Fall 1995

Part I Synthesis and study of cyclic sulfamates Part II Investigation of endocyclic nucleophilic substitution at tetracoordinate sulfur(VI)

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PART I. SYNTHESIS AND STUDY OF CYCLIC SULFAMATES. PART II. INVESTIGATION OF ENDOCYCLIC NUCLEOPHILIC SUBSTITUTION AT TETRACOORDINATE SULFUR (VI).

BY

MARTIN G. KOCIOLEK
BA, Syracuse University, 1990.

DISSERTATION

Submitted to the University of New Hampshire
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Doctor of Philosophy

in

Chemistry

September, 1995.

This dissertation has been examined and approved.

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July 14/1995
Date

DEDICATION

This thesis is dedicated to Mom, Dad and Tina.

Their love, support and encouragement has meant so much to me throughout the last five years.

ACKNOWLEDGEMENTS

First and foremost, I wish to express my sincere appreciation to Dr. Kenneth K. Andersen, "boss", for his patience, encouragement and insight throughout the past five years. It has been a pleasure to work for and work with him. In the time I spent at UNH I learned so much and matured greatly as a scientist, much of this due to KKA, thanks.

I also wish to thank several faculty members: Dr. Wong, Dr. Jones, Dr. Johnson, Dr. Zercher, Dr. Weisman and Dr. Planalp. Each of these men, at one time or another, contributed to my education and I thank them for that.

I met a great many people in my time at UNH, the most important of which was Tina. A former student who quickly became the love of my life. I don't think she realizes what she has done for me in the time we've been together. Her love and support has meant the world to me. I am not sure how I will repay her, but I'm ready to start trying.

Lastly, I want to thank all the friends I've made in the years I've been here. Unfortunately, I can't name them all, but there are a few I need to mention. A thanks to everyone, past and present, who was a member of the infamous Buckyballs. From the "early years", I wish to thank John K. and Ken D. for their support, advice and most importantly friendship. A special thanks to Craig W., a good friend and colleague. This "experience" was made a little easier by going through each step along with someone, thanks.

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by

Martin G. Kociolek
University of New Hampshire, September, 1995

Part I. 5-Nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide was synthesized and reacted with various nucleophiles. Nitrogen nucleophiles attacked the exocyclic sulfur atom resulting in cleavage of the tosyl group. This is due in part to the acidity of the parent benzoxathiazole ring. A series of substituted *N*-H-1,2,3-benzoxathiazole-2,2-dioxides were synthesized and their pK_a values were determined. An *ab initio* study was also undertaken on a simple sulfamate model in order to determine the origin of the increased acidity of the cyclic sulfamates, compared to their acyclic analogues. It was determined that the increased acidity was directly affected by the conformation of the neighboring heteroatoms. This is primarily due to heteratom-sulfur delocalization. Investigations of the role of *d*-orbitals on the stabilization of the system were inconclusive. An *ab initio* study of the increased acidity of the cyclic compounds compared to their acyclic analogues of sulfamide, methyl sulfonamide and vinyl sulfonamide was undertaken. The sulfamide and methyl sulfonamide models gave results consistent with experimental results, the former showing an increased acidity, the latter

showing no change in acidity. Vinyl sulfonamide gave results contrary to those observed experimentally. The calculation suggested no increase in acidity, although one is observed experimentally.

Part II. The synthesis was undertaken of several compounds capable of endocyclic nucleophilic substitution through a five-membered intermediate or transition state. The synthesis of two amino alcohols was unsuccessful. *N*-methyl-*N*-*p*-toluenesulfonyl-2-phenyl-ethylenediamine was synthesized and treated with *n*-butyllithium and lithium diisopropylamide. In each case, the anticipated rearrangement product was not observed. *N*-*p*-toluenesulfonyl-1,8-naphthosultam was also synthesized and treated with *n*-butyllithium and lithium diisopropylamide. The former resulted in nucleophilic attack of the base and ring opening. The latter resulted in an elimination-addition reaction yielding an undesired sultam. *N*-2-bromobenzyl-1,8-naphthosultam was also synthesized and treated with *n*-butyllithium. The sultam rearranged to a thiazocine through an endocyclic nucleophilic substitution, presumably by way of a five-membered intermediate or transition state, thus providing the first example of a rearrangement through this intermediate.

PART I

SYNTHESIS AND STUDY OF CYCLIC SULFAMATES.

Historical

Cyclic sulfamates.

The differences in reactivity toward nucleophiles of cyclic sulfur (IV) and sulfur (VI) esters and amides compared to their acyclic analogues has been the topic of some interest[1a-f], particularly stimulated by the work of Kaiser[2].

Kaiser showed that some cyclic sulfur (VI) compounds reacted faster than their acyclic analogues. o-Phenylene sulfate (**1**) was shown to hydrolyze 2 x 10^7 faster in base than diphenyl sulfate (**2**). Similarly, sulfonate **3** was shown to react 7 x 10^6 faster than its acyclic counterpart (**4**). In addition, the six-membered cyclic sulfonate **5** was shown to react 10^4 times less rapidly than the five-membered compound.

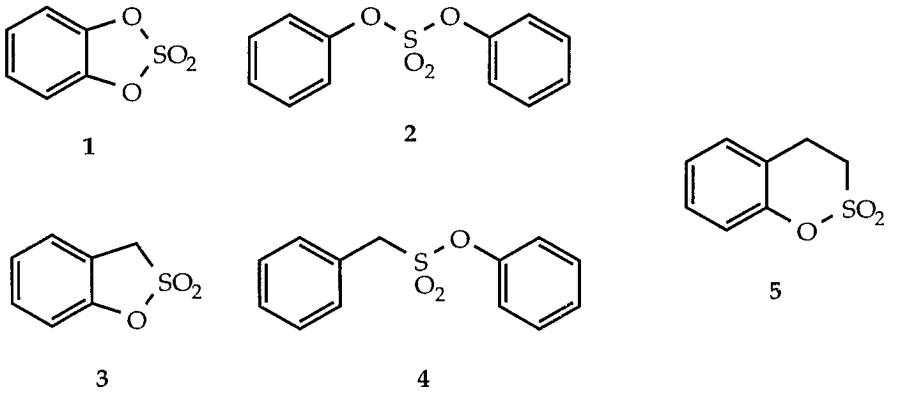
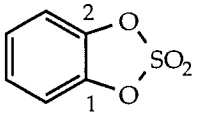


Figure 1. Cylic sulfur esters studied by Kaiser and coworkers.

These results lead to an order of reactivity: five-membered ring >> six-membered ring > open chain analogue. The driving force for the rapid ring opening of the five-membered heterocycles has been shown by

thermochemical measurements to be relief of ring strain. The structure of **1** was determined by x-ray crystallography and it was found that all of the bond angles and distances in the five-membered ring showed evidence of ring strain.[3].



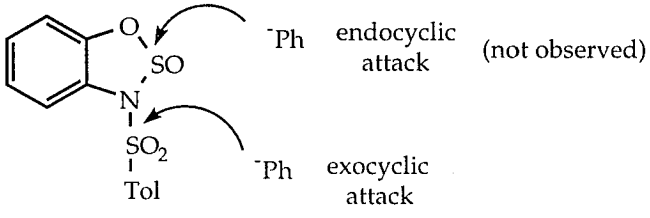
1

$-C_1-C_2-O-$	111.6°
$-C_2-O-S-$	108.6°
-O-S-O-	97.1°

Figure 2. Experimentally determined bond angles in catechol sulfate.

The results for the cyclic sulfates and sulfonates are analogous to those previously observed for structurally similar cyclic phosphates and phosphonates, which also undergo basic hydrolysis very rapidly compared to their acyclic counterparts[4a-f]. This increase in reactivity, however, is not observed in all sulfur (VI)[5a-b] or sulfur (IV)[6a-b] compounds.

As part of a study of nucleophilic substitution at tetracoordinate sulfur by Chumpradit[7], the first example of the 1,2,3-benzoxathiazole-2,2-dioxide (**6**) system was synthesized and reacted with phenyllithium.

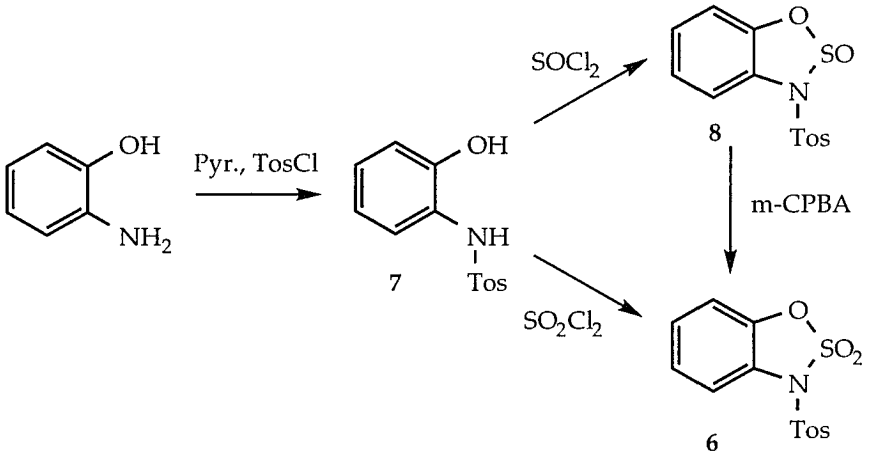


6

It was initially believed that the nucleophile would attack the endocyclic ring sulfur and cleave either the N-S or O-S bond of the five-membered ring, this being analogous to Kaiser's saponification studies of cyclic sulfates and sulfonates. The results, however, were contrary to this expectation. The nucleophile attacked the exocyclic tosyl sulfur atom and cleaved the exocyclic N-S bond.

These results led to the study, by Andersen[8] and co-workers, of the reactions of a series of substituted cyclic sulfamates of this type with hydroxide ion, as well as the reaction of **6** with other nucleophiles.

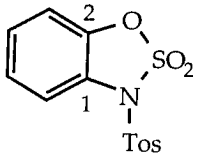
The synthesis of the cyclic sulfamate **6** was accomplished in two ways as shown in Scheme 1.



Scheme 1. Synthesis of cyclic sulfamate **6**.

Capuano[9] and co-workers reported the preparation of **8** by the reaction of **7** with thionyl chloride. Chumpradit was then able to synthesize **6** by oxidizing **8** with *m* -chloroperbenzoic acid. Later, Chumpradit prepared **6** by the direct reaction of **7** with freshly distilled sulfuryl chloride. Direct

attempts to prepare a cyclic sulfamate from *o*-aminophenol and either thionyl chloride or sulfuryl chloride were unsuccessful; only unreacted starting material was recovered. The structure of cyclic sulfamate **6** was confirmed by single-crystal x-ray analysis[10]. Similar to Kaiser's catechol sulfate, the cyclic sulfamate showed bond angles indicative of strain in the five-membered ring.

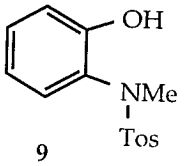


6

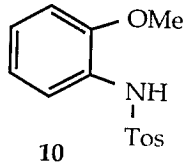
$-C_1-C_2-O-$	112.5°
$-C_2-O-S-$	111.2°
$-O-S-N-$	95.0°
$-S-N-C_1-$	108.6°
$-N-C_1-C_2-$	110.6°

Figure 3. Experimentally determined bond angles in cyclic sulfamate **6**.

When cyclic sulfamate **6** was treated with aqueous NaOH, it was shown to give the ring-opened product resulting from nucleophilic attack at the ring sulfur atom, this being analogous to the results observed by Kaiser for the sulfates. In order to determine which bond, O-S or N-S, was cleaving during ring opening, the UV spectrum of **6** in aqueous hydroxide was compared to the spectra of model compounds **9** and **10** in aqueous hydroxide. The spectrum of the hydrolysis product most closely resembled that of **10**, indicating that ring opening must proceed by way of N-S bond cleavage to **11**.



9



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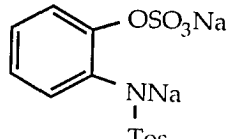
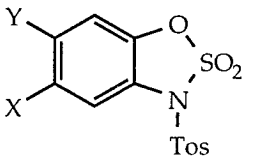


11

Clark was able to use the same synthetic procedure to prepare a series of 5-substituted cyclic sulfamates from the appropriately substituted amino phenols and sulfuryl chloride[11].

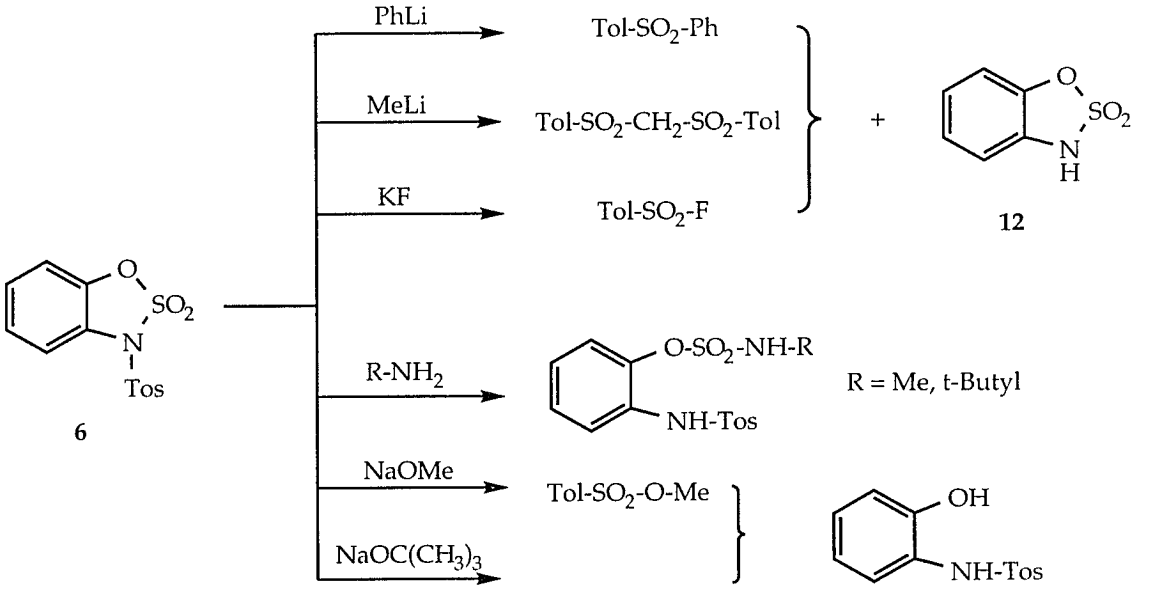


6	X	Y
a	H	H
b	Me	H
c	Cl	H
d	*t*-Bu	H
e	Acyl	H
f	Br	H
g	NO_2	H
h	H	NO_2

The rates of the base induced hydrolysis of the series of 5-substituted cyclic sulfamates (**6a-g**) were measured in acetonitrile. The cyclic sulfamates showed a mechanistic profile similar to the analogous sulfates and sulfonates, undergoing rapid alkaline hydrolysis compared to structurally similar acyclic analogues. The Hammett plots of the psuedo-first order rate constants for the saponification of the series of cyclic sulfamates gave a rho value of +1.83, with the best correlation obtained with σ^- substituent constants. This was interpreted as meaning that there is a significant build-up of negative charge on the nitrogen in the transition state. This is only possible if the endocylic N-S bond, and not the S-O bond, cleaves during hydrolysis.

Although cyclic sulfamate **6** is sensitive to hydroxide ion reacting with it to open the ring, it is very stable toward acid. Attempts at nitration of **6** directly with concentrated or fuming nitric acid and concentrated sulfuric or glacial acetic acid failed, with only starting material being recovered.

Chumpradit[7] reacted **6** with other nucleophiles, however, these results which were not all analogous to Kaiser's saponification studies. The results of these reactions are summarized in Scheme 2.



Scheme 2. Reaction of cyclic sulfamate **6** with nucleophiles.

As previously mentioned, the treatment of **6** with phenyllithium yielded *p*-tolylsulfone as the major product, this arising from the attack of the nucleophile on the tosyl sulfur atom and cleavage of the exocyclic N-S bond. A similar reaction of **6** with methyllithium gave bis(*p*-tolylsulfonyl)-methane, this arising from initial attack at the tosyl sulfur, to form methyl *p*-tolylsulfone. This sulfone was then deprotonated and served as a nucleophile to give the product. Exocyclic attack was also observed when **6** was treated with potassium fluoride in aqueous acetonitrile. This reaction yielded *p*-toluenesulfonyl fluoride, which suggests that the fluoride ion attacks the tosyl sulfur. It is possible, however, that the fluoride ion opened the ring, but that the reaction was rapidly reversible and the ring reclosed.

However, the reaction was monitored by ^{19}F NMR and only signals for fluoride ion and *p*-toluenesulfonyl fluoride were observed.

The treatment of **6** with amines (methyl and *t*-butyl) yielded the ring opened products, resulting from attack at the endocyclic sulfur atom. Similar to the reaction with hydroxide, the endocyclic N-S bond, and not the O-S bond, was cleaved.

When **6** was treated with sodium methoxide in methanol, two major products were observed: methyl *p*-toluenesulfonate, resulting from attack at the exocyclic sulfur, and the *N*-tosyl-*o*-aminophenol, resulting from attack at the endocyclic sulfur atom.

The chemoselectivity of the nucleophilic attack could not be explained fully. However, it was suggested that sulfamate **12** may be expected to be quite acidic, therefore its conjugate base would act as a good leaving group. This may be one reason to explain why the exocyclic sulfur undergoes nucleophilic attack. The varying reactivity of different nucleophiles, however, remains unexplained.

Acidity of sulfamates and related sulfonyl-containing compounds.

The acidity of the hydroxyl hydrogen of sulfamic acid, H_2NSO_2OH, has seen considerable study, however, only a few values have been reported for the deprotonation of the nitrogen on sulfamic acid or its esters (sulfamates).

Spillane[12] and co-workers have reported the pK_a's for the deprotonation at nitrogen in a series of *N*-alkylsulfamic acid anions (Figure 4), as measured by potentiometric and ^{13}C NMR methods. The sulfamate nitrogen was found to be only slightly more basic than the analogous sulfonamide nitrogen in *N*-

alkylsulfonamides, such as $MeSO_2NHMe$ and $PhSO_2NHMe$ (pK_a 11.79 and 11.43, respectively).

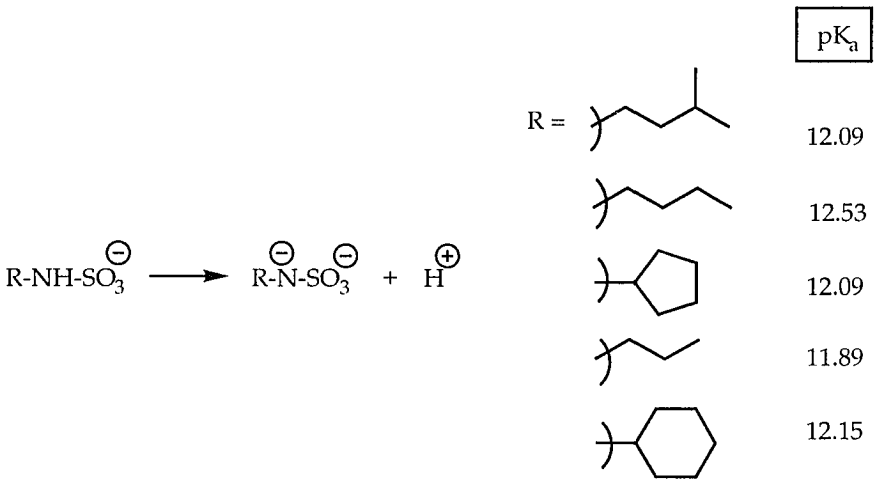
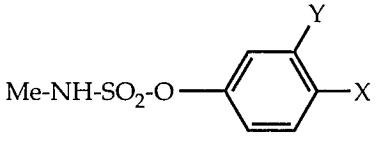


Figure 4. pK_a values for sulfamates studied by Spillane and coworkers.

In the study of the hydrolysis of *O*-aryl-*N*-methylsulfamates, Williams[13] and Douglas reported the pK_a values for a series of these sulfamates (Figure 5).

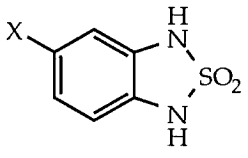


Y	X	pK_a
H	NO_2	8.88
NO_2	H	8.70
Cl	H	9.48
H	Cl	9.80
H	H	10.53

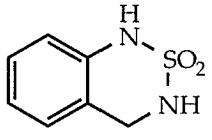
Figure 5. pK_a values for sulfamates studied by Williams and Douglas.

To date, no values for the acidity of cyclic sulfamates have been reported, however the acidities of cyclic sulfamides have been investigated. These cyclic sulfamides are structurally analogous to the cyclic sulfamates, with the sulfamate ring oxygen being replaced by a nitrogen.

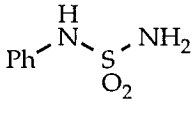
Spillane[14] and co-workers have shown 2,1,3-benzothiadiazoles (**13**) to be quite acidic. The unsubstituted compound (X = H) was shown to have a pK_a of 6.41. The most acidic of the series being when X = NO_2; the pK_a was 2.85. Spillane pointed out that these cyclic sulfamides are considerably more acidic (approximately 4 pKa units) than their acyclic analogues. The acyclic sulfamides **15**, **16** and **17**, which can be considered acyclic analogues of **13**, have been reported to have pK_a values of 11.10[14], 10.13[15] and 11.04[14], respectively. In addition, the six-membered sulfamide, **14**, (pK_a 8.79) was shown to be more acidic (approx 2 pK_a units) than the acyclic analogues but less acidic (approximately 2 pK_a units) than the five-membered analogue.



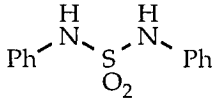
13 (6.41)



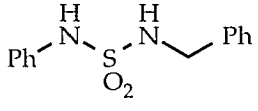
14 (8.79)



15 (11.10)



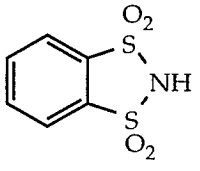
16 (10.13)



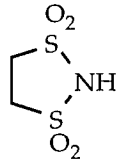
17 (11.04)

The origins of this "acid-strengthening" effect are unclear. Spillane speculated that ring strain may play a role in this effect, however, it seems unlikely that this is the major cause for such a large increase. Also suggested was that overlap of the lone pairs of the nitrogen with the sulfur *d*-orbitals may play a role.

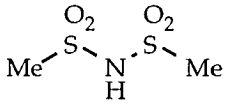
This acid strengthening effect has also been observed in the case of five-membered disulfonamides. King[16] and co-workers have reported the H_o values at half protonation of the disulfonamides **18** and **19** to be -4.1 and -3.1, respectively. These compounds are considerably more acidic than the acyclic analogues **20**[16] and **21**[16,17], whose values have been reported to be -1.8 and -1.7, respectively.



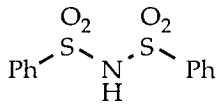
18 (-4.1)



19 (-3.1)

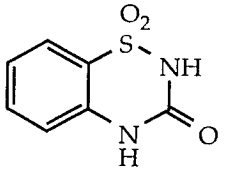


20 (-1.8)

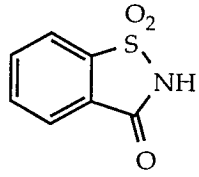


21 (-1.7)

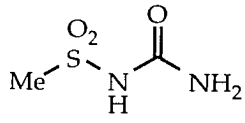
Similarly, certain *N*-acyl cyclic sulphonamides have been shown to be more acidic than their *N*-acyl acyclic analogues. The pKa of 1,2,4-benzothiadiazine **22** and saccharin **23**[18] , have been shown to be 2.90 and 1.8 respectively. Their acyclic analogues **24**[19] and **25**[16] are considerably more basic with pK_a values of 5.10 and 5.13, respectively. As was the case with the sulphamides, ring strain may play a role, however it has been suggested that stereoelectronic factors may have an affect. This has yet to be investigated.



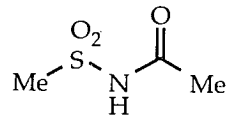
22 (2.90)



23 (1.80)

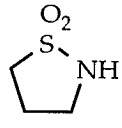


24 (5.10)

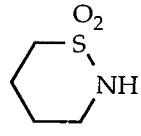


25 (5.13)

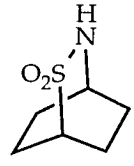
Interestingly, not all cyclic sulfonamides show an increased acidity compared to their acyclic analogues. The five-membered (**26**), six-membered (**27**) and bicyclic (**28**) sulfonamides (pK_a values 11.54, 12.34 and 11.65 respectively) show very little difference from the acyclic sulfonamide **29**, whose pK_a has been reported to be 11.79[16].



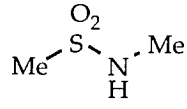
26 (11.54)



27 (12.34)

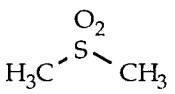


28 (11.65)



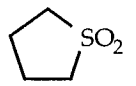
29 (11.79)

This acid stengthening effect is also not observed in the acidity of sulfones. Bordwell[20] and co-workers reported the acidity of a number of sulfones. The pK_a of dimethyl sulfone (**30**) in dimethyl sulfoxide was reported to be 28.5. The pK_a values of cyclic analogues with four, five and six-membered rings (**31-33**) all were found to be less acidic (1.5-2.5 units higher) than their acyclic counterparts.

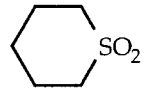


30 (28.5)

31 (>30)



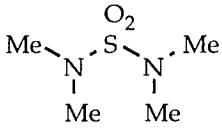
32 (>31)



33 (>31)

The existence of delocalization in α-hetero sulfonyl compounds has been suggested previously.

Lipscomb[21] and coworkers reported the first x-ray crystal structure of tetramethylsulfamide (**34**). Lipscomb observed that the geometry of the nitrogens indicated an hybridization intermediate between sp^3 and sp^2. This hybridization was similar to that suggested for α-sulphonyl carbanions (**36**).



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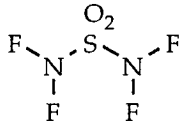

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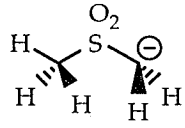


36

Previously, it had been suggested that the retention of configuration for these carbanions may be due to a barrier of rotation. In an effort to understand this barrier, Lipscomb examined the isoelectronic tetrafluorosulfamide **35**. The results of this study suggested that the barrier of rotation may arise from interactions involving replusion between the *d*-orbitals localized on sulfur and the *p*-orbitals localized on nitrogen.

A study of the basicity of *N*-methyl, *N*-ethyl and *N*,*N* -dimethyl sulfonamides by Laughlin[22] and coworkers showed that these sulfonamides are markedly less basic than simple amines. It was suggested that the difference in acidity between RSO_2NHR and R_2NH (about 16 pK_a units) was too large to be solely due to inductive effects. He argued that these results indicated a delocalization between the nitrogen and sulfonyl sulfur.

Figure 6. N-S delocalization proposed by Laughlin.

This hypothesis was investigated by King[23] and coworkers who utilized a search of the Cambridge Crystalographic Data Center and found that a majority of sulfonamides had a C-S-N-C dihedral angle between 60°and120°. This suggested that the most favorable arrangement for N-S delocalization is $\theta = 80°$, therefore, a sulfonamide with $\theta = 0°$ would have less N-S delocalization. This, in turn, would be reflected in an increase in base strength.

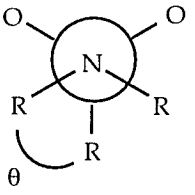
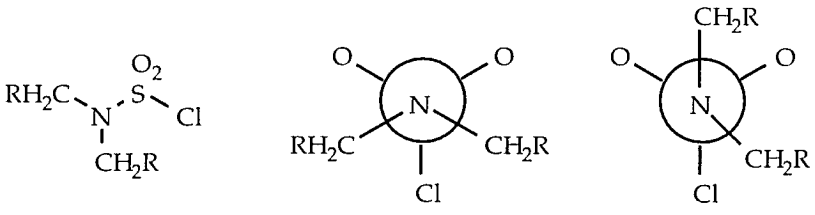


Figure 7. Newman projection of sulfonamide conformation.

In accordance with this, King found the *N*-methylated analogues of **26, 27** and **28** are considerably more basic than their acyclic analogues[16].

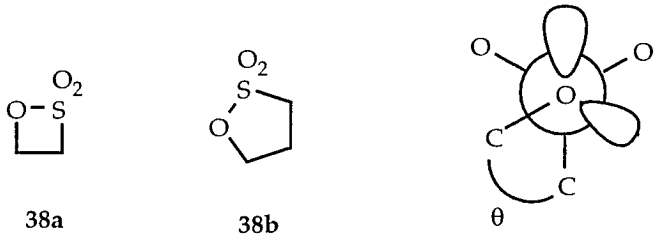
The existence of a barrier to rotation in α-heterosulfonyl compounds was reported by Jennings and Spratt[24]. ^{1}H NMR studies of *N,N*-dialkylsulfamoyl chlorides (**37**) indicated a barrier to rotation of 11.5 kcal/mol. The observation of diastereotopic methylene protons in the low temperature ^{1}H NMR spectra was consistent with **37a** as the ground state conformation, but inconsistent with **37b**. The ground state conformation of these compounds was shown to be similar to that for an α-sulfonyl carbanion. It was suggested that this barrier of rotation arose from an overlap of the nitrogen *p*- orbital with the sulfur *d*-orbitals.



37 37a 37b

Figure 8. Conformations of sulfamoyl chlorides studied by Jennings and Spratt.

The stereoelectronic effects in sulfonyl compounds were addressed by King[25] and co-workers in a study of the alkaline hydrolysis of the four and five-membered sultones, **38a** and **38b**.



38a 38b

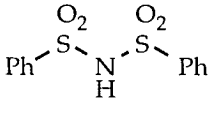
Figure 9. Sultones studied by King and co-workers.

Sulfonic esters typically undergo nucleophilic attack at carbon, resulting in cleavage of the carbon-oxygen bond[26]. King showed, however, that sultones **38a** and **38b** undergo hydrolysis with cleavage of the sulfur-oxygen bond. He proposed that there is delocalization between the sulfur and the lone pairs on the adjacent atom, similar to that proposed by Laughlin for sulfonamides.

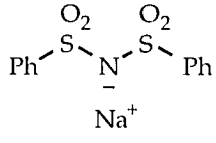
This delocalization varies with the C-S-X-C dihedral angle (θ) with the greatest delocalization being when θ is approximately 75° and the least delocalization being when θ = 0°. In sultones **38a** and **38b** the ring geometry forces a reduction in this delocalization. This reduction in delocalization (a) leads to a lowering of the S-O bond order, (b) decreases the partial positive charge on the carbon and (c) increases the partial positive charge on sulfur. These factors all facilitate nucleophilic attack at the sulfur atom.

King also suggested that this stereoelectronic effect should appear in the conformational preferences of sulfonic esters. A search of the Cambridge Crystallographic Data Center (1986) indicated that a majority of the sulfonic esters have C-S-O-C dihedrals between 60° and 90°. Aryl sulfones also show this trend with 94% having C-S-C_{ipso}-C_{ortho} dihedrals of 60°-120°.

Additional evidence for N-S delocalization in both a sulfonamide and its conjugate base is shown by N-S bond lengths determined by x-ray crystallography. Cotton and Stokely[27] reported the structure of the disulfonamide **39a** and its sodium salt **39b**. The N-S bond lengths were 1.65 and 1.58 Å, respectively, both below the 1.7 Å estimated for a N-S single bond from covalent radii.



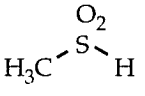
39a



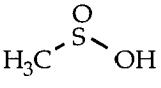
39b

The theoretical investigation of the participation of *d*-orbitals on sulfur in the bonding of α-heterosulfonyl groups has not been reported. These compounds, however, can be considered isoelectronic to α-sulphonyl carbanions, whose structure and bonding have been examined computationally.

One of the first studies to examine the role of the *d*-orbitals of sulfur was reported by Wolfe[28] and co-workers, who choose the carbanion of **40a** as a model. The examination of the optimized structures with (3-21G* basis set) and without (3-21G) *d*-orbitals, as well as examination of the wavefunction, led Wolfe to conclude that *d*-orbitals indeed play a role in stabilization of the anion.



40a



40b

However, it was later suggested by Streitweiser[29,30] that this may not be an accurate model for true compounds. This was based on the fact that **40a** does not exist, as it rapidly rearranges to methysulfinic acid (**40b**). In addition, it was pointed out that hydrogen is a poor model for a methyl group, the methyl group being bulkier and more polarizable. In an effort to provide a more reasonable model, Streitweiser reported the study of the carbanion of dimethyl sulfone. The analysis of the role of *d*-orbitals in the stabilization of adjacent carbanions was examined by analyzing four factors: (1) structural changes in formation of the anion, (2) rotational potential surface of the anion, (3) proton affinity and (4) integrated spatial electron populations. The analysis of the structural changes upon formation of the anion revealed that

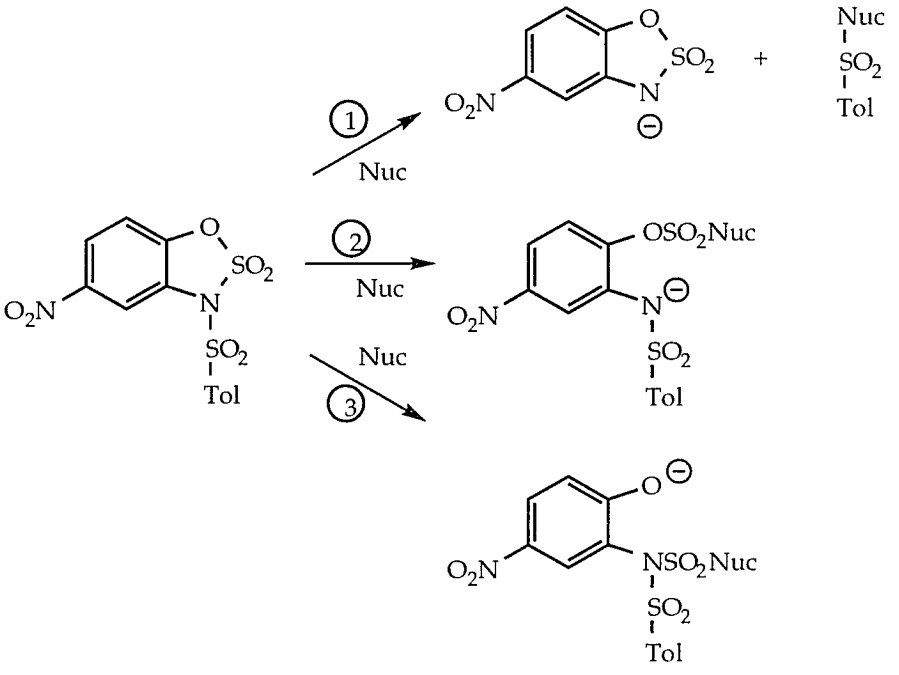
similar changes occurred in both cases, with and without d-orbitals. The rotational potential energy surface provided no significant evidence one way or the other. The calculation of the proton affinities showed little difference when calculated with and without d-orbitals, one would expect a smaller proton affinity if d-orbital were involved in stabilization of the anion. A detailed analysis of the electron densities with and without d-orbitals showed similar patterns of charge polarization, suggesting a lack of participation by the d-orbitals. Streitweiser's overall conclusion was that d-p π conjugation is not an important factor in stabilizing the anion. Instead, coulombic interactions play a dominant role.

Results and Discussion

Reactions of 5-Nitro-1,2,3-Benzoxathiazole-2,2-Dioxide with Nucleophiles.

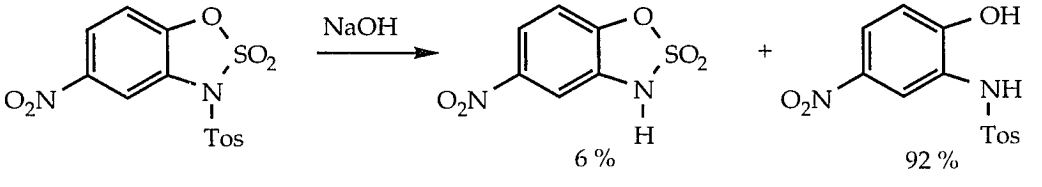
The initial aim of this research was to investigate the reactions of 5-nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (**6g**) with various nucleophiles and compare these results to those previously reported for the unsubstituted case, *N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (**6**). This would provide information about the effect of ring substitution on the site of nucleophilic attack and on the stability of the five-membered ring.

The attack of a nucleophile on these compounds could proceed along three different pathways: (1) attack at tosyl sulfur atom, resulting in cleavage of the exocyclic N-SO_2 bond, (2) attack at the ring sulfur atom with cleavage of the endocyclic N-SO_2 bond and (3) attack at the ring sulfur atom with cleavage of the endocyclic O-S bond (Scheme 3).



Scheme 3. Possible pathways for the reaction of 5-nitro-1,2,3-benzoxathiazole-2,2-dioxide with nucleophiles.

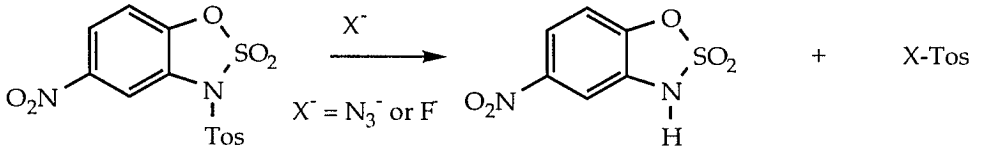
The synthesis of 5-nitrosulfamate **6g** was analogous to that of sulfamate **6** (Scheme 1)[11], starting with commercially available 4-nitro-2-aminophenol. Analogous to the reactions of the unsubstituted cyclic sulfamate (**6**) previously reported, the 5-nitro compound was reacted with various nucleophiles. The cyclic sulfamate was reacted with one equivalent of sodium hydroxide in acetonitrile/water (5:1).



6g **41** **42**

After work-up, the reaction yielded a small amount (6%) of the *N*-unsubstituted sulfamate **41**, indicating that the reaction proceeded in part through pathway (1). The major product (92%) was 4-nitro-2-(*N*-tosyl)-aminophenol (**42**); this product most likely arises through attack at the endocyclic sulfur atom, either pathway (2) or (3). The acidic workup results in loss of the sulfate group yielding the same product for either pathway. Therefore, we cannot determine if ring opening proceeds through O-S of N-S bond cleavage after initial attack of the nucleophile. The attack at the ring sulfur is analogous to that reported for the treatment of the cyclic sulfamate **6** with sodium hydroxide[7]. As previously mentioned, it was determined experimentally that the ring opening proceeds by way of N-S bond cleavage. Hammett correlations of the rate constants for the saponification of a series of these cyclic sulfamates suggested that the ring opening of the 5-nitro sulfamate may also proceed by way of N-S bond cleavage. The reaction of **6** with hydroxide ion, however, showed no evidence for attack on the N-tosyl sulfur atom.

The reaction of **6g** with either sodium azide or potassium fluoride in acetonitrile/water at room temperature resulted in nucleophilic attack at the tosyl sulfur atom (pathway 1).

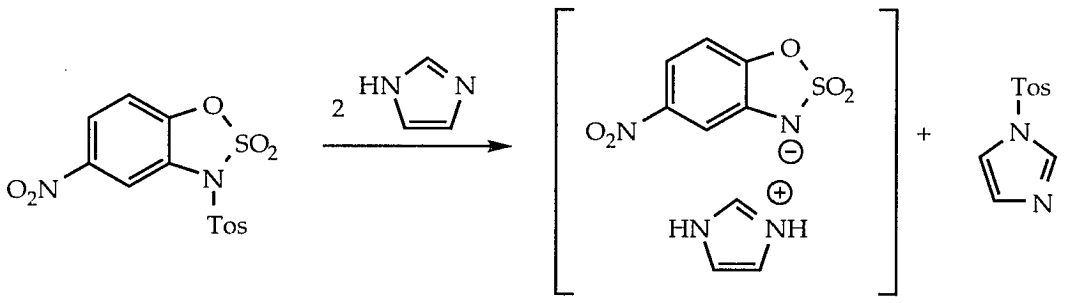


6g **41**

Both reactions resulted in the formation of the N-H sulfamate **41** and tosyl fluoride or tosyl azide, respectively. The reaction with potassium azide was very rapid, went to completion in 15 minutes, and yielded **41** in 93% yield. The reaction with potassium fluoride required 12 hours for completion, yielding **41** in 81% yield.

Several attempts were made to react **6g** with carbon nucleophiles. Treatment with sodium cyanide in acetonitrile/H_2O resulted in a brown sticky solid which showed several spots on tlc; no pure compounds could be isolated from the mixture. Similar results were observed when **6g** was reacted with *t*-butylmagnesium chloride in THF.

Sulfamate **6g** was then reacted with several amine nucleophiles. The reaction with imidazole provided some interesting results. Initially, the sulfamate was reacted with one equivalent of imidazole in an acetonitrile/H_2O solution. After acidic workup, three compounds were isolated, the detosylated sulfamate (**41**), *p*-toluenesulfonyl imidazole and half of the starting material. The reaction was repeated, using a neutral aqueous workup. The aqueous layer yielded a yellow solid which was identified as the imidazolium salt of the sulfamate anion (**43**). It seems that two equivalents of the imidazole are necessary for the reaction to run to completion. The first attacks the tosyl sulfur to form the tosyl imidazole and the second forms a salt with the sulfamate anion.



43

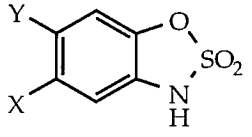
Similar results were observed when **6g** was reacted with benzyl or *t*-butyl amine. The amine appears to attack the tosyl sulfur atom forming the tosyl amine and a second equivalent of base forms a salt with the cyclic sulfamate anion.

Compound **6g** was also treated, under analogous conditions, with one equivalent of pyridine. It was envisioned that if nucleophilic attack occurred at the tosyl sulfur atom, the resulting *N*-*p*-toluensulfonylpyridiniun ion would form a salt with the sulfamate anion. This reaction, however, returned only the starting *N*-tosylsulfamate. We cannot rule out that nucleophilic attack occurred, however, it may be rapidly reversible.

The results from the reactions with imidazole and the two primary amines provided evidence for the increased acidity of the benzo-fused five-membered cyclic sulfamate **6g**, as was previously suggested. The formation of the imidazolium salts indicates that the pK_a of the cyclic sulfamate must lie below that of protonated imidazole (ca. 7). This is considerably lower than the pK of previously reported acyclic sulfamates. It seems that the "acid strengthening "effect" observed for sulfamides, aryl sulfonamides and disulfonamides may also be observed for the case of cyclic sulfamates.

Synthesis of Cyclic Sulfamates

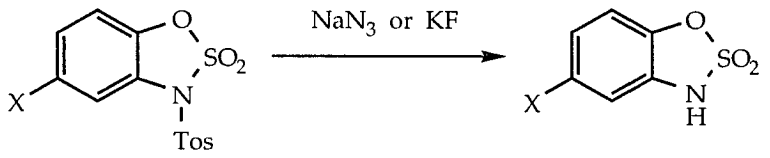
These results prompted the experimental investigation of the acidity of these cyclic sulfamates. A series of eight substituted cyclic sulfamates was synthesized for pK_a determinations.



#	X	Y
41a	NO_2	H
41b	H	H
41c	Me	H
41d	Br	H
41e	Cl	H
41f	Cl	Cl
41g	H	NO_2

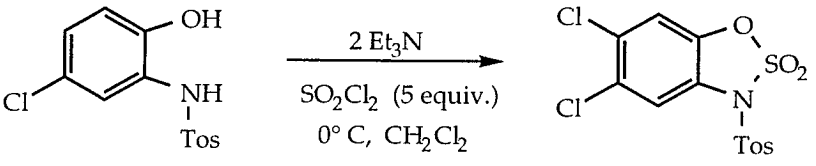
41h 

Compounds **41a-e** were derived from the *N*-tosylsulfamates, whose synthesis has been previously described[11]. Removal of the tosyl group was accomplished by treatment of the *N*-tosyl compounds with either potassium fluoride or sodium azide in acetonitrile/water (5:1, v/v).



X = NO_2, H, Me, Br, Cl **41a-e**

Compound **41f** was synthesized by a modified procedure used for the synthesis of compound **41e**.



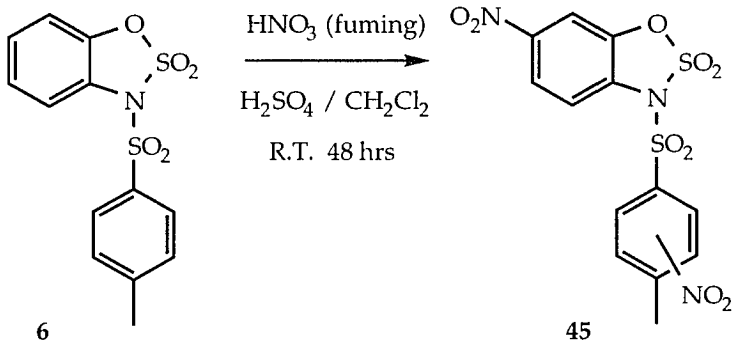
41f

N-(2-hydroxy-5-chlorophenyl)-*p*-toluenesulfonamide was treated with two equivalents of triethylamine and a five-fold excess of sulfuryl chloride at 0 °C. The results were formation of the five-membered cyclic sulfamate as well as chlorination at the 6-position to give dichlorosulfamate **41f**. Detosylation was accomplished by treatment with sodium azide as described previously.

The synthesis of the 6-nitrosulfamate **41g**, was envisioned to proceed from the *N*-tosylated analogue, in the manner in which **41a-e** were prepared. However, the synthesis of the *N*-tosyl compound from 2-amino-5-nitro phenol gave very low yields. Significant amounts of this compound could not be obtained, so alternate method were desired.

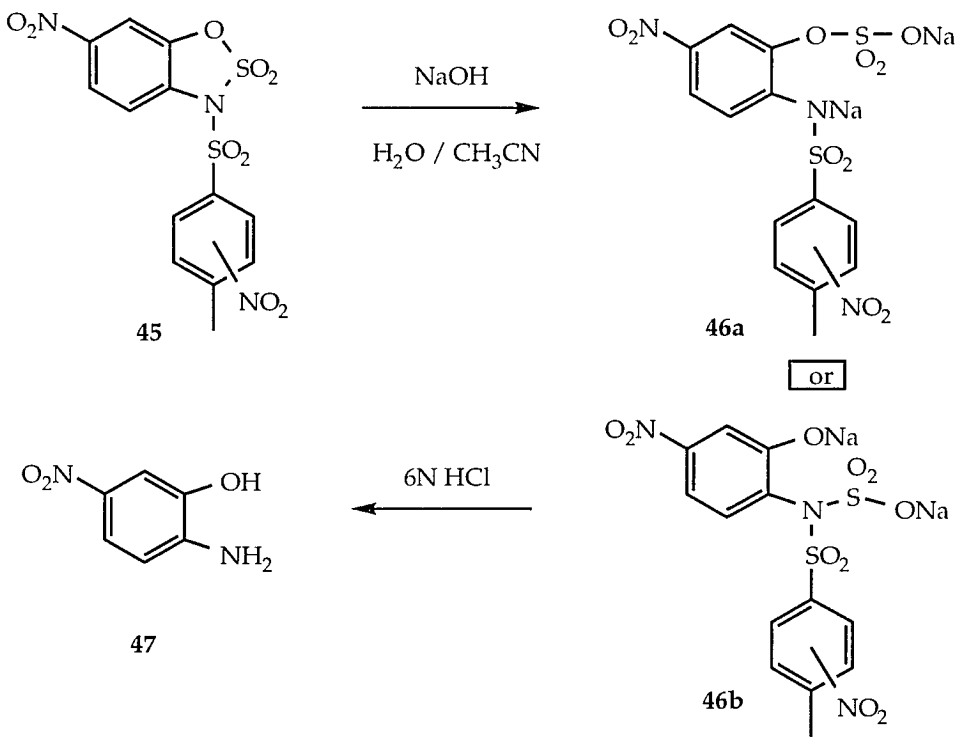
Initially, the nitration of the unsubstituted sulfamate **6** was attempted by stirring the sulfamate with an excess of sodium nitrite in trifluoroacetic acid at room temperature for 3 days. The starting sulfamate was the only compound recovered after aqueous work-up.

The nitration of sulfamate **6** was previously reported using a two phase system of methylene chloride and a fuming nitric acid/sulfuric acid mixture[31]. The solution was stirred rapidly for two days at room temperature.



6 45

The methylene chloride layer yielded a dinitrated sulfamate whose structure was proposed to be that of the **45**. The exact location of the nitro group on the tosyl ring was not unequivocally assigned. However, in our case, the sulfonate group was to be removed to get the desired product, so its exact location was not relevant. The nitro group on the benzoxathiazole ring was believed to be in the six position by comparison of the aromatic region of the ^{1}H NMR spectrum of **45** with that of a spectrum of authentic 6-nitro *N*-tosyl sulfamate synthesized as previously mentioned. This location was verified by conversion to 5-nitro-2-aminophenol as shown in Scheme 4.

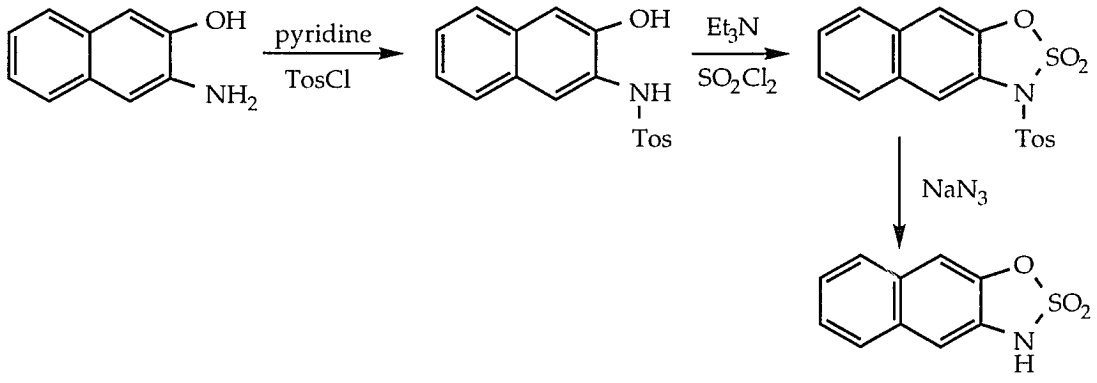


Scheme 4. Conversion of dinitro sulfamate to 5-nitro-2-aminophenol.

The dinitrated species was hydrolyzed with aqueous NaOH in acetonitrile, to give a yellow solid whose structure was not determined; it could be either of the two ring-opened products (**46a-b**). This solid was then refluxed in 6N HCl for 20 hours. Neutralization of the reaction mixture followed by extraction with diethyl ether yielded a yellow solid whose mp and ^1H NMR spectrum matched that of 5-nitro-2-aminophenol (**47**).

Once the position of the nitro group was established to be at the 6-position of the aromatic ring, the dinitrated species was then treated with 2 equivalents of imidazole in acetonitrile, yielding **41g** in a 71% yield.

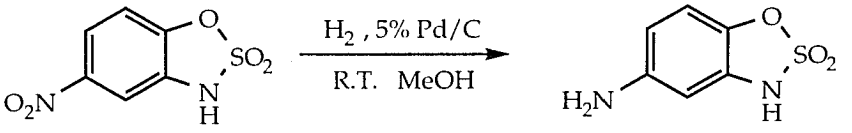
The previously unreported naptho-fused sulfamate (**41h**) was prepared by the same methods as those for the compounds for **41a-e**, starting with 3-amino-2-naphthol.



41h

3-Amino-2-naphthol was selectively tosylated at nitrogen using pyridine and tosyl chloride. The *N*-tosyl sulfamate was then prepared by treatment with triethylamine and sulfuryl chloride. Removal of the tosyl group was accomplished as previously described with sodium azide to give **41h** in 89% yield.

The syntheses of the 5- and 6- amino sulfamates, **48**, were also attempted by reduction of the corresponding nitro compounds. Compound **41a** (or **41g**) was dissolved in MeOH and stirred with 5% palladium on carbon under a hydrogen atmosphere.

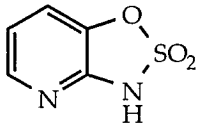


not observed

41a **48**

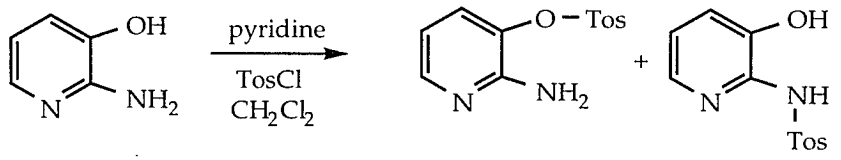
The mixture was stirred until loss of the bright yellow color of the starting sulfamate was evident. Upon opening the reaction mixture to the atmosphere and filtering of the catalyst, the filtrate immediately turned dark brown. A dark brown to black solid was recovered, however, no pure compounds could be isolated.

The synthesis of the pyridino-fused sulfamate was also attempted. It was envisioned that this compound could be synthesized in an analogous manner to other sulfamates, starting with the 2-amino-3-hydroxypyridine.

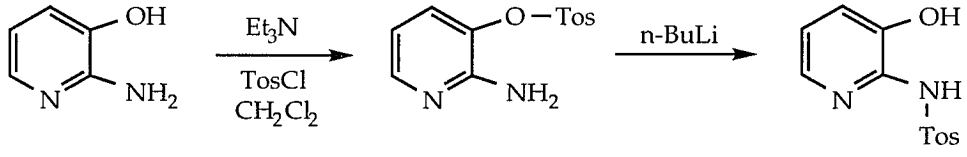


49

2-Hydroxy-3-aminopyridine was treated with pyridine and tosyl chloride in methylene chloride in an attempt to selectively tosylate the amino nitrogen. However, these conditions resulted in a mixture of what appeared, by ^{1}H NMR, to be the N-tosyl and O-tosyl compounds.

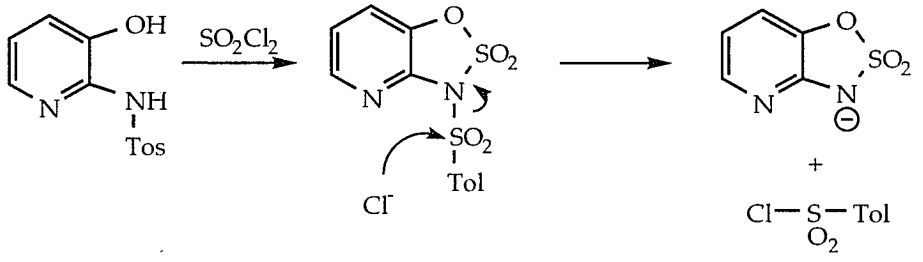


The desired *N*-tosyl aminohydroxypyridine was previously reported to be accessible from the *O*-tosyl aminohydroxypyridine by way of a base-induced rearrangement[32]. The *O*-tosyl compound was prepared by treatment of 2-amino-3-hydroxypyridine with triethylamine and tosyl chloride. Subsequent treatment with a 30-fold excess of *N*-butyllithium yielded the *N*-tosyl compound in 55% yield.



The *N*-tosyl compound was then treated with triethylamine (2 equiv.) and sulfuryl chloride in CH_2Cl_2 at -78°C (Scheme 5), followed by warming to room temperature. After washing with water and evaporation of the solvent a brown sticky solid remained. Analysis by tlc showed one major spot and several brown streaky spots. The compound giving the major spot was isolated and was determined to be *p*-toluenesulfonyl chloride. Numerous attempts were made varying the amounts of reagents, reaction time and reaction temperature. In all cases, tosyl chloride was the only isolable product. Analysis by tlc early in the reaction showed a spot for the tosyl chloride as well as a spot where the product would be expected to be seen.

The compound giving this spot quickly disappeared as the reaction progressed and the tosyl chloride spot grew. Attempts to stop the reaction and isolate the compound giving this spot were unsuccessful. One explanation for these results is the formation of the *N*-tosyl sulfamate followed by rapid nucleophilic attack at the tosyl sulfur by chloride anion.



Scheme 5. Attempted synthesis of pyrido-fused sulfamate.

Unsuccessful attempts to isolate *N*-tosyl sulfamate by stopping the reaction before completion suggests that the compound may undergo nucleophilic attack as rapidly as it is formed. The rapid nucleophilic attack at the tosyl sulfur may be a consequence of the acidity of **49.** The pyrido-fused sulfamate would be expected to be very acidic, therefore, its conjugate base would be a very good leaving group. Numerous attempts at isolation of **49** or its anion were unsuccessful.

pK_a Determinations

The pKa values for the eight cyclic sulfamates were determined by potentiometric methods as described by Albert and Serjeant[33]. The samples were run at 0.01M concentration (0.25 g in 25 mL) in 60% (v/v) $EtOH/H_2O$.

The samples were titrated with 0.1N NaOH which was prepared and standardized with KHP daily. A typical data table for a pK_a determination is shown in Table 1, tables for **41a,c-h** are shown in Appendix.

Table 1. Data table for pK_a determination of sulfamate **41b**.

% ion.	mL base	[HA]	[A-]	$\{H^+\}$	pH	pK_a
10	0.25	0.009	0.001	0.000188	3.73	4.68
20	0.50	0.008	0.002	0	4.01	4.61
30	0.75	0.007	0.003	0	4.23	4.60
40	1.00	0.006	0.004	0	4.43	4.60
50	1.25	0.005	0.005	0	4.62	4.61
60	1.50	0.004	0.006	0	4.81	4.63
70	1.75	0.003	0.007	0	5.02	4.65
80	2.00	0.002	0.008	0	5.32	4.71

averages: 10-80% (8 points) 4.64 ± 0.07
10-70% (7 points) 4.63 ± 0.05
20-70% (6 points) 4.62 ± 0.03

The pH values were recorded as the acids were titrated at 9 intervals between 10-90% ionization. The pK_a values at each interval were calculated using equation (1), which includes a correction for hydrogen ion activity $\{H^+\}$(2). This correlation need only be applied for pH values below 4.0; at higher values the hydrogen activity is essentially zero.

$$pK_a = pH + \log_{10} [HA] - \{H^+\} / [A^-] + \{H^+\} \quad (1)$$

$$\{H^+\} = 10^{-pH} \quad (2)$$

The most reliable results for the calculation of a pK_a value lie in the 20-80% ionization range. A typical titration curve has a steep slope in the area of 10% and 90% ionization, therefore, these values are not accurate and are often not averaged into the overall pK_a value. The pK_a values are reported along with the ionization range over which the data was taken. In addition, the degree of precision was calculated in the form of scatter. The scatter represents the largest deviation from the average for that particular data set and is reported along with the number of points taken. The pK_a values determined for the eight cyclic sulfamates are shown in Table 2.

Table 2. Potentiometrically determined pK_as for cyclic sulfamates **41a-h**.

comp.	pK_a	scatter (#)	% ion.
41a	2.76	±0.07 (5)	30-70
41b	4.62	±0.03 (6)	20-70
41c	4.73	±0.03 (7)	10-70
41d	3.47	±0.05 (5)	30-70
41e	3.72	±0.05 (6)	30-80
41f	2.87	±0.04 (6)	20-70
41g	2.33	±0.04 (5)	40-80
41h	3.84	±0.02 (5)	30-70

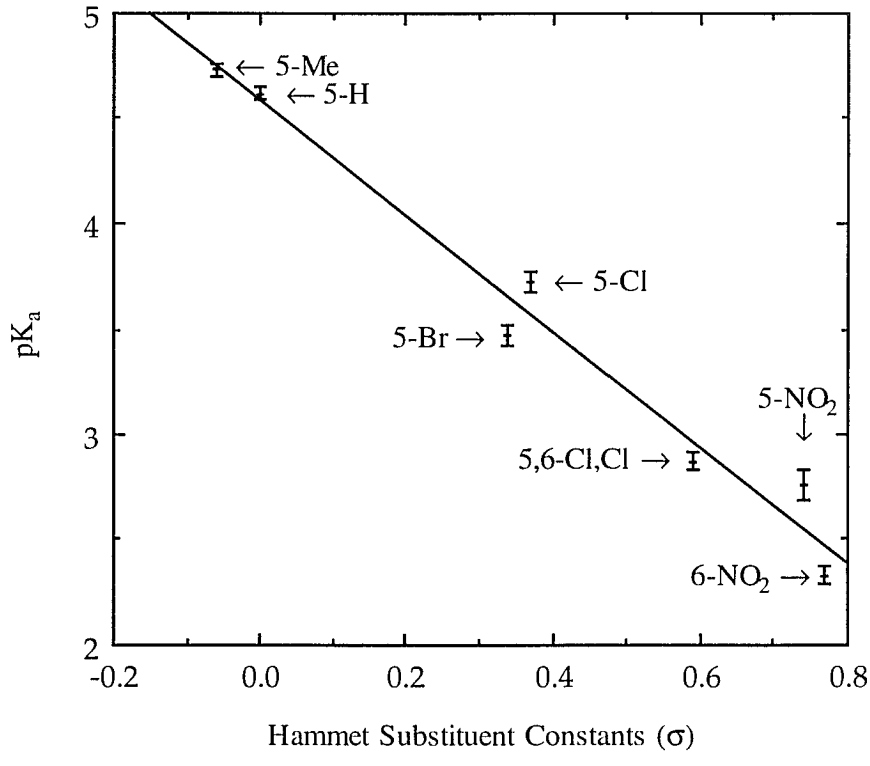
The pK_a values for compounds **41a-g** were then used to construct Hammett plots to evaluate the correlation and determine the substituent

constant. The σ values[34] for each compound are shown in Table 3. For compounds **41a-e** , σ_m was used, for compound **41g** ,σ_p was used and for **41f**, $\sigma_m+\sigma_p$ was used.

Table 3. Substituent constants used for Hammett plots of pK_a values of **41a-g**.

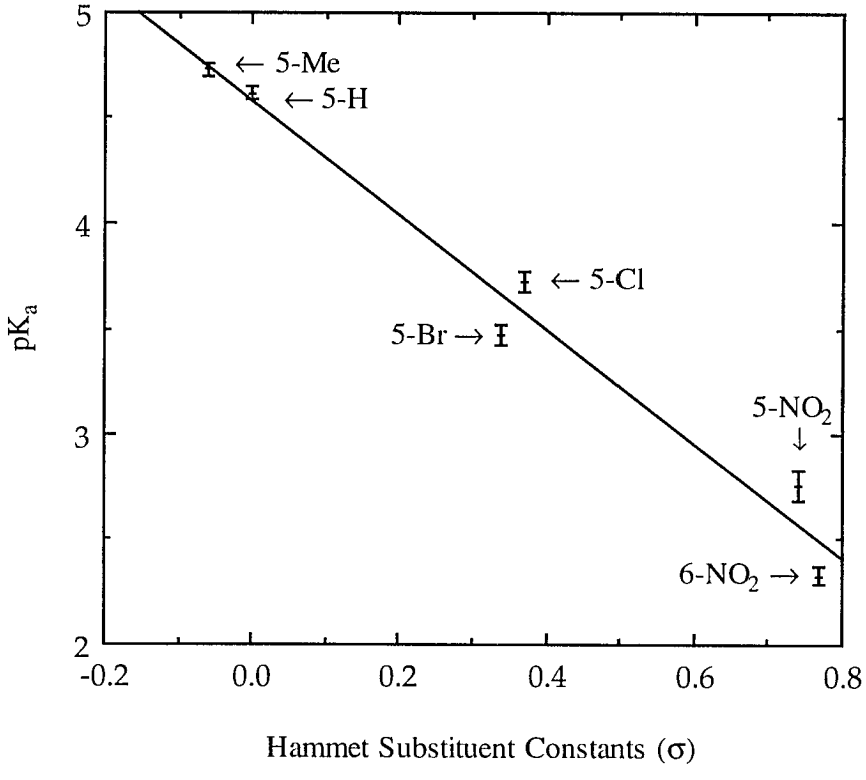
compound	σ constant	σ value
41a	σ_m	0.74
41b	σ_m	0
41c	σ_m	-0.06
41d	σ_m	0.34
41e	σ_m	0.37
41f	$\sigma_m + \sigma_p$	0.59
41g	σ_p	0.77

Graph 1. Hammett plot for sulfamates **41a-g.**



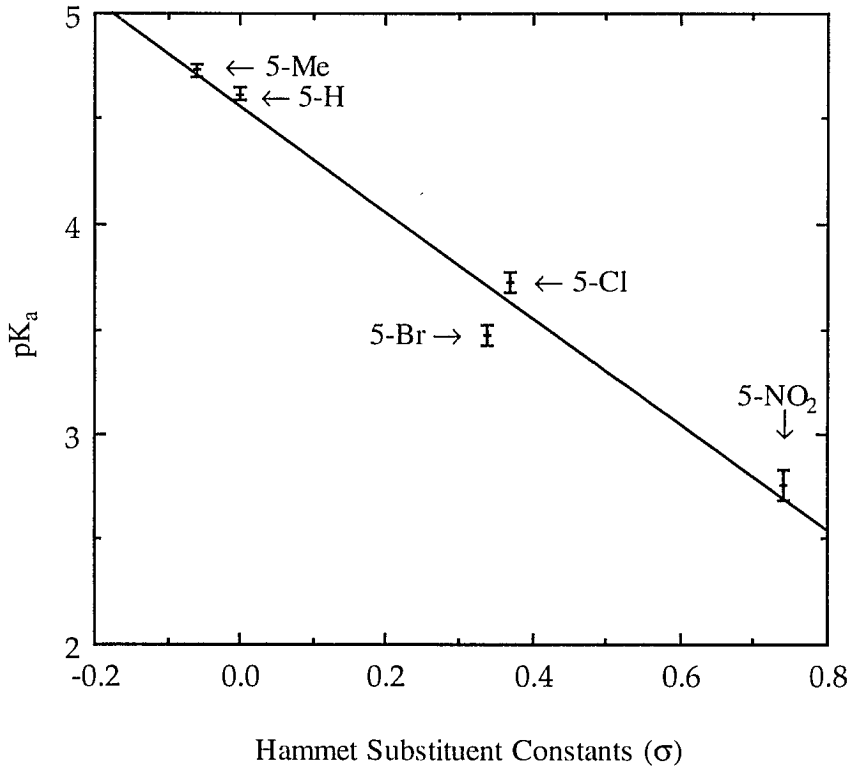
$\rho = 2.74$ $r = 0.975$ $s = 0.16$

Graph 2. Hammett plot for sulfamates **41a-f.**



$\rho = 2.71 \quad r = 0.974 \quad s = 0.17$

Graph 3. Hammett plot for sulfamates **41a-e**.



$\rho = 2.52 \quad r = 0.974 \quad s = 0.15$

From the Hammett plots, the reaction constant (ρ), the correlation coefficient (*r*) and standard error (*s*) were calculated. The results of the three plots are summarized in Table 4.

Table 4. Results of Hammett plots for compounds **41a-g**.

compounds	ρ	*r*	*s*
41a-g	2.74	0.975	0.16
41a-f	2.71	0.974	0.17
41a-e	2.52	0.974	0.15

All three plots gave a straight line with satisfactory correlation. Removal of the dichloro compound (**41f**) and/or the 6-nitro compound (**41g**), shown in Graphs 2 and 3, had no effect on the correlation or error of the plots. The reaction constants obtained were consistent with those previously reported for the ionization of a series of cyclic sulfamides (2.8) and for a series of sulphamate esters, $MeNHSO_2OAr$ (2.5).

The relative gas phase acidities for this series of cyclic sulfamates were also calculated using semi-empirical (AM1)[35] methods. The relative acidities were determined by the calculation of the energy change for the isodesmic reaction shown in Figure 10.

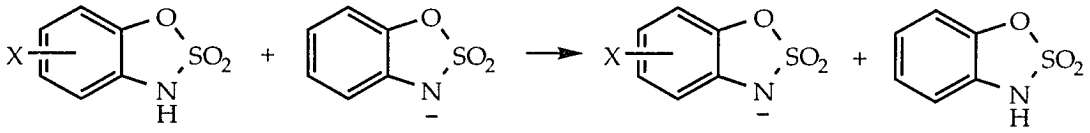


Figure 10. Isodesmic reaction used to calculate relative acidities for substituted benzo-fused five-membered cyclic sulfamates.

The heats of formation for the neutral and anionic sulfamates were calculated at AM1 level. The structures were optimized at the same level, cartesian coordinates are shown in Appendix. The values obtained are shown in Table 5.

Table 5. Calculated (AM1) heats of formation (kcal/mol) for neutral and anionic sulfamates.

X	NH	N^-
H	-70.563	-109.859
Me	-78.105	-117.095
5-NO_2	-65.030	-117.773
6-NO_2	-64.500	-120.311
Br	-64.747	-108.920
Cl	-76.731	-120.431
5,6-Cl,Cl	-81.324	-128.791
Nap	-52.546	-95.629

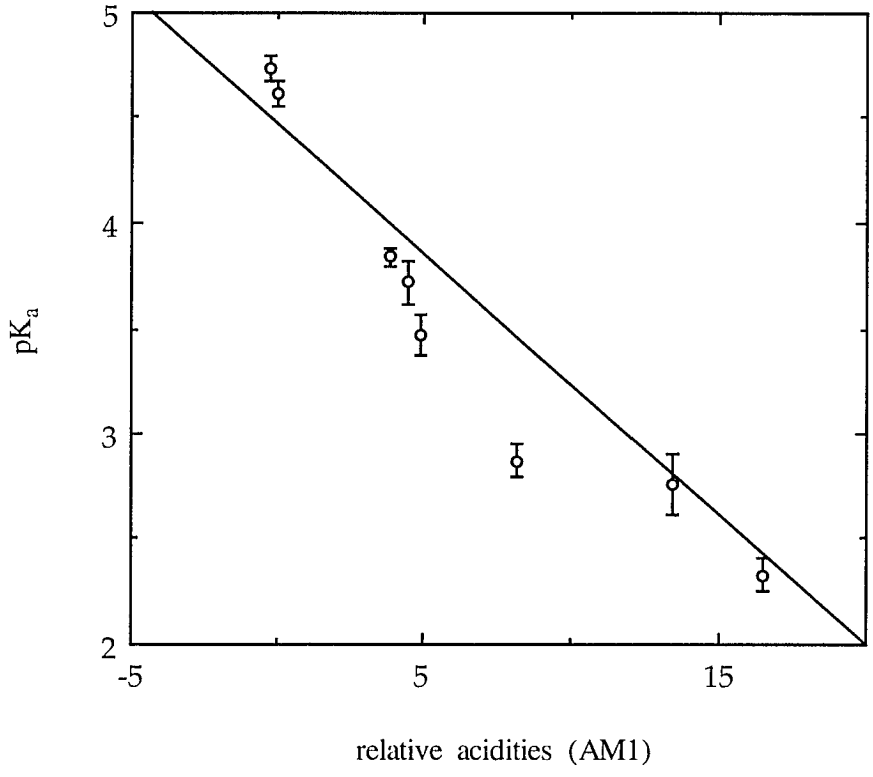
The relative acidities (ΔE for the reaction) calculated using the isodesmic equation are shown in Table 6.

Table 6. Relative acidities of substituted sulfamates.

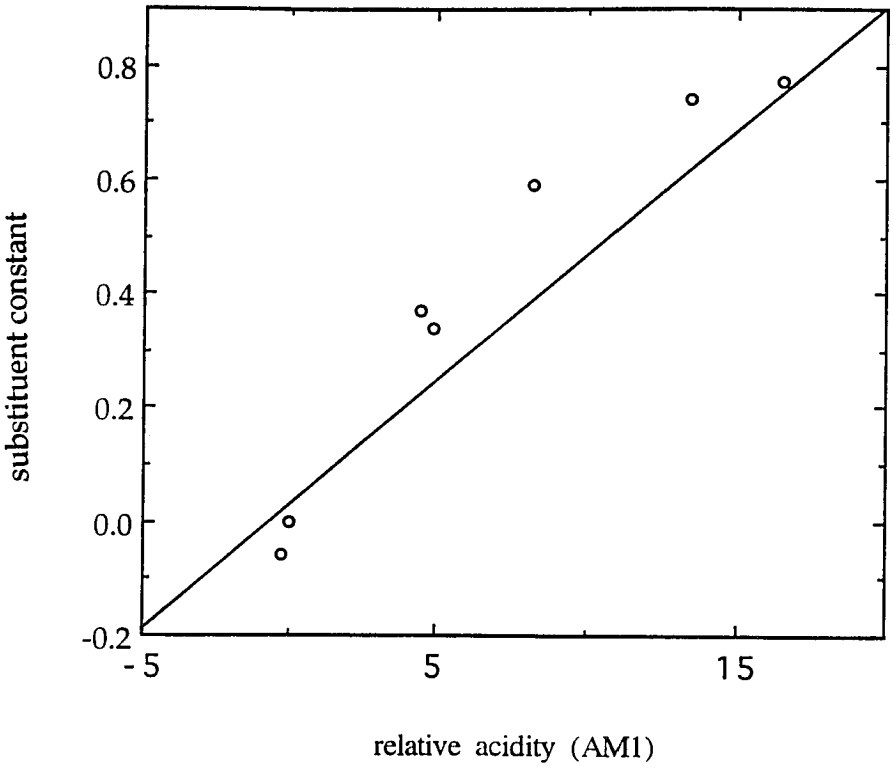
compound	X	ΔE (kcal/mol)
41a	5-NO_2	13.447
41b	H	0
41c	Me	-0.306
41d	Br	4.877
41e	Cl	4.404
41f	5,6-Cl,Cl	8.171
41g	6-NO_2	16.515
41h	Nap.	3.787

Hammett plots (Graph 4 and 5) were constructed plotting the calculated relative acidities *vs* experimentally determined pK_a and *vs* Hammett substituent constants.

Graph 4. Plot of the calculated relative acidities (AM1) *vs* experimental pK_a for substituted benzo-fused five-memebered cyclic sulfamates.



Graph 5. Hammett plot of relative acidities (AM1) *v s* substituent constants for substituted benzo-fuse five-membered cyclic sulfamates.



The plot of calculated relative acidity *v s* experimental pK_a gave a satisfactory correlation with a reaction coefficient (r) = 0.914 and a standard error (s) = 0.279. The Hammett plot also gave average correlation with r = 0.923 and s = 0.102. The less than excellent correlation of the calculated values is a reflection of the low level at which they were calculated. The semi-empirical (AM1) level provided an adequate description of the the general trend in relative acidity but was not precise in descibing the exact acidity.

An attempt was made to calculated solution phase acidities by incorporating heats of solvation into the calculations. Geometry

optimization and single point energies were calculated at the AM1 semi-empirical level incorporating the Cramer-Truhlar solvation parameters[36]. The relative acidities from these calculation are shown in Table 7.

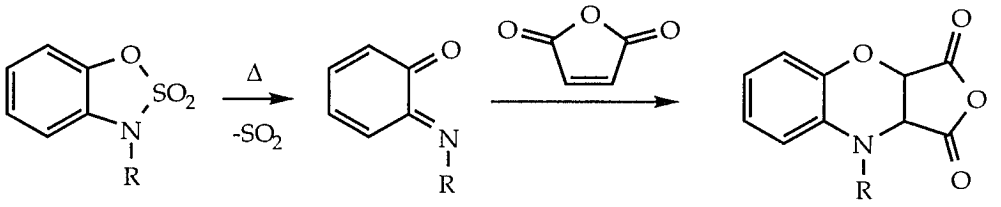
Table 7. Relative acidities calculated incorporating Cramer-Truhlar solvation parameters.

compound	X	ΔE (kcal/mol)
41a	5-NO_2	2.708
41b	H	0
41c	Me	1.009
41d	Br	3.081
41e	Cl	1.014
41f	5,6-Cl,Cl	2.516
41g	6-NO_2	5.429
41h	Nap.	0.352

The calculated values indicate that the Cramer-Truhlar solvation model did not provide an accurate description for the sulfamate. The order of acidity was very much inconsistent with that predicted by gas phase calculations as well as with the experimental results.

Attempted Synthesis of *o*-Monoquinoneimine from Cyclic Sulfamates

The cyclic sulfamates were evisioned to be a possible source of *o*-quinoneimine[37]. It was believed that upon heating the sulfamate would extrude sulfur dioxide to give the unstable *o*-quinoneimine which could then be trapped with an alkene to give the Diels-Alder adduct (Scheme 6).

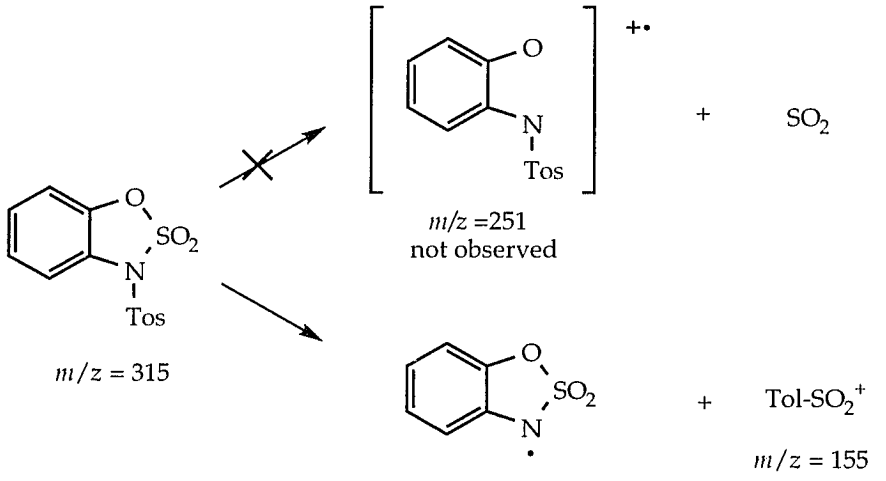


Scheme 6. Proposed formation and trapping of *o*-quinioneimine.

N-Tosyl sulfamate **6** was initially refluxed in a variety of high boiling solvents and the disappearance of starting material monitored by tlc. It was found that the starting material rapidly disappeared when refluxed in 1,2 dichlorobenzene (bp 180°C); also, the evolution of sulfur dioxide was observed by holding a wet piece of litmus paper over the neck of the flask.

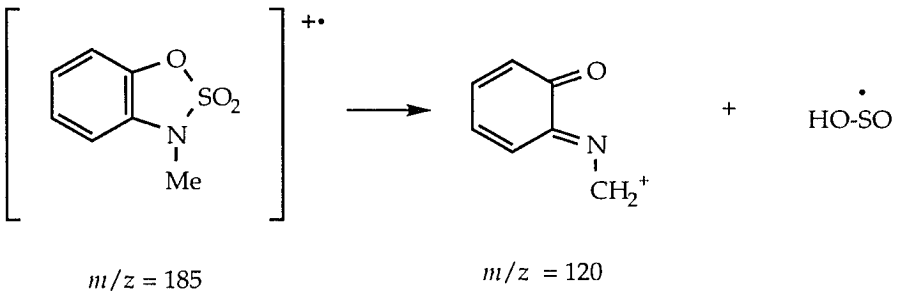
Compound **6** was refluxed in dichlorobenzene in the presence of an excess of maleic anhydride. The reaction mixture, which turned dark brown over time, was refluxed for 5 hours. It was believed that none of the Diels-Alder adduct was formed. The tlc of the reaction mixture showed several highly colored spots all of which were present when the sulfamate was heated in the absence of maleic anhydride.

It was believed that the tosyl group may be the cause of further decomposition aside from the extrusion of sulfur dioxide. It has been shown that there exists a correlation between the electron impact-induced fragmentation of a molecule and its thermolysis products. The EI-mass spectrum of **6** gave a molecular ion at *m* /*z* = 325 and shows no significant peak at *m* /*z* = 261 resulting from initial loss of SO_2. The first peak in the spectrum appears at *m* /*z* = 155 indicating the formation of the tosyl ion (Scheme 7).



Scheme 7. Initial EI-MS fragmentation of *N*-tosyl cyclic sulfamates.

This data might indicate that the *N*-tosyl is likely to fragment under the high temperature reflux conditions. In order to eliminate this possibility, the *N*-methyl sulfamate was synthesized as previously reported by Chumpradit. The EI-mass spectrum showed a parent ion at *m* /*z* = 185, and a base peak at m/z = 120, which arises from the initial loss of SO_2H (Scheme 8).



$m/z = 185$ $m/z = 120$

Scheme 8. Initial EI-MS fragmentation of *N*-methyl cyclic sulfamates.

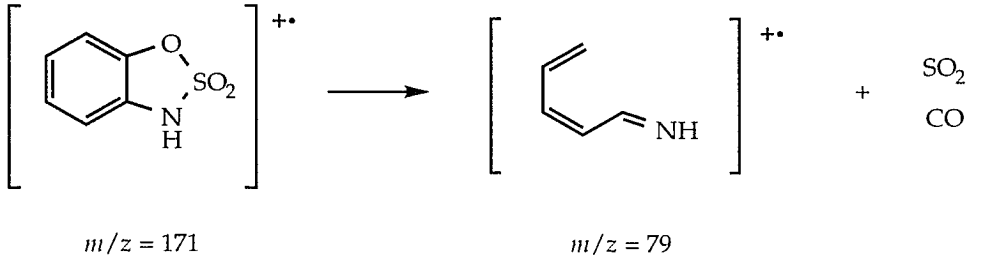
It was hoped that the fragment with $m/z = 120$ was the desired *o*-quinoneimine and that this fragment could be formed under thermal conditions. The *N*-methyl compound was then refluxed in 1,2-dichlorobenzene together with maleic anhydride. The solution was refluxed for 18 hours, becoming a dark orange color. Tlc showed a large dark streaky spot. Removal of the solvent gave a dark solid, which was very insoluble in chloroform. No pure compounds could be isolated from the mixture. An analogous reaction was carried out using dimethyl maleate in the place of maleic anhydride. The results were similar; no Diels-Alder adduct could be isolated.

It was thought that substitution on the aromatic ring of the benzoxathiazole might allow extrusion to occur under conditions which were less harsh. The *N*-methyl-5-nitrosulfamate was synthesized and refluxed in mesitylene in the presence of acenaphthylene for 18 hours. Removal of the solvent left a brown-orange oil. Tlc indicated that some starting material was left as well as another compound. The unknown compound was isolated. Its ^{1}H NMR spectrum showed numerous peaks, none of which were thought to correspond to the desired Diels-Alder adduct. It appeared that the sulfamates were indeed extruding sulfur dioxide; however, the formation of the

quinoneimine could not be demonstrated. The high temperatures may be causing further decomposition to occur before the quinoneimine can react to form the Diels-Alder adduct.

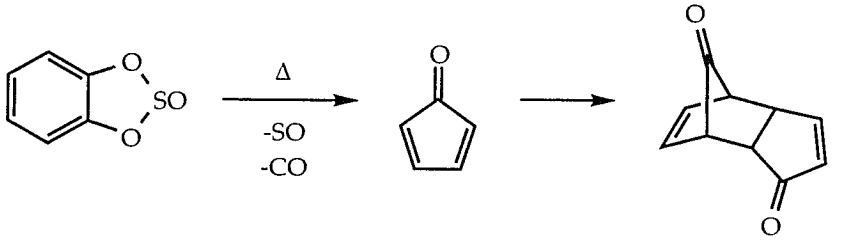
It was thought that the extrusion of sulfur dioxide could possible be induced photochemically. A solution of the *N*-methyl sulfamate in acetonitrile was irradiated in a Rayonet apparatus for 8 hours until the starting material had disappeared (tlc). The solution turned dark red and a black solid deposited in the reaction vessel as the reaction proceeded. The solid was found to be insoluble in chloroform. A ^{1}H NMR spectrum measured in acetone showed numerous peaks. The reaction was run again in the presence of maleic anhydride. The solution again turned red and a solid deposited as the reaction proceeded. The resulting solid was the same as was formed in the analogous reaction run in the absence of maleic anhydride.

Interestingly, the EI-mass spectrum of the *N*-H sulfamates was not analogous to that of the *N*-methyl compounds. The former sulfamates gave a molecular ion peak at *m /z* = 171, however, a peak was not observed at *m /z* = 106 or 107, which would be expected from loss of SO_2 or SO_2H. The largest peak in the spectrum was at *m /z* = 79, a loss of 92 mw, which is believed to result from initial loss of SO_2 and CO (Scheme 9).



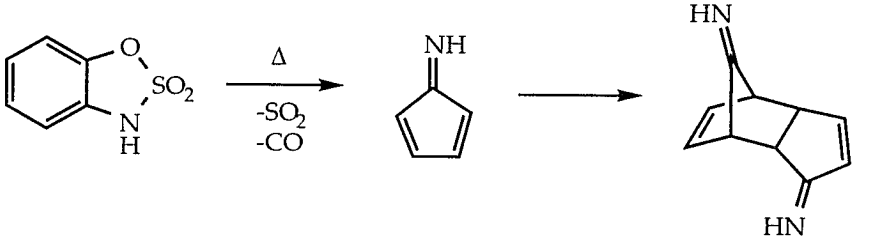
Scheme 9. Initial EI-MS fragmentation of N-H cyclic sulfamates.

These results are analogous to those observed by DeJongh[38a-b] and co-workers for *o*-phenylene sulfite, which fragments with loss of SO and CO. These fragmentation patterns were duplicated in the gas-phase pyrolysis of the sulfite, which resulted in the formation of cyclopentadieneone dimer (Scheme 10).



Scheme 10. Pyrolysis of *o*-phenylene sulfite reported by DeJongh.

It was envisioned that the *N*-H sulfamate, under gas-phase pyrolysis conditions, might undergo the loss of SO_2 and CO to give the cyclopentadieneimine which might dimerize similarly to cyclopentadieneone (Scheme 11).



Scheme 11. Proposed pyrolysis of N-H cyclic sulfamate.

The *N*-unsubstituted sulfamate was heated under vacuum and passed through a quartz tube containing glass beads. Several attempts were made, each varying the temperature of the quartz tube, from 250 to 400 °C. In all cases, no solid was collected in the dry ice/acetone trap at the end of the

apparatus. However, a brown orange solid deposited in the quartz tube just at the very exit of the oven. Tlc analysis of this compound showed several spots. The ^1H NMR spectrum showed many peaks including some in the aromatic region. No single compound could be isolated from the mixture. Also, in most cases, a good portion of the starting material turned brown and appeared to be decomposing in the heating flask.

It appears that in the case of the benzofused five-membered cyclic sulfamates, the decomposition pathway, either thermal or light induced, is not simply the loss of sulfur dioxide, but involves more extensive decomposition. These results indicate that the sulfamates do not provide a source of *o*-quinoneimines.

Theoretical Investigation of Sulfamate Model

The origins of the acid strengthening effect, which has been previously observed in sulfamides, disulfonamides and certain sulfonamides, and now in sulfamates has not been fully investigated. It has been suggested that ring strain may play an important role in the lowering of the pK_as of these compounds. However, the magnitude of the change seems too large to be due to this alone. Stereoelectronic effects involving the sulfonyl sulfur and neighboring heteroatoms have also been observed and have been suggested to play some role. The degree to which each of these factors affects the change in acidity has not been theoretically investigated. In an effort to understand the contribution of each of these factors to the acid strengthening effect, an *ab initio* study of a simple sulfamate model was undertaken.

Sulfamic acid was chosen as a simple model to study the effect of conformational change on the pK_a of sulfamates. By applying various

constraints to the molecule we could model a sequence of conformations of the sulfamate going from an acyclic-like geometry to a ring-like geometry and assess the degree to which each of these changes affects the pK_a.

The geometries of all the conformations (applying constraints where necessary) were optimized at the RHF/3-21+G(*)[39] level, cartesian coordinates for all structures are shown in Appendix. This level incorporates *d*-orbitals on the sulfur atom and also diffuse functions necessary for proper treatment of the anionic species. By calculating the energies for both the neutral and anioic species, ΔH for the deprotonation at nitrogen was obtained. The ΔH values for each conformation were then compared to judge the relative acidity of each conformation. Three factors which were thought to contribute to the overall lowering of the pK_a were examined. These three factors included O-S bond rotation, N-S bond rotation and ring contraction.

Initially, the model was allowed to optimize to its lowest energy conformation (**50a**), in which the H_1-O_2-S-N dihedral = 180° (hydroxyl hydrogen bisects the sulfonyl oxygens) and the O_2-S-N-(lone pair) dihedral = 180° (nitrogen lone pair bisects the sulfonyl oxygen). The molecule was then subjected to a series of conformational changes, to evaluate the three factors mentioned above, until the ring-like geometry was reached. The optimized structures representing these changes in conformation are shown in Figure 11.

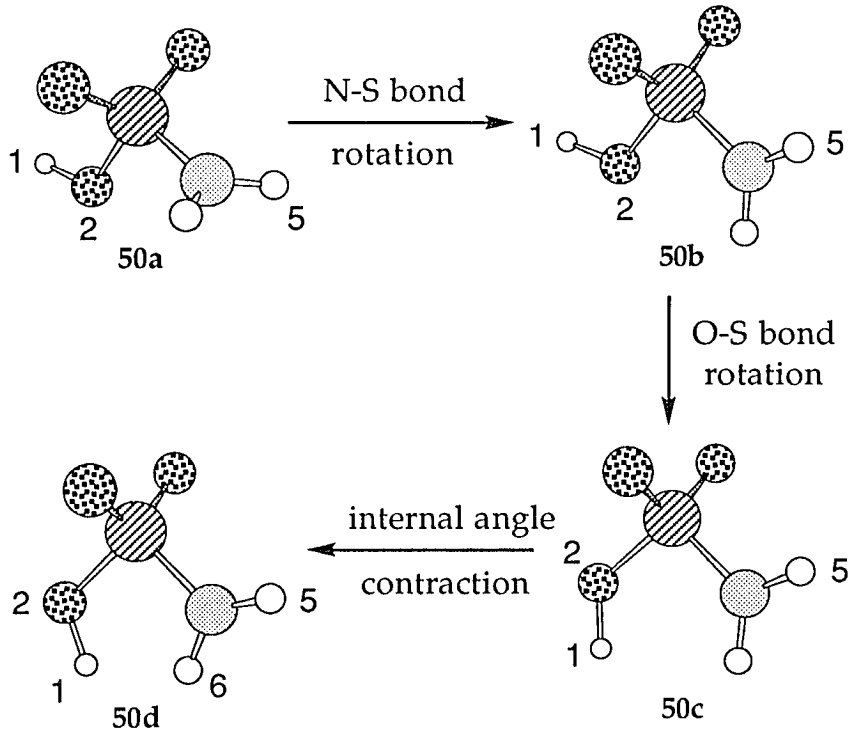


Figure 11. Conformation of sulfamic acid model.

The conformation of the nitrogen in relation to the sulfur atom is consistent with the experimental results observed in other systems containing a sulfonyl sulfur with a neighboring nitrogen, such as sulfonamides. The conformation of the oxygen, however, seems inconsistent with the geometry observed in similar systems, such as the sultones studied by King. As previously mentioned, most sultones prefer a geometry with a C-O-S-C dihedral of 75-90°. Structure **50a** was compared to a structure whose H_1-O_2-S-N dihedral was constrained to 90°, and the two were shown to be very close in energy with **50a** being only 1 kcal/mol lower in energy. The preference for that conformation in sultones may solely arise from steric interactions between an alkyl group on the oxygen and the sulfonyl oxygens.

The possibility was also raised that, hydrogen bonding between the hydroxyl hydrogen and sulfonyl oxygens might stabilize structure **50a**. An analysis of the Mulliken bond order of this compound, however, reveals no significant hydrogen bonding.

The single point energies of the neutral and anionic forms of **50a-d** from which the pK_a changes were calculated, as well as the relative energies of the different conformations, are shown in Table 8.

Table 8. Calculated (3-21+G(*)) energies for **50a-d** and their anions.

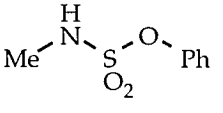
compound	E (NH_2)	E_{rel} (NH_2)	E (NH^-)	E_{rel} (NH^-)
50a	-674.929742	0	-674.376334	0
50b	-674.921973	4.9	-674.369018	4.6
50c	-674.905323	15.3	-674.356589	12.4
50d	-674.889493	25.2	-674.343595	20.6

The first conformational change examined was N-S bond rotation. The O_2-S-N-(lone pair) dihedral was constrained to 90° and the H_1-O_2-S-N dihedral at 180°, the optimized structure is represented **50b**. The resulting 90° rotation of the N-S bond caused a difference in energy of the two neutral species (**50a** to **50b**) of +4.9 kcal/mol and a difference between the anions of +4.6 kcal/mol. The difference between the two ΔH values of the two conformations was -0.3 kcal/mol. This translates to a ΔpK_a of -0.22 units resulting from the N-S bond rotation; *i.e*, the acidity was increased on going from **50a** to **50b**.

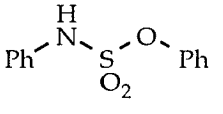
The O_2-S bond was then rotated, with the H_1-O_2-S-N dihedral angle constrained at 0°, keeping the O_2-S-N-(lone pair) dihedral at its previous value of 90°. This conformational changing resulted in a difference in energies from **50b** to **50c** of 10.4 kcal/mol for the neutral species and 7.8 kcal/mol for the anions. The difference in the two ΔH values was -2.65 kcal/mol, which leads to a ΔpK_a of -2.03 units.

The internal angle of **50c** were then constrained to resemble the ring-like geometry of the five-membered cyclic sulfamate. The internal angles were taken from the crystal structure of the *N*-tosyl sulfamate previously mentioned. The angles were constrained as follows: H_1-O_2-S = 112°, O_2-S-N = 95°, S-N-H_6 = 108°. The effects of constraining these internal angles were changes of 9.9 kcal/mol and 8.2 kcal/mol for the neutral molecules and anions, respectively. The ΔH value going from **50c** to **50d** was -1.78 kcal/mol, which leads to a ΔpK_a of -1.36 units.

The calculations suggest that the overall pK_a change in going from the acyclic structure to the cyclic structure is 3.6 pK_a units. To properly test the validity of these results, the experimentally determined pK_a for a cyclic sulfamate must be compared to an acyclic analogue. A proper compound to compare to cyclic sulfamate **6** would be phenyl *N*-phenyl aminosulfonate (**52**). The pK_a value for this compound has not yet been reported. A similar compound, **51**, has been reported to have a pK_a in 50% EtOH/H_2O of 10.53.



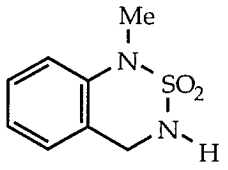
51



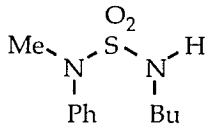
52

This value is approximately 5.8 units higher that that of the cyclic compound **6**. The computational results suggest that the difference should be smaller, around 3.6 pK_a units. It is conceivable, however, that the presence of a phenyl group attached to the nitrogen in place of the methyl could increase the acidity by as much as 2.5 pK_a units. This has been shown experimentally in the case of $PhNHSO_2Ph$ versus $MeNHSO_2Ph$ where the pK_a values differ by 2.67 units, with the former sulfonamide being more acidic. If the sulfamate were analogous to the sulfonamide, then the pK_a of **52** is predicted to be around 8 (10.53 - 2.67). This would bring the change in pK_a between the cyclic and acyclic sulfamates in the range of the theoretical model (3.6). These results are analogous to experimental results seen in cyclic sulfamides; cyclic sulfamide **13** (pK_a = 6.4) is approximately 3.7 pK_a units more acidic than its acyclic analogue (pK_a = 10.1).

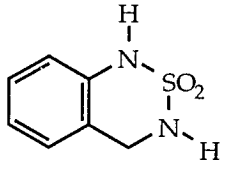
One other factor which may serve to lower the pK_a of the cyclic structure is the conformation of the aromatic ring in regard to the adjacent heteroatoms. In the acyclic compound the aromatic ring can adopt a conformation maximizing the interaction between the ring and the lone pairs on the heteroatoms. The constrained geometry of the cyclic structure might change this interaction, having a subsequent effect on the acidity of the compound. It has been experimentally shown in the case of six-membered sulfamides that this factor may not provide a significant change in the acidity.



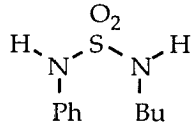
53 (10.66)



54 (13.28)



55 (8.79)



56 (11.34)

Sulfamide **53** (pK_a = 10.66)[17], which does not have an aromatic ring adjacent to the nitrogen was shown to be 2.62 pK_a units more acidic than acyclic analogue **54** (pK_a = 13.28)[40]. Sulfamide **55** (pK_a = 8.79)[17], which does possesses an aromatic ring adjacent to the nitrogen was shown to be 2.55 pK_a units more acidic than its acyclic analogue **56** (pK_a = 11.34)[40]. If the conformation of the aromatic ring in regard to the nitrogen did play a significant role in the increased acidity the difference between **53** and **54** would be expected to be larger than that between **55** and **56.**

It appears that the increase in acidity for the five-membered sulfamates is directly dependent on the amount of delocalization present between the lone pairs on the hetero-atoms and the sulfur atom. This delocalization is directly effected by bond rotation and angle contraction going from **50a** to **50d** and is reflected in the O-S and N-S bond lengths (Table 9)

Table 9. Selected bond lengths for **50a-d** and their anions.

	N-S (NH)	N-S (N^-)	O-S (NH)	O-S (N^-)
50a	1.58	1.52	1.59	1.65
50b	1.60	1.52	1.58	1.65
50c	1.62	1.53	1.58	1.66
50d	1.65	1.58	1.61	1.69

As the conformation of the neutral species is changed to provide for less and less delocalization, there is a corresponding increase in the appropriate bond lengths. This inhibition of delocalization has a direct effect on the acidity of the compound. The expected shortening of the N-S bond length in the anion compared to the neutral compound resulting from an increase in N-S delocalization is also seen. This causes the expected increase in O-S bond length. Evidence for this N-S delocalization has been determined by x-ray crystallography. Cotton and Stokely reported the crystal structures of $(PhSO_2)_2NH$ and $(PhSO_2)_2N^-Na^+$ whose N-S bond lengths were 1.65 and 1.58 Å, respectively[27].

The results of the theoretical study indicate that, for the case of cyclic sulfamates, the nitrogen-sulfur delocalization plays a minor role in the observed increase in acidity. The major contribution seems to arise from inhibition of oxygen-sulfur delocalization caused by rotation of the O-S bond. As previously suggested, ring strain does play a role in the increased acidity, in so much as it directly affects both the O-S and N-S delocalization as is apparent from the observed increases in bond lengths.

It seems that systems which are capable of this type of delocalization (Figure 12) with the sulfonyl sulfur atom are likely to exhibit the observed "acid strengthening" effect.

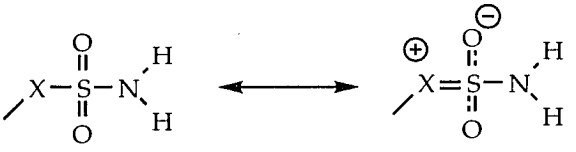
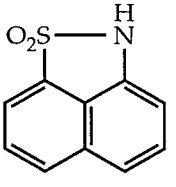


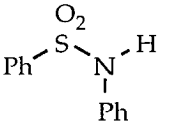
Figure 12. Heteroatom-sulfur delocalization observed in sulfamate model.

Our calculations show this to be the case for sulfamates. By analogy, this type of delocalization may also play a significant role in the cyclic sulfamides (nitrogen analogues of sulfamates) previously mentioned.

This explanation may not be limited to only heteroatom-sulfur delocalization, but may also apply to the case of aryl sulfonamides. The cyclic sulfonamide **57** (pK_a = 6.2)[41] has been shown to be 2.2 pK_a units more acidic than its acyclic analogue **58** (pK_a = 8.4).



57 (6.2)



58 (8.4)

This increase in acidity may arise from inhibition of delocalization between the aromatic ring and the sulfonyl sulfur. This would increase the

positive charge on sulfur, in turn making the sulfonamide hydrogen more acidic. In systems where this type of delocalization is not possible, such as the aliphatic sulfonamides **26-29**, no increase in acidity is observed for the cyclic analogues.

To further investigate the acid strengthening effect, calculations were performed on other heteroatom-sulfonyl systems to determine the theoretical changes in acidity and compare them to known values. The systems investigated were the sulfamides and aryl sulfonamides which have been shown experimentally to exhibit an increased acidity, and aliphatic sulfonamides which do not exhibit an increase.

Sulfamide, $H_2N\text{-}SO_2\text{-}NH_2$, was used as the model for the sulfamide functional group. The acyclic model, both the neutral and anionic compounds (**59a-b**) were allowed to optimize without constraints. The cyclic model (**60a-b**) was constrained in a five-membered ring-like geometry, applying the following constraints: $\angle H_1\text{-}N\text{-}S = 108°$; $\angle N\text{-}S\text{-}N = 95°$; $\angle H_2\text{-}N\text{-}S = 108°$; $H_1\text{-}N\text{-}S\text{-}N$ dihedral = 0°; $H_1\text{-}N\text{-}S\text{-}N$ dihedral = 0°. These angles were determined by geometry optimization, using a lower level basis set (HF/STO-3G), of a five-membered cyclic sulfamide. The remaining bond lengths and angles were allowed to optimize to the lowest energy conformation. The optimized structure and calculated energies (hartrees) are shown in Figure 13.

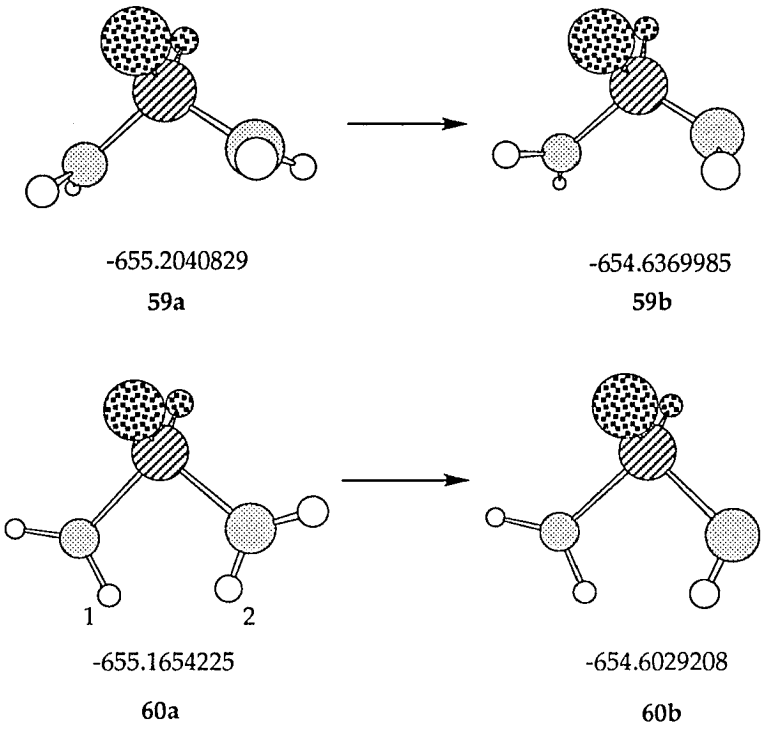


Figure 13. Optimized geometries and energies (hartrees) for sulfamide.

The differences between the ΔH values for the deprotonation of the cyclic and acyclic sulfamides was calculated to be 2.875 kcal/mol lower for the cyclic compound. This results in a pK_a 2.20 units lower for the cyclic compound compared to that of the acyclic compound. Experimentally, for benzo-fused five-membered sulfamides (**13**), it has been shown that the pK_a of the cyclic compound **13** is approx. 3.7 units lower than the acyclic compound **16**. Although there is a difference of 1.5 pKa units between experimentally observed value and the calculated values, the acid strengthening affect is still observed in the case of sulfamides. The difference might arise from changes in the geometry of the nitrogens. The calculated values were obtained on a structure with primarily planar nitrogens. The lack of experimental structure data on these five-membered sulfamides makes it impossible to know

whether the nitrogen atoms are actually planar. Slight differences in the geometries could account for relatively small energy differences in the compounds. A change in energy of only 1 kcal/mol could account for the discrepancy between the calculated change in pK_a and the expermintally observed value.

Similar calculations were performed on methyl sulfonamide, CH_3-SO_2-NH_2. For the acyclic model (**61a-b**), both the neutral and anionic compounds were allowed to optimize to their lowest energy geometries. In order to properly model the cyclic compound, the geometry of the five-membered saturated sulfonamide was optimized using a lower basis set. The two carbon atoms β to the sulfur atom were then removed, to give methyl sulfonamide (**62a-b**). The appropriate bond angle and dihedral angle were then constrained in the five-membered ring geometry as follows: $\angle H_1$-C-S = 108°, $\angle$C-S-N = 98°, $\angle$S-N-H_2 = 107° , H_1-C-S-N dihedral = 13° and C-S-N-H_2 dihedral = 0°.

Important to note is that the five-membered sulfonamide ring is not planar, but slightly puckered by rotation around the carbon sulfur bond, presumably to relieve steric interaction caused by the eclipsed conformation of the methyl hydrogen and the sulfonyl oxygens. The optimized structure and energies (hartrees) are shown in Figure 14.

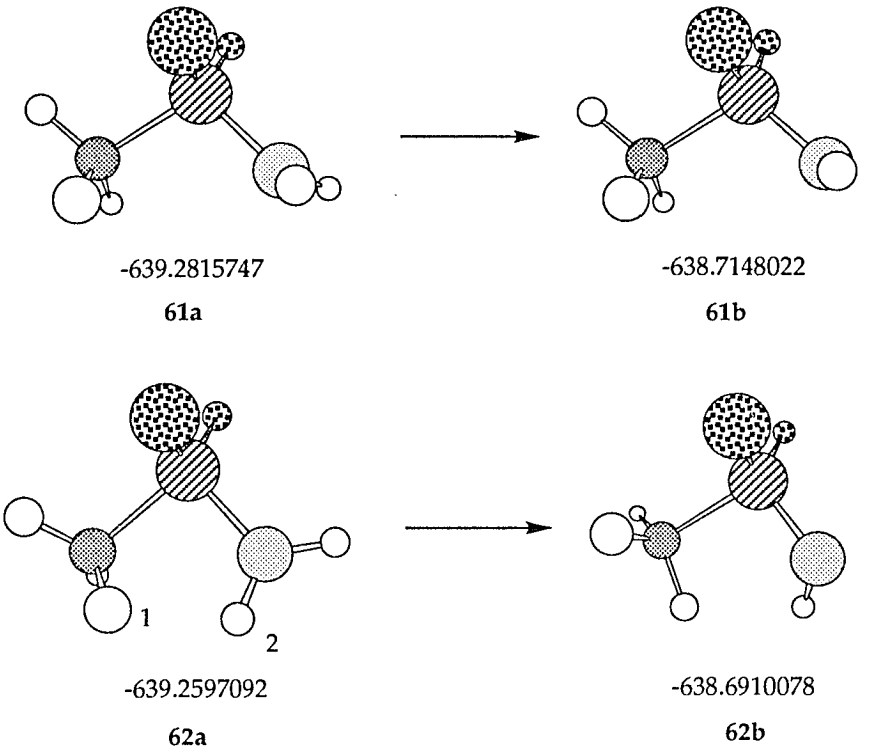
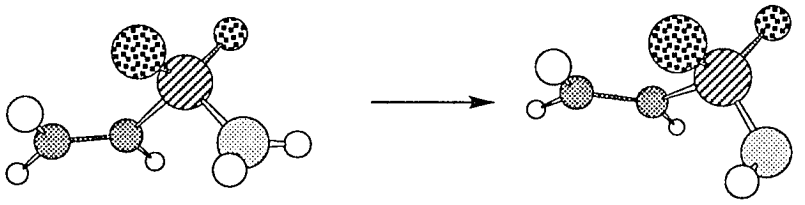


Figure 14. Optimized structures and energies (hartrees) for methyl sulfonamide.

The results of the calculations show a ΔH value for the cyclic sulfonamide which is 1.21 kcal/mol larger than that of the acyclic compound. The suggests that the acidity of the cyclic compound should be approx. 0.9 units higher; *i.e. less acidic,* than the acyclic compound. These results seem to correlate reasonably well with experimental results which show that aliphatic sulfonamides show no increase in acidity when incorporated into ring structures. The five-membered saturated sulfonamide **26** has been shown to have almost the same pK_a as acyclic analogue **29**. The six-membered compound **27** has been shown to be 0.55 units less acidic than **29**.

In order to examine the acid strengthening effect in aryl sulfonamides, vinyl sulfonamide (CH_2=CH-SO_2-NH_2) was used as a model. It was hoped that the alkene would serve as an appropriate mimic for a phenyl group attached to the sulfur atom. As done previously, the acyclic compounds were allowed to optimized to their lowest geometry. The vinyl sulfonamide, however, would not act as an appropriate model for the cyclic compounds. By constraining the internal angle in a ring-like geometry, the sulfonamide hydrogen and a vinyl hydrogen were put in very close proximity, providing substantial steric interactions. The α,β-unsaturated five-membered cyclic sulfonamide was used in its place. The optimized geometries and energies (hartrees) are shown in Figure 15.

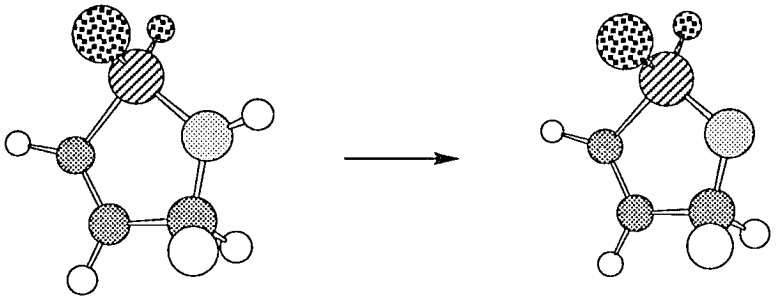


-676.9134612

63a

-676.3481080

63b



-714.5585798

64a

-713.9911229

64b

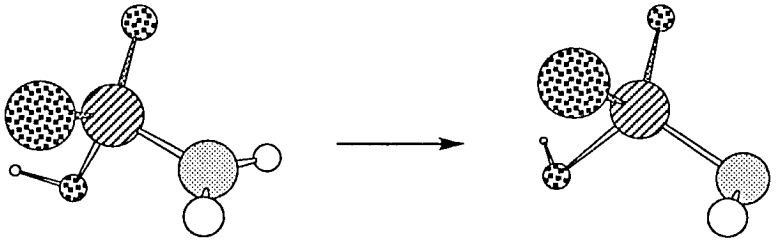
Figure 15. Optimized geometries and energies (hartrees) for vinyl sulfonamide models.

The calculations showed results similar to those observed for the methyl sulfonamide. The cyclic compounds was calculated 1.0 pK_a units less acidic that the acyclic compound. As previously mentioned, aryl sulfonamides have been shown experimentally to display an increase in acidity when incorporated into a ring structure, however these results do not corroborate this. It is quite conceivable that **63a** and **64a** do not adequately mimic the stereoelectronic factors in aryl sulfonamides.

Much controversy has surrounded the area of *d*-orbitals on sulfur and their effect on stabilizing adjacent anions. In an effort to examine this role in

the case of the cyclic sulfamates, the sulfamic acid model previously mentioned was further examined.

Previously the geometries of sulphamic acid and its anion were optimized at the 3-21+G(*) level, which incorporates *d*-orbital on the sulfur atom. To examine the effects of these orbitals, the compounds were reoptimized at the 3-21+G[39] level, without *d*-orbitals. The reoptimized structures are shown in Figure 16.



-674.62919800 -674.091720700

65a 65b

Figure 16. Optimized geometries and energies for sulfamic acid without *d*-orbitals (3-21+G).

The analysis of the role of *d*-orbitals on the stabilization of the anion was approached in two ways: (1) examination of the structural changes upon formation of the anion and (2) comparison of the proton affinities with and without *d*-orbitals. Select bond distances are shown in Table 10.

Table 10. Selected bond distances (Å) for sulfamic acid, with and without *d*-orbitals.

	with d-orbitals		without d-orbitals	
	NH	N^-	NH	N^-
S-N	1.573	1.521	1.657	1.677
S-O	1.600	1.648	1.677	1.724
S=O	1.430	1.460	1.589	1.606

The examination of the structural changes upon formation of the anion can be primarily focused on the changes in the length of the N-S bond. In the structure without *d*-orbitals the N-S bond lengthens 0.02 Å when the anion is formed, with *d*-orbitals this bond shortens 0.052 Å. The shortening of this bond with *d*-orbitals suggests that they have some stabilizing effect on the anion, resulting in an increase in the N-S delocalization reflected by the shortened bond length.

An examination of the proton affinities (difference in the energies of the neutral and anionic compounds) of the two compounds, however, suggests otherwise. If *d*-orbital participation were indeed important in stabilizing the anion, the proton affinity of the compound with *d*-orbitals should be lower than that without, due to extra stabilization afforded by the *d*-orbitals. In the sulphamic acid case, however, the proton affinity of the compound with *d*-orbitals is 9.73 kcal/mol larger than the compounds without *d*-orbital. This suggests that the *d*-orbitals do not serve to stabilize than anion and may in fact, serve to destabilize it.

Conclusions

In summary, 5-nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (**6g**) was shown to react with nucleophiles differently than the parent *N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (**6a**). Amine nucleophiles were shown to attack the exocyclic sulfur atom and cleave the tosyl group. This reactivity was, in part, thought to be caused by the acidity of the benzoxathiazole ring. To further investigate this, a series of substituted *N*-H-1,2,3-benzoxathiazole-2,2-dioxides (**41a-h**)(cyclic sulfamates) was synthesized and their pK_as determined. The cyclic sulfamates were shown to be more acidic than their acyclic analogues. The origins of this "acid stengthening" effect in sulfamates was investigated by *ab initio* calculations, using sulfamic acid as a model. The overall pK_a change was shown to arise from three factors: N-S bond rotation, O-S bond rotation and ring contraction. O-S rotation was responsible for the largest contribution, followed by ring contraction and lastly, N-S bond rotation. It has been previously suggested that the delocalization between the sulfur atom and the atom being deprotonated (in the case of sulfamates, nitrogen) was a major contributor to this effect. The results on the sulfamate model lead to the conclusion that this delocalization plays a minor role and the primary contributor is the delocalization between the sulfur atom and the heteroatom on the opposite side of the sulfur from the atom being deprotonated (in the case of sulfamates, oxygen). This conclusion may be extended to other systems capable of this type of delocalization which have shown this acid strengthening effect.

The contribution of *d*-orbitals to the stabilization of the sulfamate anion was also investigated using *ab initio* methods. These results were ambiguous,

providing no certain evidence either way of the role of *d*-orbitals in this system.

Lastly, the acid strengthening effect in other sulfonyl-containing heterocycles was investigated by *ab initio* methods. The sulfamide model was consistent with experimental results, in that the cyclic compound was shown to be more acidic than the acyclic analogue. The methyl sulfonamide was also consistent with experiment in that there is no difference between the cyclic and acyclic compounds. Results for the vinyl sulfonamide, used as a model for aryl sulfonamides, was inconsistent with experiment. The calculations suggest no difference between the acyclic and cyclic compounds. However, experiment has shown otherwise, with the cyclic compound being more acidic. This inconsistency may be the result of lack of a proper model.

Further work that could be done in this area includes continued investigation into the chemoselectivity of nucleophilic attack on the N-tosyl sulfamate. The reasons why certain nucleophiles attack the exocylic sulfur whereas others attack the endocyclic sulfur remain unexplained. Insight might be gained by substituting the sulfonyl aryl group and investigating how the different substituents affect the selectivity of nucleophilic attack. In addition, further computational investigations into the acid strengthening effect in other sulfonyl-containing heterocycles would provide useful information regarding hetero atom-sulfur delocalization. Higher level computations also might provide further insight into the role of *d*-orbitals in these systems.

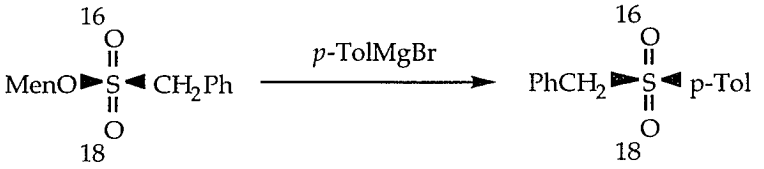
PART II

INVESTIGATION OF ENDOCYCLIC SUBSTITUTION AT TETRACOORDINATE SULFUR (VI).

Nucleophilic Substitution at Tetracoordinate Sulfur (VI)

Nucleophilic substitution reactions at tetracoordinate sulfur (VI) have been the topic of some interest and have been reviewed[42-46].

The stereochemistry of nucleophilic substitution at tetracoordinate sulfur (VI) was first described by Andersen[47] and coworkers. When (-)-menthyl-(*S*)-phenylmethanesulfonate-$^{16}O,^{18}O$ (**66**) was treated with *p*-tolylmagnesium bromide, optically active benzyl p-tolyl sulfone-$^{16}O,^{18}O$ (**67**) was obtained. The absolute configuration of the sulfone was assigned as *S*, indicating that the nucleophilic attack proceeded with inversion of configuration at sulfur.



66 **67**

Two mechanisms have been considered for nucleophilic substitution at tetracoordinate sulfur (VI) (Figure 17).

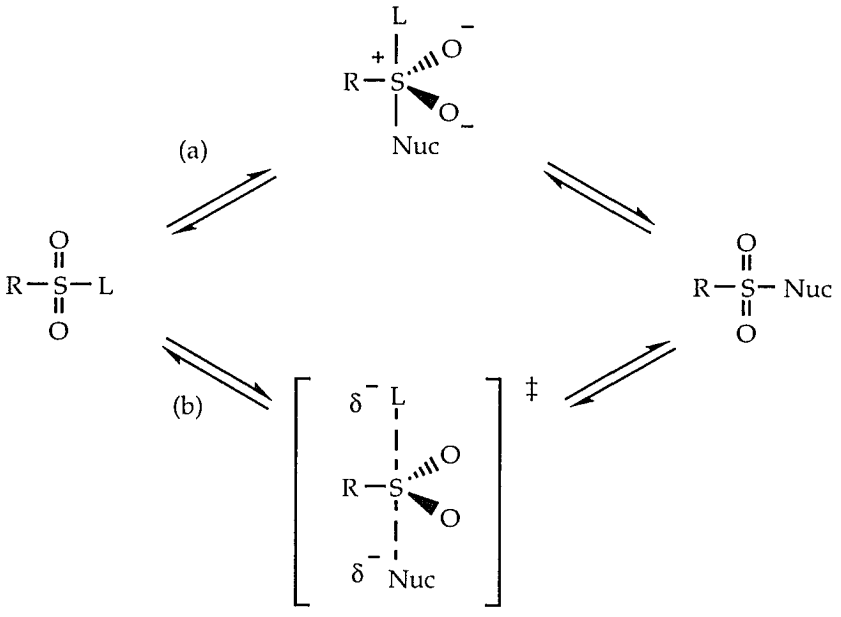
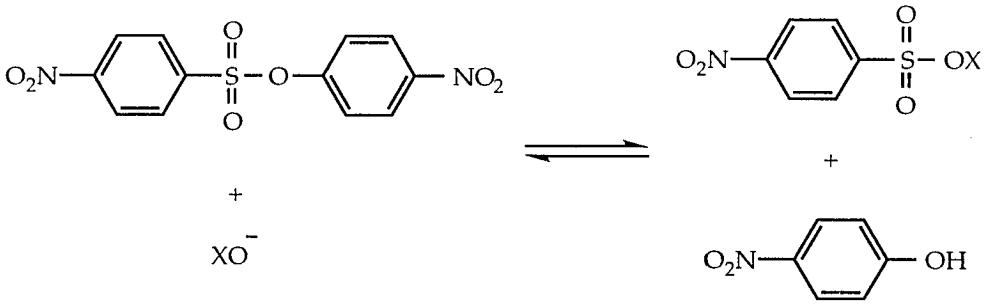


Figure 17. Pathways for sulfonyl transfer reaction.

The reaction may proceed through a concerted mechanism (b), involving and S_N2-like transition state. Alternatively, it could go through a two-step process (a), involving a pentacoordinate trigonal bipyramidal sulfurane intermediate. The question of a concerted or step-wise mechanism is still disputed; arguments for both pathways have appeared in the literature.

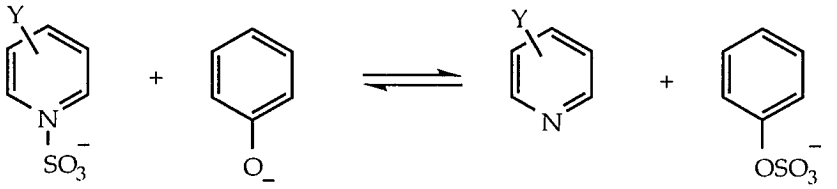
Williams[48] and coworkers have presented evidence for a single transition state, therefore a concerted mechanism in sulfonyl transfer between oxyanions and nitroaryl esters of 4-nitrobenzenesulfonic acid (Scheme 12).



Scheme 12. Sulfonyl transfer between oxyanions and nitoaryl ester of 4-nitrobenzenesulfonic acid.

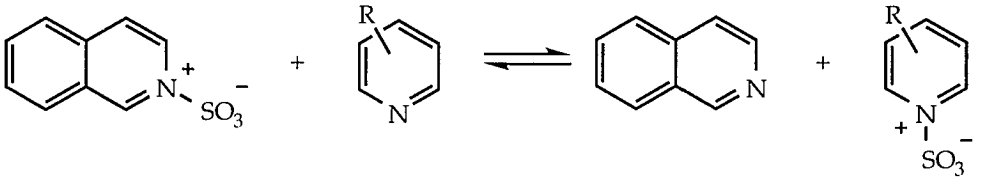
A series of oxyanions with basicities both smaller and larger than 4-nitrophenolate were used as nucleophiles. Should this reaction follow a step-wise mechanism, a change in the rate-determining step should have occurred as the incoming group became more or less basic than the leaving group. This would have given a Brønsted relationship which was non-linear, with break at $\Delta pK_a = 0$ resulting from a stepwise mechanism with two electronically distinct transition states. The Brønsted relationship observed was linear, suggesting a single transition state concerted mechanism. The possibility of the intermediate being in a shallow energy well with two electronically similar transition states cannot be ruled out unequivocally.

A similar study was also reported by Williams[49] and coworkers which involved the sulfonyl transfer between substituted pyridines and phenolate anion in aqueous solutions (Scheme 13). Analogous to the previous study, a single transition state, concerted mechanism, was supported by the Brønsted plot data.



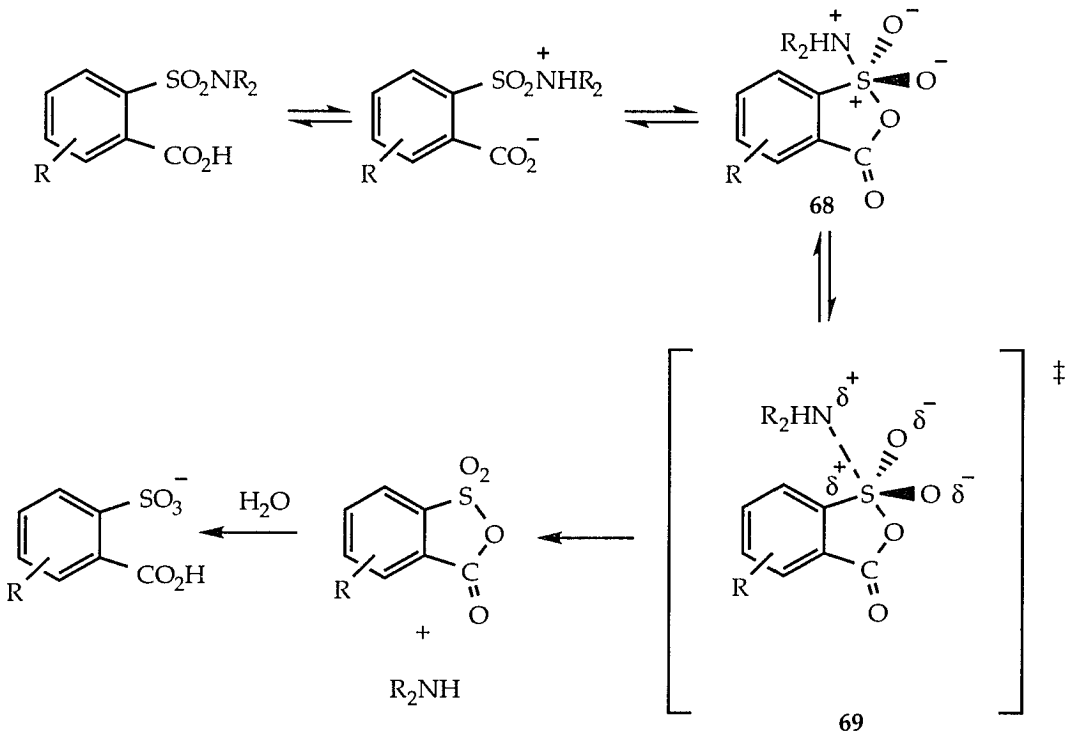
Scheme 13. Sulfonyl transfer between substituted pyridines and phenol.

Williams[50] and coworkers presented further evidence to support a concerted mechanism in the sulfonyl transfer between isoquinoline-N-sulfonate and substituted pyridines (Scheme 14). A Brønsted study was conducted between pH 7-8. If a stepwise mechanism is operative, the Brønsted plot would exhibit a break at the pK of isoquinoline. If a concerted mechanism is operative, the plot would be linear. The reaction obeyed a linear plot suggesting a concerted mechanism.



Scheme 14. Sulfonyl transfer between subtituted pyridine and isoquinoline.

Engberts[51] and coworkers presented evidence for the formation of a pentacoordinate intermediate (**68**) in the intramolecular carboxyl-catalyzed hydrolysis of sulfonamides (Scheme 15).

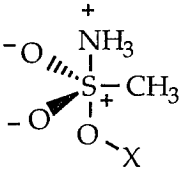


Scheme 15. Engbert's intramolecular carboxyl-catalyzed hydrolysis of sulfonamides.

The main argument put forth for a stepwise mechanism was based on the negative ρ value (-0.54 ± 0.02) for the acid catalyzed hydrolysis of aromatic sulfonamides with substituents *meta* and *para* to the carboxyl functionality. This negative value is consistent with a reduction of electron density on the carboxyl group in the transition state compared to the initial state. This implies that the new sulfur-oxygen bond is already fully formed in the transition state of the slow step. The sulfur-nitrogen bond is partially broken. The leaving group ρ value is very small and negative, signifying that the nitrogen must carry a small positive charge in the transition state. The ρ value for the sulfonyl center (-0.58 ± 0.01) implies a reduction of electron density on going to the transition state. The effects of the substituents are

consistent with a transition state structure in which all three centers, carboxyl, sulfonyl and nitrogen, are more electron deficient than in their initial state. The transition state that fits these requirements is that for the breakdown of the pentacoordinate intermediate. Engberts concluded a stepwise mechanism involving a sulfurane intermediate.

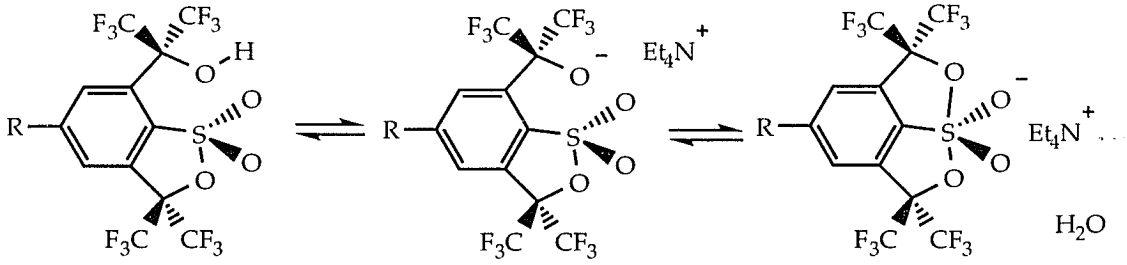
Engberts[52] and coworkers reported further support for this stepwise mechanism in the form of *ab inito* calculations. The preference rules for pentacoordinate phosphorus compounds were applied to sulfur compounds; the structure **70** was found to be the most favorable structure. This compound has a structure in which the ring would be attached via apical-equatorial positions with the C-S-O_{ax} angle equal to 90°.



70

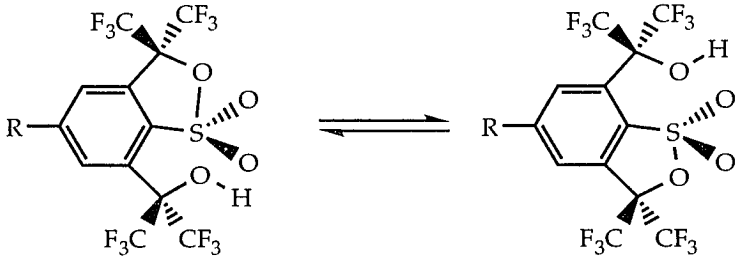
Calculations on different conformations of this intermediate showed a clear preference for the trigonal bipyramidal structure with apical bonds to the incoming nucleophile and the leaving amine.

Martin[53] and coworkers synthesized the analogue of the sulfurane intermediate expected from endocyclic substitution at sulfur (VI). The sulfanilide dioxide **71d** resulted from the treatment of conjugate acid **71** with tetraethylammonium hydroxide.



71a,b 71c 71d

The dynamic interconversion between conjugate acids **71a** and **71b** was evident by the coalescence, at high temperatures, of two ^{19}F NMR singlets into one. Base catalysis was postulated to go through the sulfuranilide dioxide **71d** as evident by a broad singlet in the ^{19}F NMR spectrum. The stabilization of the anion of **71c** by bridging to form **71d** would lower the energy of the equilibrium and explain a large increase in the rate of base-catalyzed equilibration.



71a 71b

The pK value for the hypothetical equilibrium between alcohol **71a** and its conjugate base (**71c**), was estimated by a Hammett correlation to be 9.1. The

observed value was 7.2. The lower value suggested that the structure in solution was that of **71d** and not the open-chained isomer **71c**.

An x-ray structure analysis was done on sulfurane **71d**. The geometry about the sulfur atom was shown to be trigonal bipyramidal. The equatorial angles were shown to be 117.8° and 122.7°, very close (less than 3° deviation) to ideal (120°). The apical O-S-O angle was shown to be 192.3°, 12° from the ideal (180°). This deformation from linearity was explained by Martin to be caused by repulsive interaction between non-bonding electrons on the equatorial oxygens and also by ring strain in the two bridged five-membered rings.

Endocyclic Substitution at Sulfur (VI)

Nucleophilic attack at sulfur is generally assumed to take place in an S_N2 like fashion, with the incoming nucleophile at an angle approximately 180° from the leaving group. This would lead to an apical-apical arrangement of the nucleophile and leaving group in the trigonal bipyramidal intermediate or transition state, leading to inversion of configuration at the sulfur. The orientation of the nucleophile and leaving group, however, can take other arrangements. The nucleophile could approach 120° to the leaving group, resulting in an equatorial-equatorial arrangement, leading to an inversion of configuration at sulfur. The nucleophile could also approach 90° to the leaving group, resulting in an apical-equatorial arrangement, leading to a retention of configuration at sulfur (Figure 18). Although there are no demonstrated cases of retention of configuration at tetracoordinate sulfur (VI), there are examples of retention in nucleophilic substitution at tricoordinate sulfur (IV)[54,55].

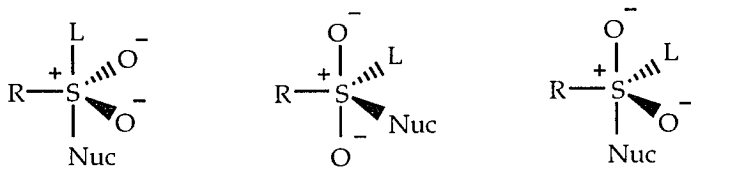
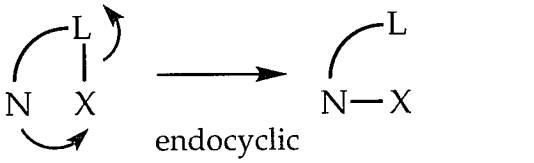
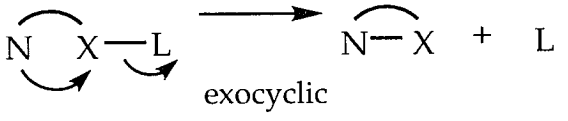


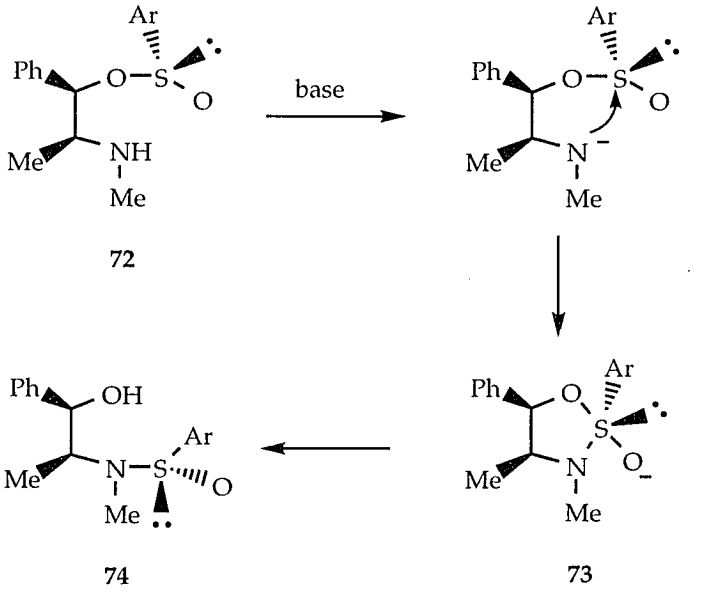
Figure 18. Stereochemical arrangements for nucleophilic substitution at sulfur (VI).

To determine if colinearity is necessary in nucleophilic substitution at sulfur (VI), endocyclic substitution[56] can be used to probe the affect of deviation from the ideal Nuc-S-L angle of 180°. In endocyclic substitution the leaving group (L) is bound directly to the nucleophile (N), so the atom being being attacked (X) is transfered intramolecularly. This is in contrast to exocylic substitution, in which the the atom being attacked (X) is attached to the nucleophile (N). Intramolecular nucleophilic attack results in ring formation and loss of the leaving (L) from the parent molecule.





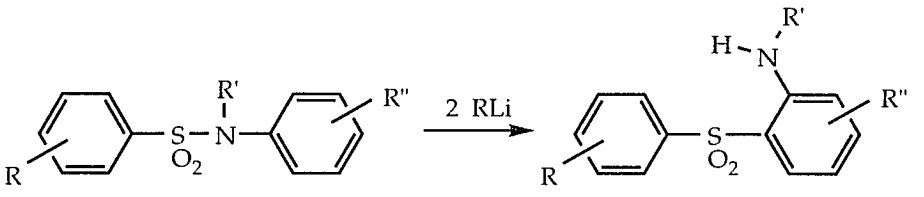
Wudl and Lee[54] first demonstrated intramolecular nucleophilic substitution at sulfinyl sulfur via a five-membered cyclic pentacoordinate intermediate or transition state (Scheme 16).



Scheme 16. Wudl's example of retention of configuration in endocyclic substitution of sulfur (IV).

When (*R*)-1-ephedrine-4-toluenesulfinate (**72**), at low concentrations, was treated with lithium dicyclohexylamide, sulfinyl transfer took place. It was determined that the transfer took place with retention of configuration. As the concentrations were increased the amount of inversion increased, due to the increase in the likelihood of intermolecular substitution. This led to the conclusion that the reaction at low concentrations was an example of intramolecular endocyclic substitution. The five-membered tetracoordinate sulfurane **73** was proposed as an intermediate.

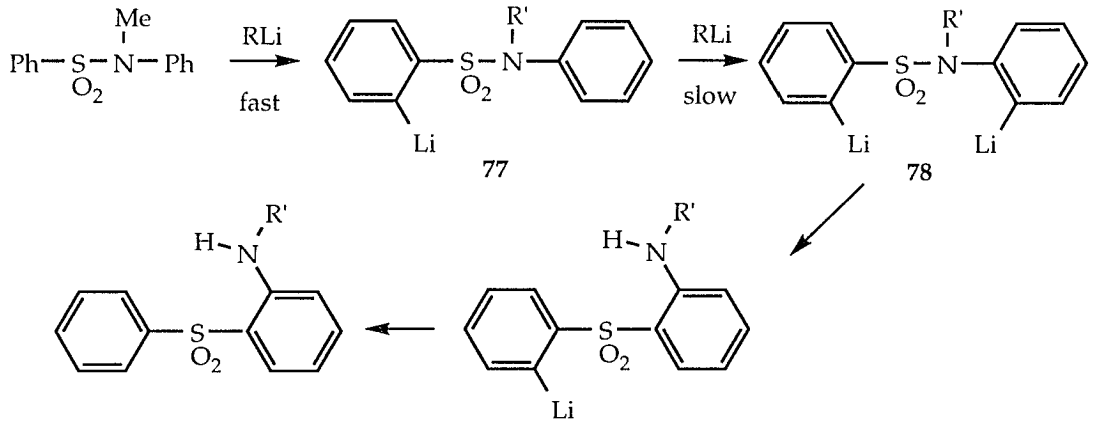
Examples of endocyclic nucleophilic substitution at sulfur (VI) have been reported by Hellwinkel[57] and Closson[58] and coworkers for sulfonamides of the general type **75**, with R, R' and R" being combinations of H, CH_3 and OCH_3. Treatment of these compounds with two equivalents of alkyllithiums (methyl and *n*-butyl) resulted in rearrangement to sulfones of the general type **76**, in moderate to good yields.



75 **76**

A crossover experiment was performed with a mixture of two sulfonamides; (1) R = CH_3, R'= CH_3, R"= H and (2) R = OCH_3, R"= OCH_3, R'= CH_3. After treatment with *n*-butyllithium, GC analysis of the product mixture showed only two products, those resulting from intramolecular rearrangement; no intermolecular products were observed.

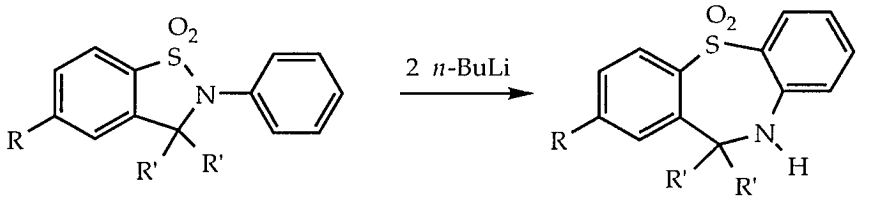
Closson postulated a mechanism for this reaction which involved the formation of a dianion **78**, prior to rearrangement (Scheme 17).



Scheme 17. Postulated mechanism for Hellwinkel-Closson rearrangement.

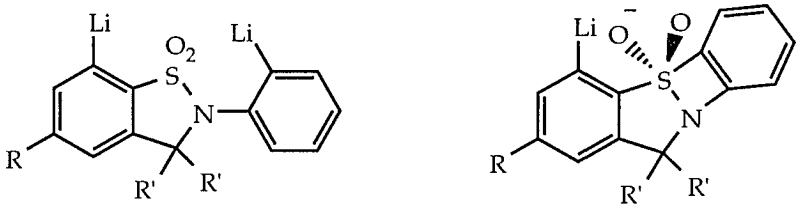
In support of the first step, *ortho* metallation, the treatment of the sulfonamide with one equivalent of the alkyllithium and quenching with methyl iodide led to the *ortho* methyl sulfonamide arising from the mono anion **77**. No evidence was offered for the existence of the dianion (**78**), however, its formation was postulated based on the following: (1) the *ortho* site is the position of sulfonyl transfer, (2) if the ortho position is blocked the reaction doesn't take place and (3) chelation of a lithium cation with a sulfonyl oxygen via a six membered ring is possible.

Hellwinkel and coworkers extended this reaction to cyclic sulfonamides of the general type **79**. Treatment with two equivalents of *n*-butyllithium caused the rearrangement to a dibenzo[*b*,*f*][1,4]thiazepine dioxide structure (**80**).



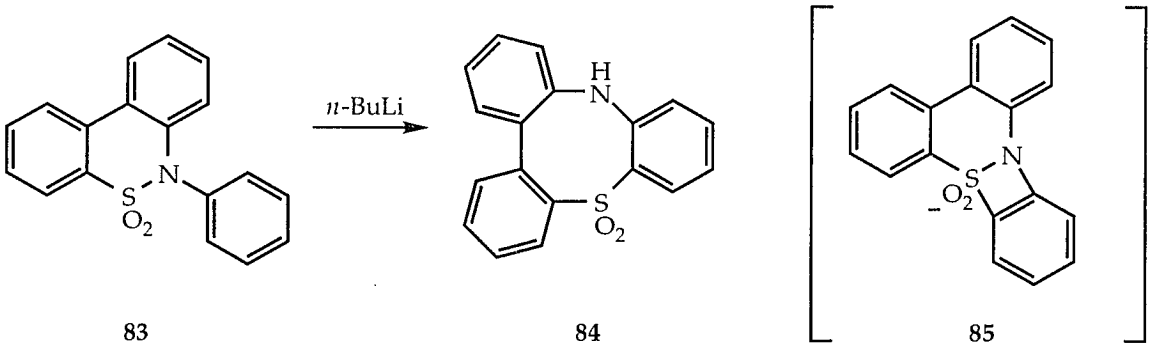
79 80

Hellwinkel[59] postulated a mechanism similar to Closson's involving formation of a dianion **81**. Treatment of **79** with one equivalent of *n*-butyllithium gave mono-metallation *ortho* to the sulfonyl group. Hellwinkel noted that this anion was too far away for an intramolecular transmetalation to occur. Once the second equivalent was added, the compound rearranged to the thiazepine. Whether structure **82** is an intermediate or transition state in the rearrangement could not be determined.



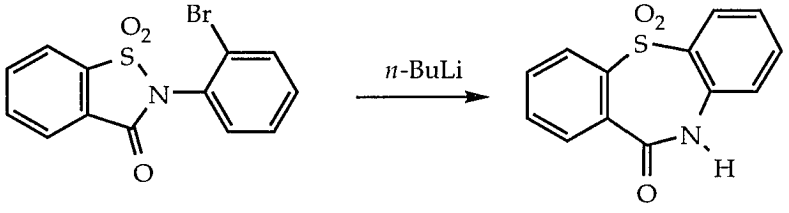
81 82

Analogously, Hellwinkel[60] treated (*N*-phenyl)-6H-dibenzo[*c*,*e*]-[1,2]thiazin-5,5-dioxide (**83**) with *n*-butyllithium at low temperature and observed a rearrangement product, 14H-tribenzo[*b*,*e*,*g*][1,4]thiazocin-9,9-dioxide (**84**). Whether structure **85** is a transition state or intermediate was not determined.



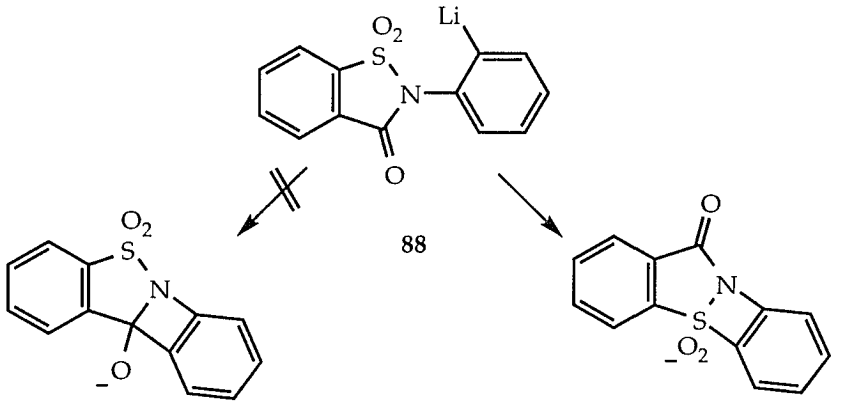
83 84 85

Hellwinkel[60] also investigated the synthetic utility of this rearrangement, as a means of making seven-membered heterocycles from five-membered heterocycles. Rearrangement of 1,2-benzisothiazolone-1,1-dioxide **86**, upon treatment with *n*-butyllithium provided the dibenzo[*b,f*][1,4]-thiazepin derivative **87**.

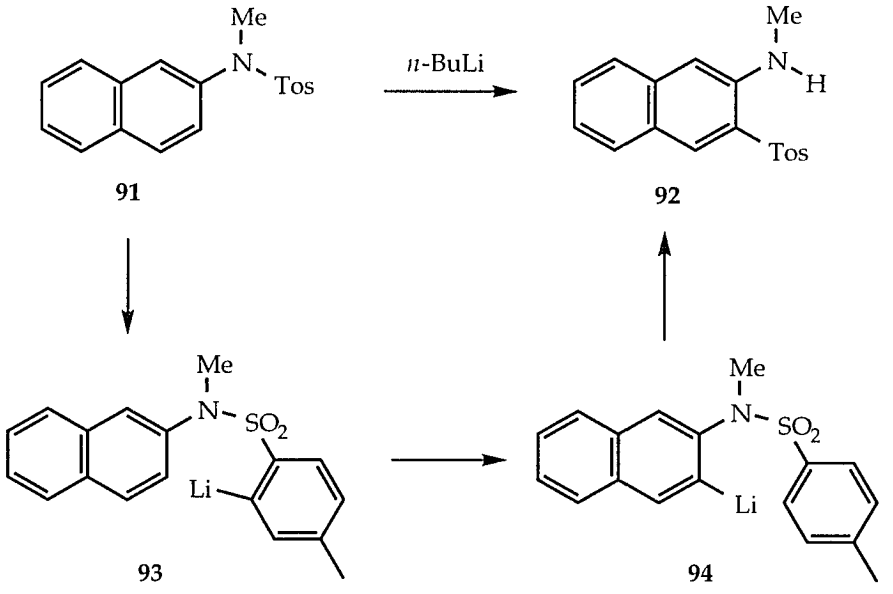


86 87

Although the carbonyl was potentially a site of nucleophilic attack by the carbanion (**88**), it was rationalized that the carbanion cannot achieve the prefered angle of attack (100°) with the carbonyl bond, in order to form intermediate **89**. It is in position, however, to attack the sulfur center to form the trigonal bipyramidal structure (**90**).

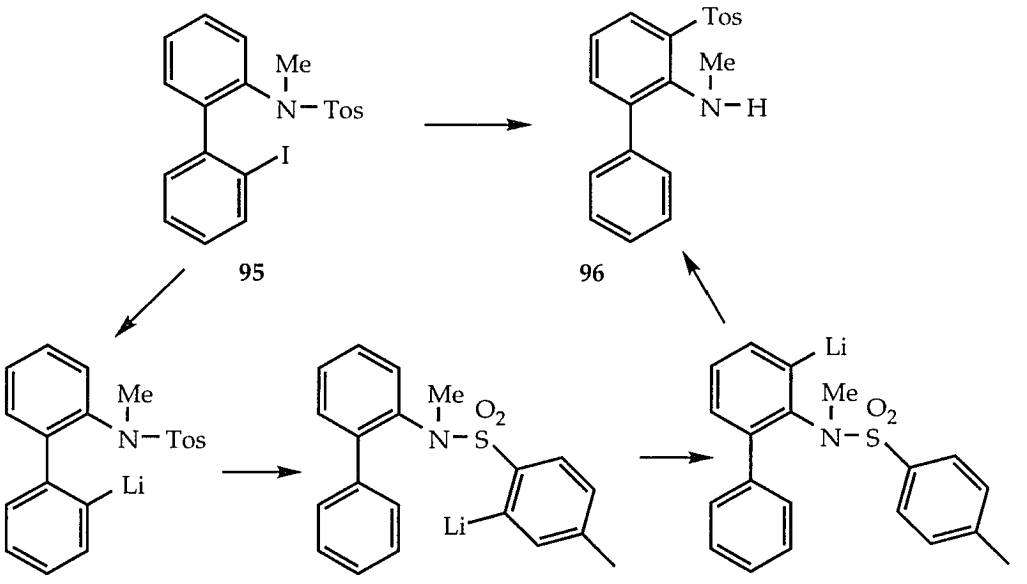


Hellwinkel and Lenz[61] further explored the rearrangement of sulfonamides (Scheme 18). *N*-Napthyl-*N*-methyl-4-toluenesulfonamide (**91**) rearranged to the aminosulfone **94** when treated with only one equivalent of *n*-butyllithium. The mechanism was postulated to be metallation *ortho* to the sulfonyl group forming anion **92**, followed by transmetallation to the position *ortho* to the nitrogen (**93**), then rearrangement.



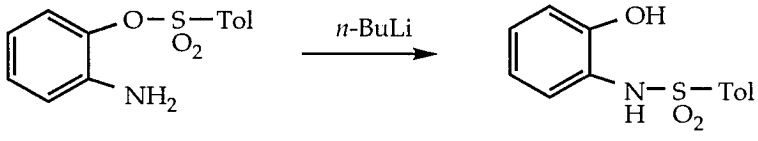
Scheme 18. Hellwinkel's transmetallation mechanism for the rearrangement of sulfonamide **91.**

A similar transmetalltion was observed when sulfonamide **95** was treated with *n*-butyllithium or *t*-butyllithium, rearrangement then led to the sulfone **96** (Scheme 19)[61]. Formation of the product was explained by initial metal-halogen exchange followed by two transmetallations, then rearrangement. It is of interest that the initial carbanion could have reacted with the sulfur atom and rearranged through a six-membered transition state or intermediate, instead transmetalation occurred and the rearrangement took place by way of a four-membered transition state or intermediate.



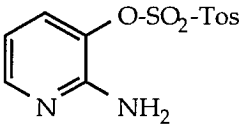
Scheme 19. Hellwinkel's transmetallation mechanism for the rearrangement of sulfonamide **95**.

An apparent example of endocylic substitution at sulfur (VI) was reported by Andersen[62] and coworkers. 2-Aminophenyl 4-toluenulfonate (**97**) was treated with *n*-butyllithium and found to rearrange to sulfonamide **98**. The reaction was found to be irreversible, by treatment of **98** with *n*-butyllithium; no sulfonate **97** was detected.

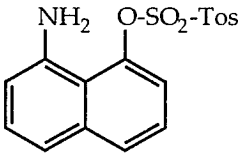


97 **98**

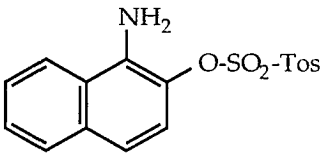
Several other sulfonates were shown to rearrange to their corresponding sulfonamides. The analogous pyridine compound **99** rearranged in a 70% yield. The two naphthyl compound, **100** and **101**, also yielded the rearranged products in low yields, 33% and 20% respectively.



99

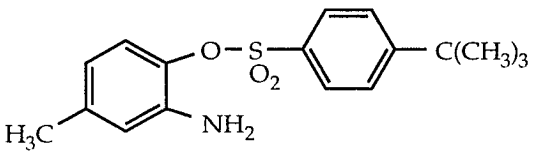


100

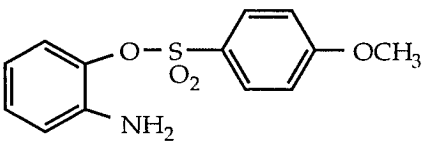


101

An initial crossover experiment was performed to determine whether this rearrangement went by way of an intramolecular or an intermolecular pathway. An equal mixture of sulfonates **102** and **103** was treated with four equivalents of *n*-butyllithium. If the reaction were going intermolecularly, the reaction mixture should contain four products. An intramolecular reaction would give only two products.



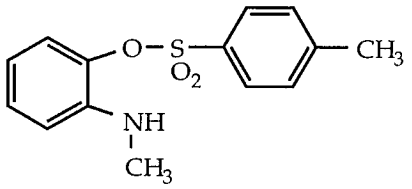
102



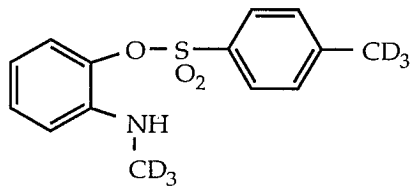
103

The ^1H NMR spectrum of the product mixture showed only two products. Comparison to spectra of all four independently synthesized possible sulfonamides showed the two products to be the ones arising from intramolecular rearrangement. It was concluded that this reaction was intramolecular; however, this was based on the assumption that the two sulfonates rearranged at the same rate. The possibility existed that one sulfonate reacted faster than the other. This would allow for the faster reacting sulfonate to react intermolecularly to completion before the slower sulfonate had reacted significantly. If this indeed were the case, only the intramolecular products would be observed even though the rearrangement might be actually occurring intermolecularly.

In an effort to rule out this possibility, a crossover experiment involving the sufonate **104** and its corresponding deuterium labeled analogue **105** was undertaken. The rates of the two compounds were not expected to differ significantly.



104

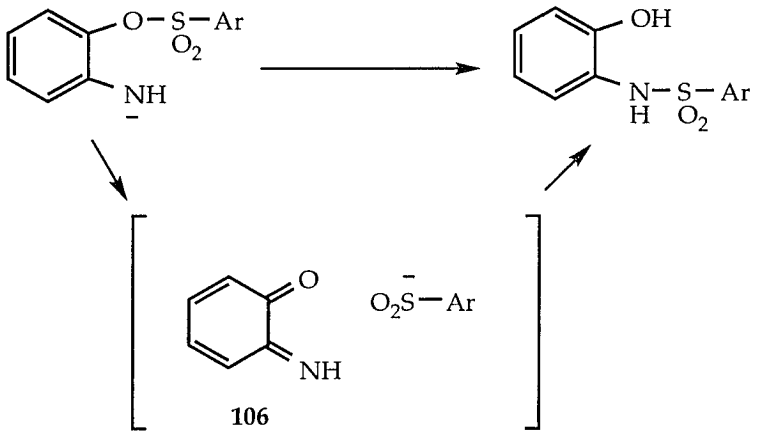


105

Compounds **104** and **105** were treated with three equivalents of lithium diisopropylamide. The deuterium distribution detected by mass spectrometry was found to be consistent with that calculated for an intramolecular reaction.

These results support the previous crossover experiment, indicating that the rate of reaction of compounds **102** and **103** are not significantly different.

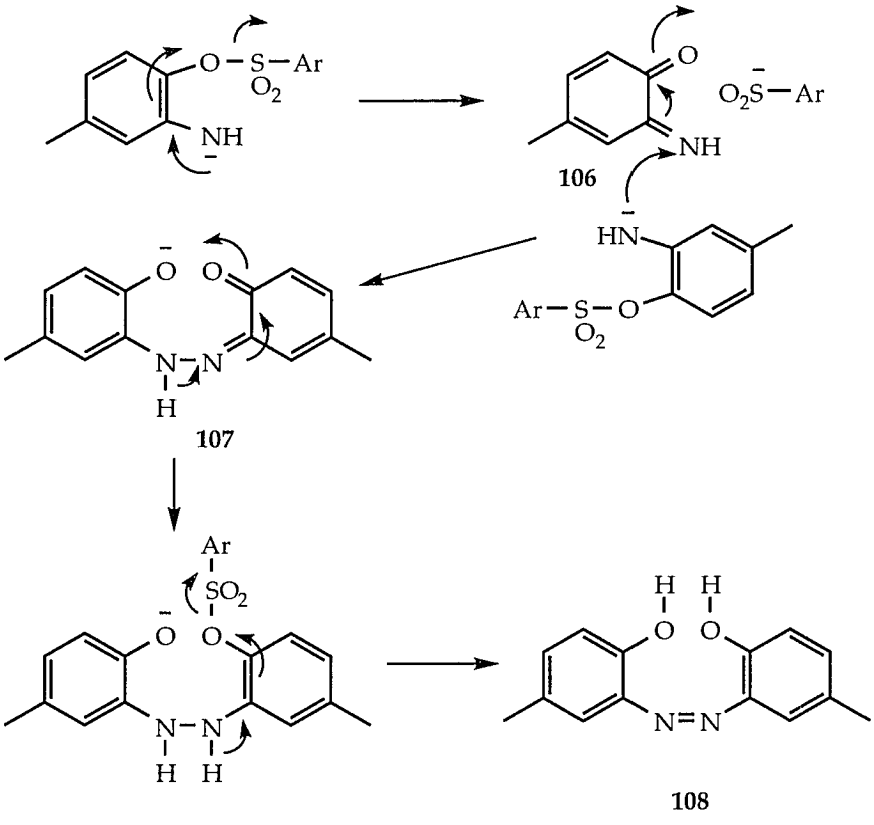
Even though the reaction was shown to be intramolecular, it was not necessarily an example of endocylic substitution. An alternative mechanism was put forth to explain the formation of the products (Scheme 20).



Scheme 20. Elimination-addition pathway for rearrangement of sulfonate **97**.

This mechanism involves the base-induced 1,4-elimination to form an *ortho*-quinoneimine **106** and *p*-toluenesulfinate anion. The ion pair could then recombine within a solvent cage to give the observed sulfonamides.

This mechanism was suspected to be involved due to the isolation of 2,2'-hydroxy-5,5'-dimethylazobenzene (**108**) from the reaction mixture (Scheme 21).

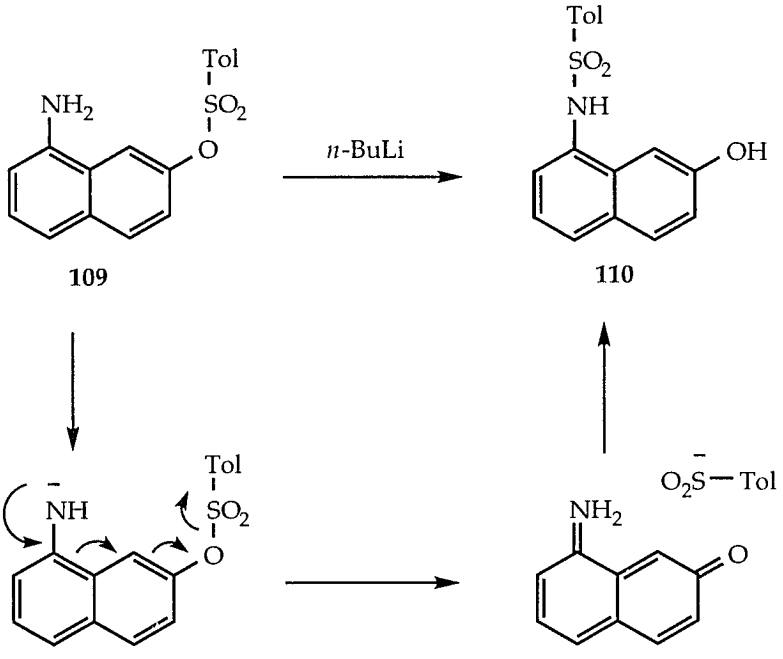


Scheme 21. Mechanism of 1,4-elimination-addition of 2-aminoaryl arenesulfonates.

This product might arise by a base-induced elimination to form the *o*-quinoneimine (**106**), followed by attack of the nitrogen anion to give **107**. A second base-induced elimination, followed by deprotonation led to the azobenzene (**108**).

To investigate the validity of the elimination-addition mechanism, 2'-(8'-amino)naphthyl-4-toluenesulfonate (**109**) was synthesized and reacted under the conditions for rearrangement (Scheme 22). Sulfonate **109** seems unlikely to undergo endocyclic substitution, because of the distance between the nitrogen and sulfur atom. This compound can, however, undergo the elimination-addition pathway. Treatment of **109** with three equivalents of *n*-

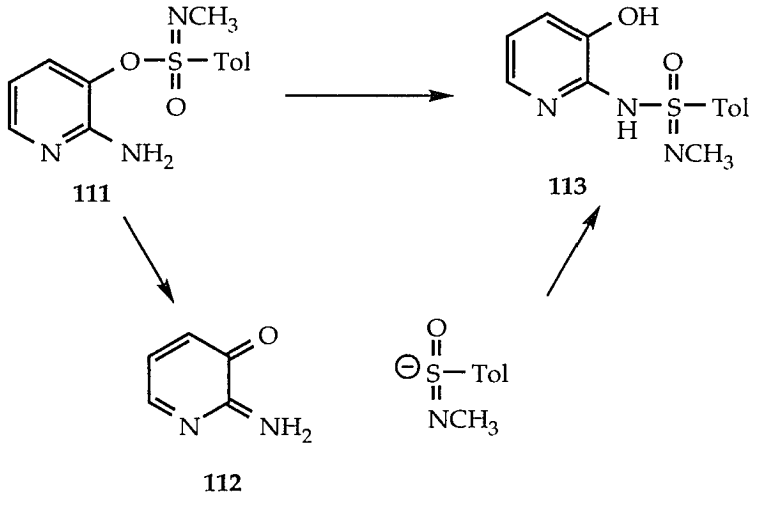
butyllithium gave sulfonamide **110** in 78% yield. This indicated that, at least in this particular case, either the elimination-addition or intermoleular substitution pathway is operative.



Scheme 22. Mechanism for rearrangement of 2'-(8'-amino)naphthyl-4-toluenesulfonate.

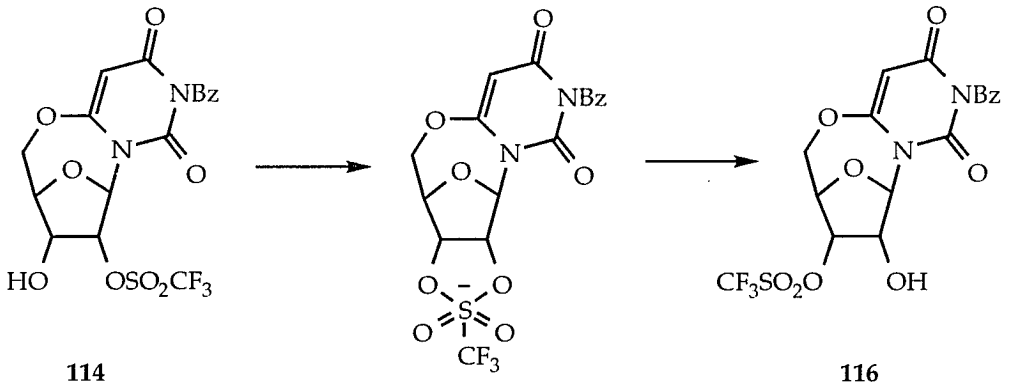
Andersen[62] and coworkers also reported the rearrangement of sulfamidates. Compound **111** when treated with lithium diisopropylamide, rearranged to **113** in 45% yield. Another compound isolated from the reaction mixture was *N*-methyl-*p*-toluenesulfinamide. It was postulated that this reaction may go through and elimination-addition mechanism (Scheme 23). Initial base-induced elimination formed quinone **112.** Approximately half of the sulfinimide anion added to this quinoneimine to give the observed rearranged product and the other half was protonated to form *N*-

methyl-*p*-toluenesulfinamide. The remaining quinoneimine was speculated to account for polymeric material recovered from the reaction mixture.



Scheme 23. Suggested rearrangement mechanism for sulfamidates.

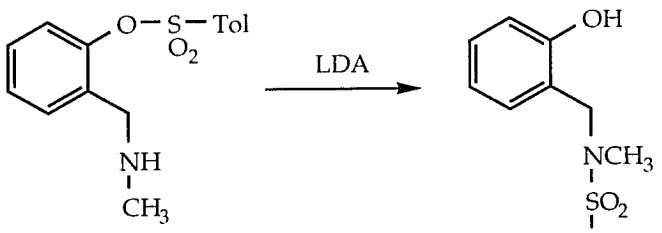
Watanabe[63] and coworkers reported that a pyridine solution of **114** rearranged to **116**. It was suggested that this reaction may go through intermediate or transition state **115**. No evidence was presented that this is in fact an intramolecular reaction. If it is, however, it would be an example of endocyclic nucleophilic substitution at sulfur (VI) through a five-membered ring.



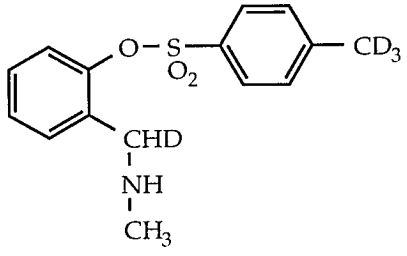
114 **115** **116**

Andersen[62] and coworkers also reported the investigation of a series of compounds, designed to rearrange by way of an endocyclic nucleophilic substitution through a six-membered transition state or intermediate.

Sulfonate **117** was reported to rearrange to the corresponding sulfonamide when treated with an excess of lithium diisopropylamide. In an effort to determine whether this reaction was intramolecular or intermolecular, equal amounts of compound **117** and its isotopomer **119** were treated under the same conditions. Sulfonamide **118** and its isotopomers were isolated from the reaction mixture. The deuterium distribution detected by mass spectrometry was found to be consistent with an intermolecular and not an intramolecular reaction.

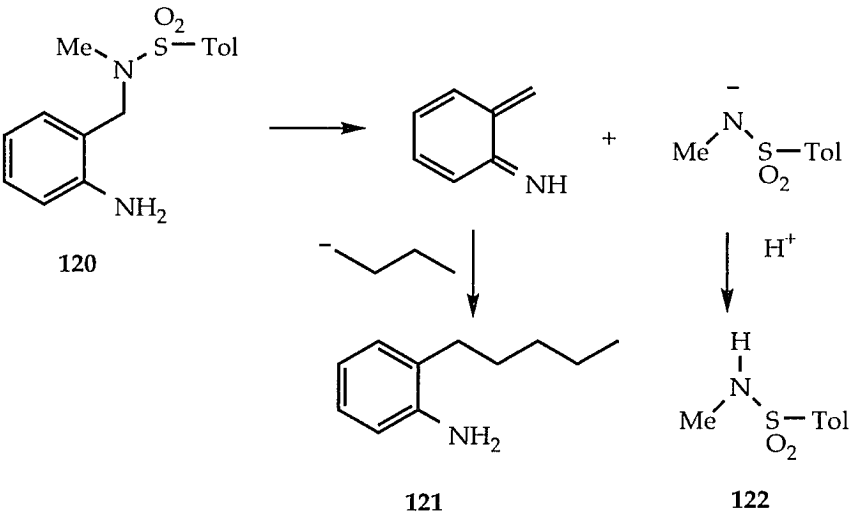


117 118



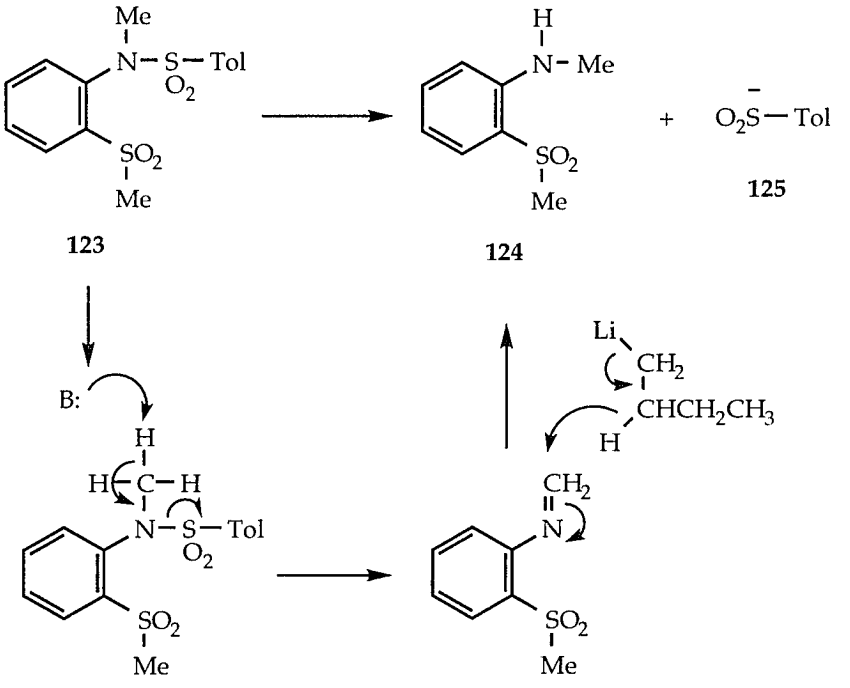
119

Sulfonamide **120** was a potential candidate for endocyclic nucleophilic substitution. Treatment of **120** with *n*-butyllithium gave none of the expected rearrangement product, but yielded 2-pentylaniline (**121**) and *N*-methyl-*p*-toluensulfonamide (**122**). The products were thought to arise from an elimination-addition mechanism as shown in Scheme 24.



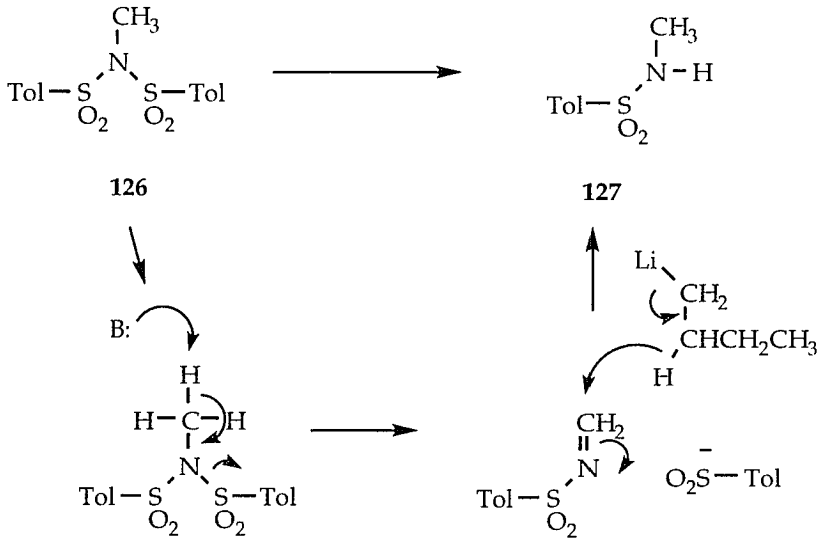
Scheme 24. Mechanism for base-induced elimination of **120**.

Two other compounds, thought to possibly undergo endocyclic nucleophilic substitution, were investigated[62]. Compound **123** when treated with a variety of bases, sodium hydride, *n*-butyllithium and lithium diisopropylamide, gave none of the expected rearrangement product. In all cases, the isolated products were aminosulfone **124** and sulfinate salt **125**. The products were thought to arise from base-induced elimination followed by hydride attack on the generated imine as shown in Scheme 25.



Scheme 25. Base-induced elimination of sulfonamide **123**.

An analogous reaction was that of disulfonamide **126**, treatment with *n*-butyllithium gave *N*-methyl sulfonamide **127**. This resulted from deprotonation of the nitrogen methyl group, followed by elimination of sulfinate anion, followed by hydride attack on the resulting imine (Scheme 26).

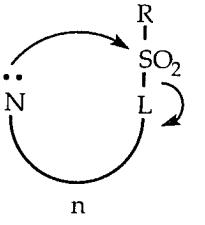


Scheme 26. Mechanism for the base-induced elimination of disulfonamide **126**.

The literature has several examples of nucleophilic substitution at sulfur (VI). The work of Hellwinkel and Closson provided several examples of endocyclic nucleophilic substitution which are presumed to proceed through a four-membered intermediate or transition state. One example of a compound which could proceed through a six-membered intermediate or transition state has been reported to rearrange through an intermolecular exocyclic substitution rather that the desired intramolecular endocyclic substitution. The case of the five-membered intermediate or transition state is still in question. Andersen has reported a five-membered case which appears to rearrange intramolecularly; however, there is a strong possibility that it may go by way of an elimination-addition mechanism. Therefore it may not be a case of endocyclic nucleophilic substitution at sulfur (VI).

Results and Discussion

The purpose of this research was to further investigate the stereochemical requirements of nucleophilic substitution at tetracoordinate sulfur (VI), by utilizing compounds of the general type **127**. These molecules are capable of undergoing substitution endocyclically, thus allowing control of the angle of approach of the nucleophile by varying the chain length n.

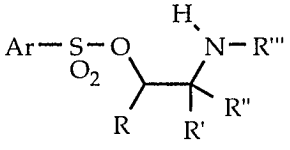


127

Previous work by Hellwinkel and Closson has shown that for compounds where n = 1, nucleophilic substitution proceeds endocyclically through a four-membered intermediate or transition state. This is preferred over exocyclic substitution. Andersen has shown that one case where a six-membered transition state is necessary for nucleophilic substitution, the exocyclic reaction is preferred over the endocyclic reaction. The case of the five-membered transition state or intermediate is less clear. Andersen has shown that for certain compounds this reaction does proceed intramolecularly, however, it seems that there is a competing elimination-addition mechanism that provides the same products as the desired endocyclic substitution mechanism. Therefore, the existence of the five-membered intermediate or transition state is still in question.

This research was directed toward the synthesis and study of molecules which are capable of undergoing endocyclic nucleophilic substitution via the five-membered intermediate, without the possibility of an elimination-addition mechanism. This would provide further insight into the possibility of a five-membered intermediate or transition state in nucleophilic substitution at sulfur (VI).

The previously mentioned aminoaryl sulfonates, which underwent the elimination-addition reaction, had the leaving group and nucleophile attached to an aromatic ring which served as a two carbon spacer. This allowed for formation of the quinonimine intermediate upon elimination. It was the original goal of this project to synthesis analogous aminoalkyl sulfonates of the general type **128**, which possessed two aliphatic carbon joining the leaving group (O) and nucleophile (N).

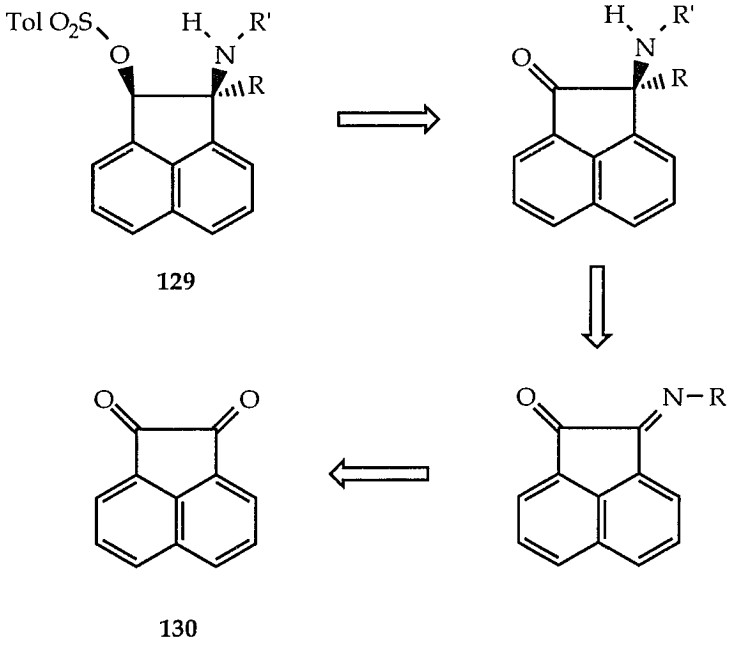


128

These compounds would be unable to undergo an elimination as did the aryl sulfonates. Initially, we felt that R, R' and R" were necessary in the model compounds. The carbon adjacent to the oxygen should be secondary to prevent nucleophilic attack at that carbon which would result in loss of the tosylate group. Additionally, this might prevent nucleophilic attack of the nitrogen and aziridine formation. It was also necessary to have a tertiary

carbon adjacent to nitrogen to prevent deprotonation and 1,2-elimination of the tosylate.

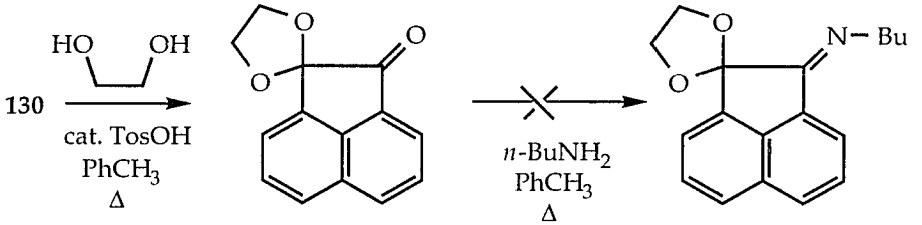
The first synthesis attempted was that of **129**. This compound seemed to be accessible in several steps from acenaphthequinone (**130**) (Scheme 27).



Scheme 27. Retro-synthesis of aminosulfonate **129**.

The acenaphthequinone (**130**) was protected as its monoketal (**131**) by treatment with one equivalent of ethylene glycol in refluxing toluene using a Dean-Stark apparatus to remove the water[64]. The mono-ketal (**131**) was separated from a small amount of diketal (5%) byproduct by recrystallization in methanol. Compound **131** was recovered in 86% yield. The mono-ketal (**131**) was then refluxed in toluene with *n*-butylamine for three hours.

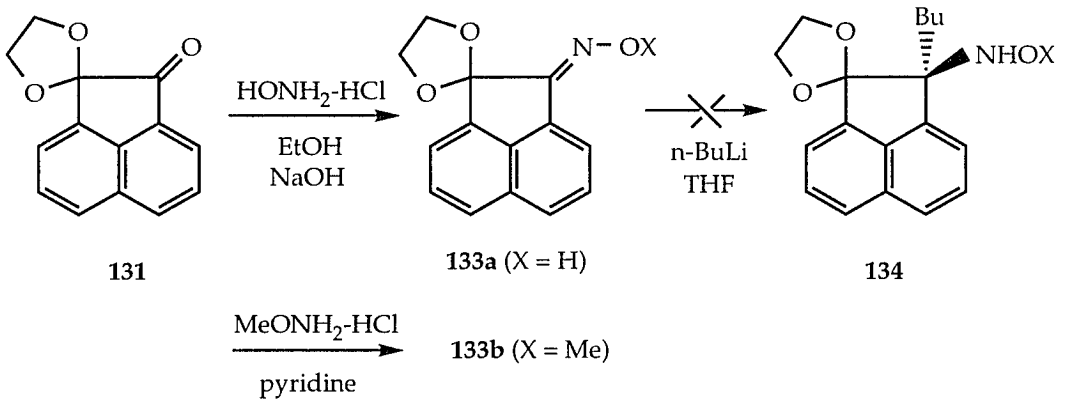
During the course of the reaction, no water was collected in the attached Dean-Stark trap. Evaporation of the reaction mixture yielded only starting material; none of the desired imine, **132**, was present. An analogous reaction was attempted using Linde 4Å molecular sieves to drive the equilibrium to the right by removing the water. Again only starting material was recovered.



131 **132**

An alternate method used to incorporated the nitrogen functionality was conversion of the protected ketone to an oxime. Ketoximes have been reported to undergo nucleophilic attack at carbon by alkyllithiums and alkyl-magnesium halides to give hydroxylamines which could be further reduced to the desired amine[65].

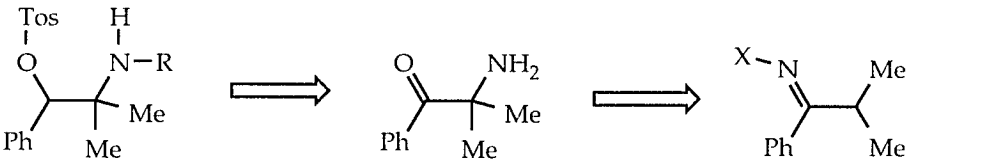
The mono-ketal (**131**) was added to a 50% aqueous ethanol solution containing hydroxylamine hydrochloride and sodium hydroxide and refluxed for thirty minutes. A mixture (5:1) of the two isomers of **133**, recovered in 84% yield, was then treated with *n*-butyllithium (four equivalents) in THF. The reaction mixture, after workup, yielded many spots on tlc; the desired hydroxylamine (**134**) could not be isolated. Reaction with two equivalents of *n*-butyllithium gave back only starting material. Analogous reactions with methyllithium and methylmagnesium iodide were also unsuccessful.



The *O*-methyl oxime (**133b**) was also prepared by reaction of **131** with *O*-methylhydroxylamine hydrochloride in pyridine at room temperature for twelve hours. The oxime **133b** was isolated in 92% yield. Reaction of the *O*-methyl oxime with methyllithium[66] (one equivalent) gave only starting material. Use of an excess of methyllithium gave a mixture which showed many spots on tlc; no single compound could be isolated.

Further attempts at synthesis of the naphtho-fused compound **129** were abandoned. It did not appear that incorporation of a tertiary amine into the five-membered naphtho-fused ring would be possible by this route.

A similar acyclic aminosulfonate, **135**, was envisioned to be a suitable model for study. The amino sulfonate seemed accessible from the analogous amino ketone (**136**) which could be synthesized by a Neber rearrangement[67] of the appropriate *N*-tosyl oxime[68] or *N*-chloroimine[69] (**137**) (Scheme 28).



135 136 137 X = OTos, Cl

Scheme 28. Retro-synthesis of aminosulfonate **135**.

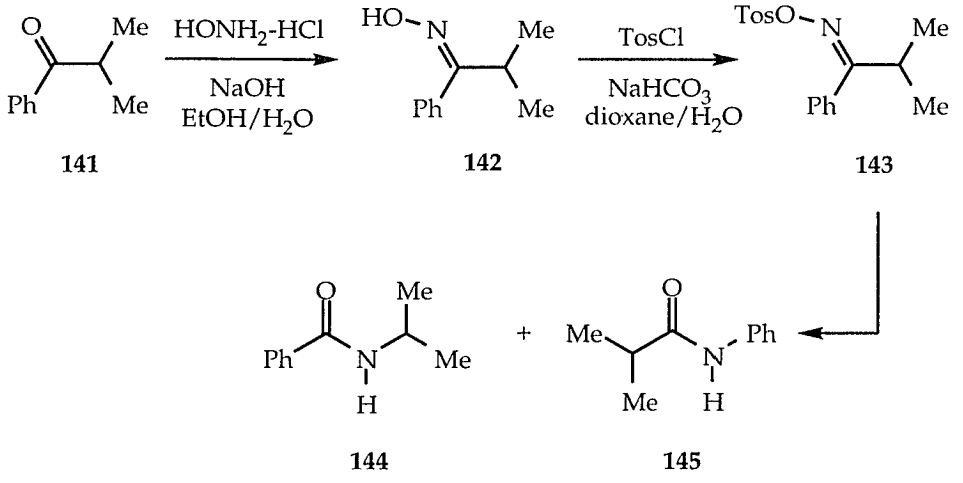
A large number of α-aminoketones have been synthesized from the appropriate oximes via the Neber rearrangement[70]. Treatment of the ketoxime (**138**) with a strong base leads to formation of the azirine (**139**) which upon acid hydroylsis gives the aminoketone hydrochloride salt (**140**) (Scheme 29).

138 139 140

Scheme 29. Neber rearrangement.

The desired starting ketone, isobutyrophenone (**141**), was commercially available. Treatment of **141** with hydroxylamine hydrochloride and sodium hydroxide in refluxing 50% aqueous ethanol for three hours gave oxime **142** in 97% yield. This oxime was treated with one equivalent of *p*-toluenesulfonyl chloride and sodium bicarbonate in 1:1 dioxane/H_2O for 18

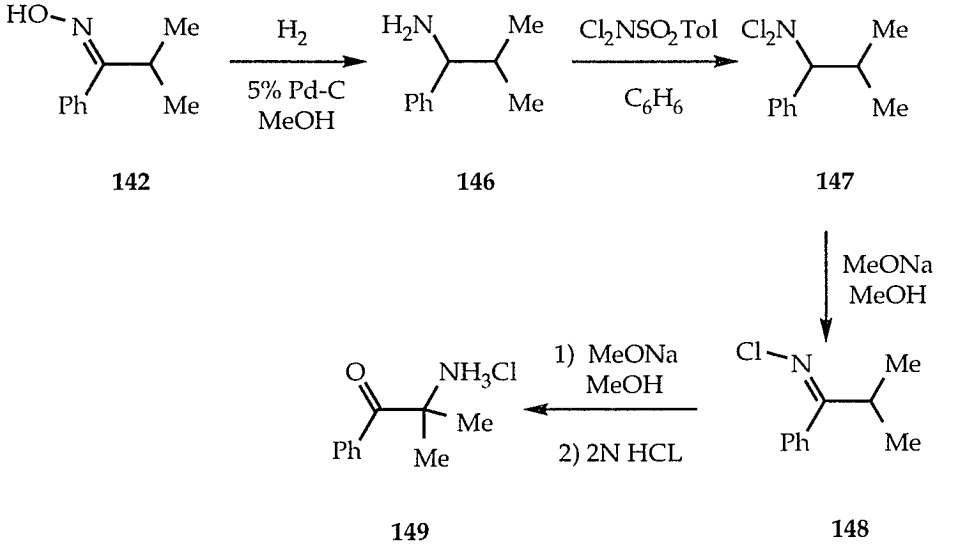
hours at room temperature. The products isolated were not the desired *O*-tosyl oxime, but a mixture of the two amides **144** and **145** resulting from a Beckmann rearrangement[71] of the *O*-tosyl oxime (**143**). Similar products were observed when the oxime was treated with *p*-toluensulfonyl chloride and pyridine in ethanol. Also treatment of **142** with potassium hydroxide and *p*-toluensulfonyl choride in 1:1 acetone/water gave a complex mixture of products.



The preparation of the *O*-tosyl oxime (**143**) did not seem possible due to the facile Beckmann rearrangement under these conditions. The alternative was the Neber rearrangement by way of the *N*-chloroimine.

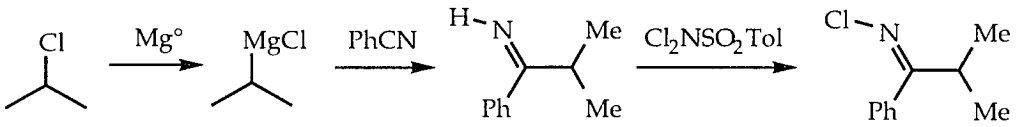
The isobutyrophenone oxime, **142**, was reduced by hydrogen using 5% palladium on carbon in methanol to give amine **146** in 65% yield. The amine was then dichlorinated using *N,N*-dichloro-*p*-toluenesulfonamide, prepared from *p*-toluenesulfonamide and chlorine bleach. The dichloroamine **147** was not isolated , but was treated with excess sodium

methoxide in methanol. This caused initial formation of the *N*-chloroimine (**148**), which upon reaction with more base formed the intermediate azirine which was hydrolyzed with 2N HCl. The aminoketone hydrochloride salt was recovered in 28% yield.



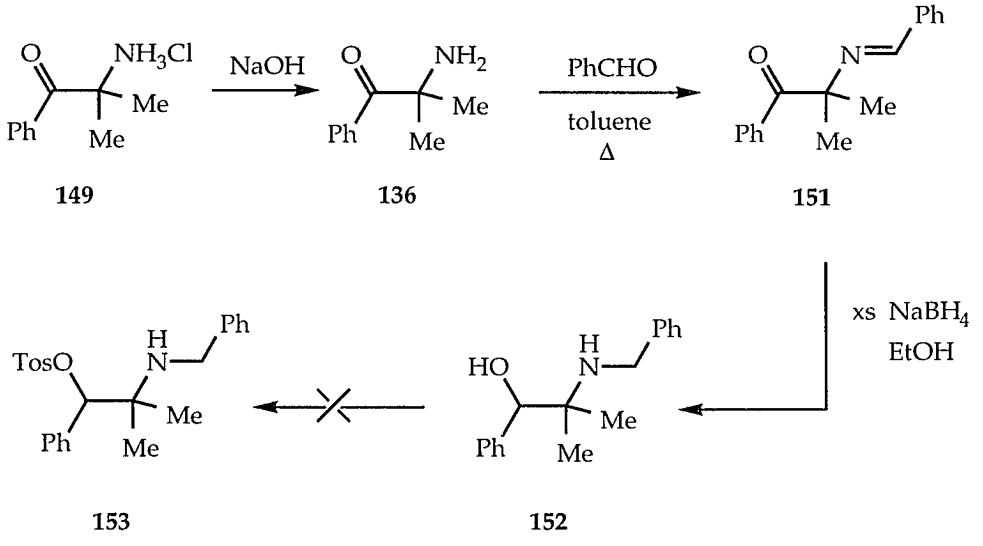
142 **146** **147** **148** **149**

An alternative synthesis of the N-chloroimine (**148**) was also used. Treatment of a solution of isopropylmagnesium chloride in diethyl ether with benzonitrile gave imine **150**, which was not isolated but immediately chlorinated with *N*,*N*-dichloro-*p*-toluenesulfonamide[72] to give *N*-chloro imine **148**. This was then treated as previously to give the aminoketone hydrochloride salt. This route provided better overall yields and was the easier of the two procedures to carry out on a larger scale.



150 **148**

The aminoketone was reductively alkylated in two steps. The amine was refluxed in toluene with one equivalent of benzaldehyde to give the keto-imine **151**, which was then reduced with excess sodium borohydride in methanol. Simultaneous reduction of the ketone and imine functionalities gave the *N*-benzyl aminoalcohol (**152**) in 65% yield.



149 **136** **151**

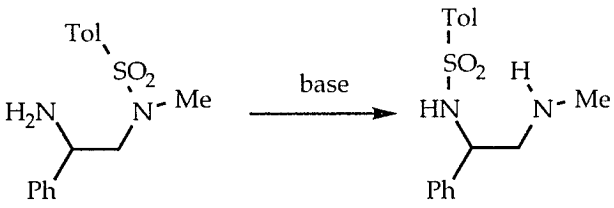
153 **152**

The tosylation of the alcohol functionality, to form the aminosulfonate **153**, was attempted under various conditions[73]. Treatment of **152** with pyridine and *p*-toluenesulfonyl chloride in methylene chloride returned

starting material as well as pyridinium tosylate and the hydrochloride salt of **152**. Using triethylamine as the base returned only starting material. Attempts at tosylation using tosyl chloride with pyridine as the solvent, as have been previously reported, were also unsuccessful. It was thought that if the nitrogen could be protected, *O*-tosylation could be done using a stronger base. Attempts to make the *N*-protected 9-fluroenylmethoxy carbonyl (Fmoc)[74] derivative were unsuccessful. The inability to protect the nitrogen most likely arose from the nitrogen being too sterically hindered which prevented attachment of the very bulky Fmoc protecting group. Tosylation using sodium hydride in THF was also unsuccessful primarily due to the insolubility of the sodium salt of the aminoalcohol.

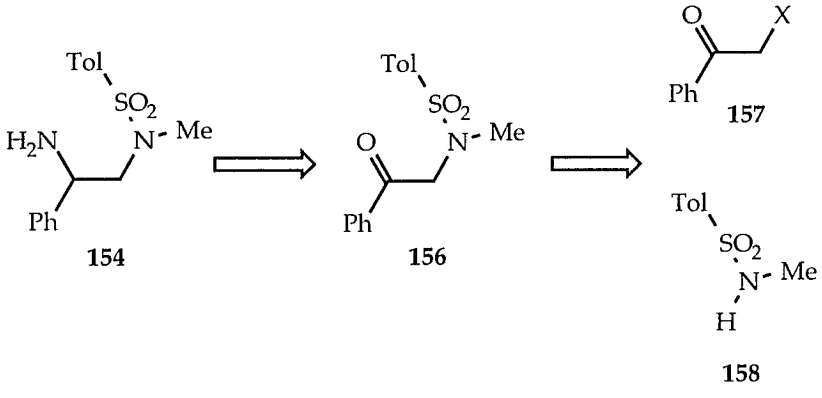
The inability to selectively tosylate the oxygen of the α-aminoalcohol was unexpected , as this has been reported to be possible in several similar systems. The problems encountered with aminosulfonate **152** may arise from steric interactions and also strong hydrogen bonding between the alcoholic hydrogen and the nitrogen. This, however, is only speculation.
With the inability to synthesize the desired amino sulfonate, an analogous nitrogen analogue model was considered.

Diamine **154** was a compound which might undergo endocyclic nucleophilic substitution. It was hoped that deprotonation of the primary amine would cause rearrangement to **155**, with the driving force being the difference between the pK_as of the primary and secondary amines. This reaction would also be irrreversible, because once the rearrangement occurred, the new sulfonamide would be deprotonated stopping any rearrangement back to **154**.



154 **155**

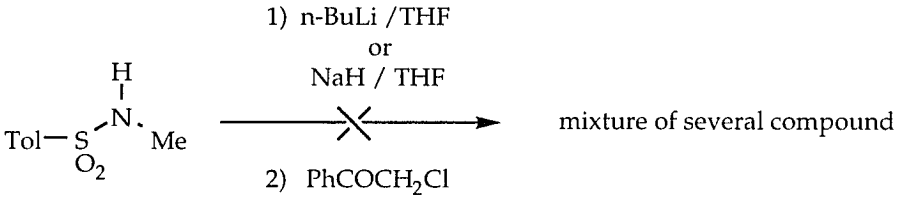
The synthesis of **154** was envisioned to be accessible from the analogous ketone **156**, which could be synthesized from ketone **157** and sulfonamide **158** (Scheme 30).



Scheme 30. Retro-synthesis of diamine **154**.

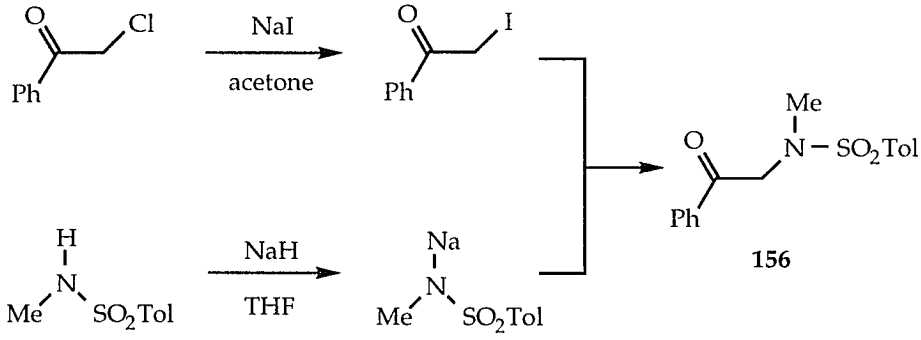
Sulfonamide **158** was deprotonated with *n*-butyllithium or sodium hydride in THF at 0 °C, α-chloroacetophenone was added dropwise and the reaction was allowed to warm to room temperature. Analysis by tlc showed five different spots. No attempt was made to isolate any products. The formation of several products might be the results of the sulfonamide anion not only acting as a nucleophile but also as a base. It is conceivable that the

sulfonamide anion could deprotonate the product, forming an enolate which could further react with a molecule of α-chloroacetophenone.

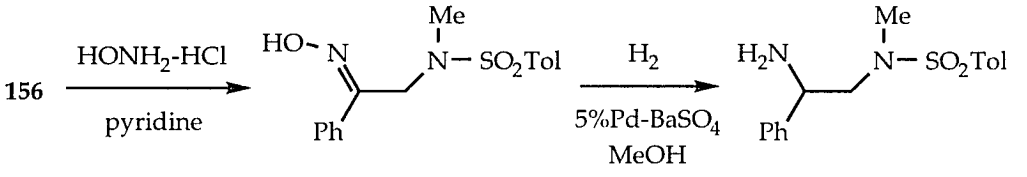


158

To avoid this potential problem, the α-chloroacetophenone was converted to the more reactive α-iodoacetophenone[75] by treatment with sodium iodide in acetone. The iodo compound was then reacted with the sodium salt of *N*-methyl-*p*-toluenesulfonamide in DMF at room temperature for one to two hours. The reaction mixture was poured over ice and **156** precipitated in a 81% yield.



The synthesis of the diamine **154** was completed by treatment of **156** with hydroxylamine hydrochloride in pyridine at room temperature for twelve hours, yielding oxime **159** in 80% yield. Reduction of the oxime was accomplished by hydrogenation using 10% palladium on barium sulfate in MeOH. The diamine **154** was isolated in 90% yield.



159 **154**

Compound **154** was reacted with two equivalents of *n*-butyllithium at -78 °C, then allowed to warm to room temperature with stirring for fifteen hours. After workup, only starting material was recovered. When three equivalents of *n*-butyllithium were used, under the same conditions, a yellow oil was recovered which showed several spots by tlc. A ^{1}H NMR spectrum showed no starting material, but many peaks. No pure compounds could be isolated from the mixture. Analogous results were observed when five equivalents were used. It is quite possible that the first two equivalents of butyllithium are forming the nitrogen anion as well as deprotonating the aromatic ring *ortho* to the sulfonyl group. The third equivalent may be acting as a nucleophile further attacking the molecule causing the formation of several side products. To eliminate this, a non-nucleophilic base was required.

The diamine **154** was treated with two equivalents of lithium diisopropylamide at -78 °C, then stirred at room temperature for fifteen

hours. After workup, only starting material was isolated. Analogous reactions were run using three and five equivalents of lithium diisopropylamide; only starting material was recovered in all cases. The lack of any decomposition products being formed when more than two equivalents were used suggests that the butyllithium, in the previous case, may have indeed been acting as a nucleophile and attacking the molecule, most likely at the sulfonyl sulfur.

The lack of intramolecular reaction when **154** was treated with base may lie in the mode of coordination of the lithium cation. The most stable conformation of the diamine **154** would be expected to be the one in which the phenyl group and the *N*-methyl nitrogen are *anti* to one another (a), as opposed to the two nitrogens being *anti* to one another (b) (Figure 19). Both conformations exhibit one gauche interaction, however, the steric interactions between the phenyl group and the tosyl methyl nitrogen in (b) would seem to rule out this conformation as being the most preferred.

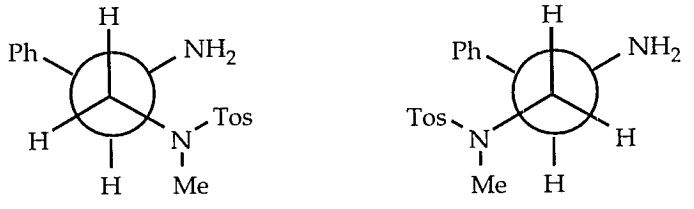


Figure 19. Conformations of diamine **154**.

Conformation (a) would be the most likely conformation for the molecule to adopt if it were to go through an intramolecular sulfonyl transfer. The question, however, remains as to how the lithium coordinates in this conformation. Two possibilities seem likely (Figure 20). The lithium cation could coordinate to both nitrogens forming a five-membered ring (I), the ring would have to adopt a puckered shape to avoid any eclipsing interaction. The other mode of coordination could be the coordination of the cation to the nitrogen anion and one of the sulfonyl oxygens (II). This would form a seven-membered ring in which the molecule could maintain the staggered conformation.

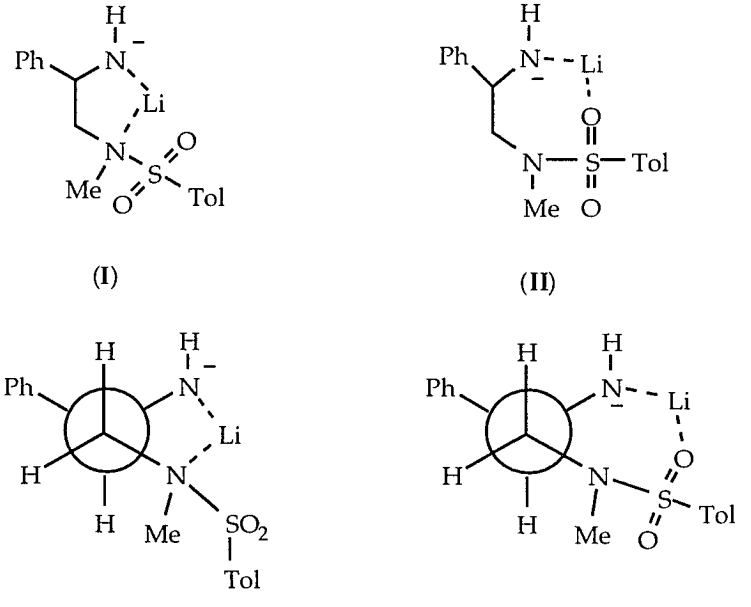


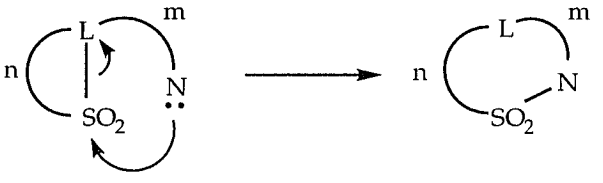
Figure 20. Proposed lithium coordination to anion of **154**.

The coordination as in (**II**) has been previously suggested in the case of intramolecular sulfinyl transfer by Wudl and coworkers[54]. Wudl suggested

that coordination in this fashion was expected to activate the sulfur toward nucleophilic attack. The other mode of coordination would have the opposite effect. Coordination of the two nitrogens to the lithium cation would seem to effectively move the sulfonyl group away from the nitrogen anion, thus making nucleophilic attack less likely.

In the case of diamine **154**, if indeed the anion is being formed, this may be a case of coordination of the type (I), which would seem to effectively negate the likelihood of intramolecular sulfonyl transfer.

The lack of success in finding a suitable acyclic compound which would undergo enocyclic nucleophilic substitution led to examination of cyclic compounds of the general type **160**.

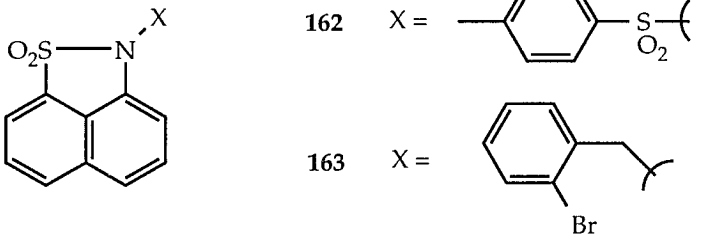


160 **161**

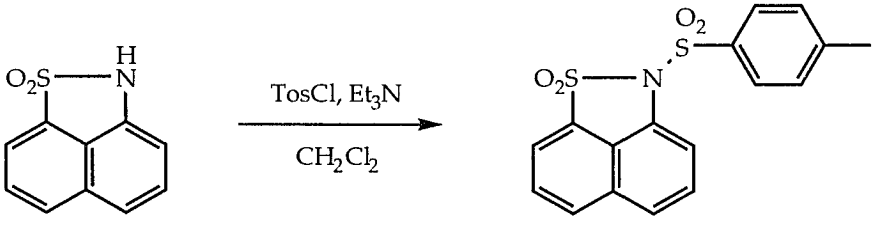
These compounds differ from the previous examples in that the leaving group and the sulfonyl sulfur atom are now contained in a ring. Attack of the nucleophile and subsequent cleavage of the SO_2-L bond leads to formation of a larger ring (**161**). As previously mentioned, Hellwinkel[59,60] studied compounds of this general type, in which n = 3 and m = 1. These compounds went through a four-membered intermediate or transition state and resulted in formation of a seven-membered ring. This research focused on examples

where n = 3 and m = 2; these compounds would go through a five-membered intermediate or transition state and result in an eight membered ring.

The synthesis of a series of *N*-substituted 1,8-naphthosultams had previously been reported during a study of their properties[31]. Two of these sultams, the *N*-tosyl (**162**) and *N*-2-bromobenzyl (**163**) appeared to be likely candidates for endocylic substitution of this type.

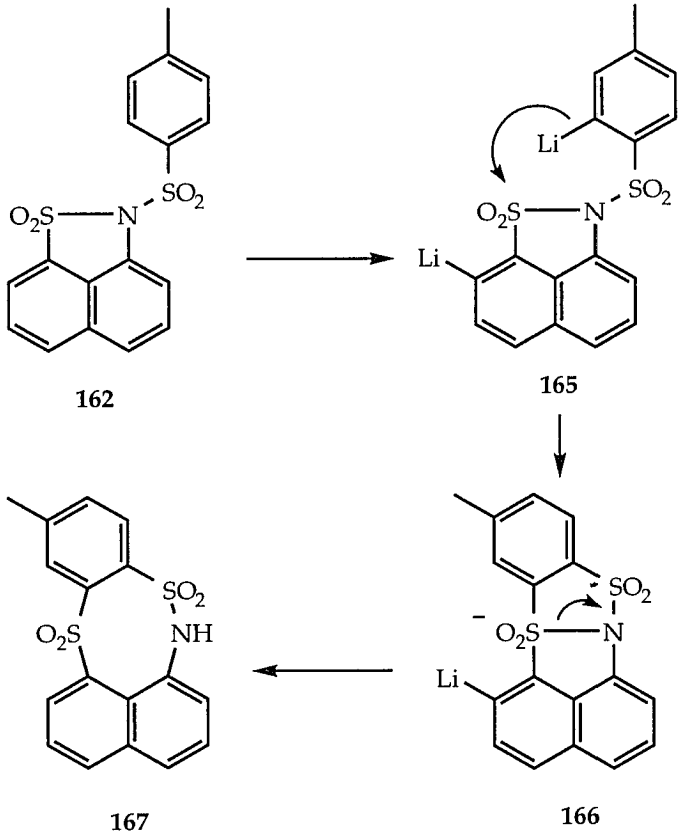


1,8-Naphthosultam (**164**) was dissolved in methylene chloride and treated with triethylamine and *p*-toluenesulfonyl chloride at room temperature for twelve hours. The *N*-tosyl compound **162** was recovered in 56% yield.



164 **162**

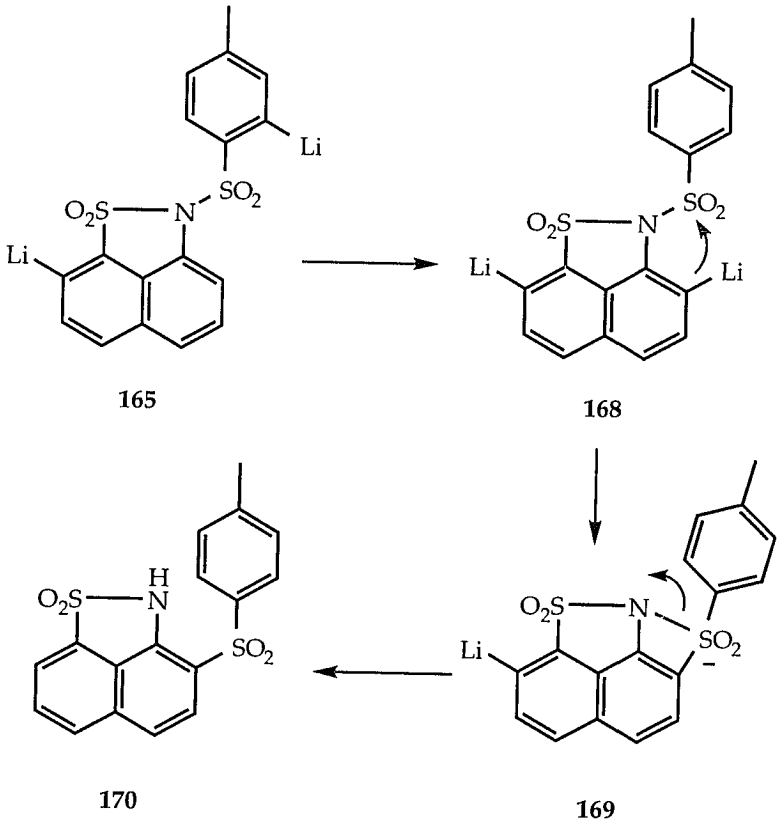
It was believed that treatment of the **162** with two equivalents of strong base would result in formation of the dianion **165**. This is analogous to results previously reported by Hellwinkel. The dianion could then react endocyclically to form the pentacoordinate intermediate **166**. Breakdown of this could form the eight-membered dithiazocine (**167**) (Scheme 31).



162 **165** **167** **166**

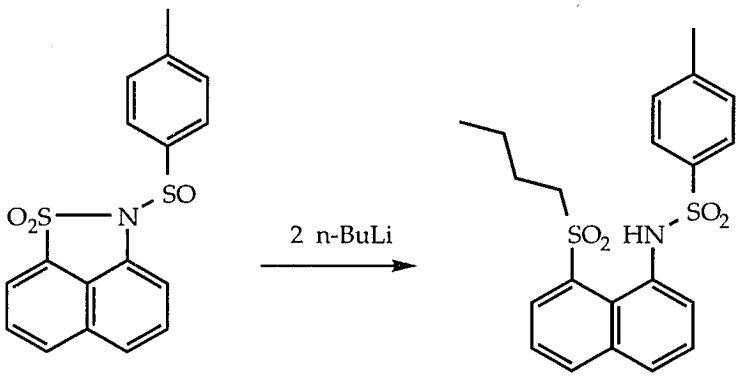
Scheme 31. Proposed rearrangement of *N*-tosyl sultam **162** to the dithiazocine **167**.

The alternative pathway would be transmetallation of **165** to form dianion **168**, which could then react endocyclically through the four-membered intermediate **161**, resulting in sultam **170**.



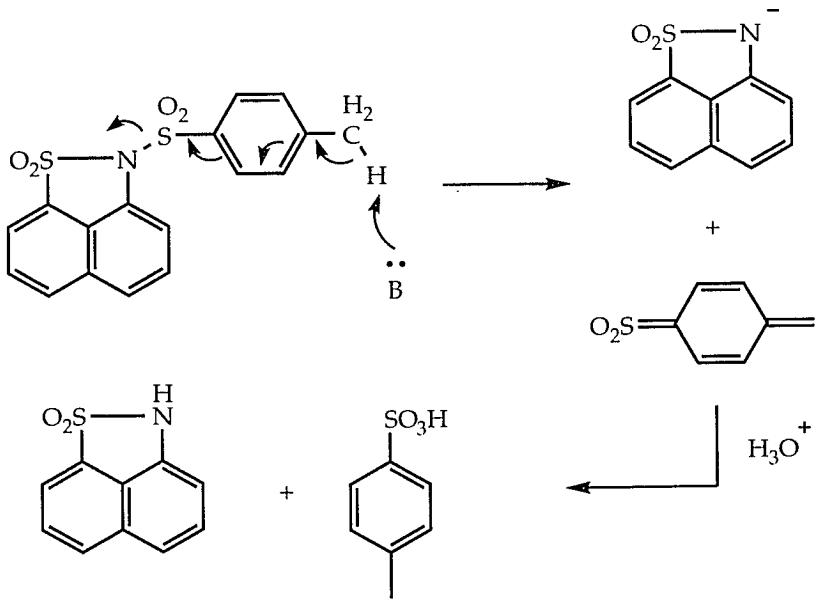
Scheme 32. Proposed rearrangement of tosyl sultam **165** to sultam **170**.

N-tosyl sultam **162** was treated with two equivalents of *n*-butyllithium in THF at -78 °C and the mixture was allowed to warm to room temperature with stirring for one hour. Analysis by tlc showed only one spot. After aqueous workup and purification on a silica gel column, a white solid was recovered. This solid was identified as sulfone **171**.



162 **171**

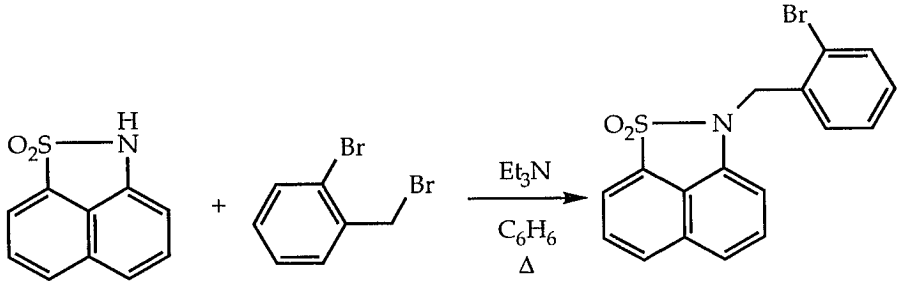
The *n*-butyllithum was evidently too good a nucleophile and opened the sultam ring. The base was then changed to a less nucleophilic base, lithium diisopropylamide. Treatment of **162** with two equivalents of LDA at -78 °C, then warming the mixture to room temperature with stirring for one hour, gave a mixture which showed two major spots on tlc After aqueous acidic workup, a yellow oil was recovered. The oil was dissolved in diethyl ether and extracted with 2H NaOH. Acidification of the aqueous extract gave a tan solid, which showed two spots on tlc; one which moved up the plate and the other remained at the baseline. The componds were separated by column chromatography on silica gel and identified as 1,8-naphthosultam (**164**) and *p*-tolueneuslfonic acid (**172**) (baseline spot). The mechanism for the formation of these products can be explained by the elimination mechanism shown in Scheme 33. Deprotonation of the tosyl methyl group lead to elimination of the sultam anion and formation of *ortho*-sulfoquinomethane Quenching with aqueous acid protonates the sultam and forms the sulfonic acid.



164 172

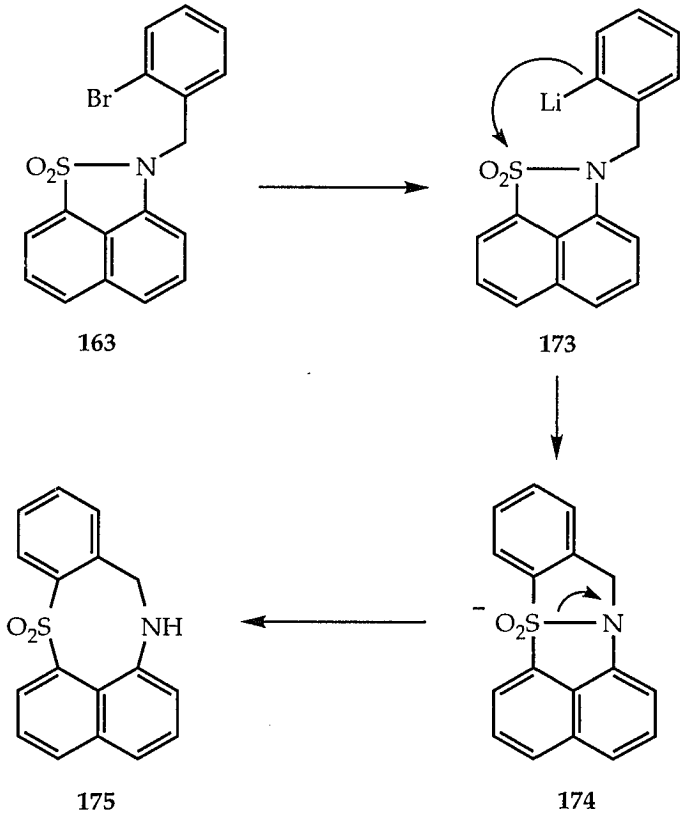
Scheme 33. Proposed reaction of *N*-tosyl sultam **162** with lithium diisopropyl amide.

The other compound investigated was the *N*-2'-bromobenzylsultam **163**. The benzyl sultam was prepared by treatment of 1,8 naphthosultam (**164**), with triethylamine and 2-bromobenzyl bromide for eighteen hours in refluxing in benzene. This yielded the desired sultam in 62% yield.



164 163

It was believed that lithium-halogen exchange should form anion **173**, which could undergo endocylic nucleophilic substitution by way of intermediate **174** to form thiazocine **175** (Scheme 34).

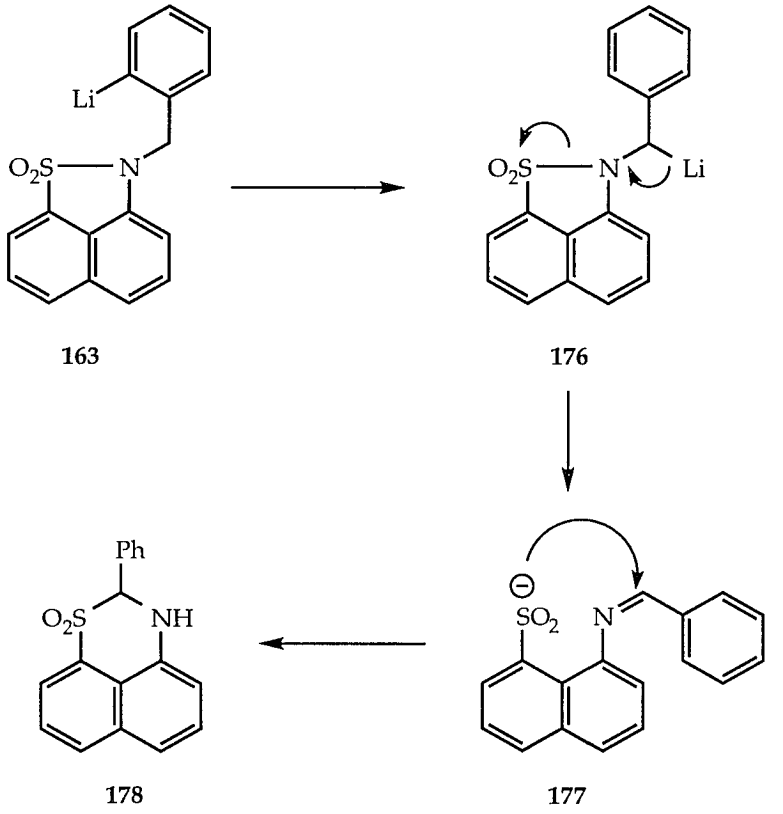


Scheme 34. Proposed rearrangement of benzyl sultam **163** to thiazocine **175**.

Sultam **163** was treated with one equivalent of *n*-butyllithium in THF at -78 °C. The mixture was allowed to warm to room temperature and stirred for 1 hour. Analysis by tlc showed one major spot. The reaction mixture was poured into diethyl ether and extracted with 2N HCl. The acidic aqueous

extract was made basic and a light yellow precipitate filtered. The ^{1}H NMR, ^{13}C NMR, infrared and mass spectra all supported thiazocine **175** as the structure.

An alternate structure **178**, which also fits the spectral data was considered. This product could arise by the mechanism shown in Scheme 35. Transmetallation of the anion **163** could form benzyl anion **176**, which could then eliminate to form imine **177**. Addition of the sulfinate anion to the imine carbon could form the six membered 1,3-thiazine **178.**



163 **176** **178** **177**

Scheme 35. Proposed rearrangemnt of benzyl sultam **163** to 1,3-thiazine **178.**

In order to differentiate between the two structures **175** and **178**, a ^{13}C NMR experiment employing a DEPT (Distortionless Enhancement by Polarization Transfer) pulse sequence was employed. This pulse sequence allows one to distinguish between carbons with different hybridization. The pulse sequence was set to allow for CH_3 and CH carbons to appear in the positive region (above the baseline) of the spectrum and CH_2 to appear in the negative. Tertiary carbons are omitted; the number of these is determined by comparison to the normal ^{13}C spectrum.

This experiment allowed a distinction to be made between **175** and **178** by the number of different types of carbons in each. Both compounds contain 17 peaks in the normal ^{13}C NMR spectrum. The DEPT of **175** should contain 10 CH peaks and 1 CH_2 peaks. The DEPT of **178** should contain only 12 CH peaks.

The DEPT and normal ^{13}C NMR spectra are shown in Figure 21. The rearranged compound shows 10 positive peaks, corresponding to CH carbons and one negative peak corresponding to a lone CH_2 carbon. By comparison to the normal ^{13}C spectrum, it was determined that the compound has 6 tertiary carbons. These results indicate that the rearranged product of the bromobenzylsultam **163** is thiazocine **175**.

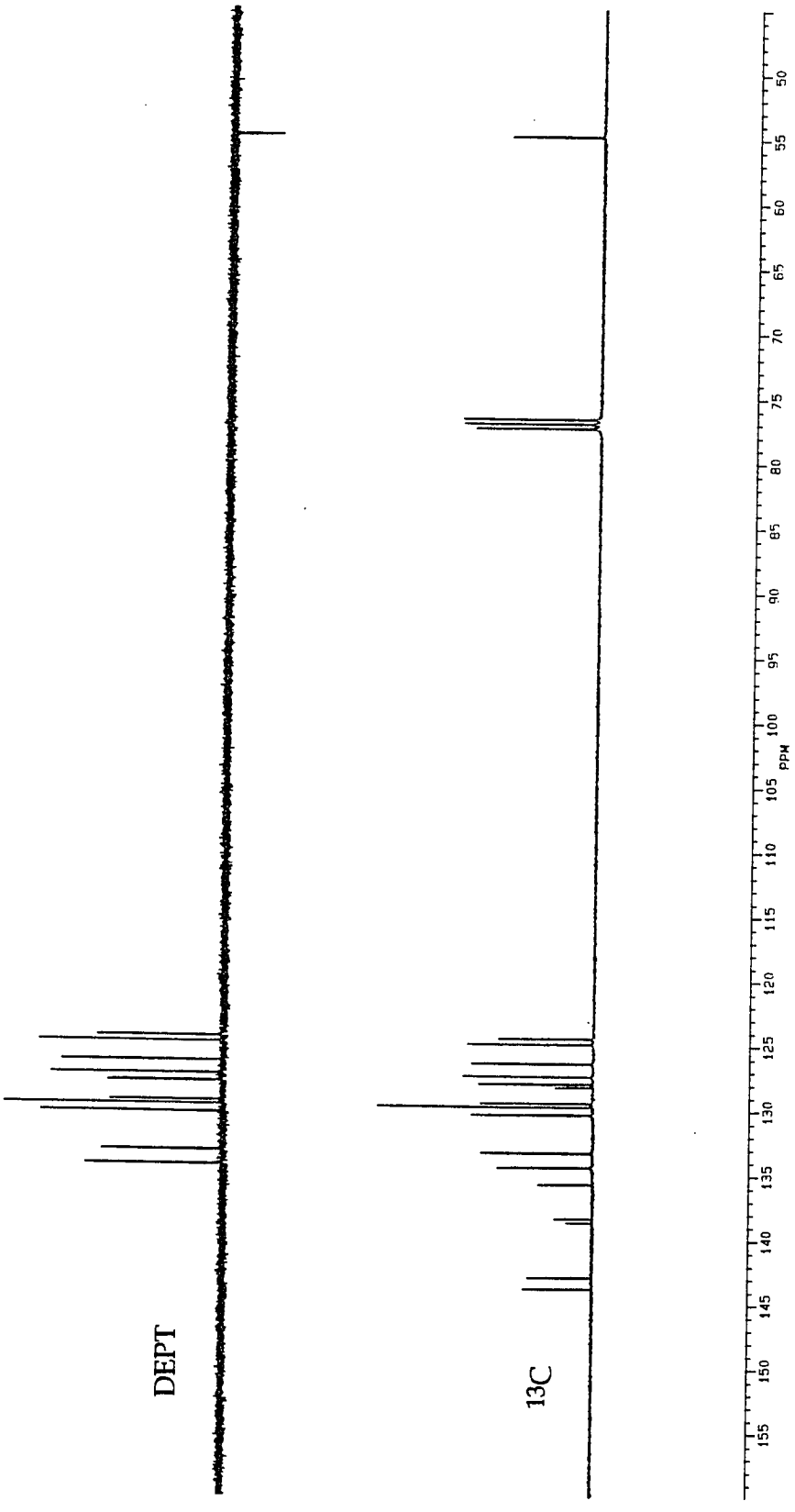


Figure 21. DEPT and ^{13}C NMR spectra for **175**.

Conclusions

In summary, the synthesis of two amino alcohols was attempted. It was thought that compounds **129** and **135** would be likely to undergo endocyclic nucleophilic substitution through a five-membered transition state or intermediate. The synthesis of these compounds, however was unsuccessful.

Diamine **154** was also investigated, as it also could undergo endocylic nucleophilic substitution through a five-membered transition state or intermediate. It was shown that treatment of this compound with strong bases resulted in no rearrangement, as primarily starting material was recovered. It is believed that the coordination of the lithium cation with the diamine could prevent transfer of the sulfonyl group.

Tosyl sultam **162** was also investigated. It was believed that deprotonation α to the sulfonyl group followed by endocyclic nucleophilic attack would result in formation of the eight-membered dithiazocine **167**. Treatment of **162** with *n*-butyllithium resulted in nucleophilic attack of the base at the sulfonamide sulfur atom resulting in ring opening. Treatment with lithium diisopropylamide resulted in elimination and loss of the tosyl group. None of the hoped for rearrangement product was observed in either case.

Benzyl sultam **163** was also investigated, as it also was capable of endocyclic substitution by way of a five-membered intermediate or transition state. Treatment of **163** with *n*-butyllithium resulted in formation of thiazocine **175**. This product can only arise from rearrangement of **163** by endocyclic nucleophilic substitution through a five-membered transition state or intermediate.

Previously, only examples of endocylic substitution through a four-membered transition state or intermediate have appeared in the literature.

The case of the five-membered intermediate, up to this point has been ambiguous. The rearrangement of 2-aminoaryl arenesulfonates (**97**) is an apparent example, however evidence for a competing elimination addition mechanism makes this rearrangement suspect. The synthesis of **175,** therefore, provides the first example of endocyclic nucleophilic substitution through a five-membered intermediate.

Future work that could be done in this area includes investigation into the stereochemistry of the products of the rearrangement of **163**. Whether this reaction proceeds with retention or inversion at the sulfonyl center would provide an important piece of information on substitution reactions at sulfur (VI). Furthermore, the synthetic usefulness of this reaction could be extended to similar systems, as it provides a route to novel eight-membered heterocycles.

Experimental

Instrumentation.

Melting points were obtained with a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Nicolet FT-IR model 205. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) soectra were obtained at 360 MHz for ^{1}H and 90.6 MHz for ^{13}C on a Bruker AM-360 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from a trimethylsilane (TMS) internal standard, unless otherwise noted. Coupling constants (J) are give in hertz (Hz). Mass spectra were obtained on a Hewlett Packard model 5988-A GC/MS quadropolar spectrometer using electron impact (EI) ionization unless otherwise stated. Elemental analyses were performed by Nancy Cherim at the University Instrumentation Center. pH values were obtained on a Orion Research model 401A digital pH meter using a standard glass electrode calibrated with pH 4 and pH 7 buffer solutions. *Ab initio* and semi-empirical calculations were carried out using Spartan (version 1.0.3) on a Silicon Graphics workstation.

Materials.

All chemicals used were reagent grade or better. Solvents were purified and dried by standard techniques. Thin layer chromatography (tlc) experiments were conducted on 0.2 mm thick pre-coated, aluminum-backed plates of silica gel (Aldrich Chemical). Column chromatography was performed using 70-230 or 200-400 mesh silica gel (Aldrich Chemical).

Known starting materials.

The synthesis of compounds **6a-c,f,g** have been previously reported.

pK_a Determinations.

Experimental pK_a values were obtained by potentiometric titration as outlined in Albert and Serjeant. The pK_a values were determined in 60% v/v EtOH/water mixtures, primarily due to the low solubility of the compounds in pure water. The samples were typically run at 0.01M concentrations (0.25 mmol in 25 mL) and titrated with 0.1N NaOH (standardized with KHP) at 25 °C. The measurements of pH were taken at nine intervals from 10-90% ionization.

Reaction of 5-nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (6g) with imidazole.

A solution of imidazole (0.050 g, 0.730 mmol) in water (2 mL) was added to a solution of **6g** (0.135 g, 0.365 mmol) in CH_3CN (10 mL). The solution was stirred at room temperature for 30 minutes. The solvent was evaporated and the residue was triturated with $CHCl_3$ (10 mL) and filtered. The organic layer yielded *p*-toluenesulfonyl imidazole (0.072 g, 89%), whose mp, IR and ^1H NMR spectra matched those in the literature. The bright yellow solid, removed by filtration, was dissolved in water (10 mL) and the solution was acidified with 6N HCl. The aqueous solution was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and evaporated to yield 5-nitro-*N*-H-1,2,3-benzoxathiazole-2,2-dioxide (**41a**) (0.054 g, 69 %): mp 147-50 °C dec; MS *m /z* 216 (M^+); IR (KBr) 3272 (NH, sharp), 1600, 1525 (NO_2), 1475, 1430, 1375, 1345 (NO_2, SO_2), 1230, 1220, 1180 (SO_2); ^1H NMR (acetone-d_6) δ 8.08 (dd, 1H, J = 2.5, 8.5 Hz), 8.00 (d, 1H, J = 2.5 Hz), 7.25 (d, 1H, J = 8.5 Hz); ^{13}C

(acetone-d_6) δ 108.5, 112.2, 120.0, 131.3, 145.5, 147.2. Anal. Calcd. for $C_6H_4N_2O_5S$: C, 33.34; H, 1.87; N, 12.96. Found C, 33.30; H, 1.89; N, 12.92.

Reaction of 5-nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (6g) with benzylamine.

Sulfamate **6g** (0.050 g, 0.135 mmol) was dissolved in CH_3CN (10 mL) and benzylamine (0.04 mL, 0.27 mmol) was added. The solution was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure and the residue triturated with $CHCl_3$ (15 mL) and filtered. Concentration yielded *N*-benzyl-*p*-toluenesulfonamide (0.031 g, 88%) whose mp and ^1H NMR spectrum matched those reported in the literature. A solution of the filtered solid in water (20 mL) was acidified with 6N HCl and then extracted with $CHCl_3$ (3 x 10 mL). The $CHCL_3$ extract was dried with magnesium sulfate and concentrated under reduced pressure to yield a yellow solid (0.025g, 86%) which was identified as **41a**.

Reaction of 5-nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (6g) with *t*-butylamine.

Sulfamate **6g** (0.100 g, 0.270 mmol) was dissolved in CH_3CN (10 mL), *t*-butylamine (0.057 mL, 0.540 mmol) was added and the solution was stirred at room temperature for 1.5 hours. The solvent was evaporated under reduced pressure and the residue was triturated with $CHCl_3$ (10 mL). The undissolved solid was dissolved in water (15 mL), The solution was cooled in an ice/water bath and acidified with 6N HCl. The resulting precipitate was filtered and dried under reduced pressure to yield a tan solid (0.031 g, 53 %) which was identified as **41a**. The *N*-*t*-butyl-*p*-toluenesulfonamide was not isolated.

Reaction of 5-nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (6g) with pyridine.

Sulfamate **6g** (0.050g, 0.135 mmol) was dissolved in $CHCl_3$ (10 mL); pyridine (0.011 mL, 0.135 mmol) was added and the solution was stirred at room temperature. After 3 hours, tlc showed the presence of starting material. An additional equivalent of pyridine (0.011 mL) was added and the solution was stirred for 24 hr; only starting material was detected by tlc.

Reaction of 5-nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (6g) with sodium azide.

Sulfamate **6g** (0.100 g, 0.270 mmol) was dissolved in CH_3CN (5 mL) and sodium azide (0.018 g, 0.260 mmol) in water (1 mL) was added. The reaction mixture was stirred for 15 minutes at room temperature. Removal of the solvent under reduced pressure gave a solid which was triturated with $CHCl_3$ (10 mL). The undissolved solid was filtered , dissolved in water (10 mL), and the solution was cooled in ice/water bath and acidified with 6N HCl. The resulting precipitate was filtered and dried under reduced pressure to give a tan solid (0.052 g, 93%) which was identified as **41a**. The $CHCl_3$ layer was concentrated under reduced pressure to give a yellow solid identified as *p*-toluenesulfonyl azide, whose mp and ^1H NMR spectrum matched those in the literature.

Reaction of 5-nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (6g) with potassium fluoride.

Sulfamate **6g** (0.100 g, 0.270 mmol) was dissolved in CH_3CN (5 mL). Potassium fluoride (0.018 g, 0.260 mmol) in H_2O (1mL) was added and the reaction mixture was stirred at room temperature for 12 hours. The solvents

were removed under reduced pressure. The residue was triturated with $CHCL_3$ (10 mL). The undissolved solid was filtered and dissolved in H_2O (10 mL), the solution was cooled in an ice/water bath and acidified with 6N HCl. The resulting precipitate was filtered and dried under reduced pressure to give a tan solid (0.045 g, 81%) which was identified as **41a**. The $CHCl_3$ layer was dried with magnesium sulfate and concentrated under reduced pressure to give *p*-toluenesulfonyl fluoride, whose mp and ^1H NMR spectrum matched those in the literature.

Reaction of 5-nitro-*N*-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole-2,2-dioxide (6g) with sodium hydroxide.

A solution of NaOH (6.4 mg, 0.16 mmol) in water (2 mL) was added to **6g** (0.058 g, 0.16 mmol) in CH_3CN (10 mL) and the mixture was stirred at room temperature for 2 hours. The solution was acidified with 6 N HCl and extracted with $CHCl_3$ (3 x 5 mL). Removal of the solvent yielded **41a** (2 mg, 6%). The aqueous layer was then extracted with Et_2O (3 x 5 mL); concentration of the organic solution yielded **42** (0.045, 92 %) whose mp, IR, ^1H NMR and ^{13}C NMR spectra matched those previously reported.

3-H-1,2,3-Benzoxathiazole 2,2-dioxide (41b).

3-Tosyl-1,2,3-benzoxathiazole 2,2-dioxide (**6a**) (2.0 g, 6.2 mmol) was dissolved in CH_3CN (100 mL). Sodium azide (0.4 g, 6.2 mmol) in water (40 mL) was added dropwise and the solution was stirred for 14 hours at room temperature. The solution was evaporated under reduced pressure leaving a tan solid which was triturated with $CHCl_3$ (50 mL) and filtered. The undissolved solid was dissolved in water (100 mL) and the solution was acidified with concentrated HCl. The resulting precipitate was filtered and dried under reduced pressure

yielding **41b** as tan needles (0.93 g, 89%). mp 76-79 °C dec; MS *m /z* (relative intensity) 171 (35, M^+), 106 (6), 79 (100). ^1H NMR (acetone-d_6) δ 7.07 (m, 5H); ^{13}C NMR (acetone-d_6) δ 111.4, 113.5, 124.3, 124.9, 129.1, 143.6. Anal. Calcd. for $C_6H_5NO_3S$: C, 42.10; H, 2.94; N, 8.18. Found: C, 41.91; H, 3.04; N, 8.02.

3-H-5-Methyl-1,2,3-benzoxathiazole 2,2-dioxide (41c).

3-Tosyl-5-methyl-1,2,3-benzoxathiazole 2,2-dioxide (**6b**) (0.2 g, 0.58 mmol) was dissolved in CH_3CN (20 mL) at room temperature. Sodium azide (0.038 g , 0.58 mmol) in water (2 mL) was added and the solution was stirred for 24 hours. The solvent was evaporated under reduced pressure to give a solid which was triturated with acetone and filtered. The undissolved solid was then taken up in water (20 mL) and acidified with concentrated HCl. A white precipitate was filtered and dried under reduced pressure giving **41c** as a white powder (0.063 g, 71 %). mp 99-100 °C dec; MS *m / z* (relative intensity) 185 (37, M^+), 93 (100); ^1H NMR (acetone-d_6) δ 2.31 (s, 3H), 6.93 (dd, 1H, J = 2, 8 Hz), 6.96 (d, 1H, J = 2 Hz), 7.11 (d, 1H, J = 8 Hz); ^{13}C NMR (acetone-d_6) δ 21.1,111.4,114.0, 124.3, 130.8, 135.8, 142.0. Anal. Calcd. for $C_7H_7NO_3S$: C, 45.40; H, 3.81; N, 7.56. Found: C, 45.40; H, 3.84; N, 7.44.

3-H-5-Bromo-1,2,3-benzoxathiazole 2,2-dioxide (41d).

3-Tosyl-5-bromo-1,2,3-benzoxathiazole 2,2-dioxide (**6f**) (0.2 g, 0.5 mmol) was dissolved in CH_3CN (8 mL). Potassium fluoride (0. 029 g, 0.5 mmol) in water (1.5 mL) was added and the solution was stirred at room temperature for 12 hours. The solution was evaporated under reduced pressure leaving a dark solid which was triturated with $CHCl_3$ (15 mL) and filtered. The undissolved solid was dissolved in water (15 mL) and acidified with concentrated HCl while cooling in an ice/water bath. The resulting precipitate was filtered and dried

under reduced pressure to yield **41d** as an off-white solid (0.051 g, 40 %). mp 178-181 °C dec; MS *m / z* (relative intensity) 251 (34, M^+), 249 (35), 159 (37), 157 (44), 78 (100); ^1H NMR (acetone-d_6) δ 7.23 (d, 1H, J = 8.6 Hz), 7.30 (dd, 1H, J = 2.1, 8.6 Hz), 7.33 (d, 1H, J = 2.1 Hz); ^{13}C NMR (acetone-d_6) δ 113.1, 115.8, 117.0, 126.1, 131.9, 142.3. Anal. Calcd. for $C_6H_4BrNO_3S$: C, 28.82; H, 1.61; N, 5.60. Found: C, 28.73; H, 1.55; N, 5.44.

3-H-5-Chloro-1,2,3-benzoxathiazole 2,2-dioxide (41e).

3-Tosyl-5-chloro-1,2,3-benzoxathiazole 2,2-dioxide (**6c**) (0.3 g, 0.8 mmol) was dissolved in CH_3CN (50 mL). Imidazole (0.057 g, 1.6 mmol) in CH_3CN (5 mL) was added and the solution was stirred at room temperature for 14 hours. The solvent was evaporated under reduced pressure. $CHCl_3$ (25 ml) was added to the residual solid. The mixture was extracted with water (2 x 10 mL). The aqueous layer was cooled in an ice/water bath and acidified with 6N HCl. A white precipitate of **41e** (0.10 g, 61 %) was filtered and dried under reduced pressure. mp 168-170 °C dec.; MS m/z (relative intensity) 207 (79, M^+), 205 (32), 113 (100), 111 (34). ^1H NMR (acetone-d_6) δ 7.27 (d, 1H, J = 8.9 Hz), 7.19 (d, 1H, J = 2.1 Hz), 7.14 (dd, 1H, J = 8.9, 2.1 Hz). ^{13}C NMR (acetone-d_6) δ 113.1, 113.5, 123.6, 130.3, 131.9, 142.3. Anal. Calcd. $C_6H_4ClNO_3S$: C, 35.05; H, 1.96; N, 6.81. Found: C, 35.00; H, 2.01; N, 6.80.

N-(2-Hydroxy-5-chlorophenyl)-4-toluenesulfonamide.

2-Amino-4-chlorophenol (10 g , 70 mmol) was dissolved in CH_2Cl_2 (150 mL) in a 500 mL round-bottom flask. The flask was flushed with nitrogen and cooled to -78°C in a dry ice/acetone bath. Pyridine (6.30 mL, 78 mmol) was added dropwise. The mixture was stirred for 20 minutes. *p*-Toluenesulfonyl chloride (15 g , 78 mmol) in CH_2Cl_2 (100 mL) was added dropwise to the stirred

solution. The mixture was allowed to warm to room temperature and was stirred for 12 hours. Water (100 mL) was added to the mixture and the two layers were stirred vigorously. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (50 mL). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure to yield a sticky brown solid. Recrystallization from hexanes/ethyl acetate (4:1) gave a tan solid (13.3 g, 62.9%). The mp and ^1H NMR spectrum matched those previously reported for this compound.

3-Tosyl-5,6-dichloro-1,2,3-benzoxathiazole-2,2,dioxide.

N-(2-Hydroxy-5-chlorophenyl)-4-toluenesulfonamide (5.0 g, 17 mmol), was dissolved in CH_2Cl_2 (100 mL) in a 250 mL three-neck round-bottom flask fitted with an addition funnel, magnetic stirrer and nitrogen inlet. The flask was cooled to 0 °C in ice water bath. Triethylamine (4.70 mL, 34 mmol) was added dropwise to the solution which was stirred for 15 minutes. Sulfuryl chloride (8.49 mL, 85 mmol) in CH_2Cl_2 (25 mL) was added dropwise over a 15 minute period. The solution was allowed to warm to room temperature and stirred for 12 hours. Water (100 mL) was added to the mixture which was then stirred vigorously for 15 minutes. The layers were separated and the aqueous portion was washed with CH_2Cl_2 (50 mL). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure. The sticky brown solid that resulted was recrystallized from benzene yielding a tan solid (2.45 g, 36.5 %) identified as 3-tosyl-5,6-dichloro-1,2,3-benzoxathiazole-2,2,dioxide. mp. 135-140 °C; ^1H NMR ($CDCL_3$) δ 2.45 (s, 3H), 7.22 (s, 2H), 7.37 (d, 2H, J = 8.0 Hz), 7.78 (s, 2H), 7.87 (d, 2H, J = 8 Hz).

3-H-5,6-Dichloro-1,2,3-benzoxathiazole 2,2-dioxide (41f).

3-Tosyl-5,6-dichloro-1,2,3-benzoxathiazole 2,2-dioxide (0.3 g, 0.73 mmol) was dissolved in CH_3CN (30 mL). Imidazole (0.099 g, 1.5 mmol) in CH_3CN (10mL) was added and the solution stirred for 12 hours at room temperature. The solvent was evaporated under reduced pressure. The residual solid was triturated with $CHCL_3$ (30 mL) for 10 minutes. The undissolved solid was filtered and dissolved in water (30 mL). The filtrate was cooled in an ice-water bath and acidified with 6N HCl. A white precipitate of **41f** (0.14 g, 75 %) was filtered and dried under reduced pressure. mp 177-181 °C dec; MS *m / z* (relative intensity) 241 (27, M^+), 239 (37), 149 (59), 147 (100), 112 (75). ^1H NMR (acetone-d_6) δ 7.59 (s, 1H), 7.39 (s, 1H); ^{13} C NMR (acetone-d_6) δ 113.6, 114.3, 123.2, 128.2, 130.2, 141.9. Anal. Calcd. for $C_6H_3Cl_2NO_3S$: C, 30.02; H, 1.26; N, 5.84. Found: C, 29.94; H, 1.32; N, 5.77.

Attempted nitration of 3-tosyl 1,2,3-benzoxathiazole 2,2-dioxide with sodium nitrite in trifluoroacetic acid.

Sulfamate **6** (2.00 g, 6 mmol) was dissolved in trifluoroacetic acid (50 mL). Sodium nitrite (2.07 g, 30 mmol) was added and the solution was stirred at room temperature for 3 days. The solution was then poured into water (25 mL). A yellow solid precipitated, which was filtered, washed with water (25 mL) and air dried. The ^1H NMR spectrum of the solid showed it to be unreacted **6**.

Dinitro 3-Tosyl-1,2,3-benzoxathiazole 2,2-dioxide (45).

Sulfamate **6** (1.6 g, 5 mmol) was dissolved in CH_2Cl_2 in a 50 mL round-bottom flask. Concentrated sulfuric acid (10 mL) was added slowly followed by the addition of 90% fuming nitric acid (5 mL). The mixture was stirred

vigorously at room temperature for 48 hours. The CH_2Cl_2 layer was evaporated by a slow stream of nitrogen, followed by addition of water (50 mL). A yellow precipitate formed and was filtered. Recrystallization from ethyl acetate gave yellow crystals of **45** (0.425 g, 20%). mp 190-192 °C; ^1H NMR ($CDCl_3$) δ 2.71 (s, 3H), 7.63 (d, 1H, J = 8.2 Hz), 7.83 (d, 1H, J = 9.0 Hz), 8.03 (d, 1H, J = 2.3 Hz), 8.16 (dd, 1H, J = 2.1, 8.2 Hz),8.26 (dd, 1H, J = 2.3, 9.0 Hz), 8.58 (d, 1H, J = 2.1); ^{13}C NMR ($CDCl_3$) δ 20.9, 108.4, 114.2, 121.80, 125.1, 130.3, 132.1, 134.3, 134.8, 139.9, 142.5, 145.2, 149.1.

4-Nitro-2-aminophenol.

The dinitrosulfamate (**45**) (0.2 g, 0.48 mmol) was dissolved in CH_3CN (5 mL). Aqueous 0.1 N NaOH (2 mL) was added dropwise and the mixture was stirred at room temperature until starting material was no longer observed by tlc. The solvent was removed under vacuum leaving a bright yellow solid. The solid was refluxed in 50% HCl (10 mL) for 20 hours. The solution was cooled, neutralized with 0.1 N NaOH and then extracted with $CHCl_3$ (2 x 10 mL). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure to give a red orange solid which was recrystallized from aqueous EtOH. The mp and ^1H NMR spectrum of this solid matched that of a known sample of 5-nitro-2-aminophenol, mp 195-200 °C dec. (lit. 198-200 °C dec); 1H NMR (acetone-d_6) δ 3.46 (broad s, 1H), 6.74 (d, 1H, J = 8.7 Hz), 7.61 (d, 1H,2.5 Hz), 7.65 (dd, 1H, J = 2.5, 8.7 Hz), 9.11 (broad s, 2H).

3-H-6-Nitro-1,2,3-benzoxathiazole 2,2-dioxide (41g).

The dinitrosulfamate (**45**) (0.1 g, 0.24 mmol) was dissolved in CH_3CN (10 mL). Imidazole (0.033 g, 0.48 mmol) was added to the solution which was stirred at room temperature for 1 hour. The solvent was removed under

vacuum leaving a bright yellow solid. $CHCl_3$ (15 mL) was added and the mixture was stirred for 5 minutes. The undissolved precipitate was filtered and dissolved in water (15 mL) which was acidified with 6N HCl. The aqueous solution was extracted with ethyl acetate (2 x 10 mL). The ethyl acetate extract was dried with calcium chloride and evaporated under vacuum to yield compound **41g**, (0.036, 71%). mp 200-202 °C dec; MS *m / z* 216 (M^+); ^1H NMR (acetone-d_6) δ 7.33 (d, 1H, J=9.4 Hz), 8.16 (m, 2H); ^{13}C NMR (acetone-d_6) δ 107.5, 111.7, 112.9, 135.9, 141.8, 143.1. Anal. Calcd. for $C_6H_4N_2O_5S$: C, 33.34; H, 1.87; N, 12.96. Found: C, 33.40; H, 1.76; N, 12.99.

3-H-1,2,3-Naphtho[2,3-*d*]oxathiazole 2,2-dioxide (41h).

3-Tosyl-1,2,3-naphtho[2,3-d]oxathiazole 2,2-dioxide (0.38 g, 1.0 mmol) was dissolved in CH_3CN (25 mL). Sodium azide (0.066 g, 1 mmol) in water (2 ml) was added and the solution was stirred for 12 hours at room temperature. The solvents were evaporated under reduced pressure leaving a tan solid, which was triturated with $CHCL_3$ (20 mL) for 10 minutes. The undissolved solid was filtered and dissolved in water (20 mL). The aqueous solution was cooled in ice/water bath and acidified with 6 N HCl. Tan needles of **41h** (0.196 g, 89 %) were filtered from the solution and dried under reduced pressure, mp 167-170 °C dec; MS *m / z* (relative intensity) 221 (15, M^+), 129 (93), 102 (100); ^1H NMR (acetone-d_6) δ 7.47 (m, 2H), 7.53 (s, 1H), 7.72 (s, 1H), 7.88 (m, 2H); ^{13}C NMR (acetone-d_6) δ 107.8, 108.9, 125.9, 126.5, 127.6, 128.2, 130.0, 130.1, 131.4, 143.0. Anal. Calcd. for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19; N, 6.33. Found: C, 54.38;, H, 3.15; N, 6.38.

2-Aminopyrid-3-yl 4-toluensulfonate .

1-Amino-2-hydroxy pyridine (3.0 g, 27 mmol) was suspended in CH_2Cl_2 (50 mL) and cooled to 0 °C in an ice/water bath. Triethylamine (3.75 mL, 27 mmol) was added and the solution was stirred for 15 minutes. *p*-Toluenesulfonyl chloride (5.14, 27 mmol) was added and the solution was allowed to warm to room temperature and was stirred for 12 hours. Water (25 mL) was added and the solution was stirred vigorously for 10 minutes. The layers were separated and the organic layer was dried with magnesium sulfate and the solvent was evaporated under reduced pressure giving a tan solid (4.65 g, 65 %), whose mp and ^1H NMR spectrum matched those previously reported for 2-aminopyrid-3-yl 4-toluensulfonate. mp 131-132 °C (lit.[32] mp 131-132 °C); ^1H NMR (acetone-d_6) δ 2.43 (s, 3H), 6.54 (dd, 1H, J= 6.0,7.7 Hz), 7.28 (dd, 1H, J= 1.5, 7.7 Hz), 7.44 (d, 2H, J= 8.0 Hz), 7.80 (d, 2H, J= 8.0 Hz), 7.84 (dd, 1H, J= 1.5, 6.0 Hz).

***N*-(3-Hydroxynapth-1-yl)-4-toluenesulfonamide.**

2-Aminopyrid-3-yl 4-toluensulfonate (0.5 g, 0.19 mmol) was dissolved in THF (50 mL) and the solution was cooled to -78 °C in a dry ice/acetone bath under nitrogen. *n*-Butyllithium (7.42 mL, 7.6 mmol) was added dropwise and the solution was slowly warmed to room temperature over a 1 hour period. Water (25 mL) was added and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (25 mL) to remove any remaining starting material. The aqueous solution was cooled in ice/water bath and carefully neutralized with 6N HCl. A tan solid precipitated which was filtered and dried under reduced pressure to give a tan solid (0.27 g, 54 %) whose mp, ^1H NMR and ^{13}C NMR spectra matched those previously reported for N-(3-Hydroxynapth-1-yl)-4-toluenesulfonamide, mp 159-162 °C (lit.[32] mp 162-165 °C);

^{1}H NMR (acetone-d_6) δ 2.36 (s, 3H), 6.71 (dd, 1H, J= 6.0, 7.7 Hz), 7.12 (dd, 1H, J= 1.5, 7.7 Hz), 7.29 (d, 2H, J = 8 Hz), 7.53 (dd, 1H, J = 1.5, 6.0 Hz), 7.84 (d, 2H, J = 8 Hz).

Reduction of 3-H-5-nitro-1,2,3-benzoxathiazole-2,2-dioxide by catalytic hydrogenation.

3-H-5-Nitro-1,2,3-benzoxathiazole-2,2-dioxide (**41a**) (0.3 g, 1.4 mmol) was dissolved in MeOH (20 mL), 5% palladium on carbon (0.05 g) was added and the mixture was stirred under a hydrogen atmosphere for 2 hours. When the bright yellow color of the nitro sulfamate was no longer evident, the reaction was stopped. The catalyst was filtered; during filtration the solution quickly turned dark brown. The MeOH was evaporated under reduced pressure giving a brown solid. The solid was only sparingly soluble in acetone, and the ^{1}H NMR spectrum showed many peaks in the aromatic region. An ^{1}H NMR spectrum in D_2O also showed numerous peaks. No attempt to isolate any pure products was made.

Reduction of 3-H-6-nitro-1,2,3-benzoxathiazole-2,2-dioxide by catalytic hydrogenation.

3-H-6-Nitro-1,2,3-benzoxathiazole-2,2-dioxide (**41g**) (0.13 g, 0.6 mmol) was dissolved in MeOH (20 mL), 5% palladium on carbon (0.05 g) was added and the mixture was stirred under a hydrogen atmosphere for 1.5 hours. When the bright yellow color of the nitro sulfamate was no longer evident, the reaction was stopped. The catalyst was filtered and washed with MeOH (10 mL). The filtrate quickly turned dark brown. The MeOH was evaporated under reduced pressure giving a sticky brown solid. A ^{1}H NMR spectrum in deuterated acetone showed many peaks in the aromatic region. An ^{1}H NMR spectrum in

D_2O also showed numerous peaks. No attempt to isolate any pure products was made.

Reaction of 6 with maleic anhydride in 1,2-dichlorobenzene.

3-Tosyl-1,2,3-benzoxathiazole-2,2-dioxide ( ) (0.33 g, 1 mmol) and maleic anhydride (0.10 g, 1 mmol) were dissolved in 1,2-dichlorobezene (3 mL) and the solution refluxed (20 hours) until all of the starting material was gone, by tlc. During the reflux period, SO_2 was detected by holding moist pH paper over the mouth of the flask. Several spots were apparent on the tlc. Attempts to isolate product by column chromatography (silica gel) were unsuccessful. Mixtures of several unidentified compounds were observed by analysis of the ^1H NMR spectra of the different fractions.

Reaction of *N*-methyl-1,2,3-benzoxathiazole 2,2-dioxide with maleic anhydride in 1,2-dichlorobenzene.

3-Methyl-1,2,3-benzoxathiazole 2,2-dioxide (0.1 g, 0.54 mmol) and maleic anhydride (0.5 g, 0.54 mmol) were refluxed in 1,2-dichlorobenzene (20 mL). The reaction was monitored for disappearance of starting material by tlc. After 20 hours, all tof he starting material had disappeared. Several spots were evident by tlc. Attempts to isolate any pure products from the black reaction mixture by column chromatography (silica gel), were unsuccessful.

An analogous reaction was carried out using dimethyl maleate instead of maleic anhydride. Similar results were observed. No pure products were isolated.

Reaction of 3-methyl-5-nitro-1,2,3-benzoxathiazole 2,2-dioxide with acenaphthylene in mesitylene.

3-Methyl-5-nitro-1,2,3-benzoxathiazole 2,2-dioxide (0.02 g, 0.09 mmol) and acenaphthylene (0.01 g, 0.09 mmol) were dissolved in mesitylene (10 ml) and the mixture was refluxed for 18 hours. The solvent was removed by distillation leaving a brown-orange oil. Analysis by tlc showed two spot, one corresponding to starting material and the other to an unknown compound. The compounds were separated by column chromatography (silica gel, 2:1 hexanes/ethyl acetate). The ^{1}H NMR spectrum of the unknown spot showed it to be a mixture of several compounds. Attempts to isolated a pure compound from this mixture were unsuccessful.

Irradiation of 3-tosyl-1,2,3-benzoxathiazole 2,2-dioxide (6a).

3-Tosyl-1,2,3-benzoxahiazole-2,2-dioxide (0.05 g, 0.15 mmol) and acenaphthylene (0.050 g, 0.32 mmol) were dissolved in ethyl ether (50 mL) in a 60 mL quartz tube under nitrogen. The solution was irradiated in a Rayonet photochemical reactor for two hours. The solution turned brown, tlc showed acenaphthylene and a brown spot at the baseline. The brown material was only sparingly soluble acetone. ^{1}H NMR spectrum showed many peaks, no pure compound could be isolated.

Pyrolysis of 3-H-1,2,3-Benzoxathiazole 2,2-dioxide (41b).

Compound **41b** (0.4 g, 2.3 mmol) was placed in a 50 mL round-bottom flask which was attacked to a quartz tube, filled with loosely packed glass beads, which was inserted into a pyrolysis oven. A dry ice/acetone trap was placed at the exit of the oven and the entire system was attached to a vacuum pump. The quart tube was heated to 400 °C and the reaction flask heated to induce

sublimation of **41b**. The pyrolysis was continued for 20 minutes. No compounds were collected in the trap, however, a brown-orange compound was deposited in the tube at the exit of the oven. The solid was taken up in $CHCl_3$ and passed through a 1 inch silica gel plug. The tlc of the $CHCl_3$ showed mainly one spot. A ^1H NMR spectrum of the material showed many peaks in the aromatic region. Attempts to isolate only one compound from the mixture were unsuccessful.

Several other attempts were made varying the oven temperature and rate of sublimation. Similar results were observed in all cases.

Acenaphthequinone mono-ethylene ketal (131).

Acenaphthequinone (10 g, 55 mmol), ethylene glycol (3.4g, 3.0 mL, 55 mmol) and *p*-toluenesulfonic acid (0.55 g) were refluxed in toluene (200 mL) in a 500 mL round bottom flask fitted with a Dean-Stark apparatus. After 4 hours, the theoretical amount of water (1 mL) had been collected in the trap so the reaction was stopped. The solution was filtered and the filtrate was washed with 20% NaOH (100 mL). The mixture was dried with magnesium sulfate and concentrated under reduced pressure giving a brown-orange oil which solidified upon cooling. The brown solid was recrystallized from MeOH, giving **131** (9.72g, 78%). mp 93-95 °C (lit.[64] mp 96-97 °C); MS *m /z* (relative intensity) 226 (25, M^+), 198 (71), 170 (100), 154 (34), 126 (88), 114 (31); ^1H NMR ($CDCl_3$) δ 4.44 (m, 2H), 4.66 (m, 2H), 7.71-8.14 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 66.4, 104.8, 121.0, 121.7, 126.9, 128.3, 128.7, 129.4, 130.4, 131.8, 134.0, 142.7, 201.4.

Reaction of 131 with *n*-butylamine.

Method A: Compound **131** (0.50 g, 2.2 mmol) and *n*-butylamine (0.22 mL, 2.2 mol) were dissolved in toluene (50 mL) in a 100 mL round bottom flask fitted

with a Dean-Stark apparatus. The solution was refluxed for 3 hours, during which time the solution became dark brown, no water was collected in the Dean-Stark trap. The solution was concentrated under reduced pressure. A ^1H NMR spectrum of the residual solid showed it to be mostly unreacted **131**.

Method B: Compound **131** (0.23 g, 1 mmol) was dissolved in *n*-butylamine (5 mL) and oven-dried Linde 4A molecular sieves were added. The solution was refluxed while being monitored by tlc for disappearance of starting material. After 3 hours the solution was dark brown and showed mostly starting material by tlc. An additional reflux for 12 hours showed no change.

Acenaphthequinone mono-ethylene ketal oxime (133a).

Hydroxylamine hydrochloride (6.0 g, 86 mmol) was dissolved in 10% NaOH (25 mL) and **131** (3.0 g, 13 mmol) was added. 95% EtOH (25 mL) was added slowly until the mixture became homogeneous. The reaction was refluxed for 1 hour. Water was added until the solution became cloudy and the solution was cooled to 0 °C overnight. A mixture of the two isomers of oxime **133a** precipitated as orange plates (2.68g, 84%). mp °C; MS *m /z* (relative intensity) 241 (6, M^+), 224 (91), 180 (100), 152 (45), 125 (7), 75 (2); ^1H NMR ($CDCl_3$) δ 1.72 (s, 1H), 4.51 (m, 8 H), 7.55-8.37 (m, 10 H), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 65.9, 67.1, 109.7, 110.1, 115.4, 117.8, 119.1, 120.2, 126.3, 126.6, 126.7, 127.8, 128.2, 128.4, 130.4, 131.5, 137.1, 137.5, 137.8, 139.4, 156.9, 158.8.

Reaction of acenaphthequinone mono-ethylene ketal oxime (133a) with *n*-butyllithium.

Method A: Oxime **133a** (0.2 g, 0.8 mmol) was dissolved in THF (5 mL) in a three-neck round bottom flask equipped with an addition funnel and

evacuated with nitrogen. The flask was cooled to 0 °C in an ice water bath and *n*-butyllithium (2 mL, 3.2 mmol) was added dropwise. The reaction was stirred for 1 hour allowing it to warm to room temperature. Water (2 mL) was added and the solution was extracted with Et_2O (2 X 5 mL). The ether extracts were dried with magnesium sulfate and concentrated under reduced pressure leaving an orange oil. Analysis by tlc and ^1H NMR showed several compounds, no pure compounds could be isolated from the mixture.

Method B: Oxime **133a** (0.2 g, 0.8 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. *n*-Butyllithium (1 mL, 1.6 mmol) was added dropwise and the the solution allowed to warm to room temperature and stirred for 4 hours. Water was added and the reaction worked-up as previously. A ^1H NMR spectrum of the residue showed only starting material.

Reaction of acenaphthequinone mono-ethylene ketal oxime (133a) with methylmagnesium iodide.

Magnesium (500 mg) was covered with THF (5 mL). Methyl iodide (0.25 mL, 4 mmol) and a small crystal of iodine were added. The reaction refluxed spontaneously for a 30 minutes. Once the reflux had ceased, **133a** (0.24 g, 1mmol) in THF (5 mL) was added dropwise. The reaction was stirred at room temperature. After 1 hour the reaction mixture showed only starting material by tlc. The solution was refluxed for 4 hours, then quenched with water (5 mL) and extracted with with Et_2O (2 X 5 mL). The ether was dried with magnesium sulfate and concentrated under reduced pressure. The residual solid was shown, by ^1H NMR, to be mainly unreacted **133a.**

Reaction of acenaphthequinone mono-ethylene ketal oxime (133a) with methyllthium.

Oxime **133a** (1 g, 4 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. Methyllithium (5.7 mL, 8 mmol) was added dropwise and the the solution was allowed to warm to room temperature and was stirred for 4 hours. Analysis by tlc showed starting material. The reaction was stirred for an additional 16 hours and quenched with MeOH (5 mL). The tlc showed mostly starting material.

O-Methylhydroxylamine hydrochloride.

NaOH (2.50 g, 61 mmol) was dissolved in 95% EtOH (500 mL). *N*-hydroxyphthalimide (10 g, 61 mmol) was added, followed by methyl iodide (20 mL, 305 mmol). The solution was stirred overnight at room temperature. The solvents were removed under reduced pressure. The residual solid was triturated with $CHCL_3$ (200 mL) and filtered. The $CHCL_3$ solution was evaporated and the residue was recrystallized in 95 % EtOH yielding white crystal of N-methoxyphthalimide. The solid was then suspended in 6N HCl (200 mL) and refluxed for 5 hours. The solvents were removed under reduced pressure and the residual solid was triturated with Et_2O (200 mL) and filtered. The undissolved solid was taken up from 95% EtOH, Et_2O was added slowly until the solution became cloudy. Upon cooling a white crystalline solid precipitated, the mp and ^1H NMR of the solid matched those for O-methylhydroxylamine hydrochloride. mp 85-86 °C (lit. mp 86-88 °C); ^1H NMR (D_2O) δ 3.72 (s).

Acenaphthaquinone mono-ethylene ketal *O*-methyl oxime (133b).

Compound **131** (0.158 g, 0,7 mmol) and *O*-methylhydroxylamine hydrochloride (0.07 g, 0.8 mmol) were stirred in pyridine (3 mL) at room temperature under a nitrogen atmosphere for 12 hours. Water (50 mL) was added and the reaction cooled to 0 °C. A white solid (0.149 g, 83 %), identified as a mixture of both isomers of **133b**, precipitated and was filtered. mp 141-143°C; MS *m /z* (relative intensity) 255 (6,M^+), 224 (79), 180 (100), 152 (78), 125 (22), 75 (8); ^{1}H NMR (acetone-d_6) δ 4.06 (s, 3H), 4.11 (s, 3 H), 4.34-4.58 (m, 8 H), 7.58-8.22 (m, 12 H); ^{13}C NMR (acetone-d_6) δ 63.1, 63.5, 66.4, 68.2, 110.1, 111.8, 118.0, 120.2, 121.3, 126.5, 126.8, 127.3, 127.4, 128.6, 128.9, 129.2, 129.3, 129.4, 129.5, 131.2, 131.3, 132.8, 137.6, 138.1, 139.3, 141.1, 156.7, 158.2.

Reaction of acenaphthaquinone mono-ethylene ketal *O*-methyl oxime (133b) with methyllithium.

Method A: Compound **133b** (0.357 g, 1.4 mmol) was dissolved in THF (10 mL) and cooled to -78 °C in a dry ice/acetone bath under a nitrogen atmosphere. Methyllithium (1 mL, 1.4 mmol) was added and the solution allowed to warm to room temperature over a 2 hour period. The reaction was quenched with MeOH (2 mL). Water (100 mL) was added and the solution stored at 0 °C overnight. White crystals were filtered and identified as unreacted **133b**.

Method B: Compound **133b** (0.15 g, 0.59 mmol) was dissolved in THF and cooled to -78 °C under a nitrogen atmosphere. Methyllithium (5 mL, 0.7 mmol) was added dropwise and the solution allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched with MeOH (5 mL). Water (50 mL) was added and the aqueous solution extracted with $CHCl_3$ (2 X 25 mL). The $CHCl_3$ layers were dried with magnesium sulfate and

concentrated under reduced pressure yielding a brown oil. The ^1H NMR showed many peaks. Several spots were observed on tlc, no pure compounds could be isolated from the mixture.

Isobutyrophenone oxime (142).

Isobutyrophenone (**141**) (10.0 g, 68 mmol) was added to a solution of hydroxylamine hydrochloride (8.0 g, 82 mmol) and NaOH (3.3 g, 82 mmol) in water (150 mL). 95% EtOH was added until the mixture became homogeneous. The solution was refluxed for 3 hours. The solution was poured over water (500 mL) and cooled overnight at 0 °C. The aqueous solution was extracted with $CHCl_3$ (2 X 150 mL). The $CHCl_3$ was dried with magnesium sulfate and evaporated under reduced pressure giving a clear oil. Upon standing the oil solidified to a white solid (10.8, 97%) identified as both isomers of **142**. mp 93-96°C (lit. mp 95-96°C); ^1H NMR ($CDCl_3$) δ 1.23 (d, 3 H, J = 6.8 Hz), 1.31 (d, 3H, J = 7.1 Hz), 2.94 (sept, 1 H, J = 6.8 Hz), 3.71 (sept, 1H, J = 7.1 Hz), 7.38-7.52 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 19.5, 20.2, 21.9, 27.9, 34.6, 127.7, 127.8, 128.2, 128.5,128.6, 133.9, 135.9, 193.1, 164.8.

Attempted tosylation of isobutyrophenone oxime (142).

Method A: Isobutyrophenone oxime (**142**) (1.0 g, 6 mmol), *p*-toluenesulfonyl chloride (1.72 g, 9 mmol) and $NaHCO_3$ (1.26g, 15 mmol) were dissolved in 3:1 water/dioxane (40 mL) and stirred vigorously for 18 hours. Water (50 mL) was added and the solution extracted with toluene (2 X 20 mL). The toluene was evaporated under reduced pressure giving a clear oil; addition of petroleum ether (20 mL) caused a solid to precipitate. The solid was tentatively identified as a mixture of *N*-isopropyl benzamide (**144**) and *N*-phenyl isobutyramide (**145**). The two compounds were not separated, only spectra of the mixture was

obtained. MS m/z 163 (M^+); ^1H NMR ($CDCL_3$) δ 1.25 (d, 6 H, J = 6.8), 1.27 (d, 6H, J = 6.4 Hz),1,17 (s, broad, 1H), 2.52 (sept, 1H, J = 6.8 Hz), 4.30 (sept, 1 H, J = 6.4 Hz),5.97 (s, broad, 1H), 7.07-7.77 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 19.6, 22.8, 36.6, 41.9, 119.7, 124.0, 126.8, 128.5, 128.9, 131.2, 134.9, 138.1, 166.8, 175.3.

Method B: Isobutyrophenone oxime (**142**)(0.5 g, 3.2 mmol) and p-toluenesulfonyl chloride (0.59 g, 3.1 mmol) were dissolved in absolute EtOH (20 mL). Pyridine (0.3 mL, 3.8 mmol) was added and the solution stirred at room temperature for 14 hours. A tlc of the reaction mixture showed several spots including starting material as well two spots corresponding to the amides **144** and **145** observed in the previous reaction. No attempt was made to isolate any products from the reaction mixture.

Method C: Isobutyrophenone oxime (**142**) (0.5 g, 3.1 mmol) and KOH (0.174 g, 3.1 mmol) were dissolved in 1:1 acetone/water (10 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (0.59 g, 3.1 mmol) in acetone (5 ml) was added dropwise over a fifteen minute period. The solution was stirred for an additional 20 minutes at 0 °C. The solution darkened with time; tlc showed many spots. No attempt was made to isolate any products from the mixture.

1-Phenyl-isobutylamine (146).

Isobutyrophenone oxime (**142**) (9.8 g, 60 mmol) was dissolved in MeOH (60 mL), 5% palladium on carbon (1 g) was added and the solution stirred under a hydrogen atmosphere for 24 hours. The solution was filtered through a sintered glass funnel to remove the catalyst, 6N HCl (15 mL) was added and the solvents evaporated under reduced pressure. The residual red solid was triturated with Et_2O (200 mL) for 30 minutes. The undissolved solid was

filtered and washed with acetone. The solid was dissolved in water and made slightly basic with 6N NaOH. The aqueous solution was extracted with Et_2O (2 X 50 mL). The ether extarct was dried with magnesium sulfate and evaporated under reduced pressure giving 5.8 g of an oil identified as **146**. ^1H NMR ($CDCl_3$) δ 0.78 (d, 3H, J = 6.7 Hz), 0.99 (d, 3H, J = 6.7), 1.47 (s, 1H), 1.84 (dsept, 1 H, J = 6.7, 7.2 Hz), 3.60 (d, 1H, J = 7.2 Hz), 7.22-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.7, 19.5, 35.2, 62.2, 126.5, 126.8, 127.6, 127.9, 145.3.

***N,N*-Dichloro-*p*-toluenesulfonamide.**

p-Toluenesulfonamide (10 g, 58.5 mmol) was dissolved in glacial acetic acid (200 mL). A commercial bleach solution (5% NaOCl) was added dropwise. As the addition proceeded a precipitate from solution. The bleach was added until no further precipitate appeared to be forming (approx 250 mL). The white solid was filtered and washed (4 X 50 mL) with water. The solid was dried under reduced pressure for 24 hours. The mp matched that reported in the literature and the ^1H NMR and ^{13}C NMR spectra were fully consistent with that expected for *N,N*-dichloro-*p*-toluenesulfonamide. mp 81-82 °C (lit.[72] mp 83 °C); ^1H NMR ($CDCl_3$) δ 2.54 (s, 3H), 7.47 (d, 2H, J = 8 Hz), 7.99 (d, 2H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 22.0, 125.9, 129.9, 131.6, 147.8.

2-Amino-isobutyrophenone hydrochloride (149).

Method A: 1-Phenyl-isobutylamine (**146**) (6.4 g, 43 mmol) was dissolved benzene (25 mL) and cooled to 0 °C in an ice water bath. *N,N*-dichloro-*p*-toluenesulfonamide (10.2 g, 43 mmol) in benzene (25 mL) was added dropwise over a 10 minute period.The reaction mixture was allowed to warm to room temperature and was stirred for an additional 2 hours, the precipitate (*p*-toluenesulfonamide) was filtered. The benzene solution was slowly added to a

solution of NaOMe in MeOH (prepared from Na metal (3.0g, 130mmol) in MeOH) dropwise over a ten minute period. The reaction mixture was then refluxed for 20 hours. The reaction was cooled to room temperature,then to 0 °C. The benzene solution was poured into 2N HCl (150 mL) and was stirred vigorously. The layers were separated and the organic layer was washed with additional 2N HCl (2 X 50 mL). The combined acidic aqueous layers were washed with Et_2O (2 X 50 mL) and then concentrated under reduced pressure. The residual solid was refluxed in 2-propanol/HCl (100:1) (150 mL) for 2 hours. The undissolved solid (NaCl) was filtered and the solution was cooled. A small amount of NaCl formed and was filtered. The 2-propanol solution was evaporated and the residue triturated with Et_2O (50 mL) and filtered. The filter cake was washed with acetone leaving a white solid, **149** (2.4g, 28%). mp 184-187 °C (lit. mp 187-188 °C);^{1}H NMR (D_2O) δ 1.71 (s, 3H), 7.44 (dd, 2H, J = 7.4, 7.6 Hz), 7.57 (t, 1 H, J = 7.6 Hz), 7.82 (d, 2H, J = 7.4 Hz); ^{13}C NMR (D_2O, dioxane used as reference) δ 25.7, 28.6, 71.5, 133.9, 134.0, 137.6, 139.0, 205.9.

Method B: Magnesium (6 g) was covered with 100 mL Et_2O, 2-chloropropane (5 mL, 55 mmol) and one iodine crystal were added. The reaction began to reflux spontaneously. The remaining 2-chloropropane (18 mL, 197 mmol) in Et_2O (100mL) was added dropwise, so as to maintain a vigorous reflux. Once the reaction had subsided, benzonitrile (10.3 mL, 100 mmol) in diethyl ether (10 mL) was added dropwise over a ten minute period. The solution was refluxed for 12 hours. The reaction flask was cooled to room temperature, followed by cooling in an an ice water bath. MeOH was added dropwise until no reaction was apparent upon further addition. The solution was filtered and the solid washed with Et_2O (2 X 50 mL). The combined ether washes were dried with magnesium sulfate and evaporated under reduced pressure. The residual oil,

imine **150**, was dissolved in benzene (50 mL) and cooled to 0 °C in an ice water bath. A solution of *N,N*-dichloro-*p*-toluenesulfonamide (11g, 45 mmol) in benzene (10 mL) was added dropwise and the reaction allowed to warm to room temperature and stirred for 4 hours. The solution was filtered, to remove *p*-toluenesulfonamide, and a solution of NaOMe in MeOH (5 g sodium in 50 mL MeOH) was added dropwise over a ten minute period. The solution was refluxed for 2 hours then cooled to 0 °C and filtered, to remove precipitated NaCl. The benzene solution was slowly poured into 2 N HCl (200 mL) with vigorous stirring. The layers were separated and the benzene layer was extracted with 2 N HCl (2 X 50 mL). The combined acidic aqueous layers were concentrated under reduced pressure. The residual solid was refluxed in 2-propanol/HCl (100:1) (200 mL). The undissolved solid was filtered and the 2-propanol solution was concentrated. The residual solid was triturated with diethyl ether (150 mL) and filtered, the filter cake was washed with acetone. A white solid (7.1 g, 36%), **149**, was recovered.

_N_-Benzylidene-2-aminoisobutyrophenone (151).

Method A: Compound **149** (0.2 g, 1.2 mmol) was dissolved in pyridine (5 ml), benzaldehyde (0.1 mL, 1 mmol) was added and the solution was refluxed for 6 hours. The pyridine was evaporated under reduced pressure leaving a yellow oil, which gave two spots on tlc. The compounds were separated by column chromatography (silica gel, 4:1 hexanes/ethyl acetate). One appeared, by ^{1}H NMR, to be due to a 1:1 mixture of benzaldehyde and **151**. The compound giving the other spot was isolated, however, its structure was not determined.

Method B: Compound **136** (0.2 g, 1.2 mmol) and benzaldehyde (0.12 mL, 1.2 mmol) were dissolved in toluene (20 mL) in a flask equipped with a Dean-Stark

apparatus. The solution was refluxed (2 hours) until the theoretical amount of water (0.2 ml) was collected. The toluene was evaporated under reduced pressure leaving a clear oil. ^{1}H NMR and ^{13}C NMR spectra showed this to be **151** containing a small amount (15 %) of benzaldehyde. Attempts to separate the compounds by column chromatography were unsuccessful. IR (KBr) 3010, 3000, 2980, 2950,2850, 1675 (C=O), 1650 (C=N)1600, 1575, 1460, 1450, 1400, 1250, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 6H), 7.37-7.49 (m, 7H), 7.77 (m, 2 H), 8.07 (d, 2H, J = 7.4 Hz), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.2, 69.9, 128.0, 128.2, 128.7, 130.6, 131.0, 132.1, 135.0, 136.4, 160.0, 202.6. (all NMR spectra were of the mixture, however, the values reported above are only those due to **151**).

***N*-Benzyl-1-phenyl-2-methyl-2-amino-1-propanol (152).**

Compound **151** (85% pure) (0.1 g, 0.4 mmol) was dissolved in MeOH (10 mL). Sodium borohydride (0.15 g, 4 mmol) was added portionwise over a 20 minute period to the vigorously stirred solution. The solution was refluxed for 2 hours. The reaction mixture was cooled to room temperature and concentrated HCl was added until the solution reached pH = 2 (by litmus paper). The solvents were removed under reduced pressure. The residual solid was washed with Et_2O. The solid was dissolved in water and made basic by addition of aqueous 2N NaOH. The aqueous solution was extracted with Et_2O (2 X 25 ml). The ether extract was dried with magnesium sulfate and evaporated under reduced pressure leaving a white solid (0.064 g, 65 %), **152**. mp 102-104°C, MS m/z (relative intensity) 296 (3, M+41), 284 (6, M+29), 256 (100,M+1), 238 (11), 148 (39), 108 (6); IR (KBr) υ_{max} (cm^{-1}) 3300-2700 (very broad, OH, NH); ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.19 (s, 1H), 3.79 (s, 2 H), 4.53 (s, 1 H), 7.25-7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.5, 46.4, 57.3, 127.1, 127.3, 127.6, 127.7, 128.2, 128.5, 140.4, 140.5.

Attempted tosylation of *N*-benzyl-1-phenyl-2-methyl-2-amino-1-propanol (152). Method A: Compound **152** (0.1 g, 3.9 mmol) was dissolved in CH_2Cl_2 (5 mL). Pyridine (0.03 mL, 4 mmol) and *p*-tolueneusulfonyl chloride (0.076 g, 4 mmol) were added and the solution was stirred at room temperature for 24 hours. A white solid was filtered which was tentatively identified, by ^1H NMR, to be the hydrochloride salt of **152**. The methylene chloride was evaporated under reduced pressure. ^1H NMR showed several compounds, unreacted **152**, pyridinium tosylate and several small unidentified peaks.

Method B: Compound 152 (0.1 g, 0.4 mmol) was dissolved in methylene chloride (15 ml) and cooled to 0 °C. Triethylamine (0.056 mL, 0.4 mmol) was added followed by *p*-tolueneuslfonyl chloride (0.76 g, 0.4 mmol), the reaction was warmed to room temperature and stirred for 18 hours. The solvents were evaporated under reduced pressure and the residual solid triturated with $CHCl_3$. The undissolved solid was filtered and the $CHCl_3$ layer was dried with magnesium sulfate and evaporated. The residual oil was identified as unreacted **152** and triethylamine.

Method C: Compound **152** (0.1 g, 0.4 mmol) was dissolved in pyridine (10 mL), *p*-toluenesulfonyl chloride (0.076 g, 0.4 mmol) was added and the solution was stirred at room temperature for 24 hours. The solution was poured into water (100 mL) and cooled at 0 °C for 18 hours. The aqueous solution was extracted with Et_2O (2 X25 mL). The ether extract was dried with magnesium sulfate and evaporated under reduced pressure. The residual solid was identified as unreacted **152**.

Attempts to protect 152 as its 9-fluorenylmethoxy carbonate derivative.

Method A: A solution of 9-fluorenylemethyl chloroformate (0.103 g, 0.4 mmol) in Et_2O (5 mL) was added to a vigorously stirred solution of **152** (0.1 g, 0.4 mmol) and K_2CO_3 (0.106 g, 1 mmol) in Et_2O (5 mL) and water (5 mL). The solution was stirred overnight at room temperature. The layers were separated and the ether layer waswashed with 15% H_2SO_4 (2 X 10 mL) and dried with magnesium sulfate. Petroleum ether was added until the solution became cloudy. The solution was cooled to 0 °C for 18 hours. A small amount of solid had precipitated and was filtered. This was identified as 9-fluorenylmethyl chloroformate. The ether solution was concentrated; the residue was identified as unreacted 9-fluorenylmethyl chloroformate and **152**.

Method B: Compound **152** (0.1 g, 0.4 mmol) and $KHCO_3$ (0.106 g, 1 mmol) were dissolved in dioxane/water (1:1) (10 ml). 9-Fluorenylmethyl chloroformate (0.103 g, 0.4 mmol) was added and the solution was stirred at room temperature for 12 hours. Water (950 mL) was added until the solution became turbid and the solution was stirred at 0 °C for 12 hours. A white precipitate was filtered and identified as unreacted 9-fluorenylmethyl chloroformate. Evaporation of the solvent gave a tan solid identified as unreacted **152**.

Attempted synthesis of *N*-methyl-*N*-tosyl-α-aminoacetophenone (156).

Method A: *N*-methyl-*p*-toluenesufonamide (1.48 g, 8 mmol) was dissolved in THF (15 mL) and cooled to -78 °C in a dry ice/acetone bath. *n*-Butyllithium (5 mL, 8 mmol) was added dropwise to the cold solution which was stirred 10 minutes. α-Chloroacetophenone (1.24 g, 8 mmol) in THF (10 mL) was added dropwise and the reaction was allowed to warm to room temperature. The reaction mixture was quenched with water (20 mL). The aqueous solution was

extracted with Et_2O (2 X 20 mL). The ether was dried with magnesium sulfate and concentrated under reduced pressure leaving an orange oil. Analysis by ^1H NMR and tlc showed several compounds, no attempt was made to isolate an pure compounds from the mixture.

Method B: *N*-methyl-*p*-toluenesulfonamide (1.48 g, 8 mmol) was dissolved in THF (15 ml) and added to a stirred slurry of NaH (0.192 g, 8 mmol) in THF at 0 °C. α-Chloroacetophenone (1.24 g, 8 mmol) in THF was added dropwise. The reaction mixuture was warmed to room temperature and was stirred for 1 hour. A number of compounds were observed by tlc of the reaction mixture, similar to previous reaction. No attempt was made to isolate any pure products from the mixture.

α-Iodoacetophenone.

NaI (5.5 g, 36.7 mmol) in acetone (50 ml) was added to a stirred solution of α-chloroacetophenone (5 g, 32.3 mmol) in acetone (50 mL). The solution was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure, the residue was triturated with Et_2O (100 mL) and filtered. The ether solution was treated with aqeuous sodium thiosulfate and dried with magnesium sulfate. Concentration of the ether solution gave a yellow oil (7.5 g, 96%) identified as α-iodoacetophenone. ^1H NMR ($CDCL_3$) δ 4.35 (s, 2H), 7.42-7.60 (m, 4H), 7.98 (d, 1H, J = 7.6 Hz).

Sodium *N*-methyl-*p*-toluenesulfonamide.

p-Toluenesulfonamide (1.85 g, 10 mmol) dissolved in THF (15 ml) was added to a stirred solution of NaH (0.4 g, 10 mmol) in THF (10 mL). The solution was stirred for 30 minutes at room temperature. The solvent was

evaporated under reduced pressure. The residual solid was triturated with Et_2O for 10 minutes and filtered. The filter cake was washed with acetone and allowed to air dry. A white solid (1.56 g, 81 %), sodium *N*-methyl-*p*-toluenesulfonamide was recovered and used without further purification. ^1H NMR (D_2O) δ 2.22 (s, 3H), 2.27 (s, 3H), 7.19 (d, 2H, J = 7.5 Hz), 7.45 (d, 2H, J = 7.5 Hz).

_N_-methyl-_N_-_p_-toluensulfonyl-α-aminoacetophenone (156).

Sodium *N*-methyl-*p*-toluenesulfonamide (0.58 g, 3 mmol) in DMF (20 mL) was added dropwise, over a 1 hour period, to a solution of α-iodoacetophenone (0.73 g, 3 mmol) in DMF (20 mL). The solution was stirred for an additional 30 minutes. The solution was poured over 100 mL of ice water and cooled at 0 °C for 18 hours. A yellowish precipitate was filtered. The solid was recrystallized from hexanes/ethyl acetate (4:1) giving yellow crystals of **156** (0.73 g, 80%). mp 115-117 °C (dec); MS *m* /*z* (relative intensity)(CI) 344 (3, M^++41), 332 (4, M^++29), 304 (100, M^++1), 186 (36), 148 (26), 123 (17), 59 (47); ^1H NMR ($CDCl_3$) δ 2.46 (s, 3H), 2.84 (s, 3H), 4.58 (s, 2H), 7.34 (d, 2H, J = 8.4 Hz), 7.49 (dd, 2H, J = 7.8, 7.4), 7.62 (t, 1H, J = 7.4), 7.73 (d, 2H, J = 8.2 Hz).

_N_-methyl-_N_-_p_-toluenesulfonyl-α-aminoacetophenone oxime (159).

N-methyl-*N*-*p*-toluensulfonyl-α-aminoacetophenone (**156**) (0.303 g, 1 mmol) was dissolved in pyridine (5 mL). Hydroxylamine hydrochloride (0.07 g, 1 mmol) was added to the solution and the reaction mixutre was stirred at room temperature for 14 hours. The pyridine solution was poured into water (30 mL) and cooled to 0 °C; a yellow oil separated. The aqueous solution was extracted with Et_2O (2 X 15 mL). The ether was dried with magnesium sulfate and evaporated under reduced pressure giving a yellow oil which solidified

upon standing. Recrystallization of the crude solid from benzene gave a white solid (0.254g, 80 %) identified as a mixture of the two isomers of **159**. mp 174-175 °C (dec); MS m/z (relative intensity)(CI) 359 (1, M^++41), 347 (4, M^++29), 319 (31, M^++1), 198 (87), 186 (29), 147 (12), 104 (23), 79 (100); ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.45 (s, 3H), 2.55 (s, 3H), 2.64 (s, 3H), 4.09 (s, 2 H), 4.39 (s, 2H), 7.27-7.80 (m, 10H), 8.33 (broad s, 1H), 8.73 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 34.3, 34.8, 42.8, 53.3, 126.8, 127.5, 127.7, 128.3, 128.5, 129.6, 129.7, 129.8, 133.1, 133.2, 143.6, 143.8, 153.6, 153.8.

_N_-Methyl-_N_-_p_-toluenesulfonyl-2-phenyl-ethylenediamine (154).

_N_-methyl-_N_-_p_-toluenesulfonyl-α-aminoacetophenone oxime (**159**) (1.5 g, 4.5 mmol) was dissolved in MeOH (50 mL) and stirred under a hydrogen atmosphere in the presence of 10% palladium on barium sulfate (0.2 g). The solution was stirred at room temperature for 2 hours. The catalyst was removed by filtration through a fritted glass funnel. The solvent was evaporated under reduced pressure to give a clear oil, **154** (1.23 g, 90%). MS _m /z_ (relative intensity)(CI) 345 (2, M^++41), 333 (4, M^++29), 305 (51, M^++1), 288 (18), 186 (6), 106 (14), 79 (100); IR (KBr) υ_{max} (cm^{-1}) 3550 (broad), 3467 (broad), 3312 (broad), 3060, 3025, 2920 (broad), 1573, 1492, 1465, 1340, 1200, 1159; ^{1}H NMR (C_6D_6) δ 1.35 (broad s, 2H), 1.87 (s, 3H), 2.40 (s, 3H), 2.61 (dd, 1H, J = 4.1, 13.3 Hz), 3.20 (m, 1H), 3.96 (dd, 1H, J = 4.1, 9.3 Hz), 6.81 (d, 2H, J = 8 Hz), 7.19 (m, 3H), 7.34 (d, 2H, J = 7.3 Hz), 7.63 (d, 2H, J = 8 Hz); ^{13}C NMR (C_6D_6) δ 21.0, 36.1, 54.8, 59.2, 127.1, 127.6, 127.7, 128.6, 128.7, 128.8, 129.6, 135.5, 142.7, 143.9.

Reaction of *N*-methyl-*N*-*p*-toluenesulfonyl-2-phenyl-ethylenediamine (154) with *n*-butyllithium.

Method A: Compound **154** (0.05 g, 0.16 mmol) was dissolved in dry THF and cooled to -78°C in a flask flushed with nitrogen. *n*-Butyllithium (0.2 mL, 0.32 mmol) was added and the solution was stirred at -78 °C for 3 hours. No change was observed by tlc; only starting material was present. The reaction mixture was allowed to warm to room temperature and was stirred for 15 hours. The reaction was quenched with water (10 mL). The aqueous solution was extracted with Et_2O (2 X 10 ml). The ether extract was dried with magnesium sulfate and evaporated under reduced pressure. A yellow oil was recovered; it was identified as unreacted **154**.

An analogous reaction was performed using three equivalents of *n*-butyllithium. After workup, a yellow oil was recovered. Analysis by ^1H NMR and tlc showed several spots. No pure compounds could be isolated from the mixture.

An analogous reaction was performed using five equivalents of *n*-butyllithium. After workup, a yellow oil was recovered. Analysis by ^1H NMR and tlc showed several spots. No pure compounds could be isolated from the mixture.

Reaction of *N*-methyl-*N*-*p*-toluenesulfonyl-2-phenyl-ethylenediamine (154) with lithium diisopropylamide.

A solution of diisopropylamine (0.084 ml, 0.64 mmol) in THF (5 mL) was cooled to -78°C. *n*-Butyllithium (0.4 mL, 0.64 mmol) was added and the solution was stirred for 1 hour at -78 °C. A solution of **154** (0.1 g, 0.32 mmol) in THF (5 mL) was added dropwise and the solution was allowed to warm to room temperature and was stirred for 15 hours. The reaction was quenched

with water (10 mL) and extracted with Et_2O (2 X 10 mL). The ether was dried with magnesium sulfate and concentrated under reduced pressure giving a yellow oil, which was identified by, ^1H NMR, as unreacted **154**.

An analogous reaction was performed using three equivalents of lithium diisopropylamide. After workup, the reaction mixture gave a yellow oil identified, by ^1H NMR , as unreacted starting material.

An analogous reaction was performed using five equivalents of lithium diisopropylamide. After workup, the reaction gave a yellow oil identified, by ^1H NMR , as primarily unreacted starting material, with a few other small peaks in the aromatic region. No attempt was made to isolate this trace compound.

***N*-*p*-Toluenesulfonyl-1,8-naphthosultam (162)[31].**

1,8-Naphthosultam (2.05 g, 10 mmol) was dissolved in CH_2Cl_2 (40 mL). Triethylamine (1.4 mL, 10 mmol) was added along with *p*-toluenesulfonyl chloride (1.91 g, 10 mmol). The solution was stirred at room temperature for 24 hours. The CH_2Cl_2 solution was washed with water (2 X 50 ml), dried with magnesium sulfate and evaporated under reduced pressure. The black residue was recrystallized from 95% EtOH giving 162 as a grey solid (2.8 g, 78%). The mp, ^1H NMR and ^{13}C NMR matched those previously reported. mp 208-210 °C (lit. mp 210-211 °C); ^1H NMR ($CDCl_3$) δ 2.34 (s, 3H), 7.27 (d, 2H, J = 8.3 Hz), 7.58-7.65 (m, 3H), 7.74 (t, 1H, J = 7.8 Hz), 7.93 (d, 1H, J = 7.3 Hz), 8.07 (d, 2H, J = 8.3 Hz), 8.08 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 109.3, 118.2, 120.1, 121.9, 128.1, 128.5, 129.2, 129.3, 129.7, 130.6, 130.7, 131.8, 134.1, 145.9.

***N*-2-Bromobenzyl-1,8-naphthosultam (163)[31].**

1,8-Naphthosultam (**164**) (0.62 g, 3 mmol) was dissolved in benzene (10 ml). Triethylamine (0.42 ml, 3 mmol) and 2-bromobenzyl bromide (1.56g, 6.2 mmol) were added and the solution was refluxed for 20 hours. The solvents were removed under reduced pressure giving a black solid residue. The major spot on tlc was isolated using column chromatography (silica gel, 4:1 hexanes/ ethyl acetate). The green solid was recrystallized from ethyl acetate giving green crystal of **163** (0.57 g, 51%). The mp, ^{1}H NMR spectrum and ^{13}C NMR spectrum matched those previously reported. mp 159-160 °C (lit. mp 160-162 °C); ^{1}H NMR ($CDCl_3$) δ 5.10 (s, 2H), 6.50 (dd, 1H, J = 1.6, 6.3 Hz), 7.17 (dt, 1H, J = 1.7, 7.6 Hz), 7.25 (dt, 1H, J = 1.2, 7.5 Hz), 7.45 (m, 2H), 7.52 (dd, 1 H, J = 1.5, 7.7 hz), 7.63 (dd, 1H, J = 1.3, 7.9 Hz), 7.78 (t, 1H, J = 7.9 Hz), 8.01 (d, 1H, J = 7.2 Hz), 8.08 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 45.6, 103.7, 118.6, 119.1, 120.0, 122.5, 128.0, 128.1, 128.6, 129.3, 129.4, 130.2, 130.6, 131.3, 132.8, 134.0, 136.1.

Reaction of *N*-*p*-toluenesulfonyl-1,8-naphthosultam (162) with *n*-butyllithium.

N-*p*-toluenesulfonyl-1,8-naphthosultam (**162**) (0.114 g, 0.32 mmol) was dissolved in THF (5 mL) and the mixture was cooled to -78 °C. *n*-Butyllithium (0.4 mL, 0.64 mmol) was added and the reaction mixture was stirred at -78 °C for 20 minutes. The tlc of the reaction mixture showed only one spot. The reaction mixture was warmed to room temperature and was stirred for 1 hour. Water (20 mL) was added and the solution was extracted with Et_2O (2 X 25 ml). The ether was dried with magnesium sulfate and evaporated under reduced pressure giving an orange oil. The compound giving the major spot was isolated using column chromatography (silica gel, 4:1 hexanes/ethyl acetate). A white solid was recovered and recrystallized from 4:1 hexanes/ethyl acetate giving white crystals of **171** (0.85 g, 62%). mp 128-130 °C; MS m/z (relative

intensity)(CI) 458 (5, M^++41), 446 (8, M^++29), 418 (100, M^++1), 298 (5), 263 (17), 157 (6), 57 (25); ^{1}H NMR (acetone-d_6) δ 0.86 (t, 3H, J = 7.6 Hz), 1.45 (sextet, 2H, J = 7.4 Hz), 1.82 (pent, 2H, J = 7.5 Hz), 2.47 (s, 3H), 3.74 (t, 2H, J = 7.9 Hz), 7.45 (d, 2H, J = 8.1 Hz), 7.48-7.55 (m, 2H), 7.76 (t, 1H, J = 7.7 Hz), 7.88 (d, 2H, J = 8.1 Hz), 7.90-7.93 (m, 1H), 8.32 (d, 1H, J = 8.2 Hz), 8.51 (d, 1H, J = 7.5 Hz), 10.53 (broad s, 1H); ^{13}C NMR (acetone-d_6) d 13.3, 20.9 21.5, 24.5, 56.8, 122.2, 125.1, 127.2, 127.5, 127.6, 130.4, 132.2, 134.2, 135.2, 136.9, 137.3,138.1, 144.5.

Reaction of *N*-*p*-toluenesulfonyl-1,8-naphthosultam (162) with lithium diisopropylamide.

A solution of diisopropylamine (0.084 mL, 0.64 mmol) in THF (5 mL) was cooled to -78 °C. *n*-Butyllithium (0.4 mL, 0.64 mmol) was added and the solution was stirred at -78 °C for 1 hour. A solution of **162** (0.114 g, 0.32 mmol) in THF (3 mL) was added and the solution was allowed to warm to room temperature and was stirred for 2 hours. The solution was quenched with water (20 mL) and extracted with Et_2O (2 X 25 mL). The ether was dried with magnesium sulfate and evaporated under reduced pressure. A small amount of yellow oil was recovered which was identified as unreacted **162**. The aqueous solution was acidified (pH=2) with concentrated hydrochloric acid and extracted with Et_2O (2 X 25 mL). The ether extract was dried with magnesium sulfate and evaporated under reduced pressure giving a tan solid, identified as 1,8-naphthosultam (**164**) (0.48 g).

Reaction of *N*-2-bromobenzyl-1,8-naphthosultam (163) with *n*-butyllithium.

N-2-bromobenzyl-1,8-naphthosultam (**163**) (0.06 g, 0.16 mmol) was dissolved in THF (5 mL) and cooled to -78°C. *n*-Butyllithium (0.1 mL, 0.16 mmol) was added and the solution was allowed to warm to room temperature and was

stirred for 18 hours. The reaction was quenched with water (1 mL), diethyl ether was added, and the solution was extracted with 2N HCl (2 X 10 mL). The aqueous extracts were made basic (pH = 11) with 2 N NaOH. A yellow solid precipitated and was filtered. The solid was purified by column chromatography (silica gel, 4:1 hexanes ethyl acetate) to give a light yellow solid (0.02 g, 42 %), identified as **175**. mp 209-210 °C (dec); MS m/z (relative intensity)(CI) 336 (4, M^++41), 324 (10, M^++29), 296 (100, M^++1); IR (KBr) υ_{max} (cm^{-1}) 3395, 3076, , 3049, 3026, 2915, 2891, 1590, 1585, 1512, 1475, 1463, 1360, 1349, 1295, 1243, 1146, 1110; ^1H NMR ($CDCL_3$) δ 6.31 (broad t, 1H), 7.29 (d, 2H, J = 7.5 Hz), 7.39-7.61 (m, 8H), 7.97 (d, 1H, J = 8.7), 7.94 (d, 1H, J = 8.9 Hz), 8.61 (d, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 54.9, 124.5, 124.9, 126.4, 127.4, 128.0, 128.3, 129.5, 129.8, 130.4, 133.3, 134.4, 135.8, 138.4, 138.7, 143.0, 143.9.

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APPENDIX

Data table for pK_a determination of sulfamate **41a**.

% ion.	mL base	[HA]	[A-]	$\{H^+\}$	pH	pK_a
10	0.25	-----	-----		-----	-----
20	0.50	0.0052	0.0013	0.0016	2.79	2.88
30	0.75	0.0046	0.0019	0.0015	2.83	2.78
40	1.00	0.0039	0.0026	0.0012	2.91	2.77
50	1.25	0.0033	0.0032	0.0010	3.00	2.73
60	1.50	0.0026	0.0039	0.0008	3.11	2.70
70	1.75	0.0019	0.0046	0.0004	3.35	2.83
80	2.00	0.0013	0.0052	0.0002	3.75	3.02

average: 30-70% (5 points) 2.76 ± 0.07

Data table for pK_a determination of sulfamate **41c.**

% ion.	mL base	[HA]	[A-]	$\{H^+\}$	pH	pK_a
10	0.25	0.009	0.001	.00015	3,81	4.76
20	0.50	0.008	0.002	0	4.11	4.71
30	0.75	0.007	0.003	0	4.33	4.70
40	1.00	0.006	0.004	0	4.54	4.71
50	1.25	0.005	0.005	0	4.73	4.73
60	1.50	0.004	0.006	0	4.92	4.74
70	1.75	0.003	0.007	0	5.13	4.76
80	2.00	0.002	0.008	0	5.42	4.81

averages: 10-80% (8 points) 4.74 ± 0.07
10-70% (7 points) 4.73 ± 0.03

Data table for pK_a determination of sulfamate **41d**.

% ion.	mL base	[HA]	[A-]	$\{H^+\}$	pH	pK_a
10	0.25	0.009	0.001	0.0010	2.96	3.92
20	0.50	0.008	0.002	0.0009	3.02	3.62
30	0.75	0.007	0.003	0.0008	3.10	3.47
40	1.00	0.006	0.004	0.0006	3.20	3.45
50	1.25	0.005	0.005	0.0003	3.45	3.45
60	1.50	0.004	0.006	0.0002	3.63	3.46
70	1.75	0.003	0.007	0.0001	3.90	3.52
80	2.00	0.002	0.008	0	4.35	3.77

average: 30-70% (5 points) 3.47 ± 0.05

Data table for pK_a determination of sulfamate **41e**.

% ion.	mL base	[HA]	[A-]	$\{H^+\}$	pH	pK_a
10	0.25	0.009	0.001	-----	-----	-----
20	0.50	0.008	0.002	0.0006	3.20	3.65
30	0.75	0.007	0.003	0.0004	3.38	3.68
40	1.00	0.006	0.004	0.0002	3.53	3.67
50	1.25	0.005	0.005	0.0001	3.72	3.71
60	1.50	0.004	0.006	0	3.98	3.74
70	1.75	0.003	0.007	0	4.14	3.73
80	2.00	0.002	0.008	0	4.48	3.76

average: 20-80% (6 points) 3.72 ± 0.05

Data table for pK_a determination of sulfamate **41f**.

% ion.	mL base	[HA]	[A-]	$\{H^+\}$	pH	pK_a
10	0.25	0.009	0.001	0.0021	2.67	3.02
20	0.50	0.008	0.002	0.0019	2.72	2.91
30	0.75	0.007	0.003	0.0015	2.81	2.90
40	1.00	0.006	0.004	0.0013	2.90	2.85
50	1.25	0.005	0.005	0.0010	3.04	2.86
60	1.50	0.004	0.006	0.0007	3.17	2.86
70	1.75	0.003	0.007	0.0005	3.33	2.85
80	2.00	0.002	0.008	0.0002	3.63	2.97

average: 20-70% (6 points) 2.87 ± 0.04

Data table for pK_a determination of sulfamate **41g**.

% ion.	mL base	[HA]	[A-]	$\{H^+\}$	pH	pK_a
10	0.25	0.0045	0.0005	-----	-----	-----
20	0.50	0.0040	0.0010	0.0020	2.70	2.54
30	0.75	0.0035	0.0015	0.0018	2.74	2.43
40	1.00	0.0030	0.0020	0.0016	2.80	2.37
50	1.25	0.0025	0.0025	0.0013	2.88	2.32
60	1.50	0.0020	0.0030	0.0010	2.99	2.30
70	1.75	0.0015	0.0035	0.0007	3.15	2.32
80	2.00	0.0010	0.0040	0.0004	3.39	2.35

averages: 30-80% (6 points) 2.35 ± 0.08
40-80% (5 points) 2.33 ± 0.04

Data table for pK_a determination of sulfamate **41h**.

% ion.	mL base	[HA]	[A-]	$\{H^+\}$	pH	pK_a
10	0.25	0.009	0.001	0.0006	3.18	4.14
20	0.50	0.008	0.002	0.0005	3.31	3.91
30	0.75	0.007	0.003	0.0003	3.48	3.85
40	1.00	0.006	0.004	0.0002	3.64	3.82
50	1.25	0.005	0.005	0.0001	3.82	3.82
60	1.50	0.004	0.006	0	4.01	3.84
70	1.75	0.003	0.007	0	4.22	3.85
80	2.00	0.002	0.008	0	4.50	3.92

averages: 20-80% (7 points) 3.86 ± 0.06
20-70% (6 points) 3.85 ± 0.06
20-70% (6 points) 3.85 ± 0.02

Compound **41a.** (AM1)

Neutral

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-1.9808149	0.0000000	1.3441395
C 2	-0.9055547	0.0000000	1.0981863
C 3	1.8957681	0.0000000	0.5274675
C 4	-0.4575337	0.0000000	-0.2159223
C 5	0.0660201	0.0000000	2.1224733
C 6	1.4404777	0.0000000	1.8497789
C 7	0.9551253	0.0000000	-0.4903757
N 8	-1.2167903	0.0000000	-1.3992589
N 9	-0.3956592	0.0000000	3.5365950
H 10	2.1713428	0.0000000	2.6784137
O 11	1.2457349	0.0000000	-1.8249479
H 12	2.9707882	0.0000000	0.2940093
S 13	-0.2582503	0.0000000	-2.7245367
H 14	-2.2006543	0.0000000	-1.3190129
O 15	-0.2662523	-1.1894280	-3.4074833
O 16	-0.2662523	1.1894280	-3.4074833
O 17	-1.5762095	0.0000000	3.7612906
O 18	0.4245634	0.0000000	4.4141285

Anion

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-1.9840802	0.0000000	1.3089701
C 2	-0.9101240	0.0000000	1.0718286
C 3	1.8927540	0.0000000	0.5196185
C 4	-0.4756234	0.0000000	-0.2500134
C 5	0.0590004	0.0000000	2.1026222
C 6	1.4331813	0.0000000	1.8412119
C 7	0.9711572	0.0000000	-0.5113429
N 8	-1.2163500	0.0000000	-1.3949291
N 9	-0.4016424	0.0000000	3.5067482
H 10	2.1593486	0.0000000	2.6685471
O 11	1.2604529	0.0000000	-1.8286974
H 12	2.9684939	0.0000000	0.3025377
S 13	-0.3541048	0.0000000	-2.6872150
O 14	0.4115244	0.0000000	4.4003242
O 15	-0.2937634	-1.1695453	-3.4581753
O 16	-0.2937634	1.1695453	-3.4581753
O 17	-1.5812269	0.0000000	3.7558616

Compound **41b**. (AM1)

Neutral

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-2.5159950	0.0000000	1.8785479
C 2	-1.4174873	0.0000000	1.8523196
C 3	1.4301593	0.0000000	1.8295760
C 4	-0.7289803	0.0000000	0.6425427
C 5	-0.6781307	0.0000000	3.0422036
C 6	0.7130346	0.0000000	3.0336601
C 7	0.7066557	0.0000000	0.6490861
N 8	-1.2426044	0.0000000	-0.6672049
H 9	-1.2181242	0.0000000	4.0014168
H 10	1.2670651	0.0000000	3.9846034
O 11	1.2582207	0.0000000	-0.6100969
H 12	2.5286929	0.0000000	1.8104191
S 13	-0.0377213	0.0000000	-1.7715395
H 14	-2.2213477	0.0000000	-0.7829986
O 15	0.0777630	-1.1873145	-2.4557797
O 16	0.0777630	1.1873145	-2.4557797

Anion

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-2.5266000	0.0000000	1.8459484
C 2	-1.4299205	0.0000000	1.8271483
C 3	1.4126633	0.0000000	1.8303270
C 4	-0.7507644	0.0000000	0.6076151
C 5	-0.6999453	0.0000000	3.0235502
C 6	0.6856994	0.0000000	3.0342870
C 7	0.7159178	0.0000000	0.6414669
N 8	-1.2515971	0.0000000	-0.6619208
H 9	-1.2512837	0.0000000	3.9749811
H 10	1.2321740	0.0000000	3.9861939
O 11	1.2688246	0.0000000	-0.6028583
H 12	2.5093357	0.0000000	1.8335630
S 13	-0.1308766	0.0000000	-1.7454169
O 14	0.0711926	1.1697721	-2.5027544
O 15	0.0711926	-1.1697721	-2.5027544

Compound 41c. (AM1)

Neutral

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-2.1838987	0.0000000	1.7854986
C 2	-1.0968716	0.0000000	1.6230060
C 3	1.7233091	0.0000000	1.2499236
C 4	-0.5629155	0.0000000	0.3396899
C 5	-0.2206198	0.0000000	2.7238742
C 6	1.1619744	0.0000000	2.5331071
C 7	0.8621282	0.0000000	0.1668559
N 8	-1.2355702	0.0000000	-0.8962765
C 9	-0.7940436	0.0000000	4.0906449
H 10	1.8331825	0.0000000	3.4058355
O 11	1.2534634	0.0000000	-1.1512862
H 12	2.8115200	0.0000000	1.0974356
S 13	-0.1768532	0.0000000	-2.1414456
H 14	-2.2210393	0.0000000	-0.8897739
O 15	-0.1481506	-1.1871293	-2.8354989
O 16	-0.1481506	1.1871293	-2.8354989
H 17	0.0084162	0.0000000	4.8682756
H 18	-1.4323011	-0.9062667	4.2427287
H 19	-1.4323011	0.9062667	4.2427287

Anion

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-2.1952569	0.0000000	1.7506196
C 2	-1.1089285	0.0000000	1.5965857
C 3	1.7102378	0.0000000	1.2518554
C 4	-0.5845963	0.0000000	0.3053352
C 5	-0.2411622	0.0000000	2.7050947
C 6	1.1379911	0.0000000	2.5360766
C 7	0.8751859	0.0000000	0.1567551
N 8	-1.2385308	0.0000000	-0.8932038
C 9	-0.8329154	0.0000000	4.0649446
H 10	1.8012242	0.0000000	3.4114069
O 11	1.2699834	0.0000000	-1.1457078
H 12	2.7994165	0.0000000	1.1226819
S 13	-0.2611794	0.0000000	-2.1067795
H 14	-1.4742414	0.9049756	4.2098469
O 15	-0.1538025	-1.1696398	-2.8832605
O 16	-0.1538025	1.1696398	-2.8832605
H 17	-0.0422158	0.0000000	4.8544426
H 18	-1.4742414	-0.9049756	4.2098469

Compound 41d. (AM1)

Neutral

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-1.8847890	0.0000000	1.0222269
C 2	-0.8182491	0.0000000	0.7512786
C 3	1.9476707	0.0000000	0.0725949
C 4	-0.4250424	0.0000000	-0.5831899
C 5	0.1772797	0.0000000	1.7418026
C 6	1.5318979	0.0000000	1.4100008
C 7	0.9730426	0.0000000	-0.9105689
N 8	-1.2288719	0.0000000	-1.7371558
Br 9	-0.3397467	0.0000000	3.5420113
H 10	2.2991273	0.0000000	2.2012775
O 11	1.2168323	0.0000000	-2.2606021
H 12	3.0133866	0.0000000	-0.1967700
S 13	-0.3154005	0.0000000	-3.0936780
H 14	-2.2081886	0.0000000	-1.6218448
O 15	-0.3583840	-1.1879584	-3.7826898
O 16	-0.3583840	1.1879584	-3.7826898

Anion

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-1.8877099	0.0000000	0.9901400
C 2	-0.8227524	0.0000000	0.7236484
C 3	1.9456123	0.0000000	0.0627503
C 4	-0.4431137	0.0000000	-0.6193118
C 5	0.1727999	0.0000000	1.7133053
C 6	1.5250618	0.0000000	1.4040086
C 7	0.9913076	0.0000000	-0.9315723
N 8	-1.2270246	0.0000000	-1.7346853
Br 9	-0.3581348	0.0000000	3.5251117
H 10	2.2860624	0.0000000	2.1961373
O 11	1.2350875	0.0000000	-2.2671474
H 12	3.0135507	0.0000000	-0.1877979
S 13	-0.3980612	0.0000000	-3.0546887
O 14	-0.3758269	1.1699155	-3.8337104
O 15	-0.3758269	-1.1699155	-3.8337104

Compound 41e. (AM1)

Neutral

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
H	1	-2.0488689	0.0000000	1.5523177
C	2	-0.9705971	0.0000000	1.3367016
C	3	1.8351260	0.0000000	0.8243553
C	4	-0.4966131	0.0000000	0.0288150
C	5	-0.0290951	0.0000000	2.3796530
C	6	1.3446440	0.0000000	2.1358734
C	7	0.9187971	0.0000000	-0.2136000
N	8	-1.2290719	0.0000000	-1.1711137
Cl	9	-0.5946914	0.0000000	3.9826322
H	10	2.0568472	0.0000000	2.9758863
O	11	1.2436471	0.0000000	-1.5477370
H	12	2.9145113	0.0000000	0.6161093
S	13	-0.2344839	0.0000000	-2.4703302
H	14	-2.2135857	0.0000000	-1.1158826
O	15	-0.2379157	-1.1878914	-3.1611870
O	16	-0.2379157	1.1878914	-3.1611870

Anion

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
H	1	-2.0488244	0.0000000	1.5301187
C	2	-0.9730997	0.0000000	1.3152602
C	3	1.8323499	0.0000000	0.8098930
C	4	-0.5173197	0.0000000	-0.0043061
C	5	-0.0278789	0.0000000	2.3528296
C	6	1.3409366	0.0000000	2.1278551
C	7	0.9334494	0.0000000	-0.2338785
N	8	-1.2357322	0.0000000	-1.1617513
Cl	9	-0.6030642	0.0000000	3.9722425
H	10	2.0500221	0.0000000	2.9654774
O	11	1.2526135	0.0000000	-1.5552644
H	12	2.9121951	0.0000000	0.6172738
S	13	-0.3309304	0.0000000	-2.4325277
O	14	-0.2667389	1.1700468	-3.2095059
O	15	-0.2667389	-1.1700468	-3.2095059

Compound 41f. (AM1)

Neutral

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-2.5267421	0.0000000	0.6672632
C 2	-1.4266675	0.0000000	0.6411754
C 3	1.4241696	0.0000000	0.6189252
C 4	-0.7367810	0.0000000	-0.5649853
C 5	-0.6902084	0.0000000	1.8388929
C 6	0.7101106	0.0000000	1.8307877
C 7	0.6997729	0.0000000	-0.5582836
N 8	-1.2497477	0.0000000	-1.8728858
Cl 9	-1.5529783	0.0000000	3.2988693
Cl10	1.5921493	0.0000000	3.2772130
O 11	1.2510303	0.0000000	-1.8146043
H 12	2.5244773	0.0000000	0.5993431
S 13	-0.0453058	0.0000000	-2.9821595
H 14	-2.2292066	0.0000000	-1.9891972
O 15	0.0717545	-1.1883773	-3.6605183
O 16	0.0717545	1.1883773	-3.6605183

Anion

Atom	Cartesian Coordinates (Angstroms) X	Y	Z
H 1	-2.5269786	0.0000000	0.6327348
C 2	-1.4294917	0.0000000	0.6119321
C 3	1.4221184	0.0000000	0.6051445
C 4	-0.7506079	0.0000000	-0.6072927
C 5	-0.6940773	0.0000000	1.8084151
C 6	0.6968150	0.0000000	1.8150295
C 7	0.7191318	0.0000000	-0.5774261
N 8	-1.2524023	0.0000000	-1.8706718
Cl 9	-1.5734754	0.0000000	3.2768472
Cl10	1.5804201	0.0000000	3.2768977
O 11	1.2653363	0.0000000	-1.8209107
H 12	2.5196418	0.0000000	0.6061511
S 13	-0.1385886	0.0000000	-2.9665751
O 14	0.0604683	1.1707094	-3.7162609
O 15	0.0604683	-1.1707094	-3.7162609

Compound **41g.** (AM1)

Neutral

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
O	1	0.0339856	-0.0803114	-1.8003580
C	2	0.0037888	0.1513043	-0.4477501
C	3	-0.0496020	0.3030406	2.3250274
C	4	0.0204315	-1.0517328	0.3392285
C	5	-0.0385689	1.4074174	0.1278715
C	6	-0.0651162	1.4623838	1.5380164
C	7	-0.0067716	-0.9607578	1.7296418
N	8	0.0641554	-2.1949982	-0.4678534
H	9	-0.0508190	2.3197195	-0.4921956
N	10	-0.1107465	2.7931091	2.2015020
H	11	0.0049106	-1.8635548	2.3577921
H	12	-0.0711998	0.3825305	3.4270037
O	13	-0.1332949	2.8394923	3.4021631
O	14	-0.1238957	3.7818243	1.5202021
O	15	-1.0875557	-2.1118503	-2.7098494
S	16	0.0833905	-1.8030728	-2.0649569
H	17	0.0776687	-3.0786796	-0.0280825
O	18	1.2915556	-2.0501000	-2.6662778

Anion

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
O	1	0.0339665	-0.0805690	-1.8153246
C	2	0.0032899	0.1540678	-0.4718837
C	3	-0.0497406	0.2767622	2.3085663
C	4	0.0209833	-1.0928771	0.3130946
C	5	-0.0387043	1.3916766	0.1144396
C	6	-0.0654383	1.4494077	1.5349950
C	7	-0.0075521	-0.9769609	1.7154998
N	8	0.0636180	-2.1971374	-0.4542053
H	9	-0.0511341	2.3103346	-0.4900883
N	10	-0.1091478	2.7553234	2.1958150
H	11	0.0041452	-1.8834165	2.3345091
H	12	-0.0712583	0.3517429	3.4088458
O	13	-0.1273578	2.8158022	3.4040018
O	14	-0.1267755	3.7673819	1.5369927
O	15	-1.0692820	-2.1566945	-2.7431810
S	16	0.0842327	-1.8689846	-2.0001589
O	17	1.2784745	-2.0952541	-2.6987718

Compound **41h**. (AM1)

Neutral

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
O	1	1.2515726	0.0000000	-1.7587423
C	2	0.7097270	0.0000000	-0.4951092
H	3	2.5279296	0.0000000	0.6549506
C	4	1.4288153	0.0000000	0.6651865
C	5	-1.4322124	0.0000000	0.6863164
C	6	0.7184134	0.0000000	1.9036637
C	7	-0.7464850	0.0000000	-0.5025516
C	8	-0.7004841	0.0000000	1.9118044
C	9	1.4179256	0.0000000	3.1390788
H	10	-2.2268100	0.0000000	-1.9387941
H	11	-2.4837097	0.0000000	3.1567286
H	12	-2.5311417	0.0000000	0.7201506
C	13	0.7317338	0.0000000	4.3307772
H	14	2.5184627	0.0000000	3.1222668
H	15	1.2738501	0.0000000	5.2881960
C	16	-0.6815857	0.0000000	4.3397098
H	17	-1.2115982	0.0000000	5.3038775
C	18	-1.3832335	0.0000000	3.1571538
S	19	-0.0423472	0.0000000	-2.9184317
O	20	0.0726145	1.1871957	-3.6029031
O	21	0.0726145	-1.1871957	-3.6029031
N	22	-1.2485039	0.0000000	-1.8160370

Anion

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
O	1	1.2626663	0.0000000	-1.7624982
C	2	0.7285283	0.0000000	-0.5161771
H	3	2.5260174	0.0000000	0.6577600
C	4	1.4289426	0.0000000	0.6534126
C	5	-1.4313313	0.0000000	0.6637938
C	6	0.7154378	0.0000000	1.8913652
C	7	-0.7603513	0.0000000	-0.5427960
C	8	-0.7061163	0.0000000	1.8874800
C	9	1.4036291	0.0000000	3.1274009
N	10	-1.2518872	0.0000000	-1.8113154
H	11	-2.4881607	0.0000000	3.1266606
H	12	-2.5282012	0.0000000	0.6919119
C	13	0.7147648	0.0000000	4.3212207

H	14	2.5035306	0.0000000	3.1178959
H	15	1.2541969	0.0000000	5.2777459
C	16	-0.6947078	0.0000000	4.3214615
H	17	-1.2316547	0.0000000	5.2800696
C	18	-1.3884396	0.0000000	3.1320026
S	19	-0.1449416	0.0000000	-2.9054150
O	20	0.0551925	1.1701013	-3.6575747
O	21	0.0551925	-1.1701013	-3.6575747

Compound 50a. (RHF/3-21+G(*))

Neutral

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	-0.0179983	0.2694298	-1.4871174
S	2	0.0470847	0.1014189	0.0895449
O	3	1.4175844	0.0882456	0.5077097
O	4	-0.8948586	0.9924367	0.6995715
O	5	-0.5155968	-1.3750577	0.2662669
H	6	0.7506907	-0.0259767	-2.0567824
H	7	-0.8557235	0.6016064	-1.9236302
H	8	-0.5793665	-1.7293374	1.1691306

Anion

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	-0.0291387	0.3572920	-1.5322380
S	2	0.0316656	0.1343929	-0.0292004
O	3	1.3746606	0.0578038	0.5714425
O	4	-0.9026385	0.9724919	0.7144527
O	5	-0.5350964	-1.3944509	0.2246211
H	6	0.7200152	-0.0820421	-2.0486378
H	7	-0.5180990	-1.6560467	1.1573800

Compound **50b.** (RHF/3-21+G(*))

Neutral

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	0.2336011	0.0000000	-1.4948953
S	2	0.1177746	0.0000000	0.1023198
O	3	0.5991877	-1.2229727	0.6791768
O	4	0.5991877	1.2229727	0.6791768
O	5	-1.4667081	0.0000000	0.1208425
H	6	-0.5924357	0.0000000	-2.0597214
H	7	1.1354581	0.0000000	-1.9284639
H	8	-1.9159624	0.0000000	0.9817667

Anion

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	0.2441360	0.0000000	-1.5506990
S	2	0.1508310	0.0000000	-0.0335278
O	3	0.6255167	-1.2108888	0.6423762
O	4	0.6255167	1.2108888	0.6423762
O	5	-1.4766532	0.0000000	0.2497378
H	6	-0.6134946	0.0000000	-2.0757163
H	7	-1.7037938	0.0000000	1.1911325

Compound **50c**. (RHF/3-21+G(*))

Neutral

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	0.7014262	0.0000000	-1.3363025
S	2	0.0629016	0.0000000	0.1533351
O	3	0.3675291	-1.2261761	0.8232109
O	4	0.3675291	1.2261761	0.8232109
O	5	-1.4759587	0.0000000	-0.1977252
H	6	1.7002160	0.0000000	-1.4219618
H	7	0.1689219	0.0000000	-2.1812307
H	8	-1.8583440	0.0000000	-1.0856251

Anion

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
O	1	1.2071733	0.0000000	-0.9119672
S	2	-0.0943793	0.0000000	0.1196512
O	3	0.0935477	-1.2156706	0.9017199
O	4	0.0935477	1.2156706	0.9017199
N	5	-1.3401595	0.0000000	-0.7736190
H	6	-1.2710558	0.0000000	-1.7751299
H	7	1.0080933	0.0000000	-1.8557362

Compound **50d.** (RHF/3-21+G(*))

Neutral

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	1.0810838	0.0000000	1.1638820
S	2	0.0253884	0.0000000	-0.1902335
O	3	0.1173169	1.3633295	-0.9819093
O	4	0.1173169	-1.3633295	-0.9819093
O	5	-1.4039209	0.0000000	0.7280752
H	6	0.5285178	0.0000000	1.9914379
H	7	2.0779818	0.0000000	1.1093131
H	8	-1.2260027	0.0000000	1.6817574

Anion

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	-1.2781757	0.0000000	0.8762323
S	2	-0.0935246	0.0000000	-0.1647441
O	3	0.0873449	-1.2137815	-0.9428986
O	4	0.0873449	1.2137815	-0.9428986
O	5	1.1414235	0.0000000	0.9880458
H	6	-0.8837317	0.0000000	1.8003656
H	7	0.7984475	0.0000000	1.8839243

Compound **59a.** (RHF/3-21+G(*))

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	0.0489825	0.0553462	-1.5542682
S	2	0.0388676	0.0696191	0.0563808
O	3	1.4131478	-0.0698728	0.4631781
O	4	-0.7883420	1.1839933	0.4404042
N	5	-0.7194174	-1.2492039	0.5857550
H	6	0.8365582	-0.3163437	-2.0463677
H	7	-0.6691139	0.5297065	-2.0639998
H	8	-1.6939851	-1.2107131	0.8078057
H	9	-0.1959764	-2.0705541	0.8136501

Compound **59b.**

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	-0.1265131	0.3104678	-1.5354533
S	2	0.0785844	0.0920729	-0.0268952
O	3	1.4573061	-0.1664008	0.4279741
O	4	-0.6186853	1.1263741	0.7469840
N	5	-0.6628622	-1.3652969	0.3534513
H	6	0.4386310	-0.3087894	-2.1031737
H	7	-1.6325405	-1.4349641	0.1096753
H	8	-0.4075305	-1.7666693	1.2364942

Compound 60a. (RHF/3-21+G(*))

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	-0.0175004	0.4092174	1.5004392
S	2	0.0949805	0.0503502	-0.1120397
O	3	1.3075427	-0.6518007	-0.4401240
O	4	-0.2001055	1.2402776	-0.8656840
N	5	-1.1566464	-1.0335955	-0.1162773
H	6	-0.7505392	-0.1377610	1.8928435
H	7	0.1671606	1.3351727	1.8328378
H	8	-1.1282505	-1.8464794	-0.6997191
H	9	-1.5359499	-1.0779425	0.8028129

Compound 60b.

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	0.7217527	0.1758824	-1.3894218
S	2	0.0919867	0.1197461	0.0574292
O	3	-0.2806354	1.4098215	0.6338764
O	4	0.7684543	-0.7419851	1.0374178
N	5	-1.3300654	-0.7342021	-0.4088442
H	6	0.1007063	-0.2970892	-2.0199158
H	7	-1.2768845	-0.9173688	-1.3840638
H	8	-1.6995383	-1.4420751	0.1946585

Compound **61a.** (RHF/3-21+G(*))

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
C	1	0.0686477	0.0725870	-1.6478974
S	2	0.0568816	0.1041767	0.1085186
O	3	1.4247627	-0.0133284	0.5586024
O	4	-0.7629681	1.2197858	0.5217297
N	5	-0.7121777	-1.2470968	0.5531364
H	6	-0.1794560	-2.0475745	0.8341017
H	7	-1.6797616	-1.2022256	0.8087032
H	8	0.5976302	-0.8039244	-1.9924490
H	9	0.5764971	0.9622631	-1.9954636
H	10	-0.9460145	0.0671304	-2.0184178

Compound **61b.**

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	-0.0309003	0.0691913	-1.5883303
S	2	0.0626156	0.1345069	-0.0443415
O	3	1.4447926	-0.0120181	0.4750739
O	4	-0.6880663	1.2656257	0.5228339
C	5	-0.7940406	-1.2848330	0.6091934
H	6	0.8209404	-0.2593834	-2.0235434
H	7	-0.7785889	-1.2422917	1.6904776
H	8	-0.3026752	-2.1867921	0.2692467
H	9	-1.8147904	-1.2678459	0.2531726

Compound **62a.** (RHF/3-21+G(*))

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
C	1	0.0519942	0.6263266	-1.5211309
S	2	-0.1166384	0.0300724	0.1557640
O	3	0.1482814	1.0975150	1.0952260
O	4	-1.3630843	-0.6874788	0.3095174
N	5	1.1404056	-1.0160343	0.1129408
H	6	1.6492139	-1.0637132	-0.7415568
H	7	0.2233262	1.6925933	-1.4956605
H	8	-0.8581693	0.4085977	-2.0608384
H	9	0.8834792	0.1344553	-1.9963001
H	10	1.3919836	-1.5791005	0.9003843

Compound **62b.**

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
S	1	0.0459346	-0.0113871	-0.1875273
C	2	-0.3129016	0.4767729	1.5260706
H	3	0.4968810	1.0964973	1.8836795
N	4	0.4244419	-1.5041617	0.0703076
H	5	-1.2380687	1.0346584	1.5455486
O	6	-1.2276958	0.2118900	-0.9083986
H	7	-0.1637039	-1.8314008	0.8260476
O	8	1.1596303	0.7914087	-0.7126107
H	9	-0.3792219	-0.4754560	2.0646592

Compound **63a.** (RHF/3-21+G(*))

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
H	1	-0.7537317	0.1868000	-3.2204472
C	2	-0.7786591	0.3579920	-2.1613845
C	3	0.0898419	-0.2322709	-1.3668437
H	4	-1.5264238	1.0265650	-1.7799621
H	5	0.8592950	-0.8938870	-1.7155955
S	6	0.1075055	0.0398986	0.3549441
O	7	1.4645436	0.3500052	0.7403391
O	8	-0.9797243	0.9364500	0.6708740
N	9	-0.2166392	-1.4001569	1.0094886
H	10	0.5237840	-1.9189340	1.4407820
H	11	-1.1638949	-1.6833471	1.1678566

Compound **63b.**

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
H	1	-0.7042954	0.1012650	-3.2162474
C	2	-0.7378430	0.2939355	-2.1579977
C	3	0.1136596	-0.2784754	-1.3302666
H	4	-1.4854915	0.9735042	-1.7950783
H	5	0.8754504	-0.9575280	-1.6666140
S	6	0.1213094	-0.0441048	0.4268248
O	7	1.4747647	0.4610801	0.6818713
O	8	-0.9706374	0.9213158	0.6737888
N	9	-0.0926348	-1.4323637	1.0691945
H	10	-1.0676572	-1.6566758	1.2234694

Compound **64a.** (RHF/3-21+G(*))

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	1.2028362	-0.0917713	0.0566114
S	2	-0.2313866	0.5761848	-0.3233776
O	3	-0.5776419	1.6476089	0.5858374
O	4	-0.3190244	0.8830253	-1.7349939
C	5	-1.0930163	-0.8934979	0.0647266
H	6	2.0480152	0.4369431	-0.0226445
H	7	1.7509997	-2.1250742	-0.1493061
C	8	-0.2943103	-1.8572196	0.4712908
H	9	-2.1564111	-0.9235570	-0.0438257
C	10	1.1763857	-1.4923984	0.5149606
H	11	-0.6211901	-2.8359415	0.7573260
H	12	1.5648406	-1.5746418	1.5219606

Compound **64b.**

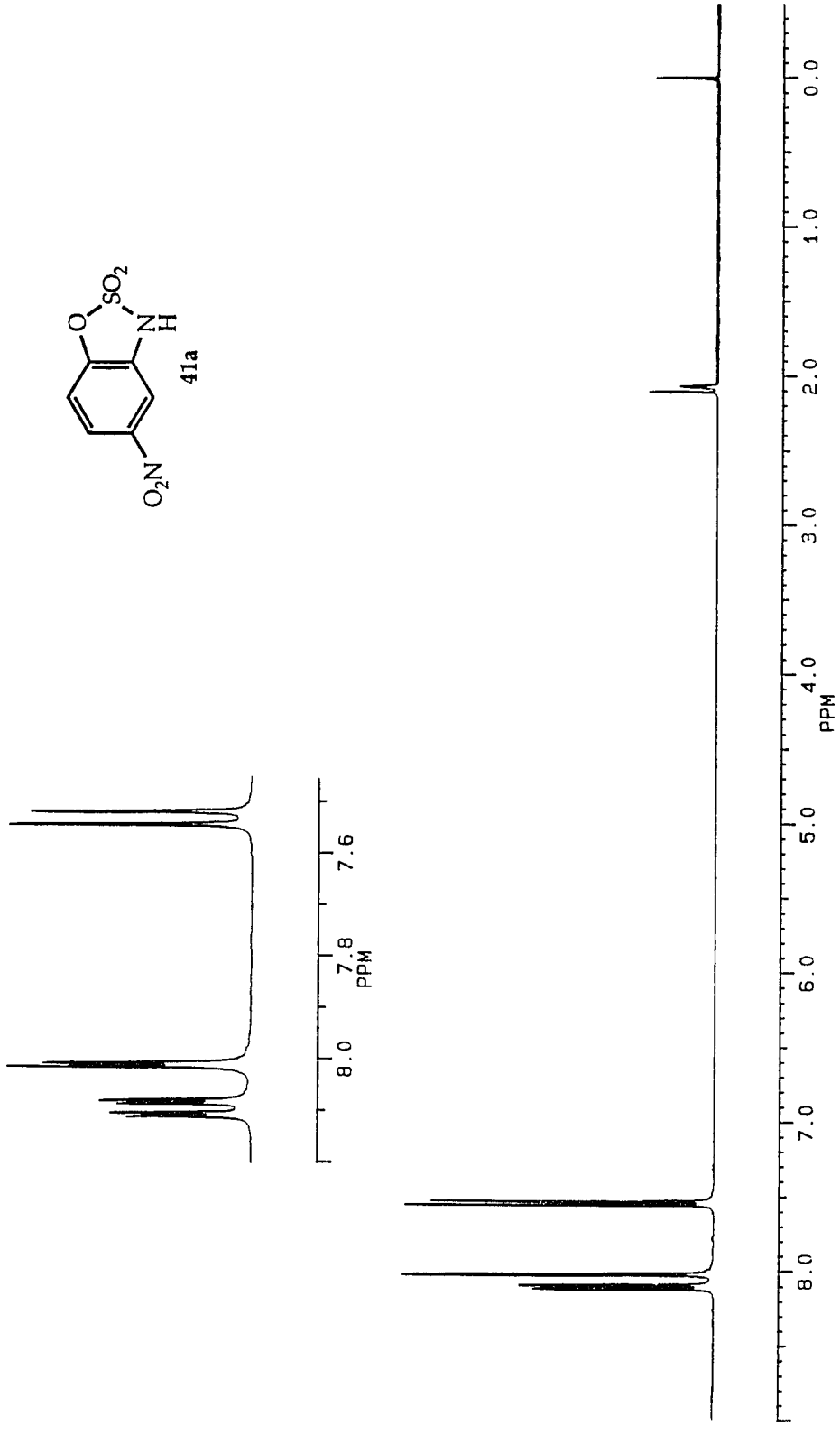
Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	0.0456375	0.5573373	-1.1779275
S	2	0.4414532	0.3416274	0.3155157
O	3	1.7925334	-0.2043821	0.5421842
O	4	0.1583965	1.4731672	1.2180750
C	5	-0.7315808	-0.9439130	0.6711953
C	6	-1.4486194	-1.2086988	-0.4008097
H	7	-0.7925451	-1.3944585	1.6399938
H	8	-1.9112923	0.2367017	-1.9357769
H	9	-2.2296850	-1.9429527	-0.4647063
H	10	-0.7359383	-0.9724782	-2.4246671
C	11	-1.0531071	-0.3397065	-1.5996520

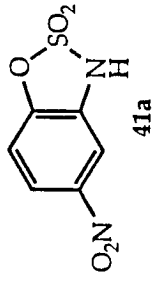
Compound **65a.** (RHF/3-21+G(*))

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	-0.0219284	0.2725304	-1.5510320
S	2	0.0512207	0.1113403	0.0970263
O	3	1.5710902	0.0982616	0.5598288
O	4	-0.9941159	1.0995510	0.7716039
O	5	-0.5433303	-1.4483281	0.2698257
H	6	0.7575699	-0.0326576	-2.1007673
H	7	-0.8711159	0.6034778	-1.9661579
H	8	-0.5975743	-1.7814097	1.1843662

Compound **65b.**

Atom		Cartesian Coordinates (Angstroms) X	Y	Z
N	1	-0.1990486	0.3313350	-1.6756524
S	2	0.0527485	0.1224291	-0.0311493
O	3	1.5770030	0.2414653	0.4626200
O	4	-1.0224698	0.9106567	0.8683381
O	5	-0.3738145	-1.4956753	0.3829085
H	6	0.6843122	0.0685253	-2.1178014
H	7	-1.0904227	-1.4860106	1.0395408





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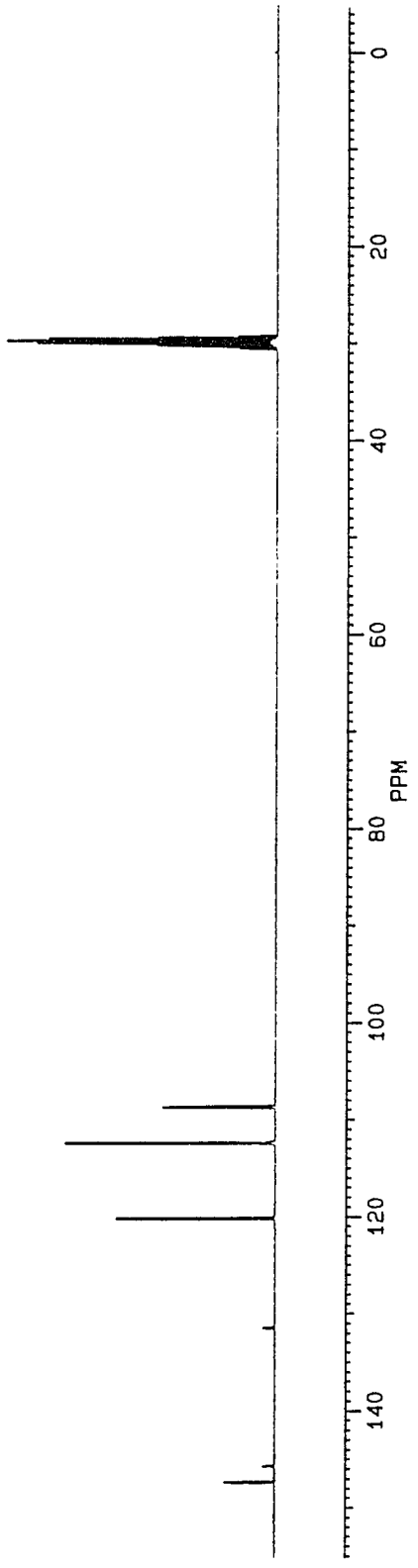
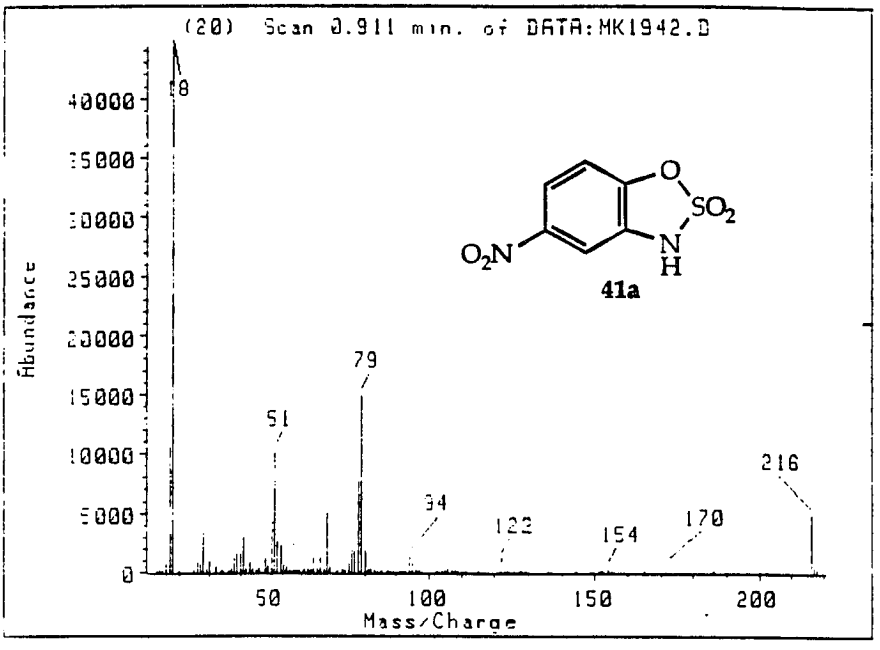
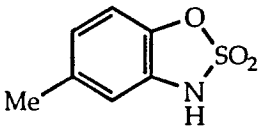




41a

AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
12.95	103.00	60.05	135.00	107.95	155.00
13.85	207.00	60.85	247.00	109.05	74.00
14.75	123.00	61.95	524.00	109.95	30.00
15.85	823.00	62.95	489.00	110.55	25.00
16.95	10570.00	63.85	1367.00	111.45	35.00
17.95	44360.00	64.85	484.00	115.05	107.00
20.05	99.00	65.95	1303.00	121.05	225.00
24.85	199.00	66.95	650.00	121.95	1165.00
25.95	735.00	67.95	4939.00	123.15	116.00
26.85	656.00	68.85	392.00	124.05	80.00
27.85	3300.00	71.05	74.00	125.25	37.00
28.85	283.00	72.95	184.00	125.45	34.00
29.85	838.00	73.95	103.00	126.05	39.00
31.95	481.00	74.95	769.00	127.45	25.00
33.65	89.00	76.05	1849.00	128.10	73.00
34.05	98.00	76.95	1817.00	129.20	66.00
36.05	76.00	77.95	7592.00	136.10	78.00
36.85	298.00	78.95	14959.00	136.90	31.00
37.95	1258.00	79.95	1761.00	144.30	69.00
38.85	1572.00	81.05	243.00	149.10	44.00
39.95	1793.00	81.95	200.00	149.30	41.00
40.95	3042.00	82.95	109.00	151.20	88.00
41.75	307.00	84.05	46.00	152.00	58.00
42.95	760.00	85.05	82.00	152.30	70.00
43.85	299.00	87.15	111.00	154.20	410.00
44.95	156.00	88.15	50.00	155.20	50.00
45.95	388.00	88.95	47.00	165.30	64.00
47.85	1116.00	90.15	50.00	170.20	147.00
48.75	606.00	91.05	111.00	171.30	46.00
49.95	4321.00	92.05	121.00	178.30	22.00
50.95	10055.00	92.95	163.00	186.00	68.00
51.95	2552.00	93.95	1350.00	186.20	67.00
52.95	2204.00	94.85	793.00	190.10	56.00
53.95	586.00	96.05	199.00	192.20	31.00
54.95	427.00	97.05	84.00	200.00	71.00
55.75	76.00	102.65	34.00	200.20	66.00
56.05	84.00	102.95	31.00	202.40	30.00
57.05	119.00	104.05	143.00	216.10	4811.00
57.85	123.00	104.95	318.00	217.10	412.00
58.45	61.00	105.95	719.00	218.10	198.00
58.95	69.00	107.05	196.00		



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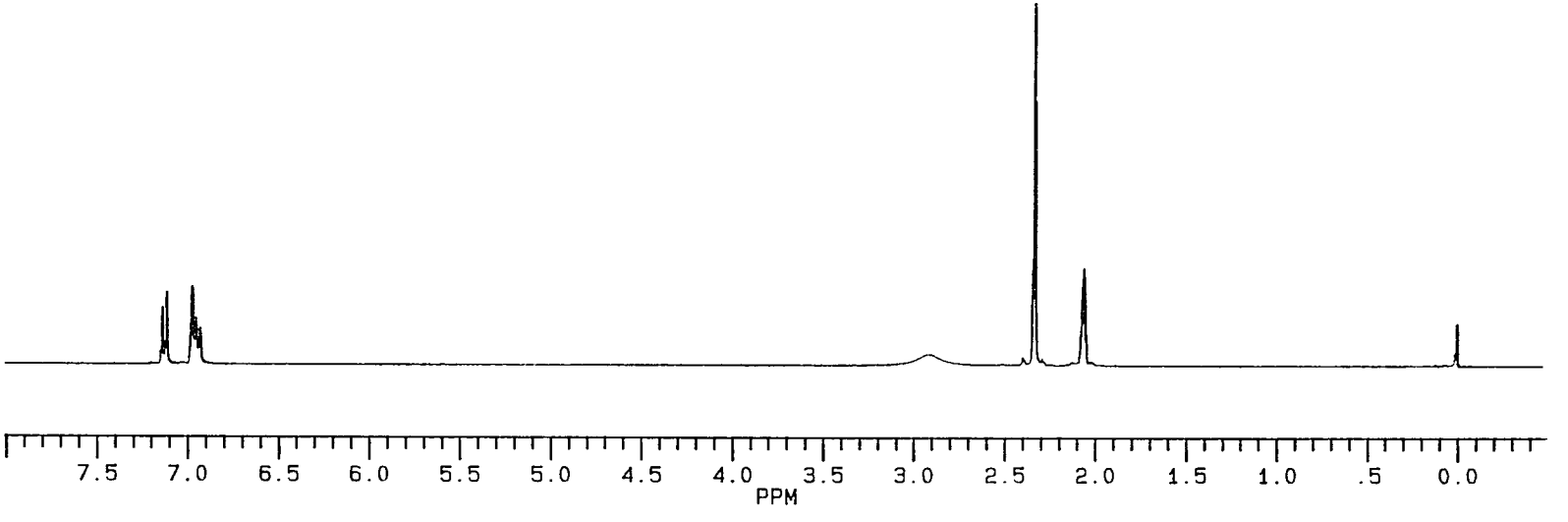

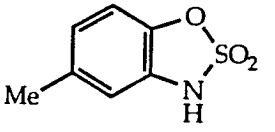

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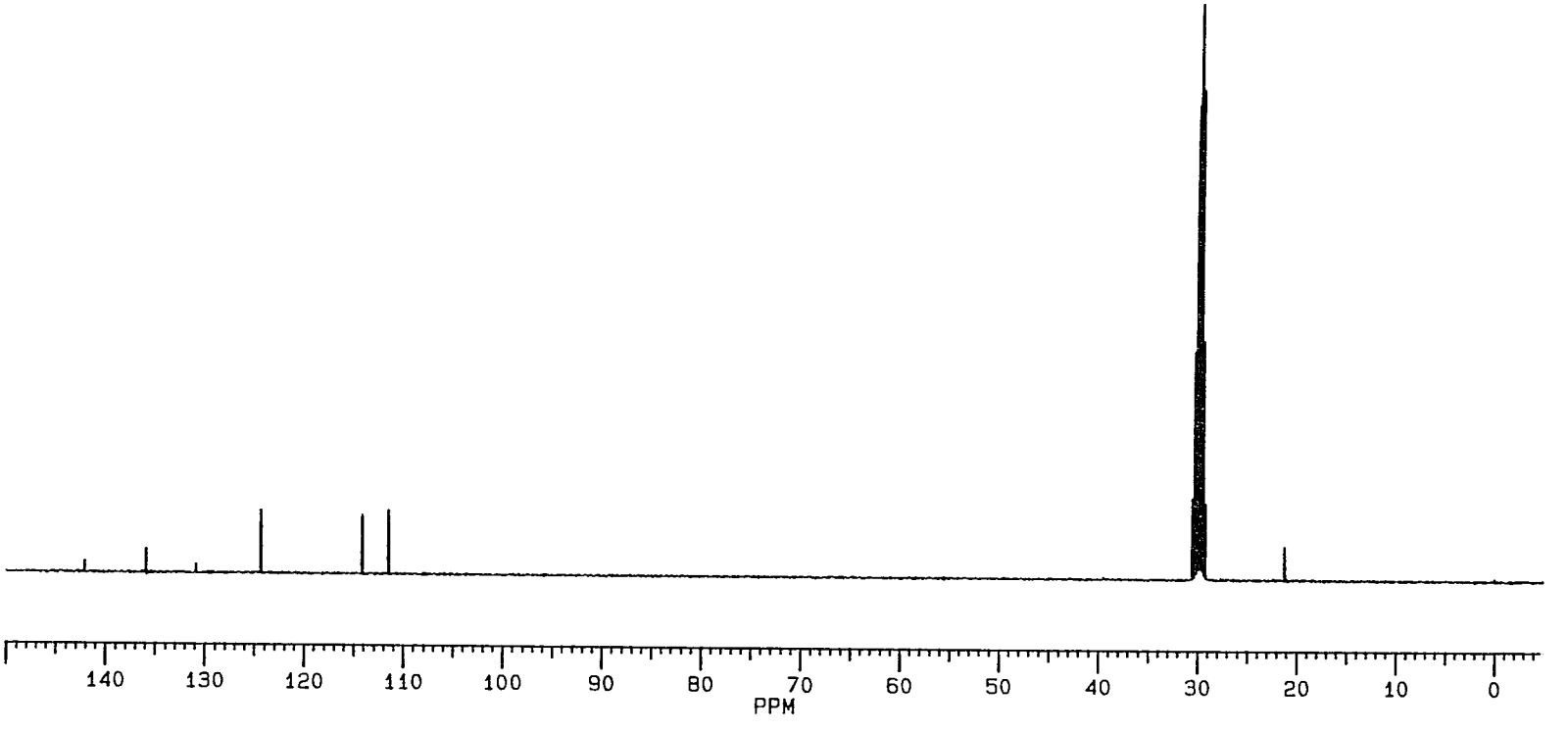
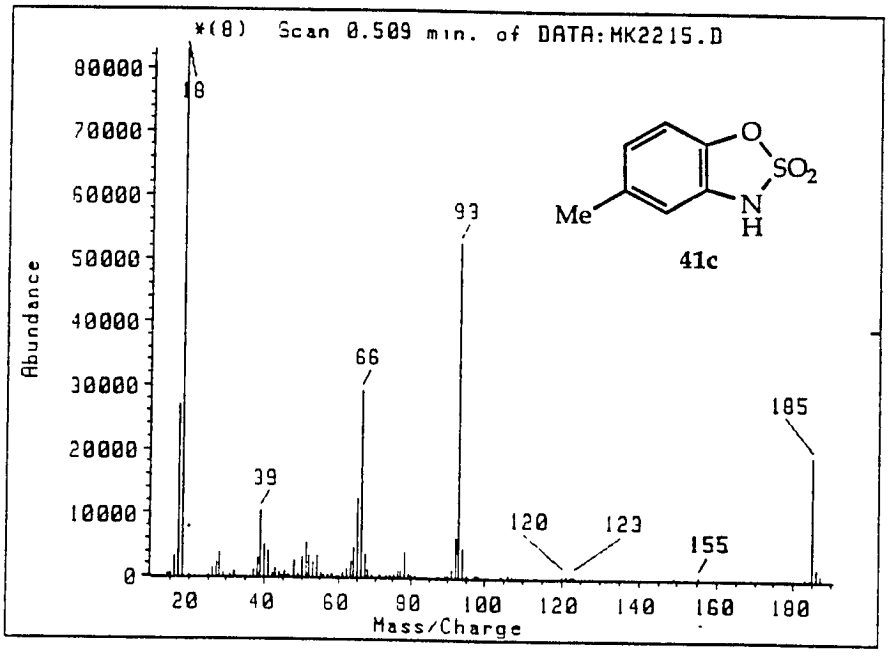
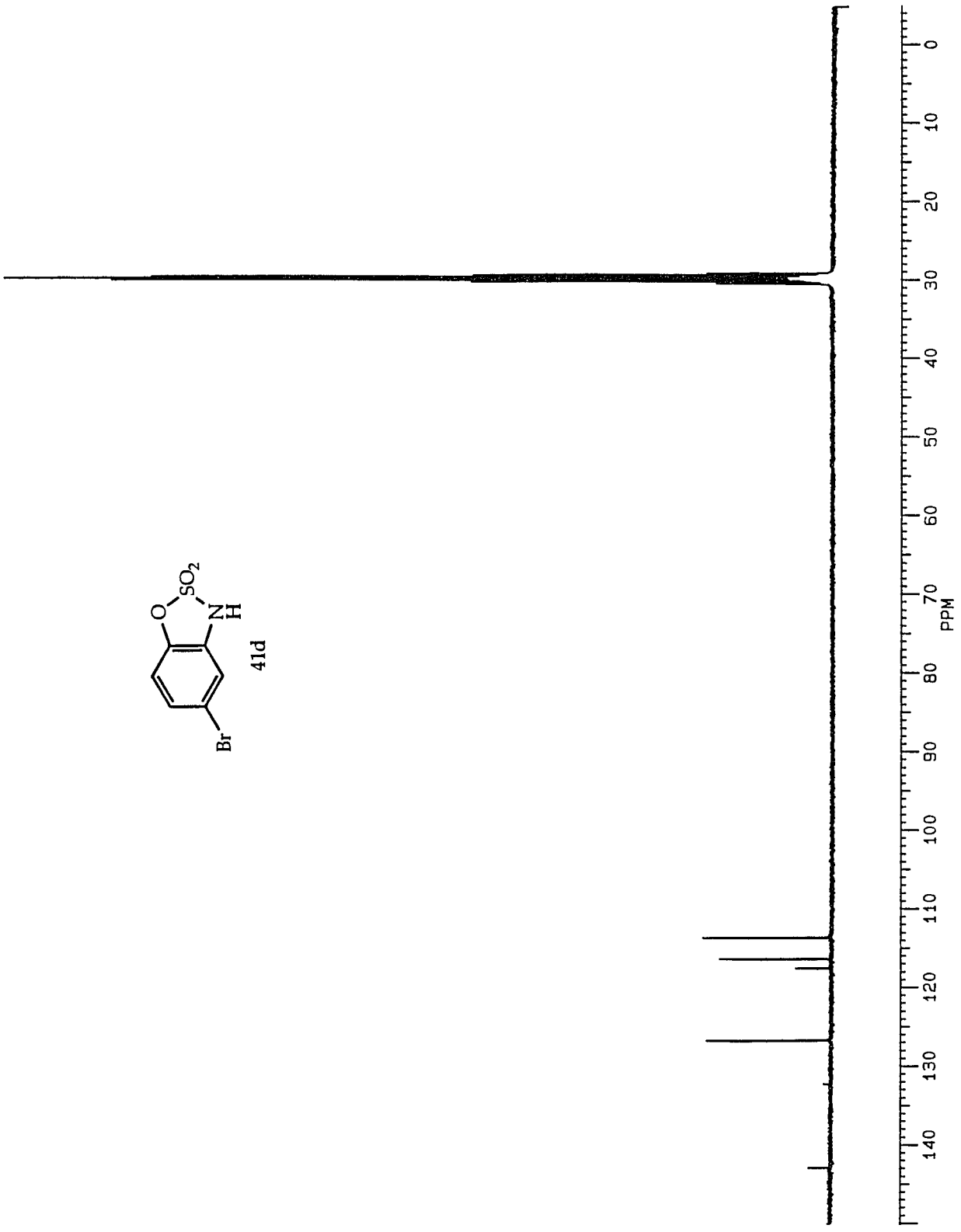
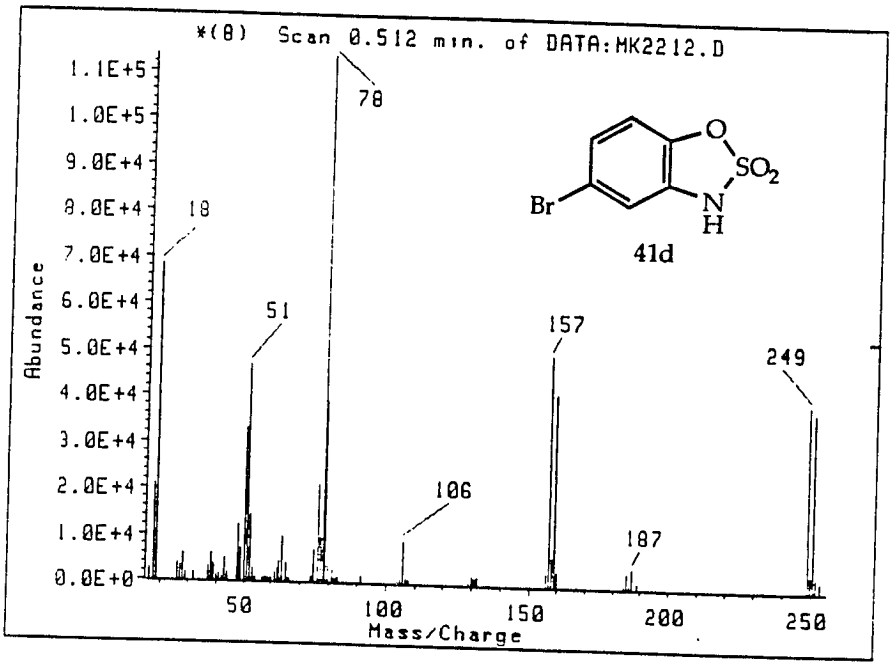


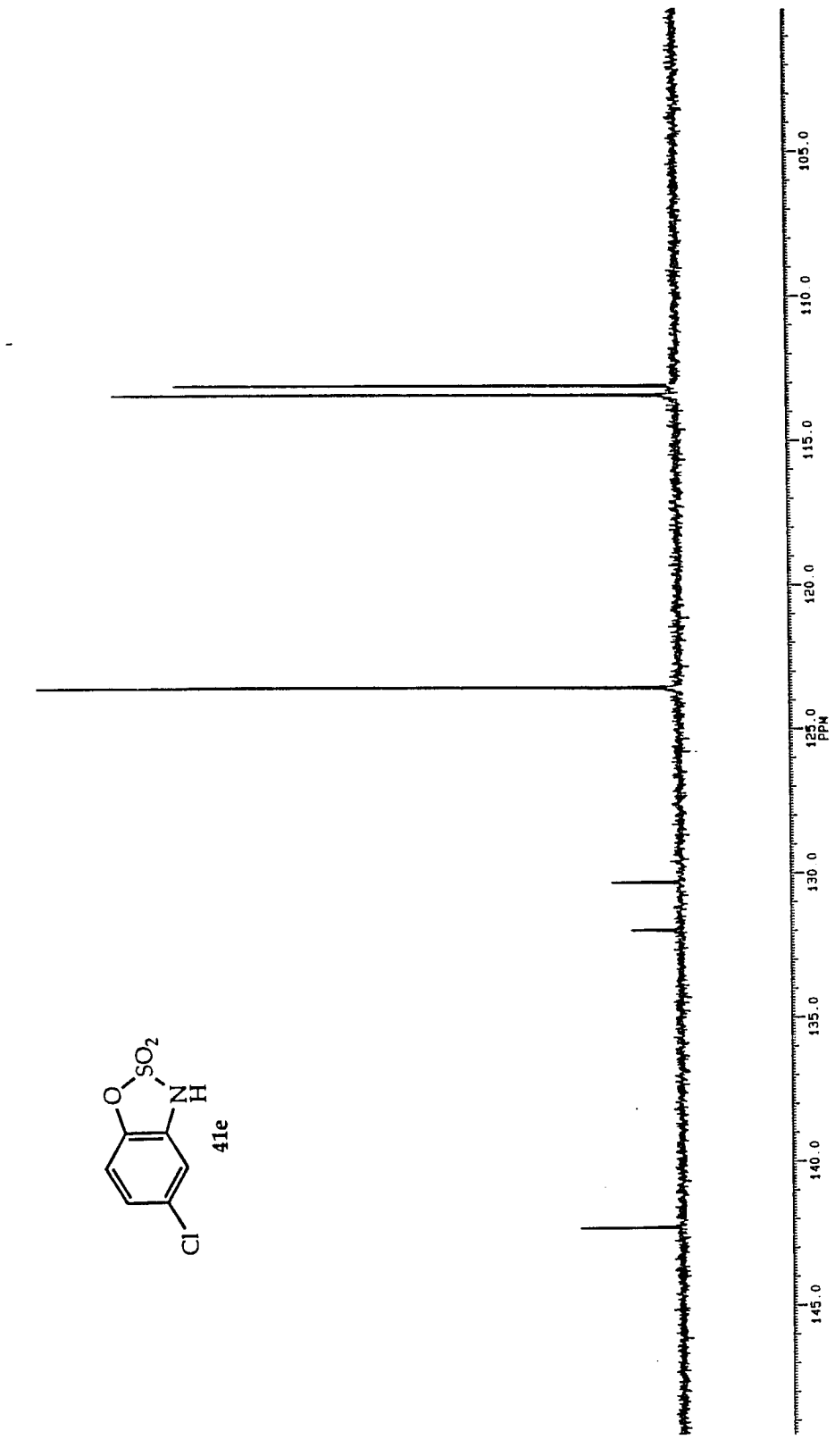


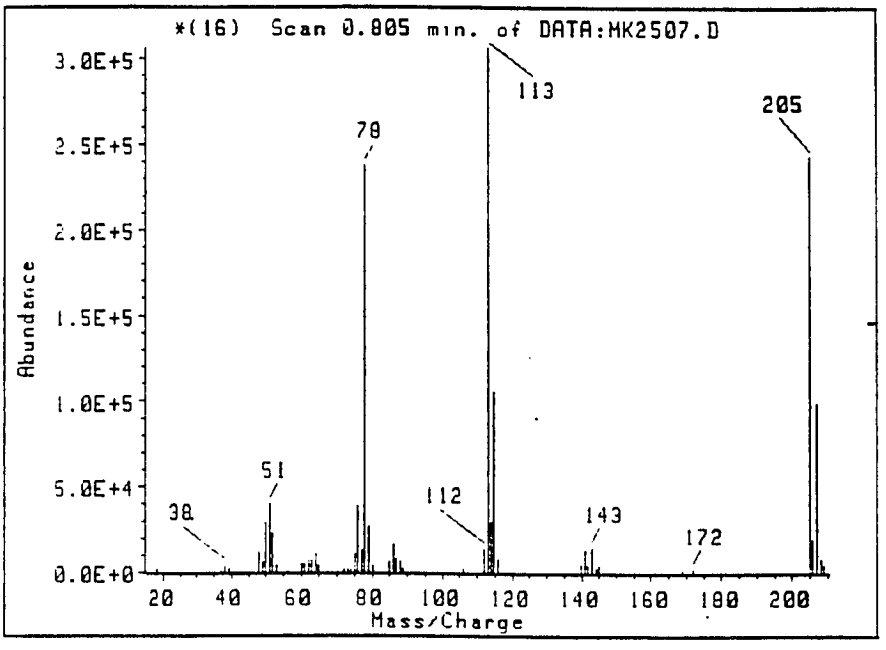
AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
14.15	417.00	52.10	3319.00	89.15	191.00
15.15	661.00	53.20	2206.00	90.15	161.00
16.15	3032.00	54.10	3247.00	91.05	1310.00
17.25	26880.00	55.10	528.00	92.05	6195.00
18.25	82776.00	56.10	118.00	93.05	52504.00
20.15	271.00	57.10	197.00	94.15	4451.00
25.05	134.00	58.10	341.00	95.15	221.00
26.15	1333.00	59.10	107.00	97.15	181.00
27.25	2237.00	60.10	107.00	98.15	114.00
28.10	3615.00	61.00	715.00	104.15	218.00
29.10	532.00	62.00	1225.00	106.05	505.00
31.10	179.00	63.10	2510.00	107.05	208.00
32.10	843.00	64.10	4546.00	108.15	108.00
37.10	998.00	65.10	12420.00	113.15	98.00
38.10	2840.00	66.10	29224.00	120.15	526.00
39.10	10232.00	67.10	3403.00	121.15	467.00
40.10	4846.00	68.10	1015.00	122.15	304.00
41.10	3918.00	69.20	137.00	123.15	304.00
42.10	459.00	71.10	163.00	149.10	177.00
43.10	1164.00	73.10	164.00	152.20	100.00
44.10	554.00	74.10	201.00	155.10	414.00
44.90	264.00	75.10	512.00	169.20	93.00
45.60	830.00	76.10	1012.00	183.05	153.00
46.20	264.00	77.10	1089.00	184.25	155.00
46.60	245.00	78.10	3851.00	185.05	19216.00
48.10	2566.00	79.05	700.00	186.15	1555.00
49.10	436.00	80.05	172.00	187.15	750.00
50.10	3170.00	81.15	159.00		
51.10	5306.00	87.15	97.00		



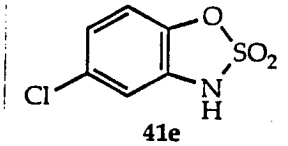


AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
16.15	2587.00	53.90	953.00	104.85	986.00
17.15	20736.00	57.10	712.00	105.95	9123.00
18.15	68136.00	58.00	875.00	106.95	1135.00
26.15	3586.00	59.00	569.00	107.95	808.00
27.15	3195.00	60.00	653.00	128.95	1003.00
28.10	5513.00	61.10	1915.00	129.95	1998.00
29.10	1562.00	62.10	2793.00	130.90	1362.00
32.00	1775.00	63.00	4160.00	131.80	1797.00
37.00	3056.00	63.90	9609.00	155.90	2879.00
38.00	5927.00	65.00	3819.00	156.90	49968.00
38.60	3811.00	66.00	646.00	157.90	6219.00
39.10	3530.00	74.00	1075.00	158.90	41432.00
40.10	1123.00	75.00	7039.00	159.90	3028.00
41.10	1510.00	76.10	21176.00	183.95	686.00
42.10	716.00	77.10	9652.00	184.95	3236.00
43.00	4825.00	78.10	113600.00	185.95	909.00
44.00	1564.00	78.95	38856.00	186.95	4179.00
48.00	12251.00	79.85	3300.00	188.85	1214.00
49.00	7068.00	80.95	2644.00	248.90	40104.00
50.10	32952.00	81.95	785.00	249.90	3403.00
51.10	46728.00	82.95	1198.00	250.90	38472.00
52.10	14267.00	91.05	1290.00	251.90	2773.00
53.00	2761.00	103.95	1433.00	252.90	1844.00





AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
18.15	2401.00	72.95	2641.00	114.85	105640.00
37.05	2976.00	73.95	1827.00	115.95	7636.00
38.05	3338.00	74.95	10826.00	139.90	4266.00
39.15	2060.00	75.95	38744.00	140.90	12631.00
47.95	11122.00	77.05	12812.00	141.90	3828.00
49.05	6376.00	77.95	237824.00	143.00	14685.00
50.05	28616.00	78.95	26760.00	144.00	1965.00
51.05	40096.00	79.95	3475.00	145.00	3556.00
51.95	22632.00	84.95	5834.00	169.00	1652.00
52.95	3491.00	85.95	16217.00	171.80	2059.00
59.95	4773.00	86.95	7315.00	204.90	242880.00
60.95	4334.00	87.95	6238.00	205.90	19152.00
61.95	7186.00	88.95	2429.00	206.90	99192.00
62.95	6995.00	105.95	1936.00	207.90	7303.00
63.95	10953.00	111.95	13839.00	208.90	4040.00
64.95	4007.00	112.95	306304.00		
71.95	1886.00	113.95	29592.00		



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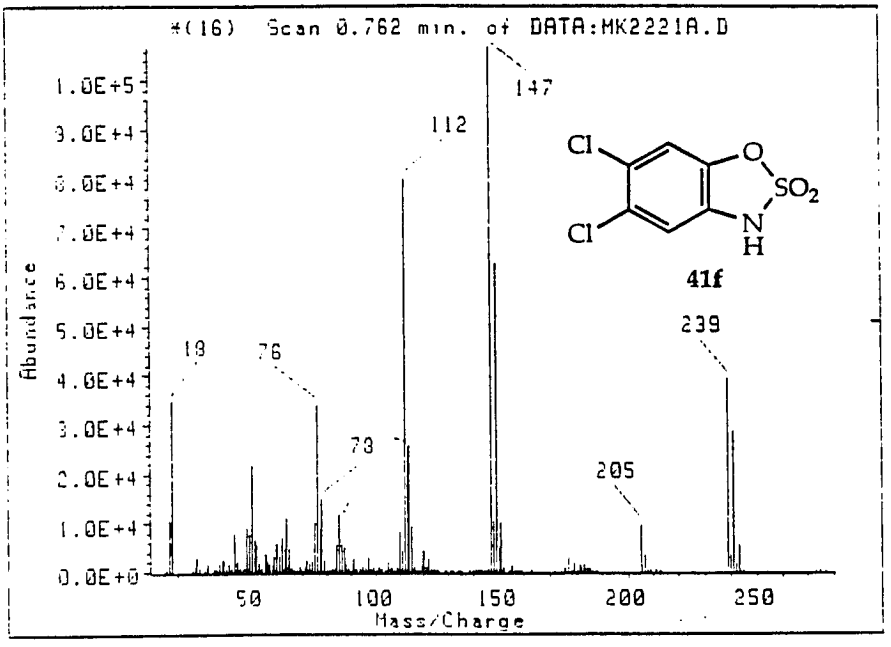
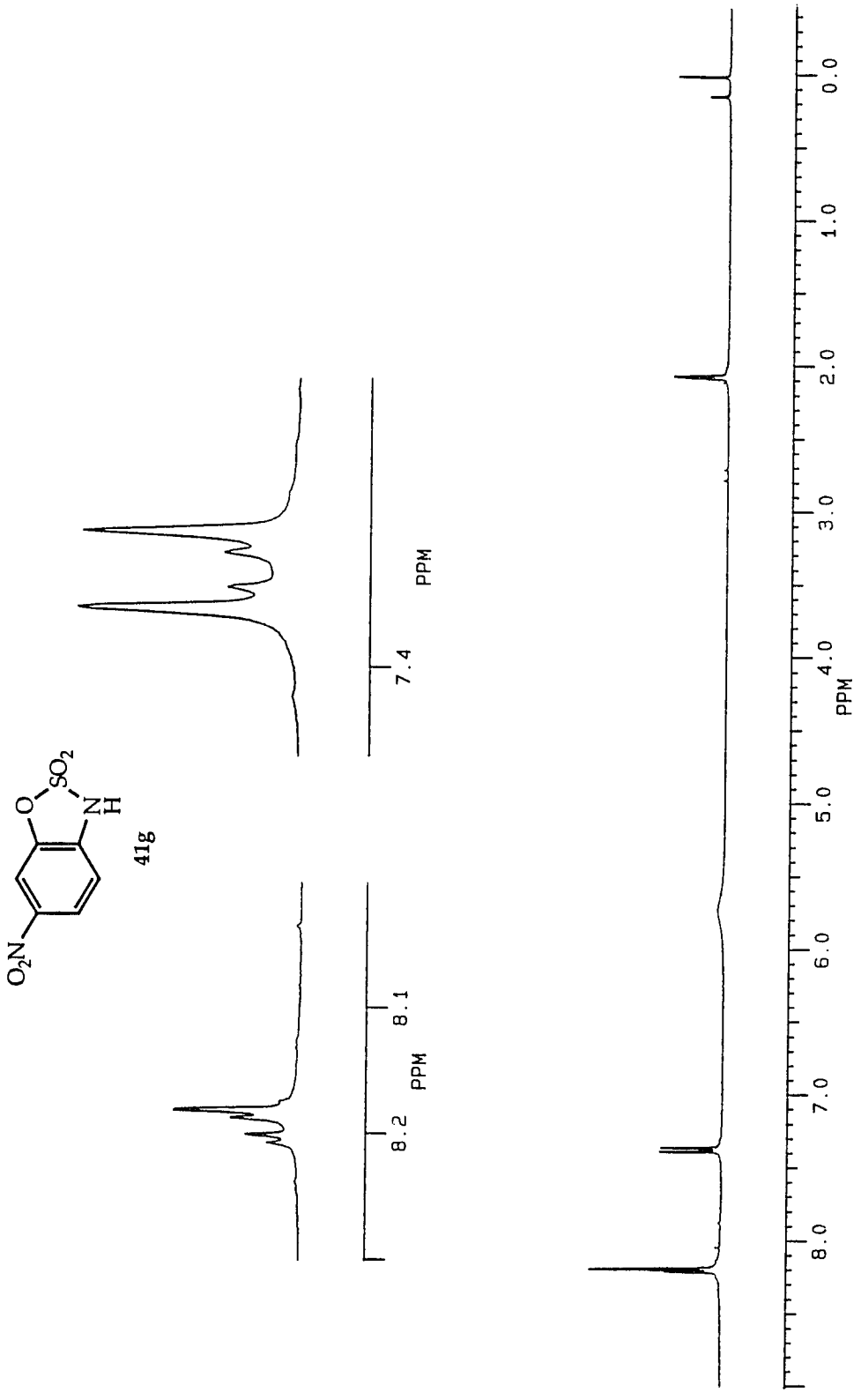
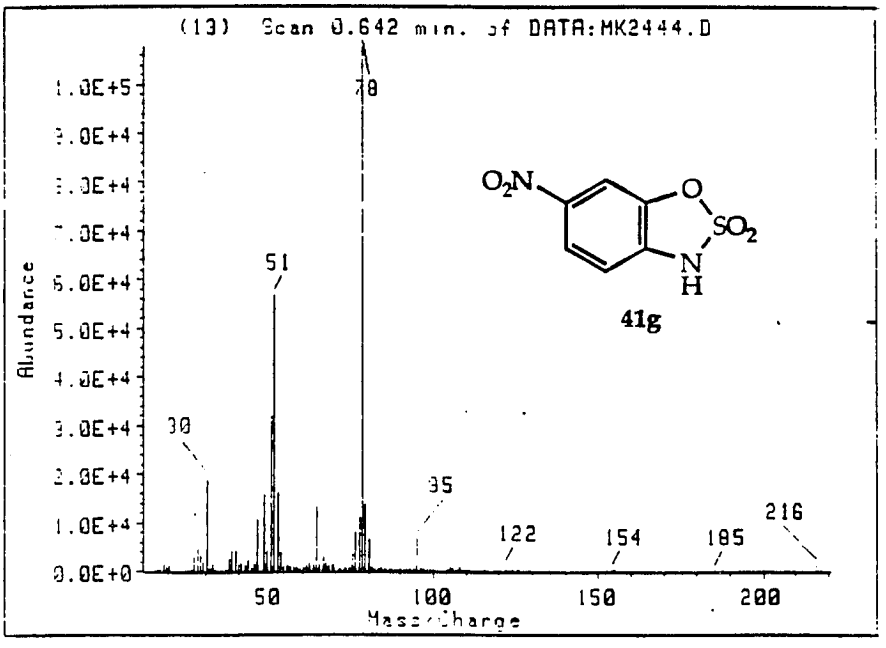


41f

AMU.	Abundance
15.20	242.00
16.10	1384.00
17.10	10684.00
18.10	34680.00
26.15	430.00
27.15	1037.00
28.05	2848.00
29.05	716.00
31.15	327.00
32.05	1468.00
35.05	524.00
36.15	657.00
37.05	1962.00
38.05	2501.00
38.35	2239.00
38.55	2275.00
40.05	584.00
41.15	1627.00
42.05	883.00
43.05	7958.00
44.05	2094.00
45.05	808.00
46.15	284.00
46.95	777.00
47.95	8907.00
48.95	7645.00
50.05	21760.00
51.05	6751.00
52.05	5703.00
53.05	1780.00
53.95	779.00
55.55	3722.00
56.15	2112.00
56.45	1522.00
56.75	1492.00
57.05	1726.00
58.05	1351.00
59.10	3093.00
60.00	5787.00
61.00	3554.00
62.00	6849.00
63.00	4804.00
64.00	11220.00
65.00	4798.00
66.10	729.00
67.10	381.00
68.10	260.00
69.10	946.00
70.00	396.00
71.10	1038.00
72.00	2326.00
73.00	1933.00
73.90	2487.00
75.00	10078.00
76.00	33952.00
77.10	8758.00
78.00	14821.00
79.00	2450.00
79.90	351.00
81.10	301.00
82.00	524.00
83.10	821.00
83.90	5625.00
84.90	11782.00
86.00	5515.00
87.00	4964.00
87.90	1673.00
88.90	920.00
90.00	400.00
91.00	2698.00
92.10	428.00
93.90	509.00
94.90	959.00
95.90	719.00
97.05	2799.00
98.15	881.00
99.05	988.00
99.95	342.00
101.05	1440.00
102.15	471.00
103.95	347.00
105.05	2082.00
105.95	757.00
106.85	717.00
107.95	344.00
108.95	1026.00
109.95	8362.00
110.95	4572.00
111.95	80120.00
112.95	25480.00
113.95	25632.00
114.95	9298.00
115.85	1087.00
116.95	251.00
117.95	220.00
118.95	1217.00
119.85	4248.00
120.85	1117.00
121.85	2598.00
122.95	520.00
124.05	607.00
124.95	238.00
125.75	231.00
128.95	220.00
130.95	247.00
131.95	307.00
133.95	271.00
135.00	229.00
138.00	275.00
140.00	920.00
140.90	804.00
142.00	675.00
143.00	593.00
144.00	255.00
144.90	223.00
145.90	4092.00
146.90	107000.00
147.90	10599.00
149.00	62976.00
149.90	5118.00
150.90	10010.00
151.90	1113.00
154.00	326.00
155.00	1417.00
155.90	360.00
156.90	336.00
157.90	234.00
159.00	252.00
162.90	502.00
171.10	238.00
173.95	811.00
174.95	960.00
175.95	790.00
176.95	3018.00
177.85	650.00
178.85	1785.00
180.05	313.00
180.95	1595.00
181.95	1003.00
182.85	1549.00
183.95	813.00
184.95	685.00
185.85	289.00
187.85	289.00
203.95	397.00
204.85	9804.00
205.85	1392.00
206.85	3383.00
207.85	603.00
208.85	422.00
211.10	410.00
212.90	312.00
238.80	39528.00
239.80	3471.00
240.80	28616.00
241.90	1951.00
242.90	5300.00
243.80	399.00
244.80	253.00
272.75	648.00
274.85	648.00
276.85	254.00

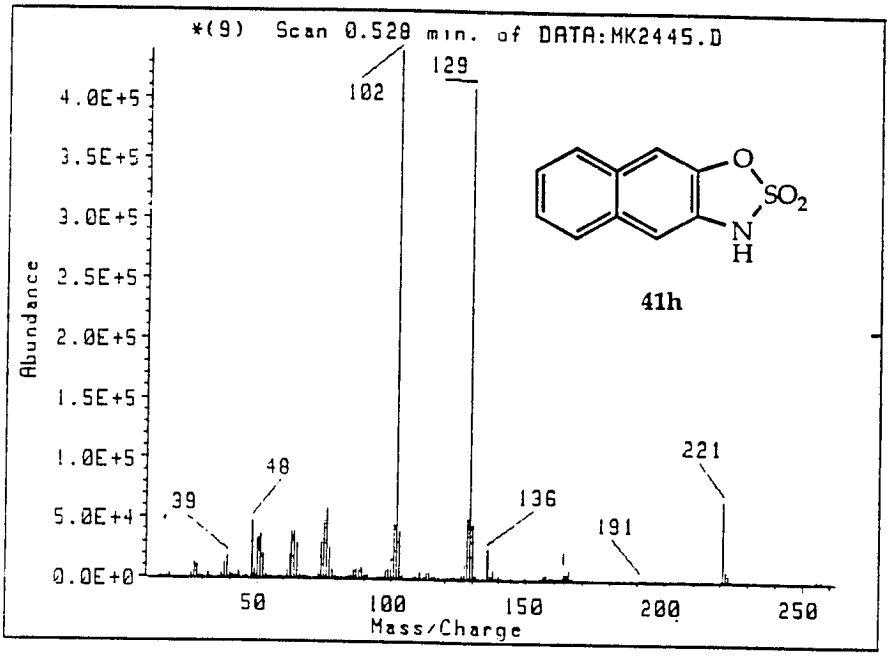




41g

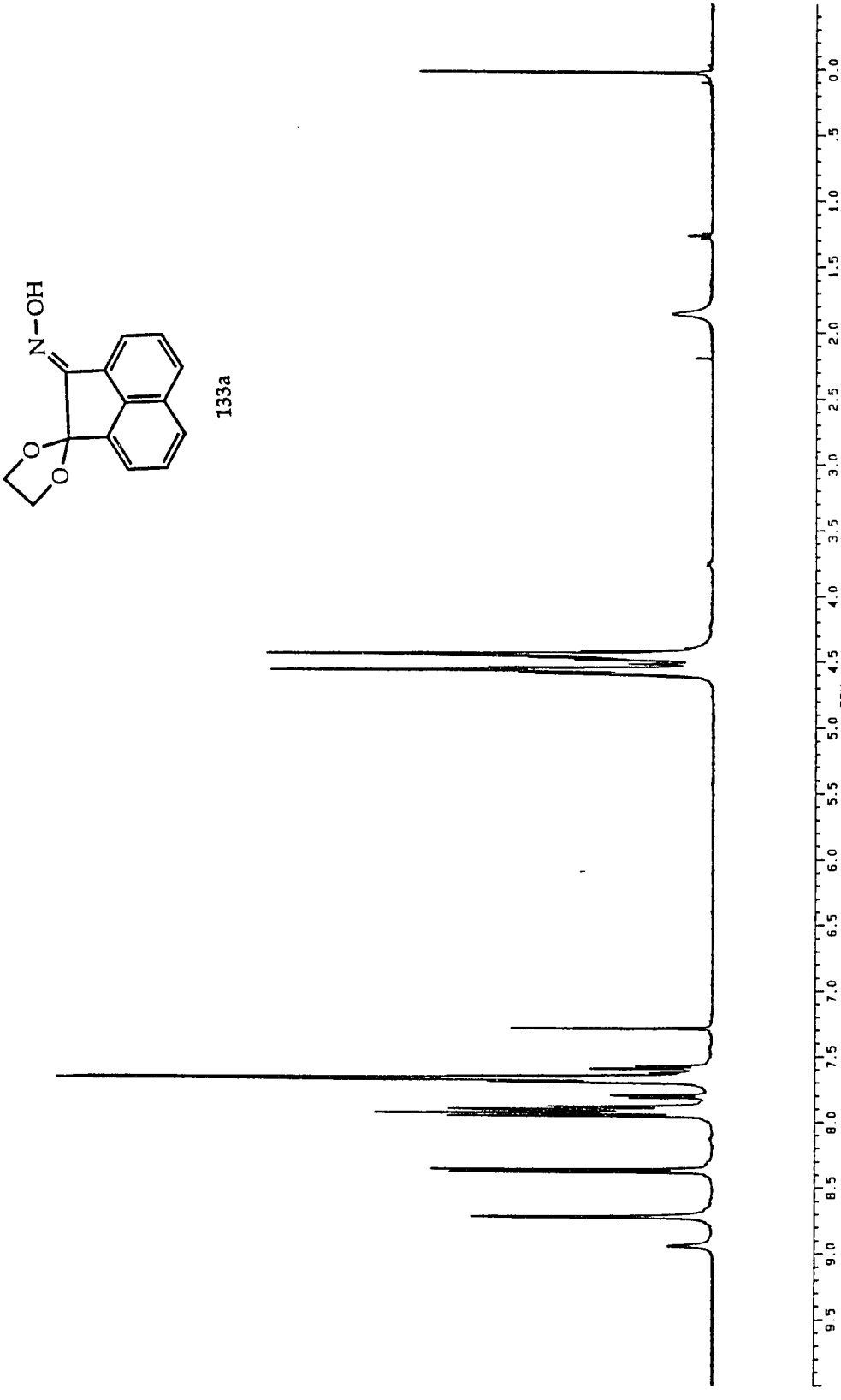
AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
13.15	129.00	60.05	622.00	99.05	107.00
14.15	201.00	61.05	1601.00	99.85	45.00
14.75	107.00	62.05	2134.00	104.05	1525.00
15.15	282.00	63.05	2456.00	105.05	761.00
16.10	1269.00	63.95	13009.00	106.05	453.00
17.10	720.00	64.95	2507.00	106.65	71.00
18.10	1015.00	66.05	2908.00	107.35	148.00
25.10	222.00	67.05	1511.00	108.05	712.00
26.10	3186.00	67.95	1188.00	109.05	70.00
27.10	4584.00	68.95	1251.00	109.25	54.00
28.10	3249.00	71.10	370.00	109.95	127.00
29.10	1858.00	72.00	81.00	110.95	81.00
30.10	18816.00	72.30	59.00	115.75	50.00
31.10	530.00	73.10	452.00	119.05	70.00
32.00	1291.00	74.00	542.00	120.35	72.00
32.90	135.00	75.00	3352.00	121.95	929.00
34.90	129.00	76.00	8035.00	122.95	139.00
36.10	226.00	77.10	10983.00	124.15	166.00
37.00	2386.00	78.00	107616.00	125.85	171.00
38.00	4144.00	79.00	13551.00	129.10	110.00
39.00	4071.00	80.00	6324.00	135.00	98.00
40.00	1462.00	81.10	916.00	149.10	51.00
41.00	1674.00	82.00	250.00	151.50	57.00
42.00	1038.00	83.10	217.00	151.80	49.00
43.00	2155.00	84.00	415.00	152.10	73.00
44.05	593.00	85.10	374.00	152.80	61.00
45.05	1467.00	86.30	106.00	154.05	152.00
46.05	10574.00	87.00	406.00	154.65	146.00
47.95	15642.00	88.20	102.00	154.85	143.00
49.05	3922.00	88.90	147.00	171.65	32.00
50.05	31760.00	89.10	145.00	181.05	24.00
51.05	56568.00	89.80	151.00	185.20	57.00
52.05	16029.00	91.00	332.00	188.10	29.00
52.95	3678.00	92.00	381.00	200.00	171.00
53.95	794.00	93.00	230.00	202.90	43.00
55.05	1020.00	94.00	1059.00	216.05	1400.00
56.05	804.00	95.00	6700.00	217.15	102.00
57.15	486.00	96.00	507.00	217.95	72.00
58.05	636.00	97.00	154.00		
59.05	303.00	98.20	61.00		

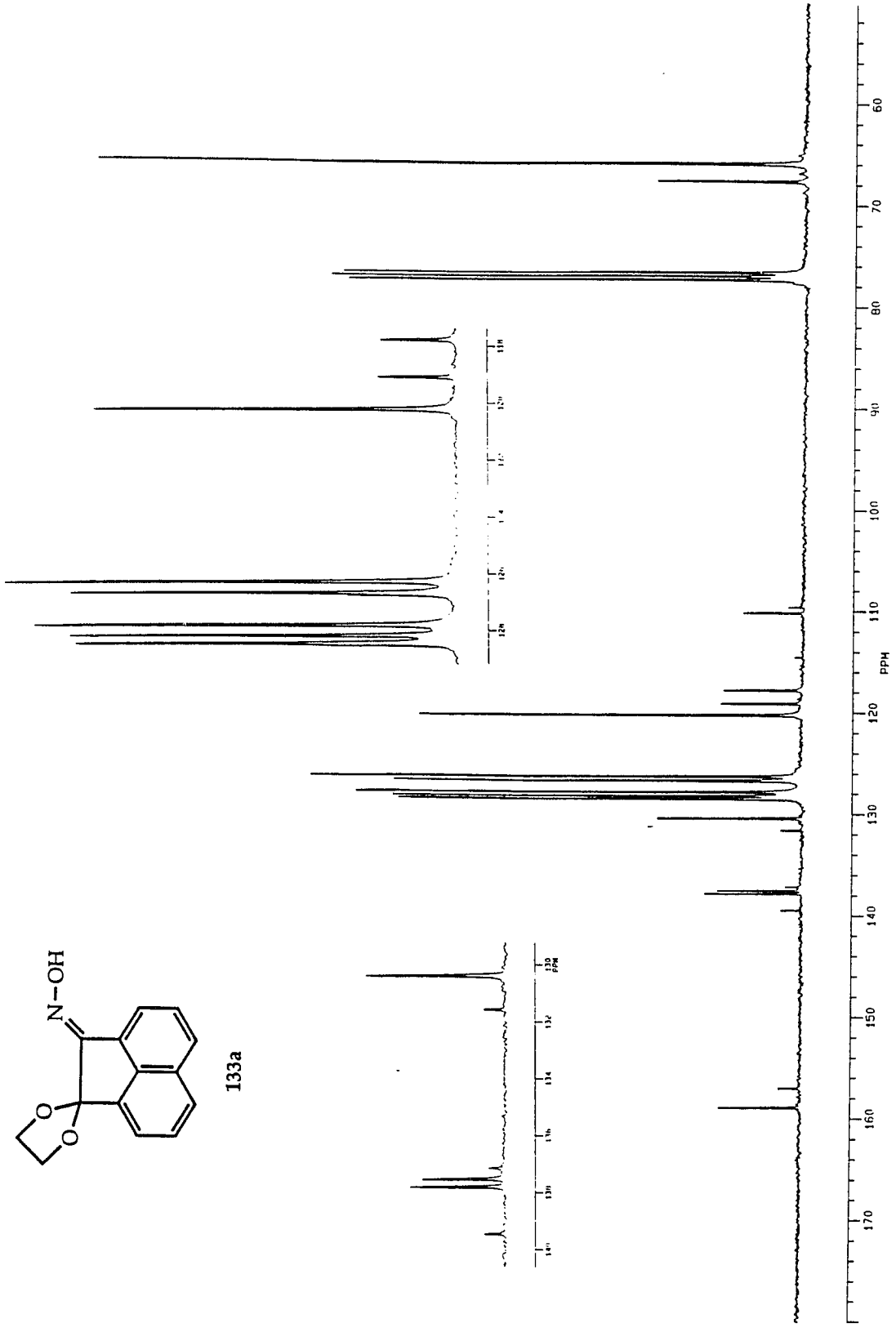
41h

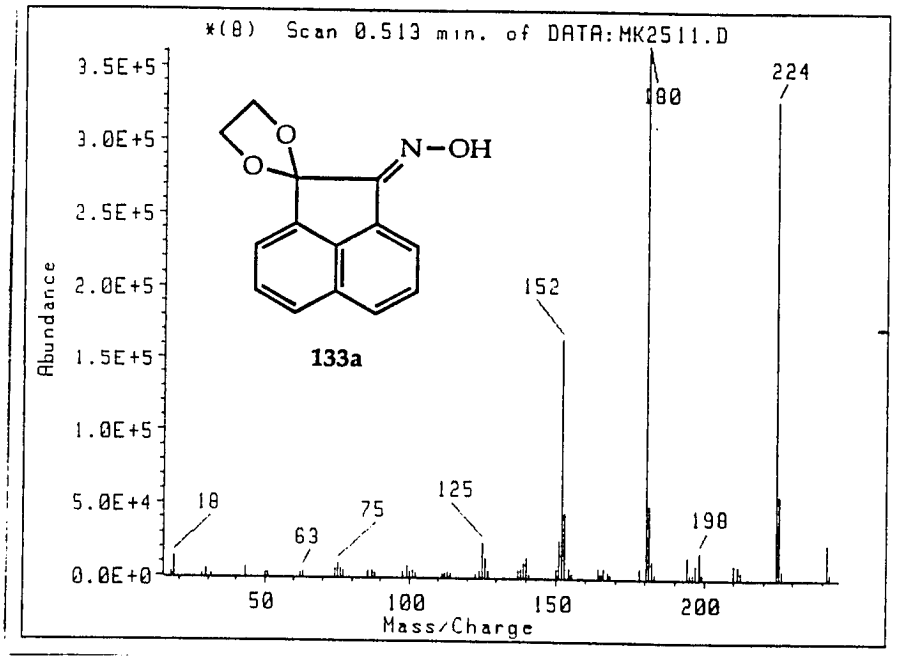


41h

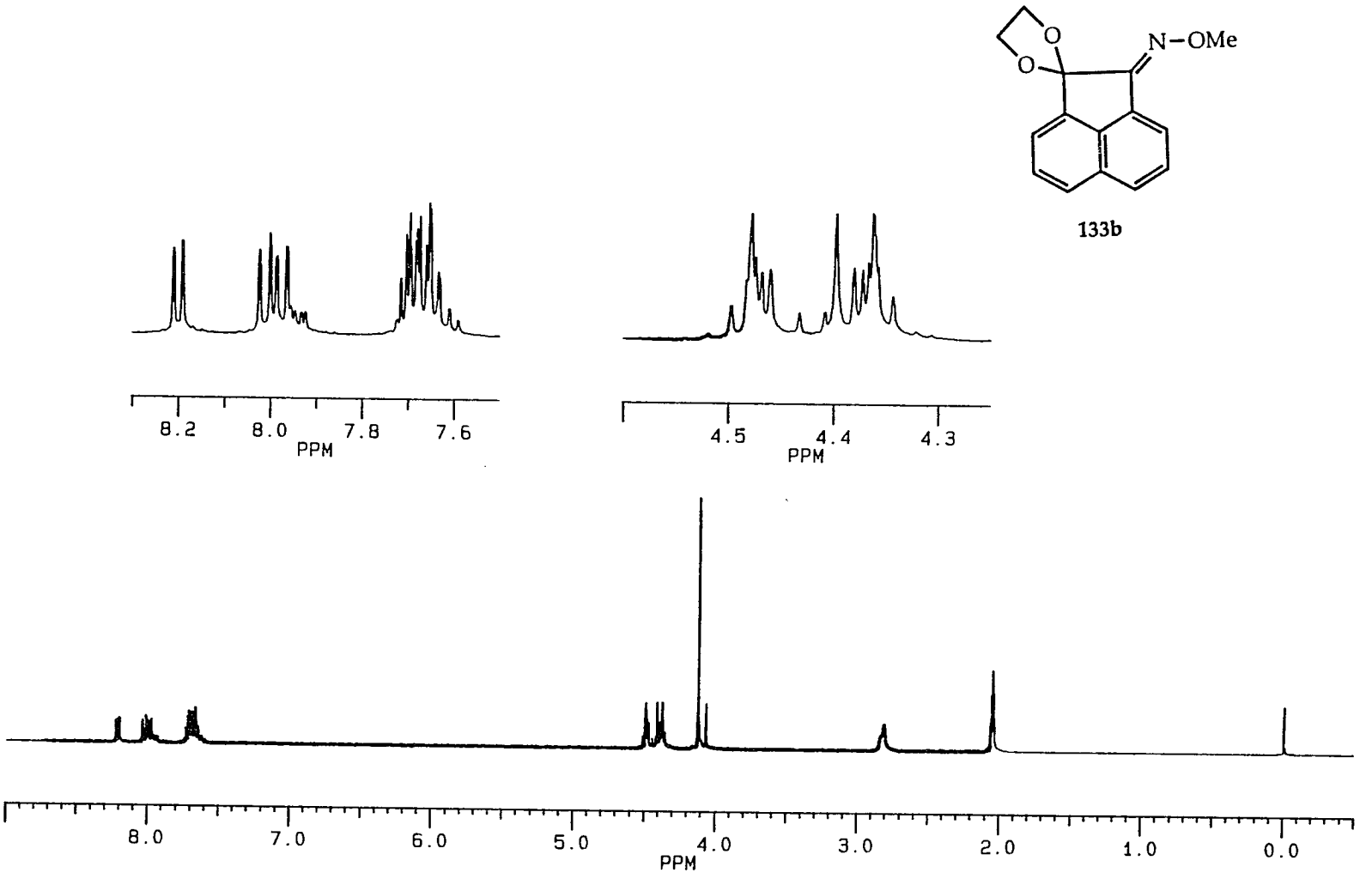
AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
14.15	251.00	73.00	3637.00	125.95	2874.00
15.15	579.00	74.00	29552.00	127.10	12253.00
16.20	465.00	75.00	48544.00	128.10	50504.00
17.10	1092.00	76.10	57936.00	129.10	409472.00
18.20	3315.00	77.00	24792.00	130.00	44848.00
26.10	3293.00	78.00	8170.00	131.00	2231.00
27.10	12256.00	79.00	981.00	132.00	297.00
28.10	9661.00	79.90	260.00	134.10	337.00
29.10	1244.00	81.40	434.00	136.00	24112.00
30.20	300.00	81.60	409.00	137.00	1827.00
32.00	3024.00	83.00	228.00	138.00	6757.00
33.00	495.00	84.00	890.00	139.00	973.00
36.10	230.00	85.00	2488.00	140.00	1832.00
37.00	2965.00	86.00	6229.00	141.00	571.00
38.00	12114.00	87.00	9264.00	144.10	389.00
39.10	17200.00	88.00	6203.00	149.10	317.00
40.10	3669.00	89.00	8340.00	150.00	248.00
41.00	1868.00	90.00	2220.00	155.05	2796.00
42.00	1000.00	91.00	2191.00	156.05	2943.00
43.00	3861.00	95.00	294.00	157.05	4437.00
45.05	596.00	96.00	344.00	158.05	575.00
46.05	628.00	97.00	1664.00	159.15	875.00
47.95	47024.00	98.00	6094.00	160.05	266.00
49.05	6521.00	99.05	8713.00	161.05	346.00
50.05	53072.00	100.05	16142.00	162.05	1320.00
51.05	36568.00	101.05	45272.00	163.05	23080.00
52.05	19304.00	102.05	439616.00	164.05	4864.00
53.05	2613.00	103.05	39328.00	165.05	7634.00
54.05	440.00	104.05	2341.00	165.95	1257.00
55.05	254.00	107.95	238.00	188.00	313.00
57.05	290.00	108.95	892.00	191.10	773.00
58.05	896.00	110.45	3854.00	192.00	265.00
59.15	350.00	111.95	853.00	192.90	579.00
60.15	467.00	113.05	4493.00	197.00	359.00
61.05	6450.00	114.05	4483.00	205.00	547.00
62.05	18736.00	114.95	1212.00	207.00	238.00
62.95	28344.00	115.95	759.00	220.15	1509.00
63.95	27792.00	117.85	382.00	221.05	66072.00
64.95	28312.00	119.85	244.00	222.05	7299.00
65.95	2597.00	120.95	439.00	223.05	3919.00
66.95	1266.00	122.05	415.00	223.95	508.00
67.95	1044.00	122.95	808.00	255.00	2585.00
68.85	521.00	124.05	488.00	256.10	339.00
72.00	561.00	124.95	232.00	257.00	853.00



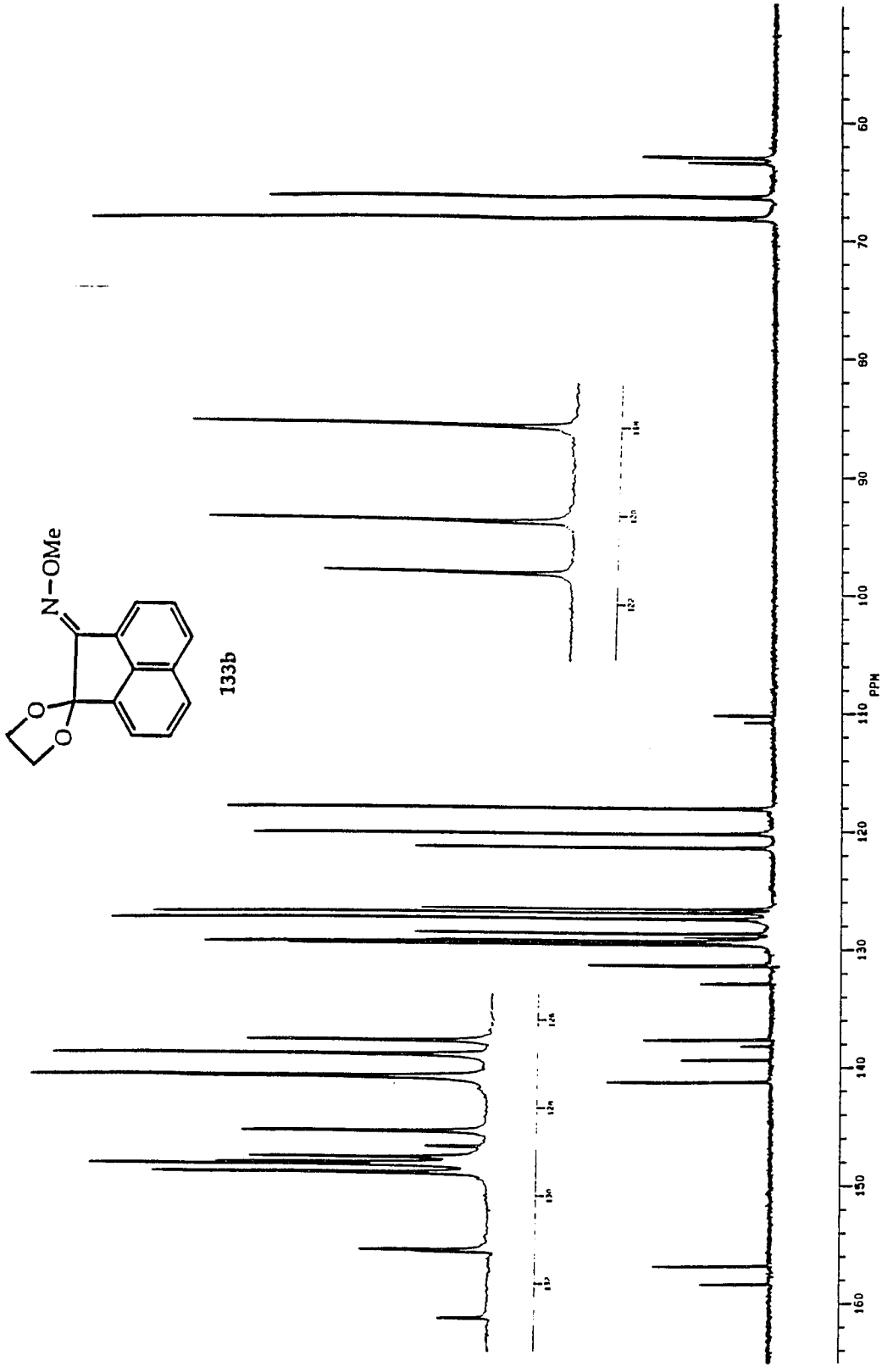


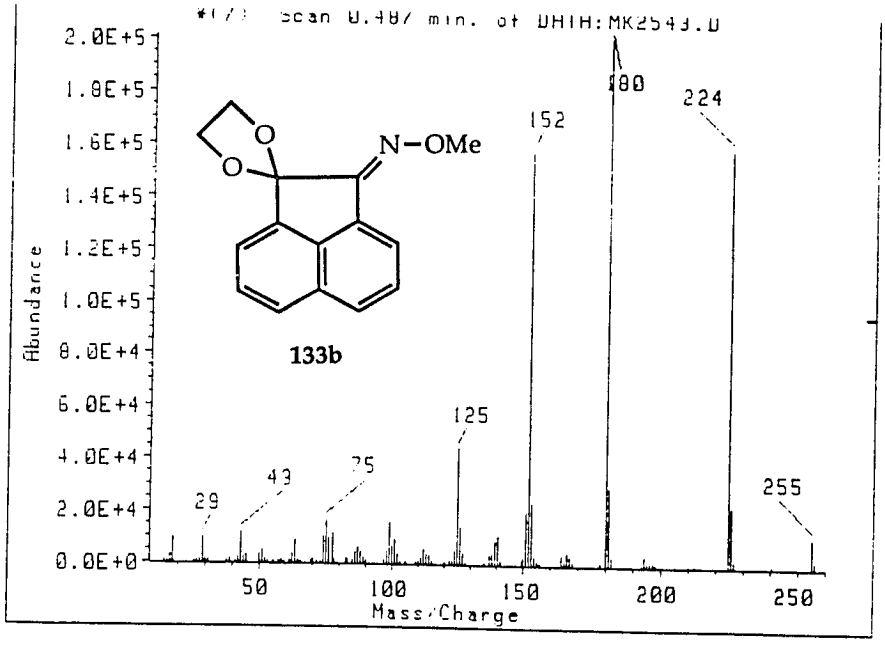


AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
17.20	2780.00	111.05	2027.00	166.10	6707.00
18.10	13623.00	111.95	2744.00	167.10	3996.00
28.10	2005.00	112.95	3750.00	168.00	1812.00
29.10	5349.00	114.05	2284.00	178.10	6481.00
31.10	1836.00	122.95	1851.00	180.10	361024.00
43.10	6558.00	124.05	4073.00	181.10	49288.00
50.05	2435.00	125.05	23608.00	182.10	11954.00
51.05	2554.00	126.05	12702.00	183.10	2326.00
62.05	2397.00	127.05	4758.00	194.10	14159.00
63.05	4003.00	137.10	4332.00	195.00	2988.00
74.05	5472.00	138.00	5578.00	196.10	2524.00
75.05	8613.00	139.10	9664.00	197.10	8802.00
76.05	4953.00	140.10	13372.00	198.10	17896.00
77.05	4627.00	141.10	2116.00	199.10	2751.00
85.95	3297.00	150.10	5500.00	210.10	8649.00
87.05	4563.00	151.10	24816.00	211.10	8443.00
88.05	2352.00	152.10	163648.00	212.10	4546.00
98.05	3361.00	153.10	44120.00	224.15	327616.00
99.05	7601.00	154.10	6691.00	225.15	56024.00
100.05	4018.00	155.10	2502.00	226.15	5234.00
101.05	4758.00	164.00	6187.00	241.15	23128.00
101.95	2270.00	165.10	2737.00	242.15	3814.00



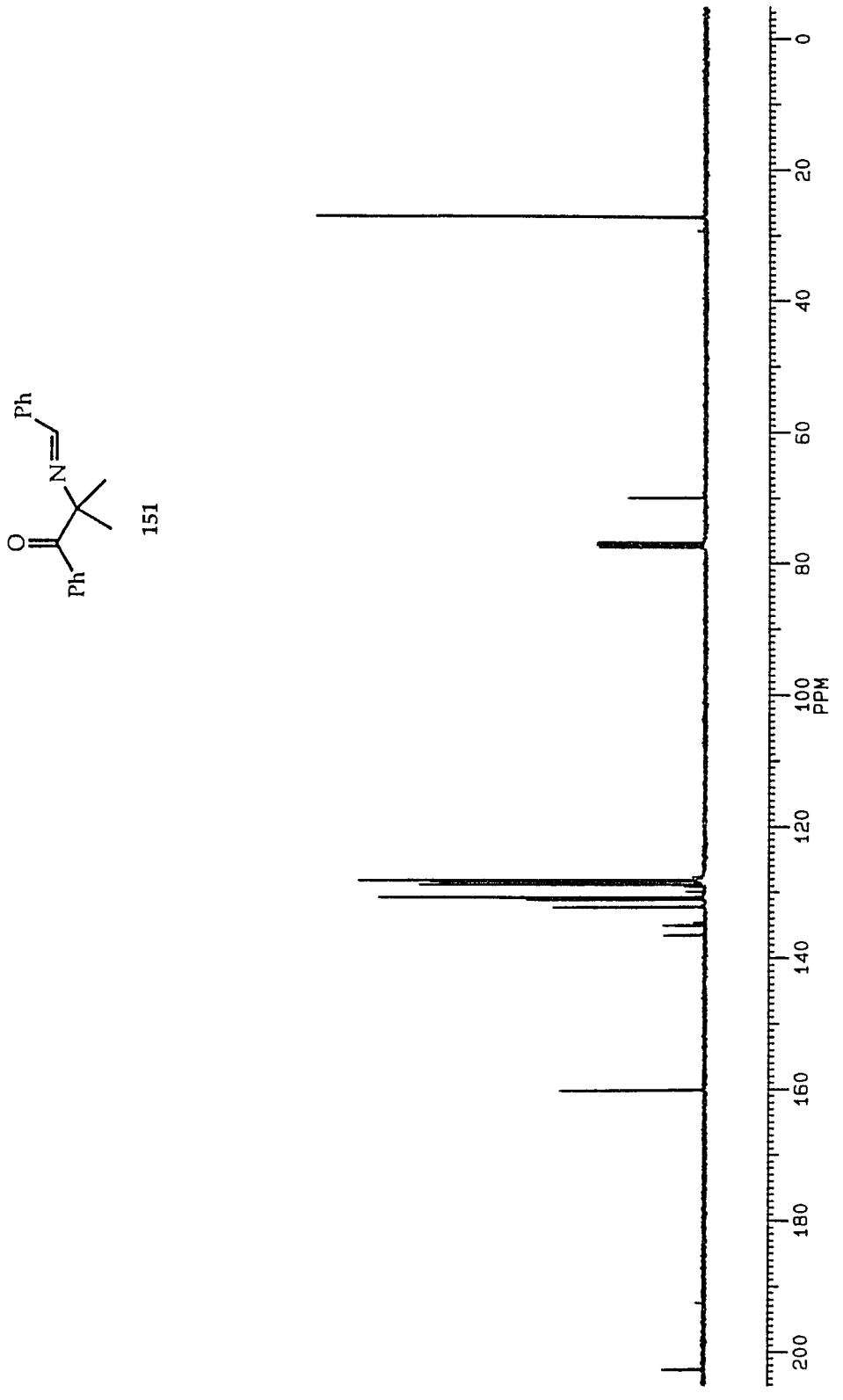
133b

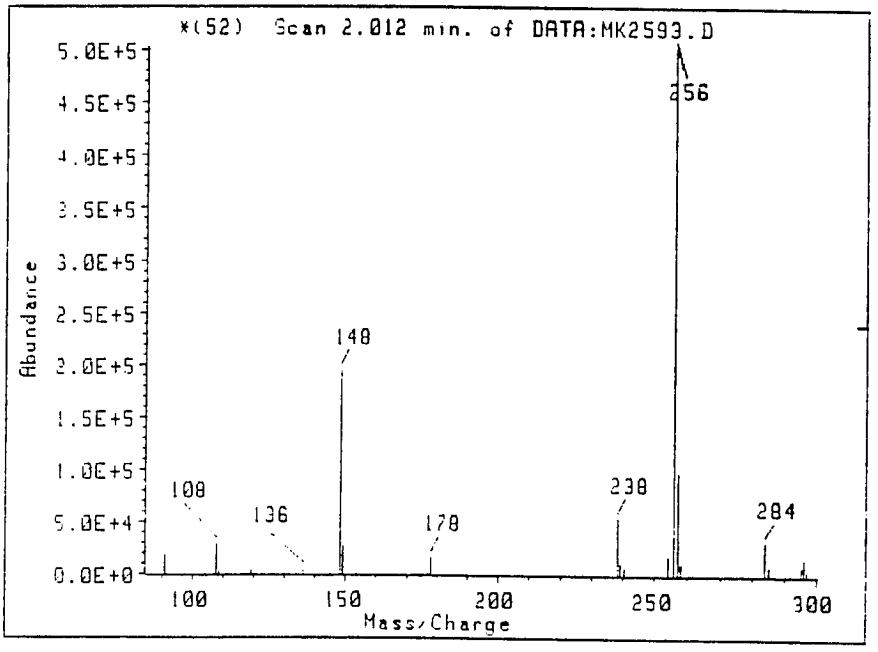




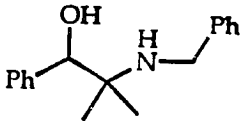
133b

AMU.	Abundance
15.20	1073.00
16.10	508.00
17.20	3119.00
18.20	9398.00
26.10	522.00
27.10	1024.00
28.10	1616.00
29.10	9607.00
30.10	1739.00
31.10	967.00
36.10	515.00
39.10	1627.00
41.10	682.00
42.10	1905.00
43.10	11343.00
44.10	2036.00
45.15	3245.00
50.15	3698.00
51.15	4499.00
52.05	1283.00
53.05	424.00
55.15	592.00
57.15	635.00
58.05	796.00
59.15	423.00
61.05	843.00
62.05	3614.00
63.05	8540.00
64.15	1159.00
65.15	659.00
69.15	1207.00
69.65	1765.00
71.15	457.00
73.05	754.00
74.05	10189.00
75.05	16176.00
76.05	9597.00
77.15	11108.00
78.05	1055.00
82.55	1677.00
83.05	1431.00
85.15	1029.00
86.05	3875.00
87.05	5956.00
88.05	5756.00
89.05	1808.00
90.05	1035.00
97.15	1274.00
98.05	4967.00
99.05	15426.00
100.05	6677.00
101.05	9221.00
102.05	3404.00
103.15	496.00
105.15	441.00
109.05	432.00
109.95	1028.00
111.05	2252.00
112.05	5528.00
113.05	3659.00
114.05	2984.00
115.05	929.00
120.05	418.00
122.05	850.00
123.05	1597.00
124.05	5235.00
125.05	43960.00
126.05	14141.00
127.05	3897.00
128.05	498.00
135.10	472.00
137.10	3689.00
138.10	3924.00
139.10	8281.00
140.10	10697.00
141.10	1399.00
149.10	1695.00
150.10	2514.00
151.10	20200.00
152.10	157632.00
153.10	23400.00
154.10	3034.00
155.10	1291.00
156.10	539.00
164.10	3392.00
165.20	1513.00
166.10	4533.00
167.10	3131.00
168.10	971.00
178.10	1083.00
180.10	201024.00
181.10	29416.00
182.10	3118.00
193.00	585.00
194.10	3333.00
195.10	930.00
196.10	1145.00
197.10	1310.00
198.10	655.00
210.20	425.00
212.20	413.00
224.15	159296.00
225.25	22560.00
226.25	2109.00
240.35	670.00
255.25	11179.00
256.25	2023.00

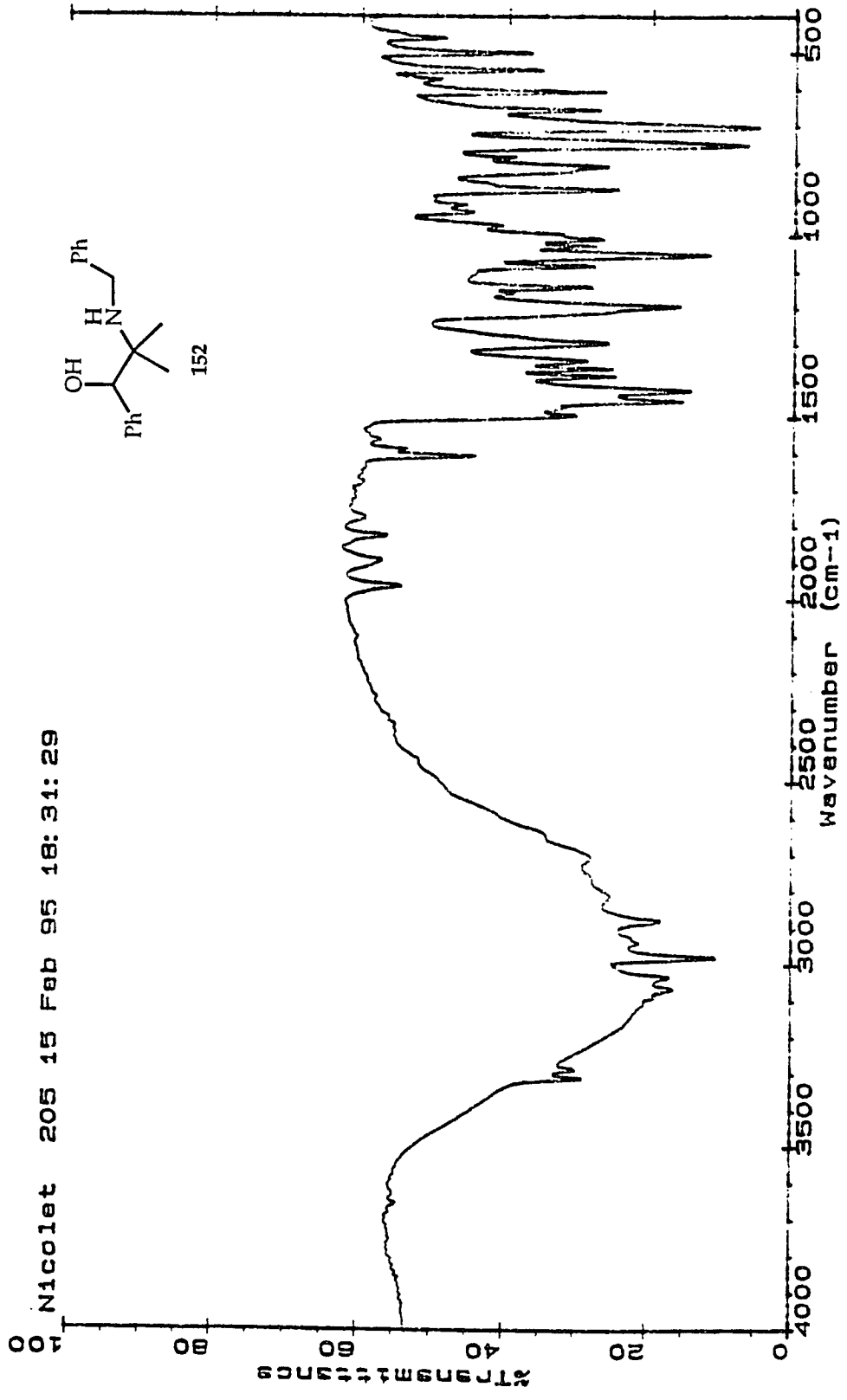


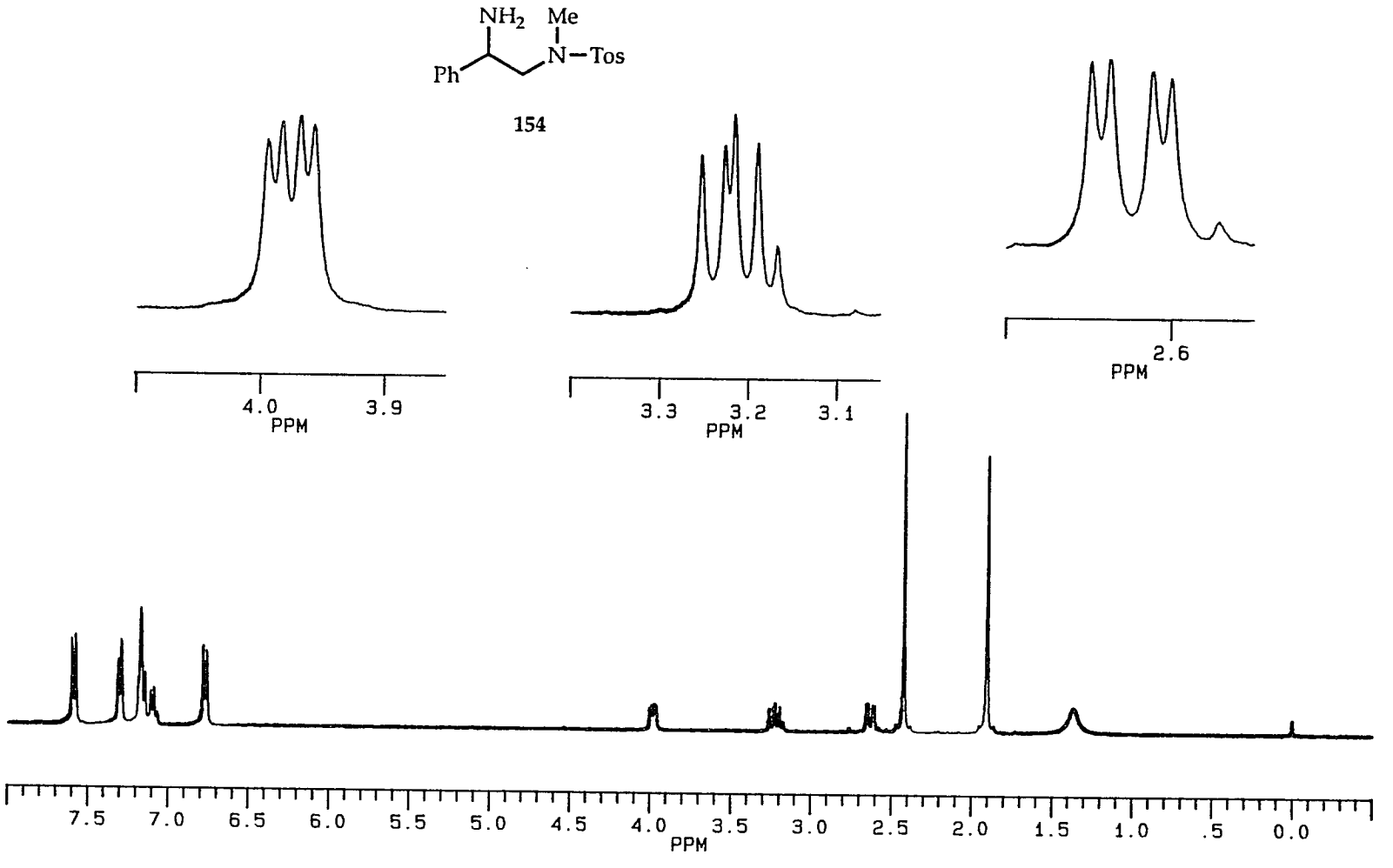


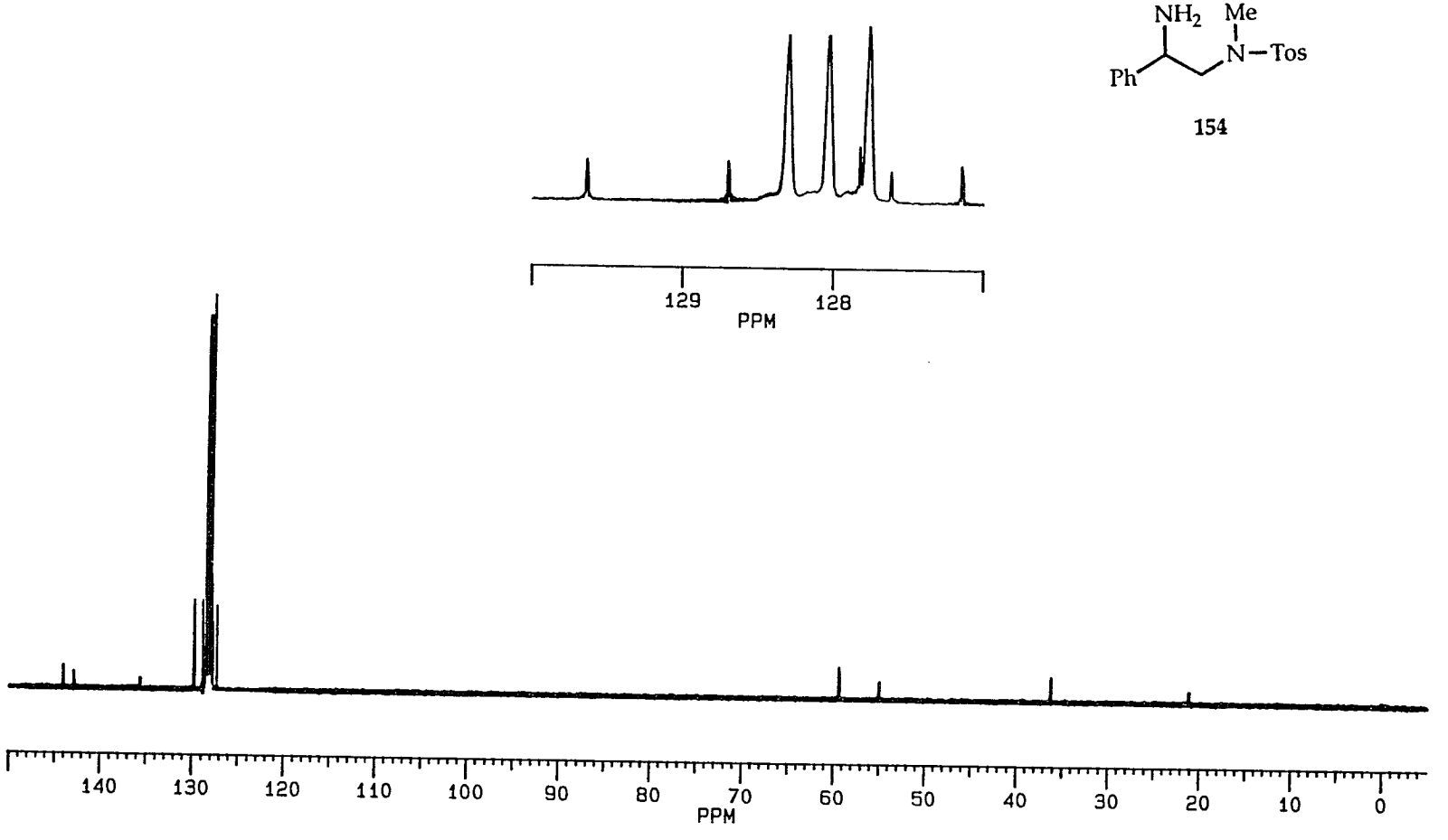
AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
90.95	17024.00	177.15	3741.00	258.20	9880.00
106.95	4304.00	178.05	16182.00	284.25	31128.00 (M+29)
[illegible]	28616.00	238.20	53784.00	285.25	7024.00
108.55	2709.00	239.20	9647.00	295.25	7405.00
118.55	4147.00	240.20	6376.00	296.25	15597.00 (M+41)
136.10	4260.00	254.20	17000.00	297.25	3929.00
148.00	194944.00	256.10	502720.00 (M+1)		
149.00	26792.00	257.10	97000.00		

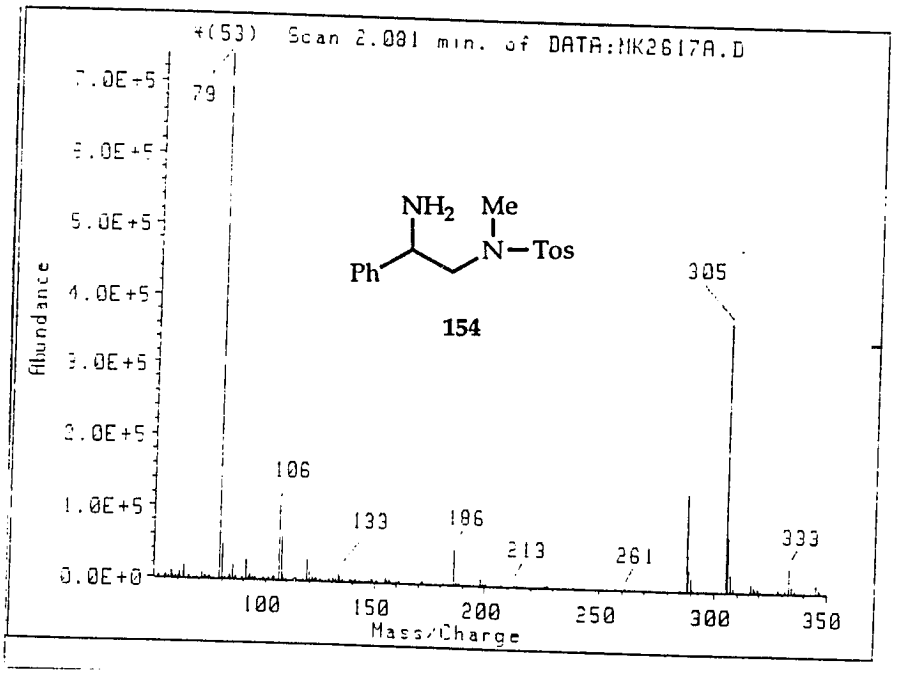


152

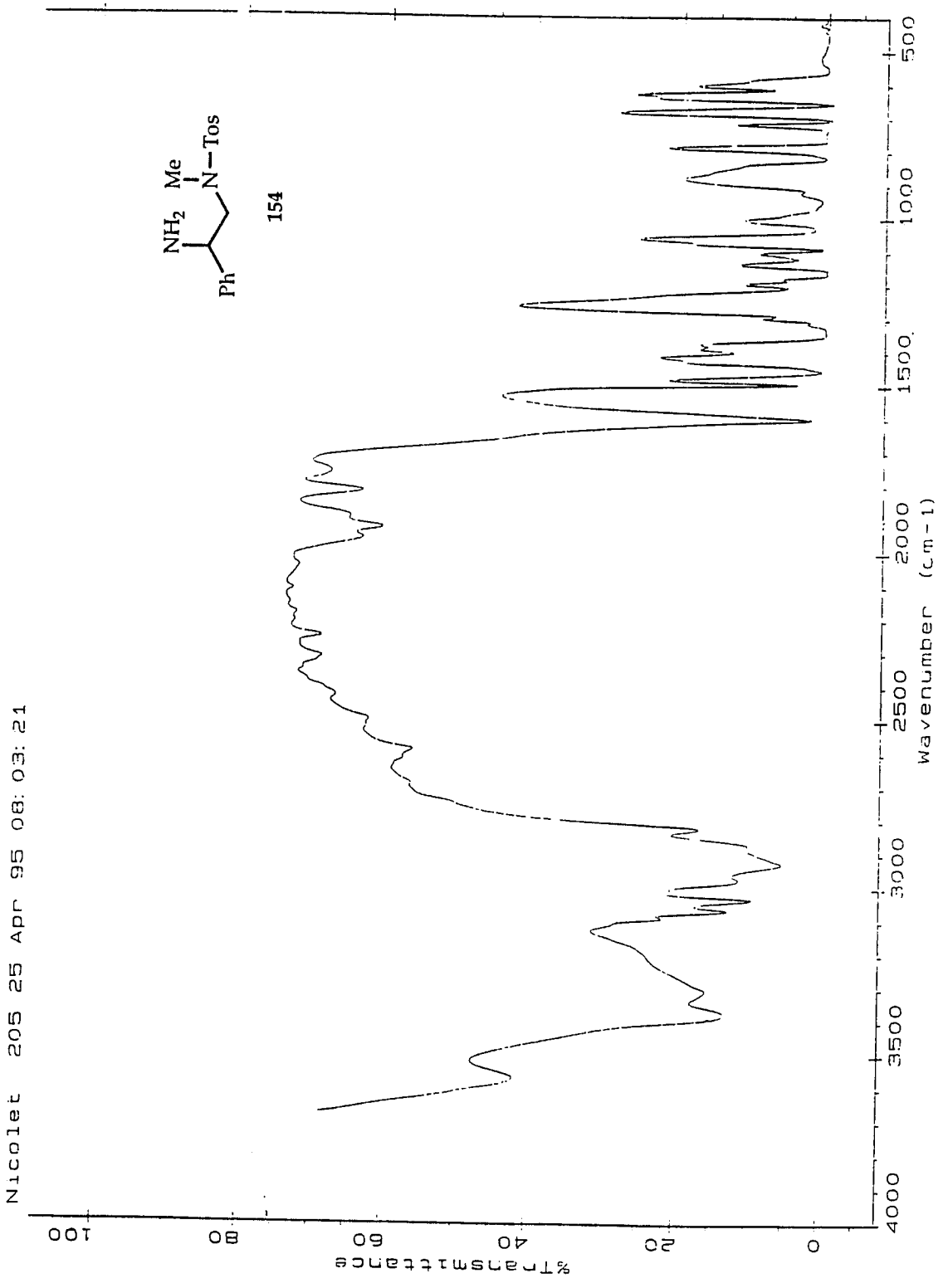


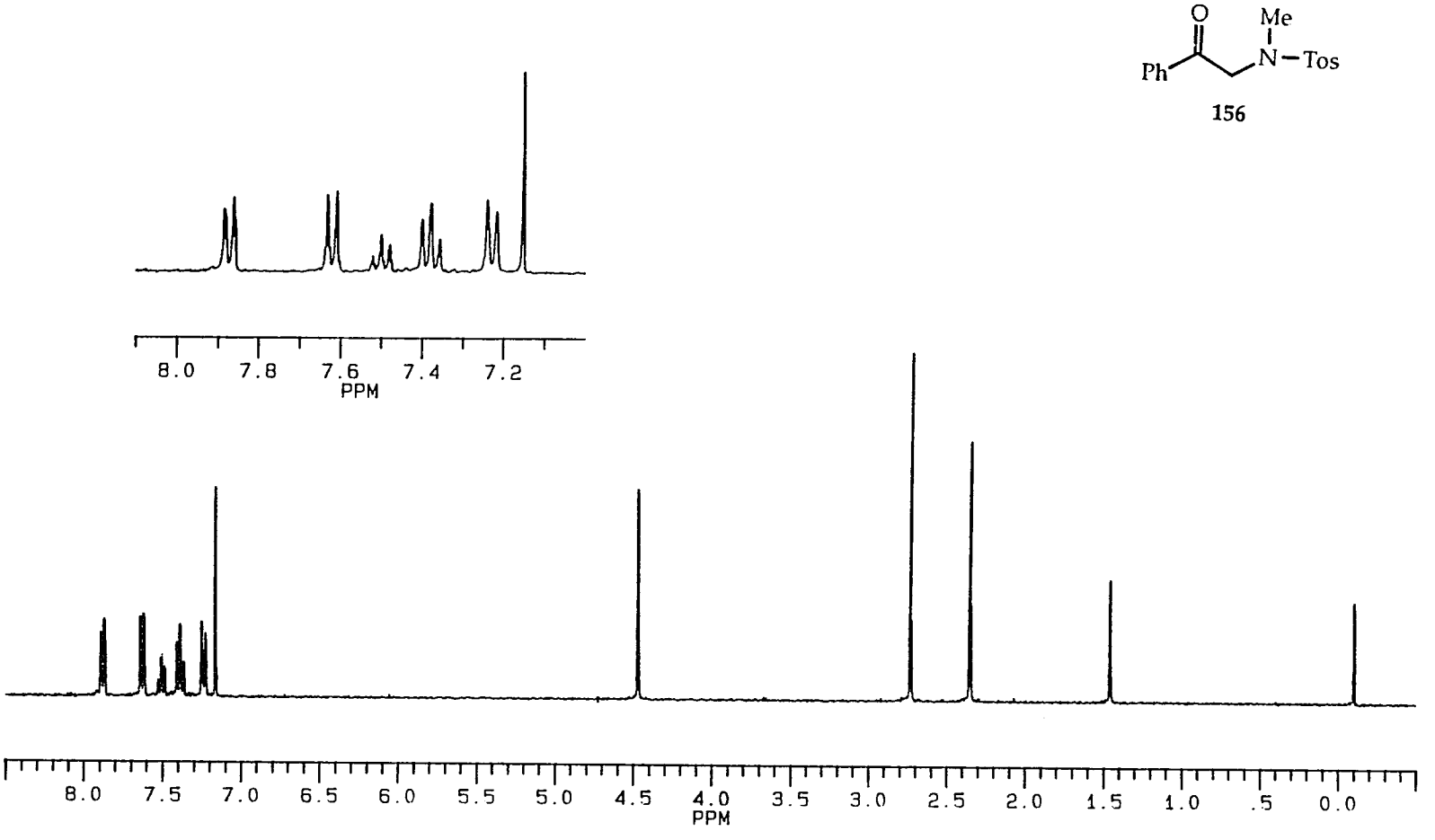


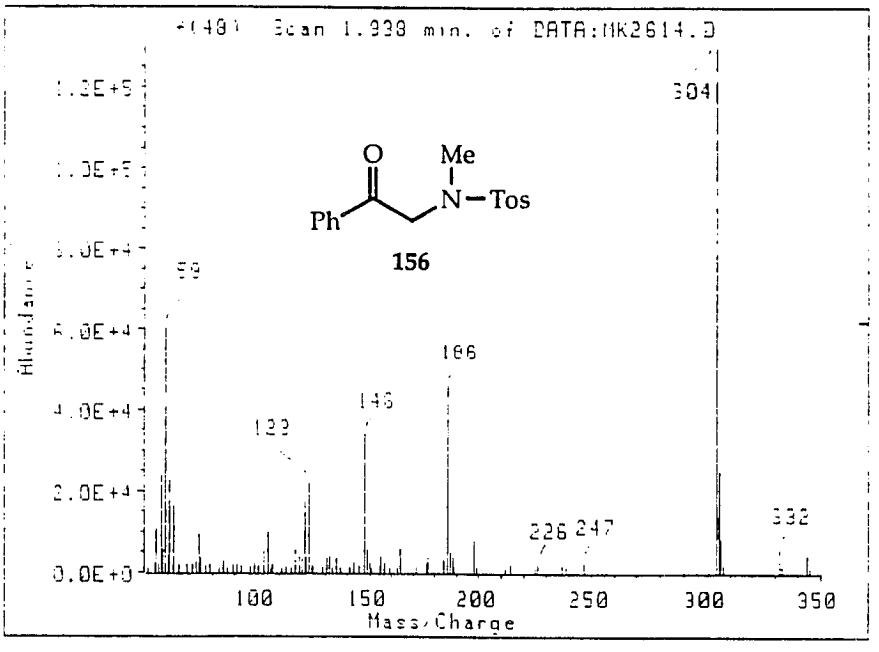




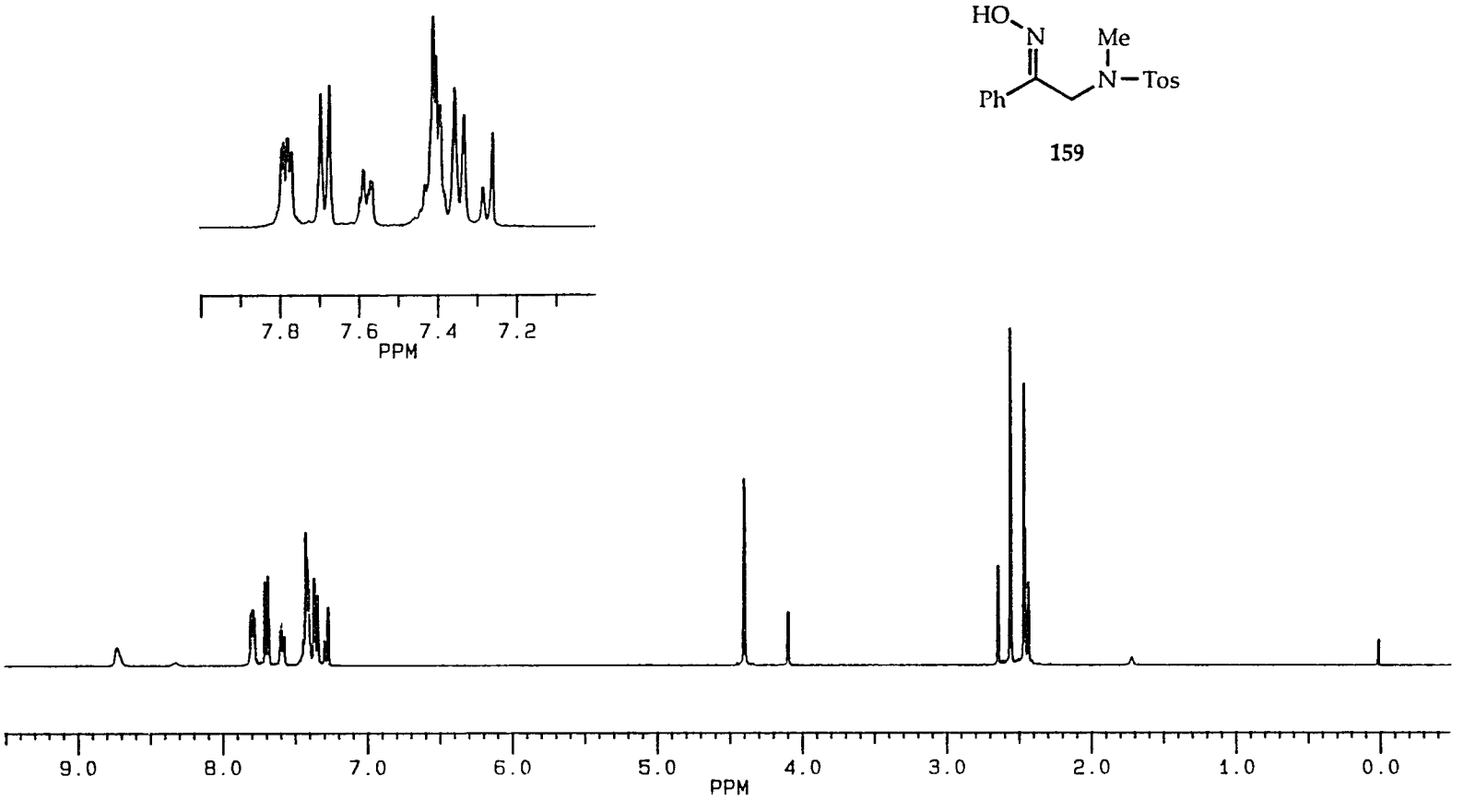
AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
51.00	1277.00	107.05	59560.00	186.95	5324.00
51.90	1057.00	108.05	5399.00	188.05	2537.00
54.00	985.00	108.95	868.00	198.05	7830.00
55.00	4452.00	113.05	2408.00	199.05	1084.00
56.00	1516.00	113.95	1210.00	200.05	1323.00
57.00	9802.00	117.05	1115.00	207.05	829.00
57.90	1831.00	118.95	26712.00	213.05	5136.00
59.00	2542.00	119.95	10406.00	214.15	3066.00
60.00	2018.00	121.10	3750.00	226.20	1913.00
61.00	7760.00	122.10	2598.00	227.20	3153.00
62.90	15690.00	123.00	2598.00	239.20	789.00
64.90	1721.00	125.00	2748.00	257.20	1018.00
68.90	745.00	129.00	999.00	261.10	1069.00
71.00	7344.00	131.00	3293.00	285.25	759.00
72.00	3304.00	132.10	2666.00	288.25	134336.00
72.90	2718.00	133.10	8442.00	289.25	27192.00
73.95	1930.00	134.10	5994.00	290.15	16193.00
74.95	1973.00	135.00	2338.00	291.15	2712.00
78.95	738560.00	139.00	1453.00	305.15	376960.00
79.95	47368.00	139.90	746.00	306.15	75520.00
81.05	2037.00	141.00	1671.00	307.25	22632.00
83.05	1988.00	143.10	946.00	308.25	3276.00
84.05	6165.00	146.10	830.00	316.20	9976.00
85.05	18248.00	147.00	2357.00	317.20	4859.00
86.05	2927.00	148.10	3524.00	318.20	1833.00
88.95	1640.00	149.10	2026.00	319.30	3360.00
91.05	24824.00	151.00	1291.00	320.30	811.00
92.05	2465.00	155.00	4809.00	328.30	3593.00
93.95	4663.00	155.90	1029.00	329.40	914.00
93.85	1314.00	157.00	4207.00	331.30	1142.00
94.95	989.00	160.10	808.00	333.30	32656.00
98.95	1144.00	161.00	1624.00	334.30	6897.00
101.05	1162.00	171.05	1079.00	335.40	2112.00
103.05	1739.00	172.05	1076.00	345.30	13476.00
103.95	4374.00	181.05	1180.00	346.30	3651.00
105.95	105464.00	186.05	46944.00	347.20	1710.00

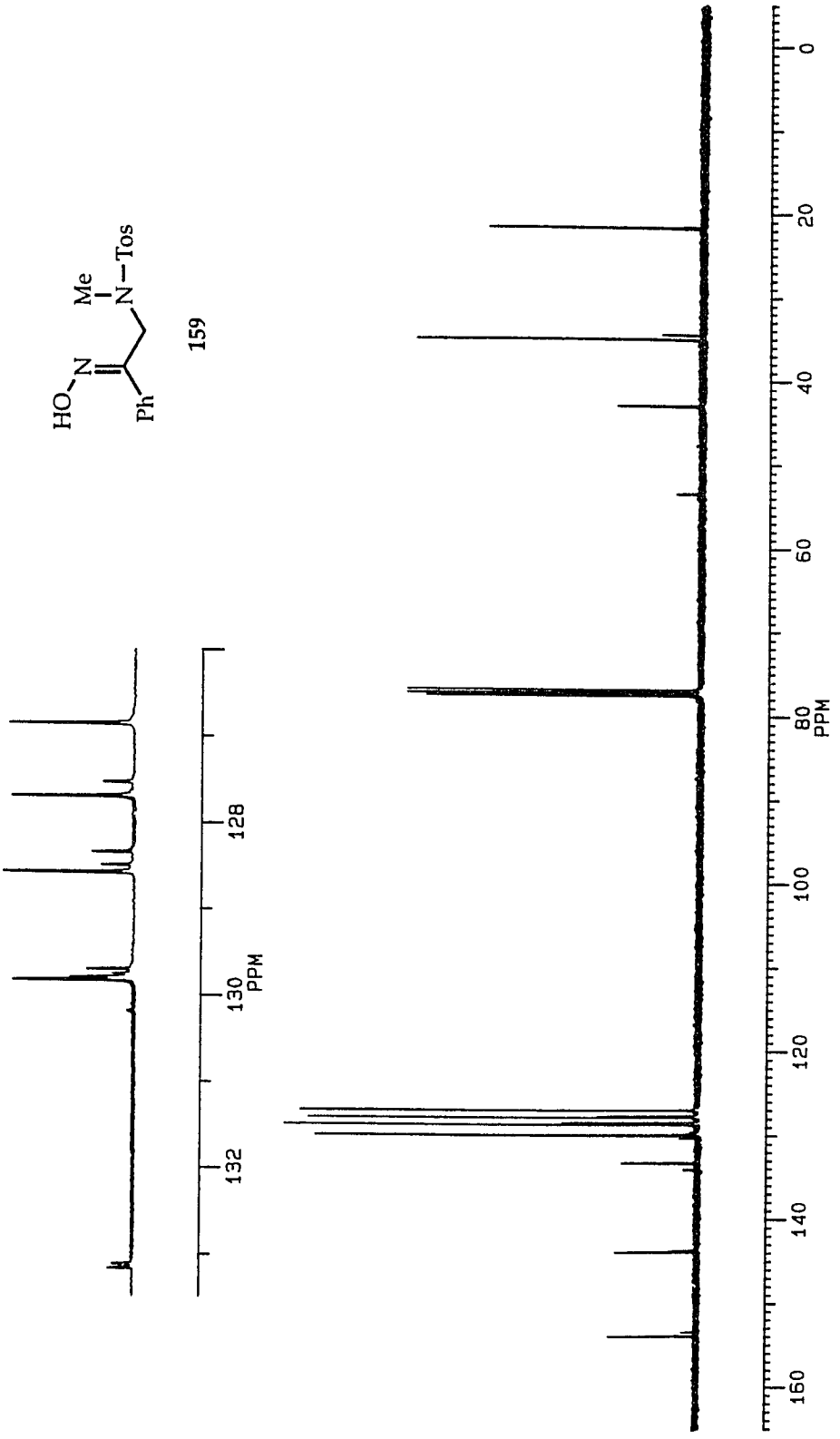


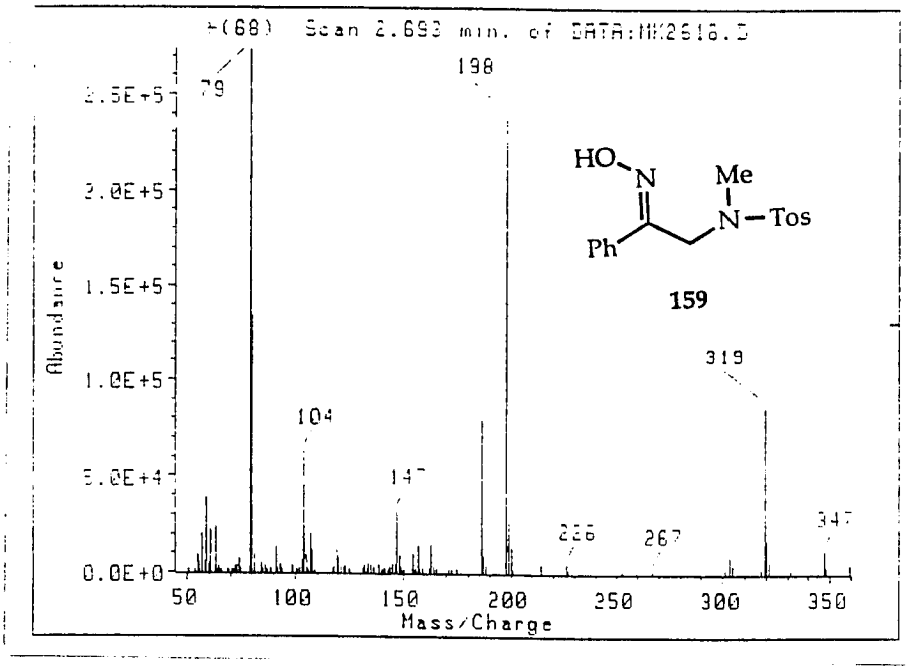




AMU.	Abundance	AMU.	Abundance	AMU.	Abundance
51.00	1072.00	105.85	1049.00	163.00	999.00
53.90	2411.00	106.95	1893.00	164.00	5828.00
54.90	10470.00	110.95	1119.00	171.15	1192.00
56.00	3573.00	112.95	1410.00	176.15	2259.00
57.05	23680.00	114.95	1074.00	177.05	3536.00
58.00	5616.00	116.95	5351.00	183.95	3137.00
59.90	61104.00	118.95	3912.00	186.05	46040.00
60.90	4312.00	119.95	3451.00	187.05	4711.00
60.90	22816.00	121.00	17424.00	188.05	4001.00
62.90	16357.00	122.00	3543.00	188.95	1215.00
64.90	1869.00	123.00	22288.00	198.05	7625.00
68.90	1945.00	124.00	1982.00	198.95	1284.00
71.00	1975.00	125.00	1445.00	211.95	981.00
73.00	2646.00	129.00	1240.00	214.05	1867.00
73.95	9203.00	131.00	3524.00	225.00	1173.00
74.95	3614.00	132.00	3959.00	226.10	1942.00
76.95	1553.00	133.00	951.00	237.10	1710.00
78.95	1791.00	135.00	3421.00	239.20	1322.00
83.05	1110.00	136.90	1085.00	247.00	3037.00
84.95	2896.00	141.00	1433.00	304.15	129608.00
86.95	1300.00	142.90	2725.00	305.15	24688.00
88.95	2054.00	145.10	1482.00	306.15	8198.00
90.95	3885.00	148.00	34016.00	307.05	1533.00
92.95	1718.00	149.00	5348.00	332.20	5804.00
96.95	1188.00	150.00	2256.00	333.10	1359.00
98.95	2681.00	151.00	938.00	344.20	4215.00
100.95	1711.00	154.90	4024.00	345.10	928.00
102.95	5001.00	157.00	2331.00		
104.85	9864.00	159.00	1083.00		







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65.90	1363.00	122.00	2843.00	188.05	3692.00
69.00	1385.00	122.90	5764.00	198.05	236928.00
70.90	1614.00	125.00	1782.00	199.05	25656.00
72.00	2431.00	131.10	1833.00	200.05	13234.00
73.00	3359.00	132.00	4124.00	200.95	1542.00
74.05	7064.00	133.00	1556.00	214.05	4346.00
74.95	2293.00	134.00	5002.00	226.10	4601.00
79.05	273792.00	135.00	4136.00	227.00	1518.00
79.95	133760.00	136.00	2486.00	252.10	1186.00
80.95	7643.00	138.90	4013.00	267.15	1436.00
83.95	4912.00	140.00	1513.00	301.25	1495.00
85.05	2196.00	141.00	1921.00	303.15	8497.00
85.85	3156.00	143.00	1520.00	304.05	3977.00
86.95	1258.00	144.00	2637.00	317.30	2104.00
88.95	1792.00	145.00	3803.00	319.20	85560.00
90.95	13088.00	146.10	4321.00	320.10	16005.00
91.95	1768.00	147.00	32432.00	321.20	5445.00
92.95	4161.00	148.00	9029.00	331.30	1189.00
93.95	2198.00	149.00	2758.00	347.20	11234.00
98.95	3315.00	150.00	1599.00	348.20	2429.00
100.95	1442.00	154.90	9837.00	359.35	3947.00
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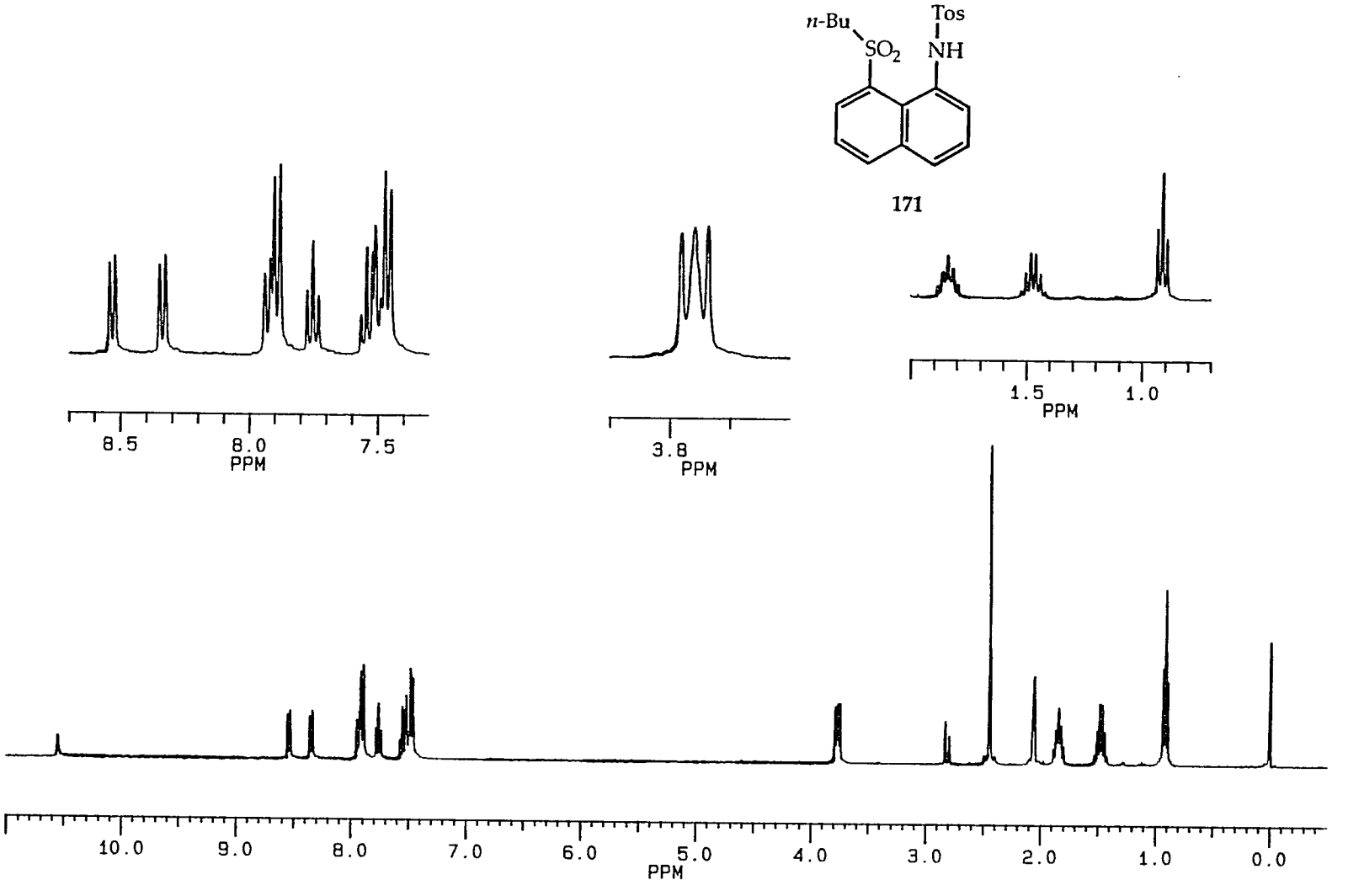

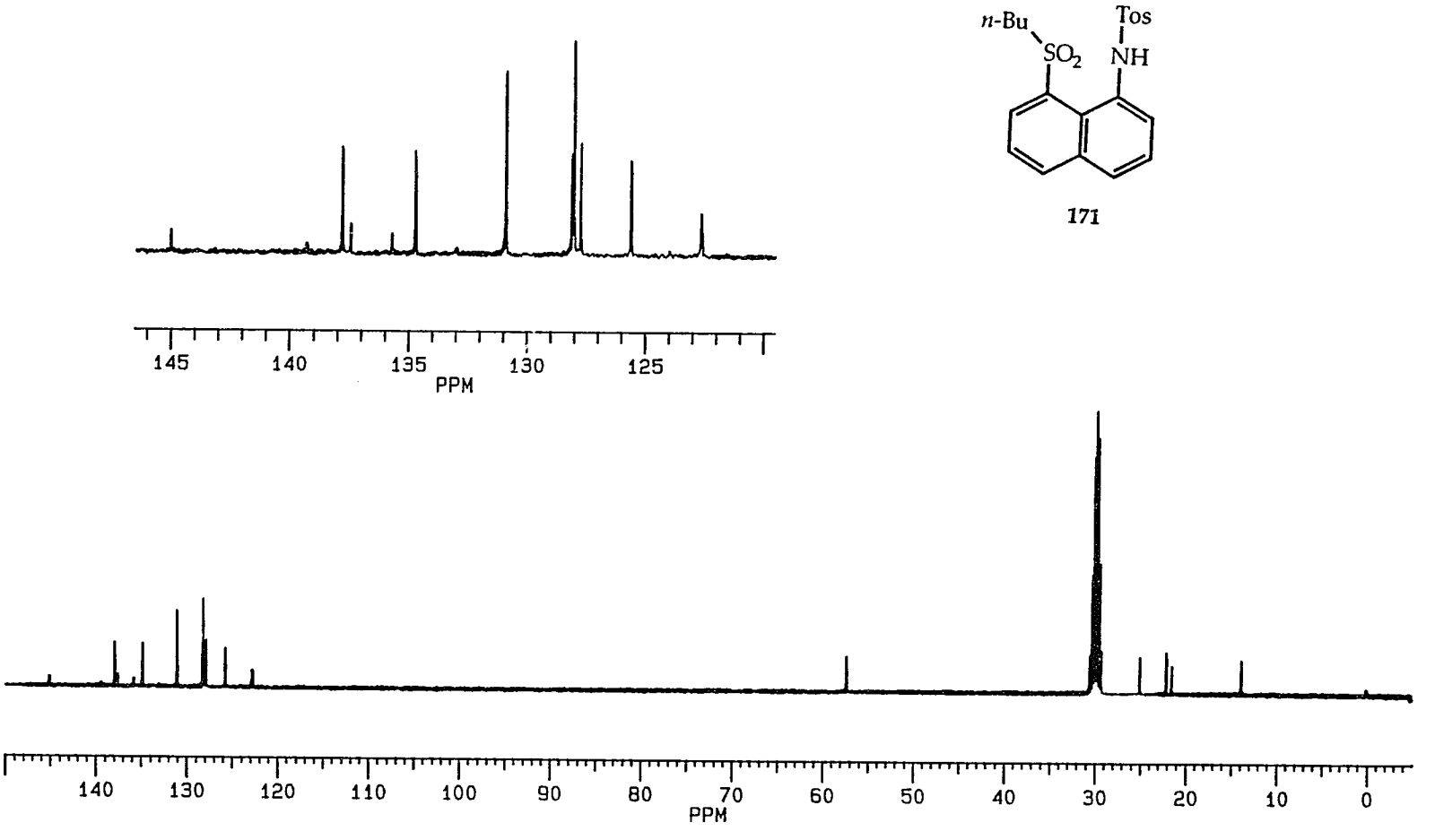

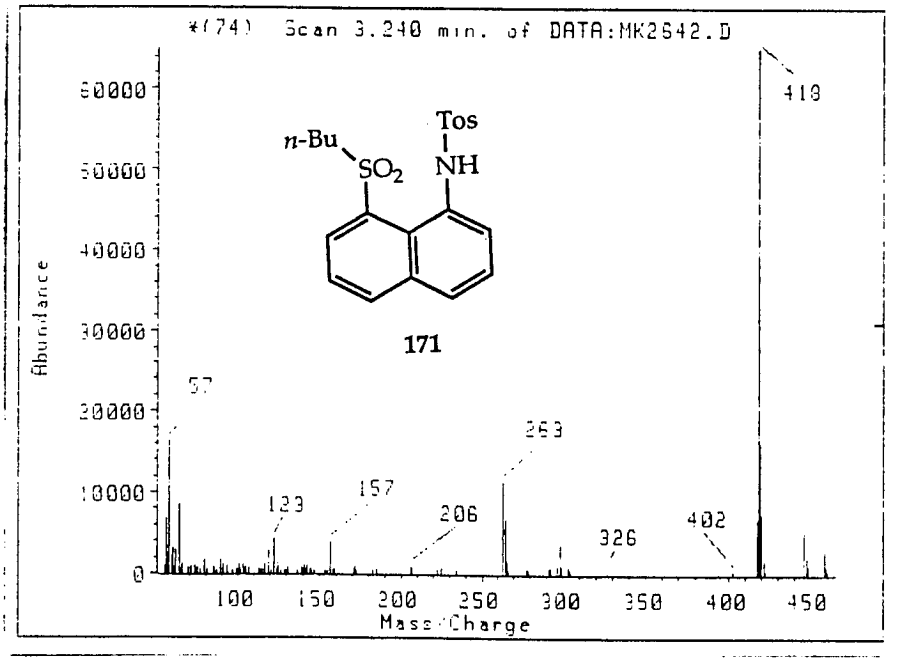

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58.00	2158.00	119.05	2692.00	263.10	11358.00
59.00	3033.00	121.10	377.00	264.25	7001.00
60.00	839.00	123.00	4225.00	265.25	1495.00
61.00	2885.00	124.10	460.00	266.05	454.00
63.00	8597.00	125.00	1275.00	278.15	419.00
63.90	459.00	127.00	361.00	279.15	399.00
64.90	1068.00	129.10	567.00	291.25	727.00
67.00	624.00	131.00	784.00	292.25	636.00
71.00	824.00	137.00	327.00	296.25	1091.00
73.00	909.00	139.00	1029.00	298.15	3529.00
73.95	502.00	140.00	431.00	299.15	849.00
74.95	695.00	141.00	1105.00	303.15	812.00
76.95	521.00	142.00	557.00	304.25	406.00
78.95	1667.00	143.00	932.00	326.20	556.00
80.95	526.00	144.10	509.00	402.25	377.00
84.95	838.00	145.10	438.00	417.20	6617.00
87.05	404.00	147.10	333.00	418.30	65064.00
89.05	1540.00	153.10	326.00	419.30	16001.00
91.05	1069.00	155.10	326.00	420.30	7308.00
93.05	984.00	157.00	3832.00	421.30	1687.00
97.05	335.00	158.10	463.00	422.20	398.00
99.05	553.00	159.10	461.00	446.30	5135.00
99.95	415.00	171.05	622.00	447.30	2006.00
100.95	1108.00	172.05	977.00	448.30	988.00
102.05	504.00	173.05	370.00	458.35	2938.00
103.05	1062.00	183.05	458.00	459.35	801.00
103.95	676.00	185.05	566.00	460.35	383.00
104.95	759.00	206.05	802.00		

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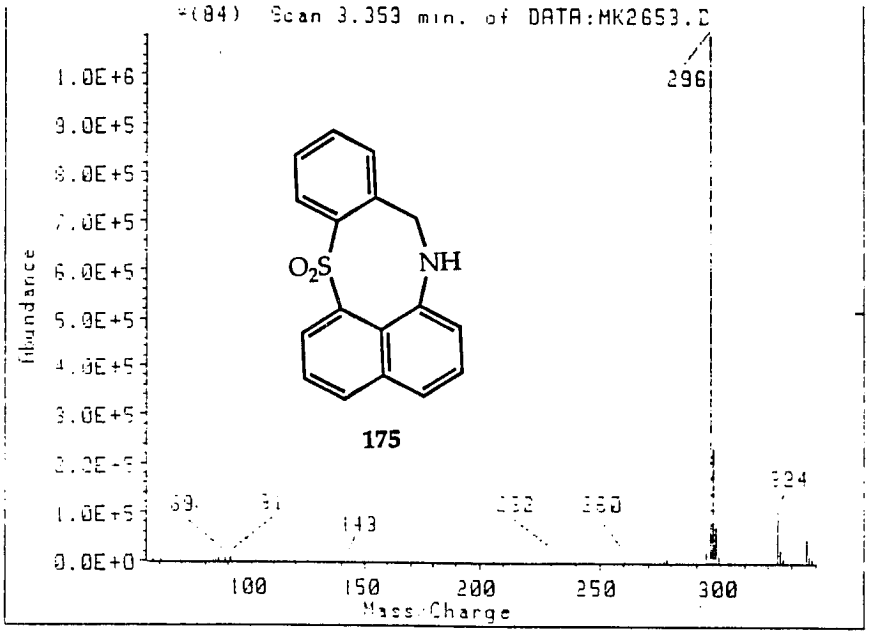

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105.05	41o4.00	252.10	7034.00	325.20	24072.00
105.85	4819.00	260.10	7208.00	326.20	7109.00
108.95	4934.00	277.05	4422.00	336.20	46744.00
109.95	7972.00	278.15	4719.00	337.20	11167.00
101.95	5507.00	294.25	24832.00	338.10	4787.00
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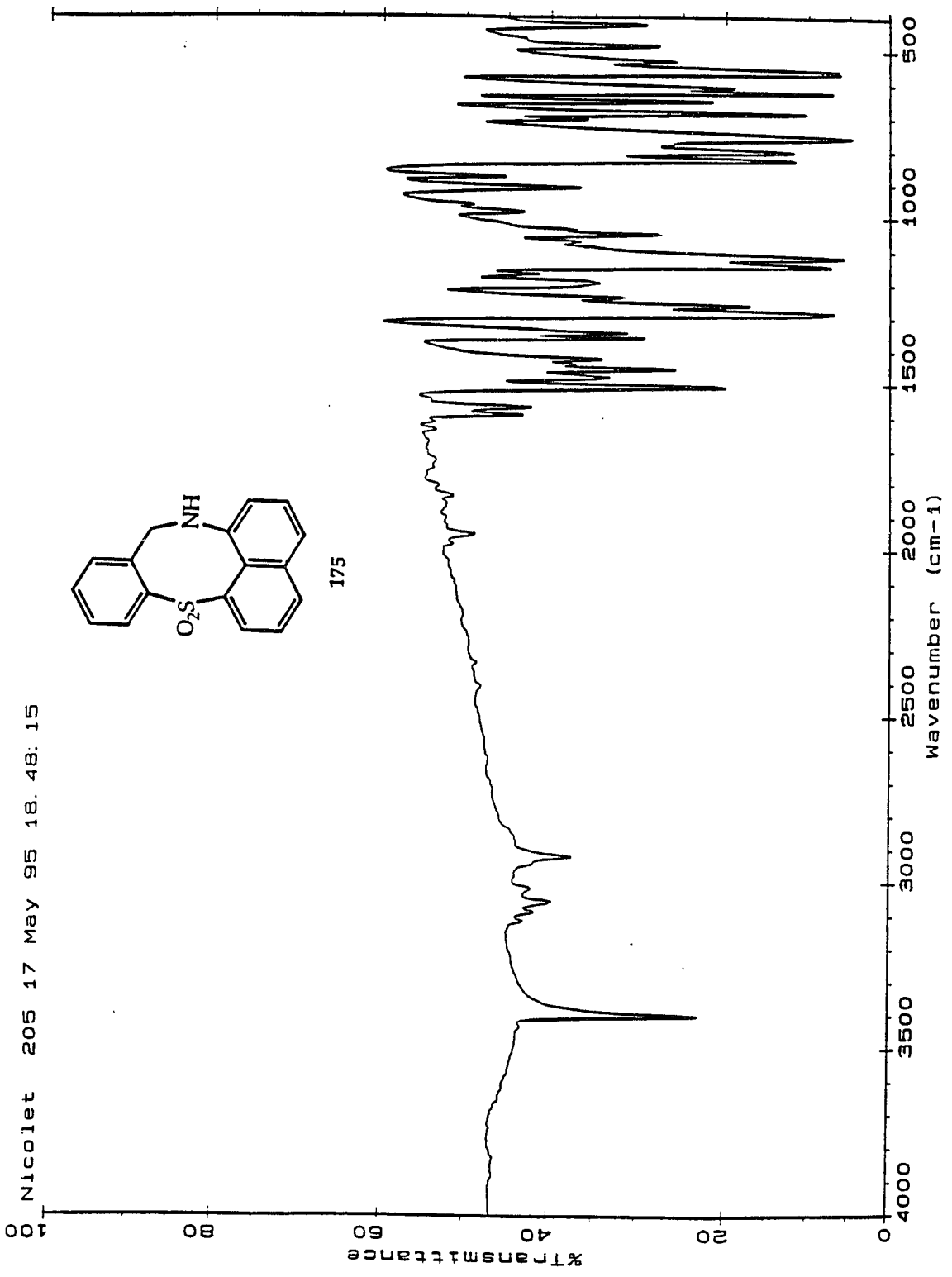

Acidity of Cyclic Sulfamates: Study of Substituted 1,2,3-Benzoxathiazole 2,2-Dioxides and Theoretical Investigation of the Effect of Conformation on Acidity

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Received December 1, 1994[⊗]

Sulfamate **1b**, 5-nitro-3-(4-toluenesulfonyl)-1,2,3-benzoxathiazole 2,2- dioxide, was treated with various nucleophiles: imidazole, benzylamine, *tert*-butylamine, sodium azide, potassium fluoride, pyridine, and sodium hydroxide. The first five attacked the exocyclic (tosyl) sulfur atom. No reaction was observed with the pyridine. The hydroxide ion attacked the endocyclic sulfur atom leading to opening of the benzoxathiazole ring. Several N-unsubstituted cyclic sulfamates, X-3*H*-1,2,3-benzoxathiazole 2,2-dioxides (**2a**, X = 5-H; **2b**, X = 5-NO_2; **2c**, X = 5-Me; **2d**, X = 5-Br; **2e**, X = 5-Cl; **2f**, X = 6-NO_2; **2g**, X = 5,6-Cl,Cl) and the naphtho-fused cyclic sulfamate (**2h**), were prepared by treatment of the respective *N*-tosyl compounds (**1a–h**) with sodium azide or potassium fluoride. The pK_a values for these compounds were determined by potentiometric titration in 60% v/v EtOH/H_2O. A Hammett plot using σ_m for **2a–e**, σ_p for **2f**, and both σ_m and σ_p for **2g** gave a $\rho = 2.74$. *Ab initio* calculations were done using sulfamic acid as a simple sulfamate model to test the effect of the geometry changes on pK_a. The calculations showed that the sulfamate with the ringlike geometry should be 3.6 pK_a units more acidic than the acyclic sulfamate. This overall change was broken down into three factors affecting the pK_a. The N–S bond rotation accounted for a change of 0.22 units, O–S bond rotation for 2.03 units, and ring strain for 1.36 units.

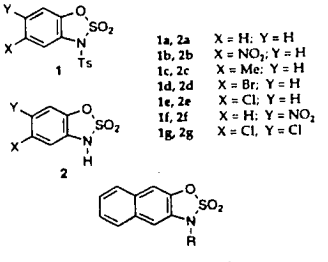
Introduction

Cyclic sulfur(VI) and sulfur(IV) esters and amides have been studied in order to compare their properties with those of their acyclic analogues.[1] These investigations have shown that cyclic compounds often differ markedly in reactivity compared to their acyclic analogues.

The reactivity of 3-tosyl-1,2,3-benzoxathiazole 2,2-dioxide (**1a**) with various nucleophiles has been examined previously.[2] Results of that study showed that the site of attack could be either the exocyclic or endocyclic sulfur atom depending on the nucleophile. Hydroxide ion and amines attacked the endocyclic sulfur atom, resulting in ring opening. Methoxide ion attacked both the endocyclic and exocyclic sulfur atoms. Organolithiums, as well as fluoride ion, attacked the exocyclic sulfur atom, cleaving off the tosyl group. In the latter cases it was suggested that **2a** was unusually acidic, since its conjugate base was a good leaving group. A variety of compounds, including sulfamides,[3] sulfonamides,[4] and disulfonamides,[5] show enhanced acidity when these functional groups are incorporated into five- or six-membered rings. This "acid strengthening" has been suggested to arise from stereoelectronic effects resulting from the ring geometry.[3a,5]

This paper reports the reaction of **1b** with several nucleophiles. The addition of the nitro group on the aromatic ring should make **2b** a stronger acid and, in turn, its conjugate base a better leaving group than the conjugate base of **2a**. This might increase the reactivity of the tosyl sulfur atom in **1b** compared to **1a**.

In addition, several of these substituted cyclic sulfamates (**2a–h**) were synthesized and their pK_a values determined. The effects of the substituents on the pK_as of these sulfamates were correlated by a Hammett plot.



1a, 2a	X = H; Y = H
1b, 2b	X = NO_2; Y = H
1c, 2c	X = Me; Y = H
1d, 2d	X = Br; Y = H
1e, 2e	X = Cl; Y = H
1f, 2f	X = H; Y = NO_2
1g, 2g	X = Cl, Y = Cl

The acid strengthening effect was examined by *ab initio* calculations using sulfamic acid as a simple sulfamate model. By calculating the energies for a variety of conformations, we were able to calculate the overall pK_a change going from an acyclic to a ring-like geometry. The overall change was broken down into three additive contributions: (1) O–S bond rotation; (2) N–S bond rotation, and (3) ring strain.

[⊗] Abstract published in *Advance ACS Abstracts*, March 15, 1995.

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(4) Girard, Y.; Atkinson, J. G.; Rokach, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1043–1047.

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Results and Discussion

Reaction of 1b with Various Nucleophiles. The reaction of **1b** with 2 equiv of imidazole in acetonitrile gave the *N*-unsubstituted cyclic sulfamate **2b** (69%) and *p*-toluenesulfonyl imidazole which arose from attack of the imidazole on the exocyclic *N*-tosyl sulfur atom. Similarly, the reaction of **1b** with two equivalents of benzyl- or *tert*-butylamine resulted in **2b** and the tosylated amines.

These reactions all required 2 equiv of the nitrogen nucleophile in order for the reactions to go to completion. One equivalent was necessary to form the *N*-tosylated compound, and the second equivalent formed an ammonium salt with the cyclic sulfamate anion. The use of 1 equiv resulted in the above mentioned products as well as recovery of half of the starting sulfamate.

Treatment of **1b** with 1 equiv of sodium azide in an aqueous acetonitrile solution gave the *N*-unsubstituted cyclic sulfamate **2b** (93%) and *p*-toluenesulfonyl azide. As monitored by TLC, this reaction went to completion in several minutes. Similarly, the reaction of **1b** with 1 equiv of potassium fluoride in aqueous acetonitrile resulted in **2b** (81%) and *p*-toluenesulfonyl fluoride. This reaction time was significantly longer.

The reaction of **1b** with 1 equiv of pyridine in acetonitrile was also attempted, but after the mixture had been stirred for 24 h at room temperature, TLC showed only starting material.

The treatment of **1b** with sodium hydroxide in aqueous acetonitrile resulted in the formation of sulfonamide **3** (92%) and a small amount of **2b** (6%). The formation of the major product arose from attack on the ring sulfur atom with cleavage of either the S–N or S–O bond. Ultimately, the acidic workup resulted in loss of a sulfate group, yielding the sulfonamide. This attack at the ring sulfur is analogous to that reported for the treatment of **1a** with sodium hydroxide, where it had been determined experimentally that the ring opening proceeded by way of N–S bond cleavage. Hammett correlation of the rate constants for the saponification of these *N*-tosyl sulfamates suggested that the ring opening of **1b** also proceeded by way of N–S bond cleavage. The reaction of **1a** with hydroxide ion, however, showed no evidence for attack on the *N*-tosyl sulfur atom.

The exocyclic sulfur atom of **1b** was the site of reaction when the nucleophiles were imidazole, azide ion, fluoride ion, or amines, and the endocyclic sulfur atom when the nucleophile was hydroxide ion. These results are analogous with those previously reported for the reaction of **1a** with fluoride ion and hydroxide ion.[2] However, in the case of the amines, opposite results were observed: endocyclic attack for **1a** and exocyclic for **1b**. The cyclic sulfamide **5a** has been shown to be quite acidic, which suggests that **2a** would also be quite acidic. The addition of a nitro group would only serve to increase the acidity of sulfamate **2b**. The conjugate base of **2b** would therefore be a better leaving group than that of **2a**. This might explain the increased reactivity of the exocyclic sulfur in **2b**. The difference in selectivity of the various nucleophiles remains unexplained.

These results led to an investigation of the acidity of a series of these NH cyclic sulfamates (**2a–h**).

Synthesis of N–H Cyclic Sulfamates. Treatment of **1a** with sodium azide in aqueous acetonitrile resulted in removal of the tosyl group and formation of the NH cyclic sulfamate, as well as *p*-toluenesulfonyl azide.

Table 1. Experimentally Determined pK_a Values

no.	pK_a[a]	scatter[b]	n[c]	no.	pK_a[a]	scatter[b]	n[c]
2a	4.62	0.03	6	**2e**	3.72	0.05	6
2b	2.76	0.07	5	**2f**	2.33	0.04	5
2c	4.73	0.03	7	**2g**	2.87	0.04	6
2d	3.47	0.05	5	**2h**	3.84	0.02	5

[a] pK_a determined at 25 °C in 60% v/v EtOH/H_2O. [b] The scatter or spread was determined as described in ref 6. [c] n = number of pK_a values averaged to obtain the value shown.

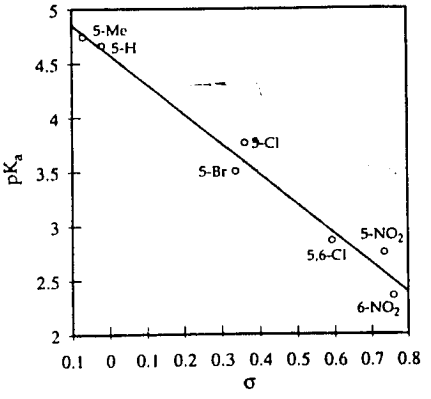

Figure 1. Hammett plot for the ionization of **2a–g** in 60% EtOH/H_2O.

Similar results were seen upon treatment of **1a** with potassium fluoride. The cyclic sulfamates **1c–h** were all treated in a similar manner, with either sodium azide or potassium fluoride, to give the N-unsubstituted cyclic sulfamates **2c–h**. The reactions of these compounds with sodium azide, in general, were faster and proceeded with very good yields. The reaction with potassium fluoride generally involved longer reaction times and resulted in lower yields.

pK_a Determinations. The pK_a values for the series of substituted cyclic sulfamates were determined in 60% v/v EtOH/H_2O. Potentiometric methods[6] were utilized with the pK_a values being calculated by using eq 1 which includes a correction for hydrogen ion activity $\{H^+\}$ (eq 2). This correction was applied only for pH values below 4.0; for values above 4.0 the hydrogen ion activity is essentially 0.

$$pK_a = pH + \log_{10}([HA] + \{H^+\}/[A^-] - \{H^+\}) \quad (1)$$

$$\{H^+\} = 10^{-pH} \quad (2)$$

The pK_a values for a series of substituted cyclic sulfamates (**2a-h**), as well as the scatter and number of pK_a values averaged, are shown in Table 1.

Hammett Plot. Several Hammett correlations using least squares analyses were carried out by plotting the experimental pK_a values (-log K) vs Hammett σ values (Figure 1). The pK_a values for compounds **2a–g** were plotted using σ_m for **2a–e**, σ_p for **2f**, and $\sigma_p + \sigma_m$ for **2g**.[7]

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Table 2. Energies (hartree) and Relative Energies (kcal mol^{-1})

no.	$E(NH_2)$	$E_{rel}(NH_2)$	$E(NH^-)$	$E_{rel}(NH^-)$
6a	−674.929742	0	−674.376334	0
6b	−674.921973	4.9	−674.369018	4.6
6c	−674.9053229	15.3	−674.356589	12.4
6d	−674.889493	25.2	−674.343595	20.6

The straight line provided a ρ value of 2.74, correlation coefficient (r) of 0.975 with a standard error (s) of 0.16. Similar plots were constructed using only values for **2a−e** and **2a−f**. The ρ,r,s values showed little change when the 6-NO_2 (**2f**) and 5,6-dichloro (**2g**) compounds were omitted. The value for these plots were as follows: (**2a−e**) $\rho = 2.74$, $r = 0.975$, $s = 0.16$; (**2a-f**) $\rho = 2.71$, $r = 0.974$, $s = 0.17$. The ρ value for this series of cyclic sulfamates, 2.74, is in the same range as the value of 2.8 observed for a series of substituted cyclic sulfamides.[3]

Computational Investigation of a Simple Sulfamate Model. Sulfamic acid was chosen as a simple model to investigate the effect of O−S, N−S, and ring strain on the pK_a of sulfamate systems. By applying various constraints to the molecule, we could assess the degree to which each of these changes in geometry effected the acidity. The geometries of all the conformations (applying appropriate constraints where necessary) was optimized at the RHF/3-21+G* level. This level incorporates d-orbitals on the sulfur atom and also diffuse functions necessary for proper treatment of the anionic species. By calculating the energies for both the neutral and anionic species (Table 2), ΔH could be obtained for the reaction (deprotonation of H_5 at nitrogen). This could be used comparatively to judge the relative acidity of each conformation. Initially, the model was allowed to optimize to its lowest energy conformation (**6a**), in which the $H-O_2-S-N$ dihedral = 180° (hydroxyl hydrogen bisects the sulfonyl oxygens) and the O_2-S-N-(lone pair) dihedral = 180° (lone pair on nitrogen bisects the sulfonyl oxygens). The model was then subjected to a series of sequential conformational changes until the ring like geometry was reached (Figure 2). Each step was evaluated to compare its contribution to the overall pK_a change.

N−S Bond Rotation. The O_2-S-N-(lone pair) dihedral angle was constrained to 90° while holding the $H-O_2-S-N$ dihedral at 180°. The result of the 90° rotation of the S−N bond was a difference in energy between the two neutral species (**6a** to **6b**) of +4.9 kcal mol^{-1} and a difference between the anions of 4.6 kcal mol^{-1}. The difference between the two ΔH values of the two conformations was −0.3 kcal mol^{-1}. This translates to a ΔpK_a of −0.22 units resulting from rotation of the H_1-S bond; i.e., the acidity was increased on going from **6a** to **6b**.

O−S Bond Rotation. The O_2-S bond was rotated and the $H-O_2-S-N$ dihedral angle constrained at 0. This change resulted in a change in energy from **6b** to **6c** of 10.4 kcal mol^{-1} for the neutral compounds and 7.8 kcal mol^{-1} for the anions. The difference between the two ΔH values was −2.65 kcal mol^{-1}, which leads to a ΔpK_a of −2.03; i.e., an increase in acidity in going from **6b** to **6c**.

Ring Strain. The internal angles of compound **6c** were then constrained to resemble the ring geometry of the five-membered cyclic sulfamate using angles taken from a crystal structure of **1a** previously reported.[8] The angles were constrained as follows: $H-O_2-S$ = 112°, O_2-S-N = 95°, $S-N-H_6$ = 108°. The effect of constraining these angles were changes of 9.9 and 8.2 kcal mol^{-1} in the energies for the neutral molecules and anions, respectively. The ΔH value going from **6c** to **6d** was calculated to be −1.78 kcal mol^{-1}, which leads to a difference between the two ΔpK_a values of −1.36; i.e., an increase in acidity going from **6c** to **6d**.

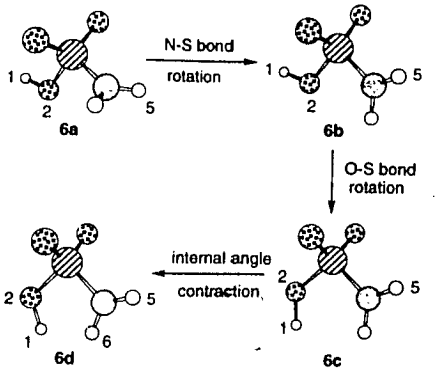

Figure 2. Representation of conformations of sulfamate model. **6a**: H_1-O_2-S-N dihedral = 180°, O_2-S-N-(lone pair) dihedral = 180°. **6b**: O_2-S-N-(lone pair) dihedral rotated to 90°. **6c**: H_1-O_2-S-N dihedral rotated to 0°. **6d**: internal angles contrained to ringlike geometry, $\angle H_1-O_2-S$ = 112°, $\angle O_2-S-N$ = 95°, $\angle S-N-H_6$ = 108°.

These results show that the change in geometry going from an acyclic to a ringlike structure has a profound effect on the energies of the compounds and, in turn, on the acidity. Overall, the neutral ringlike structure **6d** is 25 kcal mol^{-1} higher in energy than its acyclic analogue. The anion is slightly less effected with the structure having ringlike geometry being 20 kcal mol^{-1} higher. These calculations suggest that this change in geometry may be responsible for a lowering of the pK_a for the ring structure by about 3.6 units, thus acounting for the increase in acidity of the cyclic sulfamates compared to their acyclic analogues. The rotation of the N−S bond seems to have the smallest effect, a change of −0.22 units. The O−S bond rotation has the most profound effect with a change of −2.03 units. The ring strain also contributed greatly to the overall ΔpK_a, providing a change of −1.36 units.

To properly test the validity of these results, the experimentally determined pK_a for a cyclic sulfamate must be compared to an acyclic analogue. A proper compound to compare to cyclic sulfamate **2a** would be phenyl (*N*-phenyl amino)sulfonate (**4a**). The pK_a value for this compound has not yet been reported. A similar compound, **4b**, has been reported to have a pK_a in 50% EtOH/H_2O of 10.53.[9] This value is approximately 5.8 units higher that that of the cyclic compound **2a**. The computational results suggest that the difference should be smaller, around 3.6 pK_a units. It is conceivable,

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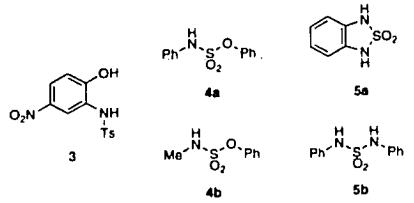
however, that the presence of a phenyl group attached to the nitrogen in place of the methyl could increase the acidity as much as 2.5 pK_a units. This has been shown experimentally in the case of $PhNHSO_2Ph$ versus $MeNHSO_2Ph$ where the pK_a values differ by 2.67 units, with the former sulfonamide being more acidic.[10] If the sulfamate were analogous to the sulfonamide, then the pK_a of **4a** is predicted to be around 8 (10.53−2.67). This would bring the change in pK_a between the cyclic and acyclic sulfamates in the range of the theoretical model (3.6). These results are analogous to experimental results seen in cyclic sulfamides; cyclic sulfamide **5a** (pK_a = 6.4)[3a,b] is approximately 3.7 pK_a units more acidic than its acyclic analogue **5b** (pK_a = 10.1).[11]



One other factor which may serve to lower the pK_a of the cyclic structure is the conformation of the aromatic ring in regard to the adjacent heteroatoms. In the acyclic compound the aromatic ring can adopt a conformation maximizing the interaction between the ring and the lone pairs on the heteroatoms. The constrained geometry of the cyclic structure might change this interaction, having a subsequent effect on the acidity of the compound.

It appears that this increase in acidity for the five-membered sulfamates is directly dependent on the amount of delocalization present between the lone pairs on the heteroatoms and the sulfur atom. This delocalization is directly effected by bond rotation and angle contraction going from **6a** to **6d**. This effect is reflected in the calculated N−S bond lengths for the neutral and anionic species of the four compounds which are as follows: (**6a**) 1.58, 1.52 Å; (**6b**) 1.60, 1.52 Å; (**6c**) 1.62, 1.53 Å; (**6d**) 1.65, 1.58 Å. As we change the conformation of the neutral species to provide for less and less delocalization, there is a corresponding increase in the N−S bond length. This inhibition of N−S delocalization has a direct effect on the acidity of the compound. We also see the expected shortening of the N−S bond length in the anion compared to the neutral compound resulting from an increase in N−S delocalization. Evidence for this type of delocalization has been determined by X-ray crystallography. Cotton and Stokely[12] reported the crystal structures of $(PhSO_2)_2NH$ and $(PhSO_2)_2N^-Na^+$ whose N−S bond lengths were 1.65 and 1.58 Å, respectively.

Similar arguments were suggested by King[5] to explain the acidity of a variety of sulfonamides. Laughlin[13] and co-workers also cited this effect to explain the basicity of *N,N*-dialkyl sulfonamides. King[14] also pointed to stereoelectronic effects of this type to explain the conformation and reactivity of sultones.

This delocalization has been considered for a number of similar compounds. Lipscomb[15] and co-workers' study of the rotational barriers in $(CH_3)_2NSO_2N(CH_3)_2$ suggested that interactions of the nitrogen lone pair and sulfur d-orbital has a profound effect on the conformations and rotational barriers of these compounds. Jennings and Spratt[16] came to similar conclusions for $ClSO_2NR_2$ and related compounds. By analogy it appears that there is a similar effect for the neutral sulfamates.

The effect of this d-orbital interaction involving anions next to a sulfonyl group is a source of some controversy. Wolfe[17] and co-workers have completed theoretical studies on carbanions adjacent to sulfur centers and suggested that these d-orbitals may indeed play some role in the stabilization of these compounds. In contrast, Streitwieser[18] has completed theoretical studies on the anion of dimethyl sulfone which suggested that the d-orbital interaction plays little role in the stabilization of the anion next to sulfonyl sulfur. Most recently,[19] Streitwieser has reported a study of the acidities of dimethyl sulfide, sulfoxide, and sulfone. They concluded that the relative acidity is inherent in the acid and is not dependent on charge delocalization within the anion.

Conclusion. The reactions of nucleophiles with **1b** did not prove totally analogous to those reaction with **1a**. The addition of the nitro group, making the conjugate base of **2b** a better leaving group, seems to have changed the reactivy of the exocyclic (tosyl) sulfur atom. Nitrogen nucleophiles, as well as fluoride ion, attack the tosyl sulfur atom and cleave the tosyl moiety, whereas hydroxide ion attacks the endocyclic sulfur atom and opens the ring. The selectivity between these two sulfur atoms remains unexplained.

The cyclic sulfamates **2a−h** have proven to be quite acidic in comparison to their acyclic analogues. This effect is analogous to that seen in sulfamides, sulfonamides, and disulfonamides. *Ab initio* studies of a simple sulfamate model suggest that the increase in acidity may arise from stereoelectronic effects which are controlled by the geometry of the system.

Experimental Section

General Methods. Melting points were determined in capillary tubes and are uncorrected. NMR spectra were obtained at 360 MHz for ^1H and at 90.6 MHz for ^{13}C on a Bruker spectrometer. All samples are in acetone−d_6 unless otherwise noted and are reported in parts per million from internal TMS. Mass spectra were obtained on a Hewlett Packard Model 5988−A GC/MS quadrupole spectrometer. IR spectra were obtained on a Nicolet model 205 FT spectrometer. Solvents were purified and dried via standard techniques.

Computational Methods. *Ab intio* calculations were carried out using Spartan (version 1.0.3) on a Silicon Graphics workstation with all compounds being optimized (applying constraints where necessary) at the HF/3-21+G* level.

Hammett Plots. The Hammett plots were constructed using the Least Squares 1.0 program, as well as DeltaGraph (version 2.0.2). Hammett σ values were obtain from ref 7.

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Acidity Measurements. Experimental pK_a values were obtained by potentiometric titration as outlined in Albert and Serjeant.[6] The pK_a values were determined in 60% v/v ethanol/water mixtures, primarily due to the low solubility of the compounds in water. The samples were typically run at 0.01 M concentrations (0.25 mmol in 25 mL) and titrated with 0.1 N NaOH (standardized with KHP) at 25° C. The measurements of pH were taken at nine intervals from 10–90% ionization.

Known Starting Materials. The syntheses of **1a–f** have been previously reported.[2] Compound **1h** was synthesized by similar methods: treatment of 3′-*N*-(2′-hydroxynaphthyl)-4-toluenesulfonamide with triethylamine and sulfuryl chloride. Compound **1g** was isolated as a product in the synthesis of **1e**.

Reaction of 1b with Imidazole. A solution of imidazole (0.050 g, 0.730 mmol) in H_2O (2 mL) was added to a solution of **1b** (0.135 g, 0.365 mmol) in acetonitrile (10 mL). The solution was stirred at room temperature for 30 min. The solvent was evaporated and the residue was triturated with $CHCl_3$ (10 mL) and filtered. The organic layer yielded *p*-toluenesulfonyl imidazole (0.072 g, 89%), whose mp, IR, and ^{1}H NMR spectra matched those in the literature. The bright yellow solid, removed by filtration, was dissolved in H_2O (10 mL), and the solution was acidified with 6 N HCl. The aqueous solution was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried over magnesium sulfate and evaporated to yield **2b** (0.054 g, 69%): mp 147–50 xa1C dec; MS *m*/*z* 216 (M^+); IR (KBr) 3272 (NH, sharp), 1600, 1525 (NO_2), 1475, 1430, 1375, 1345 (NO_2, SO_2), 1230, 1220, 1180 (SO_2); ^{1}H NMR δ 8.08 (dd, 1H, *J* = 2.5, 8.5 Hz), 8.00 (d, 1H, *J* = 2.5 Hz), 7.25 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR δ 108.5, 112.2, 120.0, 131.3, 145.5, 147.2. Anal. Calcd for $C_6H_4N_2O_5S$: C, 33.34; H, 1.87; N, 12.96. Found: C, 33.30; H, 1.89; N, 12.92.

Reaction of 1b with Benzylamine. Benzylamine (0.040 mL, 0.260 mmol) was added to a solution of **1b** (0.050 g, 0.135 mmol) in acetonitrile (10 mL). The solution was stirred at room temperature for 30 min. The solvent was evaporated and the residue triturated with $CHCl_3$ (15 mL) and filtered. Removal of the $CHCl_3$ yielded *N*-benzyl-*p*-toluenesulfonamide (0.031 g, 88%) whose mp and ^{1}H NMR spectra matched those in the literature. The undissolved solid was dissolved in H_2O and acidified with 6 N HCl and extracted with $CHCl_3$ (3 × 10 mL). Removal of the $CHCl_3$ yielded **2b** (0.025 g, 86%).

Reaction of 1b with *t*-Butylamine. An analogous reaction to the one with benzylamine was carried out with **1b** (0.100 g, 0.270 mmol) and *tert*-butylamine (0.057 mL, 0.540 mmol). Workup yielded **2b** (0.031 g, 53%). The *N*-*tert*-butyl-*p*-toluenesulfonamide was not isolated.

Reaction of 1b with Pyridine. An analogous reaction was carried out using **1b** (0.050 g, 0.135 mmol) and pyridine (0.011 mL, 0.135 mmol). The reaction was stirred for 24 h with only starting material detected by TLC.

Reaction of 1b with Sodium Azide. An analogous reaction was carried out using **1b** (0.100 g, 0.270 mmol) in acetonitrile (5 mL) and sodium azide (0.018 g, 0.260 mmol) in H_2O (1 mL). The reaction was complete in 15 min. Similar workup, using acetone in place of chloroform, yielded *p*-toluenesulfonyl azide, whose mp and ^{1}H NMR matched those in the literature. The reaction also yielded **2b** (0.052 g, 93%).

Reaction of 1b with Potassium Fluoride. An analogous reaction was carried out using **1b** (0.100 g, 0.270 mmol) in acetonitrile (5 mL) and potassium fluoride (0.018 g, 0.260 mmol) in H_2O (1 mL). The reaction was complete in 12 h. Workup yielded *p*-toluenesulfonyl fluoride, whose mp and ^{1}H NMR matched those in the literature. The reaction also yielded **2b** (0.045 g, 81%).

Reaction of 1b with Sodium Hydroxide. A solution of sodium hydroxide (6.4 mg, 0.16 mmol) in H_2O (2 mL) was added to **1b** (0.058 g, 0.16 mmol) in acetonitrile (10 mL), and the mixture was stirred at room temperature for 2 h. The solution was acidified with 6 N HCl and extracted with chloroform (3 × 5 mL) which upon removal of the solvent yielded **2b** (2 mg, 6%). The aqueous layer was then extracted with diethyl ether (3 × 5 mL); concentration of the organic solution yielded **3** (0.045, 92%) whose mp, IR, ^{1}H NMR, and ^{13}C NMR matched those previously reported.[2]

Synthesis of 2a,c–h. The compounds **2a,c–h** were synthesized by methods analogous to the reactions of **1b** with sodium azide or potassium fluoride as mentioned above. The IR spectra for the compounds below all showed the characteristic absorption bands of the cyclic sulfamate ring, most notably the single sharp NH stretch around 3200 cm^{-1}.

3*H*-1,2,3-Benzoxathiazole 2,2-dioxide (2a): mp 76–79 °C dec; MS *m*/*z* (relative intensity) 171 (35, M^+), 106 (6), 79 (100); ^{1}H NMR δ 7.07 (m, 5H); ^{13}C NMR δ 111.4, 113.5, 124.3, 124.9, 129.1, 143.6. Anal. Calcd for $C_6H_5NO_3S$: C, 42.10; H, 2.94; N, 8.18. Found: C, 41.91; H, 3.04; N, 8.02.

3*H*-5-Methyl-1,2,3-benzoxathiazole 2,2-dioxide (2c): mp 99–100 °C dec; MS *m*/*z* (relative intensity) 185 (37, M^+), 93 (100); ^{1}H NMR δ 2.31 (s, 3H), 6.93(dd, 1H, *J* = 2, 8 Hz), 6.96 (d, 1H, *J* = 2 Hz), 7.11 (d, 1H, *J* = 8 Hz); ^{13}C NMR δ 21.1, 111.4, 114.0, 124.3, 130.8, 135.8, 142.0. Anal. Calcd for $C_7H_7NO_3S$: C, 45.40; H, 3.81; N, 7.56. Found: C, 45.40; H, 3.84; N, 7.44.

3*H*-5-Bromo-1,2,3-benzoxathiazole 2,2-dioxide (2d): mp 178–181 °C dec; MS *m*/*z* (relative intensity) 251 (34, M^+), 249 (35), 159 (37), 157 (44), 78 (100); ^{1}H NMR δ 7.23 (d, 1H, *J* = 8.6 Hz), 7.30 (dd, 1H, *J* = 2.1, 8.6 Hz), 7.33 (d, 1H, *J* = 2.1 Hz); ^{13}C NMR δ 113.1, 115.8, 117.0, 126.1, 131.9, 142.3. Anal. Calcd for $C_6H_4BrNO_3S$: C, 28.82; H, 1.61; N, 5.60. Found: C, 28.73; H, 1.55; N, 5.44.

3*H*-5-Chloro-1,2,3-benzoxathiazole 2,2-dioxide (2e): mp 168–170 °C dec; MS *m*/*z* (relative intensity) 207 (79, M^+), 205 (32), 113 (100), 111 (34); ^{1}H NMR δ 7.27 (d, 1H, *J* = 8.9 Hz), 7.19 (d, 1H, *J* = 2.1 Hz), 7.14 (dd, 1H, *J* = 8.9, 2.1 Hz); ^{13}C NMR δ 113.1, 113.5, 123.6, 130.3, 131.9, 142.3. Anal. Calcd $C_6H_4ClNO_3S$: C, 35.05; H, 1.96; N, 6.81. Found: C, 35.00; H, 2.01; N, 6.80.

3*H*-6-Nitro-1,2,3-benzoxathiazole 2,2-dioxide (2f): mp 200–202 °C dec; MS *m*/*z* 216 (M^+); ^{1}H NMR δ 7.33 (d, 1H, *J* = 9.4 Hz), 8.16 (m, 2H); ^{13}C NMR δ 107.5, 111.7, 112.9, 135.9, 141.8, 143.1. Anal. Calcd for $C_6H_4N_2O_5S$: C, 33.34; H, 1.87; N, 12.96. Found: C, 33.40; H, 1.76; N, 12.99.

3*H*-5,6-Dichloro-1,2,3-benzoxathiazole 2,2-dioxide (2g): mp 177–181 °C dec; MS *m*/*z* (relative intensity) 241 (27, M^+), 239 (37), 149 (59), 147 (100), 112 (75). ^{1}H NMR δ 7.59 (s, 1H), 7.39 (s, 1H); ^{13} C NMR δ 113.6, 114.3, 123.2, 128.2, 130.2, 141.9. Anal. Calcd for $C_6H_3Cl_2NO_3S$: C, 30.02; H, 1.26; N, 5.84. Found: C, 29.94; H, 1.32; N, 5.77.

3*H*-1,2,3-Naphtho[2,3-*d*]oxathiazole 2,2-dioxide (2h): mp 167–170 °C dec; MS *m*/*z* (relative intensity) 221 (15, M^+), 129 (93), 102 (100); ^{1}H NMR δ 7.47 (m, 2H), 7.53 (s, 1H), 7.72 (s, 1H), 7.88 (m, 2H); ^{13}C NMR δ 107.8, 108.9, 125.9, 126.5, 127.6, 128.2, 130.0, 130.1, 131.4, 143.0. Anal. Calcd for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19; N, 6.33. Found: C, 54.38;, H, 3.15; N, 6.38.

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Supplementary Material Available: Cartesian coordinates for compounds **6a–d** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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