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Cyclopolyamines: Synthesis of Cyclospermidines and Cyclospermines, Analogues of Spermidine and Spermine

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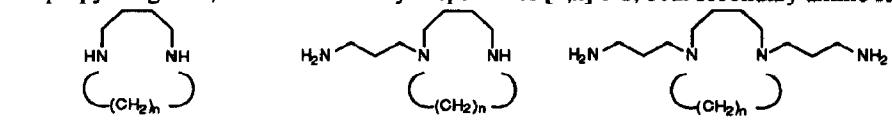
Abstract: The synthesis of a series of cyclic analogues of the naturally occurring polyamines putrescine, spermidine and spermine was achieved. The cyclic analogues of putrescine named cycloputrescine [4,n] were composed of cycloputrescine in which the two primary amines were connected with a polymethylene chain of variable length (n = 3, 4, 5). Cyclospermidines [4,n] and Cyclospermines [4,n] were composed of a cycloputrescine [4,n] moiety mono- or di-functionalized with an aminopropyl chain respectively.

Among various biogenic polyamines, putrescine, spermidine and spermine are ubiquitous in a large variety of biological materials.[1] Although spermine was first isolated from human semen by Leeuwenhoek as early as 1677, as spermine phosphate crystals, only in recent years has much attention been focused on naturally occurring polyamines and their analogues. Since the early 1970s, the literature dealing with these compounds has been grown considerably. Putrescine, spermidine and spermine are found in a wide variety of animals, bacteria, yeasts and plants and are associated with a tremendous variety of biological activity. For example, they have been proposed to stabilise membranes such as *E-coli* spheroplasts [2], isolated mitochondria [3], to facilitate transfection by phage DNA of *E-coli* spheroplasts,[4] and to modulate membrane functions [5]. They also play important roles in proliferative processes.[6] In particular, they were shown to be involved in the processes of neoplastic growth [1,6] as well as, in chemical carcinogenesis.[7] In this regard, an interesting observation was that in dividing cells, in particular in cancerous cells, the level of polyamines such as putrescine, spermidine and spermine was substantially higher than in other cells.[8] Based on these observations, the control and the modification of polyamines level was exploited in chemotherapy.[9] Many polyamines analogues have been prepared and their inhibition effects tested.[10] The control of polyamines level has been also explored by blocking their biosynthesis using D,L-α-difluoromethylornithine (DFMO)[11], the most well known specific inhibitor of ornithine decarboxylase.[12]

We report here the design and synthesis of a series of spermidine and spermine analogues named cyclospermidine [4,n] and cyclospermine [4,n] respectively. Our design was based on the rigidification of spermidine and spermine structures by interconnection of their two secondary amines with a $-(CH_2)_n-$ (n = 3, 4, 5) bridge. Thus, these compounds are all based on a cycloputrescine [4,n] core (**1-3**). In the case of

cyclospermidines [4,n] **4,5**, their corresponding cycloputrescines [4,n] (n = 4, 5) were monofunctionalized with one aminopropyl fragment, whereas for the cyclospermines [4,n] **6-8**, both secondary amino functions of



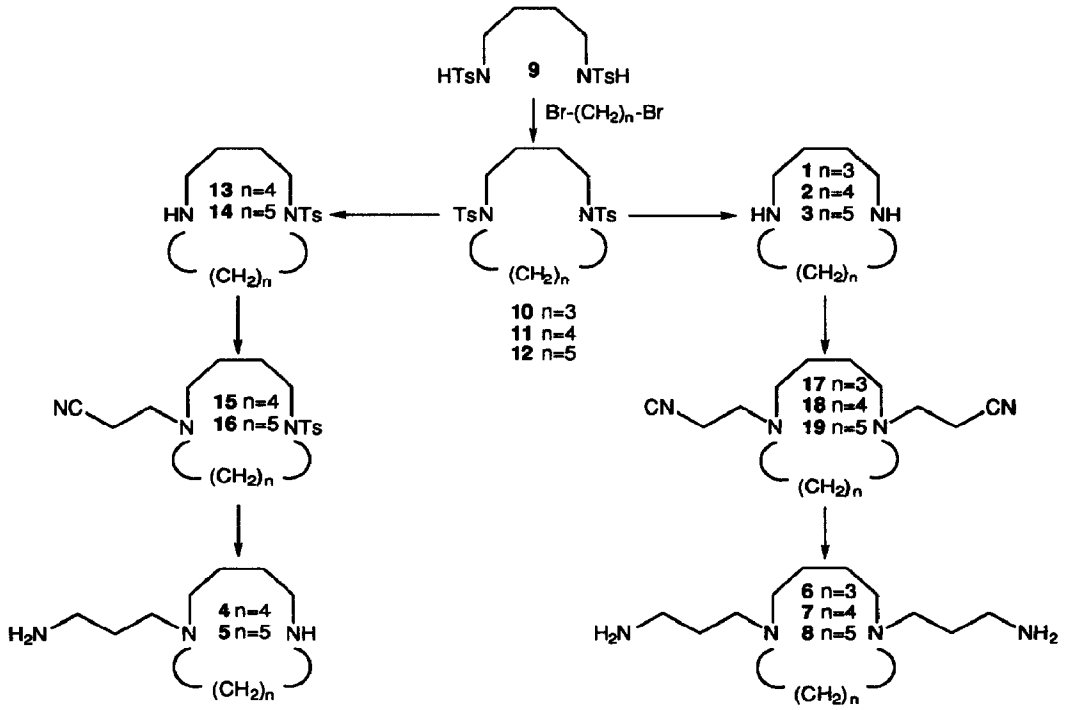
1 n=3; [4,3]cycloputrescine
2 n=4, [4,4]cycloputrescine
3 n=5, [4,5]cycloputrescine

4 n=4, [4,4]cyclospermidine
5 n=5, [4,5]cyclospermidine

6 n=3, [4,3]cyclospermine
7 n=4, [4,4]cyclospermine
8 n=5, [4,5]cyclospermine

the cycloputrescines [4,n] (n = 3, 4, 5) bear an aminopropyl moiety. Our aim being that these compounds either inhibit the transport of circulant polyamines from outside into the cell, or, if transported, being structural analogues, they may alter cell functions and they may inhibit or at least decrease tumour cells proliferation.

Our strategy for the synthesis of cyclospermidine **4,5** and of cyclospermidine **6-8** was based on a stepwise and convergent scheme starting from putrescine. After diprotection of the latter with tosyl group (compound **9**), the medium size cycles **10-12**[13] were obtained in 8-18 % yield by treatment of the disodium salt of **9** with Br-$(CH_2)_n$-Br; n = 3-5 in DMF, following the Richmond and Atkins cyclization procedure.[14] **10-12** were the common intermediates for the synthesis of both cyclospermidines and cyclospermines. Attempts to increase the reaction yield by modification of the cyclization conditions failed. For example the use of K_2CO_3 or Cs_2CO_3 or different addition rate of the dibromo compound did not improve the yield. Since **10-12** are medium size cycles with a ring size of 9 to 11, the results obtained are not surprising. Using the same type of reaction, the effect of the ring size on the yield has been extensively studied by Kellog et al. .[15] Our strategy for the preparation of **4** and **5** required first the synthesis of the monoprotected compounds **13** and **14**.



The synthesis of these two compounds was based on an interesting observation during the deprotection of **10-12** to **1-3** using the standard HBr/AcOH/phenol method.[16] Indeed, the treatment of **11** and **12** by this mixture afforded the monoprotected compounds **13** and **14** in rather high yields.[17] The introduction of the aminopropyl fragment was achieved in two steps by first treatment of **13** or **14** by acrylonitrile[18] in toluene, affording nitriles **15** and **16** in high yields[19], followed by a $LiAlH_4$ reduction in THF of the cyano group to the primary amine **4** and **5**.[20] For the synthesis of **6-8**, cycloputrescines **1-3** were first prepared by the Li/NH_3 reductive cleavage of the tosyl groups. **1-3** were also previously prepared using many different methods.[21] The double alkylation of **1-3** by acrylonitrile afforded the dicyano compounds **17-19**[22] which were transformed into the desired **6-8** [23] by treatment with BH_3/THF.

The biological effects of **1-8** as well as their protonation constants will be reported elsewhere.

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13. **General procedure for the synthesis of 10-12.**: In a 1 l flask dry MeOH (400 ml) and Na (2.9 g, 126 mmol) were stirred until dissolution. To the sodium methoxide solution thus obtained, **9** (20 g, 50.4 mmol) was added and the mixture stirred under N_2 at 60 °C for 2 h. before the solvent was removed. To the white solid DMF (400 ml) was added and the mixture stirred under N_2 at 110 °C before the α,ω-dibromo compound (1.1 eq.) was added dropwise (60 min) and the mixture further stirred at 100 °C overnight. The solvent was removed leaving an oil which was dissolved in CH_2Cl_2 (200 ml) and washed successively with H_2O (100 ml), aqueous NaOH (100 ml, 2.5 N) and aqueous HCl (100 ml, 10%). The organic layer was dried ($MgSO_4$). Filtration over alumina and removal of the solvent left a solid which was recrystallized from hexane/$CHCl_3$. The crystals obtained were further purified by chromatography (Al_2O_3, CH_2Cl_2/hexane). For all compounds satisfactory elementary analysis on C, H, and N were obtained.

    10 : 1,3-dibromopropane (7.6 g, 37.6 mmol), yield = 8.5 % (2.6 g). M. P. > 250 °C (decomp.); ^{1}H-NMR ($CDCl_3$) : 1.87 (br.t, 4H, $NCH_2CH_2CH_2CH_2N$), 2.21 (q, 2H, $NCH_2CH_2CH_2N$), 2.44 (s, 6H, CH_3); 3.08-3.16 (br.m, 8H, NCH_2), 7.30-7.35, 7.66-7.69 (m, 8H, arom.); ^{13}C-NMR ($CDCl_3$) : 21.6 (CH_3), 21.9, 25.2, 44.7, 50.6 (CH_2), 127.6, 129.8, 134.1, 143.6 (arom.).

    11: 1,4-Dibromobutane (10.9 g, 50.5 mmol), yield = 16 % (5.5 g). M. P. > 250 °C (decomp.): ^{1}H-NMR ($CDCl_3$) : 2.01 (br. q, 8H, NCH_2CH_2); 2.43 (s, 6H, CH_3), 3.19 (br.t, 8H, NCH_2), 7.29-7.33, 7.63-7.66 (m, 8H, arom.); ^{13}C-NMR ($CDCl_3$) : 21.6 (CH_3), 24.9, 51.1 (CH_2), 127.6, 129.7, 134.2, 143.4 (arom.).

    12: 1,5-Dibromopentane (11.6 g, 50.4 mmol), yield = 14 % (4.9 g). M. P. > 250 °C (decomp.); ^{1}H-NMR ($CDCl_3$) : 1.58 (br.q, 2H, $CH_2CH_2CH_2N$); 1.89 (br.m, 8H, NCH_2CH_2), 2.42 (s, 6H, CH_3), 3.08 (br.m, 8H, NCH_2), 7.28-7.32, 7.63-7.67 (m, 8H, arom.); ^{13}C-NMR ($CDCl_3$) : 21.6 (CH_3); 24.2, 25.4, 28.5, 51.1, 52.1 (CH_2), 127.4, 129.7, 135.3, 143.3.(arom.).
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17. **General procedure for the synthesis of 13 and 14.**: In a 500 ml flask **11** or **12**, phenol (2 g), and HBr/AcOH (130 ml, 33 %) were heated to 80 °C for 16 h. The mixture was allowed to cool to r. t. before ether (250 ml) was added and the precipitated hydrobromide salt was filtered and further washed with ether (3x100ml). The coloured solid was passed over a

Dowex anion exchange resin in its basic form (H_2O/EtOH: 50/50) affording the desired pure compound **13** or **14** as white solids.

13: **11** (5.55 g, 12.3 mmol), yield = 68 % (2.5g). ^{1}H-NMR ($CDCl_3$) : 1.19 (br.t, 1H, NH), 1.61 (br.m, 4H, C*H*$_2$CH$_2$NH), 1.77 (br.m, 4H, C*H*$_2$CH$_2$NTs), 2.31 (s, 3H, *CH*$_3$), 2.73 (br.m, 4H, CH$_2$*H*NH); 3.03 (br.t, 4H, C*H*$_2$NTs), 7.18, 7.22, 7.52, 7.56 (m, 4H, H arom.); ^{13}C-NMR ($CDCl_3$) : 21.5 (CH_3), 25.5, 26.2, 47.5, 51.0 (CH_2), 127.8, 129.5, 133.5, 143.2 (arom.).

14: **12** (4.9 g, 10.5 mmol), yield = 52% (1.7 g). ^{1}H-NMR ($CDCl_3$) : 1.65-1.85 (br.m, 10H, C*H*$_2$C*H*$_2$CH$_2$N, C*H*$_2$CH$_2$N), 2.42 (s, 3H, *CH*$_3$), 2.82-2.89 (br.m, 4H, C*H*$_2$NTs), 3.06-3.12 (br.m, 4H, C*H*$_2$NH), 7.28, 7.32, 7.65, 7.69 (m, 4H, H arom.); ^{13}C-NMR ($CDCl_3$) : 21.5 (CH_3), 24.8, 25.5, 26.3, 27.4, 28.0, 48.0, 48.7, 50.0, 50.3 (CH_2), 127.3, 129.6, 135.9, 143.0 (arom.).

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19. **General procedure for the synthesis of 15 and 16.**: In a 250 ml flask, **13** or **14** in dry toluene (80ml) and acrylonitrile (16ml) were refluxed. The reaction was followed by TLC and after 5 days, the liquid was separated and the residue washed with toluene. Washes were combined with the supernatant and the solvent removed affording a solid. The desired compounds **15** and **16** were obtained after chromatography (Al_2O_3, CH_2Cl_2) and were recrystallized from CH_2Cl_2/hexane.

15: **13** (2.2 g, 7.4 mmol), yield 96 % (2.5 g). M. P. = 112 °C, ^{1}H-NMR ($CDCl_3$) : 1.56 (br.t, 2H, C*H*$_2$CN); 1.86 (br.m, 8H, C*H*$_2$C*H*$_2$N); 2.42 (s, 3H, *CH*$_3$), 2.48 (br.t, 2H, NC*H*$_2$CH$_2$CN), 2.62 (br.t, 4H, C*H*$_2$NTs), 3.0 (t, 4H, C*H*$_2$N), 7.28, 7.32, 7.60, 7.64 (m, 4H, H arom.); ^{13}C-NMR ($CDCl_3$) : 15.9 (CH_2CN), 21.5 (CH_3), 23.7, 24.6, 49.8, 50.6, 51.1 (CH_2), 119.5 (CN), 127.7, 129.6, 133.4, 143.3 (arom.).

16: **14** (1.4 g, 4.5 mmol), yield 92 % (1.5 g). M. P. = 116 °C, ^{1}H-NMR ($CDCl_3$) : 1.55 (br.m, 2H, C*H*$_2$CN), 1.69-1.97 (br.m, 10H, C*H*$_2$C*H*$_2$N), 2.42 (s, 3H, *CH*$_3$)), 2.46-2.55 (br.m, 2H, NC*H*$_2$CH$_2$CN), 2.74 (t, 4H, C*H*$_2$NTs), 3.06 (t, 4H, C*H*$_2$N), 7.26, 7.31, 7.64, 7.68 (m, 4H, H arom.); ^{13}C-NMR ($CDCl_3$) : 16.2 (CH_2CN), 21.5 (CH_3), 24.3, 25.1, 25.4, 26.0, 28.2, 51.4, 52.6, 55.0 (CH_2), 119.4 (CN), 127.3, 129.6, 135.7, 143.0 (arom.).

20. **General procedure for the synthesis of 4 and 5**: **15** or **16** was refluxed with 20 eq. of $LiAlH_4$ in THF for 6 days. 100 eq of NaF was added, the excess of $LiAlH_4$ was destroyed with a H_2O/THF : 50/50 mixture. The slurry was filtered and the solid washed with hot $CHCl_3$. The filtrate and washes were combined and evaporated affording an oil which was dissolved in a mixture of MeOH/conc. HCl (50:50, 100 ml) and further washed with $CHCl_3$ (3x100 ml). The desired hydrochloride salts of cyclospermidines **4** and **5** were obtained as oils after evaporation of the aqueous phase.

4: **15** (0.98 g, 2.88 mmol), yield = 90 % (0.80 g). ^{1}H-NMR (D_2O) : 1.95-2.15 (br.m, 10H, C*H*$_2$CH$_2$N), 2.72-3.6 (br. m, 12H, C*H*$_2$N). ^{13}C-NMR (D_2O) : 22.6, 24.1, 36.5, 45.2, 51.8, 52.9, 56.0 (CH_2).

5: **16** (1.1 g, 3.03 mmol), yield = 70 % (0.68 g). ^{1}H-NMR (D_2O) : 1.83-2.09 (br.m, 12H, C*H*$_2$C*H*$_2$CH$_2$N), 3.22-3.50 (br.m, 12H, C*H*$_2$N). ^{13}C-NMR (D_2O) : 21.9, 23.1, 24.2, 38.9, 47.4, 53.5, 59.7 (CH_2).

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22. **General procedure for the synthesis of 17-19**: In a 250 ml flask, toluene, **1**,**2** or **3** and acrylonitrile (20 eq.) were refluxed under N_2 for 10 days. The solvent was removed and the solid was taken up in CH_2Cl_2 and washed with H_2O (3x20 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The desired compounds were obtained by chromatography (Al_2O_3, CH_2Cl_2).

17: **1** (2.5 g, 19.5 mmol), yield = 29 % (1.34 g). ^{1}H-NMR ($CDCl_3$) : 1.30 (q, 2H, NCH$_2$C*H*$_2$CH$_2$N), 1.62 (br.m, 4H, C*H*$_2$CH$_2$N), 2.37 (br.m, 8H, C*H*$_2$C*H*$_2$CN); 2.61-2.70 (br.m, 8H, C*H*$_2$N); ^{13}C-NMR ($CDCl_3$) : 16.8 (*C*H$_2$CN), 22.3, 27.5, 46.7, 52.3, 53.5 (CH_2), 119.6 (CN).

18: **2** (1.0 g, 7.8 mmol), yield = 33 % (0.61 g). ^{1}H-NMR ($CDCl_3$) : 1.68 (br.m, 8H, C*H*$_2$CH$_2$N), 2.45 (br.m, 4H, C*H*$_2$CN), 2.51 (br.m, 4H, C*H*$_2$CH$_2$CN), 2.63 (br.m, 8H, C*H*$_2$N); ^{13}C-NMR ($CDCl_3$) : 15.5 (CH_2CN), 24.1, 49.6, 51.6 (CH_2), 119.6 (CN).

19: **3** (1.4 g, 9.0 mmol), yield = 21 % (0.50 g). ^{1}H-NMR ($CDCl_3$) : 1.55 (br.m, 10H, C*H*$_2$C*H*$_2$CH$_2$N), 2.40 (br.m, 12H, C*H*$_2$CN), 2.64 (t, 4H, C*H*$_2$CN); ^{13}C-NMR ($CDCl_3$) : 15.7 (CH_2CN), 24.9, 25.9, 26.3, 50.7, 53.6, 54.5 (CH_2), 119.6 (CN).

23. **General procedure for the synthesis of 6-8**: **17**, **18** or **19** was refluxed in BH_3/THF (15 eq. , 1M) for 2 days. The excess of BH_3 was cautiously destroyed with H_2O/THF : 50/50 mixture before the solvents removed. To the residue a solution of H_2O/MeOH/HCl : 1/6/1 was added and the mixture refluxed for 6 h. The mixture was evaporated to dryness and the residue coevaporated with absolute EtOH before it was taken up in aqueous NaOH (100 ml, 2.5 N) and extracted with CH_2Cl_2. The desired tetraamine was obtained as an oil after removal of the solvent. Compounds **6**-**8** were stored as their hydrochloride salts.

6: **17** (1.2 g, 5.1 mmol), yield = 70 % (1.4 g). ^{1}H-NMR (D_2O) : 2.29 (br.m, 10H, C*H*$_2$CH$_2$N); 3.29-3.70 (br.m, 16H, C*H*$_2$N). ^{13}C-NMR (D_2O) : 22.8, 24.7, 26.1, 39.1, 55.4, 57.0, 58.4 (CH_2).

7: **18** (0.30 g, 1.2 mmol), yield = 90 % (0.45 g). ^{1}H-NMR (D_2O) 2.26 (br.m, 12H, C*H*$_2$CH$_2$N); 3.35-3.80 (br.m, 16H, C*H*$_2$N). ^{13}C-NMR (D_2O) : 2.24 (br.m, 14H, C*H*$_2$CH$_2$N); 3.24-3.70 (br.m, 16H, C*H*$_2$N); ^{13}C-NMR (D_2O) : 26.1, 28.4, 39.7, 53.8, 57.4 (CH_2).

8: **19** (0.50 g, 1.9 mmol), yield = 92 % (0.83 g). ^{1}H-NMR (D_2O) : 2.24 (br.m, 14H, C*H*$_2$CH$_2$N); 3.24-3.70 (br.m, 16H, C*H*$_2$N); ^{13}C-NMR (D_2O) : 25.0, 25.9, 26.1, 31.3, 40.7, 52.9, 53.8, 54.7 (CH_2).

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