Unusual reactions of 6,8-dialkyl-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octan-7-one 3,3-dioxides under conditions of acid hydrolysis and acetylation

Galina A. Gazieva,* Angelina N. Kravchenko and Yurii A. Strelenko

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation. Fax: +7 095 135 5328

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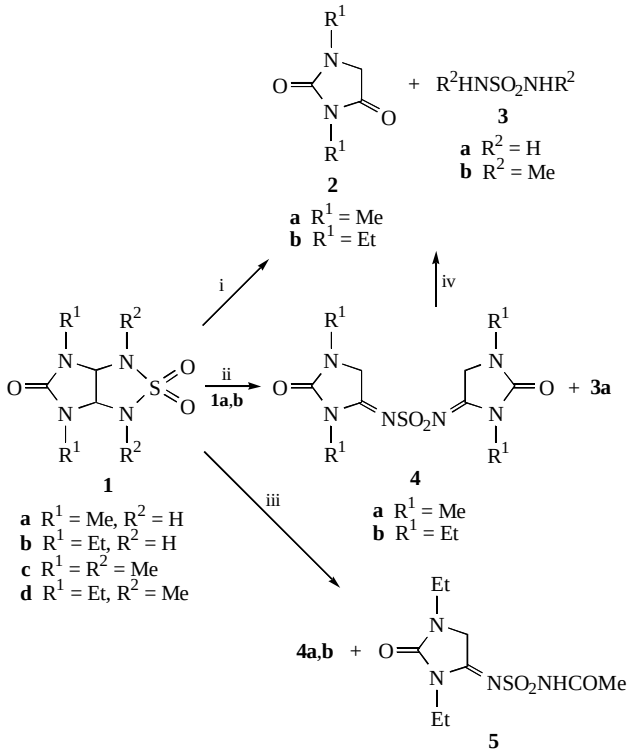
The title compounds were found to transform into 4,4′-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) under the action of acids (pH 1) or acetyl chloride.

Cyclic sulfamides are of considerable interest because they can exhibit biological activity.[1] Previously, new bicyclic compounds, *viz*., 6,8-dialkyl- and 2,4,6,8-tetraalkyl-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octan-7-one 3,3-dioxides **1** (Scheme 1), which are monosulfo analogues of 2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-diones, were prepared by the condensation of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones with sulfamides.[2]

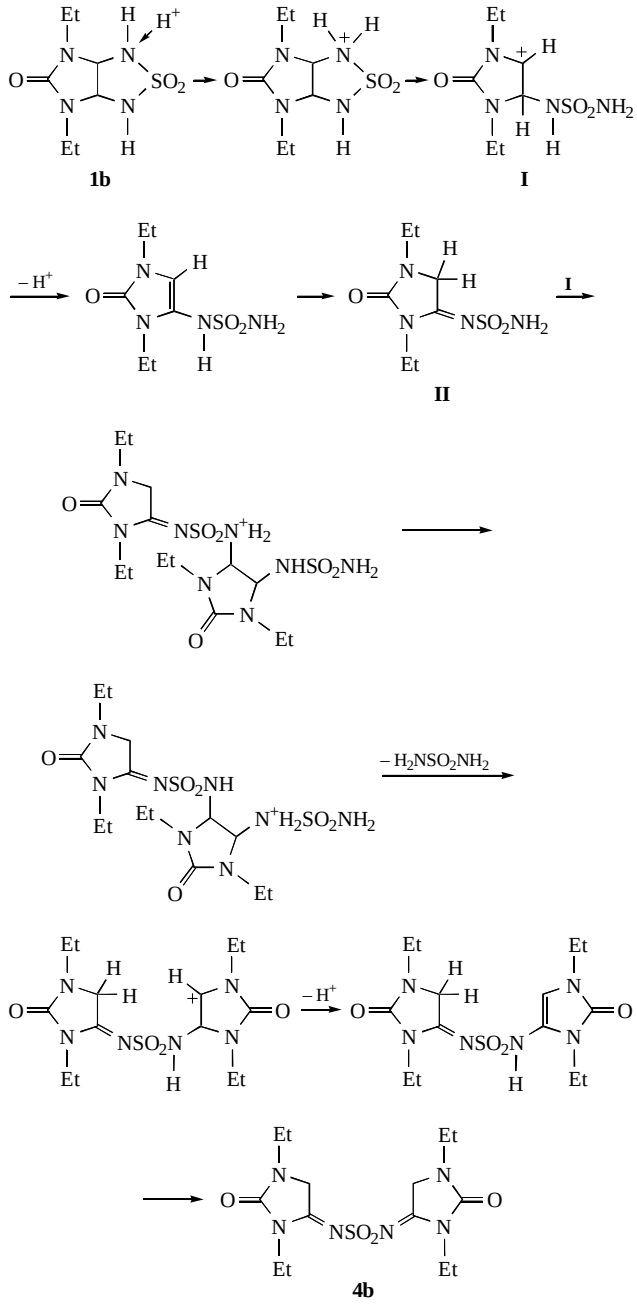


Scheme 1 *Reagents and conditions*: i, 25% H_2SO_4, reflux, 0.2–5 h; ii, pH 1 (1 M HCl or TFA), 60 °C, H_2O, 0.5 h; iii, AcCl, Py; iv, pH < 1, 90 °C, > 1 h.

The stability of compounds **1** to acid hydrolysis was examined. The experiments were performed on reflux in 25% sulfuric acid, on heating in water in the presence of hydrochloric or trifluoroacetic acid (TFA) at pH 1 and in DMSO in the presence of TFA at 30 °C.

It is well known that 2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-diones are stable to acid hydrolysis. For example, Mebicar (2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-dione) was completely hydrolysed in 51 h on boiling in 25% sulfuric acid. 1,3-Dimethylurea and 1,3-dimethylhydantoin are the main hydrolysis products of Mebicar.[3]

We found that 3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octan-7-one 3,3-dioxides **1a**–**d** were completely hydrolysed in 0.2–5 h under analogous conditions. Similarly to Mebicar, the main hydrolysis products for compounds **1a**–**d** were identified as corresponding 1,3-dialkylhydantoin **2** and sulfamide **3** (Scheme 1). The rate of reaction and the qualitative composition of hydrolysis products were examined by TLC and ^{1}H NMR spectroscopy.



Scheme 2

When the hydrolysis of **1a**,**b** was performed with hydrochloric acid or TFA (in water) at pH 1 and 60 °C, the reaction unusually proceeded with the formation of 4,4′-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) **4a**,**b**† and sulfamide **3a** (Scheme 1).

It was found that an increase in the acidity, temperature and reaction time (> 1 h) resulted in the degradation of imino derivative **4** to a 1,3-dialkylhydantoin and a sulfamide (Scheme 1).

The course of the reaction was followed by TLC and ^{1}H NMR spectroscopy.‡ Compound **1b** was used as a substrate for ^{1}H NMR monitoring; the rate of reaction was judged from a decrease in the integral intensity of the singlet of bridging CH–CH protons, δ 5.31 ppm.

In DMSO in the presence of TFA (approximately 0.125 mol dm^{-3}) at 30 °C, compound **1b** was converted into **4b** by 50% for 1 h. At a constant proton concentration, the reaction was of pseudo-first order with the apparent rate constant k = $= 7.92 \times 10^{-3}$ min^{-1}.

† Previously, compounds **4** were prepared from 4,5-dihydroxyimidazolidin-2-ones and a sulfamide.[4]

‡ The ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer (300.13 MHz). Chemical shifts were measured with reference to residual protons of [$^2H_6$]DMSO (2.50 ppm). The mass spectra were measured on a Varian MAT-CH-6 instrument; the IR spectra were recorded on a UR-20 spectrometer (in KBr pellets). TLC was performed with the use of the chloroform–methanol system (9:1).

1a: yield 45–49%, mp 201–203 °C, R_f 0.14 (visualisation with I_2). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.69 (s, 6H, NMe), 5.22 (s, 2H, CH), 7.66 (s, 2H, NH). IR (KBr, ν/cm^{-1}): 3272, 3104 (NH), 2984 (Me), 1684 (C=O), 1344, 1168 (SO_2). MS, m/z: 206 (M^+).

1b: see ref. 2, R_f 0.29 (I_2).

2a: R_f 0.37 (visualisation with an alkaline solution of sodium nitroprusside, orange colour). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.71 (s, 6H, NMe), 3.76 (s, 2H, CH_2).

2b: R_f 0.69 (visualisation with an alkaline solution of sodium nitroprusside, brick-red colour). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.04 (t, 6H, Me), 3.28 (q, 2H, NCH_2), 3.35 (q, 2H, NCH_2), 3.82 (s, 2H, CH_2).

3a: R_f 0.22 (I_2). ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.05 (NH).

3b: R_f 0.31 (I_2). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.42 (s, 6H, NMe), 6.60 (NH).

4a: yield, 65–70%, see ref. 4, R_f 0.82 (visualisation with I_2 and an alkaline solution of sodium nitroprusside, white colour).

4b: yield, 66–70%, see ref. 4, R_f 0.88 (visualisation with I_2 and an alkaline solution of sodium nitroprusside, white colour).

5: yield, 13.9%, mp 156–159 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.13 (t, 6H, Me), 1.96 (s, 3H, COMe), 3.29 (q, 2H, NCH_2), 3.51 (q, 2H, NCH_2), 4.59 (s, 2H, CH_2), 11.69 (s, 1H, NH). IR (KBr, ν/cm^{-1}): 3488, (NH), 1728, 1708 (C=O), 1604 (C=N), 1336, 1160 (SO_2). MS, m/z: 276 (M^+).

A singlet due to protons of the ring CH_2 group of imino derivative **4b** at δ 4.47 ppm appeared in the ^{1}H NMR spectra almost immediately; the intensity of this signal increased with time. Moreover, we detected an additional singlet at δ 4.58 ppm, whose intensity changed only slightly during the reaction time and which disappeared almost simultaneously with the signal of the starting compound. We believe that this signal can be attributed to the protons of the ring CH_2 group of intermediate 1,3-diethyl-4-aminosulfonyliminoimidazolidin-2-one **II**. The reaction can proceed according to Scheme 2, which is similar to the formation of compounds **4** from 4,5-dihydroxyimidazolidin-2-ones and a sulfamide.[4]

The acylation of **1a**,**b** with acetyl chloride also resulted in the formation of 4,4′-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) **4a**,**b** in 50% yields. A small amount of *N*-(1,3-diethyl-2-oxoimidazolidin-4-ylidenaminosulfonyl)acetamide **5** was isolated from the reaction mixture in addition to **4b** (Scheme 1). Evidently, under the action of acetyl chloride, the ring containing a sulfamide unit in 6,8-dialkyl-3-thia-2,4,6,8-tetraazabicyclo-[3.3.0]octan-7-one 3,3-dioxides undergoes degradation similarly to the above reaction under exposure to acids. This reaction scheme is supported by the isolation of *N*-(1,3-diethyl-2-oxoimidazolidin-4-ylidenaminosulfonyl)acetamide.

The kinetics of acid hydrolysis of compound **1** to form **4** will be studied in detail at a later time.

References

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