemical oxidation as a function of the electronic properties of the aryl substituent in the 4 position of the heterocycle and the 2-alkylthio substituent. X-ray diffraction data indicate the existence of a hydrogen bond between the C=O of the 2-carbamoylmethylthio substituent and the NH of the hydrogenated heterocycle, which explains the more facile oxidation of the studied compounds compared with 2-methylthio-substituted 1,4-dihydropyridines.

Keywords: 1,4-dihydropyridines, hydrogen bond, one-pot multicomponent method, electrochemical oxidation, X-ray diffraction analysis.

Nitriles of 2-alkylthio-4-aryl-1,4-dihydropyridine-3-carboxylic acids are of interest as potential antioxidants [1, 2] that are also distinguished by cardiovascular [3, 4] and hepatoprotective [5] activity.

Continuing a study of the chemical and electrochemical properties of 2-alkylthio-1,4-dihydropyridines [4, 6] and methods for obtaining them [7, 8], we have synthesized a series of novel 4-aryl-2-carbamoylmethylthio-5-ethoxycarbonyl-6-methyl-1,4-dihydropyridine-3-carboxylic acid nitriles **1**, in which we varied the substituents on the 4-phenyl ring over a broad range. We carried out a comparative analysis of the capability for electrochemical oxidation of 2-alkylthio-4-aryl-5-ethoxycarbonyl-1,4-dihydropyridine-3-carboxylic acid nitriles **1** and **4** as a function of the electronic properties of the aryl substituent on the 4 position of the heterocycle and the 2-alkylthio substituent, since the corresponding values of the potentials quantitatively characterize the antioxidant properties of the compounds. The electrochemical oxidation data were used for a more targeted search for biologically active substances.

* Dedicated to Academician V. Minkin to show our appreciation for his contribution to organic chemistry and his wonderful humanity, remembering his collaboration with his colleagues from Riga.

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4-Aryl-2-carbamoylmethylthio-5-ethoxycarbonyl-1,4-dihydropyridine-3-carboxylic acid nitriles **1** were obtained by condensation of: A) 2-arylidene acetoacetic acid ethyl ester, 2-cyanothioacetamide, piperidine, and iodoacetamide; B) acetoacetic acid ethyl ester, 3-aryl-2-cyanothioacrylamide, piperidine, and iodoacetamide; C) acetoacetic acid ethyl ester, an aromatic aldehyde, 2-cyanothioacetamide, piperidine, and iodoacetamide, and D) by alkylation of 4-aryl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxylic acid nitriles **2** by iodoacetamide (Scheme 1). For the comparative analysis, we obtained compound **1g** by all four methods. Multicomponent synthesis methods A (yields of compounds calculated based on the aldehyde, 47%-60%), B (54%-62%), and C (68%-85%) have advantages over method D (stepwise synthesis, 33%-50%). The five-component method C proved to be the most efficient and the most "green" in the studied cases (the need to synthesize lacrimators, 3-aryl-2-cyanothioacrylamides, was dropped).

These observations are consistent with data on synthesis of 2-methylthio-1,4-dihydropyridine-3-carboxylic acid nitriles **4**. It has been established [4] that design of the 1,4-dihydropyridine-2(3H)-thione ring is a very complicated problem, since these compounds are readily oxidized in dilute solutions (compound **1d** cannot be obtained by method D). We need to find conditions allowing them to be rapidly separated from the reaction medium or transformed to more stable 2-alkylthio-1,4-dihydropyridines, which is possible when using methods A-C. On the other hand, 2-arylideneacetoacetic acid ethyl esters, obtained from an aromatic aldehyde and acetoacetic acid ethyl ester (the starting materials for method A), are formed as a mixture of *cis* and *trans* isomers [9], and their separation is occasionally prolonged and labor-intensive, since upon heating the products of further Michael reaction are formed with participation of acetoacetic acid ethyl ester as the methylene component. The lacrimators 3-aryl-2-cyanothioacrylamides, obtained from an aromatic aldehyde and 2-cyanothioacetamide (the starting materials for method B), tend toward dimerization in the presence of bases [10]. Furthermore, 2-arylideneacetoacetic acid ethyl esters and 3-aryl-2-cyanothioacrylamides, in contrast to aromatic aldehydes, are not oxidized during storage and therefore in a number of cases are used as the starting components when using less efficient synthesis methods (A, B, or D).

Application of methods A-C leads to formation of 1,4-dihydropyridines **1** with 6-hydroxy-1,4,5,6-tetrahydropyridines **3** as an impurity. When the reaction mixture containing compounds **1** and **3** is acidified, final dehydration of hydroxy derivatives **3** occurs with formation of exclusively 1,4-dihydropyridines **1**.

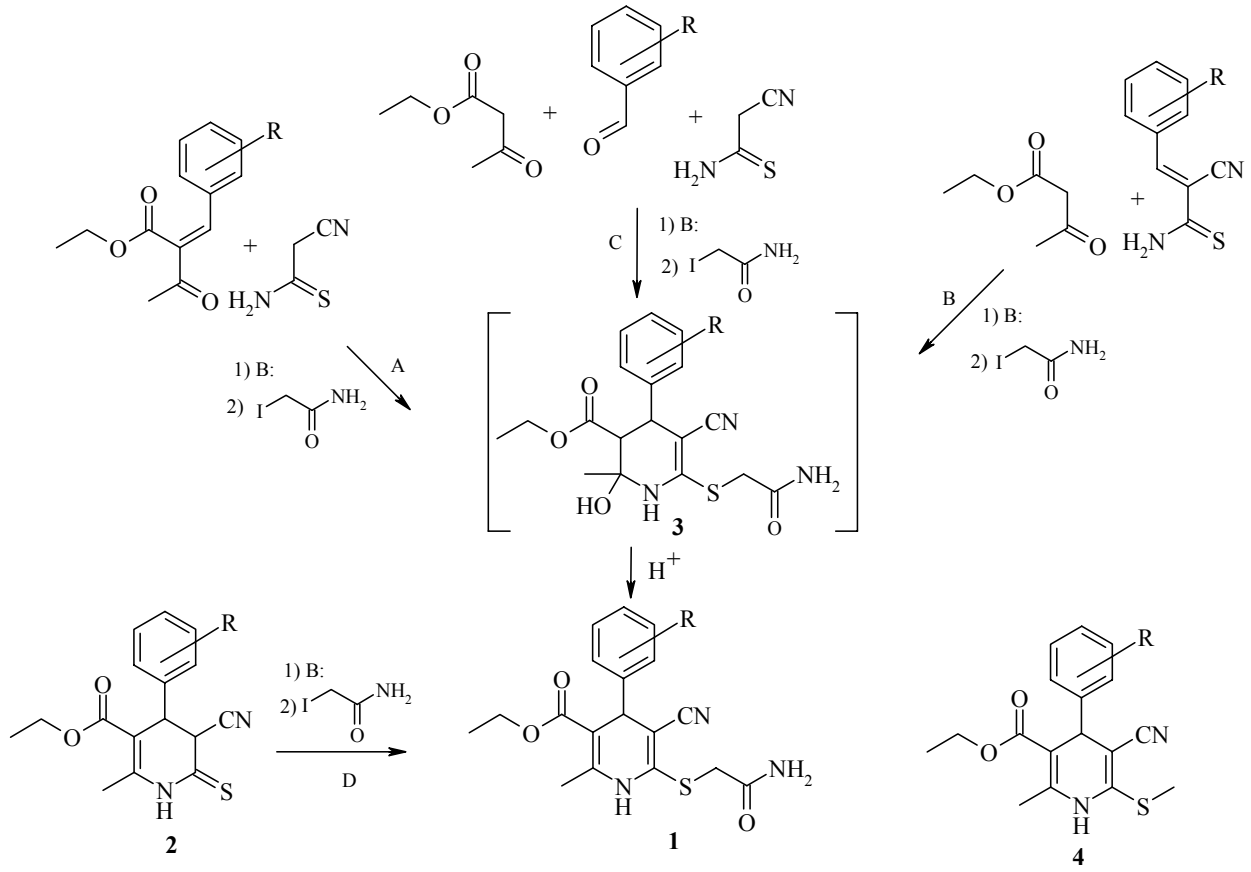
The structure of compounds **1** is proved spectroscopically. In the IR spectra, the most characteristic features are absorption bands for the stretching vibrations of the cyano groups at 2190-2200 cm^{-1} and the three bands for the C=O groups at 1686-1707 cm^{-1} (COOEt), 1670-1692 cm^{-1} ($CONH_2$), and 1632-1652 cm^{-1}. The latter band may be assigned to stretching vibrations of the C=O of the amide group, which takes part in hydrogen bond formation. In the ^1H NMR spectra, we observe signals from the H-4 protons at 4.42-5.12 ppm, confirming the 1,4-dihydropyridine structure of compounds **1**.

The characteristics of the synthesized compounds and the IR and ^1H NMR spectral data are shown in Tables 1 and 2.

During electrochemical oxidation of compounds **1a-j** in anhydrous acetonitrile on a stationary glassy carbon electrode, we recorded one oxidation peak in the potential range from 1.18 V to 1.29 V relative to the aqueous saturated calomel electrode. For compound **1a**, we also recorded electrochemical oxidation polarograms on a rotating disk electrode, and on a ring electrode we recorded the reduction waves for the oxidized products. We found that electrochemical oxidation occurs along previously established pathways [6]: on the disk electrode we recorded one oxidation wave with half-wave potential $E_{1/2}$ = 1.09 V, and on the ring electrode we recorded a reduction wave for the product (the protonated pyridine) at a potential $E_{1/2}$ = -1.12 V (relative to $Ag/AgNO_3$).

The electrochemical oxidation potentials of compounds **1a-j** are not very sensitive to a change in the electron-donor properties of the substituent on the phenyl ring, in the 4 position of the 1,4-dihydropyridine ring. Going from a clearly electron-donor substituent *para*-OCH_3 (compound **1c**) to a strong electron-acceptor *para*-NO_2 (compound **1h**) increases the electrochemical oxidation potential by only 60 mV (Table 3). The same

Scheme 1



a R = H, **b** R = 4-OH; **c** R = 4-OMe; **d** R = 2-OMe; **e** R = 4-Cl; **f** R = 3-Cl; **g** R = 2-Cl; **h** R = 4-NO_2; **i** R = 3-NO_2; **j** R = 4-CN; B: = piperidine

TABLE 1. Characteristics of Synthesized Compounds **1**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Method	Yield, %*
		C	H	N	S			
1a	$C_{18}H_{19}N_3O_3S$					194-196 [7]	A D	75 (60) 79 (50)
1b	$C_{18}H_{19}N_3O_4S\cdot 1/2\ H_2O$	56.31 / 56.53	5.27 / 5.27	10.92 / 10.98	8.49 / 8.38	202-204	B	94 (54)
1c	$C_{19}H_{21}N_3O_4S$					173-175 [4]	B	83 (60)
1d	$C_{19}H_{21}N_3O_4S$	58.88 / 58.90	5.42 / 5.46	10.81 / 10.84	8.25 / 8.28	203-205	B C	84 (60) 68 (68)
1e	$C_{18}H_{18}ClN_3O_3S$	54.81 / 55.17	4.66 / 4.63	10.58 / 10.72	8.07 / 8.18	193-195	A	72 (54)
1f	$C_{18}H_{18}ClN_3O_3S$	55.17 / 55.17	4.48 / 4.63	10.78 / 10.72	8.19 / 8.18	189-191	C	85 (85)
1g	$C_{18}H_{18}ClN_3O_3S$	55.21 / 55.17	4.52 / 4.63	10.75 / 10.72	8.19 / 8.18	193-195	A B C D	84 (60) 84 (62) 82 (82) 87(33)
1h	$C_{18}H_{18}N_4O_5S$	53.68 / 53.72	4.38 / 4.51	13.80 / 13.92	7.99 / 7.97	185-187	A	71 (47)
1i	$C_{18}H_{18}N_4O_5S$					184-186 [7]	D	84 (41)
1j	$C_{19}H_{18}N_4O_3S$					184-186 [8]	C D	73 (73) 73 (49)

* Calculated based on the aldehyde.

TABLE 2. Spectral Characteristics of Compounds **1**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)
1	2	3
1a	1642, 1676, 1700 (C=O); 2195 (C≡N); 3160, 3328 (NH, NH_2)	1.00 and 3.91 (5H, t and q, OC_2H_5); 2.24 (3H, s, CH_3-6); 3.55 and 3.68 (2H, d and d, *J* = 14.4, SCH_2); 4.47 (1H, s, H-4); 7.1-7.3 (5H, m, C_6H_5); 7.58 and 7.88 (2H, br. s and br. s, $CONH_2$); 10.40 (1H, s, NH)
1b	1637, 1670, 1686 (C=O), 2190 (C≡N), 3270, 3360, 3458 (NH, NH_2, OH)	1.10 and 3.97 (5H, t and q, OC_2H_5); 2.30 (3H, s, CH_3-6); 3.63 and 3.72 (2H, d and d, *J* = 14.4, SCH_2); 4.42 (1H, s, H-4); 6.72 and 6.98 (4H, d and d, C_6H_4), 7.62 and 7.92 (2H, br. s and br. s, $CONH_2$); 9.34 (1H, s, OH); 10.32 (1H, s, NH)
1c	1652, 1678, 1700 (C=O), 2200 (C≡N), 3214, 3362 (NH, NH_2)	1.10 and 3.92 (5H, t and q, OC_2H_5); 2.28 (3H, s, CH_3-6); 3.58 and 3.72 (2H, d and d, *J* = 14.6, SCH_2); 3.68 (3H, s, OCH_3); 4.54 (1H, s, H-4); 6.84 and 7.07 (4H, d and d, C_6H_4); 7.57 and 7.86 (2H, br. s and br. s, $CONH_2$); 10.32 (1H, s, NH)
1d	1645, 1675, 1690 (C=O), 2190 (C≡N), 3165, 3198, 3350 (NH, NH_2)	1.02 and 3.88 (5H, t and q, OC_2H_5); 2.33 (3H, s, CH_3-6); 3.58 and 3.70 (2H, d and d, *J* = 14.4, SCH_2); 3.76 (3H, s, OCH_3); 4.97 (1H, s, H-4); 6.8–7.3 (4H, m, C_6H_4); 7.60 and 7.88 (2H, br. s and br. s, $CONH_2$); 10.33 (1H, s, NH)
1e	1643, 1688, 1707 (C=O), 2198 (C≡N), 3160, 3338 (NH, NH_2)	1.08 and 3.97 (5H, t and q, OC_2H_5); 2.32 (2H, s, CH_3-6); 3.62 and 3.74 (2H, d and d, *J* = 14.4, SCH_2); 4.54 (1H, s, H-4); 7.72 and 7.38 (4H, d and d, C_6H_4); 7.58 and 7.87 (2H, s and s, $CONH_2$); 10.42 (1H, s, NH)

TABLE 2 (continued)

1	2	3
1f	1650, 1672, 1700 (C=O), 2190 (C≡N), 3180, 3350 (NH, NH_2)	1.08 and 3.96 (5H, t and q, OC_2H_5); 2.32 (2H, s, CH_3-6); 3.62 and 3.74 (2H, d and d, J = 14.4, SCH_2); 4.56 (1H, s, H-4); 7.05-7.45 (4H, m, C_6H_4); 7.60 and 7.90 (2H, s and s, $CONH_2$); 10.45 (1H, s, NH)
1g	1643, 1692, 1705 (C=O), 2196 sh, 2200 (C≡N), 3150, 3330 (NH, NH_2)	1.00 and 3.86 (5H, t and q, OC_2H_5); 2.34 (2H, s, CH_3-6); 3.60 and 3.72 (2H, d and d, J = 14.8, SCH_2); 5.12 (1H, s, H-4); 7.2-7.5 (4H, m, C_6H_4); 7.62 and 7.90 (2H, s and s, $CONH_2$); 10.44 (1H, s, NH)
1h	1647, 1680, 1707 (C=O), 2190 (C≡N) 3160, 3340 (NH, NH_2)	1.08 and 3.97 (5H, t and q, OC_2H_5); 2.36 (2H, s, CH_3-6); 3.56 and 3.78 (2H, d and d, J = 14.4, SCH_2); 4.74 (1H, s, H-4); 7.52 and 8.26 (4H, d and d, C_6H_4); 7.66 and 7.96 (2H, s and s, $CONH_2$); 10.58 (1H, s, NH)
1i	1632, 1671, 1686 (C=O); 2192 (C≡N); 3140, 3208, 3318, 3342 (NH, NH_2)	1.09 and 3.95 (5H, t and q, OC_2H_5); 2.31 (3H, s, CH_3-6); 3.75 and 3.64 (2H, d and d, J = 14.4, SCH_2); 4.70 (1H, s, H-4); 7.1-8.1 (4H, m, C_6H_4); 7.56 and 7.87 (2H, br. s and br. s, $CONH_2$); 10.42 (1H, s, NH)
1j	1646, 1683, 1704 (C=O); 2196, 2228 (C≡N); 3160, 3348 (NH, NH_2)	1.07 and 3.95 (5H, t and q, OC_2H_5); 2.35 (3H, s, CH_3-6); 3.64 and 3.74 (2H, d and d, J = 14.8, SCH_2); 4.64 (1H, s, H-4); 7.38 and 7.78 (4H, m, C_6H_4); 7.62 and 7.90 (2H, br. s and br. s, $CONH_2$); 10.49 (1H, s, NH)

TABLE 3. Values of the Oxidation Peak Potentials for Cyclic Potential Scanning on a Stationary Electrode (E_n) for Compounds **1a-j** in Acetonitrile in the Supporting Electrolyte 0.1 M $(C_4H_9)_4NPF_6$*

Compound	E_n, V	Compound	E_n, V
1a	1.26	**4a**	1.32
1b	1.23	**4b**	1.32
1c	1.22	**4c**	1.33
1d	1.18	**4d**	1.28
1e	1.28	**4e**	1.42
1f	1.27	**4f**	1.42
1g	1.28.	**4g**	1.36
1h	1.28	**4h**	1.44
1i	1.29	**4i**	1.42
1j	1.28	**4j**	1.42

* For comparison, we give the values of the electrochemical oxidation potentials for compounds **4a-j** [4].

replacement of substituents in 4-aryl-5-ethoxycarbonyl-2-methylthio-1,4-dihydropyridine-3-carboxylic acid nitriles **4** shifts the oxidation potential toward the positive region by 110 mV [4], in symmetric 4-aryl-3,5-di(ethoxyethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridines, by 120 mV [1], and in 4-aryl-3,5-di(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridines, by 240 mV [12]. The low sensitivity and the poor correlation of the electrochemical oxidation potentials with the Hammett's σ*-constants for compounds **1** indicate a role for new effects besides a purely electronic effect.

All the studied 2-carbamoylmethylthio-1,4-dihydropyridines **1a-j** have one common feature: they are more readily oxidized than the corresponding 2-methylthio-1,4-dihydropyridines **4a-j** [4,6]. For the 4-phenyl derivative **1a**, the difference in the potentials for the corresponding compounds of the two series is 60 mV, and

as the electron-donor or electron-acceptor properties of the substituent on the phenyl ring increase, the difference becomes as much as 160 mV (see Table 3 and [4]). This is not consistent with ideas about the effect of donor or acceptor properties of a substituent on the electrochemical oxidation potentials of the starting compounds, since the carbamoyl group in the 2 position of the 1,4-dihydropyridine ring has electron-acceptor properties and should hinder abstraction of the first electron in the electrochemical process. 2-Methylthio-1,4-dihydropyridines **4** [4] were studied in acetonitrile with camphor as an additive; in this work, there was no need for such an addition due to the low adsorbability of the substance on the electrode surface. We established that the values of the oxidation peak potentials in pure acetonitrile and in acetonitrile with camphor additive coincide for compounds **1a** and **1j**. Consequently, we should look elsewhere for the reasons for the anomaly found.

We carried out X-ray diffraction analysis for representatives of the series of compounds to be compared. Single crystals were grown for 2-carbamoylmethylthio-1,4-dihydropyridine **1e** and its analog 2-methylthio-1,4-dihydropyridine **4e**. Three-dimensional models of the compounds **1e** and **4e** are shown in Figs. 1 and 2; the bond lengths and bond angles in the molecules of both compounds as well as some parameters characterizing the conformation of these molecules are given in Table 4. X-ray diffraction analysis clearly shows that there is a hydrogen bond in the molecule of compound **1e**, in contrast to **4e**. By means of an intramolecular hydrogen bond N(1)–H(1)···O(10), in the molecule of compound **1e** a seven-membered ring is formed that is condensed with the dihydropyridine ring. The length of the hydrogen bond is 2.789(12) Å (H(1)···O(10) = 2.0(1) Å, the angle N(1)–H(1)···O(10) = 168(9)°), which corresponds to a hydrogen bond of average strength [13]. The dihydropyridine rings in the **1e** and **4e** molecules have a flattened *boat* conformation and in molecule **1e** the degree of flattening is higher, which probably is promoted by intramolecular hydrogen bond formation.

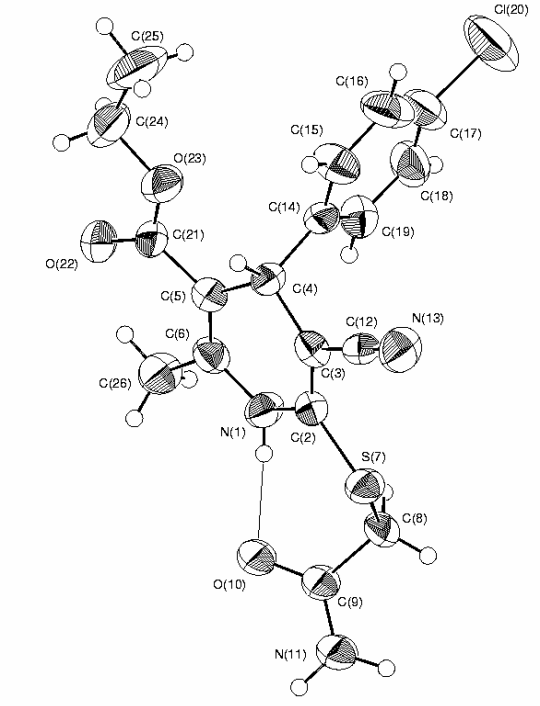


Fig. 1. Three-dimensional molecular model of compound **1e**, designating the atoms and showing their thermal vibration ellipsoids.

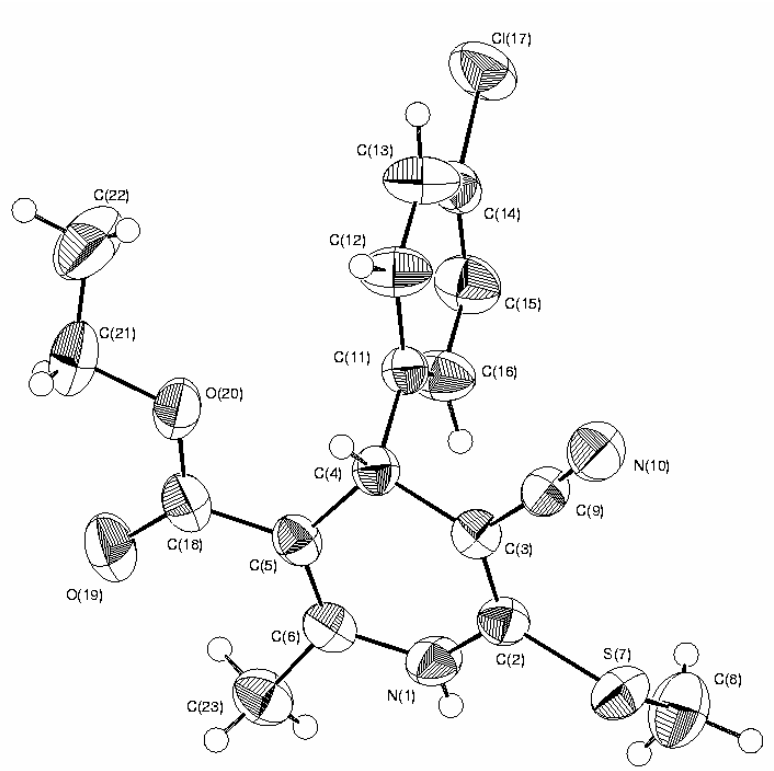


Fig. 2. Three-dimensional molecular model of compound **4e**, designating the atoms and showing their thermal vibration ellipsoids.

In the studied crystals of both compounds, there are also intermolecular hydrogen bonds (Table 6). In the structure of compound **1e**, the lengths of the intermolecular hydrogen bonds are close to the statistical average values for hydrogen bonds of the NH···O and NH···N type [14]. In the structure of **4e**, the hydrogen bond is forked, so the corresponding N···O and N···Cl distances are longer than the statistical average values [19]. Figs. 3 and 4 illustrate the packing of the molecules in crystals of **1e** and **4e**. In the crystal structure of **1e**, there is the disordered ethanol C_2H_5OH molecule (single crystals of **1e** were grown in an acetone–ethanol mixture, 1:1). For all the atoms of the ethanol molecule, the *g*-factors are equal to 0.5.

In the course of the X-ray diffraction studies of compound **1e**, we observed an intramolecular hydrogen bond between the proton on the nitrogen atom in the heterocycle and the oxygen atom of the carbamoyl group, while this was absent for compound **4e**, which probably explains the indicated effect of ease of electrochemical oxidation for compound **1e**. The lower bond multiplicity at the nitrogen atom in the 1 position and at the carbon atom in the 4 position of the heterocycle indicates a decrease in conjugation between the 1 position, where the electron density is concentrated, and the 4 position of the 1,4-dihydropyridine ring. N-Substituted 1,4-dihydropyridines are more readily oxidized electrochemically than N-unsubstituted derivatives. Thus the oxidation potential of 3,5-di(ethoxycarbonyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine is 90 mV higher than for its N–CH_3 derivative [15, 16]; the oxidation potential for 3,5-di(methoxycarbonyl)-4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine is 61 mV higher than for its N–CH_2CH_3 derivative [17]; and for 4-(4-nitrophenyl)-1,4-dihydropyridine, it is 57 mV higher than for the N–CH_2CH_3-substituted derivative [17]. On the other hand, the substituent on the nitrogen atom creates steric hindrances to free rotation of the substituents in the

TABLE 4 Bond Lengths (*l*) and Bond Angles (ω) of the Molecules of Compounds **1e** and **4e***

Bond	*l*, Å	
	1e	**4e**
N(1)–C(2)	1.382(9)	1.374(3)
N(1)–C(6)	1.388(9)	1.383(4)
C(2)–C(3)	1.355(10)	1.351(4)
C(3)–C(4)	1.528(10)	1.526(4)
C(4)–C(5)	1.518(10)	1.525(4)
C(5)–C(6)	1.345(10)	1.354(4)
C(2)–S(7)	1.752(7)	1.763(3)
Angle	ω, deg.	
C(2)–N(1)–C(6)	121.9(7)	123.2(3)
N(1)–C(2)–C(3)	120.0(7)	119.2(2)
N(1)–C(2)–S(7)	119.7(6)	119.2(2)
C(3)–C(2)–S(7)	120.1(6)	121.3(2)
C(2)–C(3)–C(4)	122.6(6)	122.0(2)
C(3)–C(4)–C(5)	109.7(6)	109.9(2)
C(4)–C(5)–C(6)	122.6(7)	121.1(2)
C(5)–C(6)–N(1)	120.6(7)	119.8(2)
C(2)–S(7)–C(8)	104.5(4)	102.4(2)
ΔN(1), Å	0.079(7)	0.114(3)
ΔC(4), Å	0.199(7)	0.274(3)
ΔS(7), Å	0.200(2)	0.3098(8)
φ_1, deg.	6.8(4)	10.1(2)
φ_2, deg.	13.2(3)	18.2(2)

* ΔN(1), ΔC(4), ΔS(7) are the deviations of the corresponding atoms from the C(2), C(3), C(5), C(6) plane; φ_1 is the dihedral angle between the C(2), N(1), C(6) and C(2), C(3), C(5), C(6) planes; φ_2 is the dihedral angle between the C(3), C(4), C(5) and C(2), C(3), C(5), C(6) planes.

TABLE 5. Crystallographic Data and Refinement Parameters of the Crystal Structures of **1e** and **4e**

Characteristic	**1e**	**4e**
1	2	3
Empirical formula	$[C_{18}H_{18}ClN_3O_3S]\cdot[C_2H_5OH]_{1/2}$	$C_{17}H_{17}ClN_2O_2S$
Color of crystals	Colorless	Yellow
Size of single crystal, mm	0.04 × 0.13 × 0.37	0.12 × 0.23 × 0.35
Crystal system	Triclinic	Monoclinic
Crystal lattice parameters, Å, degrees		
a	8.413(1)	13.1194(7)
b	10.403(2)	9.8636(7)
c	14.168(3)	13.4731(9)
α	68.482(7)	90
β	87.997(8)	104.225(3)
γ	68.23(1)	90
Unit cell volume *V*, Å^3	1063.9(3)	1690.0(2)
Space group	$P\,\bar{1}$	$P\,2_1/n$

TABLE 5 (continued)

1	2	3
Z	2	4
$F(000)$	434	728
Density, D_x, g/cm^3	1.295	1.371
μ, mm^{-1}	0.30	0.36
$2\theta_{max}$, °	50.0	55.0
Number of reflections		
measured	5537	6402
independent	3506	4136
used in least-squares method	1605 ($I > 2\sigma_I$)	2535 ($I > 3\sigma_I$)
Number of refined parameters	255	276
R-factor	0.089	0.052
wR_2	0.226	0.207
$\Delta\rho_{max}$, e/Å^3	0.32	0.41
$\Delta\rho_{min}$, e/Å^3	-0.25	-0.53

positions 2 and 6 and the for substituents in the 3 and 5 positions of the heterocycle. The hydrogen bond H···O=C(NH_2)– weakens the N–H bond, thus facilitating the process of deprotonation and abstraction of an electron. Consequently, the presence of a hydrogen bond at the nitrogen atom may be a factor promoting abstraction of an electron in compounds **1** with a thiomethylcarbamoyl group compared with compounds **4**, having a thiomethyl group in the 2 position of the 1,4-dihydropyridine ring.

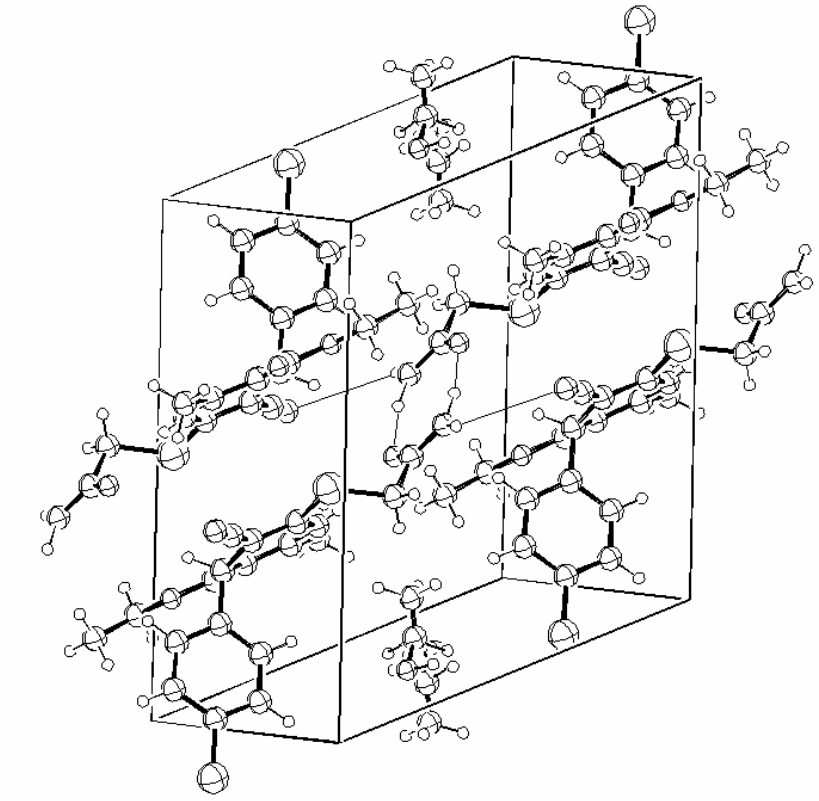


Fig. 3. Three-dimensional model of molecular packing in the unit cell of **1e** crystals.

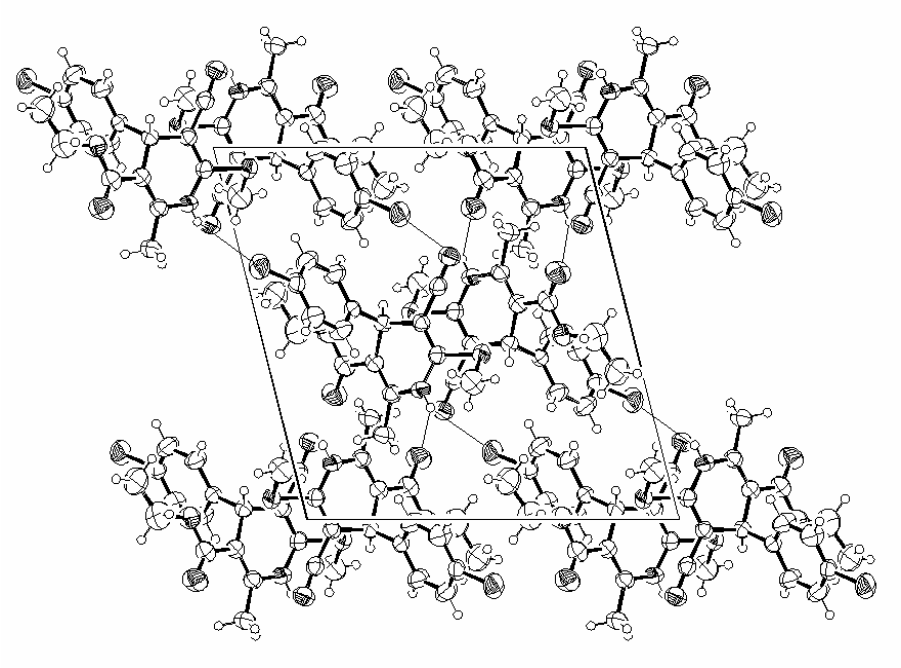


Fig. 4. Crystal structure of **4e** in the projection on the (010) crystallographic plane.

TABLE 6. Parameters of Intermolecular Hydrogen Bonds in the Crystal Structures of **1e** and **4e**

Com-pound	Bond D–H···A	Length of H-bond D···A, Å	Distance D···A, Å	Angle, D–H···A, deg.	Symmetry of A atoms
1e	N(11)–H(111)···O(10)	2.896(12)	1.84(7)	165(5)	$2 - x, -y, -z$
	N(11)–H(112)···N(13)	3.019(13)	2.05(8)	173(6)	$1 - x, 1 - y, -z$
4e	N(1)–H(1)···O(19)	3.060(4)	2.40(4)	142(3)	$3/2 - x, 1/2 + y, 3/2 - z$
	N(1)–H(1)···Cl(17)	3.715(3)	3.30(3)	116(2)	$1/2 + x, 1/2 + y, 3/2 + z$

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer 580B spectrometer in vaseline oil. The ^{1}H NMR spectra were recorded on a WH 90/DC (90 MHz) spectrometer in DMSO-d_6, internal standard HMDS (δ, 0.05 ppm). The course of the reaction and the purity of the substances were monitored using TLC on Silufol UV-254 plates; eluent, chloroform–hexane–acetone 2:1:1. The compounds were recrystallized from ethanol. The synthesis of compounds **1a** (method A and D) and **1i** (method D) is described in [7]; the synthesis of **1c** (method B) is described in [4], and the synthesis of **1j** (method D) is described in [8]. The starting 2-arylideneacetoacetic acid ethyl esters were synthesized according to the organic chemistry laboratory manual [18], while the 3-aryl-2-cyanothioacrylamides were synthesized as in [10]. Product yields: 2-benzylideneacetoacetic acid ethyl ester,

80%; 2-(4-chlorobenzylidene)acetoacetic acid ethyl ester, 75%; 2-(2-chlorobenzylidene)acetoacetic acid ester, 72%; 2-(4-nitrobenzylidene)acetoacetic acid ester, 66%; 2-(3-nitrobenzylidene)acetoacetic acid ethyl ester, 80%; 2-cyano-3-(4-hydroxyphenyl)thioacrylamide, 57%; 2-cyano-3-(4-methoxyphenyl)thioacrylamide, 81%; 2-cyano-3-(2-methoxyphenyl)thioacrylamide, 72%; and 3-(2-chlorophenyl)-2-cyanothioacrylamide, 76%.

The cyclic voltammetric curves were recorded with a PAR-170 electrochemical system, using a three-electrode cell on a stationary glassy carbon electrode. The reference electrode was an aqueous saturated calomel electrode fitted with a bridge junction for working in nonaqueous solvents. Electrochemical studies using the rotating ring-disk electrode method with a ring were conducted on an apparatus consisting of a Ring–Disk-Electrode System Model 636 (PAR) electrode rotation system and a Bruker E-350 dual potentiostat. The disk and ring electrodes were made from glassy carbon. The calculated electrode efficiency coefficient was 0.39 [19], the electrode rotation speed was 2000 min^{-1}. All the potentials were measured relative to a 0.1 N silver reference electrode ($Ag/AgNO_3$). All the studies were conducted in anhydrous acetonitrile purified by the procedure in [20]. The depolarizer concentration was $5 \cdot 10^{-4}$ $mol \cdot l^{-1}$. The supporting electrolyte was $1 \cdot 10^{-1}$ $mol \cdot l^{-1}$ tetrabutylammonium hexafluorophosphate.

For the X-ray diffraction analysis, single crystals of compound **1e** were grown in a mixture of solvents, acetone–ethanol (1:1), and single crystals of compound **4e** were grown in chloroform. The crystal structure of compounds **1e** and **4e** were determined using a Nonius KappaCCD automatic diffractometer (the data collection were taken at room temperature, molybdenum radiation with $\lambda = 0.71073$ Å, graphite monochromator, φ and ω scanning). The structures were solved by the procedure in [21] and refined by the full-matrix least-squares method using the program in [22] (for **1e**) and [23] (for **4e**). The main crystallographic characteristics for **1e** and **4e** are given in Table 5.

General Methods for Synthesis of 4-Aryl-2-carbamoylmethylthio-5-ethoxycarbonyl-6-methyl-1,4-dihydropyridine-3-carboxylic Acid Nitriles (1). A. A mixture of 2-arylideneacetoacetic acid ethyl ester (5 mmol), 2-cyanothioacetamide (5 mmol) in ethanol (15-20 ml), and piperidine (6 mmol) was heated briefly until dissolved, and then after 10 min iodoacetamide (5.5 mmol) was added. The mixture was boiled for 1-2 min on a water bath and then 3 M HCl in ethanol (2 ml) was added. The precipitate formed was filtered out and then washed with ethanol (5-10 ml) (cooled down to 0°C) and water (10 ml). Compounds **1a,e,g,h** were obtained.

B. A mixture of acetoacetic acid ethyl ester (5 mmol), 3-aryl-2-cyanothioacrylamide (5 mmol) in ethanol (15-20 ml), and piperidine (6 mmol) was heated briefly until dissolved, and then after 10 min iodoacetamide (5.5 mmol) was added. The mixture was boiled for 5 min on a water bath and 3 M HCl in ethanol (2 ml) was added. The precipitate formed was filtered out and then washed with ethanol (cooled down to 0°C) (5-10 ml) and water (10 ml). Compounds **1b-d,g** were obtained.

C. A mixture of an aromatic aldehyde (5 mmol), 2-cyanothioacetamide (5 mmol) in ethanol (15-20 ml), and piperidine (1 mmol) was heated briefly until dissolved. Then, while the reaction mixture was stirred at room temperature, acetoacetic acid ethyl ester (5 mmol) and piperidine (5 mmol), and (after 10 min) iodoacetamide (5.5 mmol) were added. The mixture was boiled for 5 minutes on a water bath, and then 3 M HCl in ethanol (2 ml) was added. The precipitate formed was filtered out and then washed with ethanol (cooled down to 0°C) (5-10 ml) and water (10 ml). Compounds **1d,f,g** were obtained.

D. A mixture of 2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxylic acid nitrile **2** (10 mmol), piperidine (11 mmol), and iodoacetamide (11 mmol) in ethanol (20-40 ml) was boiled for 2-5 min on a water bath and stirred for 5-10 min at room temperature. The precipitate formed was filtered out and then washed with ethanol (cooled down to 0°C) (5-10 ml) and water (10 ml). Compounds **1a,g,i,j** were obtained.

The characteristics of the synthesized compounds are given in Tables 1 and 2.

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