

## RESEARCH ON NITROGEN AND SULFUR-CONTAINING HETEROCYCLES

## VI. 3H-Pyrido[2,3-b][1,4]thiazines\*

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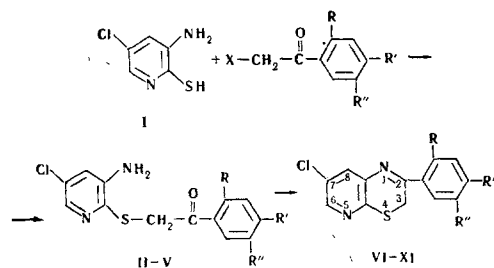
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2-Mercapto-3-amino-5-chloropyridine reacts with phenacyl halides to yield 2-phenacylmercapto-3-amino-5-chloropyridines and 2-aryl-7-chloro-3H-pyrido[2,3-b][1,4]thiazines.

In continuation of our work on the synthesis of bicyclic compounds containing the 1,4-thiazine ring [1], we have prepared some derivatives of pyrido[2,3-b][1,4]thiazine. This structure has been little investigated, either from the chemical or biological point of view. Derivatives of 1H-pyrido[2,3-b][1,4]thiazine have been obtained by the reaction of 2-mercapto-3-amino-6-chloro- and 2-mercapto-3-amino-6-methoxy-pyridines with  $\alpha$ -haloketones and esters of  $\alpha$ -halo- $\beta$ -ketoacids [2,3].

In order to obtain new derivatives of pyridothiazine, we have examined the reaction of 2-mercapto-3-amino-5-chloropyridine (I) with various phenacyl halides. It has been shown that, depending on the reaction conditions and on the nature of the substituents in the benzene ring of the ketone, reaction of I with phenacyl halides gives either 2-phenacylmercapto-3-amino-5-chloropyridines (II-V, table) or the corresponding derivatives of 3H-pyrido[2,3-b][1,4]thiazine (VI-XI, table). The nomenclature used is that of the Ring Index, second edition.



Compounds II-V were obtained by reaction of I with the appropriate phenacyl halides in alcoholic alkali at

\*For part V, See [11].

$-10^{\circ}\text{C}$  for 15-30 min. They separated from the reaction mixture after this time. However, if they were not isolated from the alcoholic alkali, they were gradually converted to the pyridothiazones VI-XI. Confirmation of structures II-V was provided by the presence in their IR spectra of bands at  $1680-1700\text{ cm}^{-1}$  characteristic of CO groups in ketones, and at  $3350-3380$  and  $3420-3350\text{ cm}^{-1}$ , characteristic of primary amino groups (Fig. 1). The carbonyl band in compound V was shifted towards lower frequencies ( $1640\text{ cm}^{-1}$ ), apparently as a result of the formation of intramolecular hydrogen bonds between the carbonyl group and the hydroxy group in the *o*-position in the benzene ring [4]. Compounds II-V are somewhat unstable, cyclizing to the corresponding pyridothiazines on standing in air, in inert and polar solvents, and with particular ease on heating. Thus, III in boiling benzene was converted to the pyridothiazine VII. The designation of VII as a derivative of 3H-pyridothiazine was confirmed by the absence from the IR spectrum (Fig. 2) of the carbonyl band (excluding the noncyclic structure III), and of the NH band (in agreement with the 3H-pyridothiazine structure, but not the 1H-structure).

If the reaction of I with phenacyl bromide, 2,5-dichlorophenacyl bromide, or 2-hydroxy-4-ethoxyphenacyl chloride was carried out at  $18-20^{\circ}\text{C}$ , however, then only the pyridothiazines VI, VIII, and IX were isolated from the reaction mixture. Absorption bands due to NH were absent from the IR spectra of these compounds. They must also, therefore, be derivatives of 3H-pyridothiazine.

Reaction of I with *m*- and *p*-nitrophenacyl chloride both at  $18-20^{\circ}\text{C}$  and at  $-10^{\circ}\text{C}$  gave only the pyridothiazines X and XI.

Starting materials were prepared by known methods, with some modifications. Thus, 2-hydroxy-3-nitro-5-chloropyridine was obtained by nitration of 2-amino-5-chloropyridine [5] with a mixture of  $\text{HNO}_3$  and  $\text{H}_2\text{SO}_4$  at  $55-60^{\circ}\text{C}$ , the amino-group being hydrolyzed simultaneously. It was observed that the 2-chlorine atom in

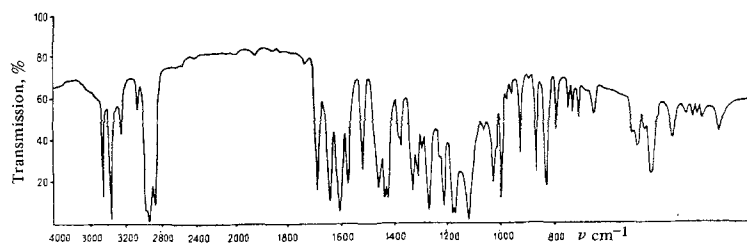
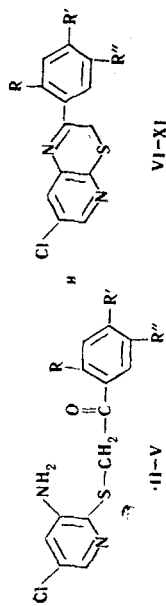


Fig. 1. IR spectrum of 2-p-methoxyphenacylmercapto-3-amino-5-chloropyridine (III).



Com- pound	R	R'	R''	Mp, °C <sup>a</sup>	Molecular formula <sup>b,c</sup>	Found, %					Calc., %					Yield, %
						C	H	Cl	N	S	C	H	Cl	N	S	
II	H	H	H	85-87	C <sub>13</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub> S	55.85	4.08	13.03	9.91	11.54	56.00	3.94	12.75	10.05	11.49	52.5
III	H	OCH <sub>3</sub>	H	143-145	C <sub>14</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> S	54.75	4.21	11.22	8.95	10.23	54.45	4.21	11.50	9.07	10.37	59
IV	Cl	H	Cl	108-110	C <sub>13</sub> H <sub>9</sub> Cl <sub>3</sub> N <sub>2</sub> O <sub>2</sub> S	44.80	2.77	30.38	7.83	9.10	44.89	2.59	30.64	8.05	9.20	56
V	OH	OC <sub>2</sub> H <sub>5</sub>	H	117-120	C <sub>15</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>3</sub> S	52.87	4.53	10.37	8.16	9.37	53.17	4.42	10.48	8.27	9.44	55
VI	H	H	H	208-210	C <sub>13</sub> H <sub>9</sub> ClN <sub>2</sub> S	60.20	3.60	13.37	10.75	12.43	59.84	3.45	13.62	10.74	12.26	67.5
VII	H	OCH <sub>3</sub>	H	232-234	C <sub>14</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub> S	57.67	3.47	12.29	9.56	10.78	57.86	3.78	12.29	9.63	11.01	83
VIII	Cl	H	Cl	100-102	C <sub>13</sub> H <sub>7</sub> Cl <sub>3</sub> N <sub>2</sub> S	47.60	2.36	32.64	8.26	9.66	47.34	2.12	32.32	8.43	9.71	84
IX	OH	OC <sub>2</sub> H <sub>5</sub>	H	183-184	C <sub>15</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> S	56.04	4.26	11.26	8.84	10.12	56.28	4.06	11.07	8.73	9.98	33
X	H	NO <sub>2</sub>	H	243-245	C <sub>13</sub> H <sub>8</sub> ClN <sub>2</sub> O <sub>2</sub> S	50.98	2.90	11.42	13.90	10.28	51.06	2.61	11.62	13.74	10.47	86
XI	H	H	NO <sub>2</sub>	>300	C <sub>13</sub> H <sub>8</sub> ClN <sub>2</sub> O <sub>2</sub> S	51.25	2.80	11.92	13.57	10.76	51.06	2.61	11.62	13.74	10.47	73

<sup>a</sup>The rate of heating for II was 3-4° C/min., for III, 1-2° C/min., and for V, 7-8° C/min. <sup>b</sup>Compounds II-V were purified for analysis by washing with water and ether. <sup>c</sup>The IR spectra (recorded on a UR-10 instrument in vaseline oil suspension) were as follows: II - νCO 1700 cm<sup>-1</sup>, νNH<sub>2</sub> 3450, 3350 cm<sup>-1</sup> (0.02% solution in CCl<sub>4</sub>); νCO 1700 cm<sup>-1</sup>, νNH<sub>2</sub> 3500, 3400 cm<sup>-1</sup>; V - νCO 1640 cm<sup>-1</sup>, νNH<sub>2</sub> 3420, 3350 cm<sup>-1</sup>; IV - νCO 1700 cm<sup>-1</sup>, νNH<sub>2</sub> 3450, 3370 cm<sup>-1</sup>.

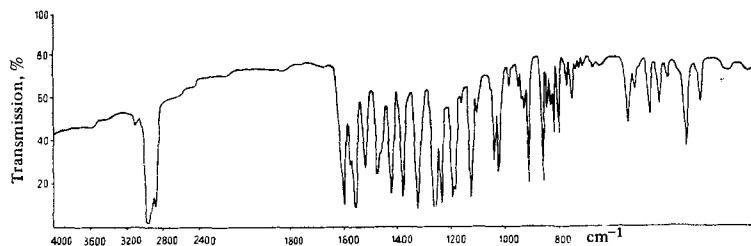


Fig. 2. IR spectrum of 2-(p-methoxyphenyl)-7-chloro-3H-pyrido[2,3-b][1,4]thiazine (VII).

2,5-dichloro-3-nitropyridine was readily replaced by the hydroxy group, so that the reaction mixture from 2-hydroxy-3-nitro-5-chloropyridine and  $\text{PCl}_5$  must be decomposed carefully with water at a temperature not above  $0^\circ\text{C}$ . 2-Mercapto-3-amino-5-chloropyridine (I) was obtained in 80% yield by carrying out the replacement of the chlorine atom in 2,5-dichloro-3-nitropyridine and the reduction of the nitro group in one stage.

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## EXPERIMENTAL

**2-Hydroxy-3-nitro-5-chloropyridine.** To a solution of 128.5 g (1 mole) of 2-amino-5-chloropyridine [5] in 500 ml of  $\text{H}_2\text{SO}_4$  (d 1.84) was added dropwise, during 5 hr, 64.5 ml (1.25 mole) of  $\text{HNO}_3$  (d 1.5) at  $55-60^\circ\text{C}$ , with vigorous stirring. After all the  $\text{HNO}_3$  had been added, the mixture was stirred at the same temperature for a further 1.5-2 hr, cooled to  $18-20^\circ\text{C}$ , poured onto ice, and worked up as described in [6]. Yield 110.6 g (63.4%), mp  $230^\circ\text{C}$  (from ethanol) (from [7], mp  $235^\circ\text{C}$ ).

**2,5-Dichloro-3-nitropyridine.** A mixture of 20 g (0.114 mole) of 2-hydroxy-3-nitro-5-chloropyridine and 20 g (0.096 mole) of  $\text{PCl}_5$  in 40 ml of  $\text{POCl}_3$  was heated at  $115^\circ\text{C}$  for 2 hr, cooled, and added slowly in small portions to ice with vigorous stirring, at such a rate that the temperature of the mixture did not exceed  $0^\circ\text{C}$ . The solid was filtered off, washed with water, and dried. Yield 14 g (63%), mp  $41-42^\circ\text{C}$  (from ethanol) (from [8], mp  $43^\circ\text{C}$ ).

**2-Mercapto-3-amino-5-chloropyridine (I).** To an alcoholic solution of potassium hydrogen sulfide, obtained by passing hydrogen sulfide into a solution of 15 g (0.268 mole) of KOH in 200 ml of methanol, was added dropwise, with stirring, a solution of 15 g (0.08 mole) of 2,5-dichloro-3-nitropyridine in 160 ml of methanol, the temperature being kept at  $18-20^\circ\text{C}$ . After stirring for 1 hr, the methanol was removed in vacuo and the residue dissolved in 5% aqueous NaOH (about 200 ml) and the solution filtered. Sodium hydrosulfite (about 4-5 moles) was added in small portions, with stirring, until an excess of the latter was present (tested for by decolorization of paper impregnated with methylene blue), and until the mixture was alkaline (pH 10-11). When all the hydrosulfite had been added, the mixture was stirred for 30 min at  $50^\circ\text{C}$ , cooled to  $18-20^\circ\text{C}$ , filtered, the filtrate acidified with glacial acetic acid, and the precipitate filtered off. Yield 10.0 g (80%), mp  $191-192^\circ\text{C}$  (from methanol) (from [9, 10], mp  $204-205^\circ\text{C}$ . Found %: C 37.29; H 3.24; Cl 21.98; N 17.71; S 19.98. Calc. for  $\text{C}_5\text{H}_5\text{ClN}_2\text{S}$ , %: C 37.38; H 3.11; Cl 22.11; N 17.44; S 19.93).

**2-Phenacylmercapto-3-amino-5-chloropyridine (II).** To a solution of 0.5 g (0.003 mole) of I in 10 ml of methanol containing 0.18 g (0.032 mole) of KOH, was added dropwise, with vigorous stirring, a solution of 0.55 g (0.002 mole) of phenacyl bromide in 10 ml of me-

thanol, the temperature being kept at  $-10^\circ\text{C}$ . After stirring for a further 30 min at this temperature, the precipitate which had separated was filtered off and washed with water and ether. Yield 0.42 g (52.5%), mp  $85-87^\circ\text{C}$ .

Compounds III-IV were prepared similarly. In the preparation of V, the solution obtained after the separation of V was stirred for 15 min at  $18-20^\circ\text{C}$ , and the IX which separated was filtered off, washed with water, and dried to give 0.15 g (33%), mp  $183-184^\circ\text{C}$  (from benzene).

Compounds II-V were gray crystalline solids, which on standing in air, or when dissolved in inert or polar solvents, turn yellow. II, III, and V do not possess characteristic melting points, since they gradually cyclize on heating to the corresponding VI, VII, and IX.

**2-Phenyl-7-chloro-3H-pyrido[2,3-b][1,4]thiazine (VI).** To a solution of 0.5 g (0.003 mole) of I in 10 ml of methanol containing 0.18 g (0.032 mole) of KOH was added, at  $18-20^\circ\text{C}$ , a solution of 0.55 g (0.002 mole) of phenacyl bromide in 10 ml of methanol. The mixture was stirred for 3-4 hr, the KBr which separated was filtered off, and the filtrate evaporated in vacuo. The residue was washed with water, dried, and dissolved in 15 ml of benzene, and the benzene solution boiled for 2-3 hr, followed by concentration in vacuo to 1/3 of its volume. After cooling, the solid was filtered off to yield 0.5 g (67.5%), mp  $208-210^\circ\text{C}$  (from benzene).

Compounds X and XI were prepared similarly, but in the case of VIII the benzene solution was not boiled, but concentrated in vacuo, without heating to 1/3 of its volume, and the solid which separated was filtered off and recrystallized from methanol.

**2-(p-Methoxyphenyl)-7-chloro-3H-pyrido[2,3-b][1,4]thiazine (VII).** A solution of 0.5 g of III in 15 ml of benzene was boiled for 2-3 hr, concentrated in vacuo to 1/3 of its volume, and cooled. The precipitate was filtered off to give 0.39 g (83%), mp  $232-234^\circ\text{C}$  (from benzene).

Compounds VI, VII, IX, and XI were yellow crystalline solids, and VIII was pale yellow. They were soluble in ether, chloroform, benzene, pyridine, and dimethylformamide, but insoluble in light petroleum.

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