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An unusual product obtained from condensation between ethylenediamine and formaldehyde in basic medium

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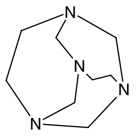
Abstract—Reaction between ethylenediamine and formaldehyde normally affords 1,3,6,8-tetraazatricyclo[4.4.1.1$^{3.8}$]dodecane (TATD) but in this case also afforded 3,3′-ethane-1,2-diyl-bis-1,3,5-triazabicyclo[3.2.1]octane (ETABOC), this being an unusual product from such condensation.

For a few years now, 1,3,6,8-tetraazatricyclo [4.4.1.1.^{3,8}]-dodecane (TATD) **1** a macrocyclic aminal obtained as described[1] by condensing formaldehyde and ethylenediamine with NaOH, has been successfully used in Mannich-type reactions in basic media[2] and in the synthesis of some heterocyclic compounds, such as 1,3,5-tris-arylhexahydro-1,3,5-triazines,[3] 1,3-bis(cyanomethyl)imidazolidines,[4] 1,3-dinitrosoimidazolidine,[5] and 1,3,6,8-tetraazatricyclo [4.3.1.1.^{3,8}]undecane a cage amine type compound.[6] A recent report[7] has described a solvent-free Mannich-type reaction of 1,3-bis(2′-hydroxy-5′-substituted-benzyl)imidazolidines with TATD to afford calix[2]imidazolidin[2]arenes.

Surprisingly low levels (<2.0%) of an unknown impurity were detected during our ongoing research for the synthetic exploitation of TATD when larger amounts of sodium hydroxide and lower temperatures than those which have been reported[1] were employed. We assigned its structure as 3,3′-ethane-1,2-diyl-bis-1,3,5-triazabicyclo[3.2.1.]octane **2** (we named it ETABOC) on the basis of NMR spectroscopic studies of a small sample isolated by recrystallization. In view of the apparent ease of formation of this unexpected compound and our own interest in such molecules it was decided to examine its mode of formation and hopefully, its chemistry.

Although the reaction for TATD preparation is known since 1898[8] to the best of our knowledge only Hocker and Wendisch[9] formerly and later Dale and Sigvartsen[10] have reported the isolation of compound 3-oxa-1,5-diazabicyclo[3.2.1]octane **3** in addition to TATD.



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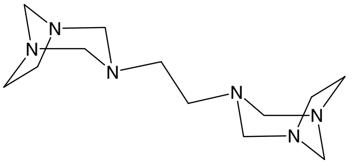

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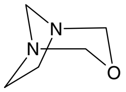

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The latter authors have proposed that the reaction for **1** and **3** forming happens via a mechanism implying the simultaneous presence of imines and methylolamines, respectively (Scheme 1).

Our NMR studies allowed us to ascertain the presence of methylolamines but not that of imines. We were also able to establish that **1** and **2** production is controlled by factors such as pH and temperature. Thus, increasing the amount of NaOH added to an ethylenediamine/formaldehyde mixture favored producing **2**. A contrary effect was presented on bringing the reaction mixture into contact with small quantities of ammonium fluoride. Regarding temperature, it was established that

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Keywords: Cyclic aminals; Ethylenediamine formaldehyde condensation.

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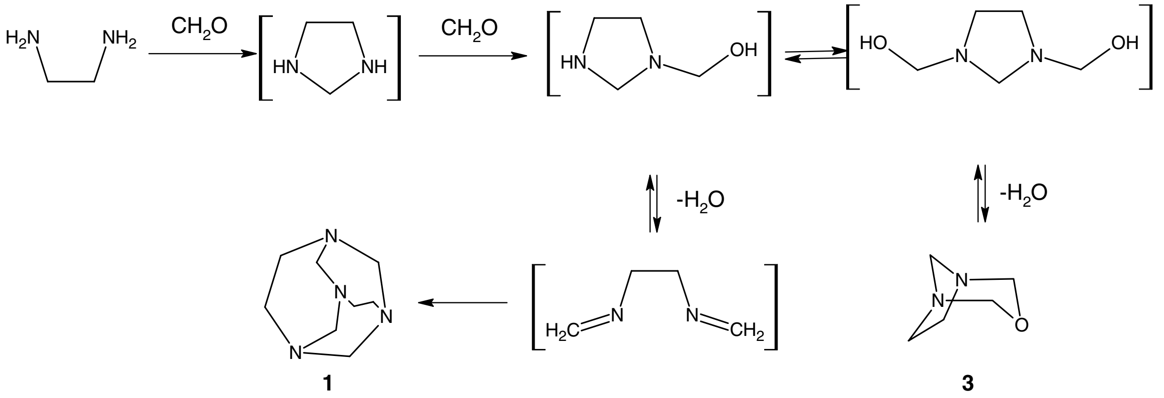


Scheme 1. Proposed mechanism[10] for obtaining compounds **1** and **3**.

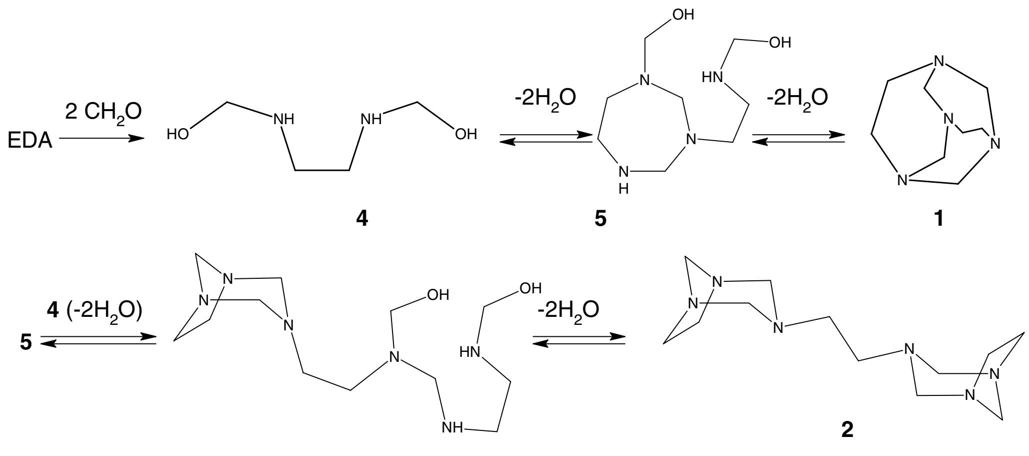
the concentration of **2** decreased if the reaction was carried out at room temperature and, on the contrary, it increased when lower temperatures were used. On the other hand, the variation in relative yield of products **1** and **2** in crude mixtures of different reactions, led us to think about the existence of a common intermediary for both, different to that proposed in the literature.[10]

In fact, NMR spectra (H_2O/D_2O) recorded 5 min after mixing ethylenediamine with formaldehyde revealed the presence of TATD, ETABOC, and methylolamines in the reaction mixture. It is interesting to note that, we were never able to detect compound **3** nor imines. These results led us to suppose that it should be referred to as equilibrium control (kinetic and thermodynamic) of product composition formed from a common intermediary. A plausible mechanism involving no imines but a common intermediary **5** that may rationalize these results is depicted in Scheme 2.

Experimental conditions in which ETABOC **2** was the major compound in the reaction mixture and in which it was isolated with an appreciable yield were established after carrying out several assays. Thus, a solution of ethylenediamine (1.6 mL, 24 mmol) in water (2.0 mL) cooled to 0 °C was slowly added (30 min) to a 25 mL single neck round bottom flask that contained formaldehyde 37% solution (3.6 mL, 48 mmol) cooled using an ice-salt bath and stirred. After stirring at −10 °C for 1 h, the solution was concentrated under reduced pressure. Crude reaction product was extracted with chloroform (10 mL × 3) and the chloroformic extract was dried with anhydrous sodium sulfate and filtered. Removal of the chloroform under reduced pressure afforded a crude product which was purified by crystallization (pet. ether) to give compound **2** (1.04 g) in 51% yield, mp 88–89 °C. From the residue compound **1** was also isolated (485 mg, 30%).

Compound **2** is stable in the absence of acids and water. ^{1}H NMR and ^{13}C NMR measurements carried out in $CDCl_3$ provide unequivocal evidence for the structure of **2**[11] especially in 2D experiments. The $\delta(^1H)$ assignments of AB and AA′BB′ spin system are based on the characteristic ^2J(H,H), ^3J(H,H) and ^4J(H,H) coupling constants as well as ^{1}H COSY and NOESY experiments.

The ^{1}H NMR spectrum consist of seven signals having intensities of 1:2:2:1:2:2:2. A singlet at 2.17 ppm which is ca. 0.80 ppm more highfield than expected was assigned to four protons of ethylenediamine exocyclic moiety. This signal correlated to a 48.5 ppm signal in the carbon domain in the HMQC two-dimensional spec-



Scheme 2. Proposed mechanism for forming **1** and **2**.

trum. A double–doublet centered on 2.75 ppm (^2J = 10.6 and ^3J = 4.4 Hz) and a double doublet-of-doublets centered at 3.13 ppm (^2J = 10.6, ^3J = 4.4 and ^4J = 1.9 Hz) clearly exhibited the general splitting pattern of an AA′BB′ system which was assigned to ethylenediamine portions conforming the 1,3,5-triaza[3,2,1]octane bicycle system. Four signals at 3–4 ppm having coupling constants about 10 Hz, characteristic of coupling between non-equivalent geminal protons, indicated the presence of two AB systems. The more shielded aminal hydrogen signal, centered at 3.30 ppm, corresponded to a double–triplet (^2J = 10.5 and ^4J = 1.5 Hz); this signal coupled with the more deshielded signal resonated at δ 3.89 as a double–triplet (^2J = 10.5 and ^4J = 1.9 Hz). The other AB system showed a doublet at 3.40 ppm and the other one at 3.62 and both exhibit ^2J = 10.7 and ^4J = 1.5 Hz.

It is noteworthy to mention that unequivocal assignments of bridgehead protons was possible because of ^4J coupling (less than 2.0 Hz) have conformational dependence[12] and are observable in cycles only when the ‘W’ path is available. Additional evidence for structure elucidation of **2** was obtained from the NOESY contour plot shown in Figure 1 where it can be seen that the double–doublet at 3.62 ppm and the singlet at 2.17 corresponded to hydrogens having *syn* distribution, the same as that presented with hydrogens appeared at 3.17 ppm. Another NOE effect was presented between the more downfield hydrogens (3.89 ppm) and those at 3.40 ppm.

The cross-peak in the HMQC two-dimensional spectrum was taken into account when assigning ^{13}C NMR signals. The signal at 51.9 ppm presented contours correlating to the AA′BB′ system (2.75 and 3.13 ppm), the signal a 76.5 ppm correlated to the (AB)2 system (3.39 and 3.62 ppm) and the signal at 76.6 ppm presented contours correlating to the AB system (3.29 and 3.86 ppm). The highest field signal (48.5 ppm) correlated to the highfield signal (2.17 ppm) which was assigned to exocyclic ethylene residue.

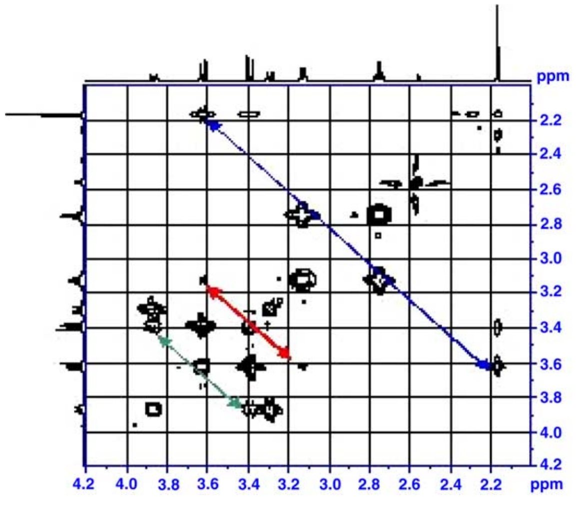
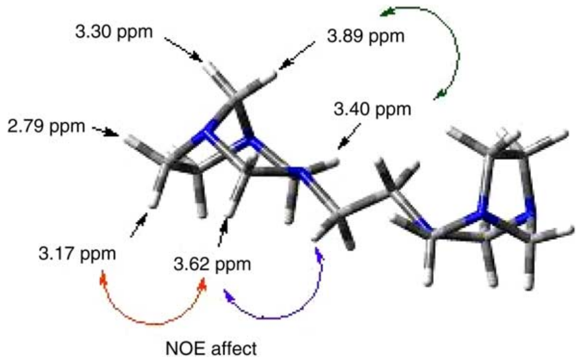


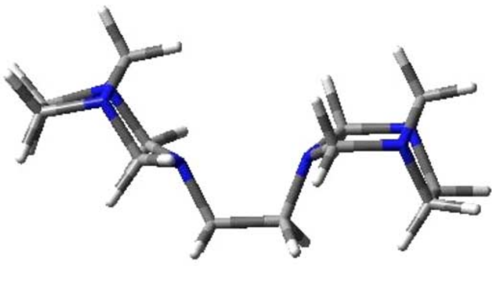
Figure 1. ETABOC **2** NOESY contour plot.



The ^{13}C NMR spectrum showed two pairs of secondary carbon atoms indicating that the molecule has symmetry. Aminalic carbon appeared at 78.5 and 76.6 ppm while ethylenic carbon resonated at 51.9 and 48.5 ppm. This fact was puzzling because at first glance the molecule appeared to be more complex. The ethylene group binding the two bicycles exhibited a surprisingly chemical equivalence of both ^{13}C nuclei and ^{1}H. This fact especially caught our attention. Such chemical and magnetic equivalence is only possible in one of two cases: when free rotation throughout this bond is not restricted or when the molecule is symmetric.

An eclipsed **6** conformation presenting a plane of symmetry is less stable than an *anti* conformation **7** presenting a C_2 axis of symmetry according to stability calculations for the two possible conformation presenting elements of symmetry, based on HF/6-31G* calculation employing Gaussian 98 computational software.[13] The difference in energy between the two conformers was 8.70 kcal/mol (HF/6-31G*).

In solution a more ‘stretched out’ geometry is adapted by the molecule. The fact that one of these two conformations predominated implies that the molecule is rigid



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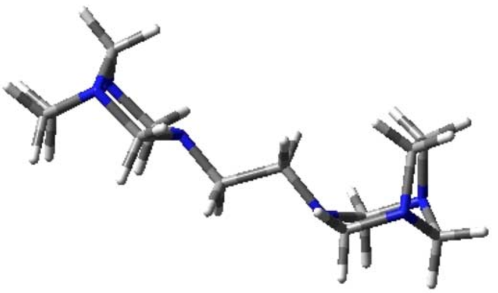

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and 'free rotation' around N3–CH_2–CH_2–N3′ bonds are restricted. The NOESY contour diagram experiment of **2** was supported because a cross-peak between ethylene hydrogens (2.17 ppm) and (AB)2 system hydrogens can be seen (Fig. 1).

The M^+ peak in HR-EIMS at 252.2062 further confirmed the structure. In conclusion, we have discovered an unknown product from condensation reaction between ethylediamine and formaldehyde and developed a mild method to obtain it in good yields.

Acknowledgements

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11. pf 88 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm (*J* Hz): 2.17 (NCH_2CH_2N, s, 4H); 2.79 (H6β, H7β, H6′β, and H7′β, dd; 10.6; 4.4); 3.17 (H6α, H7α, H6′α, and H7′α, ddd; 10.6; 4.4; 1.9) 3.30 (H8b and H8′b, dt: 10.5;1.5); 3.40 (H2β, H4β, H2′β, and H4′β, d; 10.7); 3,62 (H2α, H4α, H2′α, and H4′α, dd: 10.7;1.5); 3.89 (H8a and H8′a, dt; 10.5; 1.9). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 76.6 (C-8 and C-8′); 76.5 (C-2, C-4, C-2′, and C-4′); 51.9 (C-6, C-7, C-6′, and C-7′); 48.5 (NCH_2CH_2N). HR-EIMS: *m*/*z* (%) [M^+]: (1.71) calcd for $C_{12}H_{24}N_6$: 252.3653. Found: 252.2062; 182.1564 (10.10); 126.1030 (87.2), 85.0728 (100).
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