Formation and Catalytic Hydrogenation of the Dimer of 1,2,3,4,5,7a-Hexahydroimidazo[1,2-*a*]pyrazine

Chad A. Mirkin [1], Joan E. Premecz, Michael E. Ford* and Thomas A. Johnson

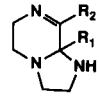
Air Products and Chemicals, 7201 Hamilton Boulevard, Allentown, Pennsylvania 18195-1501, USA

Received March 8, 1993

Reaction of diethylenetriamine with glyoxal or *N,N'*-dicyclohexylethylenediimine forms the novel heterocycle 1,2,3,4,5,7a-hexahydroimidazo[1,2-*a*]pyrazine **1** ($R_1 = R_2 = H$) which is isolated as its dimer. Catalytic hydrogenation converts **1** into *N*-(2-aminoethyl)piperazine in high yield.

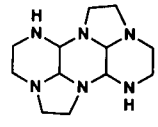
J. Heterocyclic Chem., **30**, 839 (1993).

Formation of saturated heterocycles by reaction of glyoxal with ethylenediamine [2], 1,3-propanediamine [3], and linear [4] and cyclic [5] aliphatic tetramines is well known. Further, the versatility of polyamine-glyoxal condensation reactions for synthesis of novel heterocycles is the object of ongoing attention [6-10]. A recent report [11] of the preparation and hydrogenolysis of 7,7a-diaryl-1,2,3,4,5,7a-hexahydroimidazo[1,2-*a*]pyrazines **1** ($R_1 = R_2$ = phenyl, *p*-substituted phenyl) prompts our disclosure of the first synthesis of the dimer of the parent heterocycle **1** ($R_1 = R_2 = H$), and its catalytic hydrogenation.



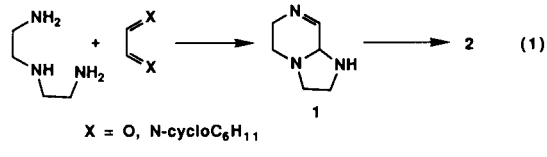
1

Reaction of diethylenetriamine (DETA) with 40% aqueous glyoxal (equation 1, 1:1 mole ratio, incremental addition of glyoxal to DETA at 0°) provided **2**, the dimer of **1** ($R_1 = R_2 = H$), albeit in low yield ($\leq 10\%$). In contrast,



2

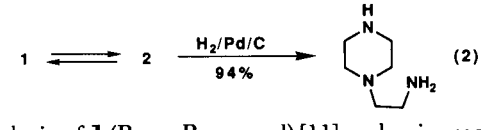
an acceptable yield of **2** (71%) was obtained by treatment of DETA with *N,N'*-dicyclohexylethylenediimine (equation 1) [12]. That the isolated product is dimeric was demonstrated by vapor phase osmometry, and ir, ^1H nmr and mass spectrometry. The ir and ^1H nmr were consistent with the presence of a cyclic aliphatic amine functionality, but characteristic bands for a cyclic imine [*eg* ν C=N at 1640-1690 cm^{-1}; δ 6.5-7.0 (m, imine hydrogen)] were absent. The existence of **2** as a dimeric structure was suggested by low resolution mass spectroscopy [m/z 250 (M+), 125 (base peak), no fragments between these ions] at a low injector port temperature ($\leq 200°$). However, at injector port temperatures of 250° and above, only **1** and its fragmentation products were observed. Formulation of **2** as a dimer was supported by high resolution ms (FAB, M+ Calcd: 250.1904. Found: 250.1704). Fragmentations corresponding to trimers or higher oligomers of **1** were not observed. Further evidence for the dimeric nature of **2** in solution was provided by vapor phase osmometry; a molecular weight of 252 (theoretical, 250) was found. Although we do not have X-ray crystallographic evidence for the pentacyclic structure postulated, this formulation is consistent with the spectroscopic data, and best accomodates the absence of imine functionality and the dimeric nature of **2**.

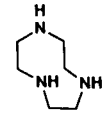


X = O, N-cycloC_6H_{11}

Isolation of **1** ($R_1 = R_2 = H$) as a dimer reflects the high susceptibility of $\Delta^{1,2}$-tetrahydropyridines and similar heterocyclic enamines to undergo addition reactions [13]. In contrast to simpler systems, which cyclotrimerize, a cyclic dimer arises here *via* double aminal formation. This may result from the relative insolubility of **2** and its precipitation from an otherwise dynamic equilibrium mixture [2,7]. Interestingly, **1** ($R_1 = R_2$ = aryl) does not dimerize, presumably for steric (and possibly electronic) reasons.

Catalytic hydrogenation of **2** provided further evidence for the equilibrium between **1** and **2** in solution. *N*-(2-Aminoethyl)piperazine was obtained in 94% yield (equation 2). In agreement with the reactivity found on hydrogenolysis of **1** ($R_1 = R_2$ = aryl) [11], only piperazine derivatives were obtained. Formation of the isomeric triazacyclononane **3** was not observed.





3

EXPERIMENTAL

Diethylenetriamine, 40% aqueous glyoxal, and cyclohexylamine were obtained from the Aldrich Chemical Co. (reagent grade) and were used as received. Melting points were determined on a Thomas Hoover capillary melting point apparatus, and are uncorrected. Microanalyses were performed by the Analytical Services Department of Air Products and Chemicals. Where appropriate, the identity of compounds was confirmed by comparison of infrared spectra, determined by the usual Nujol mull and liquid film techniques on an Analect Instruments Model FX-6200 FTIR, and nmr spectra, determined as solutions in perdeuteriomethanol on an IBM Sy-200 FT NMR Spectrometer, with TMS as internal standard. Osmometry was carried out in methanol solvent with a Knauer Vapor Phase Osmometer. The gc analyses were carried out on a Varian Model 3700 gas chromatograph equipped with a capillary injection port for use with fused-silica columns, Model 8000 autosampler, and flame ionization detection. Separations were effected with a fused-silica DB-5 column (30 m x 0.32 mm; 1.0 μm film thickness). Quantitation was based on the use of triethylene glycol dimethyl ether as the internal standard. The autosampler was controlled, and integrations performed, by a Varian VISTA 402 chromatography data system. Low resolution mass spectra were determined with a Hewlett-Packard Model 5988A GC/MS; molecular weights and the number of nitrogen-bonded hydrogens were confirmed by chemical ionization (perdeuterioammonia). High resolution mass spectra were determined with a VG ZAB EQ High Resolution MS. High resolution FAB analyses were carried out using glycerol solvent.

Preparation of 1,2,3,4,5,7a-Hexahydroimidazo[1,2-*a*]pyrazine (**2**) from Glyoxal.

Diethylenetriamine (9.7 g, 0.094 mole) was added to a 50 ml round bottom flask equipped with a magnetic stirrer and cooled to 0° in an ice bath. Aqueous (40%) glyoxal (14.5 g, 0.100 mole) was added dropwise with stirring over 0.5 hour. As the glyoxal was added, the temperature of the reaction rose to 20°. After addition was complete, the mixture was allowed to stand at room temperature overnight. Filtration and washing with cold (0°) absolute ethanol provided 1 g (9%) of **2**, mp 194-195°; ^{1}H nmr: δ 3.75 (s, 2H), 2.10-3.20 (m, 20H); ir: ν NH 3180 and 1490 cm^{-1}, ν C-N 1150 cm^{-1}, ν CH_2 3000-2700 and 1468 cm^{-1}; ms: m/z 250 (12), 125 (16), 110 (16), 97 (100).

Preparation of 1,2,3,4,5,7a-Hexahydroimidazo[1,2-*a*]pyrazine (**2**) from *N,N'*-Dicyclohexylethylenediamine.

A solution of *N,N'*-dicyclohexylethylenediimine (16.5 g, 0.075 mole) and DETA (14.4 g, 0.140 mole) in absolute ethanol (50 ml) was heated under reflux for 24 hours. Cooling to room temperature and filtration gave 5.0 g (53%) of **2**, mp 194°. Cooling to -20° and filtration provided an additional 1.7 g (18%) of **2**, mp 194-195°. Melting point and spectroscopic data (ir, ^{1}H nmr, and ms) were identical to those found above.

Anal. Calcd. for $C_{12}H_{22}N_6$: C, 57.57; H, 8.86; N, 33.57. Found: C, 57.31; H, 8.84; N, 33.36.

Catalytic Hydrogenation of **2**.

A solution of **2** (5.0 g, 0.02 mole) in absolute ethanol (25 ml) and 5% palladium/carbon (0.1031 g, 2.1 wt%, based on **2**) were charged into a 100 ml 316 stainless steel autoclave. Reduction was carried out at 125°/800 psig for 6 hours. After cooling and filtration, quantitative glc analysis showed complete conversion of **2**, and the presence of *N*-(2-aminoethyl)piperazine, 94 wt% of the product mixture. Identity of the major product as *N*-(2-aminoethyl)piperazine was verified by gc-ms.

REFERENCES AND NOTES

[1] Summer research associate, May-August 1986. Currently Assistant Professor of Chemistry, Northwestern University.

[2a] B. Fuchs and A. Ellencweig, *Recl. Trav. Chim. Pays-Bas*, **98**, 326 (1979); [b] I. J. Ferguson, A. R. Katritzky and R. Patel, *J. Chem. Soc., Perkin Trans. 2*, 1564 (1976); [c] B. Fuchs, S. Weinman, U. Schmuel, A. R. Katritzky and R. Patel, *Tetrahedron Letters*, **22**, 3541 (1981).

[3] D. St. C. Black, D. C. Craig, O. Giitsidis, R. W. Read, A. Salek and M. A. Sefton, *J. Org. Chem.*, **54**, 4771 (1989).

[4] J. Jazwinski and R. A. Kolinski, *Tetrahedron Letters*, **22**, 1711 (1981).

[5a] G. R. Weisman, S. C. H. Ho and V. Johnson, *Tetrahedron Letters*, **21**, 335 (1980); [b] P. W. R. Caulkett, D. Greatbanks, R. W. Turner and J. A. J. Jarvis, *J. Chem. Soc., Chem Commun.*, 150 (1977).

[6] J. M. Edwards, U. Weiss, R. D. Gilardi and I. L. Karle, *J. Chem. Soc., Chem. Commun.*, 1649 (1968).

[7] R. L. Willer, D. W. Moore, C. K. Lowe-Ma and D. J. Vanderah, *J. Org. Chem.*, **50**, 2368 (1985) and references therein.

[8] E. Tauer, K.-H. Grellmann, M. Noltemeyer and G. M. Sheldrick, *Angew. Chem., Int. Ed. Engl.*, **28**, 338 (1989).

[9] A. T. Nielsen, R. A. Nissan, D. J. Vanderah, C. L. Coon, R. D. Gilardi, C. F. George and J. Flippen-Anderson, *J. Org. Chem.*, **55**, 1459 (1990).

[10] D. C. Craig, M. Kassiou and R. W. Read, *J. Chem. Soc., Chem. Commun.*, 607 (1991).

[11] T. Okawara, K. Uchiyama, Y. Okamoto, T. Yamasaki and M. Furukawa, *J. Chem. Res. (S)*, 264 (1992).

[12] J. M. Kliegman and R. K. Barnes, *Tetrahedron*, **26**, 2555 (1970).

[13a] C. Schopf, H. Arm and F. Braun, *Chem. Ber.*, **85**, 937 (1952); [b] C. Schopf, A. Komzak, F. Braun, E. Jacobi, M.-L. Bormuth, M. Bullheimer and I. Hagel, *Liebigs Ann. Chem.*, **559**, 1 (1948); [c] F. Chioccara and E. Novellino, *J. Heterocyclic Chem.*, **24**, 1741 (1987); [d] O. Crescenzi, G. Prota, T. Schultz and L. J. Wolfram, *Tetrahedron*, **44**, 6447 (1988).