PHOTOCHEMICAL REMOTE OXIDATION OF OLEYL ESTER OF p-BENZOYLBENZOIC ACID

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Photochemical Remote Oxidation of Oleyl ester of p-benzoylbenzoic Acid

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To my parents

for understanding my deepest desire for

education and making it possible

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ABSTRACT

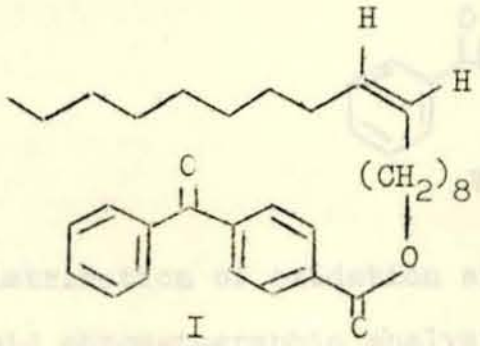
PHOTOCHEMICAL REMOTE OXIDATION OF OLEYL ESTER OF p-BENZOYLBENZOIC ACID

by

Sendaba Gerba

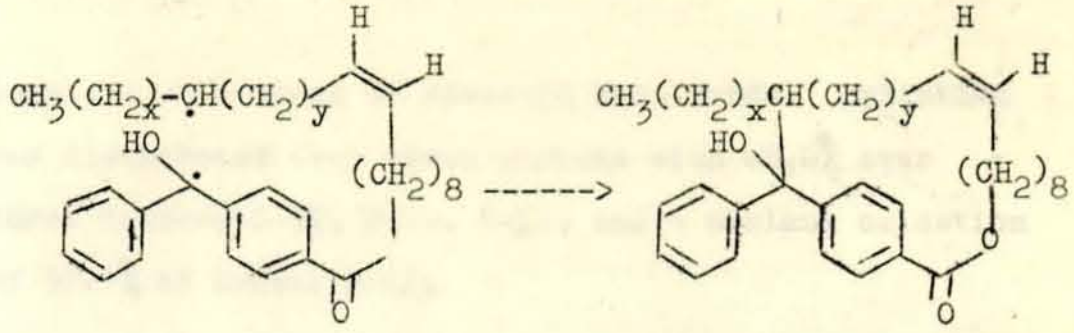
Research advisor: Berhanu Abegaz

Oleyl ester of p-benzoylbenzoic acid (I) was irradiated in carbontetrachloride. The triplet state of benzophenone served to abstract hydrogen, intramolecular to, but structurally remote from the excited carbonyl.



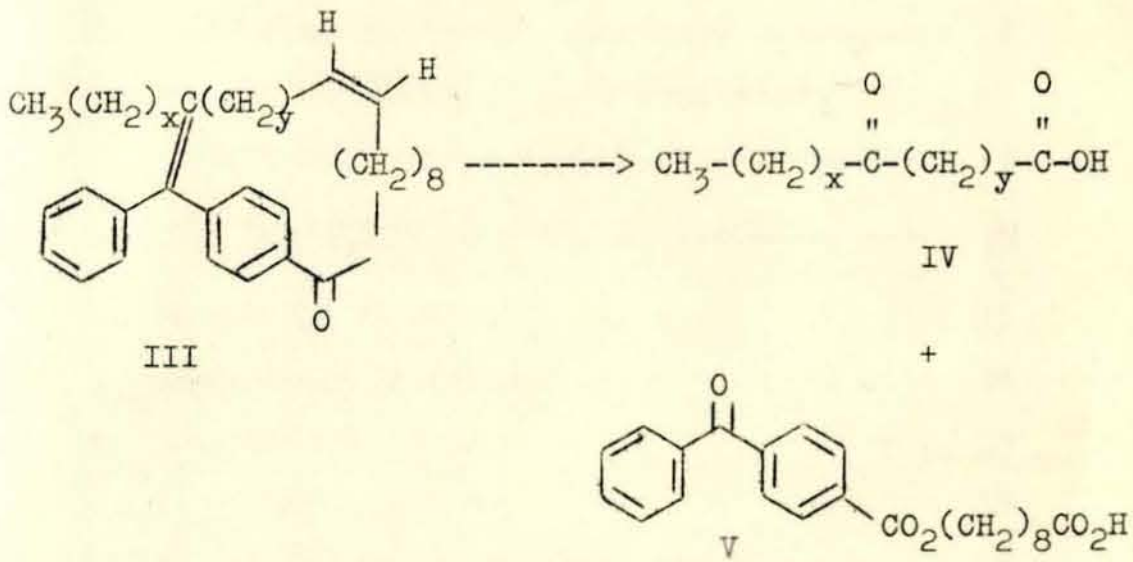
I

The photolysis produced a diradical which cyclized predominantly at the ketyl position to yield the lactone (II).



II x + y = 6

Compound II was dehydrated to III, which was then ozonized to IV and V.



III

IV

V

The distribution of oxidation sites was determined by gas liquid chromatographic analysis of IV. Retention time was

compared with those of standard keto acids. Oxidation was distributed over seven carbons with 88.6% over three centers C-12, C-14, C-15, and a maximum oxidation of 37.7% at carbon C-12.

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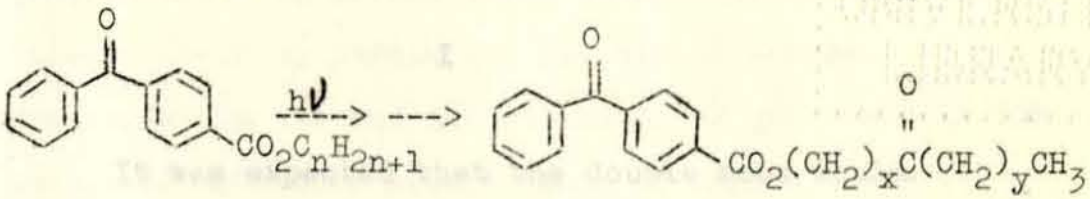
I INTRODUCTION

In 1969 Breslow and Winnik[1] reported a chemical method for functionalizing unactivated methylenes in long chain fatty alcohols. This was accomplished by photolysis of compounds of type 1.



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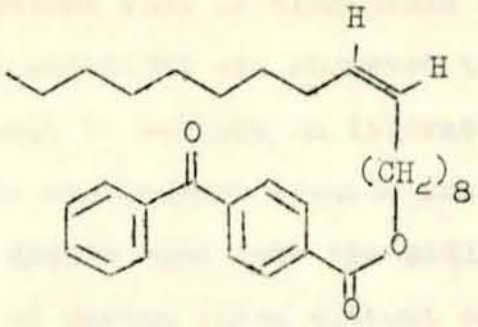
However, these attempts led to indiscriminate attack on methylene groups giving several products. The main reason for this appears to be the lack of rigidity of saturated side-chain. In the work described in this thesis an attempt was made for the first time to functionalize the methylene groups of a compound containing cis-double bond in the alkyl chain of type I by irradiating in carbon tetrachloride.



I

It was expected that the double bond would increase the rigidity of the alkyl chain resulting in a more discrete functionalization than that of saturated long chain fatty alcohols.

II. BACKGROUND

It is apparent that in biogenesis several selective stereospecific reactions are observed that appear to be very difficult to perform in laboratories. For example, nature can convert stearic into oleic acid, by introducing a double bond into the middle of a homogeneous chain of carbon atoms without activating these carbons by particular functional groups. Similarly, in steroid metabolism it is quite simple for nature to introduce double bonds or oxygen atoms at particular sites.

The mechanism of desaturation is not completely understood. K. Bloch[2] suggests that an appropriately placed iron in the form of reduced ferredoxin might deliver molecular oxygen to the specific carbon attacked, followed by the specific removal of an adjacent hydrogen to form a double bond.

The superiority of natural enzymatic reactions over common synthetic reactions is due to their selectivity and high velocity; high speed being less important than high selectivity. If one could achieve high speed and selectivity in the laboratory, one would have the possibility of carrying out similar reactions which nature does by the use of enzymes.

Chemists have worked for many years on the imitation of natural pathways. These attempts have resulted in the development of a new branch of chemistry, biomimetic chemistry, providing additional power to organic chemical synthetic procedures.

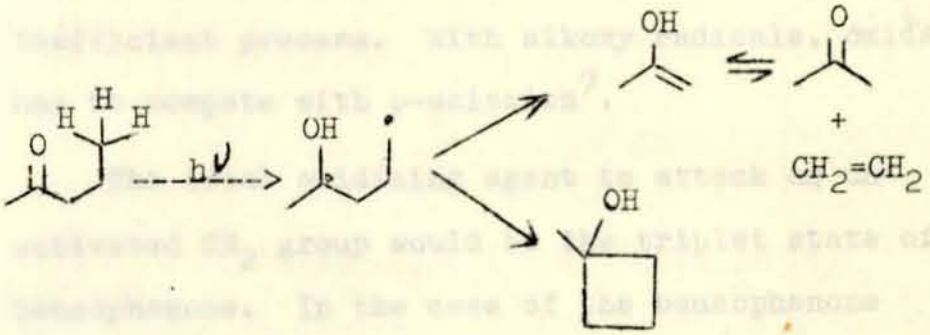
Any intrinsic reactivity of the substrate, which is dictated by its own functional groups, can be overridden by combining the substrate with a reagent (i.e., the enzyme) whose selectivity is dominant. In particular, even a single unactivated CH_2 group of a chain can be attacked selectively within an enzyme-substrate complex by steric approximation to the attacking atom. This chapter treats some of the chemical examples of the application of this principle.

1. Remote Oxidation

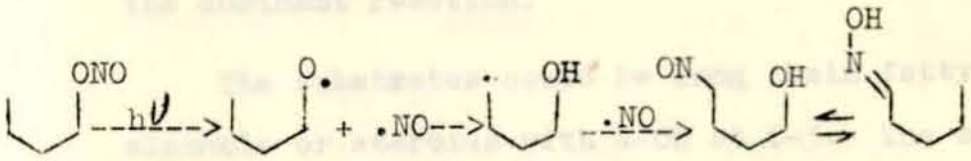
New methods of organic synthesis have been developed by the utilization of intramolecular, free-radical decomposition of certain alcohol derivatives. Lead tetraacetate oxidation of alcohols[3], photolysis of nitrites[4], and thermolysis or pyrolysis of hypohalites[5] have permitted functionalization of saturated hydrocarbon centers in close proximity to the original hydroxy function. All involve the production of a reactive hetroatom

radical in a molecule which then, by intramolecular attack on a hydrogen atom, initiates functionalization of a position which is not chemically activated in the usual sense.

The idea of remote oxidation sees its precedence in the reactions of Young[6] (scheme 1) and Barton[4] (scheme 2). In these reactions, a hydrogen on a carbon γ to an excited carbonyl or alkoxy radical is abstracted specifically. The formation of a six-membered ring transition state affords the proper orientation of only that hydrogen.



Scheme 1



Scheme 2

The extension of such a stereospecific oxidation to more complex systems would allow hydrogen abstraction to take place at larger distances than six atoms. For example an alkoxy radical located at a position structurally remote from a hydrocarbon chain might, if appropriately oriented, prefer to abstract hydrogen in a selective fashion.

2. Oxidizing Agents and Substrates

Any alkoxy radical is capable of abstracting a hydrogen from a saturated C-H bond. However, directed hydrogen abstraction is likely to be an inefficient process. With alkoxy radicals, oxidation has to compete with β-scission[7].

The ideal oxidizing agent to attack an unactivated CH_2 group would be the triplet state of benzophenone. In the case of the benzophenone triplet, competition is between abstraction of H and return to the ground state[8], the former being the dominant reaction.

The substrates could be long chain fatty alcohols or steroids with α-OH at C-3. The substrate and the oxidizing agent are attached by a covalent bond or alternatively simple complexing forces (i.e., hydrogen bonding) may be employed to allign them[9].

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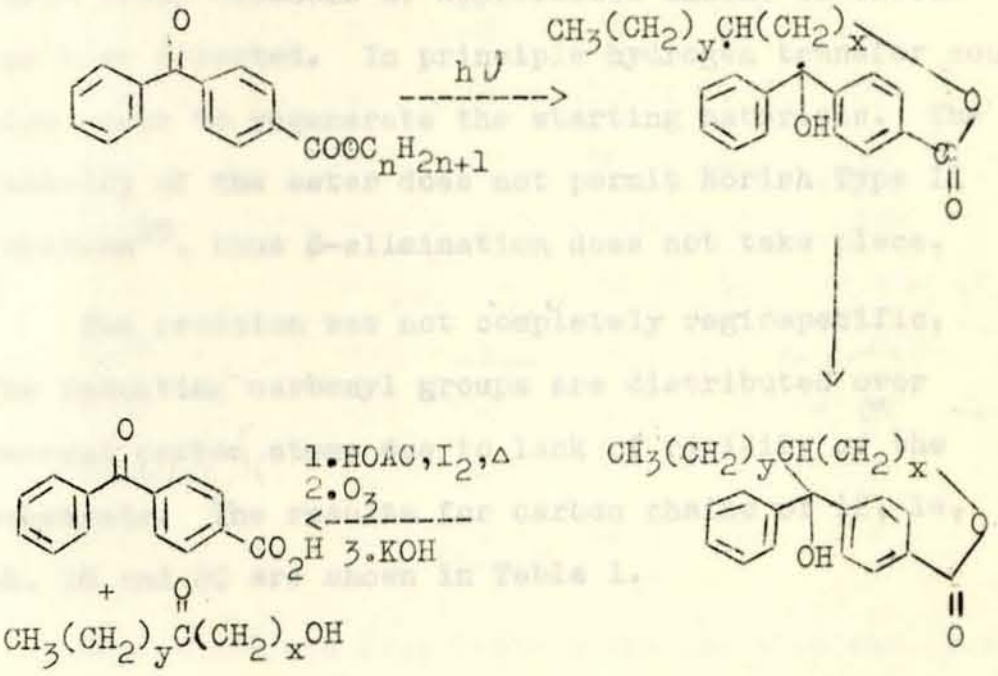
3. Remote Oxidation of Unactivated Methylene

It has proved possible to convert the CH_2 group of long chain fatty alcohols to C=O groups even if they are not near any functional groups[1]. The sequence for such reaction is as follows: esterification of the alcohol with p-benzoylbenzoic acid, photolysis, dehydration, ozonolysis, and hydrolysis (scheme 3).



Scheme 3

The chemistry involved is the oxygen atom of the benzophenone triplet attacks a particular hydrogen or set of hydrogens in the substrate to form a diradical. This diradical can then either collapse to form a new carbon-carbon bond, or undergo hydrogen transfer to form a double bond in the substrate and a reduced carbonyl group in the benzophenone. In studies sofar done on flexible substrates such as saturated long chain fatty alcohols no appreciable amount of olefin has been detected. In principle hydrogen transfer could also occur to regenerate the starting materials. The geometry of the ester does not permit Norish Type II reaction[10], thus β-elimination does not take place.

The reaction was not completely regiospecific. The resulting carbonyl groups are distributed over several carbon atoms due to lack of rigidity of the substrate. The results for carbon chains of 12, 14, 16, 18 and 20 are shown in Table 1.

Table 1 Percent Oxidation[1]

	Number of Carbons in Ester Alkyl Chain				
Oxidation Site	C-12	C-14	C-16	C-18	C-20
C-8	1	0	0	0	0
C-9	6	1.4	1.1	0.1	<2
C-10	28	3	7.8	8	5
C-11	65	11	12	17	15
C-12	0	49	13	21	20
C-13	-	22	10	18	19
C-14	-	0	56	12	19
C-15	-	-	7	5	13
C-16	-	-	0	13	8
C-17	-	-	-	6	0.7
C-18	-	-	-	0	0
C-19	-	-	-	-	0
C-20	-	-	-	-	-

As can be seen from Table 1 the reaction was less regiospecific for longer chains and better selectivity was achieved with relatively short chains. No functionalization closer than C-8 was observed presumably due to geometric restrictions or inaccessiblity. The terminal methyl groups are not attacked. The absence of attack on the methyl is apparently the result of the

chemical selectivity of the benzophenone triplet[11], since the methyl hydrogens are less reactive than methylene hydrogens. The penultimate carbon also shows a decreased reactivity.

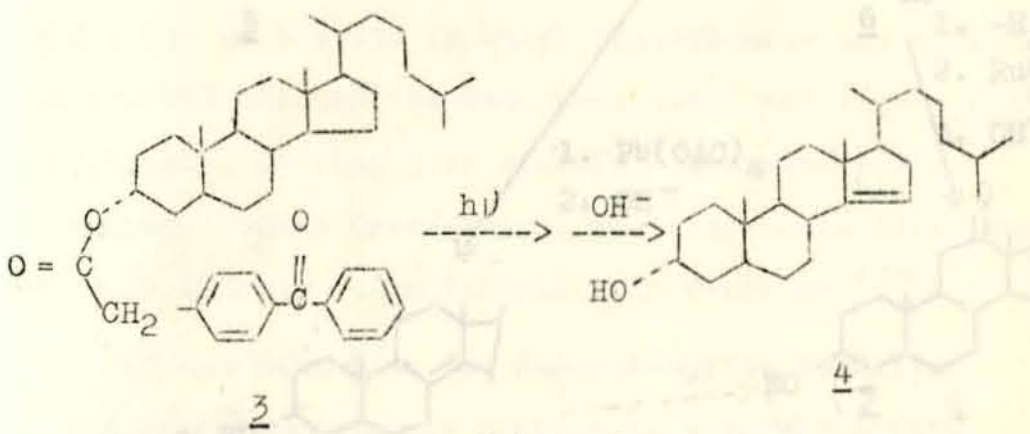
With steroids, in contrast to long chain fatty alcohols remote oxidation affords high selectivity of functionalization. This is mainly due to the rigidity of the substrate and the limited number of accessible axial hydrogens on the bottom of the steroid.

The sequence followed is identical with that of long chain fatty alcohols: esterification, photolysis, oxidation and hydrolysis. The chemistry involved is the attack by the excited carbonyl of benzophenone on the steroid substrate to produce a diradical. This diradical can then either collapse to form a new carbon-carbon bond, or it may undergo a direct hydrogen transfer to form a double bond in the substrate.

The ease and also the specificity of the steroid functionalization mainly depends on the geometry of the ester. One can then achieve regiospecific functionalization by constructing a reagent substrate combination of the right geometry.

Photolysis of benzophenone-4acetic ester of 3α-cholestanol (3) gives Δ^{14}-cholesten-3α-ol (4) as the

only steroidal product detectable in 35% yield (scheme 4).[12, 13]



3 4

Scheme 4

Irradiation of benzophenone-4-propionic acid ester of 3α-cholestanol (5)[12, 13, 14] gives 35% of steroidol olefin (4) by hydrogen transfer and 50% of (6) in which new carbon-carbon bonds have been formed by coupling of the intermediate diradical. When (6) is dehydrated and the resulting olefin is oxidatively cleaved 12-keto-cholestan-3α-ol (7) and 7-keto-cholestan-3α-ol (8) are produced.[12, 13, 14] Lead tetraacetate cleavage of (6) gives a mixture of three olefines $\Delta^{8(14)}$-cholesten-

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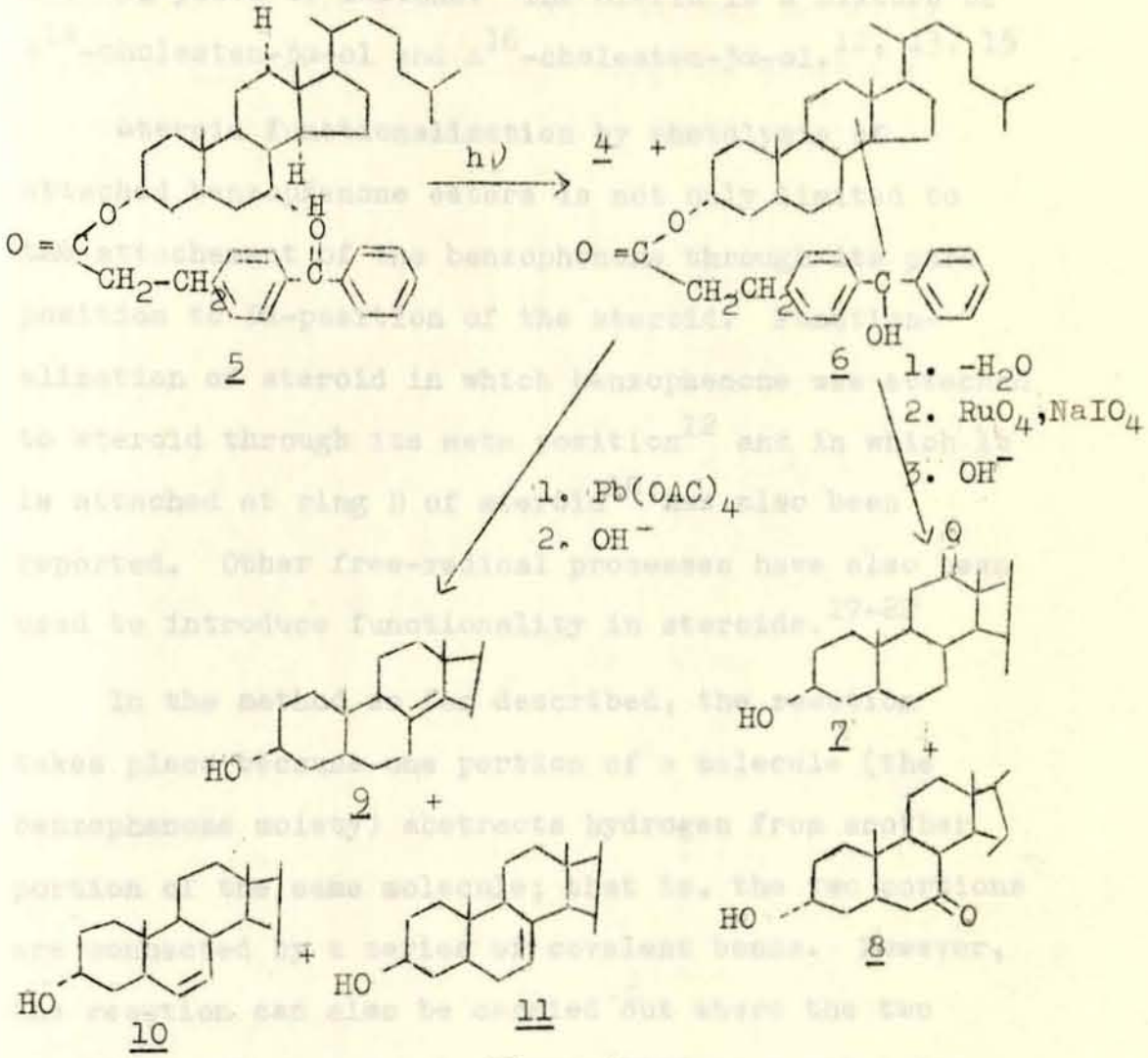
3α-ol (9), Δ^6-cholesten-3α-ol (10) and Δ^7-cholesten-3α-ol (11)[12, 13, 14] (scheme 5).



Scheme 5

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Photolysis of benzophenone-4-pentanoic acid ester of 3α-cholestanol gives a 53% direct yield of olefin and 25% yield of lactone. The olefin is a mixture of Δ^{14}-cholesten-3α-ol and Δ^{16}-cholesten-3α-ol.[12, 13, 15]

Steroid functionalization by photolysis of attached benzophenone esters is not only limited to the attachement of the benzophenone through its para position to 3α-position of the steroid. Functionalization of steroid in which benzophenone was attached to steroid through its meta position[12] and in which it is attached at ring D of steroid[16] has also been reported. Other free-radical processes have also been used to introduce functionality in steroids.[17-22]

In the method so far described, the reaction takes place because one portion of a molecule (the benzophenone moiety) abstracts hydrogen from another portion of the same molecule; that is, the two portions are connected by a series of covalent bonds. However, the reaction can also be carried out where the two reacting centers are actually in different molecules, providing the two molecules are held together by hydrogen bonding.[9]

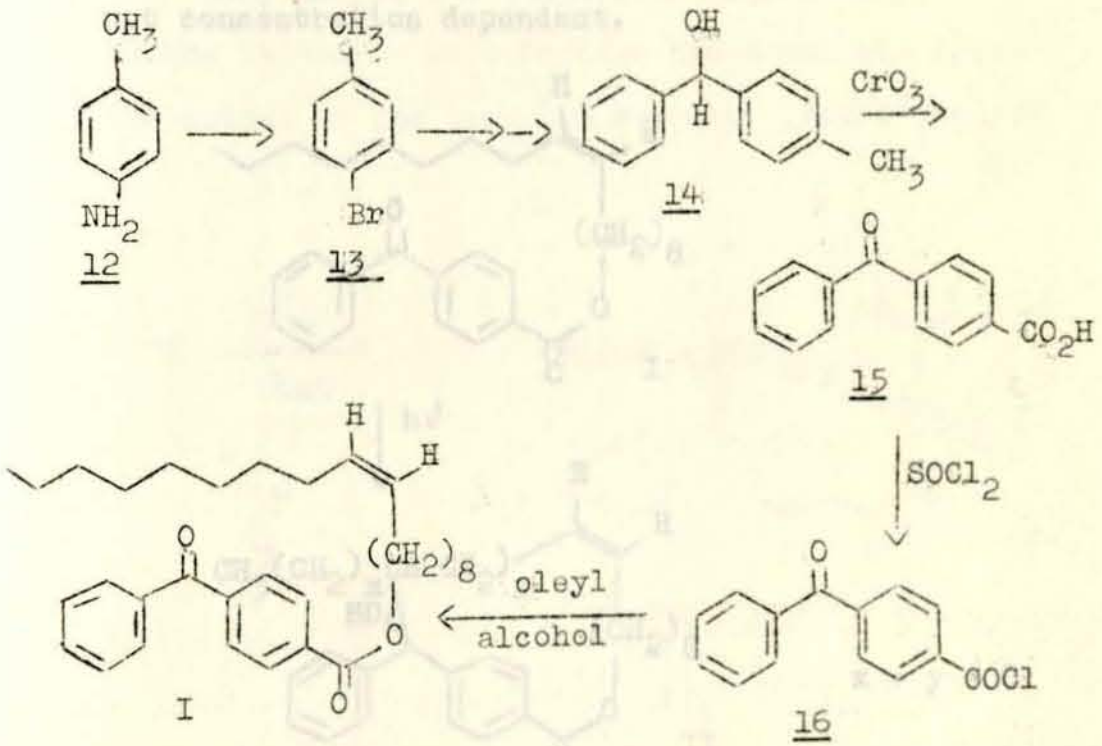
It is clear from the forgoing survey that this approach leads to potentially useful synthesis in functionalization of specific sites in the steroid

field. However, it is seen that saturated fatty alcohols give a variety of products. It was therefore of interest to use alcohols derived from naturally occuring cis-unsaturated fatty acids as substrates and examine if better selectivity could be achieved.

III. RESULTS AND DISCUSSION

1. Synthesis of Ester

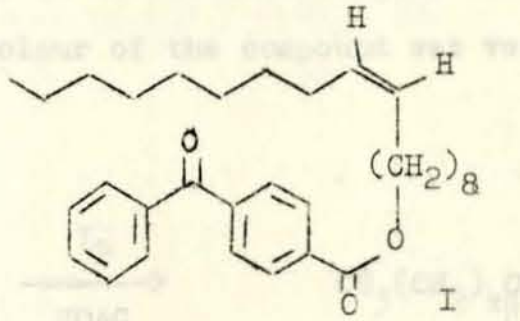
The Sandmeyer reaction was used to prepare p-bromotoluene from p-toludine (12)[23] which was converted to the corresponding Grignard reagent and reacted with benzaldehyde to give phenyl-p-tolylcarbinol (14). This intermediate alcohol was oxidized with CrO_3[24] and p-benzoylbenzoic acid (15) was obtained in good yield. Compound (15) was converted to the acid chloride (16) with thionyl chloride which was then reacted with oleyl alcohol to give ester (I).



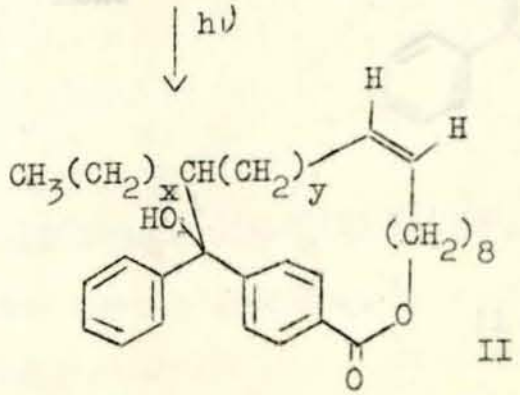
The molecular ion peak of ester I appeared at 476 which is consistent with the molecular formula of $C_{32}H_{44}O_3$.

2. Photolysis of Ester I

A solution of ester I (6.7×10^{-4}M) in CCl_4 was irradiated for 10 hrs. At this dilute concentration it is expected that intermolecular reactions would not compete with intramolecular reactions. The relative amount of intermolecular reaction varies linearly with concentration while the relative amount of intramolecular reaction is not concentration dependant.



I



II

x + y = 6

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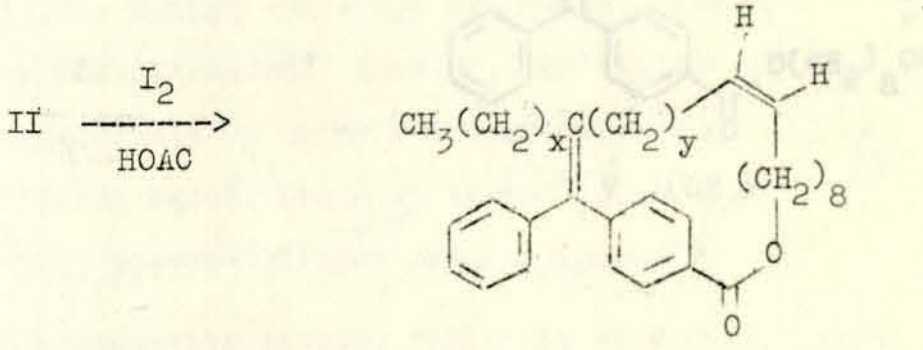
Irradition resulted in the dissapperance of the ketone carbonyl at 1670 cm^{-1} in the ir. Sodium chloride cavity cells (path length 2.5 mm) permitted us to follow the disappearance of the carbonyl absorption band without concentrating the solution. The ketone was completely photoreduced after 10 hrs of irradiation. The solution was then concentrated to yield compound II, a dirty red-brown oil. Compound II showed strong absorption at 3500 cm^{-1} indicating the presence of an alcohol.

3. Dehydration of II

Compound II was dehydrated with a trace of iodine in acetic acid to give red-brown oil III. The colour of the compound was very little changed.



III x + y = 6

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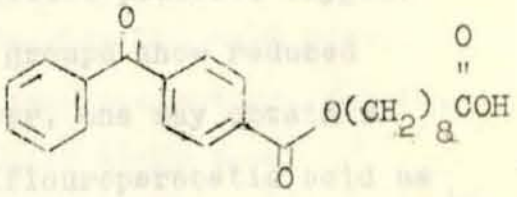
The disapperance of the alcohol absorption at 3500 cm^{-1} indicated that II had undergone dehydration to give III.

4. Ozonolysis of III

A solution of III in CH_2Cl_2 and CH_3OH was treated with excess ozone at -35°. Ater oxidative work-up with H_2O_2, a mixture of IV and V was obtained.

III $\xrightarrow[2.\ H_2O_2]{1.\ O_3}$ $CH_3(CH_2)_x\overset{O}{\overset{\|}{C}}(CH_2)_y\overset{O}{\overset{\|}{C}}OH$ (IV) $\qquad x + y = 6$

+  (V)

5. Distribution of Oxidation Sites

The method developed by Breslow and Winnik[1] for the photolysis of the saturated fatty alcohol

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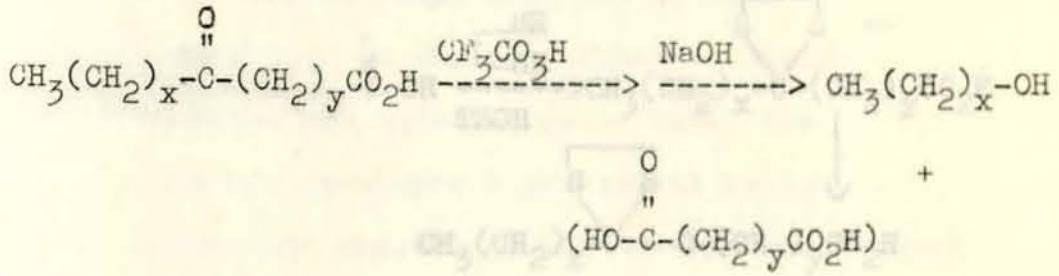
esters involves Baeyer-Villager oxidation of the mixture followed by saponification and gas liquid chromatographic (glc) analysis of the simple alcohols produced (scheme 6)



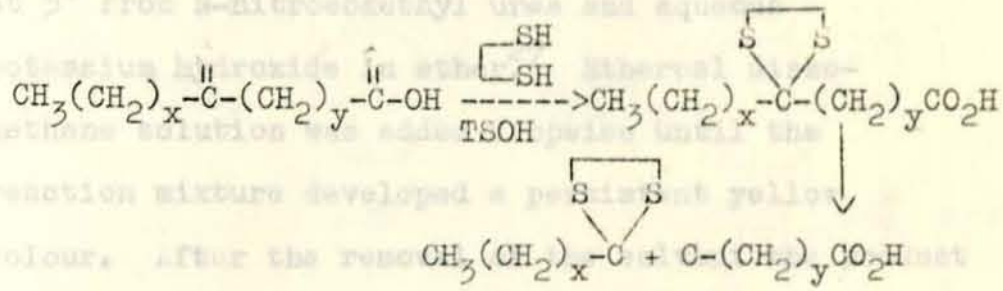
Scheme 6

The assumption here is that the amount of $CH_3(CH_2)_x$-OH is directly proportional to the amount of IV which has its new carbonyl group on $CH_3(CH_2)_{x+1}$.

This method has a draw-back since Baeyer-Villager reactions are believed to be governed by electronic factors in the migration to electro positive oxygen.[25] For example, methyl and ethyl groups show reduced tendency for migration. However, one may obtain a reasonable result by using triflouroperacetic acid as the oxidizing agent, since it is the least discriminating Baeyer-Villager reagent known.[26]

An alternative method, which can be used to locate the position of functionalization involves the conversion of the resulting carbonyl into thioketal with ethylene dithiol followed by examination of the mass spectrum

of the resulting product mixture.[9] At a low ionizing voltage mass spectrum fragmantation occurs very largely at the carbon carrying the sulphurs (scheme 7).



scheme 7

The method choosen to determine the site of oxidation involved the identification of mixture IV obtained by ozonolysis of III. The entire ozonolysis product (IV and V) was methylated with diazomethane, and was subjected to glc analysis. It was assumed that IV contains a mixture of ketononanoic acids with the keto group at different positions. With this assumption, 8-keto, 7-keto, 6-keto, and 5-ketononanoic acids were synthesized. The keto-acids synthesized were methylated with CH_2N_2 and injected into glc. The peaks of the methylated standard keto acids were then correlated with those of the peaks obtained for the methylated ozonolysis product.

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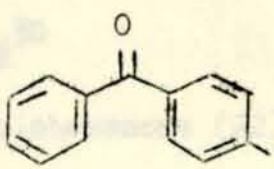
5.1 Methylation of the Ozonolysis Product

The entire ozonolysis product of III, (IV and V), was treated with excess diazomethane generated at 5° from N-nitrosomethyl urea and aqueous potassium hydroxide in ether.[27] Ethereal diazomethane solution was added dropwise until the reaction mixture developed a persistent yellow colour. After the removal of the solvent the product obtained was a mixture of VI and VII.

IV and V ----------> $CH_3(CH_2)_x-\overset{O}{\overset{\|}{C}}-(CH_2)_y-\overset{O}{\overset{\|}{C}}-OCH_3$ (VI)

+



$CO_2(CH_2)_8\overset{O}{\overset{\|}{C}}OCH_3$ (VII)

5.2 Synthesis of the Standard Keto Acids

5.2.1 8-Ketononanoic Acid

Oxidation of cyclooctanol (17) with CrO_3[28] gave cyclooctanone (18) which was then reacted with methylmagnesium iodide to yield 1-methylcyclooctanol (19). Dehydration of (19) was attempted with 50% aqueous sulphuric acid[29] as well as with thionyl chloride. The treatment of alcohol (19) with 50% sulphuric acid proceeded satisfactorily to give the desired olefin (20).

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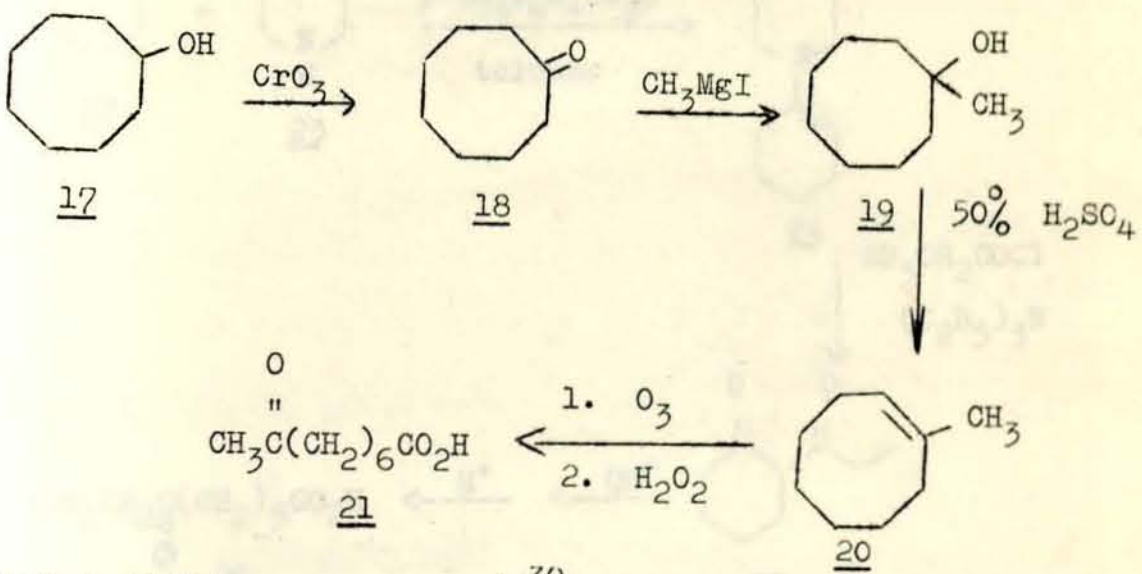
Compound (20) was ozonized oxidatively with hydrogen peroxide to yield 8-ketononononanoic acid (21).



5.2.2 7-Ketononononanoic Acid[30]

A mixture of cyclohexanone (22), morpholine (23) and p-toluenesulphonic acid in toluene was refluxed in a Dean-Stark apparatus until water was completely removed. After cooling, washing, and removal of the solvent the residue was distilled under reduced pressure to give morpholinocyclohexene (24). Treatement of the enamine (24) with propionyl chloride in the presence of $(C_2H_5)_3N$ gave, after work-up, a β-diketone (25) which upon treatement with

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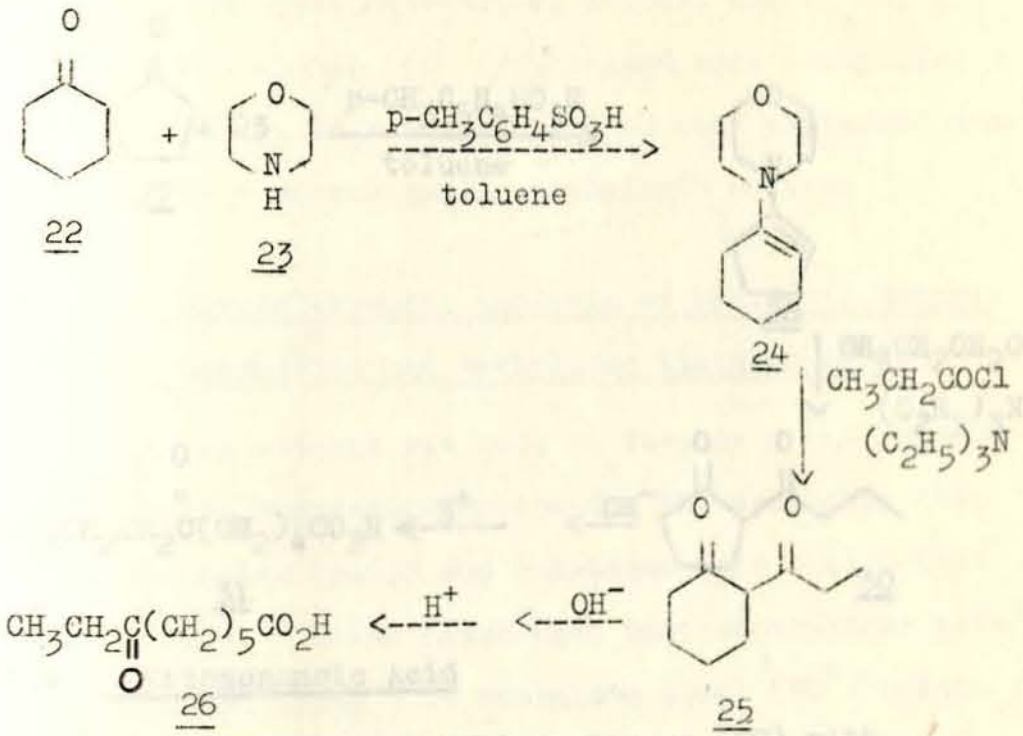
base gave 7-ketononanoic acid (26).



22 23 24 25 26

5.2.3 6-Ketononanoic Acid[30]

Cyclopentanone (27) was prepared from adipic acid and barium hydroxide[31] and reacted with morpholine (23) as described for (22) above to yield morpholinocyclopentene (28). Reaction of (28) with butyryl chloride (29) (prepared from butyric acid and thionyl chloride) produced a β-diketone (30) which upon treatement with base gave 6-ketononanoic acid (31).

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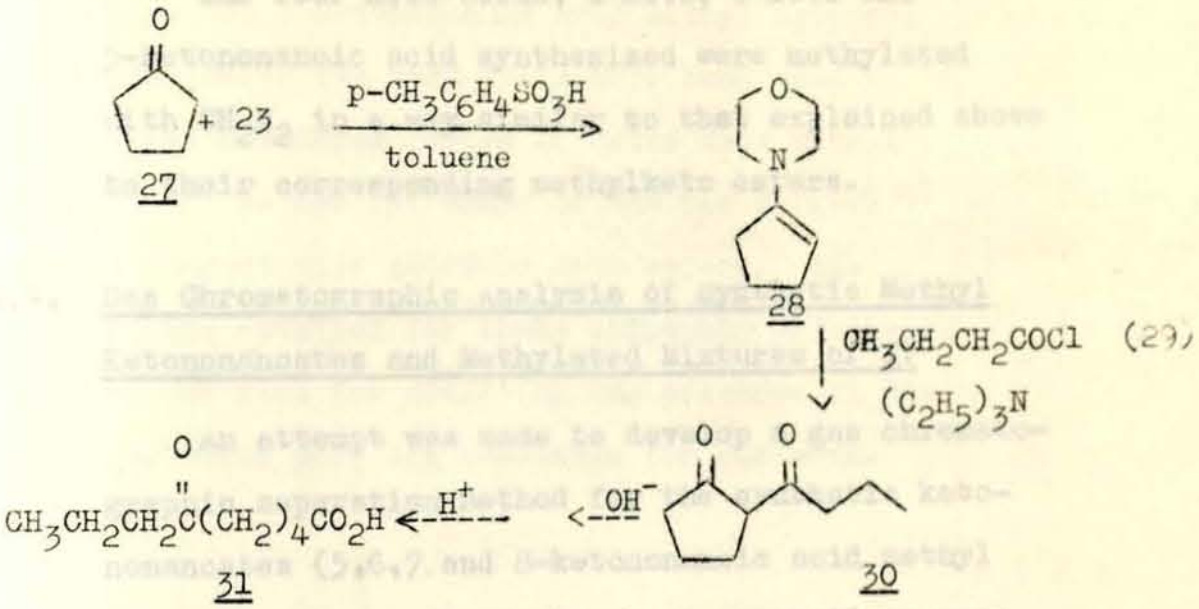
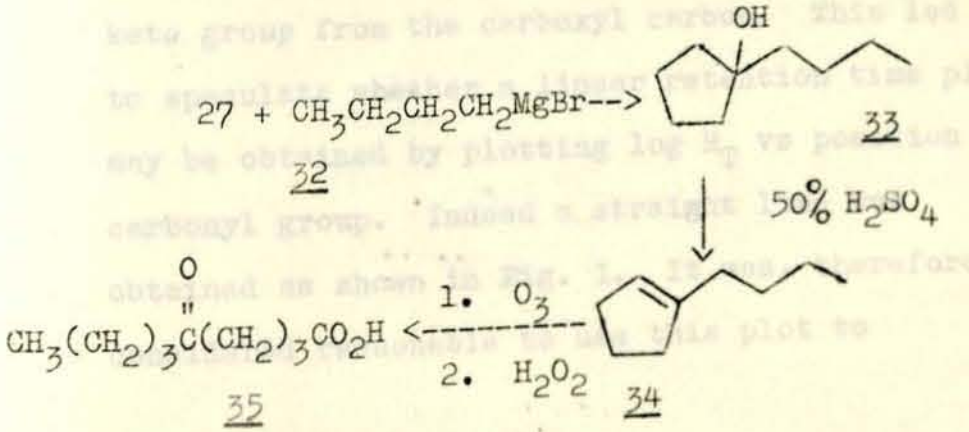


5.2.4 5-Ketononanoic Acid

Treatment of cyclopentanone (27) with butylmagnesium bromide (32) gave 1-butylcyclopentanol (33). Dehydration of (33) with 50% aqueous sulphuric acid[29] followed by ozonolysis of the intermediate olefin (34) resulted in 5-ketononanoic acid (35).



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5.3. Methylation of the Standard Keto-acids

The four keto-acids, 8-keto, 6-keto and 5-ketononanoic acid synthesized were methylated with CH_2N_2 in a way similar to that explained above to their corresponding methylketo esters.

5.4. Gas Chromatographic Analysis of Synthetic Methyl Ketononanoates and Methylated Mixtures of IV

An attempt was made to develop a gas chromatographic separation method for the synthetic ketononanoates (5,6,7 and 8-ketononanoic acid methyl esters). It was found that best separations were obtained using 5 ft stainless steel (1/8") column packed with 10% carbowax 20 M terminated with terphthalic acid (10%) on 100/120 Gaschrom Q. Carbowax 20 M gave poorly resolved peaks. The retention times of the isomeric methylketononanoates are given in table II. It is noted that the retention time increases with increased distance of keto group from the carboxyl carbon. This led us to speculate whether a linear retention time plot may be obtained by plotting log R_T vs position of carbonyl group. Indeed a straight line was obtained as shown in Fig. I. It was, therefore, considered reasonable to use this plot to

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identify the other isomeric methyl-ketononanoates (i.e., 4,3, and 2 ketononanoic acid methyl esters). Even though retention time plots have been used to characterize homologus series of fatty acid methyl esters,[32, 33] we are not aware of the use of such plots to characterize isomeric keto esters. The straight line obtained for these compounds encouraged us to use the plot for detecting the presence of the keto acids which were not available for our work.

TABLE II

Retention times of the isomeric methyl ketononanoates and methylated mixtures of IV.

Mdthyl keto esters	Retention time (sec)	Log R_T	Identified as	% distribution
Standard Sample				
8-keto	554.40	2.74		
7-keto	477.6	2.68		
6-keto	410.4	2.61		
5-keto	357.6	2.55		
4-keto	302	2.48		
3-keto	263.01	2.42		
2-keto	223.87	2.35		
Mixtures of IV				
Unknown A	225.6	2.35	2-keto	7.5%
Unknown B	254.4	2.41	3-keto	37.7%
Unknown C	295.2	2.47	4-keto	1.3%
Unknown D	338.4	2.53	5-keto	28.3%
Unknown E	410.4	2.61	6-keto	22.6%
Unknown F	487.2	2.69	7-keto	1.3%
Unknown G	561.6	2.75	8-keto	1.3%

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Fig. 1: log R_T VS Position of Keto group

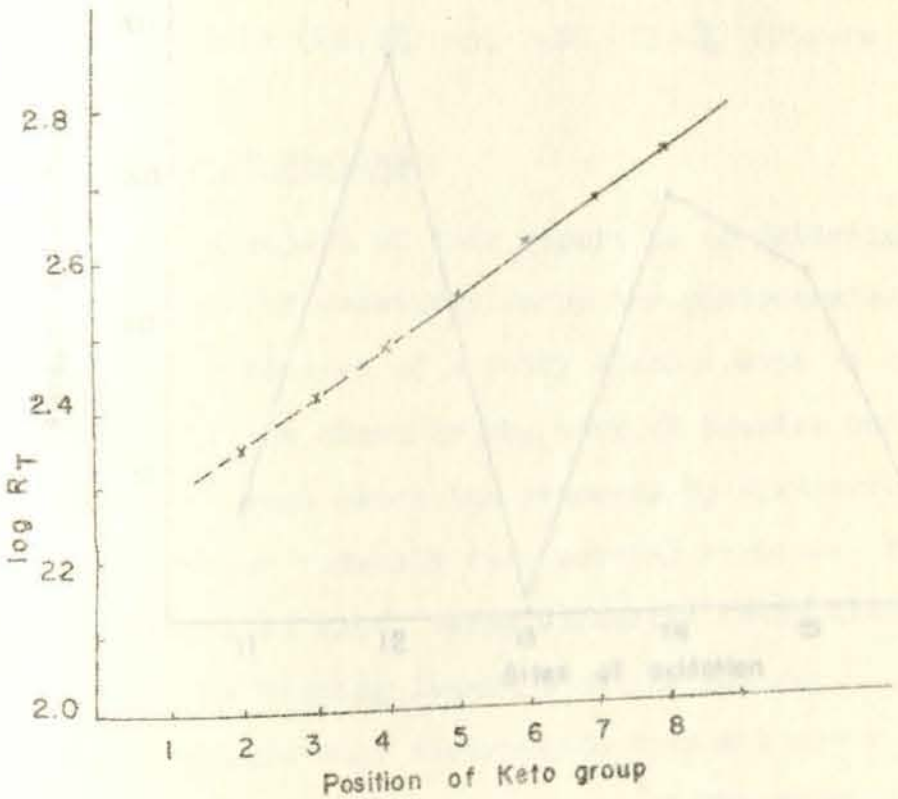
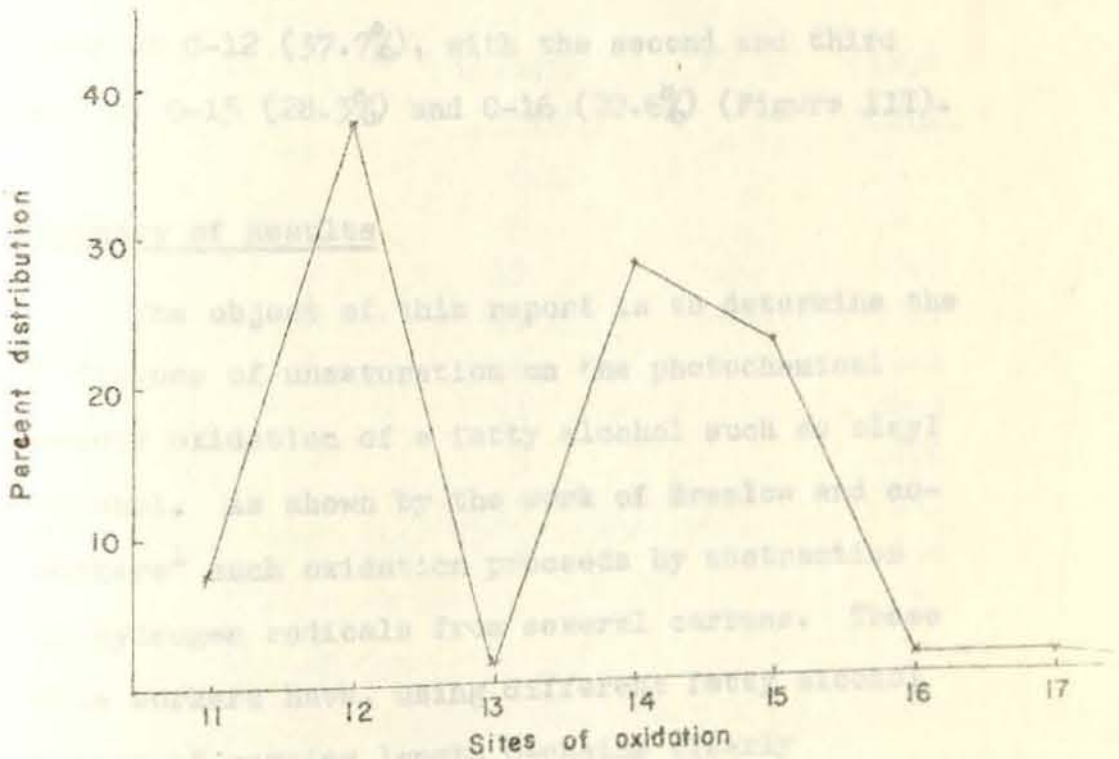


Fig.2 : Distribution of oxidation sites



As can be seen from table II the retention times of the unknown methylketoesters of A,B,C,D,E,F and G correlate with those of 2-keto, 3-keto, 4-keto, 5-keto, 6-keto, 7-keto and 8-ketononanoate esters respectively.

The oxidation was distributed over seven carbons with 88.6% over three centers. Maximum oxidation appeared at C-12 (37.7%), with the second and third maximum at C-15 (28.3%) and C-16 (22.6%) (Figure III).

6. Summary of Results

The object of this report is to determine the influence of unsaturation on the photochemical remote oxidation of a fatty alcohol such as oleyl alcohol. As shown by the work of Breslow and co-workers[1] such oxidation proceeds by abstraction of hydrogen radicals from several carbons. These same workers have, using different fatty alcohol esters of varying length C-chains clearly demonstrated that abstraction does not occur from any of the first eight carbons of the alcohol chain indicating that the ketocarbonyl does not attack any of these sites.

The effect of introducing a double bond in the fatty alcohol may be seen from a comparison of the

relative distribution of photochemical oxidation sites in stearly and oleyl alcohol (Table III).

TABLE III

Relative distribution of Photochemical Oxidation in stearyl and Oleyl Esters of p-Benzoylbenzoic Acid

Carbon No.	Stearyl ester	Oleyl ester
9	0.1	-
10	8	-
11	17	7.5
12	21	37.7
13	18	1.3
14	12	28.3
15	5	22.6
16	13	1.3
17	6	1.3
18	-	-

Oxidation occurs mainly at the 12th carbon in both instances even though, higher yields are observed for oleyl than for stearyl alcohol. It may thus be possible to conclude that the conformation of both molecules

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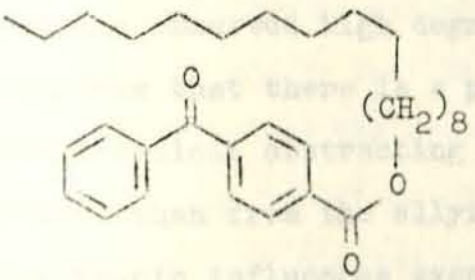
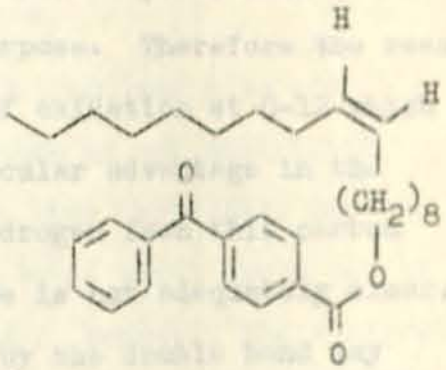
under the irradiation conditions, is such that this carbon spends more time in the vicinity of the carbonyl group than do any others.



Stearyl ester of
p-benzoylbenzoic acid



Oleyl ester of
p-benzoylbenzoic acid

One of the most important factors that facilitate the ease of hydrogen abstraction in free radical reactions is the inherent stability of the resulting radical. It was rather surprizing, therefore, to see a low level of abstraction from the eleventh carbon in view of the fact that the radical formed would be an allylic one. One explanation for this could be that a radical of this type, because of the adjacent double bond, may have two possible sites for formation of a C-C bond with the ketyl radical. If this indeed happens,

the product arising by coupling of C-9 with the ketyl radical would result in the formation of octanoic acid. However, the glc analysis of IV did not show the presence of octanoic acid when compared with standard octanoic acid used for this purpose. Therefore the reason for the observed high degree of oxidation at C-12 which suggests that there is a particular advantage in the ketyl radical abstracting a hydrogen from this carbon rather than from the allyic one is not adequately clear. Electronic influences exerted by the double bond may have some influence but we cannot argue this factor would exceed the relatively greater ease with which an allyic hydrogen is abstracted over a regular methylene hydrogen.

A further difference in the two systems is that in the case of oleyl alcohol nearly 90% of the oxidation takes place among the three carbons 12,14 and 15 while for stearly carbons 80% of the oxidation takes place among the five carbons 11,12,13,14, and 16.

The method of analysis employed in this work does not show whether oxidation has taken place on C-18. However, in the work done by Breslow and co-workers[1] on different fatty alcohols attack on the CH_3 group was not observed. This was explained by the fact that

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benzophenone triplet slects strongly against primary hydrogens. Because of this no further analytical methods which would enable detection of the amount of oxidation on C-18 were attempted.

The amount of oxidation on C-10 was also not determined due to the limitations of our analytical procedure, since the attack at this particular carbon leads to the formation of a lactone which could not be dehydrated and cleaved by ozone. However, the abstraction of hydrogen from this carbon is less likely due to the relatively large bond dissociation energy of vinylic hydrogen and some electronic influences expected to be exerted by the double bond.

The percentage distribution of the oxidation sites reported here are relative values since they compare only components which were identified, normalized to 100.

IV. EXPERIMENTAL

All the solvents used were redistilled. Melting points were determined in a capillary tube on a Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 727B grating instrument. Nuclear magnetic resonance spectra were obtained in CCl_4 on a Varian T-60A spectrometer. Values are given in δ(p.p.m) down field from tetramethylsilane. Mass spectra were determined on Finnigan Model 3200F GC/MS spectrometer attached with Finnigan Model 6100 data system. Column chromatography was performed using silica gel 60 (70-230 mesh). Gas chromatograms were obtained on a Hewlett Packard Model 5710A gas chromatograph equipped with flame ionization detector (FID). Nitrogen was used as carrier gas.

1. Preparation of p-Bromotoluene[23]

A solution of copper (I) bromide was prepared in a 2.5 l three necked flask by heating under reflux 31.5 g (0.124 mol) copper sulphate, 10 g (0.158 mol) copper turnings, 77 g (0.55 mol) sodium bromide, 15 g (8.2 ml) conc. H_2SO_4 and 500 ml water.

In a separate flask 53.3 g (0.5 mol) p-toludine, 400 ml H_2O, 98 g (53.5 ml) conc. H_2SO_4 were mixed and cooled in an ice bath to 5°. To the contents of the flask sodium nitrite solution (35 g/60 ml H_2O) was added slowly with frequent shaking keeping the temperature below 10°.

The flask containing CuBr solution was then equipped for steam distillation and heated so that the solution boiled. While steam was passing rapidly through the mixture the toluene-p-diazonium sulphate solution prepared as described above was added during 30 min from a separatory funnel fitted with a tube leading almost to the bottom of the flask through the side neck. The steam distillation was continued until no more organic matter distilled. The distillate was rendered alkaline with 20% NaOH and the crude p-bromotoluene separated was washed successively with concentrated H_2SO_4 (50 ml), H_2O, NaOH solution

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and finally with water. After drying over $CaCl_2$ the product was filtered and distilled through an air cooled condenser to yield 32 g (37%); mp 25-26° (lit[23] 25-26°).

2. Preparation of Phenyl-p-tolylcarbinol

Magnesium turnings (7.1 g) were washed with sodium dried ether, dried in an oven at 100-110°, and allowed to cool in a dessicator. A solution of 42.75 g p-bromotoluene in 300 ml dry ether was poured into a pressure equalizing separatory funnel and 15 ml of the p-bromotoluene solution was introduced into the flask which contained 7.1 g of magnesium and a crystal of iodine. It was warmed in the water bath to start the reaction. The ether refluxed when the reaction commenced. The water bath was removed and 50 ml of dry ether was added to cover the magnisium. The remaining etheral solution of p-bromotoluene was added dropwise during 40 minutes with stirring. When the reaction became vigorous, the flask was cooled in an ice bath. The reaction was completed in about 2 hrs. This solution of p-toluene magnesium was reacted with benzaldehyde as outlined below.

A solution of 36.75 g (35.13 ml) freshly

prepared benzaldehyde (washed with $NaHCO_3$, dried over Na_2CO_3 and vacuum distilled) in dry ether (200 ml) was added during 30 min to a solution of p-CH_3-C_6H_4-MgBr (Grignard Reagent) with stirring. The mixture was stirred for an additional 90 min. The mixture was then cooled by adding crushed ice and vigorously stirred to complete the decomposition. The stirred solution was treated with saturated solution of NH_4Cl and the ether layer separated was washed successively with $NaHSO_4$ and water. An oily product was recovered from the ether which was then chromatographed on slica gel eluted with ether/hexane solvent gradient. The compound eluted with 25% ether/hexane gave a yield of 8 g (16.2%) which solidified upon standing; δ2.3 (s, 3H, Me), δ3.1 (s, 1H, OH), δ5.53 (s, 1H, Ar-$\underset{OH}{C}$H-Ar), δ7.1 p.p.m (m, 9H, Ar); ir (neat) 3400 cm^{-1} (OH).

3. Preparation of p-Benzoylbenzoic acid[24]

Phenyl-p-tolylcarbinol (9.8 g) was dissolved in acetic acid (52 ml) under reflux condenser. A solution of 19 g CrO_3 in 43.4 ml H_2O, 52 ml acetic acid and 13.6 ml conc. H_2SO_4 was added slowly through the condenser keeping the reaction mixture below its boiling point. The reaction mixture was

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boild for 45 min. The liquid protion was then decanted into cold water to give 800 ml solution. The solid which preciptated was collected by filtration and washed with cold water. It was dissolved in hot water by adding excess conc. HCl. After filtration and washing with cold water, recrystallization from ethanol gave 5 g (44% yiels); mp 197-200°; (lit[24] 197-200°); m/e 226 (M^+).

4. Preparation of Oleyl Ester of p-Benzoylbenzoic Acid (Ester I)

To 1 g (4.4 millimole) p-benzoylbenzoic acid purified $SOCl_2$ (0.8 g, 6 millimole) was added with stirring in water bath under reflux conditions. Refluxing was continued for about 3 hrs.

The excess $SOCl_2$ was removed under vacuum and 1.19 g (4.4 millimole) oleyl alcohol was added with stirring in a water bath under reflux conditions. After 3 hrs refluxing the solution was taken up in benzene (50 ml) and washed successively with sodium bicarbonate solution and water. The benzene layer was concentrated and chromatographed on silica gel and eluted with benzene/hexane solvent gradient. The compound eluted with 30% benzene/hexane gave .8 g (39.5% yield) of ester free of unreacted alcohol; ir (neat) 1670 cm^{-1} (ketone C=O), 1720 cm^{-1} (ester C=O), 1275, 1110 cm^{-1}

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(benzoate C-O); m/e 476 (M^+); δ0.9 (t, 3H, Me), δ1.27 (m, 24H, aliphatic), δ1.92 (m, 4H, allylic), δ4.2 (t, 2H, CH_2O), δ5.2 (t, 2H, vinylic), δ7.2 p.p.m (m, 9H, Ar).

5. Photolysis of Ester (I)

Ester I (0.134 g) in 420 ml of redistilled carbon-tetrachloride was degassed with a stream of nitrogen for 10 minutes. The solution was irradiated for 10 hrs with Hanovia 450 watt high pressure mercury lamp using a pyrexfilter. The lamp was situated inside a double-walled glass well through which cooling water was passed.

Irradiation was monitored by the disapperance of ketone carbonyl at 1670 cm^{-1} in the ir by running spectra every 2 hours using sodium chloride cavity cells, path length of 2.5 mm, without concentrating the solution. After ten hours the solution was concentrated to yield 0.19 g red-brown oil (II); ir (neat) 3500 cm^{-1} (OH), 1720 (ester C=O), 1280, 110 cm^{-1} (benzoate C-O).

6. Dehydration of II

Ester II (0.18) was dissolved in 65 ml of acetic acid and when brought to reflux 0.01 gm iodine crystals

were added. The reflux was continued for one hour. Concentration on rotatory evaporator removed most of the iodine. A benzene solution of the reaction product was washed successively with sodium sulphite solution, water and saturated sodium sulphate solution, and dried ($CaSO_4$). After the removal of the solvent 0.16 gm of III was obtained, ir (neat) 1720 cm^{-1} (ester C=O), 1280, 1100 Cm^{-1} (benzoate C-O).

7. Ozonolysis of III

The entire dehydrated product (III) was dissolved in 5 ml of CH_2Cl_2 and 50 ml of methanol and cooled to $-35^{o}C$. Excess ozone was passed through the solution until potassium iodide trap placed behind the reacting mixture changed colour from colourless to intense red indicating that the reaction is complete. After the removal of the solvent on rotatory evaporator 5 ml of 30% H_2O_2 was added and refluxed for 45 minutes. After cooling, the whole content was dissolved in 100 ml of ethyl acetate and the aqueous layer was separated. The organic layer was washed with 25 ml of H_2O and dried (Na_2SO_4). Evaporation of the solvent gave 0.15 gm of IV and V.

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8. Methylation of IV and V

Diazomethane generated from 4.12 gm of N-nitrosomethyl urea and 10 ml of 50% KOH solution and 40 ml of ether cooled to 5°C was added drop by drop to the cooled etheral solution of a mixture of IV and V until the colour of the mixture was changed to yellow. After drying (Na_2SO_4) and removal of the solvent a mixture of VI and VII was obtained.

9. Preparation of Cyclooctanone[28]

In a 500 ml two necked round bottomed flask fitted with mechanical stirrer 21.3 gm of cyclooctanol in 417 ml of acetone was cooled to 20°C. To the cooled solution 41.7 ml of $H_2Cr_2O_7$ (prepared by dissolving 22.3 gm CrO_3 in 41.7 ml H_2O and mixing with 19.3 ml H_2SO_4) was added slowly with vigorous agitation until excess $H_2Cr_2O_7$ was present. The mixture was neutralized with 21 gm $NaHCO_3$, filtered and the filtrate was concentrated to 37 ml. Saturated NaCl solution (167 ml) was then added to the filtrate and the resulting mixture was extracted with ethet. The extract was washed with water and dried (Na_2SO_4). After removal of the solvent, the residue was distilled under reduced pressure to give 12 gm

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(52.7%) of cyclooctanone, mp 28° (lit[28] 28°).

10. Preparation of 1-methylcyclooctanol

In a one liter three-necked flask equipped with sealed stirrer, separatory funnel, condenser and water bath 2 gm of magnesium (washed with dry ether in 30 ml of dry ether) was transferred. After addition of few crystals of iodine a portion of a solution of 5 ml CH_3I (0.08 mole) in 50 ml of dry ether from the funnel was introduced. As the vigorous reaction commences, the stirrer was set in motion and the remainder of the methyl iodide was added at such a rate that a steady refluxing of the reaction was maintained. After completion of the addition, refulxing was continued in a hot water bath for 45 minutes. A solution of 10 gm (0.08 mole) of cyclooctanone in 50 ml of dry ether was introduced drop by drop during 30 min and refluxing was continued for one hour. After cooling, the reaction mixture was transferred to 200 gm of crushed ice and treated with saturated NH_4Cl solution and the organic layer was extracted with ether. The ether extracts were combined, dried (K_2CO_3), and the solvent removed. The residue was distilled under reduced pressure to yield 1.5 gm of pure

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1-methylcyclooctanol; ir (neat) 3400 cm^{-1} (OH).

11. Dehydration of 1-methylcyclooctanol

1-methylcyclooctanol (1 g) was dissolved in 25 ml of cyclohexane to which 10 ml of 50% H_2SO_4 was added. The mixture was stirred at room temperature for one hour. It was then washed with H_2O, $NaHCO_3$, and again with water, dried over Na_2SO_4. After removal of the solvent 0.8 gm (92% yield) of 1-methylcyclooctene was obtained; ir (neat) 3100, 1680 cm^{-1} (olefin), δ1.4 (m, 8H, $-(CH_2)_4-$) δ1.66 (s, 3H, Me), δ2.13 (m,4H, allylic), δ5.33 p.p.m (t, 1H, vinylic).

12. Ozonolysis of 1-Methylcyclooctene

1-methylcyclooctene (0.5 g) was dissolved in 5 ml CH_2Cl_2 and 50 ml CH_3OH and excess ozone was passed through it. After the removal of the solvents, 3 ml 30% H_2O_2 was added to it and refluxed for 45 minutes. The whole content was dissolved in hexane (50 ml) and the organic layer was separated. After drying (Na_2SO_4) and filtering the solvent was removed and the residue was re-crystallized from ethanol to give 0.35 g

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(50.7% yield) of 8-ketononanoic acid.

13. Preparation of Morpholinocyclohexene[30]

One mole (98 gm) of cyclohexanone, 1.2 moles (104.4 g) of morpholine, 0.2 gm of p-toluenesulphonic acid and 200 ml of toluene was taken in a 500 ml round bottomed flask equipped with a mechanical stirrer, a water separator (Dean-stark trap) and a reflux condenser. The mixture was refluxed on oil bath until about 18 ml of water was collected; it was then cooled, washed with small amount of water, (to remove p-toluenesulphonic acid) dried over Na_2SO_4 and filtered. After the removal of the solvent the residue was distilled under vacuum to give 54 g (32.3% yield) of morpholinocyclohexene.

14. Acylation of Morpholinocyclohexene[30]

In a 500 ml three necked flask equipped with a dropping funnel, a reflux condenser and stirrer, 0.2 moles of the enamine (morpholinocyclohexene), 0.2 moles (24.24 gm) triethylamine and 300 ml of benzene was taken. The mixture was heated to 35°C and 0.12 moles (22.2 gms) of propionyl chloride was added drop by drop keeping the temperature at

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35°. After the addition was complete, the mixture was heated for one hour keeping the temperature at 35°. Then 100 ml of 20% HCl was added and the mixture was refluxed for 30 min under stirring. The aqueous layer was removed and the organic layer was washed with water until it was neutral. The aqueous portion was brought to pH 6 by addition of dilute NaOH and was extracted twice with benzene. The benzene extracts were combined and dried over Na_2SO_4 and filtered. Evaporation of the solvent gave a yield of 16.9 g (55%).

15. Preparation of 7-Ketononanoic Acid[30]

To 0.19 moles of propionylcyclohexanone, 3 times molar quantity of hot 60% NaOH at 100° was added under stirring, and the mixture was kept at the same temperature for further 15 minutes. The mixture was then cooled, and dissolved in about 200 ml of H_2O. To the solution concentrated HCl was added drop by drop until it become about pH of 8 and then it was extracted with ether. The aqueous phase was strongly acidified with concentrated HCl and was extracted with chloroform. The extracts were combined and the solvents were evaporated. The residue was then distilled under vacuum to give 10.5 g (32%) of 7-ketononanoic acid; mp 29°,

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(lit[30] 29°); ir (neat) 3600-2200 cm^{-1} (acid OH), 1720 cm^{-1} (acid and ketone C=O); δ1.02 (t, 3H, Me), δ1.4 (m, 6H, $-CH_2-$), δ2.35 (m, 6H, $-CH_2\overset{O}{\overset{\|}{C}}-$), δ11.1 p.p.m (s, 1H, OH).

16. Synthesis of 6-ketononanoic Acid[30]

In procedure identical to that outlined above, cyclopentanone (84 g), morpholine (104.4 g), p-toluenesulphonic acid (0.2 g), in toluene (200 ml) were reacted to give 94 g (61.4% yield) of morpholinocyclopentene. This intermediate enamine (0.2 mole) was then reacted with butyrylchloride (0.24 mole) in the presence of 0.2 moles of $(CH_2)_3N$ in benzene (300 ml) to produce 16.3 g (53%) of butyrylcyclopentanone. This β-diketone (0.1 mole) when treated with three times molar quantity of 60% NaOH at 100° gave 9.3 g (54.7/) of 6-ketononanoic acid; mp 35° (lit[30] 35°); ir (neat) 3600-2300 cm^{-1} (acid OH), 1710 cm^{-1} (acid and ketone C=O); δ0.87 (t, 3H, Me), δ1.57 (m, 6H, $-CH_2-$), δ2.26 (m, 6H, $-CH_2-\overset{O}{\overset{\|}{C}}-$), δ11.1 p.p.m. (s, 1H, OH).

17. Preparation of 1-Butylcyclopentanol

In a one liter three-necked flask equipped with sealed stirrer, separatory funnel and condenser, arranged to be heated in the bath of hot water, 6 gm

of magnesium in 48 ml of dry ether was transferred. After addition of few crystals of iodine a portion of a solution of butylbromide (34.25 g) in dry ether (50 ml) from the funnel was introduced. As the vigorous reaction commences, the stirrer was set in motion and the remainder of the butylbromide was added at such a rate that a steady refluxing of the reaction was maintained. After completion of the addition, refluxing was continued for 30 minutes, followed by addition of cyclopentanone (21 g) in 35 ml of dry ether and the mixture was stirred for a further one and half hours. The mixture was then transferred to 150 g of crushed ice and treated with a solution of NH_4Cl (30 g/41.6 ml H_2O) and the organic layer was extracted with ether. The ether extracts were dried over K_2CO_3, filtered, and the solvent was evaporated. The residue was distilled under reduced pressure to yield 7.3 g (20.6%) of pure 1-butylcyclopentanol; ir (neat) 3400 cm^{-1} (OH).

18. Dehydration 1-butylcyclopentanol

1-butylcyclopentanol (1 g) was dissolved in cyclohexane (25 ml) and 10 ml of 50% aqueous H_2SO_4 was added to it. The mixture was stirred at room temperature for one hour. It was then washed with

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$NaHCO_3$, H_2O, and dried over Na_2SO_4. After removal of the solvent 0.8 g (92%) of 1-butylcyclopentene was obtained; ir (neat) 3100, 1670 cm^{-1} (olefin); δ0.95 (t, 3H, Me), δ147 (m, 4H, $-CH_2-CH_2-$), δ2.23 (m, 6H, allylic), δ5.17 p.p.m.(t, 1H, vinylic).

19. Ozonolysis of 1-butylcyclopentene

1-butylcyclopentene (0.5 g) dissolved in 5 ml CH_2Cl_2 and 45 ml of CH_3OH was treated with excess ozone at -35°. After the removal of the solvent, 3 ml of 30% H_2O_2 was added to it and refluxed for 45 minutes. To the whole content 50 ml of hexane was added and the organic layer was separated from the aqueous layer. After drying, filtering and evaporation of the solvent, the residue was re-crystallized from ethanol to give 0.47 g (68.1%) of 5-ketononanoic acid; mp 53°(lit[30] 54).

20. Methylation of the Standard Keto Acids

Approximately 30 mg of each of the keto acids in ether was treated with CH_2N_2 as outlined above to give the corresponding methylketononanoates.

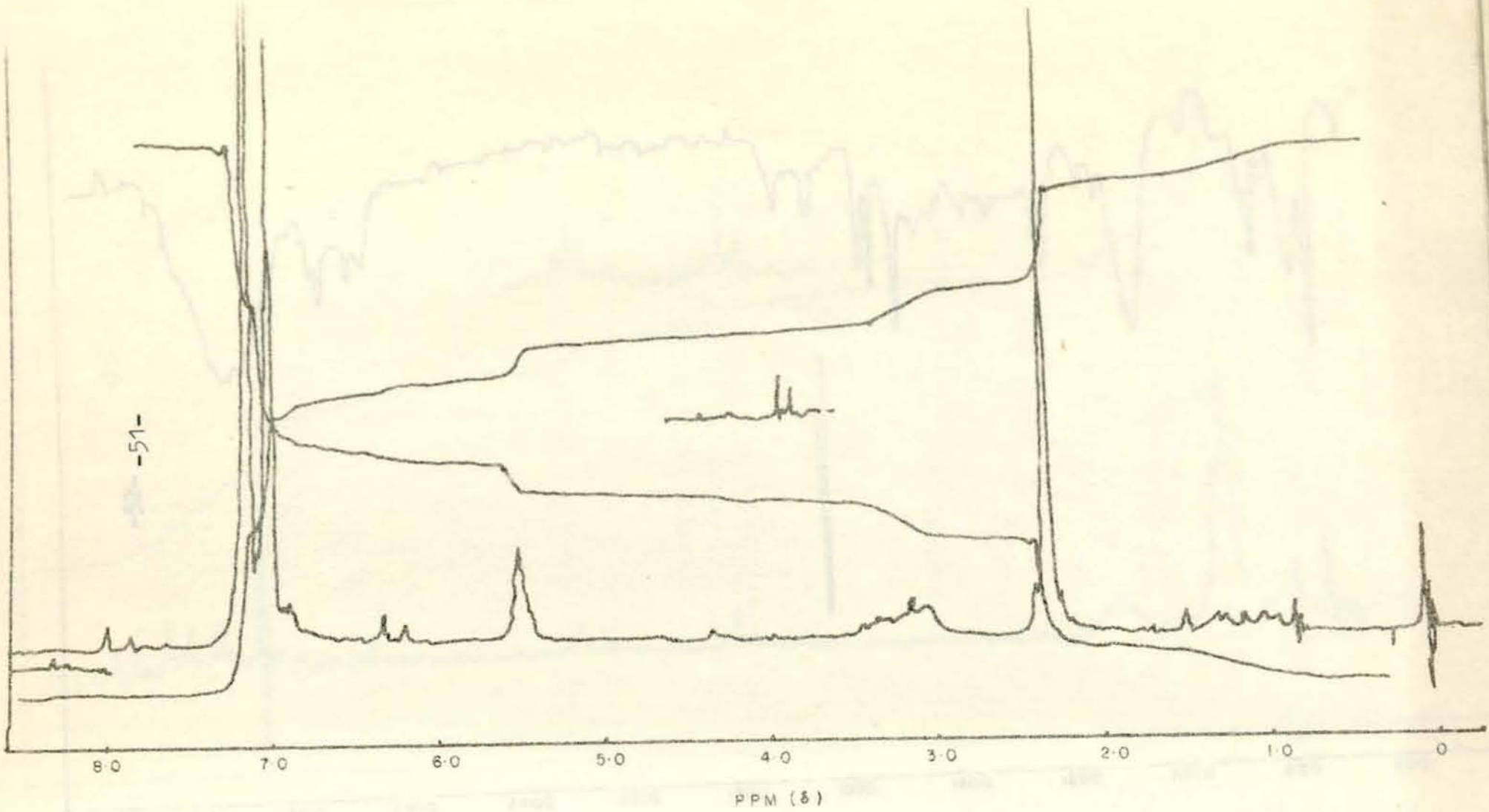
21. Gas Chromatographic Analysis

A 5 ft stainless steel (1/8") column packed

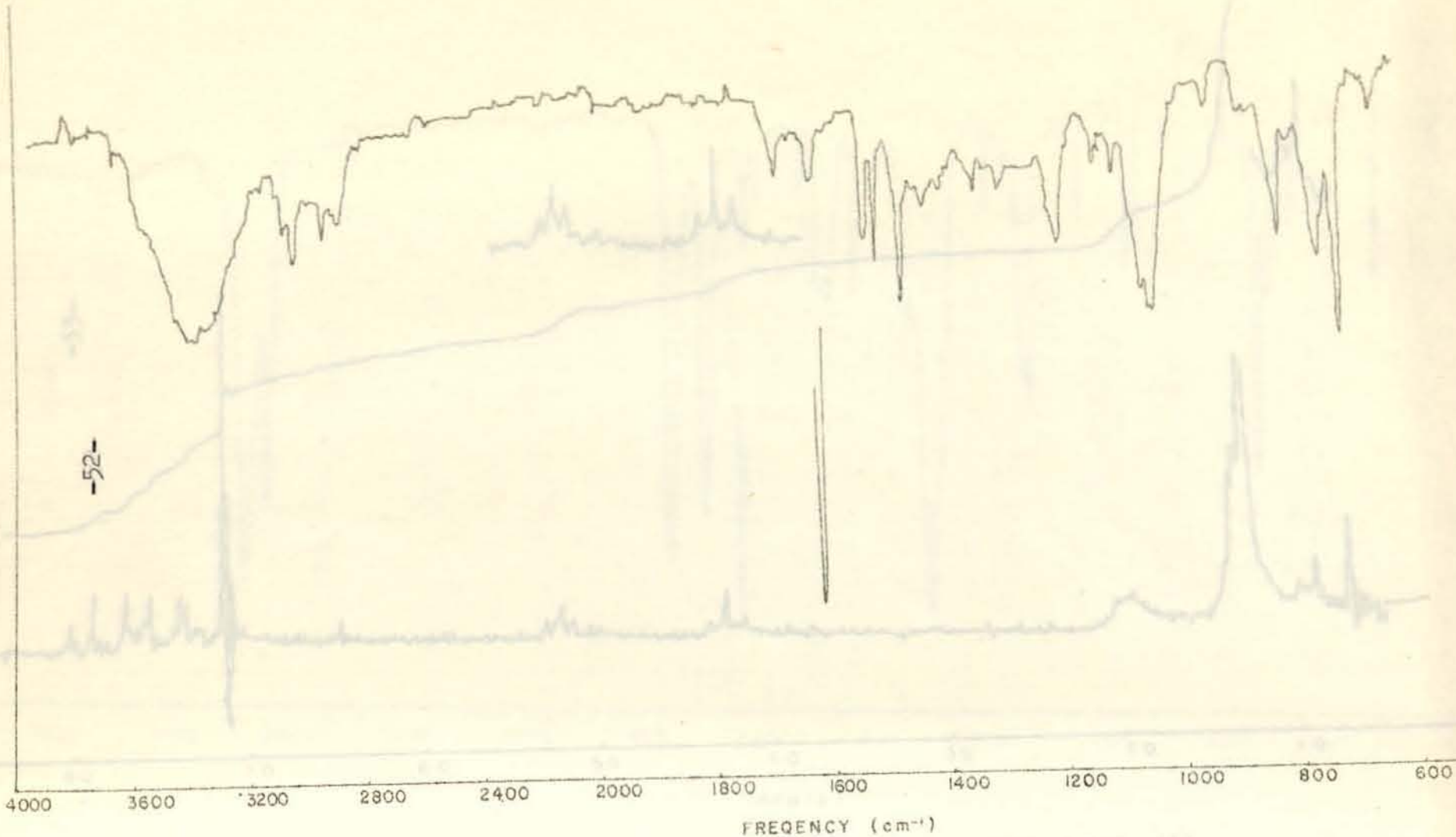
with 10% carbowax 20 M terminated with terephthalic acid (10%) on 100/120 Gaschrome Q was used in this analysis. The methylated unknown mixture and synthesized standard compounds were chromatographed on the column mentioned above at iso-thermal oven temperature under the following conditions.

Column temperature	150°
Inlet temperature	200°
Detector temperature	250°
Chart speed	15 in/hr
Injector volume	2 µl

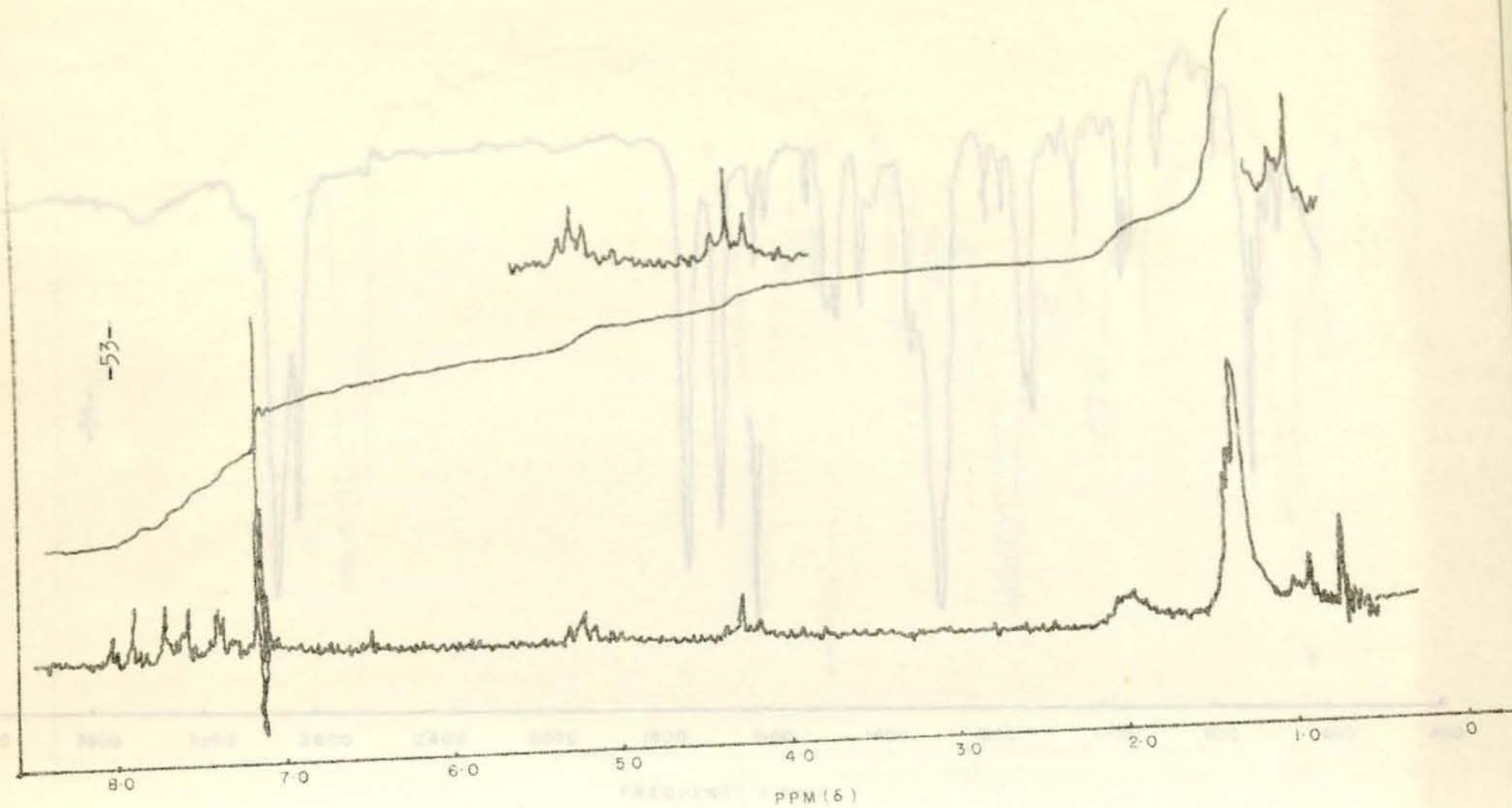
The retention times of the standard compounds and unknown mixture were correlated. The areas of the peaks identified were calculated and the total area was normalized to 100 to give the percentage distribution of the oxidation sites.



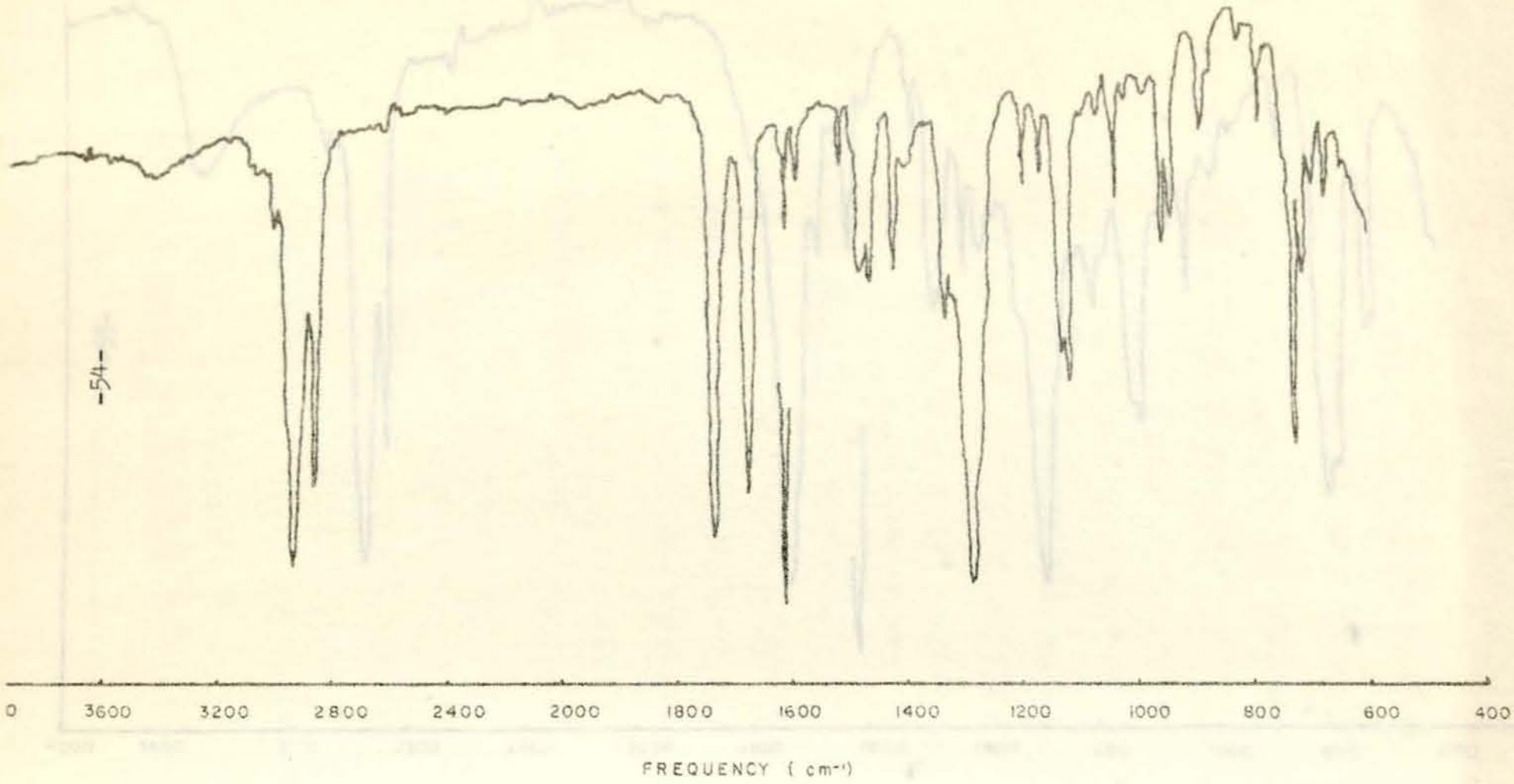
Nmr Spectrum of Phenyl - P - Tolylcarbinol



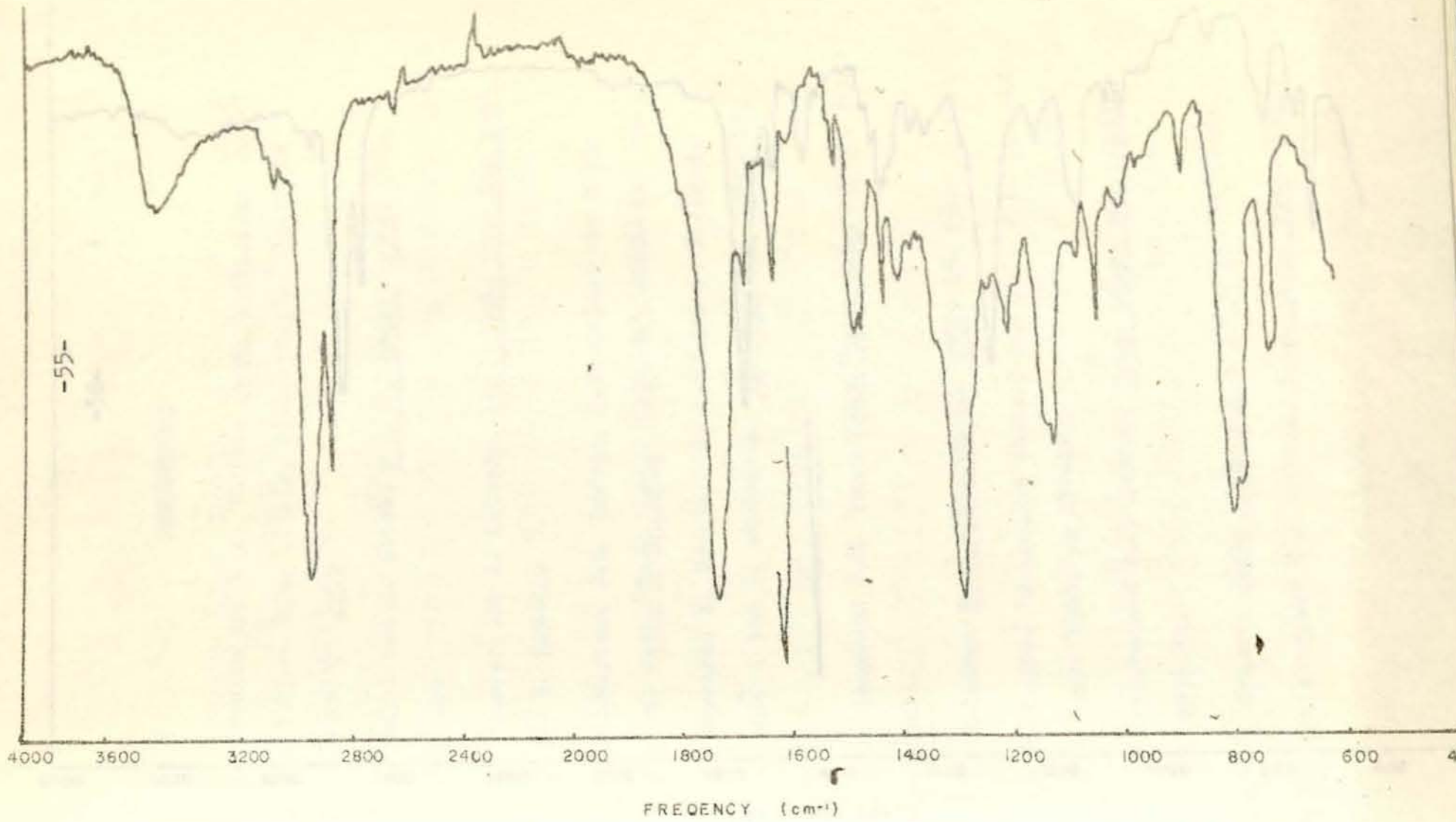
Ir Spectrum of PHENYL-P-TOLYLCARBINOL (20)



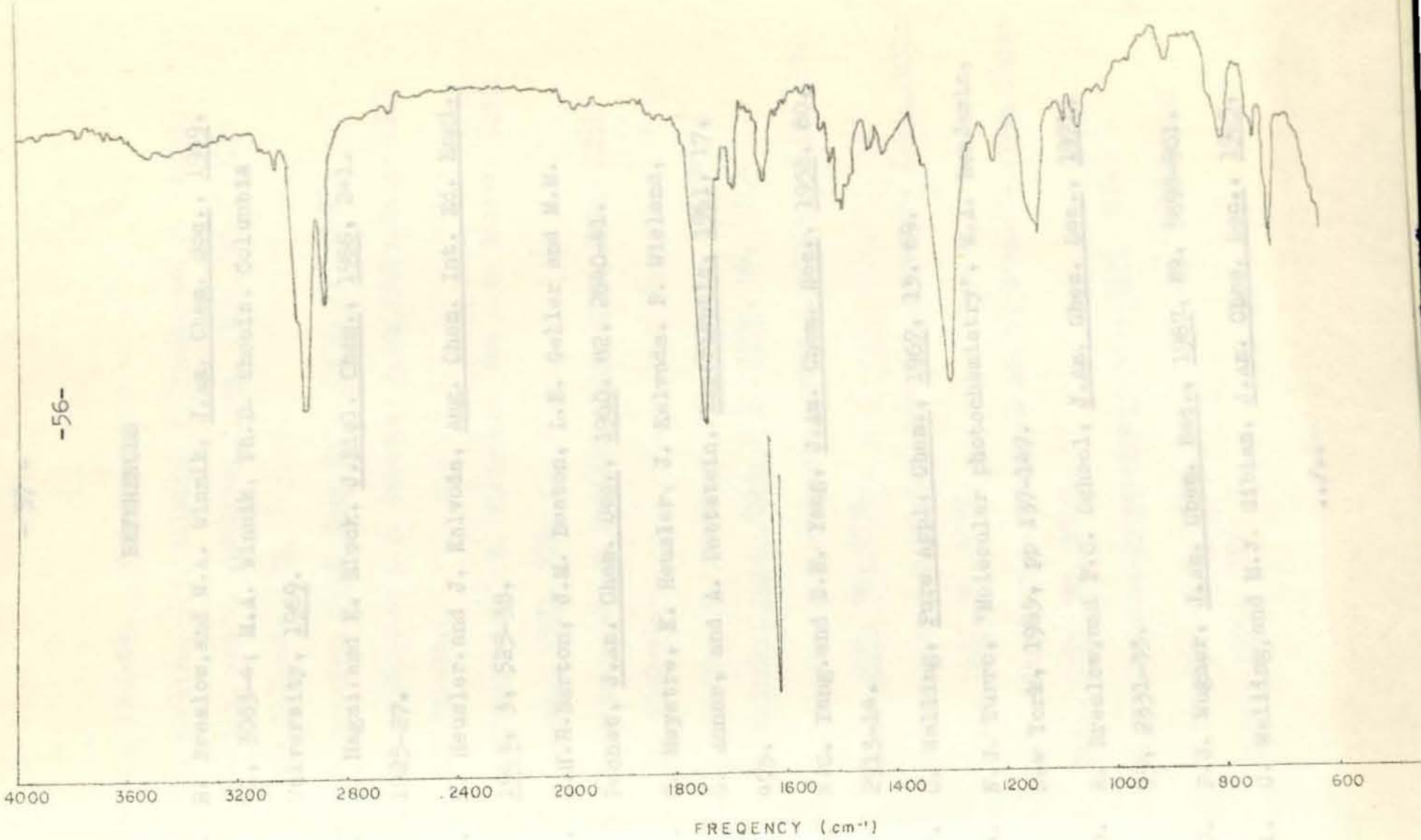
Nmr Spectrum of OLEYL ESTER of P-BENZOYL BENZOIC ACID (I)



Ir Spectrum of OLEYL ESTER of P-BENZOYLBENZOIC ACID (ester I)



Ir Spectrum of II



Ir Spectrum of III

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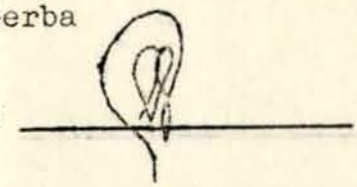
D E C L A R A T I O N

I, the undersigned, declare that this thesis is my work and that all sources of material used for the thesis have been duly acknowledged.

Sendaba Gerba

Signature 

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