A STUDY OF NITROGEN- AND SULFUR- CONTAINING HETEROCYCLES

VII. The Reaction of 3-Amino-6-chloro-2-mercaptopyridine with Phenacyl Halides*

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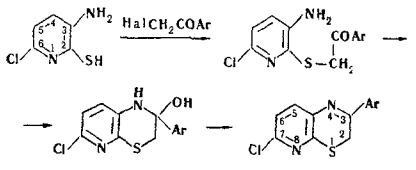
The reaction of 3-amino-6-chloro-2-mercaptopyridine with phenacyl halides has been studied, and a number of 3-aryl-7-chloro-2H-pyrido-[2,3-b]-1,4-thiazines have been synthesized. Two types of intermediate compounds have been isolated: 2-amino-6-chloro-2-phenacylthiopyridines and 3-aryl-7-chloro-3-hydroxy-1,2-dihydropyrido[2,3-b]-1,4-thiazines.

The preparation of several derivatives of 7-chloro- and 7-methoxypyrido- [2,3-b]-1,4-thiazines by means of the reaction of 3-amino-7-chloro(methoxy)-2-mercaptopyridine (II) with α-halogenoketones has been reported [1,2]. In one paper [1], these compounds are ascribed the structure of 4H-pyrido [2,3-b]-1,4-thiazines and in the other [2] the structure of 2H derivatives.

Continuing our investigation [3] with the aim of obtaining derivatives of 7-chloropyrido [2,3-b]-1,4-thiazine and establishing their structure, we have investigated the reaction of I with phenacyl halides containing electron-donating and electron-accepting substituents. Depending on the conditions of carrying out this reaction and the structure of the α-halogenoketones, three types of compound have been isolated: 3-amino-6-chloro-2-phenacylthiopyridines (II-V), 7-chloro-3-hydroxy-3-p-nitrophenyl-3,4-dihydropyrido [2,3-b]-1,4-thiazines (the carbinol amine XII) and 3-aryl-7-chloro-2H-pyrido [2,3-b]-1,4-thiazines (VI–XI). Thus, the formation of the pyridothiazines, like that of the pyrimidothiazines [4], takes place in the following way:



It was possible to isolate compounds II–V, like the 3-amino-5-chloro-2-phenacylthiopyridines, by carrying out the reaction of I with the corresponding phenacyl halides in an ethanolic solution of alkali at −10° C. Under similar conditions, I and p-nitrophenacyl bromide gave a carbinol amine XII. The reaction of I with α-halogenoketones at 18–20° C led to the formation of the final reaction products, the pyridothiazines VI–IX.

The 3-amino-6-chloro-2-phenacylthiopyridines II–V cyclize very readily to form the pyridothiazines VI–IX on storage in the air or in solution, when subjected to thin-layer chromatography (silica gel–gypsum), and, especially, when heated. The more stable carbinol amine XII dehydrates to form the pyridothiazine X only on boiling in benzene for several hours.

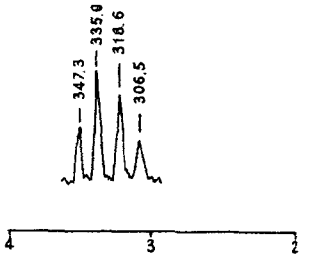


Fig. 1. PMR spectrum (in pyridine) of 7-chloro-3-nitrophenyl-3,4-dihydropyrido [2,3-b]-1,4-thiazine (XII).

The structure of the compounds synthesized was confirmed by their IR, UV, and PMR spectra. The IR spectra of substances II–V have bands of a CO group (1720–1750 cm^{-1}) and of an NH_2 group (3200, 3360 cm^{-1}); in the case of the carbinol amine XII, there is no band of a CO group and in the high-frequency region there are bands of NH and OH groups (3400, 3500 cm^{-1}). In the IR spectra of the phyridothiazines VI–XI, there are no bands of an NH group, which shows their structure as 2H derivatives. The UV spectra of the 7-chloropyridothiazines VI and IX–XI are similar to those of the 6-chloro-2H-pyridothiazines that we have synthesized previously [3] and have two characteristic maxima in the 270–285 and 350–380 nm regions. The PMR spectrum of the carbinol amine XII has a quartet corresponding to the signals of the two protons of the CH_2 group in position 2 in the 3.06–3.47 ppm region (Fig. 1). This splitting of the signals of the protons of the CH_2 group is apparently due to the fact that the dihydrothiazine ring has a nonplanar structure. In the PMR spectra of the pyridothiazines VI–X (Fig. 2) there is a single signal with a chemical shift of 3.75–4.07 ppm corresponding to the two protons of the CH_2 group, which again confirms the structure of the compounds that we obtained as 2H- and not 4H-pyridothiazines [1].

EXPERIMENTAL

3-Amino-6-chloro-2-mercaptopyridine (I). This was obtained by heating 7 g (0.037 mole) of 2-amino-6-chloropyrido[2,3-d]thiazole in 70 ml of 20% NaOH solution at 130° C for 15–20 hr. Yield 4 g (65%), mp 170° C (decomp.). In an attempt to synthesize I by the method of Yamamoto and Takahashi [5], N-(6-chloro-2-mercaptopyrid-3-yl) urea, mp 184–186° C, was obtained with a yield of 90%.

*For part VI, see [3].

3-Amino-6-chloro-2-phenacylthiopyridines (II–V) and 3-Aryl-7-chloro-2H-pyrido-[2,3-b]-1,4-thiazines (VI–IX)

Compound	R	R¹	R²	Mp, °C	Empirical formula	Found, %					Calculated, %					Yield, %
						C	H	Cl	N	S	C	H	Cl	N	S	
II	H	H	H	a, b	$C_{13}H_{11}ClN_2OS$	56.29	4.14	13.00	10.23	11.51	56.00	3.94	12.75	10.05	11.49	76
III	H	OCH_3	H		$C_{14}H_{13}ClN_2O_2S$	54.58	4.01	11.70	9.36	10.65	54.45	4.21	11.50	9.07	10.37	63
IV	OH	OC_2H_5	H		$C_{15}H_{15}ClN_2O_3S$	53.53	4.56	10.76	8.48	9.30	53.17	4.42	10.48	8.27	9.44	52
V	H	Br	H		$C_{13}H_{10}BrClN_2OS$	43.94	3.00	32.28[g]	7.92	9.16	43.65	2.79	32.29	7.83	8.95	54
VI	H	H	H	141—143[c,d]	$C_{13}H_9ClN_2S$[e,f]	59.57	3.47	13.80	10.56	12.47	59.84	3.45	13.62	10.74	12.28	96
VII	H	OCH_3	H	203—205	$C_{14}H_{11}ClN_2OS$	57.47	3.88	12.50	9.77	11.01	57.86	3.78	12.22	9.63	11.01	86
VIII	OH	OC_2H_5	H	190—191	$C_{15}H_{13}ClN_2O_2S$	56.60	4.08	11.25	8.71	9.97	56.28	4.06	11.07	8.73	9.98	73
IX	H	Br	H	182—184	$C_{13}H_8BrClN_2S$	46.32	2.49	33.98[g]	7.99	9.70	45.99	2.35	33.99	8.24	9.42	72
X	H	NO_2	H	174—176	$C_{13}H_8ClN_3O_2S$	51.12	2.76	11.82	13.72	10.60	51.06	2.61	11.62	13.74	10.47	80
XI	H	H	NO_2	178—180	$C_{13}H_8ClN_3O_2S$	51.19	2.83	11.38	13.60	10.26	51.06	2.61	11.62	13.74	10.47	84

[a]Compounds II–V formed colorless crystals having no sharp melting point, and to obtain analytically pure samples they were washed 2-3 times with water and dried; on heating and recrystallization, they cyclized into VI–IX. [b]The IR spectra (taken in paraffin oil on a UR-10 instrument), cm^{-1}: II–ν_{CO} 1720; ν_{NH_2} 3230, 3360; III–ν_{CO} 1720; ν_{NH_2} 3230, 3360; IV–ν_{CO} 1720; ν_{NH_2} 3200,3703; V–ν_{CO} 1720; ν_{NH_2} 3330, 3400; in VI–IX bands of CO and NH groups were absent. [c]Compounds VI–IX form yellow crystals and X brown crystals; VI was recrystallized from methanol, VII from dimethylformamide–water (2 : 1), and VIII–XI from acetone. [d]When VI–XI were chromatographed in a thin layer (KSK silica gel–gypsum) in the benzene–n-heptane–ethyl acetate (19 : 1 : 1) system and the chromatograms were treated with conc. H_2SO_4, spots with the following R_f values were obtained: VI–0.76; VII–0.72; VIII–0.73; IX–0.78; X–0.68; XI–0.69. [e]UV spectra (taken on a EPS-3 recording spectrophotometer), λ_{max}, nm (log ε): VI–277 (4.34); 352 (3.94); IX–282 (4.42); 355 (4.02); X–286 (4.38); 378 (3.98); XI–269 (4.27); 362 (3.74). [f]PMR spectra (taken on a INM-4H instrument (100 MHz, internal standard TMS), δ, in ppm: VI (in $CDCl_3$) is 3.78 (2H–3CH_2,); VII (in pyridine) is 3.94 (2H–3CH_2,); IX (in $CDCl_3$) is 3.75 (2H–3CH_2); X (in pyridine) is 4.07 (2H–3H_2,). [g]For compounds V and IX the total halogen contents (Cl + Br) are given.

3-Amino-6-chloro-2-phenacylthiopyridine (II). At −10° C, a solution of 0.55 g (0.002 mole) of phenacyl bromide in 10 ml of methanol was added to a solution of 0.5 g (0.003 mole) of I in 10 ml of methanol containing 0.18 g (0.003 mole) of KOH. After stirring at the same temperature for 1 hr, the precipitate that had deposited was filtered off, washed with water, and dried in the vacuum desiccator. This gave 0.65 g (75.6%) of colorless crystals. The filtrate remaining after the separation of the II was evaporated to dryness in vacuum, and the residue was triturated with water, filtered off, and dried in the air to form 0.13 g (16%) of VI, mp 141–143° C (from ethanol). Compounds III–V were prepared similarly. After being stirred for 2 hr, the filtrates obtained after the separation of the III–V yielded compounds VII–IX, and they were filtered off, washed with water, and recrystallized. The yield of VII was 14.4%, of VIII 33.3%, and of IX 37%.

7-Chloro-3-phenyl-2H-pyrido[2,3-b]-1,4-thiazine (VI). This was obtained in a similar manner to compound II from 0.5 g (0.003 mole) of I and 0.55 g (0.0035 mole) of phenacyl bromide by performing the reaction at 18–20° C for 3 hr. Yield 0.78 g (96.2%), mp 141–143° C. According to the literature [2], mp 148–149° C. Compounds VII–XI were obtained similarly.

7-Chloro-3-hydroxy-3-p-nitrophenyl-3,4-dihydropyrido[2,3-b]-1,4-thiazine (XII). This was obtained from 0.5 g (0.003 mole) of I and 0.7 g (0.003 mole) of p-nitro-phenacyl bromide in a similar manner to II. Yield 0.95 g (95%). For analysis it was recrystallized from methanol. Yellow crystals having no definite melting point, soluble in acetone, dioxane, dimethylformamide, ethyl acetate, pyridine, chloroform, and benzene, and insoluble in carbon tetrachloride, ether, and petroleum ether. IR spectrum, cm^{-1}: 3400, 3500 (NH, OH); no CO group present. PMR spectrum (in pyridine), δ, ppm: 3.06, 3.18, 3.35, 3.47 (quartet 2H–3CH_2). Found, %: C 48.40; H 3.29; Cl 11.00; N 12.79; S 9.90. Calculated for $C_{13}H_{10}ClN_3O_3S$, %: C 48.22; H 3.09; Cl 10.97; N 12.98; S 9.89.

7-Chloro-3-p-nitrophenyl-2H-pyrido[2,3-b]-1,4-thiazine (X). A solution of 0.4 g (0.012 mole) of XII in 20 ml of benzene was boiled for 5 hr and was evaporated to dryness in vacuum, after which the residue was triturated with water and filtered off to give 0.37 g (97.3%) of product with mp 168–170° C.

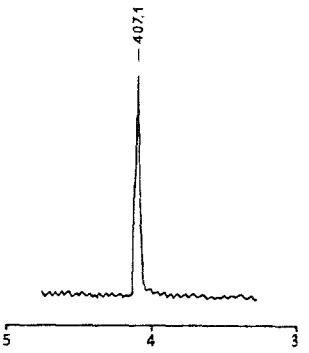


Fig. 2. PMR spectrum (in pyridine) of 7-chloro-3-(4'-nitrophenyl)-2H-pyrido-[2,3-b]-1,4-thiazine (X).

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