SYNTHESIS OF ETHOXYCARBONYL-1,4- AND -1,2-DIHYDROPYRIDINECARBOXYLIC ACID AMIDES

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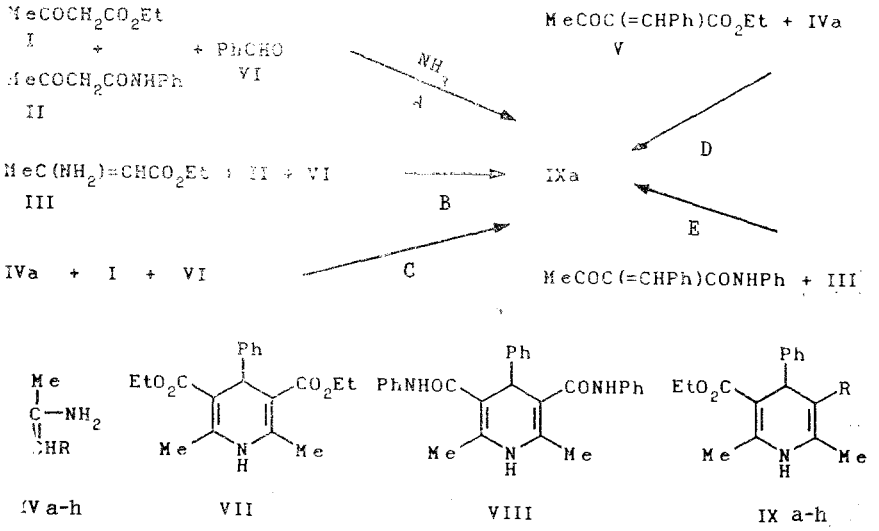
3-Carbamoyl derivatives of 4-phenyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine were obtained by cyclocondensation of 2-benzylideneacetoacetic ester with β-aminocrotonic acid amide or anilides. In the alkylation of 4-phenyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine-3-carboxylic acid anilides the amido group is initially alkylated, after which the ring NH group is alkylated, while the thiocarbamoyl group is converted to a cyano group. Reduction of the pyridinium salts gave 3- and 5-carbamoyl derivatives of 4-phenyl-1,2,6-trimethyl-1,2-dihydropyridine-5- and -3-carboxylic acids.

In contrast to 1,4-dihydropyridine(DHP)-3,5-dicarboxylic acid derivatives, 1,2-DHP-3,5-dicarboxylic acid derivatives with various carbofunctional substituents attached to the $C_{(3)}$ and $C_{(5)}$ atoms can exist in the form of two structural isomers, for example, 3-ethoxycarbonyl-1,2-DHP-5-carboxylic acid amide and 5-ethoxycarbonyl-1,2-DHP-3-carboxylic acid amide. For a comparative study of the reactivities of 1,2-DHP-3,5-dicarboxylic acid derivatives we set out to obtain 1,2-DHP that simultaneously contain both ester and amide functions.

In using the previously developed [1] scheme for obtaining 1,2-DHP (through a step involving the synthesis of N-methyl derivatives of 1,4-DHP and pyridinium salts with subsequent reduction of the latter) the first task is the development of a satisfactory method for the synthesis of 5-ethoxycarbonyl-1,4-DHP-3-carboxylic acid amides.

The synthesis of known (up to this time) 1,4-DHP-3,5-dicarboxylic acid derivatives that simultaneously contain amide and ester functions [2-4] was accomplished by the condensation of β-aminocrotonic acid amides, acetoacetic ester, and an aldehyde. The yields of the desired products reach 12-20%.

Scheme 1



IV a-h VII VIII IX a-h

IV, IX a R=CONHPh; b R=CONHC$_6$H$_4$CH$_3$-*p*; c R=CONHC$_6$H$_4$OCH$_3$-*p*; d R=CONHC$_6$H$_4$Cl-*p*; e R=CONHC$_6$H$_4$NO$_2$-*p*; f R=CSNHPh; g R=CONH$_2$; h R=CSNH$_2$

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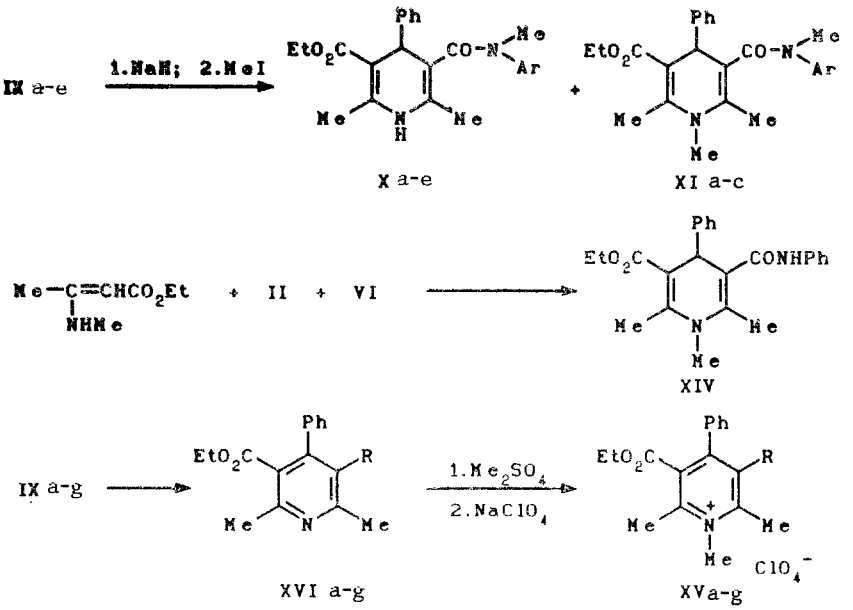
Scheme 2



X, XI a Ar=Ph; b Ar=$C_6H_4CH_3$-*p*; c Ar=$C_6H_4OCH_3$-*p*; d Ar=C_6H_4Cl-p; e Ar=$C_6H_4NO_2$-*p*. IX, XV, XVI a R=CONHPh; b R=$CONHC_6H_4CH_3$-*p*; c R=$CONHC_6H_4OCH_3$-*p*; d R=$CONHC_6H_4Cl$-*p*; e R=$CONHC_6H_4NO_2$-*p*; f R=CSNHPh; g R=$CONH_2$

Our condensation of equimolar amounts of benzaldehyde (VI), ammonia, acetoacetic ester (I), and acetoacetic acid anilide (II) under the conditions of the Hantzsch reaction (pathway A) gives a mixture of products (20.4% VII, 19.8% VIII, and 46.5% IXa, according to HPLC) that is separable only by means of chromatography. In the reaction of ethyl β-aminocrotonate (III) with anilide II and aldehyde VI (pathway B) product IXa is formed in 11% yield after fractional crystallization, while the reaction of ester III with aldehyde VI and thioanilide IVf gives 1,4-DHP IXf in 13% yield. Variants of the synthesis of IXa from aminocrotonic acid anilide IVa and ester I (pathway C, 21% yield) are unsuitable, as is the condensation of ester III with the benzylidene derivative of acetoacetic acid anilide (pathway E, 15% IXa). The condensation of ester V with β-aminocrotonic acid anilides IVa-e (pathway D), including β-aminothiocrotonic acid anilide (IVf), is most suitable for the preparative production of anilides IXa-f. However, it should be noted that the yields of amides IXg, h obtained via this scheme reach only 15% and 38%, respectively.

In the methylation of 1,4-DHP IX with both methyl iodide and dimethyl sulfate it was established that both the NH group of the DHP ring and the NH group of the side chain, which undergoes the reaction first, are capable of alkylation in the anionic form. In the case of the alkylation of anilide IXa it was shown that a mixture of N-methyl-N-phenylamide Xa and starting IXa is isolated if 1.0-1.5 equivalents of sodium hydride are used for the formation of the anion. An increase in the amount of the base leads to the formation of a mixture of mono- (Xa) and dialkyl (XIa) products. Only dialkyl product XIa is obtained when a threefold to fivefold amount of NaH with respect to the DHP is used.

The structures of the alkylation products were established by analysis of their PMR spectra. A comparison of the PMR spectra of 1,4-DHP-carboxylic acid anilides IX in d_6-DMSO with the spectra of dianilide VIII and diester VII makes it possible to assign the signal at 8.2-8.6 ppm to the NH proton of the 1,4-DHP ring and the signal at 9.2-10.8 ppm to the NH proton of an amide function. When d_6-DMSO is replaced by $CDCl_3$, the signals of the protons of the NH groups undergo a significant strong-field shift: the ring NH signal is found at 5.6-6.0 ppm, while the proton of the CONHAr group is overlapped by signals of protons of aromatic substituents (~7.3 ppm). The behavior of the signals of the 2,6-CH_3 groups of anilides IX is also characteristic — in the spectra of solutions in d_6-DMSO they are individual signals at ~2.0 and ~2.3 ppm. In the spectra of solutions in $CDCl_3$ they merge to give a single signal at ~2.2 ppm.

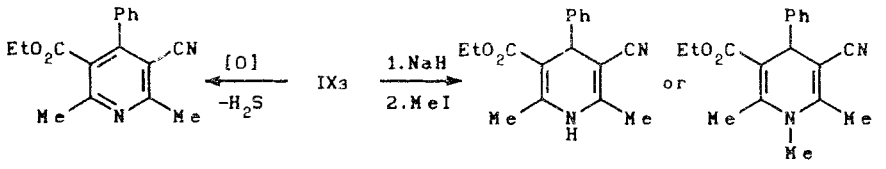
Depending on the reaction conditions, either nitrile XII or its 1-methyl derivative XIII is formed in the alkylation of thioamide IXh. This is explained by initial alkylation of the thioamido group, which leads to an imino ester, which in an alkaline medium splits out methyl mercaptan and forms nitrile XII. 1-Methyl derivative XIII is formed in the presence of large excess amounts of NaH and the alkylating agent:

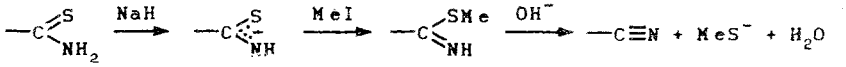
TABLE 1. Characteristics of the Synthesized IX, XV, XVI, XVIII, and XIX

Compound	Empirical formula	mp, °C	Yield, %	Compound	Empirical formula	mp, °C	Yield, %
IXa	$C_{23}H_{24}N_2O_3$	190...192	96,0	XVIa	$C_{23}H_{22}N_2O_3$	169...171	88,0
IXb	$C_{24}H_{26}N_2O_3$	196...200	77,2	XVIb	$C_{24}H_{24}N_2O_3$	78...80	76,7
IXc	$C_{24}H_{26}N_2O_4$	97...99	69,9	XVIc	$C_{24}H_{24}N_2O_4$	178...180	72,5
IXd	$C_{23}H_{23}ClN_2O_3$	213...215	70,3	XVId	$C_{23}H_{21}ClN_2O_3$	75...77	91,3
IXe	$C_{23}H_{23}N_3O_5$	197...199	48,4	XVIe	$C_{23}H_{21}N_3O_5$	219...221	56,3
IXg	$C_{17}H_{20}N_2O_3$	193...195	20,2	XVIf	$C_{23}H_{22}N_2O_2S$	186...188	47,2
XVa	$C_{24}H_{25}ClN_2O_7$	182...184	57,3	XVIg	$C_{17}H_{18}N_2O_3$	169...171	71,8
XVb	$C_{25}H_{27}ClN_2O_7$	219...221	46,7	XVIIIa	$C_{24}H_{26}N_2O_3$	138...140	40,8
XVc	$C_{25}H_{27}ClN_2O_8$	187...189	44,2	XVIIIb	$C_{25}H_{28}N_2O_3$	150...152	53,8
XVd	$C_{24}H_{24}Cl_2N_2O_7$	209...211	46,4	XVIIIc	$C_{25}H_{28}N_2O_4$	115...118	60,7
XVe	$C_{24}H_{24}ClN_3O_9$	234...236	93,8	XVIIId	$C_{24}H_{25}ClN_2O_3$	147...149	67,2
XVf	$C_{24}H_{25}ClN_2O_6S$	174...176	22,0	XVIIIe	$C_{24}H_{25}N_3O_5$	153...155	32,6
XVg	$C_{18}H_{21}ClN_2O_7$	124...126	33,4	XVIIIf	$C_{24}H_{26}N_2O_2S$	131...133	22,5
XIXa	$C_{24}H_{26}N_2O_3$	134...136	17,5	XVIIIg	$C_{18}H_{22}N_2O_3$	164...166	22,5
XIXc	$C_{25}H_{28}N_2O_4$	152...154	10,6	XIXb	$C_{25}H_{28}N_2O_3$	180...182	8,8
				XIXd	$C_{24}H_{25}ClN_2O_3$	151...153	7,4

TABLE 2. PMR Spectra of Pyridinium Perchlorates XVa-e

Compound	Chemical shifts, δ, ppm (in $CDCl_3$)							
	1-CH_3 (s 3H)	2-CH_3 (s 3H)	6-CH_3 (s 3H)	$-COOCH_2CH_3$		- CONHAr		4-Ph (s 5H)
				CH_3 (t 3H)	CH_2 (q 2H)	NH s 1H)	Ar	
XVa	4,16	2,80	2,90	0,86	4,01	8,99	6,98...7,30 (s 5H)	7,36
XVb	4,16	2,80	2,91	0,87	4,01	8,91	2,23 (s 3H) 6,97 (d 2H) 7,19 (d 2H)	7,36
XVc	4,17	2,82	2,93	0,89	4,04	8,91	3,72 (s 3H) 6,73 (d 2H) 7,22 (d 2H)	7,38
XVd	4,20	2,86	2,92	0,89	4,07	9,59	7,56 (d 2H) 7,19 (d 2H) 8,08 (d 2H)	7,35
XVe	4,18	2,81	2,91	0,88	4,02	9,04	7,11 (d 2H) 7,29 (d 2H)	7,36





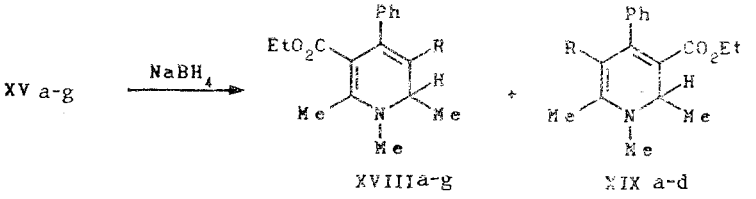
Attempts to obtain 1-methyl derivative XIV starting from β-methylaminocrotonic acid derivatives were unsuccessful. 1-Methyl-1,4-dihydropyridine XIV was isolated in 7-8% yield from the reaction mixture obtained by condensation of the ethyl ester of the acid mentioned above with benzaldehyde and acetoacetic acid anilide. The condensation of β-methylaminocrotonic acid anilide with benzylidene derivative V under the conditions of the Hantzsch reaction results in the formation of a product with a carbocyclic structure, regarding which information will be reported separately.

Because of the lack of a preparative method for the synthesis of 1-methyl-DHP of the XIV type and, consequently, the possibility of their oxidation to pyridinium salts (XIV → XV), to obtain the latter we used pyridines XVIa-g — the products of oxidation of 1,4-DHP IXa-g. The oxidation of these DHP with sodium nitrite in glacial acetic acid presents no difficulties, except for thioamide IXh, which, under the reaction conditions, splits out hydrogen sulfide and forms 5-ethoxycarbonyl-4-phenyl-2,6-dimethylpyridine-3-carboxylic acid nitrile (XVII). Pyridinium perchlorates XVa-g were obtained by methylation of pyridines XVIa-g with methyl iodide with subsequent exchange of the anion.

TABLE 3. PMR Spectra of 1,4-Dihydropyridines IXa-h (in d_6-DMSO)

Compound	Chemical shifts, δ, ppm								
					—COOCH$_2$CH$_3$		—CONHAr		
	1-H (s 1H)	2-CH$_3$ (s 3H)	6-CH$_3$ (s 3H)	4-H (s 1H)	CH$_3$ (t 3H)	CH$_2$ (q 2H)	NH	Ar	4-Ph (s. 5H)
IXa	8,26	2,01	2,24	4,83	1,06	3,89	9,28 (s 1H)	6,84 ... 7,56 (m 10H)	
IXb	8,40	2,03	2,23	4,97	1,08	4,00	9,36 (s 1H)	2,29 (s 3H) 7,02 (d 2H) 7,42 (d 2H)	7,13
IXc	8,28	1,93	2,19	4,80	1,00	3,84	9,22 (s 1H)	3,60 (s 3H) 6,70 (d 2H) 7,38 (d 2H)	7,08
IXd	8,56	2,04	2,30	4,98	1,08	4,00	9,64 (s 1H)	7,37 (d 2H) 7,68 (d 2H)	7,23
IXe	8,36	2,08	2,28	4,94	1,11	3,98	9,90 (s 1H)	7,79 (d 2H) 8,12 (d 2H)	7,15
IXf	8,31	1,91	2,27	5,29	1,02	3,91	10,80 (s 1H)	7,16 ... 7,42 (m 10H)	
IXg	8,19	2,00	2,16	4,71	1,04	3,88	6,66 (s 2H)		7,06
IXh	8,18	1,89	2,22	5,27	1,07	3,89	8,82 (d J = =54 Hz 2H)		7,09

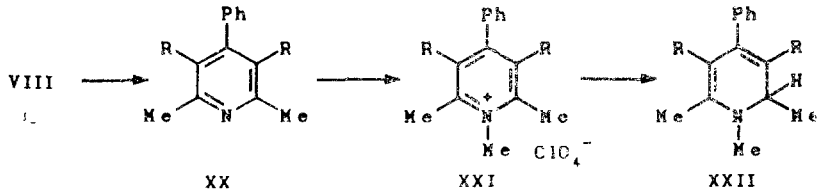
As one should have expected, the reduction of pyridinium salts XV, which have unsymmetrical substituents attached to the $C_{(3)}$ and $C_{(5)}$ atoms, with sodium borohydride gives mixtures of 1,2-dihydropyridine-3- (XVIIIa-g) and -5-carboxylic acid amides (XIXa-d):



XVIIIa-g XIX a-d

XV, XVIII, XIX a R=CONHPh; b R=CONHC$_6$H$_4$CH$_3$-*p*; c R=CONHC$_6$H$_4$OCH$_3$-*p*; d R=CONHC$_6$H$_4$Cl-*p*; XV, XVIII e R=CONHC$_6$H$_4$NO$_2$-*p*; f R=CSNHPh; g R=CONH$_2$

4-Phenyl-1,2,6-trimethyl-1,2-dihydropyridine-3,5-dicarboxylic acid dianilide (XXII) was also synthesized in accordance with the scheme presented above:



XX XXI XXII

XX - XXII R = CONHPh

The classification of the compounds obtained as 1,2-DHP-3- and -5-carboxylic acid derivatives was made by comparison of the PMR spectra of amides XVIII and XIX with the spectrum of ethyl 1,2-DHP-5-monocarboxylate XXIIIa [1], as well as with the spectra of various 5-ethoxycarbonyl-1,2-DHP-5-carboxylic acid esters XXIIIc [5]. Because of hindered rotation, in the PMR spectra of ethyl 1,2-DHP-5-carboxylates XXIIIa-c one observes nonequivalence of the methylene protons of the OCH_2CH_3 group (a multiplet, the most intense middle quartets of which are shifted 0.02-0.06 ppm relative to one another; ^3J = 7.0 Hz). The same nonequivalence of the protons of the CH_2 group is characteristic for amides XVIIIa-g. The signal of the CH_2 protons of the ester group of amides XIXa-d is a distinct quartet that is similar to the corresponding signal of the CH_2 protons of ethyl 1,2-DHP-3-carboxylate (see Fig. 1). It is characteristic that the signals of the protons of the ester group of 3-carboxylic acid amides XVIIIa-g are located at stronger field than the corresponding signals of 5-carboxylic acid amides XIXa-d: the signals of the CH_3 protons by 0.16 ppm, and the signals of the CH_2 protons by 0.20 ppm. In turn, the quartet of the 2-H protons of amides XVIII is located at weaker field by ~0.06 ppm than the corresponding signal of amides XIX.

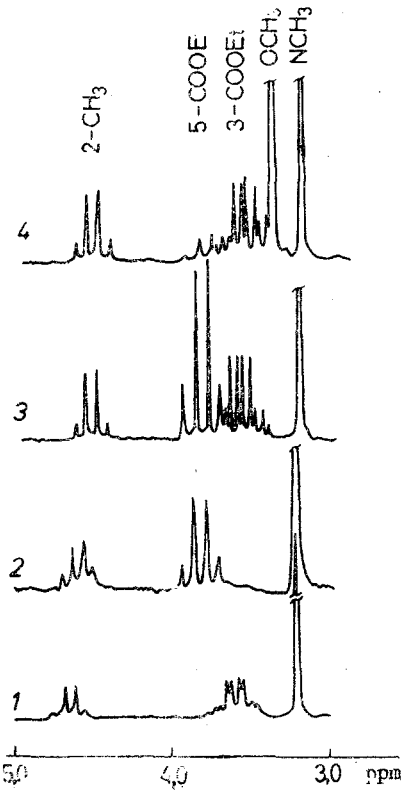
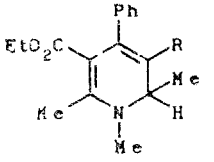


Fig. 1. PMR spectra (δ 3-5 ppm) of 1,2,6-trimethyl-4-phenyl-1,2-dihydropyridine derivatives in $CDCl_3$: 1) XVIIIa; 2) XIXa; 3) XXIIIb; 4) XXIIIc (Alk = Me).



XXIII a-c

XXIII a R=H, b R=CO_2Et , c R=CO_2Alk

The UV and IR spectra of 1,2-DHP-3-carboxylic acid anilides XVIIIa-g do not differ substantially from the corresponding characteristics of 1,2-DHP-dicarboxylic acid diesters: for example, the UV spectrum of ester XXIIIb contains absorption maxima at 283 and 388 nm, as compared with 295 and 385 nm for anilide XVIIIa; the IR spectrum of ester XXIIIb contains an absorption maximum at 1690 cm^{-1}, as compared with 1688 cm^{-1} for anilide XVIIIa. The absorption maxima in the IR spectra of 5-carboxylic acid anilides XIXa-d are decreased by ~20 cm^{-1} as compared with 3-carboxylic acid anilides XVIIIa-g (for example, 1672 cm^{-1} for anilide XIXa). A new maximum at 247 nm appears in the UV spectrum of anilide XIXa [for anilide XVIIIa the spectrum in the examined region is sloping with significant absorption ($\log \varepsilon = 4.13$)], while the long-wave maximum is shifted bathochromically to 403 nm. The maximum at 290 nm is weakly expressed and shows up in the form of an increased shoulder at 300 nm.

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord M-40 spectrophotometer. The IR spectra of suspensions in mineral oil were obtained with a PE 580-B spectrometer. The PMR spectra were recorded with

TABLE 4. PMR Spectra of 1,4-Dihydropyridines Xa-e and XIa-c (in $CDCl_3$)

Compound	Chemical shift, δ, ppm								
	1-R, s	2-CH_3 (s 3H)	6-CH_3 (s, 3H)	4-H (s 1H)	—$COOCH_2CH_3$		—$CON(CH_3)Ar$		4-Ph
					CH_3 (s 3H)	CH_2	NCH_3 (s 3H)	Ar	
Xa	5,30 (1H)	1,88	2,27	4,64	1,07	3,91 (q 2H)	3,19	6,98 (m, 2H) 7,22 (m 8H)	
Xb	5,66 (1H)	1,84	2,26	4,56	1,07	3,91 (q 2H)	3,16	2,32 (s 3H); 6,88 (d 2H); 7,09 (d 2H)	7,23 (s 5H)
Xc	5,54 (1H)	1,84	2,28	4,67	1,09	3,93 (q 2H)	3,16	3,80 (s 3H); 6,77 (d 2H); 6,91 (d 2H)	7,24 (s 5H)
Xd	5,50 (1H)	1,84	2,30	4,69	1,09	3,96 (q 2H)	3,18	7,23 (m 7H)	
Xe	5,58 (1H)	1,83	2,29	4,70	1,03	3,93 (q 2H)	3,18	6,89 (d 2H); 7,10 (d 2H); 8,10 (d 2H)	7,21 (s 5H)
XIa	3,01 (3H)	2,00	2,37	4,54	1,13	3,92 (m 2H)	3,27	7,12 (m, 10H)	
XIb	3,04 (3H)	2,00	2,38	4,58	1,14	3,93 (m 2H)	3,26	2,30 (s, 3H); 6,92 (d 2H); 7,06 (d 2H)	7,18 (s 5H)
XIc	3,05 (3H)	2,01	2,38	4,64	1,17	4,00 (m 2H)	3,27	3,79 (s 3H); 6,82 (d 2H); 7,10 (d 2H)	7,33 (s 5H)

TABLE 5. PMR Spectra of 1,2-Dihydropyridines XVIII and XIX (in $CDCl_3$)

Compound	δ, ppm		SSSC, $^7J_{H-CH_3}$, Hz	δ, ppm				SSSC, ^3J, Hz*	δ, ppm		SSCC, J, Hz**	δ, ppm, 4-Ph
	2-CH_3 (d 3H)	2-H (q 1H)		1-CH_3 (s, 3H)	6-CH_3 (s, 3H)	—$COOCH_2CH_3$			—CONHAr			
						CH_3 (t, 3H)	CH_2 (2H)		NH	Ar		
XVIIIa	1,24	4,66	6,2	3,21	2,46	0,62	3,61 m	7,0	6,54 (br.s., 1H)	6,73 ... 7,27 (m 5H)		7,33
XIXa	1,24	4,59	5,9	3,21	2,39	0,79	3,82 q	7,0	6,36 (br.s, 1H)	6,77 ... 7,14 (m 5H)		7,22
XVIIIb	1,28	4,63	6,0	3,20	2,46	0,61	3,60 m	6,8	6,48 (br.s., 1H)	2,20 (s 2H); 6,72 (d 2H); 6,90 (d 2H)	8,2	7,32
XIXb	1,23	4,58	6,0	3,18	2,37	0,77	3,81 q	6,8	6,32 (br.s., 1H)	2,19 (s 3H); 6,70 (d 2H); 6,88 (d 2H)	8,6	7,20
XVIIIc	1,29	4,63	6,0	3,21	2,46	0,62	3,61 m	6,8	6,43 (br.s., 1H)	3,70 (s 3H); 6,63 (d 2H); 6,82 (d 2H)	8,6	7,33
XIXc	1,23	4,58	6,4	3,17	2,36	0,77	3,81 q	6,8	6,27 (br.s., 1H)	3,68 (s 3H); 6,58 (d 2H); 6,76 (d 2H)	9,0	7,20
XVIIId	1,28	4,64	6,0	3,20	2,46	0,62	3,61 m	7,0	6,52 (br.s., 1H)	6,78 (d 2H); 7,06 (d 2H)	8,4	7,33
XIXd	1,24	4,58	5,8	3,21	2,40	0,79	3,81 q	6,8	6,34 (br.s., 1H)	6,78 (d 2H); 7,00 (d 2H)	8,6	7,22
XVIIIe	1,29	4,71	6,2	3,24	2,47	0,63	3,63 m	6,8	6,83 (br.s., 1H)	6,84 (d 2H); 7,97 (d 2H)	9,0	7,30
XVIIIf	1,29	4,64	6,0	3,21	2,44	0,62	3,60 m	6,8	6,53 (br.s., 1H)	6,73 ... 7,11 (m 5H)		7,32
XVIIIg	1,22	4,63	6,4	3,18	2,41	0,61	3,58 m	6,8	4,84 (2H)			7,26 (m)

*For —$COOCH_2CH_3$.

**For —CONHAr.

a WH-90 spectrometer with tetramethylsilane (TMS) as the internal standard. Preparative chromatography was carried out on plates (30 by 30 cm) with silica gel L 40/100 (the thickness of the absorbing layer was 2-3 mm). If not specified otherwise, ethanol was used for crystallization.

The characteristics of the synthesized compounds are presented in Tables 1-5.

The results of elementary analysis were in agreement with the calculated values. Crotonic acid amide and anilides IVa-e were synthesized from acetoacetic acid amide and anilides by the method in [6]. β-Aminothiocrotonic acid amide and anilide were obtained by the methods in [7, 8].

General Method for Obtaining 1,4-Dihydropyridines IXa-e, g. Equimolar amounts (50 mmole) of 2-benzylideneacetoacetic ester (V) and anilide IVa-e or β-aminocrotonic acid amide (IVg) were refluxed in 80 ml of ethanol for 6 h. The mixtures were cooled, and the colorless precipitates were removed by filtration and recrystallized. The resulting crystal hydrates were dried in vacuo.

4-Phenyl-5-ethoxycarbonyl-2,6-dimethyl-3-thiocarbamoyl-1,4-dihydropyridine (IXh, $C_{17}H_{20}N_2O_2S$). A 7.75-g (35 mmole) sample of ester V and 4.10 g (35 mmole) of β-aminothiocrotonic acid amide were refluxed in 50 ml of absolute ethanol and 1 ml of glacial acetic acid for 7 h. The solvent was evaporated in vacuo to 25 ml, the concentrate was cooled, and the yellow crystals were removed by filtration to give 4.21 g (38%) of amide IXh with mp 207-209°C [from ethanol—acetic acid (2:1)].

3-Ethoxycarbonyl-4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3-thiocarboxylic acid anilide (IXf, $C_{23}H_{24}N_2O_2$) was similarly obtained. The product had mp 208-210°C and was obtained in 65% yield.

4-Phenyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine-3-carboxylic Acid N-Phenyl-N-methylamide (Xa, $C_{24}H_{26}N_2O_3$). A 0.3-g (12.5 mmole) sample of sodium hydride was added to a solution of 3 g (8 mmole) of dihydropyridine IXa in 10 ml of hexametapol, and the mixture was stirred for 30 min at 20°C. Methyl iodide (1.8 ml) was added, and the mixture was stirred for another 15 min and then diluted with 100 ml of water. The colorless oil was separated, washed with water (2 × 30 ml), and dissolved in chloroform (10 ml). The solution was dried over Na_2SO_4, the solvent was removed by distillation, and the residue was separated chromatographically in chloroform—ethyl acetate (5:1). Workup of the band that absorbed UV light gave 0.86 g (28%) of amide Xa with mp 202-204°C, while workup of the band that fluoresced in UV light gave 1.38 g (46%) of starting IXa.

4-Phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,4-dihydropyridine-3-carboxylic Acid N-Phenyl-N-methylamide (XIa, $C_{25}H_{28}N_2O_3$). A 1-g (2.7 mmole) sample of dihydropyridine IXa and 0.15 g (6 mmole) of sodium hydride were stirred in 10 ml of hexametapol for 15 min at room temperature, after which 0.6 g (10 mmole) of methyl iodide was added, and the mixture was stirred for 15 min. The mixture was treated with 0.15 g of NaH and, after 15 min, another 0.6 ml of methyl iodide, and stirring was continued for another 15 min. The reaction mixture was then diluted with 100 ml of water, and the colorless oil was separated and dissolved in 20 ml of chloroform. The chloroform solution was washed with water (2 × 50 ml) and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was recrystallized to give 0.49 g (46%) of amide XIa with mp 131-133°C. Dialkyl derivative XIa was also obtained by alkylation of monoalkyl derivative Xa.

Amides Xb-e and XIb, c were similarly obtained.

4-Phenyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-DHP-3-carboxylic Acid N-(p-Tolyl)-N-methylamide (Xb, $C_{25}H_{28}N_2O_3$). This compound had mp 91-93°C and was obtained in 59.2%.

4-Phenyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-DHP-3-carboxylic Acid N-(p-Methoxyphenyl)-N-methylamide (Xc, $C_{25}H_{28}N_2O_4$). This compound had mp 114-116°C and was obtained in 53.4% yield.

4-Phenyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-DHP-3-carboxylic Acid N-(p-Chlorophenyl)-N-methylamide (Xd, $C_{24}H_{25}ClN_2O_3$). This compound had mp 121-122°C and was obtained in 72% yield.

4-Phenyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-DHP-3-carboxylic Acid N-(p-Nitrophenyl)-N-methylamide (Xe, $C_{24}H_{25}N_3O_5$). This compound had mp 179-180°C and was obtained in 39% yield.

4-Phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,4-DHP-3-carboxylic Acid N-(p-Tolyl)-N-methylamide (XIb, $C_{26}H_{30}N_2O_3$). This compound had mp 165-167°C and was obtained in 42.7% yield.

4-Phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,4-DHP-3-carboxylic Acid N-(p-Methoxyphenyl)-N-methylamide (XIc, $C_{26}H_{30}N_2O_4$). This compound had mp 111-113°C and was obtained in 57.2% yield.

Alkylation of 4-Phenyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine-3-thiocarboxylic Acid Amide (IXh). **A.** A 0.95-g (3 mmole) sample of amide IXh was dissolved in 40 ml of absolute dimethoxyethane in an argon atmosphere with cooling of the flask in an ice bath, and 0.36 g (15 mmole) of sodium hydride was added. After 10 min, 1.8 ml (30 mmole) of methyl iodide was added dropwise, and the mixture was stirred for another 10 min. It was then diluted with 100 ml of

water, and the aqueous mixture was extracted with ethyl acetate (2 × 50 ml). The extract was washed with water, dried over Na_2SO_4, and distilled in vacuo. The residue was crystallized from dilute (1:1) methanol to give 0.49 g (58%) of 3-cyano-4-phenyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (XII), which was identical with respect to its PMR spectrum and a mixed-melting-point determination to a genuine sample synthesized by the method in [9]. PMR spectrum ($CDCl_3$): 1.10 (3H, t, OCH_2CH_3), 2.04 (3H, s, 2-CH_3), 2.33 (3H, s, 6-CH_3), 4.03 (2H, q, OCH_2CH_3), 4.64 (1H, s, 4-H), 6.16 (1H, broad s, 1-H), 7.29 ppm (5H, s, 4-Ph).

B. A 0.1-g (4 mmole) sample of sodium hydride was added in an argon atmosphere at 20°C to a solution of 0.63 g (2 mmole) of amide IXh in 45 ml of absolute dimethoxyethane. After 30 min, 0.6 ml (10 mmole) of methyl iodide was added, another 0.1 g of NaH was added, and the mixture was refluxed for 30 min. The mixture was then treated with 0.6 ml of CH_3I, and refluxing was continued for another 30 min. The reaction mixture was cooled and diluted with 100 ml of water, and the colorless precipitate was removed by filtration to give 0.48 g (85%) of **3-cyano-4-phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,4-dihydropyridine (XIII, $C_{18}H_{20}N_2O_2$)** with mp 85-88°C (from dilute ethanol).

4-Phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,4-dihydropyridine-3-carboxylic Acid Anilide (XIV, $C_{24}H_{26}N_2O_3$). Equimolar amounts (10 mmole) of anilide II, benzaldehyde, and ethyl β-methylaminocrotonate were refluxed in 50 ml of ethanol for 5 h, after which the solvent was evaporated, and the residue was triturated with 100 ml of ether and cooled in a vessel containing dry ice. The colorless precipitate that formed overnight was removed by filtration to give 0.27 g (7%) of anilide XIV with mp 159-161°C. PMR spectrum (d_6-DMSO): 1.07 (3H, t, J = 7.3 Hz, OCH_2CH_3), 2.07 (3H, s, 2-CH_3), ~2.41 (3H, s, 6-CH_3), 3.11 (3H, s, 1-CH_3), 3.98 (2H, q, J = 7.3 Hz, OCH_2CH_3), 4.81 (1H, s, 4-H), 6.87-7.43 (8H, m) and 7.59 (2H, d, J = 8.0 Hz, aromatic protons), 9.67 ppm (1H, s, NH).

Pyridines XVIa-g were obtained by oxidation of dihydropyridines IXa-g with sodium nitrite in glacial acetic acid at 70-80°C by the method in [10]. Oxidation of amide IXh gave 3-cyano-4-phenyl-5-ethoxycarbonyl-2,6-dimethylpyridine (XVII, $C_{17}H_{16}N_2O_2$), with mp 93-95°C, in 43% yield. PMR spectrum ($CDCl_3$): 0.9 (3H, t, OCH_2CH_3), 2.62 (3H, s, 2-CH_3), 2.80 (3H, s, 6-CH_3), 4.01 (2H, q, OCH_2CH_3), 7.36 ppm (5H, m, 4-Ph).

Perchlorates XVa-g were obtained by methylation of pyridines XVI with methyl iodide with subsequent anion exchange by the method in [10].

Synthesis of 1,2-Dihydropyridines XVIIIa-g and XIXa-d. A 0.95-g (25 mmole) sample of $NaBH_4$ was added with stirring in the course of 20 min to a solution of 10 mmole of salts XVa-g in 20 ml of acetonitrile, after which the solvent was evaporated in vacuo, 100 ml of water was added to the residue, and the aqueous mixture was extracted with chloroform (2 × 25 ml). The chloroform layer was dried and evaporated, and the residue was chromatographed in ethyl acetate—chloroform (5:1). Workup of the first (reckoned from the front) yellow band gave amides XVIII, while workup of the second band gave amides XIX.

4-Phenyl-2,6-dimethylpyridine-3,5-dicarboxylic acid dianilide (XX, $C_{27}H_{23}N_3O_2$) was obtained by oxidation of the corresponding 1,4-dihydropyridine [11]. The product had mp > 360°C and was obtained in 84.6% yield.

4-Phenyl-2,6-dimethyl-3,5-di(phenylcarbamoyl)pyridinium perchlorate (XXI, $C_{28}H_{23}ClN_3O_2$) was obtained in the same way as salts XV. The product had mp 310-312°C and was obtained in 55% yield.

4-Phenyl-2,6-dimethyl-1,2-dihydropyridine-3,5-dicarboxylic acid dianilide (XXII, $C_{28}H_{27}N_3O_2$) was obtained by reduction of salt XXI with sodium borohydride and had mp 187-189°C. PMR spectrum ($CDCl_3$): 1.32 (3H, d, J = 6.0 Hz, 2-CH_3), 2.41 (3H, s, 6-CH_3), 3.21 (3H, s, 1-CH_3), 4.68 (1H, q, J = 6.0 Hz, 2-H), 6.38 (1H, s, 3-CONH), 6.49 (1H, s, 5-CONH), 6.73-7.11 (10H, m, NHPh), 7.36 ppm (5H, s, 4-Ph). The yield was 51.3%.

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SYNTHESIS AND PROPERTIES OF 6-METHYL-4-(m-NITROPHENYL)-3-CYANOPYRIDIN-2(1H)-ONES, THE CORRESPONDING PYRIDINE-2(1H)-THIONES, AND THEIR HYDROGENATED ANALOGS

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The condensation of 4-pyridylacetone, m-nitrobenzaldehyde, and cyanoacetamide (cyanothioacetamide) in the presence of bases was used to obtain 5-pyridyl-substituted 6-methyl-4-(m-nitrophenyl)-3-cyanopyridin-2(1H)-ones, the corresponding pyridine-2(1H)-thiones, and their hydrogenated analogs. 2-Carbamoylmethylthiopyridine was isolated in the alkylation of 5-(4'-pyridyl)pyridine-2(1H)-thione with iodoacetamide under mild conditions, while 2-carbamoylthio-5-(N-carbamoylmethyl-4'-pyridyl)pyridine iodide was isolated under more severe conditions.

3,4'-Dipyridyls are of interest as cardiotonic agents. Among them have been discovered the preparations amirinone and milrinone — 5-(4'-pyridyl)-substituted pyridin-2(1H)-ones, which have a positive inotropic effect on the heart while simultaneously displaying a vasodilating effect [1-6]. 3,4-Dihydropyridin-2(1H)-ones also increase the force of contraction of the papillary muscles [7].

Cardiotonic properties have recently also been discovered for 5-(4'-pyridyl)-substituted pyridine-2(1H)-thiones [8].

In continuing our research on partially hydrogenated pyridin-2(1H)-ones and pyridine-2(1H)-thiones [9, 10] we synthesized 5-(4'-pyridyl)-substituted di- and tetrahydropyridin-2(1H)-ones and dihydropyridine-2(1H)-thiones and accomplished their oxidation and alkylation.

Of the possible methods for the synthesis of these compounds [7, 10-13] we selected the method of unsymmetrical three-carbon condensation [10, 13]. The condensation of 4-pyridylacetone, m-nitrobenzaldehyde, and cyanoacetamide in the presence of strong bases at high temperatures proceeds with the formation of a complex mixture of products. 3-Cyanopyridin-2(1H)-one (IV), 6-hydroxy-3-cyano-3,4,5,6-tetrahydropyridin-2(1H)-one (II), and 3-carbamoyl-3,4-dihydropyridin-2(1H)-one (IIIb) were obtained in low yields when the reaction was carried out at room temperature using an equimolar amount of piperidine as the condensing agent with subsequent treatment of the reaction mixture with excess acetic acid and neutralization with ammonium hydroxide. The corresponding 3-cyano-3,4-dihydropyridin-2(1H)-one (IIIa) was isolated by brief heating of 6-hydroxy derivative II with HCl in ethanol.

The progress of this reaction can be represented in the following way: the initially formed δ-keto amide I undergoes subsequent intramolecular cyclization with the participation of both the amido and cyano groups, which leads to a mixture of hydrogenated 3-cyano- and 3-carbamoyl-substituted pyridin-2-ones II and IIIb. As compared with 3-carbamoyl-substituted IIIb, hydrogenated 3-cyanopyridin-2-ones II and IIIa are distinguished by greater instability; this is explained by their more facile oxidizability in the anionic form [15] and makes it possible to isolate pyridin-2-(1H)-one IV immediately from the reaction

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