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HETEROCYCLES WITH A BRIDGING NITROGEN ATOM. 15*. THE NOVEL RECYCLIZATION OF DIPYRIDO[1,2-*a*:1',2'-*c*]-IMIDAZOLIUM SALTS TO PYRIDO[1,2-*a*]-BENZIMIDAZOLE-8-CARBOXALDEHYDES

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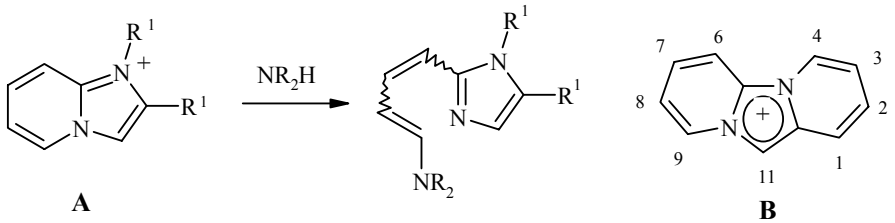
A previously unknown recyclization of an 11-acyldipyrido[1,2-a:1',2'-c]imidazolium cation to 8-formyl-9-methyl(aryl)pyrido[1,2-a]benzimidazoles has been discovered. The proposed reaction mechanism includes a selective opening of one of the pyridinium rings and the formation of a benzaldehyde fragment via condensation of the intermediate with the participation of the acyl group.

Keywords: dipyrido[1,2-*a*:1',2'-*c*]imidazoles, pyrido[1,2-*a*]benzimidazole, tricyclic aromatic heterocycles with a bridging nitrogen atom, recyclization, synthesis of aldehydes, transformation of a pyridine ring to benzene.

We have previously shown [2] that imidazo[1,2-*a*]pyridinium salts **A** undergo opening of the pyridine ring in the presence of secondary amines to form 1-amino-4-(imidazol-2-yl)-1,3-dienes.



A **B**

The formation of such azolyldienes is also typical for other azolopyridinium salts [2] with a bridging nitrogen atom [3]. We were interested in the reactivity of the dipyrido[1,2-*a*:1',2'-*c*]imidazolium system **B**, for which a reaction with nucleophiles has not been studied up to this time.

The tricyclic heterocycle **B** contains two unsymmetrically positioned pyridinium fragments, the imidazole ring also taking part in the delocalization of the positive charge. A priori, it is not evident at which of the three rings the attack of a nucleophile might occur and what is the nature of the covalent structures of the compounds if ring opening of one of the rings occurs. In this work we have discovered the first (and very unexpected) example of the transformation of the **B** system in the presence of base.

* For Communication 14 see [1].

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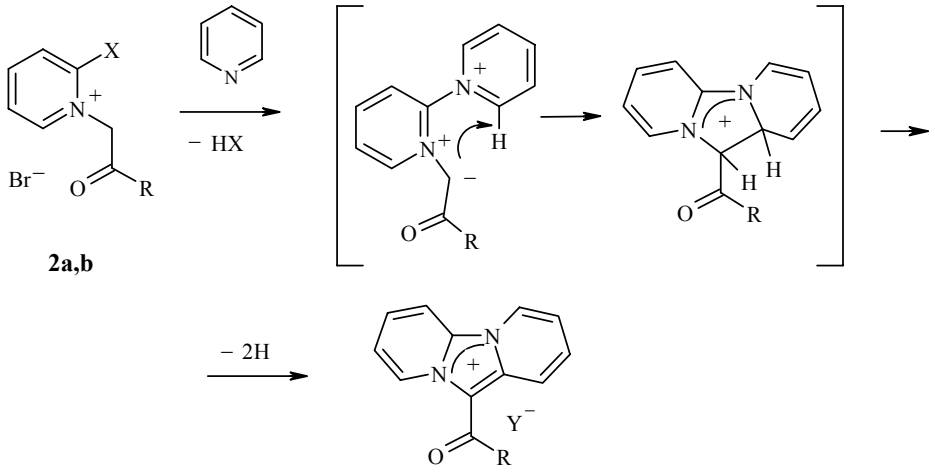
The most readily available derivatives of system **B** are compounds **1**, which contain an acyl group in position 11. They are prepared by the reaction of 2-halopyridinium salts **2** (e.g. X = Cl) with pyridine [4]. The stepwise process mechanism includes the substitution of the halogen atom in the salts **2** by pyridine with subsequent closing of the imidazoline ring and final oxidative aromatization to give the cation **1**.



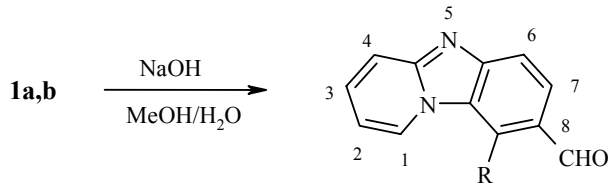
2a,b

1a,b

1,2 a R = *p*-BrC_6H_4; **b** R = Me; **1 a** Y = Br, **b** Y = ClO_4 (from Y = Br with $HClO_4$); **2a,b** X = Br

We have used the 2-bromopyridinium salts **2a,b** to prepare the tricyclic heterocycles **1** which were separated as the bromide (**1a**) or perchlorate (**1b**) salts. Although the bromo derivatives react under rather more rigid conditions than the 2-chloropyridinium salts, such a change does not affect the yields.

Upon short heating in basic solution the salts **1** undergo a previously unknown recyclization to form pyrido[1,2-*a*]benzimidazole derivatives **3** which contain an aldehyde group.



3a,b

The ^1H NMR spectra of compound **3** show the preservation of the signals of one of the pyridinium rings of the starting system **1**. The signals for the four protons of the second pyridinium ring are changed to a pair of doublets for the newly formed benzene ring in the region of about 8 ppm and a new, low field singlet for the aldehyde group. The mass spectra of the covalent compounds **3** show a molecular ion peak and the IR spectra a characteristic aldehyde C=O group vibration at 1690 cm^{-1}. The heterocyclic aldehydes **3** are soluble in acids and readily form oximes and hydrazones. Through the interpretation of 2-D heteronuclear magnetic resonance it was possible to assign the carbon atom signals in the ^{13}C NMR spectrum of compound **3a** (see Fig. 1).

The reaction evidently occurs via an ANRORC type mechanism and may include the following stages. Under the influence of hydroxide ion the cation **1** is converted to the zwitterionic adduct with an ylide structure **A** or enolate structure **B**. Opening of the dihydropyridine ring gives the covalent intermediate **C** which contains a conjugated diene fragment. (Formation of the conjugated system is indirectly confirmed by the transient appearance of a red-brown color which disappears at the end of the reaction).

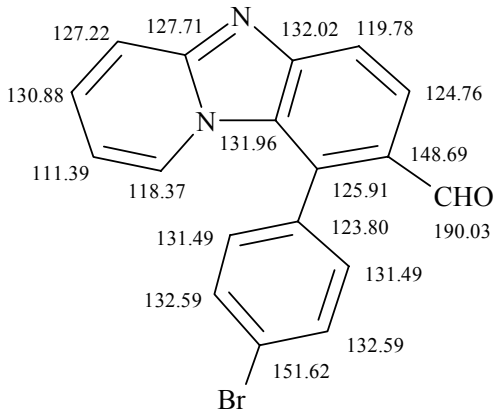
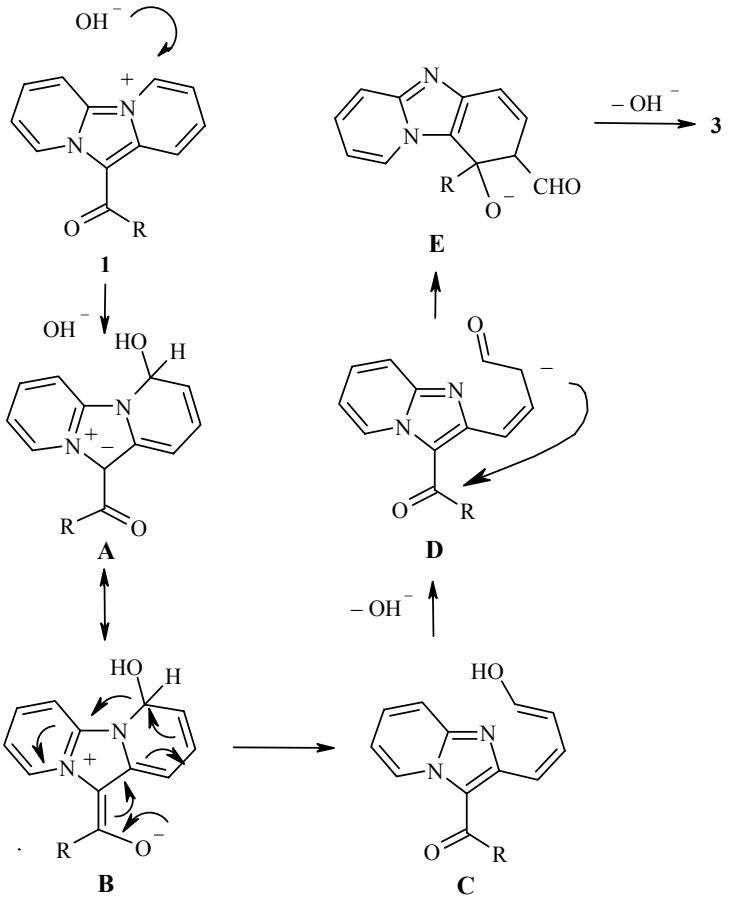


Fig. 1. Complete assignment of signals in the ^{13}C NMR spectrum of compound **3a**.

The open form **D** enolate contains a conjugated 1,7-dicarbonyl compound fragment and can undergo an intramolecular aldol-crotonic condensation. The carbonyl component is evidently the acyl group which is situated on the imidazole fragment of intermediate **D**. As a result of this condensation the new, six-membered carbocycle of the tricyclic system **E** closes. The final process is the aromatization of adduct **E** to the benzaldehyde **3**.



The reaction yield varies from 93% in the case of **3a** to 43% for **3b**. A similar lowering of the yield when exchanging the aroyl group in the cation **1** for acetyl can be explained by side condensation processes in which the methyl group of the COMe residue can be involved as an additional nucleophilic center.

Pyrido[1,2-*a*]benzimidazoles are often biologically active. Hence even the simplest homologs of the starting tricycle show analgesic properties [5] and examples of antiviral and psychotropic activity are known in a series of different derivatives [6]. It should be noted that 4-carboxy derivatives of this system are GABA receptor ligands and can bind to the benzodiazepine site of this receptor [7]. In this connection it was interesting to find that the subclass of pyridobenzimidazoles with an aldehyde group in the 8 position that we have discovered have not been reported to this time.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 400 (360 and 90 MHz respectively) using DMSO-d_6 solvent and mass spectra of an MS 5988 instrument with direct introduction and an ionization energy of 70 eV. The starting bromopyridinium salts **2** were prepared by a reported method [4] using the reaction of 2-bromopyridine with bromoketones.

N-(4-Bromophenacyl)-2-bromopyridinium Bromide (2a). Yield 84%, mp 226-228°C (mp 228-230°C [4]).

N-Acetonyl-2-bromopyridinium Bromide (2b). Yield 49%, mp 119-120°C (mp 118°C [4]).

Synthesis of Acylpyrido[1,2-*a*:1',2'-*c*]imidazolium Salts 1a,b (General Method [4]). A stream of oxygen (prepared by heating solid potassium permanganate) was passed slowly through a suspension of the pure bromide **2** (0.002 mol, dried in vacuo at 80-100°C) in freshly distilled pyridine (15 ml). The mixture was stirred at 40°C. After 30 min the precipitate had dissolved and yellow crystals were obtained from the solution. The mixture was held for 7 h and then left overnight at 0°C. The precipitate was filtered off, washed with a small amount of ice cold ethanol, acetone, and ether, and dried in air to give the bromide **1** which was recrystallized from ethanol. The perchlorate salt was prepared by dissolving it in ethanol and stirring with 2 equivalents of perchloric acid.

11-(4-Bromophenyl)pyrido[1,2-*a*:1',2'-*c*]imidazol-10-ium Bromide (1a). Yield 1.21 g (85%). Yellow crystals; mp 294-295°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.98 (1H, d, J_{34} = 7.1, H-4); 9.49 (1H, d, J_{89} = 6.6, H-9); 9.16 (1H, d, J_{67} = 8.8, H-6); 8.43 (1H, m, H-7); 8.08 (1H, m, H-8); 7.76 (1H, m, H-2); 7.79 (4H, m, Ar); 7.47 (1H, m, H-3); 7.21 (1H, d, J_{12} = 9.7, H-1). The salt was used in the subsequent reaction without additional purification.

11-Acetylpyrido[1,2-*a*:1',2'-*c*]imidazol-10-ium Perchlorate (1b). Yield 0.89 g (64%). Yellow crystals; mp 250-253°C (mp 253°C [4]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.28 (1H, d, J_{89} = 7.0, H-9); 9.61 (1H, d, J_{34} = 7.3, H-4); 9.19 (1H, d, J_{67} = 7.9, H-6); 8.83 (1H, m, H-7); 8.42 (1H, d, J_{12} = 9.0, H-1); 8.08 (1H, m, H-2); 7.85 (1H, m, H-8); 7.60 (1H, m, H-3); 2.89 (3H, s, CH_3).

Reaction of the Salts 1 with Base. An aqueous solution of sodium hydroxide (1 molar, 3 ml) was added to a solution of the dipyridoimidazolium salt **1** (0.002 mol) in methanol (5 ml) at room temperature. The solution immediately became light-brownish in color. The reaction mixture was heated on a water bath, the color of the solution became more intense, and developed a red shade. After 15 min heating the solution became lighter and brown flakes form. It was then cooled at room temperature for 20 min. At this time the reaction mixture became light-yellow and the flocculated, flaked precipitate settled to the base of the vessel. The precipitate was then filtered off, washed twice with water, and dried in air. The following were prepared:

9-(4-Bromophenyl)pyrido[1,2-*a*]benzimidazole-8-carboxaldehyde (3a). Yield 0.65 g (93%); R_f 0.90 ($CHCl_3$–MeOH, 8:1, Silufol), mp 195-198°C. Mass spectrum, *m/z* (*I*, %): 353 [M^+] (100). IR spectrum (vaseline oil), ν, cm^{-1}: 1692 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.84 (1H, s, 8-CHO); 8.21 (1H, d, J_{76} = 8.7, H-7);

7.99 (1H, d, J_{67} = 8.7, H-6); 7.41-7.79 (4H, m, Ar); 7.74 (1H, d, J_{12} = 9.2, H-1); 7.48 (1H, m, H-3); 7.44 (1H, d, J_{43} = 7.2, H-4); 6.65 (1H, m, H-2). The ^{13}C NMR data are given on Fig. 1. Found, %: C 61.28; H 3.39; N 7.99. $C_{18}H_{11}BrN_2O$. Calculated, %: C 61.56; H 3.16; N 7.98.

Derivatives of aldehyde **3a**. **2,4-Dinitrophenylhydrazone.** Yield 91%; mp 295-297°C, R_f 0.65. **Oxime.** Yield 80%; mp 199-201°C, R_f 0.80.

9-Methylpyrido[1,2-*a*]benzimidazole-8-carboxaldehyde (3b). According to TLC data the product prepared using the method described above contains at least 4 substances. The dried residue was dissolved in chloroform and chromatographed on a silica gel column using $CHCl_3$–MeOH (20:1) as eluent. The first fraction was collected (R_f 0.75, $CHCl_3$–MeOH, 8:1, Silufol). Yield 43%; mp 126-129°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.44 (1H, s, 8-CHO); 9.04 (1H, d, J_{12} = 8.3, H-1); 8.06 (1H, d, J_{76} = 8.1, H-7); 7.96 (1H, m, H-3); 7.65-7.95(2H, m, H-4 and H-6); 7.07 (1H, m, H-2); 3.13 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 210 [M^+]. Compound **3b** decomposes upon storage and satisfactory elemental analytical data could not be obtained.

2,4-Dinitrophenylhydrazone of 3b. Yield 94%; mp 228-230°C, R_f 0.75 ($CHCl_3$–MeOH, 8:1, Silufol).

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