Azatriquinanes. 2.[1] Synthesis of Azatriquinadiene and Azatriquinacene

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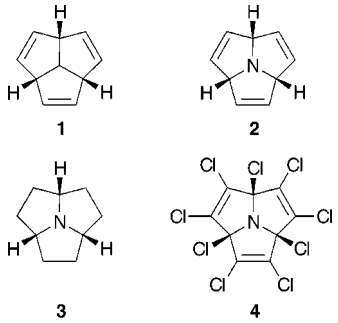
The tricyclic hydrocarbon triquinacene **1**, first synthesized by Woodward in 1964,[2] remains the object of substantial attention: Over 150 variously substituted triquinacenes have since been described,[3] and many more publications address homoaromaticity arguments,[4] rearrangement chemistry,[5] ions and radicals,[6] metal complexation,[7] and its potential for electrocyclic dimerization to dodecahedrane.[8]

We recently identified the aza analogue of **1**, i.e. 10-azatriquinacene **2**, as an attractive synthetic target due, of course, to its congruities with **1** but also its significant electronic differences, which should confer unique reactivity. In our original report of the synthesis of azatriquinane **3**,[1] we commented that the halogenation-dehydrohalogenation-reduction protocol originally used by Jacobson[9] to convert triquinane to triquinacene did not work for **3**. Although perchloroazatriquinacene **4** could be derived from **3** in high yield, all attempts to reduce it directly to the target material **2** have failed. We have since learned that *stepwise* reduction of **4** to azatriquinacene **2** is possible, and we now report the synthesis of **2** as well as an independent route to the corresponding diene, **6**.

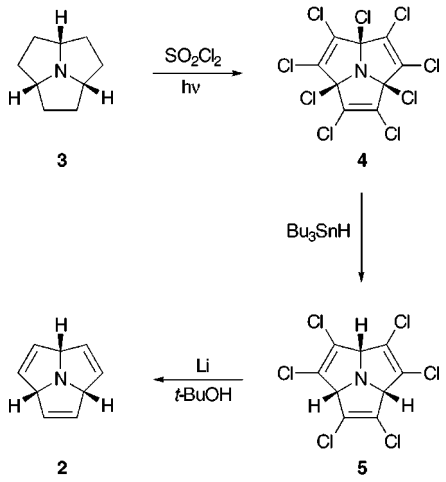


1 **2** **3** **4**

Results and Discussion

As noted, direct exposure of the nonachloride **4** to lithium in *tert*-butyl alcohol as described by Jacobson[9] for perchlorotriquinacene resulted only in decomposition. We subsequently became interested in acquiring 2,3,5,6,8,9-hexachloroazatriquinacene **5** in an independent pursuit and treated **4** with the mild hydride transfer agent Bu_3SnH in hopes of selectively reducing the more reactive α-chlorines. The reaction went smoothly and provided **5** in 53% yield (Scheme 1). It was recognized that this result potentially offered a new approach to **2**, and accordingly, reaction of **5** with lithium and *tert*-butyl alcohol gave the completely dehalogenated product in an acceptable 32% yield.

Scheme 1



3 **4** **5** **2**

Azatriquinacene **2** was analyzed as its trifluoroacetate salt but could be converted to the free base by addition of aqueous hydroxide and extraction into dichloromethane. Like the previously described azatriquinane **3**,[1] the free base is a waxy, low-melting, volatile, white solid. Its proton NMR spectrum in $CDCl_3$ consists of two singlets at δ 5.79 and 4.87, compared to 5.63 and 3.70 for **1**.[10]

Crystals of the tetrafluoroborate salt of **2**, prepared by dissolving the trifluoroacetate in concentrated aqueous sodium tetrafluoroborate and extracting with dichloromethane, produced the X-ray crystal structure shown in Figure 1. The tricycle and its counterion lie across a crystallographic mirror plane, which in the cation passes through C1 and N and bisects the C5−C5A double bond. Except for the shortening of the C−N bonds relative to **1** and the resulting minor angles changes, the structures are indistinguishable.[11] An N−H···F hydrogen bond (N···F, 2.77 Å and N−H···F, 178°) links the cation and the anion, which pack in alternating corrugated layers.

It had been speculated that the aqueous solubility of **2** and its perturbed electronics relative to **1** might prove advantageous in the photochemical [2+2+2+2+2+2] dimerization reaction which would give diazadodecahedrane, a reaction which has never actually been observed

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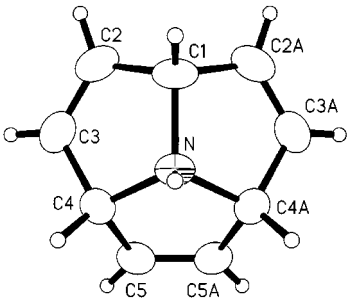


Figure 1. X-ray crystal structure of **2**·HBF_4. The counterion is omitted for clarity.

for **1**. Indeed, [4+2] cycloadditions are known to be substantially accelerated in aqueous media due to the formation of aggregation structures that increase the probability of achieving the reactive configuration.[12] Indications are, however, that neither **2** nor its salts are more reactive than **1** in this capacity, and no evidence of diazadodecahedrane has yet been found. In fact, compound **2** appears to be curiously inert, failing to react at all under conditions known to induce various photochemical transformations in **1**.[5]

Judging both from our results and those of others,[8] we suggest that a solution-state 12π photodimerization is unlikely to ever be observed for a triquinacene, although a topochemical route may yet be an option. Triquinacene itself crystallizes with the C_3 related double bonds of neighboring molecules adjacent and in the correct relative orientation (i.e. rotated 60° to each other), but a 7 Å translational offset of the faces prevents dimerization, even under very high pressure.[13] In compound **2**, on the other hand, there is no close approach of the endo faces. It is at least possible, however, that the required juxtaposition of the hemispheres may eventually be achieved in the solid state, and exo face substituted derivatives of **2** (*N*-alkyl, Lewis acid complexes or metal complexes) are prime candidates for such endeavors.[14]

Triquinadiene, or 2,3-dihydrotriquinacene, had been prepared by Bischof et al.[15] by partial hydrogenation of triquinacene. The interesting photochemistry of this material[16] prompted us to attempt the synthesis of the aza analogue **6** by the same method. However, the resulting, virtually inseparable mixture of di- and tetrahydro products alongside unreacted **2** indicated that this would not be a preparative route to **6**. An opportunity to approach this problem in a concise manner was nonetheless realized when the treatment of the bridgehead enamine **7**[1] with bromine followed by aqueous workup led unexpectedly to the tetrabromohemiaminal **8**, whose structure was confirmed by X-ray crystallography (Figure 2). The effects of crowding the four bromine substituents together can be seen in the considerable distortion of the normally bowl-shaped azatriquinane framework. Molecules of **8** pack in the crystal as centrosymmetric, hydrogen-bonded dimers, with an O···N distance of 2.89 Å and an O−H···N angle of 161°. Dehydrohalogenation of **8** with potassium hexamethyldisilazide (KHMDS) was facile, and the vinyl halogen and hemiaminal functions could be simultaneously reduced with lithium aluminum hydride to give the target material **6** in good overall yield (Scheme 2).

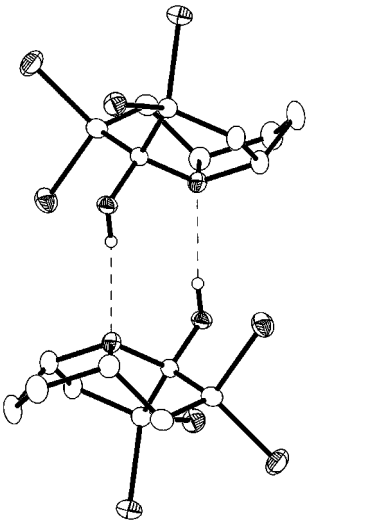
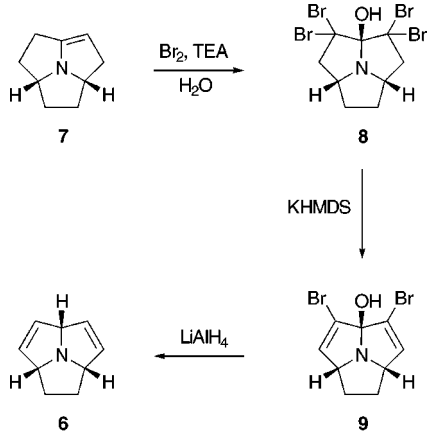


Figure 2. X-ray crystal structure of **8**. The OH hydrogen atom is shown, but the CH hydrogens are omitted for clarity.

Scheme 2



In summary, efficient routes to 10-azatriquinacene **2** and 10-azatriquinadiene **6**, respectively eight and seven steps from pyrrole, are described. These compare favorably with the most efficient literature synthesis of **1**, which is eight steps from cyclopentadiene.[10] We anticipate that the availability of these rigid, apically functional, unsaturated tricycles will stimulate investigations of theoretical, structural, and chemical issues analogous to those of their hydrocarbon relatives.

Experimental Section

***cis,cis,cis*-2,3,5,6,8,9-Hexachloro-10-azatricyclo[5.2.1.0^{1,10}]-deca-2,5,8-triene (5).** Tributyltin hydride (0.756 g, 2.60 mmol) was added dropwise to a stirred solution of **4** (0.265 g, 0.601 mmol)[1] in benzene (20 mL) under nitrogen at room temperature. After 16 h, the mixture was concentrated in a vacuum and the residue chromatographed (10:1 light petroleum/ethyl acetate) to give **5** (0.108 g, 53%) as a white solid: mp 152−154 °C; ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 4.75 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.4, 76.8; HRMS (EI) found, *m*/*z* 334.8407 (M^+), $C_9H_3Cl_6N$ requires 334.8397.

***cis,cis,cis*-10-Azatricyclo[5.2.1.0^{1,10}]deca-2,5,8-triene (2).** Lithium metal (0.234 g, 33.7 mmol) was added in small pieces over 5 min to a stirred solution of **5** (0.338 g, 1.00 mmol) and *tert*-butyl alcohol (1.4 g, 19 mmol) in THF (40 mL). A slow stream of nitrogen was passed over the mixture, which was stirred for 20 min and then heated at reflux for 2.5 h. The reaction was allowed to cool to room temperature and poured into a mixture of ice/water/concentrated HCl (30 g/20 mL/5 mL) and stirred for 20 min. The mixture was washed with dichloromethane and the aqueous layer basified with NaOH and extracted with dichloromethane. Trifluoroacetic acid (0.34 g, 3.0 mmol) was added to the organic phase, which was then dried, and the solvent was evaporated to give the trifluoroacetate salt of **2** (79 mg, 32%) as a white solid: mp 178−180 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (6 H, s), 5.69 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.8, 78.6; HRMS (EI) found, *m*/*z* 131.0735 (M^+), C_9H_9N requires 131.0735. The tetrafluoroborate salt (**2**·HBF_4) was prepared for X-ray analysis in essentially quantitative yield by dissolving the trifluoroacetate salt in a 20-fold molar excess of saturated aqueous $NaBF_4$ followed by extraction with dichloromethane. The free base **2** was obtained by introducing the trifluoroacetate salt (0.102 g, 0.416 mmol) into a mixture of dichloromethane (5 mL) and aqueous KOH (2 M, 1 mL). After vigorous agitation for 2 min, the layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was dried and the majority of the solvent cautiously evaporated at room temperature to give **2** as a colorless, volatile solid: ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (6 H, s), 4.87 (3 H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 130.3, 78.6; HRMS (EI) found, *m*/*z* 131.0735, (M^+), C_9H_9N requires 131.0735.

***cis,cis,cis*-2,2,9,9-Tetrabromo-10-azatricyclo[5.2.1.0^{1,10}]-decan-1-ol (8).** A solution of enamine **7** (1.24 g, 9.17 mmol) in dichloromethane (5 mL) was added dropwise to a stirred solution of bromine (7.40 g, 46.3 mmol) in dichloromethane (30 mL) at −78 °C under nitrogen. After 5 min, a solution of triethylamine (4.66 g, 46.1 mmol) in dichloromethane (12 mL) was added dropwise, and the mixture was stirred for an additional 5 min. The −78 °C bath was then replaced by an ice-acetone bath (−5 °C) and stirring was continued for 10 min. Water (10 mL) was added and the mixture was stirred for a further 20 min. The layers were then separated and the aqueous phase was extracted with dichloromethane. The combined organic extract was washed with sodium hydrogen carbonate (1 M, 80 mL) and water then dried. The solvent was evaporated to leave a brown solid which was triturated with dichloromethane (20 mL) to give pure **8** (0.843 g) as a white crystalline solid, mp 132−134 °C. The dichloromethane triturate could be chromatographed (4:1 light petroleum/ethyl acetate) to give additional **8** (0.748 g) as a yellow solid (total yield 1.59 g, 37%): ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (2 H, m), 3.35 (4 H, m), 2.26 (2 H, m), 2.02 (2 H, m); ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 103.3, 70.3 (br), 61.4, 53.8, 29.1; HRMS (ES) found, *m*/*z* 469.7610 ([M + H]$^+$), $C_9H_{12}{}^{79}Br_2{}^{81}Br_2NO$ requires 469.7612. Anal. Calcd for $C_9H_{11}Br_4NO$: C, 23.1; H, 2.4; N, 3.0. Found: C, 23.0; H, 2.3; N, 2.9.

***cis,cis,cis*-2,9-Dibromo-10-azatricyclo[5.2.1.0^{1,10}]deca-2,8-dien-1-ol (9).** A solution of potassium hexamethyldisilazide (0.5 M in toluene, 20 mL, 10 mmol) was added dropwise to a stirred solution of **8** (1.17 g, 2.50 mmol) in THF (125 mL) at −78 °C under nitrogen. The reaction was stirred for 12 h, during which it was allowed to come to room temperature. Water (150 mL) and dichloromethane (150 mL) were added, and stirring was continued for 5 min. The layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic extract was dried and the solvent evaporated to give **9** (0.649 g, 85%) as colorless crystals: mp 110−112 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.09 (2 H, s), 4.18 (2 H, m), 2.09 (2 H, m), 1.80 (2 H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 134.9, 122.1, 106.3, 68.4, 31.8; HRMS (ES) found, *m*/*z* 305.9142 ([M + H]$^+$), $C_9H_{10}Br_2NO$ requires 305.9129.

***cis,cis,cis*-10-Azatricyclo[5.2.1.0^{1,10}]deca-2,8-diene (6).** A solution of lithium aluminum hydride (1 M in THF, 14.0 mL, 14.0 mmol) was added to a stirred solution of **9** (0.611 g, 1.99 mmol) in THF (40 mL) under nitrogen. The mixture was then heated at reflux for 36 h and cooled to 0 °C, and water (2 mL) was cautiously added followed by aqueous NaOH (2.0 M, 10 mL). The resulting slurry was stirred at room temperature for 30 min and then solid potassium carbonate (10 g) was added. The mixture was stirred for a further 1 h at room temperature and filtered. The solid residue was washed with dichloromethane and aqueous HCl (0.5 M, 150 mL) was added to the filtrate. The layers were separated, and the aqueous phase was washed with dichloromethane. The aqueous layer was then basified with NaOH (2 M) and extracted with dichloromethane. Trifluoroacetic acid (0.68 g, 6.0 mmol) was added to the combined organic extract, which was then dried. The solvent was evaporated to give the trifluoroacetate salt of **6** (0.371 g, 75%) as a white solid: mp 179−181 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (2 H, dd, *J* 6.3, 1.5), 5.69 (2 H, dd, *J* 6.3, 1.5), 5.46 (1 H, s), 4.90 (2 H, br s), 2.35 (2 H, m), 1.90 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 128.0, 127.9, 116.4, 77.7, 64.8, 32.3; HRMS (EI) found, *m*/*z* 133.0894 (M^+), $C_9H_{11}N$ requires 133.0892. Anal. Calcd for $C_{11}H_{12}F_3NO_2$: C, 53.4; H, 4.9; N, 5.7. Found: C, 53.4; H 5.0; N, 5.4. The free base **6** was obtained by introducing the trifluoroacetate salt (0.152 g, 0.615 mmol) into a mixture of dichloromethane (2 mL) and aqueous KOH (2 M, 2 mL). After vigorous agitation for 2 min, the layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was dried and the majority of the solvent cautiously evaporated at room temperature to give **6** as a colorless, volatile solid: ^1H NMR (400 MHz, $CDCl_3$) δ 5.62 (2 H, ddd, *J* 5.9, 1.8, 1.8), 5.50 (2 H, ddd, *J* 5.9, 1.8, 1.8), 4.62 (1 H, s), 4.00 (2 H, m), 1.86 (2 H, m), 1.45 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.5, 130.0, 78.0, 71.2, 32.3; HRMS (EI) found, *m*/*z* 133.0896 (M^+), $C_9H_{11}N$ requires 133.0892.

Crystallographic Studies. Crystal Data for 2·HBF_4: $C_9H_{10}N^+BF_4^-$, M = 218.99, monoclinic, a = 6.8915(11) Å , b = 9.236(2) Å, c = 7.7114(13) Å, β = 98.676(3)°, U = 485.2(2) Å^3, T = 150(2) K, space group $P2_1/m$ (No. 11), Z = 2, D_c = 1.499 g cm^{-3}, μ(Mo $K\alpha$) = 0.141 mm^{-1}, 1017 unique reflections were measured (R_{int} 0.024) and used in all calculations. The BF_4^- anion suffered disorder in its F atoms and was modeled using alternative, partial occupancy sites and geometric restraints. Final R_1 [907$F \geq 4\sigma(F)$] = 0.0474 and wR (all F^2) was 0.124.

Crystal Data for 8: $C_9H_{11}Br_4NO$, M = 468.83, triclinic, a = 7.556(4) Å , b = 7.959(3) Å , c = 11.517(6) Å, α = 98.83(4) °, β = 102.56(4) °, γ = 112.76(4)°, U = 601.3(5) Å^3, T = 150(2) K, space group $P\bar{1}$ (No. 2), Z = 2, D_c = 2.590 g cm^{-3}, μ(Mo $K\alpha$) = 13.359 mm^{-1}, 2364 unique reflections were measured, corrected for absorption (R_{int} 0.029), and used in all calculations. Final R_1 [2056$F \geq 4\sigma(F)$] = 0.0347 and wR(all F^2) was 0.0866.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **2**, **5**, **8**, and **9**, and tables of X-ray crystallographic data for compounds **2**·HBF_4 and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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