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REACTION OF α-(THIO)AMIDOALKYLATION IN THE SYNTHESIS OF α-CYANO-SUBSTITUTED CYCLIC (THIO)UREAS AND DITHIOCARBAMATES

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It was shown that the reaction of the readily accessible 4-azido-, 4-acetoxy-, 4-arylsulfonyl, 4-ethoxythiocarbonylthio-, or 4-isothiocyanatohexahydropyrimidine-2-thiones/ones and 4-azidotetrahydro-1,3-thiazine-2-thiones with sodium cyanide leads to the selective formation of the corresponding 4-cyano derivatives. The diastereoselectivity of the reactions depends on the structure of the heterocycle and the solvent, and is practically independent of the nature of the leaving group. The preferableness of the axial orientation of the cyano group in the molecules of the compounds synthesized was established; this is explained by the development of the anomeric effect.

The reaction of α-(thio)amidoalkylation is widely employed in the chemistry of heterocyclic compounds to introduce different groups into the α-position, relative to nitrogen, of heterocyclic amides and thioamides [1-5], particularly at the position 4 of the molecules of hexahydropyrimidine-2-thiones/ones and tetrahydrohydro-1,3-thiazine-2-thiones. In the indicated case, the amidoalkylating systems usually utilized were the readily accessible 4-hydroxy- or 4-alkoxyhexahydropyrimidine-2-thiones/ones, 1,2,3,6-tetrahydropyrimidine-2-thiones/ones, 4-hydroxy- or 4-alkoxytetrahydro-1,3-thiazine-2-thiones, which are converted to the corresponding 4-substituted hexahydropyrimidine-2-thiones/ones [6-16] and tetrahydro-1,3-thiazine-2-thiones [17] by different nucleophilic reagents in the presence of acidic or basic catalysts. At the same time as reactions of the amidoalkylating systems, indicated above, with O-, S-, N-, and H-nucleophiles are well shown in the literature [7-17], their reaction with C-nucleophiles is only described in a few works [6-8], whereby only substituted phenols were utilized as the nucleophilic reagents. It seemed expedient to study the possible application of the α-(thio)amidoalkylation reaction as a general method for the formation of the carbon–carbon bond at the position 4 of the hexahydropyrimidine-2-thione/one and tetrahydro-1,3-thiazine-2-thione molecules. The present work describes the utilization of this reaction for the introduction of the cyano group into the indicated heterocyclic systems.

We showed that the direct substitution of the hydroxyl group in the 4-hydroxyhexahydropyrimidine-2-thiones by the cyano group is unsuccessful under different conditions. Thus, for example, trans-4-hydroxy-6-methylhexahydropyrimidine-2-thione (I) [10] does not react with sodium cyanide in DMF when the mixture is heated in water in the presence of hydrochloric acid (20-95°C) or sodium bicarbonate (90°C), or with acetone cyanohydrin in water with an acid (HCl or TsOH, 65-95°C) or a base (KOH, 50-70°C). Attempts to accomplish the reaction of trans-4-hydroxy-3,6-dimethylhexahydropyrimidine-2-thione (II) [10] with sodium cyanide in the presence of an acid also proved to be unsuccessful. At the same time, as described in the works [10-14], the compounds (I) and (II) react easily with different O-, S-, N-, and H-nucleophiles. The absence of the reaction between the 4-hydroxyhexahydropyrimidine-2-thiones and sodium cyanide under different conditions is probably caused by the unfavorable combination of the nucleophilic properties of the reagent and the nucleofugic properties of the leaving group (see scheme at top of following page).

Raised activity of the 4-azido- and 4-isothiocyanato- [18], 4-acetoxy- [19], 4-arylsulfonyl- and 4-ethoxythiocarbonylthio derivatives [12] toward different O-nucleophiles was previously found in the series of 4-functionally substituted hexahydro-

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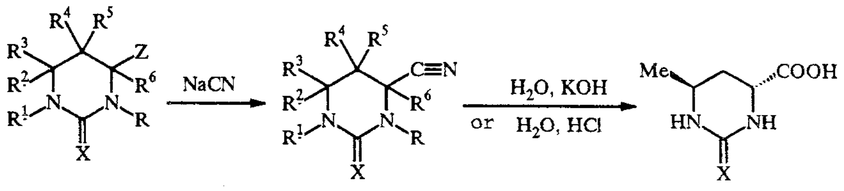
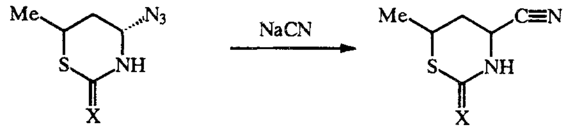


III a-i, IV a,b
Va-c, VI, VIIa,b

VIII a-i

XI



IX

X

III э–i $Z = N_3$; IVa,b $Z = OAc$; Va– b$Z = SO_2Ar$; VI $Z = SC(S)OC_2H_5$; VIIa, b $Z = NCS$. III a-f,
VIII a-f $X = S, R^1 = R^4 = H$; a$R = R^2 = R^3 = R^5 = R^6 = H$; b$R = R^3 = R^5 = R^6 = H, R^2 = CH_3$; c$R = R^2 =$
$= CH_3, R^3 = R^5 = R^6 = H$; d$R = R^2 = R^3 = R^6 = H, R^5 = CH_3$; e$R = R^2 = R^3 = R^5 = H, R^6 = CH_3$; f$R =$
$= R^5 = H, R^2 = R^3 = R^6 = CH_3$; g-i $X = O, R^3 = H, R^4 = CH_3$; g$R = R^1 = R^5 = CH_3, R^2 = R^6 = H$; h$R =$
$= R^1 = R^6 = H, R^2 = CH(CH_3)_2, R^5 = CH_3$; $R = R^1 = R^2 = R^5 = H, R^6 = CH_3$. IV, VII $R^1 = R^3 = R^4 =$
$= R^5 = R^6 = H, R^2 = CH_3$; a$R = H$, b$R = CH_3$. V $R^1 = R^3 = R^4 = R^5 = R^6 = H, R^2 = CH_3$; a$R = H, Ar =$
$= C_6H_5$; b $R = H, Ar = 4\text{-}CH_3C_6H_4$; c $R = CH_3, Ar = 4\text{-}CH_3C_6H_4$. VI $R = R^1 = R^3 = R^4 =$
$= R^5 = R^6 = H, R^2 = CH_3$

pyrimidine-2-thiones/ones which we synthesized [10-14, 18, 19]. It could be assumed that these compounds will also be effective for the (thio)amidoalkylation of other nucleophiles, particularly the cyanide anion.

In fact, the 4-azido- (IIIa-f), 4-acetoxy- (IVa, b), 4-arylsulfonyl- (Va-c), 4-ethoxythiocarbonylthio- (VI), and 4-isothiocyanatohexahydropyrimidine-2-thiones (VIIa, b) react readily with sodium cyanide at room temperature in different solvents resulting in the formation of the corresponding 4-cyanohexahydropyrimidine-2-thiones (VIIIa-f) with yields up to 94% (Tables 1, 2). When DMF or DMSO are utilized as solvents, the reactions are completed in 1-2 h. When the reactions are performed in acetonitrile or pyridine, the reaction mixtures have to be maintained for 3-24 h. Under analogous conditions, the 4-azidohexahydropyrimidin-2-ones (IIIg-i) react with NaCN to give the 4-cyanopyrimidinones (VIIIg-i).

It should be noted that the reaction of the azidopyrimidine trans-(IIIc) with sodium cyanide also proceeds successfully in methanol. However, in this case, 3,6-dimethyl-4-(methoxycarbonimidoyl)hexahydropyrimidine-2-thione (XII), which is formed as a result of the addition of a molecule of methanol to the cyano group in the 4-cyanopyrimidine (VIIIc) obtained, results as a by-product with the yield of 15%. Besides the absorption bands of the pyrimidine (VIIIc) (Table 2), the IR spectrum of the synthesized substance also contains a band at 1644 cm^{-1}, caused by the stretching vibrations of the C=N bond of the imidoyl fragment of compound (XII). The PMR spectrum of the reaction product in DMSO-D_6 has signals of the protons in the cyanopyrimidine (VIIIc) (Table 3), as well as signals of protons in the compound (XII) [8.10 ppm (s, NH), 7.60 ppm (s, =NH), 4.20 ppm (dd, 4-H, $J_{4,5e} = 2.0$, $J_{4,5a} = 5.7$ Hz), 3.67 ppm (s, OCH_3), etc.].

The described reaction of amidoalkylation can probably serve as a convenient method for the introduction of the cyano group into not only the pyrimidine ring, but also into other nitrogen-containing heterocyclic systems. Thus, we synthesized the 4-cyanothiazinethione (X) by the reaction of trans-4-azido-6-methyltetrahydro-1,3-thiazine-2-thione (IX) with sodium cyanide.

The reactions studied are characterized by high diastereoselectivity (58-100%), whereby the preferred retention of the relative configuration of the heterocyclic compound is observed in all cases (Table 1). Thus, for example, the reaction of trans-4-azido-6-isopropyl-5,5-dimethylhexahydropyrimidin-2-one [trans-(IIIh)] with NaCN gives exclusively the trans-cyanopyrimidinone [trans-(VIIIh)]. Trans-4-azido-6-methyl- and 4-azido-3,6-dimethylhexahydropyrimidine-2-thiones [trans-(IIIb, c)] give the mixtures of the cis and trans isomers of the cyanopyrimidines (VIIIb, c) with the significant predominance of the latter (the diastereomeric excess of 60-88%). Cis-4-azido-5-methylhexahydropyrimidine-2-thione [cis-(IIId)] gives the mixture of the cis and trans isomers of the cyanopyrimidine (VIIId) in the ratio of (79-98):(21-2) correspondingly. The analogous results are observed in the reaction of NaCN with other 4-functionally substituted hexahydropyrimidine-2-thiones (IV)-(VII) (Table 1).

Besides the dependence on the structure of the heterocyclic compound, the diastereoselectivity of the reaction also depends on the nature of the solvent. The maximal diastereoselectivity is observed when the reactions are performed in strongly

TABLE 1. Reaction of the 4-Functionally Substituted Hexahydropyrimidine-2-thiones/ones (IIIa-i), (IVa, b), (Va-c), (VI), and (VIIa, b) with Sodium Cyanide at 20°C*[1]

Compound	Solvent	Reaction product	Ratios of isomers*[2]	Yield, %	Compound	Solvent	Reaction product	Ratios of isomers*[2]	Yield, %
IIIa	DMF	VIIIa	—	55	trans-IIIa	Pyridine	VIIIc	80 : 20	67
	CH_3CN	VIIIb	—	69		Methanol	VIIIc	93 : 7	48*
trans-IIIb	DMF	VIIIc	*5	87	trans-IVb	DMF	VIIIc	85 : 15	91
IIIb	DMF	VIIIb	92 : 8	84	trans-Vc	DMF	VIIIc	84 : 16	75
	CH_3CN	VIIIb	92 : 8	83	VIIb	DMF	VIIId	*5	36
trans-IVa	DMF	VIIIb	94 : 6	85	cis -IIId	DMF	VIIId	2 : 98	51
	CH_3CN	VIIIb	*5	69		DMSO	VIIId	2 : 98	50
Va *3	DMF	VIIIb	*5	83		CH_3CN	VIIId	21 : 79	67
Vb *4	DMF	VIIIb	*5	61		Pyridine	VIIId	10 : 90	54
trans-VI	DMF	VIIIb	95 : 5	84	IIIe	DMF	VIIIe	—	68
VIIa	DMF	VIIIb	*5	52	IIIf	DMF	VIIIf	—	89
tans-IIIc	DMF	VIIIb	90 : 10	84	IIIg	CH_3CN	VIIIg	—	98
	DMF	VIIIc	90 : 10	94	trans-IIIh	CH_3CN	VIIIh	>98 : 2	82
	CH_3CN	VIIIc	82 : 18	87	IIIi	DMF	VIIIi	*5	33

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*[1]The molar ratio NaCN:pyrimidine comprises (1.60-1.80):1.0.

*[2]According to the data of PMR spectroscopy, the cis:trans isomeric ratio (in %) is presented for the unpurified substances.

*[3]The 93:7 mixture of trans and cis isomers [12].

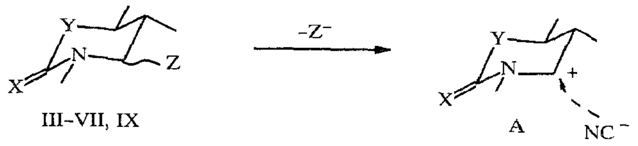
*[4]The 88:12 mixture of trans and cis isomers [12].

*[5]The ratio of isomers was not determined.

*[6]The imidate (XII) is formed besides the compound (VIIIc) with the yield of 15%.

polar aprotic solvents such as DMSO or DMF. This is marked especially well taking the example of the reaction of cis-4-azido-5-methylpyrimidine [cis-(IIId)] with NaCN, where the diastereoselectivity of the reaction increases from 58% to 96% in the transition from acetonitrile to DMF as the solvent (Table 1). It is also important to note that the diastereoselectivity of the reaction of NaCN with different 4-functionally substituted hexahydropyrimidine-2-thiones is virtually independent of the nature of the leaving group.

The obtained data on the selectivity of the reactions described above may be explained in the framework of the S_N1 mechanism for the process with the intermediate formation of the compressed carbenium ions (A), which further undergo the addition of the cyanide anion with the preferred formation of stereoisomers in which the unshared pair of electrons of the $N_{(3)}$ nitrogen atom are antiperiplanar to the new $C_{(4)}-CN$ bond (the kinetic anomeric effect [20]).



III-VII, IX

A

X = O, S; Y = S, NR; Z = N_3, OAc, SO_2Ar, SC(S)OEt, NCS

TABLE 2. Characteristics of the Synthesized Compounds (VIIIa-f, h), (X), and (XI)

Compound	Empirical formula	mp, °C	R_f*2	UV spectrum (methanol), λmax, nm log ε)	IR spectrum, ν, cm^{-1}					Yield, %
					NH	CN	thioamide-II	region of ~1300 cm^{-1}	region of ~1200 cm^{-1}	
VIII a	$C_5H_7N_3S$	158,5...159,5 ethanol	0,17	204 (3,98), 250 (4,18)	3170	2235	1570, 1542, 1522	1307	1217, 1197	69
trans-VIII b	$C_6H_9N_3S$	235...237 ethanol	0,26	204 (4,01), 250 (4,16)	3180	2235	1572, 1534	1304	1215	87
trans-VIII c	$C_7H_{11}N_3S$	202...204 ethanol	0,46	208 (4,04), 251 (4,19)	3215	2237	1530, 1508	1293	1203	94
VIII d	$C_6H_9N_3S$	205,5...206 ethanol	0,28	205 (3,99), 249 (4,18)	3185	2235	1581, 1522	1267	1217	67
VIII e	$C_6H_9N_3S$	232...232,5 ethanol	0,32	204 (4,00), 250 (4,19)	3160	2224	1575, 1527	1343	1209	68
VIIIe	$C_8H_{13}N_3S$	295...296 methanol	0,37	205 (4,03), 250 (4,21)	3190	2234	1565, 1523	1257	1206	89
trans-VIII g	$C_{10}H_{17}N_3O$	177...178 ethyl acetate	—	—	3236, 3084	2243	—*3	1270	—	82
trans-X	$C_6H_8N_2S_2$	184...184,5 methanol	0,31	205 (3,93), 240 (3,91), 292 (4,16)	3116	2236	1522	1320, 1309	—	44
XI	$C_6H_{10}N_2O_2S$	221,5...222 water	0	204 (4,10), 245 (4,24)	3325, 3245	—*4	1563, 1539	1303	1209, 1177	84

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*1The compounds (VIIIb, d-f), (X), and (XI) melt with decomposition.

*2In the 13:1 system of chloroform–methanol; standard conditions of chromatography [26].

*31700 (amide-I), 1527 cm^{-1} (amide-II).

*42462 (ν_{OH}; the strongest of six bands in the range 2353-2743), 1703 cm^{-1} ($\nu_{C=O}$).

Therefore, the 4-functionally substituted hexahydropyrimidine-2-thiones/ones and tetrahydro-1,3-thiazine-2-thiones, containing the N_3, OAc, SO_2Ar, SC(S)OEt, and NCS groups at the $C_{(4)}$ carbon atom, show high effectiveness for the (thio)amidoalkylation not only of O-nucleophiles [12, 18, 19], but also of C-nucleophiles (NaCN). It should however be noted that the most promising of the compounds indicated are the 4-azido- and 4-arylsulfonyl derivatives; this is determined by their high availability [12, 13, 18], their stability on storage, their high reactivity, and the absence of secondary reactions when they are utilized as (thio)amidoalkylation reagents.

The cyano-substituted heterocycles (VIIIa-i) and (X), which we synthesized, may be initial substances for the isolation of various pyrimidine and 1,3-thiazine derivatives due to the presence of highly reactive functional groups in their molecules. Thus, for example, the hydrolysis of the cyanopyrimidine trans-(VIIIb), which occurs when it is heated in water in the presence of HCl or KOH, results in the formation of trans-4-carboxy-6-methylhexahydropyrimidine-2-thione (XI) with yields of 75-84%.

The UV spectra (Table 2) of the pyrimidinethiones (VIIIa-f) and (XI) in methanol contain two absorption bands, characteristic of the thioureide chromophore [21], with maxima in the ranges 204-208 nm (log ε 3.98-4.10) and 245-251 nm (log ε 4.16-4.24). The UV spectrum of the thiazinethione (X) in methanol contains three intense absorption bands with maxima at 205, 240, and 292 nm caused by the dithiocarbamate chromophore in their molecules [22].

The IR spectra of the pyrimidinethiones (VIIIa-f) and (XI) are characterized by a series of strong absorption bands associated with vibrations of the atoms of the thioureide fragment of the molecules [23], namely the bands of the stretching vibrations of the N–H group(s) in the region of 3160-3325 cm^{-1}, the thioamide-II bands in the range 1508-1581 cm^{-1}, and bands in the region ~1300 cm^{-1} and the region ~1200 cm^{-1} (Table 2). In the spectrum of the thiazinethione (X), the vibrations of the atoms of the dithiocarbamate part of the molecule [24] appear at 3116 cm^{-1} (νN–H), 1522 cm^{-1} (thioamide-II), and 1309 cm^{-1}, and the ureide fragment in the molecules of the pyrimidinones (VIIIg-i) determines the presence of the absorption bands at 3080-3236 cm^{-1} [νN–H for (VIIIh, i)], 1623-1700 cm^{-1} (amide-I), and 1525-1527 cm^{-1} [amide-II for (VIIIh, i)]. Besides the absorption bands, described above, in the IR spectra of the cyanopyrimidines (VIIIa-i) and the cyanothiazine (X), a weak

TABLE 3. PMR Spectra of the Compounds (VIIIa-f, h), (X), and (XI) in DMSO-D_6

Compound	Configuration (conformation)	Chemical shift, δ, ppm (SSCC, J. Hz)							
		4-H ($J_{4,5e}$; $J_{4,5a}$)	5a-H ($J_{5a,6a}$)	5e-H ($J_{5e,5a}$)	6a-H ($J_{5e,6a}$)	6e-H ($J_{6e,6a}$)	$N_{(1)}$—H ($J_{NH,6-H}$)	$N_{(3)}$—H ($J_{NH,4-H}$)	other protons
VIIIa	— (4a)	4,64 (3,2; 5,0) ($J_{4e,6e}$ = 1,3)	1,99 (11,1) ($J_{5a,6e}$ = 5,5)	2,15 (13,8) ($J_{5e,6e}$ = 3,1)	3,20 (4,2)	3,29 (13,5)	8,56 (~0; >0)	8,56 (~4,0)	—
VIIIb*1	trans (4a,6e)	4,63 (2,2; 5,3)	1,69 (11,5)	2,21 (13,9)	3,51 (3,9)	—	8,56 (~0)	8,57 (3,5)	1,20 (d J = 6,3, 6-CH_3)
VIIIc*2	trans (4a,6e)	4,92 (2,3; 5,1)	1,87 (11,8)	2,32 (14,0)	3,54 (3,8)	—	8,55 (~0)	— ($J_{NH,5e}$ = −1,6)	3,31 (s N—CH_3), 1,19 (d, J = 6,4, 6-CH_3)
VIIId	cis (4a,5e)	4,54 (—; 4,8) ($J_{4e,6e}$ = 1,6)	2,17 (11,4) ($J_{5a,6e}$ = 4,8)	—	2,83 (—)	3,23 (13,3)	8,45 (~0; 4,6)	8,53 (~3,7)	1,04 (d, J = 6,7, 5-CH_3)
VIIIe	trans (4a,5a)	4,27 (4,5; —)	— ($J_{4e,6e}$ = 1,2)	2,28 ($J_{5e,6e}$ = 4,5)	3,28 (4,5)	2,92 (13,9)	8,42...8,59*4		0,99 (d, J = 7,0, 5-CH_3)
	—	—	1,82 (11,5) ($J_{5a,6e}$ = 6,0)	2,27 (13,7) ($J_{5e,6e}$ ~ 2,0)	3,21 (3,9)	3,30 (13,6)	8,57 (~0; 2,5)	8,73 (—)	1,58 (s, 4-CH_3)
VIIIf	—	—	1,73 (—)	2,32 (14,3)	—	—	8,70 (—)	8,81 (—)	1,61 (s, 4-CH_3), 1,37 1,21 s (6-CH_3)
VIIIh	trans (4a,6e)	4,19 (—; —)	—	—	3,07 ($J_{CH,6a}$ = 1,7)	—	6,65 (~0)	7,17 (3,8)	1,94 (m, $\underline{CH}(CH_3)_2$, 1,12 s, 1,01 s (5-CH_3), 0,99 d, 0,85 d (J = 6,8, $\underline{CH_3}CH_2CH_2$)
X*3	trans (4a.6e)	5,01 (3,2; 4,0)	1,89 (12,3)	2,55 (14,6)	3,56 (3,8)	—	—	10,80	1,26 (d, J = 6,6, 6-CH_3)
XI	trans (4a,6e)	3,92 (3,1; 5,7)	1,60 (10,2)	2,03 (13,5)	3,23 (3,9)	—	8,08 (~0)	8,01 (3,0)	1,12 (d, J = 6,4, 6-CH_3)

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*1Signals of the protons of the cis isomer of compound (VIIIb): 1.81 ppm (dt, $J_{4,5a}$ ~ $J_{5a,6}$ ~ 7.6 Hz; $J_{5e,5a}$ = 13.6 Hz, 5a-H).

*2Signals of the protons of the cis isomer of compound (VIIIc): 8.66 ppm (br.s, N−H), 3.30 ppm (s, N−CH_3), 2.39 ppm (dt, $J_{4,5e}$ ~ $J_{5e,6}$ ~ 5.6 Hz, 5e-H), 2.03 ppm (dt, $J_{4,5a}$ ~ $J_{5a,6}$ ~ 6.0 Hz; $J_{5e,5a}$ = 13.9 Hz, 5a-H), and 1.23 ppm (d, J = 6.6 Hz, 6-CH_3).

*3The signals of the protons of the cis isomer of compound (X): 4.94 ppm (dd, $J_{4a,5e}$ = 4.1 Hz, $J_{4a,5a}$ = 10.0 Hz, 4e-H), 2.55 ppm (m, $J_{5e,6a}$ ~ 4.0 Hz, 5e-H), and 2.02 ppm (m, $J_{5a,6a}$ = 10.0 Hz, $J_{5e,5a}$ = 14.0 Hz, 5a-H).

*4The signals are superimposed by the signals of the analogous protons of the cis isomer.

absorption band of the stretching vibrations of the $C\equiv N$ bond is observed in the range of 2224-2243 cm^{-1}, and the bands of the stretching vibrations of the $O-H$ group (2353-2743 cm^{-1}) and the $C=O$ group (1703 cm^{-1}) are present in the spectrum of the acid (XI).

Analysis of the SSCCs of the protons of the pyrimidine ring in the PMR spectrum of the cyanopyrimidine (VIIIa) (Table 3) shows that the molecules of this compound in solutions exist in the chair-type conformation with the axial orientation of the cyano group. This conclusion follows from the low SSCCs of the 4-H proton with the 5a-H and 5e-H protons, equal to 5.0 and 3.2 Hz. Additional confirmation of this conclusion is the development of the distant spin–spin interaction of the 4-H proton with the 6e-H proton ($J_{4e,6e}$ = 1.3 Hz) and the presence of the $J_{NH,4e}$ SSCC of ~4.0 Hz, which is only possible for the conformer with the equatorial orientation of the 4-H proton [11, 25]. The axial position of the CN group is also characteristic of the cyanopyrimidinone (VIIIg) ($J_{4e,6e}$ = 2.0 Hz). The preferableness of the axial orientation of the cyano group in the molecules of the compounds (VIIIa, g) can probably be explained by the development of the anomeric effect in the $N_{(3)}-C_{(4)}-C\equiv N$ system.

We established analogously on the basis of the data of PMR spectroscopy that the substituent at the $C_{(4)}$ carbon atom (the CN or COOH group) occupies an axial position in the molecules of the compounds trans-(VIIIb, c, h), cis-(VIIId), trans-(X), and (XI), and the substituent at the $C_{(6)}$ carbon atom [for the compounds (VIIIb, c, h), (X), and (XI)] or at the $C_{(5)}$ carbon atom [for the compound cis-(VIIId)] has the equatorial orientation. The conformation with the diequatorial position of both substituents is characteristic for the compounds cis-(VIIIb, c) and cis-(X), and the conformation with the diaxial position is characteristic for the compound trans-(VIIId).

EXPERIMENTAL

The IR spectra were recorded on the Specord IR-75 instrument for suspensions in mineral oil. The UV spectra were registered on the Shimadzu UV-240 spectrophotometer for the solutions of the compounds in methanol with the concentration of $5\cdot 10^{-5}$ M. The PMR spectra were obtained on the Bruker WM-250 or Bruker MSL-200 spectrometers for solutions of the samples in DMSO-D_6; the internal standard was HMDS. Thin layer chromatography was performed on plates of Kieselgel 60 F_{254} (Merck) in the 13:1 system of chloroform–methanol; spots were detected in UV light or in iodine vapor.

The synthesis of the 4-azido- and 4-isothiocyanatohexahydropyrimidine-2-thiones/ones (IIIa-h) and (VIIa, b) was described in the works [13, 18]. The isolation of the 4-acetoxyhexahydropyrimidine-2-thiones (IVa, b) was described in the work [19]. The isolation of the 4-arylsulfonyl- and 4-ethoxythiocarbonylthiohexahydropyrimidine-2-thiones (Va-c) and (VI) was described in the work [12]. The compounds (III)-(VII) which were separated from the reaction mixtures were utilized further in the reactions with NaCN without additional purification.

The data of the elemental analysis for C, H, N, and S for the compounds (VIIIa-f, h), (X), and (XI) correspond with the calculated data.

6-Methyl-4-cyanohexahydropyrimidine-2-thione (VIIIb). A. The mixture of 4.360 g (25.46 mmoles) of the azidopyrimidine trans-(IIIb), 2.169 g (44.26 mmoles) of sodium cyanide, and 20 ml of dry DMF is stirred at room temperature for 2.2 h. The turbid solution obtained is poured into 70 ml of ice water. The precipitated residue is filtered off, washed with ice water, and dried. Compound (VIIIb) is obtained with the yield of 3.439 g (87.0%) in a chromatographically pure form. The recrystallization from ethanol leads to the isolation of the individual trans-isomer of compound (VIIIb).

Compound (VIIIb) is also synthesized by an analogous method in the reaction of the 4-substituted 6-methylhexahydropyrimidine-2-thiones trans-(IVa), (Va, b), trans-(VI), and (VIIa) with sodium cyanide (Table 1).

By analogy, the azidopyrimidines (IIIa, e, f) and cis-(IIId) afford the cyanopyrimidines (VIIIa, d-f),* and the 4-substituted 3,6-dimethylhexahydropyrimidine-2-thiones trans-(IIIc), trans-(IVb), trans-(Vc), and (VIIb) afford the cyanopyrimidine (VIIIc). The recrystallization of compound (VIIIc) (the 90:10 mixture of the trans and cis isomers) and compound (VIIId) (the 2:98 mixture of the trans and cis isomers) from ethanol gives the individual compounds trans-(VIIIc) and cis-(VIIId).

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*Compound (VIIIf) is obtained as the mixture with 4,6,6-trimethyl-1,2,3,6-tetrahydropyrimidine-2-thione (10%), and is purified from the last using the twofold crystallization of the reaction product from methanol.

The cyanopyrimidines (VIIIb-d) are synthesized analogously by the reaction of the azidopyrimidines trans-(IIIb, c) and cis-(IIId) with NaCN with the utilization of dry DMSO as the solvent.

The yields and isomer compositions of the resulting cyanopyrimidines (VIIIa-f) are presented in Table 1.

B. The mixture of 0.685 g (4.00 mmoles) of the azidopyrimidine trans-(IIIb), 0.333 g (6.79 mmoles) of sodium cyanide, and 8 ml of dry acetonitrile is stirred at room temperature for 24 h with the monitoring by TLC. The mixture is concentrated to dryness in vacuo, and 10 ml of water are added to the residue. The mixture is cooled to 0°C, and the residue is filtered off, washed with ice water, and dried. Compound (VIIIb) is obtained with the yield of 0.516 g (83%) in a chromatographically pure form. The substance is the mixture of the trans and cis isomers in the ratio of 92:8. The recrystallization from ethanol gives the individual trans diastereomer of compound (VIIIb).

By the analogous method, the cyanopyrimidines (VIIIa-d, h) are synthesized by the reaction of the azidopyrimidines (IIIa), trans-(IIIb, c, h), and cis-(IIId) with NaCN in acetonitrile or pyridine (Table 1).

1,3,5,5-Tetramethyl-4-cyanohexahydropyrimidin-2-one (VIIIg). The mixture of 0.489 g (2.48 mmoles) of the azidopyrimidine (IIIg), 0.206 g (4.21 mmoles) of sodium cyanide, and 4 ml of dry acetonitrile is stirred at room temperature for 3.3 h. The solvent is distilled off in vacuo. To the residue is added 1 ml of water, and the mixture is extracted with 5 × 4 ml of ether; the extract is dried with anhydrous $MgSO_4$. After the distillation of the solvent in vacuo, 0.440 g (98%) of compound (VIIIg) is obtained as a colorless oil with the n_D^{25} 1.4855. The IR spectrum (thin layer) is as follows: 2224 cm^{-1} ($\nu C{\equiv}N$), 1623 cm^{-1} (amide-I), and 1496 cm^{-1}. The PMR spectrum ($CDCl_3$) is as follows: 3.74 ppm (1H, d, 4e-H, $J_{4e,6e}$ = 2.0 Hz), 3.44 ppm (1H, d, 6a-H, $J_{6e,6a}$ = 12.3 Hz), 3.04 ppm (3H, s, 3-CH_3), 2.96 ppm (3H, s, 1-CH_3), 2.83 ppm (1H, dd, 6e-H), and 1.23 and 1.22 ppm (6H, two s, 5-CH_3).

4,5-Dimethyl-4-cyanohexahydropyrimidin-2-one (VIIIi). This compound is obtained by analogy with the compound trans-(VIIIb) by the method A from 0.215 g (1.27 mmoles) of the azidopyrimidine (IIIi), synthesized by the reaction of 4,5-dimethyl-1,2,3,6-tetrahydropyrimidin-2-one [8] with HN_3 (water, 76°C, 3 h) using the method of [19], 0.100 g (2.04 mmoles) of sodium cyanide, and 1.5 ml of dry DMF. The yield of compound (VIIIi) comprises 0.063 g (32.6%). The PMR spectrum (Bruker HX-90E) of the substance obtained contains the spectral indications of only one diastereomer. The compound was purified by the recrystallization from ethanol. It has the mp 217.5-218.5°C (with decomp.; ethanol). The IR spectrum (in mineral oil) is as follows: 3230 cm^{-1}, 3080 cm^{-1} ($\nu N{-}H$), 2225 cm^{-1} ($\nu C{\equiv}N$), 1688 cm^{-1} (amide-I), and 1525 cm^{-1} (amide-II). The PMR spectrum (DMSO-D_6) is as follows: 7.22 ppm (1H, br.s, $N_{(3)}{-}H$), 6.73 ppm (1H, br.s, $N_{(1)}{-}H$), ~3.15 ppm (1H, m, 6e-H), 2.87 ppm (1H, dd, $J_{5a,6a}$ = 11.7 Hz, $J_{6e,6a}$ = 11.7 Hz, 6a-H), 1.87 ppm (1H, m, $J_{5a,6e}$ ~ 5 Hz, 5a-H), 1.48 ppm (3H, s, 4-CH_3), and 1.00 ppm (3H, d, J = 6.7 Hz, 5-CH_3).

6-Methyl-4-cyanotetrahydro-1,3-thiazine-2-thione (X). The mixture of 0.1975 g (1.05 mmoles) of the azidothiazine (IX) [18], 0.0565 g (1.15 mmoles) of sodium cyanide, and 1 ml of dry DMF is stirred at 20°C for 1 h. The mixture is applied to a column with silica gel L 40/100 μ (10 g) prior to the elution with chloroform and further with the 40:1 system of chloroform–ethanol. The cyanothiazine (X) is obtained with the yield of 0.0798 g (44%), and is recrystallized from methanol. After the first crystallization, the ratio of the trans and cis isomers comprises 94:6.

Trans-4-carboxy-6-methylhexahydropyrimidine-2-thione (XI). A. The solution of 3.841 g (24.75 mmoles) of the cyanopyrimidine trans-(VIIIb) in 20 ml of concentrated HCl is heated with boiling and stirring in the course of 3 h. The mixture with the precipitated crystalline residue is cooled to 0°C. The crystals are filtered off, washed with ice water, and dried. The yield of 3.075 g (71%) of compound (XI) is obtained. Treatment of the mother liquors gives the additional 0.560 g of the compound. The total yield comprises 3.635 g (84%). The compound (XI) is purified by recrystallization from water.

B. The solution of 0.124 g (0.80 mmole) of the cyanopyrimidine trans-(VIIIb) and 0.095 g (1.69 mmoles) of KOH in 0.7 ml of water is heated at 95°C for 2 h. The mixture is cooled and neutralized with concentrated HCl to the pH 1. The mixture with the precipitated residue is cooled again to 0°C, and the residue is filtered off and washed with ice water. The yield of 0.104 g (74%) of compound (XI) is obtained.

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