Vicinal Tetraamines of Defined Geometry: Potential Scaffolds for Assembly

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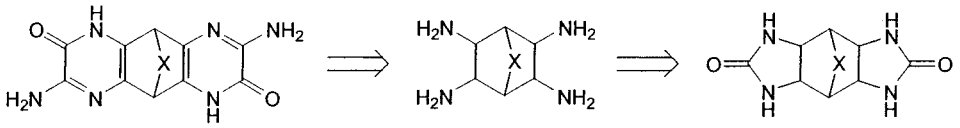
The syntheses of tetraamines **10** (*Scheme 3*) and **17** (*Scheme 4*), which might be useful as rigid organizing scaffolds in dynamic or standard combinatorial chemistry, are described. The *Diels-Alder* reaction of the electron-rich dienophile 1,3-diacetyl-2,3-dihydro-1*H*-imidazol-2-one (**5**) with benzo[*c*]thiophene or 2*H*-pyran-2-one is the key step in their preparation. The intermediate fused cyclic diureas **9** and **16** are dimethylglycoluril analogues, and their crystal structures are examined. Diurea **9** (*Fig. 2*) crystallizes as a hydrate and forms undulating chains through a network of H-bonds. These chains are interconnected through H-bonds to the H_2O molecules. H_2O Molecules are not incorporated in the crystal of 'bis-urea' **16** (*Fig. 3*), the molecules of which associate through an extended three-dimensional H-bonding network.

Introduction. – Molecules with a rigid skeleton and oriented functional groups play an important role in molecular recognition [1] and are used as templates in combinatorial chemistry [2]. Vicinal diamines and their metal complexes are of medicinal importance and can serve as intermediates in the synthesis of polyamines, heteromacrocycles, and bifunctional chelating agents [3].

In the course of a research project aimed at the preparation of aminopyrazinones of type **I** (*Scheme 1*) and the study of their self-assembly through H-bonds, the preparation of rigid bicyclic vicinal tetraamines **II** was required. We report here our synthetic strategy towards these compounds and the crystal-packing features of the corresponding fused cyclic 'bis-ureas' **III**.

Scheme 1. *Retrosynthetic Analysis of Aminopyrazinones* **I** (X = C_6H_4, C_2H_4)



I II III

Results and Discussion. – *Synthesis of Tetraamine* **10**. Benzo[*c*]thiophene (**2**; *Scheme 2*) can be conveniently prepared from 1,2-bis(bromomethyl)benzene (**1**) by the *S*-oxide route [4][5], and it is a versatile synthetic equivalent of *o*-quinodimethane [6]. It reacts readily with electron-poor dienophiles [5][7], such as maleic anhydride or

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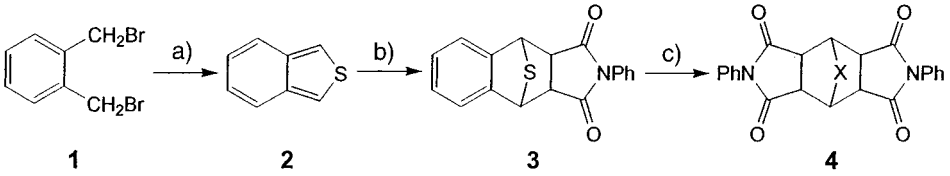
N-phenylmaleimide, to yield the corresponding *Diels-Alder* adducts (**3**). It has been demonstrated [8] that subsequent oxidation of the sulfide bridge to the corresponding sulfone, followed by thermal extrusion of SO_2, regenerates the *o*-quinoid system. This can be trapped in the presence of *N*-phenylmaleimide to yield a fused polycyclic diimide **4**. The structural similarity of **4** to the targeted tetraamine, and the encouraging results obtained in the case of benzo[*c*]furan [9], prompted us to investigate the reaction of benzo[*c*]thiophene with the electron-rich dienophile 1,3-diacetyl-2,3-dihydro-1*H*-imidazol-2-one (**5**, see *Scheme 3*) [10].

Scheme 2. *Preparation of Polycyclic Diimide* **4** *by Sequential* Diels-Alder *Reactions* ($X = C_6H_4$)



1 **2** **3** **4**

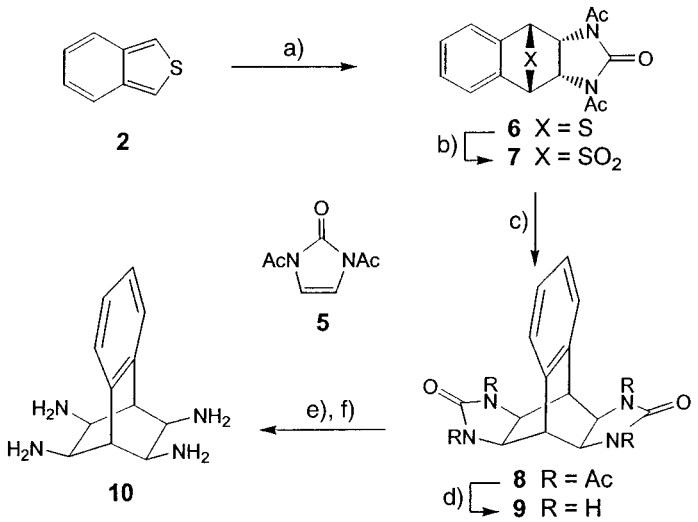
a) [10]. b) [5]. c) [8].

In an attempt to generate and trap *in situ* the highly reactive benzo[*c*]thiophene [5], 1,3-dihydrobenzo[*c*]thiophene 2-oxide, and 1,3-diacetyl-2,3-dihydro-1*H*-imidazol-2-one (**5**) were refluxed in Ac_2O. Disappointingly, very complex reaction mixtures were obtained, and only traces of the required *Diels-Alder* adduct could be isolated. However, when a solution of freshly prepared benzo[*c*]thiophene [4] and 1,3-diacetylimidazolin-2-one in *m*-xylene was heated at reflux for 24 h the *Diels-Alder* adduct **6** (*Scheme 3*) was isolated in 53% yield. Only one stereoisomer (*endo*) could be detected, in analogy to the reaction of benzo[*c*]furan [9] with the same dienophile.

In preparation for the second *Diels-Alder* cycloaddition, the sulfide bridge was oxidized to the corresponding dioxide **7**. Subsequent thermolysis in the presence of the dienophile furnished in high yield the fully protected tetraamine **8** as a single stereoisomer (*endo*,*endo*). Treatment of **8** with 2N aqueous HCl or 10N aqueous NaOH at reflux failed to fully unmask the targeted tetraamine; hydrolysis progressed only to the bis-urea stage. However, more vigorous conditions (excess $Ba(OH)_2$ at 140° for 24 h) yielded tetraamine **10** as the sulfate salt. The free tetraamine was subsequently obtained upon treatment with saturated ammoniacal $CHCl_3$ [11–13].

Synthesis of Tetraamine **17**. In analogy to the preparation of tetraamine **10** described above, a double *Diels-Alder* reaction of 2*H*-pyran-2-one (**11**) [14] with 1,3-diacetyl-2,3-dihydro-1*H*-imidazol-2-one (**5**) was anticipated to result in formation of the central C-framework of tetramine **17** (*Scheme 4*). However, heating at reflux a solution of **11** and **5** in toluene or *m*-xylene failed to yield any of the desired product. The ability of 2*H*-pyran-2-one (**11**) to act both as a diene and as a dienophile to yield dimers and polymers [15] in conjunction with the poor dienophilic character of **5** [10] were thought to be responsible for these disappointing results. Nevertheless, it was possible to obtain, albeit in low yield, the desired double *Diels-Alder* adduct **14** by heating at 180° a mixture of **11**, excess **5**, and *m*-xylene in a sealed tube for 72 h. Along with **14**, a second compound, **13**, was obtained, presumably through dimerization of the postulated intermediate **12**. It is noteworthy that, due to steric hindrance around the C=C bond of

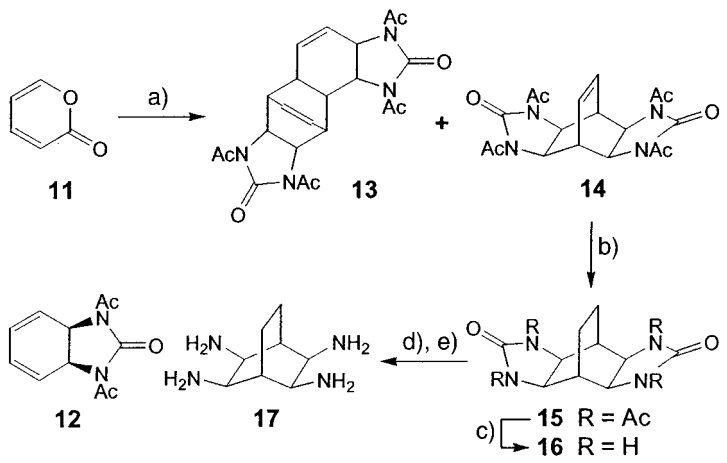
Scheme 3



a) Xylenes, **5**, reflux; 24 h, 53%. b) AcOH, 30% H_2O_2, cat. H_2SO_4, r.t., 2 d; 87%. c) Triethylene glycol dimethyl ether (TEGDME), **5**, 180°, 45 min; 95%. d) K_2CO_3, EtOH/H_2O 7:1, reflux, 5 h; 98%. e) $Ba(OH)_2/H_2O$, 140°, sealed tube, 24 h; CO_2, 1N H_2SO_4. f) $NH_3(g)$, $CHCl_3$; 80%.

14, its reduction, under an atmosphere of H_2 and in the presence of a catalytic amount of Pd/C, required prolonged reaction time (1 week). Unmasking of the tetraamine required again the use of excess $Ba(OH)_2$ at 140° in a sealed tube for 24 h. In this case, however, efficient formation of the tetraamine **17** from its sulfate salt required

Scheme 4



a) *m*-Xylene, **5**, 180°, sealed tube, 72 h; (**13**): 17%, **14**: 15%. b) 10% Pd/C, 1 atm H_2, r.t., AcOEt/EtOH 1:1, 1 week; 100%. c) K_2CO_3, EtOH/H_2O 7:1, reflux, 5 h; 77%. d) $Ba(OH)_2 \cdot 8H_2O$, 140°, sealed tube, 24 h; 1N H_2SO_4. e) $NH_3(g)$, EtOH; 62%.

treatment with saturated ammoniacal EtOH. Use of saturated ammoniacal $CHCl_3$ failed to liberate the tetraamine.

Crystal Packing of Cyclic 'Bis-ureas' **9** *and* **16**. Cyclic ureas are known to self-assemble in a variety of different H-bonding motifs [16]. In the case of dimethylglycoluril (*Fig. 1*), both halves of the molecule form independent tapes resulting in a layer arrangement [16].

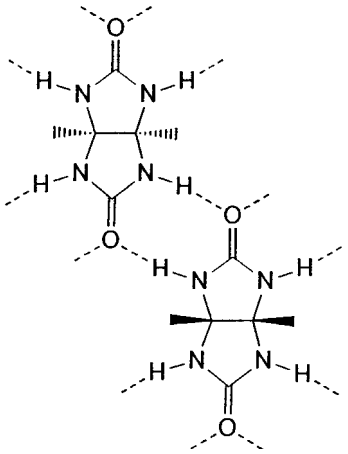


Fig. 1. *Schematic representation of the crystal structure of dimethylglycoluril* [16]

Cyclic 'bis-ureas' **9** and **16** are analogues of dimethylglycoluril (glycoluril = imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione). They can be easily obtained by methanolic base treatment of intermediates **8** and **15** mentioned above. It is interesting to note the profound differences observed in the H-bonding motifs of these closely related compounds.

Compound **9** crystallizes as a hydrate. The molecules are assembled into infinite undulating chains through a H-bonding network (*Fig. 2*,*a*). Two successive molecules in a chain (for example molecules A and B, *Fig. 2*,*a*) are associated through two strong H-bonds (N–H···O 2.85 Å, <NHO 180°; N–H···O 2.88 Å, <NHO 159°). This dyad is associated to the next through two weaker H-bonds (N–H···O 2.93 Å, <NHO 133°; N–H···O 2.90 Å, <NHO 154°). Four such chains are arranged around the H_2O molecules (*Fig. 2*,*b*). Successive H_2O molecules are positioned on two different parallel lines. H_2O Molecules on the same line (for example molecules w1 and w2, *Fig. 2*,*a*) are positioned at regular intervals (O···O 8.42 Å). Each H_2O molecule is connected through H-bonds to all four chains. It is noteworthy that all available H-bonding functional groups are utilized.

In contrast, the cyclic 'bis-urea' **16**, under identical conditions, does not form a hydrate. The molecules are arranged in layers (*Fig. 3*,*a*). Within each layer, the molecules form in two rows and have the same orientation, while molecules of neighboring layers have opposite orientation. Each molecule (*Fig. 3*,*b*) is associated with *i*) four neighboring molecules (molecules A, B, C, D; *Fig. 3*,*b*) of the same layer through six H-bonds (two cyclic bidentate: N–H···O 2.85 Å, <NHO 164°; N–H···O 2.92 Å, <NHO 158° and two monodentate interactions: N–H···O 2.85 Å, <NHO 154°) and *ii*) a molecule of the next layer (molecule E; *Fig. 3*,*b*) through a

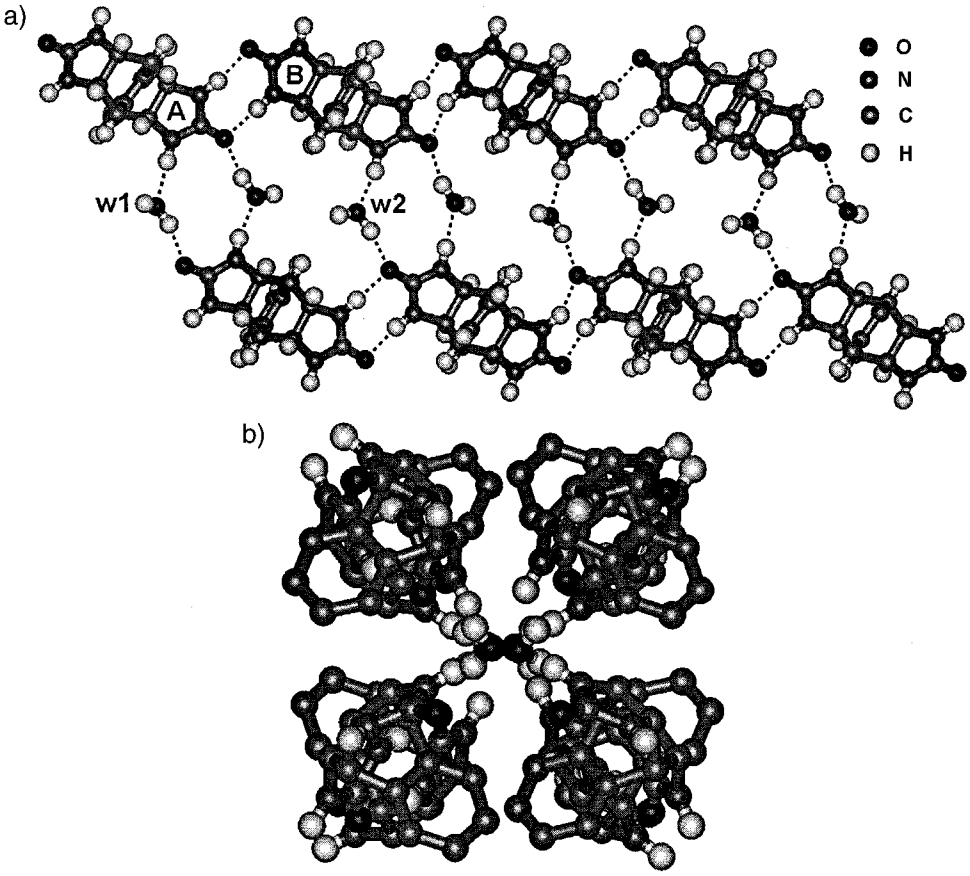


Fig. 2. *X-Ray crystal structure of* **9**. *a*) View perpendicular to the long axis of the undulating chains; two additional chains positioned symmetrically above and below the H_2O molecules are not shown for clarity. *b*) View parallel to the long axis of the chains; H atoms not involved in H-bonds are omitted for clarity.

centrosymmetric cyclic H-bonding network (N–H···O 2.88 Å, $<$NHO 155°). Once more, all available H-bonding sites are utilized.

Conclusion. – An efficient synthetic strategy towards rigid tetraamines was developed based on sequential *Diels-Alder* reactions of diacetyldihydroimidazolone with either benzo[*c*]thiophene or 2*H*-pyran-2-one. Although the intermediate cyclic 'bis-ureas' have similar structures and identical H-bonding groups, they form different patterns of H-bonds in the crystalline state.

Attempts to prepare the aminopyrazinones **I** from these tetraamines were unsuccessful, however, they might be useful as rigid organizing scaffolds in dynamic [17] or standard combinatorial chemistry [2].

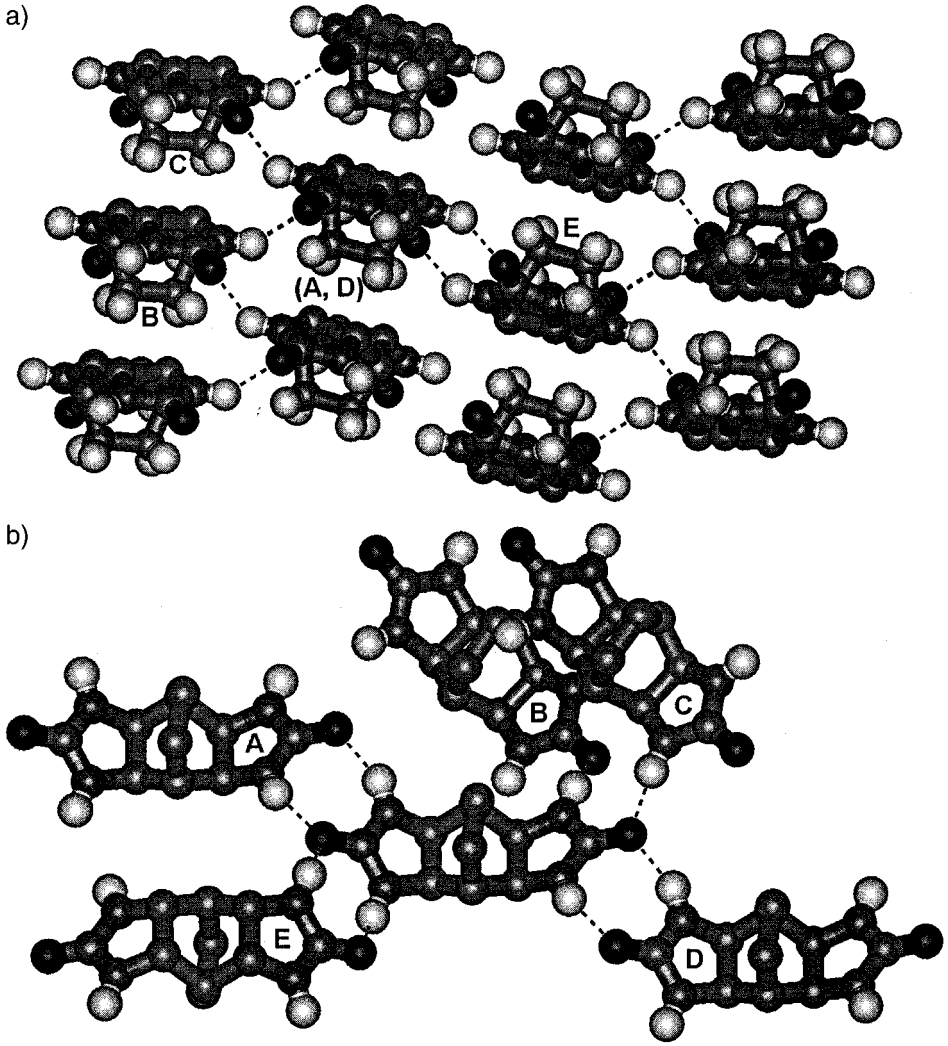


Fig. 3. *X-Ray crystal structure of* **16**. Some (*a*) or all (*b*) the H-atoms not involved in H-bonds are not shown for clarity.

Experimental Part

General. All commercially available chemicals employed were of reagent grade and used without further purification. All reactions were carried out under a dry Ar atmosphere with anh., freshly distilled solvents under anh. conditions unless otherwise noted. All reactions were magnetically stirred with *Teflon* stir bars, and temp. was measured externally. THF and toluene were freshly distilled over sodium benzophenone ketyl. Reactions were monitored by TLC carried out on 0.25-mm precoated glass plates (*Merck* silica gel *60 F_{254}*). Visualization was effected with UV light (254 nm), I_2 vapor chamber, 7% ethanolic phosphomolybdenic acid and heat, or *p*-anisaldehyde soln. (2.5% *p*-anisaldehyde, 3.4% H_2SO_4, 1% AcOH in 95% EtOH) and heat as developing agent. Prep. column chromatography (CC): silica gel (*Merck Si 60:* 40–63 μm). M.p.: *Electrothermal* digital m.p. apparatus; no corrections. IR: *Perkin-Elmer FT-IR-1600*; in cm^{-1}. ^{1}H-NMR: *Bruker AC-200*; δ in ppm relative

to Me_4Si with residual solvent peak as standard, *J* in Hz. ^{13}C-NMR: broad-band decoupled. MS: *m*/*z*, fast atom bombardment (FAB, positive mode) and electron impact (EI) were performed at the Laboratoire de Spectrometrie de Masse, Strasbourg.

10,12-Diacetyl-14-thia-10,12-diazatetracyclo[6.5.1.0^{2,7}.0^{9,13}]tetradeca-2,4,16-trien-11-one (**6**). To a stirred soln. of *1,3-diacetyl-2,3-dihydro-1*H-*imidazol-2-one* [10] (**5**; 4.86 g, 28.9 mmol) and a trace of hydroquinone in dry and degassed *m*-xylene (100 ml), freshly prepared benzo[*c*]thiophene [4] **2** (3.0 g, 22.4 mmol) was added. The mixture was heated at reflux under Ar for 24 h. The mixture was allowed to cool to r.t., and then it was evaporated to dryness *in vacuo*. The residue was purified by FC (AcOEt/hexane 5% → 10%), followed by crystallization (Et_2O) to yield 3.59 g (53%) of **6**. Colorless crystals. M.p. 151–152°. R_f (10% AcOEt/hexane) 0.09. IR (thin film): 3060, 3040, 3018, 2992, 2959, 2933, 1786, 1754, 1598, 1659, 1465, 1457, 1430, 1420, 1386, 1358, 1349, 1315, 1297, 1237, 1201. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.13–7.03 (*m*, 4 H); 4.98 (*s*, 4 H); 2.28 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.6; 150.9; 142.0; 127.4; 122.2; 57.6; 55.1; 24.3. FAB-MS: 303.1 ($[M+1]^+$). Anal. calc. for $C_{15}H_{14}N_2O_3S$: C 59.59, H 4.67, N 9.27; found: C 59.71, H 4.55, N 9.39.

10,12-Diacetyl-14-thia-10,12-diazatetracyclo[6.5.1.0^{2,7}.O^{9,13}]tetradeca-2,4,16-trien-11-one 14,14-Dioxide (**7**). To a soln. of **6** (3.44 g, 11.4 mmol) in glacial AcOH (250 ml), at r.t., was carefully added 30% H_2O_2 (190 ml), and the mixture was stirred for 48 h. It was then poured into H_2O (250 ml) and extracted with $CHCl_3$. The org. phase was washed sequentially with a sat. aq. soln. of $NaHCO_3$ (until the aq. wash was neutral) and brine, and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure, followed by purification of the residue by FC (AcOEt/hexane 30 → 50%) and crystallization (CH_2Cl_2/hexane) yielded 3.3 g (87%) of **7**. Colorless solid. M.p. = 184–186° (dec.). R_f (AcOEt/hexane) 0.5. IR (thin film): 3052, 3029, 3011, 1774, 1702, 1466, 1420, 1361, 1322, 1296, 1275, 1243, 1187. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.51–7.43 (*m*, 2 H); 7.39–7.31 (*m*, 2 H); 5.22–5.14 (*m*, 4 H); 2.30 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.2; 150.6; 132.2; 130.0; 125.7; 64.4; 52.0; 23.9. FAB-MS: 335.2 ($[M+1]^+$). Anal. calc. for $C_{15}H_{14}N_2O_5S$: C 53.88, H 4.22, N 8.38; found: C 53.89, H 4.08, N 8.49.

N,N′,N″,N‴-*Tetraacetyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-triene-9,10 : 11 : 12-bis[dicarboximide]* (**8**). To a stirred soln. of **7** (2.15 g, 6.43 mmol) in triethylene glycol dimethyl ether (650 ml), **5** (3.27 g, 19.4 mmol) was added, and the resulting soln. was degassed. It was then heated to 180° under Ar for 45 min. The mixture was allowed to cool to r.t., and then the majority of the solvent (*ca*. 600 ml) was removed *in vacuo* (0.1 Torr). The resulting residue was recrystallized from Et_2O to yield 2.69 g (95%) of **8**. White solid. M.p. > 340°. R_f (AcOEt/hexane 50%) 0.20. IR (thin film): 1753, 1689, 1416, 1383, 1366, 1348, 1319, 1279, 1245, 1210. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.33–7.29 (*m*, 2 H); 7.07–7.03 (*m*, 2 H); 4.61 (*s*, 4 H); 4.57 (*s*, 2 H); 2.31 (*s*, 12 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.3; 151.6; 132.9; 129.0; 127.9; 50.8; 37.6; 24.4. FAB-MS: 439.3 ($[M+1]^+$). Anal. calc. for $C_{22}H_{22}N_4O_6$: C 60.27, H 5.06, N 12.78; found: C 60.28, H 5.07, N 12.64.

Tricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-triene-9,10 : 11,12-bis[dicarboximide] (**9**). A mixture of **8** (234.5 mg, 0.53 mmol) and K_2CO_3 (0.85 g, 6.2 mmol) in EtOH/H_2O 7 : 1 (7 ml) was heated to reflux for 5 h. The mixture was allowed to cool to r.t., and it was then concentrated (*ca*. 1 ml) under reduced pressure. The mixture was neutralized by careful addition of 1M HCl soln., and then the solvents were removed under reduced pressure. The resulting white solid was washed with H_2O (2 × 2 ml) and then dried *in vacuo* over P_2O_5 to yield 140.4 mg (98%) of **9**. Crystallization from H_2O yielded crystals suitable for X-ray analysis. Crystal data and parameters used in the structural determination are given in the *Table*. M.p. > 340°. IR (KBr): 3200, 3118, 3076, 2917, 2855, 1692, 1488, 1465, 1430, 1322, 1310, 1277. ^{1}H-NMR (200 MHz, (D_6)DMSO): 7.23–7.17 (*m*, 2 H); 7.13–7.07 (*m*, 2 H); 5.99 (*s*, 4 H); 3.92 (*s*, 4 H); 3.09 (*s*, 2 H). ^{13}C-NMR (50 MHz, (D_6)DMSO): 161.7; 136.0; 128.4; 126.2; 51.7; 44.6. FAB-MS: 271.1 ($[M+1]^+$).

Tricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-triene-9,10,11,12-tetraamine (**10**). A heavy-walled glass tube equipped with a magnetic stirring bar was charged with a mixture of **9** (855.3 mg, 1.95 mmol), $Ba(OH)_2 \cdot 8\,H_2O$ (19.5 g, 62 mmol), and H_2O (10 ml). The tube was sealed and heated to 140°. The initial solid mixture became a thick suspension when the oil-bath temp. reached 80° and, at that time, stirring was commenced. Heating and stirring was continued for 24 h, and then the mixture was allowed to cool to r.t. The contents of the tube were transferred quantitatively with H_2O (*ca*. 100 ml) to a 500-ml *Erlenmeyer* flask. CO_2 was bubbled through the mixture until a pH of 7 was reached. The precipitated $BaCO_3$ was removed by filtration through *Celite*, the cake was carefully washed with hot H_2O (3 × 50 ml), and the washings were combined with the filtrate. The clear soln. thus obtained was acidified to pH 1–2 by addition of an aq. 1N H_2SO_4 soln. The $BaSO_4$ formed was removed by filtration through *Celite*, the cake was washed with H_2O (2 × 50 ml), and the washings were combined with the filtrate. The clear aq. soln. thus obtained was concentrated under reduced pressure to *ca*. 100 ml. Upon careful addition of MeOH (*ca*. 300 ml) a white precipitate appeared. The mixture was allowed to stand at 0° overnight, and the white precipitate was collected by filtration and dried under vacuum over P_2O_5. It was then treated with dry sat. ammoniacal $CHCl_3$ (100 ml) for 1 h. The precipitated $(NH_4)_2SO_4$ was removed by filtration, and the

cake was resuspended in dry sat. ammoniacal $CHCl_3$ (100 ml) and stirred for 1 h at r.t. The mixture was then filtered, the two filtrates were combined, and removal of the solvent under reduced pressure yielded 341.8 mg (80%) of free **10**. White solid. M.p. 75–76°. IR (KBr): 3351, 2935, 2863, 1599, 1462, 1369, 1312. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.25–7.15 (*m*, 4 H); 3.26 (*s*, 4 H); 2.79 (*s*, 2 H); 0.93 (*s*, 8 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 138.5; 126.7; 127.1; 53.2; 51.5. FAB-MS: 219.1 ($[M+1]^+$). Anal. calc. for $C_{12}H_{18}N_4$: C 66.02, H 8.31, N 25.67; found: C 65.78, H 8.09, N 25.74.

3,5,9,11-Tetraacetyl-3,5,9,11-tetraazatetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradec-13-ene-4,10-dione (**14**). A heavy-walled pressure glass tube with *Teflon* bushing, equipped with a magnetic stirring bar, was charged with *m*-xylene (30 ml), and Ar was bubbled through for 45 min. Compound **5** (3.0 g, 17.8 mmol) and 2*H*-pyran-2-one (0.7 ml, 8.7 mmol) were then added, and the tube was sealed and immersed in an oil bath. The mixture was heated with stirring to 180° for 72 h. During this period the mixture was occasionally (3–4 times) allowed to cool to r.t., and the tube was opened under continuous sparging with Ar to obtain aliquots for monitoring the progress of the reaction by TLC analysis (AcOEt/hexane 20%). The mixture was allowed to cool to r.t., and the contents of the tube were transferred quantitatively with CH_2Cl_2 to a round-bottomed flask, and the solvents were removed under reduced pressure. The residue was dissolved in a minimum amount of CH_2Cl_2 (*ca.* 100 ml), and Et_2O was added until no more precipitate formed. The white precipitate was isolated by filtration and further purified by FC (AcOEt/CH_2Cl_2 10 → 50%) to yield 506.8 mg (15%) of **14** and 651.4 mg (17%) of **13**, both as white solids. Compound **5** (1.0 g) could be recovered from the filtrate upon removal of the solvents under reduced pressure and further purification by FC (AcOEt/hexane 10%).

Data of **14**: M.p. > 340°. R_f (AcOEt/CH_2Cl_2) 0.14. IR (thin film): 1757, 1700, 1401, 1364, 1322, 1272, 1243. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.11 (*q*, *J* = 4.9, 3.9, 2 H); 4.39 (*s*, 4 H); 4.24–4.19 (*m*, 2 H); 2.45 (*s*, 12 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 166.3; 148.5; 126.9; 46.7; 29.6; 20.7. FAB-MS: 389.1 ($[M+1]^+$). Anal. calc. for $C_{18}H_{20}N_4O_6$: C 50.67, H 5.19, N 14.43; found: C 50.68, H 5.10, N 14.69.

Data of **13**: M.p. > 300° (dec.). R_f (AcOEt/CH_2Cl_2 20%) 0.34. IR (thin film): 1753, 1695, 1685, 1383, 1362, 1299, 1269, 1258, 1247, 1205. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.26–6.06 (*m*, 2 H); 5.77 (*s*, 2 H); 4.42–4.27 (*m*, 3 H); 4.14–4.09 (*m*, 1 H); 3.66–3.62 (*m*, 1 H); 3.42–3.38 (*m*, 1 H); 2.73–2.66 (*m*, 1 H); 2.52 (*s*, 3 H); 2.48 (*s*, 3 H); 2.47 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 172.3, 170.9, 170.6, 152.7, 152.2, 133.2, 131.2, 130.9, 122.4, 54.1, 53.9, 53.7, 48.7, 37.9, 37.7, 34.3, 34.2, 25.4, 24.7, 24.6. FAB-MS: 441.2 ($[M+1]^+$). Anal. calc. for $C_{22}H_{24}N_4O_6$: C 59.99, H 5.49, N 12.72; found: C 59.81, H 5.99, N 12.74.

3,5,9,11-Tetraacetyl-3,5,9,11-tetraazatetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradecane-4,10-dione (**15**). To a degassed soln. of **14** (1.4758 g, 3.8 mmol) in AcOEt/EtOH 1:1 (2.7 l) was added a cat. amount of 10% Pd/C and the mixture was stirred at r.t. and under H_2 for a week. Filtration through *Celite* and removal of the solvents under reduced pressure yielded 1.4921 g (100%) of **15**. White solid. M.p. > 300° (dec.). IR (thin film): 1755, 1698, 1352, 1271, 1244. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.35 (*s*, 4 H); 3.05 (*s*, 2 H); 2.55 (*s*, 12 H); 1.34 (*s*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.6; 152.6; 50.2; 27.0; 24.7; 12.7. FAB-HR-MS: 391.1602 ($[M+1]^+$); calc. for $C_{18}H_{22}N_4O_6$: 391.1617.

3,5,9,11-Tetraazatetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradecane-4,10-dione (**16**). A mixture of **15** (199.1 mg, 0.51 mmol) and K_2CO_3 (0.85 g, 6.2 mmol) in EtOH/H_2O 7:1 (8 ml) was heated to reflux for 8 h. The mixture was allowed to cool to r.t., and it was then concentrated (*ca.* 1 ml) under reduced pressure. The mixture was neutralized by careful addition of 1M HCl soln., and then the solvents were removed under reduced pressure. The resulting white solid was washed with H_2O (2 × 2 ml) and then dried *in vacuo* over P_2O_5 to yield 87.1 mg (77%) of **16**. Crystallization from H_2O yielded crystals suitable for X-ray analysis. Crystal data and parameters used in the structural determination are given in the *Table*. M.p. > 340° (dec.). IR (thin film): 3214, 3071, 2958, 2931, 2908, 2868, 1675, 1645, 1481, 1340, 1290, 1275, 1239. ^{1}H-NMR (200 MHz, (D_6)DMSO): 6.21 (br. *s*, 4 H); 3.58 (br. *s*, 4 H); 3.27 (br. *s*, 2 H); 1.52 (br. *s*, 4 H). FAB-MS: 223.1 ($[M+1]^+$).

Bicyclo[2.2.2]octane-2,3,5,6-tetraamine (**17**). A heavy walled glass tube equipped with a magnetic stirring bar was charged with a mixture of **15** (505.1 mg, 1.29 mmol), $Ba(OH)_2 \cdot 8\,H_2O$ (13.43 g, 42.6 mmol) and H_2O (6.9 ml). The tube was sealed and heated to 140°. The initial solid mixture became a thick suspension when the oil-bath temp. reached 80° and, at that time, stirring was commenced. Heating and stirring was continued for 24 h, and then the mixture was allowed to cool to r.t. The contents of the tube were transferred quantitatively with H_2O (*ca.* 150 ml) to a 500-ml *Erlenmeyer* flask. CO_2 was bubbled through the mixture until a pH of 7 was reached. The precipitated $BaCO_3$ was removed by filtration through *Celite*, the cake was carefully washed with hot H_2O (3 × 50 ml), and the washings were combined with the filtrate. The clear soln. thus obtained was acidified to pH 1–2 by addition of an aq. 1N H_2SO_4 soln. The $BaSO_4$ formed was removed by filtration through *Celite*, the cake was washed with H_2O (3 × 50 ml), and the washings were combined with the filtrate. Upon careful addition of EtOH (*ca.* 300 ml), a white precipitate appeared. The mixture was allowed to stand at 0° overnight, and the white precipitate was collected by filtration and dried under vacuum over P_2O_5. It was then

Table. *Crystal Data and Parameters Pertaining to Structural Analyses of* **9** *and* **16**

	9	**16**
Crystallization solvent	H_2O	H_2O
Chemical formula	$C_{14}H_{14}N_4O_2 \cdot H_2O$	$C_{10}H_{14}N_4O_2$
Formula weight	288.31	222.25
Crystal system	Monoclinic	Monoclinic
Cell constants a [Å]	16.590(5)	6.4890(4)
b [Å]	12.667(4)	24.699(1)
c [Å]	13.781(4)	6.4670(4)
β [deg]	107.90(2)	92.300(3)
V [Å^3]	2755(2)	1035.6(2)
Z	8	4
Density calc. [g cm^{-3}]	1.39	1.43
Absorption coefficient [mm^{-1}]	0.101	0.103
Space group	$P2_1/c$	$P2_1/c$
Crystal size [mm]	$0.32 \times 0.25 \times 0.20$	$0.20 \times 0.16 \times 0.10$
Diffractometer	*Enraf Nonius MACH3*	*Nonius-KappaCCD*
Radiation	MoK_α graphite monochromated	
Wavelength [Å]	0.71073	
Temperature [K]	294	
Measurement method	$\theta/2\theta$	*phi* scans
θ Limits (deg)	2.5/26.29	2.5/28.11
Absorption correction applied and limits	0.94/1.00	none
Method used to solve and refine structure	Direct methods	
Treatment of H-atoms	Riding, C–H = 0.95, B(H) = 1.3/B_{eqv}(C)	
Use of F magnitudes in least-squares refinement		
Measured reflections	6109	6866
Observed reflections	2097	1653
Criterion	$I > 3\sigma(I)$	$I > 3\sigma(I)$
Number of parameters refined	369	145
$R = \Sigma \lvert \lvert F_o \rvert - \lvert F_o \rvert \rvert / \Sigma \lvert F_o \rvert$	0.047	0.057
$wR = [\Sigma w(\lvert F_o \rvert - \lvert F_c \rvert)^2 / \Sigma w \lvert F_o \rvert^2]^{1/2}$	0.061	0.075
$s = [\Sigma w(\lvert F_o \rvert - \lvert F_c \rvert)^2 / (N_o - N_v)]^{1/2}$	1.154	1.009
Max. positive electron density in final *Fourier* synthesis [eA^{-3}]	0.46	0.26
Computer programs used	Open MoleN[a])	Open MoleN[a])

[a]) Open MoleN, Interactive Structure Solution, *Nonius B.V.*, The Netherlands, 1997.

treated with dry sat. ammoniacal EtOH (100 ml) for 1 h. The precipitated $(NH_4)_2SO_4$ was removed by filtration, and the cake was resuspended in dry sat. ammoniacal EtOH (100 ml) and stirred for 1 h at r.t. The mixture was then filtered, the two filtrates were combined, and removal of the solvent under reduced pressure yielded 168.6 mg (77%) of free **17**. White solid. M.p. 163–164°. IR (thin film): 3404, 3318, 3252, 3127, 2928, 1593, 1558, 1478, 1385, 1308. ^{1}H-NMR (200 MHz, CD_3OD): 4.65 (br. *s*, 8 H); 3.01 (br. *s*, 4 H); 1.59 (br. *s*, 4 H); 1.56 (br. *s*, 2 H). ^{13}C-NMR (50 MHz, CD_3OD): 51.4, 41.1; 12.4. FAB-HRMS: 171.1608 ($[M+1]^+$); calc. for $C_8H_{18}N_4$: 171.1610.

X-Ray Crystal-Structure Determination of Compounds **9** *and* **16**. The crystallographic parameters for compounds **9** and **16** are listed in the *Table*. Crystallographic data (excluding structure factors) for compounds **9** and **16** have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC 149247 and 149248, resp. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

REFERENCES

[1] D. Mink, S. Mecozzi, J. J. Rebek, *Tetrahedron Lett*. **1998**, *39*, 5709.
[2] E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. Fodor, M. A. Gallop, *J. Med. Chem*. **1994**, *37*, 1385.
[3] D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.*, *Int. Ed*. **1998**, *37*, 2580.
[4] R. P. Kreher, J. Kalischko, *Chem. Ber.* **1991**, *124*, 645.
[5] M. P. Cava, N. M. Pollack, O. A. Mamer, M. J. Mitchell, *J. Org. Chem*. **1971**, *36*, 3932.
[6] J. L. Segura, N. Martin, *Chem. Rev.* **1999**, *99*, 3199.
[7] M. P. Cava, N. M. Pollack, *J. Am. Chem. Soc*. **1966**, *88*, 4112.
[8] M. P. Cava, J. McGrady, *J. Org. Chem*. **1975**, *40*, 72.
[9] S. V. D'Andrea, J. P. Freeman, J. Szmuszkovicz, *J. Org. Chem*. **1990**, *55*, 4356.
[10] R. A. Whitney, *Tetrahedron Lett*. **1981**, *22*, 2063.
[11] R. C. F. Jones, J. Schofield, *J. Chem. Soc.*, *Perkin Trans. 1*, **1990**, 375.
[12] S. V. D'Andrea, J. P. Freeman, P. F. VonVoigtlander, J. Szmuszkovicz, *Tetrahedron* **1991**, *47*, 6157.
[13] H. Flaster, H. Kohn, *J. Heterocycl. Chem.* **1981**, *18*, 1425.
[14] F. Effenberger, T. Ziegler, *Chem. Ber.* **1987**, *120*, 1339.
[15] W. H. Pirkle, C. A. Eckert, W. V. Turner, B. A. Scott, L. H. McKendry, *J. Org. Chem.* **1976**, *41*, 2495.
[16] J. C. MacDonald, G. M. Whitesides, *Chem. Rev.* **1994**, *94*, 2383.
[17] J.-M. Lehn, *Chem.-Eur. J.* **1999**, *5*, 2455.

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