2-(ACYLMETHYLMERCAPTO)-3-AMINO- AND 2-(ACYLMETHYLMERCAPTO)-3-ACETAMIDOPYRIDINES

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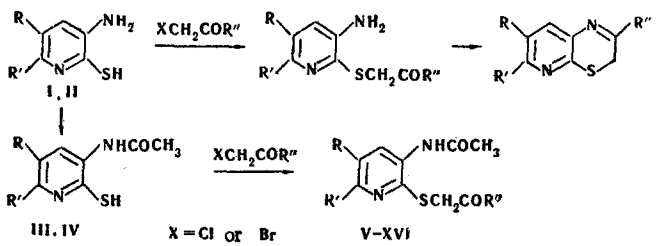
The reaction of 2-mercapto-3-acetamido-5-(or 6-)chloropyridines with phenacyl bromide and substituted phenacyl bromides yielded 2-(phenacylmercapto)-3-acetamidopyridines, while the reaction of the former with γ-chloroacetoacetic ester yielded 2-(carbethoxyacylmethylmercapto)-3-acetamidopyridines.

In developing the research in [1,2], it seemed of interest to investigate the properties of 2-(acylmethylmercapto)-3-aminopyridines and to obtain some of their derivatives. It was found that 2-(acylmethylmercapto)-3-aminopyridines are completely dehydrated to pyridothiazines under the influence of the Fischer reagent. Absorption maxima corresponding to pyridothiazines are observed in the UV spectra of alcohol solutions of these compounds.

Pyridothiazines, rather than the corresponding hydrazones, are also obtained by the treatment of 2-phenacylmercapto-3-amino-5-chloro- and 2-phenacylmercapto-3-amino-6-chloropyridines with 2,4-dinitrophenylhydrazine hydrochloride. 2-(2',5'-Dichlorophenacylmercapto)-3-acetamidopyridine (XI) (36%) and bis{6-(2',5'-dichlorophenyl)pyrido[2,3-b][1,4]thiazinyl} (XX) (21%) were isolated in an attempt to acetylate 2-(2',5'-dichlorophenacylmercapto)-3-aminopyridine with acetic anhydride. Compound XI and 2-phenacylmercapto-3-acetamidopyridines V-X are obtained in better yields by the reaction of 2-mercapto-3-acetamido-5-chloropyridine (III) with 2,5-dichlorophenacyl chloride and the appropriate phenacyl bromides in alcohol in the presence of alkali. 2-(Acylmethylmercapto)-3-acetamido-6-chloropyridines (XII-XIV) are similarly synthesized by the reaction of 2-mercapto-3-acetamido-6-chloropyridine (IV) with phenacyl halides. 2-(Carbethoxyacylmethylmercapto)-3-acetamidopyridines (XV and XVI, respectively) are obtained by the reaction of mercaptopyridines III and IV with γ-chloroacetoacetic ester.



The structures of V-XVI were confirmed by IR and PMR spectroscopic data. Thus the absorption bands of a ketone carbonyl group (1670-1740 cm^{-1}) and of an amide group (1640-1680 cm^{-1}) are present in the IR spectra of V-XIV; in addition to these bands, there is carbonyl absorption of an ester group at ~1740 cm^{-1} in the spectra of XV and XVI. The PMR spectra of V-XIV contain signals from the protons of a methylene (4.7-4.75 ppm) and methyl group (2.2-2.3 ppm), while the signals of the protons of an ester group (~1.3 and 4.2 ppm) are also observed in the spectra of XV and XVI.

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TABLE 1. 2-Acylmethylmercapto-3-acetamidopyridines (V-XVI)

Comp.	R	R'	R''	Mp, °C*	Empirical formula	Found, %					Calculated, %					Yield, %
						C	H	Cl	N	S	C	H	Cl	N	S	
V	Cl	H	C_6H_5	148—149	$C_{15}H_{13}ClN_2O_2S$	56,4	4,1	11,3	8,6	10,1	56,2	4,0	11,1	8,7	10,0	91
VI	Cl	H	p-$CH_3OC_6H_4$	219—220	$C_{16}H_{15}ClN_2O_2S$	54,8	4,5	10,3	8,1	9,3	54,8	4,3	10,1	8,0	9,1	98
VII	Cl	H	2-HO-4-$C_2H_5OC_6H_3$	183—184	$C_{17}H_{17}ClN_2O_3S$	53,5	4,4	9,5	7,4	8,2	53,6	4,5	9,3	7,4	8,4	91
VIII	Cl	H	p-BrC_6H_4	180—181	$C_{15}H_{12}BrClN_2O_2S$	45,3	3,1	29,0†	7,0	8,2	45,1	3,0	28,9†	7,0	8,0	91
IX	Cl	H	p-$O_2NC_6H_4$	191—193	$C_{15}H_{12}ClN_3O_4S$	49,0	3,3	10,0	11,4	9,0	49,3	3,3	9,7	11,5	8,7	98
X	Cl	H	m-$O_2NC_6H_4$	150—152	$C_{15}H_{12}ClN_3O_4S$	49,4	3,1	10,0	11,5	9,0	49,3	3,3	9,7	11,5	8,7	93
XI	Cl	H	2,5-$Cl_2C_6H_3$	175—177	$C_{15}H_{11}Cl_3N_2O_2S$	46,3	2,9	27,3	7,4	8,4	46,2	2,8	27,3	7,2	8,2	96
XII	H	Cl	C_6H_5	166—167	$C_{15}H_{13}ClN_2O_2S$	55,9	4,1	11,3	8,6	10,1	56,2	4,0	11,1	8,7	10,0	83
XIII	H	Cl	p-$CH_3OC_6H_4$	178—180	$C_{16}H_{15}ClN_2O_2S$	54,8	4,2	10,4	8,0	9,1	54,8	4,3	10,1	8,0	9,1	87
XIV	H	Cl	2,5-$Cl_2C_6H_3$	206—207	$C_{15}H_{11}Cl_3N_2O_2S$	46,1	2,6	27,6	7,1	8,5	46,2	2,8	27,3	7,2	8,2	91
XV	Cl	H	$CH_2COOC_2H_5$	146—148	$C_{13}H_{15}ClN_2O_4S$	47,2	4,8	10,9	8,5	9,7	47,2	4,5	10,7	8,5	9,6	97
XVI	H	Cl	$CH_2COOC_2H_5$	143—144	$C_{13}H_{15}ClN_2O_4S$	47,5	4,6	11,0	8,5	9,8	47,2	4,5	10,7	8,5	9,6	96

*Purified by crystallization: V, IX, and X from methanol, XI-XVI from ethanol, VI from dimethylformamide—CH_3OH (1:2), and VII and VIII from acetone.

† The total halogen content is presented.

2-(Acylmethylmercapto)-3-acetamidopyridines V-XVI are more stable substances than 2-(acylmethylmercapto)-3-aminopyridine. They do not cyclize to the corresponding pyridothiazines on heating with acetic anhydride or phosphorus pentoxide in dimethylformamide or under the influence of other dehydrating agents. Dinitrophenylhydrazones XVII-XIX are formed by treatment of 2-phenacylmercapto-3-acetamidopyridines V, XII, and XVI with 2,4-dinitrophenylhydrazine hydrochloride.

In contrast to 2-phenacylmercapto-3-aminopyridines, intense absorption maxima, apparently caused by the presence of carbonyl chromophores (see Table 2), are observed in the UV spectra of 2-(acylmethylmercapto)-3-acetamidopyridines. These spectra differ from the UV spectra of pyrido[2,3-b][1,4]thiazines [2].

EXPERIMENTAL

The IR spectra of mineral oil emulsions were recorded with a UR-10 spectrophotometer. The PMR spectra of $CDCl_3$ (V), $CHCl_3$ (XV and XVI), and C_5H_5N (IX and XI) solutions were recorded with a JNM-100 spectrometer. The purity of the compounds was confirmed by means of thin-layer chromatography (KSK silica gel—gypsum).

2-Mercapto-3-acetamido-5-chloropyridine (III). A mixture of 7.0 g (0.042 mole) of 2-mercapto-3-amino-5-chloropyridine (I) [1] and 7 ml (0.074 mole) of acetic anhydride was stirred at 18-20° for 3 h, 50-70 ml of 20% NaOH solution was added, and the mixture was stirred until the substance dissolved completely. The solution was filtered, and the filtrate was acidified with glacial acetic acid. The precipitate was removed by filtration, washed with water, and dried to give 7.0 g (80%) of III with mp 185-187°. Recrystallization from methanol gave colorless crystals with mp 193-195° that were soluble in ethyl acetate, chloroform, acetone, pyridine, and dimethylformamide (DMF). IR spectrum: 1670 cm^{-1} (amide CO), 3310 cm^{-1} (NH). Found: C 41.6; H 3.5; Cl 17.8; N 13.8; S 15.8%. $C_7H_7ClN_2OS$. Calculated: C 41.5; H 3.4; Cl 17.5; N 13.8; S 15.8%.

2-Mercapto-3-acetamido-6-chloropyridine (IV). This compound was obtained by the method in [3] from 2-mercapto-2-amino-6-chloropyridine (II) [2,4].

6-(2',5'-Dichlorophenyl)pyrido[2,3-b][1,4]thiazine. This compound was obtained by treatment of 2-(2',5'-dichlorophenacylmercapto)-3-aminopyridine with the Fischer reagent or with 2,4-dinitrophenylhydrazine hydrochloride.

2-(2,5-Dichlorophenacylmercapto)-3-acetamidopyridine (XI) and bis{6-(2,5-dichlorophenyl)pyrido[2,3-b]-[1,4]thiazinyl} (XX). A mixture of 0.25 g (0.007 mole) of 2-(2,5-dichlorophenacylmercapto)-3-amino-5-chloropyridine in 2 ml (0.021 mole) of acetic anhydride was heated at 90-100° for 2 h. The precipitate was removed by filtration

TABLE 2. UV Spectra of 2-Acylmethylmercapto-3-acetamidopyridines (in alcohol)

Compound	λ_{max}, nm	lg ε
V	255	4,33
	310	3,71
VI	222	4,34
	272	4,36
VII	277	4,27
	315	4,13
VIII	262	4,49
	309	3,74
IX	263	4,43
	305	3,87
X	226	4,50
	256	4,35
	307	3,75
XI	215	4,51
	255	4,18
	308	3,73
XII	253	4,33
	302	3,81
XIII	220	4,33
	273	4,36
XIV	215	4,51
	254	4,14
	302	3,83
XV	254	4,23
	305	3,75
XVI	220	4,07
	257	4,07
	304	3,82

and washed with water and alcohol to give 0.1 g (21%) of yellow crystals of XX with mp 243-245° that were insoluble in alcohol, ethyl acetate, acetone, pyridine, and chloroform and soluble in DMF. Carbonyl group absorption bands were absent in the IR spectrum. Found: C 47.5; H 1.9; Cl 32.3; N 8.4; S 9.9%. $C_{26}H_{12}Cl_6N_4S_2$. Calculated: C 47.5; H 1.8; Cl 32.4; N 8.5; S 9.7%.

The filtrate after removal of XX was vacuum-evaporated, and the residue was removed by filtration, washed with water, and dried to give 0.1 g (36%) of XI with mp 163-165°. Recrystallization from ethanol gave a product with mp 175-177°.

2-Phenacylmercapto-3-acetamido-5-chloropyridine (V). A solution of 0.45 g (0.002 mole) of phenacyl bromide in 10 ml of methanol was added to a solution of 0.5 g (0.0024 mole) of I in 10 ml of methanol containing 0.18 g (0.003 mole) of KOH. The mixture was stirred at 18-20° for 3 h, and the precipitate was removed by filtration, washed with water, and dried to give 0.57 g of V with mp 145-147°. An additional 0.15 g of V was obtained from the filtrate after vacuum evaporation. The overall yield of product with mp 148-149° (from methanol) was 91%. Compounds VI-XI and XV were similarly obtained (see Table 1).

2-Phenacylmercapto-3-acetamido-5-chloropyridine 2,4-Dinitrophenylhydrazone (XVII). Three to four drops of concentrated hydrochloric acid and 0.16 g (0.0005 mole) of V were added to a mixture of 0.1 g (0.0005 mole) of dinitrophenylhydrazine in 5 ml of ethanol, and the mixture was heated for 5-7 min. The precipitate was removed by filtration, washed with water, and dried to give 0.23 g (96%) of XVII with mp 237-238° [from DMF–water (2:1)]. Found: C 50.7; H 3.7; Cl 7.4; N 16.9; S 6.3%. $C_{21}H_{17}ClN_6O_5S$. Calculated: C 50.3; H 3.4; Cl 7.1; N 16.8; S 6.4%.

The following hydrazones were similarly obtained: XVIII [mp 196-197° (from ethanol)]. Found: C 50.2; H 3.4; Cl 7.3; N 17.1; S 6.3%. $C_{21}H_{17}ClN_6O_5S$. Calculated: C 50.3; H 3.4; Cl 7.1; N 16.8; S 6.4%. XIX [mp 183-185°] from DMF–methanol (1:2)]. Found: C 44.5; H 3.8; Cl 6.9; N 16.3; S 6.2%. $C_{19}H_{19}ClN_6O_7S$. Calculated: C 44.7; H 3.7; Cl 6.9; N 16.4; S 6.2%.

2-Phenacylmercapto-3-acetamido-6-chloropyridine (XII). This compound was synthesized from IV and phenacyl bromide under the conditions used to obtain V. Compounds XIII, XIV, and XVI were similarly synthesized (see Table 1).

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