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

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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). 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. Differential N-substitution of the four amino nitrogens in cyclen still represents a challenge. N-Monoalkylation has been effected by the use of a large excess of cyclen (× 5–10) relative to electrophilites. This methodology is undesirable for less accessible or expensive electrophilites. With highly sterically hindered alkyllating agents, selective N-monoalkylation has been effected using equimolar amounts of reactants. Alternative methods reported for monooalkylation include triprotection of cyclen as boron, phosphorus, group VI metal carbonyl and silicon derivatives before the alkylation reaction. However, these methods are not general. 1,7-N,N-Dialkylation of cyclen has been reported using an N,N,N′,N″-diprotected cyclen intermediate, 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,N,N′,N″-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. The salt 2 was transformed into the tetracyclic amine 3 on treatment with base. Singlets in the 13C NMR spectra at 169.15 (CN3) and at 127.66 (CN4) ppm agree with the salt structure 2 and the free amine 3. Conformational properties of both these compounds have been elucidated. 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 A2B2 systems. The 13C NMR spectra of the structures 4a-d showed the four CH2 signals expected for these structures. Rapid nitrogen inversion would explain the fact that the two protons of each ring CH2 group gave only one signal in the 1H NMR spectrum. The 13C NMR signal for CN3 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-monoalkylated 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 13C 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. The urea 5 showed high resistance to both base and acid hydrolysis. Likewise, exchange reactions with 1,3-propanediamine failed to remove the urea moiety. 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 13C NMR spectrum of the product, which gave

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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)aluminum hydride (Red-Al). Conditions for clean reduction with LAH were not found, and reduction reactions with the carbocation scavenger Et$_3$SiH gave less satisfactory results. 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 $^1$H 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 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 $^1$H 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

\[ \text{Red-Al} \]  
Et$_2$O or toluene  
20 °C, 12–65 h  
56–82%  

\[ \text{EtOH, H$_2$O} \]  
20 °C, 24 h  
>95%  

\[ 6 \text{ M HCl} \]  
rfx, 14 h  

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 orthoamidine; 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 HCN2 group in the 13C 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 13C NMR spectra which showed four different ring CH2 groups; the alternative 1,7-N,N-alkylation would lead to the more symmetrical product with only two different ring CH2 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 13C 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 13C 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 a 1,7-benzylcyclen in which only two different ring C atoms would be observed. 7c,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 13C 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-5H-4a,7,9a-triaza-2a-azonia-cycloocta[c/d]/pentalaene 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 orthoformate (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–Et2O; yield 618 mg (96%), m.p. 135–140 °C (lit.8 133–136 °C). 1H NMR (CD3OD, 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 × CH2]. 13C NMR (CD3OD): δ 46.21 (CH2), 169.15 (CN3)°. 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-tetraazapentalene[1,6-cd]/pentalaene (3). 1,2,3,4,6,7,8,9-Octahydro-5H-4a,7,9a-triaza-2a-azonia-

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cycloocta[cd]pentacene 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°9 C (lit.° 97°105 °C). 1H NMR (CD2OD): δ 2.99 (16 H, s, 8 × CH2); (C6D6): δ 2.45–2.53 (8 H, m, 4 × CH2), 2.88–2.95 (8 H, m, 4 × CH2). 13C NMR (CDCl3): δ 49.11 (CH2), 127.66 (CN3), MS(El): 180 (76, M+), 152 (77), 125 (76), 124 (100), 98 (50), 70 (25).

1.2,3,4,6,7,8,9-Octahydro-7-benzyl-5H-4a,7,9a-triaza-2-azacycloocta[cd]pentacene bromide (4a). Benzyl bromide (415 mg, 2.43 mmol) was added to a solution of octahydro-2a,4a,6a,8a-tetraazapentalenol[1,6-cd]pentacene (433 mg, 2.40 mmol) in dry toluene (8 ml under N2) 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. 1H NMR (CD2OD): 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 CH2], 3.81 (2 H, s, CH2Ph), 7.38 (3 H, s, Ph), 7.40 (2 H, s, Ph). 13C NMR (CD2OD): δ 45.62, 46.15, 52.42, 55.68 (ring CH2), 63.57 (CH2Ph), 128.75, 129.47, 130.62, 140.20 (Ph), 169.27 (CN3). IR (film): 1626s, 1570s, 1452cm–1.

2.4-Benzyl-1,4,7,10-tetraazabicyclo[8.2.1]tridecan-13-one (5a). 1.2,3,4,6,7,8,9-Octahydro-7-benzyl-5H-4a,7,9a-triaza-2-azacycloocta[cd]pentacene 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 (MgSO4), filtered and evaporated; yield 133 mg (>95%) of an oily material. 1H NMR (CDCl3): δ 2.32–3.12 (10 H, m), 3.42–3.82 (5 H, m) [7.5 × ring CH2], 3.69 (2 H, s, CH2Ph), 3.98–4.14 (1 H, m, 1/2 × ring CH2), 7.21–7.40 (5 H, m, Ph). 13C NMR (CDCl3): δ 40.78, 43.56, 45.13, 48.12, 51.16, 54.72 (ring CH2), 59.89 (CH2Ph), 126.67, 127.84, 128.97, 138.22 (Ph), 164.24 (N2=C=O), MS(El–C2H5): 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.

1.2,3,4,6,7,8,9-Octahydro-7-allyl-5H-4a,7,9a-triaza-2-azacycloocta[cd]pentacene bromide (4c) was prepared as above using an equimolar amount of allyl bromide (2.60 mmol) for the alklylation at 50 °C; yield 81% of a yellow solid, m.p. 81–85 °C. 1H NMR (CDCl3): δ 2.95 (4 H, t, J 6.5 Hz, 2 × ring CH2), 3.32 (2 H, d, J 1.4 Hz, CH2C=), 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 CH2], 5.12–5.25 (2 H, m, =CH2), 5.70–5.90 (1 H, m, CH=). 13C NMR (CDCl3): δ 44.32, 44.69, 50.14, 54.16 (ring CH2), 60.86 (CH2C=), 117.91 (=CH2), 134.20 (CH=), 167.07 (CN3). MS(El): 221 (100, [M–Br]+), 179 (11), 138 (10), 128 (17), 124 (17), 92 (21), 94 (13), 80 (79). IR film): 1638s, 1569s, 1469cm–1.

1.2,3,4,6,7,8,9-Octahydro-7-(2-iodobenzyl)-5H-4a,7,9a-triaza-2-azacycloocta[cd]pentacene chloride (4d) was prepared as above using an equimolar amount of 2-iodobenzyl chloride (836 mg, 3.31 mmol) for the alklylation under reflux for 16 h; yield 73% of a white solid, m.p. 176–179 °C. 1H NMR (CDCl3): 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 CH2], 3.88 (2 H, s) (CH2C=CH2), 7.05, 7.44 7.92 (CH2). 13C NMR (CDCl3): δ 44.96, 45.47, 52.06, 55.36 (ring CH2), 66.40 (CH2C=CH2), 102.09, 129.28, 130.58, 132.59, 140.79, 142.21 (CH2C=), 168.06 (CN3). MS(El): 397 (23, [M–Cl]+), 271 (79), 128 (100), 91 (89), 83 (55), 69 (66). IR (film): 1637s, 1575s, 1466cm–1.

2-Benzyl-1,4,7,10-tetraazabicyclo[8.2.1]tridecan-13-one (5a).

1.2,3,4,6,7,8,9-Octahydro-7-benzyl-5H-4a,7,9a-triaza-2-azacycloocta[cd]pentacene 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 (MgSO4), filtered and evaporated; yield 133 mg (>95%) of an oily material. 1H NMR (CDCl3): δ 2.32–3.12 (10 H, m), 3.42–3.82 (5 H, m) [7.5 × ring CH2], 3.69 (2 H, s, CH2Ph), 3.98–4.14 (1 H, m, 1/2 × ring CH2), 7.21–7.40 (5 H, m, Ph). 13C NMR (CDCl3): δ 40.78, 43.56, 45.13, 48.12, 51.16, 54.72 (ring CH2), 59.89 (CH2Ph), 126.67, 127.84, 128.97, 138.22 (Ph), 164.24 (N2=C=O), MS(El–C2H5): 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.

1-Benzyl-1,4,7,10-tetraazacyclododecan (6).

LiAlH4 (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 N2 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 (2 ml). The product was extracted into chloroform, washed with water, dried
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7-Benzyl-octahydro-5H,9bH-2a,4a,7,9a-tetraazaacycloocta[c,d]pentaleine (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-5H-4a,7,9a-triaza-2-azoniacycloocta[c,d]pentaleine bromide (55 mg, 0.16 mmol) in dry diethyl ether (15 ml) under N₂ at ambient temperature and the mixture stirred for 15 h. The reaction mixture was worked up as above; yield 48 mg (59%). ¹H NMR (CD₂Cl₂): δ 2.47 (7 H, br s), 2.70 (7 H, br s), 2.70 (7 H, br s), 2.99 (2 H, br s) [8 × ring CH₂], 3.62 (2 H, s, CH₂C₆H₅), 5.31 (1 H, s, HCN₃), 6.54 (1 H, 6.97 (1 H), 7.43 (1 H), 7.68 (1 H) [C₆H₄]. ¹³C NMR (CD₂Cl₂): δ 51.36, 51.88, 52.65, 55.63 (ring CH₃), 67.84 (CH₂C₆H₅), 98.19 (HCN₃), 100.69, 128.18, 128.75, 131.03, 139.63, 142.06 (C₆H₄), MS (EI): 398 (10, M⁺), 274 (5), 217 (8), 181 (100), 152 (49), 91 (12), 83 (12).

7-Benzyl-1,4,7,10-tetraazaacyclodecane-1-carbaldehyde (8a). A solution of 7-benzyl-octahydro-5H,9bH-2a,4a,7,9a-tetraazaacycloocta[c,d]pentaleine (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, and the remaining mixture extracted with chloroform and the dried (MgSO₄) chloroform solution evaporated; yield 68 mg (>95%) of a white powder, m.p. 61–64 °C (lit. 86–65 °C).

7-Ethyl-octahydro-5H,9bH-2a,4a,7,9a-tetraazaacycloocta[c,d]pentaleine (7b) was prepared as above from 1,2,3,4,6,7,8,9-octahydro-7-ethyl-5H-4a,7,9a-triaza-2-azoniacycloocta[c,d]pentaleine iodide (0.35 mmol); yield >95% of an oily material. ¹H NMR (CD₂Cl₂): δ 1.03 and 2.68 (CH₂C₆H₅), 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 CH₂], 8.29 (1 H, s, NCHO). ¹³C NMR (CD₂Cl₂): δ 11.72 (CH₃), 43.70, 45.13, 45.69, 46.01, 47.23, 49.25, 49.32, 50.02, 50.60 (ring CH₂ and CH₂C₆H₅), 164.42 (NCHO). MS (CI–C₆H₅): 257 (7, [M + C₆H₅]⁺), 230 (18), 229 (100, [M + 1]⁺), 227 (11), 211 (19). IR (film): 3412 cm⁻¹, 2925 cm⁻¹, 2834 cm⁻¹, 1665 cm⁻¹, 1453 cm⁻¹⁻¹.

7-Allyl-octahydro-5H,9bH-2a,4a,7,9a-tetraazaacyclodecane-1-carbaldehyde (8c) was prepared as above from 7-allyloctahydro-5H,9bH-2a,4a,7,9a-tetraazaacycloocta[c,d]pentaleine (27 mg, 0.12 mmol); yield >95% of an oily material. ¹H NMR (CD₂Cl₂): 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 CH₂], 3.15–3.22 (4 H, m, ring CH₂ and CH₂C₆H₅), 3.61 (2 H, t), 3.69 (2 H, t) [2 × ring CH₂], 5.13 (1 H, s), 5.20 (1 H, d), 5.70–5.90 (1 H, m, CH–CH₂), 8.24 (1 H, s, NCHO). ¹³C NMR (CD₂Cl₂): δ 43.70, 46.01, 46.29, 46.56, 8.26, 48.91, 49.46, 52.02 (ring CH₂), 59.35 (CH₂C₆H₅), 118.33 (CH₂C₆H₅), 134.62 (CH=), 164.40 (NCHO). MS (Cl–C₆H₅): 269 (7, [M + C₆H₅]⁺), 242 (16), 241 (100, [M + 1]⁺), 239 (13), 229 (9), 223 (27), 215 (3), 84 (5). IR (film): 3423 cm⁻¹, 2319 br, 2927s, 2855s, 1667s, 1455 cm⁻¹⁻¹.
7-(2-Iodobenzyl)-1,4,7,10-tetraazaacyclocodecane-1-carbaldheyde (8d) was prepared from 7-(2-iodobenzyl)-octahydro-5H,9H-f2a,4a,7,9a-tetraazaacyclocta[cdf]-pentalenale (40 mg, 0.10 mmol) as above: yield 42 mg (>95%) of an oily material. 1H NMR (CDCl3): δ 2.57-2.66 (2H, m), 2.63 (6H, s), 2.75 (2H, t), 2.87 (2H, t), 3.44-3.55 (4H, m) [8 x ring CH2], 3.69 (2H, s, CH2-C6H5), 6.93 (1H, 7.31-7.43 (2H, m), 7.79 (1H, ddd) [C6H4] 8.24 (1H, s, NCHO). 13C NMR (CDCl3): δ 44.56, 46.93, 47.36, 47.45, 47.76, 50.10, 51.20, 51.88 (ring CH2), 64.49 (CH2-Ph), 99.99, 128.32, 129.91, 130.95, 134.40, 141.10 (C6H4), 164.55 (NCHO). MS([Cl-C6H4], 445 (7, [M+C2H5]+), 418 (21), 417 (100, [M+1]+), 345 (25), 399 (24), 291 (27), 273 (10), 152 (12). IR (film): 3480nm br, 3308m, 3233m, 2929s, 2877m, 2819s, 1671s, 1449m cm⁻¹.

1-Benzyl-1,4,7,10-tetraazaacyclocodane (9a). 7-Benzyl-1,4,7,10-tetraazaacyclocodane-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 x 20 ml), and the chloroform extracts dried (MgSO4), filtered and evaporated; yield 32 mg (>95%) of a white solid, m.p. 81-83°C (lit. 85°C). 1H NMR (CDCl3): δ 2.52-2.64 (8H, m), 2.64-2.74 (4H, m), 2.74-2.86 (4H, m) [8 x ring CH2], 3.61 (2H, s, CH2-Ph), 7.22-7.37 (5H, m, Ph). 13C NMR (CDCl3): δ 44.96, 46.24, 47.04, 51.12, ring CH2), 59.13 (CH2-Ph), 126.99, 128.25, 129.97, 138.97 (Ph).

1-Ethyl-1,4,7,10-tetraazaacyclocodane (9b) was prepared as above from 7-ethyl-1,4,7,10-tetraazaacyclocodane-1-carbaldehyde (0.02 mmol); yield 39 mg (91%) as an oily material. 1H NMR (CDCl3): δ 1.04 (3H, t, J 7.0 Hz, CH3), 2.48-2.69 (14H, m, 6 x ring CH2 and CH2CH2), 2.76-2.81 (4H, m, 2 x ring CH2). 13C NMR (CDCl3): δ 11.90 (CH3), 44.96, 45.86, 46.85 (ring CH2), 47.87 (CH2CH2), 50.72 (ring CH2).

1-allyl-1,4,7,10-tetraazaacyclocodane (9c) was prepared as above from 7-allyl-1,4,7,10-tetraazaacyclocodane-1-carbaldehyde (0.10 mmol); yield 20 mg (91%) of an oily material. 1H NMR (CD3OD): δ 2.07-2.12 (12H, m), 2.23-2.29 (4H, m) [8 x ring CH2], 2.64 (2H, dt, J 6.3, 1.3 Hz, CH2CH2), 4.69-4.84 (2H, m, =CH2), 5.41-5.61 (1H, m, CH=). 13C NMR (CDCl3): δ 45.11, 45.97, 47.0, 50.88 (ring CH2), 57.63 (CH2-CH=), 117.69 (=CH2), 135.38 (CH=).

1-2-Iodobenzyl-1,4,7,10-tetraazaacycldocane (9d) was prepared as above from 7-(2-iodobenzyl)-1,4,7,10-tetraazaacyclocodane-1-carbaldehyde (0.065 mmol); yield 25 mg (>95%) of an oily material. 1H NMR (CDCl3): δ 2.56-2.61 (8H, m), 2.68-2.70 (4H, m), 2.79-2.84 (4H, m) [8 x ring CH2], 3.65 (2H, s, CH2-CH3), 6.93 (1H, 7.30-7.42 (2H, m), 7.82 (1H, ddd) [C6H4], 13C NMR (CDCl3): δ 44.90, 46.19, 47.05, 51.40 (ring CH2), 63.89 (CH2-CH3), 100.31, 128.12, 128.69, 130.95, 139.39, 140.52 (CH2).
References


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