INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XXX.* REACTION OF 2-MERCAPTO-3-UREIDO-6-CHLOROPYRIDINE WITH PHENACYL HALIDES

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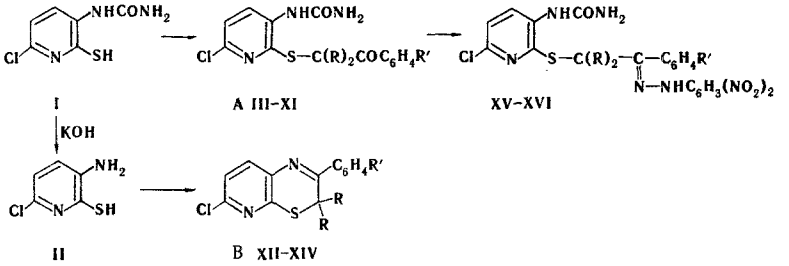
2-Mercapto-3-ureido-6-chloropyridine reacts with the ortho, meta, and para derivatives of phenacyl halides to give 2-phenacylthio-3-ureido-6-chloropyridines, which are readily cyclized to 6-arylpyrido[2,3-b][1,4]thiazines regardless of the presence or absence of a substituent in the meta and para positions of the benzene ring.

In order to synthesize 6-arylpyrido[2,3-b][1,4]thiazines from 2-mercapto-3-ureido-6-chloropyridine (I), we investigated the reaction of I with the ortho, meta, and para derivatives of phenacyl halides. Compound I reacts with o-chloro-, o-boromo-, o-iodo-, o-methyl-, o-, m-, and p-fluoro, and o,p-dimethoxyphenacyl halides and bromophenyl isopropyl ketone to give 2-phenacylthio-3-ureido-6-chloropyridines (III-XI, Table 1). In the preparation of IV and V, we also isolated 6-arylpyrido[2,3-b][1,4]thiazines (XII and XIII). Compounds III and VI-X, which have a substituent in the ortho position of the benzene ring of the carbonyl fragment of the molecule, do not change on standing in air and in solution and during recrystallization from polar solvents and form hydrazones XV and XVI. On the other hand, regardless of the presence or absence of a substituent in the meta and para positions, IV, V and XI are unstable, and are cyclized to 6-arylpyridothiazines (XII-XIV) on standing in alcoholic alkali solutions or on heating with dimethylformamide (DMF). This process is accompanied by facile splitting out of a urea residue. Compounds III and VI-X, in which the ortho substituent sterically hinders the formation of an N_5-C_6 bond, are not cyclized to 6-arylpyridothiazines. A urea residue is not split out in this case even under more severe conditions.



III R=H, R¹=*o*-F; IV R=H, R¹=*m*-F; V R=H, R¹=*p*-F; VI R=H, R¹=*o*-Br; VII R=H, R¹=*o*-Cl; VIII R=H, R¹=*o*-CH_3; IX R=H, R¹=*o*p-$(CH_3O)_2$; X R=H, R¹=*o*-I; XI R=CH_3; R¹=H; XII R=H, R¹=*m*-F; XIII R=H, R¹=*p*-F; XIV R=CH_3, R¹=H; XV R=H, R¹=*o*-F; XVI R=H, R¹=*o*-Br

6-Arylpyridothiazines XIII and XIV were also synthesized by reaction of 2-mercapto-3-amino-6-chloropyridine (II) with p-fluorophenacyl halide and bromophenyl isopropyl ketone, respectively.

*See [1] for communication XXIX.

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TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C[a]	Empirical formula	Found, %					Calc., %					Yield, %
			C	H	Cl	N	S	C	H	Cl	N	S	
III	195—197	$C_{14}H_{11}ClFN_3O_2S$	49,6	3,0	10,5	12,2	9,6	49,5	3,2	10,4	12,4	9,4	99
IV	217—219	$C_{14}H_{11}ClFN_3O_2S$	49,8	3,1	10,2	12,2	9,2	49,5	3,2	10,4	12,4	9,4	53
V	205—207	$C_{14}H_{11}ClFN_3O_2S$	49,8	2,9	10,4	12,4	9,7	49,5	3,2	10,4	12,4	9,4	59
VI	205—207	$C_{14}H_{11}BrClN_3O_2S$	42,0	3,0	28,7*	10,5	8,3	41,9	2,7	28,8*	10,5	8,0	88
VII	184—185	$C_{14}H_{11}Cl_2N_3O_2S$	47,2	3,3	19,6	12,1	9,4	47,3	3,1	19,7	11,8	9,0	75
VIII	190—192	$C_{15}H_{14}ClN_3O_2S$	53,8	4,2	10,4	12,3	9,6	53,6	4,2	10,6	12,5	9,5	85
IX	175—177	$C_{16}H_{16}ClN_3O_4S$	50,2	4,4	9,1	11,2	8,5	50,3	4,2	9,3	11,0	8,4	77
X	187—189	$C_{14}H_{11}ClIN_3O_2S$[b]	37,3	2,2	—	9,3	7,1	37,5	2,4	—	9,4	7,1	84
XI	170—172	$C_{16}H_{16}ClN_3O_2S$	54,7	4,4	10,0	11,8	9,4	54,9	4,6	10,1	12,0	9,1	57
XII	152—154	$C_{13}H_8ClFN_2S$	56,4	3,0	—	10,3	11,9	56,0	2,9	—	10,0	11,5	34
XIII	142—144	$C_{13}H_8ClFN_2S$	55,8	3,1	—	10,4	11,5	56,0	2,9	—	10,0	11,5	75
XIV	95—96	$C_{15}H_{13}ClN_2S$	62,3	4,6	12,5	10,0	11,3	62,4	4,5	12,3	9,7	11,1	66
XV	225—227	$C_{20}H_{15}ClFN_7O_5S$	46,3	3,2	6,7	18,8	6,8	46,2	2,9	6,8	18,9	6,2	88
XVI	188—190	$C_{20}H_{15}BrClN_7O_5S$[c]	41,3	2,4	20,2	—	5,9	41,3	2,6	19,9	—	5,5	82

[a]Compounds III, X-XIII, and XVI were crystallized from ethanol, IV-IX and XV were crystallized from dimethylformamide–water (1 : 2), and XIV was crystallized from benzene. [b]Found: I 28.9%. Calculated: I 28.4%. [c]Found: Br + Cl 16.6%. Calculated: Br + Cl 16.9%.

The structures of 2-phenacylthio-3-ureidopyridines III-XI and 6-arylpyridothiazines XII-XIV were confirmed by means of IR and PMR spectroscopy. The IR spectra of III-XI contain the absorption bands of ketone and amide CO groups (1650-1690 cm^{-1}) and NH and NH_2 groups (3450-3480, 3340-3360, and 3250-3290 cm^{-1}), which are absent in the spectra of XII-XIV. A singlet from the protons of the CH_2 group is observed in the PMR spectra of XII and XIII; this is in agreement with their 7H structure.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer spectrometer. The UV spectra of alcohol solutions were recorded with an EPS-3 spectrophotometer. The PMR spectra were recorded with a JNM 4H spectrometer (100 MHz) with tetramethylsilane as the internal standard. The compounds were chromatographed on Silufol UV-254 in benzene–n-heptane–ethyl acetate–ethanol (19 : 1 : 2 : 2). The chromatograms were developed with concentrated H_2SO_4 and examined in UV light. Data on III-XIV are presented in Table 1.

2-Fluorophenacylthio-3-ureido-6-chloropyridine (III). A solution of 0.8 g (4.8 mmole) of a o-fluorophenacyl chloride in 5 ml of ethanol was added at 18-20° to a solution of 1.0 g (4.8 mmole) of I in 15 ml of ethanol containing 0.3 g (4.9 mmole) of KOH, and the mixture was stirred for 3 h. The resulting precipitate was removed by filtration, washed successively with water and petroleum ether, and dried to give 1.44 g of colorless crystals. PMR spectrum in C_5D_5N: 4.71 ppm (2H, CH_2).

Compounds X and XI were similarly obtained. PMR spectrum of XI in $CDCl_3$: 1.58 ppm (6H, two CH_3 groups).

4-Fluorophenacylthio-3-ureido-6-chloropyridine (V) and 2-Chloro-6-(4-fluorophenyl)-7H-pyrido-[2,3-b][1,4]thiazine (XIII). The method used to prepare compound III was used to obtain these compounds from 1.5 g (7.3 mmole) of I and 1.2 g (6.8 mmole) of 4-fluorophenacyl chloride. The reaction was carried out at −5 to −10°, and the yield of colorless crystals of V with R_f 0.09 was 1.47 g (59%). The filtrate remaining after separation of V was poured into water, and the resulting precipitate was removed by filtration, washed successively with water and petroleum ether, and dried to give 0.51 g of light-yellow needles of XIII (25%). PMR spectrum in $CDCl_3$: 4.02 ppm (2H, 7-CH_2).

The method used to prepare V was used to synthesize IV and VI-IX. In the preparation of IV, pyridothiazine XII was additionally isolated from the filtrate. PMR spectra: 3.18 ppm (2H, CH_2) for VI in $CDCl_3$, 2.43 ppm (3H, CH_3) for VIII in C_5D_5N, and 4.65 ppm (2H, CH_2).

2-Chloro-6-(4-fluorophenyl)-7H-pyrido[2,3-b] [1,4]thiazine (XIII). A) A mixture of 0.3 g (0.88 mmole) of V in 6 ml of dimethylformamide and 1.5 ml of water was refluxed for 3-5 h, after which 10-15 ml of water was added, and the resulting precipitate was removed by filtration, washed with water, and dried to give 0.18 g (75%) of light-yellow needles of XIII with mp 142-144°.

B) A solution of 1.0 g (5.9 mmole) of 4-fluorophenacyl chloride in 10 ml of methanol was added to a solution of 1.0 g (6 mmole) of II in 15 ml of methanol containing 0.36 g (6 mmole) of KOH, and the mixture was stirred at 18-20° for 3-5 h and then allowed to stand for 12 h. The resulting precipitate was removed by filtration, washed successively with water and petroleum ether, and dried to give 1.1 g (63%) of XIII with mp 142-144° and R_f 0.55 (yellow spot). The IR spectra and chromatograms of the substances obtained by methods A and B were identical.

2-Chloro-6-phenyl-7,7-dimethylpyrido[2,3-b][1,4]thiazine (XIV). A) The method used to prepare XIII (method A) was used to obtain 0.47 g of light-yellow crystals of this compound.

B) A solution of 0.5 g (3 mmole) of II containing 0.18 g (3 mmole) of KOH was added to a solution of 0.6 g (2.6 mmole) of bromophenyl isopropyl ketone in 10 ml of methanol, and the solution was then stirred at 60° for 3 h, cooled, and filtered. The filtrate was vacuum evaporated to one third of its original volume, and 15-20 ml of water was added. The resulting precipitate was removed by filtration and worked up as indicated for XIII (method B) to give 0.59 g (66%) of a product with R_f 0.88. PMR spectrum in $CDCl_3$: 1.52 ppm (6H, two CH_3 groups).

2,4-Dinitrophenylhydrazones XV and XVI. These compounds were obtained as yellow crystals. IR spectrum of XV: 3500, 3240-3340 cm^{-1} (NH, NH_2), 1650 cm^{-1} (amide CO). IR spectrum of XVI: 3460, 3280-3350 cm^{-1} (NH, NH_2), 1680 cm^{-1} (amide CO); UV spectrum, λ_{max}, nm (log ε): 260 (4.18), 361 (4.16).

LITERATURE CITED

1. N. V. Sazonov and T. S. Safonova, Khim. Geterotsikl. Soedin., 1694 (1973).