

THE MECHANISM OF THE LEUCKART REACTION

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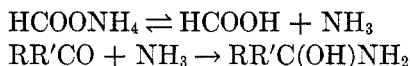
The Leuckart reaction is perhaps best defined as a process for the reductive amination of aldehydes or ketones by formamide, ammonium formate, or formic acid with formamide. The reaction is carried out by heating a mixture of the carbonyl compound and the amide or its derivative. Primary and secondary amines produced in the reaction are obtained as the formyl derivatives; tertiary amines are obtained as the formates. The reaction can be illustrated by the following general equations:



The reaction was discovered by Leuckart (1), who in 1885 reported the results of an attempt to prepare benzylidenediformamide by heating benzaldehyde with formamide. Instead of the expected product, he obtained benzylamine, dibenzylamine, and tribenzylamine, as well as the formyl derivatives of the first two.

In spite of the large quantity of work which has appeared upon the subject, there is little agreement concerning the mechanism of the reaction among the workers in the field. In fact, there has been no published hypothesis which covers more than the first steps.

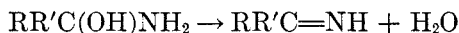
Wallach (2) proposed that the initial steps of the reaction are as follows:



Formic acid then reduces this product to the amine, which subsequently reacts with more formic acid to give the final product, a substituted formamide. Novelli (3) later showed that the reaction could be used to prepare secondary amines by reacting monosubstituted formamides with ketones.

Crossley and Moore (4) published a report of a comparison of the efficiency of the various reactants which may be used in the Leuckart reaction. They reported that formamide, ammonium formate, a mixture of formamide and formic acid, or a mixture of formamide and ammonium formate may be used with a carbonyl compound to give the reaction and that the mixture of formamide and formic acid produces the best yields.

In their short discussion of the mechanism they repeat the proposal of Wallach, while suggesting the following as a possibility:

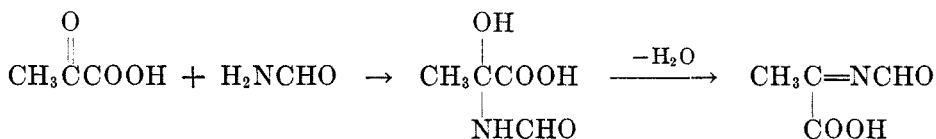


The resulting imine is then reduced by formic acid.

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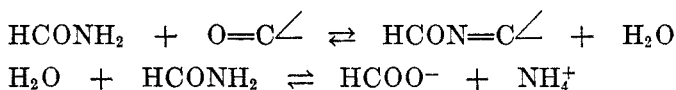
At about the same time, Doevre and Courtois (5) suggested that the initial step in the reaction was the addition of formamide to the carbonyl carbon, $RR'CO + H_2NCHO \rightarrow RR'C(OH)NHCHO$; while Davies and Rogers (6) thought that both of the proposed mechanisms might be operative.

In 1946 Shive and Shive (7) reported that at room temperature formamide adds to pyruvic acid to give α -hydroxy- α -formamidopropionic acid. Upon dehydration, α -formimidopropionic acid was obtained:



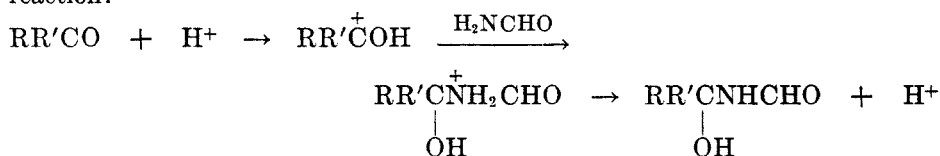
They were able to isolate both of these compounds in fair yields. This reaction, they stated, shows that the addition of formamide to the carbonyl group is the first step in the Leuckart reaction.

The next attempt to clarify the mechanism of the reaction was made by Alexander and Wildman (8). The object of their work was to determine if there were conditions such that the reaction could be carried out with ammonium formate but not with formamide. They found that when acetophenone was heated with formamide in diethylene glycol at 120–130°, no reaction occurred even after as long as 15 hours, while a yield of 10% was obtained with ammonium formate and acetophenone after four hours. In order to explain the fact that formamide is a satisfactory reagent at higher temperatures, they proposed that the following equilibrium operates at temperatures above 165°



and that the ammonium formate thus produced is the material which enters into the Leuckart reaction. They also found that the addition of anhydrous calcium sulfate to a mixture of formamide and acetophenone reacting at 165–170° lowered the yield from 30 to 17%. They regarded this fact as supporting evidence for the equilibrium proposed above. On the basis of this work, they stated that ammonium formate is the required reactant and that the mechanism proposed by Wallach is correct.

Almost simultaneously with the proposal of Alexander and Wildman came the work of Webers and Bruce (9). They found that when formamide is used as the reactant, acid catalysts increase the yield markedly. In direct contrast to the work discussed above, they proposed that the required reactant is formamide and that the function of the acid catalyst is to increase the polarity of the carbonyl group. They suggested the following as the first step of the Leuckart reaction:



During the following year, Bennett and Marks (10) found that acid catalysts increase the yield of tertiary amines prepared from substituted formamides and ketones.

At about the same time, Staple and Wagner (11) published their study of the Wallach reaction, which consists of the reaction of an amine with an aldehyde or ketone and formic acid. This, of course, is closely related to the Leuckart reaction. They were able to show that this reaction does not normally proceed by way of the formyl derivative of the amine. They felt that it is probable that the two reactions, the Leuckart and the Wallach, have essentially the same mechanism. In support of this view, they quoted the work of Wallach and of Alexander and Wildman.

In his recently published book Alexander (12) repeated his statement that ammonium formate is the required reactant and that the correct mechanism is that originally proposed by Wallach. He did not mention any other possibility. Moore (13), in his recent review of the Leuckart reaction, discussed both of the proposed mechanisms but did not reach a definite conclusion as to which is correct.

TABLE I
THE EFFECT OF THE REMOVAL OF WATER UPON REACTION TEMPERATURES AND YIELD

LIQUID REMOVED, ML.	TEMPERATURE, °C.	YIELD, ^a %
None	135	16
36	141	42
65	151	69
72	157	60

^a Four moles of ammonium formate and one mole of acetophenone; four hours reaction time.

A COMPARISON OF THE LEUCKART REAGENTS

A study of the literature on the Leuckart reaction reveals several factors which must be considered in any comparison of the efficiency of the various reagents which may be used.

Some workers have removed water from the mixture during the course of the reaction, while others either have not done so or have not reported the fact. It seems clear that the removal of water increases the yield when any reagent other than formamide is used. It is not clear, however, whether the presence of water decreases the yield because it causes the reaction temperature to be lower or because it is itself involved in the reaction.

In an effort to determine the role of the water, the runs recorded in Table I were carried out. These data show that water is involved in the reaction. As more and more water is removed, the temperature increases, but yields are decreased if an amount of water approaching the theoretical quantity is removed.

A comparison of the efficiency of the various reagents is shown in Table II. This series of reactions was carried out without the removal of water at 135°, the highest temperature at atmospheric pressure at which such a comparison could be made.

Before any mechanism can be proposed for the reaction, one other source of confusion must be removed. The contention of Alexander and Wildman that ammonium formate is the required reactant cannot readily be reconciled with the other experimental data which have been reported. Therefore, it was decided to attempt some low-temperature runs with acetophenone and formamide. A comparison of several of the Leuckart reagents at low temperatures, with and without solvent, is shown in Table III. Although the yields obtained with formamide are low, they are real.

Using formamide as the reagent, Alexander and Wildman failed to obtain a yield at low temperatures. It should be noted, however, that they carried out

TABLE II
A COMPARISON OF REAGENTS AT 135°

REAGENT (MOLES PER MOLE OF ACETOPHENONE)	YIELD, %
Ammonium formate (four)	16
Ammonium formate (two) and formamide (two)	28
Formamide (two) and formic acid (two)	21
Formamide (four)	5

TABLE III
LOW TEMPERATURE LEUCKART REACTIONS

REAGENT	SOLVENT	TIME, HOURS	TEMPERATURE, °C.	YIELD, %
Acetophenone (1 mole) plus:				
Formamide (4 moles)	None	4	135	5
Formamide (4 moles)	Benzene	30	115	21
Ingersoll ^a (4 moles)	Benzene	25	113	25
Formamide (4 moles) and formic acid (1 mole)	Butanol	24	130	50
Formamide (4 moles)	Butyl formate	4	131	7
Formamide (4 moles) and formic acid (4 moles)	Butyl formate	4	123	13

^a Ingersoll's Reagent: Water is distilled from a mixture of 210 ml. of formic acid and 215 g. of commercial ammonium carbonate until the pot temperature reaches 165°. The resulting mixture is used as the reagent.

the reaction in diethylene glycol at 130°; the present work was concerned with the reaction in various solvents at their boiling points. Furthermore, when an alcohol was the solvent, a portion of the formamide was removed from the reaction due to the formation of a formate ester of the alcohol. Further investigation may show whether this fact is significant.

A SUMMARY OF THE FACTORS AFFECTING THE REACTION

A careful study of the literature and of the work which has just been outlined yields a number of facts concerning the reaction. They can be best summarized as follows:

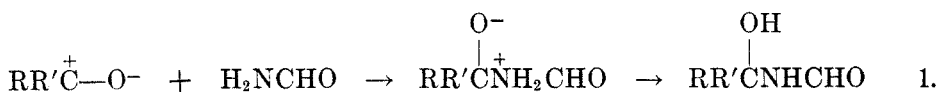
1. When water is removed, a mixture of formamide and formic acid gives the best yields.
2. When water is removed, ammonium formate gives better yields than formamide, although it does not give yields as high as formic acid and formamide combined.
3. When water is removed, a mixture of formamide and ammonium formate is as good as, but no better than, ammonium formate alone.
4. At low temperatures when water is not removed a mixture of ammonium formate and formamide is best.
5. With any reagent other than formamide, yields are improved when water is removed from the reaction mixture.
6. The yield is lowered when a dehydrating agent is used along with formamide.
7. Secondary and tertiary amines may be prepared by use of substituted formamides.
8. Acid catalysts increase the yield when formamide is used as the reagent.
9. A reducing agent is required.

It will be observed that in every case formamide is initially present or can easily be formed by dehydration of ammonium formate, that water must be somehow concerned in the reaction, and that a reducing agent is required. Furthermore, the familiar resonance forms of the ketone ($RR'CO \rightleftharpoons RR'C^+O^-$) must also be considered for their effect upon any possible mechanism.

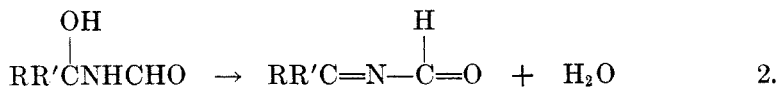
A PROPOSED MECHANISM

On the basis of the preceding summary, it is possible to propose a general mechanism for the Leuckart reaction which accounts for all the facts:

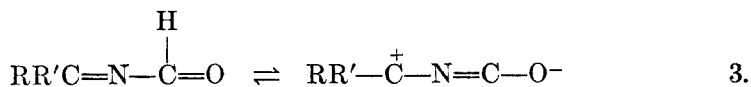
Case I. Reactant: Formamide. The first step is the addition of formamide to the carbonyl carbon:



At the temperature of the reaction (125° or higher), water is split out:



The product of step 2, having a conjugate system of two double bonds, should have the following resonance forms:



The water obtained in step 2 then hydrolyzes some formamide to give a small concentration of ammonium formate which can serve as the reducing agent which the reaction requires. The introduction of a dehydrating agent would de-

other than formamide is used. There are obviously two reasons for this. First of all, the removal of water facilitates the formation of formamide from the ammonium formate as well as the formation of the intermediate of step 2. Furthermore, the presence of a large quantity of water keeps the temperature comparatively low. Note, however, that according to the data of Table I, it is unwise to remove too much water. When this is done, substantially all the ammonium formate has been converted to formamide at the expense of the reducing agent, and yields are decreased.

Case IV. Reactants: Formamide and ammonium formate. When water is removed, mixed formamide and ammonium formate is as good as ammonium formate alone but no better. However, when no water is removed, the mixture is better than ammonium formate alone.

The same general mechanism fits the behavior of the reaction mixture when both formamide and ammonium formate are present. Some water is removed in order to force step 2 forward, since this water is not consumed in the formation of a reducing agent. In this case only a small amount of water should be removed, much less than when ammonium formate alone is present.

When no water is removed, as was the case with the data of Table II, the mixture is better than ammonium formate alone, because the concentration of formamide is much higher.

This general mechanism, therefore, seems to fit all the facts concerning all the possible reactants used in the Leuckart reaction.

THE PROOF OF THE PROPOSED MECHANISM

In order to investigate a mechanism it is necessary to determine the order of the reaction. Unfortunately, the Leuckart reaction, as it is normally carried out, does not lend itself to kinetic investigations. One of the basic conditions of the kinetic theory of solutions is that the medium in which the reaction occurs must be reasonably constant. Since in most cases the Leuckart reaction is carried out without a solvent, the concentrations are very high and the medium therefore changes constantly as the reaction proceeds.

Furthermore, when the reactants present are only a ketone and formamide or ammonium formate, no reliable method for determining concentrations is available. The most reliable method for following the course of the reaction, the measurement of carbon dioxide evolved, is unsuitable because part of the carbon dioxide is trapped in the condenser in the form of ammonium carbamate.

Thus, it seems that only the reaction between formamide, formic acid, and a ketone can be adapted to a kinetic study, since in this case no ammonia can be evolved.

In order to determine the order of the first step of the reaction, it is necessary to avoid the possibility of the reduction step being the rate-determining one. This may be most easily accomplished by the use of formic acid as the solvent. Under these conditions the acid concentration is much greater than that of the other reactants; the reduction step should occur much more rapidly than the initial step.

Several preliminary runs were carried out in order to determine the most practical conditions for kinetic measurements. It was found that comparatively low temperatures and high concentrations are required. When water is not removed, the reflux temperature of the reaction mixture decreases as the reaction proceeds. It is therefore necessary to carry out the reaction at a temperature below the reflux temperature of the mixture at the completion of the reaction. For this reason, it was decided to operate at a temperature of 125°.

TABLE IV
RATE CONSTANTS OF THE LEUCKART REACTION

INITIAL CONCENTRATION IN MOLES PER LITER		RATE CONSTANT (TIME IN HOURS)
Ketone ^a	Amide ^a	
4	4	2.4×10^{-3}
4	4	2.2×10^{-3}
2	4	1.5×10^{-3}
4	2	1.3×10^{-3}
3	3	1.1×10^{-3}

^a Acetophenone and formamide in 90% formic acid.

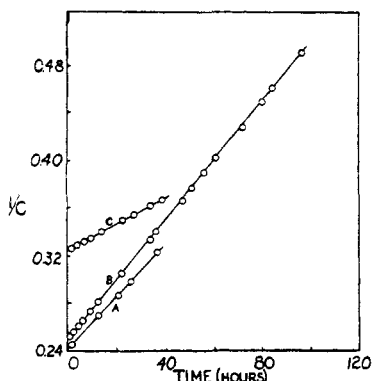


FIG. 1

FIGURE 1. KINETICS OF THE LEUCKART REACTION. Solvent, 90% formic acid; temperature, 125°. A, B: 4 *M* acetophenone and 4 *M* formamide. C: 3 *M* acetophenone and 3 *M* formamide.

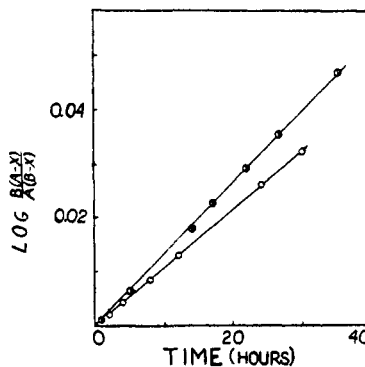


FIG. 2

FIGURE 2. KINETICS OF THE LEUCKART REACTION. Solvent, 90% formic acid; temperature, 125°. ●: 2 *M* acetophenone, 4 *M* formamide. ○: 4 *M* acetophenone, 2 *M* formamide.

At this temperature solutions in which both formamide and acetophenone were 2 *molar* reacted at rates which were much too slow to be practical. Even with concentrations of 3 *molar*, the reaction would be one-half complete only after about 330 hours.

The rate constants which have been obtained are compiled in Table IV. The determinations of reaction order are shown in Figures 1 and 2.

Examination of Figures 1 and 2 reveals that the reaction under these condi-

tions is most certainly second order. Very excellent straight lines were obtained when the proper identities for a second order reaction were plotted.

The data which are compiled in Table IV, however, show that the values for the rate constant do not check very well. Note that the value is fairly constant when the total concentration of reactants is 6 *molar*, but that the value obtained when both amide and ketone are 4 *molar* does not check with the other three.

It must be concluded, therefore, that the concentrations used in these determinations are too high. The requirement that the reaction medium be constant has not been met.

It will be recalled that it was proposed that the first step in the Leuckart reaction consists of the addition of formamide to the ketone. When this is the rate-determining step, as it should be under the conditions outlined above, the reaction should indeed be second order. The fact that the kinetic study discussed above shows this to be true constitutes excellent support for this step of the proposed mechanism. Obviously, the kinetic studies just outlined can be of value only for the clarification of the first step of the reaction.

It now becomes necessary to advance some proof of the presence of an intermediate of the type $RR'C=NCHO$.

Note that in the case of a simple aliphatic ketone, of formic acid, of formamide, and of the substituted formamide, the final product of the reaction, only one double bond is present. The proposed intermediate, however, contains a conjugate system of two double bonds. For this reason the ultraviolet absorption curves of the reaction mixture after reaction has occurred should be markedly changed from that of a mixture of the reactants and products.

Preliminary determinations of the absorption curve of the reaction mixture of acetophenone and formamide indicated that the use of this mixture is inadvisable. Acetophenone has such intense absorption maxima that the absorption maxima of a compound present in low concentration would be completely obscured, if they should be close to those of acetophenone. In order to avoid such interference, which is due to the resonance of the benzene ring, it was decided to use methyl isobutyl ketone instead of acetophenone when the ultraviolet absorption curves were to be determined.

The absorption curves, of formamide, methyl isobutyl ketone, and 2-methyl-4-formamidopentane, the final product of the reaction, are shown in Figure 3. Note that the two amides do not show an absorption maximum above 220 $m\mu$, while methyl isobutyl ketone has a maximum at 280 $m\mu$.

Figures 4 and 5 depict typical absorption curves of the Leuckart reaction mixtures after reaction has occurred.

The reaction mixture represented by the curve of Figure 4 initially contained formamide, formic acid, and methyl isobutyl ketone. The reaction was continued until most of the ketone had been consumed. Note the appearance of a new maximum at 340 $m\mu$ and a new shoulder which represents a maximum at about 240 $m\mu$.

Curve A, Figure 5, was obtained from a reaction in which only formamide and the ketone were initially present. Note that in this case, the maximum at

340 $m\mu$ is almost completely obscured by the intense absorption of the ketone.

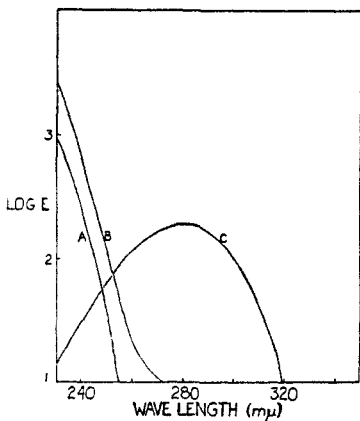


FIG. 3

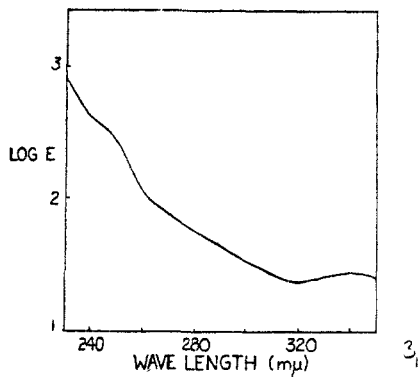


FIG. 4

FIGURE 3. ULTRAVIOLET ABSORPTION. A: Formamide. B: 2-Methyl-4-formamidopentane. C: Methyl isobutyl ketone; solvent, ethanol.

FIGURE 4. ULTRAVIOLET ABSORPTION OF A LEUCKART REACTION MIXTURE AFTER 12 HOURS. Reaction of methyl isobutyl ketone, formamide, and formic acid; solvent, ethanol.

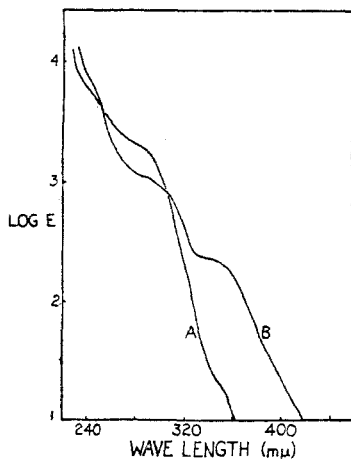


FIGURE 5. ULTRAVIOLET ABSORPTION OF LEUCKART REACTION MIXTURES AFTER 4 HOURS. A: Methyl isobutyl ketone and formamide. B: Methyl isobutyl ketone and formamide, with anhydrous calcium sulfate added; solvent, ethanol.

The reaction mixture which furnished Curve B, Figure 5, also contained formamide and the ketone; and in addition, a small amount of anhydrous calcium sulfate was present. In this case the shoulder at 340 $m\mu$ is much more pronounced.

If these new absorption maxima are due to the presence of a formimido com-

pound, the presence of a dehydrating agent would be expected to cause its absorption to be more intense. Since the addition of anhydrous calcium sulfate does indeed cause a more intense absorption at 240 and 340 $m\mu$, and since these new maxima cannot be attributed to the starting materials or products, it seems entirely reasonable to conclude that an intermediate of the type $RR'C=N-C=O$ is indeed formed during the course of the Leuckart reaction.

H

EXPERIMENTAL DETAILS

The acetophenone, methyl isobutyl ketone, and formamide used in this research were C. P. chemicals, carefully dried and redistilled before use. The formic acid used was commercial 90% formic acid.

The comparative runs listed in Tables I and III were carried out at a temperature such that a gentle reflux was maintained. The runs compiled in Table II were maintained at constant temperature by means of a Brown indicating controller.

The *product* of all runs of the Leuckart reaction listed in this work was isolated according to the following general method: The reaction mixture was allowed to cool and was washed three times with water. In order to speed up the separation of layers, 50 ml. of benzene was added to the mixture. After separating as much water as possible, the benzene layer was subjected to azeotropic distillation, with separation and removal of the lower layer of the distillate, in order to dry the material thoroughly.

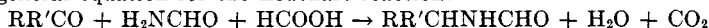
The resulting dry mixture was then distilled through a small column capable of effecting a separation equivalent to about six theoretical plates. The fraction boiling at 138–141° at 2 mm. was collected and reported as the yield of α -phenylethylformamide.

The *kinetics measurements* were obtained as follows: The starting materials were weighed to the nearest milligram, made up to 100 ml. with formic acid, and placed in the reaction flask. This flask was fitted with a reflux condenser attached to an absorption train consisting of two traps containing concentrated sulfuric acid and one containing anhydrous calcium chloride. The entire system was swept by a stream of nitrogen which had been first passed through sulfuric acid and Ascarite.

The amount of carbon dioxide evolved was determined by passing the effluent gases through tared tubes containing Ascarite and observing the change in weight over a measured period of time.

It was found unnecessary and undesirable to sweep nitrogen through the system continuously, since an appreciable amount of formic acid was picked up by the current of nitrogen. Therefore, the system was swept out with nitrogen for ten minutes just before a sample was to be weighed. This sweeping time was found to be sufficient to carry the carbon dioxide into the weighing tube.

The use of carbon dioxide measurements to follow the course of the reaction is based upon the general equation for the Leuckart reaction:



For every mole of carbon dioxide produced, one mole of ketone and one mole of formamide are consumed.

Ultraviolet absorption curves were obtained by means of a Beckman Model DU Quartz Spectrophotometer. All solutions were originally diluted to a concentration of 10.0% in absolute ethanol, and further dilutions were made, as necessary, in steps of one-tenth. In most cases, solutions of 10.0, 1.0, 0.1, and 0.01% were required for the complete absorption curve. The value of $\text{Log } I_0/I$ was read directly from the instrument. A modified extinction coefficient was then obtained by dividing this value by the concentration of the solution being measured. Thus, the values plotted in Figures 3, 4, and 5 were obtained from the equation:

$$\text{Log } E = \log \frac{\log I_0/I}{c}$$

Readings were taken at 2-m μ intervals at critical points on the curve and at 5-m μ intervals over the remaining range.

Acknowledgements: The authors express sincere appreciation to Dr. A. H. Gropp and Dr. C. E. Ried for their suggestions in connection with this work.

SUMMARY

A complete mechanism for the Leuckart reaction has been proposed. The results of all the published investigations of the Leuckart reaction, with the exception of a small portion of the work of Alexander and Wildman, support this mechanism.

Comparative data on various Leuckart reagents have been tabulated; kinetic and spectrophotometric studies have been presented.

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