DERIVATIVES OF CONDENSED PYRIMIDINE, PYRAZINE, AND PYRIDINE SYSTEMS

XXXIII.* 6-AMINOPYRIMIDO[4,5-b]-1,4-THIAZINES

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4-Amino-, 4-methylamino-, and 4-dimethylamino-6-aminopyrimido[4,5-b]-1,4-thiazines were obtained. Some of the properties and transformations of 6-aminopyrimido[4,5-b]-1,4-thiazines – their behavior with respect to acids, reductive desulfuration under the influence of Raney nickel, and reaction with hydrazine – were studied.

We previously reported the synthesis of 6-aminopyrimido[4,5-b]-1,4-thiazines, which we undertook in order to find antitumorigenic preparations [2-4]. In the present research we used a similar method to obtain new derivatives of this system and studied the properties of both the newly and previously obtained 6-aminopyrimidothiazines.

The reaction of 4,5-diamino-, 4-methylamino-5-amino- [5], and 4-dimethylamino-5-amino-6-mercapto pyrimidines (I-III) with chloroacetonitrile was used to synthesize S-cyanomethyl-substituted pyrimidines (IV, V), which were converted to the corresponding 6-aminopyrimidothiazines (VI-VII) by treatment with a methanol solution of potassium hydroxide. In the case of III, 4-dimethyl-amino-6-aminopyrimidothiazine (VIII) was obtained without isolation of the intermediate cyanomethylthiopyrimidine.

In [3] it was noted that the 6-amino group in pyrimido[4,5-b]-1,4-thiazines is cleaved hydrolytically under the influence of aqueous alkali, as a result of which pyrimido-6-thiazinones are formed [6]. However, this process occurs much more readily in the presence of acids. 4-Methoxypyrimido-6-thiazinone (X) was obtained by treatment of 4-methoxy-6-aminopyrimidothiazine (IX) [3] with aqueous hydrochloric acid. When IX is refluxed in concentrated hydrochloric acid, the 4-methoxy group is hydrolyzed along with the 6-amino group to give 4-hydroxyprimido-6-thiazinone (XI).

In contrast to benzothiazine derivatives, which form indoles upon reductive desulfuration under the influence of Raney nickel [7], VI, VIII, and IX, as well as 2-amino-4-methyl-, 4-methylthio-, and 4-methoxy-7-phenyl-6-aminopyrimidothiazines (XII-XIV) [3], are converted under these conditions to N-(5-pyrimidyl) acetamidines (XV-XX), which are quite soluble in water and give strongly alkaline solutions (pH 9-10).

The structures of XV-XX were confirmed by the presence in their IR spectra of absorption bands of a primary amino group and by the presence in their PMR spectra of signals of protons of both methyl groups at 2-2.2 ppm and of protons of the pyrimidine ring at 6-7 ppm. (See scheme on following page.)

The reaction of 6-aminopyrimido[4,5-b]-1,4-thiazines with hydrazine [8] proceeds ambiguously, and the structures of the final products depend both upon the character of the substituents in the pyrimidine ring and on the reaction conditions. Thus 6-hydrazino-substituted compounds (XXI-XXIII) are formed in the reaction of 6-aminopyrimidothiazines (VI, XII, and XIII) with hydrazine hydrate in refluxing ethanol. 4,6-Dihydrazinopyrimido[4,5-b]-1,4-thiazine (XXIV) is obtained when 4-methoxy-6-aminopyrimido[4,5-b]-1,4-thiazine (IX) is refluxed in 99% hydrazine hydrate, whereas N,N'-di(4-methoxypyrimido-6-thiazinyl)hydrazine (XXVI) is obtained when this reaction is carried out in refluxing ethanol. The analogous N,N'-di(4-

*See [1] for communication XXXII.

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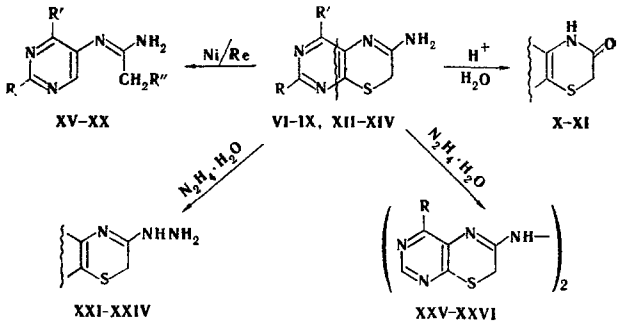
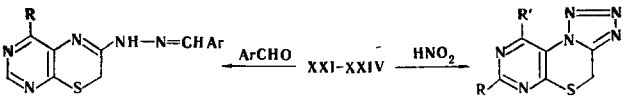


dimethylaminopyrimido-6-thiazinyl)hydrazine (XXVI) was obtained by refluxing VIII in excess 99% hydrazine hydrate. In the latter case, replacement of a dimethylamino group by a hydrazine residue, as was observed for the 4-methoxy group in IX, did not occur. Compound VIII does not react with hydrazine in refluxing ethanol. In contrast to the IR spectra of 6-hydrazinopyrimidothiazines (XXI-XXIV), the IR spectra of XXV-XXVI contain a distinct single band of a secondary amino group (3400 cm^{-1}).

The hydrazine group in XXI-XXIV reacts readily with aromatic aldehydes to give benzylidene derivatives XXVII-XXVIII. Like 6-aminopyrimidothiazines, 6-hydrazinopyrimidothiazines are readily hydrolyzed by mineral acids to give the corresponding pyrimido-6-thiazinones.



The reaction of 6-hydrazinopyrimidothiazines (XXI-XXIII) with HNO_2 gives representatives of a new three-ring system – tetrazalo[1,5-f]pyrimido[4,5-b]-1,4-thiazine (XXX-XXXII). The absorption band of an azide group is absent in the IR spectra of these compounds, and this excludes the possibility of an alternative structure for XXX-XXXII, namely, 6-azidopyrimido[4,5-b]-1,4-thiazine. It is interesting to note that in the reaction of hydrazino derivative XXII with HNO_2 replacement of the amino group in the 2 position by

TABLE 1. 4-R-5-Amino-6-cyanomethylthiopyrimidines IV and V and 4-R-6-Aminopyrimido[4,5-b]-1,4-thiazines VI-VIII

Compound	R	mp, °C*	Empirical formula	Found, %				Calculated, %				Yield, %
				C	H	N	S	C	H	N	S	
IV	NH_2	191—193	$C_6H_7N_5S$	39.7	3,9	38,4	17,8	39.8	3,9	38,6	17.7	82
V	$NHCH_3$	129—130	$C_7H_9N_5S$	43,4	4,7	35.9	16,4	43.1	4,6	35.9	16,4	71
VI	NH_2	241—242	$C_6H_7N_5S$	39,7	3,8	38,4	18,1	39,8	3.9	38.6	17,8	86
VII	$NHCH_3$	185—187	$C_7H_9N_5S$	43,0	4,9	35,4	16,3	43,1	4,6	35.6	16,4	75
VIII	$N(CH_3)_2$	213—214	$C_8H_{11}N_5S$	46,0	5,5	33,9	15.1	45,9	5.3	33.5	15.3	84

*Compounds IV and VI-VIII were purified by recrystallization from water, and V was purified by recrystallization from benzene.

TABLE 2. N-(5-Pyrimidyl)acetamidines XV-XX

Compound	R	R′	R″	mp, °C*	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
XV	H	NH_2	H	130—132	$C_6H_9N_5$	47,3	6,2	—	47,7	6,0	—	71
XVI	H	$N(CH_3)_2$	H	164—165	$C_8H_{13}N_5$	53,4	7,3	38,6	53,6	7,3	39,1	71
XVII	H	OCH_3	H	140—142	$C_7H_{10}N_4O$	50,5	5,9	33,6	50,6	6,1	33.7	70
XVIII	NH_2	CH_3	H	165—167	$C_7H_{11}N_5$	51,0	6,6	42,1	50,9	6,7	42,4	82
XIX	H	H	H	141—143	$C_6H_8N_4$	53,2	6,1	40,9	52,9	5,9	41,1	39
XX	H	OCH_3	C_6H_5	136—138	$C_{13}H_{14}N_4O$	64,7	5,8	23,2	64,4	5.8	23,1	50

*Compounds XV, XVI, and XIX were purified by recrystallization from benzene, XVIII was purified by recrystallization from benzene–alcohol (20 : 1), and XX was purified by recrystallization from cyclohexane.

TABLE 3. 6-Hydrazinopyrimido[4,5-b]-1,4-thiazines (XXI-XXIV) and Their Benzylidine Derivatives (XXVII, XXVIII) and Tetrazolo[1,5-f] pyrimido[4,5-b]-1,4-thiazines (XXX-XXXII)

Compound	R	R'	R''	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	N	S	C	H	N	S	
XXI	H	NH_2	NH_2	281—282	$C_6H_8N_6S$	36,9	4,27	43,0	16,3	36,7	4,16	42,8	16,3	83
XXII	NH_2	CH_3	NH_2	>300	$C_7H_{10}N_6S$	40,1	4,7	39,0	15,3	40,0	4,8	39,0	15,2	88
XXIII	H	SCH_3	NH_2	>300	$C_7H_8N_6S_2$	37,1	3,7	31,4	28,5	37,0	4,0	30,8	28,5	75
XXIV	H	$NHNH_2$	NH_2	251—253	$C_6H_9N_7S$	34,1	4,5	46,5	15,3	34,1	4,3	46,4	15,2	74
XXVII	NH_2	CH_3	N=CHC$_6$H$_5$	226—227	$C_{14}H_{14}N_6S$	56,0	4,8	27,7	10,8	56,3	4,7	28,2	10,7	91
XXVIII	NH_2	CH_3	N=CHC$_6$H$_4$NO$_2$-p	272—273	$C_{14}H_{13}N_7O_2S$	49,3	3,9	28,7	9,6	49,0	3,8	28,6	9,3	97
XXX	H	NH_2	—	227 (dec.)	$C_4H_5N_7S$	34,9	2,5	47,3	15,4	34,8	2,5	47,3	15,5	75
XXXI	OH	CH_3	—	>300	$C_5H_6N_6OS$	37,7	2,7	37,9	14,3	37,8	2,7	37,8	14,4	75
XXXII	H	SCH_3	—	181 (dec.)	$C_5H_6N_6S_2$	35,6	2,4	35,5	26,6	35,3	2,5	35,3	26,9	66

*Compounds XXI-XXIV and XXXI were purified by recrystallization from water, XXVII was purified by recrystallization from ethanol, XXVIII was purified by recrystallization from DMFA–water, and XXX and XXXII were purified by recrystallization from DMFA–alcohol.

a hydroxyl group occurs simultaneously with the formation of the tetrazole ring, whereas under similar conditions the 4-amino group in XXI remains unchanged.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra of D_2O solutions were recorded with a JNM 4H-100 spectrometer. 4,5-Diamino-6-mercaptopyrimidine (I) was obtained in 67% yield by the method in [9] by treatment of 4,5-diamino-6-chloropyrimidine with P_2S_5 in pyridine. 4-Dimethylamino-5-amino-6-mercaptopyrimidine (III) was obtained from 4-dimethylamino-5-nitro-6-chloropyrimidine under the conditions of the synthesis of 4-methylamino-5-amino-6-mercaptopyrimidine [5]. The yield of III with mp 190-192° was 71%. Found: C 42.3; H 6.1; N 33.1; S 18.5%. $C_6H_{10}N_4S$. Calculated: C 42.3; H 5.9; N 32.9; S 18.3%. 6-Cyanomethylthiopyrimidines IV and V and 6-aminopyrimido [4,5-b]-1,4-thiazines VI-VIII were obtained by the method in [3] (Table 1).

4-Methoxypyrimido[4,5-b]-1,4-thiazin-6-one (X). A solution of 1 g of 4-methoxy-6-aminopyrimido[4,5-b]-1,4-thiazine (IX) in 10 ml of 5% hydrochloric acid was allowed to stand at room temperature for 10 h. The resulting precipitate was removed by filtration to give 0.75 g (75%) of X with mp 191-193° (from alcohol). No melting-point depression was observed for a mixture of this product with a genuine sample [6].

4-Hydroxypyrimido[4,5-b]-1,4-thiazinone (XI). A solution of 0.8 g of XI in 4 ml of concentrated HCl was refluxed for 30 min, after which it was cooled to 0°, and the resulting precipitate was removed by filtration and washed with alcohol to give 0.51 g (67%) of a product with mp 263-265° (from water). No melting-point depression was observed for a mixture of this product with a genuine sample [6].

General Method for the Preparation of XV-XX (Table 2). A tenfold amount (by weight) of Raney nickel paste was added to a solution of 5 mmole of the appropriate 6-aminopyrimidothiazine in alcohol, and the mixture was refluxed with vigorous stirring for 6 h. It was then filtered, and the solid on the filter was washed with boiling alcohol. The combined alcohol filtrates were vacuum evaporated, and the residue was triturated with ether. The solid was then removed by filtration and recrystallized.

General Method for the Preparation of XXI-XXIII (Table 3). A solution of 10 mmole of VI, XII, and XIII and 10 ml of 99% hydrazine hydrate in methanol was refluxed for 4 h. The solvent was then removed by distillation, the residue was triturated with water, and the resulting solid was removed by filtration.

4,6-Dihydrazinopyrimido[4,5-b]-1,4-thiazine (XXIV) (Table 3). A solution of 1 g of IX in 15 ml of 99% hydrazine hydrate was refluxed for 2 h, after which it was cooled to 20°, and the resulting precipitate was removed by filtration to give XXIV.

Bis-N,N'-(4-methoxypyrimido[4,5-b]-1,4-thiazin-6-yl]hydrazine (XXV). This compound, with mp 250-252° (from DMF), was obtained in 90% yield by reaction of IX with hydrazine hydrate under the conditions of the synthesis of XXI-XXIII. Found: C 42.8; H 3.8; N 29.0; S 16.2%; M 390 (mass-spectrometric determination). $C_{14}H_{14}N_8O_2S_2$. Calculated: C 43.1; H 3.6; N 28.7; S 16.4%; M 390.

Bis-N,N'-(4-dimethylaminopyrimido[4,5-b]-1,4-thiazin-6-yl)hydrazine (XXVI). A solution of 1 g of VIII in 20 ml of 99% hydrazine hydrate was refluxed for 30 min, after which the excess hydrazine hydrate was removed by vacuum distillation, and the residue was treated with 20 ml of water. The aqueous mixture was filtered, and the filtrate was neutralized with acetic acid and allowed to stand at 0° for 12 h. The resulting precipitate was removed by filtration, washed with alcohol, and air dried to give 0.7 g (70%) of a product with mp 292-294° (from DMF). Found: C 46.1; H 4.8; N 34.0; S 15.5%. $C_{16}H_{20}N_{10}S_2$. Calculated: C 46.1; H 4.8; N 33.6; S 15.4%.

General Method for the Preparation of XXVII and XXVIII (Table 3). An alcohol solution of equimolecular amounts of XXII and benzaldehyde or p-nitrobenzaldehydl was refluxed in the presence of a few drops of acetic acid for 2 h, after which the mixture was cooled to 18-20°, and the resulting precipitate was removed by filtration and recrystallized.

General Method for the Preparation of XXX-XXXII (Table 3). A solution of 5.7 mmole of $NaCO_2$ in 10 ml of water was added dropwise at 0° to a solution of 4.5 mmole of XXI-XXIII in 25 ml of 7% hydrochloric acid, after which the mixture was stirred at 0° for 1 h, and the resulting precipitate was removed by filtration and washed with water.

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