REACTIVITIES OF HETEROCYCLIC AMIDES AND THIOAMIDES

ALKYLATION OF 4-HYDROXYHEXAHYDRO- AND 1,2,3,6-TETRAHYDRO-PYRIMIDINE-2-THIONES

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2-Alkylmercapto-4-hydroxy-3,4,5,6-tetrahydro- and 2-alkylmercapto-3,6-dihydropyrimidines were synthesized by the reaction of substituted 4-hydroxyhexahydro- and 1,2,3,6-tetrahydropyrimidine-2-thiones with alkyl halides. It is shown that the nucleophilic center in the alkylation is the sulfur atom. The capacity of the synthesized compounds for prototropic ring-chain tautomerism was established.

In the development of our studies [1,2] of the synthesis and investigation of the tautomerism and reactivities of hydrogenated pyrimidine-2-thiones, we turned to a study of the nucleophilic substitution reactions in the case of the alkylation of our previously obtained [1,3] 1,2,3,6-tetrahydropyrimidine-2-thiones (I) and 4-hydroxyhexahydropyrimidine-2-thiones (II) [3]. In investigating this reaction, we were primarily interested in the "site" of alkylation as a characteristic of the relative nucleophilicity of the two reaction centers – the nitrogen and sulfur atoms of the thioamide group. In addition, the diverse biological activity of alkylmercaptopyrimidines [4-6] and the high polyfunctional activity of I [7] and II in polymer materials are known. In this plan, the directed synthesis of hydrogenated 2-alkylmercaptopyrimidines is of independent interest.

Methyl iodide, ethyl bromide, benzyl chloride, and chloroacetic acid were used as alkylating agents. The reaction was carried out in acetone, and the yields of the hydrohalide salts of the 2-alkylmercapto derivatives (III and IV, Tables 1 and 2) were almost quantitative. Free bases V and VI (Table 3) were isolated from the salts at 0°C with ammonium hydroxide. Attempts to obtain V and VI directly from the

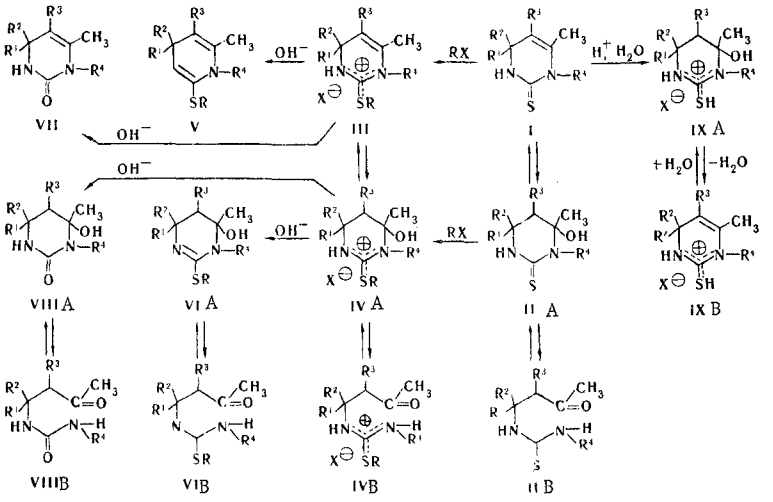

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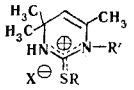
TABLE 1.

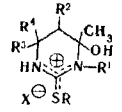


Comp.	R	R′	X	mp, °C (from acetone)	Empirical formula	Found, %			Calc., %			IR spectra, ν, cm^{-1} (NH – C=S, C=N, C=C)	UV spectra, λ_{max}, nm (log ε)	Yield, %
						N	S	X	N	S	X			
IIIa	CH_3	H	I	130,5—131	$C_8H_{14}N_2S \cdot HI$	9,4	10,6	42,7	9,4	10,7	42,6	—	222 (4,19)	92
IIIb	CH_3	CH_3	I	119 —120	$C_9H_{16}N_2S \cdot HI$	8,9	10,3	39,8	9,0	10,3	40,6	1520, 1595, 1690	223 (4,22)	97
IIIc	CH_3	C_6H_5	I	156 —156,5	$C_{14}H_{18}N_2S \cdot HI$	7,5	—	33,6	7,5	—	33,9	1515, 1565, 1710	221 (4,42)	95
IIId	CH_3	$C_6H_4CH_3$-*p*	I	163,5—164,5	$C_{15}H_{20}N_2S \cdot HI$	7,2	7,8	32,2	7,2	8,2	32,7	1515, 1565, 1710	221 (4,45)	94
IIIe	CH_3	$C_6H_4OCH_3$-*p*	I	174,5—175	$C_{15}H_{20}N_2OS \cdot HI$	6,8	7,9	31,5	6,9	7,9	31,4	1515, 1565, 1710	220 (4,34)	93
IIIf	CH_3	$C_6H_4CH_3$-*m*	I	153,5—154,5	$C_{15}H_{20}N_2S \cdot HJ$	7,0	8,3	32,7	7,2	8,3	32,7	1519, 1560, 1710	220 (4,35)	92
IIIg	CH_3	C_6H_4CN-*p*	I	167,5—168,5	$C_{15}H_{17}N_3S \cdot HJ$	10,5	8,1	31,9	10,5	8,0	31,8	1515, 1590, 1710	223 (4,57)	87
IIIh	CH_3	C_6H_4Cl-*p*	I	146 —148	$C_{14}H_{17}ClN_2S \cdot HI$*	—	—	30,0	—	—	31,1	1515, 1565, 1710	223 (4,48)	85
IIIi	CH_3	C_6H_4Cl-*m*	I	153,5—154,5	$C_{14}H_{17}ClN_2S \cdot HI$†	—	—	31,1	—	—	31,1	1510, 1573, 1715	216 (4,42)	89
IIIj	CH_3	$C_6H_4COOC_2H_5$-*p*	I	153 —154	$C_{17}H_{22}N_2O_2S \cdot HI$	6,3	7,0	28,3	6,3	7,2	28,4	1515, 1565, 1710	223 (4,48)	83
IIIk	C_2H_5	C_6H_5	Br	171 —172	$C_{15}H_{20}N_2S \cdot HBr$	8,2	—	23,4	8,2	—	23,4	1515, 1575, 1710	—	78
IIIl	CH_2COOH	H	Cl	139 —140	$C_9H_{14}N_2O_2S \cdot HCl$	11,1	—	14,1	11,2	—	14,1	1522, 1560, 1695	—	82

* Found %: Cl 8.7. Calculated %: Cl 8.7.

† Found %: Cl 8.6. Calculated %: Cl 8.7.

TABLE 2.



Comp.	R	R¹	R²	R³=R⁴	X	mp, °C (from acetone)	Empirical formula	Found, %			Calc., %			IR spectrum, ν, cm^{-1}	UV spectra, λ max, nm (log ε)	Yield, %
								N	S	X	N	S	X			
IVa	CH_3	CH_3	CH_3	H	I	118—119	$C_8H_{16}N_2OS \cdot HI$	8,9	10,5	40,3	8,9	10,1	40,1	1517, 1600	222 (4,28)	95
IVb	CH_3	C_2H_5	CH_3	H	I	119,5—120	$C_9H_{18}N_2OS \cdot HI$	8,7	9,8	—	8,5	9,8	—	1529, 1600	222 (4,38)	94
IVc	CH_3	C_3H_7	CH_3	H	I	146,5—147,5	$C_{10}H_{20}N_2OS \cdot HI$	8,4	9,4	—	8,1	9,3	—	1514, 1595	222 (4,30)	87
IVd	CH_3	CH_3	H	CH_3	I	151—152	$C_9H_{18}N_2OS \cdot HI$	8,5	9,7	38,6	8,5	9,7	38,4	1530, 1590	221 (4,26)	96
IVe	C_2H_5	H	H	CH_3	Br	129,5—130	$C_9H_{18}N_2OS \cdot HBr$	10,2	10,9	28,2	9,9	11,3	28,2	1533, 1590	—	80
IVf	$CH_2C_6H_5$	CH_3	H	CH_3	Cl	99,5—100	$C_{15}H_{22}N_2OS \cdot HCl$	9,0	9,7	11,3	8,9	10,2	11,3	1530, 1590	—	79

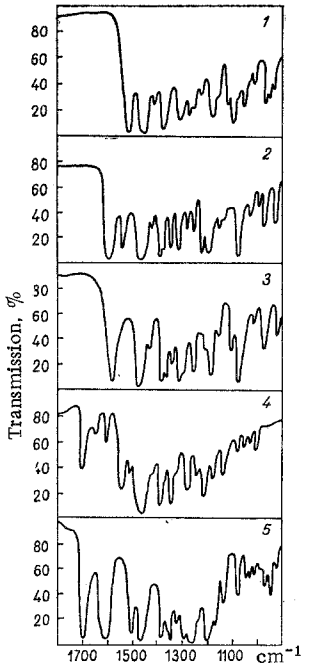


Fig. 1. IR spectra: 1) 3,4,6,6-tetramethyl-4-hydroxyhexahydropyrimidine-2-thione; 2) IVd; 3) VIc; 4) 4,6,6-trimethyl-3-phenyl-1,2,3,6-tetrahydropyrimidine-2-thione; 5) Va.

starting I and II in alkaline media using various basic reagents were unsuccessful because of the side processes that occur under these conditions. The alkylmercapto group is hydrolyzed to form the corresponding 1,2,3,6-tetrahydropyrimidin-2-ones (VII) and 4-hydroxyhexahydropyrimidin-2-ones (VIII) when salts III and IV are heated with aqueous alkalis.

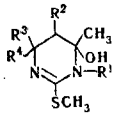
In analogy with thioureas [8-10] and heterocyclic thioamides [11-14], it might be expected that the nucleophilic center of the thioureido group of I and II in alkylation reactions would be the sulfur atom. A study of the IR and UV absorption spectra of the bases of alkylmercaptopyrimidines V and VI confirmed this assumption. The absorption bands at 1520-1540 cm^{-1} characteristic for the thioamide group [15] vanish in the IR spectra of V and VI, and intense bands of the stretching vibrations of the N=C group appear at 1585-1600 cm^{-1} (Fig. 1). The IR spectra of V also contain a band at 1700 cm^{-1} that is related to the vibrations of the C=C bond in analogy with the absorption of this group in the starting I [2, 16].

The UV spectra of the products of alkylation (V and VI), in which a strong hypsochromic shift of the absorption band is observed (Fig. 2), are also proof of the S-alkylation of I and II.

The structure of the cations of hydrohalide salts III and IV apparently should be represented as mesomeric structures with a fixed position of the proton and a positive charge delocalized between the three heteroatoms and the carbon atom. The IR spectra of salts III and IV reflect the contribution to the mesomeric structure of both the N=C bond (band at 1565-1600 cm^{-1}) and the NH−C=S (thioamide) group (band at 1515-1530 cm^{-1}) in which the latter band is considerably less intense than in the starting thioamides (I and II).

Pyrimidinethiones I and II are weak bases and are not titrated in methanol by perchloric acid. We were able to obtain the hydrochloride salts IXa ($R^1 = R^2 = CH_3$, $R^3 = H$, $R^4 = C_6H_4CH_3$-p) and IXb ($R^1 = R^2 = CH_3$, $R^3 = H$, $R^4 = C_6H_4OCH_3$-p) by treatment of the corresponding I with concentrated hydrochloric acid at 20°. Hydration of the double bond of I occurred simultaneously to form IIA as the molecule was protonated.

TABLE 3.



Compound	R¹	R²	R³=R⁴	mp, °C (from hexane)	Empirical formula	Found, % N	Found, % S	Calc., % N	Calc., % S	IR spectrum, ν C=N, cm^{-1}	UV spect. λ_{max}, nm (log ε)	Yield, %
VIa	CH_3	CH_3	H	75,5—76	$C_8H_{16}N_2OS$	15,2	17,1	14,9	17,0	1585	220 (3,93)	84
VIb	C_2H_5	CH_3	H	78,5—79,5	$C_9H_{18}N_2OS$*	—	—	—	—	1595	—	81
VIc	CH_3	H	CH_3	59 —60	$C_9H_{18}N_2OS$	13,5	15,3	13,9	15,8	1590	<215	72
VId	C_6H_5	H	CH_3	44,5—45,5	$C_{14}H_{20}N_2OS$	10,5	12,1	10,6	12,1	1590	<215 (4,10) †	84
VIe	$C_6H_4CH_3$-*p*	H	CH_3	19 —20	$C_{15}H_{22}N_2OS$	9,9	11,4	10,1	11,5	1590	<215 (4,16) †	79
VIf	$C_6H_4OCH_3$-*p*	H	CH_3	29 —30	$C_{15}H_{22}N_2O_2S$	—	10,5	—	10,9	1590	<215 (4,27) †	81

* Found %: C 53.6; H 8.8. Calculated %: C 53.4; H 9.0.

† ε was determined at 220 nm.

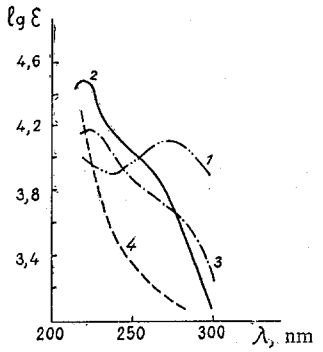


Fig. 2. UV spectra: 1) 4,6,6-trimethyl-3-(p-tolyl)-1,2,3,6-tetrahydropyrimidine-2-thione; 2) IIId; 3) IXa; 4) Vb (in alcohol, c · 10^{-4} M).

The IR spectra of IXa and IXb indicate that the sulfur atom is also protonated: the bands at 1575 and 1535 cm^{-1} reflect the fraction of participation in the mesomeric electronic structure of cation IX of both the N=C bond and the C=S bond. The UV spectra of I and II in 1 N hydrochloric acid, in which a hypsochromic shift of the band by 40-50 nm as compared with the starting I and II, which is similar to the shift in S-alkylated compounds V and VI and their salts (III and IV), is observed are also evidence in favor of protonation at the sulfur atom.

Appreciable attention has been directed to the problem of the relative basicities of the nitrogen and sulfur atoms in thioamides in recent years [17-21]. Our data regarding the center of protonation and alkylation of pyrimidine-2-thiones are in good agreement with the results in the literature.

We have shown that when III and IV are heated briefly in aqueous acids they are interconverted (monitoring by means of thin-layer chromatography). Starting pyrimidinethiones I and II behave similarly in acids.

In the crystalline state IV and VI exist as cyclic structures. It was demonstrated by means of the IR spectra that the ring undergoes partial opening in $CHCl_3$ or CCl_4 solutions, and equilibrium is established between two tautomeric forms – a cyclic form (A) and a chain form (B). The prototropic ring-chain tautomerism was previously studied by us for compounds II [1]. The results of the investigation of the ring-chain tautomerism of IV and VI will be described in a separate communication.

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrophotometer. The UV spectra of alcohol solutions (10^{-5} M) were measured with an SF-4 spectrometer.

4,6,6-Trimethyl-3-phenyl-2-methylmercapto-3,6-dihydropyrimidine Hydriodide (IIIc). A mixture of 8 g (0.035 mole) of 4,6,6-trimethyl-3-phenyl-1,2,3,6-tetrahydropyrimidine-2-thione and 5.4 g (0.038 mole) of methyl iodide in 70 ml of acetone was allowed to stand at room temperature for 6-8 h. The solvent was removed by vacuum distillation, and the residue was recrystallized from acetone.

Compounds IIIa-j were similarly obtained.

3,4,6,6-Tetramethyl-2-benzylmercapto-4-hydroxy-3,4,5,6-tetrahydropyrimidine Hydrochloride (IVf). A mixture of 5 g (0.029 mole) of 3,4,6,6-tetramethyl-4-hydroxyhexahydropyrimidine-2-thione and 4.46 g (0.035 mole) of benzyl chloride in 90 ml of acetone was refluxed for 3 h. The solvent was removed by vacuum distillation, and the residue was recrystallized from acetone.

Compounds IVe and IIIk were similarly prepared.

4,6,6-Trimethyl-2-carboxymethylmercapto-3,6-dihydropyrimidine Hydrochloride (IIIl). A mixture of 3.5 g (0.022 mole) of 4,6,6-trimethyl-1,2,3,6-tetrahydropyrimidine-2-thione and 3.18 g (0.034 mole) of chloroacetic acid in 50 ml of acetone was refluxed for 3 h. The reaction mass was cooled, and the precipitate was removed by filtration, washed with acetone–ether (1:1), and recrystallized from acetone.

3,4,6,6-Tetramethyl-1,2,3,6-tetrahydropyrimidin-2-one (VIIa). A solution of 6 g (0.019 mole) of IIIb in 250 ml of 0.2 N potassium hydroxide (0.05 mole) was heated at 125° for 2 h with vigorous stirring. The reaction mass was cooled and extracted with six 35-ml portions of ether. The ether extract was dried with magnesium sulfate, and the ether was removed by distillation to give 1.82 g (61%) of VIIa with mp 130.5-131.5° (from ethanol). Found %: N 18.0. $C_8H_{14}N_2O$. Calculated %: N 18.2.

Similarly obtained were 4,6,6-trimethyl-3-phenyl-1,2,3,6-tetrahydropyrimidin-2-one (VIIb) [in 9% yield with mp 167-168° (from ethanol). Found %: N 12.6. $C_{13}H_{16}N_2O$. Calculated %: N 13.0] and 4,5-dimethyl-3-ethyl-4-hydroxyhexahydropyrimidin-2-one (VIIIa) [in 57% yield with mp 91.5-92° (from hexane)]. Found %: C 55.7; H 9.3; N 16.2. $C_8H_{16}N_2O_2$. Calculated %: C 55.7; H 9.4; N 16.3.

4,6,6-Trimethyl-3-phenyl-2-methylmercapto-3,6-dihydropyrimidine (Va). Compound IIIc [6 g (0.016 mole)] was treated with 15 ml of 10% ammonium hydroxide at 0° and extracted with ether. The ether extract was dried with magnesium sulfate, and the ether was removed by distillation to give 3.21 g (81%) of Va with mp 39.5-40.5° (from hexane). Found %: C 68.7; H 7.4; N 11.4. $C_{14}H_{18}N_2S$. Calculated %: C 68.3; H 7.4; N 11.4. IR spectrum, ν, cm^{-1}: 1685 (C=C), 1600 (C=N). UV spectrum; λ_{max} < 215 nm, log ε_{220} 4.10.

Compounds Vb-c and VIa-f were similarly obtained.

4,6,6-Trimethyl-3-(p-tolyl)-2-methylmercapto-3,6-dihydropyrimidine (Vb). This compound was obtained in 79% yield and had mp 100.5-101.5° (from acetone). Found %: N 10.6; S 12.1. $C_{15}H_{20}N_2S$. Calculated %: N 10.8; S 12.3. IR spectrum, ν, cm^{-1}: 1680 (C=C), 1600 (C=N). UV spectrum: λ_{max} < 215 nm, log ε_{220} 4.14.

4,6,6-Trimethyl-3-(p-methoxyphenyl)-2-methylmercapto-3,6-dihydropyrimidine (Vc). This compound was obtained in 80% yield and had mp 58.5-59° (from hexane). Found %: N 10.2; S 11.4. $C_{15}H_{20}N_2OS$. Calculated %: N 10.1; S 11.6. IR spectrum, ν, cm^{-1}: 1680 (C=C), 1600 (C=N). UV spectrum: λ_{max} < 215 nm, log ε_{220} 4.25.

4,6,6-Trimethyl-3-(p-tolyl) -4-hydroxyhydropyrimidine-2-thione (IXa). 4,6,6-Trimethyl-3-(p-tolyl)-1,2,3,6-tetrahydropyrimidine-2-thione [2 g (0.008 mole)] was treated with 20 ml of concentrated hydrochloric acid. The acid was removed by vacuum distillation at 30-40°, and the crystals were washed with a large amount of ether to give 1.91 g (78%) of IXa with mp 167.5-168°. Found %: C 55.9; H 7.0; N 9.3. $C_{14}H_{19}N_2OS \cdot HCl$. Calculated %: C 55.7; H 7.1; N 9.3. IR spectrum, ν, cm^{-1}: 1575 (C=N), 1530 (NH−C=S).

4,6,6-Trimethyl-3-(p-methoxyphenyl)-4-hydroxyhexahydropyrimidine-2-thione Hydrochloride (IXb). This compound was similarly obtained in 82% yield and had mp 172-173°. Found %: Cl 11.5. $C_{14}H_{19}N_2O_2S \cdot HCl$. Calculated %: Cl 11.2. IR spectrum, ν, cm^{-1}: 1578 (C=N), 1530 (NH−C=S).

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