1,4-DIHYDROPYRIDINE-3,5-DICARBOTHIONIC ACID S-ESTERS

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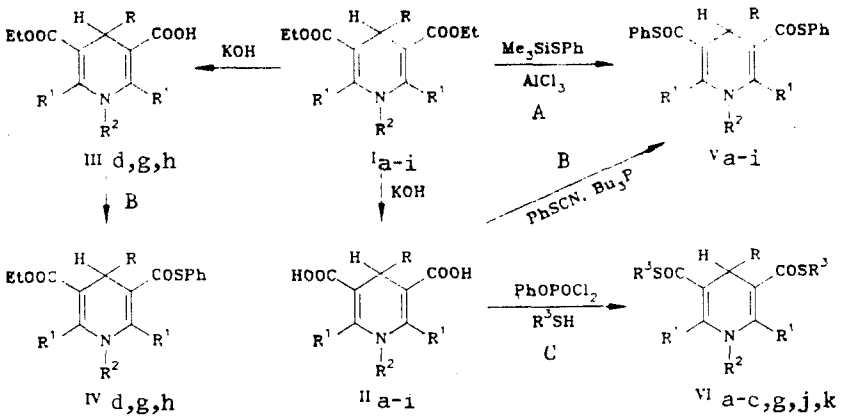
Procedures have been developed for the synthesis of 1,4-dihydropyridine-3,5-dicarbothionic acid S-esters via the direct thiolysis of 1,4-dihydropyridine-3,5-dicarboxylic acids and their ester derivatives. The use of different acid activating agents and thiolysis agents is discussed.

We have recently prepared 2,6-dimethyl-1,4-dihydropyridine-3- and 3,5-dicarbothionic acid S-alkyl ester derivatives, which exhibit high biological activity and unique, inherent chemical reactivity [2, 3], via condensation reactions of acetothioacetate S-esters [1].

Our goal in the present paper was to study the thiolysis of 1,4-dihydropyridine-3,5-dicarboxylic acids (IIa-i), their diesters (Ia-i), and monoacid esters (IIId, g, h), in order to develop new methods for the synthesis of a new class of 1,4-dihydropyridines (1,4-DHP), namely 2,6-unsubstituted 1,4-dihydropyridine-3-mono- (IVd g, h) and 3,5-dicarbothionic acid S-esters (Va-i VIa-c, g, j, k). In contrast to their 2,6-dimethyl-substitute analogs, S-esters V and VI are not accessible via Hantzch synthesis reactions, since the corresponding thiopropiolate S-alkyl (S-aryl) esters required for the synthesis are not known. Our attempts to prepare the latter synthons via thiolysis of propiolic acid with thiols in the presence of phenyl dichlorophosphate [4] or dicyclohexylcarbodiimide [5] as acid activating agents led only to addition of the mercaptan to the triple bond in propiolic acid.

A variety of methods are known for the thiolysis of carboxylic acid esters using trimethylsilyl sulfides [6] and aluminum, boron [7], or dimethylaluminum thiophenolates [8] as thiolating agents. We have selected for study trimethyl(phenylthio)silane [6], which is commercially available and undergoes reactions with 1,4-DHP-3,5-dicarboxylic acid esters (Ia, b, d, e) in the presence of aluminum chloride (see Scheme, method A):

Scheme



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The reaction course depends on the structure of the 1,4-DHP substrate; in the case of 1,2,6-unsubstituted 1,4-DHP (Ia, b) the yield is 30%; introduction of a substituent at the nitrogen atom (Id, e) increases the yields of S-phenyl esters to 60%. In contrast, however, 2,6-dimethyl 1,4-DHP derivatives (Ih, i), regardless of the presence of a substituent at the nitrogen atom, do not undergo thiolysis in this reaction, apparently due to steric hindrance blocking approach of the reagent.

Although esters are used in the synthesis of thiol esters, carboxylic acids are generally more widely used; the latter undergo reaction with thiols in the presence of acid activating agents (YX). The role of the activating agent YX involves replacement of the carboxylic hydrogen atom by group Y to form new, intermediate activated ester derivatives in which the new OY functional group represents a more active leaving group than hydroxyl, and is thus easily displaced by an alkyl (aryl)mercapto group.

$$RCOOH \xrightarrow{YX} [\ RCOOY + HX\ ] \xrightarrow{R^1SH} RCOSR^1$$

The most widely used activating agents at the present time are a variety of (alkyl-, aryl)chlorophosphates [4, 9], 4-dimethyl-3-butyn-2-one [10], 1-acylimidazoles [11], and tributylphosphine [12]. Also, in addition to thiols, the following types of compounds also undergo thiolysis reactions: methyl thiolates [9, 10], disulfides [13], and phenyl thiocyanate [12].

4-Aryl-1,4-DHP-3,5-dicarboxylic (IIa-i) and 5-alkoxycarbonyl-3-carboxylic acids (IIId, g, h) undergo facile thiolation by phenyl thiocyanate in the presence of an equimolar amount of tributylphosphine (Scheme, method B). This reaction is carried out at room temperature in dry methylene chloride solvent under an argon atmosphere. The reaction course can be monitored by TLC. In the majority of cases the S-ester products can be isolated by preparative TLC. In the case of N-substituted 1,4-DHP derivatives (IIe-i) the yields of S-phenyl esters are as high as 80%, while the yields of S-esters from N-unsubstituted substrates (IIa-c) are around 50%. According to TLC analysis, the reaction mixture in these reactions contains the acid starting material, is oxidized form, and monothiolate ester. The reduced yield of S-phenyl esters from N-unsubstituted dicarboxylic acids (Va-c) is apparently due to limited solubility of the acid starting materials in methylene chloride. Substitution at the nitrogen atom significantly improves the solubility of 1,4-DHP-3,5-dicarboxylic acids. It should also be noted in this regard that N-substituted 2,6-dimethyl-1,4-DHP dicarboxylic acids (IIh, i) and monocarboxylic acid IIIh also undergo thiolysis in the presence of phenyl thiocyanate, but the yields are lower than for the corresponding 2,6-unsubstituted 1,4-DHP derivatives (IId-g). N-Unsubstituted 2,6-dimethyl-1,4-DHP-3,5-dicarboxylic acids are not available to undergo this type of thiolysis reaction, since the corresponding esters are unreactive to basic hydrolysis without concomitant destruction of the 1,4-DHP ring; this can be attributed to steric shielding of the ester carbonyl groups in these compounds by substituents in the 2-, 4-, and 6-positions [14, 15].

Use of ethyl thiocyanate in place of phenyl thiocyanate in the above reaction did not lead to the formation of S-ethyl esters VIa-c, i.e., this method seems to be limited exclusively to the introduction of a (phenylthio)carbonyl group in 1,4-DHP.

A more general method for the synthesis of thiol ester derivatives of 1,4-DHP-dicarboxylic acids involves direct thiolysis of the corresponding acids by mercaptans in absolute dimethoxyethane in the presence of phenyl dichlorophosphate as acid activating agent (cf. Scheme, method C). The yield of 1,4-DHP-3,5-dicarbothionic acid S-esters VIa-c, g, j depends on the nature of the thiol used; in the case of thiophenol, for instance, the yield of Va using method C is 74%, while in the case of ethanethiol as the thiolating agent the yields of S-ethyl esters are lower (Table 1).

In contrast to 4-aryl 1,4-DHP derivatives II, 1,4-DHP-3,5-dicarboxylic acid, which is unsubstituted in the r-position, does not undergo thiolysis reactions with mercaptans in the presence of phenyl dichlorophosphate, due to its low stability and easy oxidizability. 3,5-Di(ethylthiocarbonyl)-1,4-DHP (VII) can be obtained in almost quantitative yield, however, by reduction of 3,5-di(ethylthiocarbonyl)-pyridine (VIII) by sodium cyanoborohydride in acetic acid:

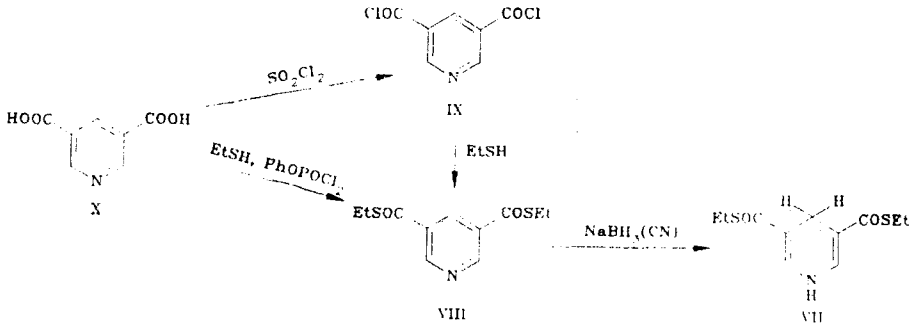

TABLE 1. Physical Characteristics of Newly Synthesized Compounds

Compound	Molecular formula	mp, °C	Long-wavelength absorption, λ max, nm (log ε)	IR spectrum, cm^{-1}	PMR spectrum, ppm (DMSO–D_6)						Yield, %		
					CH_2CH_3, t	CH_2CH_3	4-H, s	2-H, 6-H (CH_3)	N–H (CH_3)	arom. protons, m	method A	method B	method C
IVd	$C_{22}H_{21}NO_3S$	131...133	402 (3,97)	1650, 1700	1,11	3,98g	4,78	7,64s	3,38s	7,13...7,31		53	
IVg	$C_{27}H_{23}NO_3S$	144	393 (4,10)	1600, 1660, 1670, 1710	1,11	4,02g	4,89	7,84s	—	7,20...7,60		55	
IVh	$C_{29}H_{27}NO_3S$	146	368 (4,13)	1600, 1620, 1660, 1700	1,22	4,16g	5,31	(1,93s	—	7,24...7,47		77	
Va	$C_{25}H_{19}NO_2S_2$	208...210	402 (4,01)	1620, 1640, 1670, 3320	—	—	4,93	7,78d	9,73t	7,16...7,44	30	37	74
Vb	$C_{26}H_{21}NO_3S_2$	173	382 (3,94)	1610, 1640, 1665, 3300	—	—	4,82	7,61d	9,64t	3,42 *; 6,67...7,40	25	39	
Vc	$C_{26}H_{19}F_2NO_3S_2$	181	408 (3,98)	1600, 1630, 1650, 1670, 3280	—	—	5,16	7,71d	9,69t	6,93...7,40**		39	
Vd	$C_{26}H_{21}NO_2S_2$	158	418 (4,14)	1650, 1670	—	—	4,89	7,67s	(3,47s)	7,13...7,31	51	77	
Ve	$C_{27}H_{23}NO_3S_2$	168	420 (4,14)	1610, 1645, 1675	—	—	4,80	7,60 s	(3,64s)	3,31 *; 6,67...7,42	47	72	
Vf	$C_{27}H_{21}F_2NO_3S_2$	146	420 (4,18)	1640, 1660	—	—	5,13	7,67s	(3,47s)	7,00...7,40**		83	
Vg	$C_{31}H_{23}NO_2S_2$	203	409 (4,14)	1600, 1650, 1670	—	—	5,00	7,89 s	—	7,22...7,58		76	
Vh	$C_{33}H_{27}NO_2S_2$	147	390 (4,15)	1640, 1660, 1675	—	—	6,09***	1,98s	—	7,00...7,44		63	
Vi	$C_{34}H_{29}NO_3S_2$	168	378 (4,16)	1620, 1660, 1670	—	—	5,51***	1,96s	—	3,76s *; 7,02...7,38		50	
VIa	$C_{17}H_{19}NO_2S_2$	149	395 (4,00)	1620, 1640, 1660, 1680, 3300	1,11	2,80g	4,98	7,51d	9,42t	7,16			47
VIb	$C_{18}H_{21}NO_3S_2$	97	400 (3,95)	1620, 1635, 1660, 1680, 3300	1,11	2,78g	4,89	7,42d	9,42t	3,67s *; 7,07...7,67			30
VIc	$C_{18}H_{18}F_2NO_3S_2$	165	395 (4,10)	1615, 1650, 1665, 1675, 3280	1,11	2,80g	4,93	7,49d	9,47t	7,00...7,44**			55
VIg	$C_{23}H_{23}NO_2S_2$	158...160	412 (4,05)	1600, 1660, 1675	1,13	2,84g	4,93	7,71s	—	7,24...7,60			65
VIg	$C_{27}H_{23}NO_2S_2$	127	402 (4,02)	1630, 1660, 3280	—	4,09s	5,18	—	6,27t	7,20			41
VIh	$C_{28}H_{25}NO_3S_2$	136	404 (4,13)	1610, 1640, 1660, 3200	—	4,07s	4,93	7,49d	9,49t	6,70...7,20			39
VII	$C_{11}H_{15}NO_2S_2$	132	420 (4,15)	1600, 1660, 3300	1,18	2,87g	3,20	7,22d	9,00t	—		85	
VIII	$C_{11}H_{13}NO_2S_2$	Oil	—	—	—	—	—	—	—	—			84

*4-OCH_3 group proton signals.

**The 2-F_2CHO group proton signal appears in the form of a triplet at 7.00 ppm, J = 72 Hz.

***The PMR spectrum was recorded in $CDCl_3$ solvent.

The pyridine starting material in this reaction was synthesized by thiolysis of either the corresponding chloroanhydride IX, or pyridine-3,5-dicarboxylic acid X by ethanethiol. The latter method is preferred, since it obviates the need for a separate step, isolation of the chloroanhydride (acyl chloride) IX.

The UV spectra of compounds IV-VI are characteristic of monocyclic 1,4-DHP, with three absorption bands (205, 270-280, and 370-420 nm). The medium- and long-wavelength absorption bands are shifted bathochromically by 30-40 nm, relative to their corresponding ethoxycarbonyl derivatives I [16, 17]; this suggests the presence of greater conjugative interaction between (ethylthio, phenylthio)carbonyl substituents and the β-aminovinyl system. The absorption band maxima in the visible region of the spectrum are listed in Table 1; this region reflects more accurately structural changes in 1,4-DHP derivatives, whereas the UV absorption region is less informative in this regard. In contrast to the behavior of 2,6-dimethyl-1,4-DHP derivatives, in which introduction of alkyl or aryl substituents at the nitrogen atom exerts a hypsochromic shift, introduction of an N-substituent to 2,6-substituted 1,4-DHP compounds results in a bathochromic shift of the long-wavelength absorption maximum (cf. Table 1), which is consistent with the general principles governing the effect of alkyl substituents in the 1-position [17]. Addition of methyl groups in the 2- and 6-positions in both 1,5-DHP I and in 3,5-di(ethylthiocarbonyl)-1,4-DHP VIa-c leads to a hypsochromic shift in the long-wavelength absorption maximum; the numerical value of the resulting shift is independent of the steric bulk of the β-substituent, which indicates that the methyl groups exert primarily an electronic effect.

The IR spectra of compounds Va-i and VIa-c, g, j in the region of double bond absorption exhibit two characteristic maxima at 1660 and 1600 cm^{-1}; these are approximately equal in intensity and are assigned to ring $>C{=}{=}C<$ vibrations. In the case of compounds VIa-c, g, j and VII the frequencies of the higher frequency band is reduced by 30-40cm^{-1} on average compared to their oxygen-containing ester analogs [18], which is analogous to the behavior observed for thiol ester derivatives in the aliphatic series [19]. Addition of S-phenyl groups in 1,4-DHP Va-i leads to an additional reduction in the position of the high-frequency absorption band, by 10-15 cm^{-1}.

The PMR spectra of compounds VIa-c indicate that the $C_{(4)}$ proton signal is shifted upfield by 0.20 ppm relative to 4-aryl-2,6-dimethyl-3,5-di(ethylthiocarbonyl)-1,4-DHP [1]. It should be noted also in this regard that the magnitude of this shift in 4-arylsubstituted 2,6-dimethyl-1,4-DHP depends primarily on the volume of the β-substituent. The absence of 2,6-methyl groups in compound VII, which is unsubstituted in the 4-position, does not result in a corresponding shift in the signal of this proton (about 0.20 and 0.40 ppm, respectively) relative to their 2,6-dimethyl analogs [1]. Introduction of a phenylthiocarbonyl substituent in the 3- and 5-positions also exerts an additional weak field shift in the NH group proton (~0.75 ppm).

Compound VIa-c and VII appear to be stronger NH acids than derivatives Ia-c: they are completely dissociated, for example, in 0.1 M KOH solution in 90% alcohol. The oxygen analogs (Ia-c) under these conditions are about 60% dissociated (as determined based on the change in the long-wavelength absorption maxima for the neutral and anionic forms in their electronic spectra).

EXPERIMENTAL

UV spectra were recorded on a Specord UV-Vis spectrophotometer using ethanol solutions; IR spectra were obtained on a UR-20 spectrophotometer (for Nujol mulls), PMR spectra on a WH-90 (90 MHz) spectrometer versus TMS as internal standard. The purity of the newly synthesized compounds was assessed by TLC analysis on Silufol UV-254 plates using hexane—chloroform—acetone (7:9:1) and hexane—n-propyl alcohol (9:1) as the eluting solvent systems. Preparative TLC was performed on loose (unmounted) silica gel (40/100μ) with hexane—chloroform—acetone (7:9:3) as eluent.

The physicochemical characteristics of compounds IVd, g, h, Va-i, and Via-c, g, j, k and VII are summarized in Table 1.

The results of C, H, N, S elemental analysis agreed with calculations.

4-Aryl-1,4-DHP-3,5-dicarboxylic acid esters Ia-f were synthesized by condensation of propiolate esters with aromatic aldehydes in the presence of ammonium acetate, according to known procedures [17, 19, 20]; esters Ig-i were prepared according to [14]. The monoacid ester derivative IId, g, h were prepared from their corresponding diesters by treatment with KOH, according to a previously published procedure [21]. Their dicarboxylic acid derivatives IIa-i were obtained by using a fivefold excess of potassium hydroxide [14, 17, 21].

General Method for the Synthesis of 4-Aryl-1,4-dihydropyridinecarbothionic Acid S-Phenyl Esters (Va, b, d, e). A. The required ester Ia, b, d, e (5 mmoles) is dissolved in 30 ml absolute tetrahydrofuran under argon at room temperature. Aluminum chloride (3 g, 15 mmoles) is added in portions. After 10 min 2.19 g (12 mmoles) trimethyl(phenylthio) silane is added dropwise with stirring. After 3 h reflux the reaction mixture is poured into a phosphate buffer solution (pH 7.0), extracted with methylene chloride, and the extract dried over anhydrous

magnesium sulfate. After solvent removal the product was isolated by TLC of the residue, in the form of brightly fluorescent substances (Va, b, d, e), which were crystallized from ethanol.

General Method for the Synthesis of 4-Aryl-1,4-dihydropyridine-3,5-dicarbothionic Acid S-Phenyl Esters (IVd, g, h and Va-i). B. To a solution of 5 mmoles of the corresponding compound IIa-i or ester IIId, g, h in 100 ml dry methylene chloride under argon was added 2.22 ml (11 mmoles) tributylphosphine. After stirring for 20 min at room temperature 1.36 g (10 mmoles) phenyl thiocyanate in 20 ml methylene chloride was added. The reaction mixture was stirred for 6 h at room temperature, poured into water, and the organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the bright yellow product (IVd, g, h and Va-i) was from the residue as described above, and crystallized from ethanol.

4-Aryl-3,5-di(alkylthiocarbonyl)-1,4-dihydropyridines (VIa-c, g, j, k). C. Compound IIa-i (10 mmoles) is dissolved in 60 ml absolute, freshly distilled (from lithium aluminum hydride under argon) dimethoxyethane. To the solution is added 9.72 ml (120 mmoles) dry pyridine and 40 mmoles of the corresponding thiol; the solution is then cooled to 0°C, stirred, and 6.3 g (30 mmoles) phenyl dichlorophosphate is added dropwise. After stirring for 14 h the reaction mixture is poured onto ice, neutralized with 1% sodium hydroxide solution, and extracted with methylene chloride. The extract is washed with water, and dried over anhydrous calcium chloride. The solvent is removed under vacuum and the residue is transferred to a chromatographic column filled with 100 g silica gel (40/100μ). The bright fluorescent zone or band is eluted with hexane—chloroform—acetone (7:9:3), and the bright yellow product is isolated, containing product VIa-c, g, j, k, which is then crystallized from ethanol.

3,5-Di(ethylthiocarbonyl)pyridine (VIII). 3,5-Pyridinedicarboxylic acid (8.35 g, 50 mmoles) is dissolved in 70 ml absolute 1,2-dimethoxyethane under argon. The solution is cooled to 0°C and 23.7 g (300 mmoles) dry pyridine is added, followed by 31.7 g (150 mmoles) phenyl dichlorophosphate (dropwise), and after 20 min, by 22.5 ml (300 mmoles) ethanethiol. After stirring for 14 h at room temperature the reaction mixture is poured into water, neutralized with 1% sodium hydroxide solution, and extracted with methylene chloride. The extract is washed with water and dried over anhydrous calcium chloride. The solvent is removed under vacuum and the residue is purified by column chromatography (with benzene eluent); the product is collected from the yellow-colored band zone. After solvent removal the resulting yellow oil is distilled under vacuum to give 10.8 g (85%) of dithiopyridine VIII, bp 205°C (25 mm Hg).

3,5-Di(ethylthiocarbonyl)-1,4-dihydropyridine (VII). Dithiopyridine VIII (1 g, 4 mmoles) is dissolved in 10 ml glacial acetic acid, cooled to 0°C, and 1 g (16 mmoles) finely powdered or ground sodium cyanoborohydride is added. After 20 min the reaction mixture is diluted with 50 ml water, and the bright yellow crystalline dihydropyridine VII is separated by filtration and crystallized from methanol.

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