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SYNTHESIS AND ELECTROCHEMICAL OXIDATION OF NITRILES OF 4-ARYL-2-CARBAMOYLMETHYLTHIO-5-ETHOXY-CARBONYL-1,4-DIHYDROPYRIDINE-3-CARBOXYLIC ACIDS

L. Baumane, A. Krauze, L. Chernova, L. Sile, G. Duburs, and J. Stradins

Nitriles of 4-aryl-2-carbamoylmethylthio-5-ethoxycarbonyl-6-hydroxy-1,4,5,6-tetrahydropyridine-3-carboxylic acids were obtained by the alkylation of 1,4,5,6-tetrahydropyridine-2-thiolate with iodoacetamide or by a three-component synthesis by condensing 2-arylmethylene-1,3-dicarbonyl compounds with 2-cyanothioacetamide in the presence of piperidine with subsequent reaction with iodoacetamide. Nitriles of 4-aryl-2-carbamoylmethylthio-5-ethoxycarbonyl-1,4-dihydropyridine-3-carboxylic acids were obtained by the dehydration of 6-hydroxy-1,4,5,6-tetrahydropyridines or with a one-reactor three-component system from 2-cyano-3-(4-methoxyphenyl)thioacrylamide, 1,3-dicarbonyl compounds, and iodoacetamide. The electrochemical oxidation of the synthesized nitriles was investigated and it was established that derivatives of 1,4,5,6-tetrahydropyridine as a rule are oxidized readily to the corresponding 1,4-dihydropyridines. A comparative analysis has been carried out of the ability of hydrogenated pyridines to be oxidized electrochemically depending on the electron-withdrawing properties of the substituents in the heterocycle.

Keywords: 6-hydroxy-1,4,5,6-tetrahydropyridines, 1,4-dihydropyridines, one-reactor three-component synthesis, electrochemical oxidation.

Many of the esters of 4-substituted 1,4-dihydropyridine-3,5-dicarboxylic acids possess a cardiovascular action [1], consequently their antioxidant and antiradical activity have been investigated [2], as also the interconnection of these forms of activity with cardiovascular properties [3, 4]. Unsymmetrical 2-alkylthio-1,4-dihydropyridines have been studied less, however marked cardiovascular [5], hepato-protecting [6], antioxidant [7], and antiradical [8] activity have also appeared among them.

In continuation of investigations on the synthesis and properties of 2-alkylthio-1,4-dihydropyridines [9,10] and condensed heterocycles based on them [11], we have synthesized a series of new nitriles of 4-aryl-2-carbamoylmethylthio-5-ethoxycarbonyl-6-methyl(phenyl or *p*-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acids (see Scheme) and have investigated their electrochemical oxidation. Data on electro-chemical oxidation are important as a quantitative characteristic of the ability of compounds to be oxidized, which enables a more purpose-directed search for biologically active substances to be carried out.

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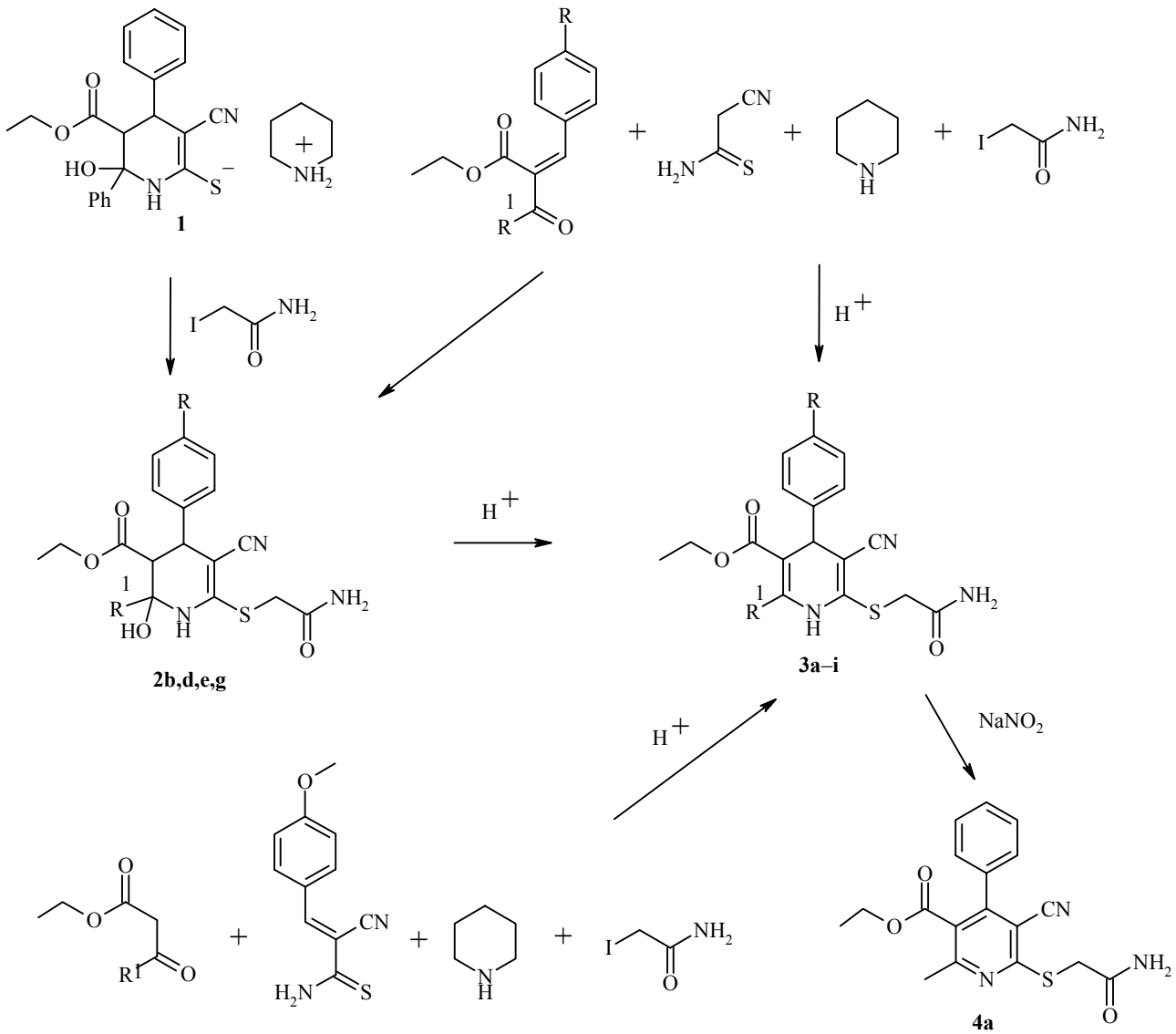

a,d,g R = H, **b,e,h** R = NO_2, **c,f,i** R = OMe; **a–c** R^1 = Me, **d–f** R^1 = Ph, **g–i** R^1 = *p*-$O_2NC_6H_4$

2-Carbamoylmethylthio-5-ethoxycarbonyl-6-hydroxy-4,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylic acid nitrile (**2d**) was obtained in 87% yield by the alkylation of 1,4,5,6-tetrahydropyridine-2-thiolate **1** with iodoacetamide.

6-Hydroxytetrahydropyrimidines **1** and **2** are unstable compounds on the whole, having a tendency to eliminate a molecule of water [12]. For this reason in certain cases it was not possible to isolate compound **1** from the reaction mixture. The nitriles of 1,4,5,6-tetrahydropyrimidine-3-carboxylic acids **2b** and **2e** were obtained with the aid of a one-reactor three-component synthesis. The advantage of this method is that the unstable intermediates of the reaction of **1** are not isolated. Compound **2b** was obtained only in this way. The low yield is explained by the fact that pure 6-hydroxytetrahydropyridine **2b** was obtained after fractional crystallization of the resulting mixture of **2b** with dihydropyridine **3b.**

The nitriles of 4-aryl-2-carbamoylmethylthio-5-ethoxycarbonyl-1,4-dihydropyridine-3-carboxylic acid **3** were obtained by three methods: A) by the dehydration of tetrahydropyridines **2** (compounds **3d,e**) or by a one-reactor three-component synthesis; B) by the condensation of 2-arylmethylene-1,3-dicarbonyl compounds with

2-cyanothioacetamide in the presence of piperidine with subsequent reaction with iodoacetamide and acidification of the reaction mixture under mild conditions (1,4-dihydropyridines **3b** and **3d** in yields of 77 and 69%); C) by the condensation of 2-cyano-3-(4-methoxyphenyl)thioacrylamide with 1,3-dicarbonyl compounds in the presence of piperidine, with subsequent reaction with iodoacetamide and acidification of the reaction mixture under mild conditions (1,4-dihydropyridines **3c** and **3f** in yields of 83 and 70%), which is a new convenient method for obtaining nitriles of 2-carbamoylmethylthio-1,4-dihydropyridine-3-carboxylic acid **3**.

The structures of compounds **2** and **3** were demonstrated spectroscopically. In the IR spectra of **2** and **3** the absorption bands of the stretching vibrations of the cyano groups at 2182-2212 cm^{-1} and the absorption bands of the stretching vibrations of the carbonyl group were the most characteristic. In the ^1H NMR spectra of compounds **2** the most characteristic signals were those of the 4- and 5-H protons as doublets with coupling constants 12-13 Hz, which indicates the *trans*-diaxial disposition of these protons. Consequently the bulky 4-aryl and 5-ethoxycarbonyl substituents are orientated *trans*-equatorially. In the ^1H NMR spectra of compounds **3** the most characteristic were the signals of 4-H at 4.48-4.74 ppm and the signals of the S-CH_2 groups as an AB quartet with $J \sim 15$ Hz, which shows the nonequivalence of the CH_2 protons due to the presence in the molecule of the asymmetric center at 4-C.

The electrochemical oxidation of compounds **2** and **3** was carried out in anhydrous acetonitrile at a rotating disk electrode with a ring and stationary glass-graphite electrode. When oxidizing the derivatives of 1,4-dihydropyridine **3a-i** and of 1,4,5,6-tetrahydropyridine **2b,d,e,g** at the rotating disc electrode one or two polarographic waves were observed. Waves for the electrochemical reduction of the oxidized products were recorded at the ring electrode. The potentials of the oxidation peaks of compounds were determined by cyclic voltammetry at the stationary electrode and the reversibility of the oxidation–reduction reactions was checked. It was established that all the compounds are oxidized irreversibly at room temperature. The results of the investigations are given in Table 1.

By analogy with the data obtained by various authors [13-17] when studying the mechanism of oxidation of 1,4-dihydropyridine derivatives, we propose that compounds **3a-i** are oxidized to the corresponding pyridines with separation of two electrons and two protons by a ECEC scheme. The values of the reduction potentials at the ring electrode of the products formed at the disc electrode indicate this, particularly the wave in the potential range -1.7 to -2.4 V, corresponding to the reduction of pyridine, and the wave in the potential range from -0.8 to -1.1 V which belongs to the reduction of the protonated form of pyridine. The oxidized form **4a** of 1,4-dihydropyridine **3a** was synthesized and an electrochemical reduction of it was carried out at the rotating ring electrode. The half-wave potential $E_{1/2}$ = -2.36 V coincides with the reduction potential of one of the products of the electrooxidation of compound **3a**. The wave at potential ~1 V shows the presence of the protonated form of the pyridine, the possibility of forming which for N-unsubstituted 1,4-dihydro-pyridines has been studied in more detail in [16].

For compounds **3d-i** containing a phenyl or *p*-nitrophenyl substituent at position 6 of the 1,4-dihydropyridine ring, a second oxidation wave was recorded at the disc electrode more or less clearly displayed. At the potentials of this wave in the case of compound **3g** a product was formed capable of being reduced electro-chemically at a more positive potential than the reduction potential of the corresponding protonated pyridine (see Table 1). The nature of the product is still not clear. Possibly this indicates a further oxidation process affecting the sulfur atom and heterocyclization with the formation of 4,7-dihydrothieno-[2,3-*b*]pyridine [18] or further oxidation of some other product.

For 1,4,5,6-tetrahydropyridine derivatives **2b,d,e** two electrooxidation waves were also recorded at the disk electrode. The values of the potentials of the first wave for compounds **2b,d,e** were greater than for the corresponding 1,4-dihydropyridines. Compound **2g** is oxidized in acetonitrile with the formation of one extremely sloping polarographic wave, the half-wave potential (1.25 V) is displaced into the positive region compared with the potential of the corresponding 1,4-dihydropyridine (Table 1). However, if the surface active substance camphor (up to 0.1%) is added to the solution, then the wave is split and it is possible to determine approximately two values for the half-wave potentials, *viz*. 1.0 and 1.4 V. For comparison we recorded the

TABLE 1. Values of Potentials for Compounds **3** and **2** in Acetonitrile on a Base of 0.1 M $(C_4H_9)_4PF_6$*

Com-pound	$E_{1/2}$, V*[2]	n	E, V	$-E_{1/2}$, V	E_p, V*[2]
3a	1.04	1.6	1.3-1.9	1.12, 2.36	1.26
4a			0	2.36	
3b	1.09	1.4	1.1-1.8	1.11, 1.98	1.28
3c	0.88	1.6	1.1-1.9	0.82, 1.73	1.22
3d	1.03 1.46	Σ1.4	1.5-1.9	0.41, 2.04	1.32
3e	1.04	1.2	1.3	0.77, 1.89	1.37
3e	0.94 1.64	1.8 1.2	1.3-1.9	0.86, 2.27	1.32
3f	0.95 1.51	0.7 1.3	1.3 1.8	0.99 0.53	1.36
3g	*0.93* *1.50*				*1.34*
3h	1.19	1.2	1.2-1.9	0.78	1.45
3i	1.04 1.68	1.2 2.0	1.2-1.9	0.71	1.42
2b	0.85 1.50	1.0 1.1	1.2 1.9	1.12 0.76	1.10 1.80
2d	0.97 ~1.8	1.0 ?	1.2 2.0	0.89, 1.9 0.69	1.34 1.78
2e	0.95 1.38	1.0 1.2	1.2-1.9	0.96	1.33
2g	1.25 *1.03* *1.40*	1.4	1.2 1.7 *1.2* *1.7*	1.15, 1.72 0.69 *1.19, 1.72* *0.77*	1.10 1.38 *1.36*

* $E_{1/2}$ is the half-wave potentials for electrochemical oxidation, where n is the number of electrons transferred at the rotating disk electrode; $-E_{1/2}$ is the half-wave potential for the electrochemical reduction at the rotating ring electrode of the products formed at potential E at the disk electrode; E_p is the potential of oxidation peaks on cyclic scanning (0.1 V/sec) at the stationary electrode. For compounds **3g** and **2g** values given in italics were obtained with the addition of 0.1% camphor to the solution being investigated.

*[2] The numerical values of potentials $E_{1/2}$ and E_p differ due to the use of different reference electrodes.

electrochemical characteristics of dihydropyridine **3g** under the same conditions. In all cases tetrahydropyridine **2g** is oxidized with more difficulty than dihydropyridine **3g**. The first polarographic waves of compounds **2b,d,e** correspond in height to the transfer of one electron, however in the cyclic voltammetric curves at a potential scanning rate up to 1 V/sec no reversibility of the electrochemical process was observed in any case.

At constant potential E at the disk electrode, corresponding to the potential for the limiting current of each of the polarographic waves, products were detected for compound **2** capable of being reduced electrochemically. As in the case of the corresponding 1,4-dihydropyridines a product is formed at the first stage of electrooxidation which is reduced at a potential of ~1 V, and in the second a product that is reduced more readily (Table 1). In addition to the oxidation products proposed for compound **3g** tetrahydropyridines may, as a result of dehydration, form either 1,4- or 3,4-dihydropyridine structures [12]. In the present work new data are

presented on the electrochemical oxidation of tetrahydropyridines **2** for which conjugation between the COOEt group in position 5 and the N atom of the heterocycle is impossible. Such a system may be converted by elimination of water into a dihydropyridine **3** (tetrahydropyridine **2b** is oxidized more readily than the corresponding 1,4-dihydropyridine **3b** and at the first stage products are formed which are reduced at the same potential). Compounds **2d** and **2e** are also oxidized more readily than their dihydro analogs, however the corresponding pyridine analogs were not recorded at the ring electrode. In the case of tetrahydropyridine **2g** oxidation proceeds with more difficulty than for dihydropyridine **3g** and reduction of the protonated pyridine was also not detected. From the data given it is impossible to establish a route for the oxidation of tetrahydropyridines **2**. They are mainly oxidized more readily than dihydropyridines **3**. For a detailed study of the mechanism of reduction of tetrahydropyridine derivatives it is necessary to use subjects which are not clogged with various electroreactive substituents, to synthesize additional model compounds, and to apply more contemporary methods of investigation, such as electrochemical oxidation with simultaneous detection and identification of the resulting intermediate products by chromato-mass spectrometry (CMS). In our case the waves of the electroreduction of the nitro groups of the initial compounds and the series of possible conversions of the substituents in positions 2 and 3 of the heterocycle significantly hinder the polarographic study of the mechanism of electrooxidation.

The effect of the donor–acceptor properties of substituents in positions 4 and 6 has been studied on the ease of electrochemical oxidation of 1,4-dihydropyridine derivatives **3a-i**. When comparing the numerical values of the electrooxidation potentials the values of E_p obtained from cyclic voltammetric curves were used, since in certain cases it is difficult to determine on the polarograms the precise values of the half-wave potentials due to their merging into one slanting wave or there is no clear plateau of limiting current.

If R^1 = Me (compounds **3a-c**) or R^1 = Ph (compounds **3d-i**), the detachment of the first electron is hindered by an increase in the electron-withdrawing properties of the substituent R. If a strong electron-withdrawing group is introduced into position 6 (compounds **3g-i**) then the ability of compounds to be oxidized electrochemically falls in the series **3g** < **3i** < **3h** and does not comply with the Hammett equation LSE (values of $E_{1/2}$ change in the same sequence). On the other hand, if compounds with unchanged substituent R in position 4 of the heterocycle are compared then in all cases the electrochemical oxidation potential is displaced towards the region of more positive values with the growth in electron-withdrawing properties of the substituent R^1, which is in agreement with the LSE principle. On comparing the results with the data of [13] we established that replacement of a methyl group by an alkylthio group in position 2 and an ethoxycarbonyl group by a cyano group in position 3 of the heterocycle hinders detachment of the first electron for compound **3c** by 220, for compound **3a** by 120, and for compound **3b** by only 20 mV. If the electrooxidation potentials of certain symmetrical 4-aryl- and 4-(*p*-nitrophenyl)-2,6-dimethyl-3,5-X-1,4-dihydropyridines [14] are compared with the electrooxidation potentials of compounds **3a** and **3b** then these compounds may be arranged in series according to electro-oxidation potential (ΔE, V is the difference in the numerical values of the electro-oxidation potentials).

for R = H	X =	$COCH_3$ <	$COOC_2H_5$ <	$COOCH_3$ <	**3a** <	CN
	ΔE =	0.20	0.12	0.08	0	-0.12
for R = NO_2	X =	$COCH_3$ <	$COOC_2H_5$ <	$COOCH_3$ <	**3b** <	CN
	ΔE =	0.12	0.02	0.01	0	-0.16

The introduction of a strong electron-withdrawing group (R = NO_2) into the substituent at position 4 of the heterocycle narrows the gap of oxidation potentials ΔE of the compounds being compared from 320 to 280 mV. In its series compound **3b** becomes more susceptible towards electrooxidation than compound **3a** in its series.

TABLE 2. Characteristics of the Synthesized Compounds **2** and **3**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, % (method)
		C	H	N	S		
2b	$C_{18}H_{20}N_4O_6S$	51.32 / 51.42	4.68 / 4.79	13.16 / 13.33	7.56 / 7.63	152-153	11
2d	$C_{23}H_{23}N_3O_4S$	62.91 / 63.14	5.21 / 5.30	9.72 / 9.60	7.45 / 7.33	148-150	87
2e	$C_{23}H_{22}N_4O_6S$	57.13 / 57.27	4.47 / 4.59	11.51 / 11.61	6.56 / 6.65	203-205	31
3b	$C_{18}H_{18}N_4O_5S$	53.52 / 53.72	4.29 / 4.51	13.80 / 13.92	7.99 / 7.97	185-187	77 (B)
3c	$C_{19}H_{21}N_3O_4S$	58.56 / 58.90	5.36 / 5.46	10.69 / 10.84	8.36 / 8.28	173-175	83 (C)
3d	$C_{23}H_{21}N_3O_3S$	65.49 / 65.85	4.81 / 5.05	10.11 / 10.02	7.75 / 7.64	223-226	72 (A) 69 (B)
3e	$C_{23}H_{20}N_4O_5S$	59.10 / 59.47	4.21 / 4.34	12.05 / 12.06	6.86 / 6.90	198-200	75 (A)
3f	$C_{24}H_{23}N_3O_4S$	64.11 / 64.13	5.15 / 5.16	9.38 / 9.35	7.14 / 7.13	205-207	70 (C)

On comparing values of electrochemical oxidation potentials of the corresponding di- and tetrahydropyridines it is evident that tetrahydropyridine **2b**, containing an electron-donating, low-volume methyl substituent in position 6 of the heterocycle, is oxidized 240 mV more readily than the corresponding dihydropyridine **3b**. However, if the methyl group in position 6 is replaced by a bulky phenyl substituent then the electron-withdrawing nitro group in position 4 hinders the electrooxidation of the dihydropyridine by 50 mV (E_p, compounds **3d**, **3e**) and the opposite is observed for tetrahydropyridine derivatives. The nitrophenyl derivative **2e** is oxidized 10 mV more readily than the phenyl derivative **2d**. If compounds **3b,d,g** and **2b,d,g** are compared then it is evident that replacement of the methyl group in position 6 of the heterocycle by phenyl and then by nitrophenyl gradually hinders electrooxidation in the compound **3** series, however in the compound **2** series transfer from a methyl to a phenyl substituent introduces the the main contribution.

The results given indicate that according to the values of both $E_{1/2}$ and E_p the tetrahydropyridines **2** are oxidized more readily than the corresponding dihydropyridines **3** (except for **2g** the oxidation peak of which at E_p = 1.1 V is not caused by the oxidation of the starting material). The tetrahydropyridine has one electron-withdrawing substituent, the cyano group, in the conjugated system, while the conjugated system of the dihydropyridine contains a second electron-withdrawing substituent, the ethoxycarbonyl group. This confirms the hypothesis that electron-withdrawing substituents in the conjugated system of hydrogenated pyridines hinder detachment of an electron and the process of electrochemical oxidation. The information given above on the noncorrespondance of the values of the electro-oxidation potentials with the LSE principle indicates only that the susceptibility of compounds of type **2** and **3** towards electrochemical oxidation is determined not only by donor–acceptor properties but also by additional effects such as steric hindrance to the access of the molecule to the electrode. The mechanism of electrochemical oxidation of tetrahydropyridines requires further study. It should be noted that the instability of the compounds hindered the work. They were fairly readily dehydrogenated in the air being converted into dihydropyridines.

EXPERIMENTAL

The electrochemical investigations by the rotating disk electrode with a ring electrode were carried out in equipment consisting of a PAR Ring–Disk–Electrode System Model 636 (USA) and a Bruker E 350 double potentiostat. The disk and ring electrodes were prepared from glass-graphite. The efficiency coefficient of the

TABLE 3. Spectral Characteristics of Compounds **2** and **3**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
2b	1690 (C=O); 2182 (C≡N); 3180, 3350 (NH, NH_2)	0.98 and 3.90 (5H, t and q, *J* = 7, OC_2H_5); 1.52 (3H, s, 6-CH_3); 2.82 and 4.12 (2H, d and d, *J* ~ 13, 5-H and 4-H); 3.62 (2H, s, SCH_2); 6.04 (1H, s, OH); 7.60 and 8.20 (4H, d and d, *J* = 7, C_6H_4); 7.58 and 7.88 (2H, s an s, NH_2); 8.88 (1H, s, NH)
2d	1673, 1731 (C=O); 2196 (C≡N); 3190, 3342, 3500 (NH, NH_2, OH)	0.48 and 3.42 (5H, t and q, *J* = 7, OC_2H_5); 2.90 and 4.10 (2H, d and d, *J* ~ 12, 5-H and 4-H); 3.60 (2H, s, SCH_2); 6.40 (1H, s, OH); 7.1-7.9 (12H, complection, 2 C_6H_5 and NH_2); 9.14 (1H, s, NH)
2e	1674, 1730 (C=O); 2192 (C≡N); 3186, 3346 (NH, NH_2)	0.48 and 3.47 (5H, t and q, *J* = 7, OC_2H_5); 3.06 and 4.30 (2H, d and d, *J* ~ 13, 5-H and 4-H); 3.62 (2H, s, SCH_2); 6.54 (1H, s, OH); 7.4-8.2 (11H, complection, C_6H_5, C_6H_4 and NH_2); 9.34 (1H, s, NH)
3b	1647, 1680, 1707 (C=O); 2190 (C≡N); 3160, 3342 (NH, NH_2)	1.08 and 3.97 (5H, t and q, *J* = 7, OC_2H_5); 2.36 (3H, s, 6-CH_3); 3.56 and 3.78 (2H, d and d, *J* ~ 15, SCH_2); 4.74 (1H, s, 4-H); 7.52 and 8.26 (4H, d and d, C_6H_4); 7.66 and 7.96 (2H, br. s and br. s, NH_2); 10.58 (1H, s, NH)
3c	1651, 1678, 1700 (C=O); 2200 (C≡N); 3214, 3362 (NH, NH_2)	1.10 and 3.92 (5H, t and q, *J* = 7, OC_2H_5); 2.28 (3H, s, 6-CH_3); 3.58 and 3.72 (2H, d and d, *J* ~ 15, SCH_2); 3.68 (3H, s, OCH_3); 4.54 (1H, s, 4-H); 6.84 and 7.07 (4H, and dd, C_6H_4); 7.57 and 7.86 (2H, br. s and br. s, NH_2); 10.32 (1H, s, NH)
3d	1673, 1710 (C=O); 2194, 2204 (C≡N); 3170, 3340, 3414 (NH, NH_2)	0.70 and 3.70 (5H, t and q, *J* = 7, OC_2H_5); 3.64 and 3.88 (2H, d and d, *J* ~ 15, SCH_2); 4.56 (1H, s, 4-H); 7.2-7.5 (10H, complection, 2 C_6H_5); 7.58 and 7.90 (2H, s and s, NH_2); 10.74 (1H, s, NH)
3e	1666, 1694 (C=O); 2198, 2204 (C≡N); 3200, 3370 (NH, NH_2)	0.70 and 3.72 (5H, t and q, *J* = 7, OC_2H_5); 3.70 and 3.94 (2H, d and d, *J* ~ 15, SCH_2); 4.70 (1H, s, 4-H); 7.48 (5H, m, C_6H_5); 7.60 and 7.97 (2H, s and s, NH_2); 7.64 and 8.80 (4H, d and d, *J* = 7, C_6H_4); 10.96 (1H, s, NH)
3f	1667, 1688 (C=O); 2205, 2212 (C≡N); 3205, 3380 (NH, NH_2)	0.70 and 3.92 (5H, t and q, *J* = 7, OC_2H_5); 3.64 and 3.82 (2H, d and d, *J* ~ 15, SCH_2); 3.70 (3H, s, OCH_3); 4.48 (1H, s, 4-H); 6.90 and 7.18 (4H, dd and dd, *J* = 8, C_6H_4); 7.40 (5H, m, C_6H_5); 7.53 and 7.88 (2H, br. s and br. s, NH_2); 10.70 (1H, s, NH)

electrodes of 0.39 was calculated by the procedure of [19], and the rotation rate of the electrodes was 2000 min^{-1}. All potentials were measured relative to a 0.1 N silver reference electrode ($Ag/AgNO_3$). Cyclic volt-ampere curves were recorded with the aid of a PAR 170 (USA) electrochemical system using a three-electrode cell and a stationary glass-graphite electrode. The reference electrode was a saturated aqueous calomel electrode fitted with a connecting bridge for working in nonaqueous solvents. All investigations were carried out in anhydrous acetonitrile purified by the method of [20]. The depolarizer concentration was $5 \cdot 10^{-4}$ M , base electrolyte was tetrabutylammonium hexafluorophosphate ($1 \cdot 10^{-1}$ M).

The IR spectra of the starting materials were taken on a Perkin–Elmer 580B spectrometer in Nujol. The ^1H NMR spectra were recorded on a WH 90/DC (90 Hz) spectrometer in DMSO-d_6, internal standard was TMS. A check on the course of reactions and the homogeneity of substances was effected by TLC on Silufol UV 254 plates, eluent was chloroform–hexane–acetone, 2:1:1. Compounds were recrystallized from ethanol. The synthesis of compounds **2g** and **3g-i** has been described in [10], and of **3a** and **4a** in [11].

The physicochemical and spectral characteristics of compounds **2** and **3** are given in Tables 2 and 3.

2-Carbamoylmethylthio-5-ethoxycarbonyl-6-hydroxy-6-methyl-4-(4-nitrophenyl)-1,4,5,6-tetrahydropyridine-3-carboxylic Acid Nitrile (2b). 2-(4-Nitrophenylmethylene)acetoacetic acid ethyl ester (1.32 g, 5 mmol) and 2-cyanothioacetamide (0.5 g, 5 mmol) were dissolved in ethanol (20 ml) by heating, then the solution was cooled to 30-40°C, and piperidine (0.6 ml, 0.5 mmol) was added. After 15 min stirring at room temperature iodoacetamide (1.11 g, 6 mmol) was added. The solid formed was filtered off after 1 h, washed with ethanol (10 ml) cooled to 0°C, and with water (20 ml). A mixture (0.96 g) of compounds **2b** and **3b** was obtained. Pure colorless compound **2b** (0.22 g, 11%) was obtained by recrystallization from ethanol. On acidifying the filtrates compound **3b** (1.23 g, 61%) was isolated. Colorless compound **2e** (31%) was obtained analogously on using the ethyl ester of 2-(4-nitrophenylmethylene)benzoylacetic acid.

2-Carbamoylmethylthio-5-ethoxycarbonyl-6-hydroxy-4,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylic Acid Nitrile (2d). Finely powdered 1,4,5,6-tetrahydropyridine-2-thiolate **1** [12] (2.33 g, 5 mmol) and iodoacetamide (1.02 g, 5.5 mmol) were dissolved with heating in ethanol (20 ml). The solution was stirred at room temperature for 15 min, the resulting solid was filtered off, washed with ethanol (10 ml) cooled to 0°C, and with water (20 ml). Colorless compound **2d** (1.90 g, 87%) was obtained.

Synthesis of 6-Substituted Nitriles of 4-Aryl-2-carbamoylmethylthio-5-ethoxycarbonyl-6-hydroxy-1,4-dihydropyridine-3-carboxylic Acids 3. A. 1,4,5,6-Tetrahydropyridine **2d** (0.44 g, 1 mmol) was dissolved with brief heating in 0.5 M HCl in ethanol (10 ml), and the solution stirred for 1 h at room temperature. The solid formed was filtered off, washed with ethanol (10 ml) cooled to 0°C, and colorless compound **3d** (0.30 g, 72%) was obtained.

Colorless compound **3e** was obtained analogously by the dehydration of tetrahydropyridine **2e** in 75% yield.

B. 2-(4-Nitrophenylmethylene)acetoacetic acid ethyl ester (1.32 g, 5 mmol) and 2-cyanothioacetamide (0.5 g, 5 mmol) were dissolved by heating in ethanol (20 ml). Piperidine (0.6 ml, 0.5 mmol) was added to the obtained solution, and after stirring for 15 min iodoacetamide (1.11 g, 6 mmol) was added. After 10 min, 1 M HCl in ethanol (10 ml) was poured in, the mixture was briefly heated to boiling and stirred for 1 h at ~20°C. The resulting precipitate was filtered off, and washed with ethanol (10 ml) cooled to 0°C, and with water (20 ml). Colorless compound **3b** (1.55 g, 77%) was obtained.

Colorless compound **3d** was obtained analogously in 69% yield using 2-(4-nitrophenylmethylene)-benzoylacetic acid ethyl ester.

C. 2-Cyano-3-(4-methoxyphenyl)thioacrylamide (1.09 g, 5 mmol) and acetoacetic acid ethyl ester (0.65 g, 5 mmol) were dissolved with heating in ethanol (20 ml). Piperidine (0.6 ml, 0.5 mmol) was added to the obtained solution, and after stirring for 15 min iodoacetamide (1.02 g, 5.5 mmol) was added. After 10 min 1 M HCl in ethanol (10 ml), was added, the mixture was heated briefly to boiling, then stirred for 1 h at ~20°C. The precipitate formed was filtered off, and washed with ethanol (10 ml) cooled to 0°C, and with water (20 ml). Colorless compound **3c** (1.60 g, 83%) was obtained.

Colorless compound **3f** was obtained analogously in 70% yield using benzoylacetic acid ethyl ester.

REFERENCES

1. D. J. Triggle, *Can. J. Physiol. Pharmacol.*, **68**, 1474 (1990).
2. G. Tirzitis, I. Kirule, and G. Duburs, *Fat Sci. Technol.*, **10**, 411 (1988).
3. N. Rojstaczer and D. J. Triggle, *Cardiovascular Drug Reviews*, **12**, 70 (1994).
4. W. F. Kauder and J. Watts, *Biochem. Pharmacol.*, **51**, 811 (1996).
5. A. A. Krauze, R. O. Vitolinya, M. R. Romanova, and G. Ya Dubur, *Khim.-farm. Zh.*, No. 8, 955 (1988).
6. A. A. Krauze, A. G. Odynets, A. A. Verreva, S. K. Germane, A. N. Kozhukov, and G. Ya. Dubur, *Khim.-farm. Zh.*, No. 7, 40 (1991).

7. I. E. Kirule, A. A. Krauze, A. Kh. Velena, D. Yu. Antipova, G. Ya. Arnitsane, I. A. Vutsina, and G. Ya. Dubur, *Khim.-farm. Zh.*, No. 11/12, 59 (1992).
8. D. Tirzite, A. Krauze, A. Zubareva, G. Tirzitis, and G. Duburs, *Khim. Geterotsikl. Soedin.*, 902 (2002).
9. A. A. Krauze, E. E. Liepin'sh, Yu. E. Pelcher, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, 124 (1987).
10. A. Krauze, J. Popelis, and G. Duburs, *Tetrahedron*, **54**, 9161 (1998).
11. A. Krauze, L. Sile, and G. Duburs, *Heterocyclic. Commun.*, **7**, 4, 375 (2001).
12. A. A. Krauze, E. E. Liepin'sh, Yu. E. Pelcher, Z. A. Kalme, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, 75 (1987).
13. Ya. P. Stradyn', G. Ya. Dubur, Yu. I. Beilis, Ya. R. Uldrikis, and A. F. Korotkova, *Khim. Geterotsikl. Soedin.*, 84 (1972).
14. J. Ludvik, J. Klima, J. Volke, A. Kurfürst, and J. Kuthan, *J. Electroanal. Chem.*, **138**, 131 (1982).
15. Ya. V. Ogle, L. Kh. Baumane, Ya. P. Stradyn', G. Ya. Dubur, V. P. Kadysh, R. A. Gavar, and V. K. Dusis, *Khim. Geterotsikl. Soedin.*, 1099 (1985).
16. J. Stradins, L. Baumane, A. Kalninsh, Ya. Uldrikis, E. Bisenieks, Ya. Poikans, and G. Dubur, *Khim. Geterotsikl. Soedin.*, 1360 (2000).
17. C. Lopez-Alarcon, L. J. Nunez-Vergara, and J. A. Squella, *Electrochim. Acta,* **48**, 2505 (2003).
18. K. Ueno and T. Umeda, *Chem. Pharm. Bull.*, **40**, 1376 (1992).
19. M. R. Tarasevich, E. I. Khrushcheva, and V. Yu. Filinovskii, *The Rotating Disk Electrode with a Ring* [in Russian], Nauka, Moscow (1987), p. 247.
20. D. Clark, M. Fleishmann, and D. Pletcher, *J. Electroanal. Chem.*, **36**, 137 (1972).