NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XX.* REACTION OF 2-MERCAPTO-3-AMINO-6-CHLOROPYRIDINE WITH CHLOROOXALACETIC ESTER

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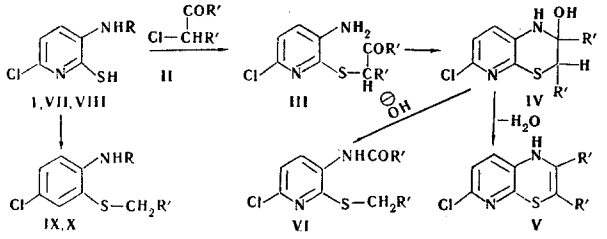
Ethyl N-(2-carbethoxymethylmercapto-6-chloro-3-pyridyl)oxamate was obtained by the reaction of 2-mercapto-3-amino-6-chloropyridine with chlorooxalacetic ester in the presence of a sesquimolar excess of potassium hydroxide. N-[2-(Carbethoxymethylmercapto)-6-chloro-3-pyridyl]urea and 2-carbethoxymethylmercapto-3-acetamido-6-chloropyridine, respectively, were isolated by the reaction of N-(2-mercapto-6-chloro-3-pyridyl)urea and 2-mercapto-3-acetamido-6-chloropyridine with chlorooxalacetic ester in the presence of excess alkali.

It was previously reported that diethyl α-(3-amino-6-chloro-2-pyridyl)mercaptooxalacetate (III), a hydroxyamino compound (IV), and 6,7-dicarbethoxypyridothiazine (V) are formed by the reaction of 2-mercapto-3-amino-6-chloropyridine (I) with chlorooxalacetic ester (II) in the presence of an equimolecular amount of alkali [1].

In a continuation of this study we have investigated the reaction of I with II in the presence of excess alkali. Ethyl N-(2-carbethoxymethylmercapto-6-chloro-3-pyridyl)oxamate (VI) is formed by the reaction of I with II in alcohol in the presence of a sesquimolar excess of potassium hydroxide at 18-20°C.



I R = H; VII, IX R = $CONH_2$; VIII, X R = $COCH_3$; II-VI, IX, X R' = $COOC_2H_5$

VI has the same elementary composition as III and IV but differs from them with respect to physical chemical properties: it has a sharp melting point that does not change on storage in air and refluxing in polar and inert solvents. The structure of VI was confirmed by the IR and PMR spectra. Thus, the IR spectrum of VI does not contain NH_2 group absorption bands but does have the intense absorption of a secondary amino group at 3370 cm^{-1} and a broad band at 1725-1750 cm^{-1}, which was ascribed to the absorption of the carbonyl groups of the ester and amide groups (Fig. 1).

In a study of the properties of III it was observed that it is readily converted to pyridothiazine V in alcohol in the absence of hydroxyl ions and in acidic media. The conversion of III to V and VI proceeds through the intermediate formation of an unstable, energy-rich compound (IV), as indicated by the following data. The UV spectrum of III, obtained immediately after its dissolving in alcohol, is similar to the spec-

*See [5] for communication XIX.

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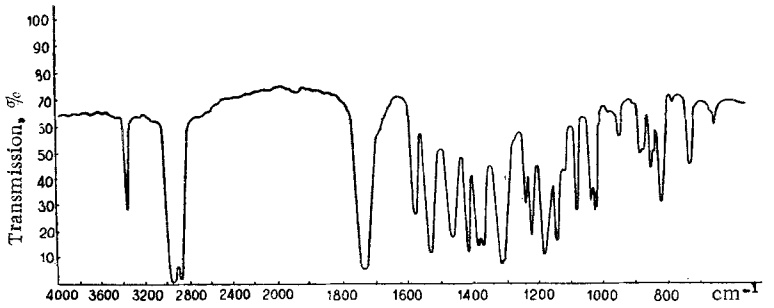

Fig. 1. IR spectrum of ethyl N-(2-carbethoxymethylmercapto-6-chloro-3-pyridyl)oxamate (VI).

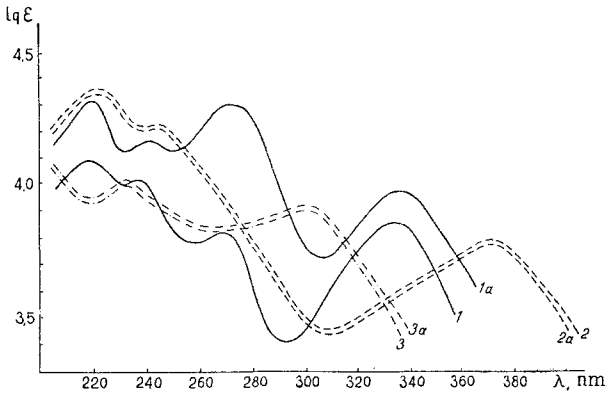

Fig. 2. UV spectra (in ethanol): 1) diethyl α-3-amino-6-chloro-2-pyridyl)mercaptooxalacetate (III), obtained immediately after dissolving; 1a) 2-chloro-6-hydroxy-6-(p-nitrophenyl)-5,6-dihydropyrido[2,3-b][1,4]thiazine; 2) III, obtained after standing for 3 h in alcohol; 2a) 2-chloro-6,7-dicarbethoxy-5H-pyrido[2,3-b][1,4]-thiazine (V); 3) III, obtained after treatment with alcoholic alkali; 3a) ethyl N-(2-carbethoxymethylmercapto-6-chloro-3-pyridyl)-oxamate (VI).

trum of 2-chloro-6-hydroxy-6-(p-nitrophenyl)-5,6-dihydropyridothizaine, the cyclic structure of which was previously established by us in [2]. When the spectrum was obtained after the compound had stood for 2-3 h in alcohol, it was identical to the spectrum of pyridothiazine V. On treatment with alcoholic alkali (at both −5° and 18-20°), III is converted to oxamic acid derivative VI rather than pyridothiazine V. In contrast to the spectrum of III, the UV spectrum of VI has two maxima at 232 and 299 nm (Fig. 2). It was also found that VI is formed from IV in the presence of a catalytic amount of alkali. In the absence of alkalis, IV is dehydrated to pyridothiazine V. Thus, depending on the conditions, IV can be stabilized in two directions: in a nearly neutral medium, dehydration of IV to the stable pyridothiazine V predominates; in an alkaline medium the attack of the hydroxyl ion is directed to the carbon atom in the 6 position, as a result of which the C_6–C_7 bond is cleaved under quite mild conditions, and the final reaction product is oxamic acid derivative VI.

As in the case of α-chloroacetoacetic ester [4], the acid cleavage characteristic for β-keto acid esters occurs under the influence of hydroxyl ions in the reaction of N-(2-mercapto-6-chloro-3-pyridyl)urea (VII) [2] and 2-mercapto-3-acetamido-6-chloropyridine (VIII) [3] with chlorooxalacetic ester in the presence of excess alkali. The major reaction products are N-[2-(carbethoxymethylmercapto-6-chloro-3-pyridyl]urea (IX), in the case of VII, and 2-carbethoxymethylmercapto-3-acetamido-6-chloropyridine (X) and bis(3-acetamido-6-chloro-2-pyridyl) disulfide (XI), in the case of VIII. The structure of IX was confirmed by the PMR spectrum and by alternative synthesis (by the reaction of VII with chloroacetate ester [4]). The structure of X was proved by comparison with an authentic sample of X obtained by the reaction of VIII with chloroacetate ester [4].

EXPERIMENTAL

Ethyl N-(2-Carbethoxymethylmercapto-6-chloro-3-pyridyl)oxamate (VI). A) A solution of 0.6 g (2.6 mmole) of II in 5 ml of ethanol was added at 18-20° to a solution of 0.5 g (3 mmole) of I in 15 ml of ethanol containing 0.28 g (5 mmole) of KOH. After the mixture was stirred for 3 h at this temperature, the resulting precipitate of KCl was removed by filtration, the filtrate was evaporated in vacuo to one third of its original volume, and 10-15 ml of water was added. The resulting precipitate was filtered, washed with water, and dried to give 0.65 g (61%) of VI with mp 95-96°; recrystallization from ethanol gave colorless crystals with mp 98-99°. PMR spectrum (in $CHCl_3$, ppm): 1.27, 1.43 (two triplets, absorption of the CH_3 groups); 4.20, 4.45 (two quartets, absorption of OCH_2C groups); 4.00 (singlet, absorption of the protons of the SCH_2CO group). Found %: C 45.12; H 4.48; Cl 10.45; N 8.08; S 9.43. $C_{13}H_{15}ClN_2O_5S$. Calc. %: C 45.02; H 4.32; Cl 10.24; N 8.08; S 9.23.

B) A mixture of 0.25 g (0.7 mmole) of III [1] in 5 ml of ethanol and 0.05 g (0.9 mmole) of KOH was stirred at −10° for 2 h. The precipitate was filtered, washed with water, and dried to give 0.1 g of VI with mp 98-99°. The filtrate was poured into 5-10 ml of water, and the resulting precipitate was filtered, washed with water, and dried to give an additional 0.1 g of VI with mp 95-96°. The overall yield was 0.2 g (80%). This substance did not depress the melting point of the compound obtained via method (A).

The yield of VI was 80% when the reaction was carried out at 18-20°.

C) A mixture of 0.2 g (0.5 mmole) of IV [1] in 5 ml of ethanol and 0.02 g (0.3 mmole) of KOH was stirred at 18-20° for 2 h. Subsequent treatment of the reaction mixture was similar to that described in method (A) to give 0.17 g (85%) of VI with mp 94-95°. The IR spectra of the compounds synthesized via methods (A) and (C) were identical.

N-[2-(Carbethoxymethylmercapto)-6-chloro-3-pyridyl]urea (IX). This compound (0.14 g) was obtained like VI [method (A)] from 0.5 g (2.4 mmole) of VII in 15 ml of ethanol containing 0.28 g (5 mmole) of KOH and 0.54 g (2.4 mmole) of II in 2 ml of ethanol and had mp 192-194°. Water (10-15 ml) was added to the alcoholic mother liquor, and the mixture was allowed to stand for 2 days. The resulting precipitate was filtered and dried to give another 0.25 g of IX. The overall yield was 0.39 g (55%). The product was obtained as colorless crystals with mp 201-202° (from ethanol) [4]. PMR spectrum ($C_5H_5N + CF_3COOH$): 1.05 ppm (triplet, absorption of the protons of the CH_3 group), 4.08 ppm (quartet, absorption of the OCH_2C group), 4.00 ppm (singlet, absorption of the protons of the SCH_2CO group).

2-Carbethoxymethylmercapto-3-acetamido-6-chloropyridine (X) and Bis(3-acetamido-6-chloro-2-pyridyl) Disulfide (XI). A solution of 0.5 g (2.4 mmole) of VIII in 12 ml of ethanol containing 0.21 g (3.7 mmole) of KOH was added at −10° to a solution of 0.54 g (2.4 mmole) of II in 2 ml of ethanol. The mixture was stirred at this temperature for 3 h to give 0.21 g (27%) of XI with mp 217-219°. Recrystallization from ethanol yielded colorless crystals with mp 230-231° (mp 232° [3]). The filtrate after removal of the precipitate was evaporated in vacuo to one third of its original volume, 10 ml of water was added, and the mixture was allowed to stand for 3-5 days to give 0.2 g (28%) of X with mp 131-132° (from ethanol). The compound was spectrally similar to the compound obtained via the method in [4]. It did not depress the melting point of a genuine sample.

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

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