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Azatriquinane, Azatriquinacene, and a Remarkable Dimerization Product

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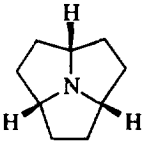
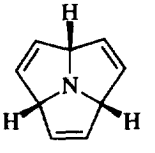
Abstract: Azatriquinane, an amine with a rigid, hemispherical topology, is synthesized in six steps from pyrrole. It is shown to be more basic than quinuclidine, and can be dimerized by N-oxidation and treatment with base to give novel, highly strained heptacycle. Oxidation with chlorine gives an azatriquinacene, a theoretical precursor to diazadodecahedrane.

In the 30 years since the first synthesis of triquinacene by Woodward,[1] no attempt has been registered to prepare an aza analogue of this topologically interesting molecule, or indeed any [2.2.2]cyclazine with a lone apical nitrogen,[2] despite an enduring interest both in triquinacene and in the [2.2.3], [2.3.3], and [3.3.3] cyclazines. Triquinacene was believed to be a precursor to dodecahedrane in a theoretically allowed [6+6]π dimerization,[3] and the latter have been extensively studied for aspects of their electronic structure.[4] The reduced form of the [2.3.3] and [3.3.3] systems also comprise a group of natural products isolated from orchids and the ladybird beetle defence secretion, respectively.[5,6]

We however became fundamentally interested in [2.2.2] cyclazine, or azatriquinane[7] (**1**) in terms of the concave/convex topology notion discussed and popularized by Cram.[8] This oblate hemispherical, non-invertable amine could be used to build up cryptands with fixed in-in[9] geometry, or be desymmetrized by substitution α to nitrogen leading to a highly rigid, novel, chiral acid/base system. Finally, if *azatriquinacene* **2** could be derived therefrom, the prospect of dimerization[3] to diazadodecahedrane cannot be completely ignored, especially since salts of **2** would be water soluble, and the effects of an aqueous environment on cycloaddition chemistry are well known.[10] We now give a preliminary report on the preparation of azatriquinane **1** and some of its chemistry, including oxidation to an azatriquinacene system.

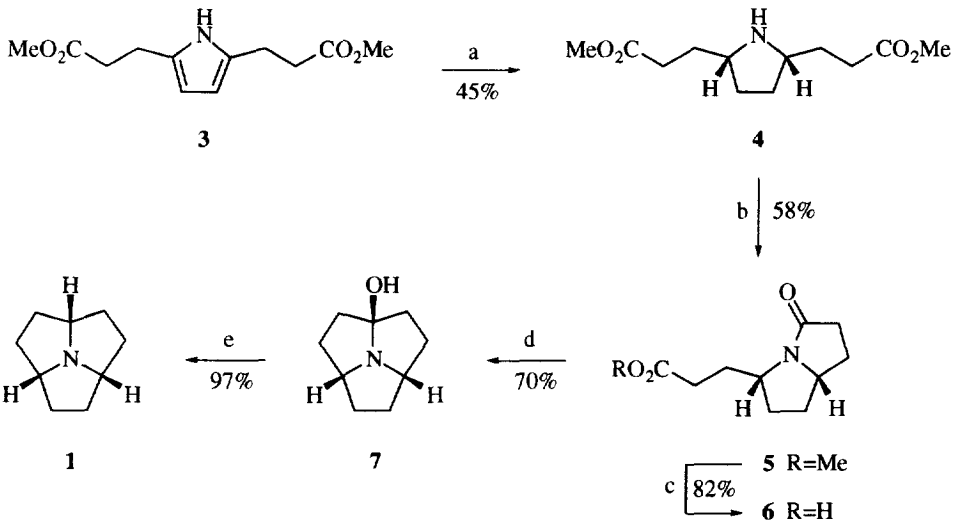


1



2

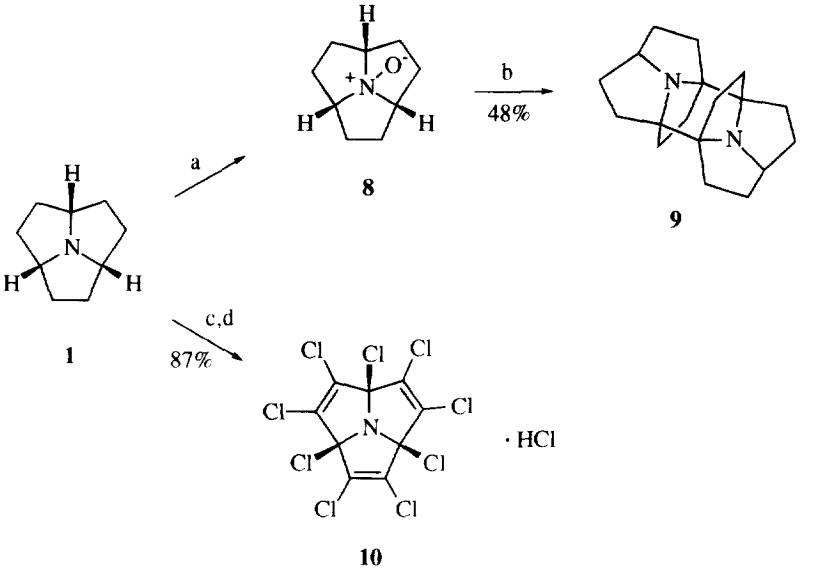
Compound **1** was approached by combining two methods used to prepare pyrrolizidines.[11,12] Thus pyrrole 2,5-bis(propanoate) ester **3**, derived from the bis addition of pyrrole to methyl acrylate,[13] was hydrogenated to give pyrrolidine **4** stereoselectively (Scheme 1). This could be cyclized in refluxing xylene to give pyrrolizidinone **5**, which was then hydrolyzed to **6**. The key step of the synthesis was the final cyclization by dry distillation of **6** from sodalime which proceeded in good yield to give the unusual, stable hemiaminal **7**. Whereas the pyrrolizidine synthesis on which this cyclization reaction was based gave the corresponding imine/enamine,[12] compound **7** is unable to dehydrate because of its rigid framework. The parent triquinane **1** could however be derived from **7** by reduction with lithium aluminium hydride under forcing conditions.[14] It is a volatile white solid with a melting point just above room temperature, and has been shown by nmr competition experiments to be among the most basic of simple amines.[15] An estimate of the pK_a was made by preparing a mixture of the HBF_4 salt of **1** with quinuclidine[16] in DMSO-d_6 and observing the position of acid-base equilibrium by nmr,[17] which led to the deduction that **1** was approximately 0.5 pK_a units more basic than quinuclidine. This may be a manifestation of the enforced and more acute pyramidalization of the nitrogen in **1** relative to quinuclidine.



Scheme 1. Reagents and conditions: (a) H_2, Rh/Al_2O_3; (b) reflux in xylenes, 52 h; (c) aq. NaOH, H^+; (d) sodalime, Δ; (e) $LiAlH_4$, THF, reflux, 62 h.

The above led us on to attempts to break the symmetry in **1** by introducing three different substituents α to the nitrogen and thereby create a basic (or acidic R_3N^+-H) site in a rigid, chiral enclosure. Accordingly, the N-oxide **8** was prepared (Scheme 2). However, on deprotonation and attempted quenching with electrophiles,[18] a dimer of **1** was observed which could only be assigned the improbable structure **9**. This was nevertheless confirmed by X-ray crystallography[19] (Figure 1). Presumably, **9** is the result of α-anion formation followed by elimination of oxide to give an iminium intermediate which again undergoes deprotonation and then 3+3 dimerization.[20] In stark contrast to **1**, compound **9** is essentially nonbasic, since modelling studies show that protonation at nitrogen seriously violates the van der Waals radii of the adjacent

hydrogens on the ethylene bridge. This hitherto unknown ring system shows the evidence of extraordinary ring strain in the length of the C–C bonds which connect the two tricycles to each other (1.583 Å). The targeted synthesis of **9** (i.e. in the absence of an electrophile) succeeds in 48% yield.



Scheme 2. Reagents and conditions: (a) 30% H_2O_2, MeOH; (b) t-BuLi, –78 to 0 °C, THF; (c) HCl, excess $NaBF_4$; (d) SO_2Cl_2, hv, 16 h.

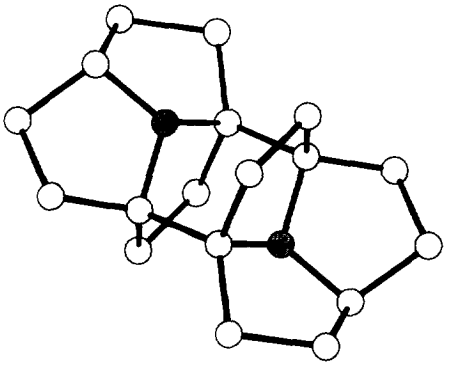


Figure 1. X-Ray crystal structure of **9**.

Finally, a number of attempts have been made to dehydrogenate **1** and derivatives thereof to the corresponding triquinacene. To date, success has only been won via a photochemical chlorination-dehydrochlorination pathway (Scheme 2). This however leads to a perchlorinated product **10** (87% yield)[21] which, although interesting in its own right, has resisted attempts at reduction to **2**. Work along these lines continues.

References and Notes

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14. Full analytical data consistent with the identity of **1** have been obtained in addition to an X-ray crystal structure of its HBF_4 salt, which will be published when the work is presented in full.
15. We define 'simple' as a trialkyl amine whose basicity is not influenced by the presence of other heteroatoms.
16. Formally 1-azabicyclo[2.2.2]octane; a consensus of literature values places the pK_a of this compound at about 11.0.
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19. Crystals of **9**: $C_{18}H_{26}N_2$, 0.6 x 0.2 x 0.1 mm, monoclinic, a = 12.166(2), b = 9.487(2), c = 13.565(3) Å, ß = 111.66(3) °, V = 1455 Å^3, D_c = 1.234 g cm^{-3}, space group *C2/c*, and Z = 4. The structure was solved by direct methods and refined on F^2 by a full matrix least squares method to R = 0.040, wR^2 = 0.099 (S = 1.018) for 1275 independent reflections.
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21. The observed isotopic peak pattern between *m/z* 486–472 in the mass spectrum matches that calculated for $C_9Cl_{10}N$ (15 peaks). The molecular ion peak at *m/z* 476 is 100% abundant. δ_c (100 MHz, CD_2Cl_2) 94.0 and 131.0. All other analytical data are consistent with the assigned structure, in particular the IR and UV spectra, which bear a strong resemblance to that of perchlorotriquinacene (Jacobson, I.T. *Acta Chem. Scand.* **1972**, *26*, 2477).

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