33-8; 3-methoxy-1-methylpyridinium ion, 54560-57-5; 1,2,5-trimethylpyrazinium ion, 58091-57-9; 2-benzylisoquinolinium ion, 38602-73-2; 2-benzylphthalazinium ion, 46818-75-1; 3-carbamoyl-1-methylpyrazinium ion, 58091-58-0; nitromethide ion, 18137-96-7; ethanethiolate ion, 20733-13-5.

Supplementary Material Available. Additional NMR data and interpretation (2 pages). Ordering information is given on any current masthead page.

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The Nature of the Carbonium Ion. XII. The *N*-*p*-Toluenesulfonyl-2-aza-5-norbornyl Cation[1a]

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The syntheses of several C_5-substituted *N*-*p*-toluenesulfonyl-2-azabicyclo[2.2.1]heptanes are described. Solvolytic studies carried out on the *exo*- and *endo*-*p*-bromobenzenesulfonates **13** and **16**, respectively, in buffered acetic acid indicate a 10^{-4}–10^{-5}-fold rate retardation for either isomer as compared with the acetolysis rate of its corresponding 2-norbornyl analogue. The **13**:**16** (exo/endo) rate ratio is 5. The endo acetate **15**, formed in a relatively high proportion, and the anticipated exo acetate **9** were primary acetolysis products from both **13** and **16**. A mechanistic interpretation of the results is presented.

In connection with our interest in heterocyclic analogues of the norbornyl skeleton, we commenced a synthetic sequence leading to the incorporation of a nitrogen atom into a two-carbon bridge of the bicyclo[2.2.1]heptane skeleton. We elected to investigate those derivatives which possess functional groups attached to the opposite bridge such that they are separated from the nitrogen atom by a minimum of three carbons. The strong structural resemblance of these derivatives to the analgetic agents meperidine and prodine suggested a potential for physiological activity in a manner originally suggested by Portoghese.[4] In addition, for most dissociation reactions of secondary 2-norbornyl derivatives which lead to carbonium ions, it is uncertain whether the C_6–C_1 σ bond is directly involved in ionization, affording a delocalized cation, or only involved in a subsequent Wagner–Meerwein shift interconverting two localized cations.[5,6] In the case of the 2-sulfonyl-2-aza 5-substituted compound, the proximity of the electron-withdrawing sulfonamide function to the C_3–C_4 ethylene bond (analogous to the C_6–C_1 bond in the 2-substituted carbocyclic compounds) promised to shed light on the electronic requirements for involvement of this bond in cation forming reactions on the opposite two-carbon bridge.

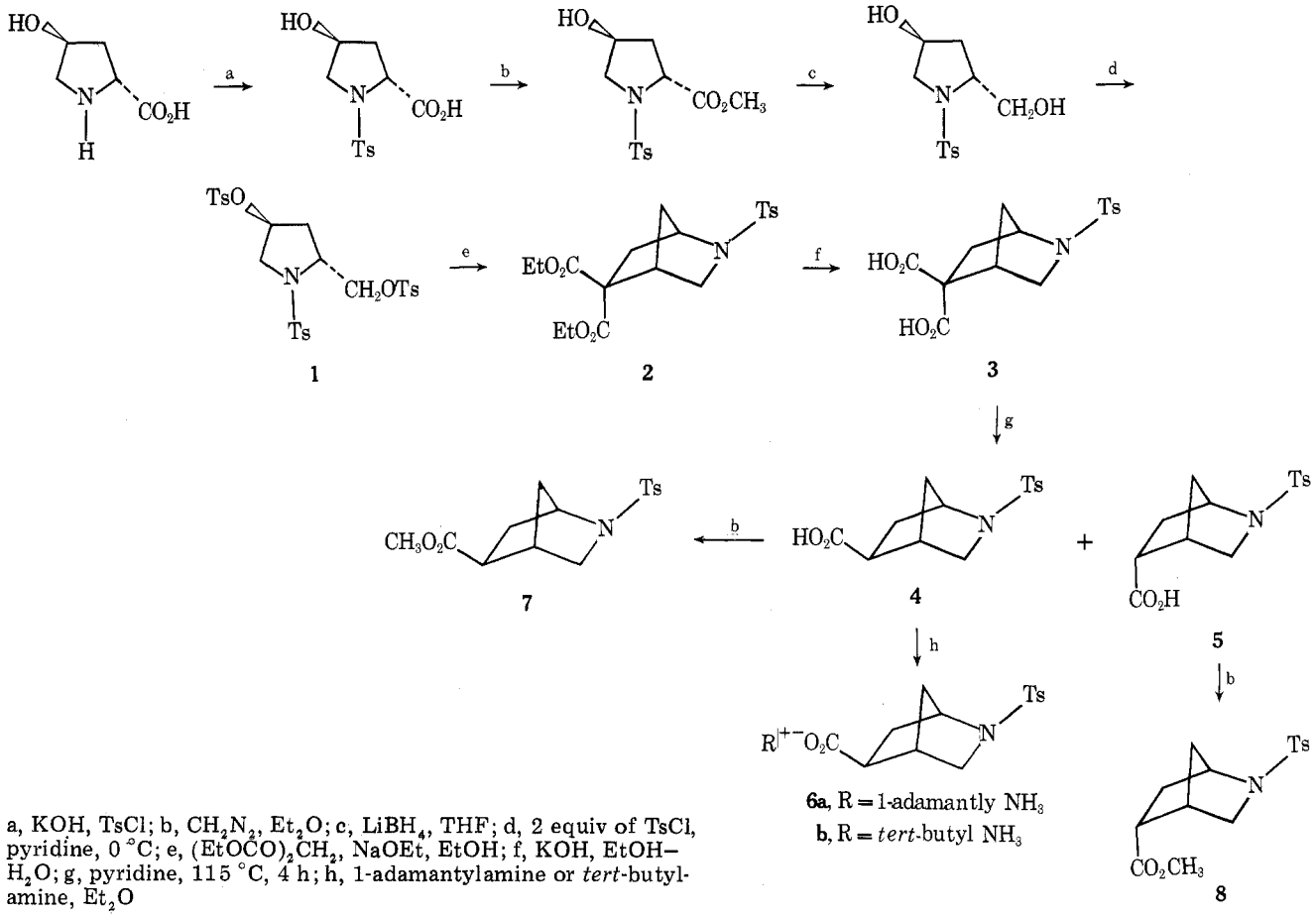
As the syntheses of C_5-substituted 2-azanorbornyl systems are rather complex, only a few derivatives with this substitution pattern have been reported.[4,7]

Results

The *N,O,O'*-tri-*p*-toluenesulfonate ester of hydroxy-L-prolinol (**1**) was prepared by the method of Portoghese[4] and employed as the chief precursor to the 2-azabicyclo-[2.2.1]hept-5-yl derivatives.[8] (See Scheme I.) Reaction of the triarenesulfonate ester **1** with sodiomalonic ester in ethanol or in diglyme effected ring closure to bicyclic diester **2**. Hydrolysis in ethanol or in diglyme afforded the corresponding geminal diacid **3**. The crude diacid was effectively decarboxylated in pyridine at reflux to yield a mixture of the epimeric monoacids **4** and **5**. The acids were shown to be in an endo/exo ratio of 80:20 by GC analysis of their methyl esters. As the endo acid **5** was substantially more hindered than its epimer, a partial purification was achieved by preferential reaction of exo acid **4** with *tert*-butylamine, generating the acid salt **6**. Regeneration of the acid and crystallization from benzene gave pure exo acid **4**. The endo acid **5** was recovered from the mother liquors of the salt forming reaction.

In an attempt to further verify the stereochemical assignments about C_5, the methyl esters **7** and **8** were pre-

Scheme I[a]



a, KOH, TsCl; b, CH_2N_2, Et_2O; c, $LiBH_4$, THF; d, 2 equiv of TsCl, pyridine, 0 °C; e, $(EtOCO)_2CH_2$, NaOEt, EtOH; f, KOH, EtOH–H_2O; g, pyridine, 115 °C, 4 h; h, 1-adamantylamine or *tert*-butylamine, Et_2O

[a] For the sake of clarity in this and subsequent schemes, the structural formulas represent the configuration corresponding to *trans*-hydroxy-D-proline. The compounds actually prepared were derived from hydroxy-L-proline.

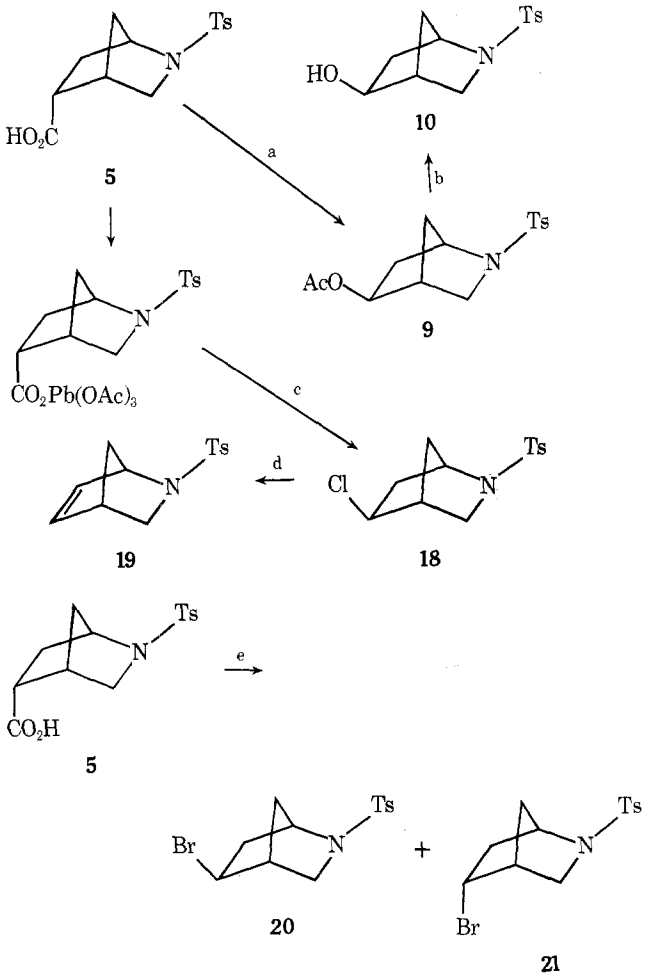
pared from the acid mixture by treatment with diazomethane. By analogy with the documented geometry of the norbornyl skeleton, we felt that steric hindrance by the endo hydrogen atom at C_3 would lead to a predominance of the exo ester upon base-catalyzed equilibration. In actuality, the exclusive formation of exo acid **4** on treatment of the endo methyl ester **8** with aqueous ethanolic potassium hydroxide proved the best support for the epimerization-based deductions leading to stereochemical assignment.

As our interests centered on placing a suitable leaving group at C_5, a pathway leading to replacement of the carboxyl group by a hydroxyl function was begun. Treatment of the endo carboxylic acid **5** with lead tetraacetate in pyridine–benzene solution afforded a mixture of the epimeric acetates **9** and **15**. Although these epimeric acetates possessed identical retention times on GC analysis, a NMR spectrum indicated that less than 10% of endo acetate had formed in the conversion of the endo acid **5** (see Scheme II). Supporting this finding was the observation that when the reaction was run for time periods less than 1 h and rapidly decanted into a 40% hydrochloric acid solution, the exo chloride **18** was the predominant product. No endo chloride was observed within the detection limits of the NMR spectrometer, or of GC analysis.

Elution of the acetate mixture from neutral alumina produced a fraction containing pure exo acetate **9**. Reduction of **9** with lithium aluminum hydride gave the exo alcohol **10** which was ultimately characterized as its *p*-bromobenzenesulfonate ester **13**. (See Scheme III.) Oxidation of exo alcohol **10** with a chromium(VI) oxide–pyridine complex[9] generated the analogous ketone **11**. The endo alcohol **12** was efficiently synthesized by reduction of ketone **11** with lithium aluminum hydride or lithium aluminum tri-*tert*-butoxyhydride. The alcohol was characterized as its acetate and *p*-bromobenzenesulfonate esters, **15** and **16**, respectively. Isotopic labeling, accomplished by reduction of ketone **11** with 99.9% lithium aluminum deuteride, afforded deuterioalcohol **14**, and allowed unequivocal assignment of the exo-C_5 proton signal in the NMR spectrum of endo alcohol **12**.

As an alternative pathway toward generation of a hydroxyl function from the original carboxyl group at C_5, we attempted a synthetic sequence beginning with the stereochemically pure exo carboxylic acid **4**. (See Scheme IV.) This acid was treated with an ethereal solution of methyllithium to give stereospecifically the exo methyl ketone **17**, which was contaminated with some exo *tert*-carbinol. Fractional crystallization from ether gave the pure methyl ketone. Treatment of methyl ketone **17** with *m*-chloroperbenzoic acid in 1,2-dichloroethane afforded only exo acetate **9**. The stereochemical integrity of this ester was established by its reduction with lithium aluminum hydride, or hydrolysis with 1 N ethanolic potassium hydroxide, exclusively to the previously characterized exo alcohol **10**. The exo alcohol obtained in this fashion was homogeneous to GC analysis. Conversion of **10** to its *p*-bromobenzenesulfonate ester **13** was accomplished by teatment with *n*-butyllithium followed by *p*-bromobenzenesulfonyl chloride. Crystallization of this exo ester, and its epimer **16**, from methylene chloride–ether produced the analytically pure samples employed in the acetolysis product studies and kinetic rate determinations subsequently described.

Scheme II



a, $Pb(OAc)_4$, pyridine, benzene; b, $LiAlH_4$, Et_2O; c, 40% HCl; d, K, *t*-BuOH; e, HgO, CCl_4, Br_2

In a further investigation of the stereoselectivity of various functional transformations at C_5, the pure endo acid **5** was treated with mercuric oxide and molecular bromine to give a mixture of epimeric bromides, **20** and **21**.

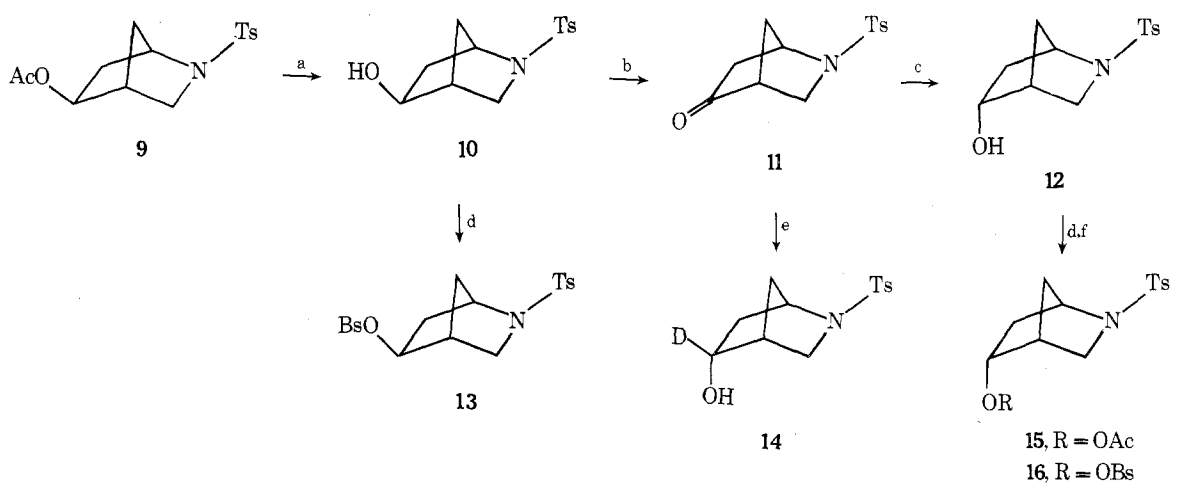
Fractional crystallization from ether separated the isomers. The ether insoluble component failed to react with alcoholic silver nitrate, whereas the isomer obtained from the ethereal mother liquor gave a silver bromide precipitate after several minutes. Similar observations of the epimeric 2-norbornyl bromides had shown that the exo isomer reacted with alcoholic silver nitrate more rapidly than the endo bromide. Our ether soluble bromide was therefore assumed to be the exo isomer **20**. As the ether insoluble bromide failed to react with silver acetate in aqueous acetone even when heated at reflux for 24 h, we assigned it the endo configuration, **21**.

Supporting these assignments were the analyses of the NMR spectra of the two isomers. The bromine in **21** induces a much greater chemical shift differentiation between the endo and exo hydrogen atoms at C_3 than is observed for the exo bromide of **20**. Furthermore, reaction of exo bromide **20** (or exo chloride **18**) with potassium *tert*-butoxide effected a slow dehydrohalogenation to generate olefin **19**. Similar treatment of the endo bromide **21** afforded only uncharacterizable products resulting from fragmentation of the bicyclic ring.

The solvolytic behaviors of the isomeric *p*-bromobenzenesulfonate esters **13** and **16** were studied in sodium acetate buffered acetic acid. Similar studies in unbuffered medium were considered and rejected on the grounds that generation of the strong acid, *p*-bromobenzenesulfonic acid, would tremendously complicate the product and kinetic studies by allowing an unknown amount of protonation of the ring nitrogen during solvolysis. Product studies were carried out at 150 °C for a minimum of 7 half-lives with 0.042 M solutions of the sulfonate esters in the buffered medium. GC analysis of the products derived from acetolysis of the endo ester **16** indicated one major component as 97% of the mixture. The minor component possessed a considerably shorter retention time. By analogy with the preferred 1,3-elimination mode of the norbornyl system, and with consideration for the probable enhanced acidity of the C_3 protons, the minor compound was tentatively assigned an azanortricyclene ring structure.

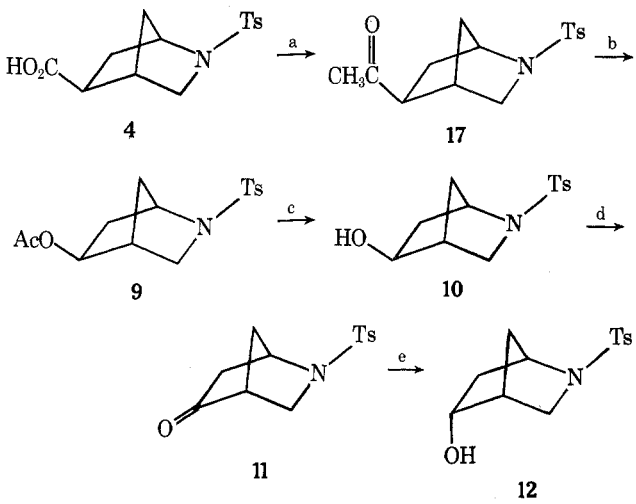
As the retention time of the major component was identical with that of both epimeric exo and endo acetates **9** and **15**, the acetolysis mixture was reduced with lithium aluminum hydride to the corresponding alcohols. GC analysis clearly showed the predominance of the exo alcohol **10** but also indicated a minor incompletely resolved peak with retention time identical with that of authentic endo alcohol **12**. Full resolution of the components was ultimately obtained by conversion of the alcoholic product mixture to

Scheme III



a, $LiAlH_4$, Et_2O; b, CrO_3–2 pyridine, CH_2Cl_2; c, $LiAlH(O\text{-}t\text{-}Bu)_3$, Et_2O; d, BsCl, pyridine, 0 °C; e, $LiAlD_4$, Et_2O; f, Ac_2O, pyridine

Scheme IV



4 17 9 10 11 12

a, CH_3Li, Et_2O, 0 °C; b, *m*-chloroperoxybenzoic acid, CH_2Cl_2; c, $LiAlH_4$, Et_2O; d, CrO_3–2 pyridine, CH_2Cl_2; e, $LiAlH(O\text{-}t\text{-}Bu)_3$

Table I. Rate Data for Sodium Acetate Buffered Acetolyses of Norbornyl *p*-Bromobenzenesulfonates

ROBS	Temp, °C	k, $s^{-1} \times 10^5$	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
13	102	0.14	27.2	−13.2
	146	6.65		
16	146	1.39	24.0	−24.2
	176	8.90		
exo-2-Norbornyl	146	2.2×10^5 [a]	25	
endo-2-Norbornyl	146	1×10^a	26	

[a] Extrapolated from rates at 25 °C.

the trimethylsilyl ethers. The major constituent (80%) of the ether mixture was shown to have the exo configuration by comparison with an authentic sample. The remaining 20% was confirmed as the endo ether.

Acetolysis of *exo*-*p*-bromobenzenesulfonate **13** followed by a similar isolation and analysis procedure indicated the acetate fraction of acetolysis to be composed of 84% exo and 16% endo acetate. The minor nonacetate component (3%) was shown to have a retention time different from that of authentic olefin **19** and so was also assumed to have the azanortricyclene structure. In a control experiment the acetate esters **9** and **15** were shown to be stable to the solvolytic conditions at 150 and 180 °C for 96 h (0.042 M solutions).

Kinetic rates for the acetolyses were determined at 102, 146, and 176 °C. The reactions exhibited linear first-order kinetics over the indicated temperature range. Reaction rates were determined from plots of ln [ROB] vs. time and represent the averages of duplicate experiments. A summary of the averaged kinetic rate data may be found in Table I.

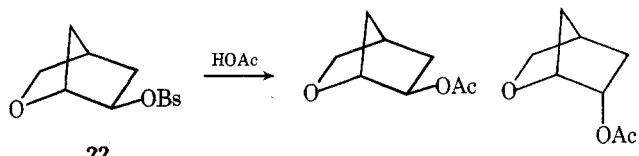
Discussion

In their investigation of the reactions of the optically active 2-norbornylcarboxylic acids with lead tetraacetate, Corey and Casanova[10] suggested that "the most obvious possibilities for the intermediate species are either the radical or the cation or both. However, rearrangement of the norbornyl radical by homolytic scission of the C_6–C_1 bond has been shown to occur only at high temperature (300 °C)"[11] The responsibility for the retention of optical activity observed in production of the exo acetate was thereby relegated to a cationic species. If this is so, the conclusion is significant: all of the norbornyl acetate is derived from a cation, which at least in the case of the optically active product must be nonsymmetrical. The absence of symmetry in this case was attributed to the rapid collapse of an initially formed intimate ion pair, resulting in a greatly shortened ion lifetime.

The oxidative decarboxylation of the 2-aza-endo acid **4** yielded both endo and exo **9** and **15.** This result suggests the presence of a symmetrical intermediate,[12] and in this case a localized cation is at least implicated in part. The most interesting feature of this ion is its unusual ability to accept nucleophilic attack at the endo face of the norbornyl skeleton.

This unusual quality of the *N*-*p*-toluenesulfonyl-2-azanorbornyl cation(s) was further shown in the acetolyses of the *p*-bromobenzenesulfonate esters **13** and **16** where both esters yielded a mixture of acetate epimers as the chief product. Interestingly, the endo acetate **15** was found to be present as 16% of the product acetates from **13** and 20% of the acetates from **16.** The formation of these relatively large amounts of endo acetate must be contrasted with the acetolyses of the 2-norbornyl *p*-bromobenzenesulfonates in which essentially no endo acetate was observed.

Nevertheless the observation of endo product from acetolyses of norbornyl esters is not without precedent. In an acetolysis study of *exo*-2-oxabicyclo[2.2.1]hept-6-yl *p*-bromobenzenesulfonate (**22**), Fayter and Spurlock[3] reported the formation of endo acetate **23** as 0.4% of the acetate products. The epimeric endo sulfonate ester afforded a slightly higher propotion of **23.** The authors have suggested that coordination of the oxygen atom in the ring with the solvent facilitates delivery of acetate to the endo face.



22 23

More recently, Gassman et al.[13] have described the syntheses and solvolytic properties of the epimeric 7,7′-dimethoxybicyclo[2.2.1]hept-2-yl *p*-toluenesulfonates. Their observation of endo product from solvolysis of the exo ester, in addition to a rate retardation of this compound as compared with its unsubstituted analogue, suggests an inefficient assistance to ionization and formation of an ion with the charge localized at C_2. On the basis of these observations the authors conclude that "substituents in the 1 or 7 positions with electron withdrawing power greater than two methoxy groups will not yield ions in which the charge will be localized in the 1 position in the transition state for ionization . . ." As we will presently reconfirm, substituents on the 6 position may be added to this statement.

Clearly, a major difference between the *N*-toluenesulfonyl-2-azabicyclo[2.2.1]heptyl skeleton and the carbocyclic 2-norbornyl one is the lessened electron density at C_3 brought on by the presence of the sulfonamide group. A rough approximation of the rate differential caused by introduction of a sulfonamide function γ to a solvolytic center in a carbocyclic molecule is 7.5.[14] Whether the inductive effect of the sulfonamide is sufficient in the case of *exo*-*p*-bromobenzenesulfonate **13** to completely quench C_3–C_4 σ-bond assistance to ionization is not clear, but the rate difference of 3×10^5 between **13** and its *exo*-2-norbornyl counterpart strongly suggests this possibility. It is at least

certain that the effect transmitted from the γ substituent to C_5 does not lead to an appreciable exo/endo rate ratio.

The ground state energy for *endo*-2-norbornanol is known to exceed that observed fo *exo*-2-norbornanol by approximately 1 kcal/mol.[15] A similar energy barrier assumed for the related sulfonate esters would allow the prediction that ionization of the endo ester should occur more rapidly than that of its exo isomer by about sixfold. In light of the actual exo/endo rate ratio at 25 °C of ~350 it has been speculated that to some degree decelerative effects must therefore operate more effectively on the transition state for solvolysis of the endo sulfonate ester than on that of the exo. To explain part of the discrepancy between prediction and observation, Sargent has argued that either steric factors more effectively inhibit dissociation of the endo ester or that solvolysis of the endo material is hindered by torsional interactions which lead to a transition state of higher energy than that from the exo ester, or that a combination of effects is operative.

Similar arguments can be advanced, in a somewhat less ambiguous example, to explain the exo/endo rate ratio of approximately 5 observed for the acetolyses of the *N*-*p*-toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl *p*-bromobenzenesulfonates, **13** and **16**. In this case, apparent means by which the solvolytic rate for exo ester **13** can be accelerated are absent, other than the distinct possibility of solvent assisted ionization.[17] This fact and the observation of a 7×10^3 fold rate retardation of **16** when compared to its *endo*-2-norbornyl analogue lead to the conclusion that a greater increase in nonbonded strain during passage from the endo ground state to its transition state must be at least partially responsible for the observed small, but positive, exo/endo rate ratio.

In summary, several facts are obtainable from the synthetic and solvolytic results. First, based on the results of equilibration studies, substituents at the exo position of C_5 are thermodynamically favored over their endo counterparts; second, removal of a carboxyl group from C_5 by either a carbonium ion generating reaction (lead tetraacetate) or radical reaction (mercuric oxide, bromine) gives a mixture of exo and endo products; third, the formation of relatively large quantities of endo acetate **15** from acetolyses of either *p*-bromobenzenesulfonate **13** or **16** suggests a localized ion at C_5 as the major product forming species; fourth, the large rate retardation (10^{-5}–10^{-4}) for acetolysis of either sulfonate ester, relative to its carbocyclic norbornyl analogue, indicates a profound detrimental inductive influence on ionization by the γ-sulfonamide group and in the endo case suggests detrimental influences of nonbonded interactions on ionization of **16**; fifth, the relatively small, but not inverse, exo/endo rate ratio for acetolyses of **13** and **16** indicates that while assistance to ionization may be mainly responsible for large exo/endo rate ratios observed in other norbornyl acetolyses, it is not the only reason for more rapid reactions by the exo compounds; sixth, and finally, the large negative entropies of activation for acetolyses of **13** and **16** imply much demand for solvent participation in the transition states to ionization of both esters.

Experimental Section[18]

***N,O,O*^{1}-Tri-*p*-toluenesulfonylhydroxy-L-prolinol (1).** The tri-*p*-toluenesulfonate **1** was prepared from hydroxy-L-proline according to the procedure of Portoghese[4] in 85% yield, mp 132–135 °C (lit.[4] mp 134.5–136 °C).

***N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-5,5-dioic Acid (3).** To 100 ml of absolute ethanol at reflux was added 4.14 g (0.18 g-atom) of sodium metal under an atmosphere of nitrogen. Upon complete reaction of the sodium, 36 g (0.225 mol) of diethyl malonate in 75 ml of ethanol was added dropwise. After 0.5 h this sodiomalonic ester was transferred to a dropping funnel and added to 25.8 g (0.045 mol) of **1** in 650 ml of ethanol at reflux. The reaction mixture was stirred for 7 h at reflux and then for 13 h at room temperature. The precipitate of sodium *p*-toluenesulfonate was removed by filtration and the filtrate diluted with 400 ml of water and concentrated under vacuum. The concentrate was saturated with sodium chloride and continuously extracted with ether to yield 15.5 g (88%) of crude diester. This material was employed without further purification. To 15.5 g (0.039 mol) of the diester in 350 ml of 80% ethanol was added 13.4 g (0.236 mol) of potassium hydroxide. The reaction mixture was heated at reflux for 10.5 h and continuously extracted with ether to yield 9.5 g of reddish oil which could be induced to crystallize after trituration with 30–60 °C petroleum ether. Recrystallization of the solid from the same solvent afforded colorless crystals: mp 168.5–170.5 °C; ir (mull) 2900–2500, 1720, 1350, 1250, 1160, 1080, 1030, 820, and 665 cm^{-1}.

***N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-5-carboxylic Acids (4 and 5).** A 9.5-g (0.028 mol) sample of crude diacid **3** was heated at reflux in 40 ml of pyridine. Evolution of carbon dioxide was observed by trapping the escaping gas in an aqueous barium hydroxide solution. After 3 h gas evolution had ceased and the reaction mixture was basified with 1 N sodium hydroxide and extracted with ether. Separation of the aqueous layer was followed by its acidification with 10% hydrochloric acid solution and subsequent extraction with ether. The extracts were dried with magnesium sulfate, filtered, and concentrated to give 4.2 g (51%) of the crude epimeric monoacids. The oily mixture was redissolved in ether and reacted with an ethereal solution of *tert*-butylamine. The precipitated salt was separated by filtration. The firtrate was acidified with 10% hydrochloric acid and extracted with ether, producing a yellow oil whose infrared spectrum suggested the predominant presence of one isomer. This was tentatively assigned the endo configuration **5**. The oil subsequently solidified and several recrystallizations from benzene afforded pure endo acid **5** as white crystals: mp 189.5–191.0 °C (lit.[8] mp 188–190 °C); NMR ($CDCl_3$) τ 1.0 (1 H, br s), 2.45 (4 H, A_2B_2), 5.70 (1 H, m), 6.75–7.30 (4 H, complex m), 7.55 (3 H, s), 7.80–8.90 (4 H, complex m).

The *tert*-butylamine salt was dissolved in water and acidified with 10% hydrochloric acid. Extraction with ether followed by drying and concentration of the solution afforded 0.9 g of a light brown solid whose infrared spectrum was different from that of the solid obtained previously. Four recrystallizations of this exo acid **4** from benzene–ether gave white needles, mp 138.5–140 °C. The exo epimer was characterized as its 1-adamantylamine salt **6**, a white solid with mp 212–215 °C dec. The pure exo acid could be regenerated from the adamantyl salt with concentrated acid: ir (mull) 3600–3000, 3050, 2900–2300, 1695, 1340, 1155, 820, and 685 cm^{-1}; NMR ($CDCl_3$) τ 1.50 (1 H, br s), 2.50 (4 H, A_2B_2), 5.7 (1 H, br m), 6.75–6.90 (2 H, m), 7.20 (1 H, br m), 7.40–7.60 (1 H, m), 7.60 (3 H, s), 7.80–9.19 (4 H, br m).

Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.87; H, 5.93; N, 4.48.

Methyl *N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-*exo*-5-carboxylate (7). To 10 mg (0.03 mmol) of the exo acid **4** in 2 ml of methylene chloride was added an ethereal solution of diazomethane (generated from Diazald) until the evolution of nitrogen ceased and the pale yellow color of diazomethane persisted. On concentration of the solution a fluffy white solid resulted: mp 148.5–149 °C; ir (CH_2Cl_2) 3060, 2950, 2900, 1740, 1600, 1440, 1350, 1220, 1100, 810, and 660 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.80 (4 H, A_2B_2), 5.70–5.90 (1 H, br m), 6.40 (3 H, s), 6.85–6.95 (2 H, m), 7.15–7.50 (2 H, m), 7.60 (3 H, s), 7.80–8.20 (2 H, m), 8.40–9.15 (2 H, complex m).

Methyl *N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-*endo*-5-carboxylate (8). A 10-mg (0.03 mmol) sample of the pure endo acid **5** was treated with diazomethane as described previously, affording the endo ester **8** as a pale yellow oil which could not be induced to solidify: ir (CH_2Cl_2) 3060, 2950, 2900, 1740, 1600, 1440, 1350, 1220, 1160, 1100, 2950, 2900, 1740, 1600, 1440, 1350, 1220, 1160, 1100, 810, and 660 cm^{-1}; NMR ($CDCl_3$) τ 2.15–2.70 (4 H, A_2B_2), 5.50–5.85 (1 H, br m), 6.35 (3 H, s), 6.70–6.85 (2 H, m), 6.90–7.30 (2 H, m), 7.60 (3 H, s), 7.80–8.10 (2 H, br m), 8.45–9.0 (3 H, m).

***exo*- and *endo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]-hept-5-yl Acetates (9 and 15).** To 17.5 g (0.05 mol) of endo acid **5** in a mixture of 300 ml of anhydrous benzene and 60 ml of pyridine under nitrogen was added 60 g (130 mmol) of lead tetraacetate which had been recrystallized from acetic acid and stored under vacuum. The solution was heated at reflux for 9 h. Work-up was accomplished by filtration through a bed of Celite 503 and succes-

sive washings of the filtrate with 500 ml of a 10% hydrochloric acid solution, 250 ml of 10% sodium hydroxide solution, and 500 ml of water. The solution was dried with magnesium sulfate, filtered, and concentrated to yield 5.5 g (35%) of a bicyclic acetate mixture contaminated with an unidentified material. The acetate mixture was triturated with *n*-pentane to remove the contaminant and used directly in the succeeding reaction: ir (film) 2950, 1740, 1600, 1500, 1340, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–3.10 (4 H, A_2B_2), 5.20–5.35 (1 H, br m), 5.90 (1 H, br s), 6.70–7.10 (2 H, br m), 7.10 (4 H, m), 8.10 (3 H, s), 8.50–9.20 (2 H, m).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptan-5-ol (10).** To 0.8 g (21 mmol) of lithium aluminum hydride in 30 ml of anhydrous ether was added 5.5 g (17 mmol) of the crude exo acetate mixture (from above) in 20 ml of anhydrous ether. The reaction mixture was stirred at room temperatue for 3 h. Work-up was accomplished by addition of 0.5 ml of water, followed by 2.5 ml of 15% potassium hydroxide solution and an additional 1 ml of water. The white salts were removed by filtration and the filtrate dried with magnesium sulfate and concentrated to yield 2.5 g (55%) of a yellow oil. A 750-mg sample of the crude alcohol mixture was chromatographed on 8 g of neutral alumina. Elution with ether gave pure exo alcohol **10** as a white, waxy solid: mp 120.5–122.5 ° C (lit.[8] mp 120–122 °C); ir (film) 3600–3450, 2950, 1600, 1500, 1340, 1300, 1160, 1090, 1040, and 820 cm^{-1}; NMR ($CDCl_3$) τ 2.30–2.80 (4 H, A_2B_2), 5.95 (1 H, br m), 6.50 (3 H, m), 6.80–7.20 (2 H, m), 7.70 (3 H, s), 8.00–9.20 (4 H, m).

***N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptan-5-one (11).** To the complex formed from the reaction of 2.69 g (0.027 mol) of chromium trioxide and 6 ml of pyridine in 60 ml of methylene chloride was added 1.2 g (4.5 mmol) of the exo alcohol **10** in 6 ml of methylene chloride. The reaction mixture was stirred overnight at room temperature and then terminated with successive washes of 250 ml of 10% hydrochloric acid solution, 250 ml of 10% sodium hydroxide solution, and 200 ml of water. The methylene chloride solution was dried with magnesium sulfate and concentrated to yield 0.91 g (83%) of the ketone as a pale oil which failed to solidify on standing: ir (film) 2950, 1750, 1600, 1500, 1340, 1160, 1100, 820, and 700 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.80 (4 H, A_2B_2), 5.50 (1 H, br m), 6.75–7.20 (3 H, m), 7.60 (3 H, s), 7.80–9.20 (4 H, br m).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl *p*-Bromobenzenesulfonate (13).** To 1.0 g (3.7 mmol) of the exo alcohol **10** in 15 ml of anhydrous ether at 0 °C was added 2.5 ml of a 1.6 M *n*-butyllithium solution in hexane. After stirring for 0.5 h, the alkoxide salt had precipitated. A solution of 1.1 g (4.1 mmol) of *p*-bromobenzenesulfonyl chloride in 10 ml of tetrahydrofuran was then added. The reaction mixture was maintained at 6 °C for 10 h and then decanted into 50 ml of water. The organic phase was collected, dried with magnesium sulfate, and concentrated to yield 1.82 g of yellow oil. The crude residue was chromatographed on 15 g of Florisil and eluted with 90:10 ether–chloroform. Crystallization from ether afforded a white solid: mp 156–158 °C dec; ir (mull) 3100, 2960, 1600, 1570, 1500, 1380, 1340, 1200, 1160, and 820 cm^{-1}; NMR ($CDCl_3$) τ 2.10–2.80 (4 H, A_2B_2), 2.25 (4 H, s), 4.70–5.50 (1 H, br m), 5.85 (1 H, br m), 6.30–6.50 (1 H, d), 6.70–7.40 (2 H, m), 7.60 (3 H, s), 7.85–9.20 (4 H, m).

Anal. Calcd for $C_{19}H_{20}S_2O_5NBr$: C, 46.93; H, 4.11; N, 2.97. Found: C, 46.84; H, 4.39; N, 2.72.

***endo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptan-5-ol (12).** To 50 mg (1.3 mmol) of lithium aluminum hydride stirring in 10 ml of ether was added 30 mg (1.14 mmol) of ketone **11** in 4 ml of ether. The reaction mixture was stirred at room temperature for 10 h. Treatment with 4 drops of water and 6 drops of 15% potassium hydroxide solution gave a white precipitate which was removed by filtration. The filtrate was dried and concentrated, producing endo alcohol **12** as a white solid: mp 144–148 °C (lit.[8] mp 146–149 °C); ir (film) 3600, 3450, 2950, 1600, 1500, 1340, 1160, 920, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.80 (4 H, A_2B_2), 5.55–6.10 (2 H, br m), 6.25–6.40 (1 H, d), 6.70–7.20 (3 H, br m), 7.60 (3 H, s), 7.80–9.20 (4 H, br m).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl *p*-Bromobenzenesulfonate (16).** To 1.42 g (5.3 mmol) of endo alcohol **12** in 10 ml of ether at 0 °C was added 4.3 ml (6.9 mmol) of a 1.6 M *n*-butyllithium solution. A white precipitate developed after 15 min and the reaction was maintained at 0 °C for 0.5 h. A solution of 1.48 g (5.0 mmol) of *p*-bromobenzenesulfonyl chloride in 10 ml of ether was then added. The reaction mixture was stored at 6 °C overnight and then decanted into 50 ml of ice water. The organic phase was separated, dried, and concentrated to give 1.9 g (73%) of **16** as a white solid: mp 142–144.5 °C; ir (mull) 3100, 2950, 1600, 1570, 1500, 1470, 1360, 1340, 1200, and 820 cm^{-1}; NMR ($CDCl_3$) τ 2.15–2.75 (4 H, A_2B_2), 2.25 (4 H, s), 4.90–5.25 (1 H, br m), 5.80 (1 H, br m), 6.20–7.00 (2 H, m), 7.25 (1 H, br m), 7.60 (3 H, s), 7.80–9.10 (4 H, br m).

Anal. Calcd for $C_{19}H_{20}S_2O_5NBr$: C, 46.93; H, 4.11; N, 2.87. Found: C, 46.76; H, 4.13; N, 2.89.

***exo*- and *endo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]-hept-5-yl Bromides (20 and 21).** To 460 mg (1.55 mmol) of endo acid **5** and 760 mg (3.50 mmol) of red mercuric oxide in 30 ml of carbon tetrachloride at reflux was added 610 mg (3.8 mmol) of molecular bromine. After stirring for 24 h in the dark, the solution was decanted into an iced 10% potassium hydroxide solution. The organic layer was separated and dried. Concentration in vacuo gave a yellow oil which on trituration with ether proved to be partially soluble. The solid insoluble material was recrystallized from methylene chloride to give 210 mg (42%) of endo bromide **21** as a white solid: mp 170.5–171.5 °C; ir (CH_2Cl_2) 2950, 1600, 1500, 1340, 1300, 1150, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.75 (4 H, A_2B_2), 5.50–6.00 (2 H, m), 6.15–6.35 (2 H, d), 6.65–7.95 (1 H, d), 7.30 (1 H, br m), 7.60 (3 H, s), 7.80–8.85 (3 H, m). The ether-soluble component was isolated by concentration of the solution to give 10 mg of exo bromide **20** as a colorless oil which could not be induced to crystallize: ir (film) 2980, 1600, 1500, 1340, 1160, 1100, 810, 705, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.75 (4 H, A_2B_2), 5.60–6.15 (2 H, br m), 6.70–6.85 (2 H, m), 7.10–7.30 (1 H, br m), 7.60 (3 H, s), 7.70–9.10 (4 H, m).

***N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-ene (19).** To 420 mg (1.3 mmol) of exo bromide **20** in 4 ml of *tert*-butyl alcohol at reflux was added 430 mg (3.8 mmol) of potassium *tert*-butoxide in 5 ml of *tert*-butyl alcohol. After 24 h, the reaction mixture was decanted into ice water and extracted with two 20-ml portions of ether. The combined extracts were dried and concentrated to give 110 mg (36%) of pure olefin **19** as a colorless oil: ir (film) 3050, 2900, 1600, 1340, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.15–2.75 (4 H, A_2B_2), 3.80–4.10 (2 H, m), 5.20–5.35 (1 H, br m), 6.55–6.75 (1 H, dd), 6.75–6.85 (1 H, br m), 7.35–7.55 (1 H, d), 7.60 (3 H, s), 8.55–8.70 (1 H, br s), 8.70 (1 H, br s).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl Chloride (18).** To 5.1 g (17 mmol) of an 80:20 mixture of acids **5** and **4**, respectively, in 10 ml of pyridine and 75 ml of benzene was added 17.1 g (3.8 mmol) of lead tetraacetate. The solution was heated at reflux for 2 h and then decanted into a 40% hydrochloric acid solution. The benzene fraction was washed with saturated sodium bicarbonate solution until neutral and dried with magnesium sulfate. Concentration of the extract afforded 1.9 g (39%) of **18** as a white solid: mp 93.5–95.5 °C; ir (CH_2Cl_2) 3000, 2950, 1600, 1500, 1350, 1160, 1100, and 820 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.75 (4 H, A_2B_2), 5.8–5.95 (1 H, br m), 5.80–6.10 (1 H, br m), 6.80–7.00 (2 H, m), 7.25–7.55 (1 H, br m), 7.60 (3 H, s), 7.70–9.30 (4 H, br m).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-5-carboxylic Acid (4) via Epimerization.** To a solution of 17.8 g (0.33 mol) of sodium methoxide in anhydrous methanol was added 10 g (33 mmol) of an 80:20 mixture of endo and exo methyl esters **8** and **7**. The solution was heated at reflux for 48 h, quenched with water, and concentrated in vacuo. The residue was treated with ether to remove residual ester (1.1 g). The ether-insoluble fraction was acidified with 10% hydrochloric acid solution and extracted with ether. The organic fraction was dried and concentrated to give 7.5 g (84%) of a white solid which was spectroscopically identical with the authentic exo carboxylic acid **4**, mp 138.5–140 °C.

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl Methyl Ketone (17).** To a vigorously stirred solution of 2.62 g (8.8 mmol) of pure exo acid **4** in 150 ml of anhydrous ether under nitrogen at 0 °C was added 9.7 ml (17.6 mmol) of a solution of methyllithium (1.8 M) in ether. During addition the reaction mixture was allowed to slowly warm to room temperature. After 2 h the reaction was quenched with 5 ml of water and 20 ml of 15% hydrochloric acid solution. The ether layer was separated, dried, and concentrated in vacuo to yield 1.85 g of exo methyl ketone **17** contaminated with the *tert*-carbinol. The residue was taken up in ether and *n*-pentane added until a yellow oil was completely deposited. This insoluble material was isolated and shown to be the exo *tert*-carbinol: ir (film) 3600–3300, 2950, 2880, 1600, 1500, 1340, 1160, 1100, 1060, and 690 cm^{-1}. The ether–pentane solution was concentrated to produce the exo methyl ketone **17** as a colorless oil which solidified on standing: mp 158–162 °C (GC analysis suggested that the ketone was 99% pure; therefore no further purification was attempted); ir (film) 2950, 2880, 1710, 1600, 1500, 1340, 1160, 1100, 760, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.75 (4 H, A_2B_2), 5.80 (1 H, m), 6.90 (2 H, m), 7.30 (2 H, br m), 7.60 (3 H, s), 7.85 (3 H, s), 8.00–8.30 (2 H, m), 7.80–9.20 (2 H, m).

***exo*-N-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl Acetate (9).** To 6.0 g (29 mmol) of *m*-chloroperbenzoic acid in 200 ml of methylene chloride was added 1.60 g (5.4 mmol) of **17** in 20 ml of methylene chloride. The reaction was heated at reflux for 24 h, cooled to room temperature, and terminated by addition of 40 ml of 20% sodium sulfite solution. After 2 h a test for the peracid with starch–iodide paper proved negative. The reaction mixture was then concentrated in vacuo. The residue was twice extracted with 50-ml portions of ether, and the combined extracts were dried with magnesium sulfate. Concentration of the solution yielded 1.3 g of crude exo acetate **9** which solidified on standing. Crystallization from ether–pentane afforded **9** as a white solid, mp 122–123.5 °C. This acetate was converted to its corresponding alcohol **10** by treatment with lithium aluminum hydride. The exo alcohol **10** obtained in this fashion appeared to be free of its endo epimer **12** when subjected to GC analysis.

Trimethylsilylation of Alcohols 10 and 12. To approximately 10 mg of either alcohol in a one-dram vial fitted with a micro magnetic stirring bar was added 1 ml of a silylating mixture composed of 10 parts pyridine, 2 parts hexamethyldisilazane, and 1 part trimethylsilyl chloride. The mixture was capped and stirred for 12 h, decanted into 30 ml of ice water, and extracted with 30 ml of ether. The ether extract was successively washed with cold 10% hydrochloric acid solution, saturated sodium bicarbonate solution, and water. The solution was then dried and concentrated to give the silyl ether samples employed for GC comparison. The authentic exo silyl ether exhibited a retention time of 3.6 min, whereas the endo epimer possessed a retention time of 4.2 min at 285 °C, 32 psi.

***endo*-N-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl Acetate (15).** To 29 g (1 mmol) of **12** stirring in 5 ml of pyridine (63 mmol) was added 12 ml (130 mmol) of acetic anhydride. The reaction mixture was stirred at 115 °C for 4 h, cooled, and decanted into 100 ml of iced 10% hydrochloric acid solution and extracted with ether. The organic solution was neutralized with sodium bicarbonate solution, dried, and concentrated to give 150 mg of **15** as a pale yellow oil: NMR analysis of the product revealed no epimeric exo acetate **9** accompanying **15**; ir (film) 2950, 1740, 1600, 1500, 1340, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.80 (4 H, A_2B_2), 4.80–5.20 (1 H, complex m), 5.90 (1 H, broad m), 6.30–6.50 (1 H, m), 6.80–7.10 (1 H, dq), 7.30 (1 H, broad m), 7.65 (3 H, s), 7.70–8.10 (2 H, complex m), 8.10 (3 H, s), 8.40–9.30 (2 H, m).

***endo*-N-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptan-5-ol-*exo*-5-*d* (14).** To 100 mg (2.6 mmol) of lithium aluminum deuteride in 10 ml of anhydrous ether was added 60 mg (0.22 mmol) of ketone **11** in 1 ml of anhydrous ether. The reaction mixture was stirred overnight at room temperature and reaction was terminated with 5 drops of water and 0.5 ml of a 15% potassium hydroxide solution. After 1 h the white salts were separated by filtration and washed twice with 10-ml portions of ether. The combined extracts were dried and concentrated to yield 45 mg (70%) of the deuterated alcohol **14**: ir (film) 3600–3200, 2950, 1600, 1500, 1340, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.95 (4 H, A_2B_2), 5.90–6.10 (1 H, broad m), 6.25–6.45 (1 H, m), 6.90–7.25 (1 H, m), 7.10 (1 H, s), 7.30 (1 H, m), 7.60–9.10 (4 H, complex m).

Acetolysis Product Studies. A 230-mg sample (0.47 mmol) of the analytically pure *endo*-*p*-bromobenzenesulfonate ester **16** and a 85-mg sample (0.17 mmol) of pure exo ester **13** were dissolved in 11 and 4 ml, respectively, of 0.085 N sodium acetate in acetic acid containing 1% by weight acetic anhydride. The solutions were sealed under nitrogen in Carius combustion tubes and heated at 150 °C for approximately 8 half-lives in an isothermal bath. The tubes were then cooled and opened and the contents decanted into 100 ml of ice water. The solutions were extracted with three 30-ml portions of ether, and the combined extracts neutralized with a saturated solution of sodium bicarbonate. The solutions were then dried and concentrated to give the samples of crude acetolysate.

A sample of the acetolysis mixture from **16** was subjected to GC analysis at 285 °C and 32 psi. One major component (97%) was noted in the product mixture. The retention time (5 min) was identical with that of both acetates **9** and **15**. A 50-mg (0.1 mmol) sample of the acetolysis residue was therefore added to 0.2 g (5.2 mmol) of lithium aluminum hydride in 30 ml of ethyl ether. The reaction mixture was stirred for 2 h and subsequently worked up with aqueous 15% sodium hydroxide solution. Concentration of the resulting ether solution afforded 35 mg of alcohol mixture. GC analysis under the aforementioned conditions indicated the predominant presence of the exo alcohol **10** along with an incompletely resolved peak having a retention time (4.7 min) similar to that of the epimeric endo alcohol **12**. Trimethylsilylation of the alcohol mixture in the manner previously described afforded 30 mg of the trimethylsilyl ethers. GC analysis of the silyl ethers indicated a product mixture consisting of 20.4% of endo ether and 79.6% of the exo ether.

GC analysis of the acetate produce mixture from exo ester **13** likewise indicated only one component with retention time identical with that of **9** and **15**. Reduction of a 30-mg portion of this acetolysate with lithium aluminum hydride, in a manner identical with that described previously, gave 20 mg of alcohol mixture. Trimethylsilylation of this mixture followed by GC analysis indicated a product composition of 83.5% exo ether and 16.5% endo ether.

Kinetic Studies. Kinetic rates for **13** and **16** were measured in buffered solutions of sodium acetate in acetic acid to which 1% acetic anhydride by weight had been added. Determination of the acetate concentration at various time intervals was accomplished by titration with standardized solutions of perchloric acid in acetic acid. All titrations were made with a 5-ml Fisher microburet, precise to 0.01 ml. An approximate 0.2% solution of crystal violet in glacial acetic acid was used as the indicator, with the end point of each titrimetric determination being taken at blue. The constant temperatures for each kinetic run were maintained with a Neslab TEX9-H isothermal bath filled with Dow Corning 200 silicone fluid. Temperatures were measured with a National Bureau of Standards thermometer calibrated to 0.1 °C.

The kinetic determinations were made by the following general procedure. A sample of the *p*-bromobenzenesulfonate was weighed into a 10-ml volumetric flask and diluted to volume with standardized sodium acetate solution. Aliquots (0.5 ml) of this solution were sealed in ampules (Kimble Neutraglas no. 12012-L) and placed in an isothermal bath.

As the acetolysis rates were sufficiently slow, zero time was taken as the time of immersion. At appropriate time intervals the tubes were withdrawn, cooled in ice water, and opened and the contents titrated with a standard perchloric acid solution. The reactions were followed through approximately 3 half-lives.

All first-order rate constants were determined using PLSTSQR, a computer program in APL language, which plots the graph of ln [ROBS] vs. time and determines a best-fit straight line to the valid points by the method of least squares.

Registry No.—**1**, 5234-75-3; **3**, 58267-19-9; **4**, 58267-20-2; **5**, 35320-35-5; **6a**, 58310-78-4; **6b**, 58310-79-5; **7**, 58267-21-3; **8**, 58267-22-4; **9**, 58229-30-4; **10**, 35299-52-6; **11**, 58267-23-5; **12**, 58267-24-6; **13**, 58229-31-5; **14**, 58310-80-8; **15**, 58267-25-7; **16**, 58267-26-8; **17**, 58267-27-9; **18**, 58229-32-6; **19**, 58229-33-7; **20**, 58229-34-8; **21**, 58267-28-0; diethyl malonate, 105-53-3; diazomethane, 334-88-3; lead tetraacetate, 546-67-8; *p*-bromobenzenesulfonyl chloride, 98-58-8; hexamethyldisilazane, 999-97-3; trimethylsilyl chloride, 75-77-4; lithium aluminum deuteride, 14128-54-2.

References and Notes

(1) (a) Presented in part at the 162d National Meeting of the American Chemical Society, Washington, D.C., Sept 1971, Abstracts, No. ORGN-133. (b) Taken in part from the Ph.D. Thesis of R.D. Gleim, Brown University, 1973.
(2) Alfred P. Sloan Fellow, 1973–1975.
(3) See, for example, (a) L. A. Spurlock and R. G. Fayter, *J. Am. Chem. Soc.*, **94**, 2707 (1972); (b) R. J. Schultz, W. H. Staas, and L. A. Spurlock, *J. Org. Chem.*, **38**, 3091 (1973).
(4) See P. S. Portoghese and A. A. Mikhail, *J. Org. Chem.*, **31**, 1059 (1966); P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968); P. S. Portoghese, *ibid.*, **8**, 609 (1965), and references cited therein.
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(16) G. D. Sargent, "Carbonium Ions", Wiley-Interscience, New York, N.Y., 1972, Chapter 24, p 1099.
(17) The relatively large amount of endo acetate **15** formed in acetolysis of *exo-p*-bromobenzenesulfonate **13** suggests that a cationic product forming intermediate does not possess sufficient steric hindrance to preclude approach from the endo face. It is therefore probable that the starting ester **13** is likewise subject, in some measure, to endo-face solvent assistance. Based on simple steric observations, the endo ester **16** should be at least equally, if not more, subject to this type of assistance.
(18) Infrared spectra were determined utilizing a Perkin-Elmer 247 grating infrared spectrometer with sodium chloride optics. Nuclear magnetic resonance spectra were obtained via a Varian Associates A-60A spectrometer; approximately 20% solutions in $CDCl_3$, acetone-d_6, or Me_2SO-d_6 were employed with teramethylsilane as the internal standard. A Perkin-Elmer 881 flame ionization gas chromatograph or a Perkin-Elmer F-11 gas chromatograph employing 20 ft × 0.125 in. columns of 3% OV-210 on Chromosorb W were used in product analyses. Elemental analyses were performed by either the Baron Consulting Co., Orange, Conn., or by Micro-Analysis, Inc., Wilmington, Del.

Synthesis of the Three Isomeric Ortho-Substituted Phenylthienyl Benzoic Acids

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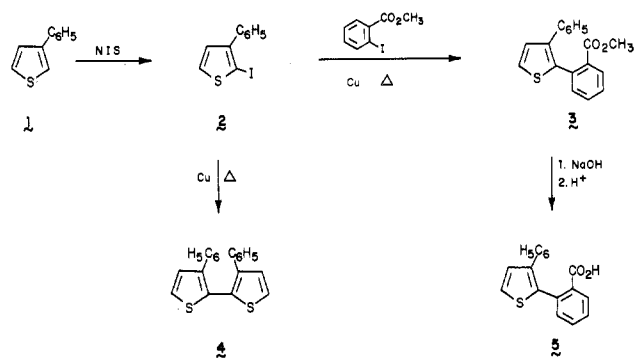
The syntheses of the three isomeric 2-(phenyl-2-thienyl)benzoic acids (**5, 19b, 19d**) are described. 2-(3-Phenyl-2-thienyl)benzoic acid (**5**) was prepared via the Ullmann biaryl synthesis from 2-iodo-3-phenylthiophene (**2**) and methyl 2-iodobenzoate. The 4- and 5-phenyl isomers (**19b, 19d**) were prepared by constructing the benzoic acid moiety by Diels–Alder reaction of butadiene with the acrylate esters (**15b, 15d**), derived from the Knoevenagel reaction of 4- and 5-phenylthiophene-2-carboxaldehydes (**14a, 14b**) with malonic acid. A cyclohexenyl group which is conjugated to the thiophene ring, as in **12a** and **12b**, was dehydrogenated rapidly to a phenyl group with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) whereas an unconjugated cyclohexenyl group, as in **17a** and **17b** was difficult to aromatize by this procedure.

Over the past several years, I have been interested in the synthesis of benzoic acid derivatives which have a heterocyclic substituent in the ortho position and the heteroatom γ to the carboxyl group.[1-4] This paper describes the syntheses of the hitherto unknown 2-(3-, 4-, and 5-phenyl-2-thienyl)benzoic acids (**5, 19b, 19d**) shown in Schemes I and II. The literature syntheses[5-7] of the parent compound, 2-(2-thienyl)benzoic acid, and its methyl ester suggest the Ullmann method as being applicable to the phenyl compounds.

The bromination or iodination of 2- and 3-phenylthiophene[8-10] was the starting point for the new compounds. The synthesis and electrophilic substitutions of these thiophenes has been extensively studied by Gronowitz[10-13] and Wynberg[11,14] and their collaborators. 2-Bromo-5-phenyl- and 2-bromo-3-phenylthiophene are readily obtained in high yield by treating 2- and 3-phenylthiophene, respectively, with NBS,[11,14] and they appeared to be good candidates with which to start the synthesis of **5** and **19d.** Bromination of 3-phenylthiophene in acetic acid[11] gives a difficultly separable mixture of 2-bromo-3-phenyl- and 2-bromo-4-phenylthiophene, in which the former predominates. In acetic acid, 2-bromo-3-phenylthiophene equilibrates with its isomer, and undergoes disproportionation to 3-phenylthiophene and 2,5-dibromo-3-phenylthiophene.[11-14] This did not appear to be a promising method of preparing quantities of 2-bromo-4-phenylthiophene to use as starting material for **19b.**

In Scheme I, attempts to condense 2-bromo-3-phenylthiophene with methyl 2-iodobenzoate using copper powder at 200 °C were unsuccessful. 2-Iodo-3-phenylthiophene (**2**), prepared from 3-phenylthiophene and *N*-iodosuccinimide in 80% yield, was successfully used to give a 45% yield of the desired ester **3** as a distillable oil. As expected in a mixed Ullmann reaction,[15,16] bibenzoic acid ester was

Scheme I



present in the reaction mixture, but 3,3′-diphenyl-2,2′-bithiophene (**4**) was not detected. Structure **4**, a new compound,[17] was prepared separately in 13% yield from **2** by the Ullmann reaction. 2-(3-Phenyl-2-thienyl)benzoic acid (**5**) was obtained in good yield by saponification of ester **3.**

The problems discussed above in preparing sufficient quantities of pure 2-bromo-4-phenylthiophene by the direct bromination of 3-phenylthiophene[11-14] required a different approach to the synthesis of 2-(4-phenyl-2-thienyl)benzoic acid (**19b**). In Scheme II, 4-bromothiophene-2-carboxaldehyde (**6a**), the aluminum chloride catalyzed bromination product of thiophene-2-carboxaldehyde,[18,19] was chosen because it was readily prepared in quantity and had the necessary orientation of functional groups which could be modified to produce **19b** in a sequence of eight steps. The product distribution in this bromination depends upon how well the reaction mixture, which has the consistency of heavy grease, is stirred. In tenth-mole runs good conversion to **6a** was observed, the minor amounts of 4,5-dibromothiophene-2-carboxaldehyde (**7**) being readily