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SYNTHESIS AND STERIC STRUCTURE OF 4-ARYLAMINOHEXAHYDROPYRIMIDINE-2-THIONES

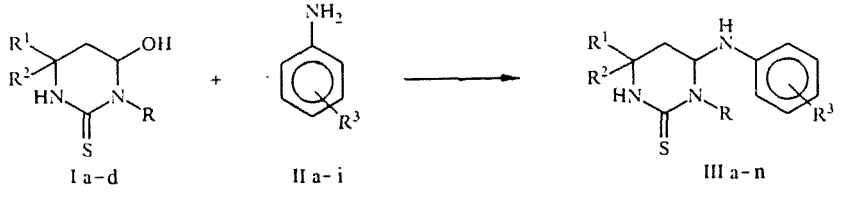
A. D. Shutalev, M. T. Pagaev, and L. A. Ignatova

Reaction of 4-hydroxy- and 4-methoxyhexahydropyrimidine-2-thiones and 6-methyl-1,2,3,6-tetra-hydropyrimidine-2-thione with primary amines occurs readily in the presence of acidic or basic catalysts to give 4-arylaminohexahydropyrimidine-2-thiones both regio- and stereoselectively. It was shown that reaction stereoselectivity depends on the structure of the starting materials and on the reaction conditions. The steric structures of the products synthesized has been studied.

4-Substituted hexahydropyrimidine-2-thiones(ones) are an extremely valuable class of compounds. On one hand this is due to their range of reactivities and can be used to synthesize pyrimidines [1-6], 1,3-thiazines [7], pyridines [8], condensed heterocyclic systems [9, 10], etc. On the other hand they show a wide spectrum of practical and useful properties. They have radioprotective properties [11], pesticidal activity [12, 13], and are used as fertilizers [14] or rubber additives [15], and in the textile industry [16], etc.

The main method for obtaining 4-substituted hexahydropyrimidine-2-thiones(ones) is the reaction of the readily available 4-hydroxy- and 4-alkoxyhexahydropyrimidine-2-thiones(ones) of 1,2,3,4-tetrahydropyrimidine-2-thiones(ones) with different nucleophilic reagents and this can be considered as an α-aminoalkylation reaction [17, 18]. The behavior of these compounds with certain O-, S-, H-, and C-nucleophiles has been reported previously [4, 5, 19-22]. The reactions with such N-nucleophiles as ureas [4], hydroxylamine [23], and phenylhydrazine [3] have been reported. However, that with N-nucleophiles has been little investigated particularly from the aspect of the reaction stereochemistry and the structure of the products. In order to extend our systematic work on the α-aminoalkylation reaction of hydrogenated nitrogen heterocycles [24-27], it was thought very appropriate to look at the reaction of 4-hydroxy- and 4-alkoxyhexahydropyrimidine-2-thiones and 6-methyl-1,2,3,6-tetrahydropyrimidine-2-thione with different arylamines. The latter are typical N-nucleophiles and able to show C-nucleophilic properties in a number of examples. We chose to examine the regio- and stereochemical aspects of the reaction and to investigate the steric structure of the products, particularly possible anomeric effects in these molecules.

It was shown that 4-hydroxyhexahydropyrimidine-2-thione (Ia), trans-(Ib, c), and cis-(Ib) react readily with arylamines (IIa-i) upon standing in 0.5-3.6% hydrochloric acid (method A) or in 10-50% acetic acid (method B) at 50-95°C. The 4-arylaminohexahydropyrimidine-2-thione (IIIa-m) products are obtained in yields up to 98% and are isolated from the reaction mixture as a water insoluble crystalline precipitate. The reaction time depends on the temperature and the structure of the heterocyclic compound. Hence at 70-95°C the reaction of arylamines with the hydroxythiones Ia, trans-Ib, and cis-Ib is complete in 0.4-1 h whereas hydroxythione trans-Ic takes 2.2-3.5 h. Products IIIa-k are usually obtained as a mixture of cis- and trans- isomers (Table 1).



I a–d II a–i III a–n

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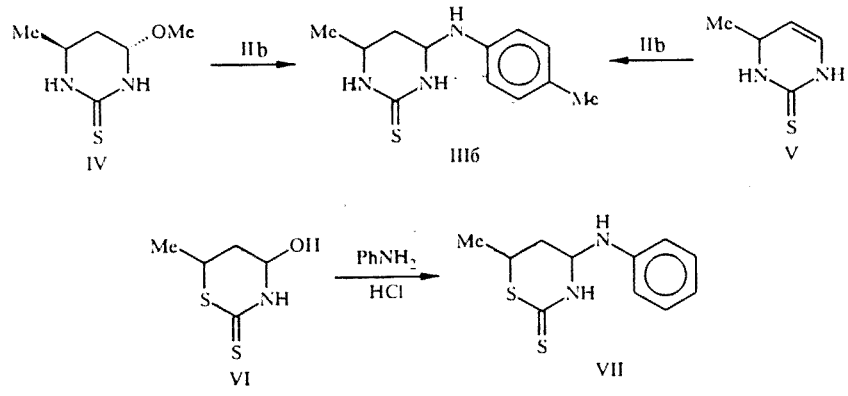

I a R = R^1 = R^2 = H; b R = R^2 = H, R^1 = CH_3; c R = R^1 = CH_3, R^2 = H; d R = H, R^1 = R^2 = CH_3.
II, IIIa—i a R^3 = 4-OCH_3, b R^3 = 4-CH_3, c R^3 = H, d R^3 = 3-Br, e R^3 = 3-Cl, f R^3 = 4-C(O)CH_3,
g R^3 = 2-COOH, h R^3 = 3-NO_2, i R^3 = 4-NO_2. IIIa— i R = R^2 = H, R^1 = CH_3. III j R = R^1 = CH_3, R^2 = =H, R^3 = 4-CH_3; k R = R^1 = CH_3, R^2 = R^3 = H; l R = R^1 = R^2 = R^3 = H; m R = R^1 = R^2 = H, R^3 = 3-Br; n R = R^3 = H, R^1 = R^2 = CH_3

Arylamine like aminoalkylation in acid media is also shown by 4-methoxyhexahydropyrimidine-2-thione (IV) and 1,2,3,6-tetrahexahydropyrimidine-2-thione (V). Heating these with p-toluidine in dilute acetic acid gives the 4-(4-methylphenylamino)pyrimidinethione IIIb in 77 and 65% yields respectively (predominantly the trans isomer). The reaction of trans-6-methyl-4-ethylthiohexahydropyrimidine-2-thione with p-toluidine under the same conditions occurs very slowly, evidently due to the low nucleophilicity of the alkylthio group.

The reaction of 4-hydroxy-6-methyltetrahydro-1,3-thiazine-2-thione (VI) with aniline also occurred readily in acidic medium (0.5% hydrochloric acid, 90-95°C) to give a 62% yield of the 4-phenylamino derivative (VII) as a mixture (45:55) of trans- and cis- isomers.

We have also been able to aminoalkylate aniline and p-toluidine with hydroxyhexahydropyrimidine trans-Ib in basic medium (aqueous NaOH, 90-95°C, method C). Under the same conditions the N_3 methyl substituted analog trans-Ic shows virtually no reaction.

In the absence of acid or base catalyst the reaction of trans-Ib with aniline in aqueous medium does not occur. However, at 80-90°C in acetonitrile (method D) or DMF (method F) a mixture of trans- and cis- isomers of the phenylamino derivative IIIc is formed, even without addition of a catalyst. In similar conditions in acetonitrile, hydroxythione Id does not react with aniline. Hydroxythione trans-Ic reacts with p-toluidine in the presence of TsOH (method E) to give the corresponding IIIn, j. (Thione Id was prepared by us by reaction of 3-iso-cyanato-3-methylbutanal (VIII) with ammonia in ether).

It was shown that, in contrast to compounds Ia-d, the reaction of 4-hydroxy-4,6,6-trimethylhexahydropyrimidine-2-thione with aniline in various conditions does not give the aminoalkylation product but forms 4,6,6-trimethyl-1,2,3,6-tetrahexahydropyrimidine-2-thione by dehydration of the starting compound. Its structure was proved by comparison with a sample synthesized by the method in [22].

Arylamines are ambident nucleophiles. As a result, reaction with Ia-d, IV-VI can occur through aminoalkylation either at the nitrogen atom or in the aromatic ring. By PMR it was shown that all the studied reactions occur exclusively at nitrogen atom of the arylamines, the products of reaction at a carbon atom not being observed. It should be noted that in the literature, reaction of certain 4-hydroxy- and 4-alkoxyhexahydropyrimidine-2-ones and 1,2,3,6-tetrahexahydropyrimidine-2-thiones(ones) with substituted phenols in acidic medium occurs via C-aminoalkylation [4, 22].

It was found that the diastereoselectivity of the aminoalkylation of the arylamines by Ib, c, IV, VI depends to a significant degree on the structure of the aminoalkylating and nucleophilic reagents, the reaction temperature, the nature of the solvent, and the type and concentration of catalyst (see Table 1). As seen in this table, the reaction of Ib, c and IV with arylamines in acidic medium (methods A and B) occurs with a quite high diastereoselectivity (mostly exceeding 50%). For reaction of hydroxythiazine VI with aniline by method A this is much lower than for trans-Ib with aniline under the same conditions (10% compared with 66%).

TABLE 1. Diasteroselective Reaction of Compounds Trans-Ib, c, Cis-Ib, IV, VI with Arylamines IIa-i

Starting material		Reaction conditions			Reaction production	Ratio of isomers,*2, trans:cis, %	Yield, %
heterocycle	arylamine	method*	T, °C	time, h			
trans-Ib	IIa	A	95	0,5	IIIa	16 : 84	88,3
		B	90	0,4	IIIa	18 : 82	87,3
	IIb	A	95	0,5	IIIb	93 : 7	91,3
		B	90	0,6	IIIb	>96 : 4	89,2
		C	90	5,0	IIIb	>96 : 4*3	74,0
	IIc	A	95	0,5	IIIc	83 : 17	90,3
		A	70	1,0	IIIc	67 : 33	89,4
		A	50	4,5	IIIc	70 : 30	90,0
		A*4	70	0,5	IIIc	70 : 30	94,5
		B	70	0,7	IIIc	91 : 9	88,9
		C	95	4,0	IIIc	64 : 36	75,5
		D	82	8,0	IIIc	57 : 43	74,8
		D	82	22,0	IIIc	53 : 47	74,8
		F	90	8,5	IIIc	72 : 28	74,8
	IId	A	95	0,5	IIId	14 : 86	83,0
		A*5	95	0,5	IIId	78 : 22	78,7
		B	90	0,8	IIId	5 : 95	95,7
	IIe	B	70	0,5	IIIe	29 : 71	87,3
	IIf	B	70	1,0	IIIf	<4 : 96*3	79,3
	IIg	B	95	0,8	IIIg	90 : 10*3	87,9
	IIh	B	90	1,0	IIIh	<4 : 96*6	94,4
	IIi	A	95	0,5	IIIi	88 : 12	90,0
		B	90	1,0	IIIi	88 : 12	91,7
cis-Ib	IIc	D	82	8,0	IIIc	65 : 35	75,7
trans-Ic	IIb	A*4	90	2,2	IIIj	69 : 31	49,6
		E	82	4,0	IIIj	67 : 33	25,6
	IIc	A*4	90	3,5	IIIk	94 : 6	68,1
IV	IIb	B	90	0,5	IIIb	92 : 8	76,6
VI	IIc	A	95	0,7	VII	45 : 55	62,4

*Using method A with 0.5% HCl (unless indicated otherwise).

*2From PMR data for unpurified products (unless indicated otherwise).

*3After washing the mixture with refluxing acetone.

*4Using 1% HCl.

*5Using 3.6% HCl.

*6After reprecipitation of the material from a solution in DMF with water, loss on purification being 5%.

In the case of the aminoalkylation of trans-Ib in acidic medium using various arylamines there is not observed an obvious correlation between the structure of the latter and the stereo direction of the reaction. Thus predominance of cis-diastereomer products occurs in reaction of trans-Ib with arylamines having both donor and acceptor substituents. Thus reaction of trans-Ib with p-anisidine or m-bromoaniline in 0.5% HCl (95°C, 30 min) gives predominantly cis-IIIa, d whereas trans-Ib with toluidine or p-nitroaniline gives mostly trans-IIIb,i under analogous conditions. On the other hand, with identical substituents in the nucleophile, change in their position can affect the reaction of trans-Ib with p-nitro- and m-nitroanilines (method B) (respectively trans- and cis- diastereoselective processes).

The effect of temperature on the reaction selectivity of arylamines with I is seen in the reaction of trans-Ib with aniline in dilute hydrochloric acid leading to IIIc. Upon decreasing the temperature from 95 to 70°C the trans isomer content of the latter decreases from 83 to 67%. Further lowering of the temperature to 50°C has virtually no effect on the product isomer ratio. Catalyst concentration also has an effect on reaction stereoselectivity. Thus reaction of trans-Ib with m-bromoaniline with 0.5% or 3.6% hydrochloric acid gives a mixture of trans- and cis- IIId in the ratio 14:86 and 78:22 respectively.

TABLE 2. Parameters for Id, IIIa-n, VII, IX

Compound	Empirical formula	Mp*, *2, °C	UV spectrum*3, λ_{max}, nm (log ∈)	IR spectrum*4, ν, cm^{-1}				Yield, *5, % (method)
				OH, NH	thioamide-II	Ar	other vibrations	
1	2	3	4	5	6	7	8	9
Id	$C_6H_{12}N_2OS$	151...152	207 (3,99), 246 (4,19)	3255, 3220	1547, 1528	—	1182, 1105	27,4
IIIa	$C_{12}H_{17}N_3OS$	180,5...181	209 (4,36), 247 (4,45), 308 (3,56)	3362, 3293, 3240	1551, 1528, 1513, 1502	3064, 1618, 813	1207	88,3 (A)
IIIb	$C_{12}H_{17}N_3S$	185...185,5	208 (4,29), 248 (4,32), 299 (3,31)	3288, 3190	1570, 1550, 1516	3016, 1615, 797	1309, 1212	94,0 (B)
IIIc	$C_{11}H_{15}N_3S$	174,5...175,5	248 (4,34), 294 (3,19)	3404, 3287, 3188	1563, 1543, 1507	1596, 747, 698	1211	97,0 (A)
IIId	$C_{11}H_{14}BrN_3S$	192,5...193	215 (4,44), 250 (4,45), 298 (3,58)	3395, 3317, 3217	1548, 1511, 1501	3065, 1601, 777	1207	97,6 (B)
IIIe	$C_{11}H_{14}ClN_3S$	192...192,5	213 (4,39), 250 (4,37), 298 (3,43)	3382, 3299, 3198	1549, 1504	3058, 1605, 776, 714	1310, 1210	87,3 (B)
IIIf	$C_{13}H_{17}ClN_3OS$	208,5...209 (decomp.)	—	3230	1552, 1512, 1500	3076, 3051, 1603, 827	1654, 1217	96,0 (A)
IIIg	$C_{12}H_{15}N_3O_2S$	192...192,5 (decomp.)	222 (4,39), 250 (4,34), 339 (3,69)	3370, 3200, 2648, 2570	1567, 1532, 1497	1600, 748	1653, 1206	87,9 (B)
IIIh	$C_{11}H_{14}N_4O_2S$	205...205,5 (decomp.)	250 (4,29), >357	3428, 3256	1545, 1530 sh 1500	3080, 1620, 799	1342, 1207	94,4 (B)
IIIi	$C_{11}H_{14}N_4O_2S$	205,5...206 (decomp.)	209 (4,11), 247 (4,22), >357	3383, 3190	1566, 1546, 1500	3100, 1598, 836	1320, 1210	91,7 (B)
IIIj	$C_{13}H_{19}N_3S$	149,5...150,5	250 (4,39), 300 (3,28)	3287	1513, 1501	3025, 1614, 812	—	49,6 (A)
IIIk	$C_{12}H_{17}N_3S$	169,5...170,5	250 (4,41), 294 (3,34)	3400, 3244	1506 sh 1487	3030, 1594, 752, 698	—	68,1 (A)
IIIl	$C_{10}H_{13}N_3S$	169...169,5	207 (4,29), 248 (4,36), 293 (3,17)	3292, 3208	1560, 1520	1593, 1487, 747, 694	1200	76,3 (A)
IIIm	$C_{10}H_{12}BrN_3S$	177...178	209 (4,53), 250 (4,39), 296 (3,35)	3334 sh 3273, 3218	1555, 1529	1597, 764, 717	1299, 1197	42,9 (A)

This stereoselectivity data for the reaction of Ib, c, IV, and VI with arylamines and an acidic catalyst in aqueous media (methods A, B) can be explained if the process occurs principally under conditions of kinetic control via an S_N1 mechanism. Moreover, the direction of attack of the nucleophile on the intermediate carbonium ions is governed by a fine balance of steric and electronic factors (the stabilizing effect of the unshared N_3 electron pair on the C_4-N bond arising upon axial attack [28]). Thermodynamic factors also affect the observed ratio of isomers in the products. Predominating stereoelectronic control is characterized in the example of the reaction of 4-hydroxy(alkoxy)hexahydropyrimidine-2-thiones with alkanethiols [19] (as a

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9
IIIn	$C_{12}H_{17}N_3S$	191...192	208 (4,34), 246 (4,43), 293 (3,24)	3431, 3260, 3200	1545	3065, 1597, 1495, 730	1172	92,7 (E)
VII	$C_{11}H_{14}N_2S_2$	148,5...149 (decomp.)	207 (4,33), 245 (4,29), 291 (4,22)	3265, 3120	1491	1601, 753, 691	1307	62,4 (A)
IX	$C_7H_{14}N_2OS$	181	207 (3,88), 247 (4,18)	3210	1567, 1527	—	1177, 1065	69,6

*Compounds Id, IIIc, IX were purified by recrystallization from MeOH, IIIa, b, k, *l*, n, VII from acetone, IIIj from EtOAc, IIIm from acetonitrile IIId, f, h, i by reprecipitation with water from DMF; solution, and IIIe,g by washing with refluxing acetone.

*2For IIIa, d-f, h the mp is given for the cis isomers, for IIIb, c, k the trans isomers, and IIIg, i, j a mixture of cis and trans isomers in the ratios 90:10, 84:16 and 70:30 respectively.

*3Compounds IIIa, b, d, e, were measured in ethanol, the rest in methanol.

*4Compounds IIIc, e, *l*-n, VII, IX were recorded as Vaseline mulls, the rest as KBr tablets.

*5Highest yields given.

result of which the thermodynamic and kinetic reaction products coincide). For the reaction of trans-Ib, c, IV, and VI with arylamines it is not so clearly seen apparently because of the weaker anomeric effect of the amino group when compared with an alkylthio group [29].

The diastereoselectivity of the reaction of I with arylamines in the presence of base was studied through treating trans-Ib with p-toluidine and aniline heated in aqueous NaOH solution (90-95°C, method C). Under these conditions the selectivity of the reaction of aniline itself is markedly lower than for acid catalysis (Table 1). Similarly low in selectivity are the reactions of trans- and cis-Ib with aniline when heated in acetonitrile or DMF. This can account for the occurrence of the reaction under thermodynamic control when it is possible to find an equilibrium between the product isomers (homogeneous medium, long reaction time). Confirmation can be found, for example, in the almost unchanged ratio of isomeric products when the reaction in acetonitrile is continued to 8 and 22 hours. Hence, under equilibrium conditions in refluxing acetonitrile, IIIc is obtained as a cis-/trans- mixture with the latter slightly predominating (53-57%). Reaction of trans-Ib with aniline in DMF (90°C) gives a mixture of trans- and cis- IIIc in the ratio 72:28. The isomer ratio is virtually unchanged after a further 2 h at 95°C in DMF. Under the same conditions (DMF, 95°C), cis-IIId is converted to an equilibrium mixture of cis- and trans- isomers in the ratio 60:40.

These results for reaction of Ib-d with arylamines in water in the presence of NaOH or in acetonitrile and DMF can apparently be rationalized in terms of a base catalyzed elimination-addition [19]. Support for this proposal comes, in particular, from the absence of a reaction between trans-Ic (having a methyl at N_3) and aniline in water in the presence of NaOH (see above). The occurrence of a reaction between trans-Ib and aniline in acetonitrile or DMF and its absence in aqueous medium without catalyst addition can also be explained in terms of this mechanism, through the significantly greater basicity of the aniline in aprotic solvents rather than water [30].

In order to correlate the conformational behavior of the 4-arylaminohexahydropyrimidine-2-thiones III and other 4-substituted hexahexahydropyrimidine-2-thiones (see further) we have synthesized 6,6-dimethyl-4-methoxyhexahydropyrimidine-2-thione (IX) by treating Id with methanol in the of TsOH.

The structure of the compounds synthesized was confirmed spectroscopically (see Tables 2, 3).

The UV spectra of Id, IX in methanol show two intense absorption bands at 207 (log ε 3.88-3.99) and 246-247 nm (log ε 4.18-4.19), characteristic of the thiourea chromophore [31]. The electronic spectra of IIIa-n are a summation of the spectra of the two virtually independent thiourea and benzene chromophoric systems. There are two strong bands at 207-222 (log ε 4.11-4.53) and 246-250 nm (log ε 4.22-4.45) as well as a rather low intensity absorption for the benzene ring at longer

TABLE 3. PMR Spectra of 4-Arylaminohexahydropyrimidine-2-thiones IIIa-n in DMSO-D_6

Compound	Chemical shift, δ, ppm, spin-spin coupling (J), Hz								
	4-H, m ($J_{4,5e}$; $J_{4,5a}$)	5-H_a, dq ($J_{5a,6a}$)	5-H_e, dt ($J_{5e,5a}$)	6-H, m ($J_{5e,6a}$)	6-CH_3, d ($J_{CH3,CH}$)	$N_{(1)}$-H ($J_{NH,6-H}$)	$N_{(3)}$-H ($J_{NH,4-H}$)	NH-Ar, d ($J_{NH,4-H}$)	Ar^{*3}, m
1	2	3	4	5	6	7	8	9	10
trans-IIIa	4,70 (*; 4,4)	1,48 (11,2)	1,90 (13,0)	*[2]	*[2]	8,18 s (0)	8,29 d (3,4)	5,66 (~10)	*[2]
cis-IIIa	4,92 (4,3; 10,5)	1,39 (12,4)	2,04 (12,9)	3,50 (2,9)	1,13 (6,7)	7,11 s (0)	8,10 s (0)	5,73 (10,2)	6,61...6,75
trans-IIIb	4,70 (2,1; 4,2)	1,46 (11,9)	1,87 (13,7)	3,61 (4,0)	1,14 (6,5)	8,19 s (0)	8,33 d (3,4)	5,86 (8,3)	6,61...6,90
cis-IIIb	4,98 (4,3; 10,3)	*[2]	*[2]	*[2]	*[2]	*[2]	*[2]	5,92 (10,1)	*[2]
trans-IIIc	4,76 (2,3; 4,2)	1,50 (11,8)	1,91 (13,0)	3,64 (3,8)	1,17 (6,3)	8,24 s (0)	8,41 d (3,5)	6,10 (7,8)	6,55...7,12
cis-IIIc	5,02 (4,3; 10,2)	1,44 (11,4)	2,08 (12,6)	3,54 (3,2)	1,16 (6,4)	7,28 s (0)	8,12 s (0)	6,15 (9,5)	6,57...7,15
trans-IIId	4,75 (*; 4,2)	1,49 (12,8)	1,89 (12,6)	3,60 (*)	1,18 (6,0)	8,26 s (0)	8,56 d (3,6)	6,40 (~8)	*[2]
cis-IIId	5,04 (4,1; 9,9)	1,40 (11,0)	2,06 (12,8	3,53 (3,3)	1,14 (6,2)	7,74 s (0)	8,09 s (0)	6,48 (9,5)	6,64...7,08
trans-IIIe	4,74 (*; 4,2)	1,47 (~12,1)	1,87 (~13,2)	*[2] (*)	1,15 (6,4)	8,24 s (0)	8,52 d (~4,0s	6,41 (8,0)	*[2]
cis-IIIe	5,01 (4,1; 10,0)	1,40 (10,7)	2,05 (12,8)	3,50 (3,3)	1,14 (6,4)	7,67 s (0)	8,06 s (0)	6,46 (9,3)	6,58...7,12
cis-IIIf	5,14 (4,2; 10,0)	1,46 (10,4	2,08 (13,0)	3,54 (3,9)	1,15 (6,5)	7,76 s (0)	8,10 s (0)	7,01 (8,8)	6,68...7,76
trans-IIIg	4,98 (~2,2; 3,8)	1,58 (12,3)	2,02 (13,0)	3,48 (3,6)	1,22 (6,5)	8,36 s (0)	8,72 d (4,2)	8,24 (7,3)	6,63...7,85

cis-IIIg	5,20 (~4; ~9)	1,45 (*)	2,19 (*)	*2	1,19 (*)	*2	*2	*2	*2
cis-IIIh	5,14 (4,3; 10,0)	1,43 (11,5)	2,09 (12,8)	3,54 (3,2)	1,14 (6,4)	7,98 s (0)	8,08 s (0)	6,87 (9,3)	7,04...7,45
trans-IIIi	4,97 (~2,2; 4,0)	1,55 (12,2)	1,93 (13,0)	3,59 (~3)	1,18 (6,3)	8,36 s (0)	8,61 d (4,0)	7,64 (7,4)	6,84 d
cis-IIIi	5,21 (4,3; 10,2)	*2	2,12 (*)	*2	*2	*2	*2	*2 (7,9)	8,02 d *2
trans-IIIj	5,00 (2,0; 4,0)	1,59 (12,3)	1,91 (13,0)	3,52 (3,4)	1,13 (6,5)	8,20 s (0)	–	6,00 (9,4)	6,63...6,93
cis-IIIj	5,10 (5,0; 10,2)	1,71 (*)	*2	*2	1,11 (6,4)	8,02 (0)	–	6,07 (9,6)	*2
trans-IIIk	5,04 (2,1; 3,9)	1,62 (12,2)	1,92 (12,8)	3,57 (3,3)	1,14 (6,3)	8,14 s (0)	–	6,16 (9,4)	6,56...7,14
cis-IIIk	5,0...5,2 (*)	*2	*2	*2	*2	7,96 s (0)	–	6,21 (8...10)	*2
III *l*	4,81 (Σ = 6,9)	1,74...1,90 m		3,10...3,45 m	–	8,22 br.s (*)	8,22 br.s (~4) *4	6,08 (8,0)	6,55...7,13
IIIm	4,79 (*)	1,70...1,90 m		3,05...3,50 m	–	8,23 br.s (*)	8,42 br.s (*)	~6,4 (*)	6,70...7,07
IIIn	4,97 (4,5; 10,2)	1,62	1,94 (13,2)	–	1,21, 1,22	7.36 s	8,20 s (0)	6,11 (9,5)	6,60...7,15

*Spin–spin coupling could not be determined.

*2Signals overlapped by those of analogous signals in the second isomer.

*3Spectra also show singlet signals for OMe at 3.63 (IIIa), Me at 2.14-2.42 (IIIb,f,j), N-Me at 3.12-3.23 (IIIj,k) and CO_2H at 12.77 ppm (IIIg).

*4Spin–spin coupling determined for the 4-H proton.

wavelength ($\lambda_{max} \geq 293$ nm, log ε 3.17-3.69). The electronic spectrum of thiazine VII shows three strong bands for the dithiocarbamate system [32] at 207, 245, and 291 nm, masking the transition bands for the benzene ring.

The IR spectra of Id, IIIa-n, IX and thiazinethione VII show absorptions for the thioamide fragment, in particular for NH at 3120-3431 and for "thioamide-II" at 1487-1570 cm^{-1}. The spectra of IIIa-n and VII also show absorption bands for the arylamino groups (Table 2).

Using PMR spectroscopy (Table 3) to study the steric structures of the compounds synthesized, it was shown that IIIl (having one chiral center at C_4) exists in DMSO-D_6 solution predominantly as a conformer with an axially orientated phenylamino group. This follows from the spin–spin coupling for the 4-H and 5-H_a, 5-H_e protons ($J_{4,5a} + J_{4,5e} = 6.9$ Hz). This is also confirmed by the coupling between 4-H and N_3-H of 4 Hz which can only be for an equatorially orientated 4-H proton according to the criteria in [19]. Hence it appears that III, as with other previously studied 4-substituted hexahydropyrimidine-2-thiones, containing the groups OH, OR, SR, SO_2Ar, SC(S)OEt, $SC(S)NH_2$, CN [5, 6, 19, 20, 27] show an anomeric effect which stabilizes the conformation with an axially orientated substituent. However, for 4-arylamino derivatives, this effect is apparently significantly weaker since 6,6-dimethyl-4-phenylaminohexahydropyrimidine-2-thione IIIn exists in DMSO-D_6 solution in a conformer with an equatorial phenylamino group ($J_{4,5a} = 10.2$, $J_{4,5e} = 4.5$, $J_{NH,4a} = 0$ Hz). By contrast, 4-hydroxy-6,6-dimethylhexahydropyrimidine-2-thione Id and its 4-methoxy derivative IX have respectively pseudoaxial and axial orientations of the hydroxy and methoxy groups (PMR spectral data, see Experimental). Hence the extent of the anomeric effect in 4-substituted hexahydropyrimidine-2-thiones decreases in the order $OCH_3 > OH > NHC_6H_5$ in agreement with previous data [29].

By PMR spectroscopy it was shown that the cis-diastereoisomers of III and VII exist in DMSO-D_6 in a chair–like conformation with an equatorial positioning of the C_4 and C_6 substituents. The trans isomers have a chair–like conformation of the ring with an equatorial orientation of 6-CH_3 and an axial one for the arylamino group.

It has been shown that 4-arylaminohexahydropyrimidine-2-thiones show extremely weak aminoalkylating properties. Thus standing IIIb in water in the absence of catalyst and also in the presence of acidic or basic catalyst at 95°C does not form the trans-Ib product. Thione IIIb reacts, however, with butanethiol in concentrated hydrochloric acid at 90°C to give trans-4-butylthio-6-methylhexahydropyrimidine-2-thione (X).

EXPERIMENTAL

IR Spectra were recorded on UR-20 or Shimadzu IR-435 instruments using Vaseline mull or KBr tablets. Electronic spectra in the region 200-400 nm were obtained on a Specord UV-vis for 5×10^{-5} molar solutions in methanol or ethanol. PMR Spectra were recorded on Bruker MSL-200 (200 MHz) or WM-250 (250 MHz) instruments for solutions in DMSO-D_6 using HMDS or TMS as internal standards. The course of the reactions and product purities were monitored using TLC on Silufol UV-254 plates (Kavalier) with chloroform–methanol (10:1) or ether–acetone (3:2) eluents and iodine vapor visualization.

Synthesis of the starting 4-hydroxyhexahydropyrimidine-2-thione IV have been reported in [5], 6-methyl-1,2,3,6-tetrahydropyrimidine-2-thione V in [26], and 4-hydroxy-6-methyltetrahydro-1,3-thiazine-2-thione VI in [25].

Experimental conditions, isomeric compositions for the products, and yields are given in Table 1. Parameters for the compounds prepared and best yields are given in Table 2, and PMR spectral data in Table 3.

Elemental analytical data for C, H, N, and S for the compounds synthesized agreed with those calculated.

3-Isothiocyanato-3-methylbutanal (VIII). Concentrated sulfuric acid (5.5 ml, 99 mmoles) in water (10 ml) was added dropwise with vigorous stirring over 45 min to a mixture of 3-methyl-2-butenal (12.06 g, 143 mmoles) and ammonium thiocyanate (15.26 g, 201 mmoles) in water (10 ml) in a nitrogen stream with cooling in an ice bath. After cooling had been stopped the reaction mixture was stirred in a nitrogen stream for 1.5 h at room temperature and then at 35-40°C for 1 h. The product was extracted with ether, the extract carefully neutralized with saturated aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. After removal of ether, the residue was redistilled *in vacuo* to give VIII (9.52 g, 46.4%) with bp 50-51°C (0.1 mm Hg) and n_D^{20} 1.5078. IR Spectrum (thin layer): 2308 (N=C=S), 1722 cm^{-1} (C=O). PMR Spectrum ($CDCl_3$): 9.82 (1H, t, J = 2.2 Hz, CH=O), 2.68 (2H, d, CH_2), 1.55 ppm (6H, s, CH_3).

4-Hydroxy-6,6-dimethylhexahydropyrimidine-2-thione (Id). Ether (100 ml) saturated with ammonia at 0°C was added to a solution of freshly prepared VIII (8.2 g, 57.3 mmoles) in ether (100 ml). Ammonia was passed through the obtained

solution at the same temperature until complete precipitation of the product (about 5 min), and the precipitate was filtered, washed with ether, and dried to give Id (2.51 g*). It was recrystallized from methanol or acetonitrile. PMR Spectrum (DMSO-D_6): 7.98 (1H, br.s, N_3-H), 7.86 (1H, br.s, N_1-H), 5.73 (1H, d, $J_{4-H,OH}$ = 5.8 Hz, OH), 4.75 (1H, m, $J_{4-H,NH}$ = 2.1 Hz, $J_{4,5'}$ = 6.1, $J_{4,5''}$ = 4.6 Hz, 4-H), 1.72 (1H, dd, $J_{5',5''}$ = 13.5 Hz, 5''-H), 1.57 (1H, dd, 5'-H), 1.23 (3H, s, 6-CH_3), 1.12 ppm (3H, s, 6-CH_3).

6-Methyl-4-phenylaminohexahydropyrimidine-2-thione (IIIc). **A**. A mixture of trans-Ib (0.270 g, 1.85 mmoles), freshly distilled aniline (0.292 g, 3.14 mmoles), and hydrochloric acid (0.5%, 0.8 ml) was stirred at 95°C for 30 min, cooled to 0°C, and the precipitated crystals filtered, and washed with cold water and ether to give IIIc (0.369 g).

Similar reactions of Ia, trans-Ib, c, and arylamines IIa-d, i gave III*l*, m, and IIIa, b, d, i-k respectively.

B. A solution of freshly distilled aniline (3.86 g, 41.4 mmoles) in isopropanol (3.9 ml) was added to a mixture of trans-Ib (2.08 g, 14.2 mmoles), acetic acid (5.8 ml), and water (23 ml). The mixture was stirred at 90°C for 40 min, cooled, and the crystalline precipitate washed with cold water and cold acetone. Drying gave IIIc (2.80 g) as a mixture (91:9) of trans- and cis- isomers. Recrystallization from methanol or acetonitrile gives trans-IIIc.

Similar treatment of trans-Ib and arylamines IIa, b, d-i gives IIIa, b, d-i and of reaction of IV or V with p-toluidine gives IIIb in 77 and 65% yields respectively.

C. A mixture of trans-Ib (0.381 g, 2.61 mmoles), aniline (0.364 g, 3.91 mmoles), sodium hydroxide (0.0104 g, 0.26 mmoles) and water (2.3 ml) was stirred at 95°C for 4 h, cooled to 0°C, and the crystalline precipitate filtered, washed with water and ether, and then dried to give IIIc (0.435 g).

Similarly, trans-Ib and p-toluidine (IIb) gave IIIb.

D. A mixture of trans-Ib (0.72 g, 4.92 mmoles), aniline (1.376 g, 14.78 mmoles), and dry acetonitrile (9 ml) was refluxed for 8 h and cooled to 0°C. The crystalline precipitate was filtered, washed with cold acetonitrile and ether, and dried to give IIIc (0.816 g).

Compound IIIc was prepared by the above method from cis-Ib and aniline.

E. Similar reactions of trans-Ic and p-toluidine and of catalytic amount of p-toluenesulfonic acid) gave IIIj, n.

F. A solution of trans-Ib (0.530 g, 3.62 mmoles) and aniline (1.1013 g, 10.88 mmoles) in dry DMF (1 ml) was held at 90°C for 8.5 h, cooled to 20°C, and poured into cold water (30 ml). The crystalline precipitate was filtered, washed with water and ether, and dried to give IIIc (0.6 g).

6-Methyl-4-phenylaminotetrahydro-1,3-thiazine-2-thione (VII). Prepared similarly to IIIc (method A) by reaction of VI with aniline and product purification by recrystallization from acetone. PMR spectrum (DMSO-D_6): 10.75 (0.45H, d, $J_{4H,NH}$ = 3.8 Hz, N_3-H trans isomer), 10.06 (0.55H, s, $J_{4H,NH}$ = 0 Hz, cis isomer), 6.61-7.16 (5H, m, aryl), 6.40 (0.55H, br.s, 4-NH cis isomer), 6.29 (0.45H, br.s, 4-NH trans isomer), 5.06-5.25 (1H, m, 4-H), 3.54-3.79 (1H, m, 6-H_a), 2.33 (0.55, m, $J_{5e,5a}$ ~ 13,8, $J_{4a,5e}$ + $H_{5e,6a}$ ~ 6.0 Hz, 5-H_e cis isomer), 2.27 (0.45H, m, $J_{5e,5a}$ ~ 14.0, $J_{4e,5e}$ + $J_{5e,6a}$ ~ 6.0 Hz, 5-H_e trans isomer), 1.73 (0.55H, m, $J_{4a,5a}$ + $J_{5a,6a}$ ~ 22.5 Hz, 5-H_a cis isomer), 1.68 (0.45, m, $J_{4e,5a}$ = 3.2, $J_{5a,6a}$ ~ 9.1 Hz, 5-H_a trans isomer), 1.23 (1.35H, d, J = 6.6 Hz, 6-CH_3 trans isomer), 1.19 ppm (1.65H, d, J = 6.6 Hz, 6-CH_3 cis isomer).

6,6-Dimethyl-4-methoxyhexahydropyrimidine-2-thione (IX). A solution of Id (0.104 g, 0.65 mmoles) in anhydrous methanol (4 ml) containing TsOH (1 mg) was refluxed for 8 h, cooled, and the crystalline precipitate filtered was washed with cold methanol and dried. The product IX (0.079 g) was recrystallized from methanol. PMR Spectrum (DMSO-D_6): 8.71 (br. d, $J_{4H,NH}$ = 4.1 Hz, N_3-H), 8.31 (1H, br. s, N_1-H), 4.36 (1H, m, $J_{4,5e}$ = 2.5, $J_{4,5a}$ = 4.5 Hz, 4-H), 3.23 (3H, s, OCH_3), 1.86 (1H, dd, $J_{5e,5a}$ = 14.2 Hz, 5-H_e), 1.65 (1H, dd, 5-H_a), 1.23 (3H, s, 6-CH_3), 1.16 ppm (3H, s, 6-CH_3).

Trans-4-butylthio-6-methylhexahydropyrimidine-2-thione (X). A mixture of IIIb (0.33 g, 1.40 mmoles), butylmercaptan (0.18 g, 2 mmoles), and concentrated hydrochloric acid (2 ml) was heated at 90°C for 1 h and evaporated *in vacuo*. The residue was neutralized with sodium bicarbonate solution, and the crystalline precipitate filtered, washed with water and ether, and dried to give X (0.06 g, 19.6%). The spectral data was in complete agreement with that reported in [19].

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*Yield not optimized.

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