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DIALKYLANILINE N-OXIDES REACTIONS OF DIALKYLANILINES WITH CHIRAL PEROXY COMPOUNDS

KAREN PATTI LONG

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by

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ABSTRACT

DIALKYLANILINE N-OXIDES. REACTIONS OF DIALKYLANILINES WITH CHIRAL PEROXY COMPOUNDS

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A series of N-methyl,N-alkylanilines (where the alkyl group was ethyl, isopropyl, t-butyl, or part of the ring of 1-methyl-1,2,3,4-tetrahydroquinoline) was oxygenated with the chiral peracids (R)- and (S)-2-phenylperbutanoic acid and (1S)-percamphoric acid. Solvent, temperature, and proportion of reagents were varied. The amine oxides formed at -70° in chloroform-ether had small optical rotations. Although the enantiomeric excess of the amine oxide could not be determined in most cases (since the maximum rotations were not known) the enantiomeric excess in the product from the oxygenation of 1-methyl-1,2,3,4-tetrahydroquinoline was about 1%. Asymmetric induction in the oxygenations of the other amines was probably of a similar order of magnitude. The products were not observed to be optically active when ethanol was used as the reaction solvent. The amine oxygenations are compared to the asymmetric oxygenation of sulfides to sulfoxides with chiral peracids.

In order to study the possible asymmetric oxygenation of tertiary anilines with chiral hydroperoxides, conditions were sought which would yield N-methyl,N-alkylaniline N-oxides from the reaction of a tertiary aniline with hydroperoxides. In some cases an amine oxide was obtained, but

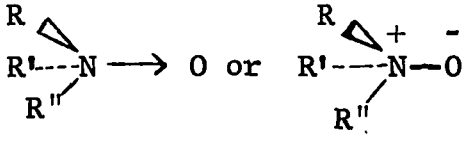
it was heavily contaminated with other nitrogenous products. It was not considered feasible to attempt to study asymmetric synthesis in this reaction. Oxygenation of methyl phenyl sulfide with a mixture of epimeric chiral hydroperoxides (bornyl and isobornyl hydroperoxides, prepared from (-)-bornyl chloride), however, gave optically active methyl phenyl sulfoxide (1% enantiomeric excess of S-(-)).

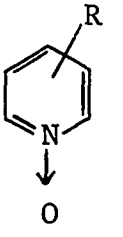
Since very little has been reported about the properties and reactions of aromatic-aliphatic amine oxides, the following observations and exploratory studies with these compounds and their hydrochlorides are described. Most of the amine oxides decomposed readily. Some amine oxide hydrochlorides decomposed in the solid state to a green material even when recrystallized and stored in the cold. When a methanolic solution of some of the amine oxides came in contact with certain metals a deep purple material was produced. Some amine oxide hydrochlorides appeared to form a stable half hydrate. Preliminary work on a study of the relative hydrogen bonding basicities of amine oxides to chloroform was carried out using nmr. A partial resolution of N-methyl,N-isopropylaniline N-oxide was accomplished. The medium to strong infrared band at 950-970 cm^{-1} assigned by others as an N-O stretch, on the basis of a comparison of the spectra of a limited number of amine oxides and their hydrochlorides with the spectra of the corresponding amines and amine hydrochlorides was found to be significantly decreased or absent in the N-methyl,N-alkylaniline N-oxides and N-oxide hydrochlorides with α-branched alkyl groups.

I. DIALKYLANILINE N-OXIDES

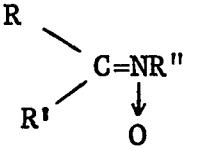
Introduction

Amine oxides were first discovered at the end of the nineteenth century.[1-7] The term amine oxide has not been clearly defined. It is usually taken to include all compounds which have an oxygen atom bonded to the nitrogen of a tertiary amine (general structures A-C). Nitrones (D) can be included, but are usually considered as a separate category of compounds, although some of the reactions they undergo are similar to those of certain heteroaromatic amine oxides (C).





C



D

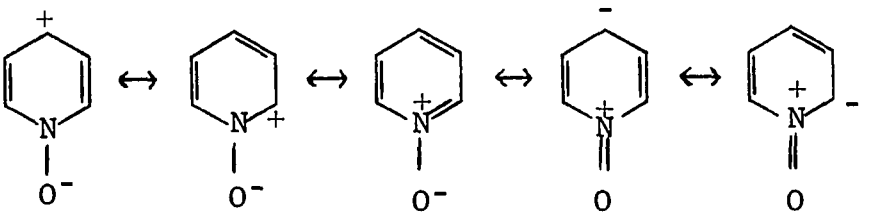
A (R,R',R" = alkyl)

B (R = aryl, R',R" = alkyl or aryl)

There are two ways to classify amine oxides; either according to the nature of the N-O bond[8] or according to the nature of the substituents on the nitrogen.[9] This matter of classification can be quite confusing. In most articles the only way to tell what type of amine oxide is meant by "aromatic amine oxide" is to find out what particular compound is being discussed.

When classified according to N-O bond type, amine oxides of types A and B are similar and different from C type compounds. The N-O bond of C has much more double bond character than that of A or B as observed by ultra-

violet and infrared studies, reactivity, and various other properties. This is due to the interaction of the N-0 bond with the ring in C which may be visualized by the following resonance structures.



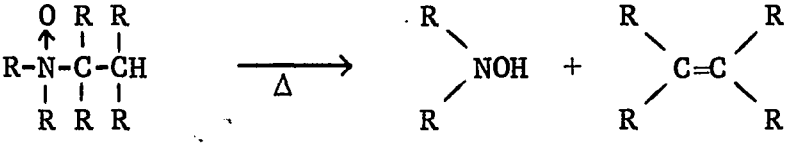
Therefore, by N-0 type classification, types A and B are aliphatic and type C is aromatic.

Classification according to nitrogen substituent type separates types A, B, and C into three distinct groups. Here type A is an aliphatic amine oxide, type B aromatic (sometimes called aromatic-aliphatic for clarity) and type C is heterocyclic or heteroaromatic. These designations will be used in this thesis since the attention here is more directed toward the nitrogen substituents than toward the nature of the N-0 bond.

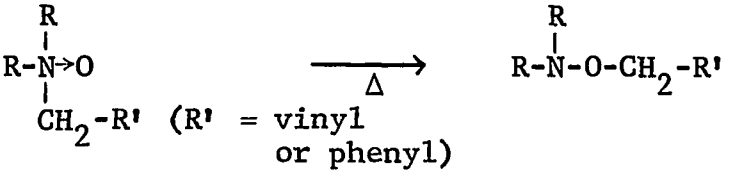
This work deals almost exclusively with amine oxides of the aliphatic-aromatic type. Aromatic-aliphatic amine oxides have been the least studied of all the classes. Long chain aliphatic amine oxides, such as N,N-dimethyldodecylamine oxide have been explored by industrial firms primarily for their utility as detergents, surfactants, dispersing agents, and foam stabilizers.*[10-13] Several N-oxides of

* The author will vouch for their marvelous ability to stabilize foams produced on attempted extraction from an organic solvent into water.

alkaloids have been studied to determine the effect of this functional change on the biological activity of the parent amines.[14-16] Other aliphatic amine oxides have been made primarily for investigating the Cope elimination reaction (eqn 1).[17] Heteroaromatic amine oxides have proven quite useful in synthetic routes to substituted heterocycles and some have been found to have antibacterial and other physiological properties.

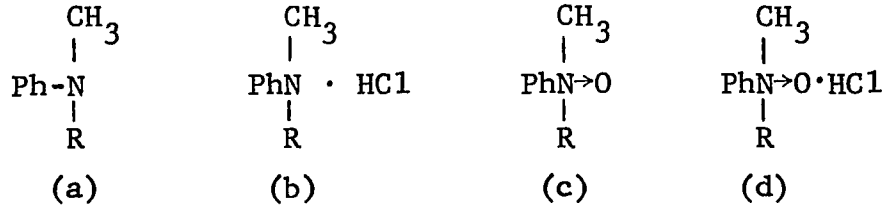
(1) 

Many of the aromatic-aliphatic amine oxides which have been synthesized have been prepared[18-21] in order to study the Meisenheimer rearrangement (eqn 2). This rearrangement occurs only when one of the groups on the nitrogen

(2) 

in the N-oxide is allylic or benzylic. Most of the other aromatic-aliphatic amine oxides which have been prepared have been N,N-dimethyl or diethyl substituted.[7a,23-26] Methyl, ethyl, and n-propyl substituents were incorporated into some unsymmetrical amine oxides prepared by Meisenheimer.[22,27] The nitrogen was included in a ring in kairoline N-oxide (5c)[27] and diphenylpiperazine dioxide.[28] Very few aniline, N-oxides with α-branched alkyl substituents have been reported.[21,29] Involved in this thesis are

the compounds listed below.* N-methyl, N-isopropylaniline, N-oxide (3c) and N-methyl, N-t-butylaniline, N-oxide (4c)** and their derivatives are new compounds.



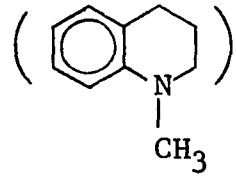
(a) (b) (c) (d)

1 (R = CH_3)

2 (R = Et)

3 (R = i-pr)

4 (R = t-bu)

5 

Our initial interest in these amine oxides, however, did not rest solely in their properties, reactions, or industrial and biological significance but in the fact that an unsymmetrically substituted tetrahedral nitrogen constitutes a chiral center. Amine oxides (N-methyl, N-ethylaniline, N-oxide, 2c) were first resolved in 1908.[30] If the oxygen atom were added by means of a chiral oxidizing agent to a tertiary amine containing three different R groups, one enantiomer of

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* The reader should note that these compounds are listed and numbered so as to facilitate easy recall. Compounds with the number 1 are derivatives of the N-methylalkylaniline with a 1-carbon alkyl group, i.e., N,N-dimethylaniline. Compounds numbered 2 are the N-methyl, N-ethylaniline derivatives, etc. Compounds numbered 5, however, are 1-methyl-1,2,3,4-tetrahydroquinoline (kairoline) derivatives.

** N-methyl, N-t-butylaniline, N-oxide was isolated only as its hydrochloride.

the amine oxide might be formed in excess, giving optically active amine oxides.

There has been much recent interest in asymmetric induction reactions as evidenced by the increasing number of articles and reviews on the subject.[31-36] Amine oxides, optically active only at nitrogen, have never been prepared by an asymmetric synthesis. The tertiary arylalkyl amines were chosen for these studies due to the relative ease of obtaining tertiary amines with three groups of different steric and electronic characteristics.

In view of the relative deficiency of literature on aromatic-aliphatic amine oxides and because a discussion of the properties of these compounds and their derivatives is necessary to the understanding of the difficulties encountered in the oxidations of amines with chiral peroxy compounds, Section I includes some review of the literature of aromatic-aliphatic amine oxides and the author's experience with these compounds. Section II is devoted to oxidations of tertiary amines with chiral peracids. The reactions of tertiary amines with hydroperoxides are in Section III. Included also in Section III is the oxidation of a sulfide with a chiral hydroperoxide which has been done as a preliminary to further work which may be carried out in these laboratories.

Preparation

The direct oxidation of a tertiary amine is the most general method of preparation of amine oxides. The oxidizing agent is usually aqueous hydrogen peroxide or an organic peracid but mono-persulfuric acid (Caro's acid),[24,27,37-40] ozone,[41,42] and periodate[43] have also been used. The uncatalyzed reaction of tertiary amines with hydroperoxides

has not been reported to give amine oxides. However, in two recent papers[44,45] Group VB and VIB metal catalysts have been used to catalyze this reaction. In Section III of this thesis, work by the author on both catalyzed and uncatalyzed oxidation of tertiary anilines with hydroperoxides is described.

Tertiary aliphatic amines are oxidized readily with hydrogen peroxide in water, alcohol, or acetic acid solvent at room temperature or below. Aromatic amines are less readily oxidized; reaction with hydrogen peroxide usually requires heat and longer reaction times. Oxidation by peracids, however, is rapid at room temperature or below and even takes place at -78° (see Section II). Increased steric bulk around the nitrogen slows the oxidation. An ortho methyl group in dimethylaniline greatly reduces its ease of N-oxygenation with Caro's acid and dimethyl-vic-m-xylidine (2,6,N,N-tetramethylaniline) remains unchanged under the reaction conditions.[37] A steric effect on the rate of both hydrogen peroxide and peracid oxidation of the N-methyl, N-alkylanilines in the present work was noted. Aromatic nitrogen heterocycles are still more difficult to oxidize and usually require peracids or hydrogen peroxide in glacial acetic acid to effect the N-oxygenation.

Since hydrogen peroxide is the least expensive and most readily available oxidizing agent, its use is usually preferred whenever possible. Several patents have been obtained in recent years for the use of hydrogen peroxide with alkali metal phosphates and bicarbonate,[46] formic acid esters,[47] inorganic per-compounds of the acid-forming elements of Groups VA, VIA, VIB and VIII,[48] or diethylenetriaminepentacetic acid[49] to oxidize amines to amine oxides.

Increased yields over the use of hydrogen peroxide alone or oxidation of less reactive amines are claimed. The oxidation of N,N-dimethylaniline with hydrogen peroxide, catalyzed by selenium dioxide in the presence of perchloric acid has also been found to give amine oxide.[50]

References to the preparation of various amine oxides are included in several reviews. A review by Swern[16] is concerned with those amines oxidized with peracids, primarily aliphatic-aromatic amines and heterocyclic aromatic amines. Freytag[51] has discussed the oxidation of some aliphatic and aliphatic-aromatic amines with either hydrogen peroxide or peracids. References to trialkylamine oxides whose elimination reactions have been studied (primarily N,N-dimethylalkylamine oxides) may be found in Cope's review of amine oxide pyrolysis[17] and in Smith's book on open chain organic nitrogen compounds.[52] Culvenor[9] summarized the preparations of different types of heterocyclic amine oxides up to 1953. An FMC Corporation publication on organic peracids[53] explores the patent literature from 1953 to 1963 and reports the preparations of a wide variety of functionally substituted heterocyclic amine oxides with peracids. An excellent general source for the preparation of heterocyclic amine N-oxides is the book by Ochiai.[8]

Other methods for the preparation of amine oxides which may be worth mentioning, although they do not have the wide applicability of N-oxygenation, are the reaction of alkyl halides with hydroxylamines (eqn 3)[40,54] and the reaction of alkyl nitro-compounds with dialkylzinc reagents (eqn 4).[55]

(3) $3NH_2OH + 3CH_3I \rightarrow (CH_3)_3N{\rightarrow}O \cdot HI + 2NH_2OH \cdot HI$

(4) $EtNO_2 + Et_2Zn \rightarrow Et_3N \rightarrow O + ZnO$

For heterocyclic N-oxides, several synthetic routes not involving direct oxidation of the amine are often available. Most of these involve cyclization reactions.[8]

Initially, N,N-dimethylaniline (1a), N-methyl, N-ethylaniline (2a), and N-methyl, N-isopropylaniline (3a) were oxidized at about 45° with 30% hydrogen peroxide in ethanol to obtain amine oxides for comparison with those from the reaction of the amines with chiral peracids (Section II). A definite decrease in oxidation rate was noticed on increasing the steric bulk of one alkyl group.

As obtained from these reactions, the amine oxides were brown oils. Amine oxides 1c[25] and 2c[27] have been reported to be white solids. Since in this work these extremely hygroscopic amine oxides were obtained by evaporation of an aqueous solution, it was difficult to get them completely dry. Small amounts of impurities were also detectable in some cases by nmr. Whether these impurities were formed as by-products of the reaction or by decomposition of the amine oxides either during the long heating (up to 48 hrs) at 45° or after workup is not known. The amine oxide samples did undergo decomposition on standing at room temperature and slowly decomposed when stored in a desiccator in a refrigerator with occasional exposure to air. The impurities were not identified.

At one point in this research it was decided to take advantage of the series of amines 1-5a which had been prepared and determine the relative basicities of the amine oxides which could be obtained from them.* Only the

* The method will be discussed under the topic of nmr spectra.

basicity of 1a had been reported in the literature.[56] Pure dry samples of amine oxide were needed. The amine oxides obtained from oxidation of the tertiary amines with 30% hydrogen peroxide were not satisfactory.

N,N-dimethylaniline N-oxide (1c) was prepared in pure dry form by reaction of the amine at 60-70° with 30% hydrogen peroxide in acetic anhydride according to the procedure of Belov and Savich.[25] Dry recrystallized 1c, sealed in bottles in a dry atmosphere and stored over phosphorous pentoxide in a desiccator under refrigeration, remained unchanged for at least one year.

From the appearance of the nmr spectrum, 3c prepared by the same method was accompanied by at least one other major product. Oxidation of the amine (3a) with monoperphthalic acid at 8° yielded 3c as a pale yellow oil which contained a small amount of impurity, possibly N-methyl, N-phenylhydroxylamine. The product solidified over a ten day period in the refrigerator in an evacuated desiccator over phosphorous pentoxide after the addition of a few drops of absolute ethanol.* The nmr of the slightly yellow oily solid showed more of the original impurity and a new component, exhibiting a weak doublet at 1.15 ppm (possibly propene).

Meisenheimer was able with difficulty to obtain pure dry crystalline 2c by slow recrystallization from dry benzene containing one drop of absolute ethanol.[27] However, recrystallization of the isopropyl analog 3c was attempted here from dry benzene-absolute ethanol, carbon tetrachloride-dry ether, chloroform-dry ether, ethyl acetate-dry ether, dry

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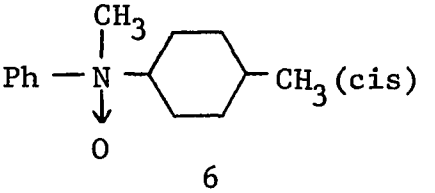
* This technique was used by Meisenheimer to obtain 2c as a solid.[27]

dimethylsulfoxide-dry ether, and dry acetone without success. Some amine oxides crystallize as the hydrate. Berti[57] claims that 6 is obtained as a crystalline hydrate by



6

crystallization of the dried oil from ether, half saturated with water. Such a procedure was also unsuccessfully tried here for 3c. Meisenheimer claimed that the crystals of 2c which he obtained were water free.

While handling the amine oxides during attempted recrystallization decomposition increased, even at room temperature. (The solutions were never warmed.) Since the basicity studies were not crucial to this research, recrystallization attempts were eventually abandoned.

N-methyl, N-ethylaniline N-oxide (2c) was likewise prepared in solid form by reaction of the amine (2a) with monoperphthalic acid and evaporation of an ethanolic solution in a vacuum desiccator over phosphorous pentoxide. The pale yellow slightly oily solid had a melting point of 70-75° (lit.[27] mp 102-103°). After three weeks of cold storage in a vacuum desiccator over phosphorous pentoxide, thin layer chromatography showed a barely visible trace of a single impurity. The amine oxide, however, continued to slowly discolor and deteriorate to an oil on long storage. From this oil a large quantity of N-methyl, N-ethylaniline (2a) was isolated.

Amine oxides are not known for great stability. The Cope elimination reaction to give olefins and hydroxylamines (eqn 1) is common for amine oxides which have β-hydrogens.[17] Warming is usually necessary for the reaction to occur but conditions are highly variable. Sahyun and Cram[58] obtained olefins in high yields at room temperature in solvents such as dioxane and dimethyl sulfoxide. Other decomposition pathways are also available to the amine oxides. Bamberger and Leyden[59] found that heating N,N-dimethylaniline N-oxide (1c) (which has no β-hydrogens) in dry state or as its hydrochloride with or without solvent at 100°, leads to a large number of products including: aniline, mono- and dimethylaniline, formaldehyde, formic acid, p-aminophenol, quinol, tetramethylbenzidine, o,o'-dimethylaminodiphenyl ether, and o,o'-dimethylaminophenylmethane. Several of the more explicit accounts of work in this area have included reports of extreme instability. The ring substituted N,N-dimethylaniline, N-oxides of Jones and Hartshorn[24] decomposed to the tertiary amine on attempted sublimation under vacuum. Quin and Shelburne[60] found tertiary amine in their amine oxides immediately after preparation by the oxidation of the tertiary amine with hydrogen peroxide. The amount of amine increased on standing. Bellucci and Berti[29,61] found that although they could isolate solid N-methyl,N-cis-4-methylcyclohexylaniline, N-oxide (6), the N-oxides of N-methyl, N-cis or trans-4-t-butylcyclohexylaniline could not be induced to crystallize and slowly decomposed even at 0° to t-butylcyclohexene.

Amine Oxide Hydrochlorides

In the present work the amine oxides were handled primarily as their hydrochlorides, which were readily made by contact of the amine oxide with aqueous hydrochloric acid or with ether saturated with hydrogen chloride. These salts could all be recrystallized from chloroform-ether as long as they were dry and reasonably pure. Some were also recrystallized from dry acetone. The hydrochlorides were much less hygroscopic than the free bases. The N-oxide hydrochloride of N-methyl, N-t-butylaniline (4d) was not noticeably hygroscopic. It would be interesting to see whether the free amine oxide (4c) is hygroscopic. The literature reports only one nonhygroscopic aniline N-oxide, that from N,N-dimethyl, p-nitroaniline.[24]

When obtained from aqueous solution and dried under reduced pressure over phosphorous pentoxide, the amine oxide hydrochloride appeared to exist as half hydrates, perhaps of a structure similar to Figure 1.

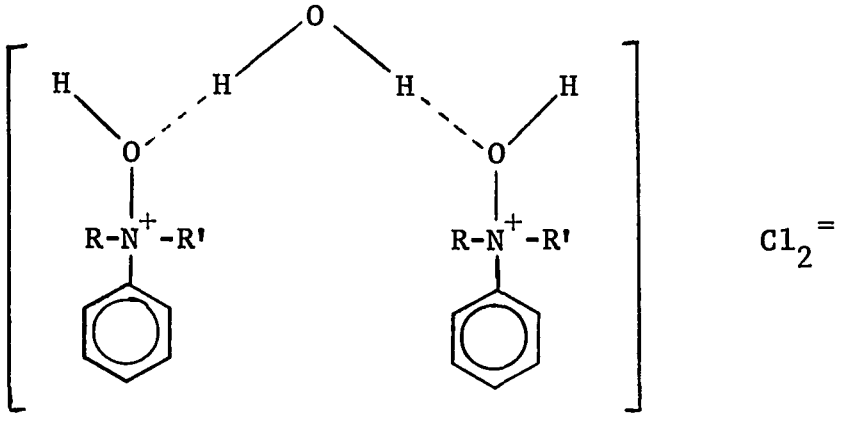


Figure 1. Possible structure of solid amine oxide hydrochlorides obtained from aqueous solution.

The nmr spectra in deuterochloroform showed two hydrogens associated with each amine oxide oxygen. A Volhard titration, however, accounted for only one chloride ion per molecule. The excess weight of the titration sample calculated to be about a half molecule of water per molecule of amine oxide. "Abnormal" salts of heteroaromatic amine oxides (fig 2) have been reported in the literature.[62,63]

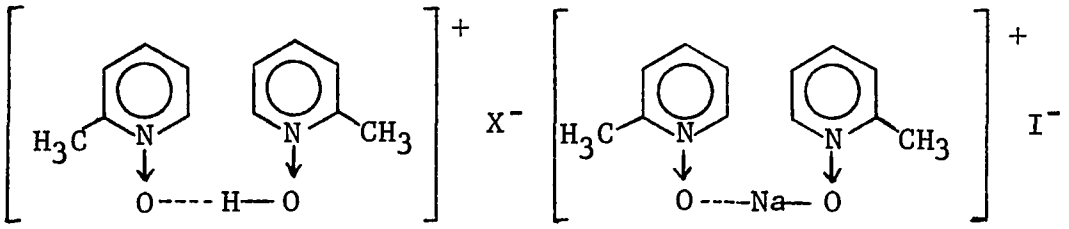


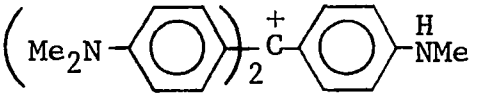
Figure 2. "Abnormal" salts of heteroaromatic amine oxides.

With one, possibly two, exceptions the dried and purified N-oxide hydrochlorides decomposed very little on long storage in the cold over phosphorous pentoxide. The white needles of recrystallized 1d decomposed in the solid state to a green material even when dried, sealed under nitrogen, and stored in the refrigerator. Decomposition of the crystals of 1d to green, dark blue, purple, or black material was observed on other occasions, sometimes in one day or less. Similar decomposition of 2d (a compound which was not handled much in this work) has been noted in the literature without explanation.[64]

When a methanolic solution of 1d was placed in the stainless steel Zeiss polarimeter cell, an intense purple color developed. The same reaction occurred with syringe needles and the metallic portions of the infrared solution

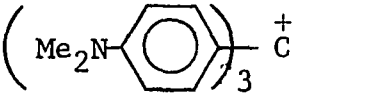
cells and glass polarimeter tubes. The colored compound changed from blue or purple in hydroxylic solvents to green in acetone and was not very soluble in any solvent. Green and purple colors were sometimes also observed with the other amine oxide hydrochlorides.

The usual products from decomposition of amine oxide hydrochlorides (by heating) are primarily aldehydes, secondary amines, and primary amines.[9] Tertiary amines which contain at least one α-CH bond, however, are also readily oxidized at the α-carbon by a variety of reagents (cupric chloride, chloranil, chlorine dioxide, mercuric acetate, manganese dioxide, potassium permanganate).[65,66] The formation of colored products from the oxidation of N,N-dimethylaniline is common.[67] Chloranil and cupric chloride oxidation of N,N-dimethylaniline produces varying amounts of the violet dyes, methyl violet (7) and crystal violet (8).[66]



Cl^-

7



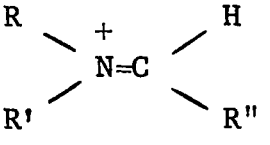
Cl^-

8

If it is assumed that the green, blue, and purple materials from the decomposition of 1d in solid state are oxidation products of either amine oxide hydrochloride or amine formed by decomposition by a different route, one may wonder what the oxidizing agent might be. Coats and Katritzky[68] have found that pyridine N-oxide hydrochloride acts as an oxidizing agent towards N,N-dimethylaniline. A solution of these compounds boiled for one minute developed an intense blue color which they identified as due to crystal violet, probably mixed with methyl violet.

With this information, it does not seem impossible that 1d could decompose in the solid state to colored compounds. The ease of the reaction may be the only surprise. Lack of decomposition of 3d and 4d may be due to steric hindrance to the reaction. It may also be due to a change incurred in going from the amorphous to the crystalline solid state; either loss of the hydrated water or a different orientation of the molecules. Compounds 3d and 4d were never obtained in good crystalline form. Compound 1d was obtained as white needles, often without recrystallizing. Shortly after recrystallization of 5d (which had been stored for several months as a white amorphous solid) to white needles, a faint bluish discoloration was noted. Meisenheimer's report[64] of 2d decomposition was with reference to recrystallized needles.

The purple color obtained from contact of the N-oxide hydrochlorides with metal surfaces may be due to similar products. The iron catalyzed dealkylation reaction of tertiary amine oxides in refluxing aqueous sulfuric acid has been studied.[69] The mechanism proposed involved initial generation of the same type of iminium ion (9) which has been proposed as the species leading to the formation of the



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violet dyes from N,N-dimethylaniline. The studies which have been made of the metal catalyzed dealkylation reactions employed primarily ferrous or cuprous salts or complexes.

In an attempt to duplicate the purple color produced at room temperature by contact of the amine oxide hydrochlorides with metal laboratory equipment, pinches of ferrous sulfate, ferrous chloride, cuprous chloride, cupric chloride, and chromium trioxide were added to samples of 1d in methanol. The solutions containing cupric chloride, cuprous chloride, or chromium trioxide turned dark green to black on standing.

Picrate derivatives of the amine oxides were also prepared. These appeared to be more stable to storage than the free bases or hydrochlorides but were not very soluble in common nmr solvents, were too highly colored for good polarimeter readings, and were difficult to convert back to pure amine oxides or oxide hydrochlorides.

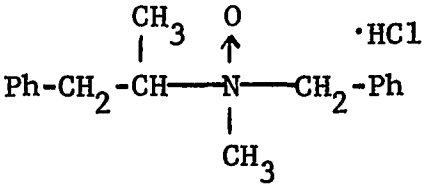
Infrared Spectra

In the infrared spectra of heterocyclic amine oxides the N-O stretch is a strong band at about 1200-1300 cm^{-1}.[70] This band is in the lower frequency range when the ring is substituted with electron donating groups and in the higher range with electron withdrawing groups. The primary literature reference,[71] however, to the infrared spectra of aliphatic-aromatic amine oxides covers only a few compounds, all of which had only straight chain alkyl groups. By comparing the spectra of the amine oxides to those of the corresponding amines, the N-O stretch was assigned to the 950-970 cm^{-1} region. The spectrum of the hydrochloride of trimethylamine oxide was also determined and was found to have an N-O band at the same wavelength as the free base but of slightly lower intensity. This reference was cited by Bellamy[72] and has been used by many workers to identify aliphatic or aliphatic-aromatic amine oxides.

Several authors have criticized the simple assignment of the band at 950 cm^{-1} in trimethylamine oxide (10) to the N-O stretch. Giguere,[73] who obtained two bands, assigned the very strong band at 937 cm^{-1} to the N-O stretch and the strong band at 945 cm^{-1} to C-N stretching. Kida[74] suggested that the most intense of the three bands he obtained for 10 in potassium bromide pellet (or the one band observed in bromoform) was due to N-O stretch with significant contributions by C-N stretching and deformation vibrations. He felt that some other bands in the spectra were also due to this combination.

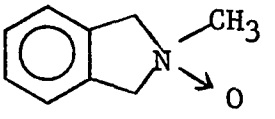
The "N-O" band in the infrared spectra reported was of either medium or strong intensity. However, as mentioned before, no amine oxides with branched alkyl groups were studied. Only one was an aromatic-aliphatic amine oxide (N,N-dimethylaniline, N-oxide). It is therefore of interest to report here the infrared spectra of some dialkylaniline N-oxides and N-oxide hydrochlorides obtained during work on other aspects of this thesis.

The infrared absorptions in the 900-1000 cm^{-1} region are listed in Table 1. In 1c the bands between 950 and 970 cm^{-1} are very strong as reported in the literature. The band at 950 cm^{-1} in 3c, however, is of only weak to medium intensity. The amine oxide hydrochlorides show the same trend, the N,N-dimethyl compound being the only one with at least medium intensity bands at about 950 cm^{-1}. The 940 and 960 cm^{-1} bands of N-benzyl, N-α-dimethylphenethylamine, N-oxide hydrochloride (11) reported in the Sadtler Spectra catalog as a mull in Nujol[75] are also only medium weak to very weak.



11

The strongest absorption in the 900-1000 cm^{-1} region in all of the amine oxides and their hydrochlorides reported in Table 1 except for 1c is at 904-913 cm^{-1}. The 909 cm^{-1} band of N-methylisoindoline, N-oxide (12) was used by one group of investigators[76] to detect its presence in a crude



12

product mixture. The vibrational origin of this band has not been investigated. The band shifts around strangely (see spectra of 1c.)

In conclusion, this work indicates that the study of the infrared spectra of amine oxides and their salts certainly needs more examples, particularly of the type with branched chain substituents. Until further data are accumulated or comparison to a known spectrum is made, the statement:

> "Possible structures containing a tertiary N-oxide grouping were eliminated on the basis of the absence of a strong band in the 950-970 cm^{-1} region in the infrared spectra of these adducts [perchlorate salts]."[17]

is, at best, a dangerous premise.

Table 1. Infrared Bands of N-Methyl, N-alkylanilines, Their Oxides and Hydrochlorides Between 900 and 1000 cm^{-1}

Spectrum Number	Compound Number	State	IR Bands				
112[a]	1c(dry)	mull[b] [c]	928(m) (934)[71]		953(vs) (955)	961(vs) (961)	993(w) (980)(997)
28	1c(wet)	$CHCl_3$	917(w)		950(sh)	967(vs)	1004(vw)
115	1c(dry)[d]	$CHCl_3$(dil)	925(s) ($CHCl_3$?)		948(sh)	963(vs)	998(w)
114	1c(dry)[d]	$CHCl_3$(conc)	909(w)		950-970(off scale)		998(vw)
27[a]	1d	mull	913(vw)		956(m)	972(w)	997(vw)
26	1b	$CHCl_3$	900(m)				996(m)
8	1a	liq.		940(ms) (942)[71]			985(ms) (991)[71]
47	3c(wet)	$CHCl_3$	906(s)		934(m)	950(w)	
109[a]	3d	mull	907(w)		935(vw)	946(sh)	990(vw)
24	3b	$CHCl_3$	900(w)	928(w)	933(w)		998(m)
9	3a	liq.			934(mw)		990(m)
111[a]	4d	mull	904(w)	926(vvw)		942(vw)	999(w)
113	4a	liq.	911(mw)	919(sh)			998(w)

Table 1. (continued)

Spectrum Number	Compound Number	State	IR Bands					
110[a]	5d	mull	909(w)	931(sh)	945(w)	953(sh)	973(vw)	994(mw)
74	5a	liq.		925(w)			1001(m)	

[a] See appendix. [b] Mulls in Nujol. [c] Probably slightly wet because mull was exposed to the air. [d] Compound stored under dry nitrogen; bottle opened and cell filled under dry nitrogen.

Nuclear Magnetic Resonance Spectra

All of the amine oxides used in this work had at least one N-methyl substituent. The chemical shift of the N-methyl peak in the nmr spectra could be used to identify the species present. In the amine oxides the resonance of this methyl group always occurred in the 3.28-3.81 ppm range in deuterium oxide* or 3.45-3.73 ppm in deuterochloroform.** In the amine it was observed at 2.58-2.67 ppm. N-Methyl groups of the hydrochlorides absorb between 3.80 and 3.96 ppm (D_2O) or 4.08 and 4.16 ppm ($CDCl_3$) for the amine oxides and 3.25 and 3.58 ppm (D_2O) or 3.25 and 3.33 ppm ($CDCl_3$) for the amines. In aqueous solutions containing both amine oxide and amine oxide hydrochloride, only one N-methyl peak was found. This peak shifted downfield on the addition of hydrochloric acid.

Nmr proved to be quite useful in the analysis of product mixtures since the N-methyl peaks in the hydrochlorides of oxide and amine were always separated by about 0.3 ppm in deuterium oxide or 0.8 ppm in deuterochloroform. Because the spectra were simple, nmr was also usually the best way to detect impurities. The results from thin layer chromatography were at best doubtful*** and gas-liquid phase chromatography was out of the question.

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* Ppm values in deuterium oxide are with respect to external TMS. With deuterochloroform internal TMS was used.

** The chemical shift is concentration dependent. Dilution causes a downfield shift.

*** In one case intensities of certain spots were observed to increase if the plates were allowed to stand a short while between spotting and eluting.

As mentioned previously, it was planned at one time to determine the relative basicities of the series of N-methyl, N-alkylaniline, N-oxides (1-5c). Amine oxides strongly bond to chloroform. Their relative hydrogen bonding basicities to chloroform could be determined by nmr. By plotting the chemical shift of the chloroform hydrogen with respect to TMS in solutions containing varying mole fractions of amine oxide versus mole fraction of chloroform, a chemical shift at infinite dilution of chloroform can be extrapolated. The difference between the shift of the chloroform proton at infinite dilution with each of the donors compared to its shift in inert hydrocarbon solvents can be used as a measure of the relative hydrogen bonding strengths of the donors. This technique has been used by other investigators for various compounds.[78-83] In some cases good correlation with basicity was claimed.

Initial data with pyridine N-oxide (13) and N,N-dimethylaniline, N-oxide (1c) gave straight lines to a concentration of at least 0.2 mole fraction of amine oxide. The differences in intercepts of these lines were qualitatively in accord with the known basicities of the two amine oxides. However, due to the inability to obtain purified samples of the other amine oxides (2-5c), these basicity studies were not carried further.

Resolution

Since Meisenheimer's initial resolution of N-methyl, N-ethylaniline, N-oxide (2c) in 1908, relatively few amine oxides have been resolved. Most of these have also been done by Meisenheimer and his patient coworkers* (Table 2).

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* Apparently at the rate of about two per student. See ref. 22.

Table 2

Amine Oxides Which Have Been Resolved

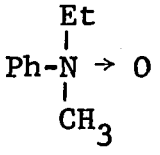
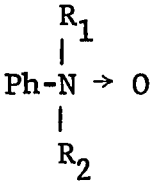
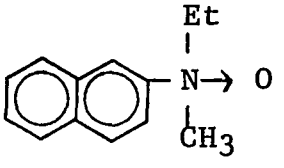
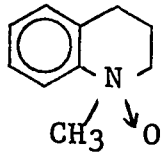
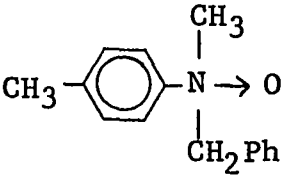
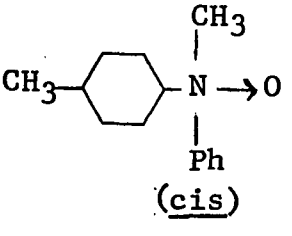
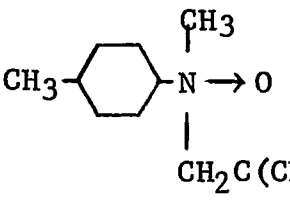
Amine Oxide	Resolving Agent	Ref.
	(+)-π-bromocamphor sulfonic acid and/or (+)-tartaric acid	27,30
 R_1=allyl, benzyl, propyl; R_2=methyl, ethyl	"	22
	"	27
	"	27
	"	22
 (cis)	(-)-dibenzoyl-tartaric acid	29

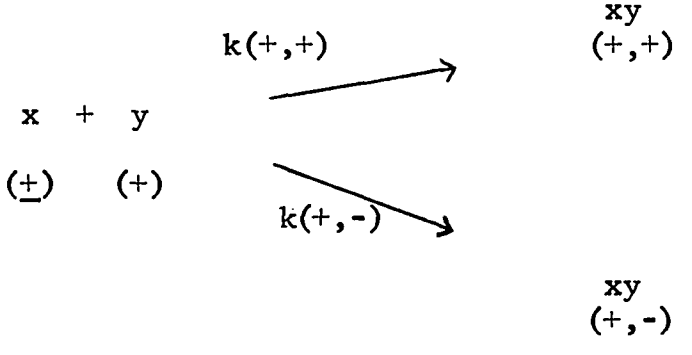
Table 2. (continued)

Amine Oxide	Resolving Agent	Ref.
 (cis and trans)	(-)-dibenzoyl-tartaric acid	86

In 1966 the configuration of (-)-2c was related to (S)-(+)-methylethylphenylphosphine oxide by a comparison of their ord curves.[84]

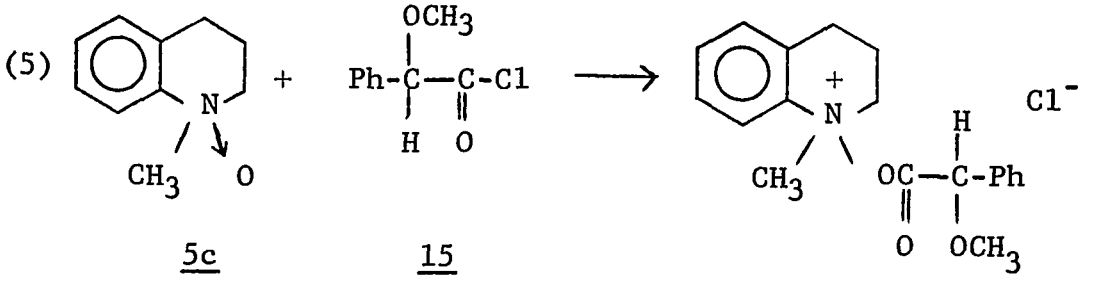
An initial attempt to determine whether it would be possible to resolve N-methyl, N-isopropylaniline, N-oxide (3c) was successful. The salt of 3c with (-)-dibenzoyl-tartaric acid (14) which crystallized slowly upon formation (no recrystallization) afforded 3c with $[\alpha]_{578}$ -19.2°, $[\alpha]_{546}$ -22.5° (c 4, 95% ethanol). N-oxide 2c may also be resolvable with this acid. Diastereomeric salts of 14 and N-methyl, N-ethyldodecylamine, N-oxide, however, could not be separated by repeated recrystallization.[85]

Cervinka has reported[84] that he obtained optically active kairoline N-oxide (5c) by a kinetic resolution. In a kinetic resolution racemic material is allowed to react with less than an equivalent amount of a chiral reagent.



The transition states are diastereomeric, therefore the activation energies will not in principle be the same. Since the rate constant k(+,+) is not equal to k(+,-), interruption of the reaction or use of insufficient chiral reagent for complete reaction will leave starting material enriched in one enantiomer. When racemic 5c was reacted with less than an equivalent amount of R-(-)-O-

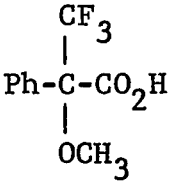
methylmandeloyl chloride (15), a precipitate formed which was presumed to be the N-acyloxyammonium salt 16 (eqn 5). The unreacted amine oxide was enriched slightly in the



5c 15 16

isomer which could be converted into the (+)-hydrochloride 5d. As could be expected, an enantiomeric excess of the (-)-hydrochloride was obtained by hydrolysis of 16.

This reaction should be tried using the acid chloride of optically active α-methoxy, α-trifluoromethylphenylacetic acid (17). This acid chloride might create larger differences



17

in diastereomeric transition state energies giving residual amine oxide of higher enantiomeric excess than that obtained by Cervinka. The groups on the asymmetric carbon in 17 are different in polarity as well as in size. An added advantage to using this acid is the possibility of being able to determine by nmr the optical purity of the N-acyloxyammonium salt formed without having to depend upon known maximum rotation values. It has been found[87] that the diastereomeric

protons in the esters or amides of optically active 17 with racemic or partially resolved alcohols or amines have different chemical shifts. These can be integrated to determine the enantiomeric excess of the alcohol or amine present. The technique has not yet been applied to amine oxides.*

The acid needed (17) was prepared, but the reaction of the acid chloride with the racemic amine oxides remains to be done in the future.

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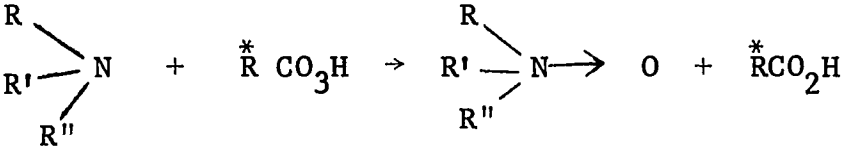
* An alternate nmr method for the direct determination of enantiomeric purities, the use of optically active solvents, has, however, recently been extended to amine oxides.[88]

II. OXIDATION OF N-METHYL, N-ALKYLANILINES WITH CHIRAL PERACIDS

Introduction

Asymmetric oxidation of achiral unsymmetrical sulfides with chiral peracids is a well known phenomenon.[89-97] Chiral sulfoxides are generally produced in low enantiomeric excess, usually no greater than 5%. Chiral peracids have also been used to oxidize disulfides,[98-101] sulfinates,[101] sulfenamides,[101] alkenes,[102] imines,[103-104] and an azo compound [105] asymmetrically.

The purpose of this work was to determine whether asymmetric induction occurs in the oxidation of achiral, unsymmetrically substituted, tertiary amines with chiral peracids (eqn 6).

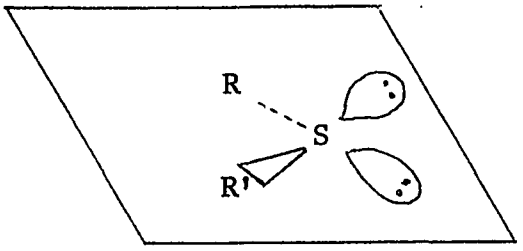


(6)

optically active?

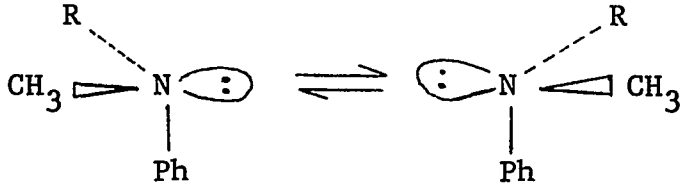
It is generally accepted that the mechanism for the oxidation of amines with peracids[40,106-110] is essentially the same as that for the peracid oxidation of sulfides,[111] i.e., nucleophilic displacement by the heteroatom on the peroxidic oxygen.

In an asymmetric synthesis an achiral unit is converted into a chiral unit in such a manner that stereoisomeric products are produced in unequal amounts. Unlike the unsymmetrically substituted sulfides (E) which are



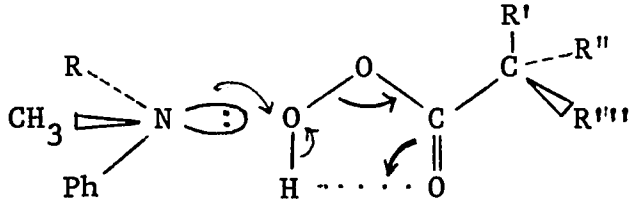
E

achiral by virtue of a plane of symmetry, unsymmetrically substituted tertiary amines are effectively achiral due to rapid inversion of enantiomeric pyramidal forms (F and G).



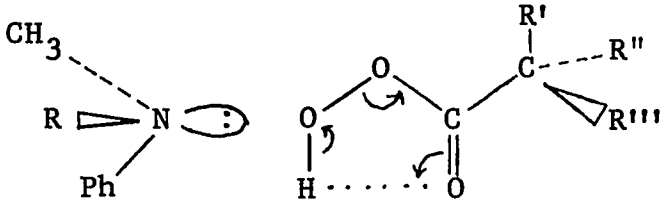
F G

The transition states H and I, generated by the attack of these two invertomers on a chiral peracid, are diastereomeric and therefore in principle of unequal energy. The



H

(Conformations at asymmetric centers are arbitrarily assumed)



I

amine oxide produced from H is the enantiomer of that from I. The ratio of the enantiomers formed depends upon the difference in the severity of the nonbonded interactions between the two asymmetric centers in the various conformations of epimeric transition states. Relatively small differences in the diastereomeric transition state energies can lead to large differences in enantiomeric purities of products. For a sulfide oxidation in which a 5% enantiomeric excess of sulfoxide is formed, the net energy difference ($\Delta\Delta G^{\ddagger}$) between the epimeric transition states is only about 0.05 kcal/mole.*

The peracid moiety in H and I is drawn as a pseudo-five membered ring because peracids are believed to exist[112] and probably to react[111,113] in the internally hydrogen bonded conformation in non-hydroxylic solvents. In the case of reaction with amines, some formation of open chain peracid-amine hydrogen bonded species in solution could be envisioned. However, reaction in the forms represented by H and I would be expected to be more facile. Evidence discussed later in this section indicates that peroxyacid ammonium salts are not involved in the reaction.

Preparation of N-methyl, N-alkylanilines

The N-methyl, N-alkylanilines 2a, 3a, and 5a were prepared in reasonable yields by methylation of the appropriate corresponding secondary amines with dimethyl sulfate. N-t-butylaniline (18), however, is not commercially available and no high yield synthesis of N-methyl, N-t-

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* $\Delta\Delta G^{\ddagger} = \Delta G_R^{\ddagger} - \Delta G_S^{\ddagger} = -RT \ln \frac{[R]}{[S]}$

butylaniline (4a) has as yet been reported.

By the usual N-alkylation methods, overall yields of 4a starting from either aniline (19) or N-methylaniline (20) are never more than about 15-20% (eqns 7, 8).

(7) $Ph\text{-}NH\text{-}CH_3 + (CH_3)_3CX \rightarrow PhN(CH_3)\text{-}C(CH_3)_3$

20 → 4a

X=Br, 15% yield[114]

X=Cl, not recommended[114]

(8) $Ph\text{-}NH_2 + (CH_3)_3CX \rightarrow PhNH\text{-}C(CH_3)_3$

19 → 18

X=Br, 27%[115]

X=I, 32%[115]

18 + $CH_3X \rightarrow PhN(CH_3)\text{-}C(CH_3)_3$

18 → 4a

X=I, 18%[115]

X=I, 58%[114]

X=I, 51%[116]

Some of the 4a for this work was prepared by van Hoek's synthesis.[114] Addition of potassium carbonate, in an attempt to remove the hydrogen bromide generated by the decomposition of the t-butyl bromide, did not increase yields over those reported.

The t-butyl group could instead be generated from a group already attached to the nitrogen by a reaction such as that of organometallic reagents with ketimines (eqn 9).

(9) $Ph\text{-}NH_2 + O{=}C(CH_3)_2 \rightarrow PhN{=}C(CH_3)_2 \xrightarrow{CH_3M} PhNH\text{-}C(CH_3)_3$

19 21 22 18

M=MgX, only starting material obtained[117]
M=Li, 61% yield 18[117]

Abstraction of one of the hydrogens α to the azomethine carbon is a major competing reaction, giving regenerated ketimine upon hydrolysis. The predominance of addition or enolization is largely determined by steric factors. Hydrogen abstraction is often the preferred process with ketimines while the addition of Grignards to aldimines can be of preparative importance.

Grignards often react with ketiminium salts, however, to give good yields of tertiary amine.[118-120] The reaction of isopropylidene N-methylanilinium perchlorate (23) with methyl magnesium iodide (eqn 12) was therefore investigated

(10) $PhNHCH_3 \xrightarrow{HClO_4} [Ph\overset{+}{N}H_2CH_3]ClO_4^-$ 49% yield

20 24

(11) 24 + $(CH_3)_2C{=}O \xrightarrow{(CH_3)_2C(OCH_3)_2} [Ph\overset{+}{N}(CH_3)=C(CH_3)_2]ClO_4^-$

21 23

73% yield

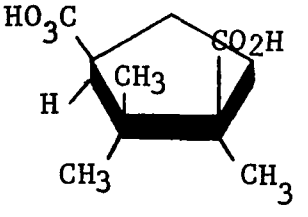
(12) 23 $\xrightarrow[Et_2O]{CH_3MgI}$ $PhN(CH_3)\text{-}C(CH_3)_3$ 19% yield

4a

as a possible route to 4a. A 19% yield (comparable to the overall yields by alkylation procedures) was obtained. The yields of 24 and 23 (prepared from very inexpensive reagents) could probably be improved, but the yields in the last step are probably limited by competing enolization.[118,119]

Preparation of Peracids

The two chiral peracids used in these studies were (1S)-percamphoric acid (25) and (R)- and (S)-2-phenylperbutanoic acid (26). Peracid 25 could be easily prepared



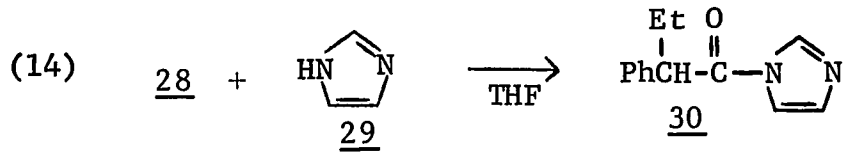
25

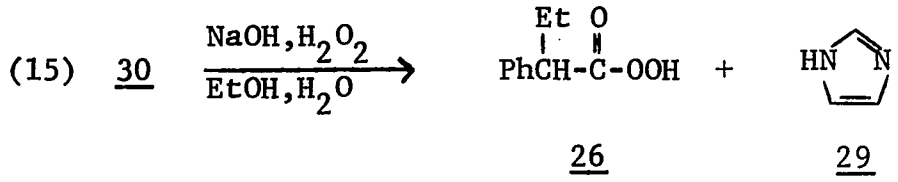
S-26

from readily available d-camphoric anhydride.[121,122] Peracid 26 was chosen because the precursor acid had been resolved previously in large quantities in this laboratory in connection with other studies. Preparation of 26 by standard methods, however, proved not to be simple.

The first attempted method of synthesis of 26 was perhydrolysis of the imidazolide of 2-phenylbutanoic acid (eqn 13-15), a synthesis used by Montanari and coworkers[92,123] to prepare optically active peracids without racemization.

(13) $\underset{\textbf{27}}{\text{Ph-CH(Et)-C(=O)-OH}} \xrightarrow{SOCl_2} \underset{\textbf{28}}{\text{PhCH(Et)-C(=O)-Cl}}$

(14) 

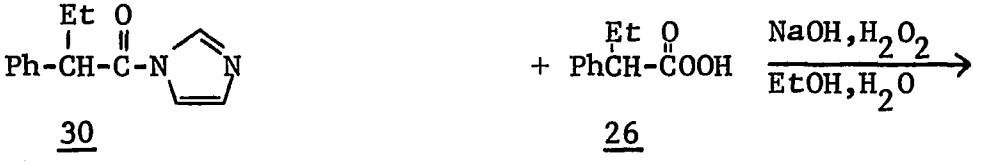
(15) 

No 2-phenyl-substituted peracids were reported in these papers although Montanari had previously used (S)-perhydrotropic (2-phenylperpropionic) acid (31) for a sulfide oxidation.[91]

The products from reactions 13 and 14 were isolated and characterized. Three attempts with reaction 15, however, gave no peracid or even diacyl peroxide as determined by iodometric titrations. The major product appeared to be the acid, 27, on the basis of its melting point and solubility in dilute base.

After 2-phenylperbutanoic acid was no longer being used in this research, a publication of further work on Montanari's preparations of peracids[96a] indicated the probable cause of the failures noted here. Imidazolide must be added rapidly to the hydrogen peroxide-sodium hydroxide mixture, the reagents being in contact for no more than ten minutes before workup. Yields of peracids are said to be considerably diminished with longer reaction times. The reaction time for the attempted preparation here was one hour as suggested by the original article.[92] Peracids are unstable in basic media, decomposing to the corresponding acid.[124] As noted later in this thesis, 26 happens to be

particularly unstable in base. Slow addition of the imidazolide could also favor the production of diacyl peroxides (eqn 16.)[125] Diacyl peroxides are rapidly

(16) 

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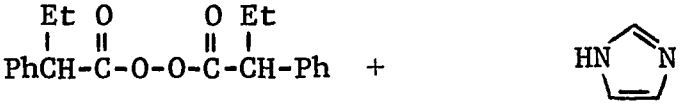
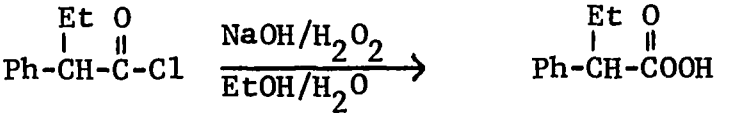


32 29

hydrolyzed with base catalysis to give acid and the desired peracid.[125] However, hydratropoyl peroxide (33) when formed in basic media is unstable even at -20°,[126] decomposing to give primarily hydratropic acid and hydratropylhydratropate but also significant amounts of styrene, acetophenone, α-phenylethanol, and 2,3-diphenyl butane. Montanari has now claimed[96a], however, a 66% yield of perhydratropic acid (31) by his improved procedure.

The second type of peracid synthesis undertaken was perhydrolysis of the acid chloride 28 (eqn 17), following

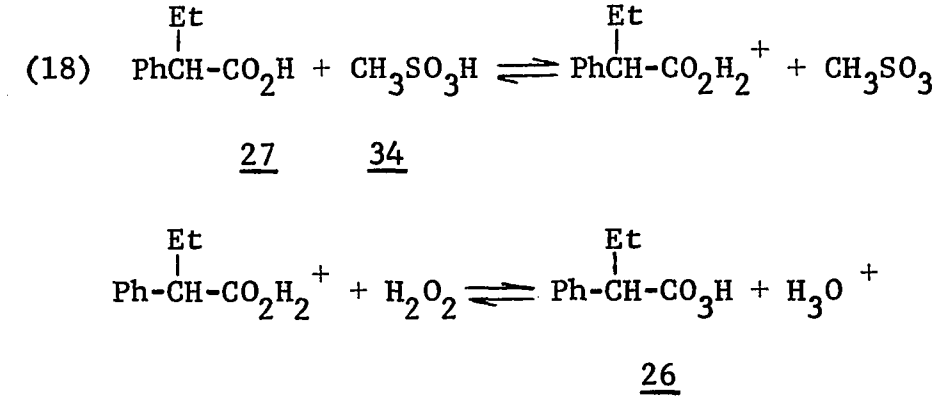
(17) 

28 26

a procedure for perbenzoic acid.[127] Less than a 1% yield of peracid was obtained. Good yields are usually obtained only from acid chlorides of relatively strong acids such as those which are aromatic or α-halogenated. However, lauroyl

chloride[128] and 2-methylbutanoyl chloride[129] have been reported to give about 30% yields of peracids.

Peracid 26 was finally obtained in 15 to 59% yields by the action of 90% hydrogen peroxide in methanesulfonic acid on the carboxylic acid, 27 (eqn 18). This procedure which was developed by Swern and coworkers[130] has been used to obtain peracids from aromatic, long chain aliphatic, α-halo, and dicarboxylic acids in 85 to 97% yields.



(18) $PhCH(Et)\text{-}CO_2H + CH_3SO_3H \rightleftharpoons PhCH(Et)\text{-}CO_2H_2^+ + CH_3SO_3^-$

27 34

$Ph\text{-}CH(Et)\text{-}CO_2H_2^+ + H_2O_2 \rightleftharpoons Ph\text{-}CH(Et)\text{-}CO_3H + H_3O^+$

26

Reaction conditions were varied in an attempt to determine optimum conditions before using resolved acid. The yields appeared to vary in no rational way, probably indicating that trace impurities or the temperature profile of the exothermic reaction were factors, since these were extremely unpredictable. In general, reaction mixtures held longer in the temperature ranges 10-25° and 30-38° appeared to give lower yields of peracid than when the temperature was held primarily between 25 and 30°. Purified methanesulfonic acid seemed to be better than practical grade although Swern found no difference. No apparent pattern of effect on the yield could be observed by changing the purity of 27 or the proportions of reagents.

The reaction was difficult to control and always became darkly colored, probably indicating charring in the strongly acidic medium. It is interesting to note that Montanari's coworkers[96a] tried Swern's procedure with 2-(α-naphthyl)-propionic acid and with 2-phenoxypropionic acid, but abandoned it because the reaction mixture turned dark upon addition of 85% hydrogen peroxide.

Optically active 26 obtained by Swern's method of preparation was shown to have the same optical purity as the acid from which it was prepared by comparison of the rotations of starting acid with that from reduction of the peracid with iodide. As was the case for sulfide oxidations,[89-97] the chiral peracids were used for the amine oxidations as crude extracts or as oils obtained by evaporation of solvent from the extracts.

Workup Procedures for the Reaction of Amines with Chiral Peracids

There are several approaches that might be used to isolate amine oxide from the reaction mixture. An insoluble derivative of the amine oxide, such as the picrate, could be precipitated. However, precipitation from a chiral medium did not seem desirable since partial resolution could possibly be effected in this process. Picrate precipitation was also found not to be quantitative.

Since only amine oxide, carboxylic acid, and unreacted starting materials should be present in the reaction mixture, the organic acids could be removed with aqueous base, leaving behind the desired product. Berti[61] used saturated sodium carbonate for this purpose. However, when a reaction of 2a and excess 2-phenylperbutanoic acid (26) in benzene was worked up in this manner, the nmr of the

benzene residue showed many unidentified multiplets in the region of amine oxide or amine resonances. It was subsequently shown that 26 decomposes very rapidly when shaken with saturated sodium carbonate solution, giving benzene-soluble material with an nmr spectrum similar to that observed from the workup of the amine oxidation. In addition, the amine oxide was found to be quantitatively extracted out of the benzene layer by the saturated sodium carbonate, making this method of workup totally inapplicable.

Alternatively, the amine oxide (and any unreacted amine) could be extracted from the reaction mixture into aqueous solution as their hydrochlorides. This involved the inconvenience of removing large quantities of water from the product by freeze-drying (and possibly allowing decomposition of the amine oxide). Aqueous extraction of the hydrochloride salts had the advantage, however, of being adaptable to low temperature reactions (-70°). The hydrochloride salts could be formed at the low temperature by the addition of hydrogen chloride in ether, thus quenching the reaction and ensuring that the product isolated was formed in the cold rather than on warming to room temperature. That hydrogen chloride effectively quenches the amine oxidation was demonstrated by adding an ethereal solution of hydrogen chloride to a solution of amine before the addition of peracid. No amine oxide was formed under conditions which for another sample without the hydrogen chloride gave a quantitative yield.

Results and Discussion

Initial reactions of dialkylanilines with chiral peracids showed no asymmetric induction (Table 3). Since the reaction at room temperature is very rapid, possibly instantaneous*, it was thought that lowering the temperature might encourage some stereoselectivity. With a slower reaction rate, small differences in transition state energies could become significant in terms of enantiomeric product composition. The decrease in conformational mobility could also increase asymmetric induction. Lowering the sulfide oxidation temperature from 0° to -50° was found to increase optical yields two- to four-fold.[96b]

The reactions of the dialkylanilines with (1S)-percamphoric acid (25) in chloroform-ether were roughly two-thirds complete in seven days at -70°. Some had reached completion by about thirteen days. Most of the reactions (Table 4) were held at -70 to -75°C for twenty-one days or longer to ensure complete reaction.

Table 4 shows that a low order of asymmetric induction was observed in the low temperature reactions. Comparison of the observed rotations of kairoline N-oxide hydrochloride (5d) with the maximum reported[27] indicates optical yields of 1% or less. N,N-dimethylaniline (1a) was oxidized and worked up concurrently with every reaction in Table 4, since its amine oxide is achiral. The lack of observed optical rotation for any of these control samples suggests that the work-up procedure removed any optically active by-products. Nmr also showed none of the camphoric acid

* The shortest reaction time used, however, was one hour.

Table 3

Reactions of Dialkylanilines with Chiral Peracids

Reaction No.	Amine	Peracid, Solvent	Temp.	Rotation of Product
1	2a	R-26[a] benzene	26°	0°[b]
2	3a	R-26[a] benzene	+7 to +11°	0°[b]
3[c]	3a	1S-25 $CHCl_3$	-10 to +7° (0.75 hr) -13 to -14° (1 hr) 25° (2 hr)	0°[b]
9	3a	1S-25 $5CHCl_3/2Et_2O$	25-31°	0°[d]

[a] 44% enantiomeric excess (e.e.)

[b] Rudolph Recording Spectropolarimeter Model 260/655/850/810-614. The ord curve was measured from 600 to about 300 nm.

[c] Conditions similar to those for the initially reported sulfide oxidations with chiral peracids.[89-95]

[d] Carl Zeiss Photoelectric Polarimeter, 0.005°. Rotations were measured at 578, 546, 436, 405, and 365 nm.

Table 4

Specific Rotations of Amine Oxide Hydrochlorides Obtained from Reactions of Dialkylanilines with (1S)-Percamphoric Acid at -70°

Reaction No.	Amine	Solvent	$[\alpha]^{a}_{578}$	$[\alpha]_{546}$	$[\alpha]_{436}$	$[\alpha]_{405}$	$[\alpha]_{365}$
			0.00,	+0.05,	+0.20,	+0.25,	+0.41,
11b	2a	$5CHCl_3/2Et_2O$	+0.05[b]	+0.10	+0.30	+0.36	+0.51
			±0.05[c]	±0.05	±0.05	±0.05	±0.05
11c	3a	"	-0.09	-0.09	-0.11	-0.14	---
			±0.03	±0.03	±0.03	±0.03	
8b	3a	"	-0.03[d]	-0.03	-0.07	-0.08	---
			±0.02	±0.02	±0.02	±0.02	
13b	4a	"	+0.31	+0.39	+0.76	---	---
			±0.03	±0.03	±0.03		
14b	5a	"	+0.26	+0.28	+0.37	---	---
			±0.03	±0.03	±0.03		
			+0.27[e]	+0.27	+0.41	+0.54	
			±0.14	±0.14	±0.14	±0.14	

Table 4. (continued)

Reaction No.	Amine	Solvent	$[\alpha]^{a}_{578}$	$[\alpha]_{546}$	$[\alpha]_{436}$	$[\alpha]_{405}$	$[\alpha]_{365}$
15b[f]	5a	$5CHCl_3/2Et_2O$	+0.43[g] ±0.14[h]	+0.53 ±0.14	---	---	---
15c[f]	5a	$5CHCl_3/2Et_2O$ 1 equiv. d-camphoric acid	+0.50[e] ±0.16[h]	+0.63 ±0.16	---	---	---
16b	5a	abs. ethanol	0[i]	0	---	---	---

[a] Rotations in spectroquality methanol unless otherwise noted.

[b] Solvent blanks read before and after the rotation of this sample was determined did not agree with each other.

[c] Deviation possible due to measuring tolerance of ±0.005° of the Carl Zeiss Photoelectric Polarimeter, 0.005° unless otherwise noted.

[d] This sample contained a trace of amine hydrochloride.

[e] Rotations in water.

[f] One-half equivalent of peracid was used.

[g] The specific rotation was based only on the weight of amine oxide hydrochloride in the sample but unreacted amine hydrochloride was also in the sample and could affect the rotation slightly.

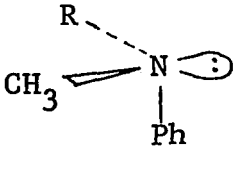
Table 4 (continued)

[h] Error includes (besides polarimeter measuring error) a weight of amine oxide hydrochloride error based on a ±2% nmr analysis error of the ratio of amine hydrochloride to amine oxide hydrochloride.

[i] If the sample had any rotation it was less than 1/3 of that obtained in reactions 15.

methyl peaks which had been observable in very low concentrations in reaction products with other workups. Infrared showed the absence of carbonyl absorption. The results were also reasonably reproducible (compare reactions 8b and 11c, and 15b and 15c). The asymmetric induction is apparently real but should be considered as essentially negligible.

If at -70° the nitrogen atom in the dialkylanilines did not invert, the amine would exist as a 50/50 mixture of enantiomeric forms. Complete N-oxygenation would give



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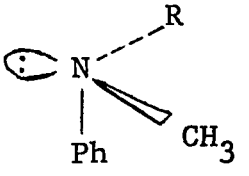

G

a racemic mixture of amine oxides whether a chiral or an achiral oxidizing agent were used because the configuration of the nitrogen (and, therefore, the ratio of enantiomers) was fixed before the reaction began. These considerations could in principle explain the lack of significant asymmetric induction observed.

It is unlikely, however, that pyramidal inversion of the free amine could be slow enough at -70° to affect the ratio of isomeric products of the reaction.* Ethylenimine

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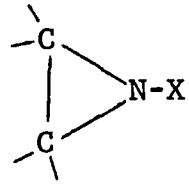
* The activation energy for the inversion process would have to be larger than the activation energy for the reaction. Otherwise, the Curtin-Hammett principle[131] would apply and the ratios of products would not depend on the ratio of the invertomers. This reaction does have a very low enthalpy of activation ($\Delta H^{\ddagger}$ = 10.13 kcal/mole for the reaction of N,N-dimethylaniline with perbenzoic acid[110]). The entropy of activation for this type of reaction is generally about -25 cal/mole °.[109,132]

derivatives (J) have been found to invert slowly, some even



J

being isolable in isomeric forms at room temperature.[133,134] However, N-alkyl substituted trimethylenimines and larger ring imines have an inversion rate too great to be measurable by nmr at temperatures above -77°.*[135] Conjugation with the nitrogen increases the inversion rate.[135]

If the amine were protonated, however, it could not invert.** Partial salt formation or hydrogen bonding could also be expected to substantially decrease the nitrogen inversion rate.[135] Since carboxylic acid could be present in the peracid extract initially and would certainly be formed during the course of the reaction, the opportunity of the amine to hydrogen bond or form salts was available.

The nmr spectra of N-methyl, N-isopropylaniline (3a) in chloroform-tetrahydrofuran with various proportions of

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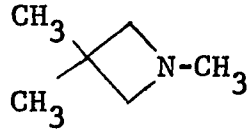
* 

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* $\Delta G^{\neq}_{inversion}$ = 8.8 kcal/mole at -98° for 1,3,3-trimethylazetidine (35)[136]

** However, if the protonation were reversible, the protonation-deprotonation rate would have to be greater than the nitrogen inversion rate in order for some configurational integrity to be maintained. There are cases in which evidence for faster protonation-deprotonation than nitrogen inversion has been obtained.[137]

camphoric acid showed no evidence of slow nitrogen inversion (which would be accompanied by increased multiplicity of the isopropyl methyls) or partial salt formation (which would be accompanied by a shift of the N-methyl to lower fields) at room temperature. Addition of up to two equivalents of optically active carboxylic acid to the reaction mixtures appeared not to inhibit complete reaction of the amine*, either at room temperature or -70°, and had no influence on the percent of asymmetric induction at -70° (reaction 15b). Although complete reaction with noninterconverting invertomers would give a racemic product, partial reaction could effect asymmetric induction whether the amine molecules were inverting or not. Reaction of kairoline (5a) with one-half of an equivalent of (1S)-percamphoric acid (25) gave product whose rotation was not significantly different from that obtained when an excess of 25 was used. In summary, there appears to be no experimental evidence at present for slow nitrogen inversion in these low temperature reactions or evidence that slow inversion is a reason for the low order of asymmetric induction observed.

Chloroform was chosen as the solvent for most of these reactions because of its use for the sulfide oxidations. Henbest and coworkers[138] in 1967 showed that chloroform gave the highest optical yields in the oxidation of olefins with peracids. Ether was added here to prevent the chloroform from freezing at -75°. Subsequent to this work, Montanari and coworkers[96b] found that of the seven solvents tried in the oxidation of sulfides with (1S)-percamphoric acid, the highest optical yields were obtained in chloroform, ether, or benzene.

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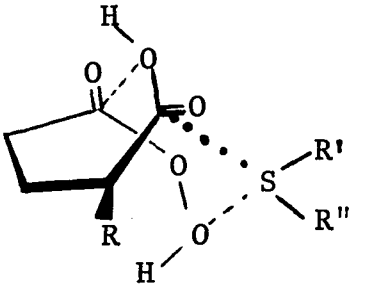
* Modena[108] also found no effect of added carboxylic acid on the rate of oxidation of pyridines with perbenzoic acid.

The overall lower optical yields from dialkylanilines than from arylalkyl sulfides indicates that there is less difference in the diastereomeric transition state energies for the amine oxidation than for the sulfide oxidation. Assuming the reaction mechanisms to be the same, larger steric and/or electronic differences must be presented by an alkyl group, an aryl group, and a pair of electrons than by an aryl group and two different alkyl groups. The difference in ability of these amines and sulfides to orient solvent may be a factor. An asymmetric solvent shell may be involved in transmitting the influence of the asymmetric center of the chiral reagent to the asymmetric center being formed.[96b,138] The effective size of the lone pair of electrons cannot be compared with certainty to the size of any covalently bonded group.[139] In determining transition state preferences, the lone pair probably plays a larger role through solvation or electronic effects than steric effects.

The sulfide oxidation with monoperoxydicarboxylic acids has been postulated to proceed through a transition state (K) in which one sulfur lone pair is interacting with the carboxylic acid function.[90]

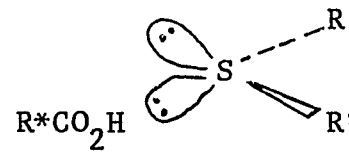


K

This pseudo-six membered ring transition state rationalizes the observation that in the few cases studied, peracids with the structure $HO_2C\text{-}\overset{*}{C}(R)\text{-}C\text{-}C\text{-}CO_3H$ gave greater asymmetric induction than peracids of other substituted dicarboxylic acids.[90]

It is interesting to consider the consequences if the sulfide oxidations, including those with monocarboxylic peroxy acids proceed at least partially through a transition state in which a molecule of carboxylic acid (or peracid) is hydrogen bonded or associated through the carbonyl with one of the sulfur lone pairs. As with the amine oxidation, carboxylic acid is always present in the reaction mixture. Since the lone pairs on the sulfide molecule are enantiotopic by internal comparison*, association of a pair of electrons with the optically active acid would lead to the diastereomeric species L and M. Oxidation by a chiral

L



M

peracid would then involve the interaction of a chiral molecule with diastereomeric substrates, not an achiral substrate as in amine oxidation. The effect of added carboxylic acid of either the same or opposite chirality to the peracid should be examined in sulfide asymmetric oxidations.

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* "Enantiotopic by internal comparison" means that the groups are in enantiomeric environments within the same molecule.[140]

Other factors, including differences in C-N and C-S bond lengths* and the possibility that the transition states for the two reactions lie at different points along the reaction coordinate, could also account for the difference in asymmetric induction with sulfides and amines.

In conclusion, asymmetric induction in the reaction of tertiary amines with peracids was found to be probably no greater than 1% in any of the cases studied. The low optical yields indicate that the diastereomeric transition states involved must be nearly isoenergetic. This is probably due to the distance between the permanent and incipient asymmetric centers and the conformational mobility of the reactants. No stereocorrelation models** for this asymmetric synthesis will be proposed since we agree[93,94] that it is not reasonable to do so for reactions with such a low order of asymmetric induction.

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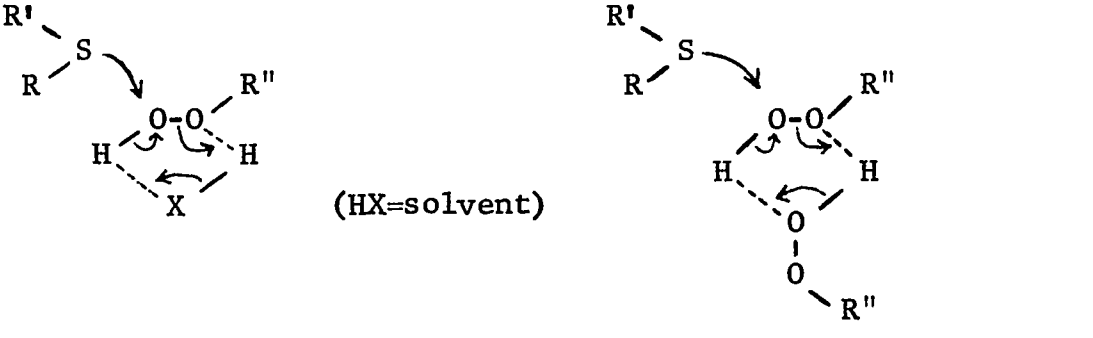
* C-N = 1.51Å; C-S = 1.81Å.

** "Stereocorrelation model" is a term proposed by J. D. Morrison. It refers to the "transition state" models often drawn by workers in the field of asymmetric synthesis to rationalize their stereochemical results. Mislow has criticized the use of "transition state" models[93,94] because the present state of knowledge about exact transition state topologies is not sufficient to warrant simple diagrams, especially where these are used for predictive purposes. The proponents of transition state models reply that the emphasis should be placed upon the word "model". The term stereocorrelation model appeases both factions because it emphasizes that the model which is used is only an attempt to correlate the configurations of the starting materials with those observed to be in excess in the product and does not imply an exact knowledge of the transition state.

III. REACTIONS OF N,N-DIALKYLANILINES AND METHYL PHENYL SULFIDE WITH HYDROPEROXIDES

Introduction

Since one possible cause of negligible asymmetric induction in the reaction of chiral peracids with tertiary amines was the distance between the existing and the incipient asymmetric centers in the reaction transition state, a system in which the two centers could be closer was sought. N-Oxygenation with chiral hydroperoxides (in which the asymmetric carbon atom could be one atom closer to the reaction site) appeared to be one way to accomplish this. If the mechanism of the N-oxidation of tertiary amines with hydroperoxides were similar to that proposed for S-oxidation of sulfides[141,142] (Fig. 3), there appeared to be a better



A (in protonic solvents) B (in nonprotonic solvents)

Figure 3. Proposed transition states for the oxidation of sulfides to sulfoxides.

chance that the differences in energies of the diastereomeric transition states would be large enough to favor the production of an excess of one enantiomer of amine oxide (Fig. 4) than was the case for N-oxidation with chiral peracids.

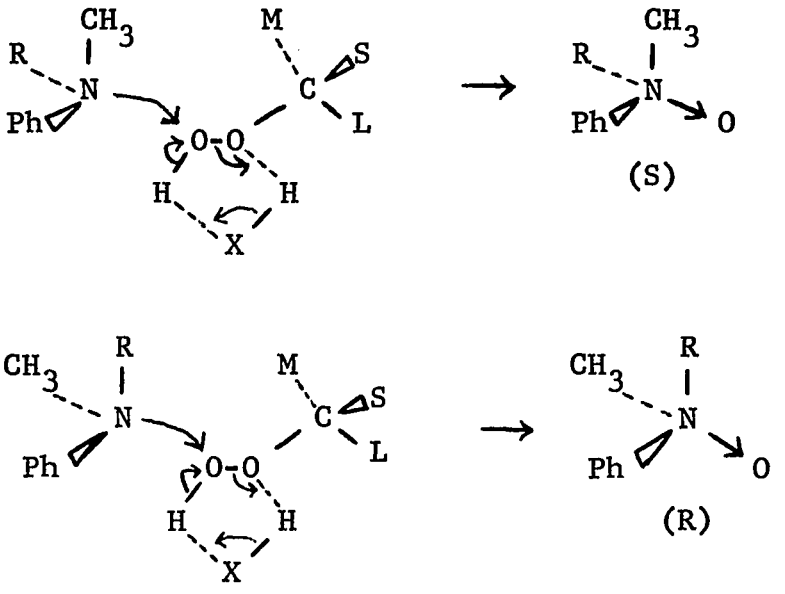


Figure 4. Possible diastereomeric transition states for reactions of N-methyl, N-alkylanilines with chiral hydroperoxides. (Conformations at tetrahedral centers drawn arbitrarily).

Neither sulfides nor amines have previously been oxygenated with chiral hydroperoxides. It was decided to study this reaction using the same N-methyl, N-alkylanilines (1-5a) which had been oxidized with chiral peracids. For reasons to be discussed later, the use of secondary chiral hydroperoxides was planned for the initial work.

Although sulfides have been oxidized routinely to sulfoxides in high yields with achiral hydroperoxides, the analogous reaction with amines has not been studied. Recently, however, amine oxides have been reported to be produced from the reaction of tertiary amines with hydroperoxides in the presence of catalytic amounts of certain Group IV and Group V metal compounds.[44,45] Trialkylamine oxides were prepared in good yields by this procedure but pyridine N-oxide could be obtained only under special

conditions. The N-oxidation of dialkylanilines was not reported.[44,45] A recent patent[143] claimed, however, that N,N-dimethylaniline had been oxidized to the N-oxide using similar catalysts. In all of this work only tertiary hydroperoxides and amylene hydroperoxide (36) (a mixture of tertiary and secondary allylic hydroperoxides) were employed. Reaction conditions (hydroperoxide, solvent, amine, temperature, and catalyst) were critical.

The reactions of tertiary amines and hydroperoxides without catalysts have been studied by various workers with different goals in mind, but amine oxides have never been identified in the product mixtures* Capp and Hawkins in 1953[144] reacted tertiary hydroperoxides with tertiary amines at temperatures from 60 to 120° and obtained, in amounts equivalent to the hydroperoxide decomposed, the corresponding alcohol and water. Non-stoichiometric amounts of the amine were recovered. Other nitrogenous products were not characterized although it was stated that the residue did not appear to contain amine oxides. Reaction of tertiary amines with primary and secondary hydroperoxides has been found to give carbonyl compounds, water, and unchanged amine.[145]

The rapid exothermic reaction of tri-n-propylamine with t-butyl hydroperoxide (37) at 92° was found to yield primarily di-n-propylamine but other unidentified nitrogenous products were also obtained.[146] Coppinger and Swalen[147] observed a nitroxide radical species in this reaction mixture by esr. Heating N,N-dimethylaniline with 37 has also been found to generate radicals useful for initiation of polymerization.[148]

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* In the catalytic N-oxygenation work [45] one reaction without catalyst was noted in a table to give some amine oxide. The reaction was not mentioned elsewhere in the article.

While looking for a free radical antioxidant species in the reaction of trialkylamine with tertiary hydroperoxides at 70°, Harris and Olcott[149] isolated dialkylhydroxylamine in 1% yield. The remainder of the product mixture was not characterized. Oswald[150] found that hydroperoxides formed isolable adducts with tertiary amines but the decomposition of these adducts was not studied.

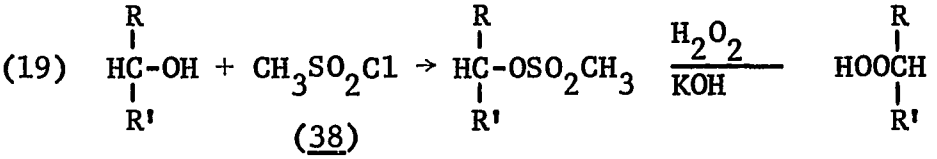
It was our feeling, in spite of the lack of literature evidence, that amine oxides ought to be produced by the reaction of tertiary amines with hydroperoxides. Most of the workers just mentioned were either not concerned with finding amine oxides or did not have good methods to detect them. Some postulated amine oxides as reaction intermediates.[146-149] It appeared to us that the reaction conditions in most of the literature references were such that amine oxide could have been destroyed even if it were formed.

The problem, therefore, became one of attempting to find conditions for the reaction of tertiary amines with hydroperoxides which would be conducive to the formation of amine oxides. Hopefully, these conditions would also allow the eventual study of asymmetric induction in the reaction of chiral hydroperoxides with N-methyl, N-alkylanilines containing in some cases branched alkyl groups.

Preparation of Hydroperoxides

There are no reported methods of preparing optically active tertiary hydroperoxides with the asymmetric center at the tertiary carbon. Optically active straight chain, saturated, secondary alkyl hydroperoxides of reasonable optical purity, however, have been prepared from resolved

alcohols according to equation 19.[151] This sequence was



attempted, but many difficulties were encountered,* the precious resolved alcohols had to be used, and the method was applicable to some compounds but not others.

It was decided to prepare chiral hydroperoxides for routine use instead by the oxygenation of organometallic reagents derived from readily obtainable optically active menthyl or bornyl compounds. Walling and Buckler have prepared the hydroperoxide from bornyl Grignard reagent in good yield by oxygenation at -75°.[152,153] Cadmium and zinc reagents have been oxygenated at higher temperatures to give hydroperoxides.[154] It is not possible by this method, however, to maintain the configurational integrity of the functionally substituted carbon in the sequence from halide to hydroperoxide. During and after formation of the Grignard reagent, equilibration of the configuration at the carbon-metal bond occurs.[155,156] The oxygenation reaction may also not be stereospecific.[152,155,157-159]

Even though the hydroperoxide obtained by oxygenating an organometallic reagent from (-)-menthyl chloride (39) or (-)-bornyl chloride (40) is not isomerically pure it still can be considered a chiral hydroperoxide reagent since the isomers present are epimers rather than enantiomers. For example, the "bornyl" hydroperoxide reagent (41) prepared from (-)-bornyl chloride is actually a mixture of the

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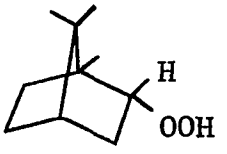
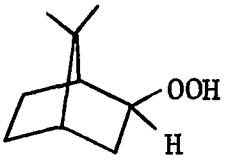
* One of the authors of the original work has pointed out that the reaction may not be general and the present author has confirmed its unpredictable nature. (Personal communication from H. S. Mosher).

hydroperoxides 41a and 41b which upon reduction give (-)-borneol and (+)-isoborneol, respectively.



41a



41b

Due to difficulty in obtaining reasonable yields of Grignard reagents from (-)-menthyl chloride (39) or (-)-menthyl bromide (42), use of the "bornyl" hydroperoxide was planned. Cyclohexyl hydroperoxide (43), prepared either from the Grignard or cadmium reagent, was employed as a model compound to study the reaction of amines with hydroperoxides.

Attempts to Obtain Amine Oxides from the Reaction of Tertiary Amines with Hydroperoxides

The attempts to obtain amine oxide from the reaction of N,N-dimethylaniline with hydroperoxides are summarized in Table 5. In many cases the reactions were begun under much milder conditions than shown but when iodometric titration*

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* Amine oxides can also be titrated iodometrically under some conditions.[160,161] A pure dry sample of N,N-dimethylaniline, N-oxide (1c) titrated only to a negligible extent by the Wibaut room temperature method of hydroperoxide titration[162], but titrated almost totally (97%) under the conditions of an alternate hydroperoxide determining procedure which involved refluxing in isopropanol.[163] Except for reactions 1, 2, and 6, the Wibaut method was used to follow the hydroperoxide-amine reactions.

Table 5

Reactions of Hydroperoxides with N,N-Dimethylaniline

No.	Reagents	Conditions under which ROOH loss occurred	Percent loss of ROOH	Products[a]
1.	0.0117 moles $C_6H_{11}OOMgCl$[b] 0.0133 moles amine 20 ml anhyd. ether (under N_2)	7° 1 hr room temp. 1 day reflux 1 hr[c]	75%	No $PhN(CH_3)_2$ (O) At least 7 compounds present[d]
2.	0.0057 moles $C_6H_{11}OOH$ 0.0200 moles amine 200 ml ether 70 ml dry isopropanol	reflux 6 hrs add 190 ml more isopropanol reflux 3 hrs	35%	Yield[e]: 60% $PhN(CH_3)_2$ (O) 11% $PhNHCH_3$ Some $PhN(CH_3)_2$ (O) may be present but quantity too small to determine[f]
3.	0.0105 moles $C_6H_{11}OOH$ 0.0210 moles amine 100 ml ether 55 ml isopropanol 25 ml water	40° 3 days	20%	Yield[e]: 74% $PhN(CH_3)_2$ (O) 10% $PhNHCH_3$ ca. 1-2% $PhN(CH_3)_2$ (O)[g]

[f]

Table 5. (continued)

No.	Reagents	Conditions under which ROOH loss occurred	Percent loss of ROOH	Products[a]
4.	0.030 moles t-butyl OOH 0.030 moles amine 75 ml H_2O 55 ml isopropanol	reflux (85°) ca. 4 1/2 days reflux 1 day[c]	49%	3 or 4 major products, two of which are $PhN^{\uparrow O}(CH_3)_2$ and $PhN(CH_3)_2$ smaller amounts of $PhNHCH_3$[f]
5.	0.0067 moles $C_6H_{11}OOH$ 0.0067 moles amine	45-50° 8 days	84%	40%[h] $PhN^{\uparrow O}(CH_3)_2$ 26% $PhN(CH_3)_2$ 34% $PhNHCH_3$ 4 minor peaks
6.	0.006 moles $C_6H_{11}OOH$ 0.010 moles amine 0.006 moles $VO(acac)_2$ 200 ml ether	reflux 2 hrs	90%[i]	85%[h] $PhN(CH_3)_2$ 15% $PhNHCH_3$ 1 minor peak No $PhN^{\uparrow O}(CH_3)_2$

Table 5. (continued)

No.	Reagents	Conditions under which ROOH loss occurred	Percent loss of ROOH	Products[a]
7.	0.020 moles t-butyl OOH 0.020 moles amine 0.06 moles t-butanol 0.025 g $VO(acac)_2$	reflux (86°) 1 1/2 hrs	---	81%[h] $PhN(\overset{\uparrow O}{C})_2$ 19% $PhN(CH_3)_2$ [j]
8.	0.00202 moles "menthyl" OOH 0.00202 moles amine 11.5 ml methanol 0.01 g $VO(acac)_2$	60-65° 2 hrs	---	89%[h] $PhN(CH_3)_2$ 11% $PhNHCH_3$ 1 minor peak No $PhN(\overset{\uparrow O}{C})_2$

[a] Aqueous HCl or water soluble products only; percentages only approximate, based on nmr analysis.

[b] C_6H_{11} = cyclohexyl. [c] Analysis before and after this time period revealed no further loss of ROOH. [d] In this case glpc analysis was done in addition to the nmr analysis.

[e] Based on starting amines. [f] Other products are also present in small amounts.

[g] Roughly 15-25% yield based on hydroperoxide conversion. [h] Percentages refer to the percent of the total identified aqueous HCl soluble material.

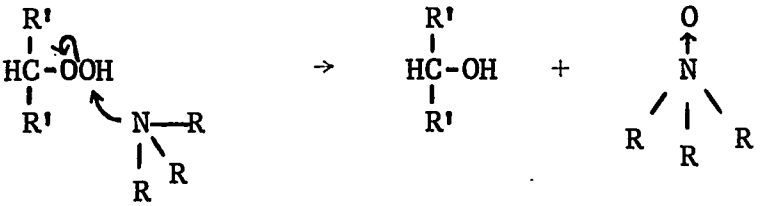
[i] The titration values for hydroperoxide are probably not valid in the presence of the vanadium compound.

[j] Possible minor components were not observable due to poor resolution of the spectrum.

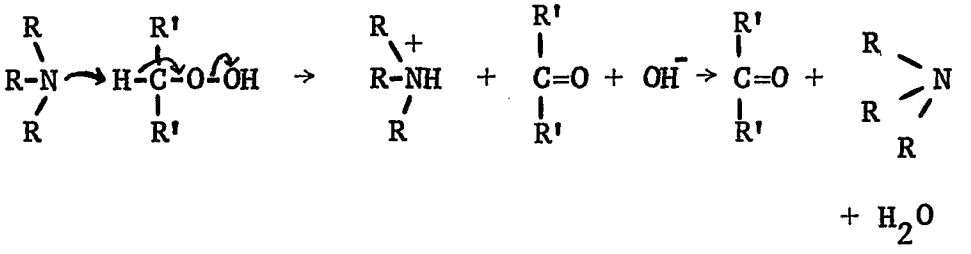
showed no loss of hydroperoxide the solvent was changed or the temperature was increased. Hydroxylic solvents increased the rate of loss of hydroperoxide. Only the products soluble in water or aqueous hydrochloric acid were analyzed. No attempt at detailed analysis of products was made because the primary concern was the detection of amine oxide in the product mixture.

Relatively large amounts of N-oxide were finally formed in uncatalyzed reactions 4 and 5 and catalyzed reaction 7. Other major products were tertiary amine 1a and secondary amine (N-methylaniline 20), but several unidentified components were also present in some product mixtures. Reactions 2,4, and 8 turned purple as loss of hydroperoxide proceeded.

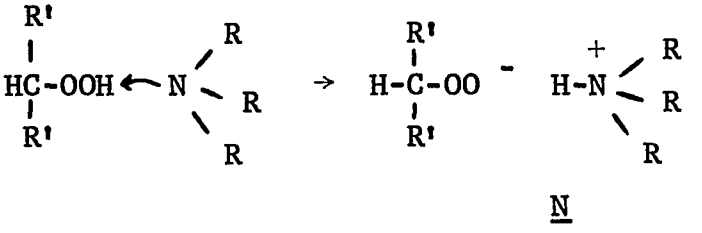
Unlike the reaction between sulfides and hydroperoxides, or amines and peracids, the reaction between tertiary amines and hydroperoxides appears to be extremely complex. Many competing reactions can be envisaged. There are three sites on a secondary alkyl hydroperoxide molecule where the amine could attack and give products by heterolytic bond breaking. These are (a) attack on the electrophilic β-oxygen to give amine oxide and alcohol (eqn 20), the reaction analogous to sulfide oxidation with hydroperoxides and amine oxidation with peracids; (b) attack on the

(20) 

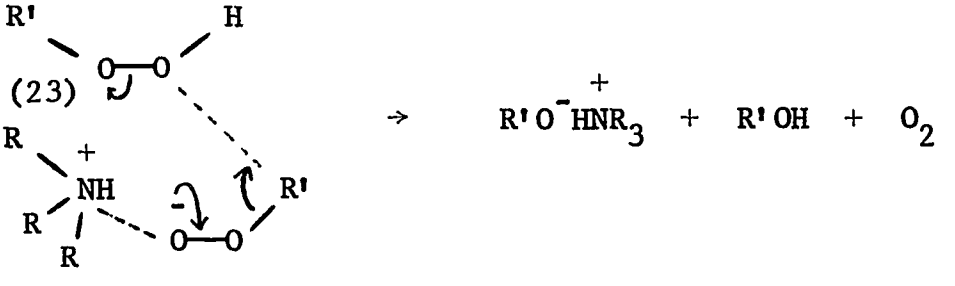
α-hydrogen to give a ketone, water, and unchanged amine[145] (eqn 21); and (c) attack on the acidic hydrogen of the

(21) 

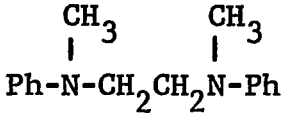
hydroperoxide to give alkylammonium peroxides (eqn 22).

(22) 

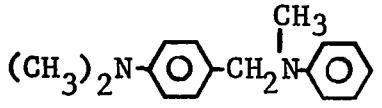
Such adducts (N) with tertiary hydroperoxides have been found to be isolable and stable at room temperature but those with secondary hydroxides slowly decomposed.[150] Decomposition products were not reported, although amine oxides might be expected by analogy to their ready formation from tertiary amine adducts with 90% hydrogen peroxide.[164] One could also write, however, reactions analogous to the mechanism proposed for the decomposition of the sodium salt of t-butyl hydroperoxide (eqn 23).[165] Other decomposition pathways might also be possible.

(23) 

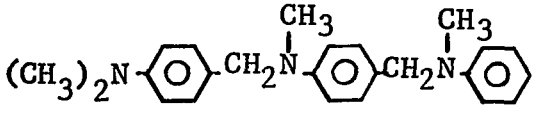
Reaction between N,N-dimethylaniline and hydroperoxides could also occur via free radical pathways. Many products, 7, 8,[66] 20,[169,171] 44-55[166-172], could arise from initially formed radicals 56[173] or 57.[174]



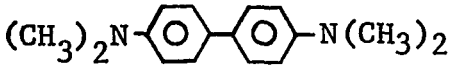
44 (ref 166)



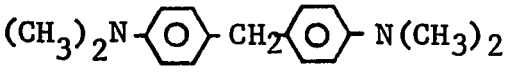
45 (ref 66,167)



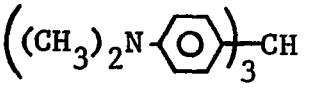
46 (ref 66,167)



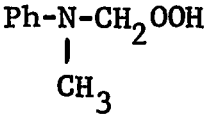
47 (ref 168)



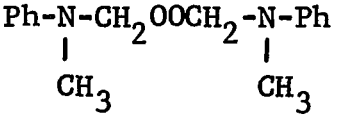
48 (ref 66)



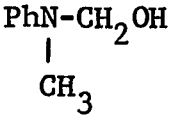
49 (ref 66)



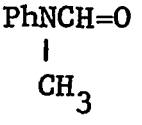
50 (ref 169)



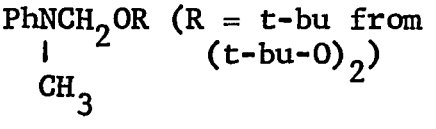
51 (ref 169)



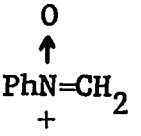
52 (ref 169)



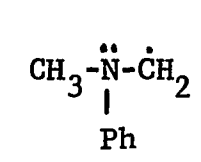
53 (ref 169,170)



54 (ref 167)



55 (ref 172)



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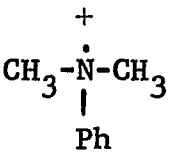

57

It could not be determined whether low yields of amine oxide were due to destruction of initially formed amine oxide under the reaction conditions or whether alternate products were formed instead. The N-methylaniline detected could have arisen by many routes; oxidative dealkylation of the tertiary amine,[171] decomposition of amine oxide,[69] or decomposition of coupling products.[69,9] Some of the N,N-dimethylaniline may have also been formed by decomposition of amine oxide or other products.

Reactions 6, 7, and 8, involve catalysis by vanadium oxyacetylacetonate (58). t-Butyl hydroperoxide in refluxing t-butanol gave good yields of amine oxide from both N-methyl, N-ethyldodecylamine (not included in Table 5) and N,N-dimethylaniline (1a). However, no amine oxide was obtained under the listed reaction conditions when the hydroperoxides were secondary.

Decomposition of the hydroperoxide to give non-amine oxide products and catalytic oxidation, to give amine oxide are competing. Since the decomposition reaction is very temperature dependent, the stability of the hydroperoxide to this reaction determines the limiting temperature for optimum yields of amine oxide. As mentioned previously, catalytic oxidations have been studied only with a very limited number of hydroperoxides. No secondary alkyl hydroperoxides were used. Secondary hydroperoxides appear to be much less stable to amines than tertiary hydroperoxides.

Catalyst, solvent type and steric properties, and amine type and steric properties, can all greatly affect the balance between the competing reactions.[45] It may be possible to find a system in which amine oxides would be produced from tertiary amines and chiral hydroperoxides but many further studies of the many variables in the reaction will be necessary.

Initial thinking on the reaction of tertiary amines with hydroperoxides was that if the reaction were run at lower temperatures than those in the literature, it might be possible to avoid generation of free radicals and decomposition of any amine oxide formed. The problem encountered was that N,N-dimethylaniline would not react with the tertiary hydroperoxide at lower temperatures. Although the energy of 0-0 homolytic bond breaking is about the same for t-butyl and cyclohexyl hydroperoxides,[175,176] cyclohexyl hydroperoxide (43) was found to be much more reactive (in terms of hydroperoxide loss) toward the amine.* This might be a consequence of the greater acidity of 43[177] which could increase the rates of reaction with the amine at both the β-oxygen (eqn 20) and the acidic hydrogen (eqn 22). If such were the case, the reaction of primary hydroperoxides with tertiary amines might be even more conducive to the production of amine oxides. However, the observed more rapid loss of 43 may be due instead to amine catalyzed decomposition to cyclohexanone (eqn 21), a reaction not possible for the tertiary hydroperoxide. The products of reaction 5 show that carbonyl forming elimination could not have been the only reaction of cyclohexyl hydroperoxide.

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* Compare reactions no. 3 and 4 (Experimental): Reaction 3 - 20% loss of hydroperoxide after three days at 40°. Reaction 4 - no loss of hydroperoxide after twelve days at 45-48°.

If it were, no N,N-dimethylaniline, N-oxide or N-methylaniline would have been formed. If, however, equation 21 does represent a major reaction of 43, little would be gained in using primary hydroperoxides which decompose in an analogous manner even more rapidly.

The lack of similarity of the reactions of hydroperoxides with amines and sulfides is probably due to the difference in basicities of the two types of compounds. The amines, being more basic, prefer to react as bases according to equations 21 and 22 rather than as nucleophiles according to equation 20. Also, since the sulfide reaction with hydroperoxides can proceed at lower temperatures than the amine reaction, it would be less likely to involve free radicals generated by thermal scission of the peroxide bond.

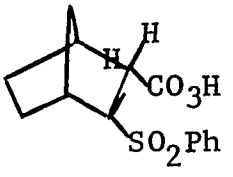
This work has shown in spite of the lack of previous evidence that under some, if not all, conditions amine oxides are produced in the reaction of tertiary amines with hydroperoxides. Although future work may show that oxidation with primary or secondary hydroperoxides can give good yields of amine oxides or that an applicable combination of conditions can be found for the metal catalyzed reaction, the present yields of amine oxide and complex product mixtures make it impossible at this time to study asymmetric induction in the hydroperoxide N-oxygenation reaction.

The Reaction of "Bornyl" Hydroperoxide with Methyl Phenyl Sulfide

Although this thesis work was initially to involve only the reactions of amines and amine oxides with chiral reagents, the oxidation of sulfides with the chiral hydroperoxide which had been prepared appeared to be a particularly propitious asymmetric synthesis to study. The reaction with achiral substrates is known and the mechanism

has been investigated (Fig 5).[141,142,178,179] A chiral sulfide has been oxidized to unequal amounts of diastereomeric sulfoxides with an achiral hydroperoxide (37),[180] but the reaction of achiral sulfides with chiral hydroperoxides has not been studied.

Chiral peracid oxidations of achiral sulfides have been discussed at length in recent years.[89-97] The optical yields of sulfoxides from these reactions usually ranged from 0 to 5%. For example, methyl phenyl sulfide (59) oxidations gave methyl phenyl sulfoxide (60) with an enantiomeric excess of 0.8% with (S)-(+)-2-methylbutyric acid and 5.4% with (3R)-(+)-2-endo-phenylsulfonylbicyclo-[2,2,1]heptane-3-endo-percarboxylic acid (61).[96b]



61

As mentioned before, oxidation with a chiral hydroperoxide might give a higher optical yield than oxidation with peracids because the asymmetric center of the hydroperoxide could be closer to the incipient asymmetric center in the reaction transition state.

When a slight excess of "bornyl" hydroperoxide (41) prepared *via* the cadmium reagent from (-)-bornyl chloride (40) was stirred with methyl phenyl sulfide (59) for five days at 40°, one equivalent of hydroperoxide was lost. The sulfoxide obtained had a rotation $[\alpha]D$ -1.89 ± 0.15 (*c* 1.75, absolute ethanol) corresponding to a 1% enantiomeric excess of the *S*-isomer. Nmr and glpc analysis showed the product to be free from impurity.

The observation of only a 1% enantiomeric excess of (S)-(-)-60 does not necessarily indicate that the reaction goes with low asymmetric induction. The chiral oxidizing agent was actually a mixture of two diastereomeric hydroperoxides (41a and 41b) and it is possible that oxidation of 59 by 41a gives the enantiomer of 60 opposite to that obtained by oxidation with 41b. The ratio of 41a to 41b prepared from the cadmium reagent has not been determined although Walling and Buckler[152] did show that when prepared from Grignard reagent the hydroperoxide contained about 56% 41a and 44% 41b.

"Bornyl" hydroperoxide reacts with 59 only slowly. If one hydroperoxide diastereomer reacts more rapidly with 59 than the other, comparison of the optical yield of 60 using an equivalent of sulfide with that using less than an equivalent would tell whether 41a and 41b produce 60 of opposite chirality. To determine what isomeric ratio of 41a and 41b had reacted, the ratio of borneol (62) to isoborneol (63) produced during the sulfide oxidation would have to be determined. If significant amounts of alcohols were formed in the oxidation of the organometallic, analysis of alcohol ratios may have to be compared before and after oxidation of the sulfide. Unreacted 41 could be decomposed by heating at 65° in benzene to (-)-camphor (64) and (-)-α-campholenic acid (65)[152] and separated out. Alternatively, aqueous sodium hydroxide extraction could remove the hydroperoxide, but lack of success with this process has been noted.[152]

The reaction will probably need to be repeated using only one chiral isomer of hydroperoxide. The preparation of such a hydroperoxide might be difficult. One could approach the problem by oxygenating a Grignard reagent which had been

enriched in one isomer (either by "isomerizing" it[157] or by reacting it with some reagent which preferentially destroys one isomer.)[156,157] However, if the oxygenation of Grignards is not stereospecific,[152,155,157-159] enriching the Grignard in one isomer would serve no purpose.

An alternate approach would be to selectively destroy one of the diastereomeric hydroperoxides before reaction with the sulfide. The bornyl hydroperoxide reagent has been found to slowly decompose with heat or base.[152] One diastereomer might decompose faster than the other.

t-Butyl phenyl sulfide (66) may prove to be a selective destructive agent by reacting preferentially with 41a and 41b to give t-butyl phenyl sulfoxide (67). After the oxidation of less than an equivalent of 66, 59 could be added to react with the remaining hydroperoxide. The sulfoxides 60 and 67 are easily separable since 60 is soluble in water and 67 is soluble in ether. Separation of 67 from the other ether soluble products (to determine asymmetric induction in its formation, if desired) can be accomplished by column chromatography.[181]

Further work on the asymmetric induction reaction of unsymmetrical sulfides with chiral hydroperoxides is being pursued in these laboratories.

EXPERIMENTAL

General

Melting Points. Melting points were determined using a Mel-Temp capillary melting point apparatus and are uncorrected.

Infrared Absorption Spectra. All infrared spectra were obtained using a Perkin-Elmer Model 337 grating spectrophotometer. Mulls of solids were prepared with Halocarbon Oil for the region from 4000 cm^{-1} to 1350 cm^{-1} and with Nujol for the region from 1350 cm^{-1} to 650 cm^{-1}. Liquids whose spectra were determined neat were run as films between salt plates. Cells for the spectra of solutions had a 0.1 mm thickness.

Ultraviolet Absorption Spectra. The ultraviolet absorption spectra were determined using a Cary Model 14 recording spectrophotometer.

Nuclear Magnetic Resonance Spectra. Nuclear magnetic resonance spectra were determined using a Varian Model A-60 Spectrometer. Unless otherwise noted the chemical shifts are given in ppm relative to an internal TMS standard when the solvent is chloroform or deuterochloroform but relative to an external TMS (in chloroform) standard when the solvent is water or deuterium oxide.

Optical Rotation Data. All optical rotation data was obtained on a Carl Zeiss Photoelectric Precision Polarimeter, 0.005° equipped with a mercury vapor lamp as the light source and filtered to be used at 578, 546, 435, 405, and 365 nm. Error limits reported are based on the $\pm$ 0.005° measuring tolerance of the instrument. Rotation readings were taken until three sets of values at all possible wave-

lengths agreed within the ± 0.005° limit. Standard Zeiss 0.5 and 1.0 dm polarimeter tubes with a 6 mm free diameter were used for precise work. For routine measurements a 1 dm end-fill and a 1 dm center-fill tube, both with approximately a 1 ml capacity, were sometimes used. Ord spectra were determined on a Rudolph Recording Spectropolarimeter Model 260/655/850/810-614.

Gas Chromatography. Gas chromatographic analyses were conducted using a Perkin-Elmer Model 154 Vapor Fractometer or a Varian Aerograph Model 90-P.

Analyses for Peroxy Compounds. Peracid yields were determined by iodometric titration according to the methods used by Braun[182] and Swern and coworkers.[130] An iodometric titration under different conditions[183] was used to detect diacyl peroxides. Titration for hydrogen peroxide in the presence of peracid was accomplished by the method of Greenspan and MacKeller.[184a]

Hydroperoxide content was determined by thiosulfate titration of the iodine liberated by the sample from (a) sodium iodide and glacial acetic acid in dry isopropanol after refluxing for 5 minutes (Wagner method)[163] or (b) a mixture of sodium bicarbonate, glacial acetic acid and 40% aqueous potassium iodide in the dark at room temperature for 10 minutes (Wibaut method).[162] Since amine oxides were found to titrate by the Wagner but not the Wibaut method, the latter was used in most cases when amine oxides were believed to be present. In the Wibaut method, oxygen is excluded by generation of a carbon dioxide atmosphere on mixing the reagents. However, the sample may not be added until evolution of carbon dioxide has ceased. This was most easily accomplished by suspending a 5 ml beaker by a thread inside a 250 ml stoppered filter flask whose side arm was

connected to a tube submerged in a beaker of water. When the reagent was ready the beaker was dropped in.

Preparation of N-Methyl, N-alkylanilines

N-Methyl, N-ethylaniline (2a), N-Methyl, N-isopropylaniline (3a), and Kairoline (5a). (Methylation of N-Alkylanilines). The following reaction procedure for the N-methylation of N-isopropylaniline (68) (Aldrich)* with dimethyl sulfate is typical of the procedures also followed with N-ethylaniline (69) (Eastman) and 1,2,3,4-tetrahydroquinoline (70) (Aldrich).

To 150.7 g (1.11 mol) of 68 warmed to about 40° in a flask fitted with a stirrer, thermometer, addition funnel, and reflux condenser, was slowly added 106 ml (141 g, 1.12 mol) of dimethyl sulfate. During the addition (1.25 hr), the temperature varied from 80-112°. After stirring for 2 hr longer at 95-105° the reaction was cooled to room temperature and 78.5 g (1.40 mol) of potassium hydroxide in 100 ml of water was added, keeping the temperature below 40°. Water (25 ml) was added to dissolve the solid formed and the layers were separated. The organic layer was combined with the residue from the evaporated ether extracts (3 x 100 ml) of the aqueous layer. An equal volume (about 100 ml) of acetic anhydride was added. After allowing the reaction mixture to stand overnight, 90 ml of concentrated hydrochloric acid in 135 ml of water was added with cooling.

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* Before N-isopropylaniline became so readily available it was prepared (in 76% yield) by the reaction of aniline with isopropyl phosphate.[184b] Isopropyl phosphate was prepared from phosphorous oxychloride and isopropanol in 71% yield by the method of Dutton and Noller.[184c]

Ether extracts (200, 100, 100 ml) of this mixture were discarded and the aqueous layer was made basic with 25% sodium hydroxide (290 ml). Two layers separated. Ethereal extracts (3 x 100 ml) of the aqueous layer were added to the organic layer and dried over magnesium sulfate. The ether was removed and the residue was distilled to give 105.8 g (64%) of tertiary amine, 3a: bp 61-61.5° (0.6 mm) [lit.[185] bp 212-213° (760 mm); ir (no. 9, neat) no N-H; nmr (no. 3225, neat, internal TMS) 0.95 (d, J = 6.5 Hz, $CH(C\underline{H}_3)_2$), 2.49 (s, $N\text{-}C\underline{H}_3$), 3.89 (m(7), J = 6.5 Hz) and 6.65-7.54 ppm (m, Ar); glpc (15% Silicone GE XE-60 (nitrile gum) on Chromosorb W, KOH washed, 151°) greater than 99% purity. A 64% yield of 3a was also obtained with a higher reaction temperature (135°).

N-methyl, N-ethylaniline (2a) was prepared in 48-50% yield by addition of dimethyl sulfate to N-ethylaniline (69) over 1 hr at about 100° and subsequent reaction at either 140-150° for 2.5 hr or at 97° for 22.5 hr;* bp 54-55° (0.3 mm) [lit.[186] bp 93-95° (12 mm)]; ir (no. 32, neat) no N-H; nmr (no. 3311, neat, internal TMS) 0.90 (t, J = 7 Hz, $CH_2C\underline{H}_3$), 2.62 (s, $N\text{-}C\underline{H}_3$), 3.14 (q, J = 7 Hz, $C\underline{H}_2CH_3$) and 6.52-7.40 ppm (m, Ar); glpc (15% Silicone GE XE-60 (nitrile gum) on Chromosorb W, KOH washed, 151°) greater than 96% purity.

Nmr dilution shifts in $CDCl_3$: (no. 3311, $CDCl_3$, 42.1 mole % amine) 1.02 (t, J = 7 Hz, $CH_2C\underline{H}_3$), 2.76 (s, $N\text{-}C\underline{H}_3$) 3.27 (q, J = 7 Hz, $C\underline{H}_2CH_3$), and 6.52-7.40 ppm (m, Ar); (no. 3311, $CDCl_3$, 18.6 mole % amine) 1.09 (t, J = 7 Hz, $CH_2C\underline{H}_3$), 2.88 (s, $N\text{-}C\underline{H}_3$), 3.37 (q, J = 7 Hz, $C\underline{H}_2CH_3$) and 6.52-7.40 ppm (m,

* After only 3 hr at 97° the ratio of tertiary to secondary amine was already 3:1 as determined by nmr (no. 5378).

Ar). The appearance of the aromatic region is quite altered on change from pure liquid to $CDCl_3$ solution and on dilution in $CDCl_3$.

Kairoline (5a) was prepared in a 34% yield by addition of dimethyl sulfate to 1,2,3,4-tetrahydroquinoline (70) at about 90° over 1 hr and stirring at about 100° for 4.5 hr. The product was distilled in the dark and stored under nitrogen because it discolored so rapidly: bp 71° (0.45 mm) [lit.[27] bp 112° (8 mm)]; ir (no. 74, neat) no N-H; nmr (no. 5803, $CDCl_3$) 1.50-1.90 (m, 2, $CH_2\underline{CH_2}CH_3$), 2.40-3.00 (m, 4, $Ar\underline{CH_2}$ and $N\text{-}\underline{CH_2}$), 2.55 (s, 3, $N\text{-}\underline{CH_3}$), and 6.29-7.14 ppm (m, 4, Ar); glpc (15% Silicone GE XE-60 (nitrile gum) on Chromosorb W, KOH washed, 151°) about 6% (by triangulation) of a lower boiling impurity which could not be removed by distillation.

N-Methyl, N-t-butylaniline (4a). (A) From N-Methylaniline and t-Butyl Bromide. In a 500 ml flask fitted with a mechanical stirrer, thermometer, and reflux condenser were placed 43.0 g (0.4 mol) of N-methylaniline, 96.7 g (0.7 mol) of anhydrous potassium carbonate, and 68.0 g (0.5 mol) of t-butyl bromide. After stirring under reflux for 1.5 hr the reaction mixture solidified. Infrared (no. 65, $CHCl_3$) showed that N-methylaniline hydrobromide had been formed. A small sample of the reaction mixture was made basic, extracted into chloroform, and dried over sodium sulfate, and the chloroform was removed to give an oil with a ratio of intensities of NH:phenyl (1600 cm^{-1}) absorption bands in the infrared (no. 67, neat) similar to that in the initial reaction mixture.

Water (100 ml) was added to the reaction mixture to dissolve the potassium carbonate, forming two liquid phases.

An additional 34.5 g (0.25 mol) of potassium carbonate and 17.0 g (0.125 mol) of t-butyl bromide were added and the mixture was heated to 65-70° for 3.75 hr, then allowed to stand at room temperature overnight. The infrared spectrum (no. 71, neat) again showed no significant change in the ratio of intensities of the NH and phenyl (1600 cm^{-1}) absorption bands. The nmr spectrum (no. 5377, neat) of the amine layer, however, showed that about 21% of the total amine was N-methyl, N-t-butylaniline (4a). The addition of 17.7 g (0.129 mol) more of t-butyl bromide and heating at 45-70° for 23 hr increased the percentage of 4a in the total amount of amine only to 25% (NMR no. 5384, neat).

Aqueous potassium hydroxide was added to the reaction mixture and the layers were separated. Ether extracts of the aqueous layer were combined with the organic layer, dried, and the ether removed. The product was allowed to stand overnight with an equal volume of acetic anhydride and 50 ml of concentrated hydrochloric acid in 100 ml of water was added. The mixture was washed with ether (7 x 50 ml) and the ether was discarded. The aqueous solution was made strongly basic and extracted with ether (3 x 50 ml). The ether extract was dried, the ether was removed, and the residue was distilled to give 8.40 g (13%) of 4a: bp 64-65° (0.7 mm) [lit. bp 93° (15 mm)[114]; 81-82° (39 mm)[116]]; ir (no. 64, neat) no N-H, 1670 cm^{-1} (trace of amide impurity); nmr (no. 5450, neat, internal TMS) 1.07 (s, 9, $C(C\underline{H}_3)_3$), 2.66 (s, 3, N-$C\underline{H}_3$) and 6.89-7.24 ppm (m, 5, Ar).

N-Methyl, N-t-butylaniline (4a). (B) From an Iminium Salt. N-Methylanilinium Perchlorate (24). Perchloric acid solution (70%, 1:1 in ethanol) was added to 33.86 g (0.320 mol) of freshly distilled N-methylaniline in

150 ml of ether until the solution became just acid to Congo red. Upon removal of solvent under reduced pressure (behind a safety shield) a pale green semisolid was obtained. Recrystallization from (1:1) ether-isopropanol (25 ml) yielded 32.76 g (49%) of 24 as waxy white plates, mp 68-71°. This procedure is similar to the perchlorate salt preparations of Leonard.[187]

Isopropylidene N-Methylanilinium Perchlorate (23). A mixture of 32.76 g (0.158 mol) of 24, 9.16 g (0.158 mol) of anhydrous acetone, and 16.40 g (0.158 mol) of 2,2-dimethoxypropane (a water scavenger) was stirred at 60-70°. The reaction was followed by observing the relative intensities of the ir peaks at 1710 cm^{-1} (C=O, acetone) and 1660 cm^{-1} ($C=\overset{+}{N}<$, iminium salt). After a reaction time of 5.5 hr the solvent was removed under reduced pressure. The white solid obtained was washed with ether and recrystallized from isopropanol to yield 28.6 g (73%) of 23 as pale gray needles: mp 116-123°; ir (no. 58, $CHCl_3$) 1660 cm^{-1} (s, $C=\overset{+}{N}<$); nmr (no. 5196, $CDCl_3$) 2.35 (s, 3), 2.84 (s, 3), 3.92 (s, 3) and 7.57 ppm (s, 5). Since it appeared that much of the solid product was lost in the recrystallization, the mother liquor was evaporated and the solid residue was analyzed by nmr: (no. 5280, 5302, D_2O) 2.85 (s, 3), 4.63 (s, 3) and 7.27 ppm (s, 5). This product was not identified.

N-Methyl, N-t-butylaniline (4a). To the Grignard reagent prepared from 32.6 g (0.230 mol) of methyl iodide in 250 ml of anhydrous ether was added slowly, under nitrogen, 27.9 g (0.113 mol) of 23. The mixture was heated under reflux for 1.5 hr and stirred overnight at room temperature. After hydrolysis with saturated ammonium chloride, the product was extracted into ether, dried over magnesium sulfate, and the ether removed by distillation. An nmr spectrum (no. 5227)

showed the crude amine (13.05 g) to be about 23% N-methyl, N-t-butylaniline and 77% N-methylaniline. Further extraction of the aqueous layer of the reaction after removal of Mg^{2+} as MgF_2[188] yielded no additional product. Workup similar to that for 4a preparation by method (A) afforded 3.48 g (19%) of 4a: bp 43-45° (2.5 mm); nmr (no. 5246, neat, external TMS) 0.74 (s, $C(CH_3)_3$, 2.32 (s, N-CH_3) and 6.66-6.89 ppm (m, Ar); glpc (15% Silicone GE XE-60 (nitrile gum) on Chromosorb W, KOH washed, 151°) greater than 96% purity.

Preparation of N-Methyl, N-Alkylaniline N-Oxides

Preparation of N-Methyl, N-isopropylaniline N-Oxide (3c) with 30% Hydrogen Peroxide. A mixture of 25.07 g (0.168 mol) of N-methyl, N-isopropylaniline (3a) and 43 ml (0.422 mol) of 30% hydrogen peroxide in 130 ml of 95% ethanol was stirred at 44-48° for 48 hr.* Excess hydrogen peroxide was destroyed by adding a pinch of platinum black** and stirring overnight at room temperature. The ethanol was evaporated at room temperature under reduced pressure and the residue was dissolved in water (30 ml) and washed with low boiling petroleum ether (4 x 50 ml). The water was removed over a seven hour period by evaporation at room temperature on a rotary evaporator with a vacuum pump. There was obtained 23.2 g (84%) of a red-brown viscous oil, primarily the N-oxide, 3c: nmr (no. 4706, H_2O) 0.97 (d, J = 6.5 Hz, $CH(CH_3)CH_3$), 1.16 (d, J = 6.5 Hz, $CH(CH_3)CH_3$),

* Previous experiments had shown that after a three hour reaction period only a 10% yield of 3c was obtained. After an eight hour period the yield was 29%.

** Caution should be observed for fires can occur.

2.97 (s), 3.39 (s, N-C$\underline{H}_3$), 3.92 (m (7), $\underline{J}$ = 6.5 Hz, C$\underline{H}$(CH_3)CH_3), and 7.35-7.78 ppm (m, Ar).

Starting material, 3a, (contaminated with impurities) was recovered in 14% crude yield by evaporation of the petroleum ether wash: nmr (no. 4707, neat, internal TMS, relative intensities given) 0.96 (d, 76, $\underline{J}$ = 7 Hz, CH($C\underline{H}_3$)$_2$), 0.98 (t, 11, $\underline{J}$ = 7-8 Hz), 1.63 (s, 5), 2.51 (s, 38, N-C$\underline{H}_3$), 3.91 (m (7), 15, $\underline{J}$ = 7 Hz, C$\underline{H}$(CH_3)$_2$, 6.53-7.45 (m, 112, Ar) and 8.14-8.29 ppm (m, 25).

After six months of cold storage in a desiccator, with an occasional exposure to air, the sample of 3c gave an nmr spectrum in which new peaks appeared at 1.20 (low field peak of what appears to be a partially concealed doublet), 1.97 (s), 2.71 (s), 3.00-3.11 (br), and 3.61-4.21 ppm (m) and the aromatic region was broadened to 6.61-7.95 ppm (NMR no. 5542, $CDCl_3$).

Heating the sample of partially decomposed 3c at 70° for 2.5 hr reduced 3c to a minor component and increased the intensities of the other peaks seen in the NMR spectrum no. 5542, allowing the doublet centered at 1.15 ppm ($\underline{J}$ = 6.5 Hz) to become clearly visible (NMR no. 5544, $CDCl_3$).

Preparation of N,N-Dimethylaniline N-Oxide (1c) and N,Methyl,N-ethylaniline N-Oxide (2c) with 30% Hydrogen Peroxide. Compounds 1c and 2c were obtained as brown oils in a manner analogous to that used to prepare 3c. The crude yield of 1c was 42% after a reaction period of 3.75 hr and that of 2c was 75% after 8.5 hr. NMR spectra: Product 1c (no. 3226, $CDCl_3$): 3.60 (s, 6, N-($C\underline{H}_3$)$_2$), 5.37 (s, 23, H_2O), and 7.21-8.30 ppm (m, 5, Ar). Product 2c (no. 3430, $CDCl_3$): 1.07 (t, $\underline{J}$ = 7 Hz, $CH_2C\underline{H}_3$), 3.60 (s, N-C$\underline{H}_3$), 3.80 (doubled quartet, $\underline{J}$ = 7 Hz, C$\underline{H}_2CH_3$), 5.05 (s, H_2O), and 7.28-8.14 ppm (m, Ar).

Preparation of N,N-Dimethylaniline N-Oxide (1c) with 30% Hydrogen Peroxide in Acetic Anhydride. Compound 1c was prepared in pure dry form by the reaction of the amine (1a) with 30% hydrogen peroxide in acetic anhydride at 70° according to the procedure of Belov and Savich.[25] The slightly yellow crystals obtained by recrystallization from large amounts (several liters) of carbon tetrachloride or from carbon tetrachloride containing small amounts of chloroform, were collected by filtration and portions were sealed in numerous small bottles in a dry atmosphere and stored over phosphorous pentoxide in a desiccator. These samples remained unchanged on storage in the refrigerator for at least one year.

Preparation of N-Methyl, N-isopropylaniline N-Oxide (3c) with 30% Hydrogen Peroxide in Acetic Anhydride. The procedure of Belov and Savich[25] for the N-oxygenation of N,N-dimethylaniline (1a) was followed using N-methyl, N-isopropylaniline (3a) as the amine. An orange oil was obtained by evaporation of the dried chloroform extract. This residue could not be induced to solidify even by removing the last traces of solvent or water by evaporation under the reduced pressure of a vacuum pump on a rotary evaporator. The nmr spectrum (no. 5422, $CHCl_3$) showed the presence of two major components, one of which was probably the desired amine oxide, 3c. Washing the crude oil with ether or low boiling petroleum ether (in which amines but not amine oxides are soluble) effected no separation of the components. Nmr peaks in addition to those assigned to 3c were present at 3.02 ppm and in the aromatic region in the ratio of 1 to 2, respectively (NMR no. 5431, $CDCl_3$). The intensity of the signal at 3.02 ppm was twice that of the peak assigned to N-CH_3 in 3c.

Preparation of N-Methyl, N-isopropylaniline N-Oxide (3c) with Monoperphthalic Acid. A solution of 8.95 g (0.06 mol) of N-methyl, N-isopropylaniline (3a) in 10 ml of anhydrous ether was added to a solution of monoperphthalic acid (0.0902 mol) in 200 ml of ether, keeping the temperature below 8°. Colorless oil immediately separated. The reaction mixture was kept in the refrigerator for about 2 hr and the ether layer was decanted from the crude oil (phthalic acid salt of 3c). Attempts to crystallize this oil neat or from ethyl acetate-ethanol solution failed. The solvent was evaporated at room temperature under reduced pressure and the residue was made basic with 40% potassium carbonate (25 ml) and then extracted with several portions of chloroform (100 ml). After drying over sodium sulfate in the refrigerator, the chloroform was removed under reduced pressure at room temperature. Portions of absolute ethanol (3 x 10 ml) were added and evaporated to give a pale yellow oil. The nmr spectrum of the oil (no. 5491, $CDCl_3$) showed peaks due to the expected product 3c, ethanol, and a small amount of impurity giving a singlet at 3.08 ppm. The oil was rinsed into a flask with a small portion of absolute ethanol and placed in a vacuum desiccator over phosphorous pentoxide. The desiccator was evacuated with a vacuum pump and stored in the refrigerator for 10 days during which time the product slowly solidified to a pale yellow solid: nmr (no. 5540, $CDCl_3$) 1.03 (d, J = 6.5 Hz, $CH(\underline{CH_3})CH_3$), 1.15 (d, J = 5-7, high field peak of doublet partially obscured), 1.38 (d, J = 6.5 Hz, $CH(CH_3)\underline{CH_3}$), 3.08 (s), 3.45 (s, $N\text{-}\underline{CH_3}$), 3.91 (m (7), J = 6.5 Hz, $C\underline{H}(CH_3)_2$) and 6.66-8.00 ppm (m). The relative intensities of the $N\text{-}CH_3$, 3.08 ppm, and 1.15 ppm peaks were 35, 22, and 4, respectively.

Preparation of N-Methyl, N-ethylaniline, N-Oxide (2c) with Monoperphthalic Acid. A procedure identical to that used to prepare 3c was followed. The product 2c started to solidify on evacuation of the vacuum desiccator and was obtained after storage for one day in the refrigerator as a pale yellow, slightly oily solid, mp 70-75° [lit.[84] mp 102-103°]. The nmr (no. 5547, $CDCl_3$) was identical to that of 2c prepared with aqueous 30% hydrogen peroxide, except that this sample showed no trace of water. A weak triplet under and slightly downfield from the $CH_2\underline{CH_3}$ triplet could be seen. After 22 days of cold storage in a desiccator over phosphorous pentoxide, thin layer chromatography on Silica GF microplates with absolute ethanol eluent showed a barely visible trace of a rapidly migrating impurity. A sample of 2c allowed to stand at room temperature before chromatography showed more of this impurity and an additional slow moving spot. The amine oxide spot was stationary. Cold storage for one year in the same manner produced a large amount of N-methyl, N-ethylaniline (2a) (NMR no. 7158, $CDCl_3$).

NMR Studies of Hydrogen Bonding of Chloroform to Amine Oxides

Amine Oxides. The N,N-dimethylaniline N-oxide (1c) used was the dry purified material prepared by oxidation of the amine with 30% hydrogen peroxide in acetic anhydride. Commercial pyridine N-oxide (13) (Aldrich) was dried in a desiccator over phosphorous pentoxide and distilled: bp 110-111° (1.15 mm) [lit.[189] bp 138-140 (15 mm)]. The distilled material was stored in a desiccator over phosphorous pentoxide in the cold.

Chloroform. Spectral grade chloroform (Fisher) containing 0.75% of ethanol as a preservative was purified by passage through an 8-1/2" column of activated neutral aluminum oxide. Glpc (10' x 1/4" FFAP 10% on Chromosorb W 60/80, 65°) showed no ethanol, water, or other impurity.

Technique. The amine oxides were transferred in varying amounts to preweighed nmr tubes with tight fitting caps in a dry nitrogen atmosphere. The capped nmr tubes were reweighed in air and then returned to the dry atmosphere. Purified chloroform was added and the tubes were weighed again. The same capillary of TMS in $CDCl_3$ was used as an external standard for each spectrum and this was also placed in the nmr tube in the dry atmosphere.

Data. See Figure 5.

Resolution of Amine Oxides with (-)-Dibenzoyltartaric Acid (14).

N-Methyl, N-isopropylaniline N-Oxide (3c). A solution of 1.65 g (0.01 mol) of 3c (prepared with 30% hydrogen peroxide) in 5 ml of absolute ethanol was added to 3.39 g (0.009 mol) of (-)-dibenzoyltartaric acid monohydrate (Aldrich), dissolved as much as possible (by boiling) in 15 ml of absolute ethanol. The mixture had to be warmed gently to effect solution. After several attempts to find proper crystallization conditions the final volume of solution was 14.5 ml of absolute ethanol and 1.5 ml of 95% ethanol. Crystals formed slowly and were collected after 7 days of storage in the refrigerator. The pale yellow hard crystals were crushed and suspended in chloroform (15 ml) and washed with saturated sodium carbonate (10 ml). The large amount of precipitate which formed was removed by filtration and washed several times with chloroform. The evaporated

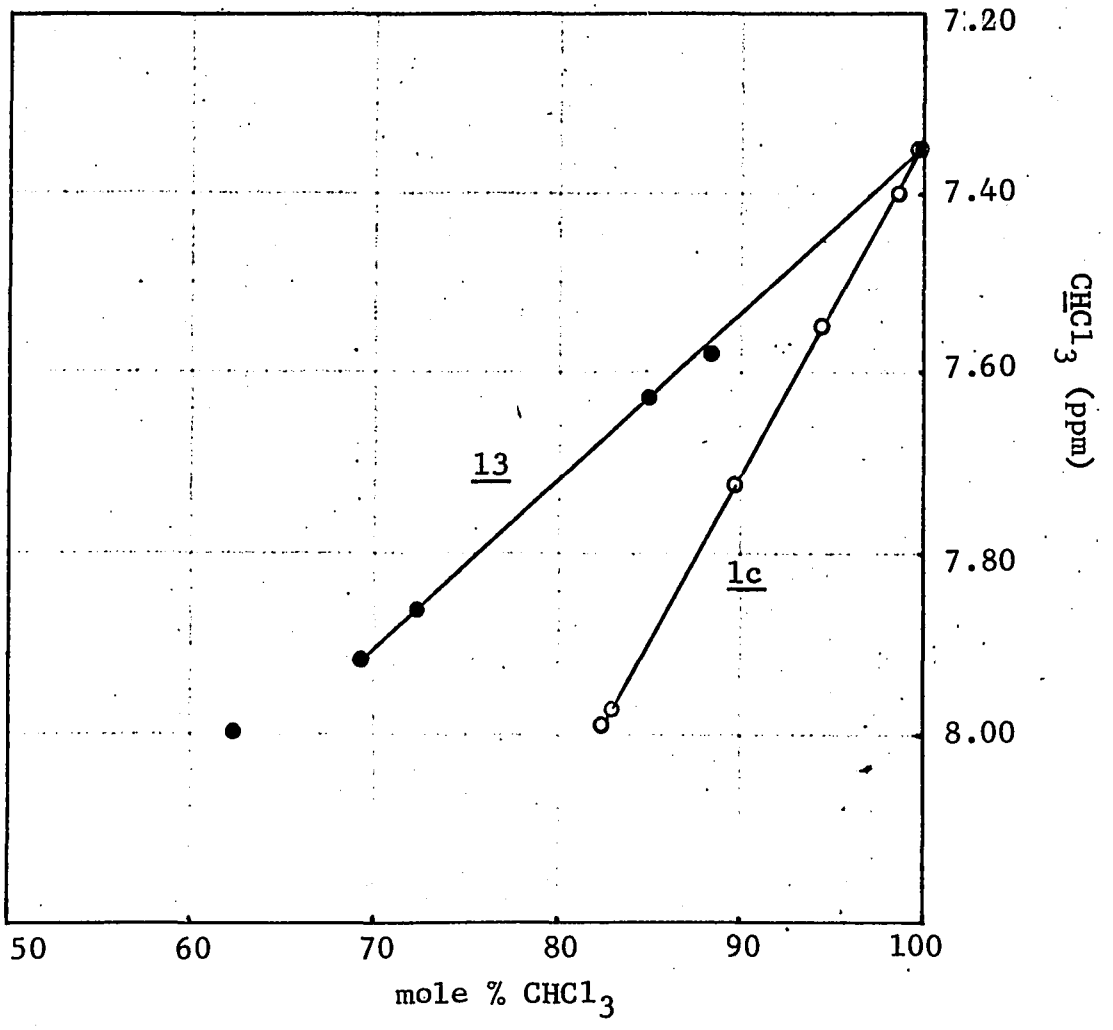

Figure 5. Plot of the chemical shift of chloroform protons in solutions containing differing amounts of amine oxide vs. mole per cent of chloroform.

Pyridine N-oxide (13): NMR no. 5571-5576.
N,N-Dimethylaniline N-oxide (1c): NMR no. 5586-5592.

filtrate was redissolved in chloroform (15 ml), washed with saturated sodium carbonate (2 x 5 ml), and dried over magnesium sulfate. The chloroform was removed at room temperature to give an oil: $[\alpha]_{578}$ -19.2, $[\alpha]_{546}$ -22.5 (c 4, 95% ethanol); ir (no. 47, $CHCl_3$) no C=O; nmr (no. 5097, $CDCl_3$) peaks in addition to those for 3c at 1.19 (t, J = 7 Hz), 3.67 (d, J = 7 Hz), 4.20 (br), 4.81 (br), and 7.44 ppm ($C\underline{H}Cl_3$).

N-Methyl, N-ethylaniline N-Oxide (2c). The (-)-dibenzoyltartaric acid salt was formed and hydrolyzed in a manner similar to 3c. The oil obtained, however, did not give clear enough solutions in water or 95% ethanol (even after filtration) to allow rotation measurements.

Preparation of α-methoxy, α-trifluoromethylphenylacetic acid (17).

The preparation of 17 was accomplished in 43% yield from trifluoromethyl phenyl ketone according to the procedure of Dale, Dull, and Mosher.[87] Part of the workup had to be modified slightly. It was not possible to extract a concentrated sulfuric acid solution of the product with ether-benzene. Water was added until no more organic solvent separated.

The trifluoromethyl phenyl ketone used in the above preparation was synthesized in 73% yield from trifluoroacetic acid and phenyl magnesium bromide.[190]

Preparation of Peracids

2-Phenylperbutanoic Acid (26). (A) Attempted Perhydrolysis of the Imidazolide of 2-Phenylbutanoic Acid. 2-Phenylbutanoyl Chloride (28). Melted 2-phenylbutanoic acid (27) was added slowly to a 25% excess of thionyl chloride,

heated under reflux for 0.5 hr, and distilled, giving an 84% yield of 28, bp 82° (0.2 mm).

N-(2-Phenylbutanoyl)imidazole (30). To a stirred solution of 10.7 g (0.157 mol) imidazole (29) in 100 ml of dry tetrahydrofuran was slowly added 14.3 g (0.0786 mol) of 2-phenylbutanoyl chloride in 100 ml of dry tetrahydrofuran. White precipitate formed immediately. After stirring at room temperature for 6 hr the mixture was filtered and the solid material (imidazole hydrochloride) was washed with dry tetrahydrofuran (50 ml), before being discarded. Solvent was removed from the filtrate and the residue, which crystallized on standing, was washed with n-hexane-benzene to give 10.8 g (64%) of crude hygroscopic 30, mp 78-81°. Alternatively, the residue could be recrystallized from benzene to give purified 30: mp 87-89° (depressed to 63-73° when mixed with imidazole, mp 88-91°); uv max (no. 4, THF) 240 and 219 nm [lit.[191] N-acetylimidazole in THF, 242.5 and 215-220 nm], (no. 3, CH_3OH, in which the imidazolide undergoes methanolysis to give imidazole and methyl 2-phenylbutanoate) 204 (ϵ 2.7 x 10^4) [lit.[192] imidazole, 204 nm (ϵ 5.0 x 10^3)] and 240-260 nm (ϵ 2.1 x 10^3) [phenyl]; ir (no. 2, $CHCl_3$) 1740 cm^{-1} [lit.[193] (N-acetyl imidazole) 1747 cm^{-1}]. The reaction procedure was suggested by those of Staab.[194]

Reactions of N-(2-phenylbutanoyl)imidazole with $NaOH/H_2O_2$. To a stirred heterogeneous mixture of 0.031 mol of sodium hydroxide and 0.016 mol of 30% hydrogen peroxide in 62 ml of ethanol and 1 ml of water at 0° was added 0.0125 mol of 30 in 7 ml of tetrahydrofuran. After stirring for 1 hr at 0°, the mixture was diluted with water (150 ml) acidified with hydrochloric acid, extracted with chloroform

(4 x 50 ml), washed with 50% ammonium sulfate (100 ml), and titrated iodometrically for peracid. No peracid was present. A titration for diacyl peroxide showed no diacyl peroxide present. The crude product which melted at 40-43° and was soluble in dilute base but not in water was probably the carboxylic acid, 27: mp 47.5°.

The procedure was repeated with identical quantities of reagents in a solvent system which allowed the reaction mixture to be homogeneous (87 ml of ethanol, 51 ml of water, and 6 ml of tetrahydrofuran) with the same results. Use of a 13.5-fold excess of sodium hydroxide and 30% hydrogen peroxide also failed to give peracid product.

(B) Attempted Perhydrolysis of 2-Phenylbutanoyl Chloride. The procedure of Kergomard and Bigou[127] for the preparation of perbenzoic acid was followed. Less than 1% yield of peracid (by titration) was obtained.

(C) Preparation of 2-Phenylperbutanoic Acid (26) by Reaction of 2-Phenylbutanoic Acid with 90% H_2O_2. The procedure followed was that of Swern et al.[130] for the preparation of aromatic and long chain aliphatic peroxy acids. According to this procedure, 94% hydrogen peroxide is added dropwise over a period of about 10-15 minutes to a solution or slurry of the carboxylic acid in practical grade methanesulfonic acid, maintaining the reaction at a desired optimum temperature for a particular acid (20, 30, 40, 50, or 60°). The reaction mixture is then stirred at that temperature for 1-3 hr longer. The reaction is worked up by the addition of ice and saturated ammonium sulfate solution and extraction of the peracid into benzene. The benzene extract is washed with saturated ammonium sulfate solution, dried over sodium sulfate, and titrated iodometrically to determine the yield. Yields are dependent upon

proportions of reactants, time, and temperature.

The procedures followed below in the preparation of 2-phenylperbutanoic acid were essentially the same as those of Swern. The biggest problem encountered was temperature control. The reaction seemed to have some critical temperature which varied from one run to the next. Below this temperature only a slight exothermic reaction occurred and above it the exothermic reaction could not be stopped. Therefore, the hydrogen peroxide was added at low temperatures and the reaction allowed to warm slowly under careful scrutiny. The reagent 90% hydrogen peroxide is not to be handled casually. The reactions must be carried out behind a safety shield in a clean and dust free beaker. Two of the seventeen preparations that were run were lost by thermal erruption. Another was lost by detonation without warning. The explosion was caused either by jarring or a small amount of talcum powder from the rubber gloves.

Table 6 gives a summary of reaction conditions and yields obtained in various experiments. Experiments where yields were not determined are not included. The product was isolated as either a benzene or chloroform extract. In some cases, the extract was evaporated to dryness to obtain a thick orange oil or semisolid. The product was shown to contain no significant amount of hydrogen peroxide by a combination of cerric ion and iodometric titrations.

Color started developing during the reactions at any time between three minutes (at 0°) to 45 minutes (at 25°) after the beginning of addition of hydrogen peroxide. The early appearance of color usually preceded poor yield. Color did not develop in a sample of acid warmed in methanesulfonic acid without the hydrogen peroxide for the same length of time. Some of the product was tested for the

Table 6

Reaction Conditions for the Preparation of 2-Phenylperbutanoic Acid

	No. 1 (one-fold)[a]	No. 5 (one-fold)	No. 6 (one-fold)
Proportions of reagents:	9MSA[b] purified 2.67 H_2O_2 1 CA racemic[c] (solid)	5MSA practical 3 H_2O_2 1 CA racemic dist. (liq.)	3MSA practical 3 H_2O_2 1 CA 44% e.e., dist. (liq.)
Addition of H_2O_2:	below 12° 12 min	10-20°, cooling in ice bath	-10-0° 5 min
Additional reaction temp. and time:	12-20° 45 min 20-53°, averaging around 30° 1.75 hr	15-30° 1 hr 30-38° 45 min	-10-+20° 30 min 20-30° 1.5 hr 34-38° 30 min
Yield:	59.2%	17.7%	39.2%

	No. 7[d] (one-fold)	No. 8 (one-fold)	No. 9 (ten-fold)
	5MSA practical 3 H_2O_2 1 CA 44% e.e., dist. (liq.)	5MSA practical 3 H_2O_2 1 CA racemic, melted (liq.)	3MSA practical 3 H_2O_2 1 CA racemic, melted (liq.)
	-10- -5° 1 min -10-+10° 30 min 10-20 20 min 20-30 1.3 hr 30-38 1 hr	-10- -5° 1 min -10-+10° 30 min 10-20 40 min 20-30 1 hr 30-38 2 hr	-1-+10° 8 min 10-22° 15 min 25-32° 2 hr
	18.8%	15.3%	49.6%

Table 6. (continued)

	No. 10 (three and one-half fold)	No. 13 (three-fold)	No. 15[e] (one-fold)
Proportions of reagents:	3MSA practical 3 H_2O_2 1 CA 44% e.e., dist. (liq.)	3MSA practical 3 H_2O_2 1 CA 87% e.e., dist. (liq.)	3MSA practical 3 H_2O_2 1 CA racemic, melted (liq.)
Addition of H_2O_2:	0-10° 7 min	-5-+4° 12 min	2-8° 4 min
Additional reaction temp. and time:	10-25° 8 min 25-29° 3.75 hr	4-25° 5 min 23-28° 30 min 25-30° 2.5 hr	2-8° 4 min 21-25° 18 min 25-28° 2.5 hr
Yield:	43.8%	34.8%	35.6%

	No. 16 (one-fold)	No. 17 (two and one-half fold)
	3MSA practical 3 H_2O_2 1 CA racemic, melted (liq.)	3 MSA practical 3 H_2O_2 1 CA 87% e.e., dist. (liq.)
	3-17° 2 min	-6-+5° 5 min
	10-18° 17 min 24° 15 min 25-30° 2.5 hr	5-25° 15 min 25-30° 30 min 30-33° 2.5 hr
	33.4%	25.6%

Table 6 (continued)

Footnotes

[a] One-fold scale reactions used 0.03 moles CA

[b] MSA = methanesulfonic acid (purified, K&K Laboratories; practical, Eastman)
H_2O_2 = 90% hydrogen peroxide (FMC Corp.)
CA = carboxylic acid = 2-phenylbutanoic acid

[c] Racemic material is practical grade

[d] Reactions no. 7 and no. 8 were run at the same time.

[e] Reactions no. 15 and no. 16 were run at the same time. A small amount of $MgSO_4 \cdot 7H_2O$ was added to the aqueous layer in the workup.

presence of sulfonated materials by a sodium fusion reaction and a subsequent test with lead acetate solution. No sulfur was found.

During the workup of many preparations a small amount of brown oil or solid separated. It was insoluble in benzene, chloroform, water, and 5% hydrochloric acid but was soluble in 5% ammonium hydroxide. The material obtained by dissolving the oily solid in 5% ammonium hydroxide and reprecipitation with hydrochloric acid turned black at about 200° and did not melt. It also did not contain sulfur. The infrared spectrum (no. 43, halocarbon mull) halocarbon showed bands at 3700-2200 (br, s), 1715 (s), 1610 (m), and 1400-1440 cm^{-1} (m, unresolved). The structure of the compound is not known.

Proof of Retention of Optical Activity in the Preparation of 2-Phenylperbutanoic Acid (26). Peracid 26 was prepared in 39.2% yield from 5.07 g (0.0309 mol) of partially resolved 2-phenylbutanoic acid, $[\alpha]_D$ -35.8° (c 20, ether), according to the usual procedure (Run no. 6). A portion of the peracid containing benzene extract (55 ml, 0.0095 mol peracid, 0.0242 mol total of peracid and acid if none were lost in the reaction procedure) was mixed with 10 g of sodium iodide, 50 ml of glacial acetic acid, 5 ml of chloroform, and enough water to effect solution, and allowed to stand for 5 min to convert all peracid (26) present to acid (27). Sodium thiosulfate solution was added to destroy the iodine formed. The acid (27) was extracted into benzene (100 ml), then into a 5% ammonium hydroxide solution. After acidifying, the aqueous mixture was extracted with ether. The ether extract was dried over sodium sulfate, the ether was removed, and the residue was distilled to yield 1.82 g (0.0111 mol) of 2-phenylbutanoic acid: bp 104° (0.24 mm);

$[\alpha]_D$ -35.8° (c 20, ether). A sample of 2-phenylbutanoic acid in 55 ml of benzene, carried through an identical workup, was recovered in 79% yield.

(E) Decomposition of 2-Phenylperbutanoic Acid (26). Peracid extract which had been evaporated to dryness and allowed to stand at room temperature until the peracid content was only 3.5% gave an nmr spectrum (no. 4312) consistent with that of authentic 2-phenylbutanoic acid except for what appeared to be a partially concealed low intensity triplet, centered at 1.02 ppm.

If, however, the peracid extract in benzene was washed with saturated sodium carbonate solution and dried over sodium sulfate before evaporating to dryness, the nmr spectrum (no. 3322) was extremely complex, exhibiting many multiplets from 0.50 to 8.85 ppm. No attempt was made to analyze this mixture further.

The process of extracting a sample of peracid from benzene into sodium carbonate solution, acidifying to pH 1, and reextracting into benzene, caused the loss of approximately two-thirds of the peracid content.

(1S)-Percamphoric Acid (25). The synthesis of 25 by Milas and McAlevy[121] was modified by the addition of a small amount of crystalline magnesium sulfate.[122] The magnesium sulfate supposedly inhibits decomposition of the peracid by trace impurities of metal ions in the reagents or on the glass, and it is claimed that this allows the peracid to be stable in the reaction mixture even at room temperature. In nine preparations by the present author, yields varied from 47 to 80%, averaging about 70%. The peracid decomposed at room temperature, sometimes very rapidly with gas evolution. The reaction had to be worked up rapidly and the product was stored in the refrigerator.

Even under these conditions the peracid content dropped significantly after a few days.

Monoperphthalic Acid. Monoperphthalic acid was prepared in 70% yield using the method of Ogata and Sawaki[195] with the exception that the reaction was run at approximately 0°, as had previously been done by Payne[196] and Böhme,[197] rather than at room temperature. The reaction was run in a Tupperware container. When the exact procedure of Ogata and Sawaki was followed (except that a glass instead of a polyethylene reaction vessel was used), a 9% rather than the expected 80% yield of peracid was realized.

Oxidation of N-Methyl,N-alkylanilines with (1S)-Percamphoric Acid at -70 to -75°C (Reactions no. 8, 11, 13-16).

General Reaction Procedure. A long-necked pyrex flask was suspended in a 2-l Dewar flask filled with Dry Ice-acetone slush. A solution of the peracid was placed in the flask and allowed to cool. When the peracid solution and a solution of the amine (cooled separately in a Dry Ice-acetone bath) had reached about -75°, the amine solution was quickly added to the reaction flask and rinsed in with a small portion of cooled solvent. During addition, the reaction temperature did not rise more than five degrees. The reaction mixture was stirred with a Hershberg stirrer (made with Nichrome wire) or a glass rod, and was then stoppered and allowed to stand with occasional stirring. The Dewar, sealed with a sandwich of glass wool between aluminum foil, had to be replenished with Dry Ice every 24-48 hrs.

Quantities of Reagents. The reagents were used in the proportions 0.0074 mol of amine: 0.0089 mol of peracid: 77 ml of solvent.

Workup. After the desired reaction time, ether saturated with hydrogen chloride (30 ml) and cooled to -75° was added to the reaction mixture. The mixture was stirred and allowed to warm to room temperature, then evaporated to a pasty mass under reduced pressure. The residue was dissolved in ether (60 ml) and water (5 ml), the layers separated and the ether layer extracted further with water (2 x 5 ml). The combined aqueous extracts were washed carefully with ether (6 x 5 ml)* and freeze-dried at room temperature on a

* Preliminary work had shown that fewer extractions with ether did not remove all of the camphoric acid.

rotary evaporator under the reduced pressure of a vacuum pump. The product was placed in a vacuum desiccator over calcium chloride and phosphorous pentoxide and the desiccator was evacuated with a vacuum pump. In some cases a few drops of ethanol were added to the product to aid crystallization. Upon storage in the refrigerator all samples became white, pale yellow, or slightly brownish solids. Yields were quantitative.

Analysis of the Products. NMR. Products were identified primarily by the chemical shift of the N-C$\underline{H}_3$ peak which for the amine oxide hydrochlorides was at 3.39-3.83 ppm (D_2O) or 4.08-4.16 ppm ($CDCl_3$) and for the amine hydrochlorides was at 3.25-3.58 ppm (D_2O) or 3.25-3.33 ppm ($CDCl_3$). Typical nmr data for the amine oxide hydrochlorides involved are listed below:

N,N-dimethylaniline N-oxide hydrochloride (1d) (no. 4791, 4638, 3.83 (s, 6 N-($C\underline{H}_2$)$_2$) and 7.47-7.91 ppm (m, 5, Ar). No. 5313-A, $CDCl_3$, ext TMS: 4.11 (s, 6, N(CH_3)$_2$), 7.48-8.18 (m, 5, Ar), and 8.43 (br, 2.5, N·H).

N-methyl, N-ethylaniline N-oxide hydrochloride (2d) (no. 4792, D_2O): 1.03 (t, J = 7Hz, $CH_2C\underline{H}_3$), 3.80 (s, N-$C\underline{H}_3$), 4.01 (q, J = 7Hz, $C\underline{H}_2CH_3$), and 7.36-7.87 (m, Ar).

N-methyl, N-isopropylaniline N-oxide hydrochloride (3d) (no. 4637, D_2O): 1.22 (d, 3, J = 12Hz, CH($C\underline{H}_3$)CH_3), 1.30 (d, 3, J = 12Hz, CH(CH_3)$C\underline{H}_3$), 3.82 (s, 3, N-$C\underline{H}_3$), 4.30 (m (7), 1, J = 12Hz, $C\underline{H}$(CH_3)$_2$), and 7.50-7.88 ppm (m, 5, Ar).

N-methyl, N-t-butylaniline N-oxide hydrochloride (4d) (no. 5312, 5313, $CDCl_3$, ext TMS): 1.53 (s, 9, C($C\underline{H}_3$)$_3$), 4.15 ppm (s, 3, N-$C\underline{H}_3$), 7.47-8.06 ppm (m, 5, Ar), and 8.57 ppm (br, 2, N·H).

Kairoline N-oxide hydrochloride (5d) (no. 5917, $CDCl_3$): 2.20-2.67 (m, 2, CH_2-$C\underline{H}_2$-CH_2), 2.90-3.30 (t, 2, J = 12-13Hz,

$PhC\underline{H}_2-CH_2$), 4.05 (s, 3, $N-C\underline{H}_3$), 4.66-4.37 (t, 2, $\underline{J}$ = 10-11Hz, $N-C\underline{H}_2CH_2$), 7.17-8.30 (m, 4, Ar), and 9.67 ppm (br, 2, $N\cdot\underline{H}$).

The camphoric acid methyl peak at 0.92 ppm ($CDCl_3$) could be observed in very low concentrations in the presence of the amine oxide hydrochlorides. No camphoric acid was observed in the nmr spectra of the reaction products reported here (no. 8, 11, 13-16).

IR. All of the infrared spectra showed the absence of carbonyl absorption. The spectra were determined in chloroform solution.

Reactions Not Reported. Several reactions are not reported in Table 7 either because the products were contaminated with optically active acid or because decomposition to colored materials during purification (or by contact with the metal portions of the polarimeter cells) made rotation readings impossible. The product from the reaction of 4a with (1S)-percamphoric acid (25) at room temperature (no. 12) turned to a dark orange-brown oil upon addition of hydrochloric acid during the workup. The products from the reactions of 3a and 1a (blank) with 25 in absolute ethanol (no. 10) showed no rotation at 578 nm. Light absorption by the samples at other wavelengths was too strong for rotations to be determined.

Estimation of the Time Necessary for Complete Oxidation of N-Methyl, N-isopropylaniline (3a) at -70°.

The reaction of 3a with 2-phenylperbutanoic acid (26) in chloroform-ether (5:2) run under the conditions described for low temperature oxidations with (1S)-percamphoric acid (25) and worked up after 48 hours gave a product whose nmr (no. 3735, $CDCl_3$) showed about a 45:55 ratio of $N-C\underline{H}_3$ intensities of the amine to amine oxide hydrochlorides.

Another experiment with the same reagents, worked up after 7 days, showed complete conversion to amine oxide (NMR no. 3933, $CDCl_3$). The reaction of 3a with 25 in chloroform-ether (2:5) was observed in one experiment to have gone to about 64% completion after 7 days (NMR no. 4364, $CDCl_3$). After 13 days in chloroform-ether (5:2), another reaction mixture was shown to contain only a small amount of amine (Reaction 8). The reactions run for 21 days (Reactions 11 and 14) showed no trace of amine hydrochloride in the product.

Oxidation of N-Methyl, N-ethylaniline with (R)-2-Phenylperbutanoic Acid (26) (Reaction No. 1).

To 90 ml of a benzene solution of (R)-2-phenylperbutanoic acid (26) (0.0355 mol of peracid; prepared from acid 27 with $[\alpha]_D$ -35.8°, 44% e.e.[198]) was added rapidly 4.0 g (0.296 mol) of N-methyl,N-ethylaniline (2a) and 10 ml of benzene. The mixture was allowed to stir at 26° for 12 hr, then it was extracted with 5% hydrochloric acid (4 x 10 ml), washed with benzene (10 ml) and the water evaporated under the reduced pressure of a vacuum pump at room temperature to give 6.38 g (more than the theoretical amount) of a mushy solid whose nmr spectrum (no. 3507, $CDCl_3$) showed only the peaks attributable to the N-oxide hydrochloride 2d. The ord spectrum (no. 743, c: 17.4, 1.74, water) showed no significant rotation between 600 and 350 nm.

Oxidation of N-Methyl,N-isopropylaniline with (R)-2-Phenylperbutanoic Acid (26) (Reaction No. 2).

The procedure was identical to that for Reaction 1 except that the reaction was run at 7-11° for 8 hr instead of at room temperature and was worked up with cold 5% hydrochloric acid. From 0.0111 mol of amine 3a and 0.0143 mol

of peracid 26 (44% e.e.) in 85 ml of benzene there was obtained 2.93 g (100%) of a yellow oil whose nmr spectrum (no. 3506, $CDCl_3$) showed the peaks attributable to the N-oxide hydrochloride 3d and a small singlet at 2.05 ppm. The ord spectrum (No. 745, c 16.5, 4.12, 1.65, water) showed no significant rotation between 611 and 300 nm.

Oxidation of N-Methyl,N-isopropylaniline (3a) with (1S)-Percamphoric Acid (25) (Reaction No. 3).

A solution of 1.31 g (0.0088 mol) of N-methyl,N-isopropylaniline (3a) in 9 ml of chloroform was cooled to -10°. While being weighed, the (1S)-percamphoric acid began to decompose rapidly with gas evolution. All of the peracid on hand (about 10 g, 0.03 mol) was quickly added to the amine solution in a small amount of chloroform (about 10 ml). The temperature of the reaction rose from -10° to +7°. Stirring was continued at -13 to -14° for 1 hr and at 25° for 2 hr. The product was extracted into 5% hydrochloric acid. The extract was filtered several times to remove suspended solid (camphoric acid), was partially evaporated, and was filtered again. Chloroform extracts of this aqueous layer were combined and dried over sodium sulfate. Upon evaporation of the chloroform solution, 0.425 g of a brownish-pink oil was obtained. The nmr spectrum of this oil (no. 3596, $CDCl_3$) showed several peaks in addition to those attributable to 3d. These were at 0.92 (s), 2.07 (s), and 2.19 (s) ppm with partially concealed multiplets between 0.93 and 1.36 ppm. The 0.92 ppm singlet and the multiplets could be assigned to traces of camphoric acid.

The oil from the chloroform extract was combined with the aqueous solution from which it had been extracted. The aqueous solution was then made basic, saturated with

sodium chloride and extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated to give 0.931 g of a yellow oil which exhibited peaks in the nmr spectrum (no. 3600, neat, internal TMS), in addition to those for the amine oxide 3c, at 1.22 (t, J = 7 Hz), 1.55-1.75 (m), 2.10 (s), 3.10 (s), and 7.16 ppm (s). The ord spectrum (c 2, methanol) from 600 - 350 nm was a straight line, only slightly under the base line.

Oxidation of N-Methyl, N-isopropylaniline (3a) with (1S)-Percamphoric Acid (25) (Reaction No. 9).

To 0.50 g (0.0034 mol) of N-methyl,N-isopropylaniline (3a) in 5 ml of ether and 10 ml of chloroform was added 1.20 g (0.0040 mol) of (1S)-percamphoric acid in 15 ml of chloroform and 5 ml of ether. After stirring at room temperature for 1 hr, the reaction mixture was treated with a saturated solution of hydrogen chloride in ether (20 ml) and was evaporated at room temperature. The residue was dissolved in ether (10 ml) and water (5 ml) and the layers were separated. Aqueous extracts (2 x 5 ml) of the ether layer were combined with the aqueous layer, washed with ether (5 ml), and evaporated to dryness giving a product which had an nmr spectrum (no. 4558, H_2O) showing peaks attributable to the amine oxide hydrochloride 3d and a possible trace of camphoric acid. The product was redissolved in water, washed several times with ether, and evaporated to give a sample which had no noticeable rotation at 578, 546, 436, 405 or 365 nm (c, 20, water).

Table 7. Reactions of N-Methyl, N-Alkylanilines with (1S)-Percamphoric Acid at -70 to -75°C.

Reaction No.	Amine	Solvent	Reaction Time (days)	Optical Rotation[a] conc. (g/ml) (solvent), temp.	Product NMR[b]	Product IR
8a	1a	$5CHCl_3$/ $2Et_2O$	12.9	0.6087 (MeOH)[c] 22°	No. 4638 (D_2O)	----
8b	3a	$5CHCl_3$/ $2Et_2O$	12.9	0.7212 (MeOH) 22°	No. 4637 (D_2O) 3-9%[d] 3b	No. 46
11a	1a	$5CHCl_3$/ $2Et_2O$	21	0.4570 (MeOH) 28°	No. 4791 (D_2O)	----
11b	2a	$5CHCl_3$/ $2Et_2O$	21	0.1955 (MeOH) 28°	No. 4792 (D_2O)	----
11c	3a	$5CHCl_3$/ $2Et_2O$	21	0.3486 (MeOH) 30°	No. 4793 (D_2O)	----

Reaction No.	Amine	Solvent	Reaction Time (days)	Optical Rotation[a] conc. (g/ml) (solvent), temp.	Product NMR[b]	Product IR
13a	1a	$5CHCl_3$/ $2Et_2O$	11.8	0.1373 (MeOH) 36°[e]	No. 5313 ($CDCl_3$)	----
13b	4a	$5CHCl_3$/ $2EtO_2$	11.8	0.1910 (MeOH) 36°	No. 5312[f] ($CDCl_3$)	No. 63
14a	1a	$5CHCl_3$/ $2Et_2O$	21	0.3694 (MeOH) 18°[g]	No. 5918 ($CDCl_3$) trace of EtOH	----
14b	5a	$5CHCl_3$/ $2Et_2O$	21	0.3513 (MeOH) 20° 0.0735 (H_2O) 18°	No. 5917 ($CDCl_3$) trace of EtOH	No. 79
15a	1a[h]	$5CHCl_3$/ $2Et_2O$	46	0.0669[i] (H_2O) 29°	No.[d] 6403 46% 1b trace of EtOH	No. 81

Reaction No.	Amine	Solvent	Reaction Time (days)	Optical Rotation[a] conc. (g/ml) (solvent), temp.	Product NMR[b]	IR
15b	5a[j]	5$CHCl_3$/ 2Et_2O	46	0.0939[i] (H_2O) 30°	No. 6404 ($CDCl_3$) 31%[d] 5b trace of EtOH	No. 82
15c	5a[k]	5$CHCl_3$/ 2Et_2O 1 eq. (+)-camphoric acid	46	0.0793[i] (H_2O) 29°	No. 6405 ($CDCl_3$) 50%[d] 5b 27 mole % EtOH	No. 83
16a	1a	absolute EtOH	52	0.1116 (H_2O) 30°	No. 6135 ($CDCl_3$) trace of EtOH	----
16b	5a	absolute EtOH	52	0.0606 (H_2O) 30°	No. 6134 ($CDCl_3$)	----

Table 7. (continued)

(a) For specific rotation data at 578, 546, 436, 405, and 365 nm see Table 4.

(b) Only peaks other than those for amine oxide hydrochloride are listed.

(c) Methanol is spectral grade.

(d) Percent of the total N-CH_3 intensity for the amine and amine oxide hydrochlorides.

(e) July.

(f) Thin layer chromatography on Silica GF showed only one spot with all of the solvents tried (ether, chloroform, ethyl acetate, acetone, water, absolute ethanol, 95% ethanol, and methanol).

(g) February.

(h) 0.49 eq. peracid.

(i) The amount of amine oxide hydrochloride in the sample.

(j) 0.54 eq. peracid.

(k) 0.39 eq. peracid.

The Effect of Added Hydrogen Chloride on the Oxidation of N-Methyl,N-isopropylaniline (3a) with (1S)-Percamphoric Acid (25).

When the procedure for Reaction 9 was followed, except that the ether in which the amine was initially dissolved had been previously saturated with hydrogen chloride, the product gave an nmr spectrum (no. 4556, H_2O) showing peaks for the amine hydrochloride 3b [1.30 (d, J = 6.5 Hz, $CH(C\underline{H}_3)_2$), 3.28 (s, N-$C\underline{H}_3$), 4.05 (m (7), J = 6.5 Hz, $C\underline{H}(CH_3)_2$), and 7.35-7.92 ppm (m, Ar)] and some peaks due to impurities [1.02 (s, camphoric acid), 1.16 (s), and 3.20 ppm (s)] but no peaks attributable to N-oxide hydrochloride 3d.

The Effect of Added (1S)-Camphoric Acid on the Oxidation of N-Methyl,N-isopropylaniline (3a) with (1S)-Percamphoric Acid (25).

When the procedure for Reaction 9 was followed, except that two equivalents of (1S)-camphoric acid were added to the peracid solution, the nmr (No. 4557, H_2O) of the product showed peaks for the N-oxide hydrochloride 3d and a trace of camphoric acid, but no peaks attributable to amine hydrochloride 3b.

NMR Spectra of N-Methyl, N-isopropylaniline (3a) and Camphoric Acid (71) in Chloroform-Tetrahydrofuran Solution.

The nmr spectra of the following solutions in chloroform-anhydrous tetrahydrofuran (5:2 by volume) were determined:

0.15 g (0.001 mol) 3a (No. 6063)

0.15 g (0.001 mol) 3a and 0.10 g (0.0005 mol) 71 (No. 6064)

0.15 g (0.001 mol) 3a and 0.20 g (0.001 mol) 71 (No. 6065)

In all cases the chemical shifts for the methyl protons (with respect to external TMS) were at 0.86 (s), 1.18 (s), and 1.26 ppm, (methyl groups in camphoric acid), 1.09 (d, J = 7 Hz, $CH(C\underline{H}_3)_2$), and 2.67 ppm (s, $N\text{-}C\underline{H}_3$).

Preparation of Hydroperoxides by Nucleophilic Displacement Reactions.

2-Octyl Methanesulfonate (72). A 76% yield of 2-octyl methanesulfonate was obtained by treatment of 2-octanol with methanesulfonyl chloride.[199] Octanol was removed from the crude product by vacuum distillation at 35-45° (0.15 mm) and the remaining material, which had an infrared spectrum (no. 39, neat) showing strong SO_2 absorptions at 1195 and 1360 cm^{-1} but no OH bands, was used without further purification. An attempt to distill the methanesulfonate at 0.3 mm (100°) resulted in vigorous decomposition with foaming.

2-Octyl Hydroperoxide (73). The procedure of Williams and Mosher[199] afforded a 1.5% yield [lit.[199] 11.3% yield] of 73 from the methanesulfonate.

Preparation of Hydroperoxides by Oxygenation of Organometallic Reagents.

Halides.

(-)-"Menthyl Chloride" (39).* The synthesis of 39 was accomplished according to the general procedure of Hückel and Pietrzok[200] with the proportions of reagents used by Hughes and coworkers.[201] From 167 g (0.803 mol) of

* The product was actually a mixture of (-)-menthyl and (+)-neomenthyl chlorides, primarily (-)-menthyl chloride. Since epimerization occurs during Grignard reagent formation, the next step in the synthesis, it was not necessary to obtain epimerically pure halide.

commercial phosphorous pentachloride, 33.3 g (0.205 mol) of anhydrous ferric chloride and 107 g (0.687 mol) of (-)-menthol a yield of 104.1 g (87%) of chloride 39 was obtained. The product was determined to be free from alkene or alcohol impurities by its infrared spectrum (no. 94, 95, neat) and glpc (20% Carbowax 20M on Chromosorb W, acid washed, DMCS, 124°).

(-)-Menthyl Bromide (42). A 500-ml flask containing 125 g of 40% hydrobromic acid was cooled in an ice bath and 35 ml of concentrated sulfuric acid was added slowly. The ice bath was removed and 95.1 g (0.609 mol) of (-)-menthol was added. The mixture was heated to reflux with stirring for 4 hr, cooled, and the layers were separated. Low boiling petroleum ether (100 ml) was added to the organic layer. The solution was washed with water (50 ml), concentrated sulfuric acid (8 x 50 ml), water (2 x 30 ml), 5% sodium bicarbonate (2 x 30 ml), and water (2 x 30 ml). The solution was dried over calcium chloride and the solvent was evaporated under reduced pressure. Distillation of the residue, carried out with magnetic stirring and with the receiver cooled in a Dry Ice-acetone bath, gave 69.8 g (52%) of 42: bp 58-60° (0.45 mm), pot temperature 75°; ir (no. 100, neat) no OH. The nmr spectra (no. 6936, neat) showed no vinyl hydrogens.

(-)-Bornyl Chloride (40). Dry hydrogen chloride was bubbled through (-)-α-pinene ($[\alpha]_D^{30.5}$ -38.07°*, neat, 74.4% e.e.[202]), at 10-20° until about 1 equiv had been taken up (2.25 hr) according to the general procedure of Long.[203] Only 24.5 g (28%) of crystalline 40 could be obtained by

* D line rotations are calculated by the Drude equation from values obtained at 578 and 546 nm.

filtration from the reaction mixture even after prolonged cooling. The remaining reaction mixture was distilled to give a further 21.4 g (24%) of crude 40: bp 85-105° (15 mm); ir (no. 84, $CHCl_3$) no OH. Further heating of the large pot residue caused evolution of hydrogen chloride. The crude product was recrystallized 3 times from ethanol-water or methanol to give purified 40: mp 119-124° [lit.[202] mp 132°*]; $[\alpha]_D^{25}$ -23.70° (c 1, 95% ethanol), 70.8% e.e.; ir (no. 90, $CHCl_3$) no OH. The purified bornyl chloride gave negative tests for olefins with 2% potassium permanganate and bromine in carbon tetrachloride.

Grignard Reagents.

General. The following Grignard reagents were prepared under dry nitrogen. Yields were determined by titration in dry tetrahydrofuran using phenanthroline indicator.[204]

"Menthyl" Magnesium Chloride (74).[205] The Grignard reagent was prepared using 6.14 g (0.252 mol) of doubly sublimed magnesium and 19.50 g (0.125 mol) of (-)-menthyl chloride (39) in 125 ml of anhydrous ether which had been distilled from lithium aluminum hydride. The reaction started slowly (with the aid of ethylene bromide) and proceeded slowly, forming a white precipitate. Stirring overnight increased the amount of precipitate. Titration showed

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* These workers have noted that literature melting points of bornyl chloride vary considerably due to the fact that the solid bornyl chloride becomes sticky shortly after isolation from the mother liquor. This observation was confirmed here. Storage in a desiccator did not solve the problem.

that this precipitate contained Grignard reagent. The approximate yield was 35%.

"Menthyl" Magnesium Bromide (75). The Grignard reagent was prepared using 1.99 g (0.82 mol) of doubly sublimed magnesium, 16.4 g (0.075 mol) of (-)-menthyl bromide (42) and 150 ml of sodium-dried anhydrous ether. After a 1 hr addition time, the reaction was stirred at room temperature for 2.5 hr. A 22% yield of homogeneous Grignard reagent was obtained.

"Bornyl" Magnesium Chloride (76). The Grignard reagent was prepared using 2.92 g (0.120 mol) of doubly sublimed magnesium, 19.1 g (0.110 mol) of (-)-bornyl chloride (40) and 165 ml of sodium-dried anhydrous ether. The reaction commenced after the addition of a small amount of ethylene bromide to a portion of the reactants but reflux could not be maintained spontaneously during the addition of the remainder of the halide solution. After an addition time of 2.5 hr the mixture was heated at reflux for 3 hr and stirred overnight at room temperature to afford a 42% yield of Grignard reagent. Some solid which did not titrate as Grignard reagent was formed.

Oxygenation of Organometallics.

General. Hydroperoxides were prepared from the Grignard reagents by three methods: (A) addition of the Grignard reagent to oxygen saturated ether; (B) formation of the organocadmium reagent followed by addition to oxygen saturated ether; or (C) formation of the organocadmium reagent and addition of oxygen to it (one-pot method).

Oxygenation of Grignard reagents must be carried out at low temperatures (-75°C) and with a large excess of oxygen and low concentration of Grignard reagent in order that hydroperoxides rather than alcohols are obtained.[152]

Alkoxide salts are formed by the facile reaction of the Grignard reagent with oxygenated Grignard reagent (eqn 24) and only alcohols are obtained when Grignard reagents are allowed to react with oxygen at room temperature.[152]

(24) $RMgX + ROOMgX \rightarrow 2ROMgX$

This competing reaction makes the oxygenation of Grignard reagents to hydroperoxides experimentally difficult. Care must be taken not to allow oxygen to come in contact with the Grignard reagent until the reagent is cooled and dilute. The reaction between the Grignard reagent and oxygen appears to occur on contact and forms solids which may clog bubblers, addition funnels, etc. Some details on the apparatus are included here.

Cadmium and zinc reagents, however, can by oxygenated to hydroperoxides in good yield at 0-15°C.[154] Hydroperoxides can also be obtained by bubbling oxygen into the organometallic at low temperatures (-50°C).[154] The yields of hydroperoxides by the latter method appear to be very sensitive to experimental conditions, particularly the oxygen flow rate (which must be extremely rapid for good yields to be realized).

Cyclohexyl Hydroperoxide (43). Method (A). Sodium-dried anhydrous ether (100 ml) was placed in a round bottom flask fitted with a mechanical stirrer, oxygen bubbler (a capillary dropper), nitrogen inlet, and a non-pressure-equalizing addition funnel. The apparatus was flushed with nitrogen and 100 ml (0.05 mol) of a filtered Grignard reagent prepared from cyclohexyl chloride was placed in the addition funnel. Oxygen was started bubbling through the ether and the reaction flask was cooled in a Dry Ice-acetone bath.

With the aid of nitrogen pressure in the addition funnel, the Grignard reagent was added over a period of 1 hr. The reaction mixture was then allowed to warm to room temperature and was hydrolyzed by pouring over ice and acidifying with hydrochloric acid. The organic layer was combined with ether extracts (4 x 50 ml) of the aqueous layer and titrated for hydroperoxide by the Wagner method. A 25% yield of 43 was obtained in several trials.

Cyclohexyl Hydroperoxide (43). Method (C). In a round bottom 3-necked flask under dry nitrogen, fitted with a mechanical stirrer and connected with a small Erlenmeyer flask containing cadmium chloride, was placed 50 ml (0.023 mol) of filtered Grignard reagent prepared from cyclohexyl chloride. The 4.1 g (0.022 mol) of anhydrous cadmium chloride (heated at 100°C for 1 day and pulverized) was added with stirring at 0°C. In 10 min a Gilman test for Grignard reagent was negative. An additional 45 ml of anhydrous ether (distilled from lithium aluminum hydride) was added to the heterogeneous mixture and the flask was cooled to -60°C. Oxygen, dried by bubbling through concentrated sulfuric acid and cooled by passage through a Dry Ice-acetone bath, was passed into the reaction mixture as rapidly as possible with vigorous stirring, keeping the temperature below -50°C. After 1.25 hr, 75ml of 2N hydrochloric acid was added and the reaction was allowed to warm to room temperature. The ether layer was washed with water, dried over anhydrous sodium sulfate in the refrigerator and titrated by the Wibaut method. A 42% yield of 43 was obtained. Use of a hollow Trubore stirrer with gas dispersion holes would possibly increase yields by better dispersion of oxygen into the solution.

Menthyl Hydroperoxide (77). Method (C). Using 140 ml (0.014 mol) of filtered Grignard reagent (75), a 28% yield of hydroperoxide was obtained.

Bornyl Hydroperoxide (41). Method (B). The cadmium reagent was prepared under dry nitrogen in the manner described above, using 162 ml (0.0445 mol) of filtered Grignard reagent 76 and 8.60 g (0.0468 mol) of anhydrous cadmium chloride.

A separate flask containing 500 ml of sodium-dried anhydrous ether and fitted with a mechanical stirrer, oxygen bubbler, addition funnel and nitrogen inlet, was cooled to -2°C, flushed with nitrogen, and connected to the cadmium reagent flask. With the cadmium reagent flask isolated from the rest of the system, oxygen was bubbled into the ether. The organocadmium reagent was then pushed into the addition funnel and added to the reaction mixture in spurts with nitrogen pressure over a period of 5 min.* The reaction was stirred for 1.75 hr with continuous flow of oxygen. It was then hydrolyzed and worked up in the same manner as described for method (C). Titration showed a 39% yield of hydroperoxide.

Reactions of N,N-Dimethylaniline (1a) with Hydroperoxides.

General. The reaction mixtures were stirred magnetically and the progress was followed by titration for hydroperoxide either by the Wagner method[163] (Reactions 1, 2, and 6) or by the Wibaut method[162] (Reactions 3-5 and 7-8).

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* This addition rate is most likely too rapid. Some difficulty was encountered at first in maintaining a large enough nitrogen pressure to push the thick cadmium reagent through the addition funnel into the reaction flask. Oxygen backed up through the stopcock into the addition funnel causing a mildly exothermic reaction. The yield reported here, therefore, may not be indicative of what could be obtained.

Reagents, experimental conditions, and percentage loss of hydroperoxide are listed for each of the reactions in Table 8. The conditions were often altered during the course of the reaction in attempts to increase the percentage loss of hydroperoxide. Reaction mixtures were worked up and the products analyzed for N,N-dimethylaniline N-oxide primarily by nmr spectroscopy as indicated in Figures 6-13.

Table 8. Experimental Conditions of the Reactions of N,N-Dimethylaniline (1a) with Hydroperoxides

Reagents	Temp.	Time (hr)	Loss of Hydroperoxide	Comments
Reaction 1:				
$C_6H_{11}OOMgX$[a] (0.0117 mol in 180 ml ether) prepared as described for $C_6H_{11}OOH$, method (A), without hydrolysis)	7°	1	66%	Reaction mixture turned lime green on addition of amine
$PhN(CH_3)_2$ (0.0133 mol in 20 ml ether) (under N_2)	25°	24	74%	
	reflux	1	75%	
Reaction 2:				
$C_6H_{11}OOH$[a] (0.0057 mol in 180 ml ether)	26°	24	0%	
$PhN(CH_3)_2$ (0.0100 mol in 20 ml ether)				
Added $PhN(CH_3)_2$ (0.0100 mol[b])	reflux	7.5	0%	
Added dry isopropanol (70 ml)	reflux	6.5	0%	
Added dry isopropanol (190 ml)	reflux	3.75	20%	began to turn purple
	reflux	2.25	25%	
	reflux	3	35%	

Table 8. (continued)

Reagents	Temp.	Time (hr)	Loss of Hydroperoxide	Comments
Reaction 3:				
$C_6H_{11}OOH$ (0.0105 mol in 95 ml ether)	26°	8.5	0%	pale yellow
$PhN(CH_3)_2$ (0.0105 mol in 5 ml ether)				
Added 0.0105 mol[b] $PhN(CH_3)_2$	26°	2.5	0%	
Added dry isopropanol (55 ml)	26°	22.5	0%	pale orange
Added water (25 ml)	26°	17	0%	
	40°	70.5	20%[c]	reddish brown
Reaction 4:				
$(CH_3)_3COOH$[d] (0.030 mol)	26°	1 day	0%	
$PhN(CH_3)_2$ (0.030 mol)				
75 ml water				
55 ml isopropanol	45-48°	12 days	0%	orange
	reflux (85°)	1 day	20%	brown
	"	3.5 days	49%	
	"	2 days	49%	strong smell of amine
Reaction 5:				
$C_6H_{11}OOH$ (0.0067 mol)	25-30°	3 days	0%	
$PhN(CH_3)_2$ (0.0067 mol)	45-50°	1 day	22%	
	"	1 day	50%	
	"	2 days	72%	
	"	3 days	83%	
	"	1 day	84%	

Table 8. (continued)

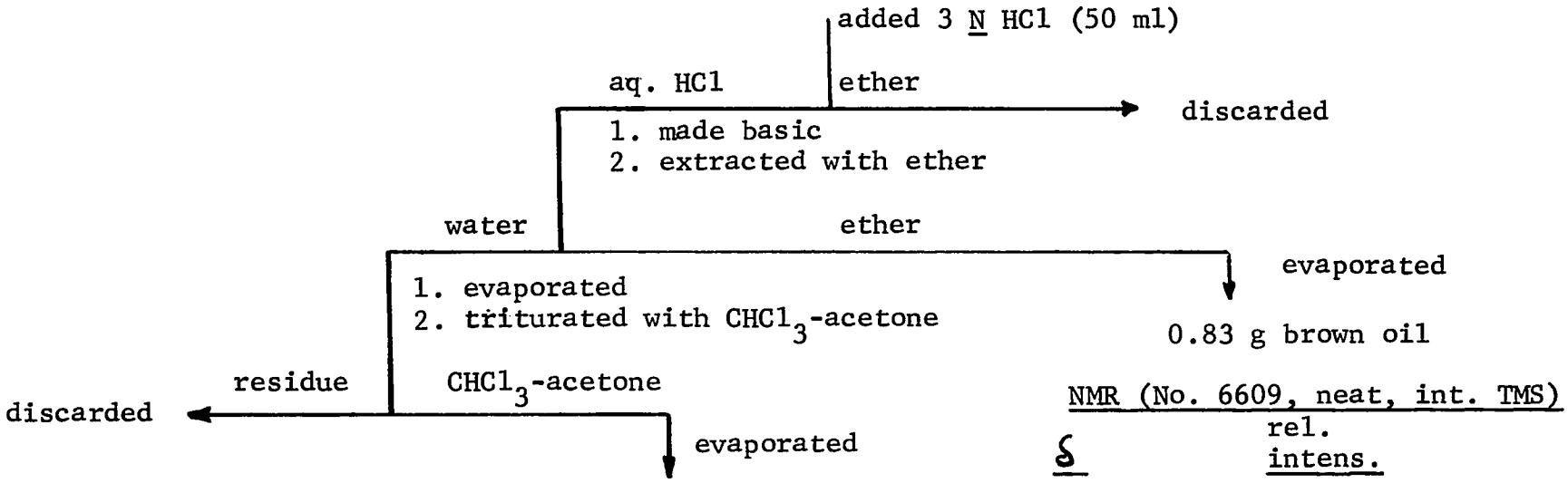
Reagents	Temp.	Time (hr)	Loss of Hydroperoxide	Comments
Reaction 6:				
$C_6H_{11}OOH$ (0.006 mol) $PhN(CH_3)_2$ (0.010 mol) $VO(acac)_2$[e] (0.00005 mol) 200 ml ether	reflux	8.5	0%	
Added 0.006 mol[b] $VO(acac)_2$	reflux	2	90%[f]	
Reaction 7:				
$(CH_3)_3COOH$ (0.020 mol) $PhN(CH_3)_2$ (0.020 mol) t-butanol (0.060 mol) $VO(acac)_2$ (0.0001 mol)	25-86°	0.5	Not Titrated	
Reaction 8:				
"menthyl" OOH (0.002 mol) $PhN(CH_3)_2$ (0.002 mol) 11.5 ml methanol	60-65°	2	Not Titrated	Purplish brown

(a) $C_6H_{11}OOMgX$ = the magnesium salt of cyclohexyl hydroperoxide; $C_6H_{11}OOH$ = cyclohexyl hydroperoxide (43). (b) The actual amount added was slightly less than the quantity listed since an adjustment was made for the amount of the compound removed in the titration aliquots.

Table 8. (continued)

(c) By the Wagner method this sample titrated for more hydroperoxide than the initial reaction mixture. (d) 67% t-butyl hydroperoxide, obtained from Matheson, Coleman & Bell. (e) Vanadium oxyacetylacetonate. (f) Titration values for hydroperoxide are probably not valid in the presence of the vanadium compound.

Figure 6. Workup of the reaction of oxygenated Grignard reagent from cyclohexyl chloride with N,N-dimethylaniline in ether. (Reaction 1)



NMR (No. 6609, neat, int. TMS)

δ	rel. intens.
2.58(d)	40
2.66(s)	61
6.20-7.33(m)	77 - aromatic

GLPC[a] (sample from NMR)

retention time(min)	approx. peak height
0.32	8.5 - CCl_4?
0.60	90
0.80	41
1.14	2
2.06	15
3.40	3

GLPC[a]

retention time(min)	approx. peak height
0.06	7.5 - $CHCl_3$
0.32	6
0.52	13

NMR (No. 6632, neat, ext. TMS)

δ	rel. intens.
1.18 (s)	49
1.55 (s)	72
2.13 (s)	26
2.60 (s)	16
4.31(br)	21
7.61	trace - $CHCl_3$

(a) 15% Silicone GE XE-60 Chromosorb W, KOH washed; 150°; 10 psi

Figure 7. Workup of the reaction of cyclohexyl hydroperoxide with N,N-dimethylaniline in ether-isopropanol. (Reaction 2)

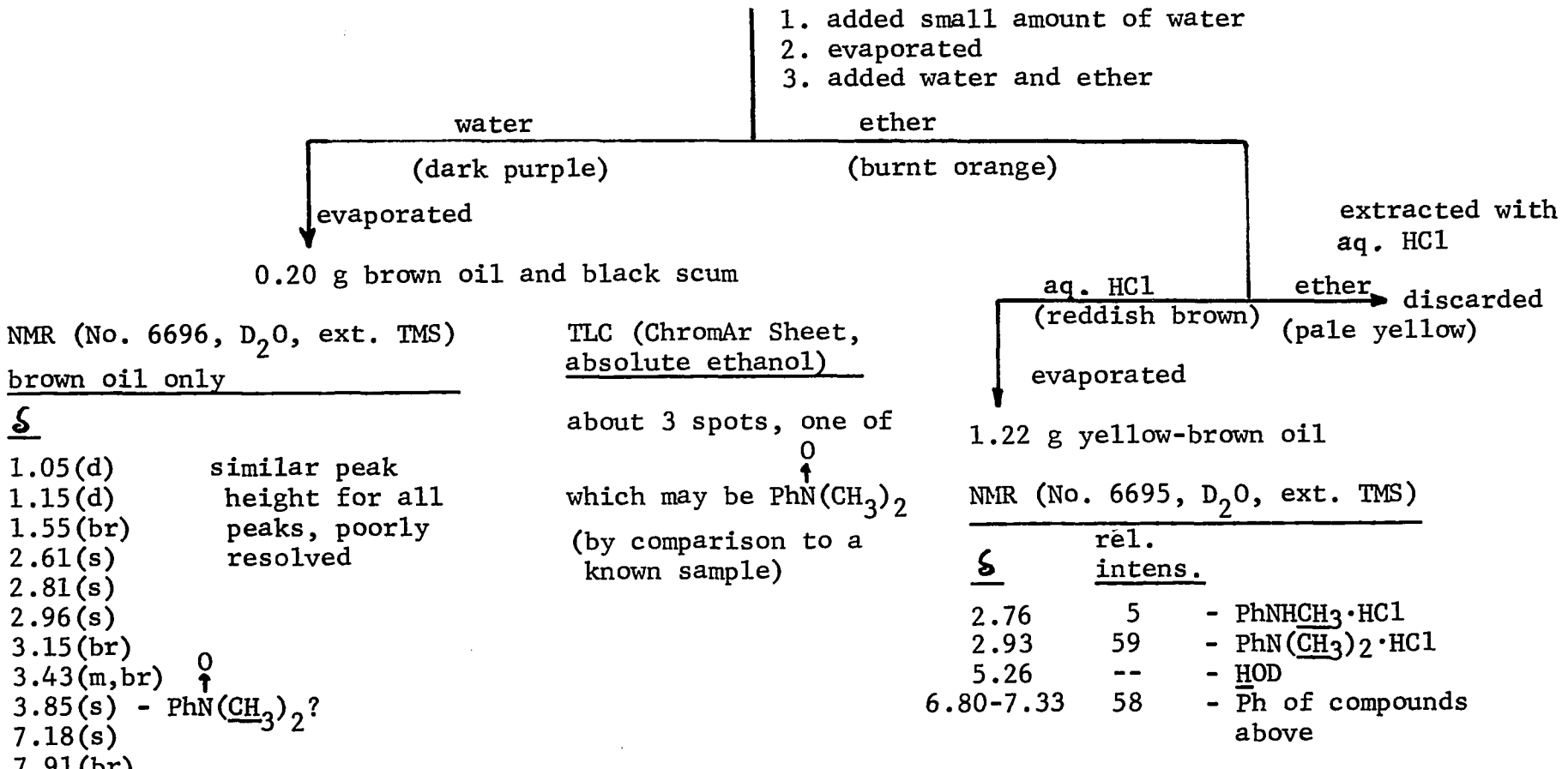


Figure 8. Workup of the reaction of cyclohexyl hydroperoxide with N,N-dimethylaniline in ether-isopropanol-water. (Reaction 3)

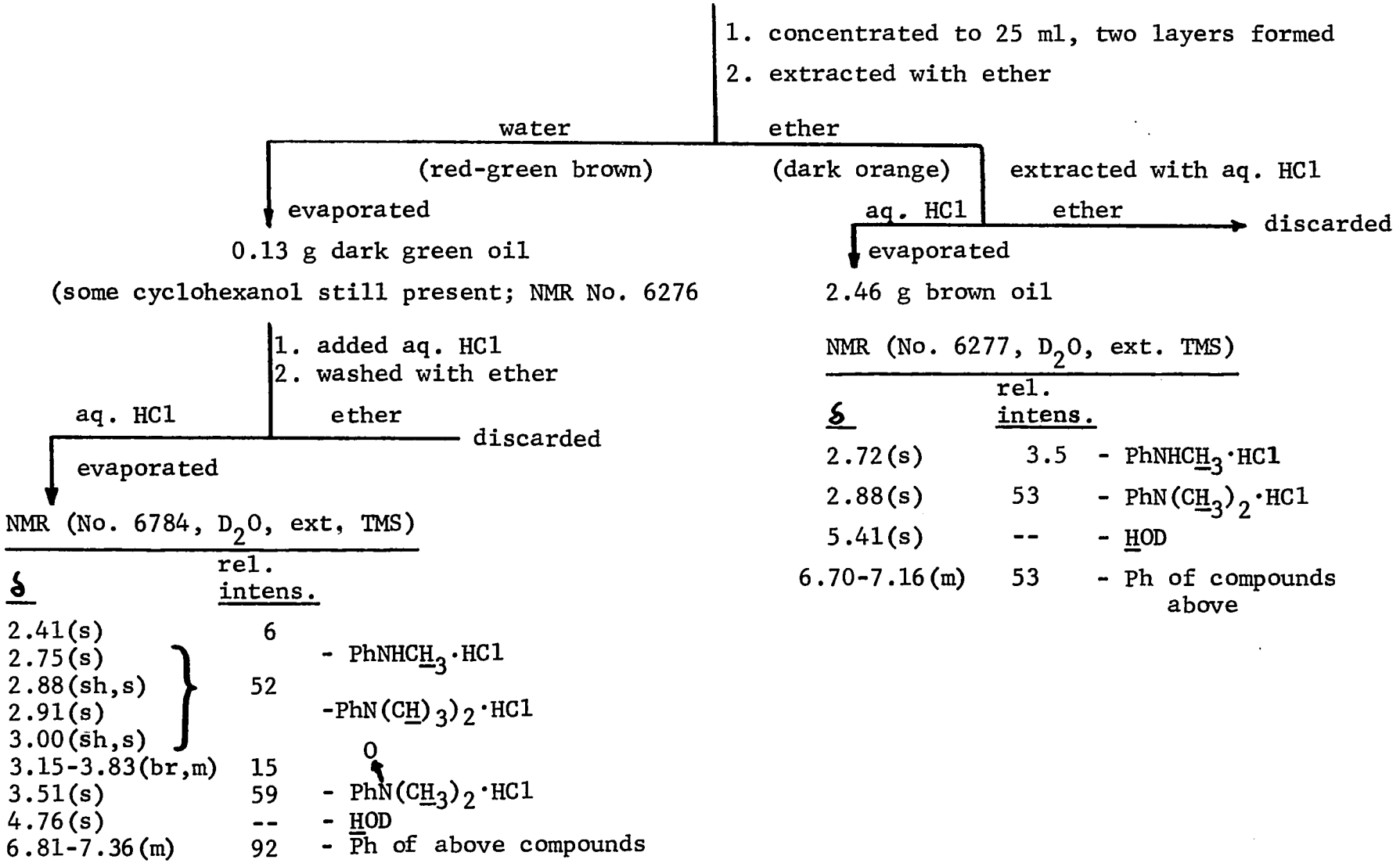
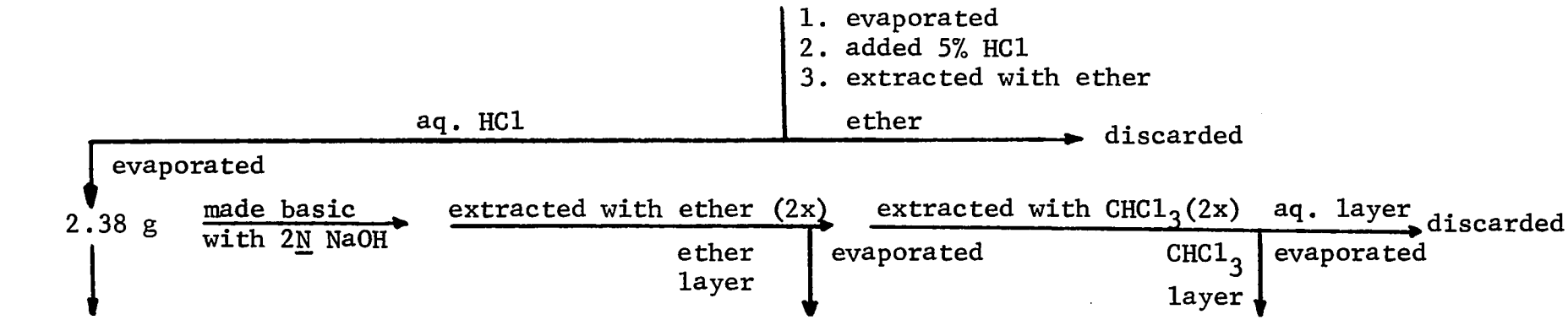


Figure 9. Workup of the reaction of t-butyl hydroperoxide with N,N-dimethylaniline in aqueous isopropanol. (Reaction 4)



NMR (No. 6995, D_2O, ext. TMS)

δ	rel. intens.	
2.65(s,br)	8	
2.89(s), 2.94(s)	16	or PhNHCH$_3$·HCl
3.07(s), 3.13(s)	77	
	(minor)	- PhN(CH$_3$)$_2$·HCl
3.77(s)	72	- PhN(CH$_3$)$_2$·HCl
5.43(s)	--	- HOD
7.06-7.81(m)	132	- Ph of above compounds

TLC(ChromAr Sheet, absolute ethanol)

3 spots

NMR(No. 7001,$CDCl_3$,int. TMS)

δ	rel. intens.	
2.61(s)	18	PhNHCH$_3$[a]
2.77(s), 2.80(s)	91	
	(minor)	PhN(CH$_3$)$_2$
3.21(s)	3	
3.75(s)	19.5	
4.76(s)	--	H_2O?
6.28-7.31(m)	92	Ph of above compounds

NMR(No. 7002,$CDCl_3$,int. TMS)

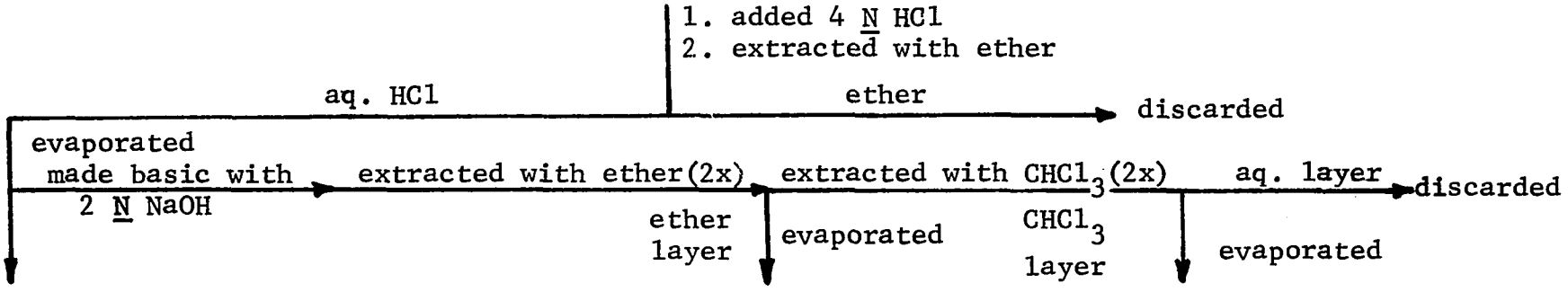
δ	rel. intens.	
1.26(m)	5.5	
2.77(s)	8	
2.88(s)	36.5	dil. → 3.55
3.52(br,s)	60	dil. → 3.58 minor PhN(CH$_3$)$_2$
3.90(s), 4.08(br)	33	O
6.40-7.60(m)	85	- Ph of above compounds
7.08(s)		- $CHCl_3$
7.60-8.08(m)	22	

IR(No. 118,neat)

942(s), 963(s) N→O present

(a) Addition of a small amount of known material increased the intensity.

Figure 10. Workup of the reaction of cyclohexyl hydroperoxide with N,N-dimethylaniline, no solvent. (Reaction 5)



NMR(No. 6999, D_2O, ext. TMS)

δ	rel. intens.	
2.95[b]	20	$PhNHCH_3 \cdot HCl$
3.11[b]	44	$PhN(CH_3)_2 \cdot HCl$
4.80(s)	69	$PhN(CH_3)_2 \cdot HCl$ (O on N)
5.83-8.30(m)	very intense	Ph of above compounds and HOD

NMR(No. 7004, $CDCl_3$, int. TMS)

δ	rel. intens.	
1.26(s)	6	
2.73(s)	27	$PhNHCH_3$[a]
2.88(s)	41	$Ph(CH_3)_2$
3.25(s)	14	
6.41-7.36(m)	94	Ph of above compounds

NMR(No. 7044,7003, $CDCl_3$, int. TMS)

δ	rel. intens.	
2.83(s)	small	
2.95(s)	small	
3.58(sh)?		
3.61(s)		$PhN(CH_3)_2$ (O on N)[a]
7.28(s)		$CHCl_3$

small multiplets under $CHCl_3$(Ph) and at 2.58-4.25 ppm

TLC(ChromAr Sheet, absolute ethanol)

2 spots

IR (No. 119, $CHCl_3$)

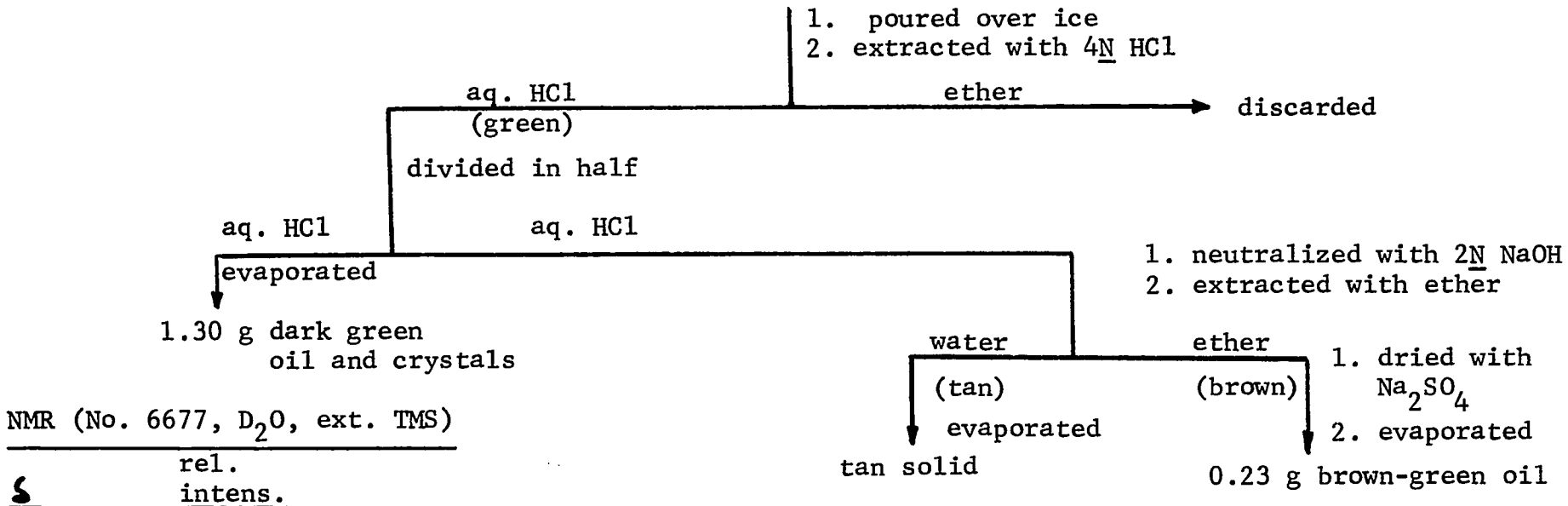
924(sh,m)
942(m) N→O present[d]

(a) Addition of a small amount of known material increased the intensity. (b) Not sharply resolved. (c) Addition of a small amount of $PhN(CH_3)_2$ (O on N) to the NMR tube (spectrum no. 7006) gave a new $N-CH_3$ peak at 207 Hz.

Figure 10. (continued)

(d) For some unexplained reason the spectrum appeared to be shifted about 20 cm^{-1} to lower wave numbers than normal.

Figure 11. Workup of the reaction of cyclohexyl hydroperoxide with N,N-dimethylaniline in ether, catalyzed by vanadium oxyacetylacetonate. (Reaction 6)



NMR (No. 6677, D_2O, ext. TMS)

δ	rel. intens.	
2.68(br)	69	Ph-NHC$\underline{H}_3$·HCl and Ph-N(C$\underline{H}_3$)$_2$·HCl
7.00(br)	54	Ph of above compounds

NMR(No. 6676, D_2O, ext. TMS)

-only peak observable even at very high amplitude was small singlet at 2.10 ppm
-solid is mostly NaCl

NMR(No. 6678, $CDCl_3$, int. TMS)

δ	rel. intens.	
2.03(s)	5	
2.68(s)	10	
2.87(s)	107	PhNHC$\underline{H}_3$
6.41-7.45(m)	114	Ph of above compounds

Figure 12. Workup of the reaction of t-butyl hydroperoxide with N,N-dimethylaniline in t-butanol, catalyzed by vanadium oxyacetylacetonate. (Reaction 7)

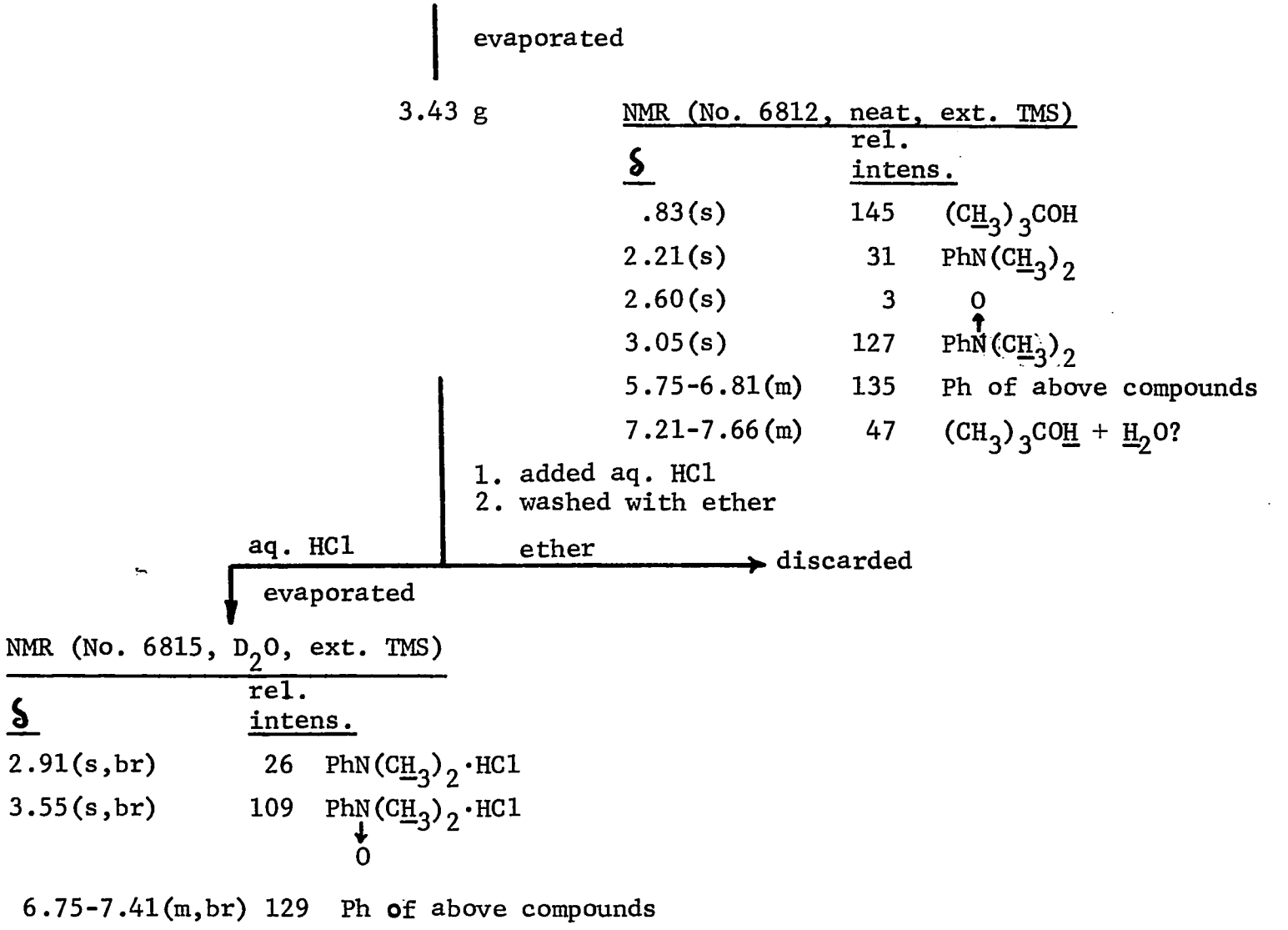
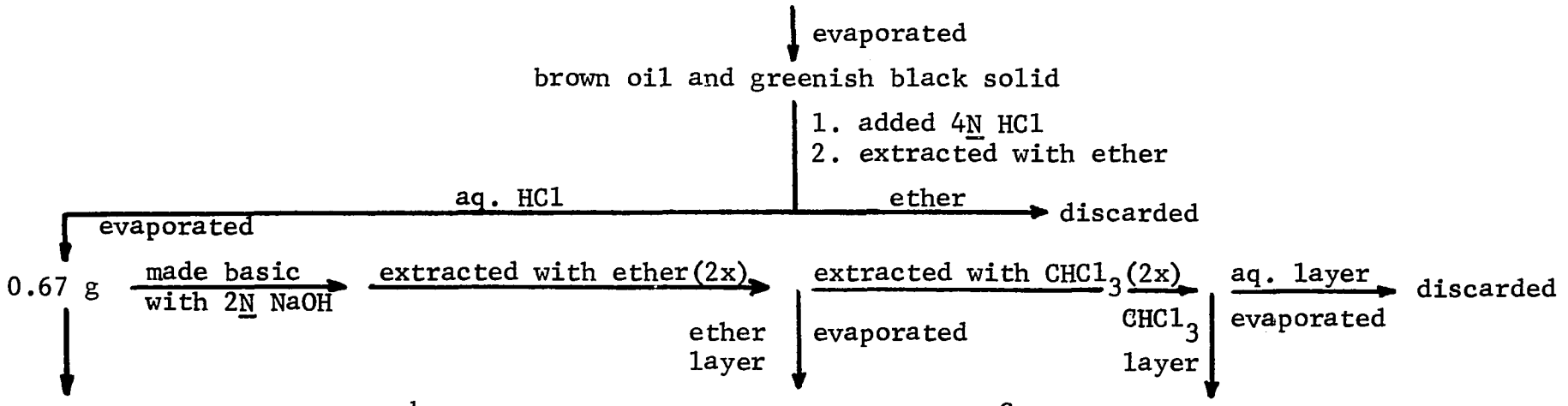


Figure 13. Workup of the reaction of menthyl hydroperoxide with N,N-dimethylaniline in methanol, catalyzed by vanadium oxyacetylacetonate. (Reaction 8)



NMR(No. 6998, D_2O, ext. TMS)[b]

δ	rel. intens.	
1.88(s)	2	solid material
2.81(s)	6	$PhNHCH_3 \cdot HCl$
3.00(s)	62	$PhN(CH_3)_2 \cdot HCl$
7.20-7.66(br)	62	Ph of above compounds

NMR(No. 7022, $CDCl_3$, int. TMS)[c]

δ	rel. intens.	
2.76(s)	4	$PhNHCH_3$
2.85(sh)	60	
2.88(s)		$PhN(CH_3)_2$[a]
6.43-7.48(m)	55	Ph of above compounds

NMR(No. 7023, $CDCl_3$, int. TMS)

δ	
many small broad peaks between 0 and 2.16 ppm	
2.93(s) small	$PhN(CH_3)_2$[a]
	d

TLC(ChromAr Sheet, absolute ethanol)

2 spots

(a) Addition of a small amount of known material increased the intensity. (b) The addition of D_2O caused a solid to precipitate. (c) Major peaks only. (d) Addition of $PhNHCH_3$ gave a new peak at 2.81.

Reaction of Methyl Phenyl Sulfide (59) with Bornyl Hydroperoxide (41).

To a solution of bornyl hydroperoxide (41) (0.178 mol, prepared by method B from (-)-bornyl chloride (40)) in anhydrous ether (9 ml) was added 1.86 g (0.0150 mol) of methyl phenyl sulfide (59) in absolute ethanol (10 ml). The reaction was stirred under nitrogen at 30° for 0.5 days, and then at 40° for 5 days at which time a titration (Wibaut method[162]) showed only 0.0029 mol of hydroperoxide remaining. The solvents were removed under reduced pressure, the residue was dissolved in ether (25 ml), and the product was extracted into water (6 x 25 ml). The combined aqueous extracts were washed with low boiling petroleum ether[206] (4 x 50 ml) and were evaporated to dryness with warming under reduced pressure to give 1.43 g (74%) of a partially solidified, pale yellow oil. The nmr spectrum (no. 7038, D_2O) showed peaks due to the desired product, 60 (2.42 ppm, s, CH_3-S(O)-Ph) contaminated with 7-8% of unreacted 59 (1.82 ppm, s, CH_3-S-Ph). Since very weak signals (0.8 and 1.23 ppm) possibly from traces of bornyl compounds could be observed at very high spectral amplitudes, the residue was redissolved in water (35 ml) and washed again with petroleum ether (25 ml). The aqueous layer was then evaporated to dryness and the residue was dissolved in chloroform and dried over anhydrous sodium sulfate. The chloroform was evaporated to yield 1.18 g (62%) of 60 as a pale yellow oil which solidified on cold storage in a vacuum desiccator over phosphorous pentoxide, and melted on warming to room temperature (lit. 29.5°[207], 29-30°[208]). Since a small solvent peak was observed by gas chromatography, the oil was placed on a rotary evaporator under the reduced pressure of a vacuum pump for 1 hr to give

pure 70: $[\alpha]_D^*$ -1.59, $[\alpha]_{578}$ -1.73, $[\alpha]_{546}$ -2.16, $[\alpha]_{436}$ -4.32, $[\alpha]_{405}$ -5.72, $[\alpha]_{365}$ -8.64 (c 4.6, absolute ethanol); $[\alpha]_D^{**}$ -1.89, $[\alpha]_{578}$ -2.00, $[\alpha]_{546}$ -2.28, $[\alpha]_{436}$ -4.28, $[\alpha]_{405}$ -5.71, $[\alpha]_{365}$ -8.86 (c 1.75, absolute ethanol); 1.06-1.26% e.e. (lit.[206a] + 149° (c 1, absolute ethanol) for the pure compound); ir (no. 105) 1040 cm^{-1} (S-O) identical to authentic material; nmr (no. 7081, $CDCl_3$) 2.67 (s, 3, $CH_3\overset{O}{\uparrow}S$-) and 7.33-7.78 ppm (m, 5, Ar); tlc (Mallinckrodt ChromAr 500 sheet) showed no spots other than methyl phenyl sulfoxide (60) using benzene or 10% methanol in ethyl acetate (eluents in which known samples of methyl phenyl sulfide, borneol, and camphor were separable from the sulfoxide); glpc (15% Silicone GE XE-60 (nitrile gum) on Chromosorb W, KOH washed, 128°, 10 psi) gave only one peak (retention time 10.5 min) corresponding to known 60. (Known samples of methyl phenyl sulfide, borneol, and camphor had retention times of 1.4 min or less).

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* All specific rotations are ±0.05°.

**All specific rotations are ±0.15°.

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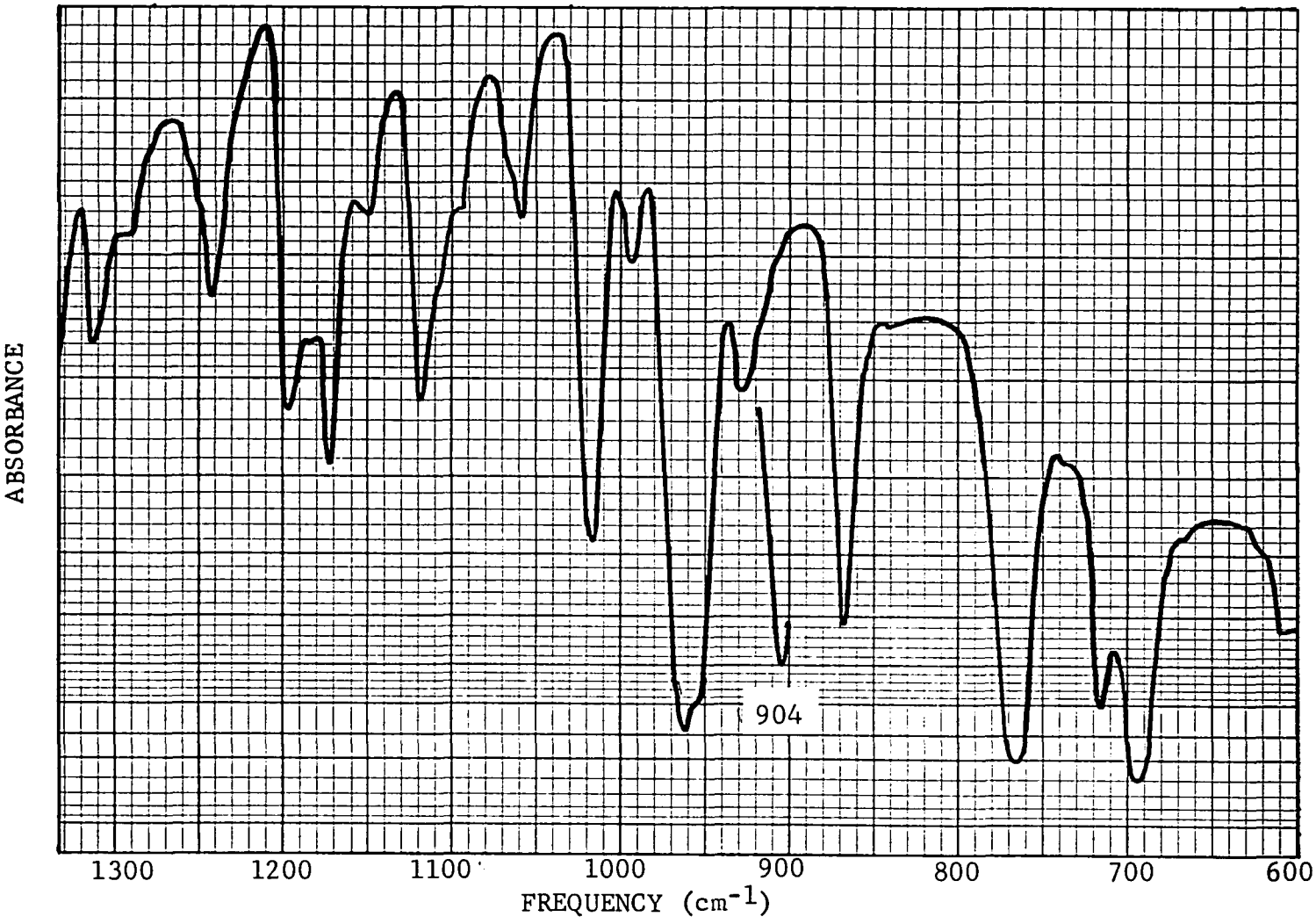

Figure 14. Infrared spectrum (no. 112) of N,N-dimethylaniline N-oxide (1c). (mull in Nujol).

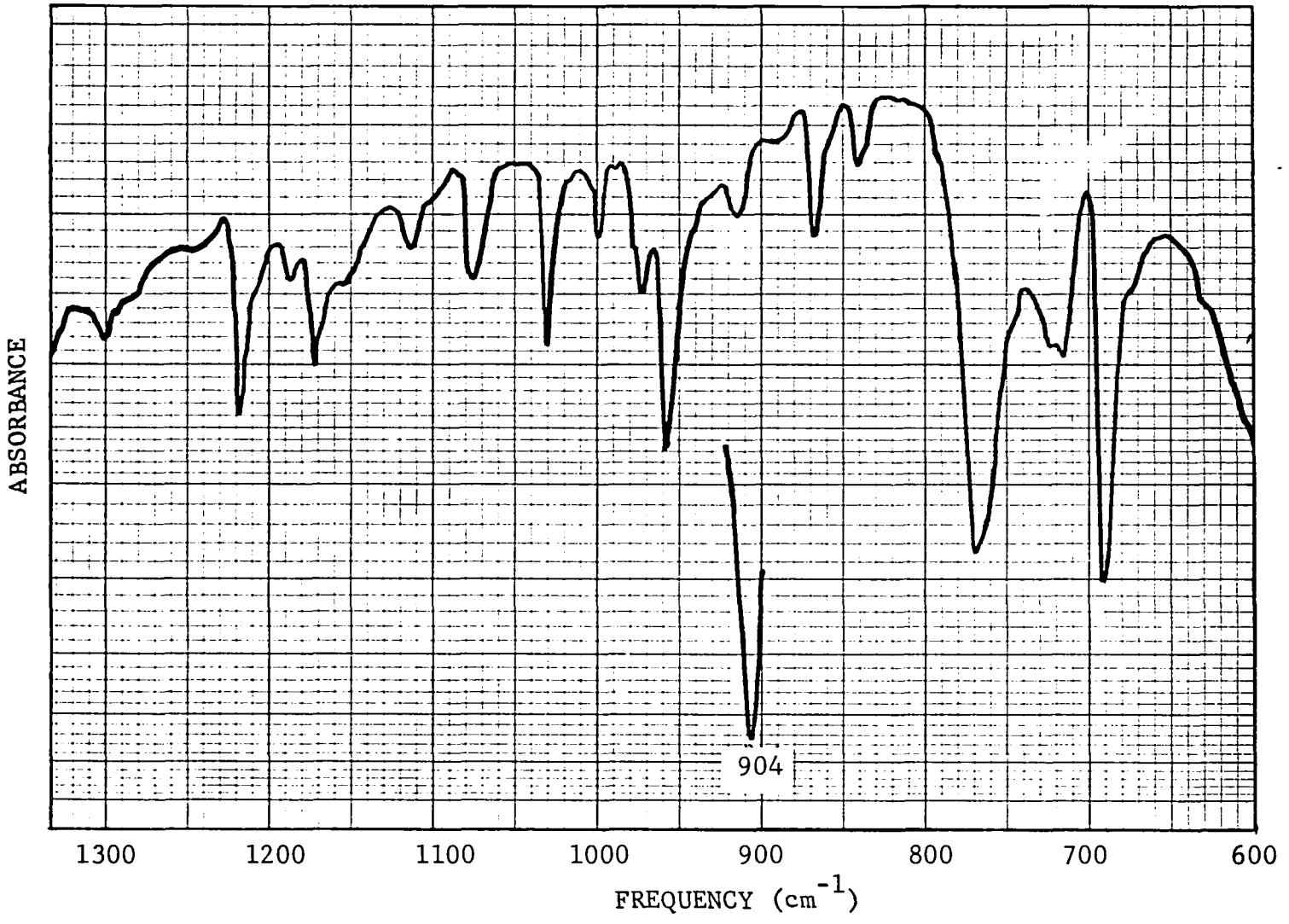

Figure 15. Infrared spectrum (no. 27) of N,N-dimethylaniline N-oxide hydrochloride (1d). (mull in Nujol).

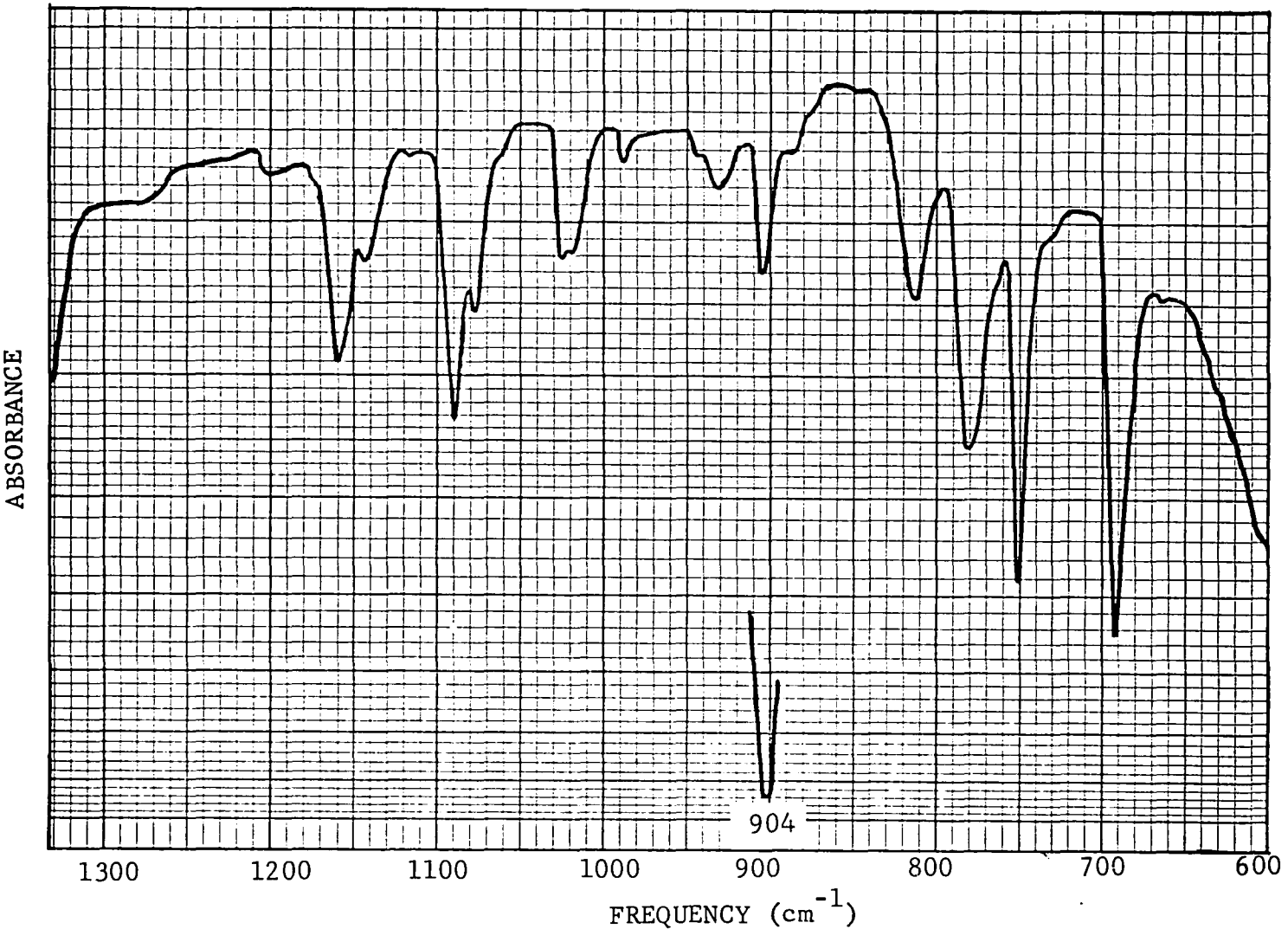

Figure 16. Infrared spectrum (no. 109) of N-methyl, N-isopropylaniline N-oxide hydrochloride (3d). (mull in Nujol).

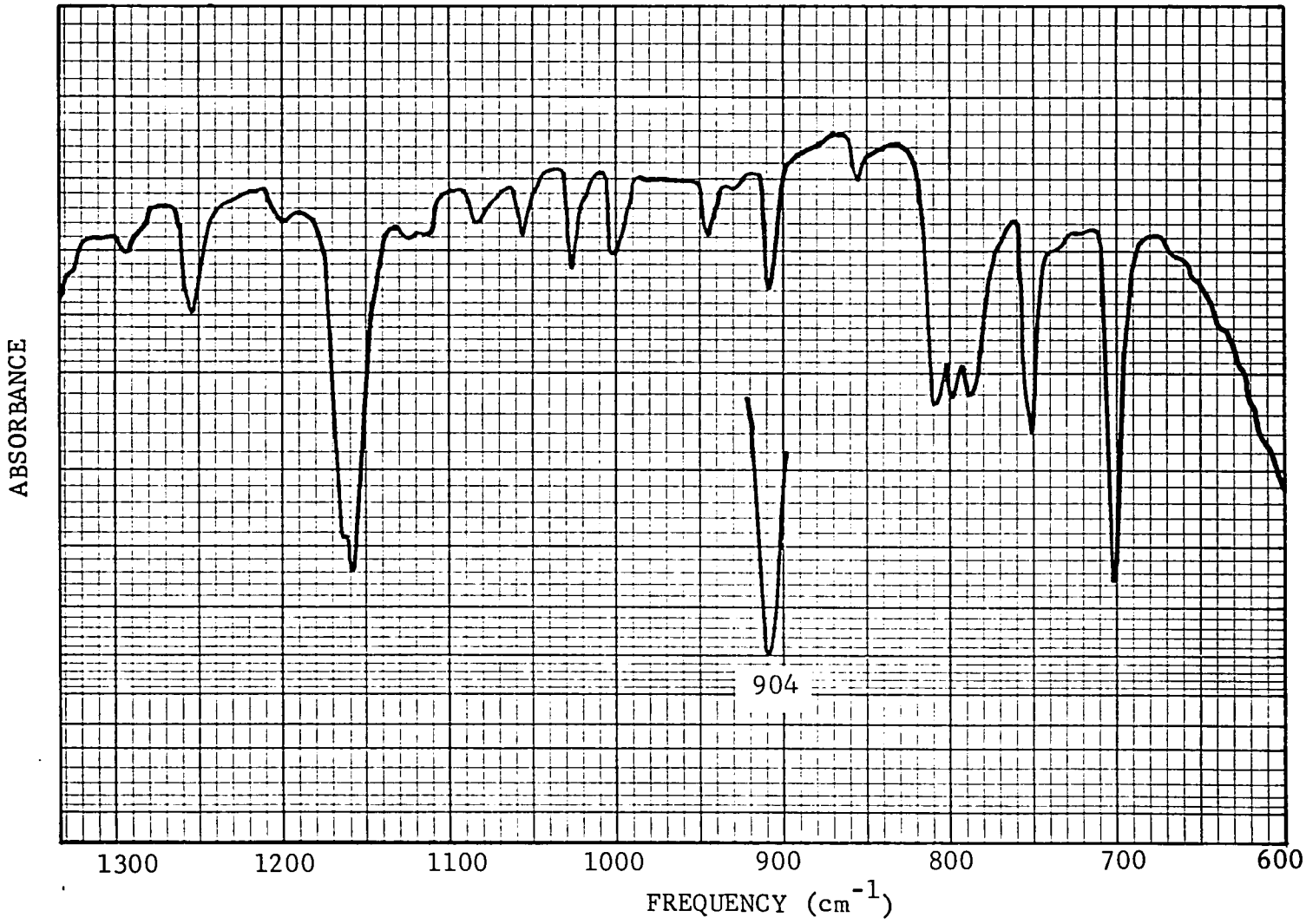

Figure 17. Infrared spectrum (no. 111) of N-methyl, N-t-butylaniline N-oxide hydrochloride (4d). (mull in Nujol).

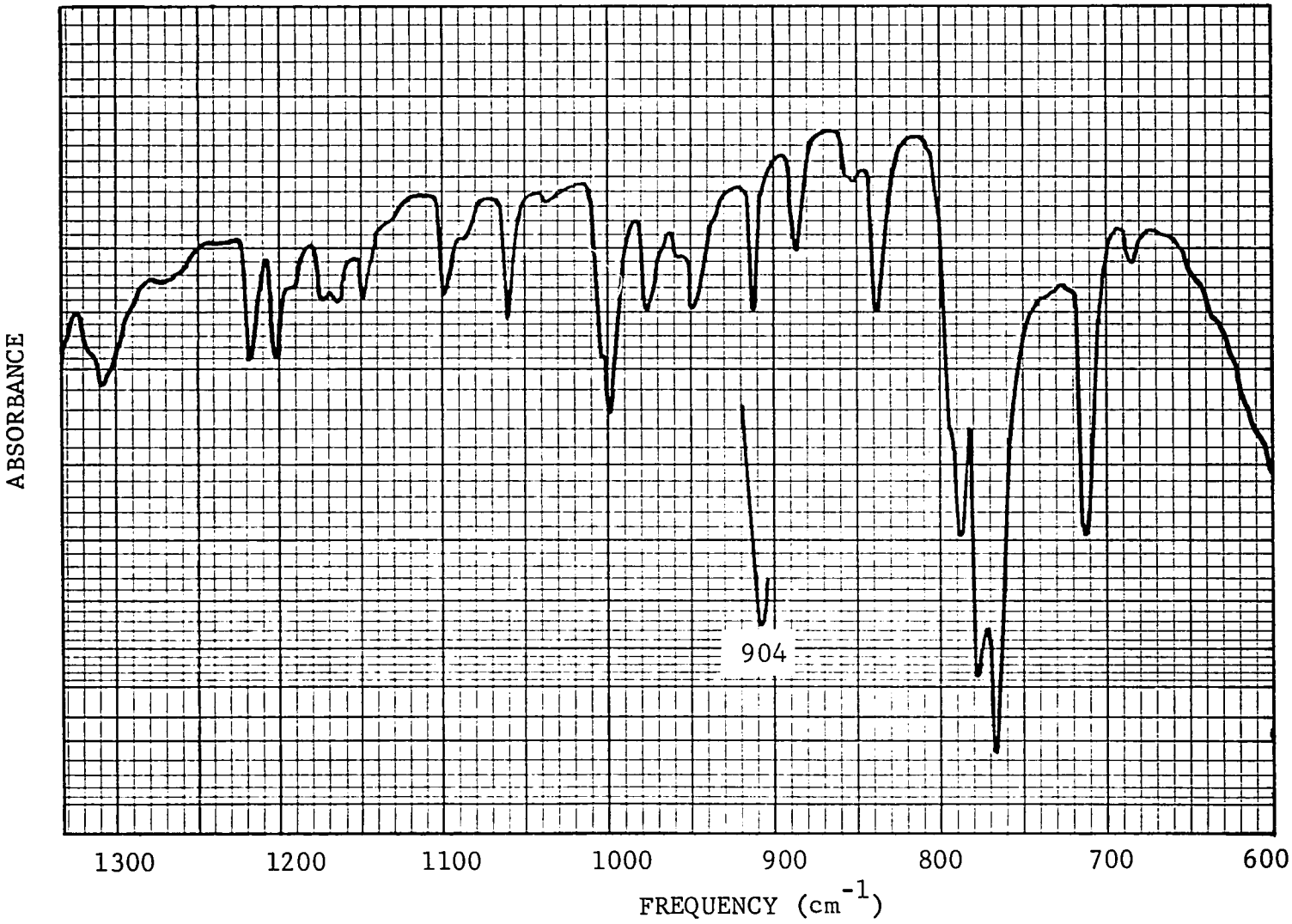

Figure 18. Infrared spectrum (no. 110) of kairoline N-oxide hydrochloride (5d). (mull in Nujol).

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