1-Phenyl-3-oxo-4-methyldihydrothieno[3,4-b]indole (XXVI). A 0.7-g (0.0025 mole) sample of II·hydrochloride was refluxed in 20 ml of alcohol and 5 ml of concentrated HCl for 4 h, after which the mixture was cooled to precipitate XXVI (Table 3) with R_f 0.56.

The same method was used to prepare XXVII and XXVIII.

Bis(1-methyl-2-hydroxymethyl-3-indolylphenylmethyl) Sulfide (XXIX). A 1.4-g (0.005 mole) sample of XXVI was reduced in ether with 0.40 g (0.012 mole) of $LiAlH_4$. After decomposition of the excess $LiAlH_4$ with water, the precipitate was removed by filtration, and the ether layer was dried with anhydrous Na_2SO_4 and evaporated to give XXIX, which was crystallized from cyclohexane. The yield of product with mp 75°C was 0.78 g (56%). Found: N 5.2; S 6.0%; $C_{34}H_{32}N_2SO_2$. Calculated: N 5.8; S 6.0%.

2-(1-Methyl-2-indolyl)-4-methylthiazole Hydrochloride (XXX). A 1.37-g (0.01 mole) sample of bromoacetone was added to 1.92 g (0.01 mole) of thioamide I in 15 ml of ethanol saturated with HCl, after which the mixture was refluxed for 5 min. It was then cooled to precipitate 2.4 g (86%) of XXX with mp 215°C (from alcohol). Substance XXX was not affected by refluxing in HCl. The 2-(1-methyl-2-indolyl)-4-methylthiazole base is incapable of forming acetyl derivatives under the influence of acetic anhydride. Found: Cl 12.6; N 4.9; S 11.0%. $C_{14}H_{10}NS \cdot HCl$. Calculated: Cl 12.7; N 5.0; S 11.4%.

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DERIVATIVES OF CONDENSED SYSTEMS BASED ON PYRIMIDINE, PYRAZINE, AND PYRIDINE

XXXVI.* SYNTHESIS OF PYRIMIDO[4,5-b]-1,4-THIAZIN-6-ONES AND PYRIMIDO[4,5-b]-1,5-THIAZEPIN-6-ONES

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Pyrimido[4,5-b]-1,4-thiazin-6-one and pyrimido[4,5-b]-1,5-thiazepin-6-one derivatives were obtained by reaction of 5-amino-6-chloropyrimidines with thioglycolic acid and 5-amino-6-mercaptopyrimidines with β-bromopropionyl chloride. The IR spectra of the compounds are presented.

We have previously reported the synthesis of pyrimido[4,5-b]-1,4-thiazin-6-ones by reaction of 5-amino-6-mercaptopyrimidines with α-halo acids [2]. During a biological study of these compounds it was observed that they inhibit the enzymes of folic acid metabolism and have antitumorigenic activity [3]. In this connection we obtained a number of new derivatives and homologs of pyrimido[4,5-b]-1,4-thiazin-6-one and investigated some of their properties.

4-Alkoxypyrimidothiazin-6-ones IV and V were obtained by reaction of 4-alkoxy-5-amino-6-chloropyrimidines I and II with thioglycolic acid. In the reaction of 4,6-dichloro-5-aminopyrimidine (III) with thioglycolic acid both chlorine atoms are replaced by carboxymethylthio groups to give derivative VI. This method for the synthesis of pyrimidothiazin-6-ones [4] has an advantage over the method described in [2] with respect to the number of steps involved.

*See [1] for communication XXXV.

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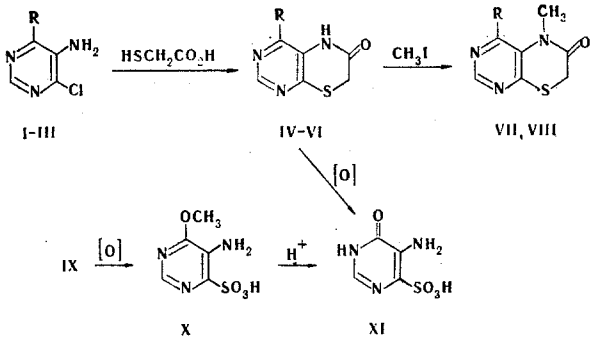
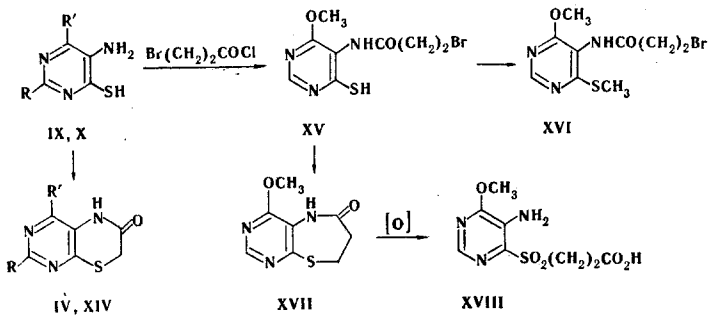
Compounds IV and V are readily alkylated to give methyl derivatives VII and VIII, in the IR spectra of which the NH absorption band present in the spectra of starting IV and V is absent and the absorption band of an amide group (1678-1680 cm^{-1}) is retained. Oxidation of IV with peracetic acid yielded sulfonic acid XI, the structure of which was proved by identification with a sample obtained by oxidation of 4-methoxy-5-amino-6-mercaptopyrimidine (IX) to X and subsequent demethylation.



I, IV, VII R = OCH_3; II, V, VII R = OC_2H_5; III R = Cl; VI R = SCH_2CO_2H

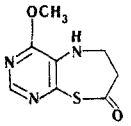
For biological study it was of interest to obtain pyrimido[4,5-b]-1,5-thiazepin-6-one derivatives, which are homologs of IV-VI. With this end in mind, we obtained the corresponding 6-thiopropionic acids XII and XIII by reaction of IX and 2,5-diamino-4-methyl-6-mercaptopyrimidine (X) with β-bromopropionic acid. An attempt to cyclize XII and XIII under the influence of $SOCl_2$ or $POCl_3$ was unsuccessful. We therefore used the more reactive haloalkanoic acid chlorides as the carbonyl component in this reaction. Initially in the case of IX and chloroacetyl chloride we ascertained that in acetone containing K_2CO_3 pyrimidothiazin-6-one IV, rather than the product of acylation of the ring nitrogen atom is formed. Similarly, 2-amino-4-methylpyrimido[4,5-b][1,4]-thiazin-6-one (XIV) was obtained by reaction of X with chloroacetyl chloride. Thus under the indicated conditions the 5-NH_2 groups is acylated and the SH group is alkylated, and the ring $N_{(1)}$ atom does not participate in the reaction.



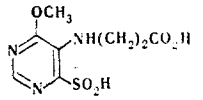
XIV R = NH_2, R' = CH_3

5-(2-Bromopropionyl)aminopyrimidine (XV) was isolated in the reaction of pyrimidine IX with β-bromopropionyl chloride. The alternative structures – products of aklylation and acylation of the S or $N_{(1)}$ atoms – are excluded by the results of elementary analysis, by the absence in the IR spectra of absorption of an NH_2 group, by the presence of absorption bands of an amide group, and by the chemical transformations of XV. Thus the reaction of XV with CH_3I gave derivative XVI, the structure of which as the SCH_3 rather than the NCH_3 derivative was proved by the presence in its PMR spectrum of the signal of an SCH_3 group (2.62 ppm). Heating XV in acetonitrile gave pyrimido[4,5-b]-1,5-thiazepin-6-one (XVII), the structure of which was proved by the presence in its IR spectrum of bands of an amide group (1670 and 3230 cm^{-1}) and by reactions: like cyclic lactams, XVII is readily alkylated by CH_3I to give the 5-methyl derivative (XIX). The IR spectrum of XIX does not contain the NH band that is present in the spectrum of starting XVII, but the band of an amide carbonyl group (1675 cm^{-1}) is retained. Oxidation of thiazepinone XVII gave acid XVIII, the IR spectrum of which contains, in addition to bands of SO_2 groups (1125 cm^{-1}) and a carboxyl group (1725 cm^{-1}), bands of an NH_2 group (3380, 3490, and 1610 cm^{-1}). The intensity of the bands related to the NH_2 group decrease markedly when acid XVIII is deuterated; this confirms the correctness of the above assignments. These data make it possible to reject alternative structures XX and XXI for acid XVIII and starting pyrimidothiazepinone XVII and consequently to exclude the possibility of migration of the acyl residue from the 5-NH_2 group to the 6-mercapto group under the conditions

of cyclization of XV to XVII:



XX



XXI

In a preparative respect thiazepinone XVII is more conveniently obtained without isolation of intermediate XV [5]. In this case the reaction product is extracted, after removal of the solvent, by refluxing acetonitrile, and XVII is obtained in 75% yield. 4-Methylthiopyrimido[4,5-b]-1,5-thiazepin-6-one (XXIII) was similarly obtained from 4-methylthio-5-amino-6-mercaptopyrimidine (XXII) and β-bromopropionyl chloride.

EXPERIMENTAL

The IR spectra of suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

The starting 4-methoxy-5-amino-6-chloropyrimidine (I) was obtained by the method in [6], 4,6-dichloro-5-aminopyrimidine (III) and 4-methoxy-5-amino-6-mercaptopyrimidine (IX) were obtained by the method in [7], and 2,5-diamino-4-methyl- and 4-methylthio-5-amino-6-mercaptopyrimidines (X and XXII) were obtained by the methods in [8, 9].

4-Ethoxy-5-amino-6-chloropyrimidine (II). This compound, with mp 54-55°C (from water), was obtained in 59% yield by the method in [6] by reaction of 4,6-dichloro-5-aminopyrimidine with sodium ethoxide in ethanol. Found: C 41.2; H 4.5; N 24.6%. $C_6H_8ClN_3O$. Calculated: C 41.5; H 4.6; N 24.2%.

General Method for the Preparation of IV, V, VI, and XIV. A) A mixture of 46 mmole of pyrimidines I-III, 40 ml of water, 123 mmole of KOH, and 80 mmole of $HSCH_2COOH$ was stirred at 90-95°C for 40 min, after which it was cooled to 20° and acidified with HCl. After 48 h, thiazinones IV-VI were removed by filtration.

B) A mixture of 6.3 mmole of IX or X, 7.5 mmole of $ClCH_2COCl$, 0.9 g of K_2CO_3, and 35 ml of dry acetone was stirred at 20°C for 16 h, after which the solvent was removed by distillation, and the residue was treated with water and neutralized with acetic acid to give thiazinones IV and XIV (see Table 1).

General Method for the Preparation of VII, VIII, and XIX. Methyl iodide (4 ml) was added to a solution of 11.4 mmole of IV, V, or XVII in 40 ml of ethanol containing 0.9 g of KOH, and the mixture was heated to 70-75°C and stirred for 5 h. It was then filtered, and the filtrate was evaporated to dryness. The residue was extracted with boiling ether, the solvent was removed by distillation, and the residue was triturated with water to give 5-N-methyl derivatives VII, VIII, and XIX (see Table 1).

General Method for the Preparation of XII and XIII. A solution of 6.5 mmole of β-bromopropionic acid in 20 ml of methanol was added to a solution of 6.4 mmole of IX in 40 ml of methanol containing 0.8 g of KOH, and the mixture was stirred at 20°C for 5 h. The solvent was removed by vacuum distillation, and the residue was dissolved in water. The aqueous solution was acidified to pH 4-5 with hydrochloric acid and extracted with ethyl acetate. The extract was evaporated, and the residue was triturated with ether to give thiopropionic acids XII and XIII (see Table 1).

4-Oxo-5-amino-3,4-dihydropyrimidine-6-sulfonic Acid (XI). A) A 3.5-ml sample of 30% H_2O_2 was added to a solution of 2 g of IV in 7 ml of glacial acetic acid, and the mixture was allowed to stand at room temperatur for 20 days. The resulting precipitate was removed by filtration to give X, with mp 250-251°C (from water), in 32% yield. IR spectrum: 1712 (amide CO), 1255 (S–O), and 3350 and 3467 cm^{-1} (NH_2). Found: C 24.9; H 2.9; S 16.6%. $C_4H_5N_3O_4S$. Calculated: C 25.1; H 2.6; S 16.8%.

B) A mixture of 1 g of X and 10 ml of 12% HCl was refluxed for 30 min, after which it was cooled to 1-3°C, and the precipitate was removed by filtration to give acid XI. The IR spectra of the samples of XI synthesized by methods A and B were identical.

4-Methoxy-5-aminopyrimidine-6-sulfonic Acid (X). A 4-ml sample of 30% H_2O_2 was added dropwise with ice cooling to a solution of 2 g of IX in 10 ml of glacial acetic acid, and the mixture was stirred at this temperature for 3 h and at 20°C for 48 h. The precipitate was removed by filtration and washed with water to give acid X, with mp 212-214°C (from water), in 41% yield. IR spectrum: 1240 (S–O) and 3340 and 3470 cm^{-1} (NH_2). Found: C 29.1; H 3.5; N 20.5; S 15.8%. $C_5H_7N_3O_4S$. Calculated: C 29.3; H 3.4; N 20.8; S 15.6%.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C*	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
IV	190—191					$C_7H_7N_3O_2S^2$					83
V	193—194	45,2	4,1	20,2	15,4	$C_8H_9N_3O_2S$	45,5	4,3	19,9	15,2	60
VI	213—215					$C_8H_6N_3O_3S^{10}$					30
XIV	>300					$C_7H_8N_4OS^2$					70
VII	129—130	45,7	4,4	19,9	15,4	$C_8H_9N_3O_2S$	45,5	4,3	19,9	15,2	63
VIII	110—112	48,0	4,7	18,7	14,1	$C_9H_{11}N_3O_2S$	48,0	4,9	18,6	14,2	81
XIX	115—117	48,4	5,1	18,8	14,1	$C_9H_{11}N_3O_2S$	48,0	4,9	18,6	14,2	47
XVII	160—162	45,7	4,2	19,9	15,0	$C_8H_9N_3O_2S$	45,5	4,4	19,9	15,2	70
XXIII	199—201	42,1	4,0	18,4	27,9	$C_3H_9N_3O_2S$	42,3	4,0	18,5	28,2	70
XII	85—87	41,8	4,7	18,1	—	$C_8H_{11}N_3O_3S$	41,9	4,8	18,3	—	67
XIII	154	42,1	5,3	24,9	—	$C_8H_{12}N_4O_2S$	42,0	5,3	24,6	—	61

*Compounds IV, XVII, XIX, and XXIII were purified by recrystallization from alcohol, VI was purified by reprecipitation from aqueous NaOH solution by the addition of hydrochloric acid, XIV was purified by recrystallization from DMF, V was purified by recrystallization from aqueous alcohol, VII and XIX were purified by recrystallization from ether, and XII and XIII were purified by recrystallization from water.

4-Methoxy-5-β-bromopropionylamino-6-mercaptopyrimidine (XV). A mixture of 1 g (6.3 mmole) of IX, 0.9 g (6.5 mmole) of K_2CO_3, 1.3 g (6.8 mmole) of $Br(CH_2)_2COCl$, and 100 ml of dry acetone was stirred at 20°C for 2.5 h, after which the precipitate was removed by filtration and extracted with boiling alcohol. The alcohol extract and the acetone filtrate were combined and evaporated to dryness, and the residue was recrystallized from alcohol to give XV in 70% yield. The product did not have a definite melting point. IR spectrum: 1672 (amide CO) and 3220 and 3260 cm^{-1} (amide NH). Found: C 33.2; H 3.6; Br 27.0; N 14.7; S 11.1%. $C_8H_{10}BrN_3O_2S$. Calculated: C 32.9; H 3.4; Br 27.3; N 14.4; S 11.0%.

General Method for the Preparation of XVII and XXIII. A mixture of 6.3 mmole of IX, 0.9 g of K_2CO_3, 6.8 mmole of $Br(CH_2)_2COCl$, and 100 ml of dry acetone was stirred at 20°C for 6 h, after which the precipitate was removed by filtration and extracted with boiling acetonitrile (two 50-ml portions). The extracts were evaporated to dryness, and the residue was treated with water and removed by filtration to give thiazepinones XVII and XXIII (see Table 1).

2-(4-Methoxy-5-amino-6-pyrimidyl)thiopropionic Acid S,S-Dioxide (XVIII). A mixture of 1 g of thiazepinone XVII, 3.5 ml of glacial acetic acid, and 1.9 ml of 30% H_2O_2 was maintained at 20°C for 20 days, after which the precipitate was removed by filtration to give XVIII, with mp 160-163°C (from water), in 36% yield. IR spectrum: 1125 (S—O), 1725 (COOH), and 3380 and 3490 cm^{-1} (NH_2). Found: C 36.5; H 4.1; N 16.6; S 12.4%. $C_8H_{11}N_3O_5S$. Calculated: C 36.8; H 4.2; N 16.1; S 12.3%.

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