ESTERS OF 1,4-DIHYDROPYRIDINE-3- AND -3,5-CARBOTHIOLIC ACIDS

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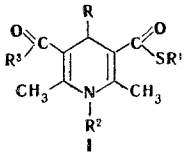
Methods for the preparation of esters of 1,4-dihydropyridine-3- and -3,5-carbothiolic acids were developed, and their structure and reactivity were studied. A comparative analysis was made of the spectroscopic characteristics of sulfur-containing esters of the 1,4-dihydropyridine series and their oxygen analogs. More strongly expressed electron-acceptor properties of the COSAlk groupings as compared with alkoxycarbonyl substituents were observed.

Highly effective coronary dilators [1, 2] and hypotensive agents [3] are found among 4-aryl- and 4-hetaryl-1,4-dihydropyridines. 4-Unsubstituted 1,4-dihydropyridines are of practical interest as potential antioxidants [4].

The aim of the present research was to synthesize and study the reactivity (in alkylation, oxidation, and transesterification) of a new series of 1,4-dihydropyridines I with alkylthio- and benzylthiocarbonyl substituents in the 3 and 3,5 positions, from which one might expect a number of specific chemical, physical, and biological properties due to the introduction of a sulfur atom in place of the oxygen atom in the ester grouping. Sulfur-containing esters of the 1,4-dihydropyridine series I ($R = R^2 = H$, R^1 = alkyl and benzyl, and R^3 = alkylthio and benzylthio) are obtained by condensation of S-substituted esters of thioacetoacetic acid urotropin in the presence of ammonium acetate by heating in dioxane.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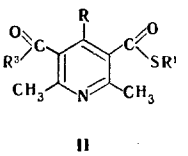
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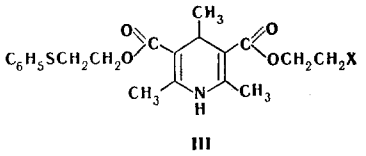
III

For the preparation of 4-substituted 1,4-dihydropyridines, S-substituted esters of thioacetoacetic acid are condensed with aldehydes and ammonia by refluxing in dioxane.

Unsymmetrical 3-O- and 5-S-substituted 1,4-dihydropyridine esters (I, $R^1 = C_2H_5$, $CH_2C_6H_5$, $R^3 = OC_2H_5$) are obtained either by condensation of ethyl β-aminocrotonate with the α-arylidene-S-ethyl ester of thioacetoacetic acid or by reaction of S-substituted esters of β-aminothiocrotonic acid with α-ethylidene and α-benzylidene derivatives of ethyl acetoacetate. The latter method is preferable, for it is technologically simpler to realize.

The oxidation of 1,4-dihydropyridines I with nitrogen oxides leads to the corresponding pyridines II (Table 2).

4-Methyl-1,4-dihydropyridines with a phenylthio substituent in the β position of the ethoxy group (III, X = H, SC_6H_5) were obtained on the basis of known key compounds, viz., the corresponding β-chloroethoxycarbonyl derivatives [5], by their reaction with sodium thiophenoxide. This expands the possibilities of modification of the substituents in the 3 and 5 positions of the dihydropyridine system.

Three absorption bands that are characteristic for monocyclic 1,4-dihydropyridines are observed in the UV region of the spectrum for I and III (Table 1); in the spectra of I one observes a 35-50 nm bathochromic shift of the average and long-wave maxima as compared with

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TABLE 1. 2,6-Dimethyl-1,4-dihydropyridine-3- and -3,5-carbothiolic Acid Esters (I, R^2 = H)

R	R^1	R^3	mp, °C	UV spectrum λ_{max}, nm (log ε)	IR spectrum at 1600-1800 and 3000-3600 cm^{-1}	Found, %				Empirical formula	Calc., %				Method of synthesis	Yield, %
						C	H	N	S		C	H	N	S		
H	C_2H_5	SC_2H_5	142—143	205 (3,94); 278 (4,26); 418 (3,94)	1600, 1655, 3360	54,3	6,9	5,0	22,4	$C_{13}H_{19}NO_2S_2$	54,7	6,7	4,9	22,5	A	74
H	$CH_2C_6H_5$	$SCH_2C_6H_5$	109—110	205 (4,39); 278 (4,28); 420 (3,90)	1600, 1670, 3320	67,3	5,5	4,1	15,1	$C_{23}H_{23}NO_2S_2$	67,5	5,7	3,4	15,7	A	70
CH_3	C_2H_5	SC_2H_5	116	205 (3,94); 255 (4,09); 277 (4,24); 390 (3,98)	1610, 1660, 3335	56,3	7,2	4,7	21,0	$C_{14}H_{21}NO_2S_2$	56,2	7,1	4,7	21,4	B	20
CH_3	$CH_2C_6H_5$	$SCH_2C_6H_5$	67	203 (4,39); 259 sh (4,13); 280 (4,28); 392 (4,01)	1600, 1650, 3300	67,9	6,0	3,1	15,3	$C_{24}H_{25}NO_2S_2$	68,1	6,0	3,3	15,1	B	35
C_6H_5	C_2H_5	SC_2H_5	132—133	204 (4,25); 273 (4,17); 390 (3,96)	1610, 1655, 3310	63,6	6,8	4,1	17,2	$C_{19}H_{23}NO_2S_2$	63,1	6,4	3,9	17,8	C	15
C_6H_5	$CH_2C_6H_5$	$SCH_2C_6H_5$	135	203 (4,42); 275 (4,24); 390 (3,96)	1600, 1645, 3300	72,0	5,9	3,1	12,8	$C_{29}H_{27}NO_2S_2$	71,7	5,6	2,9	13,2	C	22
$C_6H_4NO_2$ (4′)	C_2H_5	SC_2H_5	150	203 (4,24); 275 (4,48); 392 (3,71)	1610, 1650, 3390	55,8	5,2	6,5	15,1	$C_{19}H_{22}N_2O_4S_2$	56,1	5,5	6,9	15,8	E	80
C_5H_4N (3′)	C_2H_5	SC_2H_5	241	205 (4,25); 264 (4,32); 385 (3,97)	1610, 1660, 3230	59,1	6,0	7,7	17,2	$C_{18}H_{22}N_2O_2S_2$	59,6	6,1	7,7	17,7	C	40
C_5H_4N (3′)	$CH_2C_6H_5$	$SCH_2C_6H_5$	255	204 (4,42); 264 (4,22); 390 (3,90)	1610, 1655, 3250	68,6	5,4	5,9	12,8	$C_{28}H_{26}N_2O_2S_2$	69,1	5,4	5,8	13,2	C	35
CH_3	C_2H_5	OC_2H_5	110—111	247 (4,20); 263 sh (4,12); 375 (4,0)	1600, 1640, 1655, 3305	59,7	7,6	5,2	10,6	$C_{14}H_{21}NO_3S$	59,3	7,5	4,8	11,3	D	69
CH_3	$CH_2C_6H_5$	OC_2H_5	153	203 (4,25); 250 sh (4,33); 270 (4,37); 378 (4,00)	1600, 1620, 1660, 3335	66,2	6,3	4,3	8,6	$C_{19}H_{23}NO_3S$	66,1	6,7	4,1	9,3	D	55
C_6H_5	C_2H_5	OC_2H_5	136—137	205 (4,09); 260 (4,23); 380 (3,81)	1600, 1660, 1690, 3340	65.7	6,6	4,4	9,5	$C_{19}H_{23}NO_3S$	66,1	6,7	4,1	9,3	D	60
C_6H_5	$CH_2C_6H_5$	OC_2H_5	159	203 (4,42); 258 (4,28); 380 (3,94)	1610, 1630, 1660, 3335	70,1	6,1	3,7	7,1	$C_{24}H_{25}NO_3S$	70,7	6,2	3,4	7,9	D	38
$C_6H_4NO_2$ (4′)	C_2H_5	OC_2H_5	130	205 (4,24); 246 (4,20); 272 sh (4,12); 375 sh (3,75)		57,8	5,6	7,1	8,0	$C_{19}H_{22}N_2O_5S$	58,4	5,7	7,2	8,2	E	75

TABLE 2. 2,6-Dimethylpyridine-3- and -3,5-carbothiolic Acid Esters (II)

R	R^1	R^3	mp, °C	IR spectrum at 1500-1800 cm^{-1}	Found, %				Empirical formula	Calc., %				Yield, %
					C	H	N	S		C	H	N	S	
H	C_2H_5	SC_2H_5	48	1540, 1590, 1670	54,3	6,0	5,1	22,4	$C_{13}H_{17}NO_2S_2$	55,1	6,0	5,0	22,6	88
H	$CH_2C_6H_5$	$SCH_2C_6H_5$	56	1550, 1595, 1670	67,8	5,2	3,5	15,3	$C_{23}H_{21}NO_2S_2$	67,8	5,2	3,4	15,7	85
C_6H_5	C_2H_5	SC_2H_5	106	1550, 1585, 1665	62,9	5,8	4,0	18,0	$C_{19}H_{21}NO_2S_2$	63,5	5,9	3,9	17,8	68
C_5H_4N (3′)	C_2H_5	SC_2H_5	107	1550, 1590, 1660	59,5	5,5	7,3	18,2	$C_{18}H_{20}N_2O_2S_2$	60,0	5,6	7,7	17,8	53
$C_6H_4NO_2$ (4′)	C_2H_5	SC_2H_5	118—119	1550, 1600, 1675	56,6	4,9	7,3	16,1	$C_{19}H_{20}N_2O_4S_2$	56,4	5,0	6,9	15,9	77
C_5H_4N (3′)	$CH_2C_6H_5$	$SCH_2C_6H_5$	104	1550, 1590, 1670	69,2	5,0	5,9	12,9	$C_{28}H_{24}N_2O_2S_2$	69,4	5,0	5,8	13,2	53
C_6H_5	C_2H_5	OC_2H_5	74	1555, 1670, 1720	65,9	6,3	4,2	8,6	$C_{19}H_{21}NO_3S$	66,4	6,2	4,1	9,3	56

TABLE 3. PMR Spectra of I in Dimethyl Sulfoxide

R	R^1	R^2	R^3	δ, ppm
H*	C_2H_5	H	SC_2H_5	1,2 (t, 6H, $2CH_3$); 2,16 (s, 6H, 2,6-CH_3); 2,87 (q, 4H, $2SCH_2$); 3,49 (s, 2H, 4-CH_2); 5,46 (s, 1H, N—H)
CH_3	C_2H_5	H	OC_2H_5	0,84 (d, 3H, 4-CH_3); 1,11 (t, 3H, SCH_3); 1,15 (t, 3H, OCH_3); 2,15 (s, 6H, 2,6-CH_3); 2,76 (q, 2H, SCH_2); 3,82 (q, 1H, 4-CH); 4,6 (q, 2H, OCH_2); 8,82 (s, 1H, N—H)
C_6H_5	C_2H_5	H	SC_2H_5	1,08 (t, 6H, $2CH_3$); 2,22 (s, 6H, 2,6-CH_3); 2,74 (q, 4H, $2SCH_2$); 5,18 (s, 1H, 4-CH); 7,11 (s, aromatic protons); 9,27 (s, 1H, N—H)
C_6H_5	C_2H_5	H	OC_2H_5	1,0 (t, 3H, SCH_3); 1,11 (t, 3H, OCH_3); 2,16 (s, 3H, 2-CH_3); 2,24 (s, 3H, 6-CH_3); 2,67 (q, 2H, SCH_2); 4,0 (q, 2H, OCH_2); 5,0 (s, 1H, 4-CH); 7,11 (s, aromatic protons); 9,04 (s, 1H, N—H)
$C_6H_4NO_2$ (4′)	C_2H_5	H	SC_2H_5	1,15 (t, 6H, $2CH_3$); 2,27 (s, 6H, 2,6-CH_3); 2,75 (q, 4H, $2SCH_2$); 5,29 (s, 1H, 4-CH); 7,38; 7,47; 7,96; 8,07 (4s, 4H, $C_6H_4NO_2$(4′)); 9,22 (s, 1H, N—H)
C_5H_4N (3′)*	C_2H_5	H	SC_2H_5	1,07 (t, 6H, $2CH_3$); 2,27 (s, 6H, 2,6-CH_3); 2,76 (q, 4H, $2SCH_2$); 5,18 (s, 1H, 4-CH); 7,33—8,31 (t, 4H, C_5H_4N(3′)); 9,4 (s, 1H, N—H)
H	$CH_2C_6H_5$	H	$SCH_2C_6H_5$	2,56 (s, 6H, 2,6-CH_3); 4,02 (s, 2H, 4-CH_2); 4,27 (s, 4H. $2SCH_2$); 7,24 (s, 10H, aromatic protons); 8,91 (s 1H, N—H)
CH_3	$CH_2C_6H_5$	H	$SCH_2C_6H_5$	0,89 (d, 3H, 4-CH_3); 2,22 (s, 6H, 2,6-CH_3); 3,78 (q, 1H, 4-CH); 4,0 (s, 4H, $2SCH_2$); 7,13 (s, 10H, aromatic protons); 9,22 (s, 1H, N—H)
C_6H_5	$CH_2C_6H_5$	H	$SCH_2C_6H_5$	2,24 (s, 6H, 2,6-CH_3); 4,02 (s, 4H, $2SCH_2$); 5,2 (s, 1H, 4-CH); 7,16 (t, 15H, aromatic protons); 9,37 (s, 1H, N—H)
CH_3	$CH_2C_6H_5$	H	OC_2H_5	0,82 (d, 3H, 4-CH_3); 1,13 (t, 3H, CH_3); 2,13 (s, 3H, 2-CH_3); 2,18 (s, 3H, 6-CH_3); 3,78 (q, 1H, 4-CH); 4,02 (q, 2H, OCH_2); 4,04 (s, 2H, SCH_2); 7,2 (s, 5H, aromatic protons); 9,56 (s, 1H, N—H)
C_6H_5	$CH_2C_6H_5$	H	OC_2H_5	1,11 (t, 3H, CH_3); 2,16 (s, 3H, 2-CH_3); 2,27 (s, 3H, 6-CH_3); 3,93 (s, 2H, SCH_2); 3,97 (q, 2H, OCH_2); 4,98 (s, 1H, 4-CH); 7,07, 7,13 (2s, aromatic protons); 10.66 (s, 1H, N—H)
H*	C_2H_5	CH_3	SC_2H_5	1,20 (t, 6H, $2CH_3$); 2,30 (s, 6H, 2,6-CH_3); 2,84 (q, 4H, $2SCH_2$); 3,09 (s, 3H, N—CH_3); 3,31 (s, 2H, 4-CH_2)
CH_3	C_2H_5	CH_3	SC_2H_5	0,83 (d, 3H, 4-CH_3), 1,18 (t, 6H, $2CH_3$); 2,28 (s, 6H, 2,6-CH_3); 2,80 (q, 4H, $2SCH_2$); 3,08 (s, 3H, N—CH_3); 4,03 (q, 1H, 4-CH)
C_6H_5	C_2H_5	CH_3	SC_2H_5	1,09 (t, 6H, $2CH_3$); 2,38 (s, 6H, 2,6-CH_3); 2,80 (q, 4H, $2SCH_2$); 3,13 (s, 3H, N—CH_3); 3,98 (s, 1H, 4-CH); 7,07 (s, 5H, aromatic protons)
$C_6H_4NO_2$ (4′)	C_2H_5	CH_3	SC_2H_5	1,11 (t, 6H, $2CH_3$); 2,36 (s, 6H, 2,6-CH_3); 2,82 (q, 4H, $2SCH_2$); 3,13 (s, 3H, N—CH_3), 5,38 (s, 1H, 4-CH); 7,24; 7,36; 7,96; 8,07 (4s, 4H, $C_6H_4NO_2$(4′)
H	$CH_2C_6H_5$	CH_3	$SCH_2C_6H_5$	2,31 (s, 6H, 2,6-CH_3); 3,11 (s, 3H, N—CH_3); 3,20 (s, 2H, 4-CH_2); 4,02 (s, 4H, $2SCH_2$); 7,18 (s, 10H, aromatic protons)

*These spectra were obtained from solutions in deuterochloroform.

the oxygen-containing analogs [6, 7], which indicates stronger conjugation between the alkylthiocarbonyl substituent and the β-aminovinyl system than in the case of oxygen esters.

The effect of the substituents in the 1 and 4 positions follows the same principles as in the 2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridine series [8]; replacement of the hydrogen atom attached to the nitrogen atom by an alkyl group gives rise to a 20-25 nm hypsochromic shift of the long-wave maximum.

For I (R^2 = H, alkyl, Tables 1 and 6) one observes a decrease in the high-frequency absorption bands in the IR spectra of, on the average, 40-50 cm^{-1} as compared with the oxygen-

containing esters [6]; this is similar to the acylthiol esters of the aliphatic and aromatic series [9-11]. The oxidized forms — pyridines of the II type — are characterized by higher values (10-15 cm^{-1}) of the high-frequency absorption bands (Table 2) than the corresponding dihydropyridines I. A second absorption band in the double bond region also appears in the case of I that are unsymmetrically substituted in the 3 and 5 positions ($R^1 = C_2H_5$, $CH_2C_6H_5$, $R^3 = OC_2H_5$) (Table 1); however, a band at 1680-1690 cm^{-1}, which can be assigned primarily to the ethoxycarbonyl substituent, is observed only when $R = C_6H_5$.

The PMR spectra of I are in agreement with structure I with respect to the chemical shifts and integral intensities of the signals (Table 3).

To establish the character of the electronic effect of alkylthiocarbonyl substituents in the investigated β-aminovinylcarbonyl grouping of the 1,4-dihydropyridine system we determined the electrochemical oxidation potentials of I (Table 4). It is known that 1,4-dihydropyridines are oxidized more easily when less effective electron-acceptor β substituents are present [12]. Replacement of one oxygen atom of the alkoxy group in the ester residue by a sulfur atom leads to a 30-40 mV increase in the electrolytic oxidation potential, whereas the introduction of sulfur atoms in place of oxygen in both ester groups leads to doubling of the effect. This confirms the more strongly expressed overall electron-acceptor effect of alkylthiocarbonyl groups than that of alkoxycarbonyl substituents. The same conclusion also follows from a determination of the rate constants for oxidation of I ($R = R^2 = H$, $R^1 = C_2H_5$, $R^3 = SC_2H_5$; $R^1 = CH_2C_6H_5$, $R^3 = SCH_2C_6H_5$) with chloranil in benzene, which are 60 and 33 K units$\cdot 10^2$ (liters-$mole^{-1}$/sec^{-1}), while the corresponding oxygen-containing esters have oxidation rate constants that are greater by a factor of ~10 (450 and 320, respectively) [13].

The introduction of a methyl or phenyl group in the 4 position of sulfur-containing esters I leads to the same increase in the electrochemical oxidation potentials as in the case of esters of the oxygen series [12, 14] (70-100 and 150-190 mV, respectively).

It was established by a study of the reactivities of esters I that they, like oxygen-containing esters [15], undergo transesterification when they are heated with alkanols in the presence of a basic catalyst (OH^-, $OAlk^-$). In the case of unsymmetrically substituted I ($R^1 = C_2H_5$, $CH_2C_6H_5$, $R^3 = OC_2H_5$) only the S-substituted ester substituent undergoes alcoholysis under certain conditions (depending on the amount of catalyst and the experimental time); this confirms that it is more reactive in transesterification. The reaction takes place faster and gives the products in higher yields in the case of 4-unsubstituted esters I ($R = R^2 = H$) (Table 5).

Compounds I ($R^2 = H$) are alkylated at the nitrogen atom by heating with alkyl halides in acetonitrile in the presence of alkali, whereas the oxygen-containing esters of the 1,4-dihydropyrimidine series, inasmuch as they are weak heterocyclic N—H acids, are alkylated only when sodium hydride is used as the basic agent [8]. 4-Substituted 1,4-dihydropyridines are the most reactive compounds in alkylation (Table 6).

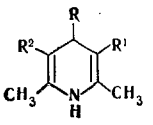
EXPERIMENTAL

The IR spectra of mineral oil or hexachlorobutadiene suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of $4 \cdot 10^{-5}$ M solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Bruker WH-90/DS spectrometer. The electrochemical oxidation potentials were determined by a previously described method with an LP-60 recording polarograph with acetonitrile as the solvent and a rotating platinum microelectrode [16]. The rate constants for oxidation with chloranil in benzene at 37°C were determined spectrophotometrically from the disappearance of the long-wave absorption maximum at 418 nm by the method in [13].

2,6-Dimethyl-3,5-bis(ethylthiocarbonyl)-1,4-dihydropyridine. A) A mixture of 2.92 g (0.02 mole) of thioacetoacetic acid S-ethyl ester, 1.38 g (0.06 mole) of urotropin, 0.7 g of ammonium acetate, and 10 ml of dioxane was refluxed for 15 min, after which it was diluted with water and allowed to stand at 0°C for 12 h. The resulting yellow precipitate was separated and crystallized from acetonitrile. The characteristics of the synthesized compounds are presented in Table 1.

2,4,6-Trimethyl-3,5-bis(ethylthiocarbonyl)-1,4-dihydropyridine. B) A mixture of 2.92 g (0.02 mole) of thioacetoacetic acid S-ethyl ester, 0.92 g (0.015 mole) of 1-aminoethanol, and 10 ml of dioxane was refluxed for 1 h, after which it was poured into water, and the resulting yellow oil was extracted with ether. The extract was dried with anhydrous sodium sulfate,

TABLE 4. Peak and Half-Wave Potentials in the Electrochemical Oxidation of Esters of Derivatives of the 1,4-Dihydropyridine Series*



R	R¹	R²	E_n, V	$E_{1/2}$, V
H	$COSC_2H_5$	$COSC_2H_5$	1,06	0,97
CH_3	$COSC_2H_5$	$COSC_2H_5$	1,12	1,08
C_6H_5	$COSC_2H_5$	$COSC_2H_5$	1,18	1,10
$C_6H_4NO_2$ (4′)	$COSC_2H_5$	$COSC_2H_5$	1,28	1,20
CH_3	$COOC_2H_5$	$COSC_2H_5$	1,08	1,06
C_6H_5	$COOC_2H_5$	$COSC_2H_5$	1,15	1,10
$C_6H_4NO_2$ (4′)	$COOC_2H_5$	$COSC_2H_5$	1,25	1,18
H	$COOC_2H_5$	$COOC_2H_5$	0,97	0,89
CH_3	$COOC_2H_5$	$COOC_2H_5$	1,04	0,96
C_6H_5	$COOC_2H_5$	$COOC_2H_5$	1,12	1,08
$C_6H_4NO_2$ (4′)	$COOC_2H_5$	$COOC_2H_5$	1,22	1,18
H	$COSCH_2C_6H_5$	$COSCH_2C_6H_5$	1,02	0,93
C_6H_5	$COSCH_2C_6H_5$	$COSCH_2C_6H_5$	1,20	1,11
H	$COOCH_2C_6H_5$	$COOCH_2C_6H_5$	0,97	0,85
C_6H_5	$COOCH_2C_6H_5$	$COOCH_2C_6H_5$	1,16	1,06
C_6H_5	$COSCH_2C_6H_5$	$COOC_2H_5$	1,20	1,10
CH_3	$COSCH_2C_6H_5$	$COOC_2H_5$	1,16	1,06

*The experimentally found peak and half-wave potentials in the electrochemical oxidation of some oxygen-containing esters differ somewhat from those presented in [12, 14].

the ether was removed, and the residue was purified by chromatography with a column filled with Al_2O_3 [elution with chloroform–hexane–acetone (9:7:1)]. The solvent was removed, and the residue was crystallized from acetonitrile–water. The characteristics of the synthesized compounds are presented in Table 1.

2,6-Dimethyl-3,5-bis(ethylthiocarbonyl)-4-phenyl-1,4-dihydropyridine. C) A mixture of 4.38 g (0.03 mole) of thioacetoacetic S-ethyl ester, 1.52 g (0.015 mole) of benzaldehyde, 1.5 ml of 25% ammonium hydroxide, and 10 ml of dioxane was refluxed for 6 h, after which it was poured into water, and the liberated yellow oil was purified by chromatography as in method B. The characteristics of the synthesized compounds are presented in Table 1.

2,4,6-Trimethyl-3-ethoxycarbonyl-5-(ethylthiocarbonyl)-1,4-dihydropyridine. D) A mixture of 2.98 g (0.02 mole) of β-aminothiocrotonic acid S-ethyl ester,* 3.12 (0.02 mole) of α-ethylideneacetoacetic ester,† and 10 ml of dioxane was refluxed for 1 h, after which it was diluted with water and cooled at 0°C for 12 h to give a yellowish substance, which was crystallized from methanol–hexane. The characteristics of the synthesized compounds are presented in Table 1.

2,6-Dimethyl-3,5-bis(ethylthiocarbonyl)-4-(p-nitrophenyl)-1,4-dihydropyridine. E) A mixture of 1.35 g (0.005 mole) of α-(p-nitrobenzylidene)-acetoacetic acid S-ethyl ester, 0.76 g (0.005 mole) of β-aminothiocrotonic acid S-ethyl ester, and 5 ml of absolute ethanol was refluxed for 2 h, after which it was diluted with water and cooled at 0°C for 12 h. The yellow precipitate was crystallized from ethanol. The characteristics of the synthesized compounds are presented in Table 1.

β-Aminothiocrotonic Acid S-Ethyl Ester. A solution of 14.6 g (0.1 mole) of thioacetoacetic acid S-ethyl ester in 20 ml of dry benzene was saturated with dry ammonia at 0°C in the course of 30 min, after which it was allowed to stand at room temperature for 24 h. It was then washed with water and dried with anhydrous sodium sulfate. The solvent was removed by distillation *in vacuo*, and the residue was crystallized from benzene–hexane to give 5.1 g (35%) of a white substance with mp 89°C. PMR spectrum: 1.07 (t, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.67 (q, 2H, SCH_2), 4.71 (s, 1H, CH=), 7.36 (s, 1H, NH), and 8.24 ppm (s, 1H, NH). Found:

*The β-aminocrotonic acid esters were obtained by the method in [17].
†The ylideneacetoacetic esters were obtained by the method in [18].

TABLE 5. Transesterification of 2,6-Dimethyl-1,4-dihydropyridine-3- and -3,5-carbothiolic Acid Esters I (R^2 = H)

Starting compound	Starting ester: potassium hydroxide	Reagent	Reaction time, h	Reaction product	Yield, %	Characteristics of the reaction product
I, $R=R^2=H$, $R^1=C_2H_5$, $R^3=SC_2H_5$	1 : 2	C_2H_5OH	4	2,6-Dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine [17]	68	
I, $R=R^2=H$, $R^1=C_2H_5$, $R^3=SC_2H_5$	1 : 2	*iso*-C_4H_9OH	1	2,6-Dimethyl-3,5-diisobutoxycarbonyl-1,4-dihydropyridine [6]	35	
I, $R=CH_3$, $R^1=CH_2C_6H_5$, $R^2=H$, $R^3=OC_2H_5$	1 : 1	C_2H_5OH	8	2,6-Dimethyl-4-methyl-3,5-diethoxycarbonyl-1,4-dihydropyridine [18]	90	
I, $R=C_6H_5$, $R^1=CH_2C_6H_5$, $R^2=H$, $R^3=OC_2H_5$	1 : 1	C_2H_5OH	18	2,6-Dimethyl-4-phenyl-3,5-diethoxycarbonyl-1,4-dihydropyridine [18]	50	
I, $R=C_6H_5$, $R^1=C_2H_5$, $R^2=H$, $R^3=OC_2H_5$	1 : 2	C_2H_5OH	12	2,6-Dimethyl-4-phenyl-3,5-diethoxycarbonyl-1,4-dihydropyridine [18]	70	
I, $R=CH_3$, $R^1=C_2H_5$, $R^2=H$, $R^3=OC_2H_5$	1 : 1	*iso*-C_3H_7OH	6	2,4,6-Trimethyl-3-ethoxycarbonyl-5-isopropoxycarbonyl-1,4-dihydropyridine	54	mp. 104—105°. Found: C 54,5; H 8,0; N 5,0%. $C_{15}H_{23}NO_4$. Calculated: C 54,0; H 8,2; N 5,0%. PMR spectrum in DMSO: 0,76 (d, 3H, 4-CH_3); 1,13 (m, 9H, $3CH_3$); 2,11 (s, 6H, 2,6-CH_3); 3,58 (q, 1H, 4-CH); 4,0 (q, 2H, OCH_2); 4,82 (m, 1H, OCH); 8,49 ppm (s, 1H, NH)
I, $R=CH_3$, $R^1=CH_2C_6H_5$, $R^2=H$, $R^3=OC_2H_5$	1 : 1	CH_3OH	21	2,4,6-Trimethyl-3-ethoxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine	80	mp. 134°. Found: C 61,9; H 7,4; N 5,6%. $C_{13}H_{19}NO_4$. Calculated: C 61,6; H 7,6; N 5,5%. PMR spectrum in DMSO: 0,84 (d, 3H, 4-CH_3); 1,12 (t, 3H, CH_3); 2,20 (s, 6H, 2,6-CH_3); 3,51 (s, 3H, OCH_3); 3,90 (q, 1H, 4-CH); 4,00 (q, 2H, OCH_2); 8,30 ppm, (s, 1H, NH)
I, $R=C_6H_5$, $R^1=C_2H_5$, $R^2=H$, $R^3=OC_2H_5$	1 : 1	CH_3OH	10	2,6-Dimethyl-3-ethoxycarbonyl-5-methoxycarbonyl-4-phenyl-1,4-dihydropyridine	62	mp. 157—158°. Found: C 68,9; H 6,7; N 4,2%. $C_{18}H_{21}NO_4$. Calculated: C 68,6; H 6,7; N 4,4%. UV spectrum, λ_{max}, 206, 242, 362 nm. PMR spectrum in DMSO—CCl_4, 1 : 2): 1,11 (t, 3H, CH_3); 2,18 (s, 6H, 2,6-CH_3); 3,49 (s, 3H, OCH_3); 3,93 (q, 2H, OCH_2); 4,73 (s, 1H, 4CH); 7,02 (s, aromatic protons); 8.40 ppm (s, 1H, NH)
I, $R=C_6H_5$, $R^1=CH_2C_6H_5$, $R^2=H$, $R^3=OC_2H_5$	1 : 1	CH_3OH	24	The same	75	

TABLE 6. 1-Alkyl-2,6-dimethyl-1,4-dihydropyridine-3- and -3,5-carbothiolic Acid Esters (I, R^2 = Alkyl)

R	R^1	R^2	R^3	Reaction time, h	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum at 1500-1800 cm^{-1}	Found, %				Empirical formula	Calc., %				Yield, %
								C	H	N	S		C	H	N	S	
H	C_2H_5	CH_3	SC_2H_5	18	136	287 (4,23); 394 (3,83)	1550, 1600, 1650	56,2	7,0	4,5	21,5	$C_{14}H_{21}NO_2S_2$	56,2	7,1	4,7	21,4	80
H	C_2H_5	C_2H_5	SC_2H_5	18	104—105	287 (4,30); 395 (3,88)	1545, 1600, 1650	57,7	7,3	4,3	20,0	$C_{15}H_{23}NO_2S_2$	57,5	7,4	4,5	20,5	49
$C_6H_4NO_2$ (4′)	C_2H_5	CH_3	SC_2H_5	2	164—165	203 (4,25); 282 (4,30); 378 (3,79)	1550, 1600, 1650	57,2	5,8	6,6	15,0	$C_{20}H_{21}N_2O_4S_2$	57,1	5,8	6,7	15,3	61
H	$CH_2C_6H_5$	CH_3	$SCH_2C_6H_5$	18	108—109	205 (4,40); 287 (4,38); 397 (3,97)	1550, 1600, 1650	67,7	6,1	3,1	14,9	$C_{24}H_{25}NO_2S_2$	68,1	6,0	3,3	15,1	50
H	$CH_2C_6H_5$	C_2H_5	$SCH_2C_6H_5$	18	97	203 (4,40); 288 (4,34); 397 (3,91)	1540, 1590, 1650	68,3	6,1	3,3	14,2	$C_{25}H_{27}NO_2S_2$	68,6	6,2	3,2	14,7	46
C_6H_5	C_2H_5	CH_3	SC_2H_5	1	180	203 (4,42); 284 (4,25); 376 (4,0)	1540, 1610, 1645	64,0	6,8	3,5	16,7	$C_{20}H_{25}NO_2S_2$	64,0	6,7	3,7	17,1	65
CH_3	C_2H_5	CH_3	SC_2H_5	6	118—119	260 sh. (4,13); 287 (4,33); 385 (4,02)	1550, 1600, 1640	57,5	7,5	4,7	19,9	$C_{15}H_{24}NO_2S_2$	57,3	7,7	4,5	20,4	81
CH_3	$CH_2C_6H_5$	CH_3	$SCH_2C_6H_5$	6	160—161	205 (4,34); 262 sh. (4,11); 288 (4,28); 390 (3,96)	1540, 1600, 1645	68,4	6,1	3,0	14,4	$C_{25}H_{27}NO_2S_2$	68,6	6,2	3,2	14,7	75

C 49.4; H 7.4; N 9.9; S 21.7%. $C_6H_{11}NOS$. Calculated: C 49.6; H 7.6; N 9.7; S 22.1%.

α-(p-Nitrobenzylidene)-S-ethyl Thioacetoacetate. A 5.8-g (0.04 mole) sample of S-ethyl thioacetoacetate and two drops of piperidine were added to a solution of 6.04 g (0.04 mole) of p-nitrobenzaldehyde in 10 ml of ethanol, and the mixture was allowed to stand at room temperature for 3 days. The precipitated substance was separated and crystallized from ethanol–hexane to give 3.9 g (36%) of a colorless substance with mp 110°C. PMR spectrum: 1.13 (t, 3H, CH_3), 2.27 (s, 3H, CH_3CO), 2.89 (q, 2H, SCH_2), 7.56-7.78 and 8.09-8.31 (m, aromatic protons), and 7.87 ppm (s, 1H, CH=). Found: C 55.6; H 4.9; N 4.9; S 11.2%. $C_{13}H_{13}NO_4S$. Calculated: C 55.9; H 4.7; N 5.0; S 11.5%.

1,2,6-Trimethyl-3,5-bis(ethylthiocarbonyl)-1,4-dihydropyridine. A 0.56-g (0.01 mole) sample of powdered potassium hydroxide was added to a solution of 1.43 g (0.005 mole) of 2,6-dimethyl-3,5-bis(ethylthiocarbonyl)-1,4-dihydropyridine in 20 ml of acetonitrile, and the mixture was heated on a water bath for 5 min. A 2.13-g (0.015 mole) sample of methyl iodide was added, and the mixture was refluxed on a water bath for 6 h. The same amounts of potassium hydroxide and methyl iodide were added, and the mixture was refluxed for 12 h. The solvent was evaporated *in vacuo*, and the residue was diluted with water. The insoluble precipitate was separated and crystallized from acetonitrile. The characteristics of the synthesized substances are presented in Table 6.

2,6-Dimethyl-3,5-bis(ethylthiocarbonyl)pyridine. A suspension of 1.43 g (0.005 mole) of 2,6-dimethyl-3,5-bis(ethylthiocarbonyl)-1,4-dihydropyridine in 5 ml of 6 N nitric acid was heated to 60°C for 5 min, after which it was cooled, and the resulting precipitate was separated and crystallized from hexane–ethanol. The characteristics of the synthesized compounds are presented in Table 2.

2,4,6-Trimethyl-3,5-bis(β-phenylthioethoxycarbonyl)-1,4-dihydropyridine (III, X = SC_6H_5). A 1.3-g (0.01 mole) sample of sodium thiophenoxide was added to a solution of 1.7 g (0.005 mole) of the dichloride prepared in [5] in a mixture of 5 ml of ethanol and 1 ml of dimethylformamide (DMF), and the mixture was refluxed for 3 h. The light-yellow solution was poured into 20 ml of water, and the liberated oil was extracted with ether. The extract was dried with anhydrous calcium chloride, the solvent was removed by distillation, and the residue was crystallized from aqueous ethanol to give 0.2 g (8.3%) of a light-yellow substance with mp 83°C. UV spectrum (in ethanol), λ_{max} (log ε): 203 (4.56), 239 (4.39), 257 (4.38), and 359 nm (3.90). Found: C 64.2; H 6.1; N 2.8; S 13.3%. $C_{26}H_{29}NO_4S_2$. Calculated: C 64.6; H 6.0; N 2.9; S 13.3%.

2,4,6-Trimethyl-3-ethoxycarbonyl-5-(β-phenylthioethoxycarbonyl)-1,4-dihydropyridine (III, X = H). As in the preceding experiment, the reaction with the monochloride [5] gave a light-yellow substance with mp 86°C (from dilute ethanol) in 27% yield. UV spectrum λ_{max} (log ε): 203 (4.30), 236 (4.33), 257 (4.34), and 360 nm (3.88). Found: C 64.0; H 6.7; N 3.5; S 8.2%. $C_{20}H_{25}NO_4S$. Calculated: C 64.0; H 6.7; N 3.7; S 8.5%.

Transesterification of 2,6-Dimethyl-3,5-bis(alkylthiocarbonyl)-1,4-dihydropyridines. A 1.12-g (0.02 mole) sample of finely ground potassium hydroxide was added to a solution of 2.85 g (0.01 mole) of 2,6-dimethyl-3,5-bis(ethylthiocarbonyl)-1,4-dihydropyridine in 5 ml of ethanol, and the mixture was refluxed for 4 h. The solvent was removed by distillation, the residue was treated with water, and the solid material was removed by filtration and crystallized from ethanol to give a light-yellow substance, the properties and physicochemical characteristics of which were in agreement with those described in the literature for 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine [19].

Transesterification of 2,6-Dimethyl-3-(alkylthiocarbonyl)-5-ethoxy-carbonyl-1,4-dihydropyridines. A 0.28-g (0.005 mole) sample of powdered potassium hydroxide was added to a solution of 2.03 g (0.005 mole) of 2,6-dimethyl-3-(benzylthiocarbonyl)-5-ethoxycarbonyl-1,4-dihydropyridine in 5 ml of methanol, and the mixture was refluxed for 16 h. It was then worked up as in the preceding experiment. The properties of the substances are presented in Table 5.

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