Formation of cyclic ketene *N*-hydroxyaminals, 2-acylmethylene-1-hydroxyimidazolidines, in the reaction of 1,2-bishydroxylamines with 1,3-ketoaldehydes

Dmitrii G. Mazhukin,* Aleksei Ya. Tikhonov, Vladimir A. Reznikov and Leonid B. Volodarsky

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 383 234 4752; e-mail: dimm@mail.nsk.ru

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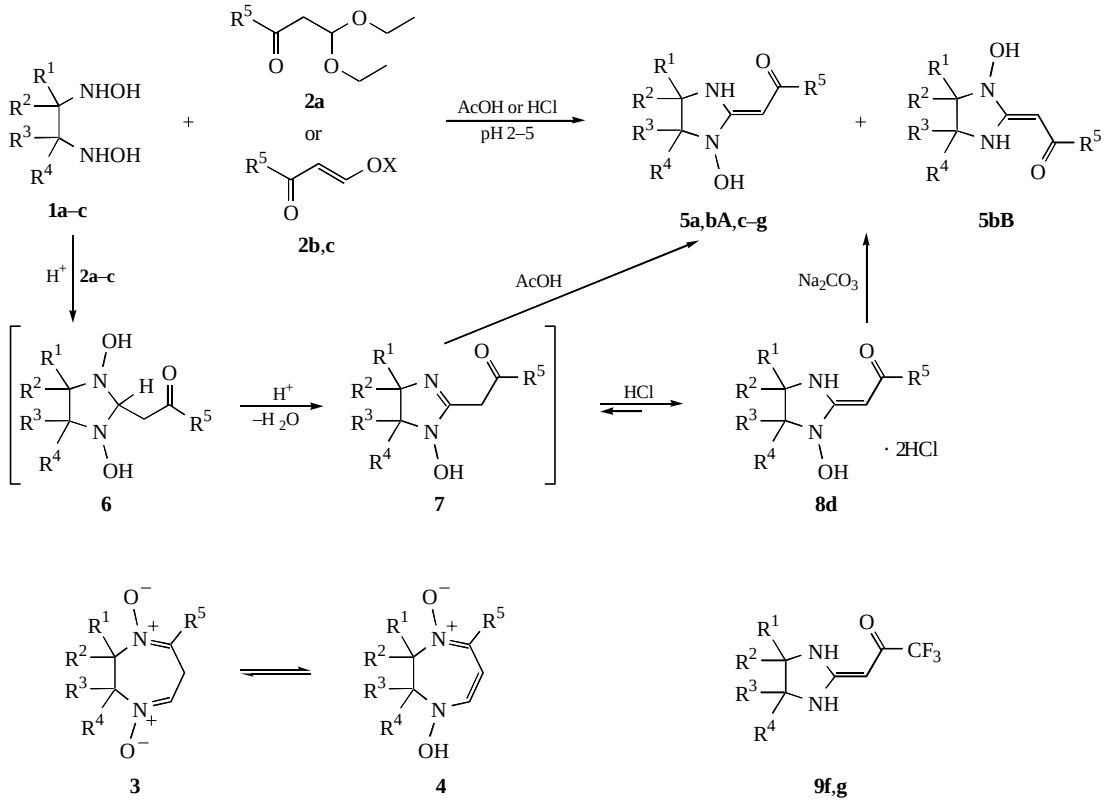
The reaction of aliphatic 1,2-bishydroxylamines with 1,3-ketoaldehydes generated *in situ* in acidic media leads to 2-acylmethylene-1-hydroxyimidazolidines, a new class of cyclic ketene *N*-hydroxyaminals.

Aliphatic 1,2-diamines react with 1,3-dicarbonyl compounds in the presence of acids with the formation of 2,3-dihydro-1,4-diazepinium salts.[1] The best yields of 1,4-diazepines were observed at pH 2–5 when the formation of accompanying enaminoketones was minimised because the equilibrium was shifted towards the thermodynamically more favourable diazepinium cation.[2] The reaction of another type of N-centered binucleophiles, aliphatic 1,2-bishydroxylamines,[3] with 1,3-dicarbonyl compounds has not so far been investigated. It is tempting to suppose that 1,3-ketoaldehydes may react with 1,2-bishydroxylamines to form 1,4-diazepine *N*-oxides or their tautomeric *N*-hydroxy derivatives.

Because 1,3-ketoaldehydes are unstable compounds, we used their synthetic equivalents, *viz*., the 1,3-ketoacetal **2a**, sodium salt **2b** or enol ether **2c**, in the reaction with 1,2-bishydroxylamines **1a**–**c**. Free 1,3-ketoaldehydes **2** were generated in the reaction mixture by acidification or acid-catalysed hydrolysis (pH 2–5) . We found that the reaction of *cis*-1,2-bis(hydroxylamino)cyclohexane **1a** with the sodium salt of 3-oxo-3-phenylprop-1-enol **2b** in glacial acetic acid was complete within 30 h at room temperature to afford a compound in 63% yield. The elemental analytical data for this compound formally corresponded to a product of condensation of the ketoaldehyde with the bishydroxylamine with elimination of two water molecules. However, the product was neither of the 1,4-diazepines **3** or **4**. As judged from the spectroscopic characteristics of this compound, it has the structure of a cyclic ketene *N*-hydroxyaminal, *viz*., 2-benzoylmethylene-1-hydroxyimidazolidine **5a**. Thus, the ^{1}H NMR spectrum of **5a** exhibits a characteristic signal (5.62 ppm) of the methyne proton at an (electron-rich) sp^2 carbon atom. The ^{13}C NMR spectrum of **5a** shows the presence of a carbonyl group (184.2 ppm) and an enamine fragment (a doublet at 75.4 ppm and a singlet at 166.9 ppm). A number of intense broad bands typical of enaminoketones[4] were observed in the IR spectrum of **5a** at 1525–1615 cm^{-1} .

Ketene aminals, including cyclic examples of the imidazolidine series, are reactive species, and convenient starting compounds for the synthesis of fused heterocycles. The chemistry of these compounds has been reviewed in refs. 5, 6. However, only one



1a, **5a** $R^1 + R^3 = (CH_2)_4$, $R^2 = R^4 = H$, $R^5 = Ph$
1b, **5b** $R^1 = R^3 = R^4 = Me$, $R^2 = H$, $R^5 = Ph$
1c, **5c** $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = Ph$
5d, **8d** $R^1 + R^3 = (CH_2)_4$, $R^2 = R^4 = H$, $R^5 = Me$
5e $R^1 = R^2 = R^3 = R^4 = R^5 = Me$
5f, **9f** $R^1 + R^3 = (CH_2)_4$, $R^2 = R^4 = H$, $R^5 = CF_3$
5g, **9g** $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = CF_3$

2a $R^5 = Me$
2b $R^5 = Ph$, X = Na
2c $R^5 = CF_3$, X = Et

Scheme 1

example of the synthesis of a cyclic ketene *N*-hydroxyaminal, by the reaction of 4,5-dihydro-1-hydroxy-2-methylimidazole with ethyl benzoate in the presence of lithium diisopropylamide (LDA), has been reported earlier.[7]

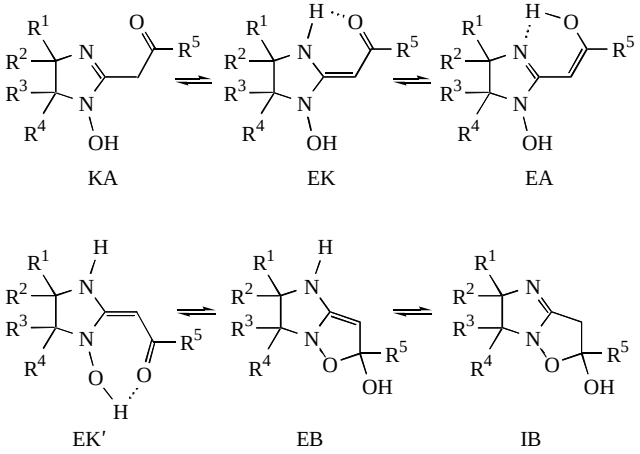
The reaction of 1,2-bishydroxylamines **1b**,**c** with 1,3-ketoaldehyde **2b** also leads to 2-benzoylmethylene-1-hydroxyimidazolidines **5**. Thus, a mixture of two isomeric imidazolidines **5bA** and **5bB** was obtained in the reaction of unsymmetrical 1,2-bishydroxylamine **1b** with the sodium salt of enol **2b**. In this reaction, the sterically hindered 1,2-bishydroxylamine **1c** gave the cyclic ketene *N*-hydroxyaminal **5c** in high yield. The formation of **5** could be rationalised as a result of dehydration of intermediate imidazolidines **6** (*cf*. ref. 8) to 4,5-dihydroimidazoles **7**, which are obviously more stable as tautomeric enaminoketones **5A**,**B**. When 1,2-bishydroxylamine **1a** reacted with acetoacetaldehyde diethyl acetal **2a** in anhydrous methanol saturated with HCl, the dihydrochloride **8d** was quantitatively precipitated from the reaction mixture. The free enaminoketone base **5d** was prepared by careful alkalination of a solution of **8d** (Scheme 1).

The reaction of 1,2-bishydroxylamines **1a**,**c** with *trans*-4-ethoxyvinyl trifluoromethyl ketone **2c**[9] in a water–methanol solution of HCl gave cyclic ketene *N*-hydroxyaminals **5f** and **5g**, respectively.† In the case of 1,2-bishydroxylamine **1c**, the cyclic ketene aminal **9g** was formed in the reaction mixture along with compound **5g** in almost equal amount. The ^{1}H NMR spectrum of crude compound **5f** exhibits low-intensity signals of a by-product that can be identified as the ketene aminal **9f**.

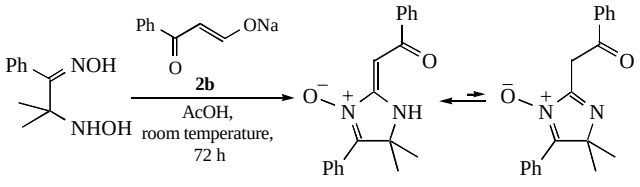
The ^{13}C NMR spectroscopy data for 2-acylmethylene-1-hydroxyimidazolidines **5**‡ indicate that these compounds exist in solution as enaminoketone EK rather than ketoamidine KA forms. The observed signals are likely due to fast proton transfer (on an NMR scale) with the formation of enol–amidine specie s EA§ and, as a consequence, with the presence of tautomeric mixture EK $\rightleftharpoons$ EA in the solution. The evident difference between the positions of long-wave maxima in the UV spectra of parent enaminoketones[11,12] (λ_{max} = 325–330 nm) and enhydroxylaminoketones[13] (λ_{max} = 350 nm), as compared with the positions of maxima for **5a**–**c** (λ_{max} = 330–333 nm) motivated us to reject alternative tautomeric form EK′. Because of the presence of carbonyl signals in the ^{13}C NMR spectra, the bicyclic tautomers, enamine EB and imine IB (Scheme 2), can be ruled out as significant contributors.

In the above reaction with 1,3-ketoaldehyde **2b**, 1,2-hydroxyaminooxime **10**,[16] a precursor of 1,2-bishydroxylamines, afforded 2,5-dihydroimidazole derivative **11**. The ^{1}H and ^{13}C NMR spectra of **11** in [^{2}H$_6$]DMSO indicated that this compound is a mixture of two tautomers **11A** and **11B** in the ratio ~10:1 (Scheme 3). The conjugation in a diazadiene fragment of 4*H*-imidazole **11B** seems to be less favourable than the formation of tautomer **11A** possessing an exocyclic double bond.

Sterically hindered 2-acylmethylene-1-hydroxyimidazolidines **5c**,**e**,**g** are of interest as possible chelating ligands for the preparation of transition metal complexes with abnormal magnetic properties. We have found that the oxidation of **5c** by PbO_2 leads to an unstable paramagnetic compound. According to the EPR spectrum, this compound has an iminonitroxide moiety (a_{N1} = 9.2 G, a_{N2} = 4.6 G), *i.e.*, it is an oxidation product of corresponding tautomeric species KA. At the same time, the reaction of **5g** with Ni, Co, Cu and Pd salts followed by oxidation of the resulting chelates with PbO_2 yielded stable paramagnetic complexes, in which the energy of exchange interactions between unpaired electrons was ~100 cm^{-1}.[17]



Scheme 2



Scheme 3

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† *Typical condensation procedure*: a solution of 15 mmol of 1,3-ketoaldehyde **2a**–**c** in 10 ml of glacial AcOH (for **2b**) or in 10 ml of methanol (for **2a**,**c**) was added dropwise to a solution of 10 mmol of 1,2-bishydroxylamine **1a**,**b**,[3(*a*)]**c**[3(*b*)] in 10 ml AcOH or 10 ml MeOH containing ~25 mmol of HCl (2.08 ml of a concentrated aqueous HCl solution) for 15 min with stirring. The reaction mixture was kept at room temperature for 30–72 h or refluxed for 3–7 h up to the disappearance of starting 1,2-bishydroxylamine and intermediate 1,3-dihydroxyimidazolidine **6** (the reaction was monitored using TLC plates treated by I_2 vapour). The solvent was removed *in vacuo*, the residue was treated with 10 ml of water, and a saturated sodium carbonate solution was carefully added to adjust pH ~8. The mixture was extracted with EtOAc (3×15 ml), and the combined organic layers were dried with anhydrous $MgSO_4$. Evaporation of the EtOAc solution gave a crude product, which was purified by silica gel chromatography (chloroform was the eluent) to yield 2-acylmethylene-1-hydroxyimidazolidines **5** (30–68% yields).

‡ All new compounds gave satisfactory elemental analysis data and were characterised by UV, IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

5a: 63% yield, mp 198–201 °C (EtOH). ^{13}C NMR (50.32 MHz, [^{2}H$_6$]DMSO) δ: 20.2, 21.3, 23.5, 28.9 (4t, CH_2), 51.6 (d, C-4), 61.7 (d, C-5), 75.4 (d, CH=), 126.4 (d, C_{meta}, Ph), 128.1 (d, C_{ortho}, Ph), 129.9 (d, C_{para}, Ph), 140.9 (s, C_{ipso}, Ph), 166.9 (s, C-2), 184.2 (s, C=O). UV [EtOH, λ_{max}/nm (lg ε)]: 243 (4.13), 333 (4.44).

5g: 33% yield, mp 208–211 °C (EtOAc–hexane). ^{13}C NMR (50.32 MHz, [^{2}H$_6$]DMSO) δ: 17.8 (q, Me), 22.2 (q, Me), 61.2 (s, C-4), 68.7 (s, C-5), 71.5 (d, CH=), 118.2 (q, CF_3, $^2J_{C–F} \approx$ 280 Hz), 163.8 (s, C-2), 171.0 (q, C=O, $^3J_{C-F} \approx$ 30 Hz).

9g: 34% yield, mp 193–194 °C ($CHCl_3$). ^{13}C NMR (50.32 MHz, [^{2}H$_6$]DMSO) δ: 22.4 (q, Me), 62.3 (s, C-4 and C-5), 71.5 (d, CH=), 117.5 (q, CF_3, $^2J_{C-F} \approx$ 280 Hz), 161.9 (s, C-2), 169.4 (q, C=O, $^3J_{C-F} \approx$ $\approx$ 30 Hz).

11: 32% yield, mp 145–147 °C (EtOAc–hexane). ^{1}H NMR (200.13 MHz, [^{2}H$_6$]DMSO) δ; **11A**: 1.75 (s, 6H, Me), 6.57 (s, 1H, CH=), 7.49–7.61, 7.93–8.01, 8.56–8.63 (3m, 10H, Ph); **11B**, 1.59 (s, 6H, Me), 4.60 (s, 2H, CH_2), 7.42–7.63, 8.01–8.08, 8.57–8.62 (3m, 10H, Ph). ^{13}C NMR (50.32 MHz, [^{2}H$_6$]DMSO) δ; **11A**: 26.1 (q, Me), 64.5 (s, C-5), 77.3 (d, CH=), 125.9 (s, C_{ipso}, Ph), 126.8, 127.7, 128.5, 128.8, 131.4 (5d, C_{ortho}, C_{meta}, C_{para}, Ph and PhC=O), 139.1 (s, C_{ipso}, PhC=O), 148.5 (s, C-4), 158.2 (s, C-2), 187.4 (s, C=O); **11B**: 24.8 (q, Me), 36.4 (t, CH_2), 73.8 (s, C-4), 126.2 (s, C_{ipso}, Ph), 126.7, 128.3, 131.0, 133.7 (4d, C_{ortho}, C_{meta}, C_{para}, Ph and PhC=O), 135.9 (s, C_{ipso}, PhC=O), 153.5 (s, C-5), 162.4 (s, C-2), 193.5 (s, C=O). The assignment of signals due to carbon atoms in the imidazole ring for tautomers **11A** and **11B** was performed on the basis of literature analogues.[10]

All spectroscopic data for compounds **5**, **8**, **9** and **11** will be published elsewhere.

§ This species was postulated previously[14,15] for 2-acylmethyleneimidazolidines.

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