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GENERAL ROUTES FOR THE SYNTHESIS OF MONO, DI AND TRI-N-SUBSTITUTED DERIVATIVES OF CYCLAM

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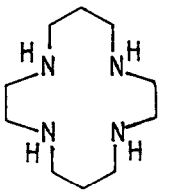
Abstract - The selective synthesis of N-substituted derivatives of 1,4,8,11-tetraazacyclotetradecane may be achieved through N-tosyl or N-benzyl intermediates, permitting for example the synthesis of 1,8 disubstituted derivatives.

The fourteen membered tetrazamacrocycle, 1,4,8,11-tetraazocyclotetradecane (cyclam) continues to attract interest as a versatile ligand in inorganic coordination chemistry.[1,2] The selective functionalisation of the basic ligand skeleton at both carbon[2,3] and nitrogen[4,5] has permitted the study of a series of derivatives and has broadened the utility of this system in catalysis and metal ion discrimination. Although there are isolated examples of N-functionalised derivatives of cyclam 1, no general synthetic routes have been developed other than the use of the tritosylamide 2[5] for the preparation of some monofunctionalised derivatives. During the course of studies directed towards the selective attachment of functionalised poly-aza macrocycles to monoclonal antibodies for tumour targetting,[2] we have developed some straightforward syntheses, often from the parent 1, that permit the preparation of any given mono, di or trisubstituted derivative of cyclam.

The mono-substituted N-alkyl derivatives e.g. 3-6 are prepared by reaction of the alkyl halide with excess cyclam (1:10) in chloroform and in the presence of K_2CO_3. Excess cyclam is removed by filtration following repeated ether extraction of the residue and is conveniently recycled following sublimation. An alternative approach which has been developed recently[5] involves formation of the tritosylamide 2. Alkylation of the secondary amine proceeds efficiently with alkyl halide in acetonitrile in the presence of Na_2CO_3, and the tosyl groups may be subsequently removed by HBr/AcOH in the presence of phenol or using Li/l.NH_3/EtOH/THF. The o-hydroxybenzyl derivative 7 was prepared following this sequence.

The formation of trisubstituted derivatives from the mono N-benzyl derivatives is aided by the ease of hydrogenolysis of the tertiary benzylic C-N bond.[6] Reaction of 4, for example, with bromoacetic acid in aqueous base led to formation of the triacid 8 which was purified by ion-exchange hplc. Minor amounts of the isomeric diacids and mono-acids could also be separated by hplc. Cleavage of the benzylic carbon-nitrogen bond proceeded smoothly (Pd/C; H_2; (3 atm); H_2O pH < 7; 20°C) to yield the triacid 9. In this particular case of the p-nitrobenzyl substituted triacid, 8, it was also possible to selectively reduce the aromatic nitro-group without concomitant hydrogenolysis, by effecting the reduction in basic media (pH > 10). The p-amino benzyl substituted triacid 10 was obtained, in this manner.



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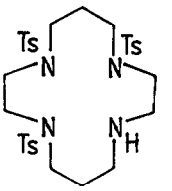

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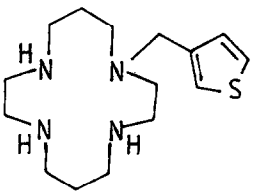

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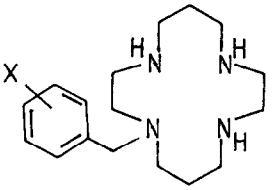
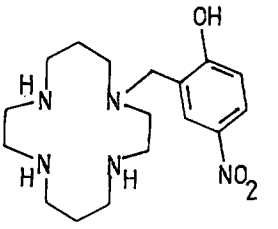


4 X = p-NO_2

5 a) X = p-CN; b) = m-CN

6 X = p-CH_2NH_2



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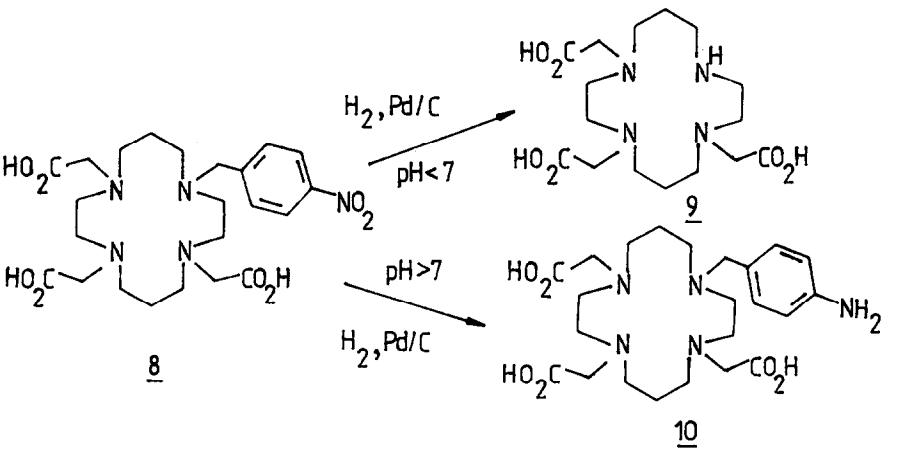

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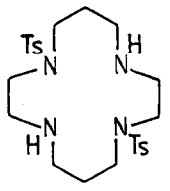
and ^{13}C nmr methods, and in the case of 11 by crystallographic analysis of a derivative. Thus, the 1,11 derivative, 12, may be distinguished from the 1,4 isomer 13 by virtue of its symmetry: for example the C-6 and C-13 methylene groups are homotopic and isochronous for 13 but are consitutionally heterotopic in 12 ($\delta_C(CDCl_3)$ = 29.0, 26.4 ppm, $\delta_H(CDCl_3)$ = 1.96, 2.02 ppm). We did not succeed in isolating 13, presumably it is formed in very low yield ($\leq$ 3.5%), under these reaction conditions. A simpler and higher yielding route to the 1,11 derivative 12 involves the intermediacy of the 'dioxo-cyclam' 14, obtained by condensation of diethyl malonate with 1,4,8,11-tetraazaundecane. Tosylation of 14 (Et_3N, CH_2Cl_2, TsCl) followed by reduction with BH_3.THF affords 12 in good yield. The ditosylamide 12 may then be used for the synthesis of any 1,11-disubstituted derivative.



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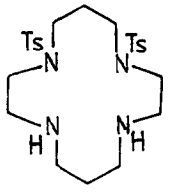

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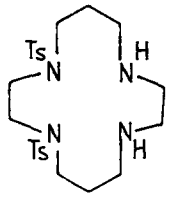

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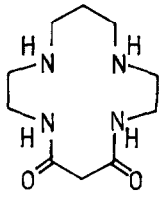
The structure of 11 has been subsequently verified by an X-ray crystal structure determination of the copper(II) complex of the derived diacid.[7] Reaction of 11 with ethyl



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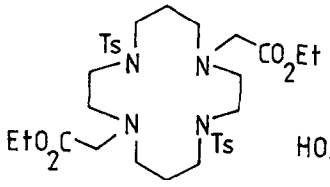

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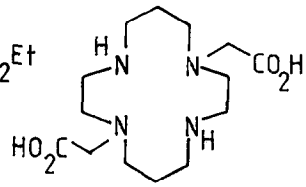

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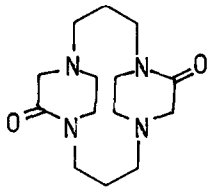

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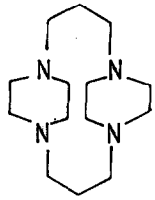

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bromoacetate in acetonitrile in the presence of sodium carbonate gave the diester 15 which was converted into the diacid 16 by treatment with HBr/AcOH in the presence of phenol. The diacid was isolated by filtration from the mixture as the hydrobromide salt. This was most convenient as in aqueous or alcoholic solution the diacid quickly lactamises to form the tricyclic lactam, 17. The consitution of the diacid and of the lactam was confirmed by the X-ray crystallographic analysis. The lactam 17 is remarkably resistant to acidic hydrolysis and may be recovered unchanged after boiling in 6 M HCl (36 h). Although the crystallographic analysis (Figure 1)[7] revealed that the 'E' stereoisomer was formed, lactamisation proceeds in solution to give an approximately 65:35 mixture of the 'E' and 'Z' diastereoisomers, as deduced by ^1H nmr integration. The resistance of the tricyclic lactam 17 to acid hydrolysis may be related to steric hindrance to the approach of a water molecule to the faces of the protonated amide carbonyl: attack at the Re face is hindered by the ring topology and the axial hydrogens in the half-chair six membered rings inhibit attack at the Si face. In some preliminary work reduction of 16 with excess BH_3.THF affords the tricyclic tetraamine 18, which forms a kinetically inert complex with copper(II) (λ_{max} (H_2O) = 538 nm), which is resistant to attack by H_2S i.e. no CuS was precipitated when H_2S was passed through an aqueous solution of the complex.

In summary, these simple methods afford practicable routes to mono, di or tri-N-functionalised derivatives of cyclam.

EXPERIMENTAL

Proton and carbon nmr spectra were recorded on a Bruker AC 250 (250.13 MHz and 62.1 MHz) spectrometer. Chemical shifts are quoted to higher frequency of Me_4Si as internal standard and are given in ppm, with coupling constants in Hz. Infra-red spectra were recorded on a Perkin-Elmer 580A Infrared Spectrophotometer, and mass spectra were recorded either in the EI, CI, DCI or FAB mode using a VG 7070E spectrometer. Thin-layer chromatography was used (Merck $60F_{254}$) to follow the reactions, and column chromatography was effected using Merck 60 7354 or 9385 for flash chromatography. HPLC analyses were carried out with a Varian 5500 instrument using both ion exchange (TSK DEAE) or reverse phase (Hypersil 5005) columns for analytical or semi-prepartive work typically using aqueous acetate/CH_3CN gradient elution. Compounds that did not give correct combustion microanalyses were examined for their purity by t.l.c. and/or HPLC and were $\geq$ 96% homogeneous.

N,N',N''-tris(p-toluenesulphonyl)-1,4,8,11-tetraazacyclotetradecane (2)

This was prepared following a similar method to that of Fabbrizzi[5] by reaction of cyclam (1) (1.0 g, 5 mmol) with p-toluenesulphonyl chloride (2.0 g, 10.4 mmol) in dichloromethane (100 cm^3) in the presence of triethylamine (1.1 g, 11 mmol), and the mixture was stirred for 3 h at 20°C. Solvent was removed under reduced pressure and the residue chromatographed on silica gel (CH_2Cl_2:MeOH; 100:1) to yield a colourless solid which was recrystallised from hot toluene (1.15 g, 51%) mp 85-7°C. Found: C, 56.4; H, 6.40; N, 8.21; S, 15.0. $C_{31}H_{41}N_4O_6S_3$ requires C: 56.3; H, 6.20; N, 8.47; S, 14.5. $\delta_H(CDCl_3)$ 1.54 (2H, quint, J = 7.4 Hz), 1.65 (2H, quint, J = 7.3), 1.92 (2H, mult), 2.36 (9H, brs), 2.55 (2H, mult), 2.70 (2H, mult), 3.26-3.00 (10H, mult)m 7.26-7.17 (6H, d+d+d), 7.65-7.55 (6H, d+d+d). $\delta_C(CDCl_3)$ 142.5, 135.7, 134.6, 133.9, 128.7, 126.1; 50.3, 48.2, 47.7, 47.2, 46.8, 46.4, 45.0, 44.4 (CH_2N); 28.6 (CH_2C), 20.4 (CH_3). m/e (CI-NH_3) 662 (M+1), 661 (M^+).

1,8-N,N'-Bis(toluenesulphonyl)-1,4,8,11-Tetraazacyclotetradecane (11)

This was prepared as described for 2, but using only 1.5 equivalents of tosyl chloride and effecting the reaction at 5°C (18 h). Separation of the ditosylated product from 2 was effected by flash chromatography on silica gel (R_f (SiO_2, 10% MeOH in CH_2Cl_2): 11, 0.45; 2, 0.7) to yield a colourless solid (0.57 g, 30%) mp 256-7°C. $\delta_H(CDCl_3)$ 2.19 (4H, quint), 2.42 (6H, s), 3.15-3.10 (12H, mult), 3.30 (4H, mult), 7.33 (4H, d, J 7.1), 7.64 (4H, d), $\delta_C(CDCl_3)$ 143.1, 131.6, 128.8, 126.4; 48.6, 48.5, 47.6, 45.0 (CH_2N), 24.8 (CH_2), 20.3 (CH_3). m/e (DCI, NH_3) 509 (M^++1), 508 (M^+). Found C, 56.6; H, 6.92; N, 11.4; S, 12.2. $C_{24}H_{34}N_4O_4S_2$ requires: C, 56.7; H, 6.69; N, 11.0; S, 12.6.

A small quantity of the constitutional isomer 12 was also produced in this reaction which could be separated by flash chromatography [R_f (SiO_2: 10% MeOH in CH_2Cl_2) 0.4], to yield a glassy solid (66 mg, 3.5%) $\delta_H(CDCl_3)$ 1.96 (2H, mult J = 5.1), 2.02 (2H, mult), 2.44 (6H, s), 3.06-2.96 (6H, mult), 3.15 (2H, mult), 3.26 (4H, t, J = 5.6), 3.34 (4H, mult), 7.37 (4H, d, J =7.2), 7.67 (4H, d). $\delta_C(CDCl_3)$ 143.8, 134.5, 129.9, 127.4; 49.9, 49.4, 49.0, 48.6 (CH_2N); 29.0, 26.4 (CH_2), 21.5 (CH_3). A higher yielding route to this 1,11-ditosylamide 12 is as follows:

1,11-N,N'-Bis(toluenesulphonyl)-1,4,8,11-tetraazacyclotetradecane, (12)

To dioxo-cyclam (912 mg, 4 mmol) in dichloromethane (100 cm^3) was added p-toluene sulphonyl chloride (1.915 g, 10 mmol) and triethylamine (1.01 g) and the solution was stirred for 18 h at 45°C. A white solid precipitated from solution and was filtered off, washed with ether and chloroform and dried to yield the diamide (1.67 g, 79%) mp > 240°C. Found: C, 53.4; H, 5.80; N, 9.61; S, 11.5. $C_{24}H_{32}N_4O_6S_2$ requires C, 53.7; H, 5.55; N, 9.72; J, 11.1. i.r. (Nujol) 3300 (NH), 1663 (CO). m/e (CI) 537 (M^++1), 536 (M^+), 447, 446, 381, 352. $\delta_H(CDCl_3)$: 7.66 (4H, d, J = 8.2), 7.36 (4H, d), 6.94 (2H, brt, NHCO), 3.59 (4H, mult), 3.25 (2H, s, CH_2CO) 3.13 (4H, brt, CH_2CN), 2.96 (4H, brt, CH_2N), 2.47 (6H, s, CH_3), 1.55 (2H, quint CH_2C).

The diamide (536 mg, 1.0 mmol) was treated with a solution of borane in THF (20 cm^3, 1 M solution) and boiled under nitrogen (42 h). After cooling to 0°C, excess borane was destroyed by careful addition of methanol (2 cm^3) and volatiles removed under reduced pressure. The residue was treated with 6 M hydrochloric acid (20 cm^3) and boiled (3 h, bath temp 110°C), evaporated, the residue taken up in 2 M KOH (10 cm^3) and extracted with dichloromethane (4 x 20 cm^3), dried (K_2CO_3) and evaporated to yield a colourless residue which was chromatographed on flash silica gel (10% MeOH/CH_2Cl_2) to yield a glassy solid (300 mg, 65%), identical to that obtained above.

N-(3-thienyl)-1,4,8,11-tetraazacyclotetradecane, (3)

To a solution of cyclam (1, 2.0 g, 10 mmol) in chloroform (100 cm^3) was added a solution of 3-bromomethylthiophene (177 mg, 1.0 mmol) in chloroform (10 cm^3) and potassium carbonate (2 g), and the mixture was stirred at 20°C (18 h). After removal of solvent under reduced pressure, the residue was extracted with diethyl ether (3 x 30 cm^3), the ether extracts were combined and solvent evaporated under reduced pressure and the procedure was repeated three times, yielding a colourless oil (207 mg, 70%). Found: C, 61.2; H, 9.30; S, 10.5; N, 19.3. $C_{15}H_{28}N_4S$ requires C, 60.8; H, 9.46; S, 10.8; N, 18.9. m/e (NH_3, CI) 298 (M^++2), 297 (M^++1), 199. $\delta_H(CDCl_3)$ 7.06 (1H, d), 7.04 (2H, mult), 3.66 (2H, s), 2.85-2.40 (16H, mult), 2.35 (3H, brs, NH), 1.85 (2H, quint, J = 5.1), 1.70 (2H, quint, J = 5.3). $\delta_C(CDCl_3)$ 139.0, 128.7, 125.1, 122.7; 54.9, 53.1, 51.7, 50.9, 49.5, 49.1, 48.1, 47.5 (CH_2N); 29.0, 26.3 (CH_2C). Unused cyclam may be recovered (typically 70%) by sublimation (0.01 mmHg, 80°C), from the residues.

N-(4-nitrobenzyl)-1,4,8,11-tetraazacyclotetradecane (4)

This was obtained in an identical manner to that described above for preparation of 3, yielding a pale yellow solid (246 mg, 72%), m.p. 31-33°C. m/e (NH_3, CI) 345 (M^++2), 344 (M^++1), 343 (M^+), 199. δ_H 8.08 (2H, d), 7.50 (2H, d), 3.58 (2H, s), 2.89-2.32 (19H, mult, CH_2N + NH), 1.80 (2H, quint), 1.62 (2H, quint). $\delta_C(CDCl_3)$ 147.1, 129.9, 129.5, 123.3, 57.6, 54.8, 53.5, 50.9, 49.3, 49.1, 48.6, 47.8, 47.1 (CH_2N); 28.2, 26.0 (CH_2C).

N-(4-cyanobenzyl)-1,4,8,11-tetraazacyclotetradecane (5a)

This was prepared as described for 3, to yield a colourless solid, (257 mg, 82%) mp 88-90°C. Found: C, 68.5; H, 9.59; N, 22.0. $C_{18}H_{29}N_5$ requires: C, 68.6; H, 9.21; N, 22.2. m/e (NH_3, CI) 317 (M^++2), 316 (M^++1), 315 (M^+), 216, 199. $\delta_H(CDCl_3)$ 7.59 (2H, d), 7.50 (2H, d), 3.61 (2H, s, CH_2Ar), 2.86-2.45 (19H, mult, CH_2N + NH), 1.86 (2H, quint), 1.71 (2H, quint). $\delta_C(CDCl_3)$ 144.9, 131.8, 129.3, 119.0, 110.5 (CN); 57.7, 55.1, 53.4, 50.1, 49.2, 49.0, 48.6, 47.9, 47.1 (CH_2N); 28.5, 26.1.

N-(3-cyanobenzyl)-1,4,8,11-tetraazacyclotetradecane (5b)

This was prepared as described above to yield a colourless solid (230 mg, 73%), mp 89-90°C. Found: C, 68.6; H, 9.59; N, 22.3. $C_{18}H_{29}N_5$ requires: C, 68.6; H, 9.21; N, 22.2. i.r. (Nujol) 3300 (br, NH), 2215 (CN), 1140, 1120, 880, 745. m/e (NH_3, CI) 316 (M^++1), 315 (M^+). δ_H 7.94 (1H, br.s), 7.52 (2H, dd), 7.39 (1H, brd), 3.58 (2H, s), 2.90 (2H, mult), 2.88-2.58 (15H, mult, CH_2N + NH), 2.45 (2H, mult), 1..86 (2H, quint), 1.69 (2H, quint).

N-(4-aminobenzyl)-1,4,8,11-tetraazacyclotetradecane (6)

The nitrile 5a (200 mg, 0.65 mmol) was treated with borane-tetrahydrofuran (7 cm^3, 7 mmol) and the solution was boiled under nitrogen (18 h). After quenching the excess borane with methanol (1 cm^3), solvents were removed under reduced pressure and the residue was treated with boiling 6 M HCl (20 cm^3, 3 h). After removal of solvents under reduced pressure, the solution was basified to pH 12 (10 cm^3, 6 M KOH), and extracted with dichloromethane (3 x 20 cm^3), from evaporation of which a colourless oil was obtained (177 mg, 85%). m/e (NH_3, CI): 321 (M^++2), 320 (M^++1), 220. $\delta_H(CDCl_3)$ 7.22 (2H, d), 7.16 (2H, d), 3.76 (2H, s, CH_2Ar), 3.49 (2H, s, CH_2Ar), 2.70-2.30 (21 H, CH_2N+NH), 1.78 (2H, quint), 1.60 (2H, quint). $\delta_C(CDCl_3)$ 141.9, 137.2, 129.4, 126.7; 57.4, 54.4, 53.3, 50.8, 49.4, 49.2, 48.9, 47.9, 47.3, 45.3 (CH_2N); 28.5, 25.2.

N-(5-nitro-2-hydroxybenzyl)-1,4,8,11-tetraazacyclotetradecane (7)

To a solution of 2 (0.53 g, 0.8 mmol) in dichloromethane (60 cm^3) was added triethylamine (0.11 g, 1.1 mol) and 2-hydroxy-5-nitrobenzyl bromide (0.19 g, 0.82 mmol) and the mixture was stirred at room temperature overnight. After filtration, solvent was removed under reduced pressure and the residue chromatographed on 'flash' silica gel (elutant 1% MeOH/CH_2Cl_2) to yield a glassy solid (0.59 g, 73%) R_f (SiO_2, 1% MeOH/CH_2Cl_2 = 0.25) i.r. (Nujol): 3400 (br, OH) 1610, 1590, 1520, 1330, 1280, 1165, 1090 cm^{-1}. $\delta_H(CDCl_3)$: 8.14 (1H, dd), 7.95 (1H, d), 7.70-7.60 (6H, mult), 7.38-7.26 (6H, mult), 6.89 (1H, d), 3.90 (2H, s), 3.26-3.14 (8H, mult), 3.09 (2H, t), 2.99 (2H, t), 2.93 (2H, t), 2.75 (2H, t), 2.46 (3H, s), 2.43 (3H, s), 2.42 (3H, s), 2.01-1.90 (4H, mult). $\delta_C(CDCl_3)$ 164.0 (ArC-O), 143.9, 143.7, 140.1, 134.9, 133.8, 133.5, 129.8, 127.5, 127.4, 127.1, 125.4, 124.8, 121.6, 116.5; 66.9, 58.0, 52.8, 51.1, 50.1, 48.8, 47.9, 47.3, 45.9, (CH_2N); 27.8, 24.5 (CH_2C); 21.4 (CH_3). m/e (NH_3, CI) 812 (M^++1), 811 (M^+), 662, 661. To the tritosylamide, obtained as above, (500 mg, 0.63 mmol) was added HBr in acetic acid (40%, 40 cm^3) and phenol (0.4 g), and the mixture was heated at 110°C (18 h). On cooling, a colourless precipitate formed which was collected by filtration, washed with diethyl ether (3 x 10 cm^3) and dried in vacuo (350 mg, 94%). mp 214-6°C; $\delta_H(D_2O)$ 7.78 (1H, d), 7.69 (1H, dd), 6.55 (1H, d), 3.75 (2H, D), 3.04-2.96 (8H, mult), 2.85-2.77 (8H, mult), 1.59-1.50 (4H, mult). $\delta_C(D_2O)$ 162.3 (C-O), 140.2 (C-N), 129.1, 128.4, 116.2, 116.1; 54.3 ($ArCH_2N$), 47.5, 44.3, 41.1, 40.7, 40.5, 36.9, 36.8, 18.5, 18.0 ppm.

1,4,11-tris(carboxymethyl)-8-(4-nitrobenzyl)-1,4,8,11-tetraazacyclotetradecane (8)

To a solution of 4 (0.57 g, 1.7 mmol) in ethanol (10 cm^3) at 0°C, was added a solution of sodium hydroxide (0.21 g) and bromoacetic acid (0.71 g, 5.1 mmol), in water (20 cm^3) and the mixture was stirred keeping the pH $\geq$ 10 and maintaining the temperature at 0°C (1 h). The mixture was stirred at 20°C (2 h) and then heated to 70°C (2 h). After cooling, c.HCl was added dropwise (pH ~ 3), and the solvents were removed under reduced pressure and the residue was passed down a short cation-exchange resin column (Amberlite 120, H^+ form). The eluates were concentrated and a pale-yellow solid precipitated slowly (pH ~ 3) and was collected by filtration and dried in vacuo (438 mg, 51%) m/e (fab, glycerol) 511 (M^++1), 510 (M^+), 374, 137, 107, 91. $\delta_H(D_2O)$ 8.05, (2H, d, J = 7.9), 7.54 (2H, d), 4.35 (2H, s, CH_2CO_2H), 4.01 (4H, s, CH_2CO_2H), 3.84 (2H, s, CH_2Ar), 3.6-2.8 (16H, mult., CH_2N), 2.03 (2H, quint, CH_2C), 1.89 (2H, quint, CH_2C).

1,4,11-tris(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane (9)

A solution of 8 (120 mg, 0.24 mmol) in water (10 cm^3, pH 4) was hydrogenated (18 h) (3 atm H_2, 20°C) over palladium on charcoal (10%, 50 mg). After filtration and removal of water in vacuo, a colourless glassy solid was obtained of the p-toluidinium salt of 9, (109 mg, 95%) $\delta_H(D_2O)$ 7.06 (2H, d, J = 8.2), 6.97 (2H, d, J = 8.2), 3.56-3.44 (4H, mult), 3.37 (2H, s), 3.25-3.18 (8H, mult), 3.03 (2H, mult), 2.89 (2H, mult), 2.74 (4H, mult), 2.05 (3H, s, CH_3), 1.91 (4H, mult). m/e (fab, glycerol) 108 $(CH_3\text{-}Ph\text{-}NH_3)^+$, 375 ($M^+$+1), 374 ($M^+$).

1,4,11-tris(carboxymethyl)-8-(4-aminobenzyl)-1,4,8,11-tetraazacyclotetradecane (10)

A solution of 8 (125 mg, 0.25 mmol) in water (10 cm^3, pH 11 [NaOH]) was hydrogenated (20 h), [3 atm H_2, 20°C] over palladium on charcoal (10%, 30 mg). After filtration and removal of water in vacuo, a glassy solid was obtained which was purified by hplc (TSK DEAE, 1.4 cm^3 min^{-1}, observed at λ = 268 nm, ternary gradient elution with A = H_2O, B = 1 M NH_4OAc (pH 7.3), C = CH_3CN starting from 75% A, 51% B, 20% C and stepping to 0% A, 80% B, 20% C after 30 minutes. The product eluted at 4.2 minutes and was re-injected on a Hypersil 5 ODS reverse phase column (A = 10 mM NH_4HCO_3, C = CH_3CN, 3 cm^3 min^{-1}, eluting with A = 95%, C = 58% and proceeding to A = 65%, C = 35% after 30 mintues) giving one single peak ($\geq$ 99%) at t = 9.7 minutes. $\delta_H(D_2O)$ 7.32 (2H, d, J = 8.4), 6.93 (2H, d), 4.18 (2H, s, CH_2), 3.77 (4H, s,

CH_2CO_2H), 3.42-2.84 (H, mult), 2.23 (2H, quint), 2.06 (2H, quint). m/e (fab, glycerol) 481 (M^++1), 480 (M^+), 375, 374.

1,8-N,N'-bis(toluenesulphonyl)-4,11-bis(carboethoxymethyl)-1,4,8,11-tetraazacyclotetradecane (15)

To a solution of 11 (0.508 g, 1 mmol) in dry acetonitrile (10 cm^3) was added anhydrous sodium carbonate (0.23 g, 2.1 mmol) and ethyl bromoacetate (0.35 g, 2.1 mmol). After boiling (18 h), the mixture was cooled, filtered and solvent removed under reduced pressure. The residue was chromatographed on 'flash' silica gel (eluting 3% MeOH in CH_2Cl_2) to yield a colourless solid (0.62 g, 91%) mp 128-9°C. Found: C, 56.2; H, 7.35; N, 8.01; S, 9.80. $C_{32}H_{48}N_4O_8S_2$ requires: C, 56.5; H, 7.06; N, 8.23; S, 9.41. $\delta_H(CDCl_3)$ 7.65 (4H, d), 7.27 (4H, d), 4.15 (4H, quart, CH_2O), 3.23 (4H, t), 3.15 (4H, t), 2.84 (4H, t), 2.64 (4H, t), 2.41 (6H, s, CH_3), 1.74 (4H, quint), 1.26 (6H, t, CH_3). $\delta_C(CDCl_3)$ 171.0 (CO_2R), 143.2, 136.3, 129.7, 127.2; 60.4, 55.7, 53.1, 51.6, 47.9, 47.8 (CH_2N); 27.1 (CH_2C), 21.5 (CH_3-Ar), 14.3 (CH_3). m/e (NH_3, DCI) 671 (M^++1), 680 (M^+).

1,8-N,N'-bis(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane (16)

To a solution of (15) [0.34 g, 0.5 mmol] in HBr-acetic acid (40%, 30 cm^3) was added phenol (0.2 g) and the mixture heated to 110°C for 36 h. After cooling to room temperature, a white precipitate formed which was collected by filtration, washed with ether (3 x 10 cm^3) and dried in vacuo to yield the dihydrobromide salt (143 mg, 60%). $\delta_C(D_2O)$ 178.6, (C=O), 59.1, 56.8, 51.8, 47.6 (CH_2N), 25.2 (CH_2C). $\delta_H(D_2O)$ 3.5-3.1 (12H, br mult, CH_2N+CH_2CO), 2.83 (8H, br s, CH_2N), 1.89 (4H, br s, CH_2C) m/e (fab, 3-nitrobenzyl alcohol) 317 (M^++1), 316 (M^+), 257, 199. The consitution of this diacid was confirmed by an X-ray crystallographic analysis of the copper(II) salt.[7]

5,18-Dioxo-1,5,8,12-tetraazatricyclo[10.2.2.2.^{5,8}]tetradecane (17)

A solution of the dihydrobromide salt of 16 (79 mg, 0.25 mmol) in 6 M hydrochloric acid (10 cm^3) was heated at 95°C (18 h). On cooling to 0°C, ethanol was added (5 cm^3) and a white precipitate of the dihydrochloride salt formed which was collected by filtration, and dried in vacuo (30 mg, 34%) m/e (NH_3, CI) 281$^+$ (M^++1), 280 (M^+). $\delta_H(D_2O)$ 4.46-4.13 (6H, mult), 3.91-3.83 (8H, mult, CH_2N), 3.57-3.44 (2H, mult), 3.20-3.12 (2H, dt+dt, J = 4.0), 3.37-3.32 (0.7 H, mult, Z-isomer), 2.92-2.79 (1.3 H, mult, E-isomer), 2.28-2.15 (4H, mult, CH_2C). One stereoisomer (E-isomer) was characterised by X-ray crystallography[7] and permitted partial assignment of the ^1H spectrum. A mixture of 65% E and 35% Z diastereoisomers were formed therefore, which do not interconvert in solution (300 K, 250 MHz). The lactam may also be isolated as the free base from solution as follows: removal of 6 M HCl yielded a residue which was taken up in water (2 cm^3), washed with chloroform, basified to pH $\geq$ 11 (NaOH) and extracted with dichloromethane (3 x 15 cm^3), dried (K_2CO_3) and evaporated to yield a colourless residue. i.r. (KBr) 1660 cm^{-1} (CO). $\delta_C(CDCl_3)$ 168.8 (major), 168.4 (minor), (amide carbonyl), 57.6 (major), 55.3 (major), 54.8 (minor), 51.2 (major); 50.3, 49.8, 47.2, 4.67 (all minor peaks), 45.8, 45.7 (both major); 21.7, 21.5 (both major). m/e (NH_3, CI) 281 (M^++1), 280 (M^+).

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