Note

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Crystal structure of a dimeric 1-benzothiepin

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Abstract: The crystal structure of the 1-benzothiepin derivative *meso*-**5** is presented. Compound **5** is the first dimeric 1-benzothiepin system.

Keywords: dimerization; meso-4,4′-bi(1-benzothiepinyl); thiepin.

1 Introduction

1-Benzothiepins (**1**) represent an important class of compounds for many applications in pharmacology and biology. Although more than 18,000 derivatives of 1-benzothiepin are registered in SciFinder, no simple dimer of 1-benzothiepin (**1**) is known. Exceptions exist only for some tetrahydrobi(dibenzothiepinyl)s **2** [1–3] and **3** [4–6], which are antihistaminic or neurotropic and psychotropic agents. We report here on an unexpected formation and the crystal structure of 4,4′,5,5′-tetrahydro-4,4′-bi(1-benzothiepinyl)-2,2′,4,4′-tetracarboxylic acid tetraethyl ester.

1.1 Results and discussion

2*H*-1-Benzothietes are versatile synthons for the preparation of various *S*-heterocycles [7–13]. Diester **4**, our starting compound, was prepared by the reaction of diethyl (*Z*)-4-diazo-2-ethoxy-pent-2-enedioate, and 2*H*-1-benzothiete in the presence of rhodium (II) acetate as catalyst [14]. We tried to transform **4** to the corresponding thiepin by ether cleavage with BBr_3 and dehydrobromination with $NaOCH_3$ (Scheme 1). Instead of the expected 1-benzothiepin diester, we got a multicomponent mixture, which refrained from separation. However, after allowing an ethanol solution of the mixture to stand for several days at 0 °C, we observed the formation of colorless crystals (13 % yield). Their crystal structure analysis revealed the structure of the dimer *meso*-**5**. As its stereoselective formation is unlikely, we assume that the stereoisomers (*R*,*R*)-**5** and (*S*,*S*)-**5** were formed as well.

Assuming that the dimerization proceeds *via* radical or ionic intermediates (Fig. 1), it may be expected that (*R*,*R*)-, (*S*,*S*)-, and (*R*,*S*)-2,2′-dimers as well as (2*R*,4′*S*)-, (2*R*,4′*R*)-, (2*S*,4′*R*)-, and (2*S*,4′*S*)-dimers could be formed in addition to (*R*,*R*)-**5**, (*S*,*S*)-**5**, and (*R*,*S*)-**5**. This might explain the complexity of the ^{1}H NMR spectra of the crude product.

Figure 2 shows the SCHAKAL plot, and Fig. 3 shows the unit cell of the X-ray diffraction of *meso*-**5**. The most important bond lengths, bond angles, and torsion angles are listed in Table 1.

The length of the σ bond between the monomer units is extended to about 1.60 Å. The seven-membered rings are tilted against each other. Moreover, they are puckered, which is indicated by the torsion angles listed in Table 1.

2 Conclusion

Besides 2,2′-bithiepan [15] and the bi(dibenzothiepinyl)s **2** and **3**, shown in Fig. 4, the compound *meso*-**5** represents one of the very few known thiepin dimers and actually the first 1-benzothiepin dimer. The crystal structure analysis revealed tilted, puckered seven-membered rings, which are connected by a σ bond with an extended length of about 1.60 Å.

3 Experimental section

3.1 Reaction of 4-ethoxy-4,5-dihydro-1-benzothiepin-2,4-dicarboxylic acid diethyl ester (4)

To **4** (60 mg, 0.17 mmol), dissolved in 5 mL of dry CH_2Cl_2, a solution of 43 mg (0.17 mmol) BBr_3 in 2 mL of dry CH_2Cl_2 was added slowly at –78 °C. The mixture was

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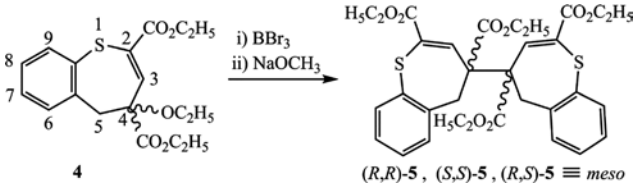

Scheme 1: Formation of dimeric 1-benzothiepin derivatives.

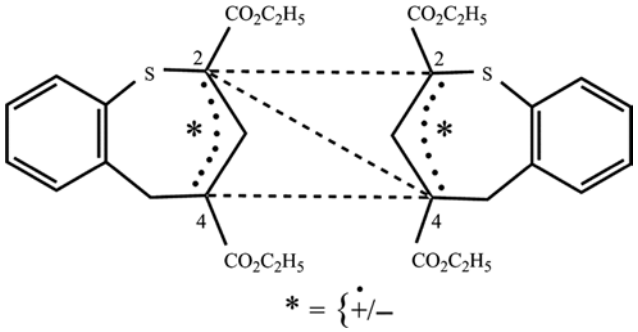

Fig. 1: Possible dimerization reactions of radical or ionic intermediates.

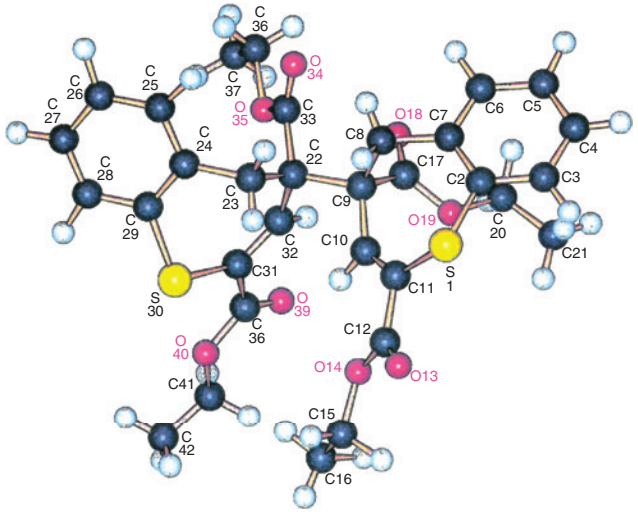

Fig. 2: Molecular structure of *meso*-**5** in the crystalline state (SCHAKAL plot).

stirred overnight, and the reaction temperature was slowly raised to room temperature. Water (10 mL) was added, and the aqueous layer was extracted with 30 mL of CH_2Cl_2. The unified organic layers were evaporated at 0.1 kPa, and the residue was treated at ambient temperature with a solution of Na (23 mg, 1.0 mmol) in 10 mL of anhydrous ethanol. A ^1H NMR probe in $CDCl_3$ revealed a complex mixture of products. However, after a few days at 0 °C, colorless crystals of *meso*-**5** (6.8 mg, 13 %, m.p. 137 °C) could be collected from the ethanol phase.

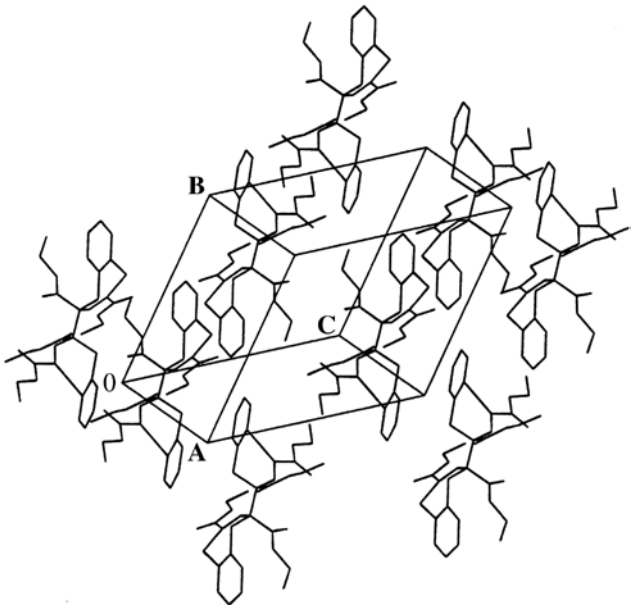

Fig. 3: Projection of the crystal structure of *meso*-**5**.

Table 1: Selected bond lengths (Å), bond angles (deg), and torsion angles (deg) of the molecular structure of *meso*-**5** in the crystal.

C(9)–C(22)	1.599(2)
C(2)–S(1)	1.757(2)
C(11)–(S(1)	1.763(2)
C(29)–S(30)	1.764(3)
C(31)–S(30)	1.761(2)
C(2)–S(1)–C(11)	106.34(9)
C(29)–S(30)–C(31)	102.98(1)
C(2)–S(1)–C(11)–C(10)	–27.8(3)
C(7)–C(8)–C(9)–C(10)	77.3(2)
C(24)–C(23)–C(22)–C(32)	–64.1(3)
C(29)–S(30)–C(31)–C(32)	38.7(3)

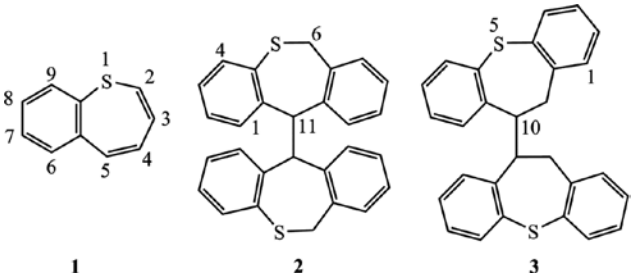

Fig. 4: 1-Benzothiepin (**1**), 6,6′,11,11′-tetrahydro-11,11′-bi(dibenzo[*b*,*e*]thiepinyl) (**2**), and 10,10′,11,11′-tetrahydro-10,10′-bi(dibenzo[*b*,*f*]thiepinyl) (**3**).

3.2 Crystal structure analysis

Details of the crystal structure analysis of *meso*-**5** are summarized in Table 2. The measurement was performed

Table 2: Crystal structure data of **5**.

Formula	$C_{32}H_{34}O_8S_2$
M_r	610.71
Habit	Colorless block
Crystal size, mm³	0.500 × 0.625 × 0.750
Crystal system	Triclinic
Space group	$P\bar{1}$
Cell parameters	
a, Å	10.2936(9)
b, Å	12.291(2)
c, Å	13.648(1)
α, deg	69.225(9)
β, deg	89.351(9)
γ, deg	76.659(9)
V, Å³	1566.1(3)
Z	2
D, g/cm³	1.295
Radiation	MoK_α
μ, mm⁻¹	0.6
F(000), e	1160
T, K	298 K
θ_{max}, deg	29.97
Measured refl	9578
Independent refl	9106
R (int)	0.008
Observed ref. [$F_o/\sigma(F_o) > 4.0$]	6328
Refined parameters	399
$R1$ ($F^2 > 2\,\sigma(F^2)$)	0.0578
$wR2$	0.1853
S	1.017
$\Delta\rho_{fin}$ (max/min), e Å⁻³	0.71/−0.38

with an Enraf-Nonius CAD-4 diffractometer applying the Enraf Nonius Software V5 [16]. Structure solution and refinement were done with the programs SIR-97 [17] and SHELXL-97 [18].

CCDC 150223 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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