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Chemistry of 1,3-Dioxepins. XVI.[1] The Synthesis, Characterization and Crystallographic Analysis of Some Arylsulphanyl-, Arylsulphinyl-, Arylsulphonyl- and Benzoyl- *N*-Substituted Derivatives of 1a,2,6,6a-Tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines*

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Chemo-selective synthesis and characterization of *N*-[(4-nitrophenyl)sulphanyl]- **2** and *N*-[(4-nitrophenyl)sulphinyl]- **3** *N*-[(4-aminophenyl)sulphonyl]- **5** and *N*-(4-aminobenzoyl)- **7** derivatives of 1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines, starting from 1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**1**), are described. Their solid state conformational behaviour based on crystallographic analysis shows that: (i) dioxepinoazirine moiety of **2**, **5** and **7** adopts a boat-chair (BC) conformation, while dioxepinoaziridine moiety of **3** adopts a twist-boat (TB) conformation; (ii) the substituent on aziridine nitrogen is always in *trans* and never in *cis* position in relation to the dioxepane ring; (iii) the orientation of sulphanyl-, sulphinyl-sulphonyl- and carbonyl- moiety in **2**, **3**, **5** and **7** are defined by torsion angles C1-S1-N1-C7 of 110.7(2)°, 82.6(2)°, 88.80(11)°and C1-C-N1-C7 of 64.9(5)°, respectively; (iv) Phenyl moiety of sulphinyl and sulphonyl derivatives, **3** and **5**, is perpendicular to the S-N bond with the torsion angles N1-S1-C1-C2 of 67.9(3)° and –92.54(13)°, respectively, while that of sulphanyl- **2** and carbonyl- **7** derivatives is coplanar to S-N or C-N bonds with the torsion angles N1-S1-C1-C2 and N1-C-C1-C2 of 168.5(2)° and 170.9(4)°, respectively. Obtained data will serve for further investigation of steric and electronic properties of studied compounds aimed at designing anti-hyperglycaemically more potent analogues.

Keywords
• chemo-selective synthesis
• 1,3-dioxepins
• 1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]-dioxepino[5,6-*b*]azirines
• sulphanyl
• sulphinyl
• crystallographic analysis
• conformational behaviour
• antihyperglycaemics

INTRODUCTION

N-Sulphonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino-[5,6-*b*]azirines known as potent antihyperglycaemics[2,3] are recognized by scientific community as a promising class under examination.[4] In order to study the importance of its sulphonyl moiety for antihyperglycaemic profile, we recently reported conformational behaviour of their different analogues bearing sulphonyl-, carbonyl- and methylene moieties.[1]

Having these data in mind, we directed our attempts to the synthesis as well as structural and conformational characterization of the novel *N*-[(4-nitrophenyl)sulphanyl]-

* Dedicated to Memory of the Late Professor Vladimir Prelog on the Occasion of the 100th Anniversary of His Birthday.

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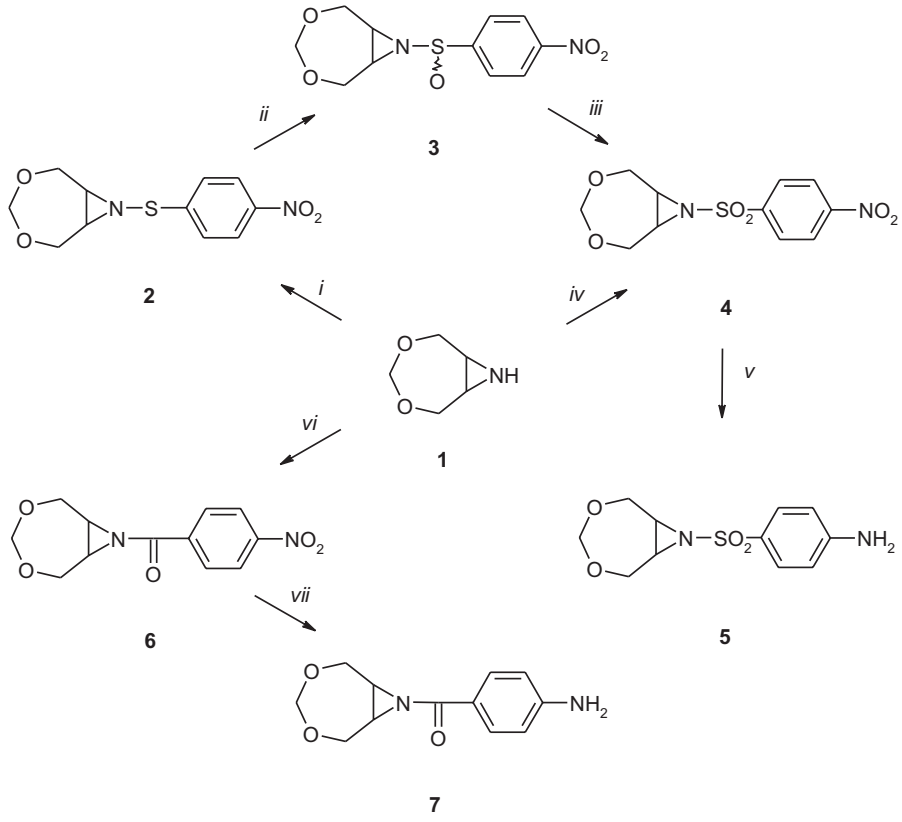

Scheme 1. Synthesis of nitro- and aminoaryl-azirines **2**–**7**. Reagents and conditions: *i*, 4-nitrobenzenesulfenyl chloride/pyridine/CH_2Cl_2, r.t., 30 min. under N_2; *ii*, *m*-CPBA/CH_2Cl_2, r.t., 2 h; *iii*, $KMnO_4$/HOAc-EtOAc, 5 °C; *iv*, 4-Nitrobenzenesulphonyl chloride/pyridine/CH_2Cl_2, 0 °C, 1 h[1]; *v*, H_2/ 5 % Pd/C, EtOAc, 1 bar, r.t., 3 h; *vi*, 4-nitrobenzoyl chloride/pyridine/CH_2Cl_2, refl., 1 h[1]; *vii*, H_2/ 5 % Pd/C, methanol, 3 bar, r.t., 3 h.

2, and *N*-[(4-nitrophenyl)sulphinyl]- **3** analogs, and *N*-[(4-aminophenyl)sulphonyl]- **5** (Ref. 5) and *N*-(4-aminobenzoyl)- **7** derivatives of already known sulfonyl and carbonyl subclasses (Figure 1, Scheme 1). Here, we report the obtained results, which will encourage further molecular modeling studies of isosterism and biosterism between sulphanyl-, sulphinyl-, sulphonyl- and carbonyl-moieties.

EXPERIMENTAL

General

Melting points were determined using a Fischer-Johns apparatus, and are uncorrected. Infrared spectra (IR) were recorded on a Nicolet Magna-IR 760 Spectrometer and the bands are given in cm^{-1}. Nuclear magnetic resonance spectra ^1H NMR and ^{13}C NMR were recorded with tetramethylsilane as internal standard on Bruker Avance DPX 300 and Bruker Avance DRX 500 spectrometers. DMSO-d_6 was used as solvent, unless otherwise stated. Chemical shifts (δ) are given in ppm relative to the tetramethylsilane (δ = 0), and coupling constants (J) in Hz. Combustion analyses were performed in our laboratory. TLC was performed using Merck Kieselgel 60 F_{254} silica plates and components were visualized using UV light and iodine vapour. Solvents and 4-nitrobenzenesulphenyl chloride (Fluka) were *p.a.* grade and were used without further purification. 1a,2,6,6a-Tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**1**)[2] as well as *N*-[(4-nitrobenzene)sulfonil]- and *N*-(4-nitrobenzoyl)- derivatives **4** (Ref. 1) and **6** (Ref. 1) were prepared by the previously reported procedures. Chemical yields were not optimized.

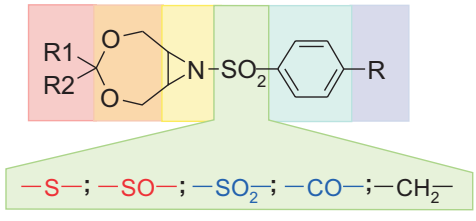

Figure 1. Variation of sulphonyl moiety of *N*-aryl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine.

Chemistry

*Reaction of 1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino-[5,6-*b*]azirine (**1**) with 4-nitrobenzenesulphenyl chloride*

Procedure 1: Under Air

A solution of dioxepinoazirine **1** (1.15 g; 10 mmol) and pyridine (1.1 mL) in methylene chloride (30 mL) was added dropwise to a solution of 4-nitrobenzenesulphenyl chloride (1.89 g; 10.00 mmol) in methylene chloride (10

mL) during 10 min at 25–30 °C. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was washed with saturated solution of sodium hydrogen carbonate (5 mL), 5 % sulphuric acid (10 mL) and water (2×10 mL) and dried over anhydrous sodium sulphate. Evaporation under reduced pressure yielded a dry residue (2.24 g), which was dissolved in methylene chloride (10 mL), and crystals of the starting 4-nitrobenzenesulphenyl chloride were precipitated (0.30 g; 16 %); m.p.; 46–48 °C. Its IR spectrum was identical to the IR spectrum of the starting 4-nitrobenzenesulphenyl chloride.

Dry residue obtained by evaporation of the mother liquor under reduced pressure was purified by column chromatography using a methylene chloride / ethyl acetate (9/1, *v*/*v*) mixture as eluent. After concentration of the selected fractions under reduced pressure, 1-[(4-nitrophenyl)sulphanyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (sulphanyl derivative **2**) (827.0 mg, 31 %) was obtained.

The analytical sample of sulphanyl derivative **2** was prepared by recrystallization from ethyl acetate, showing m.p. 110–111 °C.

IR (KBr) ν_{max}/cm^{-1}: 3444, 3104, 3020, 2963, 2935, 2877, 2796, 1591, 1575, 1506, 1476, 1452, 1409, 1337, 1301, 1247, 1181, 1147, 1102, 1062, 998, 936, 913, 848, 743, 700, 670, 612. ^{1}H NMR (DMSO-d_6)/300 MHz δ/ppm: 8.23 and 7.61 (2d, 4H, H-arom, J = 8.9 Hz), 4.80 and 4.47 (2d, 2H, H-C4, J = 6.7 Hz), 4.16–4.04 (m, 4H, H-C2,6), 2.66 (s, 2H, H-C1a,6a). ^{13}C NMR (DMSO-d_6) δ/ppm: 151.0 (s), 144.4 (s), 124.2 (d), 122.4 (d) (C-arom), 98.1 (t, C4), 67.5 (t, C2,6), 47.8 (d, C1a,6a).

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$ (M_r = 268.29): C 49.25, H 4.51, N 10.44, O 23.85, S 11.95 %; found: C 49.27, H 4.47, N 10.49, S 11.93 %.

MS (ESI): 268.1 M$^+$.

By evaporation of the other pool of fractions, 1-[(4-nitrophenyl)sulphinyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (sulphinyl derivative **3**) was isolated (747.0 mg, 26 %); m.p. 94–96 °C. The analytical sample of sulphinyl derivative **3** was prepared by recrystallization from methanol showing m.p. 102–106 °C.

IR (KBr) ν_{max}/cm^{-1}: 3449, 3095, 3072, 2960, 2902, 2867, 2800, 1606, 1525, 1478, 1454, 1351, 1312, 1286, 1255, 1227, 1150, 1133, 1092, 1030, 997, 937, 854, 789, 743, 726, 683, 633. ^{1}H NMR (DMSO-d_6)/300 MHz δ/ppm: 8.42 and 7.99 (dd, 4H, H-arom, J = 8.9 Hz, J = 1.9 Hz), 4.78 and 4.30 (2d, 2H, H-C4, J = 7.1 Hz), 4.00 and 3.90 (2dd, 2H, H-C2,6, J = 13.7 Hz, J = 1.7 Hz) and 4.19 and 3.51 (2dd, 2H, H-C1a,6a, J = 13.7 Hz, J = 2.6 Hz). ^{13}C NMR (DMSO-d_6) δ/ppm: 152.0 (s), 149.5 (s), 126.5 (d), 124.4 (d) (C-arom), 97.8 (t, C4), 66.9 and 66.8 (2t, C2,6), 40.16 and 39.60 (2d, C1a,6a).

Anal. Calcd. for $C_{11}H_{12}N_2O_5S$ (M_r = 284.29): C 46.47, H 4.25, N 9.85, O 28.14, S 11.28 %; found: C 46.49, H 4.27, N 9.82, S 11.25 %.

MS (ESI): 284.1 M$^+$.

Also, a small quantity of sulphonyl derivative **4** were detected by TLC (methylene chloride/ethyl acetate (9/1, *v*/*v*)), but no product was isolated.

Procedure 2: Under Nitrogen

A mixture of azirine **1** (0.98 g, 8.51 mmol) and pyridine (0.8 mL) in methylene chloride (40 mL) was added dropwise into the solution of 4-nitrobenzenesulphenyl chloride (1.61 g, 8.66 mmol) in methylene chloride (10 mL) and stirred for 15 min at room temperature under a nitrogen atmosphere. The reaction mixture was washed with a saturated solution of sodium hydrogen carbonate (15 mL), sulphuric acid 5 % (15 mL) and with water (2×15 mL). Organic layer was separated and dried over anhydrous sodium sulphate and evaporated to dryness. The solid residue (2.17 g) was chromatographed using methylene chloride/ethyl acetate mixture (9/1, *v*/*v*). Besides the desired sulphanyl derivative **2** (1.37 g, 60 %), sulphinyl derivative **3** (161.0 mg, 7 %) and sulphonyl derivative **4** (26.0 mg, 1 %) were isolated.

The IR spectra of thus obtained **2**, **3** and **4** were identical to the IR spectra of sulphanyl derivatives **2** and **3** obtained by Procedure 1 as well as to the authentic sample of **4** described earlier.[1]

*1-[(4-Nitrophenyl)sulphinyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**3**)*

Sulphanyl derivative **2** (150.0 mg, 0.56 mmol) and *m*-CPBA (70 %, 137.8 mg, 0.56 mmol) in methylene chloride (10 mL) were stirred under a nitrogen atmosphere at room temperature. Immediately after *m*-CPBA addition, the yellow solution became colourless. According to TLC, the methylene chloride / ethyl acetate (9/1, *v*/*v*) reaction was over. The reaction mixture was washed with 5 % sodium pyrosulphite ($Na_2S_2O_5$) (5 mL) and with water (5 mL). Organic layer was dried over anhydrous sodium sulphate, and concentrated under reduced pressure, yielding the crude product (294.0 mg). It was purified by column chromatography using a methylene chloride / ethyl acetate mixture (9/1, *v*/*v*) as eluent. After concentration of selected fractions under reduced pressure, sulphinyl derivative **3** was obtained (107.0 mg, 67 %); m.p. 98–100 °C. IR spectrum of thus obtained sample was identical to the IR spectrum of sulphinyl derivative **3** described above.

By evaporation of the other pool of fractions, 1-[(4-nitrophenyl)sulphonyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (sulphonyl derivative **4**) was isolated (40.0 mg, 24 %); m.p.195–198 °C. The analytical sample of **4** was prepared by recrystallization from ethyl acetate–methanol (6/1, *v*/*v*); m.p. 207–209 °C. (lit.[1] m.p. 208–210 °C). The IR spectrum of thus obtained **4** was identical to the IR spectrum of the authentic sample described previously.[1]

*1-[(4-Nitrophenyl)sulphonyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**4**)*

Sulphinyl derivative **3** (91.0 mg, 0.32 mmol) was dissolved in a mixture of acetic acid (80 %, *v*/*v*) (2 mL) and ethyl acetate (2.5 mL). The resulting solution was cooled to 5 °C and a saturated aqueous solution of potassium permanganate (1.1 mL) was added under stirring as long as the rose colour persisted. After addition of water (2 mL), the solution was discoloured with 30 % H_2O_2. White crystals started to

TABLE I. Crystallographic data for *N*-substituted dioxepinoazirines **2**, **3**, **5** and **7**

Parameter	**2**	**3**	**5**	**7**
Formula	$C_{11}H_{12}N_2O_4S$	$C_{11}H_{12}N_2O_5S$	$C_{11}H_{14}N_2O_4S$	$C_{12}H_{14}N_2O_3$
M_r	268.29	284.29	270.30	234.25
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/c$ (No.14)	$P2_1/n$ (No.14)	$P\bar{1}$ (No.2)	Cc (No.9)
a /Å	4.5540(10)	12.933(3)	5.994(3)	5.9900(10)
b /Å	22.389(3)	6.591(3)	9.091(3)	16.2720(10)
c /Å	12.308(3)	14.839(3)	12.490(3)	11.649(7)
α /°	90	90	93.11(2)	90
β /°	98.50(2)	95.39(2)	102.308(6)	95.21(2)
γ /°	90	90	105.063(10)	90
V/Å^3	1241.1(4)	1259.3(7)	637.8(4)	1130.7(7)
Z	4	4	2	4
ρ_{calc} / Mg cm^{-3}	1.436	1.499	1.408	1.376
μ /cm^{-1}	2.7	2.8	2.6	8.3
F_{000}	560.0	592.0	284	496
Unique refl.	3627	3686	3716	694
Refined parameter.	160	172	172	162
R_F	0.0627	0.0690	0.0383	0.0358
wR_{F2}	0.0751	0.1262	0.1020	0.0903
$\Delta\varphi_{max,min}$ /e Å^{-3}	0.18, –0.23	0.28, –0.39	0.04, –0.26	0.04, –0.16

precipitate and the suspension was stirred in an ice bath for 30 min. Crystals were suctioned off and washed with water (2×2 mL). After drying at room temperature for 24 hours, the TLC pure crude sulphonyl derivative **4** was obtained (65.0 mg, 68 %); m.p. 199–201 °C. The analytical sample of **4** was prepared by recrystallization from ethyl acetate–methanol (6/1, *v*/*v*); m.p. 206–208 °C. The IR spectrum of thus obtained **4** was identical to the IR spectrum of the authentic sample.[1]

*1-[(4-Aminobenzene)sulphonyl)]-1a,2,6,6a-tetrahydro-1*H,*4*H*-[1,3]dioxepino[5,6-*b*]azirine (**5**)*

Sulphonyl derivative **4** prepared previously[1] (300.0 mg, 1.00 mmol) was hydrogenated in ethyl acetate (60 mL) in the presence of 5 % palladium on charcoal catalyst (50.0 mg) at room temperature and hydrogen pressure of 1 bar for 3 hours. The catalyst was separated by filtration and after evaporation of solvent under reduced pressure, the crude TLC pure foamy amino derivative **5** (251.0 mg, 93 %) was obtained.

The analytical sample of **5** was prepared by recrystallization from ethyl acetate; m.p. 177–178 °C.

IR (KBr) ν_{max}/cm^{-1}: 3483, 3381, 2965, 2922, 2858, 1631, 1597, 1504, 1441, 1377, 1308, 1261, 1240, 1181, 1153, 1104, 1072, 1023, 993, 944, 916, 829, 767, 737, 694. ^{1}H NMR (DMSO-d_6)/300 MHz δ/ppm: 7.49 and 6.65 (2dd, 4H, H-arom. J = 8.5 Hz, J = 2.3 Hz), 6.20 (s, 2H, NH_2), 4.75 and 4.29 (2dd, 2H, H-C4, J = 7.1 Hz, J = 2.4 Hz), 3.93 (s, 4H, H-C2,C6), 2.89 (s, 2H, H-C1a,6a). ^{13}C NMR (DMSO-d_6) δ/ppm: 112.9 (d), 121.4 (s), 129.9 (d) and 154.10(s) (C-arom.), 97.7 (t, C4), 66.3 (t, C2,6), 43.5 (d, C1a,6a).

Anal. Calcd. for $C_{11}H_{14}N_2O_4S$ (M_r = 270.30): C 48.87, H 5.23, N 10.37, O 23.66, S 11.86 %; found: C 49.01, H 5.18, N 10.52, S 11.95 %.

MS (ESI): 271 M$^+$.

*1-(4-Aminobenzoyl)-1a,2,6,6a-tetrahydro-1*H,*4*H*-[1,3]dioxepino[5,6-*b*]azirine (**7**)*

Nitrobenzoyl derivative **6** prepared previously[1] (1.00 g, 3.24 mmol) was hydrogenated in methanol (200 mL) in the presence of 5 % palladium on charcoal catalyst (100.0 mg) at room temperature and hydrogen pressure of 3 bar for 3 hours. The catalyst was separated by filtration and after evaporation of solvent under reduced pressure, the crude foamy, TLC pure amino derivative **7** (820.0 mg, 91 %) was obtained.

The analytical sample of **7** was prepared by recrystallization from ethyl acetate; white crystals, m.p. 173–175 °C.

IR (KBr) ν_{max}/cm^{-1}: 3447.15, 3345.86, 3218.75, 2977.89, 1659.92, 1628.92, 1593.62, 1567.88, 1519.75, 1319.55, 1284.95, 1177.42, 1107.95, 1060.89, 1018.80, 967.80, 921.83, 860.08, 689.11, 649.13, 585.77. ^{1}H NMR (DMSO-d_6)/300 MHz δ/ppm: 7.60 and 6.59 (2d, 4H, H-arom, J = 8.6 Hz), 5.96 (s, 2H, NH_2), 4.87 and 4.38 (2d, 2H, H-C4, J = 7.1 Hz), 4.19 and 4.01 (2d, 4H, H-C2,6, J = 13.5 Hz), 2.78 (s, 2H, H-C1a,6a). ^{13}C NMR (DMSO-d_6) δ/ppm: 178.0 (a, CO), 153.2 (s), 130.7 (d), 119.1 (s) and 112.6 (d, C arom), 98.1 (t, C4), 67.5 (t, C2,6), 41.2 (d, C1a,6a).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$ (M_r = 234.25): C 61.52, H 6.04, N 11.96, O 20.48 %; found: C 61.58, H 6.09, N 12.20 %.

MS (ESI): 234.1 M$^+$.

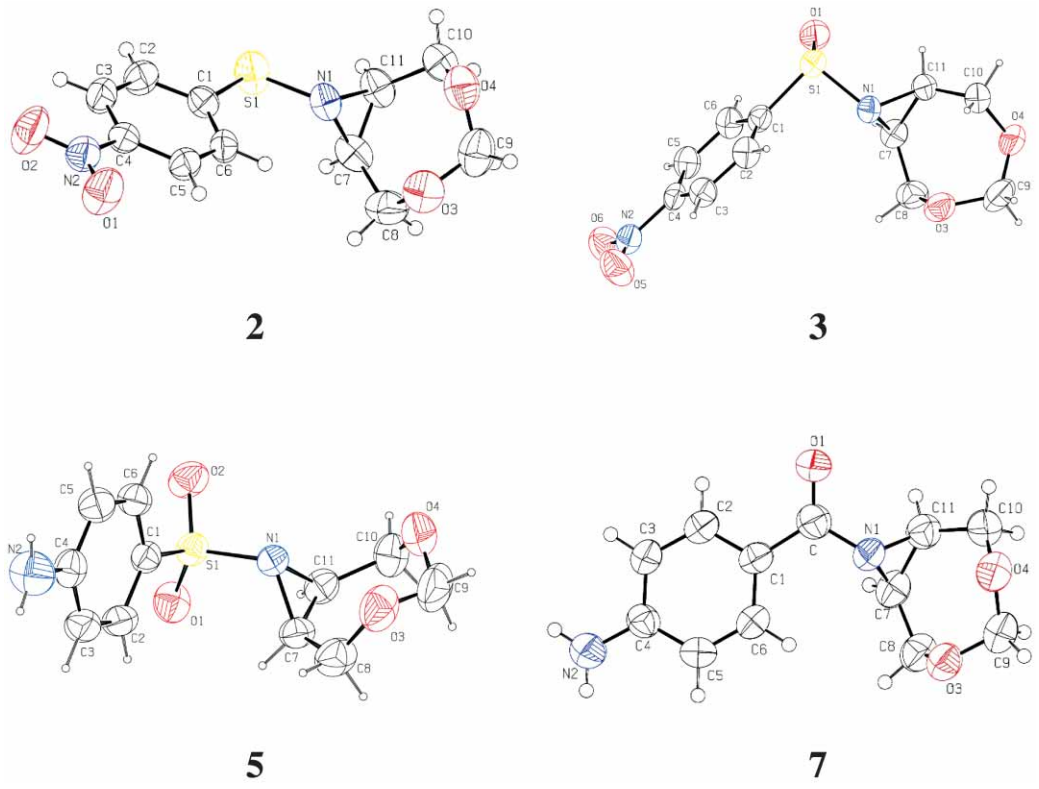

Figure 2. TEP of **2**, **3**, **5** and **7** crystal structures with atomic numbering (Ellipsoids drawn at 50 % probability level).

Crystallography

The X-ray diffraction data for sulphanyl- **2**, sulphinyl- **3,** sulphonyl- **5** and carbonyl- **7** derivatives were collected on a PHILIPS PW1100 automatic four-circle diffractometer (Stoe/Cie upgrade) using graphite monochromatized Mo-Kα (λ = 0.71069 Å) and Cu-Kα (λ = 1.54178 Å) radiation at room temperature and controlled by the STADI4 programme.[6] The measured intensities were corrected for Lorentz and polarization effects, but not for absorption by the XRED programme.[7] Molecular and crystal structures were solved by direct methods implemented in the program SIR97 (Ref. 8) and refined on F^2 with anisotropic displacement parameters for all non-hydrogen atoms by SHELXL97.[9] All hydrogen atoms except that on the nitrogen amino group of **5** and **7** were generated on geometrical grounds. The essential crystallographic data are presented in Table I. Crystallographic data sets for all compounds are deposited with the Cambridge Crystallographic Data Centre and are available on request.

RESULTS AND DISCUSSION

Chemistry

Sulphanyl derivative **2** was prepared in 31 % yield by reaction of aziridine **1** with 4-nitrobenzenesulphenylchloride in methylene chloride at room temprerature. The reaction was fast, but non-selective, yielding additionally 26 % of sulphinyl derivative **3**, and according to TLC, a small, not isolated, quantity of sulphonyl derivative **4** as the highest level oxidation products. Performing the reaction under a nitrogen atmosphere increased the yield of **2** to 60 %, and subsequently decreased the yields of **3** to about 7 %. Besides these products, the sulphonyl derivative **4** was isolated in 1 % yield, all indicating the air-sensitive behaviour of sulphanyl moiety under the studied reaction conditions.

Oxidation of **2** by *m*-CPBA in methylene chloride at room temperature under nitrogen predominantly led to the formation of sulphinyl derivate **3** (67 %) in the mixture with sulphonyl derivative **4** (24 %). Oxidation of **3** by a saturated aqueous solution of potassium permanganate, in acetic acid–ethyl acetate solution at 5 °C, furnished sulphonyl derivate **4** (68 %), identical to the previously obtained authentic sample, by the reaction of 4-nitrobenzenesulphonyl chloride with aziridine **1** (68 %).[1]

The amino derivative **5** was prepared in 93 % yield by hydrogenation of **4** in the presence of 5 % Pd/C in ethyl acetate under hydrogen pressure of 1 bar at room temperature for 3 hours. On the other hand, the amino derivative **7** was prepared in an overall yield of 55 % by reaction of dioxepinoazirine **1** with *p*-nitrobenzoyl chloride as described previously,[1] followed by hydrogenation of thus obtained nitrobenzoyl derivative **6** (61 %) in the presence of Pd/C catalyst in methanol under hydrogen pressure of 3 bar at room temperature for 3 hours (Scheme 1).

X-ray Diffraction Study

The thermal ellipsoid plots (TEP) of azirine compounds **2**, **3**, **5** and **7** with the atomic numbering scheme were prepared with the PLATON[10] program (Figure 2). Crystallographic analysis shows that dioxepinoaziridine moiety of **2, 5** and **7** adopts a boat-chair (BC) conformation, the same as for **4** found previously,[1] while dioxepinoaziridine moiety of **3** adopts a twist-boat (TB) conformation. In all cases, the substituent on aziridine nitrogen is in *trans* position in relation to the dioxepane ring, supporting our previous results.[1,3] The aziridine nitrogen atoms in all structures are sp^3 hybridized in accordance with a previous study.[1]

In addition, sulphanyl moiety in **2** adopts conformation **a** in relation to the aziridine ring with torsion angle C1-S1-N1-C7 of 110.7(2)°. Orientation of sulphinyl moiety in **3** is defined by the angle C1-S1-N1-C7 of 82.6(2)° and by the conformation **b**. Sulphonyl group of **5** adopts only one, *i.e.,* **d** of the two possible (**d** and **e**) conformations in relation to the aziridine ring determined by torsion angle C1-S1-N1-C7 of 88.80(11)° (corresponding angle O1-S1-N1-LP ≅ 180°; LP = lone pair) (Figure 3). We named this conformation BC*, and found it to be the most frequent in the crystal state of

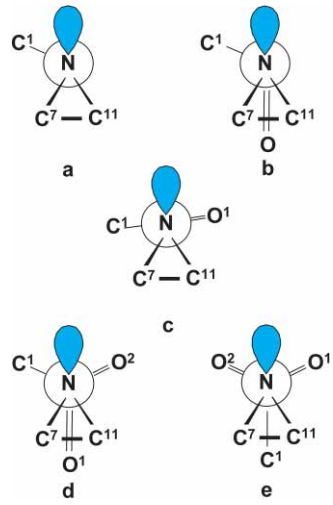

Figure 3. Solid state conformations: Sulphanyl-, sulphinyl-, and carbonylaziridine moieties of **2**, **3**, and **7** adopt conformations **a**, **b** and **c**, while sulphonylaziridine moiety of **5** adopts only conformation **d** of the two possible ones, **d** and **e**.

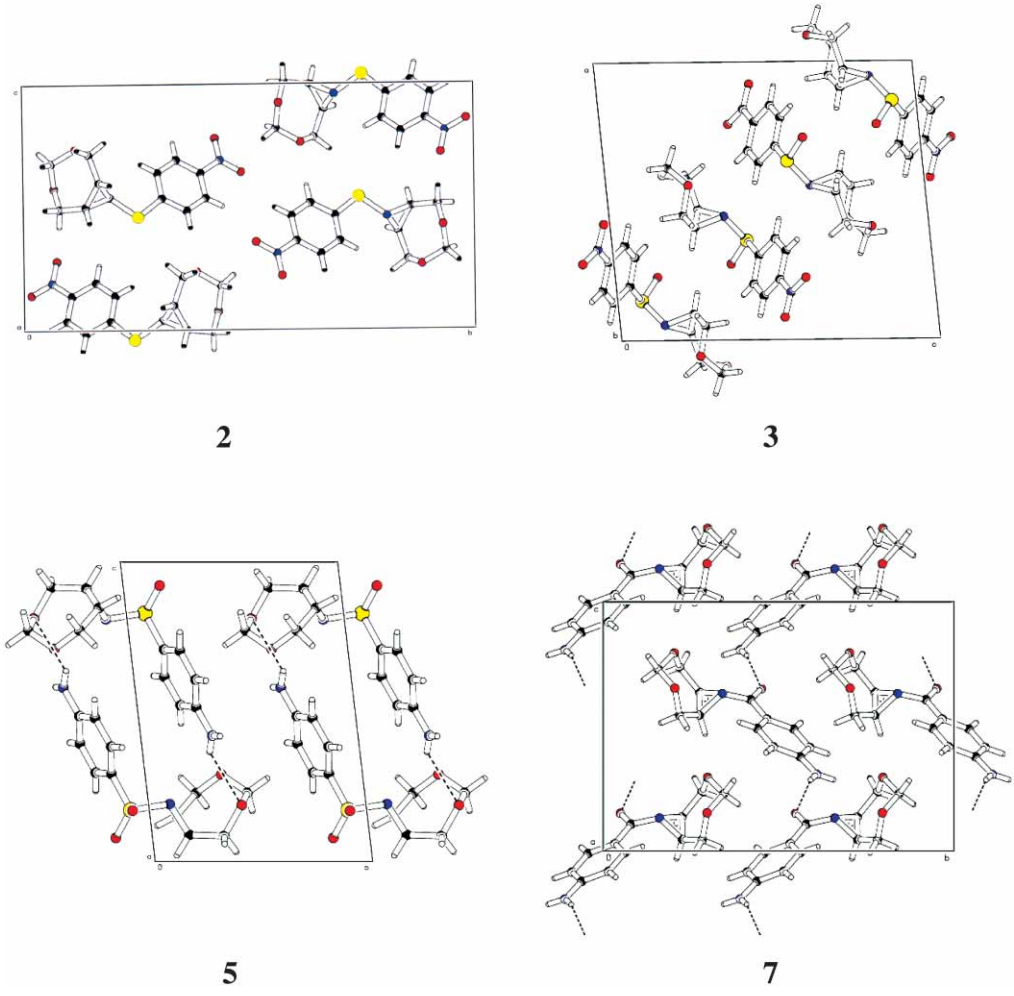

Figure 4. Crystal packing of azirines **2**, **3**, **5** and **7**.

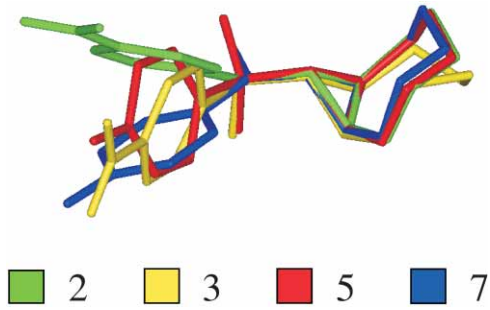

Figure 5. Superposition of solid state conformations of azirines **2**, **3**, **5** and **7**.

sulphonyldioxepinoazirines.[1,3] Orientation of carbonyl moiety in **7** is defined by torsion angle C1-C-N1-C7 of 64.9(5)°, which is in good agreement with the conformation of carbonyl moiety of previously published carbonyl analogues.[1]

Phenyl moiety of sulphinyl and sulphonyl derivatives, **3** and **5,** is oriented in a similar way, *i.e.,* perpendicular to the S-N bond with the torsion angles N1-S1-C1-C2 of –67.9(3)° and –92.54(13)°, respectively. On the other hand, sulphanyl and carbonyl derivatives **2** and **7** have the phenyl group coplanar to S-N and C-N bonds with the torsion angles N1-S1-C1-C2 and N1-C-C1-C2 of 168.5(2)° and 170.9(4)°, respectively.

Therefore, sulphinyl and sulphonyl derivatives **3** and **5**, on the one side, and sulphanyl and carbonyl derivatives **2** and **7,** on the other side, could have *o*- and *m*-substituents pointing to the same direction in space.

Nitro groups **2** and **3** and amino groups of **5** and **7** are approximately coplanar to the phenyl ring plane.

None of the studied molecules of **2** and **3** possesses H-donating groups or the ability to form H-bonds. Therefore, only van der Waals interactions stick the molecules together in their crystal lattices (Figure 4). However, in the structure of amino derivative **5** exist the weak, donor bifurcated hydrogen bonds d(N2···O4) = 3.264 (3) Å, forming the dimmers of **5** as building blocks. On the other hand, in the structure of amino derivative **7**, the molecules are interconnected by the weak hydrogen bond d(N2···O1) = 3.065(5) Å forming chains along *b* axis.

Superposition of the crystal state conformation shows that **2**, **5** and **7** are similar in dioxepinoazirine moiety but they differ substantially in the aromatic part of the molecule. Otherwise, **3** and **5** are similar in the aromatic part, but differ in the dioxepinoazirine moiety (Figure 5).

The described crystallographic and conformational data of the studied sulphanyl and sulphinyl derivatives **2** and **3** as well as sulphonyl and carbonyl derivatives **5** and **7** have extended our knowledge of the conformational behaviour of *N*-substituted dioxepinoazirines. This will serve for further investigation of steric and electronic properties of the studied compounds and their biosterism, as well as for designing antihyperglycaemically more potent analogues.

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Supplementary Materials. – Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 122333 6033; e-mail: deposit@ccdc.cam.ac.uk) and can be obtained on request, free of charge, by quoting the publication citation and the deposition number 275726 (for **2**), 275727 (for **3**), 275728 (for **5**), or 275729 (for **7**).

REFERENCES

1. For Part XV see: M. Orešić, D. Filić, B. Prugovečki, M. Vinković, and M. Dumić, *Croat. Chem. Acta* **74** (2001) 667–682.
2. M. Dumić, D. Filić, M. Vinković, B. Jamnicky, and B. Kamenar, *Tetrahedron Lett.* **34** (1993) 3639–3642.
3. M. Dumić, M. Vinković, D. Filić, B. Jamnicky, M. Eškinja, and B. Kamenar, *J. Med. Chem*. **38** (1995) 3034–3042.
4. Anonymous, *Chem. Brit.* **31** (3) (1995) 184.
5. M. Dumić, D. Filić, M. Vinković, and B. Jamnicky, US 5,286,744, Feb. 15, 1994.
6. Stoe & Cie, STADI4. Diffractometer Control Program, Stoe & Cie, Darmstadt, Germany, 1995.
7. Stoe & Cie, XRED. Data Reduction Program, Stoe & Cie, Darmstadt, Germany, 1995.
8. A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, M. C. Burla, G. Polidori, M. Camalli, and R. Spagna, SIR 97: A Package for Crystal Structure Solution by Direct Methods and Refinement, Roma, Italy, 1997.
9. G. M. Sheldrick, SHELXL97: Program for the Refinement of Crystal Structures, Universität Göttingen, Germany, 1997.
10. T. Spek, PLATON98: A Multipurpose Crystallographic Tool, University of Utrecht, Utrecht, The Netherlands, 1998.

SAŽETAK

Kemija 1,3-dioksepina. XVI.[1] Sinteza, karakterizacija i kristalografska analiza nekih arilsulfenil-, arilsulfinil-, arilsulfonil- i benzoil- *N*-supstituiranih derivata 1a,2,6,6a-tetrahidro-1*H*,4*H*-[1,3]dioksepino[5,6-*b*]azirina

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Opisana je kemo-selektivna sinteza i karakterizacija *N*-[(4-nitrofenil)sulfenil]- (**2**) i *N*-[(4-nitrofenil)sulfinil]- (**3**) *N*-[(4-aminofenil)sulfonil]- (**5**) i *N*-(4-aminobenzoil)- (**7**) analoga antihiperglikemičkih *N*-sulfonil-1a,2,6,6a-tetrahidro-1*H*,4*H*-[1,3]dioksepino[5,6-*b*]azirina, polazeći od 1a,2,6,6a-tetrahidro-1*H*,4*H*-[1,3]dioksepino[5,6-*b*]-azirina (**1**). Njihovo konformacijsko ponašanje u čvrstom stanju, temeljeno na provedenoj kristalografskoj analizi pokazuje da: (i) dioksepinoazirinski dio molekule u spojeva **2**, **5** and **7** zauzima čamac-stolac (BC), dok u spoju **3** zauzima konformaciju izvijenog čamca (TB); (ii) supstituent na aziridinskom dušiku je uvijek u *trans*, a nikad u *cis* položaju u odnosu na dioksepanski prsten; (iii) orijentacija sulfenilne-, sulfinilne-, sulfonilne- i acilne-skupine u spojeva **2**, **3**, **5** i **7** definirana je torzijskim kutovima C1-S1-N1-C7 od 110.7(2)° i 82.6(2)°, 88.80(11)° odnosno C1-C-N1-C7 od 64.9(5)°; (iv) Fenilna skupina od sulfinil- i sulfonil derivata **3** i **5** je okomita na S-N vezu s torzijskim kutovima N1-S1-C1-C2 od 67.9(3)° i –92.54(13)°, dok je ona u sulfenil- **2** i karbonil- **7** derivata koplanarna sa S-N ili C-N vezom, s torzijskim kutovima N1-S1-C1-C2 i N1-C-C1-C2 od 168.5(2)° odnosno 170.9(4)°. Dobiveni podaci služit će za daljnja istraživanja steričkih i elektronskih svojstava studiranih spojeva, usmjerena dizajnu antihiperglikemički djelotvornijih analoga.