Nicholas, Elaine C.

STUDIES IN ORGANOSULFUR CHEMISTRY

City University of New York PH.D. 1982

STUDIES IN ORGANOSULFUR CHEMISTRY

by

ELAINE C. NICHOLAS

A dissertation submitted to the Graduate Faculty
in Chemistry in partial fulfillment of the
requirements for the degree of Doctor of Philosophy,
The City University of New York.

1982

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

6/16/82
date

William Frost Sherk
Chairman of Examining Committee

6/29/82
date

David C. Lorde
Executive Officer

Herbert Meislich

John Fryd

Supervisory Committee

To my family,

Abstract

STUDIES IN ORGANOSULFUR CHEMISTRY

by

Elaine C. Nicholas

Advisor: Professor W.F. Berkowitz

The reaction of NBS, dry DMSO and alkenes to produce bromo ketones was explored. Conditions were sought in which the amount of dibromide would be reduced (varying time, temperature , addition of additives such as alkyltrimethylammonium tetrafluorborate resins, etc.). Yields for the reaction with cyclohexene were 18% of 2-bromocyclohexanone and 13% of 1,2-dibromocyclohexane. Instead of using DMSO, different amine oxides were tried. The best results were obtained using quinuclidine oxide which gave upon reaction with cyclohexene 47% of 2-bromocyclohexanone and 6% of 1,2-dibromocyclohexane.

Explorations were made into the synthesis and use of tosylmethyl THP ether as an acyl anion equivalent. It was synthesized from toluenesulfinic acid and formalin to give tosylmethanol (88%) which was treated with dihydropyran (using pyridinium toluenesulfinate as a weak acid catalyst) to give tosylmethyl THP ether (67%). This was reacted with alkyl halides (octyl bromide, benzyl bromide, cinnamyl bromide) and then hydrolyzed to give the corresponding aldehyde plus one additional carbon in good yield.

Acknowledgements

I would like to express my sincere appreciation to Dr. Berkowitz for his unending patience and his encouragement throught the work.

Also, I would like to thank all of the faculty and staff for their help and assistance throught the years.

Finally, I would like to thank my fellow lab. mates (past and present), fellow graduate students and post-doctoral students for their help and assistance through out the years.

CONTENTS

A. Introduction

The work presented here is in two parts: first, work done on the reaction of NBS and DMSO (amine oxides) with alkenes to produce bromo ketones and second, work done on the synthesis and use of tosylmethyl THP ether as an acyl anion equivalent.

For each of the parts a few chapters of historical information will be presented which pertains to the use of such compounds and other relevant information such as closely related mechanistic work, next the proposal, followed by the discussion of the experimental work which we did (Results and Discussion). This is followed by the experimental section for both parts and then the tables.

B. 1. Uses of Halo Ketones

Halo ketones are useful synthetic intermediates because they possess functional groups on adjacent carbon atoms. In some cases, it is possible to cause one of these groups to react selectively while leaving the other intact. Their uses include: 1) base induced ring contraction or Favorskii rearrangement, 2) dehydrohalogenation reaction to the enone, 3) reduction to the ketone, 4) reduction to the halohydrin, 5) reduction of halo group with metals followed by alkylation, 6) substitution reactions in which the halide is a leaving group, and 7) reactions which make use of the halo ketone's bifunctional nature, such as those in which heterocycles are formed. Each of these topics shall be reviewed and some relevant examples will be given.

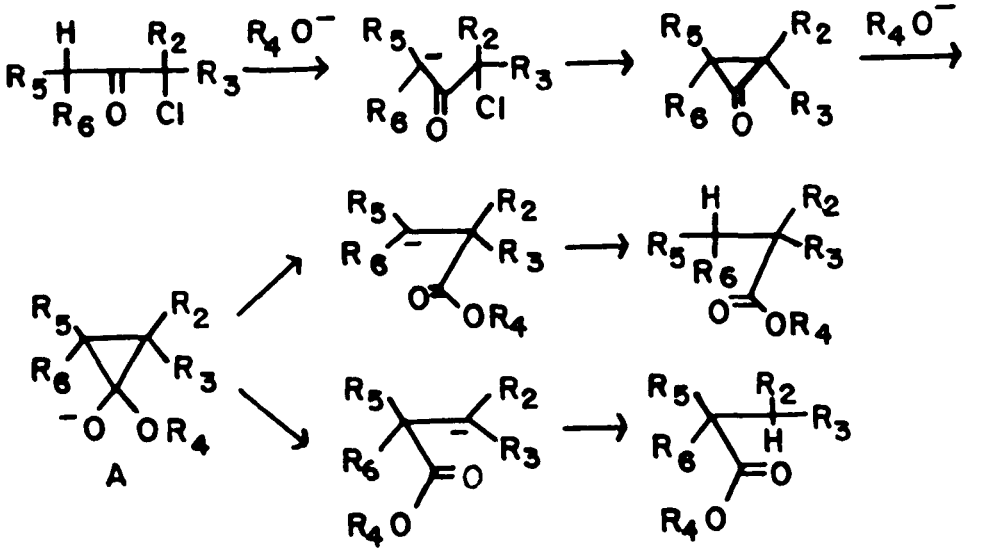
Halogenation of ketones followed by dehydrohalogenation is a method which has been used for many years to convert ketones to enones. Highly basic reagents are to be avoided as the products may undergo a Favorskii rearrangement. To avoid this problem, one can protect the halo ketone as the halo ketal and get elimination of HX by treating it with strong bases such as sodium methoxide or potassium t-butoxide. After deketalization the unsaturated ketone is produced (1).

A more direct method to produce enones is by heating the halo ketone in a weaker base such as collidine or lithium chloride in dimethylformamide (2). In both cases, the reagents are basic enough to cause the desired eliminations but not too basic such that a Favorskii rearranged product is obtained. Another more recent method is to heat the halo ketone in HMPA (approximately 120^{o}C for 12 hours) to give the unsaturated ketone in good yield. It appears that HMPA is sufficiently basic to cause this elimination (3).

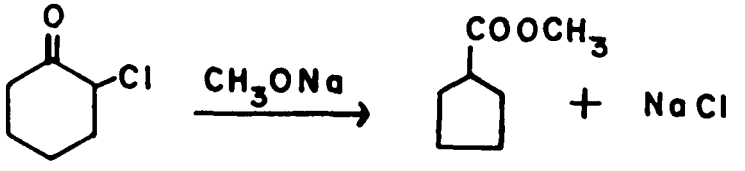
Halo ketones undergo the Favorskii rearrangement when they are reacted with strong bases. Many mechanistic studies have been done on the Favorskii rearrangement and it is still a topic of controversy and further study. The mechanism (4) shown in scheme 1 is probably the most commonly accepted mechanism. It was determined by C-14 labelling studies and studies in which the substituents were changed.

Intermediate A undergoes a ring opening reaction in the direction to produce the most stabilized carbanion. A typical example of this reaction is shown in equation 1 (5). The yield for this reaction is approximately 60%. This reaction is a useful way in which rings can be contracted to one having one less carbon atom in the ring.

Halo ketones can be dehalogenated to produce ketones without the halo group. This can be accomplished by using



Scheme 1



Equation 1

various kinds of reagents. Perhaps the oldest method is reduction of the halogen substituent by warming the mixture of bromo ketone in acetic acid and zinc dust (6).

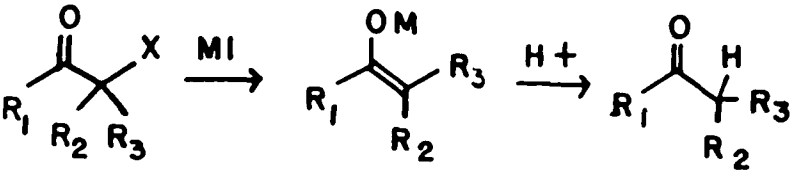
Metal carbonyl complexes also have been found to be useful in reducing halo ketones. Examples of these are molybdenum hexacarbonyl (7) and iron pentacarbonyl (8) which give yields of approximately 80% and 60% respectively.

This type of reduction can also be done by transition metals in low valency states. Halo ketones can be reduced to ketones by chromium(II) acetate (9). In addition, titanium trichloride can be used to give the corresponding ketones in very good yield ($\geq$ 84%) (10).

A number of iodide reagents have been developed for reducing halo ketones. Among them are lithium iodide and boron trifluoride (11), cerium(III) iodide (12), sodium iodide and trimethysilyl chloride (13), and sodium iodide in aqueous acid-THF (14). The mechanism of these reductions are outlined in equation 2. Isolated yields for most of these reactions were very good (generally $\geq$ 90%).

Sodium cyanoborohydride is a reducing agent for alkyl iodides and bromides but it can also be used to to reduce iodo and bromo ketones to the unhalogenated ketone. Sodium cyanoborohydride (15) is thought to reduce organohalides by nucleophilic hydride attack (S_N2) in polar aprotic solvents.

Halo ketones can be treated with zinc to produce a zinc enolate. This zinc enolate can be alkylated by being



Equation 2

treated with electrophiles such as methyl iodide (16), chlorosulfides (17), and aldehydes (16,18). This type of reaction is similar to the classical Reformatsky reaction and appears to be a good way to alkylate the original site of the bromide in bromo ketones, even when the corresponding zinc enolate is the less stable one. While methyl iodide gives good yields other alkyl halides do not. By alkylating with aldehydes followed by dehydration, alkylidene ketones were obtained in good yields. These presumably can be reduced to give the alkylated product in good yield (16). Russian workers (17) solved this problem by using chlorosulfides, making it possible to produce a fully alkylated a-position.

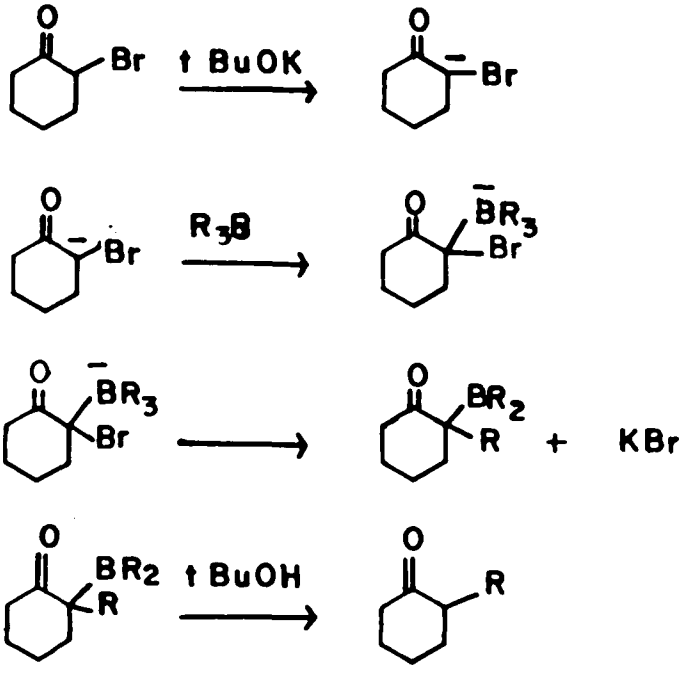
Japanese (18) workers treated bromo ketones with zinc and diethyl aluminium chloride in THF at low temperatures. This produces an aluminium enolate, which can then be treated with aldehydes to produce B-hydroxy ketones in excellent yields ($\geq$ 92%).

Bromo ketones can be alkylated by using copper lithium reagents (19,20). The desired product is formed by direct substitution of bromide by the copper lithium reagent. Unfortunately, yields for this reaction tend to be low, especially for bulky cuprates and/or hindered ketones.

Alkylations of bromo ketones were also done using trialkylboranes and potassium t-butoxide in THF. The

mechanism (21) is shown in scheme 2. A caveat in this reaction is the possibility that when halo ketones are treated by strong bases, a Favorskii rearranged product may result. Yields for straight chain alkyl boranes were generally good, but with secondary and tertiary alkyl boranes, reported yields were 0%.

Halo ketones can be reduced selectively at the carbonyl carbon while leaving the carbon-halogen bond intact to produce the corresponding bromohydrins. This has been done by using aluminium isopropoxide and by using sodium borohydride (22). The stereoisomer obtained in this manner

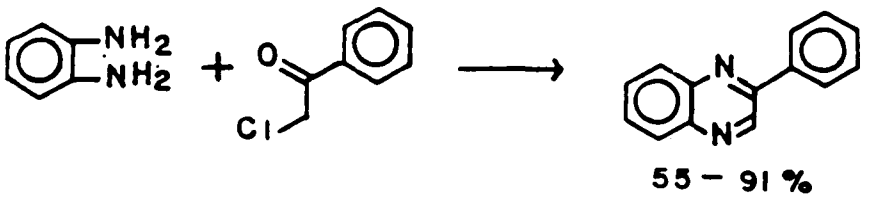


Scheme 2

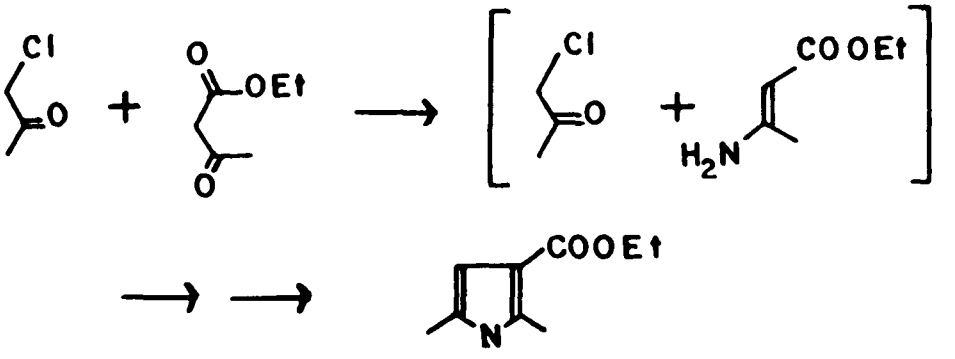
is often different than that obtained through other methods of bromohydrin formation.

Halo ketones are used extensively in the synthesis of heterocycles. Heterocycles are often synthesized from the fragments to produce the heterocycle with the desired substituents already built in rather than through substitution reactions as is done in benzene chemistry. Halo ketones are good fragments because they have three points of nuleophilic attack on only two carbon atoms.

One classical example of the use of halo ketones in heterocycles is in the Hantzsch synthesis of pyrroles (23). The mechanism is outlined in equation 3. Generally, the halo ketones used in heterocyclic synthesis are simple ones, made from either symmetrical ketones or from ketones which have only one position with enolizable hydrogens such as acetophenone. Such an example is shown in the synthesis of quinoxaline (24) by treating a substituted phenacyl chloride with ortho-diaminoaniline as shown in equation 4.



Equation 3



Equation 4

In conclusion, halo ketones can be reduced to either ketones or halohydrins. They can be alkylated and, upon base treatment, can undergo the Favorskii rearrangement. They are used in the synthesis of heterocycles. Thus, halo ketones are very useful intermediates because of the wide variety of reactions that they can undergo.

2. Ways to Form Halo Ketones from Ketones

The most common way to form bromo ketones is by treatment of a ketone with a brominating agent. There are many different aspects involved such as the effect of substituents, acid- vs. base-catalysis, type of brominating agents, concentration, free-radical vs. ionic conditions, etc.. Although this is a rather complex topic, major trends shall be discussed as background material for the proposal at hand. In this discussion, brominations shall be emphasized rather than chlorinations, because the proposal (see Chapter 8) involves a bromination reaction.

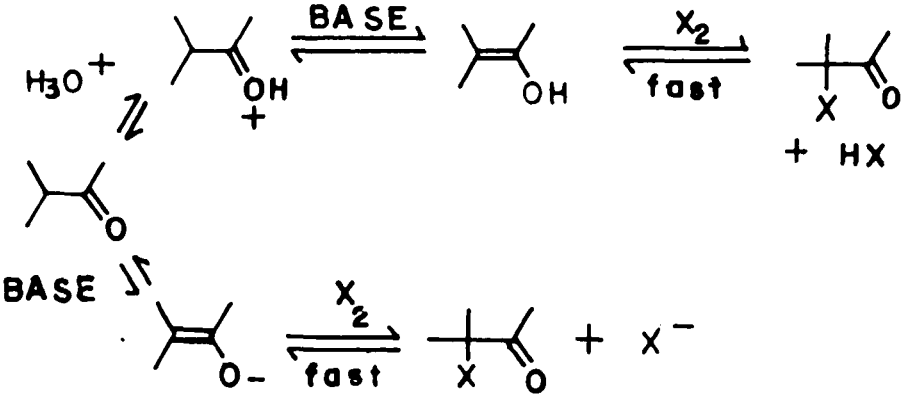
Most of the studies presented in this section were done using bromine as the brominating agent. Other brominating agents are available, but these shall be discussed in a special section.

The mechanisms (25) of acid- and base-catalyzed halogenations of ketones are shown in scheme 3.

The intermediate involved in the acid-catalyzed route is the enol, whereas, in the base-catalyzed route, it is the enolate. For monohalogenations, the acid-catalyzed route is preferred because monohalogenated ketones are less basic and therefore, less prone to undergo enolization and subsequent halogenation than the unhalogenated ketones. The use of

acid-catalyzed halogenations generally allows one to produce monohalogenated ketones. The reverse is true for base-catalyzed halogenations. Halo ketones are more acidic than unhalogenated ketones so they form enolates more readily, which undergo subsequent halogenation. Base-catalyzed halogenation of ketones is generally avoided because the product is a mixture of di- and tri-halogenated products (25).

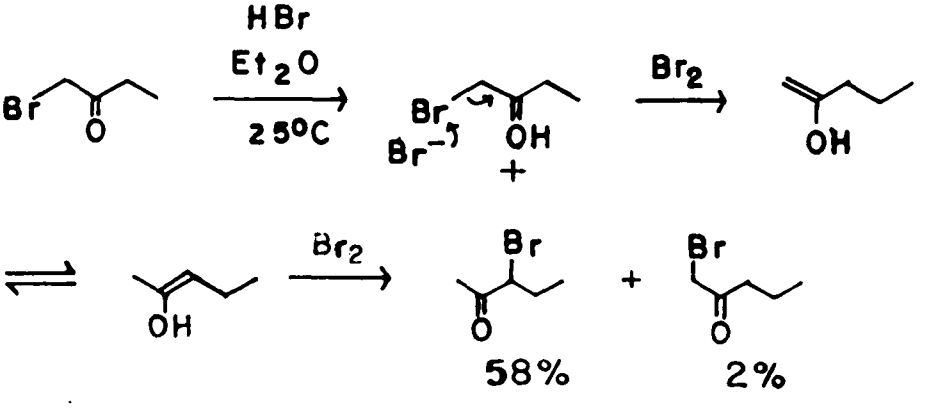
Halogenations of unsymmetrical ketones generally take place with a greater percentage of halogen at the more highly substituted a-position. Thus reaction at a CH group is perferred over a CH_2 group, which is preferred over a CH_3 group. This is because the more highly substituted enol is the major product due to thermodynamic control (26). This is further is complicated because bromo ketones are readily isomerized under acid-catalyzed



Scheme 3

conditions as shown in scheme 4 (27). Although bromination is perferred at the more highly substituted carbon atom, one generally obtains mixtures of the *a* and *a'* monohalogenated products.

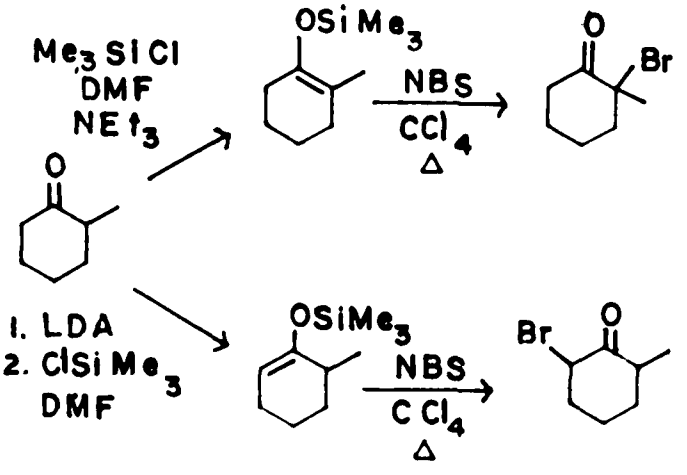
Unsymmetrical ketones can be regiospecifically halogenated by treating silyl enol ethers (28), enol acetates (29), enol ethers (30), or lithium enolates (29) with a halogenating agent. The more highly substituted enolate can be generated under thermodynamically controlled conditions and trapped by reaction with an electrophile such as trimethylsilyl chloride to produce the silyl enol ether or acetic anhydride to produce the enol acetate. Under kinetically controlled conditions, such as treatment of the ketone with a strong base followed by addition of an electrophile, the less highly substituted enol ether will be produced (31).



Scheme 4

The protected enol ethers are deprotected by appropriate means such as treatment with fluoride ion to deprotect silyl enol ethers and with treatment of enol acetates with methyl lithium to produce the corresponding lithium enolates. These resulting enolates are not allowed time to equilibrate, but instead are immediately treated with a halogenating agent which produces the halo ketone regiospecifically as shown in scheme 5 (29). Thus, through the use of kinetic vs. thermodynamic product control, it is possible to trap the desired enol which can then be halogenated to yield the desired halo ketone.

Although most of the above noted work dealt with bromine as the brominating agent, many different brominating agents have been developed which are now currently being used.



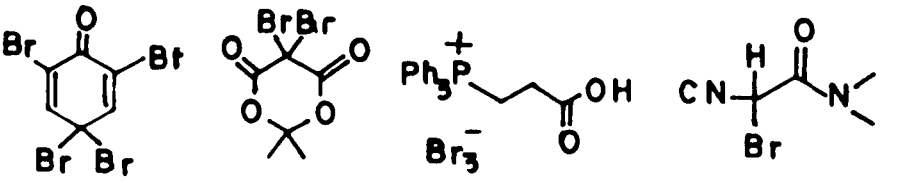
Scheme 5

Pyridine hydrobromide perbromide has been used to brominate ketones (32). It is a crystalline, stable salt. Small quantities can be easily weighed, in contrast, to bromine. Reactions were performed by warming the ketone and the salt in acetic acid, ethanol or a solution of ethanol and chloroform.

Phenyl trimethylammonium perbromide (33-35) is a brominating agent which is similar to pyridinium hydrobromide perbromide, but it is even more stable. It is soluble in THF and the by-product, phenyltrimethylammonium bromide, is insoluble thus making the isolation process easier. It is used to a-brominate ketones and acetals. It showed some selectivity in the bromination of ketones in the presence of double bonds.

Pyrrolidone hydrotribromide, another brominating agent, is even more selective in bromination of ketones in the presence of double bonds (36,37).

The brominating agent, 2,4,4,6-tetrabromo-cyclohexan-2,5-dienone, B, (38) can be used to a' brominate a,B unsaturated ketones. The reaction is enhanced by addition of gaseous HCl or HBr which reacts to form bromine (or bromochloride) and 2,4,6-tribromophenol. The low concentration of bromine thus produced is the actual brominating agent.



B C D E

A similar brominating agent is 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane, C (39). It is similar to 2,4,4,6-tetrabromocyclohexa-2,5-dienone in that it is used to a' brominate a,B unsaturated ketones and the reaction is enhanced by addition of a small amount of HBr.

2-Carboxyethyl triphenylphosphonium perbromide, D, (40) can also be used to brominate ketones in the presence of double bonds. It can also be used to brominate the a' position of a,B unsaturated ketones. This reagent is thought to be a bromine (Br_2) transfer agent.

2-Bromo-2-cyano-N,N-dimethyl acetamide, E, (41) can be used to a' brominate a,B unsaturated ketones. It can also be used to selectively brominate the a-carbon of ketones on the side favorable to enolization. It is thought to proceed via radical mechanism because reaction times are reduced upon addition of the initiator, AIBN, and product formation is restrained upon addition of p-benzoquinone.

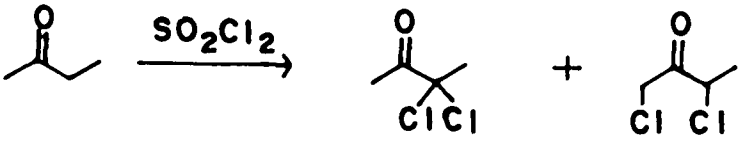
Sulfuryl chloride has been used in the chlorination of ketones. Regiospecificity is not high and dichloro products

are often produced as shown in equation 5. It probably reacts via a radical mechanism (42).

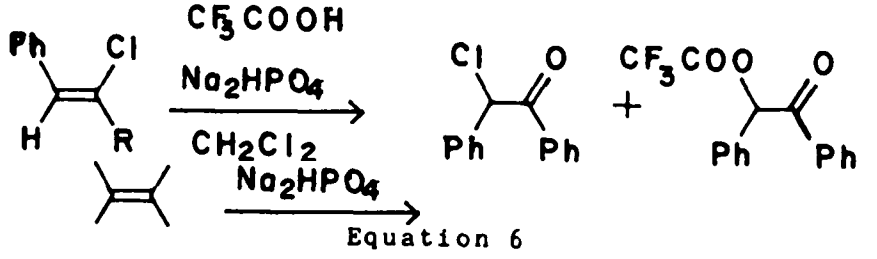
Hydrobromous acid and NBS, used in the presence of light irradiation or radical initiators, are thought to react also via a radical mechanism (43).

Copper(II) bromides and chlorides have been used in the bromination of ketones (44-48). The mechanism is thought to proceed through a copper halide catalyzed enolization. Next, a halogen atom is transferred to the enolate. Chlorination takes place at the more highly substituted carbon atom (48).

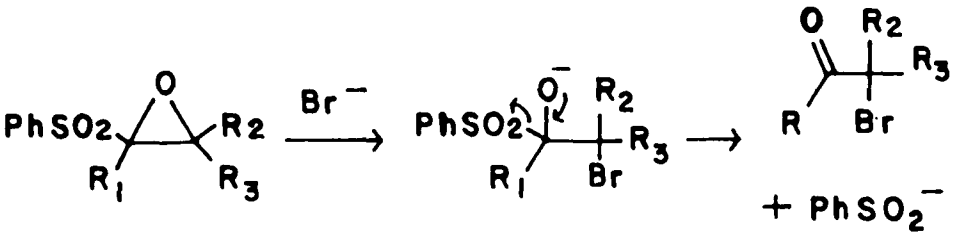
Bromo ketones have also been produced through intramolecular rearrangement as shown in equations 6 and 7. While these reactions do form halo ketones, the reactants involved (the chloroalkene and sulfone epoxide) are not as readily available as in some reactions.



Equation 5



Equation 6



Equation 7

In conclusion, much work has gone into the regiospecific formation of halo ketones from symmetrical and unsymmetrical ketones. Acid-catalyzed bromination of unsymmetrical ketones usually gives the more highly substituted bromo ketone. The most regiospecific bromo ketone formation is from trapped enolate derivatives such as silyl enol ethers. Although much work has gone into the development of new brominating agents, etc., and into greater regiospecificity in bromination of ketones, undoubtedly in upcoming years even more work will be directed in these areas.

While these ways are of interest, the proposal (Chapter 8) involves work done on a reaction of alkenes to form bromo ketones. The next chapter deals with ways this problem has been solved in the past.

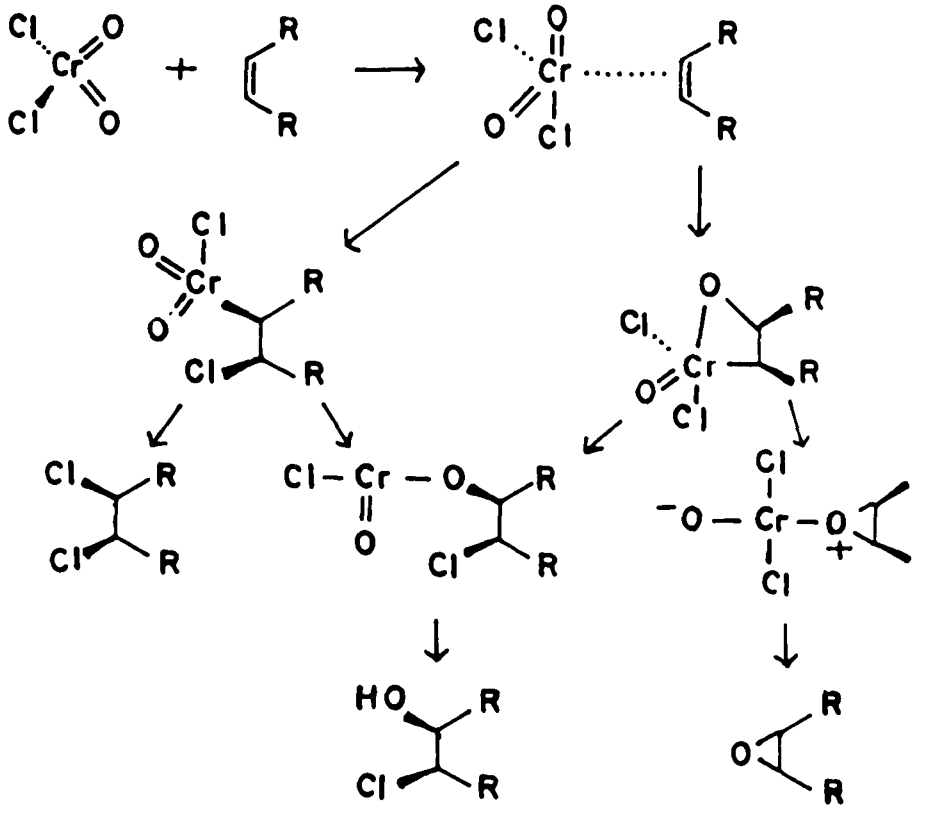
3. Conversion of Alkenes to Halo Ketones

There are several ways in which alkenes can be converted into halo ketones. Some of these involve just one step, whereas others involve two steps in which the intermediate may need to be isolated.

Sharpless reported (49) that reaction with di- and tri-substituted alkenes with chromyl chloride in acetone forms the chloro ketone in good yield. When this reaction is run using methylene chloride as the solvent instead of acetone the reaction products are the chlorohydrin, the epoxide, and the dichloride (50,51).

Results were reported mainly for symmetrical alkenes giving the expected chloro ketone in approximately 70% yield. Trans alkenes gave higher yields than cis alkenes. For example, trans-5-decene gave 81%, whereas cis-5-decene gave 65% of the chloro ketone (52). Results on the unsymmetrical alkene, trans-2-octene, indicate that a 1:1 mixture of the two chloro ketones was produced. When 4,4-dimethyl-trans-2-pentene was treated, it resulted in a 10:1 mixture of the 4,4-dimethyl-3-chloro-2-pentanone and 4,4-dimethyl-2-chloro-3-pentanone. The only result reported for a tri-substituted alkene was 2-methyl-2-heptene which gave that 45% of 2-chloro-2-methyl-3-heptanone plus 32% of

an unidentified chlorohydrin (49). The chlorohydrin with a tertiary hydroxyl group may have been produced but since it could not be further oxidized, it remained as such. A mechanism was presented in a later paper (51) for chlorohydrin, epoxide, and dichloride formation but not for chloro ketone formation. Sharpless postulated the mechanism shown in scheme 6 for the production of cis-dichloride, cis-chlorohydrin, and epoxide.

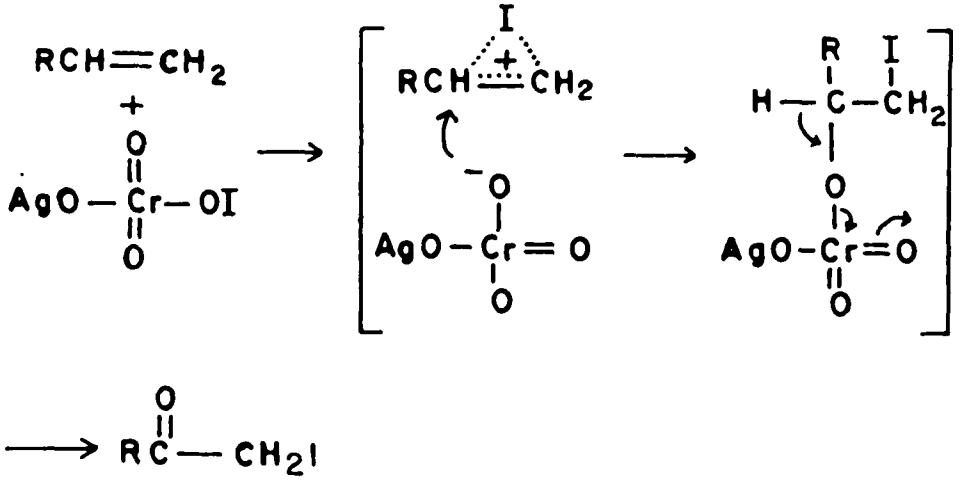


Scheme 6

The possibility of side reactions from the use of a strong oxidizing agent such as chromyl chloride may hinder the utility of this method as a one step preparative method to synthesize halo ketones (53,54,55).

Cardillo and Shimizu (56) reported a method for synthesizing iodo ketones from alkenes using silver chromate and iodine. The proposed mechanism for this reaction is shown in scheme 7. This reaction gave a range of yields. The primary alkene, 1-octene, gave 86% isolated yield of the corresponding iodo ketone, whereas cyclohexene gave a 60% yield of iodo ketone.

Iodo ketones are relatively unstable (56) and are often reduced to the corresponding ketone. Thus the best use of this type of transformation is from alkene to ketone. Many times the halo ketone is what is desired because of the reactivity of the halogen in addition to the keto group.



Scheme 7

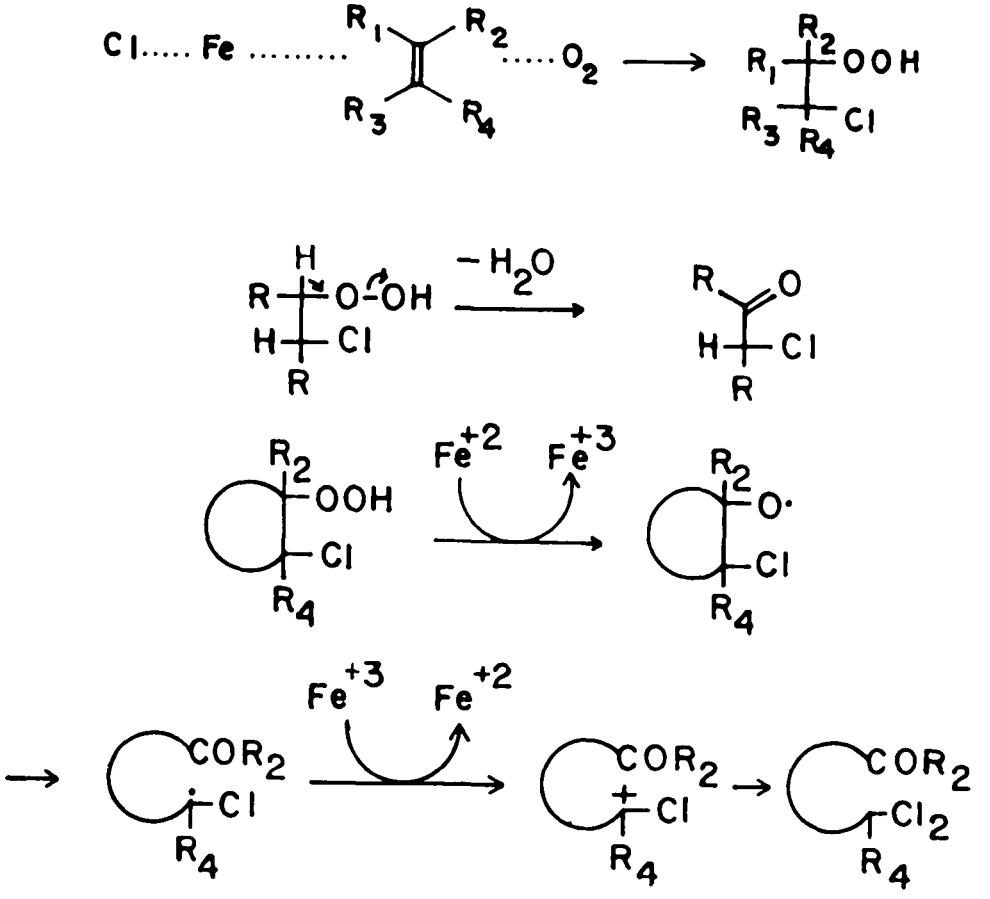
If the halo functionality is desired, it may not be the best strategy to make the iodo ketone because of the instability of the iodo group and possible decomposition to the unhalogenated ketone. Another problem is the cost of the reagent, silver nitrate, needed to make the silver chromate. This reaction or a large scale may be cost prohibitive (57).

Piancatelli *et al*. reported a method of synthesizing cyclic iodo ketones from cycloalkenes using pyridinium dichromate and iodine (58). This reaction works for cyclic olefins. When linear olefins were used, unidentified mixtures resulted which decomposed despite attempts to isolate them. The yields on this reaction range from 50-70% (58). In addition, this method has the drawback of producing iodo ketones which may not be sufficiently stable if a-functionality is required.

Japanese workers reported (59,60) that chloro ketones can be made from mono- or di-substituted olefins. A solution of the alkene in pyridine was irradiated with Pyrex-filtered light in the presence of iron(III) chloride while oxygen gas was being bubbled through. Tri- and tetra-substituted olefins gave dichloro ketones which had undergone a C-C bond cleavage. The mechanism (60) which the authors proposed is shown in scheme 8. Originally , a radical mechanism was proposed but was later revised after it was observed that radical inhibitors did not affect the

formation of chloro ketones from olefins. A major drawback to this scheme is that for tri-substituted olefins, a product is formed which results from C-C bond cleavage.

Another method of conversion of alkenes to chloro ketones is by reaction with nitrosyl chloride to produce the chloro oxime. This can then be hydrolyzed to render the corresponding chloro ketone (61). These authors found that the chloro oximes could be hydrolyzed through warming to



Scheme 8

50°C a mixture of the chloro oxime, levulinic acid, and hydrochloric acid. Overall yields of the chloro ketone from the starting alkene were approximately 65%.

Corey (62) reported a method of reductive hydrolysis of chloro oximes to ketones using conditions which acid and base sensitive functional groups could survive. According to this strategy, the oxime could be acetylated by reaction with acetic anhydride at 20°C. This oxime O-acetate and excess chromous acetate in THF/water were stirred at moderate temperatures and then worked up to give a good yield (>80%) of the corresponding ketone. When this method was applied to chloro oximes the product was the ketone. For example, the chloro oxime of cyclooctene gave cyclooctanone in 88% yield.

Through the use of nitrosyl chloride, alkenes can be converted into ketones using Corey's method (62) or can be converted to chloro ketones using fairly acidic condtions. The latter method has the disadvantage that acid sensitive groups, such as THP ethers, can be cleaved under these conditions.

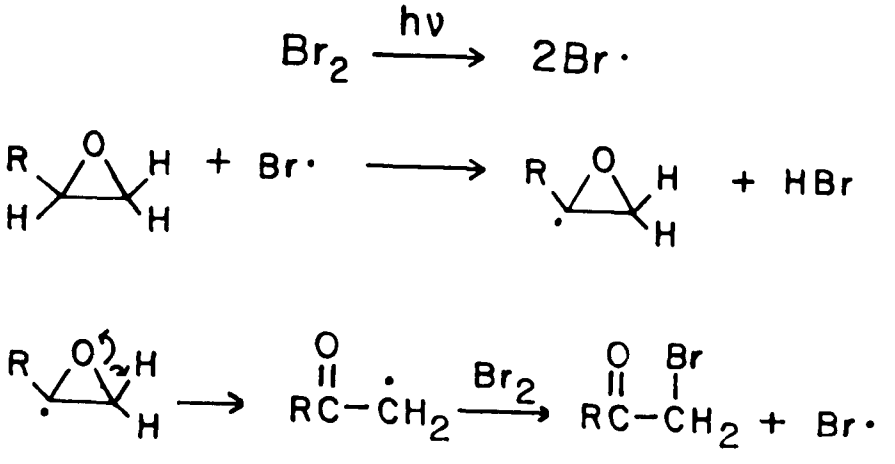
Two other methods have been used by which halo ketones can be made from alkenes and again both of these are two step procedures. The first method (63) is by reaction of the epoxide (which can be readily made from the alkene) with one equivalent of bromine under photolytic condititons. The

mechanism is shown in scheme 9. Average yield of the resulting bromo ketone from the epoxide was 85% or better.

The second method of formation of halo ketones from epoxides is that of Olah (64) in which he treated the epoxide with halodimethylsulfonium halides. The intermediate involved here was probably the halo sulfoxonium salt which then decomposes to the halo ketone. This method is discussed in more detail in Chapter 6.

The final method to be discussed is that by which the alkene can be converted to the bromohydrin which can then be oxidized to the bromo ketone. Formation of bromohydrins from alkenes is a well known reaction and is discussed in Chapter 5.

The most common method of oxidizing bromohydrins is through chromic acid oxidation. Stork (65) oxidized the prostaglandin intermediate F to the corresponding bromo

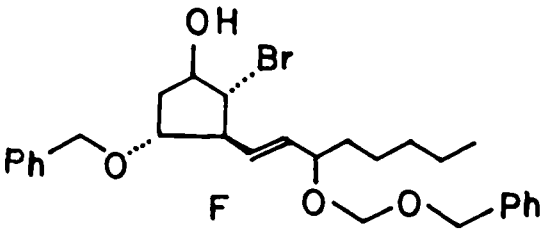


Scheme 9

ketone in quantitative yield by using Jones' reagent. Other examples of this type of oxidation are available, although not always in quantitative yield (66-68).

Oxidation of epoxides and bromohydrins to bromo ketones have the drawback in that they are multi-step processes. In some cases it is probably necessary to isolate intermediates. This is not only time consuming, but also yields are often reduced significantly in such procedures, because the overall yield is the product of the yields for the individual steps.

In conclusion, while methodology has been developed for the conversion of alkenes to halo ketones, most of the methods involve rather strong reagents, harsh conditions, or multi-step sequences. Thus, it would be desirable to be able to do such a transformation in one pot using inexpensive reagents under mild conditions.



4. N-Bromosuccinimide

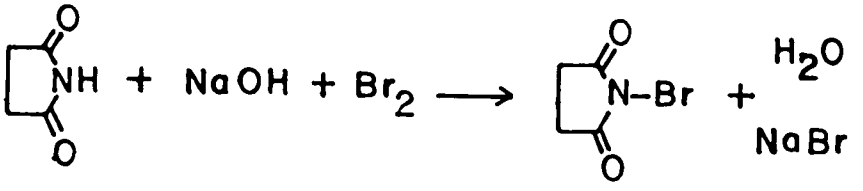
N-Bromosuccinimide (NBS) is known to react in two ways, either by a free radical mechanism (as in allylic bromination) or by an ionic mechanism.

Commercial NBS generally has a pale yellow color due to the occlusion of bromine on the normally white NBS (69). This can be removed by recrystallization from a large volume of water.

NBS has an almost non-polar N-Br bond. This allows homolytic fission to give a Br atom (70). NBS has a dipole moment of 2.10, whereas NCS has a dipole moment of 2.86 and NIS has a dipole moment of 0.97 (71).

It can be formed upon reaction of succinimide with sodium hydroxide and bromine as shown in equation 8. Generally N-halo imides are rather stable (72).

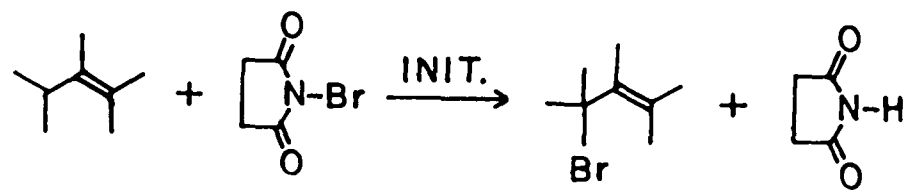
The most well known reaction of NBS is the allylic bromination of alkenes, which is shown in equation 9. The reaction is best run using CCl_4 as the solvent. Neither



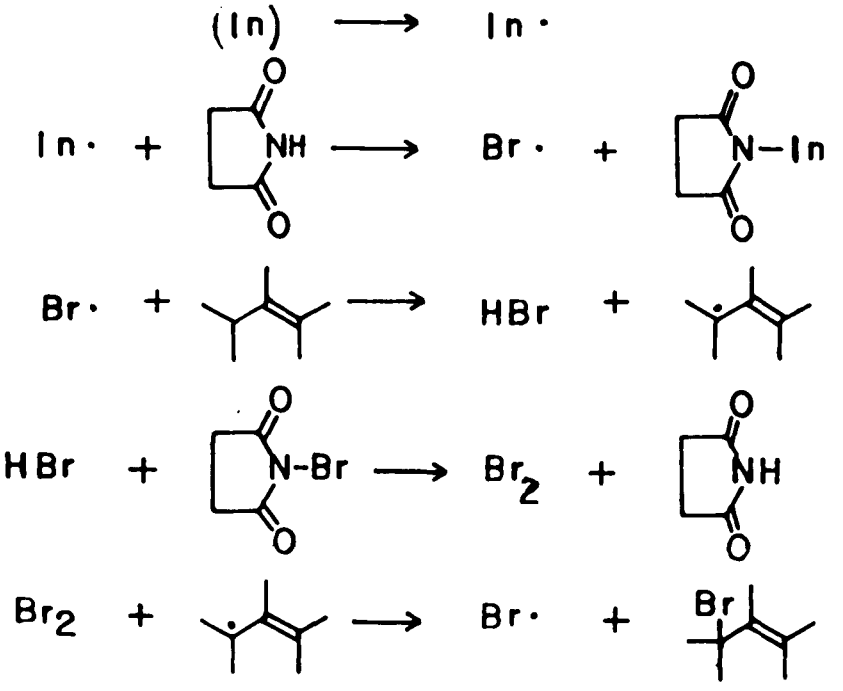
Equation 8

NBS nor succinimide are soluble in CCl_4. The alkene, initiator, NBS, and CCl_4 are combined. NBS is more dense than CCl_4 so it starts out on the bottom of the reaction vessel. As the reaction proceeds, succinimide is produced which is less dense than CCl_4. The reaction is followed by observing the loss of solid on the bottom of the reaction vessel being replaced by the formation of solid near the surface of solvent (73).

The reaction proceeds by a free radical mechanism. The reaction does not proceed unless a trace of initiator is present. It is sensitive to the presence of both initiators and inhibitors. The mechanism of allylic bromination is thought to be that presented in scheme 10 (73). The reaction is thought to take place on the surface of the solid NBS. When the surface area of solid NBS was increased by putting it on a silica gel carrier, there was an increase in the rate of allylic bromination. When the NBS was dissolved in a slightly more polar solvent, allylic bromination no longer took place, but instead, bromination of the double bond predominated (74).



Equation 9



Scheme 10

In the regular allylic bromination reaction, it is thought that bromine does not add to the double bond to produce the dibromide because the bromine concentration in CCl_4 is so low. One bromine atom can add but to get the dibromide, it is necessary to have another bromine atom add. Because of the dilute concentration it is more likely that the bromine atom will be lost thus regenerating the alkene, rather then reacting with another bromine atom (75).

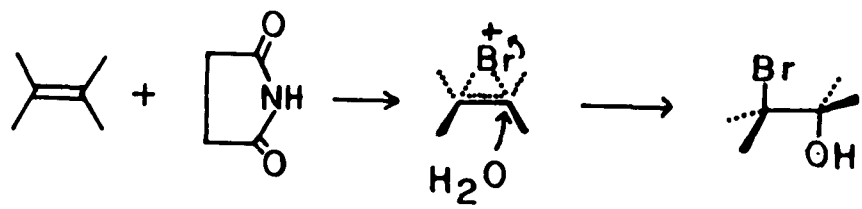
Under less polar conditions, in the presence of an initiator, NBS is thought to undergo free radical reactions. However, in polar solvents NBS is thought to undergo ionic reactions (76). In this case, NBS can be thought of as a

positive source of bromine. Bromine can also still be present due to even trace impurities of HBr which upon reaction with NBS produces Br_2.

Dalton *et al.* proposed (82) the possibility that DMSO may be oxidized by NBS with concommitant formation of bromine. Since they found dibromide only in one sterically hindered case, they concluded that it was not a problem in the synthesis of bromohydrins.

An example of ionic type reaction is the formation of bromohydrins from alkenes. In the case of the reaction of NBS, alkene, water and some solvent, the mechanism is thought to proceed as shown in equation 10. This reaction involves trans addition of the elements of HOBr across the alkene double bond (77). Had this reaction been a radical reaction, trans stereospecificity would not bave been observed.

In conclusion, NBS can react under two mechanisms. In the presence of an initiator and with a non-polar solvent, NBS reacts according to a free radical mechanism, often with a low concentration of bromine dissolved in the non-polar



Equation 10

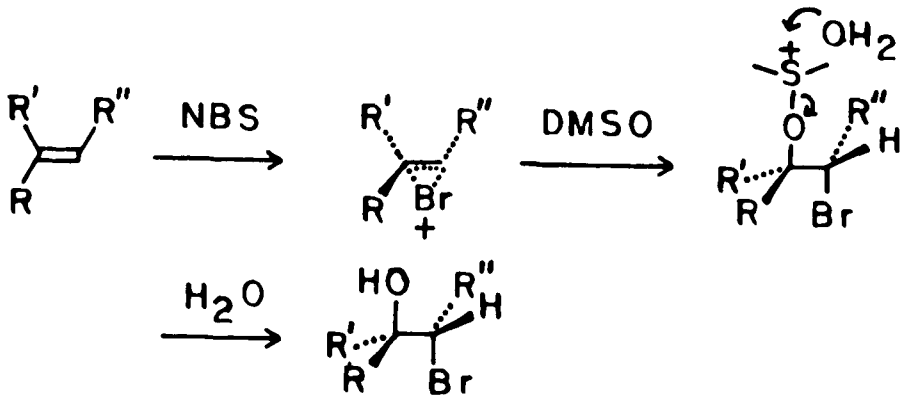
solvent. In the absence of a free radical initiator, and in more polar solvents, NBS is thought to react through an ionic mechanism. In the presence of small amounts of HBr, it is possible that HBr reacts with NBS generating Br_2. This may not be a negligible concentration. Thus, although NBS is thought of as a source of positive bromine, molecular bromine may also be present reacting possibly in undesired ways.

5. Formation of Bromohydrins using Dimethyl Sulfoxide

Bromohydrins can be formed by the addition of the elements of HO-Br to olefins. The reagent "HOBr" can be used for this purpose, which can be formed in situ by the reaction of water and bromine. It is then treated with the olefin to form the bromohydrin. Another method used for the preparation of bromohydrins is by reacting water, NBS (or N-bromoacetamide), and the olefin. These reactions have the drawback that olefins are generally not soluble in water. To avoid this problem, it was necessary to use emulsions or mixed solvent systems (79,80).

Dalton reported a new method for producing bromohydrins in a single solvent system. He utilized the fact that most olefins are soluble in DMSO that contained a small amount of water. He found that if the olefin, DMSO and water were stirred at a temperature slightly less than room temperature, after aqueous work-up, good yields of bromohydrin were obtained (81). The suggested mechanism is shown in scheme 11 (82,83).

The mechanism of this reaction involves Markownikoff addition of positive bromine to the carbon-carbon double bond resulting in the formation of an unsymmetrically bridged bromonium ion for unsymmetrical alkenes. If a



Scheme 11

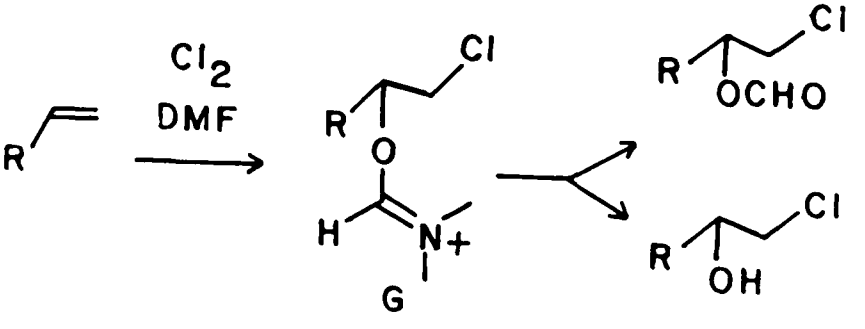
B-bromo carbonium ion were formed, there would have been considerable rearrangement and possibly elimination. No rearrangement products were observed and only one elimination product was observed. 2,4,4-Trimethylpent-1-ene gave 56% of the expected bromohydrin plus 24% of the elimination product, 2-bromomethyl-4,4-dimethylpent-1-ene. This suggested that an unsymmetrically bridged B-bromo carbocation was formed rather than a full carbocation.

The next step in the mechanism is attack of the unsymmetrically bridged bromonium ion by the oxygen atom of DMSO resulting in the formation of the trans-B-bromosulfoxonium ion. In this case, the attack is by the solvent DMSO. Similar reactions have been observed in which alkenes were treated with chlorinating (or brominating) agents in DMF which resulted in formation of immonium ions, such as G, as shown in equation 11. This

intermediate can be treated with a nucleophile to form the cis B-chloro product (84) or hydrolyzed to form the B-chloro formate ester (84-87).

Heasley *et al.* showed that both DMSO and MeOH compete in attacking the bromonium ion of cyclohexene. Attack by methanol resulted in formation of B-bromo methoxy compound whereas attack by DMSO resulted in, after hydrolysis, bromohydrin. They showed that DMSO is more nucleophilic than methanol in attacking the bromonium ion of cyclohexene (88). This again shows that polar solvents attack bromonium ions.

Getting back to the Dalton reaction, oxygen-18 labelling studies were performed using trans-stilbene as the olefin. These studies were run varying the reactant containing the O-18 label (DMSO, H_2O initially in the DMSO, and H_2O used to quench the reaction). The results obtained indicated that the trans-bromohydrin was formed and that the



Equation 11

oxygen came from the DMSO (82). This indicated the trans B-bromo sulfoxonium was formed which was later hydrolyzed by a backside attack by water on the positively charged sulfur, resulting in formation of protonated DMSO plus trans-bromohydrin.

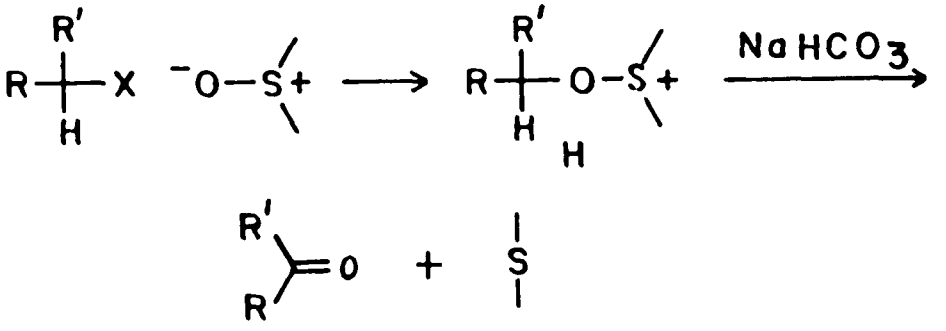
An anticipated problem was formation of dibromide which could result from attack of the bromonium ion by bromide rather than dimethyl sulfoxide. Bromine is thought to be formed in low concentrations by traces of HBr reacting with the NBS (89). It was also proposed that DMSO may be oxidized by NBS to produce bromide ion which may react with NBS to form bromine (82). Generally, even though dibromide product was sought, none could be detected (82). The only case in which dibromide production was found was with the highly hindered olefin, 2,3,3-trimethylbut-1-ene which can produce a stabilized carbocation at carbon-2. The expected bromohydrin was formed, but also considerable amounts of dibromide. This happened because presumably reaction with DMSO was slow due to steric hindrance of the bromonium ion. Because of this, attack by bromide is more favorable, resulting in considerable amounts of dibromide.

6. Dimethyl Sulfoxide as an Oxidizing Agent

Dimethyl sulfoxide has many interesting properties both as a solvent and as a reactant. One of its uses as a reactant is its ability to act as an oxidizing agent. Through the efforts of organic chemists during the past twenty-five years, many discoveries, advances, and modifications have been made in its usage to make it now one of the most versatile reagents to oxidize alkyl halides and alcohols to carbonyl compounds under essentially neutral, mild conditions.

Kornblum, in 1957 (92), reported that bromo ketones could be stirred in DMSO, for a number of hours at room temperature to produce corresponding the glyoxal compound. This work was later extended to alkyl halides and to tosylates which, upon being heated with a mixture of DMSO and sodium bicarbonate, resulted in the production of corresponding carbonyl compounds (93-96).

The mechanism (97) was later envisioned to be that which is presented in equation 12. In this case, the oxygen of DMSO was the nucleophile which attacked the electrophile, the carbon of the alkyl halide, to produce the intermediate sulfoxonium ion, H. This intermediate, either with or without base treatment, formed the carbonyl compound plus dimethyl sulfide.



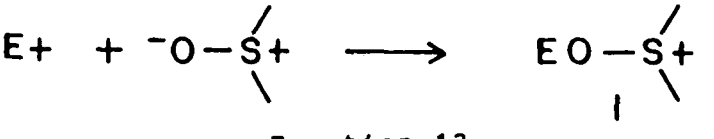
Equation 12

This method was improved upon by Ganem and Boeckman (98). Instead of using the high temperatures necessary in the Kornblum oxidation, they found that if the alkyl bromide was added to a solution of $AgBF_4$ in DMSO and stirred for 18 hours, the expected carbonyl compound could be obtained in excellent yield. Addition of the silver salt facilitated leaving group departure and nucleophilic attack to produce the sulfoxonium salt.

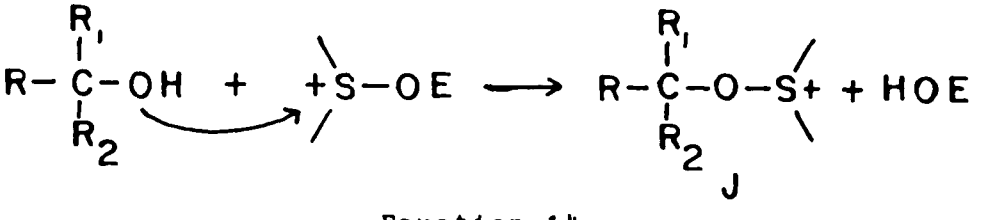
Another way in which the intermediate sulfoxonium ion has been produced is by reaction of alcohols with "activated" (99,100) dimethyl sulfoxide. DMSO was treated with an electrophile to produce an oxygen protected sulfoxonium salt, I, as shown in equation 13. The DMSO was then activated such that if attacked by a nucleophile such as an alcohol a new sulfoxonium salt was formed by the expulsion of the leaving group, EO^-, as shown in equation 14. The sulfoxonium ion, upon treatment with base,

decomposes to produce the carbonyl compound and dimethyl sulfide by the mechanism shown in equation 15. This mechanism was determined by labelling studies shown in equation 16 and 17.

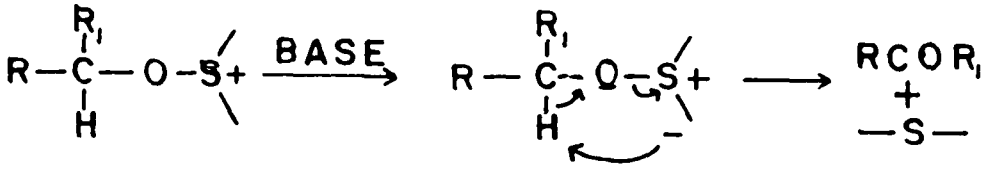
From this, one can see that the decomposition of the sulfoxonium ion generally proceeds by an intramolecular cyclic mechanism. Thus the sulfoxonium salts H and J (above) are identical compounds but formed by different routes. In the case of H, the alkyl halide was the electrophile which was attacked by the nucleophile, DMSO, to form G. In the case of J, the "activated" DMSO was the



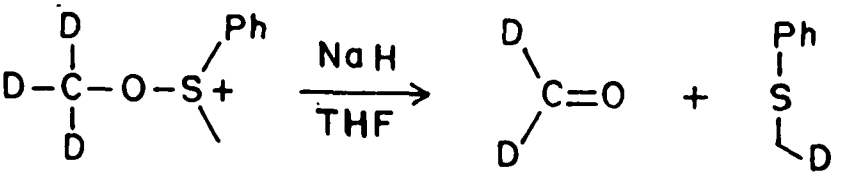
Equation 13



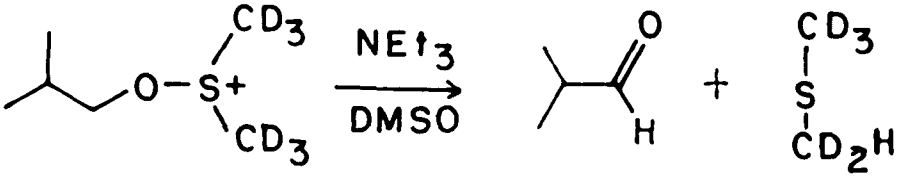
Equation 14



Equation 15



Equation 16

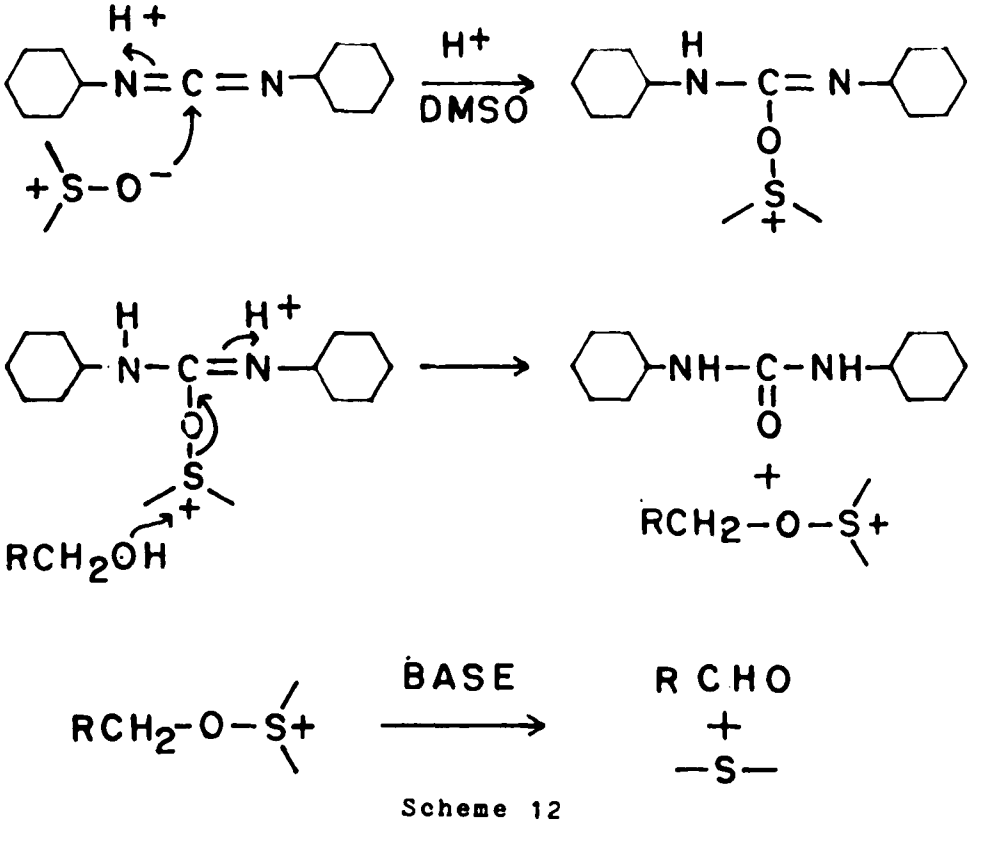


Equation 17

electrophile which was attacked by the nucleophile, which was the alcohol to be oxidized. A variety of different reagents have been used to activate the DMSO.

The well-known Pfitzner-Moffatt oxidation is an example of this type of oxidation. It involves treatment of DMSO with DCC and a proton source such as anhydrous phosphoric acid or pyridinium trifluoroacetate (105). The mechanism (106), shown in scheme 12, was demonstrated through oxygen-18 and deuterium labelling studies.

The reaction was generally complete in a few hours at room temperature to produce the corresponding carbonyl compound in good to excellent yield (107). An improved method was developed which used different carbodiimides (108) which resulted in the formation of water soluble urea compounds. This aided greatly in the isolation of the



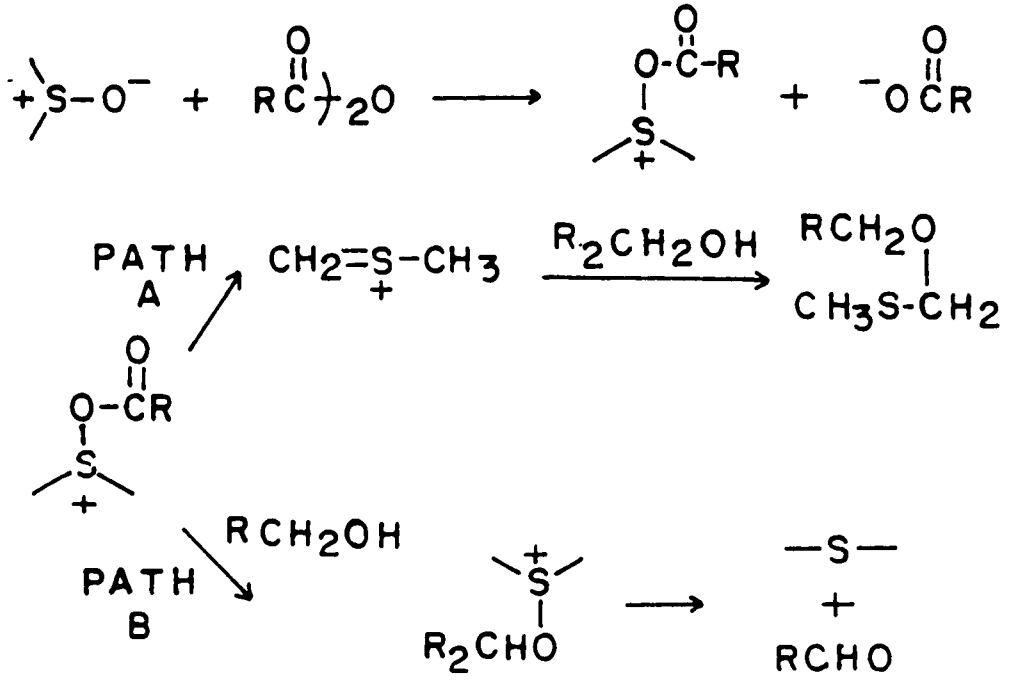
Scheme 12

desired carbonyl compound from the urea by-product, which had been a problem in the regular Pfitzner-Moffatt oxidation.

Anhydrides are also used to activate DMSO. The two most often used are acetic anhydride and trifluoroacetic anhydride. The mechanism (109) is shown in scheme 13. Reactions with acetic anhydride have been used extensively in the carbohydrate field. It appeared to be more effective in the oxidation of hindered alcohols than unhindered alcohols (110). Here, it was more effective than the

Pfitzner-Moffatt oxidation (111). Drawbacks of this method are that reactions are performed at room temperature, but require long reaction times (i.e. 24 hours) and produce substantial amounts of methyl thiomethyl ethers, via a Pummerer rearrangement as shown in scheme 13, path B (99). This type of rearrangement can also take place in the Pfitzner-Moffatt oxidation (112).

When trifluoroacetic acid was used as the anhydride, reactions had to be performed at low temperatures (-60°C) (99). At room temperature, the reaction can be explosive, and if the resulting sulfoxonium salt was allowed to warm up beyond -30°C, it would spontaneously undergo

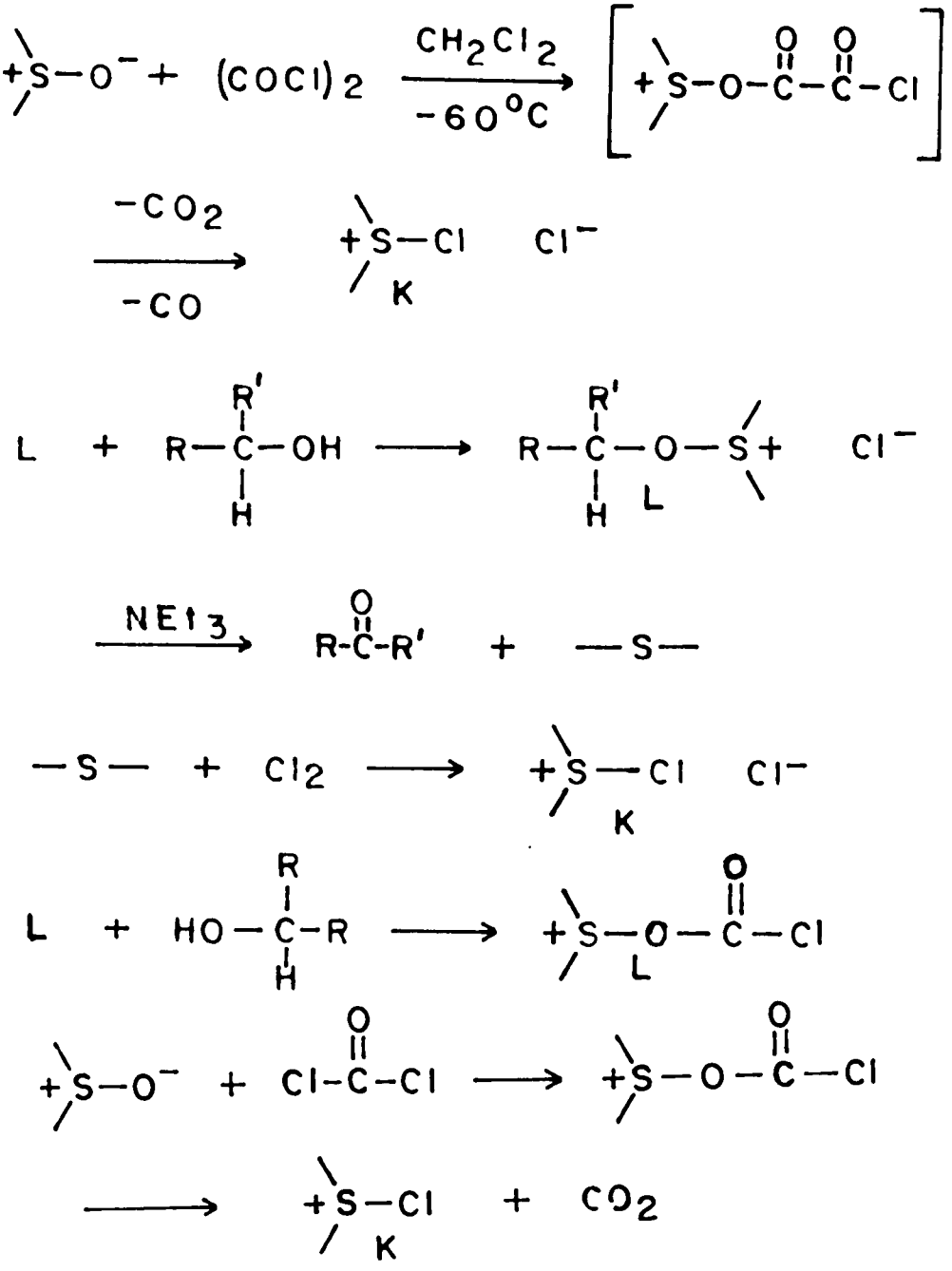


Scheme 13

the Pummerer rearrangement (99). This reagent worked well when reaction temperatures were kept below -30°C. The advantage of this reagent when used at low temperatures is its short reaction times, high yields, and minimal amount of Pummerer rearrangement product (99, 113).

Sulfur trioxide in pyridine, thionyl chloride, and sulfuryl chloride were all used as electrophiles to activate DMSO. These reactions usually took only a few minutes and products were easily isolated through acidification and precipitation with water (99, 114). This by-passed the difficult step of removing the urea by-product in the Pfitzner-Moffatt oxidation. Many of the activated DMSO reagents gave higher yields in the oxidation of more hindered alcohols, but using DMSO/SO_3/pyridine even straight chain, unhindered alcohols were oxidized to carbonyls in >90% yield (110) with negligible formation of methyl thiomethyl ethers.

A lot of work was done most recently by Swern (99,110) on the use of DMSO and oxalyl chloride. Since oxalyl chloride and DMSO reacted violently at room temperatures, reactions generally were performed at low temperatures (-60°C). The reactions for the formation of the intermediate and its reaction with alcohol and base are shown in scheme 14.



Scheme 14

DMSO was reacted with one mole of oxalyl chloride in a non-polar solvent at low temperature to form the unstable acid chloride sulfoxonium ion which spontaneously lost carbon dioxide and carbon monoxide and formed the intermediate K (115), which was reacted with an alcohol to form the sulfoxonium ion, L. The same intermediate K was made by Corey and Kim, (116), as shown in scheme 14, by the addition of Cl_2 to dimethyl sulfide at low temperatures. Intermediate L was also the reactive intermediate found in the Barton oxidation, also shown in scheme 14, which was formed by the treatment of the alcohol with ether which was saturated with phosgene to produce the chloroformate of the alcohol. The chloroformate was then treated with DMSO for 2 minutes at 15°C, followed by triethylamine. Thus, all three ways were used to make the same "activated" DMSO intermediate.

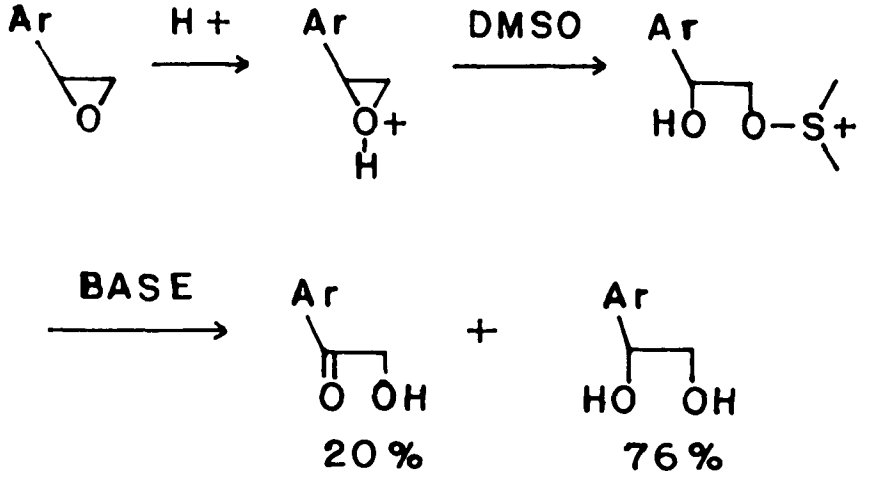
Swern examined (99) many of these "activated" DMSO oxidizing agents and concluded that DMSO-oxalyl chloride was, in general, the most effective. It oxidized primary, secondary, hindered, benzylic, and allylic alcohols to the corresponding carbonyl compound in excellent yields with a minimum amount of methyl thiomethyl, Pummerer rearrangement by-product.

DMSO was also used in the conversion of bromo ketones to diketones (118). The bromide was lost through an S_N2

displacement by DMSO to form the B-oxo-sulfoxonium ion which decomposed to form the diketone and dimethyl sulfide.

Swern and Santosusso (119) reported the acid-catalyzed reaction of epoxides with DMSO formed the intermediate hydroxy sulfoxonium ion which, upon base treatment, formed the hydroxy ketone as shown in equation 18. This reaction was shown to be regiospecific in the ring opening of styrene oxide and p-nitrostyrene oxide and stereospecific in the ring opening of cyclohexene oxide and cis- and trans-9,10-epoxystearic acid. Upon base treatment, 1,2-ketols and glycols were found, but with the yield of glycol predominating.

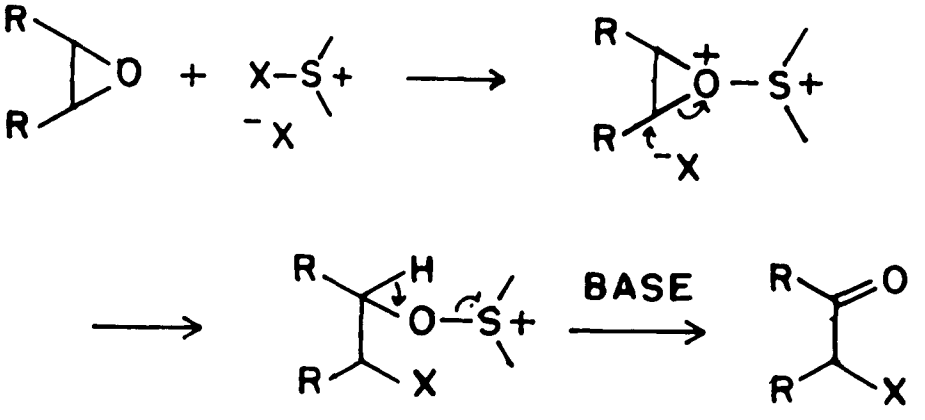
Olah et al. (64) reported that epoxides ring opened to produce a sulfoxionium ion, as shown in the equation 19 (120), which eventually produced halo ketones. Most of this



Equation 18

work was performed on symmetrical epoxides. No comment was made on its regioselectivity.

In conclusion, sulfoxonium ions can be formed through a variety of ways: reaction of DMSO with alkyl halides, reaction of "activated" DMSO with alcohols, and reaction of DMSO or "activated" DMSO with epoxides. Sulfoxonium ions can then be treated with base which results, through an intramolecular cyclic decomposition, to the corresponding carbonyl compound plus dimethyl sulfide.

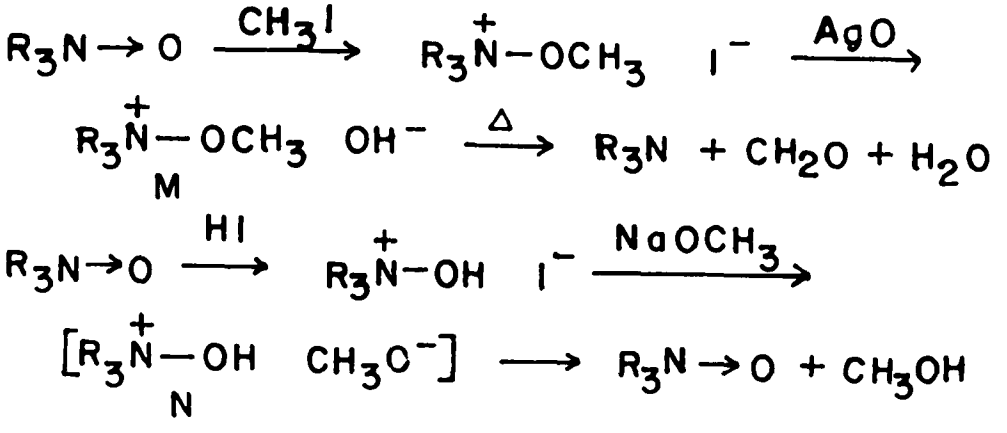


Equation 19

7. Oxidations using Amine Oxides

The structure of amine oxides was first determined by Meisenheimer who synthesized the isomeric compounds M and N by different routes as shown in scheme 15. The two isomers M and N differ in the pyrolytic decomposition products they produce (121).

Amine oxides can also be prepared from the oxidation of tertiary amines by a variety of oxidizing agents such as hydrogen peroxide and peroxy acids. They tend to be hydroscopic, very water soluble, and not soluble in non-polar organic solvents. It was demonstrated that they have a tetrahedral configuration by the fact that unsymmetrically substituted amine oxides have been resolved into enantiomers, by formation of diasteriomeric salts, separation and regeneration (122).

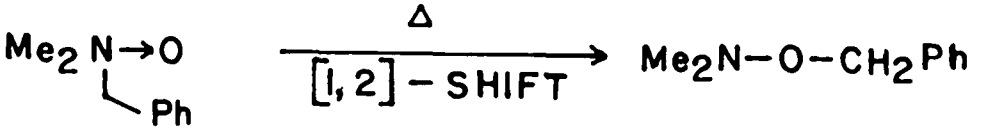


Scheme 15

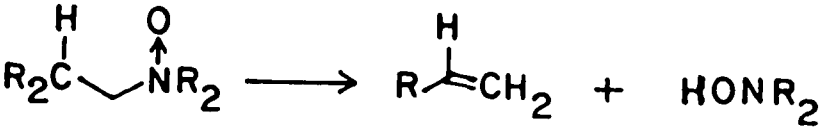
The two most well known reactions (122) of amine oxides are the Meisenheimer rearrangement shown in equation 20 and the Cope elimination shown in equation 21. The Meisenheimer rearrangement is thermally induced. Studies using CIDNP have established that is proceeds by a radical mechanism. The Cope elimination is also thermally induced. For this reaction to occur it is necessary to have a beta-hydrogen available which is oriented in such a way to permit a five membered cyclic transition state.

Oxidations using amine oxides can be traced all the way back to the original work of Meisenheimer (which was shown in scheme 15) in which $(R_3NOCH_3)^+ OH^-$, upon heating gives formaldehyde and the corresponding amine (121).

Early work was done using pyridine oxide as the amine oxide. Reaction of pyridine oxides with benzylic halides produced arylalkylammonium salts which underwent



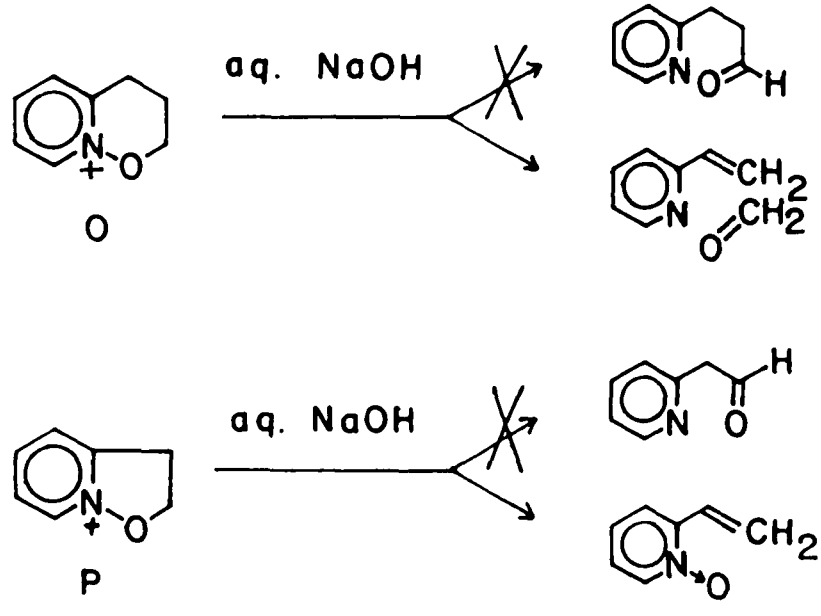
Equation 20



Equation 21

decomposition when warmed in the presence of dilute aqueous sodium hydroxide (123). Boekelheide used this reaction to produce aromatic aldehydes in good yields (124). This is applicable only to actived substrates such as benzyl bromide, due to the low nucleophilicity of pyridine oxides (125). Later, when this reaction was done on O and P, as shown in scheme 16, the desired aldehydes were not produced (125). Instead of abstracting the proton alpha to the oxygen, the benzylic proton in each case was abstracted.

Franzen and Otto (127) reported alkyl halides or tosylates were oxidized to the corresponding aldehydes in yields of 30 - 60% using trimethylamine oxide. The alkyl halide (or tosylate) and trimethyl amine oxide were refluxed



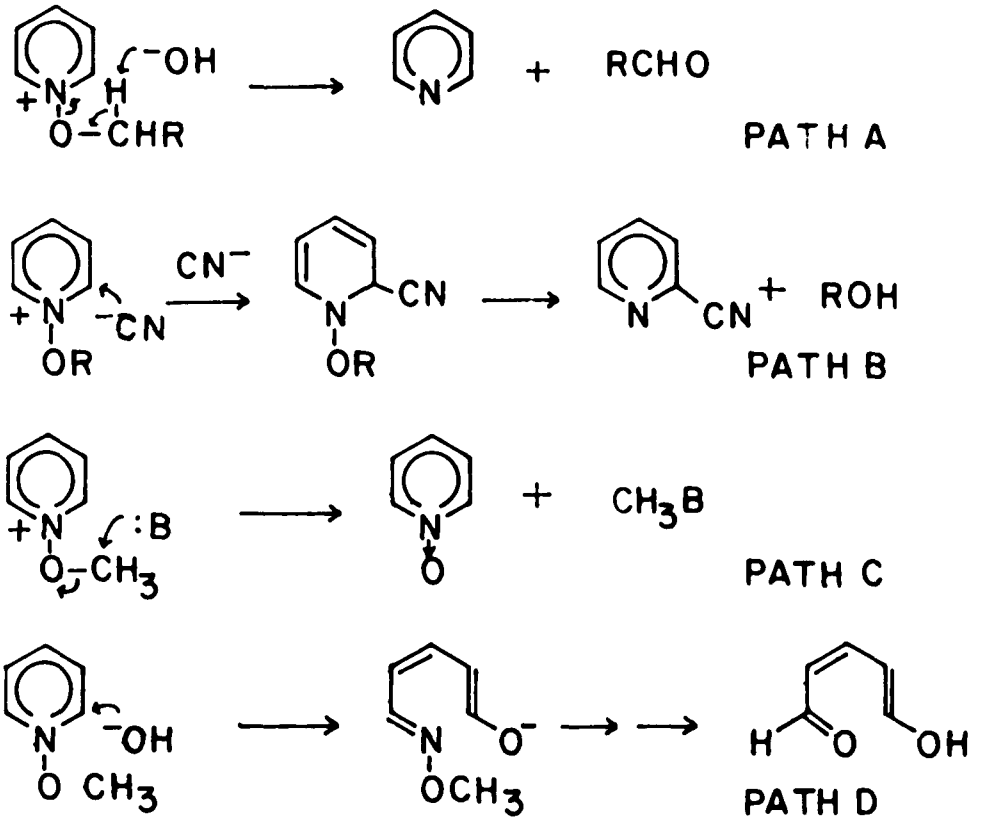
Scheme 16

in chloroform for thirty minutes to produce the corresponding aldehyde. Typical reactions were the reaction of n-hexyl bromide to give n-hexanal in 48%, isopentyl bromide to give isovaleraldehyde in 66%, and benzyl bromide to give benzaldehyde in 45% yields.

In a recent paper along these lines, Japanese workers (128) demonstrated that various kinds of alkyl halides could be oxidized to aldehydes or ketones in high yields using 4-dimethylaminopyridine oxide followed by treatment with a base such as DBU. Using this reaction primary and secondary halides can be used to produce aldehydes and bromo esters can be used to give keto esters, both in high yield.

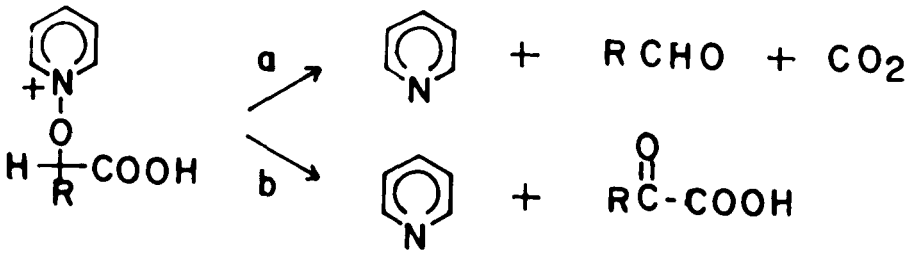
A disadvantage in using pyridine oxide or a substituted pyridine oxide is the variety of products that can be produced. Katritzky (129,130) showed that there are four ways that nucleophiles can react with N-alkoxy pyridium salts as shown in scheme 17.

Path A is the route by which alkyl halides can be oxidized to aldehydes. Path D is, however, a reaction by which glutaconic dialdehyde can be produced. This is a reactive dialdehyde which can undergo further intramolecular reactions or possibly react further with the N-alkoxy pyridinium salt. Reactions of this sort not only complicate matters by giving a number of products in the reaction mixture (which must be separated) but also can severly reduce yields.

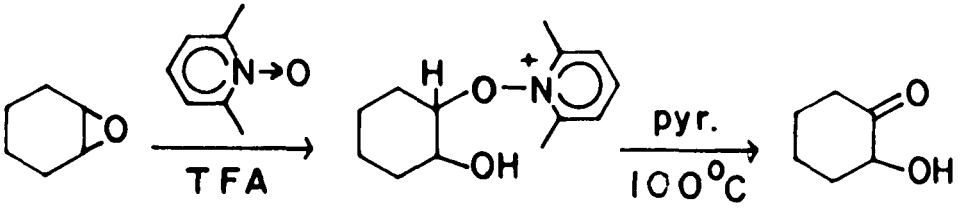


Scheme 17

Much work has been done on the reaction of pyridine oxides on haloacids (131-133) and on haloesters (133,134). This is a rather versatile reaction because decomposition of the intermediate N-alkoxy pyridinium salt can proceed selectively in either of the two routes shown in scheme 18 (133). Similarly, Swern and Marmer (135) showed that pyridine oxides (or 2,6-lutadine oxide) could be reacted with epoxides to produce a-hydroxy ketones as shown in equation 22.



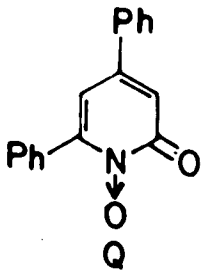
Scheme 18

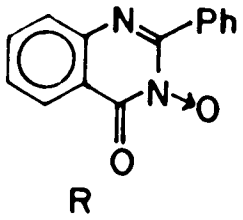


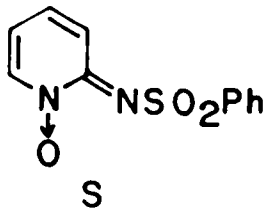
Equation 22

Katritzky and coworkers developed (136) three additional heterocyclic amine oxide oxidizing agents, Q, R, and S. These were designed to have electron withdrawing substituents built into the ring, thus making decompostion more favorable. The decompostion step was done either thermolytically or photolytically. For non-heat sensitive compounds, thermolytic cleavage is the better route as pure products in higher yields are obtained. For heat sensitive compounds, photolytic cleavage is an alternative, however, the product is often contaminated with the corresponding alcohol, and the yields are generally lower.

Katritzky concluded that this route is synthetically useful for the synthesis of aromatic aldehydes and ketones





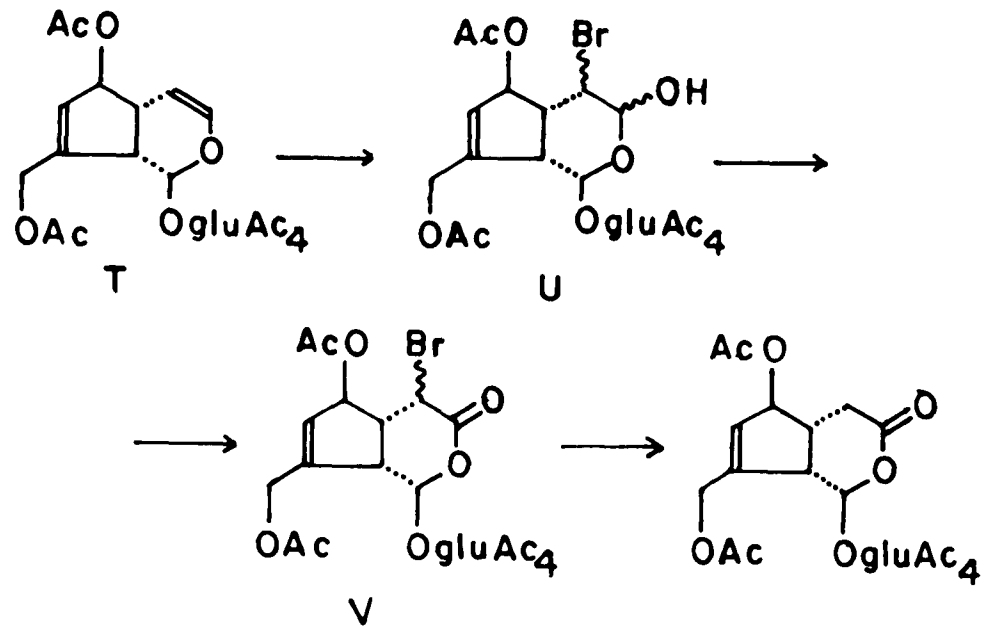


from benzyl halides. However this route is not synthetically useful for the synthesis of carbonyl compounds from aliphatic halides due to formation of side products (the corresponding alcohol) and to low yields.

In conclusion, oxidation of alkyl halides to the corresponding carbonyl compounds by the use of amine oxides is a method that is synthetically useful and is currently being used (137,138). The reaction proceeds through nucleophilic attack by the oxygen of the amine oxide on the electrophilic alkyl halide to form a N-alkoxy ammonium salt. This can then be decomposed to form the corresponding carbonyl compound plus the amine.

8. Proposal

Recent work in Dr. Berkowitz's lab involved the conversion of aucubin hexaacetate, T, to the corresponding bromolactone, V, as shown in equation 23. This was accomplished in two steps by treating aucubin hexaacetate with NBS and wet DMSO to produce the bromolactol (bromohydrin), U, according to the Dalton procedure (83) for bromohydrin synthesis. This bromolactol, U, was then oxidized to give the bromolactone (bromo ketone), V, in high yield.



Equation 23

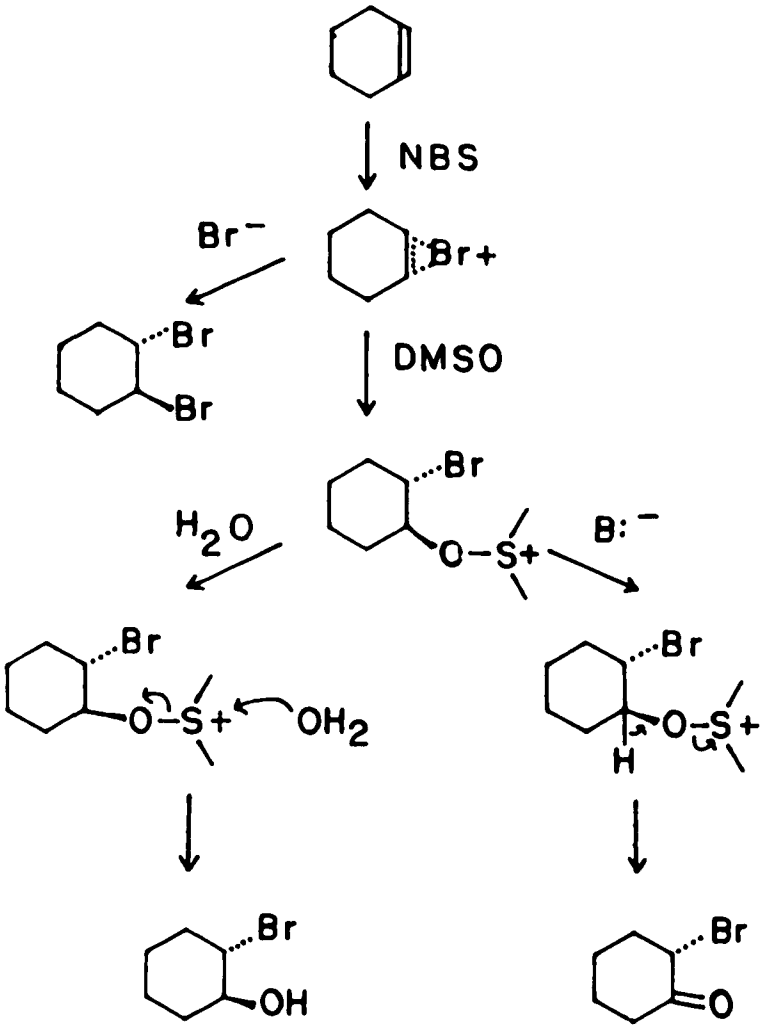
When repeating this work, the Dalton reaction was attempted in the absence of additional water. This was later repeated using dry DMSO (distilled from CaH_2) and it was observed that the bromo lactone was produced directly in high (85%) yield (139).

Although the original work on aucubin hexaacetate involved the reaction of an enol ether with NBS and DMSO, it is reasonable that this type of reaction could be performed on alkenes because the intermediate is the B-bromo sulfoxonium ion which is the same intermediate in the Dalton reaction (83).

The proposal at hand is to explore this reaction. From the above discovery, it appears to be a way in which enol ethers could be used to synthesize bromo lactones and alkenes could produce bromo ketones both under rather mild conditions. This reaction could be used to convert alkenes to bromo ketones under rather mild conditions.

The mechanism for this can be envisioned as shown in scheme 19. Basic parts to this mechanism were presented in earlier chapters which include the reaction of alkenes, DMSO and water to form bromohydrins and reaction of sulfoxonium ions with or without base to give the corresponding carbonyl compound.

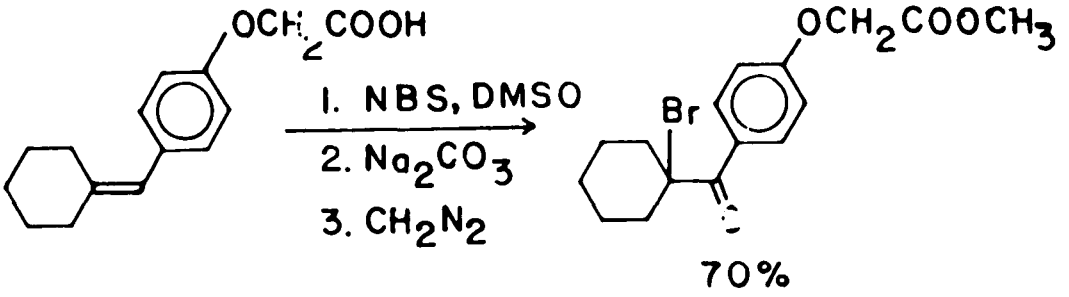
There is one example of a reaction of this type in the literature as shown in equation 24 (91). It may be a



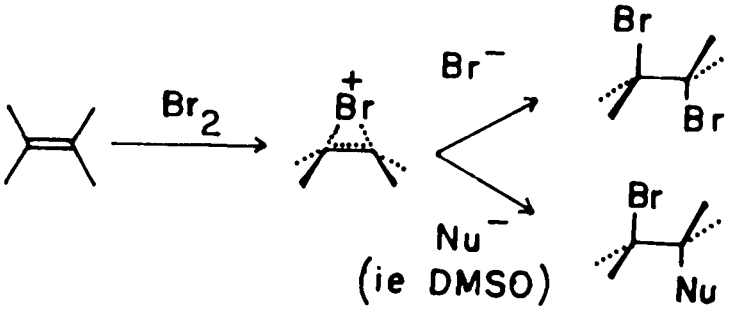
Scheme 19

special case in that it is a styrene derivative. General utility of this method was not explored.

One caveat to be aware of is the presence of a low concentration of bromine in NBS reactions. This could be a serious problem because bromine reacts with alkenes to form the trans-dibromide as shown in equation 25.



Equation 24



Equation 25

In this proposal, it is desired that the bromonium ion would react with DMSO and not with bromide. However, depending on cage effects of bromonium ion - bromide complex, the availability of bromide ion (possibly from other sources), and the nucleophilicity of DMSO vs. bromide, dibromide or B-bromo sulfoxonium ion (or a mixture of both) could be formed.

Chen and Wang (90) reported formation of trans-stilbene dibromide upon reaction of trans stilbene, dry DMSO, and N,N-dibromobenzene sulfonamide. Also, Dalton and Dutta (83) reported the formation of dibromide when the

bromohydrin reaction was attempted on the hindered alkene, 2,3,3-trimethylbutene.

Thus, the proposal at hand is to investigate the reaction of alkenes (and enol ethers) with dry DMSO and NBS possibly followed by treatment with base to produce bromo ketones (and bromo esters). General applicability shall be explored and conditions found to, hopefully, develop this into a synthetically useful method.

9. Results and Discussion of the Bromo Ketone Reaction

Much of the work done on the reaction of alkenes with NBS and dry DMSO was done on cyclohexene which would, hopefully, react to form 2-bromo cyclohexanone. Cyclohexene was chosen for these initial studies because it is a symmetrical, stable, readily-available and inexpensive alkene.

The first attempt at this reaction was done by equilibrating 1 equivalent of cyclohexene and 25 equivalents of dry DMSO (distilled under reduced pressure from CaH_2) at a temperature just under 20°C. To this solution, 2 equivalents of NBS were added. After 15 minutes, this reaction mixture was poured into a large excess of water, extracted with ether, washed with solutions of sodium thiosulfate, and sodium bicarbonate, dried and distilled. This mixture was then analyzed by gas chromatography (GC) to give three products. These products were later shown to be (in relative yields) 8% 2-bromocyclohexanol (hereafter referred to as bromohydrin, BrOH), 23% 2-bromo cyclohexanone (hereafter referred to as bromo ketone, BrC=O), and 69% 1,2 dibromocyclohexane (hereafter referred to as dibromide, Br_2). These relative yields were determined by comparing the area under the curve of bromohydrin, bromo ketone and

dibromide from the recorder paper of the GC run. Reaction products were collected from the GC and compared individually to bromohydrin, bromo ketone and dibromide made by other methods. NMR, IR, and GC retention times upon co-injection were identical. At this point only relative yields were determined. Absolute yields were determined later through the use of an internal reference.

Bromohydrin was made according to Dalton's procedure (alkene, NBS, wet DMSO) (140). Bromo ketone was synthesized in two ways. The first way was by oxidizing the product from the Dalton reaction using Corey's pyridinium chlorochromate (141). This method had the drawback that the bromohydrin from the Dalton reaction was contaminated with dibromide. Since the boiling points were sufficiently close (BP: bromohydrin 63-5°C at 4 mm Hg (=205°C); bromo ketone, 102°C at 29 mm Hg (=205-210°C); dibromide, 99-103°C at 16 mm Hg (=210°C)), and simple distillation would not separate them. It was necessary to separate them by collection from the GC since it was undesirable to have bromo ketone contaminated with one of the other anticipated products. A much cleaner way the bromo ketone, free of dibromide, was synthesized was by heating cyclohexanone with copper (II) bromide in $CHCl_3$/EtOAc (47). Dibromide was synthesized (142) by adding a solution of bromine in CCl_4 to a solution of

cyclohexene, CCl_4, and a small amount of absolute ethanol at $-5^{o}C$.

If the amount of DMSO had an effect on the amount of (undesired) dibromide in the Dalton procedure, it may also have an effect on the amount of dibromide in the bromo ketone preparation. Tables 1 - 11 which shows variations and final results are located in the Experimental Section. Table 1 shows that by increasing the ratio of moles of DMSO to moles of cyclohexene, dibromide formation was significantly reduced.

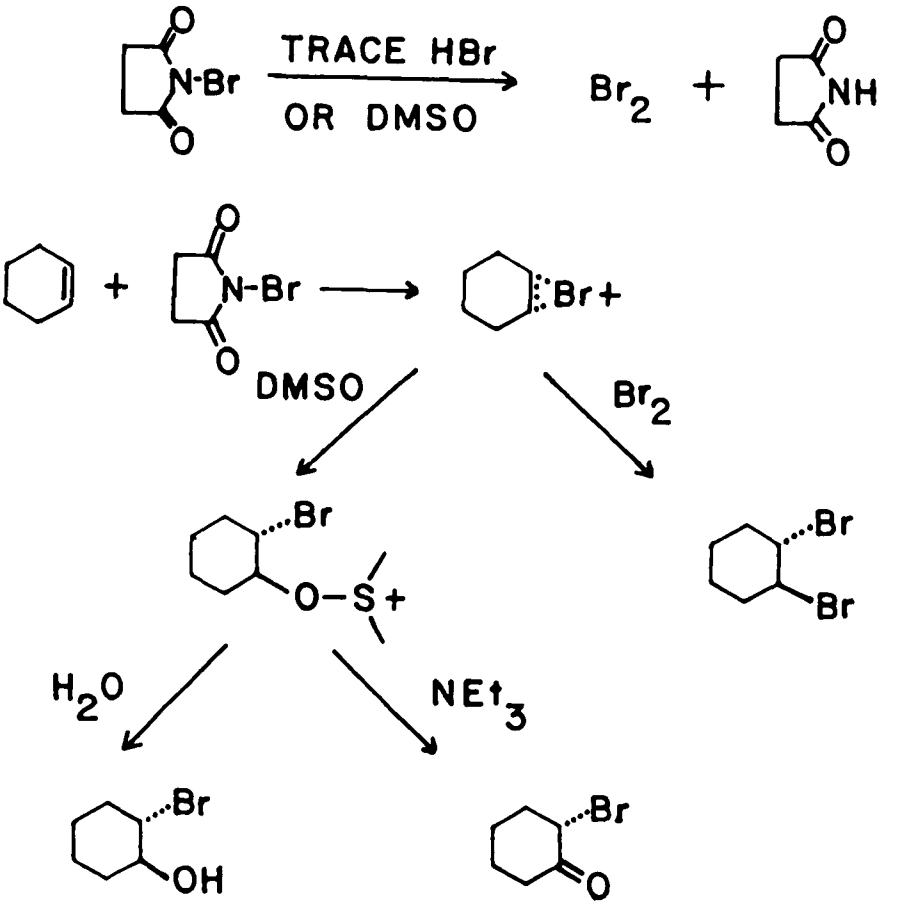
This data also revealed that, by increasing the amount of DMSO, the absolute yield of bromohydrin was decreased. This was presumably because the products were lost in the work-up. Since the products are soluble in DMSO and since DMSO is soluble in water, it is possible that, due to the large amount of DMSO and the large amount of water used to quench the reaction (water was scaled up to the relative amount of DMSO), losses were due in part to mechanical losses. This explanation could account for the lower absolute yields of bromohydrin with increasing amounts of DMSO.

The ratio of moles of dry DMSO to moles of cyclohexene were varied to observe the effects on the relative yields of the three products. These results are presented in Table 2.

As seen in Table 2, increasing the amount of DMSO decreased the amount of dibromide and increased the sum of the amount of bromohydrin and bromo ketone. It was decided to use the standard ratio, that of 1.5 mL of cyclohexene to 75 mL of dry DMSO, because it gave somewhat reduced amounts of dibromide at fairly manageable amounts of DMSO.

At this point, it was of interest to decrease the amount of dibromide. This undesired side product represented a large percentage of the reaction mixture and could considerably hinder the usefulness of the reaction by lowering yields. Both the bromohydrin and the bromo ketone were presumably formed through an intermediate B-bromosulfoxonium salt. This salt, upon base treatment, can undergo decomposition to produce bromo ketone as shown in scheme 20 as indicated by Torssell's work (102).

Much of the following work was done on the basis of relative yields to see the effect of various changes. After a series of changes, the best improvements were incorporated, and absolute yields were determined. Some of the variations which were tried included the following: 1.) running the reaction at 0°C (because DMSO has a melting point of 18.5°C, it was necessary to dilute the reaction mixture with methylene chloride), 2.) giving it a reaction time of one hour, 3.) using hydroquinone as a radical inhibitor (to determine whether it was going by a radical



Scheme 20

mechanism), 4.) using oven dried equipment, and 5.) using recrystallized NBS. None of these changes significantly reduced the amount of dibromide.

When the reaction was run at 0°C using methylene chloride as a co-solvent for 15 minutes, followed by addition of triethylamine, the amount of bromohydrin significantly decreased and the amount of bromo ketone increased, while the amount of dibromide remained relatively

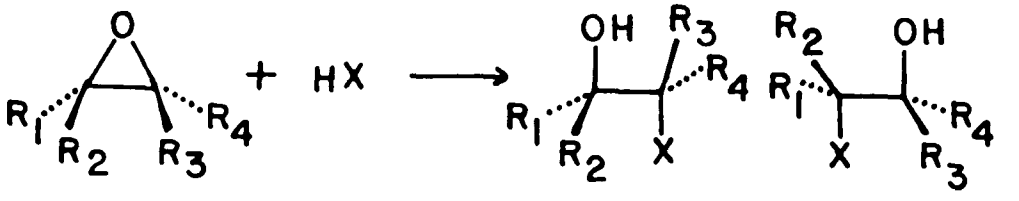
the same. As mentioned previously, both proceeded from an intermediate B-bromosulfoxonium ion as shown in scheme 20.

This reaction shall hereafter be referred to as the "standard" reaction. It was performed in the following manner: cyclohexene was dissolved in a solution of DMSO and methylene chloride and then cooled to $0^{o}C$. NBS was added slowly (approximately 0.3 g at 5 sec. intervals). After 15 minutes of stirring, triethylamine was added in one portion. After 15 minutes more, the reaction mixture was poured into water extracted into ether, washed with a solution of sodium thiosulfate, dried and distilled. This produced relative yields of 9% of bromohydrin, 51% of bromo ketone and 40% of dibromide.

Other variations were also tried. When the triethylamine was added 5 minutes after the NBS was added, the ratios were slightly better: 8% BrOH, 64% BrC=O, and 28% Br_2. When the reaction was run with propylene oxide (1 and 3 equivalents), the relative yields produced were similar. This gave average yields of 7% BrOH, 63% BrC=O, and 30% Br_2.

Propylene oxide was added to the reaction mixture because oxiranes are known (143-146) as anion traps, as shown in equation 26 (143).

This type of ring opening can occur under neutral, acidic, or basic conditions. Epichlorohydrin has been used



Equation 26

for this purpose. We used propylene oxide instead to avoid any possibility of introducing chloride ion into the reaction mixture. Variations are shown in Table 3.

Quaternary Ammonium Resins as Bromide Traps

The problem at this point was reduced yields due to dibromide formation. A solution to this problem would be to reduce or eliminate the bromide ion present in the reaction mixture. If bromide ion were not present or could be kept away from the bromonium ion, then DMSO would be the only nucleophile which could attack the bromonium ion. This would result in a greater yield of B-bromosulfoxonium ion, and greater yields of bromo ketone.

We thought that if a quaternary ammonium resin with a non-nucleophilic anion was added, the bromide ion would be attracted by the positively charged nitrogen. This would, hopefully, keep the bromide in the vicinity of the solid resin and away from the bromonium ion which is in solution.

Many reactions were run using approximately 2000 equivalents of resin (as determined by the number of moles of quaternary ammonium salts per gram of resin as it came out of the bottle and after it was dried). The resin was treated in various ways (as will be described later) and finally it was dried in the drying pistol overnight over P_2O_5 to remove any traces of water.

These reactions are summarized in Table 4.

The first counter anion tried was trifluoroacetate which gave only slightly less dibromide than the reactions without resin.

The previously made trifluoroacetate resin was washed with a sodium chloride solution to remove the trifluoroacetate anion. It was then washed with 1M $NaBF_4$ until the filtrate no longer showed a precipitate when tested with an $AgNO_3$ solution, then rinsed with absolute ethanol and dried.

When approximately 2000 equivalents of this resin were added to the standard reaction, the relative yields obtained were: 4% BrOH, 83% BrC=O, and 13% Br_2. Thus using this resin, the relative yield of dibromide, on a small scale, was reduced. The resin that was used was Amberlite IRA-400 resin. It was later determined that this resin was of the type made before 1975. It seems that in 1975 they changed their formula for making IRA-400 resin, even though it maintained the same number.

The old resin which had been converted to BF_4^- resin gave better results than the new resin which had also been converted to BF_4^- resin. However, fortunately, the new BF_4^- resin gave good relative yields (81% BrC=O, 14% Br_2) when the resin was pre-soaked for 35 minutes at room temperature in anhydrous DMSO, followed by the regular routine of washes which included the $NaBF_4$ wash.

Many different variations were tried as can be seen in Table 4. Among these included trying many different quaternary ammonium salt resins which were converted to BF_4^- resins by washing the resins first with brine and then with sodium tetrafluoroborate solutions.

Resins such as Dowex 1-X8, Dowex 1-X8-400, Dowex 2-X8, Amberlite IRA-400AR, Amberlite IRA-400CP, Bio-rad AG1-X8, Bio-rad AGMP-1, Amberlite IRA-900 powder, Amberlite IRA-900 liquid, and Amberlite IRA-402 liquid all gave unacceptably high yields of dibromide.

Dowex 1 1X8-400 resin which had been pre-dried on the drying pistol, was pre-soaked in DMSO, then washed with a NaCl solution, followed by a wash with 1M $NaBF_4$ solution. It was then rinsed with ethanol and again dried in the drying pistol. Two batches of resin were prepared according to this procedure. In both runs, the relative yield of dibromide was decreased (9% and 14%), but the

relative yield of bromohydrin increased significantly (39% and 19%). In these two runs, the relative yield of bromo ketone was typical (55% and 67%). Generally, large amounts of bromohydrin indicate the presence of water. Other resins which had been prepared according to the same procedure did not show such large amounts of bromohydrin. This indicates that this resin probably had water trapped inside the particles which was released during the reaction.

Absolute yields by using the GC were determined by "spike" analysis using 1-bromoadamantane as the internal standard. The ratio of weight to area of known amounts of the spike and the three products were determined individually. Then, to the reaction mixture a known amount of spike was added, and from the relative areas, the weight of each product was determined.

Table 5 shows the absolute yields which were determined. The resin used in that run was pre-dried Dowex 1 1X8-400 which had been soaked (35 minutes at room temperature) in DMSO, then washed with aqueous NaCl, and aqueous $NaBF_4$, rinsed with absolute ethanol and finally dried in the drying pistol.

To our dismay, while the resins did cut down on dibromide formation on a small scale, this effect was not noticeable when run on a larger scale (3X small scale run). Also, the absolute yield of bromo ketone was lower in the

resin run than in the non-resin run. This is presumably due to the organic products adhering to the organic resin. Even though the resin was washed with 150 mL of ether four times, there must still have been residual trapping of the products by the resin.

It was somewhat encouraging to see that the absolute yield of bromo ketone was 40% when 2.0 equivalents of NBS were used (this was without resin). Previously, only 1.2 equivalents of NBS had been used as an effort to limit bromine formation in the reaction mixture.

Reactions Run Using Different Amine Oxides as Oxidizing Agents

Since the bromonium ion has two possible ways of reacting, as shown in scheme 20, if a nucleophile could be found which was even more nucleophilic than DMSO, this route would be preferred rather than attack of the bromonium ion by bromide ion. We thought that amine oxides may be more nucleophilic than DMSO, thus increasing the amount of bromo ketone formed and decreasing the amount of dibromide formed.

A number of variations were run using pyridine oxide as the oxidizing agent instead of DMSO as shown in Table 6. Reactions were run using different solvents and combinations of solvents (EtOAc, DMSO/CH_2Cl_2, benzene,

CH_2Cl_2) and different temperatures. When DMSO and methylene chloride were used as the solvent approximate relative yields were 25% BrOH, 25% BrC=O and 50% Br_2. When ethyl acetate was used as the solvent and $AgNO_3$ was added, practically pure bromohydrin was the only product. This actually may be a good way to synthesize bromohydrin which is uncontaminated by dibromide. Dalton (82) reported that dibromide was not produced (except for very hindered alkenes) in his reaction of alkenes with wet DMSO and NBS to produce bromohydrins. In our hands, dibromide was produced in each instance as reported in Table 1.

In the remaining cases, when solvents such as EtOAc, CH_2Cl_2, and benzene were used, worthless mixtures of solid and liquid were obtained as shown in Table 6. Although some bromo ketone was produced in some cases, a white solid was also produced after the product was worked up in the usual way. Some of these mixtures showed multiple high retention time peaks on GC and/or multiple spots in TLC.

One way to explain these results is by assuming other undesirable reactions such as opening of the pyridine ring are taking place as Katritsky reported (147). As evident from these results, this is not a useful way to synthesize bromo ketones, so other amine oxides were investigated.

Another amine oxide which was tried was N-methylmorpholine oxide. This was synthesized (148) by adding hydrogen peroxide to N-methylmorpholine and heating. As shown in Table 7, using N-methylmorpholine oxide in different solvents (CH_2Cl_2 or DMF), and with or without $AgNO_3$, large amounts of dibromide were produced. In most cases, although some bromohydrin was produced, no bromo ketone was observed. Reactions of the various amine oxides are summarized in Table 7.

N-Methylmorpholine oxide was tried because it was thought that it was a less hindered amine oxide than an average amine oxide such as triethylamine oxide. This was because two of the alkyl groups were pulled back in a ring. Apparently, it was too hindered, thus not nucleophilic enough to produce the desired results.

Another amine oxide which was tried was diazabicyclo(2.2.2)octane mono oxide, W (hereafter referred to as dabco monoxide). It was produced (149) by adding 1 equivalent of 30% hydrogen peroxide to a solution of dabco in benzene. This reaction gave absolute yields of 48% BrOH, 8% BrC=O, and 2% Br_2. This seems like a fairly good way to make bromohydrin with not much dibromide produced.

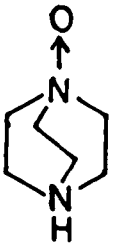
The best results were obtained using quinuclidine N-oxide, X, as the amine oxide. Both quinuclidine N-oxide and dabco mono-oxide are tertiary amine oxides with all

three alkyl groups tied back in a rather unstrained fashion. Both of them are rather unhindered amine oxides.

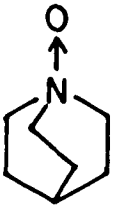
When the reaction was run using quinuclidine oxide as the oxidizing agent and DMF as the solvent, the absolute yields produced were a trace of BrOH, 47% BrC=O, and 7% Br_2. The remainder was unreacted cyclohexene. Crude analysis estimated there to be approximately 40% of unreacted cyclohexene. This appeared to be a fairly good way to make bromo ketones. (This implies 78% of BrC=O and 12% of Br_2 when the amount of unreacted cyclohexene is taken into account.)

Other variations were tried such as increasing the reaction temperature, varying the reaction time, and having the triethylamine in the reaction mixture from the start. All of these variations produced mainly dibromide.

When the reaction using quinuclidine oxide was done on cyclododecene unreacted cyclododecene was obtained. This reaction was done increasing time and temperature and still



W



X

only unreacted cyclododecene was obtained. It is surprising that the dibromide at least was not produced.

Reactions on Alkenes Other than Cyclohexene in NBS, DMSO Reaction

A fair amount of work was done on cyclopentene. The standard reaction was performed using cyclopentene as the alkene rather than cyclohexene. The double bond in cyclopentene is more strained than in cyclohexene and thus more reactive. This could explain the different results which were obtained.

In most cases, the relative yield of bromo ketone was roughly equal to the relative yield of dibromide plus bromohydrin. Thus, the maximum absolute yield could be 50%. The mixture of product also appeared to be rather temperature sensitive. After distilling the material, the remainder in the distillation head turned black within a half-hour.

When the reaction was run using pyridine as the solvent, the main products were bromohydrin and bromo ketone. Attempts were made to remove the pyridine by reduced pressure distillation but there was significant decomposition.

Thus, the results obtained from the reaction on cyclopentene were not encouraging. This could be due, however, to the increased reactivity due to the additional strain on the double bond.

Another alkene tried was trans-stilbene. This, too, is not a typical alkene because the double bond is conjugated with a phenyl ring at each end.

From this reaction a solid product was obtained which was soluble in $CDCl_3$. The dibromide of trans-stilbene is known to be insoluble in everything except hot xylene. The fact that the product here was soluble indicates that, if any of the dibromide was present at all, it was present in very low concentration. The relative yields of product obtained from the integration by NMR showed the following: 61% unreacted trans-stilbene, 31% bromo ketone, and 9% bromohydrin. A couple of other reactions were run which also suggested the product was largely the unreacted starting material.

Dihydropyran was also used as an alkene, even though it is an enol ether. This was thought to be more reactive than a regular olefin due to the electron-donating ability of the adjacent oxygen atom. In addition, aucubin hexaacetate reacted at a substituted dihydropyran moiety.

When the Dalton (140) reaction was tried on dihydropyran, the GC of small samples showed one fairly pure

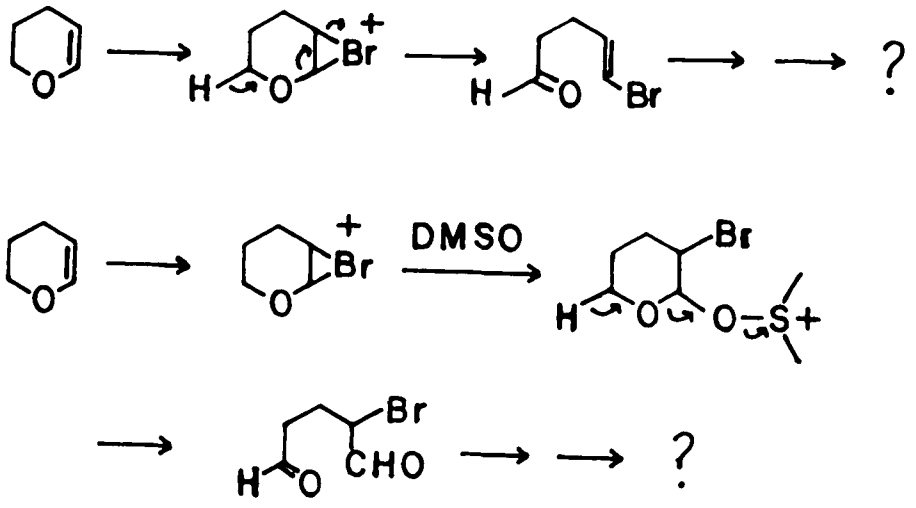
peak which was not starting material. When large samples were injected, as when collection was to be made, the product decomposed such that it could not even be seen on the recorder paper. When the product was distilled under high vacuum, it turned blackish (decomposition and/or polymerization). The crude IR did show a faint carbonyl at 1730 cm^{-1}. However, the NMR did not match the expected a-bromo-δ-valerolactone.

When the dihydropyran was reacted in the usual manner with dry DMSO and NBS, the IR showed a strong carbonyl stretch at 1725 cm^{-1}. However, it did show an OH-group (wet?). This product could not be collected off the GC or distilled. The IR and NMR spectra did look good. However, TLC analysis showed at least four spots as is shown after column chromatopraphy and then TLC analysis.

Different reactions can be envisioned to take place which may explain the large number of products. These are shown in scheme 21.

10. Conclusion

In conclusion, while yields of bromo cyclohexanone were greatly improved from the original runs of these reactions, the best results were obtained by using quinuclidine oxide as the oxidizing agent. The yield of bromo cyclohexanone



Scheme 21

obtained was approximately 50%. Reactions on other alkenes did not seem too promising.

1. Concept of Acyl Anion Equivalent

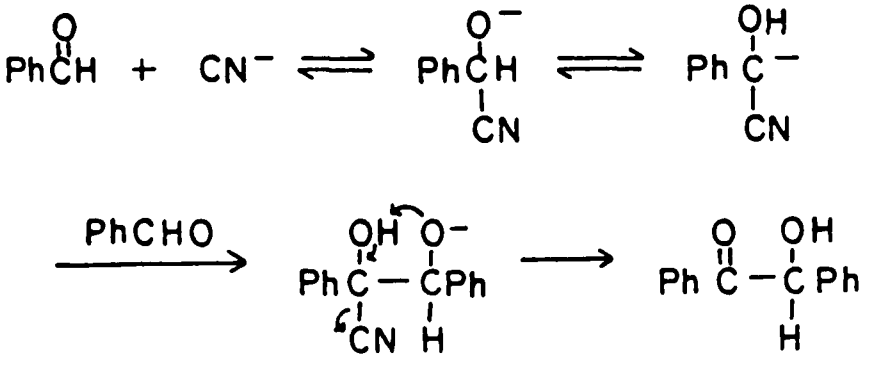
A current area of interest in organic chemistry is devising methods to reverse the normal polarity of functional groups. This type of change has been termed "umpolung". For example, aldehydes are generally sites of electrophilic attack. However, with the use of activating and/or protecting groups, they can be made to be nucleophilic reagents. Table 8 (150) shows some of the reversals of polarity which have been accomplished. A number of review articles are available which deal with the topic of umpolung (150-156).

The area of nucleophilic anion equivalents is so vast that a number of recent reviews are exclusively devoted to this topic (150-153). The topic of formyl anion equivalent falls under the broad heading of acyl anion equivalent. Since the work presented in this part of the thesis involves synthesis and reactions of a sulfone formyl anion equivalent, the material presented in this section will mainly concentrate on formyl anion equivalents which involve sulfur and their reactions with alkyl halides which, upon hydrolysis, produce aldehydes.

A well known reaction which makes use of an acyl anion equivalent is the benzoin condensation which is depicted in

scheme 22. In this classical reaction, the equivalent of Ph-CO$^-$ is generated which attacks nucleophilically another molecule of benzaldehyde. Upon elimination of cyanide ion, the final product is produced. In this case, it is not necessary to protect the alcohol moiety of the cyanohydrin because the negative charge is stabilized by the phenyl group. Generally, it is necessary to protect the alcohol group because it would interfere with the remaining reactions.

Stork and Maldonado (157) made use of this concept in their method of ketone synthesis which is known as the Stork-Maldonado reaction. This series of reactions is shown in scheme 23. They treated an aldehyde with cyanide to produce the cyanohydrin. This was then treated with ethyl vinyl ether to produce the ethoxyethyl cyanohydrin of the aldehyde (157). In this example, Y is acting as an acyl anion equivalent, which can be depicted as Z. This is then

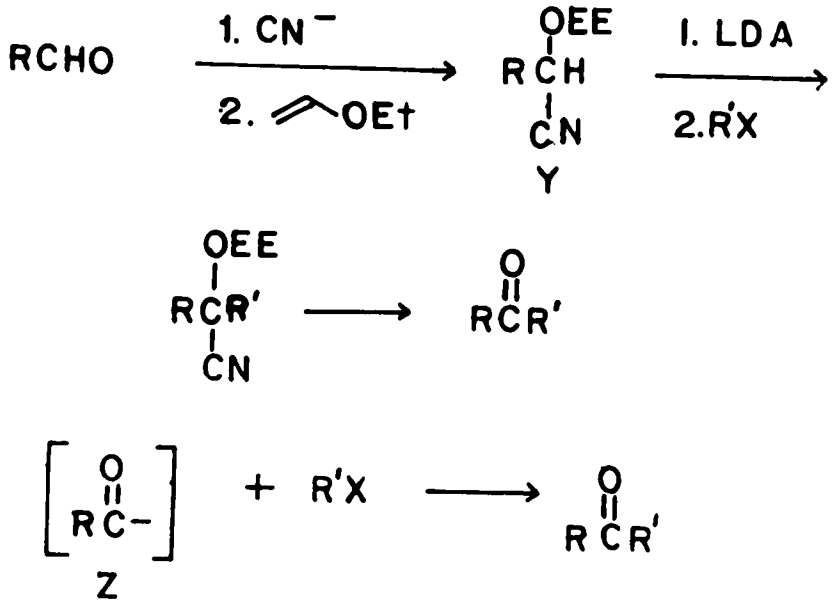


Scheme 22

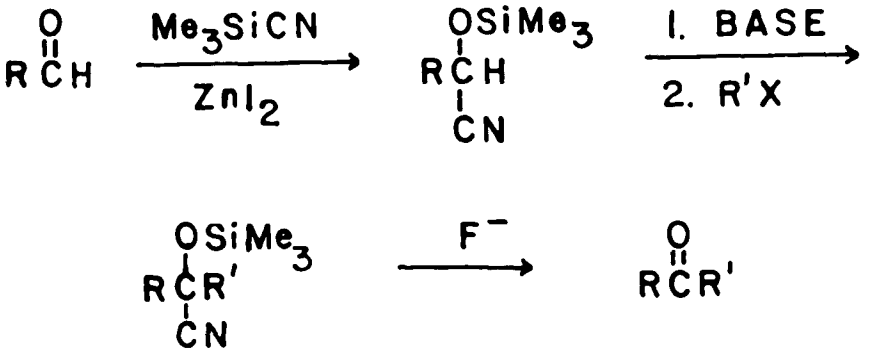
treated with base, followed by alkylating agent to produce the alkylated reagent. Upon hydrolysis the ketone is generated.

Evans (158) demonstrated that trimethylsilyl cyanide can be treated with aldehydes to produce the O-trimethylsilyl cyanohydrin in one step, which can then be alkylated. Upon hydrolysis, for example with fluoride (159) ion, the alkylated cyanohydrin is generated which can be decomposed to the ketone. These reactions are shown in equation 27.

Many acyl anion equivalents have been developed which make use of either one or two sulfur atoms adjacent to the anionic carbon atom. These reagents make use of the sulfur atom in different oxidation levels; sulfide, sulfoxide, and



Scheme 23



Equation 27

sulfone. It has been postulated that anions adjacent to sulfur are stabilized through p-d backbonding. Although there is some controversy in this matter, it is generally thought that vacant d-orbitals on the sulfur allow this extra stabilization. This effect is not observed, for example, in substituted dialkoxymethanes, because oxygen does not have these vacant d-orbitals.

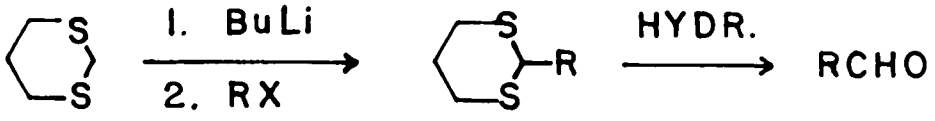
One of the first sulfur acyl anion equivalents developed was 1,3-dithiane (usually called simply dithiane). It is now commercially available from Aldrich (160). It can be made by treating 1,3-dithiopropandiol with dimethoxymethane using boron trifluoride etherate as the catalyst. After recrystallization, the yield of the pure product is 78 - 84% (161).

Dithiane can be metalated by reaction with butyl lithium in THF at -20°C. This lithiated species thus produced can be alkylated with primary or acyclic secondary iodides

or bromides (as shown in equation 28) and carbonyl compounds (162).

Although dithioketals are generally resistant to acidic and basic hydrolysis, there are now procedures available for cleaving the alkylated dithiane and thereby generating the carbonyl compound. These procedures (162) include hydrolysis with metallic ions (such as Hg(II), Cu(II), Ag(I) or Tl(III)), with alkylating agents (such as methyl iodide or methyl fluorosulfonate) or with oxidizing agents (such as N-halosuccinimide, peracids, ceric ammonium nitrate or concentrated sulfuric acid). The most commonly used method of hydrolysis is through the use of mercuric salts or N-halosuccinimide.

S,S-Acetal S-oxides have also been used as acyl anion equivalents. The dimethyl and diethyl formyl anion equivalents AA and BB are commercially available from Aldrich (163) and Fluka (164), respectively. The cyclic sulfoxide, CC, was alkylated (165) although in quite low yield. Methyl iodide and benzyl bromide gave alkylated product in 14% and 24% yield respectively. Ogura (166)

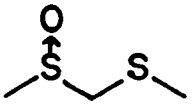


Equation 28

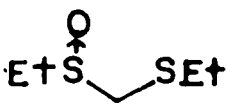
reported CC was alkylated by different alkyl halides in high yields (85 - 91%). When trying to duplicate these results, Schlessinger (167) reported that he only got modest yields. He found that BB was a far superior reagent because it not only gave high yields on monoalkylation, but that it also could be dialkylated and that it underwent a Michael type addition to enones.

Reagent BB can be prepared as shown in equation 29. Dimethoxymethane was treated with 2 equivalents of ethanethiol to give the thioacetal DD. Upon oxidation with sodium meta-periodate, DD was converted into the monosulfoxide BB in 90% yield. Alkylation proceeds as shown in equation 30.

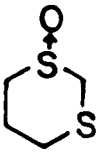
While hydrolysis can be accomplished using a catalytic amount of sulfuric acid (166), or using a catalytic amount of 70% perchloric acid (167), the product is contaminated with ethyl disulfide which can be difficult to remove. Schlessinger found (167) that hydrolysis can be effected by treating the alkylated product with mercuric chloride suspended in a solution of THF and 9N HCl. This was stirred



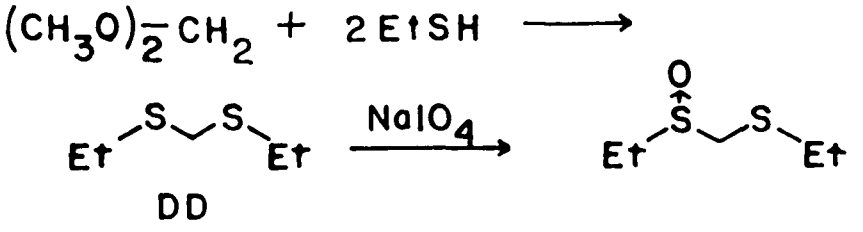
AA



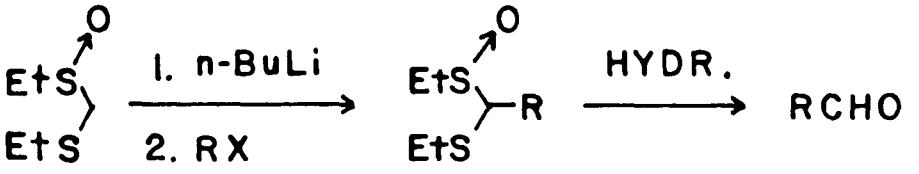
BB



CC



Equation 29



Equation 30

at 0°C for 1.5 hours to produce the aldehyde or ketone in 80 - 95% yield without disulfide.

A number of advantages of using the S,S acetal S-oxide rather than dithiane have been presented. These reasons (150) include the following:

a) Alkylated S-oxides are easier to hydrolyze. They can be hydrolyzed readily in acidic media. (This is their main advantage.)

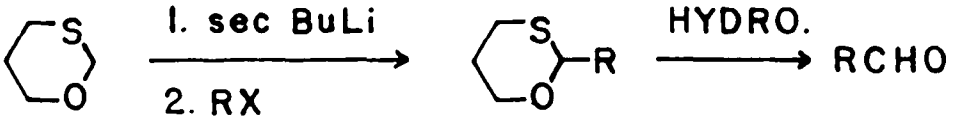
b) S-Oxides are more acidic, thus their anions are easier to generate.

c) These anions are more nucleophilic. They can be reacted with more kinds of electrophiles.

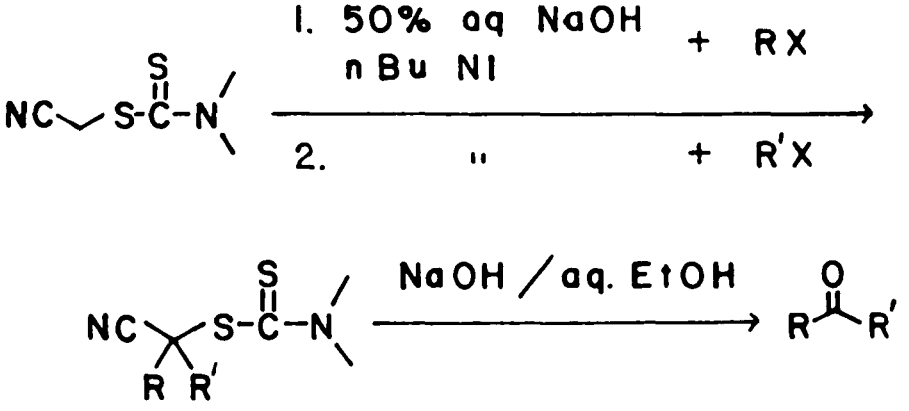
d) S-Oxides add 1,4 to enones, whereas dithiane adds 1,2.

Oxathianes (168) can be alkylated and then hydrolyzed to form aldehydes, as shown in equation 31. Oxathianes can be synthesized by treating the aldehyde (presumably formaldehyde, also) with 3-mercaptopropanol in methylene chloride plus a catalytic amount of p-toluenesulfonic acid. They can be alkylated with primary iodides in good yields. Alkylation with secondary iodides gives generally much lower yields (i.e. sec-propyl iodide gives 35% of the alkylated product). Oxethianes are stable under alkaline and neutral reaction conditions and can be cleaved by mineral acids in alcohols (or dioxane) or by mercuric salts (169).

Cyanomethyl-N,N-dimethyldithiocarbamate (170) was used as a formyl anion equivalent. It was synthesized by reacting chloroacetonitrile with sodium N,N-dimethyl-dithiocarbamate in methanol. Since it is activated by two very strong electron withdrawing groups, it is more acidic than, for example, dithiane. It can be alkylated under phase-transfer catalysis conditions as shown in scheme 24. This reagent can be monoalkylated selectively because dialkylation requires much more time.



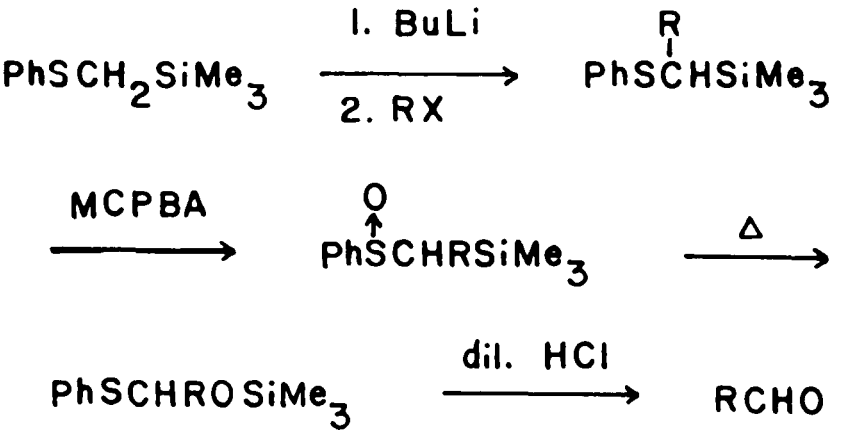
Equation 31



Scheme 24

Phenylthiotrimethylsilylmethane has also been used as a formyl acyl anion equivalent (171,172). It was prepared by refluxing thioanisole in nBuLi in ether for 18 hours and quenching with trimethylsilylchloride to give the expected product in 95% yield. Scheme 25 shows the alkylation and hydrolysis steps. Alkylation was done in high yield. Cleavage involved three steps with an overall yield of approximately 70%. This reagent has the drawback that it can not be dialkylated (173).

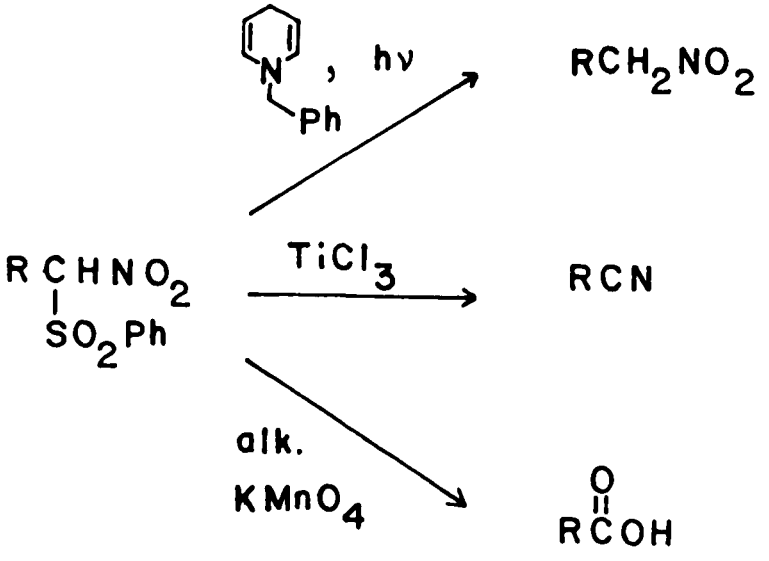
The remaining reagents to be presented in this section involve sulfone acyl anion equivalents. Phenylsulfonyl nitromethane (174) can be alkylated by benzylic halides and primary alkyl iodides in good yields (54 - 73%). As shown in scheme 26, the resulting product was desulfonated to give the nitro product, or reduced to give the nitrile, or oxidized to give the carboxylic acid. Hydrolysis to the



Scheme 25

carbonyl compound was not mentioned. Thus, at this time, it has not been used as an acyl anion equivalent.

The next reagent is slightly different in that it was oxidized after the alkylation step had been performed. Scheme 27 shows the sequence of steps used to produce

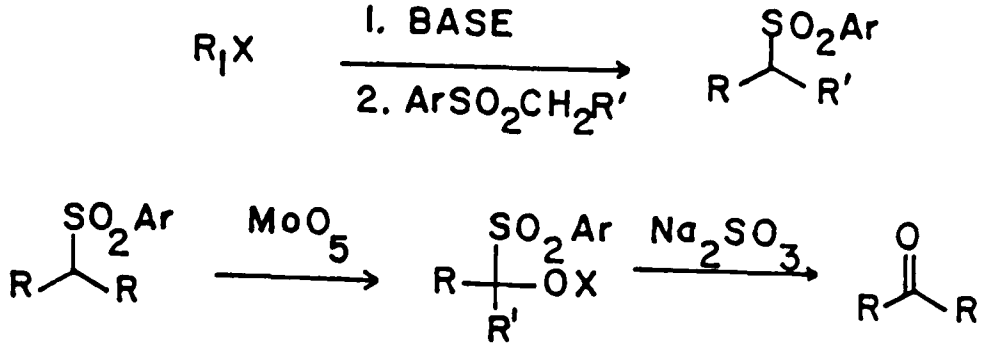


Scheme 26

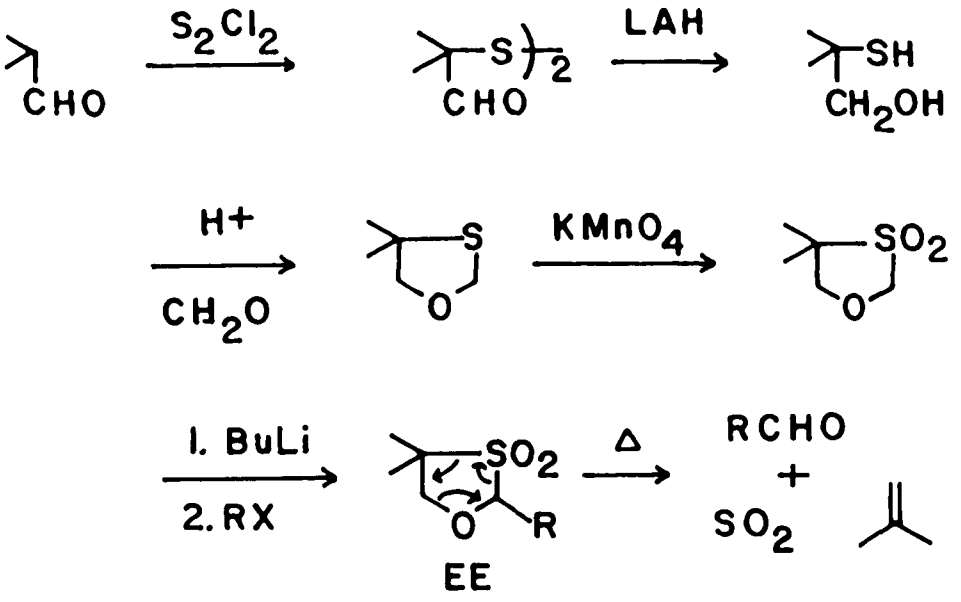
ketones from sulfones (175). Overall yields from the sulfone to the ketone range from 51 to 97%.

Another carbonyl anion equivalent is 4,4-dimethyl-1,3-oxathiolane-3,3-dioxide. It was synthesized as shown in scheme 28 (176). The reported yields for the alkylation step using primary alkyl halides ranged from 57 to 84%. Deprotection was achieved by either refluxing EE in benzene for five hours or by subliming it through a column maintained at 400°C at a pressure of 0.1 mm Hg. Yields were reported for the pyrolysis deprotection but not for the deprotection by refluxing in benzene.

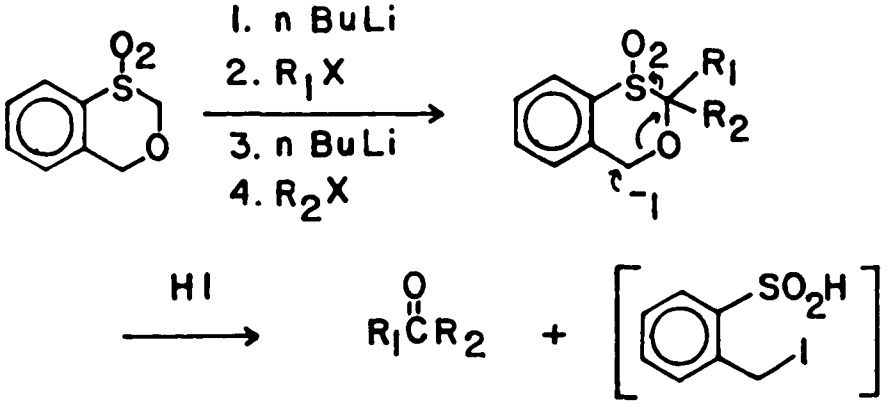
Another sulfones acyl anion equivalent is the alkoxy sulfone (177) as shown in scheme 29. Details for this reagent have not been published, it was only mentioned in a review article.



Scheme 27



Scheme 28



Scheme 29

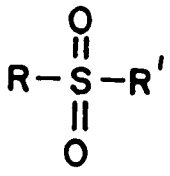
Unfortunately, information concerning this reagent was published while our work was in progress. Since this work was so close to our work, reactions of this reagent will be compared and contrasted in the Results and Discussion section.

In conclusion, because methodology for so many acyl anion equivalents is now available, due to constraints of space, it is not practical to mention them all. In these preceeding paraghaphs, acyl anion equivalents, especially formyl anion equivalents of the type $X-CH_2-Y$ have been presented. Special emphasis of sulfur acyl anion equivalents was given because the proposal at hand involves a sulfone formyl anion equivalent.

2. General Information on Sulfones

Although organic chemists have known about the sulfone group for more than a century (177), it has only been within the past few decades that much work has been done to understand more about their chemistry. Work done on sulfones can roughly be divided into two categories (179): before 1967 and after 1967. The work done before 1967 generally dealt with stereochemical behavior, whereas that after 1967 generally dealt with synthetic applications of sulfones.

The general formula of the sulfone group is depicted as FF. R and R' can be alkyl, aryl, vinyl or alkynyl groups. The sulfone group is an electron withdrawing group, as is the sulfoxide group. Because of this, protons alpha to the sulfone group are acidic. The alpha protons of sulfones are more acidic than those of sulfoxides. This is seen by the fact that the pKa of dimethyl sulfone is 28.5, whereas that of dimethyl sulfoxide is 33.5 (179).

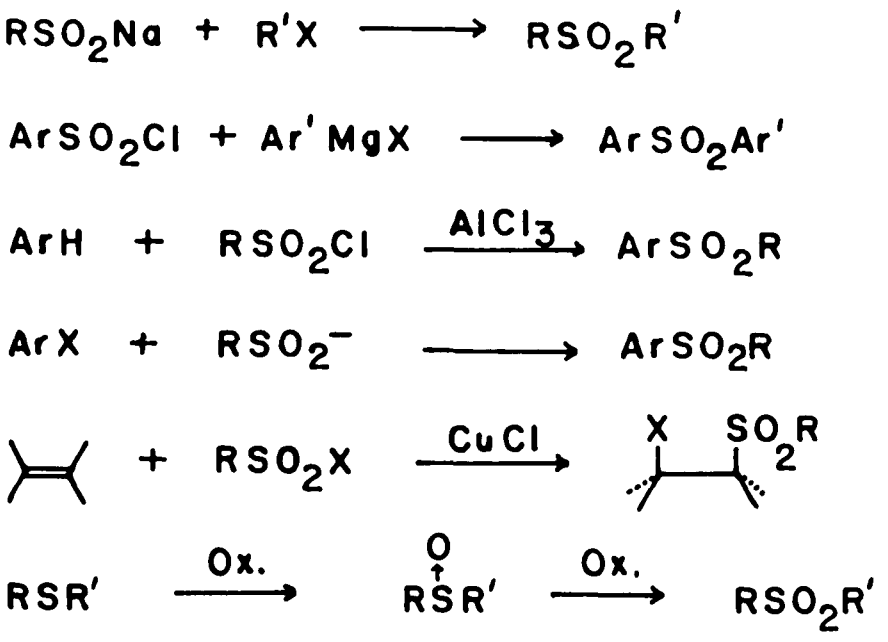


FF

Much work has gone into discovering reasons why alpha anions are stabilized. It had been thought this was because of p-d overlap of the orbitals of the carbanion with the vacant d-orbitals of the sulfur. Wolfe and coworkers (179,180) concluded, after having done *ab initio* calculations, that d-orbitals are insignificant in stabilizing the adjacent carbanion. Their results indicated that the stabilization was due to the long C-S bond and to the fact that the sulfur atom is more polarizable so that the negative charge can be dispersed.

Sulfones can be synthesized in several ways, some of which are shown in scheme 30 (180-186). Sulfides can be oxidized to sulfoxides by using one equivalent of an oxidizing agent. Sulfoxides can be further oxidized to sulfones by using another equivalent of the oxidizing agent. Isolation of the sulfoxide is not necessary. Oxidizing agents which have been used include 30% H_2O_2, m-chloroperbenzoic acid, sodium meta-periodate, and potassium permanganate (179,181).

Sulfinic acids can be alkylated by reacting alkyl halides at 20 - 40° for 2 to 4 hours. Alkyl halides which have been used include primary alkyl, allylic, and benzylic halides in addition to bromo ketones (179). Generally, the S-atom is alkylated to yield sulfones, but if very reactive alkylating agents (such as Et_3O^+



Scheme 30

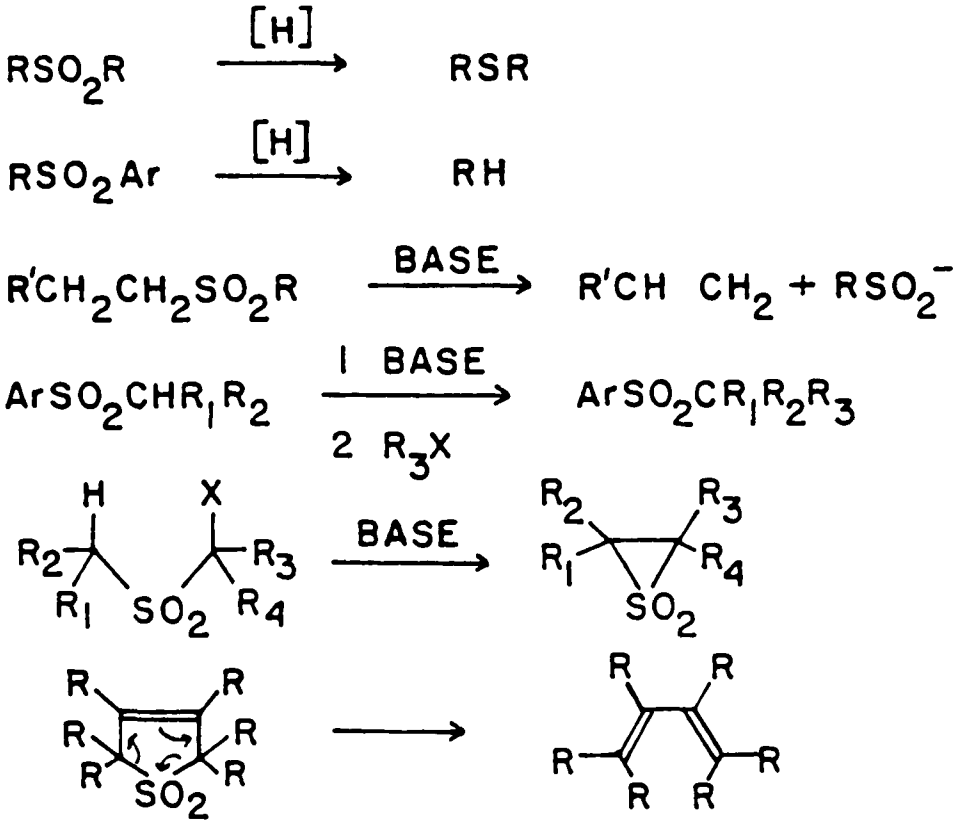
BF_4^-) are used, the O-atom is alkylated to yield sulfinate esters. Usually sulfinate esters thermally rearrange to sulfones anyway (181).

Sulfones can undergo a number of reactions. Some of these are shown in scheme 31 (179,182). Sulfones are generally resistant to reducing agents. LAH has been used to reduce four and five membered ring sulfones to sulfides. However, it does not affect six membered ring or acyclic sulfones. This could be due to alpha anion formation which makes the sulfone inert (179). Another way to reduce sulfones to the sulfides is to heat them in the presence of elemental sulfur. The oxygens are removed by reacting with

the sulfur and are lost in the form of sulfur dioxide (182).

More recently sulfones have been used to activate the adjacent C-H bond. Through this effect, C-C bond formation can be brought about. If the sulfone group is no longer needed it can be removed by the use of Raney nickel in ethanol, Na(Hg), Al(Hg) in phosphate buffer, or lithium in ethylamine. They have also been reduced electrochemically and photochemically (179).

Sulfones with beta hydrogens can undergo elimination when treated with a strong base or when heated. The



Scheme 31

resulting products are the alkene and the sulfinate salt (which is a good leaving group). The ease of elimination depends on the acidity of that beta hydrogen. This elimination has been used effectively in some natural product synthesis (179).

Probably the most well known reaction of sulfones in years past is that of the Ramberg-Backlund reaction. In this reaction, an a-halo sulfone which possesses an a'-hydrogen is treated with base. This results in the formation of an episulfone. The episulfone looses sulfur dioxide, thus rendering the alkene (179). The most useful feature of this reaction is its ability to form a carbon-carbon double bond regiospecifically. Because other such methods are now available, it is not used as much as it once was (177).

Alkylation of alpha-sulfonyl carbanions is of special interest here as it was used in the synthesis at hand. References closely associated with the work actually done are presented in the Results and Discussion section.

A number of studies were done on alpha-sulfonyl carbanions to determine whether they are planar, sp^2-hybridized or pyramidal, sp^3-hybridized. Many of these studies were performed on optically active sulfones in which the rate of H-D exchange was compared to the rate of racemization. It is now thought that the a-sulfonyl

carbanions are pyramidal, sp^3-hybridized. Since the sulfone on which the work was done is not optically active and since, as far as this work is concerned, the kind of hybridization involved is not crucial, these topics shall not be discussed further.

Treatment of the dialkylsulfone or alkyl arylsulfone with an appropriate base generates the corresponding alpha-sulfonyl carbanion. For sulfones which are not further activated, this is often accomplished by using n-butyl lithium. For doubly activated sulfones, such as beta-ketosulfones such strong base treatment is not necessary. These can generally be alkylated using phase transfer conditions (179).

Alkylating agents such as allylic, benzylic, and primary halides often give excellent yields upon reaction with alpha-sulfonyl carbanions. For secondary alkyl halides, it has been found advantageous to add HMPA to the reaction mixture (179). Generally alpha-sulfonyl carbanions do not add 1,4 to enones, but instead add 1,2 (177). This could be due to the steric bulk of the sulfone group which is comparable in size to the neo-pentyl group.

Internal alkylations have been performed which produce sulfonyl substituted carbocycles. Three, five and six membered rings have been prepared in this way. Potassium amide in ammonia as the base gives better results than

sodium ethoxide in ethanol because the latter gives elimination products and products of intermolecular substitution (179).

Using 2 equivalents of BuLi, it is possible to produce 1,1 dianions of alkyl arylsulfones. These have been treated with aldehydes to produce arylsulfone alkenes (179).

In conclusion, sulfones are useful in synthetic organic chemistry largely because of the wide variety of reactions they can undergo. The most outstanding feature is their ability to activate adjacent C-H bonds. This aspect is used in C-C bond formation. Once that bond is formed, the sulfonyl group can be allowed to remain, be reduced, or be eliminated.

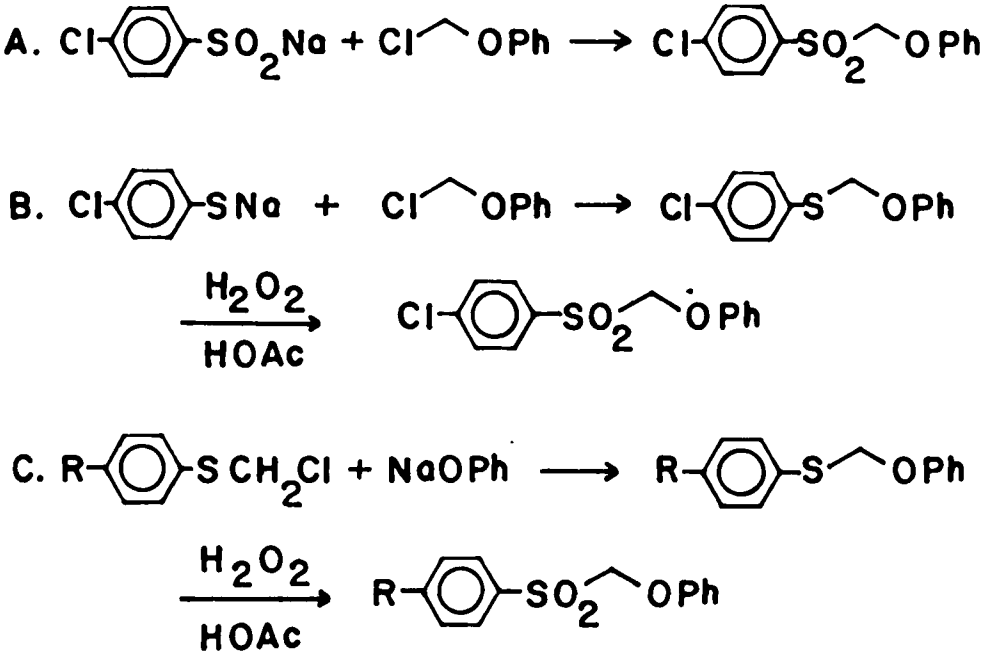
3. Arylsulfonylmethyl Methyl Ethers and Related Work

Kurt Schank and coworkers of the University of Saarlandes, Germany, have done much work on alpha-sulfonyl methyl ethers. Some aspects of this work shall be presented here and the more closely related work shall be discussed in the Results and Discussion section.

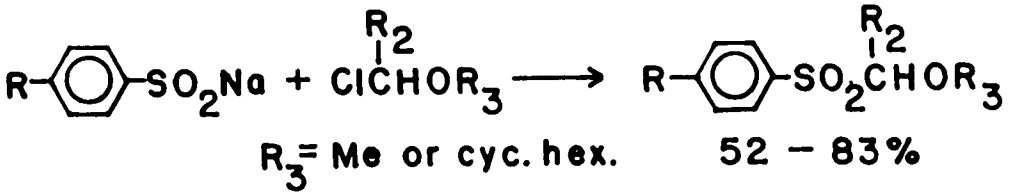
Schank reported (187) three ways in which arylsulfonyl methyl ethers could be synthesized. These are shown in scheme 32. Method A can give either S-alkylation or O-alkylation depending on reaction conditions. The product of O-alkylation, the arylsulfinic ester, is unstable and decomposes into the S-alkylated product under acid, base or neutral conditions (188).

Arylsulfonylmethyl methyl ethers were produced in the following two ways (189) as shown in equations 32 and 33: Of interest is the latter route because this closely resembles the alkylation step in the proposal. The only products which were made by this route were GG, HH, II, and JJ.

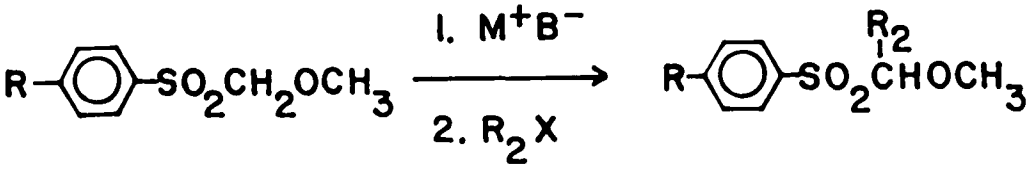
Schank tried different metalating conditions and found the best to be n-BuLi at -70°C for 3 hours or KOtBu at 25°C for 1 hour. Even so, the yields in the alkylation step by this method were low. Using MeI or Me_2SO_4,



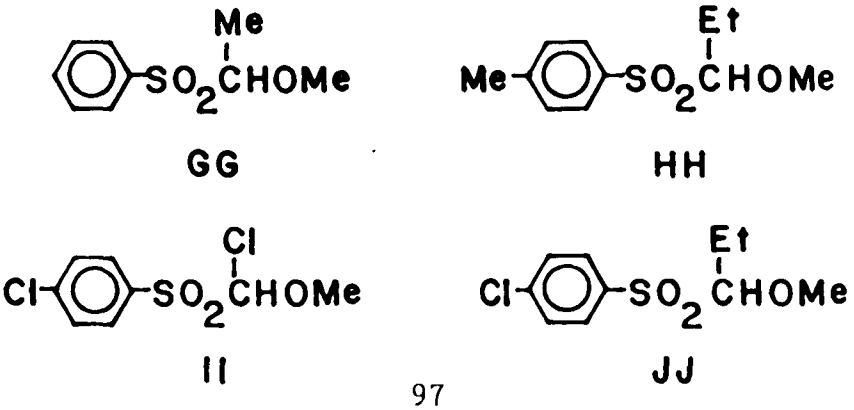
Scheme 32



Equation 32



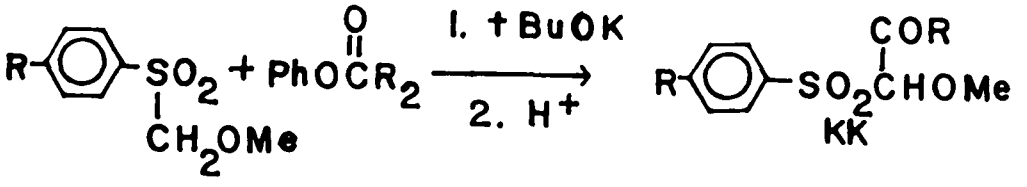
Equation 33



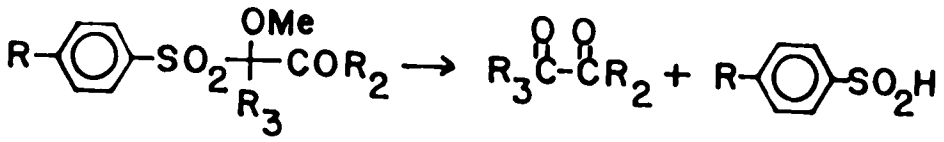
GG HH II JJ

the yields ranged from 26 to 43%. With benzyl chloride as the alkylating agent, none of the substituted product was obtained. Because of low yields and lack of general applicability, they resorted to the method shown in equation 32 (189). Because this paper (189) was so closely related to the proposal at hand, it shall be discussed further in the Results and Discussion section.

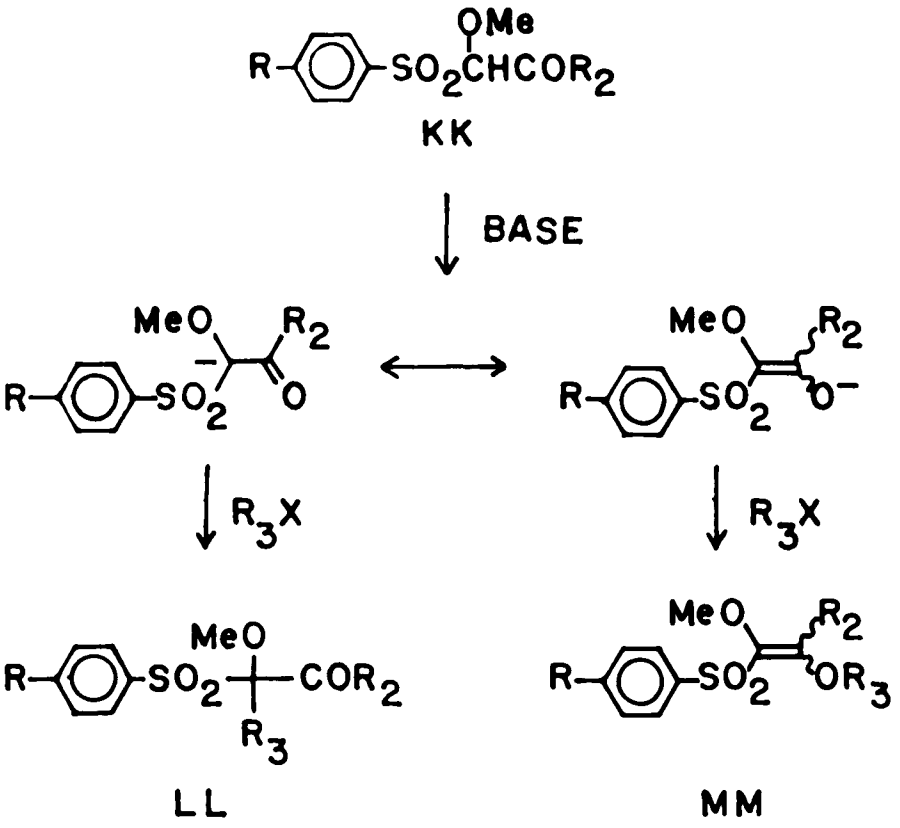
Arylsulfonylmethyl methyl ethers were acylated using a variety of substituted phenyl benzoates (190) as shown in equation 34 to give products of the type KK. The products, KK, upon further base treatment and alkylation, gave products LL and MM as shown in scheme 33. Products of C-alkylation, LL, were obtained when "soft" alkylating agents such as alkyl halides without beta hydrogens were used. Products of O-alkylations, MM, were obtained when "hard" alkylating agents such as acyl halides or chloromethyl methyl ether was used. Mention (190) was made that product LL, which was persubstituted, decomposed into the 1,2 diketone and the sulfinic acid as shown in equation 35.



Equation 34



Equation 35



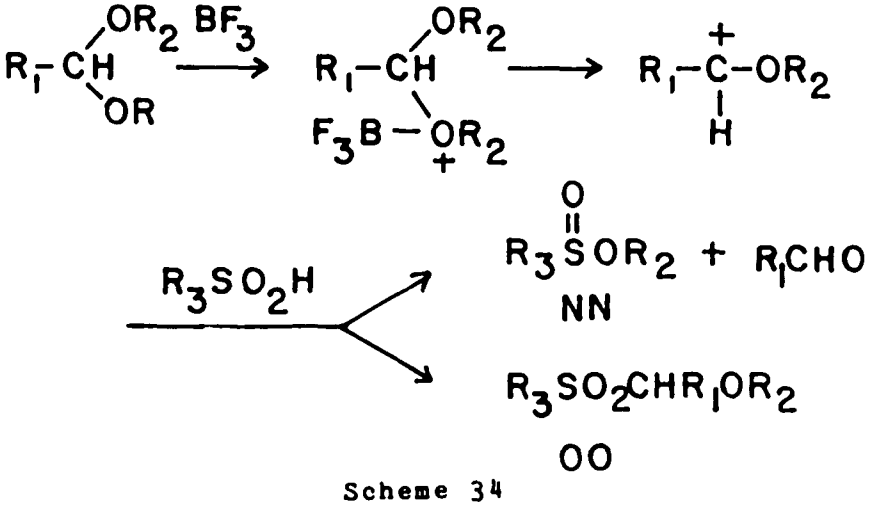
Scheme 33

Also of interest is the reaction (184) of acetals with sulfinic acids in the presence of BF_3-Et_2O to yield either sulfinic ester NN or sulfonylethers OO in good yield as shown in scheme 34. The product NN does not incorporate

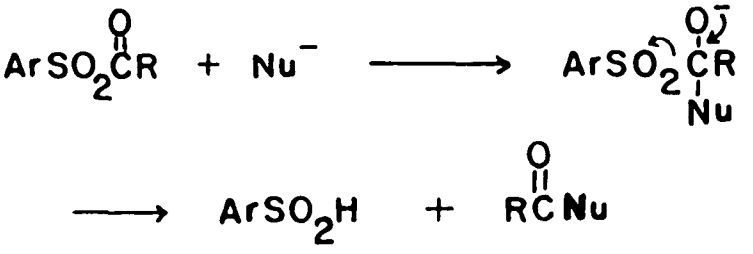
the acetal and is a by-product in the synthesis of OO. Product OO is produced in yields ranging from 38 to 88% (184).

Another type reaction sulfones can be used for is shown in scheme 35. It was thought that through this series of reactions, a compound on the oxidation level of a carboxylic acid could be converted to a ketone. For this reaction to be useful, it is necessary to be able to produce alpha-oxo sulfones. Schank and coworkers synthesized alpha-oxo sulfones by two methods (192) shown in scheme 36.

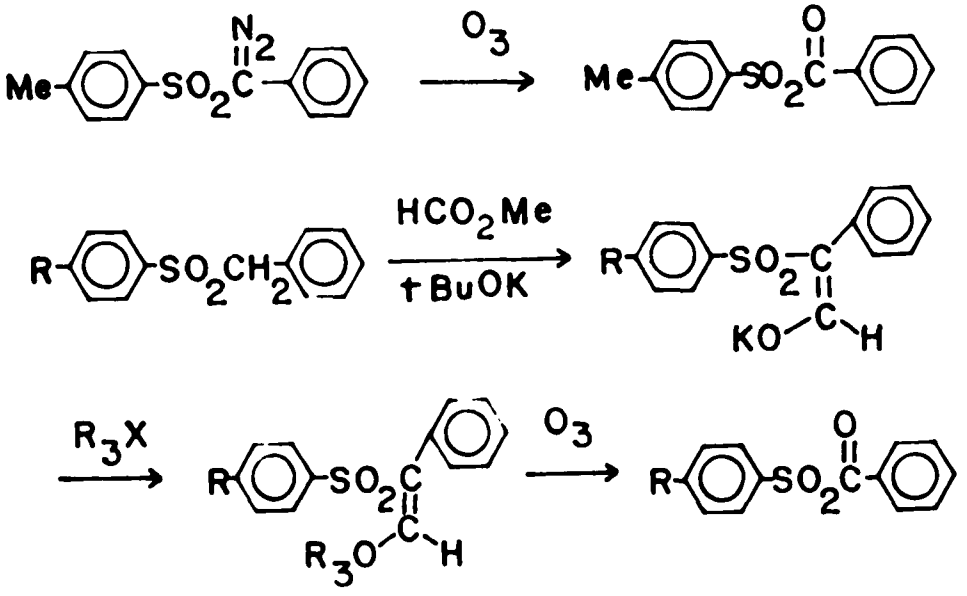
These alpha-oxo sulfones thus produced reacted (186) with protic and aprotic nucleophiles. With protic solvents as the nucleophile, the products were the sulfinic acid and substituted benzoate ester as shown in equation 36. With aprotic solvents as the nucleophile, different results were



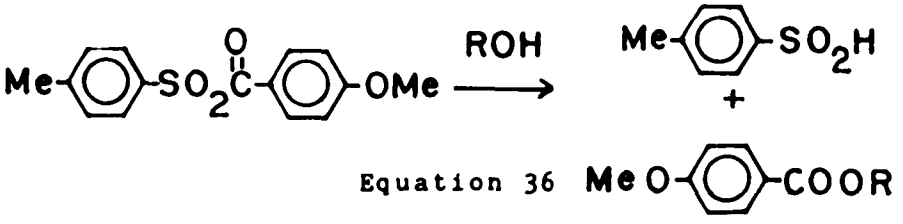
Scheme 34



Scheme 35



Scheme 36



Equation 36

obtained depending on the nucleophile in question. Nucleophiles such as amines, DMSO, and diazomethane were used.

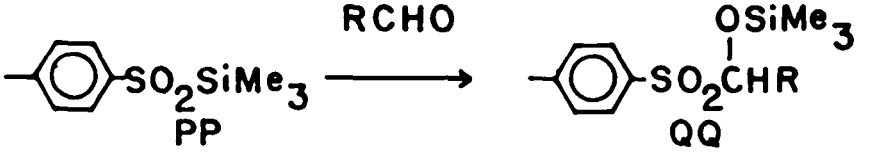
In conclusion, general information on arylsulfonyl methyl ethers has been presented with an emphasis toward reactions involved in the proposal at hand.

4. Proposal for alpha-Alkoxy Sulfone Work

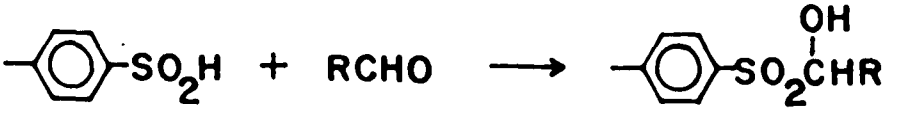
The project at hand was to develop methodology in the use of alpha-alkoxy sulfones as acyl anion equivalents. It was desired to have an acyl anion equivalent that is easy to make from low cost commercially available starting materials via procedures which are easy-to-perform and relatively safe.

The original proposal was to make the trimethylsilyl ester of toluenesulfinate, PP. This was to be reacted with aldehydes to produce the protected aldehyde, QQ, as shown in equation 37.

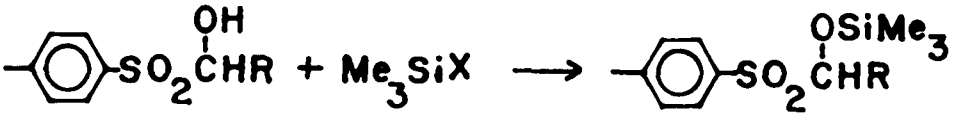
Because compounds like PP are not stable, it was decided to change the original intent slightly and prepare QQ in two steps, as shown in equation 38 and 39.. Unfortunately, there was difficulty in putting the trimethylsilyl group on (even through the two step process), and we decided to change the protecting group altogether to the tetrahydropyranyl protecting group. The protected aldehyde is shown in equation 40 - 41.



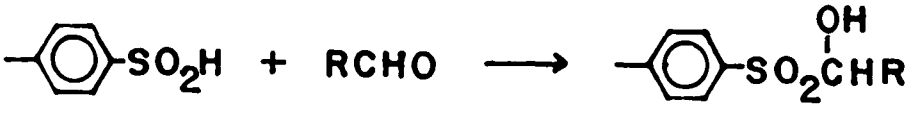
Equation 37



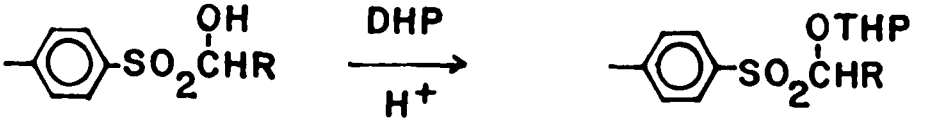
Equation 38



Equation 39

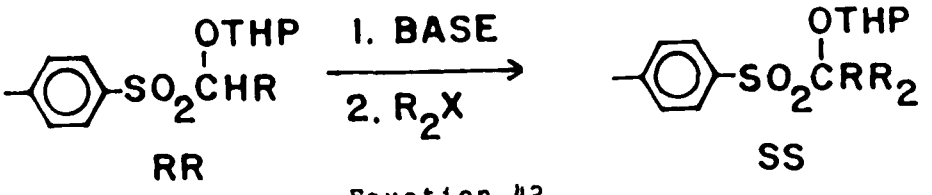


Equation 40

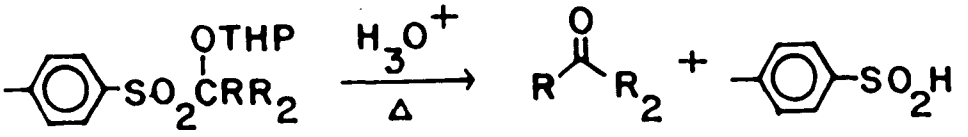


Equation 41

It was envisioned that compound RR could be alkylated according to known procedures for alkylation of sulfones as shown in equation 42. The compound thus produced, SS, could then be deprotected via one of the many published procedures for removing the tetrahydropyranyl group, eg. acid, as shown in equation 43.



Equation 42

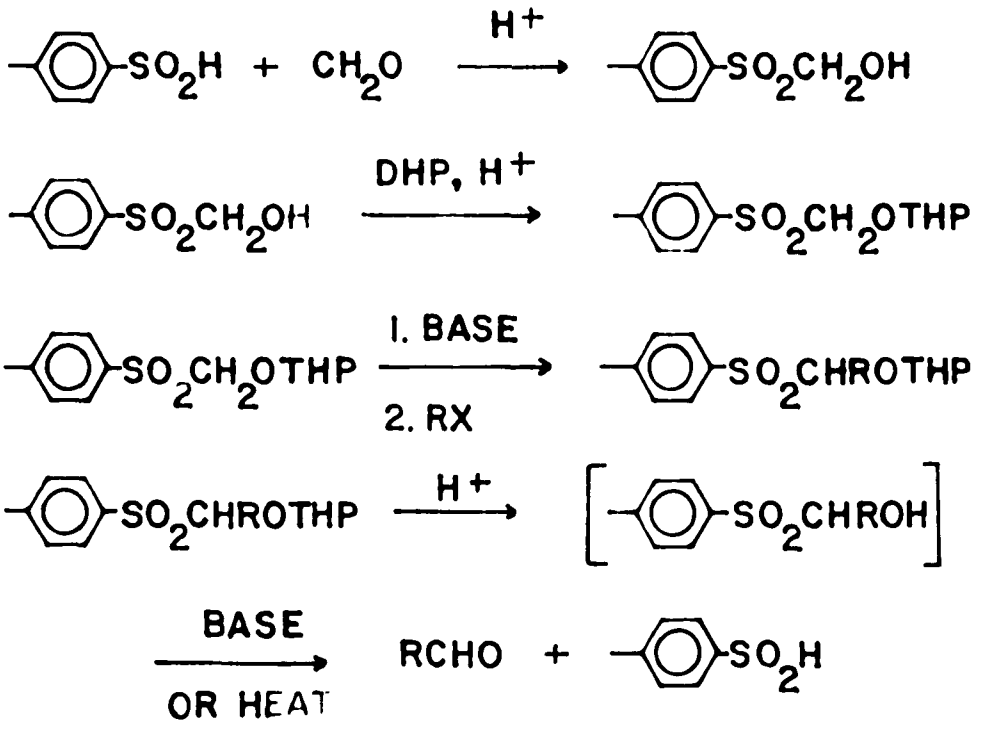


Equation 43

As as in the basic concept of acyl anion equivalents of aldehydes, this proposal is to convert aldehydes to ketones by replacing the aldehydic proton with an alkyl group. The first half of the project was to develop the methodology for the smallest aldehyde available, formaldehyde. The actual reactions that were to be done are shown in scheme 37. This scheme proposed a method of forming an acyl anion equivalent of formaldehyde which would result in the synthesis of higher aldehydes or ketones (by mono or dialkylation, respectively).

The alkylating agent could, hopefully, be an alkyl halide or an enone which could presumably add 1,2 or 1,4.

An extension of the work would be to start with aldehydes higher than formaldehyde. This would be a more general type of reaction in which aldehydes could be converted to ketones, as shown in equations 40 - 43.



Scheme 37

This work was planned to be done, realizing there may be problems in the alkylation due to steric hindrance from the fairly bulky sulfone group.

Thus the proposal which was explored is that summarized in scheme 37.

5. Results and Discussion on Alkoxyl Sulfones

Choise of a Protecting Group

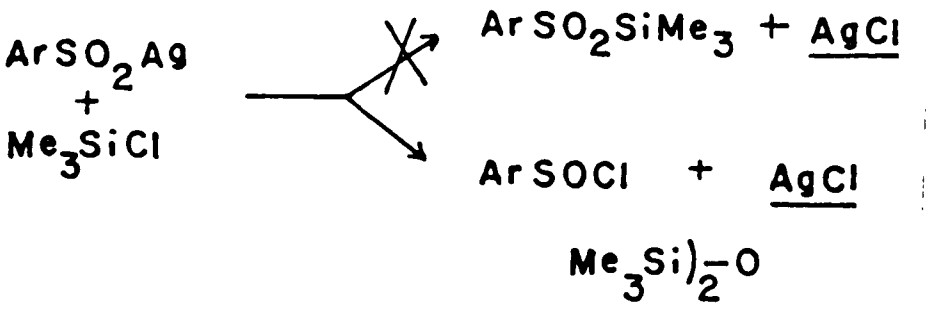
Some trimethyl metal esters of sulfinic acids have been synthesized, but not trimethylsilyl esters of arylsulfinic acids. Lindner and Schardt (194) reported that they made the trialkylgermanium ester of arylsulfinic acids by reaction of trimethylgermanium bromide with the silver salt of arylsulfinate as shown in equation 44.

When the analogous reaction was tried with trimethylsilyl chloride, they obtained the acid chloride of the arylsulfinic acid instead, as shown in equation 45. They reported that possibly the trimethylsilyl ester was obtained but due to its instability it further reacted to form the arylsulfenyl chloride.

Lindner and Schardt (195) also reported that they formed $MeSiO_2SCH_3$ and Ph_3SiO_2SPh. $Me_3SiO_2SCH_3$ was unsuitable for our purposes because it would have another removable proton alpha to the

$$ArSO_2Ag \xrightarrow{R_3GeBr} ArSO_2GeBr + \underline{AgCl}$$

Equation 44



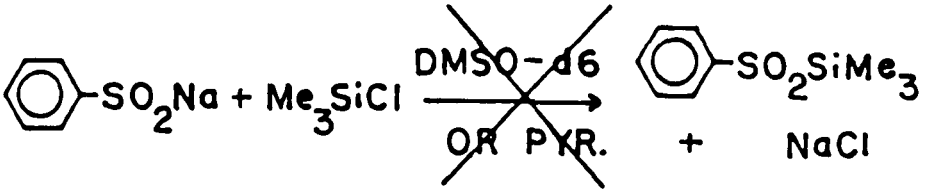
Equation 45

sulfone group in the product which was to be alkylated. The triphenylsilyl ester would be quite bulky due to those three phenyl groups on silicon.

In another paper Lindner and Ansorge (196) reported that they made di- and tri-sulfinic esters of silicon of the type $R_2Si(O_2SAr)_2$ and $RSi(O_2SAr)_3$. Again this type of compound may not be useful due to its increased steric hindrance in a position which is already fairly hindered due to the adjacent sulfone group. They also reported that compounds of this type are extremely sensitive to hydrolysis.

Our attempts at making this type of compound, although limited, appeared to be unsuccessful. The reaction which we attempted is shown in equation 46.

The sodium salt of benzenesulfinic acid was dissolved in DMSO-d6 in a NMR tube. Trimethylsilyl chloride was then added and a precipitate was obtained. Presumably this precipitate was sodium chloride which is not soluble in



Equation 46

DMSO. There was also an insoluble liquid layer on the top. There had been a water peak observable in the NMR of sodium benzenensulfinate which now had disappeared when the trimethylsilyl chloride was added. This solution was filtered to remove that cloudy precipitate, and the NMR was taken of the lower layer. It only showed a trace of methylsilane protons, presumably trimethylsilyl chloride was dissolved in DMSO. The integration of aromatic protons to trimethylsilyl protons in the desired compound is 5:9. If the correct compound were obtained, the ratio should have been 211 based on 117 for the aromatic protons. The ratio observed was only 3 to 117 which indicated the product was not present. It is presumed that the reaction that took place is shown in equation 45 as Lindner and Schardt observed.

It had been postulated by us that trimethylsilyl arylsulfinate could be a stable reagent. From Lindner and Schardt's work and our (limited) work and from the fact that these kinds of compounds are very moisture sensitive, it was decided not to pursue the one step synthesis of arylsulfonyl

trimethylsilyl protected aldehydes but to instead attempt it through two steps. This would be accomplished by first making the alpha-hydroxy sulfone and second, protecting the alcohol function with the trimethylsilyl group.

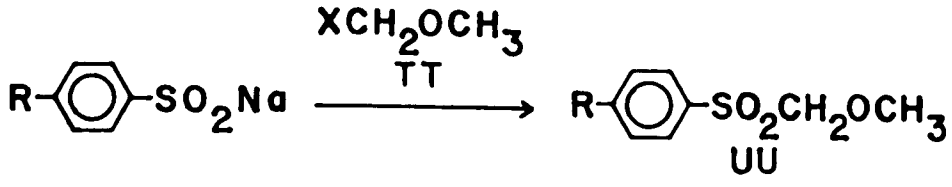
Some work was done in which toluenesulfinic acid was treated with formalin to give tosylmethanol. This was then treated with trimethylsilyl chloride to give not the expected tosylmethyl trimethylsilyl ether but what appears to be bis-(tosylmethyl) ether. This shall be discussed towards the end of this chapter.

Because efforts at silylation of tosylmethanol did not give the desired product, we decided to try another protecting group. This protecting group should meet the conditions of being base stable (because alkylation was to be done with a strong base) and easily removable under fairly mild conditions.

Schank (189) described alkylating arylsulfonylmethyl methyl ether. These compounds were synthesized (188) as shown in equation 47. The substituent X of compound TT could be Cl, Br, or tosyl. Reagents of this type are highly carcinogenic. Also if methyl ethers such as UU were to be used as acyl anion equivalents (which has not yet been reported) it would be necessary to cleave the methyl ethers to generate the aldehyde. Generally these are cleaved with BCl_3 or more recently developed methodology using

Me_3SiI (197). It is not a simple process as cleaving THP ethers with mild acid hydrolysis.

It was decided to use tetrapyranyl group as the hydroxy protecting group (198). Since the THP group can be used to protect primary, secondary, or tertiary alcohols, a point of concern because work on the reaction of aldehydes with arylsulfinic acids would produce a rather hindered secondary alcohol. THP ethers are stable in strong bases such as lithium alkyls and cleaved by dilute aqueous acid. The group is fairly easy to introduce by reaction with dihydropyran and acid catalyst. One concern was, however, the fact that it is possibly less stable than may be desired. It has been reported that "THP ethers are usually very sensitive to acid and should be prepared just prior to use or else stored in the dry state at lowest possible temperature" (199). It was also reported (199) that some THP ethers can be hydrolyzed readily by $MgSO_4$. Thus, although this was the protecting group that was actually used here, these compounds were always kept at room temperature a minimum amount of time and were stored in the



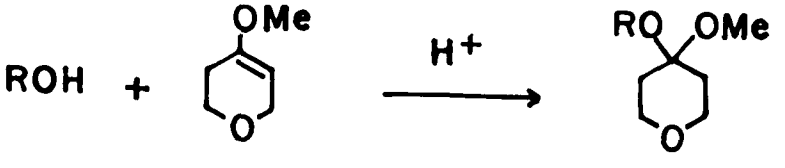
Equation 47

freezer. The ethoxyethyl (EE) group was considered as a protecting group but it was not used because it is even more labile than the THP group (200).

A possible problem with using the THP group or EE group was the fact that each possessed an asymmetric center. Since the types of compounds we eventually wanted to produce by this method do not have a asymmetric center at the carbon in question and since THP ethers were so widely used and studied, it was decided to use this route unless problems arose. Other symmetrical acetal protecting groups (201) have been developed such as that shown in equation 48. This group is three times as acid labile as the THP group. The starting material is not as readily available as dihydropyran. In addition, it is less widely used so there is not as much methodology developed concerning its use.

Synthesis of Tosylmethyl THP Ether

Since we abandoned the one step approach, we decided to approach the problem through a two step approach. The first

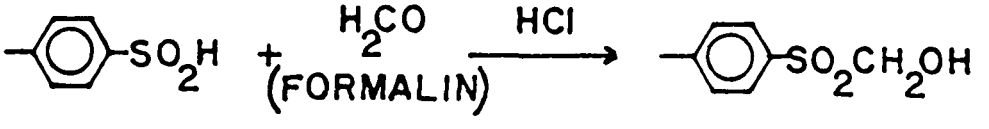


Equation 48

step would be to treat the arylsulfinic acid with the aldehyde and the second step would be to protect of the resulting sulfonyl alcohol with dihydropyran. The information presented in this section is work done on the smallest aldehyde, formaldehyde. Work on larger aldehydes is presented in the following section.

Tosylmethanol was first reported in 1901 (202), which was then modified in 1954 (203). The reaction is run as shown in equation 49. Toluenesulfinic acid and formalin plus a trace of HCl were warmed to 65-70°C. The published procedure (203) reported that this resulted in the formation of a crystalline mass which was squeezed to remove excess solvent and dried in a desiccator. Then it was recrystallized from benzene. The reported yield was 80%.

p-Toluenesulfinic acid is not commercially available from Aldrich; however, its sodium salt is. The reason (204) for this is that it is difficult to dry the sulfinic acid without partial oxidation to the sulfonic acid. The sulfinic acid can be obtained by dissolving its sodium salt in cold water and by adding the exact amount of aqueous HCl. Immediately white flaky crystals precipitate which are



Equation 49

collected by extracting several times with ether, drying over $MgSO_4$, gravity filtering, and finally rotary evaporating to remove the solvent.

Since the sodium salt is the starting material rather than the sulfinic acid, we devised a more direct method to synthesize tosylmethanol. Using the same proportions as before, the sodium salt was suspended in the required amount of formalin. Then the amount of HCl equivalent to the amount of sodium salt was added to give an oily, two-phase mixture. This mixture was heated to 70°C until most of the solid was dissolved. After cooling to room temperature, a crystalline mass was formed. This mixture was then extracted twice with ether, dried and rotary evaporated. It was recrystallized from benzene to give a product with a mp of 92.9-93.6°C in 88% yield.

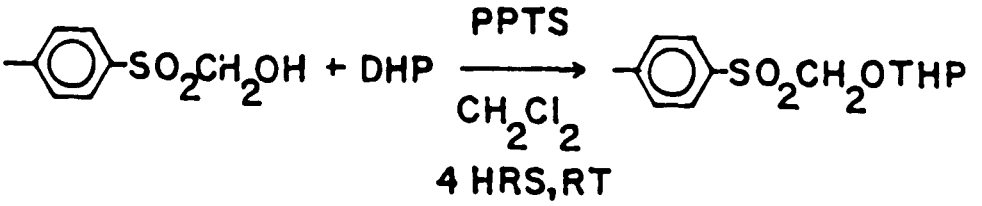
The reference cited (203) stated that the reaction was catalyzed by small amounts of HCl. The resulting crystalline mass was squeeze dried and finally dried in a desiccator. When we followed this procedure, the product which resulted from recrystallization from benzene still had the traces of HCl. When it was dried on the vacuum pump for a prolonged period of time, in order to remove the benzene from large quantities of product, the product turned tannish. This was probably due to partial decomposition of the tosylmethanol by residual amounts of HCl.

Thus, our new modified procedure gave better yields of more pure tosylmethanol from commercially available starting materials.

After it had been decided to use the THP group as the hydroxy protecting group, methods for this transformation were sought. The most common method for putting on the THP group is by dissolving (205) the hydroxy compound in dihydropyran and then adding a small amount of HCl to this solution. When applied to our tosylmethanol, the HCl droplet did not dissolve in the solution, but rather sank to the bottom and became a reddish color. Eventually, the whole solution was red-brown. After work-up, the resulting oil gave large, inseparable masses on TLC. Thus, due to the apparent problems when applying this method, other means of synthesizing THP ethers of fairly acid sensitive compounds were sought.

Grieco (206) reported a new catalyst for the synthesis of THP ethers of acid sensitive alcohols, pyridinium p-toluenesulfonate (PPTS). He reported that the yields of this reaction were practically quantitative. This method applied to our alcohol is shown in equation 50.

Following Grieco's procedure, the tosylmethanol was dissolved in methylene chloride. To this solution, a solution of PPTS in methylene chloride was added followed by dihydropyran. (The tosylmethanol had to be sufficiently



Equation 50

dry such that the NMR integration gave the expected ratios. If it were wet, the yield of product would be significantly decreased, and a lot of yellow impurity would be formed). This solution was stirred for 4 hours at room temperature. The reported work-up consisted of washing with half-saturated brine. In addition, we washed it twice with a saturated solution of sodium bicarbonate and dried it with potassium carbonate to remove any traces of acid which may remove the protecting group. Then it was gravity filtered and rotary evaporated. The resulting product was an oil which could then be crystallized by the addition of hexane and cooling it in the freezer. If the resulting crystals were white with good melting point (53.8-55°C) and one spot on TLC, it was not necessary to run a column to purify the compound further. This was desirable, because prolonged exposure at room temperature resulted in partial decomposition. If the resulting crystals were yellowish, it was necessary to purify them by flash chromatography (207). This yellow impurity is more pronounced when wet

tosylmethanol is used. It was probably formed by reaction of water and dihydropyran, possibly a polymerization type reaction. The yield was observed to be as high as 81% if chromatography were not necessary. The average final yield if chromatography were required was 67%.

The Japanese workers who investigated this type of reaction (178) used as their formyl anion synthon, benzenesulfonylmethyl ethoxyethyl ether. They made it by stirring a solution of benzenesulfonylmethanol, ethyl vinyl ether, and a catalytic amount of p-toluenesulfonic acid in methylene chloride at 0°C for three hours. It was worked-up in a similar way and purified by alumina chromatography to give 52% yield of desired product.

Reaction of Higher Aldehydes with Aryl Sulfinic Acids

As stated in the proposal, one of the main avenues that was worthy of investigating in this project was the conversion of aldehydes to ketones using this method of protecting the aldehyde with both a sulfone group and ether moiety, then alkylation, and next deprotection to produce the desired ketone. It was thought that it would be best if the aldehyde could be reacted directly with the sulfinic acid without the need to go through an activated form of the aldehyde such as an acetal or substituted chloro methyl ether.

H. Bredereck and E. Bader (203) reported a procedure for reacting sulfinic acids with aldehydes. The sulfinic acid and the aldehyde were refluxed in ether, cooled, and a crystalline product was obtained (which was rather unstable). This reaction is shown in equation 40.

We followed this procedure using heptanal as the aldehyde. After some of the ether was evaporated, the solution was put in the freezer. Instead of precipitation of the product, as expected, the whole thing froze, most likely due to low melting point of heptanal (melting point = 8°C). After some modification of the procedure, we obtained a product with a melting point of 58-60.5°C. Bredereck and Bader (203) reported a melting point of 58-68°C. The NMR of our material seemed to indicate the addition product plus unreacted aldehyde. This procedure was repeated without isolation of the addition product and the procedure for making THP ether was followed (DHP, PPTS, CH_2Cl_2, 4 hours, room temperature). Products were obtained through crystallization and then flash chromatography. TLC showed multiple spots and the integration did not match up.

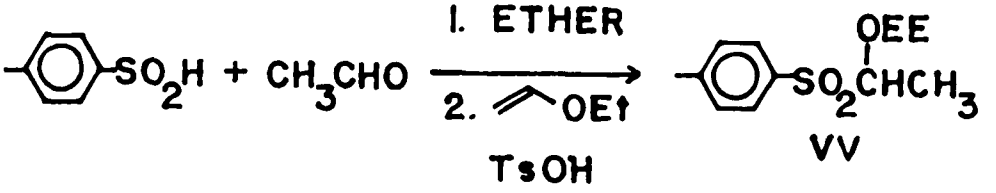
Although we had run a few reactions of this type, at the time we were concentrating on the reactions of the formaldehyde acyl anion equivalent. It was during this time that the paper was published which reported similar work

(178). Our work was stopped due to the publication of this paper.

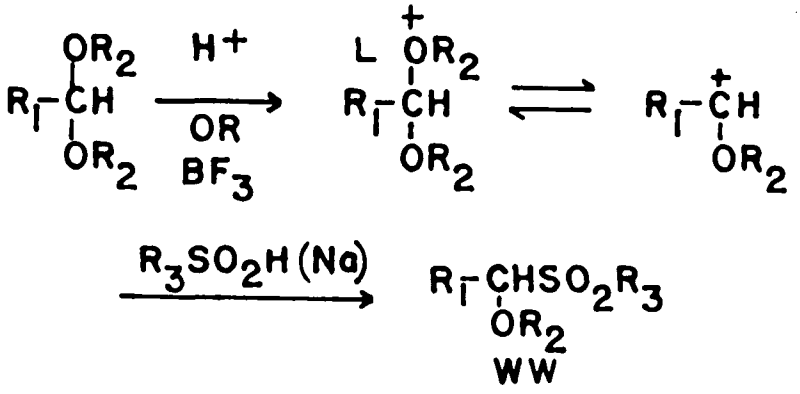
In this paper, the Japanese authors (178) reported only the reaction of benzenesulfinic acid with acetaldehyde. They did this by refluxing an etheral solution of benzenesulfinic acid with excess aldehyde and then adding to it ethyl vinyl ether in dichloromethane and a catalytic amount of p-toluenesulfonic acid. This resulted in a 60% yield of expected compound as shown in equation 51. Compound VV was alkylated in yields of approximately 50%.

As background for this type of reaction, Schank and Schmitt (191) reported the reaction of acetals with benzenesulfinic acid to produce alkoxy sulfones as shown in scheme 38. Presumably they had to go through the acetal in making compound WW due to no product formation or low yields.

Bredereck and Bader (203) reported synthesis of a alpha-hydroxy sulfones by refluxing the arylsulfinic acid and the aldehyde in an ethereal solution as shown in equation 52. Some of the ether was distilled, and, upon



Equation 51



Scheme 38

cooling in an ice bath, the product crystallized out. The product was recrystallized from ether. Yields were not reported.

Although we had planned to investigate this reaction more thoroughly, we did only preliminary work in this area due to the publication of similar work.

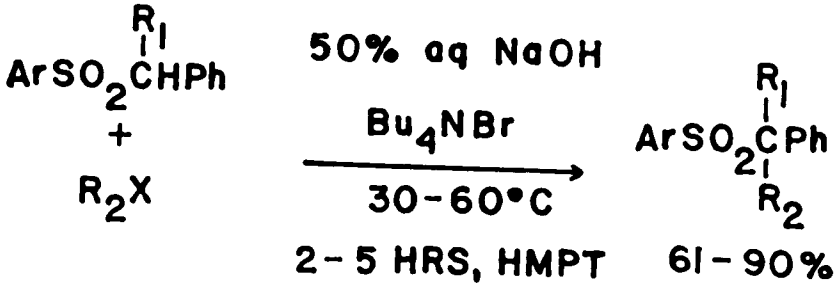
Alkylation of Tosylmethyl THP Ether

One of the most crucial steps in this sequence is the alkylation of the acyl anion equivalents, which in this case is the formyl acyl anion equivalent.

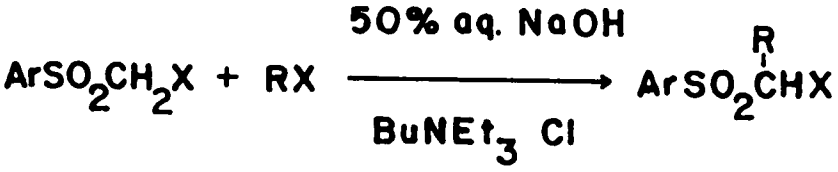
Equation 52

A method was used recently was alkylation of aryl benzylsulfones (208) or halomethyl arylsulfones (209) using phase transfer catalysis as shown in equation 53 - 55.

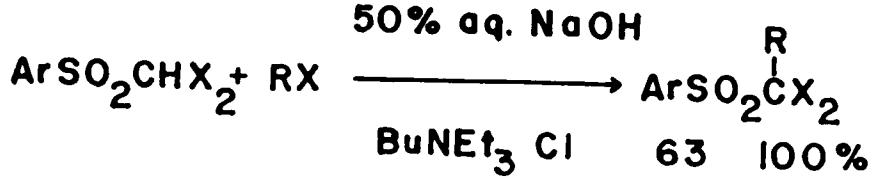
In both cases, the resulting carbanions were stabilized not only by the electron withdrawing sulfone group, but also by a phenyl group or by halogen substituents. Although references in the literature were not promising, for alkylation of alkyl arylsulfones, we did perform two



Equation 53



Equation 54



Equation 55

reactions of this type. The first (209) used triethylbenzylammonium chloride as the catalyst, benzene as the solvent, 50% sodium hydroxide, and a limiting amount of benzyl chloride as alkylating agent. This mixture was stirred by a vibro mixer for 3 hours at 65°C. After hydrolysis, work-up and distillation, 54% of benzyl bromide was recovered plus only a trace of phenyl acetaldehyde, as determined by NMR. The remainder of benzyl bromide probably reacted with the sodium hydroxide to form benzyl alcohol which was lost in the aqueous work-up.

The second phase transfer attempt was done with the same amounts of reagents as before but without the solvent, benzene. However, it was stirred for 6 hours at 60°C. After hydrolysis, work-up and distillation, 17% of benzyl bromide was obtained plus a trace amount of phenyl acetaldehyde. As before, probably the rest of the benzyl bromide was lost as benzyl alcohol. Thus, using phase transfer catalysis as the base to alkylate the tosylmethyl THP ether did not prove to be a satisfactory method to alkylate our sulfone.

Schank accessed the utility of various bases for metallating arylsulfonyl methyl methyl ethers (189) (see above) using the following bases: potassium t-butoxide, butyl lithium, sodium hydride and ethyl magnesium bromide. Deuterium oxide was added to the anions produced. The

product was extracted into chloroform, dried with $MgSO_4$, concentrated, and crystallized by adding methanol to the resulting oil. The amount of deuterium substitution was estimated by comparison of the integration of the methylene proton(s) versus the integration of the methoxy protons. Thus the percentages that were reported are not absolute percentages, but relative percentages. He obtained 100% deuteration by generating the anion using potassium t-butoxide under dry N_2 at 25°C for one hour and by using 1 equivalent of BuLi at -70°C for three hours. The best results reported using sodium hydride were 40% deuteration at 25°C after 1 hour. Using ethyl magnesium bromide, an average of 57% was obtained at room temperature for 1 hour followed by warming it to 40°C. From these results, butyl lithium and potassium t-butoxide appeared to be the most promising bases.

Anions so generated were alkylated with methyl iodide, dimethyl sulfate and ethyl bromide. Alkylation of tosylmethyl methyl ether using MeI gave a 42% yield when BuLi was the base and 29% with KOtBu. Thus the absolute yields of alkylated product were higher when the base was BuLi as opposed to KOtBu.

This was a concern to our project, because even though the electrophiles Schank (189) used were the smallest available, he only achieved absolute yields using BuLi of

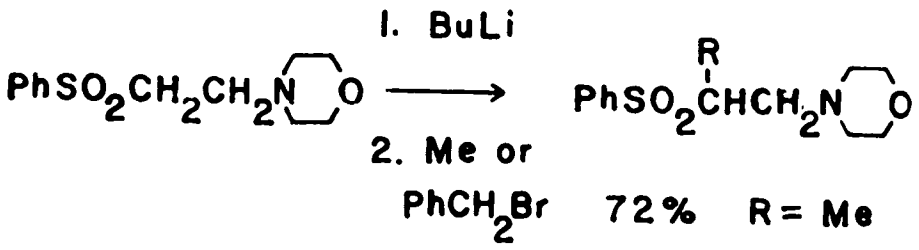
approximately 38%. If this were the maximum yield obtainable on our acyl anion equivalent, it would severely limit its usefulness because the maximum overall yield can not be higher than the lowest yield step. Furthermore, our arylsulfonylmethyl alkyl ether was even more hindered than Schank's.

General Procedure

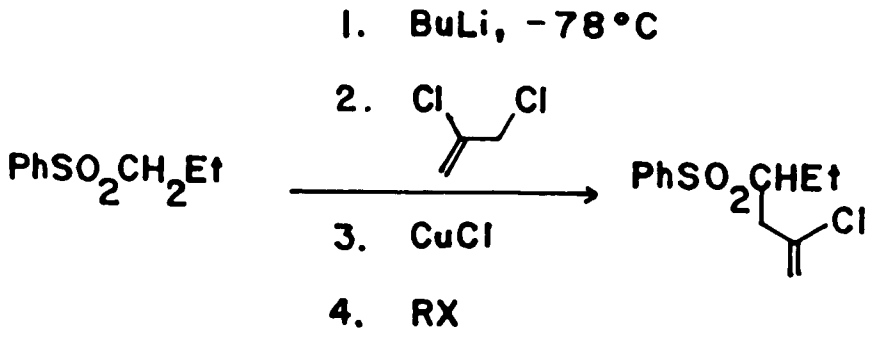
Upon searching the literature, two closely related systems were found. They are presented in equations 56 (210) and 57 (211).

The procedure we used to alkylate tosylmethyl THP ether was a modification of that found in equation 57. The sulfone compound was dissolved in THF and cooled to -78°C. The temperature was allowed to slowly rise to -20°C and then cooled back down to -78°C. A solution of the alkylating agent in THF was added and the temperature was allowed to slowly come to room temperature. When benzyl bromide was used as the alkylating agent, a 60% isolated yield of benzylated product was obtained as shown in equation 58.

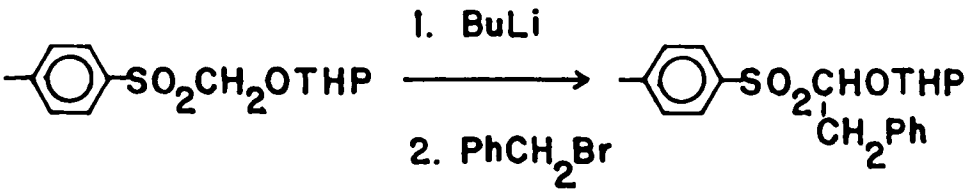
Yields obtained from the overall process of alkylation and hydrolysis indicate that these yields are actually higher. Losses were probably due to problems in isolation.



Equation 56



Equation 57



Equation 58

Initially, it was thought that hexamethylphosphoric amide (HMPA) would help improve (212) our yields, so reactions were routinely run with it. It was found that the more HMPA that was used, the lower the yields. For example, in the benzylation reaction with no HMPA, the overall yield was 83%. With 0.8 molar equivalents, 45% was obtained. With

4.0 molar equivalents, only 1.4% of the expected product was obtained. Possibly the low yields were due to dissolved water in the HMPA which had not been removed by distillation

The Japanese workers (178) performed their alkylation step in a slightly different way. They made a solution of 1 equivalent of LDA and 1 equivalent of HMPA in THF and cooled it to -78°C under N_2. To this, they added their formyl anion equivalent, benzenesulfonylmethyl ethoxyethyl ether, which was dissolved in THF, dropwise and stirred the resulting solution for 1 hour. To this, they then added the alkylating agent in THF dropwise and stirred it at -78°C for 2 hours and at room temperature for 16 hours. Next they proceeded directly to the hydrolysis step.

The BuLi was titrated using the procedure of Watson and Eastham (213, 214) nBuLi forms a red colored complex with 1,10-phenanthroline. This solution was titrated by a solution of sec-butanol in xylene. The end point was that volume necessary to decompose the nBuLi-1,10--phenanthroline complex as indicated by a decoloration of the solution.

Hydrolysis of THP Ether and Generation of the Aldehyde

THP ethers are easily hydrolyzed by dilute acid to regenerate the alcohol functional group. THP ethers can be cleaved (215) by treatment with 0.01N HCl at 22°C for 67

minutes or by treatment of 0.10N HCl at 22°C for 4 minutes. Procedures for the removal of the THP group in recent natural product syntheses (216) include hydrolysis using aqueous hydrochloric acid, and p-toluenesulfonic acid in methanol or aqueous acetic acid in THF.

In our original scheme, it was thought that after alkylation, the solution could just be acidified and worked-up to yield the product. This is basically what was done later in the steam distillation hydrolysis procedure.

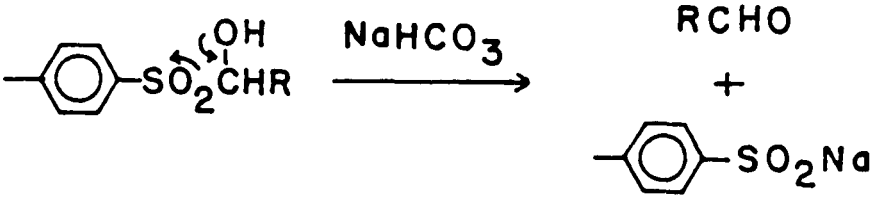
Initially small amounts of the isolated benzylated tosylmethyl THP ether were hydrolyzed. It was later decided that after alkylation, the resulting solution should be worked-up (extracted with ether several times, washed with brine, dried, rotary evaporated) without purifying the crude alkylated product. Next the whole crude batch would be hyrolyzed. It was thought that working with larger amounts would give more accurate results as to the yield and purity of the product.

E.J. Corey (217) hydrolyzed a THP ether by heating it with a solution of HOAc: water: THF (3:1:1) at 45°C for 3 hours. This procedure, when applied to our THP ether did remove the THP group, as observed in the NMR of the product after work-up. This was the method of hydrolysis used most frequently because it seemed to work well (Method A).

After hydrolysis, the product was extracted with ether. To remove traces of acetic acid and to decompose the hydroxy methyl sulfone as shown in equation 59, the ether solution was washed repeatedly with saturated aqueous sodium bicarbonate until the aqueous layers remained slightly basic. The ether layer was further washed with brine, dried over $MgSO_4$, concentrated and the residue was distilled under vacuum to give the product of rather high purity.

The Japanese workers (178) used a similar hydrolysis step. After their alkylation step, the reaction mixture was quenched with methanol and then treated with a large quantity of 2M HCl. After extraction with several portions of ether, the combined ether layers were treated with an aqueous solution of sodium bicarbonate for 4 hours and then dried. Solvent was removed and the product was purified by vacuum distillation.

Thus both their strategy and ours were basically the same although accomplished in different ways. Both hydrolyzed the acid-labile protecting group followed by base treatment to release the resulting carbonyl compound.



Equation 59

Another method of hydrolysis and isolation (Method E) was addition of the alkylation reaction mixture to a rather large quantity of water, acidification with concentrated HCl to pH=2, and then steam distillation. This distillate mainly consisted of product, THF, and water. The resulting product by this method was of comparable purity to the product obtained by hydrolysis via Corey's method, work-up and distillation. For even greater purity, the product can be redistilled.

Originally tosylmethyl THP ether was used as the limiting reagent with an excess (1.3 equivalents) of benzyl bromide and (1.1 equivalents) of nBuLi. The resulting product, phenyl acetaldehyde, was contaminated with benzyl bromide, a considerable problem, as their boiling points are very close together: BP ($PhCH_2CHO$) = 195°C and BP ($PhCH_2Br$) = 201°C. It turns out that many halides and their respective formylated equivalents have very close boiling points so a general method was necessary for separating the unreacted starting material from the product. Several procedures for removing the benzyl bromide were tried.

Since the alkylated tosylmethyl THP ether has a much higher boiling point than the benzyl bromide, it was thought that before hydrolysis, the benzyl bromide could be distilled off under high vacuum.

Note that in the data for the next few trials to be discussed, all runs contained 1.0 equivalent of HMPA.

The crude benzyl tosyl THP ether was put under vacuum (0.15 mm Hg) to hopefully remove excess benzyl bromide and then cooled to room temperature. Two drops of H_2SO_4 were added and the resulting product was then vacuum distilled (Method B). It was thought that slight contact of H_2SO_4 would release the aldehyde from its alpha-alkoxy sulfone form, enabling it to distill when heated under high vacuum. By this method, low yield (19% of phenyl acetaldehyde contaminated with benzyl bromide) plus extensive charring was observed.

It was thought that a milder acid might serve better and after the crude benzylated product was heated in an oil bath to 80°C under 0.15 mm Hg. This was then cooled down to room temperature and decomposed with 1 drop of concentrated H_3PO_4 (Method C). Distillation gave a low yield of 36% (with some contamination by benzyl bromide) and there was charring.

The final attempt along these lines of reasoning was to use a weaker acid still such as benzoic acid (0.1 equivalent). The yield of phenyl acetaldehyde was only 36% (benzyl bromide was not present in large quantities). The benzoic acid sublimed into the head of the distillation set-up, but it just remained there. It did not contaminate the distillate (Method D).

Since benzyl bromide is soluble in hexane and the more polar benzylated tosyl ether is not, it should have been possible to wash away the excess benzyl bromide with hexane. The yield of phenyl acetaldehyde obtained after washing the crude alkylation product with hexane, hydrolysis (Method A), and then distillation was only 24%. The product was still contaminated with benzyl bromide as (not including the amount of benzyl bromide which was equimolar to phenyl acetaldehyde).

Since attempts to remove the excess benzyl bromide from the crude benzylated product gave unsatisfactory results, it was decided to switch the limiting reagent from the tosylmethyl THP ether to the alkylating agent itself. In this way, hopefully, all the alkylating agent would be consumed and there would not be the need to devise another step to remove it.

We had been performing the alkylation step in the presence of HMPA, but since we later discovered that it reduced the yields of the aldehyde, we stopped using it. The following reactions were run in the absence of HMPA.

Another variation was the addition of 1.4 equivalent of TMEDA to the alkylation reaction mixture. The yield obtained with this modification was 42%.

A still other variation was to add the BuLi to the reaction mixture and let it warm up to 2^{o}C slowly. It

was kept at 2°C for 2 1/2 hours. Then the rest of the scheme was followed as before. The idea behind this was that possibly, in the regular scheme, not enough time was allowed for the BuLi to deprotonate the tosylmethyl THP ether to form the anion. The yield was 31% of phenyl acetaldehyde (it was contaminated with benzyl bromide).

Final Results

The overall yields for the regular reaction (work-up, hydrolysis at 45°C, 4 hours using HOAc: H_2O: THF (3:1:1) and reduced pressure distillation) are presented in Table 11.

A successful modification (no HMPA, benzyl bromide as the limiting reagent) was the use of acidification followed by steam distillation (Method E). It was thought that heating such aldehydes to their distillation temperatures (even though under reduced pressure) may cause the aldehydes to undergo acid-catalyzed aldol condensation, especially in the presence of a trace of acid. Using the technique of steam distillation, the aldehydes would be diluted and thus less likely to undergo aldol condensations. After alkylation, the reaction mixture was poured into 500 mL of water. This mixture was acidified to about pH 2, and then steam distilled. These results are also shown in Table 9 and 10.

When benzyl bromide was the alkylating agent, the amount of product obtained from the steam distillate 102% (of rather high purity as determined by NMR). This was then vacuum distilled to obtain a final yield of 79%. From the regular reaction, the overall yield was 83%. Possibly in both cases, there were rather significant lossed in yield in the final distillation.

Steam distillation also proved to be benefical in the reaction in which the alkylating agent was cinnamyl bromide. The yield after distillation obtained was 50%. An interesting observation was that after the steam distillate was acidified, if it were neutralized with saturated sodium bicarbonate to pH 7, the yield was only 33%!

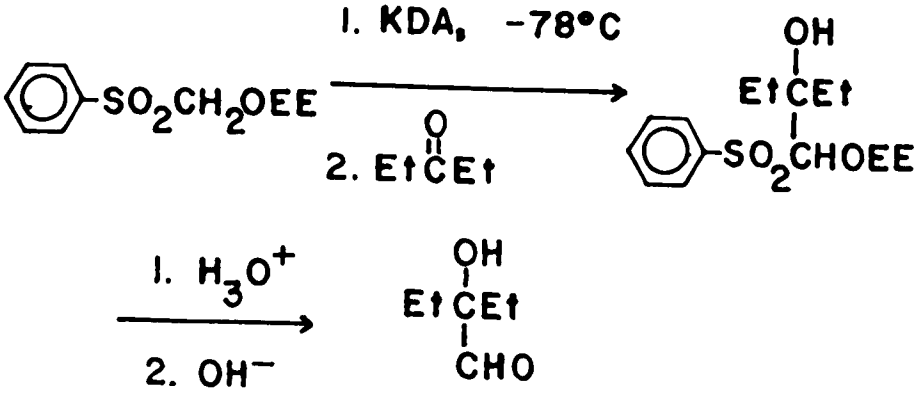
Tables 10 and 11 show the results obtained using other alkyl halides. Allyl bromide was also used as an alkylating agent. The expected product was 3-butenal which has a boiling point of 100° C, which is fairly close to the boiling point of THF (67°C). We tried an 8 inch spinning band column to distill the ethers, but at temperatures necessary for such a distillation, the aldehyde may have undergone further reactions (such as isomerization or polymerization), and no product was obtained.

In addition to work similiar to ours, the Japanese workers (178) reported one reaction in which the electrophile was a ketone. They treated phenylsulfonylmethyl

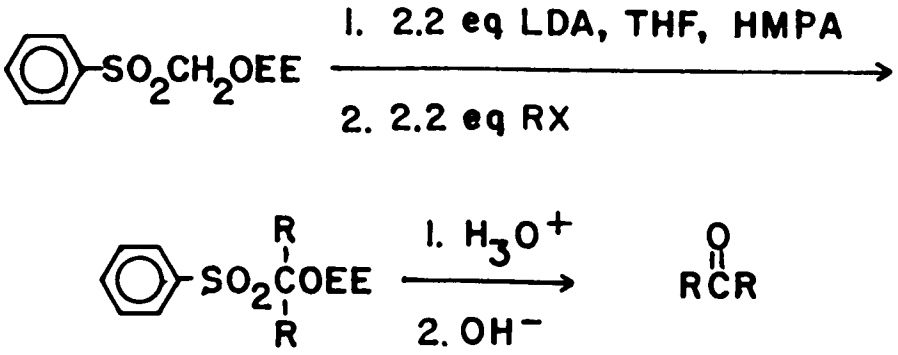
EE ether with 1.2 equivalents of potassium diisopropyl amide in THF at -78°C. They mentioned that lithium diisopropyl amide could not be used successfully in this reaction. To the metalated product, 4-heptanone was added. After acidic hydrolysis and base treatment, the expected product was obtained in 63% yield as shown in equation 60.

Their formyl anion equivalent was also dialkylated as shown in equation 61. This synthesis of symmetrical ketones produced the expected products in 52 - 72% yield.

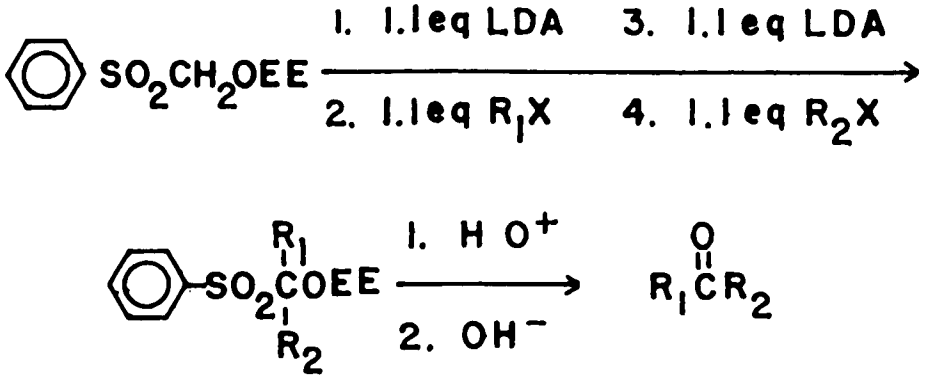
Synthesis of an unsymmetrical ketone as shown in equation 62 was not as successful. Results were reported for only one attempt at this kind of reaction. For R_1=Hex-Br and R_2=EtBr, the products obtained were 14% of the expected product, ethyl hexyl ketone, and 37% and 14% of the symmetrical products, dihexyl ketone and diethyl ketone, respectively. Thus, this reagent does not appear to be useful for synthesizing unsymmetrical ketones.



Equation 60



Equation 61



Equation 62

The Reaction of Tosylmethanol with Trimethylsilyl Chloride and Hexamethyldisilazane

The original protecting group we intended to use for the hydroxyl group (formerly the oxygen of the aldehyde) was the trimethylsilyl group. When we realized that the one step method (using trimethylsilyl toluenesulfinate) was not

working, we decided to use a two step method in which the aldehyde would be reacted with toluenesulfinic acid to produce the alpha-hydroxy sulfone. We planned to again use the trimethylsilyl group as a protecting group for the alcohol moiety because it was known to be easy to put on and easy to remove. Since we had made tosylmethanol from the smallest aldehyde, formaldehyde, we decided to try to trimethylsilate it.

One of the most common (218) ways to protect an alcohol with the trimethylsilyl group is by heating a mixture of the alcohol, pyridine, trimethylsilyl chloride and ether at 60°C for 2 hours. The published procedure reported that the alcohol should be completely consumed . Because we suspected that our alcohol was base sensitive, we tried heating it in a solution of pyridine and ether (in the same proportions as in the procedure), but without the trimethylsilyl chloride. During this time a solid sublimed into the reflux condenser. This solid was, presumably, paraformaldehyde. The solution was washed with water, dried with $MgSO_4$, and rotary evaporated to give a solid which indicated a 77% recovery. The NMR integration showed a greater amount of aromatic protons compared to methylene protons. This indicated that the alcohol was losing formaldehyde to give a mixture of alcohol and toluenesulfinic acid. The procedure (using the

trimethylsilyl chloride) was tried and the product appeared to be a mixture of the alcohol and toluenesulfinic acid. Thus the alcohol appeared to be base sensitive and methods avoiding highly basic conditions were sought.

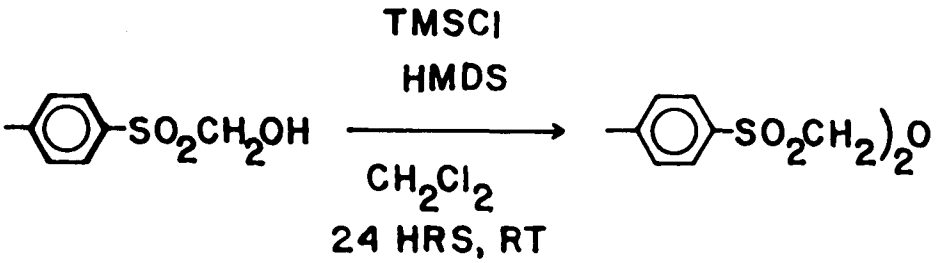
We decided to try a mixture of trimethylsilyl chloride (TMSCl) and hexamethyldisilazane (HMDS) (219). We chose this because mixtures of TMSCl and HMDS, in general, give better yields than either silylating agent alone. According to A.E. Pierce (219), the solvent of choice depends on the solubility of the substance to be silylated: usually THF or chloroform for steroids and pyridine for carbohydrates. We chose methylene chloride which was previously distilled from P_2O_5.

The alcohol, TMSCl, HMDS, and methylene chloride were stirred for 24 hours at 48°C. This solution was then washed with saturated aqueous $NaHCO_3$, brine, next dried with $MgSO_4$ and rotary evaporated to give a substance which looked like melted (vanilla) icing. This was then dissolved in EtOAc and cooled overnight in the freezer to give powdery, white crystals (EN-G-31-3)(23% yield, mp 118-119°C). These crystals had an NMR which only showed protons corresponding to the C-H protons of the original alcohol but no hydroxyl proton peak. The integration showed these to be exactly in the same proportion as in the alcohol. The IR showed a peak at 1320 and 1140 cm^{-1}

which correspond to sulfone peaks. A strong peak at 1080 cm^{-1} was present which may be due to the presence of an ether functional group. TLC showed one spot plus a small origin spot with various solvents. The reaction which we envisioned to be taking place is shown in equation 63.

The reason for this speculation was that the integration from the NMR spectrum (which was very clean) showed this expected ratio exactly. The IR seemed to confirm it and TLC seemed to indicate one compound (or if more, they were not separated on TLC using various solvents). This compound was recrystallized twice in the same manner to give a compound (EN-G-36-5) (mp 136.5-139) in 57% recovery with same NMR, IR, and TLC characteristics.

Other results were not as confirmatory. The analysis of EN-G-31-3 and EN-G-36-5 were almost identical to each other. The hydrogen and sulfur results were acceptable, but carbon was off by approximately 1.15%. (Analysis observed: EN-G-31-3 - 55.40%C, 5.36%H, 18.45%S, EN-G-36-5 - 55.33%C, 5.25%H, 18.34%S. Calc.: 54.22%C, 5.12%H, 18.09%S).

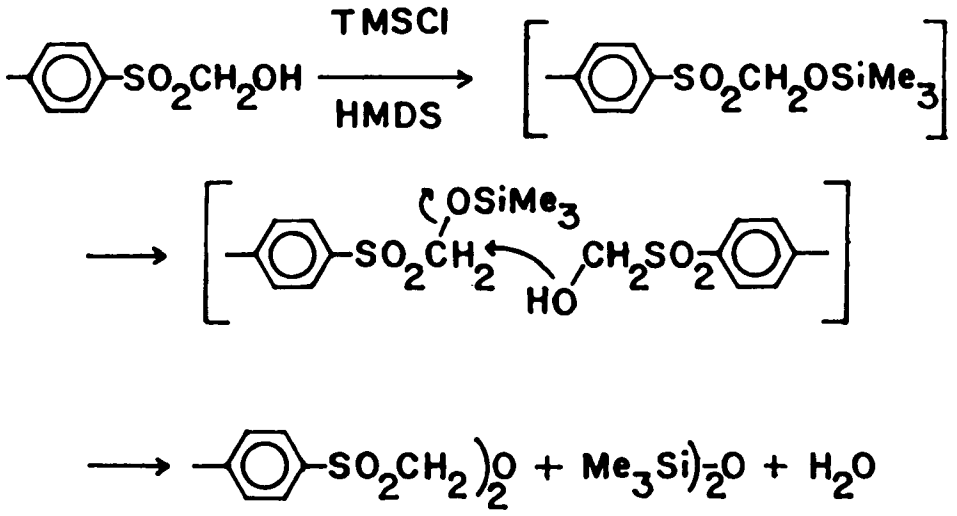


Equation 63

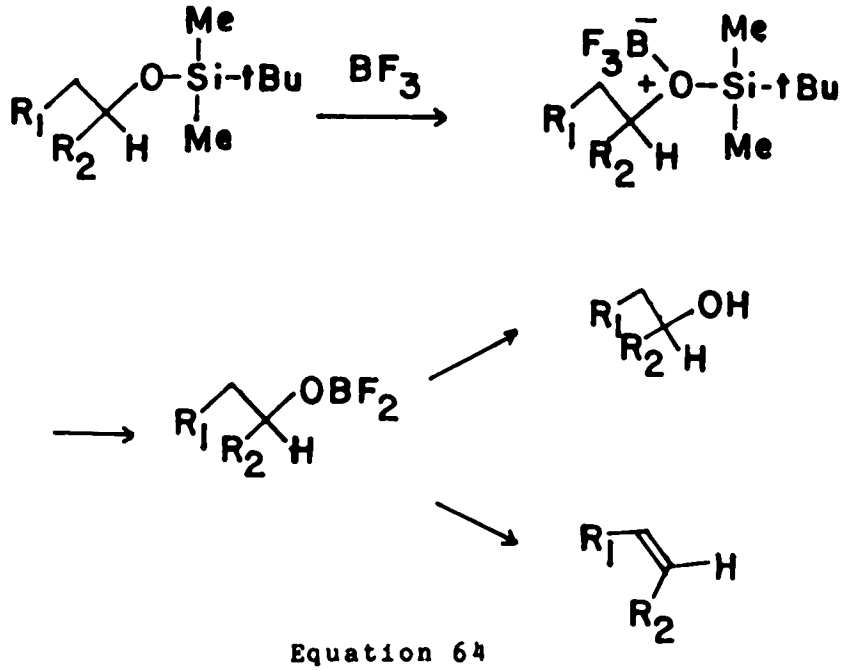
The mass spectra for EN-G-31-3 and EN-G-36-5 was nearly identical. They showed peaks at 139, 157, 198, 279, 366, 382, and 416 (relative intensities were approximately 3: 10: 7: 9; 1: 1: 1, respectively). From these results, we assumed the molecular weight was 416 whereas the ether has a molecular weight of 354. This difference of 62 could be made up of CH_2SO (not acceptable because no additional methylene protons were found by NMR) or NSO (not acceptable because no reasonable mechanism has been found). Note that addition of either of these fragments to the formula for the bis-(tosylmethyl) ether we propose does not give a formula which corresponds to the analytical results (eg. $C_{16}H_{18}SO_5$ + NSO gives (calc.) 46.2%C, etc.). We have tried to propose other structures but that of the bis ether seems to be the one that fits the data more closely than the others. The mechanism which we have postulated is shown in scheme 39.

The reaction (220) shown in equation 64 is an example of a trialkylsiloxy group (upon treatment with BF_3-Et_2O) leaving to form the alkene. The specific example which the authors showed was that of a silyl protected allylic alcohol eliminating to form the alkene.

Another example of trimethylsilanol as a leaving group is from the work of Olah (221,222) in which he treated alcohols with trimethylsilyl chloride and lithium bromide



Scheme 39



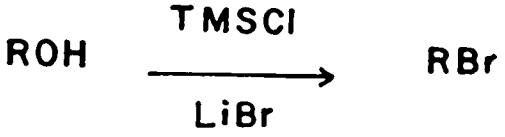
Equation 64

(221) or sodium iodide (222). Although the mechanism was not

discussed in these papers, it is probably that shown in equation 65. In this example, the trimethylsiloxy group is displaced by the nucleophilic halide ion.

The drawbacks to this mechanism are that groups alpha to a sulfone group are not generally easily displaced due to the electron withdrawing nature and steric effect of the sulfone group. In addition, a thorough search of the literature was made and, as far as we found, no other reactions of this type have been reported.

In conclusion, while attempting to silylate the tosylmethanol, we obtained a compound without trimethylsilyl protons which after addition recrystallization gave the same analytical results despite a change in melting point. postulated the structure of this compound to be bis-(tosylmethyl) ether. The drawbacks to this proposed structure are the analysis, which was off by >1% for carbon, and the mass spectra which indicated a molecular weight of 62 g/mole greater than for our structure. The mechanism we proposed, althought it has no precedent in the literature, does appear to be reasonable.



Equation 65

6. Conclusion of alpha-Alkoxy Sulfone Work

Table 12 shows a comparison of some of the sulfur reagents (160,164) available for this type of transformation. "Synthesized" prices were obtained from equimolar amounts of reagents assuming 100% yields. Prices (160) do not take into account solvents, catalysts, etc.. As seen in Table 12, both dithiane and ethyl ethylthiomethyl sulfoxide cost about the same when "synthesized". They both have the drawback that they are synthesized from mercaptans. The cyclic alkoxy sulfone is made from inexpensive reagents. It has the drawback that it is made from a four step procedure. It is synthesized by way of a route that produces mercaptans and uses LAH.

Section D. Experimental

Melting points were determined using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Proton spectra were recorded at 60 MHz on a Varian EM360 instrument with TMS as an internal standard. Chemical shifts were recorded in parts per million downfield from TMS with the multiplicity (s=singlet, d=doublet, dd=doublet of doublets, t=triplet, m=multiplet, br= broad). Infrared spectra were recorded on Perkin Elmer IR 598 instrument, unless otherwise indicated. Absorptions are reported in reciprocal centimeters with intensity in parentheses (s=strong, m=moderate, w=weak).

Silica gel thin layer chromatography was performed using Polygram pre-coated silica gel plates (0.2 MN silica gel N-HR, distributed by Brinkmann Instruments, Inc.) Visualization was performed by placement in an iodine chamber. Dimethyl sulfoxide (referred to as dry DMSO) was dried by distillation from calcium hydride at reduced pressure and stored over 4A molecular sieves (which had been dried by heating several hours at 300°C). DMSO specified as wet was commercial grade which was reported to contain 99+% DMSO. Methylene chloride was distilled from phosphorous pentoxide and stored over 4A molecular sieves. Cyclohexene was purified by a simple distillation. Dimethyl

formamide was purified by azeotropic distillation from benzene, followed by shaking with barium oxide, distilling under reduced pressure, and storing over 4A molecular sieves.

Microanalysis was performed by Schwarzkopf (Woodside, N.Y.) or by Galbraith (Knoxville, Tenn.) Laboratories.

Gas chromatography was performed on a Perkin Elmer 900 with a DC 710 W 9' x 1/4" column.

Flash chromatgraphy was performed using Silica Gel 60 (particle size 0.040-0.063, EM Reagents).

Experimental Work on the Reaction of Alkenes with NBS and Dry DMSO

1. Synthesis of 2-Bromo cyclohexanone by known routes.

Method A: PCC oxidation of 2 bromocyclohexanol (141). To a 100 mL RBF was added PCC (6.46 g, 0.03 moles), 40 mL methylene chloride (previously distilled from P_2O_5) and EN-A-48-1 (3.58 g, this consisted of 74% BrOH, 5% BrC=O, and 21% Br_2 relative yields as determined by GC) and stirred for 5 1/2 hours at room temperature. Progress of the reaction was followed by GC. When it appeared that the amount of BrC=O was not increasing, additional PCC (2.15 g, 0.01 moles) was added and the mixture was stirred an

additional hour. Ether (40 mL) was added and the solution was decanted from the resulting solid. The solid was washed with more ether (3 x 10 mL). The combined ether layers were then rotary evaporated and distilled to give four fractions with relative yields as determined by GC of 7% BrOH, 77% BrC=O, and 17% Br_2 (34%). The bromo ketone was collected off the GC using a small bent glass tube immersed in an isopropanol/dry ice slurry. It was identical upon reinjection and coinjection.

BP (obs.): 31.8°C at 0.08 mm Hg

(lit.): 90°C at 14 mm Hg = 30°C at 0.08 mm Hg
(estimated from the nomagraph)

Method B: Cupric bromide (47) (11.17 g, 0.05 moles) and 25 mL ethyl acetate were brought to reflux on a hot plate. To this mixture, cyclohexanone (3.0 mL, 0.03 moles) in 25 mL of hot chloroform was added. The resulting mixture was refluxed with vigorous stirring for 1 1/4 hours, filtered, dried with $MgSO_4$, filtered, rotary evaporated and distilled under reduced pressure giving 1.87 g (35%) of EN-B-65-1. This was further purified by collection off GC.

BP (obs.): 37°C at 0.025 mm Hg.

(lit.): 90°C at 14 mm Hg = 20°C at 0.025 mm Hg

GC: Rt = 7 min. T inj. = 160

T col. = 150

Flow rate = 2.4 sec/10 mL

NMR (CCl_4, ppm): 2.0 and 2.9 (br m, 8H), 4.28 (br t, 1H) (identical by Method A, Method B and product collected off GC)

IR (CCl_4, cm^{-1}): 2940 (m), 1725 (s), 1450 (m), 1430 (m), 1310 (m), 1210 (m), 1190 (m), 1115 (m), 1055 (m), 970 (m), 920 (m), 835 (m).

2. Synthesis of 1,2 Dibromocyclohexane (142)

To a 3N 100 mL RBF equipped with pressure equalizing addition funnel and magnetic stirrer, cyclohexene (15.2 mL, 0.15 moles), 1.5 mL abs. ethanol, 14.5 mL CCl_4 (previously distilled) were added and cooled down to -15.5°C using a CCl_4/dry ice slurry. To this solution, bromine (21.4 g, 0.13 moles) was added slowly enough to keep the temperature of the solution below -10°C, which took 1 1/4 hours. Excess CCl_4 and cyclohexene were distilled away. This solution was then washed with 20 mL of 20% alc. KOH, water (6 x 100 mL), brine, dried with $MgSO_4$ and finally distilled at reduced

pressure to give 14.8 g (46%) of EN-A-36-(1-4). GC indicated 96% Br_2 plus 4% BrOH.

BP (obs.): 99°C at 11 mm Hg

(lit.): 101°C at 16 mm Hg = 97°C at 11 mm Hg.

GC: Rt = 10 min T inj. = 180

T col. = 160

T det. = 200

Flow rate = 1.9 sec./10mL = 316 mL/min.

NMR ($CDCl_3$, ppm): 2.0 (br m, 8H), 4.45 (m, 2H).

IR (CCl_4, cm^{-1}): 2960 (s), 2880 (s), 1440(s), 1330 (w), 1250 (w), 1175 (s), 990 (s), 895 (m), 850 (m), 710 (m), 690 (m), 640 (m).

3. Synthesis of 2 bromo-cyclohexanol by Dalton's Procedure (140)

Bromohydrin was synthesized according to the procedure given in section 4 in which the 70.9 mL of commercial DMSO and 1.35 mL of water were used to give absolute yields of 27% BrOH and 2% Br_2 (as determined by spike analysis, which will be explained later for EN-A-43-1). The

bromohydrin was collected off the GC using a small bent glass tube immersed in a slurry of isopropanol/dry ice. It was identical upon reinjection and coinjection. (In the first attempts we used to synthesize bromo ketones, the relative amounts of the products were 8% BrOH, 23% BrC=O, 69% Br_2. It was difficult to collect from the GC the small amount of bromohydrin because its percentage was so low. Because of this, the product that we did collect was contaminated with bromo ketone as can be seen by the peak in the carbonyl region of the IR. Initially, the only difference between our procedure and Dalton's was the amount of water in the reaction mixture.)

BP (obs.): 30°C at 0.025 mm Hg.

(lit.): 64°C at 4 mm Hg = 15°C at 0.025 mm Hg.

GC: Rt = 4.0 min T inj. = 170

T col. = 155

T det. = 202

Flow rate = 2.1 sec/10 mL. = 286 mL/min.

NMR ($CDCl_3$, ppm): 1.7 (br m, 8H), 2.65 (br s, 1H, dis. with D_2O), 3.7 (br m, 2H)

IR (CCl_4, cm^{-1}): 3630 (m), 2925 (s), 2830 (s), 1750 (m,

contamination from BrC=O), 1470 (s), 1380 (s), 1350 (s), 1230 (s), 1190 (s), 1125 (m), 1080 (s), 1040 (m), 960 (s), 830 (s), 690 (s)

4. Varying the Amount of DMSO in the Dalton Reaction on Cyclohexene (140)

Cyclohexene (3.0 mL, 0.030 moles), commercial DMSO (28.4 mL, 0.40 moles) and water (1.35 mL, 0.075 moles) were combined (in a flask that had previously been purged with nitrogen) and cooled to 19°C with the use of an ice water bath. N-bromosuccinimide (NBS) (10.68 g, 0.060 moles was added slowly with stirring (approximately 0.3 g every 10 seconds). This mixture was stirred for 15 minutes and then poured into 300 mL of water and extracted with ether (5 x 50 mL). The combined ether extracts were washed with 5% aqueous $NaHCO_3$ (3 x 100 mL), saturated aqueous NaCl (3 x 65 mL), then dried with $MgSO_4$, filtered, and rotary evaporated to give a yellowish liquid. This was distilled at reduced pressure to give 3.31 g of oily product which was analyzed by GC for relative yields (comparison of area under the peak) and for absolute yields (by comparison of an internal standard which was added after the product was distilled, in this case it was 1-bromo adamantane).

The reaction was repeated with varying amounts of DMSO. Results are summarized in Table 1.

GC: Rt BrOH = 3.7 min T inj. = 156
Rt Br_2 = 6.6 min T col. = 148
Rt spike= 12.7 min T det. = 243
Flow rate = 2.0 sec/10 mL
= 300 mL/min

5. Sample Calculation of Using Spike Analysis
EN-A-61-1

Aw=wt. of bromohydrin =0.0869 g
Cw=wt. of spike =0.0877
Aa=area of bromohydrin =1251
Ca=area of spike =1656

$$f = \frac{Aw}{Cw} \cdot \frac{Aa}{Ca} = \frac{0.0869}{0.0877} \cdot \frac{1251}{1656} = 1.32$$

Aw'=wt of sample EN-A-42-1 used= 0.1794 g
Cw'=wt of spike =0.0497 g
Aa'=area of bromohydrin =2941

Ca'=area of spike =1125

$$\frac{Aw'}{Aa'} \quad \frac{X}{2941}$$

$$f = \frac{Cw'}{Ca'} = \frac{.0497}{1125} = 1.32 \quad x = 0.1715 \text{ g}$$

$$\frac{\text{Wt of bromohydrin}}{\text{Wt of sample}} = \frac{\text{total wt of BrOH}}{\text{total wt of sample}}$$

$$\frac{0.1715}{0.1794} = \frac{x}{3.31} \qquad x = 3.16 \text{ g}$$

$$\% \text{ yield} = \frac{\text{wt. obs.}}{\text{wt. theo.}} \quad \frac{3.16}{6.37} \text{ g} = 49.6\%$$

6. Reactions shown in part 4, except under Anhydrous Conditions

These reactions were repeated as above, except that in each case the DMSO used had been distilled under reduced pressure from CaH_2, and no water was added. Results are summarized in Table 2.

7. Bromo Ketone Reaction with CH_2Cl_2, Run at 2°C Upon Which Other Variations were Tried

Cyclohexene (1.5 mL, 0.015 moles), methylene chloride (30 mL, 0.47 moles) and dry DMSO (75 mL, 0.52 moles) were combined under nitrogen, and cooled to 2°C using an ice water bath. NBS (5.34 g, 0.030 moles) was added. The temperature rose to 10°C and then dropped back down to 2°C. The mixture was stirred for 30 minutes. Next, NEt_3 (2.1 mL, 0.015 moles) was added. The mixture was stirred for an additional 15 minutes, and poured into 300 mL of water, and then extracted with ether (1 x 100 mL, then 3 x 50 mL). The combined ether extracts were washed with 10% aqueous $Na_2S_2O_3$ (4 x 22 mL), saturated aqueous $NaHCO_3$ (2 x 45 mL) and brine (2 x 45 mL), then dried over $MgSO_4$, filtered, rotary evaporated, and distilled (33°C at 0.08 mm Hg). Relative yields were determined by GC under same conditions as previously stated.

Variations tried and their results are shown in Table 3.

8. Bromo Ketone Reactions run in the Presence of Resins

A. Typical conversion of Cl^- resin into BF_4^- resin.

Actual preparation of B-40 resin.

Amberlite resin (IRA-400, 15.9 g) and DMSO (distilled from CaH_2, 50 mL) were combined and stirred under N_2 for 35 minutes at room temperature, then poured into 300 mL water and vacuum filtered through a coarse sintered glass funnel. The residue was transferred to a 3/4 inch diameter column which had a glass wool plug at the bottom and washed in series with:

1. distilled water 88 mL
2. 1M NaCl 175 mL
3. distilled water 175 mL
   (no ppt when tested with 1 M $AgNO_3$)
4. 1M $NaBF_4$ 262 mL
   (until only a faint ppt. appeared when the effluent was tested with 1M $AgNO_3$)
5. distilled water 175 mL
6. abs. EtOH 150 mL
7. anhyd. ether 110 mL

The washed resin was placed in drying pistol (40°C, approx. 0.10 mm Hg) and dried approximately 22 hours.

B. Preparation of other resins shown in Table 4.

C. Reaction run on resins.

Resins (prepared shown in Table 4), (10.64 g, 2000 eq, cyclohexene (1.5 mL, 0.015 moles, dry DMSO (75 mL, 1.1 moles) and methylene chloride (30 mL, 0.015 moles) were combined under N_2 and cooled to 2°C in an ice water bath. NBS (3.20 g, 0.018 moles) were added, and the mixture was stirred for 15 minutes. Then, NEt_3 (2.1 mL, 0.015 moles) was added and the mixture was stirred for an additional 15 minutes, then poured into 300 mL of water. The resin was filtered and washed with two 100 mL portions of ether. The aqueous filtrate was washed with an additional two 50 mL portions of ether and the combined organic layers were washed with two 44 mL portions of 10% aqueous $Na_2S_2O_3$, two 44 mL portions of saturated aqueous $NaHCO_3$, and two 44 mL portions of brine. The resulting organic layer was dried over $MgSO_4$, gravity filtered, rotary evaporated, and the residue was distilled, and analyzed by GC (same conditions as previously indicated.) Results are shown in Table 4 and 5.

9. Reactions using Pyridine Oxide (135), rather than than DMSO in attempting to Synthesize Bromo Ketones.

Presented here is EN-C-39-1, other reactions are variations of this, with changes as indicated in Table 6.

Pyridine oxide (commercial product which had been dried in a drying pistol for 25 hours at 40°C at 0.10 mm Hg, 5.7, 0.06 moles), EtOAc (100 mL), $AgNO_3$ (1.27 g, 0.0075 moles) and cyclohexene (1.5 mL, 0.015 moles) were combined and cooled to 2°C. NBS (3.2 g, 0.018 moles) was then added. (In this case a white precipitate formed.) After stirring for 30 minutes, the reaction mixture was poured into 300 mL water. (In this case it was filtered to remove AgBr). The organic material was extracted using one 100 mL and then two 50 mL portions of ether which were combined and washed with two 44 mL portions of 10% aqueous $Na_2S_2O_3$, followed by two 44 mL portions of 5% aqueous $NaHCO_3$, and finally two 44 mL portions of brine. The resulting ethereal solution was dried over $MgSO_4$, gravity filtered, and rotary evaporated. The residue was distilled and then analyzed by GC (conditions previously specified).

For other variations and results, see Table 6.

10. Synthesis of Diazabicyclo(2.2.2)octane Monoxide (223)

Diazabicyclo(2.2.2)octane (Dabco) (purchased from Aldrich, 11.2 g, 0.10 moles) was dissolved in 50 mL of benzene at room temperature. Hydrogen peroxide (11.3 g of 30% H_2O_2, 0.10 moles) was added from an addition funnel at a rate of approximately 1 drop/second. Foaming and fairly rapid boiling ensued. The mixture was kept at room temperature overnight. Platinum-on-carbon (0.11 g) was added. Celite (2.78 g) was then added and the mixture was suction filtered. The resulting filtrate was rotary evaporated with the water bath temperature increasing from room temperature to 90°C. The residue was placed on the vacuum pump and shortly thereafter it crystallized. It was kept on the vacuum pump at RT for 6 1/2 hours to remove any traces of water. The weight of dried product (EN-G-40-1) was 9.82 g (78%).

MP (obs.): 89°C

(lit.): 121-3°C

NMR ($CDCl_3$, ppm): 3.20 (s)

(pyridine, ppm): 3.15 (br d)

IR ($CHCl_3$, cm^{-1}): 3660-3000 (s), 2960-2840 (s), 1455 (s), 1320 (s), 1240 (m), 1065 (m), 1040 (s), 930 (s), 830 (m), 650 (s).

11. Synthesis of Quinuclidine Oxide (224)

To a solution of quinuclidine (9.8 g, 0.09 moles) dissolved in 11 mL of methanol was added CH_2Cl_2 (29.7 g, 0.26 moles) dropwise. After standing overnight, the mixture was determined to be no longer basic by testing a drop of reaction mixture in a small amount of phenolpthalein. Pt/C (caution: fire hazard) (0.0485 g) was added and allowed to stand 4 hours, after which the mixture no longer showed the presence of peroxides (as tested with an aqueous solution of potassium iodide.) After addition of celite (1.07 g), the mixture was filtered and heated from room temperature to 60°C on the rotary evaporator and then under vacuum (0.10 mm Hg, 95°C) to remove traces of water. Weight of the product (EN-G-39-1) was 11.2 g (approx. 100% yield).

MP (obs.): 70 - 72.5°C

(lit.): 110°

NMR ($CDCl_3$, ppm): 2.08 (br t, 7H) 3.45 (br t, 6H) 4.55 (s, H_2O - absorbed possibly during weighing)

IR ($CHCl_3$, cm^{-1}): 3650 (m), 3600-3040 (br, s), 2900 (br, s), 1630 (m), 1455 (s), 1345 (m), 1250 (m), 1060 (s), 930 (s), 910 (m), 820 (m), 645 (s).

12. Reactions using Different Amine Oxides and Different Solvents

Actual Reaction using Quinuclidine Oxide and DMF (EN-D-24-1)

Quinuclidine oxide (6.5 g, 0.58 moles), DMF (50 mL) and cyclohexene (1.5 mL, 0.015 mL) were combined and cooled to 2°C. NBS (5.27 g, 0.03 moles) was added and the resulting mixture was stirred for 18 minutes. Triethylamine (2.1 mL, 0.015 moles) was then added and the resulting mixture was stirred for an additional 15 minutes. This mixture was then poured into 300 mL of water and extracted with one 100 mL portion and two 50 mL portions of ether. The combined ethereal extracts were washed with two 75 mL portions of 10% aqueous $Na_2S_2O_3$ and two 50 mL portions of brine. The resulting mixture was dried with $MgSO_4$ and the ether was distilled away. The absolute yields were determined on GC using an added internal standard, as before.

13. Reactions and Results of Reactions using Other Amine Oxides are Shown in Table 7.

Experimental Work on the Use of Tosylmethyl THP Ether As an Acyl Anion Equivalent

1. Formation of Tosyl Hydroxy Methane

Hydrated sodium toluenesulfinate (4.3-H_2O) (98.055 g, 0.384 moles) was added to 46.9 g (0.58 moles) of formalin. Concentrated HCl (31.45 mL, 0.0384 moles) was added and the mixture was heated to 70°C, and then cooled to room temperature. A solid clump was formed which was dissolved in 700 mL of ether and was washed with 70 mL of water, dried with $MgSO_4$, filtered, and rotary evaporated to produce white crystals. This was then recrystallized from benzene to yield 59.8 g (88%) of tosylmethanol (EN-F-54-2).

MP (obs.)= 92.9 - 93.6°C

(lit.)= 90°C (202)

(lit.)= 95°C (203)

TLC: one spot using various solvents

Eluting Solvents	Rf
Ethanol	0.65
Acetone	0.03
EtOAc, $CHCl_3$, CH_2Cl_2	0.00

NMR ($CDCl_3$, ppm): 2.4 (s, 3H), 4.5 (s, 1H, disappears with D_2O), 4.6 (s, 2H), 7.45 (q, 4H)

IR ($CHCl_3$, cm^{-1}): 3400 (s), 3020 (m), 2900 (m), 1595 (s), 1490 (m), 1400 (m), 1300 (s) 1140 (s), 1080 (s), 1020 (m), 920 (s), 810 (s), 620 (m), 540 (s)

2. Formation of Tosylmethyl THP Ether (206)

Tosylmethanol (EN-F-54-2, 34.42 g, 0.185 moles), pyridinium toluenesulfonate (206) (5.0144 g, 0.020 moles), dihydropyran (distilled from sodium, 27.36 mL, 0.30 moles) and CH_2Cl_2 (distilled from P_2O_5, 950 mL) were combined and stirred for 4 hours at room temperature. This was then washed with half-saturated brine (2 x 100 mL) and saturated $NaHCO_3$ (2 x 125 mL). The aqueous layers were back washed with 50 mL CH_2Cl_2 and the combined organic layers were dried with K_2CO_3, filtered and

oil and the mixture was then placed in the freezer. If the resulting crystalline product was yellowish, it was necessary to remove the yellow impurity using flash chromatography (4/1: hexane/ethyl acetate). The yellow impurity stayed at the top of the column. The appropriate fractions (Rf = 0.3, 4/1: hexane/ethyl acetate) were concentrated, then washed with saturated $NaHCO_3$ (2 x 40 mL). The aqueous layers were back washed with ether (40 mL) and the organic layers were combined, dried with K_2CO_3, filtered and rotary evaporated. Hexane was then added to this oil, and it was placed in the freezer. The resulting crystalline material was vacuum filtered to yield 33.5 g (67%) of EN-F-67-6.

MP (obs.): 53.8 - 55.0°C

Analysis (obs.): C: 57.68% H: 6.68% S: 11.60%
(calc.): C: 57.76% H: 6.71% S: 11.86%

TLC: one spot solvent 3/1: Hex/EtOAc Rf = 0.53

NMR ($CDCl_3$, ppm): 1.66 (m, 6H), 2.5 (s,3H), 3.6 (m,2H), 4.7 (q, 2H), 5.0 (m, 1H), 7.63 (q, 4H)

IR ($CHCl_3$, cm^{-1}): 3020 (m),2945 (s), 2875 (m),

1600 (s), 1440 (m), 1310 (s), 1140 (s), 1070 (s), 1030 (s), 960 (s), 925 (s), 900 (s), 865 (s), 815 (s), 630 (m), 570 (m)

3. Benzylation of Tosylmethyl THP Ether (211)

Tosylmethyl THP ether (1.14 g, 0.0042 moles) was dissolved in 8 mL of freshly distilled (from LAH) THF under N_2. It was cooled to -65°C and nBuLi (3.0 mL of 1.55 M, 0.0046 moles) was added by a gas tight syringe. The mixture was then allowed to warm to -20°C in approximately 30 minutes and then cooled back down to -65°C. Benzyl bromide (0.79 g, 0.0046 moles) was added dropwise. The temperature was allowed to slowly rise to room temperature during a period of 5 hours. The reaction mixture was then neutralized by adding 20 mL of 0.1 N HCl. The product was extracted with ether (2 x 20 mL, 1 x 10 mL), washed with saturated $NaHCO_3$ (20 mL), dried with $MgSO_4$, filtered, and rotary evaporated. Hexane was added to the resulting oil, and white crystals were formed, 0.48 g of EN-E-64-2 (51%) . This produce was not routinely isolated, but alkylated products were directly hydrolyzed. Yield was not optimized here.

MP (obs.): 75 - 76°C

TLC: solvent 7/1 Hex/EtOAc Rf = .15 major
Rf = .31 minor
(phenyl acetaldehyde)

NMR ($CDCl_3$, ppm): 1.6 (m, 6H), 2.46 (s, 3H), 2.78 (br s, 2H), 3.43 (q, 2H), 4.94 (q, 1H), 5.18 (br s, 1H), 7.24 (s, 5H), 7.56 (q, 4H)

4. General Alkylation Procedure (211)

Tosylmethyl THP ether (which had been stored in the freezer) (5.54 g, 0.021 moles) was dissolved in 40 mL freshly distilled (from LAH) THF. It was cooled under N_2 to -67°C and nBuLi (13.6 mL of 1.55 M, 0.021 moles) was added by a gas tight syringe. The mixture was then allowed to warm to -20°C in approximately 30 minutes, and then cooled back down to -67°C. The alkylating agent (approximately 0.015 moles) was added in a 50% THF solution by gas tight syringe. The mixture was then cooled down to -67°C and the temperature was allowed to slowly rise to room temperature during a period of 5 hours.

Next the reaction mixture was poured into 25 mL of brine and extracted with ether (4 x 30 mL). The combined organic layers were washed with 25 mL of brine, dried with K_2CO_3, filtered, and rotary evaporated. The resulting crude concentrate was then hydrolyzed as detailed below. Variations and final results are shown in Tables 9, 10, and 11.

5. Hydrolysis of Alkylated Tosylmethyl THP Ether

Method A: Corey's (217) method. A mixture of 18 mL of acetic acid, 6 mL of THF and 6 mL of H_2O were added to the crude concentrate and stirred for 4 hours at approximately 45°C, then poured into 25 mL of brine and extracted with ether (4 x 30 mL). The combined organic layers were washed with brine (60 mL), saturated $NaHCO_3$ (4 x 50 mL), and again with brine (60 mL), then dried with $MgSO_4$ and rotary evaporated. The crude residue was distilled at pressure reduced sufficiently to give a boiling point of approximately 60°C. The resulting aldehyde was analyzed by TLC, NMR and in some cases by derivative formation.

Phenyl acetaldehyde: (EN-F-25-4)

BP (obs.): 57°C at 4 mm Hg

(lit.): 195°C at 760 mm Hg = 55°C at 4 mm Hg (225)

Derivative (semicarbazone): (226)

MP (obs.): 150.2-151°C

MP (lit.): 156°C (227)

TLC: Solvent 4/1: Hex/EtOAc Rf = 0.57 major
(phenyl acetaldehyde)
= 0.82 trace
= 0.42 trace

NMR ($CDCl_3$, ppm): 3.68 (d, 2H), 7.24 (m, 5H), 9.66 (t, 1H), 0.9 - 2.1 (small amount of impurities), 4.8 - 5.9 (small amount of impurities)

IR (CCl_4, cm^{-1}): 3010 (m), 2920 (m), 2860 (m), 2720 (w), 1740 (s), 1600 (w), 1595 (m), 1500 (m), 1410 (w), 1100 (m)

Method B, C, D, and E. Addition of Concentrated Acid to Crude Alkylated Tosylmethyl THP Ether.

(This method was tried when alkylating agent was in excess as part of an attempt to separate the excess

alkylating agent from the sulfone, then quickly decomposing it to the aldehyde.)

Method B: The crude benzylated sulfone was put under vacuum (0.15 mm Hg) for approximately 30 minutes. The vacuum was then released and two drops of concentrated H_2SO_4 were added and resulting mixture was then distilled under reduced pressure.

Method C: The crude benzylated sulfone was heated to 80°C under vacuum (0.15 mm Hg) over a period of approximately 30 minutes. It was cooled to room temperature and the vacuum was then released. Next, one drop of H_3PO_4 was added and the resulting mixture was distilled at reduced pressure.

Method D: The crude benzylated sulfone was heated to 96°C over a period of approximately 30 minutes under vacuum (0.12 mm Hg). Benzoic acid (0.10 eq.) was added in a methylene chloride solution and then the methylene chloride was removed by rotary evaporation. As the temperature increased (as was necessary for distillation), the benzylated sulfone decomposed to the aldehyde which then distilled over. A problem with this method is that the benzoic acid sublimed into the distillation head but it remained there, thereby, not contaminating the product.

Method E: The crude alkylated product was added to 500 mL water. The reaction vessel was then rinsed with 20 mL of

THF. Concentrated HCl (0.7 mL) was added until the pH was 2 as indicated by pH paper. This mixture was steam distilled until 250 mL of distillate (which contained a large amount of THF) separated into two layers upon standing. The aqueous layer was washed with ether (3 x 20 mL). The combined organic layers were washed with 30 mL brine, dried with $MgSO_4$, filtered, rotary evaporated, and the residue was distilled under reduced pressure.

Data on Other Aldehydes Made in this Manner:

Nonanal: (EN-F-94-3)

BP (obs.): 75°C at 8 mm Hg

(lit.): 93.5°C at 23 mm Hg = 73°C at 8 mm Hg

Derivative (semicarbazone): (226)

MP (obs.): 94.2 - 95.8°C

MP (obs. on commercial nonanal): 94.2 - 96.5°C

MP (lit.): 100°C

TLC: Solvent 3/1 $CHCl_3$/Hexane Rf = 0.68 major (nonanal)

= 0.08 trace

NMR ($CDCl_3$, ppm): 0.9 (t, 3H), 1.3 (m, 12H), 2.4 (m, 2H),
9.68 (t, 1H)

IR ($CHCl_3$, cm^{-1}): 2918 (s), 2720 (w), 1715 (s),
1455 (m), 1405 (m), 1370 (m), 1260 (s),
1100 (s), 1065 (s), 1030 (s), 810 (m)

4-Phenyl 3-butenal; (EN-F-86-3) (228)

BP (obs.): 65°C at 0.3 mm Hg.

(lit.): 131°C at 14 mm Hg = 67°C at 0.3 mm Hg

TLC: Solvent 4/1 Hexane/EtOAc Rf = 0.42 major
= 0.69 trace
= 0.17 trace

NMR ($CDCl_3$, ppm): 3.38 (dd, 2H), 6.4 (m, 2H),
7.35 (s, 5H), 9.78 (t, 1H),

IR (CCl_4, cm^{-1}): 3080 (m), 3060 (m), 3020 (s),
2940 (m), 2820 (s), 2720 (s), 1730 (s),
1495 (s), 1450 (s), 1395 (m), 1120 (m),
1070 (m), 1030 (m), 965 (s), 695 (s)

6. Reaction of Tosyl Hydroxy Methane with TMSCl and HMDS

Tosylmethanol (6.7 g, 0.036 moles), TMSCl (5.1 mL, 0.024 moles), HMDS (3.0 mL, 0.024 moles) and CH_2Cl_2 (60 mL, distilled from P_2O_5) were stirred at 48°C for 24 hours. This was then washed with brine (1 x 30 mL, 2 x 20 mL), then saturated, aqueous Na_2CO_3 (1 x 40 mL, 1 x 20 mL), brine (20 mL), dried with $MgSO_4$, filtered, rotary evaporated to give a gummy solid which looked like melted icing (6.37 g). This was then dissolved at room temperature in EtOAc (33 mL) and placed in the freezer overnight to give 1.47 g (23%) of nice, powdery, white crystals (EN-G-31-3). This was then dissolved in 21.9 mL EtOAc, in the same manner, to give 1.19 g of EN-G-35-1 (19% overall yield). EN-G-35-1 was again recrystallized using 94.5 mL to give 0.836 g of EN-G-36-5 (13.5% overall yield, after two recrysallizations).

MP (obs.): EN-G-31-3: 118-119°C
EN-G-36-5: 136.5-139°C (difference due to different crystal structure (?))

TLC: Various solvents: one spot plus trace origin spot.

Solvent	Rf
Hex/EtOAc	0.37
$CHCl_3$/Ether	0.50
CH_2Cl_2/MeOH (50/1)	0.90

Analysis (Galbraith Lab., Inc.):

EN-G-31-3 55.40% C, 5.36% H, 18.45% S

EN-G-36-5 55.33% C, 5.25% H, 18.34% S

Calc. 54.22% C, 5.12% H, 18.09% S

(for bis-(tosylmethyl) ether)

NMR ($CDCl_3$, ppm): 2.38 (s, 3H), 4.38 (s, 2H), 7.50 (q, 4H)

IR ($CHCl_3$, cm^{-1}): 3010 (m), 2920 (m), 1595 (s), 1490 (m), 1410 (m), 1300 (s), 1210 (s), 1140 (s), 1080 (s), 1020 (m), 920 (m), 750 (br, s) 660 (s).

Table 1. Dalton Reaction of Cyclohexene with Varying Amounts of DMSO. Amounts Not Specified: Cyclohexene (3.0 mL, 0.03 moles), Water (1.35 mL, 0.075 moles), NBS (10.68 g, 0.060 moles), Temperature <20C, Time 15 min.

		Relative Yields		
Number	DMSO	BrOH	BrC=O	Br2
EN-A-41-1	28 mL, 0.4 m	73	-	27
EN-A-43-1	71 mL, 1.0 m	69	-	31
EA-A-44-1	150 mL, 2.1 m	94	-	6
EN-A-44-2	213 mL, 3.0 m	93	trace	1

-

Table 2. Anhydrous Reaction of Cyclohexene with NBS and Varying Amounts of DMSO. Amounts Not Specified: Cyclohexene (3.0 mL, 0.030 moles), NBS (10.68 g, 0.060 moles), Temperature <20C, Time 15 min.

		Relative Yields		
Number	DMSO	BrOH	BrC=O	Br2
EN-A-70-1	28 mL, 0.4 m	15	27	58
EN-A-71-1	71 mL, 1.0 m	15	36	49
EN-A-71-2	150 mL, 2.1 m	24	35	42
EN-A-72-1	284 mL, 4.0 m	37	30	33

Table 3. Variations Made on the Reaction of Cyclohexene, NBS, and DMSO. Amounts of Reactants Not Specified: Cyclohexene (1.5 mL, 0.015 moles), DMSO (75 mL, 1.1 moles).

Number	CH_2Cl_2	NBS	Time	Temp.	NEt3	Additive	Relative Yields BrOH	BrC=O	Br_2
EN-A-74-1	30 mL	0.030 moles	30 min.	2C	none	none	33	19	48
EN-A-74-2	"	"	"	"	"	"	30	17	53
EN-A-76-1	none	"	"	<20C	"	hyd.quin.	32	29	39
EN-A-80-1	none	"(rec.)	"	"	"	none	33	28	39
EN-A-82-1	none	"	"	"	"	oven dry	31	22	46
EN-A-85-1	none	0.018	"	"	"	none	34	24	42
EN-A-88-1	30 mL	"(rec.)	"	2C	0.017 moles	none	9	51	40
EN-A-89-1	"	"	5	"	"	none	8	64	28
EN-B-8-1	"	"	15	"	"	1 eq pr.ox.	8	62	29
EN-B-9-5	"	"	"	"	"	3 eq "	6	64	30
EN-B-16-1	"	"(unrec.)	"	"	"	none	5	59	36
EN-C-91-2	"	0.030	"	"	0.045	none	7	48	45
EN-C-92-1	120 mL	"	2 1/4 hrs	18C	0.015	none	tr	61	39
EN-C-93-1	30 mL	"	15 min	2C	"	20g sieves	8	45	46

Table 4. Relative Yields Obtained Upon the Reaction of Cyclohexene, NBS, DMSO, CH2Cl2, followed by the Addition of NEt3 in the Presence of Resins.

Resin Number	Reaction Number	Description of Resin Preparation	Relative Yield BrOH	BrC=O	Br2
A-98	EN-B-11-1	CF3COONa	23	47	30
B-14	EN-B-18-1	Same as A-98 (made on a larger scale)	6	64	23
B-20	EN-B-24-1	Pre-used B-14 resin, NaCl, NaBF4	4	83	13
B-20	EN-B-26-1	Old Bottle resin, KPF6	3	60	36
B-28	EN-B-30-1	Bottle resin, CF3COONa	4	59	37
B-34	EN-B-35-2	Bottle resin, NaBF4	6	64	30
B-36	EN-B-39-1	Used CF3COO- resin, NaCl, NaBF4	3	83	14
B-38	EB-B-39-2	New resin, NaCl, NaBF4	6	55	39
B-40	EN-B-42-5	New resin, DMSO, NaCl, NaBF4	5	81	14
B-43	EN-B-44-1	New resin, comm. DMSO, NaCl, NaBF4	10	76	14
B-46	EN-B-48-1	New resin, dried 24 hours, NaCl, NaBF4	7	26	67
B-48	EN-B-50-1	New resin, DMSO, NaCl, KPF6	9	72	19
B-50	EN-B-52-1	New resin, NaCl, CF3COONa	6	65	24
B-78	EN-B-82-1	New resin, DMSO, NaBF4 (large batch)	4	58	38
B-87	EN-B-91-1	New resin, DMSO, (24 hrs) (large batch)	7	67	26
B-94	EN-B-95-2	New resin, DMSO, (24 hrs), NaCl NaBF4 (large batch)	7	67	27
B-87	EN-B-97-2	See above, reaction done with 2 eq. NaBF4	7	54	40
B-87	EN-B-97-1	See above, reaction done with 2 eq. Li2CO3	4	61	35
B-98	EN-B-99-1	DMSO, NaCl,NaBF4	5	65	31
C-9	EN-C-13-2	DMSO, NaCl, NaBF4 (old good resins, EN-B-42-5 & EN-B-24-1)	24	65	11
C-14	EN-C-17-1	Amberlite IRA-400AR (not pre-dried), NaCl, NaBF4	20	43	33
C-16	EB-C-19-1	Same as C-14, but pre-dried	19	59	22
C-21	EN-C-24-1	Old, no good resins (B-20) DMSO, NaCl, NaBF4	11	69	20
C-24	EN-C-26-1	Redid C-16 resin (DMSO redistilled)	12	60	28
C-25	EN-C-27-1	Dowex 1-X8, 20-50 Mesh, pre-dried, DMSO, NaCl, NaBF4	9	56	35
C-26	EN-C-27-2	Dowex 1 1X8-400, pre-dried DMSO, NaCl, NaBF4	39	52	9
C-28	EN-C-32-1	Dowex 2-X8, pre-dried, DMSO, NaBF4	10	45	45
C-30	EN-C-34-1	Same as C-26 but 4 times	11	64	26
C-33	EN-C-35-1	Amberlite IRA-400CP, pre-dried, DMSO, NaCl, NaBF4	10	55	35

Resin Number	Reaction Number	Description of Resin Preparation	Relative Yield BrOH	BrC=O	Br2
C-36	EN-C-37-1	"Ion-Exchange Resin A-540", pre-dried, DMSO, NaCl, NaBF4	15	62	23
C-37	EN-C-38-1	Amberlite IRA-400AR, pre-dried, DMSO, NaBF4	10	57	33
C-38	EN-C-42-1	Used C-24 resin, DMSO,NaCl, NaBF4	16	60	24
C-45	EN-C-48-2	Dowex 1 1X8-400, pre-dried, DMSO, NaCl, NaBF4	19	67	14
C-46	EN-C-48-2	Bio-rad's AG1-X8 (OH resin)	67	22	12
C-53	EN-C-54-1	Bio-rad's AGMP-1, (Cl resin), pre-dried, DMSO, NaCl, NaBF4	12	62	27
C-55 (small scale)	EN-C-56-2	Dowex 1 1X8-400, pre-dried, DMSO, NaCl, NaBF4	13	64	22
C-55	EN-C-57-2	See above	3 (absolute yields)	10	7
C-64	EN-C-67-1	Amberlite IRA-900 Powder, DMSO NaCl, NaBF4		52	
C-65	EN-C-67-2	Amberlite IRA-900 Liquid	10	65	25
C-71	EN-C-75-1	Amberlite IRA-402 Liquid, DMSO, NaCl, NaBF4	31	29	41

Table 5. Absolute Yields for the Reaction of DMSO, NBS, and Cyclohexene. Reactants: DMSO (75 mL, 1.1 moles), NBS (3.20 g, 0.018 moles), Cyclohexene (1.5 mL, 0.015 moles), CH_2Cl_2 (30 mL, 0.5 moles), NEt_3 (2.1 mL, 0.015 moles).

Reaction Number	Scale	NBS (moles)	Spike Anal.	Absolute Yields BrOH	BrC=O	Br_2
EN-C-53-1	X3	0.018	undistilled	5	19	13
			distilled	6	18	18
EN-C-57-2	X3	"	undistilled	3	10	7
			distilled	3	9	7
EN-C-88-1	X1	"(rec)	spike		20	
EN-C-90-1	"	0.030	spike	3	40	43
EN-C-91-1	"	0.060	spike	13	21	10

Table 6. Reaction of Pyridine Oxide, Cyclohexene, NBS, and Base (Triethylamine unless otherwise specified). Pyridine oxide (5.7 g,0.06 moles), Cyclohexene (1.5 mL, 0.015 moles), NBS (3.2 g, 0.018 moles).

Reaction Number	Variation	Solvent	Amt (mL)	Temp. (C)	Time (min.)	NEt3 (moles)	Relative Yields BrOH	BrC=O	Br2	Anal.
EN-C-22-1	1/2 scale	EtOAc	50	16-RT	30	0.015	Bromo ketone, plus 5 other products			GC
EN-C-32-2		DMSO & CH2Cl2	75	"	"	"	28	30	42	GC
EN-C-34-2	plus 51 mg. hydro-quinone	CH2Cl2	50	"	"	"	got white ppt. 4 peaks on GC 4 spots on TLC			
EN-C-39-1	AgNO3 (0.0075m.) before NBS	EtOAc	100	"	"	"	100	None	None	GC
EN-C-43-1	Diff. temp	"	"	"	"	"	got white ppt. 5 spots on TLC one corr. to bromo ketone			
EN-C-44-1	Diff. solv.	Benzene	100	20-RT	50 min 6.5 hr	"	got white ppt. bromo ketone plus others			GC

Reaction Number	Variation	Solvent	Amt (mL)	Temp. (C)	Time (min.)	NEt3 (moles)	Relative Yields BrOH	BrC=O	Br2	Anal.
EN-C-49-1	0.0075 moles $AgNO_3$ added before NBS	EtOAc	"	2	30 min	"	got white ppt. None	None	None	GC
EN-C-51-1	$AgNO_3$;NaOH	"	"	"	"	1 eq 10% NaOH	Mainly			GC,IR,NMR
EN-C-56-1	" ;2 eq NaOH	"	"	"	"	2 eq 10% NaOH	Mainly	Small	None	GC
EN-C-59-1	" ;10 eq NaOH	"	"	"	"	10 eq 10% NaOH	Most plus other earlier peaks plus later solid peaks	Next	None	GC

Table 7. Reactions of Other Amine Oxides, Alkenes, and NBS. Reactants not specified; Cyclohexene (1.5 mL, 0.015 moles), DMF (solvent, unless otherwise specified).

Reaction Number	Var.	Amt. (Moles)	Solvent (mL)	Temp. (C)	NBS (Moles)	Time (Min)	NEt3 (Moles)	Time (Min)	Results BrOH	BrC=O	Br2	Anal.
N-Methyl Morpholine Oxide												
EN-C-83-1 (Solvent: CH2Cl2)		0.06	50	2	0.018	30	0.015	30	17	9	57	GC
EN-D-4-1		0.074	75	RT	0.030	"	----	---	trace	none	mainly	GC
EN-D-7-2 (+ 2 eq. AgNO3)	X0.63	0.075	100	"	0.030	"	0.03	30	18	none	82	GC
EN-D-11-1 (+ 4 eq. AgNO3 added before NBS)	X1.16	"	50	"	"	1.5 hrs.	"	"	9	none	91	GC
Dabco Mono-oxide												
EN-D-45-1		0.050	"	4	"	30	0.015	"	got decomposed BROH and a small amt. of Br2			GC

Reaction Number	Var.	Amt. (Moles)	Solvent (mL)	Temp. (C)	NBS (Moles)	Time (Min)	NEt3 (Moles)	Time (Min)	Results BrOH	BrC=O	Br2	Anal.
EN-D-64-1	X1/2	0.057	"	2	"	60	0.030	"	48	8	2	spike
Quinuclidine Oxide												
EN-D-22-1 (cyclohexene added after NBS)		0.048	"	"	"	18	0.015	15	3	86	11	GC
EN-D-24-1		0.051	"	"	"	"	"	--	46	7	spike	
EN-D-29-1	"	0.053	"	"	"	30	"	30	-- (absolute yields) Crude estimates of cyclohexene are 51%, 30%, 29%	48	6	spike
EN-D-52-2 (repeat of EN-D-29-1)		0.054	"	"	"	"	"	"	-- (absolute yields)	47	8	spike
EN-D-51-1	X1/2	0.059	25	100	"	2hrs.	0.030	15	--	--	mainly	spike
EN-D-52-1	"	0.054	50	33	"	24hrs.	"	15	--	--	mainly	spike
EN-D-53-1	"	0.054	"	2-RT	"	30	0.015	30 at RT	--	--	mainly	spike

Reaction Number	Var.	Amt. (Moles)	Solvent (mL)	Temp. (C)	NBS (Moles)	Time (Min)	NEt3 (Moles)	Time (Min)	Results BrOH	BrC=O	Br2	Anal.
EN-D-58-1	"	0.053	50	-20	0.030	3	0.015	2	--	32 (absolute yield)	2	spike
EN-D-60-1 (NEt3 from start)	"	0.051	42	2	"	1	0.030		--	---	only	GC
EN-D-64-1	"	0.055	50	-20	"	3	"	2 at RT	--	--	only	GC
EN-D-67-1 (blank; no NBS added)	"	0.051	"	-20	"	3hrs	"	1	(cyclohexene; 51% or 30% depending on how analyzed)			
EN-D-41-1		0.021	5	RT (35)	0.011	1hr.	--	--	NR, cyclododecene greater than 95% weak carbonyl			GC IR
EN-D-42-1		0.022	10	100	"	2hrs.	0.044	15min. at RT	NR, GC & IR almost exactly like IR cyclododecene			GC
EN-D-43-1	"	0.021	"	RT	"	24hrs.	"	"	same as EN-D-42-1			

Table 8: Reversal of Polarities

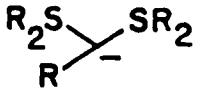
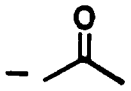
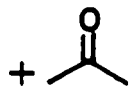
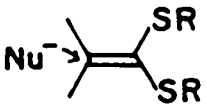
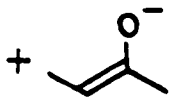
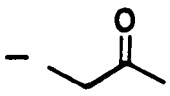
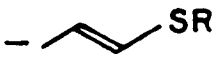
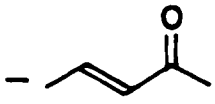
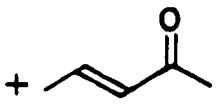
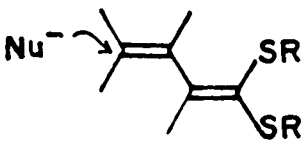
Normal Reactivity	Reactivity with Umpolung	Types of Reagents Which Accomplish This
		
		
		
		

Table 9. Results of Alkylation, Hydrolysis, and Distillation Steps from Various Modifications on Reaction of Benzyl Bromide with Tosylmethyl THP Ether.

Reaction Number	Sulfone Number	Sulfone (Eq)	BuLi (Eq)	RX (Eq)	HMPA (Eq)	Hydrol. Number	Hydrol. Method	Yield of PhCH2CHO
Tosylmethyl THP Ether as the Limiting Agent								
EN-E-92	EN-E-90-3	1	1.09	1.47	1	E-94	A	56% (contam. with PhCH2Br)
EN-E-98	"	1	1.10	1.33	1	F-6	B	24 "
EN-F-7	"	1	1.10	1.33	1	F-8	C	36 "
EN-F-7	"	1	1.10	1.34	1	F-9	D	36 "
Benzyl Bromide as the Limiting Agent								
EN-F-10	"	1.51	1.02	1	1	F-13	A	45
EN-F-14	EN-E-93-4	1.35	1.02	1	0.82	F-18	A	46
EN-F-20	"	1.61	1.28	1	3.3	F-23	A	1.4
EN-F-22	"	1.50	1.29	1	0	F-25	A	83
Other Variations								
EN-F-61 (added 1.35 eq. of distilled TMEDA)	EN-F-45-3	1.48	1.23	1	-	F-62	A	42

Reaction Number	Sulfone Number	Sulfone (Eq)	BuLi (Eq)	RX (Eq)	HMPA (Eq)	Hydrol. Number	Hydrol. Method	Yield of PhCH2CHO	
EN-F-65	"	1.49	1.32	1	-	F-67	A	73	(contam. with PhCH2Br)
(after BuLi added: T;-67C to 2C, 45 min., the T:2C, 30 min.)									
EN-F-70	"	1.58	1.31	1	-	F-72	A	41	
(added 1.3 eq. of freshly distilled TMEDA)									
Phase Transfer Catalysis									
EN-F-57	"	1.13	34.3 eq NaOH	1	-	F-59	A	54 of recovered PhCH2Br (plus a trace of PhCH2CHO)	
(added 0.035 eq. of PTC and 10 mL of benzene, 3 hrs, RT)									
EN-F-58	"	1.05	34.3 eq NaOH	1	-	F-59	A	17 of recovered PhCH2Br	
(added 0.035 eq. of PTC, no benzene, 6 hrs, 55-60C)									

Table 10. Results of Alkylation, Hydrolysis, and Distillation Steps from Various Modifications of Reactions of Alkyl Halides with Tosylmethyl THP Ether.

Reaction Number	Sulfone Number	Sulfone (Eq)	BuLi (Eq)	RX (Eq)	HMPA (Eq)	Hydrol. Number	Hydrol. Method	Yield of RCHO
Octyl Bromide								
EN-F-24	EN-E-93-4	1.71	1.42	1	1	F-27	A	41%
EN-F-28	EN-F-21-3	1.94	1.61	1	-	F-30	"	83
EN-F-29	"	1.56	1.34	1	-	F-32	"	58 (?)
EN-F-92	EN-F-51-3	1.64	1.72	1	-	F-94	"	69
Cinnamyl Bromide								
EN-F-83	EN-F-60-8	1.51	1.42	1	-	F-86	"	25
EN-F-88	EN-F-64-6	1.47	1.60	1	-	F-89	" (T=RT, not 45C)	13
EN-F-91	"	1.53	1.41	1	-	F-93	A	23
Allyl Bromide								
EN-F-76	EN-F-60-8	1.49	1.41	1	-	F-78	"	

(Used spinning band to remove ether, made 2,4 DNP: mp 152-165 unrec.)

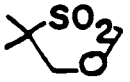
Reaction Number	Sulfone Number	Sulfone (Eq)	BuLi (Eq)	RX (Eq)	HMPA (Eq)	Hydrol. Number	Hydrol. Method	Yield of RCHO
EN-F-76	"	1.51	1.39	1	-	F-82	"	

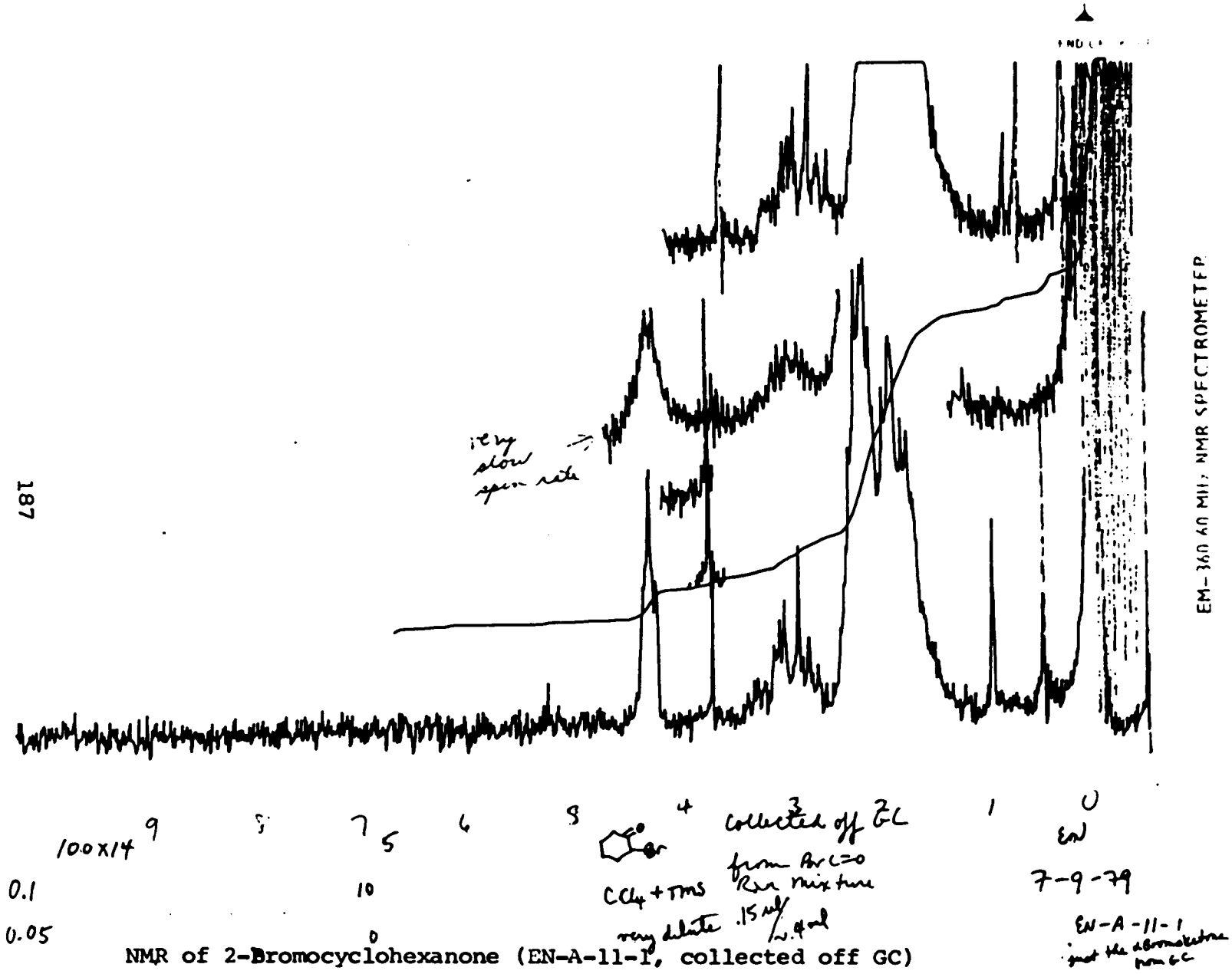
Made 2,4 DNP:
1st crop 0.8282 g (TY=3.42 g) mp: 157.5-158
2nd crop 0.7269 g mp: 145.5-152
Recrystallized 1st crop:
1st crop mp: 158-158.4
2nd crop mp: 155.1-156
3rd crop mp: 153.5-156
4th crop mp: 155-156
Mp (lit.): 160, 165, 190, 195.

Table 11. Yields Obtained After Alkylation, Hydrolysis, and Distillation, from the Reaction of Alkyl Halides with Tosylmethyl THP Ether.

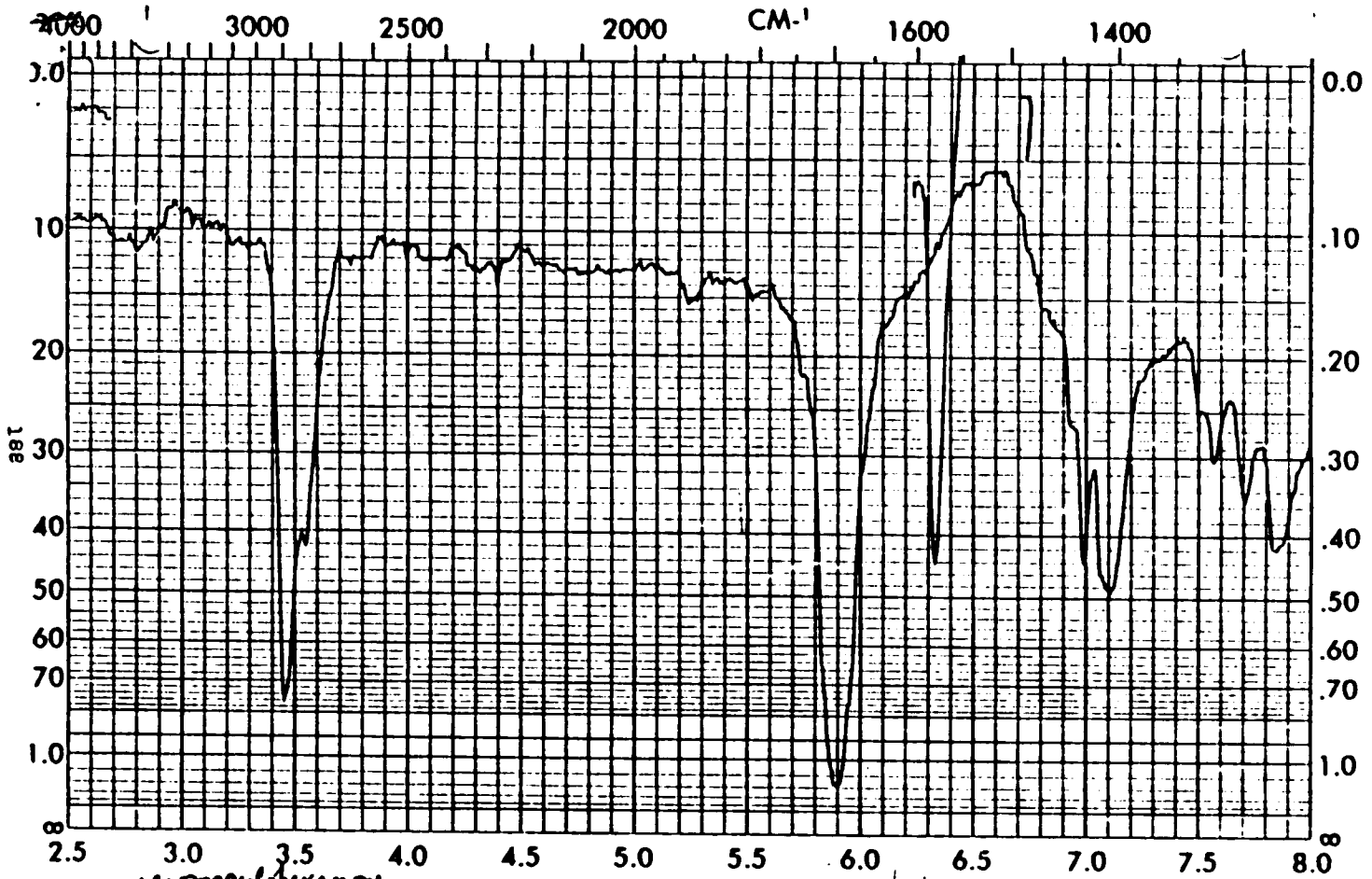
Alkyl Halide	Product	"Corey" Hydrolysis	Steam Distillation
Benzyl Br	PhCH2CHO	83	79
Oct Br	Nonanal	68	--
Cin Br	4-Phenyl-3-butenal	24	50

Table 12. Price (160) of One Mole of Formyl Anion Equivalent.

Reagent	"Synthesized"	Commercial	Drawbacks
Dithiane	$42.17	$141.20	Stench: $HS(CH_2)_3SH$
Ethyl ethyl thiomethyl sulfoxide	47.49	422.07 (164)	Stench: EtSH
	9.12	not available	Four step synthesis: using mercaptans, LAH.
Tosylmethyl			
THP ether	35.98	"	
EE ether	30.19	"	Less stable

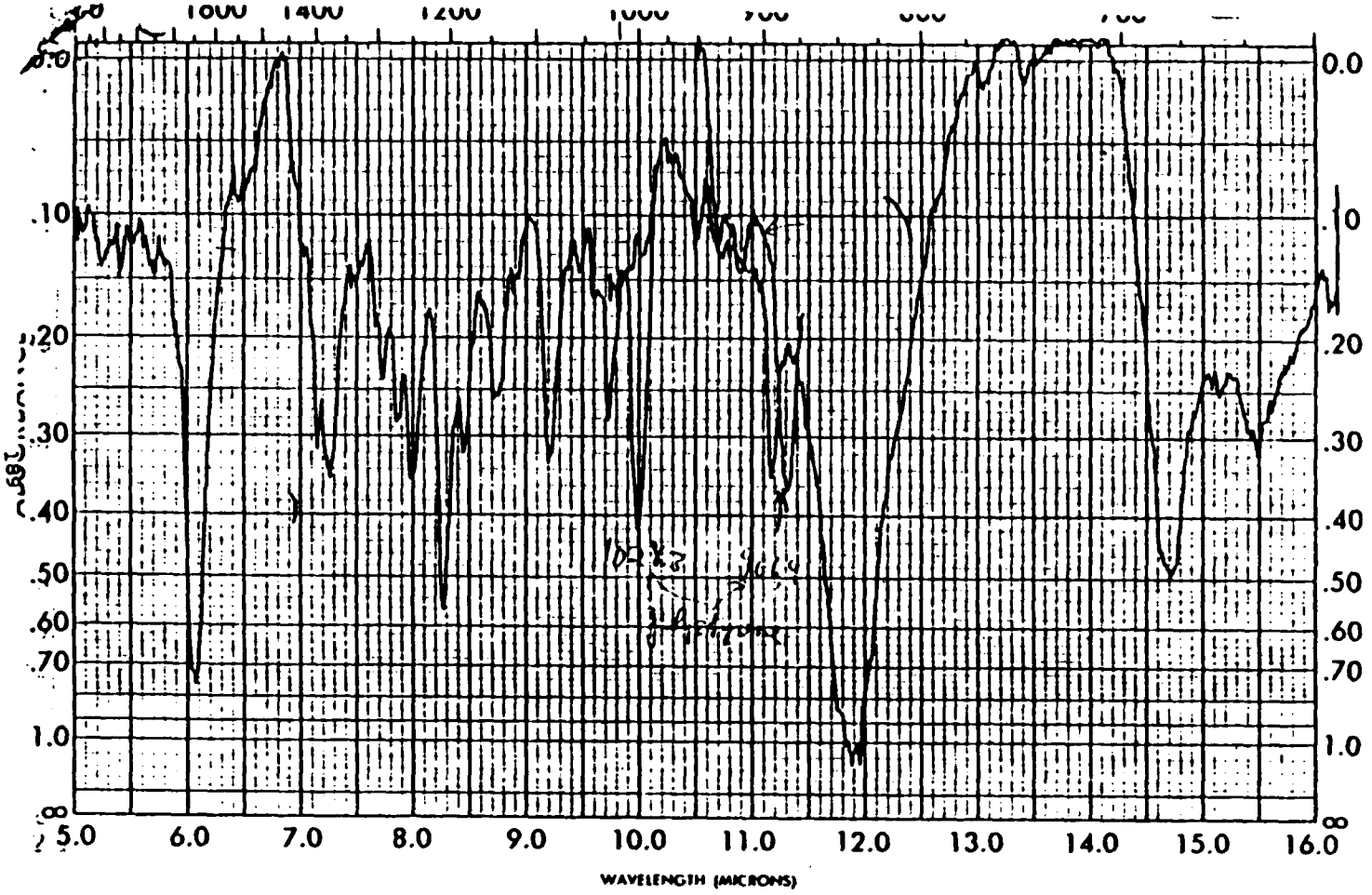


NMR of 2-Bromocyclohexanone (EN-A-11-1, collected off GC)

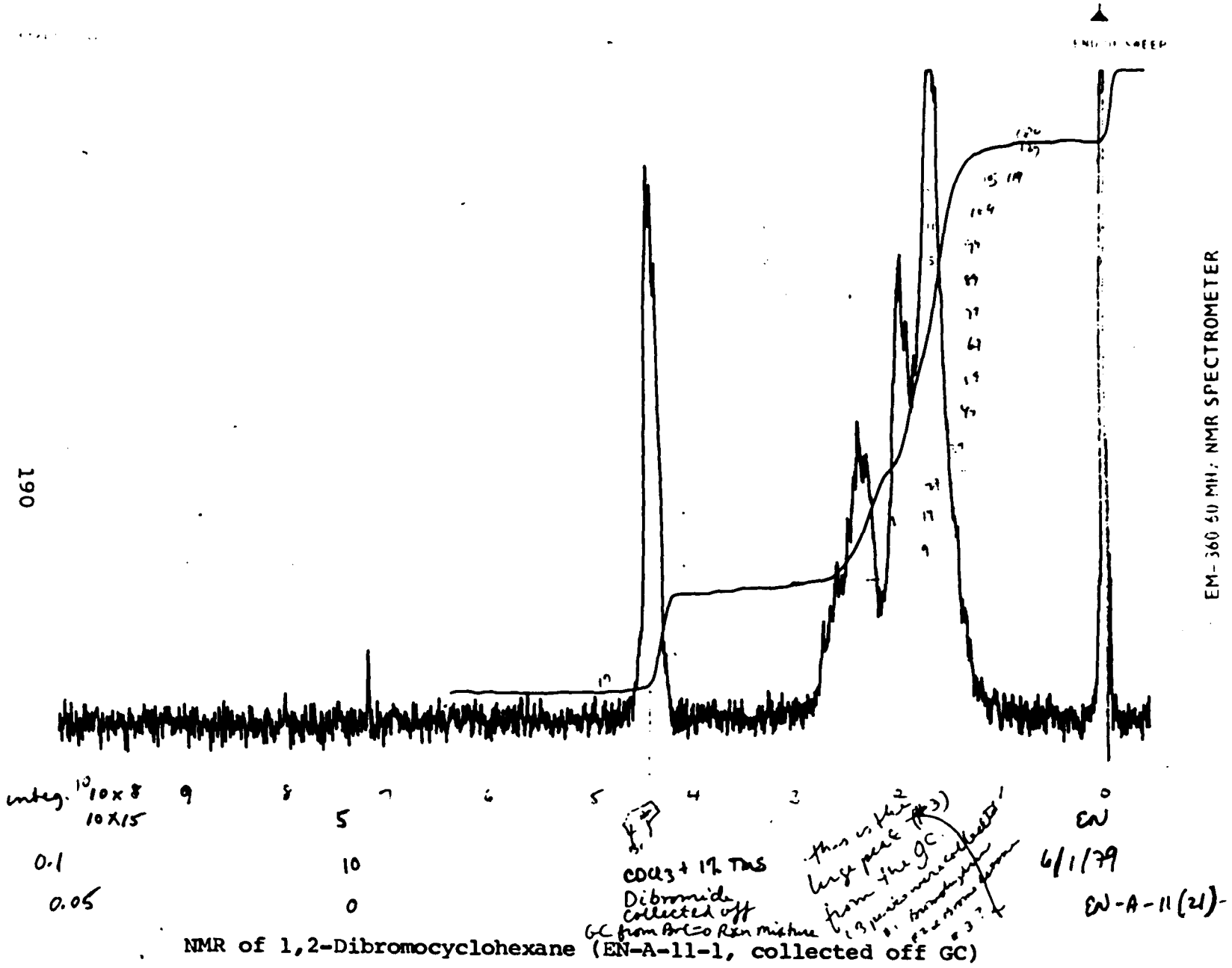


2 bromocyclohexanone
2 Bromoketone → G.C. purified – collected off G.C.

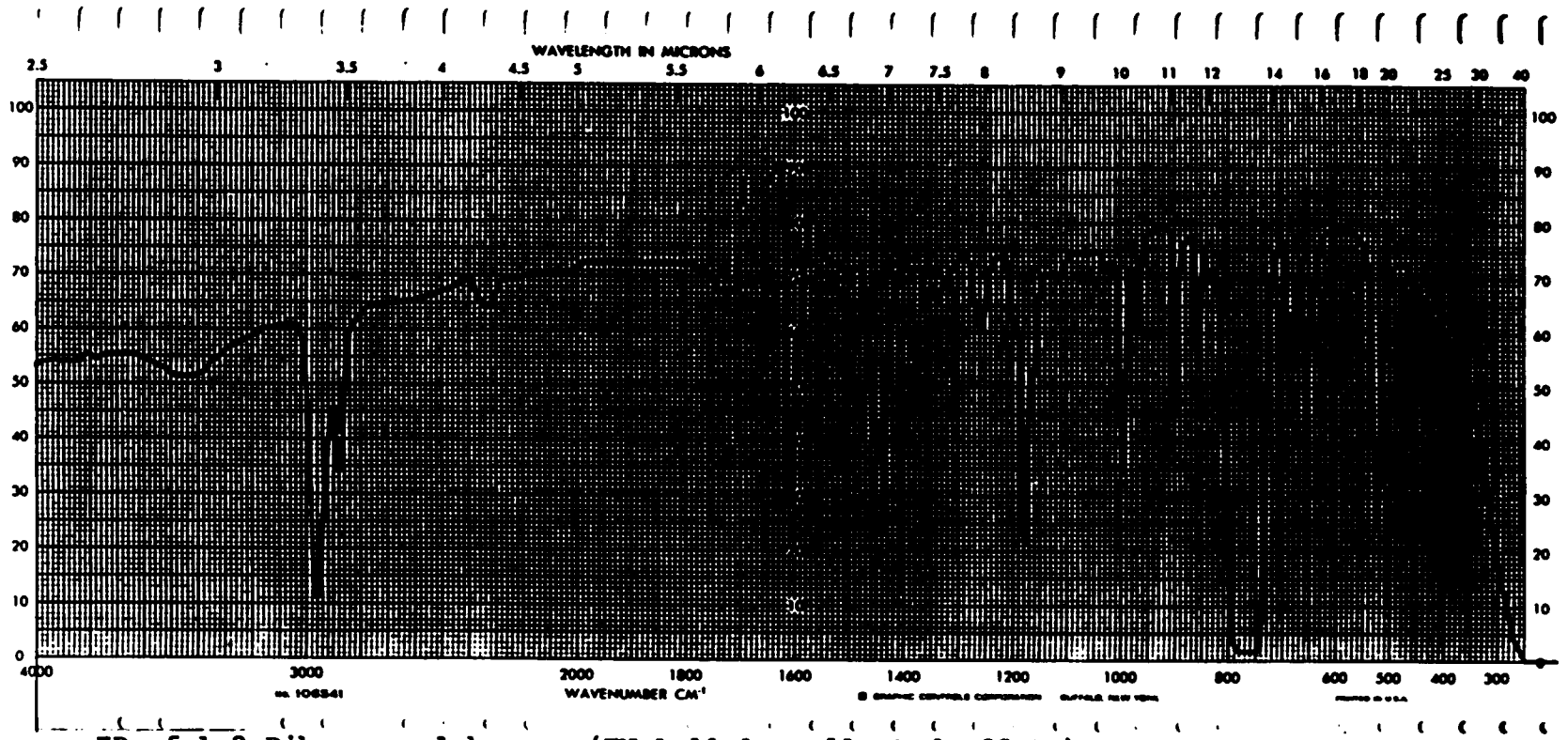
SAMPLE from EW-A-11-1	CURVE NO. from Br C=O Rxn mixture	SCAN SPEED F	OPERATOR EW
	CONC. ~15 µl / .4 ml	SLIT N	DATE 7-9-79
ORIGIN NBS, dry DMSO, hv	CELL PATH	REMARKS	
SOLVENT CCl4 + trace TMS	REFERENCE CCl4 ℓ		



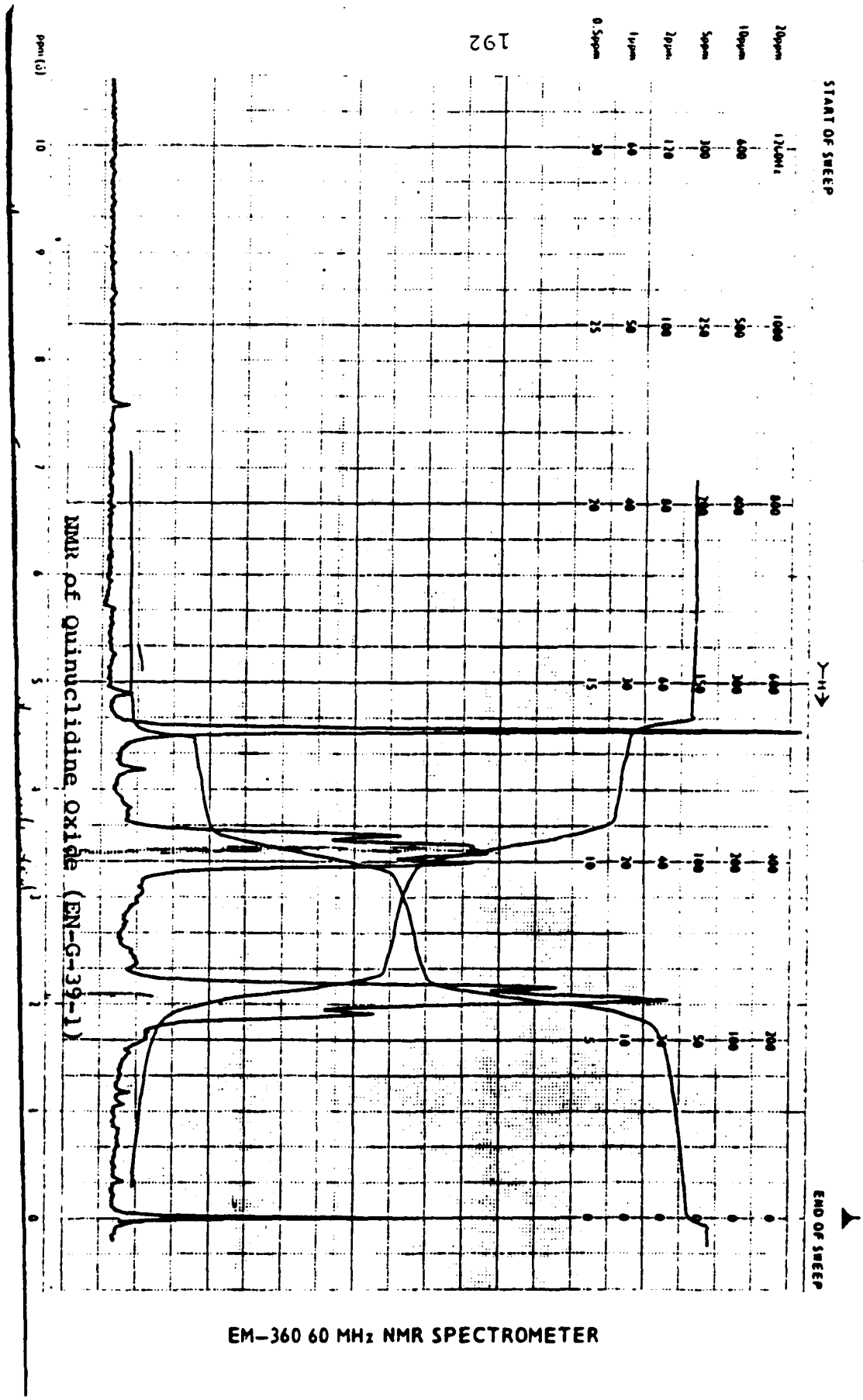
SAMPLE d-Bromocyclohexanone from EW-A-11 g.c purified	CURVE NO.	SCAN SPEED F	OPERATOR EW
ORIGIN NBS, dry DMSO,	CONC. ~15 µl/.4 ml	SLIT N	DATE 7-9-79
SOLVENT CCl4 + trace TMS	CELL PATH	REMARKS	
	REFERENCE CCl4		



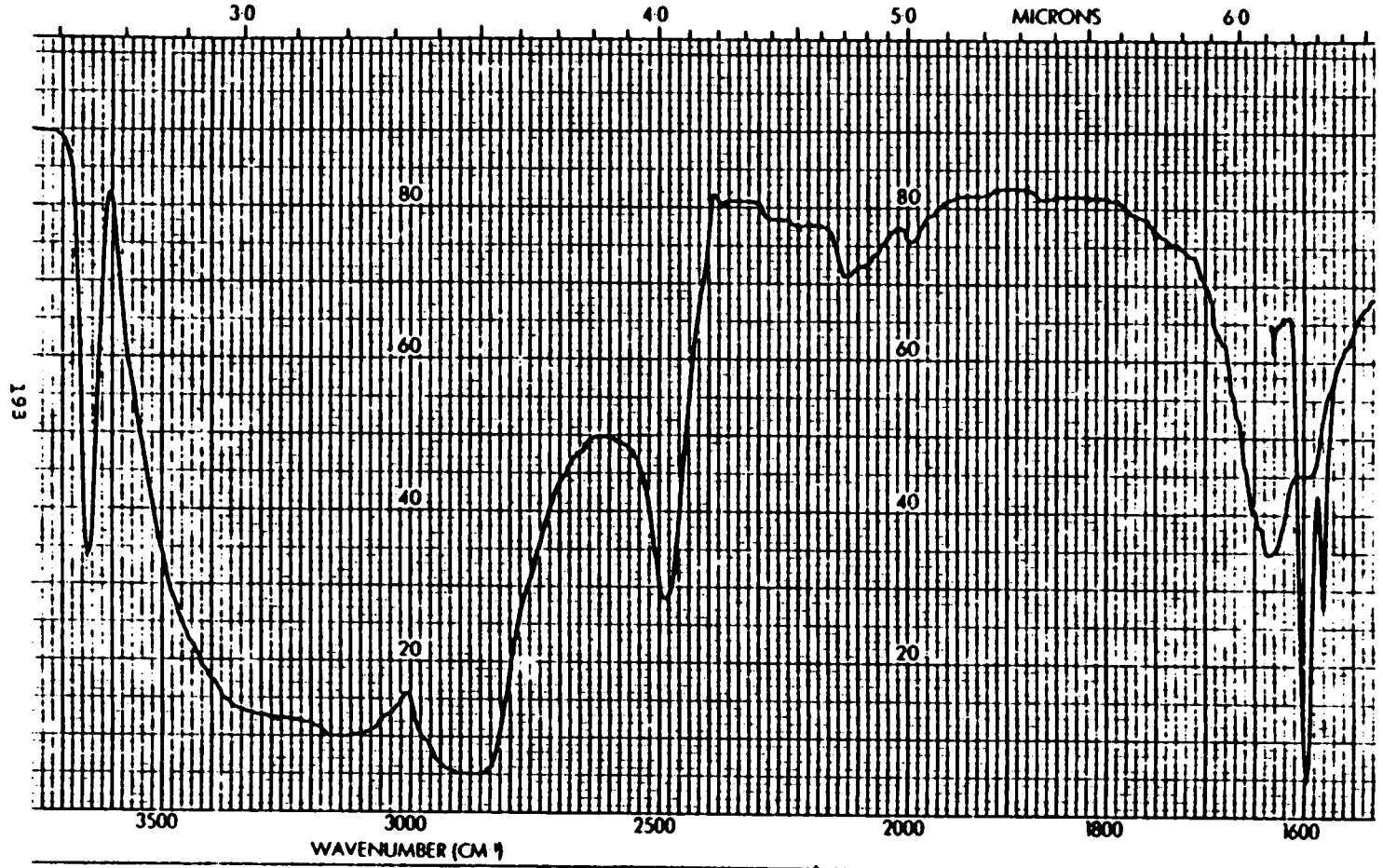
NMR of 1,2-Dibromocyclohexane (EN-A-11-1, collected off GC)



IR of 1,2-Dibromocyclohexane (EN-A-11-1, collected off GC)



EM–360 60 MHz NMR SPECTROMETER



EN-G-39-1

Guaiazulene Oxide

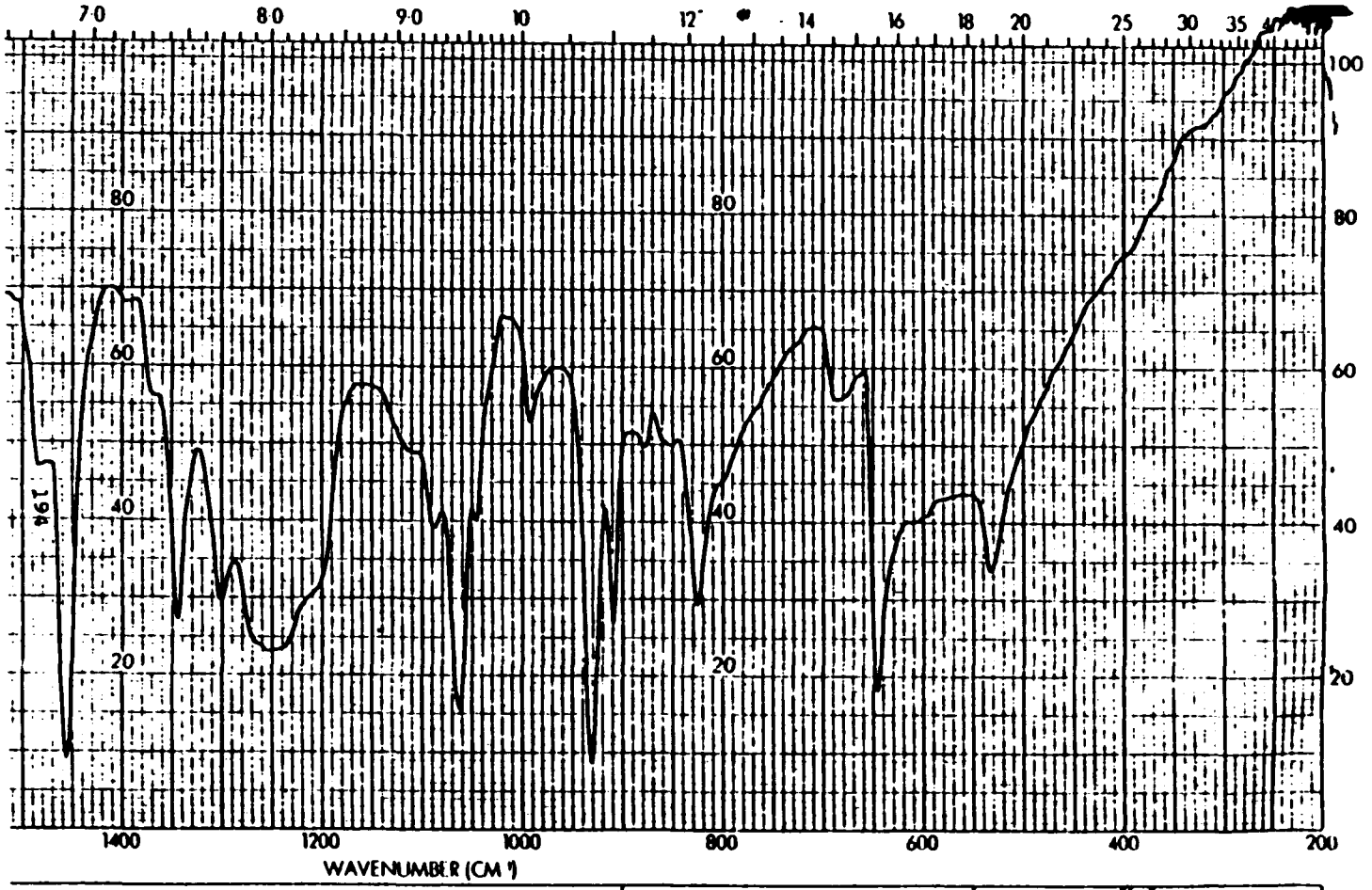
SOLVENT $CHCl_3$

CONCENTRATION 11.2 mg in 100 ml

CELL PATH

REFERENCE $CHCl_3$

REMARK

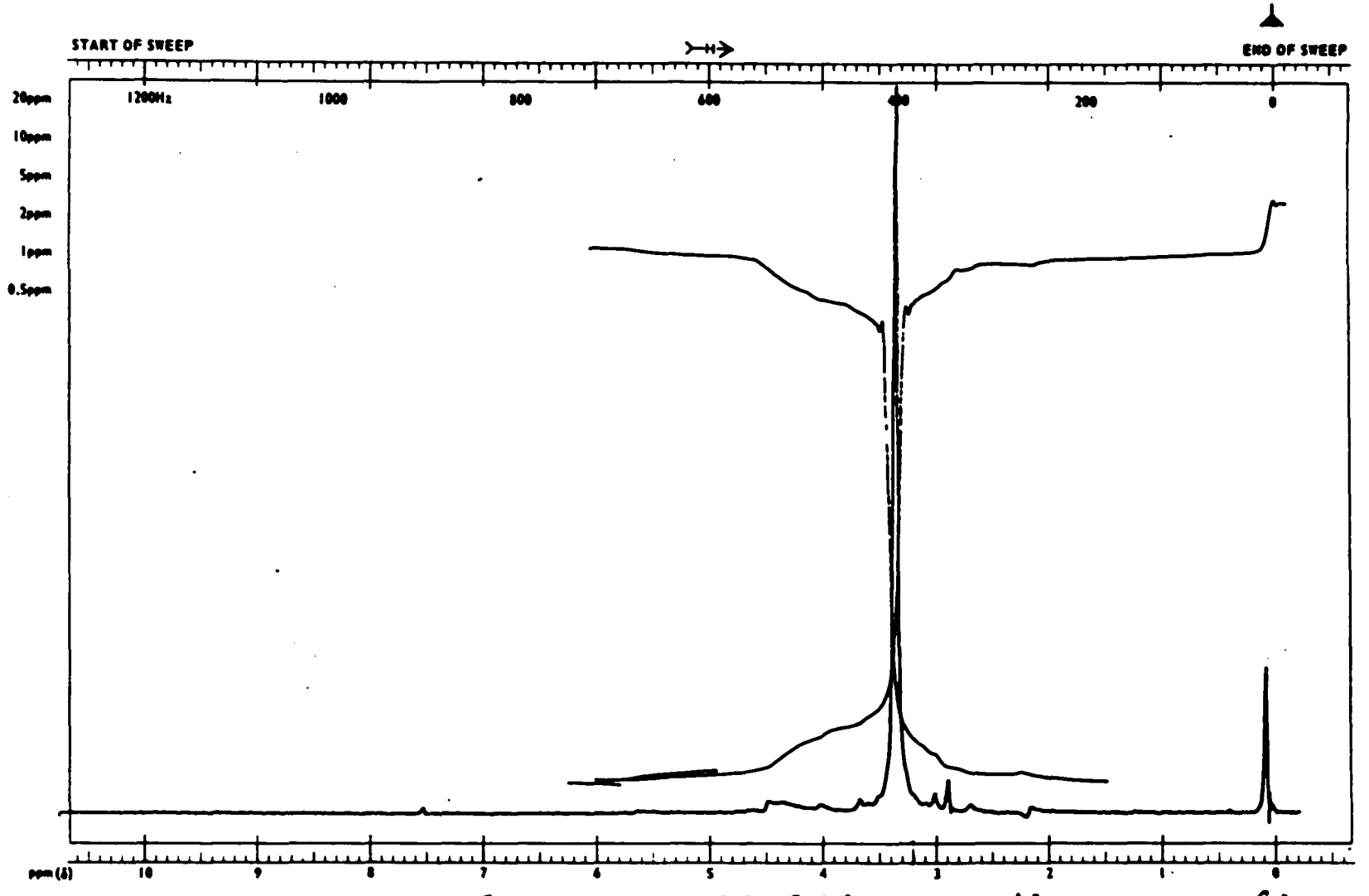


EN-G-39-1
Guanidine Oxide

SCAN MODE 12 min
SLIT M TIME CONSTANT

OPERATOR CN
DATE 4/15/82

REF No.



NORELL, INC.
314 ARBOR AVENUE
LANDISVILLE, N.J. 08326
Phone (609) 697-0020

CHART # NV EM-360-H-10
PRINTED IN U.S.A.

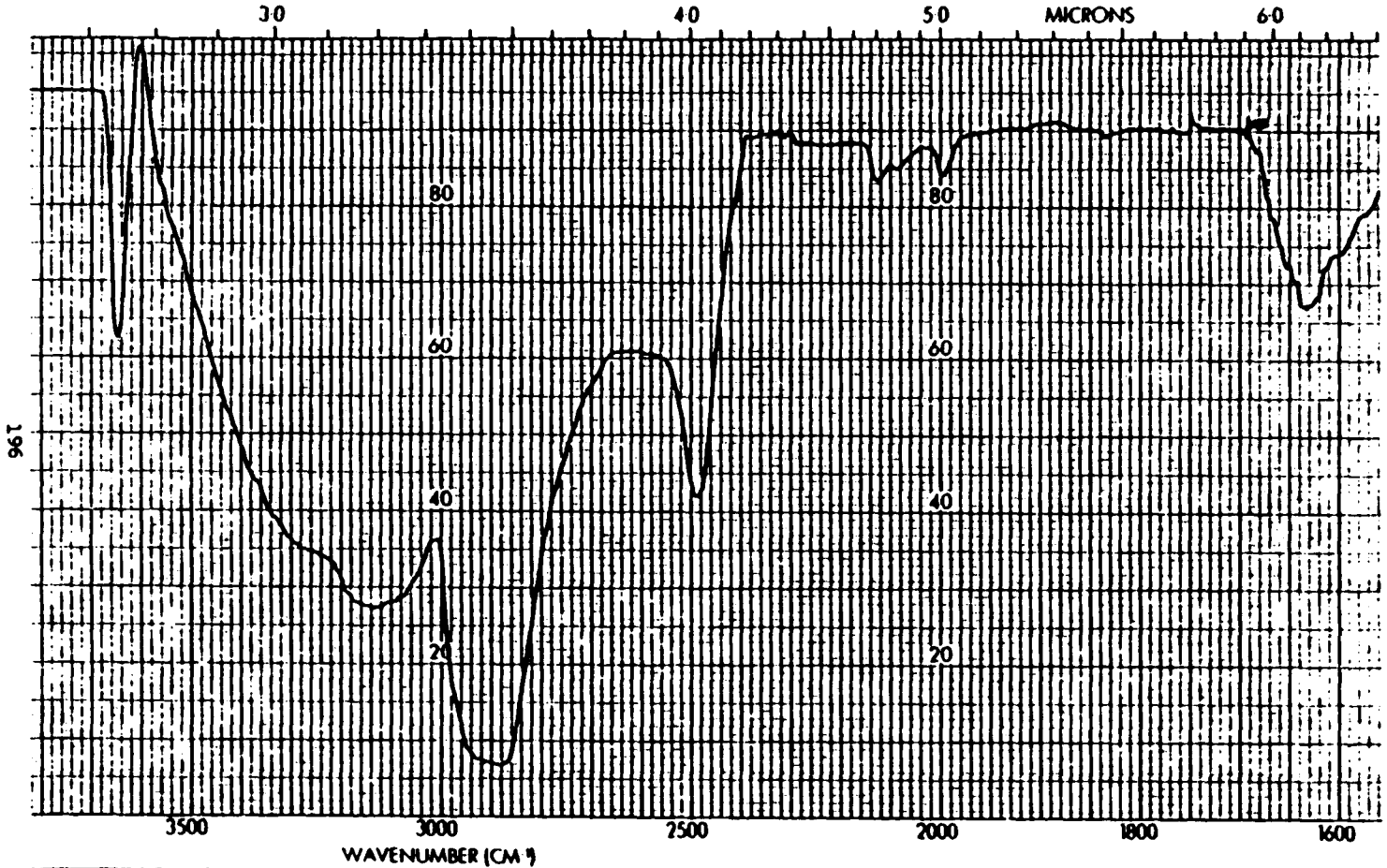
EM-360 60 MHz NMR SPECTROMETER

195

SPECTRUM AMPL. 10 x 9 | SWEEP TIME 5 min. | SAMPLE: NMR of Dabco mono-oxide EN-G-40-1 Dabco monooxide | REMARKS: 0.0481 g in 0.5 ml $CDCl_3$ +12 rms | OPERATOR EN

FILTER 0.1 sec | SWEEP WIDTH 10 ppm or Hz | DATE 4/16/82

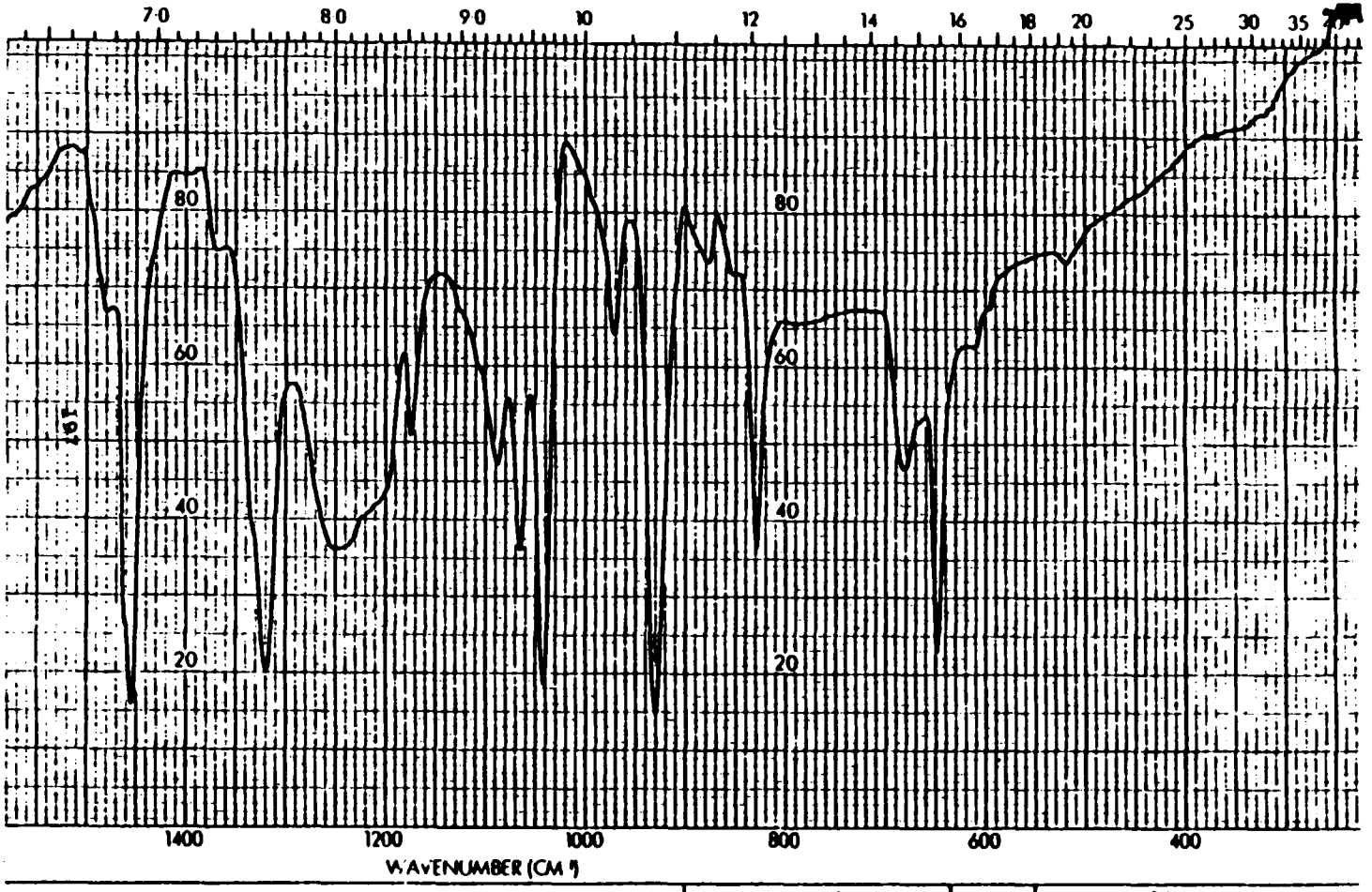
RF POWER 0.05 mG | END OF SWEEP 0 ppm or Hz | SOLVENT: monooxide | SPECTRUM NO.



EN-G-40-1
Dabco mono oxide

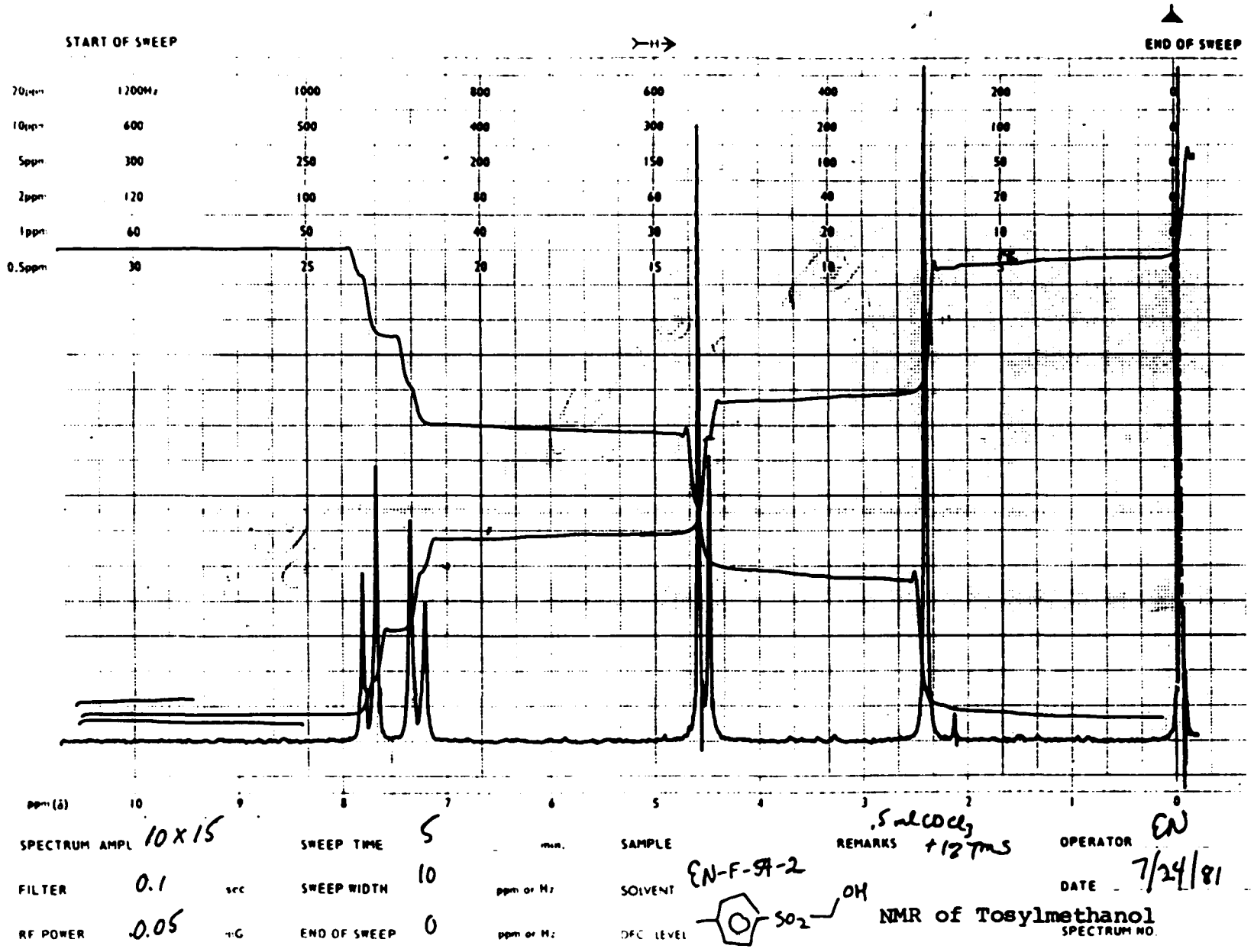
SOLVENT $CHCl_3$
CONCENTRATION
CELL PATH
REFERENCE $CHCl_3$

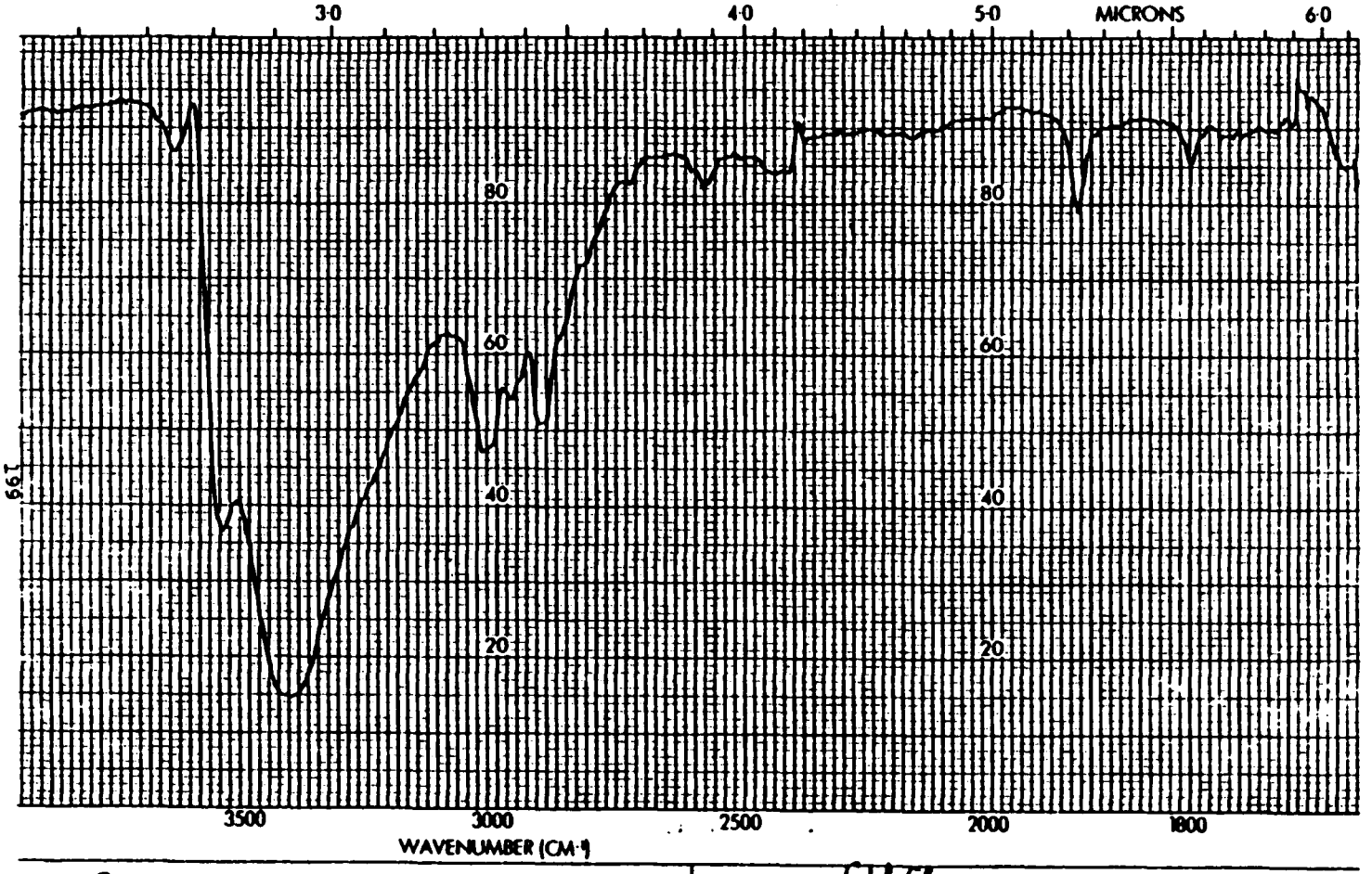
REM.



REMARKS EN-G-40-1
Dabco - Mono Oxide

SCAN MODE 12 mm
SLIT mm TIME CONSTANT
OPERATOR Ed
DATE 4/14/82
REF No.


START OF SWEEP
END OF SWEEP
20ppm 1200Hz 1000 800 600 400 200 0
10ppm 600 500 400 300 200 100 0
5ppm 300 250 200 150 100 50 0
2ppm 120 100 80 60 40 20 0
1ppm 60 50 40 30 20 10 0
0.5ppm 30 25 20 15 10 5 0
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
SPECTRUM AMPL 10 X 15
SWEEP TIME 5 min.
SAMPLE .5 ml CDCl3 + 1% TMS
REMARKS
OPERATOR EN
FILTER 0.1 sec
SWEEP WIDTH 10 ppm or Hz
SOLVENT
DATE 7/24/81
RF POWER 0.05 mG
END OF SWEEP 0 ppm or Hz
DEC LEVEL
EN-F-54-2
SPECTRUM NO.
NMR of Tosylmethanol
EM-360 60 MHz NMR SPECTROMETER
CHART NO WCV-360X-10
WILMAD GLASS CO. INC
198



SAMPLE CN-F-54-2 Tosylmethanol

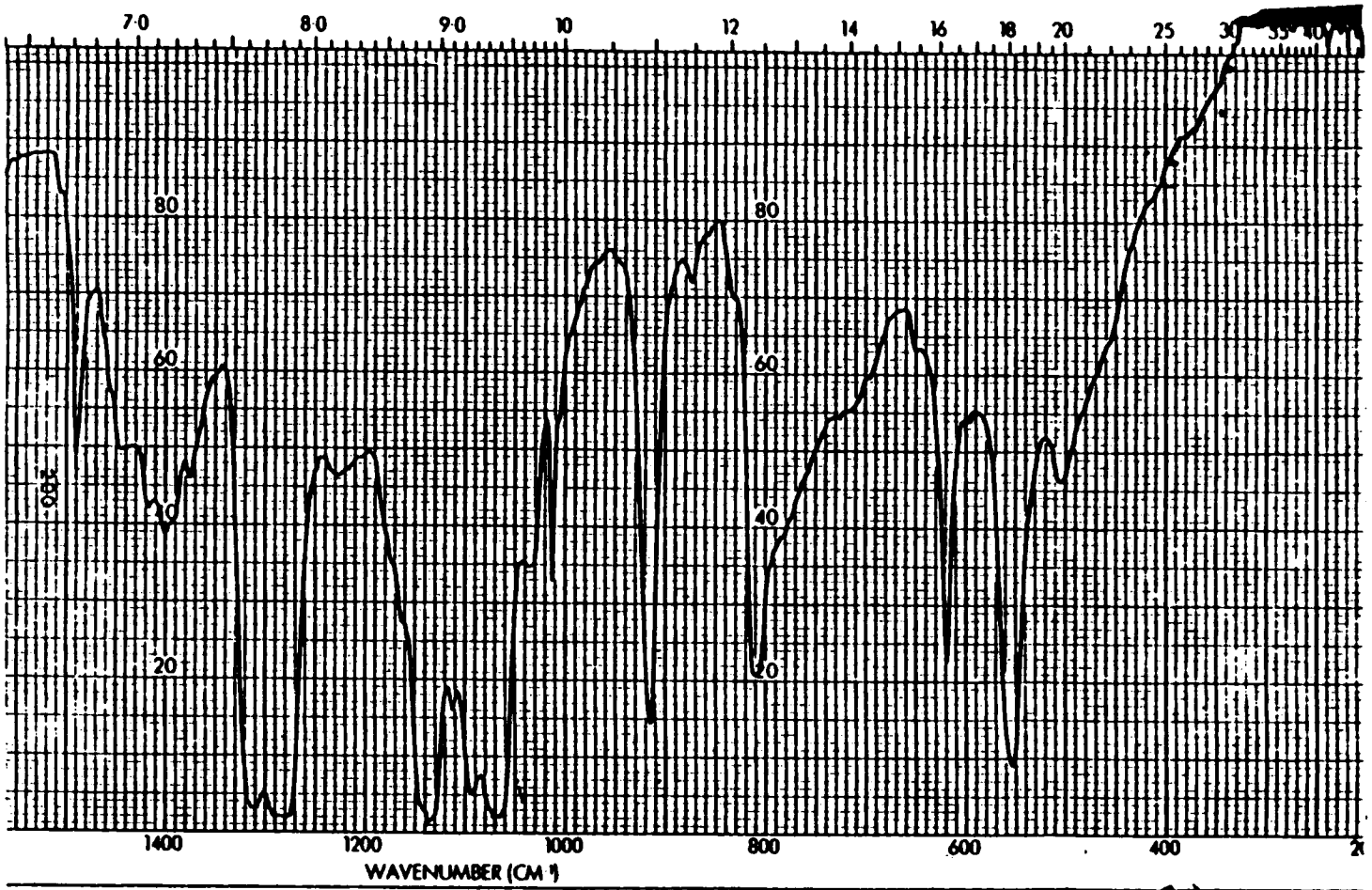
ORIGIN

SOLVENT $CHCl_3$

CONCENTRATION 10 mg in 100 ml

CELL PATH

REFERENCE $CHCl_3$



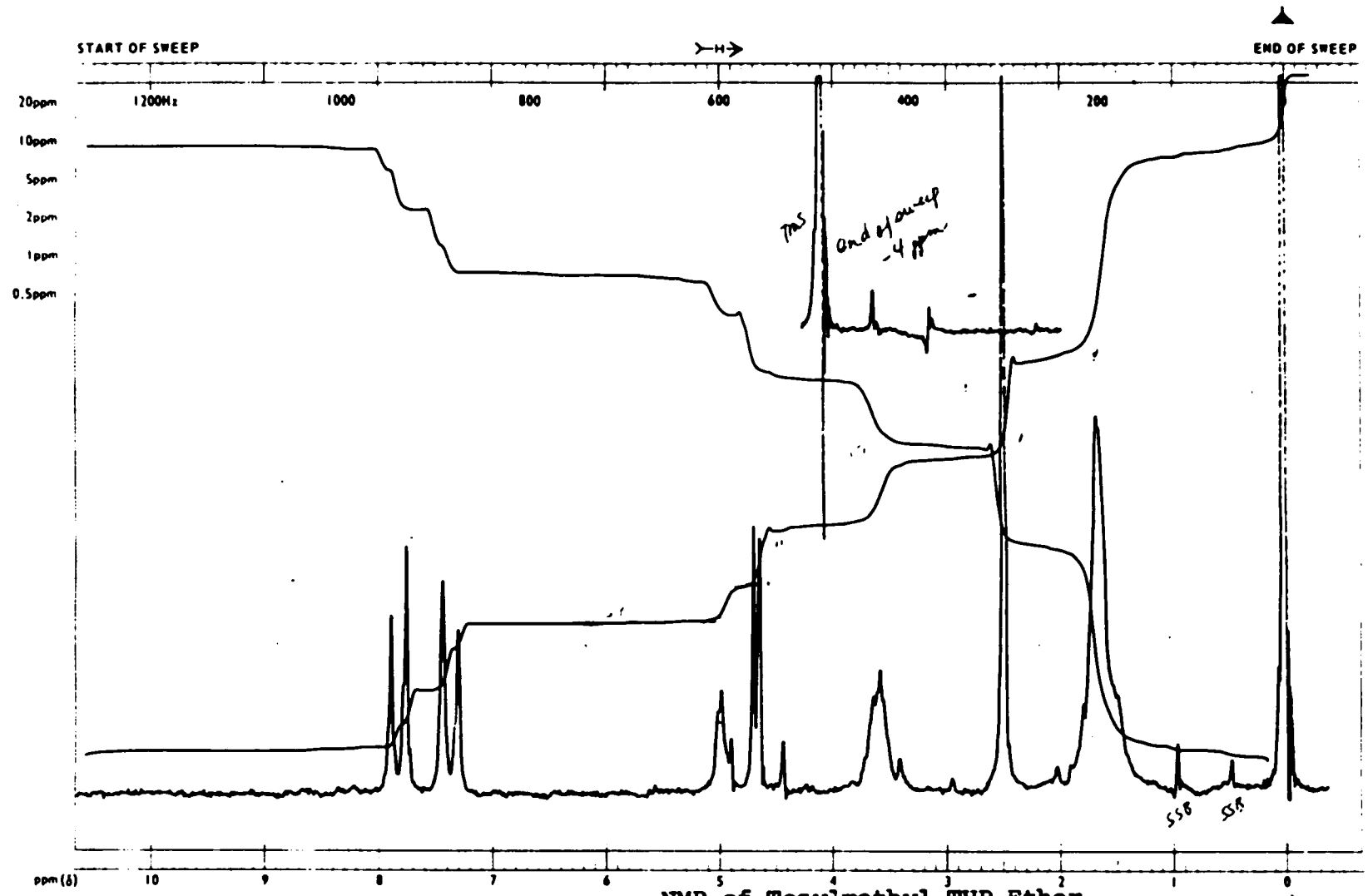
ARKS EN-F-54-2
Tosylmethanol

SCAN MODE 12 min
SLIT M TIME CONSTANT 12 min

PERKIN-ELMER
GRAPHIC CONTROLS CORPORATION
BUFFALO NEW YORK
No. PR 5100 4367

OPERATOR EN
DATE

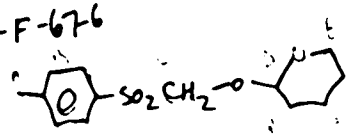
REF No.



NMR of Tosylmethyl THP Ether

SPECTRUM AMPL. 10 X 19 | SWEEP TIME 5 min. | SAMPLE GW-F-676 | REMARKS | OPERATOR GW

FILTER 0.1 sec | SWEEP WIDTH 10 ppm or Hz | DATE 8/21/81

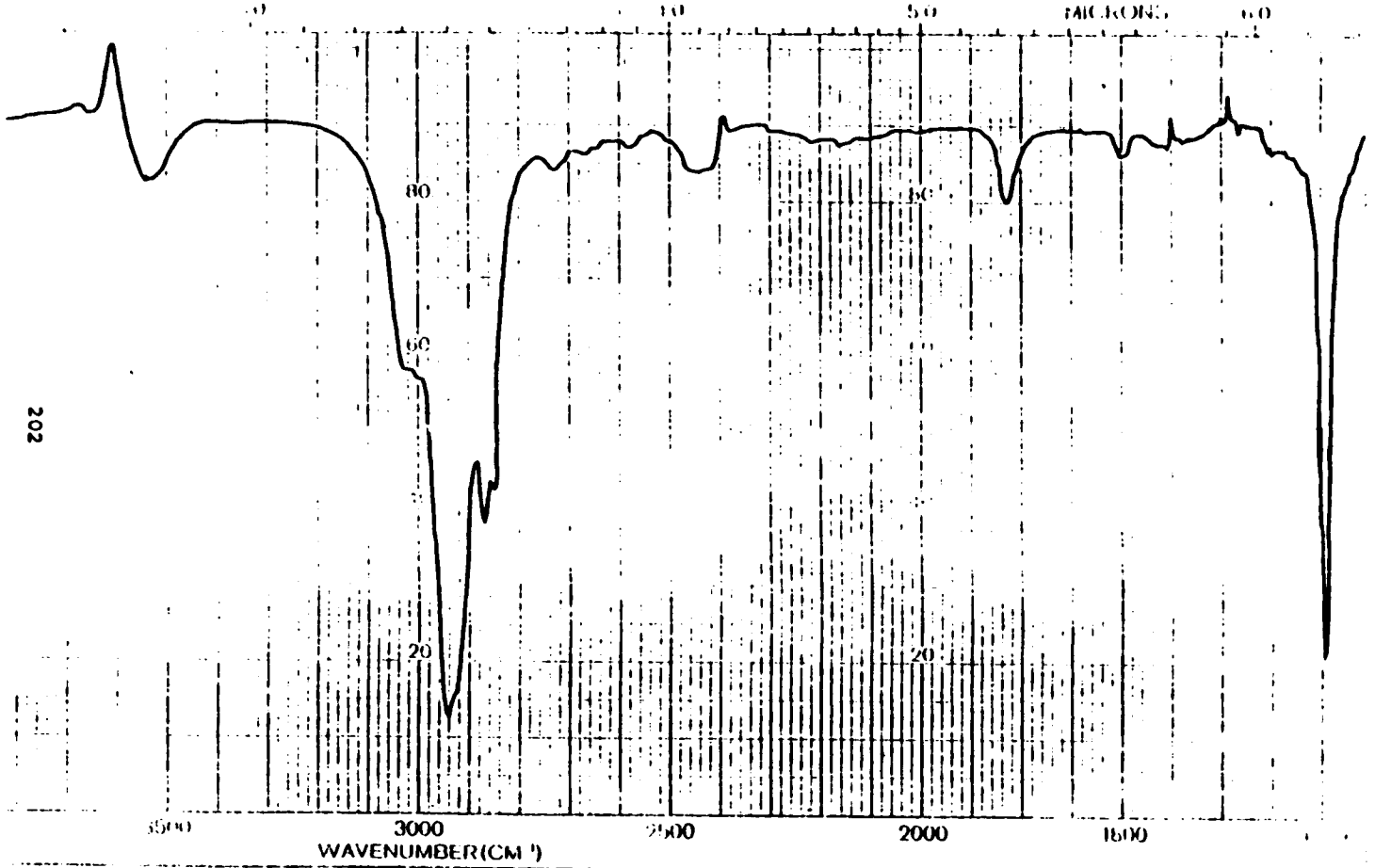
RF POWER 0.05 mG | END OF SWEEP 0 ppm or Hz | SOLVENT  | SPECTRUM NO.

201

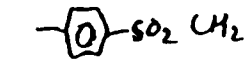
NORELL, INC.
314 ARBOR AVENUE
LANDISVILLE N.J. 08326
Phone (609) 697 0020

CHART # NV EM 360 R-10
PRINTED IN U.S.A.

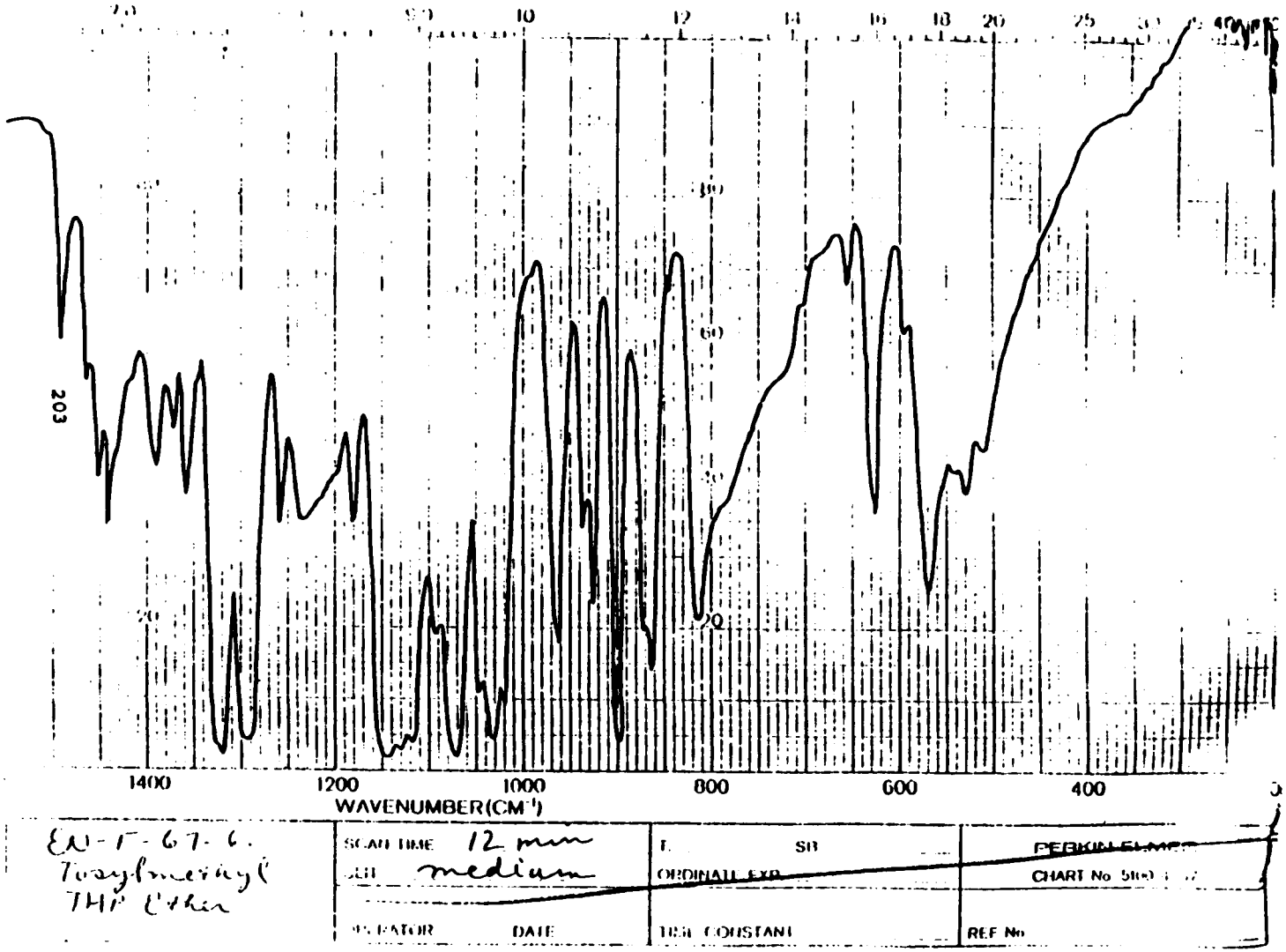
EM-360 60 MHz NMR SPECTROMETER



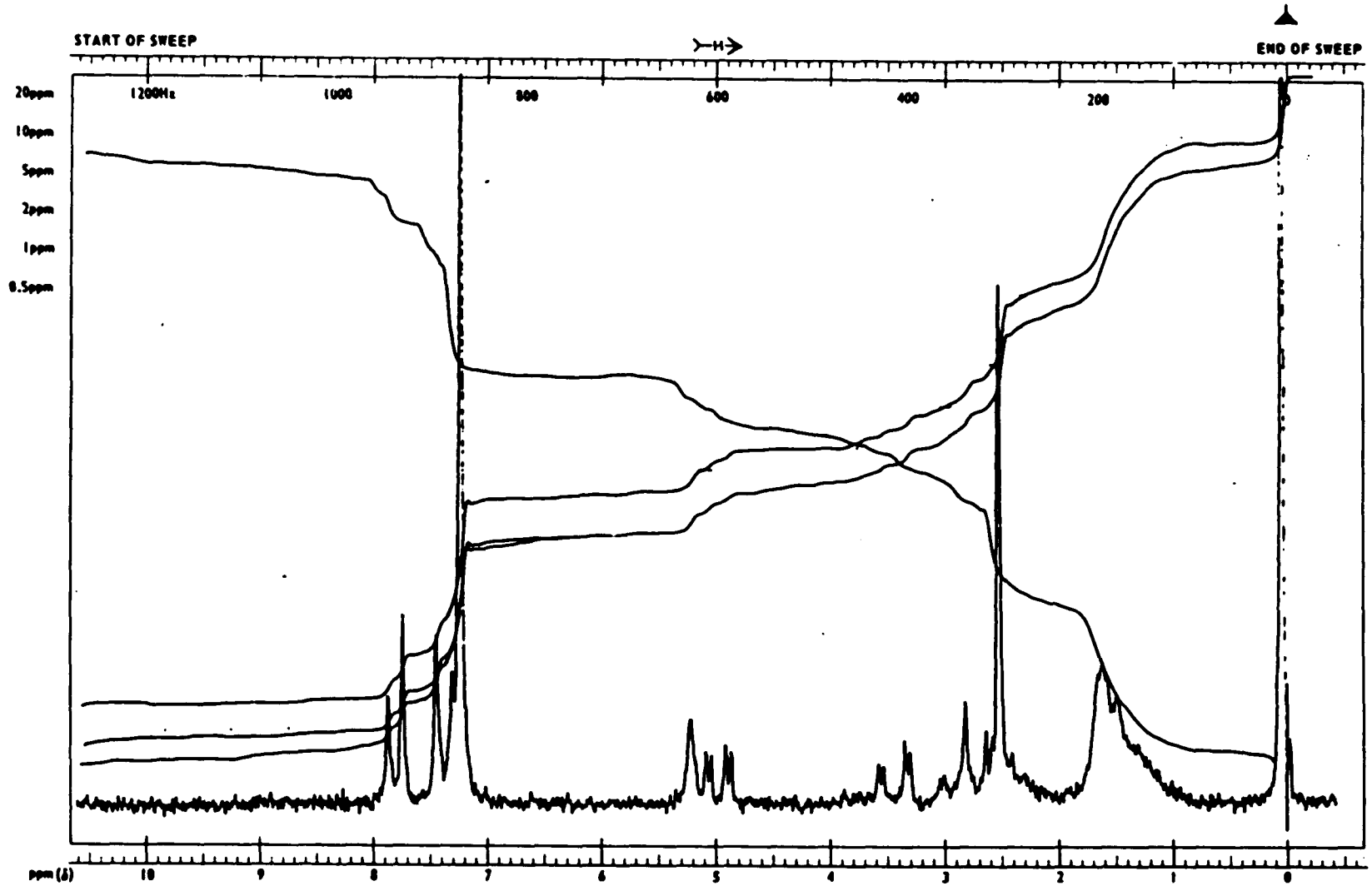
EN-F-67-6 Tosylmethyl THP Ether



SOLVENT $CHCl_3$
CONCENTRATION 10 mg in 100 ml
CELL PATH
REFERENCE $CHCl_3$



EN-T-67-6.
Tosylmercaptyl
THP Ether



NORELL, INC.
314 ARBOR AVENUE
LANDISVILLE, N.J. 08326
Phone (609) 697-0020

204

CHART # NV EM-360-K-10
PRINTED IN U.S.A.

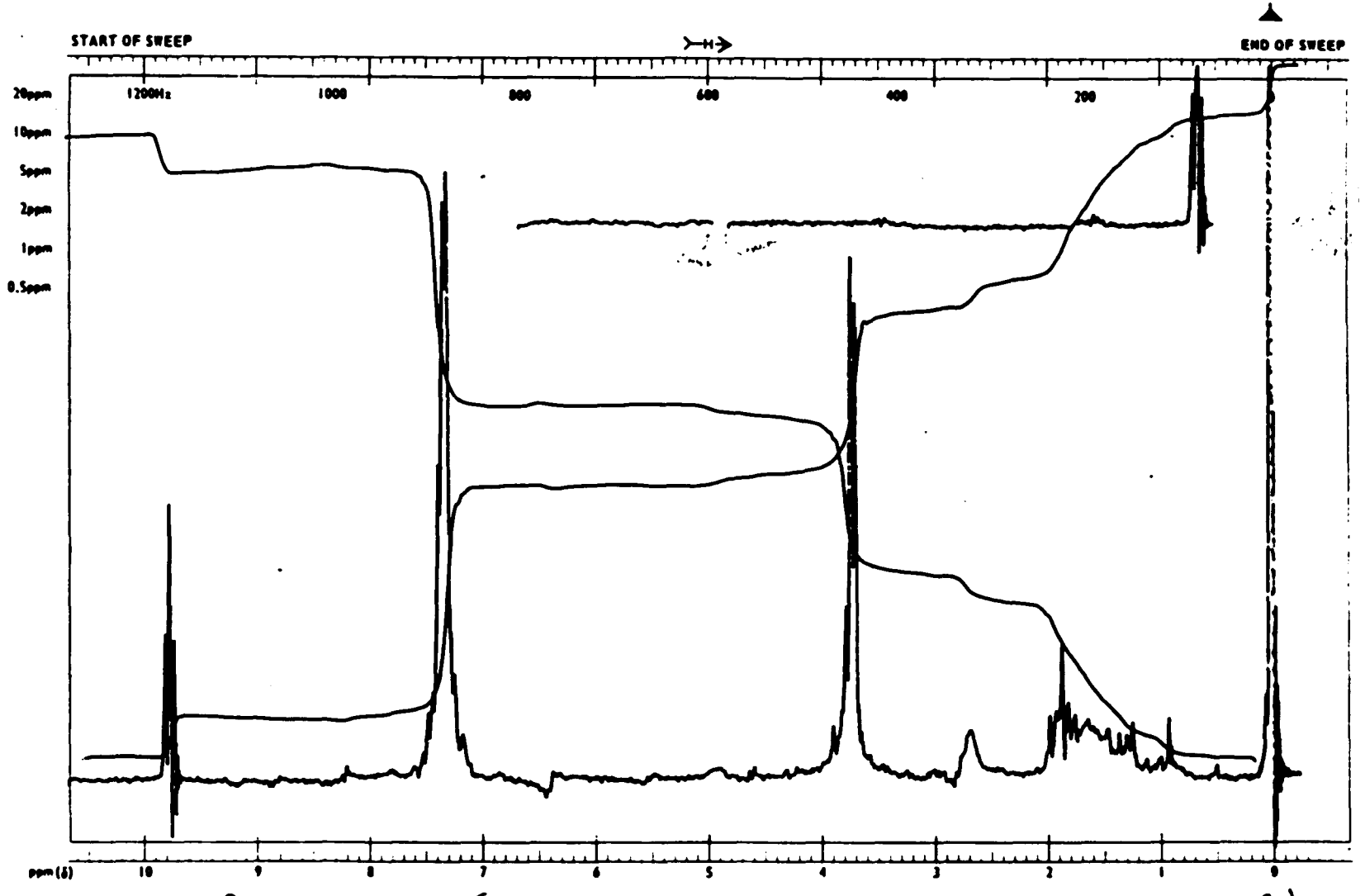
EM-360 60 MHz NMR SPECTROMETER

NMR of Benzyltosylmethyl THP Ether

SPECTRUM AMPL. 100X9.0 | SWEEP TIME 5 min. | SAMPLE: | REMARKS: | OPERATOR EN

FILTER 0.1 sec | SWEEP WIDTH 10 ppm or Hz | EN-E-64-1 | DATE 4/21/81

RF POWER 0.05 mG | END OF SWEEP 0 ppm or Hz | SOLVENT: | SPECTRUM NO.



NORELL, INC.
314 ARBOR AVENUE
LANDISVILLE, N.J. 08326
Phone (609) 697-0020

CHART # NV EM-360-H-10
PRINTED IN U.S.A.

205

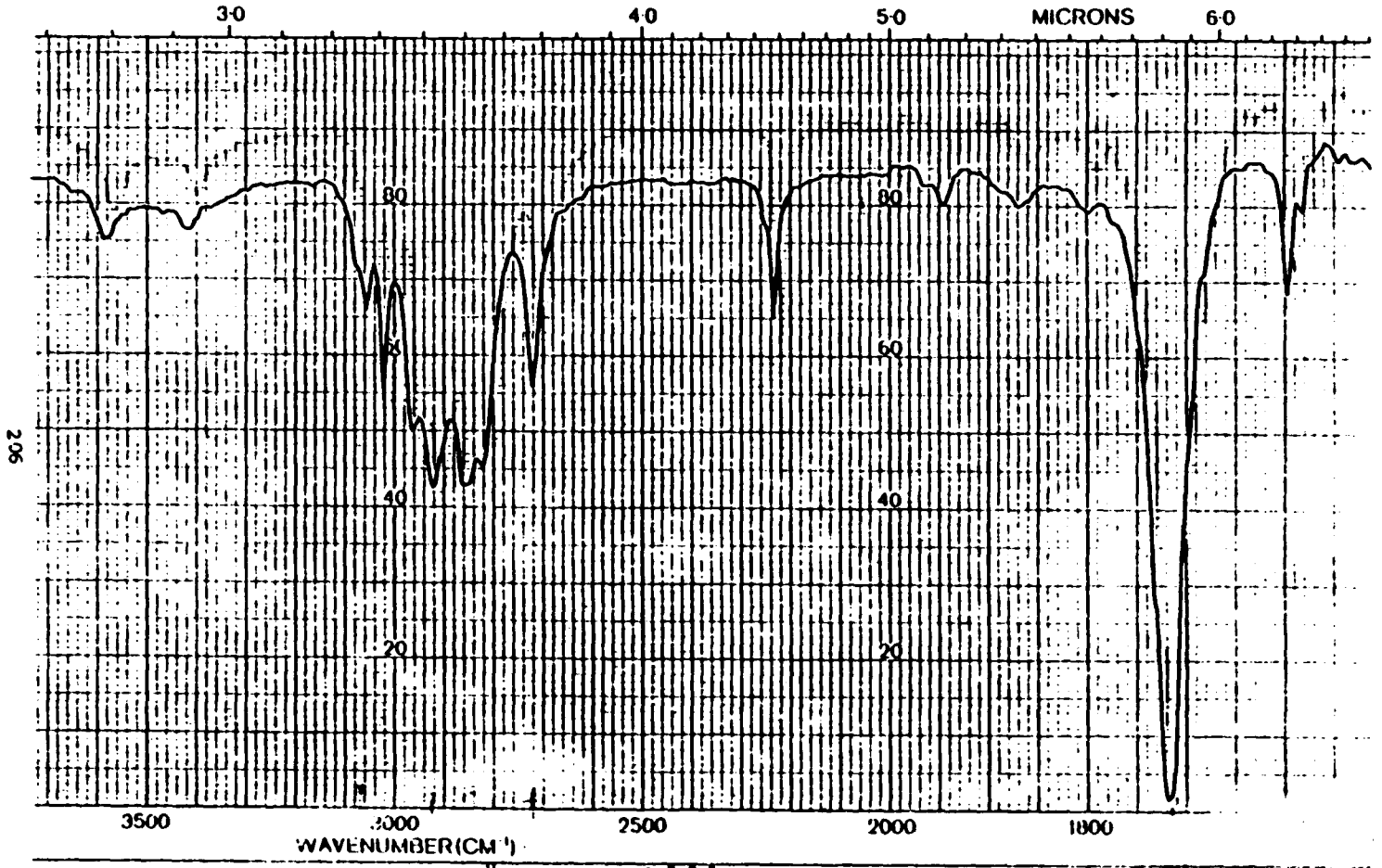
EM-360 60 MHz NMR SPECTROMETER

SPECTRUM AMPL. 10X18 | SWEEP TIME 5 min. | SAMPLE: EN-F-96-2 crude | REMARKS: .5 ml $CDCl_3$ + 1 drop TMS | OPERATOR EN

FILTER 0.1 sec | SWEEP WIDTH 10 ppm or Hz | DATE 10/21/81

RF POWER 0.05 mG | END OF SWEEP 0 ppm or Hz | SOLVENT | SPECTRUM NO.

NMR of Phenylacetaldehyde
(after steam distillation, before final dist.)



EN-F-96-2 Phenylacetaldehyde (before final distln, after steam distillation)

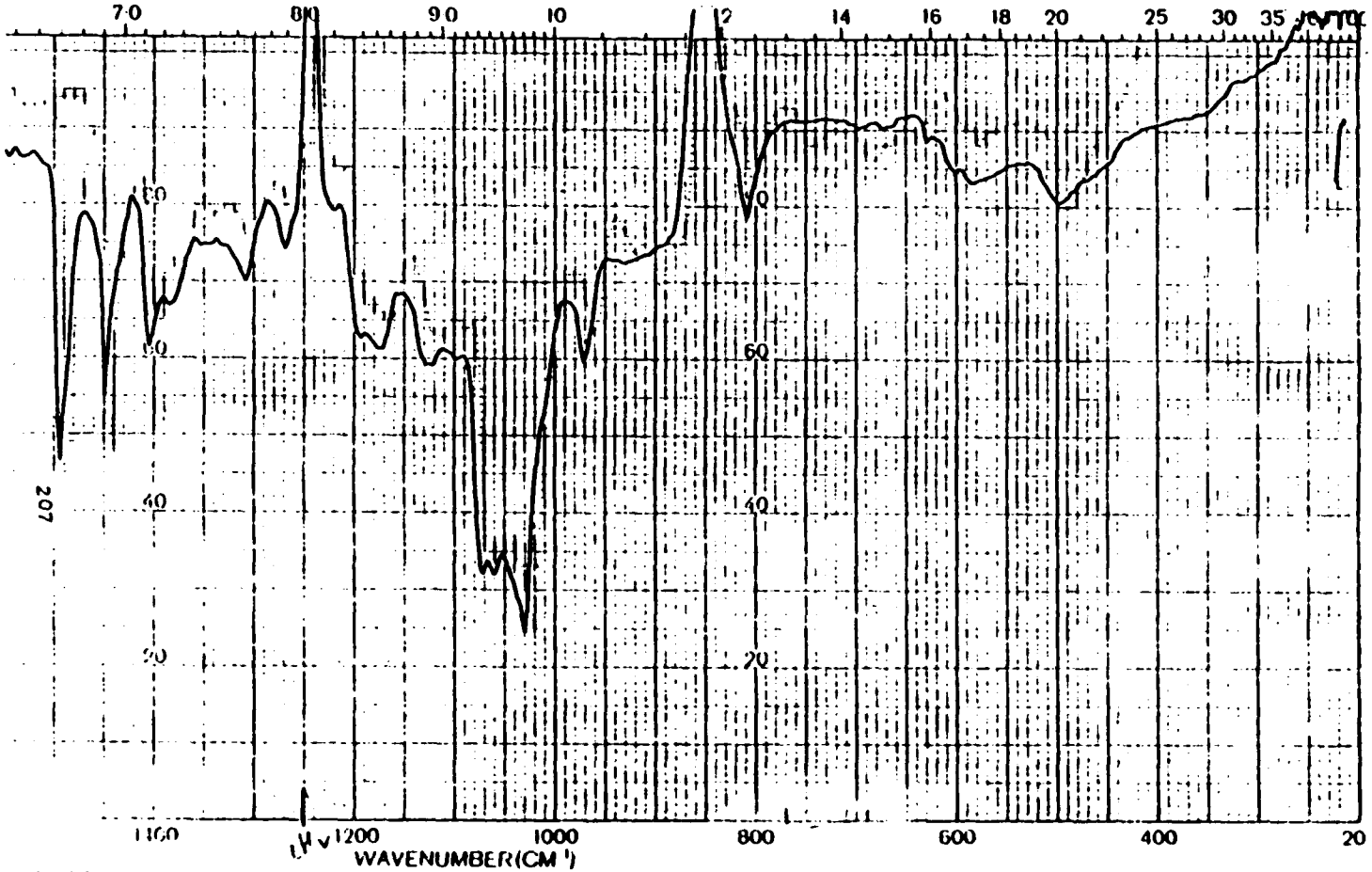
SOLVENT $CDCl_3$

CONCENTRATION Neat sample : $CDCl_3$ 1 : 1

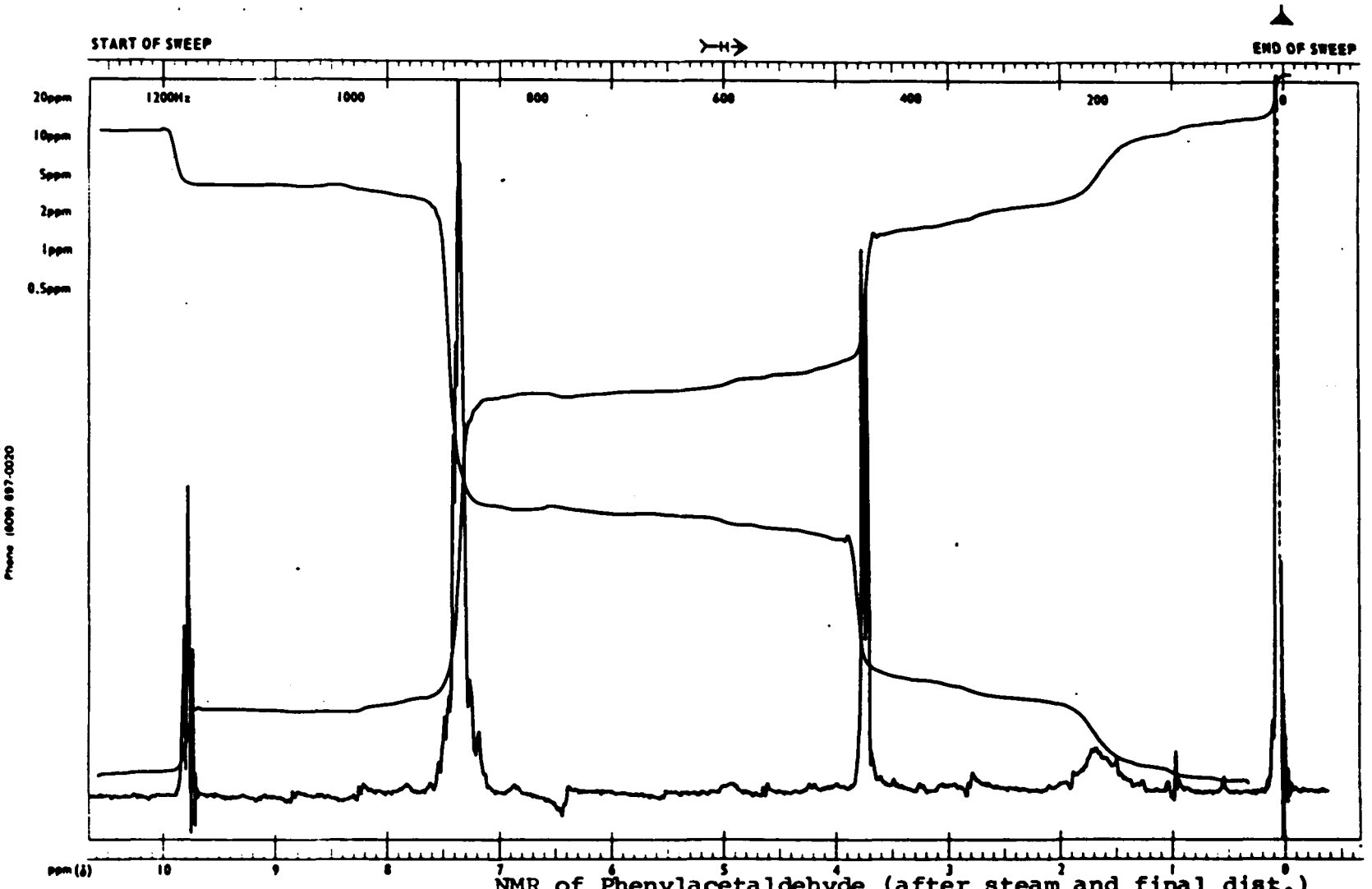
CELL PATH

REFERENCE $CDCl_3$

REMARKS



EN-F-96-2 Phenylacetaldehyde (after steam distillation, before final distillation)	SCAN TIME 4	T SB	PERKIN ELMER
	SLIT med	ORDINATE EXP	CHART No 5100 4367
	OPERATOR EN DATE 10/22/81	TIME CONSTANT	REF No



NMR of Phenylacetaldehyde (after steam and final dist.)

EM-360 60 MHz NMR SPECTROMETER

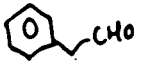
NORELL, INC.
314 ARBOR AVENUE
LANDISVILLE, NJ 08326
Phone (609) 697-0020

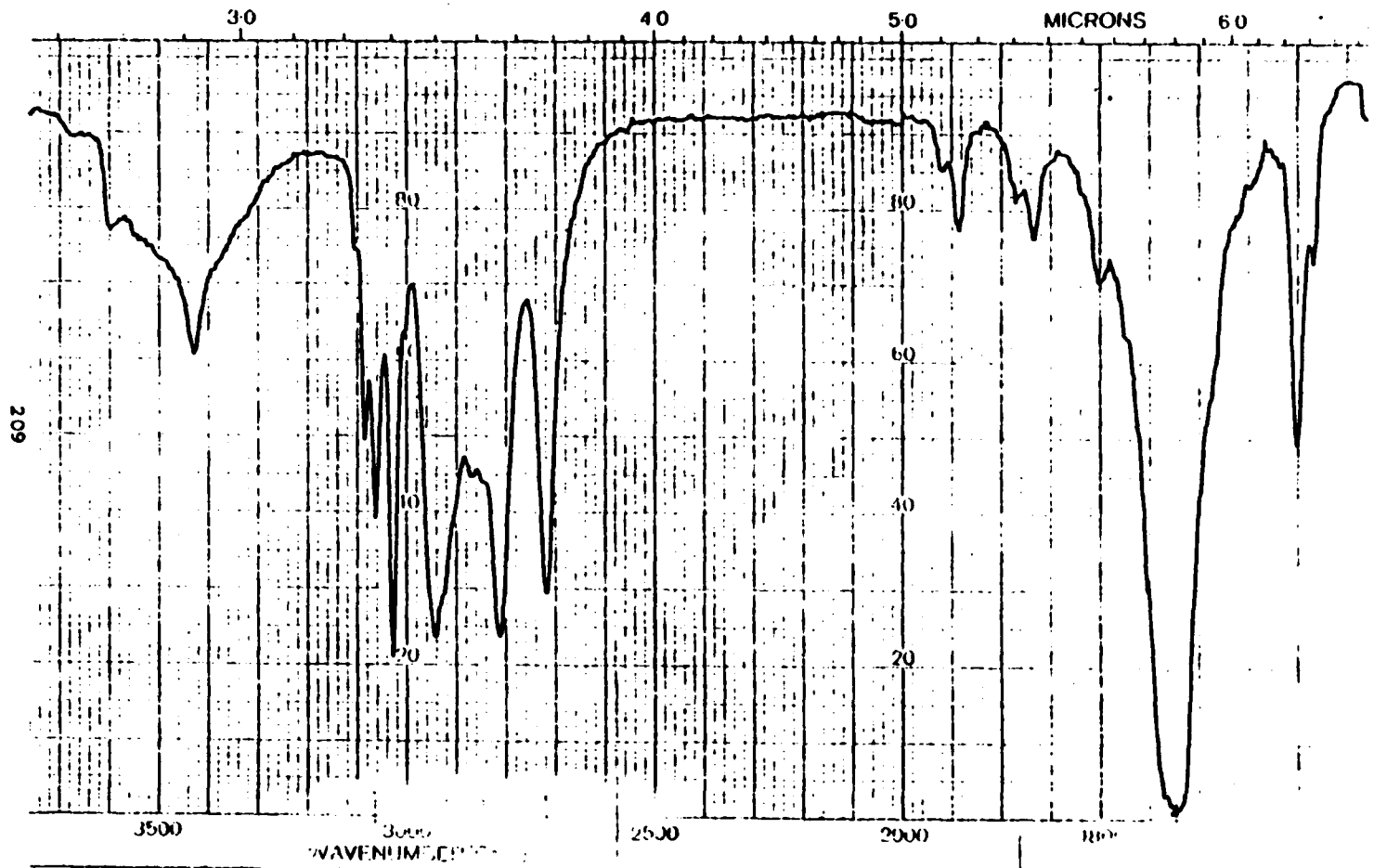
208

CHART # NV EM-360-H-10
PRINTED IN U.S.A.

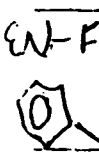
SPECTRUM AMPL. 100 x 2 | SWEEP TIME 5 min. | SAMPLE: EN-F-96-4B | REMARKS: +.5 ml $CDCl_3$ + 1% TMS | OPERATOR EN

FILTER 0.1 sec | SWEEP WIDTH 10 ppm or Hz | DATE 10/21/81

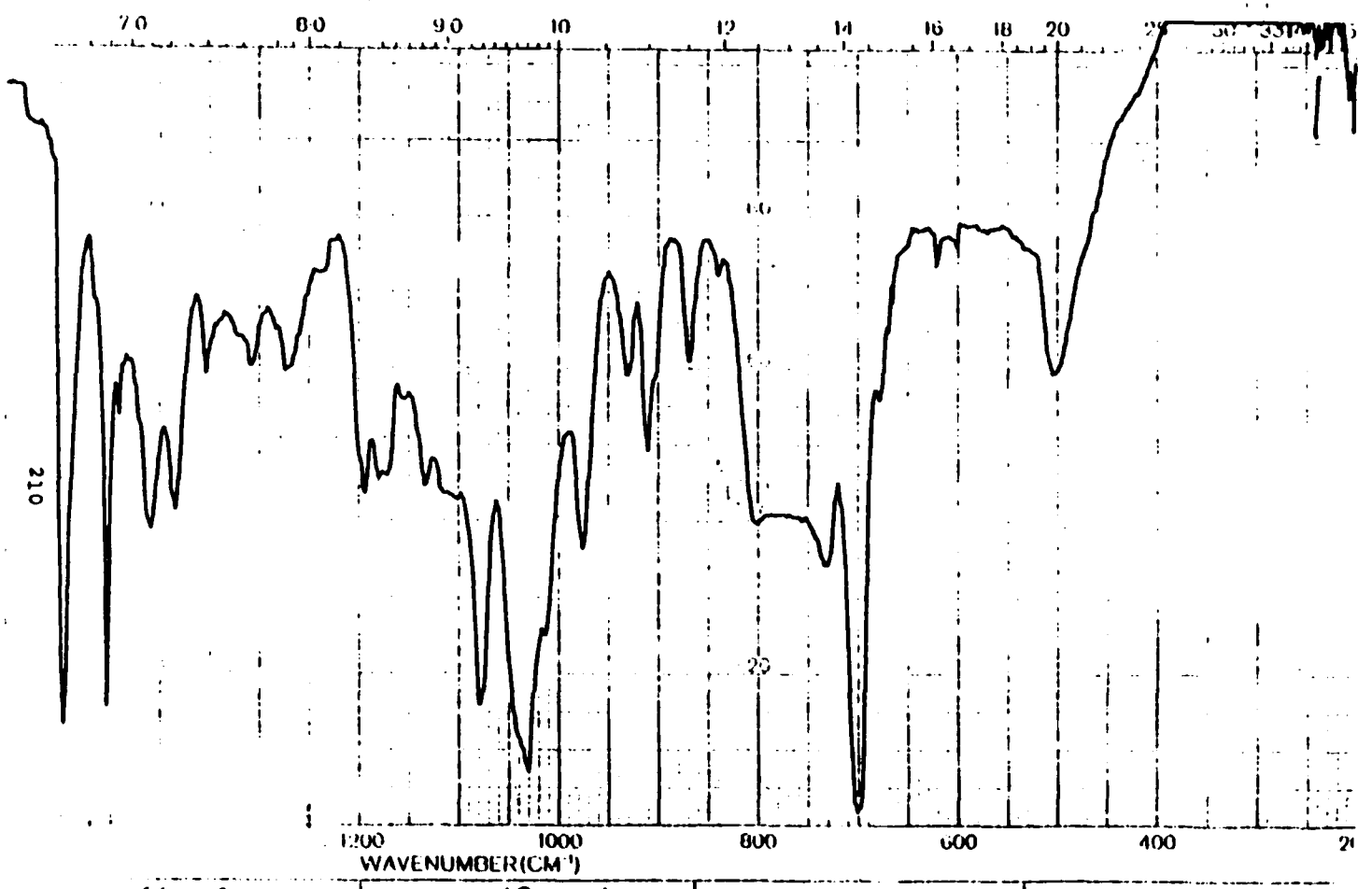
RF POWER 0.05 mG | END OF SWEEP 0 ppm or Hz | SOLVENT:  | SPECTRUM NO.



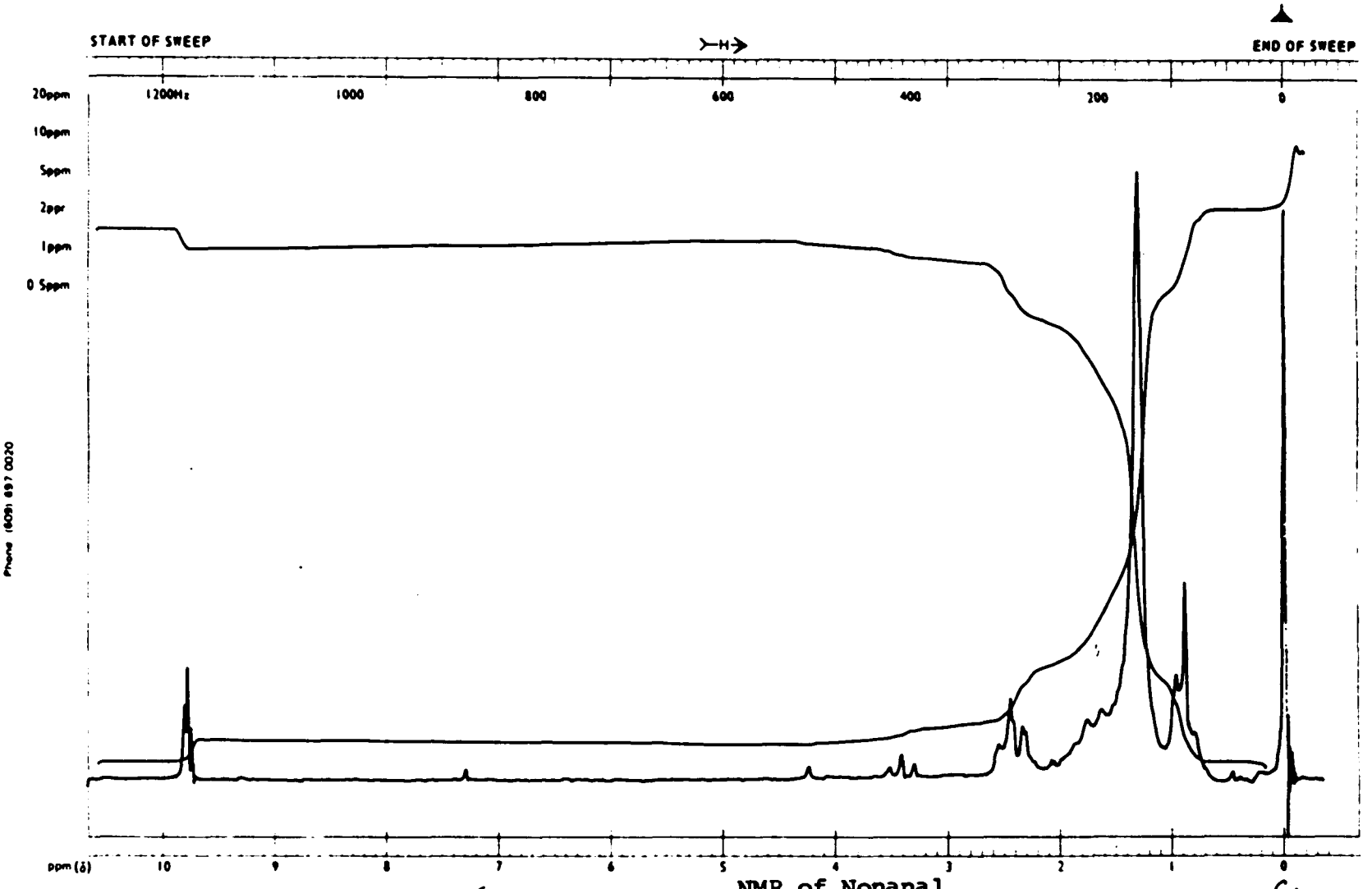
EN-F-96-4B Phenylacetaldehyde (after steam and final distillation).



SOLVENT	CCl_4
CONCENTRATION	ca. 100 : 1
CELL PATH	
REFERENCE	CCl_4



EN-F-96-4B
Phenylacetaldehyde
(after steam / funnel
distillation)



NMR of Nonanal

EM-360 60 MHz NMR SPECTROMETER

NORELL, INC.
314 ARBOR AVENUE
LANDISVILLE N.J. 08326
Phone (609) 697-0020

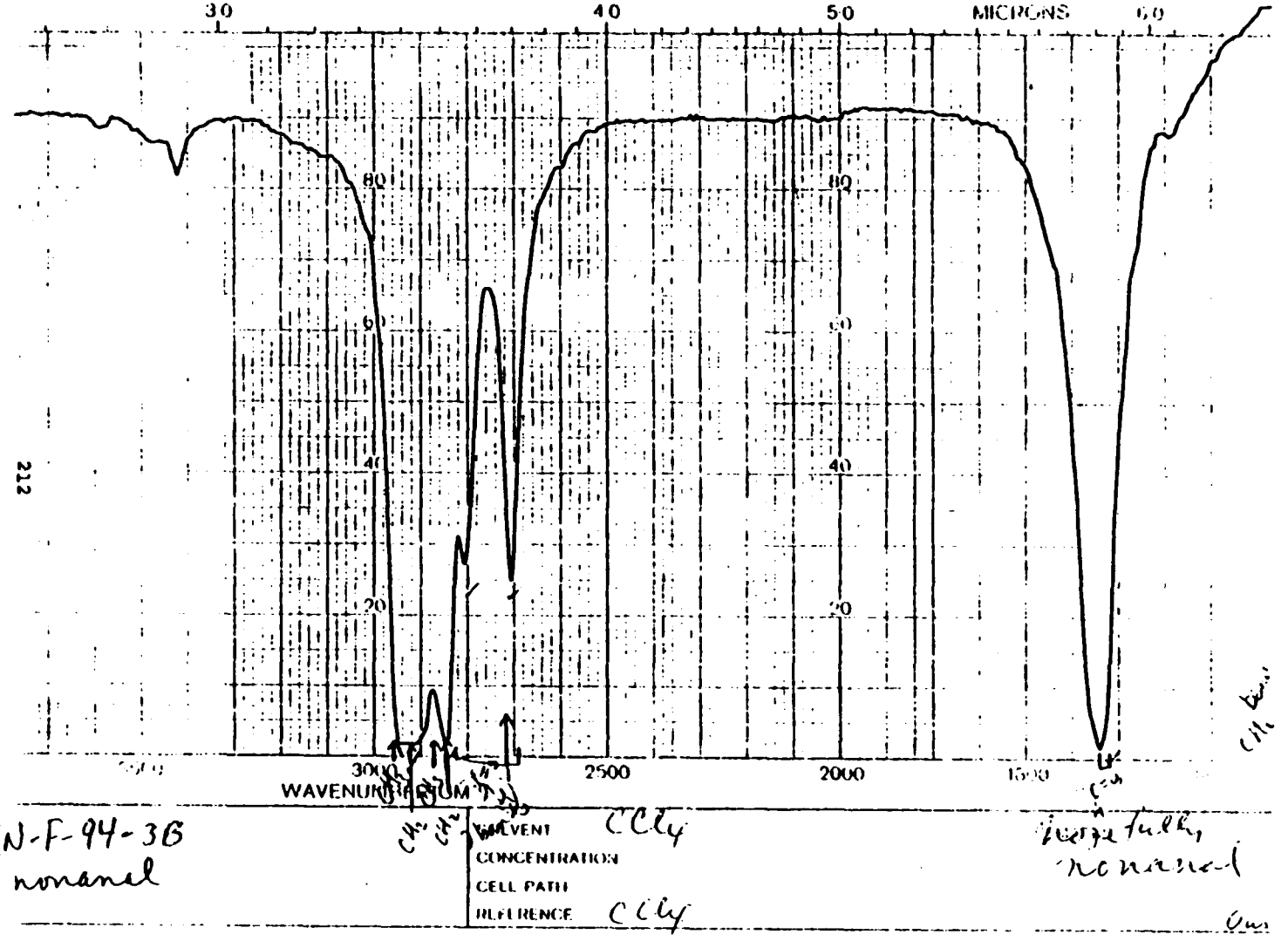
CHART # NV EM 360 R 10
PRINTED IN U.S.A.

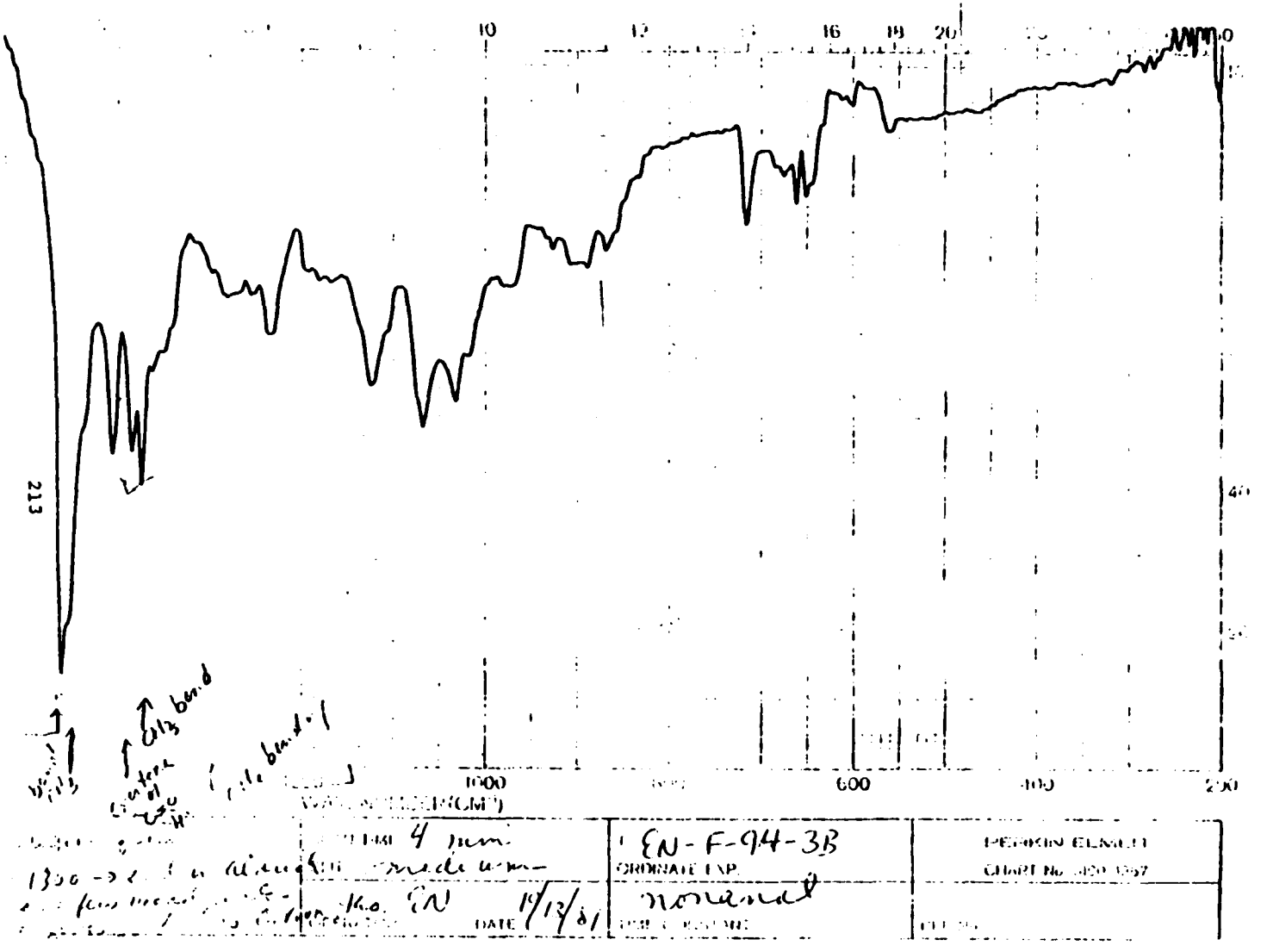
21

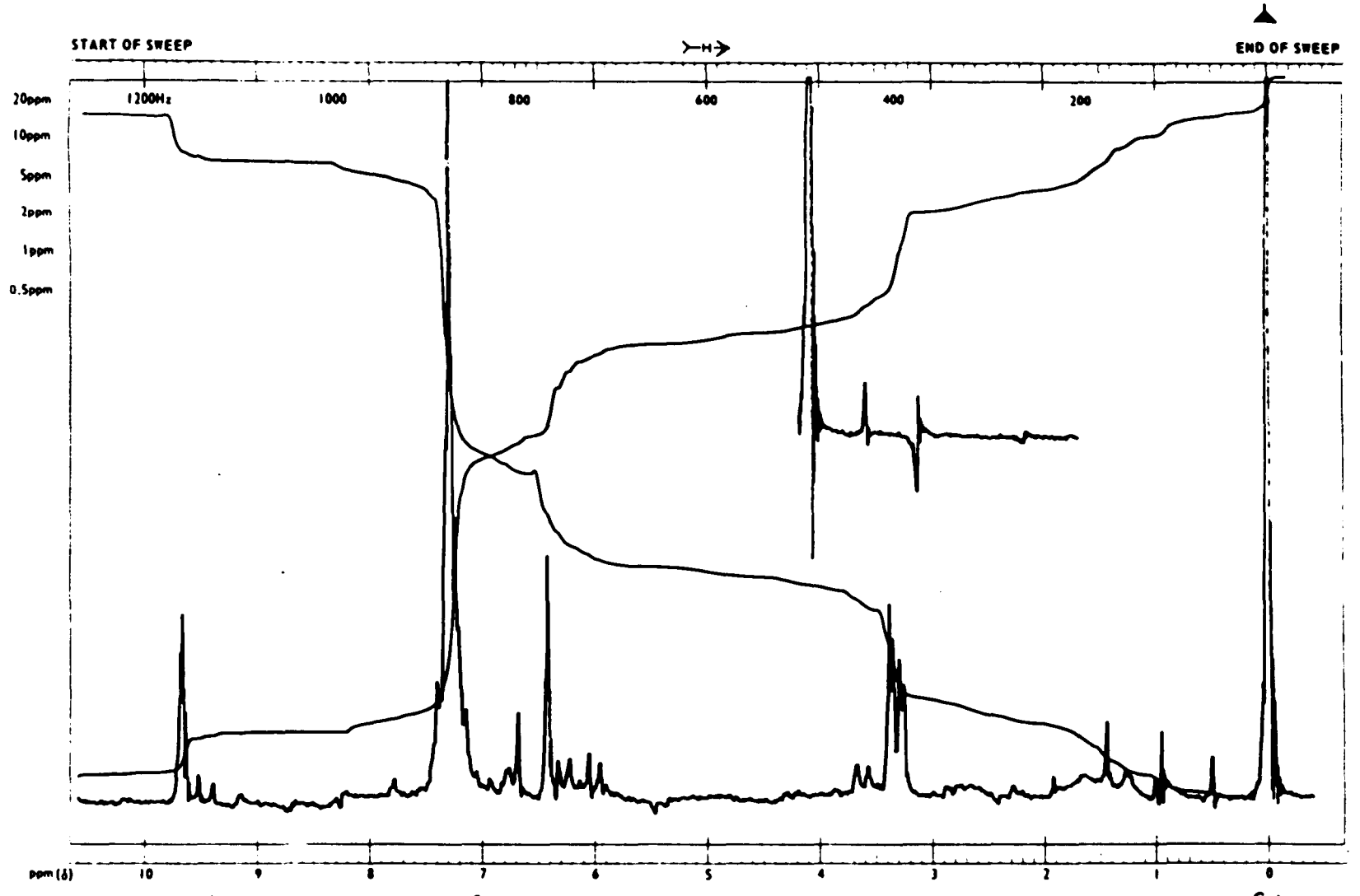
SPECTRUM AMPL. 10 X 10 | SWEEP TIME 5 min. | SAMPLE | REMARKS | OPERATOR GW

FILTER 0.1 sec | SWEEP WIDTH 10 ppm or Hz | GW-F-94-3B | .5 ml $CDCl_3$ | DATE 10/13/81

RF POWER 0.05 mG | END OF SWEEP 0 ppm or Hz | SOLVENT | SPECTRUM NO.


30
40
50
MICRONS
60
80
60
40
20
212
2500
2000
1500
WAVENUMBER (cm⁻¹)
EN-F-94-3B
nonanol
SOLVENT CCl4
CONCENTRATION
CELL PATH
REFERENCE CCl4
liquid film
nonanol


10
12
16
18
20
213
1600
600
EN-F-94-3B
PERKIN ELMER
DATE 10/13/81



EM-360 60 MHz NMR SPECTROMETER

214

NORELL, INC.
314 ARBOR AVENUE
LANDISVILLE N.J. 08326
Phone (609) 697 0020

CHART # NV EM 360 K 10
PRINTED IN U.S.A.

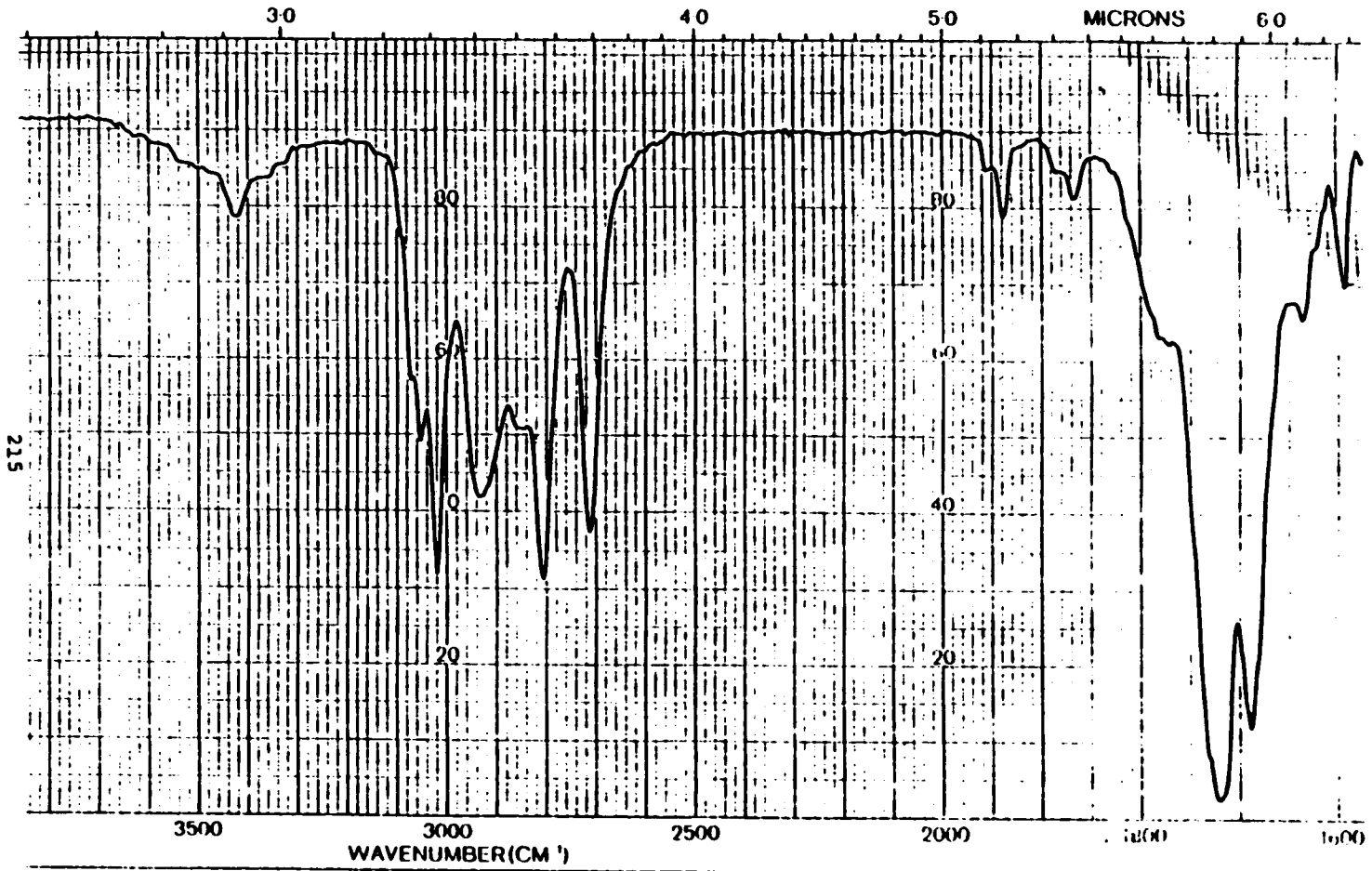
SPECTRUM AMPL. 10 X 16 | SWEEP TIME 5 min. | SAMPLE EN-F-99-4B | REMARKS | OPERATOR EN

FILTER 0.1 sec | SWEEP WIDTH ± 10 ppm or Hz | DATE 11/3/99

RF POWER 0.05 mG | END OF SWEEP 0 ppm or Hz | SOLVENT

NMR of Phenylacetaldehyde (Steam Distillation)

SPECTRUM NO.



EW-F-99-4B

ϕ CH_2CHO (pretty pure)

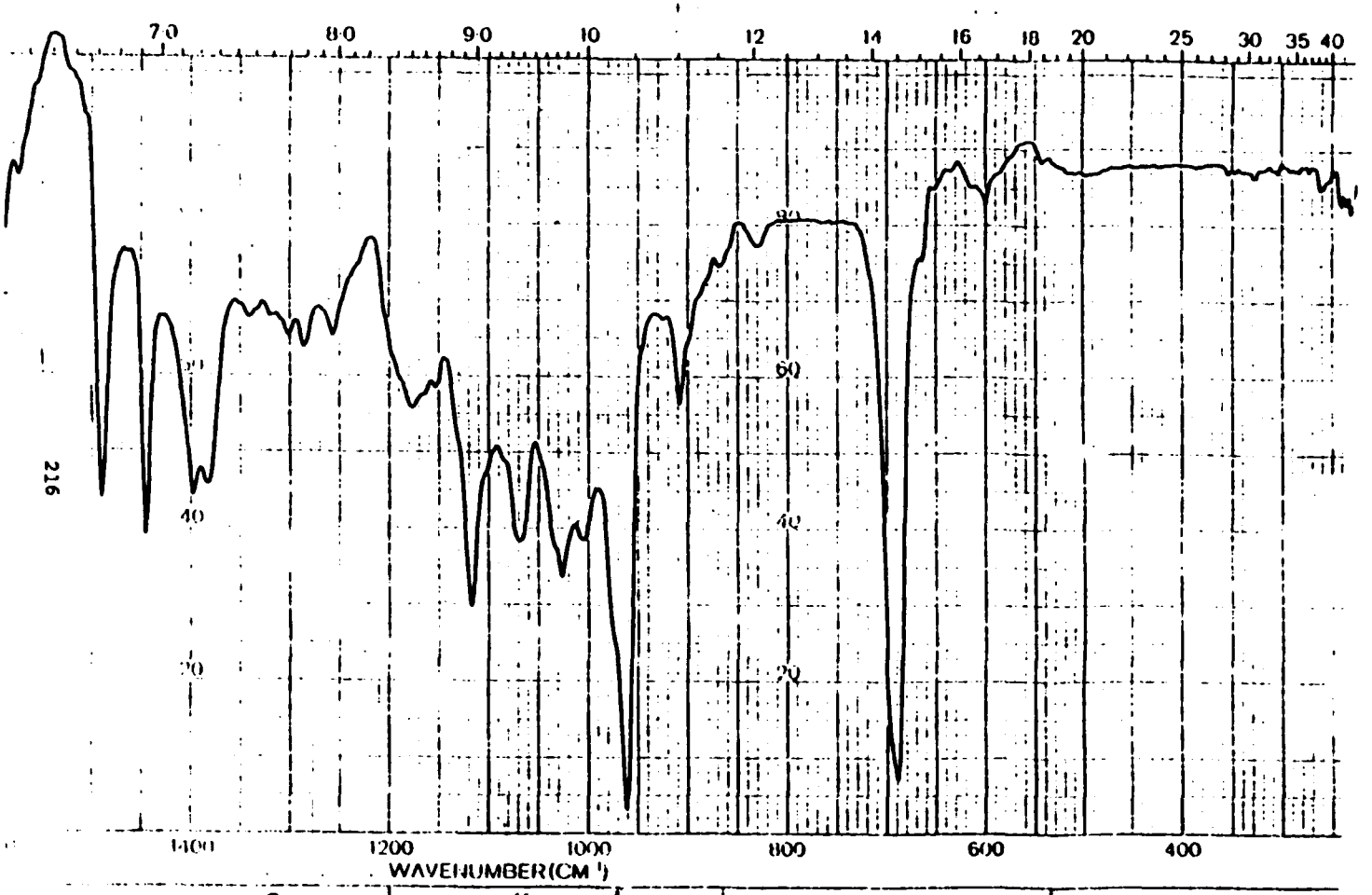
SOLVENT CCl_4 in 100 µl

CONCENTRATION

CELL PATH

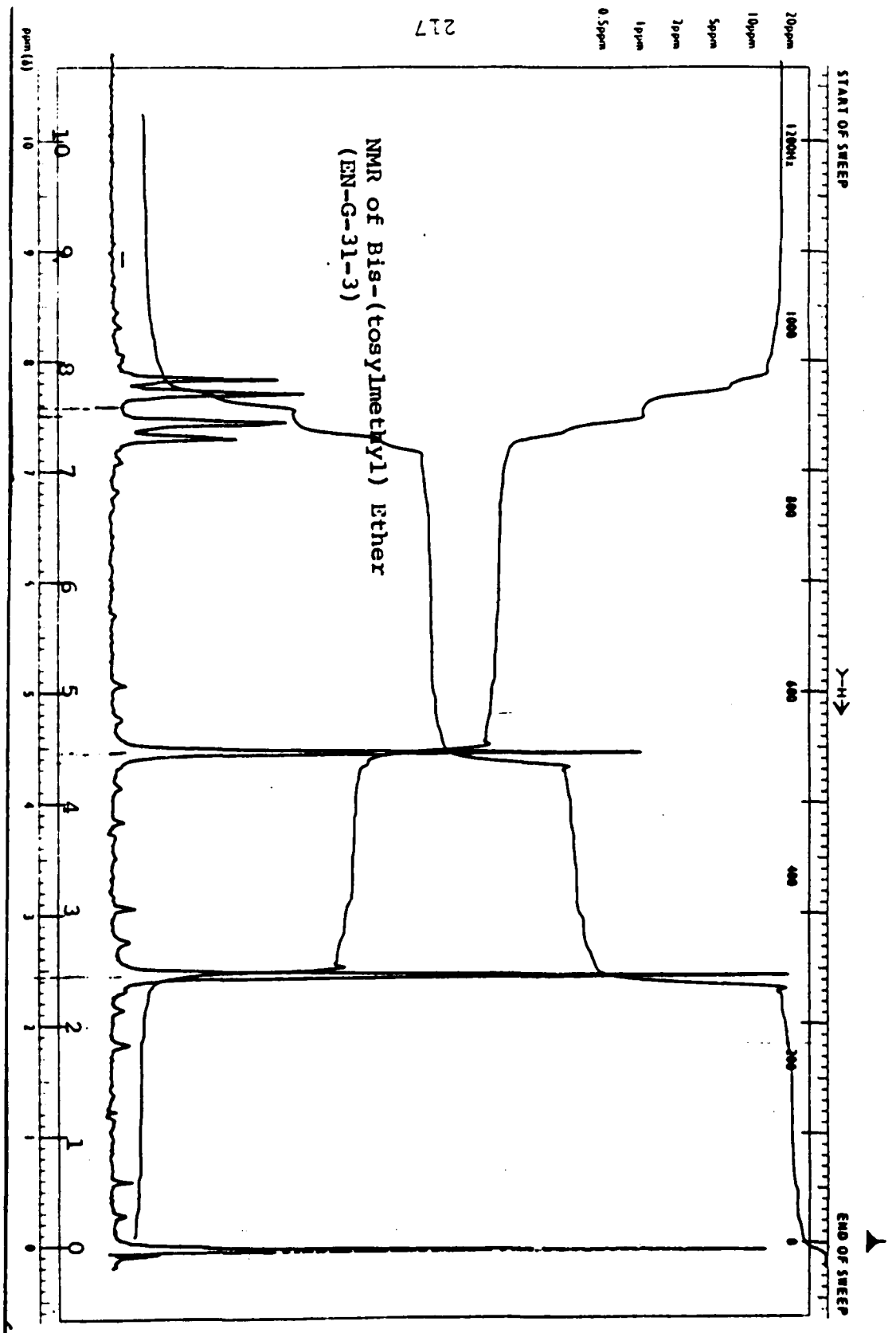
REFERENCE CCl_4

REMARKS

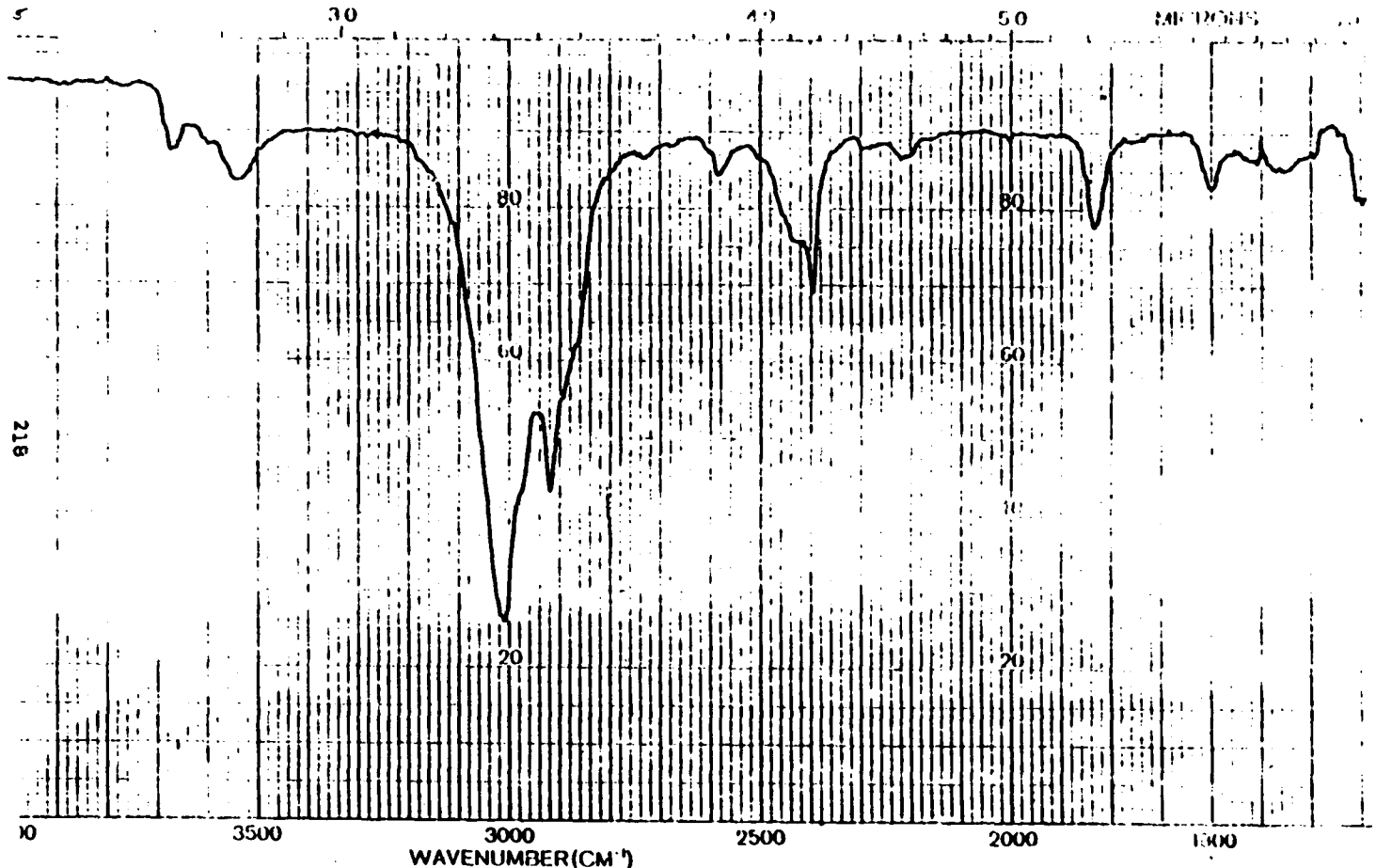


EN-F-99-45

SCAN TIME 4 minutes	T SB	PERKIN ELMER
SLIT medium	ORDINATE EXP	CHART No 5100 4367
OPERATOR EN DATE 11/3/81	TIME CONSTANT	REF No



EM-360 60 MHz NMR SPECTROMETER



SAMPLE EN-G-31-3

ORIGIN

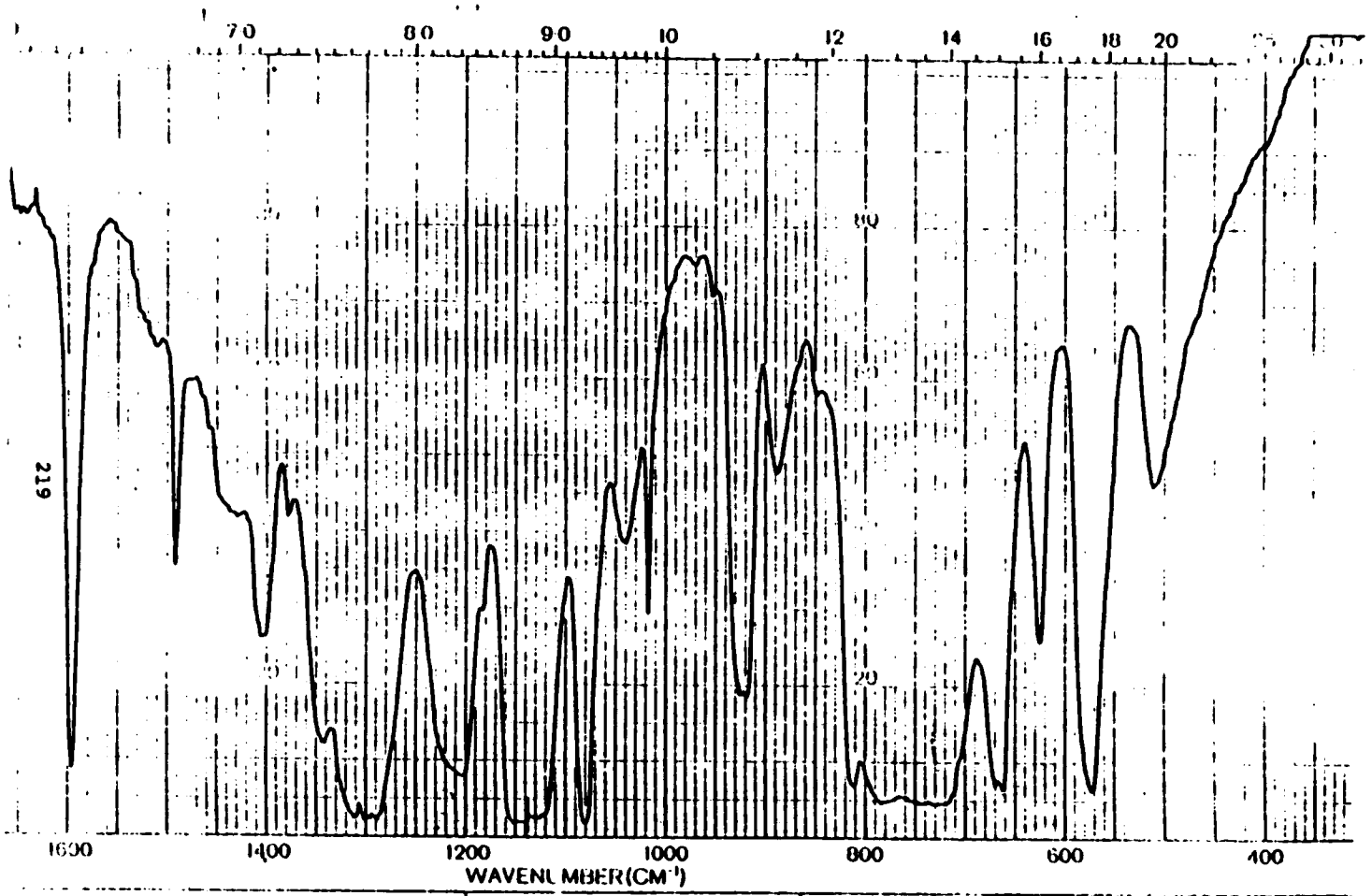
SOLVENT $CHCl_3$

CONCENTRATION

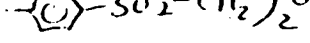
CELL PATH

REFERENCE $CHCl_3$

REMARKS



EN-G-31-3



SCAN TIME 12

SLIT medium

1/4/92

T SB

ORDINATE EXP

PERKIN ELM

CHART No 5100

References

1. Johnson, W.S.; Bass, J.B.; Williamson, K.L. Tet., 1963, 19, 861.

2. Warnhoff, E.W.; Martin, D.G.; Johnson, W.S. Org. Syn.: Coll. Vol. 4, 1963, 162.

3. Hanna, R. Tet. Lett., 1968, 17, 2107.

4. Turro, N. Acc. Chem. Res. 1969, 2, 25.

5. Goheen, D.W.,; Vaughan, W.R. Org. Syn. Coll. Vol. 4, 1963, 594.

6. Sauers, R.R.; Hu, C.K. J. Org. Chem. 1971, 36, 1153.

7. Alper, H.; Pattee, L. ibid, 1979, 44, 2568.

8. Luh, T.-Y.; Lai, C.-H.; Lei, K.-L.; Tam, S.-W. ibid 1979, 44, 641.

9. Hanson, J.R.; Premuzic, E. Angew Chemie. I.E., 1968, 7, 247.

10. Ho, T.-L.; Wong, C.M. Syn. Comm. 1973, 3, 237.

11. Townsend, J.M.; Spencer, T.A. Tet. Lett. 1971, 137.

12 Ho, T.-L. Syn. Comm. 1979, 9, 241.

13 Olah, G.A.; Arvanaghi, M.; Vankar, Y.D. J. Org. Chem. 1980, 45, 3531.

14. Gemal, A.L.; Luche, J.L. Tet. Lett. 1980, 3195.

15. Hutchins, R.O.; Maryanoff, B.E.; Milewski, C.A. J. Chem. Soc. Chem. Comm. 1971, 1097.

16. Spencer, T.A.; Britton, R.W.; Watt, D.S. J. Org. Chem. 1967, 89, 5727.

17. Saitkulova, F.G.; Abashev, G.G.; Lapkin, I.I. Zh. Org. Khim. 1973, 9, 1405.

18. Marvoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. J. Am. Chem. Soc. 1977, 99, 7705.

19. Dubois, J.E.; Lion, C. Tet. 1975, 31, 1227.

20. Dubois, J.E.; Lion, C.; Moulineau, C. Tet. Lett.

1971, 177.

21. Brown, H.C.; Rogic, M.M.; Rathke, M.W. J. Am. Chem. Soc. 1968, 90, 6218.

22. Fieser, L.F.; Dominquez, X.A. J. Am. Chem. Soc. 1953, 75, 1704.

23. Hantzsch, A. Ber. 1890, 23, 1474.

24. Figueras, J. J. Org. Chem. 1966, 31, 803.

25. Waring, A. In "Comprehensive Organic Chemistry", Barton, D. and Ollis, W.D., ed.; Pergamon Press: New York, 1979: Vol. 1, p. 1036.

26 Dick, C.R. J. Org. Chem. 1962, 27, 272.

27. Mehta, M.D.; Miller, D.; Tidy, D.J.D. J. Chem. Soc. 1963, 4614.

28. Blanco, L.; Amico, P.; Conia, J.M. Syn. 1976, 194.

29. Stotter, P.L.; Hill, K.A. J. Org. Chem. 1973, 38, 2576.

30. Gaudry, M.; Marquet, A. Bull. Soc. Chim. Fr. 1969, 4169.

31. House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. J. Org. Chem. 1969, 34, 2324.

32. Djerassi, C.; Scholz, C.R. J. Am. Chem. Soc. 1948, 70, 417.

33. Marquet, A.; Dvolaikzky, M.; Kagan, H.B.; Mamlok, L,; Quannes, C.; Jacques, J. Bull. Soc. Chim. Fr. 1961, 1822.

34. Marquet, A.; Jacques, J. Bull. Soc. Chim. Fr. 1962, 90.

35. Fieser, L.F.; Fieser, M. "Reagents for Organic Synthesis" John Wiley and Sons, Inc.: New York, 1967; Vol I, p. 855.

36. Awang, D.V.C.; Wolfe, S. Can. J. Chem. 1969, 47, 706.

37. Fieser and Fieser, Vol 3, p. 240 (see ref. 35)

38. Calo, V.; Lopez, L.; Pesce, G.; Todesco, P.E. Tet.

1973, 29, 1625.

39. Block, R. Syn. 1978, 140.

40. Armstrong, V.W.; Chishti, N.H.; Ramage, R. Tet. Lett. 1975, 6, 373.

41. Sekiya, M.; Ito, K.; Suzuki, K. Tetr. 1975, 31, 231.

42. Waring, A.J. in "Comprehensive Organic Chemistry", Vol I, p. 1037. (see ref. 25)

43. Ibid, p. 1038.

44. Fort, A.W. J. Org. Chem. 1961, 765.

45. Kosower, E.W.; Cole, W.J.; Wir, G.-S.; Cardy, D.E.; Meisters, G. ibid 1963, 28, 630.

46. Kosower, E.W.; Wu, G.-S. ibid 1963, 28, 633.

47. King, L.C.; Ostrum, G.K. ibid 1964, 29, 3459.

48. Deno, N.C.; Fishbein, R. J. Am. Chem. Soc. 1973, 95, 7445.

49. Sharpless, K.B.; Teranishi, A.Y. J. Org. Chem. 1973, 38, 137.

50. Backvall, J.E.; Young, M.W.; Sharpless, K.B. Tet. Lett. 1977, 3523.

51. Sharpless, K.B.; Teranishi, A.Y.; Backvall, J.E. J. Am. Chem. Soc. 1977, 99, 3120.

52. Authors report yields determined by GLC.

53. San Filippo, J.; Chern, C.I. J. Org. Chem. 1977, 42, 2182.

54. Dr. Berkowitz's Bromo Ketone Grant Proposal, p. 11.

55. Hartford, W.H.; Darrin, M. Chem. Rev. 1958, 58, 1.

56. Cardillo, G.; Shimizu, M. J. Org. Chem. 1977, 42, 4268.

57. Dr. Berkowitz's Bromo Ketone Grant Proposal, p. 11.

58. D'Ascoli, R.; D'Aurie, M.; Nucciarelli, L.; Piancatelli, G.; Scettri, A. Tet. Lett. 1980, 21, 4521.

59. Murayama, E.; Kohda, A.; Sato, T. Chem. Lett. 1978, 161.

60. Kohda, A.; Ueda, K.; Sato, T. J. Org. Chem. 1981, 46, 509.

61. Ponder, B.M.; Walker, D.R. J. Org. Chem. 1967, 32, 4136.

62. Corey, E.J.; Richman, J.E. J. Am. Chem. Soc. 1970, 92, 5276.

63. Calo, V.; Lopez, L.; Valentino, D.S. Syn. 1978, 139.

64. Olah, G.A.; Vankar, Y.D.; Arvanaghi, M. Tet. Lett. 1979, 38, 3653.

65. Stork, G.; Isobe, M. J. Am. Chem. Soc. 1975, 97, 4745.

66. Bordwell, F.G.; Frame, R.R.; Strong, J.G. J. Org. Chem. 1968, 33, 3385.

67. Denis, J.N.; Krief, A. Tet. Lett. 1981, 1431.

68. Wendt, W.; Haegele, W.H.; Simonitsch, E.; Schmid, H. Helva. Chim. Acta. 1960, 43, 1440.

69. Fieser and Fieser, Vol. I, p. 78. (see ref. 35)

70. Horner, L.; Winkelmann, E.H. in "Newer Methods of Preparative Organic Chemistry", Foerst, W. Ed.; Academic Press: New York, 1964; Vol. III, p. 151.

71. Ibid. p. 156.

72. Campaigne, E.; Tullar, B.F. Org. Syn. Coll. Vol. 4. 1963, 921.

73. Dauben, H.J.; McCoy, L.L. J. Am. Chem. Soc. 1959, 81, 4863.

74. Horner and Winkelmann, pp. 159-160.

75. McGrath, B.P.; Tedder, J.M. Proc. Chem. Soc. 1961, 80.

76. Garwood, R.F. In "Rodd's Chemistry of Carbon Compounds", Coffey, S., Ed.; Elsevier Publishing Co.: New York, 1964; Vol. IA, Chapter 2, p. 420.

77. VanTamelen, E.E.; Storni, A.; Hessler, E.J.;

Schwartz, M. J. Am. Chem. Soc. 1963, 85, 3295.

78. Wilkinson, S.G. in "Comprehensive Organic Chemistry" Vol. 1, p. 648 (see ref. 25)

79. Boguslavskaya, L.S. Russ. Chem. Rev. 1972, 41, 740.

80. Guss, C.O.; Rosenthal, R. J. Am. Chem. Soc. 1955, 77, 2549.

81. Dalton, D.R.; Hendrickson, J.B. ; Jones, D. J. Chem. Soc. Chem. Comm. 1966, 591.

82. Dalton, D.R.; Dutta, V.P.; Jones, D.C. J. Am. Chem. Soc. 1968, 90, 5498.

83. Dalton, D.R.; Dutta, V.P. J. Chem. Soc. B 1971, 85.

84. Lasne, M.C.; Masson, S.; Thuillier, A. Bull. Soc. Chim. Fr. 1973, 5, 1751.

85. DeRoocker, A.; DeRadzitzky, P. Bull. Soc. Chim. Belg. 1970, 79(9-10), 531.

86. DeRadzitzky, A.; DeRoocker, A.J.G. U S Patent 3,786,084.

87. Ibid. 3,793,380.

88. Heasley, V.L.; Skidgel, R.A.: Heasley, G.E.: Strickland, D. J. Org. Chem. 1974, 39, 3953.

89. Adam, J.; Gosselain, P.A.; Goldfinger, P. Bull. Soc. Chim. Fr. 1965, 65, 533.

90. Chen, C.T.; Wong, M.Y. CA 1968, 68, 12581.

91. Morrison, G.A.; Qureshi, M.I. Tet. 1972, 4239.

92. Kornblum, N.; Powers, J.W.; Anderson, G.J.; Jones, W.J.; Larson, H.O.; Levand, O.; Weaver, W.M. J. Am. Chem. Soc. 1957, 79, 6562.

93. Kornblum, N.; Jones, W.J.; Anderson, G.J. J. Am. Chem. Soc. 1959, 81, 4113.

94. Nace, H.R.; Monagle, J.J. J. Org. Chem. 1959, 24, 1792.

95. Johnson, A.P.; Pelter, A. J. Chem. Soc. 1963, 520.

96. Jones, D.N.; Saeed, M.A. ibid 1963, 4657.

97. Torssell, L. Tet. Lett. 1966, 4445.

98. Ganem, B.; Boeckman, R.K. Tet. Lett. 1974, 917.

99. Mancuso, A.J.; Swern, D. Syn. 1981, 165.

100. Huang, S.L.; Omura, K.; Swern, D. Syn. 1978, 297.

101. Johnson, C.R.; Phillips, W.G. J. Org. Chem. 1967, 32, 1926.

102. Torssell, K. Acta. Chem. Scand. 1976, 21, 1.

103. Johnson, C.R.; Phillips, W.E. Tet. Lett. 1965, 2101.

104. Torssell, Tet. Lett. 1966, 4445.

105. Fenselau, A.H.; Moffatt, J.G. J. Am. Chem. Soc. 1966, 88, 1762.

106. Harmon, R.E.; Zenarosa, C.V.; Gupta, S.K. Tet. Lett. 1969, 3781.

107. Fieser and Fieser, Vol 1, p. 305 (see ref. 35)

108. Fieser and Fieser, Vol. 2, P. 162. (see ref. 35)

109. Durst, T. in "Comprehensive Organic Chemistry", Vol 3, p. 135. (see ref. 25)

110. Omura, K.; Swern, D. Tet. 1978, 34, 1651.

111. Durst, p. 138. (see ref. 25)

112. Fieser, Vol. 5, p. 266. (see ref. 35)

113. Huang, S.L.; Omura, K.; Swern, D. Syn. 1978, 297.

114. Fieser, Vol. 2, p. 165. (see ref. 35)

115. Mancuso, A.J.; Brownfain, D.S.; Swern, D. J. Org. Chem. 1979, 44, 4148.

116. Corey, E.J.; Kim, C.U. J. Am. Chem. Soc. 1972, 94, 7586.

117. Barton, D.H.R.; Garner, B.J.; Wightman, R.H. J. Chem. Soc. 1964, 1855.

118. Iacona, R.N.; Rowland, A.T.; Nace, H.R. J. Org. Chem. 1964, 29, 3495.

119. Santosusso, T.M.; Swern, D. J. Org. Chem. 1975, 40, 2764.

120. The mechanism shown in equation 19 is slightly different in the paper.

121. Meisenheimer, J.; Ann. 1913, 397, 273.

122. Roberts, J.S. in "Comprehensive Organic Chemistry" pp. 201-203. (see ref. 25)

123. Feely, W.; Lehn, W.L.; Boekelheide, V. J. Org. Chem. 1957, 22, 1135.

124. Feely, W.; Lehn, W.L.; Boekelheide, V. J. Org. Chem. 1957, 22, 1135.

125. Mukaiyama, S.; Inanga, J.; Yamaguchi, M. Bull. Chem. Soc. Jpn. 1981, 54, 2221.

126. Boekelheide, V.; Feely, W. J. Am. Chem. Soc. 1958, 80, 2217.

127. Franzen, V.; Otto, S. Chem Ber. 1961, 94, 1360.

128. Mukaiyama, S.; Inanaga, J.; Yamaguchi, M. Bull. Chem. Soc. Jpn. 1981, 54, 2221.

129. Eisenthal, R.; Katritzky, A.R. Tet. 1965, 21, 2205.

130. Lunt, E.; Katritzky, A.R. ibid 1969, 25, 4291.

131. Cohen, T.; Song, I.H. J. Org. Chem. 1966, 31, 3058.

132. Cohen, T.; Song, I.H.; Fager, J.H.; Deets, G.L. J. Am. Chem. Soc. 1967, 89, 4968.

133. Sliwa, H.; Tartar, A. J. Org. Chem. 1976, 41, 160.

134. Tien, H.-J.; Yeh, M.-Y.; Tien, J.M. J. Chin. Chem. Soc. 1977, 24, 115.

135. Marmer, W.N.; Swern, D. J. Am. Chem. Soc. 1971, 93, 2719.

136. Katritzky, A.R.; Cook, M.J.; Brown, S.B.; Cruz, R.; Millet, G.H.; Anani, A. J. Chem. Soc., Perkin I 1979, 2493.

137. Baumgarten, H.E.; Barkley, R.P.; Chui, S.H.L.; Thompson, R.D. J. Hetero. Chem. 1981, 18, 925.

138. Moriya, B.T.; Pabiot, M.; Pichat, L. J. Labell. C.R. 1981, 18, 963.

139. Berkowitz, W.F.; Sasson, I.; Sampathkumar, P.S.; Hrabie, J.; Choudhry, S.; Pierce, D. Tet. Lett. 1979, 1641.

140. Dalton, D.R.; Jones, D.G. ibid 1967, 2875.

141. Corey, E.J.; Suggs, J.M. ibid 1975, 2647.

142. Snyder, H.R.; Brooks, L.A. Org. Syn. Coll. Vol. 2. 1943, 171.

143. Wilkinson, S.G. in "Comprehensive Organic Chemistry", Vol 1, Chapter 4, p. 866 (see ref. 25)

144. Kobal, V.M.; Gibson, D.T.; Davis, R.E.; Garza, A. J. Am. Chem. Soc. 1973, 95, 4419.

145. Liston, A.J.; Howarth, M. J. Org. Chem. 1967, 32, 1034.

146. Sato, D.K.; Kojima, Y.; Sato, H. ibid 1970, 35, 2374.

147. Eisenthal, R.; Katritzky, A.R. Tet. 1965, 21, 2205.

148. Oswald, A.A.; Guertin, D.L. J. Org. Chem. 1973, 28, 651.

149. Farkas, A.; Mascioli, R.L.; Miller, F.; Strohm, P.F.; J. Chem. Eng. Data 1968, 278.

150. Grobel, B.T.; Seeback, D. Syn. 1977, 357.

151. Lever, O.W. Tet. 1976, 32, 1943.

152. Seeback, D. Angew. Chemie. I.E. 1969, 8, 639.

153. Hase, T.A.; Koskimies, J.K. Aldrich Chem. Acta. 1981, 14, 73.

154. Evans, D.A.; Andrews, G.C. Accts. Chem. Res. 1974, 7, 147.

155. Callear, A.B.; Fleming, I.; Ottewill, R.H.; Wainwright, K.; Warren, S. Chem. Ind. 1974, 910.

156. Seebach, D. Angew. Chemie. I.E. 1979, 18, 239.

157. Stork, G.; Maldonado, L. J. Am. Chem. Soc. 1971, 93, 5286.

158. Evans, D.A.; Truesdale, L.K.; Carroll, G.L. J. Chem. Soc., Chem. Comm. 1973, 55.

159. Hunig, S.; Wehner, G. Syn. 1975, 180.

160. "1981-1982 Aldrich Catalog Handbook of Fine Chemicals" Chemical Co.: Milwaukee, Wisc., 1980; p. 418.

161. Corey, E.J.; Seebach, D. Org. Syn. 1970, 50, 72.

162. Seebach, D.; Corey, E.J. J. Org. Chem. 1975, 40, 231.

163. "1981-1982 Aldrich Catalog", p. 652.

164. "1979 Catalog, Tridom Chemical Inc." Tridom Chemical Inc.: New York, 1978, p. 256.

165. Carlson, R.M.; Helquist, P.M. J. Org. Chem. 1968, 33, 2596.

166. Ogura, K.; Tsuchihashi, G. Tet. Lett. 1971, 34, 3151.

167. Richman, J.E.; Herrmann, J.L.; Schlessinger, R.H. ibid 1973, 3267.

168. Fuji, K.; Ueda, M.; Fujita, E. J. Chem. Soc., Chem. Comm. 1977, 814.

169. Angyal, S.J.; Anderson, L. Adv. Carbo. Chem. 1959, 14, 135.

170. Masuyama, Y.; Ueno, Y.; Okawara, M. Tet. Lett. 1976, 2967.

171. Ager, D.J.; Cookson, R.C. ibid 1980, 1677.

172. Kocienski, P.J. ibid 1980, 1559.

173. Ager, D.J. ibid 1980, 4759.

174. Wade, P.A.; Hinney, H.R.; Amin, N.A.; Vail, P.D.; Morrow, S.D. Hardinger, S.A; Saft, M.S. J. Org. Chem. 1981, 46, 765.

175. Little, R.D.; Myong, S.O. Tet. Lett. 1980, 3339.

176. Gokel, G.W.; Gerdes, H.W. ibid 1979, 3375.

177. Magnus, P.D. Tet. 1977, 33, 2019.

178. Tanaka, K.; Matsui, S.; Kaji, A. Bull. Chem. Soc. Jpn. 1980, 53, 3619.

179. Durst, in "Comprehensive Organic Chemistry" Vol. 3, pp. 174-188. (see ref. 25)

180. Wolfe, S. Accts. Chem. Res. 1972, 5, 102.

181. Meek, J.S.; Fowler, J.S. J. Org. Chem. 1968, 33, 3422.

182. Oae, E.; Kawamura. Bull. Chem. Soc. Jpn. 1963, 36 163.

183. Graybill, B.M. J. Org. Chem. 1967, 32, 293.

184. Parker, A.J. In "Organic Sulfur Compounds," Karasch, N., Ed.; Pergamon Press: New York, 1961; Vol. I, p. 103.

185. Truce, W.E.; Goralski, C.T.; Christiansen, L.W.; Bavry, P.H. J. Org. Chem. 1970, 35, 4217.

186. Venier, C.G.; Barager, H.J. Org. Prep. Proced. Int. 1974, 6, 77

187. Schank, K.; Schmitt, H.-G. Chem. Ber. 1978, 111, 3497.

188. Schank, K.; Schmitt, H.-G. ibid 1974, 107, 3026.

189. Schank, K.; Schmitt, H.-G.; Schroeder, F.; Weber, A. Leibigs 1977, 1116.

190. Schank, K.; Hasenfratz, H.; Weber, A. Chem. Ber. 1973, 106, 1107.

191. Schank, K.; Schmitt, H.-G. ibid 1977, 110, 3235.

192. Schank, K.; Werner, F. Leibigs 1979, 12, 1977.

193. Schank, K.; Werner, F. ibid 1980, 1477.

194. Olapinski, H.; Schaible, B.; Weidlein, J. J. Organomet. Chem. 1972, 44, 111.

195. Lindner, E.; Schardt, K. J. Organomet. Chem. 1974, 81, 145.

196. Lindner, E.; Ansorge, U. J. Organomet. Chem. 1978, 153, 209.

197. Jung, M.E.; Lyster, M.A. J. Org. Chem. 1977, 42, 3761.

198. Parham, W.E.; Anderson, E.L. J. Am. Chem. Soc. 1948, 70, 4187.

199. Fieser and Fieser, Vol. 1, p. 256. (see ref. 35)

200. Chladek, S.; Smrt, J. Chem. Ind. 1964, 1719.

201. Reese, C.B.; Saffhill, R.; Sulston, J.E. J. Am. Chem. Soc. 1967, 89, 3366.

202. von Meyer, E. J. Prakt. Chem. 1901, 63, 167.

203. Bredereck, H.; Bader, E. Chem. Ber. 1954, 87, 129.

204. "The Merck Index", 9th ed.; Merck & Co., Inc.: Rahway, N.J., 1976, p. 1226.

205. Ott, A.C.; Murray, M.F.; Pederson, R.L. J. Am. Chem. Soc. 1952, 74, 1239.

206. Miyashita, M.; Yoshikoshi, A.; Grieco, P.A. J. Org. Chem. 1977, 42, 3772.

207. Stille, W.C.; Kahn, M.; Mitra, A. ibid 1978, 43, 2923.

208. Golinski, J.; Jonczyk, A.; Makosza, M. Syn. 1979, 461.

209. Jonczyk, A.; Banko, K.; Makosza, M. J. Org. Chem. 1975, 40, 266.

210. Drozd, V.N.; Sergeichuk, V.V. J. Org. Chem. U.S.S.R. 1979, 15, 649.

211. Julia, M.; Basioli, C. Bull. Soc. Chim. Fr. 1976, 11-12, Pt. 2, 1941.

212. Kondo, K.; Tunemoto, D. Tet. Lett. 1975, 1397.

213. Watson, S.C.; Eastham, J.F.; J. Organomet. Chem. 1967, 9, 165.

214. Brown, H.C. "Organic Synthesis via Boranes", John Wiley and Sons, Inc.: New York, 1975; pp. 248-249.

215. Griffin, B.E.; Jarman, M.; Reese, C.B. Tet. 1968, 24, 639.

216. Bindra, J.S.; Bindra, R.; "Prostaglandin Synthesis", Academic Press: New York, 1977.

217. Corey, E.J.; Nicolaou, K.C.; Shibasaki, M. J. Chem. Soc., Chem. Comm. 1975, 658.

218. Gerrard, W.; Kilburn, K.D. J. Chem. Soc. 1956, 1536.

219. Langer, S.H.; Connell, S.; Wender, I. J. Org. Chem. 1958, 23, 50.

220. Kelly, D.R.; Roberts, S.M.; Newton, R.F. Syn. Comm. 1979, 9, 295.

221. Olah, G.A.; Gupta, B.G.G.; Malhotra, R.; Narang, S.C. J. Org. Chem. 1980, 45, 1638.

222. Olah, G.A.; Narang, S.C.; Gupta, B.G.G.; Malhotra, R. J. Org. Chem. 1977, 44, 1247.

223. Farkas, A.; Mascioli, R.L.; Miller, F.; Strohm, P.F. J. Chem. Eng. Data 1968, 278.

224. Naumann, K.; Zon, G.; Mislow, K. J. Am. Chem. Soc. 1969, 91, 7012.

225. "Handbook of Chemistry and Physics", 56th ed.; Weast, R.C., Ed.; CRC Press: Cleveland, Ohio, 1975, p. C-76.

226. Shriner, R.L.; Fuson R.C.; Curtin, D.Y.; Morrill, T.C. "The Systemic Identification of Organic Compounds", 6th ed.; John Wiley and Sons: New York, 1980, p. 179.

227. Ibid., p. 537.

228. "Handbook of Chemistry and Physics", p. C-223.