α-AMIDO(THIOAMIDO)ALKYLATION OF DITHIOCARBAMIC, O-ETHYLDITHIOCARBONIC, AND ARYLSULFINIC ACIDS BY 4-HYDROXY(ALKOXY)HEXAHYDROPYRIMIDINE-2-THIONES(ONES)

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The reaction of dithiocarbamic, O-ethyldithiocarbonic, and arylsulfinic acids with 4-hydroxy(methoxy)hexahydropyrimidine-2-thiones(ones) results in the regio- and stereoselective formation of 4-(aminothiocarbonylthio)-, 4-(ethoxythiocarbonylthio)-, and 4-(arylsulfonyl)hexahydropyridimidinethiones(ones) for which the reaction with O-nucleophiles was studied. It was found that the axial orientation of the functional groups at the $C_{(4)}$ atom is preferential in the molecules of the compounds obtained.

It was previously shown [1] that 4-hydroxy-, 4-alkoxy-, and 4-ureidohexahydropyrimidin-2-ones react in an acid medium with thiophenols and alkanethiols with the formation of 4-arylthio- and 4-alkylthiohexahydropyrimidin-2-ones. The nucleophilic substitution reaction of hydroxy or alkoxy groups in the molecules of 4-hydroxy- or 4-alkoxyhexahydropyrimidine-2-thiones by alkylthio groups by the action of alkanethiols proceed with similar ease, whereby the reaction is catalyzed not only by acids, but also by bases [2]. In continuation of our investigations [1, 2], it was of interest to study the use of other S-nucleophiles besides mercaptans in the nucleophilic substitution reactions at the $C_{(4)}$ atom in the molecules of 4-hydroxy(alkoxy)hexahydropyrimidine-2-thiones(ones). The results are reported in the present work of the investigation of this reaction, classifiable as α-amidoalkylation reaction [3] (more accurately, ureidoalkylation), using dithiocarbamic, O-ethyldithiocarbonic, and arylsulfinic acids as S-nucleophiles.

We showed that in the reaction of 4-hydroxyhexahydropyrimidine-2-thiones (Ia-c) with benzene- or p-toluenesulfinic acids (IIa, b) in water at 20°C for several hours, 4-(arylsulfonyl)hexahydropyrimidine-2-thiones (IIIa-f) are formed in high yields. We found from the PMR data (see below) that the reaction of trans-pyrimidines Ib, c with compounds IIa, b proceeds highly stereoselectively with the preferential retention of the configuration, as a result of which sulfones IIIc, f are formed as pure trans-diastereomers, while sulfones IIIb, e are formed as a mixture of trans- and cis-isomers in ratios of 93:7 and 88:12, respectively.

Compound IIIb is also obtained in the reaction of cis-hydroxypyrimidine IV or methoxypyrimidine V with acid IIa in water at 20°C.

4-Hydroxyhexahydropyrimidin-2-ones also undergo reaction with sulfinic acids, as we have shown using the example of the reaction of VI with acid IIb, as a result of which 6-isopropyl-5,5-dimethyl-4-(p-tolylsulfonyl)hexahydropyrimidin-2-one (VII) was formed.

It should be noted that the reaction of compounds Ia-c, IV-VI with acids IIa, b proceeds regioselectively and the sulfur atom of sulfinic acids exclusively undergoes thio(ureido)alkylation.

We showed that, unlike the reaction of Ia, b with alkanethiols [2], the reaction of Ib with sulfinic acids is not catalyzed by alkalies. Thus, when a solution of compounds Ib and IIa in water is held (up to 19 days) in the presence of 1.2 equivalent of sodium hydroxide at 20°C or on boiling this solution for 1 h, sulfone IIIb is not formed. This is possibly due to the considerably greater nucleofugacity of arylsulfonyl groups compared with alkylthio groups [4] (see scheme at top of page 190).

Compounds Ia-c also react readily and regioselectively in water with dithiocarbamic acid (VIII), which results in the quantitative formation of 4-(aminothiocarbonylthio)hexahydropyrimidine-2-thiones (IXa-c). The reaction of compounds Ib, c with acid VIII proceeds stereoselectively with preferential formation of trans-diastereomers of compounds IXb, c (the ratio of trans- and cis-isomers IXb, c obtained at 20°C is 82:18 and 88:12, respectively). Compound IXb is also formed in quantitative yield as a mixture of trans- and cis-isomers (82:18) in the reaction of methoxypyrimidine V with acid VIII (water, 20°C, 1 h).

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TABLE 1. Characteristics of Compounds IIIa-f, VII, IXa-c, and XIa-c

Compound	Empirical formula	Mp, °C	UV spectrum (in acetonitrile), λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}**					Yield, %
				N—H	thioamide-II	SO_2	Ar	C—O—C	
IIIa	$C_{10}H_{12}N_2O_2S_2$	151.5 ... 152	220 (4.18), 259 (4.24)	3383, 3163	1556, 1516	1300, 1137	3057, 723	—	71 (A)
IIIb	$C_{11}H_{14}N_2O_2S_2$	167 ... 168	220 (4.25), 259 (4.33)	3180 sh 3143	1576, 1527	1302, 1139	3077 n.i, 735	—	86 (A)
trans-IIIc	$C_{12}H_{16}N_2O_2S_2$	141.5 ... 142	219 (4.28), 259 (4.32)	3178	1545, 1494	1293, 1141	3031 n.i, 1579, 729	—	82 (A)
IIId	$C_{11}H_{14}N_2O_2S_2$	164.5 ... 165	224 (4.34), 259 (4.33)	3382, 3163	1557, 1518	1301, 1138	3061, 1596, 809	—	97 (A)
IIIe	$C_{12}H_{16}N_2O_2S_2$	170 ... 170.5	224 (4.34), 260 (4.34)	3358, 3197	1561, 1499	1285, 1131	3083, 1591, 808	—	100 (A)
trans-III	$C_{13}H_{18}N_2O_2S_2$	162.5 ... 163	226 (4.31), 259 (4.32)	3195	1550, 1495	1297, 1143	3037, 1593, 816	—	100 (A)
VII	$C_{16}H_{22}N_2O_3S$	165.5 ... 166	226 (4.15), 263 (3.19)	3245	—***	1283, 1133	3087, 1591, 823	—	87 (A)
IXa	$C_5H_9N_3S_3$	134 ... 135	206 (4.38), 260 (4.31), ~280 sh	3289 sh 3227, 1610	1540	—	—	—	88
IXb	$C_6H_{11}N_3S_3$	142 ... 143	209 (4.29), 262 (4.38), ~280 sh	3226, 3110sh 1596	1547, 1516	—	—	—	100 (b)
IXc	$C_7H_{13}N_3S_3$	155 ... 155.5	213 (4.27), 261 (4.37), ~280 sh	3279, 3223, 3059, 1613	1527	—	—	—	86
XIa	$C_4H_{12}N_2OS_4$	118 ... 119	210 (4.19), 217 sh 261 (4.23), 277 (4.19)	3185	1559, 1533	—	—	1057	91
XIb	$C_5H_{14}N_2OS_3$	132 ... 133	211 (4.21), ~215 sh, 262 (4.27), 277 (4.23)	3178	1565, 1520	—	—	1048	97
XIc	$C_6H_{16}N_2OS_3$	124 ... 125	217 (4.30), 262 (4.27), 278 (4.31)	3200	1530, 1499	—	—	1034, 1051	43

*Compounds IIIa-f, VII, and IXc were crystallized from acetonitrile, compounds XIa-c from acetone; compounds IIIa-f, IXa-c, and XIa-c melt.

**Compounds IXb and XIa were recorded in KBr tablets and the remaining compounds in mineral oil.

***1691 (amide I), 1526 cm^{-1} (amide II).

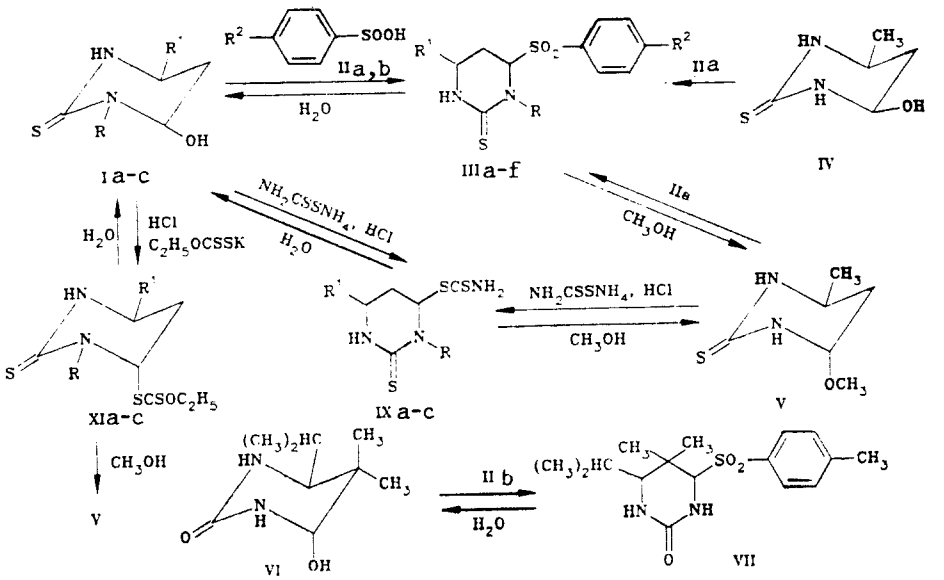
TABLE 2. PMR Spectra of Compounds IIIa-f, VI, IXa-c, and XIa-c in DMSO-D_6

Compound	Config. (con.)	Chemical shift, δ, ppm (SSCC, J, Hz)								
		4-H ($J_{4,5e}$; $J_{4,5a}$)	5-H_a ($J_{5a,6a}$)	5-H_e ($J_{5e,5a}$)	6-H_a ($J_{5e,6a}$)	6-H_e ($J_{6e,6a}$)	6-CH_3 ($J_{CH_3,6a}$)	$N_{(1)}$—H ($J_{NH,CH}$)	$N_{(3)}$—H ($J_{NH,CH}$)	other signals
IIIa	— (4a)	4,72 (~2,3; 6,1)	1,96 (12,9) ($J_{5e,6e}$ ~ 2,3)	2,30 (14,9)	3,29 (4,6) ($J_{5a,6e}$ = 6,1)	3,16 (12,9)	—	8,54 (4,5)	8,54 (3,5)	7,65 ... 7,88 (m, C_6H_5)
IIIb	trans (4a6e)	4,73 (1,4; 6,0)	1,65 (12,0)	2,37 (15,0)	3,60 (4,5)	—	1,14 (6,6)	8,55 (~0)	8,58 (5,4)	7,66 ... 7,94 (m, C_6H_5)
IIIc	trans (4a6e)	5,32 (1,6; 5,5)	1,79 (12,4)	2,33 (15,0)	3,62 (4,8)	—	1,11 (6,4)	8,57 (~0)	—	3,06 (s, N—CH_3); 7,56 ... 7,94 (m, C_6H_5)
IIId	— (4a)	4,67 (~2,3; 6,0)	1,95 (13,0) ($J_{5e,6e}$ ~ 2,3)	2,27 (15,0)	3,27 (4,6) ($J_{5a,6e}$ = 6,0)	3,16 (13,0)	—	8,50 (~5,0)	8,52 (~4,0)	2,45 (s CH_3); 7,47 ... 7,76 (m, Ar)
IIIe*	trans (4a6e)	4,66 (~1,5; 6,0)	1,64 (12,0)	2,34 (15,0)	3,58 (4,0)	—	1,12 (6,2)	8,52 (~0)	8,53 (~5,2)	2,45 (s CH_3); 7,47 ... 7,76 (m, Ar)
IIIf	trans (4a6e)	5,24 (1,8; 5,5)	1,77 (12,1)	2,32 (14,6)	3,58 (4,8)	—	1,10 (6,2)	8,51 (~0)	—	2,45 (s, CH_3); 3,08 (c, N—CH_3); 7,50 ... 7,82 (m, Ar)
VI	trans (4a6e)	3,99	—	—	3,12 ($J_{6a,CH}$ = 1,6)	—	—	6,06 (~0)	6,67 (4,0)	0,81 and 0,89 (s, 5-CH_3); 0,87 and 0,98 (d, J=7,0 Hz, CH_3 in i-C_3H_7); 1,85 (m CH in i-C_3H_7); 5,49 (d OH, J=5,1 Hz)
IXa	— (4a)	5,35 (3,2; 3,2)	2,00 ... 2,31 м		3,10 ... 3,38 м		—	8,39 (4,5)	8,41 (4,8)	9,35 and 9,68 (s, NH_2)
IXb	trans (4a6e)	5,33 (2,2; 4,3)	1,83 (11,6)	2,20 (14,0)	3,45 (3,3)	—	1,16 (6,6)	8,42 (~0)	8,44 (4,5)	9,34 and 9,69 (s NH_2)
	cis (4e6e)	5,37 (4,8; 8,4)	1,71 (8,4)	2,36 (13,6)	3,44 ... 3,60** (4,8)	—	1,16 (6,6)	7,91 (~0)	8,41 ... 8,46**	9,45 and 9,80 (s, NH_2)
IXc	trans (4a6e)	5,66 (2,4; 3,8)	2,08 (11,6)	2,22 (14,0)	3,49 (4,0)	—	1,18 (6,3)	8,37 (~0)	—	3,25 (s, N—CH_3); 9,48 and 9,80 (s, NH_2)
	cis (4e6e)	5,83 (Σ=10,4) ($J_{4a,5e}$ + + $J_{5e,6a}$ = =11,6)	1,99 ... 2,16**	2,66 (14,0)	3,40 ... 3,56**	—	1,21 (~6,0)	8,50 (~0)	—	3,20 (c, N—CH_3); 9,51 and 9,85 (c, NH_2)
XIa	— (4a)	5,39 (2,6; 2,6)	2,11 ... 2,24 м		3,00 ... 3,50***		—	8,49	8,62 (4,5)	1,37 (t, J=7,0 Hz, CH_3 in OCH_2CH_3); 4,61 and 4,66 (d.q, the AB system, J_{AB}=10,9, CH_2 c OCH_2CH_3)
XIb	trans (4a6e)	5,37 (2,4; 4,0)	1,88 (11,7)	2,23 (14,2)	3,20 ... 3,67*** (3,7)	—	1,18 (6,5)	8,48 (~0)	8,64 (4,5)	1,37 (t, J=7,0, CH_3 in OCH_2CH_3); 4,62 and 4,66 (d.q, the AB system, J_{AB}=10,8, CH_2 в OCH_2CH_3)
XIc	trans (4a6e)	5,59 (2,2; 3,8)	2,09 (11,8)	2,31 (14,0)	3,13 ... 3,62*** (3,7)	—	1,18 (6,3)	8,44 (~0)	—	1,38 (t J=7,1, CH_3 in OCH_2CH_3); 3,28 (s, N—CH_3); 4,66 (q, CH_2 in OCH_2CH_3)

*The cis-isomer IIIb: 1.09 (d, J = 6.6 Hz, 6-CH_3); 4.91 ppm (d, d, $J_{4a,5e}$ = 6.3; $J_{4a,5a}$ = 9.7; $J_{N(3)H,4-H}$ = 0 Hz, 4-H); cis-isomer IIIe: 1.08 (d, J = 6.2 Hz, 6-CH_3); 1.34 (d.q, $J_{5a,6a}$ = 9.8; $J_{5e,5a}$ = 13.4 Hz; 5-H_a); 4.86 ppm (d.d, $J_{4a,5e}$ = 6.3; $J_{4a,5a}$ = 9.8; $J_{N(3)H,4-H}$ = 0 Hz, 4-H).

**Overlap with the trans-isomer signals.

***The signals overlap with the signal of HOD in DMSO-D_6, and also with proton signals of the hydrolysis products.

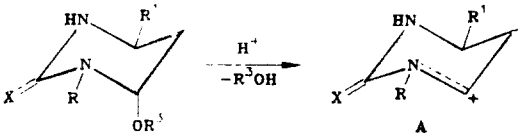


I, IX, XI a R=R¹=H; б R=H, R¹=CH₃; в R=R¹=CH₃; II a R²=H, б R²=CH₃; III a R=R¹=R²=H; б R=R²=H, R¹=CH₃; в R=R¹=CH₃, R²=H; г R=R¹=H, R²=CH₃; д R=H, R¹=R²=CH₃; е R=R¹=R²=CH₃

O-Ethyldithiocarbonic acid (X) undergoes α-amidoalkylation by the action of hydroxypyrimidines Ia, b, as a result of which 4-(ethoxythiocarbonylthio)hexahydropyrimidine-2-thiones (XIa, b) are formed in high yields. A similar reaction of compound Ic with acid X does not proceed to completion, and pyrimidine XIc is isolated from its mixture with compound Ic by crystallization from acetone. We should note that compounds XIb, c are formed as pure trans-isomers.

The use of methoxypryimidine V for the amidoalkylation of acid X leads to the formation of a mixture of compound XIb and the starting pyrimidine, which is possibly due to the lower nucleofugacity of the methoxy group compared with the hydroxy group.

The reactions studied by us possibly proceed by an S_N1 mechanism through the formation of intermediate cations of type A which are further subjected to attack by an S-nucleophile, whereby the direction of the attack is determined mainly by thermodynamic factors, i.e., products are preferentially formed in which the $C_{(4)}$—S bond is present in an antiperiplanar disposition to the unshared pair of electrons of the $N_{(3)}$ atom (see below) [5]. It should be noted that the sulfur acids used act not only as S-nucleophiles, but also as acid catalysts of the reaction:



X=O, S, R³=H, CH₃

The above-described transformations are possibly the first example discovered of an α-amidoalkylation reaction of free dithiocarbamic, O-ethyldithiocarbonic, and sulfinic acids by the action of α-hydroxy(alkoxy)amides.

Because of the high nucleofugacity of arylsulfonyl groups present in the α-position to the amide group [6], it was of interest to study the behavior of pyrimidines IIIa-f and VII that we synthesized, and also IXa-c and XIa-c with respect to various nucleophiles.

We showed that on boiling in water for 1 h, 4-(phenylsulfonyl)pyrimidine IIIb hydrolyzes with the formation of hydroxypyrimidine Ib. The shift of the equilibrium in the direction of compound Ib is possibly promoted by the instability of benzenesulfinic acid [4] that separates out under the reaction conditions. We found by the TLC method that acid IIa is not present among the hydrolysis products. As expected, the hydrolysis of IIIb is considerably accelerated in an alkaline medium and compound Ib separates out on boiling sulfone IIIb in water in the presence of sodium hydroxide for 5 min. The hydrolysis of compounds IXb and XIb proceeds readily and to completion when they are heated in water (95-100°C, 7-45 min) with the formation of hydroxypyrimidine Ib. In a DMSO-D_6 solution, in the presence of D_2O, the hydrolysis of compounds VII and XIa-c proceeds rapidly (up to 30 min) even at 20°C, as we have found using the PMR spectroscopy. Under these conditions, compounds IIIa-f and IXa-c were found to be more stable to hydrolysis.

The functional groups at the $C_{(4)}$ atom in the molecules of pyrimidines IIIb, IXb, and XIb also become substituted by the methoxy group by boiling in methanol for 15 min to 1 h 50 min, and as a result methoxypyrimidine is formed. Methanolysis of compounds IIIb and XIb is accelerated in the presence of 1.2 equivalent of sodium methylate and proceeds even at 20°C.

Thus, in the study of the reaction with O-nucleophiles* we noted a high amidoalkylating ability of the 4-functionally substituted pyrimidines of type III, IX, and XI. It should be noted that we were unable to find any examples in the literature of the α-amidoalkylation reaction using aminothiocarbonylthio- and ethoxythiocarbonylthio groups as the leaving groups.

The structure of the synthesized compounds IIIa-f, VII, IXa-c, and XIa-c was established on the basis of a combination of the IR, UV, and PMR spectroscopy data.

In the UV spectrum of pyrimidinone VII in acetonitrile, an intense absorption band is observed at 226 nm ($\log \varepsilon$ 4.15) and also a band with a maximum at 263 nm ($\log \varepsilon$ 3.19) (Table 1), belonging to the benzene chromophore of arylsulfones [7], while in the electronic spectrum of pyrimidinone VI in acetonitrile the absorption bands above 200 nm are absent.

The UV spectra of the 4-functionally substituted hexahydropyrimidine-2-thiones IIIa-f, IXa-c, and XIa-c are a sum of spectra of two practically independent chromophore systems; thioureido, on the one hand, and arylsulfonyl (in IIIa-f) dithiocarbamate (in IXa-c) or dithiocarbonate (in XIa-c), on the other. Thus, in the UV spectra of sulfones IIIa-f, two intense absorption bands are observed with maxima in the 219-226 ($\log \varepsilon$ 4.18-4.34) and 259-260 nm ($\log \varepsilon$ 4.24-4.34) region (Table 1). We assigned the low-frequency band to the π—π^*-transition of the thioureido chromophore [8], masking a weak "benzene" band of the arylsulfonyl chromophore. The high-frequency band is also caused by the superposition of absorption bands of the two chromophores, which becomes evident on comparison of the UV spectra of sulfones IIIa-f and pyrimidinethione Ib in acetonitrile [λ_{max}, nm ($\log \varepsilon$): 204 (4.04), 253 (4.27) (see [2, 9])].

The electronic spectra of compounds IXa-c and XIa-c (Table 1) also agree well with the presence of thioureido and dithiocarbamate or dithiocarbonate chromophores in the molecules of these compounds [10].

In the IR spectra of pyrimidinethiones IIIa-f, IXa-c, and XIa-c (Table 1), broad stretching vibration bands of the N—H groups are observed in the 3100-3400 cm^{-1} region, while in the 1494-1576 cm^{-1} region there are one or two intense absorption bands due to the vibrations of the atoms of the thioureido fragment of the molecules [9, 11]. In the IR spectrum of pyrimidinone VII there are strong absorption bands at 3245 (ν_{NH}) 1691 (amide I) and 1526 cm^{-1} (amide II). Moreover, in the IR spectra of compounds IIIa-f, VII, IXa-c, and XIa-c bands are observed due to the presence of a substituent at the $C_{(4)}$ atom.

On the basis of the high value (12.0-12.4 Hz) of the SSCC of the 5-H_a proton with the 6-H proton in the PMR spectra of compounds trans-IIIb, c, e, f (Table 2) we concluded that the orientation of the methyl group at the $C_{(6)}$ atom is equatorial. On the contrary, the SSCC of the 4-H proton with 5-H_a and 5-H_e protons in the PMR spectra of these compounds are 5.5-6.0 and 1.4-1.8 Hz, respectively, which indicates an axial (more accurately pseudoaxial) orientation of the arylsulfonyl groups in the molecules of compounds trans-IIIb, c, e, f. According to a criterion proposed in [2], these conclusions are additionally confirmed by the presence of an SSCC between the $N_{(3)}$—H and 4-H protons (5.2-5.4 Hz) and the absence of an SSCC between the $N_{(1)}$—H and 6-H protons in the PMR spectra of sulfones trans-IIIb, c, e, f in DMSO-D_6. Compounds cis-IIIb, e are present in a conformation with an equatorial orientation of both substituents (Table 2).

Because of the similarity of the SSCC of the 4-H protons with 5-H_a and 5-H_e in the PMR spectra of sulfones trans-IIIb, c, e, f having a fixed configuration and conformation and sulfides IIIa, d ($J_{4,5a}$ = 6.0-6.1; $J_{4,5e}$ ~ 2.3 Hz) and also because of the presence in the spectra of the latter of an SSCC between the $N_{(3)}$—H and 4-H protons (3.5-4.0 Hz), we concluded that, despite the substantial bulk of the aryl sulfonyl groups [12], these groups preferentially occupy the (pseudo)axial positions in the molecules of compounds IIIa, d in a DMSO-D_6 solution.

In a similar way, on the basis of the SSCC of the N—H, 4-H, 5-H, and 6-H protons in the PMR spectra in compounds trans-IXb, c, XIb, c (Table 2), we reached conclusions on the existence of these compounds in a conformation with an equatorial orientation of the 6-CH_3 group and an axial orientation of the substituent at the $C_{(4)}$ atom. Compounds IXa and XIa, having one chiral center, are preferentially present in a conformation with an axial disposition of the substituent ($J_{4,5}$ = 2.6-3.2; $J_{N(3)H,4\text{-}H}$ = 4.5-4.8 Hz).

We explain the preferability of the axial orientation of aryl sulfonyl, aminothiocarbonylthio- and ethoxycarbonylthio groups at the $C_{(4)}$ atom as a manifestation of an anomeric effect [5]. It is interesting to note that 2-

*The reactions with other nucleophiles will be described in forthcoming publications.

(phenylsulfonyl)tetrahydropyrans, for which the presence of the anomeric effect is also possible, have an equatorial orientation of the phenylsulfonyl group [13]. This difference in the conformation of the above compounds and sulfones IIIa, d is possibly due to smaller steric hindrances in the molecules of the latter.

The high diastereoselectivity during the amidoalkylation of dithiocarbamic, O-ethyldithiocarbonic, and arylsulfinic acids by 4-hydroxy(methoxy)hexahydropyrimidine-2-thiones, and also in the reaction of compounds IIIb, c, e, f, VII, IXb, c, and XIb, c with O-nucleophiles are readily explained by the occurrence of the anomeric effect [5].

Since we were unable to obtain a satisfactory PMR spectrum of compound VII because of its poor solubility and the ease of its hydrolysis to compound VI by traces of water in solvents, we were unable to reach an unequivocal conclusion on the configuration and conformation of this compound.

We assigned pyrimidinone VI to the trans-series with an equatorial orientation of the isopropyl group and axial orientation of the hydroxy group based on SSCC $J_{N(3)H,4-H} = 4.0$ and $J_{N(1)H,6-H} \sim 0$ Hz.

EXPERIMENTAL

The IR spectra were recorded on Specord IR-75 or UR-20 spectrophotometers in the form of a suspension in mineral oil or in KBr tablets. The electronic spectra in the 200-400 nm region were obtained on a Shimadzu UV-240 spectrophotometer in acetonitrile (Merck). The PMR spectra were run on a Bruker MSL-200 spectrometer for solutions of the samples in DMSO-D_6, and further in DMSO-D_6 + D_2O, using TMS or HMDS* as internal standard. The course of the reaction and the purity of the compounds obtained were monitored by the TLC method on Silufol UV-254 plates in an ether—acetone 2:1 system; the spots were developed by iodine vapor.

The data of the elemental analysis for C, H, N, and S corresponded to the calculated values.

The starting 4-hydroxypyrimidinethiones Ia-c, IV, and 4-methoxypyrimidinethione V were prepared by the method described in [9] and pyrimidinone VI by the method in [14].

6-Methyl-4-(phenylsulfonyl)hexahydropyrimidine-2-thione (IIIb). A. An 18-ml portion of water was added to a finely divided mixture of 1.428 g (9.77 mmoles) of hydroxypyrimidine Ib and 1.665 g (11.71 mmoles) of benzenesulfinic acid, and the suspension obtained was shaken at room temperature for 2 h. The precipitate was filtered off, washed on the filter with cold water, and dried. Yield 2.272 g of sulfone IIIb in the form of a mixture of trans- and cis-isomers, 93:7.

Sulfones IIIa and trans-IIIc were obtained in a similar way by the reaction of Ia, c with IIa, and **sulfones IIId and IIIe** — (a mixture of trans- and cis-isomers; 88:12) and by the reaction of Ia-c, VI with IIb.

B. The compound was obtained by method A by the reaction of 4-methoxypyrimidine V or cis-4-hydroxypyrimidine IV with IIa (yields 86 and 95%, respectively.

4-(Aminothiocarbonylthio)hexahydropyrimidine-2-thione (IXa). A solution of 0.243 g (2.21 mmoles) of ammonium dithiocarbamate in 0.5 ml of water was added dropwise, with stirring, at 20°C, in the course of 3-5 min, to a suspension of 0.148 g (1.12 mmoles) of hydroxypyrimidine Ia in a mixture of 0.19 ml (2.21 mmoles) of concentrated HCl and 1.7 ml of water. An abundant white precipitate separated out, which after 2 h was stirred at 20°C, filtered off, washed with ice water, and dried. Yield 0.205 g of compound IXa, which was purified by washing in boiling acetonitrile.

Compound IXc was obtained in a similar way in the form of a mixture of trans- and cis-diasteromers, 88:12.

4-(Aminothiocarbonylthio)-6-methylhexahydropyrimidine-2-thione (IXb). A. A warm solution of 0.437 g (2.99 mmoles) of hydroxypyrimidine Ib in a mixture of 0.35 ml (4.08 mmoles) of concentrated HCl and 4 ml of water was added dropwise, with stirring, in the course of 5 min, to a solution of 0.463 g (4.20 mmoles) of ammonium dithiocarbamate in 4 ml of water. The mixture obtained was heated at 95°C for 30 sec, and then allowed to stand for 1 h at 20°C, the precipitate was filtered off, washed with ice water, and dried. Yield 0.594 g (89%) of compound IXb in the form of a mixture of trans- and cis-isomers, 76:24. Compound IXb was purified by washing in boiling acetone.

B. The compound was obtained in a similar way as compounds IXa, c in a quantitative yield from hydroxypyrimidine Ib or methoxypyrimidine V. In both cases the ratio of the trans-cis isomers was 82:18.

4-(Ethoxythiocarbonylthio)hexahydropyrimidine-2-thione (XIa). A solution of 0.344 g (2.15 mmoles) of potassium xanthate in 0.4 ml of water was added at 20°C, with stirring, in the course of 5 min, to a mixture of 0.142 g (1.07 mmoles) of hydroxypyrimidine Ia, 0.18 ml (2.10 mmoles) of concentrated HCl and 1.6 ml of water. A white flocculent precipitate separated out which, after stirring of the mixture for 1 h, was filtered off, washed with ice water, and dried. Yield 0.231 g of compound XIa.

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trans-6-Methyl-4-(ethoxythiocarbonylthio)hexahydropyrimidine-2-thione (XIb) was obtained in a similar way from Ib.

trans-3,6-Dimethyl-4-(ethoxythiocarbonylthio)hexahydropyrimidine-2-thione (XIc). A. A solution of 1.264 g (7.89 mmoles) of potassium xanthate in 2.5 ml of water was added dropwise, with stirring, in the course of 3 min, to a suspension of 1.110 g (6.93 mmoles) of hydroxypyrimidine Ic in a mixture of 0.7 ml (8.16 mmoles) of concentrated HCl and 6.3 ml of water. The mixture was heated at 95°C for 30 sec, then cooled to 20°C, the precipitate was filtered off, washed with cold water, and dried. Yield 1.615 g of compound XIc with an admixture of the starting hydroxy pyrimidine Ic. After recrystallization from acetone, 0.793 g of pure compound XIc was obtained.

B. The compound was obtained in a similar way as compounds XIa, b with admixture of the starting pyrimidine Ic.

Hydrolysis of 6-Methyl-4-(phenylsulfonyl)hexahydroxypyrimidine-2-thione (IIIb). A. A mixture of 0.470 g (1.74 mmoles) of sulfone IIIb and 10 ml of water was boiled for 1 h (TLC monitoring). The solution formed with oily drops in it was extracted with ether (3 × 10 ml), the aqueous phase was evaporated under vacuum to a volume of 1 ml, cooled, the precipitate was filtered off, washed with cold water, and dried. Yield 0.122 g (48%) of compound Ib.

B. A mixture of 0.290 g (1.07 mmoles) of sulfone IIIb, 0.065 g (1.62 mmoles) of sodium hydroxide and 4 ml of water was boiled for 5 min, the solution was neutralized with dilute acetic acid to pH 7-8, filtered and evaporated to dryness. Four drops of water were added to the solid residue, the mixture was cooled, the precipitate was filtered off, washed with ice water, and dried. Yield 0.103 g (66%) of compound Ib.

Hydrolysis of trans-6-Methyl-4-(ethoxythiocarbonylthio)hexahydroxypyrimidine-2-thione (XIb). A suspension of 0.043 g (0.17 mmole) of compound XIb in 3.2 ml of water was heated at 95-100°C for 45 min to the complete dissolution of XIb. The solution was evaporated to dryness. Hydroxypyrimidine Ib was obtained in a quantitative yield.

The **hydrolysis of IXb** was carried out in a similar way, time of reaction 7 min.

Methanolysis of 6-Methyl-4-(phenylsulfonyl)hexahydropyrimidine-2-thione (IIIb). A. A solution of 0.288 g (1.06 mmoles) of sulfone IIIb in 10 ml of anhydrous methanol was boiled for 1 h 50 min. The mixture was evaporated to a volume of 1 ml, the residue was cooled, the precipitate filtered off, washed with cold methanol, and dried. Yield 0.090 g (80%) of compound V.

The **methanolysis of compounds IXb and XIb** was carried out in a similar way, the time of reaction being 15 and 45 min, respectively. Methoxypyrimidine V was formed in a yield of 99-100%.

B. A 0.232-g portion (0.859 mmole) of sulfone IIIb was added to a solution of 0.024 g (1.03 mmoles) of sodium in 2 ml of anhydrous methanol. The precipitate dissolved rapidly at 20°C on stirring, and after 5 min methoxypyrimidine V began to separate out from the solution. The mixture was allowed to stand at 20°C for 5 h and was then cooled to −15°C. The precipitate was filtered, washed on the filter with cold methanol, and dried. Yield 0.090 g (65%) of compound V.

Methoxypyrimidine V was obtained in a similar way from compound XIb in a yield of 69%.

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INVESTIGATION OF COMPLEX FORMATION AND RELATIVE REACTIVITY OF PYRROLOQUINOLINES AND PYRROLOISOQUINOLINES BY MEANS OF NMR SPECTROSCOPY

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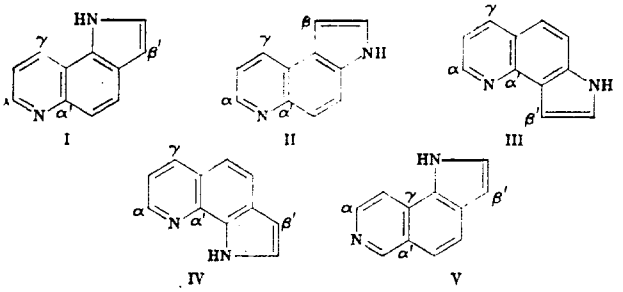
The series of isomeric pyrroloquinolines and pyrroloisoquinolines has been studied by means of multinuclear NMR spectroscopy. It is shown that in inert media all of the compounds form complexes of the NH · · · H type, cyclic or linear, depending on the type of annelation of the pyrrole ring. A spectroscopic estimation of their proton-donating and proton-accepting properties has been made. The protonation (deuteration) of the pyrrole fragment of the methiodides of the pyrroloquinolines has been studied. A reaction profile of the protonation of the pyrroloquinolines as a function of the acidity of the medium has been obtained. A comparative evaluation of the reactivity of the pyrroloquinolines has been carried out.

According to [1-3], the isomeric pyrroloquinolines to be discussed, 1H-pyrrolo[2,3-f]quinoline (I), 3H-pyrrolo[3,2-f]quinoline (II), 3H-pyrrolo[2,3-h]quinoline (III), 1H-pyrrolo[3,2-h]quinoline (IV), and 1H-pyrrolo[2,3-f]isoquinoline (V), display a different reactivity in electrophilic and nucleophilic substitution reactions. For a number of reasons related to the conditions of preparation and isolation of the pyrroloquinolines, it does not appear possible to compare the reactivities of the entire series of compounds (I-V) from the yields of a single kind of reaction. Nor do the available quantum chemical calculations by the MOKh and RMKh methods permit a judgment of the relative reactivities of compounds I-V [4].

The purpose of the present work was to seek sound criteria affording an explanation and, possibly, a prediction of the relative reactivities of the isomers. Since the molecules investigated possess two nitrogen atoms, one of which is a proton-donating and the other a proton-accepting center, a potential criterion for evaluating differences in the chemical behavior of compounds I-V could be information obtained by studying the acid-base reaction with formation of complexes of the NH · · · H type. The stability of the complex is related to the extent of the change in the electron density in the π-rich (indole) and π-deficient (pyridine) fragments of the molecules of the different isomers. This, in turn, must be reflected in their reactivity, first in electrophilic substitutions (for example protonation of the β'-carbon atom of the pyrrole ring), and second in nucleophilic substitutions (the Chichibabin reaction).



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