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HETEROCYCLES WITH A BRIDGING NITROGEN ATOM. 17*. UNEXPECTED FORMATION OF INDOLIZINE DURING THE PREPARATION OF (2-THIOXOPYRIDIN-1-YL) ACETATE

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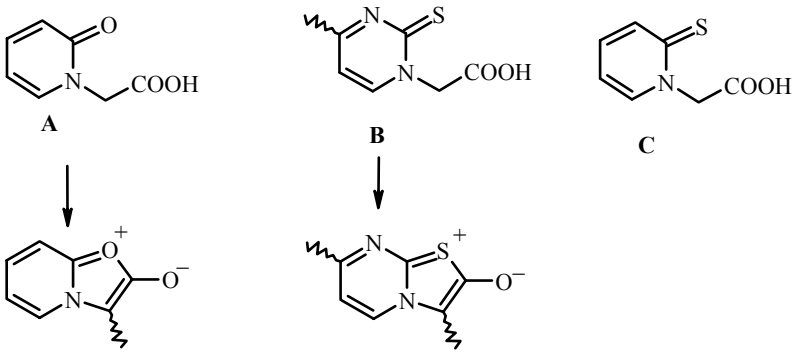
Ethyl 2-hydroxy-1-(2-thioxopyridin-1(2H)-yl)indolizin-3-carboxylate was formed along with ethyl (2-thioxopyridin-1(2H)-acetate from the reaction of 2-bromo-1-(ethoxycarbonylmethyl)pyridinium bromide with sodium sulfide. The structures of all compounds were confirmed by X-ray crystallography.

Keywords: pyridine-2-thione, 2-bromopyridinium salts, sodium sulfide, ethyl (2-thioxopyridin-1(2H))-yl)acetate, ethyl 2-hydroxy-1-(2-thioxopyridin-1(2H)-yl)indolizin-3-carboxylate, synthesis of indolizine.

Pyridoneacetic acid **A** [2,3] and its analog **B**, containing the pyrimidinethione-2 fragment [4], are capable of undergoing cyclization to form mesoionic azolo[3,2-*a*]azinium-2-olates which possess interesting structural and chemical properties [5]. Between them, a close thio-analog of **A** is the pyridinethione **C** (a potential source of new *meso*-ionic bicycles) which was not known until now.



Acid **A** and its esters are readily prepared by selective N-alkylation of pyridone-2 with derivatives of haloacetic acids. However this method is not used for the synthesis of the thio-analog **C** and its esters since it is known that pyridine-2-thiones are readily S-alkylated with various ethyl haloacetates [6]. (We note that the corresponding pyrimidinthiones **B** are obtained by a multistage synthesis, but not by N-alkylation).

The aim of this work was to study the possibility of the synthesis of ester **1** (a precursor to acid **C**) by an alternative strategy – the reaction of a bromopyridinium salt **2** with sodium sulfide or hydrosulfide:

* For Communication 16, see [1].

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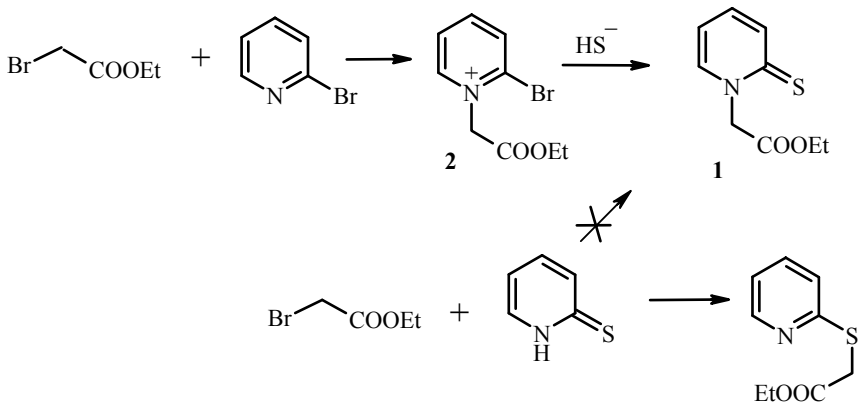


It is clear that this method the problem of selectivity of alkylation disappears, since the order of formation of the NC and CS bonds in the pyridine ring is changed. The strategy of obtaining N-alkylpyridine-2-thiones by the reaction N-alkyl-2-halopyridinium salts with aqueous solutions of sodium sulfide is well known (for example, N-phenacylpyridine-2-thiones were made in this way [7, 8]). In its turn, the bromopyridinium salt starting material **2** has been described [9], but the possibility of its conversion into the thione **1** has not been studied.

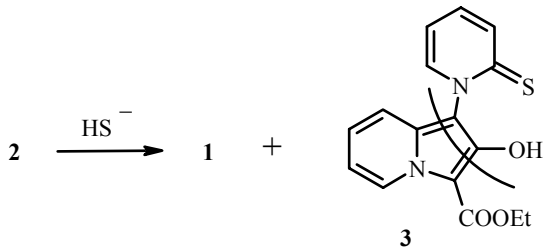
Salt **2** was prepared in high yield by quaternization of 2-bromopyridine with ethyl bromoacetate. The structure of salt **2** was confirmed by X-ray crystallography (Fig. 1).

The following thionation stage required a careful choice of conditions. Salt **2** is very sensitive to traces of base so that use of aqueous solutions of sodium sulfide or hydrogen sulfide (which clearly contain base because of strong hydrolysis) appeared unacceptable.

We succeeded in obtaining the expected conversion of salt **2** into the thione **1** in ~50% yield by use of anhydrous NaSH in absolute methanol. However this method id poorly reproducible and the preparation of anhydrous sodium hydrogen sulfide is sufficiently difficult. (The procedure for its synthesis includes the passage of H_2S through sodium methoxide and requires an enormous excess of ether to precipitate the required compound which is very soluble in methanol).

A successful and acceptable synthesis for the conversion of salt **2** into thione **1** was carried out in acetic acid. The weakly acid medium prevents the hydrolysis of the sulfide and permits reaction with commercially available the hydrate $Na_2S{\cdot}9H_2O$. We have succeeded in choosing optimal conditions in which compound **1** was formed in 60-70% yield. The structure of the thione was confirmed by X-ray crystallography (Fig. 1).

Apart from the required compound **1** another substance was isolated from the reaction mixture. The ^{1}H NMR spectrum of this compound showed signals of two different pyridine units. The structure of the unknown compound was determined by X-ray crystallography to be ethyl 2-hydroxy-1-(2-thioxopyridin-1(2H)-yl)indolizin-3-carboxylate (**3**).



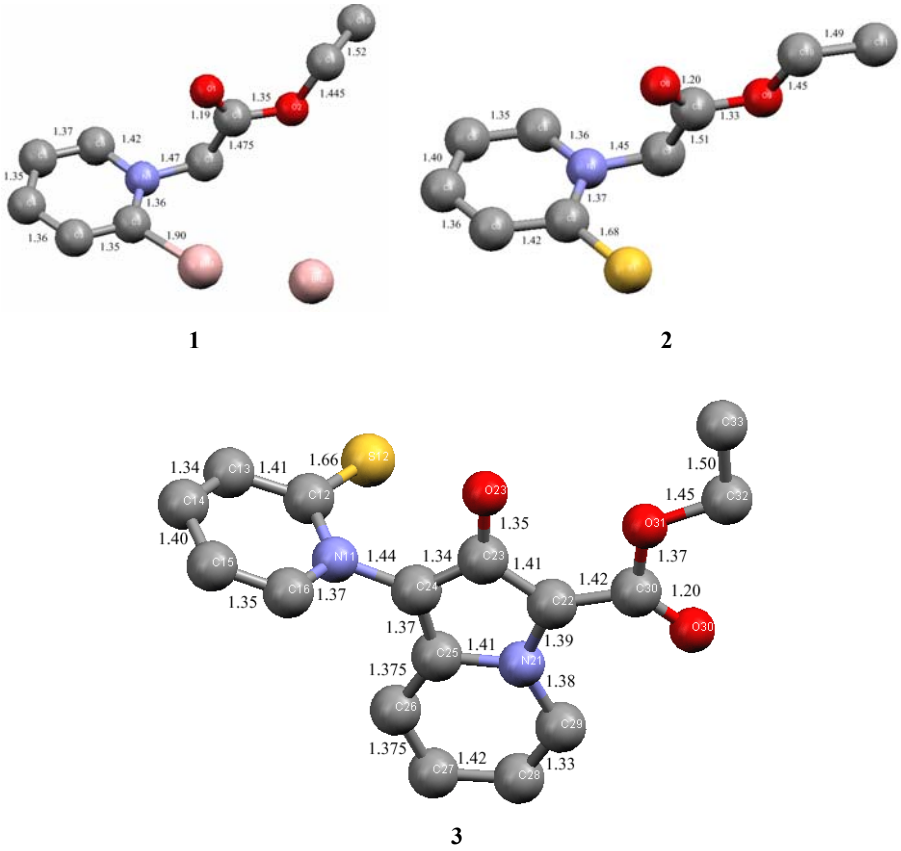


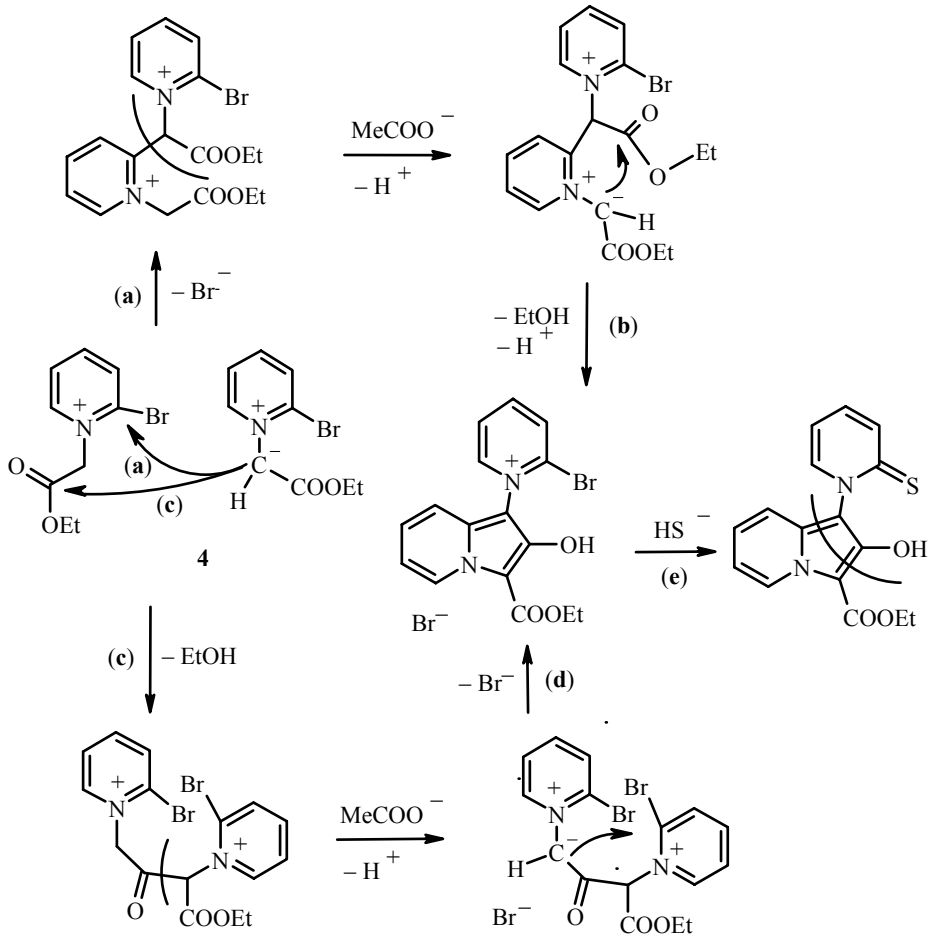
Fig. 1. X-ray Crystallographic Results and Bond Lengths in Molecules of Compound **1-3**

From the mutual positions of the two pyridine residues in molecule **3** it is clear that the assembly of the pyrrole ring occurs at the C(2)–C(3) and C(8a)–C(1) bonds of indolizine (the fragments which form these bonds are separated by heavy lines in the scheme). However the reason and sequence of the formation of these bonds is not obvious (Scheme 1).

We are convinced that the pyridinethione **1** is not converted into the indolizine **3** and consequently the formation of indolizine can only be linked to the conversion of salt **2**. It is evident that the CH_2CO group in the pyridinium salt **2** possesses high CH acidity and under the influence of bases (hydrogen sulfide or acetate ions) may be readily deprotonated to give the ylide **4**. Subsequent processes are probably linked with completion of the cyclization by nucleophilic attack of the carbanion center of the ylide at the electrophilic center of a second molecule of salt **2** (or a second ylide molecule). Note that molecule **2** has two electrophilic centers – the α-position of the pyridine ring (with an excellent leaving group) and the ester group (inclined to condensation). Consequently the mechanism of the process depends on which of the two electrophilic centers of salt **2** undergoes nucleophilic attack by the ylide **4** first.

There are two such mechanisms. The first mechanism (the upper part of the scheme) includes (**a**) the initial substitution of the bromine atom of salt **2** by the carbanion center of the ylide **4** with subsequent (**b**) intramolecular ester cyclocondensation with closing of the indolizine bicycle. In the second mechanism the stages are reversed, i.e., the ylide **4** initially undergoes condensation (**c**) with the ester group of salt **2** and then displacement of the halogen atom occurs (**d**). In one stage (probably the last (**e**))nucleophilic substitution of the second bromine atom occurs under the influence of the hydrogen sulfide ion. The first mechanism appears the more likely because of the know mobility of a halogen atom in the α-position of a pyridinium salt.

Scheme 1



We note that the assembly of the pyrrole ring of an indolizine of this type (with the formation of the C(2)–C(3) and C(8a)–C(1) bonds) is known. It occurs, for example, in the reactions of N-phenacyl-2-chloropyridinium salts with β-dicarbonyl compounds [10] , where the source of the C(1)–C(2) bond in the forming indolizine is the CH_2CO group of the dicarbonyl compound. In the conversion described here the same C(1)–C(2) fragment of the bicyclic skeleton comes however from the CH_2CO unit of a second molecule of the pyridinium salt **2**.

The bond lengths in molecules **1-3** are cited in Fig. 1 (the details of the geometry will be reported in a separate paper). We not only that the X-ray crystallographic data confirm the enolic structure of compound **3**.

EXPERIMENTAL

^{1}H NMR spectra were recorded with Bruker AC 400 (360 MHz) instrument.

2-Bromo-1-(ethoxycarbonylmethyl)pyridinium Bromide (2) was prepared by the reaction of 2-bromopyridine with ethyl bromoacetate [9]. Yield 76%; mp 183°C (mp 183-184°C [9]). The X-ray crystallographic results are give in Fig. 1.

Reaction of 2-Bromo-1-(ethoxycarbonylmethyl)pyridinium Bromide (2) with Sodium Sulfide. Salt **2** (40 g, 123 mmol) was heated and stirred in water (50 ml). The solution was cooled to room temperature and poured into methanol (50 ml) and acetic acid (15 ml). A filtered solution of sodium sulfide (55 g, 230 mmol)

($Na_2S·9H_2O$) in a minimum of water was added dropwise to the reaction mixture over 40 min, and then stirred for 30 min. The precipitate was filtered off and dissolved in benzene (100 ml). If the precipitate separated as an oily mass, the reaction mixture was extracted with benzene (2 × 50 ml) and the extract was treated with water.

Ethyl 2-Hydroxy-1-(2-thioxopyridin-1(2H)-yl)indolizin-3-carboxylate (3). On treatment of the benzene extract with water a substance was separated which was insoluble in water and poorly soluble in benzene. The precipitate of indolizine **3** was filtered off. Yield 5-15%; mp 185°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.24 (1H, d, *J* = 7.3, H-5 [indolizin]); 7.75 (1H, d, *J* = 6.4, H-6' [thioxo]); 7.58 (1H, d, *J* = 8.6, H-8); 7.33 (1H, m, H-7 or H-4'); 7.15 (1H, m, H-7 or H-4'); 7.01 (1H, d, *J* = 8.9, H-3'); 6.88 (1H, m, H-6 or H-5'); 6.75 (1H, m, H-6 or H-5'); 4.43 (2H, q, *J* = 7.1, CH_2); 2.9 (1H, br, OH); 4.43 (2H, t, *J* = 7.1 ,CH_3).

Ethyl (2-Thioxopyridin-1(2H)-yl)acetate (1). The filtered benzene extract was washed with sodium hydrogen carbonate solution, then twice with water, and dried over sodium sulfate. The extract was evaporated to a volume of 20-25 ml and then cooled. The crystals formed were filtered off and washed with cod benzene to give compound **1** (16.2 g, 67%); mp 71°C (benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.09 (1H, d, *J* = 6.4, H-6); 7.48 (1H, d, *J* = 8.1, H-3); 7.38 (1H, m, H-4); 6.82 (1H, m, H-5); 5.26 (2H, s, NCH_2); 4.16 (2H, q, *J* = 7, OCH_2); 1.21 (3H, t, *J* = 7, CH_3).

In order to avoid the formation of the indolizine **3** and to obtain the pure ester **1** it is necessary to add the sodium sulfide solution to the reaction mixture with a pH not exceeding 7 and the temperature should not exceed 30°C.

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