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BICYCLIC BASES[1, 2]

SYNTHESIS, CONFIGURATION, AND NMR ANALYSIS OF N-TOSYL-2-THIA-5-AZABICYCLO[2.2.1]HEPTANE-2-OXIDES[3]

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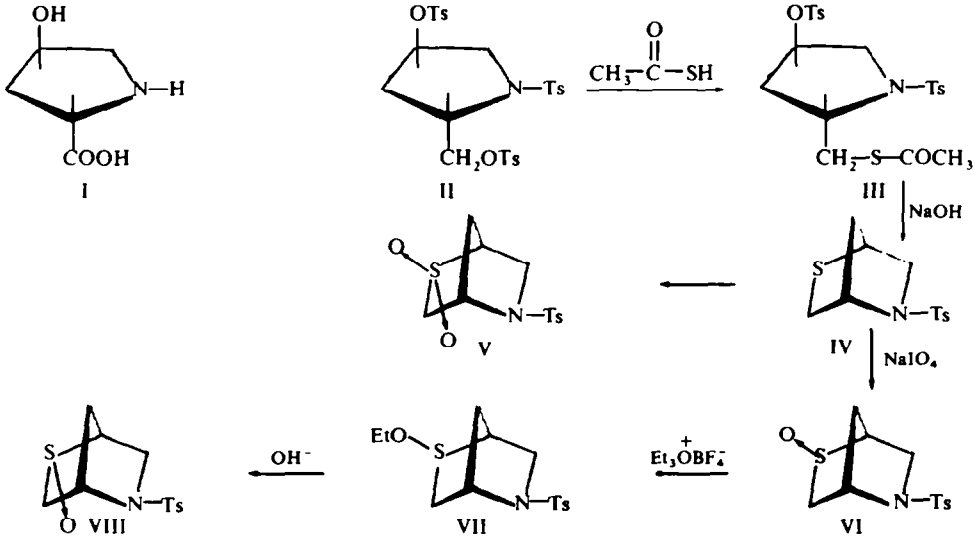
Abstract—The novel bicyclic system, N-tosyl-2-thia-5-azabicyclo[2.2.1]heptane (IV), was synthesized from tritosylhydroxy-L-prolinol and thioacetate anion. Sodium metaperiodate oxidation of (IV) yielded exclusively the *exo* sulfoxide (VI) from which the isomeric *endo* product (VIII) was obtained by treatment with ethyloxonium fluoroborate. Thermally induced equilibration studies demonstrated that the *exo*-oxide is thermodynamically more stable than the *endo*-oxide. The sulfone (V) was prepared by oxidation with H_2O_2. The identity of all proton resonances in the 100-MHz NMR spectra of (IV–VI, VIII) were deduced from spin-decoupling experiments.

WE PREVIOUSLY have reported on the synthesis of chiral norbornanes containing endocyclic heteroatoms (O,N) at the 2- and/or 4-position.[2, 4–6] Because of their conformational rigidity these compounds have been useful in stereochemical studies.[2, 5, 6] We now describe an extension of this synthetic route to prepare N-tosyl-2-thia-5-azabicyclo[2.2.1]heptane (IV) for the purpose of investigating the stereochemistry of sulfur oxidation. Moreover, the first-order NMR spectral properties of key protons in this novel bicyclic system provides an excellent opportunity to study the acetylene-like anisotropy of the S → O bond.[7–11]

Hydroxy-L-proline (I) was converted to tritosylhydroxyprolinol (II) by the procedure of Portoghese and Mikhail.[4] Reaction of (II) with thioacetate afforded the



expected intermediate (III) which, upon base hydrolysis *in situ*, cyclized to give N-tosyl-2-thia-5-azabicyclo[2.2.1]heptane (IV) in an overall yield of 60 per cent. Oxidation of (IV) using sodium metaperiodate[12] gave exclusively the *exo* sulfoxide (VI). The *endo* isomer (VIII) was obtained by treatment of (VI) with ethyloxonium fluoroborate,[13] followed by base hydrolysis of the oxonium salt (VII). The sulfone (V) was prepared by oxidation of (IV) with 30% H_2O_2.

In order to determine the thermodynamic stabilities of the isomeric sulfoxides, thermally induced equilibrations[14] of (VI) and (VIII) were carried out. When the two sulfoxides were heated together or separately in decalin only the *exo* isomer was detected by glc. It is noteworthy that the retention time of (VI) is greater than that of (VIII). Similarly, (VI) has lower Rf than (VIII). This is consistent with other studies[15, 16] which have shown that the accessibility of the sulfoxide oxygen for the stationary phase is greater in less hindered diasteromers. Thus it appears that the thermodynamically more stable isomer possess the *exo* configuration. It recently has been reported that this also is the case for the S-oxide of 2-thiabicyclo[2.2.1]heptane.[15]

The NMR data for compounds (IV), (V), (VI) and (VIII) are listed in Table 1. The chemical shifts and the coupling constants were deduced from spin decoupling experiments. All four compounds showed very similar spectral characteristics and therefore only one analysis, that of the sulfone (V), will be discussed in detail.

The lowest field signal in the 100 MHz NMR spectrum is an unresolved multiplet centered at δ 4·62. This peak is assigned to H_4, since its chemical shift is very close to that found for the bridgehead protons in N,N-ditosyl-2,5-diazabicyclo[2.2.1]heptane.[4] The other bridgehead proton H_1, also an unresolved multiplet, appears at δ 3·58. The methylene protons at C_3 and C_6 showed coupling patterns typical for those reported for the analogous carbocyclic systems,[17, 18] except that the resonances of both the C_3 and C_6 *exo* protons occurred at higher field than the corresponding *endo* protons. The doublet centered at δ 3·95 was assigned to *endo* proton H_6 and the doublet of doublets at δ 3·38 to *exo* proton H_6'. These assignments were confirmed by double resonance experiments. Irradiation of the multiplet at δ 3·58 (H_1) caused the doublet of doublets at δ 3·38 (H_6') to collapse to a doublet (J = 10·5 Hz) and irradiation of the doublet at δ 3·95 (H_6) resulted in the H_6' doublet of doublets to collapse to a doublet (J = 3·5 Hz). Consequently, the doublet of doublets arises from H_6' coupling to both the bridgehead proton H_1 and *endo* proton H_6, since it has been demonstrated that the vicinal coupling between the bridgehead proton and the adjacent *endo* proton is essentially zero in azabicyclo[2.2.1]heptane systems.[4, 6] Similarly, the doublet at δ 3·17 and the doublet of doublets at δ 2·97 were assigned to the *endo* (H_3) and *exo* (H_3') protons. Double resonance studies once again confirmed these assignments.

Since long range coupling between protons in the "planar M" configuration is well documented,[18, 19] verification of the assignments for the bridge protons at δ 2·35 and δ 1·75 was obtained from the observed long range coupling between an *endo* proton at either C_3 or C_6 and the corresponding *anti* proton at C_7 (i.e. J_{3-7} and $J_{6-7'}$). Irradiation of the δ 1·75 multiplet simultaneously narrowed the multiplet at δ 2·35 and the doublet corresponding to H_3. Hence, the signal at δ 1·75 was assigned to H_7, since only this proton assumes a "planar M" arrangement with H_3. Similarly, irradiation at δ 2·35 narrowed the signal for H_6.

Similar spin decoupling experiments were carried out for the *exo* and *endo* sulfoxides (VI and VIII) and the sulfide (IV), and in all cases complete spectral interpretations were made utilizing the above mentioned analysis.

Foster *et al*[9] have studied the NMR spectra of 1,4-Oxathiane-S-oxides oxides and observed a significant deshielding of protons that are *syn*-axial to an axial S → O bond. The authors called this the "*syn*-axial effect" and assigned it to an acetylenic-type of anisotropy of the sulfoxide bond. Johnson[16] has used this effect to assign the sulfoxide configuration to some 3-substituted thietane-1-oxides. Although the 2-thia-5-azabicyclo[2.2.1]heptane ring system is somewhat different from both Foster's and Johnson's[16] models, the same rationale can be used to assign the configuration of (VI) and (VIII). Molecular models show that only $H_{7'}$ of the *exo* sulfoxide (VI) and the sulfone (V) are close enough to the S → O bond to be influenced by this proximity effect. Consequently, one would expect that the chemical shift of $H_{7'}$ should be similar in (V) and (VI). The values (Table I) show that these chemical shift differ by only 0·06 ppm, whereas in the case of *endo* sulfoxide (VIII) and sulfone (V), it differs by 0·68 ppm. Similarly, *endo* proton H_6 in (V) and (VIII) would be expected to experience a deshielding effect. Thus, the chemical shift difference for H_6 in (V) and (VIII) is 0·3 ppm compared to a difference of 1·07 ppm between (V) and (VI) for the same proton.

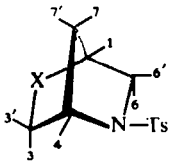
These assignments were verified further by comparing the chemical shifts of the protons at C_6 and C_7 in the two sulfoxides. The chemical shift difference for the C_6 methylene protons in (VI) should be considerably smaller than that for the C_7 protons since $H_{7'}$ is in the deshielding zone of the S → 0 bond. Accordingly, a chemical shift difference of 0·42 ppm is observed between the C_6 methylene protons in (VI), while the difference between C_7 protons is 0·79 ppm. For (VIII), the reverse would be predicted. The observed chemical shift difference between the protons at C_6 is 0·74 ppm while there is no significant difference in chemical shift between the protons at C_7.

The magnitude of the deshielding caused by the sulfoxide group can be estimated by comparing the chemical shifts of protons in the sulfide to those in the isomeric sulfoxides. In *exo* sulfoxide (VI), $H_{7'}$ is deshielded by 0·7 ppm. Similarly, H_6 in the *endo* sulfoxide (VIII) is deshielded by 0·68 ppm. The C-3 methylene protons that are *cis* to the S→O bond in (VI) and (VIII) are shielded while those that are *trans*-oriented are deshielded. Interestingly, the magnitude of shielding of H_3 in the *endo* isomer (VIII) is greater (0·77 ppm) than that observed for $H_{3'}$ in the *exo* isomer (VI) (0·55 ppm). Conversely, the deshielding affect on H_3 in (VI) is much larger (0·51 ppm) when compared to that for $H_{3'}$ (0·17 ppm) in (VIII).

Although carbocyclic bicyclo[2.2.1]heptanes are considered to be rigid, it is possible that introduction of a sulfur atom confers this system with a degree of flexibility so that there is a difference in the O←S—C—H torsion angle between (VI) and (VIII). Conceivably, such an effect could be an important factor influencing the shielding or deshielding of the C-3 protons.

A small yield (<2%) of a second bicyclic sulfoxide was isolated from the $NaIO_4$ oxidation of an unpurified sample of (IV). The IR spectrum of the compound showed the characteristically strong S → O absorption at 1030 cm^{-1}[20] and the elemental analysis indicated the presence of a third sulfur atom. On the basis of IR, NMR and mass spectral data, structure (XII) was tentatively assigned to this compound. A

TABLE 1. NMR DATA[a] FOR 2-THIA-5-AZABICYCLO[2.2.1]HEPTANE DERIVATIVES



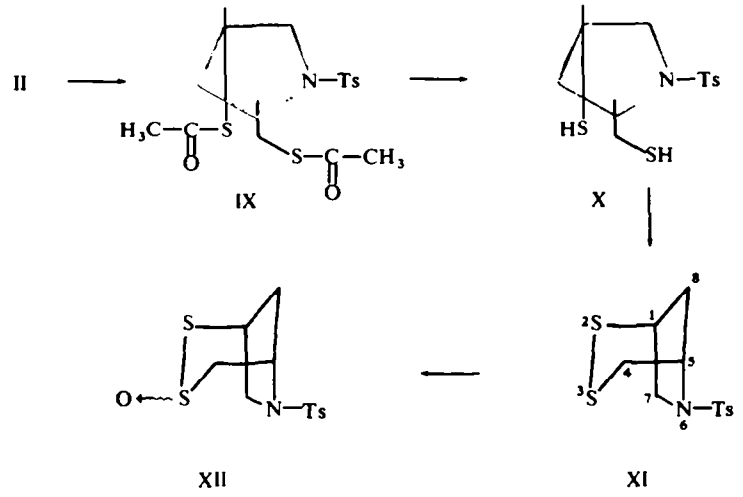
Compound	X	H_1	H_3	H_3'	H_4	H_6	H_6'	H_7	H_7'	J_{1-6}	$J_{1-6'}$	$J_{3-3'}$	$J_{3'-4}$	J_{3-4}	J_{3-7}	$J_{6\,6'}$	$J_{6\,7'}$
IV	S	3·47 $W_{\frac{1}{2}}$ = 3 Hz	3·06 d of m	2·88 d of d	4·59 $W_{\frac{1}{2}}$ = 5 Hz	3·57 d	3·40 d of d	1·6 m	1·7 m	*b*	2·5	10·0	2·5	*b*	1·0	15·0	*b*
V	SO_2	3·58 $W_{\frac{1}{2}}$ = 7·5 Hz	3·17 d of m	2·97 d of d	4·62 $W_{\frac{1}{2}}$ = 9 Hz	3·95 d	3·38 d of d	1·75 d of m	2·35 d of m	*b*	3·5	12·5	3·0	*b*	2·5	10·5	0·7[c]
VI	*exo* S → O	3·61 $W_{\frac{1}{2}}$ = 7 Hz	3·57 d of m	2·33 d of m	4·57 $W_{\frac{1}{2}}$ = 6·5 Hz	2·88 d	3·30 d of d	1·62 d of m	2·41 d of m	*b*	5·0	12·0	3·0	*b*	1·5	12·0	0·5[c]
VIII	*endo* S → O	3·88 $W_{\frac{1}{2}}$ = 6 Hz	2·29 d of m	3·05 d of d	4·57 $W_{\frac{1}{2}}$ = 7 Hz	4·25 d	3·51 d of d	1·67 m	1·67 m	*b*	4·0	13·5	3·0	*b*	3·0	10·5	*b*

[a] Compounds (IV–VI) were obtained at 100 MHz except (VIII) which was obtained at 60 MHz. Chemical shifts are given in ppm and J values in Hz. The letters d and m refer to doublet and multiplet.

[b] $J < \frac{1}{2}$ Hz.

[c] Obtained by observing the difference in $W_{\frac{1}{2}}$ before and after decoupling.

plausable pathway leading to (XII) involves displacement of both tosyloxy groups of (II) by thioacetate and hydrolysis to dithiol (X) followed by periodate oxidation. Under these conditions the dithiol first would be cyclized to disulfide (XI) and then oxidized further to the thiosulfinate (XII). The assignment of the sulfoxide group at the 3-position was made from consideration of generally accepted mechanism of $NaIO_4$ oxidation[21] of sulfide. Since cyclic six membered disulfides have been reported to exist in chair conformation,[22–25] it might be expected that (XII) would exist as depicted. Molecular models reveal that S-3 is sterically better able to accommodate the necessary cyclic intermediate with the oxidizing agent.[21] The analogous intermediate for oxidation at S-2 involves considerably more steric hindrance. In support of the above assignment the C-4 protons adjacent to the



sulfoxide center show a chemical shift difference (0·61 ppm) characteristic of methylene protons adjacent to a sulfoxide center. This effect is similar to that observed in *exo* or *endo* sulfoxides. However, the present data does not allow the assignment of the orientation of the oxygen atom at S-3.

EXPERIMENTAL

M.p.s are uncorrected. IR spectra were measured with Perkin–Elmer Model 237 B grating spectrometer. NMR spectra were obtained on a Varian A-60D and HR 100 MHz spectrometer using TMS as internal standard. Optical rotations were determined using a Perkin–Elmer 114 polarimeter and a 1 dm cell. Elemental analysis were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York and by the Microanalytical Laboratory, University of Minnesota, Minneapolis, Minnesota.

N-*Tosyl-2-thia-5-azabicyclo*[2.2.1]*heptane* (IV). A soln of 0·58 g (0·001 mole) of II[4] in CH_3CN (10 ml) was added to 1 g of anhydrous K_2CO_3. To this mixture at reflux was added dropwise a soln of 0·084 g (0·011 mole) thioacetic acid in CH_3CN (5 ml). After one hr reflux, the mixture was cooled and the solvent removed *in vacuo*. The oily residue was dissolved in 1 *N* methanolic NaOH (1 ml) and the mixture allowed to stand at room temperature for 10 hr. Removal of MeOH afforded a residue which was dissolved in $CHCl_3$, washed with $NaHCO_3$ (8%), and dried (Na_2SO_4). Removal of $CHCl_3$ yielded a solid residue which was recrystallized (EtOAc-Pet. ether) to give 0·16 g (60% yield) of product, m.p. 111–112°, $[\alpha]_D^{23}$ – 30·4 (c 1%, MeOH). (Found: C, 53·71; H, 5·55; N, 5·01. $C_{12}H_{15}NO_2S_2$ requires: C, 53·50; H, 5·58; N, 5·21%).

N-*Tosyl-2-thia-5-azabicyclo*[2.2.1]*heptane-2-exo-oxide* (VI). A soln of 1·35 g (0·005 mole) of (IV) in

CH_3OH (5 ml) was added dropwise to an aqueous soln of 1·2 g (0·0055 mole) of $NaIO_4$ with cooling and the mixture was stirred at room temp for 3 hr. The ppted $NaIO_3$ was filtered and the solvent removed under reduced pressure. The oily residue was extracted with EtOAc, washed several times with H_2O, and dried (Na_2SO_4). Evaporation of EtOAc yielded a yellow solid which was purified on column; Rf, 0·50 (Silica-gel; EtOAc-Acetone, 1:1). One recrystallization (EtOAc-Hexane) gave 1·15 g (80%) of product, m.p. 140–141·5°, $[\alpha]_D^{23}$ + 14·07 (c 1%, MeOH); IR (KBr) 1026 cm^{-1} (S → O).[20] (Found: C, 50·39; H, 5·20; N, 5·02. $C_{12}H_{15}NO_3S_2$ requires: C, 50·50; H, 5·29; N, 4·90%).

N-*Tosyl*-2-*thia*-5-*azabicyclo*[2.2.1]*heptane*-2,2-*dioxide* (V). To a soln containing 0·54 g (0·002 mole) of (IV) in glacial acetic acid (3 ml) maintained at 80° was added dropwise 2 ml of H_2O_2 (30%) and the reaction mixture stirred for 2 hr. The solvent was removed, the residue dissolved in $CHCl_3$, washed with H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ gave a white solid, recrystallized from MeOH-ether to yield 0·48 g (80%) of product, m.p. 105–106°, $[\alpha]_D^{23}$ – 27·3 (c 1%, MeOH); IR (KBr) 1149 and 1310 cm^{-1} (O=S=O).[26] (Found: C, 47·90; H, 5·28; S, 21·11 $C_{12}H_{15}NO_4S_2$ requires: C, 47·82; H, 5·01, S, 21·27%).

N-*Tosyl*-exo-2-*ethoxy*-2-*thia*-5-*azabicyclo*[2.2.1]*heptane fluoroborate* (VII). To a soln of 0·29 g (0·001 mole) of (VI) in 2 ml of CH_2Cl_2 was added 0·19 g (0·001 mole) of triethyloxonium fluoroborate.[27] After stirring for 30 min. it was cooled to 0° and dry ether added until turbid. Evaporation of solvent afforded an oil which when triturated several times with ether yielded a solid residue. One recrystallization from CH_2Cl_2-ether gave 0·37 g (91%) of (VII), m.p. 128–130°. (Found: C, 41·75; H, 4·96; N, 3·22. $C_{14}H_{20}BF_4NO_3$ requires: C, 41·90; H, 5·02; N, 3·49%).

N-*Tosyl*-2-*thia*-5-*azabicyclo*[2.2.1]*heptane*-2-*endo*-*oxide* (VIII). An aqueous soln of 0·2 g (0·001 mole) of (VII) was neutralized with 0·01 N NaOH, extracted with CH_2Cl_2, washed with H_2O and dried (Na_2SO_4). Evaporation of solvent left a solid residue which upon recrystallization from EtOAc-Hexane gave 0·12 g (84·2%) of (VIII), m.p. 144–145°, $[\alpha]_D^{23}$ – 32·2° (c 1%, MeOH); IR (KBr) 1032 cm^{-1} (S → O).[20] Rf, 0·58 (silica-gel; EtOAc: Acetone 1:1) (Found: C, 50·53; H, 5·23; N, 4·63; $C_{12}H_{15}NO_3S_2$ requires: C, 50·50; H, 5·29; N, 5·90%).

N-*Tosyl*-2,3-*dithia*-6-*azabicyclo*[3.2.1]*octane*-3-*oxide* (XII). This was isolated in a small quantity (0·27 g) during the oxidation of an impure sample (1·35 g) of (IV) with $NaIO_4$ in a manner described for (VI). The product was separated on column (Silica-gel; EtOAc-Acetone 1:1). One recrystallization from EtOAc-hexane, gave white solid, m.p. 127–128°, $[\alpha]_D^{23}$ – 277·1° (c, 1% MeOH); IR (KBr) 1030 cm^{-1} (S → O);[20] mass spectrum, molecular ion peak at *m/e* 317; NMR ($CDCl_3$), δ 1·65 (broad multiplet, 2H, H_6 and H_6'), δ 3·05 (d of d, H_4'), δ 3·66 (d of d, H_4), δ 3·75 (m, H_1), δ 3·75 (broad singlet 2H, H_8 and H_8'), δ 4·48 (d of d, H_5). (Found: C, 45·67; H, 4·72 N, 4·43; S, 30·10. $C_{12}H_{15}NO_3S_3$ requires: C, 45·40; H, 4·76; N, 4·76; S, 30·30%).

Equilibration Studies. A 1% soln of the *exo* (VI) and *endo* (VIII) sulfoxides were heated separately in freshly distilled decalin at 190° under N_2 for 1 hr. The soln was analyzed on Perkin–Elmer model 900 gas chromatograph equipped with 6′ × 1/8″ column packed with a 3% O.V. on Chromosorb W (HP). The column was silylated with silyl 8 before use. An injection temp. of 290°, manifold at 200° and column at 260° with a carrier gas flow at 35 ml/min, proved to be ideal requirements for the good separation of the two sulfoxides. The *endo* and *exo* isomer had a retention time of 12·75 and 19·75 min., respectively.

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