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Preparation of cage amine 1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane

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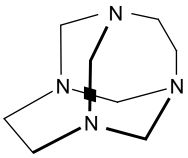
Abstract—Reaction between cage amine 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) and ammonium fluoride affords 1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane, the missing link between 1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane (urotropine) and TATD. The structure was established mainly from 2D NMR measurements.

1,3,6,8-Tetraazatricyclo[4.4.1.1^{3,8}]dodecane (**1**), or TATD, known since 1898,[1] and 1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane (**3**), or urotropine, known since 1859,[2] are important industrial chemicals produced commercially via reaction of formaldehyde with ethylenediamine[1,3] and ammonia,[2] respectively. Compound **1** has been used in organic synthesis[4] and in the preparation of resins based on phenol, urea, or melamine, in which formaldehyde is replaced entirely or partially by **1**.[5] Compound **3** has been used in organic synthesis,[6–9] and in several industrial fields, such as anti-moisture agent, hardener of resins, accelerator in sulfuration, pharmaceutical derivation, in the manufacture of high explosives such as RDX, as urinary antiseptic drug and in areas of nonlinear optics.[10] Surprisingly, during the long time that has elapsed since the discovery of **1** and **3**, no significant efforts were developed for the preparation of 1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane (**2**), hereafter referred to as TATU, despite its interest due to symmetry considerations and putative industrial applications.

In the course of our studies of the reactivity of aminals, we described several reactions of TATD (**1**), a cage amine type [(1^4.2^2)]adamanzane with phenols,[11] primary aromatic amines,[12] cyanide anion,[13] and electrophiles such as nitrosonium ion,[14] which afford 3,4-dihydro-3,6-disubstituted-2*H*-1,3-benzoxazines, 1,3-bis(2′-hydroxy-5′-substituted-benzyl)-imidazolidines, 1,3-bis(cyanomethyl)-imidazolidine, 1,3,5-tris-arylhexahydro-1,3,5-triazines, and 1,3-dinitrosoimidazolidine, respectively. In continuing our studies, we became interested in exploring the reactivity of **1** in basic media, which resulted in the preparation of the new cage amine [(1^5.2^1)]adamanzane (**2**) that we named TATU. Analogues of **2**, substituted at the ethylene residue, were prepared[15] by reaction of **3** with phenacyl bromides.



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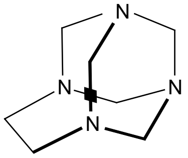

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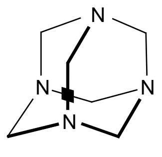

3

We initially prepared the macrocyclic aminal cage **2** by reaction of **1** using either an ammonium hydroxide (37%) solution obtained from a commercial source, or by bubbling ammonia gas into the aqueous reaction medium. However these procedures afforded low yields (12%) of the desired molecule, and therefore it was decided to perform the reaction at lower pH values. Thus, in the final procedure **1** (1.0 g, 5.95 mmol) was dissolved in distilled H_2O (5.0 mL) and ammonium fluoride

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Keywords: Adamanzanes; Aminals; Cage amines.

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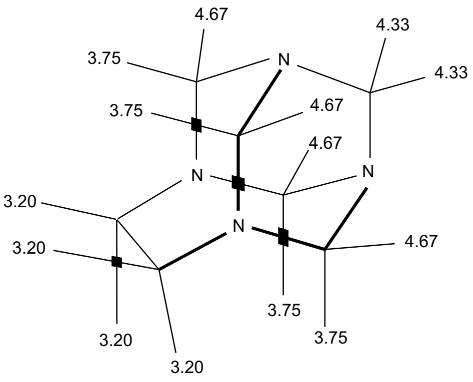
(0.35 mg, 9.52 mmol) was added, after which the reaction mixture was left stirring at room temperature for 5 h. The solvent was evaporated under reduced pressure and the solid residue was extracted with dichloromethane (3 × 5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent evaporated under reduced pressure. The crude reaction product was purified by column chromatography on Si-gel, eluting with a dichloromethane–ethanol (1:4) mixture, to yield 460 mg of **2** (63% yield) as a white solid. Other chromatographic fractions contained yellow resins that could not be characterized. The reaction yield is calculated taking into account the fact that five molecules of **1** can only afford four molecules of **2**, according to the balance

$$5C_8H_{16}N_4 + 8NH_3 \rightarrow 4C_7H_{14}N_4 + 6H_2NCH_2CH_2NH_2$$

since a carbon–carbon cleavage of an ethylene residue, to extrude a methylene group, seem extremely unlikely and therefore the only expected source to generate the fifth methylene present in **2** appears to be as originated by decomposition of another molecule of **1**.

The molecular structure of **2**[16] became evident from NMR measurements (in $CDCl_3$) and in particular from those performed in two dimensions. Thus, the ^{13}C NMR spectrum, obtained at 75.4 MHz revealed the presence of only three methylene signals at 57.4, 72.3, and 73.4 ppm,[17] suggesting that the first signal corresponds to a CH_2 group directly attached to one nitrogen atom, while the remaining two signals correspond to CH_2 groups bonded to two nitrogen atoms in each case. For comparison purposes, in the case of **1** the ethylene carbon atoms appear at 58.2 ppm, while the NCH_2N signal appears at 73.8 ppm.



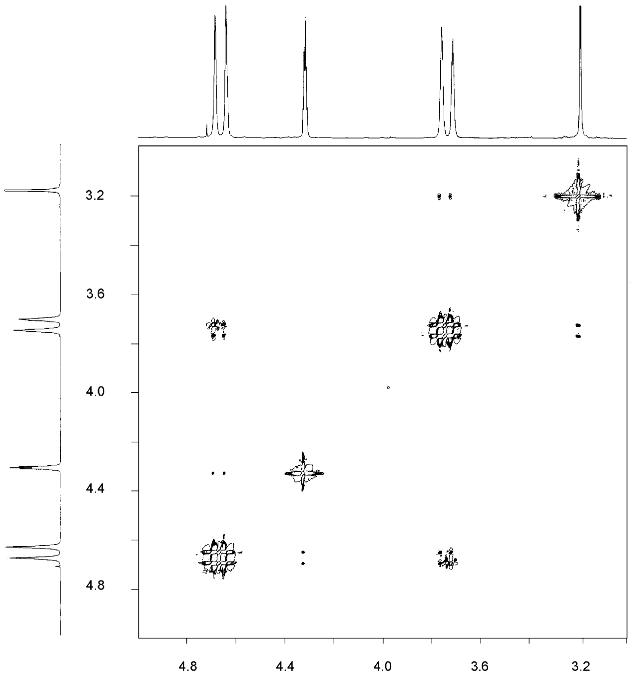


Figure 1. NOESY contour plot of TATU (**2**).

The ^1H NMR spectrum exhibits four signals with relative intensities 2:2:1:2. A singlet at 3.20 ppm, having a cross-peak in the two-dimensional gHSQC contour plot to the signal at 57.4 ppm in the carbon domain, corresponds to the four hydrogen atoms of an ethylene residue. A double doublet at 3.75 ppm ($J = 13.5$, 1.3 Hz), a homonuclear long-range coupled quintet ($J = 1.3$ Hz) at 4.33 ppm and a doublet at 4.67 ppm ($J = 13.5$ Hz) complete the spectrum. The homonuclear small coupling constant value is due to a long-range W coupling between the hydrogen atoms at 3.75 and 4.33 ppm. Each hydrogen atom at 4.33 ppm is coupled only to two of the hydrogens at 3.75 ppm but virtual coupling makes it appear as if coupled to all four hydrogens, with the apparent multiplicity of a quintet. This virtual coupling effect is not so clearly evidenced in the signal at 3.75 ppm, which should appear as a double triplet, but is in fact observed as a double doublet with a further unresolved coupling.

The quintet in the hydrogen domain is cross-coupled to the carbon signal at 72.3 ppm, while the AB proton system is cross-coupled to the carbon signal at 73.4 ppm. Cogent evidence for the molecular structure of **2** arose from the NOESY contour plot shown in Figure 1, where it can be observed that the doublet at 4.67 ppm and the quintet at 4.33 ppm correspond to *syn* distributed hydrogens, as is also the case for those protons originating the signals at 3.75 and 3.20 ppm.

Acknowledgements

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16. Compound **2** shows mp 213–215 °C (decomposition) when measured in a capillary tube. EIMS (70 eV) *m/z* (%): 154 (72), 126 (6), 112 (18), 86 (24), 57 (15), 42 (100). Anal. Calcd for $C_7H_{14}O_4$: C, 54.52; H, 9.15; N, 36.33. Found: C, 54.62; H, 8.91; N, 36.47.
17. A proton coupled ^{13}C NMR spectrum showed the signal at 57.4 ppm as a triple triplet ($J = 135.8$, 9.1 Hz), the signal at 72.3 ppm as a triple quintet ($J = 148.7$, 6.5 Hz) and the signal at 73.4 ppm as a triplet ($J = 147.5$ Hz) with further unresolved long-range spin–spin interactions.