A study of chloretone and related compounds

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A STUDY OF CHLORETON & RELATED COMPOUNDS

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In 188, Willgerodt (16) prepared acetone chloroform by condensing acetone with chloroform by means of pulverized potassium hydroxide. This compound, also known as trichloro-tertiarybutyl alcohol, is a white crystalline substance possessing a camphor-like odor and taste.

A few years later, J. A. Abel (15) made an investigation of this compound to determine its effects upon the body. His study showed that the compound, when given in proper doses, produced in the lower animals a profound sleep with complete anaesthesia without the respiration or blood pressure being seriously affected. After further investigation, Abel, in 1894, introduced Willgerodt's compound under the name of Chloretone as an anaesthetic and hypnotic.

Chloretone never became very extensively used as an anaesthetic, however, except in the physiological laboratory, although it has been commonly used as an hypnotic and local anaesthetic. It also has a number of other uses which make it an important medicinal compound (6). When taken internally, it has no irritant action on the stomach. On the contrary, it has a sedative as well as an anaesthetic action, and very favorable results have attended its use in sea-sickness, vomiting, chorea, etc. It is the chief ingredient in the proprietary medicine known as "Zotos". It also possesses antiseptic powers, and occasionally has been used for this purpose. In some cases, it has been employed as a local
anaesthetic for the mucous membrane of the larynx, and its solution in liquid petrolatum along with menthol and aromatic oils affords relief in irritable conditions of the nasal, pharyngeal and bronchial mucous membranes (11).

A consideration of these many uses of Chloretone, together with the apparent lack of information regarding analogous compounds derived from ketones related to acetone led to this present investigation. It was thought desirable to discover whether or not a number of other ketones would also condense with chloroform in a manner similar to that in which acetone did. It was further hoped that these new compounds might find a useful application in medicine.

It was proposed, therefore, to prepare first the compound, Chloretone, then to carry out a series of similar experiments using ethyl methyl ketone, diethyl ketone, and some related ketones in place of acetone.
THEORETICAL DISCUSSION

The discussion about to follow will consist mostly of a consideration of the compound Chloretone with various literature references, followed by a brief review of the physiological effects of some of the radicals which make up the compounds concerned in the investigation.

The references to the preparation of Chloretone are not very numerous. Willgerodt first prepared the compound in 1881 (16). He observed that acetone chloroform will always result if one allows solid, pulverized caustic potash to react with a quite arbitrary mixture of acetone and chloroform.

\[ \text{Acetone} \quad \text{KOH} \quad \text{Chloroform} \quad \text{Chloretone} \quad \text{Trichlorotertiarybutyl alcohol} \]

At first he used the proportions of 25 gm. of acetone to 25 gm. of chloroform and added gradually 5 gm. of pulverized potassium hydroxide. He noticed that after a few additions of potassium hydroxide were made, further additions caused a violent reaction and the flask had to be cooled before adding more of the alkali.

Now, an interesting thing about Willgerodt's preparation is that he always stopped adding the alkali while there still remained in the flask uncondensed chloroform and ketone. To use up all the materials, he filtered off the precipitate formed,
and washed this with ether. Then he distilled off the ether, chloroform and acetone and used this mixture for further preparation of Chloretone. He added 5 gm. of alkali to this mixture, as in the first case, and then proceeded as above. He repeated this procedure until further additions of potassium hydroxide showed no reaction. In this manner he was able to prepare quite large amounts of Chloretone. The Chloretone was recovered by pouring the oily liquid remaining in the flask into water. Transparent needle-like crystals of Chloretone were obtained.

In the above reaction, Willgerodt spoke of a white precipitate being formed which consisted mostly of potassium chloride. This white precipitate is due to the reaction between the chloroform and the potassium hydroxide (14), thus:

\[
\begin{align*}
\text{CHCl}_3 & \quad \text{3KOH} & \quad \text{HCOOH} & \quad 3\text{KCl} & \quad \text{H}_2\text{O} \\
\text{Chloroform} & \quad \text{Potassium hydroxide} & \quad \text{Formic acid} & \quad \text{Potassium chloride} \\
\text{HCOOH} & \quad \text{KOH} & \quad \text{HCOOK} & \quad \text{H}_2\text{O} \\
& \quad \text{Potassium formate}
\end{align*}
\]

So, in this white precipitate formed, there must be potassium chloride, potassium formate and any excess potassium hydroxide. This reaction takes place even when the mixture is kept at 0°C.

Now, the action of the potassium hydroxide in forming Chloretone is catalytic, so it can be seen that, since the above reaction takes place with the chloroform, the amount of
the alkali to be used is somewhat of a problem. This is especially true on account of the fact that the alkali will decompose the Chloretone formed if too great an amount of the alkali is present. The reaction, therefore, must proceed very slowly and it seems that the ideal place to stop would be at the point where all the chloroform has been used up in the two reactions that take place. It was shown in the laboratory, however, that as the Chloretone becomes more concentrated in the excess ketone and chloroform left, the further additions of the alkali will cause the decomposition of the product.

In this first experiment, Willgerodt discovered the solid acetone chloroform. Later a more extensive study was made of the compound by Willgerodt in conjunction with Genieser (17).

They used the proportions 500 gm. acetone to 100 gm. chloroform and added the pulverized potassium hydroxide over a period of two days while cooling the mixture with ice. It was then allowed to stand at room temperature for a further one and one-half days. After fractionating the liquid, they concluded that the acetone chloroform existed in two forms. The first form was a heavy liquid boiling at 167°. It was found to polymerize quickly in light and to go over into the solid form in damp air. The liquid acetone chloroform is poisonous and destroys organic matter. Somewhat doubtfully, the formula \( \text{C}10-\text{C(CH}_3)_2-\text{CHCl}_2 \) was ascribed to it.

In this same investigation, Willgerodt and Genieser studied further the solid acetone chloroform. This was formed by pouring the liquid acetone chloroform in water. The solid was considered to have the following formula:
The compound consists of crystals that have an odor like that of camphor and melt at 80–81°. It loses its water of crystallization upon being distilled, is soluble in 125 parts of water and very soluble in organic solvents. This form is stable in light and more reactive than the liquid form.

The compound acetone chloroform or trichlorotertertiary-butyl alcohol was also later prepared by Marcel Guedras (9) by dropping the mixture of acetone and chloroform upon the potassium hydroxide and then heating the mixture to 60°.

The most recent procedure, and the one followed in this present work, was found in "Organic Medical Chemistry" by Barrowcliff and Carr (1).

After preparing and investigating other properties of Chloretons, Willgerodt and Genieser made a number of derivatives of Chloreton by reaction between it and other substances (2). It also should be mentioned that a compound, acetone bromeform, or Brometone was made by Willgerodt (16). No references, however, could be found where chloroform was condensed with other ketones.

Although Willgerodt did not state that he was attempting to prepare a compound that might be useful in medicine, nevertheless, he prepared an excellent substitute for chloral hydrate. Chloral hydrate was the first artificial hypnotic, but had many draw backs (7). It possesses an unpleasant taste
and produces a burning feeling in the stomach. It also has a harmful by-effect upon the heart. Chloretone, on the other hand produces the same desired physiological effects without the accompanying injurious effects of chloral hydrate. However, Chloretone is a solid and cannot be as readily used as an anaesthetic like ether, although Chloretone has anaesthetic properties due to its narcotic action. This narcotic property of Chloretone is probably due to the chlorine in the molecule.

Certain radicals, such as the alkyl radical also seem to cause a narcotic action. It might be well, here, to discuss just briefly some of the characteristic physiological effects of some of the radicals or groups that are present in the compounds concerned in this work.

First it should be pointed out that a hypnotic is used primarily to produce sleep; a general anaesthetic causes insensibility to pain, together with unconsciousness; and a narcotic is used to produce a kind of stupor (10). Substances used as anaesthetics are considered to have narcotic properties, the general anaesthetics being substances like ether and chloroform that can be inhaled readily and thus become absorbed quickly and act at once. Anaesthetics, then, are narcotics.

Narcotic action is produced by the aliphatic hydrocarbons (8), the higher members possessing greater properties than the lower ones up to a certain point. Likewise, the alkyl radicals indicate a narcotic action, and the ethyl radical is more effective than the methyl. For example, methyl alcohol, although possessing toxic properties, has no narcotic action,
while ethyl alcohol has.

In the case of ethyl alcohol the narcotic property is considered to be due to the ethyl radical rather than the hydroxyl group. The hydroxyl group shows evidence of being able to become anchored to certain special tissues. The part which it plays, therefore, is that of localizing the action of the drug. In nearly every case, local anaesthetics contain the hydroxyl group. The effect of increasing the number of hydroxyl groups in aliphatic compounds, however, tends to decrease the physiological action of the compound. For example, the narcotic alcohols, which are mono-hydroxy alcohols, are transformed into the harmless glycols, glycerol, the poly-hydroxy alcohols, etc. Another observation concerning alcohols is that primary alcohols are less active than secondary alcohols, and secondary alcohols are less active than tertiary.

It has been mentioned that the introduction of chlorine into the molecule causes the substance to have a narcotic action. This is true as a general rule, and in most cases the greater the number of chlorine atoms the greater the narcotic action, as for example:

Methane, \( \text{CH}_4 \), has no narcotic action.

Methyl Chloride, \( \text{CH}_3\text{Cl} \), has a narcotic action.

Chloroform, \( \text{CHCl}_3 \), has a greater narcotic action.

The increased narcotic action caused by chlorine is usually accompanied by a depressing action on the heart, although Chloretone is considered to be without this effect. Chloretone, it will be observed, contains three atoms of
chlorine, an hydroxyl group, and two methyl radicals. It is also a tertiary alcohol.

Compounds analogous to Chloretone could have, in place of one methyl radical, a higher alkyl radical, or they might have both methyl radicals replaced by higher alkyl radicals. A ring ketone could take the place of both methyl radicals, as in the case of the compound, cyclohexanone.
The experimental work of this investigation involved the preparation or attempted preparation of Chloretone, itself, and compounds related to it. Chloretone, as has been stated, results from the condensation of acetone and chloroform under the catalytic action of potassium hydroxide. Other ketones may possibly condense in a similar way yielding analogues of Chloretone. The work, therefore, may be divided as follows:

I. Preparation of Chloretone.
II. Condensation of Ethyl Methyl Ketone and Chloroform.
III. Condensation of Diethyl Ketone and Chloroform.
IV. Condensation of Normal-hexyl Methyl Ketone and Chloroform.
V. Condensation of Acetophenone and Chloroform.
VI. Condensation of Cyclohexanone and Chloroform.
VII. Condensation of Camphor and Chloroform.
VIII. Condensation of Acetone and Chloroform with Sodaamide as the Catalyst.

Aside from the preparation of Chloretone, only one of the above condensations was successful, that of cyclohexanone and chloroform.

The apparatus used for all these experiments consisted of a three necked flask and a mechanical stirrer operated by an electric motor. As the liquids used were volatile, a mercury sealed stirrer was used, and the two outside openings of the flask were kept corked. Additions of potassium hydroxide were made through one of these openings.
I. The Preparation of Chloratone

The method used is a modification of Willgerodt's method (16) taken from Barrowcliff and Carr's "Organic Medical Chemistry".

### Materials Used

<table>
<thead>
<tr>
<th>Material</th>
<th>Amount</th>
<th>M.W.</th>
<th>B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>50 gm.</td>
<td>56.05</td>
<td>56.50</td>
</tr>
<tr>
<td>Chloroform</td>
<td>100 gm.</td>
<td>119.38</td>
<td>61.20</td>
</tr>
<tr>
<td>Potassium Hydroxide</td>
<td>32.5 gm.</td>
<td>86.0</td>
<td></td>
</tr>
</tbody>
</table>

### Condensation Reaction

\[
\begin{align*}
\text{CHCl}_3 & \xrightarrow{\text{KOH}} \text{CH}_3--\text{C}--\text{CH}_3 \\
\text{Chloroform} & \xrightarrow{\text{Acetone}} \text{Chloratone} \\
\end{align*}
\]

### Yield

Theoretical: ------------ 150 gm.
Actual: ------------ 10 gm.

\[6.7\%\]

Procedure: To a mixture of 50 gm. dry acetone and 100 gm. of chloroform, cooled to below 0° and continuously stirred, were added gradually, over a period of two and one-half days, 32.5 gm. of finely powdered potassium hydroxide. The caustic potash was added during about fifteen minute intervals. At the end of each day, the flask containing the reaction mixture was packed in ice and placed in a refrigerator.

After being allowed to stand at room temperature for a further one and one-half days, with intermittent stirring, the mass was filtered and the residue washed with acetone.
The combined filtrate and washings were then distilled; unchanged chloroform and acetone were recovered, and the fraction passing over between 168° and 172° was collected separately.

This fraction was then shaken with a little water. Crystallization set in and when this was complete, the solid was filtered off and recrystallized from a mixture of alcohol and water. As Chloroform is extremely volatile, the product, consisting of needle-like crystals, was dried by pressing between filter paper and placed in a tightly corked sample bottle.

The properties of this compound have been described in the previous section.
II. Condensation of Ethyl Methyl Ketone and Chloroform

A preliminary test showed no evidence of the violent reaction, characteristic of the preparation of Chloroetone, when pulverized potassium hydroxide was added to a mixture of ethyl methyl ketone and chloroform. For this reason, the cooling of the reaction mixture with ice was considered unnecessary.

**Materials Used**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Amount (gm.)</th>
<th>M.W.</th>
<th>B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl methyl ketone</td>
<td>25</td>
<td>72.06</td>
<td>80.80</td>
</tr>
<tr>
<td>Chloroform</td>
<td>42</td>
<td>119.38</td>
<td>61.2</td>
</tr>
<tr>
<td>Potassium hydroxide</td>
<td>15</td>
<td>56.</td>
<td></td>
</tr>
</tbody>
</table>

**Desired Reaction**

\[
\begin{align*}
\text{Ethyl methyl ketone} & \quad \text{CH}_3--\text{C}--\text{C}_2\text{H}_5 \\
\text{Chloroform} & \quad \text{CHCl}_3 \\
\text{Potassium hydroxide} & \quad \text{OH} \\
\text{Product} & \quad \text{CH}_3--\text{C}--\text{C}_2\text{H}_5 \quad \text{CCl}_3
\end{align*}
\]

**Theoretical yield**--------67 gm.

**Actual yield**-----------none.

**Procedure:** To a mixture of 25 gm. of ethyl methyl ketone and 42 gm. of chloroform 15 gm. of pulverized potassium hydroxide were added, during constant stirring, over a period of two and one-half days. After several additions of the potassium hydroxide had been made a yellowish color was imparted to the liquid.

The stirring was allowed to continue through the night and throughout the entire operation.

At the expiration of one and one-half days following the final additions of the potassium hydroxide, the mixture
was filtered and the precipitate thoroughly washed with chloroform.

The precipitate was further washed with alcohol and dried. 9 gm. of white solid were recovered. This was found to be very soluble in water and non-alkaline. Tests showed the presence of large amounts of chlorine and potassium and the mass, undoubtedly, consisted mostly of potassium chloride.

The filtrate was distilled and the majority of the liquid came over between the temperatures of 61° to 83°. This liquid consisted of the unchanged ketone and chloroform.

A very small amount of dark colored liquid remained in the flask, and, upon further distillation, yielded a small quantity of yellow liquid boiling at a rising temperature upwards to 180°.

This last portion had a rather pungent, sickly odor. A test for chlorine was made in the following manner:

A small quantity of the liquid was placed in a test tube and a little solid silver nitrate added together with a few cc. of concentrated nitric acid.

The test tube was then heated gently over a free flame. If any of the desired condensation product were present, this would be decomposed by the nitric acid and a white precipitate of silver chloride would be formed. No precipitate resulted, and the desired reaction was concluded not to have taken place.

A variation of the above procedure was tried in the following manner:
To the mixture of 25 gm. of ethyl methyl ketone and 42 gm. of chloroform were added, during constant stirring, 15 gm. of pulverized potassium hydroxide over a period of five minutes. This mixture was allowed to stand for one and one-half days with constant stirring. At the end of this time, the reaction mixture was treated in the manner described above and the results obtained were very similar, no condensation product of the ketone and chloroform being recovered.

A further attempt to condense ethyl methyl ketone was made. In this experiment 28 gm. of ethyl methyl ketone and 41.5 gm. of chloroform were used. The quantity of potassium hydroxide was increased to 20 gm.

Since unpurified ethyl methyl ketone had been previously used, it was first dried over calcium chloride and then distilled, the fraction boiling between 79° to 84° being used.

The ketone and chloroform were mixed in the reaction flask and then kept cool with ice. The 20 gm. of pulverized potassium hydroxide were added gradually over a period of one and one-half days. At the end of this time 15 gm. of chloroform were added to the mixture and the additions of potassium hydroxide continued for a further one and one-half days.

After standing at room temperature with intermittent stirring, the precipitate was filtered off and washed and thoroughly pressed in a Büchner funnel. The yellowish
colored filtrate contained a small amount of darker yellow liquid separated in a layer on top of the filtrate. This layer was separated, found to be strongly alkaline to litmus and readily taken up by calcium chloride. It was concluded that this layer consisted of water due to the reaction between the chloroform and potassium hydroxide as previously described.

The unchanged chloroform and ketone were distilled off from the main portion of the filtrate. A quantity not exceeding 5 cc. remained in the distilling flask, and this distilled over between 140° and 150°. The resulting liquid was yellow in color, contained the same disagreeable odor that was obtained in the two previous experiments and showed no test for chlorine.
III. Condensation of Diethyl Ketone with Chloroform

In a preliminary test repeated additions of pulverized potassium hydroxide to a mixture of diethyl ketone and chloroform showed no evidence of the violent reaction with the evolution of heat characteristic of the Chloretone experiment.

Materials Used

<table>
<thead>
<tr>
<th>Material</th>
<th>M.</th>
<th>B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl Ketone</td>
<td>34 gm.</td>
<td>36</td>
</tr>
<tr>
<td>Chloroform</td>
<td>47.3 gm.</td>
<td>119.38</td>
</tr>
<tr>
<td>Potassium hydroxide</td>
<td>32.6 gm.</td>
<td></td>
</tr>
</tbody>
</table>

Desired Reaction

\[
\begin{align*}
\text{Diethyl ketone} & \quad \text{KOH} \\
\text{C}_2\text{H}_5-\text{C}-\text{C}_2\text{H}_5 & \quad \text{CHCl}_3
\end{align*}
\]

Theoretical yield—81.3 gm.
Actual yield—None.

In the preparation of Chloretone, 0.65 gm. of potassium hydroxide was used for each gram of acetone used. Instead of using similar amounts in this experiment, it was decided to use 1.46 times the amount used in the Chloretone experiment, since the molecular weight of diethyl ketone is 1.46 times that of acetone. This corresponds to 0.96 gm. of potassium hydroxide to one gram of diethyl ketone or 32.6 gm. when using 34 gm. of diethyl ketone.

The amounts of chloroform and acetone taken were in equal molecular quantities.
Procedure: The 34 gm. of diethyl ketone and the 47.3 gm. of chloroform were mixed in the reaction flask and the pulverized potassium hydroxide added gradually over a period of two and one-half days with constant stirring and the mixture kept cool with ice. After standing the customary one and one-half days at room temperature and with continued stirring, the white precipitate was filtered off and washed with chloroform.

Two layers were evident in the filtrate. The smaller lower layer, yellowish in color, was drawn off in a separatory funnel. It was found to be strongly alkaline and was concluded to be water as in the case of the experiment with ethyl methyl ketone.

The colorless layer was dried over calcium chloride and distilled. Most of the liquid distilled at 100–105° and consisted of the unchanged diethyl ketone. A very small portion came over at a rising temperature reaching 180°. This had a strong rather disagreeable odor and was colored yellow during the last few days.

The usual test for chlorine in this liquid failed. The desired condensation evidently did not take place.

The above experiment was repeated with the reaction mixture at room temperature instead of cooling it with ice. The results were practically the same and no condensation product was obtained.
IV. Condensation of N-Hexyl Methyl Ketone with Chloroform

Materials Used

<table>
<thead>
<tr>
<th>Material</th>
<th>Weight</th>
<th>M.P.</th>
<th>B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Hexyl methyl ketone</td>
<td>25 gm.</td>
<td>128.13</td>
<td>172.50</td>
</tr>
<tr>
<td>Chloroform</td>
<td>23.3 gm.</td>
<td>119.38</td>
<td>61.20</td>
</tr>
<tr>
<td>Potassium hydroxide</td>
<td>8.2 gm.</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

Desired Reaction

\[
\text{CH}_3\text{--C--C}_6\text{H}_{13} + \text{CHCl}_3 \rightarrow \text{CH}_3\text{--C--C}_6\text{H}_{13} + \text{CCl}_3
\]

N-hexyl methyl ketone

Procedure: Unpurified ketone was used. This was first distilled and 25 gm. boiling at 170.5 was collected and used in the experiment. This was mixed with 23.3 gm. chloroform and cooled with ice. The pulverized potassium hydroxide was added gradually over a period of two and one-half days as in previous experiment.

The first additions of alkali formed a lumpy mass which settled to the bottom. A yellowish color appeared which later seemed to disappear. After the customary standing for one and one-half days, the liquid was slightly yellow in color. A white precipitate was present which was filtered off with suction and washed with chloroform. The liquid reacted alkaline to litmus and upon distilling a white precipitate settled out.

After most of the chloroform was apparently distilled off, the white precipitate continued to settle out when the liquid was heated for further distillation. This white precipitate was evidently potassium chloride formed by the
reaction of the alkali with chloroform that still remained. To remove alkali, the liquid was washed with water. An emulsion persisted for some time, but was broken by saturating with sodium chloride. The clear liquid was now decanted and the water layer separated. The liquid containing the ketone was now dried over calcium chloride and distilled up to 175°C, a little above the boiling point of the ketone.

The liquid remaining in the distilling flask was then distilled under about 15 mm pressure. A small amount of yellowish colored liquid came over between 130° and 160° leaving a heavy tarry mass in the distilling flask.

The collected fraction showed no test for chlorine. The tarry mass also showed no test for chlorine. The condensation evidently did not take place.

V. Condensation of Acetophenone with Chloroform

Materials Used

<table>
<thead>
<tr>
<th>Material</th>
<th>Amount</th>
<th>M.W.</th>
<th>B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetophenone</td>
<td>25 gm.</td>
<td>120.06</td>
<td>202°</td>
</tr>
<tr>
<td>Chloroform</td>
<td>25 gm.</td>
<td>119.33</td>
<td>61.2°</td>
</tr>
<tr>
<td>Potassium hydroxide</td>
<td>12 gm.</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

Desired Reaction

\[
\begin{align*}
\text{C}_6\text{H}_5-\text{C}-\text{CH}_3 & \quad \text{CHCl}_3 \\
\text{CHCl}_3 & \quad \text{C}_6\text{H}_5-\text{C}-\text{CR}_3
\end{align*}
\]

Acetophenone Chloroform

Theoretical yield———50 gm.
Actual yield———None.
Procedure: The 25 gm. acetophenone were mixed with 25 gm. chloroform and the pulverized potassium hydroxide was added gradually with constant stirring. The mixture was cooled with ice during the reaction.

Upon adding the potassium hydroxide, a brownish color was imparted to the liquid. An investigation showed that this color was due to the action of the alkali on the acetophenone; for, when potassium hydroxide was added to acetophenone, a dark brown color appeared. An odor resembling the odor of orange blossoms was detected from this mixture. The same odor was evolved from the reaction mixture. Two and one half days were taken for the addition of the potassium hydroxide and the mixture was allowed to stand for a day and a half, as in previous experiments. The liquid was a dark brown color and seemed to have the solid matter suspended throughout. A deep white precipitate settled out upon the addition of alcohol.

The white precipitate was filtered off and the filtrate distilled. Unchanged chloroform, alcohol, and acetophenone were recovered. There remained back in the flask a thick brown mass which hardened upon cooling. This mass was undoubtedly formed by the action of the alkali upon the acetophenone. As the material was not the desired condensation product, no attempt was made here to discover its identity other than that it did not distill over at a very high temperature.

A second attempt to condense acetophenone with chloroform was made. In this case, 25 gm. of acetophenone and 25 gm. of
chloroform were used together with 25 cc. of alcohol, and
the pulverized potassium hydroxide was added to this mixture
as above.

At the end of the reaction a dark brown colored liquid
and a white precipitate remained, as in the first experiment.
The white precipitate settled in this liquid.

The alcohol and chloroform were distilled off and the
liquid remaining in the flask allowed to stand for some time;
as it happened in this case, the liquid stood over the week-
end. Upon examining the mixture, distinct crystals were
apparent in the dark colored liquid. These were filtered
on a Witt filter and washed with cold alcohol until pure
white. The crystals were then dried on filter paper and
placed in a sample bottle.

OBSERVED under a microscope the crystals appeared to be
flat needle-like bodies.

A small portion placed on a piece of platinum foil and
heated over a free flame entirely vanished, leaving no trace
of ash. The material was concluded to be organic matter.

A test for chlorine was made in the following manner:(12)
A small piece of sodium about the size of a pea was placed
in a test tube and heated in a flame until vapors were seen to
rise in the test tube. At this point, a small sample of the
white crystals was allowed to drop in the sodium vapor and
the test tube again heated gently. The hot test tube was now
lowered into a small quantity of distilled water (about 10 cc.) and the bottom allowed to crack out. The sodium salt was then dissolved by heating the water gently and stirring. The mixture was filtered and the filtrate acidified with nitric acid and treated with a solution of silver nitrate. No white precipitate formed, indicating the absence of chlorine in the compound.

A third experiment was carried out using 26 gm. of acetophenone and 25 gm. of chloroform together with 25 cc. of alcohol. The mixture was cooled and the pulverized potassium hydroxide added very slowly. At the end of two days, 7.5 gm. had been added. The mixture was allowed to be stirred during the night at room temperature and was found to be very alkaline the next morning. It was decided to allow the mixture to stand for a day without further additions of the alkali. The precipitate was then filtered and washed with alcohol. The filtrate was distilled to remove alcohol and chloroform. The liquid remaining in the flask was a dark brown as before. The flask was placed into an ice and salt mixture in an attempt to crystallize out the white product which previously had crystallized out of a similar solution, upon standing for a day and a half. No crystals seemed to appear with this treatment.

Upon standing for a day, however, the white crystals appeared. These were extracted as before.

The brown liquid was now evaporated for several hours on a steam bath, then a little chloroform added. Upon standing a while, more crystals appeared. These were also extracted
and a total of one gram recovered. A test for chlorine failed to show any chlorine present.

The melting point of the compound was found to be between 86° and 88°. As the compound was evidently not the compound sought, no more efforts were made to identify it. It was found to be very soluble in water and soluble in alcohol. It was less soluble in chloroform and could be crystallized from chloroform.

VI. Condensation of Cyclohexanone with Chloroform

As in the previous experiments, equimolecular quantities of the ketone and chloroform were taken. The amount of potassium hydroxide used was based upon the proportion corresponding to that taken in the Chlorotone experiment. In the Chlorotone experiment, 0.325 of the alkali was used for each gram of chloroform used; so, for each gram of chloroform used, .325 gram of potassium hydroxide was used.

Materials Used

<table>
<thead>
<tr>
<th></th>
<th>M.W.</th>
<th>B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexanone</td>
<td>25 gm.</td>
<td>93.08</td>
</tr>
<tr>
<td>Chloroform</td>
<td>30.30 gm.</td>
<td>119.38</td>
</tr>
<tr>
<td>Potassium hydroxide</td>
<td>9.70 gm.</td>
<td>56</td>
</tr>
</tbody>
</table>
**Reaction**

\[
\begin{array}{ccc}
\text{H}_2\text{C} & \text{CH}_2 & \text{CHCl}_3 \\
\text{H}_2\text{C} & \text{CH}_2 & \text{H}_2\text{C} \\
\text{H}_2 & & \text{H}_2
\end{array}
\]

Cyclohexanone  Chloroform

Theoretical yield———55 gm.
Actual yield———1.3 gm.

**Procedure:** The 30.3 gm. of chloroform were mixed with 23 gm. of cyclohexanone in the reaction flask. With constant stirring, the finely pulverized potassium hydroxide was added in small amounts, at first, without cooling. When approximately 3 gm. had been added, further small additions produced a lively reaction accompanied by the evolution of heat. Small bits of matter appearing to be charred were observed in the mixture, suggesting probable decomposition taking place.

At this point, the reaction mixture was cooled with ice and salt and additions of the alkali continued.

When the alkali was not immediately stirred into the mixture, but allowed to float a time on top, the formerly observed lively reaction again became evident. This behavior resembled strikingly that characteristic of the Chloroetone experiment.

At the end of the first day, it was decided to add 16 gm. of cyclohexanone and 19 gm. of chloroform to make allowance
for any decomposition of the condensation product that might have resulted from the observed lively reactions that took place thus far. (The amounts were arbitrary).

At the close of each day, the reaction flask was thoroughly packed with ice and the mixture allowed to be stirred during the night. On the following day, the flask was freshly packed with ice and the additions of pulverized potassium hydroxide continued. The addition of 9.7 gm. was made during a space of two and one half days, after which the mixture was stirred at room temperature for a further one and a half days.

The white precipitate formed in the reaction was now filtered off with suction and washed with chloroform. The filtrate was distilled to remove unchanged chloroform and ketone. When the temperature had reached 140°, a white precipitate was observed to be separating out in the distilling flask. The distillation was stopped and the liquid found to be alkaline. To remove any alkali that might be present, the liquid was filtered and the filtrate treated with water and extracted with ether. The ether layer was separated and dried over calcium chloride.

After distilling off the ether on a water bath, the remaining liquid was distilled at about 13-15 mm. pressure. Two fractions were collected, as the amount of liquid was small. Between 45° to 55° about half the liquid came over. The temperature then rose rapidly to 80° and the receiving flask was changed. The temperature gradually rose to 123° and remained here until most of the remaining portion was distilled. A small amount of thick substance remained
in the distilling flask which turned into a sticky hard mass upon cooling.

After standing over the week-end, the second fraction became tinted yellowish. Several clear crystals were observed in the neck of the flask. The flask was cooled in a mixture of ice and water with the result that nearly all the liquid crystallized into clear white crystals. These were filtered on a Witt filter and pressed to draw out as much liquid as possible. A clear white crystalline product was obtained which was pressed between filter paper and placed in a bottle.

The product contained a decided camphor-like odor resembling somewhat that of Chloretone.

The product clinging to the receiving flask was dissolved in ether, and the ether allowed to evaporate. Crystals were obtained upon cooling which were likewise filtered and collected; 1.8 gm. were recovered in all.

A small portion of the substance was tested for chlorine by adding concentrated nitric acid and solid silver nitrate and heating in a test tube. An abundant white precipitate resulted.

The product seemed to melt at slightly above room temperature.

The results of the first experiment with cyclohexanone and chloroform seemed to indicate that a condensation had taken place between these two compounds. It was desired to prepare a quantity large enough to use for a more complete identification.
Materials Used

<table>
<thead>
<tr>
<th>Substance</th>
<th>Mass (gm)</th>
<th>M.</th>
<th>B. F.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexanone</td>
<td>100</td>
<td>98.08</td>
<td>185-70</td>
</tr>
<tr>
<td>Chloroform</td>
<td>121.5</td>
<td>119.38</td>
<td>61.2</td>
</tr>
<tr>
<td>Potassium hydroxide</td>
<td>36</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

Theoretical yield——---221.5 gm.
Actual yield----------10 gm.

The cyclohexanone was purified by redistillation and 100 grams boiling between 154° and 160° were mixed with 121.5 gm. of chloroform. The mixture was cooled with ice and the pulverized potassium hydroxide gradually added over a period of two and one-half days with constant stirring. After standing for one and one-half days at room temperature with stirring, the mixture was filtered and the precipitate washed with chloroform.

As the liquid was alkaline to litmus it was decided to try to wash the liquid with water at this point. A milky emulsion resulted which was separated in a separatory funnel. The yellowish layer was extracted several times with ether and the ether distilled. Only a very small quantity, approximately 5 cc. remained.

Cyclohexanone is very soluble in water, the liquids were all combined again and the water saturated with sodium chloride. Ether was added and the layer containing ether, chloroform, etc. was separated off. Three more extractions were made of the salt solution with ether and the combined extractions distilled to free from ether and chloroform, after having been dried over calcium chloride.

The liquid was further distilled up to 160°. The remain-
ing liquid in the flask was then distilled at about 13 to 15 mm. pressure.

The following fractions were collected.

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Temperature Range</th>
<th>Pressure Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>45° to 75°</td>
<td>(13-15 mm.)</td>
</tr>
<tr>
<td>Second</td>
<td>75° to 120°</td>
<td>(13-15 mm.)</td>
</tr>
<tr>
<td>Third</td>
<td>120° to 140°</td>
<td>(13-15 mm.)</td>
</tr>
</tbody>
</table>

The third fraction crystallized in the receiving flask. Both second and third became tinted pink.

The second fraction was redistilled and the fraction 110° to 125° (13-15 mm.) collected. This crystallized on standing. It amounted to 6.5 gm.

This fraction was united with the third fraction and redistilled at 13-15 mm. The following three fractions were collected:

A. 90° to 115°

About half of this fraction formed white crystals turning pinkish.

B. 115° to 128°.

All of this crystallized in the receiving flask. This also was tinted pink.

C. 120° to 130°.

Most of this formed white crystals with a pinkish tint finally appearing.

Fraction "B", was melted by heating the flask in hot water. The melted product was then poured into a small wide mouthed bottle where it recrystallized on cooling. The crystallized mass weighed ten grams. It was removed with a spatula to a large filter paper and repeatedly pressed between filter papers.
until dry. It was then allowed to stand in the air for one hour. The final product was very slightly tinted pink and now weighed 7.4 gm. This sample was used in the following tests.

**Fractions A. & C.**

Excess liquid was poured off in a small beaker and the crystals dissolved in a little ether. To this was added, also, the ether washings of the filters used in drying fraction B. The ether was allowed to evaporate in a small wide mouthed sample bottle. A yellowish liquid remained out of which crystallized a quantity of the product weighing 2.6 gm., making a total of 10 gm. in all.

**Identification of the Product**

**Molecular Weight Determination by the Lowering of the Freezing of Benzene.**

If the cyclohexanone condensed with the chloroform, the resulting compound should have the formula

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{Cl}_2 \\
\text{C} & \\
\text{H}_2\text{C} & \quad \text{CH}_2 \\
\text{H}_2\text{C} & \quad \text{CH}_2 \\
\text{C} & \\
\text{H}_2 &
\end{align*}
\]

The molecular weight of this compound would be 217.46. The compound was very soluble in benzene, so a molecular weight determination was made by determining the lowering of the freezing point of benzene by a definite amount of the compound (4).
The molecular weight was then determined from the relation

\[ M = K \frac{w}{d/\eta} \]

where \( M \) equals the molecular weight of the substance; \( K \) is a constant, 5120; \( w \) is the weight of the product taken; \( \eta \) is the weight of the solvent; and \( d \) is the amount of the lowering of the freezing point.

After setting the Beckman thermometer so that the temperature 5.4°C left the thread of mercury above the center of the scale, 25 cc. of benzene, or 25 times 21.37 (sp. gr.) = 210.97 gm. were measured out and the freezing point found. A known weight of the product was then introduced and the freezing point of this mixture determined. Three determinations were made.

Results

First Molecular Weight Determination

<table>
<thead>
<tr>
<th>t. benzene taken</th>
<th>21.97 gm.</th>
<th>Freezing point</th>
<th>1.395</th>
</tr>
</thead>
<tbody>
<tr>
<td>t. product added</td>
<td>0.1160 gm.</td>
<td></td>
<td>1.430</td>
</tr>
<tr>
<td>Lowering of freezing point</td>
<td>0.1280</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Molecular weight = \( 5120 \times \frac{0.1160}{125 \times 21.97} = 316.2 \)

Second Molecular Weight Determination

<table>
<thead>
<tr>
<th>Weight of benzene</th>
<th>21.81 gm.</th>
<th>Freezing Point</th>
<th>1.385</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of product added</td>
<td>0.2080 gm.</td>
<td>1.642</td>
<td></td>
</tr>
<tr>
<td>Lowering of freezing point .3370</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Molecular weight = \( 5120 \times \frac{0.3090}{.337 \times 21.81} = 214.6 \)
Third Molecular Weight Determination

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Freezing point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of benzene</td>
<td>21.81 gm.</td>
<td>2.016</td>
<td></td>
</tr>
<tr>
<td>Weight of product added</td>
<td>0.3677 gm.</td>
<td>2.413</td>
<td>3.97°</td>
</tr>
<tr>
<td>Lowering of freezing point</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[
M = 5120 \times \frac{0.3677}{0.297 \times 21.81} = 217.4
\]

The molecular weights found in the first and third of these experiments give a fairly certain indication that the desired product was attained.

Chlorine Determination

If the ketone and chloroform had condensed, the molecule of the condensation product would contain three atoms of chlorine. Under the conditions of the experiment, the only way that three atoms of chlorine could get into the molecule would be by the chloroform condensing with the cyclohexanone in the manner indicated in the preparation. Accordingly, a chlorine determination was made.

For this determination, a Parr Peroxide Bomb was used in which to decompose the product (13). The chlorine was precipitated by a standard solution of silver nitrate and the excess silver nitrate titrated with standard potassium thiocyanate (3).

A solution of 0.09653 normal silver nitrate was prepared. In approximately 0.05 N potassium thiocyanate solution was also prepared and this was titrated against the silver nitrate solution.
Results

AgNO₃          KSCN
10 cc. = 10 cc. = 17.4 cc.
10 cc. = 17.4 cc.
10 cc. = 17.4 cc.
AgNO₃ = \( 0.09653 \) M
KSCN = \( \frac{10 \times 0.09653}{17.4} \) = \( 0.05548 \) M

1 cc. of \( 0.09653 \) M AgNO₃ = 1.74 cc. of \( 0.05548 \) M KSCN

A ferric alum indicator was used. 30 cc. of water being saturated with ferric alum. Enough nitric acid (sp. gr. 1.20) to impart a faint yellow color to the solution was added.

Three chlorine determinations were made.

Determination of Chlorine I.

Procedure: (13), (5) One gram of powdered potassium nitrate was placed in the cup of the Farr bomb and one measure (about 14 gm.) of sodium peroxide added. These were mixed thoroughly and 0.36538 gm. of the sample together with 0.5 gm. powdered granulated sugar were now added and the entire mass thoroughly mixed. The cap was placed on the cup and the collar screwed firmly into place.

Ignition of the mass was effected by causing a small hot flame from a hand gas torch to impinge upon the bottom of the cup. Ignition was shown by the spreading of a dull red color over the surface of the cup. In ten or fifteen seconds after ignition, the bomb was cooled under a tap.

The contents of the cup were then dissolved in 150 cc. boiling water by laying the cup in a large beaker on its side.
The beaker was covered with a watch glass and the contents boiled for five minutes. After removing and washing the cup, the mixture was acidified with concentrated nitric acid. An excess of the standard silver nitrate was now added from a burette and the mixture heated to boiling. Five cc. of ferric alum indicator and 10 cc. freshly boiled nitric acid (sp.gr.1.20) were added. Standard potassium thiocyanate was now added till a faint pink endpoint was reached which persisted for at least one minute.

Results

\[ \text{AgNO}_3 (.09653N) = 58.2 \text{ cc.} \]
\[ \text{KSCN (.05548N)} = 14.6 \text{ cc.} \]

Since 1 cc. \( \text{AgNO}_3 \) is equivalent to 1.74 cc. KSCN

\[ \frac{14.6}{1.74} = 8.39 \text{ cc. } \text{AgNO}_3 \text{ excess} \]

\[ \text{AgNO}_3 (.09653N) = 49.31 \text{ cc.} \]
\[ \text{AgNO}_3 \text{ Normal equivalent} = 4.81 \text{ cc.} \]

Since 1 cc. \( \text{AgNO}_3 \) (Normal) is equivalent to \( .1483 \text{ gm.} \text{AgCl} \)

\[ \left( \frac{\text{Cl}}{\text{AgCl}} = 35.46 \right) \times .6890 = .175 \text{ gm. Chlorine} \]

The theoretical amount of chlorine in the .3638 gm. of sample taken was

\[ \frac{106.39}{217.46} \times .3638 = .178 \text{ gm.} \]

Second Determination of Chlorine in Product

A second determination was made with the following results:

Weight sample-------------4246 gm.
Theoretical Chlorine in sample

Chlorine equivalent = 7.767 g.

Third Determination of Chlorine in Product

Weight sample = 0.3729 gm.

\[ \text{AgNO}_3 (0.09653\text{H}) = 56.15 \text{ cc.} \]
\[ \text{AgNO}_3 (\text{Normal}) = 5.420 \text{ cc.} \]
\[ \text{AgCl equivalent} = 7.767 \text{ gm.} \]

Theoretical amount in sample = 0.1824 gm.

Summary of the Three Determinations

<table>
<thead>
<tr>
<th>Theory</th>
<th>Found</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>gm.</td>
<td>%</td>
<td>gm.</td>
</tr>
<tr>
<td>I.</td>
<td>0.1780</td>
<td>48.92</td>
</tr>
<tr>
<td>II.</td>
<td>0.2077</td>
<td></td>
</tr>
<tr>
<td>III.</td>
<td>0.1824</td>
<td></td>
</tr>
</tbody>
</table>

These results show, conclusively, that in one molecule of the product there must be three atoms of chlorine.

These chlorine determinations, together with the molecular weight determinations, were considered as good evidence that the compound formed was the compound having the structure indicated (Page 29).
VII. Condensation of Camphor and Chloroform

Camphor is a compound containing the carbonyl group (C=O) characteristic of ketones. It forms oximes with hydroxyl amine and reacts in general like ketones. Accordingly, an experiment was made to see if camphor, the formula of which is given below, would condense with chloroform.

Materials Used

<table>
<thead>
<tr>
<th>Material</th>
<th>M.W.</th>
<th>B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camphor</td>
<td>152.13</td>
<td>205.3°</td>
</tr>
<tr>
<td>Chloroform</td>
<td>92.11</td>
<td>61.2°</td>
</tr>
<tr>
<td>Potassium hydroxide</td>
<td>56.</td>
<td></td>
</tr>
</tbody>
</table>

Desired Reaction

\[
\begin{align*}
\text{Camphor} & : \quad \text{CH}_3\text{C} = \text{CH}_3 \\
\text{Chloroform} & : \quad \text{CH}_2\text{Cl}_2
\end{align*}
\]

Procedure: The 25 gm. of camphor were dissolved in the 19.6 gm. of chloroform and the mixture cooled. The potassium hydroxide was then added gradually as it had been in other experiments. After the reaction mixture had stood for the usual time and all the chloroform had been distilled off, the camphor solidified in the flask upon cooling. A sample of this was tested in the usual way for chlorine and the results were negative.
Condensation of Acetone and Chloroform Using Sodamide as Catalyst

All the experiments thus far described in this investigation were carried out with potassium hydroxide as the condensing agent or catalyst. It is not unlikely that some other condensing agent may be able to effect this type of condensation of chloroform with ketones. A very brief test was made using sodamide in place of potassium hydroxide. The condensation that took place was the same as indicated in the formation of Chlorotone by the use of potassium hydroxide.

About 5 cc. of acetone and 10 cc. of chloroform were mixed together and a small amount of sodamide was added in the course of one half hour.

After standing for one and one half days, the mixture was filtered and the filtrate distilled. Less than a gram of Chlorotone was recovered.

As there was not a plentiful supply of the sodamide at this time, no further investigations were made with this substance.
CONCLUSION

In this investigation a series of ketones were studied to effect a condensation with chloroform of the same nature as that taking place between acetone and chloroform with the formation of Chloretone. The results obtained were:

1. Ethyl methyl ketone, negative
2. Diethyl ketone, "
3. N-hexyl methyl ketone "
4. Acetophenone, "
5. Camphor, "
6. Cyclohexanone, positive.

From cyclohexanone by condensation with chloroform using potassium hydroxide as catalyst was obtained a new compound resembling Chloretone in odor and general properties. The formula of this compound as substantiated by analysis for chlorine and by molecular weight determination is probably:

\[ \text{H}_2\text{C} \quad \text{CH}_2 \]
\[ \text{H}_2\text{C} \quad \text{CH}_2 \]
\[ \text{C} \quad \text{H}_2 \]

The physiological properties of this compound were not investigated.

Finally, it may be observed that the number of ketones studied here includes only a very small amount of the supply of
ketones available. Also, it is realized that this work has not conclusively proved that the formation of the compounds attempted is entirely impossible or improbable. The technique of the method of forming these, on the other hand, will undoubtedly have to be different from that of the condensation of acetone and chloroform.
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ACKNOWLEDGMENT

To Dr. Chamberlain special acknowledgement is due for his selection of the topic of this thesis and his very helpful suggestions throughout the investigation.
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