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1-Sulfonyl-1a,2,6,6a-tetrahydro-1H,4H-[1,3]-dioxepino[5,6-b]azirines: A Novel Class of Fused Dioxepins, Potent Hypoglycemic Agents[1,§]

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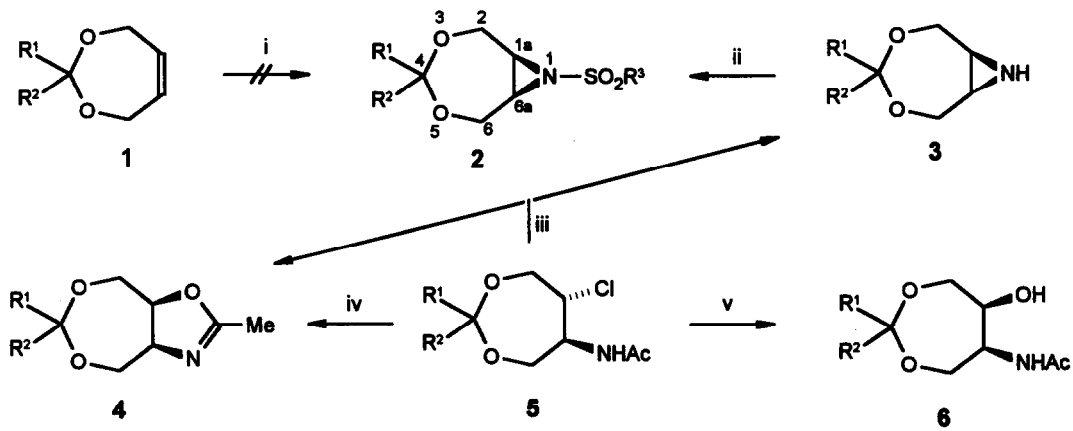
Key words: [1,3]-dioxepino[5,6-b]azirine; N-sulfonyl-dioxepinoazirine; hypoglycemic activity; X-ray diffraction.

Abstract: *The new hypoglycemics, 1-sulfonyl-dioxepinoazirines 2, derived from a novel heterocyclic system, 1a,2,6,6a-tetrahydro-1H,4H-[1,3]-dioxepino[5,6-b]azirine, have been synthesized starting from trans-6--acetylamino-5-chloro-1,3-dioxepanes 7 via azirines 3. Their structure has been confirmed by the single crystal X-ray diffraction of 1-(4-acetylaminobenzenesulfonyl) derivative 2b.*

In the context of an investigation into hypoglycemics,[2] the N-sulfonyl derivatives **2**, of the previously unknown heterocycle **3** were required. Among numerous methods existing for the syntheses of azirines,[3] the single approach involving the addition of sulfonylazides to dihydrodioxepins **1** was unsuccessful.[4]



Scheme 1 *Reagents and conditions:* i, RSO_2N_3/CH_3CN, reflux, 30 hrs.; ii, RSO_2Cl/pyridine/CH_2Cl_2, r.t., 1 hr.; iii, 2.5 M KOH in H_2O, 25 °C to 90 °C, 15 min.; iv, 2.5 M KOH in EtOH, reflux, 1 hr. (ref. 7); v, Na_2CO_3/H_2O, reflux, 5 hrs. (ref. 6).

§ Dedicated to Professor Vladimir Prelog on the Occasion of his 87th Birthday.

It was well known that *vic*- acylaminohalogeno compounds serve as good intermediates in the syntheses of azirines.[3] Therefore, we directed our attention to the synthesis of **2** starting from acetylaminochlorodioxepanes **5**,[5] *via* azirines **3**. Unfortunately, treatment of **5** with boiling aqueous sodium carbonate solution afforded *cis*-acetylaminodioxepanols **6** in high yields[6], whereas our attempt of ring-closure dehydrohalogenation of **5** in refluxing ethanolic potassium hydroxide solution resulted in the convenient method for the preparation of *cis*-dioxepinooxazolines **4** in high to excellent (up to 95%) yields.[7,8]

In spite of that, we found that warming of **5** in aqueous potassium hydroxide solution up to 90 °C for a short time resulted in the formation of the novel 1a,2,6,6a-tetrahydro-1H,4H-[1,3]-dioxepino[5,6-b]azirines **3** in moderate yields as the mixture with oxazolines **4** (scheme 1).

Thus, *trans*-acetylaminochlorodioxepane **5a** (R^1=R^2=H) was warmed in 2.5 M aqueous potassium hydroxide solution from temperature up to 90 °C in 15 minutes to produce *cis*-dioxepinooxazoline **4a** (R^1=R^2=H, identical to the authentic sample[7]) and azirine **3a** (R^1=R^2=H, bp 90-95 °C/2.1 kPa) in 58.2 % and 30.4 % yields, respectively. In an analogous manner **3b** (R^1=H, R^2=*i*Pr) and **3c** (R^1=R^2=Me) were obtained (Table 1).

All the synthesized azirines **3** were isolated by column chromatography as viscous oils. Only the azirine **3b** was additionally purified by recrystallization.

The target compounds, 1-sulfonyl-dioxepinoazirines **2** were prepared by mixing crude azirines **3** with the corresponding sulfonyl chlorides in methylene chloride for one hour at the room temperature and in the presence of pyridine (Table 1).

Table 1 1a,2,6,6a-Tetrahydro-1H,4H-[1,3]-dioxepino[5,6-b]azirines **2** and **3**.

Compd.	R^1	R^2	R^3	Yield[a] (%)	mp (t/°C)	Cryst. Solvent[b]
2a	H	H	CH_3	46.3	98-100	EA/PE
2b	H	H	4-AcNH-C_6H_4-	83.3	210-212	EA/M
2c	H	*i*Pr	4-NO_2-C_6H_4-	90.4	143-145	EA/PE
2d	Me	Me	4-AcNH-C_6H_4-	80.5	214-216	EA/M
3a	H	H	-	30.4	oil	-
3b	H	*i*Pr	-	28.2	56-58	PE
3c	Me	Me	-	33.0	oil	-

a) Isolated yields; b) EA=ethyl acetate, PE=light petroleum, M=methanol;

The structures of the new azirines **3** were assigned from their spectral data,[9] and were additionally confirmed by the spectral data of their corresponding N-sulfonyl-derivatives **2a-d**,[10] and the single crystal X-ray diffraction of **2b**, the asymmetric unit of which contains two molecules, one of them having a dioxepane pattern of a twist boat and the other one of a chair conformation (Figure 1).[11] The position of O1 opposite to the lone pair at the azirine N1 atom and the inequality of the bond angels O1-S1-N1 >> O2-S1-N1 suggest an n-σ^* interaction of the lone electron pair with the S^{VI}[O,O',N,C] tetrahedral moiety.[12] The shape and conformation around the sulfonamide group in **2** is determined by this interaction.

Finally, the target sulfonylazirines **2** were tested for hypoglycemic activity on the model of alloxan--induced diabetes in mice and rats[13] in comparison with metformin. They displayed strong hypoglycemic activity irrespective of the route of application, *e.g.* intravenous, subcutaneous or by stomach tube. Thus, sulfonylazirine **2b** four hours after the subcutaneous administration at the dose of 20 mg/kg, decreased the blood glucose levels in alloxan-induced diabetic mice and rats to 53 % and 67% of the initial concentration, respectively.

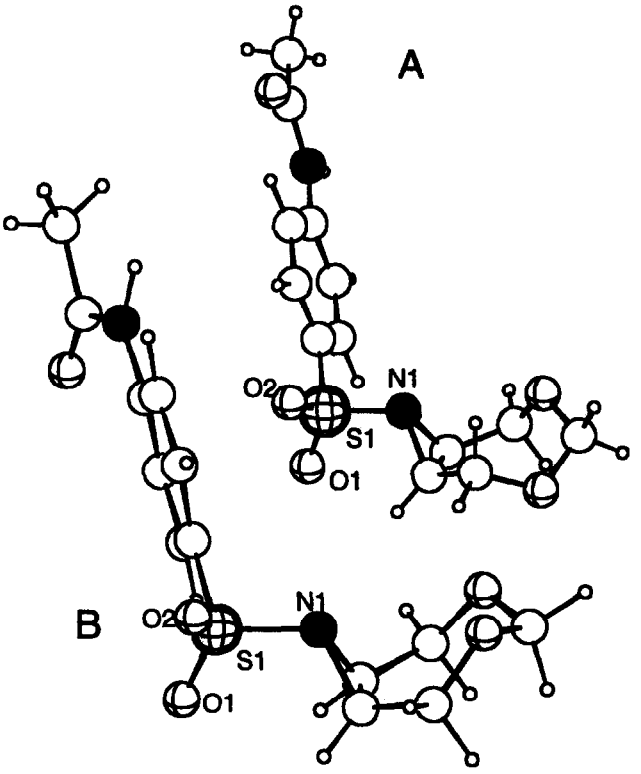


Fig. 1 PLUTON plot of the structure **2b** showing two conformations of the dioxepane pattern of molecules: A) twist-boat; B) chair.

On the other hand the new compounds **2** did not reduce the blood glucose concentration in healthy (nondiabetic, control) animals.

Therefore, 1-sulfonyl-1a,2,6,6a-tetrahydro-1H,4H-[1,3]-dioxepino[5,6-b]azirines **2** may represent a new class of potent hypoglycemic agents, the significance of which is still under investigation.

Acknowledgements: Financial support by the Ministry of Science, Technology and Informatics of the Republic of Croatia is gratefully acknowledged.

References and Notes:

1. Chemistry of 1,3-Dioxepins. Part 6. For Part 5 and Part 4 see refs. 8 and 7, respectively.
2. Mohrbacher, R. J.; Kiorpes, T. C.; Bowden, C. R. *Annu. Rep. Med. Chem.*, **1987**, 22, 213; Steiner, K. E.; Lien, E. L. *Prog. Med. Chem.*, **1987**, 24, 209; Larson, E. R.; Clark, D. A.; Stevenson, R. W. *Annu. Rep. Med. Chem.*, **1989**, 25, 205.
3. Dermer, O. C.; Ham, G. E. *Ethylenimine and Other Aziridines, Chemistry and Applications*, Academic Press, New York, London, 1969.
4. The addition of 4-acetylaminobenzenesulfonylazide to the dioxepine **1a** (R^1=R^2=H) was performed in refluxed acetonitrile producing **2b** only in traces.
5. Dumić, M.; Proštenik, M. V.; Butula, I. *Croat. Chem. Acta*, **1979**, 51, 259; *Chem. Abstr.*, **1979**, 90, 152144w.
6. Sovak, M.; Ranganathan, R. US 4.389.526 (Jun. 21, 1983); *Chem. Abstr.*, **1983**, 99, 88240f.
7. Dumić, M.; Butula, I.; Vinković, M.; Kamenar, B. *Org. Prep. Proced. Int.*, **1992**, 24, 536.
8. Vinković, M.; Dumić, M.; Kamenar, B. *Acta Crystallogr., Sect. C*, **1992**, 48, 1352.
9. The representative spectroscopic data for compound **3a**:
   ^{1}H-NMR, δ_H ($CDCl_3$, 300 MHz): 4.96 and 4.01 (ABq, 2H, J 7.2 Hz, O-CH_2-O); 4.23 and 4.02 (ABq, 4H, J 13.4 Hz, O-CH_2-C); 2.18 (s, 2H, CH-N) and 1.25 (br., 1H, NH); ^{13}C-NMR, δ_C ($CDCl_3$, 75 MHz): 99.30 (t, O-C-O); 68.49 (t, O-C-) and 35.31 (d, C-N).
10. The representative spectroscopic data for compound **2a**:
    IR ν_{max} (KBr): 1300 and 1150 (both SO_2-N) cm^{-1}; ^{1}H-NMR δ_H ($CDCl_3$, 300 MHz): 3.11 (s, 2H, -CH-N); 3.27 (s, 3H, CH_3); 4.10 and 4.25 (ABq, 4H, J 13.7, O-CH_2-C) and 4.46 and 4.93 (ABq, 2H, J 7.1, O-CH_2-O); ^{13}C-NMR δ_C ($CDCl_3$; 75 MHz): 39.05 (q, S-C); 43.34 (d, -C-N); 66.28 (t, O-C-) and 97.73 (t, O-C-O).
11. *Crystal data* for **2b**. *Mr*=312.34, monoclinic, I 2/a, *a*=24.898(7), *b*=8.349(7), *c*=29.252(7) Å, β=109.60(5)°, *V*=5728(6) Å^3, *Z*=16, *Dc*=1.45, *Do*=1.46 g cm^{-3} (floating method), μ(*Mo-K*α)=2.38 cm^{-1}, *T*=293 K, colourless crystal, 0.57*0.38*0.12 mm size, Mo-Kα radiation (λ=0.71069 Å), graphite monochromator, 7738 reflections measured on a Philips PW 1100 (ω scan technique), range 2<Θ<30° and -34≤*h*≤33, 0≤*k*≤11, -41≤*l*≤41; 4399 unique reflections (R_{int}=0.042) and 3870 observed [I > 3 σ(I)]. Absorption correction not applied. The structure was solved by direct methods (SIR 88) and anisotropically refined (SHELX 76) to final *R*=0.046 (436 parameters and unit weights). Maximum shift/error=0.088, maximum residual electron density 0.37 e Å^{-3}. Atomic co-ordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
12. Kálmán, A.; Czugler, M.; Argay, G. *Acta Crystallogr., Sect. B*, **1981**, 37, 868.
13. Mordes, J. P.; Rossini, A. A. Animal Models of Diabetes Mellitus. In *Joslin's Diabetes Mellitus*, 12th Ed., Lea & Febinger, Philadelphia, 1985, p. 110.

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