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Preparation of quaternary ammonium salts with a perhydroimidazo[1,5-*c*]oxazolium molecular skeleton

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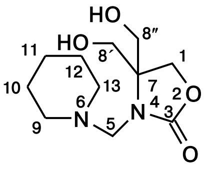
In studies on N-aminomethylation (the Mannich reaction[1,2]) of 4,4-bis(nitroxymethyl)oxazolidin-2-one (**1**) with piperidine (**2**) and dimethylamine (**3**) as the amino components, we found that it was not the expected Mannich bases **4** and **5** that formed as the final stable reaction products but rather quaternary ammonium salts **6** and **7** (Scheme 1).

We assume that the nitroxy group in the transient compounds **4** and **5** undergoes intramolecular nucleophilic substitution[3—5] by the nitrogen atom of a tertiary amine, with concominant elimination of the nitrate anion and the nitrogen atom quaternisation.

The structures of compounds **6** and **7** were established based on data from ^{1}H, ^{13}C and ^{14}N NMR spectroscopy. The signal assignment is based on a comparison of chemical shifts, multiplet forms, and signal integrated intensities for products **6** and **7** and compounds **1** and **8**, as well as literature data[6—8] for related compounds, and data from DEPT-135 and COSY ^{13}C—^{1}H experiments.

In the ^{1}H NMR spectra of compounds **1** and **8**, CH_2 protons of the oxazolidine ring and NCH_2N protons of compound **8** resonated as singlets. In the CH_2ONO_2 group (compound **1**) and in the CH_2OH group (compound **8**), the observed magnetic nonequivalence (0.05 and 0.12 ppm, respectively) is typical of such compounds.[6] Cyclisation with formation of rifid structures **6** and **7** makes all geminal positions nonequivalent. Hence a complex overlapping AB-type pattern is observed at δ 3.5—5.1, as well as poorly resolved (even on a 500 MHz instrument) piperidine ring multiplets at δ 1.5—3.8 in compound **6** and two methyl group singlets in compound **7** that became nonequivalent are observed. ^{13}C—^{1}H correlation spectroscopy was used for the assignment. In the ^{13}C-NMR spectrum of compound **6**, two broad signals at δ 66.6 and 76.0 were observed (broadening occurs probably due to spin-spin coupling with the quaternary nitrogen atom), which were



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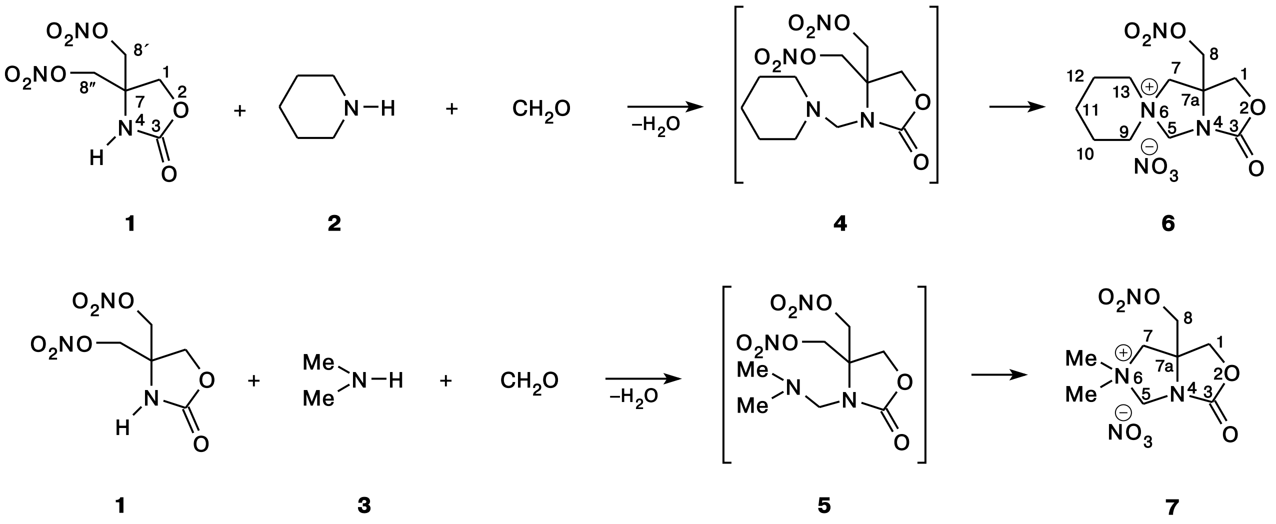
Scheme 1



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† Deseased.

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assigned to positions 7 and 5, respectively, taking into account electronegativity and magnetic anisotropy of the amide group. The magnetic nonequivalence values of the geminal protons in the bicycle formed are ~0.2 ppm for $CH_{2a,b}$ in positions 1 and 8, 0.25 ppm in position 7; in position 5, the inequivalence is 1 ppm in **6** and 0.75 ppm in **7**, which is due to proximity of the $C(5)H_{2ab}$ fragment to the amide C=O double bond. The methyl groups in **7** and the corresponding methylene fragments in **6** also become significantly nonequivalent, which is in agreement with literature data.[7,8] The ^{14}N NMR spectrum of **6** also proves the presence of a quaternary nitrogen atom with characteristic chemical shift of δ −297.3 and relatively small line width $\Delta \approx 200$ Hz.

Thus, we have discovered a new version of the use of the Mannich reaction leading to quaternary ammonium salts with unique structures. The essence of this version is aminomethylation of a heterocyclic NH acid bearing an α-nitroxyalkyl substituent.

The starting NH acid **1** was synthesized according to a known procedure.[9] The IR spectra were recorded on a Specord M-82 spectrophotometer. The NMR spectra were recorded on Bruker DRX-500 Avance and Bruker DPX-200 spectrometers with respect to Me_4Si as the internal standard, the ^{14}N NMR spectra were recorded on a Bruker Avance 2 300 spectrometer, nitromethane was used as the external standard.

6,6-Pentamethylene-7a-(nitroxymethyl)-3-oxo-perhydroimidazo[1,5-*c*]oxazol-6-ium nitrate (6). Piperidine (0.43 g, 5 mmol) and H_2O (4 mL) were added with stirring to a mixture of **1** (1.19 g, 5 mmol), H_2O (8 mL), AcOEt (6 mL), and 30% formalin (0.5 g, 5 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 2h and for 2 h at 60 °C. The aqueous layer was separated and concentrated on a watch-glass in an air flow. The solid residue was triturated with a mixture of Pr^iOH (2 mL) and MeOH (4 mL), the crystals were filtered off and recrystallized from Pr^iOH—MeOH (1 : 1.5, 20 mL). Yield 0.89 g (53%), m.p. 133—135 °C. IR (KBr), ν/cm^{-1}: 1765 (C=O); 1163, 1045 (C—O, C—N); 1646, 1284, 845, 749 (ONO_2); 1363 (NO_3^-); 3045, 3012, 2969, 2941, 2861, 1842, 1451 (CH_2). ^1H NMR (500 MHz, *J*/Hz, DMSO-d_6 + CCl_4), δ: 1.45—1.95 (m, 6 H, $H_{ab}(10) + H_{ab}(11) + H_{ab}(12)$, piperidine); 3.20—3.47 (m, 4 H, $H_{ab}(9) + H_{ab}(13)$, piperidine); 3.89 и 4.14 (both d, 1 H each, $H_a(7)$ and $H_b(7)$, $J_{gem} = 13.0$); 4.623 и 4.776 (both d, 1 H each, $H_a(1)$, $H_b(1)$, $J_{gem} = 10.0$); 4.665 и 5.593 (both d, 1 H each, $H_a(5)$ and $H_b(5)$, $J_{gem} = {}^2J_{AB} = 11.0$); 4.81 и 4.99 (both d, 1 H each, $H_a(8)$ and $H_b(8)$, $J_{gem} = 11.2$). $^{13}C\{^1H\}$ NMR, $^{13}C\{^1H\}$DEPT NMR, COSY $^{13}C—^1H$ (δ): 22.1, 22.6, 23.5 (C(10), C(11), C(12), piperidine); 62.2, 62.5 (C(9), C(13), piperidine); 66.6 (C(7)); 66.8 (C(7a)); 72.5 (C(1)); 73.6 (C(8)); 76.0 (C(5)); 160.4 (C=O). ^{14}N NMR (δ, (Δ/Hz)): −297.3 (br.s., N^+, $\Delta \approx 200$ Hz); −45.0 (br.s., ONO_2, $\Delta \approx 900$ Hz); −4.38 (s, NO_3^-). Found (%): C, 39.38; H, 5.60; N, 16.51. $C_{11}H_{18}N_4O_8$. Calculated (%): C, 39.52; H, 5.43; N, 16.76.

6,6-Dimethyl-7a-(nitroxymethyl)-3-oxo-perhydroimidazo-[1,5-*c*]oxazol-6-ium nitrate (7) was obtained analogously to **6** from **1** (1.19 g, 5 mmol), 30% formalin (0.5 g, 5 mmol), and 33% aqueous dimethylamine (0.68 g, 5 mmol). Yield 0.65 g (44%), m.p. 141—142 °C. IR (KBr), ν/cm^{-1}: 1782 (C=O); 1228, 1167, 1035 (C—O, C—N); 1636, 1281, 867, 755 (ONO_2); 1357 (NO_3^-); 3038, 2976, 2930, 2872, 1476, 1451 (CH_2, CH_3). ^1H NMR (200 MHz, *J*/Hz, Δ/Hz, DMSO-d_6 + CCl_4): 3.11, 3.36 (both s, 3 H each, NMe); 3.98 (m, 2 H, $H_{a,b}(7)$, AB, $\Delta\nu_{AB} = 55.4$; $^2J_{AB} = 13.5$); 4.71 (m, 2 H, $H_{a,b}(1)$, AB, $\Delta\nu_{AB} = 25.2$; $^2J_{AB} = 10.1$); 4.92 (m, 2 H, $H_{a,b}(8)$, AB, $\Delta\nu_{AB} = 41.3$; $^2J_{AB} = 11.2$); 5.06 (m, 2 H, $H_{a,b}(5)$, AX, $\Delta\nu_{AX} = 152.4$; $^2J_{AX} = 10.8$). $^{13}C\{^1H\}$ NMR and $^{13}C\{^1H\}$DEPT NMR (δ): 52.5 (Me); 54.3 (Me); 67.3 (C(7a)); 70.6 (C(7)); 72.8 (C(1)); 73.7 (C(8)); 77.6 (C(5)); 160.4 (C=O). Found (%): C, 32.42; H, 4.60; N, 19.23. $C_8H_{14}N_4O_8$. Calculated (%): C, 32.66; H, 4.80; N 19.04.

4,4-Bis(hydroxymethyl)-3-(piperidin-1-ylmethyl)oxazolidin-2-one (8). A mixture of 4,4-bis(hydroxymethyl)oxazolidin-2-one[9] (0.73 g, 5 mmol), H_2O (11 mL), 30% formalin (0.5 g, 5 mmol), and piperidine (0.42 g, 5 mmol) was stirred at 20 °C for 1 h and for 1 h at 60 °C. The obtained solution was concentrated on a watch-glass in an air flow. The residue was triturated with propan-2-ol, the crystalline substance was filtered off and dried. Yield 0.32 g (27%). M.p. 120—122 °C (from toluene). ^1H NMR (200 MHz, *J*/Hz, $CDCl_3$): 1.40—1.68 (m, 6 H, H(10), H(11), H(12), piperidine); 2.57 (m, 4 H, H(9), H(13), piperidine); 3.67 (m, 4 H, $H_{ab}(8')$, $H(8'')$, AB, $\Delta\nu_{AB} \approx 24.75$; $^2J_{AB} \approx 12.2$); 3.87 (s, 2 H, H(5)); 4.102 (s, 4 H, H(8′) and H(8″)); 5.410 (br. s, 2 H, OH). Found (%): C, 54.31; H, 8.46; N, 11.45. $C_{11}H_{20}N_2O_4$. Calculated (%): C, 54.08; H, 8.25; N, 11.47.

References

1. B. Reichert, *Die Mannich-Reaktion*, Springer-Verlag, Berlin, Göttigen-Heidelberg, 1959.
2. A.G. Agababyan, G. G. Gevorgyan, O. L. Midzhoyan, *Usp. Khim.*, 1982, **51**, 678 [*Russ. Chem. Rev.* (*Engl. Transl.*), 1982, **51**].
3. E. Buncel, A. N. Bourns, *Canad. J. Chem.*, 1960, **38**, 2457.
4. A. I. Titov, *Zh. Obshch. Khim.*, 1946, **16**, 2011 [*J. Gen. Chem. USSR* (*Engl. Transl.*), 1946, **16**].
5. P. M. Kochergin, L. S. Blinova, G. A. Karpov, I. S. Mikhailova, Ye. V. Aleksandrova, O. V. Korol', *Khim. Farm. Zh.*, 1999, **33**, № 1, 40 [*Pharm. Chem. J.* (*Engl. Transl.*), 1999, **33**, No. 1].
6. L. B. Romanova, L. S. Barinova, V. V. Zakharov, L. T. Eremenko, G. G. Aleksandrov, I. L. Eremenko, *Izv. AN. Ser. Khim.*, 2010, 1026 [*Russ. Chem. Bull., Int. Ed.*, 2010, **59**, No. 5].
7. K. F. Turchin, L. G. Levkovskaya, N. P. Solov′eva, T. S. Safonova, Yu. N. Sheinker, *Dokl. AN SSSR, Khimiya,* 1987, **293**, 3792 [*Dokl. Chem.* (*Engl. Transl.*), 1987, **293**].
8. M. Witanowski, L. Stefaniak, G. A. Webb, *Ann. Rep. NMR Spectrosc.*, 1986, **18**, 164.
9. A. T. Blomquist, F. T. Fiedorek. US Pat. 2 485 855 (Oct 25, 1949); *Chem. Abstr.*, 1950, **44**, 3516.

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