NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XIX.* 7H-4-CHLORO-6-ARYL- AND 5H-PYRIMIDO[4,5-b][1,4]THIAZINES

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4-Chloro-5-amino- and 4-chloro-5-methylamino-6-phenacylmercaptopyrimidines (II-V and XVI-XX) were obtained by the reaction of 4-chloro-5-amino- and 4-chloro-5-methylamino-6-mercaptopyrimidines (I and XV) with phenacyl halides. It is shown that II-V are cyclized by alkalis to 4-chloro-6-aryl-6-hydroxy-5,6-dihydropyrimido[4,5-b][1,4]thiazines (VI-IXa), while both II-IXa and XVI-XIX, respectively, are converted to 7H-4-chloro-6-aryl- (X-XIII) and 5H-4-chloro-5-methyl-6-arylpyrimido[4,5-b][1,4]thiazines (XX-XXIII) under the influence of acidic reagents.

In a supplement to [1, 2] involving a study of the mechanism of thiazine-ring closing, it was observed that the reaction of 4-chloro-5-amino-6-mercaptopyrimidine (I) with phenacyl bromide and its p-bromo and m-nitro derivatives in a nearly neutral medium leads to 4-chloro-5-amino-6-phenacylmercaptopyrimidines (II-IV, Table 1). VI-IXa were also obtained by the reaction of I with phenacyl halides in the presence of excess alkali. The latter are converted to 7H-4-chloro-6-arylpyrimido[4,5-b][1,4]thiazines (X-XIII, Table 2) by treatment with an alcoholic solution of hydrogen chloride. It was found that the dehydration of VI-IXa to X-XIII is catalyzed to a greater degree by acids than by alkalis. Consequently, on treatment of II-V with acidic reagents the process does not stop at the step involving hydroxyamino compounds VI-IXa but leads to pyrimidothiazines X-XIII [3]. The solvent and physical properties of the intermediates (II-IXa) also affect the results of the reaction. Thus, the reaction of I with p-nitrophenacyl bromide leads to IX in dimethylformamide and to V in alcohol. V, because of its low solubility in alcohol, is precipitated and thereby removed from the reaction sphere. One peculiarity of VI-IXa is their capacity to form adducts with alcohols and nonpolar solvents, for example, toluene.

The structures of II-XIII were proved by means of IR and PMR spectroscopy. The IR spectra of II-V contain CO absorption bands (1690-1700 cm^{-1}) and NH_2 bands (3200-3300, 3390-3490 cm^{-1}). The absorption bands of these groups are absent in the spectra of VI-IXa. The PMR spectrum of III contains a singlet from the $-S-CH_2-$group with a chemical shift of 4.75 ppm and an intensity of two proton units; the signals of the benzene protons, which constitute an A_2B_2 system with centers at 7.65 and 7.93 ppm and $J \sim 0.7$ Hz, and a singlet from the C_2 proton with a chemical shift of 8.13 ppm are also observed in the spectrum. In contrast to the spectra of III, the signals from the protons of the $-S-CH_2-$ group in the PMR spectra of VII, VIIa, and IX are manifested as a quartet of the AB type with a geminal interaction constant of $\sim$12-13 Hz; the signals of the doublet at weaker field are split with a long-range interaction constant of $\sim$1.5-2 Hz. An examination of three-dimensional models of hydroxyamino compounds VI-IXa indicates that the C_7 protons are not equivalent because of different environments. The dihydrothiazine ring in these compounds can exist in two semichair conformations, during which the conformation with an equatorial hydrogen atom on N_5 (relative to the plane of the ring) is more favorable than an axial hydrogen. The shielding of the C_7 protons can change during rapid conversion of the thiazine ring, but not to such a degree as to lead to equalization of the chemical shifts of these protons.

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*See [5] for communication XVIII.

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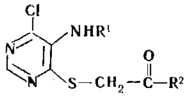
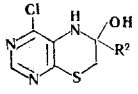
TABLE 1



II-IV, XVI-XIX



VI-Xa

Compound	R^1	R^2	Mp., °C	Empirical-formula	Found, %					Calculated, %					Yield, %
					C	H	Cl	N	S	C	H	Cl	N	S	
II	H	C_6H_5	123—125[1]	$C_{12}H_{10}ClN_3O_5S$[4]	51,96	3,8	—	—	—	51,52	3,60	—	—	—	60
III	H	p-Br-C_6H_4	150—151	$C_{12}H_9BrClN_3OS$	40,40	3,46	—	—	—	40,18	2,53	—	—	—	63
IV	H	m-O_2N-C_6H_4	154—156	$C_{12}H_9ClN_4O_3S$	44,18	2,83	10,73	17,18	10,12	44,38	2,8	10,9	17,25	9,87	69
VI	—	C_6H_5	118—120	$C_{12}H_{10}ClN_3OS \cdot CH_3OH$	50,33	4,11	—	—	—	50,08	4,52	—	—	—	40
VII	—	p-Br-C_6H_4	92—93	$C_{12}H_9BrClN_3OS \cdot CH_3OH$	40,11	3,29	—	—	—	39,96	3,35	—	—	—	71
VIIa	—	p-Br-C_6H_4	138—140	$C_{12}H_9BrClN_3OS \cdot C_2H_5OH$	41,80	3,70	—	—	—	41,54	3,73	—	—	—	36
VIII	—	m-O_2N-C_6H_4	— [2]	$C_{12}H_9ClN_4O_3S$	44,47	2,87	—	—	—	44,38	2,79	—	—	—	65
IX	—	p-O_2N-C_6H_4	145—146[3]	$C_{12}H_9ClN_4O_3S$	44,07	2,84	—	—	—	44,38	2,79	—	—	—	75
IXa	—	p-O_2N-C_6H_4	— [2]	$C_{12}H_9ClN_4O_3S \cdot H_2O$	42,04	3,23	—	—	—	42,05	3,23	—	—	—	80
XVI	CH_3	C_6H_5	92—94	$C_{13}H_{12}ClN_3OS$	53,32	4,21	11,97	14,31	10,91	53,15	4,12	12,07	14,30	10,91	45
XVII	CH_3	p-Br-C_6H_4	125—127	$C_{13}H_{11}BrClN_3OS$	42,13	2,98	—	—	—	41,89	2,97	—	—	—	70
XVIII	CH_3	m-O_2N-C_6H_4	119—120	$C_{13}H_{11}ClN_4O_3S$	46,29	3,10	—	—	—	46,09	3,27	—	—	—	87
XIX	CH_3	p-O_2N-C_6H_4	151—152	$C_{13}H_{11}ClN_4O_3S$	45,70	3,40	10,24	16,70	9,41	46,09	3,27	10,47	16,54	9,46	67

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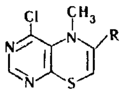
[1] II, III, VI, VII,XVI, and XVII were recrystallized from methanol for analysis, IV was recrystallized from toluene, and VIII, IX, XVIII, and XIX were recrystallized from alcohol.

[2] VIII and IXa do not have sharp melting points and are converted to XII and XIII on heating.

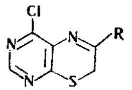
[3] IX was obtained by carrying out the reaction in dimethylformamide or by drying IXa in vacuo for 3 h at 80°. An adduct with empirical formula $C_{12}H_9ClN_4O_3S \cdot C_6H_5CH_3$ was obtained on crystallization of IX from toluene. Found %: C 54.30; H 4.20. Calc. %: C 54.74; H 4.11.

[4] The IR spectra of mineral oil pastes were obtained with a UR-10 spectrometer. The following are the absorptions of the CO and NH_2 groups for II-IV, the NH and OH absorptions for VI-IXa, and the CO and NH absorptions for XVI-XIX: II 1690, 3200, 3300, and 3440 cm^{-1}; III 1690, 3400, and 3490 cm^{-1}; IV 1700, 3220, 3320, and 3430 cm^{-1}; VI 3350 (broad) and 3400 cm^{-1} (narrow); VII 3240-3350 and 3390 cm^{-1}; VIIa 3400 cm^{-1} (broad); VIII 3400-3500 cm^{-1}; IX 3400 and 3380 (broad); IXa 3220-3380, 3400, and 3580 cm^{-1}; XVI 1690 and 3350 cm^{-1}; XVII 1690 and 3400 cm^{-1}; XVIII 1700 and 3400 cm^{-1}; XIX 1700 and 3400 cm^{-1}.

TABLE 2



XX-XXIII



X-XIII

Compound	R	Mp, °C	Empirical formula	Found, %					Calculated, %					Yield, %
				C	H	Cl	N	S	C	H	Cl	N	S	
X	C_6H_5[1]	137—139	$C_{12}H_8ClN_3S$[3]	—	—	—	—	—	—	—	—	—	—	54
XI	p-Br-C_6H_4[1]	150—152	$C_{12}H_7BrClN_3S$	—	—	—	—	—	—	—	—	—	—	61
XII	m-O_2N-C_6H_4[2]	180—181	$C_{12}H_7ClN_4O_2S$	46,75	2,51	—	—	—	46,98	2,3	—	—	—	91
XIII	p-O_2N-C_6H_4	179—181	$C_{12}H_7ClN_4O_2S$	46,85	2,47	12,07	18,67	10,58	26,98	2,3	11,56	18,27	10,45	79
XX	C_6H_5	73—75	$C_{13}H_{10}ClN_3S$	56,40	3,50	13,2	14,97	11,47	56,62	3,65	12,86	15,24	11,63	78
XXI	p-Br-C_6H_4	134—135	$C_{13}H_9BrClN_3S$	44,38	2,59	32,98[4]*	11,58	9,01	44,02	2,56	32,52[4]*	11,84	9,04	67
XXII	m-O_2N-C_6H_4	144—145	$C_{13}H_9ClN_4O_2S$	48,90	2,78	11,34	17,36	9,89	48,67	2,83	11,05	17,47	10,0	85
XXIII	p-O_2N-C_6H_4	156—158	$C_{13}H_9ClN_4O_2S$	48,67	3,05	10,08	17,21	10,18	48,67	2,83	11,05	17,47	10,0	79

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[1] See [1].

[2] For analysis, X-XIII and XX-XXIV were recrystallized from alcohol, while XX could be recrystallized from petroleum ether.

[3] The PMR spectra [obtained with a JEOL JNM 4H-100 spectrometer with $Si(CH_3)_4$ as internal standard] are presented in the following order: compound, solvent, chemical shift in parts per million: X, $CDCl_3$, 3.87 (7-CH_3 –, singlet); XI, $CDCl_3$, 3.85 (7-CH_2 –, singlet); XX, pyridine, 5.73 (7-CH=, singlet); XXIII, pyridine, 6.22 (7-CH=, singlet).

[4] The analytical data for the sum of the halogens (Br + Cl) are given.

4-Chloro-5-methylamino-6-phenacylmercaptopyrimidines (XVI-XIX, Table 1) were obtained by the reaction of 4-chloro-5-methylamino-6-mercaptopyrimidine (XV) with the above-listed phenacyl halides. The data of the IR and PMR spectra are in agreement with the structures of these compounds. Thus the IR spectra contain CO absorption bands (1690-1700 cm^{-1}) and NH absorption bands (3350-3400 cm^{-1}). The PMR spectra of XIX contains a singlet from the $-S-CH_2-$ group at 4.95 ppm and a signal from the NCH_3 group at 2.93 ppm in the form of a doublet (J ~ 6 Hz) due to interaction with the proton attached to the exocyclic nitrogen atom.

The corresponding hydroxyamino compounds could not be isolated by the action of an alcoholic solution of alkali on XVI-XIX, but, like II-V, XVI-XIX are dehydrated by acidic reagents to 5H-pyrimido[4,5-b][1,4] thiazines (XX-XXIII, Table 2).

The structures of the 7H-pyrimidothiazines (X-XIII) and 5-H-pyrimidothiazines (XX-XXIII) were confirmed by the absence in the IR spectra of an absorption band for the NH groups and by the presence in the PMR spectra of X and XI of a singlet from the CH_2 group at 3.85-3.87 ppm, and the presence in the spectra of XX and XXIII of a signal from the proton attached to the carbon atom with a double bond at the 7 position with a chemical shift of 5.73 and 6.22 ppm, respectively.

EXPERIMENTAL

4-Chloro-5-amino-6-(p-bromophenacylmercapto)pyrimidine (III). A solution of 0.7 g (0.0025 mole) of p-bromophenacyl bromide in ethanol was added at −10 to −5° to a solution of 0.5 g (0.0031 mole) of I in 20 ml of ethanol containing 0.2 g (0.0035 mole) of KOH. The mixture was stirred at this temperature for 3 h, and the precipitate was filtered and washed with water and a small amount of cooled ethanol. The filtrate yielded VIIa.

II, IV, VII, and XVI-XIX were similarly obtained in methanol, while IX was obtained from I and p-nitrophenacyl bromide in dimethylformamide.

4-Chloro-6-hydroxy-6-(p-bromophenyl)-5,6-dihydropyrimido[4,5-b][1,4]thiazine (VII). Several drops of an 8% solution of KOH in methanol were added at −5° to a suspension of 0.5 g of III in 10 ml of methanol. The mixture was stirred at this temperature for 4 h, and the precipitate was filtered and washed with water until it gave a neutral reaction. VII, which was identical to the compound obtained under the conditions for the synthesis of III, was thus obtained.

VI, VIIa, VIII, and IXa were similarly obtained.

4-Chloro-6-(p-nitrophenyl)pyrimido[4,5-b][1,4]thiazine (XIII). Several drops of an alcoholic solution of HCl were added to a solution of 0.4 g of IX in refluxing ethanol. The precipitate of XIII that resulted on cooling of the mixture to 20° was filtered.

X-XII and XX-XXIII were similarly obtained.

4-Chloro-5-methyl-6-phenylpyrimido[4,5-b][1,4]thiazine (XX). A mixture of 5 ml of $POCl_3$ and 0.45 g of XVI was held at 20° for 5 h, and poured into ice water to precipitate XX.

XXIII was similarly obtained. XX and XXIII were identical to the compounds obtained under the conditions used for the synthesis of XIII.

4-Chloro-5-methylamino-6-mercaptopyrimidine (XV). 4,6-Dichloro-5-methylaminopyrimidine [4] [4.4 g (0.025 mole)] was refluxed with a solution of KSH in methanol (obtained by saturation of a solution of 2.8 g of KOH in methanol with hydrogen sulfide) for 2 h, the solvent was removed by vacuum distillation, and the residue was dissolved in 50 ml of 2 N KOH. The solution was filtered and acidified with glacial acetic acid to give 3.8 g (88%) of XV with mp 113-115° (from ethanol). Found %: C 34.43; H 3.69; Cl 20.04; N 23.56; S 18.38. $C_5H_6ClN_3S$. Calc. %: C 34.21; H 3.44; Cl 20.19; N 23.93; S 18.26.

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