AN INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XXVIII.* REACTION OF 3-AMINO-6-CHLORO-2-MERCAPTOPYRIDINE WITH ortho-SUBSTITUTED PHENACYL HALIDES

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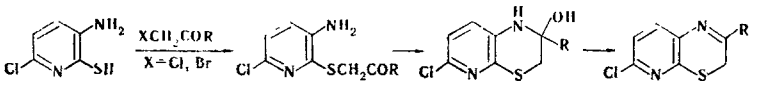
The reaction of 3-amino-6-chloro-2-mercaptopyridine with ortho-substituted phenacyl halides has been investigated. Two types of intermediate compounds have been isolated: 3-amino-6-chloro-2-(phenacylthio)pyridines and 2-aryl-2-hydroxy-1,2-dihydro-3H-pyrido[2,3-b][1,4]thiazines. Boiling 3-amino-6-chloro-2-mercaptopyridine with ortho-substituted phenacyl halides in ethanol has given 2-aryl-3H-pyrido[2,3-b][1,4]thiazines.

In continuation of investigations [2, 3] on the production of derivatives of pyrido[2,3-b][1,4]thiazine, we have investigated the reaction of 3-amino-6-chloro-2-mercaptopyridine (I) with ortho-substituted phenacyl halides. It has been shown that the nature of the substances formed and their properties and structures are determined both by the nature of the ortho substituent and by the conditions of performing the reaction. Thus, the reaction of compound (I) with o-fluorophenacyl chloride in ethanol in the presence of an equimolecular amount of alkali at a temperature from −5 to −10°C yielded the extremely unstable 3-amino-6-chloro-2-(o-fluorophenacylthio)pyridine (II) and the 2-(o-fluorophenyl)-2-hydroxydihydropyridothiazine (VI). If the aminopyridine (II) was not separated from the reaction mixture, two hours after the beginning of the reaction it was possible to isolate only the pyridothiazine (VI). An increase in the volume of the ortho substituent in the phenacyl component increases the stability of the intermediate substances of types A and B. Thus, the reaction of (I) with o-bromophenacyl bromide gave more stable compounds (III and VII) than the fluorine derivatives.

Unlike compounds (II) and (VI), compounds (III) and (VII) have clear melting points and do not change on recrystallization. The properties of the intermediate substances (II-V) and (VI-VIII) are affected not only by the volume but also by the electronic properties of the ortho substituent. The introduction into the ortho position of the benzene ring of electron-donating groups passivating the carbonyl carbon atom against nucleophilic attack considerably stabilizes the open structure (II-V). Compounds (IV) and (V), obtained by the reaction of (I) with o-methyl- and 2,4-dimethoxyphenacyl halides, withstand storage in the air and heating with alcohols. In the case of (I) and o-methylphenacyl chloride, in addition to (IV) the hydroxyamino compound (VIII) was isolated.



I II-V VI-VIII IX-XIV

The IR spectra of compounds (II-V) have the band of a ketone CO group (1670-1720 cm^{-1}), and in the high-frequency region bands of the NH_2 group are observed (3340-3360; 3440-3450 cm^{-1}). The spectra of the hydroxyamino compounds (VI-VIII) lack the absorption band of a CO group and have the bands of NH

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TABLE 1. 3-Amino-6-chloro-2-phenacylthiopyridines (II-V), 2-Aryl-6-chloro-2-hydroxy-1,2-dihydropyrido[2,3-b][1,4]thiazines (VI-VIII), and 2-Aryl-6-chloro-3H-pyrido[2,3-b][1,4]thiazines (IX-XIV)

Comp.	R	mp, °C	Empirical formula	Found, %					Calculated, %					Yield, %
				C	H	Cl	N	S	C	H	Cl	N	S	
II	2-FC_6H_4	67—69	$C_{13}H_{10}ClFN_2OS$	52,7	3,2	11,8	9,2	11,0	52,6	3,4	12,0	9,4	10,8	42
III	2-BrC_6H_4	82—84	$C_{13}H_{10}BrClN_2OS$	43,5	2,6	31,9[a]	8,0	9,2	43,6	2,8	32,0[a]	7,8	8,9	73
IV	2-$CH_3C_6H_4$	80—82	$C_{14}H_{13}ClN_2OS$	57,7	4,4	12,4	9,3	11,1	57,4	4,4	12,1	9,6	10,9	88
V	2,4-$(CH_3O)_2C_6H_3$	165—167	$C_{15}H_{15}ClN_2O_3S$	53,5	4,4	10,2	7,9	9,3	53,2	4,4	10,5	8,3	9,4	95
VI	2-FC_6H_4	80—82	$C_{13}H_{10}ClFN_2OS$	52,8	3,4	12,2	9,6	11,1	52,6	3,4	12,0	9,4	10,8	43—83
VII	2-BrC_6H_4	156—157	$C_{13}H_{10}BrClN_2OS$	43,9	2,5	31,8[a]	7,8	9,1	43,6	2,8	32,0[a]	7,8	8,9	63
VIII	2-$CH_3C_6H_4$	145—147	$C_{14}H_{13}ClN_2OS$	57,3	4,1	12,4	9,9	11,1	57,4	4,4	12,1	9,6	10,9	—
IX	2-FC_6H_4	268—270	$C_{13}H_8ClFN_2S$	55,8	2,8	—	10,0	11,5	56,0	2,9	—	10,0	11,5	69
X	2-BrC_6H_4	279—281	$C_{13}H_8BrClN_2S$	45,9	2,1	—	7,9	9,3	46,0	2,3	—	8,2	9,4	52
XI	2,4-$(CH_3O)_2C_6H_3$	218—220	$C_{15}H_{13}ClN_2O_2S$	56,5	4,0	11,0	8,4	9,9	56,2	4,0	11,1	8,7	10,0	46
XII	2,5-$Cl_2C_6H_3$	282—283	$C_{13}H_7Cl_3N_2S$	47,8	2,1	—	8,5	9,5	47,4	2,1	—	8,5	9,7	60
XIII	2-ClC_6H_4	236—238	$C_{13}H_8Cl_2N_2S$	53,2	2,5	23,5	9,3	10,6	53,1	2,7	23,8	9,5	10,9	50
XIV	2-IC_6H_4	>300	$C_{13}H_8ClIN_2S$	40,3	1,8	33,0[b]	7,1	8,5	40,4	2,1	32,8[b]	7,2	8,3	52

[a]The total Cl and Br content is given. [b]Iodine content given.

and OH groups (3240-3420 cm^{-1}). The PMR spectra of (IV) and (V) show the singlet signal of the protons of a CH_2 group. In the spectrum of the hydroxyamino compound (VI), the signals of the protons of the CH_2 group appear in the form of two doublets with a geminal coupling constant J = 12.5 Hz, and in the spectrum of (VIII) the corresponding signal is a singlet. By means of PMR spectroscopy with compound (IV) as example it has been possible to observe the transformation of the open form into the cyclic form. The spectrum of (IV) taken at 18-20°C in $CDCl_3$ shows the signals of the open form (singlet at δ 4.52 ppm). Heating the solution to 40°C causes the appearance of the signals of the cyclic form (singlet at δ 3.65 ppm) (Fig. 1), the intensity of the latter rising with an increase in the time of heating.

Boiling (I) with ortho-substituted phenacyl halides gave 2-aryl-3H-pyrido[2,3-b][1,4]thiazines (IX-XII). Compounds (XIII) and (XIV) were prepared similarly to (V) (Table 1). The structure of (IX-XIV) was confirmed by IR and PMR spectroscopy. The IR spectra of (IX-XIV) lack the absorption band of an NH group, which shows the structure of the substances synthesized as 3H derivatives. In the PMR spectra of the pyridothiazines there are signals assigned to the protons of the 3-CH_2 group in the δ 2.50-3.82 ppm region.

EXPERIMENTAL

The IR spectra were taken in paraffin oil on a Perkin-Elmer 457 instrument and the UV spectra in 95% ethanol on an EPS-3 spectrophotometer. The PMR spectra were obtained on a JNM-4H-100 instrument with TMS as internal standard.

3-Amino-6-chloro-2-(2-fluorophenacylthio)pyridine (II) and 6-Chloro-2-(2-fluorophenyl)-2-hydroxy-1,2-dihydropyrido[2,3-b]-[1,4]thiazine (VI). A. A solution of 0.5 g (3 mmoles) of (I) in 10 ml of ethanol containing 0.18 g (3 mmoles) of caustic potash was added dropwise to a solution of 0.5 g (3 mmoles) of 2-fluorophenacyl chloride in 5 ml of ethanol at −10°C. After 15 min, the precipitate was filtered off, washed with water, and with petroleum ether, and dried. This gave 0.39 g (42%) of (II). Colorless crystals with mp 67-69°C. IR spectrum: 3320, 3400 cm^{-1} (NH_2); 1690 cm^{-1} (CO of a ketone); in 4% $CHCl_3$ solution: 3380-3500 cm^{-1} (NH_2); 1690-1700 cm^{-1} (CO of a ketone).* UV spectrum, λ_{max}, nm (log ε): 240 (4.09), 333 (3.83). The filtrate was stirred at a temperature of −10 to 0°C for 2 h, 15-20 ml of water was added, and the precipitate was filtered off, washed with water and with petroleum ether, and dried. This gave 0.4 g (43%) of (VI), mp 80-82°C, light-yellow crystals. IR spectrum: 3180-3420 cm^{-1} (NH, OH). UV spectrum, λ_{max}, nm (log ε): 240 (4.0), 270 (4.03), 336 (3.87). PMR spectrum in C_5D_5N: 3.17 ppm (doublet), 3.74 ppm (doublet) − (VI); in $CDCl_3$: 2.94 ppm (doublet), 3.52 ppm (doublet) − (VI); 3.86 ppm (doublet), 3.76 ppm (doublet) − (IX). In a mixture of $CDCl_3$ and DCl: 3.86 ppm (doublet), 3.76 ppm (doublet) − (IX).†

B. When the reaction was performed at a temperature of from −5 to −10°C for 2 h, the main product was compound (VI). Yield 0.75 g (83%), mp 80-82°C. The IR spectra of the samples of compound (VI) obtained by methods A and B were identical.

*According to the IR spectrum (absence of NH_2 and CO groups), after 3 h 30 min in $CHCl_3$ compound (II) is converted into the pyridothiazine (IX).

†According to the PMR spectrum, (VI) is dehydrated to the pyridothiazine (IX).

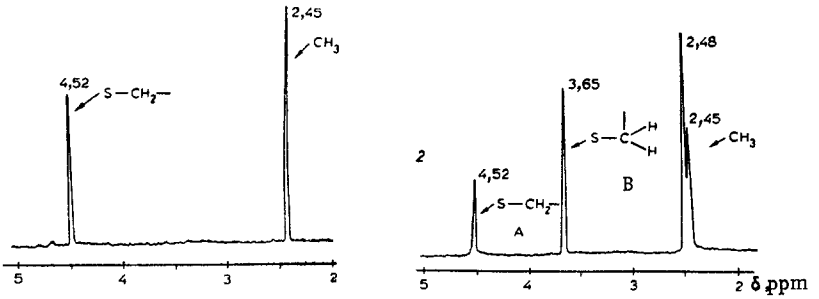

Fig. 1. PMR spectra of 6-chloro-2-hydroxy-2-(o-tolyl)-1,2-dihydropyrido[2,3-b][1,4]thiazine (IV) in $CDCl_3$: 1) at 18-20°C; 2) at 40°C after 25 min.

3-Amino-6-chloro-2-(2-methylphenacylthio)pyridine (IV). This was obtained from 0.5 g (3 mmoles) of (I) and 0.5 g (3 mmoles) of 2-methylphenacyl chloride in a similar manner to (II) (method B). Yield 0.25 g, mp 80-82°C. The filtrate was evaporated to one-third of its volume, 15-20 ml of water was added, and the precipitate was filtered off, washed with water and with petroleum ether, and dried. This gave 0.55 g, mp 73-75°C. Total yield 0.8 g (88%). Colorless crystals, mp 80-82°C (from ethanol). IR spectrum: 3360, 3450 cm^{-1} (NH_2); 1680 cm^{-1} (CO of a ketone). UV spectrum, λ_{max}, nm (log ε): 252 (4.17), 325 (3.79).

3-Amino-2-(2-bromophenacylthio)-6-chloropyridine (III) was obtained similarly from 1.0 g (6 mmoles) of (I) and 0.8 g (4 mmoles) of 2-bromophenacyl bromide, with the difference that the reaction was performed for 5 h, the solution was filtered, the filtrate was evaporated to one-third of its volume, the residue was triturated with water, and the precipitate was filtered off, and the further treatment was as for compound (IV). Yield 1.6 g (73%), mp 73-75C. Colorless crystals with mp 82-84°C (from ethanol). IR spectrum: 3200-3220 cm^{-1} (NH_2), 1715 cm^{-1} (CO of a ketone); in saturated $CHCl_3$ solution: 3390, 3430 cm^{-1} (NH_2), 1720 cm^{-1} (CO of a ketone). UV spectrum, λ_{max}, nm (log ε): 258 (4.12), 334 (3.63).

3-Amino-6-chloro-2-(2,4-dimethoxyphenacylthio)pyridine (V). At 18-20°C, a solution of 0.6 g (3 mmoles) of 2,4-dimethoxyphenacyl chloride in 20 ml of methanol was added to a solution of 0.5 g (3 mmoles) of (I) in 10 ml of methanol containing 0.18 g (3 mmoles) of KOH, and the mixture was stirred for 3 h and was left to stand for 12 h. The precipitate was filtered off, washed with water and petroleum ether, and dried to give 0.4 g of (V), mp 165-167°C. The filtrate was worked up as described for (IV). This gave an additional 0.6 g, mp 143-145°C. The total yield was 1.0 g (95%). Light-yellow crystals, mp 165-167°C (from acetone). IR spectrum: 3360, 3440 cm^{-1} (NH_2); 1670 cm^{-1} (CO of a ketone). PMR spectrum in $CDCl_3$: δ 3.79 ppm (singlet, SCH_2), 3.84 and 3.86 ppm (two OCH_3 groups).

2-(2-Bromophenyl)-6-chloro-2-hydroxy-1,2-dihydropyrido[2,3-b][1,4]thiazine (VII). This was obtained in a similar manner to (V). Yield 0.7 g (63%), mp 147-149°C. Light-yellow crystals with mp 156-157°C (from ethanol). IR spectrum: 3100-3200 cm^{-1} (NH, OH); CO group absent. UV spectrum, λ_{max}, nm (log ε): 236 (4.24), 260 (4.12), 326 (3.86).

6-Chloro-2-hydroxy-2-(o-tolyl)-1,2-dihydropyrido[2,3-b][1,4]thiazine (VIII). A solution of (IV) in ethanol was left at 18-20°C for 1-2 days, the ethanol was evaporated off in vacuum, and the precipitate was filtered off. Yellow crystals, mp 145-147°C. IR spectrum: 3050, 3140 cm^{-1} (NH, OH); CO absent. UV spectrum, λ_{max}, nm (log ε): 235 (4.14), 268 (4.13), 322 (3.63).

6-Chloro-2-(2-fluorophenyl)-3H-pyrido[2,3-b][1,4]thiazine (IX). To a solution of 0.5 g (3 mmoles) of 2-fluorophenacyl chloride in 10 ml of ethanol was added 0.5 g (3 mmoles) of (I) in 10 ml of ethanol containing 0.18 g (3 mmoles) of KOH. The mixture was boiled at 80-85°C for 4 h and was left to stand for 12 h. The precipitate was filtered off and was washed with water and with petroleum ether and dried. This gave 0.59 g of (IX) (69%), mp 255-257°C. Yellow crystals, mp 268-270°C (from chloroform). IR spectrum: NH and CO groups absent. UV spectrum, λ_{max}, nm (log ε): 266 (4.44); 364 (3.72).

Compounds (X-XII) were prepared similarly. Compounds (XIII) and (XIV) were obtained similarly to (V).

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