PART 1

B-LACTAM CARBANIONS

PART 11

THE REACTIONS OF SULFOXIDES WITH ALKYLLITHIUMS

by

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A THESIS SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR M.Sc. IN CHEMISTRY

ABSTRACT

PART 1

A number of β-lactams were converted to a variety of 3-derivatives by the condensation of carbonyl compounds with β-lactam carbanions. A method for the N-alkylation of β-lactams and a 1,2 carbanion rearrangement of β-lactams to yield five or seven numbered rings is also described.

PART 11

The results of a number of reactions of racemic and optically active sulfoxides with alkyllithiums are presented. A number of mechanisms to explain the reactions of sulfoxides with alkyllithiums are considered and critically evaluated in the light of the results.

ACKNOWLEDGEMENTS

The author wishes to express his sincere gratitude to the following:-

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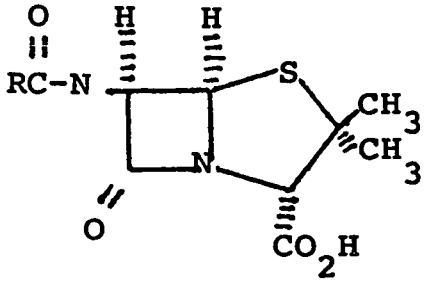
PART 1

β-LACTAM CARBANIONS

INTRODUCTION

Interest in β-lactams is derived from the fact that they comprise part of the skeleton of both penicillins 1 and cephalosporins 2, two classes of compounds which have long been known to show antibacterial action.



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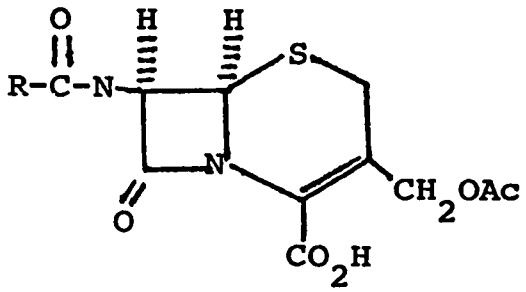


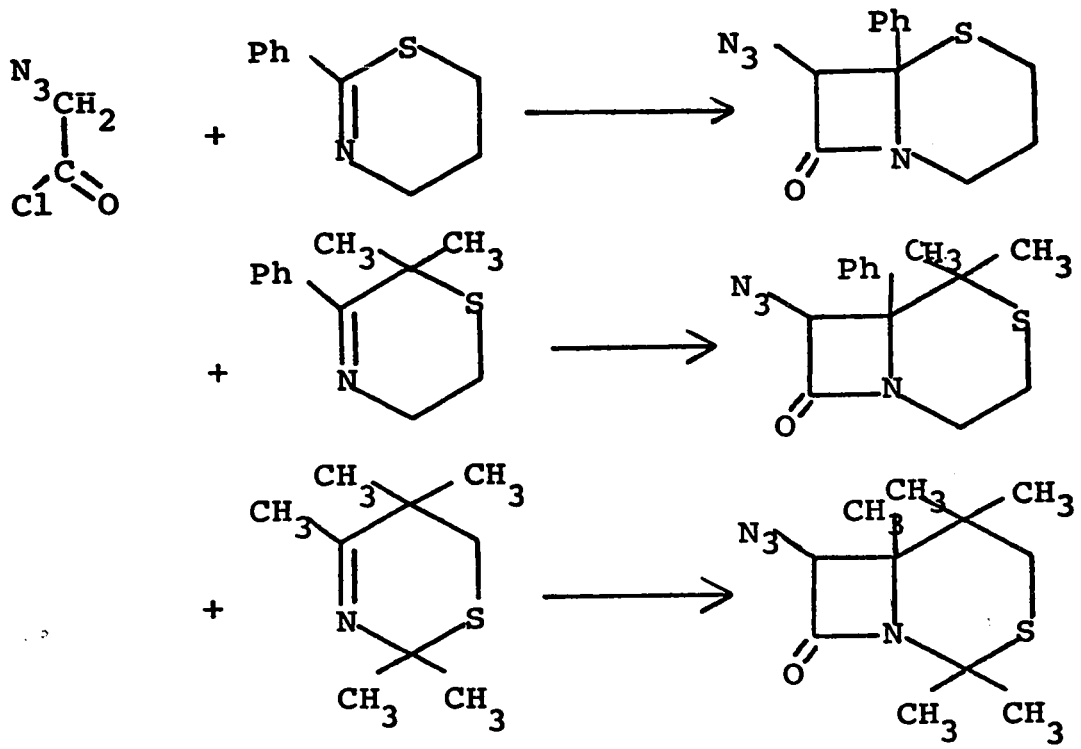
2

Much effort has been spent in the past in producing semisynthetic penicillins by acylating 6-aminopenicillanic acid with various acids with the hope of obtaining materials having enhanced therapeutic properties and fewer adverse effects than the naturally produced penicillins.

Only recently has attention been given to the synthesis of compounds in which the substitution pattern in the thiazolidine or thiazoline ring is different from

that of 1 or 2 with the hope that some of these compounds may have interesting antibiotic properties.

For example, Bose and co-workers (1) have reported the synthesis of the three isomers of the cepham ring system, the 6,4 fused ring system of the cephalosporins. The synthesis was carried out by reacting the appropriate thiazane with azidoacetyl chloride in methylene chloride in the presence of triethylamine.

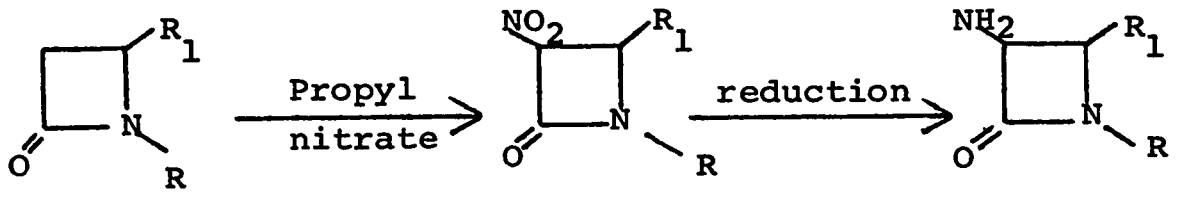


This route has the desirable feature of introducing the required nitrogen substituent in the cyclization step but suffers from very low yields unless the imine double bond is fully substituted.

Recently, in these laboratories, Boucher (2) was able to prepare the unsubstituted "cepham" ring isomer 3, by the approach outlined in Scheme 1. Since this route does not provide for the required nitrogen function α to the carbonyl group, it became the purpose of this work to investigate the feasibility of introducing such a substituent at some stage of the scheme.

It was hoped to accomplish the introduction of a nitrogen substituent via a β-lactam carbanion, for example, as outlined in equation 1.

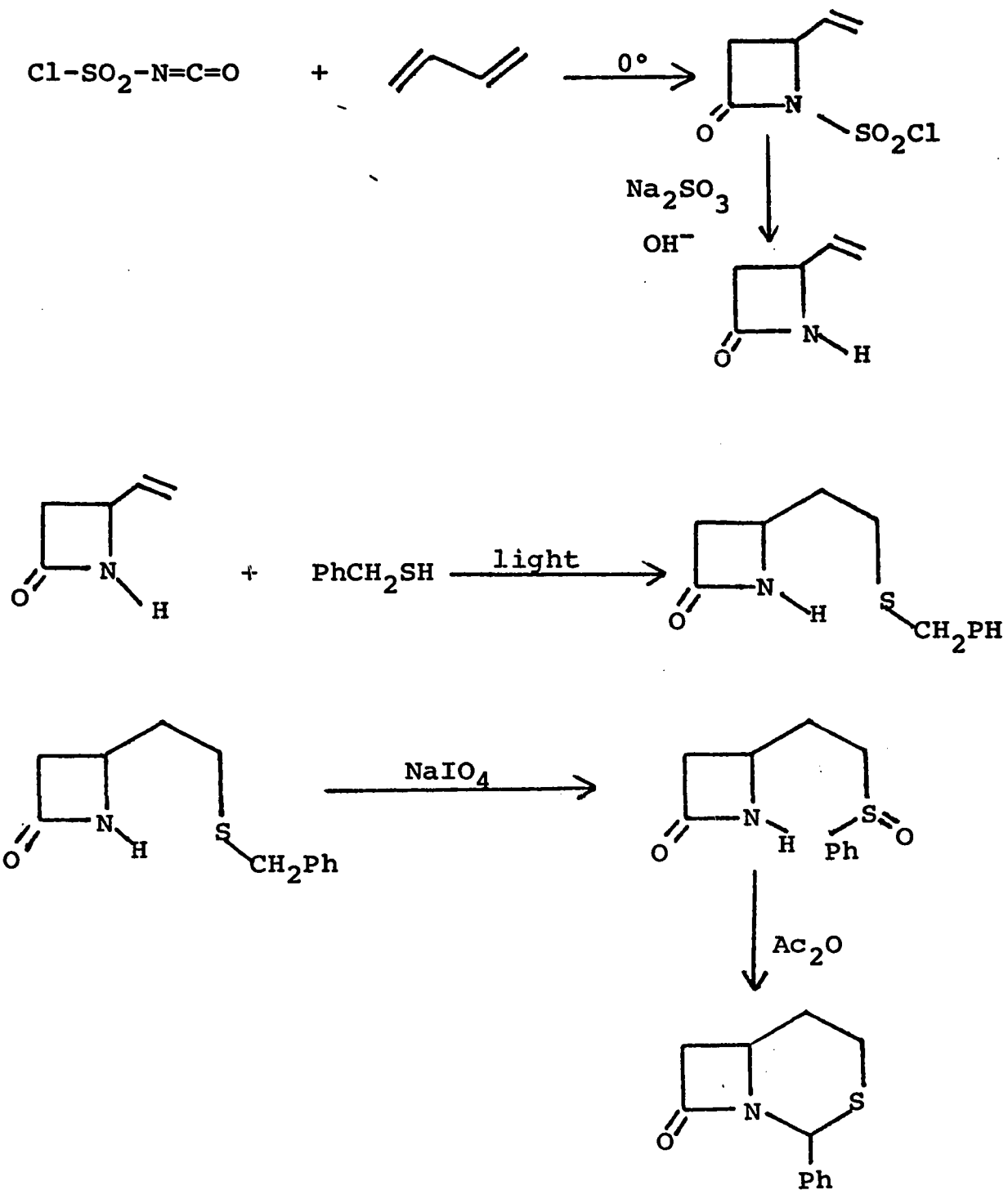
[1]



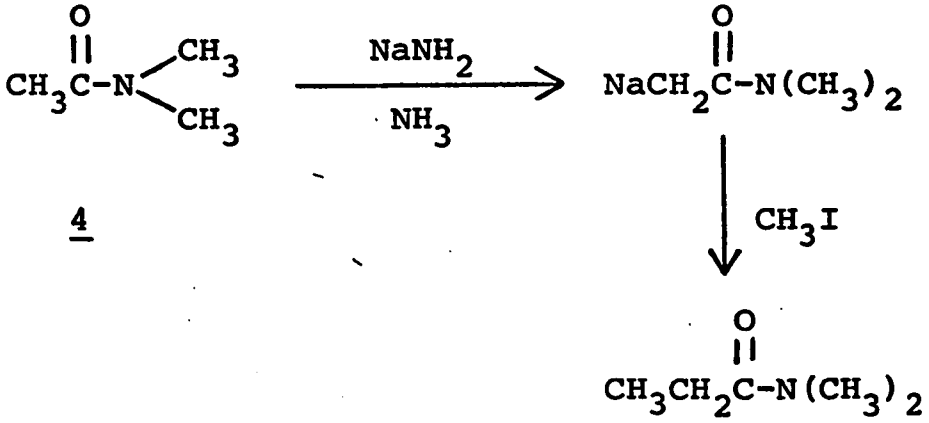
Conversion of the acid attainable by quenching the carbanion with carbon dioxide via the acyl azide to the desired amine was also considered a possibility. Success in preparing the required carbanions was considered highly likely in view of the previously published work which is discussed below.

A number of authors have reported that the interaction of N,N-disubstituted alkyl amides, for example 4, with strong bases such as sodium amide (3), n-butyllithium (4), or lithio S-trithiane (5) led to carbanions which

Scheme 1


Cl-SO2-N=C=O
+
0°
SO2Cl
Na2SO3
OH⁻
PhCH2SH
light
CH2PH
NaIO4
Ph
Ac2O

could be alkylated with a variety of alkyl halides or condensed with carbonyl compounds.

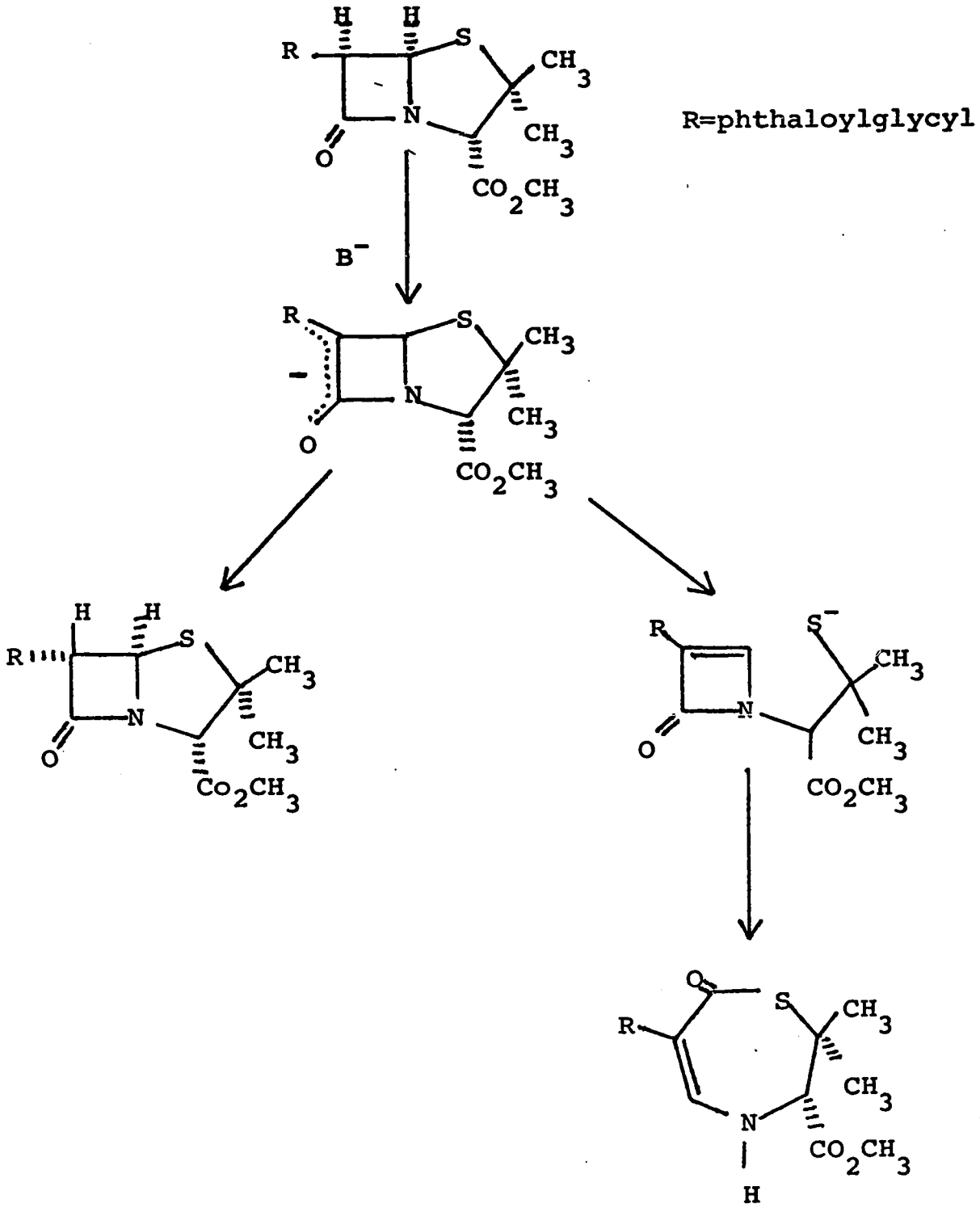


4

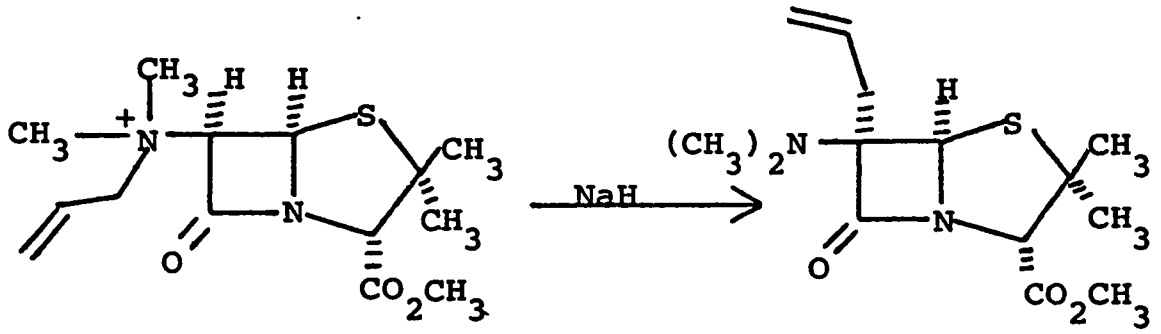
The formation of β-lactam carbanions in the penicillin and cephalosporin series has been investigated by a number of groups (6). In these examples, two types of reactions have generally been observed: epimerization of the naturally occurring cis β-lactam to the more stable trans configuration and β-elimination of the thiolate moiety followed by further rearrangements. See Scheme 2. The bases used to initiate these reactions were triethylamine (a,c,d,h), sodium hydroxide (f,g), sodium hydride (e) and potassium t-butoxide (i).

Two recent reports have shown the synthetic potential of β-lactam carbanions. The first, by Kaiser, Ashbrooke, and Baldwin (7), showed that treatment of the allyldimethylammonium salt 5 with sodium hydride resulted

Scheme 2

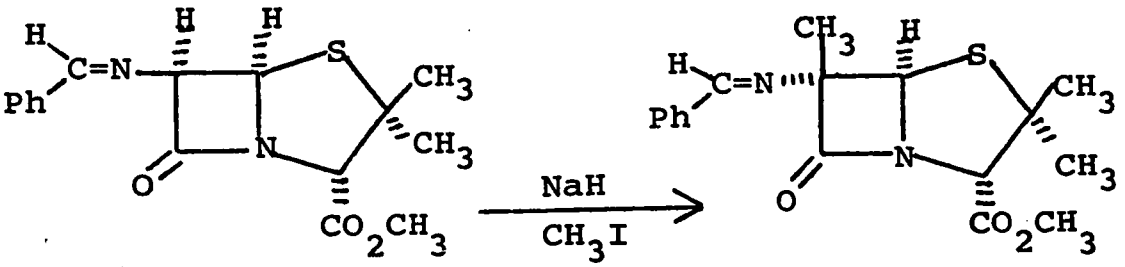


in the intramolecular migration of the allyl group from nitrogen to carbon thereby forming 6.

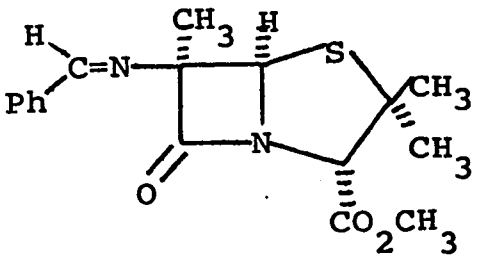


5 6

More pertinent to the work to be discussed later are the results of Bohme (8) who was able to transform methyl N-benzylidene-6-aminopenicillanate 7 into a mixture of the epimeric 6-methyl derivatives 8 and 9 upon reaction in sodium hydride followed by methyl iodide.

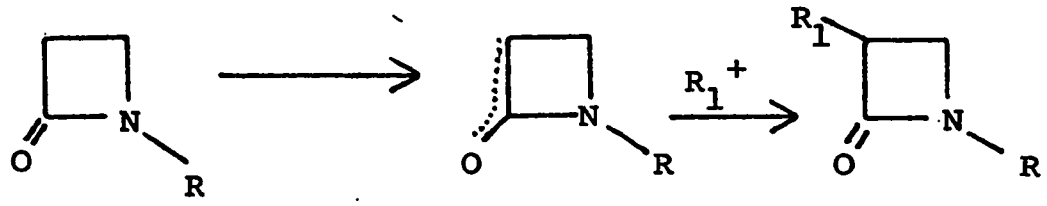


7 8 5%

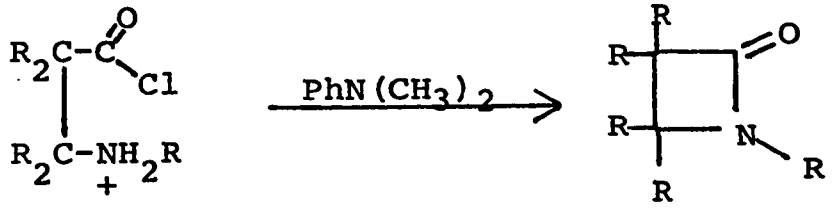


9 90%

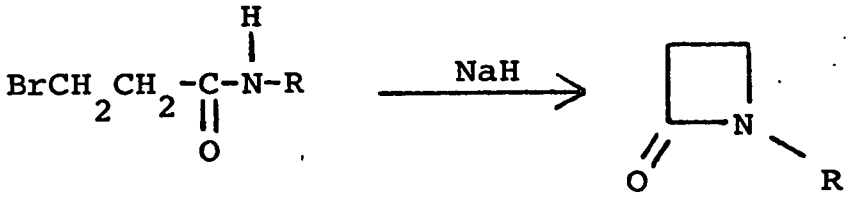
If β-lactam carbanions could be successfully prepared and reacted with a variety of electrophiles, a method would become available for the synthesis of a wide variety of rather complex β-lactams from some more readily available simple β-lactams.



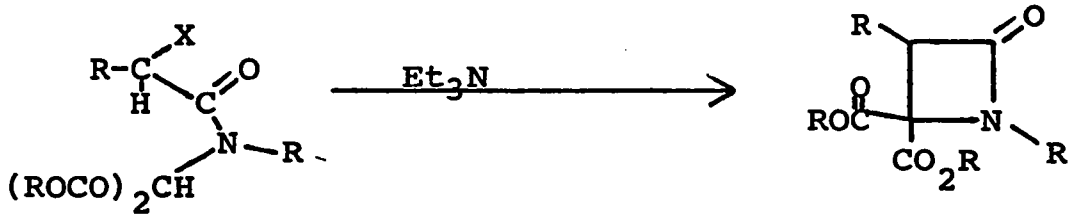
The methods of synthesis of β-lactams may be divided into two types: (a) cyclization of acyclic precursors and (b) cycloaddition reactions. Of the cyclization methods, that of Blicke (9) and Testa (10), reaction 2, is synthetically most useful.

[2] 

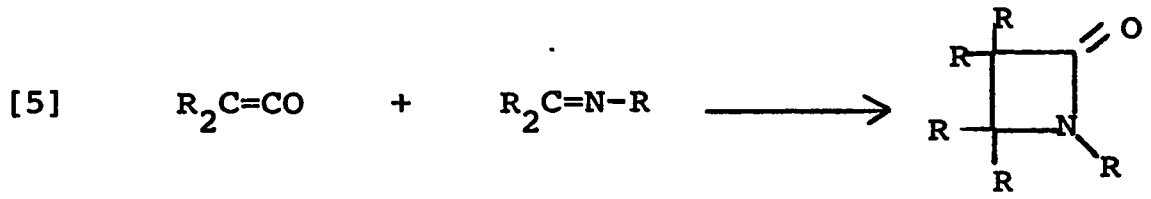
Blicke (9) also found it possible to cyclize β-bromopropionamides, reaction 3.

[3] 

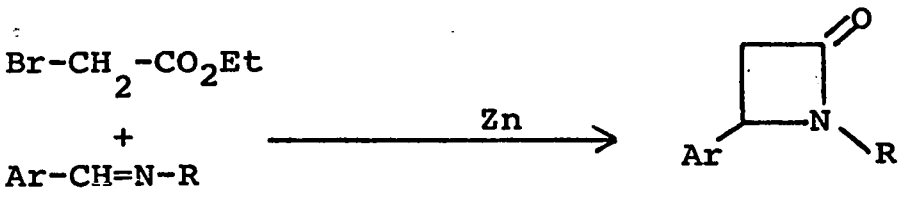
Ring closure at the C_3-C_4 bond was reported in 1950 by Sheehan (11) who was able to cyclize an α-haloacylamino-malonic ester, reaction 4.

[4] 

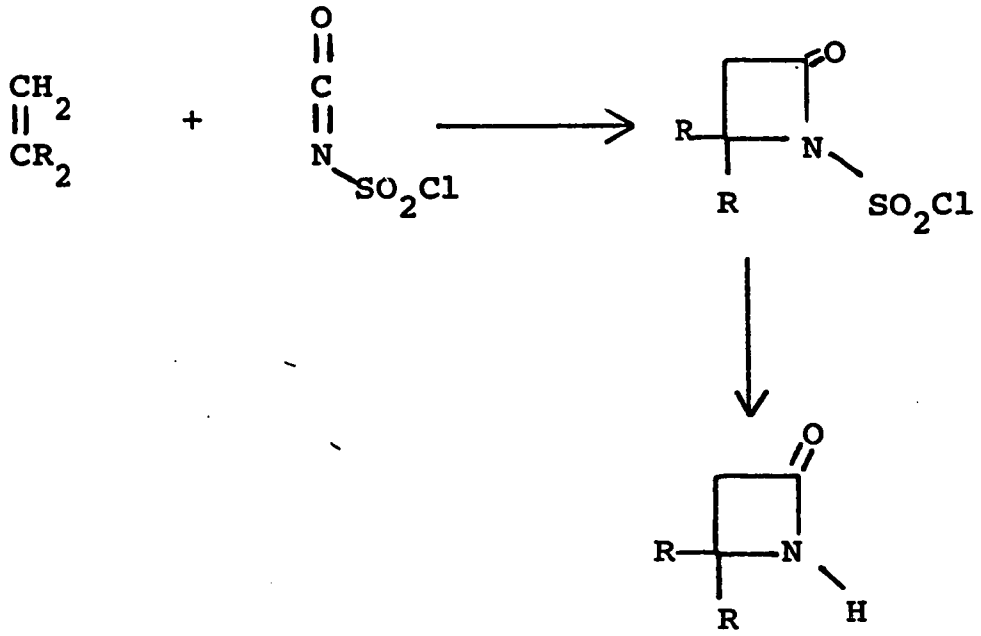
Staudinger (12) was the first to report the cycloaddition of a ketene to a Schiff base, reaction 5.

[5] 

More recently, Pfleger (13) prepared a number of β-lactams by this method. Gilman and Speeter (14) reported an anil and an α-bromoester under the conditions of the Reformatsky reaction yielded β-lactams, reaction 6.

[6] 

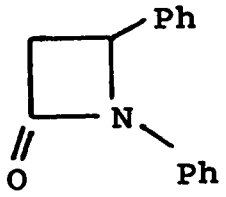
Graf (15) and Moriconi (16) have prepared β-lactams by the cycloaddition of chlorosulfonyl isocyanate to olefins, reaction 7.

[7] 

PART 1

RESULTS AND DISCUSSION

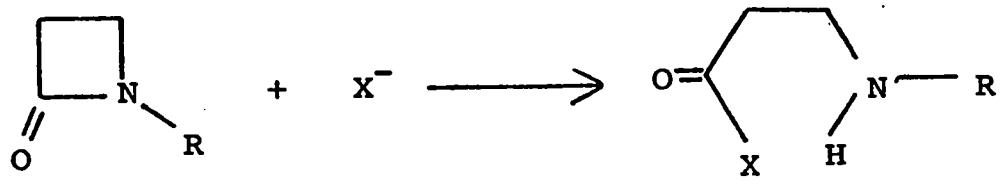
For initial investigations regarding the stability of β-lactam carbanions and their use in the preparation of 3-substituted derivatives, a compound readily available in quantity was most desirable. For this purpose, the β-lactam 10 was found to be suitable.



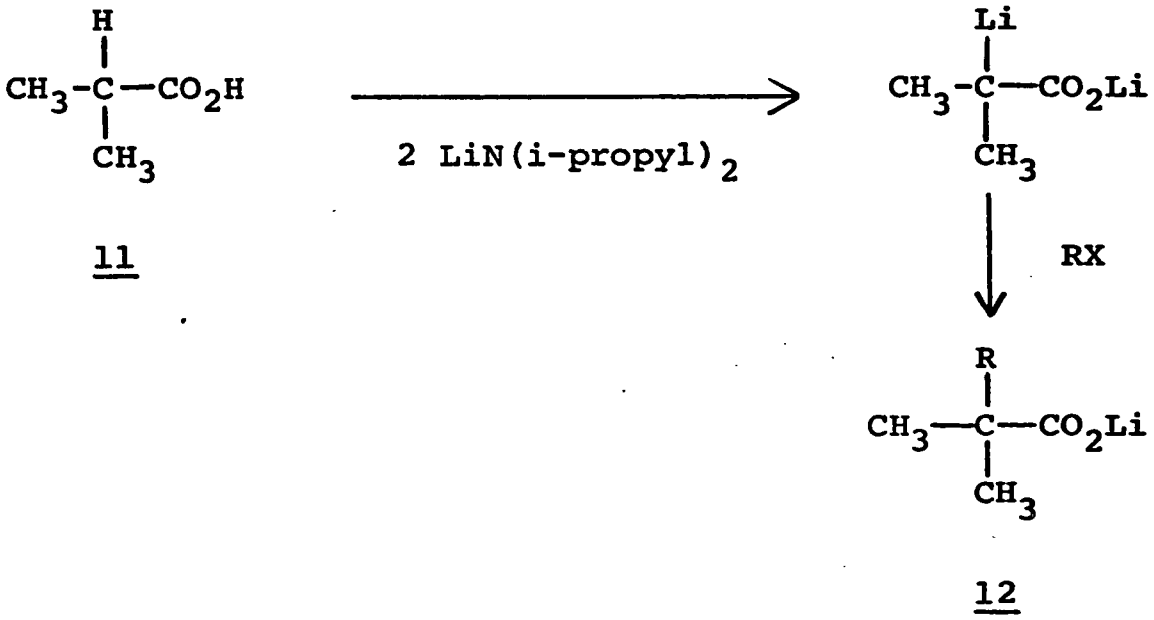
10

Compound 10 was prepared by the method of Gilman and Speeter (14) from ethyl bromoacetate and benzylidene aniline.

The choice of base for generation of the anions was important because β-lactams are known to be susceptible to nucleophilic attack at the carbonyl group and yield acyclic products.



A number of authors (17,18,19) have found lithium diisopropylamide to be of use when a strong base with low nucleophilicity is required for anion formation. Creger (17) found that treatment of isobutyric acid 11 with two equivalents of lithium diisopropylamide and subsequent reaction with an alkyl halide led to α-substituted acids, 12.



11

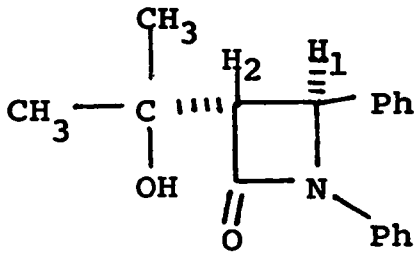
12

Previously, reaction of carboxylic acids with alkyllithiums had been shown to lead to ketones (20).

The carbanion reactions were carried out by addition of one equivalent of n-butyllithium to a tetrahydrofuran solution of diisopropylamine at -78°. The β-lactam was then added to this solution and after about thirty seconds an electrophile was added. The β-lactam

was added to the lithium diisopropylamide solution in order to minimize self condensation. The reactions were worked up by the addition of water and extraction of the solution with methylene chloride. The crude product was usually purified by preparative thin-layer chromatography (t.l.c.).

In this manner, 1,4-diphenyl-2-azetidinone[(a)], 10, was converted to its acetone derivative 13 in 58% yield.



13

Compound 13 was obtained as a white powder, m.p. 148-149.5°. The n.m.r. spectrum of 13 showed two singlets at 1.30 and 1.43 δ corresponding to the two methyl groups, a singlet at 1.85 δ due to the hydroxyl proton, and a multiplet over the range 6.94-7.46 δ due to the two phenyl groups. The proton H_1 occurred at 5.00 δ as a doublet, J=2.0 Hz. and H_2 appeared at 3.10 δ as a doublet with J=2.0 Hz. The i.r. spectrum showed a strong carbonyl band at 1730 cm^{-1} indicating the

(a) In I.U.P.A.C. nomenclature β-lactams are referred to as 2-azetidinones. Thus, 3-anilino-3-phenyl propionic acid β-lactam, 10, can be named 1,4-diphenyl-2-azetidinone.

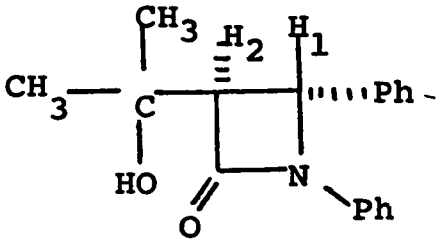
β-lactam ring was still intact. A coupling constant of 2.0 Hz. between H_1 and H_2 is indicative of trans stereochemistry. Kagan et al. (21) and others (22,23) have observed that J_{cis} is equal to about 6 Hz. and J_{trans} is equal to about 2 Hz. Construction of molecular models shows that the dihedral angle between H_1 and H_2 is close to 0° in the cis isomer and about 120° in the trans isomer.

Table 1 shows the 3-derivatives of 10 that were prepared.

Similarly, it was possible to convert 10 to its cyclohexanone derivative, 14, in 41% yield. Again, the i.r. spectrum indicated the β-lactam ring to be intact (C=O, 1760 cm^{-1}). The n.m.r. spectrum of 14 indicated a multiplet at 1.15-2.15 δ corresponding to the cyclohexane ring and the hydroxyl proton and 6.81-7.39 δ due to the two phenyl groups. Protons H_1 and H_2 appearred at 5.03 and 3.13 δ as doublets (J=2.0 Hz.) indicating the trans configuration at carbons 3 and 4.

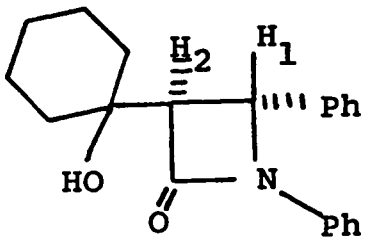
Conversion of 10 to its 3-benzoyl derivative 15 was carried out by reaction of the anion of 10 with methyl benzoate. The i.r. spectrum of 15 showed two carbonyls at 1740 (β-lactam) and 1670 cm^{-1} (aryl ketone). The n.m.r. spectrum showed a multiplet at 8.03-8.25 δ corresponding to the two aromatic protons ortho to the ketone carbonyl and a multiplet at 6.95-7.65 due to the 13 remaining aryl

Table 1. 3-Derivatives of 1,4-diphenyl-2-azetidinone (10)



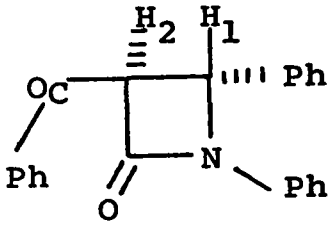
58%

13



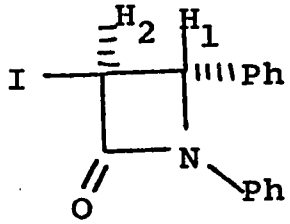
41%

14



61%

15



29%

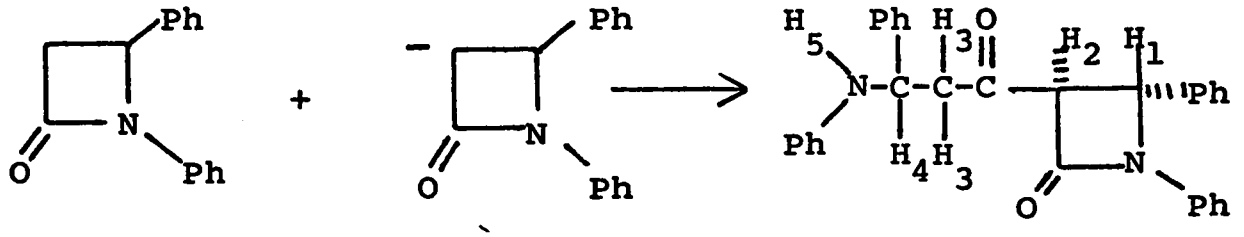
16

hydrogens. H_1 and H_2 occurred at 5.75 and 4.79 δ respectively and again $J_{12}=J_{21}=2.0$ Hz.

Compound 16, the 3-iodo derivative of 10 was prepared in 29% yield from the anion of 10 and iodine. The i.r. spectrum showed a strong carbonyl at 1755 cm^{-1}. The n.m.r. spectrum indicated a multiplet at 7.04-7.47 δ due to the aromatic protons and H_1 and H_2 appeared at 5.14 and 4.72 δ (J=2.0 Hz.). The mass spectrum contained the parent peak at m/e = 349. This derivative was of special interest since it was hoped a displacement of the iodide would yield a derivative with cis stereochemistry at carbons 3 and 4. However, all attempts to observe such a reaction were unsuccessful. Both azide (N_3-) and benzyl mercaptide ($PhCH_2S$-) failed to yield any products when heated for 7 hours at 90-100° in dimethylformamide. When the reactions were heated to higher temperatures, decomposition occurred. The inertness of 16 is not totally unexpected since earler attempts to displace chloride (24) or methane sulfonate (25) from the 6 position in penicillanates also were unsuccessful.

The poor yields of derivatives of 10 as indicated in Table 1 are due to the reaction of the anion of 10 with 10 itself to yield 17. It was found that 17 was always a biproduct in the formation of 3-derivatives of 10. Its yield was increased to 27% by allowing the anion of 10 to stir at room temperature for twenty minutes. The i.r.

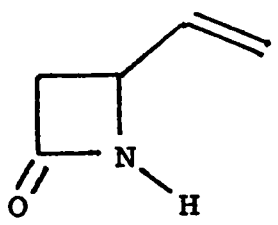
spectrum of 17 showed a weak band at 3380 cm^{-1} (N-H) and strong bands at 1740 (β-lactam C=O) and 1710 (ketone C=O).



17

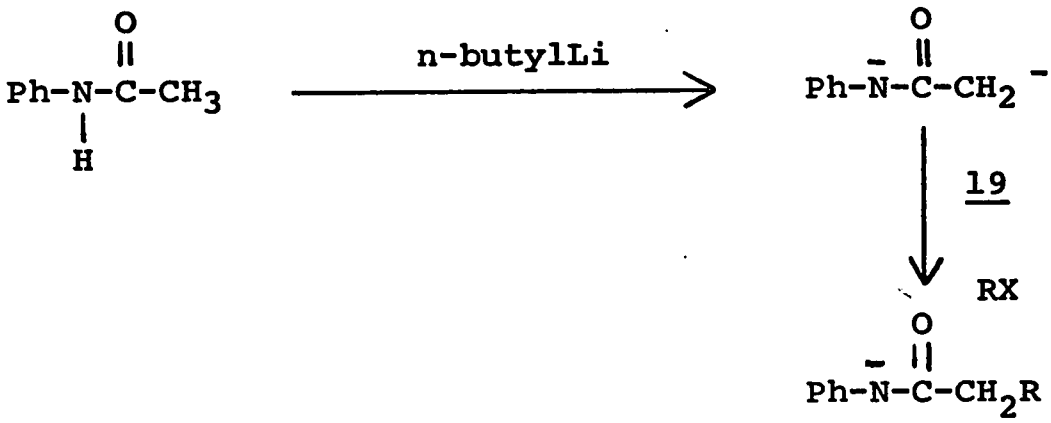
The mass spectrum showed the molecular ion at m/e = 446. The n.m.r. spectrum of 17 contained a multiplet at 2.78-3.48 δ, (H_3), a doublet at 4.57, J=2.5 Hz., (H_2), a multiplet at 4.72-5.08, (H_4), a doublet at 5.42, J=2.5 Hz. (H_1), a doublet at 6.06, J=7.5 Hz., (H_5), a doublet at 6.48 corresponding to the protons ortho and para to the nitrogen and a multiplet at 6.82-7.60 δ due to the remaining 17 aromatic protons.

Since this initial investigation proved that the β-lactam carbanions were reasonably stable, a number of other β-lactams were prepared. The 4-vinyl-2-azetidinone, 18, was prepared by the method of Moriconi (16) from chlorosulfonyl isocyanate and butadiene followed by reduction by the method of Durst and O'Sullivan (26).



18

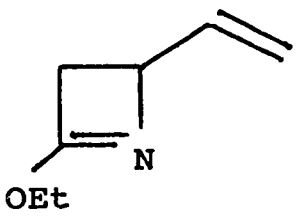
Introduction of a 3-substituent into 18 was of interest since the last step in the preparation of bicyclic β-lactams by the Boucher procedure required the presence of an N-unsubstituted β-lactam. The feasibility of this conversion was suggested by the work of Hauser et al. (27) who reported C-alkylation of acetanilide by quenching the dianion, 19, (generated by addition of two equivalents of n-butyllithium to acetanilide) with an alkyl halide.



However, reaction of 18 with 2.0 equivalents of lithium diisopropylamide and subsequent quenching with methyl iodide or acetone yielded no 3-substituted β-lactams. Only starting material was recovered (approximately 90% recovery). Since the C-alkylation of 18 was not successful, it was decided to further investigate the anion formation of a variety of N-substituted β-lactams.

The availability of a large variety of N-unsubstituted β-lactams via the chlorosulfonyl isocyanate-olefin

reaction required the development of a method for the N-alkylation of β-lactams of the type 18. Reaction of 18 with 1.0 equivalent of lithium diisopropylamide and subsequent quenching with methyl iodide gave no N-methylated material. An attempt was also made to convert 18 to its imino ether 20 by the use of Meerwein's reagent (28) but no product was obtained even though Paquette (29) has been able to isolate imino ethers of β-lactams. Attempted conversion of 18 to 21 using methyl trifluoromethane sulfonate also failed. The n.m.r. spectrum of a mixture of equimolar amounts of 18 and the sulfonate ester led to the disappearance of the sulfonate methyl absorption at 4.21 δ and the appearance of another singlet at 4.27 δ presumably due to the methyl of the imino ether.

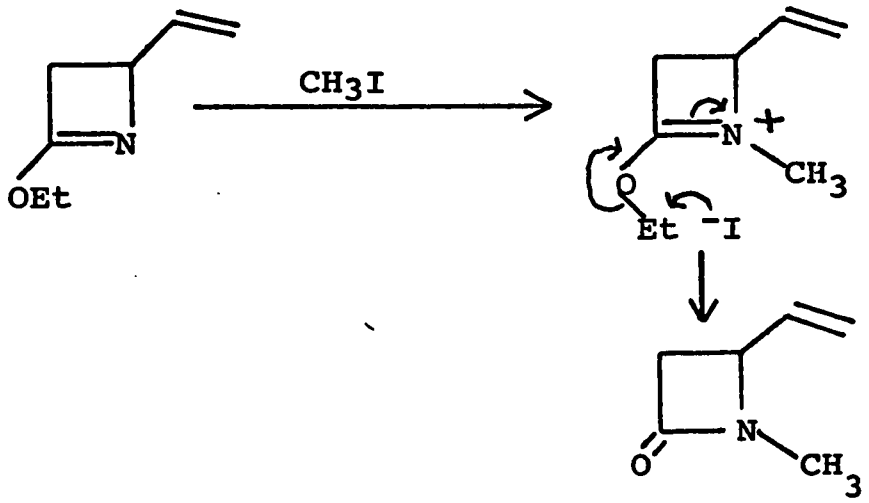


20

However, attempts to isolate 20 failed. It was hoped that treatment of the imino ether with methyl iodide prior to isolation would lead to the N-methylated derivative 21. Methyl iodide was chosen because it would be capable of methylating the nitrogen and the iodide might be basic

enough to remove the O-ethyl, reaction 8. This approach too was unsuccessful.

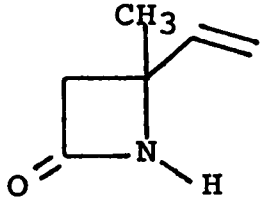
[8]



21

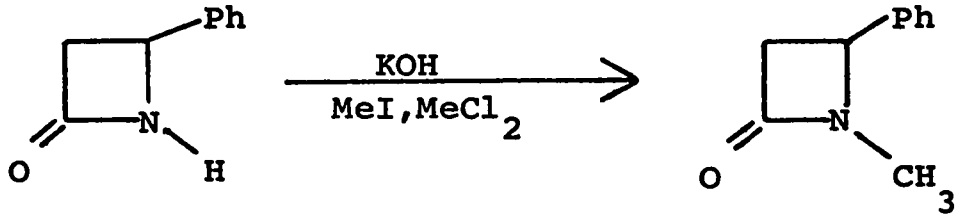
Methylation of 18 using methyl trifluoromethane sulfonate in the presence of bases such as calcium oxide, sodium bicarbonate, and triethylamine also failed.

Eventually it was found that 18 could be methylated in quantitative yields by the use of methyl iodide and potassium hydroxide. The reaction conditions consisted of mixing the β-lactam with 1-2 equivalents of methyl iodide and adding to this 1 equivalent of freshly powdered dry potassium hydroxide. After 10-15 minutes, methylene chloride was added and the precipitated salt filtered off. Evaporation of the solvent yielded pure product. This method was also applied to β-lactam 22 with similar results.



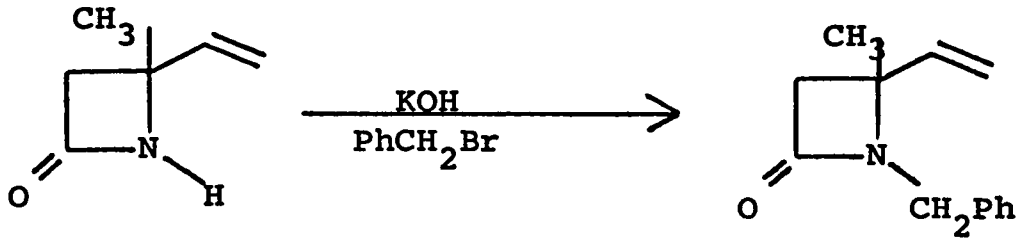
22

β-Lactam 23 was converted to 24 in 31% yield by the foregoing procedure with the exception that the reaction was carried out in methylene chloride.



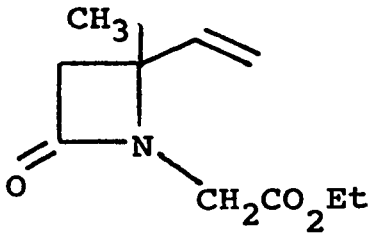
23 24

The alkylation reaction appeared to be successful for only the most reactive halides. Thus, β-lactam 22 could be converted to N-benzylated 25 in 49% yield.



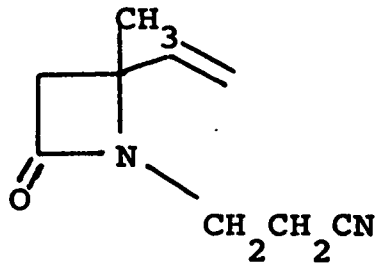
22 25

But reaction of 22 with ethyl bromoacetate failed to yield 26. This failure may have been due to the condensation of ethyl bromoacetate with itself.



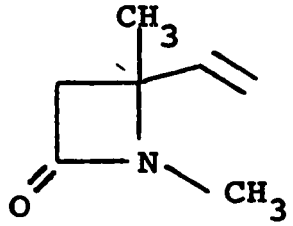
26

Reaction of 22 with acrylonitrile and potassium hydroxide in dioxane (30) afforded the cyanoethylated β-lactam 27 in 92% yield.



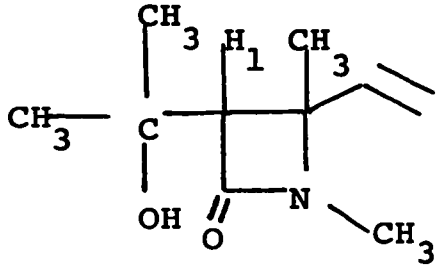
27

The N-methylated derivative of 22, β-lactam 28

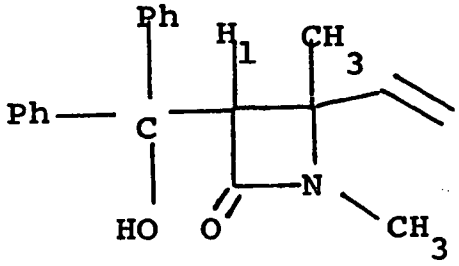


28

was converted to its acetone 29 and benzophenone 30 derivatives in 77 and 75% yield respectively.



29

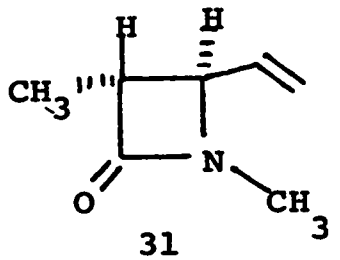


30

Compound 30 was isolated as a mixture of diasteriomers. This was determined from an n.m.r. spectrum of 30 which indicated two methyl peaks at 1.05 and 1.37 δ and two singlets attributable to H_1 at 2.81 and 3.05 δ. Compound 29 was presumably also a mixture of diasteriomers. No attempt was made to separate the mixtures. However, an attempt to convert 28 to its 3-n-butyl derivative by

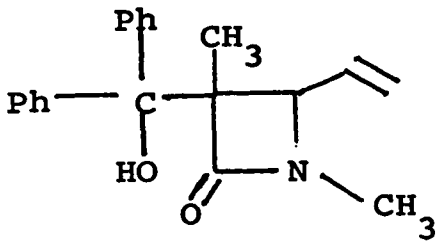
addition of n-butylbromide to the anion of 28 resulted only in recovered starting material.

But it was possible to convert β-lactam 21 to its 3-methyl derivative 31 in 59% yield. The n.m.r. spectrum



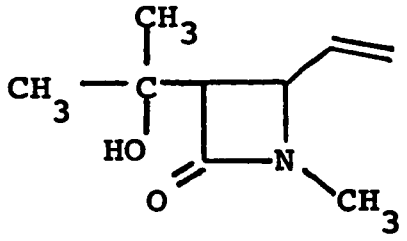
31

of 31 indicated the trans stereochemistry as shown. An attempt to epimerize 31 at C_3 by addition to one equivalent of lithium diisopropylamide and subsequent quenching with water yielded only 31 with retained stereochemistry. But quenching of the reaction mixture with benzophenone gave a 30% yield of β-lactam 32.



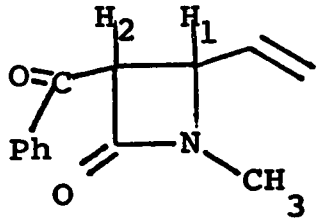
32

β-Lactam 21 was also converted to its acetone derivative, 33 in 80% yield.



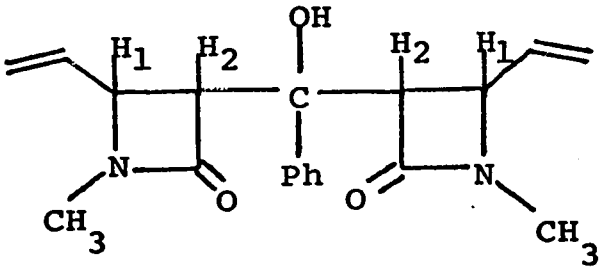
33

When the anion of 21 was quenched with methyl benzoate, a 28% yield of the expected product 34 resulted.



34

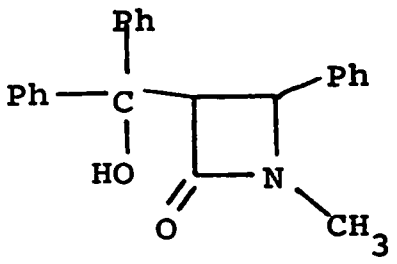
The i.r. spectrum of 34 showed strong bands at 1750 and 1680 cm^{-1}. The n.m.r. spectrum showed a singlet at 2.80 δ due to the N-methyl protons, a multiplet at 4.50-4.70 δ ascribed to H_1 and H_2, a multiplet at 5.24-6.00 δ corresponding to the vinylic protons, another multiplet at 7.91-8.24 δ due to the hydrogens ortho to the carbonyl and a 3 proton multiplet at 7.24-7.59 δ due to the three remaining aromatic protons. There also resulted a 50% yield of 35 which gave a molecular ion of m/e = 326.



35

The i.r. spectrum showed bands at 3580 and 3400 cm^{-1} (bonded and free OH) and a strong band at 1745 cm^{-1} (C=O). The n.m.r. spectrum showed 3 singlets in the range 2.42-2.75 δ corresponding to N-methyl protons, a hydroxyl singlet at 3.10, a multiplet in the range 3.48-4.00 due to H_1 and H_2, a 6 proton multiplet at 4.84-6.09 δ corresponding to vinylic protons and phenyl absorption at 7.09-7.60 δ. The compound melted over a broad range (128-151°) which is not unexpected since it contains five asymetric centres.

β-lactam 24, 1-methyl-4-phenyl-2-azetidinone, was converted to its benzophenone adduct 36 in 50% yield.

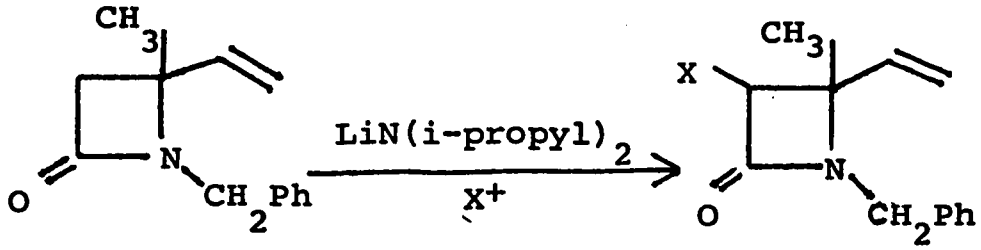


36

The N-benzylated β-lactam 25 was of special interest because it was hoped that 25 could be converted to a useful 3-derivative 37 by a carbanion reaction and that the N-benzyl group could be removed by hydrogenolysis to give an N-unsubstituted β-lactam 38 which could be subjected to the cyclization sequence in Scheme 1 and afford a bicyclic 7-substituted β-lactam 39. Scheme 3.

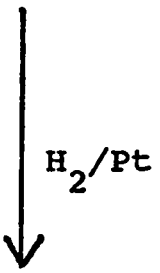
The attempted conversion of 1-benzyl-4-methyl-

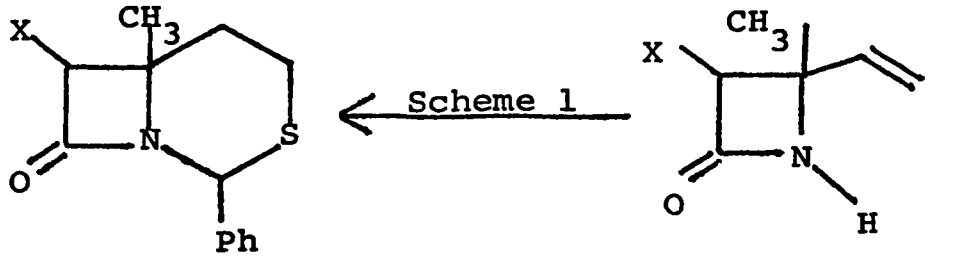
Scheme 3



25

37

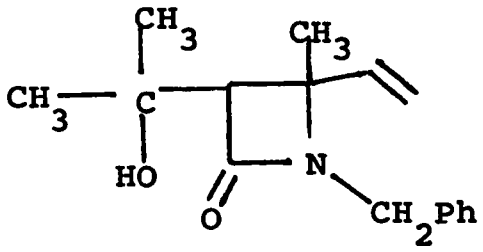




39

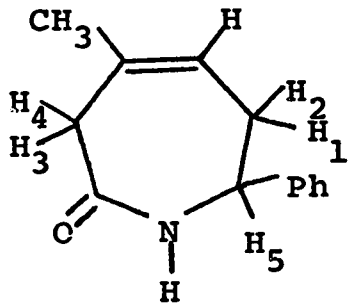
38

4-vinyl-2-azetidinone, 25, to its acetone derivative 40 failed.



40

Instead, a 35% yield of 41 was obtained.

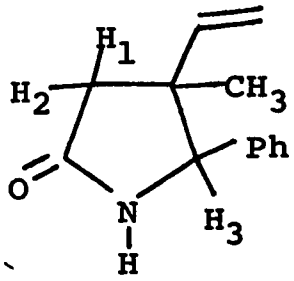


41

The mass spectrum of 41 indicated a molecular ion at m/e = 201. The i.r. spectrum indicated bands at 3400 cm^{-1} (N-H) and 1650 cm^{-1} (C=O). The n.m.r. spectrum showed a three proton singlet at 1.79 δ due to the methyl group, a multiplet at 2.20-2.90 δ corresponding to H_1, the proton H_2, and half the AB quartet corresponding to H_3 and H_4. The other half of the AB was situated at 3.70. The olefinic proton appeared at ~~4.85~~ 5.46 as a broad ~~multiplet~~ singlet and a broad ~~singlet~~ multiplet at ~~5.46~~ 4.85 δ was ascribed to H_5. The N-H appeared at 5.91 and the aromatic protons at 7.32 δ as a

singlet.

Another product was also obtained in 5% yield to which we have assigned structure 42.

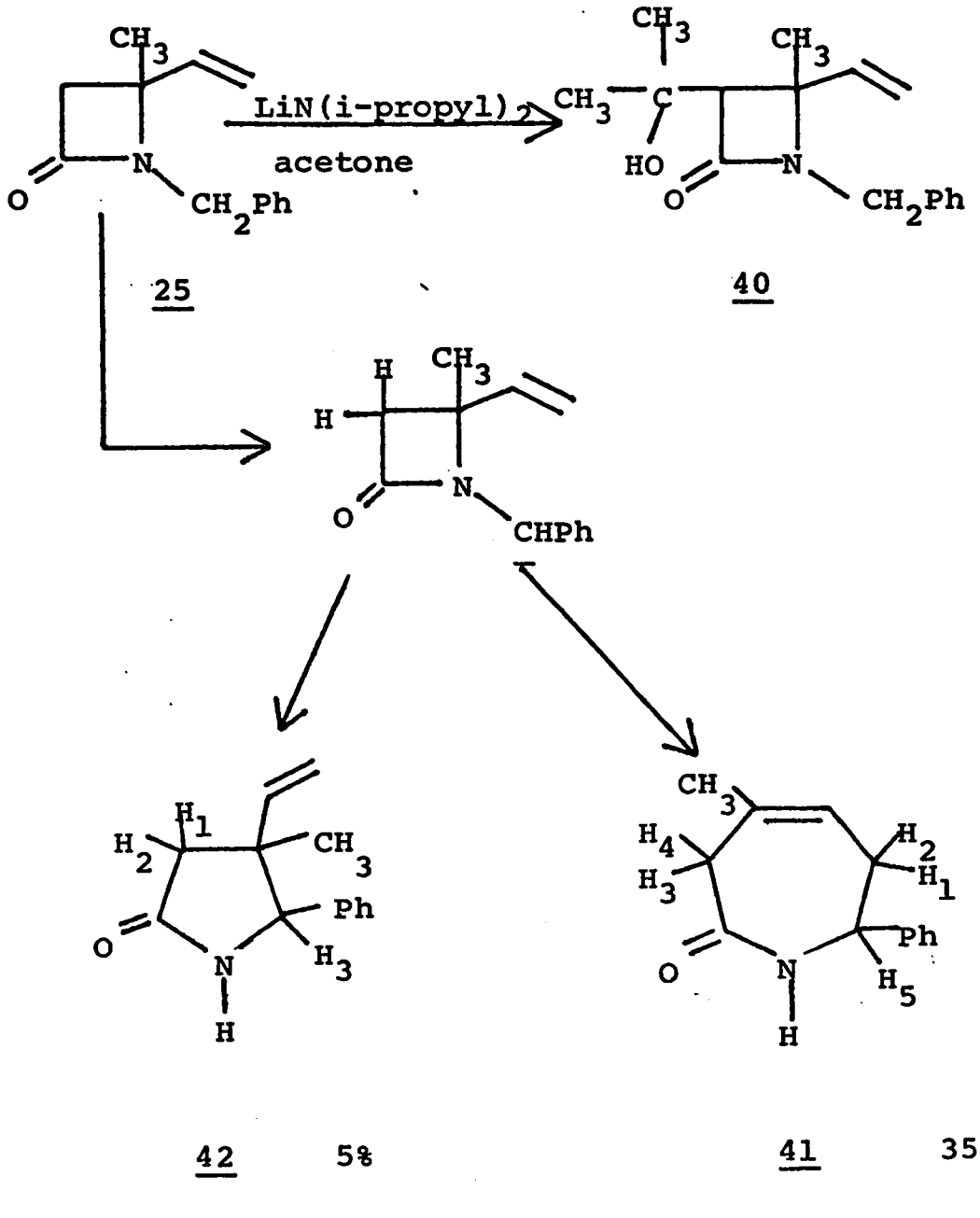


42

The i.r. spectrum of 42 showed the N-H at 3450 cm^{-1} and the carbonyl at 1700 cm^{-1}. The terminal vinyl group gave peaks at 1005, 920, and 1410 cm^{-1}. The n.m.r. spectrum of 42 showed two singlets at 0.73 and 1.35 δ due to the methyl group, an AB quartet situated at 2.40 δ corresponding to H_1 and H_2, and another pair of singlets at 4.46 and 4.59 due to H_3. The terminal vinyl absorption appeared at 4.74-5.50 δ, the N-H as a broad peak at 5.85-6.33 and the phenyl group as a multiplet at 7.01-7.45 δ.

The conversion of 25 to 41 and 42, Scheme 4, most likely occurs by a concerted mechanism. This rearrangement is similar to other 1,2 carbanion rearrangements such as those of Stevens and Wittig. However, whereas in the Stevens rearrangement the nitrogen undergoes a change of charge of +1 to 0, in the rearrangement of the N-benzyl lactam, the nitrogen acquires a negative charge. It is

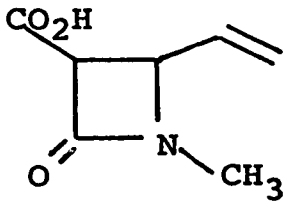
Scheme 4



most likely that the driving force for the reaction is relief of ring strain in going from a four membered to either a five or seven membered ring.

An attempt to observe another rearrangement of this type with 1-(2-cyanoethyl)-4-methyl-4-vinyl-2-azetidinone, 27, failed. It appeared that in this reaction elimination of the cyanoethyl group was preferred to rearrangement.

The reactions of β-lactam carbanions with either an alkyl nitrate or crushed dry ice failed to yield either of the expected products. Reaction of β-lactam 21 with propyl nitrate afforded only recovered starting materials. Reaction of the anion of 21 with carbon dioxide failed to yield the acid 43.

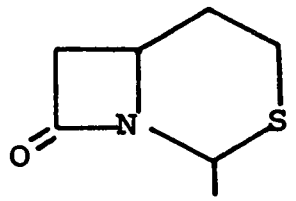


43

The failure to isolate 43 was probably due to the work-up procedure since Tin[a] found these acids to be quite soluble in water when he eventually prepared them.

(a) K. C. Tin. Private communication.

Attempted conversion of bicyclic β-lactam 3 to its acetone derivative failed.



3

Instead of the expected product, a white solid, m.p. 132-135°, that remains unidentified was obtained (compound 3 has a melting range of 101-104°). This compound seemed to exhibit two carbonyl frequencies (1720 and 1750 cm^{-1}) whereas the starting material showed only one carbonyl band at 1755 cm^{-1}. Other parts of the i.r. spectrum were different for the two compounds. The n.m.r. spectrum of the unknown material showed multiplets from 1-2 δ, 2-3.3 δ and 3.6-3.7, singlets at 5.00 and 7.25 δ and another multiplet at 7.30-7.40 δ. The peaks had an integration ratio of 67:149:16:14:114:26 which is almost 5:10:1:1:8:2. The highest peak in the mass spectrum of the material appeared at m/e = 219 which is the molecular weight of the starting material. The peaks in the mass spectrum of the unknown were quite different from those in the mass spectrum of the starting material.

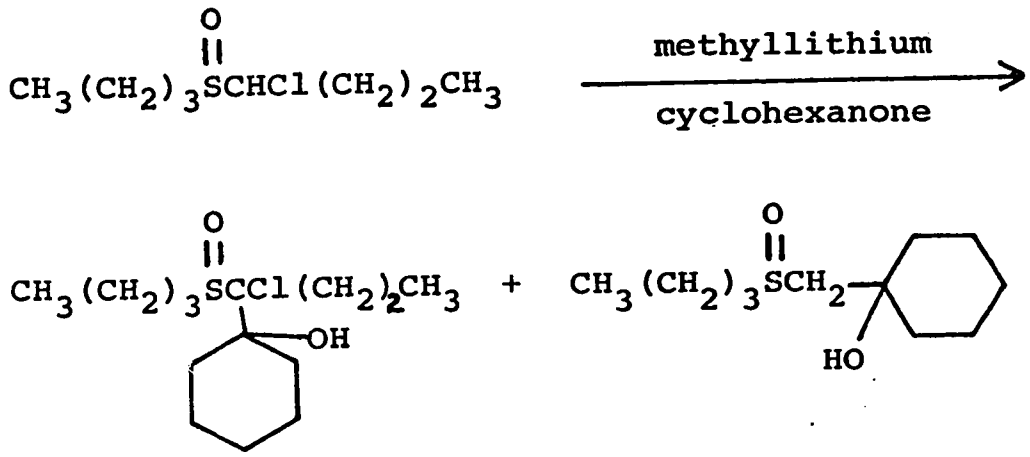
PART II

REACTIONS OF SULFOXIDES WITH ALKYLLITHIUMS

INTRODUCTION

Since Franzen (1) reported that the reaction of dimethyl sulfoxide with alkyllithiums resulted in exchange of alkyl groups, few workers have investigated this reaction.

Tin (2) has recently observed that the reaction of sulfoxides with alkyllithiums and subsequent quenching of the resulting carbanions with electrophiles yielded products arising from cleavage of the sulfoxide.



The two alkyl group exchange reactions shown above are

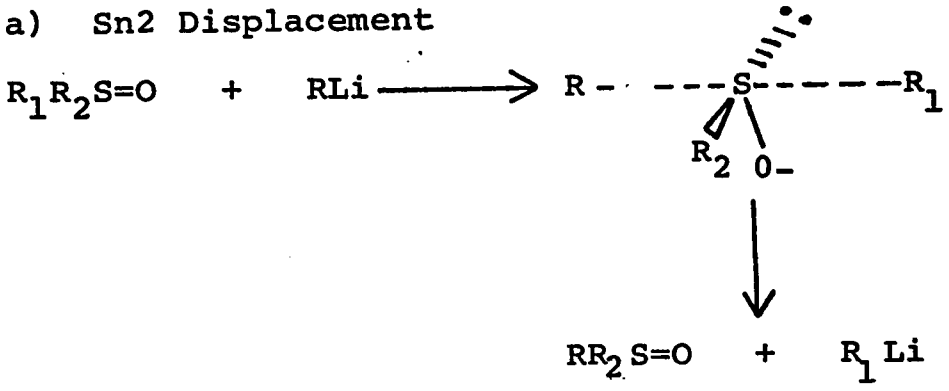
apparently general for dialkyl or aralkyl sulfoxides.

Andersen has reported (3,4) that the reaction of diaryl sulfoxides with aryllithiums leads exclusively to sulfides and arenes.

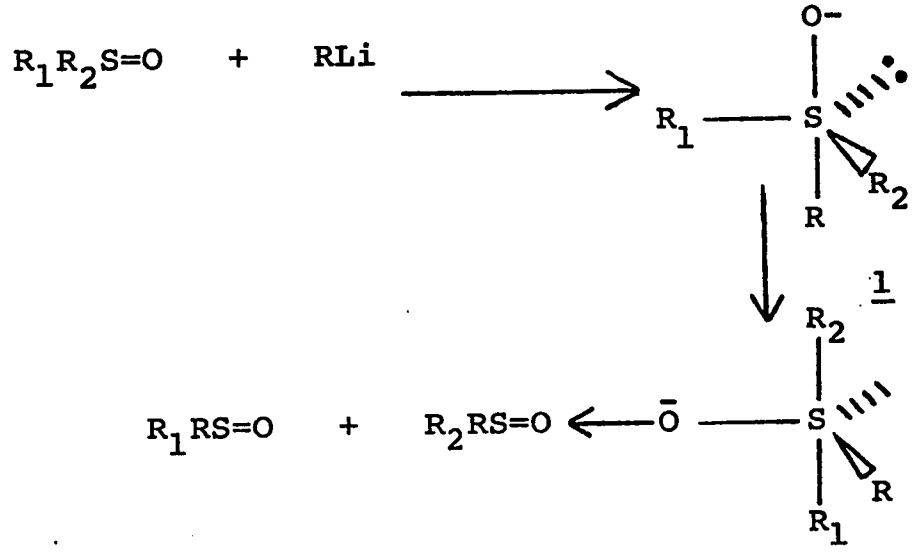
$$Ar_2S{=}O \quad + \quad ArLi \longrightarrow Ar_2S \quad + \quad ArH$$

There are three possible mechanisms to explain the exchange of alkyl or aryl groups of a sulfoxide with that of an alkyl or aryllithium.

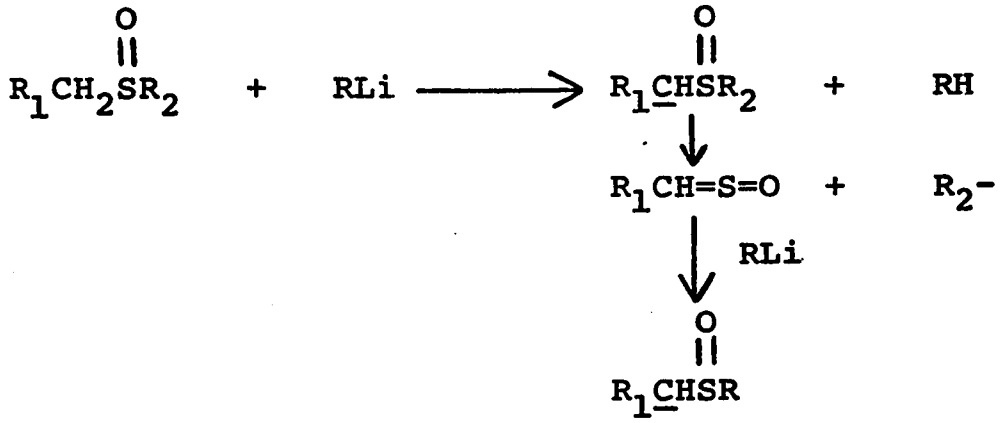
a) Sn2 Displacement



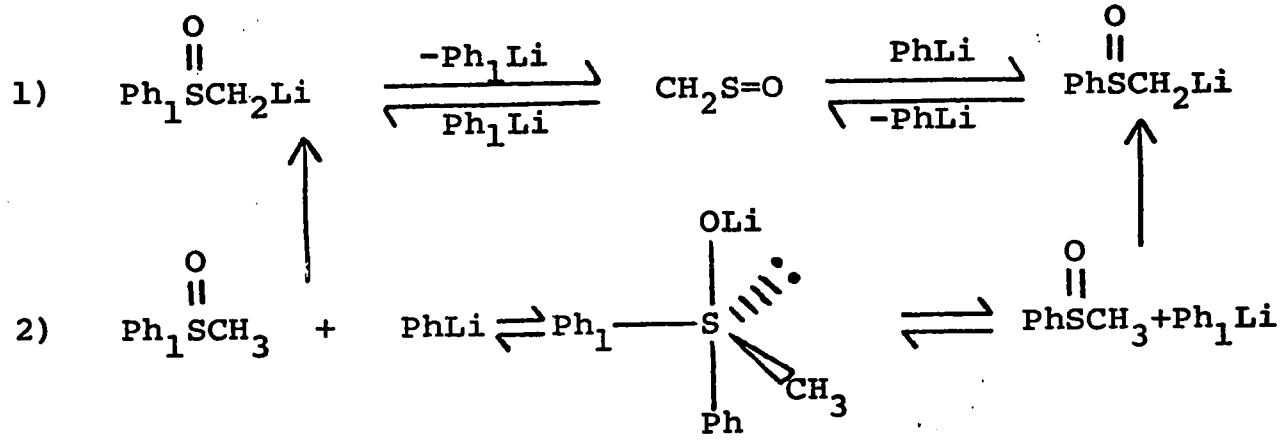
b) Formation of a pentacovalent intermediate of the type 1 (oxygen apical) followed by pseudorotation to 2 and loss of an alkyl group from an apical position.



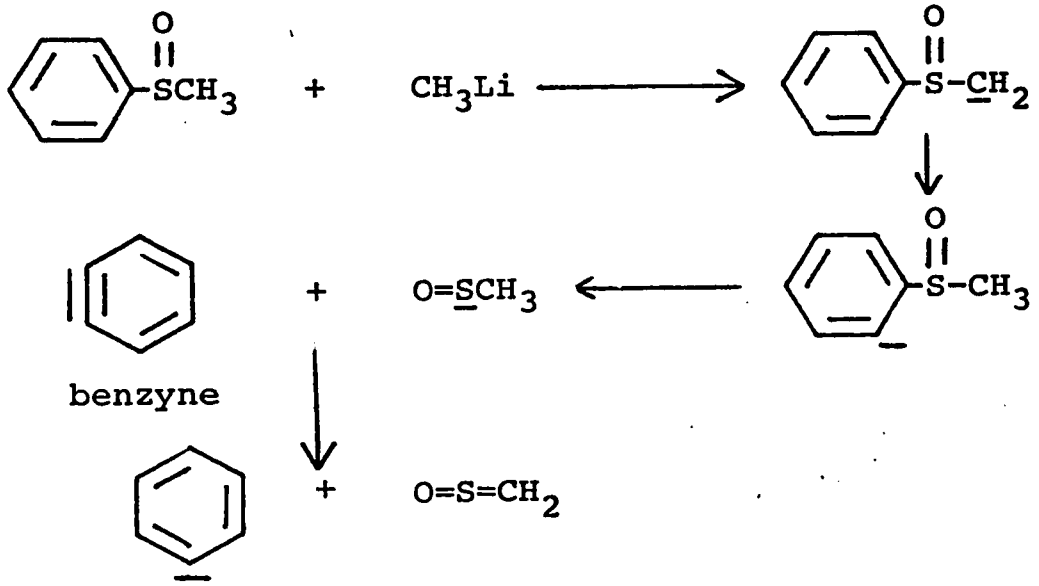
c) Sulfine mechanism



In 1967, Jacobus and Mislow (5) investigated the reactions of optically active aryl methyl sulfoxides with methyl and phenyllithium. They observed both exchange of aryl groups and racemization of recovered starting material. They favoured the two mechanisms which have been denoted as b) bipyramidal and c) sulfine. For example, for the reaction of methyl phenyl sulfoxide with phenyllithium, the following two-path mechanism was proposed.

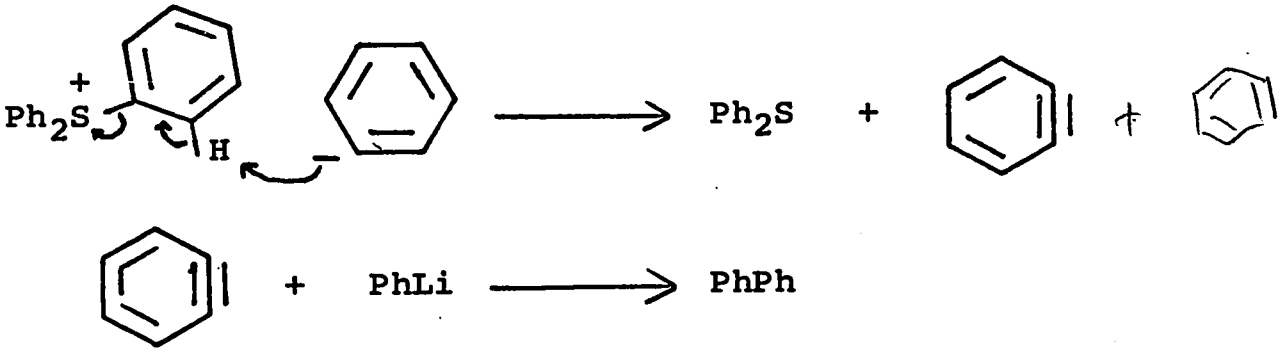


Pathway 1, the sulfine mechanism, is claimed to be predominant over 2, the bipyramidal pathway. Both pathways allow for exchange of aryl groups but only the bipyramidal mechanism allows for exchange of alkyl groups. Their preference for the sulfine mechanism resulted from the following observation: reaction of $^{13}CH_3$- enriched methyl phenyl sulfoxide with CH_3Li under conditions sufficient to give 13% racemization of optically active methyl phenyl sulfoxide gave recovered sulfoxide of unaltered ^{13}C content. They introduce the bipyramidal mechanism to explain the fact that reaction of phenyl-^{14}C methyl sulfoxide with phenyllithium under conditions sufficient to give 50% racemization of an optically active unlabelled sample yielded recovered sulfoxide with loss of 11.2% of the ^{14}C label. Mislow also suggested the possibility that a sulfine could arise through a benzyne intermediate.



Benzyne intermediates have been proposed by Andersen (3) to explain the decomposition of diphenyl sulfoxide on reaction with phenyllithium.

$Ph_2S{=}O + PhLi \longrightarrow Ph_3\overset{+}{S}\ \overset{-}{O}Li$



$PhLi \longrightarrow PhPh$

Overall: $Ph_2S{=}O + 3\ PhLi \longrightarrow Ph_2S + PhPh$

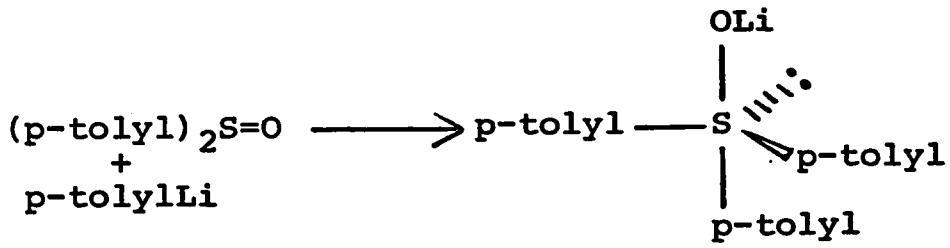
However, this mechanism fails to explain the products when substituted aryl groups, such as p-tolyl, replace phenyl.

In 1970, Andersen (4) described the reactions of di-p-tolyl sulfoxide and tri-p-tolyl sulfonium bromide with p-tolyllithium. From these two reactions he obtained the following products.

$(p\text{-tolyl})_2S{=}O$ + p-tolyllithium ⟶ 66.1% $(p\text{-tolyl})_2S$
31.4% pp' ditolyl
25.6% mp' ditolyl

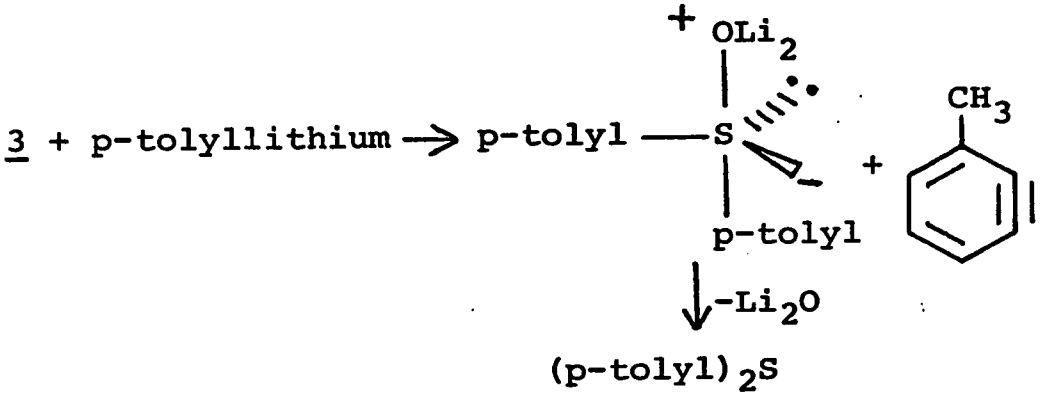
$(p\text{-tolyl})_3\overset{+}{S}\ \underline{Br}$ + p-tolyllithium ⟶ 86.8% $(p\text{-tolyl})_2S$
71.5% mp' ditolyl
5.1% mp' ditolyl

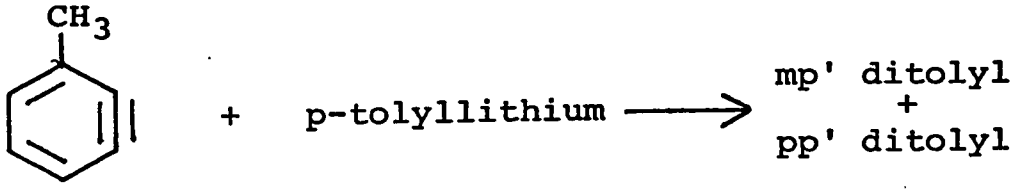
Since the sulfonium salt yielded so little mp'ditolyl, he ruled it out as the major intermediate in the reaction pathway leading from sulfoxide to sulfide and arene. To accommodate his results he proposed one major and two minor mechanisms. The first step is the formation of a bi-pyramidal pentacovalent sulfur intermediate 3, which may then react in three ways.



3

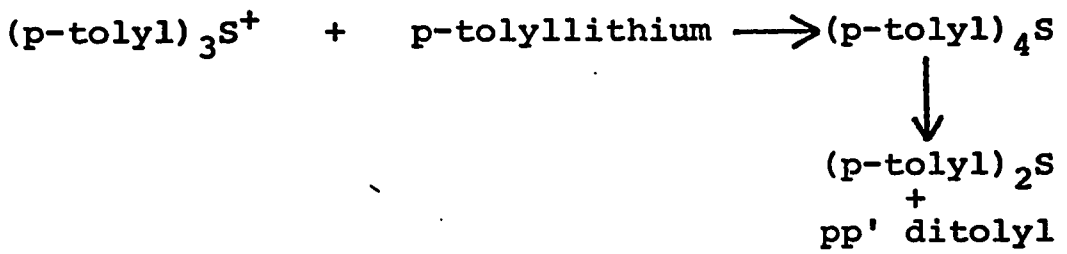
a) Aryne





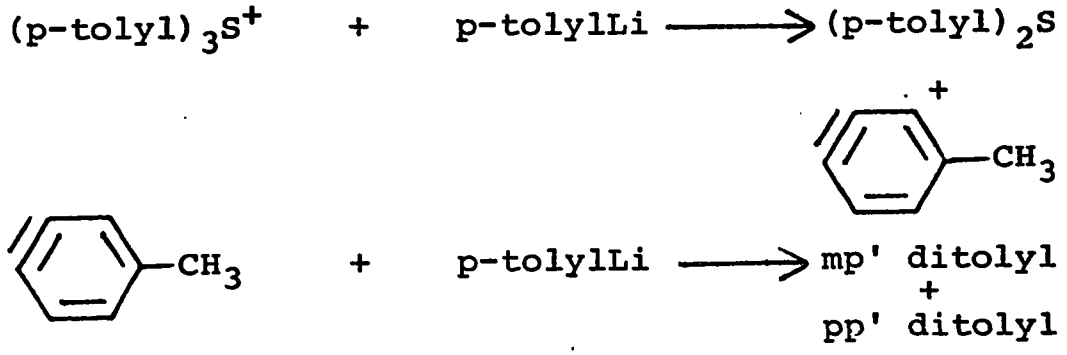
b) Sulfonium Cation

which may in turn react via a tetraaryl sulfur intermediate previously proposed by Franzen (6).

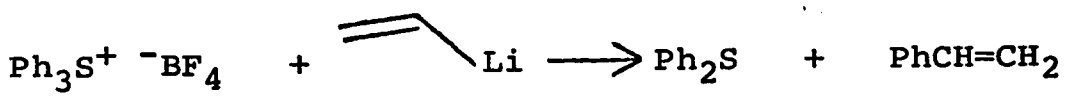


Since a small amount of mp' ditolyl is obtained from the sulfonium salt, at least part of this reaction was suggested to proceed via an aryne intermediate arising from the cation.

c) Aryne (derived from the sulfonium cation)

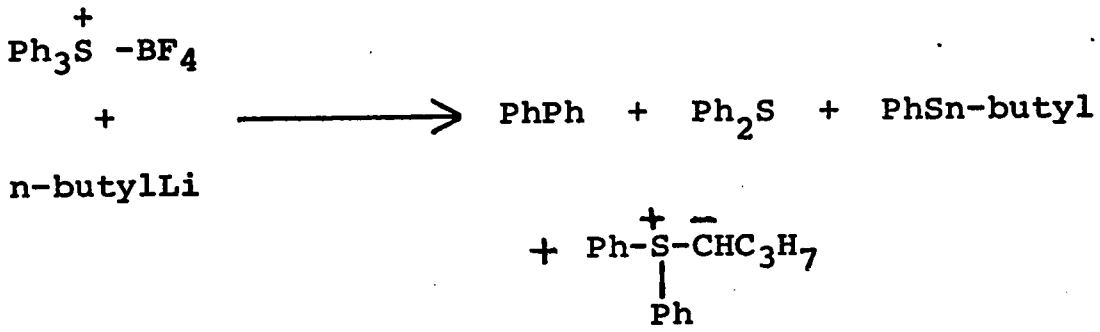


Shortly thereafter, Trost (7) reported that triphenyl sulfonium tetrafluoroborate and vinyllithium in equimolar quantities gave a quantitative yield of diphenyl sulfide and styrene.



It should be noted, however, that Andersen's experiments were carried out in boiling ether in the presence of 4-5 moles of aryllithium and Trost's reactions were done at -78° in tetrahydrofuran.

The reactions of triphenyl sulfonium salts with alkyllithiums reported by Trost do not always lead to such a simple mixture of products; for example, triphenyl sulfonium tetrafluoroborate and n-butyllithium afford four products. Even in this case only one equivalent of n-butyllithium was required to complete the reaction as demanded by the bipyramidal intermediate.

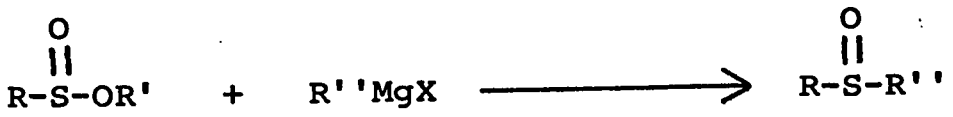


PART II

RESULTS AND DISCUSSION

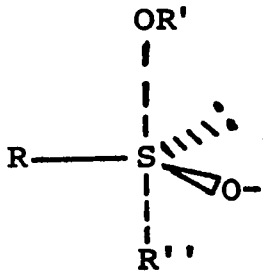
In discussing the alkyl group exchange of dimethylsulfoxide with alkyllithiums, Franzen (1) described it as "common for sulfoxides". In view of this statement and the lack of experimental proof by the author, we set out to investigate the reactions of various sulfoxides with alkyllithiums, the results of which should lead to a better understanding of the mechanism by which this interchange occurs.

The reaction of sulfinate esters 4 with Grignard reagents occurs with inversion of configuration at sulfur and has therefore been classed as an Sn2 type reaction.



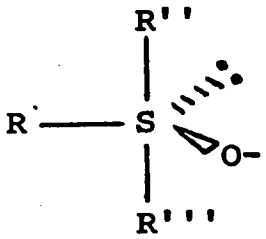
4

The transition state for an Sn2 displacement, 5, is similar in appearance to a bipyramidal sulfur species whether it be an intermediate or transition state.



5

We hoped that replacing the alkoxide group in 5 by an alkyl group which is a poor leaving group, might increase the possibility of observing a bipyramidal intermediate 6, which might be capable of undergoing pseudorotation.



6

It was hoped the formation of 6 would be demonstrated in the reactions of optically active sulfoxides with alkyllithiums.

Reaction of Sulfoxides with Alkyllithiums

Reaction of methyl phenyl sulfoxide with t-butyllithium in tetrahydrofuran (under a nitrogen atmosphere) yielded a mixture of methyl phenyl sulfoxide and t-butyl methyl sulfoxide. The ratio of these two products depended considerably on the reaction conditions. The results of a series of reactions are shown in Table 1. The products were conveniently analyzed by n.m.r. The

Table 1 - Reaction of Methyl Phenyl Sulfoxide with t-Butyllithium[a]

Reaction Number	Temp.	No. of Equiv. of RLi	Rate of Addition[b]	Products	
1.	-78°	3.0		33% Ph-S-CH_3 (O)	66% t-butyl-S-CH_3 (O)
2.	-78°	1.0		50% "	50% "
3.	25°	1.0		80% "	20% "
4.	-78°	1.0	slow	66% "	33% "
5.	-78°	1.0	fast	53% "	47% "
6.	25°	1.0	slow	75% "	25% "
7.	25°	1.0	fast	72% "	28% "

(a) All reactions were allowed to stir at the indicated temperature for ten minutes.

(b) Refers to rate with which the alkyllithium was added to the reaction mixture; slow corresponds to a dropwise addition and fast designates that the alkyllithium was added as quickly as possible. When this column is blank, the rate of addition was not strictly controlled.

methyl groups of the two products mentioned above are separated by 16 Hz. (2.66 and 2.40 δ respectively) at 60 MHz. Integration of these two peaks indicated the relative abundance of these two sulfoxides in the crude reaction product. However, this method was limited to the analysis of only these two products; that is, the presence or absence of t-butyl phenyl sulfoxide could not be determined by n.m.r. since the t-butyl groups of both sulfoxides occur at the same δ values. Furthermore, comparison of the integration of the phenyl and t-butyl groups was not possible due to the presence of high field absorption in the 1-2 δ range. This absorption is presumably due to products arising from the decomposition of tetrahydrofuran by t-butyllithium. The absence of appreciable amounts of t-butyl phenyl sulfoxide was shown by oxidation to the corresponding sulfones and analysis by gas chromatography.

Similarly, n-butyl phenyl, ethyl phenyl, phenyl i-propyl and di-n-butyl sulfoxides were reacted with t-butyllithium. The results are shown in Table 2. The products from these reactions could not be analyzed by n.m.r. due to the complexity of the crude spectra. Therefore it was necessary to employ analytical gas chromatography, g.c. Since sulfoxides are relatively thermally unstable and quite polar, it was convenient to oxidize the total crude reaction mixture with an excess of m-chloro-

Table 2 - Reaction of Sulfoxides with t-Butyllithium[a]

Reaction Number	Sulfoxide	Duration (Minutes)	Temp.	Rate of Addition[b]	Products
1.	Ph-S(=O)-n-butyl[c]	10	-78°		64% Ph-S(=O)-n-butyl 36% t-butyl-S(=O)-n-butyl
2.	Ph-S(=O)-CH_2CH_3	10	-78°	slow	50% Ph-S(=O)-Et 50% t-butyl-S(=O)-Et
3.	Ph-S(=O)-CH_2CH_3	10	25°	slow	70% " 30% "
4.	Ph-S(=O)-i-propyl	10	25°	slow	85% Phenyl-S(=O)-i-propyl 15% t-butyl-S(=O)-i-propyl
5.	Ph-S(=O)-i-propyl	10	-78°	slow	62% Phenyl-S(=O)-i-propyl 38% t-butyl-S(=O)-i-propyl

Table 2 - Reaction of Sulfoxides with t-Butyllithium[a] Cont'd

Reaction Number	Sulfoxide	Duration (Minutes)	Temp.	Rate of Addition[b]	Products
6.	$(n\text{-butyl})_2S{=}O$	10	-78°	slow	94% $(n\text{-butyl})_2S{=}O$ 6% t-butyl-S(=O)-n-butyl
7.	$(n\text{-butyl})_2S{=}O$	30	-78°	slow	Same as Reaction 6

(a) All reactions were carried out using 1 equivalent of t-butyllithium.

(b) See (b), Table 1.

(c) Products ratios from this reaction are based on isolated materials.

peroxybenzoic acid, M.C.P.A. The resulting sulfones were then analyzed by g.c. using benzophenone as standard. In order to ensure validity of the g.c. method, a reaction mixture was analyzed by both n.m.r. and g.c. The n.m.r. analysis of the products from a reaction of methyl phenyl sulfoxide with t-butyllithium indicated a ratio of starting material to t-butyl methyl sulfoxide of 0.97. Oxidation of this mixture and g.c. analysis indicated a ratio of 1.07. The g.c. chromatograms obtained from the analysis showed no significant volatile side products. The percentages of products shown in the tables are the average results of a number of runs. Variations in the ratios from successive runs under the same conditions were generally in the 5-10% range. For instance, the reaction of phenyl i-propyl sulfoxide with t-butyllithium at -78° (Reaction 5, Table 2) was carried out twice and the following results were obtained.

Run No.	% PhS(O)-i-propyl	% t-butS(O)-i-propyl
1	60	40
2	64	36

Chloromethyl phenyl and α-chloroethyl phenyl sulfoxides were reacted with alkyllithiums at -78° and the results are summarized in Table 3. The products from these reactions were also analyzed by g.c.

Table 3 - Reaction of Chloromethyl Phenyl and Chloroethyl Phenyl Sulfoxides with Alkyllithiums[a]

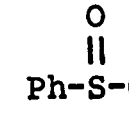
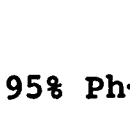
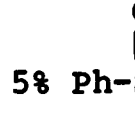
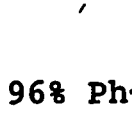
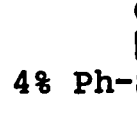
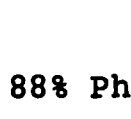
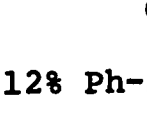
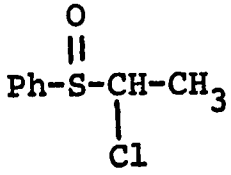
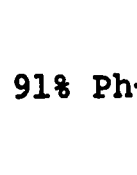
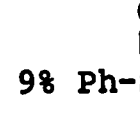
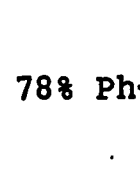
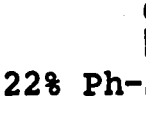
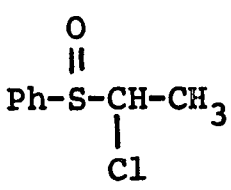
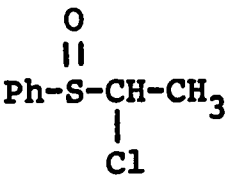
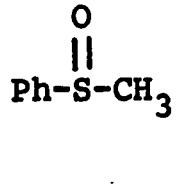
Reaction Number	Sulfoxide	Alkyllithium	No. of Equiv. of RLi	Products	
1.		t-butyl	1.0	95% 	5% 
2.	"	n-butyl	1.1	96% 	4% 
3.	"	methyl	1.0	88% 	12% 
4.		t-butyl	1.0	91% 	9% 
5.	"	n-butyl	1.1	78% 	22% 

Table 3 - Reaction of Chloromethyl Phenyl and Chloroethyl Phenyl Sulfoxides with Alkyllithiums[a] Cont'd

Reaction Number	Sulfoxide	Alkyllithium	No. of Equiv. of RLi	Products
6.		methyl	1.0	64%  36% 

(a) All reactions were allowed to stir at -78° for ten minutes. Slow[b] addition of alkyllithium was employed in all reactions.

(b) See (b), Table 1.

Table 4 contains the results of the reactions of benzenesulfinyl methide and ethide anions with t-butyllithium. The anions were generated by addition of 1.0 equivalent of methyllithium to the appropriate sulfoxide approximately five minutes before the introduction of 1.0 equivalent of t-butyllithium. Analysis was accomplished by use of the n.m.r. method for reactions 1 and 2 and v.p.c. analysis was performed on the mixtures obtained from reactions 3 and 4.

The fact that the product ratios were not significantly affected by extraction technique was illustrated by one experiment. The anion of methyl phenyl sulfoxide was reacted with t-butyllithium at -78° and n.m.r. analysis of the crude reaction mixture indicated a ratio of methyl phenyl sulfoxide to t-butyl methyl sulfoxide of 73:32 (Reaction 2, Table 4). The mixture was then subjected to the workup procedure again and analysis of recovered sulfoxides indicated the ratio to be 74:31. It seems very unlikely that reduction of sulfoxides to sulfides occurred to any appreciable extent since no peaks that could be attributed to sulfides were present in the n.m.r. of the crude products derived from the reaction of methyl phenyl sulfoxide with t-butyllithium.

The results of the reactions of methyl phenyl sulfoxide with n-butyllithium and phenyl i-propyl sulfoxide

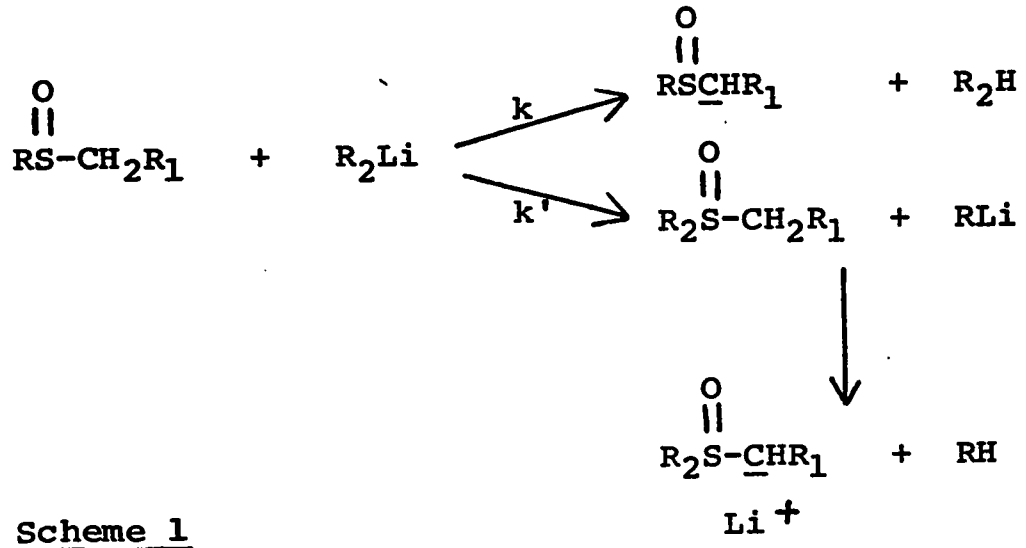
Table 4 - Reaction of Benzenesulfinyl Methide and Ethide Anions with t-Butyllithium[(a)]

Reaction Number	Anion	Temp.	Rate of Addition of RLi	Products	
1.	$Ph-\overset{\overset{O}{\|\|}}{S}-CH_2-$	-78°	slow	66% $Ph-\overset{\overset{O}{\|\|}}{S}-CH_3$	33% t-butyl-$\overset{\overset{O}{\|\|}}{S}-CH_3$
2.	$Ph-\overset{\overset{O}{\|\|}}{S}-CH_2-$	-78°	fast	70% "	30% "
3.	$Ph-\overset{\overset{O}{\|\|}}{S}-\underline{C}HCH_3$	-78°	slow	65% $Ph-\overset{\overset{O}{\|\|}}{S}-CH_2CH_3$	35% t-butyl-$\overset{\overset{O}{\|\|}}{S}-CH_2CH_3$
4.	$Ph-\overset{\overset{O}{\|\|}}{S}-\underline{C}HCH_3$	25°	slow	100% $Ph-\overset{\overset{O}{\|\|}}{S}-CH_2CH_3$	

(a) All reactions were carried out in the presence of 1.0 equivalent of t-butyllithium and were stirred for ten minutes after addition was complete.

with methyllithium are shown in Table 5.

All of the results can be rationalized in terms of two competing reactions, a) proton abstraction to give an α-lithio sulfoxide and, b) displacement of an aryl or alkyl group, Scheme 1.



Scheme 1

Scheme 1 indicates that only 1 equivalent of alkyllithium is required and that the sulfoxide products are generated as the anions. The latter was demonstrated as follows. Methyl phenyl sulfoxide was allowed to react with t-butyllithium and the reaction was quenched with deuterium oxide. From the integration of an n.m.r. spectrum of the crude products, it was determined the methyl groups of both products had incorporated almost one atom of deuterium.

A trend that is noticeable throughout the results

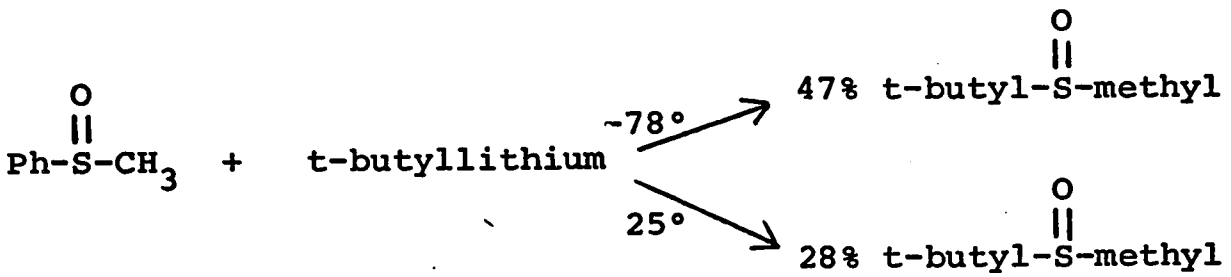
Table 5 - Reactions of Methyl Phenyl and Phenyl Isopropyl Sulfoxides with n-Butyl and Methyllithiums Respectively[a]

Reaction Number	Sulfoxide	Alkyllithium	Time in Minutes	Products[b]
1.	$Ph-\overset{\overset{O}{\|\|}}{S}-CH_3$	n-butylLi	10	70% $Ph-\overset{\overset{O}{\|\|}}{S}-CH_3$ 30% $n\text{-butyl}-\overset{\overset{O}{\|\|}}{S}-CH_3$
2.	$Ph-\overset{\overset{O}{\|\|}}{S}\text{-i-propyl}$	methyl	30	100% $Ph-\overset{\overset{O}{\|\|}}{S}\text{-i-propyl}$

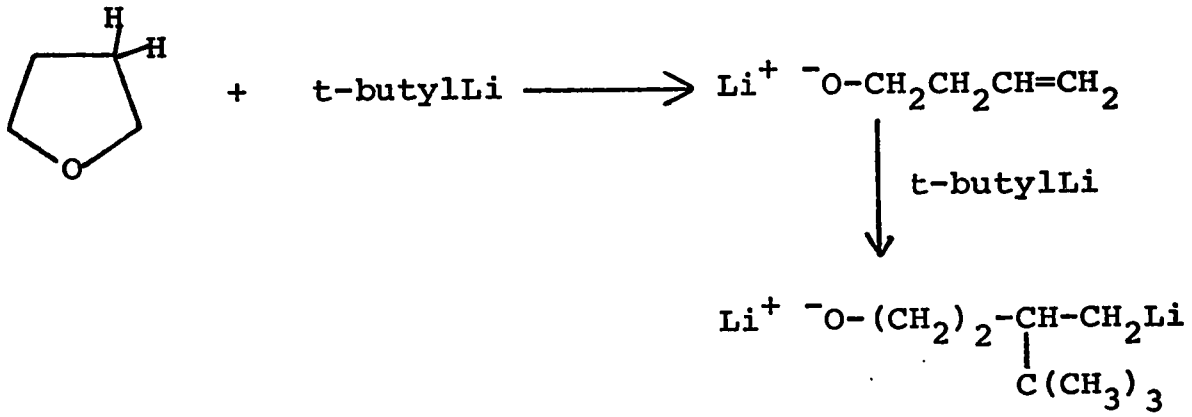
(a) All reactions were carried out at 25° in the presence of 1.0 equivalent of alkyllithium.

(b) As determined from n.m.r. spectra of crude products.

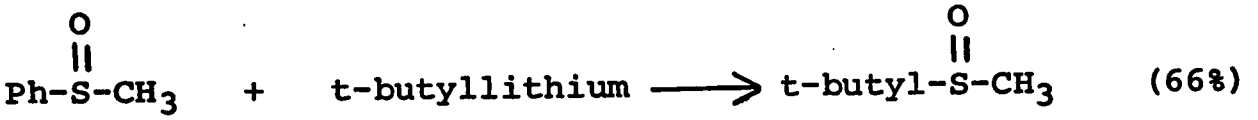
is the increase of alkyl or aryl group exchange at lower temperature, for example, reactions 5 and 7, Table 1, the results of which are shown below.

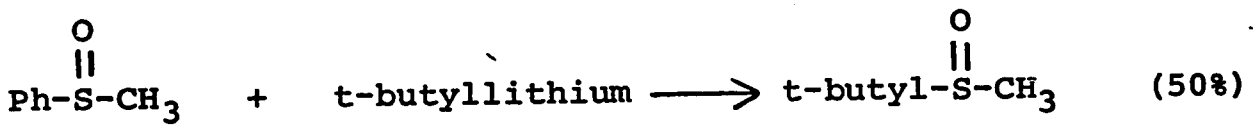


The results would seem to indicate that proton abstraction is favoured with increasing temperature. However, it is more probable that the reaction of t-butyllithium with tetrahydrofuran causes this effect. The rate of this reaction should increase with increasing temperature thereby reducing the amount of alkyllithium available for reaction with sulfoxide. This reaction is analogous to that reported by Bartlett (8) between ethyl ether and alkyllithiums.



The use of excess t-butyllithium gave an increase in the amount of exchange product.





This result can be rationalized as the result of a displacement reaction on the lithiosulfoxide by the excess t-butyllithium.

To substantiate this proposal, the lithio sulfoxide was prepared from methyl phenyl sulfoxide and methyllithium and reacted with one equivalent of t-butyllithium. Analysis showed that 30% t-butyl methyl sulfoxide was formed.

The observation that sulfinyl carbanions undergo displacement is somewhat surprising in view of the fact that the electron density about sulfur in the anion would be expected to be greater than in the sulfoxide. Comparison of the results of the reactions of sulfinyl anions, Table 4, with those from the reactions of the sulfoxides under identical conditions, either Table 1 or Table 2, indicate, however, that the anions do undergo less

displacement than the corresponding sulfoxides. For example,

Table 4, Reaction 2

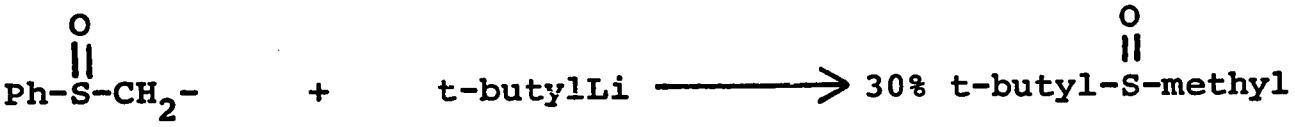
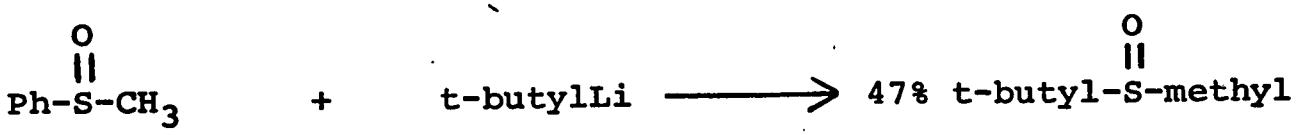


Table 1, Reaction 5



In addition to the temperature effect previously mentioned, steric factors and the acidity of α protons may also effect the degree to which exchange occurs. The results of the reactions of three sulfoxides with t-butyllithium at -78° are shown below.

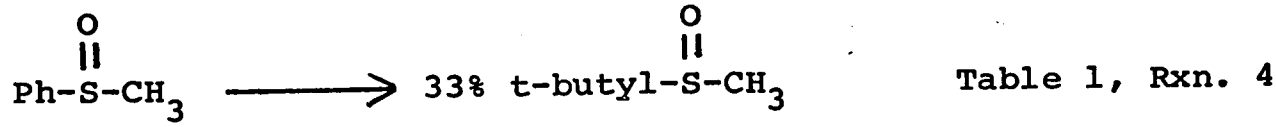


Table 1, Rxn. 4

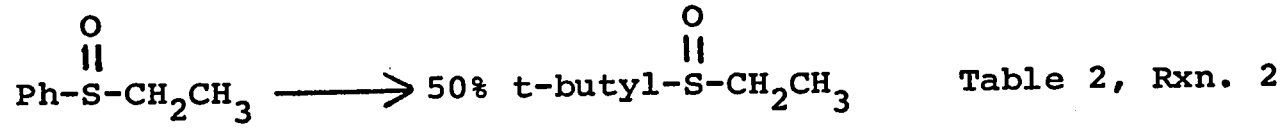


Table 2, Rxn. 2

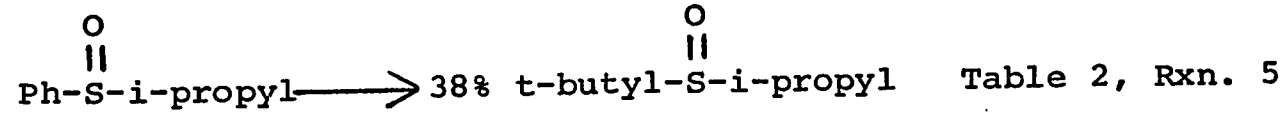


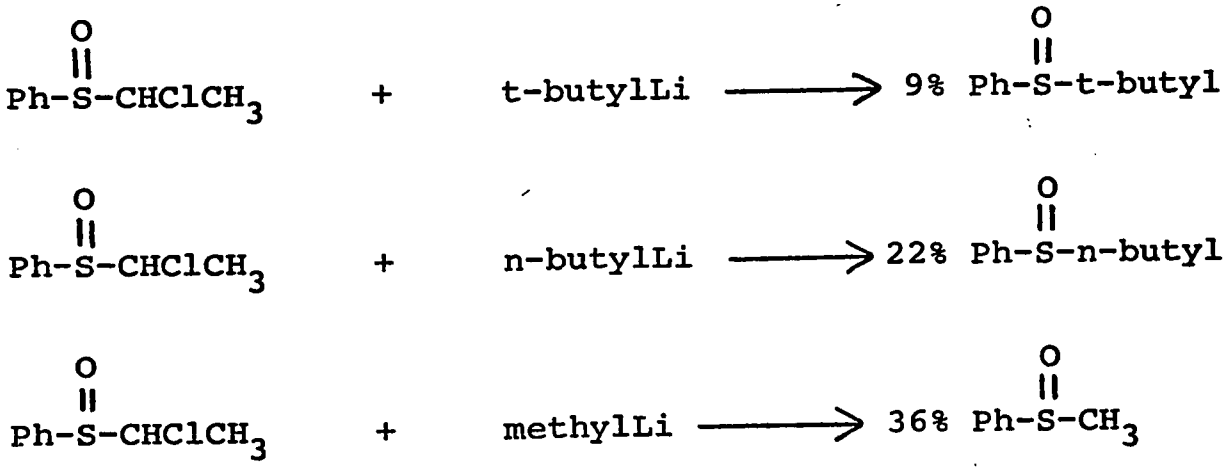
Table 2, Rxn. 5

Bearing in mind that proton abstraction is a reaction com-

peting with displacement, the above results can be interpreted in the following manner. Although being the least hindered at sulfur, phenyl methyl sulfoxide also favours proton abstraction over the other two since its α protons are more acidic and more numerous. For this sulfoxide, formation of anion is predominant over aryl group displacement. On the other hand, phenyl isopropyl sulfoxide would be expected to give slowest anion formation but steric effects impede attack at sulfur. Ethyl phenyl sulfoxide presents a balance of competing reactions and yields the greatest amount of aryl group displacement.

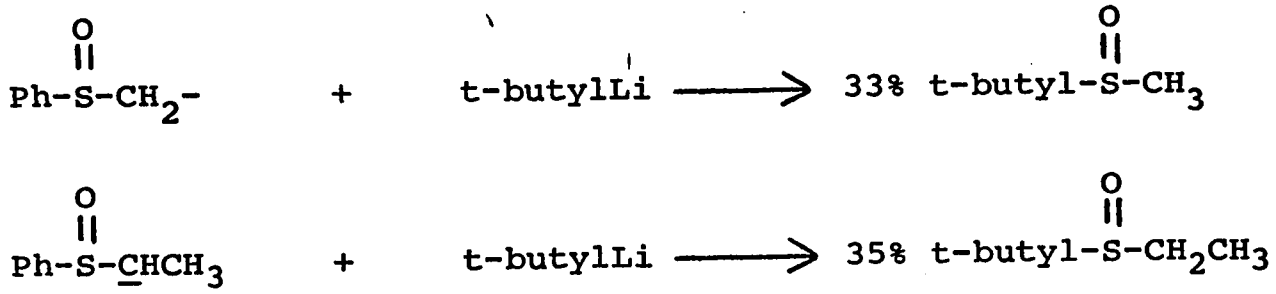
The effect of the size of the attacking group also substantiates the proposal of steric inhibition to exchange.

Table 3, Reactions 4, 5 and 6



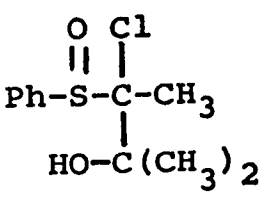
Shown above are the reactions of α-chloroethyl phenyl sulfoxide with t-butyl-, n-butyl-, and methyllithium.

Chloromethyl phenyl sulfoxide also behaves in a similar way although the effect is not as marked. These results indicate that the smaller attacking group yields more exchange. α-Chloroethyl phenyl sulfoxide would be expected to yield more displacement than chloromethyl phenyl sulfoxide for the same reason that ethyl phenyl sulfoxide undergoes more displacement than methyl phenyl sulfoxide, that is acidity of α protons. If acidity were the major factor in decreasing the yield of displacement product in methyl phenyl sulfoxide relative to ethyl phenyl sulfoxide, one would expect the anions of the two sulfoxides to yield equivalent amounts of exchanged product providing that steric factors do not greatly depress the amount of displacement occurring with the benzenesulfinyl ethide anion. Shown below are the results of the two displacement reactions, Table 4, Reactions 1 and 3.



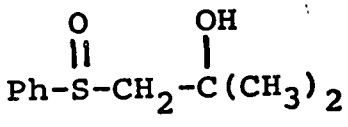
Within experimental error, these results indicate the two anions yield equivalent amounts of exchanged product.

In the alkyl phenyl sulfoxides, the phenyl group was displaced [a]. In contrast, the chloroalkyl group was found to be exclusively exchanged in the chloroalkyl phenyl sulfoxides. These results indicate that the displaced group leaves as an anion. Phenyl anion (benzene, pk_a=37 (9)) would be expected to be a better leaving group than methyl (methane, pk_a=40 (9)) or ethyl (ethane, pk_a=42 (9)). However, substitution of an α hydrogen in the alkyl group with chlorine could provide sufficient anion stabilization thus making it a better leaving group than phenyl. Surprising as the results from the reactions of chlorosulfoxides may be, our results agree quite well with those of K. C. Tin (2) who found that reaction of α-chloroethyl phenyl sulfoxide with methyllithium and subsequent quenching of the reaction with acetone yielded the two alcohols 7 and 8 in the following yields.



34%

7



18%

8

(a) Generally, it was found that displacement of the alkyl group in methyl, ethyl, and isopropyl phenyl sulfoxides by t-butyllithium comprised 1% or less of the total crude.

The results from the reactions of optically active methyl p-tolyl sulfoxide and ethyl p-tolyl sulfoxide with t-butyllithium are shown in Table 6. It is interesting to note that ethyl p-tolyl sulfoxide yields 20% t-butyl p-tolyl sulfoxide in view of the fact that ethyl phenyl sulfoxide yields 1% or less. The product ratios in reactions 1 and 2 are derived from n.m.r. spectra; those in reactions 3 and 4 refer to isolated materials.

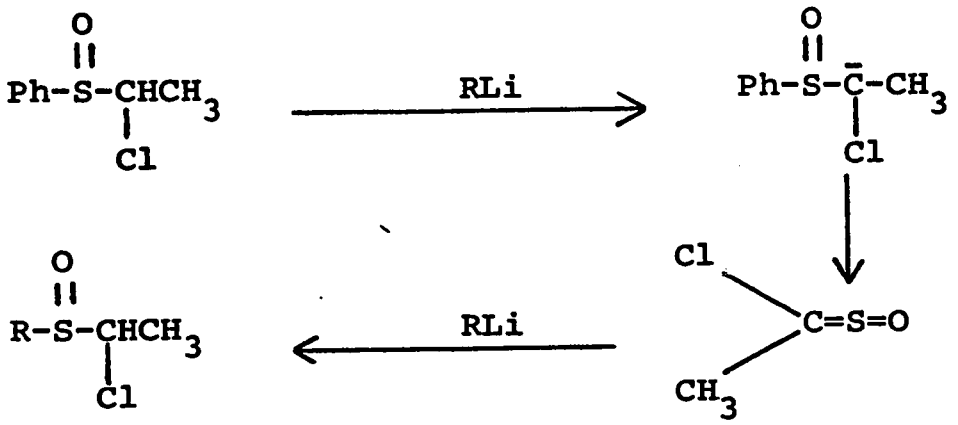
The results from the reactions of t-butyl p-tolyl sulfoxide with t-butyllithium and n-butyl p-tolyl sulfoxide with n-butyllithium are shown in Table 7.

Throughout both Tables 6 and 7, it can be seen that the recovered starting material has undergone partial racemization with the exception of t-butyl p-tolyl sulfoxide which in two cases, Table 7, reactions 2 and 3, was completely racemized. Moreover, ethyl p-tolyl sulfoxide yielded t-butyl p-tolyl sulfoxide with net inversion of configuration at sulfur.

It is now necessary to critically discuss the mechanisms by which the cleavage and racemization of sulfoxides might occur, namely Sn2 displacement, formation of a bipyramidal intermediate, or Mislow's sulfine mechanism.

The sulfine mechanism can be eliminated as a major pathway leading to exchange for the following reasons. The sulfine mechanism is unable to account for the products

arising from the reactions of chloroalkyl phenyl sulfoxides with alkyllithiums. The sulfine mechanism does not allow for exchange of the chloroalkyl group.



Yet we have found the chloroalkyl group is exclusively exchanged. In addition, it would be expected that the sulfinyl anion would yield greater amounts of exchanged product than the sulfoxides themselves since sulfines are reactive species and would be expected to react quickly with alkyllithiums.

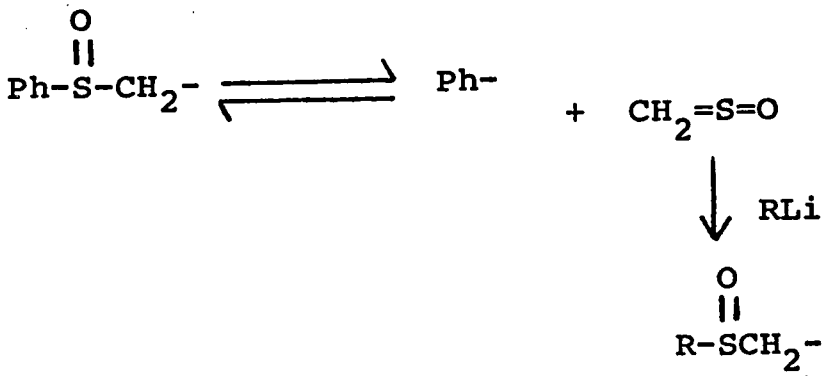


Table 6 - Reactions of Optically Active Methyl and Ethyl p-Tolyl Sulfoxide with t-Butyllithium[a]

Reaction Number	Sulfoxide	Products	
1.	p-tolyl-S(=O)-CH_3 $[\alpha]_D = 145°$	66% p-tolyl-S(=O)-CH_3	33% t-butyl-S(=O)-CH_3 $[\alpha]_D = -0.5°$
2.	p-tolyl-S(=O)-CH_3 $[\alpha]_D = 145°$	75% p-tolyl-S(=O)-CH_3 $[\alpha]_D = 140°$ (97% retention)	25% t-butyl-S(=O)-CH_3
3.	p-tolyl-S(=O)-CH_2CH_3 $[\alpha]_D = 164.5°$	80% p-tolyl-S(=O)-CH_2CH_3 $[\alpha]_D = 160°$ (97.5% retention)	20% t-butyl-S(=O)-p-tolyl $[\alpha]_D = -24.4°$

Table 6 - Reactions of Optically Active Methyl and Ethyl p-Tolyl Sulfoxide with t-Butyllithium[a] Cont'd

Reaction Number	Sulfoxide	Products
4.	p-tolyl-S-CH_2CH_3 (O) $[\alpha]_D = 154°$	60% p-tolyl-S-CH_2CH_3 (O) $[\alpha]_D = 142°$ (92% retention) 20% t-butyl-S-p-tolyl (O) $[\alpha]_D = -8.9°$ 20% t-butyl-S-CH_2CH_3 (O) [b]

(a) All reactions were allowed to stir at -78° for ten minutes in the presence of 1.0 equivalent of t-butyllithium.

(b) Estimated from an n.m.r. of a mixture of p-tolyl-S-CH_2CH_3 (O) and t-butyl-S-CH_2CH_3 (O) that was isolated.

Table 7 - Reactions of t-Butyl p-Tolyl Sulfoxide and n-Butyl p-Tolyl Sulfoxide with Alkyllithiums[a]

Reaction Number	Sulfoxide	Alkyllithium	No. of Equiv. of RLi	Products
1.	t-butyl-S(=O)-p-tolyl $[\alpha]_D = 94°$	t-butylLi	0.3	t-butyl-S(=O)-p-tolyl $[\alpha]_D = 80°$ (85% retention)
2.	t-butyl-S(=O)-p-tolyl $[\alpha]_D = 30°$	"	1.0	t-butyl-S(=O)-p-tolyl $[\alpha]_D = 0°$
3.	t-butyl-S(=O)-p-tolyl $[\alpha]_D = 114°$	"	0.5	t-butyl-S(=O)-p-tolyl $[\alpha]_D = -0.5°$

Table 7 - Reactions of t-Butyl p-Tolyl Sulfoxide and n-Butyl p-Tolyl Sulfoxide with Alkyllithiums[a] Cont'd

Reaction Number	Sulfoxide	Alkyllithium	No. of Equiv. of RLi	Products
4.	p-tolyl-S(=O)-n-butyl	n-butylLi	1.5	60% p-tolyl-S(=O)-n-butyl $[\alpha]_D$ = 115° (91% retention) 40% $(n\text{-butyl})_2S{=}O$

(a) Reactions 1-3 were allowed to stir at -78° for 10 minutes, reaction 4 for 15 minutes.

Moreover, the displacement reaction should be independent of alkyllithium used since all organolithiums are able to generate sulfinyl carbanions. However, the reaction was found to have a marked dependence on the alkyllithium. Compare Table 5, reaction 2; Table 2, reaction 4.

A discussion of bypyramidal intermediates follows and although their existence cannot be decisively eliminated, neither do our findings substantiate their participation in the mechanism of the exchange reaction.

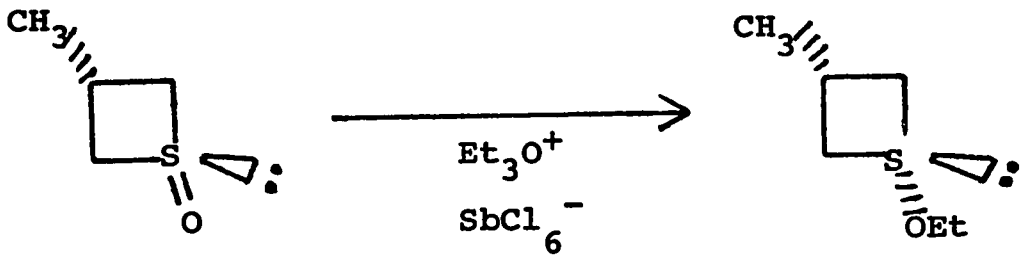
Aside from the evidence previously presented regarding the existence of pentacoordinated sulfur compounds by Andersen (3,4) and Trost (7), recent work by Sheppard (10) suggests the formation of a pentacoordinated sulfur species in solution at -80°. The ^{19}F n.m.r. spectrum of a mixture of either (pentafluorophenyl) trifluorosulfurane or sulfur tetrafluoride and pentafluorophenyl lithium at -80° leads to the disappearance of the S-F resonance and the appearance of three new resonances in the ratio of 1:2:2 corresponding to para, meta, and ortho fluorines. The observation of only three fluorine resonances implies either a rapid scrambling of ligands (pseudorotation) in a tetraaryl sulfur species as has been found in SF_4 at 25° (11) or the presence of a species such as Ar_4SF^- which would exhibit the symmetry properties necessary to render the four pentafluorophenyl ligands equivalent.

However, Tang and Mislow (12) have investigated the base catalysed solvolysis of cis and trans-1-ethoxy-3-methylthietanium hexachloroplatinates 9 and their results suggest the absence of any bipyramidal sulfur intermediates. Scheme 2. A consideration of the possible bipyramidal intermediates leading from cis-10 to trans-9 yields three diasteriomers each consisting of a pair of enantiomers, 11, a-c. (See Scheme 2). Of these 11-c may be ruled out since the lone pair occupies an apical position contrary to SF_4 in which it occupies an equatorial position and the two most electronegative groups occupy the equatorial position which is also unfavourable (13,14). Moreover, 11-a arises from hydroxide attack on an edge of the sulfur tetrahedron rather than a face (equatorial versus apical insertion) and this situation has proven unfavourable in phosphorous compounds (15). Species 11-a and 11-b are interconvertible by pseudorotation but both give starting material with retention of configuration. Inversion has been found to occur to an extent of at least 95%.

In order to explain the inversion, either an Sn2 displacement occurs or the thietane ring occupies a di-equatorial position in a bipyramidal intermediate. A structure such as 12 incorporates both alternatives.

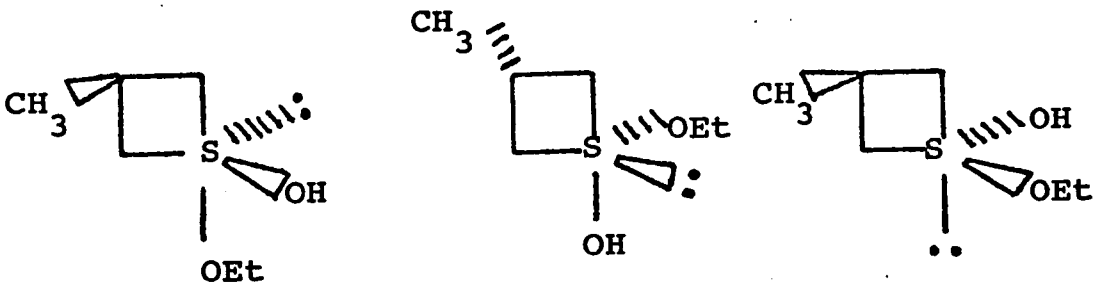
Presented in Scheme 3 are the possible bipyramidal intermediates leading from ethyl p-tolyl sulfoxide to

Scheme 2



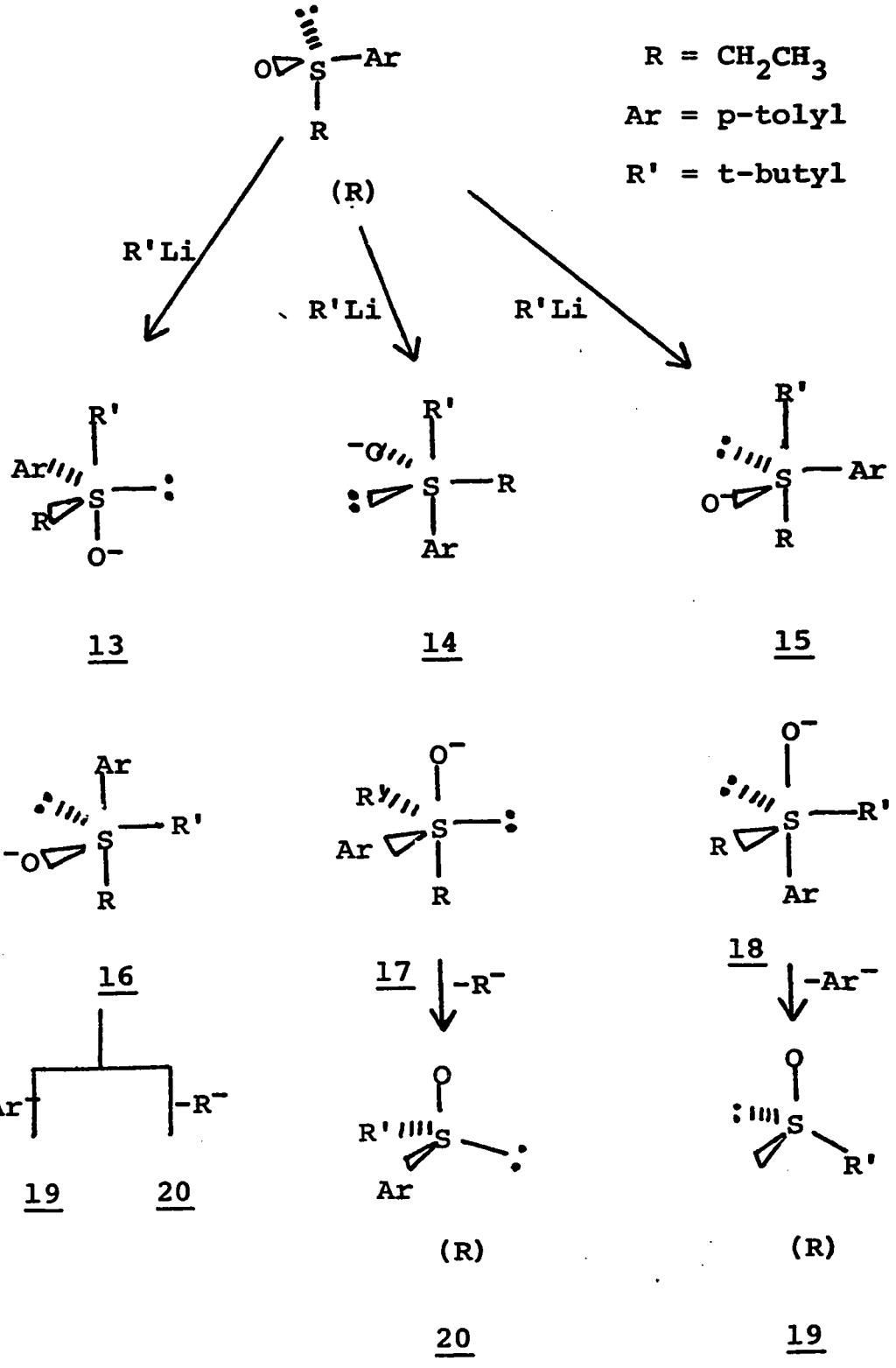
cis-9 cis-10

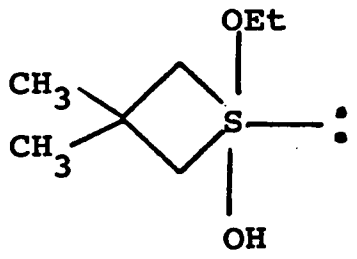
trans-9



11a 11b 11c

Scheme 3 - Bipyramidal Intermediates in the Reaction of Ethyl p-Tolyl Sulfoxide with t-Butyllithium





12

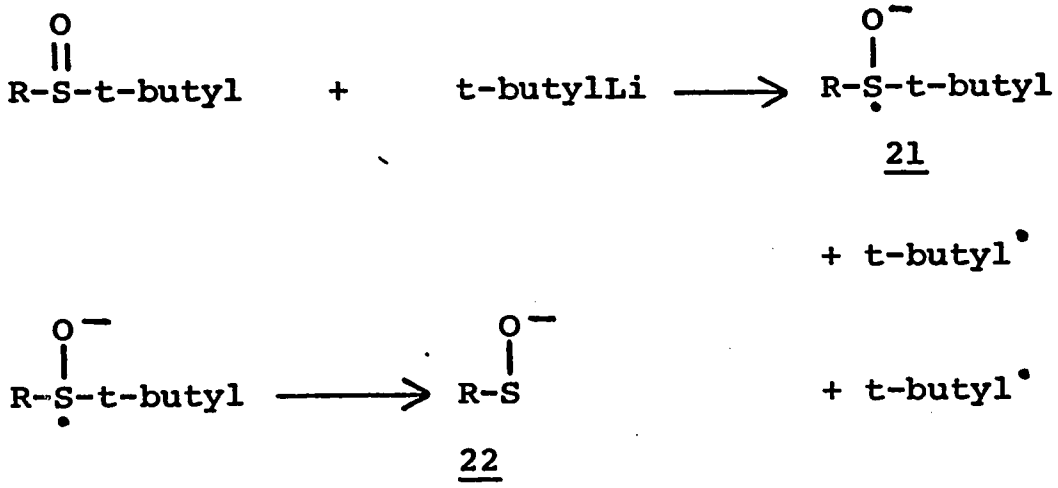
products upon reaction with t-butyllithium. Structures having an apical lone pair which is an unfavourable conformation have been omitted. Intermediates 13, 14 and 15 are the pyramidal structures obtained by facial attack of t-butyllithium upon the sulfoxide (apical insertion). If these intermediates are pseudorotated, we obtain structures 16, 17 and 18 of which the latter two can yield only one sulfoxide each (leaving group departing only from the apical position), t-butyl p-tolyl and t-butyl ethyl respectively. Intermediate 16 can yield either of the foregoing sulfoxides. However, it will be noted that in all cases the product sulfoxides have retained the stereochemistry at sulfur. Therefore, these bipyramidal intermediates account for neither the inversion associated with the displacement reaction of ethyl p-tolyl sulfoxide nor the observed racemization of the starting material and must be discounted as the major reaction pathway. Further pseudorotations of 16, 17 and 18 which would eventually lead to inverted products have not been carried out since it would involve placing a lone pair in an apical position.

The Sn2 displacement best accounts for all the results. This mechanism is able to accommodate both the steric effects and leaving group effects mentioned in connection with the reactions of racemic sulfoxides. Moreover, it is the most plausible mechanism to account for the observed net inversion at sulfur that occurs during the course of a displacement of an aryl or alkyl group. The t-butyl methyl sulfoxide produced from the reaction of methyl p-tolyl sulfoxide is racemic, Table 6, reaction 1. This may be due to the fast racemization of product in the presence of t-butyllithium. We have observed that t-butyl p-tolyl sulfoxide racemizes completely within ten minutes at -78° in the presence of less than one equivalent of t-butyllithium, Table 7, reaction 3. Thus small variations in the optical purity of the product sulfoxides due to slight variations of t-butyllithium concentration and rate of addition are not completely unexpected. For example, two consecutive reactions of ethyl p-tolyl sulfoxide with t-butyllithium yielded t-butyl p-tolyl sulfoxide with rotations of $[\alpha]_D$= -24.4° (15.1% optically pure) and -8.9° (5.5% optically pure).

The anomalous behaviour of t-butyl sulfoxides (their rapid racemization in the presence of t-butyllithium) may be due to their participation in a mechanism especial to themselves such as shown in Scheme 4.

The racemization of sulfoxide may be due to a more rapid pyramidal inversion of 21 relative to the sulfoxide.

Scheme 4



Another mechanism providing for racemization is cleavage of the radical anion 21 to yield a sulfenate anion 22 and a t-butyl radical. A mechanism of this type is favoured over an Sn2 since the latter would be expected to lead to rapid racemization whenever the attacking and leaving groups were identical. However, Mislow (5) has found that reaction of methyl phenyl sulfoxide with phenyllithium for 22 hours leads to only 50% racemization of recovered material.

A mechanism involving radicals is also suggested by the observation that essentially no di-t-butyl sulfoxide results from the reaction of t-butyl p-tolyl sulfoxide with t-butyllithium. From the reactions of both racemic and optically active sulfoxides, if displacement occurred, it

would be expected that the tolyl group would be the preferred leaving group over t-butyl and for this reason also an Sn2 mechanism must be excluded as that accounting for the rapid racemization of t-butyl sulfoxides.

Finally, the slight loss of optical activity of the recovered starting materials (Tables 6 and 7) may be due to the slight contribution of Mislow's sulfine mechanism or the sulfinyl carbanions generated in the reaction exhibit a lower barrier to inversion than the corresponding sulfoxides which would be analogous to Darwish's (16) observation that sulfonium ylids exhibit a lower barrier to inversion (approximately 23 Kcal/mole) than the corresponding sulfonium salts (25-29 Kcal/mole).

PART 1

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Boiling points are also uncorrected. Nuclear magnetic resonance (n.m.r.) spectra were recorded as $CDCL_3$ solution on Varian T-60 and HA-100 spectrometers. Peak positions are quoted in δ units. Infrared (i.r.) spectra were determined in $CHCl_3$ solution unless otherwise indicated on a Beckman IR-20 spectrophotometer. For the sake of unambiguous designations, the 2-azetidinone nomenclature will be used in the experimental section.

1,4-Diphenyl-2-azetidinone (10)

This 2-azetidinone was prepared by the method of Gilman and Speeter (14) as found in Organic Reactions (31).

4-Vinyl-2-azetidinone and 4-methyl-4-vinyl-2-azetidinone (18) and (22)

These 2-azetidinones were prepared by the method of Moriconi (16) except that reduction of the 1-chlorosulfonyl-2-azetidinone was carried out with sodium sulfite (26).

4-Phenyl-2-azetidinone (23)

This was similarly prepared by the method of reference (16) from styrene and chlorosulfonyl isocyanate using methylene chloride as solvent with subsequent sulfite reduction of the crude product. Chromatography yielded a white solid, m.p. 106-108° (methylene chloride-ether-pentane), reported (15), 108-109°.

Attempted N-alkylation of 2-azetidinones

a) With lithium diisopropylamide and methyl iodide

β-Lactam 18, 345 mg, was added to 1.0 equivalent of lithium diisopropylamide in tetrahydrofuran at -78° and stirred for one minute. An excess of methyl iodide was then added and the reaction stirred a further five minutes. The reaction was quenched with water and extraction yielded 350 mg of material that was determined to be starting material by n.m.r.

b) Via the imino ether

To 750 mg of 18 in 20 ml of methylene chloride was added 3.11 g of triethyloxonium tetrafluoroborate, two equivalents, and the solution allowed to stand at room temperature for 22 hours. The solution was hydrolysed with a 50% solution of potassium carbonate and extracted with methylene chloride to afford 986 mg of oil. Preparative t.l.c. of this material yielded no product with an N-methyl peak in the n.m.r.

c) Calcium oxide, 80 mg, and 170 mg of 18 were mixed in 10 ml of methylene chloride and 1 ml of methyl trifluoromethane sulfonate was added. The reaction was allowed to stand for 3 hours. Ten milliliters of water was added and the aqueous extracted to yield 95 mg of oil. The n.m.r. spectrum of the product indicated the presence of no N-methylated material.

d) Methyl trifluoromethane sulfonate, 164 mg, and 97 mg of 18 (1 equivalent) were dissolved in $CDCl_3$ in an n.m.r. tube. After 70 minutes, the methyl ester peak at 4.21 δ had almost disappeared and another singlet at 4.27 δ had appeared and the integration and rest of the spectrum was consistent with that expected of the imino ether. The contents of the n.m.r. tube were poured into methylene chloride and extracted once with 10% sodium bicarbonate solution. Evaporation of the solvent yielded a small amount of oil of which an n.m.r. indicated decomposition had occurred.

e) Methyl trifluoromethane sulfonate, 328 mg, and 194 mg of 18 (1 equivalent) were dissolved in 2 ml of $CHCl_3$ and 100 mg of sodium bicarbonate was added. The mixture was stirred for 30 hours. Additional chloroform was added and the mixture filtered. The filtrate was evaporated to yield an oil. An n.m.r. spectrum indicated the amide proton was still present.

f) To 676 mg of 18 was added 1.0 equivalent of methyl trifluoromethane sulfonate in 4 ml of methylene chloride and the reaction stirred for 21 hours. Then 690 mg of triethylamine was added. Another equivalent of ester was added and the solution stirred 4 hours. Thin layer chromatography indicated the absence of N-methylated β-lactam.

Attempted 3-hydroxyalkylation of 4-vinyl-2-azetidinone with n-butyllithium and acetone

To 2.0 equivalents of n-butyllithium in tetrahydrofuran at -78° was added 1.0 equivalent of 18. The reaction was allowed to stir for 3 minutes and an excess of acetone was added. The reaction was poured into 20 ml of water and the aqueous extracted with methylene chloride to give 333 mg of oil. An n.m.r. spectrum of the crude indicated no product was present.

N-methylation of 2-azetidinones - General Procedure

The 2-azetidinone was mixed neat with 2-3 equivalents of methyl iodide if liquid and in a minimum of methylene chloride if solid. The mixture was cooled to 0° and 1 equivalent of freshly powdered dry potassium hydroxide was added with stirring. The mixture was then stirred at the temperatures and for the times indicated. The workup consisted in adding methylene chloride and filtering the mixture. The methylene chloride was dried over magnesium sulfate and evaporated to give near pure products.

1-Methyl-4-vinyl-2-azetidinone (21)

To 8.32 g (85 mmoles) of 4-vinyl-2-azetidinone and 12 g (1 equivalent) of methyl iodide was added 4.85 g (1.05 equivalents) of potassium hydroxide. After five minutes another 6 g of methyl iodide was added and the mixture stirred a further 10 minutes. Workup gave 6.64 g yellow liquid (72%) which was pure by n.m.r. The product can be distilled to give a colourless liquid, b.p. 34-35°/0.35 mm. The n.m.r. spectrum showed peaks at δ=2.75 (s, 3H), 2.45-3.39 (m, 2H), 3.78-4.09 (m, 1H), and 5.12-6.18 (m, 3H). The i.r. spectrum showed bands at 1735 (s) 1410 (m), 1390 (m), 990 (m), and 930 (m). The mass spectrum gave a molecular ion at m/e=111.

1,4-Dimethyl-4-vinyl-2-azetidinone (28)

To 2.65 g (2.38 mmoles) of 4-methyl-4-vinyl-2-azetidinone and 6.8 g (2 equivalents) of methyl iodide was added 1.34 g (1 equivalent) of potassium hydroxide and the reaction stirred for 10 minutes. Workup gave 2.78 g yellow oil (90%) which was pure by n.m.r. The product can be distilled to give a colourless liquid, b.p. 40-50°/0.35 mm. The n.m.r. spectrum indicated peaks at δ=1.75 (s, 3H), 2.69 (s, 3H), 2.81 (s, 2H) and 5.00-6.21 (m, 3H). The i.r. spectrum showed bands at 1735 (s), 1410 (m), 1390 (m), 995 (m), and 930 (m) cm^{-1}. The mass spectrum indicated a molecular ion at m/e=125.

1-Methyl-4-phenyl-2-azetidinone (24)

2-Azetidinone, 1.72 g (11.7 mmoles), and 2.4 g (1.5 equivalents) of methyl iodide were dissolved in 10 ml of methylene chloride and 690 mg of potassium hydroxide was added. After the vigorous reaction had subsided the mixture was refluxed for 40 minutes. Workup gave 760 mg yellow oil. Purification by preparative t.l.c. gave 580 mg (31%) of 24 (9) as an oil. The i.r. spectrum showed the β-lactam carbonyl at 1740 cm^{-1}. The N-methyl group appeared at 2.72 δ in the n.m.r. spectrum.

Formation of 3-substituted-2-azetidinones - General Procedure

To a tetrahydrofuran solution of 1.1 equivalents of diisopropylamine under nitrogen atmosphere at -78° was added 1.0-1.1 equivalents of n-butyllithium (Foote Mineral Co., 1.6 in hexane). After five minutes a tetrahydrofuran solution of the 2-azetidinone which had been cooled to -78° was added to the first solution and this stirred for 0.5-1.5 minutes. A selected electrophile was then added, either neat if liquid, or as a tetrahydrofuran solution if solid. The reaction was stirred at -78° for the times specified. The solution was then poured into water and the aqueous saturated with sodium chloride. The products were extracted with methylene chloride and dried over magnesium sulfate. The products were usually purified by preparative thin-layer (t.l.c.) or column chromatography. Yields refer to purified materials.

3-Derivatives of 1,4-diphenyl-2-azetidinone (10)

a) 3-Iodo derivative (16)

A solution of 2.23 g (0.01 mmoles) of 2-azetidinone and 1.1 equivalents of lithium diisopropylamide was stirred for 3 minutes. Iodine (2.54 g, 1 equivalent) was added; the reaction was stirred for a further 30 minutes. The workup was carried out as usual except that the aqueous layer was saturated with sodium sulfite. Column chromatography (pentane - ether) of the crude product yielded 1.022 g grey solid (29%), m.p. 106.5-108° (ether - pentane). The n.m.r. spectrum indicated peaks at δ=4.72 (d, J=2.0 Hz, 1H), 5.14 (d, J=2.0 Hz, 1H), 7.04-7.47 (m, 10H). The i.r. spectrum showed bands at 1755 (s), 1600 (m) and 1374 (m) cm^{-1}. The mass spectrum of the compound indicated the parent peak at m/e=349. Since the compound tended to decompose, it was not analyzed.

b) Cyclohexanone derivative (14)

To a solution of 3.14 mmoles of the lithio salt of 1,4-diphenyl-2-azetidinone was added cyclohexanone (310 mg, 3.14 mmoles) and the reaction stirred for 10 minutes. Column chromatography of 700 mg of crude product gave 416 mg (41%) of pale yellow solid. Recrystallization from methylene chloride - ether - pentane gave white needles, m.p. 163-164°. The i.r. spectrum showed bands at 3580 (w), 3430 (b), 2940 (s), 1735 (s), 1600 (m), 1495 (m), 1380 (m)

and 1145 (m) cm^{-1}. The n.m.r. spectrum showed peaks at δ=1.06-2.10 (m, 11H), 3.16 (d, J=2.5 Hz, 1H), 5.06 (d, J= 2.5 Hz, 1H) and 7.00-7.48 (m, 10H).

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21. Found: C, 78.35; H, 7.21.

c) Acetone derivative (13)

1,4-diphenyl-2-azetidinone (3.97 mmoles) was stirred with 1.0 equivalent of lithium diisopropylamide for 30 seconds and 3 ml (10 equivalents) of acetone was added. The reaction was stirred for 10 minutes. Workup gave 1.18 g of yellow solid. Column chromatography yielded 643 mg (58%) of white solid, m.p. 148-149.5° (methylene chloride - ether - pentane). The n.m.r. spectrum showed peaks at δ=1.32 and 1.43 (two singlets, 6H), 1.87 (s, 1H), 3.10 (d, J=2.5 Hz, 1H), 5.00 (d, J=2.5 Hz, 1H), and 7.00-7.45 (m, 10H). The i.r. spectrum showed bands at 3580 (w), 3460 (b), 1725 (s), 1600 (m), 1350 (m) and 1375 (m) cm^{-1}.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.97. Found: C, 76.25; H, 6.77; N, 4.90.

d) Benzoyl derivative (15)

1,4-diphenyl-2-azetidinone (1.22 g, 5.49 mmoles) was stirred with 1.05 equivalents of lithium diisopropyl-amide for 30 seconds and 1 equivalent of methyl benzoate was added. After 10 minutes the reaction was worked up to give 1.85 g of yellow solid. Column chromatography yielded

1.1 g (61%) of white solid, m.p. 133-136° (methylene chloride - ether - pentane). The n.m.r. spectrum showed peaks at δ=4.80 (d, J=2.0 Hz, 1H), 5.75 (d, J=2.0 Hz, 1H), 6.95-7.61 (m, 13H), 8.05-8.25 (m, 2H). The i.r. spectrum showed bands at 1740 (s), 1682 (s), and 1600 (m) cm^{-1}.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.24; N, 4.28. Found: C, 80.48; H, 5.47; N, 4.20.

Decomposition of the lithio salt of 1,4-diphenyl-2-azetidinone

To a solution of 1.1 equivalents of lithium diisopropylamide was added 2.80 mmoles of 2-azetidinone and the solution allowed to warm to room temperature over twenty minutes. Workup yielded 630 mg of crude material which was recrystallized from methylene chloride - ether to give 167 mg (27%) of 17 as a white solid, m.p. 182-183°. The i.r. spectrum (KBr pellet) showed bands at 3380 (w), 1740 (s), 1710 (s), 1600 (m), 1490 (m), 1360 (m), 750 (m) and 690 (m) cm^{-1}. The n.m.r. spectrum (DMSO-d_6) showed peaks at 2.78-3.48 (m, 2H), 4.57 (d, J=2.5 Hz, 1H), 4.72-5.08 (m, 1H), 5.42 (d, J=2.5 Hz, 1H), 6.06 (d, J=7.5 Hz, 1H), 6.48 (d, J=6.5 Hz, 2H), 6.82-7.60 (m, 18H).

Anal. Calcd. for $C_{30}H_{26}N_2O_2$: C, 80.69; H. 5.87; N, 6.27. Found: C, 80.58; H, 5.95; N, 6.25.

Formation of 3-derivatives of 1,4-dimethyl-4-vinyl-2-azetidinone (28)

a) Acetone derivative (29)

A solution of the lithio salt of 28 prepared from 334 mg (2.7 mmoles) of 2-azetidinone was reacted with 3 ml of acetone for 5 minutes at -78°. Workup gave 538 mg of colourless oil which after purification by preparative t.l.c. gave 377 mg (77%) of white solid, m.p. 64.5-70.5° (methylene chloride - ether - pentane). The n.m.r. spectrum showed peaks at δ=1.16-1.75 (m, 9H), 2.42-3.09 (m, 5H), and 5.00-6.45 (m, 3H). The i.r. spectrum showed bands at 3580 (m), 3440 (b), 2980 (s), 1730 (s), 1375 (s), 999 (m) and 925 (m).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.45; H, 9.16; N, 7.62.

b) Benzophenone derivative (30)

To a solution of 3.0 mmoles of the lithio salt of 28 was added 550 mg (3.0 mmoles) of benzophenone. The reaction was worked up after five minutes to yield 850 mg of crude product. Column chromatography (silica gel, Chloroform-methanol) gave 683 mg (75%) of adduct as a mixture of diastereomers, m.p. 147-152° (methylene chloride - ether). The n.m.r. spectrum showed peaks at δ=1.05 and 1.37 (two singlets, 3H), 2.67 (d, J=1 Hz, 3H), 2.81 and 3.03 (two singlets, 2H), 4.23 (s, 1H), 4.83-5.93 (m, 3H), and 7.00-7.80 (m, 10H). The i.r. spectrum showed bands at 3420 (b), 1730 (s), 980 (w), and 920 (w) cm^{-1}.

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.03; H, 6.96; N, 4.53.

Formation of 3-derivatives of 1-methyl-4-vinyl-2-azetidinone (21)

a) Acetone derivative (33)

To a solution of 3.88 mmoles of the lithio salt of 21 was added 3 ml (10 equivalents) of acetone. The reaction mixture was stirred for 5 minutes at -78°. Workup gave 704 mg of a colourless oil from which 522 mg (80%) of 33 was isolated as a pale yellow oil by preparative t.l.c. using 5% methanol in chloroform as eluent. The i.r. spectrum showed strong bands at 3440 and 1730 cm^{-1}; n.m.r. peaks occurred at δ=1.24 and 1.43 (two singlets, 6H), 2.60 (s, 1H), 2.75 (s, 3H), 2.75-2.95 (m, 1H), 3.90 (d of d, J=2 and 8 Hz, 1H) and 5.16-6.10 (m, 3H).

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.79; H, 8.97; N, 8.40.

b) 3-Methyl derivative (31)

A solution of 8.5 mmoles of the lithio salt of 21 and 3 ml (50 mmoles) of methyl iodide were allowed to react for 10 minutes. Workup followed by purification by preparative t.l.c. gave 630 mg (59%) of 31 as an oil. The n.m.r. spectrum showed peaks at δ=1.30 (d, J=7.5 Hz, 3H), 2.72 (s, 3H), 2.66-2.94 (m, 1H), 3.50 (d of d, J=8.0 and 2.0 Hz, 1H), 5.10-6.10 (m, 3H).

Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.89; H, 9.01; N, 11.02.

c) Benzoyl derivatives (34) and (35)

From the reaction of 4.1 mmoles of the lithio salt of 21 and 550 mg (4.5 mmoles) of methyl benzoate was obtained 862 mg of crude product. Preparative t.l.c. gave on development with 5% methanol in chloroform two products. The upper fraction was obtained as a yellowish solid, 240 mg (28%), which was recrystallized from ether-pentane to give 34 as white needles, m.p. 66.5-67.5°. The i.r. spectrum showed strong bands at 1750 and 1680 cm^{-1}; the n.m.r. spectrum showed peaks at δ=2.80 (s, 3H), 4.50-4.70 (m, 2H), 5.24-6.00 (m, 3H), 7.24-7.59 (m, 3H), and 7.91-8.24 (m, 2H).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.48; H, 6.01; N, 6.51.

A lower fraction was extracted from the plate (20% methanol in ether) to yield 336 mg (50%) of white solid, m.p. 128-151° (methylene chloride - ether - pentane) to which we have assigned structure 35. The n.m.r. spectrum showed peaks at δ=2.42-2.75 (m, 6H), 3.28-4.00 (m, 5H), 4.84-6.09 (m, 6H), 7.09-7.60 (m, 5H). The i.r. spectrum showed bands at 3580 (w), 3400 (b), 1745 (s), 1542 (w), 988 (m) and 930 (m) cm^{-1}.

Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.96; H, 6.80; N, 8.60.

Attempted epimerization of 1,3-dimethyl-4-vinyl-2-azetidinone (31)

To 1.1 equivalents of lithium diisopropylamide was added 107 mg (0.86 mmoles) of 2-azetidinone and the solution stirred for 1.5 minutes. Workup gave 92 mg yellow oil. The n.m.r. spectrum was identical to that of the starting material.

Benzophenone derivative of 1,3-dimethyl-4-vinyl-2-azetidinone (32)

To 220 mg (1.76 mmoles) of 31 and 1.1 equivalents of lithium diisopropylamide was added 320 mg (1.0 equivalent) of benzophenone. The reaction was stirred for 10 minutes. Workup gave 558 mg of crude product which was recrystallized to give 195 mg of white solid which was then chromatographed on silica to give 162 mg (30%) of pure 32, m.p. 171-172.5° (methylene chloride - ether - pentane). The i.r. spectrum showed bands at 3600 (w), 3460 (b), 1735 (s), 1020 (w) and 925 (w) cm^{-1}. The n.m.r. showed peaks at δ=1.30 (s, 3H), 2.46 (s, 3H), 3.36 (broad singlet, 1H), 3.90 (d, J=7 Hz, 1H), 5.03-6.06 (m, 3H), and 7.12-7.69 (m, 10H).

The mass spectrum of the compound indicated the parent peak at m/e=307.

Benzophenone adduct of 1-methyl-4-phenyl-2-azetidinone (36)

A solution of the lithio salt of 24 was prepared by reacting 371 mg (2.3 mmoles) of 2-azetidinone with 2.5

mmoles of lithium diisopropylamide for 1 minute. Benzophenone (420 mg, 2.6 mmoles) was then added and the reaction mixture stirred for 6 minutes. Workup gave 750 mg of an orange solid from which 390 mg (50%) of adduct was obtained as a white powder, m.p. 216-217° (methylene chloride - ether). The i.r. spectrum had bands at 3560 (w), 3360 (b) and 1726 (s) cm^{-1}. The n.m.r. peaks occurred at δ=2.75 (m, 4H), 4.00 (broad singlet, 1H), 4.33 (d, J=2.0 Hz, 1H) and 7.00-7.66 (m, 15H).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.32; H, 6.01; N, 4.07.

N-benzylation of 4-methyl-4-vinyl-2-azetidinone (22)

To 1.57 g (14.2 mmoles) of 22 and 5 g of benzyl bromide (2.0 equivalents) was added 400 mg (1.1 equivalents) of potassium hydroxide at 0°. After the vigorous reaction had subsided, the reaction mixture was heated to 70° for 15 minutes. Workup as per the methylation yielded an undetermined amount of crude product which was immediately chromatographed on 60 g of silica gel using chloroform-methanol as eluent to give 1.39 g (49%) of N-benzylated material, 25. The n.m.r. spectrum of 25 showed peaks at δ=1.24 (s, 3H), 2.82 (s, 2H), 4.09 and 4.42 (AB, J=15 Hz), 4.97-6.09 (m, 3H), and 7.27 (s, 5H). The i.r. spectrum showed the β-lactam carbonyl at 1735 cm^{-1}.

Rearrangement of 1-benzyl-4-methyl-4-vinyl-2-azetidinone (25)

The 2-azetidinone, 509 mg (2.54 mmoles), was allowed to react with 1.1 equivalent of lithium diisopropylamide at -78° for 1 minute. An excess of acetone was then added and the reaction stirred a further 5 minutes. Usual workup gave 590 mg of yellow solid. The crude was recrystallized from methylene chloride - ether - pentane to give 195 mg of white crystals. This was chromatographed on a small silica column to yield 177 mg (35%) of 41, m.p. 115-116.5° (methylene chloride - ether - pentane). The i.r. spectrum of this material indicated bands at 3400 (w) and 1650 (s) cm^{-1}. The n.m.r. spectrum indicated peaks at δ=1.79 (s, 3H), 2.20-2.90 (m, 3H), 3.70 (d, half AB situated at 2.76 δ, 1H), 4.85 (m, 1H), 5.46 (broad singlet, 1H), 5.91 (broad singlet, 1H), and 7.32 (s, 5H). The mass spectrum gave a molecular ion at m/e-201.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.38; H, 7.46; N, 6.91.

Chromatography of the mother liquor afforded 27 mg (5%) of 42. The i.r. spectrum showed bands at 3450 (m), 1700 (s), 1410 (m), 1005 (m), and 920 (m) cm^{-1}. The n.m.r. spectrum indicated peaks at δ=0.73 and 1.35 (2s, 3H), 2.22 and 2.56 (AB, J=17 Hz, 2H), 4.46 and 4.59 (2s, 1H), 4.74-5.50 (m, 3H), 5.85-6.33 (broad singlet, 1H) and 7.01-7.45 (m, 5H). Due to the small amount of pure material, 42 was

not analyzed.

1-(2-cyanoethyl)-4-methyl-4-vinyl-2-azetidinone (27)

4-Methyl-4-vinyl-2-azetidinone, 1.0 g and 600 mg of acrylonitrile (1.2 equivalents) were dissolved in 40 ml of dioxane and two pellets of potassium hydroxide were added. The reaction was stirred at room temperature for 10 minutes, at 40-50° for 1 minute, and a further 7 minutes at room temperature. The reaction mixture was worked up as usual to give 1.42 g of oil containing 6% dioxane (92%). The n.m.r. spectrum of 27 indicated peaks at δ=1.57 (s, 3H), 2.73 (m, 2H), 2.88 (s, 2H), 3.33 (m, 2H) and 5.06-6.27 (m, 3H). The i.r. spectrum showed the β-lactam carbonyl at 1730 cm^{-1} and absorption due to the cyano group at 2250 cm^{-1}.

Attempted rearrangement of (27)

2-Azetidinone 27, 533 mg, was allowed to react with 1.0 equivalent of lithium diisopropylamide at -78° for 1.5 minutes. An excess of acetone was added and the reaction stirred a further 5 minutes. Workup gave 522 mg of oil. The n.m.r. spectrum of this indicated elimination of the cyanoethyl moity had occurred due to the appearance of a broad N-H singlet. Starting material could also be detected.

Attempted conversion of bicyclic 2-azetidinone 3 to it's acetone derivative

To 307 mg of 3 was added 1.0 equivalent of lithium diisopropylamide and the reaction stirred at -78° for 3 minutes. An excess of acetone was added and the solution stirred for 5 minutes. Usual workup afforded 290 mg of crude material. Purification by preparative t.l.c. yielded 100 mg of white solid, m.p. 132-135° (methylene chloride - ether - pentane). The i.r. spectrum of this material showed two carbonyl bands at 1720 and 1750 cm^{-1}. The highest peak in the mass spectrum occurred at m/e=219. The n.m.r. spectrum contained multiplets from 1-2 δ, 2.3-3.3 δ and 3.6-3.7 δ, singlets at 5.00 and 7.25 δ and another multiplet at 7.30-7.40 δ. These peaks had an integration ratio of 5:10:1:1:8:2 respectively.

Attempted conversion of 1-methyl-4-vinyl-2-azetidinone to it's 3-carboxyl derivative

To 350 mg of 21 and 1.0 equivalent of lithium diisopropylamide at -78° was added an excess of freshly crushed dry ice. The reaction was stirred for 5 minutes and the solution poured into water. The aqueous was acidified and extracted with methylene chloride. Evaporation of the methylene chloride yielded a yellow liquid which was redissolved in methylene chloride and extracted with 5% sodium bicarbonate. The aqueous was acidified but cooling produced

no precipitated acid.

Attempted conversion of 21 to it's 3-nitro derivative

To 2.45 mmoles of the lithio salt of 21 was added 1.0 equivalent of propyl nitrate and the solution stirred for 20 minutes at -78°. Usual workup afforded an oil which gave an n.m.r. spectrum identical to that of 21.

Attempted nucleophilic displacement on the 3-iodo derivative of 1,4-diphenyl-2-azetidinone with sodium azide.

a) 2-Azetidinone 16, 200 mg, was dissolved in 4 ml of dimethylformamide (DMF) and heated to 100°. Sodium azide, 800 mg, was added as an aqueous solution and the reaction was heated at 90-100° for 7.5 hours. The reaction mixture was then poured into 40 ml of water and extracted with three 25 ml portions of methylene chloride. Drying and evaporating gave 245 mg of oil. An n.m.r. of this indicated it to be starting material containing some DMF.

b) The above procedure was repeated except that the reaction mixture was refluxed for 11 hours. An n.m.r. of the crude product obtained indicated the β-lactam ring had been destroyed due to the absence of the characteristic doublets arising from H_1 and H_2.

Attempted displacement of iodide from the 3-iodo derivative of 1,4-diphenyl-2-azetidinone with benzyl mercaptan

To 53 mg of benzyl mercaptan and 24 mg of potassium hydroxide in 1 ml of methanol was added 150 mg of

2-azetidinone in 6 ml of DMF. The reaction mixture was allowed to stand for 23 hours at room temperature. The crude product was chromatographed to yield two products. The top fraction was a yellow solid which was determined to be dibenzyl disulfide (48 mg). The bottom fraction was an unidentified oil. An n.m.r. of this indicated the absence of the characteristic doublets due to H_1 and H_2.

Attempted conversion of 1,4-dimethyl-4-vinyl-2-azetidinone to it's 3-n-butyl derivative

To the lithio salt of 28 derived from 614 mg of 2-azetidinone was added 1 equivalent of n-butylbromide and the solution allowed to stir at -78° for 8 minutes. Usual workup afforded 514 mg of material which had an n.m.r. spectrum identical to 28.

PART II

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Boiling points are also uncorrected. Infrared spectra were determined on a Beckman IR-20 spectrophotometer in chloroform solution. Nuclear magnetic resonance spectra were recorded on a Varian model T-60 spectrometer. Optical rotations were determined on a Perkin Elmer model 141 polarimeter. Gas-liquid chromatographic analyses were performed on a Varian Series 1200 aerograph with a 10' X 1/8" 10% B.D.S. on Chromosorb W A/W DMCS column. A Speedomax W equipped with a Disc integrator was used to record chromatograms[a].

Preparation of Sulfides - General Procedure

The appropriate thiol was dissolved in a methanol solution containing 1-1.5 equivalents of potassium hydroxide. To this was then added in methanol 1-1.1 equivalents of alkyl halide. The reaction mixture was stirred for a length of time depending on the reactivity of the halide.

(a) Our thanks to Dr. R. R. Fraser for the use of his g.c. equipment.

Enough water was then added to dissolve the potassium salt that had precipitated and the solution was extracted with methylene chloride. The methylene chloride was then washed with 10% potassium hydroxide, dried over anhydrous magnesium sulfate and evaporated. The sulfides had n.m.r. spectra in agreement with their structures.

Phenyl isopropyl sulfide

The sulfide was prepared in 90% yield from 30 g of benzenethiol and 33.5 g (1 equivalent) of isopropylbromide.

n-Butyl phenyl sulfide

Benzenethiol, 30 g (0.273 mole) and 41 g (0.30 mole) of n-butylbromide yielded 41 g (90%) of sulfide.

Ethyl phenyl sulfide

To 30 g of benzenethiol in 180 ml of saturated methanolic potassium hydroxide was added 46 g of ethyliodide to give 30 g of sulfide (73%).

t-Butyl isopropyl sulfide

t-Butylthiol, 20 g, was reacted with 30 g of isopropylbromide (1.1 equivalents) to give 15.7 g of sulfide (54%).

t-Butyl phenyl sulfide

To 11.0 g (0.10 mole) of benzenethiol in 100 ml of methanolic potassium hydroxide was added 12 g of t-butylchloride (1.1 equivalents). The reaction was stirred at room temperature for 50 hours and a further 6 hours at 70°.

Water was added as usual and the solution extracted with ether. The ether was dried and evaporated to give 2.1 g (13%) of sulfide. This sulfide must not be extracted with methylene chloride since a product results due to the displacement of chloride from methylene chloride to give Ph-S-CH_2-S-Ph. In one attempt to prepare t-butyl phenyl sulfide, this biproduct was obtained in 50% yield. It can be distilled, b.p. 156-157°/0.25 mm. and recrystallized from pentane to give white needles, m.p. 37-38°, reported (17), 40°.

Preparation of Sulfoxides - General Procedure

An example of the oxidation of sulfide to sulfoxide follows. To 25 g of methyl phenyl sulfide (Aldrich Chemical Co.) in 1 liter of a 50% methanol-water mixture at 0° was added dropwise and with stirring 1 equivalent of sodium metaperiodate as a saturated aqueous solution. When addition was complete, the reaction was allowed to warm to room temperature and stir overnight. The precipitate of sodium iodate was removed by filtration and the filtrate extracted 3 times with 125 ml portions of methylene chloride. The methylene chloride solution was dried over magnesium sulfate and evaporated to give 19 g (67%) of sulfoxide which was distilled at 100-101°/0.8 mm., reported (18), 83-85°/0.1 mm. This and the following sulfoxides had n.m.r. spectra compatible with their structures.

Either sulfide or sulfoxide was converted to sulfone by dissolving about 1.0 g in methylene chloride and adding 2.1 or 1.1 equivalents of m-chloroperoxybenzoic acid, M.C.P.A., (Aldrich Chemical Co.) and stirring overnight. Workup was accomplished by filtering the solution and washing the filtrate with 10% sodium sulfite and 10% sodium bicarbonate. The methylene chloride was then dried and evaporated to give sulfone in near quantitative yields. In all cases the sulfones were solid and could be recrystallized from methylene chloride-pentane.

Phenyl isopropyl sulfoxide (19)

Phenyl isopropyl sulfide, 41.3 g (0.246 mole), was oxidized with 53 g (0.246 mole) of sodium metaperiodate to give 20 g (48%) of phenyl isopropyl sulfoxide.

n-Butyl phenyl sulfoxide

n-Butyl phenyl sulfide, 41 g, was oxidized to give an undetermined amount of sulfoxide, b.p. 107-108°/0.8 mm., reported (20), 92-96°/0.5 mm.

t-Butyl isopropyl sulfoxide

t-Butyl isopropyl sulfide, 15.7 g, was oxidized to yield 14 g (84%) of sulfoxide. The n.m.r. spectrum indicated peaks at δ=1.16 (s, 9H), 1.10 and 1.25 (two doublets, J=7.0 Hz, 6H) and 2.95 (m, 1H).

t-Butyl ethyl sulfoxide (21)

Oxidation of 13.9 g of sulfide gave 10 g (60%) of sulfoxide.

t-Butyl methyl sulfoxide and sulfone

Dimethylsulfoxide, 2.52 g (32.3 mmole), which had been freshly distilled from calcium hydride was dissolved in 70 ml of ethyl ether (dried over sodium) and the solution cooled to -78°. To this was added 32 ml of t-butyllithium (1.8 equivalents) and the solution allowed to warm to room temperature over a period of 45 minutes. The reaction was quenched with 10 ml of water and the ethereal layer separated. The ethereal solution was washed twice with water to give 300 mg of crude t-butyl methyl sulfoxide (8%) containing 5% dimethylsulfoxide. The crude was then oxidized to sulfone by the method mentioned previously to give 390 mg of crude material. Sublimation afforded 175 mg of t-butyl methyl sulfone.

α-Chloroethyl phenyl sulfoxide

Ethyl phenyl sulfoxide, 4.4 g, was converted to 3.6 g (65%) of α-chloroethyl phenyl sulfoxide by the method of K. C. Tin and T. Durst (22).

Chloromethyl phenyl sulfoxide

To 16.3 g of methyl phenyl sulfide (0.131 mole) in 100 ml of methylene chloride at 25° was added 10.65 ml of sulfuryl chloride and the reaction allowed to stir overnight. The reaction mixture was then carefully poured into 200 ml of saturated sodium carbonate. The methylene chloride layer was separated and the aqueous further extracted with three 30 ml portions of methylene chloride. The combined

organic extracts were dried and evaporated to give 20.6 g of material containing 14% of dichlorinated material. The total crude was dissolved in 100 ml of methylene chloride and cooled to 0°. To this was added dropwise 26.1 g M.C.P.A.[a] (1 equivalent) in methylene chloride. When addition was complete, the reaction mixture was allowed to warm to room temperature and stir overnight. Workup was accomplished by reducing the volume of the solution to 100 ml, cooling to 0°, and filtering to remove the m-chlorobenzoic acid which had precipitated. The filtrate was washed with 10% sodium bicarbonate, dried, and evaporated to give 15 g of pure sulfoxide (64%) which was distilled, b.p. 140-141°/2.5 mm., reported (2), 138-139°/2mm.

Preparation of Optically Active Sulfoxides - General Procedure

To an ether or tetrahydrofuran solution of l-menthyl-p-toluenesulfinate was added dropwise a solution of the appropriate Grignard reagent. The reactions were stirred for the specified times and then a saturated solution of ammonium chloride was added. The ether layer was separated and the aqueous extracted with methylene chloride. Drying and evaporating the solution afforded crude product which could be purified by thin layer chromatography (t.l.c.).

(a) Use of sodium metaperiodate in this case leads to decomposition. Private communication, K. C. Tin.

n-Butyl p-toluene sulfoxide

To 1.714 g of 1-menthyl-p-toluenesulfinate, $[\alpha]_D$= -199.2° (reported (23), $[\alpha]_D$=-199.19°), in tetrahydrofuran at 0° was added 3 equivalents of n-butylmagnesiumbromide from 400 mg of magnesium and 2.3 g of n-butylbromide also in tetrahydrofuran. After addition was complete, the reaction was stirred a further two hours at room temperature. Workup yielded 1.89 g of colourless oil which was purified by t.l.c. to give 575 mg (53%) of sulfoxide. The sulfoxide was passed through a small silica column to yield a colourless oil, $[\alpha]_D$=126.5° (c. 1.82, acetone), reported (24), $[\alpha]_D$=187.0° (c. 2.5, acetone).

t-Butyl p-toluene sulfoxide

a) To 1.053 g of sulfinate ester in tetrahydrofuran at -78° was added 2.0 ml of t-butyllithium (1 equivalent) and the reaction mixture was stirred for 10 minutes at which time 30 ml of water was added, the tetrahydrofuran layer separated, the aqueous saturated with sodium chloride, and extracted with methylene chloride. The solvent was dried and evaporated to give 1.19 g of crude material. Preparative t.l.c. afforded 330 mg (47%) of sulfoxide which was sublimed to give pure material, m.p. 66-67°, $[\alpha]_D$=30° (c. 1.48, acetone), reported (24), $[\alpha]_D$=161°.

b) To 2.02 g (6.87 mmole) of ester in 80 ml of dry ether at 25° was added 3.50 ml of t-butylmagnesium-

chloride (1.05 equivalents) in 35 ml of ether. After 70 minutes, the usual workup and purification by t.l.c. yielded 390 mg (29%) of pure sulfoxide, $[\alpha]_D$=41.3° (c. 2.06, acetone).

c) To 2.02 g of ester (6.53 mmole) in ether at 25° was added 3 ml of t-butylmagnesiumchloride (0.95 equivalent) and the reaction mixture stirred for 35 minutes. Usual isolation procedures afforded 520 mg (40%) of sulfoxide. An attempt to sublime the material resulted in partial decomposition. Only 100 mg (8%) of pure sulfoxide was obtained, $[\alpha]_D$=137° (c. 2.50, acetone).

d) To 2.03 g of sulfinate ester in ether at 25° was added 0.95 equivalents of t-butylmagnesiumchloride and the reaction stirred for 35 minutes. Bulb to bulb sublimation of the sulfoxide at 60-65°/10μ gave 334 mg (25%), $[\alpha]_D$=94° (c. 2.50, acetone).

Methyl and Ethyl p-tolyl sulfoxides (24)

Both of these sulfoxides were available in these laboratories.

Reaction of Sulfoxides with Alkyllithiums - General Procedure

Approximately 300 mg of sulfoxide was dissolved in 15-20 ml of tetrahydrofuran (distilled from lithium aluminum hydride) in a two necked flask equipped with a serum cap and nitrogen inlet. The solution was either cooled to -78° in a dry-ice-acetone bath or allowed to remain at room temperature. The alkyllithium was then added by means of

syringe. After addition was complete, the reaction was stirred for the specified times. The reactions were worked up in one of two ways. The first method consisted of adding about 0.5 ml of water, evaporating the solution, redissolving the residue in methylene chloride, drying the solution, and evaporating to give crude products. The second method consisted of pouring the whole reaction mixture into 30 ml of water, separating the tetrahydrofuran layer, saturating the aqueous with sodium chloride, and extracting with three 30 ml portions of methylene chloride. The solvent was then dried and evaporated to yield crude products.

When analysis of the crude reaction mixture was possible by n.m.r., some of the crude was immediately dissolved in deuterated chloroform for determination of product ratios. When necessary, the individual products were isolated by preparative t.l.c. (optically active sulfoxides and reaction 1, Table 5). When a v.p.c. analysis was to be performed, the sample was obtained in the following way. Having quenched the reaction mixture by the first method, 1.5-2.0 equivalents of M.C.P.A. was added to the tetrahydrofuran solution, the mixture stirred overnight, and refluxed the next day for 3-8 hours. Then about 30-40 ml of methylene chloride was added, the solution washed with about 15 ml each of saturated solutions of sodium sulfite and sodium bicarbonate. The solvent was then dried and evaporated to

give a mixture of sulfones. The sulfones were then redissolved in about 10 ml of methylene chloride. About 0.5-1.0 µl of this solution was used each time an analytical run was performed. Usually 3-4 injestions were made to obtain an average of the products ratios.

Methyl phenyl sulfoxide with n-butyllithium at 25°

Methyl phenyl sulfoxide, 852 mg (6.09 mmole), was allowed to react with 1.1 equivalents of n-butyllithium (Foote Mineral Co., 1.6 M in hexane) for 5 minutes. Workup yielded 960 mg of crude as an oil. An n.m.r. of this material indicated aliphatic absorption at 0.72-1.94 as a multiplet and integrating to 7 protons due to the propyl hydrogens of n-butyl methyl sulfoxide. The methyl of the two products absorbed at 2.69 (methyl phenyl sulfoxide) and 2.53 δ (n-butyl methyl sulfoxide). The total integration of these two peaks was 29 but also in this region is the methylene group of n-butyl methyl sulfoxide which would account for 5. In consideration of the propyl group absorption, the methyl group of exchanged product should account for 7.5 leaving 16.5 due to the methyl group of the starting material. These integration values demand a product ratio of 70% methyl phenyl sulfoxide to 30% n-butyl methyl sulfoxide.

Methyl phenyl sulfoxide with t-butyllithium

a) Methyl phenyl sulfoxide, 493 mg (3.52 mmole) and 1.0 equivalent of t-butyllithium were allowed to react

at -78° for 10 minutes and the reaction was quenched with 2 ml of deuterium oxide. An n.m.r. of the crude indicated aromatic absorption of intensity 76 (5H), CH_2D (methyl phenyl sulfoxide) of intensity 32 (2H), CH_2D (t-butyl methyl sulfoxide) of intensity 16 (2H) and a large singlet due to the t-butyl group of intensity 80 (9H).

b) Methyl phenyl sulfoxide, 460 mg, was reacted with 3.0 equivalents of t-butyllithium at -78° for 10 minutes. An n.m.r. of the crude indicated aromatic absorption of intensity 20 (5H), methyl (methyl phenyl sulfoxide) of intensity 11.5 (3H), methyl (t-butyl methyl sulfoxide) of intensity 22 (3H); the t-butyl absorption was complicated by high field absorption of impurities.

c) To 629 mg of sulfoxide was added 1.0 equivalent of t-butyllithium. The reaction was allowed to stir at -78° for 10 minutes. Workup yielded 588 mg of crude material. An n.m.r. of this indicated the following integration:

phenyl, 58 (5H); $Ph-\overset{\overset{O}{\|}}{S}-\underline{CH_3}$, 35 (3H); $t\text{-butyl}-\overset{\overset{O}{\|}}{S}-\underline{CH_3}$, 36 (3H), t-butyl, 110 (9H).

d) Methyl phenyl sulfoxide, 526 mg, was allowed to react with 1.0 equivalent of t-butyllithium at 25° for 10 minutes. An n.m.r. of the crude indicated the following integration:

phenyl, 100 (5H); $Ph-\overset{\overset{O}{\|}}{S}-\underline{CH_3}$, 60 (3H); $t\text{-butyl}-\overset{\overset{O}{\|}}{S}-\underline{CH_3}$, 14.5 (3H); t-butyl, 48 (9H).

e) Methyl phenyl sulfoxide, 190 mg, and 1.0 equivalent of t-butyllithium (dropwise addition) were allowed to stir at -78° for 10 minutes. The n.m.r. spectrum of the crude indicated the following integration for the methyl groups of the products:

$\mathrm{Ph\text{-}\overset{O}{\overset{\|}{S}}\text{-}\underline{CH}_3}$, 58 (3H); $\mathrm{t\text{-}butyl\text{-}\overset{O}{\overset{\|}{S}}\text{-}\underline{CH}_3}$, 31 (3H).

f) To 224 mg of methyl phenyl sulfoxide was added 1.0 equivalent of t-butyllithium (fast addition) at -78° and the reaction allowed to stir for 10 minutes. Workup yielded 175 mg of crude material an n.m.r. of which indicated the following integration:

$\mathrm{Ph\text{-}\overset{O}{\overset{\|}{S}}\text{-}\underline{CH}_3}$, 39 (3H); $\mathrm{t\text{-}butyl\text{-}\overset{O}{\overset{\|}{S}}\text{-}\underline{CH}_3}$, 34 (3H).

g) Methyl phenyl sulfoxide, 262 mg, was allowed to react with 1.0 equivalent of t-butyllithium (dropwise addition) at 25° for 10 minutes. Usual workup afforded 239 mg of crude material. An n.m.r. indicated a product ratio of 3 methyl phenyl sulfoxide (CH_3=75) to 1 t-butyl methyl sulfoxide (CH_3=25).

h) To 229 mg of sulfoxide was added 1.0 equivalent of t-butyllithium (rapid addition) at 25° and the reaction allowed to stir for 10 minutes. An n.m.r. of the crude (180 mg) indicated the following integration: methyl

phenyl sulfoxide (CH_3=56); t-butyl methyl sulfoxide (CH_3=22).

i) To 211 mg of methyl phenyl sulfoxide at -78° was added 1.0 equivalent of methyllithium (Foote Mineral Co.) and the solution stirred for 5 minutes. To this was then added 1.0 equivalent of t-butyllithium (dropwise addition) and the solution stirred a further 10 minutes. An n.m.r. of the crude (180 mg) indicated the following integration:

$Ph-\overset{O}{\overset{\|}{S}}-\underline{CH_3}$, 80; t-butyl-$\overset{O}{\overset{\|}{S}}-\underline{CH_3}$, 40.

j) Reaction i) was repeated with 240 mg of sulfoxide under identical conditions except that the t-butyllithium was added quickly. An n.m.r. of the crude (203 mg) indicated the following integration:

$Ph-\overset{O}{\overset{\|}{S}}-\underline{CH_3}$, 73; t-butyl-$\overset{O}{\overset{\|}{S}}-\underline{CH_3}$, 32.

As a check on extraction technique, 191 mg of crude was dissolved in 25 ml of tetrahydrofuran and 25 ml of water was added. The organic layer was separated and the aqueous extracted with four 25 ml portions of methylene chloride. The solvent was dried and evaporated to give 182 mg of crude material. An n.m.r. of this indicated the following integration:

$Ph-\overset{O}{\overset{\|}{S}}-\underline{CH_3}$, 74; t-butyl-$\overset{O}{\overset{\|}{S}}-\underline{CH_3}$, 31.

Phenyl isopropyl sulfoxide and methyllithium

Phenyl isopropyl sulfoxide, 546 mg, was allowed to react with 1.0 equivalent of methyllithium at 25° for 30 minutes. Usual workup gave 418 mg of crude product of which an n.m.r. was identical with that of pure starting material.

Phenyl isopropyl sulfoxide and t-butyllithium

a) Phenyl isopropyl sulfoxide, 297 mg, was allowed to react with 1.0 equivalent of t-butyllithium (dropwise addition) at 25° for 10 minutes. Oxidation and workup afforded 325 mg of crude sulfones. Analysis (g.c.) indicated a product ratio of 85 phenyl isopropyl sulfone to 15 t-butyl isopropyl sulfone.

b) To 301 mg of sulfoxide was added 1.0 equivalent of t-butyllithium (dropwise addition) at -78° and the reaction allowed to stir for 10 minutes. Oxidation and workup gave 281 mg of crude sulfones. Analysis by g.c. indicated a product ratio of 64 phenyl isopropyl sulfone to 36 t-butyl isopropyl sulfone.

Ethyl phenyl sulfoxide and t-butyllithium

a) Ethyl phenyl sulfoxide, 247 mg, and 1.0 equivalent of t-butyllithium (dropwise addition) were allowed to react at -78° for 10 minutes. Analysis of the resulting sulfones (240 mg) by g.c. indicated equimolar amounts of ethyl phenyl and t-butyl ethyl sulfone. t-Butyl phenyl sulfone was detected and amounted to approximately 1% of

the total crude.

b) To 269 mg of sulfoxide was added 1.0 equivalent of t-butyllithium (dropwise addition) at 25° and the reaction allowed to stir for 10 minutes. Analysis of the resulting sulfones by g.c. indicated a product ratio of 71 ethyl phenyl sulfone to 29 t-butyl ethyl sulfone.

c) Ethyl phenyl sulfoxide, 290 mg, was allowed to react with 1.0 equivalent of methyllithium at 25° for 5 minutes. To this was then added 1.0 equivalent of t-butyllithium (dropwise addition) and the reaction allowed to stir for 10 minutes. Analysis of the resulting sulfones (284 mg) by g.c. indicated less than 1% of t-butyl ethyl sulfone present.

d) Reaction c) was repeated with 303 mg of sulfoxide at -78°. Analysis of the sulfones (304 mg) indicated a product ratio of 65 ethyl phenyl sulfone to 35 t-butyl ethyl sulfone.

Di-n-butyl sulfoxide and t-butyllithium

a) To 285 mg of sulfoxide was added 1.0 equivalent of t-butyllithium (dropwise addition) at -78° and the reaction allowed to stir for 10 minutes. Analysis of the resulting sulfones (370 mg) by v.p.c. indicated a ratio of di-n-butyl sulfoxide to n-butyl t-butyl sulfoxide of 94 to 6.

b) Di-n-butyl sulfoxide, 289 mg, was allowed to

react with 1.0 equivalent of t-butyllithium at -78° for 30 minutes. Oxidation and analysis of the sulfones yielded the same product ratio as in a).

Chloromethyl phenyl sulfoxide

a) With t-butyllithium

Chloromethyl phenyl sulfoxide, 352 mg, was allowed to react with 1.0 equivalent of t-butyllithium at -78° for 10 minutes. Analysis of the oxidized crude product by g.c. indicated a ratio of 95 chloromethyl phenyl sulfone to 5 t-butyl phenyl sulfone.

b) With n-butyllithium

To 325 mg of sulfoxide at -78° was added 1.1 equivalent of n-butyllithium and the reaction allowed to stir for 10 minutes. Analysis of the sulfones obtained by oxidation of the crude product indicated the presence of only 4% n-butyl phenyl sulfone.

c) With methyllithium

To 277 mg of chloromethyl phenyl sulfoxide at -78° was added 1.0 equivalent of methyllithium and the reaction allowed to stir at -78° for 10 minutes. Analysis of the resulting sulfones indicated a product ratio of 89 chloromethyl phenyl sulfone to 11 methyl phenyl sulfone.

α-Chloroethyl phenyl sulfoxide

a) With t-butyllithium

α-Chloroethyl phenyl sulfoxide, 383 mg, and 1.0

equivalent of t-butyllithium were allowed to stir at -78° for 10 minutes. Analysis of the oxidized crude product indicated a ratio of α-chloroethyl phenyl sulfone to t-butyl phenyl sulfone of 91 to 9.

b) With n-butyllithium

To 337 mg of sulfoxide at -78° was added 1.1 equivalent of n-butyllithium. The reaction was allowed to stir for 10 minutes. Analysis of the resulting sulfones indicated a product ratio of 78 α-chloroethyl phenyl sulfone to 22 n-butyl phenyl sulfone.

c) With methyllithium

To 262 mg of sulfoxide at -78° was added 1.0 equivalent of methyllithium and the reaction allowed to stir for 10 minutes. Analysis of the sulfones (333 mg) indicated a ratio of α-chloroethyl phenyl sulfone to methyl phenyl sulfone of 64 to 36.

t-Butyl p-tolyl sulfoxide with t-butyllithium

a) t-Butyl p-tolyl sulfoxide, 180 mg, $[\alpha]_D$=30° (c. 1.6, acetone), 18.6% optically pure, was allowed to react with 1.0 equivalent of t-butyllithium at -78° for 10 minutes. Usual workup afforded 160 mg of crude sulfoxide which was purified by preparative t.l.c. The sulfoxide was then sublimed to give 80 mg of pure material, $[\alpha]_D$=0°.

b) To 334 mg of sulfoxide, $[\alpha]_D$=94° (c. 2.20, acetone), 58% optically pure, at -78° was added 0.30

equivalent of t-butyllithium and the reaction allowed to stir for 10 minutes. Workup yielded 250 mg of material which was sublimed to give pure sulfoxide, $[\alpha]_D$=80° (c. 1.83, acetone), 50% optically pure.

c) To 273 mg of t-butyl p-tolyl sulfoxide, $[\alpha]_D$= 114° (c. 2.31, acetone), 71% optically pure, at -78° was added 0.5 equivalent of t-butyllithium and the reaction allowed to stir for 10 minutes. Workup afforded 225 mg of sulfoxide which was sublimed to give pure material, $[\alpha]_D$= -0.5° (c. 3.28, acetone).

Ethyl p-tolyl sulfoxide and t-butyllithium

a) Ethyl p-tolyl sulfoxide, 622 mg, $[\alpha]_D$=164.5° (c. 2.23, acetone), 88% optically pure, was allowed to react with 1.0 equivalent of t-butyllithium for 10 minutes at -78°. Usual workup afforded 525 mg of crude material. Preparative t.l.c. of part of the crude yielded 19 mg (0.097 mmole) of t-butyl p-tolyl sulfoxide and 82 mg (0.488 mmole) of ethyl p-tolyl sulfoxide, $[\alpha]_D$=159.9° (c. 2.23, acetone), 97.5% retention. Further chromatography of the crude yielded a total of 36 mg of t-butyl p-tolyl sulfoxide, $[\alpha]_D$=-24.4° (c. 2.24, acetone), 15% optically pure.

b) To 456 mg of sulfoxide, $[\alpha]_D$=154° (c. 3.07, acetone), 82.5% optically pure, was added at -78° 1.0 equivalent of t-butyllithium and the reaction allowed to stir for 10 minutes. Chromatography of the crude (391 mg) yielded

47 mg (0.236 mmole) of t-butyl p-tolyl sulfoxide, $[\alpha]_D$=-8.9° (c, 1.08, acetone), 5.5% optical purity; 125 mg (0.745 mmole) of ethyl p-tolyl sulfoxide, $[\alpha]_D$=142° (c. 2.04, acetone), 92% retention; and 55 mg of a mixture of ethyl p-tolyl sulfoxide and t-butyl ethyl sulfoxide. An n.m.r. of this mixture indicated 66% t-butyl ethyl sulfoxide present equivalent to 35 mg (0.260 mmole).

Methyl p-tolyl sulfoxide and t-butyllithium

a) Methyl p-tolyl sulfoxide, 508 mg, $[\alpha]_D$=145° (c. 1.6, acetone), 99% optically pure, was allowed to react with 1.0 equivalent of t-butyllithium at -78° for 10 minutes. An n.m.r. of the crude (419 mg) indicated a product ratio of 3 methyl p-tolyl sulfoxide to 1 t-butyl methyl sulfoxide. Preparative t.l.c. afforded pure methyl p-tolyl sulfoxide, $[\alpha]_D$=140° (c. 1.6, acetone), 97% retention. No pure methyl t-butyl sulfoxide was isolated.

b) To 800 mg of sulfoxide, $[\alpha]_D$=145° (c. 1.6, acetone), 99% optical purity, was added 1.0 equivalent of t-butyllithium at -78° and the reaction allowed to stir for 10 minutes. An n.m.r. of the crude (705 mg) indicated a product ratio of 2 methyl p-tolyl sulfoxide to 1 t-butyl methyl sulfoxide. Preparative t.l.c. afforded pure t-butyl methyl sulfoxide, $[\alpha]_D$=0.5° (c. 2.23, acetone).

n-Butyl p-tolyl sulfoxide and n-butyllithium

To 260 mg of sulfoxide, $[\alpha]_D$=126.5° (c. 1.82,

acetone), 67.5% optically pure, was added 1.5 equivalents of n-butyllithium at -78° and the reaction allowed to stir for 15 minutes. Preparative t.l.c. of the crude (225 mg) and Soxhlet extraction of the silica with ether yielded 110 mg of t-butyl p-tolyl sulfoxide, $[\alpha]_D$=115° (c. 1.83, acetone), 91% retention, and 61 mg of di-n-butyl sulfoxide.

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CLAIMS TO ORIGINAL RESEARCH

1. A method for the N-alkylation of β-lactams was developed.

2. The synthesis of some 3-alkylated β-lactams is described.

3. A 1,2 carbanion rearrangement of β-lactams resulting in ring expanded products is also described.

4. The cleavage of a number of sulfoxides upon reaction with alkyllithiums was observed. A discussion of the results favours an Sn2 mechanism.