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PREPARATION AND REACTIONS OF CERTAIN HALOGENATED 2,5-CYCLOHEXADIENONES

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

William Xavier Bajzer, B.S., M.S.

* * * * * *

The Ohio State University
1968

Approved by

[Signature]
Adviser
Department of Chemistry
ACKNOWLEDGMENT

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VITA

June 17, 1940  . .  Born - Cleveland, Ohio

1963  . . . . . .  B.S., Case Institute of Technology, Cleveland, Ohio

1963-1965  . . .  Chemist on Organofluoride Research, Dow Corning Corporation, Midland, Michigan

1965-1966  . . .  Teaching Assistant, Department of Chemistry, The Ohio State University, Columbus, Ohio

1966  . . . . . .  M.S., The Ohio State University, Columbus, Ohio

1966-1967  . . .  Chief Teaching Assistant, Department of Chemistry, The Ohio State University, Columbus, Ohio

1967-1968  . . .  Goodyear Research Fellow and Dissertation Research Fellow, The Ohio State University

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INTRODUCTION (section A)

(1) The research described in this dissertation is presented in two sections. Research under the directorship of Dr. Melvin S. Newman is discussed in section A and commenced April, 1967. The research discussed under section B was pursued from September, 1966 to April, 1967 under the late Dr. Albert A. Henne.

Since the discovery of a method of preparation for a series of 4-methyl-4-trichloromethyl-2,5-cyclohexadienones (I) as well as a preparation for a series of 4-dichloromethyl-4-methyl-2,5-cyclohexadienones (II), the chemistry of the former class of compounds has been investigated rather comprehensively, while the latter class has received periodic and incomplete attention. For the past several years in this laboratory, a great deal of interest has
IIa, $R_1 = R_2 = \text{H}$
IIb, $R_1 = \text{H}, R_2 = \text{CH}_3$
IIc, $R_1 = R_2 = \text{CH}_3$
IID, $R_1 = \text{CH}_3, R_2 = \text{H}$
IIe, $R_1 = \text{CH}_3, R_2 = \text{C}_2\text{H}_5$

(5) R. L. Tse and M. S. Newman, ibid., 21, 638(1956)
(10) M. S. Newman and J. A. Eberwein, ibid., 29, 2516(1964)

been centered on the chemistry of the series Ia-Ie. These dienones and their carbonyl addition products were observed
to undergo three types of rearrangement: (1) a 1,2-

(11) These include the rearrangements reported in the older literature. The terms 1,2-, 1,3- and
1,5-migrations are synonymous with $\alpha,\beta-$, $\alpha,\gamma-$ and $\alpha,\delta-$migrations, respectively, and in no way
are related to the numbering system of a specific compound.

(12) T. Zincke and F. Schwabe, Ber., 41, 897(1908)
migration of the 4-methyl group, (2) a 1,3-migration of the 4-trichloromethyl group onto the ring or a side chain and (3) a 1,5-migration of the 4-trichloromethyl group. In some cases, side products were obtained in which the trichloromethyl group had been lost.

The chemistry of the series IIa-IIId and their carbonyl addition products has received little attention over the past forty years. However, the rearrangements seemingly parallel those cited above, except only two types of rearrangements are known: (1) a 1,2-migration of the 4-methyl group and (2) a 1,5-migration of the 4-dichloromethyl group. Reaction of IIc with zinc-acetic acid was reported to give 2,4,5-trimethylphenol and

methylenec, This is the sole literature report of
products arising from loss of the 4-dichloromethyl group.

No 1,3-migrations of the 4-dichloromethyl group are known.

Tables 1-5, shown on the following pages, give examples of all these rearrangements.
TABLE 1. 1,2-Migration of the 4-methyl group

\[
\begin{align*}
\text{CH}_3\text{CCl}_3 & \xrightarrow{\text{PCl}_5} \text{CO}_2\text{HCH}_3 \\
\text{Ia} & \quad \text{Cl} \\
\text{CH}_3\text{CCl}_3 & \xrightarrow{\text{PPA}} \text{CO}_2\text{HCH}_3 + \text{CH}_3 \quad \text{Cl} \\
\text{CH}_3\text{CCl}_3 & \xrightarrow{\text{H}^+} \text{CO}_2\text{HCH}_3 + \text{C}_6\text{H}_5 \\
\text{CH}_3\text{CCl}_3 & \xrightarrow{\text{PCl}_5} \text{CO}_2\text{HCH}_3 \quad \text{ref. 13} \\
\text{Ia} & \quad \text{Cl} \quad \text{ref. 6} \\
\text{CH}_3\text{CCl}_3 & \xrightarrow{\text{H}^+} \text{CO}_2\text{HCH}_3 + \text{C}_6\text{H}_5 \quad \text{ref. 7}
\end{align*}
\]
TABLE 2. 1,3-Migration of the 4-trichloromethyl group

\[
\begin{align*}
\text{CH}_3 & \quad \text{CCl}_3 \\
\text{CH}_2 \text{R}_2 & \quad \text{R} \\
\hline
\text{Ib}, \quad \text{R}_1 = \text{R}_2 = \text{H} & \quad \text{CH}_3 \quad \text{CCl}_3 \\
\text{Ic}, \quad \text{R}_1 = \text{CH}_3, \quad \text{R}_2 = \text{H} & \quad \text{CH}_3 \quad \text{CH}_2 \text{R} \\
\text{Id}, \quad \text{R}_1 = \text{H}, \quad \text{R}_2 = \text{CH}_3 & \quad \text{CH}_3 \quad \text{CCl}_3
\end{align*}
\]

[ref. 6(Ib), 8(Ic), 9(Id)]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CCl}_3 \\
\text{CH}_2 \text{R} & \quad \text{Ac}_2 \text{O} \\
\hline
\text{Ib}, \quad \text{R} = \text{H} & \quad \text{CH}_3 \quad \text{CCl}_3 \\
\text{Id}, \quad \text{R} = \text{CH}_3 & \quad \text{CH}_3 \quad \text{CH}_2 \text{R}
\end{align*}
\]

[ref. 9]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CCl}_3 \\
\text{CH}_3 & \quad \text{P} \text{PA} \\
\hline
\text{Ib} & \quad \text{CH}_3 \quad \text{CCl}_3 \\
\text{Ic} & \quad \text{CH}_3 \quad \text{P} \text{PA}
\end{align*}
\]

[ref. 6]

[ref. 8]
TABLE 3. 1,5-Migration of the 4-trichloromethyl group

III, \( R = H \)

IV, \( R = CH_3 \)

V, \( R = CH, \)

VI

VII

VIII

[ref. 13(III), 7(IV)]

[ref. 5]

[ref. 5(Va), 10(Vb), 10(Vc)]

[ref. 5, 13]
TABLE 4. 1,2-Migration of the 4-methyl group

<table>
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<tr>
<th>Reaction</th>
<th>Product</th>
<th>References</th>
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| \[
\begin{align*}
\text{CH}_3\text{CHCl}_2 & \overset{\text{PCl}_5}{\rightarrow} \text{CHOCH}_3 \\
\text{CH}_3\text{CH}_2\text{C} & \overset{\text{H}^+}{\rightarrow} \text{CHOCH}_3 \\
\text{Cl}\text{CHCl}_2 & \overset{\text{H}^+}{\rightarrow} \text{CHOCH}_3 \\
\text{CH}_3\text{CH}_2\text{C} & \overset{\text{H}^+}{\rightarrow} \text{CHOCH}_3 \\
\end{align*}
\] | \[
\begin{align*}
\text{Cl} & \\
\text{CH}_3 & \\
\text{CHO} & \\
\text{CH}_3 & \\
\text{Cl} & \\
\text{CH}_3 & \\
\text{CHO} & \\
\text{CH}_3 & \\
\end{align*}
\] | [ref. 13, 21] [ref. 15] [ref. 22] [ref. 15] |
TABLE 5. 1,5-Migration of the 4-dichloromethyl group

R = H, alkyl, aryl

IXa, $R_1 = R_2 = H$  Xa  XIa [ref. 14, 18]
IXb, $R_1 = H, R_2 = CH_3$  Xb  XIB [ref. 15, 16]
IXc, $R_1 = CH_3, R_2 = H$  Xc  XIC [ref. 15, 16]
IXd, $R_1 = R_2 = CH_3$  Xd  XID [ref. 15, 16]

R = H, CH$_3$

XIIa, $R_1 = H, R_2 = Cl$  XIIa [ref. 22]
XIIb, $R_1 = R_2 = Cl$  XIIb [ref. 22]
XIIc, $R_1 = H, R_2 = Br$  XIIc [ref. 23]
XIId, $R_1 = R_2 = Br$  XIIId [ref. 23]

[ref. 24]
(⋆) Only one of the possible geometric isomers is used for illustration.

(★★) Triene shown is a postulated intermediate and was not isolated.

(#) Triene shown is an isolated intermediate.

(21) K. von Auwers and G. Keil, *Ber.*, 38, 1693(1905)

(22) K. von Auwers, *Ber.*, 44, 788(1911)


A recent report from this laboratory established the mechanism of the 1,5-migration of the 4-trichloromethyl group as a free radical process. Also racemization prevailed if optically active material was utilized for the rearrangement study.

Recent interest in the preparation and rearrangements of dienones containing the 4-tribromomethyl group has prompted further research on halogenated dienones. This work was directed along two main routes: (1) the synthesis and investigation into the chemistry of the unknown dienones XIV and XV, which contain a 4-polyfluoromethyl group and (2)
the study of the unreported 1,3-migration of the 4-dichloro-

\[ \text{XIV, } R = H, \text{CH}_3 \quad \text{XV, } R = H, \text{CH}_3; \quad Y = H, \text{Cl} \]

methyl group and an examination of the mechanism of this
type of rearrangement. Furthermore formation of an optically-
ly active product (XVI) from the carbonyl addition product
of IIe would give support for a stereospecific 1,3-migra-
tion of the dichloromethyl group.

IIe, optically active

(XVI)

(28) One enantiomer is used for illustration. The result is independent of which one is used.
HISTORICAL (section A)

While no reports of the preparation of fluorinated dienones are to be found in literature, the introduction of fluorine is accomplished in a number of ways. The action of metal fluorides on organic chlorides serves as a general method for preparation of the corresponding fluorinated derivative. Numerous examples can be found for such exchange reactions and the ease of fluorination stands in the order: \(-\text{CH}_2\text{Cl} < -\text{CHCl}_2 < -\text{CCl}_3\), which favors introduction of a 4-trifluoromethyl group on a dienone framework.


(31) A. L. Henne, Org. Reactions, 2, 56(1944)

The work of Zinke and Suhl suggested utilization of
some of the fluorochloromethanes for preparation of mixed

(32) T. Zincke and R. Suhl, Ber., 39, 4152 (1906)

fluorochloromethyl substituted dienones from the corresponding phenol.

\[
\begin{align*}
\text{OH} & \quad + \\
\text{CH}_3 & \quad \text{CFCl}_3(\text{CF}_2\text{Cl}_2) \\
\rightarrow & \quad \text{AlCl}_3
\end{align*}
\]

The Reimer-Tiemann reaction\(^\text{33}\) has been shown to involve


formation of dichloromethylene.\(^\text{33-35}\) Besides the "normal"

(34) J. Hine, J. Amer. Chem. Soc., 72, 2438 (1950)


Reimer-Tiemann product, hydroxyaryl aldehydes, the "abnormal" product or dienones containing the 4-dichloromethyl group are also formed. The use of "dihalomethylene", generated from a number of reagents, could supplement the above series. Presumably the use of difluoromethylene could also result in dienone formation.

\[
\begin{align*}
\text{OH} & \quad + \\
\text{CH}_3 & \quad :\text{CF}_2 \\
\rightarrow & \quad \text{H}
\end{align*}
\]
Migrations in such fluorinated dienones, during their rearomatization processes, should supply invaluable information in the area of rearrangements of 4-polyhalomethyl substituted dienones and serve as a basis of comparison (or contrast) between dienones containing the halogens fluorine, chlorine and bromine.

While numerous dienones containing the 4-dichloromethyl group have been reported since the first investigation\(^{36}\), no reports of a 1,3-migration of the 4-dichloromethyl group are to be found. The analogous 4-trichloromethyl substituted dienones readily undergo 1,3-migrations (see Table 2) and serve as ample precedent for such a migration of the 4-dichloromethyl group, when the series of dienones IIa-IIId is subjected to conditions which favor 1,3-migrations (see Table 2). In light of the known \(^{25}\) radical nature of the 1,5-migrations of the 4-trichloromethyl group, now a test for the presence of a similar type of process in migrations of the 4-dichloromethyl group is in order. It is also plausible to anticipate trapping an intermediate, such as the triene XVIII, by a good dienophile.

\(^{36}\) K. von Auwers, Ber., 17, 2976 (1884)
Finally resolved dienone (IIe) could serve as a model for study of retention or loss of optical activity during rearrangement. If a free radical mechanism is operative, attack by the dichloromethyl radical could occur stereospecifically on the face of the molecule on which the 4-methyl group is located. The product (XVI) would then be expected to retain some optical activity.

![Structural diagram](image)

A recent method for dienone resolution has been reported, i.e., utilization of the oxime transfer reaction with (+)-α-(isopropylideneaminooxy)propionic acid, followed by acid hydrolysis.

DISCUSSION OF RESULTS (section A)

Initial attempts for introduction of fluorine into dienones involved halogen exchange on a trichloromethyl-substituted diene. The diene chosen for study was 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadiene (Ib). Fluorine exchange using a metal fluoride on polychloromethyl groups works best when the group is the trichloromethyl group. However, while halogen exchange on Ib appears facile, the molecule is a dienone and thereby susceptible to rearrangement in an aromatization process. Aromatization could be catalyzed by the action of a metal halide. Therefore the metal fluoride had to be chosen with care.

Arsenic trifluoride has been used\(^{38}\) to effect halogen exchange on aliphatic and olefinic halides and yet is a mild fluorinating agent. The reagent was conveniently prepared\(^{39}\) in a 58% yield by heating a mixture of arsenic trioxide and calcium fluoride with concentrated sulfuric acid. Refluxing a solution of Ib in methylene chloride with arsenic trifluoride containing a catalytic amount of antimony pentachloride


\(^{39}\) J. C. Bailar, Inorg. Syn., IV, 150(1953)
gave quantitative recovery of Ib, even after 24 hr. at reflux. While no fluorination occurred, Ib was stable toward the action of a Lewis acid such as arsenic trifluoride.

The use of anhydrous potassium fluoride was tried next. Reaction of Ib with a ten-fold excess of anhydrous potassium fluoride under the following conditions gave quantitative or near quantitative recovery of unchanged starting material: refluxing in dimethylformamide (DMF) for 1½ hr. or 24 hr., as well as reaction in tetramethylene sulfone at 150°C for 15 hr. Use of a longer reaction time, such as refluxing 7 days in DMF, gave considerable decomposition and formation of tars which were free of fluorine. At no time was a fluorinated dienone observed.

The unusual stability of Ib toward the former fluorinating agents prompted use of the classical reagent for such reactions, antimony trifluoride. Swarts utilized this

(40) F. Swarts, Bull.acad.roy.Belg., 24, 474(1892)

potent reagent, usually with 2 to 5% of a pentavalent antimony salt, to successfully prepare numerous aliphatic fluorides by exchange with the corresponding chloride or bromide. No solvent was employed in these reactions.

Table 6 shows the results of a number of attempts at fluorination of Ib using various antimony fluorides. Use of antimony trifluoride alone gave recovery of starting
TABLE 6
Antimony Fluoride Fluorination of 3,4-Dimethyl-4-trichloromethyl-2,5-cyclohexadienone (Ib)

<table>
<thead>
<tr>
<th>Weight</th>
<th>Weight</th>
<th>Weight</th>
<th>Temperature</th>
<th>Reaction Time</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dienone</td>
<td>SbF$_3$</td>
<td>SbX$_5$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0 g.</td>
<td>15.0 g.</td>
<td>-</td>
<td>152°</td>
<td>7 min.</td>
<td>94% recovered dienone</td>
</tr>
<tr>
<td>6.1 g.</td>
<td>25.0 g.</td>
<td>-</td>
<td>free flame</td>
<td>5 min.</td>
<td>charring</td>
</tr>
<tr>
<td>5.0 g.</td>
<td>15.0 g.</td>
<td>0.05 g.</td>
<td>186°</td>
<td>7 min.</td>
<td>charring + some recovered dienone</td>
</tr>
<tr>
<td>7.0 g.</td>
<td>9.0 g.</td>
<td>0.60 g.</td>
<td>free flame</td>
<td>15 min.</td>
<td>charring + Q</td>
</tr>
<tr>
<td>10.0 g.</td>
<td>-</td>
<td>10.0 g.</td>
<td>free flame</td>
<td>10 min.</td>
<td>charring + Q</td>
</tr>
<tr>
<td>11.0 g.</td>
<td>-</td>
<td>6.5 g.</td>
<td>free flame</td>
<td>10 min.</td>
<td>charring + Q</td>
</tr>
</tbody>
</table>

Q = 4-chloro-o-xylene
material at 152° but use of temperatures above 200° gave complete charring. Study of the fluorination\(^1\) of benzal chloride and \(m\)-nitrobenzal chloride showed that certain fluorinations with antimony trifluoride proceed successfully only within narrow temperature intervals (sometimes as sharp as 10°). Attempts to determine the temperature interval, if this phenomenon is present when Ib is fluorinated, gave an interval centered around 186°. At this temperature, some material was recovered and some charred. However no fluorinated product was observed. Utilization of catalytic amounts of Sb\(\text{Cl}_5\) gave rise to formation of 10-15% of 4-chloro-o-xylene, even when Sb\(\text{F}_3\text{Cl}_2\)\(^2\) or Sb\(\text{F}_5\) alone was employed. Therefore it appears evident, at least in the Sb\(\text{F}_5\) run, that the chlorine atom came from the trichloromethyl group, since this was the only source of chlorine in the reaction and workup. Besides 4-chloro-o-xylene, no other organic products were isolated and the predominant reaction

\[\text{CH}_3\begin{array}{c}
\text{CCl}_3
\end{array}\begin{array}{c}
\text{CH}_3
\end{array}\begin{array}{c}
\text{O}
\end{array}\rightarrow \text{CH}_3\begin{array}{c}
\text{CH}_3
\end{array}\begin{array}{c}
\text{Cl}
\end{array}\]  

\(10-15\%\)
was charring of the organic material present.

Since the use of antimony fluorides gave rise to aromatization and no fluorination, it was felt that perhaps the carbonyl group of Ib was being polarized by the antimony halide acting as a Lewis acid to coordinate with the unshared pairs of electrons on oxygen. Such a polarization process could lead to a facile electron shift with loss of the trichloromethyl group and achieve aromatization at the expense of the fluorination process.

In an attempt to prepare the ethylene ketal of Ib, it was heated in a benzene solution of ethylene glycol containing 4-toluene sulfonic acid with removal of water, until infrared analysis of the reaction mixture indicated absence of the carbonyl band. A crystalline aromatized product was isolated but no ethylene ketal was found. The product was characterized by nmr spectroscopy as 1,2-bis(3-(β,β,β-trichloroethyl)-4-methylphenoxy)ethane. This material resulted from an acid catalyzed 1,3-migration of the 4-

\begin{align*}
\text{CH}_3 & \quad \text{OCH}_2\text{CH}_2\text{O} \\
\text{CH}_2\text{CCl}_3 & \quad \text{CH}_3 \\
\text{CH}_2\text{CCl}_3 & \quad \text{CH}_3
\end{align*}

trichloromethyl group and reaction with ethylene glycol. Therefore if polarization of the carbonyl group in Ib was the deterrent to fluorination, it could not be tested by ketal formation.

In the light of the lack of success with the halogen
exchange reaction on dienones, attempts were made to prepare dienones by classical methods such as the Zincke-Suhl reaction.

The model phenol used for the following study was 3,4-dimethylphenol because of its ready availability and the structural feature of an alkyl group in the 3 position, which was necessary for subsequent 1,3-migration studies. Reaction of 3,4-dimethylphenol with slightly more than two equivalents of aluminum chloride in carbon disulfide solution gave the chloroaluminum salt of the phenol. Subsequent treatment with fluorotrichloromethane (Freon 11) at 0-5° for 2 hr. gave a 30% yield of 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadienone (Ib), identical in all respects to authentic material. While the C-F bond is undoubtedly stronger than the C-Cl bond in Freon 11, it seems unlikely on the basis of known bond strengths that the C-F bond was broken preferentially to form Ib. Variation of the ratio of the amount of aluminum chloride to the amount of 3,4-dimethylphenol used gave the following results: ratio, % of Ib formed; 2.58, 30%; 1.69, 32%; 1.04, 16%. Even when only a slight excess of aluminum chloride was used, i.e., excess over that necessary for formation of the chloroaluminum salt of 3,4-dimethylphenol, Ib was still formed in a significant amount (16%). All runs were accompanied by some tar formation as well as recovered 3,4-dimethylphenol.

In order to avoid the formation of Ib above as the
sole diene product, a run was conducted using dichlorodifluoromethane (Freon 12). Reaction with the chloroaluminum salt of 3,4-dimethylphenol at -30° for 2 hr. gave 99% of recovered starting material plus 1% of Ib. Another run in a sealed bomb at 25° for 19 hr. gave only unchanged starting material. Therefore it was now evident that

![Chemical structure](image)

breakage of a C-F bond preferential to a C-Cl bond on Freon 11 does not occur, but rather disproportionation of Freon 11 and Freon 12 with aluminum chloride occurred to form carbon tetrachloride which led to formation of Ib. The disproportionation was checked by showing that Freon 11 and aluminum chloride gave carbon tetrachloride and aluminum fluoride in a rapid exothermic reaction. The extent of disproportionation seemed to be determined only by the amount of aluminum chloride present.

Since aluminum chloride effected disproportionation in the cases of Freon 11 and Freon 12, the possibility of using aluminum fluoride in the Zincke-Suhl reaction was investigated. However aluminum fluoride did not react with 3,4-dimethylphenol. Aluminum fluoride exists in the solid state as a high melting, ionic salt which has been reported by
Sidgwick to be extremely inert chemically. Aluminum chloride on the other hand is a covalent, dimeric species, readily vulnerable to coordination and reaction with Lewis bases such as phenols.

While use of an alkylated phenol with a fluorinated methane in the Zincke-Suhl reaction did not give a fluorinated dienone, the converse was also unlikely. The use of $p$-trifluoromethylphenol might be considered as a plausible approach to the fluorinated dienone problem. However the compound was unusually unstable toward mineral acids, Lewis acids and bases. Only a highly purified sample stored under neutral conditions was stable for an indefinite period. Also the effect of aluminum chloride on benzotrifluoride was reported to give benzotrichloride by halogen exchange.

![Chemical Structure](image)
Therefore in light of the instability of such phenols and the lability of aryl trifluoromethyl groups toward aluminum chloride, it appears unlikely that the harsh conditions of the Zincke-Suhl reaction, or any other dienone synthesis starting with the appropriate fluorinated phenol, could result in a fluorinated dienone.

Another classical route for synthesis of dienones from alkylated phenols is the Reimer-Tiemann reaction. Here a substituted phenol is reacted with chloroform and aqueous base to give hydroxyaryl aldehydes as the major product plus minor amounts of the dichloromethyl substituted dienones IIa-IId. If dienones IIa-IIId arise from attack of dichloromethylene on the appropriate phenol, it was thought that difluoromethylene could lead to formation of an interesting series of difluoromethyl substituted dienones. The use of chlorofluoromethylene would give rise to the mixed halogenated dienones.

The mode of attack on the problem was first to utilize Reimer-Tiemann conditions (aqueous reaction system) before investigating the use of other sources of dihalomethylene (usually non-aqueous conditions). A preliminary reaction of 3,4-dimethylphenol with chlorofluoromethylene, generated
from dichlorofluoromethane (Freon 21) and aqueous sodium hydroxide at room temperature in a bomb, gave mainly unreacted 3,4-dimethylphenol plus some O-alkylated material. A strongly positive chloride ion test indicates that Freon 21 had reacted but no C-alkylated products, neither the normal Reimer-Tiemann product nor dienone, were observed. Similar results were observed by two different groups 46,47


when they reacted various alkylated phenols with difluoromethylenegenerated from chlorodifluoromethane (Freon 22) and aqueous base. Only O-alkylated products besides unchanged phenol were collected. They interpret the absence of any C-alkylation as due to the fact that under the conditions cited dichloromethylenegenerated from phenyl(trichloromethyl)mercury 48

has been reported by Seyferth and coworkers. Utilization
of this reagent with both 3,4-dimethylphenol and sodium 3,4-dimethylphenoxide in dry 1,2-dimethoxyethane gave nearly quantitative recovery of starting phenol. No C- or O-alkylated products could be found. The latter is not surprising in the light of the known hydrolytic instability of dichloromethyl ethers.

Another source of dichloromethylene and difluoro-
methylene is thermal decomposition of dry sodium trichloro-
acetate and sodium chlorodifluoroacetate, respectively. Reaction of either reagent with 3,4-dimethylphenol in dry 1,2-dimethoxyethane gave unchanged phenol. In all runs, carbon dioxide was evolved during thermal decomposition, and the aqueous workup solutions exhibited strongly positive chloride ion tests. Use of sodium chlorodifluoroacetate with sodium 3,4-dimethylphenoxide in dry 1,2-dimethoxyethane or dry dimethylsulfoxide gave the same results, however the latter run was accompanied by formation of considerable amounts of dimethylsulfide, presumably due to deoxygenation of the solvent by difluoromethylene. The ability of difluoromethylene and dichloromethylene to abstract oxygen from solvent is known. 50,51
At this point, rather than investigate the use of difluoromethylene derived from the more exotic organometallic reagents, further research on this approach to the synthesis of fluorinated dienones was discontinued.

The last approach considered was a condensation method usually employed to prepare aryl and alkyl substituted dienones. The method is shown below.

\[
\begin{align*}
\text{CH}_3 \\
\text{CF}_3\text{CHCOCH}_3 & + \text{CH}_2=\text{CHCOCH}_3 & \text{Base} \\
\text{CH}_3 & & \\
\text{CH}_3 & & \\
\text{CF}_3 & & \\
\text{CH}_3 & & \\
\uparrow & & \\
\text{XX} & & \\
\text{CH}_3 & & \\
\text{CF}_3 & & \\
\text{CH}_3 & & \\
\text{SeO}_2 & & \\
\text{CH}_3 & & \\
\text{CF}_3 & & \\
\text{CH}_3 & & \\
\end{align*}
\]

This route is a general one employed by Zimmerman

(54) For example, see H. E. Zimmerman and J. O. Grunwald, J. Amer. Chem. Soc., 89, 5163 (1967)
dienones to be used for photochemical studies. The only difficulty in such an approach was the fact that the starting ketone, 3-methyl-4,4,4-trifluoro-2-butanone (XX), was unknown. A possible route to XX is depicted below.

\[
\begin{align*}
\text{CF}_3\text{CH}_2\text{CH}_2\text{Br} & \quad \text{---} \quad \text{CF}_3\text{CH}_2\text{CH}_2\text{OH} & \quad \text{---} \quad \text{CF}_3\text{CH}_2\text{CO}_2\text{H} \\
\text{CH}_3 & \quad \text{CF}_3\text{CHCOCH}_3 & \quad \text{CH}_3 & \quad \text{CF}_3\text{CHCO}_2\text{CH}_3 \\
XX & \quad \text{XXII} & \quad \text{XXI} \\
\end{align*}
\]

The 3,3,3-trifluoropropionic acid was prepared in an overall yield of 19% from 3,3,3-trifluoropropyl bromide via oxidation of the Grignard reagent followed by chromic acid oxidation of the 3,3,3-trifluoropropanol.

Treatment of methyl 3,3,3-trifluoropropionate (XXI) with sodium methoxide in methanol followed by methyl iodide did not give the alkylated ester (XXII) (recovered XXI was the only ester observed). Use of trityl sodium readily gave the anion of XXI, since addition was accompanied by a rapid dissipation of the red color. Subsequent treatment with methyl iodide gave sodium iodide and recovered XXI. O-alkylation followed by hydrolysis to XXI during workup was assumed, although not proved.

No further investigation of this method was made and the general problem of preparation of fluorinated dienones was abandoned.

The second phase of the research program was to examine possible 1,3-migrations of the 4-dichloromethyl group in
certain substituted dienones and their carbonyl addition products. As stated earlier a 1,3-migration of the 4-dichloromethyl group had not been found. Therefore in order to find an example of this reaction, dienones IIa-IIId (page 2) were prepared as minor products from the Reimer-Tiemann reaction on the appropriate alkylated phenol. Some benzo analogs of dichloromethyl substituted dienones are known, i.e., IIf and IIg. Treatment of IIg with the ethyl Grignard reagent, followed by heating the resulting alcohol product gave a 1,5-migration of the 4-dichloromethyl group (see Table 5, page 9). While the dichloromethyl group in IIg is

![Chemical Structures](image)

IIf  
IIg  
IIh

incapable of a 1,3-migration to an alkyl group, the dichloromethyl group in IIh could undergo this type of rearrangement. The new compound (IIh) was synthesized by a five-step sequence shown below. Bromination of 2-methylnaphthalene gave a 98% yield of 1-bromo-2-methylnaphthalene. Conversion to the Grignard reagent followed by treatment with dimethylsulfate gave a 77% yield of 1,2-dimethylnaphthalene. Sulfonation followed by fusion of the sodium salt of the aryl sulfonic acid with potassium hydroxide gave upon neutralization a 35% yield of 3,4-dimethyl-1-naphthol.
Reaction of the latter with chloroform and aqueous sodium hydroxide gave 12% of purified 4-dichloromethyl-3,4-dimethyl-1-keto-1,4-dihydronaphthalene (IIh). An nmr spectrum of IIh is found in Figure 1.

While the reactions of IIf with bases are known to give ring-opened products, no reports are found regarding migration of the dichloromethyl group. In the interest of studying the chemistry of IIf under conditions of aromatization, this dienone was also prepared as shown below. A Vilsmeir reaction on 2-ethoxynaphthalene gave a 93% yield of 2-ethoxynaphthaldehyde. A Wolff-Kishner reduction gave a 91% yield of 2-ethoxy-1-methylnaphthalene. Ether cleavage using pyridine hydrochloride gave 1-methyl-2-naphthol in a
Figure 1. Nmr Spectrum of 4-Dichloromethyl-3,4-dimethyl-1-keto-1,4-dihydronaphthalene
95% yield. Finally reaction of this material with chloroform and aqueous sodium hydroxide gave a 75% yield of 1-dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene (IIf).

The unknown trichloromethyl analog (Ilf) would be a valuable compound for comparative studies with the reactions of IIIf. However attempts to prepare this dienone from 1-methyl-2-naphthol via a Zincke-Suhl reaction were unsuccessful.

There are three main reagents (see Table 2, page 6) which cause a 1,3-migration of the 4-trichloromethyl group in dienones Ia-Id: (1) acetic anhydride containing a
mineral acid, (2) phosphorus pentachloride and (3) phenyl-
magnesium bromide followed by treatment of the resulting
tertiary alcohol with acid or heat. These reaction
conditions were used in part on the various dienones IIa -
IIf and IIh to effect migrations of the dichloromethyl group
and to investigate the possibility of 1,3-migration of the
4-dichloromethyl group whenever this rearrangement could
occur.

Dienones containing the dichloromethyl group are soluble
and stable\(^{56,57}\) in cold concentrated sulfuric acid, but begin

\(^{(56)}\) H. Budzikiewicz, Tetrahedron Letters, \#7, 12(1960)

to decompose upon heating in solution. The first reaction
tried was treatment of IIb at reflux for 23 hr. with acetic
anhydride containing a catalytic amount of sulfuric acid. A
large amount of tar was formed as well as 14% of 3,4-
dimethylphenyl acetate, arising from loss of the 4-dichloro-
methyl group. Substitution of the mineral acid by BF\(_3\) gave
an 11% yield of 3,4-dimethylphenyl acetate, besides tar,
when conducted at reflux for 2 hr. Use of milder conditions
(room temperature for 4 days) and use of only a catalytic
amount of BF\(_3\) gave the same product along with some unreacted
IIb. Again some decomposition was found even under the mild
reaction conditions. No evidence of a 1,3-migration of the
4-dichloromethyl group was found by nmr analysis of the crude
Thus it appears that the use of acetic anhydride containing a mineral or Lewis acid does not effect a 1,3-migration of the 4-dichloromethyl group in contrast to the known 1,3-migrations of the 4-trichloromethyl group under similar conditions. The only product from dienones containing the 4-dichloromethyl group under these conditions was that derived from loss of this group during aromatization.

The reaction of phosphorus pentachloride with various dienones was tried next. The product from reaction of IIa with phosphorus pentachloride was reported\textsuperscript{13,21} to be 2-methyl-4-chlorobenzal chloride, arising from a 1,2-migration of the 4-methyl group. Reexamination of the reaction confirmed this report but also established the presence of some p-chlorotoluene, arising from loss of the 4-dichloromethyl group during aromatization. The major product was
characterized by oxidation with neutral potassium permanganate to the known 2-methyl-4-chlorobenzoic acid (77% yield) followed by comparison of the acid with an authentic sample.

The reaction of IIa with phosphorus pentachloride in methylene chloride was observed to be quite sluggish. Use of phosphorus oxychloride (POCl₃) in place of methylene chloride gave a marked decrease in the time necessary for complete reaction to occur. Therefore it was of interest to examine qualitatively this solvent effect. Solutions of IIa in four common solvents (methylene chloride, acetonitrile, nitromethane and POCl₃) were heated at reflux and periodically analyzed by infrared spectroscopy. Complete reaction time was defined as the time necessary to cause disappearance of the carbonyl stretching band in IIa. Reaction in methylene chloride was still incomplete after 19 hr., at reflux (40°). Reaction in acetonitrile (82°) required 2-3½ hr., while use of nitromethane (101°) or phosphorus oxychloride (107°) both shortened the reaction time to only ½ hr. For rapid reactions of dienones with phosphorus pentachloride, the latter two appear to be the solvents of choice.

The reaction of IIb with phosphorus pentachloride in phosphorus oxychloride for 4 hr. at reflux gave the first example of a 1,3-migration of the 4-dichloromethyl group. The new compound, 3-(β,β-dichloroethyl)-4-methylchlorobenzene, was formed in a 74% yield. Proof of structure was accomplished by degradation with basic potassium permanganate.
to the known 2-methyl-5-chlorobenzoic acid in 66% yield, followed by comparison with an authentic sample. No evidence of a product arising from loss of the 4-dichloromethyl group was observed.

Since reaction of IIb with phosphorus pentachloride has now been shown to undergo a 1,3-migration of the dichloromethyl group, a comparison with the known 1,3-migration of the 4-trichloromethyl group of Ib was made. Identical solutions of Ib and IIb in methylene chloride were made up in separate flasks and refluxed with one equivalent of phosphorus pentachloride. Aliquots were analyzed by infrared spectroscopy to determine the time necessary for complete reaction. Complete reaction with Ib occurred in 4-6 min., while IIb required 24-26 min. This reflects a greater stability of IIb relative to Ib toward PCl5. Similar stability \(^{56,57}\) of IIb to mineral acids was mentioned earlier.

A reaction of phosphorus pentachloride with IID, which is incapable of giving a 1,3-migration of the dichloromethyl group to an alkyl group, gave two products characterized by nmr as dimethylchlorobenzal chlorides. The two structures
shown were assigned by analogy with the known 1,2-migrations of the 4-methyl group (see Tables 1 and 4) in similar systems.

While 1-dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene (IIf) is also incapable of a 1,3-migration of the 4-dichloromethyl group to an alkyl group, it was of interest to see if the group would migrate. A preliminary reaction showed IIf to be inert toward reaction with acetic anhydride containing a mineral acid. A similar lack of reactivity was observed with phosphorus pentachloride in methylene chloride. However use of phosphorus pentachloride in phosphorus oxychloride gave a 49% yield of 2-chloro-1-methylnaphthalene plus some recovered IIf.

The structure of the product was verified by degradation with dilute nitric acid in 96% yield to the known 2-chloro-1-naphthoic acid. The latter was identical in all respects with an authentic sample synthesized in a 32% yield from
2-hydroxy-1-naphthoic acid and phosphorus pentachloride followed by acid hydrolysis. No aromatized product containing the dichloromethyl group was found.

The chemical fate of the dichloromethyl group during this reaction was questioned. If the reaction of IIIf with $\text{PCl}_5$ is an ionic process, the dichloromethyl group could be

\[
\begin{align*}
\text{CH}_3\text{CHCl}_2 & \quad \text{IIIf} \\
\text{CH}_3\text{CHCl}_2 & \quad \text{PCl}_5 \\
\text{PCl}_5 & \quad \text{PCl}_3 \\
\text{PCl}_6 & \\
\text{CH}_3\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

ejected as a cation during aromatization. The cation could then lose a proton and give rise to dichloromethylene.

Therefore a trapping experiment was conducted by reacting IIIf with phosphorus pentachloride in cyclohexene at reflux for 65 hr. Analysis of the reaction mixture showed the presence of unchanged IIIf, 2-chloro-1-methylnaphthalene and 37% of $\text{trans}-1,2$-dichlorocyclohexane. The latter arises from attack of phosphorus pentachloride on the solvent.

This observation has been reported earlier. Since 2-chloro-1-methylnaphthalene was also formed, the dichloro-
methyl group had been lost but not captured by the solvent. That authentic trapping product, 7,7-dichloronorcarane, was stable under the reaction conditions was shown by a blank run with PCl₅ and cyclohexene at reflux for 65 hr. Thus if dichloromethylenene was the result from loss of the dichloromethyl group, some or all of it should have been trapped by solvent. Since no 7,7-dichloronorcarane was observed by infrared and v.p.c. analysis of the reaction mixture, dichloromethylenene was not formed. The fate of the supposed dichloromethyl cation remains unknown.

The third type of reaction examined was the treatment of dienones with phenylmagnesium bromide followed by treatment of the resulting tertiary alcohol with acid or heat. The reaction of I Ib with excess phenylmagnesium bromide gave a 78% yield of purified 4-dichloromethyl-3,4-dimethyl-1-phenyl-2,5-cyclohexadienol (XVII). The yield of crude XVII was nearly quantitative, but traces of biphenyl in most samples required purification before further study was
conduted. The alcohol (XVII) slowly lost water and rearranged upon standing at room temperature.

Heating a sample of XVII in methylene chloride or reaction of XVII with 91% formic acid at 0-5° effected both dehydration and rearrangement to 3-(ß,ß-dichloroethyl)-4-methylbiphenyl (XIX). The product of a 1,3-migration of the 4-dichloromethyl group was thought to proceed through the intermediate 6-dichloromethyl-6-methyl-1-methylene-3-phenyl-2,4-cyclohexadiene (XVIII). Degradation of XIX with basic potassium permanganate gave an 88% yield of known 2-methyl-5-phenylbenzoic acid, identical in all respect to an authentic sample.

The triene intermediate (XVIII) now became the center of attention insofar as isolation or trapping of this intermediate is the only proof for its existence in the dehydration and rearrangement of XVII. The use of maleic anhydride to trap similar trienes has been reported and is shown

\[(59)\] K. Alder, R. H. Flack and H. Lessenich, Ber., 90, 1709 (1957)

below:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{X} & \quad \text{O, CH}_2
\end{align*}
\]

Thus a solution of freshly sublimed maleic anhydride and pure alcohol (XVII) in methylene chloride was heated at reflux for 18 hr. The water eliminated by XVII was picked up by the maleic anhydride and maleic acid was isolated. Two other components were also present and assigned the structures of XVIII and XIX based on an nmr spectrum of the binary mixture. Heating the mixture briefly at 100° gave complete conversion to XIX alone, which is consistent with the nature of XVIII.

Despite the fact that some intermediate triene (XVIII) was still present in the original mixture, no Diels-Alder type adduct was formed with the maleic anhydride or the maleic acid. Therefore a more powerful dienophile, tetracyanoethylene \(61-63\), was employed.

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(63) J. Sauer, H. Wiest and A. Mielert, Ber., 97, 3183(1964)

A solution of XVII with one equivalent of tetracyanoethylene in methylene chloride was heated for 30 min., to
give a 91% yield of a 1:1 adduct. The NMR spectrum of the adduct in acetone-$d_6$ (quintet centered at 2.07 ppm is due to the presence of some acetone-$d_5$) is shown in Figure 2. Tetracyanoethylene reacts with conjugated dienes to give Diels-Alder addition. A 1,2-cycloaddition of tetracyano-

(64) D. N. Dhar, Chem. Rev., 67, 614(1967)

ethylene with a 1,3-diene system occurs when Diels-Alder addition is impossible, such as with 1-methyl-3-methylene-cyclobutene. Other 1,2-cycloadditions of tetracyanoethylene are found only with electron rich olefins (vinyl ethers).

(65) J. K. Williams, J. Amer. Chem. Soc., 81, 4013(1959)


While the intermediate triene (XVIII) is far from being an electron rich olefin, it is therefore capable of only one 1,4-addition (to the "cisoid" diene system) since the structural features of XVIII prevent a 1,6-addition as well as the other possible 1,4-addition (to the permanent "transoid" diene system). Therefore the adduct is depicted as:
Figure 2. Nmr Spectrum of 1:1 Adduct of 6-Dichloromethyl-6-methyl-1-methylene-3-phenyl-2,4-cyclohexadiene (XVIII) with Tetracyanoethylene
Consideration of the three possible (a, b or c) 1,2-cycloadditions of tetracyanoethylene to XVIII showed these can all be eliminated as structures for the adduct.

Addition of tetracyanoethylene to the exocyclic double bond as in (a) or to the trisubstituted internal double bond as in (b) would not give the proper vinyl proton integrations. An nmr spectrum of the adduct showed one vinyl proton (besides the proton for the dichloromethyl group) in the 6-7 ppm region and two methylene type protons at 4.18 and 5.00 ppm. Addition to the disubstituted internal double bond as in (c) would give rise to two vicinal methine protons which would split each other by at least 3 Hz. Since the two

methine protons in the nmr spectrum of the adduct (Figure 2) are not split, these protons are assigned as bridge head hydrogens in a Diels-Alder addition product and the question of 1,2-cycloaddition of tetracyanoethylene to XVIII can be dropped. All other resonances in the spectrum of the adduct are in accord with the assigned structure.

The 1,5-migration of the 4-trichloromethyl group has been shown to be a radical process. The observed 1,3-migration of the 4-dichloromethyl group was accelerated by use of heat and light. One inhibited rearrangement of XVIII using iodine proved to be very efficient. None of the rearrangement product (XIX) was formed. These data are consistent with a radical mechanism for the 1,3-migration of the 4-dichloromethyl group of XVIII.

The 1,3-migration was also observed in 4-dichloromethyl-3,4-dimethyl-1-keto-1,4-dihydonaphthalene (IIt) (a benzo analog of IIb). Thus IIt was reacted with excess phenylmagnesium bromide to give 57% of unchanged IIt and the tertiary alcohol. The alcohol was not isolated but heated

IIIh

directly at 120° for 5 min. to give the rearrangement product, 3-(β,β-dichloroethyl)-4-methyl-1-phenynaphthalene
(characterized by nmr and by mass spectrometry), in a 84% yield.

Once the previously unknown 1,3-migration of the 4-dichloromethyl group had been effected and the presence of the intermediate triene (XVIII) established by trapping experiments, the question of a stereospecific migration of the dichloromethyl group was raised. The dienone has an asymmetric carbon atom and in principle could be resolved. If a stereospecific 1,3-migration of the 4-dichloromethyl group to a 3-ethyl group in a resolved dienone occurred, the rearrangement product (possessing a different asymmetric center) would also be optically active.

The dienone chosen for study was the unknown 4-dichloromethyl-2,4-dimethyl-5-ethyl-2,5-cyclohexadienone (IIe). The reasons for this choice were: (1) IIe has an ethyl group positioned such that a 1,3-migration of the 4-dichloromethyl group could occur and (2) the presence of a 2-methyl group favors anti oxime formation during resolution (use of an oxime transfer process) and thereby might facilitate the resolution process, which previously gave much difficulty.
A five step synthesis for the preparation of IIe is depicted below:

\[
\begin{align*}
\text{IIe} & \quad \xrightarrow{\text{Acetylation}} \quad \text{XXV} & \quad \xrightarrow{\text{Nitration}} \quad \text{XXIV}
\end{align*}
\]

Acetylation of m-xylene with acetyl chloride and anhydrous ferric chloride at 0-5° afforded 2,4-dimethylacetophenone in 68-77% yield. Nitration with 90% nitric acid at -10° to -5° gave a quantitative yield of mono-nitratated product. The product was primarily the 5-nitro isomer (XXIII) but some of the 3-nitro isomer was also present. Due to the very similar properties of these two isomers, complete separation was not successful and the mixture was used as such for the next steps.
The use of hydrazine to reduce aryl nitro compounds to the corresponding amino compound has been reported. \(^{70}\) Therefore the reduction of XXIII (containing some of the 3-nitro isomer) by heating in ethylene glycol with four or more equivalents of hydrazine hydrate until nitrogen evolution ceased, followed by treatment of the mixture with potassium hydroxide (Wolff-Kishner reaction)\(^{71}\) gave a 71\% yield of

\(\text{(70) R. Mohlau, H. Beyschlag and H. Kohres, } \textit{Ber.}, \textit{45}, 133(1912)\)

2,4-dimethyl-5-ethylaniline (XXIV), containing some of the isomeric 2,6-dimethyl-3-ethylaniline. The isomeric impurity was not evident in an nmr spectrum of the mixture, since both compounds seem to have identical resonances for their respective protons.

Reduction of the mixture of XXIII and its 3-nitro isomer under conditions which normally convert substituted \(m\)-nitroacetophenones into the corresponding \(m\)-ethylanilines was not successful. The use of iron and acetic acid\(^{72}\) the Clemmensen reduction\(^{73}\) and catalytic hydrogenation with Raney nick-

\(\text{(72) F. Mayer and F. A. English, } \textit{Ann.}, \textit{417}, 82(1918)\)

\(\text{(73) E. L. Martin, } \textit{Org. Reactions}, \textit{1}, 155(1942)\)

el\(^{74}\), platinum and palladium\(^{75}\) all gave partial reduction or tar formation.

\(\text{(74) } \textit{\ldots}\)

\(\text{(75) } \textit{\ldots}\)
Diazotization of a mixture of XXIV and its isomeric aniline, followed by hydrolysis gave a mixture of the expected 2,4-dimethyl-5-ethylphenol (XXV) and some of the isomeric 2,6-dimethyl-3-ethylphenol in a 98% yield. An nmr spectrum of the product mixture clearly showed the presence of both isomers (two different ethyl groups are observed). Since only XXV possesses a 4-methyl group, the subsequent dienone formation reaction could only occur with XXV and not with the isomeric 2,6-dimethyl-3-ethylphenol. Therefore the presence of the latter fortunately did not complicate the problem of preparation of IIE. Attempts were made however at separation using fractional extraction with various concentrations of base. However separation was unsuccessful since both of the isomers were extracted equally.

Finally reaction of XXV (accompanied by its isomer) with aqueous base and chloroform gave 3-6% yields of IIE. An nmr spectrum of IIE is shown in Figure 3. All attempts to raise the yield of dienone were unsuccessful (variation of reaction conditions and concentrations).

A reaction of the mixture of XXV and 2,6-dimethyl-3-ethylphenol with carbon tetrachloride and aluminum chloride in carbon disulfide at room temperature gave the expected...
Figure 3. Nmr Spectrum of 4-Dichloromethyl-2,4-dimethyl-5-ethyl-2,5-cyclohexadienone (IIe)
dienone (Ie) (15%), identical in all respects to material prepared earlier, and further supports the structure

![Structure of Ie]

assigned to XXV in the isomeric mixture.

Resolution of Ile was attempted by the method described. Oxime transfer using the optically active oxime, (+)-\( \alpha \)-((isopropylidencaminoxy)propionic acid$^{37}$, gave an 89% yield of (+)- and (-)-\( \alpha \)-((4-dichloromethyl-2,4-dimethyl-5-ethyl-2,5-cyclohexadienylideneaminoxy)propionic acid (XXVI)

![Structure of Ile and XXVI]

as an acidic oil [\( \alpha \)]$_D$ = -50° (c 0.07, methanol). Attempts at crystallization of XXVI from pentane, hexane, ethanol, ethanol-water, methanol, ethyl acetate, benzene and carbon tetrachloride were unsuccessful. Reaction of XXVI with amines, such as pyrrolidine, piperidine, ephedrine, cinchonine and dehydroabietylamine$^{76}$, also gave oils. No crystalline salt was found after repeated attempts at crystallization from the usual solvents. Unchanged XXVI
could be quantitatively recovered from these oily salts, such as the salt with cinchonine.

The structure of XXVI was confirmed by conversion to its liquid methyl ester with diazomethane in 84% yield. An nmr spectrum of methyl (4)- and (5)-α-(4-dichloromethyl-2,4-dimethyl-5-ethyl-2,5-cyclohexadienyldeneaminoxy)propionate (XXVII), \([\alpha]_D^{22} = -38.9^\circ \) (\(c \approx 0.58\), methanol), is shown in Figure 4 and is consistent with the structure assigned for XXVII and thus for XXVI also.

\[
\begin{align*}
\text{XXVII} & \quad \begin{array}{c}
\text{CH}_3 \\
\text{CHCl}_2 \\
\text{C}_2\text{H}_5 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{N} \\
\text{O} \\
\text{CHCO}_2\text{CH}_3
\end{array} \\
\end{align*}
\]

Since both XXVI and XXVII retain optical activity, resolution of IIe is still possible, but only if crystallization occurs. To date no crystals of either diastereomer have been observed in all attempts examined.

The poor yields of IIe and other dichloromethyl substituted dienones IIa - IID hamper large scale production of these dienones. A recent report of preparation of
Figure 4. NMR Spectrum of Methyl (†)- and (‡)-α-(4-Dichloromethyl-2,4-dimethyl-2,5-cyclohexadienyldeneaminooxy)propionate (XXVII)
dichloromethyl substituted dienones from the corresponding trichloromethyl substituted dienone by treatment with triphenyl- and trialkylphosphines could be a better synthetic route to IIe. The trichloromethyl substituted dienones are always prepared in greater yields by the Zincke-Suhl reaction on the appropriate substituted phenol. An experiment where Ib was treated with tri-n-butylphosphine in benzene at reflux for 6 hr. gave one part of unreacted Ib and two parts of the corresponding dichloromethyl substituted dienone (IIb). Therefore in the future, it appears to be advantageous to convert the appropriate phenol to the trichloromethyl substituted dienone followed by reaction with a trialkylphosphine to produce the corresponding dichloromethyl substituted dienone on a large scale.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CCl}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CHCl}_2 & \quad \text{CH}_3 \\
\text{Ib} & \quad \rightarrow & \quad \text{IIb}
\end{align*}
\]
INTRODUCTION (section B)

The methods for synthesis of nuclear fluorinated aryl amines and their derivatives usually involve introduction of the fluorine atoms before the other substituents, such as the amino group. The syntheses of the three fluoroanilines involve conversion of the corresponding nitroanilines into the fluoronitrobenzene followed by reduction to the appropriate fluoroaniline. While the latter process proceeds without complication, the former process (Balz-Schiemann reaction)\(^{79}\) is troublesome, difficult to control and results in very poor yields. The cause of the difficulty rests with the presence of the nitro group. If a means of preparation of nuclear fluorinated amines could be achieved by introduction of fluorine into preformed aryl amines using a halogen exchange method, the difficulties in the above route would be circumvented.

Exchange methods employing anhydrous alkali metal fluorides with or without solvents to effect nucleophilic substitution are receiving wider interest. The only requirement for nucleophilic substitution is a suitably activated aromatic nucleus. The free amino group in halogenated aryl amines would deactivate the aromatic ring toward nucleophilic
substitution. Thus in order to prepare nuclear fluorinated aryl amines by halogen exchange, the amino group must be masked. This can best be accomplished through protonation or conversion to the corresponding quaternary ammonium salt, which in effect masks the amino group and further activates


the nucleus toward attack by a nucleophile. After substitution by fluorine, the fluorinated aryl amine can be isolated by suitable procedures.

The problem therefore involved preparation of certain substituted anilines and N,N-dimethylanilines, followed by fluorination of their protonated or quaternized counterparts. The end result would be preparation of fluorinated aryl amines by an improved synthetic route.
The Balz-Schiemann reaction \(^{81}\) (preparation of aryl fluorides by diazotization of the corresponding aryl amines in fluoroboric acid) has classically served as an excellent method for limited introduction of fluorine on the aromatic ring. The reaction can be generally applied for preparation of mono-, di- and trifluorobenzenes and benzene derivatives, usually in very good yields. When the presence of nitro groups ortho and/or para to the diazotizable amino group causes poor yields in the Balz-Schiemann reaction, the introduction of fluorine can best be facilitated by taking advantage of the activating effect of ortho and/or para nitro groups on aryl halides and performing a nucleophilic displacement of the halide group with fluoride ion. Thus the Balz-Schiemann reaction of 2,4-dinitroaniline \(^{82}\) gives poor yields of 2,4-dinitrofluorobenzene, whereas reaction \(^{83}\) of


\[\text{(83) G. C. Finger and J. L. Finnerty, } \textit{Biochem. Preparations}, \textit{3}, 120(1953)}\]

2,4-dinitrochlorobenzene with potassium fluoride gives
respectable yields of the same aryl fluoride. The solvents employed were polar, aprotic media such as diethylene glycol dimethyl ether, nitrobenzene, dimethylformamide, N-methyl-2-pyrrolidone and dimethyl sulfoxide. Mono-, di- and trinitrofluorobenzenes have been prepared in this manner.\(^{84}\)


The nucleophilic reaction of fluoride ion with mixed nitro and halogen substituted aromatics works best when these groups are numerous. Thus reaction of potassium fluoride with mono-, di- and trihalobenzenes gave unchanged starting material, but sym-tetrahalobenzene\(^{85}\) through hexahalobenzene\(^{86}\) readily gave fluorination. Similarly penta-

\[\text{(85) Imperial Chemical Industries, Ltd., Brit. 989, 504 (1965); Chem. Abstr. 63: 4205}\]


chloronitrobenzene and 1,4-dinitrotetrachlorobenzene gave fluorinated products but with loss\(^{84}\) of the nitro group as well as loss of the chloro group. The reaction has been shown to proceed\(^87\) by nucleophilic displacement of a group

\[\text{(87) J. T. Maynard, ibid., 28, 112 (1963)}\]

at a site ortho and/or para to the site of attack. Results show that the nitro group is more activating\(^{87,88}\) toward
nucleophilic attack than the chloro or bromo group, as would be expected from electronic considerations. Activation similar to that of the nitro group has been observed for carboxyl, sulfonyl, trifluoromethyl, and the cyano groups. Similar activation is also found when these groups are substituted on heterocycles such as pyridine or quinoline.

A logical extension of the substituent variation study should be consideration of the use of the ammonium ion group or the quaternary ammonium ion group. The substituents mentioned above are neutral moieties, while the ammonium ion group is a charged species, better lending its compatibility with an ionic reaction system (attack by fluoride ion) in a polar solvent, and more importantly it is stronger than the trifluoromethyl group and as powerful as the nitro group in
The ammonium ion group withdraws electrons inductively only, since resonance withdrawal is impossible. The order of these groups by electron withdrawal is that established on the basis of a Hammett treatment of nucleophilic attack directly on the benzene ring.
DISCUSSION OF RESULTS (section B)

Therefore in order to test this ability of the ammonium ion group or the quaternary ammonium ion group on an aromatic ring to enhance nucleophilic attack by fluoride ion, experiments were designed to prepare and subsequently transform a number of ortho and/or para substituted aryl amines into their analogous protonated and quaternized salts. When this was accomplished, the basic problem of nucleophilic fluorination of such salts by fluoride ion would follow.

The net result of such a study would be introduction of fluorine on the ring and expulsion of a group (chloro, bromo or nitro) from the ring.

\[ R_4N^+ \cdot + \text{KF} \rightarrow R_4N^+ \cdot + \text{KF} \]

\[ X = \text{ortho or para Cl, Br, NO}_2 \]

\[ R = \text{H, CH}_3 \]

Readily available aryl amines were considered for study. These included the various ortho and/or para bromo- and nitro-substituted anilines and \( N,N \)-dimethylanilines.

The real problem however soon became apparent, namely preparation and maintainance of the ammonium ion group on benzene rings containing other deactivating groups. Thus
2,4-dinitroaniline and 2,4,6-tribromoaniline are readily soluble in liquid anhydrous hydrogen fluoride, inferring protonation to the expected anilinium fluorides (since the corresponding 2,4-dinitrohalobenzene and tetrahalobenzenes all are not soluble in the same medium). However upon removal of the hydrogen fluoride, the free nitrogen base was recovered unchanged. No salt was found.

The use of an acid medium, such as KF • x HF, throughout the fluorination step should maintain some degree of protonation and thereby allow nucleophilic attack. The hydrogen fluoride adducts of potassium fluoride are known (where x = 1 to 5). Two of these, where x is approximately 2 and 5, were prepared and used both as a fluorinating agent and solvent.

Preliminary runs were made on a nucleophilically labile compound. Thus reactions of KF • 1.9 HF and KF • 5.1 HF with 2,4-dinitrochlorobenzene at 230° for 30 minutes gave unreacted starting material. No chloride exchange occurred as evidenced by a negative chloride ion test. The reason for the lack of exchange in this system, as opposed to its reported facile exchange in polar solvents, was insolvability. At no time during the attempted fluorination does a

(97) W. Klatt, Z.anorg.allgern.Chem., 222, 225(1935); ibid., 289(1935)

homogeneous mixture occur.

While 2,4-dinitroaniline and 2,4,6-tribromoaniline are soluble in the KF \( \cdot \) x HF media, no fluorination occurred even at 280°. Unchanged material was recovered in all runs. Whereas the fluorinating ability of the KF \( \cdot \) x HF system could be the subject of conjecture here, the problem of paramount interest is the extent of protonation. Solubility of these aryl amines suggests protonation but solubility in anhydrous hydrogen fluoride and KF \( \cdot \) x HF systems could be accompanied by formation of chains through hydrogen-fluorine bonding and thereby never give rise to discretely protonated amines. Without formation of protonated aryl amines, the basis for nucleophilic attack is removed and fluorination becomes impossible.

The logical extension of the problem was to quaternize the appropriately substituted aryl amine and thereby insure the existence of a positively charged nitrogen atom attached directly to the aromatic ring.

Logical quaternary ammonium compounds for consideration would be a series of aryltrimethylammonium halide salts. The halide anion of such salts, during attack by fluoride ion, would probably be exchanged along with groups on the aromatic ring, so to minimize complications only aryltrimethylammonium fluorides were considered.

Few quaternary ammonium fluorides are known. Tetra-
methylammonium fluoride was reported to be prepared from
the corresponding iodide by treatment with hydrogen fluoride. Use of excess reagent gave tetramethylammonium bifluoride. Reports of preparation of aryltrimethylammonium fluorides or bifluorides are unknown. Synthesis of three aryltrimethylammonium bifluorides was achieved via the following routes.

Direct bromination of N,N-dimethylaniline gave a 50% yield of purified N,N-dimethyl-4-bromoaniline. Quaternization of the latter with methyl iodide gave a 96% yield of the corresponding iodide salt and treatment with excess anhydrous hydrogen fluoride gave an 83% yield of the desired 4-bromophenyltrimethylammonium bifluoride (I).

Similarly N,N-dimethylaniline when treated with two equivalents of bromine followed by addition of sodium acetate gave a 45% yield of N,N-dimethyl-2,4-dibromoaniline. An alternate approach through acid hydrolysis of 2,4-dibromoacetanilide followed by N-methylation of the 2,4-dibromoaniline with dimethyl sulfate was more attractive on a yield basis but the desired N,N-dimethyl-2,4-dibromoaniline was always contaminated with mono-methylated material. Quatern-
Br  
NaOAc  
CH₃I  

\[
\begin{align*}
\text{Azation (97% yield) of N,N-dimethyl-2,4-dibromoaniline with methyl iodide followed by treatment with hydrogen fluoride gave the desired 2,4-dibromophenyltrimethylammonium bisfluoride (II).} \\
\text{Finally bromination of aniline gave a 91% yield of 2,4,6-tribromoaniline. N-methylation using paraformaldehyde and acid gave an 89% yield of the tertiary amine. Quaternization with methyl iodide was accompanied by thermal}
\end{align*}
\]
reversibility, so conversions were low, usually in the area of 10%. Quaternization could also be achieved using dimethyl sulfate, but this quaternary ammonium salt was not studied further. Treatment of the quaternary ammonium iodide with anhydrous hydrogen fluoride gave 91% of 2,4,6-tribromophenyltrimethylammonium bifluoride (III).

The compounds I, II and III are completely water soluble, giving aqueous solutions which show a positive fluoride ion test and a negative iodide ion test. All are ether insoluble and titratable with two equivalents of base (indicative of the presence of the bifluoride ion). One equivalent of base neutralizes the bifluoride ion and the second reacts with the quaternary ammonium fluoride to form the quaternary ammonium hydroxide. Both I and III are crystalline salts, while II is a glass. Only I is not hygroscopic.

Attempted fluorination of I in refluxing dimethylformamide (DMF) with potassium fluoride gave a nearly quantitative yield of N,N-dimethyl-4-bromoaniline, presumably accompanied by liberation of methyl fluoride. Melting of I (131°) also proceeds with decomposition to the same tertiary amine.

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{(CH}_3\text{)}_3\text{NHF}_2^- & \quad \text{(CH}_3\text{)}_2\text{N} \\
\text{DMF / 155°} & \quad + \text{CH}_3\text{F} + \text{KHF}_2
\end{align*}
\]
Use of a lower boiling polar solvent, such as acetonitrile (b.p. 81-2°) gave unchanged starting material. Apparently the thermal decomposition point, near or slightly above the m.p. of the salt, determines the upper limit of an exchange reaction. However attempted exchange was not successful in the allowed temperature range. Either no reaction or thermal decomposition occurred, depending on the temperature.

Thermal decomposition of aryltrimethylammonium halides, or a retro-quaternization process, is a known phenomenon. Hofmann first noted that phenyltrimethylammonium iodide was thermally transformed into N,N-dimethylaniline and methyl iodide at 150°. Later reports on the retro-quaternization of this salt and the corresponding bromide supported the generality of the phenomenon. While the thermal decomposition is a reversible dealkylation process, the recent report by Walsh and Long shows that a photochemical retro-quaternization in alcohol solvents is also possible. In contrast to the thermal process, the photo-
chemical process is accompanied by irreversible loss of the aryl group and formation of the corresponding aryl hydrocarbon and trimethylamine.

Since III has a m.p. of 58°-62° (with retro-quaternization) and even undergoes retro-quaternization on standing at room temperature for 1-2 weeks, the fluoride exchange reaction with III became impractical. For similar reasons, II was also not subjected to a fluorination reaction.

Thus the study of the effect of an ammonium ion group on an aryl halide subjected to attack by fluoride ion was inconclusive due to the inability of maintaining the desired group. Quaternization of the tertiary aryl amine readily gave the quaternary ammonium salt, which also was labile to retro-quaternization, and thereby gave the same inconclusive results. No further extentions of this system were considered in the light of the observed complications.
Experimental

Generalizations

1. Refractive indices were measured on an Abbe Refractometer Model A marketed by Carl Zeiss, Oberkochen, Wuerttemberg in West Germany. The apparatus was equipped with three measuring prisms for measurement of low ($n_D 1.17-1.56$), medium ($n_D 1.30-1.70$) and high ($n_D 1.45-1.85$) refractive indices.

2. Nuclear magnetic resonance (nmr) spectra were determined at 60 MHz. with a Varian Associates high resolution spectrometer, Palo Alto, California. Carbon tetrachloride solutions were employed, except where otherwise noted and the nmr spectra were measured relative to tetramethylsilane as an internal standard. The resonances reported are in $\delta$ (ppm) units and were exactly measured using the "side banding" technique. Abbreviations used are: singlet (s), doublet (d), triplet (t), quartet (q), and broad (b).

3. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark and the Alfred Bernhardt Microanalytical Laboratory at the Max-Planck Institute, Mulheim (Ruhr), West Germany.

4. Boiling points and melting points are all
uncorrected. The same thermometer was used for all reported melting points.

5. The infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The absorption bands are described as: strong (s), medium (m) and weak (w).

6. A Varian Aerograph Model A90-P3 gas chromatograph was used for gas-liquid chromatographic analyses. The column employed for all analyses was a 15 ft., 1/4 in., 20% FS-1265 fluorosilicone oil (10,000 cs., supplied by the Dow Corning Corp., Midland, Michigan) on 45-60 mesh Chromasorb P. The carrier gas was helium at 40 ml./min.

7. The phrase "worked up in the usual manner" used throughout this section refers, with minor variations, to the handling of organic solutions in the following manner. The organic solution was washed successively with water and saturated sodium chloride solution, dried by filtering through a bed of anhydrous magnesium sulfate and the solvent removed in vacuo.

8. Optical rotations were determined with a J. and J. Fric polarimeter which could be read directly to hundredths of a degree.

9. Thin layer chromatography (t.l.c.) was done on 20 cm. plates of alumina or silica gel developed in hexane or hexane-ether.
Preparation of 3,4-Dimethyl-4-trichloromethyl-2,5-cyclohexadienone (Ib)

A preparation of the above dienone followed that already reported. To a slurry of 30.5 g. (0.23 mole) of aluminum chloride in 100 ml. of carbon disulfide at room temperature was added a solution of 12.6 g. (0.103 mole) of 3,4-dimethylphenol in 100 ml. of carbon disulfide over a period of 30 minutes. Once the chloroaluminum salt of the 3,4-dimethylphenol had been formed, the solution was cooled to 0-5° and 100 ml. of carbon tetrachloride was added over a period of 20 minutes. The color change on addition was light green to red to deep red-brown. After complete addition, the mixture was stirred for 2 hr. and worked up as usual. Acidification of the basic wash gave 4.9 g. (39%) of recovered 3,4-dimethylphenol. The crude product was rectified to give 11.2 g. of a pale yellow liquid, b.p. 122-90/1 mm., which solidified on standing, and 2.7 g. of a black residue. Recrystallization gave 9.0 g. (60.5%) of 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadienone, m.p. 59-60° (from hexane) [Lit. : m.p. 60-61°].

Other runs where carbon disulfide was not employed gave lower yields of dienone and more resinification. The best yield of purified dienone based on unrecovered starting material was about 60%.

Preparation of Arsenic Trifluoride

The preparation of arsenic trifluoride from calcium fluoride, arsenuous oxide (As₂O₃) and sulfuric acid was con-
ducted as reported in literature. Redistillation of crude arsenic trifluoride, dried over anhydrous potassium fluoride, gave a pure water-white product, b.p. 57-9°C [Lit.: b.p. 58°C], in 58% yield. Prolonged storage was best effected in polyethylene bottles.

Fluorination of 3,4-Dimethyl-4-trichloromethyl-2,5-cyclohexadienone (Ib)

A. Use of Arsenic Trifluoride

A 250 ml. three-necked flask, equipped with a stirrer, dropping funnel and water-cooled condenser, was charged with 12.5 g. (0.095 mole) of arsenic fluoride and 3 drops of antimony pentachloride. To this solution at room temperature was added a solution of 6.15 g. (0.026 mole) of 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadienone (Ib) in 30 ml. of methylene chloride. An exothermic reaction occurred on mixing. After refluxing for 24 hr., the reaction mixture was cooled and poured into 200 ml. of 5% hydrochloric acid at 35°C. After shaking, the organic phase was washed with 1% sodium hydroxide solution, water and dried over anhydrous magnesium sulfate. After removal of solvent, 6.10 g. (99%) of recovered material was obtained. No detectable amount of fluorination had occurred.

B. Use of Antimony Trifluoride

A mixture of antimony trifluoride and 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadienone (Ib) in a 4:1 weight ratio was ground to a fine powdery consistency and heated in a glass flask with or without any antimony (V) salt and
worked up as in A above, except that 1:1 ether-benzene was used to extract the organic material. The results of a number of runs are found in Table 6. The runs involving no antimony (V) salts gave recovered dienone, whereas use of antimony (V) salts in catalytic and greater amounts gave a vigorous reaction (charring) plus one isolable organic product, 4-chloro-o-xylene. It was surprising that the run with SbF$_5$ alone also gave this material since the sole source of chlorine was the trichloromethyl group. The 4-chloro-o-xylene formed amounted to about 1.0 g. for each run where it was detected. Characterization rested on b.p. 186-7$^\circ$ (micro), $n_D^{25} = 1.5164$, $d^{25} = 1.08$ [Lit. : b.p. 191.5$^\circ$, $d^{15} = 1.07$], infrared and nmr spectra were consistent with the structure. The latter showed a 6 proton singlet at 2.22 ppm (benzylic) and a 3 proton multiplet in the range 6.95-7.05 ppm (aromatic).

No evidence of a fluorinated dienone in any run with the antimony fluorides was observed.

C. Use of Potassium Fluoride

A 1000 ml. three-necked flask equipped with a stirrer, water-cooled condenser and thermometer was charged with 11.4 g. (0.048 mole) of 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadienone (Ib), 30.5 g. (0.53 mole) of anhydrous potassium fluoride and 500 ml. of dry dimethylformamide. The mixture
was heated to 150-155° for 90 min, cooled, poured into 1000 ml of water and the organic material was taken up in ether. After removal of solvent, only unreacted dienone was recovered. An identical run at 150-155° for 24 hr, gave unreacted dienone plus some tars. A third run for 7 days gave more tar and no evidence of recovered dienone nor a fluorinated dienone.

A reaction run in tetramethylene sulfone (Sulfolane A from Shell Chemical Company) at 150° for 15 hr, gave recovered dienone plus a trace of tars. No evidence of fluorination could be found.

**Attempted Preparation of 3,4-Dimethyl-4-trichloromethyl-2,5-cyclohexadienone Ethylene-ketal**

A 500 ml. flask was equipped with a phase separating head (Dean-Stark trap) topped with a water-cooled condenser. To the flask was added 20.0 g. (0.083 mole) of 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadienone (Ib), 0.1 g. of p-toluenesulfonic acid monohydrate, 5.5 g. (0.089 mole) of ethylene glycol and 250 ml. of benzene. The solution was refluxed for 24 hr. and the water removed by azeotropic distillation. An aliquot was removed from the reaction flask and analyzed by infrared spectroscopy to show some carbonyl containing dienone still present by the strong band at 5.99μ, 1669 cm⁻¹. Therefore an additional 6.0 g. ethylene glycol and 0.1 g. of p-toluenesulfonic acid monohydrate was refluxed for 48 hr., whereupon an infrared spectrum showed a very weak carbonyl band at 6.00μ, 1667
To the reaction mixture was added 2 ml. of triethyl amine. After filtration, the solvents were removed in vacuo to give an oil which began to crystallize on standing. Recrystallization from benzene gave white crystals, m.p. 122.0-122.5°, amounting to 4.8 g. A second crop amounted to 5.6 g. and was identical to the former material and both contained no carbonyl or hydroxyl bands. From the mother liquor, after removal of solvent, was recovered 10 g. of an oil, which also crystallized upon standing for two weeks. Attempted hydrolysis in dilute aqueous hydrochloric acid did not give starting diene. An nmr spectrum of the material showed an absence of the resonance for the aliphatic 4-methyl group and the remainder of the spectrum was consistent with the structure of the unknown 1,2-bis(3-(β,β,β-trichloroethyl)-4-methylphenoxy)ethane. The nmr data are shown below.

Calculated for C_{20}H_{20}Cl_{6}O_{2}: 47.6 C, 4.0 H, 42.1 Cl;

Found: 47.8 C, 4.1 H, 41.7 Cl

**Reaction of 3,4-Dimethylphenol with CFCl_3/AlCl_3**

The same procedure employed for preparation of 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadienone (Ib) was used here, except that CFCl_3 (from the Matheson Company, Inc.) was substituted for carbon tetrachloride. The reaction
temperature, time and workup were identical except that some benzene was added during workup to aid in the washing procedure. The results were a 37.7% recovery of unreacted 3,4-dimethylphenol and 4.5 g. of a yellow oil, b.p. 122-130°/2 mm., along with 4.8 g. of residue in the distillation flask. Recrystallization from benzene gave 3.3 g. of white Ib, m.p. (and mixed m.p. with authentic material) 60-61°. The infrared spectra were identical. No other dienone could be detected in the crude product mixture or in the distillation residue. Variation of the amount of aluminum chloride used from a catalytic amount (i.e., excess over that required to form the chloroaluminum salt of the phenol) to a 100% excess of theory did not alter the results.

Mixing CFCl₃ with aluminum chloride gave an immediate exothermic reaction and resulted in generation of carbon tetrachloride and fluoroaluminum salts. This rapid disproportionation of CFCl₃, generating carbon tetrachloride, led solely to formation of Ib.

Recation of 3,4-Dimethylphenol with CF₂Cl₂/AlCl₃

A 500 ml. three-necked flask was equipped with a stirrer, dry ice-cooled condenser and dropping funnel. To a slurry of 36.0 g. (0.27 mole) of aluminum chloride and 100 ml. of carbon disulfide in the flask was added a solution of 14.4 g. (0.12 mole) of 3,4-dimethylphenol in 150 ml. of carbon disulfide over a period of 20 min. After complete formation of the chloroaluminum salt of 3,4-dimethylphenol,
the solution was cooled to 0-5° and the dropping funnel was
replaced with a gas inlet tube. A dry ice trap containing
about 90 ml. of CF₂Cl₂ (from the Matheson Co., Inc.) at dry
ice temperature was warmed gradually and the CF₂Cl₂ was
transferred to the flask through the gas inlet tube. The
color change during addition was grey to green to brown. As
more CF₂Cl₂ was added, the temperature of the reaction mix-
ture fell to the b.p. of CF₂Cl₂ (-29°). After complete
addition, the mixture was stirred for 2 hr., warmed to 0°,
whereupon the excess CF₂Cl₂ was vented from the system and
the remainder of the flask contents was poured over crushed
ice. After separation of the organic phase and workup as
usual, 0.3 g. of dark red oil was recovered when the solvent
was removed. An infrared spectrum of this oil corresponded
in all respects to 3,4-dimethyl-4-trichloromethyl-2,5-
cyclohexadienone contaminated with some 3,4-dimethylphenol.
No other dienone could be detected. The basic aqueous
washes yielded 14.2 g. (98%) of recovered 3,4-dimethylphenol
upon acidification.

Another run done at room temperature in a steel bomb
for 19 hr. gave similar results.

Reaction of 3,4-Dimethylphenol with CFG₁₃/AlF₃

Into a 500 ml. three-necked flask equipped with a stir-
rer, dropping funnel and water-cooled condenser was added a
mixture of 200 ml. of dry carbon disulfide, 12.5 g. (0.10
mole) of 3,4-dimethylphenol and 19.2 g. (0.23 mole) of AlF₃.
The mixture was stirred at room temperature for 1 hr. and at reflux for 2 hr. No hydrogen fluoride was liberated and the AlF₃ appeared to be insoluble throughout this time. After addition of 100 ml. of CFCl₃ and refluxing the resulting mixture overnight, the mixture was stirred for 6 days at room temperature. Filtration gave 18.8 g. of recovered AlF₃. Workup of the filtrate gave quantitative recovery of 3,4-dimethylphenol. No dienone was formed.

Reaction of 3,4-Dimethylphenol with CHCl₂F and Aqueous Base

A 300 ml. iron bomb was charged with 10 g. of sodium hydroxide, 100 ml. of water and 12.0 g. (0.10 mole) of 3,4-dimethylphenol. The bomb and its contents were cooled in a dry ice-acetone bath and 30 ml. (at -78°) of CHCl₂F (Freon 21) was transferred to the bomb by standard vacuum transfer techniques. After sealing, the bomb was warmed to ambient temperature and shaken for 16 hr. before venting. The bomb contents were poured into 100 ml. of water and the organic phase was taken up in ether. The aqueous phase plus basic washes of the ether phase were combined and acidified to give 7.6 g. (63.3%) of unchanged 3,4-dimethylphenol. The ether phase was worked up as usual to give about 3 g. of a brown semi-solid. Attempts at recrystallization from the usual solvents gave oils. A small amount (0.5 g.) of crystals, m.p. 87-89°, was obtained from chloroform-ethanol. An infrared spectrum of this solid showed no carbonyl or hydroxy bonds in the usual regions. An nmr showed a six
proton singlet at 2.21 ppm (benzylic), one proton singlet at 6.28 ppm and three protons in the region 6.75-7.0 ppm (aromatic). The structure assigned was 4-dichloromethoxy-1,2-dimethylbenzene. Since a sodium fusion gave a positive test for chloride ion and a dubious weakly positive test for fluoride ion, the dihalomethoxy group was assumed to be a dichloromethoxy group because the presence of fluorine would definitely have created a marked splitting of the geminal proton resonance in the nmr and this was not observed.

Further attempts at recrystallization of the oil and/or the above 4-dichloromethoxy-1,2-dimethylbenzene gave rise to formation of 3,4-dimethylphenol, especially when hydroxylic solvents were employed. This was consistent with the structure assigned. No carbonyl containing products could be isolated and at no time was there any evidence of dienone formation.

**Preparation of Phenylmercuric Bromide**

A solution of 1.20 moles of phenylmagnesium bromide was generated in a 3 l. three-necked flask from 29.2 g. of magnesium turnings and 190 g. of bromobenzene in 1 l. of ether. To the Grignard solution was portionwise added 381 g. (1.06 mole) of mercuric bromide through an 8" piece of Gooch tubing connected to one of the necks of the reaction flask. The exothermic addition was so vigorous that external cooling by means of an ice bath was necessary. After complete addition, the grey-white slurry was refluxed for 1 hr., cooled
and added with stirring to a mixture of ice and methanol. After filtration, the solid product was slurried with twice its weight of absolute methanol and filtered. The grey-white solid was digested in boiling benzene for 30 min. (to remove any diphenylmercury), filtered and air dried to give 352.5 g. (82.1%) of phenylmercuric bromide.

Preparation of Phenyl(trichloromethyl)mercury

A 2 l. three-necked flask was equipped with a stirrer, dropping funnel and an 8" piece of Gooch tubing connecting one of the necks of the flask to a 125 ml. Erlenmeyer flask filled with 42 g. (0.78 mole) of commercial sodium methoxide. To the flask was added 1000 ml. dry reagent benzene, 120 g. (0.63 mole) of redistilled ethyl trichloroacetate and 66 g. (0.19 mole) of phenylmercuric bromide. The flask mixture was cooled to 0-5° by means of an ice bath and the sodium methoxide was added portionwise over a period of 20 min. The color change during addition was clear white to light green. Vigorous stirring was required for optimum reaction. After complete addition, the slurry was stirred for 1 hr. at 0-5°, then poured into 500 ml. of water and the benzene layer was separated. The aqueous phase was extracted twice with 150 ml. each of benzene and the benzene phases were combined, filtered and worked up as usual. The dry benzene phase was allowed to evaporate to dryness in a well-ventilated hood to give 22.5 g. of crude phenyl(trichloromethyl)mercury. The crude product was washed with hexane and 20 ml. of cold
absolute methanol to give 16.8 g. (23%) of purified material, m.p. 111-112° [Lit. 106: m.p. 114-115°]. Care must be exercised in taking the melting point since the product decomposed thermally. The melting point apparatus was pre-


heated to about 100° and then the sample was introduced for the melting point determination. In this way, a reproducible melting point could be achieved.

The yields of phenyl(trichloromethyl)mercury in a number of runs never exceeded 37%. Pure material was always used as soon as possible after preparation. Storage was in a darkened storage compartment.

Reaction of 3,4-Dimethylphenol with Phenyl(trichloromethyl)-mercury

The iodide ion modification 48 of dichloromethylene generation from phenyl(trichloromethyl)mercury was employed. A 250 ml. three-necked flask was equipped with a stirrer, water-cooled condenser and a thermometer. To the flask was added 5.6 g. (0.038 mole) of sodium iodide, 7.0 g. (0.018 mole) of phenyl(trichloromethyl)mercury, 12.0 g. (0.099 mole) of 3,4-dimethylphenol and 100 ml. of dry redistilled 1,2-dimethoxyethane. An immediate color change from grey-white to light green took place upon mixing. No exothermic reaction was noted so the mixture was stirred for 48 hr. at ambient temperature, filtered and the filtrate concentrated
on a rotary evaporator to give a viscous yellow oil. After treatment of the oil with water, the organic material was taken up with 1:1 ether-hexane. The solid collected was not soluble in ether and therefore was not phenyl(trichloromethyl)mercury. The m.p. was greater than 200° and strong heating liberated mercury. The solid was presumably phenyl-mercuric iodide\(^{107}\) \([\text{m.p. } 265^\circ]\). After removal of the solvent from the filtrate on a rotary evaporator, the yellow oil was recrystallized from hexane to give 11.95 g. (99%) of recovered 3,4-dimethylphenol, whose m.p. was not depressed by authentic material.

**Reaction of Sodium 3,4-Dimethylphenoxide with Phenyl(trichloromethyl)mercury**

The reaction of sodium 3,4-dimethylphenoxide with phenyl(trichloromethyl)mercury was conducted in the same fashion as the reaction of 3,4-dimethylphenol with the same reagent, except a reaction time of 66 hr. was utilized. Workup gave a 93% recovery of 3,4-dimethylphenol upon acidification. No evidence of dienone formation was detected by infrared spectral analysis of the reaction products.

**Preparation of Sodium Trichloroacetate**

A sample of trichloroacetic acid was dissolved in a five fold weight of water and titrated with standard sodium
hydroxide solution to the phenolphthalein end point. The water was removed on a rotary evaporator and the sodium trichloroacetate collected was dissolved in a minimal amount of absolute ethanol and reprecipitated by addition of chloroform. The salt was collected by filtration, dried in an Abderhalden drying apparatus (using steam as the source of heat) and stored in well-stoppered bottles under a dry nitrogen atmosphere.

**Preparation of Sodium Chlorodifluoroacetate**

A sample of chlorodifluoroacetic acid was dissolved in a five fold weight of water and titrated with a standard sodium hydroxide solution to the phenolphthalein end point. The water was removed on a rotary evaporator using a temperature no greater than 40° to assist in removal of the water. The sodium chlorodifluoroacetate collected was further dried in vacuo in an Abderhalden drying apparatus (using boiling chloroform as the source of heat). The dry salt, a known compound, was stored under dry nitrogen in well-stoppered bottles.

**Reaction of 3,4-Dimethylphenol with Sodium Trichloroacetate**

A 250 ml. three-necked flask was equipped with a dropping funnel, stirrer and phase separating head (Dean-Stark trap) topped with a water-cooled condenser. To the flask was added 100 ml. of dry 1,2-dimethoxyethane and 13.2 g. (0.11 mole) of 3,4-dimethylphenol and the resulting solution was brought to reflux. A solution of 21.8 g. (0.12 mole) of dry
sodium trichloroacetate in 500 ml. of dry 1,2-dimethoxyethane was added dropwise over a period of 90 min. During addition, solvent was removed gradually via the Dean-Stark trap to maintain the reaction flask half full. After complete addition, the mixture was refluxed for an additional 4 hr., cooled and worked up as usual. After removal of solvent, 2.0 g. of a dark oil, which slowly crystallized, was collected and proved to be solely crude 3,4-dimethylphenol. The aqueous base washes gave 11.0 g. of 3,4-dimethylphenol upon acidification for a total recovery of 98% of starting material. No carbonyl containing material was detected by infrared analysis of the recovered material.

**Reaction of 3,4-Dimethylphenol with Sodium Chlorodifluoroacetate**

A 250 ml. three-necked flask was equipped with a stirrer, dropping funnel and a phase separating head (Dean-Stark trap) fitted with a water-cooled condenser. To the flask was added 100 ml. of dry distilled 1,2-dimethoxyethane and 15.0 g. (0.123 mole) of 3,4-dimethylphenol. The slurry was brought to reflux (85°) and a solution of 22.3 g. (0.146 mole) of sodium chlorodifluoroacetate in 500 ml. of dry 1,2-dimethoxyethane was added dropwise over a period of 1 hr. During addition, the 1,2-dimethoxyethane was partially removed via the Dean-Stark trap so as to maintain the reaction flask half full. After complete addition, the flask contents were refluxed for an additional 64 hrs., cooled, filtered, and worked up as usual. The solvent was removed on a rotary
evaporator to give 2.70 g. of a viscous oil. Recrystallization from hexane gave 1.3 g. of 3,4-dimethylphenol and a thick oil was recovered from the mother liquor. An infrared spectrum of this oil showed it to be crude 3,4-dimethylphenol. No dienone was detected. The above recovered 3,4-dimethylphenol along with that from the basic washes amounted to 14.65 g. or 97.8% recovery of unreacted starting material.

Reaction of Sodium 3,4-Dimethylphenoxide with Sodium Chlorodifluoroacetate

A sample of 3,4-dimethylphenol was added to the theoretical amount of 3 N sodium hydroxide and the water removed from the neutral solution on a rotary evaporator to give the light tan colored solid, sodium 3,4-dimethylphenoxide. The material was not hygroscopic but was stored under dry nitrogen to avoid possible oxidation.

A 500 ml. three-necked flask was equipped with a dropping funnel, stirrer and water-cooled condenser. The apparatus was flushed with dry nitrogen for 30 min. and then to the flask was added 12.0 g. (0.083 mole) of dry sodium 3,4-dimethylphenoxide, 14.0 g. (0.092 mole) of dry sodium chlorodifluoroacetate and 100 ml. of dimethyl sulfoxide (dried and distilled over calcium hydride; b.p. 85°/ 2 mm.). The exit tube from the water-cooled condenser vented in a tube inverted in a reservoir of water (to measure the amount of carbon dioxide liberated). The flask contents were heated gradually with stirring to 140°, whereupon about 2000 ml. of
water insoluble gas was liberated (theory for carbon dioxide was 2060 ml.). The liberated gas smelled strongly of dimethyl sulfide. The temperature was raised to $150^\circ$ and held there for 4 hr. The color change during this period of heating was a clear yellow to milky white emulsion. After cooling, the reaction mixture was added to 250 ml. of water and extracted with 1:1 hexane-ether. The aqueous phase gave a strongly positive test for chloride ion and a negative test for fluoride ion. The organic phase was worked up as usual and the solvent was removed on a rotary evaporator to give 4.70 g. of a pale yellow oil. Repeated crystallization from aqueous ethanol gave white needles m.p. 122.5-123.0$^\circ$. The infrared spectrum showed no hydroxide band, but a carbonyl stretching band at 5.70$\mu$, 1754 cm$^{-1}$ was present. Attempted formation of a 2,4-dinitrophenylhydrazone was unsuccessful. A microanalysis indicated the sample was free of fluorine. Nmr analysis showed the presence of only benzylic and aromatic protons. Since the compound did not analyze for fluorine and a rough molecular weight determination in bromoform gave a value of 309 (nearly three times the expected molecular weight), further elucidation of this material was not pursued.

Another run in 1,2-dimethoxyethane at $85^\circ$ for 4 hr. gave 96.2% of recovered 3,4-dimethylphenol upon workup and acidification. No evidence of dienone formation was observed.
Preparation of 3,3,3-Trifluoropropionic Acid

The conversion of 3,3,3-trifluoropropyl bromide\textsuperscript{108} to

\begin{equation}
\text{(108) Generous gift from the Dow Corning Corp, Midland, Michigan}
\end{equation}

3,3,3-trifluoropropanoic acid via oxidation of the Grignard reagent, followed by chromic acid oxidation of the 3,3,3-trifluoropropanol, was conducted as described.\textsuperscript{109} The 3,3,3-

\begin{equation}
\end{equation}

trifluoropropionic acid was purified as its methyl ester, (XXI), b.p. 94-5\textdegree/740 mm., n\textsubscript{D}^{25\textdegree} = 1.3273.

The overall yield for the two steps was 19\%. The infrared spectrum was consistent with the structure and the nmr showed a sharp singlet (3 protons) at 3.75 ppm and a quartet (2 protons) centered at 2.10 ppm with J\textsubscript{HF} = 11 Hz.

**Attempted Preparation of Methyl 2-Methyl-3,3,3-trifluoropropionate (XXII)**

*As* A 250 ml. three-necked flask was dried at 120\degree and equipped with a stirrer, dropping funnel and water-cooled condenser fitted with a drying tube. A solution of 5.60 g. (0.104 mole) of commercial sodium methoxide in 150 ml. of anhydrous methanol was added to the flask. The solution treated with 14.2 g. (0.100 mole) of methyl 3,3,3-trifluoropropionate, followed by dropwise addition of 23.6 g. (0.166 mole) of methyl iodide. Both additions were conducted
at ambient temperature. After refluxing for 4 hr., an aliquot was removed, poured into 50 ml. of water and the organic phase was taken up in ether. The aqueous phase was basic and contained iodide ion but no fluoride ion. Analysis of the organic phase by v.p.c. showed only the presence of unreacted methyl 3,3,3-trifluoropropionate (XXI). Additional sodium methoxide (8.75 g.) was added to consume the remainder of the methyl iodide under reflux for 26 hr. When a fresh aliquot was quenched, no increase in pH of the aqueous phase of the quenching mixture was observed. Thus all the methyl iodide had reacted.

Then 3.8 g. (0.071 mole) of sodium methoxide was added and the reaction mixture refluxed for 1 hr. before addition of 13.7 g. (0.098 mole) of methyl iodide. Reflux was continued for 1 hr., followed by cooling, addition to 100 ml. of water, extraction with ether and distillation of the ether phase to give recovered methyl 3,3,3-trifluoropropionate.

Another similar run involved treatment of 7.1 g. (0.05 mole) of methyl 3,3,3-trifluoropropionate in 100 ml. of dry ether with an equivalent of trityl sodium in ether. The apparatus was flushed with dry nitrogen throughout the reaction. The red color of the trityl sodium was rapidly dissipated to yellow upon addition, giving evidence for proton transfer. After addition of 21 g. of methyl iodide and refluxing for 3 hr., the mixture was cooled, poured into water and the organic material taken up in ether.
Analysis of the ether phase by v.p.c. again showed unreacted methyl 3,3,3-trifluoropropionate as the sole constituent besides solvent. This result was born out by infrared analysis of the recovered ester. The aqueous phase gave a positive iodide ion test.

**Preparation of 4-Dichloromethyl-4-methyl-2,5-cyclohexadienone (IIa)**

The synthesis of 4-dichloromethyl-4-methyl-2,5-cyclohexadienone from p-cresol, chloroform and 19% sodium hydroxide solution proceeded in an 11.8% yield to give material m.p. 54.5-55.5° [Lit. 3: m.p. 55°].

**Preparation of 4-Dichloromethyl-2,4-dimethyl-2,5-cyclohexadienone (IIb)**

The reaction of 3,4-dimethylphenol, chloroform and 12% sodium hydroxide solution gave a 14.3% yield of product, m.p. 55-6° [Lit. 57: m.p. 55.5-57.5°].

**Preparation of 4-Dichloromethyl-3,4-dimethyl-2,5-cyclohexadienone (IIc)**

The reaction of 3,4-dimethylphenol, chloroform and 15% sodium hydroxide solution gave 14.6% yield of 4-dichloromethyl-3,4-dimethyl-2,5-cyclohexadienone, m.p. 100-101° [Lit. 3: m.p. 102-3°].

**Preparation of 3,4-Dimethyl-1-naphthol**

The four step synthesis after the method of Kruber and Schade was employed. Bromination of 2-methylnaphthalene in carbon tetrachloride at 3-5° gave a 97.8% yield of distilled 1-bromo-2-methylnaphthalene, b.p. 98-100°/1 mm. [Lit. 110:
b.p. 152-6°/14 mm.). Conversion to the Grignard reagent followed by treatment with dimethyl sulfate gave a 76.5% yield of 1,2-dimethylnaphthalene, b.p. 265-7°/749 mm., n_D^20 = 1.6150 [Lit. 111, 112: b.p. 265-7°/752 mm., n_D^20 = 1.6142].

Some 2-methylnaphthalene was also formed and was recycled. Sulfonation of 1,2-dimethylnaphthalene with 98% sulfuric acid, followed by neutralization and fusion of the dry salt with potassium hydroxide gave a 35% yield (for the two steps) of 3,4-dimethyl-1-naphthol, m.p. 117-117.5° (from hexane) [Lit. 111: m.p. 114-5°].

Preparation of 4-Dichloromethyl-3,4-dimethyl-1-keto-1,4-dihydonaphthalene (IIh)

A mixture of 30.0 g. (0.174 mole) of 3,4-dimethyl-1-naphthol and 1000 ml. of 20% aqueous potassium hydroxide was added to a 2000 ml. three-necked flask. The flask was equipped with a stirrer, dropping funnel and water-cooled condenser. After warming to 65°, 200 g. of chloroform was added over a period of 1 hr. Upon complete addition, the flask contents were refluxed for 2 hr. and stirred at room temperature overnight before adding to an equal volume of water. A large amount of granular matter was present which
was insoluble in ether and hexane. Filtration, followed by extraction with hexane gave an organic phase which was worked up as usual to afford 8.0 g. of a dark oil. Distillation and collection of the cut b.p. 167-190°/1 mm. gave 5.5 g. (12.4%) of 4-dichloromethyl-3,4-dimethyl-1-keto-1,4-dihydronaphthalene, m.p. 87.5-88.5° (from benzene-hexane), ir, 6.04μ, 1656 cm⁻¹ (s, >C=O). The nmr spectrum was consistent with the assigned structure and is found in Figure 1, page 31. The nmr data are tabulated below.

\[
\begin{align*}
\text{a} & \quad \text{CH₃} \\
\text{b} & \quad \text{CHCl₂} \\
\text{c} & \quad \text{CH₃} \\
\text{d} & \quad \text{H}
\end{align*}
\]

(a) 1.81 ppm (s, 3H)
(b) 2.29 ppm (d, 3H)
(c) 6.19 ppm (s, 1H)
(d) 6.48 ppm (m, 1H)

Aromatic region 7.4-8.2 ppm (m, 4H)

Calculated for C₁₃H₁₂Cl₂O: 61.2 C, 4.7 H, 27.8 Cl;
Found: 61.1 C, 5.0 H, 27.8 Cl

Preparation of 1-Methyl-2-naphthol


48-9° [Lit.\textsuperscript{114}: m.p. 50°], and yellow diazine, m.p. 178-9°.

(114) L. Gattermann, Ann., 357, 367(1907)

Recycling the diazine raised the yield to 91% for the reduction step. Finally ether cleavage utilizing pyridine hydrochloride gave the desired product, m.p. 110-111° [Lit.\textsuperscript{115}: m.p. 110-111°], in a 95% yield. The infrared spectrum was identical to that reported earlier.\textsuperscript{116}

(115) K. Fries and E. Hubner, Ber., 39, 442(1906)

Preparation of 1-Dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene (IIf)

The preparation of 1-dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene from 1-methyl-2-naphthol, chloroform and aqueous sodium hydroxide was conducted as described to give a 77% yield of the desired product, m.p. 60.5-61.5° [Lit.\textsuperscript{117}: m.p. 64-5°].

(116) U. S. Bureau of Mines Rept. Invest., #5505, p.87 (1959); Chem.Abstr. 54:4151


Attempted Preparation of 1-Methyl-1-trichloromethyl-2-keto-1,2-dihydronaphthalene (If)

A 1000 ml. three-necked flask was equipped with a dropping funnel, stirrer and water-cooled condenser. A slurry of 43 g. (0.32 mole) of aluminum chloride and 75 ml. of carbon
disulfide was added to the flask and to this slurry at room temperature was added a solution of 33.0 g. (0.21 mole) of 1-methyl-2-naphthol in 350 ml. of carbon disulfide. After complete addition, 100 ml. of carbon tetrachloride was added dropwise over a period of 20 min. An exothermic reaction occurred and was moderated with a water bath. The green-black mixture was stirred at room temperature for 18 hr., then added to water and the resulting mixture filtered to remove black solid matter. The organic phase was separated and worked up as usual to give 7.0 g. of a black oil. Infrared analysis showed that the oil was crude 1-methyl-2-naphthol.

Another run conducted solely in carbon tetrachloride at room temperature for 1½ hr. gave 83% recovery of unreacted starting material. Again utilizing carbon disulfide as the co-solvent, a third run at 0-5° for 1 hr. gave 25% recovered starting material plus a considerable quantity of tar. No carbonyl containing product was observed by infrared analysis of the recovered organic material.

Reaction of 4-Dichloromethyl-3,4-dimethyl-2,5-cyclohexadienone (IIb) with Acetic Anhydride and Sulfuric Acid

A solution of 10.5 g. (0.051 mole) of 4-dichloromethyl-3,4-dimethyl-2,5-cyclohexadienone (IIb) in 75 ml. of freshly distilled acetic anhydride containing 5 drops of concentrated sulfuric acid was refluxed for 23 hr., cooled and poured over 200 g. of ice. The organic material was taken
up in ether and worked up as usual to give 10.7 g. of a dark oil. Distillation gave 0.6 g. (14%) of 3,4-dimethylphenyl acetate as a forecut, b.p. to 118°/0.5 mm., 5.1 g. (49%) of unreacted dienone, b.p. 118-122°/0.5 mm., m.p. 98-99°, and 3.7 g. of tar in the flask. No rearrangement product was found by infrared and v.p.c. analysis of the reaction mixture before distillation. The only product formed is that due to loss of the dichloromethyl group.

**Reaction of 4-Dichloromethyl-3,4-dimethyl-2,5-cyclohexadienone with Acetic Anhydride / BF₃**

A 100 ml. flask was charged with a solution of 5.0 g. (0.027 mole) of 4-dichloromethyl-3,4-dimethyl-2,5-cyclohexadienone (IIb) in 50 ml. of freshly distilled acetic anhydride. A gas inlet tube was positioned above the surface of the solution and BF₃ gas was added until a color change of water-white to yellow to dark brown had occurred. The resulting hot solution was then heated to reflux for 2 hr., cooled and poured over 100 g. of ice. The organic material was taken up in ether and worked up as usual to give 3 g. of a dark red-brown syrup. Distillation gave 0.45 g. (11%) of 3,4-dimethylphenyl acetate, b.p. 107-110° / 2 mm., and the remainder of the material carbonized in the distilling flask. The infrared spectrum was identical to that of an authentic sample prepared from 3,4-dimethylphenol by heating with acetic anhydride containing a trace of p-toluenesulfonic acid.

Use of only a catalytic amount of BF₃ with a solution
of 1.0 g. (0.005 mole) of the above dienone in 12 ml. of freshly distilled acetic anhydride gave some unchanged starting material and 3,4-dimethylphenyl acetate after 100 hr. at room temperature. An aliquot analyzed by nmr showed no evidence of any rearrangement product containing the dichloromethyl group.

**Reaction of 4-Dichloromethyl-4-methyl-2,5-cyclo-hexadienone (IIa) with PCl₅**

A 250 ml. flask was charged with 5.0 g. (0.031 mole) of IIa, 13.0 g. (0.063 mole) of PCl₅ and 100 ml. of methylene chloride. The mixture was refluxed for 19 hr. and an aliquot removed for infrared analysis. The infrared spectrum of the water washed and dried aliquot showed a strong band at 5.95 μ, 1681 cm⁻¹ for unreacted dienone.

The methylene chloride (90 ml.) was removed by strip distillation and 100 ml. of POC₁₃ was added to the flask. The solution was refluxed for 2 hr., strip distilled to remove 93 ml. of solvent and the black residue was poured into 200 ml. of iced water. The organic matter was taken up in ether and the resulting solution was filtered and worked up as usual. After removal of the ether, distillation of the remainder gave 0.70 g., b.p. 185-230°, 5.1 g., b.p. 242-263°, and 2.0 g. of black residue. The first cut was predominantly one component, separated by preparative v.p.c. to give 0.45 g. (17.5%) of p-chlorotoluene, n_D = 1.5193 [Lit. : n_D = 1.5190]. The infrared spectrum was identical in all respects to an authentic sample. The other cut
was also a single component, characterized as 2-methyl-4-chlorobenzal chloride, \( n^2 \text{D} = 1.5683 \), and formed in a yield of 77.8%. Nmr analysis gave a three proton singlet at 2.43 ppm (benzylic), one proton singlet at 6.71 ppm (-CHCl\(_2\) group) and a three proton multiplet in the aromatic region, 7.0-8.0 ppm. Oxidation of 1.28 g. of 2-methyl-4-chlorobenzal chloride with 2.00 g. of KMnO\(_4\) in 100 ml. of water at 100\(^\circ\) for 1 hr. gave 0.8 g. (77%) of 2-methyl-4-chlorobenzoic acid, m.p. 163-4\(^\circ\) (from water) \([\text{Lit.}^6 : \text{m.p.} \ 168.5-170.0\,^\circ]\) after filtration and acidification. Mixture with an authentic sample gave an undepressed m.p., while mixture with the isomeric acid, 2-methyl-5-chlorobenzoic acid, gave a markedly depressed m.p..

**Reaction of 4-Dichloromethyl-4-methyl-2,5-cyclohexadienone (IIa) with PCl\(_5\) - Solvent Effects**

Reaction of IIa with one equivalent of PCl\(_5\) was examined in four different solvents at reflux. The reaction was monitored by infrared analysis of aliquots removed periodically. Complete reaction was determined by absence of the carbonyl stretch band 5.99\(\mu\), 1670 cm\(^{-1}\). The times necessary for complete reaction are: greater than 19 hr. in methylene chloride, 2-3\(\frac{1}{2}\) hr. in acetonitrile and \(\frac{1}{2}\) hr. for both nitromethane and POC\(_5\). The latter two seem to be the solvents of choice for rapid reaction between PCl\(_5\) and dienones.
Reaction of 4-Dichloromethyl-3,4-dimethyl-2,5-cyclohexadienone (IIb) with PCl₅

A solution of 15.0 g. (0.073 mole) of IIb and 15.2 g. (0.074 mole) of PCl₅ in 160 ml. of phosphorus oxychloride solvent was refluxed for 4 hr., then strip distilled to remove 75% of the solvent. The remainder was left at room temperature overnight and then poured over ice. The organic material was taken up in ether and worked up as usual. Distillation of the residue gave 12.1 g. (74%) of water-white 3-(β,β-dichloroethyl)-4-methylchlorobenzene, b.p. 82.5-83.5° / 0.20 mm., n_D^26 = 1.5614.

Calculated for C₉H₇Cl₂: 48.4 C, 4.1 H, 47.6 Cl;

Found: 48.2 C, 4.2 H, 47.6 Cl

Some runs in both phosphorus oxychloride or nitromethane gave material of a higher refractive index and a wider b.p. range. The material was a binary mixture by v.p.c. analysis and all attempts at separation were unsuccessful. The other component was thought to be the dehydrochlorination product, 3-(β-chlorovinyl)-4-methylchlorobenzene, since both are degraded to the same acid, 5-chloro-2-methylbenzoic acid.

Proof of Structure of 3-(β,β-Dichloroethyl)-4-methylchlorobenzene

A solution of 1.00 g. (4.5 mmole) of 3-(β,β-dichloroethyl)-4-methylchlorobenzene in 15 ml. of pyridine was treated with a solution of 1.5 g. of potassium permanganate in 25 ml. of water containing 15 ml. of pyridine. After
stirring at room temperature for 2 hr., the mixture was heated at 60° for 4 hr. and then left to cool overnight. After filtration, an ether extraction gave 0.60 g. of recovered material. Acidification of the aqueous phase gave 0.20 g. (66%) of 5-chloro-2-methylbenzoic acid, m.p. 169-170° [Lit. 6: m.p. 169.5-171°]. A mixed m.p. with authentic material was undepressed and the infrared spectra of both acids were identical.

**Comparative Reactions of PCl₅ with 4-Dichloromethyl- and 4-Trichloromethyl-3,4-dimethyl-2,5-cyclohexadienone**

Identical concentrations (2.5 M) of 4-dichloromethyl-3,4-dimethyl-2,5-cyclohexadienone and 4-trichloromethyl-3,4-dimethyl-2,5-cyclohexadienone with one equivalent of PCl₅ in methylene chloride solvent were made up in separate flasks. Each was heated to reflux and aliquots were removed and analyzed by infrared analysis. Complete reaction was determined by absence of the carbonyl stretching band at 5.99μ, 1670 cm⁻¹. The former dienone required 24-26 min. for complete reaction while the latter compound only required 4-6 min.

**Reaction of 4-Dichloromethyl-2,4-dimethyl-2,5-cyclohexadienone (IId) with PCl₅**

A solution of 5.0 g. (0.024 mole) of IId and 14.0 g. of PCl₅ in 70 ml. of PCl₃ was refluxed for 2 hr., followed by strip distillation of the solvent, b.p. 103-110°. The yellow residue was poured into 100 ml. of iced water. The organic material was taken up in ether and worked up as usual
to give 6.0 g. of yellow oil. V.p.c. analysis showed two peaks, but distillation gave a continuous b.p. range of 76°-114° / 0.5 mm. No clean separation resulted by using preparative v.p.c. Nmr analysis of the mixture gave a singlet at 2.45 ppm (6H) and a multiplet in the region 6.8-7.8 ppm (3H). No evidence of formation of the -CH₂CHCl₂ group was found.

Reaction of 1-Dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene with Acetic Anhydride and Sulfuric Acid

A 250 ml. three-necked flask was equipped with a stirrer, thermometer and water-cooled condenser topped with a drying tube. A solution of 8.80 g. (0.037 mole) of 1-dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene and 0.8 ml. of concentrated sulfuric acid in 125 ml. of acetic anhydride was added to the flask and refluxed for 16 hr. Strip distillation gave 105 ml. of recovered acetic anhydride, b.p. 135-140°, and a dark liquid residue. The residue was poured into 200 ml. of cold water and the organic phase taken up in 1:1 ether-benzene, filtered and worked up as usual. The residue was distilled at reduced pressure to give 7.5 g. (85%) of recovered 1-dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene, b.p. 132-155° / 1 mm., m.p. 61-2°, and 2.3 g. of residue in the flask.

Reaction of 1-Dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene with PCl₅

A 250 ml. flask was charged with 13.0 g. (0.063 mole) of PCl₅, 11.9 g. (0.050 mole) of 1-dichloromethyl-1-methyl-2-
keto-1,2-dihydrornaphthalene and 150 ml. of methylene chloride. No exothermic reaction was noted upon mixing. After refluxing for 1 hr., the solvent, b.p. 45-103°, was strip distilled and the residue taken up in carbon tetra-chloride and worked up as usual. Infrared analysis showed complete recovery of unreacted starting material.

Therefore the recovered starting material was added to 25 g. (0.120 mole) of PCl₅ in 250 ml. of POCl₃ and the mixture refluxed for 1½ hr. After strip distillation of 225 ml. of the POCl₃ solvent, b.p. 103-109°, the residue was poured into 200 ml. of iced water and the organic material taken up in benzene and worked up as usual. Distillation of the oily residue gave 0.3 g. of a forecut, b.p. up to 100°/2 mm., 1.60 g. of a single component, nD₂⁵ = 1.6235, b.p. 100-134°/2 mm., 5.3 g. of a 1:1 mixture of this same component plus unreacted starting material, b.p. 134-157°/2 mm., and 4.1 g. of residue in the flask. Besides unreacted starting material, only one component was formed and gave an nmr spectrum showing a sharp singlet (benzylic) at 2.71 ppm and a multiplet in the 7.1-8.1 ppm aromatic region in a ratio of 3:6. The infrared spectrum was consistent with a methyl- and chloro-substituted naphthalene ring and no band appeared in the carbonyl stretching region.

Degradation followed a general method for oxidation of alkyl substituted naphthalenes. A mixture of 1.60 g. of the above disubstituted naphthalene was refluxed with 75 ml.
of dilute nitric acid (diluted with 12 parts of water) for 18 days. The result was 0.4 g. of recovered material and 1.35 g. of a base soluble fraction. Recrystallization of the base soluble fraction from aqueous methanol gave needles, m.p. 149-150°. Authentic 2-chloro-1-naphthoic acid was prepared (32% yield) by reaction of 2-hydroxy-1-naphthoic acid with PC1₅ at 180-190° in a sealed tube to give needles, m.p. 148-9° [Lit.: m.p. 152-3°]. Mixture of the former needles with authentic 2-chloro-1-naphthoic acid gave an undepressed m.p. Infrared spectra of both were identical in all respects.

Preparation of 7,7-Dichloronorcarane

Into a 2000 ml. three-necked flask equipped with a stirrer, water-cooled condenser and thermometer was placed a mixture of 125 g. (0.68 mole) of dry sodium trichloroacetate (dried at 60° over P₂O₅), 550 ml. of cyclohexene and 250 ml. of 1,2-dimethoxyethane (dried by distillation from calcium hydride at reduced pressure).

The mixture was stirred at reflux for 5 days, followed by cooling, dilution with 1000 ml. of water and separation of phases. The organic layer was worked up as usual and distilled to give 28.5 g. (26%) of 7,7-dichloronorcarane,
The amount of unreacted sodium trichloroacetate present after 5 days at reflux was small, if any at all, based on the reported rate of decomposition of this salt.

Reaction of 1-Dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene with PCl₅ - Dichloromethylene Trapping Experiment

A mixture of 3.7 g. (0.015 mole) of 1-dichloromethyl-1-methyl-2-keto-1,2-dihydronaphthalene and 5.6 g. (0.027 mole) of PCl₅ in 75 ml. of cyclohexene was refluxed for 65 hr., cooled and poured into an equal volume of water and worked up as usual. Distillation gave 68 ml. of recovered cyclohexene, b.p. 83-4⁰, 1.5 g. (37%) of trans-1,2-dichlorocyclohexane, b.p. 38-41⁰/8 mm., b.p. 183.5-184.0⁰, \( n_D^{25} = 1.4861 \) [Lit. : b.p. 189⁰, \( n_D = 1.4879 \)] and 3.5 g. of residue in the flask. Infrared analysis of the distillation residue showed it to be a binary mixture of unchanged starting material and 1-methyl-2-chloronaphthalene. Authentic trans-1,2-dichlorocyclohexane could be prepared by
heating PCl₅ with cyclohexene for 18 hr., and was identical in all respects to material formed in the trapping experiment.

That 7,7-dichloronorcarane was stable to the dichloromethylene trapping experimental conditions was born out by strongly refluxing 3.0 g. of 7,7-dichloronorcarane with 2.0 g. of PCl₅ in 20 ml. of cyclohexene for 65 hr. using the strong infrared band at 12.58μ, 795 cm⁻¹ as a criteria for the presence of 7,7-dichloronorcarane. The material was stable and was not destroyed by the PCl₅.

Reaction of 4-Dichloromethyl-3,4-dimethyl-2,5-cyclohexadienone (IIb) with Phenylmagnesium Bromide

A solution of phenylmagnesium bromide was generated under dry nitrogen atmosphere in 400 ml. of dry ether from 1.00 g. (0.041 mole) of magnesium metal turnings and 7.0 g. (0.045 mole) of bromobenzene. To the Grignard reagent was added dropwise a solution of 5.00 g. (0.027 mole) of IIb in 200 ml. of dry ether. After complete addition, the solution was refluxed for 2 hr., cooled and poured over 400 g. of crushed ice. The ether phase was worked up as usual to give 10.4 g. of a semi-solid. Upon standing for 20 min., the slush was filtered and the clear crystals (7.5 g.) collected were recrystallized from hexane to give 4-dichloromethyl-3,4-dimethyl-1-phenyl-2,5-cyclohexadienol (XVII) as clear cubes, m.p. 90-91° (the capillary was immersed in the m.p. bath initially at 80° and the m.p. taken - otherwise thermal decomposition gave lower observed
values for the m.p.). Yield was nearly quantitative. The infrared spectrum showed no carbonyl band and the sharp unassociated hydroxyl band at 2.73μ, 3663 cm⁻¹ was observed. The nmr assignments are shown below.

![Diagram of molecule XVII]

- a CH₃ b CHCl₂ d (a) 1.41 ppm (s, 3H)
- (b) 1.82 ppm (d, 3H)
- (c) 5.65 ppm (bs, 1H)
- (d) 5.88 ppm (s, 1H)
- (e) 6.02 ppm (d, 2H)

Vinyl proton and aromatic protons in region 7.0-7.5 ppm (m, 6H)

The alcohol product was thermally unstable, losing water and rearranging. Samples of solid alcohol were kept for no longer than two days at room temperature. Solutions of the alcohol could be kept for no more than 24 hrs.

**Dehydration and Rearrangement of 4-Dichloromethyl-3,4-dimethyl-1-phenyl-2,5-cyclohexadienol (XVII)**

A mixture of 7.5 g. (0.027 mole) of XVII and 100 ml. of 91% formic acid in a 250 ml. flask at 0-5⁰ was stirred for 7 hr. The yellow mixture was poured over 400 g. of crushed ice and the organic material was taken up in 300 ml. of ether. The ether phase was worked up as usual to give 6.9 g. of an orange oil. These same results occur if a solution of XVII in methylene chloride was heated at reflux for 1-2 hr. or if neat XVII was heated at 120⁰ for 5 min.

The orange oil was subjected to distillation and gave 5.10 g. (72.8%) of 3-(β,β-dichloroethyl)-4-methylbiphenyl, (XIX), b.p. 138-140⁰/ 0.30 mm., nD²⁶ = 1.6059.

The infrared spectrum showed no hydroxyl band. An nmr
spectrum gave data shown below. All resonances are con-

(a) 2.37 ppm (s, 3H)
(b) 3.49 ppm (d, 2H)
(c) 5.77 ppm (t, 1H)
Aromatic region 7.0-7.5 ppm (m, 8H)

XIX

sistent with the structure proposed.

Calculated for C₁₅H₁₄Cl₂: 68.0 C, 26.8 Cl;
Found: 68.0 C, 26.8 Cl

Proof of Structure of 3-(β,β-Dichloroethyl)-4-
methylbiphenyl (XIX)

Refluxing a sample of XIX with sodium methoxide in
methanol or potassium t-butoxide in t-butanol gave unchanged
material. A 1.3 g. sample dissolved in 30 ml. of pyridine
was added to a solution of 2.0 g. of KMnO₄ in 45 ml. of
water and the mixture refluxed for 18 hr. After cooling
and filtering, the filtrate was extracted with ether to re-
cover 0.1 g. of unchanged material. Acidification of the
filtrate with hydrochloric acid, followed by extraction with
ether, gave after workup in the usual manner, 1.05 g. (87.5%)
of 2-methyl-5-phenylbenzoic acid, m.p. 205-6°. Mixture with
an authentic sample was undepressed and the infrared spectrum
of the acid was identical to that of authentic material.

Trapping of 6-Dichloromethyl-6-methyl-1-methylene-3-phenyl-
2,4-cyclohexadiene (XVIII)

A. With Maleic Anhydride

A solution of 1.00 g. (0.0035 mole) of freshly prepared
4-dichloromethyl-3,4-dimethyl-1-phenyl-2,5-cyclohexadienol
(XVII) and 0.36 g. (0.0035 mole) of freshly sublime maleic anhydride in 35 ml. of dry methylene chloride was refluxed for 18 hr., during which time a yellow-green color developed. The solvent was allowed to evaporate under a current of dry nitrogen to give 1.4 g. of a yellow residue. The residue began to solidify and treatment with ether gave 0.30 g. of maleic acid, m.p. 133-135°, which was sparingly soluble in ether. Sublimation of the acid gave maleic anhydride, m.p. 52-3°, identical in all respects to authentic material.

The ether phase was concentrated and an nmr spectrum of the orange residue showed the presence of 3-(β,β-dichloroethyl)-4-methylbiphenyl (XIX) and another component possessing a number of resonances in the vinyl region and an aliphatic methyl singlet but no allylic methyl resonance. The residue was thus assumed to be the triene intermediate (XVIII) plus XIX. None of the starting alcohol (XVII) remained. Heating of this residue at 100° for 5 min. gave a red-orange oil whose nmr spectrum now showed resonances due to XIX alone.

B. With Tetracyanoethylene

A solution of 1.2 g. of XVII and 0.55 g. of tetracyanoethylene in 30 ml. of dry methylene chloride was heated to reflux for 30 min. and stirred overnight at room temperature. A color change of yellow to green to red occurred during heating. The solvent was evaporated to dryness under a stream of nitrogen to give 1.50 g. (90.5%) of a tan adduct.
Recrystallization of the adduct from chloroform-hexane gave 1.2 g. of white plates, m.p. 184-5° with decomposition (sealed tube - melting point bath preheated to 170°).

Attempts at sublimation of the adduct gave decomposition of the sample. An infrared spectrum of the adduct in a potassium bromide pellet showed bands at 4.50μ, 2222 cm⁻¹ (m, -C≡N), 6.00μ, 1667 cm⁻¹ (m, C=C) and a number of bands in the region of 12.8μ- 14.8μ, 781 -676 cm⁻¹ (C-Cl). A nmr spectrum of the adduct in acetone- d₆ is shown in Figure 2. Besides the quintet centered at 2.07 ppm (due to the presence of acetone-d₅, a common contaminant in all acetone-d₆), the nmr data is shown below.

Calculated for C₂₁H₁₄Cl₂N₄ : 18.0 Cl, 14.3 N;
          Found : 18.8 Cl, 14.5 N

The adduct did not analyze well due to decomposition of the sample upon standing, however all analyses gave the proper N / Cl ratio of 4:2.

Analysis of the adduct by mass spectrometry at 70 eV. gave proper parent, parent +2 and parent +4 ions at m/e 392, 394 and 396, respectively, in a ratio of 1:0.66:0.14
(calculated ratio on the basis of relative isotopic abundances for two chlorine atoms present gave 1:0.65:0.11). Other characteristic ions present were at m/e 357 and 359 (corresponding to loss of a chlorine atom from parent and parent +2) and at m/e 264 and 266 (corresponding to loss of tetracyanoethylene from parent and parent +2 in a reverse Diels-Alder process).

C. With Iodine

A mixture of 1.00 g. of XVII and 1.0 g. of iodine in 40 ml. of methylene chloride was refluxed for 7 days, cooled and shaken with a dilute solution of sodium thiosulfate. After workup as usual, a tacky oil was recovered which did not contain XIX by v.p.c., nmr and infrared analysis. The oil darkened with time and decomposition prevented attempts to characterize the material.

Reaction of 4-Dichloromethyl-3,4-dimethyl-1-keto-1,4-dihydronaphthalene (IIh) with Phenylmagnesium Bromide

A solution of 3.00 g. (0.0118 mole) of 4-dichloromethyl-3,4-dimethyl-1-keto-1,4-dihydronaphthalene in 200 ml. of ether was added at room temperature to a solution of phenylmagnesium bromide (prepared from 0.02 mole of bromobenzene in 300 ml. of ether). After stirring overnight at this temperature, the mixture was poured over 200 g. of crushed ice and worked up as usual to give 4.5 g. of an oil. The alcohol was not isolated but heated at 120° for 5 min. and cooled. An nmr spectrum of the material indicated the presence of unchanged starting material plus 3-(β,β-dichloroethyl)-4-
methyl-1-phenylnaphthalene, characterized by the distinctive resonances due to the -CH₂CHCl₂ group. Distillation gave 1.7 g. (57%) of recovered starting material, b.p. 149-168°/0.21 mm., and 1.9 g. of residue in the flask. The residue was chromatographed over silica gel and purified by molecular distillation to give 1.3 g. (84%) of 3-(β,β-dichloroethyl)-4-methyl-1-phenylnaphthalene, nD²⁵ = 1.6246, crystals from hexane gave m.p. 81-2°. Nmr data are shown below.

Calculated for C₁₉H₁₆Cl₂: 72.4 C, 5.1 H, 22.5 Cl;
Found: 72.2 C, 5.1 H, 22.7 Cl

Analysis of the above sample by mass spectrometry at 70 eV. gave the expected parent, parent +2 and parent +4 ions at m/e 314, 316 and 318, respectively, in a ratio of 1:0.64:0.13 (calculated ratio on the basis of relative isotopic abundances for two chlorine atoms present gave 1:0.65:0.11).

Preparation of 2,4-Dimethylacetophenone

The preparation followed the method reported.¹²⁴


Acetylation of m-xylene with acetyl chloride using an equivalent of anhydrous ferric chloride at 0-5° was con-
ducted on a four mole scale to give, in a number of runs, a
68-77% yield of 2,4-dimethylacetophenone, b.p. 101-102°/
9 mm., n_D^26 = 1.5293, ir, 5.97μ, 1675 cm^-1 (s, ≥C=O)
[Lit. 125 : b.p. 108°/ 12 mm., n_D^20 = 1.5340].

(125) A. Klages, Ber., 35, 2245(1902)

Preparation of 2,4-Dimethyl-5-nitroacetophenone

The nitration of 2,4-dimethylacetophenone proceeded
by dropwise addition of 1 mole of 2,4-dimethylacetophenone
to 400 ml. of stirred 90% nitric acid (density = 1.52) held
at -10° to -5°. After complete addition, the solution was
diluted three-fold with cold water. The organic material
was extracted with ether and worked up as usual. The crude
yield was quantitative for mono-nitrated material. The 2,4-
dimethyl-5-nitroacetophenone was an oil which slowly
crystallized as yellow needles, m.p. 65-66° (from aqueous
ethanol) [Lit. 126 : m.p. 67°]. Despite repeated recrystall-
lizations, the material was contaminated with significant
amounts of the isomeric 2,4-dimethyl-3-nitroacetophenone
[Lit. 126 : m.p. 72°], as was born out by subsequent reac-
tions. Attempted distillation at reduced pressure was an
unsuccessful method for purification due to extensive
thermal decomposition during distillation. Therefore crude
2,4-dimethyl-5-nitroacetophenone as a semi-solid was
employed in the following reactions.

**Reduction of 2,4-Dimethyl-5-nitroacetophenone**

**A. Use of Iron / Acetic Acid**

A 3000 ml. three-necked flask was equipped with a stirrer, dropping funnel and water-cooled condenser. To the flask was added 177 g. of iron powder, 35 ml. of glacial acetic acid and 700 ml. of water. The stirred mixture was heated on a steam bath while 107 g. of crude 2,4-dimethyl-5-nitroacetophenone was added dropwise over a period of 30 min. After complete addition, 210 ml. of glacial acetic acid was added and reflux was continued for 1½ hr. After cooling, the thick black mass was filtered, made basic with sodium hydroxide and the organic material was taken up in ether and worked up as usual to give 10-15 g. of a dark oil. Infrared analysis indicated the presence of an amino group and a carbonyl group. The major portion of the reaction mixture was polymeric material which was insoluble in ether and other common organic solvents.

**B. Use of Raney Nickel and Hydrogen**

A 1.5 l. stainless steel bomb was charged with a solution of 120.5 g. of crude 2,4-dimethyl-5-nitroacetophene in 300 ml. of absolute ethanol with 40 g. of active Raney nickel (No. 28 Raney active nickel catalyst packaged in water from W. R. Grace & Co., S. Pittsburg, Tenn.). The bomb was mounted in a rocking autoclave. After flushing the system with nitrogen, a hydrogen pressure of 1450 psi was employed
at 100° for 7 hr. Initially a mild exothermic reaction ensued (the temperature rose to 144°) and then subsided. After cooling, the contents were filtered and the organic material was taken up in ether and worked up as usual to give 40.5 g. of a thick oil. Infrared analysis as in part A indicated the same incomplete reduction had occurred. Likewise black, polymeric material was formed and was insoluble in the usual solvents.

C. Use of Platinum and Hydrogen

A similar run using platinum oxide and a hydrogen pressure of 1400 psi at 125° for 12 hr. gave the same results cited under part B. Again polymer formation was the predominant result.

D. Use of Palladium and Acid

A reduction method used for similar systems was adapted for use here. A mixture of 5.4 g. of crystalline 2,4-dimethyl-5-nitroacetophenone, 3.5 g. of 5% Pd-C (200 mesh powder - 50% wet with water), 50 ml. of glacial acetic acid, 3.7 g. of 96% sulfuric acid and 31 g. of acetic anhydride was hydrogenated in a Paar hydrogenation apparatus at 32 psi of hydrogen. After 12 hr., only 15% of the theoretical amount of hydrogen was absorbed. No further uptake was observed upon prolonged reaction. Only unreacted starting material was recovered. No evidence of reduction was observed.
E. Clemmensen Reduction

A mixture of 20 g. of mercuric chloride, 200 g. of mossy zinc, 300 ml. of water and 10 ml. of concentrated hydrochloric acid was shaken for 5 minutes. After decanting the aqueous phase, the amalgamated zinc was added to a mixture of 150 ml. of water, 350 ml. of toluene and 100 g. of crude 2,4-dimethyl-5-nitroacetophenone in a 2000 ml. three-necked flask. The flask was equipped with a thermometer, stirrer and a water-cooled condenser. The stirred mixture was heated at reflux for 18 hr., during which time, 200 ml. of additional concentrated hydrochloric acid was added in four portions (about every four hours). After cooling and filtering, the organic phase was worked up as usual to give 36.5 g. of unchanged starting material. The aqueous phase was made basic with sodium hydroxide, extracted with ether and worked up as usual to give a thick oil, whose infrared spectrum showed both amino and carbonyl bands in the usual positions.

F. Wolff-Kishner Reduction

A mixture of 290 g. (1.50 mole) of crystalline 2,4-dimethyl-5-nitroacetophenone, 300 g. of hydrazine hydrate and 400 ml. of ethylene glycol was refluxed in a 2000 ml. stainless steel flask until nitrogen evolution had moderated (7 hr.). After cooling, 150 g. of potassium hydroxide was added and reflux continued overnight. Removal of the water before addition of the potassium hydroxide did not
give any improvement in the yield of product. The cooled mixture was added to twice its volume of water and the organic material was taken up in ether and worked up as usual. After removal of the solvent on a rotary evaporator, distillation gave 3 g. of a forecut, b.p. to 88°/1 mm., 159 g. (71.2%) of 2,4-dimethyl-5-ethylaniline, b.p. 88-90°/1 mm., \( n_D^{26} = 1.5454 \) [Lit.\(^{127} \): b.p. 144-5°/20 mm.].

\(^{127}\) A. Tohl and A. Geyger, Ber., 25, 1535(1892)

Despite the sharp b.p. range and the fact that purified starting material was employed in the reduction, the 2,4-dimethyl-5-ethylaniline was contaminated by some of the isomeric 2,6-dimethyl-3-ethylaniline as was evidenced by subsequent work. This contamination was not apparent by t.l.c., v.p.c., infrared or nmr analysis.

**Preparation of 2,4-Dimethyl-5-ethylphenol (XXV)**

Reduction of purified 2,4-dimethyl-5-nitroacetophenone gave what was believed to be pure 2,4-dimethyl-5-ethylaniline. A sample was subjected to diazotization and hydrolysis. Thus to a solution of 50 g. (0.34 mole) of 2,4-dimethyl-5-ethylaniline in 450 ml. of 9% sulfuric acid at 5-10° was added a solution of 24 g. (0.39 mole) of sodium nitrite in 200 ml. of water over a period of 20 min. The cold, brown diazonium salt solution was added to a boiling solution of 100 ml. of concentrated sulfuric acid in 300 ml. of water in a 3000 ml. three-necked flask. The flask was
also equipped with a steam inlet and a distilling head to allow steam distillation of the phenol as it formed. The steam inlet was regulated so as to maintain a liquid level of half-full or less in the flask. After complete addition and after no more organic material would steam distill, the distillates were washed with ether and the ether phase worked up as usual to give 50 g. (98%) of crude product. Distillation gave material, b.p. 168-173°/ 95 mm., n_D^26 = 1.5300 [Lit. 128 for 2,4-dimethyl-5-ethylphenol: b.p. 242-40°, m.p. 39-40°], and very little residue in the flask. V.p.c.


Analysis showed two components present in a ratio of 70:30. Attempted separation by distillation at a lower pressure was unsuccessful and the use of atmospheric pressure gave decomposition during distillation.

Attempted fractional separation through use of an extraction process gave partial extraction from an ether solution of the phenol mixture using 10% through 30% aqueous sodium hydroxide solutions. All of the material extracted was a binary mixture in the same ratio as the original sample. Use of Claisen's alkali gave complete extraction of both phenols from the ether phase.

Whereas an nmr spectrum of the corresponding aniline mixture did not show the presence of two components, the nmr spectrum of the phenol mixture showed two different ethyl
groups as the sole difference between the two phenols present, namely 2,4-dimethyl-5-ethylphenol and 2,6-dimethyl-3-ethylphenol. The mixture was used as such for subsequent dienone formation.

**Preparation of 4-Dichloromethyl-2,4-dimethyl-5-ethyl-2,5-cyclohexadienone (IIc)**

A 2000 ml. three-necked flask was equipped with a dropping funnel, stirrer and water-cooled condenser. The flask was charged with a mixture of 131 g. (0.875 mole) of 2,4-dimethyl-5-ethylphenol (contaminated by the 3-ethyl isomer) and 700 ml. of 30% aqueous potassium hydroxide solution. To this solution at 65° was added 300 g. of chloroform over a period of 1 hr., followed by refluxing the resulting mixture for 7 hr. After cooling, the mixture was left at room temperature overnight and then added to twice its volume of water. The organic material was taken up in hexane and extracted with 30% aqueous base and then with Claisen's alkali until the extracts were clear. Acidification of the combined base extracts gave 101 g. (76%) of recovered starting material. Washing the hexane phase with water until neutral, followed by washing with saturated sodium chloride solution and drying through anhydrous magnesium sulfate gave 40 g. of residue after removal of solvent on a rotary evaporator. Distillation and collection of the cut, b.p. 120-145°/ 0.7 mm., gave 2.6 g. (5.6%) of 4-dichloromethyl-2,4-dimethyl-5-ethyl-2,5-cyclohexadienone (IIe), m.p. 61.0-61.5° (from hexane), ir,
6.00 μ, 1667 cm\(^{-1}\) (s, =C=O).

Calculated for \(\text{C}_{11}\text{H}_{14}\text{Cl}_{2}\text{O}\) : 56.7 C, 6.1 H, 30.4 Cl;

  Found : 56.4 C, 6.3 H, 30.3 Cl

The nmr spectrum was consistent with the structure proposed. The nmr spectrum is shown in Figure 3, page 50, and the data are tabulated below.

\[
\begin{array}{c}
\text{b} & \text{CH}_3 & \text{CHCl}_2 & \text{CH}_2\text{CH}_3 & (a) 1.26 \text{ ppm (t, 3H)} \\
\text{g} & \text{H} & \text{d} & \text{H} & (b) 1.48 \text{ ppm (s, 3H)} \\
\text{c} & \text{CH}_3 & \text{e} & \text{f} & (c) 1.99 \text{ ppm (d, 3H)} \\
& \text{CH}_2\text{CH}_3 & & (d) 2.34 \text{ ppm (dq, 2H)} \\
& & \text{H} & & (e) 6.13 \text{ ppm (s, 1H)} \\
& & & \text{f} & (f) 6.27 \text{ ppm (bt, 1H)} \\
& & & & (g) 6.90 \text{ ppm (dq, 1H)}
\end{array}
\]

I\(\text{i}\)e

Attempts to raise the yield of dienone by variation of temperature, reaction time, base concentration and chloroform concentration gave a range of 3-5% yields, except where methanol was used as a co-solvent and the yield fell to zero.

**Preparation of 3,4-Dimethyl-5-ethyl-4-trichloromethyl-2,5-cyclohexadienone (Ie)**

To a slurry of 105 ml. of carbon disulfide, 39 g. of aluminum chloride and 31 g. of carbon tetrachloride at room temperature was added a solution of 21 g. of 2,4-dimethyl-5-ethylphenol (contaminated by the isomeric phenol) in 75 ml. of carbon disulfide over a period of 30 min.

After stirring for 5 hr., the mixture was poured over 100 g. of ice containing 30 ml. of concentrated hydrochloric acid. The organic phase after work up as usual gave 3.9 g. (15%) of Ie, b.p. 122-4\(^0\)/0.55 mm. [Lit. : b.p. 112-116\(^0\)/0.30 mm.]. The infrared spectrum of Ie was identical to that.
prepared\textsuperscript{69} earlier in a 38% yield from authentic 2,4-di-
methyl-5-ethylphenol. If the amount of this latter phenol
present in the binary phenol mixture above is taken into
consideration, the yield of the Ie becomes 32%.

**Reaction of Tri-n-butylphosphine with 3,4-Dimethyl-4-tri-
chloromethyl-2,5-cyclohexadienone (Ib)**

A solution of 5.0 g. (0.02 mole) of Ib and 5.2 ml.
(0.02 mole) of tri-n-butylphosphine in 50 ml. of dry ben-
zene was refluxed for 6 hr. under a dry nitrogen atmosphere.
The reaction mixture darkened during heating. Analysis of
an aliquot by t.l.c. and nmr showed the presence of one part
of Ib and two parts of 4-dichloromethyl-3,4-dimethyl-2,5-
cyclohexadienone (IIb) besides unreacted tri-n-butylphosphine
and some decomposition products. Addition of 50 ml. of
absolute ethanol to the reaction system followed by refluxing
for 18 hr. gave no change in the ratio of dienones present.
IIb was not separated from the mixture with Ib due to the
close physical properties of the two dienones. The reaction
must go to completion by addition of excess tri-n-butyl-
phosphine before isolation of IIb becomes possible.

**Preparation of (\(\dagger\))- and (\(\ddagger\))-a-(4-Dichloromethyl-3,4-dimethyl-
5-ethyl-2,5-cyclohexadienyldieneaminoxy)propionic Acid**

A solution of 4.20 g. (18.0 mmole) of IIe and 2.55 g.
(17.6 mmole) of (\(\dagger\))-a-(isopropylideneaminoxy)propionic
acid\textsuperscript{37}, \([\alpha]_D^{27} = \mp 31.5^\circ (c 0.02,\text{ water})\), in 60 ml. of 92%
aqueous acetic acid containing 0.5 g. of p-toluenesulfonic
acid monohydrate was heated to reflux for 5 hr.. A stream
of nitrogen was employed to sweep out acetone as it formed. After the first hour, 15 ml. of additional 92% aqueous acetic acid was added. After cooling the solution was poured into 100 ml. of water and the organic material was taken up in ether. The ether phase was extracted with base to separate the product from 3.3 g. (78.6%) of unreacted Ile. Acidification of the basic washes gave 1.1 g. (89%) of (S)- and (R)-(4-dichloromethyl-2,4-dimethyl-5-ethyl-2,5-cyclohexadienylideneaminoxy)propionic acids as an acidic oil. Variation of the concentration of aqueous acetic acid from 92% to 100% acetic acid gave no improvement in the extent of oxime transfer. In all runs, transfer occurred to an extent of 10-50% whereas the yield based on unrecovered Ile was always 80% or greater. The recovered Ile was optically inactive, therefore a oxime transfer process followed by hydrolysis of XXVI was not operative. The acidic oil gave 

\[ [\alpha]_D^{28} = -50^\circ \] (c 0.07, methanol).

Repeated attempts at recrystallization of the acidic oil from pentane, hexane, ethanol, ethanol-water, methanol, ether, ethyl acetate, benzene and carbon tetrachloride did not successfully give crystals of either enantiomer; "oiling out" was the result in all cases.

Attempts to form salts with cinchonine, ephedrine, piperidine, pyrrolidine, guanidine and dehydroabietylamine also gave oils which resisted crystallization from the usual solvents.
Esterification of the acidic oil with diazomethane gave an 84% yield of methyl (\(\ddagger\))- and (\(\ddagger\))-\(\alpha\)-(4-dichloromethyl-2,4-dimethyl-5-ethyl-2,5-cyclohexadienylideneaminoxy)propionate, b.p. 139-141\(^\circ\)/0.30 mm., \(n^2_D = 1.5274\), \([\alpha]^{22}_D = -38.9^\circ\) (c 0.58, methanol). Calculated for \(C_{15}H_{21}Cl_2NO_3\): 53.9 C, 6.3 H, 21.2 Cl, 4.2 N; Found: 54.0 C, 6.4 H, 21.1 Cl, 4.2 N

An nmr spectrum is shown on p. 53 in Figure 4 and the data are shown below.

\[
\begin{align*}
&b \text{ CH}_3 \quad \text{CHCl}_2 \quad h \\
i \quad \text{H} \quad \text{CH}_2\text{CH}_3 \quad e \quad a \\
d \quad \text{CH}_3 \quad H \quad j \\
\text{O-CH(\text{CH}_3)CO}_2\text{CH}_3 \\
g \quad c \quad f \\
&\begin{align*}
(a) & 1.25 \text{ ppm (t, 3H)} \\
(b) & 1.38 \text{ ppm (s, 3H)} \\
(c) & 1.52 \text{ ppm (d, 3H)} \\
(d) & 1.98 \text{ ppm (d, 3H)} \\
(e) & 2.28 \text{ ppm (q, 2H)} \\
(f) & 3.78 \text{ ppm (s, 3H)} \\
(g) & 4.78 \text{ ppm (q, 1H)} \\
(h) & 6.07 \text{ ppm (s, 1H)} \\
(i) & 6.18 \text{ ppm (dq, 1H)} \\
(j) & 6.98 \text{ ppm (dt, 1H)}
\end{align*}
\]

**XXVII**

**Preparation of KF \(\times\) HF**

A commercial sample of anhydrous potassium fluoride was further dried and pulverized in a porcelain evaporating dish at 250\(^\circ\) until the solid was flowy in consistency. The hot potassium fluoride was transferred to dry glass storage vessels until cool and later transferred again to dry polyethylene bottles for prolonged storage.

A 1000 ml. polyethylene Erlenmeyer was charged with 200 g. of dry potassium fluoride and cooled in a dry ice-acetone bath. To the cold potassium fluoride was added the
calculated amount of liquid hydrogen fluoride (also at dry ice-acetone temperature) to form KF - 2 HF. The reaction was strongly exothermic. After complete addition, the mixture was warmed to ambient temperature and the resulting solid was broken up and stored in dry polyethylene bottles. The yield of adduct was 329 g. which corresponded roughly to KF - 1.9 HF, m.p. 85-90° [Lit.: for KF - 2 HF, m.p. 65.8° and 71.7°].

A sample of KF - 5.1 HF was prepared in a similar fashion and exhibited m.p. 57-58° [Lit.: m.p. @ 60°].

Attempted Preparation of Substituted Anilinium Fluorides

A sample of 2,4,6-tribromoaniline (TBA) dissolved in liquid hydrogen fluoride at dry ice-acetone temperature to give a clear brown solution. The solution was allowed to warm to room temperature and left overnight in a well-ventilated hood to give unchanged TBA, identical in all respects to starting material.

A similar reaction with 2,4-dinitroaniline (DNA) gave a clear brown solution. Removal of the hydrogen fluoride gave unchanged DNA. No evidence of salt formation was found.

In both cases, the recovered substituted aniline weighed the same as that which had been added initially and there was no evidence at any time of an isolable salt with hydrogen fluoride.

Reaction of 2,4-Dinitrochlorobenzene with KF - x HF

A mixture of 20 g. (0.099 mole) of 2,4-dinitrochloro-
benzene (DNC) and 51.0 g. of KF $\cdot$ 1.9 HF was added to a 200 ml. silver flask, heated to 280° for 30 min., cooled, added to 300 ml. of water and extracted five times with 50 ml. each of ether to give 20 g. of recovered DNC. The aqueous phase gave a negative test for chloride ion. During the reaction, it was noted that the DNC was not soluble in the KF $\cdot$ 1.9 HF and the reaction mixture was a binary mixture of two liquid phases throughout the course of this reaction.

A similar run employing KF $\cdot$ 5.1 HF again gave a binary immiscible melt and 94% of the DNC was recovered after workup. No chloride ion was detected in the aqueous workup solution.

**Reaction of 2,4-Dinitrochlorobenzene with KF $\cdot$ x HF in a Solvent**

The fluorination of 2,4-dinitrochlorobenzene (DNC) with anhydrous potassium fluoride in dimethylformamide gave a 60% yield of purified 2,4-dinitrofluorobenzene, identical in all respects to that reported earlier for this same reaction.

Therefore a 250 ml. three-necked flask, equipped with a stirrer, water-cooled condenser and thermometer, was charged with 24 g. of KF $\cdot$ 1.9 HF, 22.5 g. (0.11 mole) of DNC and 100 ml. of dry dimethylformamide (DMF). After refluxing for 6 hr., the mixture was added to 500 ml. of water and extracted seven times with 50 ml. each of ether to give 20.0 g. of yellow crystals, m.p. 71-2° (from aqueous acetone). A molecular weight determination in
bromoform gave 232 \(^\circ\). A positive aromatic nitro group test\(^{129}\) was observed as well as a negative fluoride test

\begin{center}
\end{center}

by sodium fusion. A private communication\(^{130}\) on this re-

\begin{center}
(130) A. L. Henne, private communication
\end{center}

action showed N,N-dimethyl-2,4-dinitroaniline was the sole product and the yellow crystals could have been the same compound.

Reactions of 2,4-Dinitroaniline with KF \(\cdot\) 5,1 HF

A 200 ml. silver flask was charged with 31 g. of KF \(\cdot\) 5,1 HF and 5.0 g. (0.027 mole) of 2,4-dinitroaniline (DNA) and heated to 250-280\(^\circ\) for 15 min. The mixture appeared to be a suspension and not a true solution. After cooling, this solid was added to 300 ml. of water, neutralized with solid potassium carbonate and extracted with three 50 ml. portions of ether to give 4.8 g. of recovered DNA. No evidence of a fluoroaromatic could be found.

Reactions of 2,4,6-Tribromoaniline with KF \(\cdot\) 1,9 HF

A 200 ml. silver flask was charged with 2.0 g. (0.006 mole) of 2,4,6-tribromoaniline (TBA) and 31.0 g. of KF \(\cdot\) 1.9 HF and heated for 10 min. in the range 160-190\(^\circ\), followed by cooling gave rise to a solid mass. After addition to 300 ml.
of water and neutralization with solid potassium carbonate, the aqueous phase was extracted with three 50 ml. portions of ether to give 1.9 g. of recovered TBA, m.p. 117-8°.

A similar run at 250-280° for 25 min. gave quantitative recovery of unreacted TBA upon workup.

Preparation of N,N-Dimethyl-4-bromoaniline

A 1000 ml. three-necked flask was equipped with a dropping funnel, stirrer and water-cooled condenser. The flask was charged with 123.5 g. (1.02 mole) of N,N-dimethyl-aniline, 500 ml. of glacial acetic acid and left overnight. The next day, 179 g. (1.12 mole) of bromine was added drop-wise over a period of 1 hr. without cooling. After complete addition, the flask contents were cooled, added to 1500 ml. of water containing 50 g. of sodium bisulfite. After making the solution basic with sodium hydroxide, the crude product was extracted with ether and the resulting ether phase was concentrated to give 165 g. of a solid product. Recrystallization from 95% ethanol gave 102 g. (50%) of N,N-dimethyl-4-bromoaniline, m.p. 51-3° [Lit. 131: m.p. 55°].

(131) A. Weber, Ber., 8, 715(1875)

Preparation of 4-Bromophenyltrimethylammonium Iodide

A 250 ml. flask was charged with 30 g. (0.15 mole) of N,N-dimethyl-4-bromoaniline, 150 ml. of 95% ethanol and 32 g. (0.23 mole) of methyl iodide. The resulting solution was refluxed for 3 hr., cooled and the solvent removed on a
rotary evaporator. The residue was treated with 100 ml. of ether and filtered. The colorless 4-bromophenyltrimethylammonium iodide weighed 43.2 g. and gave a m.p. 185-6° with decomposition (sealed tube) \[ \text{Lit.}^{132} : \text{m.p.} 185° \]. From the ethereal filtrate was recovered 3.8 g. of unreacted N,N-di-

(132) C. Wurster and A. Scheibe, \textit{Ber.}, \textbf{12}, 1819(1879)

methyl-4-bromoaniline for a yield of 96.3% of the quaternary ammonium iodide based on unrecovered starting amine.

\textbf{Preparation of 4-Bromophenyltrimethylammonium Bifluoride}

To a 100 ml. silver flask was added 20 g. (0.059 mole) of 4-bromophenyltrimethylammonium iodide. After cooling in a dry ice-cooled bath, 8 ml. of liquid hydrogen fluoride (also at dry ice-acetone temperature) was added. The flask contents were agitated and subjected to reduced pressure overnight by means of a water aspirator. The residue was taken up in 125 ml. of dry acetone, dried over anhydrous potassium fluoride, filtered and the solvent removed on a rotary evaporator. The white solid (12.5 g.) which remains was completely soluble in water, insoluble in ether, gave a positive fluoride ion test and a negative iodide ion test. The solid was further dried at 1 mm. pressure over phosphorus pentoxide in a Abderhalden drying apparatus (boiling chloroform used as a heat source) to give m.p. 129-31°.

A 2.00 g. sample of the solid was dissolved in 50 ml. of distilled water and titrated with standard base. Since
15.61 meq. of base were consumed (phenolphthalein end-point), the bifluoride anion must be present and not the fluoride ion because two equivalents of base were required to neutralize one equivalent of the salt. Since excess hydrogen fluoride was employed in the synthesis, it was reasonable to expect the bifluoride anion to be found in the quaternary amine salt, since the only anion present in hydrogen fluoride is the bifluoride ion. Thus the salt formed was 4-bromophenyltrimethylammonium bifluoride.

When a sample of the above salt was neutralized with two equivalents of sodium hydroxide and the water removed from the neutral solution on a rotary evaporator 98% of theory of solid sodium fluoride was collected along with an oil. The oil was strongly basic to pH paper, and was tentatively assigned the structure of 4-bromophenyltrimethylammonium hydroxide. No amines were isolated from the oil.

Preparation of N,N-Dimethyl-2,4-dibromoaniline

A 3000 ml. three-necked flask was equipped with a stirrer, dropping funnel and water-cooled condenser. A solution of 242 g. (2.00 mole) of N,N-dimethylaniline in 1 l. of glacial acetic acid was added to the flask and then 640 g. (4.00 mole) of bromine was added dropwise while cooling by means of an ice bath. After complete addition, the red-brown slurry of 4-bromophenyltrimethylammonium bromide perbromide was treated portionwise with a slurry of 160 g. (1.95 mole) of anhydrous sodium acetate in 1000 ml. of gla-
cial acetic acid. After complete addition, the mixture was heated for 1 hr., cooled and poured into five times its volume of cold water. The resulting mixture was extracted with ether and the ether phase in turn was worked up as usual. After removal of the solvent on a rotary evaporator, the residue was subjected to distillation and gave 248.7 g. (44.6%) of N,N-dimethyl-2,4-dibromoaniline, b.p. 133-5°/7 mm., \( n_D^{24} = 1.6127 \) [Lit.: b.p. 275°/740 mm.], and 48.5 g. of residue. The product was pure by v.p.c. analysis.

(133) K. Fries, *Ann.*, 346, 189(1906)

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A 2000 ml. three-necked flask was equipped with a stirrer and water-cooled condenser. A mixture of 200 g. (0.683 mole) of commercial 2,4-dibromoacetanilide, 1000 ml. of 95% ethanol and 600 ml. of concentrated hydrochloric acid was added to the flask, refluxed for 1 hr., and then the condenser was replaced with a distilling head and 750 ml. of distillate (b.p. 78-95°) was removed. The residue in the flask was diluted with 500 ml. of water and poured over 2000 g. of crushed ice. Sufficient 40% sodium hydroxide was added to make the mixture basic. After filtration, washing with water and air drying for one day, 170.4 g. (99.3%) of white crystalline 2,4-dibromoaniline, m.p. 77.5-78.5° [Lit.\(^{134}\): m.p. 79°], was collected.

A 1000 ml. three-necked flask was equipped with a stirrer and water-cooled condenser. The flask was charged with
71.0 g. (0.28 mole) of 2,4-dibromoaniline and 120 g. of dimethyl sulfate was added portionwise to the flask followed by sufficient 30% sodium hydroxide to assure a basic solution (phenolphthalein indicator added to flask contents). Upon complete addition, the mixture was refluxed for 4 hrs., cooled and filtered. The red filtrate was extracted with 400 ml. of ether and the ether phase was worked up as usual. After removal of solvent on a rotary evaporator, the light brown oil (85.4 g.) was rectified to give 70 g. (88.8%) of N,N-dimethyl-2,4-dibromoaniline, b.p. 136-8°/8 mm., n_D^{15} = 1.6266 [Lit. 133: b.p. 275°/749 mm.] and 15 g. of residue. The product was contaminated by mono-methylated material which apparently codistilled with di-methylated product.

Preparation of 2,4-Dibromophenyltrimethylammonium Iodide

A mixture of 50 g. (0.18 mole) of N,N-dimethyl-2,4-dibromoaniline, 39 g. (0.28 mole) of methyl iodide and 200 ml. of 95% ethanol was added to a 500 ml. flask and refluxed for 48 hr. After cooling, the solvents were removed on a rotary evaporator and the residue treated with 200 ml. of ether and filtered. From the filtrate 24.8 g. of unreacted amine was recovered. The solid collected was washed with ether and dried to give 37 g. (97%) of 2,4-dibromophenyltrimethylammonium iodide, m.p. 117-8° (with decomposition). The
material was not hygroscopic.

**Preparation of 2,4-Dibromophenyltrimethylammonium Bifluoride**

Into a 100 ml. silver flask was placed 50 g. (0.12 mole) of 2,4-dibromophenyltrimethylammonium iodide. After cooling in a dry ice-acetone bath, 20 ml. of liquid hydrogen fluoride (also at dry ice-acetone temperature) was added. The mixture was allowed to warm to room temperature and subjected to reduced pressure via a water aspirator. The residue was taken up in excess absolute ethanol, filtered through anhydrous potassium fluoride and then the solvent was removed on a rotary evaporator. An ether insoluble oil (27.4 g.) was collected but resisted all attempts to crystallize from such solvents as ethanol and acetonitrile. Attempted drying over phosphorus pentoxide in an Abderhalden drying apparatus (using boiling chloroform as source of heat) also did not yield crystalline material. It was therefore assumed that the 2,4-dibromophenyltrimethylammonium bifluoride was an oil. The sample is completely soluble in water to give a positive fluoride ion test and a negative iodide ion test.

**Preparation of 2,4,6-Tribromoaniline**

A 2000 ml. three-necked flask was equipped with a dropping funnel, stirrer and water-cooled condenser. To the flask was added 600 ml. of glacial acetic acid and 100 ml. (1.10 mole) of aniline. The flask contents were cooled to 15° and 169 ml. of bromine was added with cooling. After complete addition, 200 ml. of additional glacial acetic acid
was added and the slurry poured over 5000 ml. of 1% NaHSO₃ solution. Filtration, followed by washing with water and air drying overnight, gave 331 g (91.2%) of 2,4,6-tribromoaniline, m.p. 118-119° (from benzene) [Lit.¹ 134: m.p. 119°].

Preparation of N,N-Dimethyl-2,4,6-tribromoaniline

A 1000 ml. three-necked flask was equipped with a stirrer and a solids introduction system, consisting of an Erlenmeyer flask connected to one of the necks of the reaction flask by means of an 8" piece of Gooch tubing. The third neck was left open. To the flask was added a mixture of 50 g. of paraformaldehyde and 250 ml. of 97% formic acid. The mixture was warmed and 200 g. (0.605 mole) of 2,4,6-tribromoaniline was added portionwise over a period of 20 min. After complete addition, the mixture was heated on a steam bath for 3 hrs. During this time, 100 ml. of additional formic acid and 20 g. of paraformaldehyde were added along with 200 ml. of ether (added in 25 ml. increments). The ether aided in achieving rapid homogeneity. After cooling, the mixture was continuously added to a solution of 450 g. of KOH and 200 g. of Na₂SO₃·7H₂O in 800 ml. of water. The resulting slurry was extracted with ether. The remaining aqueous slurry was filtered to give 76.5 g. of recovered 2,4,6-tribromoaniline.

The ether extracts were combined and concentrated on a rotary evaporator. The resulting oily residue was rectified at reduced pressure to give 119.0 g. (88.7%) of N,N-dimethyl-
Preparation of 2,4,6-Tribromophenyltrimethylammonium Iodide

A 500 ml. round bottom flask was charged with 88 g. (0.25 mole) of N,N-dimethyl-2,4,6-tribromoaniline, 200 g. of methyl iodide and 100 ml. of absolute ethanol. The solution was refluxed for 48 hrs., cooled, and added to an equal volume of ether. The solid material was collected by filtration to give 10 g. of 2,4,6-tribromophenyltrimethylammonium iodide, m.p. 135-60°. The latter dissolved in water and gave a positive iodide ion test with silver ion. Also heating of the quaternary ammonium iodide under reduced pressure gave methyl iodide and N,N-dimethyl-2,4,6-tribromoaniline. Therefore care must be exercised in order to maintain quaternization.

Attempts to obtain better yields of the quaternary ammonium iodide using absolute methanol, methanol-benzene, ethanol-benzene mixtures and even no solvent were not successful. However trace amounts of water in commercial methyl iodide were definitely detrimental to yields of the quaternary ammonium iodide. Therefore vigorous drying of reactants and solvents was necessary for maximum quaternization of N,N-dimethyl-2,4,6-tribromoaniline.
Preparation of 2,4,6-Tribromophenyltrimethylammonium Methyl Sulfate

A 100 ml. flask was charged with 10 g. (0.028 mole) of N,N-dimethyl-2,4,6-tribromaniline, 3.5 g. (0.028 mole) of dimethyl sulfate, 20 ml. of absolute methanol and 20 ml. of dry benzene. After refluxing for 28 hr., the flask contents were cooled to room temperature and the solvents removed on a rotary evaporator. The residue was treated with ether to recover 4 g. of ether soluble N,N-dimethyl-2,4,6-tribromoaniline. The ether insoluble fraction (8 g.) was completely soluble in water and therefore was assumed to be the expected 2,4,6-tribromophenyltrimethylammonium methyl sulfate formed in nearly quantitative yield based on unrecovered starting material. Attempted distillation of the salt at reduced pressure gave the tertiary amine back along with dimethyl sulfate.

Preparation of 2,4,6-Tribromophenyltrimethylammonium Bifluoride

A 2 oz. polyethylene bottle was charged with 2.8 g. (0.0056 mole) of 2,4,6-tribromophenyltrimethylammonium iodide and then portionwise with 2 ml. of liquid hydrogen fluoride at dry ice-acetone temperature. The resulting pink solution was subjected to reduced pressure via a water aspirator. The resulting white solid (2.1 g.), m.p. 58-62°, was completely soluble in water, giving a positive fluoride ion test and a negative iodide ion test. The salt was not soluble in ether. Since the 2,4,6-tribromophenyltrimethyl-
ammonium bifluoride was extremely hygroscopic, it was difficult to determine the m.p. to any greater accuracy. Also due to the fact that excess hydrogen fluoride was employed in the synthesis, the bifluoride salt, not the fluoride salt, was formed.

**Fluorination of 4-Bromophenyltrimethylammonium Bifluoride**

**A.** A 250 ml. three-necked flask equipped with a stirrer, water-cooled condenser and thermometer was charged with 6.0 g. (0.11 mole) of anhydrous potassium fluoride, 5.0 g. (0.020 mole) of 4-bromophenyltrimethylammonium bifluoride and 160 ml. of dry dimethylformamide (DMF). The mixture was heated to reflux for 6 hr., then cooled and an aliquot removed and tested for the presence of bromide ion. The result was negative. After pouring the crude reaction mixture into 500 ml. of water, followed by extraction with 200 ml. of ether, the ether phase was washed with water, saturated sodium chloride solution and filtered through anhydrous magnesium sulfate. After removal of solvent on a rotary evaporator, 3.65 g. (93%) of N,N-dimethyl-4-bromoaniline, m.p. 53.5-54.5°, was recovered. The melting point was not depressed upon mixing with an authentic sample.

**B.** An identical run using acetonitrile in place of DMF was refluxed for 16 hr., cooled and filtered. The salts collected by filtration were dissolved in water and gave a negative bromide ion test. The filtrate was concentrated on a rotary evaporator and the ether insoluble
residue (4.6 g.) dissolved completely in water to give a positive fluoride ion test and a negative bromide ion test. Therefore the use of acetonitrile (b.p. 81-2°) gave recovery of unreacted starting material since none of the free tertiary amine was recovered as above.