New condensation methods in the synthesis of bicyclic bisureas

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

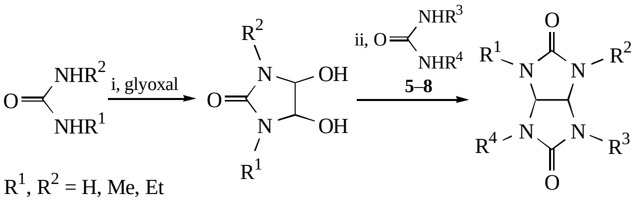
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation.
Fax: +7 095 135 5328

DOI: 10.1070/MC2000v010n01ABEH001186

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 ^{1}H NMR spectroscopy and TLC control. We found that it results in corresponding mono-*N*-alkyl-4,5-dihydroxyimidazolidin-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.



1–4 **9–14**

1 R^1 = H, R^2 = Me
2 R^1 = H, R^2 = Et
3 R^1 = R^2 = Me
4 R^1 = R^2 = Et

5 R^3 = R^4 = Me
6 R^3 = R^4 = Et
7 R^3 = H, R^4 = Me
8 R^3 = H, R^4 = Et

9 R^1 = H, R^2 = R^3 = R^4 = Me
10 R^1 = H, R^2 = Me, R^3 = R^4 = Et
11 R^1 = H, R^2 = Et, R^3 = R^4 = Me
12 R^1 = H, R^2 = R^3 = R^4 = Et

13 R^1 = R^2 = R^3 = R^4 = Me
14 R^1 = R^2 = R^3 = R^4 = Et

Scheme 1 *Reagents and conditions*: i, H_2O, pH 4–5, 45–50 °C, 2 h; ii, H_2O, 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-dihydroxyimidazolidin-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 sceleton are characteristic of bicyclic bisureas. Therefore, a chiral environment is created for any pair of geminal protons or N-substituent groups (for example, for CH_2 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 ^{1}H 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 AMX_3 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 $\delta_{A'}$ 3.51, $\delta_{M'}$ 3.31 and $\delta_{X'}$ 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 ^{1}H 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 AMX_3 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 ^{1}H 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 nonequivalent; this fact manifests itself as three AMX_3 systems in the spectrum. Two of these systems exhibit similar spectrum charac-

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[†] ^{1}H NMR spectra were recorded on a Bruker spectrometer at 250 MHz in $CDCl_3$. Mass spectra were measured on a Varian MAT-311A (EI, 70 eV). Column chromatography was performed using Silica Gel L (100/160 μm) and $CHCl_3$–MeOH (10:1) as an eluent.

9: mp 126–128 °C, R_f 0.26. ^{1}H 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, CHCH, 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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Received: 8th July 1999; Com. 99/1514