INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XXVII.* DERIVATIVES OF N-(3-PYRIDYL)HYDROXAMIC ACID

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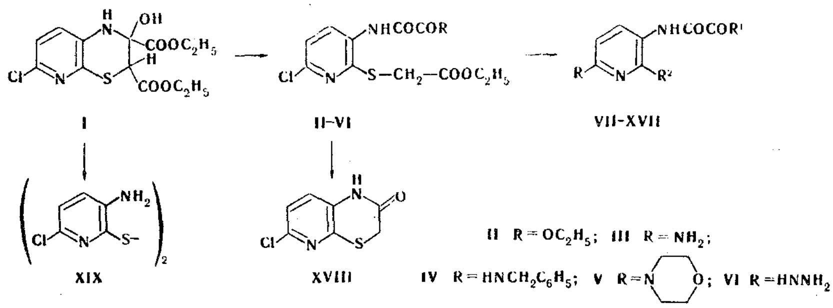
The corresponding N-(3-pyridyl)hydroxamic acid derivatives were obtained by reductive desulfuration of [2-(ethoxycarbonylmethylthio)-6-chloro-3-pyridyl]hydroxamic acid amide, benzylamide, and morpholide. The amides were synthesized by reaction of [2-(ethoxycarbonylmethylthio)-6-chloro-3-pyridyl]hydroxamic acid ester with diethylaminoethylamine and pyrrolidine. Heating of the ester and morpholide of [2-(ethoxycarbonylmethylthio)-6-chloro-3-pyridyl]hydroxamic acid with H_2SO_4 gives 2-chloropyrido[2,3-b][1,4]thiazin-6-one.

It has been shown that [2-(ethoxycarbonylmethylthio)-6-chloro-3-pyridyl] hydroxamic acid ester (II) or its amides (III-VI) are formed by the action of alkalies and amines on 2-chloro-6-hydroxy-6,7-di(ethoxycarbonyl)dihydropyridothiazine (I) [2, 3].

In a continuation of our earlier research [3], we investigated the properties and transformations of II, amides III-V and X-XIII, and hydrazide VI. It was shown that dehalogenation occurs along with desulfuration in the reductive desulfuration of III-V by means of Raney nickel, and amides of N-(3-pyridyl)-hydroxamic acid (VII-IX) are formed in 60-67% yields (Table 1).

The structures of VII-IX were confirmed by the spectral data. The absorption of an ester CO group is absent in the IR spectra. The UV spectra contain one absorption maximum at 247-267 nm, in contrast to the starting substances, for which two maxima are characteristic [3]. The PMR spectrum is also in complete accordance with the indicated structure. The formation of VII-IX during desulfuration of III-V proves that the amide group in starting substances III-V is in the oxamate residue rather than in the 2 position.



It was observed that the desulfuration of VI in alcohol with Raney nickel leads to amide VII rather than the hydrazide. The identical character of the VII obtained from amide III and hydrazide VI was proved

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*See [1] for communication XXVI.

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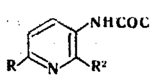
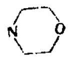
TABLE 1. N-(3-Pyridyl)hydroxamic Acid Derivatives



Com-pound	R	R'	R²	mp, °C	Empirical formula	Found, %					Calculated, %					UV spectra		Yield, %
						C	H	Cl	N	S	C	H	Cl	N	S	λ_{max}	lg ε	
VII	H	NH_2	H	250—251	$C_7H_7N_3O_2$	51,0	4,4		25,2		50,9	4,2		25,4		267	3,9	60
VIII	H	$HN-CH_2C_6H_5$	H	167—168	$C_{14}H_{13}N_3O_2$	65,7	5,2		16,6		65,9	5,1		16,5		255	4,1	68
IX	H		H	86—87	$C_{11}H_{13}N_3O_3$	56,2	5,8		17,7		56,2	5,5		17,9		247	4,2	63
X	Cl	$HN-(CH_2)_2N(C_2H_5)_2$	$S-CH_2-CO_2C_2H_5$	80—81	$C_{17}H_{25}ClN_4O_4S$	48,8	6,1	8,3	13,6	7,8	49,0	6,0	8,5	13,4	7,7	236, 284, 306	4,2; 4,0 3,9	95
XI	Cl	$HN-(CH_2)_2N-(C_2H_5)_2$	$S-CH_2CONH_2$	134—136	$C_{15}H_{22}ClN_5O_3S$	46,7	5,9	9,0	17,7	8,1	46,4	5,7	9,2	18,1	8,2			55
XII	Cl		$S-CH_2-CO_2C_2H_5$	127—129	$C_{15}H_{16}ClN_3O_4S$	48,7	4,7	9,7	11,5	8,7	48,4	4,8	9,5	11,3	8,6	231, 306	4,2; 3,7	93
XIII	Cl		$S-CH_2-CONH_2$	173—175	$C_{13}H_{15}ClN_4O_3S$	45,9	4,5	10,2		9,3	45,5	4,4	10,4		9,3	232, 306	4,2; 3,8	94
XIV	Cl	$HN-N=CH_2$	$S-CH_2-CO_2C_2H_5$	217—218	$C_{12}H_{13}ClN_4O_3S$	42,1	3,9	10,1	16,2	9,5	41,8	3,8	10,3	16,2	9,3			98
XV	Cl	$HN-N=CH-C_6H_4-p\text{-}OCH_3$	$S-CH_2-CO_2C_2H_5$	213—214,5	$C_{19}H_{19}ClN_4O_5S$	50,6	4,4	7,6	12,5	7,2	50,6	4,2	7,9	12,4	7,1			88
XVI	Cl	$HN-N=CH-CH=CH-C_6H_5$	$S-CH_2-CO_2C_2H_5$	221—222	$C_{20}H_{19}ClN_4O_4S$	53,7	4,0	7,6	12,2	7,4	53,7	4,2	7,9	12,3	7,2			88
XVII	Cl	$HN-N=CH-C_6H_3-m,p\text{-}(OCH_3)_2$	$S-CH_2-CO_2C_2H_5$	210—212	$C_{20}H_{21}ClN_4O_6S$	49,7	4,5	7,4	11,8	7,0	49,9	4,4	7,4	11,6	6,6			95

by a comparison of the spectral and analytical characteristics of these substances. Hydrazones XIV-XVII were obtained from hydrazide VI.

Amides X and XII, which were converted to diamides XI and XIII by the action of 25% ammonium hydroxide, were synthesized by reaction of ester II with diethylaminoethylamine and pyrrolidine.

When II and V are heated with 80% H_2SO_4, the amide bond of the oxamate residue is hydrolyzed with simultaneous cyclization to 2-chloropyrido[2,3-b][1,4]-thiazin-6-one (XVIII). The structure of XVIII was confirmed by alternative synthesis from 2-mercapto-3-amino-6-chloropyridine and chloroacetic acid [4] or from 2-ethoxycarbonylmethylthio-3-acetamido-6-chloropyridine [5]. Under similar conditions – when I is heated with 80% H_2SO_4 – the thiazine ring is opened, and bis(3-amino-6-chloro-2-pyridyl) disulfide (XIX) is formed.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the synthesized compounds were recorded with a Perkin-Elmer-457 spectrometer, the UV spectra (in alcohol) on an EPS-3 spectrophotometer, and the PMR spectra were recorded with a JNM-4H spectrometer with an operating frequency of 100 MHz and tetramethylsilane as the internal standard. The proton signals are presented on the δ scale.

N-(3-Pyridyl)oxamic Acid Amide (VII). A. A 1.0-g (3 mmole) sample of III was refluxed in 50 ml of ethanol with 10.0 g of Ni for 2 h. The catalyst was removed by filtration and washed several times with hot ethanol. The filtrate was vacuum-evaporated to one-third of its original volume, and the precipitate was removed by filtration and dried to give 0.31 g (60%) of a product with mp 246-248°. Recrystallization from ethanol gave colorless crystals with mp 250-251°. IR spectrum, cm^{-1}: 3400, 3370, 3320 (NH, NH_2); 1660-1710 (amide CO). UV spectrum: λ_{max}, nm (log ε): 267 (3.95).

B. The reaction of 0.7 g (2 mmole) of VI and 7.0 g of Ni as indicated in method A gave 0.15 g (44%) of a product with mp 245-246°. Recrystallization from ethanol gave a product with mp 250-251°. The IR spectra of the compounds obtained by methods A and B were identical. Compounds VIII and IX were similarly prepared. IR spectrum, cm^{-1}: VIII 3280, 3300 (two NH groups), 1650-1655 (amide CO), IX 3310 (NH), 1700-1715 (amide CO). PMR spectrum of IX in $CDCl_3$: 3.75 ppm (8-H, $-\underbrace{O-(CH_2)_2-(CH_2)_2N}$).

Compounds X-XIII were obtained by the method in [3]. IR spectra, cm^{-1} (the frequencies of the CO vibrations of the ester, amide, and NH group for X and XII are presented): X 1740, 1665, 3280; XII 1730, 1700, 1650, 3280. The frequencies of the CO vibrations of amides and of NH and NH_2 groups for XI and XIII are as follows: XI 1650-1680, 3420, 3295, 3210; XIII 1650, 1700, 3380, 3200, and 3280 cm^{-1}.

[2-(Ethoxycarbonylmethylthio)-6-chloro-3-pyridyl]oxamic Acid N-Methylenehydrazide (XIV). A mixture of a solution of 0.5 g (1.5 mmole) of VI in 10-15 ml of ethanol and 0.05 g (1.6 mmole) of formaldehyde was refluxed for 1 h. The precipitate was removed by filtration, washed with water, and dried to give 0.5 g (98%) of a product with mp 217-218°. Recrystallization from ethanol gave colorless crystals with mp 217-218° (from ethanol). IR spectrum, cm^{-1}: 3220, 3240 (two NH groups); 1735 (ester CO), 1665 (amide CO).

Compounds XV-XVII were similarly prepared. IR spectra of XV-XVII (the frequencies of the CO vibrations of the ester and amide groups and of the NH groups are presented), cm^{-1}: XV 1735, 1665, 3220, 3260; XVI 1730, 1670, 3200, 3240; XVII 1735, 1695, 3190, 3240.

2-Chloropyrido[2,3-b][1,4]thiazin-6-one (XVIII). A. A solution of 1.0 g (2.5 mmole) of V in 10 ml of 80% H_2SO_4 was refluxed at 100° for 1 h, after which it was poured into 20 ml of water. The precipitate was removed by filtration, washed with water, and dried to give 0.5 g (98%) of a product with mp 248-250°. Recrystallization from ethanol gave colorless crystals with mp 249-251.5° (from ethanol). IR spectrum, cm^{-1}: 3100, 3200 (associated NH group), 1680 (ketone CO). The melting point of a mixture with an authentic sample was not depressed.

B. The compound was obtained from 1.0 g (2.8 mmole) of II as indicated in method A. The yield of material with mp 249-251.5° was quantitative.

C. The compound was obtained from 0.7 g (2.4 mmole) of 2-(ethoxycarbonylmethylthio)-3-acetamido-6-chloropyridine as indicated in method A. The product [0.45 g (93%)] had mp 248-250°.

Bis(3-amino-6-chloro-2-pyridyl) Disulfide (XIX). This compound [0.32 g (50%)], with mp 198-202°, was obtained from 0.7 g (2 mmole) of I by method A used to prepare XVIII. Recrystallization from ethanol gave a product with mp 208-210°. No melting-point depression was observed for a mixture with a known sample.

LITERATURE CITED

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