NITROGEN-, OXYGEN-, AND SULFUR-CONTAINING HETEROCYCLES.

43.* SYNTHESIS AND PROPERTIES OF 6-OXO-5H-PYRIDO[2,3-b][1,4]THIAZINES

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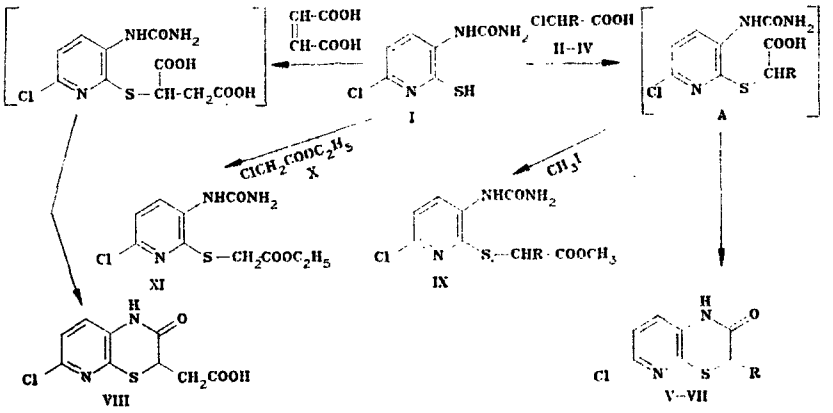
It has previously been observed that the carbamide residue in 2-phenacyl-3-ureido- and 2-cyanomethylpyridine is readily cleaved on cyclization to pyridothiazines [1-4]. It was of interest to establish whether a similar process occurs when the carbonyl component is an α-halo- or unsaturated acid. If this were the case, this reaction could be used to obtain 6-oxopyrido[2,3-b][1,4]thiazines.

It has been shown that 2-mercapto-3-ureido-6-chloropyridine (I) reacts with chloroacetic (II), α-bromobutyric (III), and α-bromovaleric acids (IV) in the presence of a twofold excess of alkali, followed by acidification with acetic acid, to give the 6-oxypyridothiazines (V-VII).



II, V R=H; III, VI R=C_2H_5; IV, VII R=C_4H_9

When this reaction was carried out with bromomalonic acid, cyclization was accompanied by decarboxylation to give in addition the pyridothiazinone (V). Reaction with unsaturated acids such as maleic acid afforded 2-chloro-6-oxo-7-carboxymethyl-5H-pyrido[2,3-b][1,4]thiazine (VIII). The reaction was carried out by heating the reactants without a solvent and in the absence of alkali.

In all instances, the cyclization proceeded so readily that it was not possible to isolate the intermediate 2-alkylthio-3-ureidoacids (A). Formation of the latter was established only when the product of the reaction of (I) with the acid (II) was treated with methyl iodide in the presence of alkali, when the ester (IX) was obtained. It was also found that when the reaction was carried out with ethyl chloroacetate (X) as the carbonyl component, the reaction stopped at the open structure, namely, the S-ethoxycarbonyalkyl derivative (XI). Examination of the properties of (IX) and (XI) showed them, unlike the intermediates (A) which have an "open" carboxyl group, to be stable compounds which did not cyclize to pyridothiazinones on treatment with alkalies or acids. The IR and PMR spectra of pyridothiazinones (V-VIII) confirmed their lactam structure. The IR spectra showed CO (1670 cm^{-1}) and amide NH absorption (3100, 3200 cm^{-1}), and the PMR spectrum of the thiazinone (V) contained signals for the aromatic protons (7.0 and 7.2 ppm) and the $C_{(7)}$ proton (3.5 ppm).

*For communication 42, see [6].

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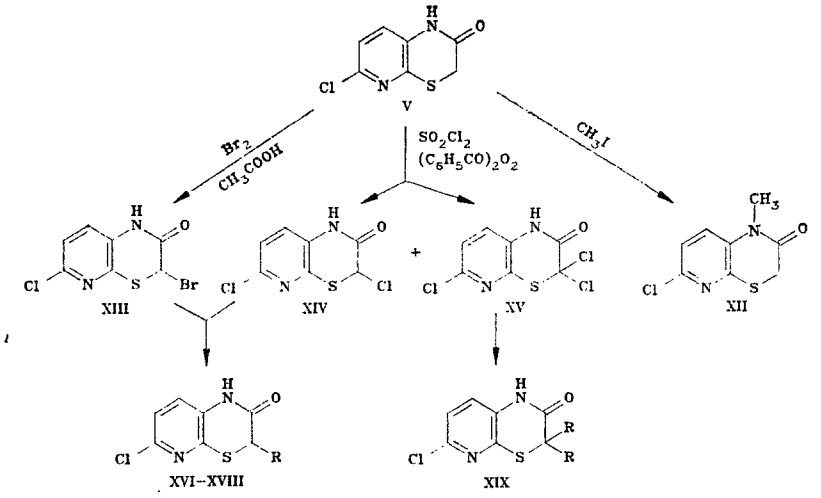
Some properties of the pyridothiazinones have been examined. Like most heterocyclic lactams, the pyridothiazinones are alkylated by alkyl halides to give the N-aryl derivatives (XII). On treatment with bromine in acetic acid, the thiazinone (V) is converted into the 7-bromothiazinone (XIII), and reaction of (V) with sulfuryl chloride in the presence of benzoyl peroxide affords the 7-chloro- (XIV) or 7,7-dichloro- (XV) derivative. The structures of the halothiazines (XIII-XV) were confirmed by their PMR spectra. In the case of the 7-halo derivatives (XIII) and (XIV), the PMR spectra contained a signal for the $C_{(7)}$ protons at 4.8-4.9 ppm, the signal for the CH_2 group present in the original compound being absent. In the spectra of the 7,7-dihaloderivatives, signals for neither the 7-CH nor 7-CH_2 were seen. It has been found that the halogen atoms in (XIII-XV) reddily undergo nucleophilic substitution.



XVI R=morpholinyl; XVII R=S—CH_2—COOH; XVIII R=$COOCH_3$; XIX R=OCH_3

Reaction of the thiazinones (XIII) and (XIV) with morpholine gives the 7-N-morpholinopyridothiazinone (XVI); reaction of the thiazinone (XIII) with thioglycollic acid gives the 7-carboxymethylthiopyridothiazinone (XVII); and reaction of the thiazinone (XIII) with sodium acetate affords the 7-methoxycarbonylpyridothiazinone (XVIII). Treatment of the thiazinone (XV) with methanol gave the 7,7-dimethoxypyridothiazinone (XIX).

EXPERIMENTAL

The IR spectra were obtained on a Perkin-Elmer twin-beam UR-10 spectrophotometer; the PMR spectra, on a JNH-4H-100 instrument, internal standard DMSO. The data are given in Table 1.

2-Chloro-6-oxo-5H-pyrido[2,3-b][1,4]thiazine (V). A. To a solution of 1 g (5 mmoles) of the pyridine (I) in 25 ml of ethanol containing 1.1 g (10 mmoles) of KOH was added at 18-20°C over 1 h a solution of 0.46 g (5 mmoles) of chloroacetic acid (II) in 15 ml of ethanol. The mixture was stirred for 4 h; the ethanol was distilled off *in vacuo*; and the residue was triturated with water, acidified with acetic acid, and extracted with ethyl acetate. The ethyl acetate was distilled off *in vacuo*, and the residue was triturated with ether to give 0.9 g of the thiazine (V).

B. To a solution of 0.6 g (2.9 mmoles) of (I) in 30 ml of ethanol containing 0.5 g (8.7 mmole) of KOH was added at 18-20°C over 30 min a solution of 0.54 g (2.9 mmoles) of bromomalonic acid in 15 ml of ethanol. The mixture was stirred for 1.5 h; the bis(3-amino-6-chloro-2-pyridyl) disulfide formed as a by-product was filtered off and washed with water. The aqueous washings were acidified with acetic acid and extracted with ether. The ether was distilled off *in vacuo* to give 0.25 g of the thiazine (V).

2-Chloro-6-oxo-7-ethyl-5H-pyrido[2,3-b][1,4]thiazine (VI). To a solution of 1 g (5 mmoles) of (I) in 20 ml of ethanol containing 0.56 g (10 mmoles) of KOH was added at 0°C over 1 h a solution of 0.84 g (5 mmoles) of α-bromobutyric acid (III) in 15 ml of ethanol. The mixture was stirred for 2 h at 18-20°C; the ethanol was distilled off *in vacuo*; and the residue was triturated with water, acidified with acetic acid, and extracted with ethyl acetate. The ethyl acetate was distilled off *in vacuo*, and the residue was triturated with

TABLE 1. Properties of (V-IX) and (XI-XIX)

Compound	M_p*, °C	IR spectrum ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm	Found, %					Empirical formula	Calculated, %					Yield, %
					C	H	Cl	N	S		C	H	Cl	N	S	
V	248—250	1670 (CO), 3200 (NH)		3,6 ($7CH_2$)	42,2	2,3	17,5	13,9	16,2	$C_7H_5ClN_2S$	41,9	2,5	17,7	13,9	16	90
VI	193—195	1670 (CO), 3200 (NH)			47,2	4,2	15,4	12,1	13,9	$C_9H_9ClN_2OS$	47,2	4,0	15,5	12,2	14,0	49
VII	206—208	1670 (CO), 3200 (NH)			51,4	4,9	13,9	11,3	12,4	$C_{11}H_{13}ClN_2OS$	51,5	5,1	13,8	10,9	12,4	52
VIII	232—234	1670 (CO амида), 1730 (CO карбоксил), 3100 (NH)	308 (3,47)		41,9	2,7	13,4	10,6	12,3	$C_9H_7ClN_2O_3S$	41,8	2,7	13,7	10,8	12,4	79
IX	206—208	1670 (CO амида)/1730 (CO), 3290, 3350, 3400 (NH, NH_2)			39,0	3,9	12,8	15,3	11,8	$C_9H_{10}ClN_3OS$	39,2	3,7	12,8	15,6	11,6	52
XI	199—201 [5]	1730 (CO эфира), 1680 (CO амида), 3280, 3460, 3320 (NH, NH_2)			41,2	3,9	12,0	14,5	11,3	$C_{10}H_{12}ClN_3O_3S$	41,4	4,1	12,2	14,5	11,1	57
XII	191—193	1670 (CO)			44,5	3,5	16,3	12,9	14,7	$C_8H_7ClN_2OS$	44,7	3,3	16,5	13,1	14,9	80
XIII	225—226	1700 (CO), 3400 (NH)	310 (3,95)	6,32 (7CH); 7,1; 7,2 (3CH, 4CH)	30,0	1,8		9,9	11,6	$C_7H_4BrClN_2OS$	30,0	1,5		10,0	11,4	70
XIV	222—224	1670 (CO), 3200 (NH)			35,6	11,7	30,2			$C_7H_4Cl_2N_2OS$	35,8	11,7	30,1			85
XV	213—214	1670 (CO), 3100 (NH)					38,9			$C_7H_3Cl_2N_2OS$			39,4			74
XVI	248—250	1680 (CO), 3350 (NH)	312 (3,92)	4,9 (7CH)	46,0	4,2	12,2	14,6	11,0	$C_{11}H_{12}ClN_3O_2S$	46,2	4,2	12,4	14,7	11,2	98
XVII	222—224	1670 (CO амида), 1700 (карбоксил), 3200 (NH)			36,9	2,2	12,3	9,4	21,6	$C_9H_7ClN_2O_3S_2$	37,1	2,4	12,2	9,6	22,0	50
XVIII	211—213	1660 (CO амида), 1760 (CO эфира), 3180 (NH)		2,0 (CH_3); 6,39 (7CH); 7,23; 7,38 (3CH, 4CH)	42,0	2,8	14,0	10,9	12,0	$C_8H_7ClN_2O_3S$	41,8	2,7	13,7	10,8	12,4	77
XIX	205—207	1670 (CO), 3150 (NH)			41,9	3,5	13,5	10,6		$C_9H_9ClN_2O_3S$	41,5	3,4	13,6	10,7		90

*Compounds (V-XII), (XVI), and (XVII) were recrystallized from ethanol, (XIII-XV) from toluene, and (XIX) from benzene.

ether to give 0.2 g of (VI). The ether mother liquors were evaporated *in vacuo* to give a further 0.35 g of (VI).

2-Chloro-6-oxo-7-butyl-5H-pyrido[2,3-b][1,4]thiazine (VII). To a solution of 0.5 g (2.5 mmoles) of (I) in 25 ml of ethanol containing 0.28 g (5 mmoles) of KOH was added at 20°C over 1 h a solution of 0.45 g (2.5 mmoles) of α-bromovaleric acid (IV) in 15 ml of ethanol. The mixture was stirred at 18-20°C for 3 h, evaporated to dryness *in vacuo*, triturated with water, and acidified with acetic acid; the solid was filtered off to give 0.25 g of (VII). A further 0.1 g of (VII) was obtained from the mother liquors.

2-Chloro-6-oxo-7-carboxymethyl-5H-pyrido[2,3-b][1,4]thiazine (VIII). A mixture of 0.5 g (2.5 mmoles) of (I) and 0.29 g (2.5 mmoles) of maleic acid was heated for 20 min at 130°C, cooled to 18-20°C, dissolved in aqueous NaOH, acidified with acetic acid, and extracted with ethyl acetate; the ethyl acetate was distilled off to dryness; and the residue was triturated with a mixture of ether and light petroleum. The solid was filtered off to give 0.5 g of (VIII).

2-Carboxymethylthio-3-ureido-6-chloropyridine (IX). To the ethanol solution from the preparation of the pyridothiazinone (V), supposedly containing 0.9 g (3.4 mmoles) of 2-carboxymethyl-3-ureido-6-chloropyridine, was added 3.5 ml of iodomethane, and the mixture was boiled for 3 h. The ethanol was removed completely *in vacuo*, and the residue was triturated with ether to give 0.5 g of (IX).

2-Ethoxycarbonylmethylthio-3-ureido-6-chloropyridine (XI). To a solution of 0.3 g (2.5 mmoles) of ethyl chloroacetate in 10 ml of ethanol was added at 0°C over 15 min a solution of 0.5 g (2.5 mmoles) of (I) in 20 ml of ethanol containing 0.14 g (2.5 mmoles) of KOH. The mixture was stirred for 1 h at 0°C, and the solid was filtered off to give 0.15 g of (XI). The alcoholic mother liquors were evaporated to dryness *in vacuo*, and the residue was triturated with water to give a further 0.25 g of (XI).

2-Chloro-5-N-methyl-6-oxopyrido[2,3-b][1,4]thiazine (XII). To a solution of 0.7 g (3.5 mmoles) of the thiazinone (V) in 30 ml of anhydrous ethanol containing 0.14 g (3.5 mmoles) of KOH was added 3 ml of iodomethane, and the mixture was boiled for 3 h. The ethanol was distilled off *in vacuo*, the residue was triturated with ether, and the solid was filtered off to give 0.6 g of the thiazine (XII).

2-Chloro-6-oxo-7-bromo-5H-pyrido[2,3-b][1,4]thiazine (XIII). To a suspension of 0.5 g (2.5 mmoles) of the thiazinone (V) in 30 ml of glacial acetic acid containing 0.2 g (2.5 mmoles) of anhydrous soidum acetate was added over 1 h at 115-118°C a solution of 0.8 g (5 mmoles) of bromine in 5 ml of acetic acid. The mixture was boiled for 2 h at 118°C, the acetic acid was distilled off to dryness *in vacuo*, the residue was triturated with water, and the solid was filtered off to give 0.5 g of the thiazine (XIII).

2,7-Dichloro-6-oxo-5H-pyrido[2,3-b][1,4]thiazine (XIV). To a suspension of 1 g (5 mmoles) of the thiazinone (V) and 0.1 g (0.4 mmoles) of benzoyl peroxide in 30 ml of dry chlorobenzene was added at 120-125°C over 15-20 min a solution of 0.68 g (5 mmoles) of sulfuryl chloride in 10 ml of chlorobenzene. The mixture was boiled at 125°C for 2 h and cooled, and the solid was filtered off to give 0.8 g of (XIV). The chlorobenzene mother liquors were evaporated to dryness, and the residue was triturated with ether to give a further 0.2 g of (XIV).

2,7,7-Trichloro-6-oxo-5H-pyrido[2,3-b][1,4]thiazine (XV). To a suspension of 1 g (5 mmoles) of the thiazinone (V) and 0.2 g (0.8 mmole) of benzoyl peroxide in 30 ml of dry chlorobenzene was added at 120-125°C over 15 min a solution of 1.36 g (10 mmoles) of sulfuryl chloride in 10 ml of chlorobenzene. The mixture was boiled at 125°C for 2 h, the solution was evaporated to dryness *in vacuo*, the residue was triturated with light petroleum, and the solid was filtered off to give 1 g of (XV).

2-Chloro-6-oxo-7-morpholino-5H-pyrido[2,3-b][1,4]thiazine (XVI). A. To a suspension of 0.6 g (2.1 mmoles) of the thiazinone (XIII) in 15 ml of dry benzene was added a solution of 0.37 g (4.2 mmoles) of morpholine in 10 ml of benzene, and the mixture was stirred for 5 h. The solid was filtered off and washed with ether and water to give 0.6 g of (XVI).

B. As in procedure A above, from 1 g (4.2 mmoles) of the thiazinone (XIV) and 0.74 g (8.4 mmoles) of morpholine there was obtained 1 g of (XVI).

2-Chloro-6-oxo-7-carboxymethylthio-5H-pyrido[2,3-b][1,4]thiazine (XVII). To a suspension of 0.5 g (1.7 mmoles) of the thiazinone (XIII) in 15 ml of water was added a solution of 0.13 g (1.7 mmoles) of thioglycollic acid in 15 ml of water containing 0.16 g (3.4 mmoles) of KOH.

The mixture was heated to 80-90°C and stirred at this temperature for 2 h; then it was filtered hot, and the filtrate was cooled, acidified, and extracted with ethyl acetate. The ethyl acetate was distilled off *in vacuo*, and the residue was triturated with ether to give 0.25 g of (XVII).

2-Chloro-6-oxo-7-methoxycarbonyl-5H-pyrido[2,3-b][1,4]thiazine (XVIII). To a solution of 0.5 g (2.5 mmoles) of the thiazinone (V) in 25 ml of glacial acetic acid containing 2 g (24 mmoles) of anhydrous sodium acetate was added at the boil over 1 h a solution of 0.8 g (5 mmoles) of bromine in 5 ml of acetic acid. The mixture was boiled for 0.5 h and evaporated to dryness *in vacuo*, and the residue was triturated with water to give 0.5 g of (XVIII).

2-Chloro-6-oxo-7,7-dimethoxy-5H-pyrido[2,3-b][1,4]thiazine (XIX). The thiazinone (XV) (0.5 g, 1.8 mmoles) was dissolved in 30 ml of hot methanol and kept for 2 days. The solution was evaporated to dryness *in vacuo*, and the residue was triturated with water to give 0.43 g of (XIX).

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