A novel heterocyclic system — dihydro-2*H*-1,5,2,4-dioxadiazine. 2,4-Dimethyldihydro-2*H*-1,5,2,4-dioxadiazine hydrochloride: synthesis and NMR study ✽

O. V. Anikin, D. L. Lipilin, P. A. Belyakov, V. Yu. Ryabtsev, and V. A. Tartakovsky*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninskii prosp., 119991 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: anikinOV@ioc.ac.ru

The first representative of a novel heterocyclic system, namely, 2,4-dimethyldihydro-2*H*-1,5,2,4-dioxadiazine hydrochloride, was synthesized.

Key words: bis(aminooxy)methane, bis(*tert*-butyloxycarbonylaminooxy)methane, 2,4-dimethyldihydro-2*H*-1,5,2,4-dioxadiazine hydrochloride, alkylation.

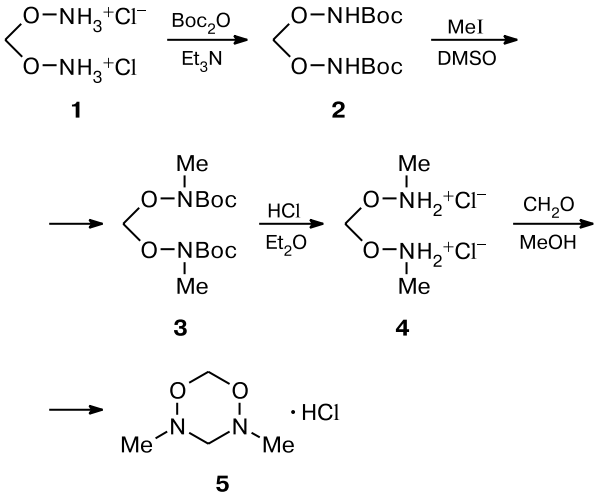
Construction of the 1,5,2,4-dioxadiazine ring has been reported only for two 2,4-dialkyl-2*H*-1,5,2,4-dioxadiazine-3,6(2,4*H*)-diones.[1] Data for dihydro-2*H*-1,5,2,4-dioxadiazine or its derivatives have not been documented to date.

Our approach to the synthesis of the target structure was as follows (Scheme 1). Bis(aminooxy)methane[2—4] (**1**) may be regarded as a heteroanalog of 1,3-diaminopropane, which is known to form hexahydropyrimidine in the reaction with formaldehyde.[5,6] An analogous reaction of bis(aminooxy)methane should give dihydro-2*H*-1,5,2,4-dioxadiazine **5**. To avoid a possible opening of the ring as a result of ring—chain tautomerism (as observed for 1,3-diaminopropane[5]), bis(aminooxy)methane **1** was replaced by its *N*,*N*′-dimethyl derivative **4** prepared by methylation of bis(*tert*-butyloxycarbonylaminooxy)methane (**2**). The reaction of salt **4** with paraform affords 2,4-dimethyldihydro-2*H*-1,5,2,4-dioxadiazine monohydrochloride (**5**) in more than 90% yield.

For recording NMR spectra, compound **5** was twice recrystallized from Pr^{i}OH.

The ^{1}H NMR spectra of product **5** at 25 °C contain strongly broadened signals for the CH_2 protons at δ ~4.2 and ~5.7. At 60 °C, these signals change to instrument-width singlets. This broadening can result from both intra- or intermolecular proton exchange of the acid and conformation processes (hindered inversion of the N atom and/or the ring (on the NMR time scale)). The hindered inversion follows from the presence of both quartets for the methylene groups upon the binding of the acid proton by pyridine added to a tube with compound **5**.

Scheme 1



Experimental

Mass spectra were recorded on Kratos MS-30 (EI, 70 eV) and Varian CH-6 instruments (ESI MS). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.5 MHz, respectively). Bis(aminooxy)methane dihydrochloride was prepared according to a known procedure.[2—4]

Di-*tert*-butyl *N*,*N*′-(methylenedioxy)dicarbamate (2). Triethylamine (9.2 mL, 66 mmol) and a solution of di-*tert*-butyl dicarbonate (14.4 g, 66 mmol) in 20 mL of anhydrous CH_2Cl_2 were added successively at 5—10 °C to a stirred suspension of dihydrochloride **1** (4.53 g, 30 mmol) in 50 mL of anhydrous CH_2Cl_2. The reaction mixture was stirred at 20 °C for 8 h, allowed to stand for ~18 h, and then poured into water (200 mL). The organic layer was separated and dried with Na_2SO_4 and the solvent was removed. The residue was recrystallized from C_6H_6 to give compound **2** (7.15 g, 86%) as colorless crystals, m.p. 109—110 °C. Found (%): C, 47.21; H, 7.83; N, 9.91.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1295—1297, June, 2004.

1066-5285/04/5306-1349

$C_{11}H_{22}N_2O_6$. Calculated (%): C, 47.47; H, 7.97; N, 10.07. ^{1}H NMR (DMSO-d_6), δ: 1.40 (s, 18 H, CMe_3); 4.81 (s, 2 H, CH_2); 9.78 (s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 27.9 ($C(\underline{C}H_3)_3$); 80.6 ($\underline{C}Me_3$); 100.6 (CH_2); 150.0 (C=O). MS, *m/z*: 278 $[M]^+$.

Di-*tert*-butyl *N,N′*-dimethyl-*N,N′*-(methylenedioxy)dicarbamate (3). A solution of MeONa (700 mg, 13 mmol) in 10 mL of anhydrous MeOH was added to a stirred solution of compound **2** (1.39 g, 5 mmol) in 5 mL of anhydrous MeOH. Stirring was continued for an additional 10 min. Then the solvent was removed and the residue was dried *in vacuo* and dissolved in 5 mL of anhydrous DMSO. Methyl iodide (1.5 mL, 25 mmol) was added at 5 °C to the stirred solution. The reaction mixture was heated at 60 °C for 1 h, cooled, and poured into water (100 mL). The product was extracted with C_6H_6 (3×30 mL). The benzene extract was washed with aqueous 10% $Na_2S_2O_3$ and water and dried with Na_2SO_4. The solvent was removed and the resulting oil was dissolved in 50 mL of hexane. The undissolved residue was filtered off, the solvent was removed, and the product was dried *in vacuo* to give compound **3** (1.35 g, 88%) as large transparent crystals, m.p. 45—48 °C. Found (%): C, 51.12; H, 8.47; N, 9.26. $C_{13}H_{26}N_2O_6$. Calculated (%): C, 50.97; H, 8.55; N, 9.14. ^{1}H NMR (DMSO-d_6), δ: 1.40 (s, 18 H, CMe_3); 3.10 (s, 6 H, NMe); 5.05 (s, 2 H, CH_2). ^{13}C NMR (DMSO-d_6), δ: 27.9 ($C(\underline{C}H_3)_3$); 38.4 (NMe); 81.3 ($\underline{C}Me_3$); 101.8 (CH_2); 156.9 (C=O). MS, *m/z*: 306 $[M]^+$.

2,6-Diaza-3,5-dioxaheptane dihydrochloride (4). Dry HCl was passed through a solution of compound **3** (1 g, 0.33 mmol) in 25 mL of anhydrous Et_2O for 5 min. The reaction mixture was left at 20 °C for 4 h. The precipitate that formed was filtered off and washed with anhydrous Et_2O to give compound **4** (0.52 g, 87%) as colorless crystals, m.p. 162—164 °C (from EtOH). Found (%): C, 20.14; H, 6.82; Cl, 39.41; N, 15.78. $C_3H_{12}Cl_2N_2O_2$. Calculated (%): C, 20.12; H, 6.76; Cl, 39.60; N, 15.65. ^{1}H NMR (DMSO-d_6), δ: 2.83 (s, 6 H, NMe); 5.64 (s, 2 H, CH_2); 9.50 (br.s, 4 H, NH_2^+). ^{13}C NMR (DMSO-d_6), δ: 37.5 (NMe); 96.4 (CH_2).

2,4-Dimethyldihydro-2*H*-1,5,2,4-dioxadiazine hydrochloride (5). Paraform (0.1 g, 3 mmol) was added to a solution of compound **4** (0.37 g, 2 mmol) in 5 mL of MeOH. The reaction mixture was stirred for 3 h, the solvent was removed, and the residue was recrystallized from Pr^iOH to give compound **5** (0.28 g, 91%) as colorless crystals, m.p. 140—141 °C. Found (%): C, 30.82; H, 7.23; Cl, 23.22; N, 17.90. $C_4H_{11}ClN_2O_2$. Calculated (%): C, 31.08; H, 7.17; Cl, 22.93; N, 18.12. ^{1}H NMR (DMSO-d_6), 25 °C, δ: 2.73 (s, 6 H, NMe); 4.20 (br.s, 2 H, NCH_2N); 5.67 (br.s, 2 H, OCH_2O); 9.91 (s, 1 H, NH^+). ^{1}H NMR (DMSO-d_6), 60 °C, δ: 2.70 (s, 6 H, NMe); 4.00 (s, 2 H, NCH_2N); 5.32 (s, 2 H, OCH_2O); 9.43 (s, 1 H, NH^+). ^{1}H NMR (DMSO-d_6—Py-d_5 (1 : 1)), 25 °C, δ: 2.49 (s, 6 H, NMe); 3.11 (m, 1 H, NCH_2N); 3.94 (m, 1 H, NCH_2N); 4.96 (m, 1 H, OCH_2O); 5.19 (m, 1 H, OCH_2O). ^{13}C NMR (DMSO-d_6), δ: 42.4 (Me); 81.1 (NCH_2N); 94.5 (OCH_2O). MS, *m/z*: 118 $[M - HCl]^+$.

References

1. J. C. Stowell and C. M. Lau, *J. Org. Chem.*, 1986, **51**, 3355.
2. C. S. McDowell and C. Merrill, US Pat. 3 714 199; *Chem. Absrts.*, 1973, **78**, 135644u.
3. C. S. McDowell and C. Merrill, US Pat. 3 714 200; *Chem. Absrts.*, 1973, **78**, 135645v.
4. K. Tollison, G. Drake, T. Hawkins, A. Brand, M. McKay, I. Ismail, C. Merrill, M. Petrie, J. Bottaro, T. Highsmith, and R. Gilardi, *J. Energetic Mater.*, 2001, **19**, 277.
5. R. F. Evans, *Aust. J. Chem.*, 1967, **20**, 1643.
6. M. M. Bagga, B. Everatt, and J. G. Hinton, *J. Chem. Soc., Chem. Commun.*, 1987, 259.

Received March 26, 2004