N-Heterocyclization in Electrophilic Haloamidation Reactions of 1,5-Cyclooctadiene. Synthesis and Rearrangements of the Granatanine and Homonortropane Skeletons†,[1]

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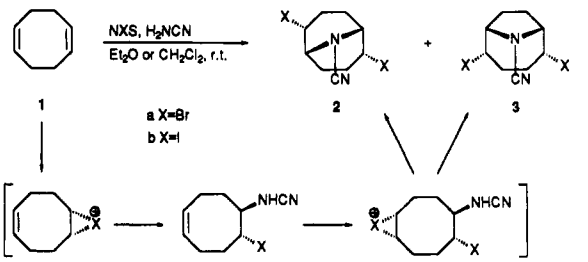
The transannular N-heterocyclization of 1,5-cyclooctadiene using either *N*-bromo- or *N*-iodosuccinimide and cyanamide is a preparatively useful method for the synthesis of 9-azabicyclononanes **2** and **3**. This reaction failed when *N*-chlorosuccinimide was employed. The chloro-substituted derivative **2c** was prepared, with retention of configuration, from both pure **2a** and from an equimolar mixture of **2a** and **3a** by nucleophilic displacement with chlorine, followed by dehydration of the resulting carboxamide **4c**. Acidic hydrolysis of the cyanamide group in **2a** and **3a** gave the ureas **4a** and **5a**. Reaction of **2a** and **3a** with tributyltin hydride gave the debrominated derivatives **8** and **9**, while treatment of the same compounds with $LiAlH_4$ afforded a single air-sensitive product which was trapped as the urea **7**. Substitution of the halogens in **2a** and **3a** (or **2b** and **3b**) by acetoxy groups using silver acetate in acetic anhydride gave **12** and **13** as a result of inversion at one side and retention of the configuration on the other side of the starting materials which was accompanied by transamidation at the nitrogen bridge. Treatment of **2a** with dicyclohexylethylamine led to complete dehydrobromination and the formation of **14**.

As an extension of our investigations on transannular reactivity of unsaturated medium sized rings, we became interested in cationic N-heterocyclization reactions of 1,5-cyclooctadiene (**1**) with *N*-bromosuccinimide (NBS) and amines.[1b] However, despite the fact that 9-azabicyclononanes can be prepared from the reaction of **1** and primary arylamines using mercury or thallium salts as electrophiles,[2,3] we were unable to observe any nitrogen participation when **1** was treated with aliphatic or aromatic amines in the presence of NBS. Other authors have reported the formation of 9-azabicyclononanes from **1** by addition of carbamates[4a,b] or *p*-toluenesulfonamide[4c] using mercury salts and by reaction of **1** with *N,N*-dibromo-*p*-toluenesulfonamide in chloroform.[5] It has also been demonstrated that acid-catalyzed addition of *N*-nitrosopiperidine to **1** led to the formation of the granatanine skeleton.[6]

In a preliminary communication,[7] we described the synthesis of **2a** and **3a** in 80% yield from diene **1**, NBS, and cyanamide.



This reaction can be rationalized on the basis of the intermediate formation of *trans*-5-bromo-6-cyanamidocyclooctene (not isolated) produced by electrophilic attack of NBS and formation of a cyclic bromonium ion followed by nucleophilic attack of cyanamide. A similar mechanism has been proposed previously by Ponsold and Ihn[8] for the reaction of steroids with cyanamide/NBS. Further electrophilic addition of a bromonium ion at the remaining double bond in the intermediate, transannular nucleophilic participation of the cyanamide moiety at one of the electron-deficient carbon atoms of the new cyclic bromonium ion, and finally deprotonation leads to the observed products **2a** and **3a**. An analogous cyanoamidation reaction has been reported recently by Salazar et al.[9] using a seleno electrophile.

We now report the preparation of other halogenated analogues of **2a** and **3a** and some transformations of these compounds. In an attempt to obtain chloro and iodo analogues of **2a** and **3a**, we first investigated the reaction

† Dedicated with best wishes to Professor Werner Schroth on the occasion of his 65th birthday.

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(1) (a) Transannular Reactions of Cycloalkenes, Cycloalkadienes and Cycloalkatrienes. 17. For 16, see: Haufe, G.; Tubergen, M. W.; Kropp, P. J. *J. Org. Chem.* **1991**, *26*, 4292. (b) For transannular O-heterocyclizations of **1** with *N*-halosuccinimides, cf. Haufe, G. *Tetrahedron Lett.* **1984**, *25*, 4365.

(2) (a) Gómez-Aranda, V.; Barluenga, J.; Asensio, G.; Yus, M. *Tetrahedron Lett.* **1972**, 3621. (b) Barluenga, J.; Pérez-Prieto, J.; Bayon, A. M.; Asensio, G. *Tetrahedron* **1984**, *40*, 1199. (c) Barluenga, J.; Pérez-Prieto, J.; Asensio, G.; García-Granda, S.; Salvado, M. A. *Tetrahedron*, **1992**, *48*, 3813.

(3) Gómez-Aranda, V.; Barluenga, J.; Aznar, F. *Synthesis* **1974**, 504.

(4) (a) Barluenga, J.; Jiménez, C.; Nájera, C.; Yus, M. *J. Chem. Soc., Perkin Trans. I* **1983**, 591. (b) Barluenga, J.; Jiménez, C.; Nájera, C.; Yus, M. *J. Heterocycl. Chem.* **1984**, *21*, 1733. (c) Barluenga, J.; Jiménez, C.; Nájera, C.; Yus, M. *J. Chem. Soc., Perkin Trans. I* **1984**, 721.

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(6) Chow, Y. L.; Pillay, S. K. *Heterocycles* **1976**, *5*, 171.

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(8) Ponsold, K.; Ihn, W. *Tetrahedron Lett.* **1970**, 1125. Cf. also: Jung, S.-H.; Kohn, H. *J. Am. Chem. Soc.* **1985**, *107*, 2931.

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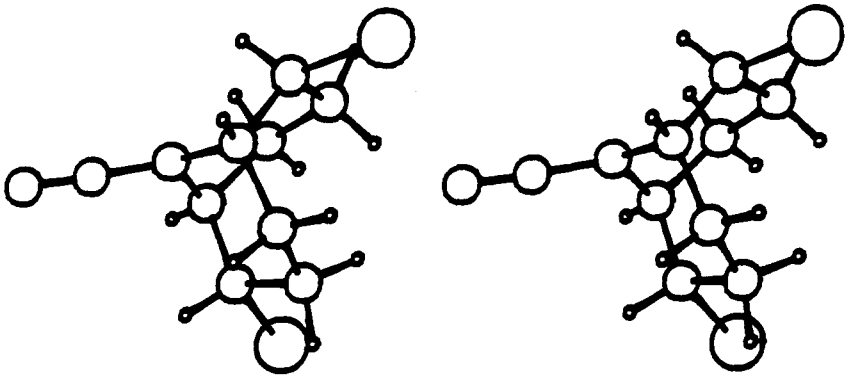


Figure 1. Stereospecific view of *endo,endo*-2,6-dibromo-9-azabicyclo[3.3.1]nonane-9-carbonitrile (**2a**).[21]

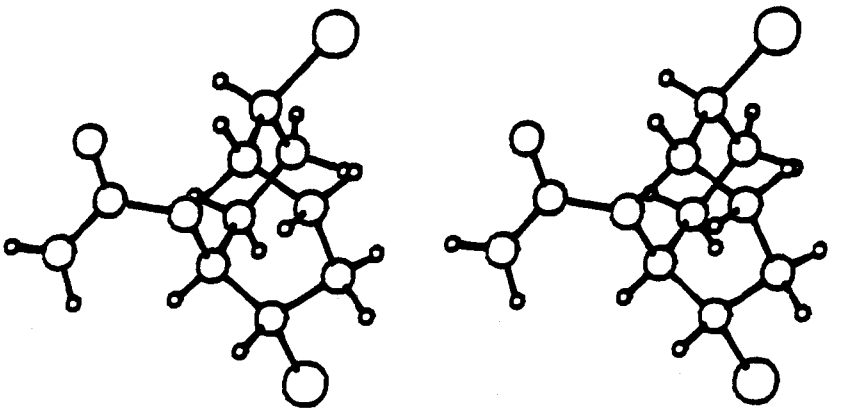
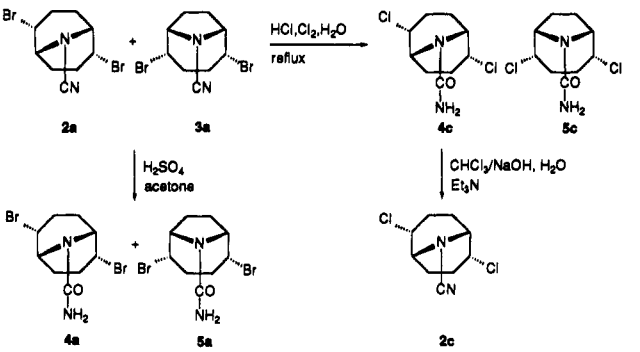


Figure 2. Stereoscopic view of *endo,endo*-2,6-dichloro-9-azabicyclo[3.3.1]nonane-9-carboxamide (**4c**).[21]

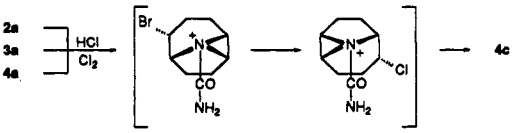
of **1** with cyanamide and both *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS). When **1** was treated with NCS/cyanamide and with NIS/cyanamide in dichloromethane (or diethyl ether), N-heterocyclization was only successful in the latter case and an equimolar mixture of the two iodo derivatives **2b** and **3b** (61% yield) was obtained.

In order to synthesize a chloro analogue of **2a**, we examined the possibility of introduction of this substituent by halogen exchange. While the usual Finkelstein reaction of alkyl halides[10] is clearly precluded, successful bromide/chloride exchange has been reported in aromatic systems using hydrochloric acid[11] or (preferably) chlorine.[12] To the best of our knowledge, no such substitutions have been reported with either aliphatic or alicyclic substrates.

When a suspension of pure **2a** in concentrated HCl containing chlorine was heated at reflux for 5 h, a single product (**4c**) (62%) was obtained. The structure of **4c** was deduced from its spectroscopic data (see Experimental Section) and proved by X-ray data (Figure 2). In the product obtained from the bromine/chlorine exchange reaction using an equimolar mixture of **2a** and **3a**, there was no indication of the isomeric 9-azabicyclo[4.2.1]nonane derivative **5c**. Thus, in addition to hydrolysis of the cyanamido function and halogen exchange, a skeletal rearrangement to the thermodynamically more stable 9-azabicyclo[3.3.1]nonane (**4c** is about 3.2 kcal mol^{-1} more stable than **5c**)[13] occurred.



However, the most important mechanistic point is that substitution proceeds with retention of configuration at C2 and C6. From an inspection of a Dreiding model of **2a** and from its X-ray crystal structure (Figure 1), it appears that nucleophilic attack from the rear of the bromo substituents is unlikely due to steric hindrance. A plausible reaction mechanism (S_N1 type, with nitrogen participation) is shown in the following scheme:



Since chlorine/bromine exchange using pure **4a** also gave **4c** without any significant change in the rate of reaction,

(10) Hudlicky, M.; Hudlicky, T. Formation of Carbon-Halogen Bonds, *The Chemistry of Halides, Pseudo-Halides and Azides*, Suppl. D; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; p 1021. Roedig, A. In *Houben-Weyl, Methoden der Organischen Chemie*; Müller, E., Ed.; Bd. V/4; Thieme: Stuttgart, 1960; p 595.

(11) Stroh, R. In *Houben-Weyl, Methoden der Organischen Chemie*; Müller, E., Ed.; Bd. V/4; Thieme: Stuttgart, 1960; p 758.

(12) Stroh, R. In *Houben-Weyl, Methoden der Organischen Chemie*; Müller, E., Ed.; Bd. V/3; Thieme: Stuttgart, 1962; p 749.

(13) AM1 calculation using MOPAC 6, QCPE Program 455, Indiana University, Bloomington, IN. Cf. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stuart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

it is not possible to deduce whether halogen exchange precedes hydrolysis of the cyanamido group. Related reactions involving substitution with retention of configuration have been reported by Stetter and Heckel[5a] and Portmann and Ganter[14] in the synthesis of 2,6-dihalo-9-azabicyclo[3.3.1]nonanes from the corresponding 2,6-diols.

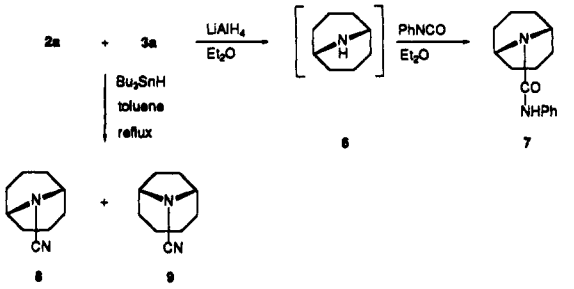
From the X-ray studies and from ^{1}H NMR data (NOE and H,H-decoupling difference spectra), **2a** and **4c** adopt the chair,chair conformation (CC) both in the solid state and in solution. For the two other possible conformations, different sets of proton signals would be expected in NMR spectra.[15]

Conversion of the chloro derivative **4c** to **2c** was accomplished using the method recommended by Schroth et al.[16] for the dehydration of ureas using dichlorocarbene. Thus treatment of **4c** with chloroform/NaOH under phase-transfer conditions in the presence of triethylamine afforded **2c** in 72% yield. No elimination of HCl was observed under these strong basic conditions.

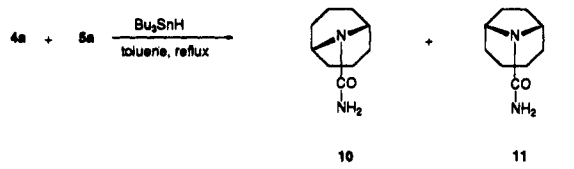
Attempted hydrolysis of the cyanamido group in an equimolar mixture of **2a** and **3a** under conditions which we hoped would lead to no substitution or rearrangement (20% aqueous sulfuric acid in acetone/room temperature/10 h) failed, and the starting materials were recovered in their original ratio. However, when this mixture was treated with 50% sulfuric acid for 8 h at the same temperature, two products (**4a** and **5a**) (in a 4:1 ratio, 92%) were obtained. The major product was purified by several recrystallizations from ethanol and its structure deduced from its spectroscopic data. The minor component could not be isolated in a pure state, but its structure was established from ^{13}C NMR measurements using an enriched sample. These results indicate that during the hydrolysis reaction, partial rearrangements of the 9-azabicyclo[4.2.1]nonane skeleton to the thermodynamically more stable (by about 3.5 kcal mol^{-1})[13] 9-azabicyclo[3.3.1]-nonane had occurred. Similar treatment of pure **2a** gave only **4a** (92% yield) with no contamination of the crude product by the isomer **5a** (^{13}C NMR). When **4a** was treated as described above with 50% sulfuric acid for 85 h, in addition to **4a** some minor decomposition products were observed, but **5a** was clearly absent in the reaction mixture.

Reduction of a mixture of **2a** and **3a** with $LiAlH_4$ in ether[7] gave an air-sensitive product (cf. ref 17), probably **6**, which was trapped as the *N*-phenylcarboxamide **7** (87%) by treatment of a dry ethereal solution of the crude reaction product with phenyl isocyanate. From NOE experiments on **7** it would appear that the bridgehead protons H1 and H5 are spatially very close to the NH group and that these may be coplanar. The absence of any isomeric product in the crystalline solid (^{13}C NMR) indicated once more that rearrangement of the 9-azabicyclo[4.2.1]nonane to the more stable skeleton had taken place. This result is in contrast to the observation of Ganter et al.,[14] who have reported that in the $LiAlH_4$ reduction of the chloro substituents in *endo,endo*-2,6-dichloro-9-methyl-9-azabicyclo[3.3.1]nonane partial isomerization occurred with the formation of 9-methyl-9-azabicyclo[3.3.1]- and -[4.2.1]-nonanes in a 3:1 ratio.

Reduction of **2a** with Bu_3SnH in toluene proceeded by a radical mechanism to give the carbonitrile **8**, while similar



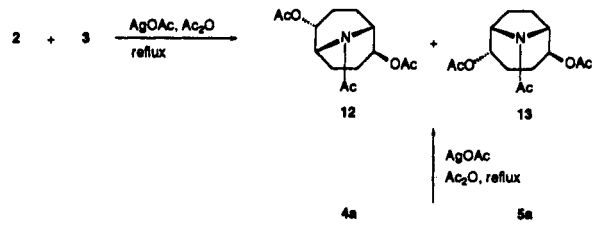
treatment of a mixture of **2a** and **3a** afforded a mixture of **8** and **9** without any alteration in the original isomeric ratio. Reduction of a mixture of the ureas **4a** and **5a** under the same reaction conditions gave **10** and **11**, again without rearrangement.



Attempted acetolysis of **2a** and **3a** was impossible using several of the usual methods of bromine → acetoxy exchange.[18] However, when pure **2a** (or a mixture with **3a**, ratio 74:26 by GC) was heated under reflux with AgOAc (2 molar equiv) in acetic anhydride in the dark, a mixture of two halogen-free compounds (92% yield, ratio 75:25 by GC) was obtained. The major product was isolated in a pure state by fractional crystallization and identified as *endo,exo*-2,6-diacetoxy-9-acetyl-9-azabicyclo[3.3.1]-nonane (**12**) from a consideration of its spectroscopic data (cf. Experimental Section). The 360-MHz ^{1}H NMR and the H,C-correlated 2D NMR spectra of **12** were particularly informative. The two-proton multiplet at δ = 4.88 correlates to the resonances of C2 and C6 at δ = 71.1 or δ = 69.9, respectively (adjacent to the acetoxy functions), while the two pseudotriplets at δ = 4.68 (J = 5.3 Hz) and δ = 3.97 (J = 5.0 Hz) correlate to the carbons at δ = 49.8 (C1) and δ = 44.1 (C5). The three methyl singlets at δ = 2.06, 2.04, and 2.00 correlate to the same carbon resonance at δ = 20.1, the integral of which is approximately three times that of the other carbon resonances. From long range H,C-correlation (CH-COLOC) the connectivity of the protons at δ = 2.06 and the carbonyl singlet at δ = 168.5 was deduced, while the other methyl singlets were found to correlate to the carbonyl signals at δ = 170.3 and 169.8, respectively. The remaining four carbon signals at δ = 25.45, 25.42, 22.8, and 22.0 correlate to the methylene proton multiplets between 1.7 and 2.0 ppm. These results show clearly that substitution of the halogen groups takes place with retention of configuration at one side of the molecule and inversion at the other with some rearrangement of the bicyclic skeleton[19] and transamidation of the ring nitrogen.

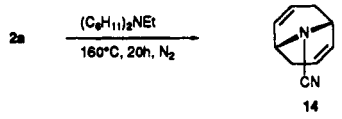
In an attempt to isolate intermediates from the above reaction, pure **2a** was heated with AgOAc (1 molar equiv) in acetic anhydride at reflux. After 1 h only 56% of the

(14) Portmann, R. E.; Ganter, C. *Helv. Chim. Acta* **1973**, *56*, 1991.
(15) Zefirov, N. S.; Palyulin, V. A. *Top. Stereochem.* **1991**, *20*, 171.
(16) Schroth, W.; Franck, R.; Schröder, H. D.; Kluge, H.; Hodeck, W. *J. Prakt. Chem.* **1983**, *325*, 787.
(17) Anastassiou, A. G.; Celluva, R. P. *J. Org. Chem.* **1972**, *37*, 3126.
(18) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 398.
(19) On the other hand, inversion of the configuration at C2 was reported in hydrolysis of an *endo*-2-bromo-*N*-acetyl-8-azabicyclo[3.2.1]octane using $AgNO_3$ in aqueous THF, which was accompanied by partial debromination and deamination of the bicyclic system: Larsen, R. D.; Davis, P.; Corley, E. G.; Reider, P. J.; Rothauser-Lamanec, T.; Grabowski, E. J. J. *J. Org. Chem.* **1990**, *55*, 299.



starting material remained, and in addition to **12** and **13** (27% and 8% respectively), three new products were detected (6%, 1%, and 2%) by GC. After 3 h two further products were evident, the percentages of **2a**, **12**, and **13** were 28%, 30%, and 9%, respectively, and those of the five new products were 10%, 4%, 11%, 1%, and 2%. These percentages were unaltered after 2 h of further heating. Unfortunately we were unable to isolate any of these new products. When the above reaction mixture was treated with a further equivalent of AgOAc and heated at reflux for 2 h, only **12** and **13** (ratio 76:24 by GC) were found in the crude product.

Treatment of a 1:3 mixture of the iodo compounds **2b** and **3b** in an analogous manner with 2 equiv of AgOAc gave **12** and **13** (83%) with very little alteration in the original isomeric ratio. From this mixture **13** was isolated and its structure established from its spectroscopic data (see Experimental Section). Compounds **12** and **13** were also obtained (87% yield, ratio 9:1) from a mixture of the ureas **4a** and **5a** using the same reagent combination, again with no significant change in the original isomeric ratio. We are unable at this time to offer any determined mechanistic explanation regarding the difference in stereochemistry encountered during substitution reactions in the 9-azabicyclononanes **2** and **3**.



Dehydrohalogenation of **2** and **3** could not be realized by treatment of the former with strong bases such as NaOMe and KO^{t}Bu in aprotic solvents such as THF or in DMSO. However, when pure **2a** was heated with excess dicyclohexylethylamine at 160 °C for 20 h under nitrogen, **14** was obtained in 43% yield. By contrast, when a 1:1 mixture of **2a** and **3a** was treated similarly, **14** was isolated as the only low molecular weight product in only 18% yield. The elimination of HBr from the ureas **4a** or **5a** could not be achieved.

Experimental Section

General. Melting points are uncorrected, IR spectra were taken from KBr disks, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO with TMS as internal standard, EI-mass spectra were recorded at 70 eV, and GC analyses were made using a 25-m capillary column HP 1, 0.25 mm id, with a temperature program starting at 100 °C with a heating rate of 5 °C/min to 280 °C.

Treatment of 1,5-Cyclooctadiene (1) with *N*-Halosuccinimides and Cyanamide. At a temperature of about 15 °C, 0.2 mol of the *N*-halosuccinimide was added in portions to a stirred solution of 10.8 g (0.1 mol) of 1,5-cyclooctadiene (**1**) and 21.0 g (0.5 mol) of cyanamide in 200 mL of ether (or CH_2Cl_2). Stirring was continued for 12 h at rt. The mixture was then washed three times with 50-mL portions of water and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The remaining 1:1 mixtures of **2** and **3** (24.6 g, 80%, **2a** and **3a**, or 24.4 g, 61%, **2b** and **3b**, respectively) were separated by several crystallizations from *n*-hexane and repeated crystallizations of the mother liquors from ethanol.

***endo,endo*-2,6-Dibromo-9-azabicyclo[3.3.1]nonane-9-carbonitrile (2a):** mp 138.5–139.5 °C (ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.16 (m, 2H, $H_{4a}H_{8a}$), 2.25–2.38 (m, 4H, H_3H_7), 2.51 (m, 2H, $H_{4e}H_{8e}$), 3.63 (t, 2H, $H_{1e}H_{5e}$, J_{1e8a} = 4.5 Hz, $J_{1e8e} \approx 0$ Hz, J_{1e2a} = 4.5 Hz), 4.50 (m, 2H, $H_{2a}H_{6a}$, J_{2a1e} = 4.5 Hz, J_{2a3e} = 10.2 Hz, J_{2a3e} = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 25.3 (C4 and C8), 31.3 (C3 and C7), 47.8 (C2 and C6), 55.6 (C1 and C5), 115.3 (CN); MS *m/z* (rel intensity) 306 (M^+, 8), 227 (100), 201 (1), 200 (2), 185 (1), 175 (7), 174 (16), 160 (9), 159 (1), 147 (29), 130 (5), 121 (40), 106 (9), 105 (23), 93 (34), 79 (42), 69 (66), 67 (30); IR (KBr) 2216 cm^{-1} (CN). Anal. Calcd for $C_9H_{12}Br_2N_2$ (308.0): C, 35.09; H, 3.93; N, 9.10; Br, 51.88. Found: 35.15; H, 3.75; N, 9.21; Br, 51.63.

***endo,endo*-2,5-Dibromo-9-azabicyclo[4.2.1]nonane-9-carbonitrile (3a):** mp 107–108 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 2.20 (m, 2H, H_7H_{8a}), 2.2–2.4 (m, 4H, H_3H_4), 2.42 (m, 2H, H_7H_{8e}), 4.27 (m, 2H, CHN), 4.44 (m, 2H, CHBr); ^{13}C NMR ($CDCl_3$, 90 MHz) 27.1 (C7 and C8), 32.2 (C3 and C4) 51.1 (C2 and C5), 65.2 (C1 and C6), 114.0 (CN); MS *m/z* (rel intensity) 306 (M^+, 7), 227 (100), 201 (1), 200 (2), 185 (1), 175 (5), 174 (12), 160 (7), 159 (1), 147 (29), 130 (8), 121 (33), 106 (11), 105 (25), 93 (51), 79 (47), 69 (54), 67 (32); IR (KBr) 2218 cm^{-1}. Anal. Calcd for $C_9H_{12}Br_2N_2$ (308.0): C, 35.09; H, 3.93; N, 9.10; Br, 51.88. Found: C, 35.22; H, 3.66; N, 9.14; Br, 51.85.

***endo,endo*-2,6-Diiodo-9-azabicyclo[3.3.1]nonane-9-carbonitrile (2b):** mp 128–129 °C (ethanol); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 2.0–2.5 (m, 8H, $-CH_2-$), 3.62 (t, 2H, CHN), 4.50 (m, 2H, CHI); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 25.7 (C4 and C8), 30.4 (C3 and C7), 33.4 (C2 and C6), 56.6 (C1 and C5), 116.4 (CN); MS *m/z* (rel intensity) 402 (M^+, 7), 275 (100), 148 (23), 147 (21), 105 (46); IR (KBr) 2186 cm^{-1}.

***endo,endo*-2,5-Diiodo-9-azabicyclo[4.2.1]nonane-9-carbonitrile (3b):** mp 107–109 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 2.0–2.5 (m, 8H, $-CH_2-$), 4.25 (m, 2H, CHI), 4.50 (m, 2H, CHN); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 28.4 (C7 and C8), 30.8 (C3 and C4), 35.7 (C2 and C5), 66.5 (C1 and C6), 114.9 (CN); MS *m/z* (rel intensity) 402 (M^+, 8), 275 (100), 148 (22), 147 (23), 105 (50); IR (KBr) 2193 cm^{-1}.

***endo,endo*-2,6-Dichloro-9-azabicyclo[3.3.1]nonane-9-carboxamide (4c).** A suspension of 3.08 g (10 mmol) of the bicycle **2a** or of a 50:50 mixture of **2a** and **3a** in 50 mL of concentrated HCl was heated to reflux while a slow stream of Cl_2 gas was introduced until no more bromine was formed (3–5 h). The mixture was poured into 100 mL of ice water. The solid material (1.47 g, 62%) was filtered off and recrystallized: mp 220–221 °C (ethanol); ^{1}H NMR (DMSO, 300 MHz) δ 1.85–2.00 (m, 2H, $H_{4a}H_{8a}$), 2.15–2.32 (m, 4H, H_3H_7), 2.38 (dt, 2H, $H_{4e}H_{8e}$), 4.31 (t, 2H, $H_{1e}H_{5e}$, J_{1e8a} = 4.5 Hz, $J_{1e8e} \approx 0$ Hz, J_{1e2a} = 4.3 Hz), 4.40 (m, 2H, $H_{2a}H_{6a}$, J_{2a1e} = 4.3 Hz, J_{2a3a} = 10 Hz, J_{2a3e} = 8 Hz), 4.58 (b, 2H, NH_2); ^{13}C NMR (DMSO, 100 MHz), δ 23.9 (C4 and C8), 31.2 (C3 and C7), 49.4 (C1 and C5), 59.4 (C2 and C6), 157.0 ($CONH_2$); MS *m/z* (rel intensity) 237 (M^+, 16), 201 (32), 192 (10), 158 (94), 122 (1), 120 (1), 118 (3), 116 (4), 96 (71), 80 (42), 69 (51), 53 (39), 41 (100); IR (KBr) 3320 and 3215 cm^{-1} (CN), 1655 cm^{-1} (CO). Anal. Calcd for $C_9H_{14}Cl_2N_2O$ (237.1): C, 45.58; H, 5.95; N, 11.81; Cl, 29.90. Found: C, 45.28; H, 5.83; N, 11.60; Cl, 29.88.

***endo,endo*-2,6-Dichloro-9-azabicyclo[3.3.1]nonane-9-carbonitrile (2c).** A mixture of 1.55 g (6.5 mmol) of **4c**, 16 mL of $CDCl_3$, 3.5 mL of 50% aqueous NaOH and 60 mg (0.58 mmol) of triethylamine was stirred for 5 h at rt. The organic phase was washed with water and an aqueous solution of NH_4Cl and dried (Na_2SO_4), and the solvent was evaporated. The solid residue was purified by recrystallization to yield 1.02 g (72%) of **2c**: mp 115–118 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03–2.18 (m, 2H, $H_{4a}H_{8a}$), 2.19–2.28 (m, 4H, H_3H_7), 2.38–2.45 (m, 2H, $H_{4e}H_{8e}$), 3.56 (t, 2H, CHN), 4.38 (m, 2H, CHCl); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5 (C4 and C8), 30.5 (C3 and C7), 55.5 (C1 and C5), 56.2 (C2 and C6), 98.1 (CN): MS *m/z* (rel intensity) 218 (M^+, 22), 183 (100), 155 (5), 119 (3); IR (KBr) 2210 cm^{-1} (CN). Anal. Calcd for $C_9H_{12}N_2Cl_2$ (219.2): C, 48.98; H, 5.48; N, 12.39; Cl, 32.25. Found: C, 49.33; H, 5.52; N, 12.78; Cl, 32.35.

Hydrolysis of Carbonitriles 2a and 3a. An equimolar mixture of 15.4 g (50 mmol) of the dibromo compounds **2a** and

3a was dissolved in 150 mL of acetone and treated under stirring at rt with 25 mL of 50% H_2SO_4. Stirring was continued for 8 h at rt. The solution was concentrated under reduced pressure and poured into 250 mL of water. The aqueous phase was extracted with ether (three 100 mL portions), and the combined ethereal extracts were washed with water, neutralized with aqueous $NaHCO_3$ (5%), and dried over Na_2SO_4. The solvent was evaporated, giving 14.9 g (92%) of a 4:1 mixture (^{13}C NMR) of the ureas 4a and 5a. The major product was purified by several recrystallizations from ethanol. The minor component was not isolated in pure form.

***endo,endo*-2,6-Dibromo-9-azabicyclo[3.3.1]nonane-9-carboxamide (4a)**: mp 198–200 °C (ethanol); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.75–2.55 (m, 8H, $-CH_2-$), 4.15 (m, 2H, CHN), 4.29 (m, 2H, CHBr), 4.50 (b, 2H, NH_2); ^{13}C NMR (DMSO, 75 MHz) δ 25.4 (C4 and C8), 31.7 (C3 and C7), 49.3 (C2 and C6), 52.2 (C1 and C5), 156.5 ($CONH_2$); MS *m/z* (rel intensity) 324 (M^+, 4), 282 (3), 265 (2), 245 (31), 203 (25), 202 (33), 185 (12), 149 (14), 123 (27), 111 (12), 105 (30), 97 (40), 95 (39), 81 (52), 79 (55), 73 (28), 71 (87), 69 (100); IR (KBr) 3232 and 3187 cm^{-1} (NH), 1664 cm^{-1} (CO). Anal. Calcd for $C_9H_{14}Br_2N_2O$ (326.0): C, 33.00; H, 3.91; N, 8.87; Br, 49.27. Found: C, 33.15; H, 4.33; N, 8.59; Br, 49.02.

***endo,endo*-2,5-Dibromo-9-azabicyclo[4.2.1]nonane-9-carboxamide (5a)**: ^{13}C NMR (DMSO, 75 MHz) δ 26.6 (C7 and C8), 32.2 (C3 and C4), 54.3 (C2 and C5), 59.4 (C1 and C6), 155.3 ($CONH_2$) (taken from a sample enriched with 55% 5a).

***N*-Phenyl-9-azabicyclo[3.3.1]nonane-9-carboxamide (7)**. A solution of 3.08 g (10 mmol) of the 1:1 mixture of 2a and 3a in 50 mL of dry ether was added dropwise at rt to a stirred suspension of 0.34 g (10 mmol) of $LiAlH_4$ in 25 mL of dry ether. After the solution was stirred for an additional 5 h, the suspension was treated carefully with water following by addition of 2 N H_2SO_4 to attain a pH near 7. The ethereal solution was dried overnight (Na_2SO_4). After filtration, the solution was treated with a solution of 1.19 g (10 mmol) of phenyl isocyanate in 10 mL of dry ether. The mixture was kept for 3 d under anhydrous conditions at rt. The solvent was removed under reduced pressure and the residue recrystallized from ethanol to yield 2.12 g (87%) of 7 as a white crystalline solid: mp 193–194 °C (ethanol); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (m, 2H, $H_{3e}H_{7e}$), 1.73 (m, 4H, $H_{2e}H_{4e}$, $H_{6e}H_{8e}$), 1.94 (m, 4H, $H_{2a}H_{4a}$, $H_{6a}H_{8a}$), 2.10 (m, 2H, $H_{3a}H_{7a}$), 4.24 (b, 2H, CHN), 6.32 (m, 2H, NH), 6.99 (m, 1H, para-H), 7.24 (m, 2H, meta-H); 7.35 (m, 2H, ortho-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3 (C3 and C7), 27.7 (C2, C4, C6 and C8), 47.1 (C1 and C5), 119.7 (ortho-C), 122.8 (para-C), 128.9 (meta-C), 154.1 (ipso-C), 164.1 (CONH); MS *m/z* (rel intensity) 244 (M^+, 54), 201 (3), 152 (100), 125 (16), 119 (11), 109 (47), 96 (23), 93 (23), 82 (52), 77 (15), 67 (53); IR (KBr) 3300 cm^{-1} (NH), 1633 cm^{-1} (CO). Anal. Calcd for $C_{15}H_{20}N_2O$ (244.3): C, 73.74; H, 8.08; N, 11.77. Found: C, 74.03; H, 8.15; N, 11.50.

9-Azabicyclo[3.3.1]nonane-9-carbonitrile (8). Under nitrogen a solution of 2.1 g (6.8 mmol) of 2a in 40 mL of dry toluene was treated with 4 g (14 mmol) of tributyltin hydride and then heated under reflux for 8 h. The solvent was removed under reduced pressure and the product (0.68 g, 67%) purified by column chromatography (silica gel, *n*-hexane/ethyl acetate 10:1), giving a white crystalline solid: mp 106–108 °C (*n*-hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.40 (b, 2H, CHN), 1.97 (m, 6H), 1.60 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6 (C3 and C7), 28.7 (C2, C4, C6, and C8), 52.4 (C1 and C5), 118.5 (CN); MS *m/z* (rel intensity) 150 (M^+, 37), 121 (26), 107 (19), 97 (28), 96 (96), 94 (14), 83 (53), 82 (100), 69 (48), 68 (33), 67 (26); IR (KBr) 2210 cm^{-1} (CN). Anal. Calcd for $C_9H_{14}N_2$ (150.2): C, 71.95; H, 9.39; N, 18.64. Found: C, 71.95; H, 9.60; N, 18.35.

9-Azabicyclo[4.2.1]nonane-9-carbonitrile (9) was separated from the crude product of a reduction of a 3:2 mixture of 2a and 3a following the above procedure. White crystalline solid: mp 114–115 °C (*n*-hexane) (lit.[20] mp 114–116 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.90 (b, 2H, CHN), 2.15–1.85 (bm, 4H), 1.65–1.35 (bm, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.8 (C3 and C4), 31.2 (C2 and C5), 34.6 (C7 and C8), 61.3 (C1 and C6), 117.2 (CN).

9-Azabicyclo[3.3.1]nonane-9-carboxamide (10) and 9-Azabicyclo[4.2.1]nonane-9-carboxamide (11). Following the preceding procedure from 2.2 g (6.8 mmol) of the 4:1 mixture of 4a and 5a after 14 h of reflux of 4:1 mixture of 10 and 11 (0.15 g, 13%) was isolated as white crystalline solid. The isomers could not be separated by column chromatography: mp 175–180 °C (*n*-hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61–1.92 (m, 12H, $-CH_2-$), 3.60–4.35 (m, 2H, CHN), 4.75 (bs, 2H, NH_2 of [4.2.1] isomer), 4.90 (bs, 2H, NH_2 of the [3.3.1] isomer); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.0 (C3 and C7), 24.0 (C2, C4, C6 and C8), 50.5 (C1 and C5), 156.4 ($CONH_2$) for the [3.3.1] isomer 10 and 20.0 (C3 and C4), 29.4 (C2 and C5), 33.8 (C7 and C8), 55.3 (C1 and C6), 157.3 ($CONH_2$) for the [4.2.1] isomer 11; MS *m/z* (rel intensity) 168 (M^+, 11), 150 (1), 124 (14); IR (KBr) 3233 cm^{-1} (NH), 1650 cm^{-1} (CO). Anal. Calcd for $C_9H_{16}N_2O$ (168.2): C, 64.25; H, 9.59; N, 16.65. Found: C, 63.91; H, 9.30; N, 16.28.

***endo,exo*-2,6-Diacetoxy-9-acetyl-9-azabicyclo[3.3.1]nonane (12)**. A 74:26 mixture of 1 g (3.25 mmol) of 2a and 3a was refluxed in the dark with silver acetate (1.08 g, 6.5 mmol) in acetic anhydride (20 mL) for 8 h. The silver salts were separated and the solvent was removed under reduced pressure. The residue (850 mg, 92%, 75:25 mixture of 12 and 13) was separated by HPLC and recrystallized from ethanol, giving pure 12 as a white crystalline solid: mp 123–125 °C (ethanol); ^1H NMR ($CDCl_3$, 360 MHz) δ 1.7–2.0 (m, 8H, $-CH_2-$), 2.00 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 3.97 (t, 1H, J = 5.0 Hz, CHN), 4.68 (t, 1H, J = 5.3 Hz, CHN), 4.88 (m, 2H, CHOAc); ^{13}C NMR ($CDCl_3$, 91 MHz) δ 20.1 (3 × CH_3), 22.0 and 22.8 (C3 and C7), 25.42 and 25.45 (C4 and C8), 44.1 (C5), 49.8 (C1), 70.2 and 71.3 (C2 and C6), 168.5 (>N—C=O), 169.8 and 170.3 (O—C=O); MS *m/e* (rel intensity) 283 (M^+, 3), 284 (M^+ + 1, 7), 240 (27), 224 (3), 198 (25), 164 (3), 138 (20), 122 (54), 109 (6), 93 (14), 80 (43), 68 (14), 55 (10), 43 (100); IR 1740 cm^{-1} (ester), 1650 cm^{-1} (amide). Anal. Calcd for $C_{14}H_{21}NO_5$ (283.3): C, 59.34; H, 7.47; N, 4.94. Found: C, 59.01; H, 7.30; N, 4.93.

***endo,exo*-2,5-Diacetoxy-9-acetyl-9-azabicyclo[4.2.1]nonane (13)**. In the same way, from a 1:3 mixture of 1 g (2.5 mmol) of 2b and 3b, 590 mg (83%) of a 1:3 mixture of 12 and 13 was obtained. Separation by HPLC and recrystallization from ethanol gave pure 13 as a white crystalline solid: mp 97–98 °C (ethanol); ^1H NMR ($CDCl_3$, 360 MHz) δ 1.7–2.2 (m, 8H, $-CH_2-$), 2.05 (s, 3H, $OCOCH_3$), 2.08 (s, 3H, $OCOCH_3$), 2.16 (s, 3H, $NCOCH_3$), 4.37 (t, 1H, CHN), 4.81 (m, 1H, CHN), 4.88 (m, 1H, CHO), 5.24 (m, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.08 ($OCOCH_3$), 21.14 ($OCOCH_3$), 21.7 ($NCOCH_3$), 23.15, 24.0, 25.0, 25.9 (C3, C4, C7, C8), 55.8 and 58.8 (CHN), 71.15 and 73.3 (CHO), 168.2 (>N—CO), 168.8 and 170.2 (O—CO); MS *m/z* (rel intensity) 283 (M^+, 12), 284 (M^+ + 1, 16), 168 (3), 242 (17), 240 (17), 223 (48), 198 (86), 181 (76), 138 (75), 122 (59), 110 (36), 94 (70), 80 (64), 68 (100); IR 1742 cm^{-1} (ester), 1658 cm^{-1} (amide). Anal. Calcd for $C_{14}H_{21}NO_5$ (283.3): C, 59.34; H, 7.47; N, 4.94. Found: C, 59.19; H, 7.32; N, 4.90.

9-Azabicyclo[3.3.1]nona-2,5-diene-9-carbonitrile (14). A solution of 6.16 g (20 mmol) of 2a in 12.6 g (60 mmol) of dicyclohexylethylamine was heated to 160 °C for 20 h under nitrogen. The waxy solid was extracted at room temperature with petroleum ether, the solvent was removed under reduced pressure, and the residue was recrystallized from *n*-hexane to yield 14 (1.0 g, 43%) as a white crystalline solid: mp 76–80 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.62 (m, 2H) and 2.69 (m, 2H) ($-CH_2-$), 4.01 (t, 2H, CHN), 5.70 (m, 2H) and 5.80 (m, 2H) (CH=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.9 (C4 and C8), 51.9 (C1 and C5), 117.2 (CN), 123.7 (C3 and C7), 127.0 (C2 and C6); MS *m/z* (rel intensity) 146 (M^+, 75), 119 (65), 108 (100); IR (KBr) 3020 cm^{-1} (=CH), 2210 cm^{-1} (CN), 1670 cm^{-1} (C=C). Anal. Calcd for $C_9H_{10}N_2$ (146.2): C, 73.94; H, 6.89; N, 19.16. Found: C, 73.68; H, 7.06; N, 18.66.

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(21) The atomic coordinates for 2a and 4c have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK.