

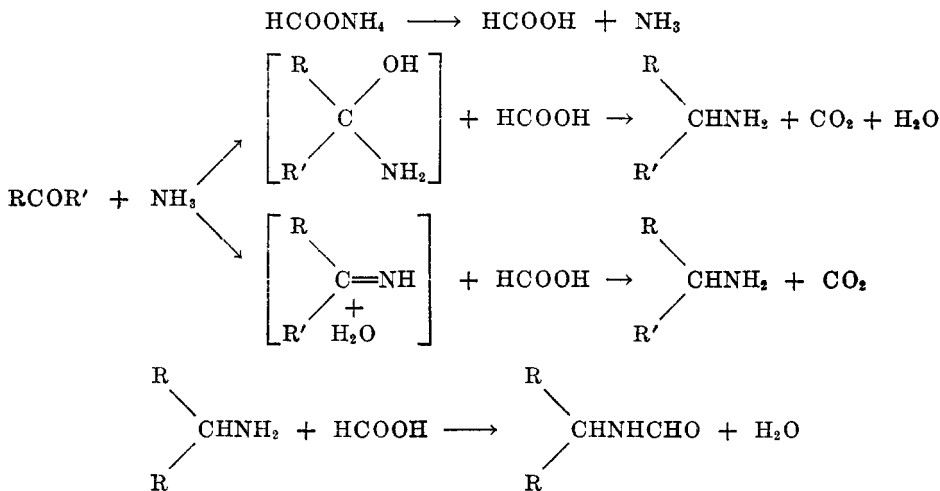
STUDIES ON THE LEUCKART REACTION

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Received July 21, 1944

In 1885, Leuckart (1) first described the conversion of certain aldehydes and ketones to the corresponding amines by heating with excess ammonium formate. Wallach (2) applied the method to a number of alicyclic and terpenoid ketones, as well as certain aldehydes, and showed its general application. Despite the excellent results reported by Wallach, the reaction had found little use by others until Ingersoll (3) and his co-workers published a review of the method and reported the synthesis of a series of substituted α -phenethylamines by an improved modification of the procedure. Since the appearance of this publication, other workers have been stimulated to use the reaction in the preparation of a number of amines with varying success.

Although the exact mechanism has not been definitely established, the reaction has been studied by Wallach (2) and Ingersoll (4) and explained by the following steps: (a) The ammonium formate dissociates into ammonia and formic acid at the temperature of the reaction; and (b) ammonia adds to the carbonyl group or condenses to form the corresponding imine. (c) The formic acid then acts as a reducing agent to remove the hydroxyl or reduce the imino group; and (d) if in excess, may form the formyl derivative which is subsequently hydrolyzed to the free amine.



Formamide (90–95%) may be substituted for ammonium formate and probably hydrolyzes in the reaction to undergo the same steps as above. Wallach (2), and more recently Nabenhauer (5), has shown that dialkylammonium formate reacts with aldehydes and ketones to give the corresponding tertiary amines,

without the formation of an intermediate formyl derivative. These observations lend support to the suggestion of an initial dissociation of the reactive agent. Ingersoll (4) has indicated recently that the presence of formic acid increases the yield when formamide is used as the reagent. Wallach has used formic acid in some of his experiments without indicating its effect upon the yields which he obtained.

Needing a supply of various aralkylamines we have used the Leuckart reaction in their preparation and have had an opportunity to study some of the experimental conditions which influence the yield of the desired product. Following Ingersoll's suggestion (3), Johns and Burch (6) used formamide as the reactive agent, but they reported yields of 10–20% less than those of Ingersoll. In order to study the effect of the reagent upon the yield of amine, we ran a series of

TABLE I
EFFECT OF VARIATION IN THE LEUCKART REAGENT ON THE CONDENSATION WITH 3-PHENYL-2-BUTANONE. ACID HYDROLYSIS OF FORMYL DERIVATIVE

RUN NO.	LEUCKART REAGENT	TEMP. °C.	TIME, HRS.	YIELDS		
				Amine, %	Un-reacted Ketone, g.	Tar, g.
1	Formamide ^a	170–180	22	27		
2	Formic acid and ammonia (5 moles each)	175–185	21	45		
3	Formamide ^a and formic acid (2.5 moles added in portions)	170–180	22	47		
4	Formic acid and ammonia (5 moles each)	170–180	14	47	3	3
5	Formamide ^a and formic acid (2.5 moles added in portions)	170–180	15	45	3	4
6	Formamide ^a and formic acid (2.5 moles added all at once)	170–180	15	48	3	3
7	Formic acid and ammonia	160–170	7	50	2	0.5
8	Formamide ^a and water (85 g.)	160–170	7	16	25	1

^a Five moles of Eastman's material used.

experiments on the condensation of formamide with 3-phenyl-2-butanone in which the source or preparation of the formamide was varied. The reactions were carried out using a ratio of five moles of reagent to one mole of ketone (3) and the formyl derivative was hydrolyzed in concentrated hydrochloric acid by refluxing for eight hours. The reagent from formic acid and ammonia was prepared according to the procedure of Novelli (7) except for the variations in temperatures as noted in the tables. Table I shows the yield of α,β -dimethylphenethylamine obtained by using the various reagents. An examination of Table I shows that the use of formamide gave a lower yield of product than that obtained from ammonia and formic acid. The addition of formic acid to formamide increased the yield to that obtained from the ammonia and formic acid reagent. It did not appear to make much difference whether the formic acid was added in portions during the condensation or all at once at the beginning of

the reaction. The addition of water to the formamide did not increase the yield of the product. The influence of formic acid upon the formamide reagent lends further support to Wallach's explanation of the reaction mechanism and may account for the low yields obtained by Read and co-workers (8) in converting carvomenthone to carvomenthylamines with dry ammonium formate at 130°, and for the need of Leuckart to heat the reagents in a sealed tube at 210–240°.

Various experimental conditions have been used in carrying out the Leuckart reaction. Ingersoll (3) heated his reaction mixture at 160–185° until the distillation of water had ceased, at which time the temperature had reached 175–185°, maintaining this temperature from three to ten hours longer. Johns and Burch (6) refluxed the ketone with formamide for thirty hours; while Novelli (7) carried out the condensation at 190–230° for four to eight hours. In order to determine the effect of temperature on the yield of product, three experiments were run on 3-phenyl-2-butanone, using the reagent from ammonia and formic acid, in which the temperature of the reaction was varied, although all were

TABLE II

EFFECT OF TEMPERATURE ON THE LEUCKART REACTION WITH 3-PHENYL-2-BUTANONE. TIME: FIFTEEN HOURS. ACID HYDROLYSIS OF FORMYL DERIVATIVE

RUN NO.	TEMPERATURE, °C.	YIELD		
		Amine, %	Unreacted Ketone, g.	Tar, g.
9	190–200	23	8	5
4	170–180	47	3	3
10	160–170	50	3	1
CONDENSATION WITH PHENYLACETONE. TIME: SIX HOURS				
11	160–170	26	0.5	7
12	140–150	25	1.0	7

heated for fifteen hours. In two experiments with phenylacetone the reaction mixture was heated for six hours. The results are shown in Table II. It is evident that the yield was influenced by the temperature at which the condensation was carried out and in these experiments the yield was twice as much at 160–170° as at 190–200°.

The effect of varying the time of heating when carrying out the condensations at various temperatures is shown in Table III. A yield of 50% was obtained when the condensation was carried out at 190–200° for five hours, while a yield of only 23% was obtained after heating for fifteen hours. The reaction may be heated for fifteen hours at 160–170° without a reduction in yield, although the same results were obtained by heating for as short a period as four hours. Similar results were obtained in the condensations with phenylacetone, although the yield from the reactions were somewhat lower.

At least two procedures have been described for the hydrolysis of the formyl derivative to the corresponding amine. In one, 30% sodium hydroxide solution was used and in the other concentrated hydrochloric acid was the hydrolytic

agent. The effect of various concentrations of these two hydrolytic agents on purified N-formyl- α,β -dimethylphenethylamine is shown in Table IV. At the same time, a study was made of the variation in time and experimental conditions on the hydrolysis of the formyl derivative from the reaction mixture without subsequent purification. These results are summarized in Table V and inspection

TABLE III
EFFECT OF TIME ON THE LEUCKART CONDENSATION WITH 3-PHENYL-2-BUTANONE.
TEMPERATURE: 190-200°. ACID HYDROLYSIS OF FORMYL DERIVATIVE

RUN NO.	TIME, HRS.	YIELD		
		Amine, %	Unreacted Ketone, g.	Tar, g.
9	15	23	8	5
13	5	50	1.5	0.5
14	3	47	2.0	0.5
TEMPERATURE: 160-170°				
10	15	50	3.0	1.0
7	7	50	2.0	0.5
15	4	48	2.0	0.5
CONDENSATION WITH PHENYLACETONE. TEMPERATURE: 160-170°				
16	8	26	0.5	7
11	6	26	0.5	7
17	3	22	0.5	8

TABLE IV
EFFECT OF TIME AND REAGENTS ON THE HYDROLYSIS OF
N-FORMYL- α,β -DIMETHYLPHENETHYLAMINE

RUN NO.	HYDROLYTIC REAGENT	TIME OF HYDROLYSIS, HRS.	YIELD OF AMINE, %
18	Conc'd. Hydrochloric acid	8	59
19	10% " "	8	75
20	10% " "	1	67
21	30% Sodium hydroxide	8	0 ^a
22	10% " "	8	71
23	6.6% " "	8	76

^a Seventeen grams of unreacted formyl derivative was recovered.

shows that the best yield was obtained by hydrolyzing the formyl derivative directly in the reaction mixture with concentrated hydrochloric acid.

Having developed a satisfactory procedure for the reaction with 3-phenyl-2-butanone, it seemed desirable to study the effect of different ketones in the reaction at 160-170° under these same experimental conditions. The results obtained in this series of experiments are summarized in Table VI. In all cases the formyl derivatives were hydrolyzed in the reaction mixture with hydrochloric acid.

A review of the data brings out the interesting observation that 3-phenyl-2-butanone gave a yield of 58% of product, while with phenylacetone a yield of only 26% resulted. This may be due to the ease of resinification of the phenylacetone, as indicated by the increased amount of tar obtained. Propiophenone

TABLE V
EFFECT OF TIME AND EXPERIMENTAL CONDITIONS OF HYDROLYSIS ON THE LEUCKART
CONDENSATION WITH 3-PHENYL-2-BUTANONE. REACTION
TEMPERATURE: 160-170°. TIME: 7 HOURS

RUN NO.	EXPERIMENTAL CONDITIONS FOR HYDROLYSIS	TIME OF HYDROLYSIS, HRS.	YIELD	
			% Amine	Unreacted Ketone, g.
18	Formyl derivative isolated, purified and hydrolyzed with conc'd hydrochloric acid	8	39	
19	Same as above but hydrolyzed with 10% hydrochloric acid	8	53	
24	Formyl derivative isolated without purification and hydrolyzed in conc'd hydrochloric acid	8	48	2
25	Formyl derivative separated as crude oil and hydrolyzed in conc'd hydrochloric acid	8	50	2
26	Formyl derivative separated as crude oil and hydrolyzed in conc'd hydrochloric acid	4	45	2
27	Formyl derivative hydrolyzed in reaction mixture with conc'd hydrochloric acid	8	58	2
28	Formyl derivative hydrolyzed in reaction mixture with 10% sodium hydroxide	8	0 ^a	3

^a Thirty-four grams of formyl derivative isolated.

TABLE VI
EFFECT OF KETONE ON THE LEUCKART REACTION AT 160-170°. ACID HYDROLYSIS OF FORMYL
DERIVATIVE IN REACTION MIXTURE

RUN NO.	KETONE	TIME, HRS.	YIELD		
			Amine, %	Unreacted Ketone, g.	Tar, g.
11	Phenylacetone	6	26	0.5	7
27	3-Phenyl-2-butanone	7	58	2	1
28	Propiophenone	7	65	0	3
29	Laurophenone	30	64	0	0
30	Benzophenone	9	80	—	0
31	<i>p</i> -Methylcaprophenone	9	63	—	0
32	<i>p</i> -Methylaurophenone	30	0	26	—
35	8-Pentadecanone	15	40		

was converted to the amine in a yield of 65% and laurophenone in a yield of 64%, although the reaction with laurophenone required thirty hours. *p*- α -Aminododecyltoluene was not isolated from *p*-methylaurophenone even though the reaction was continued for thirty hours. Unreacted ketone was the only definite product

recovered. Such a marked effect of the methyl group upon the lauryl derivative is surprising, particularly in view of the fact that *p*-methylcaprophenone gave a yield of 63%. However, three separate runs led to the same negative results.

The aliphatic ketone, 8-pentadecanone, gave a 40% yield of 8-aminopentadecane after heating for fifteen hours. These results indicate that the Leuckart reaction may be used to prepare amines in satisfactory yields from a large number of ketones with only a slight modification of the experimental conditions.

Substitutions in the ammonium formate had considerable influence upon the yield of the products from the reaction. The results of experiments with the Leuckart reagent prepared from various substituted amines are recorded in Table VII. Methylamine and formic acid converted phenylacetone to *N*, α -dimethylphenethylamine in a yield of 43%, while ammonia and formic acid produced a yield of only 26% of α -methylphenethylamine under the same conditions. In condensations with 3-phenyl-2-butanone, ammonia and formic acid gave a

TABLE VII
EFFECT OF SUBSTITUTION IN THE LEUCKART REAGENT ON THE REACTION AT 160–170°. ACID
HYDROLYSIS OF FORMYL DERIVATIVE IN REACTION MIXTURE

RUN NO.	KETONE	LEUCKART REAGENT	TIME, HRS.	YIELD		
				Amine, %	Unreacted Ketone, g.	Tar, g.
11	Phenylacetone	Formic acid and ammonia	6	26	0.5	7
36	"	Formic acid and methylamine	7	43	1.0	2
37	"	Formic acid and <i>n</i> -butylamine	6	5	20	4
38	3-Phenyl-2-butanone	Formic acid and ammonia	7	58	2	1
39	"	Formic acid and methylamine	6	41	4	0
40	"	Formic acid and <i>n</i> -butylamine	24	16	9	2
29	Laurophenone	Formic acid and ammonia	30	64	0	0
42	"	Formic acid and dimethylamine	28	0	75	

higher yield of product than methylamine and formic acid. When butylamine and formic acid were used both phenylacetone and 3-phenyl-2-butanone gave a lower yield of the amines than was obtained with either ammonia or methylamine and formic acid. Attempts to carry out the condensation using dimethylamine with laurophenone proved unsuccessful.

These data indicate that the higher alkyl substituted ammonium formates are more difficult to condense with the ketones, and it may be desirable to use higher temperatures in these reactions. This aspect of the problem needs further investigation.

EXPERIMENTAL

All melting points reported are uncorrected.

The following procedures are typical examples of the experiments reported in the preceding tables.

α , β -Dimethylphenethylamine. To a three-necked flask, equipped with a dropping-fun-

nel, thermometer, and down-directed condenser, was added with care 105 g. (1.72 moles) of 28% ammonia and 88 g. (1.72 moles) of 90% formic acid. The temperature of the solution was raised to 160° by distilling out water, and 51 g. (0.344 mole) of 3-phenyl-2-butanone was added at one time. The temperature was maintained at 160–170° for seven hours and any ketone which distilled was returned to the flask at intervals. The formyl derivative was hydrolyzed in the reaction mixture by refluxing for eight hours with 120 cc. of concentrated hydrochloric acid. After standing overnight, the mixture was diluted with 200 cc. of water and extracted with 100 cc. of benzene¹ to remove water-insoluble material. The aqueous solution was treated with a little charcoal (Norit), made alkaline with ammonia and the oil thus produced extracted with benzene. The benzene solution was washed three times with water, dried with sodium sulfate and the benzene removed by distillation under reduced pressure. The residue gave 30 g. (58%) of α,β -dimethylphenethylamine, boiling at 66–69° at about 1 mm., n_D^{25} 1.5146.

α -Aminododecylbenzene. Following the above procedure, 89.5 g. (0.344 mole) of laurophenone was added to the ammonium formate mixture and the temperature maintained at 160–170° for thirty hours. The formyl derivative was hydrolyzed by refluxing for eight hours with 120 cc. of concentrated hydrochloric acid. After standing overnight, 200 cc. of water was added and the compact crystalline mass of hydrochloride salt broken up. The α -aminododecylbenzene hydrochloride was collected on a Büchner funnel and washed three times with small portions of cold water. To a hot alcoholic solution of the crude hydrochloride, an excess of 28% ammonia was added and after dilution with cold water, the free amine was extracted with benzene. The benzene extract was distilled and the α -aminododecylbenzene collected at 170–172° (1–2 mm.) (n_D^{25} 1.4903) yield 64%. The hydrochloride prepared from this amine melted at 118–118.5°.

Unreacted laurophenone was the only product isolated from the reaction of dimethylamine and formic acid in the above procedure.

SUMMARY

1. A study has been made of some of the factors affecting the Leuckart reaction.

2. The use of formamide in the reaction gave a lower yield of primary amine than that obtained from the use of ammonia and formic acid. The addition of formic acid to formamide increased the yield obtained, while the addition of water had no effect.

3. In the condensation of the reagent from ammonia and formic acid with 3-phenyl-2-butanone, a reaction temperature of 160–170° for fifteen hours or a temperature of 190–200° for three to five hours gave the best yields of primary amine. A longer period of heating at the higher temperature reduced the yield. Similar results were obtained in the condensation with phenylacetone, although the yields were lower.

4. In the hydrolysis of the formyl derivative to the corresponding amine the best yield was obtained by hydrolyzing directly in the reaction mixture with concentrated hydrochloric acid.

5. A series of ketones were converted to the corresponding primary amines by the Leuckart reaction at 160–170° under the same experimental conditions. All gave excellent results except *p*-methylaurophenone which failed to react even when heated for thirty hours.

6. Alkyl substituted ammonium formates were more difficult to condense with

¹ Two grams of unchanged ketone and one gram of tar were recovered from the benzene.

the ketones and attempts to carry out the condensation of dimethylamine and formic acid with laurophenone were unsuccessful.

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