

Bicyclic Bases (1,2). Synthesis and Stereochemical Studies of  
Chiral 5-Substituted *N*-Tosyl-2-azabicyclo[2.2.1]heptanes.

*P. S. Portoghese, D. L. Lattin, and V. G. Telang*

Department of Medicinal Chemistry, College of Pharmacy,  
University of Minnesota, Minneapolis, Minnesota 55455

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The synthesis of chiral *exo* and *endo* 5-substituted *N*-tosyl-2-azabicyclo[2.2.1]heptanes is reported. The nearly identical *exo-endo* equilibrium ratios of the title compounds and the carbocyclic analogs suggest that their geometries and steric interactions are quite similar.

The rigid azabicyclo[2.2.1]heptane system (2-9) has proved to be useful in a variety of stereochemical studies where conformational homogeneity is required. As a continuation of our work in this area we have prepared the title compounds for use as key intermediates in the synthesis of conformationally rigid atropine analogs. We describe herein the synthesis of these compounds by a route that establishes the chirality of the bicyclic system together with stereochemical studies which lead to the assignments at the C-5 group position.

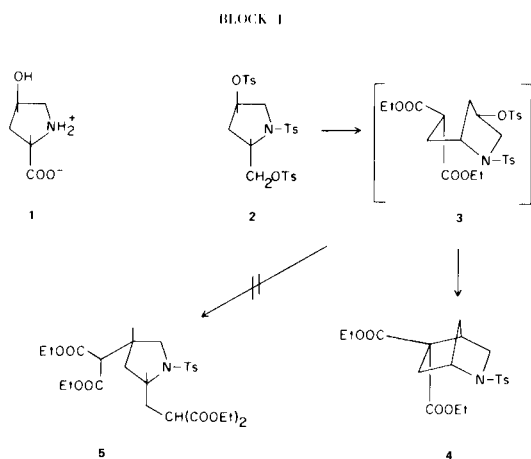
It has been reported that hydroxy-*L*-proline (1) can be utilized in the synthesis of chiral azabicyclo[2.2.1]heptane systems containing different endocyclic heteroatoms (2-5, 7-9). A similar approach was employed for the synthesis of the title compounds, since it was desirable to know the chiralities of these intermediates.

Hydroxy-*L*-proline (1) (10) was converted to *N,O*-tritosylhydroxy-*L*-prolinol (2) by the method of Portoghese and Mikhail (3). This intermediate then was condensed with diethylmalonate anion to afford the bicyclic diester

(4) in 83% yield. Presumably, the reaction involves displacement of the primary tosylate of 2 by diethylmalonate carbanion followed by internal nucleophilic displacement of the secondary tosylate in 3. It is noteworthy that neither 3 nor 5 were detected in the reaction mixtures. This suggests that the rate of formation of 3 is slow compared to the cyclization step.

Hydrolysis of 4 in ethanolic potassium hydroxide afforded the dicarboxylic acid (6) which was smoothly decarboxylated to a mixture of isomeric acids (8a, b) by heating in DMF. Conversion of the mixture to the corresponding methyl esters (9a, b) with diazomethane followed by gas chromatography (gc) revealed the 8a:8b ratio to be 20:80. Attempts to separate 9a from 9b either by fractional crystallization or column chromatography were unsuccessful. However, fractional crystallization of 8a, b from benzene did afford a partial separation. The first crop of crystals afforded pure 8b as indicated by gc of the methyl ester. Concentration of the filtrate afforded another crystalline fraction which was found to be a mixture of isomers. Further fractional crystallizations of this fraction failed to afford isomerically pure 8a.

Cope and co-workers (11) equilibrated 2-carbomethoxybicyclo[2.2.1]heptane in methanolic sodium methoxide and found that the *exo* isomer was thermodynamically favored over the *endo* ester. Using a similar approach, the isomerically pure methyl ester 9b derived from 8b and a mixture of the methyl esters (9a:9b = 63:37) were each equilibrated in methanolic sodium methoxide and the isomer compositions were determined by gc. The equilibrium mixtures derived from the isomerically pure ester and from the isomeric mixture of esters afforded an isomer ratio of 70:30 (9a:9b). By analogy with the norbornane system, the more stable isomer (9a) tentatively was assigned the *exo* configuration and the less stable isomer (9b) the *endo* configuration. Since 9b was obtained from



isomerically pure **8b**, this acid also must have the *endo* configuration.

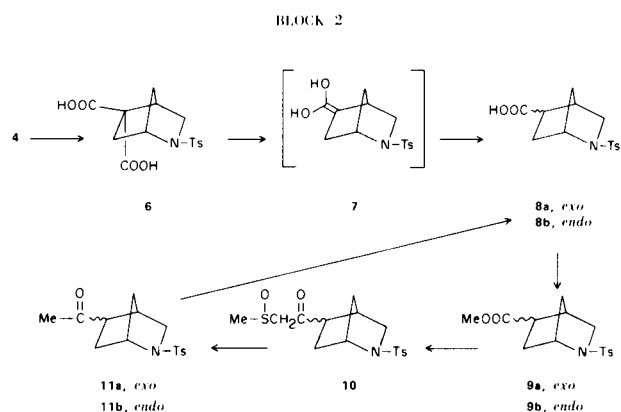
The fact that *endo* acid **8b** was the predominant isomer obtained by decarboxylation of **6** suggested that this decarboxylation was kinetically controlled. Zimmerman and colleagues (12) have extensively studied the stereochemistry of ketonization. Studies relevant to this research were those concerning the stereochemistry of decarboxylation of 2- and 4-phenylcyclohexane-1,1-dicarboxylic acid (13,14). They found that upon decarboxylation the *cis* isomers predominated. As the *trans* isomers were found to be thermodynamically favored, it was concluded that the kinetically controlled protonation of an unstable enol intermediate was the primary factor determining the stereochemical course of these decarboxylations. Since a high degree of stereoselectivity was observed for the decarboxylation of **6** in DMF, it was of interest to determine the effect on stereoselectivity by several methods of decarboxylation. Neat decarboxylation and decarboxylation in collidine afforded *exo:endo* isomer ratios of 28:72 and 22:78, respectively. These results suggest that **6** undergoes decarboxylation *via* enol intermediate **7** under a variety of conditions and that the *endo* acid **8b** results from the kinetically controlled protonation of this intermediate from the less hindered *exo* face of the molecule.

An isomeric mixture of the methyl esters (**9a, b**) was treated with the carbanion of dimethylsulfoxide according to the procedure of Corey (15) to afford the  $\beta$ -ketosulfoxides (**10**). No attempt was made to use isomerically pure methyl esters because it was assumed that epimerization of either **9** or **10** would occur under these highly basic conditions. Optimum yields were achieved using three equivalents of dimethylsulfoxide carbanion. At the end of the reaction period thin-layer chromatography (tlc) indicated the absence of **9** and the presence of both isomers of **10**, although no attempt was made to separate these isomers.

Reduction of **10** with aluminum amalgam (15) gave the bicyclic ketones (**11a, b**) in an overall yield of 89%. Gc revealed that this product was a mixture of two isomers consisting of 58% of a short-retention-time isomer and 42% of a long-retention-time isomer which were later assigned the *exo* (**11a**) and *endo* (**11b**) configurations, respectively. Although complete separation was not achieved, **11a** was obtained in 95-97% isomeric purity by column chromatography or fractional crystallization. Attempts to purify **11b** by fractional crystallization were unsuccessful.

In order to assign the configuration about C-5, mixtures of **11a** and **11b** with isomer ratios of 97:3 and 66:34 were each equilibrated in methanolic sodium methoxide and the isomer ratios determined by gc. The average

isomer ratio was found to be 75:25 which is almost identical to the equilibrium composition of *exo*- and *endo*-2-acetylbicyclo[2.2.1]heptane (**16**). In the case of the carboxylic analog it was concluded that the *exo* isomer was thermodynamically more stable because of the unfavorable steric interaction between the acetyl group and *endo* proton at C-6 and it is presumed that a comparable steric interaction between the C-5 *endo* acetyl function and the C-3 *endo* hydrogen in **11b** determines the equilibrium composition in a similar fashion.

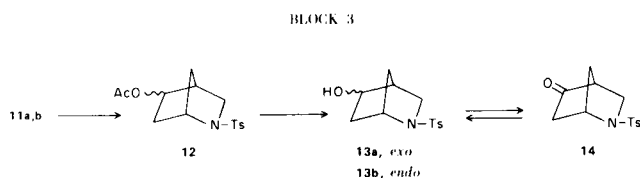


In order to corroborate further the stereochemical assignment of **11**, the haloform reaction (17) was investigated as a means of converting the ketone back to the acid **8**. If this reaction were to proceed with little or no epimerization at C-5, it would serve to relate the stereochemistry of ketones **11a** and **11b** to that of the corresponding acids (**8a, b**) and methyl esters (**9a, b**). A mixture of **11a** and **11b** (84:16) was treated with iodine-potassium iodide solution (18) to afford 62% of unreacted **11a, b** (*exo:endo* = 86:14) and 32% of **8a, b** which was converted to the methyl esters (**9a, b**). Gc analysis of this mixture revealed an *exo:endo* isomer ratio of 90:10. Although the yield of **8** was rather low, the products and recovered ketone accounted for 94% of the starting material. Inasmuch as the *exo:endo* composition of recovered **11** was only slightly different from that of the starting mixture it appears that the haloform reaction proceeded with little epimerization. The similarity in isomer ratio of recovered **11** to that of the starting mixture also indicates that product **8** was not the result of preferential oxidation of one isomer of **11**. Since the *exo:endo* ratio of the products is in close agreement with that of the starting material (**11a, b**), the above reaction chemically interrelates the stereochemical configuration at C-5 in **11a** to that in **8a** and **9a** and supports the assignment based on the equilibration of **11**.

The final step in the synthesis involved Baeyer-Villiger oxidation of **11**. A mixture of **11a** and **11b** (58:42) was

treated with *m*-chloroperoxybenzoic acid to form intermediate **12** which was hydrolyzed without isolation to afford **13a, b** in an overall yield of 30%. Gc analysis indicated that **13** was composed of two isomers in a ratio of 68:32. Since it has been found (19) that peracid oxidation of 2-acetylnorbornane proceeds with retention of configuration, the isomer present in higher quantity was tentatively assigned the *exo* configuration (**13a**).

The low yield of this reaction raised the possibility that preferential oxidation of one isomer (**11a** or **11b**) might have occurred due to the fact that functional groups with the *endo* configuration are more sterically hindered than those with the *exo* configuration (11,16). It is conceivable that this had occurred with **11** since the *exo-endo* ratio of the product is greater than that of the reactant ketones.



Column chromatography of the mixture of alcohols (**13**) afforded the pure *exo* isomer (**13a**). Attempts to isolate **13b** in pure form were unsuccessful, and the maximum purity obtained was 90%. Since only the *exo* alcohol (**13a**) was isolated isomerically pure, an effort was made to stereoselectively synthesize the *endo* isomer (**13b**). Brown and colleagues (20,21) have reported a high degree of stereoselectivity (up to 98% *endo* alcohol) upon hydride reduction of norcamphor to norbornanol. Oxidation of *exo* alcohol (**13a**) with chromic acid-sulfuric acid followed by reduction of ketone **14** with lithium aluminum hydride afforded **13b** in 93% isomeric purity. These results indicate that the stereoselectivity for the reduction is similar to that reported for the norbornane system. Column chromatography afforded **13b** in about 99% isomeric purity.

Further support for the stereochemical assignment of the hydroxyl groups in **13a, b** was obtained from their 100 MHz nmr spectra. The carbinol proton resonance was seen as a doublet of multiplets ( $\delta = 3.87$ ;  $J = 7$  Hz;  $w_{1/2} = 13$  Hz) in **13a** and as a broad multiplet ( $\delta = 4.18$ ;  $w_{1/2} = 21$  Hz) in **13b**. It is noteworthy that a similar relationship has been reported (22,23) for *exo*- and *endo*-2-norbananol in that the carbinol proton of the *exo* isomer is upfield and narrower than that of the *endo*-isomer. By analogy with the norbornanes (24), the greater  $w_{1/2}$  for the carbinol proton of **13b** relative to **13a** is related to the fact that *exo-exo* vicinal protons in the former display greater coupling than *endo-exo* coupling in the latter. In addition, **13a** should have  $J_{4,5} \sim 0$  Hz as predicted by the Karplus

(25) relationship, since their dihedral angle is  $\sim 90^\circ$  (3,8,9,24). On the other hand,  $J_{4,5} \sim 2-3$  Hz would be expected for **13b** (3,8,9). Consequently, the carbinol proton of **13a** is seen as a narrower and less complex peak than that of **13b**.

## EXPERIMENTAL

All melting points are uncorrected. A Perkin-Elmer Model 237B spectrophotometer was employed for the infrared spectra. The routine nmr spectra were obtained using a Varian A 60D spectrometer and the 100 MHz spectra were recorded by Midwest Research Institute, Kansas City, Missouri; tetramethylsilane was the internal reference standard in deuteriochloroform solutions and 2,2-dimethyl-2-silapentane-2-sulfonate was the internal reference standard in deuterium oxide solutions. Optical rotations at the sodium *D* line were obtained using a Perkin-Elmer Model 114 polarimeter and a 1 dm. cell. Gas chromatographic analyses were obtained using a Perkin-Elmer Model 900 or a Varian Aerograph Model 700 gas chromatograph. The columns used were a six foot OV-17/s (3%), a six foot (OV-210 (3%), and a 20 foot SE-30 (30%). Mass spectral data was obtained from the Mass Spectrometry Laboratory, University of Minnesota, employing a Hitachi Perkin-Elmer Model RMU-6D spectrometer.

### *N*-Tosyl-5,5-Dicarbethoxy-2-azabicyclo[2.2.1]heptane (**4**).

Diethylmalonate (29.02 g., 0.18 mole) in dry diglyme (150 ml.) was added dropwise with cooling to a suspension of sodium hydride (8.21 g. of a 50.6% mineral oil dispersion, 0.17 mole) in dry diglyme (50 ml.) under a nitrogen atmosphere. *N,O*-Tritosylhydroxy-L-prolinol (**2**) (3) (20.00 g., 0.035 mole) in dry diglyme (350 ml.) was added to the above solution and the mixture was heated at 123-128° for 12 hours. The reaction mixture was cooled, filtered, and acidified to pH 1 with 10% hydrochloric acid. Removal of solvent afforded an oil which crystallized upon trituration with petroleum ether (30-60°) to give 11.30 g. (83% yield) of **4**, m.p. 105-108°. Recrystallization (ether) gave m.p. 108-109°;  $[\alpha]_D^{20} -39.04$  ( $c$  1.05, CHCl<sub>3</sub>); ir (potassium bromide) 1730 (ester C=O), 1340 (SO<sub>2</sub>), 1160 cm<sup>-1</sup> (SO<sub>2</sub>); nmr (deuteriochloroform)  $\delta$  7.50 (m, 4), 4.17 (m, 5), 3.10 (s, 3), 2.62 and 2.55 (two d, 1), 2.40 (s, 3), 2.10 and 1.87 (two d, 1), 1.60 (d, 1), 1.20 (m, 7). The mass spectrum possessed a molecular ion of *m/e* 395 (theoretical molecular weight = 395.45).

*Anal.* Calcd. for C<sub>19</sub>H<sub>25</sub>NO<sub>6</sub>S: C, 57.71; H, 6.37; N, 3.54. Found: C, 57.63; H, 6.57; N, 3.51.

### *N*-Tosyl-5,5-dicarboxy-2-azabicyclo[2.2.1]heptane (**6**).

Diester **4** (11.30 g., 0.029 mole) was dissolved in 260 ml. of 2 *N* ethanolic potassium hydroxide and allowed to stand at room temperature for 24 hours. The precipitate (the potassium salt of **6**) was collected, washed with ethanol, dissolved in water, and acidified to pH 1 with concentrated hydrochloric acid. After the solution was refrigerated overnight, the solid was collected and dried to afford 9.52 g. (97% yield) of the diacid (**6**), m.p. 169-170° dec.; ir (potassium bromide) 3600-2300 (acid OH), 1735 (acid C=O), 1340 (SO<sub>2</sub>), 1160 cm<sup>-1</sup> (SO<sub>2</sub>). A portion of the potassium salt of **6** was recrystallized from ethanol-water for an analytical sample; ir (potassium bromide) 1575 (COO<sup>-</sup>), 1405 (COO<sup>-</sup>), 1310 (SO<sub>2</sub>), 1155 (SO<sub>2</sub>), 1090 cm<sup>-1</sup>; nmr (deuterium oxide)  $\delta$  7.63 (m, 4), 4.13 (m, 1), 2.93 (m, 3), 2.52 (m, 4), 1.92 (m, 1), 1.42 (m, 1), 0.85 (m, 1).

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>6</sub>SK<sub>2</sub>: C, 43.36; H, 3.64; N, 3.37. Found: C, 43.16; H, 3.57; N, 3.26.

*N*-Tosyl-5-carboxy-2-azabicyclo[2.2.1]heptane (**8a**, **b**).

Diacid **6** (14.64 g., 0.042 mole) was dissolved in DMF and heated at 130° (external) for 4 hours. The solvent was removed and the residue was dissolved in saturated sodium bicarbonate solution and washed with chloroform. The aqueous solution was cooled, acidified to pH 1 with concentrated hydrochloric acid and the precipitate was collected and dried to afford 12.21 g. (98% yield) of **8**, m.p. 139-187°; ir (potassium bromide) 3600-2400 (acid OH), 1690 (acid C=O), 1345 (SO<sub>2</sub>), 1155 cm<sup>-1</sup> (SO<sub>2</sub>). Fractional crystallization of **8** (5.71 g.) from benzene afforded **8b** (4.07 g.), m.p. 188-190.5°;  $[\alpha]_D^{20} + 15.29$  (c 1.02, chloroform); ir (potassium bromide) 3600-2400 (acid OH), 1700 (acid C=O), 1340 (SO<sub>2</sub>), 1155 cm<sup>-1</sup> (SO<sub>2</sub>); nmr (deuteriochloroform)  $\delta$  8.58 (broad s, 1), 7.52 (m, 4), 4.25 (m, 1), 3.03 (m, 4), 2.45 (s, 3), 1.72 (m, 4). Removal of solvent from the filtrate and recrystallization (benzene) afforded **8a** (1.22 g.), m.p. 139-140°; ir (potassium bromide) 3600-2300 (acid OH), 1690 (acid C=O), 1340 (SO<sub>2</sub>), 1155 cm<sup>-1</sup> (SO<sub>2</sub>); nmr (deuteriochloroform)  $\delta$  8.22 (broad s, 1), 7.52 (m, 4), 4.25 (m, 1), 3.18 (m, 2), 2.63 (m, 5), 1.55 (m, 4).

Acid **8a**.

*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub>S: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.68; H, 5.64; N, 4.56.

Acid **8b**.

*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub>S: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.87; H, 5.93; N, 4.48.

*N*-Tosyl-5-carbomethoxy-2-azabicyclo[2.2.1]heptane (**9a**, **b**).

Acid **8b** (2.00 g., 0.0068 mole) was dissolved in methanol, cooled, and treated with an excess of ethereal diazomethane. After removal of solvent the residue was dissolved in chloroform and washed with saturated sodium bicarbonate solution. The chloroform solution was dried (magnesium sulfate) and the solvent removed. The crystalline residue was recrystallized from acetone-petroleum ether (30-60°) to afford the methyl ester **9b**, 1.78 g. (84% yield), m.p. 149-150°; ir (potassium bromide) 1740 (ester C=O), 1330 (SO<sub>2</sub>), 1160 cm<sup>-1</sup> (SO<sub>2</sub>); nmr (deuteriochloroform)  $\delta$  7.52 (m, 4), 4.22 (m, 1), 3.65 (s, 3), 3.17 (m, 2), 2.82 (m, 2), 2.42 (s, 3), 1.58 (m, 4).

*Anal.* Calcd. for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub>S: C, 58.23; H, 6.19; N, 4.53. Found: C, 57.93; H, 6.13; N, 4.30.

Acid **8a** (0.50 g., 0.0017 mole) was treated as above to afford the methyl ester **9a**, 0.49 g. (90% yield), m.p. 97-142°; nmr (deuteriochloroform)  $\delta$  7.52 (m, 4), 4.23 (m, 1), 3.65 (s, 3), 3.10 (m, 2), 2.73 (m, 2), 2.43 (s, 3), 1.57 (m, 4).

*Anal.* Calcd. for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub>S: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.22; H, 6.03; N, 4.44.

Tlc (silica gel, ether) of methyl esters **9a** and **9b** indicated that **9b** consisted of only one isomer ( $R_f = 0.47$ ) and **9a** contained both isomers ( $R_f = 0.47$  and 0.54). Gc (OV-17/s, 245°) of **9a** and **9b** also revealed one isomer for **9b** (retention time = 8.0 minutes) and both isomers in **9a** (retention times = 7.5 minutes and 8.0 minutes) in a ratio (**9a:9b**) of 63:37.

Thermodynamic Equilibration of *exo*- and *endo*-*N*-Tosyl-5-carbomethoxy-2-azabicyclo[2.2.1]heptane (**9a**, **b**).

Esters **9b** (0.050 g.) and **9a** (0.051 g.) were each dissolved in 7 ml. of a *N* solution of sodium methoxide in absolute methanol and were allowed to stand at room temperature (31°) while aliquots were withdrawn at 0.5 and 1 hour intervals for gc analysis (OV-17/s, 245°). After 6 hours both solution had attained

equilibrium. The equilibrium isomer ratio (**9a:9b**) was determined to be 70:30.

Decarboxylation of *N*-Tosyl-5,5-dicarboxy-2-azabicyclo[2.2.1]heptane.

## a. Decarboxylation in Collidine.

Dicarboxylic acid **6** (0.335 g., 0.0099 mole) was dissolved in 7 ml. of freshly distilled collidine and heated at 160° (external) for 1 hour. The reaction mixture was cooled, diluted with 50 ml. of ether and the ethereal solution was extracted with two 20-ml. portions of *N* sodium hydroxide. The aqueous solution was cooled, acidified to pH 1 with concentrated hydrochloric acid and the precipitate was collected and dried to afford a mixture of acids **8a** and **8b**, 0.230 g. (79% yield), m.p. 137-186°. This product (0.020 g.) was dissolved in methanol and treated with an excess of ethereal diazomethane. The solvent was removed and the product was analyzed by gc (OV-17/s, 245°). The *exo:endo* isomer ratio (**9a:9b**) was 22:78.

## b. Neat Decarboxylation.

Dicarboxylic acid **6** (0.020 g.) was heated at its m.p. (169-170°) for 1 hour and analyzed as the methyl ester as described previously. The isomer ratio **9a:9b** was 28:72.

## c. Decarboxylation in Dimethylformamide.

Dicarboxylic acid **6** (0.100 g.) was dissolved in DMF and heated at 130° for 1 hour. Analysis of the methyl ester as described previously afforded **9a:9b** in a ratio of 20:80.

Methylsulfinylmethyl *N*-Tosyl-2-azabicyclo[2.2.1]hept-5-yl Ketone (**10**).

Methyl ester **9** (11.35 g., 0.04 mole) was dissolved in dry, freshly distilled THF (300 ml.) and added dropwise with stirring to an ice-cold solution of sodium methylsulfinyl carbanion obtained from sodium hydride (6.18 g. of a 50.6% mineral oil dispersion, 0.13 mole sodium hydride), DMSO (85 ml.) and THF (85 ml.) according to the procedure of Corey (15). The mixture was stirred at room temperature for 25 minutes and poured into a mixture of 500 ml. of water and 500 g. of ice. This solution was acidified to pH 5 with 10% hydrochloric acid and thoroughly extracted with chloroform. The chloroform solution was separated, dried (sodium sulfate), and the chloroform was removed to afford 16.40 g. of an oil (This weight was too high for 100% yield; however, this oil was very viscous and it was difficult to remove all the chloroform) which yielded a crystalline product, m.p. 121-142°, from boiling ethanol-petroleum ether (30-60°). Three additional recrystallizations (ethyl acetate-cyclohexane) afforded chromatographically pure **10** [tlc (silica gel, acetone-ethyl acetate, 3:1) revealed two isomers (*exo* and *endo* **10**)], m.p. 144-150°; ir (potassium bromide) 1705 (C=O), 1330 (SO<sub>2</sub>), 1155 (SO<sub>2</sub>), 1060 cm<sup>-1</sup> (S=O); nmr (deuteriochloroform)  $\delta$  7.55 (m, 4), 4.25 (m, 1), 3.82 (m, 2), 2.92 (m, 7), 2.43 (s, 3), 2.03 (m, 2), 1.18 (m, 2).

*Anal.* Calcd. for C<sub>16</sub>H<sub>21</sub>NO<sub>4</sub>S<sub>2</sub>: C, 54.06; H, 5.96; N, 3.94. Found: C, 54.14; H, 5.92; N, 3.73.

Methyl *N*-Tosyl-2-azabicyclo[2.2.1]hept-5-yl Ketone (**11a**, **b**).

The  $\beta$ -ketosulfoxide (**10**) (16.40 g., 0.04 mole) was dissolved in 785 ml. of 10% aqueous THF and treated with aluminum amalgam prepared from 9.99 g. (0.4 mole) of aluminum foil according to the procedure of Corey (15). The mixture was stirred while refluxing for 1 hour after which time tlc (alumina, chloroform) indicated the absence of starting material. The reaction mixture was filtered and the solids were washed with THF. Removal of

the THF afforded an aqueous mixture which was extracted with chloroform. The chloroform was separated, dried (sodium sulfate) and removed *in vacuo* to afford 11.72 g. of product. Recrystallization (ethyl acetate-cyclohexane) afforded ketones **11a, b**, 9.55 g. (89% yield based on the methyl ester, **9**), m.p. 121-148°; *ir* (potassium bromide) 1710 (ketone C=O), 1330 (SO<sub>2</sub>), 1155 cm<sup>-1</sup> (SO<sub>2</sub>). Tlc (silica gel, ether) of **11** gave R<sub>f</sub> values of 0.38 and 0.49 for the isomeric ketones; when employing neutral alumina eluted with ether, the R<sub>f</sub> values were 0.43 and 0.58. Gc (OV-17/s, 235°) revealed two isomers with retention times of 28.30 and 31.95 minutes. The isomer with the shorter retention time constituted 58% of the mixture and the other was 42%. An isomeric mixture (88% of the short-retention-time isomer) of **11** (0.846 g.) was chromatographed (silica gel, ether-petroleum ether, 30-60°) three times to afford 0.028 g. of a mixture of ketones, m.p. 158-160.5°; gc revealed that this was composed of the short-retention-time isomer containing approximately 5% of the long-retention-time isomer. Also obtained from this chromatographic procedure was 0.614 g. of a mixture of ketones, m.p. 121-148°, which was recrystallized (ethyl acetate-cyclohexane) to afford 0.308 g. of a mixture of ketones (**11a**), m.p. 159-161°. This was composed of the short-retention-time isomer contaminated with about 3% of the isomeric ketone; nmr (deuteriochloroform)  $\delta$  7.52 (m, 4), 4.20 (m, 1), 3.10 (d, 2), 2.70 (m, 2), 2.42 (s, 3), 2.13 (s, 3), 1.88 (m, 2), 1.08 (m, 2). *Anal.* Calcd. for C<sub>15</sub>H<sub>19</sub>NO<sub>3</sub>S: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.61; H, 6.50; N, 4.62.

The solvent was removed from the above mother liquor and the residue was recrystallized (ethyl acetate-cyclohexane) three times to afford 0.189 g. of a mixture of ketones (**11**), m.p. 129-146°; nmr (deuteriochloroform)  $\delta$  7.52 (m, 4), 4.22 (m, 1), 3.19 (d, 2), 2.72 (m, 2), 2.42 (s, 3), 2.12 (two s, 3), 2.07-0.95 (m, 4). Gc analysis (OV-210, 235°) indicated this mixture consisted of 66% of the short-retention-time isomer and 34% of the long-retention-time isomer.

Thermodynamic Equilibration of Methyl *exo*- and *endo*-*N*-Tosyl-2-azabicyclo[2.2.1]hept-5-yl Ketone (**11a, b**).

Ketones **11a** (0.025 g., isomer ratio = 97:3) and **11b** (0.025 g., isomer ratio = 66:34) were each dissolved in 4 ml. of *N* methanolic sodium methoxide and the solutions were maintained at 24°. After 60 hours each solution was determined by gc (OV-210, 235°) to have an *exo:endo* ratio of 75:25.

Haloform Reaction of Methyl *exo*- and *endo*-*N*-Tosyl-2-azabicyclo[2.2.1]hept-5-yl Ketone (**11a, b**).

Iodine-potassium iodide solution (18) was added dropwise to an isomeric mixture (*exo:endo* = 84:16) of ketone **11** (0.100 g., 0.0034 mole) in dioxane (5 ml.) and 2 *N* sodium hydroxide (1 ml.) until the reaction mixture was no longer decolorized. This solution was then heated in an oil bath maintained at 60° and the addition of the iodine-potassium iodide solution was continued until decolorization ceased. The total consumption of iodine-potassium iodide solution was 3 ml. An additional 0.1 ml. of 2 *N* sodium hydroxide was added (to discharge the iodine color), the reaction mixture was extracted with chloroform and the chloroform was washed with 10% sodium bisulfite, separated, and dried (magnesium sulfate). Removal of the chloroform afforded 0.064 g. (62% recovery) of the unreacted ketones. Gc (OV-17/s, 245°) afforded an *exo:endo* isomer ratio of 86:14. The aqueous solution from the chloroform extracts was acidified (pH 1) with 10% hydrochloric acid, 5 ml. of 10% sodium bisulfite was added, and the mixture was extracted with chloroform. The chloroform solution was separated, dried (magnesium sulfate), and the chloro-

form removed to afford a mixture of **8a** and **8b** (0.032 g., 32% yield). This was dissolved in methanol and treated with an excess of ethereal diazomethane which, after removal of solvent, afforded a mixture of *exo* and *endo* esters having an *exo:endo* (**9a:9b**) ratio of 90:10.

*exo*- and *endo*-*N*-Tosyl-5-hydroxy-2-azabicyclo[2.2.1]heptane (**13a, b**).

An isomeric mixture (*exo:endo* = 58:42) of **11** (2.93 g., 0.01 mole) and 85% *m*-chloroperoxybenzoic acid (20.30 g., 0.1 mole) was dissolved in 1,2-dichloroethane (250 ml.) and the solution was refluxed for 4 hours. Gc (OV-210, 225°) indicated the presence of two new compounds (**12**) with retention times of 14.50 and 15.25 minutes. The compound with shorter retention time represented 54% of the total. This mixture was washed with 10% sodium bisulfite solution, saturated sodium bicarbonate solution, and dried (magnesium sulfate). The solvent was removed to afford 3.31 g. of an oil which was dissolved in *N* ethanolic potassium hydroxide (25 ml.) and allowed to stand at room temperature for 1 hour. Gc analysis (OV-210, 225°) indicated that hydrolysis was complete by disappearance of the peak corresponding to **12** and the appearance of two new peaks later assigned to **13a** and **13b**, with retention times of 10.5 and 11.0 minutes. The reaction mixture was poured into water (100 ml.) extracted with chloroform, dried (magnesium sulfate), and the solvent removed to afford 1.31 g. of an oil; *ir* (potassium bromide) 3600 (OH), 1730 (ester C=O), 1715 cm<sup>-1</sup> (ketone C=O). Gc (OV-210, 225°) indicated the presence of small amounts of unoxidized ketone (**11**) and unhydrolyzed ester (**12**) as well as the alcohols, **13a** and **13b**, which constituted the bulk of the mixture. The *exo:endo* ratio (**13a:13b**) of the isomeric alcohols was 68:32. This mixture was subjected to column chromatography on neutral alumina eluted first with chloroform to afford 0.27 g. of a mixture of **11** and **12**. Elution with 0.5% methanol-chloroform gave 0.21 g. of the pure **13a** and a second fraction (0.50 g.) of containing **13a:13b** having an isomer ratio of 40:60. The yield of **13a, b** was 0.71 g. (30%).

The pure *exo* alcohol (**13a**) was recrystallized (ether-petroleum ether, 30-60°), m.p. 121-123°;  $[\alpha]_D^{20} + 9.06$  (c 1.17, chloroform); *ir* (chloroform) 3600 (non-bonded OH), 3500 (bonded OH), 1340 (SO<sub>2</sub>), 1160 cm<sup>-1</sup> (SO<sub>2</sub>); nmr (deuteriochloroform)  $\delta$  7.52 (m, 4), 4.07 (m, 2), 2.98 (m, 2), 2.22 (m, 6), 1.28 (m, 3). *Anal.* Calcd. for C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub>S: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.60; H, 6.53; N, 5.11.

The mixture of alcohols (**13a, b**) was chromatographed ten times using the above procedure to obtain 0.06 g. of a 10:90 ratio of **13a:13b** with the rest of the sample eluted as pure **13a**. *endo*-*N*-Tosyl-5-hydroxy-2-azabicyclo[2.2.1]heptane (**13b**).

Jones reagent (26) (0.3 ml.) prepared from chromic anhydride (27.72 g.), sulfuric acid (23 ml.), and enough water to make 100 ml. was added to a cooled solution of **13a** (0.27 g., 0.002 mole) in acetone (10 ml.). This solution was maintained at 0° for 15 minutes and then was diluted with water (50 ml.) and thoroughly extracted with chloroform. The chloroform solution was washed with water, dried (sodium sulfate) and the solvent was removed to afford 0.31 g. of an oil which solidified on standing. Gc (OV-210, 225°) revealed that this solid was a mixture of approximately 16% of **13a** and 84% of a new compound (**14**) with a retention time of 16.75 minutes. Column chromatography (neutral alumina, chloroform) afforded pure **14** (0.19 g.) which was dissolved in dry, freshly distilled THF (20 ml.), and LAH (0.08 g., 0.002 mole) was added. This was refluxed for 3 hours, cooled, and treated with 1 ml. of water, 1 ml. of 10% sodium hydroxide, and finally

with 3 ml. of water. This mixture was filtered, the solids were washed with THF and the filtrate was saturated with sodium chloride, and extracted with chloroform. The chloroform solution was dried (sodium sulfate) and the chloroform was removed to afford 0.11 g. of product. Gc analysis indicated the presence of **13a** and **13b** (7:93). Column chromatography (neutral alumina, chloroform with 0.5% methanol) afforded 0.059 g. of product which was recrystallized (ethyl acetate-cyclohexane) to afford 0.042 g. of **13b** in 99% isomeric purity, m.p. 144-155°; ir (chloroform) 3600 (non-bonded OH), 3500 (bonded OH), 1345 (SO<sub>2</sub>), 1165 cm<sup>-1</sup> (SO<sub>2</sub>); nmr (deuteriochloroform)  $\delta$  7.52 (m, 4), 4.25 (m, 2), 3.72 (d, 1), 3.00 (m, 1), 2.18 (m, 6), 1.25 (m, 3).  
*Anal.* Calcd. for C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub>S: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.44; H, 6.46; N, 5.04.

## REFERENCES

- (1) This investigation was supported by NIH grant GM 09402.
- (2) Previous paper in this series: P. S. Portoghese and D. T. Sepp, *J. Heterocyclic Chem.*, **8**, 531 (1971).
- (3) P. S. Portoghese and A. A. Mikhail, *J. Org. Chem.*, **31**, 1059 (1966).
- (4) P. S. Portoghese, A. A. Mikhail and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968).
- (5) A.-M. Sepulchre, J. Cleophax, J. Hildesheim, and S. D. Gero, *Compt. Rend.*, **268**, 849 (1969).
- (6) J. Cleofax, A.-M. Sepulchre, A. Gaudemer, and S. D. Gero, *ibid.*, **268**, 983 (1969).
- (7) P. S. Portoghese and J. G. Turcotte, *J. Med. Chem.*, **14**, 288 (1971).
- (8) P. S. Portoghese and J. G. Turcotte, *Tetrahedron*, **27**, 961 (1971).
- (9) P. S. Portoghese and V. G. Telang, *ibid.*, **27**, 1823 (1971).
- (10) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, John Wiley and Sons, New York, 1961, p. 191.
- (11) A. C. Cope, E. Ciganek, N. A. LeBel, *J. Am. Chem. Soc.*, **81**, 2799 (1959).
- (12) H. E. Zimmerman and P. S. Mariano, *ibid.*, **90**, 6091 (1968).
- (13) H. E. Zimmerman and T. W. Cutshall, *ibid.*, **80**, 2893 (1958).
- (14) H. E. Zimmerman and H. J. Giallombardo, *ibid.*, **78**, 6259 (1956).
- (15) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).
- (16) J. G. Dinwiddie, Jr. and S. P. McManus, *J. Org. Chem.*, **30**, 766 (1965).
- (17) R. C. Fuson and A. B. Benton, *Chem. Rev.*, **15**, 275 (1934).
- (18) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, p. 137.
- (19) J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **81**, 4088 (1959).
- (20) H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965).
- (21) H. C. Brown, P. Heim, and N. M. Yoon, *ibid.*, **92**, 1637 (1970).
- (22) E. W. C. Wong and C. C. Lee, *Can J. Chem.*, **42**, 1245 (1964).
- (23) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963).
- (24) L. M. Jackman and S. Sternhell, Applications of "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Ed. Pergamon Press, New York, 1969, p. 289.
- (25) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
- (26) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).