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Original Scientific Paper

Chemistry of 1,3-Dioxepins. X.[#] Regio and Stereocontrolled Syntheses of Antihyperglycemic *N*-Sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]-dioxepino[5,6-*b*]azirines *via* Isomeric *cis*- and *trans*-Sulfonamidodioxepanols[##,*]

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Regio- and stereocontrolled syntheses of 1-sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine **1**, the lead compound of a novel class of potent antihyperglycemics, *via* isomeric *cis*- and *trans*-sulfonamidodioxepanols **6** and **13** are described. The constitution and configuration of the key intermediates **6** and **13** were elucidated by independent syntheses and confirmed by the X-ray structure analysis.

INTRODUCTION

In the context of our research into hypoglycemics, we have synthesized 1-sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines, representatives of a novel class of fused dioxepins and a novel class of potent antihyperglycemics.[1–4] A synthetic strategy based on retrosynthetic analysis afforded this class of compounds, starting from the commercially available, *cis*-2-butene-1,4-diol (Scheme 1).

Unfortunately, the direct approach involving addition of sulfonylazides to dihydrodioxepins (path A) was unsuccessful.[2] Some aspects of path

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[#] Part IX, Ref. 1
[##] Part of projected PhD thesis of D. Filić.
[*] Dedicated to Professor Vladimir Prelog on the occasion of his 90th birthday.
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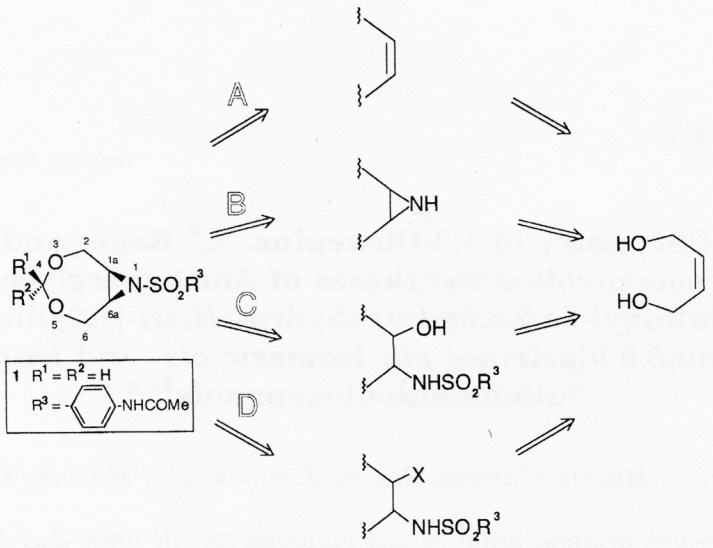
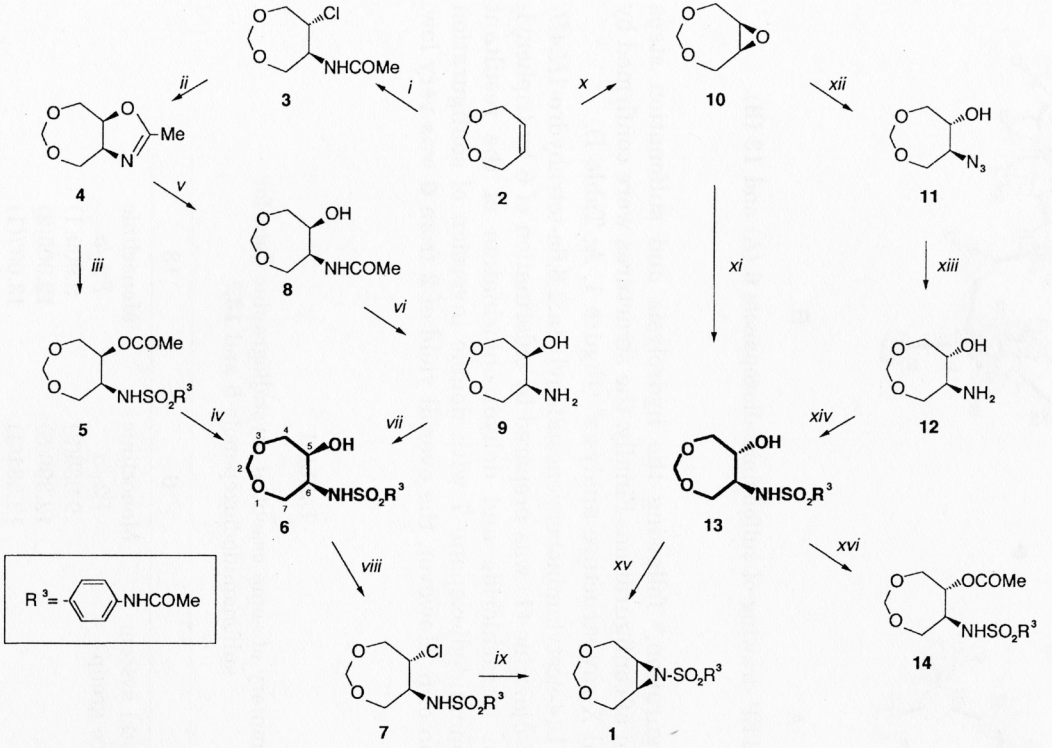


Scheme 1. Retrosynthetic strategy for antihyperglycemic sulfonyldioxepinoaziridines.

B have alreeady been published.[1,2] Now, we would like to report the results of the synthetic approach *via* path C *i.e. via* isomeric *cis*- and *trans*-sulfonamidodioxepanols detailed in the Scheme 2. This approach is exemplified by the synthesis of 1-(4-acetylaminobenzene)sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine **1**, a compound which has hitherto shown the best antihyperglycemic profile.[1]

RESULTS AND DISCUSSION

The isomeric, *cis*- and *trans*-sulfonamidodioxepanols **6** and **13** were both synthesized starting from 4,7-dihydro-1,3-dioxepin (**2**), easily prepared by the well-known Brannock and Lappin acetalization of *cis*-2-butene-1,4-diol.[5] The first two steps to **6**, *i.e.* the synthesis of *trans*-acetylaminochlorodioxepane **3**[6] and *cis*-tetrahydro-[1,3]dioxepino[5,6-*d*]oxazole **4**[7] have been published previously. Treatment of **4** with 4-acetylaminobenzenesulfonyl chloride followed by hydrolysis led to *cis*-5-acetoxy-6-(4-acetylaminobenzenesulfonamido)-1,3-dioxepane (**5**), characterized by a very strong ester carbonyl stretching band at 1730 cm^{-1} in the IR spectrum. Ammonolysis by ethanolic-ammonia afforded *cis*-sulfonamidodioxepanol **6**. Configurational assignments given in Scheme 2 followed from an independent unequivocal two step synthesis of **6**, starting from 6-acetylamino-1,3-dioxepan-5-ol (**8**), of the



Scheme 2. Preparation of sulfonyldioxepinoaziridine **1** *via cis-* and *trans*-sulfonamidodioxepanols **6** and **13**. *Reagents and conditions*: *i*, NO_2Cl/acetonitrile/H_2O/^-OH (Ref. 6); *ii*, KOH/EtOH, refl., 1 h (Ref. 7); *iii*, R^3SO_2Cl/pyridine/CH_2Cl_2, 0 °C, 5 h; *iv*, NH_3/H_2O/EtOH, r.t., 3 h; *v*, KOH/H_2O, refl., 1 h (Ref. 7); *vi*, KOH/H_2O, refl., 27 h; *vii*, R^3SO_2Cl/pyridine/CH_2Cl_2, 0 °C, 1 h; *viii*, TPP/CCl_4/acetonitrile, refl., 3 h; *ix*, NaOEt/EtOH, r.t., 30 min; *x*, *m*-CPBA/CH_2Cl_2, refl.,16 h; *xi*, $R^3SO_2NH_2$/pyridine, 150 °C, 15 min; *xii*, NaN_3/aq. acetone, refl., 6 h; *xiii*, H_2/5% Pd-C/MeOH, 2 bar, r.t., 1 h; *xiv*, R^3SO_2Cl/pyridine/CH_2Cl_2, 0 °C, 1 h; *xv*, TPP/DEAD/acetonitrile, 0 °C, 30 min, r.t., 45 min; *xvi*, Ac_2O/pyridine, r.t., 16 h (R^3 = 4-MeCONH-C_6H_4-).

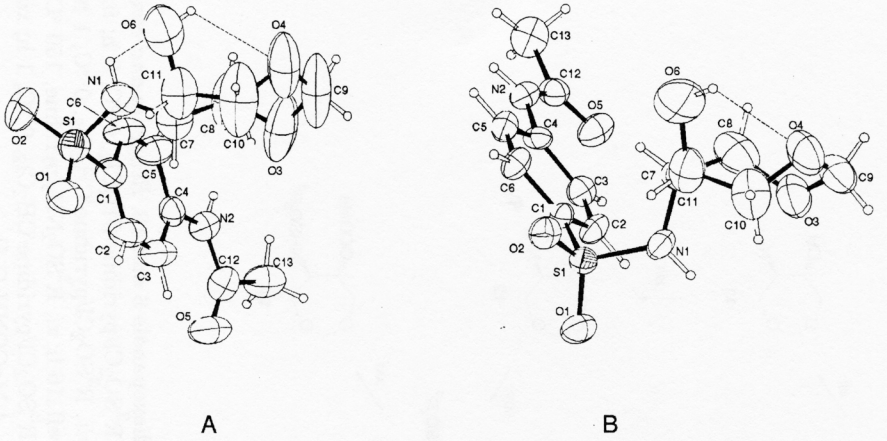


Figure 1. The ORTEP drawing of sulfonamidodioxepanols **6** (A) and **13** (B).

known *cis* configuration,[8] following the hydrolysis and sulfonation steps without inversion of configuration. Finally, the structures were confirmed by the single crystal X-ray structure analysis[9] (Figure 1, A; Table I).

The target 1-(4-acetylaminobenzenesulfonyl)-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**1**) was prepared by chlorination of **6** by triphenylphosphine/carbon tetrachloride and dehydrochlorination of the resultant *trans*-chlorosulfonamidodioxepane **7** with double inversion of configuration at the C5 position of **6**. However, the overall yield of **2** from **6** was very low.

TABLE I

Summary of some essential crystallographic data for sulfonamidodioxepanols **6** and **13**.[a]

	6	**13**
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/a$	$P2_1/a$
a/Å	9.938(3)	9.909(1)
b/Å	12.396(3)	12.005(2)
c/Å	13.531(4)	13.037(1)
β/°	110.28(2)	105.83(1)
V/Å^3	1563.6(8)	1492.0(3)

[a] X-ray diffractions were measured on a Phillips PW 1100 diffractometer with Mo-Kα radiation and graphite monochromator. For further details of the crystal structure determinations see Ref. 9.

Therefore, we turned our attention to the synthesis of *trans*-sulfonamidodioxepanol **13** and its conversion to the target sulfonyldioxepinoazirine **1**.

Treatment of epoxide **10**, prepared by modification of the known procedure,[10] with 4-acetylaminobenzenesulfonamide led directly, with epoxide ring-opening, to *trans*-sulfonamidodioxepanol **13** (47.5 %). An identical sample of **13** was also obtained by a parallel three-step synthesis. The process included the reaction of epoxide **10** with sodium azide, hydrogenation of the *trans*-azido alcohol **11** formed, and finally regio controlled sulfonation of the thus obtained *trans*-aminodioxepanol **12**[11] to **13**. Because of very small differences between both the ^{1}H- and the ^{13}C-NMR spectral data for **6** and **13**, the *trans* configuration of **13** was additionally deduced by its conversion to *trans*-5-acetoxy-6-(4-acetylaminobenzenesulfonamido)-1,3-dioxepane (**14**), which significantly differed from the corresponding *cis* isomer **5** by physical and spectral data, respectively.[12] Finally, after several attempts, the *trans* configuration of **13** was confirmed by a single crystal X-ray diffraction study (Figure 1, B; Table I).[9]

Mitsunobu[13] dehydration of **13** by diethylazodicarboxylate (DEAD) and triphenylphosphine (TPP) led to the target sulfonyldioxepinoaziridine **1** in 90.7% yield.

The overall yield *via* three steps **2** → **10** → **13** → **1** of 35.5% shows the *trans*-sulfonamidodioxepanol approach to be shorter and more efficient, *i.e.*, this should be route of choice for the synthesis of sulfonyldioxepinoazirine **1**, as well as other compounds in this series. Otherwise, the synthesis of *trans*-chlorosulfonamidodioxepane **7** and its conversion to **1** opened a new approach to sulfonyldioxepinoaziridine hypoglycemics, *i.e. via* path D outlined in Scheme 1.

In addition, the synthesized sulfonamidodioxepanols **6** and **13** were tested for hypoglycemic activity on the models of alloxan and streptozotocin induced diabetes in mice.[14] The compounds displayed strong hypoglycemic activity in comparison to the known hypoglycemic agent metformin and similar activity to that of sulfonyldioxepinoaziridine **1**. Therefore, sulfonamidodioxepanols **6** and **13** are not only intermediates in the syntheses of sulfonyldioxepinoaziridine **1**, but they may represent a new class of potent hypoglycemic agents, the significance of which is still under investigation.

EXPERIMENTAL

Melting points were determined using a Fischer-Johns apparatus, and were uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. ^{1}H- (300 MHz) and ^{13}C- (75 MHz) NMR spectra were recorded on a Varian XL-GEM 300 spectrometer, with TMS as internal standard; the values of chemical shifts (δ) were given in ppm and coupling constants (J) in Hz; DMSO-d_6 was used as solvent, unless otherwise stated. TLC was performed using Merck Kieselgel 60 F_{254} silica plates and components were visualized using UV light, iodine vapour or ninhydrin. Compounds were purified by column chromatography using

Merck Kieselgel 60 (0.063–0.200 mm, 70–230 mesh), and were homogeneous by TLC. Solvents and reagents were *p.a.* grade and were obtained from commercial sources and were used without further purification. *trans*-Acetylaminochlorodioxepane **3**,[6] tetrahydrodioxepino[5,6-*d*]oxazole **4**[7] and acetylaminodioxepanol **8**[7] were prepared previously. Chemical yields were not optimized.

cis-*5-Acetoxy-6-(4-acetylaminobenzenesulfonamido)-1,3-dioxepane* (***5***)

A mixture of dioxepinooxazoline **4**[7] (1.00 g, 0.0064 mol), 4-acetylaminobenzenesulfonyl chloride (1.49 g, 0.0064 mol) and pyridine (1.03 mL, 0.00128 mol) in 15 mL of dry methylene chloride was stirred at 0 °C for 5 hours. An additional amount of methylene chloride (50 mL) was added to the reaction mixture. The resulting solution was washed with water (2 × 10 mL), dried (Na_2SO_4) and concentrated. The oily residue was purified by column chromatography using an ethyl acetate/methanol (9.8 : 0.2, v/v) mixture as eluent, furnishing after concentration of selected fractions in vacuo the crude **5** (0.82 g, 34.6 %), m.p. 178–180 °C. After recrystallization from ethyl acetate/methanol (6 : 1, v/v), the sample displayed m.p. 182–184 °C. IR(KBr) ν_{max}/cm^{-1}: 3350, 3220, 2980, 2940, 2900, 1730, 1695, 1590, 1535, 1450, 1400, 1370, 1340, 1320, 1260, 1160, 950 and 730; ^{1}H-NMR (DMSO-d_6) δ: 10.22 (s, 1H, NHCO), 7.75 (s, 4H, H-arom.), 7.72 (s, 1H, $NHSO_2$), 4.69 (s, 1H, H-C5), 4.65 (s, 2H, H-C2). 3.79–3.43 (m, 5H, H-C4, 6 and 7), 2.10 (s, 3H, $NHCOCH_3$), 1.97 (s, 3H, $OCOCH_3$); ^{13}C-NMR δ: 169.43 (s, NHCO), 168.80 (s, OCO), 142.69 (s), 135.21 (s), 127.31 (d) and 118.60 (d) (C-arom.), 93.55 (t, C2), 71.71 (d, C5), 65.19 (t, C4), 64.22 (t, C7), 54.41 (d, C6), 23.96 (q, $NHCOCH_3$), 20.67 (q, $OCOCH_3$).

Anal. Calcd. for $C_{15}H_{20}N_2O_7S$ (M_r = 372.40): C 48.38, H 5.41, N 7.52%; found C 48.25, H 5.57, N 7.46%.

cis-*6-Amino-1,3-dioxepan-5-ol* (***9***)

A mixture of *cis*-6-acetylamino-1,3-dioxepan-5-ol (**8**)[7,8] (7.43 g, 0.0424 mol) and potassium hydroxide (5.93 g, 0.106 mol) was refluxed in 115 mL of demineralized water for 27 hours. After evaporation of water at reduced pressure the oily residue was partitioned between chloroform and water. The chloroform layer was washed with water, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography using methylene chloride/methanol/25% ammonia (8 : 2 : 0.2, v/v) as eluent. which yielded TLC homogeneous *cis*-6-amino-1,3-dioxepan-5-ol (**9**) as a viscous oil (5.12 g, 90.7%). A sample for analysis was obtained by repeated column chromatography as a viscous pale yellow oil. IR(film) ν_{max}/cm^{-1}: 3360, 2930, 2880, 1585, 1460, 1450, 1330, 1270, 1240, 1125, 1050, 995, 930, 880, 785 and 715; ^{1}H-NMR (DMSO-d_6) δ: 4.66 (s, 2H, H-C2), 3.65–3.50 (m, 5H, H-C4,5,7), 2.96 (br., 3H, OH and NH_2), 2.84–2.81 (m, 1H, H-C6); ^{13}C-NMR δ: 93.97 (t, C2), 71.04 (d, C5), 67.02 (t, C4), 66.94 (t, C7), 54.09 (d, C6).

Anal. Calcd. for $C_5H_{11}NO_3$ (M_r = 133.15): C 45.10, H 8.33, N 10.52%; found C 45.27, H 8.03, N 10.82%.

cis-*6-(4-Acetylaminobenzenesulfonamido)-1,3-dioxepan-5-ol* (***6***)

Procedure 1: Hydrolysis of ***5***

A mixture of acetoxy derivative **5** (0.16 g, 0.00043 mol), 3.0 mL of aqueous ammonia (25%, w/w) and 6 mL of absolute ethanol was stirred at room temperature

for 3 hours and concentrated in vacuo. The residue (0.16 g) was crystallized from ethyl acetate to give *cis*-sulfonamidodioxepanol **6** (0.10 g, 70.5%), m.p. 157–160 °C. After recrystallization from ethyl acetate, the sample displayed m.p. 158–160 °C. IR (KBr) ν_{max}/cm^{-1}: 3400, 3200, 2960, 2900, 1700, 1600, 1520, 1450, 1400, 1320, 1260, 1150, 1080, 1050, 920, 900, 830 and 725; ^{1}H-NMR (DMSO-d_6) δ: 10.30 (s, 1H, NHCO), 7.77 and 7.75 (dd, 4H, J = 9.0, H-arom.), 7.31 (d, 1H, J = 6.3, $NHSO_2$), 4.62 and 4.59 (ABq, 2H, J = 4.9, H-C2), 4.93 (d, 1H, J = 5.4, OH) 3.64–3.53 (m, 4H, H-C4, 7), 3.27–3.23 (m, 2H, H-C5,6), 2.09 (s, 3H, $COCH_3$). ^{13}C-NMR δ: 169.05 (s, CO), 142.75 (s), 135.21 (s), 127.71 (d), 118.58 (d) (C-arom.), 93.74 (t, C2), 69.20 (d, C5), 67.69 (t, C4), 64.69 (t, C7), 57.02 (d, C6), 24.19 (q, $COCH_3$).

Anal. Calcd. for $C_{13}H_{18}N_2O_6S$ (M_r = 330.36): C 47.26, H 5.49, N 8.48%; found C 47.39, H 5.71, N 8.25%.

Procedure 2: From Aminodioxepanol ***9***

A mixture of *cis*-6-amino-1,3-dioxepan-5-ol (**9**) (0.33 g, 0.0025 mol), 4-acetylaminobenzenesulfonyl chloride (0.64 g, 0.0027 mol) and pyridine (0.40 mL, 0.005 mol) in 10 mL of dry methylene chloride was stirred at 0 °C for 1 hour. After acidification to pH = 5.5 by acetic acid, the reaction mixture was concentrated in vacuo. The concentrate was extracted with absolute ethanol, the solvent evaporated under reduced pressure and the residue was purified by column chromatography using a methylene chloride/methanol (8 : 2, v/v) mixture as eluent. After concentration of selected fractions TLC-homogeneous *cis*-6-(4-acetylaminobenzenesulfonamido)-1,3-dioxepan-5-ol (**6**) (0,45 g, 55.0%), m.p. 156–159 °C was obtained. After recrystallization from ethyl acetate/methanol (4 : 1, v/v), the sample displayed m.p. 159–161 °C. Its IR spectrum was identical to the spectrum of an autenthic sample from procedure 1 (see above).

trans-*6-(4-Acetylaminobenzenesulfonamido)-5-chloro-1,3-dioxepane (**7**)*

A mixture of *cis*-6-(4-acetylaminobenzenesulfonamido)-1,3-dioxepan-5-ol (**6**) (0.16 g, 0.00048 mol), carbon tetrachloride (0.2 mL, 0.002 mol), and triphenylphosphine (0.26 g, 0.001 mol) was stirred in 2.5 mL of dry acetonitrile at room temperature for 20 minutes, additionally refluxed for 3 hours, and concentrated under reduced pressure. The oily residue (0.51 g) was purified by column chromatography using methylene chloride/methanol (9 : 1, v/v) as eluent, which yielded crude chloro derivative **7** (0.13 g, 77.0 %), m.p. 190–200 °C. After recrystallization from ethyl acetate, the sample showed m.p. 198–200 °C. IR(KBr) ν_{max}/cm^{-1}: 3360, 3200, 2900, 2880, 1675, 1595, 1530, 1450, 1400, 1330, 1315, 1260, 1210, 1155, 1120, 1095, 1065, 1025, 950, 905, 840, 780, 725, 635 and 620; ^{1}H-NMR (DMSO-d_6) δ: 10.35 (s, 1H, NHCO), 7.77 (s, 4H, H-arom.), 8.09 (d, 1H, J = 7.9, $NHSO_2$), 4.64 (s, 2H, H-C2), 3.97–3.37 (m, 4H, H-C4,7), 3.81 (br, 1H, H-C5), 3.37 (br, 1H, H-C6), 2.09 (s, 3H, $COCH_3$); ^{13}C-NMR δ: 169.44 (s, CO), 143.22 (s), 135.06 (s), 128.03 (d), 118.82 (d) (C-arom.), 93.50 (t, C2), 66.14 (t, C4), 65.13 (t, C7), 60.99 (d, C5), 59.42 (d, C6), 24.25 (q, $COCH_3$).

Anal. Calcd. for $C_{13}H_{17}ClN_2O_5S$ (M_r = 348.81): C 44.76, H 4.91, N 8.03%; found C 44.95, H 5.19, N 8.27%.

*5,6-Epoxy-1,3-dioxepane (**10**)*

A solution of 4,7-dihydro-1,3-dioxepin (**2**) (10.00 g, 0.10 mol) in 100 mL of dried methylene chloride was added over a 20 min period to a solution of *m*-chloroperbenzoic acid (33.33 g of 55% pure, 0.106 mol) (Fluka, Art. No. 25800) in 150 mL of dried

methylene chloride. The mixture was allowed to reflux for 16 hours, and after addition of a further 50 mL of methylene chloride, it was cooled to 0 °C to precipitate the *m*-chlorobenzoic acid formed. The solid was filtered off, the methylene chloride solution was washed with saturated sodium bicarbonate solution until all traces of acid were removed, and dried over sodium sulfate. Removal of solvent under reduced pressure (30–35 kPa) left 9.57 g (82.4%) of crude **10**, m.p. 53–55 °C. After recrystallization from diethyl ether, the sample showed m.p. 55–56 °C (lit.[10]: Y = 45%, m.p. 57–58 °C/petroleum ether). IR(KBr) ν_{max}/cm^{-1}: 2965, 2920, 2880, 2810, 2740, 1485, 1455, 1390, 1195, 1110, 990, 925, 870, 675 and 660; ^{1}H-NMR ($CDCl_3$) δ: 4.88 and 4.45 (ABq, 2H, J = 6.3, H-C2), 4.24 and 4.03 (dd, 4H, J = 13.9, H-C4,7), 3.23 (s, 2H, H-C5,6); ^{13}C-NMR δ: 97.00 (t, C2), 66.06 (t, C4,7), 56.29 (d, C5,6).

trans-*6-Azido-1,3-dioxepan-5-ol (**11**)*

A mixture of epoxydioxepane **10** (5.00 g, 0.043 mol) and sodium azide (9.74 g, 0.15 mol) in 130 mL of aqueous acetone (1:1, v/v) was refluxed for 6 hours. The mixture was cooled to room temperature, extracted with chloroform, and the organic solution was washed with water, dried over Na_2SO_4. Removal of solvent in vacuo furnished the oily residue (8.74 g) which, after purification by column chromatography using ethyl acetate petroleum ether (6 : 4, v/v) as eluent, yielded compound **11** (6.19 g, 90.3%) as a pale yellow oil. A sample for analysis was obtained by repeated column chromatography. IR(film) ν_{max}/cm^{-1}: 3700–3100, 2940, 2900, 2800, 2110, 1670, 1465, 1290, 1250, 1140, 1065, 1005, 960, 920 and 850; ^{1}H-NMR (DMSO-d_6) δ: 4.66 and 4.64 (ABq, 2H, J = 4.7, H-C2), 3.83–3.44 (m, 6H, H-C4,5,6 and 7), 5.47 (d, 1H, J = 4.8, OH); ^{13}C-NMR δ: 94.34 (t, C2), 72.94 (d, C5), 67.90 (t, C4), 65.85 (d, C6), 64.64 (t, C7).

Anal. Calcd. for $C_5H_9N_3O_3$ (M_r = 159.15): C 37.74, H 5.70, N 26.40%; found C 38.02, H 6.00, N 26.69%.

trans-*6-Amino-1,3-dioxepan-5-ol (**12**)*

trans-6-Azido-1,3-dioxepan-5-ol (**11**) (0.46 g, 0.00289 mol) was hydrogenated in 30 mL of methanol in the presence of 5% palladium on charcoal catalyst (0.046 g) (Aldrich, Art. No. 20.568–0) at room temperature and hydrogen pressure of 2 bar for 1 hour. The catalyst was separated by filtration and, after evaporation of solvent at reduced pressure, the crude oily product (0.4 g) was purified by column chromatography using methylene chloride/methanol/25% ammonia (8 : 2 : 0.2, v/v) as eluent. Evaporation of the solvents yielded the TLC homogeneous *trans*-6-amino-1,3-dioxepan-5-ol (**12**) (0.36 g, 93.5%) as a viscous pale yellow oil. A sample for analysis was obtained by repeated column chromatography. IR(film) ν_{max}/cm^{-1}: 3700–3000, 2880, 1600, 1460, 1370, 1290, 1240, 1130,1030, 935, 860 and 760; ^{1}H-NMR (DMSO-d_6) δ: 4.63 and 4.61 (ABq, 2H, J = 4.7, H-C2), 3.69–3.31 (m, 4H, H-C4,7), 3,25–3.17 (m, 1H, H-5), 3.00 (br., 3H, OH and NH_2), 2.62–2.55 (m, 1H, H-C6); ^{13}C-NMR δ: 93.73 (t, C2), 74.72 (d, C5), 67.70 (t, C4), 66.87 (t, C7), 57.05 (d, C6).

Anal. Calcd. for $C_5H_{11}NO_3$ (M_r = 133.15): C 45.10, H 8.33, N 10.52%; found C 45.39, H 8.04, N 10.78%.

trans-*6-(4-Acetylaminobenzenesulfonamido)-1,3-dioxepan-5-ol* (***13***)

Procedure 1: From Epoxydioxepane ***10***

A mixture of epoxydioxepane **10** (0.50g, 0.0043 mol), pyridine (0.20 mL, 0.0025 mol) and 4-acetylaminobenzenesulfonamide[15] (0.92 g, 0.0043 mol) was heated in a sealed tube at 150 °C for 15 minutes. After cooling to room temperature, the mixture was purified by column chromatography using ethyl acetate/methanol (9.5 : 0.5, v/v) as eluent. Unreacted starting 4-acetylaminobenzenesulfonamide (0.21 g, m.p. 212–215 °C; lit.[15] m.p. 218 °C) was obtained from the first fractions. *trans*-6-(4-Acetylaminobenzenesulfonamido)-1,3-dioxepan-5-ol (**13**) (0.52 g, 47.5%, m.p. 206–209 °C), was the second. After recrystallization from ethyl acetate/methanol (6 : 1, v/v), the sample showed m.p. 209–211 °C. IR(KBr) ν_{max}/cm^{-1}: 3510, 3300, 3270, 3110, 2950, 2870, 1665, 1590, 1530, 1400, 1320, 1260, 1150, 1080, 1060, 920, 850 and 710; ^{1}H- NMR (DMSO-d_6) δ: 10.31 (s, 1H, NHCO), 7.77 and 7.75 (dd, 4H, J = 9.0, H-arom.), 7.63 (s, 1H, $NHSO_2$), 4.91 (d, 1H, J = 5.7, OH), 4.59 (s, 2H, H-C2), 3.71–3.60 (m, 2H, H-C4), 3.50–3.44 (m, 1H, H-C5), 3.34–3.28 (m, 2H, H-C7), 3.05 (br, 1H, H-C6), 2.09 (s, 3H, $COCH_3$); ^{13}C-NMR δ: 169.11 (s, NHCO), 142.73 (s), 135.53 (s), 127.75 (d), and 118.57 (d) (H-arom.), 93.39 (t, C2), 71.38 (d, C5), 66.94 (t, C4), 64.48 (t, C7), 58.71 (d, C6), 24.26 (q, $COCH_3$).

Anal. Calcd. for $C_{13}H_{18}N_2O_6S$ (M_r = 330.36): C 47.26, H 5.49, N 8.48%; found C 47.31, H 5.75, N 8.76%.

Procedure 2: From Aminodioxepanol ***12***

A mixture of *trans*-6-amino-1,3-dioxepan-5-ol (**12**) (0.33 g, 0.0025 mol), 4-acetylaminobenzenesulfonyl chloride (0.64 g, 0.0027 mol) and pyridine (0.4 mL, 0.005 mol) was stirred in 10 mL of dry methylene chloride at 0 °C for 1 hour. After acidification to pH = 5.5 by acetic acid, the reaction mixture was concentrated in vacuo. The concentrate was extracted with absolute ethanol, the solvent evaporated under reduced pressure and the residue was purified by column chromatography using methylene chloride/methanol (10 : 1, v/v) as eluent. After concentration of selected fractions, the TLC homogeneous *trans*-6-(4-acetylaminobenzenesulfonamido)-1,3-dioxepan-5-ol (**13**) (0.26 g, 31.8%), m.p. 206–208 °C was obtained. After recrystallization from ethyl acetate/methanol (9.5 : 0.5, v/v), the sample displayed m.p. 210–211 °C. Its IR spectrum was identical to the spectrum of an autenthic sample from procedure 1 (see above).

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

Procedure 1: From Chlorosulfonamidodioxepane ***7***

A mixture of chlorosulfonamidodioxepane **7** (0.12 g, 0.000344 mol), and sodium ethoxide (0.06 g, 0.00088 mol) was stirred in 5 mL of abs. ethanol at room temperature for 30 minutes. The pH of reaction mixture was adjusted to 6.5 by addition of dilute hydrogen chloride/ethanol solution, the precipitated sodium chloride was removed by suction and the mother liquid was concentrated under vacuo to dryness giving the crude, TLC pure, sulfonyldioxepinoaziridine **1** (0.08 g, 74.5%), m.p. 206–208 °C. After recrystallization from ethyl acetate/methanol (1 : 1, v/v), the sample displayed m.p. 210–212 °C (lit.[3]: m.p. 210–212 °C).

Procedure 2: From Sulfonamidodioxepanol ***13***

To a solution of *trans*-6-(4-acetylaminobenzenesulfonamido)-1,3-dioxepan-5-ol (**13**) (0.07g, 0.00021 mol) and triphenylphosphine (0.16 g, 0.00061 mol) in 4.5 mL of dry acetonitrile a solution of diethylazodicarboxylate (38% in toluene, 0.30 mL, 0.00062 mol) in 0.5 mL of dry acetonitrile was added dropwise at 0 °C during 30 minutes. The mixture was warmed up to room temperature, stirred for a further 45 minutes at the same temperature and concentrated under reduced pressure. The oily residue (0.45 g) was purified by column chromatography using methylene chloride/methanol (9 : 1, v/v) as eluent, which yielded compound **1** (0.06 g, 90.7%) as a solid, m.p. 205–209 °C. After recrystallization from ethyl acetate/methanol (1 : 1, v/v), the sample displayed m.p. 210–212 °C (lit.[3]: m.p. 210–212 °C). Its IR spectrum was identical to the spectrum of an autenthic sample from procedure 1 (see above).

trans-*5-Acetoxy-6-(4-acetylaminobenzenesulfonamido)-1,3-dioxepane (****14****)*

A mixture of *trans*-sulfonamidodioxepanol **13** (0.20 g, 0.0006 mol), acetic anhydride (0.40 g, 0.0039 mol) and pyridine (2.0 mL, 0.0248 mol) was stirred at room temperature for 16 hours. Methanol (6.0 mL) was added, and the mixture was concentrated under reduced pressure. The obtained oily residue was purified by column chromatography using a methylene chloride/methanol (9 : 1, v/v) mixture as eluent, furnishing after concentration of selected fractions in vacuo the crude **14** (0.21 g, 93.2%), m.p. 140–145 °C. After recrystallization from ethyl acetate, the sample showed m.p. 149–151 °C. IR(KBr) ν_{max}/cm^{-1}: 3305, 3180, 2890, 1720, 1680, 1590, 1535, 1330, 1315, 1260, 1240, 1160, 1075, 875, 835, 750 and 720; ^{1}H-NMR (DMSO-d_6) δ: 10.34 (s, 1H, NHCO), 7.95 (d, 1H, J = 7.2, $NHSO_2$), 7.77 (s, 4H, H-arom.), 4.68 and 4.61 (ABq, 2H, J = 4.5, H-C2), 4.58–4.53 (m, 1H, H-C5), 3.80–3.46 (m, 4H, H-C4,7), 3.31–3.28 (m, 1H, H-C6), 2.10 (s, 3H, $NHCOCH_3$), 1.80 (s, 3H, $OCOCH_3$); ^{13}C-NMR δ: 169.47 (s, NHCO), 168.08 (s, OCO), 142.88 (s), 135.04 (s), 127.74 (d) and 118.68 (d) (C-arom.), 94.24 (t, C2), 73.65 (d, C5), 66.01 (t, C4), 64.81 (t, C7), 56.11 (d, C6), 24.22 (q, $NHCOCH_3$), 20.72 (q, $OCOCH_3$).

Anal. Calcd. for $C_{15}H_{20}N_2O_7S$ (M_r = 372.40): C 48.38, H 5.41, N 7.52%; found C 48.21, H 5.70, N 7.82%.

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REFERENCES

1. M. Dumić, M. Vinković, D. Filić, B. Jamnicky, M. Eškinja, and B. Kamenar, *J. Med. Chem.* **38** (1995) 3034.
2. M. Dumić, D. Filić, M. Vinković, B. Jamnicky, and B. Kamenar, *Tetrahedron Lett.* **34** (1993) 3639.
3. M. Dumić, D. Filić, M. Vinković, and B. Jamnicky, USP 5 286 744/1994.
4. M. Vinković, M. Dumić, and B. Kamenar, *Acta Crystallogr., Sect. C.* **49** (1993) 1661.
5. K. C. Brannock and G. R. Lappin, *J. Org. Chem.* **21** (1956) 1366.

6. M. Dumić, M. V. Proštenik, and I. Butula, *Croat. Chem. Acta* **51** (1978) 259.
7. M. Dumić, I. Butula, M. Vinković, and B. Kamenar, *Org. Prep. Proced. Int.* **24** (1992) 545 and Erratum *Org. Prep. Proced. Int.* **25** (1993) 373.
8. M. Vinković, M. Dumić, and B. Kamenar, *Acta Crystallogr., Sect. C.* **48** (1992) 1352.
9. M. Vinković and M. Dumić, to be published.
10. M. H. Gianni, R. Cody, M. R. Asthana, K. Wursthorn, P. Patanode, and H. G. Kuivila, *J. Org. Chem.* **42** (1977) 365.
11. *trans*-Aminodioxepanol **12** was previously prepared by ammonolysis of **10** (sat. NH_3 in MeOH, 120 °C, 6 h, steel bomb) and without further purification was used in a biotin synthesis; see: A. V. Rama Rao, T. Ravindranathan, S. V. Hiremath, and D. Rajagopala Reddy, *Indian J. Chem., Sect. B.* **22** (1983) 419.
12. The signals of C5 and C6 atoms in ^{13}C-NMR spectra of *trans* derivatives **12**, **13** and **14** are centered in a significantly lower field (1.7–3.7 ppm), than the corresponding *cis* isomers **9**, **6** and **5**, respectively.
13. O. Mitsunobu, *Synthesis* (1981) 1.
14. M. Dumić, D. Filić, M. Vinković, and B. Jamnicky, EP Appl. 0 668 274 A1/1995.
15. Prepared by ammonolysis of 4-acetylaminobenzenesulfonyl chloride according to A. I. Vogel, *Elementary Practical Organic Chemistry, Part 1: Small Scale Preparations*, Second Ed., Longman, London, 1970, p. 367.

SAŽETAK

Kemija 1,3-dioksepina. X. Regio- i stereokontrolirane sinteze antihiperglikemičkih *N*-sulfonil-1a,2,6,6a-tetrahidro-1*H*,4*H*-[1,3]dioksepino[5,6-*b*]azirina preko izomernih *cis*- i *trans*-sulfonamidodioksepanola

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Opisane su regio- i stereoselektivne sinteze 1-sulfonil-1a,2,6,6a-tetrahidro-1*H*,4*H*-[1,3]dioksepino[5,6-*b*]azirina **1**, vodećeg spoja nove klase jakih antihiperglikemika, preko izomernih *cis*- i *trans*-sulfonamidodioksepanola **6** i **13**. Konstitucija i konfiguracija ključnih međuprodukata **6** i **13** utvrđene su neovisnim sintezama i potvrđene rentgenskom strukturnom analizom.