INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

V. The Reaction of 5-Amino-6-mercaptopyrimidines with Phenacyl Chlorides*

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The reaction of 5-amino-4-chloro- and -4-methoxy-6-mercaptopyrimidines with 4-methoxy-, 4-amino-, and 2,4-diethoxyphenacyl chlorides has yielded 5-amino-4-chloro- and -4-methoxy-6-phenacylthiopyrimidines. The reaction of 2,5-diamino-4-methyl-6-mercaptopyrimidine with 4-methoxyphenacyl chloride has yielded 2-amino-6-hydroxy-6-(4'-methoxyphenyl)-4-methyl-5,6-dihydropyrimido[4,5-b]-1,4-thiazine, and that with 4-aminophenacyl chloride has yielded the corresponding 7H-pyrimido[4,5-b]-1,4-thiazine.

In development of previous work [1], we have studied the reaction of 5-amino-4-chloro-6-mercaptopyrimidine (I), 5-amino-4-methoxy-6-mercaptopyrimidine (II), and 2,5-diamino-4-methyl-6-mercaptopyrimidine (III) with phenacyl halides having electron-donating substituents in the benzene ring.

The reaction of I and II with 4-methoxy- and 4-aminophenacyl chlorides and of II with 2,4-diethoxyphenacyl chloride in ethanolic solution in the presence of alkali at 0 to -5° C has given 5-amino-6-phenacylthiopyrimidines (IV, VI–IX, Table 1) with yields of 66–87%. When the reaction of I with 2,4-diethoxyphenacyl chloride was carried out at 18–20° C, the S-phenacyl derivative V (Table 1) was isolated, while II and 4-methoxyphenacyl chloride gave, under similar conditions, the pyrimidothiazine **XV** (Table 2). The structures of IV–IX and **XV** were confirmed by their IR spectra. The spectra of substances **IV–IX** have absorption bands for a CO group (1650–1680 cm^{-1}) and for a primary amino group (3230–3480 cm^{-1}). These bands are not observed in the IR spectrum of compound **XV** (see figure). In the reaction of 2,5-diamino-4-methyl-6-mercaptopyrimidine (III) with 4-methoxyphenacyl chloride we succeeded in isolating a very unstable carbinol amine **X**. In favor of structure **X** was the absence from the IR spectrum of the band of a CO group. By boiling **X** in dimethylformamide and by the reaction of III with 4-aminophenacyl chloride we obtained the pyrimidothizines XI and XII, respectively (Table 2).

Thus, it has been shown that the reaction of 5-amino-6-mercaptopyrimidines I and II with phenacyl chlorides containing electron-donating substituents in the benzene ring forms the S-phenacyl derivatives IV–IX. By the reaction of III with these ketones either the carbinol amine **X** or the pyrimidothiazines XI and XII are obtained. As already shown [1], under analogous conditions compounds I and II react with phenacyl halides having electron-accepting groups with the formation of carbinol amines, while compound III gives only pyrimidothiazines. This difference in the course of reaction is explained by the fact that in the compounds of structure A, the electron-donating groups (OCH$_3$, NH$_2$, OC$_2$H$_5$) passivate the carbonyl group with respect to the nucleophilic reactant as a consequence of the decrease in the position charge on the carbonyl carbon atom. In view of this, the reactions of compounds I and II with phenacyl chlorides can be stopped at the stage of the S-phenacyl derivatives. The presence in the derivatives **B** of electron-accepting groups leads to the impoverishment of the electrons of the carbonyl carbon atom, which facilitates the reaction of the CO group with the nucleophilic amino group. In this case the main reaction products are carbinol amines or pyrimidothiazines.

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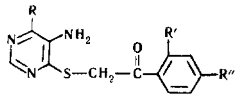
*For part IV, see [1].

Table 1



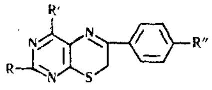
Compound	R	R'	R''	Mp, ° C[a]	Empirical formula[b]	Found, %					Calculated, %					Yield %
						C	H	Cl	N	S	C	H	Cl	N	S	
IV	Cl	H	OCH$_3$	137—138	$C_{13}H_{12}ClN_3O_2S$	50.33	3.72	11.56	13.35	10.19	50.40	3.90	11.45	13.56	10.35	71.5
V	Cl	OC$_2$H$_5$	OC$_2$H$_5$	150—151	$C_{16}H_{18}ClN_3O_3S$	52.21	5.21	9.40	11.48	8.53	52.24	4.93	9.64	11.42	8.72	66
VI	Cl	H	NH$_2$	300	$C_{12}H_{11}ClN_4S$	49.20	3.92	12.18	18.57	10.78	48.89	3.76	12.03	19.00	10.88	86
VII	OCH$_3$	H	OCH$_3$	101—103	$C_{14}H_{15}N_3OS$	55.25	5.05	—	13.39	10.59	55.65	4.98	—	13.76	10.50	78
VIII	OCH$_3$	OC$_2$H$_5$	OC$_2$H$_5$	102—104	$C_{17}H_{21}N_3O_4S$	56.14	5.78	—	11.43	8.94	56.18	5.82	—	11.56	8.82	76
IX	OCH$_3$	H	NH$_2$	в	$C_{13}H_{14}N_4O_2S$	53.76	5.0	—	19.50	10.76	53.77	4.86	—	19.30	11.04	87

[a] Compounds IV, V, and VIII were crystallized from benzene, VI is from isopropanol, and IX from ethanol. IV, V, VII, and VIII are colorless and VI and IX, pale yellow crystalline substances.

[b] The IR spectra of the compounds were taken on a UR-10 instrument in the form of mulls in paraffin oil. $\nu_{C=O}$: 1680 cm^{-1}; ν_{NH_2}: 3350, 3370, 3430, 3480 cm^{-1}; V: $\nu_{C=O}$: 1655 cm^{-1}; ν_{NH_2}: 3360, 3440 cm^{-1}; VI: $\nu_{C=O}$: 1655 cm^{-1}; ν_{NH_2}: 3230, 3350, 3440 cm^{-1}; VII: $\nu_{C=O}$: 1680cm^{-1}; ν_{NH_2}: 3360, 3450 cm^{-1}; VIII: $\nu_{C=O}$: 1650 cm^{-1}; ν_{NH_2}: 3370, 3450 cm^{-1}; IX: $\nu_{C=O}$: 1650 cm^{-1}; ν_{NH_2}: 3240, 3340, 3430, 3480 cm^{-1}.

[c] Has no clear melting point; undergoes dehydration on heating, being converted into the pyrimidothiazine XV.

Table 2



Compound	R	R′	R″	Mp, ° C*	Empirical formula	Calculated, %				Found, %				Yield %
						C	H	N	S	C	H	N	S	
XI	NH_2	CH_3	OCH_3	296—298	$C_{14}H_{14}N_4OS$	58.80	5.08	19.53	11.38	58.72	4.93	19.57	11.2	76
XII	NH_2	CH_3	NH_2	262—264	$C_{13}H_{13}N_5S$	57.44	4.86	25.56	11.67	57.54	4.83	25.80	11.81	75
XIII	H	OCH_3	OCH_3	135—137	$C_{14}H_{13}N_3O_2S$	58.85	4.51	14.34	11.13	58.52	4.56	14.63	11.16	64
XIV	H	OCH_3	NH_2	220—222	$C_{13}H_{12}N_4OS$	57.15	4.30	20.86	11.88	57.33	4.44	20.57	11.77	91
XV	H	Cl	OCH_3	186—187	$C_{13}H_{10}ClN_3OS$	53.24	3.41	—	—	53.51	3.45	—	—	53

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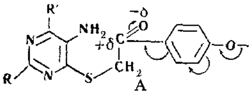
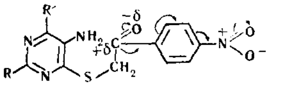
*Compounds XI-XV are yellow crystalline substances.



A



B

The nature of the substances formed in the reaction of 5-amino-6-mercaptopyrimidines with phenacyl chlorides is not determined only by the degree of activity of the carbonyl group in the ketone. An important influence on this is possessed by the nucleophilicity of the amino group in position 5 of the pyrimidine ring. Thus, the reaction of compound II with 4-methoxyphenacyl chloride gave the S-phenacyl derivative VII, while the reaction of compound III, in which the nucleophilicity of the amino group in position 5 is greater than in compound II with the same ketone, gave the carbinol amine X.

The stability of the S-phenacyl compounds IV–IX also depends on the nucleophilicity of the amino group. Substances VII and IX cyclize into pyrimidothiazines even on standing in the air, on recrystallization, and on heating in vacuum. Compound IV, in which the nucleophilicity of the amino group is lower than in VII and IX, is converted into the pyrimidothiazine on being heated with acetic anhydride. The cyclization of compounds IV–IX also apparently takes place through the carbinol amines. However, we were unable to isolate these intermediates. The presence of electron-donating substituents in position 6 of the carbinol amines creates an increased electron density on the oxygen atom of the hydroxy group, which is responsible for their instability and their capacity for readily undergoing dehydration to the corresponding pyrimidothiazines. We confirmed the capacity of the S-phenacyl derivatives IV–IX for undergoing conversion into the carbinol amines only indirectly—their different behavior with respect to the Karl Fischer reagent. It is known [2] that in the isoquinoline series carbinol amines and the corresponding amino aldehydes readily undergoing conversion into carbinol amines react with one equivalent of the Fischer reagent, which corresponds to the determination of one molecule of water in these substances. Negative results obtained with this reagent serve as a proof of the presence of a stable open amino aldehyde structure. In our case, one molecule of water was determined in each of compounds VIII and IX. A comparison of these results with the IR spectra (presence of a CO group, see figure) permits the conclusion that compounds VIII and IX form carbinol amines under conditions of determining water by the Karl Fischer method. In the determination of water in compounds V and VI we obtained negative results, which confirm that these substances have a stable noncyclic structure.

EXPERIMENTAL

4-Aminophenacyl chloride was prepared by Kunckell's method [3] with the difference that in the preparation of the 4-acetylaminophenacyl chloride, dichloroethane was used as the solvent instead of carbon disulfide. The yield of unpurified ketone was 70%, mp 205–207° C; according to Kunckell [3], mp 212° C.

4-Methoxyphenacyl chloride was obtained by the method of Volovel'skii and Khukhryanskii [4].

2,4-Diethoxyphenacyl chloride. At 10° C, a mixture of 11.3 g (0.1 mole) of chloroacetyl chloride and 16.6 g (0.1 mole) of 1,3-diethoxybenzene in 30 ml of dichloroethane was added to a suspension of 13.4 g (0.1 mole) of $AlCl_3$ in 50 ml of dichloroethane. The mixture was stirred at this temperature for 3 hr and was left overnight. Then it was poured into a mixture of ice and concentrated hydrochloric acid, the organic layer was separated off, washed with water to neutrality, and dried with sodium sulfate, the solvent was distilled off, and the residue was triturated with petroleum ether and filtered off. Yield 9.7 g (40%). Colorless crystals, mp 65–67° C (methanol), soluble in the usual organic solvents. Found, %: C 59.31; H 6.07; Cl 14.79. Calculated for $C_{12}H_{15}ClO_3$, %: C 59.38; H 6.23; Cl 14.60.

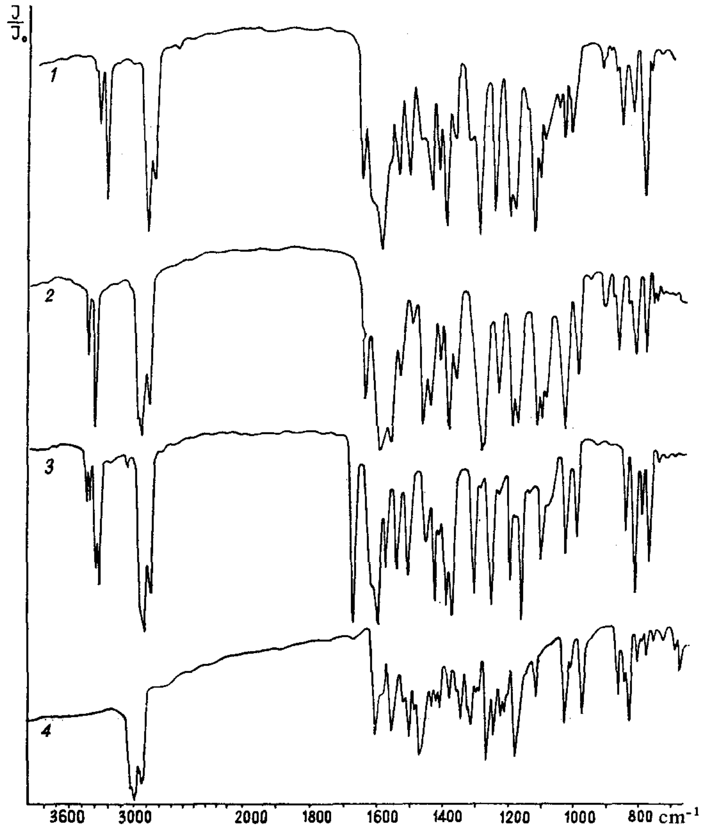
General method of preparing compounds IV, VI–IX. A solution of 0.032 mole of the 5-amino-6-mercaptopyrimidine I or II in 20 ml of ethanol containing 0.035 mole of KOH was cooled to -5 to 0° C and to it was added a solution of 0.027 mole of the appropriate α-halo ketone in 20–25 ml of ethanol. The reaction mixture was stirred at the same temperature for from 3 to 10 hr, the change in the pH of the medium being followed. At pH 7–8 stirring was discontinued, and the precipitate that had deposited was filtered off, washed with water and a small amount of cold ethanol, and recrystallized.

Compounds V and XIII were obtained similarly with the difference that the reaction was carried out at 18–20° C for 24 hr.

2-Amino-6-hydroxy-4-methyl-6-(4′-methoxyphenyl)-5,6-dihydropyrimido[4,5-b]-1,4-thiazine (X). This was obtained by the reaction of III with 4-methoxyphenacyl chloride under conditions similar to those for the synthesis of IV. Yield 86%. Colorless crystalline substance with a yellow tinge, converted into the pyrimidothiazine XI on heating. Found, %: C 55.16; H 5.15%. Calculated for $C_{14}H_{16}N_4O_2S$, %: C 55.24; H 5.30.

Compound XII was synthesized similarly (crystallized from dimethylformamide).

2-Amino-4-methyl-6-(4′-methoxyphenyl)pyrimido[4,5-b]-1,4-thiazine (XI). A solution of 0.7 g of X in 5 ml of dimethylformamide was boiled for 10 min and cooled to 18–20° C, and then 15 ml of water was added and the precipitate was filtered off. Yield 0.5 g (76%), mp 296–298° C (decomp., dimethylformamide).



IR spectra: 1) 5-amino-4-chloro-6-(2',4'-diethoxyphenacylthio)pyrimidine (**V**); 2) 5-amino-4-methoxy-6-(2',4'-diethoxyphenacylthio)pyrimidine (**VIII**); 3) 5-amino-4-chloro-6-(p-methoxyphenacylthio)pyrimidine (**IV**); 4) 4-chloro-6-(p-methoxyphenyl)pyrimido [4,5-b]-1,4-thiazine (**XV**).

4-Chloro-6-(4'-methoxyphenyl)pyrimido[4, 5-b]-1, 4-thiazine (XV). A mixture of 0.4 g of IV and 4 ml of acetic anhydride was heated in the water bath for 7 hr; then it was cooled to room temperature and the precipitate was filtered off. Yield 0.2 g (53%), mp 186–187° C (dimethylformamide).

4-Methoxy-6-(4'-aminophenyl)pyrimido[4, 5-b]-1, 4-thiazine (XIV). 0.35 g of IX was heated in a vacuum of 10 mm at 140° C for 7 hr, giving 0.3 g of XIV (91.5%), mp 220–222° C (ethanol).

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