1,2-Bis(2-hydroxyethyl)hydrazine and Derivatives[1]

Arnold T. Nielsen* and G. William Lawrence[2]

Organic Chemistry Branch, Chemistry Division, Research Department, Code 3856, Naval Weapons Center, China Lake, California 93555

Received March 15, 1977

Glycolaldehyde was condensed with 2-hydroxyethylhydrazine to yield hydrazone **2** which has been hydrogenated (Pd/C catalyst) to produce the title compound (**3**). The tetraacetyl and *N,N'*-diacetyl derivatives of **3** (**7** and **8**, respectively) and the oxidation product, bis(2-hydroxyethyl)diazene (**6**), are described. The nuclear magnetic resonance spectra of the new compounds, including rotamers of **8**, are discussed.

Hydrazine reacts with various alkylating agents to yield principally the unsymmetrical 1,1-disubstituted product. Michael addends such as acrylonitrile, as well as alkyl halides, behave in this fashion.[3,4] Ethylene oxide, for example, forms 1,1-bis(2-hydroxyethyl)hydrazine (**1**).[5] Symmetrical derivatives of this type—1,2-dialkylhydrazines having reactive functional groups attached to alkyl—are available by various other routes, e.g., hydrazoacetic acid[6] and hydrazoisobutyronitrile.[7]

$$N_2H_4 \xrightarrow{2\,\triangledown O} H_2NN(CH_2CH_2OH)_2$$

1

In the present work, as part of a study of new polyhydrazine compounds,[8,9] 1,2-bis(2-hydroxyethyl)hydrazine (**3**) and some of its derivatives have been synthesized. Glycolaldehyde, generated in situ, was condensed with 2-hydroxyethylhydrazine forming hydrazone **2** which was hydrogenated with palladium/charcoal catalyst to yield **3**.

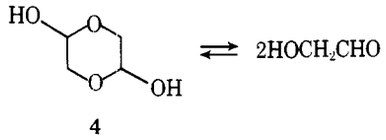
$$HOCH_2CHO + H_2NNHCH_2CH_2OH \rightarrow HOCH_2CH{=}NNHCH_2CH_2OH$$

2

$$\xrightarrow{H_2,Pd/C} HOCH_2CH_2NHNHCH_2CH_2OH$$

3

Two procedures leading to **3** were developed. In one, commercially available crystalline glycolaldehyde dimer (principally **4**)[10] was employed in ethanol, in which solvent it exists



4

primarily as the monomer and its hemiacetal.[10,11] Reaction of **4** with 2-hydroxyethylhydrazine in absolute ethanol containing Drierite led to hydrazone **2** which was isolated as an oil. Hydrogenation of **2** with 10% palladium/charcoal catalyst (50 psi, 25 °C) gave pure diol **3** in 50% overall yield from glycolaldehyde. Identical results were achieved without isolation of **2**.

In a second route leading to **3**, glycolaldehyde diethyl acetal (**5**) was the glycolaldehyde precursor.[12] The acetal was conveniently prepared from chloroacetaldehyde diethyl acetal by reaction with excess aqueous potassium hydroxide at 125 °C by an improved procedure (60–70% yield).

$$ClCH_2CH(OC_2H_5)_2 \xrightarrow[125\ °C]{aq\ KOH} HOCH_2CH(OC_2H_5)_2$$

5

$$\xrightarrow{H^+} HOCH_2CHO$$

Hydrolysis of **5** in 1 N aqueous hydrochloric acid at 25–30 °C, followed by adjustment of the pH to 6–6.5 and addition of 2-hydroxyethylhydrazine, led to formation of hydrazone **2** in aqueous medium. Without isolation, **2** was hydrogenated to diol **3** (50% yield from acetal **5**). 1,2-Bis(2-hydroxyethyl) hydrazine (**3**) is a stable, white, crystalline solid, mp 58–60 °C, in contrast to the unsymmetrical diol **1** which is described as an oil.[5]

A few glycolaldehyde hydrazones have been described previously, including those derived from phenylhydrazine[13] and 1,1-dimethylhydrazine.[14] The latter derivative has been reduced to 1,1-dimethyl-2-(2-hydroxyethyl)hydrazine by sodium cyanoborohydride (23% overall yield from glycolaldehyde).[14]

Bis(2-hydroxyethyl)diazene (**6**) was prepared readily by mercuric oxide oxidation of **3** in ether or ether–methanol solvent.

$$3 \xrightarrow{HgO} HOCH_2CH_2N{=}NCH_2CH_2OH \rightleftarrows 2$$

6

It was isolated in high yield as a low-melting crystalline solid (mp 19–20 °C). In protic solvents such as methanol or water it tautomerizes slowly to hydrazone **2** (assay by NMR spectroscopy). The diazene was characterized by its bisphenylurethane derivative.

Acetylation of hydrazine **3** with excess acetic anhydride produced the tetraacetyl derivative **7**. Fractional saponification of **7** was achieved by slow addition of aqueous sodium

$$3 \xrightarrow{Ac_2O} CH_3CO_2CH_2CH_2N(COCH_3)-NCH_2CH_2O_2CCH_3\ (COCH_3)$$

7

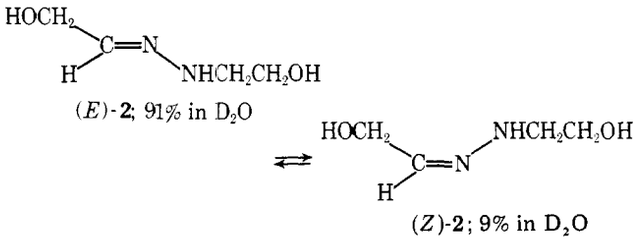
$$\xrightarrow[pH\ 10\text{–}12]{aq\ NaOH} HOCH_2CH_2N(COCH_3)NCH_2CH_2OH\ (COCH_3)$$

8

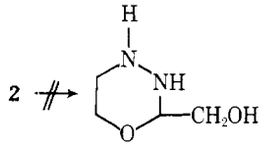
hydroxide (10%) while maintaining the pH below 12 throughout the reaction period. Acetyl derivatives **7** and **8** were obtained in high purity and high yield (isolated as oils, purified by column chromatography).

Structures of **3** and its derivatives are supported by molecular formulas and spectra. The nuclear magnetic resonance spectrum of crude **2** (in D_2O) reveals two vinyl proton signals and two methylol methylene signals in a ratio of ca. 10:1, suggesting a mixture of *Z* and *E* forms with (*E*)-2 predominating. Tautomerization of **6** to **2** in D_2O also yields the same equilibrium mixture.

In agreement with the studies of Potekhin and Vikulina[15] no evidence was found for formation of the hexahydro-1,3,4-oxadiazine tautomer **9** derived from **2** in chloroform or D_2O solvents. It has been established that only 4-substituted

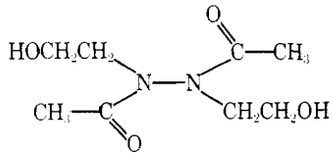


derivatives of **9** exist in tautomeric equilibrium with the parent hydrazone.[15]

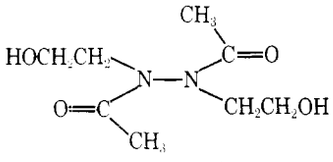


9

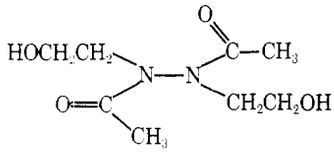
The NMR spectrum of the *N,N'*-diacetyl derivative **8** reveals a four-line methyl signal corresponding to the three possible rotamers (cis,cis, trans,trans, and cis,trans, respectively).[16,17] The proportions of the three forms were determined from the integrated peak intensities (measurements in $CDCl_3$ and D_2O). The results are similar to those reported previously for 1,2-diacetyl-1,2-dimethylhydrazine (**10**, measurements in pentachloroethane and D_2O).[17] In both compounds the predominant form in aprotic solvents is trans,trans (78% for **10**) and the minor one is cis,cis (4% for **10**). In D_2O the ratios of the three forms for the two compounds (**8**, **10**) are very similar (34% trans,trans and 12% cis,cis for **10**). In the tetraacetyl derivative **7** the four-line signal found in **8** is obscured by the intense acetoxy methyl singlet.



cis, cis-**8**
in D_2O 19%
in $CDCl_3$ 20%



trans, trans-**8**
in D_2O 32%
in $CDCl_3$ 48%



cis, trans-**8**
in D_2O 49%
in $CDCl_3$ 32%

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 137, ^1H NMR spectra on a Varian EM 360 or XL-100. Chemical shifts determined at ca. 30 °C are referenced to tetramethylsilane internal standard [sodium 3-(trimethylsilyl)-1-propanesulfonate in deuterium oxide]. Melting points were determined on a Kofler hot stage and are corrected unless otherwise noted. Elemental analyses and molecular weights (by vapor osmometry) were determined by Galbraith Laboratories, Knoxville, Tenn. Organic solutions were dried over $MgSO_4$ unless otherwise stated.

2,2-Diethoxyethanol (5). A mixture of 61.0 g (0.40 mol) of chloroacetaldehyde diethyl acetal (Aldrich Chemical Co.), KOH (45.0 g of 85% assay, 0.60 mol), and water (1 L) was heated at 125 ± 2 °C in a 1.5-L stainless steel bomb (Aminco) with gentle rocking for 120 h. The clear, yellow liquid product was extracted once with 150 mL of ether; after drying and concentration the extract yielded 7.7 g of an oily mixture of reactant chloroacetal (75%) and product **5** (25%) by NMR assay. The aqueous part was treated cautiously with 900 g of anhydrous K_2CO_3 with stirring and ice-bath cooling (temperature below 35 °C) until a clear solution resulted. The solution was extracted three times with ether (150-mL portions). The dried extracts on concentration gave an oil which was distilled through a short column to yield at 17 mm: (1) 1.0 g of a forerun, bp 40–70 °C; (2) 33 g (62%) of pure acetal **5**, bp 70–72 °C; and (3) 0.5 g of residue; fraction 2 NMR ($CDCl_3$) δ 4.58 (t, 1, CH), 3.4–3.9 (m, 6, CH_2), 2.32 (s, 1, OH), 1.26 (t, 6, CH_3) [lit. bp 74–74.5 °C (14 mm)].[12] Repeat runs gave yields of **5** of 60–70%.

The above procedure was repeated except for reaction times of 45 and 78 h to provide yields of **5** of 22 and 53%, respectively (recovered unreacted chloroacetaldehyde diethyl acetal was isolated in yields of 63 and 27%, respectively). Substitution of bromoacetaldehyde diethyl acetal for chloroacetaldehyde acetal in the above procedure gave yields of **5** of ca. 70%.

3,4-Diaza-2-hexene-1,6-diol (2). A solution of 2-hydroxyethylhydrazine (Aldrich, 1.52 g, 0.020 mol) and glycolaldehyde dimer (Aldrich, 1.20 g, 0.020 mol of glycolaldehyde) in 2 mL of water and 50 mL of absolute ethanol was concentrated at 30 mm to remove volatiles (water bath temperature below 48 °C) during 1.5 h. A second 50-mL portion of absolute ethanol was added to the residue and Drierite (10 g) added. After standing at 25 °C overnight the mixture was filtered and concentrated, followed by final pumping at 0.1 mm, 25 °C, to constant weight to yield 2.30 g (97%) of **2** as a colorless oil: IR (film) 1620 cm^{-1} (C=N); NMR (D_2O) δ 7.32, 6.78 (t, J = 5 Hz, 1 proton total, =CH, ratio of signals 10:1, respectively), 4.84 (s, 3, NH and OH), 4.28, 4.18 (d, J = 5 Hz, 2 protons total, =CHC**H**$_2$OH, ratio of signals 1:10, respectively), 3.72 (t, 2, HOC**H**$_2$CH$_2$NH), 3.19 (t, 2, HOCH$_2$C**H**$_2$NH).

Diol **2** was hydrogenated to 1,2-bis(2-hydroxyethyl)hydrazine (**3**) by the procedure described below (method A; 90% yield of crude product).

1,2-Bis(2-hydroxyethyl)hydrazine (3). Method A. Glycolaldehyde dimer (6.0 g, 0.10 mol of glycolaldehyde) was added to a solution of 2-hydroxyethylhydrazine (7.6 g, 0.10 mol) in 50 mL of absolute ethanol. After stirring for 10 min the glycolaldehyde dimer had dissolved and the temperature risen from 25 to 31 °C. After the solution had stood at 25–30 °C for 3 h, 6.0 g of 10% Pd/C catalyst was added and the mixture shaken with hydrogen in a Parr apparatus (ca. 50 psi, 25 °C) until hydrogen uptake ceased (2 h, 1.0 molar equiv of hydrogen absorbed). The mixture was filtered through Celite and washed several times with absolute ethanol. Concentration of the filtrate under reduced pressure at 25 °C gave 10.8 g (90%) of crude **3** as waxy crystals, mp 40–48 °C. The product was purified by crystallization from 2-propanol as small, rectangular prisms, mp 55–56 °C (56% recovery, 50% yield); recrystallization gave mp 58–60 °C (70% recovery).

Method B. To 33.5 g (0.25 mol) of 2,3-diethoxyethanol (**5**) was added 1 N hydrochloric acid (125 mL). After an initial temperature rise to 30 °C, the solution was allowed to stand at ambient temperature for 2 h; it was then concentrated under reduced pressure at 25 °C to remove ethanol during 1.5 h. Aqueous NaOH (35 mL of a 10% solution) was added to the solution slowly (with ice-bath cooling keeping the temperature below 25 °C) to adjust the pH to ca. 6–6.5. 2-Hydroxyethylhydrazine (18.9 g, 0.25 mol) was then added with ice-bath cooling keeping the temperature below 25 °C. After the solution had stood at 25 °C for 3 h, 10.0 g of 10% Pd/C catalyst was added and the mixture hydrogenated in a Parr apparatus (40–50 psi, 25 °C) until hydrogen uptake ceased (6 h). The mixture was filtered through Celite and the catalyst washed thoroughly with water. The filtrate was concentrated to remove volatiles under reduced pressure. The oily residue was dissolved in absolute ethanol (200 mL) and the solution again concentrated to remove solvents; the process was repeated and the residue finally pumped at 0.1 mm until reaching constant weight (25.7 g, 88% of crude **3** as oily crystals). Recrystallization from 2-propanol (25 mL) gave 13.2 g (48%) of **3** as chunky crystals, mp 43–51 °C; a second recrystallization gave 8.85 g of pure **3**, mp 58–60 °C (capillary). An analytical sample was prepared by

dissolving in absolute methanol and adding Drierite. After filtration and removal of solvents from the filtrate an anhydrous product of unchanged melting point was obtained. The material is quite hygroscopic: NMR (D_2O) δ 4.88 (s, 4, NH, OH), 3.70 (t, J = 5 Hz, CH_2O), 2.90 (t, J = 5 Hz, 4, CH_2N).

Anal. Calcd for $C_4H_{12}N_2O_2$: C, 39.98; H, 10.07; N, 23.32; mol wt, 120.15. Found: C, 39.85; H, 10.14; N, 23.11; mol wt, 125 (H_2O).

Bis(2-hydroxyethyl)diazene (6). A mixture of pure 1,2-bis(2-hydroxyethyl)hydrazine (**3**, 1.20 g, 0.010 mol), mercuric oxide (2.50 g, 0.011 mol), and 50 mL of ether was stirred magnetically at 25 °C for 3 h. Methanol (10 mL) was added and stirring continued for an additional 1 h. The mixture was filtered and the precipitate washed with ether–methanol (5:1). Drierite (4 g) was added to the filtrate and the mixture stirred for 30 min. After filtration and removal of solvents by pumping at 25 °C (0.1 mm) there remained 1.13 g (96%) of **6** as a hydroscopic oil, mp 16–18 °C. In a parallel run, omitting the addition of methanol (3 h stirring), there was obtained a 66% yield of **6**: mp 19–20 °C; NMR ($CDCl_3$) δ 4.08 (s, 8, CH_2), 3.28 (s, broad, 2, OH); NMR (D_2O) δ 4.72 (s, 2, OH), 4.05 (s, 8, CH_2), =CH peaks absent. On standing for several hours the =CH peaks of **2** isomers appeared in the same 10:1 ratio. Elemental analysis indicated the presence of oxygenated impurity, possibly water, in the unrecrystallized crude product. Anal. Calcd for $C_4H_{10}N_2O_2 \cdot 0.25H_2O$: C, 39.18; H, 8.63; N, 22.84. Found: C, 39.25; H, 8.90; N, 22.46.

A solution of 0.236 g (2.0 mmol) of diol **6** and phenyl isocyanate (0.476 g, 4.0 mmol) in 3.0 mL of chloroform was stored at 25 °C for 16 h. Chilling at −15 °C deposited 0.22 g (30%) of the crystalline bisphenylurethane derivative, mp 137–140 °C; the melting point was unchanged on recrystallization from chloroform; NMR ($CDCl_3$) δ 6.8–7.5 (m, 12, C_6H_5 and NH), 4.66, 4.10 (A_2B_2 m, $J_{AB} \simeq$ 5 Hz, 8, CH_2CH_2).

Anal. Calcd for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72; mol wt, 356.37. Found: C, 60.56; H, 5.77; N, 15.49; mol wt, 350 (C_6H_6).

1,2-Bis(2-acetoxyethyl)-1,2-diacetylhydrazine (7). 1,2-Bis(2-hydroxyethyl)hydrazine (**3**, 5.0 g, 0.0416 mol) was dissolved in 50 mL of acetic anhydride; a slightly exothermic reaction resulted. After remaining at ambient temperature for 2.5 h the solution was heated on the steam bath for 2.5 h, then concentrated under reduced pressure on the steam bath to remove volatiles including acetic acid (final pressure 0.1 mm). The process was repeated after addition of a second portion of 50 mL of acetic anhydride to yield ultimately 11.8 g of an oil (98% yield of high-purity **7** as indicated by infrared and NMR spectra). An analytical sample was obtained by column chromatography on alumina (elution with methylene chloride containing 1% methanol gave pure **7** in the first eluate fractions); some hydrolysis occurred on the column during the chromatography. The eluate was shaken with Drierite and filtered and solvents were removed at 0.1 mm to yield pure **7** as a colorless oil: IR (film) 1725 (C=O, ester), 1670 cm^{-1} (C=O, amide); NMR ($CDCl_3$) δ 4.32, 3.84 (A_2B_2 m, $J \simeq$ 5 Hz, 8, CH_2CH_2), 2.22, 2.10 (major), 1.97 (m, 12, CH_3).

Anal. Calcd for $C_{12}H_{20}N_2O_6$: C, 49.99; H, 6.99; N, 9.72, mol wt, 288.3. Found: C, 49.83; H, 7.05; N, 9.74; mol wt, 288 (C_6H_6).

1,2-Bis(2-hydroxyethyl)-1,2-diacetylhydrazine (8). To 1,2-bis(2-acetoxymethyl)-1,2-diacetylhydrazine (**7**, 25.0 g, 0.0865 mol) was added dropwise, with stirring during 1.5 h, 53 mL of 10% aqueous NaOH solution, keeping the temperature at 20 °C by ice-bath cooling. The pH of the reaction mixture was monitored continuously keeping its value between 10 and 12 during the addition. The mixture was treated immediately with sufficient K_2CO_3 to obtain a saturated solution and then extracted with five 50-mL portions of methylene chloride–methanol (15% methanol). The combined extracts were dried over K_2CO_3 and filtered through Celite; concentration of the filtrate gave 17.3 g (98%) of crude diol **8**. Chromatography on an alumina column [elution with methylene chloride–methanol (3% methanol)] gave, after drying with Drierite, 12.5 g (70%) of high-purity **8** as a viscous oil: IR (film) 3400 (OH), 1670 cm^{-1} (C=O, amide), ester C=O absent; NMR ($CDCl_3$) δ 4.47 (s, 2, OH), 3.3–4.0 (m, 8, CH_2), 2.28 (trans,trans), 2.26, 2.02 (cis,trans), 2.08 (cis,cis) (four lines, 12, CH_3); NMR (D_2O) δ 4.80 (s, 2, OH), 3.6–4.0 (A_2B_2 m, 8, CH_2), 2.30 (trans,trans), 2.27, 2.05 (cis,trans), 2.12 (cis,cis) (four lines, 12 CH_3); discussion of peak intensities in text.

Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.90; N, 13.72; mol wt, 204.2. Found: C, 46.85; H, 7.80; N, 13.63; mol wt, 200 (H_2O).

Acknowledgment. The authors are indebted to D. W. Moore for assistance in securing some of the experimental data and for helpful discussions.

Registry No.—*E*-**2**, 62562-61-2; *Z*-**2**, 62562-62-3; **3**, 2488-95-1; **5**, 621-63-6; **6**, 62562-63-4; **6** bisphenylurethane derivative, 62562-64-5; **7**, 62562-65-6; **8**, 62562-66-7; chloroacetaldehyde diethyl acetal, 621-62-5; 2-hydroxyethylhydrazine, 109-84-2; glycolaldehyde, 141-46-8; phenyl isocyanate, 103-71-9.

References and Notes

(1) Presented, in part, at the 31st Northwest Regional Meeting of the American Chemical Society, Reno, Nev., June 15, 1976.
(2) National Research Council Postdoctoral Research Associate, 1973–1974.
(3) S. Patai, Ed., "The Chemistry of the Hydrazo, Azo and Azoxy Groups", Parts 1 and 2, Wiley, New York, N.Y., 1975.
(4) R. Ohme and A. Zubek, *Z. Chem.*, **8**, 41 (1968).
(5) (a) L. Knorr and H. W. Brownsdon, *Chem. Ber.*, **35**, 4474 (1902); (b) R. Preussmann, *Arzneim.-Forsch.*, **12**, 260 (1962); (c) I. V. Podgornaya and I. Ya. Postovskii, *Zh. Obshch. Khim.*, **33**, 744 (1963).
(6) B. Gisin and M. Brenner, *Helv. Chim. Acta*, **53**, 1030 (1970).
(7) J. Thiele and K. Heuser, *Justus Liebigs Ann. Chem.*, **290**, 1 (1896).
(8) A. T. Nielsen, *J. Heterocycl. Chem.*, **12**, 1233 (1975).
(9) A. T. Nielsen, *J. Heterocycl. Chem.*, **13**, 101 (1976).
(10) H. Michelsen and P. Klaboe, *J. Mol. Struct.*, **4**, 293 (1969).
(11) G. C. S. Collins and W. O. George, *J. Chem. Soc. B*, 1352 (1971).
(12) E. Gryszkiewicz-Trochimowski, O. Gryszkiewicz-Trochimowski, and R. S. Levy, *Bull. Soc. Chim. Fr.*, 605 (1958).
(13) H. Simon, G. Heubach, and H. Wacker, *Chem. Ber.*, **100**, 3106 (1967).
(14) D. F. Morrow, P. C. Johnson, H. Torabi, D. Williams, D. L. Wedding, J. W. Craig, and R. F. Majewski, *J. Med. Chem.*, **16**, 736 (1973).
(15) (a) A. A. Potekhin and M. N. Vikulina, *Khim. Geterotsikl. Soedin.*, 1167 (1971); (b) A. A. Potekhin and B. D. Zaitsev, *ibid.*, 301 (1971); (c) A. A. Potekhin, *Zh. Org. Khim.*, **7**, 16 (1971).
(16) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).
(17) F. Conti and C. Franconi, *Ric. Sci.*, **36**, 1205 (1966); *Chem. Abstr.*, **66**, 120640t (1967).