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

Biserka Prugovečki,a Marina Marinković,b Mladen Vinković,b,** and Miljenko Dumićb,***

aLaboratory of General and Inorganic Chemistry, Faculty of Science, University of Zagreb, Kralja Zvonimira 8, 10000 Zagreb, Croatia

bPLIVA Research and Development Ltd., Prilaz baruna Filipovića 29, 10000 Zagreb, Croatia

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Chemo-selective synthesis and characterization of N-(4-nitrophenyl)sulphanyl-2 and N-(4-nitrophenyl)sulphinyl-3 derivatives of 1a,2,6,6a-tetrahydro-1H,4H-[1,3]dioxepino[5,6-b]azirines, starting from 1a,2,6,6a-tetrahydro-1H,4H-[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- and sulphonyl- moieties 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 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-1H,4H-[1,3]-dioxepino[5,6-b]azirines
• sulphanyl
• sulphinyl
• crystallographic analysis
• conformational behaviour
• antihyperglycaemics

INTRODUCTION

N-Sulphonyl-1a,2,6,6a-tetrahydro-1H,4H-[1,3]dioxepino[5,6-b]azirines known as potent antihyperglycaemics2,3 are recognized by scientific community as a promising class under examination. 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)sulphonyl]-
2, and N-[(4-nitrophenyl)sulphinyl]- 3 analogs, and N-[(4-aminophenyl)sulphonyl]- 5 (Ref. 5) and N-(4-amino- benzoyl)- 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 \(^1\)H 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 (\(\delta\)) are given in ppm relative to the tetramethylsilane (\(\delta = 0\)), 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)sulphonil]- and N-(4-nitrobenzoyl)- derivatives 4 (Ref. 1) and 6 (Ref. 1) were prepared by the previously reported procedures. Chemical yields were not optimized.

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-nitrobenzensulphenyl 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-nitrobenzensulphenyl 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)sulphenyl]-1a,2,6a-tetrahydro-1H,4H-[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) δ/ν ppm: 152.0 (s), 149.5 (s), 126.5 (d), 124.4 (d) (C-arom), 8.23 and 7.61 (2d, 4H, H-arom, J = 13.7 Hz), 4.80 and 4.47 (2d, 2H, H-C4, J = 8.9 Hz), 4.78 and 4.19 (2dd, 2H, H-C2,6, J = 1.9 Hz), 4.19 and 3.51 (2dd, 2H, H-1a,6a, J = 13.7 Hz, J = 1.7 Hz) and 4.19 and 3.51 (2dd, 2H, H-1a,6a, J = 13.7 Hz, J = 2.6 Hz). 13C NMR (DMSO-d6) δ/ν 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).


MS (ESI): 268.1 M+. 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)sulphenyl]-1a,2,6a-tetrahydro-1H,4H-[1,3]dioxepino[5,6-b]azirine (sulphanyl derivative 3) was isolated (747.0 mg, 26%); m.p. 94–96 °C. The analytical sample of sulphanyl derivative 3 was prepared by recrystallization from methanol showing m.p. 102–106 °C.

IR (KBr) δ/ν ppm: 3449, 3095, 3072, 2960, 2902, 2867, 2800, 1606, 1525, 1478, 1454, 1351, 1312, 1286, 1255, 1227, 1150, 1133, 1092, 1030, 997, 937, 879, 743, 726, 683, 633. 1H NMR (DMSO-d6) δ/ν 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). 13C NMR (DMSO-d6) δ/ν 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).


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 sulphonl derivative 2 (1.37 g, 60 %), sulphonyl derivative 3 (161.0 mg, 7 %) and sulphonl 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 sulphonl derivatives 2 and 3 obtained by Procedure 1 as well as to the authentic sample of 4 described earlier.

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

Sulphonyl 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 (Na2S2O5) (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, sulphonyl 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 sulphonyl derivative 3 described above.

By evaporation of the other pool of fractions, 1-[4-(Nitrophenyl)sulphonyl]-1a,2,6a-tetrahydro-1H,4H-[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 sulphonl derivative 4 was prepared by Procedure 1 as well as to the authentic sample described earlier.

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

Sulphonyl 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 discoulered with 30 % H2O2. White crystals started to form.
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 sulphonyl derivative 4 was obtained (65.0 mg, 68 %); m.p. 199–201 °C. The IR spectrum of thus obtained 4 was identical to the IR spectrum of the authentic sample.1

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

Nitrobenzoyl derivative 6 prepared previously1 (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) νmax/cm–1: 3447.15, 3345.86, 3218.75, 2977.89, 2977.89, 1659.92, 1628.29, 1593.62, 1579.47, 1504.17, 1468.06, 1442.87, 1407.43, 1396.32, 1345.92, 1305.87, 1284.95, 1177.42, 1107.95, 1060.89, 1018.80, 967.90, 921.83, 860.08, 689.11, 649.13, 585.77. 1H NMR (DMSO-d6)/300 MHz δ/ppm: 7.60 and 6.59 (2d, H-arom, J = 8.6 Hz), 5.96 (s, 2H, NH2), 4.87 and 4.38 (2d, 2H, H-C4, J = 7.1 Hz), 4.19 and 4.01 (2d, 4H, H-C2,6), 2.78 (s, 2H, H-C1a,6a). 13C NMR (DMSO-d6) 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).

Analytical data for N-substituted dioxepinoazirines 2, 3, 5 and 7

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**Anal.** Calcd. for C11H14N2O3S (Mr = 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⁺.
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 F² 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-nitrobenzenesulphonylchloride in methylene chloride at room temperature. 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 derivate 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-nitrobenzoyle chloride as described previously,5 followed by hydrogenation of thus obtained nitrobenzoyl derivate 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).

Figure 2. TEP of 2, 3, 5 and 7 crystal structures with atomic numbering (Ellipsoids drawn at 50 % probability level).
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\textsuperscript{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,\textsuperscript{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.\textsuperscript{1,3} The aziridine nitrogen atoms in all structures are sp\textsuperscript{3} hybridized in accordance with a previous study.\textsuperscript{1}

In addition, sulphonyl 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 sulphynyl 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 2](image2.png)
![Figure 3](image3.png)
![Figure 4](image4.png)

sulphonyldioxepinoazirines. 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. 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, sulphonyl 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 sulphonyl and sulphanyl 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 anti-hyperglycaemically 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
SAŽETAK

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

Biserka Prugovečki, Marina Marinković, Mladen Vinković i Miljenko Dumić

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 antihiperlimičkih N-sulfonil-1a,2,6,6a-tetrahidro-1H,4H-[1,3]dioksepino[5,6-b]azirina, polazeći od 1a,2,6,6a-tetrahidro-1H,4H-[1,3]dioksepino[3,6-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 sulfenil-, sulfinil-, sulfonil- i acilne-skupine u spojeva 2, 3, 5 i 7 definirana je tozijskim 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 tozijskim kutovima N1-S1-C1-C2 od 67.9(3)° i –92.54(13)°, dok je ona u sulfenil- 2 i karbonil- 7 deriva-ta koplanarna sa S-N ili C-N vezom, s tozijskim 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.