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N-3-OXOALKYLAMIDES AND -THIOAMIDES IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS. 6*. THE EFFECT OF STRUCTURAL FACTORS ON THE REGIODIRECTION OF CYCLIZATION OF PYRIDINIUM DERIVATIVES OF N-(3-OXOALKYL)CHLOROACETAMIDES. STRUCTURE OF 1-(4-HYDROXY-4,6,6-TRIMETHYL-2-OXO-3-PIPERIDYL)PYRIDINIUM CHLORIDE

A. S. Fisyuk and N. V. Poendaev

The structure of 1-(4-hydroxy-4,6,6-trimethyl-2-oxo-3-piperidyl)pyridinium chloride has been established. Reasons have been found influencing the regiodirection of cyclization of pyridinium derivatives of N-(3-oxoalkyl)chloroacetamides.

Keywords: 1-(4-hydroxy-2-oxo-3-piperidyl)pyridinium chlorides, N-(3-oxoalkyl)chloroacetamides, pyridinium salts, intramolecular cyclization, NMR spectra.

Pyridinium salts **2a-d**, depending on the nature of the substituent on the 3-oxoalkyl fragment, are cyclized in basic media into 1-(4-hydroxy-2-oxo-3-piperidyl)pyridinium chlorides **3a,b** or undergo more extensive conversion with the formation of 2-pyridones **4c,d** [1].

It should be noted that two new asymmetric centers are formed on cyclization of compounds **2a,b** into 1-(4-hydroxy-2-oxo-3-piperidyl)pyridinium chlorides **3a,b**. The presence in the NMR spectra of these compounds of signals of only a single isomer indicates the diastereospecificity of the reaction, the reasons for which remain unclear. With the aim of discovering the reasons influencing the regiodirection of the cyclization we have studied the structure of 1-(4-hydroxy-4,6,6-trimethyl-2-oxo-3-piperidyl)pyridinium chloride (**3b**).

In the ^{1}H NMR spectrum of compound **3b** in DMSO-d_6 solution signals are present for two magnetically nonequivalent protons at $C_{(5)}$ (AB system), singlet signals of protons of the three methyl groups, a hydroxyl and the NH proton. The signals of the pyridinium cation are observed as a broad singlet for α-H at 8.99 and two triplets at 8.75 (γ-H) and 8.22 ppm (β-H), which indicates the restraint on its rotation about the $C_{(3)}$–Py bond. On this basis it is possible to assume the presence in heterocycle **3b** of a donor-acceptor interaction between the π-deficient pyridinium substituent and the *p*-electrons of the hydroxyl group oxygen stabilizing the conformation with their *trans*-diequatorial disposition in *trans*-**3b**. A similar intramolecular interaction was noted for 5-cyano-2-hydroxy-3-(1-pyridyl)-1,2,3,4-tetrahydropyridine-6-thiolates [2].

* For Part 5 see [1].

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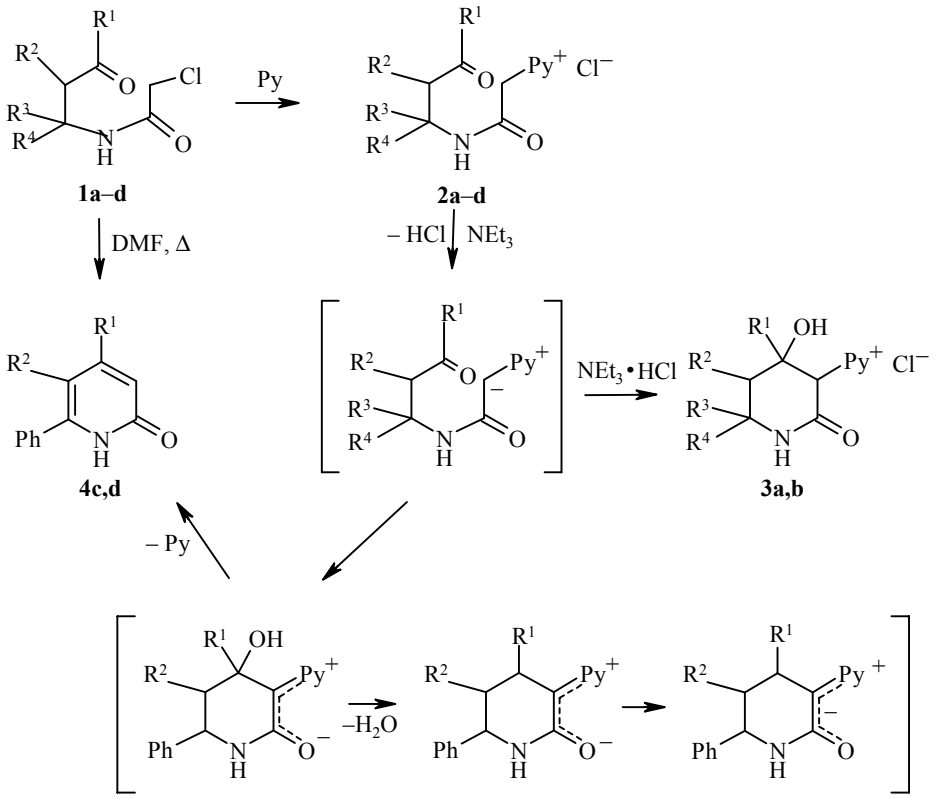
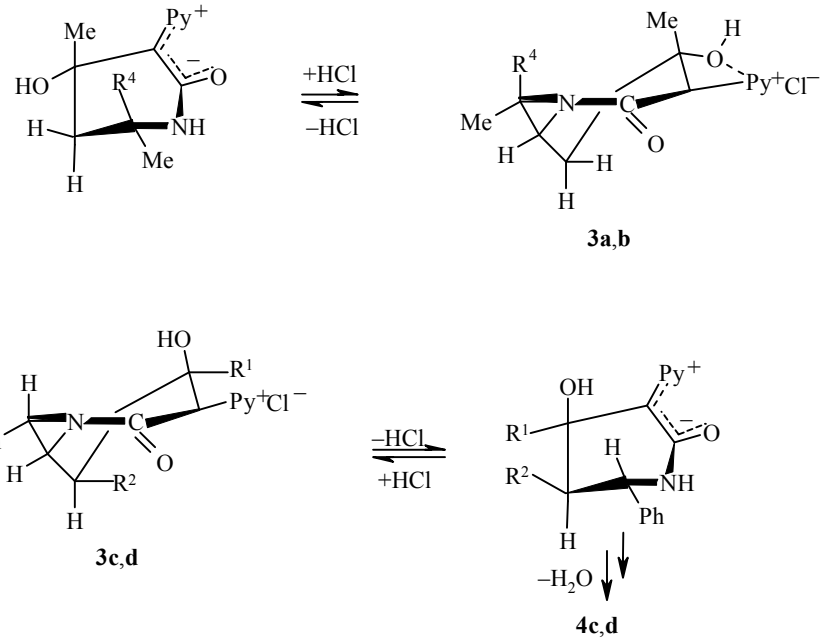


1–3 a $R^1 = R^3 = Me$, $R^2 = R^4 = H$, **b** $R^1 = R^3 = R^4 = Me$, $R^2 = H$; **1**, **2**, **4 c** $R^1 = R^3 = Ph$, $R^2 = R^4 = H$, **d** $R^1 + R^2 = (CH_2)_4$, $R^3 = Ph$, $R^4 = H$

Addition of catalytic amounts of deuterotrifluoroacetic acid to a solution of compound *trans*-**3b** in DMSO-d_6 leads to the proton signal of the α-H of the pyridine ring narrowing and resolving into a doublet. Probably, on protonation of the hydroxyl group the donor-acceptor interactions are weakened, which leads to an increase in the lability of the pyridinium cation.

In the spectrum of compound **3b** in CD_3OD solution the signals of the NH and OH protons are absent due to exchange with the solvent. The α-H protons of the pyridinium cation proved to be magnetically equivalent. Their signal is at 8.98 ppm as a doublet, which indicates the free rotation of Py^+ about the $C_{(3)}$–Py bond. The high conformational lability of compound **3b** in methanol compared with the solution in DMSO is caused by the formation of hydrogen bonds with the solvent, blocking the *p*-electrons of the hydroxyl group oxygen, which also leads to a weakening of the donor-acceptor interactions of the pyridinium cation with hydroxyl. A reduction in temperature leads to inhibition of such rotation. The pyridinium α-H (-7°C) and β-H (-25°C) are fixed initially as broadened singlets, and then at -30°C each proton of the pyridinium cation gives a separate signal.

The hydrogen atom is mobile and at a temperature of ~30°C is subject to deuterium exchange with a time for half-exchange of 0.5 h. Cleavage of the 3-H proton in compound **3b** must probably lead to the formation of a betaine, stabilized by the charge distribution in the Py^+ fragment and $C_{(3)}{=}CO^- \leftrightarrow {}^-C_{(3)}C{=}O$. It should be noted that as a result of deuterium exchange no change in the configuration of *trans*-**3b** occurred, which indicates that deuterium enters the same side of the molecule from which the proton is split off.



On the basis of the above it may be assumed that the regiodirection of cyclization of N-(3-oxoalkyl)amides **2a-d** is controlled by the nature of the substituent found in α-position to the carbonyl group, but the possibility of further conversions forming heterocycles **3** depends on their configuration. When R^1 and R^2 are linked in a ring, and also when a bulky R^1 substituent is present, the axial orientation of R^1 in the resulting compound **3** becomes disadvantageous. In difference to the methyl-substituted compounds **2a,b**, on cyclization of **2c,d** the structural factors aid the formation of the *cis* isomers **3c,d**, having an equatorial disposition of the substituents R^1 and Py^+. Probably, cleavage of water from compound **3** proceeds by a one-stage synchronous mechanism, requiring an *anti*-periplanar disposition of the proton and leaving group, which happens in *cis*-**3c,d**. Further conversions of the resulting intermediates are linked with the migration of the double bond to position $C_{(5)}=C_{(6)}$ and subsequent cleavage of pyridinium hydrochloride.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of compound **3b** were recorded on a Bruker AC 200 P instrument (200 and 50 MHz respectively), internal standard was TMS.

Compound 3b was obtained by the procedure of [1].

1-(4-Hydroxy-4,6,6-trimethyl-2-oxo-3-piperidyl)pyridinium Chloride (3b). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 8.98, 8.71, 8.16 (5H, d, t, t, Py); 5.89 (1H, s, $C_{(3)}$–H); 2.18 (2H, s, $C_{(5)}$–H_2); 1.54 (3H, s, $C_{(6)}$–CH_3); 1.29 (3H, s, $C_{(6)}$–CH_3); 1.13 (3H, s, $C_{(4)}$–CH_3); (DMSO-d_6): 8.99, 8.75, 8.22 (5H, br. s, t, t, Py); 8.50 (1H, s, NH); 6.15 (1H, s, OH); 5.90 (1H, s, $C_{(3)}$–H); 2.11 (1H, d, ^2J = 14.5, $C_{(5)}$–H); 2.02 (1H, d, ^2J = 14.5, $C_{(5)}$–H); 1.45 (3H, s, $C_{(6)}$–CH_3); 1.28 (3H, s, $C_{(6)}$–CH_3); 1.04 (3H, s, $C_{(4)}$–CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 163.4 (NCO); 146.5, 146.5, 146.4, 127.1, 127.1 (Py); 75.4 ($C_{(3)}$); 70.5 ($C_{(4)}$); 51.4 ($C_{(5)}$); 45.9 ($C_{(6)}$); 32.7 ($C_{(6)}$–CH_3); 30.6 ($C_{(6)}$–CH_3); 25.8 ($C_{(4)}$–CH_3).

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