SYNTHESIS, STRUCTURE, AND REACTIVITY OF 1,2,3,6-TETRAHYDROPYRIMIDINE-2-THIONES

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Dehydration of 4-hydroxyhexahydropyrimidine-2-thiones formed 1,2,3,6-tetrahydropyrimidine-2-thiones containing no substituent at the $C_{(4)}$ carbon atom. It is shown that the synthesized compounds, in contrast to their 4-alkyl-substituted analogs, react easily with various nucleophilic reactants (alcohols, butylmercaptan, benzenesulfinic acid, hydrazoic acid, p-toluidine) to form the corresponding 4-functionally substituted hexahydropyrimidine-2-thiones.

The paths of synthesis of 1,2,3,6-tetrahydropyrimidine-2-thiones described in the literature are based on the formation, by some method, of 4-hydroxyhexahydropyrimidine-2-thiones with their subsequent dehydration [1]. Thus, for example, 1,2,3,6-tetrahydropyrimidine-2-thiones are obtained as a result of reactions of α,β-unsaturated ketones with thiourea [1-3] or ammonium thiocyanate [1], β-isothiocyanatocarbonyl compounds with amines [4-6], β-oxocarbonyl compounds with aldehydes and thiourea (Biginelli synthesis) [7], etc.

The presence of the entioureide fragment in molecules of 1,2,3,6-tetrahydropyrimidine-2-thiones accounts for their high reactivity, and this makes it possible to use these compounds in the synthesis of various derivatives of pyrimidine and other heterocyclic systems. The chemical transformations of 1,2,3,6-tetrahydropyrimidine-2-thiourea may be classified into the following basic types: a) reactions at the thioamide group—oxidation [1] and alkylation [8]; b) reactions of addition at the carbon—carbon double bond of certain nucleophilic reactants (methanol [1, 9], water [10], xylenol [1, 2], 1,2,3,6-tetrahydropyrimidine-2-thiones [1, 11], hydroxylamine [9]) and electrophilic reactants (dihalocarbenes [12]); c) reactions with electrophilic reactants at the $C_{(5)}$ carbon atom [2]; d) condensations in which 4-methyl-1,2,3,6-tetrahydropyrimidine-2-thiones act as C—H acid components, namely reactions with aromatic aldehydes and the Mannich reaction [1, 10]; e) Dimroth's rearrangements of 4-methyl-1,2,3,6-tetrahydropyrimidine-2-thiones [5, 13, 14].

The majority of previously synthesized and studied 1,2,3,6-tetrahydropyrimidine-2-thiones contain an alkyl or aryl group attached to the $C_{(4)}$ carbon atom. In our view, the presence of such substituents should have appreciably altered the reactivity of these compounds as compared to their $C_{(4)}$-unsubstituted analogs, particularly with respect to nucleophilic reactants. The check this assumption, and from the standpoint of specifically studying the chemistry of functionally substituted hydrogenated pyrimidines, we undertook the synthesis and study of the structure and activity of certain 1,2,3,6-tetrahydropyrimidine-2-thiones, both with and without a substituent at the $C_{(4)}$ carbon atom.

The chief method of synthesizing 1,2,3,6-tetrahydropyrimidine-2-thiones (Ia-f) was dehydration of 4-hydroxyhexahydropyrimidine-2-thiones (IIa-f), which we obtained by reacting the corresponding β-isothiocyanatocarbonyl compounds (IIIa-d) with ammonia or methylamine. We showed that dehydration of 4-hydroxy-4-methylhexahydropyrimidine-2-thiones (IIe, f) takes place readily when solutions of these compounds are heated even in the absence of catalysts, for example during boiling in acetonitrile or toluene, this being consistent with data reported in the literature [10]. At the same time, the detachment of a water molecule from 4-hydroxypyrimidines IIa-d takes place only under fairly stringent conditions, namely during boiling in toluene or xylene in the presence of zinc chloride or p-toluenesulfonic acid. In this case, as a result of the formation of several by-products of the reaction, in particular 5-(2-thioxohexahydropyrimidin-4-yl)-1,2,3,6-tetrahydropyrimidine-2-thiones (see below), the yields of compounds Ia-d are moderate, 19-53%. We also carried out the dehydration of pyrimidine trans-IIb by heating this compound with silica gel at 150-160°C or by keeping a solution of the compound trans-IIb in DMSO in the presence of sulfuric acid at 20°C, but were unable to obtain a high yield of tetrahydropyrimidine Ib.

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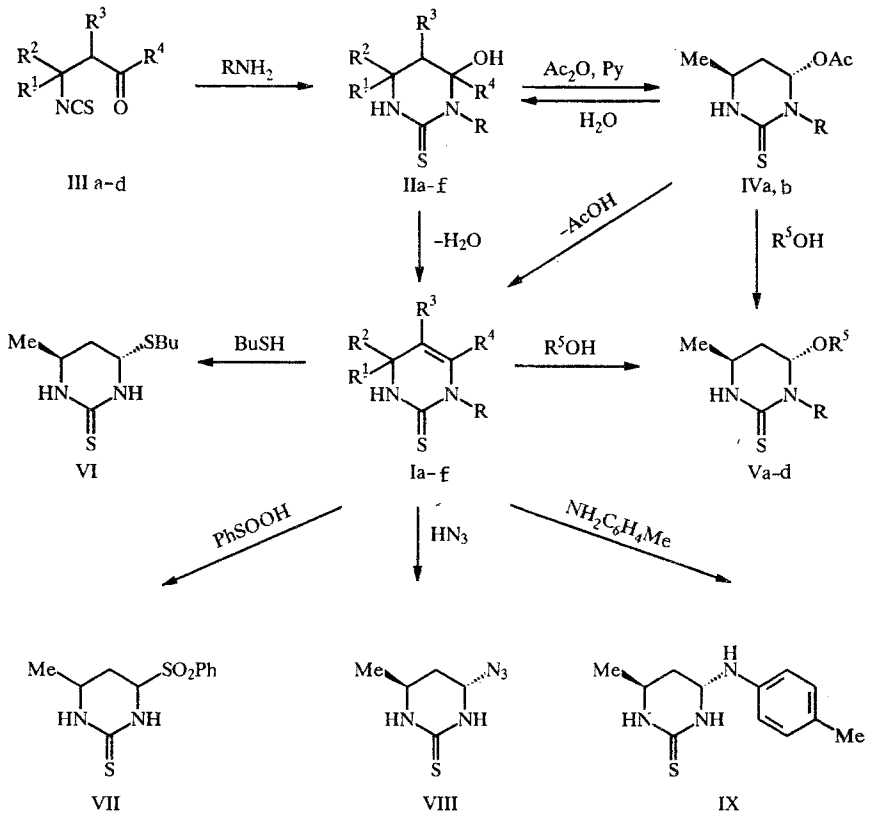
0009-3122/93/2909-1077$12.50 © 1994 Plenum Publishing Corporation

We also obtained compounds Ib, c in 79-92% yields as a result of detachment of acetic acid from 4-acetoxyhexahydropyrimidine-2-thiones (IVa, b), which was accomplished by boiling solutions of these compounds in toluene We synthesized acetoxypyrimidines IVa, b in 81-85% yields by reacting hydroxypyrimidines trans-IIb, c with acetic anhydride in pyridine at 20°C. It is interesting to note that when the cis isomer of compound IIb is acetylated under similar conditions, trans-acetoxypyrimidine IVa is also obtained as a result of a configuration inversion at the $C_{(4)}$ carbon atom.

We studied the reactivity of $C_{(4)}$-unsubstituted tetrahydropyrimidine-2-thiones Ia-d toward certain O-, S-, and N-nucleophilic reactants. These reactions were found to be catalyzed by acids and bases and to lead to the formation of the corresponding 4-functionally substituted hexahydropyrimidine-2-thiones. Thus, compounds Ib, c, boiling in methanol in the presence of p-toluenesulfonic acid, are converted to the corresponding 4-methoxyhexahydropyrimidine-2-thiones (Va, c) in 60-85% yields. In the reaction of tetrahydropyrimidine Ib with ethanol in the presence of KOH, ethoxypyrimidine Vb is formed in 77% yield. When compound Ib is heated with butyl mercaptan in dilute HCl, 4-butylthiohexahydropyrimidine-2-thione (VI) is obtained in 74% yield. Arylsulfinic acids also add to the carbon—carbon double bond of tetrahydropyrimidines (I); we showed this by the example of the reaction of compound Ib with benzenesulfinic acid (water, 20°C), which resulted in the formation of 4-phenylsulfonylpyrimidine VII in 73% yield.

We found that the reaction of tetrahydropyrimidine Ib with hydrazoic acid in water at 28°C takes place very slowly, so that a mixture of the initial pyrimidine Ib and 4-azidohexahydropyrimidine-2-thione (VIII) is formed. However, when compound Ib is heated in aqueous HN_3 in an ampul at 76°C for 3-4 h, complete conversion of compound Ib to the azide VIII, which was formed in 82% yield, is observed. Tetrahydropyrimidine Ib also reacts readily with p-toluidine when heated in dilute acetic acid at 90-95°C, forming 4-(p-tolylamino)hexahydropyrimidine-2-thione (IX) (yield 73%).

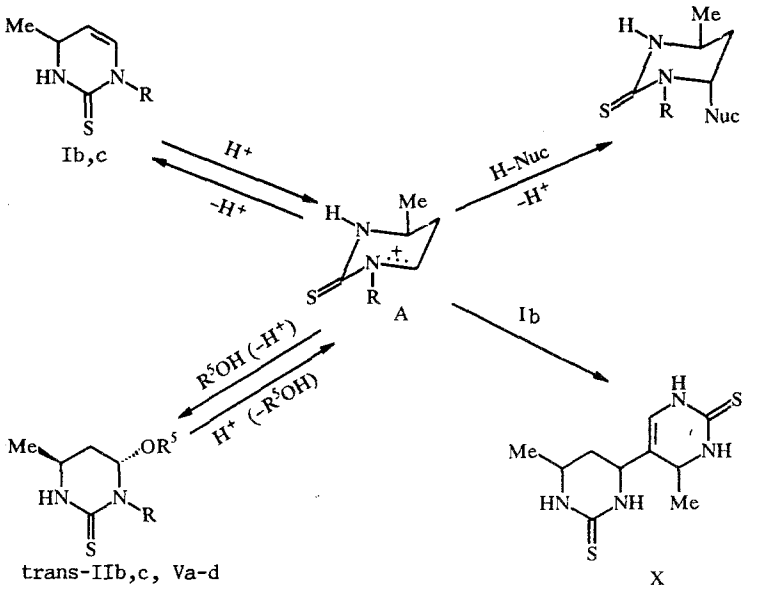
The reactions of 6-methyltetrahydropyrimidinethiones Ib, c with all the nucleophiles indicated above take place with a high degree of diastereoselectivity, and as a result, according to PMR spectroscopy data, compounds Va-c, VI, VIII, and



I, II a R = R^1 = R^2 = R^3 = R^4 = H; b R = R^2 = R^3 = R^4 = H, R^1 = Me; c R = R^1 = Me, R^2 = R^3 = R^4 = H; d R = R^1 = R^2 = R^4 = H, R^3 = Me; e R = R^3 = H, R^1 = R^2 = R^4 = Me; f R = R^1 = R^2 = R^4 = Me, R^3 = H; III a R^1 = R^2 = R^3 = R^4 = H; b R^1 = Me, R^2 = R^3 = R^4 = H; c R^1 = R^2 = R^4 = H, R^3 = Me; d R^1 = R^2 = R^4 = Me, R^3 = H; IV a R = H, b R = Me; V a R = H, R^5 = Me; b R = H, R^5 = Et; c R = R^5 = Me; d R = Me, R^5 = Et

IX are obtained exclusively in the form of trans diastereoisomers. Compound VII is also formed selectively with an appreciable predominance of the trans isomer, as was established by the complete identity of the IR spectrum of the compound obtained in the 700-4000 cm^{-1} region with the spectrum of the sample described in [15], with a known ratio (93:7) of trans to cis isomers.

We should note that the 4-alkyl-substituted 1,2,3,6-tetrahydropyrimidine-2-thiones are appreciably less reactive to nucleophilic reactants than their $C_{(4)}$ unsubstituted analogs. Indeed, in contrast to compound Ib, tetrahydropyrimidine Ie does not react with p-toluidine when the reactants are heated in dilute acetic acid at 90-95°C. When a solution of tetrahydropyrimidine If is boiled in methanol in the presence of TsOH, the product of addition at the carbon—carbon double bond is not formed either. Under analogous conditions, tetrahydropyrimidine Ie forms an equilibrium mixture (~1:1) of two compounds — pyrimidine Ie and a new, chromatographically less-mobile product, apparently 4,6,6-trimethyl-4-methoxyhexahydropyrimidine-2-thione. The same mixture is formed when 4-hydroxypyrimidine IIe is boiled in methanol in the presence of a catalytic amount of TsOH. In the IR spectrum of the mixture obtained, in addition to the absorption bands of tetrahydropyrimidine Ie [3200 (νN—H), 1705 (νC=C), and 1574 cm^{-1} ("thioamide-II")], bands due to vibrations of atoms of 4,6,6-trimethyl-4-methoxyhexahydropyrimidine-2-thione are also observed, in particular strong absorption bands at 1518 cm^{-1} ("thioamide-II") and 1085 cm^{-1} (νC—O).



R = H, Me; R^5 = H, Me, Et; H—Nuc = R^5OH, BuSH, $PhSO_2H$, HN_3, $NH_2C_6H_4Me$

The above reactions are of α-thioureidoalkylation type [7] and take place in an acidic medium, as, apparently, do the analogous reactions of 4-hydroxy- and 4-alkoxyhexahydropyrimidine-2-thiones [16], via the formation of immonium cations (A), which then react with nucleophilic reactants; the preferred direction of attack by the latter is determined by the action of stereoelectronic factors [17].

The intermediate formation of immonium cations (A) is confirmed not only by the stereochemical directivity of the studied reactions but also by the formation of the dimerization products of these cations in a number of cases. Above, we noted the formation of these products in the dehydration of 4-hydroxyhexahydropyrimidine-2-thiones in the presence of acid catalysts In the case of dehydration of hydroxypyrimidine trans-IIb, dimer X obtained was isolated in the pure state by column chromatography and was characterized as 6-methyl-5-(trans-5-methyl-2-thioxohexahydropyrimidin-5-yl)-1,2,3,6-tetrahydropyrimidine-2-thione. The latter compound is also formed when hydroxypyrimidine trans-IIb is heated in 95% formic acid or in 0.5-3.6% HCl, and also when acetoxypyrimidine IVa is heated at 150-155°C for 20 min. It should be noted that compound X, which has three chiral centers, is obtained in the form of only two diastereoisomers (Xa:Xb = 63:37), each of which has a trans location of the substituents at the hexahydropyrimidine ring The key stage of formation of dimer X appears to be the stereoselective attack on the $C_{(4)}$ carbon atom of the corresponding cation (A) by the nucleophilic $C_{(5)}$ carbon atom of tetrahydropyrimidine Ib. Obviously, as a result of the low nucleophilicity of this atom, the formation of dimer X becomes appreciable only in the absence of sufficiently strong proton acceptors in the reaction mixture. It should be noted that the formation of dimerization products of certain 1,2,3,6-tetrahydropyrimidine-2-thiones(ones) is also described in [1, 11, 18].

TABLE 1. Properties of the Compounds Ia-d, IId, IVa, b, VIII-X, and XIa, b

Compound	Empirical formula	T_m, °C (solvent)	R_f	UV spectrum,, λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}				Yield, %
					OH, NH	thioamide II	of the region ~1300 cm^{-1} ~1200 cm^{-1}	other vibrations	
Ia	$C_4H_6N_2S$	161...161,5 (toluene)	0,26	207 (3,66), 264 (4,05),*2 291 (3,57)	3222	1590, 1504	1313, 1225	1676 (C=C), 715 (=C–H)	34
Ib	$C_5H_8N_2S$	139,5...140,5 (toluene)	0,29	207 (3,81), 265 (4,08),*3 289 (3,45)	3210	1590, 1510	1302, 1222	1680 (C=C), 735 (=C–H)	92
Ic	$C_6H_{10}N_2S$	82...82,5 (toluene)	0,55	209 (3,88), 265 (4,07), 292 (3,56)	3227	1535	1315, 1295, 1221	1683 (C=C), 736 (=C–H)	79
Id	$C_5H_8N_2S$	193,5...195,5 (toluene)	0,29	209 (3,84), 259 (3,97), 290 (3,83)	3205	1582, 1525	1283, 1220	1700 (C=C)	42
cis-IIId	$C_5H_{10}N_2OS$	196...197,5	0,23	206 (3,90), 245 (4,17)	3305sh, 3229	1554	1279, 1206	1082 (C–O)	75
II									
IVa	$C_7H_{12}N_2O_2S$	124,5...125 (acetonitrile)	–	257 (4,25)*4	3183	1568, 1529	1304, 1193	1742 (C=O), 1236 (C–O)	81
IVb	$C_8H_{14}N_2O_2S$	113...113,5 (ethylacetate)	–	255 (4,28)*4	3251	1529, 1513	1314	1737 (C=O), 1222 (C–O)	85
VIII	$C_5H_9N_5S$	155,5...156 (dec.) (acetrontrile)	0,26	210 (4,11), 259 (4,33)	3171	1574, 1527	1293, 1206	2098 (N_3)	82
IX	$C_{12}H_{17}N_3S$	185...185,5 (acetone)	0,45	*1 208 (4,29), 248 (4,32), 299sh(3,31)	3288, 3190	1570, 1550sh, 1516	1309, 1212	1615 (C=C), 797 (=C–H)	73
X	$C_{10}H_{16}N_4S_2$	269 (dec.) (methanol)	0,26	207 (4,16), 249 (4,21), 276 (4,15)	3225, 3160	1570, 1550, 1515 sh	1209	1691 (C=C)	~100
XIa	$C_5H_8N_2S \cdot HI$	146...146,5	–	222 (4,20), 285 (3,41)	3257, 3157, 3108	1614, 1530	1234	1681 (C=C), 1725 (=C– H)	82
XIb	$C_6H_{10}N_2S \cdot HI$	121...122	–	222 (4,21), 280 (3,50)	3250, 3186, 3146, 3080	1594, 1551	1228	1680 (C=C), 735 (=C–H)	94

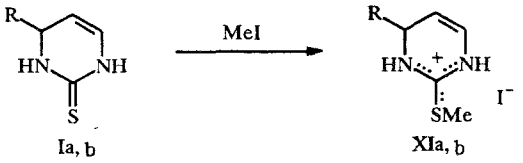
*1Solvent—ethanol.

*2λ_{max} 282 nm (in ether).

*3λ_{max} 277 nm (in acetonitrile), 283 nm (in ether), 285 nm (in heptane), 286 nm (in methylene chloride).

*4Only the π—π^* transition band is given.

Nucleophilic properties in molecules of 1,2,3,6-tetrahydropyrimidine-2-thiones are also manifested by the sulfur atom, as we showed by using the example of the reaction of compounds Ia, b with methyl iodide (acetone, 20°C), which forms hydroiodides of 2-methylthio-3,6-dihydropyrimidines (XIa, b).



Ia, b XIa, b

I, XI a R = H, b R = Me

We observed a high reactivity of 4-acetoxyhexahydropyrimidine-2-thiones (IVa, b) to nucleophilic reactants. Compounds IVa, b hydrolyze rapidly or undergo alcoholysis when heated for a short time in water or alcohols (methanol, ethanol), so that the corresponding 4-hydroxy- or 4-alkoxyhexahydropyrimidine-2-thiones (trans-IIb, c, Va, d) are formed. It was shown that the rate of these reactions increases appreciably in the presence of bases. For example, compound IVa reacts with sodium methoxide in methanol even at room temperature to form methoxypryimidine Va.

The structure of all the synthesized compounds was established on the basis of the body of data on the UV, IR, and PMR spectra (Tables 1, 2, 3).

In the UV spectra of solutions of hexahydropyrimidine-2-thiones cis IId, IVa, b, VIII, and IX in methanol or acetonitrile, two intense ($\log \varepsilon$ 3.90-4.33) absorption bands with maxima in the ranges 206-210 nm and 245-259 nm, characteristic of the nonconjugated thioureide chromophore [19, 20], are observed. In addition to the two indicated bands, the electron spectrum of 4-arylaminopyrimidinethione IX contains a "benzene" band with a maximum at 299 nm (Table 1).

The electron spectra of 1,2,3,6-tetrahydropyrimidine-2-thiones Ia-d in methanol contain an intense absorption band in the 207-209 nm range ($\log \varepsilon$ 3.66-3.88) as well as a strong band with a maximum in the 259-265 nm range, which has a shoulder on its long-wavelength portion. We decomposed the latter complex absorption band into two partial bands with maxima at 259-265 nm ($\log \varepsilon$ 3.97-4.08) and 289-292 nm ($\log \varepsilon$ 3.45-3.83), in accordance with the method described in [21] (Table 1).

Using the example of compound Ib, we showed that the intense band at 265 nm shifts into the short-wavelength region of the spectrum as the solvent polarity increases in the series heptane—ether—acetonitrile—methanol (Table 1), this being in good agreement with the nature of the influence of the solvent on the position of the π—π^* transition band in thioureide-containing compounds [20]. On this basis, the absorption band of compounds Ia-d in the 259-265 nm range may be attributed to the π—π^* transition of the thioureide chromophore. In this case, the replacement of an aprotic solvent by a protic one has a particularly marked effect. Thus, when the solvent is changed from acetonitrile to methanol, the band shifts by 12 nm in the short-wavelength direction.

We assigned the absorption band at 289-292 nm in the UV spectra of tetrahydropyrimidinethiones Ia-d to the π—π^* transition in the double bond of the enamine fragment of the molecules. This assignment is supported by the high strength of this band, and this indicates that the latter may be due to the forbidden transition n—π^* [22], and by the constancy of the position and strength of the band in going from the tetrahydropyrimidinethiones Ia, b to the corresponding hydroiodides of 3,6-dihydropyrimidines XIa, b. In the latter compounds, in addition to the band of the π—π^* transition in the carbon—carbon double bond, an intense absorption band of the thiouronium chromophore at 222 nm is also observed. The electron spectrum of compound X, which has a fragment of hexahydropyrimidine-2-thione and a fragment of 1,2,3,6-tetrahydropyrimidine-2-thione, is a superposition of the spectra of the two corresponding chromophore systems (Table 1).

A characteristic feature of the IR spectra of hexahydropyrimidine-2-thiones cis-IId, IVa, b, VIII, IX, 1,2,3,6-tetrahydropyrimidine-2-thiones Ia-d, X, and hydroiodides of 3,6-dihydropyrimidines XIa, b is the presence of intense absorption bands in the 1500-1600 cm^{-1} region (thioamide II) as well as broad bands of stretching vibrations of the N—H group(s) in the 3080-3288 cm^{-1} range. In addition to the above bands, the spectra of tetrahydropyrimidine-2-thiones also show the stretching-vibration bands of the C=C bond, and the spectra of 4-functionally substituted hexahydropyrimidine-2-thiones show the presence of bands due to vibrations of substituents at the $C_{(4)}$ carbon atom (Table 1).

On the basis of PMR spectroscopy data (Table 3), we concluded that the hexahydropyrimidine ring of compounds cis-IId, IVa, b, VIII-X has a chair conformation with an axial orientation of the substituent at the $C_{(4)}$ carbon atom and an equatorial position of the second substituent. This conformation is preferred apparently because of the presence of the anomeric effect in the molecules of these compounds. Previously [15, 16, 23], a manifestation of this effect had been observed in molecules of other 4-functionally substituted hexahydropyrimidine-2-thiones.

TABLE 2. PMR Spectra of 1,2,3,6-Tetrahydropyrimidine-2-thiones (Ia-d), Tetrahydropyrimidine Fragment of Compound X, and Hydroiodides of 2-Methylthio-3,6-dihydropyrimidines (XIa, b)

Compound	Chemical shift, δ, ppm (coupling constant, J, Hz)							
	4-H (J_{45})	5-H (J_{56})	6-H (J_{46})	5- or 6-CH_3 ($J_{CH3,CH}$)	N(1)—H ($J_{NH,6-H}$; $J_{NH,5-H}$)	N(3)—H ($J_{NH,4-H}$; $J_{NH,5-H}$)	other protons	solvent
Ia	6,10 (8,0)	4,96 (3,1)	3,99 (1,5)	—	7,50 (1,7;~1,5)	8,49 (4,6;~1,5)	—	Acetone D_6
Ib	5,93 (8,0)	4,81 (3,2)	4,21 (1,4)	1,29 (6,5)	7,42 (1,7; 2,2)	8,51 (4,8; 1,8)	—	$CDCl_3$
Ic	5,94 (8,0)	4,91 (3,3)	4,19 (1,5)	1,28 (6,4)	6,76 (~0; 2,4)	—	3,40 (s, NCH_3)	$CDCl_3$
Id	5,70	—	3,67	1,51	8,14	9,11	—	DMSO-D_6
Xa	5,83	—	3,81...3,98*	1,09...1,14**	8,63 (~1,8; -)	9,60 (4,6; -)	See Table 3	DMSO-D_6
Xb	5,59	—	3,81...3,98*	1,09...1,14**	8,54 (~1,5; -)	9,53 (4,9; -)	See Table 3	DMSO-D_6
XIa	6,26 (8,0)	5,24 (3,2)	4,09 (1,6)	—	10,31		2,62 (s, SCH_3)	DMSO-D_6
XIb	6,30 (7,7)	5,25 (3,8)	4,36 (0,9)	1,26 (6,4)	10,44		2,65 (s, SCH_3)	DMSO-D_6

*The signals overlap with those of the analogous proton of the second isomer and with the signals of the 4′-H proton of both isomers.

**The signals overlap with those of the analogous proton of the second isomer and with the signals of the 6′-CH_3 protons of both isomers.

EXPERIMENTAL

The IR spectra were recorded with Perkin—Elmer 1310 or UR-10 instruments on compounds in the form of suspensions in Vaseline oil (compounds Ib, d, cis-IId, VIII, and XIa, b) or in KBr pellets (compounds Ia, c, IVa, b, IX, and X). The electron spectra in the 200-400 nm range were obtained with Specord UV-Vis or Beckman DU-6 spectrophotometers for solutions of the compounds in methanol (Ia-d, cis-IId, X, XIa, b) or acetonitrile (Merck) (IVa, b, VIII) in a concentration of $5 \cdot 10^{-5}$ mole/liter. The PMR spectra were recorded with Bruker MSL-200 (200 MHz) and Bruker WM-250 (250 MHz) spectrometers for solutions of samples in DMSO-D_6 or $CDCl_3$, with HMDS as the internal standard. The course of the reaction and the purity of the products were monitored by TLC on plates of Kieselgel 60 F_{254} (Merck) in the system, chloroform—methanol 19:1 (compounds Ia-d, VIII) or 9:1 (compounds cis-IId, IX, X), and the spots were developed in UV light or in iodine vapor. The R_f values were determined under standard conditions of Stahl chromatography [24]. The column chromatography was carried out on L40/100 μ silica gel (Czechoslovakia).

The data of ultimate analysis of the synthesized compounds for C, H, N, and S correspond to the calculated data.*

1,2,3,6-Tetrahydropyrimidine-2-thione (Ia). A. Into a round-bottom flask provided with a stirrer and a Dean—Stark receiver are poured 0.2314 g (1.751 mmoles) of hydroxypyrimidine (IIa) [23], 0.0020 g (0.012 mmoles) of p-toluenesulfonic acid, and 100 ml of toluene. The mixture is heated with boiling and vigorous stirring for 1.5 h, the solution is filtered off, cooled to −15°C, and the precipitate is filtered off, washed with toluene and hexane, and dried. Compound Ia, recrystallized from toluene, is obtained in the amount of 0.669 g (33.5%).

*We were unable to obtain a satisfactory ultimate analysis for compound X.

TABLE 3. PMR Spectra of Hexahydropyrimidine-2-thiones IId, IVa, b, VIII, and IX and of the Hexahydropyrimidine Fragment of Compound X in DMSO-D_6

Compound	Chemical shift, δ, ppm (coupling constant, J, Hz)							
	4-H_e ($J_{4e,5e}$; $J_{4e,5a}$)	5-H_a ($J_{5a,6a}$)	5-H_e ($J_{5e,5a}$)	6-H ($J_{5e,6a}$)	5- or 6-CH_3 ($J_{CH3,CH}$)	N(1)—H ($J_{NH,6-H}$)	N(3)—H ($J_{NH,4-H}$)	other protons
cis-IId	4,43 (–; 2,7) ($J_{4e,6e}$~0,8)	1,76 (11,6) ($J_{5a,6e}$ = 6,1)	— (–)	2,87...2,96 m (–) ($J_{6e,6a}$ = =12,4)	0,86 (6,6)	8,15 (*1)	8,42 (4,5)	5,79 (d OH, J=5,4)
IVa	5,76 (1,9; 2,9)	1,52 (12,3)	1,97 (14,0)	3,48 (4,0)	1,16 (6,4)	8,66 (~0)	8,70 (4,8)	2,04 (s CH_3C=O)
IVb	6,04 (2,4; 2,8)	1,70 (12,6)	2,05 (14,0)	3,50 (4,0)	1,15 (6,5)	8,64 (~0)	—	3,24 (s, N—CH_3), 2,08 (s, CH_3C=O)
VIII	5,08 (2,2; 3,6)	1,46 (12,0)	1,85 (13,7)	3,40 (3,8)	1,15 (6,5)	8,55 (~0)	8,97 (4,6)	—
IX	4,70 (2,1; 4,2)	1,46 (11,9)	1,87 (13,7)	3,61 (4,0)	1,14 (6,5)	8,19 (~0)	8,33 (3,4)	6,88 (d, CH(Ar), J=8,3); 6,63 (d, CH(Ar)); 5,86 (d, NHAr, $J_{NH,4e}$=8,3); 2,14 (s, CH_3Ar)
Xa	3,81...3,98 (*1; 5,0) *2	1,50 (9,8)	~1,88 (13,4)	3,26 (~4,5)	1,09...1,14 (~6,5) *3	8,06 (~0)	8,17 (2,6)	See Table 2
Xb	3,81...3,98 (*1; 5,0) *2	1,37 (10,4)	~1,88 (13,4)	3,17 (~3,7)	1,09...1,14 (~6,5) *3	8,01 (~0)	8,12 (3,3)	See Table 2

*1The coupling constant cannot be determined.

*2The signals overlap with those of the analogous proton of the second isomer and with those of the 6-H proton of the tetrahydropyrimidine fragment of both isomers.

*3The signals overlap with those of the analogous proton of the second isomer and with those of 6-CH_3 protons of the tetrahydropyrimidine fragment of both isomers.

B. A mixture of 2.70 g (20.4 mmoles) of hydroxypyrimidine IIa, 4.5 g of molecular sieves (4 Å), 60 ml of p-xylene, and a few crystals of zinc chloride is heated with boiling and vigorous stirring for 30 min. The solution above the precipitate is decanted, the residue is similarly treated four times with boiling xylene (in 60-ml portions) in the presence of zinc chloride, and the combined xylene solution is evaporated under reduced pressure. Compound Ia, obtained in the amount of 0.44 g (18.9%) is purified by chromatographing on a column with silica gel (15 g) and eluted with ether. Pyrimidine Ia, recrystallized from isopropyl alcohol, is obtained in the amount of 0.24 g.

6-Methyl-1,2,3,6-tetrahydropyrimidine-2-thione (Ib). A. It is obtained in the same manner as compound Ia, in 38.3% yield, by method **A** from hydroxypyrimidine trans-IIb. It is purified by recrystallization from toluene.

B. Into a two-neck round-bottom flask with a Stark—Dean receiver are poured 10.05 g (68.7 mmoles) of hydroxypyrimidine trans-IIb, 175 ml of toluene, and a few crystals of zinc chloride are added. The mixture is boiled for 4 h with stirring. The hot solution is filtered through a layer of Al_2O_3 (2 cm), and the solvent is driven off under reduced pressure. Pyrimidine Ib is obtained in the amount of 4.66 g (52.9%) with an admixture of compound X. Column chromatography on silica gel (eluent, ether—hexane, 1:2 → 3:1) is used to separate 3.74 g of compound Ib, which is recrystallized from isopropyl alcohol. From the fractions containing a substance with R_f 0.26 (Kieselgel 60 F_{254}, 9:2 chloroform—methanol), 0.10 g of compound X is obtained.

An analogous method is used with hydroxypyrimidine trans-IIc to synthesize 3,6-dimethyl-1,2,3,6-tetrahydropyrimidine-2-thione (Ic), which is recrystallized from toluene.

C. A mixture of 0.0899 g (0.478 mmole) of acetoxypyrimidine IVa and 5 ml of toluene is heated with boiling for 2 h, the solution is filtered off, and the solvent is driven off under reduced pressure. Compound Ib is obtained in the amount of 0.0562 g (91.8%).

Similarly, tetrahydropyrimidine Ic is obtained from acetoxypyrimidine IVb in 79.1% yield.

D. A mixture of 0.407 g (2.78 mmoles) of hydroxypyrimidine trans-IIb and 1.2 g of silica gel (40/100μ) is heated for 10 min for 150-160°C, then cooled to room temperature, and the product is extracted with chloroform. After the solvent is driven off, 0.166 g (46.5%) of compound Ib is obtained.

E. A solution of 0.200 g (1.37 mmoles) of hydroxypyrimidine trans-IIb in 2 ml of DMSO, containing 1 drop of concentrated sulfuric acid, is kept for 2 h at room temperature, 4 ml of water is added, the product is extracted with chloroform (3 × 3 ml), and the extract is washed with water (6 ml) and dried over calcium chloride. After the solvent is driven off, 0.027 g (15.4%) of compound Ib is obtained.

5-Methyl-1,2,3,6-tetrahydropyrimidine-2-thione (Id). A. It is obtained, like compound Ia, by method **A** from hydroxypyrimidine cis-IId in 41.7% yield. Compound Id is purified by recrystallization from toluene.

B. It is obtained, like compound Ia, by method **B** from hydroxypyrimidine cis-IId in 42.2% yield. It is recrystallized from isopropyl alcohol.

4,6,6-Trimethyl-1,2,3,6-tetrahydropyrimidine-2-thione (Ie). A mixture of 0.950 g (5.45 mmoles) of hydroxypyrimidine IIe and 10 ml of acetonitrile is boiled with stirring for 5 h, evaporated down to a volume of 3 ml, cooled, and the precipitate is filtered off, washed with cold acetonitrile, and dried. Compound Ie is obtained in the amount of 0.782 g (91.8%), and its properties agree with reported data [1].

Tetrahydropyrimidine If, whose properties are consisted with reported data [10], is synthesized in 90.9% yield from hydroxypyrimidine IIf by a similar method.

trans-4-Hydroxy-6-methylhexahydropyrimidine-2-thione (trans-IIb). A. It is obtained by the method described in [23] by the reaction of 3-isothiocyanatobutanol (IIIb) [25] with ammonia in ether.

B. To a mixture of 100.60 g (1.435 moles) of freshly distilled crotonaldehyde, 195.0 g (2.007 moles) of potassium thiocyanate, 0.5 g of hydroquinone, and 150 ml of water in a nitrogen atmosphere is added, with vigorous stirring at 0°C for 3 h, a solution of 57 ml (104.88 g; 1.046 moles) of concentrated sulfuric acid in 100 ml of water. The reaction mixture is stirred for 3 h at 20°C, then for 1 h at 30-35°C, 120 ml of ether is added, the organic layer is separated, neutralization with a saturated aqueous solution of sodium bicarbonate is carried out until the color of the mass changes from red to lemon yellow, and the mass is washed with water (2 × 100 ml). To the obtained ether solution of 3-isothiocyanatobutanal is added 10 ml of isopropyl alcohol, and 102 g (1.497 moles) of a 25% aqueous solution of ammonia is added dropwise for 1 h with stirring in a current of nitrogen at —10 to —15°C, and the precipitate is filtered off, washed with cold water and cold acetone, and dried. The product, recrystallized from water, is obtained in the amount of 123.19 g (58.7%).

A similar procedure is used with crotonaldehyde to obtain trans-4-hydroxy-3,6-dimethylhexahydropyrimidine-2-thione (trans-IIc) in 58% yield.

C. A mixture of 0.621 g (3.30 mmoles) of acetoxypyrimidine IVa and 2 ml of water is heated with boiling for 5 min, the solution is cooled, and the precipitate is filtered off, washed with cold water, and dried. Compound trans-IIb is obtained in the amount of 0.364 g (75.5%).

A similar procedure is used to obtain compound trans-IIc in 83.2% yield by hydrolysis of acetoxypyrimidine IVb.

cis-4-Hydroxy-5-methylhexahydropyrimidine-2-thione (cis IIb). To a solution, cooled to 0°C, of 18.33 g (0.142 mole) of 3-isothiocyanato-2-methylpropanol (IIIc) [25] in 200 ml of dry ether is poured 250 ml of dry ether saturated with ammonia at 0°C. Through the mixture obtained is passed a current of ammonia at 0°C until the precipitation of the product is complete. The ether is decanted, the residue is treated several times with fresh portions of dry ether, and the precipitate is filtered off, washed with ether, and dried. Compound cis-IId, purified by washing with cold THF or cold acetone, is obtained in the amount of 15.70 g (75.7%). Compound cis-IId can then be recrystallized from acetone or acetonitrile, but according to the data of IR and PMR spectroscopy such purification gives rise to an admixture of a second diastereoisomer — compound trans-IId.

trans-4-Acetoxy-6-methylhexahydropyrimidine-2-thione (IVa). A mixture of 20.00 g (137 mmoles) of compound trans-IIb, 19.5 ml (21.10 g; 207 mmoles) of freshly distilled acetic anhydride and 70 ml of dry pyridine is stirred at 20°C. After 1 h, crystals of compound IVa begin to separate out of the solution formed. The stirring is continued for 12 h, the mixture is cooled to 0°C, the precipitate is filtered off, washed with cold pyridine, cold acetone, and ether, then dried, and 15.29 g of compound IVa is obtained. Treatment of the mother liquor is used to separate an additional 5.53 g of pyrimidine IVa. The total yield is 20.82 g (80.8%). The substance is purified by recrystallization from acetonitrile.

Acetoxypyrimidine IVa is also obtained in 66.3% yield by a similar procedure by reacting compound cis-IIb [23] with acetic anhydride in pyridine.

Similarly, compound trans-IIc is used to obtain in 85.4% yield trans-4-acetoxy-3,6-dimethylhexahydropyrimidine-2-thione (IVb), which is recrystallized from ethyl acetate.

trans-6-Methyl-4-methoxyhexahydropyrimidine-2-thione (Va). A. A solution of 0.118 g (0.920 mmole) of tetrahydropyrimidine Ib and 0.0007 g of $TsOH \cdot H_2O$ in 4 ml of methanol is boiled for 2 h, dried almost to dryness, then cooled, and the precipitated crystals are filtered off, washed with cold methanol, and dried. Compound Va is obtained in the amount of 0.126 g (85.4%).

A similar procedure is used to obtain methoxypyrimidine Vc in 60.3% yield from tetrahydropyrimidine Ic.

B. A mixture of 0.557 g (2.96 mmoles) of acetoxypyrimidine IVa and 4 ml of anhydrous methanol is heated with boiling for 1 h, then cooled, and the precipitate is filtered off, washed with cold methanol, and dried. Compound Va is obtained in the amount of 0.387 g (81.7%).

A similar procedure is used to synthesize ethoxypyrimidine Vd in 85.3% yield by boiling acetoxypyrimidine IVb in ethanol.

C. To a solution of 0.052 g (2.245 mmoles) of sodium in 2 ml of anhydrous methanol is added 0.354 g (1.881 mmoles) of acetoxypyrimidine IVa. The mixture obtained is stirred for 12 h at room temperature, then cooled, and the precipitate is filtered off, washed with cold methanol, and dried. Compound Va is obtained in the amount of 0.244 g (80.9%).

The physical constants and spectral properties of the alkoxypyrimidines Va, c, d obtained are consistent with reported data [23].

trans-6-Methyl-4-ethoxyhexahydropyrimidine-2-thione (Vb). A mixture of 0.020 g (0.156 mmole) of tetrahydropyrimidine Ib, 0.020 g (0.339 mmole) of KOH, and 0.6 ml of 80% ethanol is allowed to stand for 2 h at 60°C, and cooled, the precipitated crystals are filtered off, and 0.021 g (77.2%) of compound Vb is obtained, whose physical constants and spectral properties are consistent with reported data [23].

trans-4-Butylthio-6-methylhexahydropyrimidine-2-thione (VI). A mixture of 0.106 g (0.83 mmole) of tetrahydropyrimidine Ib, 0.097 g (1.08 mmoles) of butanethiol, and 0.3 ml of 9% hydrochloric acid is heated for 10 min at 95°C, then cooled, the precipitated is filtered off, washed with water on a filter, and dried. Compound VI, whose spectral properties are consistent with reported data [16], is obtained in the amount of 0.135 g (74.4%).

6-Methyl-4-phenylsulfonylhexahydropyrimidine-2-thione (VII). A mixture of 0.2118 g (1.652 mmoles) of tetrahydropyrimidine Ib, 0.2844 g (2000 mmoles) of benzenesulfonic acid, and 3 ml of water is stirred for 24 h at room temperature, cooled, and the precipitate is filtered off, washed with cold water, and dried. Compound VII, whose spectral properties are consistent with reported data [15], is obtained in the amount of 0.3259 g (73.0%).

trans-4-Azido-6-methylhexahydropyrimidine-2-thione (VIII). An ampul is loaded with 0.438 g (3.42 mmoles) of tetrahydropyrimidine Ib, 0.377 g (5.80 mmoles) of sodium azide, and 2.2 ml of water, then cooled to 0°C, and to the mixture obtained is added a solution, cooled to 0°C, of 0.5 ml (5.83 mmoles) of concentrated hydrochloric acid in 0.4 m of water. The ampul is sealed and heated with periodic shaking for 3.5 h at a bath temperature of 76°C. After cooling, the ampul is opened, and the precipitate is filtered off, washed with cold water, and dried. Compound VIII is obtained in the amount of 0.482 g (82.3%) in a chromatographically pure form, and the compound is purified by recrystallization from ethyl acetate.

trans-6-Methyl-4-(p-tolylamino)hexahydropyrimidine-2-thione (IX). A mixture of 0.2474 g (1.930 mmoles) of tetrahydropyrimidine Ib, 0.4849 g (4.525 mmoles) of p-toluidine, 0.75 ml of acetic acid, and 1.5 ml of water is heated with stirring for 50 min at 95°C, then cooled, and the precipitate is filtered off, washed on a filter with water, cold acetone, and ether, and dried. Compound IX, purified by recrystallization from acetone, is obtained in the amount of 0.3299 g (72.6%).

6-Methyl-5-(6-methyl-2-thioxohexahydropyrimidin-4-yl)-1,2,3,6-tetrahydropyrimidine-2-thione (X). A. A solution of 0.430 g (2.94 mmoles) of hydroxypyrimidine trans-IIb in 0.5 ml of 0.5% hydrochloric acid is heated for 1.5 h at 95°C, and the precipitate is filtered off, washed with water and acetone, and dried. Compound X, which is purified by recrystallization from methanol, is obtained in the amount of 0.210 g (55.7%).

Compound X is also obtained in 99.5% yield by a similar method involving heating of hydroxypyrimidine trans-IIb in 3.6% hydrochloric acid.

B. A solution of 0.235 g (1.61 mmoles) of hydroxypyrimidine—trans-IIb in 1.2 ml of 85% formic acid is boiled for 1 h, then cooled, and the precipitate is filtered off, washed with water and acetone, and dried. Compound X is obtained in the amount of 0.151 g (73.2%) in the form of a mixture of two diastereoisomers in the ratio 63:27.

C. It is obtained in quantitative yield by heating 0.0405 g (0.215 mmole) of acetoxypyrimidine IVa at 150-155°C under reduced pressure (20-30 torr) for 20 min.

6-Methyl-2-methylthio-3,6-dihydropyrimidine Hydroiodide (XIb). To a mixture of 0.45 g (3.5 mmoles) of tetrahydropyrimidine Ib and 5 ml of acetone is added 1.5 ml (3.42 g; 24.1 mmoles) of methyl iodide, and the solution formed is allowed to

stand in the dark at room temperature for 24 h, then the precipitate is filtered off, washed with acetone, and dried. Compound XIb is obtained in the amount of 0.57 g. Treatment of the mother liquor yields an additional 0.32 g of product. The total yield of compound XIb is 0.89 g (93.9%).

Compound XIa is obtained in 81.5% yield by a similar procedure in which tetrahydropyrimidine Ia is reacted with methyl iodide.

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