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Synthesis and Isomerization of Epoxides Derived from 7-Phenylsulfonyl- and 7-Methylsulfonyl-6-methylidenebicyclo[3.1.1]heptanes

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Abstract—Oxidation of *exo*-7-phenylsulfonyl- and *exo*-7-methylsulfonyl-6-methylidenebicyclo[3.1.1]heptanes with *m*-chloroperoxybenzoic acid gave the corresponding epoxy derivatives, *anti*-7-phenylsulfonyl- and *anti*-7-methylsulfonyl-*endo*-2'-oxaspiro[bicyclo[3.1.1]heptane-6,2'-cyclopropanes]. Treatment of the phenylsulfonyl-substituted epoxide with potassium *tert*-butoxide in THF led to the 1,3-cyclization product, 7-phenylsulfonyl-tricyclo[4.1.0.0^{2,7}]hept-1-ylmethanol. *anti*-7-Methylsulfonyl-*endo*-2'-oxaspiro[bicyclo[3.1.1]heptane-6,2'-cyclopropane] under analogous conditions underwent 1,6-cyclization, being converted into 6-hydroxy-3λ^6-thiatricyclo[4.4.0.0^{2,7}]decane 3,3-dioxide.

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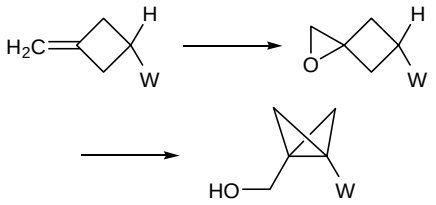
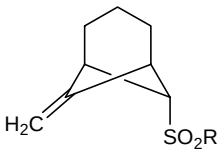
We previously showed [1] that methylidenecyclobutane containing an electron-acceptor group (W = CN, CO_2Me) in position *3* can be converted into the bicyclo[1.1.0]but-1-ylmethanol system via tandem epoxidation–isomerization process (Scheme 1).

Scheme 1.

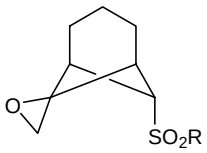


In the present work we made an attempt to effect an analogous transformation of 6-methylidenebicyclo-[3.1.1]heptane having an electron-acceptor substituent on C^7. The 3-substituted methylidenecyclobutane fragment in the initial molecule is fixed in a *butterfly* conformation. As starting compounds we used sulfones **I** and **II** which were prepared from 1-methyltricyclo-[4.1.0.0^{2,7}]heptane by successive sulfobromination and dehydrobromination according to [2, 3]. The R-sulfonyl group in molecules **I** and **II** plays the role of acceptor substituent. Insofar as its electronic effect is similar to that of cyano or alkoxycarbonyl group, the sulfonyl group could not hamper the above transformation.

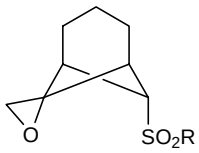
In agreement with the procedure for their preparation, the sulfo group in molecules **I** and **II** is oriented *exo*. This fact seemed to be especially favorable, for epoxidation of these compounds was expected to occur mainly from the *endo* side of the C=C bond due to steric shielding of the opposite side by the sulfonyl group. As a result, compounds **IIIa** and **IVa** rather than **IIIb** and **IVb** should be formed; intramolecular opening of the strained oxirane ring is possible only in the former.



I, **II**



IIIa, **IVa**



IIIb, **IVb**

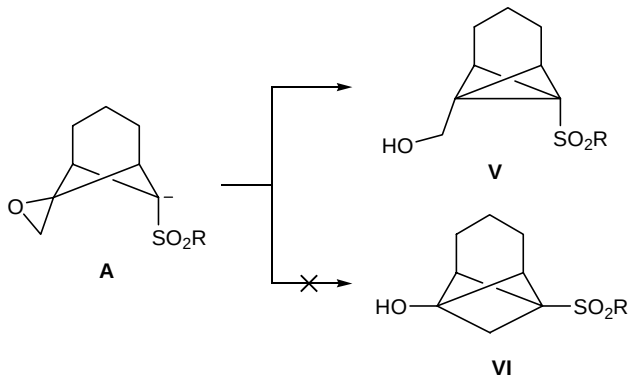
I, **III**, R = Ph; **II**, **IV**, R = Me.

In fact, by oxidation of sulfones **I** and **II** with *m*-chloroperoxybenzoic acid at 20°C we obtained spiro epoxy derivatives **IIIa** and **IVa**, respectively, as the major products, and they were readily purified from

epimeric epoxides **IIIb** and **IVb** by crystallization. The structure and configuration of compounds **IIIa** and **IVa** was reliably confirmed by the ^{1}H and ^{13}C NMR spectra. In particular, the *anti* orientation of the SO_2R group follows from the presence of a singlet signal from the 7-H proton, as in the spectra of initial compounds **I** and **II** [2, 3]. The configuration at the spiro-carbon atom in epimeric sulfones **IIIa** and **IIIb** was assigned on the basis of the difference in the chemical shifts of methylene protons in the oxirane ring: the CH_2 signal in the spectrum of isomer **IIIa** is located in a weaker field ($\Delta\delta$ = 0.35 ppm) due to deshielding by the sulfonyl group. Sulfone **IVa** was assumed to have the same configuration taking into account that the chemical shift of the OCH_2 protons in **IVa** was similar to that found for compound **IIIa**.

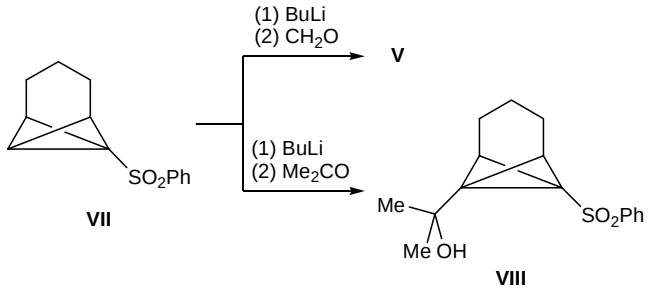
Treatment of phenylsulfonyl derivative **IIIa** with potassium *tert*-butoxide in THF induced its isomerization into tricycloheptylmethanol **V**, thus confirming the expected analogy in the behavior of epoxide **IIIa** and methylidenecyclobutane derivative [1]. Obviously, the reaction involves intermediate formation of carbanion **A**; intramolecular nucleophilic attack on the oxirane ring in intermediate **A** conforms to the stereoelectronic requirement according to which the trajectory of nucleophile approach is colinear to the C–O bond being broken [1, 4], i.e., 3-*exo* cyclization is favored (Scheme 2). Another possible direction of intramolecular nucleophilic attack on the oxirane ring would give rise to tertiary alcohol **VI** as a result of 4-*endo* cyclization; however, it does not fit the stereoelectronic requirement. In fact, no alcohol **VI** was detected in the reaction mixture.

Scheme 2.



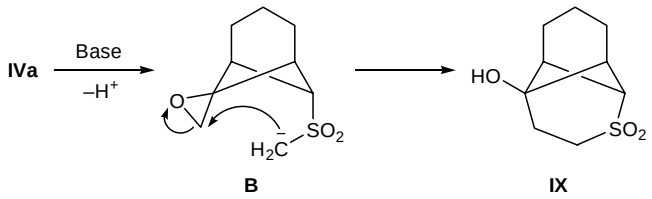
Compound **V** was also synthesized by independent method via metalation of known [5] sulfone **VII** with butyllithium, followed by reaction with formaldehyde. By analogous reaction using acetone instead of formaldehyde, we obtained tertiary alcohol **VIII** (Scheme 3). The structure of compounds **V** and **VIII** was proved by ^{1}H and ^{13}C NMR spectroscopy with account taken of the known data for structurally related substituted tricycloheptanes [2, 5–7].

Scheme 3.



A different transformation occurred under similar conditions with methylsulfonyl derivative **IVa**. Treatment of **IVa** with potassium *tert*-butoxide in THF resulted in the formation of tertiary alcohol **IX** as the only product. There are reasons to believe that in this case the key intermediate is carbanion **B** (Scheme 4). Intramolecular nucleophilic attack on the oxirane ring in anion **B** follows the 6-*endo*-cyclization pattern, i.e., in keeping with the stereoelectronic requirements [4]. This isomerization direction appears to be more favorable than 3-*exo*-cyclization which is also allowed from the viewpoint of stereoelectronic considerations. The 6-*endo* cyclization is facilitated by both kinetic (higher acidity of the CH_3SO_2 group compared to $CHSO_2$), and thermodynamic factors (formation of unstrained six-membered ring).

Scheme 4.



The ^{1}H and ^{13}C NMR spectra of compound **IX** reliably confirmed its structure. As might be expected, the spectral parameters of the norpinane skeleton in alcohol **IX** and epoxide **IVa** were similar.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker DPX-300 spectrometer at 300.130 and 75.468 MHz, respectively. Analytical

thin-layer chromatography was performed on Silufol UV-254 plates. The products were isolated and purified by column chromatography on silica gel L 40/100 μm.

exo-7-Phenylsulfonyl- and *exo*-7-methylsulfonyl-6-methylidenebicyclo[3.1.1]heptanes **I** (mp 83–84°C [2]) and **II** (mp 101–102°C [3]) and 1-phenylsulfonyltricyclo[4.1.0.$0^{2,7}$]heptane (**VII**) (mp 55–56°C [4]) were synthesized by known methods.

***anti*-7-Phenylsulfonyl-*endo*-2'-oxaspiro[bicyclo-[3.1.1]heptane-6,1'-cyclopropane] (IIIa).** A solution of 0.76 g (3.5 mmol) of 80% *m*-chloroperoxybenzoic acid in 10 ml of methylene chloride was added to a solution of 0.75 g (3 mmol) of compound **I** in 10 ml of methylene chloride, and the mixture was stirred for 3 h at 20°C, the progress of the reaction being monitored by TLC. An additional portion of *m*-chloroperoxybenzoic acid, ~0.15 g, was added to complete the oxidation. The precipitate of *m*-chlorobenzoic acid was filtered off, the filtrate was washed with an aqueous solution of K_2CO_3 and water and dried over $MgSO_4$, and the solvent was removed to obtain a crystalline product which, according to the ^{1}H NMR data, was compound **IIIa** containing ~10% of diastereoisomer **IIIb**. The latter showed the following signals in the ^{1}H NMR spectrum, δ, ppm: 2.69 s (2H, OCH_2), 2.81 br.s (2H, 1-H, 5-H), 3.32 s (1H, 7-H). Compound **IIIa** was purified by recrystallization. Yield 0.58 g (73%), mp 128–129°C (from hexane–methylene chloride. ^{1}H NMR spectrum, δ, ppm: 1.58–1.72 m (1H) and 1.80–1.95 m (1H) (3-H); 1.92–2.05 m (2H) and 2.15–2.32 m (2H) (2-H, 4-H); 2.92 br.s (2H, 1-H, 5-H); 3.04 s (2H, OCH_2); 3.25 s (1H, 7-H); 7.60 t (2H), 7.69 t (1H), and 7.94 d (2H) (C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 14.9 (C^3); 27.3 (C^2, C^4); 43.0 (C^1, C^5); 53.9 (OCH_2); 63.1 (C^7); 63.8 (C^6); 128.0 (2C); 129.2 (2C); 133.6, 138.7 (C_6H_5). Found, %: C 63.76; H 6.12. $C_{14}H_{16}O_3S$. Calculated, %: C 63.61; H 6.10.

***anti*-7-Methylsulfonyl-*endo*-2'-oxaspiro[bicyclo-[3.1.1]heptane-6,1'-cyclopropane] (IVa)** was synthesized in a similar way from compound **II**. The product was purified by recrystallization. Yield 52%, mp 102–103°C (from hexane–methylene chloride). ^{1}H NMR spectrum, δ, ppm: 1.65–1.80 m (1H) and 1.84–2.0 m (1H) (3-H); 2.0–2.13 m (2H) and 2.21–2.35 m (2H) (2-H, 4-H); 2.90 br.s (2H, 1-H, 5-H); 2.92 s (3H, SO_2Me); 3.04 s (2H, OCH_2); 3.19 s (1H, 7-H). ^{13}C NMR spectrum, δ_C, ppm: 14.9 (C^3), 27.1 (C^2, C^4), 39.6 (SO_2Me), 42.7 (C^1, C^5), 53.9 (OCH_2), 61.2 (C^7), 63.8 (C^6). Found, %: C 53.50; H 6.91. $C_9H_{14}O_3S$. Calculated, %: C 53.44; H 6.97.

(7-Phenylsulfonyltricyclo[4.1.0.$0^{2,7}$]hept-1-yl)-methanol (V). *a*. Compound **IIIa**, 265 mg (1 mmol), was added to a solution of 170 mg (1.5 mmol) of potassium *tert*-butoxide in 10 ml of THF under stirring at 20°C in an argon atmosphere. When the reaction was complete (TLC), 10 ml of a saturated solution of ammonium chloride and 10 ml of diethyl ether were added to the mixture. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2×15 ml). The extracts were combined with the organic phase and dried over $MgSO_4$, the solvent was removed, and the residue was purified by recrystallization. Yield 196 mg (74%), mp 181–182°C (from hexane–methylene chloride). ^{1}H NMR spectrum, δ, ppm: 1.10–1.32 m (2H, 4-H), 1.32–1.56 m (4H, 3-H, 5-H), 2.87 s (1H, OH), 3.36 br.s (2H, 2-H, 6-H), 4.37 s (2H, OCH_2), 7.47–7.65 m (3H) and 7.85–7.96 m (2H) (C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 19.3 (C^3, C^5); 19.9 (C^4), 32.8 and 38.2 (C^1, C^7); 46.4 (C^2, C^6); 58.4 (OCH_2); 126.2 (2C), 129.0 (2C), 132.8, 142.3 (C_6H_5). Found, %: C 63.83; H 6.18. $C_{14}H_{16}O_3S$. Calculated, %: C 63.61; H 6.10.

b. A solution of 234 mg (1 mmol) of sulfone **VII** in 15 ml of THF was cooled to –35°C, and 3 ml (1.5 mmol) of a 0.5 M solution of butyllithium in pentane was slowly added under stirring in an argon atmosphere. The cooling bath was removed, the mixture was stirred for 30 min and cooled again to –30°C, and a stream of formaldehyde (prepared by pyrolysis of paraformaldehyde) was passed through the resulting suspension in a weak stream of argon. The cooling bath was removed, and the mixture was stirred for 1 h, diluted with 50 ml of diethyl ether, and filtered. The filtrate was washed with water, a saturated solution of ammonium chloride, and water again, dried over Na_2SO_4, and evaporated, and the product was purified by flash chromatography on silica gel. Yield 130 mg (49%), mp 181–182°C.

2-Methyl-2-(7-phenylsulfonyltricyclo[4.1.0.$0^{2,7}$]-hept-1-yl)propan-2-ol (VIII). A solution of 234 mg (1 mmol) of sulfone **VII** in 15 ml of THF was cooled to –30°C, and 3 ml of a 0.5 M solution of butyllithium in pentane was added under argon. The cooling bath was removed, the mixture was stirred for 1 h, and the resulting suspension was transferred using a siphon into a flask containing a mixture of 0.23 g (4 mmol) of acetone and 4 ml of THF, cooled to –30°C. The mixture was stirred for 2 h, allowing it to gradually warm up to room temperature, diluted with 30 ml of diethyl ether, washed with a solution of ammonium

chloride and water, and dried over Na_2SO_4. The product was purified by column chromatography on silica gel. Yield 181 mg (62%), mp 98–99°C (from hexane–diethyl ether). ^{1}H NMR spectrum, δ, ppm: 1.12–1.32 m (2H, 4-H), 1.32–1.52 m (4H, 3-H, 5-H), 1.57 s (6H, CH_3), 2.80 br.s (1H, OH), 3.38 br.s (2H, 2-H, 6-H), 7.52–7.69 m (3H) and 7.90–7.98 m (2H) (C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 19.3 (C^3, C^5); 19.9 (C^4); 28.7 (2C, CH_3); 36.4 and 46.9 (C^1, C^7); 44.1 (C^2, C^6); 68.3 (COH); 126.3 (2C), 129.1 (2C), 132.8, 142.5 (C_6H_5). Found, %: C 65.67; H 6.91. $C_{16}H_{20}O_3S$. Calculated, %: C 65.72; H 6.89.

6-Hydroxy-3λ^6-thiatricyclo[4.4.0.0^{2,7}]decane 3,3-dioxide (IX). Compound **IVa**, 202 mg (1 mmol), was added under argon to a solution of 170 mg (1.5 mmol) of potassium *tert*-butoxide in 10 ml of THF, and the mixture was stirred for 3 h at 25°C. When the reaction was complete (TLC), the mixture was diluted with 30 ml of diethyl ether and treated with 10 ml of a saturated solution of ammonium chloride. The organic phase was separated, washed with water, and dried over Na_2SO_4. The product was isolated by column chromatography on silica gel. Yield 148 mg (73%), mp 183–184°C. ^{1}H NMR spectrum, δ, ppm: 1.53–1.73 m (2H, 9-H), 1.92–2.20 m (4H, 8-H, 10-H), 2.30 s (1H, OH), 2.31 t (2H, 5-H), 2.90 br.s (2H, 1-H, 7-H), 3.27 s (1H, 2-H), 3.43 t (2H, 4-H). ^{13}C NMR spectrum, δ_C, ppm: 13.9 (C^9), 22.0 (C^8, C^{10}), 30.6 (C^5), 46.6 (C^1, C^7), 48.0 (C^4), 57.8 (C^2), 72.0 (C^6). Found, %: C 53.18; H 6.82. $C_9H_{14}O_3S$. Calculated, %: C 53.44; H 6.98.

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