A STUDY OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES XIV*. THE REACTION OF 3-AMINO-2-MERCAPTOPYRIDINES WITH α-CHLOROACETOACETIC ESTER†

T. S. Safonova and L. G. Levkovskaya

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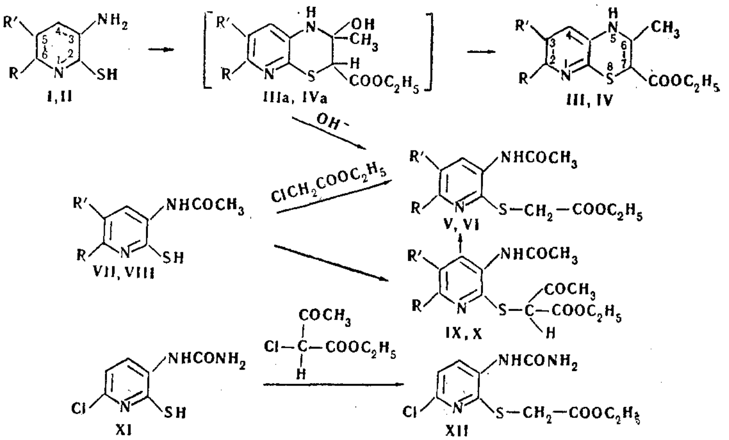
The reaction of 3-amino-6-chloro-2-mercaptopyridine (I) and the corresponding 5-chloro compound (II) with α-chloroacetoacetic ester in ethanol in the presence of 1 mole of alkali leads to 2- and 3-chloro-7-ethoxycarbonyl-6-methyl-5H-pyrido[2,3-b]-[1,4]-thiazines (III and IV) while in the presence of 2 moles of alkali it leads to 3-acetamido-6-chloro-2-ethoxycarbonylmethylthiopyridine (V) and the corresponding 5-chloro compound (VI). The reaction of 3-acetamido-6-chloro-2-mercaptopyridine (VII) and the corresponding 5-chloro compound (VIII) with α-chloroacetoacetic ester in the presence of 1 mole of KOH has given 3-acetamido-2-(α-acetylethoxycarbonylmethylthio)-6-chloropyridine (IX) and the corresponding 5-chloro compound (X). The action of ethanolic alkali on IX and X has given V and VI. N-[6-chloro-2-(ethoxycarbonylmethylthio)pyridin-3-yl]urea (XII) has been obtained by the reaction of N-(6-chloro-2-mercaptopyridin-3-yl)urea (XI) with α-chloroacetic ester in ethanol in the presence of 2 moles of KOH.

Continuing previous work [3,4], we have investigated the reaction of 3-amino-6-chloro-2-mercaptopyridine (I) and 3-amino-5-chloro-2-mercaptopyridine (II) with α-chloroacetoacetic ester. It was found that the performance of this reaction in ethanol in the presence of 1 mole of alkali at 18-20°C forms 2- and 3-chloro-7-ethoxycarbonyl-6-methyl-5H-pyrido[2,3-b]-[1,4]-thiazines‡ (III and IV) with yields of 77-80%.



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*For Communication XIII, see [1].

†For a preliminary communication, see [2].

‡The compounds have been named in accordance with the nomenclature which we adopted for the pyrimido-[4,5-b]-[1,4]-thiazines and pyrazino[2,3-b]-[1,4]-thiazines [1].

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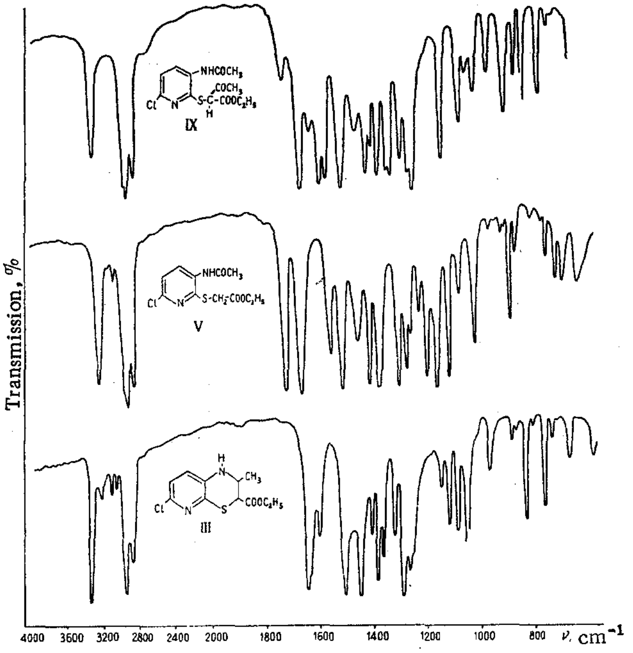

Fig. 1. IR spectra of 2-chloro-7-ethoxycarbonyl-6-methyl-5H-pyrido[2,3-b]-[1,4]-thiazine (III), 3-acetamido-6-chloro-2-ethoxycarbonylmethylthiopyridine (V), and 3-acetamido-2-(α-acetylethoxycarbonylmethylthio)-6-chloropyridine (IX).

The IR spectra of III and IV, unlike those of the 6-arylpyridothiazines [4] have the absorption band of an NH group (3300–3340 cm^{-1}), which shows their structure as 5H derivatives (Fig. 1).

The reaction of I and II with α-chloroacetoacetic ester under the conditions given above but in the presence of 2 moles of alkali yielded 3-acetamido-6-chloro-2-ethoxycarbonylthiopyridine (V) and the corresponding 5-chloro compound (VI). The individuality of compounds V and VI was confirmed by the fact that in chromatograms they each gave one spot with R_f 0.58. The structures of V and VI were shown by the independent synthesis from the corresponding 3-acetamidochloro-2-mercaptopyridines (VII and VIII), by reaction with ethyl chloroacetate, and by spectroscopy. Thus, the IR spectra of compounds V and VI obtained by the two methods have the absorption bands of an amide group (1670 and 3270–3290 cm^{-1}) and of an ester group (1740 cm^{-1}) (Fig. 1). In the UV region there are the three absorption maxima that are characteristic for 3-acetamido-2-acylmethylpyridines [5]. The PMR spectra of V and VI exhibit the signals of the protons of methylene, methyl, and ester groups, which is in harmony with the proposed structure.

It has also been shown that the reaction of compounds VII and VIII with α-chloroacetoacetic ester under the conditions for preparing V and VI (in the presence of 2 moles of KOH) leads to the cleavage of the carbon-carbon bond in the acetoacetic residue and the formation of V and VI. When these reactions were carried out in the presence of 1 mole of KOH, the intermediates IX and X were isolated. The structures of IX and X were shown by IR and UV spectroscopy and by chemical reactions. Thus, in the IR spectra of IX and X taken in the solid state there is the absorption of an amide CO group (1640 cm^{-1}), a ketone (1670–1680 cm^{-1}) and a NH group (3280–3310 cm^{-1}). The band of the ester CO group (1730 cm^{-1} in paraffin oil and 1755 cm^{-1} in dioxane) is weak, which is apparently due to the formation of an intramolecular hydrogen bond between the carboxyl and NH groups (Fig. 1). The UV spectra of IX and X are similar to the UV spectra of V and VI and have three maxima (223, 255–257, and 300–309 nm).

Compounds IX and X readily undergo the cleavage reactions that are characteristic of esters of α-substituted β-keto acids [6]. Thus, the action on IX and X of ethanolic alkali (1 mole of KOH) gave V and VI with yields of 85–92%.

Similar results were obtained in the reaction of N-(6-chloro-2-mercaptopyridin-3-yl)urea (XI) with α-chloroacetoacetic ester in ethanol in the presence of two moles of alkali, which yielded N-[6-chloro-2-(ethoxycarbonylmethylthio)pyridin-3-yl]urea (XII). The structure of XII was shown by independent synthesis from XI and ethyl chloroacetate, and also by spectroscopy. The PMR spectra of XII revealed the protons of CH_2 and $COOC_2H_5$ groups.

The material presented shows that the reactions of I and II with α-chloroacetoacetic ester in the presence of an equimolecular amount of alkali lead, as in the case of phenacyl halides [3,4], to the pyridothiazines III and IV. The formation of III and IV apparently takes place through the intermediate hydroxy compounds IIIa and IVa which, in a medium close to neutrality, dehydrates to III and IV. If the reaction under consideration is performed in the presence of an excess of alkali, the carbon-carbon bond in the intermediate hydroxy compounds cleaves with the formation of the 3-acetamido-2-(ethoxycarbonylmethylmercapto)-pyridines V and VI. Where, in the initial compounds VII, VIII, and XI, the 3-NH_2 group is replaced by acetyl or carbonyl residues, their reaction with α-chloroacetoacetic ester in the presence of an excess of alkali leads to acid cleavage, which is accompanied by the rupture of the bond between the α and β carbon atoms in the acetoacetic residue. As a result, the final reaction products are V, VI, and XII.

EXPERIMENTAL

2-Chloro-7-ethoxycarbonyl-6-methyl-5H-pyrido[2,3-b]-[1,4]-thiazine (III). At 18-20°C, a solution of 0.5 g (3 mmoles) of α-chloroacetic ester in 2 ml of ethanol was added to a solution of 0.5 g (3 mmoles) of I [4] in 10 ml of ethanol containing 0.18 g (3 mmoles) of KOH, and the mixture was stirred for 3 hr and filtered; the filtrate was poured into 15 ml of water, and the precipitate was filtered off, washed with water, and dried. This gave 0.68 g (80.9%) of yellow crystals, mp 203-204°C (from ethanol). According to the literature [8], yield 24%, mp 203-204°C (from methanol). IR spectrum in paraffin oil, cm^{-1}: 1640 (ester C = 0); 3340 (NH); in $CHCl_3$ solution: 1700-1730 (ester CO); 3430 (NH).

3-Chloro-7-ethoxycarbonyl-6-methyl-5H-pyrido[2,3-b]-[1,4]-thiazine (IV). This was obtained in a similar manner to III from II [3] and α-chloroacetoacetic ester. Yield 77.3%. Bright yellow crystals with mp 208-210°C (from ethanol). R_f 0.34 (in system 1, orange spot)*. IR spectrum in paraffin oil, cm^{-1}: 1710 (ester CO), 3300 (NH); in $CHCl_3$ solution: 1710-1730 (ester CO), 3430 (NH). Found, %: C 48.44; H 3.83; Cl 12.90; N 10.10; S 11.60. Calculated for $C_{11}H_{11}ClN_2O_2S$, %: C 48.78; H 4.06; Cl 13.11; N 10.35; S 11.83.

3-Acetamido-6-chloro-2-(ethoxycarbonylmethylthio)pyridine (V). a. At 18-20°C, a solution of 0.5 g (3 mmoles) of α-chloroacetoacetic ester in 5 ml of ethanol was added to a solution of 0.5 g (3 mmoles) of I in 15 ml of ethanol containing 0.36 g (6 mmoles) of KOH, and then the process was as described in the preparation of III, with the only difference that the filtrate was first evaporated in vacuum to 1/3 of its initial volume. Yield 0.5 g (56.2%) of colorless crystals with mp 131-132°C (from ethanol). R_f 0.58 (in system 2, light yellow spot). IR spectrum, cm^{-1}: 1740, 1670 (ester and amide CO), 3290 (NH). λ_{max} 218, 256, 302 nm, log ε 4.07, 4.04, 3.81 (in ethanol). PMR spectrum (in $CDCl_3$), ppm: 1.29 (triplet), 4.21 (quartet – OCH_2CH_3), 2.22 (singlet – 3H, 3-CH_3), 3.95 (singlet – 2H, 2-CH_2). Found, %: C 46.04; H 4.78; Cl 12.40; N 9.66; S 11.00. Calculated for $C_{11}H_{13}ClN_2O_3S$, %: C 45.75; H 4.50; Cl 12.30; N 9.70; S 11.09.

b. At 18-20°C, a solution of 0.25 g (2 mmoles) of ethyl chloroacetate was added to a solution of 0.5 g (2.4 mmoles) of VII [5,7] in 10 ml of ethanol containing 0.18 g (3 mmoles) of KOH, and the subsequent procedure was as described for III. Yield 0.59 g (83%), mp 131-132°C (from acetone). A mixture with the substance obtained by method (a) gave no depression of the melting point. The IR, UV, and PMR spectra of the substance synthesized by methods (a) and (b) were identical.

c. A solution of 0.25 g (7 mmoles) of IX in 5 ml of ethanol containing 0.04 g (7 mmoles) of KOH was stirred at 18-20°C for 3 hr. The solution was filtered, and the filtrate was poured into 5-10 ml of water and left for 2-3 days. The precipitate that had deposited was filtered off, washed with water, and dried. This gave 0.18 g (85.7%) of V, mp 131-132°C (from ethanol). A mixture with the substance obtained by method (a) gave no depression of the melting point. The identity of the substances synthesized by methods (a) and

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*The chromatography of the compounds was carried out in a fixed layer (KSK silica gel–gypsum) using systems 1 [benzene–n-heptane–ethylacetate (19:1:1)] and 2 [benzene–n-heptane–ethyl acetate–96% ethanol (19:1:2:2)]. The spots on the chromatograms were revealed with conc. H_2SO_4.

(c) was confirmed by chromatography in system 2. The reliability of the separation was shown in the case of a mixture of the starting material IX and compound V: R_f for IX 0.47 (orange spot); R_f for V – 0.58 (light yellow spot).

3-Acetamido-2-α-acetylethoxycarbonylmethylthio-6-chloropyridine (IX). This was obtained in a similar manner to the III from VII and α-chloroacetoacetic ester, the filtrate being evaporated in vacuum to 1/3 of its original volume before dilution with water. Yield 75.3%, mp 80-82°C. For analysis, the substance was reprecipitated with water from ethanolic solution. Colorless crystals, mp 85-87°C. IR spectrum, cm^{-1}: 1730, 1670, 1640 (ester, ketone, and amide CO groups); 3310 (NH). λ_{max} 255, 300 nm, log ε 4.17, 3.87 (in ethanol). Found, %: C 46.87; H 4.60. Calculated for $C_{13}H_{15}ClN_2O_4S$, %: C 47.20; H 4.53.

3-Acetamido-5-chloro-2-(ethoxycarbonylmethylthio)pyridine (VI). **a.** This was obtained in a similar manner to V [method (a)] from 0.5 g (3 mmoles) of II and α-chloroacetoacetic ester. Yield 60%. Colorless crystals, mp 124-126°C (from ethanol). IR spectrum, cm^{-1}: 1740, 1670 (ester and amide CO groups); 3270 (NH). λ_{max} 222, 257, 308 nm, log ε 4.12, 4.14, 3.74 (in ethanol). Found, %: C 45.79; H 4.40; Cl 12.28; N 9.66; S 10.91. Calculated for $C_{11}H_{13}ClN_2O_3S$, %: C 45.75: H 4.50; Cl 12.30; N 9.70; S 11.09.

b. The substance was obtained in a similar manner to V [method (b)] from VIII [7] and ethyl chloroacetate. Yield 91.5%, mp 124-126°C (from ethanol). A mixture with the substance obtained by method (a) gave no depression of the melting point. The IR and UV spectra and chromatograms of the compounds obtained by methods (a) and (b) were identical.

c. The substance was obtained from VIII and α-chloroacetoacetic ester by analogy with the preparation of V [method (a)]. Yield 63.3%, mp 124-126°C (from ethanol). A mixture with the substance obtained by method (a) gave no depression of the melting point. The IR spectra and chromatograms of the compounds synthesized by methods (a) and (c) were identical.

d. The substance was obtained in a similar manner to V [method (c)] from X. Yield 92.3%, mp 124-126°C (from ethanol). A mixture with the substance obtained by method (a) gave no depression of the melting point. The identity of the substances synthesized by methods (a) and (d) was also confirmed by chromatography in system 2: R_f of X 0.51 (orange spot): R_f of VI obtained by methods (a) and (d) 0.58 (light yellow spot).

3-Acetamido-2-(α-acetylethoxycarbonylmethylthio)-5-chloropyridine (X). This was obtained in a similar manner to IX from VIII and α-chloroacetoacetic ester. Yield 91.3%, mp 86-88°C. Colorless crystals, mp 97-99°C (from ethanol). IR spectrum in paraffin oil, cm^{-1}: 1730, 1680, 1640 (ester, ketone, and amide CO groups), 3280 (NH); in 3% solution in dioxane: 1755, 1700-1715 (ester, ketone, and amide CO groups), 3300 (NH). λ_{max} 223, 257, 309 nm, log ε 4.10, 4.15, 3.72 (in ethanol). Found, %:C 47.00; H 4.67; Cl 10.62; N 8.52; S 9.81. Calculated for $C_{13}H_{15}ClN_2O_4S$, %: C 47.20; H 4.53; Cl 10.74; N 8.47; S 9.62.

N-[6-Chloro-2-(ethoxycarbonylmethylthio)pyridin-3-yl]urea (XII). **a.** At 18-20°C, a solution of 0.4 g (2.4 mmoles) of α-chloroacetoacetic ester in 5 ml of ethanol was added to a solution of 0.5 g (2.4 mmoles) of XI [4] in 15 ml of ethanol containing 0.3 g (5 mmoles) of KOH, and then the mixture was treated as in the preparation of V. Yield 0.40 g (56.3%). Colorless crystals, mp 201-202°C (from ethanol). IR spectrum, cm^{-1}: 1730, 1680 (ester and amide CO groups), 3470, 3370, 3300 (NH, NH_2). λ_{max} 217, 259, 306 nm, log ε 4.18, 4.11, 3.83 (in ethanol). PMR spectrum (in $C_5H_5N + CF_3COOH$): 1.05 ppm (triplet) and 4.08 ppm (quartet – OCH_2CH_3), 4.00 ppm (singlet – 2H, 2-CH_2). Found, %: C 41.47; H 4.02; Cl 12.35; N 14.59; S 11.21. Calculated for $C_{10}H_{12}ClN_3O_3S$, %: C 41.45; H 4.14; Cl 12.26; N 14.50; S 11.05.

b. The same compound was obtained from equimolar amounts of XI, KOH, and ethyl chloroacetate in ethanol at 18-20°C as in the preparation of V [method (a)]. Yield 87.3%: mp 201-202°C (from ethanol). A mixture with the substance obtained by method (a) gave no depression of the melting point. The IR, UV, and PMR spectra of the substances obtained by methods (a) and (b) were identical.

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