Mechanistic studies on the oxidation of alkyl substituted tetrahydrobenzofurans with m-chloroperbenzoic acid
by Samuel Beryl Gingerich

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University
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Abstract:
The reaction of a series of alkyl substituted tetrahydrobenzo-furans with m-chloroperbenzoic acid has been explored. The furan substrates used included 3-methyl-4,5,6,7-tetrahydrobenzofuran, 1,2,3,4,5,6,7,8-octahydrodibenzofuran, 2-methy1-4,5,6,7-tetrahydro-benzofuran and 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran. The products arising from the oxidation of these substrates have been isolated and their structures determined. These substrates have also been prepared labeled with oxygen-18. These labeled substrates were also oxidized and the position of the label in the products determined by carbon-13 NMR spectroscopy. On the basis of the data obtained from these experiments, a detailed mechanistic scheme was developed. Initial attack of the furan moiety by m-chloroperbenzoic acid occurs to form an epoxide which subsequently undergoes ring openings to form a cis-enedione. These compounds are postulated as intermediates in all the reactions studied even though such a compound was isolated in only one case. These enediones undergo rapid Baeyer-Villiger oxidation with a second equivalent of m-chloroperbenzoic acid. In certain cases, the reaction with a third equivalent of m-chloroperbenzoic acid has been observed and, again, this is viewed as a Baeyer-Villiger oxidation.

MECHANISTIC STUDIES ON THE OXIDATION

OF ALKYL SUBSTITUTED TETRAHYDROBENZOFURANS

WITH m-CHLOROPERBENZOIC ACID

by

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A thesis submitted in partial fulfillment
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APPROVAL

of a thesis submitted by

Samuel Beryl Gingerich

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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ABSTRACT

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furans with m-chloroperbenzoic acid has been explored. The furan
substrates used included 3-methyl-4,5,6,7-tetrahydrobenzofuran,
1,2,3,4,5,6,7,8-octahydrodibenzofuran, 2-methyl-4,5,6,7-tetrahydro-
benzofuran and 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran. The
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isolated and their structures determined. These substrates have also
been prepared labeled with oxygen-18. These labeled substrates were
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mined by carbon-13 NMR spectroscopy. On the basis of the data
obtained from these experiments, a detailed mechanistic scheme was
developed. Initial attack of the furan moiety by m-chloroperbenzoic
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perbenzoic acid. In certain cases, the reaction with a third equiva-
lent of m-chloroperbenzoic acid has been observed and, again, this is
viewed as a Baeyer-Villiger oxidation.

INTRODUCTION

The chemistry of furans has attracted the interest of many researchers over the years. However, of this work, little has centered on the oxidation of furans. In reviewing the literature, one finds that a few workers have carried out extensive studies in this area. A literature review also shows that most of the reports dealing with the oxidation of furans come from those whose research interests have impinged on this area of furan reactivity for other reasons. One example of this latter case would be reports stemming from the oxidation of furans with a specific reagent or procedure in which the primary interest of the author lies in the oxidative process used rather than in the furan moiety. In other cases, furans have appeared in synthetic schemes in which they have been transformed by oxidation into a desired product. Examples can also be found in which natural products containing the furan moiety have been oxidized to assist in structure elucidation.

A few techniques for the oxidation of furans have received repeated use over extended periods of time. Two of these will be discussed. Attention will then be turned to the use of organic peracids as oxidants and the results which have been obtained in these systems.

One method that has been extensively utilized since its development by Clauson-Kaas is the electrochemical oxidation.[1] In this

process, alcohols are used as solvents with ammonium bromide as a

buffer and a platinum electrode is generally employed. Oxidations of

this type can convert furan 1 into 2,5-dialkoxy-2,5-dihydrofurans 2

(equation 1). These compounds, which are useful as synthetic inter-

$$RO \diagdown \diagup_O \diagdown OR \qquad (1)$$

1 2
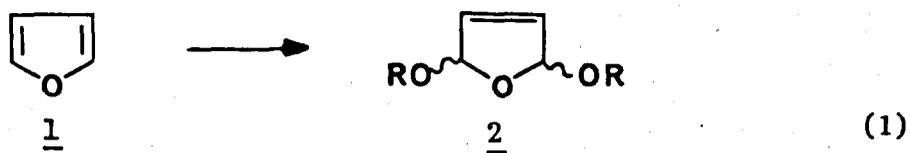
mediates, can be prepared in excellent yields. This electrochemical

oxidation process was developed to replace the bromoalkoxylation reac-

tion.[2] In these instances, bromine was used as the oxidant and simi-

lar products were obtained. However, yields were generally lower and

the resulting products were often contaminated with a small amount of

bromine. This greatly decreased their stability since these compounds

are acid sensitive. Interest is still shown in the synthesis of these

useful intermediates as evidenced by a recent report that cited use

of vanadium(V) oxide to catalytically convert hydroperoxides formed

from the photooxidation of furans to synthons of this type.[3]

A second type of furan oxidation which has received considerable

attention has been the dye sensitized photooxidation.[4] This process

results in the formation of endoperoxides 4 if the reaction is carried

out in aprotic solvents (equation 2). These products can be converted

$$ \textbf{3} \xrightarrow[\text{sens}]{h\nu, O_2} \textbf{4} \xrightarrow{\text{ROH}} \textbf{5} \qquad (2) $$
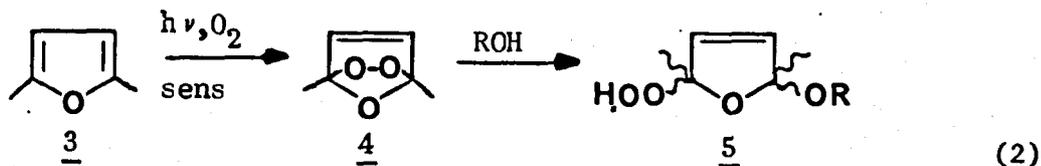
to hydroperoxides 5 by action of alcohol or the furan 3 can be con-
verted directly to 5 by carrying out the oxidation using an alcohol
as the solvent. Interest has been expressed in the endoperoxides 4
for a number of reasons. Initially, they were studied as stable
ozonides.[5] These compounds can be considered as the ozonides of
cyclobutadienes and the comment has been made that this is probably
the only case where an ozonide was isolated before the parent com-
pound.[6] Attention to the endoperoxides 4 has also persisted because
of the interesting chemistry that they afford. Recent work by Adam
has shown that these compounds are capable of epoxidizing olefins.[7]
Work continues on the mechanism of this reaction.[8] Interest is also
expressed in other conversions of these compounds as evidenced in the
report noted above with vanadium(V) oxide.[3]

In reviewing the literature on the oxidation of furans with
organic peracids, one notes discrepancies which seem to arise. As
observed previously, some of these may occur since the stated purpose
of the research relates to the peracid oxidation of a furan as a
desired chemical transformation. Thus, details of the reaction are
not reported that would be useful in a mechanistic study. Yet in

other cases, the results seem contradictory and obviously further

studies are needed. Perhaps the most relevant observation is that

there are very few references to research in this area.

Initially, attention will be directed to the oxidation of benzo-

furans or aryl substituted furans. This class of compounds is segra-

gated in this way as a matter of convenience, rather than because they

exhibit markedly different reactivities.

One of the earliest reports in this area is an article by Lutz.[9]

One primary interest of his research group was the chemistry of

substituted dibenzoylethylene. In this light, he reported that the

oxidation of tetraphenylfuran 6 proceeds to give 7 and 8 (equation

3). A variety of oxidizing agents were used including, chromic acid,
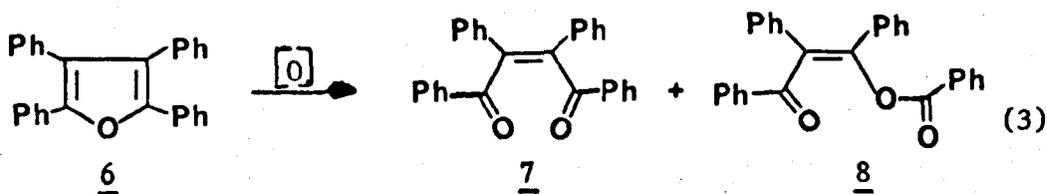
hydrogen peroxide, ozone and perbenzoic acid in acetic acid. Yields

of 7 reportedly ranged between 40-80% and yields of 8 between 10-20%.

It is inferred that under any of these conditions 7 can be oxidized

to 8; but, given the brevity of this report, this point is not clear.

Specific reaction conditions are also not noted and, therefore, yields

with a given reagent are left in doubt. Because of the lack of

experimental detail in this communication, its value is truly limited.

This area was approached next in an article by Boyer.[10] In this

report attention was directed toward the oxidation of the singlet

oxygen acceptors 1,3-diphenylisobenzofuran 9 and 2,5-diphenylfuran

11. It was noted that the treatment of 9 with one equivalent of

m-chloroperbenzoic acid (mCPBA) for two hours in refluxing methylene

$$\text{(4)}$$
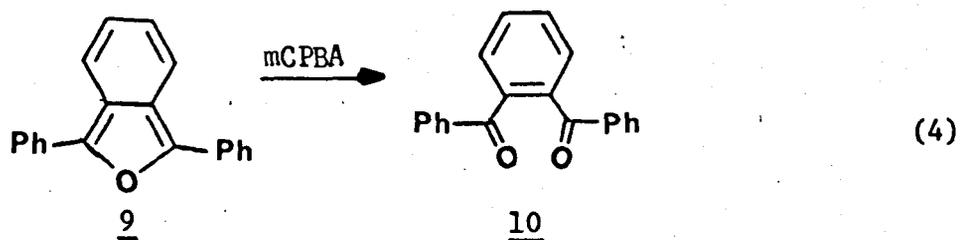
chloride in the dark gave o-dibenzoylbenzene 10 in 90% yield (equa-

tion 4). It was noted that the identical product was obtained by the

photooxidation of 9. Similarly, 2,5-diphenylfuran 11 gave cis-

dibenzoylethylene 12 in 85% yield when treated with one equivalent of

mCPBA and reflux was continued for four hours (equation 5). Again,

$$\text{(5)}$$
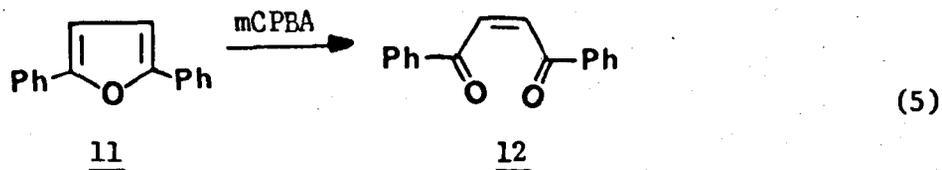
it was noted that the same product could be isolated by the singlet

oxygen oxidation of 11. On the basis of further experimentation, the

reaction with peracid was shown not to proceed through a singlet

oxygen mechanism and the epoxide 13 was suggested as the type of intermediate involved in the peracid oxidation.
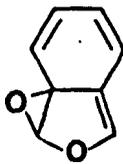
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Considering the oxidation of furan itself with organic peracids, one again finds a progression of studies. The earliest reference dates from 1931.[11] In this case, it was noted that the oxidation of furan 1 with peracetic acid as a 6% solution in acetic acid proceeded slowly, requiring three days to go to completion as noted by the disappearance of the peracid. At the end of this time, attempts to isolate the product by removing the acetic acid by distillation afforded a resinous material whose molecular weight was found to be greater than 780. On the basis of this information, two intermediates
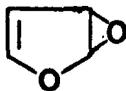
14

15

were proposed: 14 or 15. The oxidation was then carried out with

perbenzoic acid in chloroform (equation 6). In this instance,

$$\text{(6)}$$
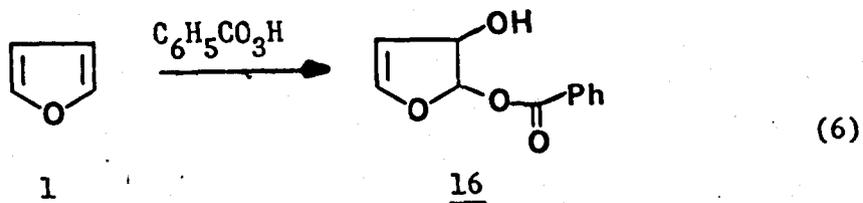
the product was determined to be 16 on the basis of carbon-hydrogen

analysis and molecular weight determination. It was therefore con-

cluded that epoxide 14 was the intermediate in both cases.

This reaction was reinvestigated by Clauson-Kaas in 1947.[12]

Again peracetic acid and perbenzoic acid were used as the oxidants.

In this case, the product was determined to be malealdehyde 17 on the

basis of the bis-phenylhydrazone which was isolated (equation 7).

$$\text{(7)}$$
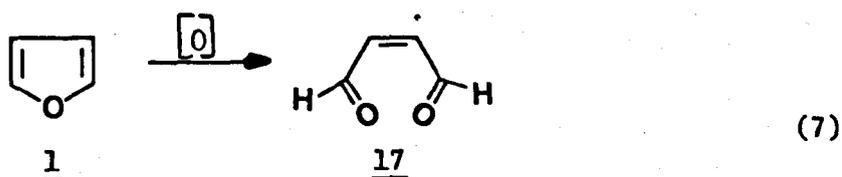
These reactions were run in a variety of solvents including chloro-

form, ether, acetic anhydride and water at temperatures ranging from

0-40°. Yields were reported to be less than 23% in all cases. No

difference was noted between the two peracids. The authors proposed

15 to be the intermediate in these reactions. In a report by the same

group five years later, they reported that oxidation of furan 1 with

lead tetraacetate gave 18 in 70-80% yield (equation 8). Compound 18

was then hydrolyzed to give 17 which was isolated and identified as

(8)
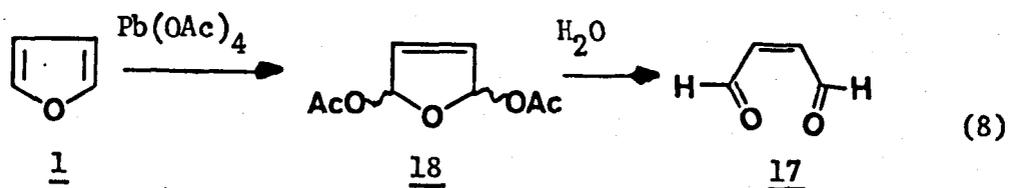
the bis-phenylhydrazone.

A final study on the oxidation of furan with peracids was

reported in 1964.[14] The result noted with p-nitroperbenzoic acid as

the oxidant was the isolation of aldehydomaleic acid 19 in 8% yield

(equation 9). The reaction was carried out in ether using 2.2

(9)
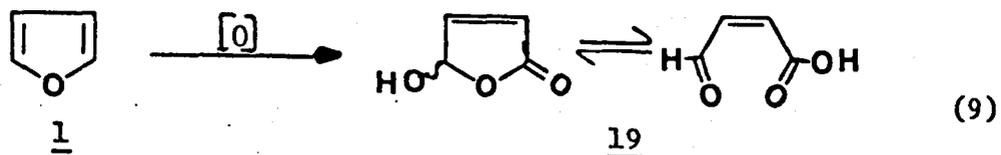
equivalents of the peracid. Reaction time was reported as two days.

The product 19 was identified on the basis of its ^{1}H NMR spectrum,

elemental analysis and the elemental analysis of a derived phenyl-

hydrazone. In this case, diepoxide 20 was proposed as the inter-

20
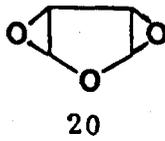
mediate in the reaction.

In analyzing the results from these three articles, it should be

noted that p-nitroperbenzoic acid is a slightly stronger oxidant than

perbenzoic acid which, in turn, is slightly stronger than peracetic

acid. This ordering is based on the concept that stronger acids yield

peracids with correspondingly stronger oxidizing ability.[15] The

result obtained with p-nitroperbenzoic acid can therefore possibly

be rationalized on the basis that a stronger oxidant was used. How-

ever, the earlier two reports are still conflicting and further

studies in this area would be useful.

Turning attention to substituted furans, Lefbvre reported on the

oxidation of 3-substituted furans with peracetic acid.[16] It was

observed that 3-isopropylfuran 21 underwent oxidation with excess

peracetic acid to give 22 (equation 10). The reaction was run in

$$CH_3CO_3H$$

(10)

21   22
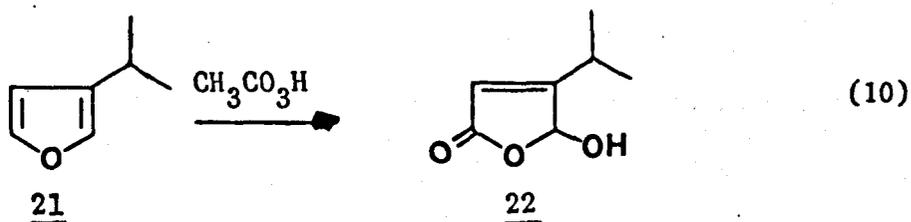
chloroform for two hours at 0-5°. Solid sodium acetate was added as

a buffer. Even though no mechanism was proposed, this reaction seems

to follow a pathway similar to that observed in the oxidation of furan

with p-nitroperbenzoic acid. In this same article, the oxidation of

a compound in the digitoxigenin series was reported (equation 11).

$$CH_3CO_3H$$

(11)
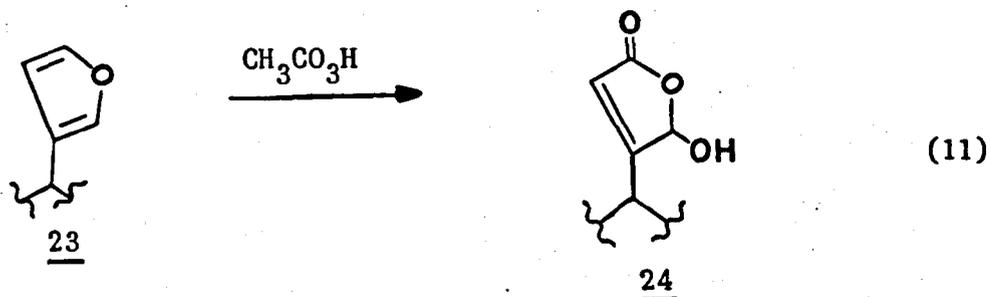
In this case the furan moiety is substituted on the D ring of a

steroidal skeleton. The furan was found to oxidize again in two

hours under similar conditions to form 24 in approximately 50% yield.

A second article by the same group followed in which they

reported the transformation shown (equation 12).[17] In this case,

(12)
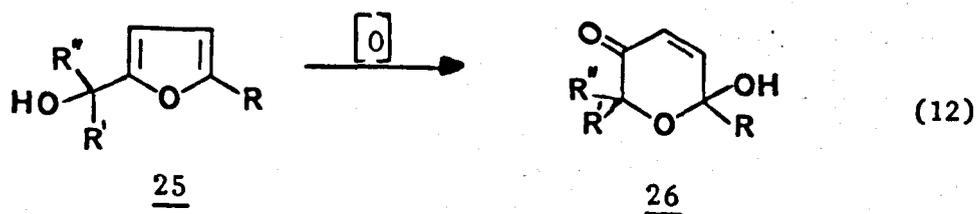
oxidation was carried out with mCPBA or peracetic acid. Reaction

times were generally short and the products were isolated in varying

yields, ranging between 50-90%, if the reaction proceeded at all. No

mechanism was proposed in this report either.

It is interesting that a similar transformation was observed

later by a group of Italian workers using pyridinium chlorochromate

(PCC) as an oxidant (equation 13).[18] Methylene chloride was used as

(13)
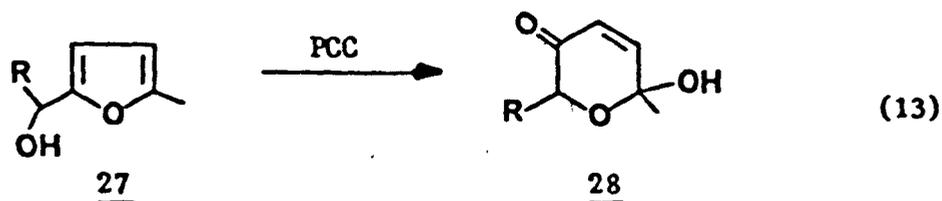
the solvent and the products were generally isolated in greater than

90% yields. No oxidation of the secondary alcohol was noted. This

work has recently been extended (equation 14).[19] These reactions were

again carried out in methylene chloride using a 2:1 molar excess of

(14)
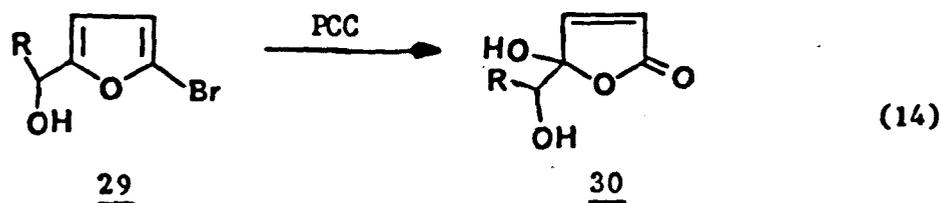
PCC. Reaction times were reported as approximately ninety minutes.

It is noteworthy that the products 30, isolated in 60-75% yields, are

of the same type one would expect from the peracid oxidation of the

furan based on the report noted above on the oxidation of 3-substi-

tuted furans.

At this point, it may be interesting to discuss a couple of

anomalies which have been reported. One case involved oxidation

reactions of biogenetic interest.[20] When epoxyazadiradone 31 was

treated with perbenzoic acid for two hours, gedunin 32 was isolated

in 90% yield (equation 15). No note was made of the quantity of

$$C_6H_5CO_3H \qquad (15)$$

$$\underline{31} \qquad\qquad\qquad \underline{32}$$
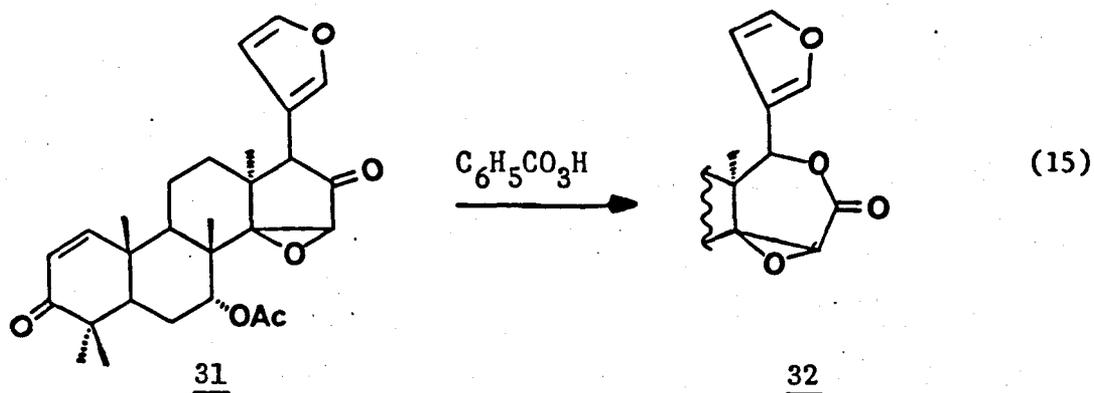
perbenzoic acid used. Similarly, 1,2-dihydroepoxyazadiradone was

reported to react with perbenzoic acid to give two products: 1,2-

dihydrogedunin and 1,2-dihydro-7α-obacunyl acetate. The latter

product arises from Baeyer-Villiger oxidation in both the A and D

rings of the steroidal nucleus. In this case reaction time was

reported as nine hours; but, again, no comment was made on the quan-

tity of perbenzoic acid used or on other conditions employed. No

products in either instance were reported arising from oxidation of

the furan moiety.

It should be noted that the furan in $\underline{31}$ is in a very similar

environment to that of the furans discussed by Lefbvre (see equations

10 and 11). As observed previously, peracetic acid, as used by

Lefbvre, is a weaker oxidant than perbenzoic acid, which was used

above. With the longer reaction times used above, one would therefore

predict some oxidation of the furan to occur. Since this was not

observed, it is obvious that further studies are needed in this area

to develop a more complete understanding of these systems.

Another paper which contained seemingly anomalous results out-
lined the synthesis of marubiin, a terrestrial natural product.[21] As
one step in this scheme, 33 was oxidized with a 4% solution of
monperphthalic acid to give the epoxide 34 as a mixture of
diastereomers (equation 16). When this reaction was run for five

$$\text{33} \xrightarrow{\quad [O] \quad} \text{34} \qquad (16)$$
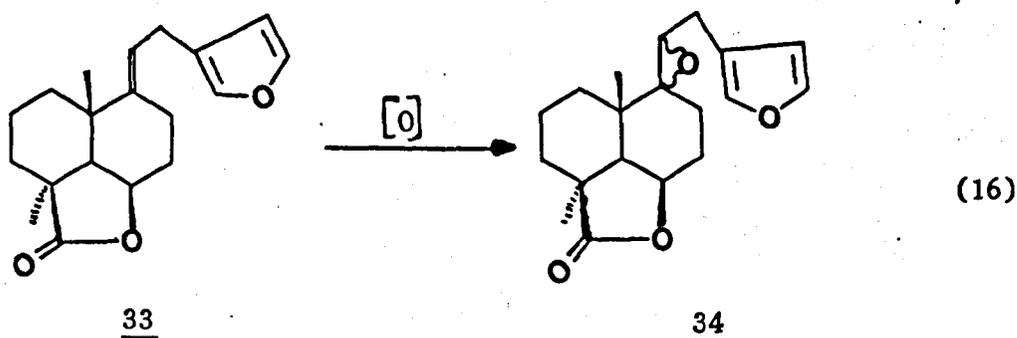
minutes at room temperature, 1.85 g of 33 reportedly gave 0.283 g of
34 and 1.475 g of 33 was recovered. Longer reaction times resulted
in a mixture of products which was not easily separated. Again, this
starting material is very similar to the 3-substituted furans noted
above. Perphthallic acid is a much stronger oxidant than peracetic
acid, yet, reaction was not reported to occur at the furan moiety.
However, this reaction may occur to some extent since longer reaction
times, as noted, led to a mixture of unidentified products.

Returning to reports in which the furan nucleus was involved in
the oxidation, an article appearing in 1964 was noted.[22] In this
instance, the oxidation was carried out as part of a degradation
scheme in a structure proof of the compound lindestrene 35. It was
observed that oxidation of this compound with 1.2 equivalents of
perbenzoic acid gave 36 in nearly quantitative yield (equation 17).

The reaction was reportedly run for thirteen hours at 0°. However,
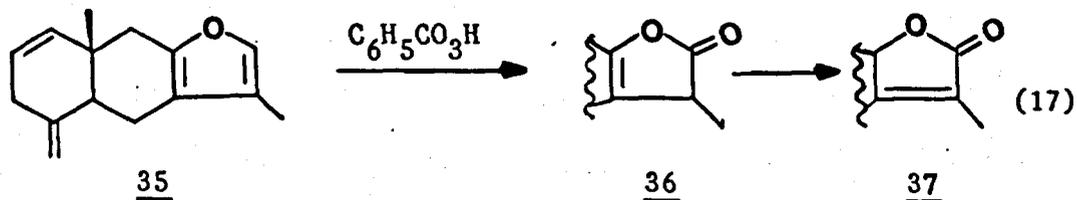
36 was identified solely on the basis of its IR spectrum (1790 cm^{-1}). It was converted to 37 by chromatography on alumina. Compound 37 was isolated in approximately 30% yield from lindestrene. It is therefore possible that materials other than 36 were in the reaction mixture. A more thorough investigation of this system would be warranted, especially in light of the work to be reported in this thesis.

In a recent report, Kuwajima detailed a synthetic scheme for the preparation of Δ^3-butenolides, compounds noted to be useful as synthetic intermediates but difficult to prepare given their propensity to rearrange.[23] This preparation involved the oxidation of 2-trimethylsilylfurans 38 with 40% peracetic acid (equation 18). The reaction conditions involved a fourfold excess of peracetic acid.
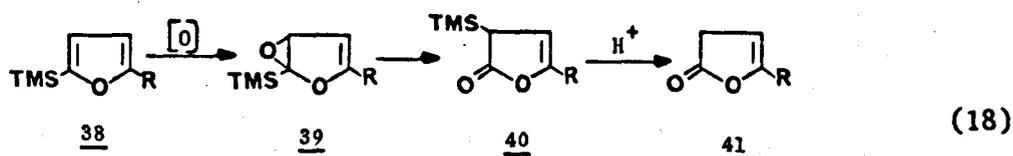
Solid sodium acetate was added as a buffer. Methylene chloride was used as the solvent and the reactions were run at 7°. The reaction

was proposed to proceed as shown from furan 38 to the butenolide 41.

It was assumed that epoxide 39 was the initially formed intermediate.

The trimethylsilyl group is electron releasing and will therefore

direct the regioselectivity of the original attack. Compound 40 was

seen by NMR spectroscopy but was too unstable to be isolated as the

TMS derivative.

Two other points from this paper are also of interest. The

authors found that mCPBA gave markedly lower yields than peracetic

acid. This was ascribed to the fact that mCPBA is a stronger oxidant

and therefore shows less regioselectivity in its attack on the furan

moiety. Another possibility, not discussed in the article, is that

mCPBA, as a stronger oxidant, carries out further chemistry on either

the intermediates or the product of this reaction, thus lowering the

yield. In this paper, it was also noted that the oxidation of

2-hexylfuran with peracetic acid or mCPBA resulted in the formation

of an intractable mixture.

A report by LeGoff in 1981 dealt with the synthesis of enedione

functionalized macrocycles by oxidative ring opening of furans.[24]

The macrocyclic furans used were tetramers 42 or hexamers synthesized

by the condensation of acetone and furan. When these were treated

with a slight molar excess of mCPBA (4.2 equivalents for the tetramer

or 6.3 equivalents for the hexammer) the furans underwent oxidative

ring opening to form the macrocycles as shown (equation 19). These

reactions were run overnight at room temperature and yields were

reported as 85% in both cases. The reaction was also attempted

utilizing bromine in methanol, as described above, followed by

hydrolysis. However, yields were significantly lower than with
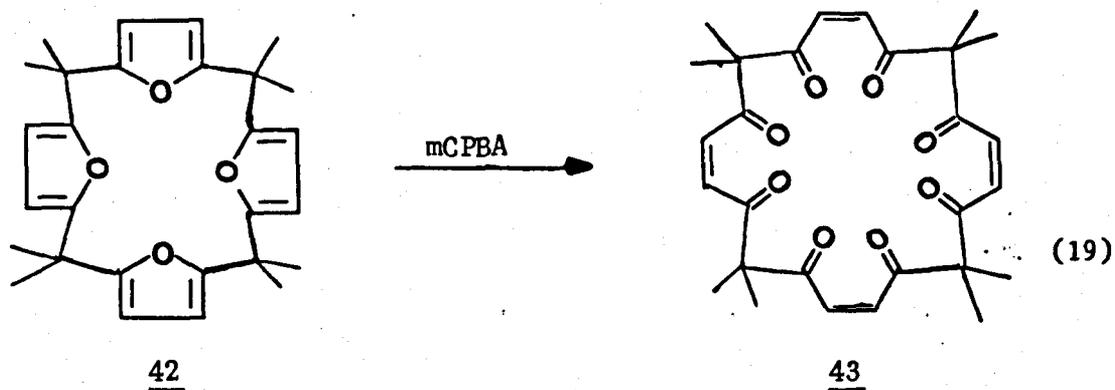
mCPBA, all the furans did not undergo ring opening, and the cis-

enediones generally underwent isomerization to the trans isomer. It

was reported that 2,5-dimethylfuran **3**, studied as a model, underwent

a similar reaction to give cis-hexene-2,5-dione **44** (equation 20). In

this case, 1.1 equivalent 5 of mCPBA were added in one portion to a
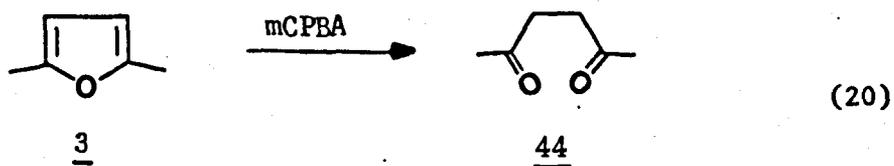
solution of the furan at -10°. The solution was allowed to warm to

room temperature and stirred overnight. Work-up led to the isolation

of **44** in 99% yield.

A report by Tada appeared in 1982 in which the oxidation of

compound **45** with two equivalents of mCPBA proceeded to give product

<u>46</u> which was isolated in high yield (equation 21).[25] The interesting

note about this reaction is that addition of one equivalent of mCPBA

$$\underset{\underline{45}}{\text{(structure)}} \xrightarrow{\text{2 mCPBA}} \underset{\underline{46}}{\text{(structure)}} \tag{21}$$
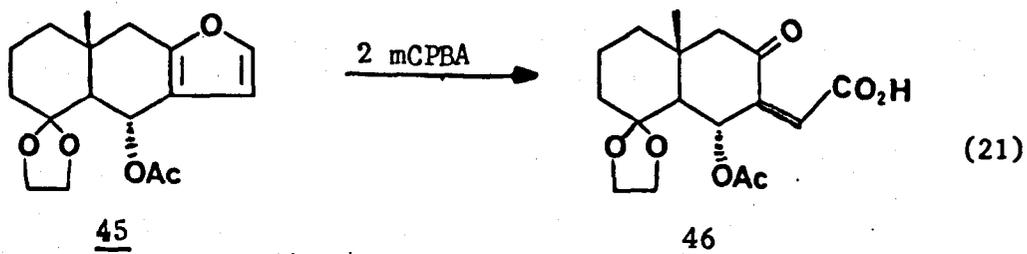
to <u>45</u> resulted in the formation of two products: the lactone <u>47</u> and

the aldehyde <u>48</u> (equation 22). The author had hoped lactone <u>47</u> would

$$\underset{\underline{45}}{\text{(structure)}} \xrightarrow{\text{1 mCPBA}} \underset{\underline{47}}{\text{(structure)}} \quad \underset{\underline{48}}{\text{(structure)}} \tag{22}$$
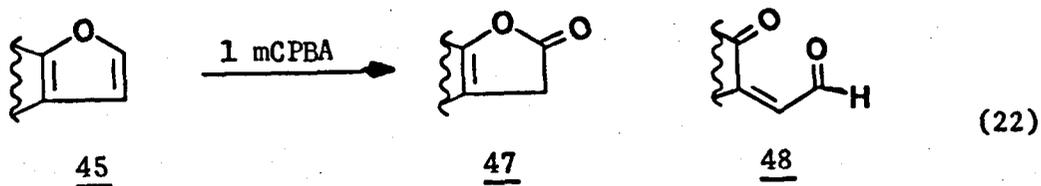
be the sole product of this reaction. This prediction was based on

the oxidation of lindestrene which was discussed above.

Finally, a report by DeShong is most enlightening.[26] This paper

dealt with the synthesis of substituted 2,9-dioxabicyclo[3.3]nonanes

as models for tirandamycin, an antibiotic. The key step in this

transformation was oxidation of the furan derivative <u>49</u> to yield

intermediates <u>50</u>. Treatment of the intermediates with dilute acid

gave <u>51</u> in 25% yield (equation 23). Since <u>49</u> would generate <u>50</u> as a

mixture of diastereomers, only one half of which would react to give

the desired product, this yield was found to be acceptable. The

oxidizing reagent for which this yield was reported was bromine in

methanol. However, it was noted that this oxidation could also be

carried out with pyridinium chlorochromate at 0°, with singlet oxygen

in methanol at -20° and with mCPBA in methylene chloride at 0°. It

$$49 \longrightarrow \underline{50} \longrightarrow \underline{51} \tag{23}$$
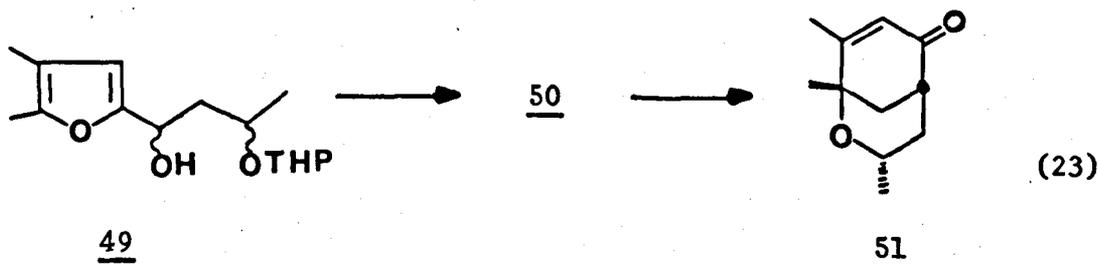
is interesting to observe that, even though these reactions probably

generate different intermediates, although this is not noted in the

article, all lie on a pathway from the furan 49 to the desired

product 51.

In reviewing these references, it is observed that there are some

unifying themes in this area as well as some discrepancies. It is

difficult to draw any real conclusions since, as stated, in many of

these cases the oxidation was not of primary importance to the author.

One can attempt to make mechanistic comparisons by analyzing reaction

conditions, but this is fraught with pitfalls. It is sufficient to

say that there have been no mechanistic studies on the oxidation of

alkyl substituted furans with peracids.

The research reported in this thesis was begun in 1979. The last

four references discussed above were published after this date. These

reports were noted as they appeared in the literature to determine how they fit in with this ongoing research project. In this light, one can see that relatively little was known concerning the oxidation of alkyl substituted furans.

STATEMENT OF THE PROBLEM

In the first half of this century, it was reported that the plant

Tetradymia glabrata, when ingested by sheep, caused numerous fatali-

ties.[27] This fact led to a study by previous workers in Dr. Jennings'

laboratory in an attempt to isolate and identify toxic constituents

of this plant. This work resulted in the characterization of

tetradymol 52 as a major toxic component of T. glabrata.[28, 29]

Further studies carried out with this furanosesquiterpene indicated

52
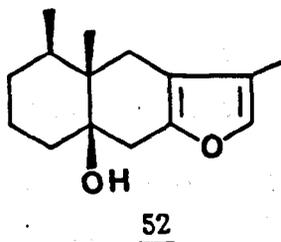
that it was oxidized by the mixed function oxidase system to form a

metabolite even more toxic than the parent compound.[30]

Interest was then directed toward possible metabolites of alkyl

substituted furans in an attempt to rationalize this enhanced toxic-

ity. In this light, in vitro metabolic studies were begun using liver

microsomal suspensions and model furan compounds. It was hoped that

this work would lead to the isolation and characterization of metabol-

ites that could be shown to cause effects similar to those of the

furan substrates.

With this as background, it was decided to pursue chemical model-
ing studies using mimics for the mixed function oxidases. These
studies were planned to parallel the in vitro experiments by using
the same model compounds. It was hoped that the chemical studies
might indicate the types of products to be expected from the in vitro
counterparts.

A literature search was then undertaken to determine the types
of chemical oxidants which have been used as mimics for the mixed
function oxidases. It was found that a wide range of compounds have
been utilized including Undenfriends reagent,[31] oxotransition metal
complexes,[32] aromatic-N-oxides,[33] hydroperoxyflavins[34] and organic
peracids.[35] A number of oxidants developed in recent years, such as
3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3H-
pyrazole,[36] 2-hydroperoxyhexafluoro-2-propanol[37] and triphenylsilyl
hydroperoxide,[38] have also been shown to afford similar reactivity
with certain systems as those reagents noted above which have been
touted as mimics.

An organic peracid, m-chloroperbenzoic acid, was selected as a
mimicking reagent in our model studies.[39] This choice was made largely
on the basis of the fact that the chemistry of this oxidant is fairly
well understood. It is also available as a solid which is easily
purified and is stable for extended periods of time.

With this choice made we therefore proposed to study the oxida-
tion of alkyl substituted furans which were models for naturally
occurring compounds with m-chloroperbenzoic acid. It was hoped that

this work would shed light on the enhanced toxicity shown when furans were oxidized in vivo.

As will be noted in the following section, initial studies led to some rather unexpected results. The goal of further research then shifted to understanding the mechanism of this observed reaction. A series of alkyl substituted tetrahydrobenzofurans were prepared and the mechanism of their oxidation with m-chloroperbenzoic acid was investigated. However, this work resulted in an understanding of these systems which may, in fact, be related to the question of metabolites of furans responsible for the toxicity evidenced in the in vivo studies.

DISCUSSION

The work presented in this thesis was directed toward elucidating

the mechanism of the oxidation of furans with m-chloroperbenzoic acid

(mCPBA). As studies were conducted, the mechanistic implications were

reviewed and new experimental approaches were proposed and carried

out. The results of these studies will be presented and discussed

from a historical perspective.

The results fit into the simplified scheme shown (equation 24).
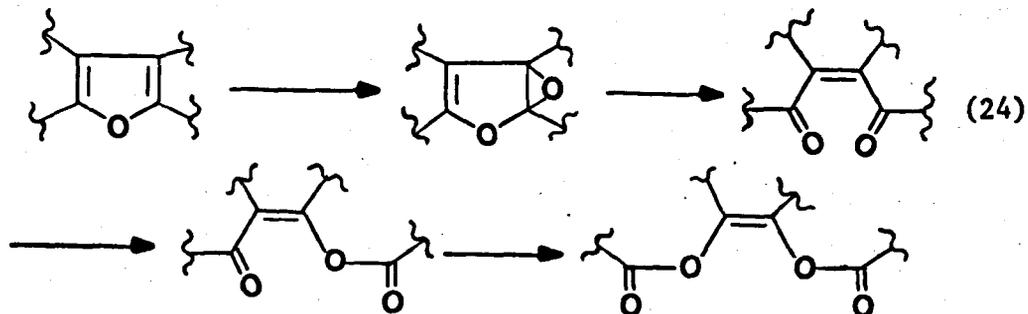
Initial attack is proposed to occur on the furan moiety to form an

epoxide. This intermediate subsequently undergoes ring opening to

yield a cis-enedione. In all cases these compounds react very rapidly

with a second equivalent of mCPBA and undergo a Baeyer-Villiger oxida-

tion. Reaction with a third equivalent of mCPBA can occur, again as a

Baeyer-Villiger oxidation. The fine points of this mechanism will be

discussed as data are presented.
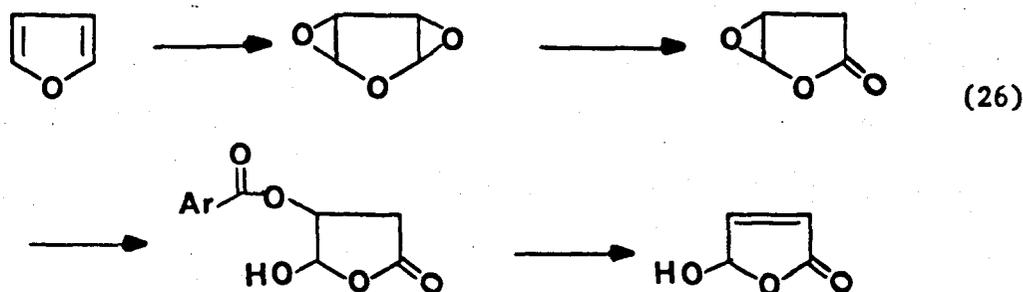
Oxidation of Furan

Initially, studies were carried out on the oxidation of furan 1 with mCPBA. This series of reactions was run in a variety of nonpolar solvents including carbon tetrachloride, chloroform, methylene chloride and benzene. The progress of the reaction was monitored by gas chromatography. Reactions were run at 0° or room temperature. Reaction times ranged from two to 24 hours.

It was observed in all these cases that addition of one equivalent of mCPBA consumed approximately 50% of the furan. Addition of a second equivalent of mCPBA carried the reaction to completion as shown by GC analysis. Attempts to isolate products from this reaction mixture were uniformly unsuccessful. m-Chlorobenzoic acid, formed as a side product, was typically removed by extracting the reaction mixture with base. When the organic layers from these reactions were subjected to this procedure, the basic aqueous layer turned brown-black. Further work-up of the organic layer led to no isolatable product.

It was noted that a procedure had been developed by Camps which utilized activated potassium fluoride to complex with m-chlorobenzoic acid and quantitatively form an insoluable precipitate.[40] Using this technique, it was possible to oxidize furan 1 with two equivalents of mCPBA and isolate aldehydomaleic acid 19 in 52% yield (equation 25). This product was identical to that prepared by Catala, who used p-nitroperbenzoic acid as an oxidant.[14] In this article, the authors

$$\text{(structure 1)} \xrightarrow{\text{2 mCPBA}} \text{(structure 19)} \qquad (25)$$
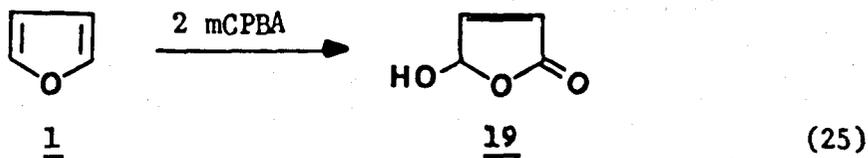
proposed the mechanism shown (equation 26). This mechanism may be

$$\text{(structures)} \qquad (26)$$

operative in our experiments with mCPBA. The only comment to be added

is that the addition of the second equivalent of mCPBA must be much

faster than initial attack of the furan by this reagent.

Since isolation of products in this instance was difficult and

because of their hydrophilic nature, it was decided to extend the

studies to substituted furans. It was hoped that products in these

cases would be more lipophilic and more easily isolated.

Studies with 3-Methyl-4,5,6,7-tetrahydrobenzofuran

When this work commenced, concurrent studies were under way util-

izing liver microsomal suspensions for in vitro oxidations of model

furan compounds. One of these model compounds was 3-methyl-4,5,6,7-

tetrahydrobenzofuran 57. It was decided to extend our studies to

this substrate since it met the requirement of being more lipophilic

than furan. Furthermore, this substituted furan is also a good model

for naturally-occurring furans and, in this sense, it tied in well with our chemical modeling studies.

Synthesis of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. The synthetic scheme utilized to prepare this compound is shown (Figure 1). The key step is the cyclization of ketal epoxide 56 to the desired furan 57. A recent report by Takahashi had been noted in which menthofuran was prepared from 9-methyl-6-(2-methyloxirane)-1,4-dioxaspiro[4.5]decane.[41] In an analogous fashion, the goal of this synthesis was 6-(2-methyloxirane)-1,4-dioxaspiro[4.5]decane 56 which could be cyclized in high yield to the furan 57.

Figure 1. Synthetic scheme followed for preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran.
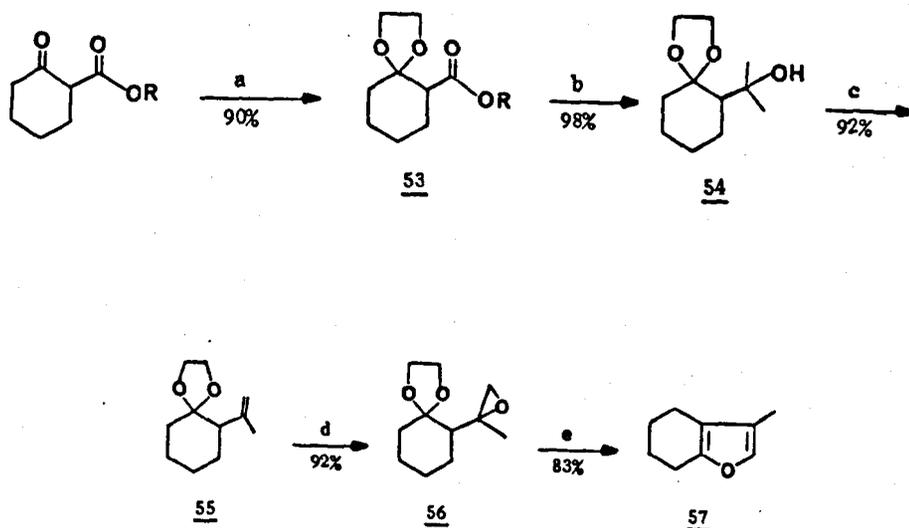
a-(HOCH$_2$)$_2$, p-TsOH, C$_6$H$_6$, Δ; b-MeMgI; c-p-TsOH, C$_6$H$_6$, Δ; d-mCPBA; e-1M HCl, pentane

The synthesis began with ethyl 2-oxocyclohexanone carboxylate

(approximately 40% corresponding methyl ester) which was ketalized.

The ketal ester 53 was converted to the alcohol 54 with methyl magnes-

ium iodide. Elimination proceeded to form the terminal alkene 55.[42]

This compound was converted to the epoxide 56 with mCPBA and then this

material was cyclized to the furan 57 as desired.

Oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. Oxi-

dation of this compound occurred with the consumption of two equival-

ents of mCPBA to afford ε-lactone 58 in nearly quantitative yield

(equation 27). The structure of 58 was deduced from its spectral

$$2 \text{ mCPBA} \qquad (27)$$
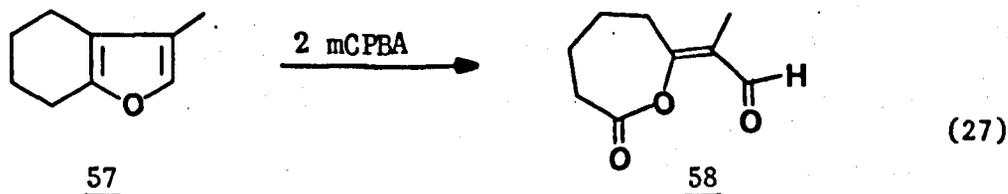
properties. The ^{1}H-decoupled ^{13}C NMR spectrum showed nine resonances,

four of which appeared at 189.8, 170.7, 164.8 and 123.9 ppm. The

resonance at 189.8 ppm was found to be a doublet in the gated decou-

pled spectrum and was assigned to the aldehydic carbon. The other

three downfield resonances noted above appeared as singlets in the

gated decoupled spectrum. The resonance at 170.7 ppm was assigned to

the carbonyl carbon of the lactone functionality. The resonance at

123.9 ppm was assigned to the olefinic carbon adjacent to the aldehyde

and the resonance at 164.8 ppm to the other olefinic carbon. The ^{1}H

NMR spectrum showed a resonance for a single proton at 10.2 ppm which was assigned to the aldehydic hydrogen. A methyl singlet was observed at 1.8 ppm. The IR spectrum showed a weak band at 2750 cm^{-1} which resulted from the carbon-hydrogen stretch of the aldehyde group. There were strong absorptions observed at 1755 and 1680 cm^{-1} assigned as the carbonyl stretching frequencies of the lactone and aldehyde groups, respectively. A moderate absorption was observed at 1640 cm^{-1} which was assigned to the carbon-carbon double bond stretching. The mass spectrum showed a molecular ion at m/e 168 indicating that two oxygens had been added to the furan substrate. This material was isolated as a clear oil which was easily converted to a 2,4-dinitrophenylhydrazone for further characterization.

When one equivalent of mCPBA was added to a solution of 57 in methylene chloride, only 50% of the substrate reacted as shown by gas chromatography and ^{1}H NMR spectroscopy. Thus, in the NMR spectrum of a sample of this reaction mixture, a resonance occurred at 1.90 ppm which was assigned to the methyl group of the furan 57 and a second resonance of equal intensity appeared at 1.80 ppm which was assigned to the methyl group of the product 58. Addition of a second equivalent of mCPBA consumed the rest of the starting furan 57.

The reaction of this substrate with two equivalents of mCPBA occurred extremely rapidly. When a solution of the furan was added to a solution of mCPBA at 0°, the reaction mixture became cloudy within seconds. After one minute, a flocculent precipitate of m-chlorobenzoic acid appeared. Analysis of the reaction mixture after five minutes showed no remaining furan.

A number of experiments were performed to determine what varia-
bles affected the course of this reaction. Addition of the furan to
a solution of two equivalents of mCPBA gave 58 in identical yield as
the addition of two equivalents of mCPBA in one portion to a solution
of the furan.

The reaction was run with or without solid sodium bicarbonate
added to determine if acid catalysis resulted because of the libera-
tion of m-chlorobenzoic acid. In both cases the yields of 58 were
identical, so this aspect was eliminated from further consideration.
A question could still be raised as to the effectiveness of solid
sodium bicarbonate as a buffer in methylene chloride. An analogy
could be drawn to the use of sodium dihydrogen phosphate as a buffer
in Baeyer-Villiger oxidations carried out with trifluoroperacetic
acid.[43] This added salt, which is an insoluble solid, was able to
suppress transesterification of the product of the oxidation and was
therefore assumed to be effective.

Oxidation of menthofuran 59. This reaction was also explored
with menthofuran 59, a close analog of 3-methyl-4,5,6,7-tetrahydro-
benzofuran 57. It was found that this reaction proceeded similarly to
that of 57 to yield ε-lactone 60 (equation 28). Again this structure

(28)

59   2 mCPBA   60
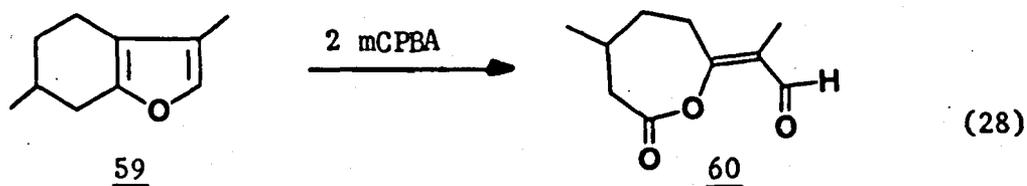
assignment was based on its spectral properties. These properties

coincided very well with those for 58 with the exception of the

perturbations introduced by the methyl group.

It was also found that lactone aldehyde 60 reacted with a third

equivalent of mCPBA to yield formate 61 (equation 29). This reaction

$$mCPBA \tag{29}$$

60   61
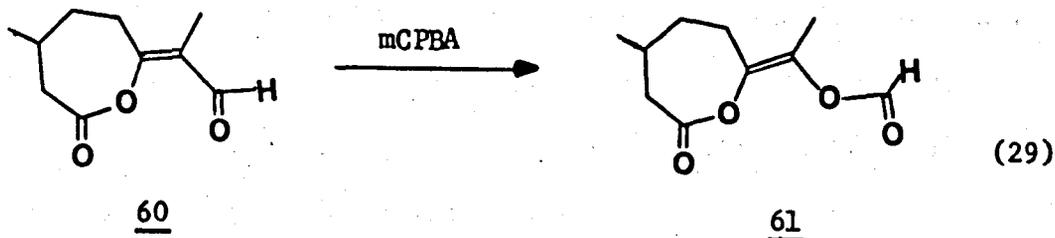
was viewed as a Baeyer-Villiger oxidation of 60 and went to completion

in four hours. The structure proposed for 61 was based on its spec-

tral properties. The ^{13}C NMR spectrum showed resonances at 171.5,

158.1, 139.0 and 133.1 ppm. The resonance at 171.5 ppm was assigned

to the carbonyl carbon of the lactone functionality. The resonance at

158.1 ppm appeared as a doublet in the gated decoupled spectrum with

a carbon-hydrogen coupling constant of 233 Hz. This was, therefore,

assigned to the formate carbon. The resonances at 139.0 and 133.1

ppm, both singlets in the gated decoupled spectrum, were assigned to

the olefinic carbons. The ^{1}H NMR spectrum showed a resonance for one

proton at 7.95 ppm which was attributed to the formate proton. A

methyl singlet appeared at 1.9 ppm and a methyl doublet at 1.1 ppm.

The IR spectrum showed an intense broad absorption at 1760 cm^{-1}

assigned to the carbonyl stretches of the lactone and formate groups.

Mass spectral analysis showed a molecular ion at m/e 198 indicating addition of three oxygens to menthofuran.

The reaction of menthofuran 59 with two equivalents of mCPBA was run in solvents of varying polarity. In nonpolar solvents (chloroform, methylene chloride and benzene), the course of the reaction was the same and the product 60 was isolated in uniformly high yields. However, as the polarity of the solvents was increased (ether, ethyl acetate, acetone and dimethyl formamide), side product formation became predominant even though 60 could be identified in the crude reaction mixtures by NMR spectroscopy.

Proposed mechanism for the oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 with a diepoxide intermediate. A mechanism for the oxidation of this substrate with two equivalents of mCPBA was proposed (Figure 2). Initial oxidation would be expected to occur at the more substituted double bond of the furan moiety to form 62.[44] Addition of the second equivalent of mCPBA would occur rapidly to form diepoxide 63. This intermediate was proposed to be a trans-diepoxide because of the repulsion between the initially formed epoxide and the approaching second equivalent of mCPBA.[45] Diepoxide 63 would then rearrange as shown to form 58.

Figure 2. Proposed mechanism for the oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran via a diepoxide intermediate.
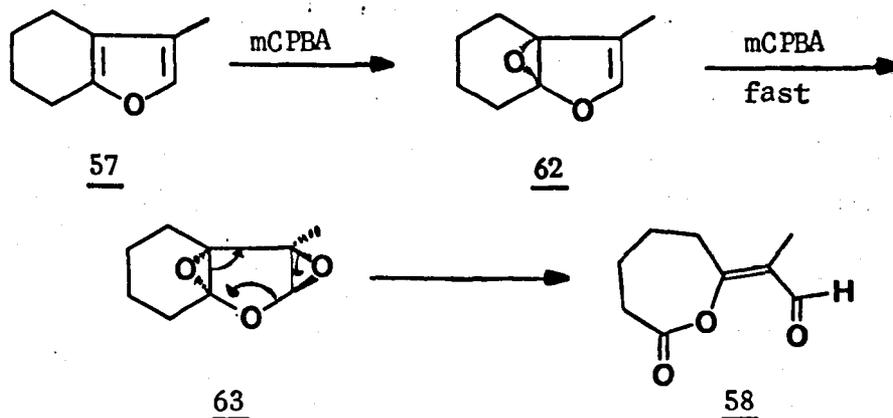

A second possible pathway considered at this point was derived

from reports by Borowitz on the oxidation of enol ethers with

mCPBA.[46, 47] This reaction was proposed to proceed to consume two

equivalents of peracid and resulted in the ring expanded product

(equation 30). However, several features of this reaction contrast

(30)
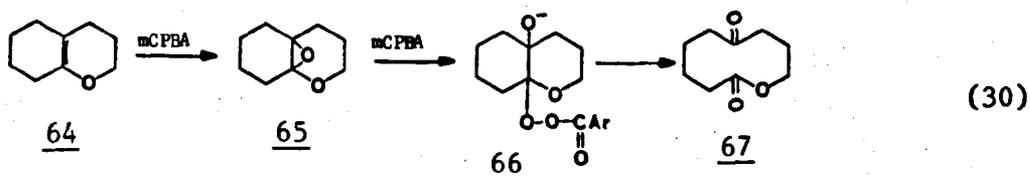
with the reaction of two equivalents of mCPBA with the furan

substrate. First, Borowitz' reaction reportedly required several

hours at room temperature to go to completion. Next, yields reported

(approximately 50%) are significantly lower than those seen with the

furan substrate. Moreover, it would be difficult to justify the

product observed in the furan case by following this mechanistic

scheme. For these reasons, it was felt that this mechanism was not

operative in the furan case and the mechanism with a diepoxide inter-

mediate was, therefore, advanced.

The inclusion of a diepoxide intermediate in the proposed mechan-

ism should cause no concern because diepoxides derived from furans

are known to exist. These compounds are generally formed from the

endoperoxides which result from the singlet oxygen oxidation of

furans. One example reported by Kraus utilized 3-methylfuran 68

(equation 31).[48] The photooxidation of 68 in methylene chloride

$$\text{68} \quad \xrightarrow[\text{sens}]{O_2, h\nu} \quad \text{69} \qquad (31)$$
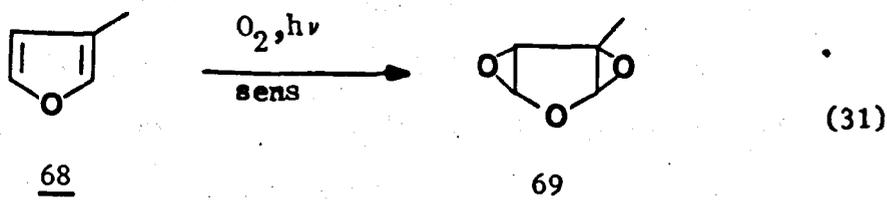
resulted in diepoxide 69 which was isolated from a mixture of

products in 23% yield. A second example was reported by Wasserman

(equation 32).[49] The sensitized photoxidation of [2.2](2.5)furan-

$$\text{70} \quad \xrightarrow[\text{sens}]{O_2, h\nu} \quad \text{71} \qquad (32)$$
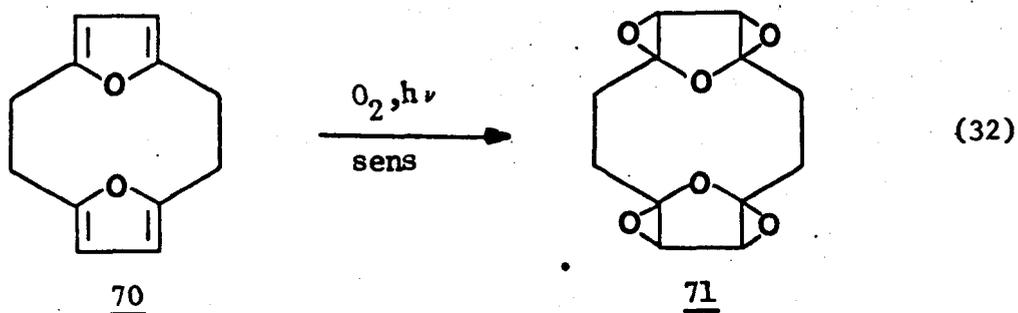
ophane 70 in methylene chloride resulted in the tetraepoxide 71, which

was isolated in high yield. Still another example showed the

endoperoxide to indeed be the intermediate of this reaction (equation 33).[55] Sensitized photooxidation of 72 afforded 73. When this

(33)
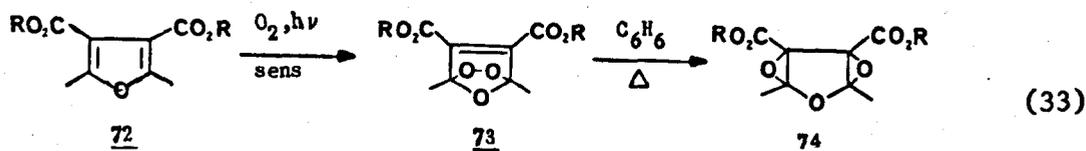
endoperoxide was heated in refluxing benzene, the diepoxide 74 was isolated, reportedly in quantitative yield.

Studies with 1,2,3,4,5,6,7,8 - Octahydrodibenzofuran

Synthesis of 1,2,3,4,5,6,7,8 - octahydrodibenzofuran 77. At this point it was decided to extend our studies to other furan substrates to see how general the reaction that we had observed was. The next substrate chosen was perhydrodibenzofuran 77. This compound was synthesized by modifying a procedure reported by Creese in the litera-ture (Figure 3).[51] Following the procedure of Wenkert, dry hydrogen chloride gas was bubbled through cyclohexanone to effect coupling.[52] The crude ketochloride which resulted was ketalized to yield ketal alkene 75. This was converted to the epoxide 76 with mCPBA. Cycli-zation was carried out to yield furan 77 using a biphasic mixture of 2 M HCl and pentane.

Oxidation of perhydrodibenzofuran 77. As in the previous exam-ples, this substrate reacted to consume two equivalents of mCPBA to give 78 as a white solid in nearly quantitative yield (equation 34).

As before, the structure of this product was elucidated from its spectral properties. The ^{13}C NMR spectrum exhibited resonances at 201.5,
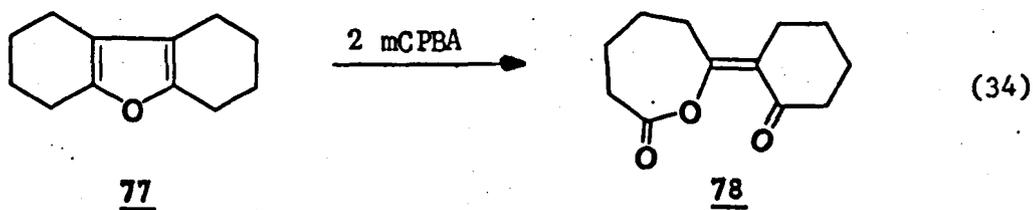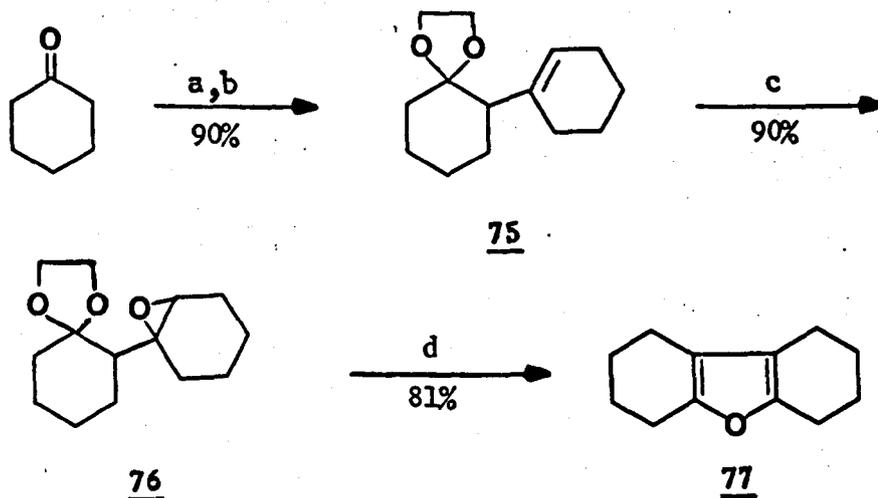

(34)

77 → 2 mCPBA → **78**

Figure 3. Synthetic scheme followed for preparation of perhydrodibenzofuran **77**.

a-HCl(g); b-$(HOCH_2)_2$, p-TsOH, $C_6H_5CH_3$, Δ; C-mCPBA; d-2M HCl, pentane

172.3, 150.6, and 125.7 ppm, all of which appeared as singlets in the gated decoupled spectrum. The resonance at 201.5 ppm was assigned to the carbonyl carbon of the ketone and that at 172.3 ppm to the

carbonyl carbon of the lactone functionality. The resonances at 150.6 and 125.7 ppm were assigned to the olefinic carbons; the upfield one to the olefinic carbon adjacent to the ketone group and the downfield resonance to the olefinic carbon adjacent to the oxygen of the lactone functionality. The IR spectrum showed strong absorptions at 1750 and 1690 cm^{-1} which were assigned as the carbonyl stretching frequencies of the lactone and ketone, respectively. A weaker band was observed at 1660 cm^{-1} and this was attributed to the carbon-carbon double bond stretching. The mass spectrum showed a molecular ion at m/e 208, again indicating addition of two oxygens.

This reaction exhibited characteristics similar to those observed for 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. The reaction was rapid, going to completion in approximately five minutes at 0°. Again, addition of one equivalent of mCPBA consumed only 50% of the substrate 77 as shown by gas chromatography and NMR spectroscopy.

Since the pattern exhibited by this reaction was similar to that shown by 3-methyl-4,5,6,7-tetrahydrobenzofuran 57, a similar mechanistic scheme was proposed (Figure 4). Initial attack would occur on either side of the furan moiety in this symmetrical molecule. Subsequent attack of this monoepoxide 79 would occur rapidly to yield diepoxide 80. This diepoxide would then rearrange to the observed product 78.

Figure 4. Proposed mechanism for the oxidation of perhydrodibenzo-
           furan 77 via a diepoxide intermediate.
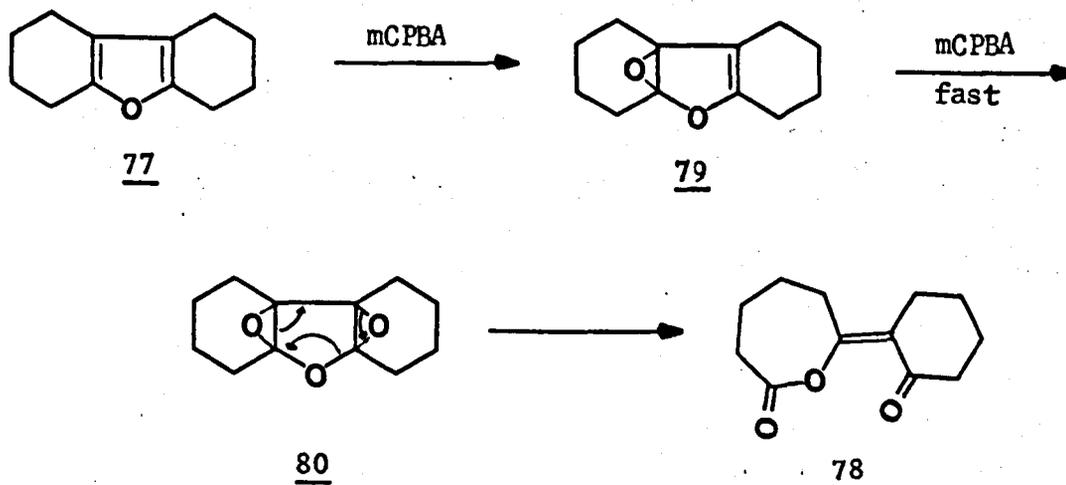
However, it was noted that in this case, if the furan reacted as

an enol ether, the product would have been 81 (equation 35). Struc-

turally, this compound is very similar to 78 and would be expected to

(35)
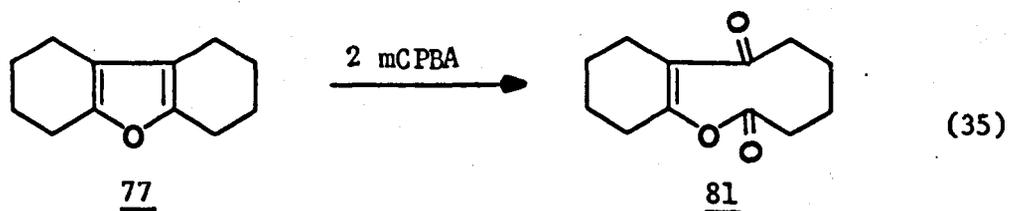
have closely related spectral properties. In order to differentiate

between these possibilities, it was elected to have a crystal struc-

ture determined.

The result of this single crystal X-ray analysis is shown

(Figure 5). Not only did this analysis demonstrate the product to

have the structure predicted, but also it determined that the stereo-

chemistry about the double bond is that of the Z-isomer, as shown.