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3,3′-Bi(6,8-dialkyl-2,4-dioxa-7-thia-6,8-diazabicyclo[3.3.0]octane 7,7-dioxides) as new heterocyclic system derivatives

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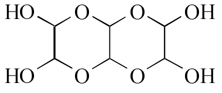
The title compounds were synthesised by condensation of *N,N′*-dialkylsulfamides with glyoxal and structurally characterised by X-ray diffraction analysis.

Cyclic sulfamides are biologically active substances.[1,2] The reactions of sulfamides and *N*-alkylsulfamides with 1,2-dicarbonyl compounds are widely used in the synthesis of 1,2,5-thiadiazole (thiadiazoline) 1,1-dioxides.[1,2]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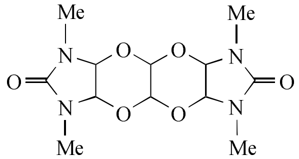
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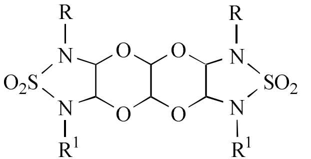
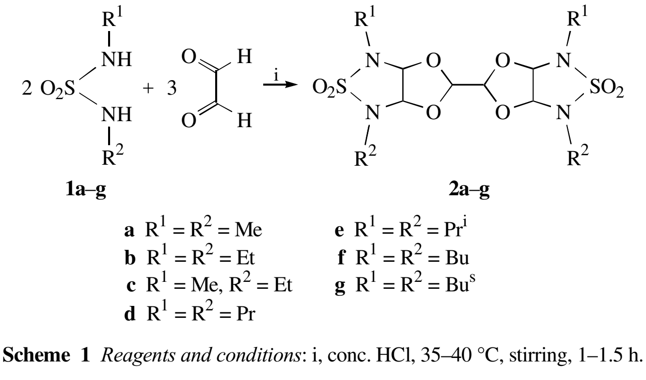

2′

Here, we studied the condensation of *N,N′*-dialkylsulfamides **1** with glyoxal and synthesised 3,3′-bi(6,8-dialkyl-2,4-dioxa-7-thia-6,8-diazabicyclo[3.3.0]octane 7,7-dioxides) **2**, the derivatives of the new [1,3]dioxolano[4,5-*c*][1,2,5]thiadiazolidine heterocyclic system (Scheme 1). The use of a trimeric dihydrate of glyoxal instead of aqueous glyoxal solution in the condensation with **1** resulted in an increase in the yield of compounds **2** from 5–11 to 54–85%.

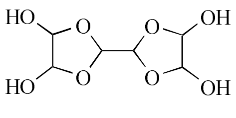


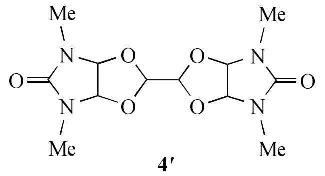
Scheme 1 *Reagents and conditions*: i, conc. HCl, 35–40 °C, stirring, 1–1.5 h.

We cannot decide between the structures of **2** and **2′** based on the data of elemental analysis, mass spectrometry and ^{1}H NMR spectroscopy.† By analogy with trimeric glyoxal dihydrate[3] **3** and the product of the condensation of *N,N′*-dimethylurea with glyoxal[4] **4**, the structure of **2′** should be attributed to the compounds.

On the other hand, the mass spectra of all the prepared compounds exhibit intense peaks corresponding to the halved molecular weight. This fact counts in favour of structure **2**. It is also well known that the oligomerisation of glyoxal in aqueous solutions results in not only dioxane but also dioxolane structures.[5,6]

A mass-spectrometric study of trimeric glyoxal dihydrate and compound **4**, which was synthesised according to a published procedure,[4] showed that their mass spectra, as well as the mass spectra of products **2**, exhibited peaks corresponding to the halved molecular weights. Thus, we can believe that these compounds can exist as dioxolane structures **3′** and **4′**.


3′


4′

To independently determine the structure of compound **2g**, a single crystal of **2g** was examined by X-ray diffraction analysis.‡ It was found that the reaction product is a compound in which two bicyclic units are connected by carbon–carbon bond (Figure 1) rather than a triply annelated tetracycle.

In the crystal of **2g** a molecule occupies a special position – the centre of symmetry lying in the middle of the C(3)–C(3′) bond. The bicyclic fragment is constructed of *cis*-combined thiadiazolidine and dioxolane rings with both hydrogen atoms at C(3) and C(3′) orientated inside the 'half-open books' of the bicycles. The thiadiazolidine ring is characterised by the conformation of flattening envelope with the deviation of the N(6) atom by 0.24 Å. The dioxolane ring is characterised by a twist conformation with the C(3) and O(2) atoms shifted by 0.37 and –0.18 Å, respectively. The relative configurations of the asymmetric centres in a bicyclic fragment are C(5) – *S*, C(1) – *R* and of the pseudo asymmetric atom C(3) – *s*.

An analysis of the crystal packing of **2g** demonstrated that shortened contacts between H(1) and H(5) atoms and oxygen atoms of sulfo group occur in the crystal. These C–H···O contacts combine molecules to form corrugated layers parallel to crystallographic plane *ab* (Figure 2).

Compounds **2** bear four asymmetric carbon atoms each (1, 5, 1′ and 5′) in bicyclic units (Figure 1).

When the substituents at nitrogen atoms are identical, the molecule of **2** has a plane of symmetry and are *meso*-forms (**2a**,**b**,**d**–**f**). When the substituents at nitrogen atoms are structurally or configurationally different (methyl or ethyl in **2c**; 1*R*- or 1*S*-methylpropyl in **2g**) the products are obtained as the mixtures of diastereomeric *meso*-forms and racemates. 3,3′-Bi{6,8-

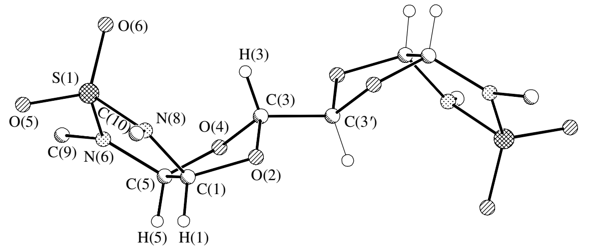
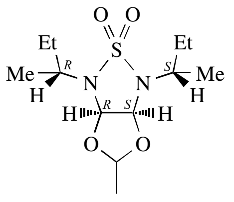
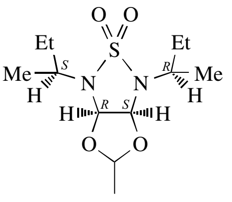


Figure 1 The general view of a molecule of **2g**. The 1-methylpropyl substituents are omitted for clarity.

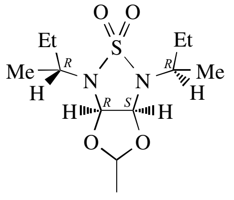
di(1-methylpropyl)-2,4-dioxa-7-thia-6,8-diazabicyclo[3.3.0]octane 7,7-dioxide} **2g** has four additional chiral centres in the substituents at nitrogen atoms. The C[3(3′)] atoms are pseudoasymmetric. Theoretically, compound **2g** can form 24 stereoisomers: the *s*, *s* and *r*, *r* configurations of C(3) and C(3′) atoms can give 7 isomers each (3 racemates and 4 *meso*-forms) and the *r*, *s* combination of configurations of these atoms can give 10 isomers (6 racemates and 4 *meso*-forms). All of these isomers are constructed of the following four stereochemically different blocks:



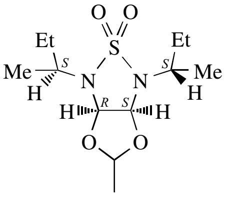
A



B



C



D

For example, the isomers with the *s*, *s* configurations of C(3) and C(3′) atoms can be presented as follows:

$$\begin{array}{ccccccc} \mathbf{A}_S & \mathbf{B}_S & \mathbf{A}_S & \mathbf{A}_S\ \ \mathbf{A}_S & \mathbf{B}_S\ \ \mathbf{B}_S & \mathbf{C}_S\ \ \mathbf{D}_S & \mathbf{C}_S \\ | & | & | & |\quad\ | & |\quad\ | & |\quad\ | & | \\ \mathbf{A}_S & \mathbf{B}_S & \mathbf{B}_S & \mathbf{C}_S\ \ \mathbf{D}_S & \mathbf{C}_S\ \ \mathbf{D}_S & \mathbf{C}_S\ \ \mathbf{D}_S & \mathbf{D}_S \\ \textit{meso}1 & \textit{meso}2 & \textit{meso}3 & \text{racemate1} & \text{racemate2} & \text{racemate3} & \textit{meso}4 \end{array}$$

In the ^{1}H NMR† spectra, the protons of the CH–CH fragment of blocks **A** and **B** exhibit two different singlets (δ 5.83, 5.88), and those of blocks **C** and **D** exhibit the AB system with the constants J_{AB} 11.7 Hz (δ_A 5.80, δ_B 5.91).

Product **2g** was separated into six fractions by HPLC. The ^{1}H

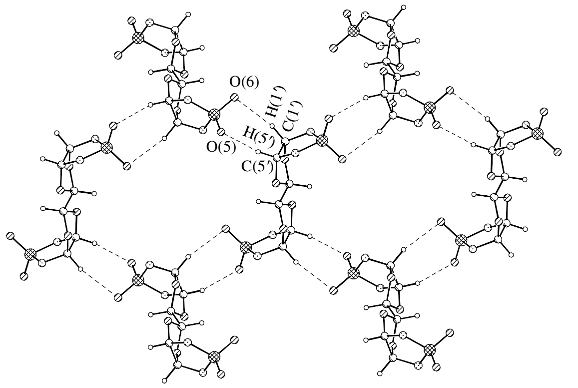


Figure 2 The C–H···O bonded corrugated layers. The 1-methylpropyl groups are omitted for clarity. The parametrs of the C–H···O contacts are H(5′)···O(5) 2.21 Å, C(5′)–H(5′)–O(5) 152°, C(5′)···O(5) 3.193(3) Å, H(1′)···O(6) 2.45 Å, C(1′)–H(1′)–O(6) 165°, C(1′)···O(6) 3.497(3) Å.

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† All new compounds gave satisfactory elemental analysis data.

^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer in a [^{2}H$_6$]DMSO solution. Chemical shifts were measured with reference to residual protons of a [^{2}H$_6$]DMSO solvent (δ 2.50 ppm). Mass spectra were measured on an MS 30 spectrometer.

2a: yield 81–85%, mp 253–254 °C (decomp.). ^{1}H NMR, δ: 2.88 (s, 12H, 4NMe), 5.03 (s, 2H, CHCH), 5.70 (s, 4H, 2CHCH). MS, *m/z* (%): 193 (26) [1/2 M$^+$], 148 (36), 83 (42).

2b: yield 54–56%, mp 219–221 °C (decomp.). ^{1}H NMR, δ: 1.30 (t, 12H, 4Me), 3.25–3.34 (m, 8H, 4NCH$_2$), 5.05 (s, 2H, CHCH), 5.77 (s, 4H, 2CHCH). MS, *m/z* (%): 441 (1), 221 (96) [1/2 M$^+$], 193 (63), 176 (92).

2c: yield 65–67%, mp 228–230 °C (decomp.). ^{1}H NMR, δ: 1.21 (t, 6H, 2Me), 2.79 (s, 6H, 2NMe), 3.21–3.30 (m, 4H, 2NCH$_2$), 5.01 (s, 2H, CHCH), 5.73, 5.88 (m, 4H, 2CHCH, AB, J_{AB} 5.8 Hz). MS, *m/z* (%): 414 (1) [M$^+$], 221 (21), 207 (100) [1/2 M$^+$], 179 (72), 162 (91).

2d: yield 72–74%, mp 173–175 °C (decomp.). ^{1}H NMR, δ: 0.98 (t, 12H, 4Me), 1.56–1.68 (m, 8H, 4CH$_2$), 3.06–3.23 (m, 8H, 4NCH$_2$), 5.03 (s, 2H, CHCH), 5.80 (s, 4H, 2CHCH). MS, *m/z* (%): 249 (87) [1/2 M$^+$], 221 (47), 204 (70) 179 (72), 111 (100).

2e: yield 54–57%, mp 229–231 °C (decomp.). ^{1}H NMR, δ: 1.30 (d, 24H, 8Me), 3.71–3.88 (m, 4H, 4NCH), 5.09 (s, 2H, CHCH), 5.88 (s, 4H, 2CHCH). MS, *m/z* (%): 498 (1) [M$^+$], 249 (61) [1/2 M$^+$], 204 (63).

2f: yield 71–72%, mp 180–182 °C (decomp.). ^{1}H NMR, δ: 0.93 (t, 12H, 4Me), 1.30–1.44 (m, 8H, 4CH$_2$), 1.56–1.68 (m, 8H, 4CH$_2$), 3.11–3.25 (m, 8H, 4NCH$_2$), 5.00 (s, 2H, CHCH), 5.75 (s, 4H, 2CHCH). MS, *m/z* (%): 277 (100) [1/2 M$^+$], 232 (81), 205 (52), 137 (42).

A mixture of **2g** stereoisomers: yield 69–71%, mp 232–234 °C (decomp.). ^{1}H NMR, δ: 0.94 (t, 6H, 2Me), 0.96 (t, 6H, 2Me), 1.23–1.37 (m, 12H, 4Me), 1.50–1.72 (m, 4H, 2CH$_2$), 1.68–1.85 (m, 4H, 2CH$_2$), 3.50–3.62 (m, 4H, NCH), 5.04 (s, 2H, CHCH), 5.79–5.92 (m, 4H, 2CHCH). MS, *m/z* (%): 553 (0.5), 277 (37) [1/2 M$^+$], 232 (95), 219 (29), 139 (100).

The diastereomers of **2c** and **2g** were separated on a Bruker LC21 liquid chromatograph at room temperature [column: Silica IBM. Eluent: light petroleum–ethyl acetate (85:15). Flow rate: 1 ml min^{-1}. Solvent: CH$_2$Cl$_2$].

Fraction 1 obtained by the HPLC separation of **2g**: ^{1}H NMR, δ: 0.85 (t, 6H, 2Me), 0.87 (t, 6H, 2Me), 1.29 (d, 12H, 4Me), 1.58–1.66 (m, 4H, 2CH$_2$), 1.66–1.74 (m, 4H, 2CH$_2$), 3.51–3.59 (m, 4H, NCH), 5.06 (s, 2H, CHCH), 5.83 (s, 4H, 2CHCH).

Fraction 2 obtained by the HPLC separation of **2g**: ^{1}H NMR, δ: 0.77 (t, 6H, 2Me), 0.79 (t, 6H, 2Me), 1.23–1.37 (m, 12H, 4Me), 1.50–1.80 (m, 8H, 4CH$_2$), 3.49–3.61 (m, 4H, NCH), 5.06 (s, 2H, CHCH), 5.83 (s, 2H, CHCH), 5.80, 5.91 (m, 2H, CHCH, AB-system, J_{AB} 11.7 Hz).

Fraction 3 obtained by the HPLC separation of **2g**: ^{1}H NMR, δ: 0.85 (t, 6H, 2Me), 0.87 (t, 6H, 2Me), 1.20–1.31 (m, 12H, 4Me), 1.48–1.78 (m, 8H, 4CH$_2$), 3.49–3.61 (m, 4H, NCH), 5.06 (s, 2H, CHCH), 5.80, 5.91 (m, 4H, 2CHCH, AB-system, J_{AB} 11.7 Hz).

Fraction 4 obtained by the HPLC separation of **2g**: ^{1}H NMR, δ: 0.85 (t, 6H, 2Me), 0.87 (t, 6H, 2Me), 1.20–1.31 (m, 12H, 4Me), 1.48–1.78 (m, 8H, 4CH$_2$), 3.49–3.61 (m, 4H, NCH), 5.06 (s, 2H, CHCH), 5.83 (s, 1H, CHCH), 5.88 (s, 1H, CHCH), 5.80, 5.91 (m, 2H, CHCH, AB-system, J_{AB} 11.7 Hz).

Fraction 5 obtained by the HPLC separation of **2g**: ^{1}H NMR, δ: 0.85 (t, 6H, 2Me), 0.87 (t, 6H, 2Me), 1.23–1.37 (m, 12H, 4Me), 1.48–1.76 (m, 8H, 4CH$_2$), 3.49–3.61 (m, 4H, NCH), 5.04, 5.08 (m, 2H, CHCH, AB-system, J_{AB} 1.4 Hz), 5.88 (s, 2H, CHCH), 5.80, 5.91 (m, 2H, CHCH, AB-system, J_{AB} 11.7 Hz).

Fraction 6 obtained by the HPLC separation of **2g**: ^{1}H NMR, δ: 0.85 (t, 6H, 2Me), 0.87 (t, 6H, 2Me), 1.23–1.37 (m, 12H, 4Me), 1.48–1.76 (m, 8H, 4CH$_2$), 3.49–3.61 (m, 4H, NCH), 5.06 (s, 2H, CHCH), 5.88 (s, 2H, CHCH), 5.80, 5.91 (m, 2H, CHCH, AB-system, J_{AB} 11.7 Hz).

3: MS, *m/z* (%): 135 (1), 117 (1), 105 (42) [1/2 M$^+$], 88 (13), 77 (8), 60 (93), 58 (98).

4: yield 18–20%, mp 236–238 °C (decomp.) [lit.,[4] 237–239 °C (decomp.)]. ^{1}H NMR, δ: 2.71 (s, 12H, 4NMe), 4.77 (s, 2H, CHCH), 5.60 (s, 4H, 2CHCH). MS, *m/z* (%): 313 (0.5) [M$^+$], 157 (46) [1/2 M$^+$], 157 (45), 129 (47), 112 (100).

‡ *Crystallographic data for* **2g**: crystals of $C_{22}H_{42}N_4O_8S_2$ are orthorhombic at 110 K, space group *Pbca*, a = 12.6834(9) Å, b = 11.5267(9) Å, c = 19.548(1) Å, V = 2857.9(4) Å^3, Z = 4, M = 554.72, d_{calc} = 1.289 g cm^{-3}, μ(MoKα) = 2.35 cm^{-1}, F(000) = 1192. Intensities of 15138 reflections were measured on a Smart 1000 CCD diffractometer at 110 K [λ(MoKa) = = 0.71072 Å, ω-scans with 0.3° step in ω and 20 s per frame exposure, $2\theta < 50°$], and 2517 independent reflections (R_{int}=0.0704) were used in further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The analysis of the Fourier synthesis has revealed that both 1-methylpropyl fragments are disordered. This disorder is the result of superposition of these fragments with different conformations along the N–C bond. The positions of the hydrogen atoms were calculated from the geometrical point of view. The refinement converged to wR_2 = 0.1866 and GOF = 0.890 for all independent reflections [R_1 = 0.0695 was calculated against F for 1348 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0 on 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.*, Issue 1, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/94.

NMR spectroscopy data of the fractions suggest that both **2g** isomers with *s*, *s* configurations of atoms C(3) and C(3′) and at least the isomers with *s*, *r* configurations were present (fraction 5[†]).

The C(3) and C(3′) atoms of 3,3′-bi(*N*-ethyl-*N*′-methyl-2,4-dioxa-7-thia-6,8-diazabicyclo[3.3.0]octane 7,7-dioxide) **2c** are asymmetric. Theoretically two *meso*-forms and four racemates of **2c** may exist. Compound **2c** gave two HPLC peaks. In the ^{1}H NMR spectra, the *meso* forms and racemates were not resolved.

Thus, a simple one-pot method was proposed for the synthesis of 3,3′-bi(6,8-dialkyl-2,4-dioxa-7-thia-6,8-diazabicyclo[3.3.0]octane 7,7-dioxides) **2** (a derivative of the new heterocyclic system [1,3]dioxolano[4,5-*c*][1,2,5]thiadiazoline) from the accessible components *N*,*N*′-dialkylsulfamides and trimeric glyoxal dihydrate. The structure of the new compound was found by X-ray diffraction analysis.

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