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DERIVATIVES OF CONDENSED PYRIMIDINE, PYRAZINE, AND PYRIDINE SYSTEMS.

XXXIV.* STRUCTURE AND PROPERTIES OF 5-AMINO-6-THIO-1,6-DIHYDROPYRIMIDINES

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It is shown by means of IR, UV, and PMR spectroscopy that 5-amino-6-thio-1,6-dihydropyrimidines exist primarily in the thione form both in the crystalline state and in solution.

Methods for the preparation of 5-amino-6-thio-1,6-dihydropyrimidines (I-IV) — starting materials in the synthesis of pyrimido[4,5-b]-1,4-thiazine derivatives — have been reported [1-3]. In the present research we investigated the structure of I-IV and their tendency to undergo thione–thiol tautomerism. Model 5-amino-6-methylthiopyrimidines (V-VIII) with a fixed thiol form were obtained by reaction of I-IV with diazomethane, dimethyl sulfate, and methyl iodide in the presence of alkaline agents. 6-Benzylthiopyrimidine IX was similarly obtained from pyrimidine I and benzyl chloride (Table 1). Reaction of thione I with dimethyl sulfate in the absence of potassium carbonate gave X, the structure of which was confirmed by the presence in its IR spectrum of absorption bands of CO (1640 cm^{-1}) and NH (3150, 3195, and 3310 cm^{-1}) groups and in its PMR spectrum of signals of SCH_3 (2.36 ppm), $N(CH_3)_2$ (2.82 ppm), and 2-H (8.20 ppm) groups. Alkylation of X with dimethyl sulfate or methyl iodide in alkaline media gave XI, the IR spectrum of which contains the absorption band of a CO group (1635 cm^{-1}); the stretching vibrations of an NH group are absent in the spectrum.

The PMR spectra of S-methyl derivatives V-VIII with a fixed thiol form contain a three-position signal at 2.5-2.6 ppm, which is characteristic for an SCH_3 group bonded to an aromatic ring (Table 2). In the alternative structure of compounds with a methyl group attached to the ring nitrogen atom the signal of the CH_3 group attached to the nitrogen atom of the thiolactam form (for example, in the case of 1-N-methyl-2-thiodihydropyridine) is found at 3.6-3.9 ppm.

An examination of the IR spectra of 5-amino-6-thiodihydropyrimidines I-IV shows that these compounds exist in the thione form in the crystalline state (from the absence of the

*See [1] for communication XXXIII.

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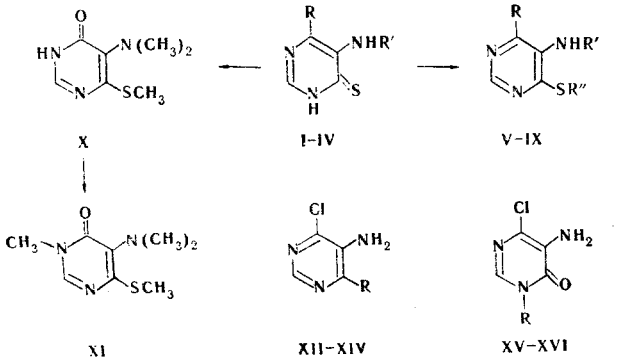

I R=OCH_3, R′=H; II R=OCH_3, R′=$COCH_2CH_2Br$; III R=Cl, R′=H; IV R=Cl, R′=CH_3; V R=OCH_3, R′=H, R″=CH_3; VI R=OCH_3, R′=$COCH_2CH_2Br$, R″=CH_3; VII R=Cl, R′=H, R″=CH_3; VIII R=Cl, R′=CH_3, R″=CH_3; IX R=OCH_3, R′=H, R″=$CH_2C_6H_5$; XII R=Cl; XIII R=OCH_3; XIV R=OC_2H_5; XV R=H; XVI R=CH_3

An examination of the IR spectra of 5-amino-6-thiodihydropyrimidines I-IV shows that these compounds exist in the thione form in the crystalline state (from the absence of the characteristic frequencies of SH bonds at 2550-2600 cm^{-1}).

Although model compounds with a thione structure could not be obtained, a comparison of the UV spectra of 5-amino-6-thiopyrimidines I-IV with the spectra of S-methyl model compounds V-IX with the spectra of S-methyl model compounds V-IX made it possible to sufficiently confidently assign a thione structure to I-IV. As in the case of the corresponding oxygen analogs — 4-chloro-5-amino-6-oxopyrimidine (XV) and its N-CH_3 (XVI) and O-CH_3 (XIII) derivatives — a substantial difference is observed in the UV spectra of these compounds. The lactam structure of XV and of 4(6)-hydroxypyrimidine and its derivatives [4, 5] follows from the UV, IR, and PMR spectra as compared with the spectra of model compounds XVI and XIII.* A comparison of the PMR spectra of I, III, and IV with the spectra of their model thiol forms V, VII, and VIII (see Table 2) shows that the difference in the chemical shifts of the 2-H protons for these groups of compounds is 0.2-0.34 ppm (in pyridine), which is close to the difference observed for oxygen analogs XIII and XV (0.35 ppm). This sort of difference in the chemical shifts also occurs in other solvents. These data also confirm that the thione-thiol equilibrium for I, III, and IV is practically completely shifted to favor the thione forms. However, in the case of 4-methoxy-5-β-bromopropionylamino-6-thiodihydropyrimidine (II) and its S-methyl derivative VI the difference in the 2-H chemical shifts in pyridine decreases to 0.11 ppm (to 0.16 ppm in DMSO), whereas in alcohol it is 0.35 ppm, as in the case of I, III, and IV. It might be assumed that this drawing together of the 2-H chemical shifts in II and VI in pyridine and DMSO is due to solvation of the amide group in the side chain. In addition, one cannot exclude the possibility that this is associated with the development in the indicated solvents of a certain amount of the thiol form in the case of II.

Thus the tautomeric equilibrium of 5-amino-6-thiodihydropyrimidines I-IV in most of the solvents used is shifted markedly to favor the thione forms. In this respect, the examined mercapto compounds are similar to 5-amino-6-hydroxypyrimidines. However, despite the almost complete similarity in the structures of I-IV and their oxygen analogs, they are alkylated primarily at the sulfur atom rather than at the ring nitrogen atom. This peculiarity in the properties of the mercapto compounds is evidently due to the high polarizability of the sulfur atom. In addition, it might be assumed that the differences in the solvation of the reaction center and steric hindrance play a certain role here.

EXPERIMENTAL

The IR spectra of crystals and mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of solutions of the compounds were recorded with an EPS-3 spectrophotometer. Alcohol, dioxane, alcohol–water, and pyridine were used as the solvents. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

*The structure of fixed hydroxy form XIII follows from the method used to prepare it, and the N–CH_3 structure of model XVI is proved by the presence of a CO absorption band in the IR spectra.

TABLE 1. 5-Amino-6-thio- and 5-Amino-6-oxo-1,6-dihydropyrimidines and Their Derivatives

Compound	mp, °C (crystallization solvent)	Found, %					Empirical formula	Calc., %					Yield, %
		C	H	Cl or Br	N	S		C	H	Cl or Br	N	S	
V	70—71[a]	42,4	5,6	—	24,7	18,8	$C_6H_9N_3OS$	42,1	5,3	—	24,5	18,7	78
VI	180—181[b]	35,4	4,0	25,7	13,3	10,6	$C_8H_{12}BrN_3O_2S$	35,3	3,9	26,1	13,7	10,5	87
VIII	48—50[c]	37,7	4,2	18,5	22,0	—	$C_6H_8ClN_3S$	38,0	4,2	18,7	22,2	—	93
IX	60—62[a]	58,7	5,4	—	16,9	13,2	$C_{12}H_{13}N_3OS$	58,3	5,3	—	17,0	13,0	Quant
X	203—205[d]	45,6	5,8	—	22,2	17,7	$C_7H_{11}N_3OS$	45,4	6,0	—	22,7	17,3	53
XI	78—79[a]	48,5	6,5	—	21,3	16,4	$C_8H_{13}N_3OS$	48,2	6,6	—	21,1	16,1	61
XIV	54—55[e]	41,2	4,5	20,6	24,6	—	$C_6H_8ClN_3O$	41,5	4,6	20,4	24,2	—	59
XV	235—236[e]	33,3	2,9	24,2	28,4	—	$C_4H_4ClN_3O$	33,0	2,8	24,3	28,9	—	51
XVI	139 b	37,9	4,1	22,5	26,4	—	$C_5H_6ClN_3O$	37,6	3,9	22,2	26,3	—	72

[a]From hexane. [b]From alcohol. [c]From petroleum ether. [d]From ethyl acetate. [e]From water.

TABLE 2. Chemical Shifts of the Protons in the PMR Spectra of 5-Amino-6-thio- and 5-Amino-6-oxo-1,6-dihydropyrimidines and Their Derivatives (δ, ppm)

Compound	2-H		CH_3
	In CD_3OD	In C_5D_5N	In C_5D_5N
I	7,78	8,21	3,94 (OCH_3)
II	8,13	8,56	4,01 (OCH_3)
III	7,65	8,19	
IV	7,66	8,20	3,17 (NCH_3)
V	8,04	8,40	3,97 (OCH_3) 2,59 (SCH_3)
VI	8,48	8,67	3,96 (OCH_3) 2,58 (SCH_3)
VII	8,12	8,46	2,67 (SCH_3)
VIII	8,26	8,54	3,08 (NCH_3) 2,61 (SCH_3)
XIII	7,75	8,16	3,94 (OCH_3)
XV		7,91	
XVI	7,45	7,80	3,45 (NCH_3)

The starting 4-methoxy-5-amino-6-thiodihydropyrimidine (I), 4-methoxy-5-β-bromopropionylamino-6-thiodihydropyrimidine (II), 4-chloro-5-amino-6-thiodihydropyrimidine (III) 4-chloro-5-methylamino-6-thiodihydropyrimidine (IV), and 4-chloro-5-amino-6-methylthiopyrimidine (VII) were obtained by the methods in [1-3, 6]; 4,6-dichloro-5-aminopyrimidine was synthesized by the method in [6], and 4-chloro-5-amino-6-methoxypyrimidine (XIII) was prepared by the method in [7].

4-Methoxy-5-amino-6-methylthiopyrimidine (V). A) A 0.8-g (6.3 mmole) sample of dimethyl sulfate was added to a suspension of 1 g (6.3 mmole) of pyrimidine I in 40 ml of anhydrous acetone containing 2 g (14 mmole) of K_2CO_3, after which the mixture was stirred at 20° for 20 h. It was then filtered, and the filtrate was vacuum evaporated. The residue was extracted with ether, and the ether was evaporated.

B) This compound was also obtained by the method in [3] by reaction of pyrimidine I with CH_3I.

Compounds VI and VIII were similarly obtained.

C) A 1-g (6.3 mmole) sample of pyrimidine I was added to an ether solution of diazomethane prepared from 15 g of nitrosomethylurea, after which the mixture was stirred at 20° for 20 h. The ether was evaporated, and the residue was triturated with water. The solid material was removed by filtration. The IR spectra of the substances obtained by methods A, B, and C were identical.

4-Methoxy-5-amino-6-benzylthiopyrimidine (IX). A 0.9-g (7.1 mmole) sample of benzyl chloride was added to a solution of 1 g (6.3 mmole) of pyrimidine I in 40 ml of ethanol containing 3.6 ml (6.4 mmole) of a 10% alcohol solution of KOH, after which the mixture was stirred at 20° for 24 h. It was then filtered, and the filtrate was vacuum evaporated. The oily residue was treated with water, and the solid material was removed by filtration.

4-Oxo-5-dimethylamino-6-methylthio-3,4-dihydropyrimidine (X). A mixture of 1 g (6.3 mmole) of pyrimidine I, 1.35 g (17 mmole) of dimethyl sulfate, and 50 ml of benzene was stirred at 80° for 15 h, after which the solvent was removed by vacuum distillation. Water (5-7 ml) was added to the oily residue, and the mixture was neutralized with sodium bicarbonate and extracted repeatedly with hot ethyl acetate. The ethyl acetate solution was treated with activated charcoal and filtered, and the filtrate was evaporated.

3-Methyl-4-oxo-5-dimethylamino-6-methylthio-3,4-dihydropyrimidine (XI). A) Methyl iodide (3 ml) was added to a solution of 0.85 g (4.6 mmole) of pyrimidine X in 50 ml of ethanol containing 0.3 g (5.3 mmole) of KOH, and the mixture was stirred at 20° for 28 h. It was then filtered, and the filtrate was vacuum evaporated. The residue was treated with 10 ml of water, and the solid material was removed by filtration.

B) A 0.72-g (5.4 mmole) sample of dimethyl sulfate was added to a mixture of 1 g (5.4 mmole) of pyrimidine X in 30 ml of anhydrous acetone containing 2 g of K_2CO_3, and the mixture was stirred at 20° for 25 h. It was then filtered, and the filtrate was vacuum evaporated. The residue was treated with ether, and the ether solution was evaporated. The IR spectra of the substances obtained by methods A and B were identical.

Compounds XVI and XV were similarly obtained.

4-Chloro-5-amino-6-ethoxypyrimidine (XIV). This compound was obtained by the method used to prepare XIII [7] by reaction of 12 g (73 mmole) of 4,6-dichloro-5-aminopyrimidine [6] and sodium ethoxide, prepared from 1.68 g of Na and 84 ml of ethanol.

4-Chloro-5-amino-6-oxo-1,6-dihydropyrimidine (XV). A 150-ml sample of 24% HCl was added to 10 g (61 mmole) of 4,6-dichloro-5-aminopyrimidine, and the mixture was stirred at 95° for 30 min. The resulting solution was treated with activated charcoal and filtered. The filtrate was vacuum evaporated, the residue was treated with alcohol, and the solid material was removed by filtration.

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