Updegraff
An Attempt to Prepare Isocyanides
Derived from Acids
AN ATTEMPT TO PREPARE ISOCYANIDES DERIVED FROM ACIDS

BY

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THESIS

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Helen Updegraff ENTITLED An Attempt to Prepare Isocyanides Derived from Acids BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE DEGREE OF Master of Arts

In Charge of Thesis

Head of Department

Recommendation concurred in:

Committee on Final Examination*

*Required for doctor's degree but not for master's.
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A few years ago Noyes and Potter prepared amino-dihydrocampholytic acid by replacing the carboxyl group, attached to the tertiary carbon atom of d-camphoric acid, with the amino group, through the amide by Hofmann's reaction. They found that aminodihydrocampholytic acid on treatment with nitrous acid yielded, among other products, trans-hydroxydihydrocampholytic acid. It had, heretofore, been assumed that the hydroxydihydrocampholytic acid formed retains the same configuration as d-camphoric acid. However, they found that the hydroxydihydrocampholytic acid formed yielded chiefly isolaurolene and campholytic acid and some campholytolactone when heated with water at 100°C while the isomeric cis-hydroxydihydrocampholytic acid under the same treatment readily goes back to campholytolactone. They were, therefore, forced to the conclusion that the trans-hydroxydihydrocampholytic acid formed must have the same configuration as isocamphoric acid. They were thus led to believe that in the decomposition of aminodihydrocampholytic acid by nitrous acid the hydroxydihydrocampholytic acid is formed by a Walden inversion.

In order to definitely prove the structure of the hydroxydihydrocampholytic acid it was decided to replace the hydroxyl group with bromine by treatment with hydrobromic acid. It was hoped that the bromine derivative thus obtained could be converted into the corresponding nitrile and this by saponification into the acid. If the acid formed in this manner proved to be isocamphoric acid, this would definitely prove that a Walden inversion had taken place.

However, attempts to convert the bromine derivative into the corresponding nitrile were unsuccessful. It was then thought that, if the hydroxy acid could be converted into the corresponding isonitrile, on heating, the isonitrile might rearrange to form the corresponding nitrile and the acid might then be obtained by saponification of the nitrile.

The general problem which then presented itself was this, viz., with an acid as a starting point, to make an isonitrile which would still contain the carboxyl group.

Nef has prepared phenyl isocyanide, o-tolyl isocyanide, and p-tolyl isocyanide by treating respectively aniline, o-toluene, and p-toluene with chloroform and potassium hydroxide in absolute alcohol. As far as could be ascertained from the available literature on the subject no one has ever applied this chloroform reaction of Hofmann to an amino acid. It would not seem unreasonable to expect that an isocyanide might be prepared in this manner from an amino acid as well as from a primary amine.

However, attempts to prepare an isocyanide in this manner were not successful. The chloroform reaction was applied to sulphanilic acid, aminodihydrocampholytic acid, and the ethyl ester of aminodihydrocampholytic acid without success.

As no promising results were obtained by this method and as Nef, in preparing isocyanides from tertiary aliphatic compounds, made use of the reaction of the halogen derivative with silver cyanide in absolute ether, it was decided to attempt to prepare the ethyl ester

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1. Annalen der Chemie 270, 274
2. " " " " " 309
3. " " " " " 320
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of hydroxydihydrocampholytic acid and to treat the iodo derivative according to this method.

\[ \begin{array}{c}
\text{II} \\
\text{Experimental 1.}
\end{array} \]

As sulphanilic acid was the only amino acid readily available it was decided to treat it with chloroform and potassium hydroxide in alcoholic solution according to the method of Nef.

The following equation represents the reaction which it was hoped would take place:

\[ \text{SO}_3\text{H} + 2\text{H}_2\text{O} + \text{CHCl}_3 + 4\text{KOH} = 3\text{KCl} + 14\text{H}_2\text{O} + \text{SO}_3\text{K} \]

\[
\begin{array}{c}
\text{N} = \text{C} \\
\text{NH}_2
\end{array}
\]

10 grams of sulphanilic acid were suspended in an excess of chloroform in a round bottom flask and a solution of alcoholic potassium hydroxide (17.6 grams, one mol, in 60 cc of absolute alcohol) were added by means of a separatory funnel.

It was found that the reaction did not go to completion, and this was thought to be due to the fact that the potassium hydroxide could not be completely dissolved in the small amount of absolute alcohol used and so probably did not come into intimate contact with the sulphanilic acid. It was, therefore, decided to dissolve the potassium hydroxide in the least possible amount of water and then to add about 100 cc of absolute alcohol to the solution shaking it up well so as to obtain a homogeneous solution. This solution was then added slowly by means of a separatory funnel to ten grams of sulphanilic acid suspended in an excess of chloroform.

The temperature was kept down by means of an ice bath while the alcoholic potassium hydroxide was added. The bath was then heat-
ed up until the reaction proceeded quietly.

A heavy white precipitate formed. The liquid portion was amber colored due, probably, to condensation products formed by the action of the potassium hydroxide on the aldehyde present in the alcohol as an impurity.

The liquid portion was separated from the precipitate by filtration and a portion of it was evaporated to dryness in a crystallizing dish. Yellow needles were deposited.

Both the solid soluble in the liquid portion and deposited on evaporation and the precipitate were found to be easily soluble in water but insoluble in ether. A small part of each was soluble in alcohol. Both gave tests for sulphanilic acid with sodium nitrite and α naphthyl amine and good flame tests for potassium. Aqueous solutions of each gave precipitates with stannous chloride, mercuric chloride and lead acetate. The precipitate formed with lead acetate was insoluble in hot water showing that it could not be lead chloride.

Some of each solid was then dissolved in water, the solution heated to boiling and lead acetate added. The precipitate obtained was of such a nature that it was exceedingly difficult to filter so that it was found almost impossible to wash it free from chlorides. It was white, putty-like, settled with great difficulty and could not be filtered by suction. This method of separation was therefore abandoned.

Extractions with hot absolute alcohol were made both in the case of the precipitate and the solid obtained by evaporating the alcoholic solution. A yellowish, flaky, crystalline product was obtained in each case. The product thus obtained was then dissolved in the least possible amount of water, the solution decolorized with bone black and evaporated in a small crystallizing dish in a vacuum
Several runs were made in this manner and the crystals examined to determine whether they were the same substance. They were also examined for impurities.

The yields obtained were very poor and very few good crystals were obtained. The best crystals gave the heaviest precipitates with silver nitrate thus indicating that they were probably largely potassium chloride. None of the crystals had definite melting points, all gave a test for sulphanilic acid with sodium nitrite and α-naphthyl amine, and all gave a strong flame test for potassium. Several potassium determinations were made on the various crystals but good checks were not obtained. The crystals were apparently quite impure and largely potassium chloride.

Having no success with sulphanilic acid it was then decided to try another amino acid containing no sulphur. It was then decided to work with aminodihydrocampholytic acid.

2. Preparation of Aminodihydrocampholytic Acid

The aminodihydrocampholytic acid used was prepared from β-camphoramidic acid by Hofmann's reaction. 19.9 grams of β-camphoramidic acid were dissolved in 100 cc of 10% NaOH. 5.1 cc's of bromine (one mol) were added to 140 cc of cold 10% NaOH, rotating the flask briskly, during the addition of the bromine. The solution of sodium hypobromite was then added immediately to the solution of the sodium salt of β-camphoramidic acid. The mixture was then warmed to 80°C. A few cc's of a strong solution of NaHSO₃ (4 cc = 1 gram) were then added to reduce the excess of sodium hypobromite and 33 cc HCl (sp. gr. 1.19) were then added carefully to neutralize the excess NaOH. The solution was then evaporated to crystallization. The aminodihydrocampholytic acid was deposited in pure white glisten-
ing scales.

3. Action of Chloroform and Alcoholic Potassium Hydroxide on Aminodihydrocampholytic Acid

The following equation represents the reaction which it was hoped would take place on the treatment of aminodihydrocampholytic acid with chloroform and alcoholic potassium hydroxide:

\[
\begin{align*}
\text{COOH} & \quad \text{COOK} \\
\text{C}_8&\text{H}_4\text{NH} + \text{CHCl}_3 + 4\text{KOH} \cdot 2\text{H}_2\text{O} = 3\text{KCl} + 12\text{H}_2\text{O} + \text{C}_8\text{H}_4\text{N} \\
& \quad \text{N} = \text{C}
\end{align*}
\]

10 grams of aminodihydrocampholytic acid were suspended in an excess of chloroform in a round bottom flask. About 24 grams of KOH (a little more than one mol) were dissolved in about 200 cc of absolute alcohol. This solution was then added, by means of a separatory funnel, to the aminodihydrocampholytic acid and chloroform.

Quite a violent reaction took place and a large white precipitate was formed. After the reaction ceased the solution was heated to boiling on the water bath. It was then allowed to cool and CO₂ was passed through the solution for an hour or so to convert the excess KOH to K₂CO₃. A little chloroform was left.

The precipitate was then filtered by suction, extracted with absolute alcohol and the alcohol extract evaporated to dryness on the water bath. A small amount of a white crystalline substance was obtained which proved to be mostly KCl and K₂CO₃.

The remaining precipitate was then dissolved in as little water as possible and HCl was added until effervescence ceased. The acid solution was then extracted with ether. A very small amount of a white, crystalline substance was obtained which proved to be
mostly KCl.

The acidified water solution was then evaporated to dryness. A large amount of a white crystalline substance was obtained which proved to be mostly KCl.

The alcoholic filtrate was evaporated to dryness and a cream-colored, slightly gummy residue was obtained. It was found that when a little of this residue was dissolved in water, acidified with HCl and extracted with ether a substance was obtained on evaporating the ether extract which was insoluble in water. The entire residue was then dissolved in the least possible amount of water, acidified with HCl and extracted with ether, and the ether evaporated. A small amount of a brown, gummy substance was obtained. A few white crystals were also deposited. The crystals proved to be mostly KCl and the potassium salt of aminodihydrocampholytic acid. The brown, oily substance charred on platinum foil and had a very characteristic odor. It may have been the product sought but not enough was obtained to work with.

The acid solution remaining after extraction with ether was then evaporated to dryness on the water bath. A cream-colored residue was obtained having a characteristic odor but it appeared to be largely KCl and aminodihydrocampholytic acid. However, an extraction of this residue was made with 30 cc of absolute alcohol and 2 or 3 cc of conc. HCl. A creamy colored substance with a characteristic odor was obtained. It was acid to litmus, gave a very slight flame test for potassium, and when ignited on platinum foil it burned leaving no appreciable residue. It was soluble in water, a small portion being more easily soluble than the rest. The substance was then treated with about 4 cc of distilled water to dissolve the most easily soluble portion, then filtered on a suction plate and the fil-
trate evaporated to crystallization. The crystals thus obtained proved to be largely aminodihydrocampholytic acid. The less soluble residue was then dissolved in the least possible amount of hot water and evaporated to crystallization. A creamy white crystalline substance was obtained which melted sharply at 189.6 °C. It was acid to litmus. On ignition on platinum foil it charred and burned leaving no residue.

Since the product thus obtained by extraction with acid alcohol appeared to be the most promising - viz., the portion least soluble in water and melting at 189.6 °C - it was decided to repeat the process, acidifying the alcoholic solution as soon as the reaction had gone to completion and to then evaporate the alcohol under diminished pressure. Since NaCl is more insoluble in alcohol than KCl it was decided to use NaOH and no water.

12 grams of NaOH were dissolved in about 300 cc of absolute alcohol and added by means of a separatory funnel to 10 grams of aminodihydrocampholytic acid suspended in about 10 or 15 grams of chloroform in a round bottom flask. A condenser was attached. No reaction took place until the flask was warmed on the water bath. Quite a vigorous reaction then took place. The flame was removed and the bubbling continued quite vigorously for about ten minutes. The contents of the flask were then brought to boiling and allowed to boil for about fifteen minutes. When the reaction took place a small amount of chloroform distilled over but there was still an excess after the reaction ceased.

The alcoholic portion was then filtered off - acidified to precipitate the NaOH dissolved as NaCl, filtered and the filtrate evaporated under diminished pressure. 10 grams of a creamy colored substance with a characteristic odor was obtained on evaporating the
alcoholic solution - [A].

[A] This substance was acid to litmus and gave a flame test for potassium. On ignition on platinum foil it sublimed, melted, then charred and burned with a luminous flame leaving practically no residue.

The substance [A] was then treated with a very small amount of water which dissolved a portion of it readily. A deep amber colored, syrupy solution was obtained. On evaporation to crystallization a considerable amount of a white, amorphous substance was obtained [B]. This was then filtered by suction and the filtrate again evaporated to crystallization [C]. The residue of [A] was then dissolved in hot water and evaporated to crystallization. A small amount of a white, crystalline substance was obtained [D].

[B] This substance, on ignition on platinum foil, charred and burned leaving no residue. On treatment with NaNO₂ and HCl a yellow oily substance was obtained which resembled very much the nitroso compound formed by the action of HNO₂ on the hydrochloride of aminodihydrocampholytic acid.

[C] This substance resembled very much the aminodihydrocampholytic acid started with. On ignition on platinum foil it charred and sublimed much like aminodihydrocampholytic acid.

[D] This substance, also, was found to behave much like the aminodihydrocampholytic acid started with, as it sublimed on platinum foil and on trying to take the melting point it sublimed and charred at about 245° C.

The results thus obtained seemed to indicate that the original reaction with CHCl₃ and KOH was simply one of neutralization. It was then decided to attempt to prepare the ethyl ester of aminodihydrocampholytic acid and to use this as the starting point.
Preparation of the Ethyl Ester of Aminodihydrocampholytic Acid.

\[
\begin{align*}
&\text{COOH} & \text{CO}_2\cdot\text{C}_2\text{H}_5^- \\
&\text{C}_8\text{H}_{14} + \text{C}_2\text{H}_5\text{OH} + \text{H}_2\text{SO}_4 = \text{C}_8\text{H}_{14} + \text{H}_2\text{O} \\
&\text{NH}_2 & \text{NH}_2\cdot\text{H}_2\text{SO}_4
\end{align*}
\]

35 grams of aminodihydrocampholytic acid was refluxed on the water bath for 60 hours with 20 cc of conc. H$_2$SO$_4$ and 150 cc of absolute alcohol. The alcohol was then distilled off under diminished pressure. 125 cc of NaOH (3 cc = 1 gram) or 41.6 grams were then added and the ester taken up in ether and dried with anhydrous Na$_2$SO$_4$. The ether was then distilled off under diminished pressure and the ester distilled at 140 °C., 20 mm pressure. 31.8 grams of the ester were obtained.


The following equation represents the reaction which it was hoped would take place:

\[
\begin{align*}
&\text{CO}_2\cdot\text{C}_2\text{H}_5^- \\
&\text{C}_8\text{H}_{14} + \text{CHCl}_3 + 3\text{KOH} = 3\text{KCl} + 3\text{H}_2\text{O} + \text{C}_8\text{H}_{14} \\
&\text{NH} & \text{N} = \text{C}
\end{align*}
\]

3 grams of the ester were shaken up in a 300 cc round bottom
flask with about 7 grams of chloroform. By means of a separatory funnel 6.1 grams of KOH dissolved in 60 cc of absolute alcohol were added. A condenser was attached. During the reaction the flask was shaken quite briskly.

For about the first ten minutes a very mild reaction took place which then became quite vigorous for about ten minutes more. The reaction then ceased quite abruptly. A copious white precipitate was formed, the solution having the amber color of the alcoholic KOH.

The precipitate was then separated from the liquid portion by suction and extracted with ether. The ether extract was added to the alcoholic solution which was then evaporated under diminished pressure.

The product thus obtained consisted of a brown oily substance with the same characteristic odor as that observed in previous runs, and in addition a white, bead-like substance was obtained.

Water was then added, the white solid going into solution, the oily substance being practically insoluble. The water solution and oil were then shaken up with ether, the oily substance going into solution in the ether. The ether layer was separated from the aqueous layer and the ether distilled over under diminished pressure in a Claisen distilling bulb. After all the ether had been driven over the product was distilled at 128° - 131° C under a pressure of 15 mm.

As the product thus obtained was strongly alkaline to phenolphthalein it was believed to consist largely of unchanged amine. It was, therefore, decided to titrate it with N/10 HCl. 0.1324 grams of the substance were weighed out in a small flask. About 10 cc of water were added and the contents were then titrated with N/10 HCl, using phenolphthalein as indicator. The product was found to contain 70.2% amine.

Since the product was found to contain about 70% amine it did
not appear very promising. However, a little more than enough HCl to react with the amine present was added and the solution was then extracted with ether. A very small amount of a yellowish characteristically smelling oil was obtained. The odor was somewhat ethereal.

Since no promising results were thus obtained and since Nef, in preparing isocyanides from tertiary aliphatic compounds made use of the reaction of the halogen derivative with silver cyanide, in absolute ether, it was decided to attempt to prepare the hydrochloride of the ester and from this to attempt to prepare the ester of hydroxydi-hydrocampholytic acid by the action of nitrous acid. By treatment of the ester of the hydroxy acid with hydriodic acid it was hoped to prepare the iodide which could then be treated with silver cyanide in absolute ether according to the method of Nef, in the hope of thus obtaining the isonitrile.


35 grams of the ester were converted into the hydrochloride by passing dry HCl gas into an ethereal solution of the ester.

\[
\text{CO}_2\text{.C}_2\text{H}_5^- + \text{HCl} = \text{CO}_2\text{.C}_2\text{H}_5^- \quad \text{C}_8\text{H}_{14} \quad \text{NH}_2
\]

\[
\text{NH}_2\quad \text{NH}_2\text{.HCl}
\]

199.2 235.6

40.5 grams of the hydrochloride were obtained — this being 97.8% of the theoretical yield 41.4 grams.
Decomposition of the Hydrochloride of the Ethyl Ester of Amino-dihydrocampholytic Acid by Nitrous Acid.

\[
\text{CO}_2 \cdot \text{C}_2\text{H}_5 + \text{NaNO}_2 = \text{NaCl} + \text{N}_2 + \text{H}_2\text{O} + \text{C}_2\text{H}_4\text{O} - \text{H}
\]

The entire amount of hydrochloride was dissolved in 162 cc H₂O. The solution was then kept cold while a solution of NaNO₂ (14.17 grams NaNO₂ in 40.5 cc H₂O) was added by carefully pouring it down the side of the flask. The flask was then shaken and conc. HCl added drop by drop till bubbles of nitrogen gas were evolved. The reaction was allowed to run over night and in the morning another drop of conc. HCl was added. The reaction was allowed to go on for about 36 hours. A green oil separated on top. The acid solution was then extracted with ether, dried with anhydrous Na₂SO₄ and the ether distilled off under diminished pressure. The product thus obtained was a greenish yellow oil. This was then subjected to fractional distillation.

Three fractions were collected.

--- Data ---

--- 1st Distillation ---

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<tr>
<td>I</td>
<td>95 - 105</td>
<td>135 - 170</td>
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<td>40.0 gms</td>
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<td>105 - 140</td>
<td>175 - 185</td>
<td>19 mm - 20 mm</td>
<td>34.0 gms</td>
<td>37.0 gms</td>
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<tr>
<td>III</td>
<td>140 - 145</td>
<td>190 - 200</td>
<td>20 mm</td>
<td>22.5 gms</td>
<td>33.0 gms</td>
<td>10.5 gms</td>
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--- 2nd Distillation ---

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<tr>
<td>I</td>
<td>95 - 96</td>
<td>135 - 160</td>
<td>15 mm</td>
<td>25 gms.</td>
<td>38.5 gms.</td>
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<tr>
<td>II</td>
<td>96 - 136</td>
<td>166 - 172</td>
<td>15 mm</td>
<td>17 mm</td>
<td>26.5 gms.</td>
</tr>
<tr>
<td>III</td>
<td>136 - 140</td>
<td>175 - 190</td>
<td>17 mm</td>
<td></td>
<td>22.5 gms.</td>
</tr>
</tbody>
</table>

The first fraction from the second distillation was believed to contain the practically pure ethyl ester of the unsaturated acid, campholytic acid -

\[
\text{CH} = \text{C} \cdot \text{CH} \\
\downarrow \\
\text{C}: (\text{CH} \_)
\]

\[
\text{CH}_2 = \text{CH}-\text{CO}_2 \cdot \text{C}_2 \text{H}_5
\]

The second fraction probably contained a mixture.

The third fraction was believed to contain the practically pure ethyl ester of one of the hydroxydihydrocampholytic acids -

\[
\text{CH}_2 - \text{C} \\
\downarrow \\
\text{CH}_3
\]

\[
\text{C}: (\text{CH}_3)\_2 \\
\downarrow \\
\text{CH}_2 - \text{C} - \text{CO}_2 \cdot \text{C}_2 \text{H}_5 \_ \\
\downarrow \\
\text{H}
\]

It was found to have a specific gravity of 1.0299 and a positive rotation of 58.01.

In order to find out whether we had a mixture of the cis and
trans hydroxy esters it was decided to saponify the ester and then acidify with HCl in order to obtain the acid.

8.

**Saponification of the Ethyl Ester of Hydroxydihydrocampholytic Acid.**

\[
\begin{align*}
O - H & \quad \quad + \quad NaOH = \quad C_H\text{H}_2\text{O}H & \quad + \quad C\text{H}_5\text{OHN}a\text{C}_2\text{O}_2\text{C}_2\text{H}_5 \\
C\text{H}_5 & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
Attempt to Prepare the Iodide from the Ethyl Ester of Hydroxydihydrocampholytic Acid.

It was then decided to attempt to prepare the iodide of the ethyl ester of hydroxydihydrocampholytic acid.

\[
\begin{align*}
CH_2\text{--} & \quad C \quad \text{(CH}_3\text{)}_2 \quad + \quad HI \quad = \quad CH_2\text{--} \quad C \quad \text{--} \quad \text{CH}_3 \\
C \quad \text{--} \quad (\text{CH}_3\text{)}_2 & \quad \text{--} \quad \text{H} \quad = \quad C \quad \text{--} \quad (\text{CH}_3\text{)}_2 \quad \text{--} \quad \text{H}_2\text{O} \\
CH_2\text{--} & \quad C \quad \text{--} \quad \text{CO}_2\text{C}_2\text{H}_5 \\
H & \quad \text{--} \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\end{align*}
\]

A preliminary run was made with only about 0.5 gram of the ester. The hydriodic acid used was generated by dropping water on a mixture of phosphorus tri-iodide and iodine.

0.5028 grams of the ester were weighed out in a U tube. The ester was then dissolved in carbon bisulphide and throughout all the subsequent operations the U. tube was kept cold by means of an ice bath. Hydriodic acid was passed through the solution for about an hour. The solution in the U tube was deeply colored with free iodine. No crystals were formed and there was no turbidity. Dry air was then passed through the solution until all the carbon bisulphide had evaporated and the excess hydriodic acid was expelled. The product thus obtained was then dried by suction for about half an hour.

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10.

Attempt to Prepare the Isocyanide from the Ethyl Ester of Hydroxydihydrocampholytic Acid.

\[
\begin{align*}
I & \quad CH_2--C--CH_3 & N = C \\
& \quad C: (CH_3)_2 & \quad CH_2--C--CH_3 \\
& \quad CH_2--C:CO_2\cdot C_2H_5 & \quad C: (CH_3)_2 \\
& \quad CH_2--C:CO_2\cdot C_2H_5 & \quad CH_2--C--CO_2\cdot C_2H_5 \\
& & H
\end{align*}
\]

It was then decided to attempt to prepare the isocyanide of the ester from the product above obtained which was hoped to be the iodide. According to the method of Nef, the product was mixed with 0.7 grams of silver cyanide in 8 cc of absolute ether and allowed to stand for 48 hours. Theoretically 0.5 grams of the ester should yield about 0.8 grams of the iodide which should react with about 0.34 grams of silver cyanide. Therefore 0.7 grams would be 2 mols which was the amount used by Nef.

After the mixture had stood 48 hours a concentrated solution of potassium cyanide was added, shaking the flask, until all the salt mass had dissolved. The ether layer was then separated from the aqueous layer and three more extractions made with ether. The ether extract was then dried with anhydrous sodium sulphate and the ether allowed to evaporate. A yellow oil having a sharp disagreeable odor was obtained.

Three drops of the oil were then subjected to fusion with metallic sodium, the fusion mixture dissolved in alcohol, two volumes of water added and the solution boiled and filtered. To a few cc of this solution five drops of FeSO₄ and one drop of FeCl₃ were

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added and the solution was then boiled for two minutes, cooled and acidified carefully with HCl. A blue precipitate of Prussian blue was obtained proving the presence of nitrogen.

11.

Second Attempt to Prepare the Iodide from the Ethyl Ester of Hydroxydihydrocampholytic Acid.

Since the results obtained above seemed to be quite promising it was decided to try the experiment with about 3 grams of the ester.

2.9763 grams of the ester were weighed out, dissolved in carbon bisulphide and treated with hydriodic acid as described above. In this case, however, hydriodic acid was not passed in after it no longer appeared to be absorbed as indicated by the fact that the acid escaping fumed at the open end of the U tube. Dry air was then passed through the solution until the excess hydriodic acid was expelled and the carbon bisulphide evaporated.

The residue which was deeply colored with free iodine was then taken up in absolute ether. About a gram of powdered potassium iodide was then added to dissolve the iodine. This did not clear the solution appreciably, so a little sodium thiosulphate solution was added until the ether layer cleared. The ether was then distilled off under diminished pressure at the temperature of the water bath in order to drive over any residual moisture. The product thus obtained weighed 4.8 grams. 2.9763 grams of the ester (C\textsubscript{11}H\textsubscript{20}O\textsubscript{3}) should yield 4.6106 grams of the iodide (C\textsubscript{11}H\textsubscript{19}O\textsubscript{2}I) theoretically.
Second Attempt to Prepare the Isocyanide from the Ethyl Ester of Hydroxydihydrocampholytic Acid.

The product obtained above (4.8 grams) which was hoped to be the iodide of the ester of hydroxydihydrocampholytic acid was then mixed with 4 grams of silver cyanide (2 mols) in about 15 cc of absolute ether and allowed to stand for 42 hours. Concentrated potassium cyanide solution was then added and the mixture shaken until the salt mass had all dissolved. The ether layer was then separated from the aqueous layer. Three more extractions were made with ether and the ether extract was then dried with anhydrous sodium sulphate. The ether was then distilled off under diminished pressure at the temperature of the water bath in order to drive off any residual moisture. A reddish oil having a green fluorescence and a characteristic odor was obtained. It was found to give a positive test for nitrogen. By the Kjeldahl method it was found to contain only 1.1% nitrogen.

The results obtained above were not very promising. It was then decided to use about 3 grams of the unsaturated ester and to somewhat modify the procedure.

13.

Attempt to Prepare the Isocyanide of the Ethyl Ester of Campholytic Acid through the Iodide.

\[
\begin{align*}
\text{CH} & \quad \rightarrow \quad \text{CH} - \text{C}_3 \text{CH}_3 \\
\text{C} : (\text{CH}_3)_2 & \quad \rightarrow \quad \text{CH}_2 - \text{I} \\
\text{CH}_2 - \text{CH} \cdot \text{CO}_2 \cdot \text{C}_2 \text{H}_5 & \quad \rightarrow \quad \text{CH}_2 - \text{C} - \text{CH}_3 \\
\text{CH}_2 - \text{CH} \cdot \text{CO}_2 \cdot \text{C}_2 \text{H}_5 & \quad \rightarrow \quad \text{CH}_2 - \text{C} : (\text{CH}_3)_2
\end{align*}
\]
3 grams of the unsaturated ester were treated, in the manner described above, with hydriodic acid. The hydriodic acid and carbon bisulphide were expelled with dry air. The product thus obtained was then taken up in ether, a little water added and then a 10 % solution of sodium thiosulphate was added drop by drop until the ether layer cleared. The ether layer was then separated and dried with anhydrous sodium sulphate. The ether solution was then poured off and treated with 2 mols of silver cyanide. The mixture was allowed to stand for 48 hours and then refluxed on the water bath for 5 hours. A concentrated solution of potassium cyanide was then added until all the salt mass dissolved on shaking the flask. The ether layer was then separated from the aqueous layer and the aqueous layer was extracted several more times with ether. The ether was then evaporated under diminished pressure. 3.3 grams of a yellow oil having a characteristic odor was obtained. Theoretically 3 grams of the ester (C_{11}H_{18}O_2) should yield 3.4 grams of the isocyanide (C_{12}H_{19}O_2N).

The product thus obtained gave a positive test for nitrogen. Two combustions were run which checked within 0.04 %.

1st combustion - - - - - - 1.44 % nitrogen.
2nd combustion - - - - - - 1.48 % nitrogen.

The isocyanide should contain 6.7 % nitrogen so the product may possibly contain 22 % of the isocyanide.

As a small amount of a compound containing nitrogen had evidently been formed it seemed worth while to repeat the experiment with a larger amount of material.
Second Attempt to Prepare the Isocyanide from the Ethyl Ester of Campholytic Acid.

10 grams of the unsaturated ester were weighed out in a distilling bulb, dissolved in carbon bisulphide, and hydriodic acid passed through the solution for half an hour after it no longer appeared to be absorbed. The excess hydriodic acid and the carbon bisulphide were then expelled with dry air. The product was then taken up in ether and 10 % sodium bisulphite solution added with shaking until the ether layer cleared. The ether layer was then separated and dried with anhydrous sodium sulphate. The ether extract was then allowed to stand for 60 hours with 14.7 grams (2 mols) of silver cyanide.

The solution in contact with the salt mass was then refluxed on the water bath for 5 hours. A concentrated solution of potassium cyanide was then added until all the salt mass dissolved on shaking the flask. Quite a violent reaction took place. The ether layer had in suspension a black, amorphous substance but on shaking up in a separatory funnel it finally disappeared very suddenly, the ether layer then becoming milky in appearance.

The ether layer was then separated from the aqueous layer. Two more extractions were made with ether and the ether extract was then dried with anhydrous sodium sulphate. The ether solution was then transferred to a Claisen distilling bulb and the ether distilled off under diminished pressure. The liquid remaining in the distilling bulb had a milky appearance and this was thought to be due to moisture. It was then decided to attempt to get rid of this moisture by distilling under diminished pressure at the temperature of
the water bath. But on warming up to the temperature of the water bath it bumped and a white solid separated and also a yellowish brown resinous substance settled to the bottom of the flask. The contents of the distilling flask had a decided ethereal odor.

Addition of low boiling ligroin was found to cause a separation of more of the white solid substance. This substance is now under investigation.