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Selective Mono- and 1,4-Di-*N*-alkylations of 1,4,7,10-Tetraazacyclododecane

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General methods for selective *N*-alkylations of the macrocycle 1,4,7,10-tetraazacyclododecane have been developed. The *N*-monoalkylation proceeds via a cyclic guanidinium derivative, and the regioselective 1,4-*N*,*N*-dialkylation via a cyclic amidinium derivative. All transformations were high yield reactions.

Over the past decade, the lanthanide complexes of 1,4,7,10-tetraazacyclododecane (cyclen) derivatives have found wide medicinal application in magnetic resonance imaging (MRI).[1] Synthesis of *N*-functionalized cyclen as ligands has received considerable attention since functionalized side chains in cyclen derivatives will affect the ligating ability of macrocycles.[2] Differential *N*-substitution of the four amino nitrogens in cyclen still represents a challenge.[1c,3,4] *N*-Monoalkylation has been effected by the use of a large excess of cyclen (× 5–10) relative to electrophiles.[2,5] This methodology is undesirable for less accessible or expensive electrophiles. With highly sterically hindered alkylating agents, selective *N*-monoalkylation has been effected using equimolar amounts of reactants.[6] Alternative methods reported for monoalkylation include triprotection of cyclen as boron, phosphorus, group VI metal carbonyl and silicon derivatives before the alkylation reaction.[7] However, these methods are not general.[7d,e] 1,7-*N*,*N*-Dialkylation of cyclen has been reported using an N^4,N^{10}-diprotected cyclen intermediate,[3f,7e,8] but so far no method for 1,4-*N*,*N*-dialkylation has been described, probably due to the difficulty of preparing a suitable 1,4-N^7,N^{10}-diprotected cyclen intermediate. Here we report a general method of *N*-monoalkylation of cyclen via a guanidinium salt and a method of 1,4-*N*,*N*-dialkylation of cyclen via an amidinium salt.

The dry HCl salt of cyclen was reacted with ethyl orthocarbonate to yield the guanidinium chloride **2** in 96% yield by a slight modification of a literature procedure.[9] The salt **2** was transformed into the tetracyclic amine **3** on treatment with base. Singlets in the ^{13}C NMR spectra at 169.15 (CN_3]$^+$) and at 127.66 (CN_4) ppm agree with the salt structure **2** and the free amine **3**. Conformational properties of both these compounds have been elucidated.[9] Reaction of the tetracyclic amine **3** with alkyl halides in toluene afforded the *N*-monoalkylated guanidinium salts **4a–d**, which crystallized out from the reaction medium. In the ^1H NMR spectra of **4a–d**, the protons of the eight methylene groups in the ring were seen as two apparent A_2B_2 systems. The ^{13}C NMR spectra of the structures **4a–d** showed the four CH_2 signals expected for these structures. Rapid nitrogen inversion would explain the fact that the two protons of each ring CH_2 group gave only one signal in the ^1H NMR spectrum. The ^{13}C NMR signal for CN_3]$^+$ in the structures **4a–d** appeared in the region 167.07–169.27 ppm. The IR spectra showed a strong absorption for the guanidinium function at 1620–1640 cm^{-1}.

The *N*-alkylated guanidinium salts **4** were not easily cleaved by HCl. Hydrolysis of **4a, b** in 1 M aq. NaOH, however, afforded the five-membered cyclic ureas **5a** and **5b** which were characterized by a carbonyl absorption in the IR spectra at 1684 cm^{-1} (**5a**) and 1669 cm^{-1} (**5b**). The signals from the urea carbon in the ^{13}C NMR spectra were at 164.24 ppm (**5a**) and 163.57 ppm (**5b**). The NMR spectra were in accordance with five-membered ring formation; alternative ring opening would result in eight-membered ring formation. A cyclen-derived tricyclic urea has also recently been reported.[10] The urea **5** showed high resistance to both base and acid hydrolysis.[11] Likewise, exchange reactions with 1,3-propanediamine failed to remove the urea moiety.[12] Reductive cleavage was subsequently investigated. By analogy with reports describing reduction of cyclic ureas with lithium aluminium hydride (LAH) to yield *gem*-diamines,[12,13] we used the latter reagent in large excess when the carbonyl group was reduced to a methyl group. The compound obtained was the 1-benzyl-7-methyl cyclen **6** in 93% yield. Structural assignment was based on the ^{13}C NMR spectrum of the product, which gave

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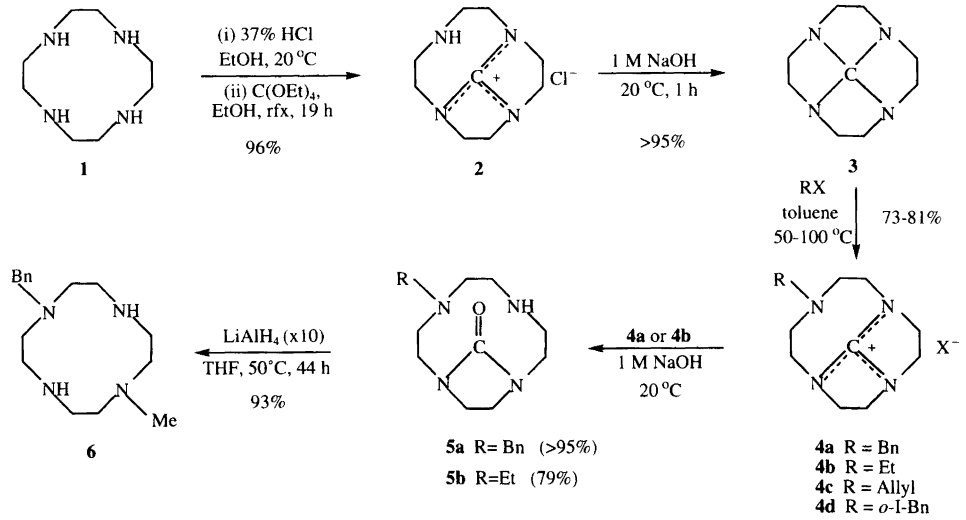


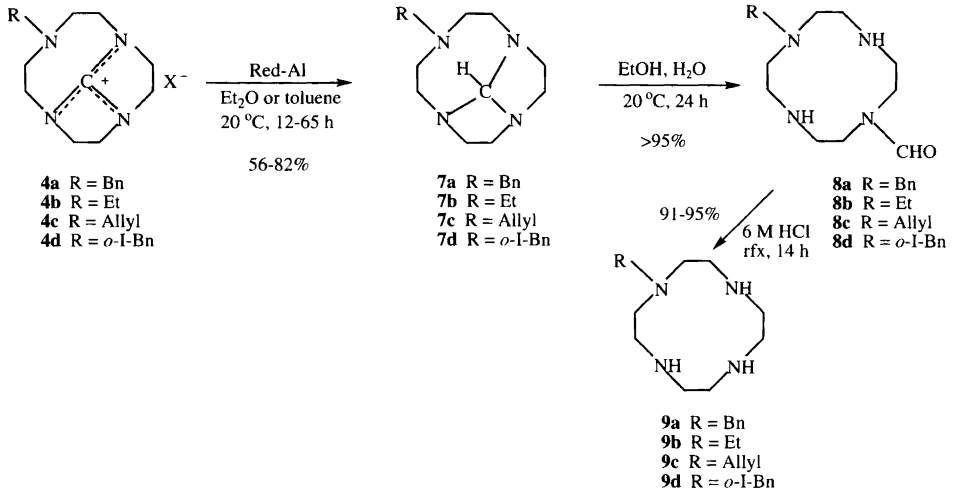
Scheme 1.

four different ring signals; alternative cleavage of the C–N bonds in the urea **5** should in principle give a product with eight different ring carbons.

In a general method for *N*-monoalkylation the guanidinium derivative **4** was reduced to a tricyclic orthoamide. Our best reagent was sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al).[14] Conditions for clean reduction with LAH were not found, and reduction reactions with the carbocation scavenger Et_3SiH gave less satisfactory results.[15] The tricyclic orthoamides **7a–d** were formed in high yields in toluene or diethyl ether solutions at ambient temperature. Individual differences for choice of optimal solvent were observed. The iodo derivative **4d** suffered largely hydrogenolysis of the iodo substituent in diethyl ether even when equimolar amounts of reactants were used, the main product isolated being **7a**. In toluene, however, the iodo substituent remained intact (**7d**). The resonances for the H–CN_3 in ^1H NMR spectra of the tricyclic orthoamides **7a–d** were in the region 4.96–5.31 ppm and the ^{13}C NMR signals in the region 97.65–98.19 ppm. Four different ring C atoms were present in the ^{13}C NMR spectra in agreement with the high symmetry of the structures **7**. Additional confirmation came from compound **7a** which has recently been prepared by an alternative route.[8b,c]

Hydrolysis of the orthoamides **7a–d** in dilute ethanol afforded the 1,7-*N*,*N*-disubstituted cyclens **8a–d**. The NCHO group in these products existed in the two usual forms and gave rise to eight carbon signals in the ^{13}C NMR spectra. The IR absorption bands for the NCHO group were in the region 1665–1671 cm^{-1}, the ^1H NMR signals in the region 8.16–8.29 ppm and the ^{13}C NMR signals in the the 163.95–164.55 ppm region. The reduction of the cyclic guanidinium derivative **4** and the subsequent hydrolysis can also be run without isolation of the intermediate orthoamide **7** in which case a higher overall yield for the two-step process was observed when effected on the guanidinium derivatives **4a–b**.

6 M HCl was used in hydrolytic cleavage of the formyl group in the structures **8a–d**; the products were the



Scheme 2.

N-monoalkylated cyclens **9a–d**. Thus, we have developed a general and convenient method of *N*-monoalkylation of cyclen with a high overall yield.

The substrate for regioselective 1,4-*N*,*N*-dialkylation was an *N*-alkyl tricyclic orthoamide; the example described in this report is the *N*-benzyl derivative **7a**, which was reacted with benzyl bromide in dry toluene at reflux. The product was the 1,4-*N*,*N*-dibenzyl amidinium salt **10**, which retained a five-membered ring in its structure. The signal for the $HCN_2]^+$ group in the ^{13}C NMR spectrum was at 157.64 ppm and the IR absorption band was at 1636 cm^{-1}. The regiochemistry was confirmed by the ^1H and ^{13}C NMR spectra which showed four different ring CH_2 groups; the alternative 1,7-*N*,*N*-alkylation would lead to the more symmetrical product with only two different ring CH_2 groups. Hydrolysis of compound **10** in 0.5 M NaOH gave the *N*-formyl derivative **11** which showed an IR absorption at 1671 cm^{-1}, ^1H NMR signals at 7.72 and 8.28 ppm and ^{13}C NMR signals at 164.0 and 164.1 ppm. The two amide conformations were also evident from the signals of the ring carbons which consisted of two sets of eight lines.

The formyl group was removed by hydrolysis using 6 M HCl. The product was the 1,4-dibenzyl cyclen **12** in 85% yield. Its structure was confirmed by the ^{13}C NMR spectrum, which showed the presence of four different ring C-atoms confirming the structure of the 1,4-dibenzylcyclen. This excludes the formation of 1,7-benzylcyclen in which only two different ring C atoms would be observed.[7e,8d]

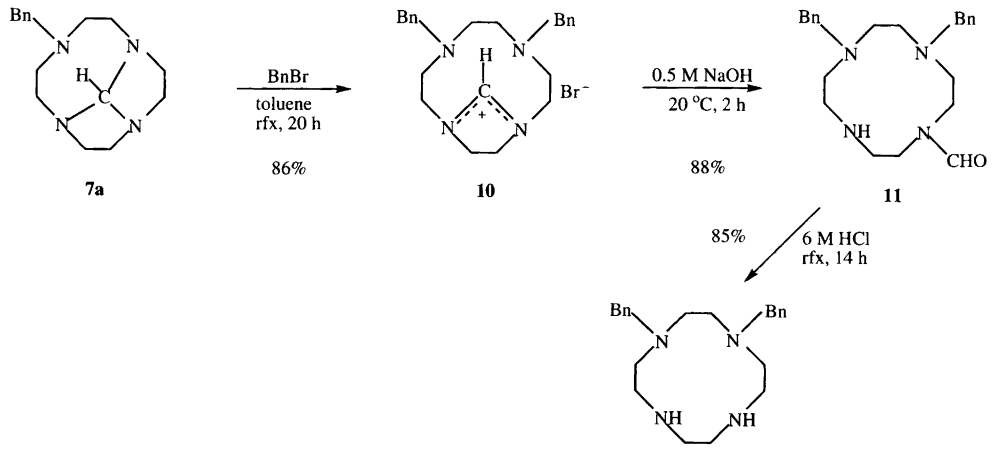
In this work we have demonstrated a general method for 1,4-*N*,*N*-dialkylation of cyclen, the total yield of **12** from cyclen (**1**) was 45%. This process allows for the use of different alkylating agents in the two alkylating steps. Furthermore, an *N*,*N*-dialkylated-*N*-formylated intermediate such as compound **11** can be alkylated with a third alkylating agent resulting in up to three different *N*-substituents. Hydrolysis of the formyl group and final *N*-alkylation could, by this process, lead to cyclens carrying four different *N*-alkyl groups.

Experimental

Melting points are uncorrected. ^1H NMR spectra were recorded at 300 MHz with a Varian XL-300 (manual) or at 200 MHz with a Varian GEMINI 200 instrument. The ^{13}C NMR spectra were recorded at 75 or 50 MHz on the same instruments. The mass spectra under electron impact conditions were measured at 70 eV ionizing potential on a Fisons VG Prospect instrument and ethane was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.). IR spectra were determined on a Magna-IR™ spectrometer 550. Dry toluene, dry THF and dry ether were prepared by distillation over sodium/benzophenone.

*1,2,3,4,6,7,8,9-Octahydro-5*H*-4a,7,9a-triaza-2a-azonia-cyclooct[*cd*]pentalene chloride* (**2**). 37% aq. HCl (296 mg, 3.00 mmol) was added dropwise to a solution of cyclen (517 mg, 3.00 mmol) in absolute ethanol (10 ml) at ambient temperature. The mixture was stirred for 2 min before the solvent was distilled off. A solution of the dried solid and ethyl orthocarbonate (750 mg, 3.9 mmol, 1.3 eq.) in absolute ethanol (12 ml) was heated under reflux for 19 h. Evaporation of the solution left a white solid which was recrystallized from MeOH–Et_2O; yield 618 mg (96%), m.p. 135–140 °C (lit.[9] 133–136 °C). ^1H NMR (CD_3OD, at −50 °C): δ 2.96 (4 H, t, *J* 6.4 Hz) 3.46 (4 H, t, *J* 7.5 Hz), 3.57 (4 H, t, *J* 6.3 Hz), 3.92 (4 H, t, *J* 7.5 Hz) [8 × CH_2]. ^{13}C NMR (CD_3OD): δ 46.21 (CH_2), 169.15 ($CN_3]^+$). MS(EI): 181 (6, [*M* −Cl]$^+$), 152 (75), 125 (66), 124 (100), 98 (51), 56 (33). IR (film): 3394s, 3281m, 1686w, 1655m, 1637w cm^{-1}.

*Octahydro-2a,4a,6a,8a-tetraazapentaleno[1,6-*cd*]pentalene* (**3**). 1,2,3,4,6,7,8,9-Octahydro-5*H*-4a,7,9a-triaza-2a-azonia-



Scheme 3.

cycloocta[*cd*]pentalene chloride (2.87 g, 13.27 mmol) was added to 1 M aq. NaOH (80 ml) and the mixture stirred at ambient temperature for 1 h. The mixture was evaporated to dryness under reduced pressure and the residual material was dried by azeotropic distillation with benzene. The residual material was triturated with benzene and the benzene extracts evaporated to dryness to leave the crude product which was used in the subsequent reactions without further purification; yield 2.39 g (>95%) as a white powder, m.p. 84–89 °C (lit.[9] 97–105 °C). ^{1}H NMR (CD_3OD): δ 2.99 (16 H, s, 8 × CH_2); (C_6D_6): δ 2.45–2.53 (8 H, m, 4 × CH_2), 2.88–2.95 (8 H, m, 4 × CH_2). ^{13}C NMR ($CDCl_3$): δ 49.11 (CH_2), 127.66 (CN_4). MS(EI): 180 (76, M^+), 152 (77), 125 (76), 124 (100), 98 (50), 70 (25).

*1,2,3,4,6,7,8,9-Octahydro-7-benzyl-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]pentalene bromide* (**4a**). Benzyl bromide (415 mg, 2.43 mmol) was added to a solution of octahydro-2a,4a,6a,8a-tetraazapentaleno[1,6-*cd*]pentalene (433 mg, 2.40 mmol) in dry toluene (8 ml) under N_2 and the mixture heated under reflux for 19 h. The insoluble product was filtered off, washed with toluene and dried; yield 740 mg (88%) of a yellow waxy solid. ^{1}H NMR (CD_3OD): δ 2.92 (4 H, t, *J* 6.5 Hz), 3.51 (4 H, t, *J* 7.8 Hz), 3.63 (4 H, t, *J* 6.5 Hz), 3.73 (4 H, t, *J* 7.8 Hz) [8 × ring CH_2], 3.81 (2 H, s, $C\underline{H}_2$Ph), 7.38 (3 H, s, Ph), 7.40 (2 H, s, Ph). ^{13}C NMR (CD_3OD): δ 45.62, 46.15, 52.42, 55.68 (ring CH_2), 63.57 ($C\underline{H}_2$Ph), 128.75, 129.47, 130.62, 140.20 (Ph), 169.27 ($C\underline{N}_3]^+$). IR (film): 1626s, 1570s, 1452m cm^{-1}.

*1,2,3,4,6,7,8,9-Octahydro-7-ethyl-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]pentalene iodide* (**4b**) was prepared as above using an equimolar amount of ethyl iodide (0.55 mmol) for the alkylation at 70 °C; yield 76% of a white powder, m.p. 139–143 °C. ^{1}H NMR (CD_3OD): δ 1.10 and 2.80 (CH_2CH_3), 2.91 (4 H, t, *J* 6.3 Hz), 3.49 (4 H, t, *J* 7.6 Hz), 3.63 (4 H, t, *J* 6.3 Hz), 3.92 (4 H, t, *J* 7.6 Hz) [8 × ring CH_2]. ^{13}C NMR (CD_3OD): δ 14.01 (CH_3), 46.16, 46.42, 51.81 (ring CH_2), 54.08 ($C\underline{H}_2CH_3$), 55.74 (ring CH_2), 168.95 ($CN_3]^+$). MS(EI): 209 (56, $[M-I]^+$), 128 (100), 127 (46). IR (film): 1672s, 1620s, 1576s, 1491m cm^{-1}.

*1,2,3,4,6,7,8,9-Octahydro-7-allyl-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]pentalene bromide* (**4c**) was prepared as above using an equimolar amount of allyl bromide (2.60 mmol) for the alkylation at 50 °C for 17 h; yield 81% of a yellow solid, m.p. 81–85 °C. ^{1}H NMR ($CDCl_3$): δ 2.95 (4 H, t, *J* 6.5 Hz, 2 × ring CH_2), 3.32 (2 H, d, *J* 1.4 Hz, CH_2C=), 3.61 (4 H, t, *J* 7.6 Hz), 3.74 (4 H, t, *J* 6.5 Hz), 4.05 (4 H, t, *J* 7.6 Hz) [6 × ring CH_2], 5.12–5.25 (2 H, m, =CH_2), 5.70–5.90 (1 H, m, CH=). ^{13}C NMR ($CDCl_3$): δ 44.32, 44.69, 50.14, 54.16 (ring CH_2), 60.86 ($C\underline{H}_2C$=), 117.91 (=CH_2), 134.20 (CH=), 167.07 ($C\underline{N}_3]^+$). MS(EI): 221 (100, $[M-Br]^+$), 179 (11), 138 (10), 128 (17), 124 (17), 112 (21), 94 (13), 80 (79). IR film): 1638s, 1569s, 1469m cm^{-1}.

*1,2,3,4,6,7,8,9-Octahydro-7-(2-iodobenzyl)-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]-pentalene chloride* (**4d**) was prepared as above using an equimolar amount of 2-iodobenzyl chloride (836 mg, 3.31 mmol) for the alkylation under reflux for 16 h; yield 73% of a white solid, m.p. 176–179 °C. ^{1}H NMR (CD_3OD): δ 2.96 (4 H, t, *J* 6.2 Hz), 3.48 (4 H, t, *J* 7.8 Hz), 3.64 (4 H, t, *J* 6.2 Hz), 3.73 (4 H, t, *J* 7.8 Hz) [8 × ring CH_2], 3.88 (2 H, s) ($C\underline{H}_2C_6H_4$), 7.05, 7.44 7.92 (C_6H_4). ^{13}C NMR (CD_3OD): δ 44.96, 45.47, 52.06, 55.36 (ring CH_2), 66.40 ($C\underline{H}_2C_6H_4$), 102.09, 129.28, 130.58, 132.59, 140.79, 142.21 (C_6H_4), 168.06 ($CN_3]^+$). MS(EI): 397 (23, $[M-Cl]^+$), 271 (79), 128 (100), 91 (89), 83 (55), 69 (66). IR (film): 1637s, 1575s, 1466m cm^{-1}.

4-Benzyl-1,4,7,10-tetraazabicyclo[8.2.1]tridecan-13-one (**5a**). 1,2,3,4,6,7,8,9-Octahydro-7-benzyl-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]pentalene bromide (162 mg, 0.46 mmol) was added to 1 M aq. NaOH (10 ml) and the mixture stirred at ambient temperature for 6 h. The product was extracted from this mixture into chloroform, and the solution dried ($MgSO_4$), filtered and evaporated; yield 133 mg (>95%) of an oily material. ^{1}H NMR ($CDCl_3$): δ 2.32–3.12 (10 H, m), 3.42–3.82 (5 H, m) [7.5 × ring CH_2)], 3.69 (2 H, s, $C\underline{H}_2$Ph), 3.98–4.14 (1 H, m, 1/2 × ring CH_2), 7.21–7.40 (5 H, m, Ph). ^{13}C NMR ($CDCl_3$): δ 40.78, 43.56, 45.13, 48.12, 51.16, 54.72 (ring CH_2), 59.89 ($C\underline{H}_2$Ph), 126.67, 127.84, 128.97, 138.22 (Ph), 164.24 (N_2C=O). MS(CI–C_2H_6): 289 (25, $[M+1]^+$), 288 (20, M^+), 287 (16, $[M-1]^+$), 271 (39), 197 (15), 169 (15), 142 (29), 134 (100), 91 (41). IR (film): 3481w br, 3337w, 2926s, 1684s cm^{-1}.

4-Ethyl-1,4,7,10-tetraazabicyclo[8.2.1]tridecan-13-one (**5b**) was prepared as above from 1,2,3,4,6,7,8,9-octahydro-7-ethyl-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]pentalene iodide (0.36 mmol); yield 79% of an oily material. ^{1}H NMR ($CDCl_3$): δ 1.03 (3 H, CH_3), 2.27–3.08 (12 H, m, 5 × ring CH_2 and CH_2CH_3), 3.40–3.71 (5 H, m), 4.01–4.16 (1 H, m). ^{13}C NMR ($CDCl_3$): δ 12.39 (CH_3), 40.57, 42.70, 43.98, 44.75, 48.54, 50.90 (ring CH_2), 53.65 ($C\underline{H}_2CH_3$), 163.57 (N_2C=O). MS(CI–C_2H_6): 255 (2, $[M+C_2H_5]^+$), 227 (65, $[M+1]^+$), 226 (27, M^+), 225 (45, $[M-1]^+$), 209 (100), 142 (20), 72 (38), 59 (34). IR (film): 3446m br, 3307m br, 2969s, 2934s, 2871s, 1669s, 1495s cm^{-1}.

1-Benzyl-7-methyl-1,4,7,10-tetraazacyclododecane (**6**). $LiAlH_4$ (62 mg, 1.63 mmol) was added to a solution of 4-benzyl-1,4,7,10-tetraazabicyclo[8.2.1]tridecan-13-one (47 mg, 0.16 mmol) in dry THF (4 ml) under N_2 and the reaction mixture stirred at 50 °C for 44 h. The reaction was quenched by addition of water (4 ml) followed by 1 M aq. NaOH (2 ml) and water (4 ml). The product was extracted into chloroform, washed with water, dried

($MgSO_4$) and the filtrate evaporated; yield 42 mg (93%) of an oily material. ^{1}H NMR ($CDCl_3$): δ 2.34 (3 H, s, CH_3), 2.59 (16 H, m, 8 × ring CH_2), 3.61 (2 H, s, CH_2Ph), 7.40–7.80 (5 H, m, Ph). ^{13}C NMR ($CDCl_3$): δ 44.01 (CH_3), 45.07, 45.15, 51.86, 54.36 (ring CH_2), 59.70 (CH_2Ph), 127.04, 128.24, 129.02, 138.81 (Ph). MS(EI): 276 (0.4, M^+), 259 (5), 218 (12), 189 (12). 177 (17), 163 (11), 142 (16), 134 (31), 113 (13), 99 (40), 91 (100).

*7-Benzyl-octahydro-5*H,*9b*H-*2a,4a,7,9a-tetraazacyclooctа[*cd*]pentalene* (**7a**). 3.5 M Red-Al in benzene (0.09 ml, 0.32 mmol) was added dropwise with stirring to a suspension of 1,2,3,4,6,7,8,9-octahydro-7-benzyl-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]pentalene bromide (55 mg, 0.16 mmol) in dry diethyl ether (15 ml) under N_2 at ambient temperature and the mixture stirred at this temperature for 40 h. Chloroform (50 ml) was then added, and the stirring continued for another 2 h before filtration and evaporation of the filtrate. The residual material was extracted into benzene and the extracts evaporated; yield 35 mg (82%) of an oily material. ^{1}H NMR ($CDCl_3$): δ 2.42–2.53 (2 H, m), 2.59–2.74 (6 H, m), 2.76–2.97 (6 H, m), 3.00–3.11 (2 H, m) [8 × ring CH_2], 3.68 (2 H, s, CH_2Ph), 5.09 (1 H, s, HCN_3), 7.21–7.39 (5 H, m, Ph). ^{13}C NMR ($CDCl_3$): δ 51.01, 51.94, 52.48, 55.30 (ring CH_2), 63.31 (CH_2Ph), 97.65 (HCN_3), 126.51, 127.71, 128.83, 139.31 (Ph). MS(EI): 272 (13, M^+), 181 (100), 152 (5), 148 (6), 138 (7), 125 (6), 97 (7), 91 (32).

*7-Ethyl-octahydro-5*H,*9b*H-*2a,4a,7,9a-tetraazacyclooctа[*cd*]pentalene* (**7b**) was prepared as above from 1,2,3,4,6,7,8,9-octahydro-7-ethyl-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]pentalene iodide (0.35 mmol); the reaction time was 65 h; yield 56% of an oily material. ^{1}H NMR ($CDCl_3$): δ 1.03 and 2.58 (CH_2CH_3), 2.70 (8 H, br s), 2.93 (8 H, br s) [8 × ring CH_2], 4.96 (1 H, s, HCN_3). ^{13}C NMR (C_6D_6): δ 13.53 (CH_3), 51.33, 52.44, 52.49 (ring CH_2), 53.03 (CH_2CH_3), 55.02 (ring CH_2), 97.89 (HCN_3). MS(EI): 210 (57, M^+), 181 (75), 152 (29), 138 (17), 124 (20), 111 (10), 97 (19), 83 (100).

*7-Allyl-octahydro-5*H,*9b*H-*2a,4a,7,9a-tetraazacyclooctа[*cd*]pentalene* (**7c**). 3.5 M Red-Al in benzene (0.27 ml, 0.95 mmol) was added dropwise to a suspension of 1,2,3,4,6,7,8,9-octahydro-7-allyl-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]pentalene bromide (144 mg, 0.48 mmol) in dry toluene (8 ml) under N_2 at ambient temperature and the mixture stirred for 12 h. The work-up of the reaction mixture was as above; yield 74 mg (70%) of an oily material. ^{1}H NMR (C_6D_6): δ 2.37–2.56 (8 H, m), 2.59–2.95 (8 H, m) [8 × ring CH_2], 3.00 (2 H, dt, *J* 6.3, 1.3 Hz, CH_2C=), 4.95–5.11 (2 H, m, =CH_2), 5.24 (1 H, s, HCN_3), 5.71–5.91 (1 H, m, CH=). ^{13}C NMR (C_6D_6): δ 51.31, 52.20, 52.56, 55.02 (ring CH_2), 62.41 (CH_2C=), 98.02 (HCN_3), 116.14 (=CH_2), 137.32 (CH=). MS(EI): 222 (28, M^+), 181 (100), 152 (8), 138 (13), 125 (14), 97 (11), 83 (39).

*7-(2-Iodobenzyl)-octahydro-5*H,*9b*H-*2a,4a,7,9a-tetraazacycloocta[*cd*]pentalene* (**7d**). 3.5 M Red-Al in benzene (0.06 ml, 0.21 mmol) was added dropwise to a suspension of 1,2,3,4,6,7,8,9-octahydro-7-(2-iodobenzyl)-5*H*-4a,7,9a-triaza-2a-azoniacycloocta[*cd*]-pentalene chloride (88 mg, 0.20 mmol) in dry toluene (10 ml) under N_2 at ambient temperature and the mixture stirred for 15 h. The reaction mixture was worked up as above; yield 48 mg (59%). ^{1}H NMR (C_6D_6): δ 2.47 (7 H, br s), 2.70 (7 H, br s), 2.99 (2 H, br s) [8 × ring CH_2], 3.62 (2 H, s, $CH_2C_6H_4$), 5.31 (1 H, s, HCN_3), 6.54 (1 H), 6.97 (1 H), 7.43 (1 H), 7.68 (1 H) [C_6H_4]. ^{13}C NMR (C_6D_6): δ 51.36, 51.88, 52.65, 55.63 (ring CH_2), 67.84 ($CH_2C_6H_4$), 98.19 (HCN_3), 100.69, 128.18, 128.75, 131.03, 139.63, 142.06 (C_6H_4). MS(EI): 398 (10, M^+), 274 (5), 217 (8), 181 (100), 152 (4), 91 (12), 83 (12).

7-Benzyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (**8a**). A solution of 7-benzyl-octahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta[*cd*]pentalene (66 mg, 0.24 mmol) in ethanol (3 ml) and water (3 ml) was stirred at ambient temperature for 24 h. The mixture was then distilled to remove most of the ethanol, the remaining mixture extracted with chloroform and the dried ($MgSO_4$) chloroform solution evaporated; yield 68 mg (>95%) of a white powder, m.p. 61–64 °C (lit.[8c] 64–65 °C).

7-Ethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (**8b**) was prepared as above from 7-ethyloctahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta[*cd*]pentalene (0.35 mmol); yield >95% of an oily material. ^{1}H NMR ($CDCl_3$): δ 1.03 and 2.68 (CH_2CH_3), 2.68–2.78 (6 H, m), 2.98 (2 H, t), 3.14 (2 H, t), 3.21 (2 H, t), 3.62 (2 H, t,), 3.69 (2 H, t) [8 × ring CH_2], 8.29 (1 H, s, NCHO). ^{13}C NMR ($CDCl_3$): δ 11.72 (CH_3), 43.70, 45.13, 45.69, 46.01, 47.23, 49.25, 49.32, 50.02, 50.60 (ring CH_2 and CH_2CH_3), 164.42 (NCHO). MS(CI–C_2H_6): 257 (7, $[M+C_2H_5]^+$), 230 (18), 229 (100, $[M+1]^+$), 227 (11), 211 (19). IR (film): 3421s br, 3225m br, 2969s, 2932m, 2834s, 1665s, 1453m cm^{-1}.

7-Allyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (**8c**) was prepared as above from 7-allyl-octahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta[*cd*]pentalene (27 mg, 0.12 mmol); yield >95% of an oily material. ^{1}H NMR ($CDCl_3$): δ 2.70–2.80 (2 H, m), 2.76 (4 H, s), 2.87–2.92 (2 H, m), 3.11 (2 H, t) [5 × ring CH_2], 3.15–3.22 (4 H, m, ring CH_2 and CH_2C=), 3.61 (2 H, t), 3.69 (2 H, t) [2 × ring CH_2], 5.13 (1 H, s), 5.20 (1 H, d), 5.70–5.90 (1 H, m, CH=CH_2), 8.24 (1 H, s, NCHO). ^{13}C NMR ($CDCl_3$): δ 43.70, 46.01, 46.29, 46.56, 8.26, 48.91, 49.46, 52.02 (ring CH_2), 59.35 (CH_2C=), 118.33 (=CH_2), 134.62 (CH=), 164.40 (NCHO). MS(CI–C_2H_6): 269 (7, $[M+C_2H_5]^+$), 242 (16), 241 (100, $[M+1]^+$), 239 (13), 229 (9), 223 (27), 213 (5), 84 (5). IR (film): 3423m br, 3219m br, 2927s, 2855s, 1667s, 1455m cm^{-1}.

7-(2-Iodobenzyl)-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (**8d**) was prepared from 7-(2-iodobenzyl)-octahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta[*cd*]-pentalene (40 mg, 0.10 mmol) as above; yield 42 mg (>95%) of an oily material. ^{1}H NMR $CDCl_3$): δ 2.57–2.66 (2 H, m), 2.63 (6 H, s), 2.75 (2 H, t,), 2.87 (2 H, t), 3.44–3.55 (4 H, m) [8 × ring CH_2], 3.69 (2 H, s, $C\underline{H}_2C_6H_4$), 6.93 (1 H), 7.31–7.43 (2 H, m), 7.79 (1 H, dd) [C_6H_4], 8.24 (1 H, s, NCHO). ^{13}C NMR ($CDCl_3$): δ 44.56, 46.93, 47.36, 47.45, 47.76, 50.10, 51.20, 51.88 (ring CH_2), 64.49 ($\underline{C}H_2$PhI), 99.99, 128.32, 129.91, 130.95, 139.40, 141.10 (C_6H_4), 164.55 (NCHO). MS(CI–C_2H_6): 445 (7, $[M+C_2H_5]^+$), 418 (21), 417 (100, $[M+1]^+$), 415 (25), 399 (24), 291 (27), 273 (10), 152 (12). IR (film): 3480m br, 3308m, 3233m, 2929s, 2877m, 2819s, 1671s, 1449m cm^{-1}.

1-Benzyl-1,4,7,10-tetraazacyclododecane (**9a**). 7-Benzyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (35 mg, 0.12 mmol) was added to 6 M HCl (10 ml), the mixture heated under reflux for 14 h, evaporated under reduced pressure and the residual material treated with 1 M NaOH (10 ml). The resultant mixture was stirred at ambient temperature for 2 h, evaporated to dryness under reduced pressure, the residual solid extracted with chloroform (3 × 20 ml), and the chloroform extracts dried ($MgSO_4$), filtered and evaporated; yield 32 mg (>95%) of a white solid, m.p. 81–83 °C (lit.[8c] 85 °C). ^{1}H NMR ($CDCl_3$): δ 2.52–2.64 (8 H, m), 2.64–2.74 (4 H, m), 2.74–2.86 (4 H, m) [8 × ring CH_2], 3.61 (2 H, s, $C\underline{H}_2$Ph), 7.22–7.37 (5 H, m, Ph). ^{13}C NMR ($CDCl_3$): δ 44.96, 46.24, 47.04, 51.12, ring CH_2), 59.13 ($\underline{C}H_2$Ph), 126.99, 128.25, 128.97, 138.85 (Ph).

1-Ethyl-1,4,7,10-tetraazacyclododecane (**9b**) was prepared as above from 7-ethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (0.22 mmol); yield 39 mg (91%) as an oily material. ^{1}H NMR ($CDCl_3$): δ 1.04 (3 H, t, *J* 7.0 Hz, CH_3), 2.48–2.69 (14 H, m, 6 × ring CH_2 and $C\underline{H}_2CH_3$), 2.76–2.81 (4 H, m, 2 × ring CH_2). ^{13}C NMR $CDCl_3$): δ 11.90 (CH_3), 44.96, 45.86, 46.85 (ring CH_2), 47.87 ($\underline{C}H_2CH_3$), 50.72 (ring CH_2).

1-Allyl-1,4,7,10-tetraazacyclododecane (**9c**) was prepared as above from 7-allyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (0.10 mmol); yield 20 mg (91%) of an oily material. ^{1}H NMR (C_6D_6): δ 2.07–2.18 (12 H, m), 2.23–2.29 (4 H, m) [8 × ring CH_2], 2.64 (2 H, dt, *J* 6.3, 1.3 Hz, CH_2C=), 4.69–4.84 (2 H, m, =CH_2), 5.41–5.61 (1 H, m, CH=). ^{13}C NMR ($CDCl_3$): δ 45.11, 45.97, 47.0, 50.88 (ring CH_2), 57.63 ($\underline{C}H_2C$=), 117.69 (=CH_2), 135.38 (CH=).

1-(2-Iodobenzyl)-1,4,7,10-tetraazacyclododecane (**9d**) was prepared as above from 7-(2-iodobenzyl)-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (0.065 mmol); yield 25 mg (>95%) of an oily material. ^{1}H NMR ($CDCl_3$): δ 2.56–2.61 (8 H, m), 2.68–2.70 (4 H, m), 2.79–2.84 (4 H, m) [8 × ring CH_2], 3.65 (2 H, s, $C\underline{H}_2C_6H_4$), 6.93 (1 H), 7.30–7.42 (2 H, m), 7.82 (1 H, dd) [C_6H_4]. ^{13}C NMR ($CDCl_3$): δ 44.90, 46.19, 47.05, 51.40 (ring CH_2), 63.89 ($\underline{C}H_2C_6H_4$), 100.31, 128.12, 128.69, 130.95, 139.39, 140.52 (C_6H_4).

4,7-Dibenzyl-4,7,10-triaza-1-azoniabicyclo[8.2.1]tridec-1(13)-ene bromide (**10**). A solution of benzyl bromide (55 mg, 0.32 mmol) and 7-benzyloctahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta[*cd*]pentalene (72 mg, 0.26 mmol) in dry toluene (8 ml) was heated under reflux for 20 h. The precipitated product was filtered off, washed with toluene and dried; yield 101 mg (86%) of a waxy solid. ^{1}H NMR ($CDCl_3$): δ 2.70 (4 H, s), 2.81 (4 H, s), 3.26 (4 H, s) [6 × ring CH_2], 3.52 (4 H, s, 2 × $C\underline{H}_2$Ph), 4.23 (4 H, s, 2 × ring CH_2), 7.14–7.33 (10 H, m, 2 × Ph). ^{13}C NMR ($CDCl_3$): δ 48.56, 49.08, 51.36, 53.88 (ring CH_2), 57.95 ($\underline{C}H_2$Ph), 127.36, 128.45, 129.29, 137.53 (Ph), 157.64 ($\underline{H}CN_2]^+$). IR (film): 3422s br, 2840s, 1636s, 1495w cm^{-1}.

4,7-Dibenzyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (**11**). 4,7-Dibenzyl-4,7,10-triaza-1-azoniabicyclo[8.2.1]tridec-1(13)-ene bromide (56 mg, 0.13 mmol) was added to 0.5 M aq. NaOH (4 ml), the mixture stirred at ambient temperature for 2 h and extracted with chloroform, and the dried ($MgSO_4$) solution evaporated under reduced pressure; yield 42 mg (88%) of an oily material. ^{1}H NMR ($CDCl_3$): δ 2.46–2.95 (12 H, m, 6 × ring CH_2), 3.37–3.69 (8 H, m, 2 × ring CH_2 and 2 × $C\underline{H}_2$Ph), 7.10–7.40 (10 H, m, 2 × Ph), 7.72 (1/2 H, s), 8.28 (1/2 H, s, NCHO). ^{13}C NMR ($CDCl_3$): δ 42.4, 46.0, 47.2, 47.4, 47.6, 48.3, 48.9, 49.8, 50.3, 51.5, 51.7, 52.3, 53.0, 53.6, 53.7, 55.7 (ring CH_2), 59.4, 60.8 ($\underline{C}H_2$Ph), 126.7, 126.8, 127.0, 127.1, 127.8, 128.0, 128.2, 128.4, 128.8, 129.0, 129.1, 129.8, 137.2, 137.6, 139.0, 139.1 (Ph), 164.0, 164.1 (NCHO). MS(CI–C_2H_6): 409 (8, $[M+C_2H_5]^+$), 382 (24), 381 (79, $[M+1]^+$), 379 (14), 291 (18), 273 (7), 241 (13), 152 (28), 75 (100). IR (film): 3247w, 3089w, 2845s, 1671s, 1495w cm^{-1}.

1,4-Dibenzyl-1,4,7,10-tetraazacyclododecane (**12**). 4,7-Dibenzyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (36 mg, 0.095 mmol) was added to 6 M HCl (10 ml), the mixture heated under reflux for 14 h and evaporated under reduced pressure, and the residual material treated with NaOH (10 ml). The resultant mixture was stirred at ambient temperature for 2 h, evaporated almost to dryness under reduced pressure, extracted with chloroform (3 × 20 ml), and the chloroform extracts dried ($MgSO_4$), filtered and evaporated; yield 28 mg (85%) of an oily material. ^{1}H NMR ($CDCl_3$): δ 2.53–2.80 (16 H, m, 8 × ring CH_2), 3.42 (4 H, s, 2 × $C\underline{H}_2$Ph), 7.24–7.29 (10 H, m, 2 × Ph). ^{13}C NMR ($CDCl_3$): δ 44.69, 46.62, 50.37, 52.09 (ring CH_2), 58.40 ($\underline{C}H_2$Ph), 126.87, 128.14, 129.10, 138.73 (Ph).

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