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Chemistry of 1,3-Dioxepins. XV.[1] Syntheses and Structure of Nitroaryl Analogues of Antihyperglycaemic *N*-Sulphonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]-dioxepino[5,6-*b*]azirines*

Marina Orešić,[a] *Darko Filić,*[a] *Biserka Prugovečki,*[b] *Mladen Vinković,*[a] *and Miljenko Dumić*[a,**]

[a]*PLIVA d.d., Research and Development, Prilaz baruna Filipovića 25, 10000 Zagreb, Croatia*

[b]*Laboratory of General and Inorganic Chemistry, Faculty of Science, University of Zagreb, Kralja Zvonimira 8, 10000 Zagreb, Croatia*

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Regio and stereocontrolled syntheses of novel nitrophenyl analogues of antihyperglycaemic *N*-sulphonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]-dioxepino[5,6-*b*]azirines: *N*-nitrobenzenesulphonylcyclohepta[*b*]azirine **6**, *N*-nitrobenzenesulphonyldioxepinoazirines **7**–**10**, *N*-nitrobenzoyldioxepinoazirine **11** and *N*-nitrobenzyldioxepinoazirine **12**, starting from cycloheptene (**2**), *trans*-6-acetylamino-2-isopropyl-5-chloro-1,3-dioxepane (**13**) and 5,6-epoxy-1,3-dioxepane (**14**), are described. Their crystallographic data show that: (a) boat-chair (BC) conformation of dioxepinoazirine and cyclohepta[*b*]azirine moieties dominates; (b) the substituent on aziridine nitrogen is always in *trans* and never in *cis* position in relation to the cycloheptane or dioxepane ring; (c) the sulphonyl group of sulphonylaziridines **6** and **8**–**10** adopts only one of the two possible conformations in relation to the aziridine ring, with torsion angles C1–S–N–C7 of ≅ 80° (corresponding angle O1–S–N–LP ≅ 180°, LP = lone pair) named by us conformation BC*; (d) orientation of the analogous carbonyl group of **11** and methylene group of **12** is defined by torsion angles

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* Dedicated to Professor Smiljko Ašperger on the occasion of his 80th birthday.

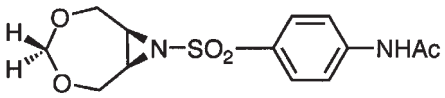
** Author to whom correspondence should be addressed. (E-mail: miljenko.dumic@pliva.hr)

C1–C0–N1–C7 of –78.3 (9)° and –93.9 (5)° respectively; (e) nitrogen atom in all studied *N*-sulphonyl-, acyl- and alkyl- aziridines is sp^3 hybridised, in contrast to other sulphonamides where sp^2 hybridisation is predominant; (f) nitrogen atom in alkylaziridine **12** is more pyramidal in relation to *N*-sulphonyl and *N*-acyl derivatives, and according to torsion angles O5–N2–C4–C5, the nitro group in all studied compounds is approximately coplanar to the phenyl ring plane. Obtained data will serve for further investigation of steric and electronic properties of studied compounds aimed at designing more antihyperglycaemically potent analogues.

Key words: 1,3-dioxepins, antihyperglycaemic activity, *N*-sulphonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines, nitroaryl analogues, regio and stereocontrolled syntheses.

INTRODUCTION

In the context of our research into hypoglycaemically active 1-sulphonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines,[2–6] the lead compound 1-(4-acetylaminobenzene)sulphonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**1**) showed the best antihyperglycaemic profile.[5]

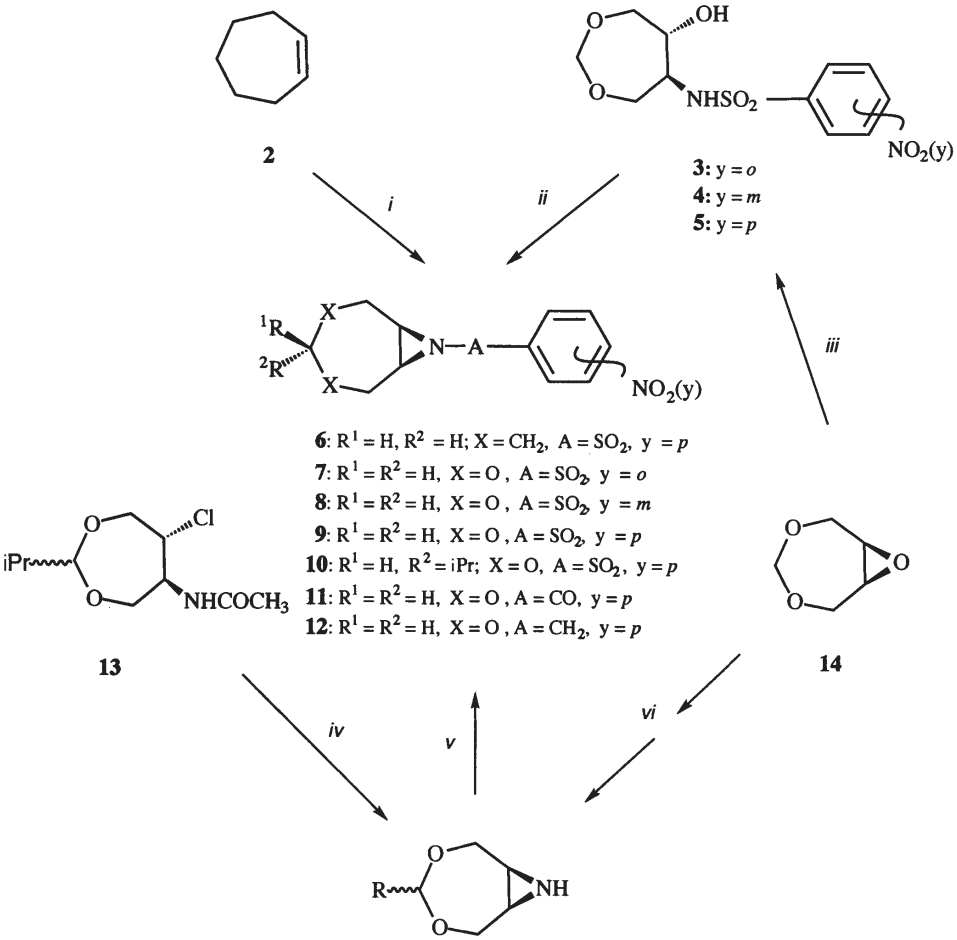


1

In order to study the importance of the sulphonyl moiety for antihyperglycaemic activity profiles, we decided to study the conformational behaviour of different sulphonyl-, carbonyl- and methylene moieties in the analogues of **1**. Therefore, we would like to report the synthesis of novel nitrophenyl analogues of **1**: *N*-sulphonylcyclohepta[*b*]azirine **6**, *N*-sulphonyldioxepinoazirines **7–10**, *N*-benzoyldioxepinoazirine **11** and *N*-benzyldioxepinoazirine **12** (Scheme 1), and the basic set of conformational data obtained from their crystallographic analysis, which will encourage further molecular modelling studies of isosterism and biosterism between sulphonyl-, carbonyl- and methylene moieties.

EXPERIMENTAL

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



(i) 4-NO_2-$C_6H_4SO_2N_3$ / acetonitrile, refl., 6.5 h
(ii) TPP / DEAD / acetonitrile, r.t., 0.5–2 h
(iii) 2-, 3- or 4- NO_2-$C_6H_4SO_2NH_2$ / pyridine, 130 °C, 15 min
(iv) KOH / H_2O, refl., 27 h (Ref. 4)
(v) 4-NO_2-$C_6H_4SO_4Cl$, 4-NO_2-C_6H_4COCl or 4-NO_2-$C_6H_4CH_2Br$ / pyridine / CH_2Cl_2, 0 °C, r.t. or refl., 1–5 h
(vi) NaN_3 / aq. acetone, refl., 6 h (Ref. 6); TPP / acetonitrile, refl. 5 h

Scheme 1.

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 F254 silica plates and components were visualised using UV light and iodine vapour. Solvents were *p.a.* grade and were used without further purification. *trans*-6-Acetylamino-2-isopropyl-5-chloro-1,3-dioxepane (**13**)[11] and 5,6-epoxi-1,3-dioxepane (**14**)[6] were prepared previously. Chemical yields were not optimised.

trans-*6-(2-Nitrobenzenesulphonamido)-1,3-dioxepan-5-ol (**3**)*

A mixture of epoxydioxepane **14** (116 mg, 1.0 mmol), pyridine (0.10 mL, 1.2 mmol) and 2-nitrobenzenesulphonamide12 (202 mg, 1.0 mmol) was heated in a sealed tube at 130 °C for 15 minutes. After cooling to room temperature, the mixture was purified by column chromatography using ethyl acetate/petroleum ether (volume ratio 7 : 3) as eluent. Unreacted starting nitrobenzenesulphonamide (71.0 mg, m.p. 185–187 °C; lit.[15] m.p. 190–191 °C) was obtained from the first fractions. By evaporation of subseqment fractions, the crude, TLC pure, sulphonamidodioxepanol **3** (103.0 mg, 32.4%) was isolated as a yellow oil. The analytical sample of **3** was prepared by crystallisation from isopropanol / petroleum ether (vol. ratio 1 : 1); m.p. 108–111 °C.

IR (KBr) ν_{max}/cm^{-1}: 3564, 3509, 3242, 2945, 2901, 1595, 1547, 1455, 1363, 1340, 1304, 1250, 1218, 1168, 1149, 1120, 1071, 1031, 956, 925, 858, 829, 785, 743, 730, 696, 655. ^1H NMR (500 MHz, $CDCl_3$) δ/ppm: 8.20–8.16 (m, 1H, H-C6'), 7.90–7.88 (m, 1H, H-C3'), 7.78–7.74 (m, 2H, H-C5' and H-C4'), 6.05 (d, 1H, NH, J = 7.9 Hz), 4.76 and 4.69 (ABq, 2H, H-C2, J = 4.5 Hz), 3.87 and 3.84 (2dd, 2H, H-C4, J = 13.0 Hz, J = 2.0 Hz), 3.83–3.79 (m, 1H, H-C5), 3.55–3.54 (m, 1H, H-C6), 3.83–3.79 (m, 1H, H-C7) and 3.47 (dd, 1H, H-C7, J = 12.5 Hz, J = 1.6 Hz), 2.62 (br, 1H, OH). ^{13}C NMR ($CDCl_3$) δ/ppm: 147.00 (s), 134.05 (d), 133.37 (s) 132.62 (d), 129.83 (d), 124.00 (d) (C-arom), 93.38 (t, C2), 71.20 (d, C5), 66.88 (t, C4), 64.40 (t, C7), 58.76 (d, C6). MS (ESI): 341.1 $(M+Na)^+$.

Anal. Calcd. for $C_{11}H_{14}N_2O_7S$ (M_r = 318.31): C 41.51, H 4.43, N 8.80%; found: C 41.52, H 4.22, N 8.61%.

trans-*6-(3-Nitrobenzenesulphonamido)-1,3-dioxepan-5-ol (**4**)*

A mixture of epoxydioxepane **14** (116.0 mg, 1.0 mmol), pyridine (0.1 mL, 1.2 mmol) and 3-nitrobenzenesulphonamide[12] (202.0 mg, 1.0 mmol) was heated in a sealed tube at 130 °C for 15 minutes. After cooling to room temperature, the mixture was purified by column chromatography using ethyl acetate/petroleum ether (volume ratio 7 : 3) as eluent. Unreacted starting nitrobenzenesulphonamide (40.0 mg, m.p. 158–161 °C; lit.[15] m.p. 162 °C) was obtained from the first fractions. By evaporation of subsequent fractions, the crude, TLC pure, sulphonamidodioxepanol **4** (61.0 mg, 19.2%) was isolated as a thick yellow oil.

IR (KBr) ν_{max}/cm^{-1}: 3288, 3113, 2933, 1607, 1532, 1455, 1433, 1354, 1286, 1170, 1133, 1091, 1039, 990, 967, 902, 877, 813, 771, 735, 664. ^1H NMR (500 MHz, $CDCl_3$) δ/ppm: 8.75 (deg dd, 1H, H-C2', J = 1.9 Hz), 8.46 (dd, 1H, H-C4', J = 7.9 Hz, J = 1.9 Hz), 8.24 (dd, 1H, H-C6', J = 7.9 Hz, J = 1.9 Hz), 7.77 (deg dd, 1H, H-C5', J = 7.9 Hz), 5.51 (d, 1H, NH, J = 8.4 Hz), 4.73 and 4.69 (ABq, 2H, H-C2, J = 18.0 Hz, J = 4.6 Hz),

3.85–3.80 (m, 3H, H-C4 and H-C5), 3.79 and 3.40 (2 × dd, 2H, H-C7, J = 3.3 Hz, J = 1.3 Hz, J = 1.3 Hz), 3.43–3.41 (m, 1H, H-C6), 2.18 (s, OH). ^{13}C NMR ($CDCl_3$) δ/ppm: 147.98 (s), 142.41 (s), 132.17 (d), 130.43 (d), 127.01 (d), 121.84 (d) (C-arom.), 93.68 (s, C2), 71.58 (d, C5), 65.32 (t, C4), 62.94 (t, C7), 57.05 (d, C6). MS (ESI): 341.0 $(M+Na)^+$.

Anal. Calcd. for $C_{11}H_{14}N_2O_7S$ (M_r = 318.31): C 41.51, H 4.43, N 8.80%; found: C 41.34, H 4.66, N 8.85%.

trans-*6-(4-Nitrobenzenesulphonamido)-1,3-dioxepan-5-ol (**5**)*

A mixture of epoxydioxepane **14** (116.0 mg, 1.0 mmol), pyridine (0.1 mL, 1.2 mmol) and 4-nitrobenzenesulphonamide[12] (202 mg, 1.0 mmol) was heated in a sealed tube at 130 °C for 15 minutes. After cooling to room temperature, the mixture was purified by column chromatography using ethyl acetate/petroleum ether (volume ratio 7 : 3) as eluent. Unreacted starting nitrobenzenesulphonamide (59.0 mg, m.p. 174–175 °C; lit.[15] m.p. 177–178 °C) was obtained from the first fractions. By evaporation of subsequent fractions the crude, TLC pure, sulphonamidodioxepanol **5** (55.0 mg, 17.3%, m.p. 117–119 °C) was isolated. The analytical sample of **5** was prepared by recrystallisation from ethyl acetate/petroleum ether (vol. ratio 1 : 1); m.p. 120–122 °C.

IR (KBr) ν_{max}/cm^{-1}: 3550, 3195, 2935, 2899, 1609, 1526, 1458, 1435, 1404, 1352, 1311, 1295, 1235, 1217, 1166, 1133, 1087, 1036, 990, 970, 905, 854, 798, 762, 738, 686, 661, 614. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 8.39 and 8.09 (2d, 4H, H-arom, J = 8.9 Hz), 8.23 (d, 1H, NH, J = 1.9 Hz), 4.90 (d, 1H, OH, J = 5.8 Hz), 4.60 (s, 2H, H-C2), 3.67 and 3.38 (2 × dd, 2H, H-C7, J = 12.0, J = 7.1, J = 2.9 Hz), 3.64 and 3.45 (2 × dd, 2H, H-C4, J = 12.0, J = 6.8, J = 2.7 Hz), 3.33–3.30, (m, 1H, H-C5), 3.13 (br, 1H, H-C6). ^{13}C NMR (DMSO-d_6) δ/ppm: 149.46 (s), 147.53 (s), 128.16 (d), 124.45 (d) (C-arom), 93.44 (t, C2), 71.44 (d, C6), 66.97 (t, C7), 64.94 (t, C4), 59.09 (d, C5). MS (ESI): 340.9 $(M+Na)^+$.

Anal. Calcd. for $C_{11}H_{14}N_2O_7S$ (M_r = 318.31): C 41.51, H 4.43, N 8.80%; found: C 41.75, H 4.22, N 8.69%.

*1-Nitrobenzenesulphonylcyclohepta[*b*]azirine (**6**)*

A mixture of 4-nitrobenzenesulphonazide (0.91 g, 4 mmol) and cycloheptene (2.33 mL, 20 mmol) in dry acetonitrile (10 mL) was refluxed for 6.5 hours. After evaporation of the solvent under reduced pressure, the mixture was chromatographed in petroleum ether/ethyl acetate (volume ratio 8 : 2) mixture. Concentration of selected fractions yielded azirine **6** (0.1997 g, 16.9%) as a yellow oil. After crystallisation from diethyl ether, the analytical sample of **6** was obtained; m.p. 115–118 °C. Besides **6**, 4-nitrobenzenesulphonylamide was isolated (0.66 g, 81%); m.p. 175–180 °C.[12]

IR (KBr) ν_{max}/cm^{-1}: 3105, 2926, 2853, 1945, 1810, 1693, 1608, 1530, 1479, 1453, 1422, 1402, 1350, 1319, 1306, 1271, 1222, 1158, 1088, 1034, 966, 941, 855, 842, 807, 788, 753, 743, 702, 682, 622. ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm: 8.45 and 8.19 (2d, 4H, H-arom, J = 9.2 Hz), 3.03–3.10 (m, 2H, H-C1a,6a), 1.74–1.88 (m, 4H, H-C2,6), 1.14–1.51 (m, 6H, H-C3,4,5). ^{13}C NMR (DMSO-d_6) δ/ppm: 150.61 (s), 143.92 (s), 129.13 (d), 125.01 (d) (C-arom), 44.87 (d, C1a,6a), 30.36 (t, C-2,6), 27.37 (t, C3,5), 24.76 (t, C4).

Anal. Calcd. for $C_{13}H_{16}N_2O_4S$ (M_r = 296.34): C 52.69, H 5.44, N 9.45%; found: C 52.80, H, 5.35, N 9.59 %.

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

Procedure 1

A solution of diethyl azodicarboxylate (38% in toluene, 0.72 mL, 1.5 mmol) in 2.0 mL of dry acetonitrile was added dropwise to a solution of nitrobenzenesulphonamidodioxepanol **3** (160.0 mg, 0.5 mmol) and triphenylphosphine (405.0 mg, 1.5 mmol) in 8.0 mL of dry acetonitrile at 0 °C during 30 minutes. The mixture was warmed up to room temperature, stirred for further 2 hours at the same temperature and concentrated under reduced pressure. The oily residue was purified by column chromatography using methylene chloride / methanol (vol. ratio 9 : 1) as eluent, which yielded crude **7** (90.0 mg, 60.0%) as a solid; m.p. 134–136 °C. The analytical sample of **7** was prepared by recrystallisation from ethyl acetate / methanol (vol. ratio 6 : 1); m.p. 141–142 °C.

IR (KBr) ν_{max}/cm^{-1}: 2980, 1590, 1550, 1440, 1365, 1335, 1300, 1250, 1170, 1160, 1130, 1105, 1070, 1030, 990, 960, 940, 920, 860, 830, 790, 770, 750, 735, 715, 685. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ/ppm: 7.94–8.04 (m, 2H, H-C4' and H-C5'), 8,23 and 8,21 (2d, 1H, H-C3', J = 1.8 Hz), 8.21 and 8.12 (2d, 1H, H-C6', J = 1.8 Hz), 4.81 and 4.34 (2d, 2H, H-C4, J = 7.0 Hz), 3.37 (s, 2H, H-C6a and H-C1a), 4.15 and 4.02 (2d, 4H, H-C6 and H-C2, J = 13.7 Hz). ^{13}C NMR (DMSO-d$_6$) δ/ppm: 136.00 (s), 133.50 (s), 131.04 (d), 130.45 (d), 125.89 (d) (C-arom), 97.64 (t, C4), 66.05 (t, C2 and C6), 46.34 (d, C1a and C6a). MS (FAB): 301 (M+H)$^+$.

Anal. Calcd. for $C_{11}H_{12}N_2O_6S$ (M_r = 300.29): C 43.99, H 4.03, N 9.33%; found: C 44.12, H 4.25, N 9.42 %.

Procedure 2

A mixture of azirine **15** (0.19 g, 1.68 mmol), 2-nitrobenzenesulphonyl chloride (0.45 g, 2.0 mmol), pyridine (0.23 mL, 2.8 mmol) and methylene chloride (7 mL) was stirred at 0 °C for 1 hour. Upon addition of additional 20 mL of methylene chloride, the mixture was worked up with aqueous NaOH solution (vol. ratio 1 : 1) (2 × 10 mL). The organic layer was separated, washed with water (10 mL), neutralised with diluted HCl up to pH = 6, washed once more with 10 mL of water and dried over anhydrous sodium sulphate. Evaporation of methylene chloride under reduced pressure yielded crude, TLC pure, sulphonylazirine **7** (0.48 g, 95.1%); m.p. 130–134 °C. The analytical sample of **7** was prepared by recrystallisation from ethyl acetate; m.p. 139–141 °C. The IR spectrum of **9** was identical to the IR spectrum of the authentic sample from procedure 1.

*1-(3-Nitrobenzenesulphonyl)-1a,2,6,6a-tetrahydro-1*H,*4*H-*[1,3]dioxepino[5,6-*b*] azirine (**8**)*

Procedure 1

A solution of diethyl azodicarboxylate (38% in toluene, 1.44 mL, 3.0 mmol) in 5.0 mL of dry acetonitrile was added dropwise to a solution of nitrobenzenesulphonamidodioxepanol **4** (318.3 mg, 1.0 mmol) and triphenylphosphine (811.0 mg, 3.0 mmol) in 15.0 mL of dry acetonitrile at 0 °C during 30 minutes. The mixture was warmed up to room temperature, stirred for a further 3 hours at the same temperature and concentrated under reduced pressure. The oily residue was purified by column chromatography using methylene chloride / methanol (vol. ratio 9 : 1) as eluent which

yielded crude **8** (250.0 mg, 83.3%) as a solid; m.p. 149–150 °C. The analytical sample of **8** was prepared by recrystallization from ethyl acetate / methanol (vol. ratio 6 : 1); m.p. 152–153 °C.

IR (KBr) ν_{max}/cm^{-1}: 3100, 2980, 2960, 2900, 2860, 1610, 1530, 1470, 1450, 1430, 1370, 1350, 1295, 1270, 1260, 1240, 1180, 1160, 1145, 1125, 1105, 1070, 1060, 1020, 995, 955, 940, 930, 920, 880, 830, 820, 775, 740, 720, 675, 660. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ/ppm: 8.57 (deg dd, 1H, H-C2', J = 7.8 Hz), 8.60 (d, 1H, H-C4', J = 7.8 Hz), 8.57–8.54 (m, 1H, H-C6'), 7.99 (deg dd, 1H, H-C5', J = 7.8 Hz), 4.79 and 4.30 (2d, 2H, H-C4, J = 7.0 Hz), 4.03 and 3.97 (2d, 4H, H-C6 and H-C2, J = 14.0 Hz), 3.29 (s, 2H, H-C1a and H-C6a). ^{13}C NMR (DMSO-d$_6$) δ/ppm: 148.38 (s), 139.31 (s), 128.85 (d), 132.07 (d), 133.77 (d), 122.48 (d) (C-arom), 97.68 (t, C4), 66.01 (t, C2 and C6), 45.05 (d, C2 and C6). MS (FAB): 301 (M+H)$^+$.

Anal. Calcd. for $C_{11}H_{12}N_2O_6S$ (M_r = 300.29): C 43.99, H 4.03, N 9.33%; found: C 44.18, H 3.96, N 9.46%.

Procedure 2

A mixture of azirine **15** (0.29 g, 2.50 mmol), 3-nitrobenzenesulphonyl chloride (0.67 g, 3.00 mmol), pyridine (0.35 mL, 4.30 mmol) and methylene chloride (7 mL) was stirred at 0 °C for 1 hour. Upon addition of additional 20 mL of methylene chloride, the mixture was worked up with aqueous NaOH solution (volume ratio 1 : 1) (2 × 10 mL). The organic layer was separated, washed with water (10 mL), neutralised with diluted HCl up to pH = 6, washed once more with 10 mL of water and dried over anhydrous sodium sulphate. Evaporation of methylene chloride under reduced pressure yielded crude, TLC pure, sulphonylazirine **8** (0.67 g, 89.25%); m.p. 149–150 °C. The analytical sample of **8** was prepared by recrystallisation from ethyl acetate; m.p. 152–153 °C. The IR spectrum of **8** was identical to the IR spectrum of the authentic sample from procedure 1.

*1-(4-Nitrobenzenesulphonyl)-1a,2,6,6a-tetrahydro-1*H,*4*H-*[1,3]dioxepino[5,6-*b*]azirine (**9**)*

Procedure 1

A solution of diethylazodicarboxylate (38% in toluene, 1.44 mL, 3.0 mmol) in 5.0 mL of dry acetonitrile was added to a solution of nitrobenzenesulphonamidodioxepanol **5** (318.3 mg, 1.0 mmol) and triphenylphosphine (811.0 mg, 3.0 mmol) in 15.0 mL of dry acetonitrile at 0 °C during 30 minutes. The mixture was warmed up to room temperature, stirred for a further 2 hours at the same temperature and concentrated under reduced pressure. The oily residue was purified by column chromatography using methylene chloride / methanol (volume ratio 9 : 1) as eluent, which yielded crude **9** (206.0 mg, 68.6%) as a solid; m.p. 206–207 °C. The analytical sample of **9** was prepared by recrystallisation from ethyl acetate / methanol (vol. ratio 6 : 1); m.p. 208–210 °C. IR spectrum of **9** was identical to the IR spectrum of the authentic sample.[5]

Procedure 2

A mixture of azirine **15** (0.29 g, 2.50 mmol), 4-nitrobenzenesulphonyl chloride (0.67 g, 3.00 mmol), pyridine (0.35 mL, 4.30 mmol) and methylene chloride (7 mL) was stirred at 0 °C for 1 hour. Upon addition of additional 20 mL of methylene chloride, the mixture was worked up with aqueous NaOH solution (volume ratio 1 : 1) (2 × 10 mL). The

organic layer was separated, washed with water (10 mL), neutralised with diluted HCl up to pH = 6, washed once more with 10 mL of water and dried over anhydrous sodium sulphate. Evaporation of methylene chloride under reduced pressure yielded crude, TLC pure, sulphonylazirine **9** (0.51 g, 68.00%) m.p. 204–206 °C. The analytical sample of **9** was prepared by recrystallisation from acetone; m.p. 206–208 °C. The IR spectrum of **9** was identical to the IR spectrum of the authentic sample.[5]

*1-(4-Nitrobenzoyl)-1a,2,6,6a-tetrahydro-1*H,*4*H-*[1,3]dioxepino[5,6-*b*]azirine (**11**)*

A mixture of **15** (0.58 g, 5.0 mmol), 4-nitrobenzoyl chloride (1.0 g, 5.4 mol), pyridine (0.8 mL) and methylene chloride (20.0 mL) was stirred at reflux temperature for 1 hour. Upon addition of an additional 20 mL of methylene chloride, the mixture was worked up with 2 × 10 mL of aqueous sodium hydroxide solution (1 : 1), the organic layer was separated, washed with 10 mL of water, neutralised with diluted hydrochloric acid up to pH = 6, washed once more with 10 mL of water, dried over anhydrous sodium sulphate and concentrated. The obtained solid residue (1.43 g) was crystallised from methylene chloride / methanol (volume ratio 1 : 2) mixture furnishing TLC pure nitrobenzoylaziridine **11** (0.80 g, 60.6%) as colourless crystals; m.p. 177–179 °C. After recrystallisation from methylene chloride / methanol (volume ratio 1 : 2) mixture, the sample showed m.p. 178–180 °C.

IR (KBr) ν_{max}/cm^{-1}: 3105, 2990, 2950, 2920, 2760, 1670, 1610, 1510, 1440, 1410, 1360, 1300, 1290, 1270, 1240, 1180, 1150, 1120, 1100, 1050, 1100, 1000, 960, 920, 880, 850, 830, 800, 760, 740, 730. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ/ppm: 8.38 and 8.10 (2d, 4H, H-arom, J = 8.7 Hz), 4.93 and 4.37 (2d, 2H, H-C4, J = 7.1 Hz), 4.46 and 3.91 (2d, 4H, H-C2,6, J = 13.9 Hz), 3.05 (s, H-C1a,6a, 2H). ^{13}C NMR (DMSO-d$_6$) δ/ppm: 176.59 (s, CO), 149.89 (s), 138.32 (s), 130.06 (d) and 124.03 (d) (C-arom), 98.25 (t, C4), 66.97 (t, C2,6), 42.18 (d, C1a,6a). MS (ESI): 286.9 (M+Na)$^+$.

Anal. Calcd. for $C_{12}H_{12}N_2O_5$ (M_r = 264.24): C 54.55, H 4.58, N 10.60%; found: C 54.52, H 4.57, N 10.61%.

*1-(4-Nitrobenzyl)-1a,2,6,6a-tetrahydro-1*H,*4*H-*[1,3]dioxepino[5,6-*b*]azirine (**12**)*

A mixture of **15** (0.70 g, 6.1 mmol), 4-nitrobenzyl bromide (1.44 g, 6.7 mmol), pyridine (1.2 mL) and methylene chloride (15.0 mL) was stirred at room temperature for 5 hours. The mixture was washed with water (4 × 10 mL), the organic layer was separated, dried over anhydrous sodium sulphate and concentrated. The oily residue (1.78 g) was crystallised from ethyl acetate furnishing TLC pure nitrobenzylaziridine **12** (0.37 g, 24.2%) as colourless crystals; m.p. 88–91 °C. After recrystallisation from ethyl acetate, the sample showed m.p. 90–92 °C.

IR (KBr) ν_{max}/cm^{-1}: 3440, 3115, 2952, 2904, 2860, 2806, 1597, 1509, 1450, 1425, 1341, 1290, 1261, 1235, 1182, 1123, 1108, 1060, 1013, 989, 944, 919, 861, 839, 789, 756, 738, 678, 660. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ/ppm: 8.21 and 7.62 (2d, 4H, H-arom, J = 8.7 Hz), 4.65 and 4.59 (ABq, 2H, H-C4, J = 6.8 Hz), 4.08 and 3.81 (2d, 4H, H-C2,6, J = 13.2 Hz, J = 4.6 Hz), 3.62 (s, 2H, H-C1a,6a), 2.05 (s, 2H, CH_2). ^{13}C NMR (DMSO-d$_6$) δ/ppm: 147.92 (s), 146.48 (s), 128.62 (d), 123.45 (d) (C-arom), 98.91 (t, C4), 69.57 (t, C2,6), 61.46 (t, CH_2), 44.06 (d, C1a,6a). MS (ESI): 250.9 (MH)$^+$.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$ (M_r = 250.25): C 57.59, H 5.64, N 11.19%; found: C 57.56, H 5.45, N 11.30%.

trans-*6-(4-Acetylaminobenzenesulphonamido)-1,3-dioxepan-5-ol (**17**)*

trans-(4-Aminobenzenesulphonylamido)-1,3-dioxepan-5-ol (**18**) (50.00 mg, 0,17 mmol) was dissolved in 1.0 mL of pyridine and the solution was cooled at 0 °C. Acetic anhydride was added (0.03 mL, 0.20 mmol) and the mixture was stirred at 0 °C for 7 hours. The reaction mixture was left at –15 °C for 2 days, the solvents were evaporated under reduced pressure and a mixture of dioxepanol **18** and *trans*-6-(4-acetylaminobenzenesulphonamido)-5-acetoxy-1,3-dioxepane (**17**) (55.00 mg) was obtained. The crude reaction mixture was chromatographed in ethylacetate / methanol mixture (volume ratio 9.5 : 0.5) and pure **17** was obtained (23.00 mg, 40.24%) as a white solid; m.p. 189–191 °C (lit. m.p. 209–211 °C). Its IR spectrum corresponds to literature data.[6]

Besides dioxepanol **17**, a mixture of dioxepanol **17** and diacetyl-derivative was obtained (26 mg).

trans-*6-(4-Aminobenzenesulphonamido)-1,3-dioxepan-5-ol (**18**)*

4-Nitrophenyl derivative **5** (100.00 mg, 0.31 mmol) was hydrogenated in ethyl acetate in the presence of 5% Pd/C catalyst (10.00 mg) under 3 bar hydrogen pressure at room temperature for 2 hours. The catalyst was separated by filtration and the solvent was evaporated under reduced pressure. The obtained crude oily **18** (99.00 mg) was crystallised from methanol, furnishing TLC pure **18** (78.00 mg, 87.3%); m.p. 124–126 °C. The analytical sample of **18** was prepared by crystallisation from methanol; m.p. 123–125 °C. After recrystallisation from methanol, the sample showed m.p. 129–130 °C.

IR (KBr) ν_{max}/cm^{-1}: 3471, 3436, 3367, 3262, 3099, 2891, 1650, 1598, 1503, 1462, 1411, 1391, 1312, 1300, 1241, 1185, 1148, 1119, 1089, 1037, 987, 967, 900, 833, 775, 683. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ/ppm: 7,46 and 6,59 (2d, 4H, H-arom, J = 8.4 Hz), 7,19 (d, 1H, $NHSO_2$, J = 8,1 Hz), 5,93 (s, 2H, NH_2), 4,58 (s, 2H, H-C2), 3,69 and 3,47 (ABq, 2H, H-C4, J = 12,3, J = 5,8 Hz), 3,59 and 3,26 (ABq, 2H, H-C7, J = 6 Hz), 3.31 (m, 1H, H-C5), 2,98-2,96 (m, 1H, H-C6). ^{13}C NMR (DMSO-d$_6$) δ/ppm: 152,70 (s), 128,67 (d), 126,90 (s), 112,83 (d) (C-arom), 93,44 (d, C2), 71,45 (d, C5), 66,97 (t, C4), 64,25 (t, C7) and 58,48 (d, C6). MS (ESI): 210.9 $(M+Na)^+$.

Anal. Calcd. for $C_{11}H_{16}N_2O_5S$ (M_r = 288.32): C 45.82, H 5.59, N 9.72%; found: C 46.02, H 5.45, N 9.66%.

The X-ray diffraction data for compounds **6** and **8–12** 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. The measured intensity data were corrected for Lorentz and polarisation effects, but not for absorption. The molecular and crystal structures were solved by direct methods implemented in the programs SIR 96 and SHELXS96 and refined on F^2 with anisotropic displacement parameters for all non-hydrogen atoms. All hydrogen atoms were generated on geometrical grounds. Essential crystallographic data are presented in Table I. Crystallographic data sets for all studied compounds are deposited with the Cambridge Crystallographic Data Centre and are available on request. Detailed analysis of molecular geometry will be published elsewhere.

RESULTS AND DISCUSSION

Chemistry

Cycloheptane analogue of **1**, *N*-sulphonylcyclohepta[*b*]azirine **6** was prepared by addition of 4-nitrobenzenesulphonylazide[7] to cycloheptene (**2**) in acetonitrile in 17% yield.[8] Nitrobenzene derivatives **7**–**9** were synthesised *via* dioxepanols **3**–**5** by reaction of epoxy derivative **14** with *o*-, *m*- and *p*-nitrobenzenesulphonamides in sealed tubes at 130 °C, catalysed by pyridine (17–32%), followed by Mitsunobu cyclisation (60–83%). Before that, derivative **9** was prepared in 68% yield, by a parallel path, *i.e.* by sulphonation of aziridine **15** by *p*-nitrobenzenesulphonyl chloride.[5] Sulphonation of isopropyl dioxepin derivative **16**, obtained by ring-closure dehydrohalogenation of the corresponding *trans*-acetylaminochlorodioxepane **13**, furnished only *exo*-4-nitrophenyl aziridine **10** in about 90% yield.[5] 4-Nitrobenzoyl derivative **11**, as well as 4-nitrobenzyl derivative **12** were prepared by reaction of aziridine **15** with 4-nitrobenzoyl chloride and 4-nitrobenzyl bromide in 61% and 24% yields, respectively.

Structures of all new nitroaziridine derivatives were assigned from their spectral data and unambiguously confirmed by the single crystal X-ray structure analyses (Figure 1, Table I). Unfortunately, an exception was the *o*-nitro derivative **7**, for which we did not obtain good quality single crystals.

Assignments of the configurations of new sulphonamidodioxepanols **3**–**5** given in Scheme 1 were based on NMR data and confirmed by an independent unequivocal two step synthesis of *trans*-6-(4-acetyl-aminobenzenesulphonamido)-1,3-dioxepan-5-ol (**17**) of the known *trans* configuration[6] by hydrogenation of 4-nitrophenyl derivative **5**, followed by acetylation of the thus obtained *trans*-6-(4-aminobenzenesulphonamido)-1,3-dioxepan-5-ol (**18**).

Finally, the *trans*-configurations of sulphonamidodioxepanols were indirectly confirmed by single crystal X-ray structure analyses of aziridines **8** and **9** (Figure 1, Table I), obtained by Mitsunobu dehydration[9] of **4** and **5**.

X-ray Diffraction Study

The thermal ellipsoid plots (TEP) of title compounds **6** and **8**–**12**, with the atomic numbering scheme, are shown in Figure 1. Crystallographic analyses show that in four out of six solved structures (for **9** and **10** only essential crystallographic data without deposition were published)[5] dioxepinoazirine and cyclohepta[*b*]azirine moieties adopt a boat-chair (BC) conformation, and only in **10** dioxepinoazirine moiety a chair-chair (CC) conformation. In all the studied cases, the substituent on aziridine nitrogen is always in *trans*

TABLE I

Crystallographic data for aziridine derivatives **6** and **8–12** [a]

Parameter	**6**	**8**	**9**	**10**	**11**	**12**
Formula	$C_{13}H_{16}N_2O_4S$	$C_{11}H_{12}N_2O_6S$	$C_{11}H_{12}N_2O_6S$	$C_{14}H_{18}N_2O_6S$	$C_{12}H_{12}N_2O_5$	$C_{12}H_{14}N_2O_4$
M_r	296.34	300.29	300.29	342.36	264.24	250.25
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group (#)	$P2_1/n$ (14)	$P2_1/n$ (14)	$I2/a$ (15)	$P\bar{1}$ (2)	$P2_1/n$ (14)	$A2/n$ (15)
a/Å	10.472(4)	6.121(2)	20.233(4)	7.057(3)	4.521(7)	19.5207(9)
b/Å	6.547(2)	19.722(8)	6.127(2)	9.615(6)	22.89(3)	5.6245(4)
c/Å	20.799(5)	11.172(3)	22.772(4)	12.022(8)	11.840(10)	24.0942(9)
α/°	90	90	90	89.98(4)	90	90
β/°	98.75(3)	101.72(2)	114.10(10)	76.97(5)	96.86(15)	113.459(5)
γ/°	90	90	90	78.52(3)	90	90
V/Å^3	1409.4(8)	1320.5(8)	2576.9(11)	778.0(8)	1216(3)	2426.7(2)
Z	4	4	8	2	4	8
ρ_{calcd} /g cm^{-3}	1.397	1.510	1.550	1.460	1.443	1.370
μ/cm^{-1}	2.44	2.73	2.79	2.41	9.71[b]	8.74[b]
F_{000}	624	624	1248	360	552	1056
Unique refl.	4127	3865	3752	4530	1468	1607
Refined paramet.	187	181	181	208	173	164
R_F	0.0584	0.0579	0.0548	0.0372	0.0830	0.0791
wR_{F2}	0.1174	0.1274	0.1429	0.1173	0.1508	0.2291
$\Delta\varphi_{max, min}$ / e Å^{-3}	0.173, –0.204	0.240, –0.317	0.214, –0.305	0.289, –0.370	0.246, –0.293	0.233, –0.252

[a] Data for compounds **6** and **8–12** were collected on a PHILLIPS PW 1100 automatic four-circle diffractometer (Stoe/Cie upgrade) using monochromatised Mo-Kα radiation (λ = 0.71069 Å) at room temperature.
[b] Monochromatised Cu-Kα radiation (λ = 1.54178 Å) was applied.

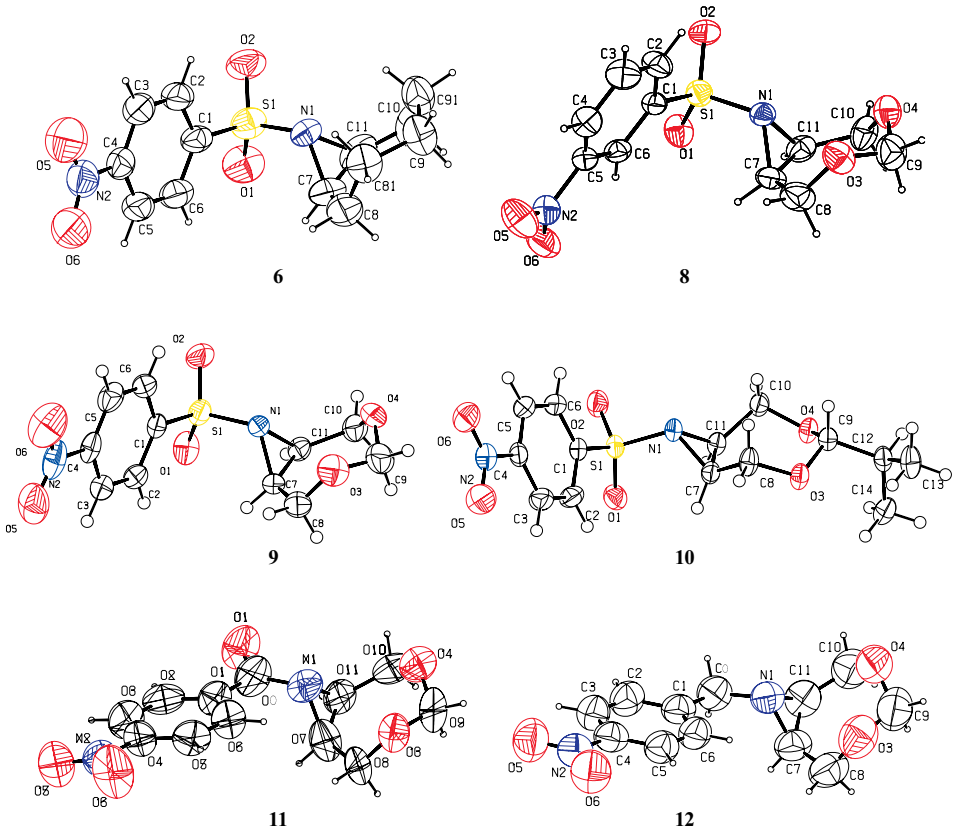


Figure 1. TEP of **6** and **8**–**12** crystal structures with atomic numbering. (Ellipsoids drawn at 50% probability level.)

and never in *cis* position in relation to the cycloheptane or dioxepane ring, supporting our previous results.[5]

In addition, the sulphonyl group of sulphonylaziridines **6** and **8**–**10** adopts only one of the two possible conformations[5] in relation to the aziridine ring,

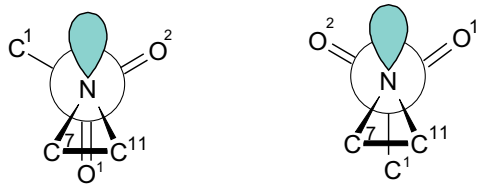


Figure 2. Sulphonylazirine moiety of **6** and **8**–**10** adopts only conformation (a) in the solid state out of the two possible ones, (a) and (b).

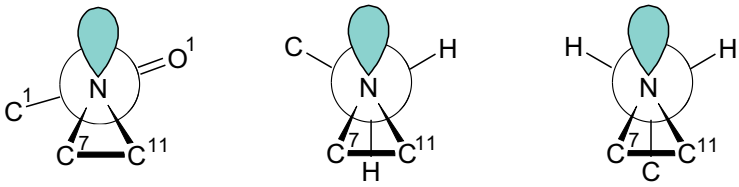


Figure 3. Acylazirine **11** can adopt only one conformation (a). Alkylazirine **12** adopts conformation (b) in the solid state out of the two possible ones, (b) and (c).

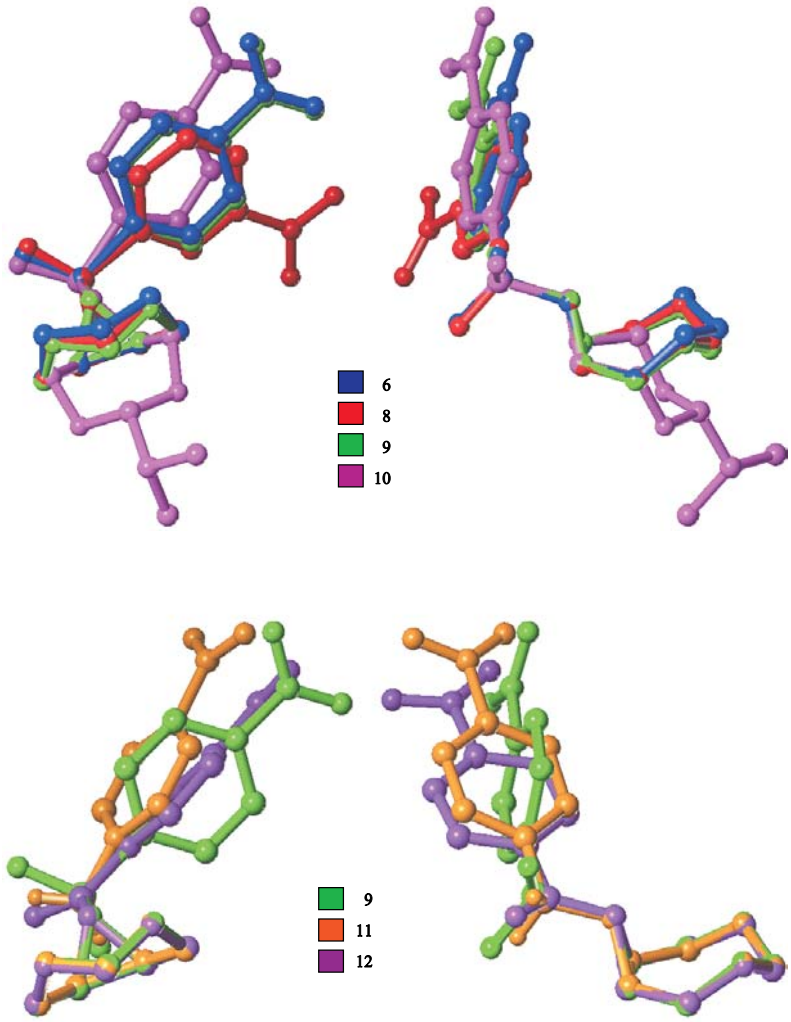


Figure 4. Superposition of crystal state conformations of nitroaziridines **6** and **8**–**12**.

with a torsion angle C1–S–N–C7 of ≅ 80° (corresponding angle O1–S–N–LP ≅ 180°; LP = lone pair) (Figure 2a). We named this conformation BC*, and found it to be the most frequent in the crystal state of sulphonyldioxepino-azirines.[5]

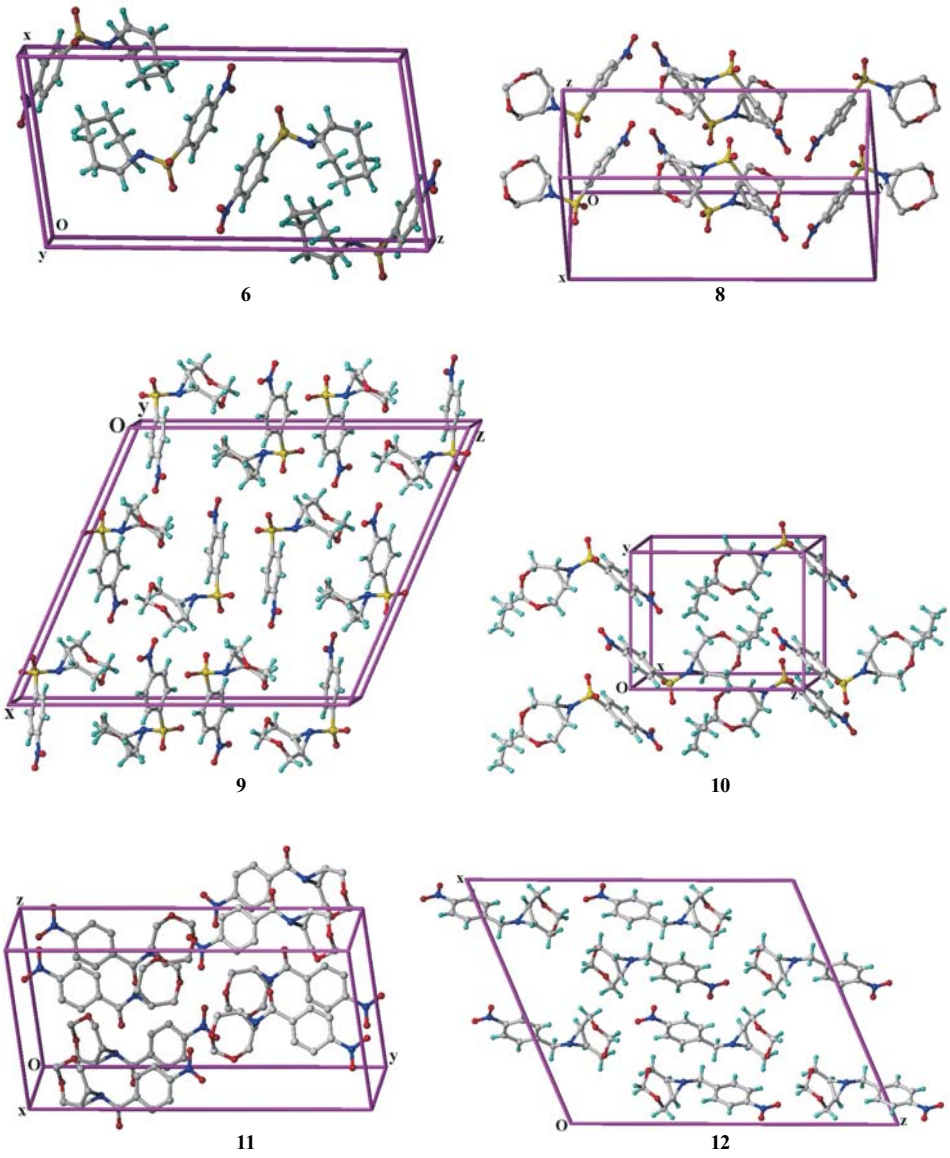


Figure 5. Crystal packing of azirines **6** and **8**–**12**. Hydrogen atoms are omitted in packing diagrams of compounds **8** and **11** for clarity.

Similarly, the orientation of the analogous carbonyl group of **11** is defined by torsion angle C1–C0–N1–C7 of –78.3(9)° (Figure 3a). Otherwise, the methylene group of **12** adopts only one (Figure 3b) of the two (Figure 3b and 3c) possible conformations[10] in relation to the aziridine ring, with a torsion angle C1–C0–N1–C7 of –93.9(5)°. Nitrogen atoms in all studied *N*-sulphonylaziridines are sp^3 hybridised, in contrast to other sulphonamides where sp^2 hybridisation predominates.[10] Similarly, the nitrogen atoms in acylaziridine **11** and alkylaziridine **12** are sp^3 hybridised as well, but the latter is more pyramidal compared to *N*-sulphonyl and *N*-acyl.[10] According to torsion angles O5–N2–C4–C5, the nitro groups in all studied compounds are approximately coplanar to the phenyl ring plane, as expected. Superposition of sulphonylaziridines **6** and **8**–**10** illustrates the above conclusions (Figure 4a) and highlights their conformational similarity.

Superposition of sulphonyldioxepinoazirine **9** with acyl- **11** and alkyl- **12** analogues (Figure 4b) shows a similarity in the dioxepinoazirine moiety and overall conformation. However, more conformational heterogeneity is observed in the orientation of the aromatic part of the molecules.

None of the studied molecules possesses H-donating groups or the ability to form H-bonds. Therefore, all the studied molecules are packed together in crystals only by van der Waals interactions (Figure 5). Aromatic parts of molecules usually stick together in dimers.

The described crystallographic and conformational data of the studied nitro derivatives will serve for further investigation of steric and electronic properties of the studied compounds and their biosterism, as well as for designing more antihyperglycaemically potent analogues.

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SAŽETAK

Kemija 1,3-dioksepina. XV. Sinteze i struktura nitroaril-analoga antihiperglikemičkih *N*-sulfonil-1a,2,6,6a-tetrahidro-1*H*,4*H*-[1,3]dioksepino[5,6-*b*]azirina

Marina Orešić, Darko Filić, Biserka Prugovečki, Mladen Vinković i Miljenko Dumić

Opisane su regio- i stereoselektivne sinteze novih nitrofenilnih analoga antihiperglikemičkih *N*-sulfonil-1a,2,6,6a-tetrahidro-1*H*,4*H*-[1,3]dioksepino[5,6-*b*]azirina: *N*-nitrobenzensulfonilciklohepta[*b*]azirina **6**, *N*-nitrobenzensulfonildioksepinoazirina **7**–**10**, *N*-nitrobenzoildioksepinoazirina **11** i *N*-nitrobenzildioksepinoazirina **12**, polazeći od cikloheptena (**2**), *trans*-6-acetilamino-2-izopropil-5-kloro-1,3-dioksepana (**13**) i 5,6-epoksi-1,3-dioksepana (**14**). Njihovi kristalografski podatci pokazuju: (a) konformacija čamac-stolac (BC) dominira za dioksepinoazirinski i ciklohepta[*b*]azirinski dio molekula; (b) supstituent na aziridinskom dušiku uvijek je u *trans*-, a nikad u *cis*-položaju u odnosu na cikloheptanski ili dioksepanski prsten; (c) sulfonilna skupina sulfonilaziridina **6** i **8**–**10** zauzima samo jednu od dvije moguće konformacije u odnosu na aziridinski prsten, s torzijskim kutevima C1–S–N–C7 od ≅ 80° (odgovarajući kut O1–S–N–LP ≅ 180°, LP = slobodan elektronski par), nazvanu po nama BC*-konformacija; (d) orijentacija karbonilne skupine u **11** i metilenske skupine u **12** definirana je torzijskim kutevima C1–C0–N1–C7 od –78.3 (9)° odnosno od –93.9 (5)°; (e) dušikov atom u svim proučavanim *N*-sulfonil-, *N*-acil- i *N*-alkil-aziridinima je sp^3-hibridiziran za razliku od ostalih sulfonamida, gdje dominira sp^2-hibridizacija; (f) dušikov atom u alkilaziridinu **12** više je piramidalan nego u *N*-sulfonil- i *N*-acil-derivatima; i (g) prema torzijskim kutevima O5–N2–C4–C5 nitro-skupina je u svim proučavanim spojevima približno koplanarna s fenilnim prstenom.

Dobiveni podatci služit će za daljnja istraživanja steričkih i elektronskih svojstava studiranih spojeva, usmjerena dizajnu antihiperglikemički djelotvornijih analoga.