INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XVII.* 5H-PYRIDINO[2,3-b]-1,4-THIAZINE

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6-Carbethoxymethyl-, 7-carbethoxy-, and 6,7-dicarbethoxy-5H-pyridinothiazines were obtained by reaction of 2-mercapto-3-amino-5-chloropyridine (I) and 2-mercapto-3-amino-6-chloropyridine (II) with esters of haloketo acids in alcohol in the presence of 1 mole of KOH. α-(3-Amino-6-chloro-2-pyridyl)mercaptooxalacetic acid diethyl ester and 2-chloro-6-hydroxy-6,7-dicarbethoxy-6,7-dihydropyridino[2,3-b]-1,4-thiazine are obtained by reaction of II with chloroxalacetic ester in alcohol in the presence of 1 mole of alkali at −10°C.

The reactions of 2-mercapto-3-amino-5-chloropyridine (I) and 2-mercapto-3-amino-6-chloropyridine (II) with esters of haloketo acids were studied in the development of investigations [1] to synthesize esters of pyridinothiazinecarboxylic, -acetic, and -dicarboxylic acids. Thus 6-carbethoxymethylpyridinothiazine (III) and 6,7-dicarbethoxypyridinothiazine (IV) (Table 1) were obtained by reaction of I with γ-chloroacetoacetic and chloroxalacetic esters in alcohol in the presence of 1 mole of alkali. 6-Carbethoxymethylpyridinothiazine (V) was similarly prepared by reaction of II with γ-chloroacetoacetic ester. It was subsequently found that 6- or 7-carbethoxy- and 6,7-dicarbethoxypyridinothiazines are more conveniently obtained by heating I or II in alcohol with the esters of the corresponding haloketo acids, in analogy with [2]. Compounds VI-X were synthesized via this method from I, α-chloroacetoacetic and chlorobenzoylacetic esters, and from II and chlorobenzoylacetic, chloroxalacetic, and bromopyruvic esters. Compounds III-X are stable, crystalline substances which, except for VIII, are quite soluble in organic solvents; III and V are colorless, while the remaining compounds are colored: IV, VI-VIII, and X are yellow, while IX is red. The structure of III-X as 5H derivatives is confirmed by spectral data, while their purity was confirmed by fixed-layer chromatography in systems 1-3.

The UV spectra of III-X differ in the position and intensity of the absorption maxima from the UV spectra of 6-aryl-7H-pyridino[2,3-b]-1,4-thiazines [3]. Thus, in the spectra of IV and VI-IX, one observes three maxima at 224-231, 243-247, and 371-375 nm for IV and VII-IX, while for VI the second maximum was shifted bathochromically by 30 nm (Table 2). In the case of 6-carbethoxymethylpyridinothiazines III and V, only two maxima are observed (at 263-267 and 333-339 nm), probably because of the absence of conjugation of the COOR group with the thiazine ring.

The IR spectra of IV and VI-X have an intense band from the NH group (3320-3330 cm^{-1}) which attests to their 5H-pyridinothiazine structure. However, the band of the NH group in the IR spectra of 6-carbethoxymethyl derivatives III and V is of low intensity and is split and shifted to 3200 cm^{-1}, probably because of association with the COOR group. The structure of compounds III and V as 5H rather than 7H derivatives is confirmed by the presence in the PMR spectra of signals from the olefin proton with chemical shifts of 4.82 and 5.45 ppm, respectively. No signals from the methine protons are observed in the PMR spectra of 6,7-disubstituted 5H-pyridinothiazines IV and IX.

*For Communication XVI, see [5].

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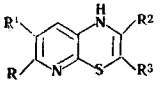
TABLE 1.



Comp.	R	R¹	R²	R³	mp	Empirical formula*	Found, %					Calc., %					Yield, %
							C	H	Cl	N	S	C	H	Cl	N	S	
III	H	Cl	$CH_2COOC_2H_5$	H	125—126	$C_{11}H_{11}ClN_2O_2S$	48,60	3,88	13,27	10,36	11,94	48,78	4,06	13,11	10,35	11,83	77
IV	H	Cl	$COOC_2H_5$	$CO_2C_2H_5$	186—187	$C_{13}H_{13}ClN_2O_4S$	47,30	3,67	10,87	8,22	9,83	47,48	3,95	10,80	8,52	9,74	99
V	Cl	H	$CH_2CO_2C_2H_5$	H	143—144	$C_{11}H_{11}ClN_2O_2S$	48,94	3,99	13,27	10,27	11,99	48,78	4,06	13,11	10,35	11,83	77
VI	H	Cl	CH_3	$CO_2C_2H_5$	208—210	$C_{11}H_{11}ClN_2O_2S$	48,44	3,83	12,90	10,10	11,60	48,78	4,06	13,11	10,35	11,83	74
VII	H	Cl	C_6H_5	$CO_2C_2H_5$	228—230	$C_{16}H_{13}ClN_2O_2S$	58,05	4,00	10,88	8,71	9,65	57,74	3,90	10,67	8,42	9,62	82
VIII	Cl	H	C_6H_5	$CO_2C_2H_5$	226—228	$C_{16}H_{13}ClN_2O_2S$	57,67	4,04	10,83	8,44	9,58	57,74	3,90	10,67	8,42	9,62	74
IX	Cl	H	$CO_2C_2H_5$	$CO_2C_2H_5$	147—148	$C_{13}H_{13}ClN_2O_4S$	47,69	3,96	11,06	8,46	9,85	47,48	3,95	10,80	8,52	9,74	90
X	Cl	H	$CO_2C_2H_5$	H	228—230	$C_{10}H_9ClN_2O_2S$	46,89	3,29	14,13	10,82	12,74	46,78	3,50	13,84	10,91	12,47	83

*The IR spectra of III-X in the form of suspensions in mineral oil were obtained with a UR-10 spectrophotometer. The vibrational frequencies of the CO groups of the ester and the NH groups are presented (cm^{-1}): III – 1670, 3230, 3270; IV – 1715, 1745, 3260; V – 1670, 3220, 3270; VI – 1710, 3300; VII – 1645, 3330; VIII – 1645, 3330; IX – 1665, 1745, 3330; X – 1730, 3360. The PMR spectra were obtained with an INM-4H-100 spectrometer at 100 MHz. The internal standard was HMDS. The compound, solvent, and chemical shift δ (ppm) are as follows: III, C_5H_5N, 1.05 (triplet), 4.11 (quartet), OCH_2CH_3, 4.70 (singlet, 2H-6-CH_2), 5.43 (singlet, 1H-7-CH); IV, CHCl, 1.29 (two triplets), 4.23 (two quartets), 2-OCH_2CH_3; V, $CHCl_3$, 1.29 (triplet), 4.18 (quartet), OCH_2CH_3, 3.55 (singlet, 2H-6-CH_2), 4.82 (singlet, 1H-7-CH); VIII, C_5H_5N, 0.70 (triplet), 3.84 (quartet), OCH_2CH_3; IX, $CHCl_3$, 1.30 (two triplets), 4.21 (two quartets), OCH_2CH_3; VI, C_5H_5N, 1.29 (triplet), 4.15 (quartet), OCH_2CH_3, 2.22 (singlet, 3H-6-CH_3). The substances were chromatographed on a fixed layer (KSK silica gel–gypsum). The chromatograms were developed with concentrated H_2SO_4 using systems 1-3. System 1 was benzene–n-heptane–ethyl acetate (19 : 1 : 1), system 2 was benzene-n-heptane–ethyl acetate–ethanol (19 : 1 : 1 : 2), system 3 was benzene-n-heptane–ethyl acetate (25 : 1 : 1). The R_f values for III, V-VI, and IX in system 1, for IV and VIII in system 2, and for VII in system 3 are indicated as follows: III, 0.54 (rose spot); V, 0.69 (yellow spot); VI, 0.34 (orange spot); IX, 0.28 (yellow spot); IV, 0.87 (yellow spot); VIII, 0.47 (yellow spot); VII, 0.52 (yellow spot).

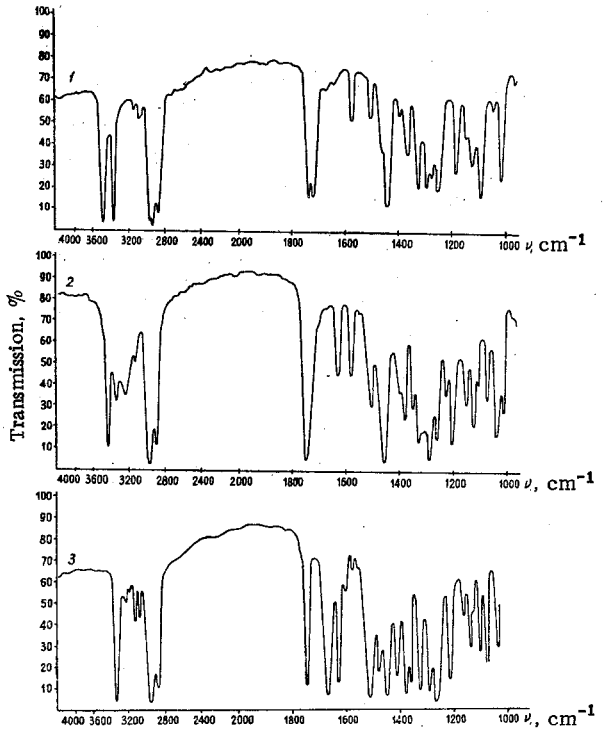


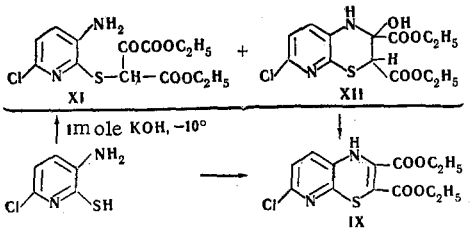
Fig. 1. IR spectra: 1) XI; 2) XII; 3) IX.

TABLE 2. UV Spectra of 5H-Pyridino[2,3-b]-1,4-thiazines (in alcohol)

Comp.	λ_{max}, nm	lg ε	λ_{min}, nm	lg ε
III	263 339	4,35 4,43	231 291	3,74 3,67
IV	227 247 375	4,20 4,19 3,61	238 306	4,15 2,65
V	267 333	4,15 4,41	231 291	3,72 3,61
VI	224 278 382	4,36 3,88 3,75	267 306	3,87 2,78
VII	231 247 377	4,17 4,17 3,41	241 316	4,17 3,13
VIII	224 244 371	4,04 4,27 3,77	239 315	4,15 3,18
IX	221 243 372	4,34 4,21 3,77	237 307	4,21 3,87

The diethyl ester of α-(3-amino-6-chloro-2-pyridyl)mercaptooxalacetic acid (XI) was obtained by reaction of II with chloroxalacetic ester under mild conditions (in alcohol at −10°, 1 mole of KOH). An extremely unstable substance, which is apparently cyclic hydroxyamino compound XII, was isolated from the alcoholic mother liquor. (See scheme, page 1274.) Only pyridinothiazine IX is obtained from the alcoholic mother liquor if it is allowed to stand for 1-1.5 h at 18-20°.

Investigation of the properties of XI indicated that, like 2-phenacylmercapto-3-aminopyridines [3,4], it is colorless, does not have a sharp melting point, and is converted to pyridinothiazine IX on standing in air, in polar solvents, and also under the influence of acetic anhydride. The IR spectrum of XI has absorption bands which correspond to the C=O groups in the ketone and ester, as well as a NH_2 group (Fig. 1).



Signals from the methine proton, with a chemical shift at 4.96 ppm, and from the protons of the $COOC_2H_5$ group are observed in the PMR spectrum, which agrees with the XI structure.

Compound XII is a cyclic isomer of XI and has the same elementary composition but, in contrast to XI, is yellow and still more unstable. The IR spectrum does not have a band at 1725 cm^{-1}, which apparently belongs to the C=O group in the ketone, while bands characteristic for cyclic hydroxyamino compounds [3] are present at 3200-3500 cm^{-1}. One of these is more intense at 3400 cm^{-1}, while the other is broad at 3200-3320 cm^{-1} (Fig. 1). Compound XII is quantitatively cyclized to pyridinothiazine IX in alcohol at 18-20°. The band at 3200-3320 cm^{-1} vanishes in the IR spectrum of IX, and a sharp band from the NH group (3400 cm^{-1}) is observed (Fig. 1).

Thus it has been established that the reaction of I and II with esters of haloketo acids in the presence of equimolecular amounts of alkali proceeds similarly to the reaction of phenacyl halides [3,4] with the formation of intermediates XI and XII.

EXPERIMENTAL

3-Chloro-6-carbethoxymethyl-5H-pyridino[2,3-b]-1,4-thiazine (III). A solution of 0.5 g (0.003 mole) of γ-chloroacetoacetic ester in 2 ml of ethanol was added to a solution of 0.5 g (0.003 mole) of I in 10 ml of ethanol containing 0.18 g (0.003 mole) of KOH at 18-20°. The mixture was stirred for 3 h and filtered. The filtrate was evaporated in vacuo to one-third of its initial volume, 10 ml of water was added to the residue, and the mixture was allowed to stand overnight. The precipitate was filtered and washed with water to give 0.65 g (77.3%) of III. This was recrystallized from ethanol (see Table 1).

Compounds IV and V were synthesized under similar conditions from I and diethylether, chloroxalacetic acid, II, and γ-chloroacetoacetic ester, respectively.

3-Chloro-6-methyl-7-carbethoxy-5H-pyridino[2,3-b]-1,4-thiazine (VI). A mixture of 0.5 g (0.003 mole) of I and 0.5 g (0.003 mole) of α-chloroacetoacetic ester in 10-15 ml of ethanol was refluxed for 30 min. The solution was poured into 15-20 ml of water, and the precipitate was filtered and washed with water to give 0.62 g (74%) of VI with mp 208-210° (ethanol).

3-Chloro-6-phenyl-7-carbethoxy-5H-pyridino[2,3-b]-1,4-thiazine (VII). A mixture of 0.5 g (0.003 mole) of I and 0.7 g (0.003 mole) of ethyl chlorobenzoyl acetate in 15 ml of ethanol was refluxed for 1.5-2 h and the precipitate was filtered and washed with water to give 0.4 g of VII with mp 222-224°. The filtrate was evaporated in vacuo to one-third of its original volume, and the precipitate was filtered and washed with water to give an additional 0.45 g of VII with mp 221-223°.

Compounds VIII and X were similarly synthesized from II and ethyl chlorobenzoylacetate and ethyl bromopyruvate, respectively.

2-Chloro-6,7-dicarbethoxy-5H-pyridino[2,3-b]-1,4-thiazine (IX). This compound was obtained in the same way as VI with the difference that the hot solution was filtered, evaporated in vacuo to one-third of its original volume, and the precipitate was filtered and washed with water.

α-(3-Amino-6-chloro-2-pyridyl)mercaptooxalacetic Diethyl Ester (XI), 2-Chloro-6-hydroxy-6,7-dicarbethoxy-6,7-dihydropyridino[2,3-b]-1,4-thiazine (XII), and 2-Chloro-6,7-dicarbethoxy-5H-pyridino-[2,3-b]-1,4-thiazine (IX). A solution of 0.6 g (0.0026 mole) of chloroxalaceticdiethyl ester in 5 ml of ethanol was added at −10° to a solution of 0.5 g (0.003 mole) of II in 10 ml of ethanol containing 0.18 g (0.003 mole) of KOH. The mixture was stirred for 2 h at this temperature, and the precipitate was filtered and washed with water to give 0.61 g (57.1%) of XI. A sample for analysis was recrystallized from ethyl acetate. The colorless crystals did not have a sharp melting point, were soluble in alcohol, acetone, chloroform, dimethylformamide, pyridine, and dioxane, and insoluble in ether and carbon tetrachloride. IR

spectrum (in mineral oil) (cm^{-1}): 1725, 1740 (ketone CO, ester); 3380, 3490 (NH). PMR spectrum (in C_5H_5N): 0.97, 1.04 ppm (two triplets); 3.98, 4.09 (two quartets, 2-OCH_2CH_3); 4.96 ppm (singlet, 1H-2-CH). Found %: C 44.93; H 4.43; Cl 10.14; N 8.18; S 9.41. $C_{13}H_{15}ClN_2O_5S$. Calculated %: C 45.02; H 4.32; Cl 10.24; N 8.08; S 9.23.

The filtrate was evaporated in vacuo to one-third of its original volume, 10-15 ml of water was added to the residue, and it was washed with water to give 0.25 g (23.3%) of XII in the form of light-yellow crystals which did not have a sharp melting point.* IR spectrum in mineral oil: 1740, 3200-3280, 3380, 3400, 3500 cm^{-1}. Found %: C 45.05; H 4.37. $C_{13}H_{15}ClN_2O_5S$. Calculated %: C 45.02; H 4.32.

The filtrate after removal of XI was evaporated to dryness in vacuo, 10-15 ml of water was added to the residue, and the mixture was allowed to stand at 18-20° for 2-3 days to give IX with mp 147-148° (ethanol). Mixing of a sample of this product with a known sample of IX did not depress the melting point. The substance was spectrally similar to IX, described above.

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*It cyclized to pyridino[2,3-b]-1,4-thiazine (IX) when attempts were made to determine the melting point, recrystallize it, and chromatograph it.