INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XXII.* N-(3-PYRIDYL)OXAMIC ACID DERIVATIVES

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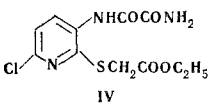
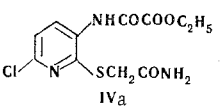
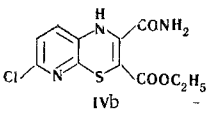
The reaction of (3-amino-6-chloro-2-pyridylmercapto)oxalacetic ester with ammonia, benzylamine, morpholine, and piperidine yielded amides, while the reaction of the ester with hydrazine hydrate gave [2-(ethoxycarbonylmethylthio)-3-pyridyl]oxamic acid hydrazide. The benzylamide and morpholide of this acid were obtained by treatment of 2-chloro-6-hydroxy-6,7-di(ethoxycarbonyl)dihydropyridothiazine with the appropriate amines. The reaction of 2-mercapto-3-amino-6-chloropyridine with chlorooxalacetic ester in the presence of alkali yielded potassium [2-(ethoxycarbonylmethylthio)-3-pyridyl]oxamate.

In a continuation of our research in [2], it was shown that (3-amino-6-chloro-2-pyridylmercapto)-oxalacetic ester (I) and 2-chloro-6-hydroxy-6,7-di(ethoxycarbonyl)dihydropyridothiazine (II) are converted by amines to amides of [2-(ethoxycarbonylmethylthio)-3-pyridyl]oxamic acid (IV-VIII) (Table 1). Thus treatment of ester I with 25% ammonium hydroxide yielded monoamide IV, for which structures IVa and IVb are also possible:


IV


IVa


IVb

The appearance of a singlet signal of a CH_2 group in the PMR spectrum of IV excludes structure IVb. Structure IV rather than IVa was adopted on the basis of the fact that the $COOC_2H_5$ group in the oxamic residue is more reactive than in the 2 position. If amide IV is not separated from the reaction medium, diamide V is formed in 3-4 h. The structure of V was confirmed by IR spectroscopy (the absence of absorption bands of the ester CO group) and also by its preparation by treatment of ethyl [2-(ethoxycarbonylmethylthio)-3-pyridyl]oxamate (III) with 25% ammonium hydroxide [3].

The reaction of ester I with benzylamine, morpholine, and piperidine in alcohol yielded the corresponding amides (VI-VIII), while the reaction of I with hydrazine hydrate gave hydrazide IX. Treatment of amide VII with 25% ammonium hydroxide yielded [2-(carboxamidomethylthio)-3-pyridyl]oxamic acid morpholide (X). Isopropylidene derivative XI was synthesized by refluxing hydrazide IX with acetone, while azide XII was synthesized by the Curtius reaction.

The formation of IV-IX from ester I probably proceeds through hydroxyamino compound II, in which the carbon-carbon bond is cleaved under the influence of alkali or amines to give diester III. The $COOC_2H_5$ group in the oxamic residue is then initially replaced by an amide group, followed by replacement of the ester grouping in the 2 position. This conclusion is confirmed by the fact that diester III is isolated after 2 h when hydroxyamino compound II is treated with morpholine in alcohol. If it is not separated from the

*See [1] for communication XXI.

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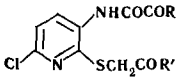
TABLE 1. 

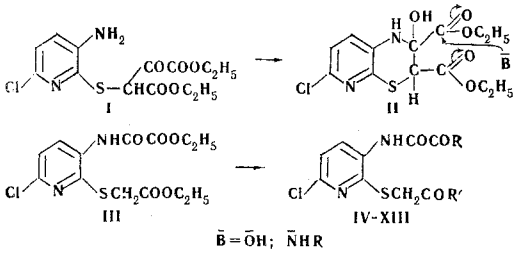
Compound	R	R′	mp, °C	λ_{max}	lg ε	Empirical formula	Found, %					Calc., %					Yield, %
							C	H	Cl	N	S	C	H	Cl	N	S	
IV	NH_2	OC_2H_5	177—179	222; 283	3,97; 3,94	$C_{11}H_{12}ClN_3O_4S$	41,2	3,8	11,1	13,2	10,1	41,6	3,8	11,2	13,2	10,1	83
V	NH_2	NH_2	238—240			$C_9H_9ClN_4O_3S$	37,7	3,1	12,1	19,1	10,8	37,4	3,1	12,3	19,4	11,1	95
VI	$NHCH_2C_6H_5$	OC_2H_5	145—147	227; 284	4,2; 4,0	$C_{18}H_{18}ClN_3O_4S$	52,6	4,4	8,7	10,5	7,9	53,0	4,4	8,7	10,3	7,8	83—97
VII	C_4H_8NO†	OC_2H_5	118—119	256; 300	4,0; 3,9	$C_{15}H_{18}ClN_3O_5S$	46,5	4,6	9,2	10,9	8,4	46,4	4,6	9,2	10,8	8,2	70—86
VIII	$C_5H_{10}N$‡	OC_2H_5	90—92	256; 300	4,0; 3,9	$C_{16}H_{20}ClN_3O_4S$	50,0	5,3	9,0	10,6	8,5	49,8	5,2	9,2	10,9	8,3	91
IX	$NHNH_2$	OC_2H_5	171—172	229; 278	4,14; 4,06	$C_{11}H_{13}ClN_4O_4S$	39,7	4,1	10,8	17,1	9,5	39,7	3,9	10,7	16,8	9,6	81
X	C_4H_8NO†	NH_2	194—196	257; 302	4,0; 3,9	$C_{13}H_{15}ClN_4O_4S$	43,1	4,3	9,8	15,8	9,1	43,5	4,2	9,9	15,6	8,9	97
XI	$NHN=C(CH_3)_2$	OC_2H_5	170—172	233; 278	4,2; 4,1	$C_{14}H_{17}ClN_4O_4S$	44,8	4,8	9,3	15,3	8,7	45,1	4,6	9,5	15,0	8,6	93
XII	N_3	OC_2H_5	73—74			$C_{11}H_{10}ClN_5O_4S$	38,4	2,9	10,3	20,4	9,3	38,4	3,1	10,4	20,6	9,2	73
XIII	OK	OC_2H_5	210—212			$C_{11}H_{10}ClN_2O_5SK$	35,8	2,9	9,9	7,6	—	36,1	2,7	9,7	7,6	—	59

*Compounds IV-XIII are colorless crystals. The following solvents were used to crystallize samples for analysis: ethanol for IV, VI-X, and XIII; dimethylformamide–water (1 : 2) for V; and acetone for XI; an analytically pure sample of XII was obtained by washing the compound two to three times with water and drying.

†Morpholino group.

‡Piperidino group.

reaction medium, morpholide VII is formed. Benzylamide VI was similarly obtained from II and benzylamine. It was demonstrated that only III is formed by the action of alcoholic triethylamine on I.



Potassium [2-(ethoxycarbonylmethylthio)-3-pyridyl]oxamate (XIII) was obtained by treatment of I and III with alcoholic alkali. In this case, just as in the case of amidation, the $COOC_2H_5$ group of the oxamic residue reacts first. It was found that the ester group in 2-(ethoxycarbonylmethylthio)-3-acetamido-6-chloropyridine [4] is not saponified under similar conditions. The structure of salt XIII was confirmed by its analytical and spectral characteristics.

Salt XIII can also be obtained by the reaction of 2-mercapto-3-amino-6-chloropyridine with chlorooxalacetic ester in alcohol in the presence of 2 moles of alkali without isolation of I-III. Under these conditions, the cyclization of I to II, cleavage of the carbon–carbon bond in II, and saponification of the ester group in III are accomplished in practically one step. Amides V and VII were similarly obtained but with 1 mole of alkali and subsequent treatment of the reaction product with the appropriate amines.

Thus it has been demonstrated that the reaction of 2-mercapto-3-amino-6-chloropyridine with chlorooxalacetic ester not only leads to pyrido[2,3-b][1,4]thiazines but also to various derivatives of 3-pyridyloxamic acid, which may be of interest for biological investigations [5].

EXPERIMENTAL

[2-(Ethoxycarbonylmethylthio)-6-chloro-3-pyridyl]oxamic Acid Amide (IV) and [2-(Carboxamidomethylthio)-6-chloro-3-pyridyl]oxamic Acid Amide (V). A mixture of 0.2 g (0.5 mmole) of I in 5 ml of 25% ammonium hydroxide was stirred at 18-20°C for 5-10 min. The resulting precipitate was filtered to give 0.15 g (83%) of IV with mp 175-176°. IR spectrum, cm^{-1}: 1715, 1670-1690 (ester CO, amide CO); 3400, 3300, 3270 (NH, NH_2). PMR spectrum (in C_5D_5N), ppm: 1.15 (triplet, CH_3), 4.16 (quartet, OCH_2), 4.20 (singlet, SCH_2). After removal of IV, the filtrate yielded (after 3-4 h) 0.02 g (12%) of V with mp 238-240°. This product did not depress the melting point of a known sample.

[2-(Carboxamidomethylthio)-6-chloro-3-pyridyl]oxamic Acid Amide (V). A) A mixture of 0.25 g (0.7 mmole) of III in 10 ml of 25% ammonium hydroxide was stirred at 18-20° for 3-4 h, and the resulting precipitate was removed by filtration to give 0.19 g (95%) of V with mp 231-233°. IR spectrum, cm^{-1}: 1700, 1670 (amide C=O); 3460, 3350, 3220 (NH, NH_2).

B) A solution of 0.6 g (2.6 mmole) of diethyl chlorooxalacetate in 5 ml of ethanol was added at -10° to a solution of 0.5 g (3 mmole) of 2-mercapto-3-amino-6-chloropyridine in 10 ml of ethanol containing 0.18 g (3 mmole) of KOH, and the mixture was stirred at this temperature for 2 h. The alcohol was removed by vacuum distillation to one third of the original volume, 10-15 ml of 25% ammonium hydroxide was added to the residue, and the mixture was worked up as in method A to give 0.56 g (63%) of a product with mp 238-240°. This product did not depress the melting point of the product obtained by method A.

[2-(Ethoxycarbonylmethylthio)-6-chloro-3-pyridyl]oxamic Acid Morpholide (VII). A) A solution of 0.46 g (5 mmole) of morpholine in 5 ml of ethanol was added at 18-20° to a mixture of 0.89 g (2.4 mmole) of I in 10 ml of ethanol, and the mixture was stirred for 5 h and allowed to stand overnight. The resulting precipitate was removed by filtration to give 0.86 g (86%) of morpholide VII with mp 110-113°. IR spectrum cm^{-1}: 1750, 1690 (ester C=O, amide C=O); 3250 (NH). PMR spectrum (in pentadeuteropyridine), ppm: 1.06 (triplet) and 4.17 (quartet, OCH_2CH_3), 3.45-3.84 [8H–$(CH_2)_2O(CH_2)_2N$]; 4.17 (singlet, 2H, 2-CH_2). Benzylamide VI and piperidide VIII were similarly obtained.

B) A solution of 0.2 g (2 mmole) of morpholine in 5 ml of ethanol was added at 18-20° to a mixture of 0.3 g (0.8 mmole) of II in 5 ml of ethanol, and the mixture was worked up as in method A to give 0.23 g (70%)

of VII with mp 118-119° (from ethanol). The IR spectra of the compounds synthesized by methods A and B were identical. Compound VI was similarly obtained.

C) A solution of 0.72 g (3.2 mmole) of diethyl chlorooxalacetate and 0.5 g (5.7 mmole) of morpholine in 5 ml of ethanol was added at 18-20° to a solution of 0.6 g (3.7 mmole) of 2-mercapto-3-amino-6-chloropyridine in 10 ml of ethanol containing 0.18 g (3 mmole) of KOH, and the mixture was stirred for 7-8 h and allowed to stand for 24-48 h to give 0.87 g (60%) of VII with mp 118-119° (from ethanol).

[2-(Ethoxycarbonylmethylthio)-6-chloro-3-pyridyl]oxamic Acid Hydrazide (IX). A solution of 0.17 g (3.4 mmole) of hydrazine hydrate in 5 ml of ethanol was added to a mixture of 0.6 g (1.7 mmole) of I in 10 ml of ethanol, and the mixture was stirred for 3 h. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.46 g (81%) of IX with mp 170-172°. IR spectrum, cm^{-1}: 1740, 1670-1690 (ester C=O, amide C=O); 3340, 3320, 3280 (NH, NH_2). The isopropylidene derivative (XI) was obtained as colorless crystals with mp 170-172° (from acetone). IR spectrum, cm^{-1}: 1740, 1670-1690 (ester C=O, amide C=O); 3260-3280 (NH).

[2-(Ethoxycarbonylmethylthio)-6-chloro-3-pyridyl]oxamic Acid Azide (XII). A solution of 0.18 g (2.6 mmole) of $NaNO_2$ in 2 ml of water was added at -5 to 0° to a solution of 0.4 g (1.2 mmole) of IX in 15 ml of glacial acetic acid, and the mixture was stirred for 1.5 h at this temperature. The mixture was filtered, and 30-40 ml of water was added to the filtrate. The precipitate was removed by filtration to give 0.3 g (73%) of colorless crystals with mp 73-74°. IR spectrum, cm^{-1}: 1720, 1690 (ester C=O, amide C=O), 3260 (NH), 2170 (N_3).

[2-(Carboxamidomethylthio)-6-chloro-3-pyridyl]oxamic Acid Morpholide (X). A mixture of 1.0 g (2.5 mmole) of VII in 10-15 ml of 25% ammonium hydroxide was held at 18-20° for 2-3 days to give 0.89 g (96%) of X with mp 190-192°. IR spectrum, cm^{-1}: 1700, 1645 (amide CO); 3380, 3310, 3180-3200 (NH, NH_2).

Potassium [2-(Ethoxycarbonylmethylthio)-6-chloro-3-pyridyl]oxamate (XIII). A) A solution of 0.6 g (2.6 mmole) of diethyl chlorooxalacetate was added at 18-20° to a solution of 0.5 g (3 mmole) of 2-mercapto-3-amino-6-chloropyridine in 10 ml of ethanol containing 0.36 g (6 mmole) of KOH, and the mixture was worked up under the conditions used to obtain VII (method A) to give 0.5 g of XIII. An additional 0.15 g of XIII was obtained from the filtrate after the ethanol was vacuum-evaporated to one third of the original volume. The overall yield of XIII was 59%. IR spectrum, cm^{-1}: 1740-1750, 1700-1710, 1645-1670 (C=O of ester, carboxyl, and amide groups).

B) A mixture of 0.3 g (0.8 mmole) of III in 5 ml of ethanol containing 0.07 g (1.2 mmole) of KOH was stirred at 18-20° and allowed to stand overnight. The resulting precipitate was removed by filtration and dried to give 0.28 g (90%) of XIII with mp 210-212°. This product did not depress the melting point of the compound obtained by method A.

C) A mixture of 0.2 g (0.6 mmole) of I in 5 ml of ethanol containing 0.05 g (0.8 mmole) of KOH was treated as described in method B to give 0.19 g (90%) of XIII with mp 210-212°. From its analytical characteristics, this compound was identical to the compound obtained by method A.

The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions were obtained with an EPS-3 spectrophotometer. The PMR spectra were measured with a JNM-4H spectrometer with an operating frequency of 100 MHz with tetramethylsilane as the internal standard. The proton signals are given in the δ scale.

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