3,7-Diazabicyclo[3.3.0]octane-2,6-diones: synthesis, NMR spectra and structures

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Parent 3,7-diazabicyclo[3.3.0]octane-2,6-dione **5**, the corresponding 1,5-dicarboxylic acid **4** and esters **3** have been synthesised for the first time; NMR spectra of the compounds were analysed, and the structures of **3b** and **5** were studied by X-ray crystallography; hydrogen bonding generates self-assembly in the form of heterochiral infinite diagonal zigzag tape in the crystal of **5**, while in the crystal structure of **3b** the H-bonded layers consist of homochiral spirals and heterochiral chains.

Bislactams of the 2,5-diazabicyclo[2.2.2]octane-3,6-dione series are capable of self-assembling only into heterochiral H-bonded suprastructures in the form of infinite linear zigzag tapes, which are packed in racemic crystals,[1–3] whereas an H-bonded self-assembly of bislactams of the bicyclo[3.3.*n*]alkane series (*n* = = 0–3) leads principally either to a heterochiral diagonal zigzag tape or to a homochiral helical structure.[4] The latter occurs in the case of a chiral glycouril such as 2,6-diethyl-2,4,6,8-tetra-azabicyclo[3.3.0]octane-3,7-dione, which gives conglomerate crystals and readily undergoes spontaneous resolution by crystallisation.[4]

Therefore, we have studied a similar system of the 3,7-diazabicyclo[3.3.0]octane-2,6-dione series (Scheme 1).
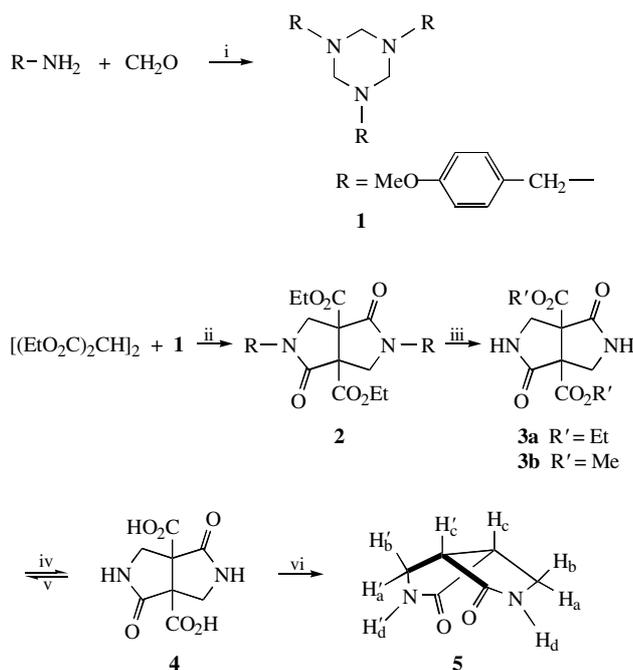
Scheme 1 *Reagents and conditions*: i, in EtOH, 1 h at 20 °C; ii, cat. amount of CF$_3$CO$_2$H, 24 h at 100–120 °C; iii, Ce(NH$_4$)$_2$(NO$_3$)$_6$ (CAN) in MeCN–H$_2$O, stirring for 1 h and standing for 2.5 days at 20 °C, then NaHCO$_3$, separation of the precipitate, extraction with Et$_2$O, evaporation and crystallisation from CCl$_4$; iv, KOH in MeOH, 18 h at 20 °C and 1.5 h refluxing, evaporation and treatment with conc. HCl in Et$_2$O, evaporation, dissolution in MeCN, filtration and crystallisation from MeOH; v, in MeOH, treatment with ether solution of CH$_2$N$_2$; vi, 5 min at 220 °C.

Bicycle **2** was synthesised on the basis of tetraethyl ethane-1,1,2,2-tetracarboxylate using the method developed by Knowles *et al.*[5,6] However, in order to ensure subsequent N-deprotection, the aminomethylation was carried out using new reagent **1**. The cleavage of *p*-methoxybenzyl groups of **2** was achieved by oxidation with cerium ammonium nitrate (CAN) using the

procedure described by Lehn *et al.*[1] Attempts of growing a crystal for the X-ray diffraction study of diethyl bislactam-dicarboxylate **3a** were unsuccessful, and the latter compound was converted into diacid **4** and then into dimethyl ester **3b**. The latter forms suitable single crystals. Unsubstituted parent bis-lactam **5** was prepared for the first time by thermal decarboxylation of diacid **4**. All of the compounds were characterised by spectroscopic data.[†] The six-spin system of the ^{1}H NMR spectrum of **5** (*cf.* similar mono- and bislactones of the 2,7-dioxabicyclo[3.3.0]alkane series[8,9]) was analysed in detail (Figure 1). The structures of **3b** and **5** were confirmed by X-ray analysis.[‡] Torsion angles HCNH found in **3b** (H$_a$CNH$_d$ 44°, H$_b$CNH$_d$ 76°) and HCCH in **5** (H$_a$CCH$_c$ 96°, H$_b$CCH$_c$ 25°, H$_c$CCH$_c'$ 23°) correspond to the observed spin coupling constants $^3J_{HH}$ (*cf.* ref. 10).[†]

The bond lengths and angles in the crystal structures of **3b** and **5** (Figures 2 and 3) exhibit expected values and are very similar to the corresponding values in bislactams of the bicyclo[2.2.2]-octane series.[1,3] Both molecules are significantly twisted, the corresponding torsion angles C(7)–C(1)–C(4)–C(9) and H(1)–C(1)–C(4)–H(4) are equal to 25° and 23.5° for **3b** and **5**,

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[†] *Characteristics and spectroscopic data.* NMR spectra were recorded on Bruker WM 400 (400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) and Bruker AM 300 (300.13 MHz for ^{1}H) spectrometers with TMS as an internal standard. ^{1}H NMR spectrum of **5** was calculated by CALM.

1: yield 90%, mp 108–110 °C (EtOH–H$_2$O, 60:40). ^{1}H NMR ([^{2}H$_8$]-toluene, 90 °C) δ: 3.34 (s, 6H, 3CH$_2$N), 3.36 (s, 9H, 3MeO), 3.49 (s, 6H, 3NCH$_2$N), 6.68 and 7.14 (d, 12H, 3C$_6$H$_4$, ^3J 7.6 Hz).

2, yield 53.4%, mp 110 °C (toluene). ^{1}H NMR (CDCl$_3$) δ: 1.14 (t, 6H, 2*Me*CH$_2$, ^3J 7.3 Hz), 3.80 (s, 6H, 2MeO), 3.82 (dd, 4H, 4,8-CH$_2$, AB spectrum, ν 60.0, ^2J –0.4 Hz), 4.11 (q, 4H, 2CH$_2$O, ^3J 7.3 Hz), 4.46 (dd, 4H, 2NCH$_2$, AB spectrum, ν 236.0, ^2J –14.7 Hz), 6.85 and 7.12 (d, 8H, 2C$_6$H$_4$, ^3J 8.5 Hz). ^{13}C NMR (CDCl$_3$) δ: 13.46 (qt, *Me*CH$_2$, ^1J 127.2 Hz, ^2J 2.9 Hz), 46.3 (ttt, CH$_2$N, ^1J 138.8 Hz, ^3J 3.6 Hz), 48.93 (tm, 4,7-CH$_2$, ^1J 148.2 Hz, ^3J 2.2 Hz), 54.83 (q, MeO, ^1J 143.1 Hz), 58.73 (m, 2,5-C, ^2J 3.6 Hz), 61.87 (tq, CH$_2$O, ^1J 149.0 Hz, ^2J 4.4 Hz), 113.77 (dd, 3'-C, ^1J 159.0 Hz, ^2J 4.4 Hz), 126.61 (m, 1'-C), 129.0 (ddt, 2'-C, ^1J 157.0 Hz, ^2J 4.4 Hz, ^3J 3.6 Hz), 158.9 (m, 4'-C), 165.9 (q, 2,6-CO, ^3J 3.6 Hz), 168.0 (m, CO$_2$).

3a: yield 63%, mp 160–161 °C (CCl$_4$). ^{1}H NMR (CD$_3$CN) δ: 1.19 (t, 6H, 2*Me*CH$_2$, ^3J 7.2 Hz), 3.76 (m, 4H, 4,8-CH$_2$, ABX spectrum, ν_{AB} 76.0, ^2J –0.4 Hz, $^3J_{H_aCNH}$ 1.2 Hz, $^3J_{H_bCNH}$ 0.0 Hz), 4.15 (m, 4H, CH$_2$O, ABX$_3$ spectrum), 6.66 (br. s, 2H, 2,7-NH). ^{13}C NMR ([^{2}H$_4$]methanol) δ: 14.25 (qt, *Me*CH$_2$, ^1J 127.2 Hz, ^2J 2.9 Hz), 46.13 (dd, 4,8-CH$_2$, ^1J 147.5 and 149.7 Hz), 62.0 (m, 1,5-C), 63.43 (tq, CH$_2$O, ^1J 149.0 Hz, ^2J 4.4 Hz), 167.82 (q, 2,6-CO, ^3J 3.6 Hz), 173.3 (qm, CO$_2$, ^3J 5.8 Hz).

3b: yield 74.2%, mp 222–223 °C (MeOH). ^{1}H NMR (CDCl$_3$) δ: 3.77 (s, 6H, 2MeO), 3.96 (m, 4H, 4,8-CH$_2$, ABX spectrum, ν_{AB} 52.0, ^2J –0.4 Hz, $^3J_{H_aCNH}$ 1.2 Hz, $^3J_{H_bCNH}$ 0.0 Hz), 6.72 (br. s, 2H, 3,7-NH).

4: yield 60%, mp 202–204 °C (MeOH). ^{1}H NMR ([^{2}H$_4$]methanol) δ: 3.81 (m, 4,8-CH$_2$, AB spectrum, ν 144.0, ^2J –0.5 Hz).

5: yield 72%, mp > 300 °C (decomp.) (H$_2$O). ^{1}H NMR ([^{2}H$_4$]methanol) δ: 3.22 (m, 2H, H$_c$, H$_c'$, $^3J_{CC'}$ 9.69 Hz), 3.54 (m, 2H, H$_b$, H$_b'$, $^2J_{ab}$ = $^2J_{a'b'}$ = –10.47 Hz, $^3J_{bc}$ = $^3J_{b'c'}$ = 1.3 Hz), 3.62 (m, 2H, H$_a$, H$_a'$, $^3J_{ac}$ = $^3J_{a'c'}$ = 7.98 Hz). ^{13}C NMR ([^{2}H$_4$]methanol) δ: 42.33 (d, 1,5-C, ^1J 145.0 Hz), 44.52 (t, 4,8-C, ^1J 146.8 Hz), 180.76 (s, 2,6-C).

Figure 2 The general view of **3b**.
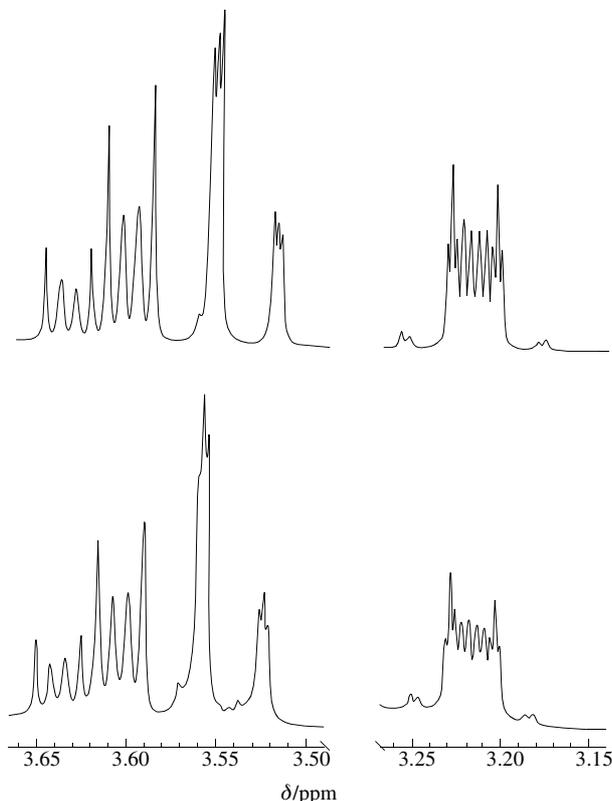

Figure 3 The general view of **5**.

Figure 1 ^{1}H NMR spectrum of **5** in [[2]H$_4$]methanol, experimental (above) and calculated (below).

respectively. The torsion angle C(2)–C(1)–C(4)–C(3) and the angle between two five-membered rings in both structures are similar and equal to 20.3° and 110.3°, respectively.

In the case of bislactam **5**, the expected self-assembly in the form of a heterochiral H-bonded [N(1)–H(1N)···O(2′) (x + x, 1 − y, x + z) N(1)O(1′) 2.860(4) Å N(2)–H(2N)···O(1″) (−x + x, 1 − y, −x + z) N(2)O(2′) 2.856(3) Å] infinite diagonal zigzag tape parallel to the crystallographic plane *ab* is observed (Figure 4).

However, in the crystal structure of **3b**, either the homochiral spirals or heterochiral zigzag tapes were not observed. The difference in the crystal packing of the centrosymmetric **5** and **3b** structures is probably caused by the CO$_2$Me 1,5-substituents. As the result of shielding due to the CO$_2$Me groups, molecules
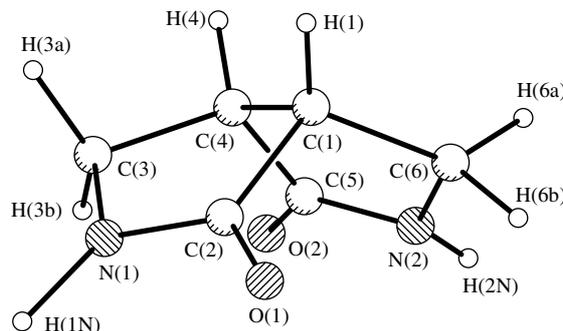
in the crystal structure of **3b** are assembled into H-bonded heterochiral layers (Figure 5) with a hydrophobic surface (CO$_2$Me groups) (Figure 5). It is noteworthy that nitrogen hydrogens [H(1N) and H(2N)] play different roles in the formation of the above layers. The H(2N) atoms [H-bond N(2)–H(2N)···O(1′) (1 − x, x + y, 3/2 − z), N(2)···O(1′) 3.039(3) Å] take part in the formation of the homochiral spirals [Figure 6(*a*)] directed along the crystallographic axes *b*, while the H(1N) atoms [H-bond N(1)–H(1N)···O(2′) (x, 3/2 − y, −x + z) N(1)···O(2′) 2.895(3) Å interlink these spirals into layers by perpendicular heterochiral chains directed along the crystallographic axes *c* [Figure 6(*b*)].
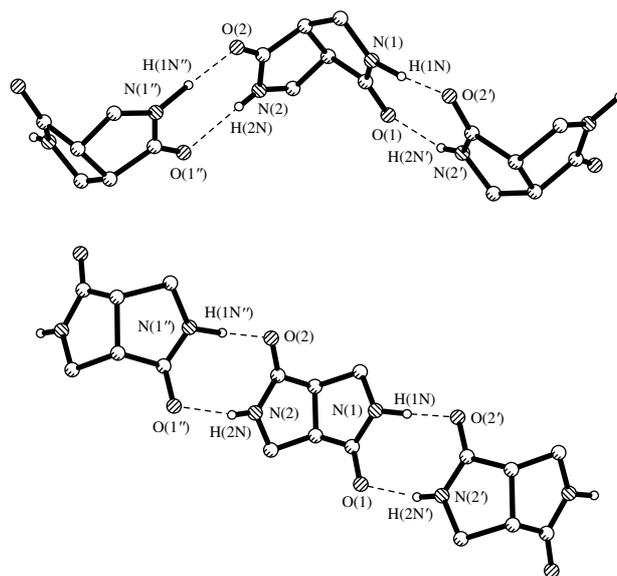

Figure 4 The zigzag heterochiral tape in two projections in the crystal structure of **5**. The hydrogens that do not take part in the formation of H-bonds are omitted for clarity.
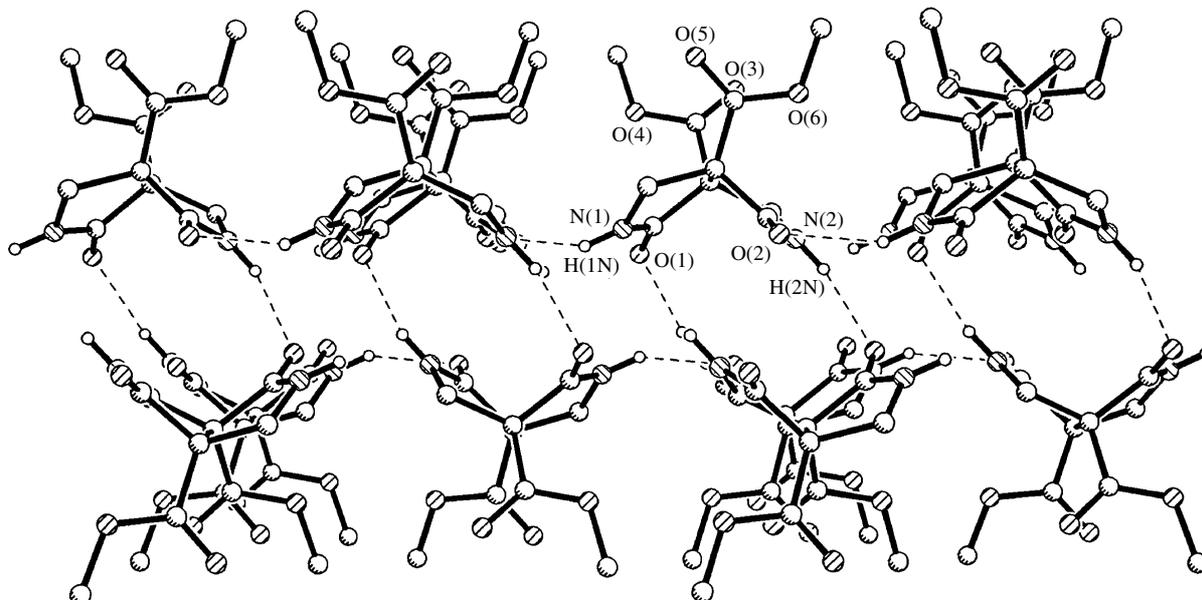
Figure 5 The H-bonded layers in the crystal structure of **3b**. The hydrogens that do not take part in the formation of H-bonds are omitted for clarity.

Apparently, a strong twist of the molecular skeleton in **5** hinders the self-assembly in a homochiral helical suprastructure because of a too small pitch of the helix.

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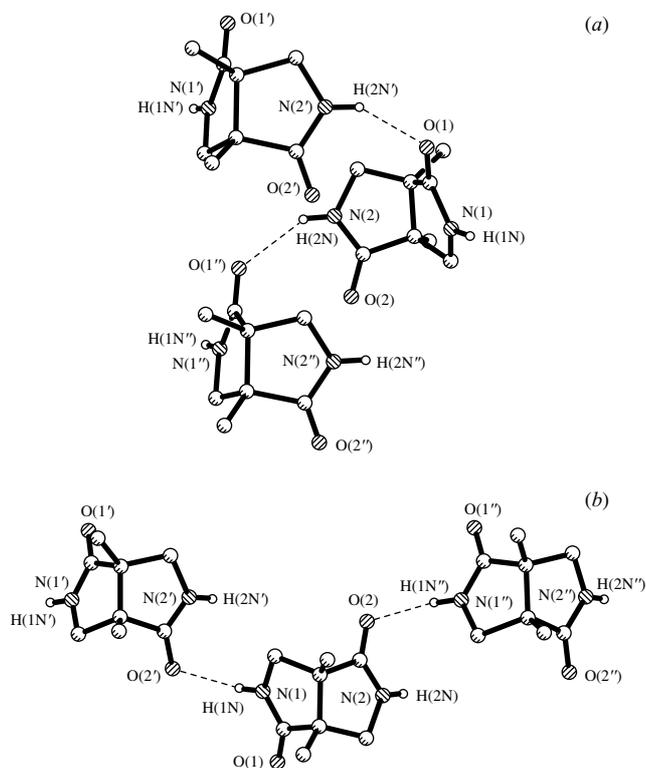
Figure 6 The H-bonded (*a*) homochiral spirals and (*b*) heterochiral chains in the crystal structure of **5**. The hydrogens of CH$_2$ groups are omitted for clarity.