

New condensation methods in the synthesis of bicyclic bisureas

Angelina N. Kravchenko,* Oleg V. Lebedev and Elena Yu. Maksareva

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation.

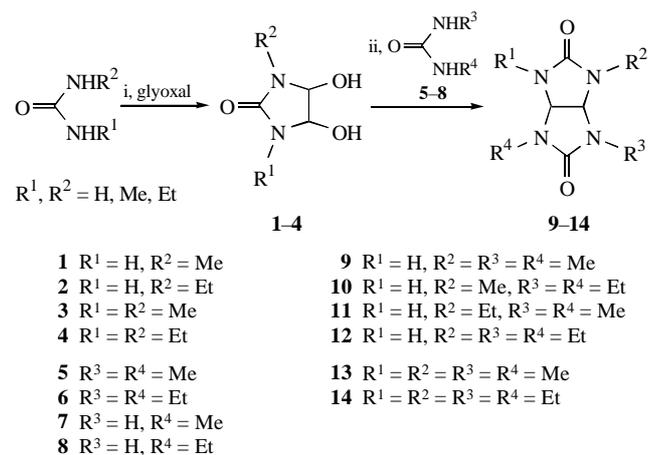
Fax: +7 095 135 5328

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For the first time, synthetic approaches to bicyclic bisureas of the octane series bearing three alkyl substituents at nitrogen atoms have been developed.

Bicyclic bisureas of the octane series, 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones (TABOD) are a new class of promising physiologically active substances.¹ Calculations performed by the QSAR method demonstrated that N-alkylated TABOD with methyl and ethyl substituents are most promising.² Published data concerning condensation methods for preparing TABOD indicate that changes in the position and number of substituents at nitrogen atoms creates some synthetic difficulties. Only mono-, di- and tetra-N-methyl(ethyl)-substituted TABOD (*cis*- and *trans*-) can be prepared by known synthetic methods. Tri-N-methyl(ethyl)-substituted TABOD derivatives were not described in the literature.

For the first time, we examined the interaction of N-methyl(ethyl)ureas with glyoxal at pH 4.5 using ¹H NMR spectroscopy and TLC control. We found that it results in corresponding mono-N-alkyl-4,5-dihydroimidazolidin-2-ones **1**, **2** (Scheme 1) which were further condensed with N,N'-dialkylureas **5**, **6**. The condensation of **1** with **5** or **6** results in **9** (yield 47–49%) or **10** (yield 40–42%), respectively, and the condensation of **2** with **5** or **6** gives **11** (yield 44–46%) or **12** (yield 37–39%), respectively.



Scheme 1 Reagents and conditions: i, H₂O, pH 4.5, 45–50 °C, 2 h; ii, H₂O, pH 1–2, 90 °C, 1 h.

This synthetic approach (method A) allowed us to obtain the following tri-N-alkyl-substituted TABOD: 2,4,6-trimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione **9**, 2,4-diethyl-6-methyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione **10**, 2,4-dimethyl-6-ethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione **11** and 2,4,6-triethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione **12**.

To confirm the structure of the compounds obtained, an independent synthesis was performed. 1,3-Dimethyl(diethyl)-4,5-dihydroimidazolidin-2-ones **3**, **4** were synthesised according to published procedures.^{4,5} These compounds (Scheme 1) reacted with N-monomethyl(monoethyl)ureas **7**, **8** to form **9–12** (method B). The reaction of **3** with **7** or **8** results in **9** (yield 32–35%) or **11** (yield 50–52%), respectively, and the reaction of **4** with **7** or **8** gives **10** (yield 60–61%) or **12** (yield 37–39%), respectively.

Both of the above approaches can be used for the synthesis of target products **9–12**. However, method A seems to be more suitable for the synthesis of **9** and **12**, and method B is better for

the synthesis of **10** and **11**. In addition, known tetra-N-alkyl-TABOD **13**, **14** (20–25%) were formed simultaneously as a result of the interaction of dimethyl- and diethylureas with glyoxal. The physico-chemical properties of tri- and tetra-alkyl-TABOD are very similar, and therefore column chromatography was used to separate individual compounds **9–12**.

Tri-N-alkyl-TABOD **9–12** are of both theoretical and practical interest. This is evident not only from the structure of **9–12**, but also from their NMR spectra.[†]

The geometrical rigidity and nonplanar structure of the molecular skeleton are characteristic of bicyclic bisureas. Therefore, a chiral environment is created for any pair of geminal protons or N-substituent groups (for example, for CH₂ of the ethyl group) to result in diastereotopy displayed in chemical nonequivalence of the above pairs of magnetic nuclei. For compounds **10–12**, these are diastereotopic methylene protons of the N-ethyl groups.

The ¹H NMR spectrum of compound **10** exhibits a singlet of N-Me protons with δ 3.03 ppm. The AB system of CH-CH protons exhibits signals with δ_A 5.23 and δ_B 5.37 ppm (J_{AB} 8.3 Hz); the former is due to H_A located between N-ethyl and N-methyl groups, and the latter, due to the H_B proton located between N-ethyl and NH groups because it is additionally split into a doublet with J 2.3 Hz as a result of vicinal spin-spin interaction with the NH proton. According to the structure of compound **10**, two N-ethyl groups exhibit the AMX₃ and A'M'X'₃ systems with the following parameters: δ_A 3.66, δ_M 3.33 and δ_X 1.29 ppm ($J_{AM} = {}^2J_{AX} = {}^2J_{MX} = 14.0$ Hz) and δ_A 3.51, δ_M 3.31 and δ_X 1.25 ppm ($J_{A'M'} = {}^2J_{A'X'} = {}^2J_{M'X'} = 14.2$ Hz), respectively. The signals due to the NH group are represented by a singlet at δ 7.18 ppm.

The ¹H NMR spectrum of compound **11** exhibits two singlets from N-Me groups with the chemical shifts δ_1 2.89 and δ_2 2.98 ppm and the AMX₃ system with the chemical shifts δ_A 3.52, δ_M 3.23 and δ_X 1.19 ppm and the spin-spin coupling constants $J_{AM} = {}^2J_{AX} = {}^2J_{MX} = 16.0$ Hz. The X-part is a triplet, and the AM-part is a doublet of sextets. The CH-CH protons manifest themselves as the AB system with the very close chemical shifts δ_A 5.16 and δ_B 5.17 ppm (J_{AB} 8.2 Hz). The NH group exhibits a singlet at δ 7.20 ppm.

The ¹H NMR spectrum of compound **12** includes the AB system of methine protons with δ_A 5.28 and δ_B 5.29 ppm (J_{AB} 8.2 Hz) and a singlet from the NH group with the chemical shift δ 7.2 Hz. All ethyl groups in compound **12** are structurally non-equivalent; this fact manifests itself as three AMX₃ systems in the spectrum. Two of these systems exhibit similar spectrum charac-

[†] ¹H NMR spectra were recorded on a Bruker spectrometer at 250 MHz in CDCl₃. Mass spectra were measured on a Varian MAT-311A (EI, 70 eV). Column chromatography was performed using Silica Gel L (100/160 μ m) and CHCl₃-MeOH (10:1) as an eluent.

9: mp 126–128 °C, R_f 0.26. ¹H NMR, δ : 2.83 (s, 3H, N-Me), 2.95 (s, 3H, N-Me), 2.99 (s, 3H, N-Me), 5.02 and 5.18 (2H, AB system, CH-CH, J_{AB} 8.20 Hz), 7.15 (s, 1H, NH). IR (KBr, ν/cm^{-1}): 1700 (C=O), 3320 (NH). MS, m/z : 184 (M⁺).

10: mp 118–121 °C, R_f 0.34. IR (KBr, ν/cm^{-1}): 1685, 1700 (C=O), 3250 (NH). MS, m/z : 212 (M⁺).

11: mp 148–149 °C, R_f 0.32. IR (KBr, ν/cm^{-1}): 1720 (C=O), 3230 (NH). MS, m/z : 198 (M⁺).

12: mp 130–131 °C, R_f 0.41. IR (KBr, ν/cm^{-1}): 1700, 1720 (C=O), 3270 (NH). MS, m/z : 226 (M⁺).

The structures of **9–12** were also confirmed by elemental analysis.

teristics as follows: $\delta_A = \delta_{A'} = 3.69$, $\delta_B = \delta_{B'} = 3.72$ and $\delta_X = \delta_{X'} = 1.18$ ppm ($J_{AM} = J_{A'M'} = {}^2J_{AX} = {}^2J_{A'X'} = {}^2J_{MX} = {}^2J_{M'X'} = 14.4$ Hz). The A'M'X'' system has the following parameters: $\delta_{A''} = 3.42$, $\delta_{B''} = 3.23$ and $\delta_{X''} = 1.14$ ppm ($J_{A'M''} = {}^2J_{A'X''} = {}^2J_{M'X''} = 14.2$ Hz).

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