OXIDATIVE REACTIONS OP ortho-HYDROXTPHENYLKETONES WITH THALLIUM (III) TRIOXGNITRATE (v) TRIHYDRATE

BY

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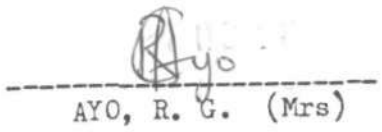
A THESIS SUBMITTED TO THE POSTGRADUATE SCHOOL, AHMADU BELLO UNIVERSITY, ZARIA, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE (ORGANIC CHEMISTRY)

DEPARTMENT OF CHEMISTRY,
FACULTY OF SCIENCE,
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ZARIA - NIGERIA.

MAY, 1989

DECLARATION

I hereby declare that this thesis has been written by me and that it is a record of my own research work. It has not been presented in any previous application for a higher degree. All quotations are indicated and the source of information are specifically acknowledged by means of references.



AYO, R. G. (Mrs)

22/9/89

Date.

CERTIFICATION

This thesis entitled, "Oxidative Reactions of ortho-Hydrophenyl-ketones with Thallium (III) trioxonitrate (V) trihydrate, by Rachael Gbekele-Oluwa Ayo meets the regulations governing the award of the Degree of Master of Science of Ahmadu Bello University and is approved for its contribution to scientific knowledge and literary presentation.

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DEDICATION

TO MY SON, **BABATOPE** AND

DAUGHTER, **IBUKUNOLUWA**

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ABSTRACT

Oxidation of ortho-hydroxyphenylketones with two molar equivalents of thallium (III) trioxonitrate (V) trihydrate (TTN) in methanol (MeOH)/ trimethyl ortho-formate (TMOF) mixture (1:1) gives the corresponding 2-alkyl-2,3,3-trimethoxy-2,3-dihydrobenzofuran in high yield. This reaction constitutes a simple and convenient method for the synthesis of benzofuran derivatives.

The ortho-hydroxyphenylketones are synthesised from the corresponding phenyl esters via Pries rearrangement.

These benzofuran derivatives are isomeric with α-methylene lactones which are of value in cancer therapy.

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ABBREVIATIONS

TTN	Thallium(III) trioxonitrate(V) trihydrate
TMOF	Trimethyl Orthoformate
MeOH	Methanol
i.r.	Infrared
n.m.r	Nuclear Magnetic Resonance
t.l.c.	Thin-layer Chromatography.

CHAPTER 1

1.0 INTRODUCTION

1.1. Properties of Thallium Compounds

McKillop and Taylor (1973) have reviewed the most important properties of thallium compounds which have been exploited in synthetic work and are given as follows:

(1) Inorganic thallium compounds are usually more stable in the (+1) valence state, while covalent organothallium compounds are stable only in the (+3) valence state.

(2) The thermodynamic ease with which transitions among the various oxidation levels can occur is evident from the standard redox potentials

$$Tl^{3+} + 2e \longrightarrow Tl^{+} \quad -1.25V$$

$$Tl^{+} + e \longrightarrow Tl \quad +0.33V$$

From these redox potentials, reduction of thallium (III) to thallium (I) is thus an especially favourable process, and one which is of critical importance in the applications of thallium compounds to organic syntheses.

(3) Tl^{3+} is a soft cation, and so TlX_3 compounds are good Lewis acids. The electrophilicity of TlX_3 derivatives can be varied substantially and in a controlled manner by variation of the nature of X.

(4) C - Tl bonds are very weak, probably of the order of 100 - 130KJmol^{-1} and cleave under both heterolytic and homolytic conditions.

(5) The thermodynamic ease of reduction of Tl (III) $\longrightarrow$ Tl (I) ensures that, given simple procedures for the preparation of

organothallium derivatives of the type $RTlX_2$, conversion of these intermediates into organic products, TlX will occur readily.

(6) Tl (III) is isoelectronic with Hg (II) and with Pb (IV) and its redox potential is intermediate between them. Hence, Tl (III) functions as efficient 2-electron oxidant, (Lee and Price, 1964):

$$Pb^{4+} + 2e \longrightarrow Pb^{2+} \quad -1.6V$$
$$Tl^{3+} + 2e \longrightarrow Tl^{+} \quad -1.25V$$
$$2Hg^{2+} + 2e \longrightarrow Hg_2^{2+} \quad -0.92V$$
$$Hg^{2+} + 2e \longrightarrow Hg^{0} \quad -0.85V$$

1.2. Organothallium Compounds

Thallium salts are becoming widely used in organic synthesis by virtue of the ease of formation and high reactivity of organothallium compounds. Example of thallium salts used in syntheses are: thallium (I) ethoxide, $TlOC_2H_5$; thallium (III) trifluoroacetate, TTFA, and thallium trioxonitrate (V), TTN.

Noyes and Garner (1936) reported that the conversion of thallium (III) to thallium (I) is the more powerful oxidizing system and under comparable reaction conditions, thallium (III) is the more selective electrophile. They also discovered that the carbon-metal bond heterolysis takes place more rapidly due to greater electron affinity of Tl(III).

The efficacy of thallium (III) salts, TlX_3, as oxidants is known to be directly related to the nature of the anionic group X, and it has been adequately demonstrated for a wide range of reactions that

the oxidizing power of the commonly available and easily handled thallium (III) salts are in the order:

nitrate > trifluoroacetate > acetate > chloride (McKillop and Taylor, 1973).

The use of thallium (III) salts as oxidants for non-aromatic unsaturated systems is a consequence of the thermal and solvolytic instability of monoalkyl thallium (III) compounds which in turn is apparently dependent on two major factors, namely: the nature of the associated anion and the structure of the alkyl group. Most of the monoalkyl thallium (III) compounds are unstable and very few have been isolated. Compounds in which the anion is a good bidentate ligand are moderately stable, for example, alkylthallium dicarboxylates. Alkyl thallium dihalides are however extremely unstable and generally decompose instantly. Methyl thallium diacetate, for example, is reasonably stable in the solid state but decomposes slowly in solution and rapidly on being heated. (McKillop and Taylor, 1973).

Monoaryl- and monovinyl thallium (III) derivatives are considerably more stable than the corresponding alkyl compounds, usually isolated and characterized without difficulty. In certain cases where the organothallium derivatives are not stable enough to be isolated, thallium is displaced by a nucleophile in the oxidative step in one of three possible fashions which are analogous to the classical S_N1, S_N2 and S_Ni mechanisms.

The simplest and general procedures for the preparation of monoalkyl and monoaryl thallium (III) compounds are via the oxythallation and thallation reactions, respectively.

1.3. Use of Thallium trifluoroacetate (TTFA) in Organic Syntheses

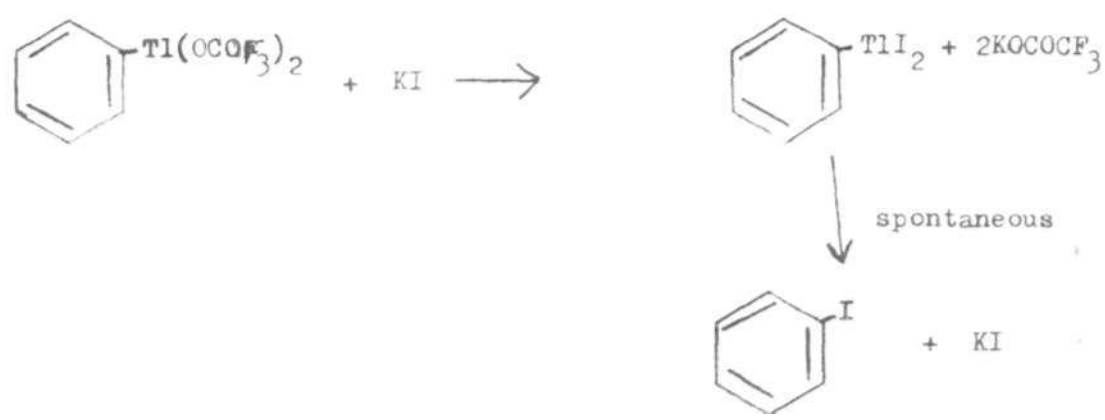
1.3.1 Thallation of Aromatic Compounds and Synthesis of Aromatic Iodides.

A solution of TTFA in trifluoroacetic acid (TFA) constitutes a powerful reaction mixture for the direct thallation of aromatic compounds (McKillop et al., 1969).

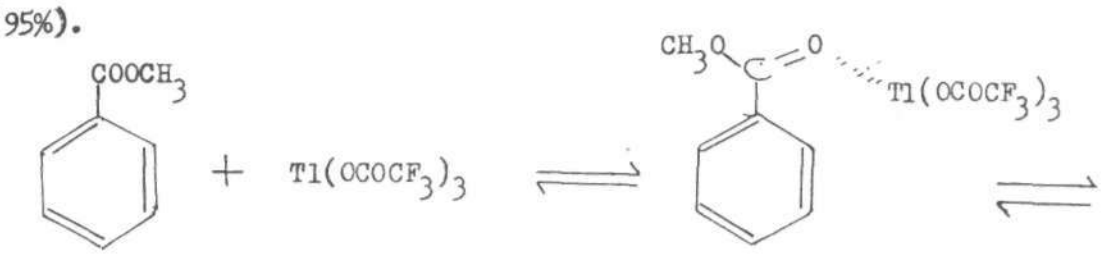
$$ArH + Tl(OCOCF_3)_3 \longrightarrow ArTl(OCOCF_3)_2 + CF_3COOH.$$

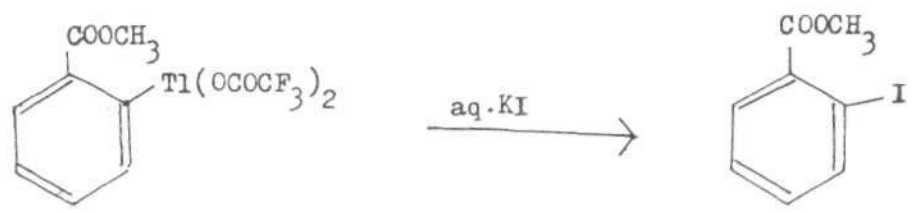
McKillop et al, (1969) found that reaction with substrates activated towards electrophilic substitution was generally complete within a few minutes at room temperature, whereas thallation of mildly deactivated substrates such as the halobenzenes required longer reaction times at room temperature or 30 minutes at reflux temperature ($73^{o}C$) The arylthallium bis-trifluoroacetates isolated were found to be stable, colourless and crystalline solids. Only a small amount of ortho-substituted products was observed with those substrates with ortho-para directing substituents. According to these workers, the overwhelming preference for para substitution may be associated with the steric bulk of thallium.

McKillop et al. (1969) also discovered that treatment of the resulting arylthallium bis-trifluoroacetates with aqueous potassium iodide at room temperature resulted in rapid precipitation of thallium(III) iodide and formation of the corresponding aromatic iodide:



Furthermore, they reported distribution rates for iodination of monosubstituted benzene derivatives under conditions of thermodynamic control (elevated temperature), meta substitution was observed. Under conditions of kinetic control (room temperature), a significant preference for para substitution is observed for compounds containing ortho - para directing substituent groups. ortho Substitution results when chelation of TTFA with the directing substituent permits intramolecular delivery of the electrophile. For example, methyl benzoate gives almost exclusively ortho-thallation (95%).



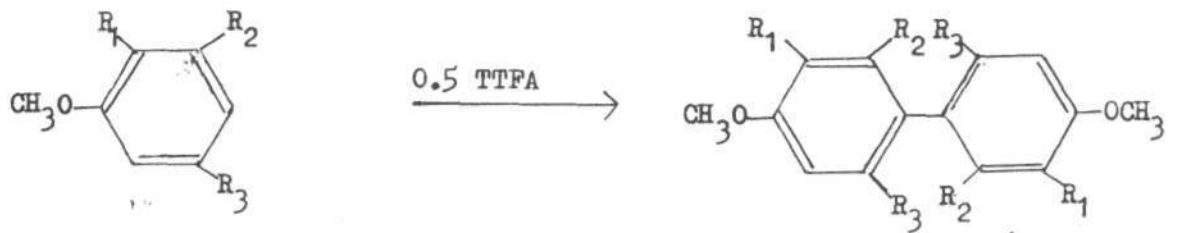


Thus, the overall process of thallation followed by treatment with iodide ion constitutes an extremely simple synthesis of aromatic iodide.

1.3.2 Oxidative Phenol Coupling with TTFA

TTFA is an effective reagent for intramolecular oxidative phenol coupling. McKillop et al. (1977) reported the oxidative coupling of aromatic compounds using TTFA in TFA or in carbon tetrachloride or

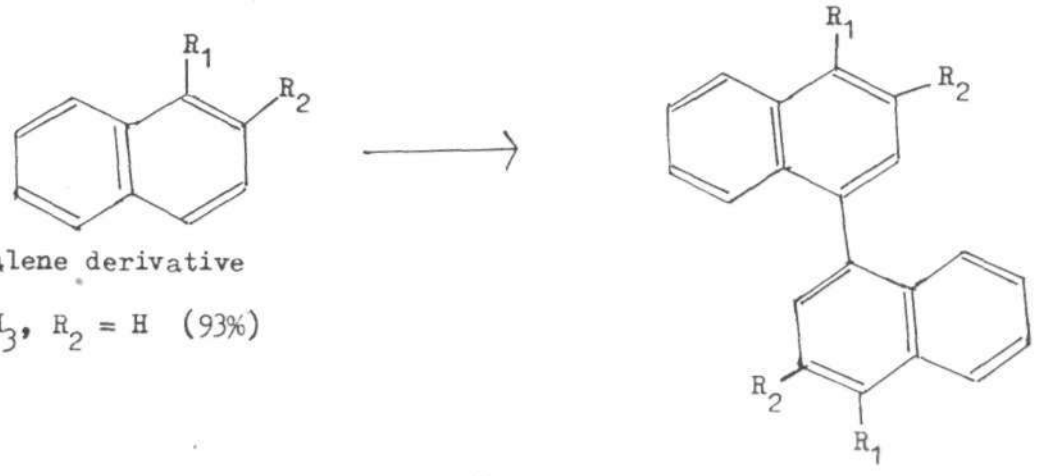
acetonitrile containing borontrifluoride etherate. The reaction was found to be smooth and rapid. The direct oxidative coupling gave symmetrical biaryls in good to excellent yield. This method constitutes a simple and effective procedure for the preparation of a variety of highly substituted biaryls in which the ring substituents are either electron donating or mildly electron withdrawing groups.



4-bromoveratrole

2,2',dibromo-4,4,5,5' tetramethoxy biphenyl

$R_1 = CH_3O$, $R_2 = H$, $R_3 = Br$ (88%)



Naphthalene derivative

$R_1 = CH_3$, $R_2 = H$ (93%)

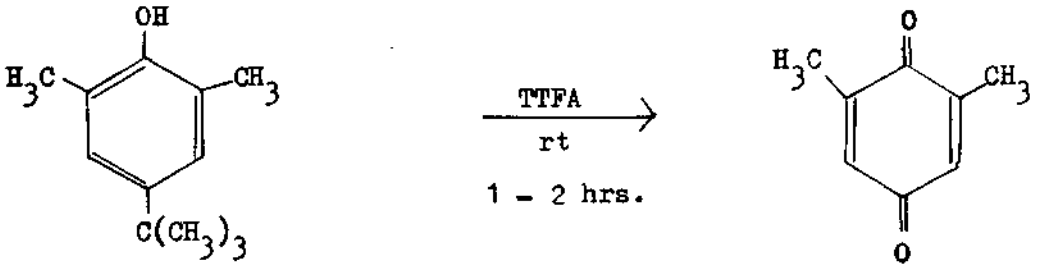
binaphthyls

Kende and Rutledge (1978) reported the selective oxidative cyclisation of diaryl butane. They found that treatment of diaryl butane derivative with 1.36 equivalents of TTFA in dichloromethane in the presence of excess borontrifluoride etherate at room teperature

afforded the 2,2 -dicarbethoxy-1- (4' hydroxy-3,5-dimethoxyphenyl) 6,7-methylene dioxytetralin in 55% yield.

1.3.3 Synthesis of p-Quinones

Treatment of 2,6-disubstituted-4-tertbutyl phenols with slight excess of two molar equivalent of TTFA in either TFA or CCl_4 results in loss of the 4-tert butyl substituent as isobutene and formation in high yield of the corresponding 2,6-disubstituted para-quinones. TTFA is highly efficient exidant for the conversion of hydroquinones and a variety of 2,4,6-trisubstituted phenols into the corresponding 2,6-disubstituted para-quinone (McKillop et al., 1970).

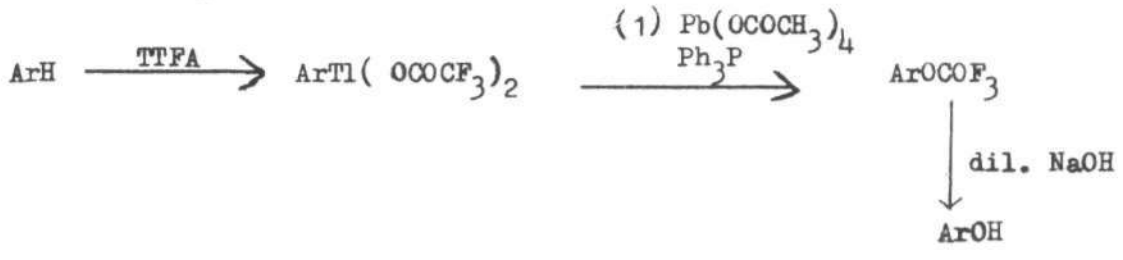


They also observed that such oxidations are possible with other groups at C-4 which are capable of departing with the bonding electron pair (NH_2, halogen, $OCOCH_3$).

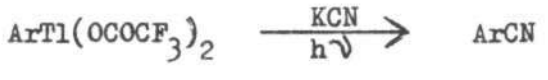
1.3.4 Synthesis of Phenols and Aromatic Nitriles

Phenols were prepared by treating the arylthallium bis-trifluoro-acetate with lead tetraacetate in TFA. The mixture was treated with one equivalent of triphenyl phosphine (Ph_3P), excess TFA removed by evaporation, and hydrochloric acid added to precipitate chlorobenzene and thallium (I) chloride. The resulting aryltrifluoroacetate is then

hydrolysed with dilute base and the phenol isolated by extraction (Taylor et al., 1970).



Treatment of the arylthallium difluoroacetates with an excess of aqueous potassium cyanide on photolysis gives the corresponding nitriles (Taylor et al., 1970).

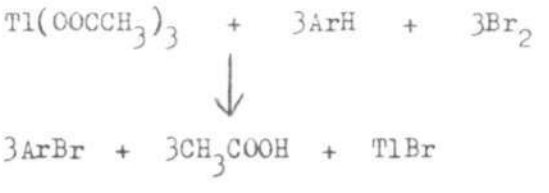


1.4. Use of Thallium (III) Acetate in Organic Syntheses

1.4.1 Preparation of Aromatic Bromides

Thallium (III) acetate displays Lewis acid properties which enables it to function as a catalyst in electrophilic aromatic substitution reactions, particularly bromination. McKillop et al., (1969) synthesised an aryl bromide by addition of a solution of thallium acetate in carbon tetrachloride containing benzene derivative. The reaction mixture was heated under reflux for 0.5 - 1hr.

These workers found that the most important advantage of the thallium (III) acetate in bromine is the remarkable specificity shown by the reagent during the electrophilic substitution process. The reaction yielded a single pure monobromic isomer in high yield.



Thallation of the aromatic ring does not occur with thallium (III) acetate but with the more electrophilic TTFA

1.4.2 Preparation of α-hydroxy carboxylic acids

Reaction of thallium (III) acetate with aliphatic carboxylic acids results in formation of α-acyloxy carboxylic acids, which are readily hydrolysed to α-hydroxy acids (Taylor et al., 1970).

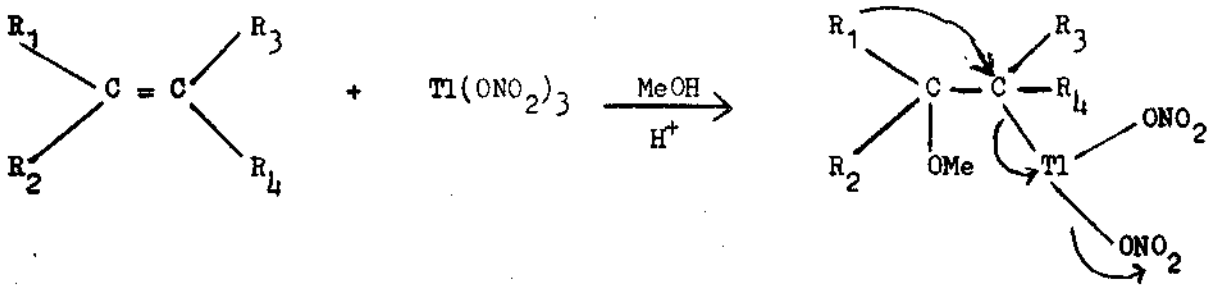
1.5 Use of Thallium (III) Trioxonitrate (V) Trihydrate, $Tl(NO_3)_3.3H_2O$, (TTN) in Organic Syntheses

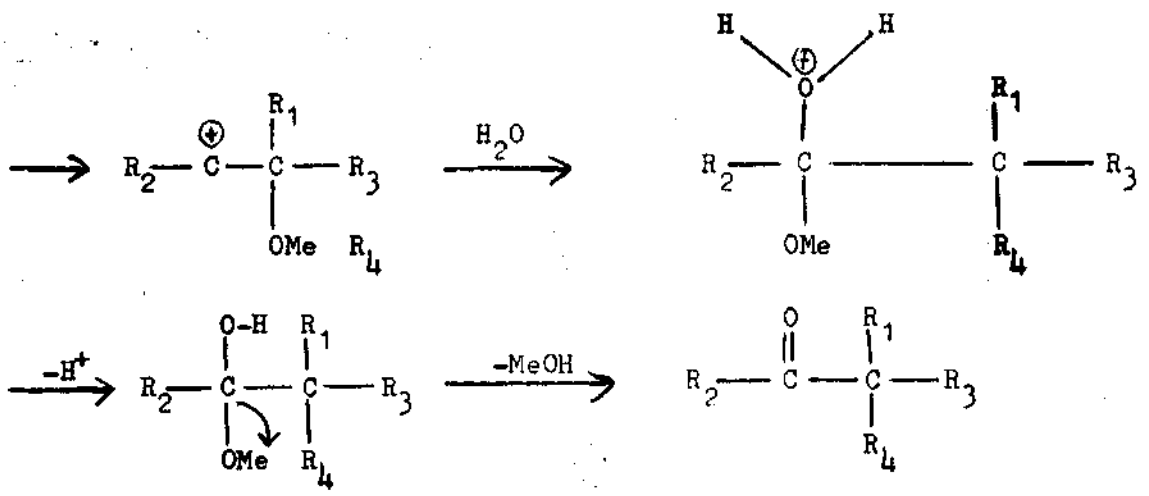
Thallium (III) trioxonitrate (V) has been found to be highly specific and often acts as a unique oxidant to effect a wide range of organic syntheses. It is an extremely effective oxidizing agent for alkenes, alkynes, ketones and other non-aromatic unsaturated systems. The most commonly used solvents for these reactions have been dilute trioxonitrate (V) acid, methanol, or aqueous glyme containing perchloric acid.

Thallium (III) nitrate (V) is capable of rapidly effecting oxythallation of carbon-carbon double and triple bonds. The resulting organothallium compound is highly unstable and can undergo decompostion in a variety of ways, depending on the substituents present. This cleavage is thought to be heterolytic resulting in the development of carbonium ion character at the carbon atom of the original C-Tl bond (McKillop and Taylor, 1973).

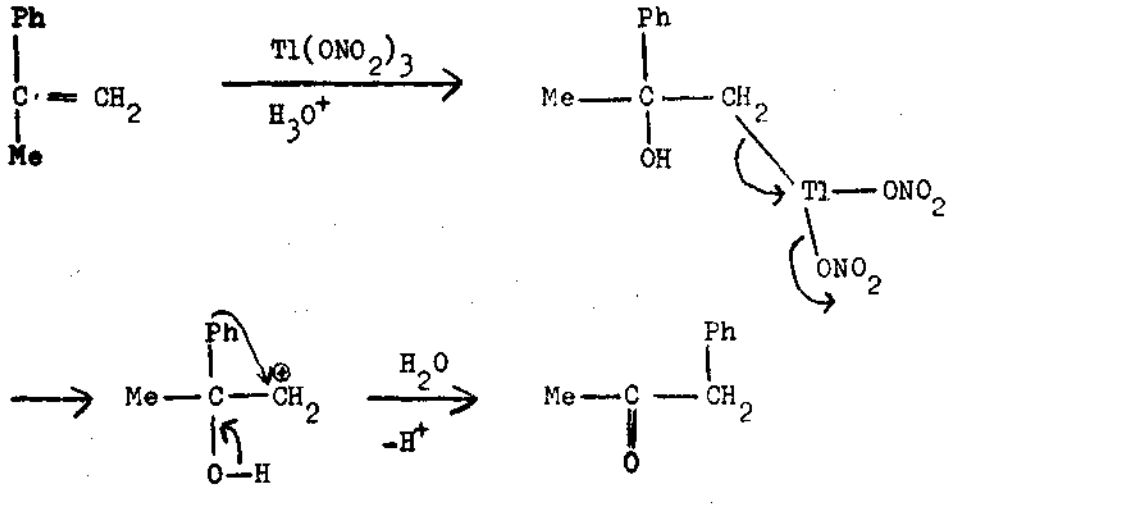
1.5.1 Oxidation of Alkenes

McKillop *et al.* (1972, 1973) reported the rapid oxidative rearrangement of alkenes using TTN/MeOH to give dimethylacetals or ketals or in dilute mineral acid to yield carbonyl compound, for example:





The carbonium ion is commonly rearranged before capturing a solvent nucleophile. For example, oxythallation of styrenes leads to benzyl ketones, the intermediate carbonium ion being stabilized by phenyl migration.



The scope, limitations and synthetic utility of TTN oxidations were also defined. The reactions were characterized by manipulative simplicity, high yield and the high state of purity of the products. McKillop et al. (1972) discovered that oxidation occured most rapidly with disubstituted alkenes and was complete within a few minutes, while trisubstituted alkenes reacted much more slowly.

1.5.2 Oxidation of Alkynes

Alkynes are smoothly oxidized by TTN (McKillop et al., 1971). Terminal alkynes undergo more extensive oxidation with two moles of TTN to afford carboxylic acids having one carbon atom less than the starting alkyne.

$$R - C \equiv C - H \xrightarrow[CH_3OH]{2TTN} R - \underset{\underset{O}{\|}}{C} - OH \qquad 80\%\ \text{yield}$$

Diarylalkyne are converted into benzils in 45 - 95% yield by treatment with TTN in either methanol or aqueous acidic (perchloric acid) glyme.

$$Ar - C \equiv C - Ar' + 2TTN \xrightarrow{H_3O^+} Ar - \underset{\underset{O}{\|}}{C} - \underset{\underset{O}{\|}}{C} - Ar'$$

Dialkylalkynes react with only one mole of TTN to give acyloins

$$R - C \equiv C - R \xrightarrow{TTN} R - \overset{\overset{O}{\|}}{C} - \overset{\overset{OH}{|}}{\underset{\underset{H}{|}}{C}} - R$$

1.5.3. Oxidation of Chalkones

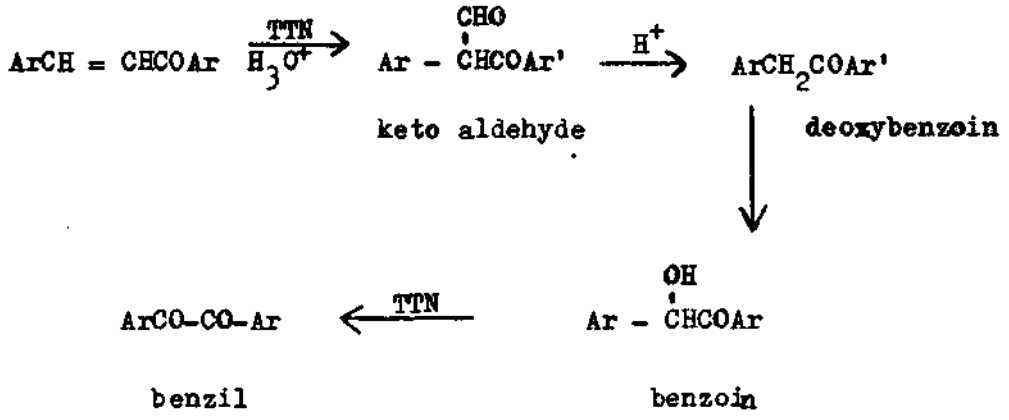
Oxidation of chalkones with three equivalents of TTN in aqueous glyme containing a little perchloric acid medium results in formation of benzils in about 50% yield (McKillop et al., 1970). They reported that three of the four distinct steps involve oxidation:

(1) Oxidative rearrangement to the ketoaldehyde;

(2) Cleavage to a deoxybenzoin;

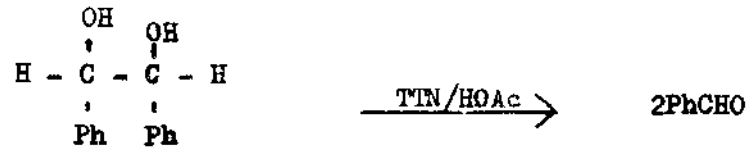
(3) Oxythallation to a benzoin and finally

(4) Oxidation to benzil.



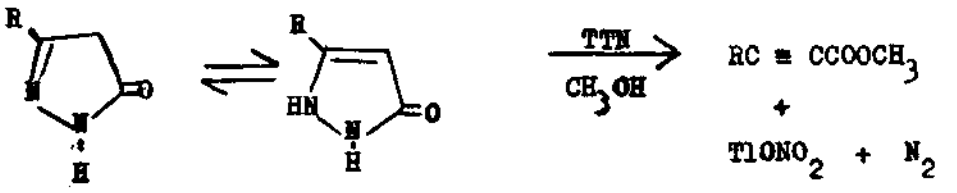
1.5.4. Oxidative Reaction of Glycols

McKillop et al. (1972) have examined the oxidative cleavage of glycols with TTN in ethanoic acid. Cleavage occurs only with glycols containing vicinal aromatic substituents.



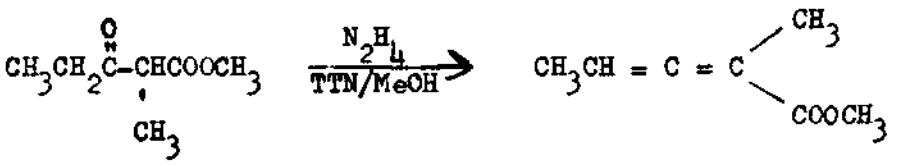
1.5.5. Oxidation of 5-Pyrazolones

5-Pyrazolones were converted by treatment with two equivalents of TTN into methylesters of α , β-alkynoic acids. Yields are high and reaction conditions are extremely mild (Taylor et al., 1972).



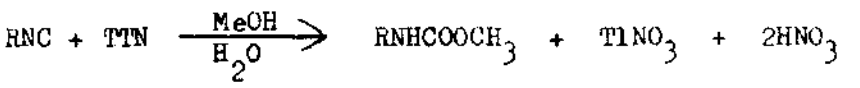
1.5.6. Oxidation of α-alkyl-β-keto esters

α-alkyl-β-keto esters were converted into allenic esters by treatment with one equivalent of hydrazine to form the 3,4-disubstituted-5-pyrazolones and then with a solution of 2 equivalents of TTN in MeOH (Taylor et al., 1972).



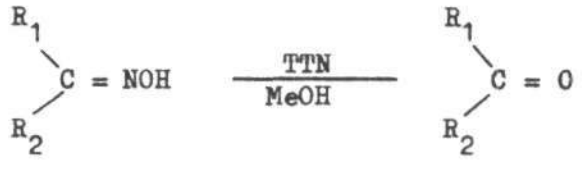
1.5.7. Oxidation of Isonitriles

TTN reacts with isonitriles in MeOH solution at room temperature within a few minutes to give carbamates in high yield (45 - 97%) (Kinenzle, 1972).



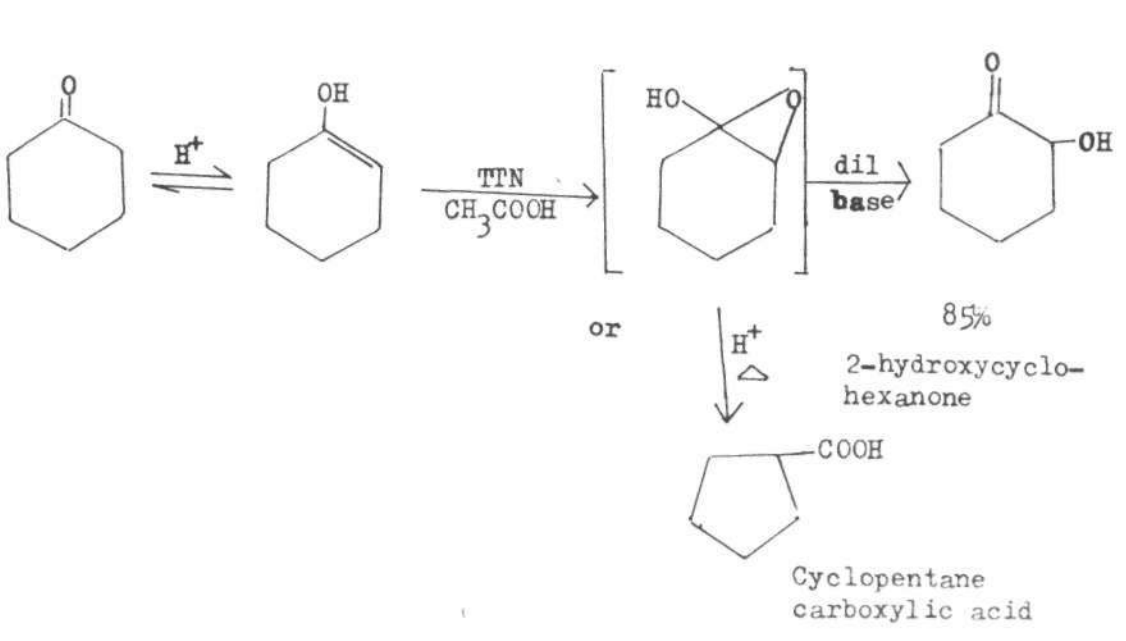
1.5.8. Oxidation of Oximes

Oximes were converted into aldehydes and ketones in yields of 70 - 95% when treated with TTN/MeOH at room temperature. The reaction was complete within few minutes (McKillop et al., 1969).



1.5.9. Oxidation of Cyclohexanone

Oxidation of cyclohexanone with TTN in ethanoic acid at room temperature proceeded rapidly to give 2-hydroxycyclohexanone in 84% yield, (McKillop et al., 1973).



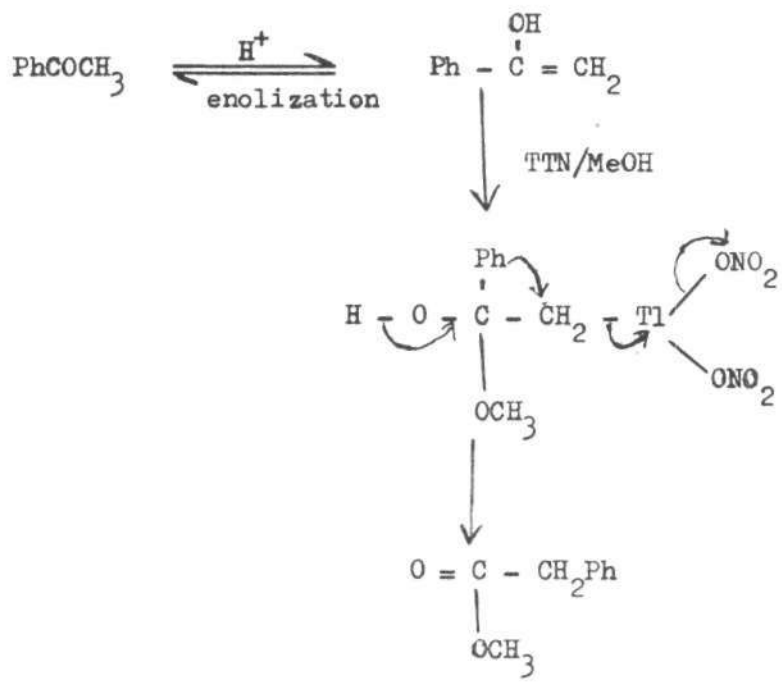
Oxidative rearrangement of alkyl arylketones to methyl phenylacetates.

The oxidative rearrangment of alkyl arylketones to methyl arylacetates by means of TTN in acidic methanol has been studied in detail (McKillop et al., 1971; McKillop et al., 1973;

Taylor et al., 1973; Belanger and Rooney, 1978). The rearrangement has been found to be applicable to a wide variety of substituted acetophenones. McKillop et al., (1973) proposed the mechanism of the rearrangement as shown in Scheme 1; that is, acid catalysed enolization of the ketone, oxythallation of the C = C thus formed, and oxidative rearrangement by 1,2 aryl migration with simultaneous reduction of Tl (III) to Tl (I).

Scheme 1: Conversion of Acetophenone to Methylphenylacetate.

Scheme 1



Other Oxidative Reactions

On examination of the oxidation of alkenes with TTN in CH_3OH, Bertsch and Quellette (1974) discovered that methoxy nitrates and dinitrate esters are also formed apart from the dimethoxy and carbonyl

compounds.

$C_8H_{17}CH{=}CH_2 \xrightarrow[MeOH,\ 0^{\circ}C]{TTN}$ $C_8H_{17}CH(OCH_3)CH_2(OCH_3)$ +

1,2 dimethoxy decane 33 - 42%

$C_8H_{17}COCH_3$ +

2-decanone 34 - 40% +

$C_8H_{17}CH(OCH_3)CH_2(ONO_2)$

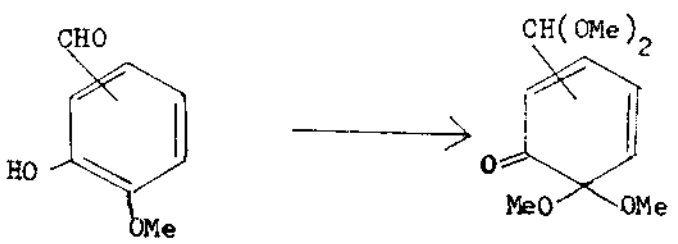
2-methoxy-1-decyl nitrate 23 - 27%.

Oxidation of alkenes and cyclopropane with TTN in pentane gave mainly dinitrate esters such as $RCH(ONO_2)CHR'(ONO_2)$ or $PhCH(ONO_2)CH_2$-CH_2ONO_2, where rearrangement products occur to a lesser extent, but there is a loss of stereospecificity as compared to the similar reaction in methanol (Quellette and Bertsch, 1976).

Oxidation of tautomeric imines with TTN in methanol gave, after hydrolytic work up, α-methoxy ketones and α-diketones. Only small amounts of methyl ester of carboxylic acids were obtained (Ahlbretch and Hagena, 1976).

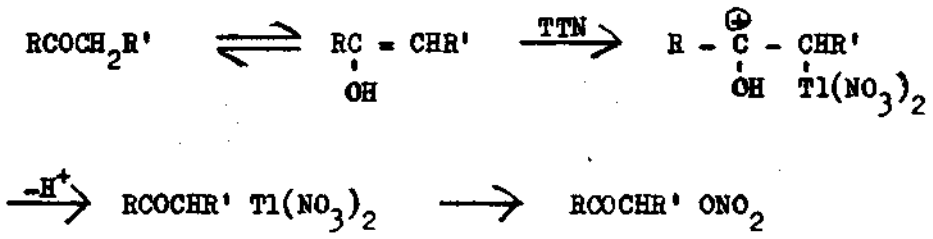
Conversion of hydroquinone monoalkyl ethers to p-benzoquinone monoketals was accomplished by using TTN in MeOH in the presence of suspended potassium hydrogen carbonate, (Buchi et al, 1978).

Oxidation of vanillins with TTN in methanol gave the dimethylacetals of 6,6-dimethoxy-2,4-cyclohexadien-1-one aldehydes, which dimerised rapidly at room temperature, (Antus et al., 1978)



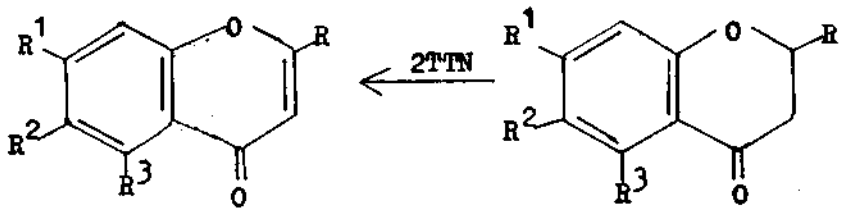
$CH(OMe)_2$ is at position 2, 3 or 4.

McKillop et al. (1978) found that oxidation of ketones with TTN in non-nucleophilic solvents such as acetonitrile or diethyl carbonate gave good yields of α-nitrato ketones instead of skeletal rearrangement.



Ketones examined include substituted acetophenone, propiophenone and some aliphatic ketones.

Varma and Varma (1982) obtained flavones (I)a in 70 - 78% yield by oxidizing the flavanones (2) with 2 moles of TTN at room temperature.



Flavones
(1)

Flavonones
(2)

R = (Ph, 2,4-$Me_2C_6H_3$)

R^1 = H, Me, OMe

R^2 = H, OMe

R^3 = H, Me

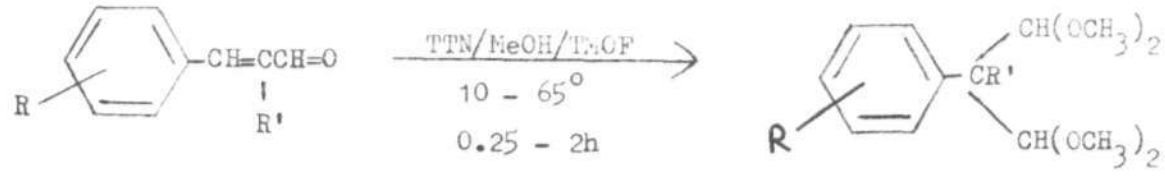
Levai and Tokes (1982) reported the oxidative rearrangement of 2'-hydroxy chalkones with TTN. The oxidation of 2'-hydroxy-3,5'-dichloro--4,6-dimethoxy-4-benzyloxychalcone with TTN gave 71.4% coumaranone (3)

obtained upon attempted oxidation of cinnamaldehyde in dilute HNO_3, four of which were identified as phenylacetaldehyde, phenylglyoxal, phenylglyoxalic acid and benzaldehyde (McKillop *et al.*, 1973). This failure led Taylor *et al.* (1976) to report the remarkable effectiveness of MeOH/TMOF (1:1) as solvents for TTN - mediated oxidations. They described novel oxidative rearrangements of unsaturated organic substrates with TTN/TMOF which do not proceed in the solvents commonly used for the reaction of TTN.

1.6.1. Oxidative Rearrangement of Cinnamaldehydes with TTN in TMOF/MeOH

The oxidation of cinnamaldehyde using TTN in MeOH/TMOF was found to proceed rapidly and clearly to give consistently high yields of aryl-malondialdehyde tetramethylacetals. The reaction was also found to be effective for the 4-nitro and the 4-methoxy derivatives, (Taylor *et al.*, 1976).

According to these workers, this transformation proceeds by an initial TTN-catalysed conversion of the cinnamaldehyde to its dimethyl acetals; the oxidative rearrangement which then follows methoxythallation is analogous to the TTN-mediated rearrangement of styrene to phenylacetaldehyde. This reaction constitutes a potential general synthetic method for the conversion of an aryl - CHO group into a tert-butyl substituent.



(a) R = R' = H, 79%

(b) R = 4-CH_3O, R' = H, 84%

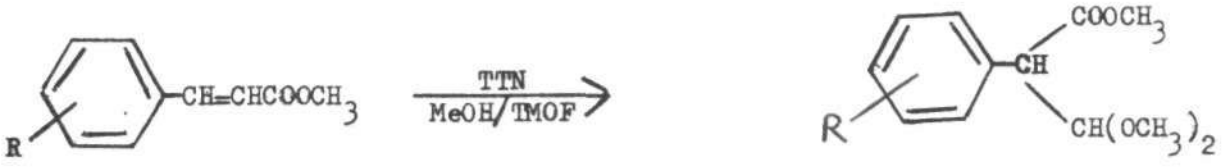
(c) R = 4-O_2N, R' = H, 63%

(d) R = H, R' = CH_3, 83%

(e) R = 3-O_2N, R' = CH_3, 50%

1.6.2. Oxidative Rearrangement of Methyl Cinnamates

Cinnamic esters have been found to rearrange smoothly with TTN/MeOH/TMOF or TTN/TMOF to methyl α-(dimethoxymethyl) arylacetates. (Taylor et al., 1976).



(a) R = H, 96%

(b) R = 4-CH_3, 96%

(c) R = 4-CH_3O, 90%

(d) R = 2-F, 83%

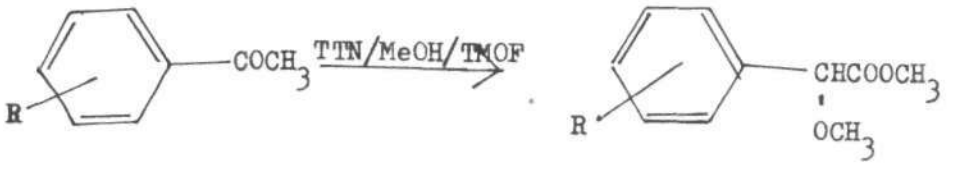
(e) R = 4-Cl, 96%

1.6.3. Oxidative Rearrangement of Acetophenones

The oxidative rearrangement of acetophenones has been studied in detail and found to be solvent dependent. Acetophenones rearrange smoothly with one equivalent of TTN in acidic methanol to give methyl arylacetates. With MeOH/TMOF as solvent, however, 2 mol. of TTN are

consumed, and the product is methyl ∝-methoxy arylacetate. According to Taylor et. al. (1976), two successive methoxythallation reactions were involved. The first utilizes ∝-methoxy styrene as substrate and involves an aryl migration; the second utilizes phenyl-ketene dimethylketal as substrate and terminates with oxidative displacement of thallium by methanol. The conversion of acetophenones to methyl ∝-methoxy phenylacetates is summarised in Scheme II.

Scheme II: Conversion of Acetophenones to Methyl ∝-methoxy arylacetates.



(a) R = H, 70%

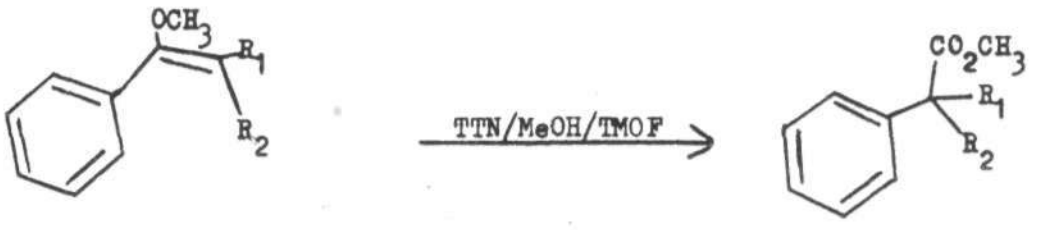
(b) R = 4-CH_3O, 81%

(c) R = 4-O_2N, 87%

(d) R = 3-C_6H_5O, 97%

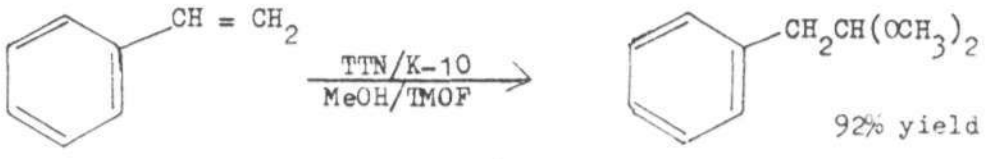
They also discovered that, in an analogous oxidative rearrangement, butyrophenone is converted to methyl-∝-ethyl phenylacetate (93%) and no ∝-methoxylation was observed, apparently for steric reasons.

Furthermore, Walker and Pillai (1977) found that arylalkylketones were converted to 2-arylalkanoic acids through in situ generation of enol ethers with TTN salts. The enol ether derivatives are oxidized very selectively to 2-aryl alkanoates:

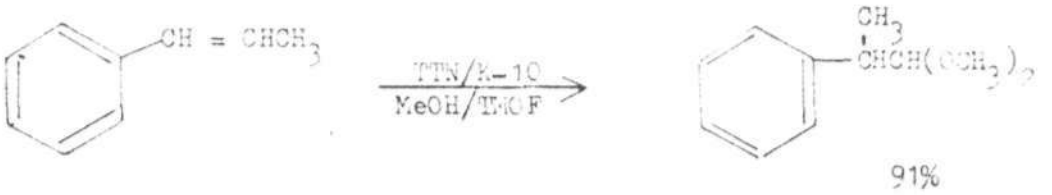


They also found that alkyl arylketones were rapidly ketalized by reagents such as TTN/MeOH/TMOF under anhydrous conditions. These workers also discovered that the use of anhydrous conditions proved convenient for the direct conversion of alkyl aryl ketones to 2-aryl alkanoates. Such conditions are <u>not</u> required for the oxidation of enol ethers with high selectivity. They also found that the intermediacy of enol ether derivatives would appear to be a major controlling factor in the facile conversion of alkyl aryl ketones to 2-aryl alkanoates with TTN.

Taylor <u>et al</u>. (1976) observed that TTN adsorbed on acidic montmorillonite clay, K-10, is a remarkably effective reagent for oxidative rearrangement of alkyl arylketones and alkenes. The superiority of TTN/K-10 over the usual TTN/MeOH system is found in the rapid, highly selective, high yield and room temperature oxidation with the former reagent. Alkenes, such as styrene and 1-phenyl-1-propene are extremely rapid in TTN/K-10 than in MeOH.



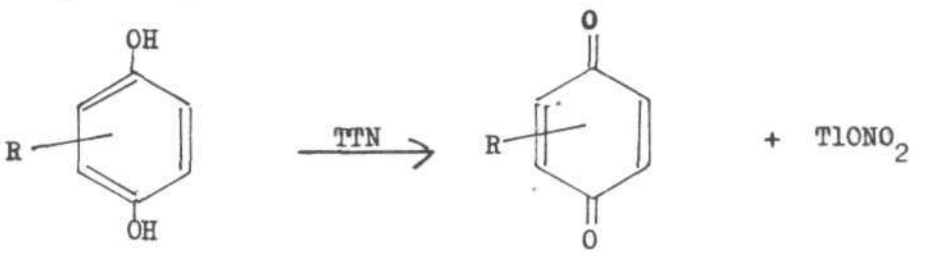
Styrene



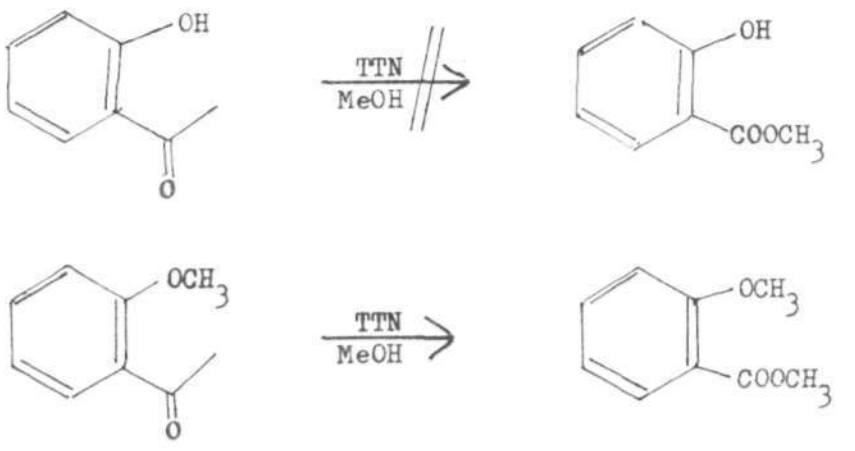
1-pheny-1-propene

1.6.4. Other Oxidative Reactions with TTN/MeOH/TMOF

McKillop et al. (1976) reported the result of a detailed investigation of the reactions of a wide range of phenols with TTN in MeOH/TMOF. The oxidation of hydroquinones to p-benzoquinones was found to take place rapidly and proceeded in excellent yields. The 2,6-disubstituted phenols are also smoothly oxidized to p-benzoquinones, while many 4-alkyl- and 4-alkoxyphenols were readily converted in good yields into 4-alkyl-4-methoxy- and 4,4-dimethoxycyclohexa-2,5-dienones, respectively.



Belanger and Rooney (1978) reported that direct rearrangement of propiophenone to methyl-α-methyl phenyl acetate under the condition of McKillop and Taylor (1973) gave a poor yield. An attempted thallium-catalysed rearrangement of o-hydroxy acetophenone at room temperature for twenty-four hours gave no reaction, while the corresponding methyl ether was converted smoothly to the phenyl acetate derivatives in fifteen minutes. Thus, blocking of phenolic ortho-hydroxy groups is a requirement in the TTN reaction.



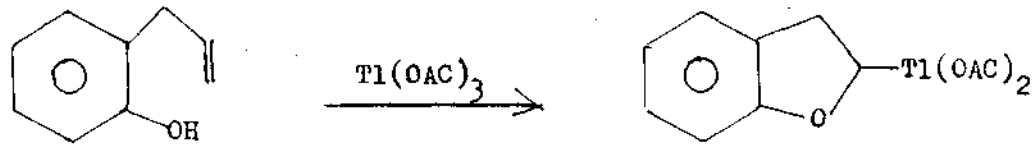
1.6.5. The Role of TMOF in the Oxidative Rearrangement

The full role of TMOF in oxidative rearrangement is not yet clear. With some carbonyl compounds, initial conversion to acetals, ketals or vinyl ethers (catalysis by TTN, are more rapid with TMOF than with MeOH alone) occurs prior to oxidation. However, an apparently important role of TMOF is to lower the dielectric constant of the reaction medium, thus favouring S_N2 as opposed to S_N1 reactions of the methoxy-thallated intermediate, (Bozimo, 1975; Taylor et al., 1976).

1.7. Oxidative Ring Closure Reactions with TTN/MeOH/TMOF

It has been discovered that reactions involving thallium rearrangement involve at some step, the displacement of thallium by a nucleophile (McKillop et al., 1970; Lethbridge et al., 1978). As a result of this property, the appropriate nucleophiles are being placed in specific positions to synthesise interesting heterocyclic compounds especially in the field of natural products.

Kabbe (1962) synthesised a benzofuran system by using a neighbouring hydroxy group of an ortho-alkenyl phenol to displace thallium from the adduct.



Therefore, it would be of interest to synthesise benzofuran derivatives from ortho-hydroxy phenyl ketones using TTN/MeOH/TMOF.

In the oxidative rearrangement of ortho-hydroxyphenylketones, both the phenyl and the hydroxy group could conceivably act as internal nucleophiles and participate as neighbouring groups in such reactions (Bozimo, 1975).

Bozimo (1975) found that the oxidative reaction of ortho-hydroxy-acetophenone with TTN/MeOH/TMOF mixture (1:1) gave ortho-hydroxy methyl α-methoxy phenylacetate while the ortho-hydroxypropiophenone underwent oxidative cyclization to yield benzofuran derivative, 2-methyl-2, 3,3-trimethoxy-2,3-dihydrobenzofuran. He also found that two moles of TTN would be required for the oxidative reactions of ortho-hydroxy-phenylketones.

It is, therefore, desired to extend the oxidative reactions to higher members of the group. The compounds chosen for the study are: ortho-hydroxybutyrophenone, ortho-hydroxyvalerophenone, ortho-hydroxyisovalerophenone and ortho-hydroxyhexanophenone.

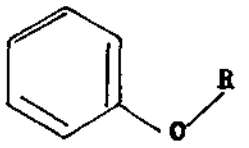
1.8. Benzofuran

Benzo [b] furan was first synthesised by Perkin in 1870 and discovered in coal tar by Kraemer and Spilker in 1890. Formation of 2-benzofurans is possible by ortho-condensation of a benzene ring with furan, depending on whether the benzene ring is condensed on the 2,3 or 3,4 positions. The 2, 3 condensation is known as benzo[b]furan or coumarone and the 3, 4 derivative as isobenzofuran or isocoumarone, (Elderfield, 1951). The importance of benzo[b]furan ring system in natural and synthetic products with pharmacologic activities explains the large number of papers published on these compounds.

1.8.1. General Approach to Syntheses of Benzofurans

According to Cagniant and Cagniant (1975), syntheses of benzofurans can be classified into three main groups.

Group 1: The starting molecule is of type A.

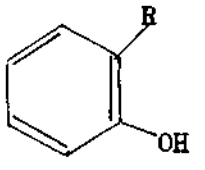


(8) Type A.

This group mainly includes aryloxylated compounds such as aryloxyacetaldehyde, aryloxyacetone, aryloxyacetic acids which can be subjected to thermal or chemical cyclodehydration of aryloxyacetones. A typical example is cyclodehydration of aryloxyacetones from the corresponding phenols and halogenoacetones, which leads to 3-aryl benzofurans (Singh and Verma, 1963; Worth et al. 1972).

The most frequently used dehydrating media are tetraoxosulphate(VI) acid, zinc chloride and phosphorous oxychloride.

Group 2: These are syntheses of benzofurans using type B molecules.



(9) Type B

This group includes substituted phenolic compounds, where R is a saturated or unsaturated alkyl radical. The benzofuran molecule can be formed by three main methods:

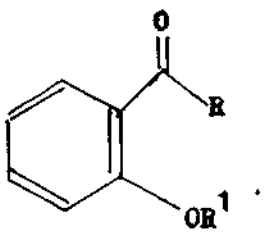
(a) Using hydroxylated alkyl compounds to form benzofurans or 2,3-dihydrobenzofurans by ring closure.

(b) When the side chain R of the type $COCH_2X$ (where X = Cl or Br, is formed by Hoesch condensation or Fries rearrangement from corresponding molecule of type (A) resulting in 3(2H)-benzofuranones.

(c) When the side chain R is of the CH_2-CO-R type the benzofuran ring is formed by cyclo dehydration.

(Spoerri, 1962; Aneja and Mukerjee, 1957).

Group 3: In this group, the starting molecule is of type C.



This group includes hydroxylated carbonyl compounds with reactive methylene groups and the ring closure is an intramolecular condensation.

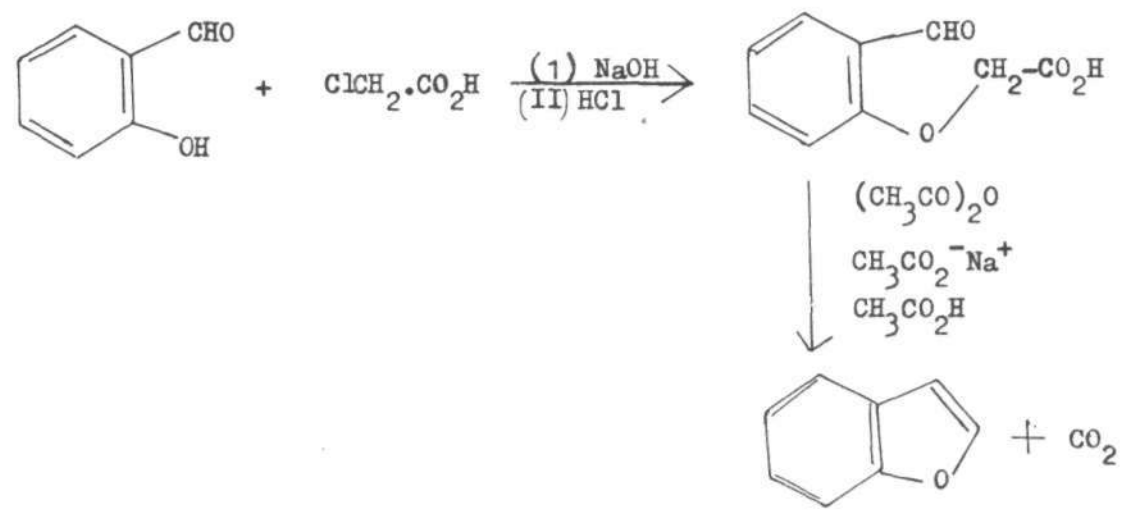
1.8.2 Specific Methods of Synthesising Benzofurans

The most often used route to benzofuran is the intramolecular cyclisation of a substituted benzene. Less commonly the system can be prepared by annulation of a furan derivative (Sergent and Cresp, 1979).

The formation of benzofurans by reaction of an ortho-halophenol with copper (I) acetylide is an example, where intermolecular coupling preceeds intramolecular cyclisation (Castro et al., 1969). Schraber and Stevenson (1976) employed this method in a short synthesis of the natural benzofuran egonol. A modification of this method employs 2-(2-chloropropenyl) phenols generated by Claisen rearrangement. Acid catalysed cyclisation follows dehydrogenation yielding benzofurans. (Anderson et al., 1976).

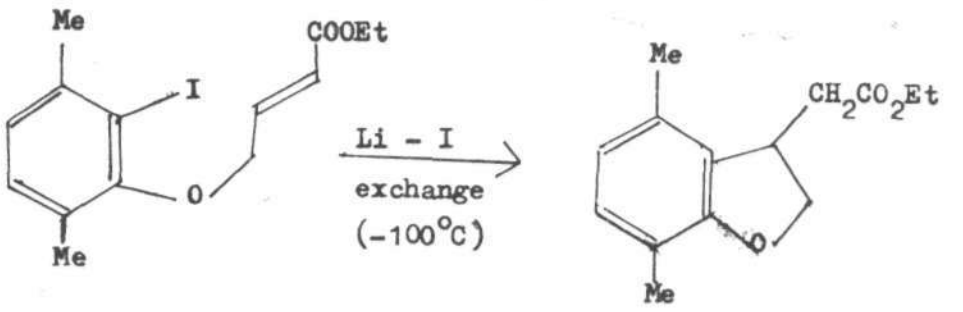
Worth et al. (1972) used the method of intramolecular aldol condensation of phenoxide ions derived from resorcinol and phloro glucinol monoacetonyl ethers to synthesis benzofuran.

Benzofuran may be prepared from salicylaldehyde by initial conversion into the corresponding aryloxyacetic acid on reaction with sodium chloroacetate in the presence of alkali. Cyclization of the product in a mixture of acetic anhydride, acetic acid and sodium acetate proceeds by way of an internal Perkin reaction accompanied by a decarboxylative dehydration, (Vogel, 1978).



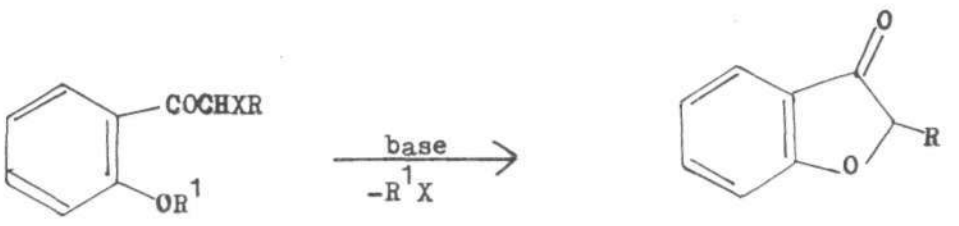
Kneen et al., (1986) reported synthesis of 4-hydroxy benzofuran from 1,3-cyclohexadione. The diketone underwent a cyclo condensation reaction with $BrCH_2COCO_2H$ to yield benzofuran.

Weartunga, et al. (1987) synthesised dihydrobenzofurans by intramolecular conjugate addition method. For example, the ortho-iodo phenoxycrotonates cyclise to dihydrobenzofuran when subjected to Lithium-Iodine exchange at $-100^{o}C$



1.8.3. Ring Closure of ortho-Haloacylphenol: 3(2H)-Benzofuranones (Coumaran-3-one)

Elimination of a hydrogen halide from halogenated ortho-hydroxy acetophenone derivatives is a common route to benzofurans (Adams and Rindfusz, 1919). Coumaran-3-one derivatives are prepared by elimination of hydrogen halides from halogenated acetophenone derivatives.



(10)

where R = H or alkyl

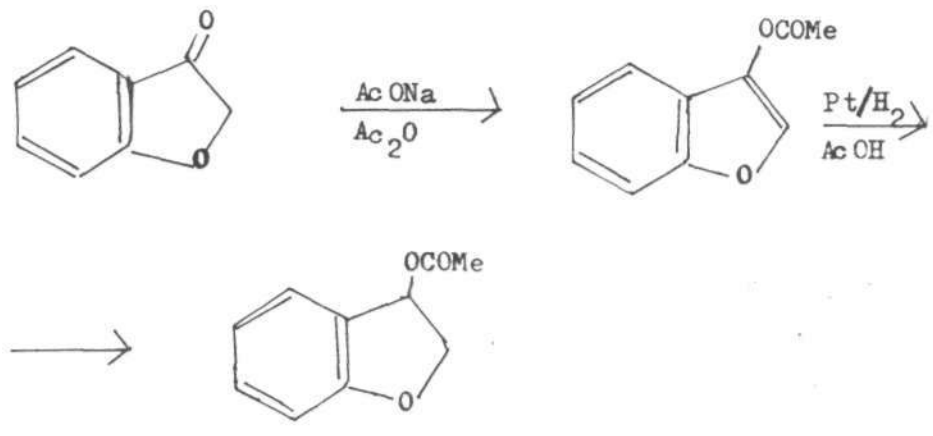
R^1 = H or acyl

Ring closure is achieved by treating the ortho-haloacylphenol with sodium acetate in ethanol or with dilute alkali, for example potassium hydroxide or with silver acetate in toluene or in acetic acid (Geissman and Hinreiner, 1951; Ramage and Stead, 1953; Chatterjea and Mehrota, 1963).

The ortho-haloacyl phenols are usually obtained from a phenol either by the Hoesch reaction involving treatment with R-CHCl-CN or by Fries rearrangement; that is, by treating first with chloro acetyl chloride, then $AlCl_3$ in nitrobenzene or from ortho-hydroxy acetophenone, notably by means of cuprous bromide in dioxan.

1.8.4. Synthesis of Benzofurans from 3(2H)-Benzofuranones (Coumaran-3-one)

Benzofuran can be prepared from coumaranones using Stiriner Anderson method, comprising reduction of 3-acetoxy derivatives. The coumaran-3-ones are heated with sodium acetate and acetic anhydride to give the 3-acetoxy derivatives which is hydrogenated (Pt in acetic acid) to benzofuran (Horning and Reishner, 1953).



1.8.5. Importance of the Benzofuran Ring System

Many natural products with benzofuran rings, are of diverse physiological, pharmacological and toxicological importance, (Cagniant and Cagniant, 1975). Chemistry of benzofuran derivatives has therefore developed in a spectacular

fashion. For example, nitrobenzofurans have been found to possess antibacterial activity. Also, α-(benzofuryloxy) acetyl derivative of 7-amino-cephalosporanic acid is a bactericidal agent (Hatteri and Hirai, 1970).

2,3-dihydro-2-hydroxy-6-methyl-3-methylene benzofuran, a simple natural benzofuran has nematocidal properties (Bohlmann et al., 1968). The 2,2,-dimethyl-2,3-dihydro benzofuran derivatives have been synthesised and found to be an effective toxophore (Cruikshnank, et al., 1970).

Many 3-alkyl-2-aryl benzofurans and 2-alkyl-3-aryl benzofurans synthesised which are of value are: 2-ethyl-3-(4-hydroxybenzoyl) benzofuran or benzorone which is a coronary vasoactive, anti-inflammatory and fibronolytic agent and 2-ethyl-3-(3-5-diiodo-4-hydroxy benzoyl) benzofuran which is a coronary vasodilator. The last two compounds are besides diuretics.

Furochromones such as khellin, a natural benzofuran, is a spasmolytic agent effective against bronchial asthma. Furocoumarins such as xanthotoxin increases the sensitivity of Ehrlich tumour cells to gammarays (Bordin et al., 1969). Linear furocoumarins such as psoralene is a photosensiting agent.

2,(4-hydroxy benzoyl) benzofuran and its 3-ethyl derivative are estrogenic (Bisagni et al., 1955).

CHAPTER 2

2.0 RESULTS AND DISCUSSION

2.1 Aim of the Project

Bozimo (1975) reported the oxidative reactions of ortho-hydroxypropiophenone in TMOF/MeOH mixture using TTN. He discovered that ortho-hydroxypropiophenone undergoes oxidative cyclisation to give benzofuran derivatives. However, Okeniyi (1983) reported that the oxidative rearrangement of ortho-hydroxyvalerophenone with TTN/TMOF/MeOH gave complex product mixtures which were difficult to resolve and characterise. Thus, it appears that the products formed on oxidation with TTN vary with experimental conditions.

Based on these findings, this work is therefore aimed at confirming and extending earlier studies of Bozimo (1975) on oxidative ring closure reactions to higher homologues of ortho-hydroxyphenylketones, using TTN/TMOF/MeOH mixture.

The first problem was to synthesize the ortho-hydroxyphenylketones from the corresponding phenyl esters by the Fries rearrangement. This was followed by oxidative cyclization reaction of the ortho-hydroxyphenylketones using two molar equivalents of TTN in TTN in TMOF/MeOH (1:1) mixture.

2.2 Previous Results

The cyclisation of ortho-hydroxyphenylketones has been studied, but the results obtained were not completely satisfactory from stand-point of yields and number of products. These reactions were initially carried out by Fries and Plaffendorf (1910), Adams and Kindfusz (1919) and Amstutz (1944). The ortho-hydroxyphenylketone was first halogenated,

dehydrohalogenated by treating it with powdered potassium hydroxide in dry ether. The coumaran-3-one obtained was isolated but the yield was poor, consequently, the reaction is of no preparative value or as synthetic route to coumaran-3-one.

Oxidation of 2-hydroxyacetophenone with SeO_2 results in the formation of minor products; 2-hydroxy-3-(2H)-benzofuranone and 2-hydroxyphenylglyoxal as the major product (Fodor and Kovacs, 1949; Howe et al., 1967).

Bohlmann and Zodero (1968) reported that the dropwise addition of w-chloro-4-methyl-2-hydroxyacetophenone in tetrahydrofuran to methyl magnesium iodide solution resulted in an abnormal Grignard reaction which led to the formation of 2,2,6-trimethyl-2,3-dihydrobenzofuran.

Nohara et al., (1974) treated a cooled solution of ortho-hydroxyacetophenone in dimethyl formamide with $POCl_3$ and allowed it to stand for thirteen hours at room temperature to obtain chromone-3-carboxyaldehyde.

ortho-Hydroxyphenylketone was thermally cyclised with $ClCH_2CONH_2$ to 58% yield of coumarilic acid amide, (Rene and Royer, 1973).

Closely related to this route is oxidation of ortho-alkenylphenol. Kabbe (1962) synthesised a benzofuran system by using a neighbouring hydroxy group of an ortho-alkenylphenol to displace thallium from the adduct. The ortho-alkenyl phenol was treated with TTN in acetic acid medium for short periods. It gave almost quantitative yields of 2,3-dihydrobenzofuranyl thallium diacetate.

Kabbe (1978) synthesised 4-chromanones by treating 2-hydroxyacetophenone with R^1COR^2 containing pyrrolidine or with the enamine of R^1COR^2; ($R^1 = (CH_2)_3NEt_2$, $R^2 = Me$).

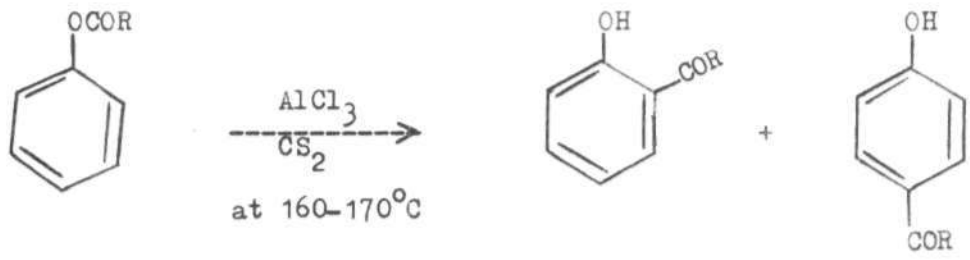
Levai and Tokes (1982) reported the oxidative rearrangment of 2' hydroxychalcone with TTN to give 71.4% coumaranone.

Forcellese (1983) found that intramolecular cyclization reaction of some 2-alkenyl phenols by TTN gave benzofuran derivatives.

2.3 Oxidative Reactions of ortho-Hydroxyphenylketones with Thallium(III) Nitrate (V) in TMOF/MeOH

2.3.1 Fries Rearrangement

The Fries rearrangement is the name for the very widespread rearrangement of phenyl esters to hydroxyphenylketones.



(1) o-hydroxyphenyl-ketone (2) p-hydroxyphenyl ketone (3)

where R is alkyl group

(a) R = $(-CH_2)_2CH_3$

(b) R = $(-CH_2)_3CH_3$

(c) R = $CH_2CH(CH_3)_2$

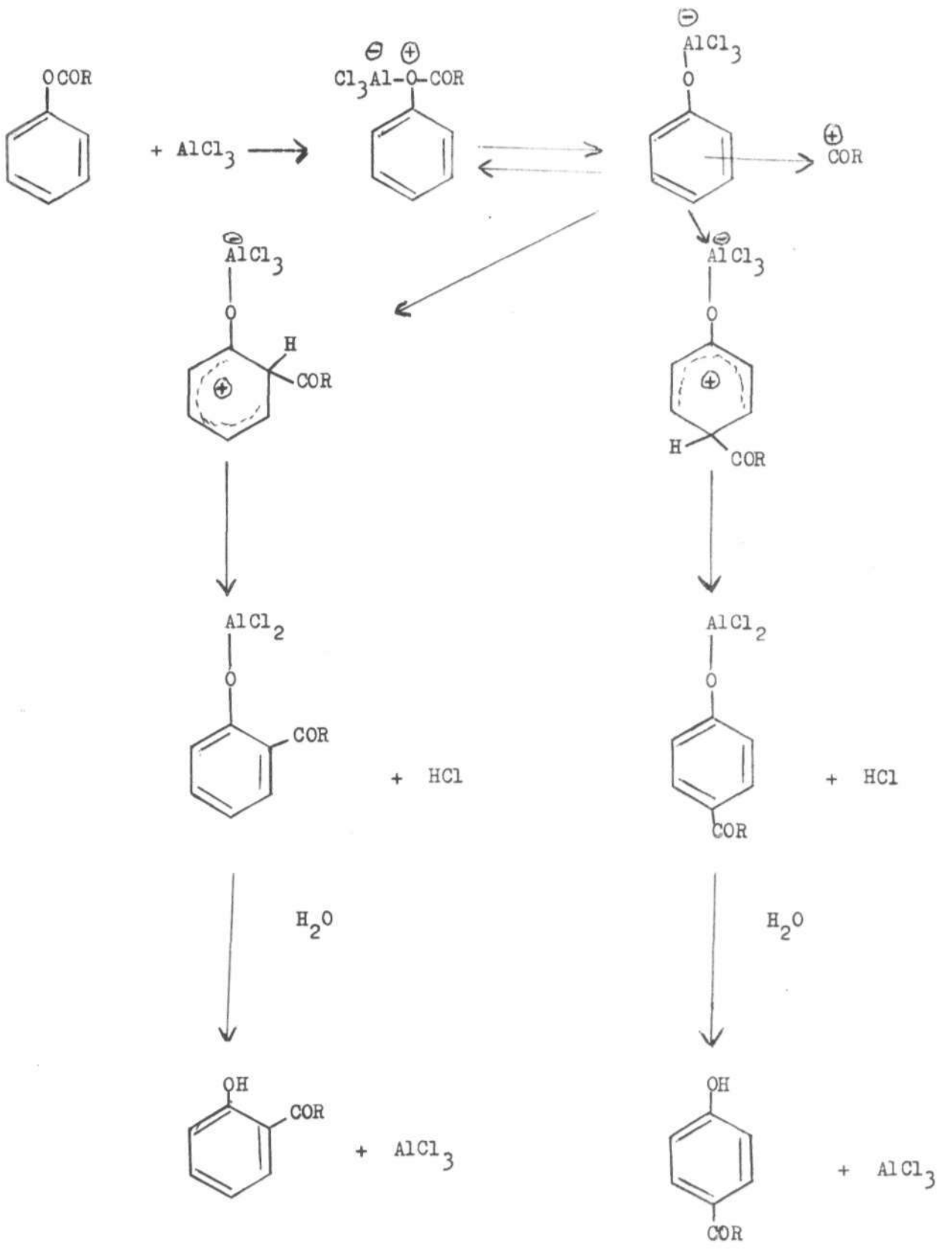
(d) R = $(-CH_2)_4CH_3$

Both the ortho- and para- - hydroxyphenylketones may be produced, and it is often possible to select conditions so that either one predominates. The ortho-/para ratio depends on the temperature, solvent and amount of catalyst used. Low temperature generally favours the para-isomer whereas high temperature, the ortho-isomer. The rearrangement was therefore done at high temperature (160° - $170^{\circ}C$). Also the Lewis acid, $AlCl_3$ was applied at 1:1 equivalent to the phenylester since the proportion of the ortho-isomer in the product is found to decrease as the amount of the aluminium halide is increased from one to two equivalents; (Hilgeteg and Martini, 1972; House 1972 ; Vogel, 1978). Moderate amount of the carbon disulphide solvent was used. Other solvents that can be used are nitrobenzene, light petroleum or chlorobenzene.

The ortho- and para-hydroxyphenylketones were separated by fractional distillation under reduced pressure through an efficient column. The ortho-hydroxyphenylketones being chelated are more steam volatile. At room temperature, the ortho-isomer is an oil whereas the para-isomer is a solid.

The details of the mechanism of the rearrangement are uncertain, but the reaction probably involves formation and migration of acylium ion. According to Ogata and Tabuchi (1964) and Dewar (1970), Fries rearrangement involves both intermolecular and intramolecular transfer of the acyl group. A proposed mechanism of rearrangement is as follows (Ogata and Tabuchi 1964):

Scheme III: Mechanism of Fries Rearrangement



The infra-red spectroscopic analysis of the ortho-hydroxy ketons gave the following absorption bands:

3500 - 3100 (strong and broad	-OH(stretching)
2960 - 2630 (w)	-CH-(stretching)
1620 - 1615 (s)	C=O(stretching)
1610 - 1600 (s)	C=C(stretching)
1380 - 1360 (m)	-OH(deformation)

The strong band at 1620 C=O (stretching) indicates a carbonyl in conjugation with the aromatic ring.

The phenylesters exhibit the ester C=O band at 1760cm^{-1}, while the C=O bands of the hydroxyphenylketones were shifted to 1620 - 1615 region. The shift may be attributed to the existence of the conjugated chelate system in the ortho-hydroxyphenylketone. These infra-red data agree very well with those of Rasmussen et al. (1949) and Hunsberger (1950).

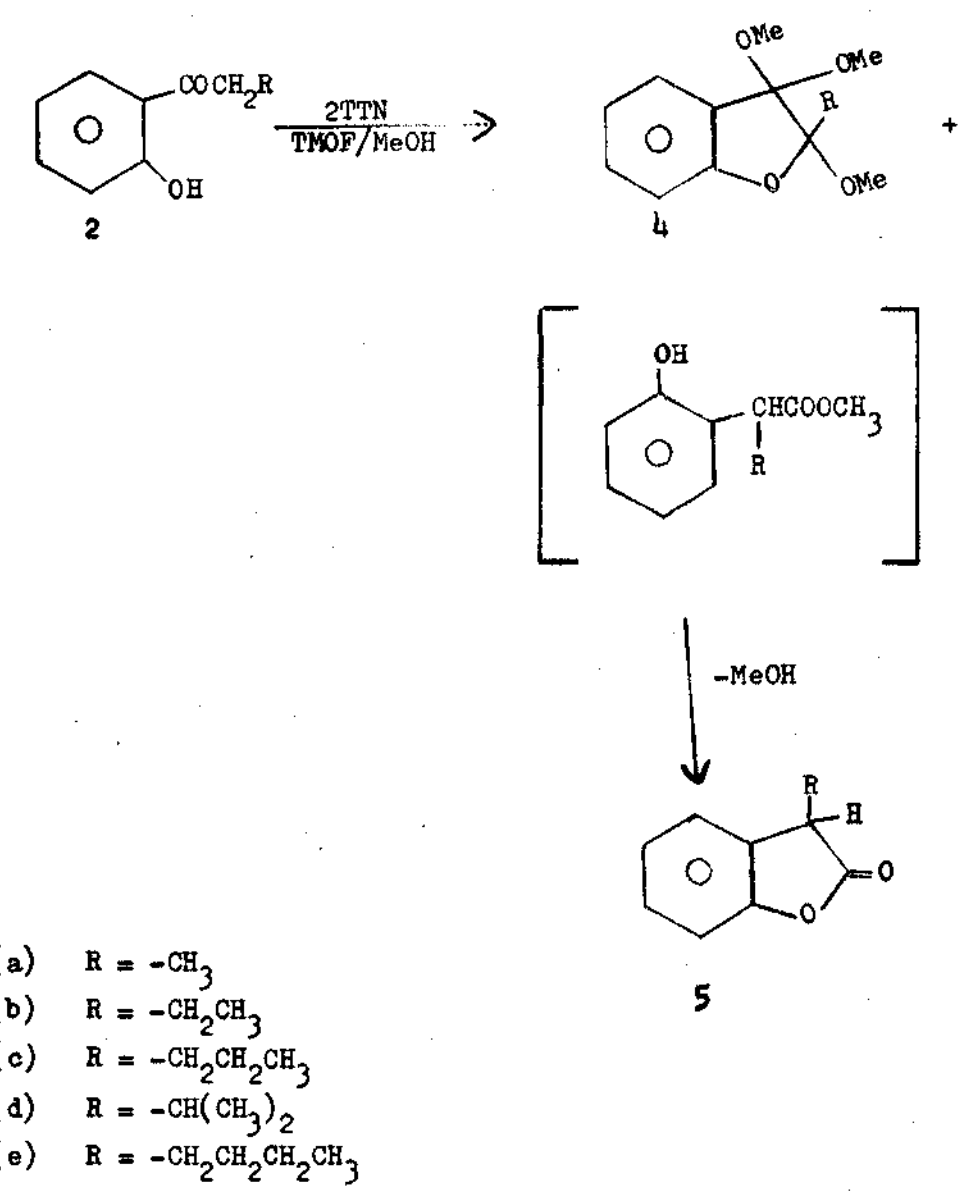
The ortho-hydroxyphenylketones exhibit strong and very broad hydroxy group (-OH) absorption extending from 3500cm^{-1} to 3100cm^{-1} as a result of 'conjugate chelation' (Rasmussen et al., 1949). According to these workers, conjugation of C=C to the ketone C=O group gives rise to typical conjugation shifts in the infra-red band and simultaneous conjugation and chelation lead to a great enhancement of its intensity and appearance of broad strong band.

The n.m.r. spectra of the ortho-hydroxyphenylketones, 2a-d agree with their structures. For example, the n.m.r. spectrum of 1-(ortho hydroxyphenyl) pentan-1-one (ortho-hydroxyvalerophenone) (Appendix VI) showed the presence of methyl protons at δ 0.9 (d, 3H), methylene protons 1.6 (m, 4H), 3.1 (t, 2H), aromatic protons δ 6.7 - 7.8 (m, 4H) and δ

12.5 (s, 1H). These data agree reasonably well with findings of Porte et al., (1950) and Pouchette and Campel (1974).

2.3.2 Oxidative Reactions of ortho-Hydroxyphenylketones Using TTN/MeOH/TMOF Mixture

Series of oxidative reactions of ortho-hydroxyphenylketones using 2 molar equivalents of TTN in MeOH/TMOF mixture (1:1) were carried out. The results are summarised below; (Table 2.3.2).



(a) R = $-CH_3$
(b) R = $-CH_2CH_3$
(c) R = $-CH_2CH_2CH_3$
(d) R = $-CH(CH_3)_2$
(e) R = $-CH_2CH_2CH_2CH_3$

Table 2.2.2

ortho-Hydroxyphenylketone	R	% Yield of Benzofuran (4)	% Yield of the Ester (5)
1-(ortho-hydroxyphenyl) propan-1-one	$-CH_3$	86	10
1-(ortho-hydroxyphenyl) butan-1-one	$-CH_2CH_3$	60	30
1-(ortho-hydroxyphenyl) pentan-1-one	$-(CH_2)_2CH_3$	86	10
1-(ortho-hydroxyphenyl) 3-methyl-butan-1-one	$-CH(CH_3)_2$	40	50
1-(ortho-hydroxyphenyl) hexan-1-one	$-(CH_2)_3CH_3$	85	10

Thin-layer chromatography was used to follow the progress of the reaction using petroleum-ether (60 - 80°); diethyl ether (1:1) developing solvent as the ∠ This consistently revealed the presence of two compounds apart from the starting material. The furan was found to run ahead of the second compound in all the chromatograms and was easily isolated.

The crude product was cleaned up by column chromatography and the two main components were separated. The less polar fraction was obtained as a yellow oil containing largely the 2,3-dihydrobenzofuran derivatives. The polar fraction was identified as esters. Thus, the two products isolated were the benzofuran, the major component, and the ester. The quantity of the benzofuran derivative obtained in the reaction of ortho-hydroxyisovalerophenone can only be due to steric effect of the isopropyl group. This is in line with the observation of Bozimo (1975) that steric factors seemed to determine whether participation by the internal hydroxy or phenyl will occur at first oxidation step.

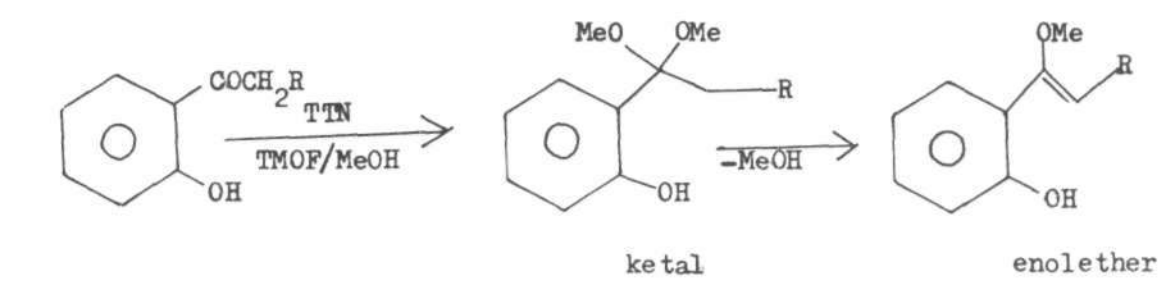
Steric factors play a very important role in the second oxidation step, and that steric bulk, either in the substrate or in the solvent, can effectively block that step.

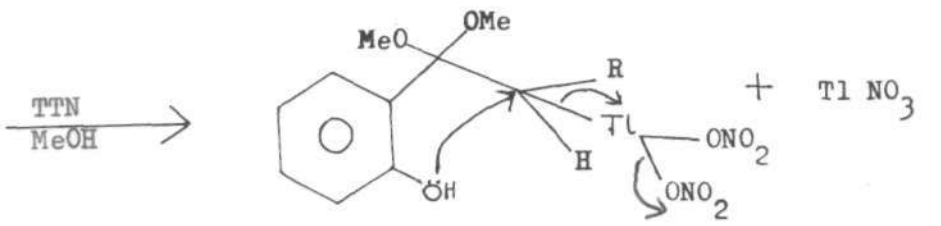
The oxidative reactions of TTN involves a prior attack by thallium and the associated nucleophile or the solvent at the two ends of the double or multiple bonds.

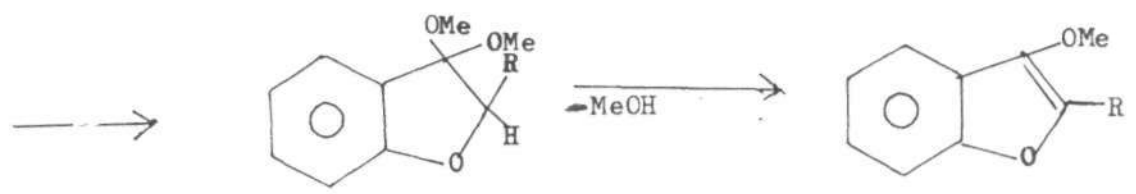
In mechanistic terms, these oxidative reactions are at first sight apparently straightforward. A plausible mechanism for the oxidative cyclization reaction of ortho-hydroxyphenylketone (2) to give the 2-methyl-2,3,3-trimethoxy-2,3-dihydrobenzofuran (4) is outlined in Scheme IV. This involves initial methoxythallation of the enol ether derivative. This is followed by the neighbouring group

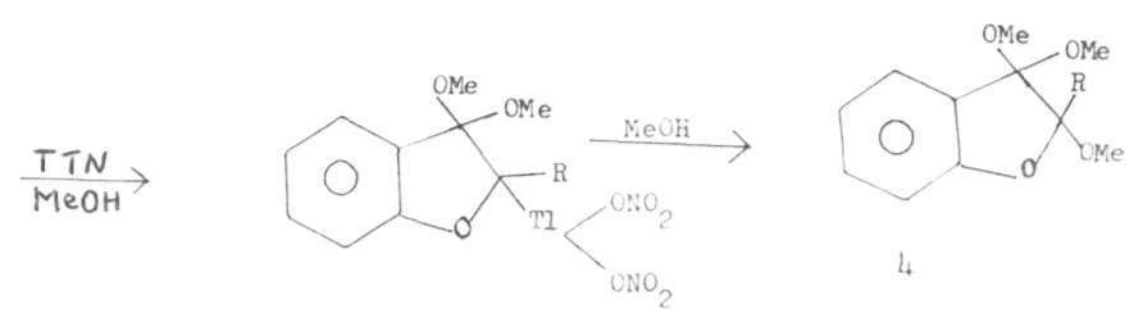
assisted cleavage of the carbon-thallium bond by the hydroxy group to effect ring closure. In this case, the hydroxy group acting as the internal nucleophile, displaces thallium in the adduct to give the benzofuran derivatives (Bozimo, 1975).

Scheme IV: Proposed Mechanism for oxidative ring closure of ortho-hydroxyphenylketone.









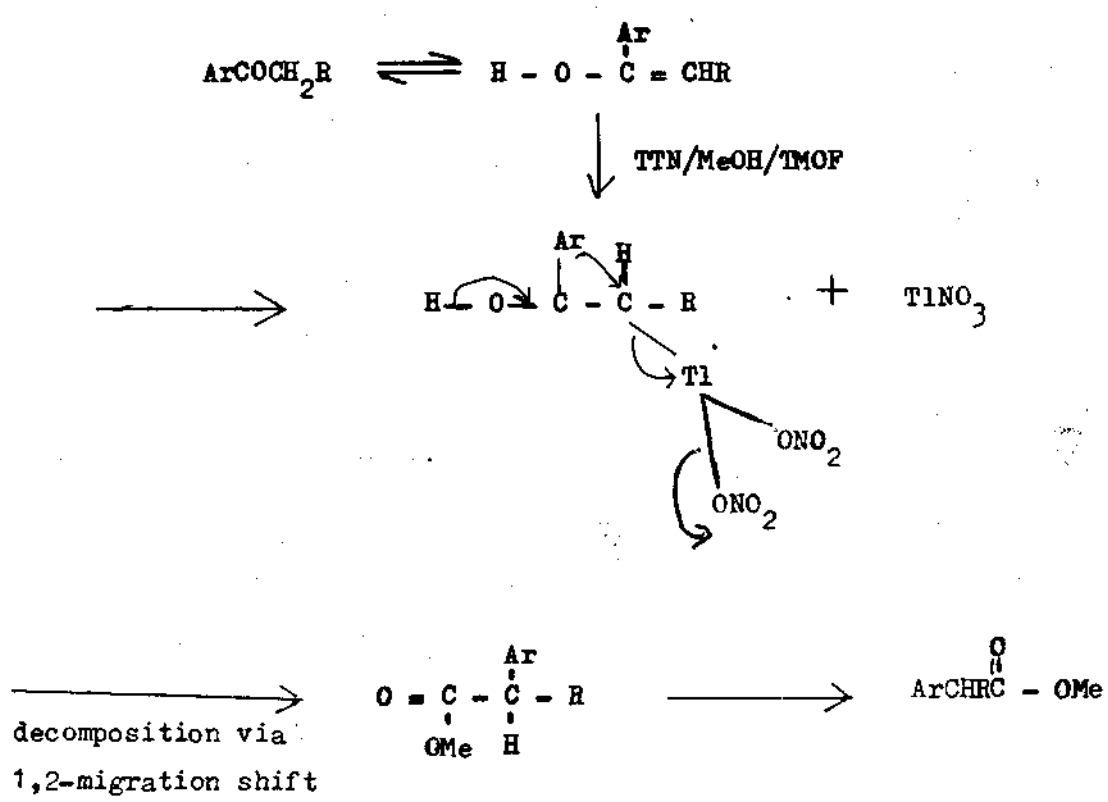
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Another simple alternative mechanism for the oxidative reaction of ortho-hydroxyphenylketones is oxidative rearrangement, outlined in Scheme V. In this transformation, a keto carbonium ion is produced and subsequent attack by the nucleophile can occur either at the carbonium ion centre or, provided an aryl migration can occur, at the adjacent carbonyl carbon.

The formation of the ester involves enolization of the ketone, followed by oxythallation leading to an unstable alkylthalliumdinitrate. Decomposition of this alkylthallium adductinvolve migration of the phenyl group. The essential feature of this mechanism is that aromatic ring migrates to displace thallium in the adduct to yield a hydroxy ester (methyl, ortho-hydroxyphenylacetate).

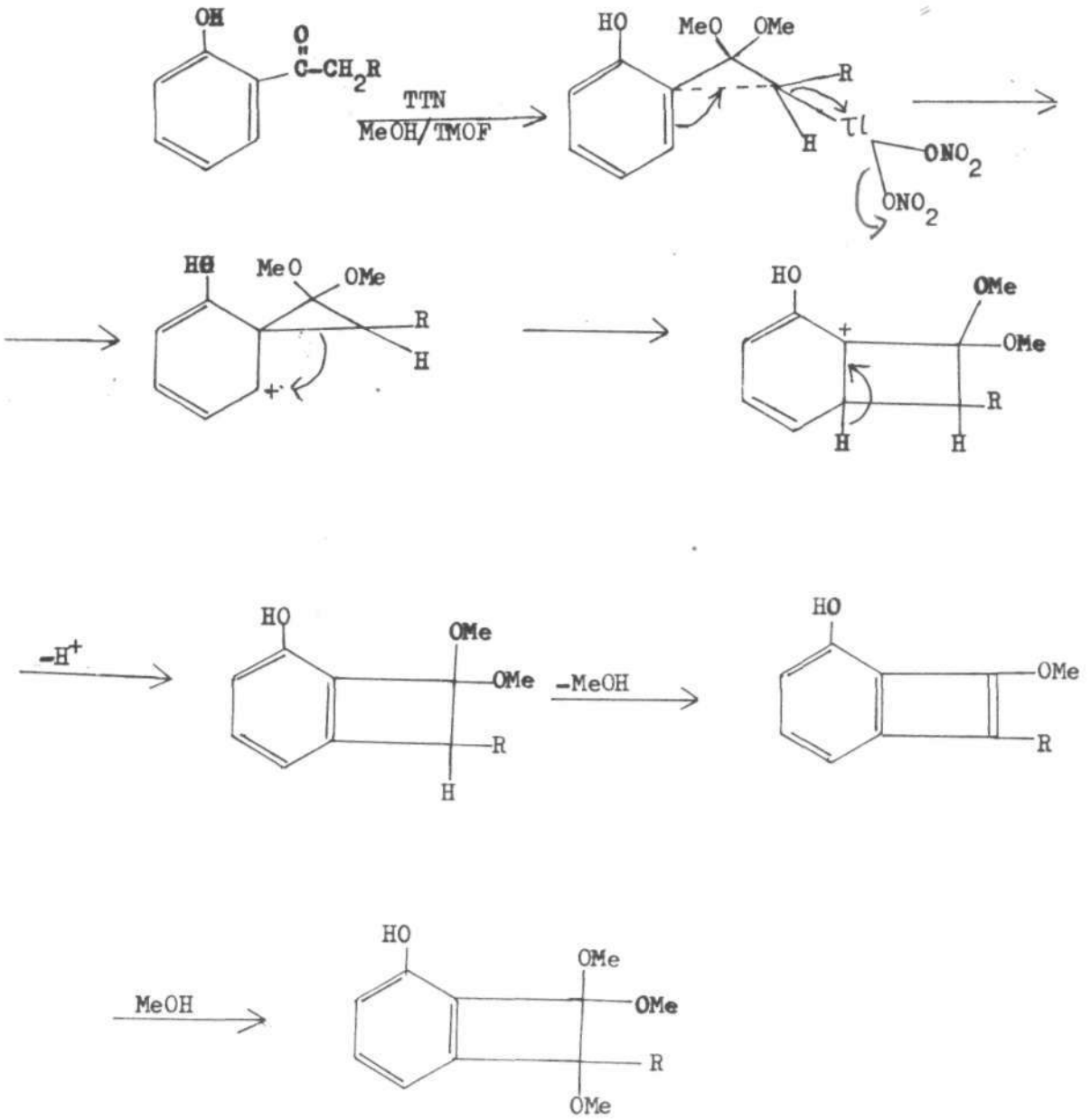
There is usually a variable concentration of enols in equilibrium with the carbonyl compounds. Gradual depletion of the enols alters the equilibrium in favour of further enolization.

Scheme V: Proposed Mechanism for Oxidative Rearrangement of ortho-hydroxyphenylketone to Alkyl, Ortho-hydroxyphenylacetate.



A third reaction pathway involves the possibility of the phenyl group acting as an internal nucleophile, thereby displacing thallium in the adduct to form the benzocyclobutane derivatives shown in Scheme VI. No product was obtained that confirms this route. It is probably not surprising since it involves higher energy transition states than those encountered in the formation of the benzofurans.

Scheme VI: Oxidative Reaction of ortho-Hydroxyphenylketone to Benzocyclobutane Derivatives.



benzocyclobutene derivatives.

The 2,3-dihydrobenzofuran derivatives (4) obtained in this oxidative reactions were characterised by spectroscopy. The identity of (4) was established by comparison of n.m.r. data with those obtained by Bozimo (1975). Most of the benzofurans are oils and possess aromatic sweet smell.

The n.m.r. spectra patterns observed for compounds 4a to 4d are in agreement with the structure of the benzofurans. The spectrum of compound 4a, (Appendix VIII) for example, showed the presence of methyl protons δ 1.60 (s, 3H), the three methoxy, $-OCH_3$ protons at δ 3.07; (s, 3H), 3.40 (s, 3H), 3.57 (s, 3H) and the aromatic ring protons at δ 6.80 - 7.4ppm (m, 4H). These data agree reasonably well with those of Bozimo (1975). Signals due to methoxy protons ($-OCH_3$) were very strong. The presence of oxygen causes a pronounced downfield shift in ring protons, especially in the α-position.

The characteristic feature of these 2,3-dihydrobenzofuran derivatives is that all of them show strong absorption bands at 1640 - 1620, 1490, 1260, 1120 and 750 cm^{-1} in the infrared region (Figure VII). These infrared absorption bands agree reasonably well with the infrared absorption bands for alkyl 2,3-dihydrobenzofuran previously reported (Shulgin and Baker, 1963; Pouchett, 1975).

The absorption bands at 2870 and 2980 cm^{-1} indicate the presence of a saturated C-H. Also, the absorption at 1240 cm^{-1} is characteristic of carbon-oxygen bond.

The infrared and n.m.r. spectroscopic data recorded for each compound are given in the experimental section.

Further evidence confirming the proposed structures is being awaited from elemental analyses and mass measurements.

The other product with lower R_f value obtained from the reaction was suspected to be an ester (Appendix IX). It was however, observed in all samples that a carbonyl (C=O) absorption at 1798 cm^{-1} occured. The corresponding hydroxyl (-OH) absorption peaks for the samples were observed to be weaker than those in the starting ortho-hydroxyphenyl-ketones. Even when the esters were hydrolysed to the corresponding acids, these carbonyl peaks were consistently strong, it was then suspected that lactonisation had taken place between the hydroxyl (-OH) group and the carboxylic ester or acid functions. Lactonisation would then involve loss of methanol and water respectively.

Further evidence showed that infrared spectrum (Appendix IX) is infact for a mixture of the ester and the lactone with carbonyl (C=O) peaks at 1740 cm^{-1} and 1798 cm^{-1} respectively. Purer samples obtained showed complete disappearance of the hydroxyl (-OH) peak at 3375 cm^{-1} and that of the carbonyl (C=O) of the ester function at 1740 cm^{-1}.

An alternative method to separate the furans from the ester is by treating the crude product with dilute methanolic sodium hydroxide. The ester is converted into the sodium salt of the corresponding carboxylic acid which is not soluble in diethyl ether. Washing the mixture with ether extracts the benzofurans neatly as oil. The furan is so stable that ring cleavage cannot easily occur since the carbonyl group is being protected with two methoxy ($-OCH_3$) groups. However, the ester will easily undergo hydrolysis to the corresponding carboxylic acid.

Finally, it was observed that in the oxidative ring closure of the ortho-hydroxyphenylketones to the corresponding benzofuran derivatives, the reactions proceeded cleanly and in high yield under anhydrous condition and only when solid crystals of TTN were used. For example, when the reaction was carried out with ortho-hydroxyvalerophenone without drying the solvents properly, the reaction was messy and low yield product, 30% of the ester and unreacted ortho-hydroxyvalerophenone were obtained.

The failure of the reaction to give benzofuran derivatives in the case of Okeniyi (1983) may be due to presence of water since the reagents may not have been properly dried.

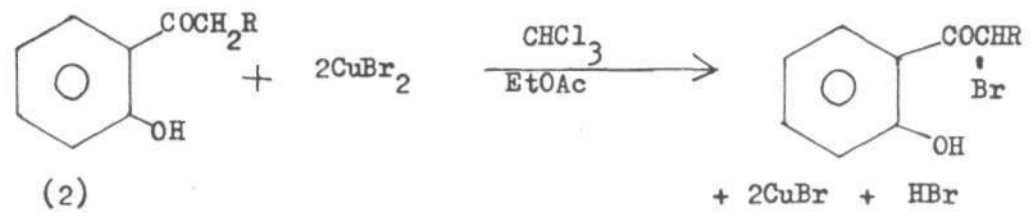
Therefore, to obtain high yield of the benzofurans, the reaction must be carried out under anhydrous condition and only the solid crystals of TTN should be used.

2.3 Cyclization of α-bromo-ortho-hydroxyphenylketones

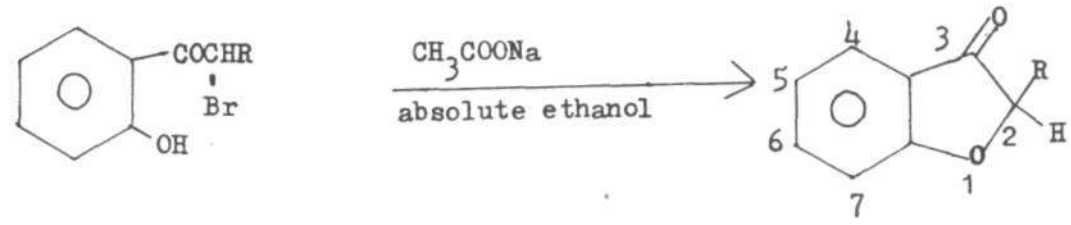
In order to confirm the structure of compound (4) via oxidative rearrangement of ortho-hydroxyphenylketone using TTN/-TMOF/MeOH, another cyclization route was followed. This cyclization route was initially carried out by Fries and Plaffendorf (1910).

The oxidative cyclization of ortho-hydroxyphenylketones was effected by first brominating the ortho-hydroxyphenylketones, followed by dehydrobromination of the product. The selective bromination was carried out using the method of King and Ostrum (1964). This was effected using copper (II) bromide in chloroform-ethylacetate mixture. The cyclization resulted in good yields when the α-bromo-o-hydroxy-phenylketones were treated with sodium ethanoate in absolute ethanol.

Thus, dehydrobromination of the ∝-bromo-o-hydroxypropiophenone (6a) resulted in 60% yield of methyl coumaran-3-one (2-methyl-2,3-dihydro-benzofuran-3-one).



(2)



(7)

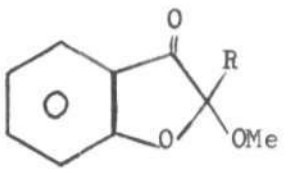
(a) R = CH_3

(b) R = $(CH_2)_2CH_3$

(c) R = $CH(CH_3)_2$

The identity of the methyl benzofuran-3-one (7a) was established by comparing the infrared spectrum of an authentic sample prepared action of 1.3M of hydrochloric acid on ∝-diazo-o-methoxyacetophenone (Bose and Yates, 1954). The infrared data agree very well with those of Bose and Yates (1954) Pouchett and Campel (1974). It is interesting to note that the infrared spectra of coumaran-3-ones exhibit broad carbonyl absorption bands and capable of further resolution into two peaks with a better instrument. The carbonyl absorption band for compound (7a) is at 1710 cm^{-1} (Appendix XIII).

Treatment of the benzofurans (4) with 3M HCl gave 2-alkyl 2-methoxybenzofuran-3-one (8a). The two protecting groups (methoxy groups at C - 3 were easily removed by acid hydrolysis. The cyclic ketal is stable to acid hydrolysis since the non-bonded p-electrons on the ring oxygen interacts favourably with the p- π electrons of benzene.



(8)

(a) R = CH_3
(b) R = $(CH_2)_2CH_3$
(c) R = $CH(CH_3)_2$

Compounds 7 and 8 are similar in structure, except for the methoxy group which replaces hydrogen atom at position C-2 of the 2-alkyl benzofuran-3-one. The structure of the compounds were confirmed by comparing the n.m.r. spectra of compounds (7c) and (8c) (Appendix 14 and 16). The n.m.r. spectrum of compound (7c) showed the presence of methyl protons δ 1.1 (m, 6H) methine proton δ 4.5 (m, 1H) and aromatic protons δ 6.8-7.8 (m, 4H). While the n.m.r. spectrum of the compound (8c) showed the presence of methyl protons δ 0.9 (m, 6H), methine proton δ 2.2 (m, 1H) and aromatic protons δ 6.8-8 (m, 4H). The n.m.r. of the compounds 7 and 8 agree with their structures.

Although this process is a unique transformation whereby ortho-hydroxyphenylketones are transformed into 2-alkyl benzofuran-3-one, the synthetic utility is, however, limited when compared with TTN/TMOF/MeOH - effected oxidation because:

(a) It involves at least a two step reaction, namely: halogenation and dehydrohalogenation.
(b) The percentage yield was low when compared with that of TTN - effect oxidative reaction.

2.5. Summary

From the examination of the oxidation reaction of ortho-hydroxy-phenylketone with TTN/MeOH/TMOF mixture, there was a considerable variation in experimental conditions. The reactions were found to proceed smoothly, cleanly, rapidly and of high yield under anhydrous condition at room temperature. The reaction was non-exothermic and was complete within three hours.

Since the yields obtained in each step were excellent this reaction may constitute a simple and convenient method for the synthesis of benzofuran derivatives.

The oxidative ring closure was found to be applicable to other homologues of acetophenones starting from ortho-hydroxypropiophenone and are of great synthetic utility.

2.6. Conclusion

In view of the fact that the starting meterials, ortho-hydroxy-phenylketones, can be easily prepared through Fries rearrangement of the appropriate esters, this route is superior to other known methods of synthesising 2,3-dihydrobenzofuran derivatives.

This simple and convenient oxidative reaction method for synthesising benzofuran derivatives resulting in clean, rapid and high yields may be used for their commercial preparation since these compounds are isomeric with α-methylene lactones possessing anticancer property (Bozimo 1975). It is recommended that further studies be conducted to test their acute and chronic toxicity as well as clinical trials. After undergoing these tests, they may be used as drugs.

CHAPTER 3

3.0 EXPERIMENTAL

3.1. Materials

Nuclear magnetic resonance (^{1}H N.M.R.) spectra were recorded on a Varian T-60 MHz instrument using tetramethyl silane (TMS) as an internal standard. All samples were run in deuteriochloroform ($CDCl_3$). Peak multiplicities are denoted by s, d, t, q and m; indicating singlet, doublet, triplet, quartet and multiplet, respectively.

Infra-red spectra (IR) were recorded on a Perkin-Elmer Model 710B spectrophotometer at FAST scan. All samples were run neat . Band intensities are denoted by s, m, w, for strong, medium and weak, respectively.

Thin-layer chromatography (t.l.c.) was carried out on plates precoated with Merck silica gel using 1:1 diethylether: petroleum ether (60 - 80°) or 1:1, diethyether: hexane, mobile phases, unless otherwise stated.

Column chromatography was performed using silica gel (0.13 to 0.25mm, 60 - 120 mesh) as stationary phase using same solvent system as above.

Solvents for both reactions and extractions were distilled and dried when required by standard methods.

Reagents

The reagents used and obtained from BDH Chemical Limited Poole, England, were:

Butanoic acid

Pentanoic acid

Hexanoic acid

Thionyl chloride

Carbon disulphide

Copper (II) bromide

Potassium hydroxide

Hydrochloric acid

Ethyl acetate

Petroleum spirit (b.p. 60 - 80°C)

Chloroform

Methanol

Acetone

Hexane

Isopropylether

Ethanol

Diethylether

Anhydrous aluminium chloride

Thallium trioxonitrate (V), trihydrate

Sodium chloride

Anhydrous sodium tetraoxosulphate (VI)

Sodium hydrogen trioxocarbonate (IV)

Silica gel (60 - 120 mesh).

The following reagents were also used and obtained from Aldrich Chemicals Company Limited, Gillingham, England.

Trimethyl orthoformate

ortho-Hydroxypropionphenone and

Triethylamine.

3.2. Preparation of Acyl Halides

Preparation of butanoyl chloride.

Redistilled thionylchloride (18g, 0.15mol) was introduced into 250cm^3 two-necked flask equipped with a reflux condenser and dropping funnel.

The flask was gently heated on a water-bath and butanoic acid (11.0g, 0.13mol.) was added through a separating funnel, cautiously over a period of thirty minutes. After the addition was completed, refluxing continued for another thirty minutes. The product was isolated by distillation (b.p. 98 - 100°C at atmospheric pressure, 12.5g, 86%).

IR ν_{max}(cm^{-1}): 2980(s), 1820(s), 1470(m), 1410(m), 1250(m), 1120(m), 1000(w), 950(w), 870(m).

^{1}H N.M.R. (ppm): δ 1.0 (t, 3H), 1.50 (m, 2H), 2.9 (t, 2H).

The same procedure was used for the preparation of pentanoyl chloride, 3-methylbutanoyl chloride and hexanoyl chloride.

Pentanoyl Chloride

Pentanoic acid (25.5g, 0.25mol.) and redistilled thionylchloride (36.0g, 0.29mol.). The yield of the title compound was 21.0g (70%), b.p. 123 - 125°C.

IR ν_{max}(cm^{-1}): 2980(s), 1810(s), 1470(m), 1410(m), 1250(m), 1110(m), 1000(w), 950(w), 870(m), 720(w).

^{1}H N.M.R. (ppm): δ 1.0 (t, 3H), 1.6 (m, 4H), 2.9 (t, 2H).

3-Methyl butanoyl Chloride

3-methyl butanoic acid (34.0g, 0.4 mol.) and thionyl chloride (47.0g, 0.50 mol.) were used. The yield of 3-methyl butanoyl chloride was 36.0g (76%), b.p. 113 - 114°C.

IR $\nu_{max}(cm^{-1})$: 2990(s), 1810(s), 1470(m), 1410(m), 1250(m), 1120(m), 1000(w), 950(m), 870(m), 720(w).

^1H N.M.R. (ppm): δ 1.1 (d, 6H), 1.6 - 2.4 (m, 2H), 2.7 (d, 1H).

Hexanoyl Chloride

Hexanoic acid (58.0g, 0.50 mol.) and thionyl chloride (72.0g, 0.6 mol) were used. The yield of the title compound was 56.0g (83%), b.p. 148 - 150°C.

IR $\nu_{max}(cm^{-1})$: 2980(s), 1820(s), 1470(m), 1410(m), 1250(m), 1110(m), 1000(w), 950(w), 870(m), 720(w).

^1H N.M.R. (ppm): δ 0.9 (t, 3H), 1.6 (m, 6H), 2.8 (t, 3H).

3.3. Preparation of Phenyl esters

Preparation of Phenyl Pentanoate

Phenol (9.4g, 0.10 mol.) was dissolved in petroleum ether (60-80°C) (150 ml.) in a 250 ml. conical flask; powdered potassium hydroxide (5.60g, 0.1 mol.) was added to the solution and the mixture stirred at room temperature for one hour, after which it was cooled in

ice. Triethylamine (15.15g, 0.15 mol.) was then added, followed by pentanoyl chloride (12.05g, 0.1 mol.). The mixture was allowed to stir for another one hour after which it was shaken with aqueous sodium trioxocarbonate (IV), extracted with diethyl ether and dried over anhydrous sodium tetraoxosulphate (VI). The mixture was filtered and concentrated using a rotary evaporator under reduced pressure. Yield was found to be 15.00g (85%).

IR $\nu_{max}(cm^{-1})$: 3050(w), 2980(s), 2900(m), 1758(s), 1598(s), 1498(s), 1198(m), 740(w).

^1H N.M.R. (ppm): δ 1.0 (t, 3H), 1.6 (m, 2H), 2.8 (t, 2H), 6.6 - 7.8 (m, 5H).

The same procedure was followed for the synthesis of phenyl butanoate, 3-methyl-1-phenyl butanoate (isovalerate) and phenyl hexanoate.

Phenyl butanoate

Phenol (28.2g, 0.30 mol.), potassium hydroxide (16.8g, 0.30 mol.), triethylamine (36.0g, 0.35 mol.) and butanoyl chloride (31.95g, 0.30 mol). Yield: (32.04g, 86%).

IR $\nu_{max}(cm^{-1})$: 3050(w), 2980(s), 2880(m), 1760(s), 1710(w), 1600(s), 1498(s), 1198(w), 740(w).

^1H N.M.R. (ppm): δ 1.0 (t, 3H), 1.7 (m, 2H), 2.5 (t, 2H), 6.7 - 7.6 (m, 5H).

3-Methyl,1-phenylbutanoate

Phenol (18.8g, 0.20 mol.), potassium hydroxide (11.20g, 0.20mol.), triethylamine (30.30g, 0.30 mol.) and 3-methylbutanoyl chloride (24.10g, 0.20 mol.). Yield: 30.1g, 85%.

IR $\nu_{max}(cm^{-1})$: 3080(w), 2980(s), 2880(w), 1760(s), 1595(s), 1490(m), 1190(w), 740(w).

^1H N.M.R. (ppm): δ 1.8 (m, 1H), 2.8 (t, 2H), 6.6 - 7.8 (m, 5H).

Phenyl hexanoate

Phenol (18.8g, 0.20 mol.), potassium hydroxide (11.3g, 0.20 mol.), triethylamine (25.25g, 0.25 mol.) and hexanoyl chloride (26.9g, 0.20 mol.).

Yield: (33.02g, 86%)

IR $\nu_{max}(cm^{-1})$: 3080(w), 2980(s), 2880(w), 1760(s), 1590(s), 1490(m), 1190(m), 740(m).

^1H N.M.R. (ppm): δ 1.0 (t, 3H), 1.8 (m, 4H), 2.8 (t, 2H), 6.6 - 7.8 (m, 5H).

3.4 Preparation of ortho-hydroxyphenylketones

Preparation of 1-(ortho-hydroxyphenyl)pentan-1-one (ortho-hydroxyvalerophenone).

A one litre three-necked round bottom flask was equipped with a dropping funnel, a sturdy mechanical stirrer and an efficient double surface reflux condenser onto which a gas trap was also attached. Anhydrous aluminium chloride (24.50g, 0.18 mol.) and carbon disulphide (150 cm^3), were placed in the flask. The suspension was stirred and the phenyl pentanoate was added dropwise at such a rate that the

solvent boils vigorously (about 45 minutes). Much hydrogen chloride was evolved and it was absorbed by the gas trap. After the addition of the ester, the reaction mixture was refluxed on a water bath until the evolution of the gas ceased (about three hours).

The reflux condenser was then turned downwards and the solvent (CS_2) was distilled off and the water bath was then replaced by oil bath maintained at 160 - 170°C and heated with stirring for about three hours. During this period, more hydrogen chloride gas was evolved, the mixture became very thick and finally became a brown resinous mass, and the stirring continued as long as possible.

The reaction mixture was then allowed to cool and the aluminium chloride complex was decomposed by slowly adding first of dilute hydrochloric acid (150cm^3) and distilled water (100ml); much heat was evolved and a dark oil collected on the surface. The mixture was then allowed to stand overnight and most of the <u>para</u>-hydroxyvalerophenone in the upper layer solidified and was filtered off.

The mixture was then extracted with diisopropylether (200 ml) and the oily layer was separated and dried over anhydrous sodium tetraoxosulphate (VI). Filteration and evaporation of the solvent gave the product which was distilled under reduced pressure. IR and N.M.R. spectra were run. The yield of 1-(<u>ortho</u>-hydroxyphenyl)pentan-1-one was found to be 14.13g (45%), b.p.; 93.9°C at 2.0mm Hg).

IR ν_{max} (cm^{-1}): 3450(s), 2980(m), 1620(s), 1600(s), 1580(s), 1295 - 1150(m), 740(w).

^{1}H N.M.R. (ppm): δ 0.9 (t, 3H), 1.6 (m, 4H), 3.1 (t, 2H), 6.7 - 7.8 (m, 4H), 12.5 (s, 1H).

The same procedure was used for the rearrangement of phenyl butanoate,3-methyl 1-phenyl butanoate and 1-phenyl hexanoate).

1-(ortho-hydroxyphenyl)butan-1-one

(ortho-hydroxy butyrophenone)

1-Phenyl butanoate (41.5g, 0.25 mol.) and aluminium chloride (33.4g, 0.25 mol.).

Yield: 18.68g, (45%)

b.p.: 69°C/1.5mm

IR $\nu_{max}(cm^{-1})$; 3300 (w), 3000(w), 1620(s), 1220(m), 1670(s), 750(m).

^1H N.M.R. (ppm): δ 0.9 (t, 3H), 1.55 (m, 2H), 2.8 (t, 2H), 6.6 - 7.8 (m, 4H), 12.5 (s, 1H).

1-(ortho-hydroxyphenyl)-3-methyl butan-1-one

(ortho-hydroxyisovalerophenone)

3-Methyl 1-phenyl butanoate (24g, 0.13 mol.) and $AlCl_3$ (20.11g, 0.135 mol.) were used.

Yield: (9.12g, 38%).

b.p.: 82 - 84°C/2.0mm.

IR $\nu_{max}(cm^{-1})$: 3400(s), 3050(w), 1640(s), 1600(s), 1500(s), 1220(s), 750(m).

^1H N.M.R. (ppm): δ 1.1 (d, 6H), 1.20 (d, 1H), 2.80 (d, 2H), 6.8 - 7.8 (m, 4H), 10.8 (m).

1-(ortho-hydroxyphenyl)hexan-1-one

(ortho-hydroxyhexanophenone)

1-Phenylhexanoate (40g, 0.208 mol.) and aluminium chloride (27.8g, 0.208 mol.).

Yield: (18.0g, 45%)

b.p.: 102°C - 104°C/1.5mm Hg.

IR $\nu_{max}(cm^{-1})$: 3450(s), 2950(m), 1620(s), 1580(s), 1200(s), 720(m).

^{1}H N.M.R. (ppm): δ 0.8 (t, 3H), 1.2 - 1.8 (m, 6H), 2.8 (t, 2H), 6.7 - 7.8 (m, 4H), 12.4 (s, 1H).

3.5 Oxidative Rearrangement of ortho-hydroxyphenylketone with TTN/TMOF/MeOH

TTN (9.8g, 0.022 mol.) was dissolved in 1:1 TMOF/MeOH mixture (10 cm^3). To the stirred solution was added dropwisely (ortho-hydroxyphenyl)pentan-1-one (1.78g, 0.01 mol.) dissolved in the solvent mixture (TMOF/MeOH) (15 cm^3). After the addition was completed, stirring continued for further 2½ hours at room temperature. At the end of the reaction time, it was then cooled in an ice bath, and the precipitated thallium (I) nitrate was filtered off on a medium porosity-sintered glass funnel.

To the filterate, chloroform (15 cm^3) was added, which was then extracted with saturated sodium hydrogen trioxocarbonate (IV) (20cm^3) solution. The aqueous layer was extracted twice with chloroform (15cm^3) and the combined organic layer was washed three times with

water (10 cm^3) and finally with saturated sodium chloride solution (15 cm^3). The organic layer was dried with anhydrous sodium tetraoxosulphate (VI). The mixture was filtered and concentrated using rotary evaporator. The compound was obtained as oil. I.R., NMR, tlc and column chromatography analyses of the resulting product were then undertaken.

Yield: (2.18g, 86%)

IR $\nu_{max}(cm^{-1})$: 2980(s), 1620(s), 1600(s), 1470(s), 1120 - 1080 730(m).

^1H N.M.R. (ppm): δ 0.8 (m, 9H), 3.1 (s, 3H), 3.4 (s, 3H), 3.5 (s, 3H), 6.80 - 7.40 (m, 4H).

The same procedure was used for the oxidative rearrangement of 1-(ortho-hydroxyphenyl)butan-1-one; 1-(ortho-hydroxyphenyl)3-methyl-butan-1-one and 1-(ortho-hydroxyphenyl)hexan-1-one. The starting materials, yields, i.r. and n.m.r. data are given below.

Oxidative Rearrangement of 1-(ortho-hydroxyphenyl)butan-1-one

TTN (9.8g, 0.022 mol.) and ortho-hydroxyphenyl-1-butanone (1.64g, 0.01 mol.) were used.

Yield: (1.45g, 60%).

IR $\nu_{max}(cm^{-1})$: 2950(s), 1620(s), 1600(s), 1470(s), 1260 - 1180, 730.

^1H N.M.R. (ppm): δ 0.9 (t, 3H), 1.1 (m, 2H), 3.1 (s, 3H) 3.25 (s, 3H), 3.7 (s, 3H), 6.80 - 7.9 (m, 4H).

Oxidative rearrangement of 1-(ortho-hydroxyphenyl)3-methyl-butan-1-one (ortho-hydroxyisovalerophenone)

TTN (9.8g, 0.022 mol.) and 1-(ortho-hydroxyphenyl)-3-methyl-butan-1-one (1.78g, 0.01 mol.) were used.

Yield: (0.87g, 40%).

IR $\nu_{max}(cm^{-1})$: 2980(s), 1610(s), 1120 - 1880 (dimer), 730(m).

^1H N.M.R. (ppm): δ 1.00 (m, 9H), 3.3 (s, 3H), 3.4 (s, 3H), 3.5 (s, 3H), 6.7 - 7.4 (m, 4H).

Oxidative rearrangement of 1(ortho-hydroxyphenyl)hexan-1-one (orthohydroxyhexanophenone)

TTN (4.9g, 0.011 mol.) and ortho-hydroxy 1-phenyl-1-hexanone (1.08g, 0.0056 mol.) were used.

Yield: (1.31g, 85%).

IR $\nu_{max}(cm^{-1})$: 2980(s), 1620(s), 1600(s), 1460 - 1440 (dimer), 730(s).

^1H N.M.R. (ppm): δ 1.0 - 2.1 (m, 11H), 3.30 (s, 3H), 3.50 (s, 3H), 3.60 (s, 3H), 6.80 - 7.40 (m, 4H).

3.6. Bromination of ortho-hydroxyphenylketones

Bromination of 1(ortho-hydroxyphenyl)propan-1-one

Copper (II) bromide (11.17g, 0.050 mol.) was placed in a quick-fit conical flask fitted with a reflux condenser on a magnetic stirrer-hot plate. The ortho-hydroxyketone (4.50g, 0.03 mol.) was dissolved or

diluted with hot chloroform ($25cm^3$) and added to the flask. The resulting reaction mixture was refluxed with vigorous stirring to ensure complete exposure of the copper (II) bromide to the reaction medium until the reaction was complete as judged by a colour change of the solution from green to amber, disappearance of all black solids and cessation of hydrogen bromide evolution. Thereafter, the reaction was left for about three hours.

At the end of the reaction time, the solid product (CuBr) was filtered off at the pump and the filtrate was extracted with diisopropyl ether. The extract was dried with anhydrous sodium tetraoxosulphate (VI). The mixture was filtered, concentrated at the rotary evaporator. The yield of crude ∝-bromo ortho-hydroxypropiophenone was found to be (6.183g, 90%).

IR $\nu_{max}(cm^{-1})$: 3250(s), 3050(w), 1720(s), 1640(s), 1480 - 1440(s/dimer), 1150 - 1280(s), 950(m), 740(s).

The same procedure was used to synthesize the ∝-bromo 1(-ortho-hydroxyphenyl)pentan-1-one and ∝-bromo 1(ortho-hydroxyphenyl)3-methyl-butan-1-one.

∝-Bromo 1-(ortho-hydroxyphenyl)pentan-1-one

Copper (II) bromide (4.85g, 0.022 mol.) and 1-(ortho-hydroxyphenyl)-pentan-1-one (2.67g, 0.015 mol.) were used.

Yield: (3.375g, 90%)

IR $\nu_{max}(cm^{1})$: 3250(s), 1710(s), 1640(s), 1600(s), 1450(m), 1360(m), 1310(m), 740(m).

α-Bromo 1-(ortho-hydroxyphenyl)3-methylbutan-1-one

Copper (II) bromide (4.85g, 0.022 mol.) and 1-(ortho-hydroxyphenyl)-3-methylbutan-1-one (2.67g, 0.015 mol.) were used.

Yield: (3.19g, 85%).

IR $\nu_{max}(cm^{-1})$: 3000(s), 1710(s), 1640(s), 1450(s), 1360(m), 1310(s), 740(m).

3.7. Cyclization of α-bromo-1(ortho-hydroxyphenyl)propan-1-one

A mixture of α-bromo-o-hydroxyphenylpropan-1-one (8.3g 0.03 mol.) of sodium ethanoate (5.0g, 0.06 mol.) absolute ethanol in $20cm^3$ was heated under reflux for thirty minutes, cooled, and poured into cold water ($50cm^3$). The crude product was separated and treated with boiling water ($30cm^3$)

after chilling, glistering yellow crystals of coumaran-3-one separated and were dried.

Yield: (5.10g, 60%)

IR $\nu_{max}(cm^{-1})$: 3050(w), 3030(s), 1710(s), 1600(s), 1450(s), 1350(m), 1310(s), 740(m).

^1H N.M.R. (ppm): δ 1.7 (d, 3H), 6.5 - 7.8 (m, 4H).

The same procedure was used for the cyclization of α-bromo 1(ortho-hydroxyphenyl)pentan-1-one and α-bromo 1(ortho-hydroxyphenyl)3-methyl-butan-1-one.

Cyclization of α-bromo 1-(ortho-hydroxyphenyl)pentan-1-one

α-bromo-o-hydroxyphenyl)pentan-1-one (3g, 0.01 mol.) and (1.64g, 0.02 mol.) of sodium ethanoate.

Yield: (1.13g, 55%).

IR $\nu_{max}(cm^{-1})$: 2990(s), 1700(s), 1602(s), 1440(s), 1300(m), 1200(s), 1120(m), 960(s), 840(m), 740(s).

^1H N.M.R. (ppm): δ 0.9 (t, 3H), 1.8 - 2.2 (m, 2H), 4.5 (m, 1H), 6.8 - 7.8 (m, 5H).

Cyclization of α-bromo 1-(ortho-hydroxyphenyl)3-methylbutan-1-one

α-Bromo-o-hydroxyphenyl-3-methylbutan-1-one (6g, 0.02 mol.) and (3.28g, 0.04 mol.) of sodium ethanoate.

Yield: (1.05g, 51%).

IR $\nu_{max}(cm^{-1})$: 2980(s), 1710(s), 1610(s), 1440(s), 1300(m), 1200(s), 1120(m), 960(s), 840(m), 740(s).

^1H N.M.R. (ppm): δ 1.1 (m, 6H), 4.5 (d, 1H), 6.8 - 7.8 (m, 4H).

REFERENCES

Adams, R. and Rindfusz, R.E. (1919). Cyclic ethers from o-allylphenols-methylene coumarans. Journal of the American Chemical Society, 41: 648 - 649.

Ahlbretch, H. and Hagena, D. (1976). Study on the reaction of tautomeric imines with TTN. Chemical Abstract, 85: 123507h

Amustutz, E.D., Cann, J.R. and Fehnel, E.A. (1944). Reaction of β-halogen ethers with metals, mechanism of the reaction and related processes. Journal of Organic Chemistry, 9: 310 - 312.

Anderson, W.K., LaVoie, E.J. and Bottaro, J.C. (1976). Use of 2,3 dichloropropene and 1,3 dichlorobut-2-ene as synthesis for heterocyclic compounds. Synthesis of 2-methyl benzo[b]furans, 2-methylbenzo[b]thiophenes and 4-methyl-2H-chromene. Journal of Chemical Society, Perkin Transaction 1, 1 - 2.

Antus, S., Nogradi, M., Baitz-Gacs, E., Radics, L., Becker, H.D., Karlsson, B. and Pilotti, A.M. (1978). Oxidation of vanillins with TTN. An exercise in NMR spectroscopy and photochemistry. Tetrahedron, 34: 2573 - 2577.

Belanger, P.C., Rooney, C.S., Robinson, F.M. and Sarett, L.H. (1978). Use of the TTN catalysed rearrangement of ketones in the synthesis of an acidic morphian derivatives. Journal of Organic Chemistry, 43: 908 - 909.

Bertsch, R.J. and Quellete, R.J. (1974). Formation of nitrate esters in TTN oxidation of alkenes. Journal of Organic Chemistry, 39: 2755 - 2759.

Bisagni, E., Buu-Hoi, N.P. and Royer, R. (1955). Oxygen heterocycles (III) reactivity of benzofuran and 2-alkylbenzofurans (IV) 2-benzoyl benzofurans and related compounds with biological interest. Chemical Abstract, 50: 9372e

Bohlman, F. and Zdero, C., (1968). Abnormal Grignard reaction. Tetrahedron Letters, 24: 3683 - 3684.

Bordin, F., Baccichetti, F., Marciani, S., Baccichett, F., Acqua, F. and Rodighiero, G. (1969). Studies on the photosensitizing properties of angelicin an angular furocoumarin forming only mono function adducts with the pyrimidine bases of DNA. Chemical Abstract, 71: 160136m.

Bose, A.K., and Yates, P. (1954). Conversion of ∝-diazo-o-methyoxy-acetophenone to coumaranone. Journal of the American Chemical Society, 74: 4703 - 4704.

Bozimo, H.T. (1975). Research Report to Professor E.C. Taylor, Princeton, PP. 1 - 31.

Buchi, G., Chu, P.S., Hoppmann, A., Mak, C.P. and Pearce, A. (1978). Oxidation of substituted hydroquinone monoalkyl ethers to p-benzo-quinone monoketals. Journal of Organic Chemistry, 43: 3983 - 3987.

Cagniant, P. and Cagniant D. (1975). Recent Advances in the Chemistry of Benzo[b]furan and its derivatives, Part I: Occurence and synthesis. In: Katritsky, A.R. and Boulton, A.J. (eds.) Advances in Heterocyclic Chemistry. Academic Press, New York, Vol. 18, PP. 337 - 482.

Castro, C.E., Havlin, R., Honwad, V.K., Malte, A. and Moje, S. (1969). Copper(I) substitutions scope and mechanisms of cuprous acetylide substitutions. Journal of the American Chemical Society, 91: 6469-6470.

Chatterjea, J.N., and Mehrota, V.H. (1963). Synthesis of furano compounds XXIV. Condensed derivatives of γbrazan. Journal of Indian Chemical Society, 40: 2003 - 2004.

Cruickshank, P.A., Lee, E.T. and Lupichuk, A. (1970). Antimalarias I. Aminoalkylamino derivatives of 2,3-dihydrofuroquinolines. Journal of Medicinal Chemistry, 13: 1110 - 1114.

Dewar, M.J.S. and Hart, L.S. (1970). Aromatic rearrangements in the benzene series I. Fries rearrangement of phenylbenzoate: the benzoylation of phenol. Tetrahedron, 26: 973 - 976.

Elderfield, R.C. and Meyer, V.B. (1951). Benzofuran and its derivatives. In: Elderfield, R.C. (ed.) Heterocyclic Compounds - John Wiley and Sons Inc., New York, Vol 2, PP. 1 - 67.

Fodor, G. and Kova'cs, O. (1949). Synthesis of adrenalinelike compounds. Journal of the American Chemical Society, 71: 1045 - 1047.

Forcellese, M., Alfonsi, C., Calvitti, S. and Mincione, E. (1983). Intramolecular cyclization reaction of some 2-alkenylphenols with TTN. Heterocycles, 20: 1559 - 1562.

Fries, K. and Plaffendorf, W. (1910). Condensation products of coumaranone and its transformation into oxindirubin. Chemical Abstract, 5: 1430.

Geissman, T.A. and Hinreiner, E. (1951). Dehydrogenation of coumaranes to prepare coumarones. Journal of the American Chemical Society, 73: 782 - 783.

Hammond, P.R. (1962). Nuclear magnetic resonance of the methyl esters of some inorganic oxyacids. Journal of Chemical Society, 1370 - 1372.

Hattori, K. and Hirai, J. (1970). -(Benzofuryloxy)acetic acid derivatives of 7-aminocephalosphoranic acid. Chemical Abstract, 72: 12747y.

Hilgetag, G. and Martini, A. (1972). Preparative Organic Chemistry. John Willey and Sons, Inc., New York, PP. 1068 - 1070.

House, H.O. (1972). Modern Synthetic Reactions. Benjamin, N.A. Inc., London, PP. 802 - 803.

Hunsberger, I.M. (1950). Determination of bond fixation in cyclic systems I - Naphthalene. Journal of the American Chemical Society, 72: 5626 - 5628.

Kabbe, H.J. (1963). Oxidation with Thallium(III) acetate. Chemical Abstract, 58: 1376c.

Kabbe, H.J. (1978). A simple synthesis of 4-chromanones. Synthesis, (12): 886 - 887.

Kende, A.S. and Rutledge, A. (1978). Product control in oxidative arylbenzyl coupling of a phenolic 1,4-diarylbutane. Synthetic Communication, 8: 245 - 250.

Kienzle, F. (1972). Reaction of isonitriles with TTN: An effective synthesis of carbamates. Tetrahedron Letters, 28: 1771 - 1774.

King, L.C. and Ostrum, K. (1964). Selective bromination with Copper(II) bromide. Journal of Organic Chemistry, 29: 3459 - 3461.

Kneen, G. and Maddocks, P.J. (1986). A convenient synthesis of 4-hydroxybenzo[b]furan, (karanjol). Synthetic Communication, 16: 1635 - 1640.

Kurosawa, H. (1978). Thallium: annual survey covering the year 1978. Journal of Organometallic Chemistry, 158: 221 - 233.

Kurosawa, H. (1979). Thallium: annual survey covering the year 1979. Journal of Organometallic Chemistry, 183: 265 - 280.

Lee, J.B. and Price, M.J. (1964). Oxidation of olefins with thallium(III) salts(I) of cyclohexene. Tetrahedron, 20: 1017 - 1019.

Lethbridge, A., Norman, R.O.C. and Thomas, C.B. (1975). Neighbouring group effects in the oxidation of olefins by mercury(II), thallium(III) and lead(IV) acetates. Journal of Chemical Society, Perkin Transaction, 2465 - 2471.

Levai, A. and Tokes, A. (1982). Synthesis of aurones by the oxidative rearrangement of 2'-hydroxy chalcones with TTN. Synthetic Communication, 12: 701 - 707.

McKillop, A. Bromley, D. and Taylor E.C. (1969). Thallium in organic synthesis (VIII). Preparation of aromatic bromides. Tetrahedron Letters, 25: 1623 - 1629.

McKillop, A., Fowler, J.S., Zelekso, M.J., Hunt, J.D., Taylor, E.C. and McGillivray, G. (1969). Thallium in organic synthesis (IX). Facile thallation of aromatic compounds with TTFA. Tetrahedron Letters, 25: 2423 - 2426.

McKillop, A., Fowler, J.S., Zelekso, M.J., Hunt, J.D., Taylor, E.C. and McGillivray, G. (1969). Thallium in organic synthesis X. A one step synthesis of aryl iodides. Tetrahedron Letters, 25: 2427 - 2430.

McKillop, A., Hunt, J.D. and Taylor, E.C. (1972). Thallium in organic synthesis (XXXV). Oxidation of cyclohexanonesto adipoins using TTN. Journal of Organic Chemistry, 37: 3381 - 3383.

McKillop, A., Oldenziel, O.H., Swann, B.P., Taylor, E.C. and Robey, R. (1971). Thallium in organic synthesis XXVIII. Selective oxidation of acetylene to carboxylic acids, acyloins, benzils and arylacetic acids with TTN. Journal of the American Chemical Society, 93: 7331 - 7333.

McKillop, A., Oldenziel, O.H., Swann, B.P., Taylor, E.C. and Robey, R.L. (1973). Thallium in organic synthesis XXXIV. Oxidation of acetylene with TTN. Journal of the American Chemical Society, 95: 1296 - 1298.

McKillop, A., Perry, D.H., Edwards, M., Antus, S., Farkas, L., Nogradi, M., and Taylor, E.C. (1976). Thallium in organic synthesis XLII. Direct oxidation of 4-substituted phenol to 4,4-disubstituted cyclohexa-2,-5-dienones using TTN. Journal of Organic Chemistry, 41: 282 - 286.

McKillop, A., Raphael, R.A. and Taylor, E.C. (1973). Thallium in Organic synthesis XXXI. Oxidation cleavage of glycols by thallium salts. Journal of Organic Chemistry, 37: 4204 - 4206.

McKillop, A., Swann, B.P., Ford, M.E., Taylor, E.C. (1973). Thallium in organic synthesis XXXVIII. Oxidation of chalcones, deoxybenzoins and benzoins with TTN. Journal of the American Chemical Society, 95: 3641 - 3646.

McKillop, A., Swann, B.P., and Taylor E.C. (1970). Thallium in organic synthesis XVI. Preparation of p-quinones by oxidation of phenols and with TTFA. Tetrahedron, 26: 4031 - 4039.

McKillop, A., Swann, B.P., Taylor, E.C. (1971). Thallium in organic synthesis XXXIII. One step synthesis of methyl aryl acetates from acetophenones using TTN. Journal of the American Chemical Society, 93: 4919 - 4921.

McKillop, A. and Taylor, E.C. (1973). Recent advances in organothallium chemistry In: Stone, F.G.A. and Robert, W. (eds.). Advances in Organometallic Chemistry, Academic Press, London, Vol. 11, PP. 147 - 206.

McKillop, A. and Taylor, E.C. (1973). Thallium in organic synthesis. A review with 54 references. Chemistry in Britain, 9: 4 - 11.

McKillop, A., Turelle, A.G. and Taylor, E.C. (1977). Thallium in organic synthesis 46. Oxidative coupling of aromatic compounds using thallium (III) trifluoroacetate. Synthesis of biaryls. Journal of Organic Chemistry, 42: 764 - 765.

McKillop, A., Young, D.W., Edwards, M., Hung, R.P. and Taylor, E.C. (1978). Thallium in Organic synthesis 51. Oxidation of enolizable ketones to α-Nitrato ketones by thallium (III) nitrate in acetonitrile. Journal of Organic Chemistry, 43: 3773 - 3774.

Mustafa, A. (1974). Benzofurans. In: Weissberger, A. and Taylor, E.C. (eds.) The Chemistry of Heterocyclic Compounds. John Willey and Sons Inc., Vol. 29, PP. 1 - 28, 251 - 279.

Nohara, A., Umetani, T. and Sanno, Y. (1974). Antianaphylactic agents II. Oxidation and reduction of 4-oxo-4H-1-benzopyran-3-carboxaldehydes. Tetrahedron, 30: 3553 - 3556.

Noyes, A.A. and Garner, C.S. (1936). Strong oxidizing agents in trioxonitrate (V) acid. Oxidation potential of thallous-thallic salts. Journal of the American Chemical Society, 58: 128 - 130.

Ogata, Y. and Tabuchi, H.C. (1964). Mechanism of the Fries reaction. Tetrahedron, 20: 1661 - 1663.

Okeniyi, O.S. (1983). Synthesis and cyclisation of α-bromo-o-hydroxy-phenylketones. Unpublished B.Sc. Dissertation, Ahmadu Bello University, Zaria - Nigeria.

Porte, A.L., Gutowsky, H.S. and Hunsberger, I.M. (1960). Determination of double-bond character in cyclic system (V). Proton chemical shifts in chelated derivatives of C_6H_5, naphthalene and phenanthrene. Journal of the American Chemical Society, 82: 5057 - 5059.

Pouchert, C.J. and Campel, J.R. (1974). The Aldrich Library of N.M.R. Aldrich Chemical Company Inc., Milwaukee, Wisconsin, Vol. VI, PP. 26c, 80A.

Pouchert, C.J. (1975). The Aldrich Library of Infrared Spectra. Aldrich Chemical Company Inc., Milwaukee, Wisconsin, PP. 762, 1099H.

Quellete, R.J. and Bertsch, R.J. (1976). Formation of nitrate esters by the oxidation of alkenes and cyclopropanes with TTN in pentane. Journal of Organic Chemistry, 41: 2782 - 2783.

Ramage, G.R. and Stead, C.V. (1953). Furanochromones derived from quinol. Journal of Chemical Society, 49: 3602 - 3603.

Rasmussen, R.S. and Brattain, R.R. (1949). Infrared spectra of carboxylic acid derivatives. Journal of the American Chemical Society, 71: 1073 - 1079.

Rasmussen, R.S., Tunnicliff, D.O. and Bratain, R.R. (1949). Infrared and ultraviolet spectroscopic studies on ketones. Journal of the American Chemical Society, 71: 1068 - 1072.

Rene, L. and Royer, R. (1973). Coumarilic acid amides and nitriles. Chemical Abstract, 79: 91982s.

Sargent, M.V. and Cresp, T.M. (1979). Benzo[b]furan and Dibenzofuran. In: Sammes, P.G. (ed.). Comprehensive Organic Chemistry (The Synthesis and Reactions of Organic Compounds). Pergamon Press, Oxford, Vol.4, PP. 736 - 738.

Schreiber, F.G. and Stevenson, R. (1976). Synthesis of 5-(3-hydroxy-propyl)-2 (3',4'-methylenedioxyphenyl)benzofuran and related styrax extracts. Journal of Chemical Society, Perkin Transaction I: 1547 - 1547.

Seshadri, T.R., Aneja, R. and Mukerjee, S.K. (1957). Chalkones and flavonones in plant products. Tetrahedron, 13: 203 - 205.

Shulgin, A.T. and Baker, A.W. (1963). Solvent effects on the Claisen rearrangement of β-methylallylphenyl ether. Journal of Organic Chemistry, 28: 2468 - 2469.

Singh, H. and Verma, J.C. (1963). Heterocyclic compounds with pharmacological possibilities -2-nitro phenylbenzofuran. Journal of Indian Chemical Society, 40: 385 - 386.

Spoerri, P.E. and Dubois, A.S. (1962). The Hoesch synthesis. In: Adams, R., Bachmann, W.E., Blatt, A.H., Fieser, L.F., Johnson, J.R. and Snyder, H.R. (eds.) Organic Reactions. John Willey and Sons, Inc., New York, Vol. 5, PP. 387 - 400.

Suresh, R.V., Rukmani, I. and Iyer, P. (1985). Synthesis of erythrinin A, a naturally occuring pyranoisoflavenols. Tetrahedron, 41: 2479-2482.

Taylor, E.C., Altland, H.W., Danforth, R.H., McGillivray, G. and McKillop, A. (1970). Thallium in organic synthesis XV. Synthesis of phenol and aromatic nitriles. Journal of the American Chemical Society, 92: 3520 - 3522.

Taylor, E.C., Altland, H.W., McGillivray, G. and McKillop, A. (1970). Thallium in organic synthesis XXIV. One step synthesis of aliphatic α-acyloxy carboxylic acids. Tetrahedron Letters, 26: 5285 - 5289.

Taylor, E.C., Chiang, C.S., McKillop A. and White, J.F. (1976). Oxidative rearrangement via oxythallation with thallium (III) nitrate supported on clay. Journal of the American Chemical Society, 98: 6750 - 6751.

Taylor, E.C., Danforth, R.H. and McKillop, A. (1973). Thallium in organic synthesis XXXV. New synthesis of arylnitroso compounds. Journal of Organic Chemistry, 38: 2688 - 2689.

Taylor, E.C., Robey, R.L., Liu, K.T., Favre, B., Bozimo, H.T., Conley, R.A. and Chiang, C.S. (1976). Novel oxidative rearrangement with thallium (III) nitrate (TTN) in trimethyl orthoformate (TMOF). Journal of the American Chemical Society, 98: 3037 - 3038.

Taylor, E.C., Robey, R.L. and McKillop, A. (1972). New synthesis of allenic ester. Journal of Organic Chemistry, 37: 2797 - 2799.

Varma, R.S. and Varma, M. (1982). Oxidation of flavonones with TTN. A convenient route to flavones. Synthetic Communication, 12: 927 - 930.

Vogel, A.I. (1978). A Textbook of Practical Organic Chemistry including Qualitative Organic Analysis. Longman Group Limited, London, PP. 268-270, 497 - 499, 744 - 752.

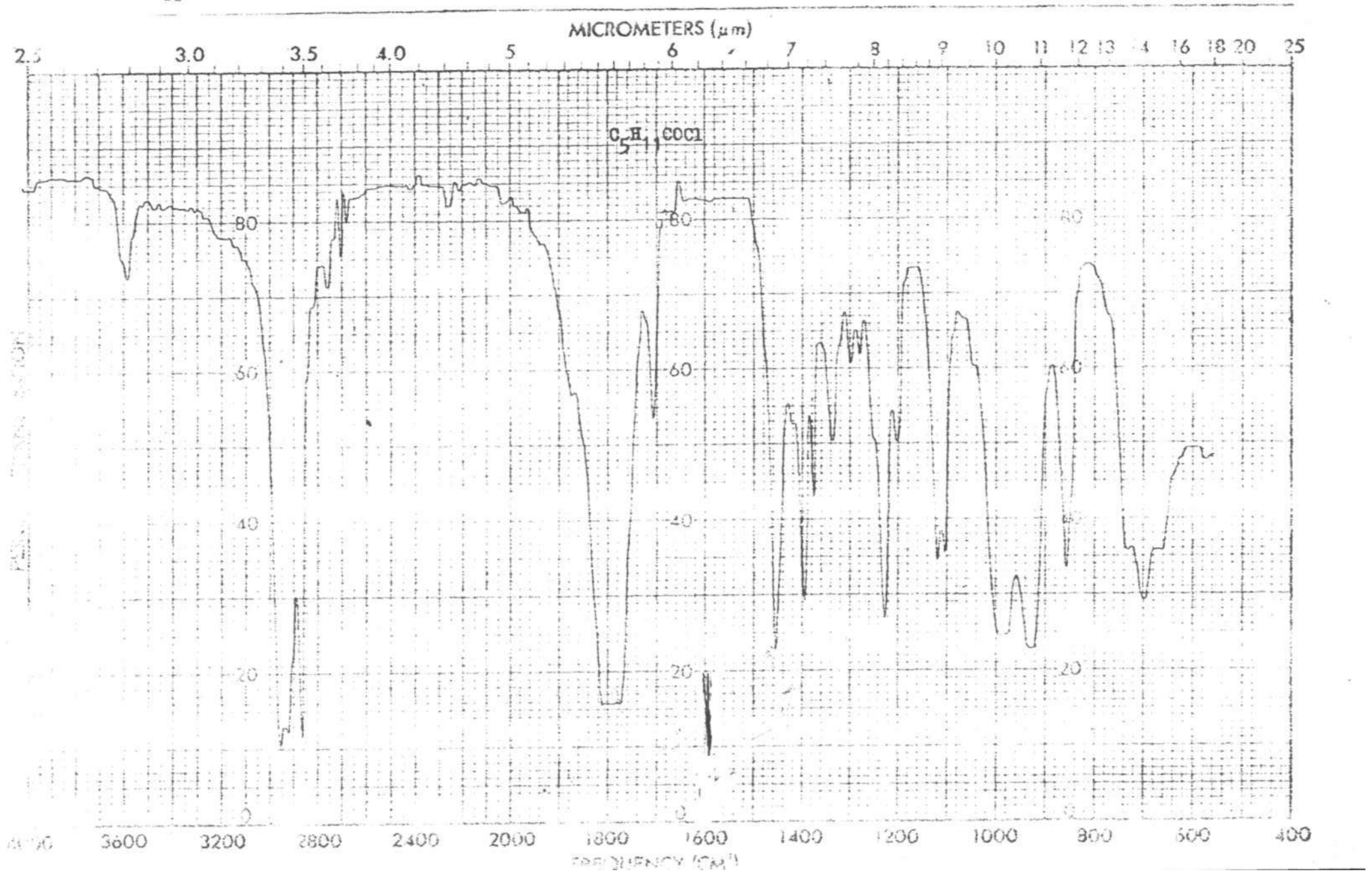
Walker, J.A. and Pillai, M.D. (1977). Oxidative rearrangement of α-methoxystyrene derivatives with thallium (III). Synthesis of 2-aryl alkanoic acids. Tetrahedron Letters, 33: 3707 - 3710.

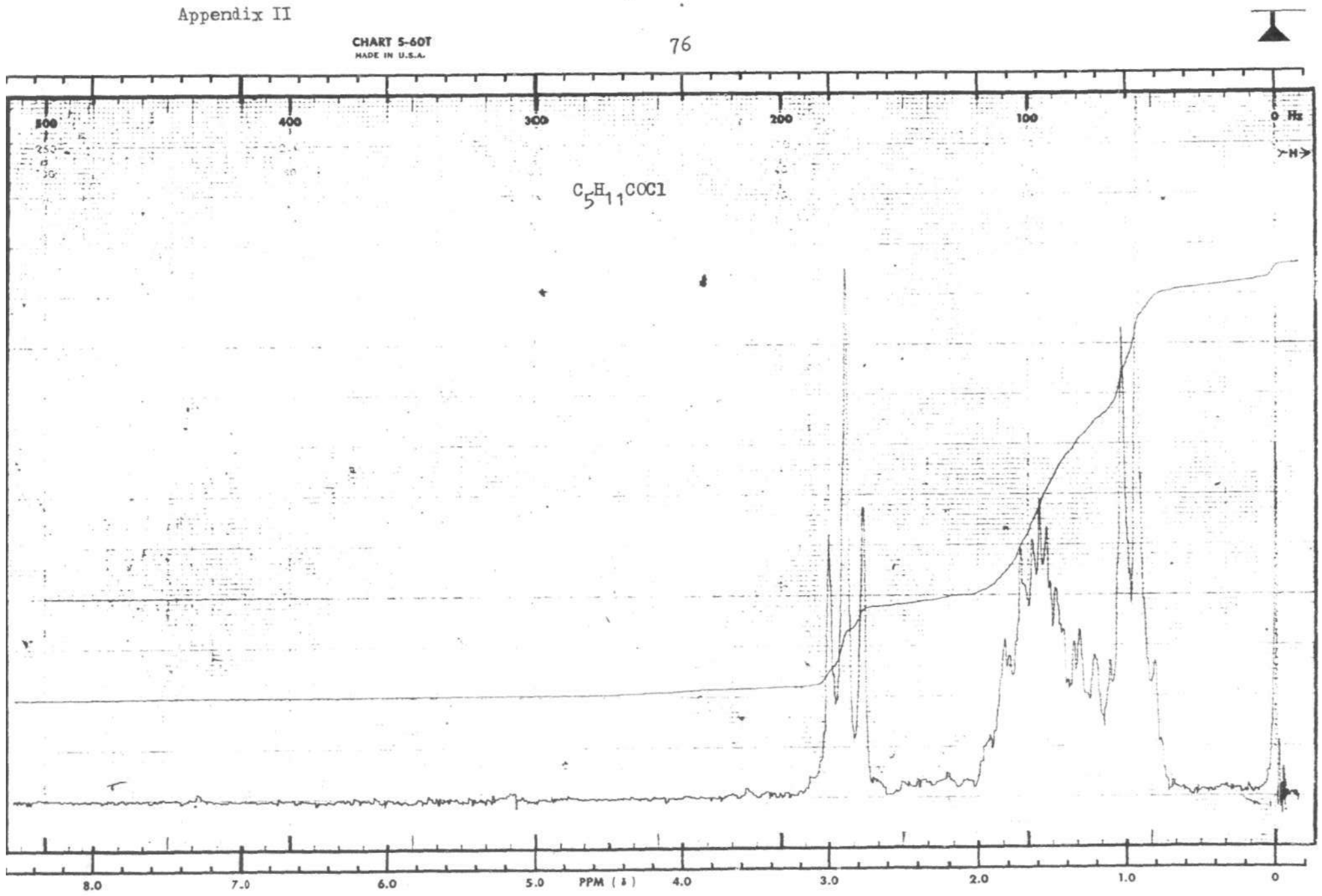
Wearatunga, G., Jaworska-Sobiesiak, A., Horne, S. and Rodrigo, R. (1987). A general synthesis of dihydrobenzofurans by intramolecular conjugate addition. Canadian Journal of Chemistry, 65: 2019 - 2023.

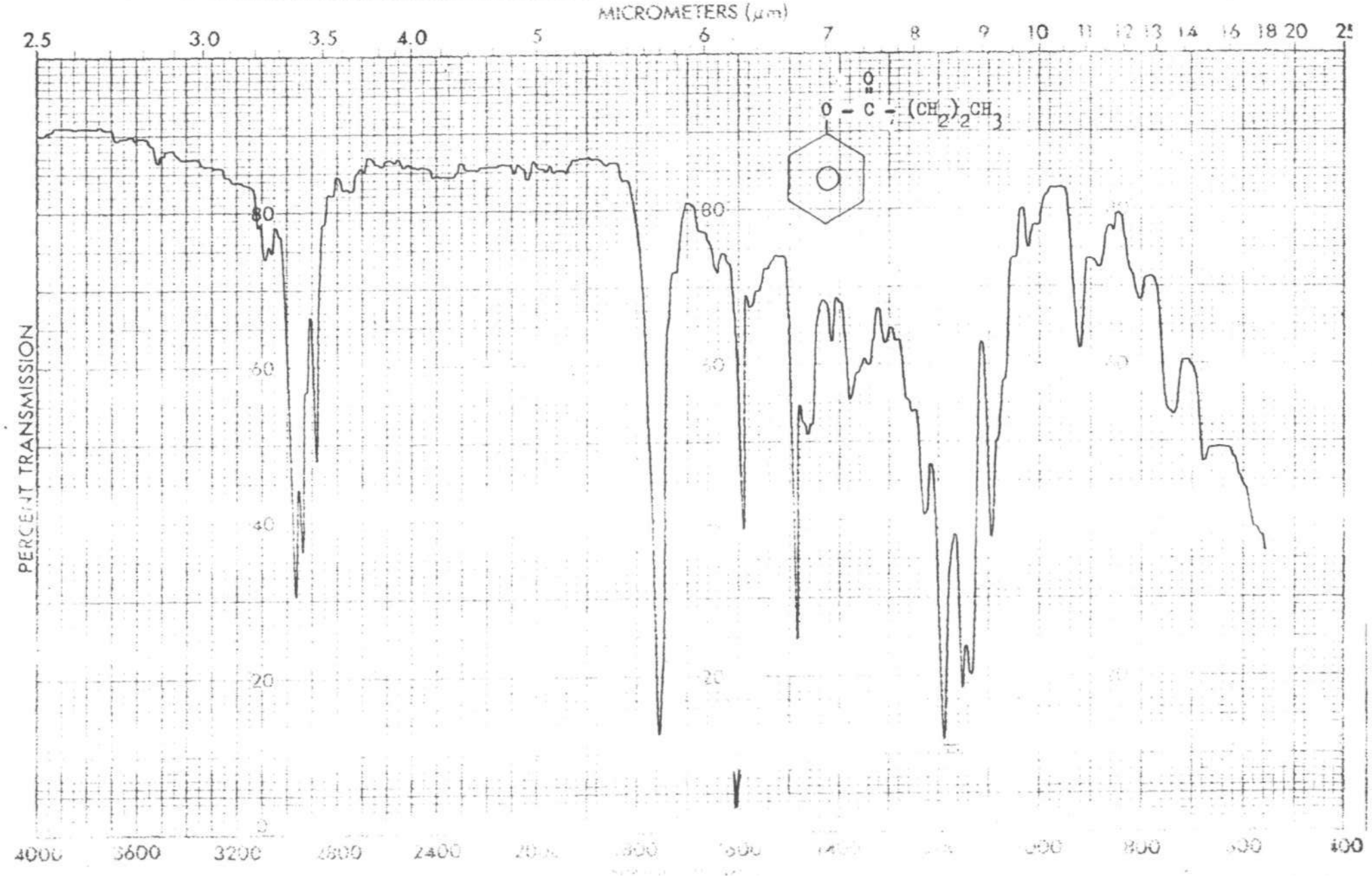
Wheeler, T.S., Philbin, E.M. and Swirski, J. (1956). Action of alkaline hydrogen peroxide on 2'-hydroxy chalkones. Chemistry and Industry, 1018 - 1019.

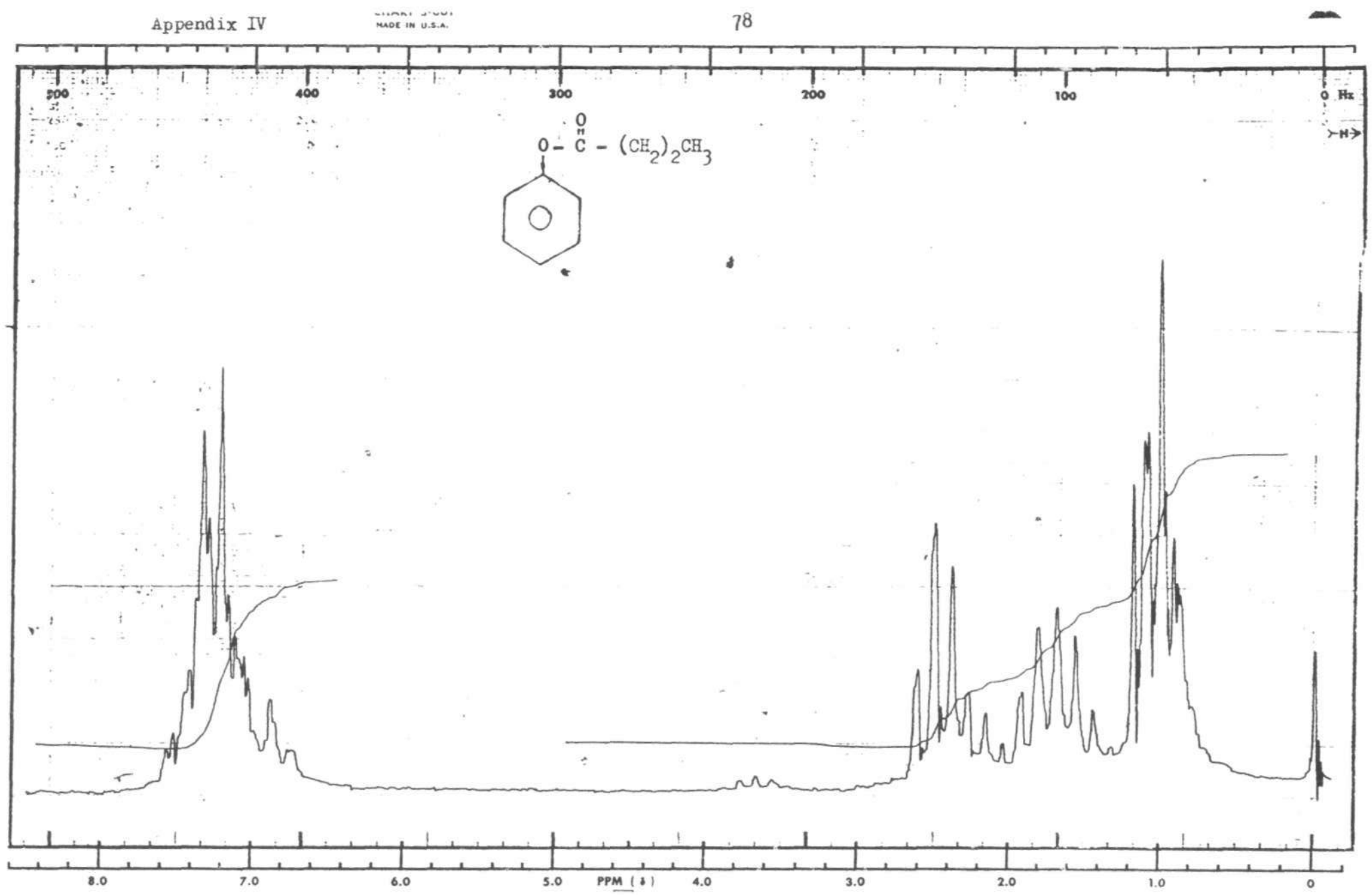
Worth, B.R., McLeod, J.K. and Wells, R.J. (1972). Synthesis of benzofuranoid systems II. Total synthesis of cyperaquinone and conicaquinone. Tetrahedron Letters, 28: 241 - 241.

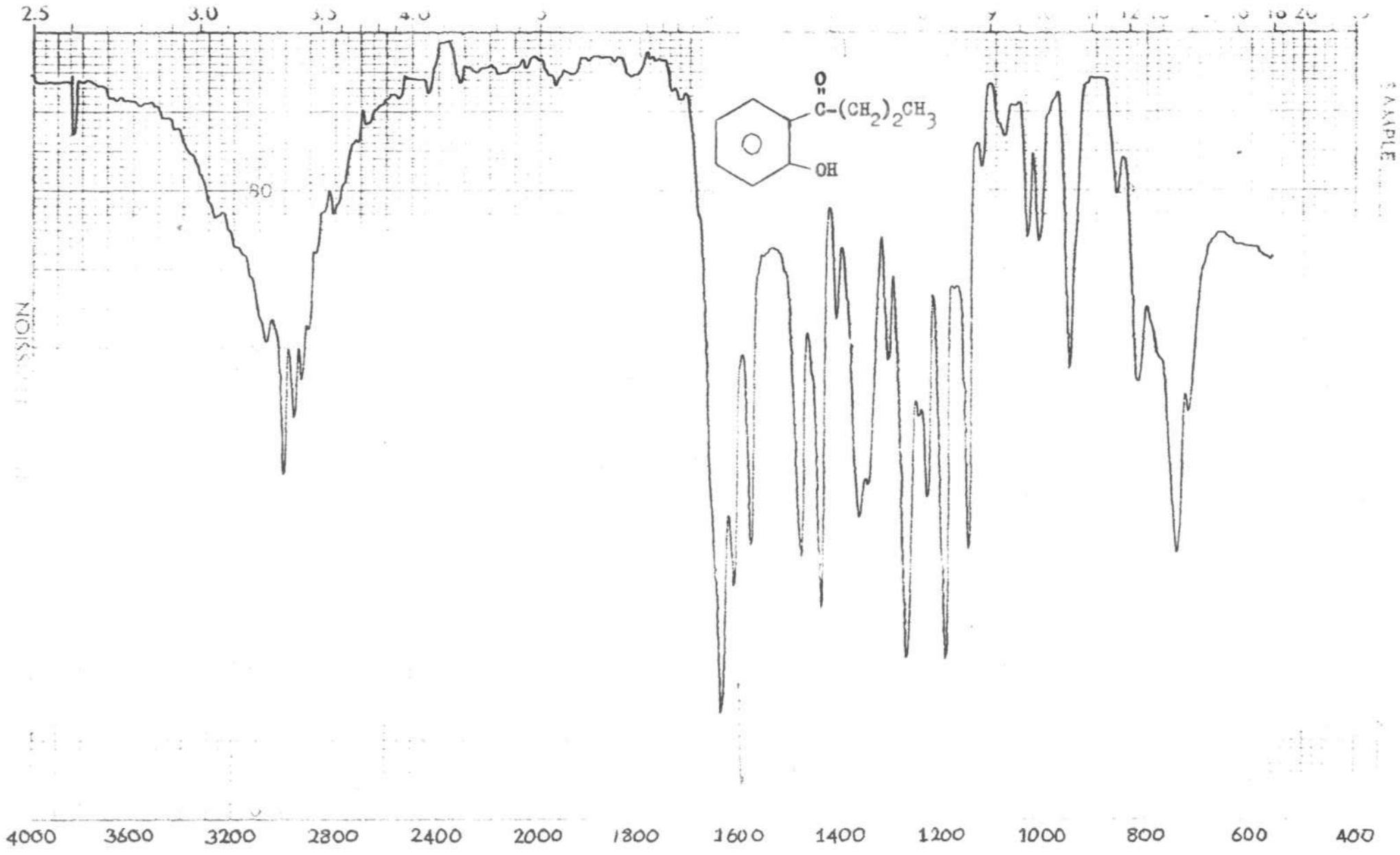
Appendix I

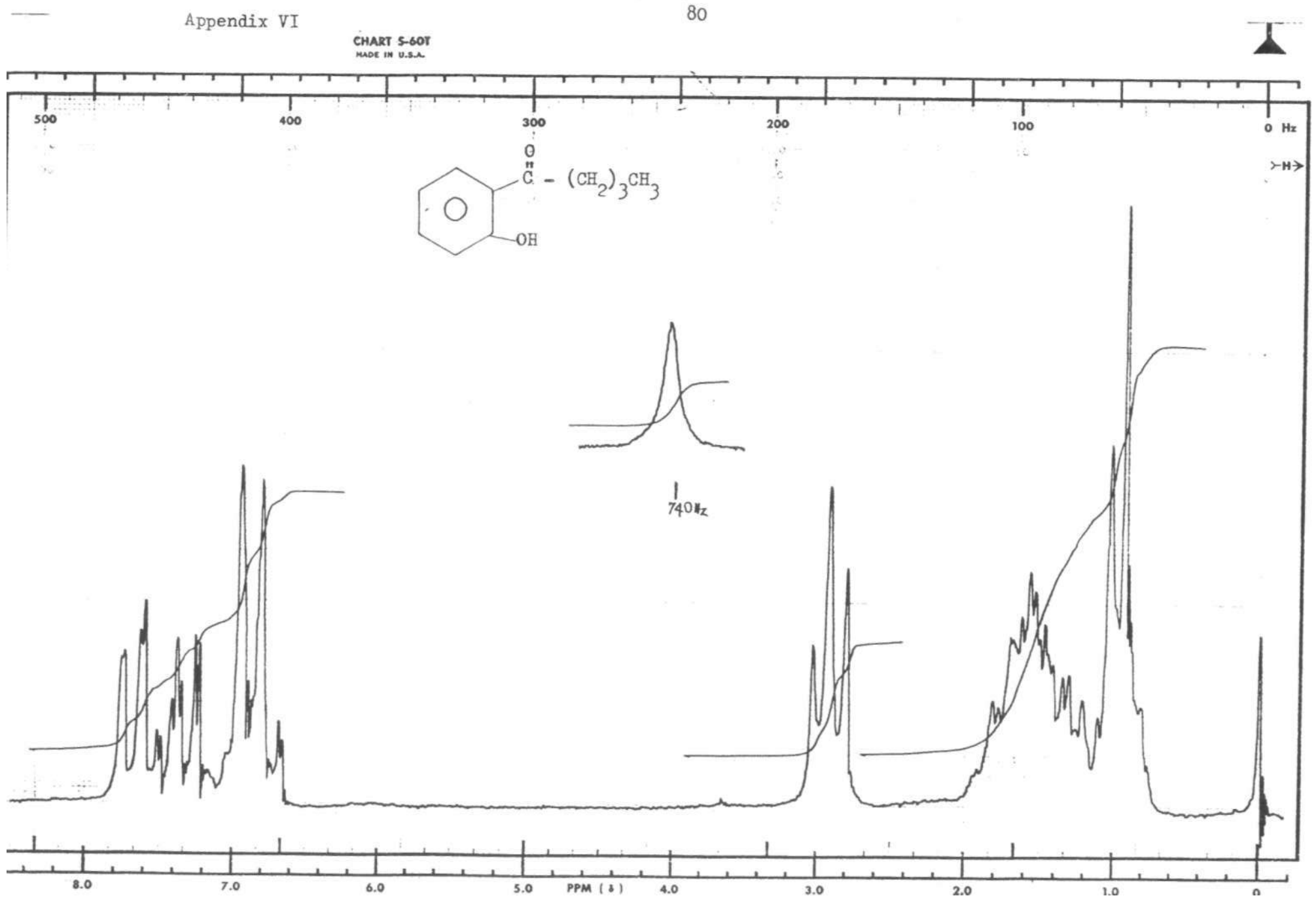

MICROMETERS (μm)
2.5
3.0
3.5
4.0
5
6
7
8
9
10
11
12
13
14
16
18
20
25
$C_5H_{11}COCl$
80
60
40
20
0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

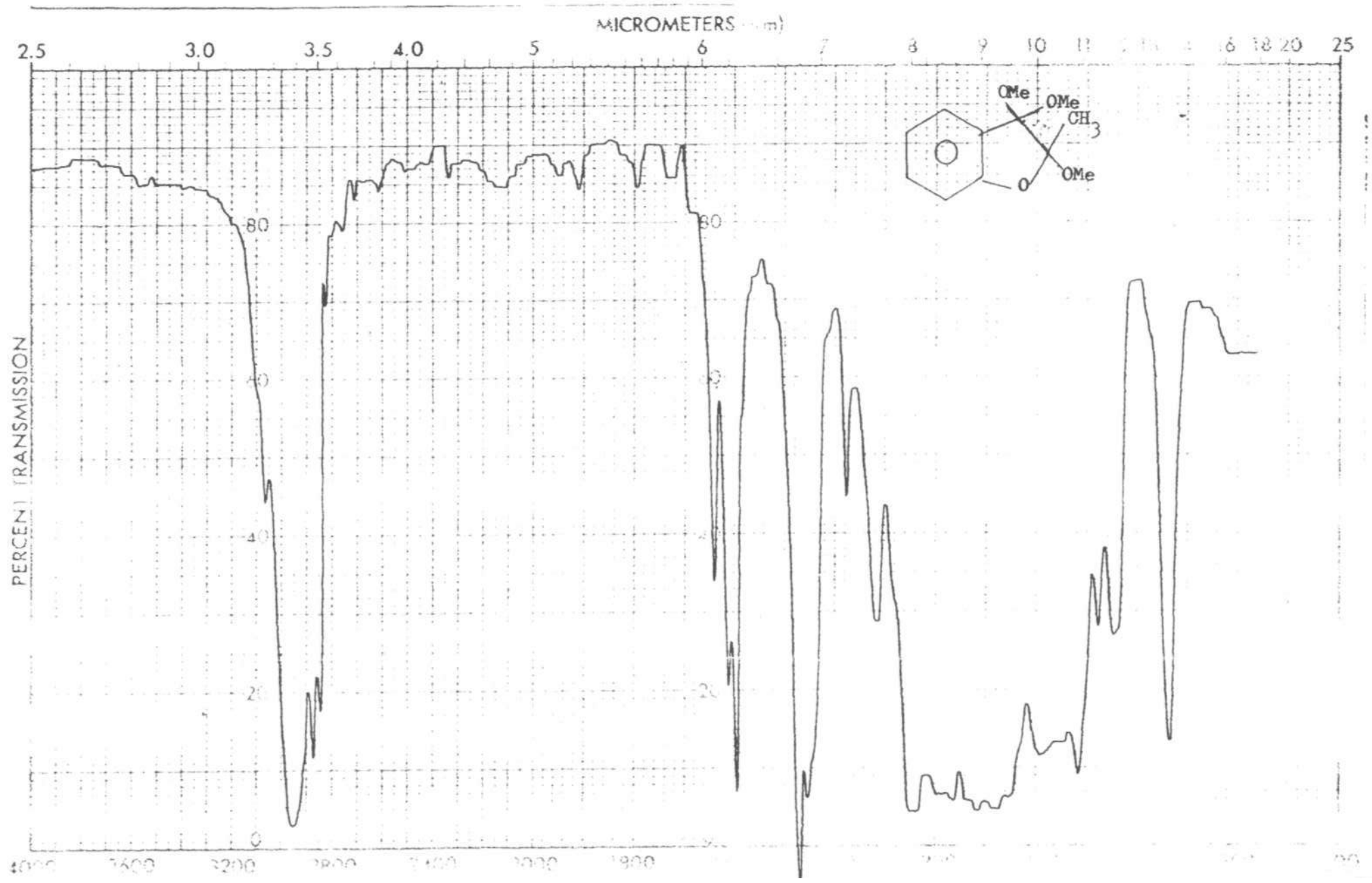

CHART 5-60T
MADE IN U.S.A.
500
400
300
200
100
0 Hz
H
$C_5H_{11}COCl$
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

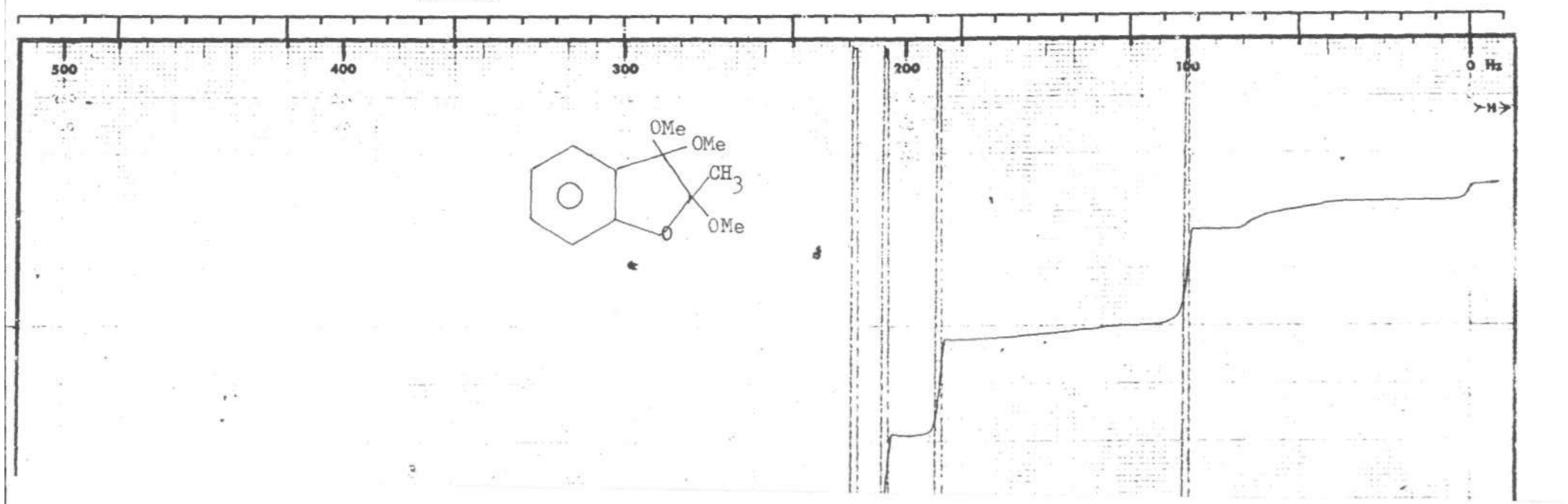

MICROMETERS (μm)
2.5
3.0
3.5
4.0
5
6
7
8
9
10
11
12
13
14
15
18
20
O
O – C – (CH2)2CH3
PERCENT TRANSMISSION
80
60
40
20
0
4000
3600
3200
2400
800
400


O
O – C – (CH2)2CH3
500
400
300
200
100
0 Hz
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

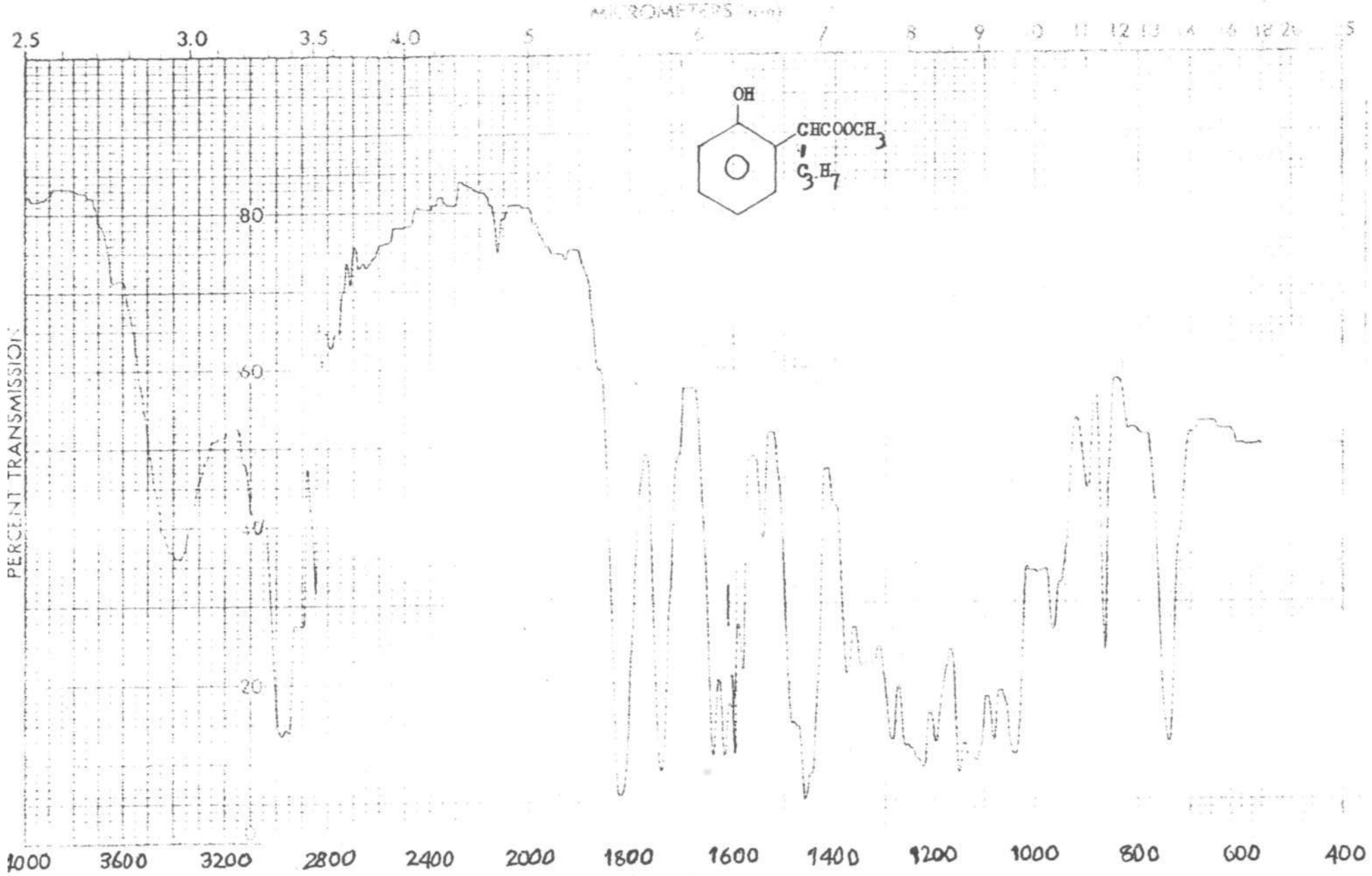

2.5
3.0
60
O
C-(CH2)2CH3
OH
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

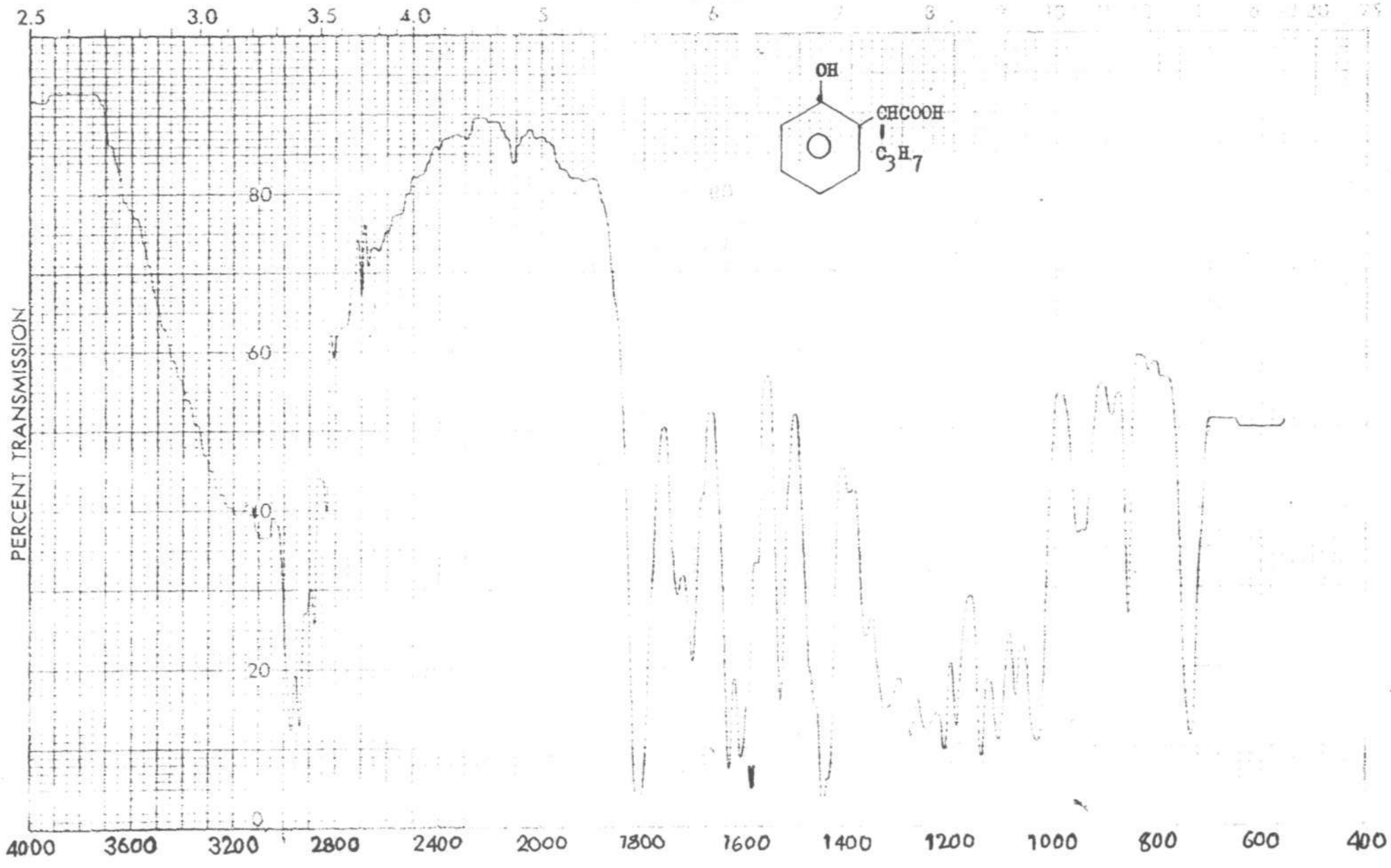

CHART S-60T
MADE IN U.S.A.
500
400
300
200
100
0 Hz
H
O
C - (CH2)3CH3
OH
740Hz
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


MICROMETERS
2.5
3.0
3.5
4.0
5
6
8
9
10
18
20
25
OMe
OMe
CH3
OMe
O
PERCENT TRANSMISSION
80
80
40
20
0
3600
3200

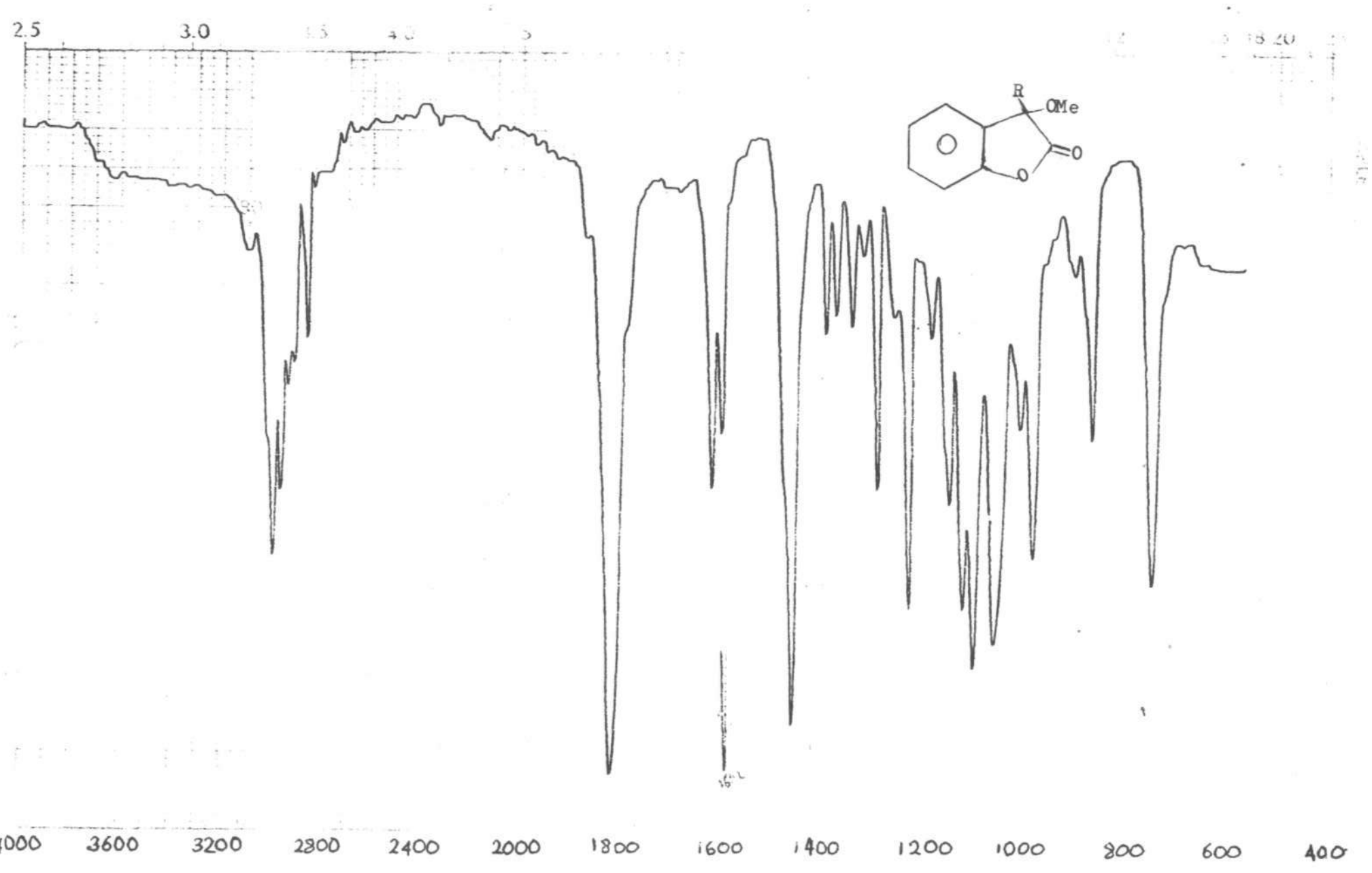

CHART S-60T
MADE IN U.S.A.
500
400
300
200
100
0 Hz
H
OMe
OMe
CH3
O
OMe

Appendix IX

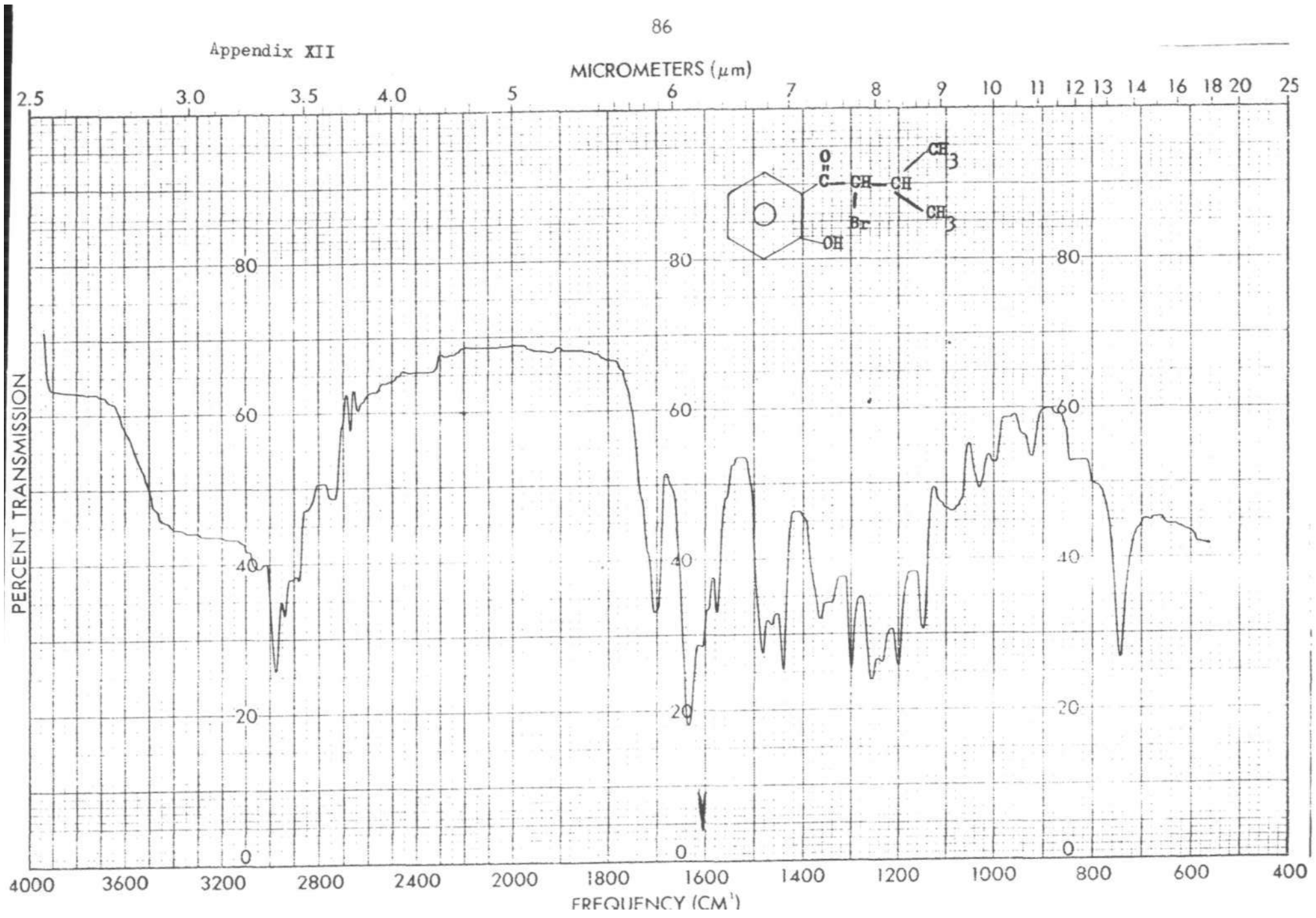

2.5
3.0
3.5
4.0
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
MICROMETERS (mm)
PERCENT TRANSMISSION
80
60
40
20
OH
CHCOOCH3
C3H7
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

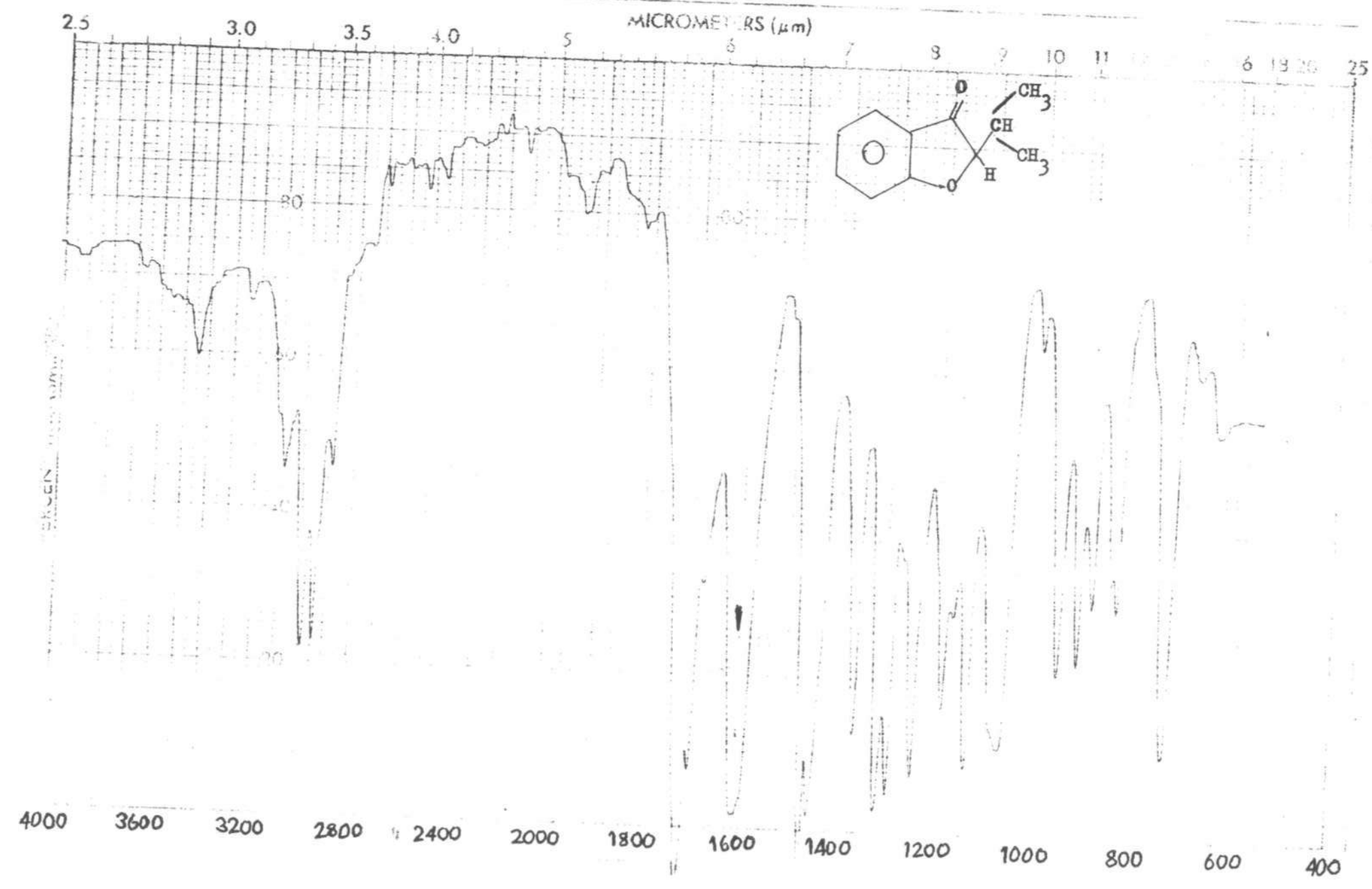

2.5
3.0
3.5
4.0
5
6
7
8
9
10
11
12
13
14
15
PERCENT TRANSMISSION
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
OH
CHCOOH
C3H7

Appendix XI

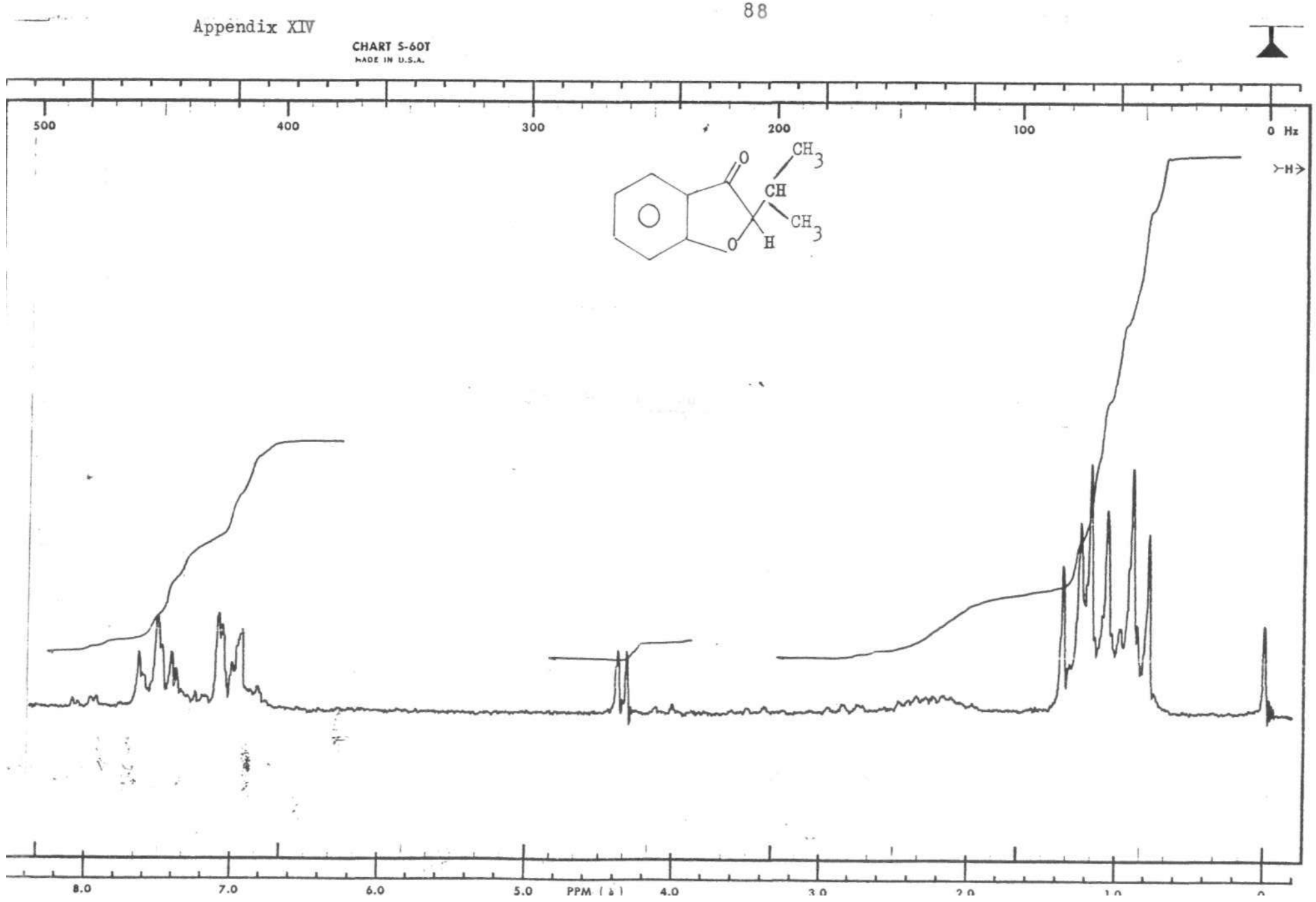

2.5
3.0
R
OMe
O
O
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

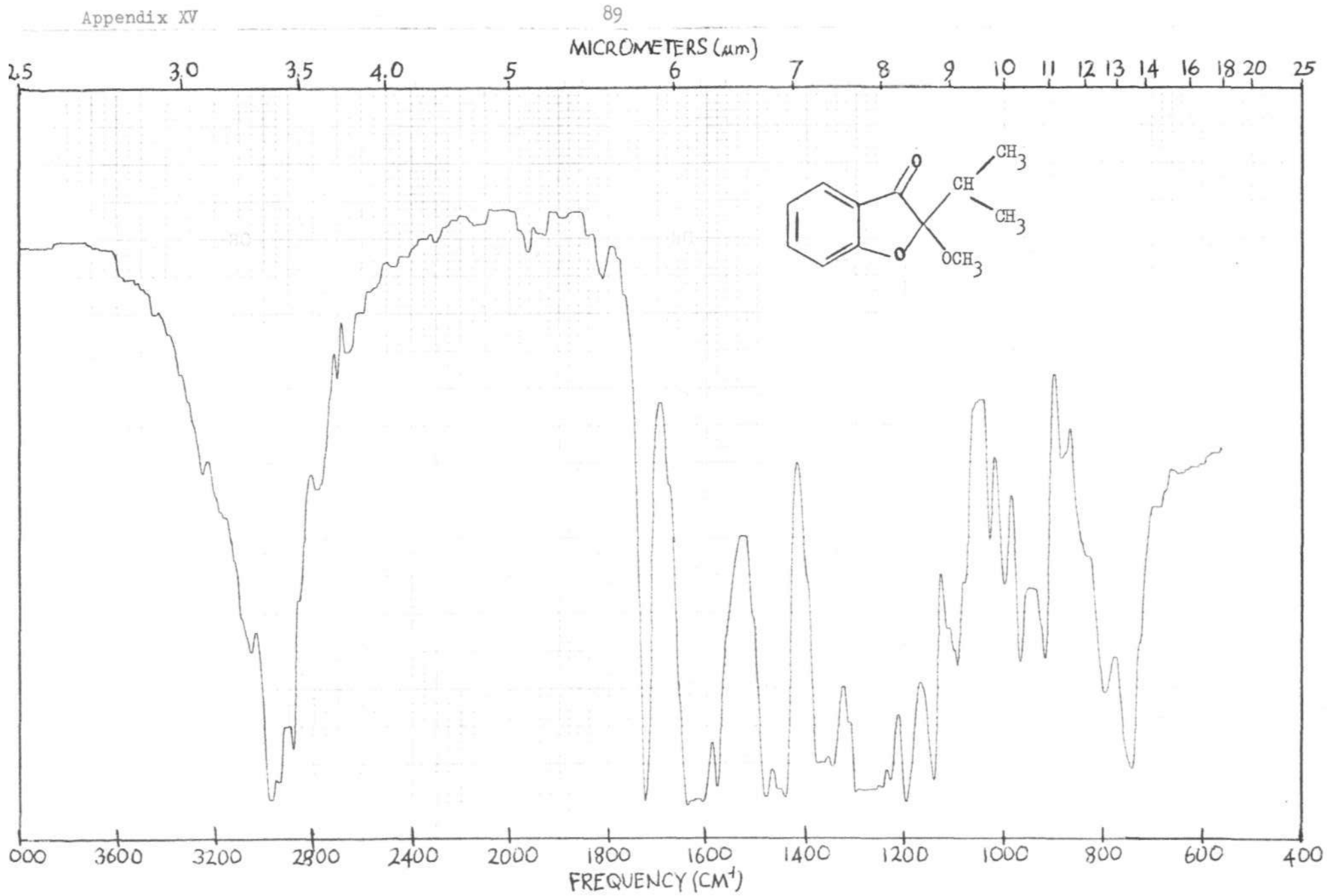
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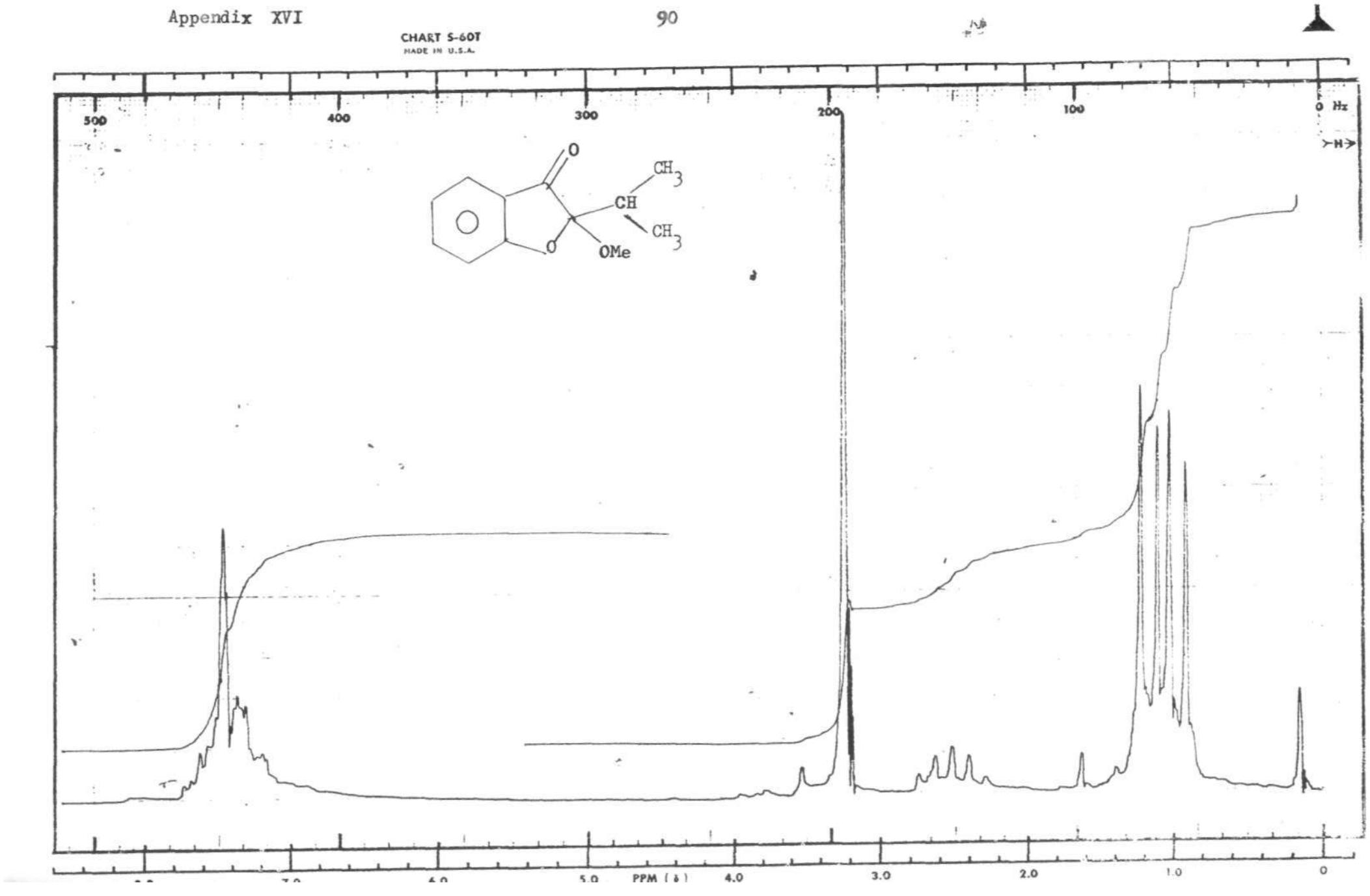



2.5
3.0
3.5
4.0
5
6
7
8
9
10
11
12
13
20
25
MICROMETERS (μm)
80
60
40
20
0
O
CH3
CH
CH3
O
H
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

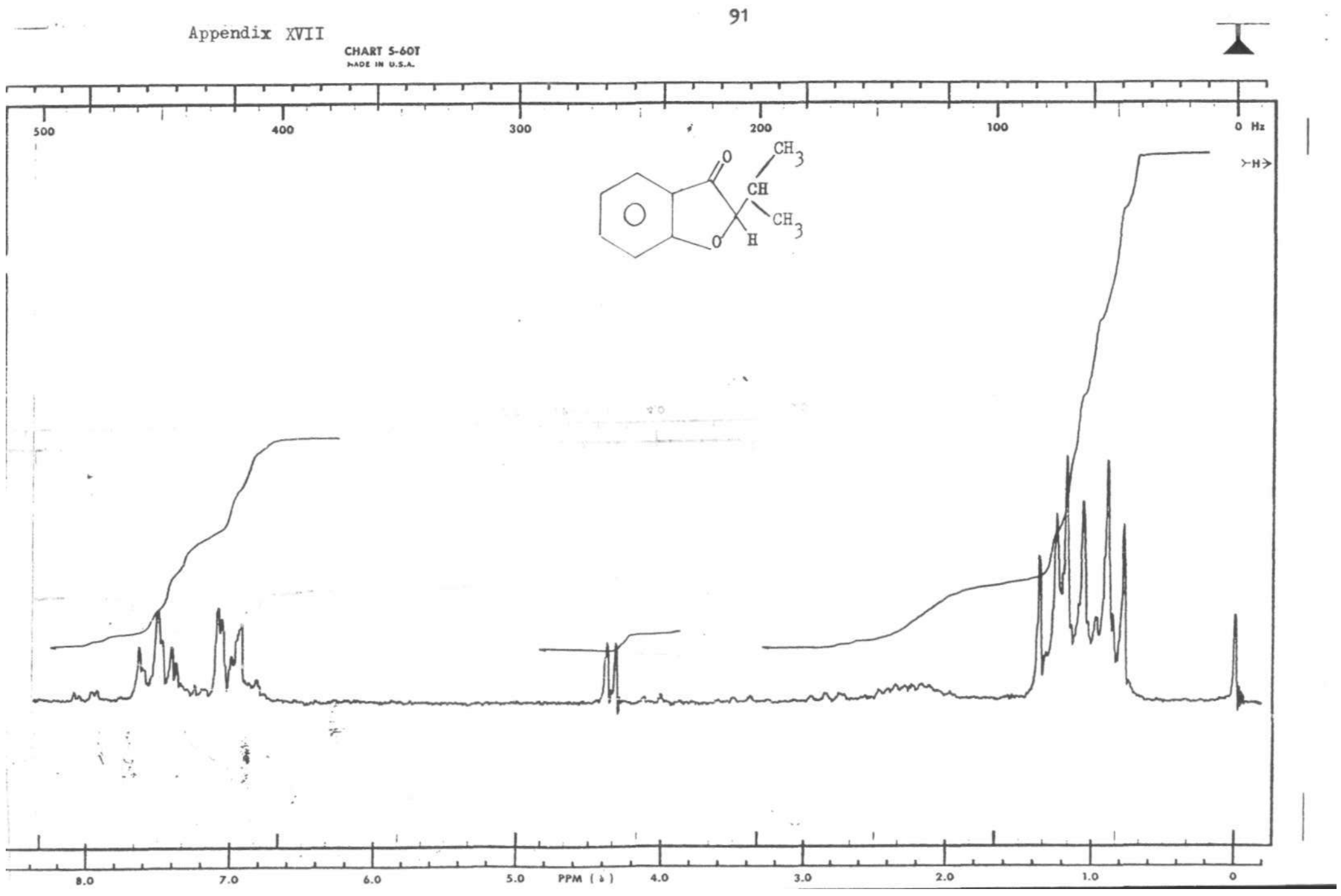
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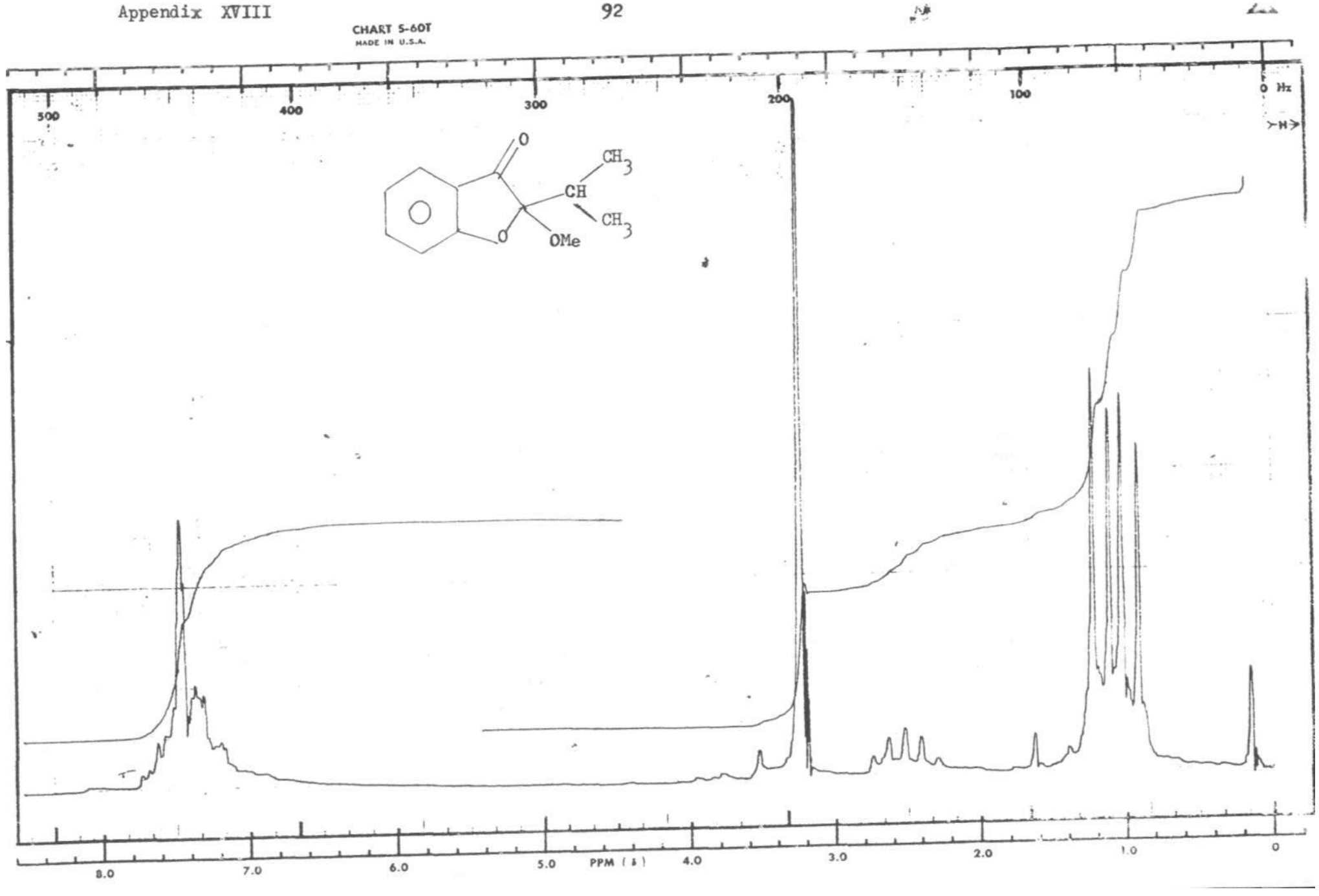



MICROMETERS (μm)
2.5
3.0
3.5
4.0
5
6
7
8
9
10
11
12
13
14
16
18
20
25
CH3
CH
CH3
O
O
OCH3
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM-1)


CHART S-60T
MADE IN U.S.A.
500
400
300
200
100
0 Hz
H
O
CH3
CH
CH3
O
OMe
PPM (δ)
4.0
3.0
2.0
1.0
0

Appendix XVII




CHART 5-60T
MADE IN U.S.A.
500
400
300
200
100
0 Hz
O
CH3
CH
CH3
O
OMe
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0