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The structure of substituted spirans derived from benzo-1,5-dithiepine and benzo-1,5-dioxepine systems. Ring-reversal isomers

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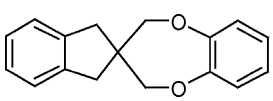
Abstract

Structural studies of newly synthesized substituted spirans, derived from methyl- and *tert*-butylbenzenes, containing either 1,5-dioxepine or 1,5-dithiepine system are reported. Crystal structures of two representative compounds were determined by X-ray diffraction. One of spirans containing 1,5-benzodithiepine appears in two isomeric forms equivalent by inversion of both spirorings. Energy calculations were carried out to find the preferred conformations. For spiran with sulfur atoms, the minimum-energy conformation is virtually identical with that in the solid state, whereas for the 1,5-dioxepine system they are different.

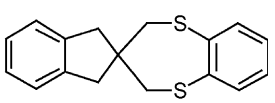
Keywords: Spiro compounds; 1,5-Dioxepine; 1,5-Dithiepine; Ring reversal; Energy calculations

1. Introduction

Interest in spiran systems has grown during the recent years because of their potential use for stereochemical studies and theoretical calculations [1,2]. Furthermore, some of these systems were detected as parts of natural products possessing antibiotic and fungicide activity [3]. Earlier studies carried out in our laboratory were connected with constitutionally symmetrical spirans [4]. Recently we have extended our investigations towards compounds containing 1,5-dioxepine (A) or 1,5-dithiepine (B) systems with various substituents.



A



B

Introduction of substituents into the aromatic moieties condensed with rings on both sides of the spiroatom was carried out as a next step to study the stereochemistry of this system. Substituents were introduced into spiro systems containing oxygen (A) and sulfur (B).

All syntheses of spiro derivatives were conducted according to Scheme 1.

As described earlier [5], the reaction derivatives of 1,2-bis(bromomethyl)benzene (**C,D,E**) with ethyl malonate gave esters (**F,1,2**), respectively, which were reduced with $LiAlH_4$ to the corresponding diols (**G,3,4**). Finally, treatment of tosylates (**H,5,6**) with the sodium salt of 1,2-benzenediol or 1,2-benzenedithiol in sealed tube afforded spirans **7–12** as stable, high-melting compounds. All new compounds were characterized by elemental analyses and spectroscopic data.

Energy calculations were carried out for compound **7** and **10** in order to establish energy preferences for various conformations. Another goal was to answer the question if the energy difference of the two isomers detected in **10** could be correlated with their occupancy factors in the solid state.

2. Experimental

2.1. General

Melting points (uncorrected): Boetius hot-stage microscope. IR spectra were recorded with a Bruker JFS 48 spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were recorded with a Bruker AMX 500 spectrometer (500 MHz proton frequency). Chemical shifts are referenced to internal

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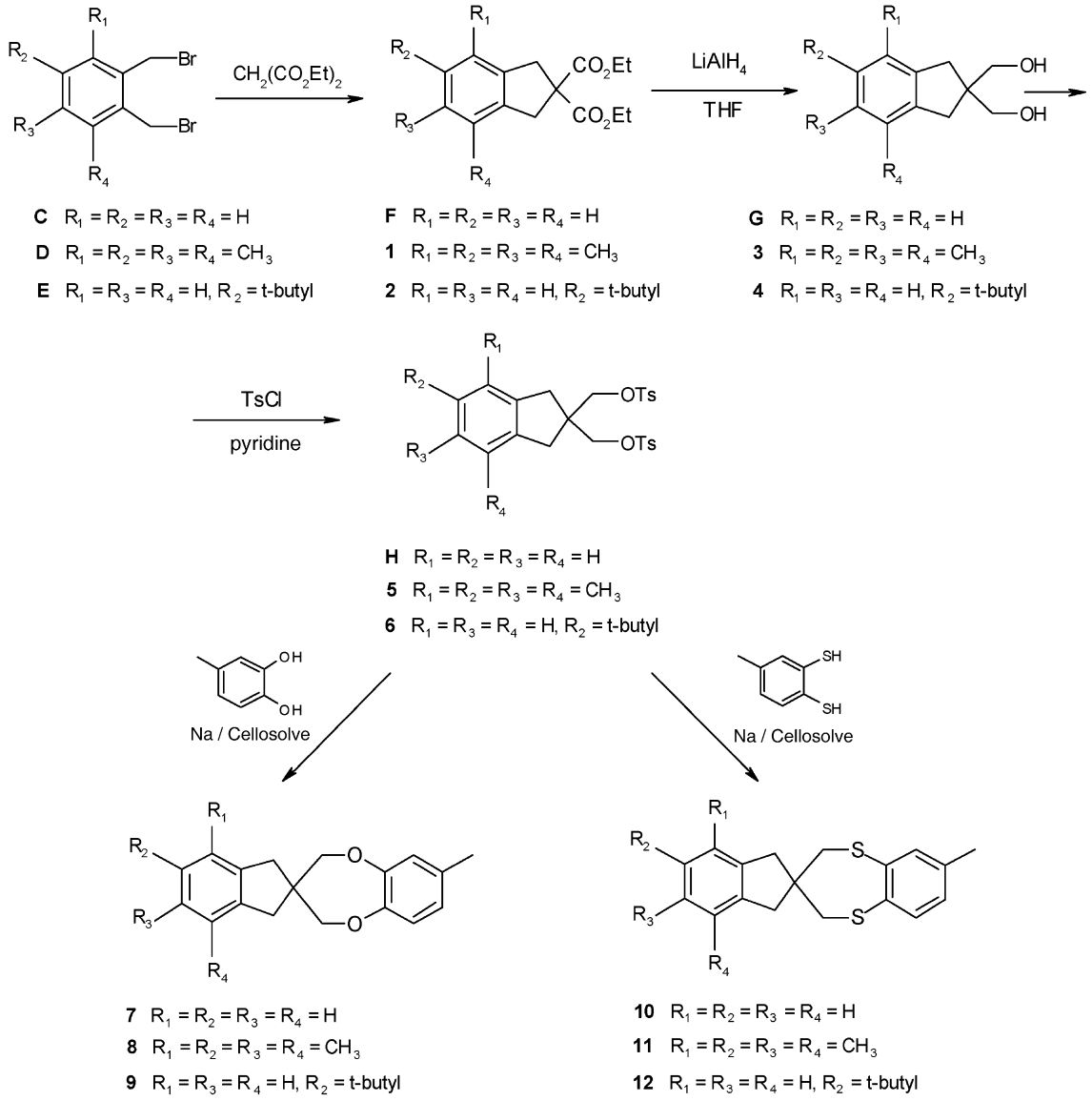

Scheme 1.

TMS. Elemental analyses: Elementar Analyzer Euro EA 3000 Eurovector; the obtained values correspond with the calculated ones within experimental error (0.4%).

*2.1.1. 2,2-Bis(ethoxycarbonyl)-4,5,6,7-tetramethyl-indan (**1**)*

Sodium (2.55 g, 110.9 mmol) was dissolved in absolute ethanol (50 ml). The mixture was cooled and a solution of diethyl malonate (8.8 g, 55.0 mmol) in absolute ethanol (25 ml) was added dropwise. The solution was stirred while **D** (13.2 g, 50.0 mmol) was added in small portions. After the reaction mixture was heated under reflux for 5 h, the ethanol was distilled off under reduced pressure. Water (100 ml) was added to the residue and the mixture was neutralized with 1 M hydrochloric acid solution. The aqueous layer was re-extracted three times with ether and ether extracts were combined with the original organic layer. The resulting ether solution was dried over anhydrous $MgSO_4$ and ether was removed. Colourless crystals (petroleum ether); 8.85 g (67.4%); m.p. 79–81 °C; IR (KBr, cm^{-1}): 2981, 2926, 2869, 1730 (C=O), 1446, 1367, 1285, 1255, 1188, 1169, 1085, 861, 801, 733; ^1H NMR ($CDCl_3$), δ: 1.26 (t, $J = 7.2$ Hz, 6H, CH_3), 2.165 (s, 6H, CH_3), 2.174 (s, 6H, CH_3), 3.55 (s, 4H, CH_2), 4.20 (q, $J = 7.2$ Hz, 4H, CH_2); ^{13}C NMR ($CDCl_3$), δ: 14.0, 15.9, 16.5, 40.3, 59.3, 61.6, 129.1, 133.6, 135.8, 172.1.

*2.1.2. 2,2-Bis(ethoxycarbonyl)-5-t-butyl-indan (**2**)*

Yellow oil; yield 58.6%; b.p. 155–160 °C/2 mmHg; IR (thin film, cm^{-1}): 2954, 2903, 2868, 1731 (C=O), 1611, 1498, 1391, 1365, 1246, 1054, 1013, 861, 822, 715; ^1H NMR ($CDCl_3$), δ: 1.25 (t, $J = 7.1$ Hz, 6H, CH_3), 1.33 (s, 9H, *tert*-butyl), 3.56 (s, 2H, CH_2), 3.58 (s, 2H, CH_2), 4.20 (q, $J = 7.1$ Hz, 4H, CH_2), 7.11 (d, $J = 7.9$ Hz, 1H, arom.H),

7.19–7.21 (m, 2H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 14.0, 31.5, 34.5, 40.1, 40.6, 60.4, 61.6, 121.0, 123.6, 124.0, 136.9, 139.8, 150.0, 171.8.

*2.1.3. 2,2-Bis(hydroxymethyl)-4,5,6,7-tetramethyl-indan (**3**)*

A solution of **1** (8.45 g, 27.8 mmol) in anhydrous THF (21 ml) was added dropwise into a solution of $LiAlH_4$ (69.5 ml of 1 M, 69.5 mmol) in anhydrous THF. The reaction mixture was heated under reflux for 4 h. Then water was added and the mixture was neutralized with 20% sulfuric acid solution. A white solid was filtered off. The filtrate was evaporated off. Resulting solid was crystallized from methanol to give 2 g (30.7%) of colourless crystals; m.p. 185–186 °C; IR (KBr, cm^{-1}): 3270 (board, O–H), 2935, 2872, 2832, 1453, 1377, 1271, 1224, 1163, 1086, 1033, 740, 686; ^{1}H NMR (DMSO-d_6), δ : 2.06 (s, 6H, CH_3), 2.09 (s, 6H, CH_3), 2.61 (s, 4H, CH_2), 3.35 (d, $J = 5.2$ Hz 4H, OCH_2), 4.52 (t, $J = 5.2$ Hz, 2H, OH); ^{13}C NMR (DMSO-d_6), δ : 15.5, 16.1, 37.4, 48.0, 64.8, 128.5, 131.6, 137.7.

*2.1.4. 2,2-Bis(hydroxymethyl)-5-t-butyl-indan (**4**)*

Colourless crystals (methanol); yield 31.4%; m.p. 123–124 °C; IR (KBr, cm^{-1}): 3285 (broad, O–H), 2962, 2871, 2837, 1495, 1380, 1362, 1082, 1048, 1018, 887, 824, 717, 604; ^{1}H NMR ($CDCl_3$), δ : 1.30 (s, 9H, *tert*-butyl), 2.78 (s, 2H, CH_2), 2.82 (s, 2H, CH_2), 2.93 (broad s, 2H, OH), 3.74 (s, 4H, OCH_2), 7.10 (d, $J = 7.9$ Hz, 1H, arom.H), 7.17–7.20 (m, 2H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 31.6, 34.5, 38.1, 38.6, 49.0, 69.5, 121.9, 123.6, 124.4, 138.5, 141.4, 149.7.

*2.1.5. Bistosylate of 2,2-bis(hydroxymethyl)-4,5,6,7-tetramethyl -indan (**5**)*

Compound **3** (2.0 g, 8.6 mmol) was dissolved in dry pyridine (10 ml). Toluene-4-sulfonyl chloride (3.5 g, 18.0 mmol) was added in small portions to cooled and stirred solution of **3**. The resulting solution was stirred overnight at room temperature and poured into cold hydrochloric acid (1:1). Colourless solid was filtered off, washed with water to pH7 and dried under vacuum. Crude product was crystallized from methanol to give 4.34 g (93.7%); m.p. 156–157 °C; IR (KBr, cm^{-1}): 3068, 2953, 2923, 2898, 2848 (CH_2, CH_3), 1596, 1465, 1376, 1359, 1176 (SO_2), 1095, 985, 966, 831, 791, 665; ^{1}H NMR ($CDCl_3$), δ : 2.04 (s, 6H, CH_3), 2.14 (s, 6H, CH_3), 2.45 (s, 6H, CH_3), 2.69 (s, 4H, CH_2), 3.95 (s, 4H, OCH_2), 7.33 (d, $J = 8.0$ Hz, 4H, arom.H) 7.74 (d, $J = 8.0$ Hz, 4H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 16.0, 16.4, 21.6, 38.1, 45.4, 71.7, 127.9, 129.7, 129.9, 132.6, 133.8, 135.4, 145.0.

*2.1.6. Bistosylate of 2,2-bis(hydroxymethyl)-5-t-butyl-indan (**6**)*

Colourless crystals (methanol); yield 91.9%; m.p. 107–108 °C; IR (KBr, cm^{-1}): 3055, 2954, 2902, 2862 (CH_2, CH_3), 1598, 1496, 1456, 1362, 1176 (SO_2), 1095, 964, 853, 787, 666; ^{1}H NMR ($CDCl_3$), δ : 1.28 (s, 9H, *tert*-butyl), 2.44 (s, 6H, CH_3), 2.70 (s, 2H, CH_2), 2.73 (s, 2H, CH_2), 3.94 (s, 4H, OCH_2), 6.99 (d, $J = 8.0$ Hz, 1H, arom.H), 7.09 (s, 1H, arom.H) 7.15 (dd, $J = 1.8$ Hz, $J = 8.0$ Hz, 1H, arom.H), 7.33 (d, $J = 8.4$ Hz, 4H, arom.H), 7.73 (d, $J = 8.4$ Hz, 4H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 21.6, 31.4, 34.5, 37.8, 38.3, 47.0, 71.3, 121.7, 124.2, 124.4, 127.9, 129.4, 132.5, 136.6, 139.5, 145.0, 150.3.

*2.1.7. Spiro[2H-(7-methylbenzo)[f]-3,4-dihydro-1,5-dioxepine-3,2′-indan] (**7**)*

A mixture of cellosolve (13 ml), sodium (0.31 g, 13.5 mmol), 4-methylcatechol (0.87 g, 7.0 mmol) and bistosylate of 2,2-bis(hydroxymethyl)-indan (3.00 g, 7.0 mmol) in sealed tube was heated at 120 °C for 80 h. After opening the tube and evaporation of the solvent the residue was dissolved in toluene and sodium tosylate was filtered off. The product **7** was chromatographed on Al_2O_3 using toluene as an eluent. Colourless crystals (chloroform–methanol); 210 mg (11%); m.p. 104–106 °C; IR (KBr, cm^{-1}): 3067, 3022, 2961, 2941, 2882, 2851 (CH_2), 1503, 1482, 1460, 1386, 1308, 1272, 1251, 1197, 1107, 1038, 1017, 922, 859, 816, 742; ^{1}H NMR ($CDCl_3$), δ : 2.25 (s, 3H, CH_3), 2.96 (s, 4H, CH_2), 4.01 (s, 2H, OCH_2), 4.02 (s, 2H, OCH_2), 6.73 (dd, $J = 1.7$ Hz, $J = 8.0$ Hz, 1H, arom.H), 6.81 (d, $J = 1.7$ Hz, 1H, arom.H), 6.88 (d, $J = 8.0$ Hz, 1H, arom.H), 7.15–7.21 (m, 4H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 20.5, 39.5, 49.6, 78.7, 78.8, 121.1, 121.9, 124.0, 125.0, 126.7, 133.2, 141.1, 149.1, 151.0.

Spiro compounds **8**, **9**, **10**, **11** and **12** were obtained according to procedures as described for **7**.

*2.1.8. Spiro[2H-(7-methylbenzo)[f]-3,4-dihydro-1,5-dioxepine-3,2′-(4′,5′,6′,7′-tetramethyl)-indan) (**8**)*

Colourless crystals (chloroform–methanol); yield 35.7%; m.p. 107–109 °C; IR (KBr, cm^{-1}): 2921, 2865 (CH_2), 1577, 1505, 1448, 1389, 1292, 1261, 1199, 1095, 1036, 1015, 922, 867, 818, 800, 756; ^{1}H NMR ($CDCl_3$), δ : 2.17 (s, 6H, CH_3), 2.20 (s, 6H, CH_3), 2.26 (s, 3H, CH_3), 2.94 (s, 4H, CH_2), 4.02 (s, 2H, OCH_2), 4.03 (s, 2H, OCH_2), 6.74 (dd, $J = 2.0$ Hz, $J = 8.1$ Hz, 1H, arom.H), 6.82 (d, $J = 2.0$ Hz, 1H, arom.H) 6.88 (d, $J = 8.1$ Hz, 1H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 16.0, 16.5, 20.5, 39.4, 48.1, 79.3, 79.4, 121.1, 121.9, 124.0, 129.9, 133.3, 133.5, 136.9, 149.2, 151.1.

*2.1.9. Spiro[2H-(7-methylbenzo)[f]-3,4-dihydro-1,5-dioxepine-3,2′-(5′-t-butyl)-indan) (**9**)*

Colourless crystals (chloroform–methanol); yield 20.2%; m.p. 102–104 °C; IR (KBr, cm^1): 3010, 2960, 2900, 2856 (CH_2), 1505, 1436, 1388, 1363, 1289, 1261, 1170, 1064, 1032, 1013, 916, 885, 826, 759; ^{1}H NMR ($CDCl_3$), δ : 1.31 (s, 9H, *tert*-butyl), 2.56 (s, 3H, CH_3), 2.92 (s, 2H, CH_2), 2.97 (s, 2H, CH_2), 4.02 (AB, $J = 12.0$ Hz, 2H, OCH_2), 4.03 (AB, $J = 12.0$ Hz, 2H, OCH_2), 6.73 (dd, $J = 2.0$ Hz, $J = 8.0$ Hz, 1H, arom.H), 6.80 (d, $J = 2.0$ Hz, 1H, arom.H), 6.87 (d, $J = 8.0$ Hz, 1H, arom.H), 7.13 (d,

$J = 8.0$ Hz, 1H, arom.H), 7.21 (dd, $J = 1.5$ Hz, $J = 8.0$ Hz, 1H, arom.H), 7.23 (s, 1H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 20.5, 31.6, 34.6, 39.1, 39.7, 49.7, 78.8, 79.0, 121.1, 121.87, 121.93, 123.8, 123.9, 124.5, 133.3, 138.1, 141.0, 149.1, 150.0, 151.0.

2.1.10. Spiro[2H-(7-methylbenzo)[f]-3,4-dihydro-1,5-dithiepine-3,2′-indan] (**10**)

Colourless crystals (chloroform–methanol); yield 3.5%; m.p. 138–139 °C; IR (KBr, cm^{-1}): 3066, 3027, 2915, 2893, 2836 (CH_2), 2362, 1584, 1481, 1458, 1433, 1398, 1280, 1091, 1040, 939, 875, 816, 746; ^{1}H NMR ($CDCl_3$), δ : 2.29 (s, 3H, CH_3), 2.92 (broad s, 8H, CH_2, SCH_2), 6.97 (d, $J = 7.1$ Hz, 1H, arom.H), 7.15–7.25 (m, 4H, arom.H), 7.45 (broad s, 2H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 20.7, 44.0, 48.4, 125.0, 126.6, 128.5, 133.3, 134.1, 137.8, 141.4.

2.1.11. Spiro[2H-(7-methylbenzo)[f]-3,4-dihydro-1,5-dithiepine-3,2′-(4′,5′,6′,7′-tetramethyl)-indan) (**11**)

Colourless crystals (chloroform–methanol); yield 7.7%; m.p. 100–102 °C; IR (KBr, cm^{-1}): 2903, 2830 (CH_2), 2363, 1626, 1587, 1459, 1376, 1285, 1260, 1155, 1041, 908, 877, 811, 737; ^{1}H NMR ($CDCl_3$), δ : 2.18 (s, 6H, CH_3), 2.19 (s, 6H, CH_3), 2.29 (s, 3H, CH_3), 2.93 (broad s, 8H, CH_2, SCH_2), 6.97 (d, $J = 7.5$ Hz, 1H, arom.H), 7.43 (broad s, 1H, arom.H), 7.47 (broad s, 1H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 16.0, 16.6, 20.7, 44.7, 46.9, 128.5, 129.9, 133.4, 134.0, 137.1.

2.1.12. Spiro[2H-(7-methylbenzo)[f]-3,4-dihydro-1,5-dithiepine-3,2′-(5′-t-buthyl)-indan) (**12**)

Colourless crystals (chloroform–methanol); yield 2.0%; m.p. 105–107 °C; IR (KBr, cm^1): 3031, 2960, 2920, 2859 (CH_2), 2365, 1584, 1491, 1458, 1432, 1359, 1279, 1120, 1037, 912, 878, 820, 713; ^{1}H NMR ($CDCl_3$), δ : 1.31 (s, 9H, *tert*-butyl), 2.29 (s, 3H, CH_3), 2.94 (broad s, 8H, CH_2, SCH_2), 6.96 (d, $J = 7.5$ Hz, 1H, arom.H), 7.12 (d, $J = 7.0$ Hz, 1H, arom.H), 7.19–7.22 (m, 2H, arom.H), 7.42 (broad s, 1H, arom.H), 7.46 (broad s, 1H, arom.H); ^{13}C NMR ($CDCl_3$), δ : 20.7, 31.6, 34.6, 44.1, 48.6, 121.9, 123.7, 124.5, 128.5, 133.4, 134.1, 138.3, 141.2, 149.9.

2.2. Energy calculations

Semi-empirical AM1 calculations were performed with the MOPAC6 [6] program package, RHF calculations with the GAUSSIAN98 [7] program and DFT with the DMOL3 [8]. In the MOPAC calculations, the keyword 'precise' was used in order to enhance criteria for terminating the energy minimization. For the RHF calculations 6-31G* basis set was used. The DFT calculations were done with DND basis set with electron non-local density approximation NLDA and electron correlation corrections such as Generalized Gradient Approximation (GGA) [9] and Perdew-Wang 91 (P91) [10]. All molecular mechanics (MM) calculations were carried out using the Dreiding2.21 generic forcefield [11] with charges assigned using the Gasteiger and Marsili (1980) method [12]. The models were built in Cerius2 molecular simulation environment [13]. All calculations

Table 1
Crystal data and structure refinement for **7** and **10**

	7	**10**
Empirical formula	$C_{18}H_{18}O_2$	$C_{18}H_{18}S_2$
Formula weight	266.32	298.47
Temperature	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system, space group	Triclinic, $P-1$	Triclinic, $P-1$
Unit cell dimensions	$a = 7.3718(2)$Å, $\alpha = 106.947(1)°$ $b = 9.2880(3)$Å, $\beta = 96.396(1)°$ $c = 11.9325(4)$Å, $\gamma = 111.975(2)°$	$a = 8.2636(3)$Å, $\alpha = 75.838(2)°$ $b = 9.5062(3)$Å, $\beta = 70.950(2)°$ $c = 10.7222(4)$Å, $\gamma = 81.142(1)°$
Volume	702.01(4)Å^3	769.43(5)Å^3
Z, Calculated density	2, 1.260 Mg/m^3	2, 1.288 Mg/m^3
Absorption coefficient	0.081 mm^{-1}	0.333 mm^{-1}
$F(000)$	284	316
Crystal size	$0.3 \times 0.2 \times 0.15$ mm^3	$0.3 \times 0.25 \times 0.08$ mm^3
θ range for data collection	3.08–30.09°	3.15–30.03°
Limiting indices	$-10 \le h \le 10, -13 \le k \le 13, 14 \le l \le 16$	$-8 \le h \le 11, -13 \le k \le 12, 15 \le l \le 15$
Reflections collected/unique	6239/4049 [R(int) = 0.0223]	6702/4436 [R(int) = 0.0205]
Completeness (to θ_{max})	98.1% (30.09°)	98.3% (30.03°)
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	4049/0/241	4436/0/247
Goodness-of-fit on F^2	1.022	1.046
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0502$, $wR2 = 0.1239$	$R1 = 0.0496$, $wR2 = 0.1229$
R indices (all data)	$R1 = 0.0700$, $wR2 = 0.1359$	$R1 = 0.0826$, $wR2 = 0.1404$
Largest diff. peak and hole	0.228 and −0.177 e Å^{-3}	0.269 and −0.430 e Å^{-3}

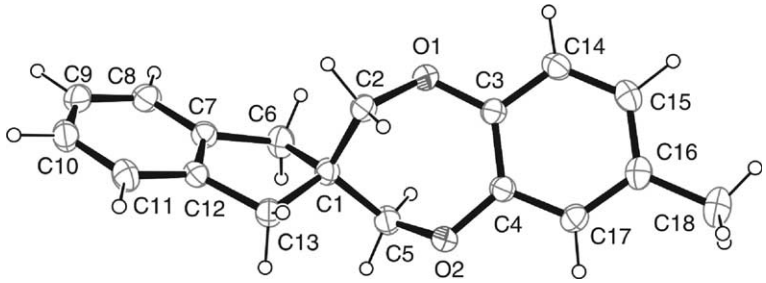

Fig. 1. A perspective view of the molecule of **7** with the crystallographic atom numbering.

were performed on a SGI 2800 supercomputer at the Academic Computer Centre Cyfronet, Kraków (Poland).

3. Results and discussion

In order to elucidate the molecular conformations for compounds containing various atoms, crystal structure analysis of compounds **7** (with oxygen atoms) and **10** (with sulfur atoms) was carried out [14]. Single-crystal diffraction data were collected using KappaCCD (Bruker–Nonius) 4-circle diffractometer and Mo Kα radiation. The structures were solved by direct methods using SHELXS97 [15] program and refined with SHELXL97 [16]. Details of crystal structure analysis of compound **7** are given in Table 1 and a perspective view of the molecule is presented in Fig. 1.

Compound **10** crystallises in the form of thin colourless plates with higher mosaicity in comparison with **7**. Significant anisotropy of mosaicity and the occurrence of overgrown forms were observed for several crystal samples of compound **10**. Single-crystal laboratory source diffraction (Mo Kα) revealed a marked decrease of intensity with the Bragg angle. The structure was solved and refined against laboratory data set giving a structural model with an ambiguity of the mutual orientation of the methyl group and the spiro rings. Independent measurements and structure solution carried out with a different sample led to an almost identical structural model. In order to decide whether this ambiguity is chemically significant or produced by insufficient data resolution, another diffraction pattern was recorded with 22.125 keV, double-monochromated synchrotron radiation at HASYLAB F1 beamline, up to the high-resolution diffraction limit determined by the sample ($d_{min} = 0.62$ Å at 295 K) [17]. Least squares refinement against both laboratory source and SR diffraction data sets resulted in consistent structural models— Fig. 2. The structural model consists of two isomeric forms. For one isomer, methyl in position 15 is in *syn* orientation with respect to the CH_2S group which is pseudoaxial with respect to the five-membered ring. For the other isomer, relevant methyl substituent is in *anti* orientation. Another way of description of both isomers is the following. Methyl substituent in position 15 is in the *meta* (*para* in the other isomer) position with respect to the sulfur atom of the CH_2S group which is pseudoaxial to the cyclopentane ring. Both isomers are ring-inversion types, since they are equivalent by inversion of both rings containing the spiroatom: the five-membered ring and the seven-membered heteroring. Both isomers are statistically distributed in the solid state with relative occupancy factors approximately 5:1. Crystal data are given in Table 1. A perspective view of the molecule with the crystallographic atom numbering is presented in Fig. 2, while the comparison of both isomers is shown in Fig. 3.

The conformations of the 7-membered heterorings in **7** and **10** are different: it is chair in **10**, but twist-boat in **7**, which may be connected with different distances of the heteroatoms within the seven-membered ring—3.33 Å in **10**, but only 2.94 Å in **7**. Also, superimposition of the molecules of **7** and **10** upon each other gives root-mean-square distance (RMSD) of the corresponding non-hydrogen atoms equal to 0.58 Å, which indicates significant difference in conformations.

Crystal structure analysis was repeated for several samples of **7** and **10** without indication of other polymorphic phases.

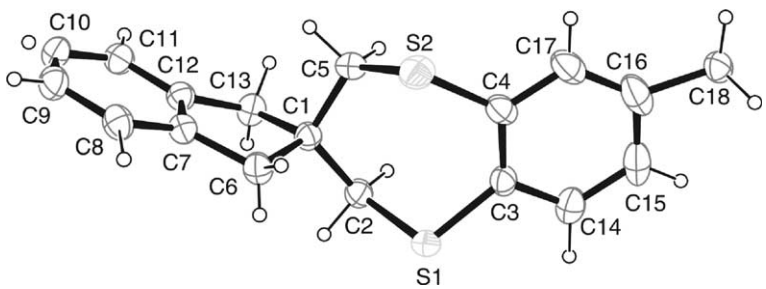

Fig. 2. A perspective view of the prevailing isomer of **10** with the atom numbering scheme.

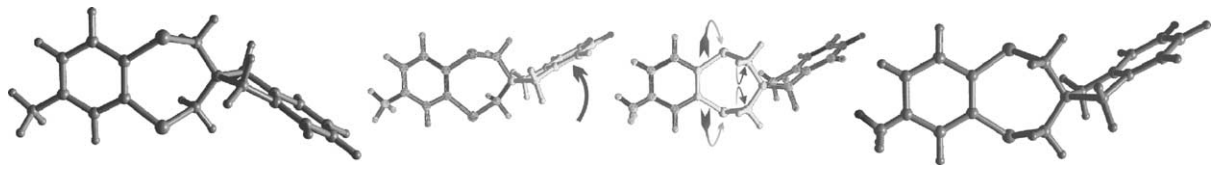

Fig. 3. Comparison of the two isomers of **10** differentiated by inversion of both seven- and five-membered spiro rings. Respective populations are: 0.17 and 0.83.

Energy calculations for **7** and **10**, conducted in order to find out about possible energy preferences for various conformations, were carried out as follows.

The models of two isomers with different positions of methyl with respect to the five-membered ring (envelope conformation) were built for each compound. Then, a simulated annealing procedure has been used to search the potential energy surface for low-energy structures. The resulting structures (100) were minimised in the Dreiding forcefield using the steepest descent and Newton–Raphson algorithms. The structure with the lowest energy has been taken as an initial structure to semi-empirical AM1 minimisation. Next, the energy optimisations procedures using DFT and RHF/6-31G* methods were carried out. The calculations for both isomers resulted in close values of energy for both **7** and **10** (Table 2). For compound **7** calculated molecular structures are different from the X-ray structure (RMSD for all non-hydrogen atoms calculated by the DFT method equal 1.302 Å). The differences are manifested in the heteroring conformations (chair for calculated and twist-boat for X-ray structure). For compound **10** minimum energy conformation calculated using the DFT procedure is virtually identical with that determined by X-ray analysis (both in chair conformation; RMSD for all non-hydrogen atoms 0.056 Å). Figs. 4–7 present superimposed calculated and experimentally

Table 2
Calculated energy differences (DE) (kcal/mol) between both isomers for **7** and **10**

Compound	DE AM1	DE RHF 6-31G*	DE GGA(P91)
7	0.00002	0.00000	0.15230
10	0.00838	0.01130	0.08007

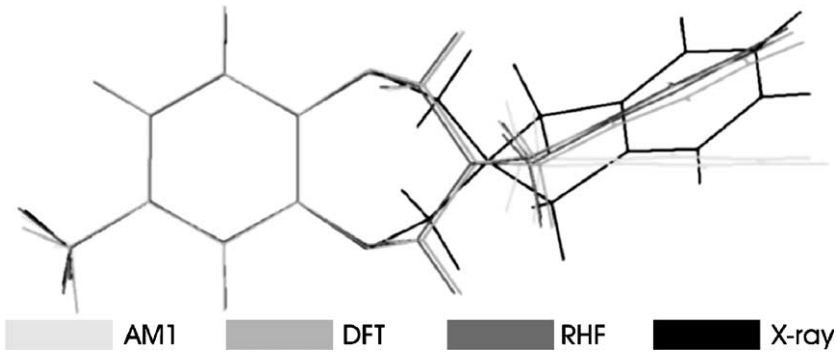

Fig. 4. Superposition of calculated and X-ray structures of compound **7**, view on plane of substituted benzo-ring. All the models were aligned to have a common rigid part.

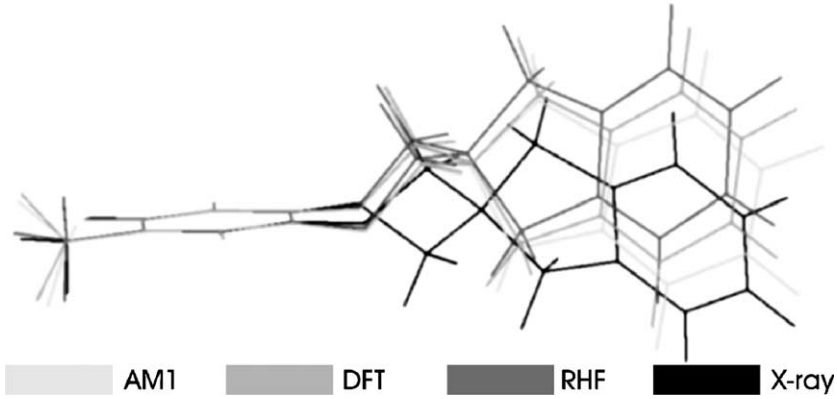

Fig. 5. Superposition of calculated and X-ray structures of compound **7**, view along the plane of substituted benzo-ring. All the models were aligned to have a common rigid part.

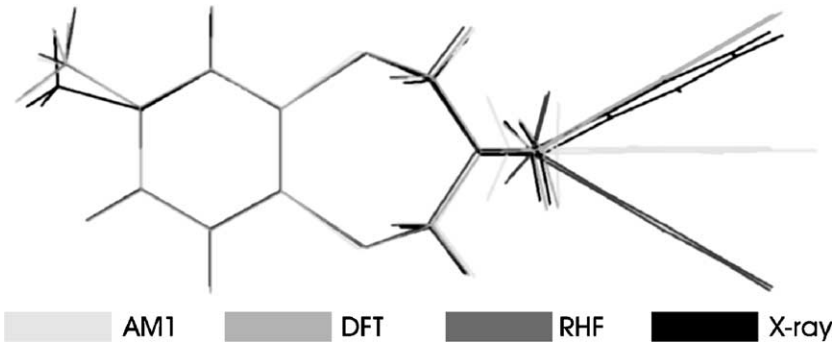

Fig. 6. Superposition of calculated and X-ray structures of compound **10**, view on plane of substituted benzo-ring. All the models were aligned to have a common rigid part.

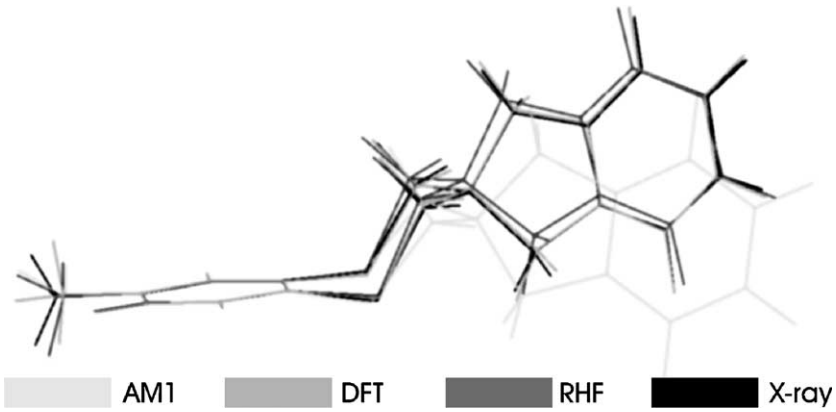

Fig. 7. Superposition of calculated and X-ray structures of compound **10**, view along the plane of substituted benzo-ring. All the models were aligned to have a common rigid part.

determined models of molecules of **7** and **10**. Energy differences calculated for both isomers of compounds **7** and **10** have very low values (Table 2), hence no energetic preferences could be attributed to any isomeric forms and their occupancy factors values in crystal structure of **10**.

The ^{1}H NMR spectra of **10**, **11** and **12** recorded at room temperature revealed broad singlets at $\delta = 2.92$, 2.93 and 2.94 for all methylene protons (CH_2, CH_2S), respectively. This result, common for **10–12**, may be attributed to an inversion of the 1,5-dithiepine ring. This was supported by ^{1}H NMR measurements of spiran **10** at low temperatures (100 °C) when the broad singlet at $\delta = 2.92$ was split. In contrast, the ^{1}H NMR spectrum of spiran **7** at room temperature exhibited three sharp singlets originating from CH_2 ($\delta = 2.96$) and CH_2O ($\delta = 4.01, 4.02$) protons. Further investigations of possible isomeric forms of all compounds in liquid and solid state are being prepared.

4. Conclusions

In summary, crystal structure analysis carried out for compounds **7** (with oxygen atoms) and **10** (with sulfur atoms) proved the identity of the products of synthesis and validity of the synthetic pathway. Introduction of methyl substituent into the 1,5-benzodithiepine moiety led to the appearance of two distinct isomeric forms in **10**. Energy calculations by the DFT method carried out for **10** led to minimum energy conformation virtually identical with that determined by X-ray analysis (RMSD for all non-hydrogen atoms as low as 0.056 Å). Energy differences for both isomeric forms of **10** detected in the solid state were very small (Table 2) giving no preference for any single isomer. For compound **7** the minimum energy conformation differs significantly from that determined by X-ray structure analysis (RMSD equal to 1.302 Å). This is particularly manifested in the heteroring conformation (chair vs. twist-boat). It follows that the experimentally determined conformation corresponds to a local rather than global minimum and the presence of polymorphic forms might be expected, especially that both crystal structures are loosely packed with no intermolecular hydrogen bonds. In seven-membered rings with two oxygen atoms twist-boat, chair conformations, or a mixture of them are reported [18].

In contrast to **10**, for compound **7,** neither NMR, nor X-ray evidence did indicate the presence of ring-reversal isomers. It could be interpreted in terms of different electronegativities of oxygen and sulfur heteroatoms, making the energetically less favourable [19] twist-boat conformation of **7** more stable in the crystallisation process.

Acknowledgements

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