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Stereochemistry of Seven-Membered Heterocycles: XLI.[1] Stereoselective Synthesis of 3-R-1,5-Dihydro-2,4-benzothiepine 2-Oxides

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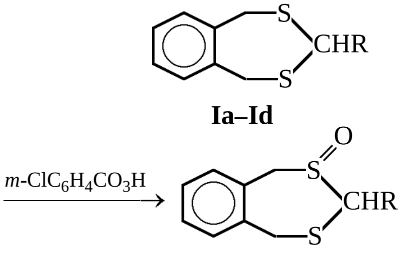
Abstract—The oxidation of 3-R-1,5-dihydro-2,4-benzothiepines with *m*-chloroperbenzoic acid occurs in a highly diastereoselective fashion. The resulting *trans*-sulfoxides at –60°C in $CDCl_3$ exist as an equilibrium mixture of the *chair* and *boat* forms with the substituents in the equatorial position. The fraction of the *boat* conformation increases in the series R = Ph, Me, *t*-Bu.

1,3-Dithiane 1-oxides are the only cyclic acetal monoxide that have found wide application for preparing various organic compounds, optically active inclusive [2].

We consider it of undeniable interest to evaluate synthetic utility of sulfoxides derived from larger cyclic dithiocetals. Here report the synthesis and stereochemical assessment of seven-membered 1,5-dihydro-2,4-benzothiepine 2-oxides.



Ia–Id

IIa–IId

R = H (**a**), CH_3 (**b**), Ph (**c**), $(CH_3)_3C$ (**d**).

In a preliminary work [3] we found that dithioacetal **Ia** is readily oxidized with *m*-chloroperbenzoic acid to the corresponding *S*-oxide **IIa**. 3-Substituted substrates **Ib**–**Id** were oxidized to the target compounds **IIb**–**IId**; therewith, the products all were isolated as a single diastereomer. To establish the configuration of the sulfoxides formed we turned to dynamic ^{1}H and ^{13}C NMR spectroscopy, since spectra recorded at room temperature showed exchange broadening.

In view of the fact that ^{13}C NMR spectroscopy is exceptionally informative as to the steric structure of dithioacetals **I** [4] which are present in solutions as an equilibrium mixture of the *chair* (*C*) and *boat* (*B*) forms [5–10], we initially examined the ^{13}C NMR spectra. As the temperature is lowered, solutions of 3-methyl(phenyl) derivatives **IIb, IIc** show a characteristic spectral pattern, and –60°C the spectra are a superposition of the spectra of two forms (Fig. 1, Table 1). At the same time, in the spectrum of compound **IId** a single conformer is only observable.

Comparison of the spectral characteristics of the *chair* form with an equatorial sulfinyl group [3], established for the model cycle **IIa**, with those for minor structures of conformationally inhomogeneous derivatives **IIb, IIc** enabled us to solve both configurational and conformational problems (Table 1). The chemical shifts of C^4 (within 1.08 ppm) and C^7 (within 0.83 ppm) proved close to each other, and the C^2 signal shifed downfield at a step of about 10 ppm in the series **IIa**–**IIc**. Analogous changes in the spectral characteristics of dithioacetal and benzyl carbon atoms are associated with the α- and γ-effects of equatorial methyl and phenyl groups in six- and eight-membered dithioacetals [4].

The information we obtained suggests that the minor conformation of sulfoxides **IIb, IIc** (0.35 and 0.46 ppm, respectively) at –60°C is a *chair* form with equatorial SO and R groups. Since the alternative *chair* form having both the substituents axial is ob-

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[1] For communication XL, see [1].

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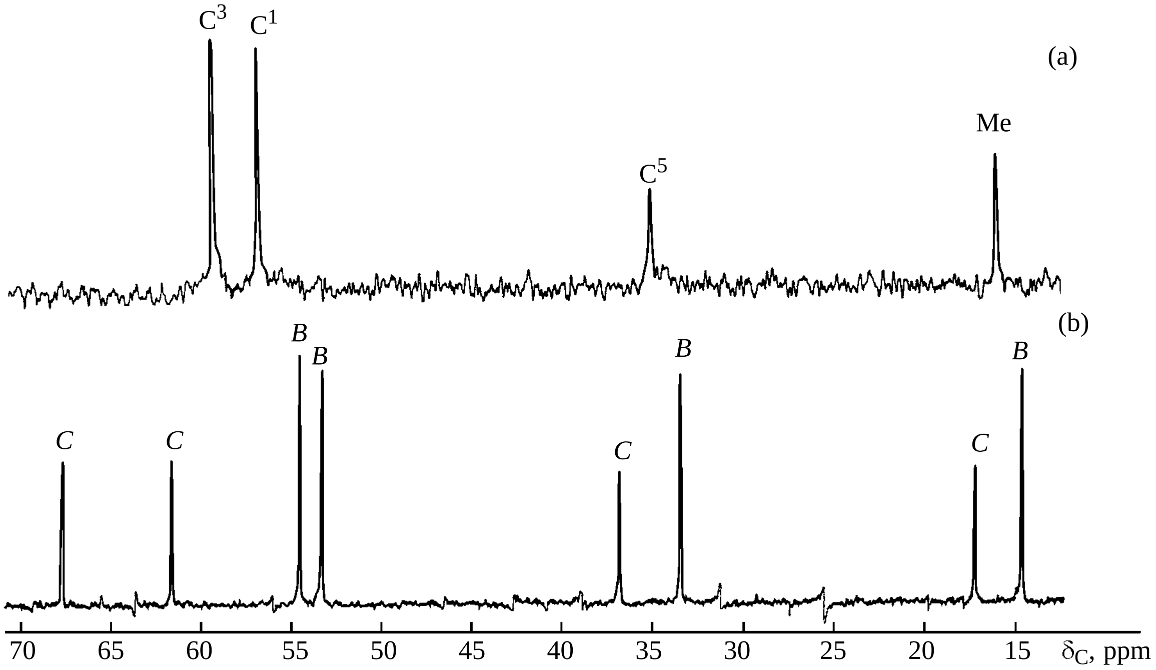
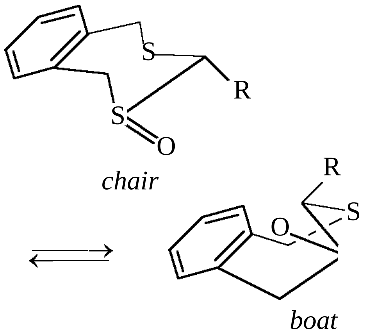


Fig. 1. ^{13}C NMR spectra of *trans*-3-methyl-1,5-dihydro-2,4-benzothiepine 2-oxide (**IIb**) in $CDCl_3$ at (a) 50 and (b) –60°C.

viously unfavored by energy [7], then the probable partner by equilibrium is a *boat* form with equatorial SO and R groups [3].

Evidence for the $C \rightleftarrows B$ equilibrium in the *trans* structures of compounds **IIb, IIc** comes from the spectral data for dominating forms. Noteworthy are larger upfield shifts of the C^1, C^3, and C^5 signals with the largest difference (>12 ppm) for the dithioacetal carbon atoms, which was earlier observed in the spectra of "frozen-out" *C* and *B* forms of compounds of the **I** series. The *ortho*-xylilene fragment proximate to C^3 in the *boat* form also exerts anisotropic effect on the more remote methyl carbons (Δδ 2.58 ppm).



The *boat* form can be assigned to 2-*tert*-butyl derivative **IId**, in view of the closeness of the chemical shifts of the benzyl carbon atoms to those for **IIb, IIc**, as well as the expected downfield shift of the C^3 signal (69.65 ppm).

Table 1. ^{13}C NMR spectra (δ_C, ppm) of 3-R-1,5-dihydro-2,4-benzothiepine 2-oxides **IIa**–**IId** in $CDCl_3$

Comp. no.	*t*, °C	C^3	C^5	C^1	R	C^{5a}–C^{9a}
IIa[a]	–70	58.38	36.84	62.50	–	128.58–135.89
	50	59.49	35.09	56.93	15.78	129.38–132.15
IIb	–60[b]	54.56 67.74	33.41 36.81	53.32 61.67	14.68 17.26	128.25–143.17
	57	69.45	35.82	57.35	128.45–133.23	
IIc	–60[b]	64.25 76.66	34.55 37.89	53.77 62.16	127.31–144.18	
IId	20	73.17	34.20	56.98	29.7 36.2	129.41–132.07
	–60	69.65	33.05	54.04	29.5 35.6	128.11–142.94

[a] The chemical shifts of the *chair-e* form are taken from [3]. Solvent $CDCl_3$–CS_2, 1:2. [b] The upper line relates to the *boat* form.

Earlier we found [3] that the ^{13}C NMR spectrum of the model sulfoxide **Ia** at –70°C contains two sets of signals of aliphatic carbon atoms, and the signals of the dominating form show tendency to exchange broadening on further lowering the temperature. These findings led us to conclude that the signals at 45.03

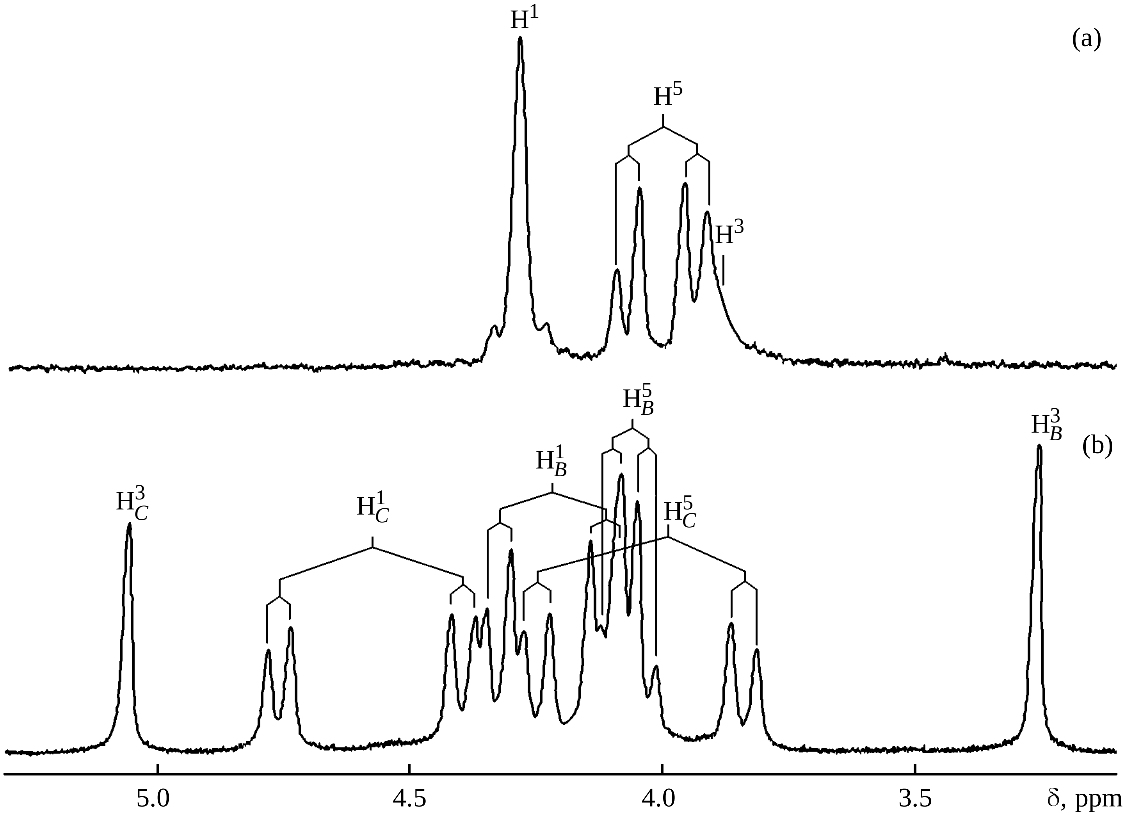


Fig. 2. ^{1}H NMR spectra of *trans*-3-phenyl-1,5-dihydro-2,4-benzothiepine 2-oxide (**IIc**) in $CDCl_3$ at (a) and –57 and (b) –60°C.

(C^3), 32.28 (C^5), and 53.05 (C^1) ppm relate to an equilibrium mixture of *boat* conformations with the equatorial and axial positions of the sufinyl group. The spectral characteristics of the *boat* forms of compounds **IIb**–**IId**, obtained in the present work, suggest an inconsiderable contribution of the axial structure of sulfoxide **IIa** in the conformational equilibrium at –70°C.

Further evidence for the prevalence of the *boat* conformation in all the cases comes from the ^{1}H NMR spectra. Lowering the temperature produces considerable changes in the spectra of compounds **IIb, IIc**. Thus, the collapse for phenyl derivative **IIc** is observed at –15°C, while at –60°C signals of both forms are observable (Table 2, Fig. 2). The benzyl hydrogen atoms have fairly close chemical shifts in the *chair* and *boat* forms. Therefore, to reveal partners in the AB quadruplets, we applied two-dimensional COSY spectra. The nonequivalence values (Δδ) for geminal hydrogen atoms in the 1 and 5 positions of compounds **IIb, IIc** are close to each other, implying similar steric structures. Note that the benzyl proton signals of both the forms of benzylidene derivative **IIc** are shifted downfield compared with those for 2-methyl analog **IIb**.

The relative positions of the H^3 signals in the "frozen-out" spectra of these compounds provide clear evidence for the shielding effect of the *ortho*-xylilene fragment in the *boat* conformation Thus, the signal of the axial hydrogen atom in the *boat* form of methyl derivative **IIb** is shifted upfield by 1.75 ppm compared with the minor *chair* form. The same is true of the *chair* and *boat* forms of compound **IIc**, where the Δδ for the H^3 signals is 1.8 ppm. Like in the ^{13}C NMR spectra, here, too, the anisotropic effect of the aromatic fragment on the methyl groups on C^3 is evident (Δδ 0.17 ppm). The populations of the *chair* and *boat* forms at –60°C, obtained by integration of signals of the methyl protons in **IIb** and of the signal of the methine proton on C^3 in **IIc** in the "frozen-out" spectra, are similar to those obtained from the ^{13}C NMR spectra.

Qualitatively new data on the conformational composition of sulfoxide **IId** could be obtained from the ^{1}H NMR spectra. This object shows an exchange process, and at –60°C the signal of the methine proton on C^3 transforms into a pair of singlets in a ~99 : 1 ratio. The stronger signal is upfield from the weaker one (Δδ 0.89 ppm); therewith, the nonequivalence of the dithioacetal hydrogen atoms has reduced by 1 ppm

Table 2. ^1H NMR spectra (δ, ppm) and spin-spin coupling constants (*J*, Hz) of 3-R-1,5-dihydro-2,4-benzothiepine 2-oxides **IIb**–**IId** in $CDCl_3$

Comp. no.	*t*, °C	H^5	H^1	H^3	R	H^6–H^9
IIb	50	3.79, 3.93	4.15	3.05	1.58 (6.9)	7.20–7.33
	–60[a]	3.93, 4.19 (–12.0)	3.93, 3.95 (–14.6)	2.38 (7.1)	1.53 (7.1)	7.16–7.44
		3.69, 4.07 (–15.1)	4.18, 4.65 (–13.2)	4.13	1.70 (7.1)	
IIc	57	3.94, 4.07 (–13.3)	4.28	3.88	7.26–7.42	
	–60[a]	4.03, 4.10 (–11.8)	4.12, 4.32	3.26	7.25–7.50	
		3.84, 4.25 (–15.1)	4.39, 4.76 (–12.9)	5.06		
IId	20	3.92, 4.33 (–13.5)	3.82	2.40	1.05	7.13–7.37
	–60[b]	3.78, 4.30 (–13.5)	3.90	2.15 3.04	1.07	7.15–7.43

[a] The upper line relates to the *boat* form. [b] The benzyl hydrogen signals of the minor form were not identified.

compared with that found in compounds **IIb, IIc**. Together with the obviously weakened α-effect of the *tert*-butyl group, these results can be explained by a certain deformation of the *boat* form produced by the bulky substituent. Evidence for this assumption is also provided by a considerable difference of the spectral parameters of the benzyl protons on C^1 and C^5 in **IId** compared with **IIb, IIc**.

Stereochemical analysis of the ^1H and ^{13}C NMR spectra of the reaction mixtures of compounds **IIb**–**IId** at ~50°C shows that the diastereoselectivity of the oxidation of dithioacetals **Ib**–**Id** is ≥90%, and the peroxy acid attacks the substrate preferentially from the side of an equatorial unshared electron pair of the sulfur atom. According to data in [11], the oxidation of 2-aryl(alkyl)substituted 1,3-dithianes with *m*-chloroperbenzoic acid and sodium metaperiodate occurs with a high diastereoselectivity with preferential formation of *trans* isomers [11]. The Kagan–Sharpless enantioselective oxidation of some 2-substituted six-membered dithioacetals was found to occur with a moderate diastereoselectivity [12, 13]. Our preliminary data show that eight-membered 3-R-2,4-dithia-3,5-dihydro-1*H*-cycloocta[*d,e*]naphthalenes that are present in solutions in the same *chair* and *boat* are preferentially oxidized from the side of an equtorial unshared electron pair of the sulfur atom.

EXPERIMENTAL

The various-temperature ^1H (300 MHz) and ^{13}C (75.43 MHz) NMR spectra of compounds **IIb, IIc** were recorded on a Varian Unity-300 spectrometer equipped with a VTC-4 thermostating unit and operating in the ^2H internal stabilization mode. Resolution 0.2 Hz with ampules 5 mm in diameter (^1H). The ^1H NMR spectra were recorded using 10°–15° pulses, pulse delay 1–2 s, spectrum width 15 ppm, scan number 8–100, no digital filtration, solvent $CDCl_3$. The ^{13}C NMR spectra were recorded using 20°–30° pulses and broad-band proton decoupling, pulse delay 5 s, spectrum width 200 ppm, scan number 400–1000, solvent $CDCl_3$.

1,5-Dihydro-2,4-benzothiepine 2-oxide was prepared by the procedure described in [3].

3-Methyl-1,5-dihydro-2,4-benzothiepine 2-oxide (IIb). To an ice-cooled solution of 0.75 g of 3-methyl-1,5-dihydro-2,4-benzothiepine (**Ib**) in 20 ml of methylene chloride we added with stirring over the course of 10 min a solution of 0.73 g of *m*-chloroperbenzoic acid (Aldrich) in 20 ml of methylene chloride. The reaction mixture was stirred for 1 h at room temperature and then washed with 10% aqueous NaOH (3 × 50 ml) and water, and dried over $MgSO_4$. The solvent was removed to obtain 0.49 g (61%) of compound **IIb** as colorless fine crystals, mp 139–140°C. IR spectrum, ν, cm^{-1}: 1030 (S=O). Found, %: C 56.71; H 5.68. $C_{10}H_{12}OS_2$. Calculated, %: C 56.57; H 5.70.

3-Phenyl-1,5-dihydro-2,4-benzothiepine 2-oxide (IIc) was prepared similarly to compound **IIb** from 0.7 g of 3-phenyl-1,5-dihydro-2,4-benzothiepine (**Ic**) and 0.51 g of *m*-chloroperbenzoic acid. Yield 0.42 g (56%), colorless crystals, mp 188°C. IR spectrum, ν, cm^{-1}: 1076 (S=O). Found, %: C 65.80; H 5.10. $C_{15}H_{14}OS_2$. Calculated, %: C 65.66; H 5.14.

3-*tert*-Butyl-1,5-dihydro-2,4-benzothiepine 2-oxide (IId) was prepared similarly to compound **IIb** from 0.5 g of 2-*tert*-1,5-dihydro-2,4-benzothiepine (**Id**) and 0.73 g of *m*-chloroperbenzoic acid. Yield 0.24 g (45%), colorless fine crystals, mp 71–73°C. IR spectrum, ν, cm^{-1}: 1035 (S=O). Found, %: C 61.55; H 7.11. $C_{13}H_{18}OS_2$. Calculated, %: C 61.38; H 7.13.

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