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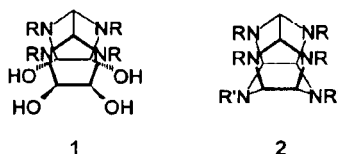
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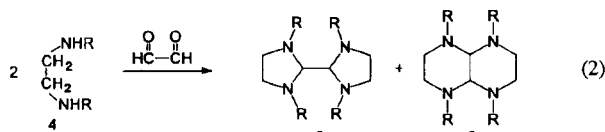
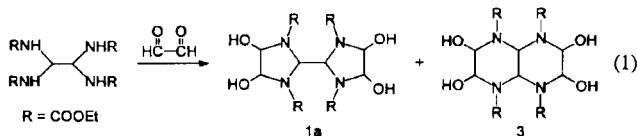
The base-promoted addition of glyoxal to 1,1,2,2-tetrakis(ethoxycarbonylamino)ethane in DMF gives a product mixture containing mostly 1,1',3,3'-tetrakis(ethoxycarbonyl)-4,4',5,5'-tetrahydroxy-2,2'-biimidazolidinyl. An alternate structure containing a tetraazadecalin system was considered less likely, since the most significant peak in the mass spectrum of this product and a tetraacetate derivative corresponded to half the mass of the parent ion. Two-dimensional nmr spectra on the major hplc fraction are more consistent with the biimidazolidinyl structure (very low  $J_{vic}$  and lack of NOE enhancement). A HETCOSY spectrum on the mixture allowed assignment of  $^1H$  nmr shifts.

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The tetrahydroxybiimidazolidinyl structure **1** is of interest for possible further transformation to the hexaazaisowurtzitane cage system **2** [2] by reactions with amines or amides  $R'NH_2$  [3].



Structure **1a** could result from addition of 2 moles of glyoxal to the known tetra(amido)ethanes. However, tetraazadecalin **3** could also be formed (eq 1) analogous to reactions of ethylenediamines **4** with glyoxal (eq 2).



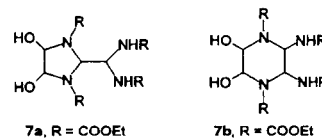
With unsubstituted ethylenediamine, the exclusive product from reaction (2) is *trans*-decalin **6** [4] and with **4** ( $R = Me$ ) the initial product is a mixture of *cis* and *trans* decalines **6** [5]. However, it was reported that **4** (where  $R$  is Ph or benzyl) gave biimidazolidinyl **5** [4b], [6]. A reinvestigation [7] of the reaction of glyoxal with several  $N,N'$ -disubstituted ethylenediamines reported that the initial product with  $N,N'$ -dibenzylethylenediamine was the biimidazolidinyl. Its yield was larger when the condensation

occurred in the presence of excess amine and in a solvent less polar than water. Thus, "inverse" addition of the amine to glyoxal in ethanol gave products **5** and **6** in an 8:2 ratio. Reaction of glyoxal with methylene bis(amides) and ureas necessarily leads to imidazolidines [8].

Glyoxal condenses readily under acidic conditions with amides and urethanes to give tetrakis(acylamino)ethanes [9]. However, further reaction to **1a** or **3** has not been observed. We now report our results on the base-promoted condensation of glyoxal with a tetrakis(acylamino)ethane.

### Results and Discussion.

Glyoxal was added to 1,1,2-tetra(ethoxycarbonylamino)ethane in DMF in the presence of potassium carbonate. Medium pressure chromatography on the crude product gave a minor amount of what is apparently mono adduct **7a** or the corresponding piperazine derivative **7b** on the basis of its nmr. This product could be readily distinguished from **1a** or **3** by the fact that it had only two exchangeable hydrogens. It was suggested [7] that the various products from eq (2) arose from rearrangement and other reactions of hydroxypiperazines analogous to **7b**.



The major product, formed in 52% yield as a colorless foam and referred to as product **A**, gave a satisfactory elemental analysis for **1a/3** but could not be crystallized. Reverse phase tlc analysis indicated the presence of several minor components which are believed to be stereoisomers (*cis/trans* hydroxy isomers) and/or structural isomers

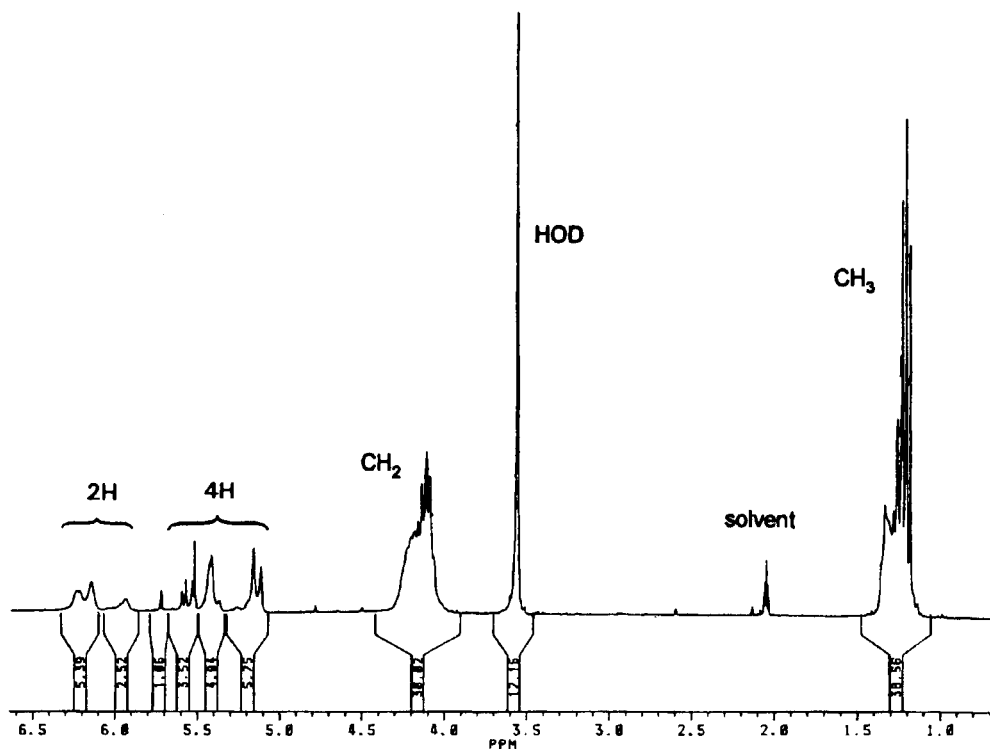


Figure 1. The  $^1\text{H}$  nmr of product A in acetone- $d_6$  after exchange with deuterium oxide.

(1a/3). Treatment of A with acetic anhydride/sulfuric acid gave a tetraacetate which likewise could not be crystallized to permit X-ray structure determination.

The  $^1\text{H}$  nmr spectrum of A (Figure 1), taken in acetone- $d_6$  after deuterium oxide exchange, shows nonequivalent ethyl groups. The downfield methine hydrogens at  $\delta$  5.9 to 6.3 were assigned to (N)CH(N) because of a relative area of 2, while those at  $\delta$  5.1 to 5.8 with a relative area of 4 to (N)CH(OH) hydrogens.

This assignment was confirmed by the HETCOSY spectrum of A in the same solvent (Figure 2). The  $^{13}\text{C}$  spectrum (top line) shows signals at ca. 72 ppm and 88 ppm which were assigned from electronegativity considerations to (N)CH(N) and (N)CH(OH) carbons, respectively. This (N)CH(N)  $^{13}\text{C}$  multiplet did indeed correlate with the more downfield hydrogens at 5.9 to 6.3 ppm.

It was thought that one way to distinguish between 1a and 3 would be to determine *vicinal* coupling constants and compare values with known biimidazolidinyls and decalins. For this purpose it was desirable to obtain spectral data on one compound. Consequently, the isomer mixture above was subjected to hplc on a 5- $\mu$ ,  $\text{C}_{18}$  column. Elution with 15% methanol/water gave three fractions corresponding to 15%, 71% and 12%. The nmr spectra described below were taken on the main fraction referred to as hplc fraction 2.

A J-resolved spectrum showed no coupling for hydrogens in the 5.1 to 6.3 ppm region (Figure 3). Also, a NOESY

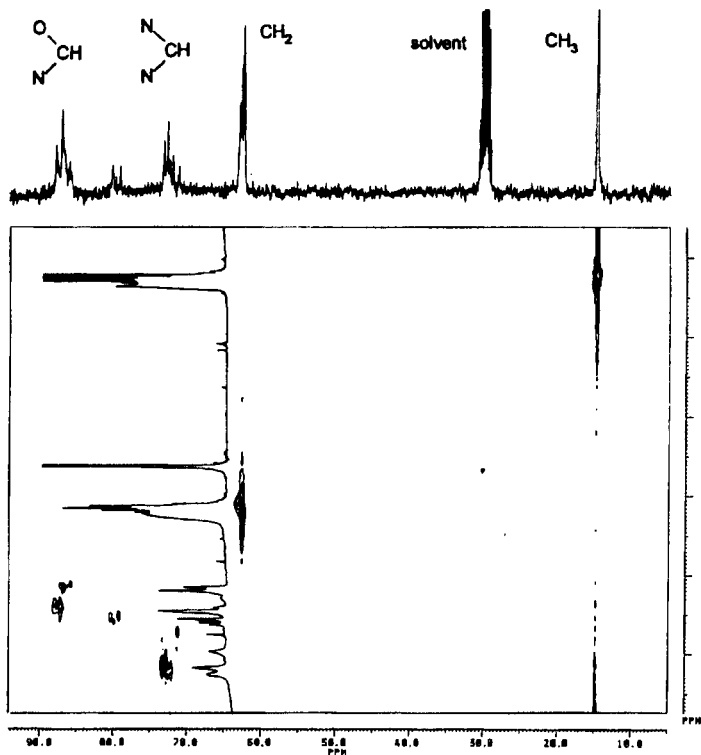


Figure 2. HETCOSY spectrum of product A in acetone- $d_6$ .

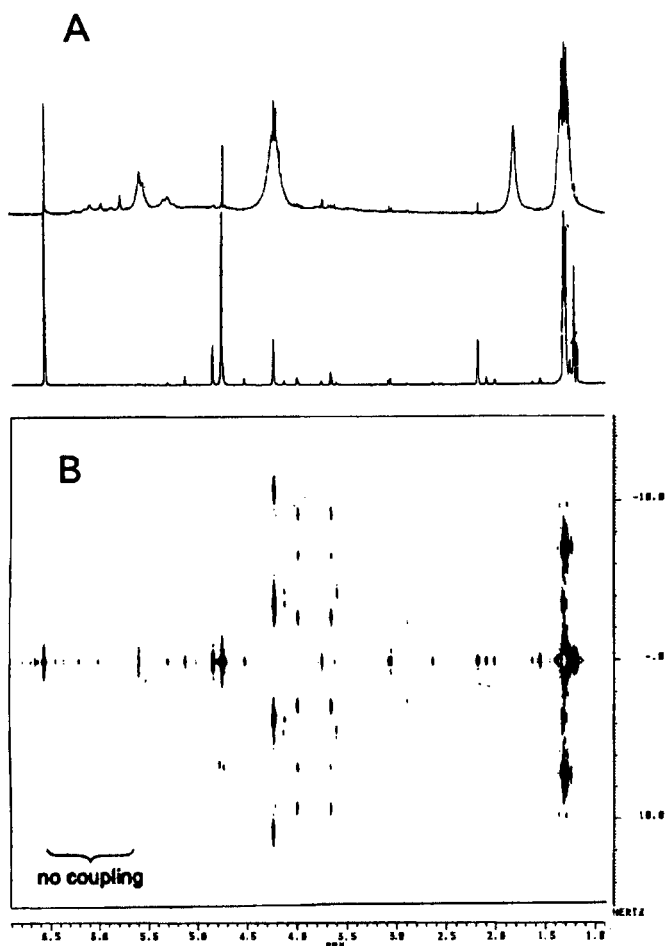


Figure 3. J-resolved spectrum of hplc fraction 2 in deuteriochloroform: (A) coupled 1D spectrum; (B) horizontal projection of the 2D matrix (decoupled spectrum).

spectrum (Figure 4) did not indicate proximal hydrogens in this region, a result found also for isomer mixture A. Finally, energy minimization with Alchemy II gave the following dihedral angles for vicinal CH(N)(N) hydrogens (averaged for a limited set of possible stereoisomers of CH(OH)):  $86 \pm 8^\circ$  for **1a**,  $52 \pm 2^\circ$  for *cis*-**3**, and  $178 \pm 1^\circ$  for *trans*-**3**.

Biimidazolidinyl structure **1a** is more consistent with these observations. One would expect a very small  $J_{vic}$  CH(N)(N) coupling constant for **1a**, since the dihedral angle is near  $90^\circ$ , and little NOE enhancement for the conformationally mobile five-membered ring system. On the other hand *cis*-**3** should have measureable *J* for bridgehead hydrogens based on the calculated dihedral angle, and non-centrosymmetric stereoisomers of *trans*-**3**, with dihedral angles near  $180^\circ$ , would have very large *J*. Centrosymmetric isomers of *trans*-**3**, where *J* is zero due to equivalent hydrogens, are ruled out by the lack of large NOE enhancements (see Figure 4) expected for a rigid, *trans*-decalin system with proximal 1,3-diaxial hydrogens.

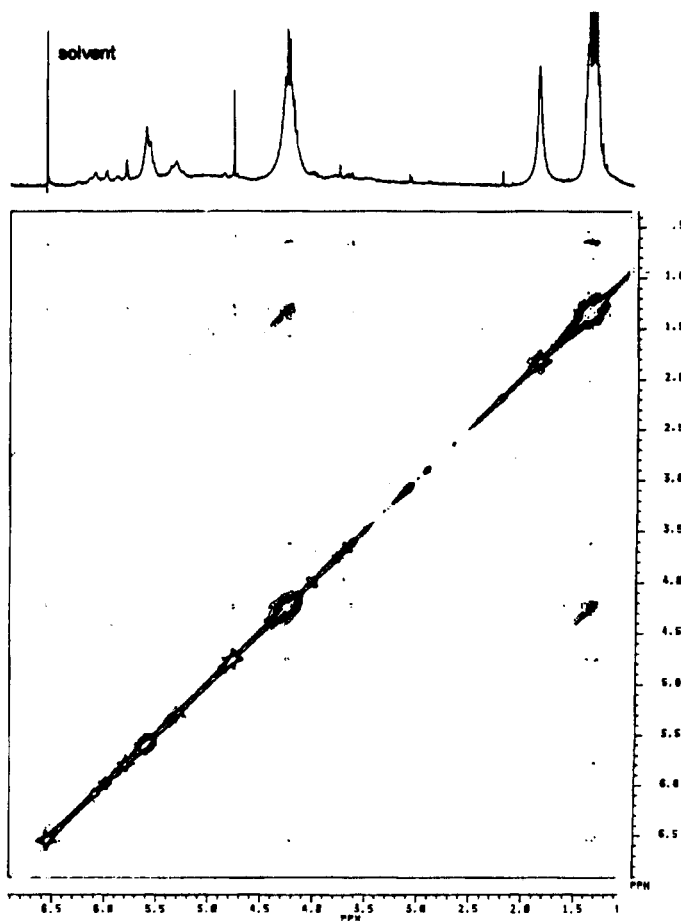


Figure 4. NOESY spectrum of hplc fraction 2 in deuteriochloroform at 100 ms mixing time.

The biimidazolidinyl structure of product A was unambiguously demonstrated by its FAB mass spectrum. The base peak was at 247 corresponding to *M*/2, and there was no observable peak at *M*. Facile cleavage into equal fragments is clearly consistent with the biimidazolidinyl structure and difficult to rationalize with a decalin or other structure. The ratio of *M*/2 to *M* peak intensities is  $>200$  in agreement with the magnitude of values reported for biimidazolidinyls **5**, e.g., 100 for *R* = benzyl [10] and  $>1000$  for *R* = phenyl [4b]. Corresponding values for the decalins **6** are much lower, ca. 5 for *R* = benzyl [10] and 1 to 2 for various methyl-substituted **6** [4b]. Similar results were found in the present study for the tetraacetate of **1a** with a base peak at 331 corresponding to *M*/2 and no observable peak at *M*.

## EXPERIMENTAL

### Instrumentation.

The nmr spectra were taken on a 300-MHz Bruker AM 300 instrument at probe temperature (ca.  $22^\circ$ ). The  $^{13}\text{C}$  spectra were taken at 75.467 MHz. All 2D spectra were obtained using stan-

standard Bruker micro programs and experimentally determined 90° or 180° pulse widths. NOESY spectra were at mixing times of 100, 200, and 500 ms. Mass spectra were taken on a Kratos 890 instrument by personnel of the Department of Chemistry, Cornell University, Ithaca, NY utilizing positive ion FAB and the following parameters: L resolution; 10 s per decade scan rate; 192 averaging rate; 68 threshold; nominal acquisition type.

#### Chromatography.

Medium pressure chromatography was carried out on Silica Gel 60 with 2-5% methanol/dichloromethane and tlc on reverse phase Si-C<sub>18</sub>F plates with 2:3 methanol/water. For hplc a Model 6000 Waters Associates Liquid Chromatograph equipped with a Model 480 LC spectrophotometer and Model 730 Data Module was used. A 1.5 µl sample was injected onto a 25 cm x 4.6 mm, 5-µ, C<sub>18</sub> Beckman column and eluted with 15% methanol/water at 1.5 kpsi and a 1.0 ml/minute flow rate. Peaks were detected by uv absorbance at 212 nm.

#### Synthesis.

To a stirred suspension of 2.27 g (6.00 mmoles) of 1,1,2,2-tetra(ethoxycarbonylamino)ethane and 0.84 g (6.1 mmoles) of potassium carbonate in 30 ml of DMF at 47° was added, dropwise and with stirring, 7.25 g (50 mmoles) of glyoxal over a period of 45 minutes. Stirring was continued at 47-52° for 22 hours. The clear, red-brown solution was then cooled to room temperature, diluted in 200 ml of acetone, filtered, and concentrated *in vacuo* to give a sticky, light tan foam. Remaining DMF was removed by co-evaporation with water. Medium pressure chromatography gave the product as a brittle white foam, 1.53 g (52%), mp 119-125°; <sup>1</sup>H nmr (acetone-d<sub>6</sub>): δ 1.2-1.4 (m, 12, CH<sub>3</sub>CH<sub>2</sub>O), 4.0-4.3 (m, 8, CH<sub>3</sub>CH<sub>2</sub>O), 5.1-6.3 (v broad m, 10, methine and OH); addition of three drops of deuterium oxide removed broad signals in the 5.1-6.3 region giving sharper multiplets 5.1-5.8 (m, 4, (N)CH(OD)), 5.9-6.3 (m, 2, (N)CH(N)).

*Anal.* Calcd. for C<sub>18</sub>H<sub>30</sub>N<sub>4</sub>O<sub>12</sub>: C, 43.72; H, 6.12; N, 11.33. Found: C, 43.61; H, 6.29; N, 10.95.

Analysis (tlc) with 1:1 methanol/water on this product showed the presence of two minor components (R<sub>f</sub> values 0.39, 0.51, and 0.73); hplc gave three fractions with the following retention times in minutes and amounts: 2.1 (15%), 3.1 (71%), 4.4 (12%).

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