

INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

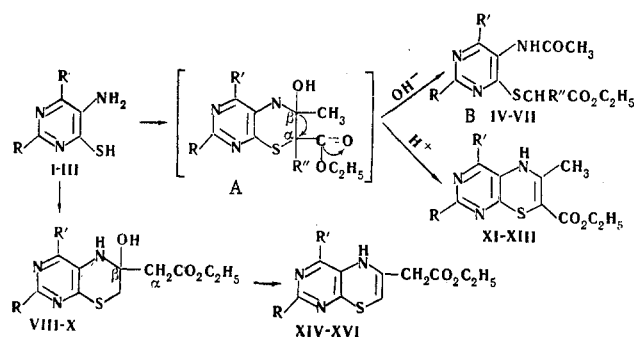
XVI.* REACTION OF 5-AMINO-6-MERCAPTOPYRIMIDINES WITH HALOKETO ACID ESTERS

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It is shown that 5-acetamido-6-carbethoxymethylmercaptopyrimidines (IV-VII) are formed by reaction of 5-amino-6-mercaptopyrimidines (I-III) with α -chloro- and α -chloro- α -methylacetoacetic esters in the presence of excess alkali, while 6-methyl-7-carbethoxypyrimidothiazines (XI-XIII) are formed in the absence of alkali; under similar conditions, hydroxyamino compounds VIII-X and 6-carbethoxymethylpyrimidothiazines XIV-XVI are obtained from I-III and γ -chloroacetoacetic ester. 6-Carbethoxy- and 7-carbethoxypyrimidothiazines XVII-XXI were synthesized from I-III and ethyl bromopyruvate, II, and chloroformylacetic ester, respectively.

In continuing our study [2] we have investigated the reaction of 2,5-diamino-4-methyl-, 4-methoxy-5-amino-, and 4-chloro-5-amino-6-mercaptopyrimidines (I-III) with haloketo acid esters. In the case of α -chloroacetoacetic ester we observed an interesting deviation of the process from the scheme described for phenacyl halides [3]. It was shown that 5-acetamido-6-carbethoxymethylmercaptopyrimidines IV-VI (Table 1) rather than pyrimidothiazines are formed by reaction of I-III with α -chloroacetoacetic ester under mild conditions (in the presence of a small excess of alkali at 18-20°). Compound VII was similarly obtained from II and α -methyl- α -chloroacetoacetic ester. The structures of IV-VII were confirmed by IR data (the presence of two carbonyl groups) and by the PMR spectra (the presence of a SCH₂ group, see Fig. 1), as well as by countersynthesis in the case of VI. Reaction of III with ethylchloroacetate yielded 4-chloro-5-amino-6-carbethoxymethylmercaptopyrimidine XXII, which was transformed to VI by reaction with CH₃COCl. The formation of IV-VII, like 6-arylpyrimidothiazines, probably proceeds through intermediate hydroxyamine compounds A. Furthermore, the bond between the α - and β -carbon atoms in compounds A is cleaved by excess alkali, similar to the acid cleavage of β -keto acids. As a result, the final products of the reaction are IV-VII rather than pyrimidothiazines XI-XIII.



*For Communication XV, see [1].

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TABLE 1. 5-Acetamido-6-carbethoxymethylmercaptopyrimidines (IV-VII) and 6-Hydroxy-6,7-dihydropyrimido[4,5-d]-1,4-thiazines (VIII-X)

Comp.	R	R'	R''	mp*	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
IV	NH ₂	CH ₃	H	190-191	C ₁₁ H ₁₆ N ₄ O ₃ S	46.5	5.6	20.1	46.5	5.7	19.7	82
V	H	OCH ₃	H	157-158	C ₁₁ H ₁₅ N ₄ O ₄ S	46.5	5.3	15.0	46.3	5.3	14.7	73
VII	H	Cl	H	127-128	C ₁₀ H ₁₂ ClN ₄ O ₃ S [†]	41.7	4.4	14.5	41.4	4.2	14.5	78
VIII	H	OCH ₃	CH ₃	71-73	C ₁₃ H ₁₇ N ₄ O ₄ S	48.0	5.8	14.0	48.1	5.7	14.0	31
IX	NH ₂	CH ₃	—	—	C ₁₁ H ₁₆ N ₄ O ₃ S	46.5	5.8	—	46.5	5.7	—	38
X	H	OCH ₃	—	100-103	C ₁₁ H ₁₅ N ₄ O ₄ S	46.3	5.1	—	46.3	5.3	—	71
	H	Cl	—	115-117	C ₁₀ H ₁₂ ClN ₄ O ₃ S [†]	41.4	4.2	14.5	41.4	4.2	14.5	78

*The compounds were purified for analysis by crystallization: IV-VI and IX-X from ethanol; VII by passing an ether solution through a column filled with Al₂O₃.

†VI: Found %: C 12.1. Calculated %: 12.2. X: Found %: C 12.4. Calculated %: 12.2.

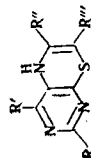


TABLE 2. Pyrimido[4,5-b]-1,4-thiazines (XI-XXI)

Comp.	R	R'	R''	R'''	mp*	Empirical formula	Found, %			Calc., %			Yield, %
							C	H	N	C	H	N	
XI	NH ₂	CH ₃	CH ₃	CO ₂ C ₂ H ₅	175-177 (dec.)	C ₁₁ H ₁₄ N ₄ O ₃ S	49.3	5.3	21.2	49.6	5.3	21.0	65
XII	H	OCH ₃	CH ₃	CO ₂ C ₂ H ₅	141-143	C ₁₁ H ₁₃ N ₄ O ₄ S	49.7	5.1	15.9	49.4	4.9	15.7	96
XIII	H	Cl	CH ₃	CO ₂ C ₂ H ₅	136-137	C ₁₀ H ₁₂ ClN ₄ O ₃ S [†]	44.0	3.5	15.5	44.2	3.7	15.5	21
XIV	NH ₂	CH ₃	CH ₂ CO ₂ C ₂ H ₅	H	198-200	C ₁₁ H ₁₄ N ₄ O ₃ S	49.4	5.5	21.2	49.6	5.3	21.0	91
XV	H	OCH ₃	CH ₂ CO ₂ C ₂ H ₅	H	120-122	C ₁₁ H ₁₃ N ₄ O ₄ S	49.1	4.6	16.0	49.4	4.9	15.7	59
XVI	H	Cl	CH ₂ CO ₂ C ₂ H ₅	H	126-128	C ₁₀ H ₁₂ ClN ₄ O ₃ S [†]	44.5	3.9	15.9	44.2	3.7	15.5	44
XVII	NH ₂	CH ₃	CO ₂ C ₂ H ₅	H	198-200	C ₁₁ H ₁₄ N ₄ O ₃ S	48.0	4.9	22.6	47.6	4.8	22.2	62
XVIII	H	OCH ₃	CO ₂ C ₂ H ₅	H	105-107	C ₁₀ H ₁₁ N ₄ O ₄ S	47.6	4.6	16.2	47.4	4.4	16.6	42
XIX	H	Cl	CO ₂ C ₂ H ₅	H	97-99	C ₉ H ₁₀ ClN ₄ O ₃ S [†]	42.2	2.9	16.2	41.9	3.1	16.3	12
XX	NH ₂	CH ₃	CO ₂ C ₂ H ₅	H	197-199	C ₁₁ H ₁₄ N ₄ O ₃ S	45.6	4.5	23.3	45.4	4.2	23.5	76
XXI	H	OCH ₃	H	CO ₂ C ₂ H ₅	208-207	C ₁₀ H ₁₁ N ₄ O ₄ S	47.6	4.2	16.6	47.4	4.4	16.6	—

*The compounds were purified for analysis by crystallization: XIV from dimethylformamide-water (1:2); XV, XVI, XI, XVII, and XX from ethanol; XIX and XXI from cyclohexane-benzene (1:1); and XII, XIII, and XVIII from cyclohexane.

†XIII: Found %: C 13.2. Calculated %: C 13.05. XVI: Found %: C 13.05. Calculated %: C 13.3. Calculated %: C 13.4. Calculated %: C 13.8.

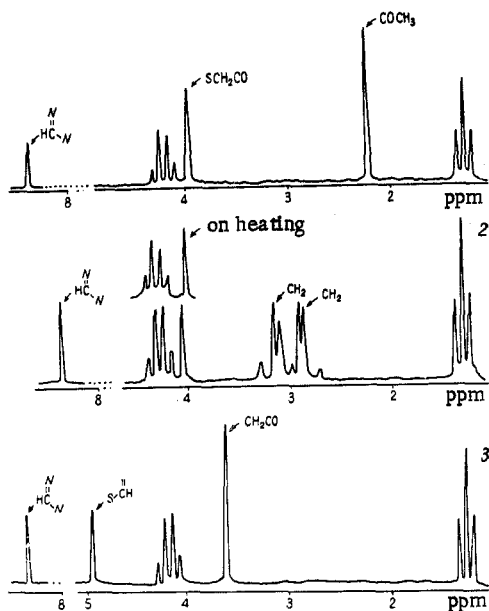


Fig. 1. PMR spectra. 1) 4-Chloro-5-acetamido-6-carbethoxymethylmercaptopyrimidine (VI) in CDCl_3 ; 2) 4-chloro-6-hydroxy-6-carbethoxymethyl-6,7-dihydropyrimido[4,5-b]-1,4-thiazine (X) in CDCl_3 ; 3) 4-chloro-6-carbethoxymethyl-5H-pyrimido[4,5-b]-1,4-thiazine (XVI) in CDCl_3 .

This concept is confirmed, first, by the fact that pyrimidothiazines XI-XIII (Table 2) are obtained by reaction of I-III with α -chloroacetoacetic ester in the absence of alkali. Second, the formation of substances with structure B does not occur when α -chloroacetoacetic ester is replaced by γ -chloroacetoacetic ester since cleavage of the bond in the 6 and 7 positions in hydroxy-amino compounds VIII-X is impossible. Thus hydroxy-amino compounds VIII-X are obtained from I-III and γ -chloroacetoacetic ester in alcoholic alkali; these compounds are readily dehydrated and transformed to pyrimidothiazines XIV-XVI in the presence of acid, followed by chromatography of their solutions on aluminum oxide.

Ethyl bromopyruvate, like γ -chloroacetoacetic ester, reacts with I-III to form 6-carbethoxypyrimidothiazines XVII-XIX. In the case of I, XX is isolated in a methanol medium as a result of transesterification. Reaction of II with ethyl chloroformylacetate gave a small yield of 4-methoxy-7-carbethoxypyrimidothiazine XXI. Compounds XI-XVI, XVIII-XIX, and XXI, in contrast to 6-arylpyrimidothiazines, have the 5H structure, while XVII and XX are 7H derivatives, as confirmed by the IR and PMR spectra. A decrease in the frequency of the ester carbonyl and the virtually complete absence of a band for the NH group are observed in the IR spectra of XV-XVI; this is explained by the formation of an intramolecular hydrogen bond between these functional groups.

EXPERIMENTAL

The starting haloketo acid esters were obtained as follows: α -chloro and γ -chloroacetoacetic esters via the methods in [4, 5], ethyl bromopyruvate via the method described in [6], ethyl chloroformylacetate via the method described in [7], and α -chloro- α -methylacetoacetic ester via the method described in [8, 9].

4-Chloro-5-acetamido-6-carbethoxymethylmercaptopyrimidine (VI). A. α -Chloroacetoacetic ester [0.52 g (0.0032 mole)] was added to a solution of 0.5 g (0.0031 mole) of III in 20 ml of ethanol containing 0.24 g (0.0042 mole) of KOH at 18–20°. The mixture was stirred for 24 h, evaporated in vacuo, and the residue was treated with water and filtered (see Table 1). Compounds IV, V, VII, IX, XIV, XVII, and XX were similarly obtained (the reaction was carried out in methanol for XX), as well as compounds XII, XVI, and XVIII, with the difference that the residue after removal of ethanol was dissolved in CHCl_3 and passed through Al_2O_3 . In the case of XII, the reaction was carried out at –5° for 2 h.

B. A solution of 0.8 g (0.01 mole) of acetyl chloride in 5 ml of benzene was added at 10° to a solution of 2.3 g (0.0093 mole) of XXII in 20 ml of benzene containing 0.9 g of pyridine. The mixture was stirred for 24 h at 18–20° and treated as indicated for VI to give 0.6 g (22%) of a product in the form of a white crystalline substance with mp 127–128° (from water). No melting point depression was observed when a sample of this product was mixed with VI obtained via method A. The IR and PMR spectra of the two substances were identical.

4-Chloro-5-amino-6-carbethoxymethylmercaptopyrimidine (XXII). This compound [0.5 g (82%)] was obtained in the same way as VI from 0.5 g (0.0031 mole) of III and 0.3 g (0.0025 mole) of ethyl chloroacetate and had mp 72–74° (from ether). Found %: C 39.0; H 4.2; Cl 14.4; N 17.1; S 12.7. $\text{C}_8\text{H}_{10}\text{ClN}_3\text{O}_2\text{S}$. Calculated %: C 38.8; H 4.1; Cl 14.3; N 17.0; S 12.9. IR spectrum: 1740 (CO); 1630, 3350, 3460 cm^{-1} (NH_2).

2-Amino-4,6-dimethyl-7-carbethoxypyrimido[4,5-b]-1,4-thiazine Hydrochloride (XI). A mixture of 0.5 g (0.0032 mole) of I and 0.55 g (0.0034 mole) of α -chloroacetoacetic ester in 20 ml of ethanol was refluxed with stirring for 2 h, cooled to 20°, and the precipitate was filtered to give 0.6 g (61%) of a bright-

red, crystalline substance with mp 278° (decomp., from ethanol). Found %: Cl 11.4; S 10.9. $C_{11}H_{14}N_4O_2S \cdot HCl$. Calculated %: Cl 11.7; S 10.6.

2-Amino-4-methyl-6-carbethoxymethyl-6-hydroxy-6,7-dihydropyrimido[4,5-b]-1,4-thiazine (VIII). A solution of 1 g (0.0061 mole) of γ -chloroacetoacetic ester in 10 ml of ethanol was added at -10° to a solution of 1 g (0.0064 mole) of I in 20 ml of ethanol containing 0.45 g (0.0078 mole) of KOH. The mixture was stirred for 1 h at -10° and for 5 h at $18-20^\circ$. The resulting precipitate was filtered and washed with water to give 0.7 g (38%) of VIII in the form of a white, crystalline substance which did not have a melting point and which was converted to pyrimidothiazine XIV on heating. Compound X was similarly obtained.

4-Methoxy-6-carbethoxymethylpyrimido[4,5-b]-1,4-thiazine (XV). A solution of 1 g (0.0064 mole) of II in 20 ml of ethanol containing 0.4 g (0.0070 mole) of KOH was added at 20° in 5 h to 1.2 g (0.0073 mole) of γ -chloroacetoacetic ester in 10 ml of ethanol. The reaction mass was allowed to stand overnight, and the mixture was filtered and evaporated to dryness to give 0.9 g (53%) of a light-yellow, crystalline substance with mp $120-122^\circ$ (from ethanol).

Similarly obtained were compounds XI (the reaction was carried out at 40°), XIII, XIX, and XXI (with the difference that the residue after removal of ethanol was dissolved in benzene, in the case of XIII and XIV, and in $CHCl_3$, in the case of XXI, and the solutions were passed through a column filled with Al_2O_3). The IR spectra were obtained with a UR-10 spectrophotometer in the form of suspensions in mineral oil. The frequencies of the vibrations of the CO, NH, NH_2 groups in the IR spectra of compounds IV-VII, XI-XIX, and XXI and of the CO, NH, and OH groups in the spectra of compounds VIII-X were as follows: (IV) 1670, 1720, 3210, 3290, 3420; (V) 1670, 1740, 3200, 3240 cm^{-1} ; (VI) 1680, 1740, 3260 cm^{-1} ; (VII) 1690, 1730, 3290 cm^{-1} ; (XI) 1640, 3200, 3320, 3460 cm^{-1} ; (XII) 1705, 3440 cm^{-1} ; (XIII) 1700, 3300 cm^{-1} ; (XIV) 1650, 3200, 3310 cm^{-1} ; (XV) 1665 cm^{-1} ; (XVI) 1670, 3200, 3100 cm^{-1} ; (XVII) 1700, 1660, 3150, 3320, 3440 cm^{-1} ; (XVIII) 1700, 3420 cm^{-1} ; (XIX) 1700, 3400 cm^{-1} ; (XXI) 1680, 3200 cm^{-1} ; (VIII) 1720, 3460, 3400, 3350, 3240 cm^{-1} ; (IX) 1720, 3380 cm^{-1} ; (X) 1720, 3160-3190, 3290 cm^{-1} .

The PMR spectra were obtained with a JNM-4H-100 spectrophotometer with tetramethylsilane as the internal standard. The compounds, solvents, and chemical shifts in ppm are as follows: VI, $CDCl_3$, 1.255 (triplet); 4.154 (quartet), $CO_2C_2H_5$; 2.181 (singlet), $3H-COCH_3$; 3.919 (singlet), $2H-CH_2CO$; 8.64 (singlet), $NH-CH=N$. X, $CDCl_3$, 1.3 (triplet), 4.25 (quartet), $CO_2C_2H_5$; 2.9 (quartet), $2H-7CH_2$; 3.25 (quartet), $2H-CH_2CO_2C_2H_5$; 4.06 (NH and OH are shifted on heating). XVI, $CDCl_3$, 1.265 ($CH_3C_2H_5$, triplet); 3.607 ($2H-COCH_2$, singlet), 4.196 ($CH_2C_2H_5$, quartet), 4.929 ($H-7CH$, singlet). XVII, pyridine, 1.085 ($CH_3C_2H_5$, triplet); 2.464 ($3H-4CH_3$, singlet); 3.87 ($2H-7CH_2$, singlet); 4.165 ($CH_2C_2H_5$, quartet), and therefore has the 7H structure. XX, pyridine, 2.48 ($3H-4CH_3$, singlet); 3.67 ($3H-OCH_3$, singlet); 3.86 ($2H-7CH_2$, singlet), and therefore has the 7H structure.

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