REARRANGEMENTS OBSERVED DURING THE TRICHLOROMETHYLATION OF SOME POLYSUBSTITUTED BENZENES

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY
JERRY FREDERICK JANSSEN
1967

THESIS

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REARRANGEMENTS OBSERVED DURING THE TRICHLOROMETHYLATION OF SOME POLYSUBSTITUTED BENZENES

presented by

Jerry Frederick Janssen

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Harold Hart
Major professor

Date November 13, 1967

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ABSTRACT

REARRANGEMENTS OBSERVED DURING THE
TRICHLOROMETHYLATION OF SOME
POLYSUBSTITUTED BENZENES

by Jerry Frederick Janssen

The reaction of carbon tetrachloride with tetrasubstituted benzenes in the presence of anhydrous aluminum chloride produces a mixture of polysubstituted benzotrichlorides. The relative rates of reaction are in the order prehnitene > isodurene ≥ 2-fluoro-1,3,5-trimethylbenzene > 2-chloro-1,3,5-trimethylbenzene > 2-bromo-1,3,5-trimethylbenzene. The chief side product in the cases of isodurene and 2-fluoro-1,3,5-trimethylbenzene are the vicinally substituted products. That is, isodurene leads to chiefly 2,3,4,6-tetramethylbenzotrichloride and 2,3,4,5-tetramethylbenzotrichloride while 2-fluoro-1,3,5-trimethylbenzene gives 3-fluoro-2,4,6-trimethylbenzotrichloride and 4-fluoro-2,3,5-trimethylbenzotrichloride. The structures of the rearranged products from the bromo- and chloro-compounds were not established but are assumed to be analogous to that derived from the fluoro-compound.

Studies of the products derived from isodurene labeled with a trideuteriomethyl group in the 2

position and again in the 5 position indicate that the reaction probably involves attack of the electrophilic reagent at various sites in the benzene ring followed by simple 1,2-shifts of methyl groups to yield the observed product mixture.

The synthesis of twenty-four new polysubstituted benzene compounds is reported.

REARRANGEMENTS OBSERVED DURING THE TRICHLOROMETHYLATION OF SOME POLYSUBSTITUTED BENZENES

By

Jerry Frederick Janssen

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
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DEDICATION

This thesis is dedicated to three teachers who have had a profound influence upon my teaching career:

Mr. Loren Grout
Roosevelt Junior High School
Mason City, Iowa

Dr. James W. Kercheval
University of Northern Iowa
Cedar Falls, Iowa

Dr. Frederick B. Dutton
Michigan State University
East Lansing, Michigan

The decision to enter upon a career of science teaching is due in part to their encouragement, support and example.

ACKNOWLEDGMENT

The author wishes to express his sincere thanks to Dr. Harold Hart for his encouragement and support throughout the pursuit of this work. Appreciation is also extended to the Chemistry Department of Michigan State University for financial support in the form of a teaching assistantship and to the E. I. du Pont de Nemours Company for a du Pont Teaching Fellowship from September, 1965 to June, 1966.

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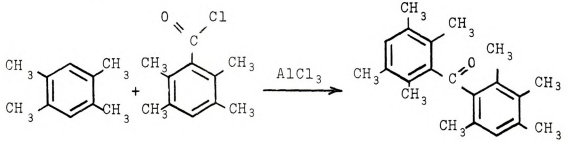
INTRODUCTION

I. Introduction

In the substitution of already highly-substituted aromatic compounds with bulky electrophiles, migration of substituents to previously unoccupied positions has frequently been observed. The most notable example of this phenomenon is the widely studied Jacobsen reaction. Several examples of similar anomalous electrophilic substitutions have been reported. Rekker and Nauta (1) have reported the reaction of durene with the acid chloride of 2,3,5,6-tetramethylbenzoic acid (I) to produce the rearranged ketone (II).



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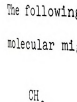



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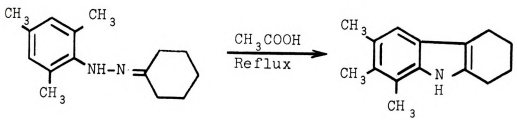
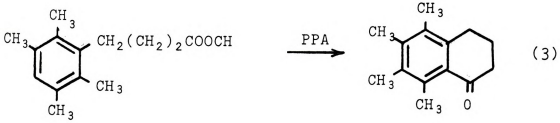


(III) (IV)

The following ring closure reactions also involve intramolecular migrations of substituent groups:



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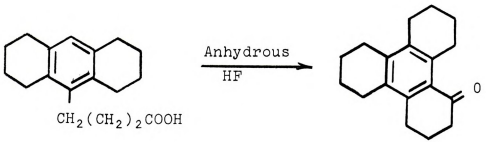

(4)

Although the above examples do not technically constitute cases of the Jacobsen reaction because there has been no sulfonation, they bear many striking similarities to it. All of the cases exhibit intramolecular migration of substituents to vicinally substituted

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products in the presence of an acid catalyst. These similarities have prompted one author (5) to suggest that the name "Jacobsen reaction" be broadened to cover all such reactions. In order to point up the similarities and differences between the Jacobsen reaction and the rearrangements observed during the trichloromethylation reactions which occupy the present study, a brief historical treatment of these two reactions will occupy the first part of this thesis.

II. The Jacobsen Reaction

A. Scope

The rearrangement of polysubstituted aromatic compounds upon sulfonation is termed the Jacobsen reaction after Oscar Jacobsen, its principal early investigator. An excellent review of the published literature prior to 1942 may be found in the first volume of Organic Reactions (6). Substituents known to migrate under the conditions of the Jacobsen reaction are iodine, bromine, chlorine and alkyl groups. Normally the substrate is mixed with concentrated sulfuric acid or fuming sulfuric acid and may then be heated briefly or allowed to stand at room temperature for extended periods. The product of this treatment is a mixture of substituted benzenesulfonic acids derived from both intra- and intermolecular migration of the substituents. The most common products

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of intramolecular rearrangements are vicinally substituted molecules. Since the sulfonic acids are easily desulfonated by steam distillation, the reaction has synthetic application in the production of the more valuable vicinal products from the more common isomers. Thus prehnitene* can be produced from durene and/or isodurene and the more valuable 3-halo-pseudocumenes from the readily available 5-bromo- and 5-chloropseudocumenes.

By-products of the Jacobsen reaction are sulfur dioxide and (often) tarry masses and polymeric materials. The ease with which rearrangement occurs depends upon the nature and number of substituents attached to the benzene ring. If only halogen is present, rearrangement will occur even if the ring is monosubstituted. Thus iodo- and bromobenzene will react in stepwise fashion to produce first p-dihalobenzene, next 1,3,5-trihalobenzene, then 1,2,4,5-tetrahalobenzene, and finally hexahalobenzene (7). The reaction conditions must be more stringent in the case of bromobenzene, and chlorobenzene does not react in this manner.

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*To facilitate the discussion, the common names of the polymethylbenzenes will be used when reference is made to the parent hydrocarbons; i.e., mesitylene (1,3,5-trimethylbenzene), pseudocumene (1,2,4-trimethylbenzene), hemimellitene (1,2,3-trimethylbenzene), isodurene (1,2,3,5-tetramethylbenzene), durene (1,2,4,5-tetramethylbenzene), and prehnitene (1,2,3,4-tetramethylbenzene). When referring to derivatives of these hydrocarbons, recourse will be made to the IUPAC naming rules to avoid ambiguity.

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A study of the polyalkylhalobenzenes (8) has shown that increasing the number of alkyl substituents favors the migration of the halogen atom but simultaneously results in the production of greater amounts of tarry by-product. The relative migratory aptitude of the halogens in these compounds seems to be in the order I>Br>Cl. For example, the monochloroxylenes merely sulfonate under conditions of the Jacobsen reaction whereas the monoiodoxylenes afford polyiodoxylenes in high yield. The reaction of the halopseudocumenes has already been cited.

With monochlorotetramethylbenzenes, migration of methyl occurs with the expected vicinally substituted products resulting. The iodotetramethylbenzenes tend to undergo disproportionation whereas the bromo-compounds fall into an intermediate class showing both inter- and intramolecular migration products. Only a few fluoro-compounds have been studied in connection with the Jacobsen reaction (9). No instance of migration of a fluorine atom has been noted.

In the case of the polyalkylbenzenes, the Jacobsen reaction is limited to tetra- or pentasubstituted benzenes containing tetramethylene rings and/or short, unbranched alkyl side chains. Mesitylene (10), pseudocumene (10), hemimellitene (11), 1,3,5- and 1,2,4-triethylbenzene (12) merely sulfonate without rearrangement. Tetraalkylbenzenes

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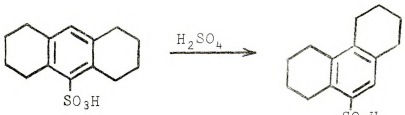
in which the substituents are isopropyl or larger tend to eliminate alkyl groups resulting in trialkylbenzenesulfonic acids (13).

Durene (10, 14) and isodurene (10, 15) react to produce prehnitenesulfonic acid although the yield is greater in the case of durene. 1,2,4,5-tetraethylbenzene and 1,2,3,5-tetraethylbenzene react in an analogous manner (12) to produce 1,2,3,4-tetraethylbenzenesulfonic acid. Prehnitene is only sulfonated without rearrangement (10). The ethyltrimethylbenzenes similarly rearrange (13, 16, 17) but migration of either methyl or ethyl or loss of either results in a complex product mixture which is difficult to analyze. Pentamethylbenzene disproportionates (18, 19) to give hexamethylbenzene and prehnitenesulfonic acid.

The Jacobsen reaction with compounds containing saturated rings fused to the benzene nucleus seems to be limited to those substances containing tetramethylene rings. Octahydroanthracene-9-sulfonic acid (V) was shown by Schroeter and Götzsky (20) to rearrange to octahydrophenanthrene-9-sulfonic acid (VI)



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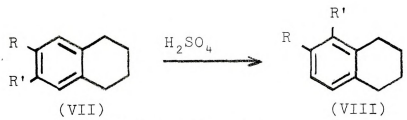
in good yield. A series of dialkyltetralins were studied by Smith and Lo (21) and although the results varied with the nature of the substituents, the results paralleled those of the tetraalkylbenzenes to which the tetralins were structurally related. When both alkyl



(VII) (VIII)

(a) R = R' = CH_3
(b) R = R' = C_2H_5
(c) R = CH_3, R' = n-C_3H_7
(VIId) R = CH_3, R' = iso-C_3H_7
(VIIId) R = CH_3, R' = H

substituents were methyl (VIIa) or ethyl (VIIb) the expected vicinal products (VIIIa) and (VIIIb) were obtained. When one of the groups was n-propyl (VIIc) the larger group was found in the 5-position (VIIIc). Since it had not undergone rearrangement to the more stable isopropyl group, the workers concluded that it was the tetramethylene ring which had opened and reclosed ortho to the n-propyl group rather than the latter migrating. Branched groups such as isopropyl (VIId) were lost resulting in monoalkyltetralins (VIIId).

s-Hydrindacene (IX) did not undergo the Jacobsen reaction (22) and 5,6,7,8-tetrahydrobenz[f]indan (X) did not rearrange but was dehydrogenated by the action



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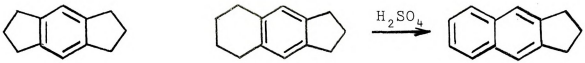

(IX) (X) (XI)

of the sulfuric acid to (XI).

B. Mechanism

The Jacobsen reaction has been the subject of much mechanistic speculation (see for example 23, 24). It has been shown that it is probably the sulfonic acid and not the parent hydrocarbon which undergoes rearrangement. Thus, Smith and Cass (10) have shown that durenesulfonic acid will rearrange to prehnitenesulfonic acid in contact with phosphorus pentoxide whereas the parent hydrocarbons are unaffected by this treatment. Support for this observation is found in the recent work of Marvell and Graybill on the rearrangement of durenesulfonic acid in polyphosphoric acid (25). They found that when in PPA all of the sulfonating agents were removed by scavenging with o-xylene, the only reaction which occurred was desulfonation.

Arnold and Barnes (22) have proposed an ionic mechanism involving the formation of an intermediate disulfonic acid. Applied to the case of durene, the mechanism is as follows:

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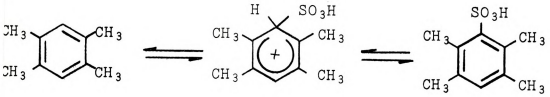
(b)

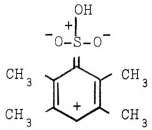
S

(a) the hydrocarbon is sulfonated



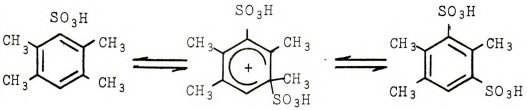
(XII)

(b) because the sulfonic group in (XII) is sterically crowded, contributions to the resonance hybrid by canonical structures such as (XIIa) are diminished.



(XIIa)

The resulting diminished positive charge in the ring permits a second sulfonation which takes place preferentially at a position meta to the first sulfonic group.



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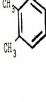

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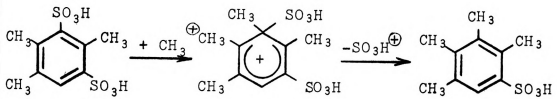
(c) attack of the displaced alkyl cation at the position of the most hindered sulfonic acid group results in the observed rearranged product.



The above mechanism is subject to the criticism put forward by Smith and Lo (21). They have showed that 6-n-propyl-7-methyltetralin (VIIc) was converted to 5-n-propyl-6-methyltetralin (VIIIc) by the action of sulfuric acid. If the migration had involved a solvated but otherwise unencumbered alkyl cation as Arnold and Barnes suggest, one would expect the n-propyl cation to rearrange to the more stable isopropyl cation. Further refutation of the above mechanism is provided by the work of Marvell and Webb (26). They found that 1,2,4,5-tetraethylbenzene labeled with C^{14} at the alpha position of the ethyl groups underwent rearrangement with better than 90% retention of labeling at the alpha position. On this basis they ruled out any process involving hydrogen-bridged structures, equilibria between ethylene and ethyl cations, or equilibria involving hydride shifts in ethyl carbonium ions. Furthermore, the

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(XIIIc).

migrating alkyl group cannot become completely free of the aromatic ring since Goto and Suzuki (13) have shown that the Jacobsen reaction with a mixture of durene and 1,2,4,5-tetraethylbenzene results predominantly in prehnitene and 1,2,3,4-tetraethylbenzene with little crossing.

The above mechanism of Arnold and Barnes can be accommodated to these criticisms if one assumes that the migrating group is never completely free of the aromatic ring. Such a mechanism for the Jacobsen reaction has been proposed by Dewar (27). He suggests that the initial sulfonation step occurs at one of the substituted positions in durene resulting in the benzenonium ion (XIII).



(XIII)

The ion (XIII) then rearranges via a series of 1,2-shifts involving alternately sigma-complexed intermediates (XIIIa) and pi-complexed intermediates (XIIIb) until the thermodynamically most stable product (XIV) is formed by the deprotonation of its conjugate acid (XIIIc).

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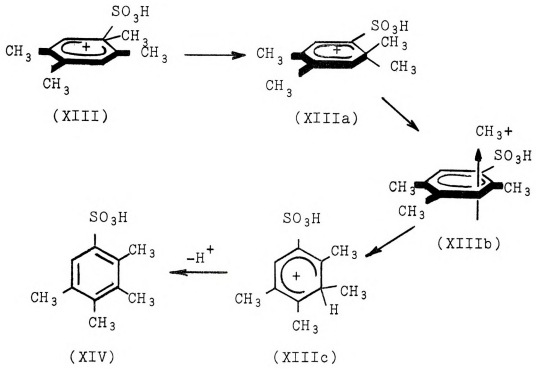

Disproportionation products such as the trimethylbenzene- and pentamethylbenzenesulfonic acids arise from S_N2 attack of an unsubstituted molecule upon a sigma complex such as (XIIIa or XIIIc).

In opposition to the above mechanisms which necessitate sulfonation and rearrangement of the sulfonic acid, Kilpatrick and Meyer (28) propose a mechanism which involves desulfonation, rearrangement of the hydrocarbon and irreversible sulfonation of the vicinally substituted benzene. Although durene and prehnitene give predominantly the more basic isodurene in mixtures of anhydrous HF and boron trifluoride (29), any of these hydrocarbons sulfonates to give almost exclusively

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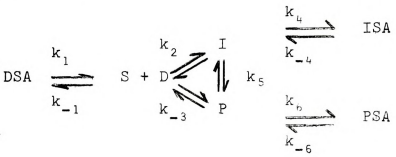
prehnitenesulfonic acid in concentrated sulfuric acid. These workers thus conclude that sulfonation, desulfonation, rearrangement and resulfonation to the stable prehnitenesulfonic acid provide a cycle which leads to an accumulation of the latter. This scheme is presented in chart form below:



DSA = durenesulfonic acid
PSA = prehnitenesulfonic acid
ISA = isodurenesulfonic acid
D = durene
P = prehnitene
I = isodurene
S = SO_3H+

For this mechanism to explain the observed facts in connection with the Jacobsen reaction it is necessary that k_{-6} in the above equilibrium be small in comparison with the other rate constants. However, serious doubt is cast upon this mechanism by the observation of Bohlmann and Riemann (30) that prehnitenesulfonic acid rapidly exchanges sulfur with S^{35} labeled sulfuric acid. Unless such exchange involves a symmetrical ion such as (XV), it is doubtful that the Kilpatrick mechanism

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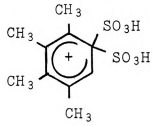
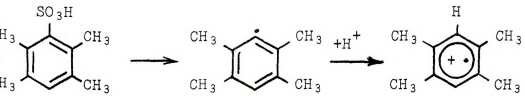


(XV)

can completely explain the course of the Jacobsen reaction of durene.

Based upon their observation that the Jacobsen reaction exhibited an induction period which disappeared upon the addition of peroxydisulfate to the reaction mixture, Bohlmann and Riemann suggest that the mechanism proceeds rather by a radical-cation mechanism. Their mechanistic proposal closely parallels that of Kilpatrick in that they suggest that it is a desulfonated species that rearranges. They suggest, however, that this species is a radical cation (XVI) formed by the dissociation of the hindered durenesulfonic acid rather than durene itself.



(XVI)

The bisulfite radical can dissociate to give sulfur dioxide and a hydroxyl radical.

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$$\cdot SO_3H \rightarrow SO_2 + \cdot OH$$

Equilibration of the radical cations of durene, isodurene and prehnitene followed by reversible sulfonation leads to an accumulation of the stable prehnitenesulfonic acid.

Although this mechanism satisfactorily accounts for the by-product sulfur dioxide it suffers from the same criticisms of the Kilpatrick mechanism. Bohlmann and Riemann showed that when the starting durene had been ring-labeled with C^{14} at the four methylated positions, the two unmethylated positions in the resulting prehnitene were not equally labeled. The position bearing the sulfonic acid group in the product contained 17.3% of the original C^{14} whereas the adjacent unsubstituted position contained only 13.0%. If this prehnitenesulfonic acid had been formed from prehnitene produced by equilibration of the hydrocarbons, these two positions should have been equally labeled.

It would appear that to date there has not been sufficient experimental data presented to define a unique mechanism for the Jacobsen reaction. Indeed, it is possible that for many of the reactions classified

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under the heading "Jacobsen reaction" the mechanism differs from that involved in the sulfonation of polyalkylbenzenes. However, there seems to be common agreement that the rearrangement probably involves protonation of the initially formed sulfonic acid followed by a series of reversible 1,2-shifts and deprotonation. The major product observed at equilibrium is then the most stable sulfonic acid which may not necessarily be that of the most stable polysubstituted substrate isomer.

III. The Trichloromethylation Reaction

A trichloromethyl group may be introduced into an organic molecule by any one of three means depending upon the method by which the $-CCl_3$ moiety is generated. Kharasch (31) demonstrated in 1945 that trichloromethyl radicals could be generated by the action of peroxide on carbon tetrachloride or chloroform and would add to olefins. Since that time the reaction has been applied to a variety of halomethanes and olefinic substrates with success (32). The trichloromethyl anion, generated by the action of bases upon chloroform adds to aldehydes (33-36) and ketones (37-40) to produce trichloromethylcarbinols. More recently (41) it has been shown that the thermal decomposition of sodium trichloroacetate in the presence of anhydrides leads to trichloromethyl keto-acids or trichloromethyllactols.

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None of the preceding reactions serves to introduce a trichloromethyl group into an aromatic nucleus, however. The generation of a trichloromethyl cation or $-CCl_3$ group in which the carbon is electron deficient is necessary for the trichloromethylation of aromatic substrates. The reaction of carbon tetrachloride with anhydrous aluminum chloride appears to provide such a species (vide infra).

The initial studies of the reaction between aromatic hydrocarbons and carbon tetrachloride comprise a part of the work performed by Charles Friedel and James Mason Crafts (42-44) on the general reaction which now bears their names. By adding anhydrous aluminum chloride to a flask containing carbon tetrachloride and benzene in a 1:20 molar ratio they were able to produce a mixture of tri- and tetraphenylmethane in which the latter compound predominated. Boeseken (45) reasoned that the reaction proceeded by a stepwise mechanism in which the chlorine atoms were successively replaced by hydrocarbon groups. Norris and Green (46), employing the technique of Friedel and Crafts, had earlier shown that chloro- and bromobenzene gave the corresponding substituted benzophenone dichlorides. Thus, it seemed possible to Boeseken to arrest the reaction at the first step to produce benzotrichlorides by adding one of these substrates to an excess of carbon tetrachloride. Using this method he was able to

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ite evidence of having produced small amounts of p-hloro- and p-bromobenzotrichloride (45). Although he lid not isolate the compounds themselves, he converted hem to the corresponding benzoic acids by hydrolysis n a mixture of glacial acetic and sulfuric acids. Vhen he attempted to prepare benzotrichloride by adding dilute solution of benzene to excess carbon tetra-hloride, he succeeded in isolating only benzophenone lichloride in 80-90% yield. A careful examination of he hydrolyzate from this reaction failed to produce evi-ience of any benzoic acid (and therefore any benzotri-hloride).

Employing this method, in which care is taken to naintain the carbon tetrachloride always in excess, Boeseken converted toluene to p,p'-dimethylbenzophenone lichloride in good yield. m-Xylene gave some resinous naterial and he was unable to isolate the dichloride vhich decomposed with the evolution of hydrogen chloride vhen he attempted its distillation.

In an extension of this work, Rolih and Peters (47) and again Hart and Fish (48) were able to produce penta-nethylbenzotrichloride by the trichloromethylation of pentamethylbenzene. Hart and Fish later employed this reaction with success in the preparation of 2,4,6-tri-nethylbenzotrichloride from mesitylene (49). However,

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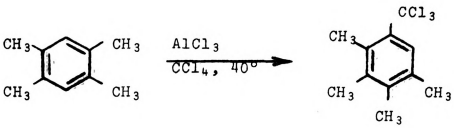
n they attempted the reaction with durene, the pro-
t was the unexpected rearranged compound 2,3,4,5-
ramethylbenzotrichloride (XVII).



(XVII)

ilarly isodurene rearranged during the course of the
ction to produce (XVII) while prehnitene reacted in a
mal fashion, also to produce (XVII).

Two notable features of the preceding reaction, in
lition to the rearrangements noted, are its color and
erogeneity. In normal practice a dilute solution of
aromatic substrate is slowly added to a stirred
pension of anhydrous aluminum chloride in a large
ess of carbon tetrachloride. The solution almost
iediately develops a red-orange color which is pre-
ably due to the formation of a complex between the
ne and aluminum chloride. As the reaction proceeds
color changes to a deep purple, the color which re-
ns until the aluminum chloride is hydrolyzed. Exami-
ion of the flask contents shows, however, that the
or resides almost exclusively in the lower semi-solid

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ase which has been spread over the walls of the reaction
ask by the stirring action; the upper carbon tetra-
loride solution is almost colorless. This suggests
at the reaction product is probably complexed with the
uminum chloride in some form and is released only in
e hydrolysis step. This conjecture is borne out by
e fact that hydrolysis and examination of the upper
rbon tetrachloride phase yields no detectable reaction
oduct.

That aromatic compounds will complex with strong
wis acids has been known since 1875 (50, 51). More
cent investigations have shown that a proton co-acid
s needed as well (52, 53). Since no precautions are
ken to dry the aluminum chloride prior to its use in
is reaction, there are undoubtedly traces of water pre-
nt in the reaction mixture. The necessary co-acid (HCl)
s therefore present and it is probable that as the
omatic material is added to the flask it becomes immedi-
ely complexed with the aluminum chloride. Brown sug-
sts (53) that the arene, aluminum chloride, and the
oton co-acid are complexed in a 1:1:1 molar ratio in
e form of a benzenonium ion salt of the hypothetical
id $HAlX_4$. This reaction is typified by the behavior
toluene shown below:

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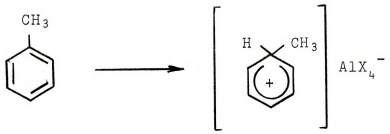

complex is capable of dissolving additional aluminum oride through the formation of complexes of the type $H)^{+}(Al_nX_{3n+1})^{-}$. This behavior is not dissimilar in e respects to the behavior of sulfur dioxide in sul- ic acid to produce the higher oxy-sulfur acids such $H_2S_2O_7$, $H_2S_3O_{10}$, etc.

Evidence has also been presented that carbon tetra- oride will weakly interact with aluminum chloride. lace and Willard (54) have shown that carbon tetra- oride will rapidly exchange its chlorine with solid minum chloride even at the freezing point of the former. ce no reaction at all occurred when the aluminum oride was dissolved or when both it and the carbon rachloride were in the vapor phase, it is evident t an aluminum chloride surface is necessary. The for- ion of carbonium ions of the type CCl_3^{+} was ruled out the basis of bond energy calculations. The authors or a mechanism in which an induced dipolar carbon rachloride molecule is adsorbed on the surface of the minum chloride lattice at a charge site. Desorption then accompanied by exchange.

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Benzene and carbon tetrachloride vapors have also
n shown to undergo a Friedel-Crafts reaction with
minum chloride, but again only when an aluminum
oride surface is present (55). These findings
ongly suggest that an excess of aluminum chloride is
essary for the trichloromethylation of aromatic sub-
nces in order to assure that there is always some
id undissolved aluminum chloride present in the lower
se of the reacting mixture. The excess carbon tetra-
oride not only serves as a diluent for the hydrocarbon
prevent formation of polynuclear products, but also
bably tends to shift the equilibrium controlling the
unt of carbon tetrachloride adsorbed on the aluminum
loride surface.

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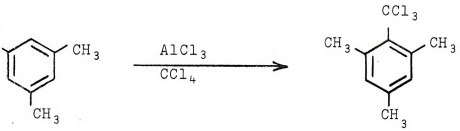
RESULTS AND DISCUSSION

The trichloromethylation of mesitylene afforded an
:llent yield of 2,4,6-trimethylbenzotrichloride (XVIII)
ı no detectable amounts of rearranged isomers being
ıed.



(XVIII)

ever, reaction of isodurene with carbon tetra-
oride in the presence of anhydrous aluminum chloride
40° produced a mixture of five polymethylbenzotri-
orides in which 2,3,4,6-tetramethylbenzotrichloride
X) and 2,3,4,5-tetramethylbenzotrichloride (XX)
dominated.

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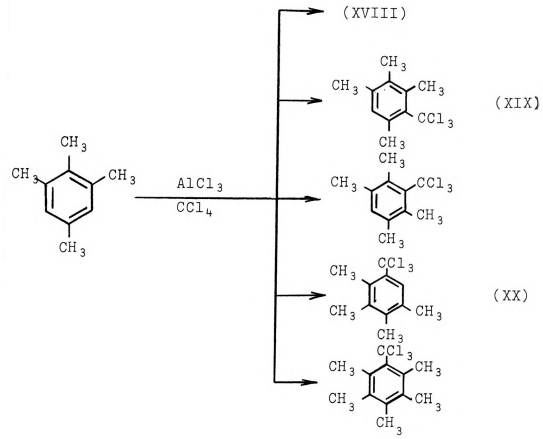
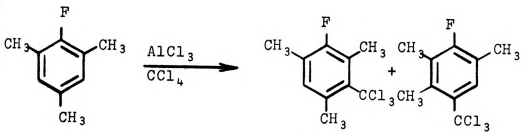


llarly 2-fluoro-1,3,5-trimethylbenzene reacted to
luce a rearranged product corresponding to (XX)
ve, but the reaction appears to be free of other re-
angement products in this case. That is, tri-
promethylation of 2-fluoro-1,3,5-trimetylbenzene at
afforded 3-fluoro-2,4,6-trimethylbenzotrichloride
X) and 4-fluoro-2,3,5-trimethylbenzotrichloride
II) but no detectable isomers.



(XXI) (XXII)

2-Chloro-, and 2-bromo-1,3,5-trimethylbenzene undergo trichloromethylation less readily than the above substrates and the amount of rearranged isomer produced in each case (assumed to correspond to (XXII above) was correspondingly reduced.

Although the rearranged isomer derived from the trichloromethylation of 2-fluoro-1,3,5-trimethylbenzene, followed by methanolysis was conclusively shown to be methyl 4-fluoro-2,3,5-trimethylbenzoate by an unambigous structure proof, the structures of the rearranged products derived from 2-chloro- and 2-bromo-1,3,5-trimethylbenzene were not determined.

These results are summarized in Table I. Because of the difficulties encountered in obtaining precise kinetic data for Friedel-Crafts reactions, the relative reactivity rates listed in Table I are only approximate. Batch work-up procedures were employed and there was difficulty in strictly reproducing reaction conditions from one experiment to another.

TABLE I

RELATIVE RATES OF AND PRODUCT DISTRIBUTION FROM THE TRICHLOROMETHYLATION OF FIVE POLYSUBSTITUTED BENZENES

Substrate	Relative Rate[a] of Trichloromethylation	Substituent X	Product Distribution[b,c]				
							
	1.00	CH_3	3%	66%	2%	22%	7%
	2.4 ± .1	CH_3				100%	
	1.0 ± 0.1	F		70%		30%	
	0.36 ± .05	Cl		88%		12%	
	0.21 ± .03	Br		93%		7%	

[a] Relative to isodurene.

[b] Expressed as percent total ester produced.

[c] X = Varying substituent, Y = $COOCH_3$.

However, the order of rates: prehnitene>isodurene>2-fluoro-,>2-chloro-,>2-bromo-1,3,5-trimethylbenzene, is clearly established. It is also clear that the amount of rearranged product in each case corresponding to methyl 2,3,4,5-tetramethylbenzoate parallels the reactivity order.

The trichloromethyl compounds produced in this study are difficult to work with for two reasons. First, the compounds hydrolyze in moist air to the corresponding benzoic acids. Second, methods of purifying individual members of the series or of separating mixtures of them meet with particular problems. The corrosive nature of the compounds precludes their separation on gas-liquid chromatographic columns or on elution columns of acidic or basic adsorbents. The tendency of some members of the series to lose hydrogen chloride when heated (56) prohibits their distillation. For these reasons the benzotrichlorides obtained in various experiments in this study were converted to their corresponding methyl benzoates by solvolysis in boiling methanol. This facilitated their separation by glc methods and their identification by comparison to known or easily prepared compounds.

Examination of the data presented in Table I indicates that in addition to the expected product the important minor product in each case is the vicinally

substituted molecule. In this regard, the trichloromethylation reaction of these substrates closely parallels the Jacobsen reaction.

There are three mechanistic possibilities leading to the formation of the rearranged vicinally substituted product: (1) the substrate could be rearranged by the action of aluminum chloride followed by trichloromethylation of the resulting mixture of hydrocarbons; (2) the substrate could be trichloromethylated and the product isomerized to the vicinally substituted isomer by the aluminum chloride; or (3) a series of competing reactions involving attack of the $-CCl_3$ moiety at various positions on the benzene ring and involving, in certain cases, 1,2-alkyl shifts leads to the product mixture observed.

In view of the fact that anhydrous aluminum chloride is known to isomerize polysubstituted aromatic compounds (57-59) the first mechanistic possibility appears at first quite reasonable. Indeed, in a simple experiment in which isodurene was shaken at 40° with aluminum chloride, a mixture of hydrocarbons was produced in which there was 1.4% prehnitene. However, although these isomerizations in the trichloromethylation reaction mixture are undoubtedly competing with the main reaction (i.e., the reaction of the hydrocarbon with carbon tetrachloride) the first mechanism cannot entirely account for the relatively large amount of rearranged material arising

from the trichloromethylation of (at least) isodurene. When isodurene was stirred with anhydrous aluminum chloride in carbon disulfide at the same "concentration"* as in the trichloromethylations of isodurene, no prehnitene was detected in the resulting hydrocarbon until 1 1/4 hours had elapsed (cf. Table II). Yet in one experiment in which a trichloromethylation reaction of isodurene was quenched after only six mintues of reaction time the product mixture contained 23% of trichloromethylprehnitene (isolated as methyl 2,3,4,5-tetramethylbenzoate). It is possible but highly improbable that the rate of isomerization of isodurene to prehnitene is sufficiently faster in carbon tetrachloride than in carbon disulfide to account for the observed results.

The second proposal cannot be entirely eliminated as the mechanistic course of the reaction, but the data presented in Table III speak strongly against it. When isodurene was trichloromethylated under varying reaction times, the ratio of trichloromethylisodurene to trichloromethylprehnitene remained substantially constant. Unless the equilibrium between these two materials was

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*The hydrocarbon reacts with the aluminum chloride to produce a lower semi-solid phase. Most of the substrate is present in this phase in equilibrium with a small amount in the upper solvent phase.

TABLE II

THE RATE OF ISOMERIZATION OF ISODURENE IN CARBON DISULFIDE AT 40°

Reaction Time (Minutes)	Grams of Isodurene (Initially)	Grams of Recovered Hydrocarbon	Composition of Recovered Hydrocarbon[a]					
								
10	1.34	1.15	---	---	---	100%	---	---
20	1.34	1.25	---	---	---	100%	---	---
30	1.34	1.19	---	---	---	100%	---	---
60	1.34	1.30	0.6%	0.4%	0.2%	98%	---	0.8%
75	1.34	1.23	1.1%	0.8%	0.2%	95%	1.6%	4.3%
2880	1.34	1.28	3.4%	5.5%	0.7%	79%	2.1%	9.3%

[a]The glc column used would not separate isodurene and durene.

TABLE III

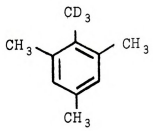
RELATIVE AMOUNTS OF TWO PRODUCTS FROM THE TRICHLOROMETHYLATION OF ISODURENE AT 40° FOR VARIOUS REACTION PERIODS

eaction Time inutes)	Percentage of Total Product Mixture[a]		Ratio
	Trichloromethyl-isodurene	Trichloromethyl-prehnitene	
6	72%	23%	3.1
20	66%	22%	3.0
20	74%	24%	3.1

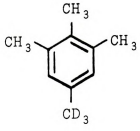
[a]Isolated as the methyl benzoates.

ablished prior to 6 minutes reaction time, it is doubt- that the rearranged product could arise from isomeri- ion of the trichloromethylisodurene.

Support for the third mechanism is found in the re- ts obtained from the trichloromethylation of 1,2,3,5- ramethylbenzene-2',2',2'-d_3 (XXIII) and 1,2,3,5- ramethylbenzene-5',5',5'-d_3 (XXIV).

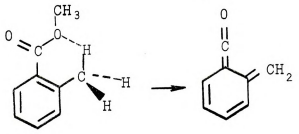


(XXIII)



(XXIV)

stated earlier, the mixture of trichloromethylated ducts derived from each substrate was solvolyzed in ling methanol to a mixture of the methyl esters of corresponding benzoic acids. The mass spectra of methyl benzoates thus obtained were instructive of product structures because of the "ortho effect" ed by McLafferty and Gohlke (60). The major frag- tation mode of methyl benzoates is the loss of hoxyl (P-31) and this is the most intense peak in ry spectrum studied. However, in those cases where re is a methyl group ortho to the carbomethoxyl group, traction of a proton and loss of methanol (P-32) often es rise to the second most intense peak in the spectrum. s process presumably occurs through a cyclic six- bered transition state as depicted in XXV.

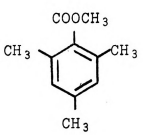


(XXV) (XXVa)

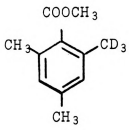
ner important peaks in the mass spectra of methyl thomethyl benzoates arise from the loss of methyl -15), loss of $COOCH_3$ (P-59) and loss of $HCOOCH_3$ -60). This last fragmentation mode is another ample of the ortho effect.

The ortho effect provided a tool by means of which he deuterium could be located in many of the products erived from XXIII and XXIV. In other cases nmr spectra rovided less precise, but meaningful data.

The mass spectrum (Figure 1) of the methyl 2,4,6- rimethylbenzoate derived from XXIII shows important eaks at m/e = 178 and 181. These are the molecular ions or XXVI and XXVII, respectively.



(XXVI)



(XXVII)

he ratio of these peak intensities suggests that the bove substances are present in a mixture of approxi- ately 48% XXVI and 52% XXVII. However, confirmatory eaks for the presence of XXVII such as m/e = 166 ($P-CH_3$), 150 ($P-OCH_3$), 149 ($P-HOCH_3$), 148 ($P-DOCH_3$), 22 ($P-COOCH_3$), 121 ($P-HCOOCH_3$) and 120 ($P-DCOOCH_3$) lthough present are too low in intensity to agree ith the above percentage of composition for the mix- ure. It must, therefore, be concluded that despite he ratio of molecular ion peaks intensities, the rimethylbenzoate derived from XXIII is predominantly

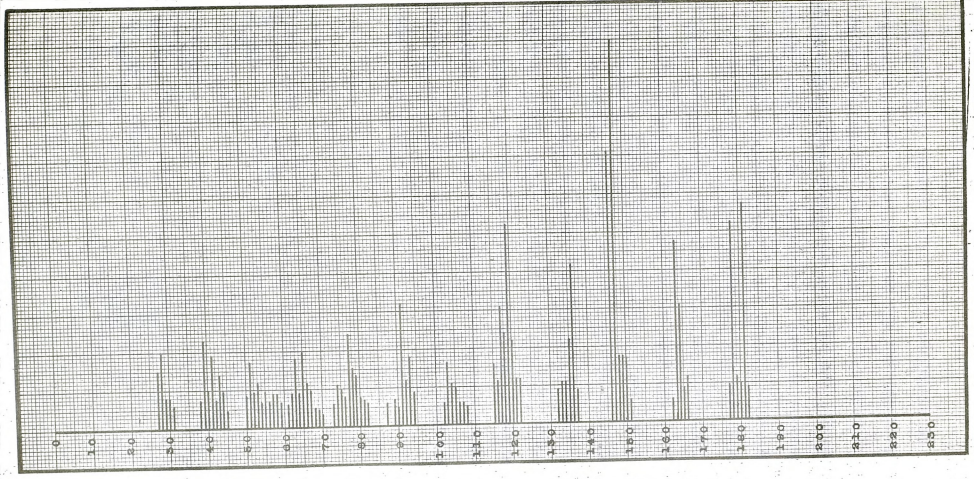
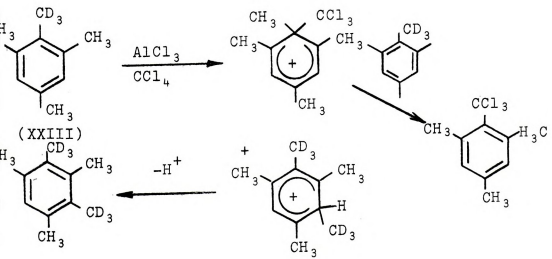


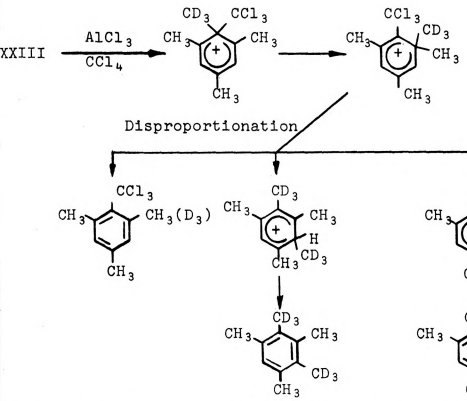
Figure 1

Mass Spectrum of Methyl 2,4,6-Trimethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3, and Subsequent Methanolysis

he undeuterated isomer XXVI. The assignment of the euterium to a position ortho to the carbomethoxy group, hile not rigorously confirmable, is supported by the ass spectral peaks mentioned above at m/e 148, and 120. hat the material is predominantly XXVI is substantiated y the intense peaks at m/e = 163 (P-CH_3), 147 (P-OCH_3, ase), 146 (P-$HOCH_3$), 119 (P-$COOCH_3$) and 118 (P-$HCOOCH_3$). Compare to the mass spectrum of authentic methyl 2,4,6-rimethylbenzoate, Figure 3c in the Appendix.) That the ethyl 2,4,6-trimethylbenzoate derived from XXIII contains ittle deuterium suggests a mechanism for its production onsonant with the proposal earlier put forward. Com-ound XXVI could arise by attack of the CCl_3 moiety at he position of the deuterated methyl group followed by disproportionation reaction with a second molecule of sodurene to produce pentamethylbenzene. This reaction cheme is presented below:



he production of compound XXVII is rationalized by a imilar mechanism which involves intramolecular migration f the deuterated methyl group prior to disproportion-tion.



his mechanism is supported by the observation that the ethyl pentamethylbenzoate derived from XXIII contains uch of the deuterium lost in the disproportionation re-ction that produces XXVI. The mass spectrum (Figure 2) of the methyl pentamethylbenzoate derived from XXIII hows molecular ion peaks at m/e = 209 (incorporation of hree deuterium atoms) and 212 (incorporation of six deuterium atoms) with the latter peak being about twice as intense as the former. That the material is pre-dominantly XXVIII below is substantiated by intense peaks

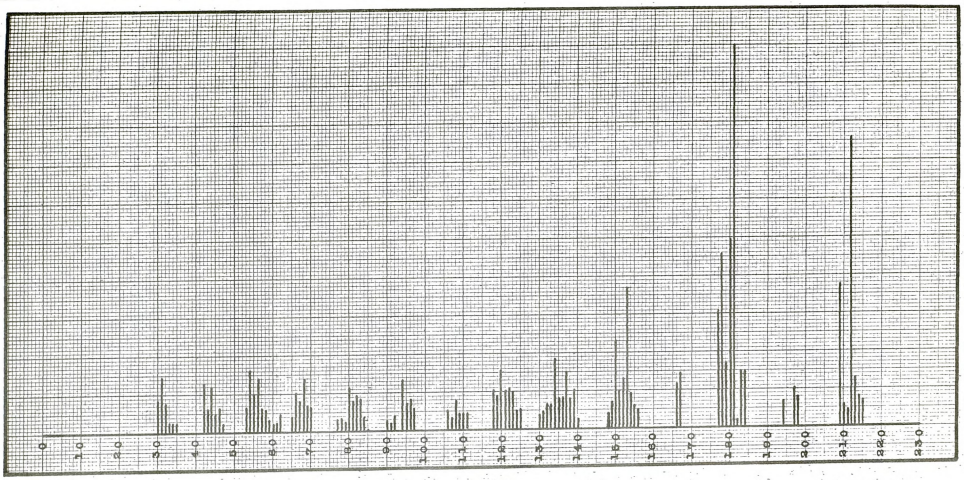


Figure 2

Mass Spectrum of Methyl Pentamethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3 and Subsequent Methanolysis

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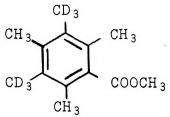
at m/e = 181 (P-OCH_3, base), 180 (P-$HOCH_3$) and 153 (P-$COOCH_3$). There is also some of the methyl pentamethylbenzoate present containing only three deuterium atoms as evidenced by less intense peaks at mass-to-charge ratios three units less than those listed above.



(XXVIII)

The mass spectrum of the methyl 2,4,6-trimethylbenzoate (Figure 3) derived from XXIV is unfortunately very poor. The sample was extremely small and subsequently the pressure in the spectrometer source reservoir dropped during the course of obtaining the spectrum. However, the weak but discernible molecular ion mass peak at 181 units is in accord with the mechanism proposed above for the production of this isomer.

The mechanism proposed for the production of this pair of disproportionation products in the trichloromethylation of isodurene is analogous in many respects to that put forward by Dewar (27) for the production of hexamethylbenzene and prehnitenesulfonic acid in the Jacobsen reaction of pentamethylbenzene. These two products are, however, only minor products in the

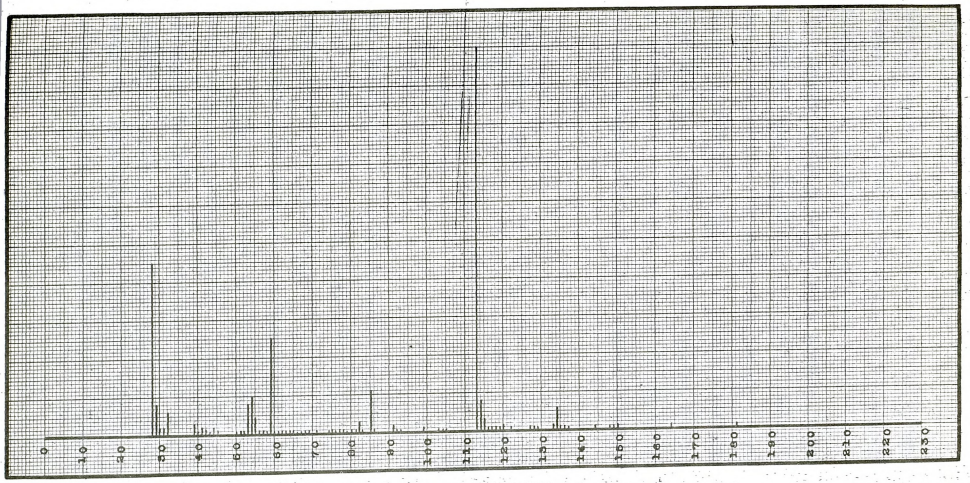
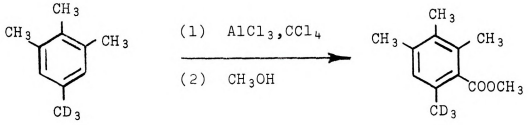


Figure 3

Mass Spectrum of Methyl 2,4,6-Trimethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3 and Subsequent Methanolysis

trichloromethylation of isodurene and attention must be focused upon the two major products, trichloromethylisodurene and trichloromethylprehnitene.

The production of the major product, trichloromethylisodurene (isolated as the methyl benzoate) is easily rationalized by the widely accepted mechanism for electrophilic aromatic substitution with, in this case, no rearrangement. This assumption is borne out by examination of the nmr spectrum of the methyl 2,3,4,6-tetramethylbenzoate-6',6',6'-d_3 (XXIX) derived from XXIV.



(XXIV) (XXIX)

The spectrum of the unlabeled ester (Figure 8b, Appendix) shows peaks in the methyl region at τ7.92, τ7.98, and τ8.03 in relative intensities of 2:1:1. The peak at lowest field is assigned to the methyl groups flanking the carbomethoxy group and shifted downfield by magnetic anisotropy effects of the carbonyl group. This assignment is made on the basis of the nuclear magnetic resonance spectra of the model compounds tabulated in Table IV. These compounds (with the exception of compound 4) were chosen because molecular symmetry

TABLE IV

SIGNAL ASSIGNMENTS IN THE NUCLEAR MAGNETIC RESONANCE SPECTRA OF FIVE POLYSUBSTITUTED METHYL BENZOATES

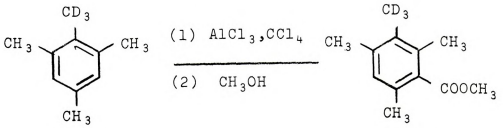
Compound	Structure[b]	Figure (Located in Appendix)	Resonance Signal Position, τ		
			Ortho	Meta	Para
1		3b	7.75	----	7.85
2		50b	7.52	7.86	7.86
3		48b	----	7.80	7.93
4[a]		54b	7.60	7.82	7.93
5		11b	7.72	7.94	----

[a] Assignments made by comparison to the spectrum of compounds 2 and 3.

[b] X = $COOCH_3$.

permitted an unambiguous assignment of the resonance signals. In every case the signal of the methyl group(s) adjacent to the carbomethoxy group is furthest downfield. In the spectrum of XXIX (Figure 4) the peak at τ7.92 has been diminished in intensity by one-half and the spectrum in the methyl region collapses to three peaks of equal intensity at τ7.92, τ7.98 and τ8.07. The mass spectrum of XXIX (Figure 5) shows a parent mass peak at m/e = 195 units and a base peak at 164 ($P-OCH_3$). The ortho effect peaks at m/e = 163 ($P-HOCH_3$) and 162 ($P-DOCH_3$) support the structural assignment for XXIX.

The reaction of isodurene labeled in the 2-position (XXIII) gives rise to an ester as the major product which on the basis of its spectral data must be methyl 2,3,4,6-tetramethylbenzoate-3',3',3'-d_3 (XXX).



(XXIII) (XXX)

It is difficult to assign the resonance signal position of the methyl group at the 3-position in the nmr spectrum of the unlabeled ester (Figure 8b, Appendix). In the spectrum of XXX (Figure 6) the peak at τ8.03 is absent.

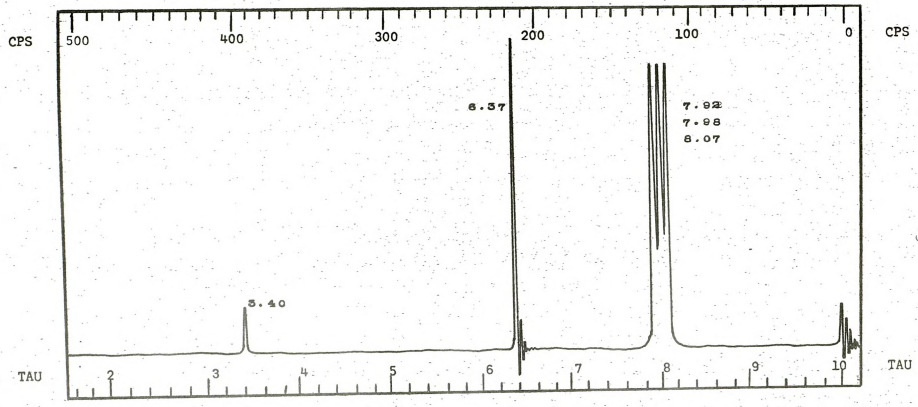


Figure 4

Nuclear Magnetic Resonance Spectrum of Methyl 2,3,4,6-Tetramethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3 and Subsequent Methanolysis

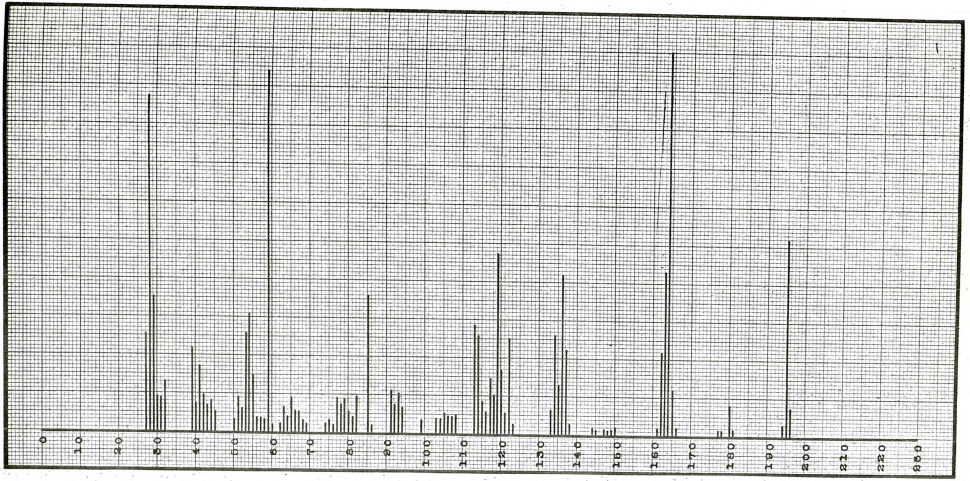


Figure 5

Mass Spectrum of Methyl 2,3,4,6-Tetramethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3 and Subsequent Methanolysis

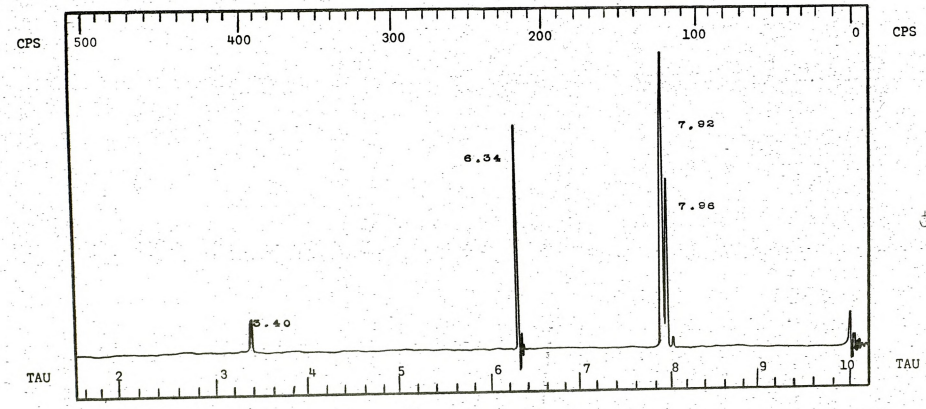
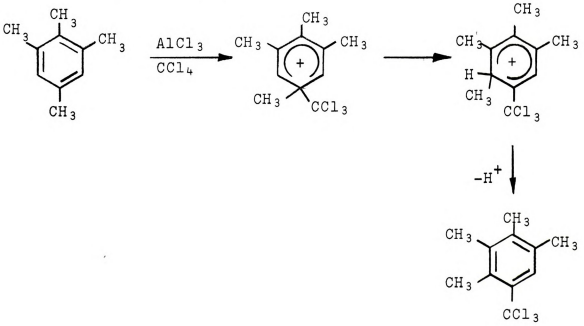


Figure 6

Nuclear Magnetic Resonance Spectrum of Methyl 2,3,4,6-Tetramethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-2',2',$2'_0$-d_3 and Subsequent Methanolysis

The mass spectrum of XXX (Figure 7) is more instructive, however. The parent mass of 195 units bespeaks of the incorporation of 3 deuterium atoms while the absence of strong ortho effect peaks at m/e = 162 ($P-DOCH_3$) and 134 ($P-DCOOCH_3$) shows that there is little if any deuterium ortho to the carbomethoxy group. Clearly the data obtained for compound XXIX are free from the ambiguities in that obtained for XXX, but taken as a whole the results are in agreement with the mechanism proposed for the production of trichloromethylisodurene from isodurene.

The most interesting product from the trichloromethylation of isodurene is trichloromethylprehnitene. The structure of the products derived from labeled starting materials seem to suggest that the production of trichloromethylprehnitene results from attack of the electrophile at the 5-position in isodurene followed by a 1,2-shift of methyl and deprotonation.



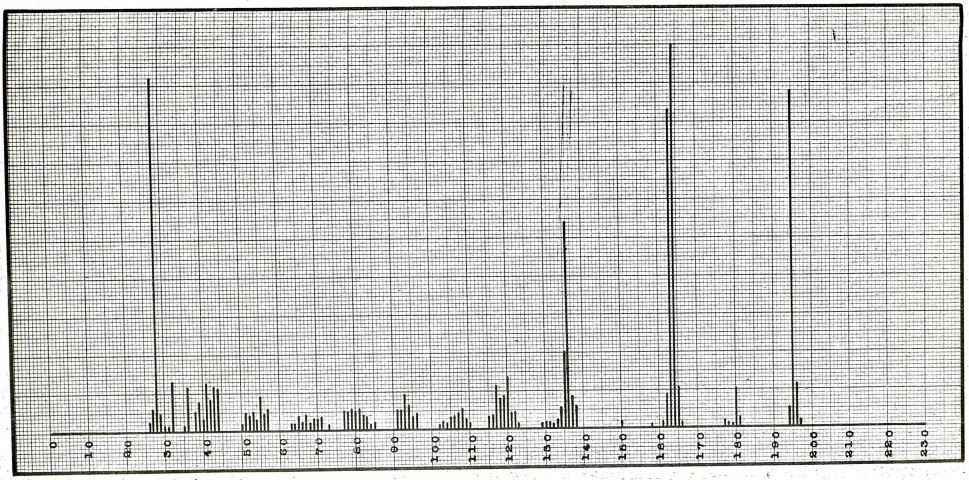
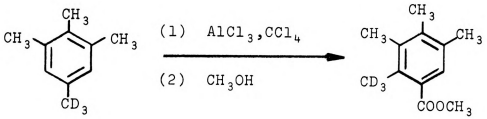


Figure 7

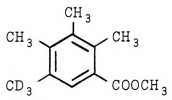
Mass Spectrum of Methyl 2,3,4,6-Tetramethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-2'-2'-2'-d_3 and Subsequent Methanolysis

The nmr spectrum of the methyl 2,3,4,5-tetramethylbenzoate (Figure 8) derived from XXIV indicates the product to be XXXI.



(XXIV) (XXXI)

The spectrum of the unlabeled isomer (Figure 16b, Appendix) shows a three-proton signal at τ7.55 which, on the basis of the data in Table IV, may be assigned to the methyl group ortho to the ester function. The nmr spectrum (Figure 8) of compound XXXI shows this peak to be essentially absent. The more revealing mass spectrum (Figure 9) shows, however, a peak at m/e = 163 ($P-HOCH_3$) in addition to the solely expected ortho effect peak at 162 ($P-DOCH_3$). Although this could arise from scrambling of the deuterium label by some unknown mechanism, it is tempting to rationalize its presence by fragmentation of a specie such as XXXII,



(XXXII)

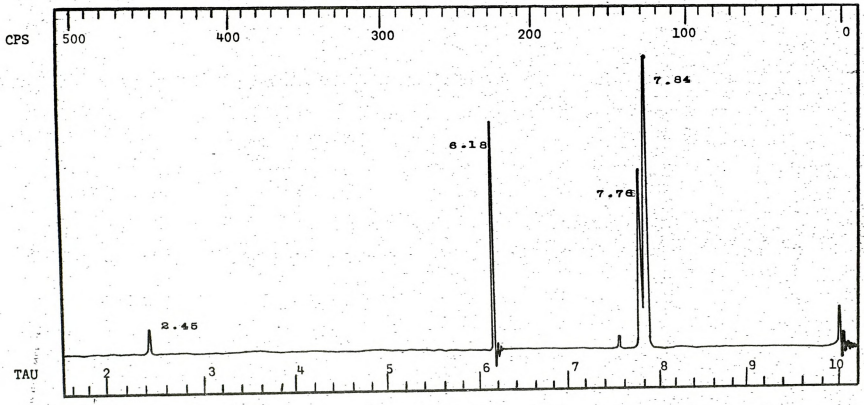


Figure 8

Nuclear Magnetic Resonance Spectrum of Methyl-2,3,4,5-Tetramethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3 and Subsequent Methanolysis

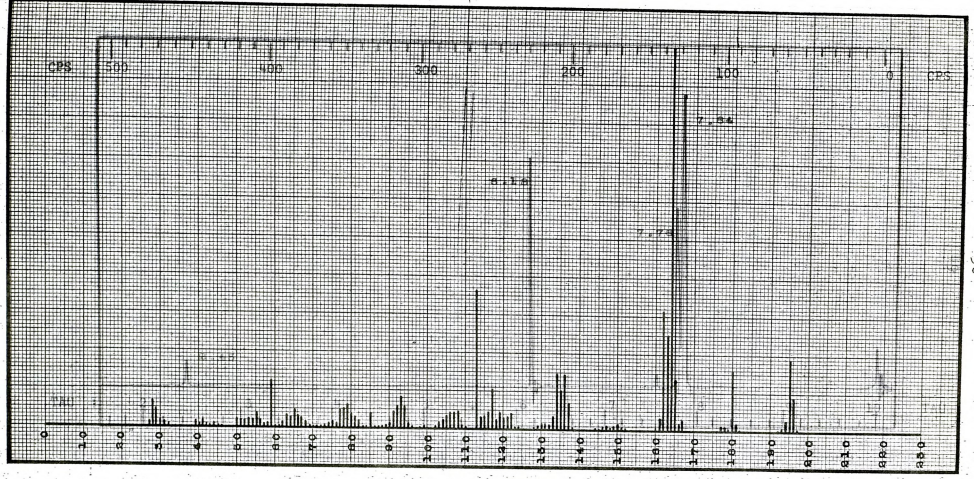
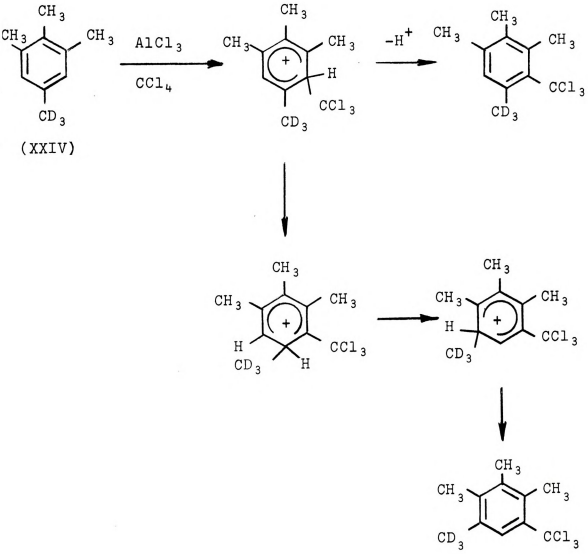


Figure 9

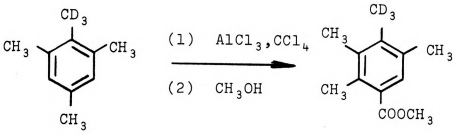
Mass Spectrum of Methyl 2,3,4,5-Tetramethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3 and Subsequent Methanolysis

which could be produced by attack of CCl_3 at position 4 in the labeled isodurene followed by two successive 1,2-shifts to relieve steric strain.



(XXIV)

The methyl 2,3,4,5-tetramethylbenzoate derived from isodurene labeled at the 2-position is predominantly the 4-labeled ester XXXIII.



(XXIII) (XXXIII)

The resonance signal at $\tau 7.84$ in the spectrum of the unlabeled material (Figure 16b, Appendix) can reasonably be assigned to the methyl groups at positions 4 and 5. In the spectrum of XXXIII (Figure 10) this peak is diminished to almost one-half the intensity of that in the spectrum of the unlabeled isomer. The mass spectrum of XXXIII (Figure 11) shows all of the expected fragmentation ions with peaks at m/e = 195 (P), 180 ($P-CH_3$), 164 ($P-OCH_3$, base), and 163 ($P-HOCH_3$). There is no evidence of an ortho effect due to loss of $DOCH_3$ which is in accord with the structural assignment of XXXIII.

The small amount of methyl 2,3,5,6-tetramethylbenzoate derived from isodurene could be explained as arising from attack of the CCl_3 electrophile at either of the equivalent positions 1 or 3 in isodurene followed by a 1,2-methyl shift and deprotonation.

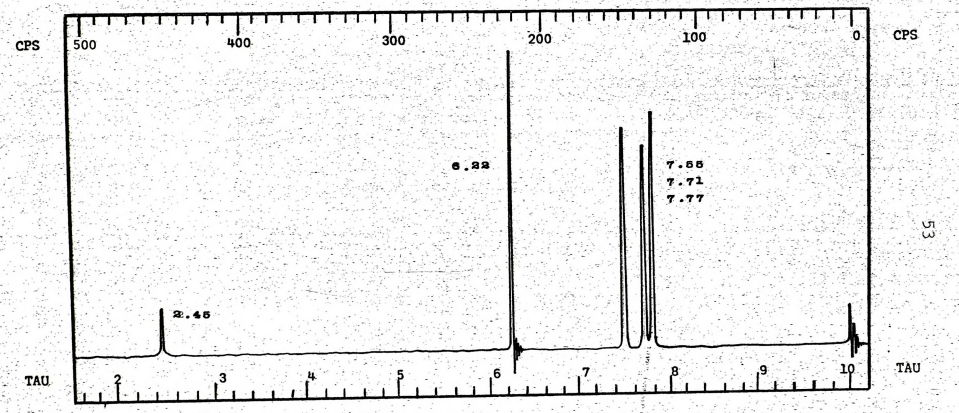


Figure 10

Nuclear Magnetic Resonance Spectrum of Methyl 2,3,4,5-Tetramethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3 and Subsequent Methanolysis

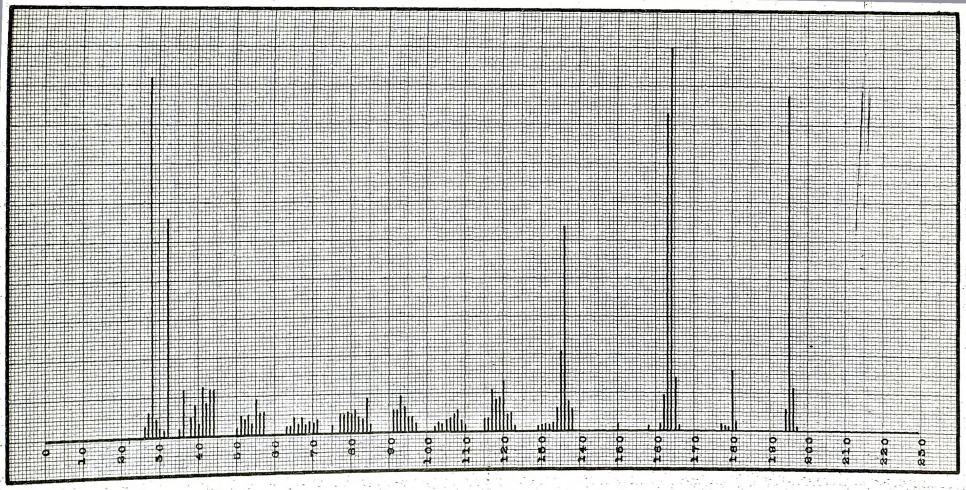
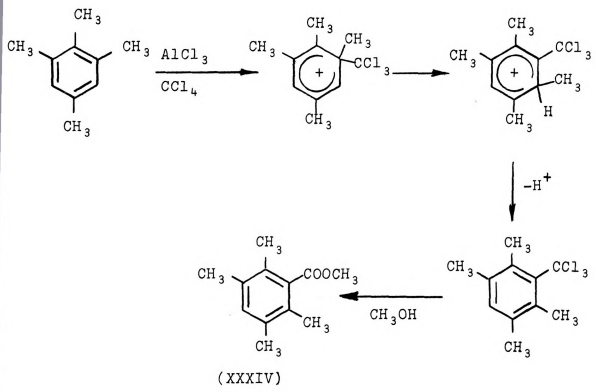


Figure 11

Mass Spectrum of Methyl 2,3,4,5-Tetramethylbenzoate Derived from the Trichloromethylation of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3 and Subsequent Methanolysis



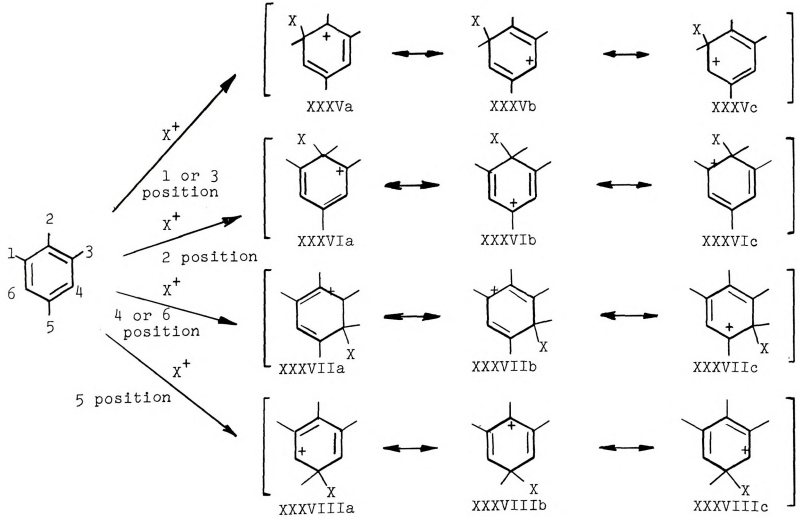
(XXXIV)

Unfortunately, as stated before, it was not possible to separate XXXIV from its isomers in the glc columns employed in the isolation of the other isomers. Thus, the structure of labeled XXXIV could not be ascertained to test the validity of the above mechanism. However, it seems reasonable in light of the previous arguments that the above mechanism could account for the small amount of XXXIV observed.

It appears that the mixtures of products arising from the trichloromethylation of the four tetrasubstituted benzenes studied result from a series of competing

reactions involving attack at each position of the substrate ring followed by deprotonation or methyl migration and deprotonation. The product mixture composition can then be viewed as reflecting the relative magnitudes of the partial rate factors for attack at each site. These in turn are affected by the activation energy requirement in reaching transition states in each case. Unfortunately there is no convenient method of predicting the relative stabilities of the transition states leading to each of the products. However, carbonium ion theory does provide a means of evaluating the relative stabilities of the reactive intermediates. Although there are objections (61) to the use of the reactive intermediates rather than the transition states for this type of argument, the conclusions drawn from such a treatment are probably valid. When this tool is applied to the problem in question, it is easy to rationalize the product mixture compositions. This has been done for the case of isodurene and the reactive intermediates in each case are depicted in chart form on the next page.

The intermediate arising from attack at the 4 or 6 position (XXXVII) is stabilized by distribution of the charge in the ring to carbon atoms bearing methyl substituents. On this basis one might expect a priori that the major product would be the one resulting from this intermediate. There is, however, some steric hindrance



$X^+ = CCl_3^+$ or its equivalent

to the formation of XXXVII. This destabilizes the intermediate bringing it closer in energy to less hindered but also less charge-stabilized species as XXXVIII. This results in greater competition for the starting material by the reaction leading through XXVIII. Using the same argument, the product arising from XXXVI might also be expected to be relatively abundant. However, the consumption of XXXVI is through a disproportionation reaction with correspondingly stringent enthalpy and entropy requirements. This militates against the loss of much starting material through this path.

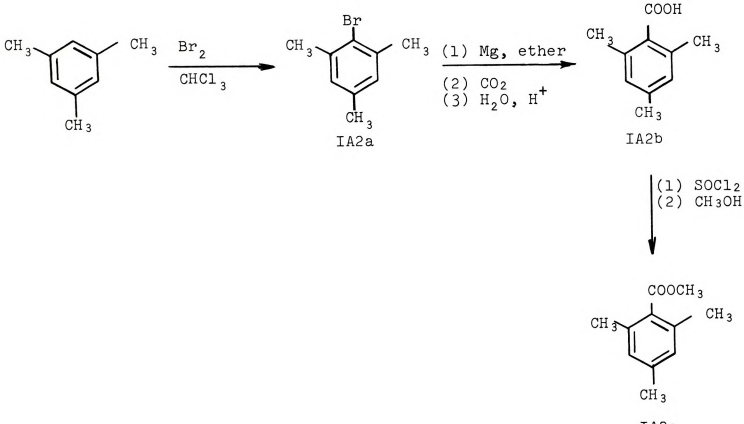
The formation of XXXV is both sterically and electronically unfavorable.

When the 2-position of the starting material is substituted with an inductively electron-withdrawing halogen atom, structures XXXV, XXXVI and XXXVIII are destabilized, although apparently the last to not as great an extent. The large amount of product arising from XXXVIII when the substituent on the 2-position is fluorine is another example of the tendency of fluorine to activate positions para to itself in electrophilic aromatic substitutions (62).

SYNTHETIC SEQUENCES

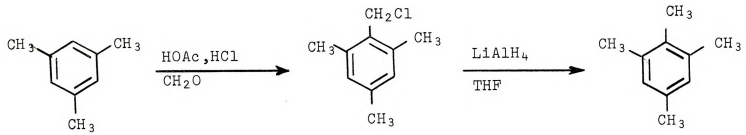
A large number of compounds were synthesized in connection with this research, some of which were previously unknown. Equations showing the structures of these compounds have been omitted from the text of the Experimental to avoid clutter. Those equations are produced below in chart form to give the reader a quick overview of the synthetic sequences employed.

Each compound is designated by a combination of letters and numbers which correspond to the position of the synthesis in the outline of the Experimental. For example, isodurene is designated IBlb since its preparation is described in the Experimental Section under Roman numeral one, sub B, sub 1, sub b. All previously unknown compounds are indicated by means of an asterisk.



IA2

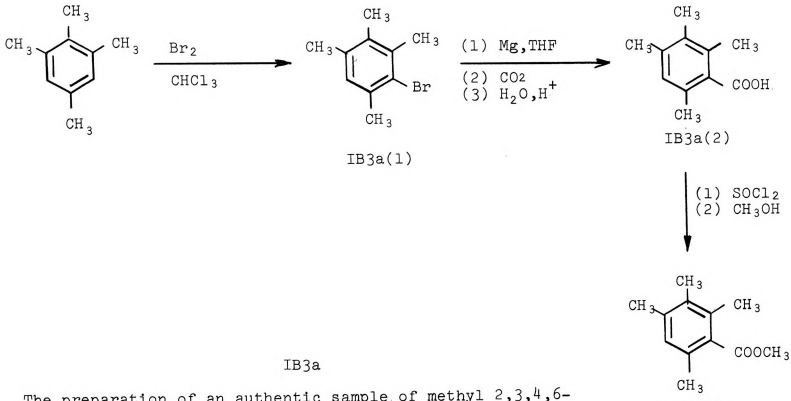
The preparation of an authentic sample of methyl 2,4,6-trimethylbenzoate



IB1a IB1b

IB1

The preparation of isodurene



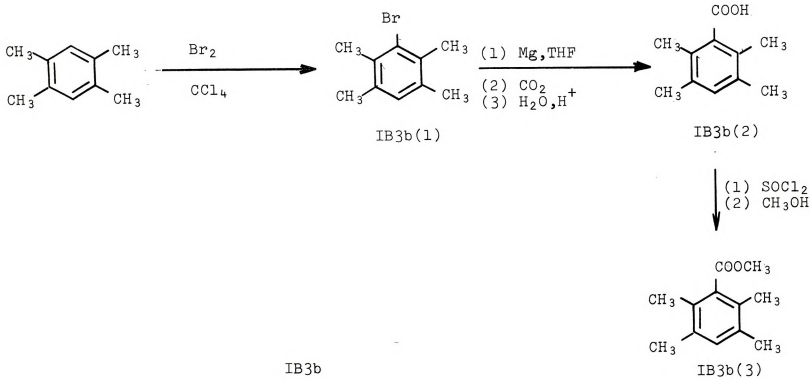
IB3a(1)

IB3a(2)

IB3a(3)

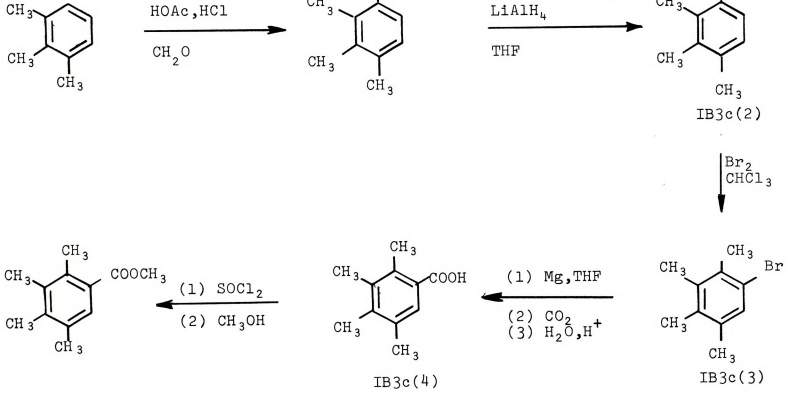
IB3a

The preparation of an authentic sample of methyl 2,3,4,6-tetramethylbenzoate



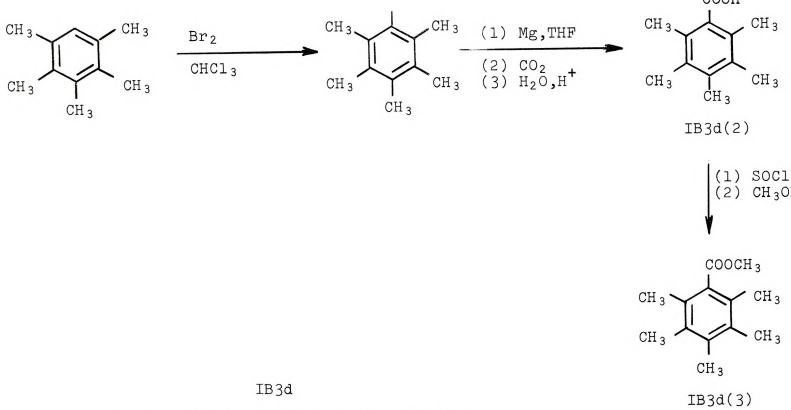
IB3b

The preparation of an authentic sample of methyl 2,3,5,6-tetramethylbenzoate



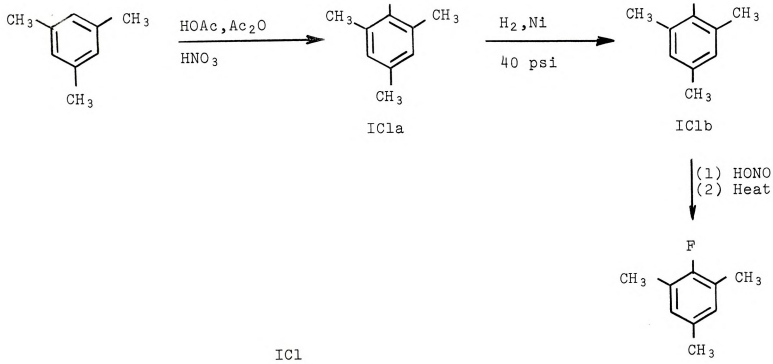
IB3c

The preparation of an authentic sample of methyl 2,3,4,5-tetramethylbenzoate



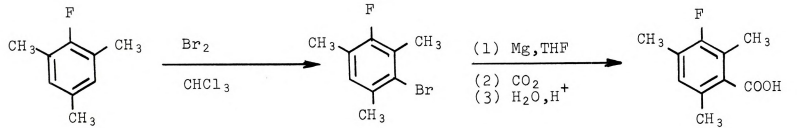
IB3d

The preparation of an authentic sample of methyl pentamethylbenzoate



IC1

The preparation of 2-fluoro-1,3,5-trimethylbenzene



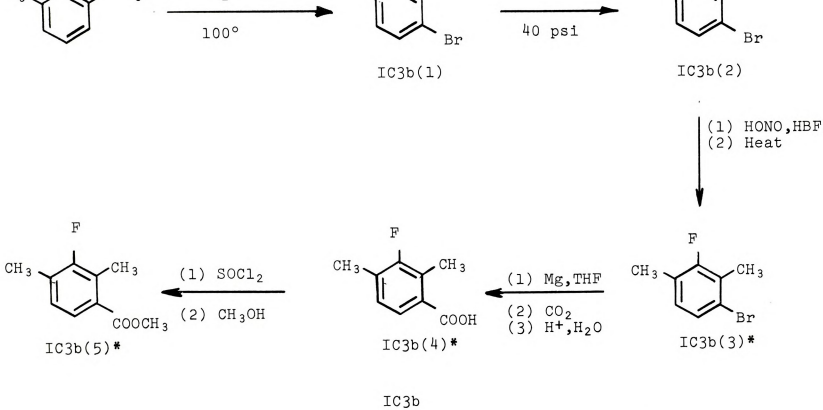
IC3a(1)

IC3a(2)*

IC3a

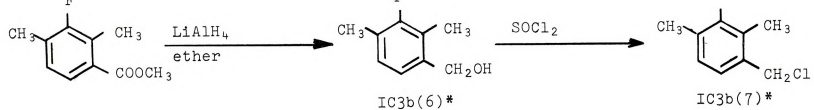
IC3a(3)*

The preparation of an authentic sample of methyl 3-fluoro-2,4,6-trimethylbenzoate



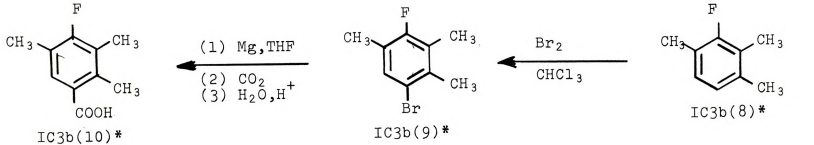
IC3b

The preparation of an authentic sample of methyl 4-fluoro-2,3,5-trimethylbenzoate



IC3b(6)*

IC3b(7)*

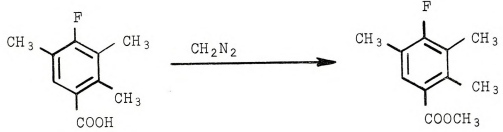


IC3b(8)*

IC3b(9)*

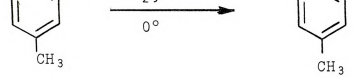
IC3b(10)*

IC3b--continued



IC3b(10) IC3b(11)*

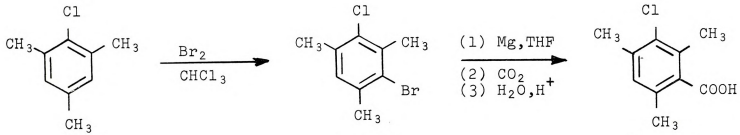
IC3b--continued



ID1

ID1

The preparation of 2-chloro-1,3,5-trimethylbenzene

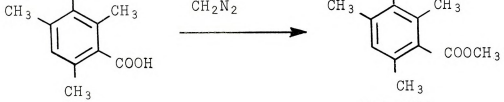


ID3a(1)*

ID3a(2)

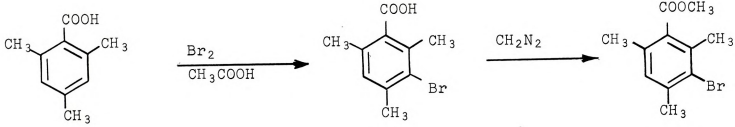
ID1

The preparation of an authentic sample of methyl 3-chloro-2,4,6-trimethylbenzoate



ID3a(3)*

ID3a--continued

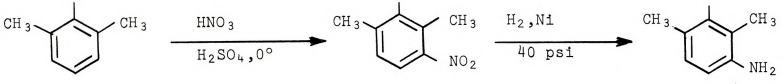


IE3a(1)

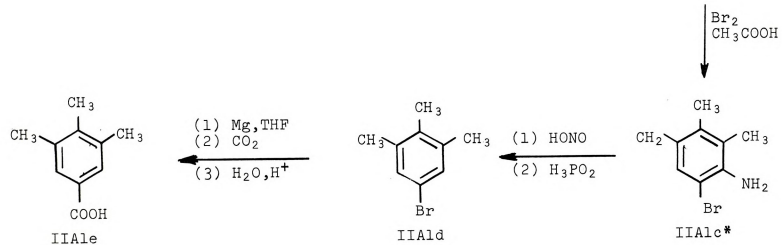
IE3a(2)*

IE3a

The preparation of an authentic sample of methyl 3-bromo-2,4,6-trimethylbenzoate



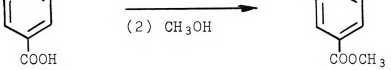
IIAla IIAlb



IIAlc* IIAld IIAle

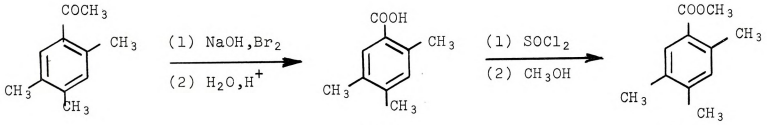
IIAl

The preparation of an authentic sample of methyl 3,4,5-trimethylbenzoate



IIA1f

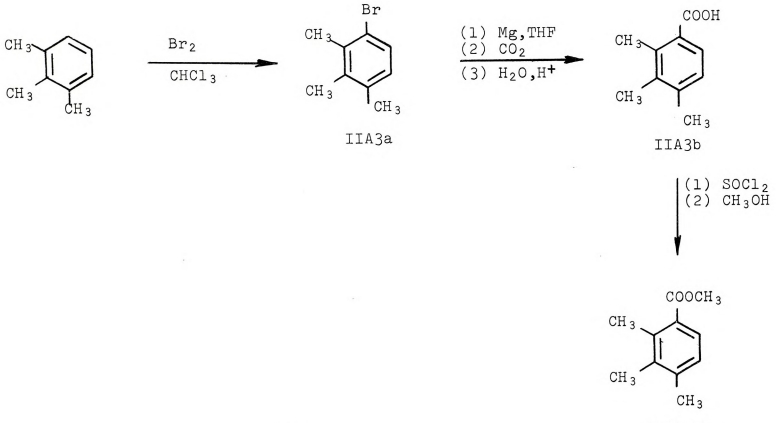
IIA1--continued



IIA2a IIA2b*

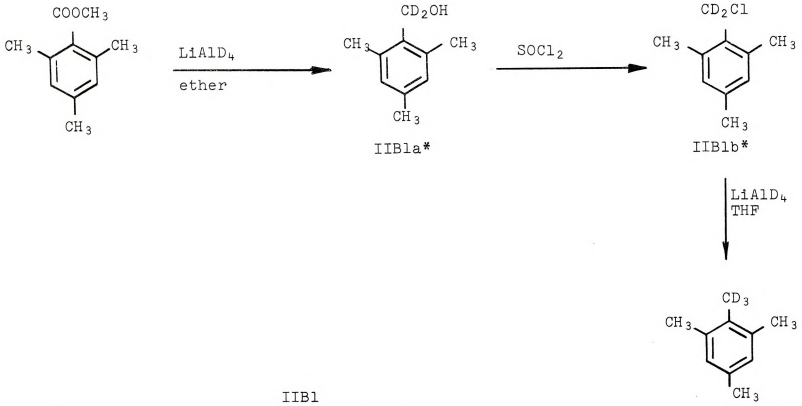
IIA2

The preparation of an authentic sample of methyl 2,4,5-trimethylbenzoate



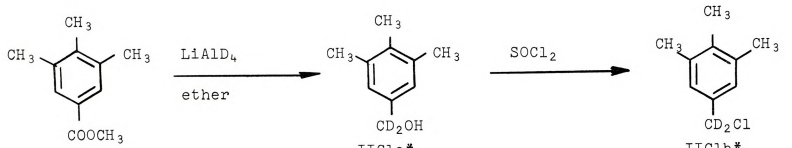
IIA3

The preparation of an authentic sample of methyl 2,3,4-trimethylbenzoate



IIB1

The preparation of 1,2,3,5-tetramethylbenzene-2',2',2'-d_3



IICla*

IIClb*

IIClc*

IICl

The preparation of 1,2,3,5-tetramethylbenzene-5',5',5'-d_3

EXPERIMENTAL

I. Trichloromethylation Reactions and Product Identification

A. The Trichloromethylation of Mesitylene

1. The Trichloromethylation of Mesitylene and Subsequent Methanolysis of the Product

Mesitylene (4.76 g, 0.039 mole) was dissolved in 200 ml of dry carbon tetrachloride and the resulting solution was added dropwise to a stirred suspension of 10.58 g (0.079 mole) of anhydrous aluminum chloride in 200 ml of dry carbon tetrachloride. Throughout the reaction the mixture was maintained at 40.0° ± 0.1. The mixture was stirred for two hours after which time the aluminum chloride was hydrolyzed by pouring the crude reaction mixture into 500 ml of ice water and shaking it in a separatory funnel. The organic layer was separated and dried over anhydrous magnesium sulfate. The carbon tetrachloride solution was concentrated to one-half its original volume on a rotary evaporator and 150 ml of methanol was added. This mixture was heated under reflux overnight after which the solvent was removed on a rotary evaporator.

The residue was analyzed by glc methods (5 ft x 0.25 inch 20% SF-96 on Chromasorb-W; helium carrier gas pressure 40 psi; temperature, 150°). The chromatogram showed only one product peak of retention time 5.3 minutes. This was shown to be methyl 2,4,6-trimethylbenzoate by comparison of its infrared and nuclear magnetic resonance spectra and glc retention times with those of an authentic sample prepared as described below. Distillation of the reaction residue yielded 6.31 g (0.035 mole, 89.7%) of methyl 2,4,6-trimethylbenzoate, bp 72-73° at 0.15 torr.

2. The Preparation of An Authentic Sample of Methyl 2,4,6-trimethylbenzoate

a. The Preparation of 2-bromo-1,3,5-trimethylbenzene (63)

One hundred grams (0.833 mole) of mesitylene were dissolved in 200 ml of chloroform. To this solution was added dropwise with stirring a solution of 134 g (0.835 mole) of bromine dissolved in 200 ml of chloroform. During the addition the mixture was kept at temperatures below 5°. After the addition was complete the mixture was allowed to warm slowly to room temperature where it was stirred for two hours. The mixture was washed with 10% sodium bisulfite solution and then water. The organic layer was separated and dried over anhydrous magnesium

sulfate and the solvent was removed on a rotary evaporator. Distillation of the residue under reduced pressure yielded 132 g (0.662 mole, 79.3%) of 2-bromo-1,3,5-trimethylbenzene, bp 80-81° at 9 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 1a and 1b, respectively.

b. The Preparation of 2,4,6-trimethylbenzoic Acid (64)

2-Bromo-1,3,5-trimethylbenzene (60 g, 0.30 mole) was dissolved in 100 ml of tetrahydrofuran which had been freshly distilled from lithium aluminum hydride. This solution was added dropwise to a stirred mixture of 7.29 g (0.30 gram-atom) of magnesium turnings and 100 ml of dry tetrahydrofuran. After the reaction had been initiated by warming the flask contents, the remainder of the bromide solution was added at such a rate as to keep the contents of the flask gently boiling. After addition was complete the mixture was stirred for two hours. At the end of this time the mixture was poured over an excess of freshly crushed dry ice and allowed to warm to room temperature. The residue was acidified with 6N hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and evaporated. The yield of crude acid was 43.0 g (0.262 mole, 87.3%). One recrystallization from benzene yielded material

melting at 153-154°. The infrared spectrum of this compound appears in the Appendix as Figure 2.

c. The Preparation of Methyl 2,4,6-Trimethylbenzoate (65)

2,4,6-Trimethylbenzoic acid (43.0 g, 0.262 mole) was placed in a 500 ml flask fitted with a condenser, addition funnel and magnetic stirrer. Thionyl chloride (35.7 g, 0.300 mole) was added cautiously to the flask. The mixture was heated under reflux for two hours. At the end of this time the excess thionyl chloride was removed by means of a water aspirator and 200 ml of methanol was slowly added to the flask contents. The resulting mixture was heated under reflux for two hours. The excess methanol was removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 35.3 g (0.186 mole, 71.2%) of methyl 2,4,6-trimethylbenzoate, bp 92-93° at 2 torr. The infrared, nmr and mass spectra of this compound appear in the Appendix as Figures 3a, 3b and 3c, respectively.

B. The Trichloromethylation of Isodurene

1. The Preparation of Isodurene

a. The Preparation of 2,4,6-Trimethylbenzyl Chloride (66)

A mixture of 300 ml of glacial acetic acid, 600 ml of concentrated hydrochloric acid, 117 g (0.975 mole) of

mesitylene and 57 g of formalin was placed in a 2 liter flask fitted with a condenser and magnetic stirrer. The mixture was heated to 40° and stirred at this temperature for four hours. At the end of this time 30 g of formalin was added and stirring was continued for four more hours. The mixture was extracted with two 150 ml portions of benzene and the benzene solutions combined and dried over anhydrous magnesium sulfate. The benzene was removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 112.2 g (0.683 mole, 70%) of 2,4,6-trimethylbenzyl chloride, bp 60-61° at 0.6 torr, mp 34-35°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 4a and 4b, respectively.

b. The Preparation of Isodurene (67)

Lithium aluminum hydride (14.2 g, 0.374 mole) was placed together with 750 ml of carefully dried tetrahydrofuran in a two-liter flask fitted with a condenser, addition funnel and stirrer. To this mixture was added dropwise with stirring a solution of 123 g (0.728 mole) of 2,4,6-trimethylbenzyl chloride dissolved in 350 ml of dry tetrahydrofuran. After addition of the substrate was complete the mixture was heated under reflux for three hours and then allowed to stand at room temperature overnight. Ice water was cautiously added to

decompose the excess hydride followed by 6N hydrochloric acid to dissolve the precipitated salts. Ether (250 ml) was added and the organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 95.5 g (0.713 mole, 97.8%) of isodurene, bp 71-72° at 7 torr. The infrared, nmr and mass spectra of this compound appear in the Appendix as Figures 5a, 5b and 5c, respectively.

2. The Trichloromethylation of Isodurene and Subsequent Methanolysis of the Product

Isodurene (6.7 g, 0.05 mole) was dissolved in 100 ml of dry carbon tetrachloride and the resulting solution was added dropwise to a stirred slurry of 13.3 g (0.100 mole) of anhydrous aluminum chloride in 100 ml of carbon tetrachloride maintained at 40.0° ± 0.1. The mixture was stirred for two hours after which time it was hydrolyzed by shaking it briefly with 500 ml of ice water. The organic layer was removed and dried over anhydrous magnesium sulfate. The solution was concentrated to one-half its original volume and 100 ml of absolute methanol was added. This mixture was heated overnight after which the solvents were removed on a rotary evaporator. The crude product mixture (weighing 9.10 g) was subjected to analysis by glc methods (5 ft x 0.25 inch 20% SF-96 on Chromasorb-W; helium carrier gas pressure 40 psi;

temperature, 175°). The recorder trace indicated four peaks in the relative areas indicated in Table V. By comparison of the infrared and nmr spectra and glc retention times of the eluted materials to those of authentic samples, the four peaks were shown to correspond to methyl 2,4,6-trimethylbenzoate (5.3 minutes), methyl 2,3,4,6-tetramethylbenzoate (10.3 minutes), methyl 2,3,4,5-tetramethylbenzoate (13.9 minutes) and methyl pentamethylbenzoate (16.0 minutes). Anomalies in the infrared and nmr spectra of the second compound eluted from the column indicated it to be impure. The nmr spectrum of methyl 2,3,4,6-tetramethylbenzoate shows a signal at τ3.39 corresponding to the single ring-bound hydrogen atom (cf. Figure 8b in the Appendix). However, the nmr spectrum of the material eluted from the glc column showed a weak signal at τ3.15 as well as anomalies in the τ7.9-8.1 region. The signal at τ3.15 was due to a small amount of methyl 2,3,5,6-tetramethylbenzoate which could not be separated from its isomer with the chromatographic column employed. Similarly disappointing results were obtained with several other columns tested.* The amount of 2,3,5,6-tetramethylbenzoate in the mixture was roughly determined by proton magnetic resonance methods

*The author is indebted to S. K. Ramaswami for the initial observation of the difficulties involved in this separation.

(vide infra) and found to constitute less than 2% of the product mixture.

TABLE V

DISTRIBUTION OF PRODUCTS OBTAINED FROM THE TRICHLOROMETHYLATION OF ISODURENE, AFTER METHANOLYSIS

Compound	Peak Area[a]	Percentage of Total Peak Area
Methyl 2,4,6-Trimethylbenzoate	0.0139	3.2
Methyl 2,3,4,6-Tetramethylbenzoate Methyl 2,3,5,6-Tetramethylbenzoate	0.2981	67.6
Methyl 2,3,4,5-Tetramethylbenzoate	0.0982	22.3
Methyl Pentamethylbenzoate	0.0305	6.9

[a]Arbitrary units. Peak areas are not corrected for differences in thermal conductivity detector response.

3. The Identification of the Products Derived from the Trichloromethylation of Isodurene, After Methanolysis

a. The Preparation of An Authentic Sample of Methyl 2,3,4,6-Tetramethylbenzoate

(1) The preparation of 4-bromo-1,2,3,5-tetramethylbenzene (68).-- Isodurene (30 g, 0.224 mole) was dissolved in 100 ml of chloroform and the resulting solution was placed in a 500 ml flask fitted with a

condenser, addition funnel and magnetic stirrer. The flask contents were cooled to 5° by means of an ice water bath. To this mixture was added dropwise with stirring a solution of 36 g (0.225 mole) of bromine dissolved in 100 ml of chloroform. The flask contents were stirred until there was no further evolution of hydrogen bromide and then washed with 10% sodium bisulfite solution and then with water. The organic layer was separated and dried over anhydrous magnesium sulfate. The chloroform was removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 38.3 g (0.180 mole, 80.2%) of 4-bromo-1,2,3,5-tetramethylbenzene, bp 55-56° at 0.1 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 6a and 6b, respectively.

(2) The preparation of 2,3,4,6-tetramethylbenzoic acid (69).--Magnesium turnings (4.37 g, 0.180 gram-atom) and 200 ml of carefully dried tetrahydrofuran were placed together in a 500 ml flask fitted with a condenser, addition funnel and magnetic stirrer. To the contents of the flask were added 38.3 g (0.180 mole) of 4-bromo-1,2,3,5-tetramethylbenzene dissolved in 100 ml of dry tetrahydrofuran. After addition of 5 ml of the bromide solution the flask was warmed to initiate the reaction. The remainder of the solution was added at such a rate as to keep the contents of the flask gently boiling. After

the addition was complete the mixture was stirred for two hours, then poured carefully over an excess of freshly crushed dry ice. The mixture was allowed to stand overnight and the residue was carefully acidified with 6N hydrochloric acid and then extracted with ether. The ether solution was separated and dried over anhydrous magnesium sulfate and the ether removed on a rotary evaporator. Two recrystallizations from aqueous acetone yielded 26.5 g (0.149 mole, 82.6%) of 2,3,4,6-Tetramethylbenzoic acid, mp 166-167°. The infrared spectrum of this compound appears in the Appendix as Figure 7.

(3) The preparation of methyl 2,3,4,6-tetramethylbenzoate (70).--2,3,4,6-Tetramethylbenzoic acid (16 g, 0.09 mole) was placed in a 200 ml flask fitted with a magnetic stirrer, condenser and dropping funnel. Thionyl chloride (12 g, 0.11 mole) was added cautiously to the flask contents. When the initial reaction had subsided the mixture was heated under reflux for two hours. At the end of this time 100 ml of absolute methanol were added to the flask and the resulting mixture was heated under reflux for one hour. The excess methanol was removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 16.9 g (0.088 mole, 96.7%) of methyl 2,3,4,6-tetramethylbenzoate, bp 71-72° at 0.03 torr. The infrared, nmr, and mass spectra of this compound appear in the Appendix as Figures 8a, 8b and 8c, respectively.

b. The Preparation of An Authentic Sample of Methyl 2,3,5,6-Tetramethylbenzoate

(1) The preparation of 3-bromo-1,2,4,5-tetramethylbenzene (71).--Durene (67 g, 0.50 mole) was dissolved in 100 ml of carbon tetrachloride and the resulting solution was placed in a 500 ml flask fitted with a condenser, stirrer and addition funnel. To the stirred contents of the flask were added dropwise 80 g (0.50 mole) of bromine dissolved in 100 ml of carbon tetrachloride. The reaction mixture was stirred at room temperature until evolution of hydrogen bromide had ceased and then it was washed successively with 100 ml of 10% sodium bisulfite and water. The organic layer was separated, dried over anhydrous magnesium sulfate and the solvent removed on a rotary evaporator. The residue was distilled under reduced pressure to yield 105.2 g (0.40 mole, 80.1%) of 3-bromo-1,2,4,5-tetramethylbenzene, bp 86-87° at 1 torr, mp 60-61°. During the distillation it was necessary to periodically warm the distillation head to prevent solidification of the distillate. The infrared and nmr spectra of this compound appear in the Appendix as Figures 9a and 9b, respectively.

(2) The preparation of 2,3,5,6-tetramethylbenzoic acid (71).--3-Bromo-1,2,4,5-tetramethylbenzene (25 g, 0.172 mole) was dissolved in 25 ml of carefully dried tetrahydrofuran. This solution was added dropwise to

a stirred slurry of 4.18 g of magnesium turnings and 100 ml of dry tetrahydrofuran. When 5 ml of the solution had been added to the flask the addition was halted and the flask was warmed to initiate the reaction. When the reaction had started, the remainder of the bromide solution was added to the flask at such a rate as to cause the contents of the flask to gently boil. When the addition was complete the mixture was stirred for two hours after which time it was poured slowly over an excess of freshly crushed dry ice and allowed to stand overnight. The residue was acidified with 6N hydrochloric acid and the acid solution was extracted with ether. After drying the ether solution and evaporation of the ether there remained 16.2 g of the crude acid (0.091 mole, 53%). Two recrystallizations from aqueous acetone yielded material melting at 173-174°. The infrared spectrum of this compound appears at Figure 10 in the Appendix.

(3) The preparation of methyl 2,3,5,6-tetramethylbenzoate (71).--Solid 2,3,5,6-tetramethylbenzoic acid (10 g, 0.056 mole) was placed in a 200 ml flask fitted with a magnetic stirrer, condenser and addition funnel. Thionyl chloride (7.0 g, 0.0588 mole) was added slowly to the flask. When the initial reaction had subsided the flask contents were heated under reflux for one hour. At the end of this time the excess thionyl chloride was removed by means of a water aspirator and

then 100 ml of absolute methanol were cautiously added to the flask. When the initial reaction had subsided the flask contents were heated under reflux for one hour at the end of which time the excess methanol was removed in a rotary evaporator. The residue was distilled under reduced pressure to yield 9.6 g (0.050 mole, 89.3%) of methyl 2,3,5,6-tetramethylbenzoate, bp 103-104° at 0.1 mm Hg pressure. The distillate solidified upon standing and two recrystallizations from pentane gave crystals melting at 58-59°. The infrared and nmr specra of this compound appear in the Appendix as Figures 11a and 11b, respectively.

c. The Preparation of An Authentic Sample of Methyl 2,3,4,5-Tetramethylbenzoate

(1) The preparation of 2,3,4-trimethylbenzyl-chloride (72).--1,2,3-trimethylbenzene (60 g, 0.50 mole) was placed together with 150 ml of glacial acetic acid, 300 ml of concentrated hydrochloric acid and 30 g of formalin in a one-liter flask fitted with a stirrer and condenser. The mixture was stirred and maintained at temperatures between 40° and 45° for four hours. At the end of this time 12 g of formalin were added to the flask contents and the heating and stirring were continued for an additional seven hours. At the end of this time 250 ml of benzene were added to the mixture and the organic layer was separated and dried over anhydrous magnesium

sulfate. The solution was concentrated on a rotary evaporator and the residue was distilled under reduced pressure to yield 5.9 g of the starting material and 55.0 g (0.326 mole, 65.2%) of 2,3,4-trimethylbenzyl chloride, bp 124-125° at 14 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 12a and 12b, respectively.

(2) The preparation of prehnitene (72).--2,3,4-trimethylbenzyl chloride (55.0 g, 0.326 mole) was dissolved in 500 ml of carefully dried tetrahydrofuran. The resulting solution was added dropwise to a stirred suspension of 6.19 g (0.163 mole) of lithium aluminum hydride contained in 500 ml of dry tetrahydrofuran. The reaction was carried out in a 2-liter flask fitted with a stirrer, addition funnel and reflux condenser. During the addition the contents of the flask were heated to 40°-45° and after the addition was complete the temperature was raised to reflux temperature where it was maintained for three hours. The mixture was then allowed to cool to room temperature and stand overnight. Water was cautiously added to the flask to decompose the excess hydride followed by 6N hydrochloric acid to dissolved the precipitated salts. The organic layer was separated and the water layer was extracted once with ether. Evaporation of the solvents after drying yielded 42.7 g of crude reaction product. Distillation of this material under reduced

pressure yielded 41.8 g (0.312 mole, 95.6%) of prehnitene, bp 63-64° at 4.5 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 13a and 13b, respectively.

(3) The preparation of 5-bromo-1,2,3,4-tetramethylbenzene (73).--Prehnitene (20 g, 0.147 mole) was dissolved in 100 ml of chloroform and the resulting solution was placed in a 500 ml flask fitted with a dropping funnel, condenser and magnetic stirrer. Bromine (24 g, 0.150 mole) was dissolved in 100 ml of chloroform and the resulting solution was added to the contents of the flask dropwise with stirring. Evolution of hydrogen bromide began after about ten minutes and continued for three hours. When gas evolution had effectively ceased the flask contents were washed with 10% sodium bisulfite solution and then with water. The chloroform solution was separated, dried over anhydrous magnesium sulfate and then stripped of solvent on a rotary evaporator. The residue was distilled under reduced pressure to yield 26 g (0.122 mole, 83%) of 5-bromo-1,2,3,4-tetramethylbenzene, bp 83-84° at 0.8 torr. Upon standing the distillate crystallized to a solid, mp 29-30°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 14a and 14b, respectively.

(4) The preparation of 2,3,4,5-tetramethylbenzoic acid (75).--5-Bromo-1,2,3,4-tetramethylbenzene (26 g, 0.122 mole) was dissolved in 25 ml of tetrahydrofuran which had been dried by distillation from lithium aluminum hydride. This solution was added dropwise to a stirred slurry of 2.96 g (0.122 g-atom) of magnesium turnings and 25 ml of dry tetrahydrofuran. After 5 ml of the substrate had been added the flask contents were warmed to initiate the reaction. The remainder of the bromide solution was added at such a rate as to cause the flask contents to gently boil. When all of the solution had been added the mixture was stirred for two hours. After this time it was carefully poured over an excess of freshly crushed dry ice and the resulting mixture was allowed to stand overnight. The residue was acidified with 6N hydrochloric acid, extracted with ether and the ether solution dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 20.5 g of the crude acid (0.115 mole, 94.5%). Two recrystallizations from aqueous acetone yielded material melting at 168-169°. The infrared spectrum of this compound appears in the Appendix as Figure 15.

(5) The preparation of methyl 2,3,4,5-tetramethylbenzoate (75).--2,3,4,5-Tetramethylbenzoic acid (10 g, 0.056 mole) was placed in a 100 ml flask fitted with a magnetic stirrer, condenser and dropping funnel. To the solid acid were slowly added 25 ml of thionyl chloride.

When the initial reaction had subsided the flask contents were stirred and heated under reflux for two hours. At the end of this time the excess thionyl chloride was removed by distillation, and 100 ml of absolute methanol were cautiously added to the flask. The mixture was stirred and heated under reflux for one hour after which time the excess methanol was removed on a rotary evaporator. The residue was distilled under reduced pressure through a six-inch Vigreaux column to remove reaction by-products. The distillate, which solidified upon standing, was recrystallized twice from petroleum ether (30-60°) to yield 9.0 g (0.047 mole, 83.8%) of methyl 2,3,4,5-tetramethylbenzoate, mp 35-36°. The infrared, nmr and mass spectra of this compound appear in the Appendix as Figures 16a, 16b and 16c, respectively.

d. The Preparation of An Authentic Sample of Methyl Pentamethylbenzoate

(1) The preparation of 6-bromo-1,2,3,4,5-pentamethylbenzene (76).--Pentamethylbenzene (20 g, 0.135 mole) was dissolved in 200 ml of chloroform and the resulting solution was placed in a 500-ml flask fitted with a condenser, addition funnel and magnetic stirrer. The upper end of the condenser was fitted with a hydrogen bromide trap. A solution of bromine (21.6 g, 0.135 mole) in 100 ml of chloroform was added dropwise with stirring to the flask contents at room temperature. When evolution

of hydrogen bromide had ceased the reaction mixture was washed with water and then dried over anhydrous magnesium sulfate. The chloroform was removed on a rotary evaporator and the solid residue was recrystallized twice from acetone to yield 24.3 g (0.107 mole, 79.3%) of 6-bromo-1,2,3,4,5-pentamethylbenzene, mp 159-160°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 17a and 17b, respectively.

(2) The preparation of pentamethylbenzoic acid (75).--6-Bromo-1,2,3,4,5-pentamethylbenzoic acid (10 g, 0.044 mole) was dissolved in 50 ml of carefully dried tetrahydrofuran. The resulting solution was added dropwise with stirring to a mixture of 1.01 g (0.044 gram-atom) of magnesium turnings and 25 ml of dry tetrahydrofuran. The mixture was warmed slightly to initiate the reaction after a few ml of the substrate solution had been added and the remainder was added at such a rate as to keep the contents of the flask gently boiling. The mixture was then heated under reflux for one hour and then poured over an excess of freshly crushed dry ice. When the residue had warmed to room temperature it was acidified with 6N hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and evaporated. The crude acid was recrystallized twice from aqueous acetone to yield 7.9 g (0.041 mole, 93.5%) of pentamethylbenzoic acid, mp 210-211°. The infrared spectrum of this compound appears in the Appendix as Figure 18.

(3) The preparation of methyl pentamethylbenzoate (77).--Pentamethylbenzoic acid (5.0 g, 0.026 mole) was placed in a 250 ml flask fitted with an addition funnel, condenser and magnetic stirrer. Thionyl chloride (3.6 g, 0.030 mole) was added and the resulting mixture was heated under reflux for one hour. At the end of this time 100 ml of absolute methanol was added and the flask contents were heated under reflux for an additional hour. The excess methanol was removed on a rotary evaporator and the flask residue was recrystallized twice from petroleum ether (30-60°) to yield 4.35 g (0.021 mole, 81.2%) of methyl pentamethylbenzoate, mp 66-67°. The infrared, nmr and mass spectra of this compound appear in the Appendix as Figures 19a, 19b, and 19c, respectively.

4. Quantitative Studies of the Proton Magnetic Resonance Spectra of Mixtures of Methyl 2,3,4,6-Tetramethylbenzoate and Methyl 2,3,5,6-Tetramethylbenzoate

Because of the difficulties encountered in attempts to separate mixtures of methyl 2,3,4,6-tetramethylbenzoate and methyl 2,3,5,6-tetramethylbenzoate by glc methods (vide supra), mixtures of these two esters obtained from the trichloromethylation-solvolysis of isodurene were analyzed by examination of their nmr spectra. The spectrum of methyl 2,3,4,6-tetramethylbenzoate (Figure 8b, Appendix) shows a signal at τ3.39 corresponding to

the single aromatic proton. The related signal in the spectrum of methyl 2,3,5,6-tetramethylbenzoate (Figure 11b, Appendix) appears at τ3.15.

Various mixtures of these two esters were prepared and the nmr spectrum of each mixture was examined at high gain and 50 cps sweep width in the region of τ3. The peak areas at τ3.15 and τ3.39 were measured using a planimeter and the relative amounts of the two esters so determined. In no case did the amount of methyl 2,3,5,6-tetramethylbenzoate in the mixture of two esters exceed 3%. Thus, the amount of this ester produced from the trichloromethylation-solvolysis of isodurene was less than 2% of the five esters produced.

C. The Trichloromethylation of 2-Fluoro-1,3,5-Trimethylbenzene

1. The Preparation of 2-Fluoro-1,3,5-Trimethylbenzene

a. The Preparation of 2-Nitro-1,3,5-Trimethylbenzene (78)

A solution of 31.5 g (0.5 mole) of fuming nitric acid in 20 g of glacial acetic acid and 20 g of acetic anhydride was prepared by slowly adding the nitric acid to the mixture of organic materials. The temperature of the mixture was kept below 20° during the addition. This solution was added dropwise with stirring to a

mixture to 40 g (0.33 mole) of mesitylene in 60 g of acetic anhydride. The mixture was maintained at temperatures below 10° during the addition. After the addition was complete the mixture was allowed to warm to room temperature and was stirred for three hours. The crude reaction mixture was poured into one liter of ice water whereupon the pale yellow solid product separated. This was filtered, washed with ice water and recrystallized from 95% ethanol to yield 36 g (0.216 mole, 66%) of 2-nitro-1,3,5-trimethylbenzene, mp 41-42°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 20a and 20b, respectively.

b. The Preparation of 2,4,6-trimethylaniline (79)

Sixty-eight g (0.41 mole) of 2-nitro-1,3,5-trimethylbenzene was dissolved in 400 ml of 95% ethanol. One-half of this solution was placed in a Parr hydrogenation apparatus together with 5 g of W-2 Raney nickel and hydrogenated at 50 psi until there was no further uptake of hydrogen. The catalyst was filtered and the solvent removed on a rotary evaporator. Similar treatment of the other half-batch and distillation of the residue under reduced pressure yielded 53.6 g (0.397 mole, 97.5%) of 2,4,6-trimethylaniline, bp 92-93° at 8.0 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 21a and 21b, respectively.

c. The Preparation of 2-Fluoro-1,3,5-Trimethylbenzene (80)

2,4,6-Trimethylaniline (14.3 g, 0.110 mole) was dissolved in 100 ml of 6M sulfuric acid and the resulting solution was cooled to 5° in an ice bath. Solid sodium nitrite was added in small batches with stirring until starch-iodide test paper indicated an excess. Fifty ml of 47% fluoroboric acid was added and the precipitate which formed was filtered and washed successively with 100-ml portions of ice water, ethanol and ether. The filter cake was dried for two hours in a vacuum desiccator. The dry powder was transferred to a one-liter flask fitted with an efficient condenser and thermally decomposed by gentle heating with a burner. The dark brown liquid residue was washed with 10% sodium hydroxide solution and then water and dried over anhydrous magnesium sulfate. Distillation under reduced pressure yielded 5.65 g (0.041 mole, 37.3%) of 2-fluoro-1,3,5-trimethylbenzene, bp 59-60° at 13 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 22a and 22b, respectively.

2. The Trichloromethylation of 2-Fluoro-1,3,5-Trimethylbenzene and Subsequent Methanolysis of the Product

2-Fluoro-1,3,5-trimethylbenzene (1.38 g, 0.01 mole) was dissolved in 75 ml of carbon tetrachloride and the

resulting solution was added to a stirred slurry of 2.68 g (0.02 mole) of anhydrous aluminum chloride in 75 ml of carbon tetrachloride. The mixture was stirred at 40.0° ± 0.1 for two hours. At the end of this time the mixture was shaken with 100 ml of ice water to decompose the aluminum chloride and then the organic layer was separated and dried over anhydrous magnesium sulfate. The solution was concentrated to one-half its original volume and 100 ml of absolute methanol was added. The resulting mixture was heated under reflux overnight after which time the solvents were removed on a rotary evaporator. The residue was analyzed by glc methods (5 ft x 0.25 inch 20% SF-96 on Chromasorb-W; temperature 175°; helium carrier gas pressure 40 psi). Two product peaks of retention times 7.8 minutes and 9.3 minutes, respectively were observed. The first peak represented 70% of the product mixture and was shown to be methyl 3-fluoro-2,4,6-trimethylbenzoate by comparison of its infrared and nmr spectra and glc retention time to those of an authentic sample prepared as described below. The second peak, representing 30% of the product mixture was similarly proven to be methyl 4-fluoro-2,3,5-trimethylbenzoate.

3. The Identification of Products Derived from the Trichloromethylation of 2-Fluoro-1,3,5-Trimethylbenzene and Subsequent Methanolysis of the Product

a. The Preparation of An Authentic Sample of Methyl 3-Fluoro-2,4,6-Trimethylbenzoate

(1) The preparation of 2-bromo-4-fluoro-1,3,5-trimethylbenzene (81).--2-Fluoro-1,3,5-trimethylbenzene (3.7 g, 0.027 mole) was dissolved in 50 ml of chloroform and the resulting solution was placed in a 250 ml flask fitted with a condenser, addition funnel and magnetic stirrer. A solution of 4.8 g (0.03 mole) of bromine in 50 ml of chloroform was added dropwise to the flask contents which were then stirred for twenty hours. At the end of this time the mixture was washed with 10% sodium bisulfite solution and then with water and dried over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 3.0 g (0.014 mole, 51.2%) of 2-bromo-4-fluoro-1,3,5-trimethylbenzene, bp 66.5-67.5° at 1.5 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 23a and 23b, respectively.

(2) The preparation of 3-fluoro-2,4,6-trimethylbenzoic acid.--2-Bromo-4-fluoro-1,3,5-trimethylbenzene (3.0 g, 0.014 mole) was dissolved in 25 ml of carefully dried tetrahydrofuran. This solution was added to a rapidly stirred suspension of 0.34 g (0.014 gram-atom) of magnesium turnings in 10 ml of dry tetrahydrofuran. The mixture was heated under reflux for one hour after which time carbon dioxide gas was passed into the flask

until the color of the flask contents had turned to white. The mixture was acidified with 6N hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from aqueous acetone to yield 0.51 g (0.003 mole, 20%) of 3-fluoro-2,4,6-trimethylbenzoic acid, mp 140.5-141°.

Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.95; H, 6.04; N.E. = 182.

Found: C, 65.94; H, 6.13, N.E. = 180.7.

The infrared spectrum of this compound appears in the Appendix as Figure 24.

(3) The preparation of methyl 3-fluoro-2,4,6-trimethylbenzoate.--3-Fluoro-2,4,6-trimethylbenzoic acid (0.4 g, 0.002 mole) was dissolved in 100 ml of ether. A solution of diazomethane, prepared from N-methyl-N-nitrosourea, was added to the acid solution until the color indicated an excess. The excess diazomethane was boiled off on a steam bath and the ether solution was dried over anhydrous magnesium sulfate and evaporated. The residue was purified by passage through a 5 ft x 0.25 inch 20% SF-96 vapor phase chromatographic column at 175°. The purified ester melted at 12.0-12.5°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 25a and 25b, respectively.

Anal. Calcd for $C_{11}H_{13}FO_2$: C, 67.32; H, 6.69.

Found: C, 67.25; H, 6.72.

b. The Preparation of an Authentic Sample of 4-Fluoro-2,3,5-Trimethylbenzoate

(1) The preparation of 4-bromo-2-nitro-1,3-dimethylbenzene (82).--2-Nitro-1,3-dimethylbenzene (75 g, 0.497 mole) was placed in a 500 ml three-neck flask fitted with a condenser, addition funnel and stirring assembly. The flask contents were heated to 100° and bromine (79.5 g, 0.500 mole) was added dropwise. Evolution of hydrogen bromide began almost immediately. When the reaction was complete the crude product was poured into 500 ml of water whereupon it solidified. The reaction flask was rinsed with benzene and these rinsings together with 200 ml of benzene were added to the flask containing the crude reaction product. The benzene solution was separated, washed with 10% sodium bisulfite solution and then with water and dried over anhydrous magnesium sulfate. The benzene was removed on a rotary evaporator. One recrystallization of the crude product from 95% ethanol yielded 85.4 g (0.372 mole, 74.6%) of 4-bromo-2-nitro-1,3-dimethylbenzene, mp 70-71°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 26a and 26b, respectively.

(2) The preparation of 3-bromo-2,6-dimethylaniline (83).--4-Bromo-2-nitro-1,3-dimethylbenzene (30 g, 0.13 mole) was dissolved in 100 ml of 95% ethanol and this solution was placed together with 5 g of W-2 Raney nickel in a Parr low pressure hydrogenation apparatus. The

mixture was shaken under hydrogen at a pressure of 40 psi until there was no further uptake of hydrogen. The catalyst was removed by filtration and the ethanol was removed on a rotary evaporator. Distillation of the residue under reduced pressure yielded 23.7 g (0.12 mole, 92.3%) of 3-bromo-2,6-dimethylaniline, bp 47-48° at 15 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 27a and 27b, respectively.

(3) The preparation of 4-bromo-2-fluoro-1,3-dimethylbenzene.--3-Bromo-2,6-dimethylaniline (33.2 g, 0.166 mole) was dissolved in 200 ml of water containing 25 ml of 18 M sulfuric acid. The mixture was cooled to 3° in an ice bath and solid sodium nitrite was added in small batches until an excess was indicated by starch-iodide paper. The solution was filtered to remove all undissolved solids and 55 g of 47% fluoroboric acid was added to the clear filtrate. The white precipitate which separated was filtered and washed successively with 100-ml portions of cold water, ethanol and ether. The filter cake was dried for five hours in a vacuum desiccator over phosphorus pentoxide. The dry powder was placed in a 1-liter flask fitted with an efficient condenser and gently heated. The solid decomposed smoothly to leave a liquid residue which was taken up in ether. The ether solution was washed with 20% sodium hydroxide solution and then water and dried over anhydrous magnesium sulfate.

Evaporation of the ether and distillation of the residue under reduced pressure yielded 25.8 g (0.127 mole, 76.6%) of 4-bromo-2-fluoro-1,3-dimethylbenzene, bp 38-39° at 0.8 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 28a and 28b, respectively.

Anal. Calcd for C_8H_8BrF: C, 47.31; H, 3.98.
Found: C, 47.41; H, 4.09.

(4) The preparation of 2,4-dimethyl-3-fluorobenzoic acid.--4-Bromo-2-fluoro-1,3-dimethylbenzene (37.6 g, 0.185 mole) was dissolved in 50 ml of carefully dried tetrahydrofuran. This solution was added dropwise to a stirred slurry of 4.5 g (0.185 gram-atom) of magnesium turnings in 50 ml of dry tetrahydrofuran. When formation of the Grignard reagent was complete, the solution was poured over an excess of freshly crushed dry ice. The mixture was allowed to warm to room temperature and then was made acid with 6N hydrochloric acid. The mixture was extracted with ether and the ether solution was dried over anhydrous magnesium sulfate and evaporated to yield 29.0 g (0.172 mole, 93%) of the crude acid. Two recrystallizations from aqueous acetone yielded needles melting at 140.5-141°. The infrared spectrum of this compound appears in the Appendix as Figure 29.

Anal. Calcd for $C_9H_9FO_2$: C, 64.27; H, 5.40; N.E. = 168.
Found: C, 64.32; H, 5.27; N.E. = 166.6.

(5) The preparation of methyl 2,4-dimethyl-3-fluorobenzoate.--2,4-Dimethyl-3-fluorobenzoic acid (20 g, 0.119 mole) was placed in a flask fitted with a condenser, addition funnel and magnetic stirrer. Thionyl chloride (30 g, 0.252 mole) was added and the mixture was heated under reflux for one hour. At the end of this time the excess thionyl chloride was removed by distillation and 100 ml of absolute methanol was cautiously added to the flask contents. The mixture was again heated under reflux for one hour after which time the excess methanol was removed on a rotary evaporator. The residue was distilled under reduced pressure to yield 18.4 g (0.101 mole, 84.9%) of methyl 3-fluoro-2,4-dimethylbenzoate, bp 53-54° at 0.15 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 30a and 30b, respectively.

Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.91; H, 6.10.
Found: C, 65.80; H, 6.13.

(6) The preparation of 2,4-dimethyl-3-fluorobenzyl alcohol.--Methyl 3-fluoro-2,4-dimethylbenzoate (14 g, 0.077 mole) was dissolved in 50 ml of dry ether and the resulting solution was added dropwise to a stirred slurry of 5.85 g (0.154 mole) of lithium aluminum hydride in 300 ml of dry ether. When addition of the substrate was complete the mixture was heated under reflux for one hour. Water was cautiously added to decompose the excess hydride followed by 6N hydrochloric acid to decompose the

precipitated salts. The ether solution was separated and dried over anhydrous magnesium sulfate and evaporated to leave a liquid residue which solidified upon standing. This residue was distilled under reduced pressure to yield 9.45 g (0.063 mole, 80%) of 3-fluoro-2,4-dimethylbenzyl alcohol, bp 74-75° at 0.3 torr. Recrystallization of the distillate from low boiling petroleum ether yielded platelets melting at 37-38°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 31a and 31b, respectively.

Anal. Calcd for $C_9H_{11}FO$: C, 70.10; H, 7.20.
Found: C, 70.16; H, 7.11.

(7) The preparation of 2,4-dimethyl-3-fluorobenzyl chloride.--2,4-Dimethyl-3-fluorobenzyl alcohol (9.3 g, 0.062 mole) was placed in a 100-ml flask fitted with a condenser, addition funnel and magnetic stirrer. Thionyl chloride (25 ml) was slowly added to the flask contents. When the initial reaction had subsided, the flask contents were heated under reflux for one hour. At the end of this time the excess thionyl chloride was removed by distillation at atmospheric pressure and the residue was distilled under reduced pressure to yield 8.1 g (0.047 mole, 76%) of 3-fluoro-2,4-dimethylbenzyl chloride, bp 49-50° at 0.35 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 32a and 32b, respectively.

Anal. Calcd for $C_9H_{10}ClF$: Cl, 20.53.

Found: Cl, 20.38.

(8) The preparation of 3-fluoro-1,2,4-trimethylbenzene.--3-Fluoro-2,4-dimethylbenzyl chloride (8.00 g, 0.046 mole) was dissolved in 25 ml of dry tetrahydrofuran. This solution was added dropwise with stirring to a suspension of 0.95 g (0.025 mole) of lithium aluminum hydride dissolved in 25 ml of dry tetrahydrofuran. After addition of the substrate was complete the mixture was heated under reflux for one hour. The excess hydride was then decomposed by cautious addition of water followed by 6N hydrochloric acid to dissolve the precipitated salts. The ether layer was removed and dried over anhydrous magnesium sulfate and evaporated on a rotary evaporator. The residue was distilled under reduced pressure to yield 5.79 g (0.042 mole, 91.2%) of 3-fluoro-1,2,4-trimethylbenzene, bp 54-55° at 15 torr, $n_D^{25} = 1.4858$. The infrared and nmr spectra of this compound appear in the Appendix as Figures 33a and 33b, respectively.

Anal. Calcd for $C_9H_{11}F$: C, 78.21; H, 8.04.

Found: C, 78.24; H, 8.15.

(9) The preparation of 3-fluoro-6-bromo-1,2,4-trimethylbenzene.--3-Fluoro-1,2,4-trimethylbenzene (5.0 g, 0.037 mole) was dissolved in 50 ml of chloroform. To this solution was added dropwise with stirring, a solution of 5.9 g (0.037 mole) of bromine in 50 ml of

chloroform. The mixture was stirred at room temperature for three hours at the end of which time the excess bromine was removed by shaking the mixture with 10% sodium bisulfite solution. The clear reaction mixture was washed with water and dried over anhydrous magnesium sulfate. The chloroform was removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 6.83 g (0.030 mole, 81%) of 3-fluoro-6-bromo-1,2,4-trimethylbenzene, bp 95-96° at 10 torr, n_D^{25}= 1.5365. The infrared and nmr spectra of this compound appear in the Appendix as Figures 34a and 34b, respectively. The bromination occurred at the position para to the fluorine as evidenced by the nmr spectrum. The coupling constant between the ring-bound proton and fluorine atom is 7.8 cps, in agreement with meta coupling (84).

Anal. Calcd for $C_9H_{10}BrF$: C, 49.78; H, 4.65.
Found: C, 49.88; H. 4.66.

(10) The preparation of 4-fluoro-2,3,5-trimethylbenzoic acid.--3-Fluoro-6-bromo-1,2,4-trimethylbenzene (3.0 g, 0.014 mole) was dissolved in 10 ml of carefully dried tetrahydrofuran and the resulting solution was added to a mixture of 0.34 g (0.014 gram-atom) of magnesium turnings and 25 ml of dry tetrahydrofuran. The mixture was heated under reflux for one hour after which time the solution was poured over an excess of freshly crushed dry ice. When the mixture had warmed to room

temperature it was acidified with 6N hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and evaporated. The yield of crude acid was 1.29 g (0.007 mole, 50%). Two sublimations of the crude acid at 0.1 torr and 100° yielded material melting at 167-168°. The infrared spectrum of this compound appears in the Appendix as Figure 35.

Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.91; H, 6.10; N.E. = 182.2.

Found: C, 65.93; H, 6.08; N.E. = 182.5.

(11) The preparation of methyl 4-fluoro-2,3,5-trimethylbenzoate.--4-Fluoro-2,3,5-trimethylbenzoic acid (0.5 g, 0.003 mole) was dissolved in 100 ml of ether. To this solution was added an ethereal solution of diazomethane prepared from N-nitroso-N-methylurea until the color indicated an excess. The excess diazomethane was boiled off on a steam bath and the remaining ether solution was dried over anhydrous magnesium sulfate and evaporated. The residue was purified by passage through a 5 ft x 0.25 inch 20% SE-30 vapor phase chromatographic column at 180°. The pure ester melted at 19.0-19.5°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 36a and 36b, respectively.

Anal. Calcd for $C_{11}H_{13}FO_2$: C, 67.32; H, 6.69.

Found: C, 67.26; H, 6.65.

D. The Trichloromethylation of 2-Chloro-1,3,5-trimethylbenzene

1. The Preparation of 2-Chloro-1,3,5-Trimethylbenzene (81)

Mesitylene (60 g, 0.500 mole) was dissolved in 200 ml of carbon tetrachloride and 1 g of degreased iron filings were added. The flask and its contents were weighed. Chlorine gas was passed into the flask and it was periodically weighed until the weight had increased by an amount corresponding to the uptake of 0.25 mole of chlorine. The flask contents were kept in the dark and at temperatures below 5° during this process. The iron filings were removed by filtration and the carbon tetrachloride solution was washed twice with 100-ml portions of 10% sodium hydroxide and then with water. The organic layer was separated, dried over anhydrous magnesium sulfate and the solvent was removed on a rotary evaporator. Distillation of the residue under reduced pressure yielded 56.5 g (0.364 mole, 73%) of 2-chloro-1,3,5-trimethylbenzene, bp 71-72° at 6 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 37a and 37b, respectively.

2. The Trichloromethylation of 2-Chloro-1,3,5-Trimethylbenzene and Subsequent Methanolysis of the Product

2-Chloro-1,3,5-trimethylbenzene (15.5 g, 0.1 mole) was dissolved in 100 ml of carbon tetrachloride and the resulting solution was added dropwise to a stirred mixture

of 26.6 g (0.2 mole) of anhydrous aluminum chloride and 100 ml of carbon tetrachloride. The mixture was maintained at 40.0° ± 0.1 and stirred for two hours. At the end of this period the aluminum chloride was hydrolyzed by shaking the crude reaction mixture with 500 ml of ice water. The organic layer was separated and dried over anhydrous magnesium sulfate and the carbon tetrachloride was removed on a rotary evaporator. The yield of crude trichloromethyl compound was 25.7 g (0.094 mole, 94%). Absolute methanol (100 ml) was added and the mixture was heated under reflux overnight. The solvent was removed on a rotary evaporator and the residue was subjected to analysis by glc methods (10 ft x 0.25 inch 20% Carbowax 20-M on Chromasorb-W; temperature 175°; helium carrier gas pressure 40 psi). Two product peaks of retention times 54.6 minutes and 71.4 minutes, respectively were observed. The ratio of peak areas was determined by weighing the paper traced out. The first peak represented 88.1% of the product mixture and was shown by comparison of its infrared and nmr spectra and glc retention time to those of an authentic sample to be methyl 3-chloro-2,4,6-trimethylbenzoate. The second peak represented 11.9% of the product mixture but the identity of this compound was not established.

3. The Identification of the Major Product Derived from the Trichloromethylation of 2-Chloro-1,3,5-Trimethylbenzene and Subsequent Methanolysis of the Product

a. The Preparation of An Authentic Sample of Methyl 3-Chloro-2,4,6-Trimethylbenzoate

(1) The preparation of 2-bromo-4-chloro-1,3,5-trimethylbenzene.--2-Chloro-1,3,5-trimethylbenzene (31.0 g, 0.20 mole) was dissolved in 100 ml of chloroform and the resulting solution was placed in a 250 ml flask fitted with an addition funnel, condenser and magnetic stirrer. The open end of the condenser was fitted with a hydrogen bromide trap. Bromine (35 g, 0.219 mole) dissolved in 50 ml of chloroform was added to the contents of the flask dropwise with stirring at room temperature. The mixture was then stirred for an additional three and one-half hours. At the end of this time the solution was washed with sodium bisulfite solution and then with water. The organic layer was separated, dried over anhydrous magnesium sulfate and the chloroform was removed on a rotary evaporator. The residue was distilled under reduced pressure to yield 33.1 g (0.142 mole, 71%) of 2-bromo-4-chloro-1,3,5-trimethylbenzene, bp 128-129° at 10.5 torr. Upon standing the distillate solidified which after one recrystallization from pentane yielded crystals melting at 57.5-58°. The

infrared and nmr spectra of this compound appear in the Appendix as Figures 38a and 38b, respectively.

Anal. Calcd for $C_9H_{10}BrCl$: C, 45.89; H, 4.29.
Found: C, 46.38; H, 4.51.

(2) The preparation of 3-chloro-2,4,6-trimethylbenzoic acid (85).--2-Bromo-4-chloro-1,3,5-trimethylbenzene (30 g, 0.129 mole) was dissolved in 150 ml of dry ether and the resulting solution was added dropwise with stirring to a mixture of 3.15 g (0.129 gram-atom) of magnesium turnings and 150 ml of ether. The reaction was initiated by the addition of a small amount of ethylmagnesium iodide solution in ether. After formation of the Grignard reagent was complete the solution was poured over an excess of freshly crushed dry ice and the resulting mixture was allowed to warm to room temperature. The residue was acidified with 6N hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and evaporated. Two recrystallizations of the crude product from aqueous acetone yielded 16.8 g (0.085 mole, 65.7%) of 3-chloro-2,4,6-trimethylbenzoic acid, mp 145-146°. The infrared spectrum of this compound appears in the Appendix as Figure 39.

(3) The preparation of methyl 3-chloro-2,4,6-trimethylbenzoate.--3-Chloro-2,4,6-trimethylbenzoic acid (5 g, 0.025 mole) was dissolved in 50 ml of ether. To this solution was added an excess of diazomethane in

ether prepared from N-methyl-N-nitrosourea. The excess diazomethane was boiled away on a steam bath and the remaining ether solution was dried over anhydrous magnesium sulfate and evaporated to yield 5.15 g (0.024 mole, 96%) of the crude ester. Two recrystallizations from petroleum ether (30-60°) yielded material melting at 34-34.5°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 40a and 40b, respectively.

Anal. Calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.17.
Found: C, 62.10; H, 6.11.

E. The Trichloromethylation of 2-Bromo-1,3,5-trimethylbenzene

1. The Preparation of 2-Bromo-1,3,5-Trimethylbenzene

The preparation of 2-bromo-1,3,5-trimethylbenzene from mesitylene has already been described in section IA2a of the Experimental.

2. The Trichloromethylation of 2-Bromo-1,3,5-trimethylbenzene and Subsequent Methanolysis of the Product

2-Bromo-1,3,5-trimethylbenzene (2.01 g, 0.010 mole) was dissolved in 50 ml of carbon tetrachloride and the resulting mixture was added dropwise to a stirred mixture of 2.70 g (0.020 moles) of anhydrous aluminum chloride in 50 ml of carbon tetrachloride maintained at 40.0° ± 0.1.

The mixture was stirred at this temperature for two hours after which time the aluminum chloride was hydrolyzed by shaking the crude reaction mixture with 500 ml of ice water. The organic layer was separated and dried over anhydrous magnesium sulfate. The carbon tetrachloride solution was concentrated to one-half its original volume on a rotary evaporator and absolute methanol (100 ml) was added. The resulting mixture was heated under reflux overnight after which time the solvents were removed on a rotary evaporator. The residue was subjected to analysis by glc methods (5 ft x 0.25 inch 20% SE-30 on Chromasorb-W; temperature 175°; helium carrier gas pressure, 40 psi). Three peaks were observed with retention times of 6.4 minutes, 24.8 minutes and 27.8 minutes, respectively. The first peak was shown to correspond to unreacted starting material and constituted 8% of the total mixture; the two remaining peaks were product peaks. The larger of these represented 93% of the product mixture and was shown by comparison of its infrared and nmr spectra and glc retention time to those of an authentic sample to be methyl 3-bromo-2,4,6-trimethylbenzoate. The second peak represented 7% of the product mixture but the identity of this compound was not established.

3. The Identification of the Major Product Derived from the Trichloromethylation of 2-Bromo-1,3,5-trimethylbenzene Followed By Methanolysis

a. The Preparation of An Authentic Sample of Methyl 3-Bromo-2,4,6-trimethylbenzoate

(1) The preparation of 3-bromo-2,4,6-trimethylbenzoic acid (85).--2,4,6-Trimethylbenzoic acid (7.0 g, 0.043 mole) was dissolved in 50 ml of glacial acetic acid and the resulting mixture was placed in a 250-ml flask fitted with an addition funnel, condenser and magnetic stirrer. The upper end of the condenser was fitted with a hydrogen bromide trap. Bromine (8.0 g, 0.05 mole) dissolved in 20 ml of glacial acetic acid was added dropwise to the stirred flask contents. After addition of the bromine was complete the mixture was heated to 60° for three hours. At the end of this time the crude reaction mixture was poured into one liter of ice water and the solid which precipitated was filtered and washed with water. Two recrystallizations from benzene yielded 7.1 g (0.029 mole, 67.6%) of 3-bromo-2,4,6-trimethylbenzoic acid, mp 161-162°. The infrared spectrum of this compound appears in the Appendix as Figure 41.

(2) The preparation of methyl 3-bromo-2,4,6-trimethylbenzoate.--3-Bromo-2,4,6-trimethylbenzoic acid (5.0 g, 0.028 mole) was dissolved in 100 ml of ether. An excess of diazomethane dissolved in ether was added to the acid. The excess diazomethane was boiled away on a steam bath and the residual ethereal solution was dried over anhydrous magnesium sulfate and evaporated.

The crude ester was recrystallized twice from petroleum ether (30-60°) to yield 6.95 g (0.027 mole, 96%) of methyl 3-bromo-2,4,6-trimethylbenzoate, mp 42.5-43°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 42a and 42b, respectively.

Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.36; H, 5.06.
Found: C, 51.49; H, 5.21.

II. Mechanism Studies--the Trichloromethylation of Deuterium Labeled Substrates

A. The Preparation of Model Compounds For the Assignment of Signals in the Nuclear Magnetic Resonance Spectrum of Methyl 2,3,4,5-Tetramethylbenzoate

1. The Preparation of An Authentic Sample of Methyl 3,4,5-Trimethylbenzoate

a. The Preparation of 4-nitro-1,2,3-trimethylbenzene (86)

A mixture of 70 g of concentrated sulfuric acid and 48 g of 70% nitric acid was added slowly to 60 g (0.500 mole) of hemimellitene which had been cooled to 5° in an ice bath. During the addition the temperature of the mixture was never allowed to rise above 10°. After addition of the acid mixture was complete the crude produce was poured into one liter of ice water. The resulting mixture was made slightly alkaline with sodium carbonate added as

a solid in small batches. The mixture was extracted with ether and the ether solution was dried over anhydrous magnesium sulfate and evaporated. The residue was distilled under reduced pressure to yield 6.5 g of starting hydrocarbon and 57.3 g (0.347 mole, 69.5%) of 4-nitro-1,2,3-trimethylbenzene, bp 147-148° at 11 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 43a and 43b, respectively.

b. The Preparation of 2,3,4-Trimethylaniline (86)

4-Nitro-1,2,3-trimethylbenzene (57.3 g, 0.347 mole) was dissolved in 150 ml of 95% ethanol and the resulting solution was placed together with 10 g of W-2 Raney nickel in a Parr low pressure hydrogenation bottle. The mixture was shaken under hydrogen pressure of 40 psi until there was no further uptake of hydrogen. The catalyst was then removed by filtration and the solvent was removed on a rotary evaporator. Distillation of the residue under reduced pressure yielded 40.8 g (0.302 mole, 88%) of 2,3,4-trimethylaniline, bp 57-58° at 0.07 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 44a and 44b, respectively.

c. The Preparation of 6-Bromo-2,3,4-trimethylaniline

2,3,4-Trimethylaniline (38 g, 0.282 mole) was dissolved in 200 ml of glacial acetic acid and the resulting

solution was placed in a 500-ml flask fitted with a stirrer, addition funnel and condenser. Bromine (45 g, 0.282 mole) dissolved in 100 ml of glacial acetic acid was added dropwise with stirring to the flask contents. Periodic cooling of the flask contents was necessary to maintain the temperature near the ambient. The product began to crystallize from the reaction mixture when about half of the bromine solution had been added. When all of the bromine had been added the mixture was stirred for an additional hour. At the end of this time the precipitate was filtered and washed with acetone to remove the acetic acid. The yield of crude 6-bromo-2,3,4-trimethylanilinium hydrobromide was 74.2 g (0.252 mole, 89.2%). Two recrystallizations from dilute hydrobromic acid yielded crystals melting at 160-162°. The free amine was rapidly oxidized by air and could not be kept for any length of time in a pure state. However, the infrared spectrum of the free amine, 6-bromo-2,3,4-trimethylaniline does appear in the Appendix as Figure 45. The compound was analyzed as the hydrobromide salt.

Anal. Calcd for $C_9H_{13}NBr_2$: C, 36.63; H, 4.45; N, 4.75.

Found: C, 36.96; H, 3.83; N, 4.76.

d. The Preparation of 5-Bromo-1,2,3-trimethylbenzene (81)

6-Bromo-2,3,4-trimethylanilinium hydrobromide (74.2 g, 0.252 mole) was dissolved in 300 ml of 1 M hydrochloric

acid. The resulting solution was cooled to 5° in an ice bath. Sodium nitrite solid was added in small batches until starch-potassium iodide test paper indicated an excess. The cold diazonium salt solution was filtered to remove all undissolved solids. Hypophosphorous acid (200 ml, 30%) was added to the solution and the resulting mixture stood overnight at room temperature. The oil which separated was taken up in ether and the water solution was extracted with ether. The combined ether solutions were dried over anhydrous magnesium sulfate and the ether was evaporated. The residue was distilled under reduced pressure to yield 33.4 g (0.167 mole, 66.4%) of 5-bromo-1,2,3-trimethylbenzene, bp 49-50° at 0.1 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 46a and 46b, respectively.

e. The Preparation of 3,4,5-trimethylbenzoic acid (88)

5-Bromo-1,2,3-trimethylbenzene (20 g, 0.100 mole) was dissolved in 25 ml of dry tetrahydrofuran and the resulting solution was slowly added to a stirred suspension of 2.43 g (0.100 gram-atom) of magnesium turnings in 50 ml of dry tetrahydrofuran. When formation of the Grignard reagent was complete the ethereal solution was poured over an excess of freshly crushed dry ice and allowed to warm to room temperature. The residue was acidified with 6N hydrochloric acid and extracted with

ether. The ether solution was dried over anhydrous magnesium sulfate and evaporated. Two recrystallizations of the crude acid from aqueous acetone yielded 11.9 g (0.073 mole, 73%) of 3,4,5-trimethylbenzoic acid, mp 214-216°. The infrared spectrum of this compound appears in the Appendix as Figure 46.

f. The Preparation of Methyl 3,4,5-Trimethylbenzoate (87)

3,4,5-Trimethylbenzoic acid (5.0 g, 0.030 mole) was placed in a 100-ml flask fitted with an addition funnel, condenser and magnetic stirrer. Thionyl chloride (5 g, 0.042 mole) was added and the resulting mixture was heated under reflux for one hour. At the end of this time 25 ml of absolute methanol was added and the mixture was again heated under reflux for one hour. The solvent was removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 4.5 g (0.026 mole, 85.2%) of methyl 3,4,5-trimethylbenzoate, bp 103-104° at 1 torr. The ester solidified in the receiver; one recrystallization from petroleum ether (30-60°) yielded plates melting at 40-41°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 48a and 48b, respectively.

2. The Preparation of An Authentic Sample of Methyl 2,4,5-Trimethylbenzoate

a. The Preparation of 2,4,5-Trimethylbenzoic Acid (89)

2,4,5-Trimethylacetophenone (20 g, 0.123 mole) was placed together with 200 ml of 10% sodium hydroxide solution in a 500-ml flask fitted with a stirrer, addition funnel and condenser. The mixture was cooled to 5° in an ice bath and bromine (56.2 g, 0.35 mole) was added dropwise over a period of two hours. When addition of the bromine was complete the mixture was allowed to warm to room temperature where it was stirred for five hours. The bromoform which had separated was removed and the basic aqueous layer was extracted once with ether. The water solution was acidified with 6N hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and evaporated. Two recrystallizations of the crude acid from aqueous acetone yielded 18.7 g (0.114 mole, 93%) of 2,4,5-trimethylbenzoic acid, mp 150-151°. The infrared spectrum of this compound appears in the Appendix as Figure 49.

b. The Preparation of Methyl 2,4,5-Trimethylbenzoate

2,4,5-Trimethylbenzoic acid (10 g, 0.061 mole) was placed in a 100 ml flask fitted with a condenser, addition

funnel and magnetic stirrer. Thionyl chloride (8 g, 0.067 mole) was added and the mixture was heated under reflux for one hour. At the end of this time 50 ml of absolute methanol was added and the mixture was again heated under reflux for one hour. The solvent was then removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 7.20 g (0.041 mole, 66.4%) of methyl 2,4,5-trimethylbenzoate, bp 90-91° at 0.6 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 59a and 50b, respectively.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.15; H, 7.86.
Found: C, 74.28; H, 7.87.

3. The Preparation of An Authentic Sample of Methyl 2,3,4-Trimethylbenzoate

a. The Preparation of 4-Bromo-1,2,3-trimethylbenzene (90)

1,2,3-Trimethylbenzene (50 g, 0.416 mole) was dissolved in 100 ml of chloroform and the resulting solution was cooled to 5° in an ice bath. To this solution was added dropwise with stirring a solution of bromine (67 g, 0.419 mole) dissolved in 100 ml of chloroform. When the addition of the bromine was complete the solution was allowed to warm to room temperature where it was stirred for four hours. At the end of this time the mixture was

washed with 10% sodium bisulfite solution and then water. The organic layer was separated and dried over anhydrous magnesium sulfate. Evaporation of the chloroform and distillation of the residue under reduced pressure yielded 69.4 g (0.348 mole, 84%) of 4-bromo-1,2,3-trimethylbenzene, bp 75-76° at 1.5 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 51a and 51b, respectively.

b. The Preparation of 2,3,4-Trimethylbenzoic Acid (91)

4-Bromo-1,2,3-trimethylbenzene (50 g, 0.250 mole) was dissolved in 50 ml of dry tetrahydrofuran and the resulting solution was added dropwise to a stirred mixture of 6.1 g (0.250 gram-atom) of magnesium turnings in 100 ml of dry tetrahydrofuran. The mixture was heated to initiate the reaction and the substrate was added at such a rate as to keep the contents of the flask gently boiling. When formation of the Grignard reagent was complete, the ethereal solution was poured over an excess of freshly crushed dry ice and the resulting mixture was allowed to warm to room temperature. Acidification of the residue with 6N hydrochloric acid followed by extraction with ether and evaporation of the dried ether solution yielded 34.5 g (0.21 mole, 84.1%) of the crude acid. One recrystallization from aqueous acetone yielded material

melting at 168-169°. The infrared spectrum of this compound appears in the Appendix as Figure 52.

c. The Preparation of Methyl 2,3,4-trimethylbenzoate

2,3,4-Trimethylbenzoic acid (10 g, 0.061 mole) was placed in a 100-ml flask fitted with a condenser, addition funnel and magnetic stirrer. Thionyl chloride (8 g, 0.067 mole) was added and the mixture was heated under reflux for one hour. At the end of this time 50 ml of absolute methanol was added and the mixture was again heated under reflux for one hour. Evaporation of the methanol on a rotary evaporator followed by distillation of the residue under reduced pressure yielded 10.0 g (0.058 mole, 95%) of methyl 2,3,4-trimethylbenzoate, bp 75-76° at 0.20 torr. The pure product solidified upon standing; one recrystallization from aqueous methanol yielded crystals melting at 52-43°. The infrared and nmr spectra of this compound appear in the Appendix as Figures 53a and 53b, respectively.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.15; H, 7.86.
Found: C, 74.19; H, 7.82.

B. The Trichloromethylation of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3

1. The Preparation of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3

a. The Preparation of 2,4,6-Trimethylbenzyl-α,α-d_2 alcohol

Lithium aluminum deuteride (2.3 g, 0.055 mole) was placed in a flask which had been fitted with a condenser, addition funnel and magnetic stirrer and which had been previously carefully dried and flushed with nitrogen. Tetrahydrofuran (100 ml) was distilled into the flask from a second flask which contained lithium aluminum hydride. To the flask containing the deuteride was added dropwise with stirring a solution of 17.8 g (0.1 mole) of methyl 2,4,6-trimethylbenzoate contained in 50 ml of carefully dried tetrahydrofuran. When the addition was complete the mixture was heated under reflux for one hour. At the end of this time water was cautiously added to decompose the excess deuteride followed by 6N hydrochloric acid to dissolve the precipitated salts. The organic layer was separated and the water layer was extracted twice with ether. The ethereal solutions were combined and dried over anhydrous magnesium sulfate. The ether solution was evaporated to yield 15.1 g (0.099 mole, 99%) of the crude alcohol. One recrystallization from petroleum ether (30-60°) gave the pure 2,4,6-trimethylbenzyl-α,α-d_2 alcohol, mp 87-88°. The infrared and nmr spectra

of this compound appear in the Appendix as Figures 54a and 54b, respectively. The literature (92) reports a melting point of 87-88° for the undeuterated isomer.

b. The Preparation of 2,4,6-Trimethylbenzyl-α,α-d_2 chloride

2,4,6-Trimethylbenzyl-α,α-d_2 alcohol (15.0 g, 0.099 mole) was placed in a 250-ml flask fitted with an addition funnel, condenser and magnetic stirrer. Thionyl chloride (14.3 g, 0.12 mole) was added and the resulting mixture was heated under reflux for one hour. At the end of this time the excess thionyl chloride was removed by means of a water aspirator and the dark flask residue was distilled to produce 7.1 g (0.042 mole, 42.4%) of 2,4,6-trimethylbenzyl-α,α-d_2 chloride, bp 52-53° at 0.1 torr. The infrared and nmr spectra of this compound appear in the Appendix as Figures 55a and 55b, respectively.

c. The Preparation of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3

2,4,6-Trimethylbenzyl-α,α-d_2 chloride (7.1 g, 0.042 mole) was reduced to 1,2,3,5-tetramethylbenzene-2',2',2'-d_3 by means of the procedure previously described for the reduction of 2,4,6-trimethylbenzyl chloride to isodurene. The yield of the deuterated hydrocarbon was 5.48 g (0.040 mole, 95.3%); bp 71-72° at 7 torr. The infrared, nmr and mass spectra of this compound

appear as Figures 56a, 56b and 56c, respectively in the Appendix. Examination of the mass spectrum of the deuterated hydrocarbon shows a peak for the molecular ion at m/e = 137 and a base peak at m/e - 122 ($P-CH_3$) in accord with that expected for the trideuterated isodurene.

2. The Trichloromethylation of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3

1,2,3,5-Tetramethylbenzene-2',2',2'-d_3 (1.37 g, 0.01 mole) was trichloromethylated in 150 ml of carbon tetrachloride with 2.68 g (0.02 mole) of anhydrous aluminum chloride using the procedure previously described for the unlabeled isodurene. The crude product mixture of esters was separated by glc methods and the infrared and mass (and in some cases nmr) spectra of the esters were obtained.

C. The trichloromethylation of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3

1. The Preparation of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3

a. The Preparation of 3,4,5-Trimethylbenzyl-α,α-d_2 alcohol

Methyl 3,4,5-trimethylbenzoate (11.0 g, 0.062 mole) was dissolved in 50 ml of tetrahydrofuran which had been previously dried by distillation from lithium aluminum

hydride. The resulting solution was added dropwise with stirring to a mixture of 1.35 g (0.032 mole) of lithium aluminum deuteride and 100 ml of carefully dried tetrahydrofuran in a 250-ml flask fitted with an addition funnel, condenser and magnetic stirrer. After addition of the substrate was complete the mixture was heated under reflux for one hour. Water was then cautiously added to decompose the excess deuteride followed by 6N hydrochloric acid to dissolve the precipitated salts. The ether layer was separated and the water layer was twice extracted with ethyl ether. The ether solutions were combined and dried over anhydrous magnesium sulfate. Evaporation of the ethers yielded 9.31 g (0.061 mole, 98.5%) of the crude alcohol. Two recrystallizations from n-pentane yielded material melting at 77-78°. The literature (93) reports a mp of 78° for the undeuterated isomer. The infrared and nmr spectra of 3,4,5-trimethylbenzyl-α,α-d_2 alcohol appear in the Appendix as Figures 57a and 57b, respectively.

b. The Preparation of 3,4,5-Trimethylbenzyl-α,α-d_2 Chloride

3,4,5-Trimethylbenzyl-α,α-d_2 alcohol (7.00 g, 0.047 mole) was placed in a 250-ml flask fitted with an addition funnel, condenser and magnetic stirrer. Thionyl chloride (6 g, 0.051 mole) was added to the flask contents and the mixture was heated to 40° for two hours. At the end of

this time the excess thionyl chloride was removed by means of a water aspirator. The crude product which appeared as a green oil was taken up in 100 ml of ethyl ether and the ether solution was washed with water. The organic layer was separated and dried over anhydrous magnesium sulfate. The ether was evaporated and the residue was recrystallized twice from n-pentane to yield 5.10 g (0.0298 mole, 64%) of 3,4,5-trimethylbenzyl-α,α-d_2 chloride, mp 35-36°. The undeuterated material, prepared as described above from the undeuterated alcohol melted at 35-36°. The infrared and nmr spectra of 3,4,5-trimethylbenzyl-α,α-d_2 chloride appear in the Appendix as Figures 58a and 58b, respectively.

c. The Preparation of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3

3,4,5-Trimethylbenzyl-α,α-d_2 chloride (5.00g, 0.029 mole) was dissolved in 15 ml of carefully dried tetrahydrofuran. This solution was added dropwise to a stirred suspension of 0.35 g (0.008 mole) of lithium aluminum deuteride in 25 ml of carefully dried tetrahydrofuran. When the addition was complete the mixture was heated under reflux for one hour and then allowed to stand at room temperature overnight. Water was then cautiously added to decompose the excess deuteride followed by 6N hydrochloric acid to dissolve the precipitated salts. The resulting mixture was extracted twice with ether and the ether

solution dried over anhydrous magnesium sulfate. The ether was removed on a rotary evaporator and the residue was distilled under reduced pressure to yield 3.12 g (0.023 mole, 78%) of 1,2,3,5-tetramethylbenzene-5',5',5'-d_3, bp 57° at 3.5 torr. The infrared, nmr and mass spectra of this compound appear in the Appendix as Figures 59a, 59b and 59c, respectively.

2. The Trichloromethylation of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3 and Subsequent Methanolysis of the Product

1,2,3,5-Tetramethylbenzene-5',5',5'-d_3 (1.37 g, 0.010 mole) was trichloromethylated in 150 ml of carbon tetrachloride with 2.66 g (0.020 mole) of anhydrous aluminum chloride using the procedure previously outlined for the unlabeled isodurene. The crude product mixture of esters was separated by glc methods and the infrared and mass (and in some cases nmr) spectra of the esters were obtained.

III. Kinetic Studies--The Relative Rates of Trichloromethylation of Five Tetrasubstituted Esters

A. The Rate of Isomerization of Isodurene in the Presence of Anhydrous Aluminum Chloride in Carbon Disulfide at 40°

In order to determine the rate at which isodurene isomerizes to other polymethylbenzenes in the presence of aluminum chloride at 40° the following experiments were

carried out. Samples of isodurene weighing 1.34 g (0.01 mole) each were dissolved in 75 ml of carbon disulfide and the solution was placed in a water bath held at 40° to thermally equilibrate. Aluminum chloride (2.68 g, 0.02 mole) samples were placed in a 250-ml flask together with 75 ml of carbon disulfide and the flask and its contents were allowed to equilibrate to 40° in the water bath. The isodurene solution was rapidly added to the stirring mixture of solvent and aluminum chloride and the resulting mixture was allowed to react for various prespecified times. The reaction was then rapidly quenched by the addition of 100 ml of ice water. The organic layer was separated and the water layer was extracted once with carbon disulfide. The carbon disulfide solutions were combined and dried over anhydrous magnesium sulfate and the solvent removed by distillation. The residual hydrocarbon was weighed and then subjected to analysis by glc methods (10 ft x 0.25 inch 20% SE-30 on Chromasorb-W; temperature, 175°; helium carrier gas pressure 40 psi). The identity of each peak was determined by peak enhancement methods; i.e., a small sample of hydrocarbon was added to an aliquot of the reaction mixture to verify the identity of each peak. The amount of each hydrocarbon present in the reaction mixture was determined by weighing the paper traced out by the recorder. The results of these experiments have been presented earlier, in Table II.

B. The Relative Rates of Trichloromethylation of Five Tetrasubstituted Benzenes at 40°

Aluminum chloride (2.68 g, 0.02 mole) was placed together with 75 ml of dry carbon tetrachloride in a 250-ml flask fitted with a condenser, stirring assembly and addition funnel. The flask and its contents were placed in a water bath and allowed to thermally equilibrate to 40.0° ± 0.1. Isodurene (0.67 g, 0.005 mole) and 0.005 mole of another tetrasubstituted benzene substrate were thoroughly mixed and a 10 µl aliquot was removed for analysis. The mixture of substrates was dissolved in 75 ml of dry carbon tetrachloride and the resulting solution was placed in the water bath to thermally equilibrate. The substrate solution was rapidly poured into the flask containing the aluminum chloride and the resulting mixture was stirred for exactly five minutes. At the end of this time the reaction was quenched by the addition of 100 ml of ice water. The organic layer was separated and the water layer was extracted once with carbon tetrachloride and the organic solutions were combined. The carbon tetrachloride was removed on a rotary evaporator and 50 ml of water and 50 ml of acetone were added to the residue. This mixture was heated under reflux for two hours. The mixture was then made alkaline and extracted with ether. The ether was evaporated and the residue of unreacted substrate was analyzed by glc methods. The ratio of amounts of the two unreacted

starting materials were determined by weighing the paper traced out by the glc recorder. This ratio was adjusted to differences in thermal conductivity detector response using glc recorder data from the aliquot of substrates previously mentioned. The rate of reaction of each substrate relative to isodurene was determined by the deviation of the ratio of recovered unreacted substrate from 1.

The rates of trichloromethylation relative to isodurene of four tetrasubstituted benzenes were determined in this manner. The substances examined were prehnitene, 2-fluoro-, 2-chloro-, and 2-bromo-1,3,5-trimethylbenzene. The results of these experiments have already been presented in Table I.

SUMMARY

1. Five tetrasubstituted benzenes were reacted with carbon tetrachloride in the presence of anhydrous aluminum chloride and the rates of trichloromethylation relative to isodurene were determined. The compounds and their relative reaction rates at 40° were prehnitene (2.4 ± 0.1), isodurene (1.00), 2-fluoromesitylene (1.0 ± 0.1), 2-chloromesitylene (0.36 ± 0.05), and 2-bromomesitylene (0.21 ± 0.03).

2. Isodurene was trichloromethylated at 40° and the resulting product mixture was solvolyzed in boiling methanol. The product mixture of methyl benzoates was analyzed by gas-liquid chromatographic means and found to consist of methyl mesitoate (3%), methyl 2,3,4,6-tetramethylbenzoate (66%), methyl 2,3,5,6-tetramethylbenzoate (2%), methyl 2,3,4,5-tetramethylbenzoate (22%) and methyl pentamethylbenzoate (7%). The identity of these products was established by comparison to samples prepared by normal routes.

3. 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3 and 1,2,3,5-tetramethylbenzene-2',2',2'-d_3 were prepared and trichloromethylated at 40°. The product mixtures were solvolyzed to mixtures of the corresponding methyl benzoates and the mixtures separated by gas-liquid chromatographic means. The structures of the deuterated methyl benzoates were inferred from their proton magnetic resonance and mass spectra. On the basis of the product structures a mechanism for the production of a mixture of isomers in the trichloromethylation of isodurene was presented.
4. 2-Fluoromesitylene was trichloromethylated at 40° and the resulting product mixture was solvolyzed in boiling methanol. The product mixture was found to consist of methyl 3-fluoro-2,4,6-trimethylbenzoate (70%) and methyl 4-fluoro-2,3,5-trimethylbenzoate (30%). The identity of the products was established by comparison to samples prepared by unambiguous routes.
5. 2-Chloromesitylene and 2-bromomesitylene were trichloromethylated at 40° and the resulting product mixtures were solvolyzed in boiling methanol. Two products were observed in each case. The major products were identified by comparison to samples prepared by unambiguous

routes. The minor product in each case was not identified but its structure was assumed by analogy to correspond to 4-halo-2,3,5-trimethylbenzoate. 2-Chloromesitylene led to methyl 3-chloro-2,4,6-trimethylbenzoate (88%) and methyl chloro-2,3,5-trimethylbenzoate (?) (12%). 2-Bromomesitylene led to methyl 3-bromo-2,4,6-trimethylbenzoate (93%) and methyl 4-bromo-2,3,5-trimethylbenzoate (?) (7%).

6. In the course of the investigation the following new compounds were synthesized and characterized:

a. 3-Fluoro-2,4,6-trimethylbenzoic acid

b. Methyl 3-fluoro-2,4,6-trimethylbenzoate

c. 4-Bromo-2-fluoro-1,3-dimethylbenzene

d. 2,4-Dimethyl-3-fluorobenzoic acid

e. Methyl 2,4-dimethyl-3-fluorobenzoate

f. 2,4-Dimethyl-3-fluorobenzyl alcohol

g. 2,4-Dimethyl-3-fluorobenzyl chloride

h. 3-Fluoro-1,2,4-trimethylbenzene

i. 6-Bromo-3-fluoro-1,2,4-trimethylbenzene

j. 4-Fluoro-2,3,5-trimethylbenzoic acid

k. Methyl 4-fluoro-2,3,5-trimethylbenzoate

l. 2-Bromo-4-chloro-1,3,5-trimethylbenzene

m. Methyl 3-chloro-2,4,6-trimethylbenzoate

n. Methyl 3-bromo-2,4,6-trimethylbenzoate

o. 6-Bromo-2,3,4-trimethylaniline

p. 3,4,5-Trimethylbenzyl chloride

q. Methyl 2,4,5-trimethylbenzoate

r. Methyl 2,3,4-trimethylbenzoate

s. 2,4,6-Trimethylbenzyl-α,α-d_2 alcohol

t. 2,4,6-Trimethylbenzyl-α,α-d_2 chloride

u. 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3

v. 3,4,5-Trimethylbenzyl-α,α-d_2 alcohol

w. 3,4,5-Trimethylbenzyl-α,α-d_2 chloride

x. 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3

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APPENDIX

INFRARED, PROTON MAGNETIC RESONANCE AND MASS SPECTRA

Infrared Spectra

All infrared spectra were recorded on a Unicam Model SP-200 Infrared Spectrophotometer and calibrated relative to polystyrene. The spectra have been reproduced in this Appendix by reducing them by a factor of 0.67 using a pantograph.

Nuclear Magnetic Resonance Spectra

All nuclear magnetic resonance spectra were recorded on a Varian Model A-60 NMR Spectrometer and a Varian Model HR-100 NMR Spectrometer and calibrated relative to tetramethylsilane used as an internal standard. The spectra have been reproduced in this Appendix by hand drawing but tau values are reported to the nearest 0.01 unit.

Mass Spectra

All mass spectra were obtained on a Consolidated Electrodynamics Corporation Model 21-103C spectrometer with ionizing voltage of 70 volts in each case.

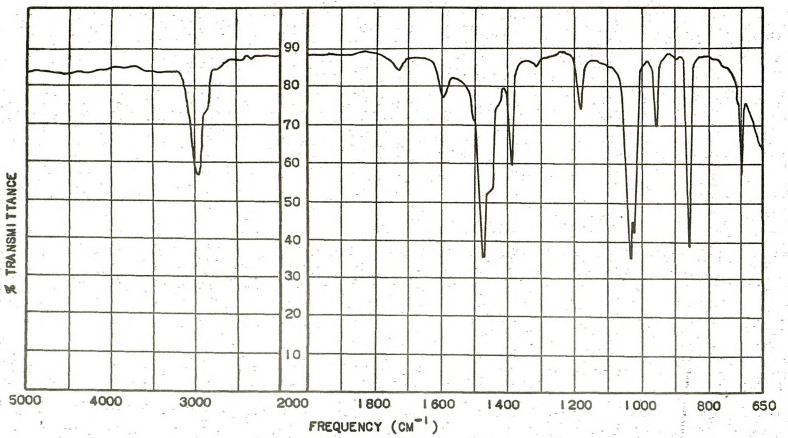

Figure 1a

Infrared Spectrum of 2-Bromo-1,3,5-trimethylbenzene

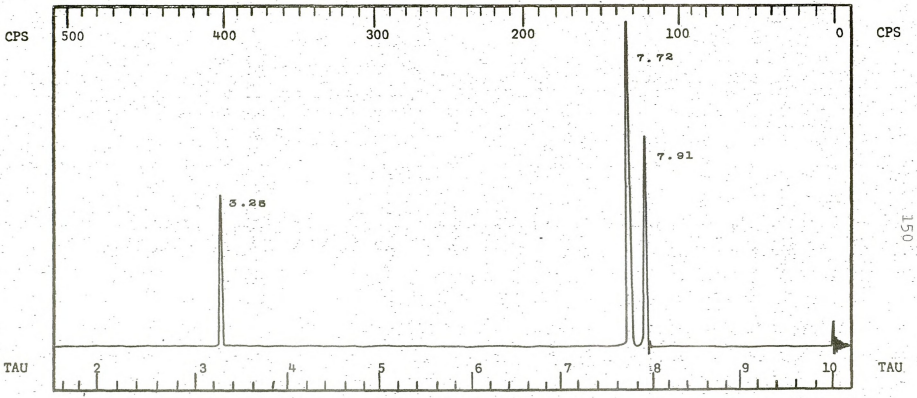

Figure 1b

Nuclear Magnetic Resonance Spectrum of 2-Bromo-1,3,5-trimethylbenzene

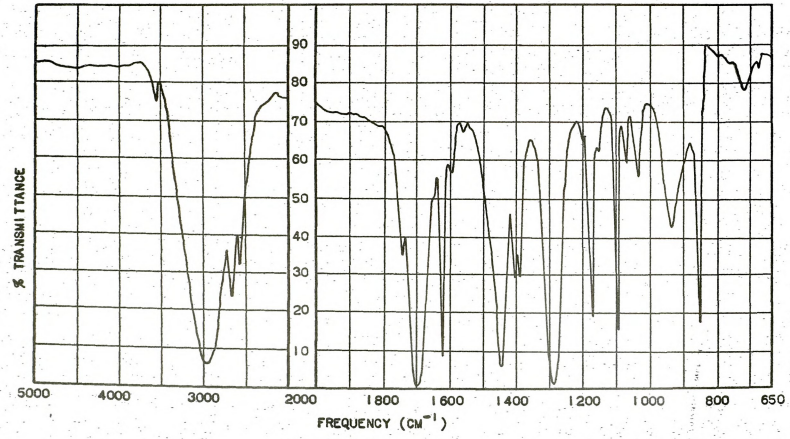

Figure 2

Infrared Spectrum of 2,4,6-Trimethylbenzoic Acid

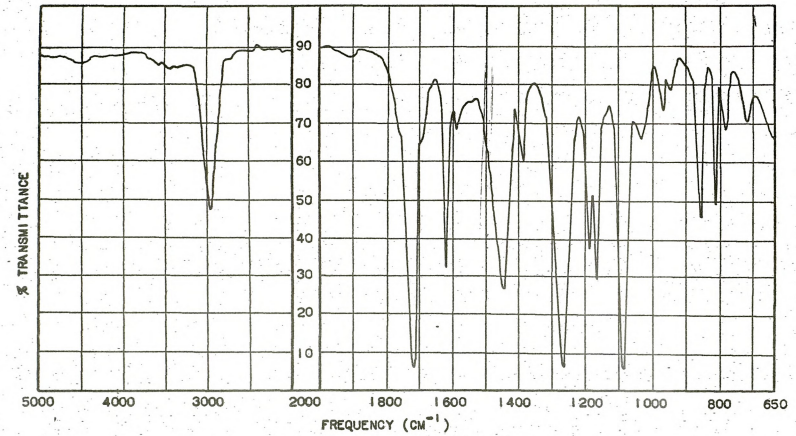

Figure 3a

Infrared Spectrum of Methyl 2,4,6-Trimethylbenzoate

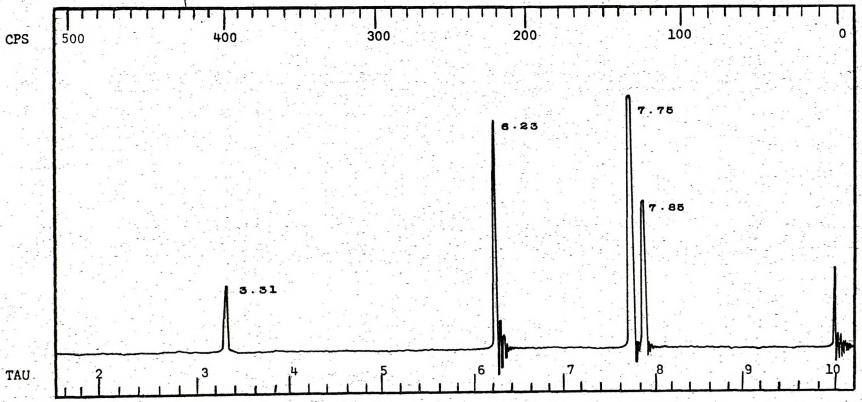

Figure 3b

Nuclear Magnetic Resonance Spectrum of Methyl 2,4,6-Trimethylbenzoate

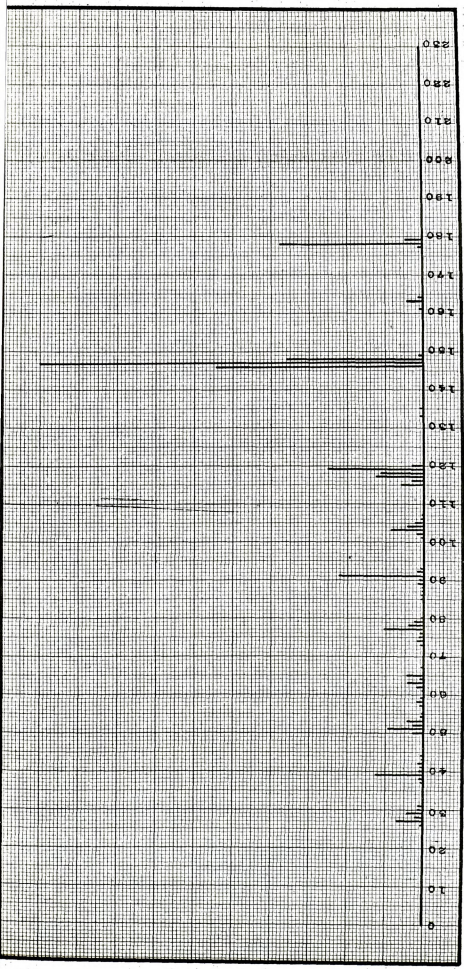

Figure 3c

Mass Spectrum of Methyl 2,4,6-Trimethylbenzoate

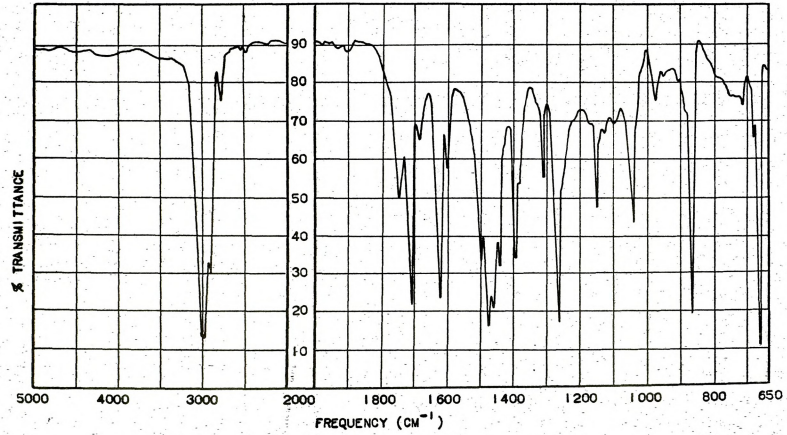

Figure 4a

Infrared Spectrum of 2,4,6-Trimethylbenzyl Chloride

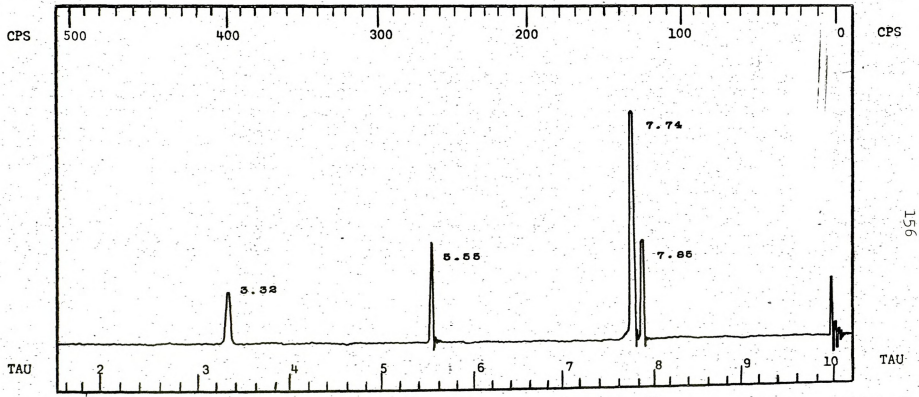

Figure 4b

Nuclear Magnetic Resonance Spectrum of 2,4,6-Trimethylbenzyl Chloride

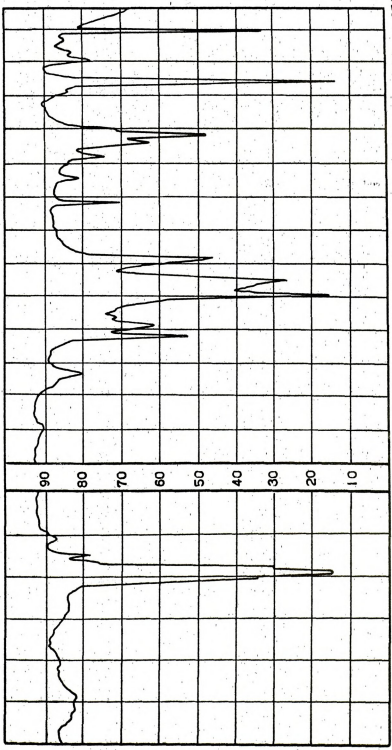

Figure 5a

Infrared Spectrum of Isodurene

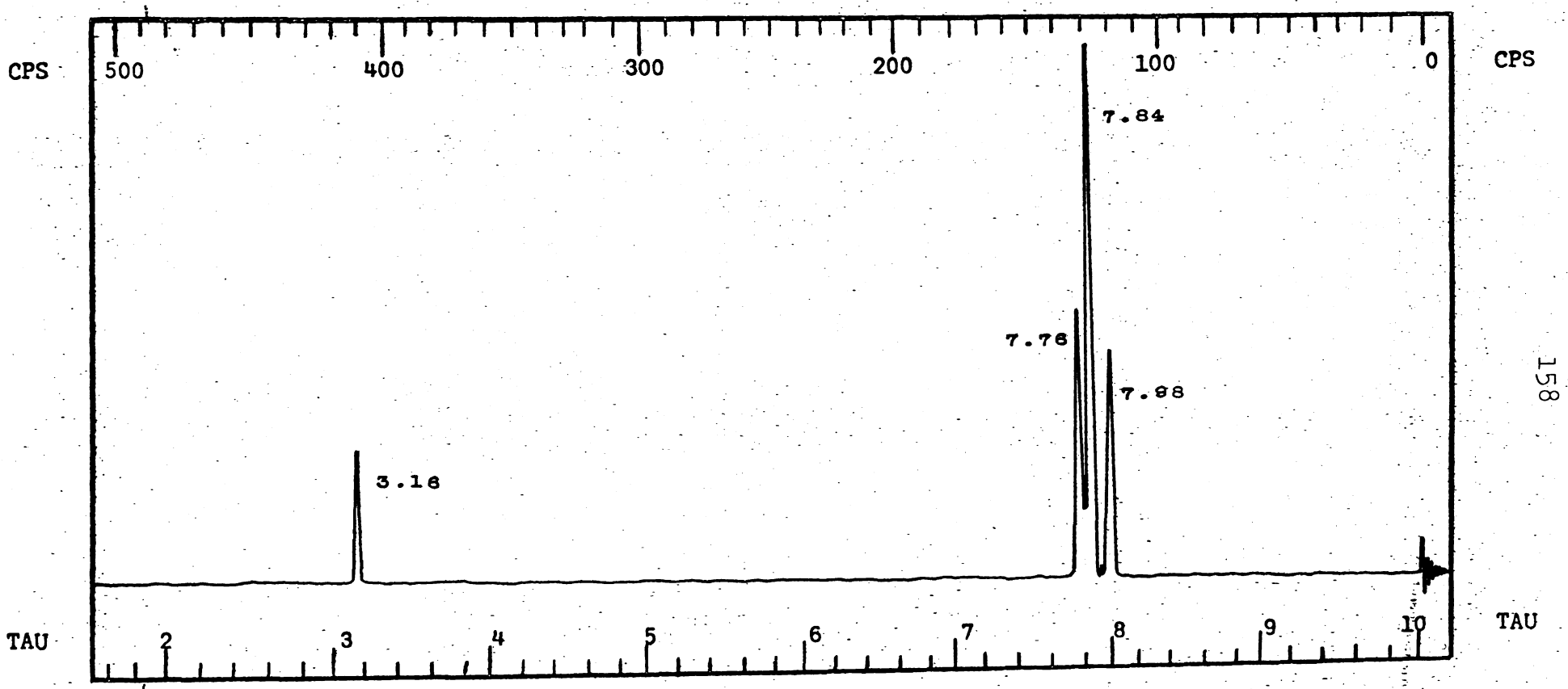

Figure 5b

Nuclear Magnetic Resonance Spectrum of Isodurene

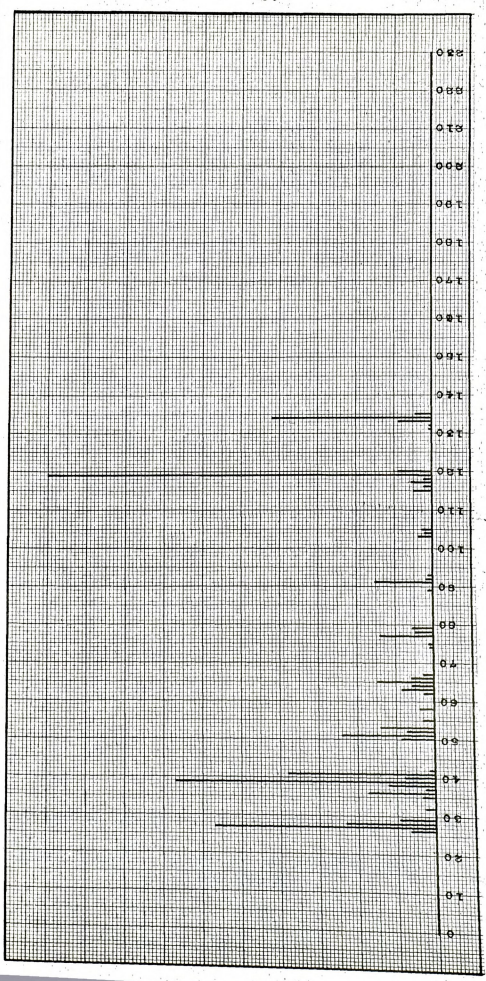

Figure 5c

Mass Spectrum of Isodurene

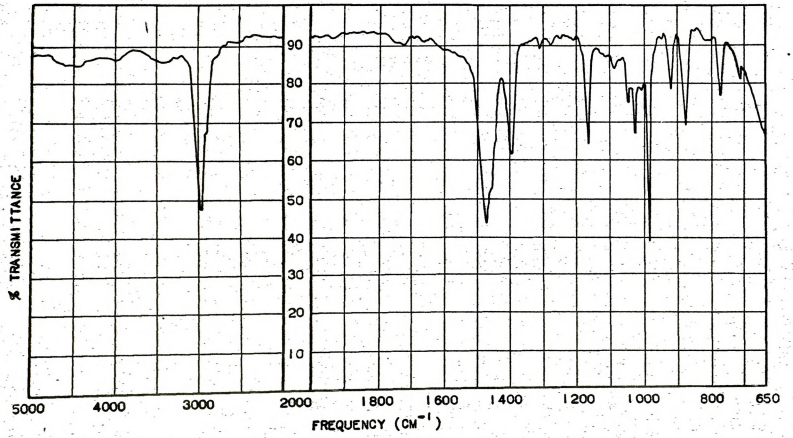

Figure 6a

Infrared Spectrum of 4-Bromo-1,2,3,5-tetramethylbenzene

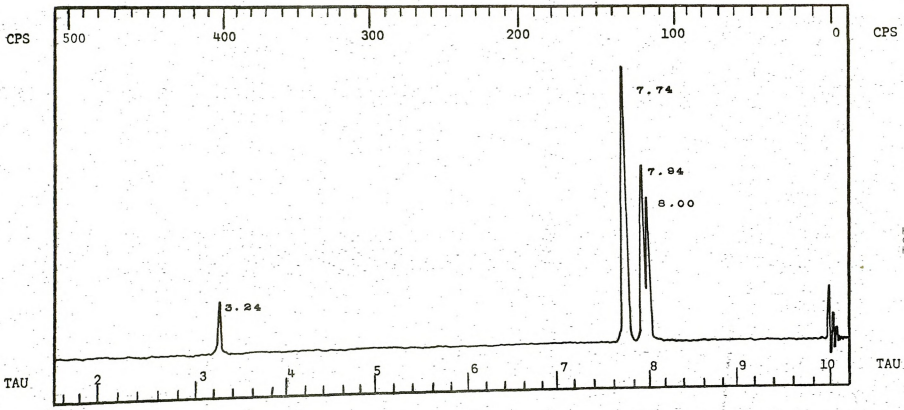

Figure 6b

Nuclear Magnetic Resonance Spectrum of 4-Bromo-1,2,3,5-tetramethylbenzene

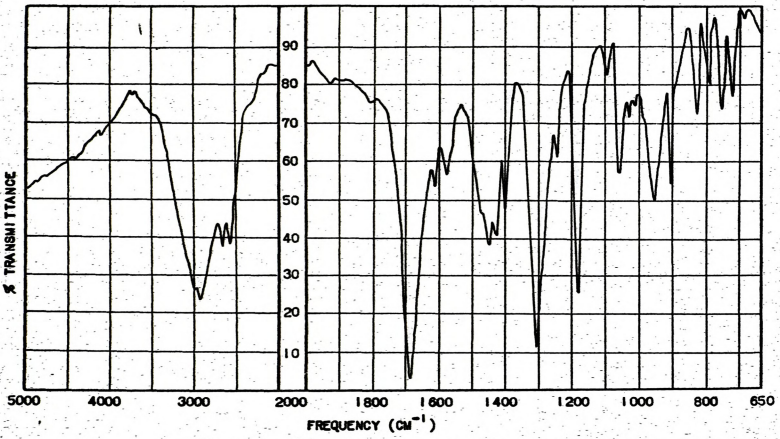

Figure 7

Infrared Spectrum of 2,3,4,6-Tetramethylbenzoic Acid

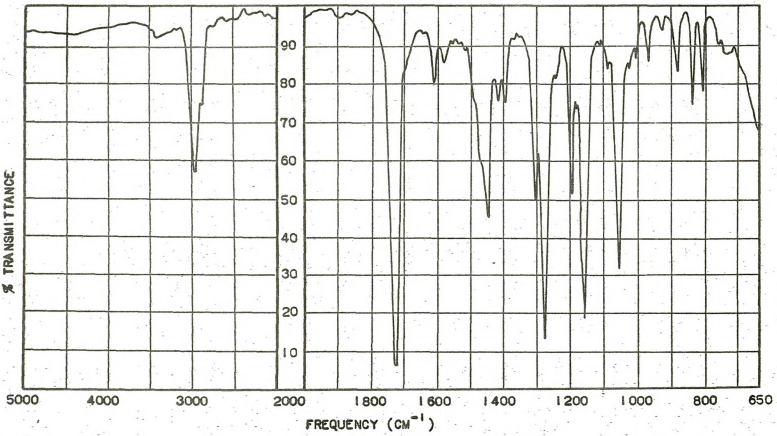

Figure 8a

Infrared Spectrum of Methyl 2,3,4,6-Tetramethylbenzoate

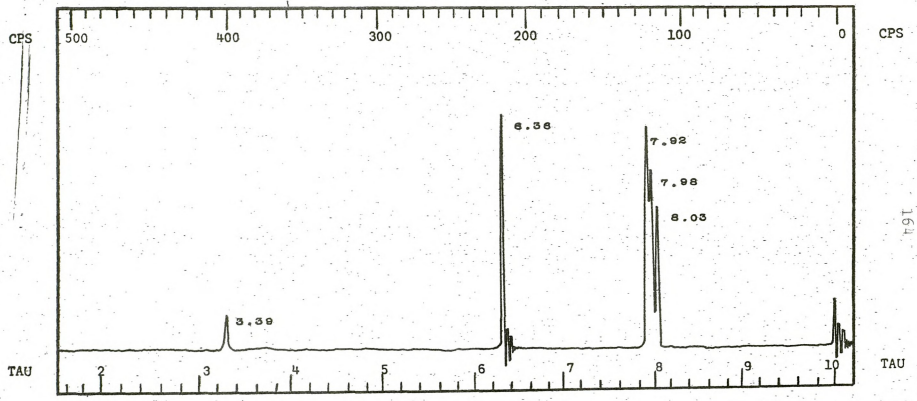

Figure 8b

Nuclear Magnetic Resonance Spectrum of Methyl 2,3,4,6-Tetramethylbenzoate

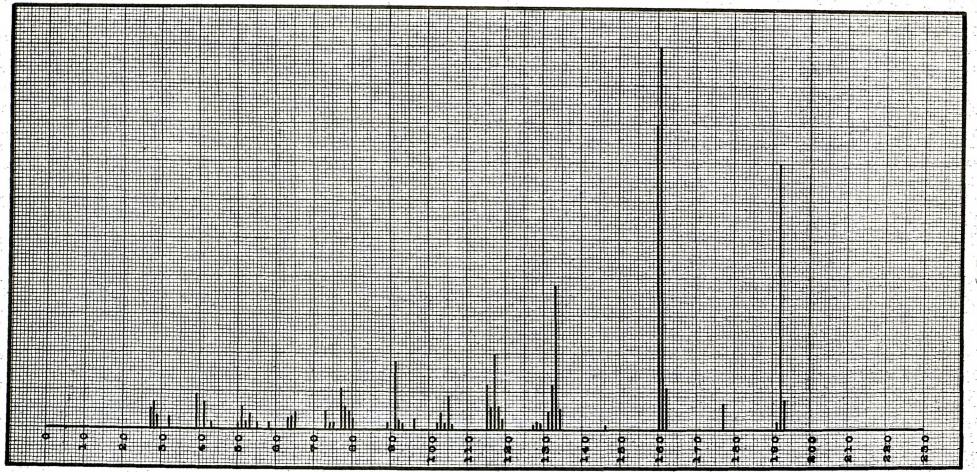

Figure 8c

Mass Spectrum of Methyl 2,3,4,6-Tetramethylbenzoate

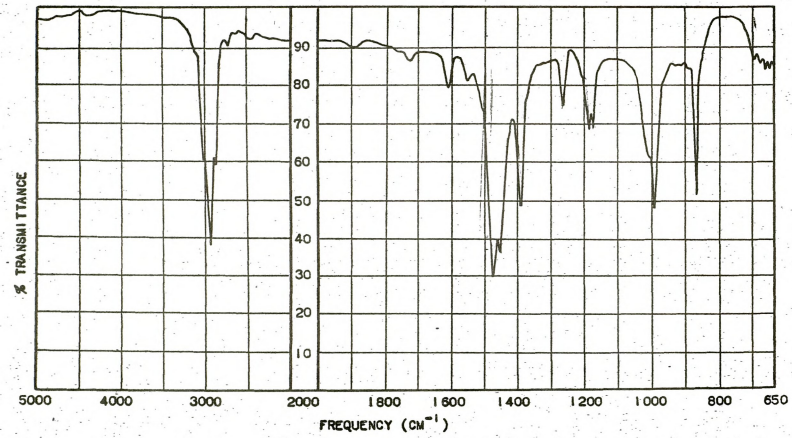

Figure 9a

Infrared Spectrum of 3-Bromo-1,2,4,5-tetramethylbenzene

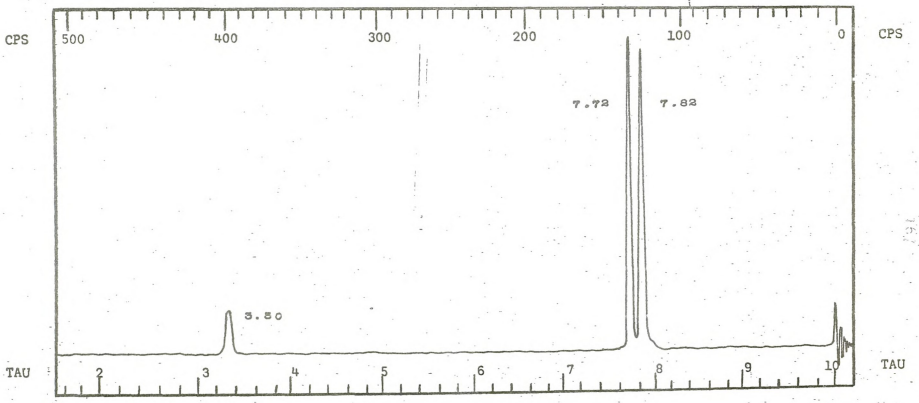

Figure 9b

Nuclear Magnetic Resonance Spectrum of 3-Bromo-1,2,4,5-tetramethylbenzene

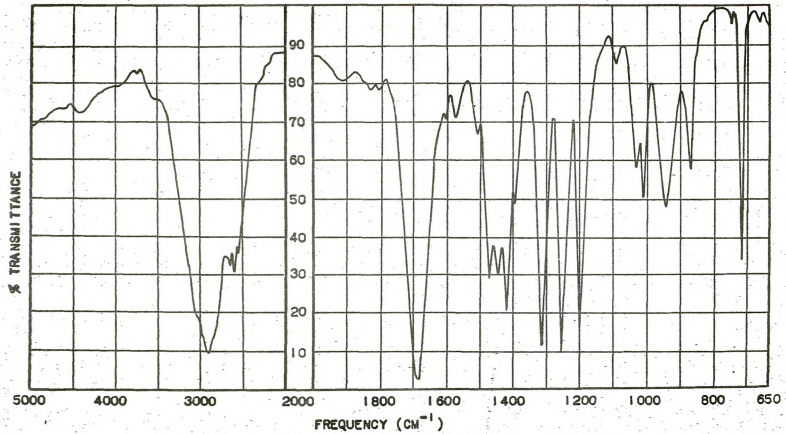

Figure 10

Infrared Spectrum of 2,3,5,6-Tetramethylbenzoic Acid

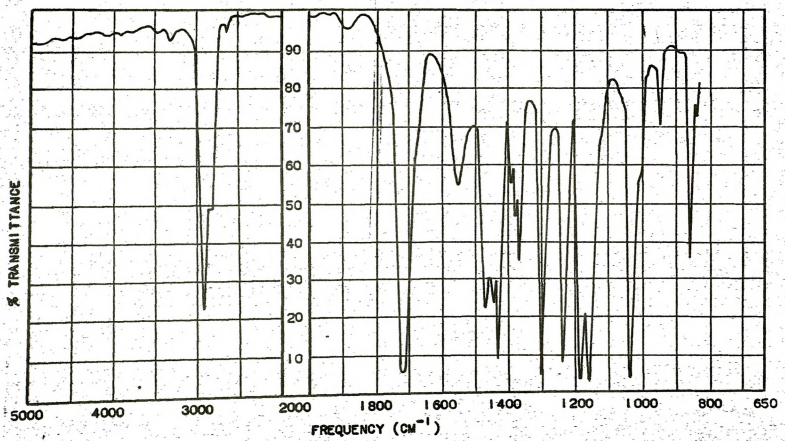

Figure 11a

Infrared Spectrum of Methyl 2,3,5,6-Tetramethylbenzoate

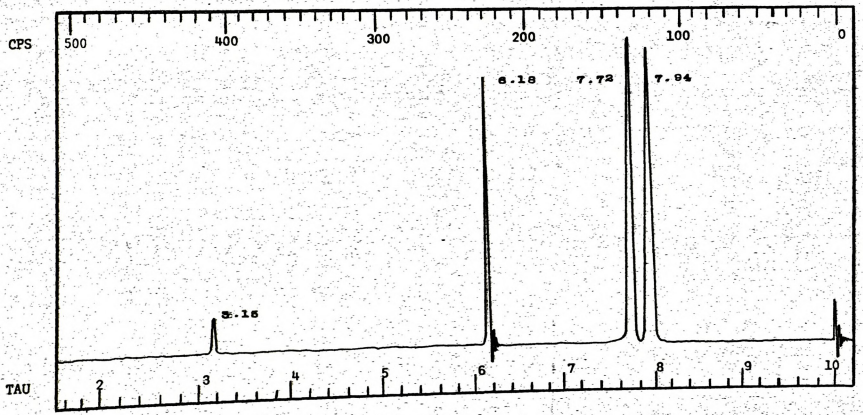

Figure 11b

Nuclear Magnetic Resonance Spectrum of Methyl 2,3,5,6-Tetramethylbenzoate

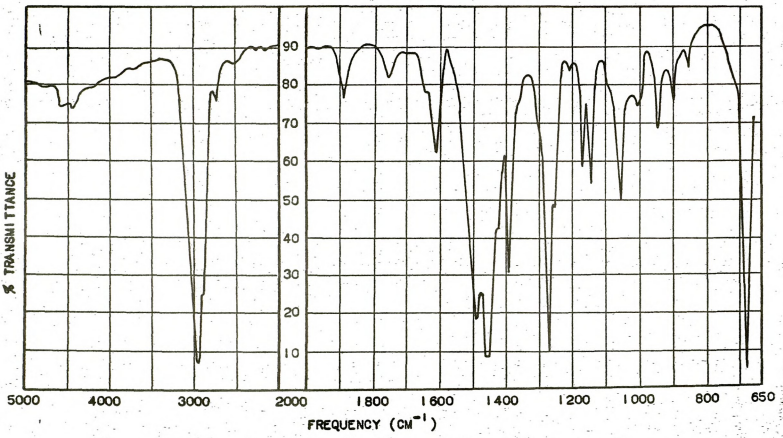

Figure 12a

Infrared Spectrum of 2,3,4-Trimethylbenzyl Chloride

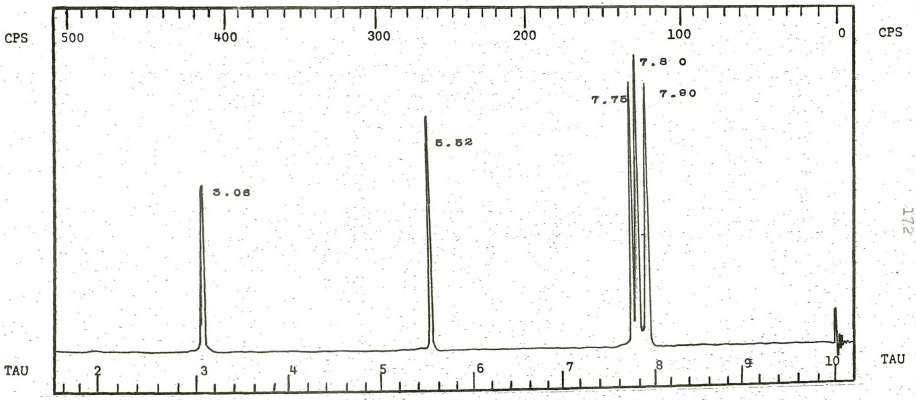

Figure 12b

Nuclear Magnetic Resonance Spectrum of 2,3,4-Trimethylbenzyl Chloride

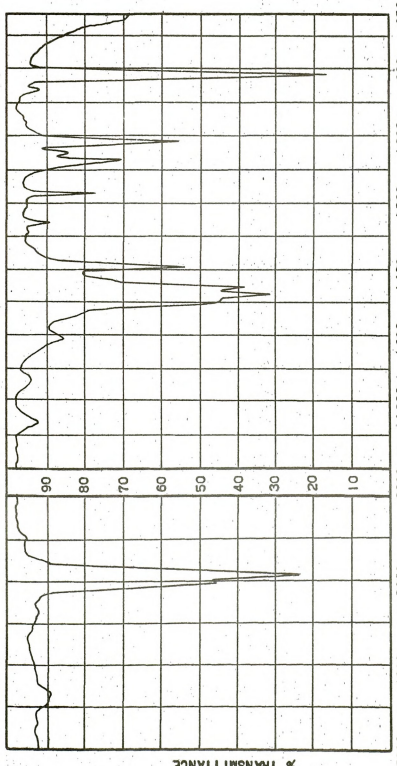

Figure 13a

Infrared Spectrum of Prehnitene

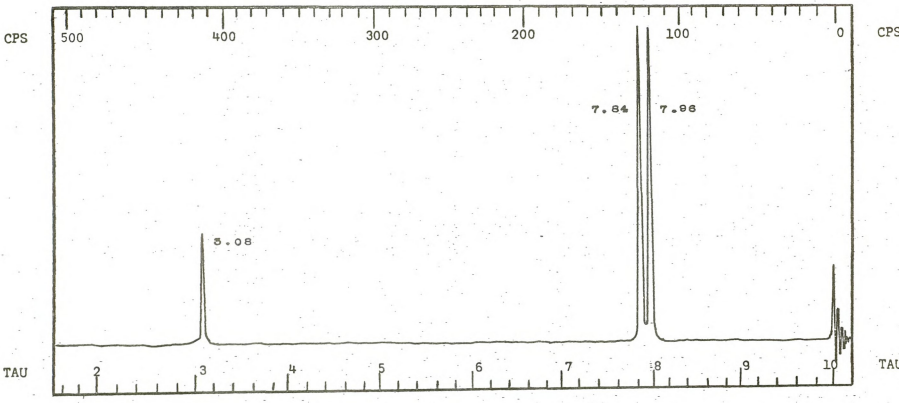

Figure 13b

Nuclear Magnetic Resonance Spectrum of Prehnitene

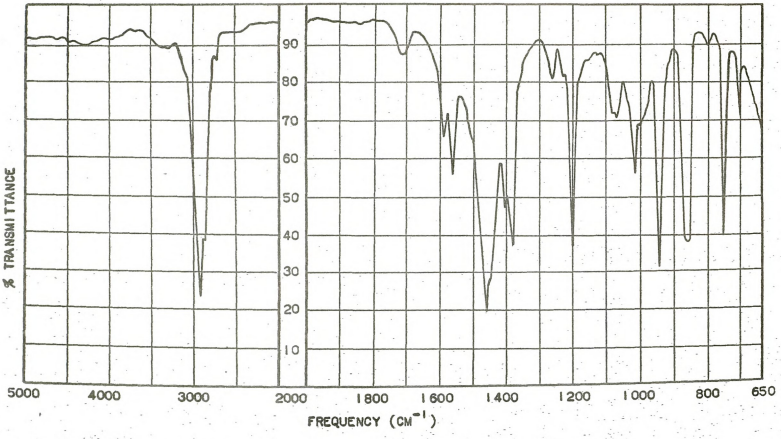

Figure 14a

Infrared Spectrum of 5-Bromo-1,2,3,4-tetramethylbenzene

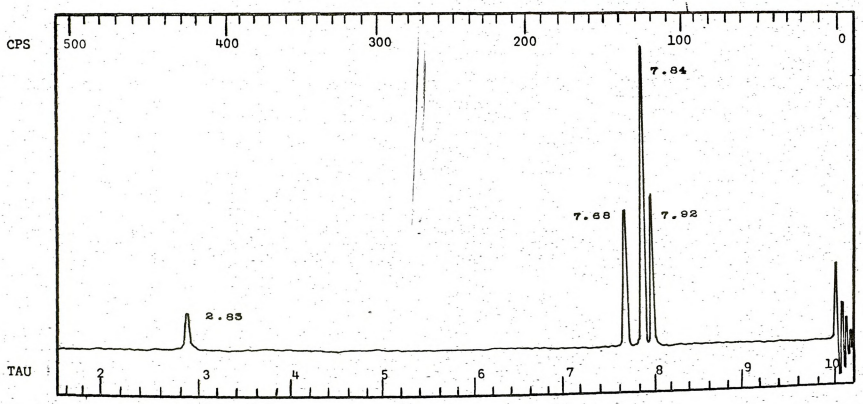

Figure 14b

Nuclear Magnetic Resonance Spectrum of 5-Bromo-1,2,3,5-tetramethylbenzene

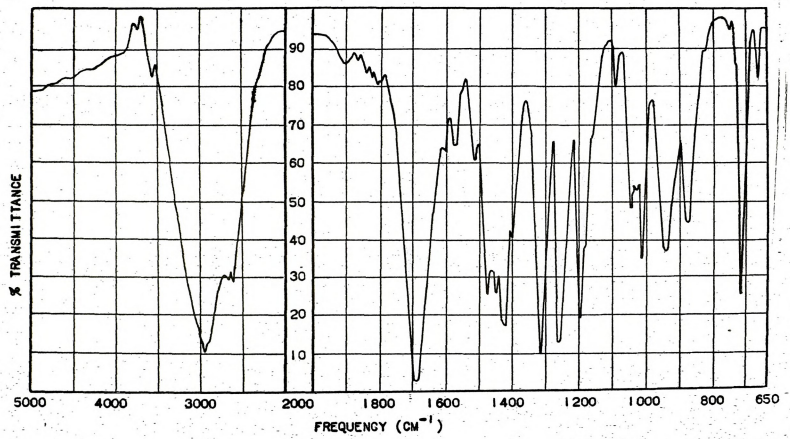

Figure 15

Infrared Spectrum of 2,3,4,5-Tetramethylbenzoic Acid

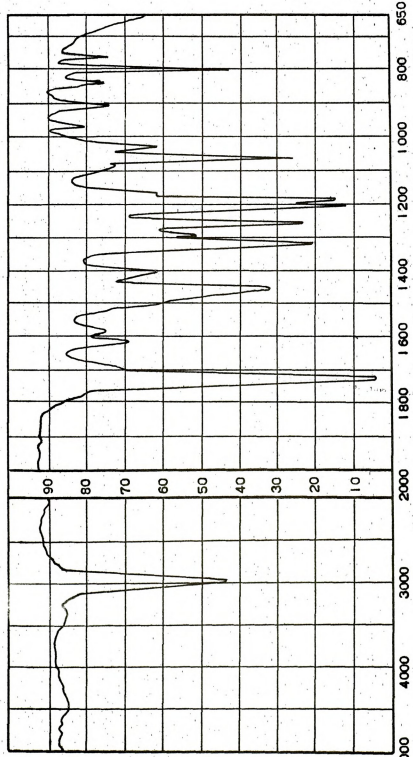

Figure 16a

Infrared Spectrum of Methyl 2,3,4,5-Tetramethylbenzoate

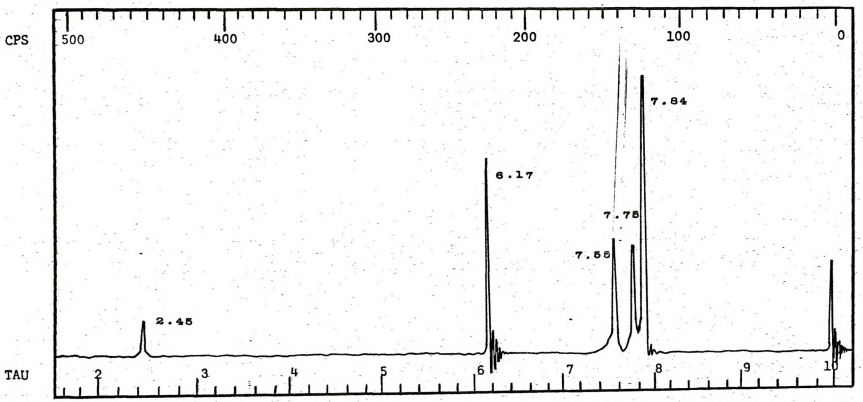

Figure 16b

Nuclear Magnetic Resonance Spectrum of Methyl 2,3,4,5-Tetramethylbenzoate

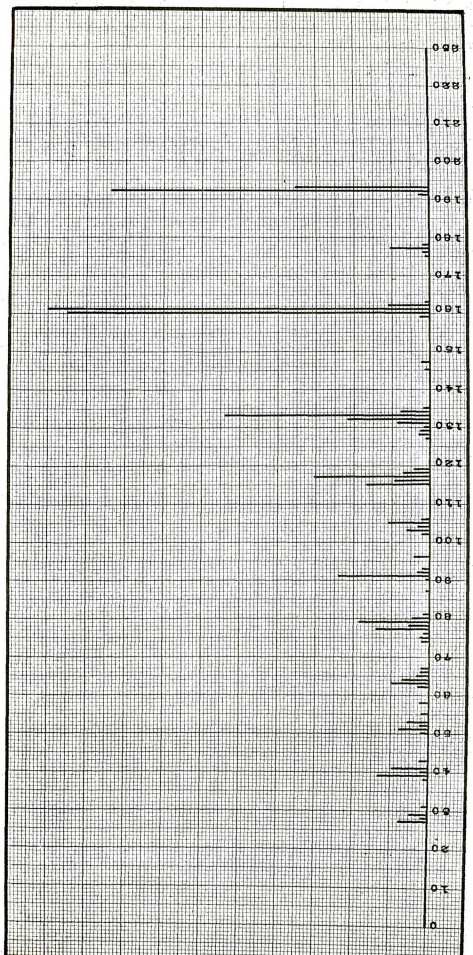

Figure 16c

Mass Spectrum of Methyl 2,3,4,5-Tetramethylbenzoate

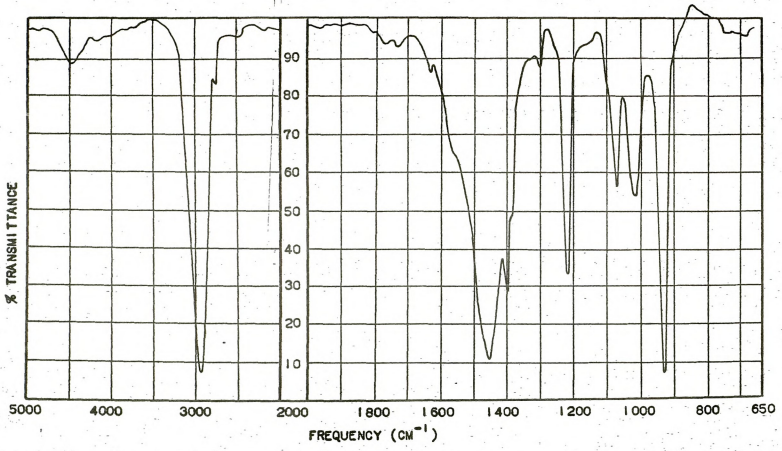

Figure 17a

Infrared Spectrum of 6-Bromo-1,2,3,4,5-pentamethylbenzene

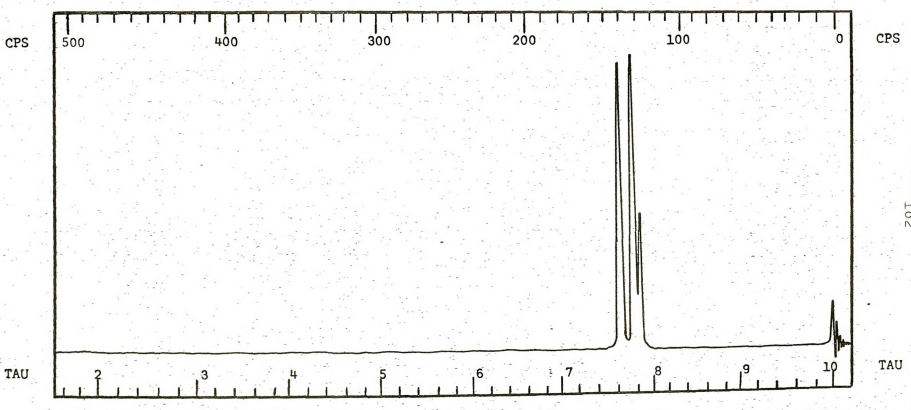

Figure 17b

Nuclear Magnetic Resonance Spectrum of 6-Bromo-1,2,3,4,5-pentamethylbenzene

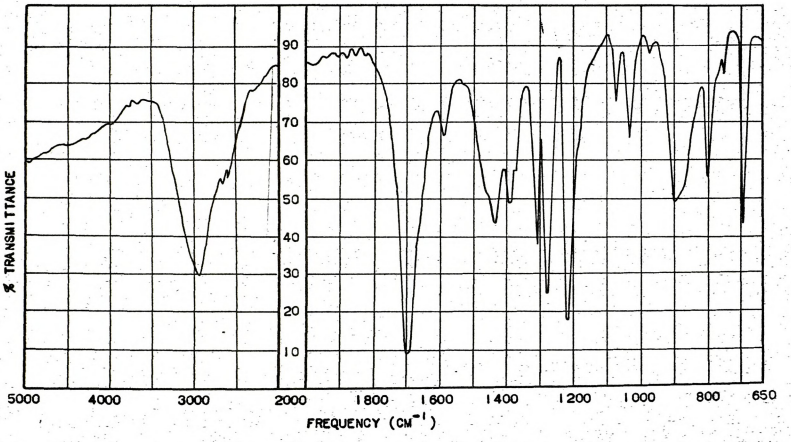

Figure 18

Infrared Spectrum of Pentamethylbenzoic Acid

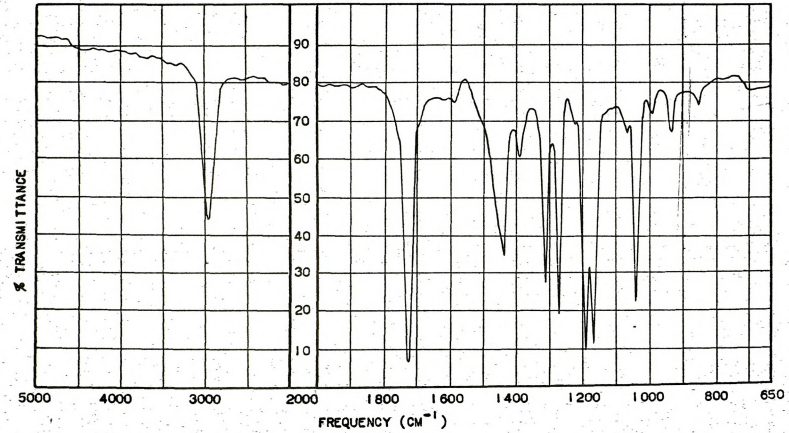

Figure 19a

Infrared Spectrum of Methyl Pentamethylbenzoate

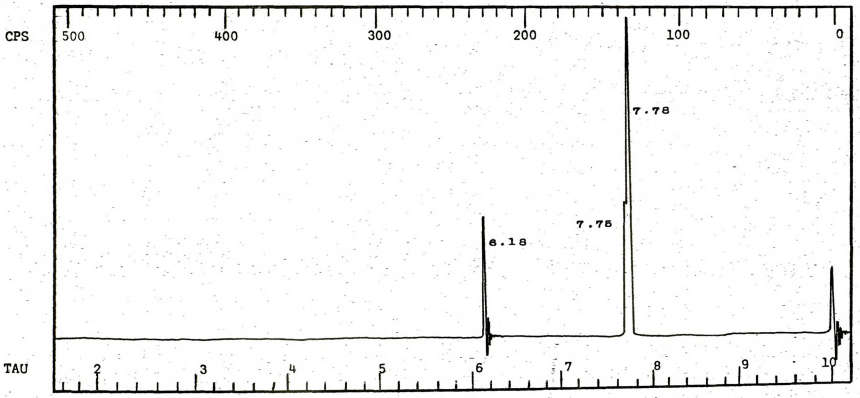

Figure 19b

Nuclear Magnetic Resonance Spectrum of Methyl Pentamethylbenzoate

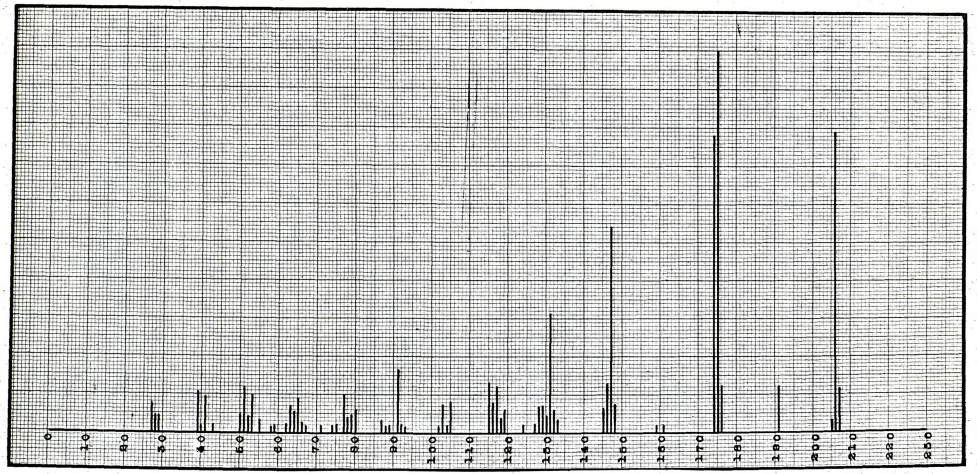

Figure 19c

Mass Spectrum of Methyl Pentamethylbenzoate

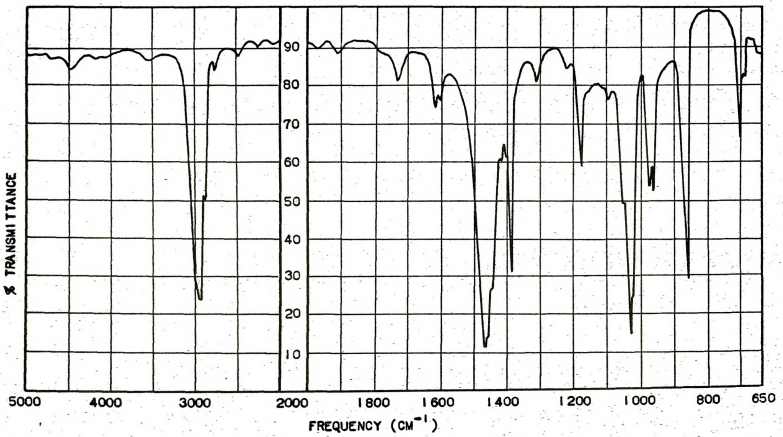

Figure 20a

Infrared Spectrum of 2-Nitro-1,3,5-trimethylbenzene

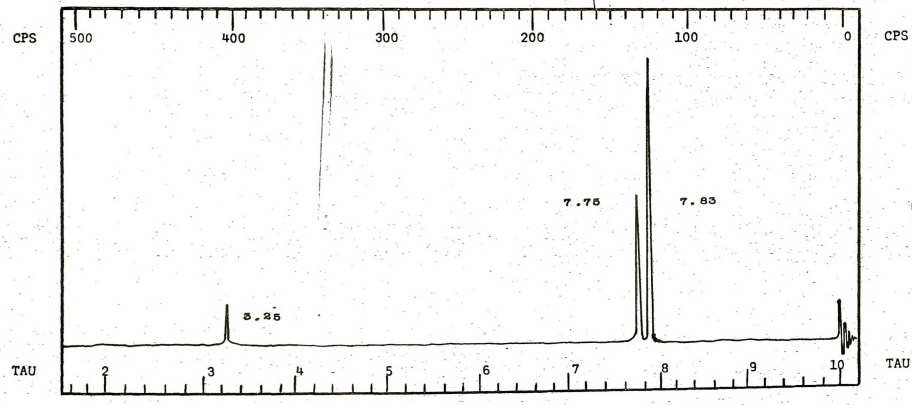

Figure 20b

Nuclear Magnetic Resonance Spectrum of 2-Nitro-1,3,5-trimethylbenzene

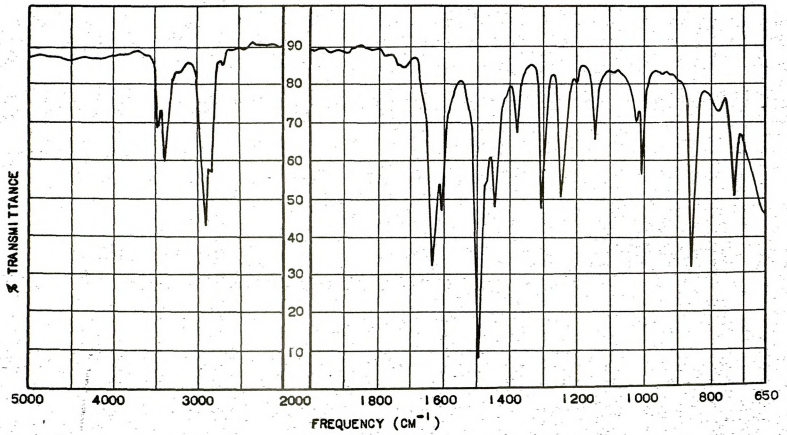

Figure 21a

Infrared Spectrum of 2,4,6-Trimethylaniline

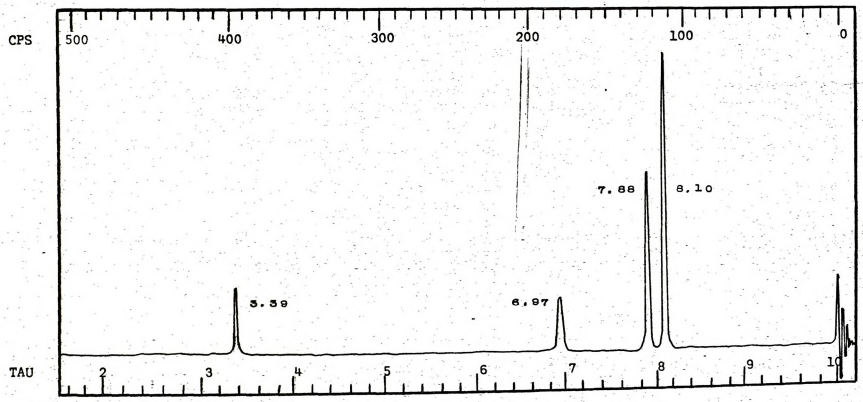

Figure 21b

Nuclear Magnetic Resonance Spectrum of 2,4,6-Trimethylaniline

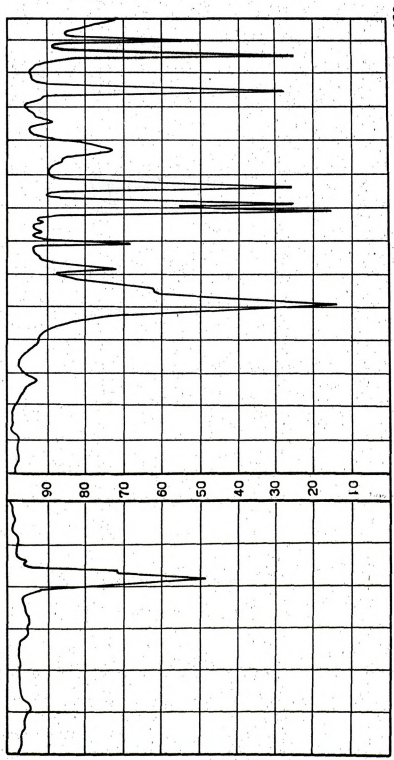

Figure 22a

Infrared Spectrum of 2-Fluoro-1,3,5-trimethylbenzene

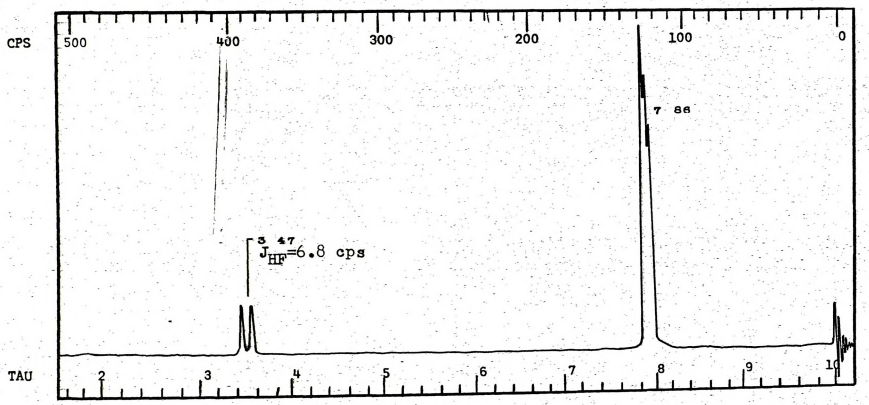

Figure 22b

Nuclear Magnetic Resonance Spectrum of 2-Fluoro-1,3,5-trimethylbenzene

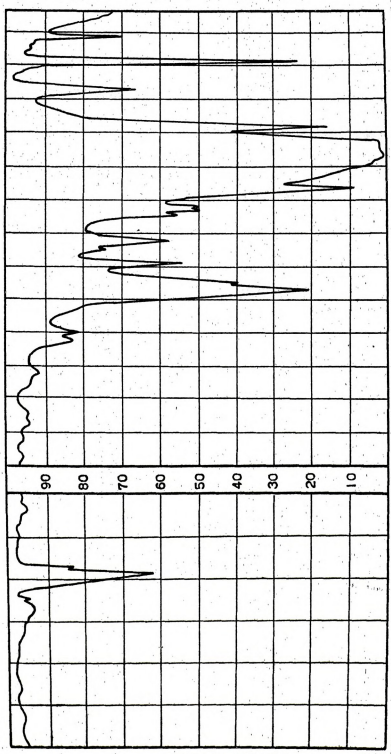

Figure 23a

Infrared Spectrum of 2-Bromo-4-fluoro-1,3,5-trimethylbenzene

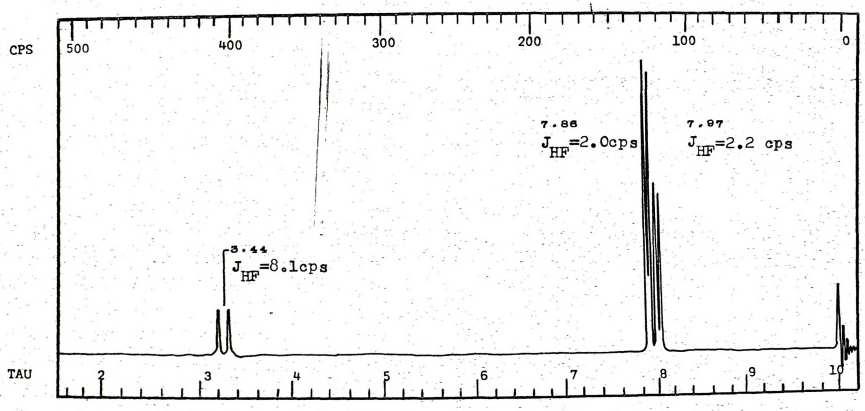

Figure 23b

Nuclear Magnetic Resonance Spectrum of 2-Bromo-4-fluoro-1,3,5-trimethylbenzene

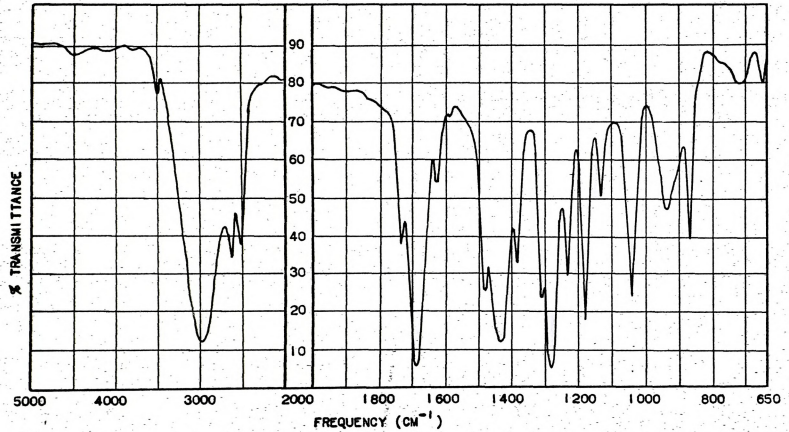

Figure 24

Infrared Spectrum of 3-Fluoro-2,4,6-trimethylbenzoic Acid

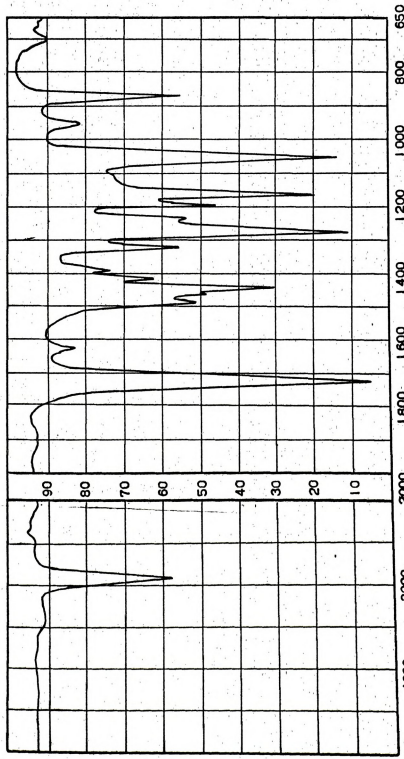

Figure 25a

Infrared Spectrum of Methyl 3-Fluoro-2,4,6-trimethylbenzoate

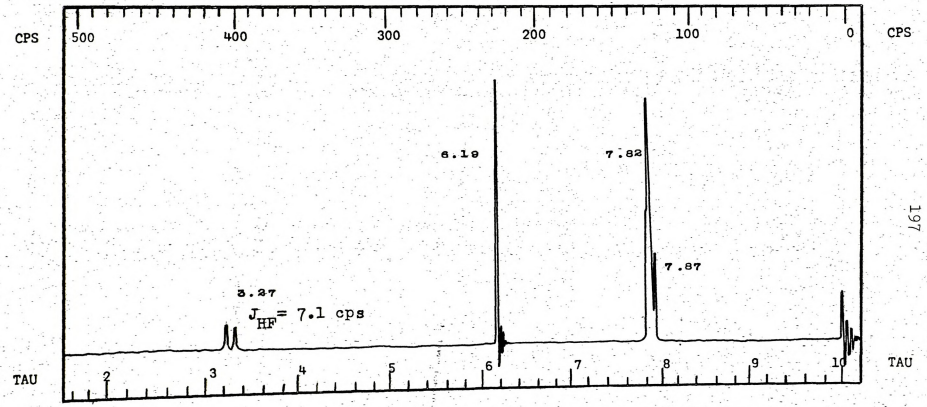

Figure 25b

Nuclear Magnetic Resonance Spectrum of Methyl 3-Fluoro-2,4,6-trimethylbenzoate

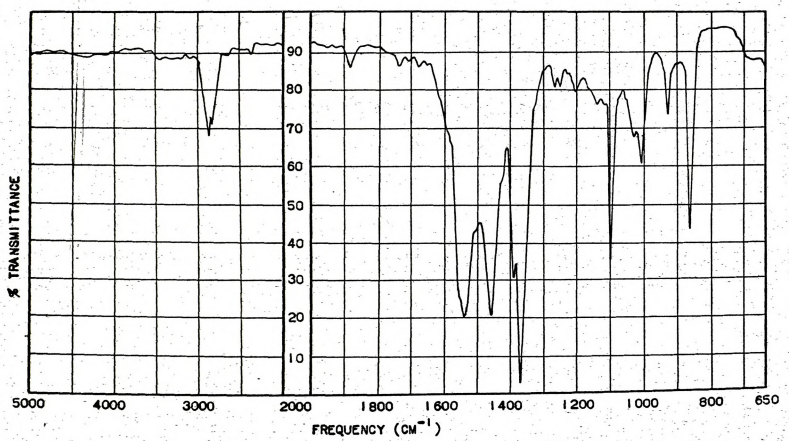

Figure 26a

Infrared Spectrum of 4-Bromo-2-nitro-1,3-dimethylbenzene

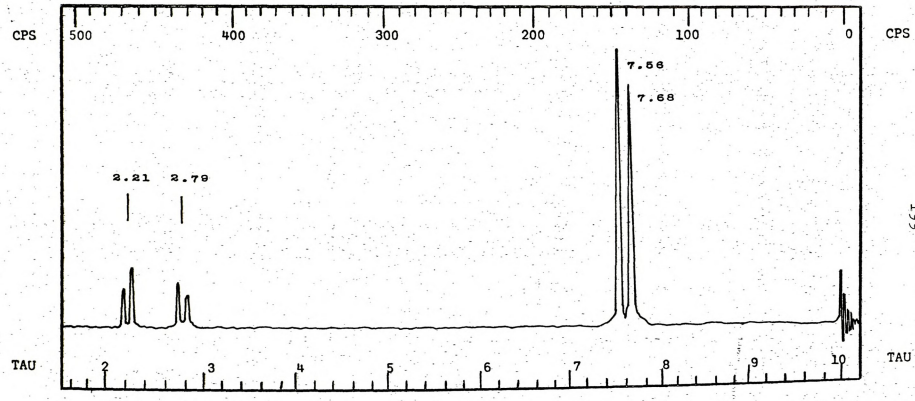

Figure 26b

Nuclear Magnetic Resonance Spectrum of 4-Bromo-2-nitro-1,3-dimethylbenzene

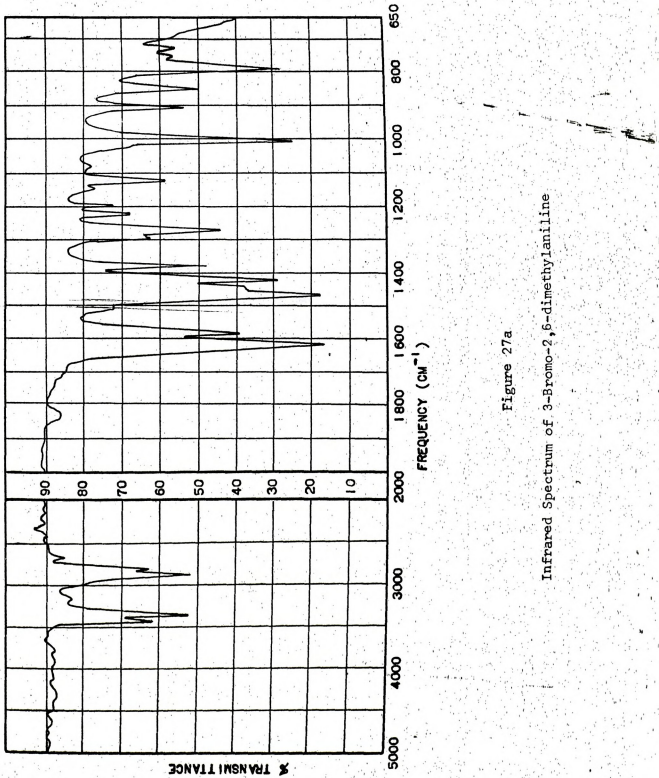

Figure 27a

Infrared Spectrum of 3-Bromo-2,6-dimethylaniline

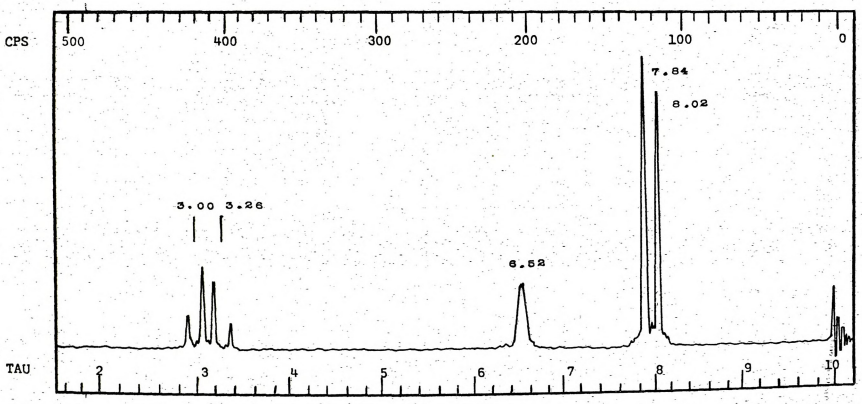

Figure 27b

Nuclear Magnetic Resonance Spectrum of 3-Bromo-2,6-dimethylaniline

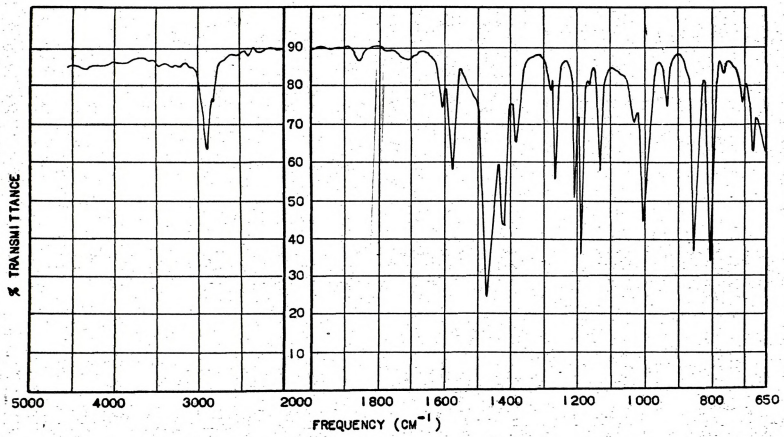

Figure 28a

Infrared Spectrum of 4-Bromo-2-fluoro-1,3-dimethylbenzene

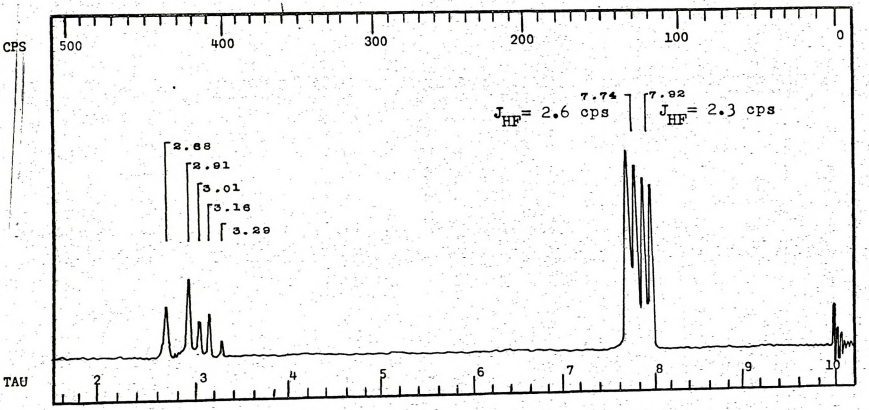

Figure 28b

Nuclear Magnetic Resonance Spectrum of 4-Bromo-2-fluoro-1,3-dimethylbenzene

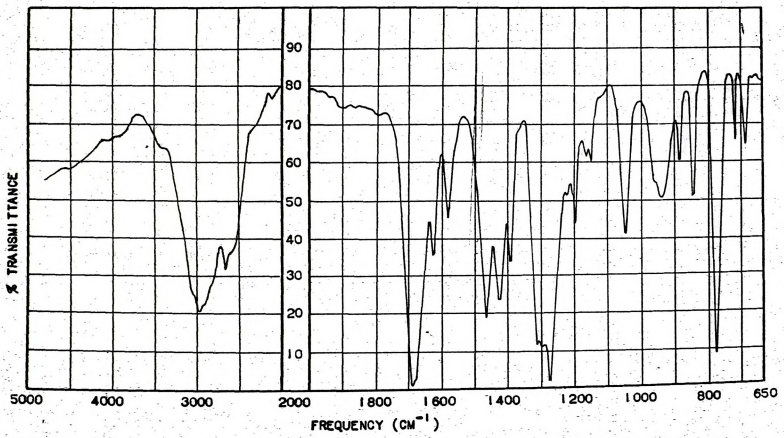

Figure 29

Infrared Spectrum of 3-Fluoro-2,4-dimethylbenzoic Acid

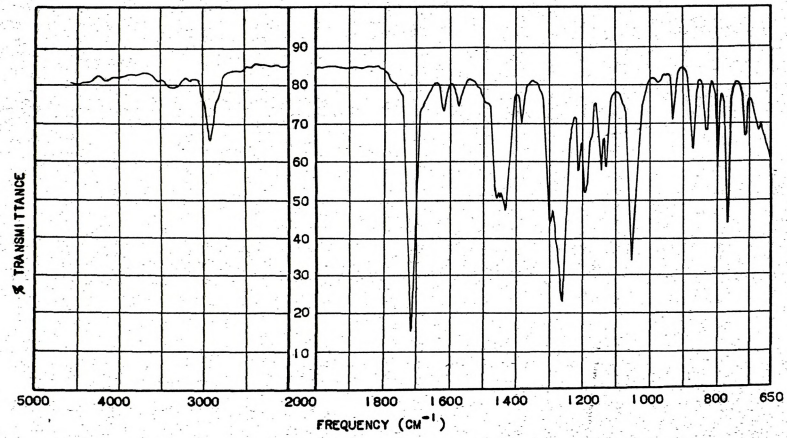

Figure 30a

Infrared Spectrum of Methyl 3-Fluoro-2,4-dimethylbenzoate

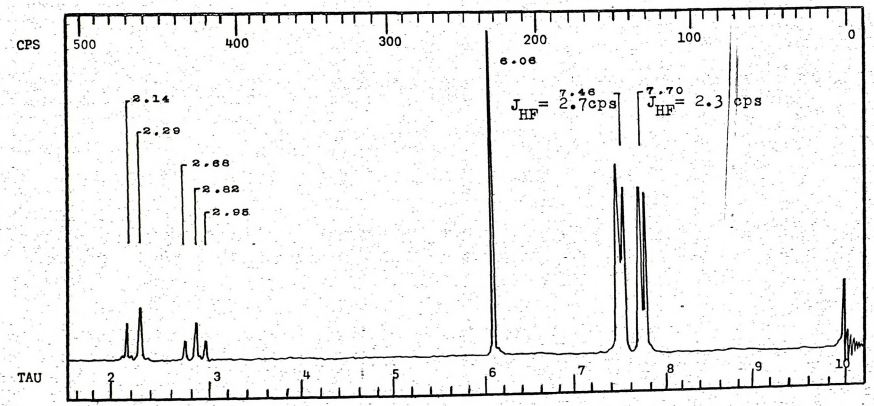

Figure 30b

Nuclear Magnetic Resonance Spectrum of Methyl 3-Fluoro-2,4-dimethylbenzoate

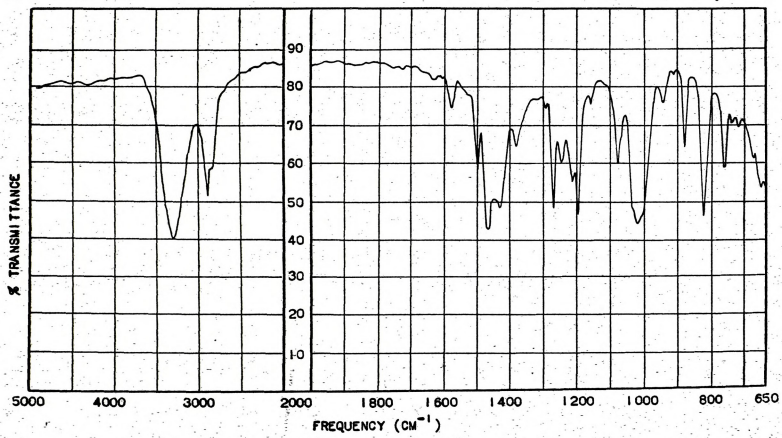

Figure 31a

Infrared Spectrum of 3-Fluoro-2,4-dimethylbenzyl Alcohol

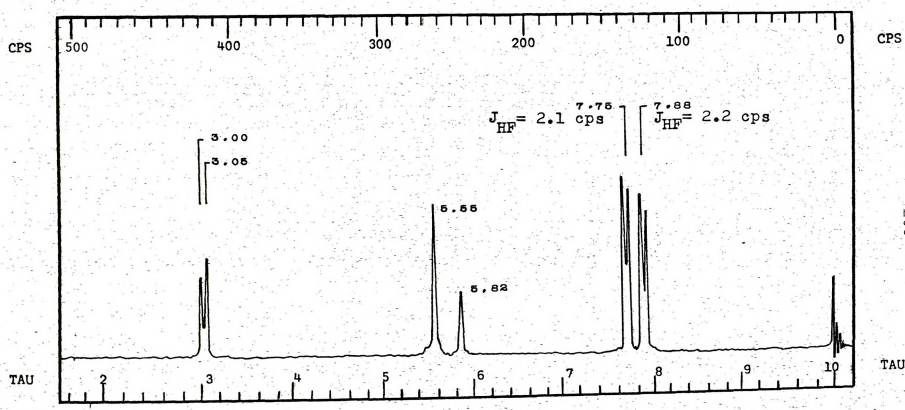

Figure 31b

Nuclear Magnetic Resonance Spectrum of 3-Fluoro-2,4-dimethylbenzyl Alcohol

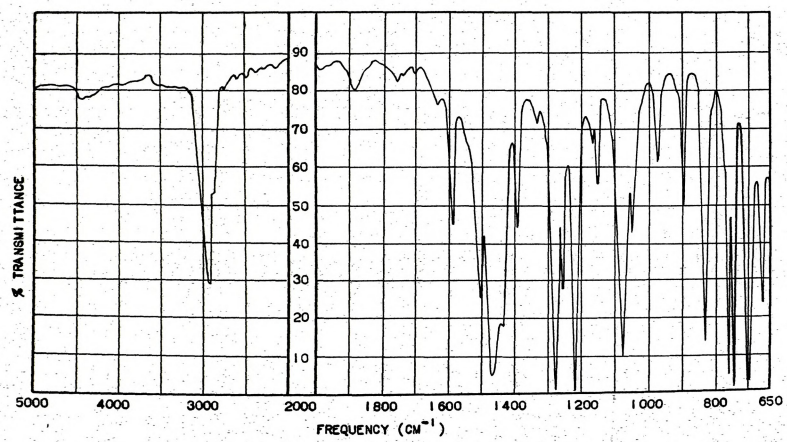

Figure 32a

Infrared Spectrum of 3-Fluoro-2,4-dimethylbenzyl Chloride

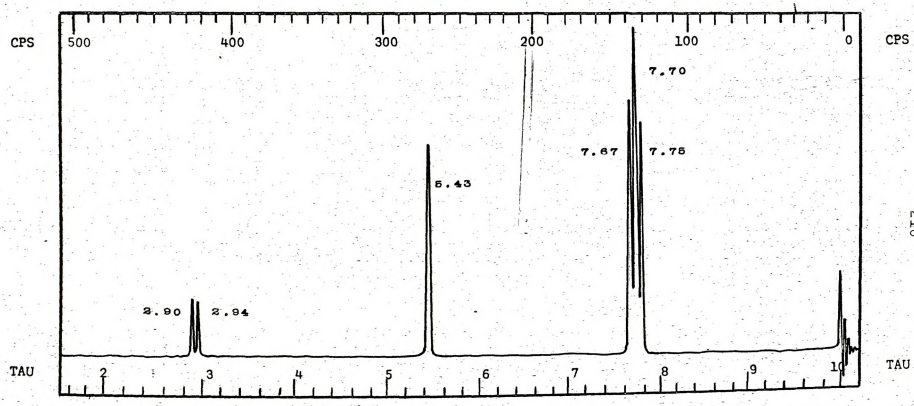

Figure 32b

Nuclear Magnetic Resonance Spectrum of 3-Fluoro-2,4-dimethylbenzyl Chloride

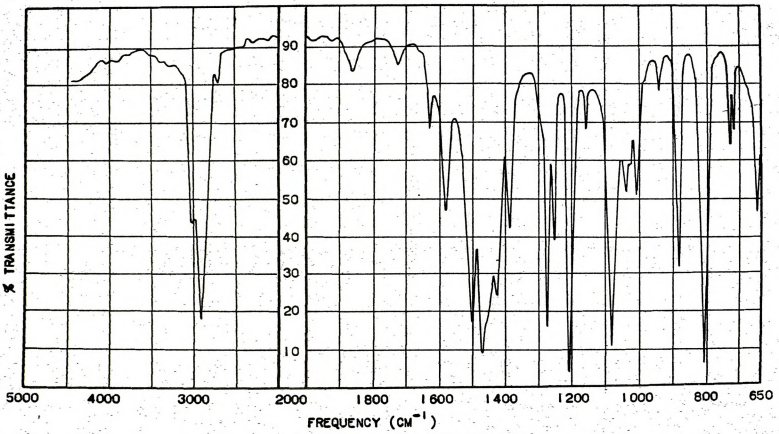

Figure 33a

Infrared Spectrum of 3-Fluoro-1,2,4-trimethylbenzene

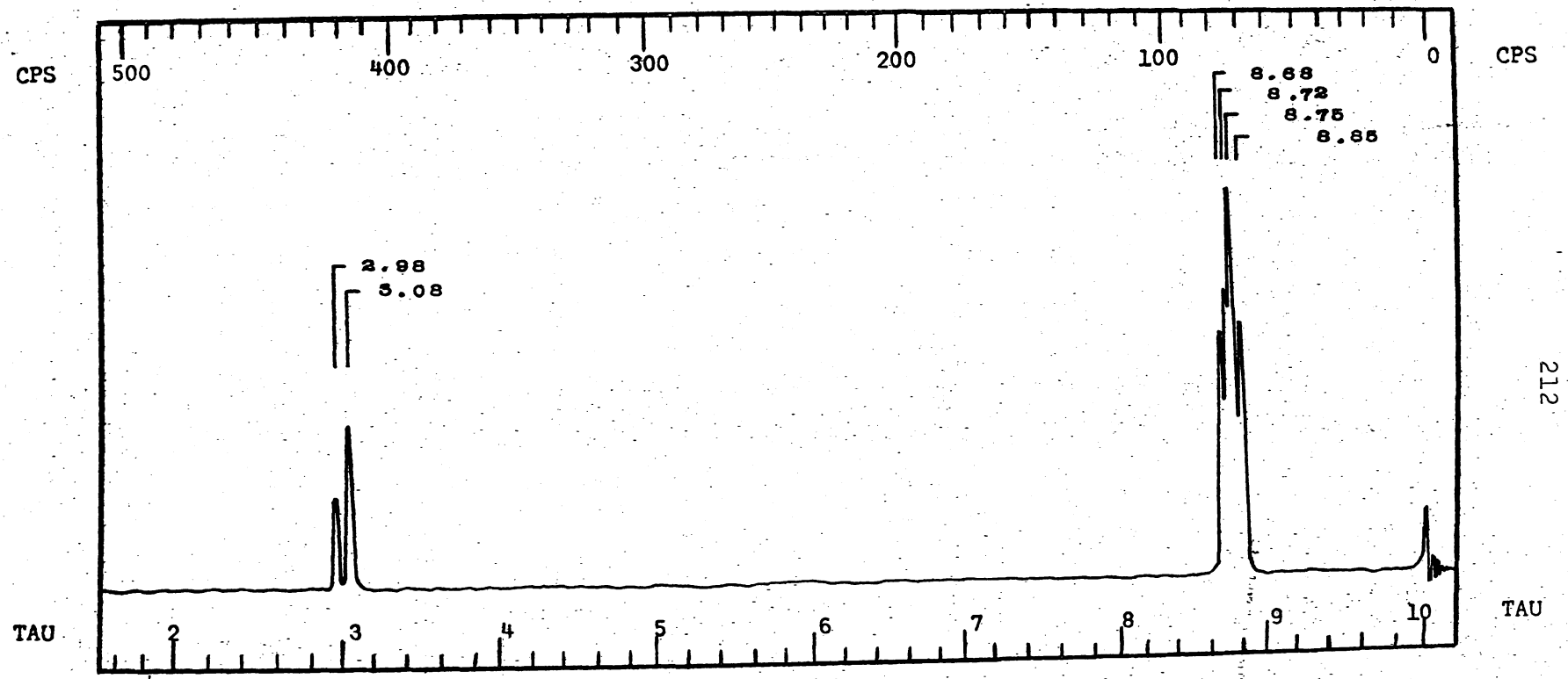

Figure 33b

Nuclear Magnetic Resonance Spectrum of 3-Fluoro-1,2,4-trimethylbenzene

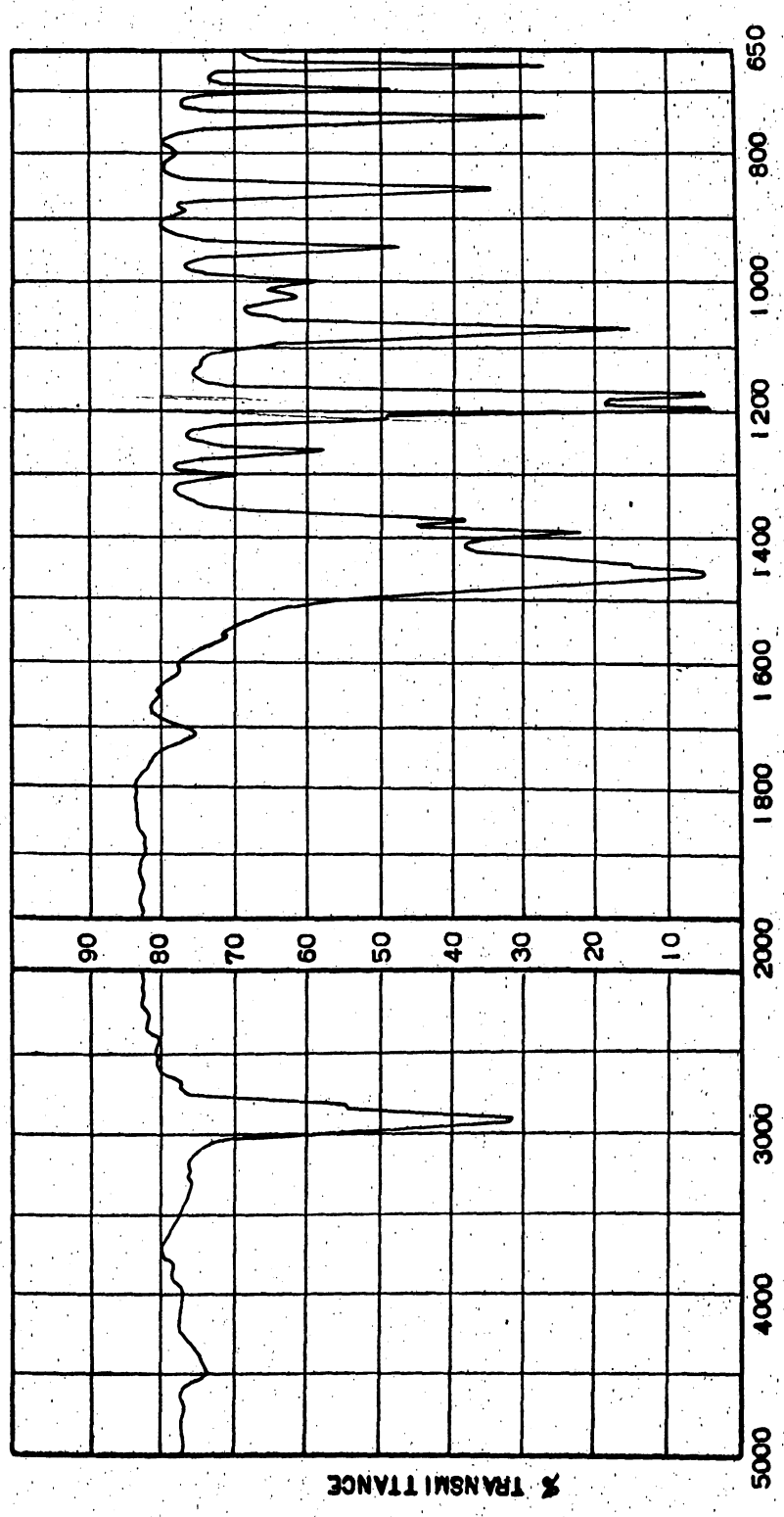

Figure 34a

Infrared Spectrum of 6-Bromo-3-fluoro-1,2,4-trimethylbenzene

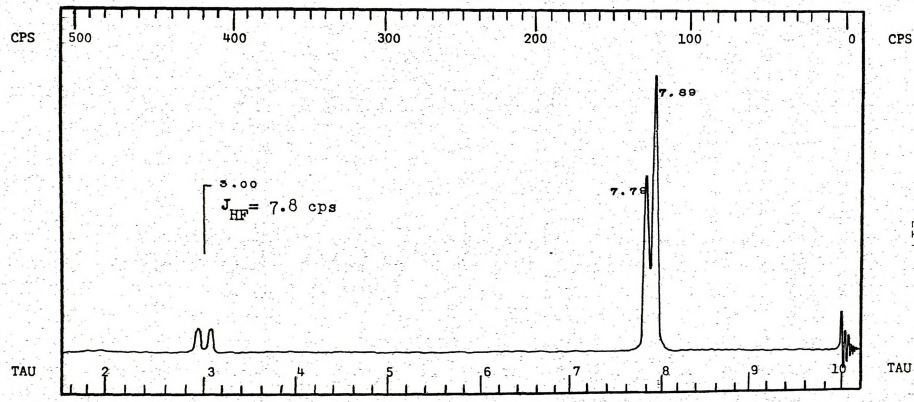

Figure 34b

Nuclear Magnetic Resonance Spectrum of 6-Bromo-3-fluoro-1,2,4-trimethylbenzene

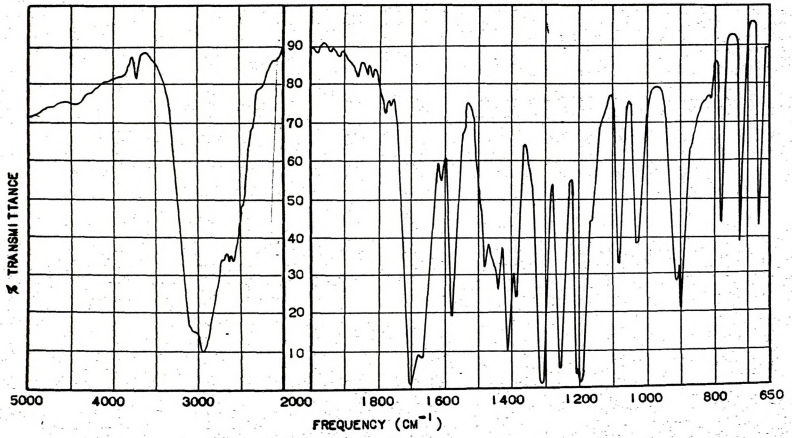

Figure 35

Infrared Spectrum of 4-Fluoro-2,3,5-trimethylbenzoic Acid

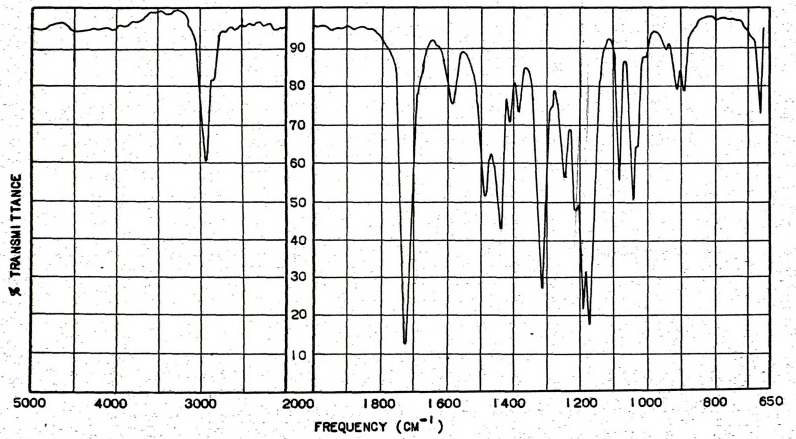

Figure 36a

Infrared Spectrum of Methyl 4-Fluoro-2,3,5-trimethylbenzoate

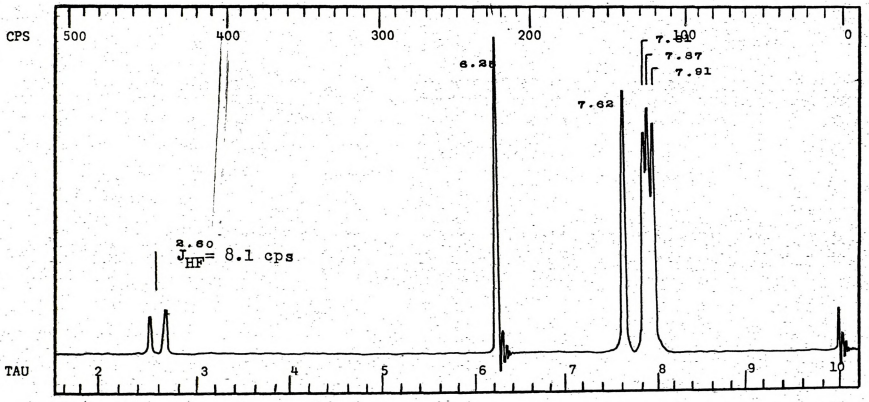

Figure 36b

Nuclear Magnetic Resonance Spectrum of Methyl 4-Fluoro-2,3,5-trimethylbenzoate

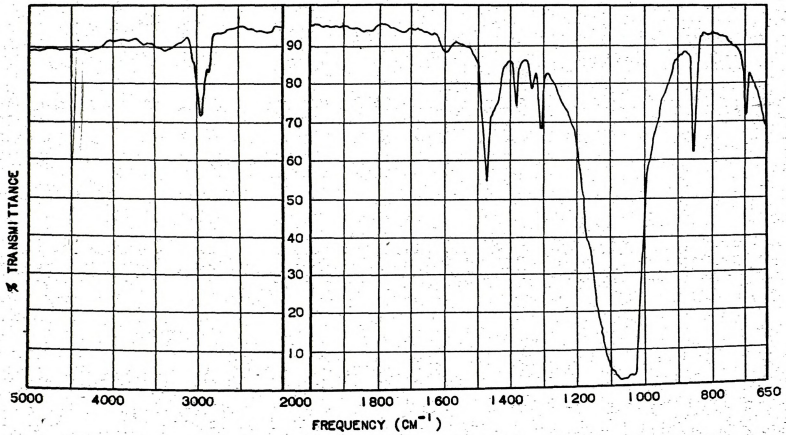

Figure 37a

Infrared Spectrum of 2-Chloro-1,3,5-trimethylbenzene

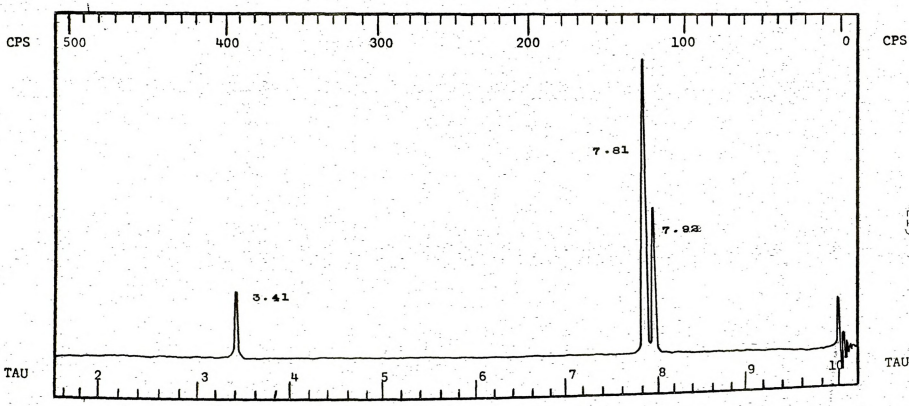

Figure 37b

Nuclear Magnetic Resonance Spectrum of 2-Chloro-1,3,5-trimethylbenzene

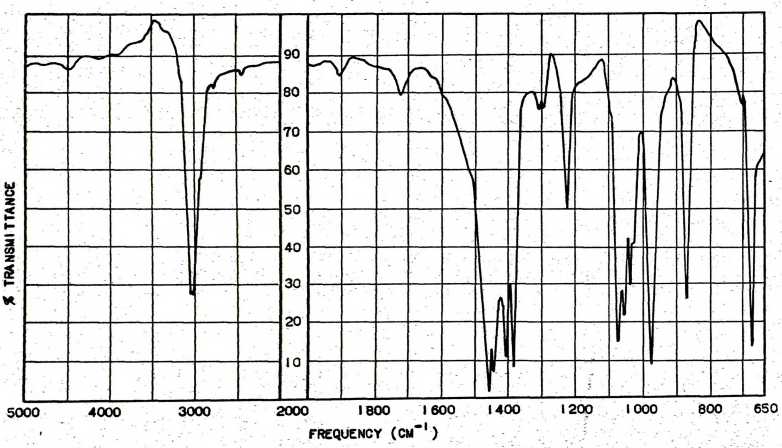

Figure 38a

Infrared Spectrum of 2-Bromo-4-chloro-1,3,5-trimethylbenzene

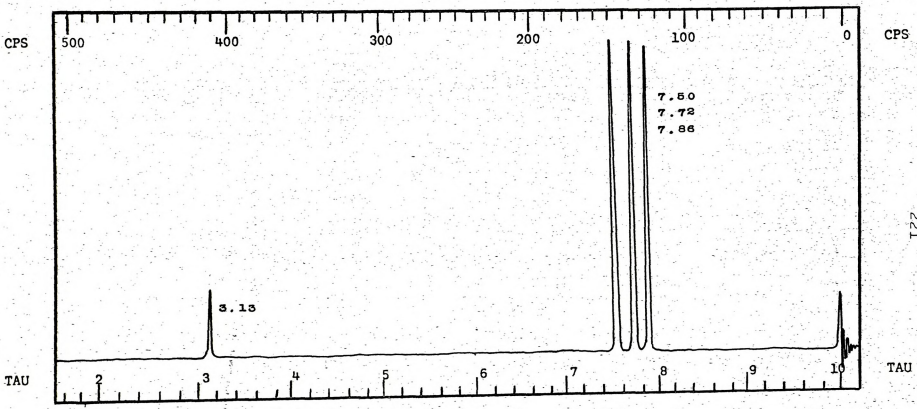

Figure 38b

Nuclear Magnetic Resonance Spectrum of 2-Bromo-4-chloro-1,3,5-trimethylbenzene

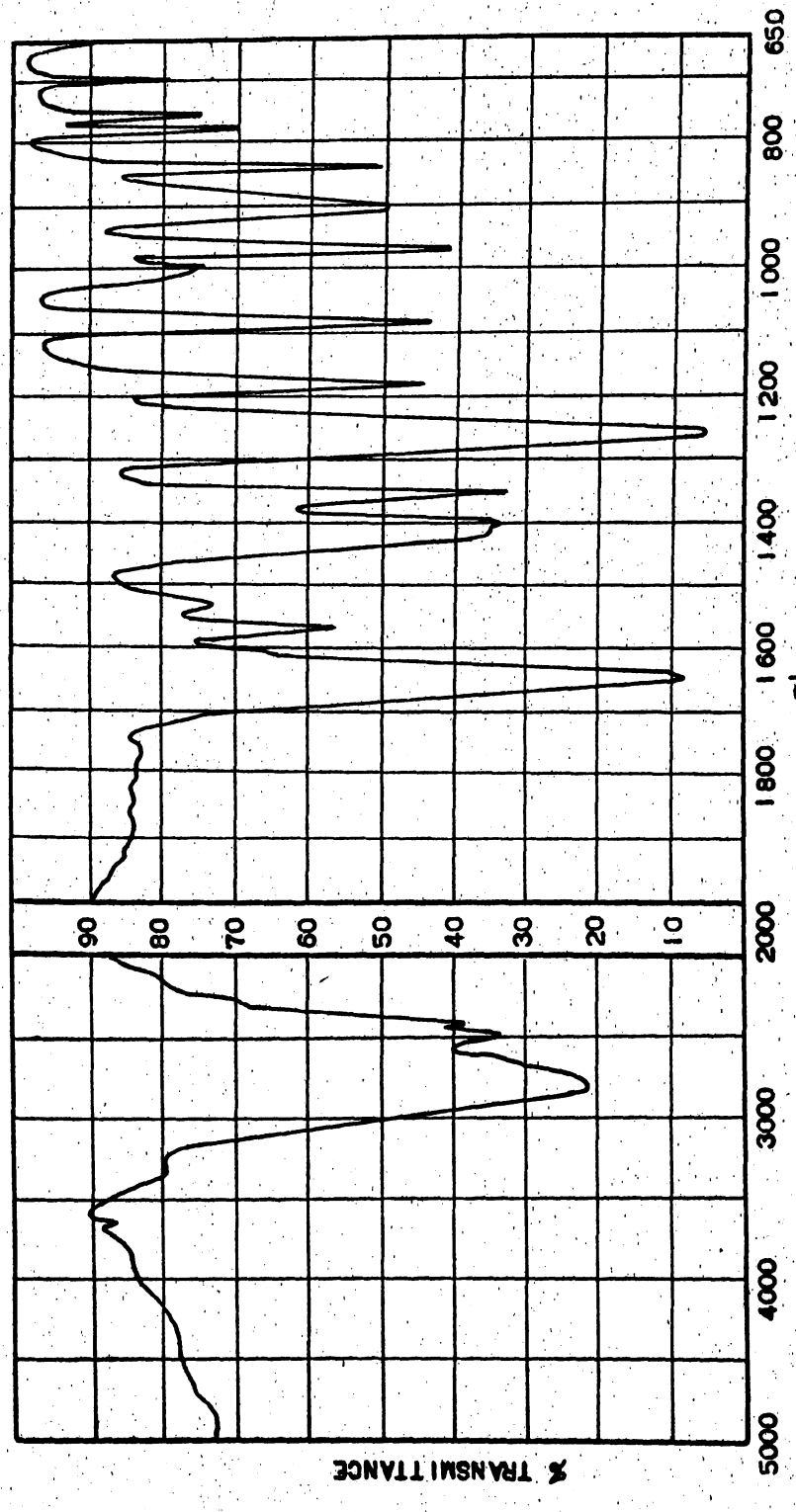

Figure 39

Infrared Spectrum of 3-Chloro-2,4,6-trimethylbenzoic Acid

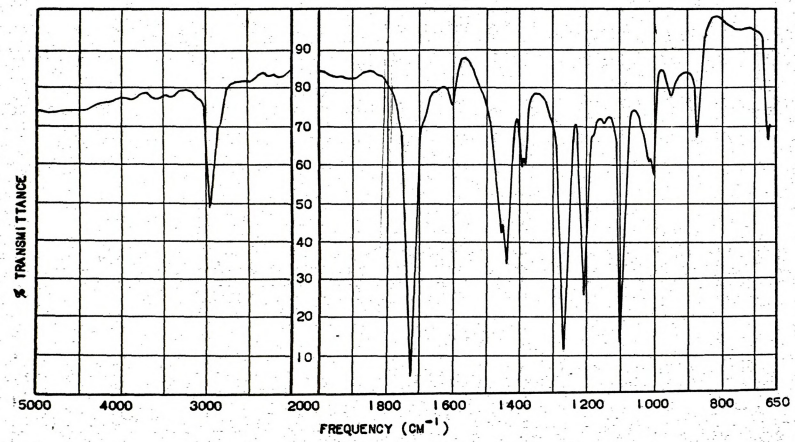

Figure 40a

Infrared Spectrum of Methyl 3-Chloro-2,4,6-trimethylbenzoate

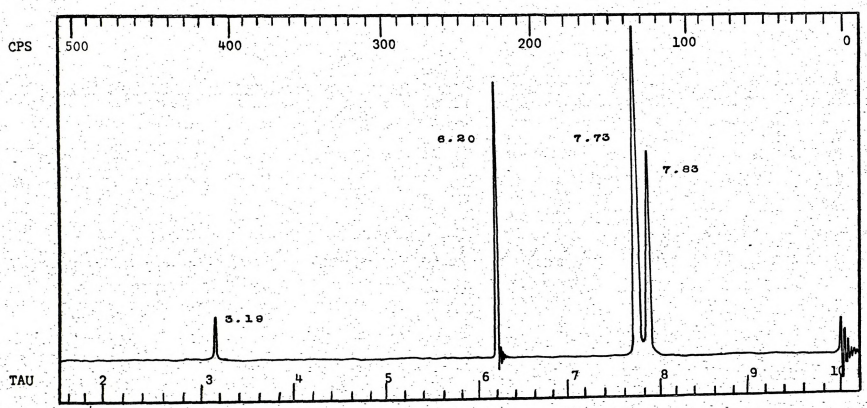

Figure 40b

Nuclear Magnetic Resonance Spectrum of Methyl 3-Chloro-2,4,6-trimethylbenzoate

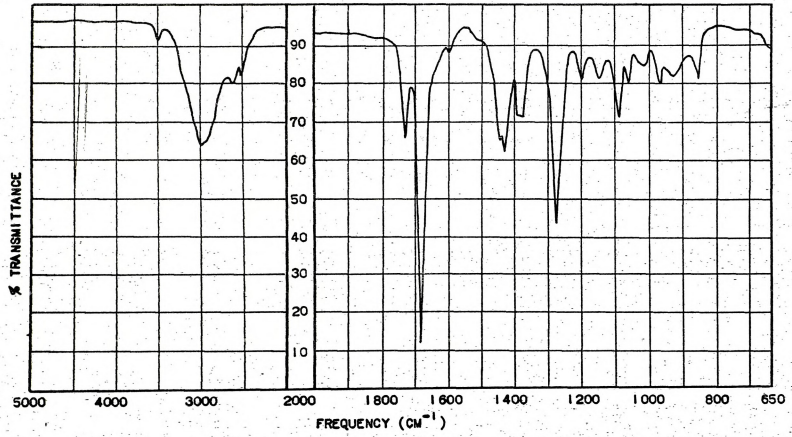

Figure 41

Infrared Spectrum of 3-Bromo-2,4,6-trimethylbenzoic Acid

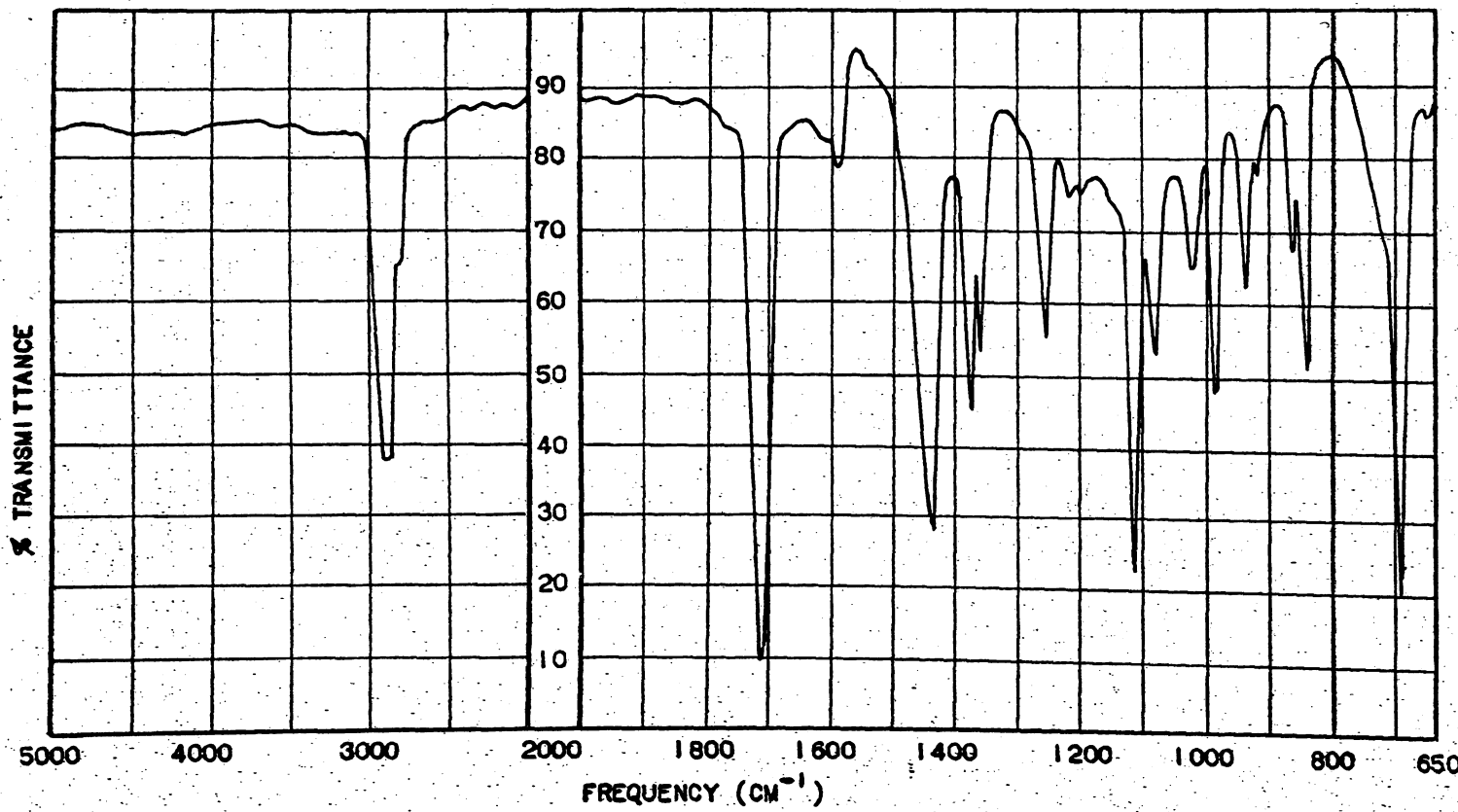

Figure 42a

Infrared Spectrum of Methyl 3-Bromo-2,4,6-trimethylbenzoate

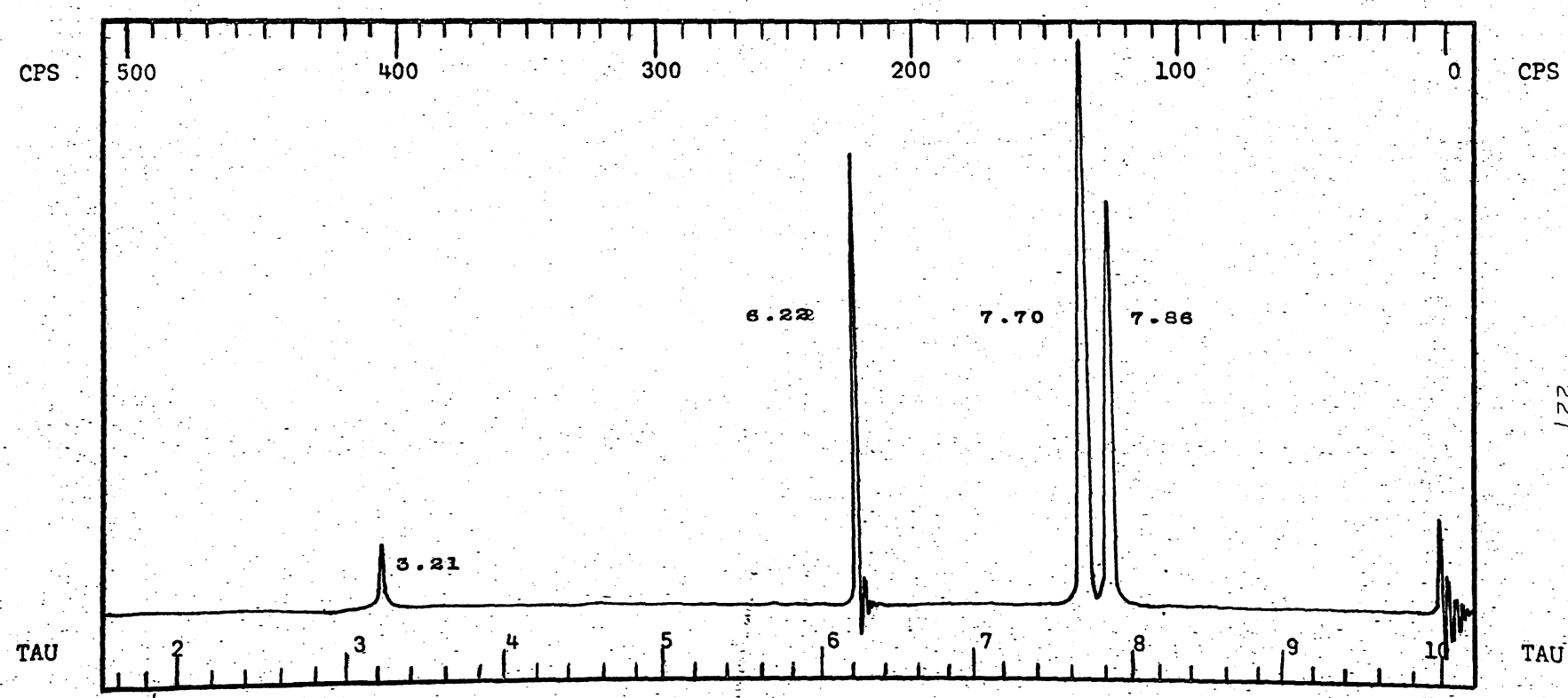

Figure 42b

Nuclear Magnetic Resonance Spectrum of Methyl 3-Bromo-2,4,6-trimethylbenzoate

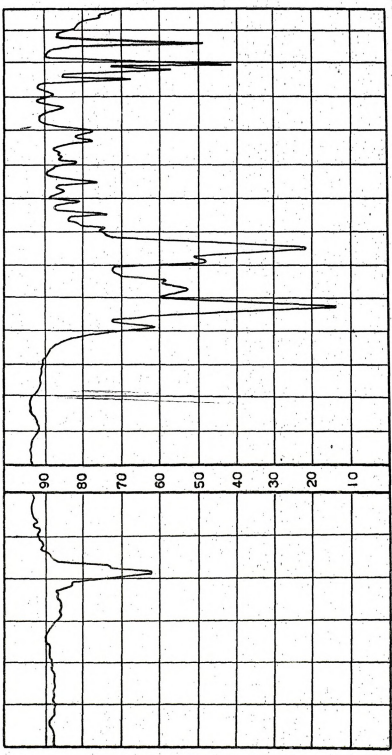

Figure 43a

Infrared Spectrum of 4-Nitro-1,3,5-trimethylbenzene

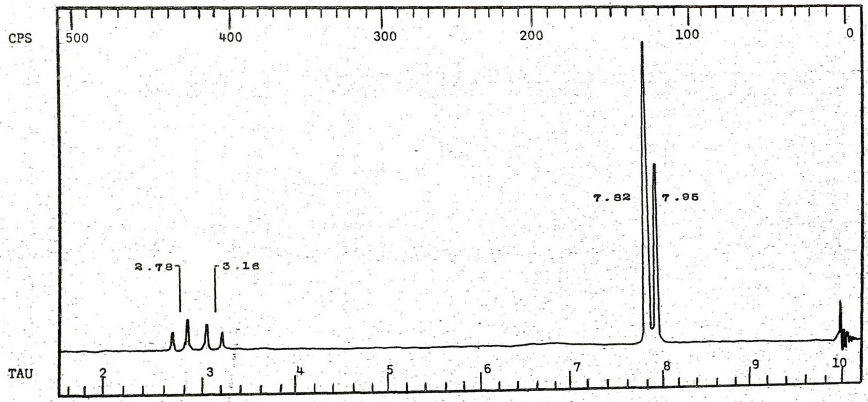

Figure 43b

Nuclear Magnetic Resonance Spectrum of 4-Nitro-1,2,3-trimethylbenzene

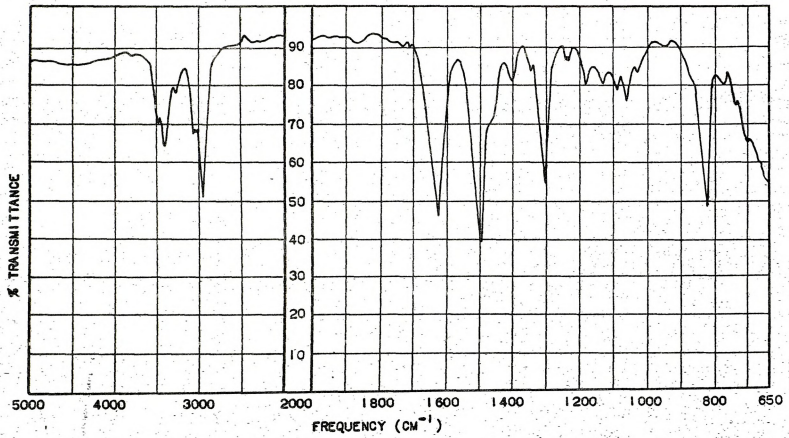

Figure 44a

Infrared Spectrum of 2,3,4-Trimethylaniline

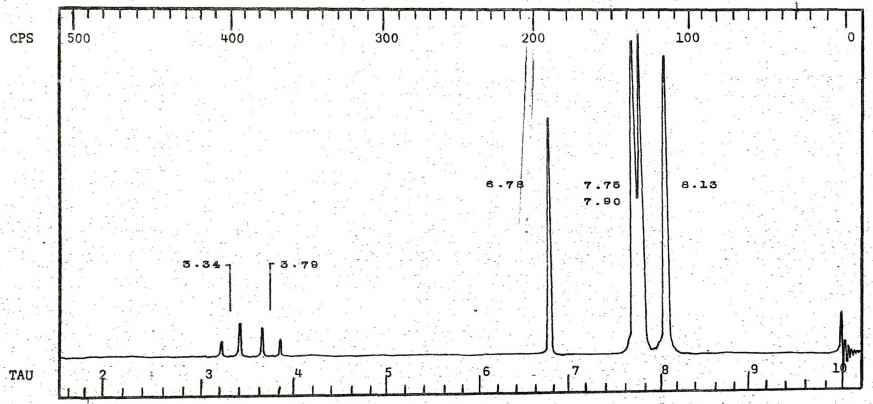

Figure 44b

Nuclear Magnetic Resonance Spectrum of 2,3,4-Trimethylaniline

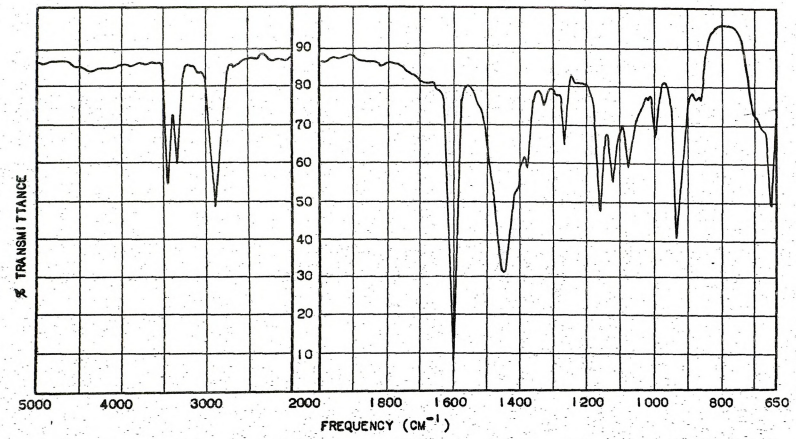

Figure 45

Infrared Spectrum of 6-Bromo-2,3,4-trimethylaniline

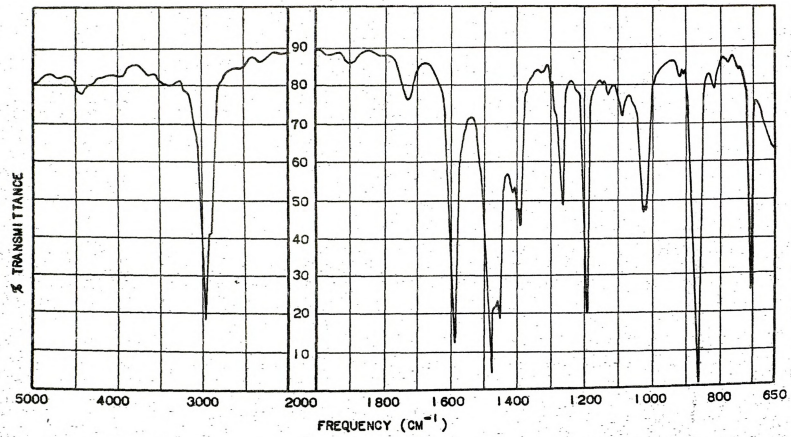

Figure 46a

Infrared Spectrum of 5-Bromo-1,2,3-trimethylbenzene

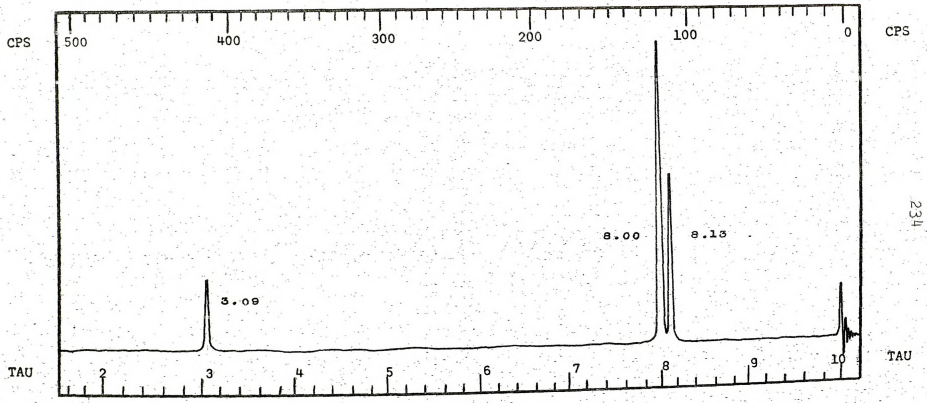

Figure 46b

Nuclear Magnetic Resonance Spectrum of 5-Bromo-1,2,3-trimethylbenzene

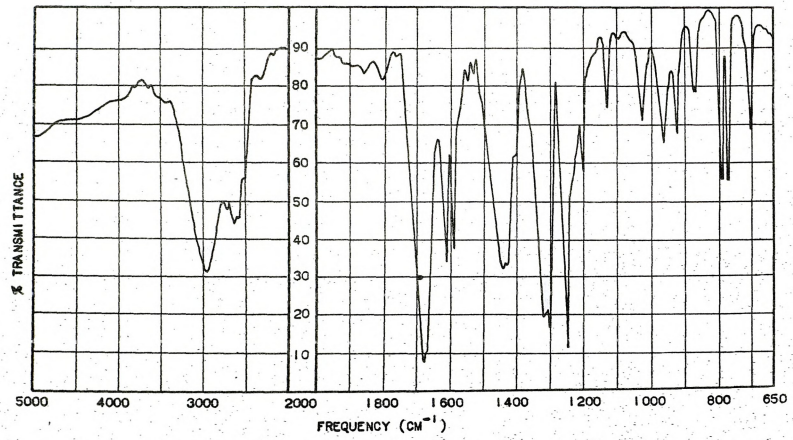

Figure 47

Infrared Spectrum of 3,4,5-Trimethylbenzoic Acid

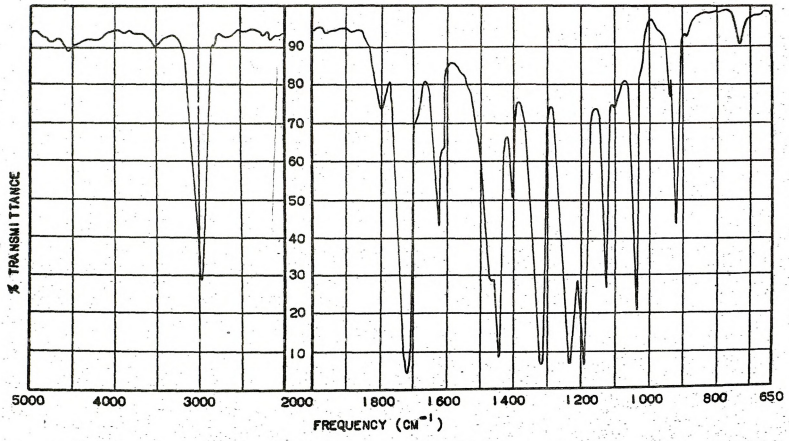

Figure 48a

Infrared Spectrum of Methyl 3,4,5-Trimethylbenzoate

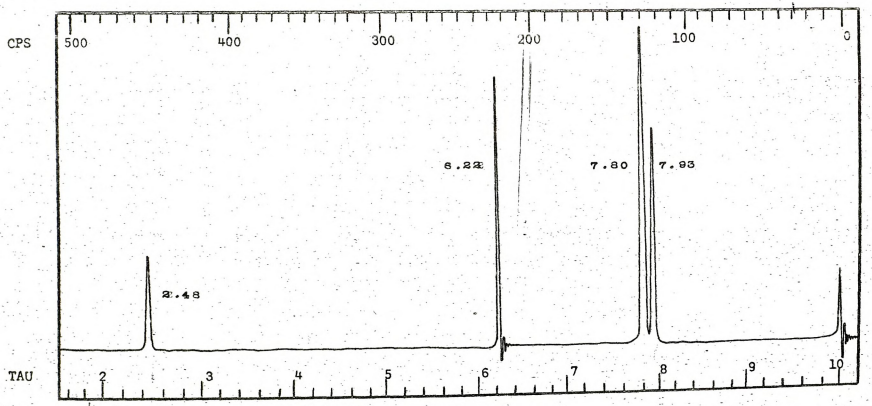

Figure 48b

Nuclear Magnetic Resonance Spectrum of Methyl 3,4,5-Trimethylbenzoate

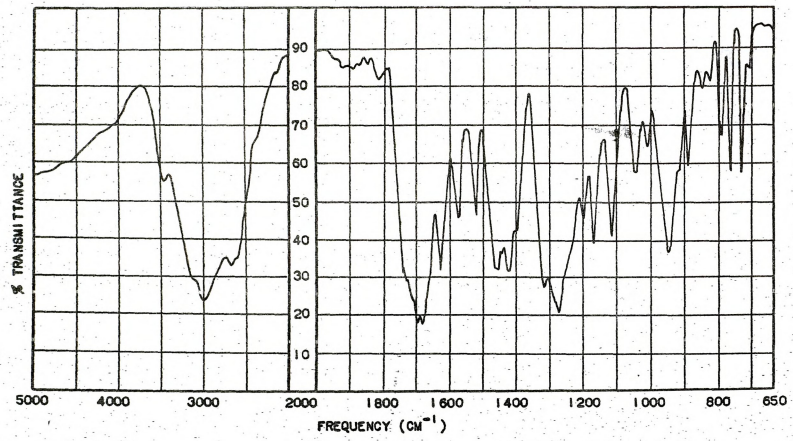

Figure 49

Infrared Spectrum of 2,4,5-Trimethylbenzoic Acid

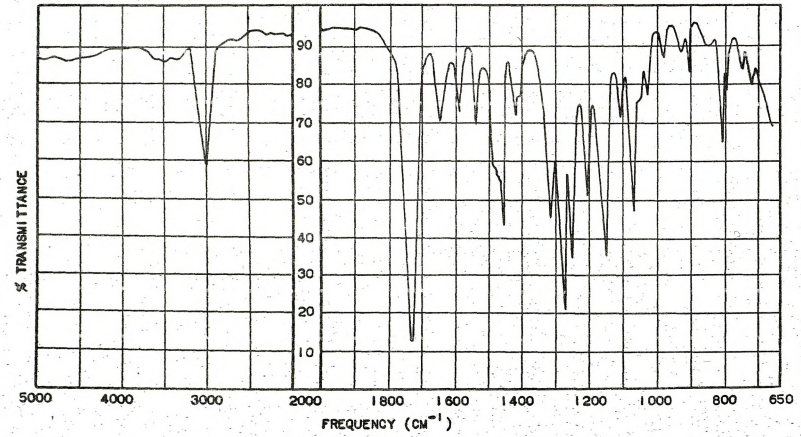

Figure 50a

Infrared Spectrum of Methyl 2,4,5-Trimethylbenzoate

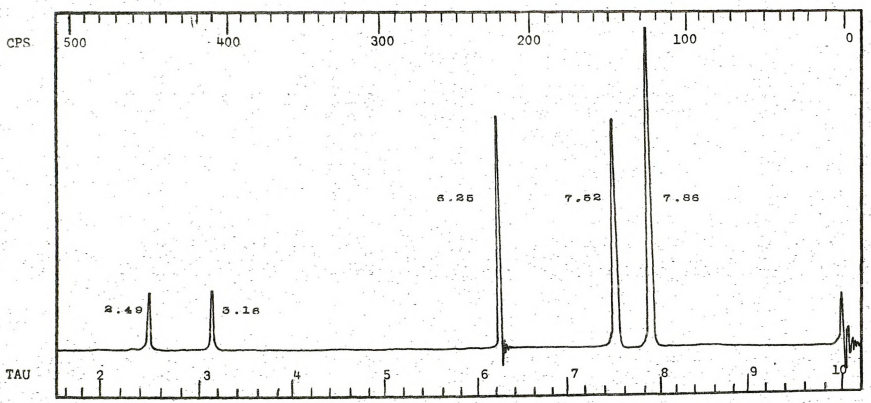

Figure 50b

Nuclear Magnetic Resonance Spectrum of Methyl 2,4,5-Trimethylbenzoate

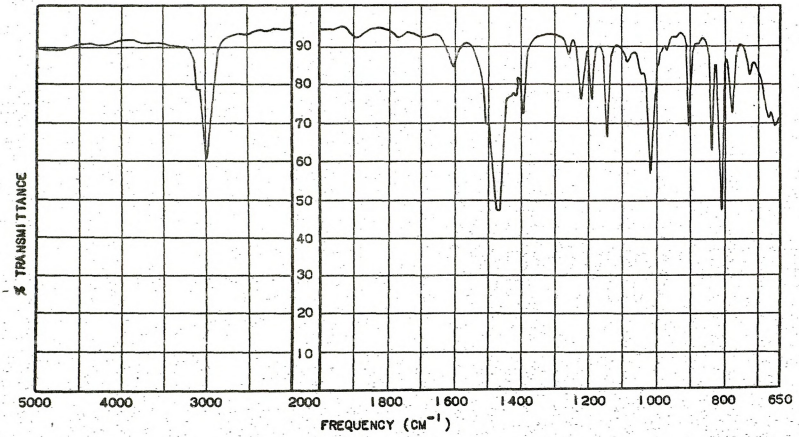

Figure 51a

Infrared Spectrum of 4-Bromo-1,2,3-trimethylbenzene

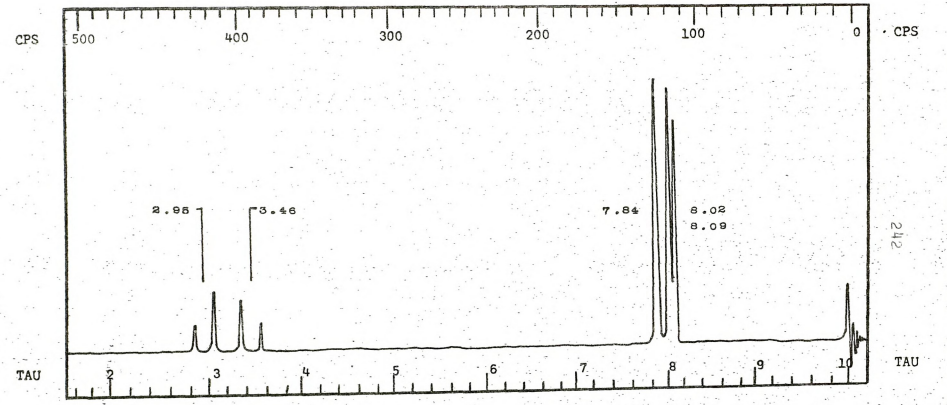

Figure 51b

Nuclear Magnetic Resonance Spectrum of 4-Bromo-1,2,3-trimethylbenzene

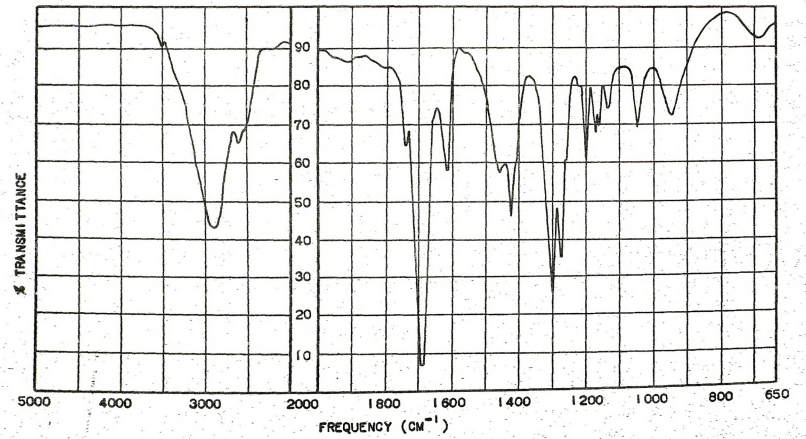

Figure 52

Infrared Spectrum of 2,3,4-Trimethylbenzoic Acid

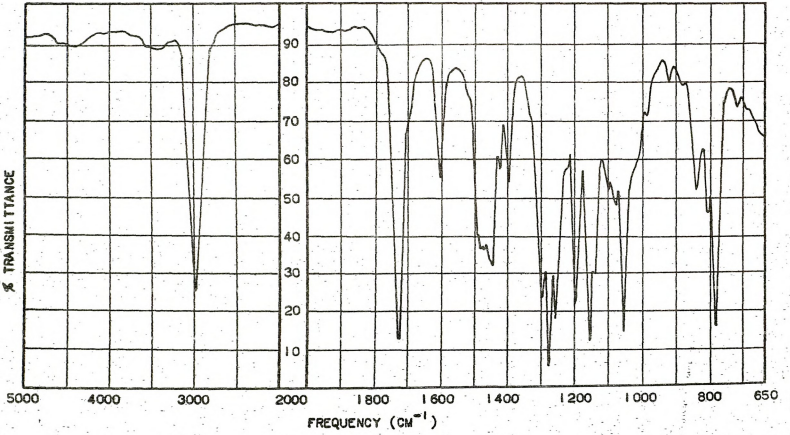

Figure 53a

Infrared Spectrum of Methyl 2,3,4-Trimethylbenzoate

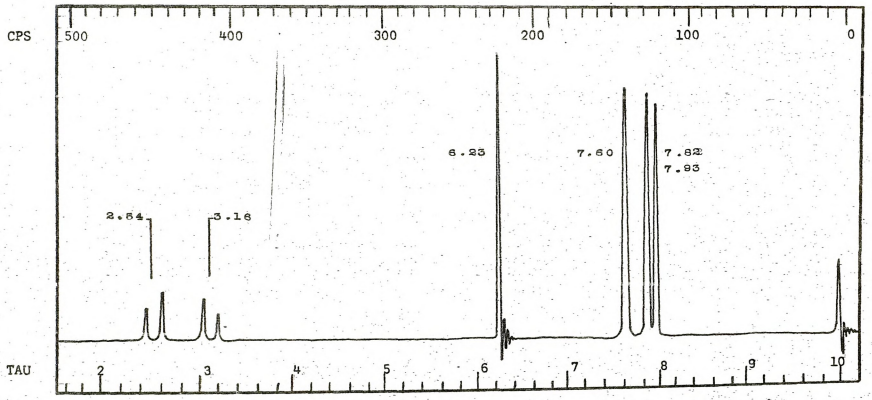

Figure 53b

Nuclear Magnetic Resonance Spectrum of Methyl 2,3,4-Trimethylbenzoate

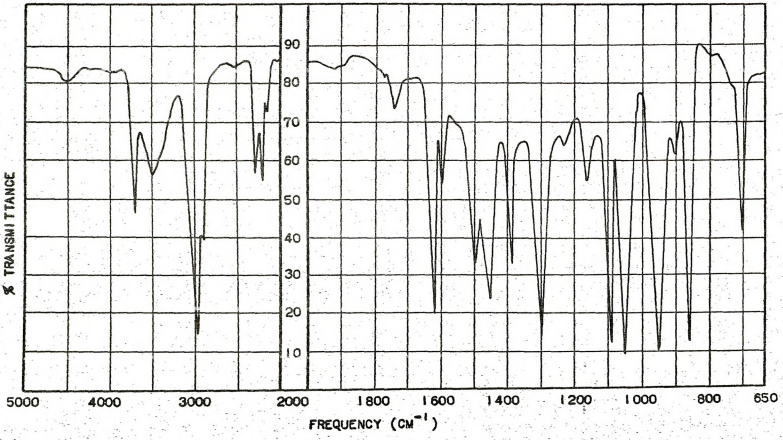

Figure 54a

Infrared Spectrum of 2,4,6-Trimethylbenzyl-α-α-d_2 Alcohol

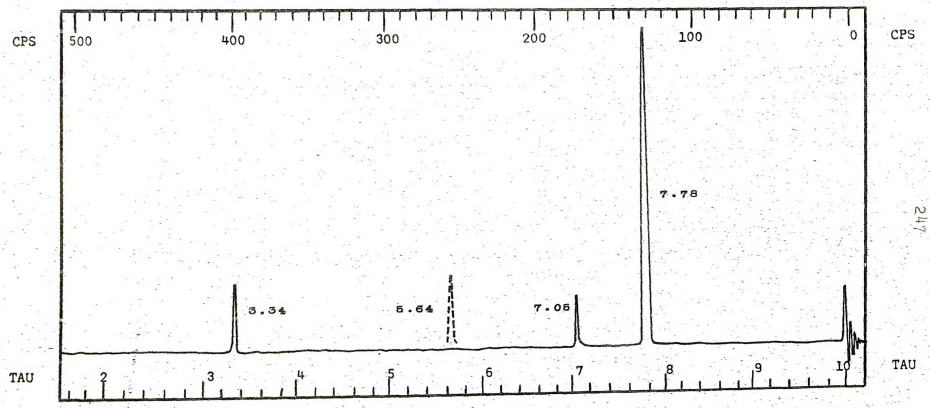

Figure 54b

Nuclear Magnetic Resonance Spectrum of 2,4,6-Trimethylbenzyl-α-α-d_2 Alcohol

(Broken line indicates the resonance signal for the benzylic hydrogens in the unlabeled isomer.)

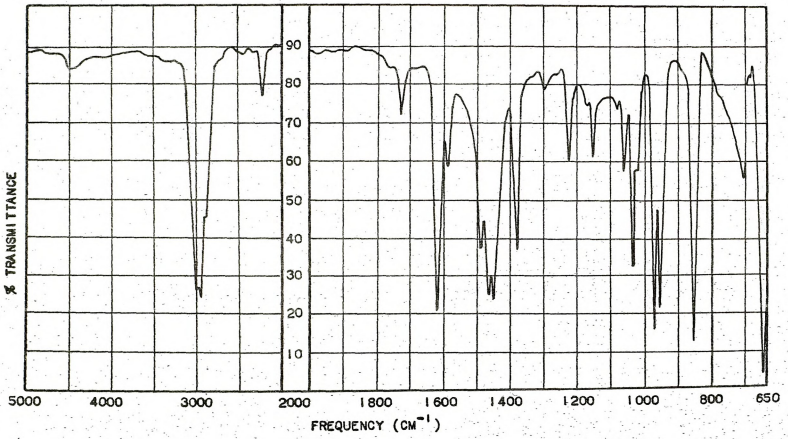

Figure 55a

Infrared Spectrum of 2,4,6-Trimethylbenzyl-α-α-d_2 Chloride

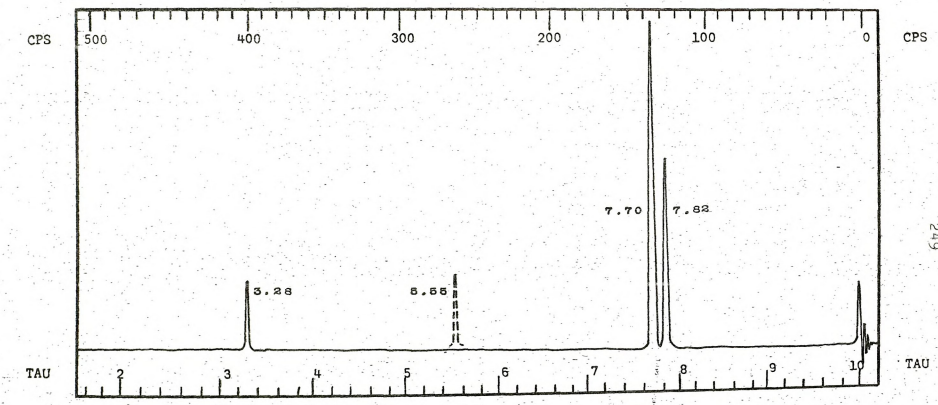

Figure 55b

Nuclear Magnetic Resonance Spectrum of 2,4,6-Trimethylbenzyl-α-α-d_2 Chloride

(Broken line indicates the resonance signal for the benzylic hydrogens in the unlabeled isomer.)

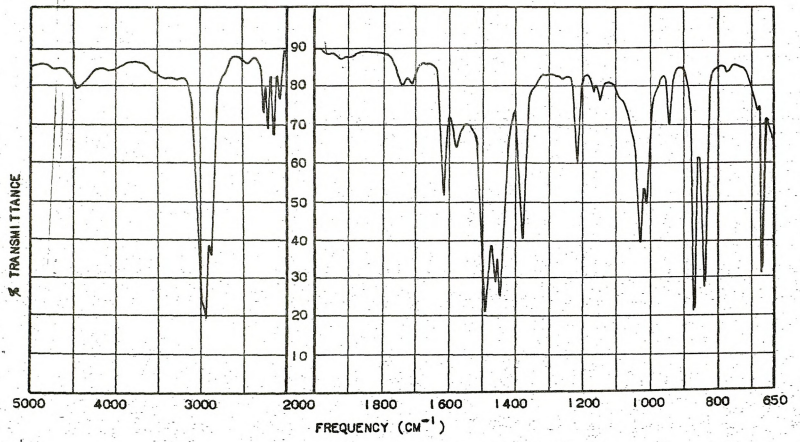

Figure 56a

Infrared Spectrum of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3

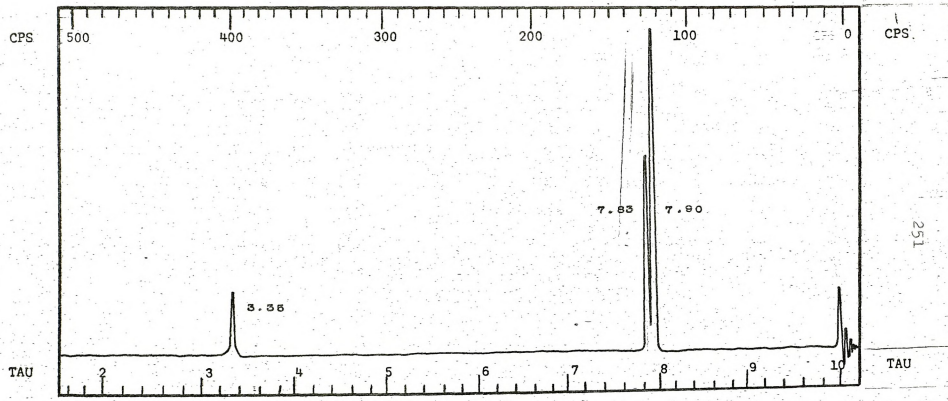

Figure 56b

Nuclear Magnetic Resonance Spectrum of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3

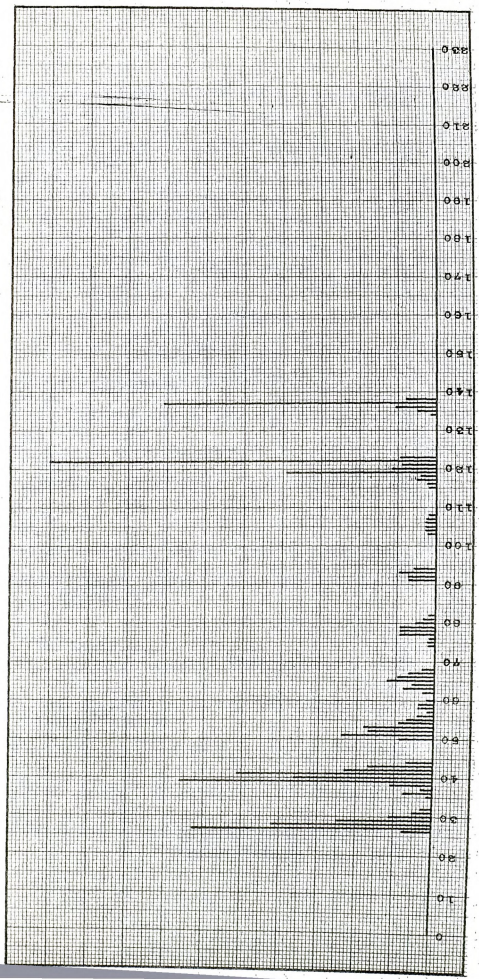

Figure 56c

Mass Spectrum of 1,2,3,5-Tetramethylbenzene-2',2',2'-d_3

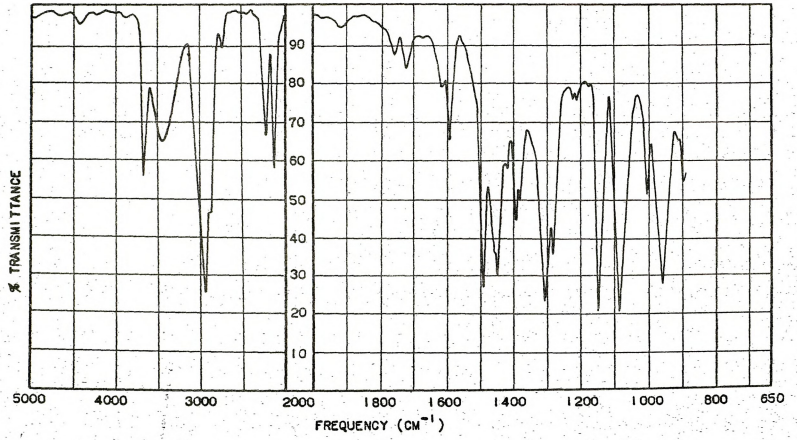

Figure 57a

Infrared Spectrum of 3,4,5-Trimethylbenzyl-α-α-d_2 Alcohol

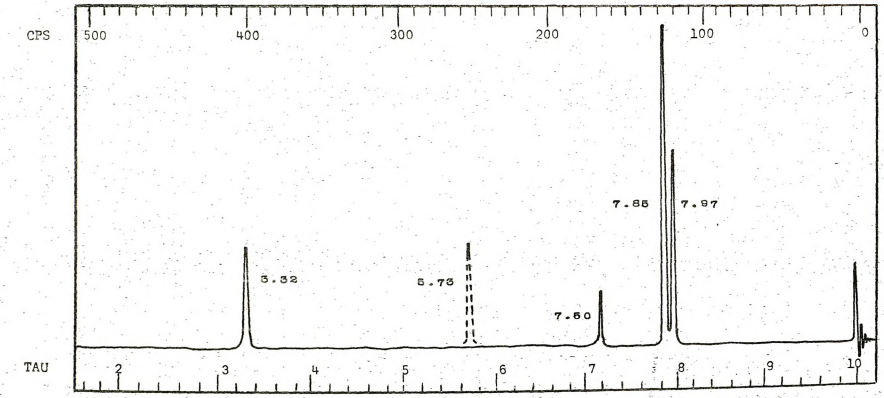

Figure 57b

Nuclear Magnetic Resonance Spectrum of 3,4,5-Trimethylbenzyl-α-α-d_2 Alcohol

(Broken line indicates the resonance signal for the benzylic hydrogens in the unlabeled isomer.)

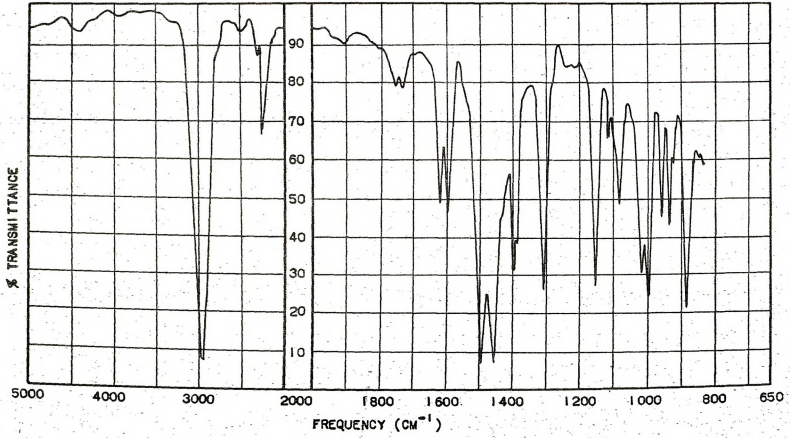

Figure 58a

Infrared Spectrum of 3,4,5-Trimethylbenzyl-α-α-d_2 Chloride

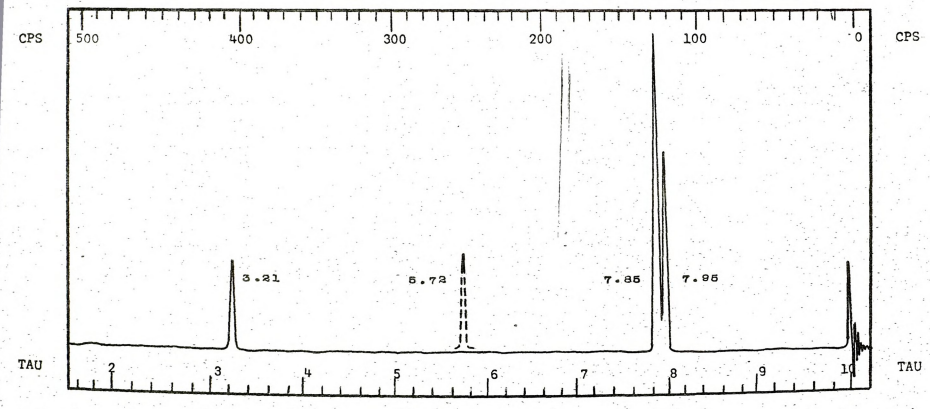

Figure 58b

Nuclear Magnetic Resonance Spectrum of 3,4,5-Trimethylbenzyl-α-α-d_2 Chloride

(Broken line indicates the resonance signal for the benzylic hydrogens in the unlabeled isomer.)

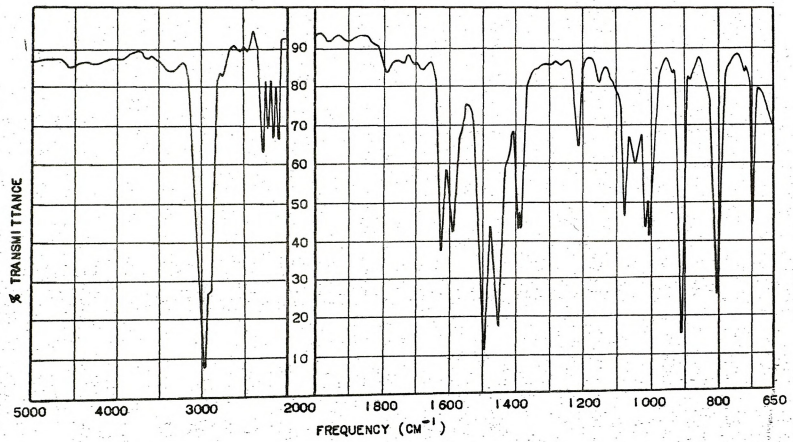

Figure 59a

Infrared Spectrum of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3

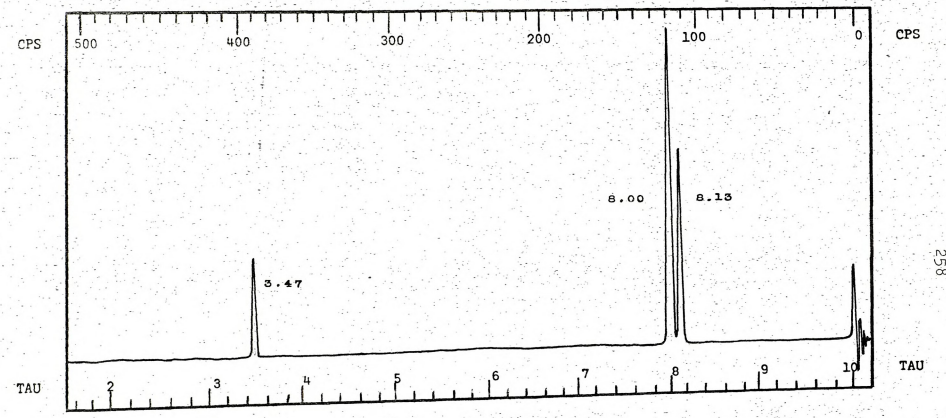

Figure 59b

Nuclear Magnetic Resonance Spectrum of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3

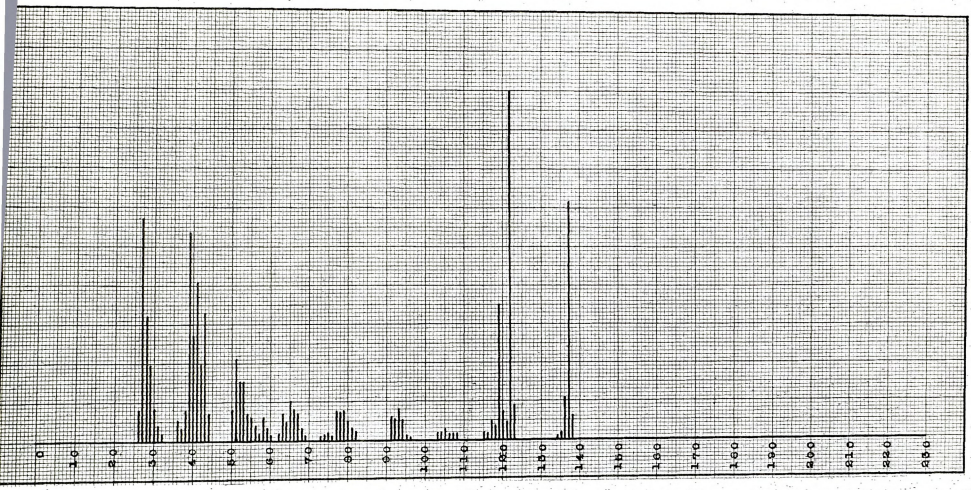

Figure 59c

Mass Spectrum of 1,2,3,5-Tetramethylbenzene-5',5',5'-d_3

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