AMINATION OF THE PYRIDINIUM CATIONS IN BETAINES. SYNTHESIS OF SUBSTITUTED PYRIMIDO[5,6-c]-1'-AZAQUINOLIZINE AND ITS DIHYDRO ANALOGS

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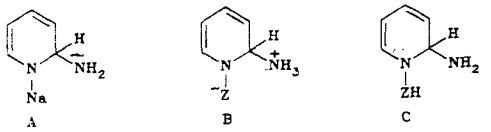
The pyridinium cations within betaines can be aminated under mild conditions with aqueous ammonia, ultimately undergoing cyclization to a new tricyclic system: 4-substituted-3,5-dioxopyrimido[5,6-c]-1'-azaquinolizine. Intermediates in the reaction are 4-substituted-3,5-dioxo-2,2-dihydropyrimido[5,6-c]-6H-1'-quinolizines.

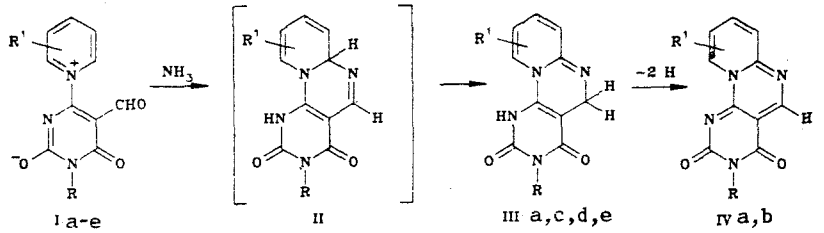
The direct amination of pyridine can be accomplished via the Chichibabin reaction [1]. An important factor in this case is the sorption of the heterocyclic base on the metal amide, promoting both an increase in the positive charge on the α-carbon and the addition of the amide ion [2].



A B C

We assumed that intermediate C, which resembles the Ziegler σ-complex (A) in the Chichibabin reaction, can also form in the reaction with ammonia due to deprotonation of the ammonium group in the σ-complex (B) by the anionlike moiety of the betaine.

In the present work we establish that uracil betaines I(a-e), which we had synthesized previously [3], may be readily aminated in aqueous solutions of ammonia and ammonium carbonate. In the first step fo the reaction 4-substituted-3,5-dioxo-2,2-dihydropyrimido[5,6-c]-6H-1'-azaquinolizines III(a, c-e) form:



I a-e II III a,c,d,e IV a,b

I—IV a $R=C_6H_5$, $R^1=H$; b $R=C_6H_5$, $R^1=3\text{-}CH_3$; c $R=p\text{-}C_6H_4\text{—}CH_3$, $R^1=H$; d $R=p\text{-}C_6H_4\text{—}OCH_3$, $R^1=H$; e $R=C_6H_5$, $R^1=D_5$

The dihydro compound III dehydrogenates partially when the reactants are heated, and completely upon treatment with chloroanil as an external oxidant, producing derivatives of 4-substituted-3,5-dioxo-pyrimido[5,6-c]-1'-azaquinolizine (IVa, b).

In the case of Ib, 4-phenyl-10-methyl-3,5-dioxopyrimido[5,6-c]-1'-azaquinolizine forms, and isolation of an intermediate of type III cannot be achieved.

The dihydro intermediate has structure III, rather than II. This follows from comparison of the NMR spectra of the dihydro products obtained from compounds Ia and from the betaine containing pyridinium D_5 (Ie). The ratio of the integrated intensities of the protons of the phenyl substituent and of the methylene group in the case of IIIa is 5:2, while in the deuterated compound IIIe it is 5:1. Consequently, formation of the methylene group in

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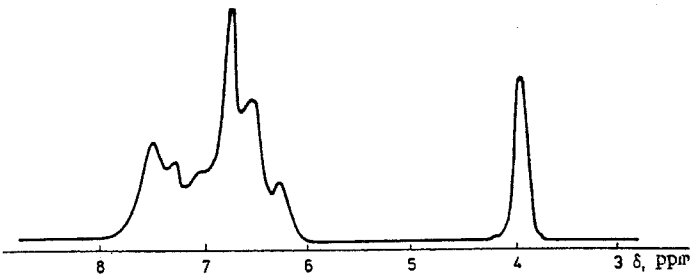


Fig. 1. NMR spectrum of 4-phenyl-3,5-dioxo-2,2-dihydropyrimido[5,6-c]-6H-1'-azaquinolizine (IIIa).

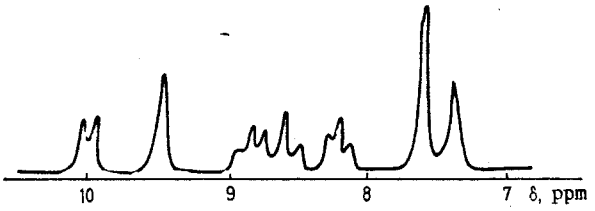
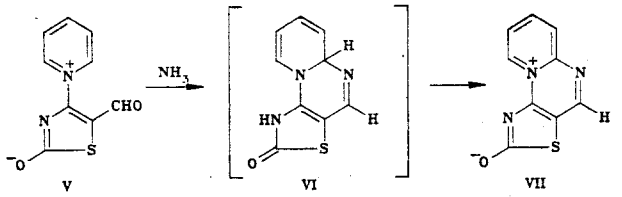


Fig. 2. NMR spectrum of 4-phenyl-3,5-dioxopyrimido[5,6-c]-1'-azaquinolizine (IVa).

compound III is coupled with transfer of an atom of hydrogen or deuterium from the α-carbon of the dihydropyridine in compound II to the carbon atom of the azomethine group.

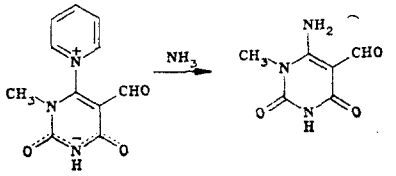
The NMR spectrum of compound IIIa is represented by the methylene proton signals (3.96 ppm) and by the multiplets of the pyridine and phenyl protons centered at 7.63 and 6.38 ppm respectively (Fig. 1). Upon chloranil oxidation of IIIa, an upfield shift of the pyridine protons is observed: the α-proton forms a doublet (10.05 ppm, J = 6 Hz), the β-protons form a doublet and a triplet with centers at 8.57 (J = 8 Hz) and 8.22 (J = 7 Hz) ppm respectively, and the γ-proton forms a triplet at 8.8 (J = 7 Hz) ppm (Fig. 2). Dehydrogenation is evidenced by the absence of the methylene group and the appearance of a methine hydrogen (9.5 ppm).

Introducing a methyl group into the β-position of the betaine pyridinium (Ib) results in formation of the dehydro species IVb under the same conditions. The NMR spectrum includes a pyridinium α-proton doublet (9.83 ppm, J = 7 Hz), γ-proton doublet (8.66 ppm, J = 6 Hz), a β-proton triplet (8.06 ppm, J = 7 Hz), and a methine proton singlet of the pyrimidine fragment (9.56 ppm). The character of the spectrum confirms unambiguously that the pyridinium C-2 participates in the cyclization. The sensitivity of the reaction to a relatively weak electron donor, such as the methyl group in compound Ib, can be linked to its direct polar conjugation with a nitrogen atom via the methylbutadiene fragment in the dihydro form of the transition state (IIb). This promotes hydride loss and formation of IVb rather than the tautomeric conversion IIb → IIIb.



The foregoing is supported by the fact that in an analogous reaction, 5-formyl-4-(1'-pyridinio)thiazole-2-oxide (V) [4], which possesses a greater basicity [5] (pK_{BH+} 0.72) than uracil betaine Ia (pK_{BH+} 0.37), does not form the tautomeric type III dihydro form but is converted directly into compound VII [6]. In this instance, the pyridinium nitrogen atom in the dihydro intermediate VI is more basic due to the absence of conjugation with the carbonyl fragment, which permits greater stabilization of the carbonium ion upon hydrogen elimination.

In the reaction of the betaines of 3-(p-anisyl)-6-(1'-pyridinio)-5-formyluracil-2-oleate (Id) and 3-phenyl-6-(1'-pyridinio-D_5)-5-formyluracil-2-oleate (Ie) with ammonia, in addition to cyclization, the direct exchange of the pyridinium cation for the amino group is observed, with formation of 3-substituted-5-formyl-6-aminouracil. The latter reaction is basic in the case of 1-methyl-6-(1'-pyridinio)-5-formyluracil-2-oleate (VIII), in which the formyl group does not participate in delocalization of the negative charge.



VIII IX

The resulting compound (IX) has previously been described [7].

EXPERIMENTAL

NMR spectra were recorded on a BS-467C instrument using trifluoroacetic acid as solvent and TMS as internal standard. IR spectra were obtained on a UR-20 instrument (vaseline).

4-Phenyl-3,5-dioxo-2,2-dihydropyrimido[5,6-c]-6H-1'-azaquinolizine (IIIa). A. To a 5-g portion (17 mmoles) of compound Ia was added 11.6 g (170 mmoles) of a 25% solution of ammonia, and the mixture was refluxed for 15 min until formation of a yellow precipitate. After cooling, compound IIIa was filtered off. Yield: 2.9 g (59%), mp 340-350°C (from DMF). IR spectrum: ν_{CO} 1650, 1715 cm^{-1}. Found: C 65.0; H 3.8; N 19.1%; $C_{16}H_{12}N_4O_2$. Calculated: C 65.8; H 4.1; N 19.2%. Evaporation of the filtrate yielded a solid which was a 1:2 mixture of compounds IIIa and IVa.

B. A 0.9-g portion (3 mmoles) of Ia was dissolved in 15 ml of water with heating. The solution was cooled to 20°C and 0.71 g (7.4 mmoles) of ammonium carbonate in 10 ml of water was added. The mixture was allowed to stand for 3 h until a precipitate of IIIa formed. Yield: 0.5 g (56%).

4-(p-Tolyl)-3,5-dioxo-2,2-dihydropyrimido[5,6-c]-6H-1'-azaquinolizine (IIIc). A 0.92-g portion (3 mmoles) of compound Ic was dissolved with heating in 10-15 ml of water, and the solution was cooled and filtered. To the filtrate was added 2.9 g (30 mmoles) of ammonium carbonate, and the mixture was refluxed for 15 min until formation of a precipitate. After cooling, IIIc was filtered off. Yield 0.6 g (60%), mp 255-256°C (crystallized form DMF). Found: C 67.3; H 4.8; N 18.5%. $C_{17}H_{14}N_4O_2$. Calculated: C 66.7; H 4.6; N 18.3%.

4-(p-Anisyl)-3,5-dioxo-2,2-dihydropyrimido[5,6-c]-6H-1'-azaquinolizine (IIId). To a 0.3-g portion (1 mmole) of compound Id was added 0.68 g (10 mmoles) of a 25% ammonia solution, and the mixture was refluxed for 15 min until formation of a white precipitate of 3-(p-anisyl)-5-formyl-6-aminouracil. Yield 0.1 g (40%), mp 260-263°C (DMF). The precipitate was filtered off. Upon evaporation of the filtrate, compound IIId was obtained. Yield 0.13 g (42%), mp 222-225°C (acetonitrile). Found: C 63.1; H 4.0; N 17.3%. $C_{17}H_{14}N_4O_3$. Calculated: C 63.4; H 4.3; N 17.4%.

4-Phenyl-3,5-dioxo-2,2-dihydropyrimido[5,6-c]-6(H–D)-1'-azaquinolizine (7,8,9,10-D_4) (IIIe). To a 1.5-g portion (5 mmoles) of compound Ie was added 3.4 g (50 mmoles) of a 25% solution of ammonia, and the mixture was refluxed for 40 min. After cooling, fine, white crystals of 3-phenyl-5-formyl-6-aminouracil were filtered off. Yield 0.36 g (30%), mp 309-312°C (DMF). Found: C 57.5; H 4.2; N 18.2%. $C_{11}H_9N_3O_3$. Calculated: C 57.1; H 4.0; N 18.2%. Evaporation of the filtrate produced IIIe. Yield 0.8 g (54%), mp 344-346°C (decomp.). The compound was crystallized from acetic acid. Found: C 63.9; H–D 4.4; N 18.5%. $C_{16}H_7D_5N_4O_2$. Calculated: C 64.6; H–D 5.7; N 18.8%.

4-Phenyl-3,5-dioxopyrimido[5,6-c]-1'-azaquinolizine (IVa). Chloranil (1.2 g, 5 mmoles) was added to a 1.4-g portion (5 mmoles) of compound IIIa in 20 ml of DMF and the mixture was refluxed for 50 min. After cooling to 20°C, 50 ml of diethyl ether was added, and the resulting precipitate of IVa was filtered off. Yield 1.1 g (78%), mp 354-356°C (acetic acid). IR spectrum: ν_{CO} 1700, 1745 cm^{-1}. Found: C 66.4; H 3.5; N 19.4%. $C_{16}H_{10}N_4O_2$. Calculated: C 64.7; H 3.4; N 20.1%.

10-Methyl-4-phenyl-3,5-dioxopyrimido[5,6-c]-1'-azaquinolizine (IVb). To a 0.75-g portion (2.5 mmoles) of compound Ib was added 1.7 g (25 mmoles) of a 25% aqueous ammonia solution, and the mixture was refluxed for 40 min. After cooling, the resulting precipitate of IVb was filtered off. Yield 0.3 g (40%), mp >350°C (DMF). Found: C 66.2; H 5.0; N 18.1%. $C_{17}H_{12}N_4O_2$. Calculated: C 67.1; H 3.9; N 18.4%.

1-Methyl-5-formyl-6-aminouracil (IX). To a 1.2-g portion (5 mmoles) of 1-methyl-6-(1'-pyridinio)-5-formyluracil-2-oleate was added 3.4 g (50 mmoles) of a 25% aqueous ammonia solution, and the mixture was refluxed for 40 min. After cooling, the precipitated compound IX was filtered off. Yield 0.59 g (68%), mp >330°C (DMF). Found: C 42.9; H 4.4; N 24.8%. $C_6H_7N_3O_3$. Calculated: C 42.6; H 4.1; N 24.8%.

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MASS-SPECTROMETRIC STUDY OF ISOMERIC 5-AMINO-1,2,3-THIADIAZOLES AND 5-MERCAPTO-1,2,3-TRIAZOLES

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The behavior of the isomeric 5-amino-1,2,3-thiadiazoles and 5-mercapto-1,2,3-triazoles under electron impact was studied. It was shown that mass spectrometry can serve as a rapid and reliable method for the identification of these compounds. Key factors in the assignment of a compound to one or the other class are the peaks of the $[M - N_2]^+$ ions, which are more intense in the case of the thiadiazoles, and the ions determined by the decomposition of the prototropic forms of the triazoles. The compositions of the ions were determined by the high-resolution mass spectra.

Either 5-amino-1,2,3-thiadiazoles or the isomeric 5-mercapto-1,2,3-triazoles are formed in the reaction of thioamides, containing acidic methylene hydrogen atoms in the α-position to the thioamide group, with tosylamides.* The structural determination of the products of this cyclization is performed by chemical methods. However, it is known that the interconversion of aminothiadiazoles and mercaptotriazoles proceeds at raised temperatures [2] and under acid-base catalysis [3]; this makes the results of the chemical proof of the structure of these heterocyclic compounds inconclusive. The mass-spectrometric experiment

*It was shown that the final stage of this reaction is the cyclization of the intermediate α-diazothioamides [1].

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