NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XVIII.* REACTION OF N-(2-MERCAPTO-6-CHLORO-3-PYRIDYL)UREAS WITH α-HALOKETONES AND ESTERS OF HALOKETO ACIDS

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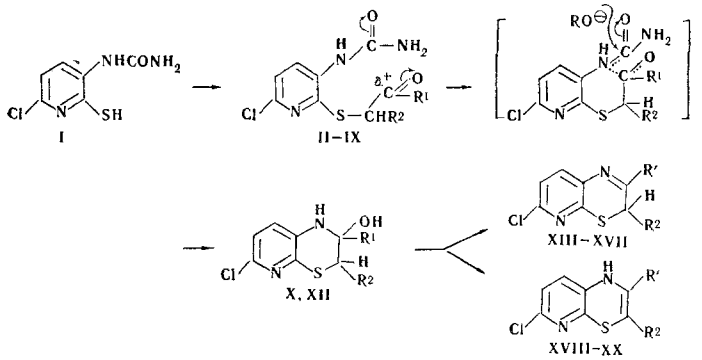
The reaction of N-(2-mercapto-6-chloro-3-pyridyl)ureas with phenacyl halide, its o-, m-, and p-substituted derivatives, chloroacetone, α-chloro- and γ-chloroacetoacetic esters, and with chlorooxalacetic ester was studied. In the process, a new method was developed for obtaining 2-chloro-6-aryl-7H-pyrido[2,3-b][1,4]thiazines, 2-chloro-6-carbethoxymethyl-, 2-chloro-7-carbethoxy-, and 6,7-dicarbethoxy-5H-pyrido[2,3-b][1,4]thiazines.

In a continuation of our studies [1, 2] to find a more accessible method for the synthesis of 2-chloropyridothiazines we investigated the reaction of N-(2-mercapto-6-chloro-3-pyridyl)ureas (I) with α-haloketones and esters of haloketo acids. It was observed that N-(2-acylmethylmercapto-6-chloro-3-pyridyl)-ureas (II-VII, Table 1) are formed by the reaction of I with phenacyl bromide, its 4-bromo, 4-methoxy, 2,5-dichloro, and 4-nitro derivatives, and with chloroacetone. At the same time, 6-aryl-7H-pyridothiazines XIV and XV are isolated from the mother liquors after separation of III and IV. Pyridothiazines XVI and XVIII are obtained under similar conditions from I and 2-hydroxy-4-ethoxyphenacyl chloride and α-chloroacetoacetic ester.

m-Nitrophenacylmercapto derivative IX and N-(2-carbethoxymethylmercapto-6-chloro-3-pyridyl)-urea were isolated from the products of the reaction of I with m-nitrophenacyl bromide and chlorooxalacetic ester, respectively, in alcoholic alkali at −10°. Unstable substances,



which apparently have the hydroxyamino structures X and XII, were obtained by rapid and careful treatment of the alcoholic mother liquors remaining after separation of IX and XI. If the alcoholic mother liquors are allowed to stand for several hours, only pyridothiazines XVII and XX can be isolated from them.

*See [2] for communication XVII.

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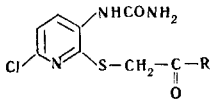
TABLE 1. N-(2-Acylmethylmercapto-6-chloro-3-pyridyl)ureas (II-IX)



Compound	R	mp[a]	Empirical formula[b,c]	Found, %					Calculated, %					Yield, %
				C	H	Cl	N	S	C	H	Cl	N	S	
II	C_6H_5	225—226	$C_{14}H_{12}ClN_3O_2S$	51,95	3,61	11,31	13,38	9,85	52,25	3,73	11,04	13,06	9,95	58
III	4-CH_3O-C_6H_4	218—220	$C_{15}H_{14}ClN_3O_3S$	51,57	4,00	10,36	11,64	9,20	51,20	3,98	10,10	11,94	9,10	70
IV	4-Br-C_6H_4	226—228	$C_{14}H_{11}BrClN_3O_2S$	42,10	2,77	29,16[d]	10,70	8,28	41,95	2,74	28,81	10,48	7,99	44
V	2,5-Cl_2-C_6H_3	205—207	$C_{14}H_{10}Cl_3N_3O_2S$	42,95	2,54	27,42	10,69	8,34	43,02	2,55	27,27	10,75	8,19	57
VI	4-NO_2-C_6H_4	214—215	$C_{14}H_{11}ClN_4O_4S$	45,61	3,16	9,84	15,27	8,60	45,86	3,00	9,68	15,01	8,73	59
VII	CH_3	187—188	$C_9H_{10}ClN_3O_2S$	41,39	3,66	13,82	16,20	12,22	41,61	3,85	13,68	16,18	12,33	43
VIII	CH_2-$COOC_2H_5$[e]	172—174	$C_{12}H_{14}ClN_3O_4S$	43,74	4,47	10,58	13,00	9,72	43,43	4,22	10,70	12,66	9,65	37
IX	3-NO_2-C_6H_4	210—212	$C_{14}H_{11}ClN_4O_4S$	45,91	3,17	9,48	15,05	8,56	45,86	3,00	9,68	15,01	8,73	63

[a]II-IX were colorless crystals which were purified for analysis by recrystallization: II from ethyl acetate, IV, V, and VII from dimethylformamide-water (2:1), and VIII from acetone; III, VI, and IX were dissolved in DMF at 18-20°, the solution was filtered, water was added to the filtrate, and the resulting precipitate was filtered, washed with water, and dried.

[b]The IR spectra (mineral oil) were obtained with a UR-10 spectrometer. The vibrational frequencies of the ketone CO, the amide CO, and the NH and NH_2 groups were: II 1720, 1700, 3470, 3360, and 3300 cm^{-1}; III 1700, 1680, 3470, 3360, and 3300 cm^{-1}; IV 1670-1680, 3470, 3360, and 3290 cm^{-1}; V 1720, 1670, 3520, 3370, and 3290 cm^{-1}; VI 1680, 1670, 3470, 3360, and 3290 cm^{-1}; VII 1720, 1675, 3470, 3360, and 3300 cm^{-1}; IX 1670-1685, 3470, 3370, and 3300 cm^{-1}. For VIII the ester CO, ketone CO, amide CO, and NH and NH_2 group frequencies were: 1745, 1720, 1680, 3470, 3360, and 3300 cm^{-1}.

[c]The UV spectra in alcohol were obtained with an EPS-3 recording spectrophotometer: λ_{max}, nm (log ε): V 215 (4.53), 257 (4.17), 307 (3.83); VII 218 (4.17), 260 (4.12), 308 (3.83); VIII 218 (4.15), 259 (4.11), 308 (3.81).

[d]The total halogen (Cl, Br) content is given.

[e]The PMR spectra were obtained with a JNM-4H spectrometer with an operating frequency of 100 MHz. The internal standard was DMSO. The proton signals are presented in the δ scale (in C_5H_5N): 1.03 ppm (triplet) and 4.06 ppm (quartet) ($-OCH_2CH_3$), 3.91 ppm (singlet, 2H from $-CH_2COOC_2H_5$), 4.22 ppm (singlet, 2H from $-SCH_2-$).

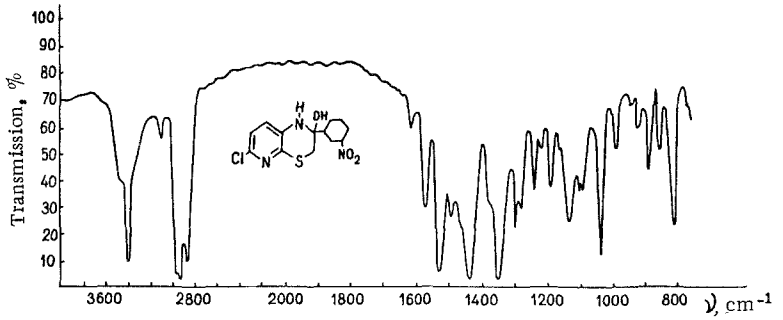


Fig. 1. IR spectrum of 2-chloro-6-hydroxy-6-(3'-nitrophenyl)-5,6-dihydropyrido[2,3-b][1,4]thiazine (X)

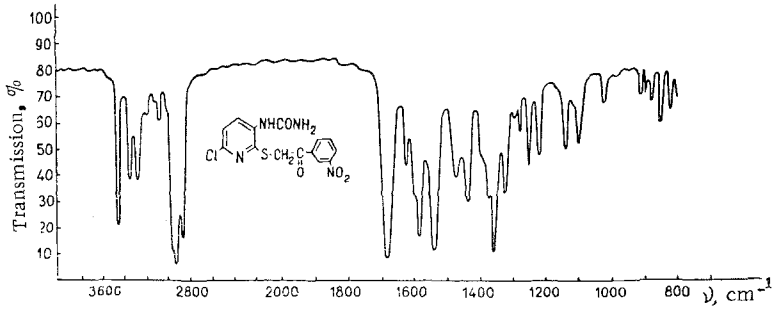


Fig. 2. IR spectrum of N-[2-(3'-nitrophenacylmercapto)-6-chloro-3-pyridyl]urea (IX).

The structure of X was confirmed by the absence in its IR spectrum of a CO-group absorption and by the presence of bands for OH and NH groups (Fig. 1). From its properties and IR spectra, XII is similar to the compound previously obtained by the reaction of 2-mercapto-3-amino-6-chloropyridine with chloro-oxalacetic ester [2].

II and IV-VII have sharp melting points that do not change on recrystallization from alcohols and storage in air, and they also form hydrazones. Thus, the corresponding dinitrophenylhydrazone is obtained by treatment of V with dinitrophenylhydrazine in the presence of hydrochloric acid. III is an exception in that it is converted to pyridothiazine XIV on standing in air and during recrystallization from alcohol.

The structures of II-IX were confirmed by IR spectroscopy (Fig. 2), and their purity was confirmed by fixed-layer chromatography.

It was found that II and VIII are converted to pyridothiazines XIII and XIX by heating in aqueous dimethylformamide. Cleavage of the amide residue and cyclization do not occur in the absence of water, alkalis, and alcohol. Thus, the starting material is recovered when VIII is refluxed in anhydrous benzene. The results indicated that facile cleavage of the urea residue takes place exclusively during the construction of 1,4-thiazine rings on the basis of N-(2-acylmethylmercapto-6-chloro-3-pyridyl)ureas. It is interesting to note that in I hydrolysis of the urea residue is accomplished completely only when it is heated with 20% aqueous alkali at 120-130° for 15-20 h. This difference is apparently explained by the fact that the presence of an electrophilic carbon atom in the ketone portion of molecules of II-IX sets up the conditions for the formation of a new C–N bond. The latter circumstance weakens the amide bond, and, under the influence of a basic reagent, it is cleaved under quite mild conditions.

The optimum conditions for the conversion of I to pyridothiazines were found during an investigation of the reaction of I with halocarbonyl compounds [3]. Thus it was shown that when phenacyl bromide and its 4-methoxy-, 2-hydroxy-4-ethoxy-, and 4-bromo-substituted derivatives and α-chloroacetoacetic ester are used, this conversion proceeds smoothly in alcohol at 18-20° in the presence of one equivalent of alkali. Under these conditions, the formation of S-acylmethylmercapto derivatives, their cyclization, and hydrolysis of the amide bond are accomplished in one operational step. If, however, more stable S-acylmercapto

derivatives or mixtures of them with pyridothiazines are obtained as, for example, in the case of γ-chloroacetoacetic ester, they are converted, without isolation in the pure state, to pyridothiazines by heating in aqueous dimethylformamide.

The identity of the pyridothiazines obtained from I and the analogous compounds [2, 3] previously synthesized from 2-mercapto-3-amino-6-chloropyridine (XXI) was confirmed by comparison of their chromatographic characteristics and their IR and PMR spectra.

The examined method for the preparation of 2-chloropyridothiazines is more convenient in a preparative respect than the method in which XXI is used as the starting material. It ensures the preparation of pyridothiazines in high yields from the more accessible I. I and XXI are obtained by hydrolysis of 2-amino-5-chlorothiazolo[5,4-b]pyridine [4], but 1 to 1.5 h are required to obtain I (90% yield), compared with 15-20 h at 120-130° to obtain XXI (60-70% yield) [1].

EXPERIMENTAL

N-[2-(4'-Methoxyphenacylmercapto)-6-chloro-3-pyridyl]urea (III) and 2-Chloro-6-(4'-methoxyphenyl)-7H-pyrido[2,3-b][1,4]thiazine (XIV). A solution of 0.45 g (2.4 mmole) of 4-methoxyphenacyl chloride in 10 ml of methanol was added at −10° to a solution of 0.5 g (2.4 mmole) of I in 10 ml of methanol containing 0.14 g (2.5 mmole) of KOH, and the resulting mixture was stirred at this temperature for 2 h. The precipitate was filtered, washed with water, and dried to give 0.6 g (70%) of III with mp 218-220°. The filtrate after removal of III was stirred at 18-20° for 2-3 h, evaporated to dryness in vacuo, and the residue was triturated with water. The solid product was filtered, washed with water, and dried to give 0.2 g (28%) of XIV with mp 203-205°. The compound obtained was chromatographically identical to an authentic sample of XIV obtained from XXI [1] (R_f 0.58, yellow-green spot, system 1).*

N-[2-(4'-Bromophenacylmercapto)-6-chloro-3-pyridyl]urea (IV) and 2-Chloro-6-(4'-bromophenyl)-7H-pyrido[2,3-b][1,4]thiazine (XV). IV was obtained from I and 4-bromophenacyl bromide under conditions similar to those used for III. The filtrate after separation of IV was treated as described for the preparation of XIV to give 36% of XV with mp 182-184°. The IR spectrum of XV was identical to that of the pyridothiazine obtained from XXI [1].

II, VI, VII, and V were similarly obtained. V gave a yellow spot (R_f 0.47) with system 2; VII gave a rose spot (R_f 0.41) with system 2. The 2,4-dinitrophenylhydrazone of V was obtained as yellow crystals with mp 168-170° (from ethanol). Found %: C 42.30; H 2.62; Cl 18.90; N 17.11; S 5.61. $C_{20}H_{14}Cl_3N_7O_5S$. Calc. %: C 42.06; H 2.47; Cl 18.66; N 17.17; S 5.60.

2-Chloro-6-phenyl-7H-pyrido[2,3-b][1,4]thiazine (XIII). A solution of 0.5 g (2.4 mmole) of phenacyl bromide was added at 18-20° to a solution of 0.5 g (2.4 mmole) of I in 10 ml of methanol containing 0.18 g (3 mmole) of KOH. The mixture was stirred at this temperature for 3 h, the methanol was removed by distillation in vacuo to dryness, and the residue was triturated with water and allowed to stand overnight. The precipitate was filtered to give 0.6 g (94%) of a product with mp 141-143° [from dimethylformamide − water (2:1)]. The IR and UV spectra were identical to the spectra of XIII synthesized from XXI. The product gave a yellow spot (R_f 0.76) which turned green.

XIV was similarly obtained in 90% yield and had mp 203-205° (from dimethylformamide).

2-Chloro-6-(2'-hydroxy-4'-ethoxyphenyl)-7H-pyrido[2,3-b][1,4]thiazine (XVI). This compound was obtained in 95% yield from I and 2-hydroxy-4-ethoxyphenacyl chloride under the conditions used to synthesize III and had mp 190-191° (from acetone).

2-Chloro-6-methyl-7-carbethoxy-5H-pyrido[2,3-b][1,4]thiazine (XVIII). A solution of 0.4 g (2.4 mmole) of α-chloroacetoacetic ester in 3-5 ml of ethanol was added at −10° to a solution of 0.5 g (2.4 mmole) of I in 10 ml of ethanol containing 0.18 g (3 mmole) of KOH. The mixture was stirred at this temperature for 3 h, the solution was filtered, and the filtrate was evaporated to dryness in vacuo. Water (10-15 ml) was added to the residue, and the mixture was allowed to stand at 0-5° for 24 h. The resulting precipitate was filtered to give 0.53 g (80%) of a product with mp 202-204° (from ethanol). The IR spectrum was identical to that of pyridothiazine XVIII synthesized from XXI.

*The chromatography was accomplished in a fixed layer (SKS silica gel − gypsum). The chromatograms were developed with concentrated H_2SO_4. System 1: benzene − n-heptane − ethyl acetate (19:11:1). System 2: benzene − n-heptane − ethyl acetate − ethanol (19:1:2:2).

N-[2-(3'-Nitrophenacylmercapto)-6-chloro-3-pyridyl]urea (IX), 2-Chloro-6-hydroxy-6-(3'-nitrophenyl)-5,6-dihydropyrido[2,3-b][1,4]thiazine (X), and 2-Chloro-6-(3'-nitrophenyl)-7H-pyrido[2,3-b][1,4]-thiazine (XVII). In analogy with the preparation of III, 63% of IX with mp 210-212° was obtained by stirring equimolecular amounts of I, KOH and 3-nitrophenacyl bromide in methanol for 3 h at −10°. The filtrate was vacuum-evaporated to one third of its original volume, and 33% of X with mp 131-133° was precipitated by the addition of water. IR spectrum: 3400-3470 cm^{-1} (NH, OH); no C=O group absorption was present. X cyclized to XVII with mp 178-180° on attempts to recrystallize it from ethanol. The product was chromatographically and spectrally identical to an authentic sample of XVII obtained from XXI and gave a yellow spot (R_f 0.66) with system 1.

N-[2-(Carbethoxymethylmercapto)-6-chloro-3-pyridyl]urea (XI), 2-Chloro-6-hydroxy-6,7-dicarbethoxy-6,7-dihydropyrido[2,3-b][1,4]thiazine (XII), and 2-Chloro-6,7-dicarbethoxy-5H-pyrido[2,3-b][1,4]thiazine (XX). A solution of 0.5 g (2.4 mmole) of I in 8 ml of a 1.8% solution (2.4 mmole) of KOH in ethanol was added at −10° to a solution of 0.54 g (2.4 mmole) of diethyl chlorooxalacetate in 5 ml of ethanol. The mixture was stirred at this temperature for 3 h, the precipitate was filtered and dissolved in 10-15 ml of water, and the solution was allowed to stand at 18-20° for 2-3 days. The resulting precipitate was filtered to give 0.32 g (45%) of XI with mp 201-202° (from ethanol). The product did not depress the melting point of an authentic sample obtained via the method in [5]. The alcoholic filtrate was evaporated to dryness in vacuo, 10-15 ml of water was added to the residue, and the solid product was filtered, washed with water, and dried to give 0.25 g (29%) of light-yellow crystals of XII with mp 90-91°.* Its IR spectrum indicated that it was identical to XII obtained from XXI [2]. If the alcoholic filtrate was allowed to stand overnight, the solution became bright-red, and XX with mp 147-148° (from ethanol) was formed.

N-[2-(Carbethoxyacetylmethylmercapto)-6-chloro-3-pyridyl]urea (VIII) and 2-Chloro-6-carbethoxymethyl-5H-pyrido[2,3-b][1,4]thiazine (XIX). A solution of 0.4 g (2.4 mmole) of γ-chloroacetoacetic ester in 2 ml of ethanol was added at 18-20° to a solution of 0.5 g (2.4 mmole) of I in 10 ml of ethanol containing 0.18 g (3 mmole) of KOH. The mixture was stirred at this temperature for 3 h, and the precipitate was filtered, washed with water, and dried to give 0.3 g (37%) of VIII with mp 172-174° (from acetone) and R_f 0.25 (rose spot, system 1). After separation of VIII, the filtrate was stirred at 18-20° for 3 h, vacuum-evaporated to one third of its original volume, water was added to the residue, and the solution was allowed to stand for 24 h to give 0.40 g (60%) of XIX [2] with mp 143-144° (from ethanol).

2-Chloro-6-carbethoxymethyl-5H-pyrido[2,3-b][1,4]thiazine (XIX). A solution of 0.15 g (0.4 mmole) of VIII in 3 ml of 50% aqueous dimethylformamide was refluxed for 2 h. The hot solution was filtered, and 5 ml of water was added to the filtrate. The resulting precipitate was filtered and washed with water to give 0.09 g (75%) of a product with mp 143-144° (from ethanol). The IR spectrum was identical to that of XIX obtained from XXI [2]. XIII was similarly obtained in 81% yield from II and had mp 141-143°.

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*The compound melted at 90-91° when the temperature was raised slowly, but had the same melting point as pyridothiazine XX on rapid heating.