INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

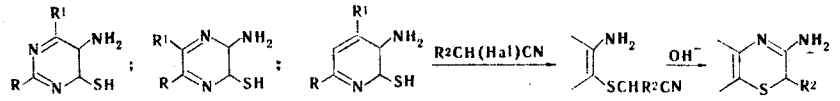
XXIII.* SYNTHESIS OF 6-AMINO DERIVATIVES OF PYRIMIDO[4,5-b]-, PYRAZINO[2,3-b]-, AND PYRIDO[2,3-b]-1,4-THIAZINES

T. S. Safonova, M. P. Nemeryuk,
L. A. Myshkina, and N. I. Traven'

UDC 547.853.7'854.1'861.6'822.7'825'869:
543.422.25.4.6

The reaction of o-aminomercapto derivatives of pyrimidine, pyrazine, and pyridine, with α-halo acid nitriles was investigated. The corresponding cyanoalkylthio heterocycles, which were converted to 6-amino derivatives of pyrimido[4,5-b]-, pyrazino[2,3-b]-, and pyrido-[2,3-b]-1,4-thiazines, were obtained. The structures of the substances obtained were confirmed by IR, UV, and PMR spectroscopy.

In connection with a search for antitumorigenic substances [1], we undertook the synthesis of previously unknown 6-amino derivatives of pyrimido- and pyrazino-1,4-thiazines [2], as well as the little-studied 6-aminopyrido-1,4-thiazine [3]. With this end in mind, we studied the reaction of o-aminomercapto derivatives of pyrimidine (Ia-f), pyrazine (IIa-c), and pyridine (IIIa-b) with α-halo acid nitriles.



Ia-f II a-c III a-b VI-XVI XVII-XXVII

5-Amino-6-cyanoalkylthiopyrimidines (VI-X, Table 1) were isolated from the reaction of 4-methoxy-, 2-amino-4-methyl-, 4-chloro-, 2-amino-4-hydroxy-, 4-methylthio-, and 4-benzylthio-5-amino-6-mercapto-pyrimidines (Ia-f) with an equimolecular amount of alkali at 40-60°C. The action of excess alkali on VI-VIII and X gave 6-aminopyrimidothiazines (XVII, XVIII, and XXI, Table 2). In the case of 2,5-diamino-4-hydroxy-6-cyanomethylthiopyrimidine (IX) under similar conditions, we isolated 2-amino-4-hydroxy-pyrimido[4,5-b]-1,4-thiazin-6-one (XXVIII), which is apparently formed as the result of hydrolysis of the corresponding 6-aminopyrimidothiazine. The structure of XXVIII was confirmed by alternative synthesis from 2,5-diamino-4-hydroxy-6-mercaptopyrimidine (Id) and chloroacetic acid.

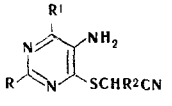
When 4-chloro-5-amino-6-cyanomethylthiopyrimidine (VIII) is heated with alcoholic KOH, replacement of the chlorine atom by a OCH_3 group occurs simultaneously with cyclization to give 4-methoxy-6-aminopyrimidothiazine (XVII).

2-Cyanoalkylthio-3-aminopyrazines (XI-XIII, Table 1) were obtained by the reaction of 5,6-dimethyl- and 5,6-diphenyl-2-mercapto-3-aminopyrazines (IIb-c) with α-halo acid nitriles under the conditions of the synthesis of VI-X. Compounds XI-XIII are more stable than the analogous pyrimidine derivatives, which is due to the α orientation of the NH_2 group with respect to the cyclic nitrogen atom. Thus XI and XIII are converted to 6-aminopyrazinothiazines (XXIII and XXV, Table 2) on refluxing with alcoholic alkali. When a phenyl group is present in the cyanomethyl grouping (XII), cyclization is accomplished by the action

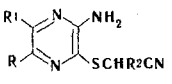
*See [10] for communication XXII.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 944-948, July, 1972. Original article submitted July 12, 1971.

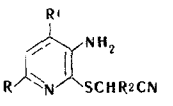
TABLE 1



VI-IX



XI-XIII



XIV-XVI

Comp.	R	R¹	R²	mp, °C *	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	S	C	H	N	S	
VI	H	OCH_3	H	102—104	$C_7H_8N_4OS$	43,2	4,2	28,3	16,7	42,8	4,1	28,5	16,3	78
VII	NH_2	CH_3	H	129—131	$C_7H_9N_5S$	42,9	4,8	36,1	—	43,1	4,6	35,9	—	86
VIII	H	Cl	H	152—153	$C_6H_5ClN_4S$	35,7	2,7	28,0	16,0	35,9	2,5	27,9	16,0	87
IX	NH_2	OH	H	>300	$C_6H_7N_5OS$	36,8	3,8	35,7	15,8	36,5	3,6	35,5	16,2	70
X	H	OCH_3	C_6H_5	145—147	$C_{13}H_{12}N_4OS$	57,1	4,3	20,2	11,9	57,3	4,4	20,6	11,8	87
XI	CH_3	CH_3	H	176—177	$C_8H_{10}N_4S$	49,5	5,4	28,9	16,8	49,5	5,2	28,9	16,5	65
XII	CH_3	CH_3	C_6H_5	156—157	$C_{14}H_{14}N_4S$	62,0	4,9	20,6	11,8	62,2	5,2	20,7	11,9	75
XIII	C_6H_5	C_6H_5	H	179—180	$C_{18}H_{14}N_4S$	68,1	4,6	17,3	9,9	68,9	4,4	17,6	10,0	82
XIV	Cl	H	H	94—95	$C_7H_6ClN_3S$	42,2	3,0	21,1	16,0	42,6	2,8	21,1	16,3	75
XV	Cl	H	C_6H_5	97—98	$C_{13}H_{10}ClN_3S$	57,0	3,6	15,0	11,4	56,6	3,6	15,2	11,6	56
XVI	OCH_3	H	H	64—65	$C_8H_9N_3OS$	49,2	4,6	21,5	16,4	48,9	4,6	21,3	16,3	88

*Compound VI was recrystallized from benzene, while the other compounds were recrystallized from water (VII-IX), alcohol (X), methanol (XI-XIII), aqueous alcohol (XIV), cyclohexane (XV), and ether–petroleum ether (XVI).

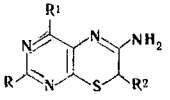
of sodium alkoxide and gives 6-amino-7-phenylpyrazinothiazine (XXIV).

The extension of the investigated reaction to 2-mercapto-3-aminopyridines (IIIa,b) made it possible to uncover peculiarities in the course of it that are caused by the nature of the pyridine ring. As a consequence of the high nucleophilic strength of the NH_2 group in IIIa,b as compared with similar pyrimidine derivatives, the primary reaction products (XIV-XVI, Table 1) can be isolated only when the process is carried out under mild conditions (0-5°). 6-Aminopyridothiazines (XXVI and XXVII, Table 2) are obtained when the S-cyanomethyl derivatives (XIV, XVI) are treated with alcoholic alkali at 18-20°.

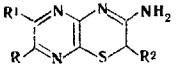
It is more convenient to obtain 6-aminopyrimido- and pyrazinothiazines (XVII-XXI, XXII-XXV) without isolation of the intermediate S-cyanoalkyl-substituted compounds. In this case, the reaction of o-aminomercaptopyrimidines and pyrazines is carried out in the presence of excess alkali. The structures of the intermediate substances (VI-XVI, Table 1) and 6-amino derivatives of the two-ring 1,4-thiazine systems (XVII-XXV, Table 2) were confirmed by means of IR, PMR, and UV spectroscopy. The IR spectra of VI-XVI contain an absorption band of a C≡N group (2000-2300 cm^{-1}), which vanishes during cyclization of these substances to 6-amino derivatives XVII-XXVII. It follows from the data of the PMR spectra of XVII, XXII, and XXVI that the double bond in the thiazine ring is in the 5,6 position (from the presence of a singlet of the 7-CH_2 group at δ 3.73-4.53 ppm). The IR spectra of the investigated amines contain absorption bands at 1590-1620, 3300-3330, and 3380-3450 cm^{-1}, which are characteristic for a primary NH_2 group, and a C=N absorption band at 1630-1670 cm^{-1}. It was also demonstrated that the intensty of bands related to the deformation vibrations of the NH_2 group (1590-1620 cm^{-1}) decreases when the compounds are deuterated by means of C_2H_5OD. The UV spectra of the 6-amino derivatives (XVII-XXVII) do not change on passing from nonpolar solvents (dioxane, chloroform) to alcohol and alcohol–water mixtures, which is evidence that the investigated compounds exist in the amino form.

The previously undescribed 2,5-diamino-4-hydroxy-6-mercaptopyrimidine (Id) was obtained by treatment of 2-amino-4-hydroxy-5-nitro-6-chloropyrimidine with alcoholic NaSH solution with subsequent reduction of the resulting nitromercapto derivatives by sodium hydrosulfite in alkali media. 4-Methylthio-5-amino-6-mercaptopyrimidine (Ie) was obtained by reaction of 4-methylthio-5-amino-6-chloropyrimidine (IV) with P_2S_5. A similar method was used to obtain 4-benzylthio-5-amino-6-mercaptopyrimidine (If). 4-Chloro-5-amino-6-methylthio- and 4-chloro-5-amino-6-benzylthiopyrimidines (IV, V) were synthesized by alkylation of 4-chloro-5-amino-6-mercaptopyrimidine (If) with methyl iodide and benzyl chloride, respectively.

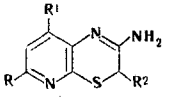
TABLE 2



XVII-XXI



XXII-XXV



XXVI-XXVII

Comp.*	R	R¹	R²	mp, °C†	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	N	S	C	H	N	S	
XVII	H	OCH_3	H	213—214	$C_7H_8N_4OS$	42,7	4,1	28,7	16,6	42,8	4,1	28,6	16,3	82
XVIII	NH_2	CH_3	H	234—235	$C_4H_9N_5S$	42,7	4,7	35,5	16,4	43,1	4,6	35,9	16,4	80
XIX	H	SCH_3	H	210—212	$C_7H_8N_4S_2$	39,4	3,7	26,1	30,4	39,6	3,8	26,4	30,2	78
XX	H	$SCH_2C_6H_5$	H	156—157	$C_{13}H_{12}N_4S_2$	53,7	4,2	19,2	22,4	54,1	4,2	19,4	22,2	67
XXI	H	OCH_3	C_6H_5	189—190	$C_{13}H_{12}N_4OS$	57,1	4,7	20,2	11,4	57,3	4,4	20,6	11,8	90
XXII	H	H	H	201—202	$C_6H_6N_4S$	43,6	3,6	33,5	19,1	43,3	3,6	33,7	19,3	48
XXIII	CH_3	CH_3	H	200—201	$C_8H_{10}N_4S$	49,6	5,0	28,8	16,4	49,5	5,2	28,8	16,5	77
XXIV	CH_3	CH_3	C_6H_5	227—228	$C_{14}H_{14}N_4S$	61,9	5,2	20,3	12,1	62,2	5,2	20,7	11,9	75
XXV	C_6H_5	C_6H_5	H	249—250	$C_{18}H_{14}N_4S$	68,0	4,2	17,6	9,9	68,0	4,4	17,6	10,1	77
XXVI	Cl	H	H	216—218	$C_7H_6ClN_3S$	42,2	3,0	21,1	16,0	42,6	2,8	21,1	16,3	80
XXVII	OCH_3	H	H	195—197	$C_8H_9N_3OS$	49,2	4,6	21,5	16,4	49,1	4,8	21,4	16,4	80

*PMR spectra: XVII 4.12 ppm (7-CH_2) (D_2O); XXIII 3.73 ppm (7-CH_2) (deuteropyridine), 4.53 (7-CH_2) (CF_3COOH); XXVI 3.73 ppm (7-CH_2) (deuteropyridine).

† Compounds XVII-XXII, XXIV, and XXVI-XXVII were recrystallized from ethanol, while XXIII and XXV were recrystallized from ethyl acetate and methanol, respectively.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions of the substances were recorded with a UR-10 spectrophotometer.

The starting 4-methoxy-5-amino-6-mercaptopyrimidine (Ia), 2,5-diamino-4-methyl-6-mercaptopyrimidine (Ib), and 4-chloro-5-amino-6-mercaptopyrimidine (Ic) were obtained by the methods in [6,7]. 2-Mercapto-3-aminopyrazine (IIa) and 2-mercapto-3-amino-5,6-dimethyl- and 2-mercapto-3-amino-5,6-diphenylpyrazines (IIb,c) were synthesized by the methods in [8]. 2-Mercapto-3-amino-6-chloro- and 2-mercapto-3-amino-6-methoxypyridines (IIIa,b) were obtained via the method in [9].

2,5-Diamino-4-hydroxy-6-mercaptopyrimidine (Id). A 13.5-g (0.07 mole) sample of 2-amino-4-hydroxy-5-nitro-6-chloropyrimidine [4] was added to a solution of NaSH obtained by saturation of a solution of 4.2 g (0.105 mole) of NaOH in 140 ml of methanol with H_2S. The mixture was stirred at 20° for 4 h, and the solvent was removed by vacuum distillation. The residue was dissolved in 10% aqueous NaOH, about 37 g (0.2 mole) of $Na_2S_2O_4$ was added in small portions to the solution, and the mixture was stirred at 50° for 30 min. The reaction mixture was tested for the presence of $Na_2S_2O_4$ (with respect to methylene blue), and when the reaction was positive the solution was filtered and acidified with acetic acid to give 7.2 g (59%) of Id with mp > 300°. The substance was purified for analysis by reprecipitation from alkaline solution by the addition of acetic acid. Found: C 30.1; H 4.0; N 35.5%. $C_4H_6N_4OS$. Calculated: C 30.4; H 3.8; N 35.4%.

4-Chloro-5-amino-6-methylthiopyrimidine (IV). A 3-ml (68 mmole) sample of CH_3I was added at 20° to a solution of 1 g (6.2 mmole) of Ic in 30 ml of methanol containing 0.4 g (7.1 mmole) of KOH, and the mixture was stirred for 20 h. The solvent was removed by distillation, and the residue was extracted with ether. The ether extracts were passed through a column filled with Al_2O_3. Evaporation of the ether eluates gave 0.8 g (73%) of IV with mp 93-95°. Found: C 34.1; H 3.4%. $C_5H_6ClN_3S$. Calculated: C 34.2; H 3.4%.

4-Chloro-5-amino-6-benzylthiopyrimidine (V). This compound was obtained in 88% yield by a method similar to that used to prepare IV by reaction of equimolecular amounts of Ic and benzyl chloride. The product had mp 75-77°. Found: C 52.4; H 4.1%. $C_{11}H_{10}ClN_3S$. Calculated: C 52.5; H 4.0%.

4-Methylthio-5-amino-6-mercaptopyrimidine (Ie). A mixture of 2 g (0.011 mole) of IV and 7 g (0.031 mole) of P_2S_5 in 50 ml of pyridine was heated at 95-98° for 2 h. The solvent was removed by vacuum distillation, 100 ml of water was added to the residue, and the mixture was refluxed for 2 h. It was then made alkaline with NaOH solution, filtered, and acidified with acetic acid to give 1.5 g (76%) of Ie with mp 241-243° (alcohol). Found: C 34.8; H 4.2; N 24.0; S 36.8%. $C_5H_7N_3S_2$. Calculated: C 34.7; H 4.1; N 24.2; S 37.0%.

4-Benzylthio-5-amino-6-mercaptopyrimidine (If) [5]. This compound was obtained in 63% yield via a method similar to that used to prepare Ie by reaction of V with P_2S_5. The product had mp 178-179° (alcohol). Found: C 52.7; H 4.2; N 16.8; S 25.3%. $C_{11}H_{11}N_3S_2$. Calculated: C 53.0; H 4.4; N 16.8; S 25.7%.

5-Amino-6-cyanoalkylthio Derivatives of Pyrimidine, Pyrazine, and Pyridine (VI-XVI). A 0.01-mole sample of the appropriate o-aminomercapto derivative in 40 ml of methanol containing 0.012 mole of KOH was added in the course of 4 h at 60° to a solution of 0.013 mole of $ClCH_2CN$ or $C_6H_5CHBrCN$ in 20 ml of methanol. The reaction mixture was held at 60° for another hour, the solvent was removed by distillation. The residue was triturated with water, and the solid was removed by filtration and recrystallized. In the preparation of XIV-XVI, the reaction was carried out at −10 to −5° (Table 1).

6-Amino Derivatives of Pyrimido[4,5-b]-1,4-thiazine (XVII-XXI). A total of 20 ml of a 4% solution of KOH in methanol was added to the reaction mass obtained under the conditions of the synthesis of VI-XIII, and the mixture was allowed to stand at 18-20° for 24 h. The solvent was removed by distillation, and the residue was triturated with water and recrystallized.

6-Amino Derivatives of Pyrazino- and Pyrido[2,3-b]-1,4-thiazine (XXIII, XXV-XXVII). These compounds were obtained by a method similar to that used to prepare pyrimidothiazines, with the difference that the reaction mixture was heated at 60° for 1 h after addition of the alkali solution. Compound XXII was obtained under the conditions of the synthesis of VI-XIII by the reaction of equimolecular amounts of IIa and $ClCH_2CN$. Compound XXIV was obtained by refluxing XII in 2% sodium methoxide solution in methanol for 30 min (Table 2).

2-Amino-4-hydroxypyrimido[4,5-b]-1,4-thiazin-6-one (XXVIII). A) A solution of 0.4 g of IX in 20 ml of 4% aqueous KOH was held at 20° for 96 h. It was then acidified with acetic acid, and the precipitate was removed by filtration to give 0.2 g (50%) of XXVIII with mp > 300° (from water).

B) A solution of 3 g (1.9 mmole) of Id and 1.8 g (1.9 mmole) of chloroacetic acid in 35 ml of 2 N KOH was heated at 95-98° for 2 h, cooled to 20°, and acidified to pH 3-2 with HCl. The mixture was heated for another 30 min at 95-98°, filtered, and neutralized with aqueous sodium acetate to give 3 g (79%) of XXVIII with mp > 300° (from water). Found: C 36.0; H 3.2; N 28.2; S 15.7%. $C_6H_6N_4O_2S$. Calculated: C 36.4; H 3.0; N 28.3; S 16.2%. The IR spectra of substances obtained by methods A and B were identical.

LITERATURE CITED

1. T. S. Safonova, M. P. Nemeryuk, V. A. Chernov, N. A. Andreeva, A. S. Sokolova, N. A. Ryabokon', A. F. Keremov, and T. P. Lapshina, in: Methods for the Synthesis and Investigation of Antitumorigenic Preparations [in Russian] (1970), No. 3, p. 91.
2. T. S. Safonova, M. P. Nemeryuk, and T. L. Lapshina, USSR Author's Certificate No. 197,599; Byull. Izobr., 13, 34 (1967).
3. Torizo Takahashi and Eiichi Yoshii, Chem. Pharm. Bull., 2, 382 (1954); Chem. Abstr., 50, 13,032 (1956).
4. G. Dovoll and D. D. Evans, J. Chem. Soc., 5041 (1960).
5. Shoji Inoue, Chem. Pharm. Bull., 6, 352 (1958).
6. E. Taylor, J. Barton, and W. Paudler, J. Org. Chem., 26, 4961 (1961).
7. F. Rose, J. Chem. Soc., 3448 (1952).
8. T. S. Safonova and L. A. Myshkina, Khim. Geterotsikl. Soedin., No. 3, 230 (1971).
9. T. S. Safonova and L. G. Levkovskaya, Khim. Geterotsikl. Soedin., 997 (1968).
10. L. G. Levkovskaya and T. S. Safonova, Khim. Geterotsikl. Soedin., 1502 (1971).