Synthesis of Benzobis[1,3]oxathiins

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In memoriam Professor *Alan R. Katritzky*

Two different synthetic concepts led to the formation of **17**, **19**, and **29**, the first structural isomeric benzobis[1,3]oxathiins. Hetero-*Diels–Alder* reactions of diethyl mesoxylate **14** and the open valence isomers of the benzobisthietes **12** and **18** yielded the linear benzobis[1,3]oxathiin **17** and its angular isomer **22**, respectively. The isomeric angular system **29** could be obtained by a twofold *O*,*S*-acetalization reaction of the dihydroxydisulfanyl compound **27** and acetone (**28**).

Introduction. – Although more than 400 different compounds were studied, which contain the skeleton of benzoxathiins **1a**, **1b**, until now none of the altogether 16 isomeric benzobis[1,3]oxathiins **2a**, **2b** – **11a**, **11b** is known – neither a parent compound nor any derivative (*Fig.*). This result of a *SciFinder* search is all the more surprising, since interesting biological or pharmacological applications of **1a** and **1b** exist [1][2]. Moreover, numerous examples of the corresponding benzobis[1,4]oxathiins were described [3 – 13]. This stimulated us to synthesize the first compounds of the types **2b**, **6b**, and **10a** (*Fig.*).

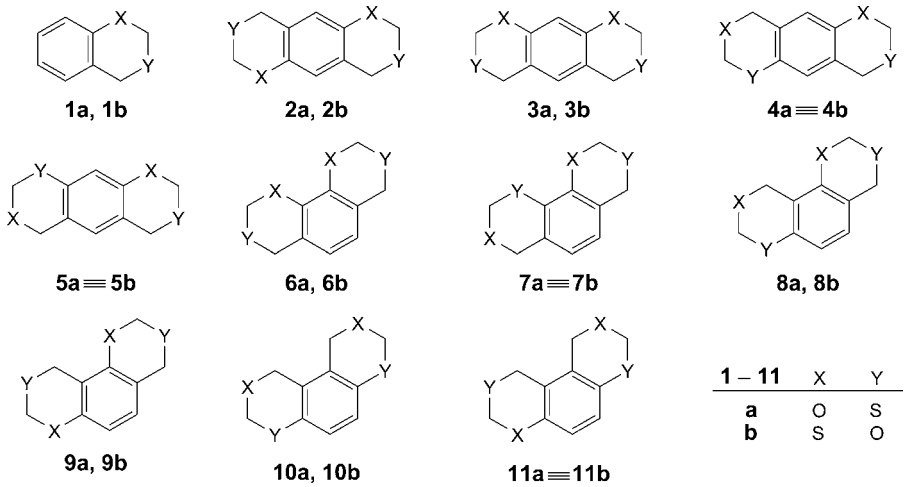


Figure. *1,3-Benzoxathiins* **1a**, **1b** *and possible benzobis[1,3]oxathiins* **2a**, **2b** – **11a**, **11b**

Results and Discussion. – Our primary synthetic concept was based on hetero-*Diels–Alder* reactions of the valence isomers of benzobisthietes (*Scheme 1*). Ring opening of 2*H*,5*H*-benzo[1,2-*b*:4,5-*b*′]bisthiete (**12**) [14] in boiling toluene generated the intermediate **13**, to which was added diethyl mesoxylate (**14**) to yield the monoadduct **15**. The second ring opening formed intermediate **16**, which entered a second hetero-*Diels–Alder* reaction to give **17** in high yield. The stepwise process was established by spectroscopic identification of the intermediate monoadduct **15**. The ^{1}H- and ^{13}C-NMR signals of the ring-CH_2 groups permit an easy pursuit of the reaction. The δ(H) and δ(C) values of the CH_2 groups in the four-membered rings differ characteristically from the corresponding δ values in the stepwise formed six-membered rings (*Table*). The hetero-*Diels–Alder* reactions proceed with high regioselectivity. Although the $[8\pi + 2\pi]$ cycloaddition can be orbital-controlled [15], a charge-controlled route would lead to the same product.

After the linear tricyclic compound **17**, we synthesized the isomeric angular system **22** by an analogous procedure (*Scheme 2*). Reaction of 2*H*,3*H*-benzo[1,2-*b*:4,3-*b*′]bisthiete (**18**) [16] with **14** gave **22** in moderate yield. The NMR spectra of the crude product revealed again the stepwise formation of the two 1,3-oxathiin rings (*Table*). In comparison to the reaction of **12**, bisthiete **18** has a much higher tendency to polymerize in boiling toluene.

Scheme 1. *Preparation of Compound* **17**

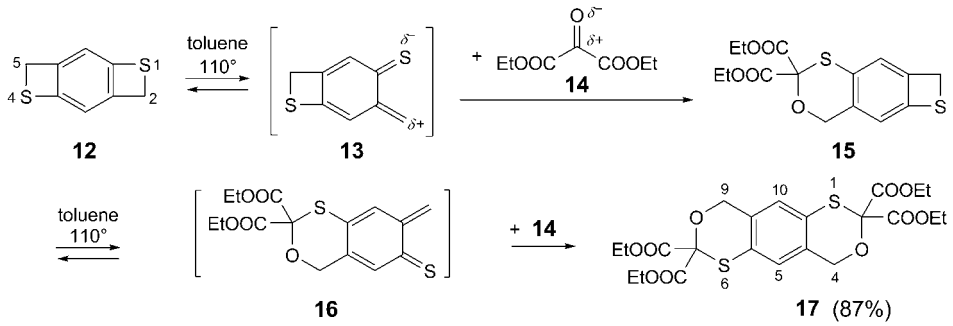
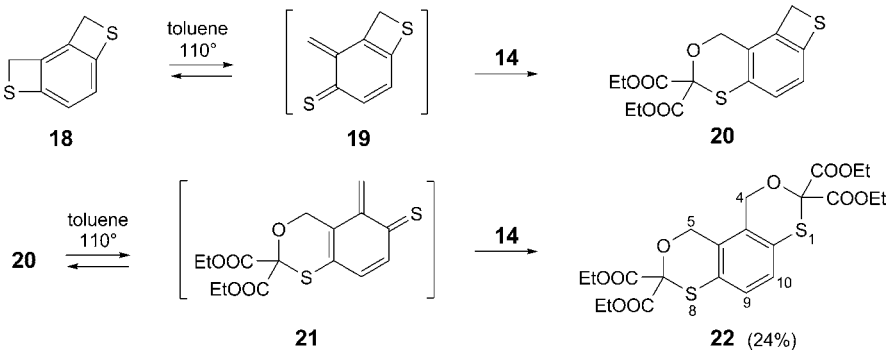


Table. *^{1}H- and ^{13}C-NMR Data* ($CDCl_3$) *of the Ring-CH_2 Groups in Compounds* **12**, **15**, **17**, **18**, **20**, **22**, **19**, *and* **30**. δ in ppm rel. to Me_4Si as internal standard.

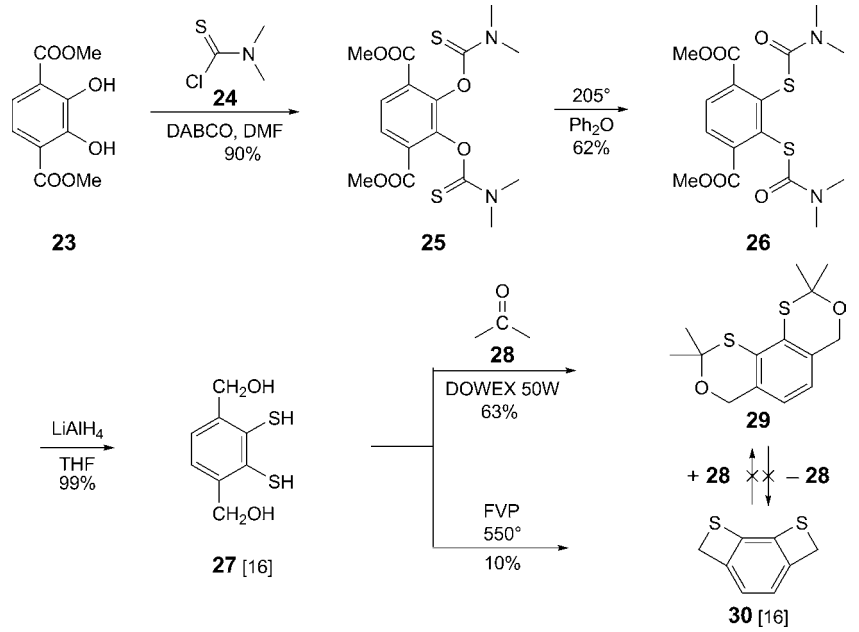
		12		**15**		**17**		**18**	
		δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
Ring size	4	4.22	36.1	4.25	36.3			4.16	34.7
	6			4.73	68.4	4.80	67.6		
		20		**22**		**29**		**30**	
		δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
Ring size	4	4.24	34.8					4.27	37.8
	6	4.70	64.0	4.88	63.5	4.84	64.6		

Scheme 2. *Preparation of Compound* **22**



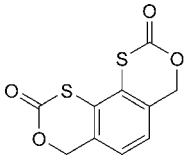
A different synthetic strategy was applied for the generation of the angular system **29** (*Scheme 3*). We started with commercially available 2,3-dihydroxyterephthalate **23**. The reaction with *N*,*N*-dimethylthiocarbamoyl chloride (**24**) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) yielded the twofold thiocarbamate **25**, which was subjected to a *Newman–Kwart* rearrangement at 205° in diphenylether to yield the isomer **26** [16]. Reduction with $LiAlH_4$ gave the bisthiol **27**. The target compound **29**, a cyclic bis-*O*,*S*-acetal, could then be obtained by the reaction of **27** with acetone (**28**) in the presence of the catalyst *DOWEX 50W*®. Flash-vacuum pyrolysis of **27** at 550° yielded the bisthiete **30** [16]. However, in contrast to the reaction of **14** with

Scheme 3. *Preparation of Compound* **30**



benzothietes and bisthietes, the reactivity of acetone (**28**) in hetero-*Diels–Alder* reactions is too low for the reaction with **30**. The reverse process **29** → **28** + **30** does also not take place – even not under flash vacuum conditions.

The chemoselective reaction of **27** and **28** is a precondition for the generation of a twofold *O*,*S*-acetal **29**. Phosgene in the form of its dimer (trichloromethyl chloroformate) or trimer (bis(trichloromethyl) carbonate) did not exhibit this selectivity. Instead of **31**, a vast mixture of cyclic dithiocarbonates **32** was obtained. Additionally, substitution reactions on the HO–CH_2 groups of **27** occurred. The δ(C) values of the C=O groups permitted an easy distinction between **31** and **32** (*Formulae*). Thiocarbonates of type **31** show δ values of *ca.* 165 ppm, whereas dithiocarbonates of type **32** have δ values of *ca.* 190 ppm [17]. The ^{13}C-NMR spectrum of the reaction mixture revealed predominantly signals in the range of 190 ppm; therefore we refrained from the isolation and a detailed characterization of the reaction products.



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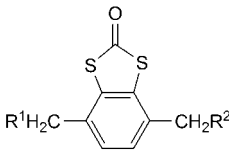

32 (R^1, R^2 = OH, Cl, ...)

The spectroscopic characterization of the benzobis[1,3]oxathiins was based on ^{1}H- and ^{13}C-NMR measurements. The most characteristic signals concern the CH_2 groups of the six-membered rings compared to the precursor systems with four-membered rings (*Table*).

Conclusions. – In this article, two methods for the preparation of benzobis[1,3]oxathiins, novel heterocyclic ring systems are described. The first method (*Schemes 1* and *2*) is based on hetero-*Diels–Alder* reactions of the open valence isomers of benzobisthietes, which react in consecutive [$8\pi + 2\pi$] processes with an electron-poor carbonyl compound. The second method (*Scheme 3*) makes use of the twofold formation of *O*,*S*-acetals from a suitable dihydroxydithiol. Both processes facilitate the accessibility of heterocyclic systems on the basis of benzothiete [18–20] or benzothiete equivalents [21–23]. From the 16 unknown benzobis[1,3]oxathiin structures shown in the *Figure*, three could be obtained by the methods described here.

Experimental Part

General. M.p.: *Büchi* melting-point apparatus. ^{1}H- and ^{13}C-NMR spectra: *Bruker AM-400* spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. FD-MS: *Finnigan-MAT-95* spectrometer, 5-kV ionization voltage; in *m*/*z*. HR-ESI-MS: *Q-TOF* with a dual source, external calibration; in *m*/*z*.

Starting Compounds: **12** [15], **18** [17], **27** [16], and commercially available **14**, **23**, **24**.

*Tetraethyl 4,9-Dihydrobenzo[1,2-*d*:4,5-*d*′]bis[1,3]oxathiine-2,2,7,7-tetracarboxylate* (**17**) *and the Intermediate Monoadduct* **15**. A soln. of benzobisthiete **12** (35 mg, 0.21 mmol) and diethyl mesoxylate (**14**) (78–87 mg, 0.45–0.50 mmol) was heated to reflux in 50 ml of dry toluene. As soon as the TLC (SiO_2;

toluene) indicated the complete consumption of **12**, the mixture was evaporated, and the crude product purified by column chromatography (CC; SiO_2, 5 × 7 cm); AcOEt/toluene gradient from 1:5 to 1:10. Yield: 94.4 mg (87%). Colorless solid. M.p. 176°. ^{1}H-NMR ($CDCl_3$): 1.25 (*t*, *J* = 7.0, 4 Me); 4.29 (*q*, *J* = 7.0, 4 CH_2O); 4.80 (*s*, H–C(4), H–C(9)); 7.23 (*s*, H–C(5), H–C(10)). ^{13}C-NMR ($CDCl_3$): 13.9 (Me); 63.1 (CH_2O); 67.4 (C(4), C(9)); 85.0 (C(2), C(7)); 126.0 (C(5), C(10)); 129.6, 135.1 (C(4a), C(5a), C(9a), C(10a)); 166.3 (CO). EI-MS: 514 (100, M^+), 441 (82), 395 (76), 267 (70). Anal. calc. for $C_{22}H_{26}O_{10}S_2$ (514.57): C 51.35, H 5.09; found: C 51.39, H 5.15.

In the first period of the reaction – in particular, when only a very small excess of dienophile **14** was applied – the intermediate monoadduct **15** could be established by its NMR data (*Table*).

*Diethyl 4,7-Dihydrothieto[2,3-*g*][3,1]benzoxathiine-2,2-dicarboxylate* (**15**). ^{1}H-NMR ($CDCl_3$): 1.23 (*t*, *J* = 7.0, 2 Me); 4.24 (*q*, *J* = 7.0, 2 CH_2O); 4.25 (*s*, H–C(5)); 4.73 (*s*, H–C(12)); 6.89, 6.97 (2*s*, H–C(2), H–C(7)). ^{13}C-NMR ($CDCl_3$): 13.9 (Me); 36.3 (C(5)); 62.9 (CH_2O); 68.4 (C(12)); 85.0 (C(10)); 119.6, 123.2 (C(2), C(7)); 126.4, 137.3, 139.7, 142.1 (C(1), C(3), C(6), C(8)); 166.6 (CO).

*Tetraethyl 1,10-Dihydrobenzo[1,2-*d*:4,3-*d′*]bis[1,3]oxathiine-3,3,8,8-tetracarboxylate* (**22**). A soln. of benzobisthiete **18** (35 mg, 0.21 mmol) and **14** (87 mg, 0.50 mmol) was heated to reflux in 50 ml of dry toluene. As soon as the TLC (SiO_2; toluene) indicated the complete consumption of **18**, the mixture was evaporated and the crude product purified by CC (SiO_2 (40 × 4 cm); petroleum ether (40–70°; PE)/AcOEt, gradient 5:1 to 3:1. Alternatively, two consecutive column chromatographies with the solvent mixtures ratio 5:1 and then 3:1 can be performed. Yield: 26 mg (24%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 1.24 (*t*, *J* = 7.0, 4 Me); 4.25 (*q*, *J* = 7.0, 4 CH_2O); 4.88 (*s*, H–C(4), H–C(5)); 7.28 (*s*, H–C(9), H–(10)). ^{13}C-NMR ($CDCl_3$): 13.9 (Me); 63.1 (CH_2O); 63.5 (C(4), C(5)); 84.7 (C(2) C(7)); 128.3 (C(9), C(10)); 129.8, 131.7 (C(4a), C(4b), C(8a), C(10a)); 166.2 (CO). HR-ESI-MS: 514.0977 (M^+, $C_{22}H_{26}O_{10}S_2^+$; calc. 514.0967).

Dimethyl 2,3-Bis[(dimethylcarbamothioyl)oxy]benzene-1,4-dicarboxylate (**25**). 2,3-Dihydroxybenzene-1,4-dicarboxylic acid dimethylester (**23**; [22], 20.0 g, 88.0 mmol), dimethylthiocarbamoylchlorid (**24**; 65.51 g, 0.53 mol) and DABCO (59.46 g, 0.53 mol) were stirred under Ar in 250 ml of dry DMF at r.t. The clear, pale yellow soln. became soon turbid. After stirring overnight, the suspension was poured on 1000 ml of an ice-water mixture. The crude product was collected, washed with H_2O and carefully dried at 105°. The obtained pale yellow product (31.87 g, 90%) melted at 146° and was analytically pure. ^{1}H-NMR ($CDCl_3$): 3.31, 3.42 (2*s*, Me_2N); 3.83 (*s*, MeO); 7.92 (*s*, H–C(5), H–C(6)). ^{13}C-NMR ($CDCl_3$): 39.0, 43.3 (Me_2N); 52.4 (MeO); 127.8 (C(5), C(6)); 128.6 (C(1), C(4)); 146.9 (C(2), C(3)); 163.5 (CO); 186.1 (CS). FD-MS: 400 (M^+, 100). Anal. calc. for $C_{16}H_{20}N_2O_6S_2$ (400.47): C 47.99, H 5.03, N 7.00, S 16.01; found: C 48 48.01, H 5.09, N 6.89, S 15.93.

Dimethyl 2,3-Bis[(dimethylcarbamoyl)sulfanyl]benzene-1,4-dicarboxylate (**26**). Ester **25** (12.0 g, 30 mmol) was heated in 180 ml of diphenylether to 205°. TLC control (SiO_2; PE/AcOEt 1:1) revealed complete consumption of **25** after approximately 45 min. The diphenylether was distilled off at 0.1 kPa and the residue purified by column filtration (SiO_2; 12 × 10 cm; PE/AcOEt 1:2). Yield: 7.54 g (63%). M.p. 96°. ^{1}H-NMR ($CDCl_3$): 2.98, 3.04 (2*s*, Me_2N); 3.81 (*s*, MeO); 7.77 (*s*, H–C(5), H–C(6)). ^{13}C-NMR ($CDCl_3$): 31.9 (Me_2N); 47.3 (MeO); 124.8 (C(5), C(6)); 131.3, 134.9 (C(1), C(2), C(3), C(4)); 160.0, 161.6 (CO). FD-MS: (400, M^+). Anal. calc. for $C_{16}H_{20}N_2O_6S_2$ (400.47): C 47.99, H 5.03, N 7.00, S 16.01; found: C 48.04, H 5.07, N 6.98, S 16.03.

(2,3-Disulfanylbenzene-1,4-diyl)dimethanol (**27**). Ester **26** (4.0 g, 10.0 mmol) suspended in 50 ml of dry THF was dropped at 0° under Ar to $LiAlH_4$ (1.90 g, 50.0 mmol) in 250 ml of dry THF. After the addition was completed, the mixture was heated to reflux. TLC control (SiO_2; PE/AcOEt) indicated the end of the reaction after 1 h reflux. AcOEt (20 ml) and H_2O (20 ml) were slowly added to the mixture at 0°. After addition of 200 ml of 2M H_2SO_4 and vigorous stirring, the mixture was extracted four times with AcOEt, 30 ml each. The combined solns. were washed with H_2O, which contained NaCl, dried ($MgSO_4$), and evaporated at 0.1 kPa. A yellow solid (2.0 g, 99%) remained, which melted at 115° and was analytically pure. ^{1}H-NMR ($CDCl_3$): 4.66 (*s*, CH_2); 7.26 (*s*, H–C(5), H–C(6)). ^{13}C-NMR ((D_6)acetone): 64.6 (CH_2); 126.0 (C(5), C(6)); 131.7 (C(2), C(3)); 140.6 (C(1), C(4)). EI-MS (70 eV): 202 (5, M^+), 166 (100, $[M - 2\ H_2O]^+$). Anal. calc. for $C_8H_{10}O_2S_2$: C 47.50, H 4.98, S 31.7; found: C 47.43, H 4.89, S 31.71.

*2,2,9,9-Tetramethyl-4,7-dihydrobenzo[1,2-*d*:6,5-*d′*]bis[1,3]oxathiine* (**29**). Diol **27** (400 mg, 2.0 mmol) was stirred in 50 ml of dry acetone (**28**) at r.t. in the presence of 50 mg of *DOWEX 50W*®, an acidic ion

exchanger. After 3 d, the excess acetone was removed, and the residue treated with PE/Et_2O 5:1. Filtration over 30 g basic Al_2O_3 led to a clear, light yellow soln. The volatile parts were evaporated. Product **29**, a highly viscous oil (353 mg, 63%), remained. ^{1}H-NMR ($CDCl_3$): 1.63 (*s*, 4 Me); 4.84 (*s*, H–C(4), H–C(7)); 6.86 (*s*, H–C(5), H–C(6). ^{13}C-NMR ($CDCl_3$): 29.9 (Me); 64.6 (C(4), C(7)); 83.3 (C(2), C(9)); 122.2 (C(5), C(6)); 129.7, 131.2 (C(4a), C(6a), C(10a), C(10b)). FD-MS: 282 (100, M^+). Anal. calc. for $C_{14}H_{18}O_2S_2$ (282.3): C 59.54, H 6.42; found: C 59.46, H 6.24.

Flash vacuum pyrolysis (FVP) of **29** at 550° and $1.5 \cdot 10^{-3}$ Pa did not yield acetone (**28**) and bisthiete **30**, which was obtained earlier by FVP of **27** [16].

When **27** was reacted with di- or triphosgene under the conditions described above, a vast mixture of products was formed, which contained – according to the ^{13}C-NMR reaction spectrum – predominantly dithioacetal structures **32**. Additionally, CH_2OH and CH_2Cl signals could be identified. A separation of the products was not performed.

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