α,α′-Diamino-α,α′-dicarboxyadipic acid tetraester: synthesis, lactamisation and dilactam structure

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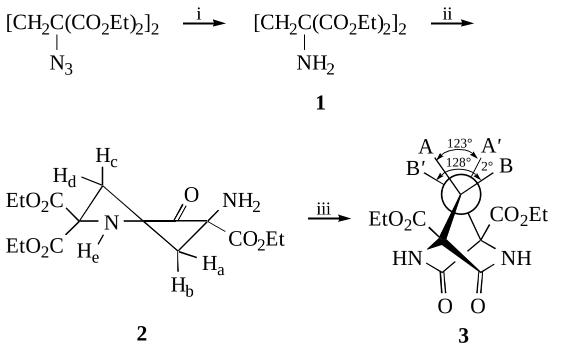
α,α′-Diamino-α,α′-dicarboxyadipic acid tetraester has been synthesised for the first time; it spontaneously cyclises into a monolactam and, under the action of bases, into a dilactam; the latter forms in the crystal a heterochiral hydrogen-bonded polymer of the linear zig-zag type.

Tetraesters of α,α′-dihydroxy-α,α′-dicarboxyadipic and -pimelic acids have been synthesised for the first time[1] and their complete autoassembling into the corresponding dilactones was effected under the conditions of base or acid catalysis (prolonged storage at 20 °C or heating, respectively).[2] The autoassembling of similar dilactams could be expected to occur substantially more easily, however, this is not the case. The above tetraacids were unknown until recently, although they are provoking interest as uncommon,[3] unnatural and unusual α-amino acids.[4–6]



Scheme 1 *Reagents and conditions*: i, $SnCl_2$ in abs. EtOH at –5 °C and 12 h at 20 °C, then $NaHCO_3$ and extraction by $MeCO_2Et$; ii, in pure form, 12 h at 20 °C; iii, cat. DBU in MeCN, 18 h at 20 °C.

As we have shown earlier,[7] the above acids could not be obtained from alkylene-bisbromomalonates. Numerous examples of the C-alkylation of *N*-acylaminomalonates[8,9] seemed to be promising as an alternative method of synthesis. However, our attempts to obtain tetraesters of α,α′-diamino-α,α′-dicarboxyadipic acid **1** by reactions of 1,2-dihaloethanes (Hal = Cl, Br) with *N*-formyl- and *N*-acetylaminomalonates failed, as previously with *N*-benzoylaminomalonate.[8]

In this work diaminotetraester **1** was synthesised by reduction ($SnCl_2$) of ethylene-bisazidomalonate (Scheme 1) which was itself obtained by reaction of azido transfer from tosyl azide to ethylene-bismalonate dianion.[10]

Diaminotetraester **1** forms stable salts (dihydrochloride and dipicrate) and undergoes a spontaneous monolactamisation under normal conditions. Dilactamisation also takes place under normal conditions on treatment with bases (DBU, Et_3N and other amines). So, the reaction of **1** with 2 equivalents of $MeNH_2$ (EtOH, 18 h, 20 °C) gives dilactam **3** in a yield of 74% and no noticeable formation of methylamides is observed. The composition and structure of all the products are confirmed by satisfactory elemental analyses and spectroscopic data† (*cf.* data for relative mono- and dilactones[2,11] and unsubstituted dilactam[12]). The NMR spectra of dilactam **3** (Figure 1) point to chirality of the molecule (non-equivalence of the methylene protons of the CO_2Et group) and its C_2 symmetry [pairwise equivalence of protons and carbons as well as AA′BB′ spectrum for the protons of the $(CH_2)_2$ bridge (Figure 1)]. This rigid bicyclic system is a matter of interest for crystal engineering by means of a stereoregular assembling of molecules using the hydrogen bonds.[13–17] On the basis of data in ref. 12 we have predicted a regular crystal structure for dilactam **3** (*cf.* ref. 16).

The molecular structure of **3** in the solid state was determined by an X-ray method‡ (Figure 2). The bond lengths and angles (Figure 2) in structure **3** have the expected values[18] and are very similar to the corresponding values in the unsubstituted 2,5-diazabicyclo[2,2,2]octane-3,6-dione.[12]

The bicyclic molecule **3** features a synchro(-,-,-)-twist conformation (*cf.* similar dilactones[19,20]). The torsion angles C(4)–N(5)–C(6)–C(1), C(4)–C(3)–N(2)–C(1) and C(4)–C(8)–C(7)–C(1) are equal to –3.1°, –3.1° and –5.0°, respectively. Nitrogen atoms N(2) and N(5) of the amido groups are characterised by a planar conformation (the deviation of the nitrogens from the plane of the neighbouring atoms does not exceed 0.09 Å).

It is noteworthy that (probably due to the packing effects in structure **3**) the ethoxycarbonyl groups are disordered (Figure 2). The OCO fragments have a slightly different orientation, disturbing the local C_2 symmetry of the rest of the molecule. The corre-

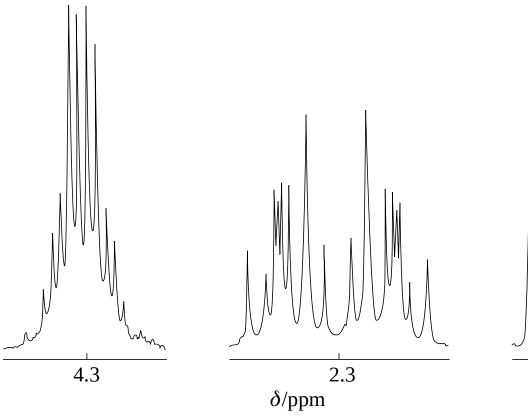


Figure 1 ^1H NMR spectrum of **3** in CD_3OD.

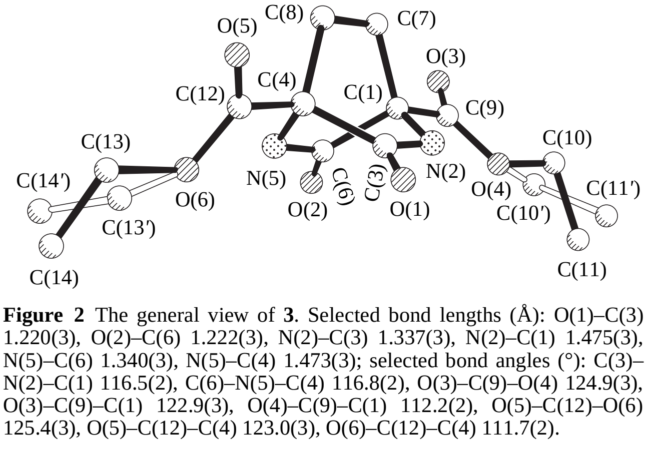


Figure 2 The general view of **3**. Selected bond lengths (Å): O(1)–C(3) 1.220(3), O(2)–C(6) 1.222(3), N(2)–C(3) 1.337(3), N(2)–C(1) 1.475(3), N(5)–C(6) 1.340(3), N(5)–C(4) 1.473(3); selected bond angles (°): C(3)–N(2)–C(1) 116.5(2), C(6)–N(5)–C(4) 116.8(2), O(3)–C(9)–O(4) 124.9(3), O(3)–C(9)–C(1) 122.9(3), O(4)–C(9)–C(1) 112.2(2), O(5)–C(12)–O(6) 125.4(3), O(5)–C(12)–C(4) 123.0(3), O(6)–C(12)–C(4) 111.7(2).

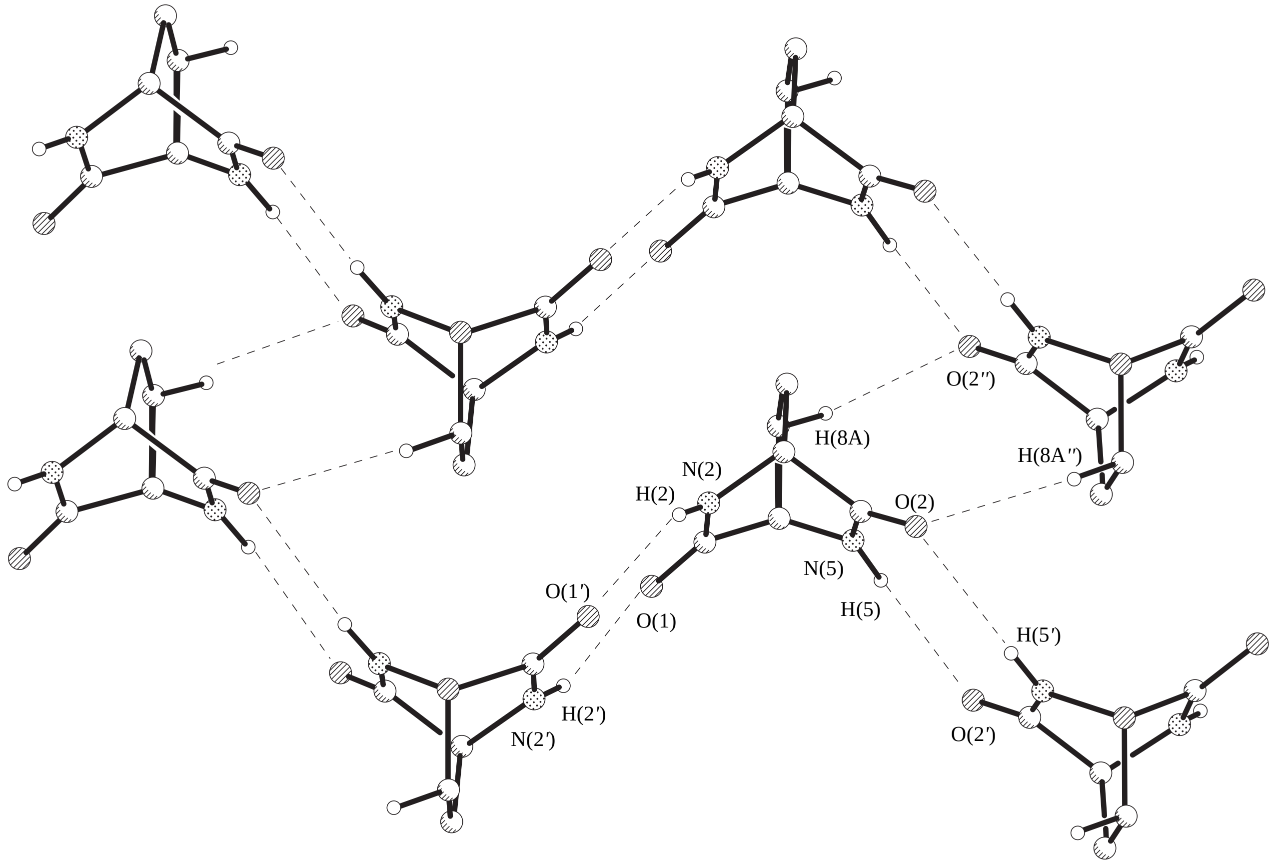


Figure 3 The formation of zig-zag chains and layers in structure **3**. The ethoxycarbonyl groups and hydrogens which do not take part in the shortened contacts are omitted for clarity.

sponding torsion angles O(5)–C(12)–C(4)–C(8) and O(3)–C(9)–C(1)–C(7) are –35.8° and –41.9°.

The molecules in the crystal structure **3** are assembled into infinite zig-zag chains of alternating (+) and (–) enantiomers directed along the crystallographic axes *a* (Figure 3) through approximately equal centrosymmetric intermolecular H-bonds: N(2)–H(2)···O(1) ($1-x$, $1-y$, $-z$) and N(5)–H(5)···O(2) ($-x$, $1-y$, $-z$) (the average N···O′, H···O′ distances and N–H–O′ angle are 2.946 Å, 2.15 Å and 157°, respectively). Moreover, the (+) and (–) enantiomers are interlinked by the intermolecular contacts C(8)–H(8A)···O(2′) ($-x$, $2-y$, $-z$) [C(8)···O(2′) 2.422(4) Å, H(8A)···O(2′) 2.42 Å, C(8)–H(8A)–O(2″) 155.1°] forming layers parallel to crystallographic plane *ab*. These C_{sp^3}H–O contacts can be considered according to Desiraju's classification,[21] as contacts of moderate strength which play a significant role in the crystal packing.[21]

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† **1**: yield 63%, colourless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 1.27 (t, 12H, 4Me, ^3J 7.0 Hz), 1.93 (br. s, 4H, $2NH_2$), 1.96 [s, 4H, $(CH_2)_2$], 4.21 (q, 8H, $4CH_2O$). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 13.06 (qt, Me, ^1J 126.4 Hz, ^2J 2.9 Hz), 28.82 [tt, $(CH_2)_2$, ^1J 132.2 Hz, ^2J 5.8 Hz], 60.75 (tq, CH_2O, ^1J 148.2 Hz, ^3J 4.4 Hz), 64.35 (s, CN), 170.33 (br. s, CO). MS (EI, 70 eV) *m*/*z*: 377 [M + 1] (1.0), 303 [M – CO_2Et] (3.0), 286 [M – CO_2Et – NH_3] (100), 257 [M – CO_2Et – NH_3 – Et] (98).

1, dihydrochloride: yield 84%, mp 173–174 °C (decomp.). ^{1}H NMR (400.13 MHz, CD_3OD) δ: 1.34 (t, 12H, 4Me, ^3J 7.0 Hz), 2.36 [s, 4H, $(CH_2)_2$], 4.39 (m, 8H, $4CH_2O$).

1, dipicrate: yield 79%, mp 168–170 °C. ^{1}H NMR (400.13 MHz, CD_3OD) δ: 1.31 (t, 12H, 4Me, ^3J 7.0 Hz), 2.40 [s, 4H, $(CH_2)_2$], 4.35 (m, 8H, $4CH_2O$), 8.77 (s, 4H, $2C_6H_2$).

2: yield 76%, mp 74–76 °C (Et_2O). ^{1}H NMR (400.13 MHz, [$^2H_8$]toluene) δ: 0.81, 0.83 and 0.91 (t, 3×3H, 3Me, ^3J 7.0 Hz), 1.59 (ddd, 1H, H_a, $^2J_{ab}$ –14.0 Hz, ^3J 7.0 Hz, ^3J 4.6 Hz), 2.0 (br. s, 2H, H_2N), 2.21 (ddd, 1H, H_b, $^3J_{bc}$ 8.9 Hz, ^3J 4.6 Hz), 2.45 (m, 1H, H_c), 2.48 (m, 1H, H_d), 3.77, 3.80 and 3.88 (m, 3×2H, $3CH_2O$), 6.9 (br. s, H_e). ^{13}C NMR (100.61 MHz, [$^2H_6$]benzene) δ: 13.8 [qt, 5,5-($Me$$CH_2O_2C$)$_2$, ^1J 127.0 Hz, ^2J 2.7 Hz], 14.0 (qt, 2-$Me$$CH_2O_2C$, ^1J 127.0 Hz, ^2J 2.7 Hz), 24.9 (ttd, 4-CH_2, ^1J 134.4 Hz, ^2J 3.6 Hz, ^3J 3.6 Hz), 30.3 (tt, 3-CH_2, ^1J 131.5 Hz, ^2J 3.6 Hz), 61.8 (m, 2-C), 61.75 (tq, 2-MeCH_2O_2C, ^1J 148.5 Hz, ^2J 4.3 Hz), 62.44 and 62.7 [tq, 5,5-(MeCH_2O_2C)$_2$, ^1J 149.0 Hz, ^2J 4.3 Hz], 66.7 (m, 5-C), 168.18 (m, CO, ^3J 4.3 Hz), 168.37 (m, CO, ^3J 3.6 and 2.9 Hz), 170.1 (br. s, CON), 173.6 (m, CO, ^3J 3.6 and 2.9 Hz). MS (EI, 70 eV) *m*/*z*: 258 [M – C_2H_4 – CO_2] (100), 243 (28), 183 (28), 155 (17), 137 (10), 128 (10), 116 (12), 111 (30), 100 (12), 42 (22), 29 (35), 28 (61).

2, hydrochloride: yield 90%, mp 126 °C (EtOH/Et_2O).

3: yield 92.7%, mp 271 °C (MeCN). ^{1}H NMR (400.13 MHz, CD_3OD) δ: 1.3 (t, 6H, 2Me, ^3J 7.0 Hz), 2.3 [m, 4H, $(CH_2)_2$, AA′BB′ spectrum, $\Delta\nu$ 41.2, $^2J_{AB}$ –13.4 Hz, $^2J_{A'B'}$ –13.4 Hz, $^3J_{AB'}$ 10.8 Hz, $^3J_{A'B}$ 10.8 Hz, $^3J_{BB'}$ 4.5 Hz, $^3J_{AA'}$ 4.2 Hz], 4.3 (m, 4H, $2CH_2O$, ABX_3 spectrum, $\Delta\nu$ 7.0, $^2J_{AB}$ –11.1 Hz). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 1.39 (t, 6H, 2Me, ^3J 7.0 Hz), 2.39 (m, 4H, $2CH_2$, AA′BB′ spectrum, $\Delta\nu$ 80.0), 4.40 (m, 4H, $2CH_2O$, ABX_3 spectrum, $\Delta\nu$ 13.0, $^2J_{AB}$ –12.0 Hz), 6.85 (br. s, 2H, HN). ^{13}C NMR (100.61 MHz, [$^2H_6$]DMSO) δ: 14.12 (qt, Me, ^1J 126.4 Hz, ^2J 2.9 Hz), 27.7 [t, $(CH_2)_2$, ^1J 138.1 Hz], 62.0 (tq, CH_2O, ^1J 148.2 Hz, ^2J 4.4 Hz), 65.31 (s, CCO_2Et), 165.85 (CO_2). MS (EI, 70 eV, resolution 5000, for M$^+$ found: 284.1008, calc. for $C_{12}H_{16}N_2O_6$: 284.100836) *m*/*z*: 284 [M$^+$] (48), 238 (38), 213 (20), 182 (12), 167 (25), 165 (57), 154 (13), 136 (12), 58 (46), 43 (100).

‡ *Crystallographic data for* **3**: $C_{12}H_{16}N_2O_6$, M = 284.1, monoclinic crystals, space group $P2_1/n$, a = 10.189(2) Å, b = 5.568(1) Å, c = 24.114(5) Å, β = 95.39(2)°, V = 1361.9(5) Å^3, Z = 4, d_{calc} = 1.386 g cm^{-3}, μ(MoKα) = = 1.12 cm^{-1}, F(000) = 600. Intensities of 2369 reflections were measured on a Siemens P3 diffractometer at 20 °C (λMoKα radiation, $\theta/2\theta$ scan technique, $2\theta < 50°$), and 2009 independent reflections were used in further calculations and refinement. The structure was solved by a direct method and refined using the full-matrix least-squares method against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the difference Fourier synthesis with the exception of the hydrogens of the ethyl groups, the positions of which were calculated and included in the further refinement using a riding motion model. The difference Fourier synthesis for **3** revealed additional peaks which were interpreted as a disorder of the ethyl groups by two positions with equal occupancies. The refinement is converged to wR_2 = 0.1823 and GOF = 1.02 for all independent reflections [R_1 = 0.0593 is calculated against F for 1520 observed reflections with $I > 2\sigma(I)$]. The number of refined parameters is 241. All the calculations were performed using SHELXTL PLUS 5.0 on an IBM PC/AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, 1998, Issue 1. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/32.

It should be noted that the present synthesis of **3** is the simplest method of functionalisation for the parent dilactam from this series (*cf*. ref. 22), derivatisation of **3** is in progress.

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