

CHAPTER 7

THE LEUCKART REACTION

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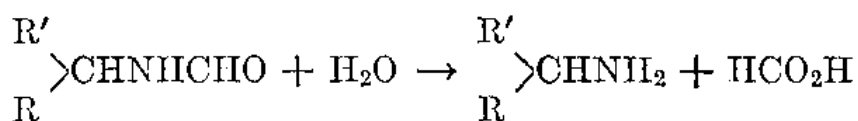
CONTENTS

	PAGE
INTRODUCTION	302
MECHANISM OF THE REACTION	303
SCOPE OF THE REACTION	306
Methylation of Amines with Formaldehyde	307
Reactions of Higher Aliphatic Aldehydes	308
Reactions of Aromatic and Heterocyclic Aldehydes	309
Reactions of Aliphatic Ketones	310
Reactions of Aliphatic-Aromatic and Aliphatic-Heterocyclic Ketones	311
Reactions of Aromatic Ketones	313
Reactions of Alicyclic Ketones	314
Reactions of Quinones	314
Reactions of a Pyrazolone and an Oxindole	315
SIDE REACTIONS	315
EXPERIMENTAL CONDITIONS	316
The Ammonium Formate or Formamide	316
Temperature	317
Solvent	317
Hydrolysis	318
Isolation	318
EXPERIMENTAL PROCEDURES	319
Tri- <i>n</i> -amylamine (Use of Ammonium Formate and Formic Acid)	319
N,N-Dimethylfurfurylamine (Use of Dimethylformamide and Formic Acid)	319
α -(β -Naphthyl)ethylamine (Preparation and Use of Formamide-Formic Acid Reagent from Ammonium Carbonate-Carbamate and Formic Acid)	320
Methyl- <i>tert</i> -butylcarbinamine (Use of a Solvent, Nitrobenzene)	321
α - <i>p</i> -Chlorophenethylamine (Use of Formamide and Formic Acid)	321
α -Aminododecylbenzene (Use of Ammonia and Formic Acid)	322
α -(<i>o</i> -Chlorobenzyl)ethylamine (Use of Formamide)	323
N,N-Dimethylbenzylamine (Eschweiler-Clarke Procedure)	323

	PAGE
TABULAR SURVEY OF THE LEUCKART REACTION	323
TABLE	
I. With Aliphatic Aldehydes	325
II. With Aromatic and Heterocyclic Aldehydes	326
III. With Aliphatic Ketones	327
IV. With Aliphatic-Aromatic and Aliphatic-Heterocyclic Ketones	328
V. With Aromatic Ketones	329
VI. With Alicyclic Ketones	330
VII. With Quinone	330

INTRODUCTION

The Leuckart reaction is a process for the reductive alkylation of ammonia or primary or secondary amines by certain aldehydes and ketones. It is distinguished by the fact that the reduction is accomplished by formic acid or a derivative of formic acid and should be compared with the reductive alkylation using hydrogen discussed in Chapter 3 of Volume IV of *Organic Reactions*. The reaction is carried out by heating a mixture of the carbonyl compound and the formic acid salt or formyl derivative of ammonia or the amine. Primary and secondary amines produced in the reaction often are obtained as the formyl derivatives and must be recovered by hydrolysis; tertiary amines are obtained as the formates. The reaction may be illustrated by the following equations.



Leuckart¹ discovered the reaction in an attempt to prepare benzylidenediformamide, $\text{C}_6\text{H}_5\text{CH}(\text{NHCHO})_2$, by heating benzaldehyde with formamide in an experiment patterned after the preparation by Roth² of the corresponding acetamide derivative. The reaction with formamide was found to take a different course, leading to benzylamine and its formyl derivative, dibenzylamine and its formyl derivative, and tribenzylamine. Ammonium formate was found to react in the same

¹Leuckart and co-workers, *Ber.*, **18**, 2341 (1885); **19**, 2128 (1886); **20**, 104 (1887); **22**, 1409, 1851 (1889).

²Roth, *Ann. Chem. Pharm.*, **154**, 72 (1870).

way as the amide, and benzophenone could be converted to benzohydrylamine by the use of conditions somewhat more drastic than those required with benzaldehyde. Leuckart's experiments with aliphatic aldehydes and ketones were not extensive,³ but Wallach⁴ and Kijner⁵ applied the reaction to many such compounds. The method received little attention from other investigators until Ingersoll and his associates⁶ reviewed the subject and applied the reaction to the synthesis of a series of substituted α -phenethylamines; since the appearance of this work the method has been employed extensively. Among the better-known modifications of the process are the preparation of trimethylamine⁷ from ammonia, formaldehyde, and formic acid and the Eschweiler-Clarke^{8,9} procedure for the methylation of primary and secondary amines by the aid of formaldehyde and formic acid.

MECHANISM OF THE REACTION

A single mechanism capable of accounting for all the variations of the Leuckart process can be postulated on the basis of the decomposition of the ammonium salt or of the amide, by thermal or hydrolytic means, respectively, to formic acid and ammonia or an amine. The base so formed may then react with the carbonyl compound to give an addition

product $\left(\begin{array}{c} \diagup \text{C} \diagdown \\ \text{OH} \\ \text{N} \end{array} \right)$ which is reduced by formic acid to an amine $\left(\begin{array}{c} \diagup \text{CH} \text{---} \text{N} \diagdown \end{array} \right)$; reaction of this amine with more formic acid leads to

the salt or the amide. These transformations appear to be the only ones concerned in the formation of a tertiary amine from a carbonyl compound and the formate or formyl derivative of a secondary amine, but there are numerous other possible intermediates in the synthesis of primary and secondary amines. For example, the addition product from a carbonyl compound and ammonia or a primary amine may undergo

³ Leuckart, *J. prakt. Chem.*, [2] **41**, 330 (1890).

⁴ Wallach and co-workers, (a) *Ber.*, **24**, 3992 (1891); (b) *Ann.*, **269**, 347 (1892); (c) **272**, 100 (1893); (d) **276**, 296 (1893); (e) **289**, 338 (1896); (f) **300**, 283 (1898); (g) **343**, 54 (1905).

⁵ Kijner, *J. Russ. Phys. Chem. Soc.*, **31**, 877, 1033 (1899); **32**, 381 (1900) [*J. Chem. Soc. (Abs.)*, **78** (i), 277, 333, 629 (1900)].

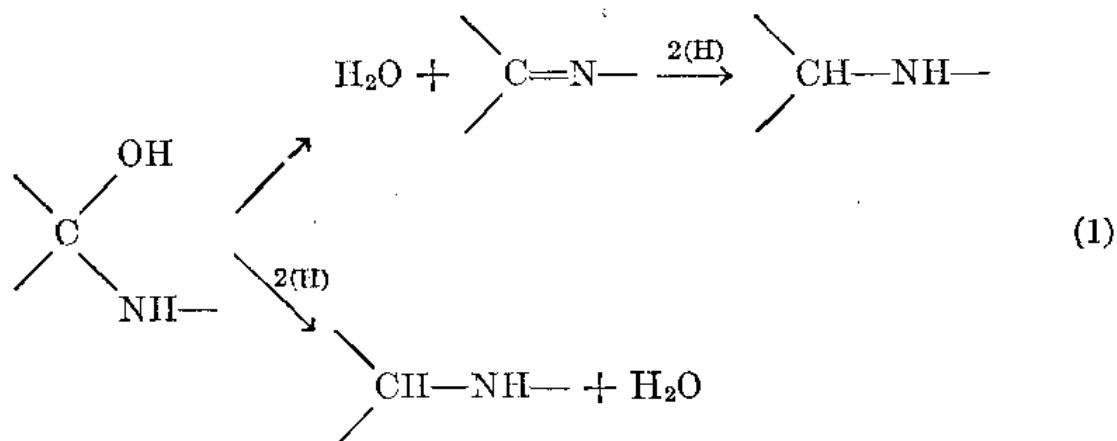
⁶ Ingersoll, Brown, Kim, Beauchamp, and Jennings, *J. Am. Chem. Soc.*, **58**, 1808 (1936).

⁷ Sommelet and Ferrand, *Bull. soc. chim. France*, [4] **35**, 446 (1924).

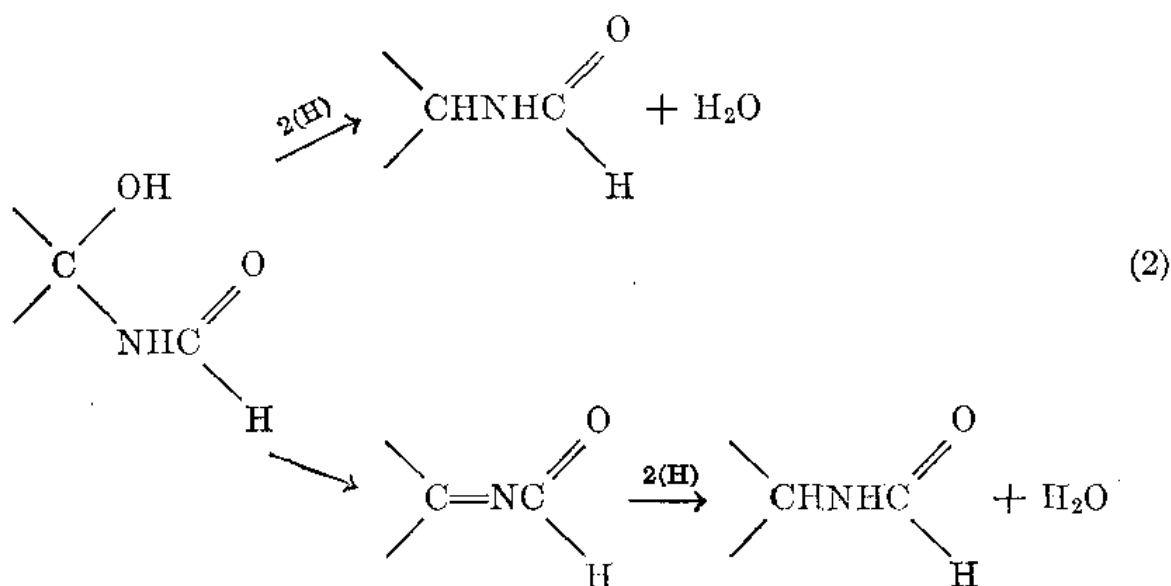
⁸ Eschweiler, *Ber.*, **38**, 880 (1905).

⁹ Clarke, Gillespie, and Weiss Haus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

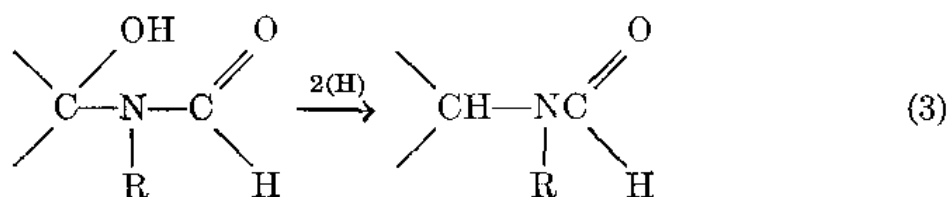
loss of water, and the imine so formed may be the intermediate which is reduced to the amine (equation 1). Furthermore, when formamide is



present in the reaction mixture (either added as such or produced by dehydration of ammonium formate) it may give rise to an addition product capable of reduction directly to the formyl derivative of the primary amine or of dehydration and reduction to the same substance.



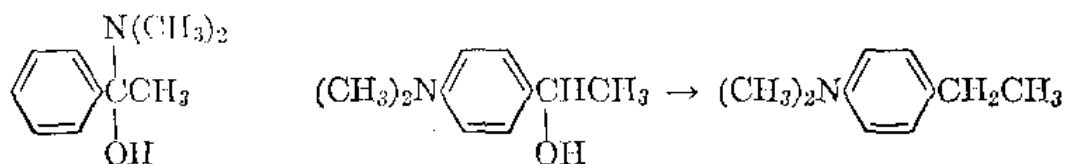
If the reacting amide is derived from a primary amine the addition product cannot undergo dehydration but must be reduced directly if it participates in the reaction. The formyl derivative of a secondary



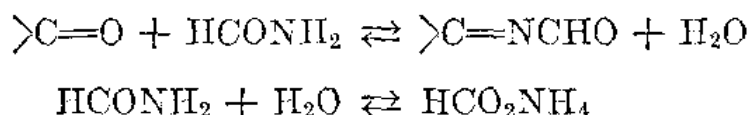
amine (HCONR_2) cannot give an addition product; evidently the first step in its reaction must be hydrolysis.

Imines, >C=N- , and addition products from carbonyl compounds and ammonia or amines, >C(OH)-N< , were suggested in the preceding

paragraphs as intermediates in the Leuckart reaction, intermediates which are reduced by formic acid. Benzalaniline, a representative imine, is reduced almost quantitatively to benzylaniline by heating at $140\text{--}160^\circ$ with triethylammonium formate.^{9a} No examples are available of the action of formic acid on the addition product of a carbonyl compound and ammonia or an amine; but *p*-dimethylaminophenylmethylcarbinol, a vinylog of the addition product from acetophenone and dimethylamine, is reduced to *p*-dimethylaminoethylbenzene in poor yield by heating at $130\text{--}135^\circ$ with triethylammonium formate.^{9a} Formic acid could not be used in these reductions since it led to the formation of resinous materials.



Much of the study^{6,10,11,12} of the mechanism of the Leuckart process has been concerned with the reactions involved in the formation of primary amines. Inasmuch as the experimental temperature (150° or higher) usually employed is above that at which ammonium formate rapidly generates formamide and water it has been considered that formamide may be the true reagent even in preparations in which ammonium formate is employed. However, acetophenone in diethylene glycol at $120\text{--}130^\circ$ does not react with formamide over a period of fifteen hours, whereas with ammonium formate under the same conditions a 10% yield of α -phenethylamine is obtained in four hours.^{9a} At the higher temperatures ordinarily used, formamide could furnish ammonium formate in the following way.



In experiments with acetophenone and formamide at $165\text{--}173^\circ$, the addition of anhydrous calcium sulfate brought down the yield of α

^{9a} Alexander and Wildman, *J. Am. Chem. Soc.*, **70**, 1187 (1948).

¹⁰ Ingersoll, Brown, Levy, and Haynes, personal communication.

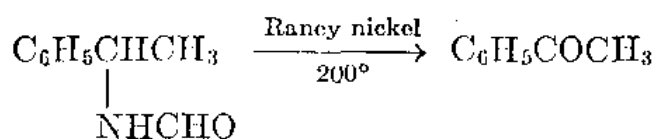
¹¹ Davies and Rogers, *J. Chem. Soc.*, **1944**, 126.

¹² Crossley and Moore, *J. Org. Chem.*, **9**, 529 (1944).

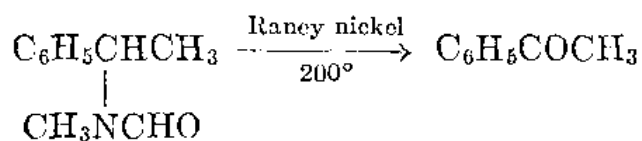
phenethylamine from 30% to 17%.^{9a} The available evidence does not permit one to exclude either of the mechanisms shown in equations 1 and 2 on p. 304; both mechanisms may be operative under appropriate experimental conditions.

The reaction between benzophenone and formamide is catalyzed by ammonium formate, magnesium chloride, or ammonium sulfate, and it has been suggested that the catalyst polarizes the carbonyl group and thus facilitates the addition of formamide or ammonia.^{12a}

Formyl derivatives of primary amines are stable substances, and many of them can be heated to 200° without undergoing any change. When they are heated to this temperature in the presence of Raney nickel, however, they furnish ketones.^{12b} Formyl derivatives of second-



ary amines undergo the same reaction, but the yields of carbonyl compounds are poor.^{12a}



SCOPE OF THE REACTION

The method appears best adapted to aromatic aldehydes and water-insoluble ketones boiling at about 100° or higher. Higher aliphatic ketones, aromatic aldehydes and ketones, and certain terpenoid ketones have been used successfully, with yields of 40–90%. The application of the reaction to aliphatic aldehydes and ketones of lower molecular weight has been very limited. The method is definitely superior to that involving the formation and reduction of aldoximes and ketoximes and has succeeded where the reduction of oximes is unsatisfactory, particularly with compounds in which functional groups are present that are readily attacked by many reducing agents. Thus, the Leuckart method gives an 82% yield of pure α -*p*-chlorophenethylamine from *p*-chloroacetophenone, whereas the reduction of *p*-chloroacetophenone oxime with sodium and ethanol, sodium amalgam and acetic acid, or by catalytic means, proceeds in all instances with extensive removal of the nuclear halogen. *p*-Bromoacetophenone and *m*-nitroacetophenone are readily

^{12a} Webers and Bruce, *J. Am. Chem. Soc.*, **70**, 1422 (1948).

^{12b} Métayer and Mastagli, *Compt. rend.*, **225**, 457 (1947).

converted to the corresponding amines without disturbance of the halogen or nitro group.

The reaction is not limited to ammonium formate or formamide. Methyl formate has been used with a few primary amines. Substituted ammonium formates, such as monomethyl- or dimethyl-ammonium formate, react satisfactorily and lead to the formation of secondary and tertiary amines of mixed type that cannot be obtained easily by other methods. Thus, the N-methyl, N-ethyl, and N-butyl derivatives of α -phenethylamine are prepared in yields of 60-70% by the action of methyl-, ethyl-, and butyl-ammonium formates on acetophenone.^{13, 14}

Methylation of Amines with Formaldehyde

The simplest aldehyde, formaldehyde, reacts very readily, and it is difficult to prevent the formation of tertiary amines. Formaldehyde reacts with ammonium formate and formic acid, but trimethylamine is the product isolated in highest yield.⁷ Formaldehyde was first used alone⁸ for the methylation reaction, but Clarke⁹ obtained better yields (80%) by using an excess of formic acid with the formaldehyde. One molecular proportion (or a slight excess) of formaldehyde and two to four molecular proportions of formic acid are used for each methyl group introduced, indicating that it is mainly the formic acid that supplies the hydrogen involved in the reduction. The reaction is carried out on the steam bath. This variant of the Leuckart reaction, as mentioned earlier, is commonly known as the Eschweiler-Clarke procedure.

Ethylamine,⁸ piperazine,⁸ anabasine,¹⁵ the benzylamines,^{8, 16, 17} phenethylamines,¹⁶ and methoxyphenethylamines¹⁷ react to give almost theoretical yields of the corresponding tertiary amines. Secondary amines react as readily as primary amines to give the corresponding methyl derivatives although N-benzyl-3,4-dimethoxyphenethylamine¹⁷ gives unsatisfactory results, probably owing to partial cyclization.¹⁸ Dibenzylamine gives a 75% yield of the anticipated methyldibenzylamine, 6-12% of a more volatile base, probably dimethylbenzylamine, and a similar amount of benzaldehyde.⁹ Further application of the process is illustrated by the complete methylation of ethylenediamine and tetramethylenediamine in yields of 92%.

¹³ Novelli, *J. Am. Chem. Soc.*, **61**, 520 (1939).

¹⁴ Busch and Ieffhelm, *J. prakt. Chem.*, [2] **77**, 21, 23 (1908).

¹⁵ Orzechoff and Norkina, *Ber.*, **65**, 724 (1932).

¹⁶ Decker and Becker, *Ber.*, **45**, 2404 (1912).

¹⁷ Buck and Baltzly, *J. Am. Chem. Soc.*, **62**, 161 (1940); **63**, 1964 (1941); **64**, 2263 (1942).

¹⁸ Buck, *J. Am. Chem. Soc.*, **56**, 1769 (1934).

The reaction fails with compounds in which strongly polar groups are attached to the nitrogen, such as amides, urea, guanidine, and hydroxylamine, as these appear to yield hydroxymethyl derivatives only. Moreover, the reaction cannot be applied successfully to the methylation of aniline, which on warming with formaldehyde and formic acid is converted into condensation products of high molecular weight.¹⁹ On the other hand, it is reported that formaldehyde reacts with *p*-toluidine in an excess of 90% formic acid to give dimethyl-*p*-toluidine,²⁰ and with 2,4,6-tribromoaniline⁹ and mesidine,²¹ in which the active positions in the benzene nucleus are occupied, to form the dimethyl derivatives in 73–77% yields.

Some of the amino acids can be methylated by treatment with formaldehyde and formic acid.⁹ For example, glycine yields 60–70% of dimethylglycine; complex, non-crystalline products as well as volatile bases, mainly trimethylamine, are formed also. α -Aminoisobutyric acid and α -phenyl- α -aminobutyric acid give 70–80% yields of the dimethyl derivatives, but the yield from β -aminopropionic acid is only 38%. However, with alanine none of the dimethyl derivative is isolated and 36% of the nitrogen is converted into methylamines. Similar results are obtained with leucine, glutamic acid, etc., in all of which an even greater proportion of the nitrogen is cleaved from the molecule.

Reactions of Higher Aliphatic Aldehydes

The Eschweiler-Clarke procedure is essentially specific for reactions with formaldehyde. Higher aldehydes usually fail to react or react in different ways at steam-bath temperatures. Thus, a mixture of acetaldehyde, ammonium formate, and formic acid yields no carbon dioxide on heating on the steam bath, and from the resulting bases only 2-methyl-5-ethylpyridine has been isolated.⁹ Acetaldehyde and propionaldehyde give only tars when heated with mesidine or 2,4,6-tribromoaniline in formic acid.²¹ However, a 63% yield of *N,N'*-dibutylpiperazine is obtained²² upon refluxing butyraldehyde with piperazine in formic acid for three hours.

In the Leuckart method, valeraldehyde reacts with ammonium formate to give triamylamine,^{4c} with aniline and formic acid to give diamylaniline, and with methylaniline and formic acid to give methylamylaniline.

¹⁹ Wagner, *J. Am. Chem. Soc.*, **55**, 724 (1933).

²⁰ Eisner and Wagner, *J. Am. Chem. Soc.*, **56**, 1938 (1934).

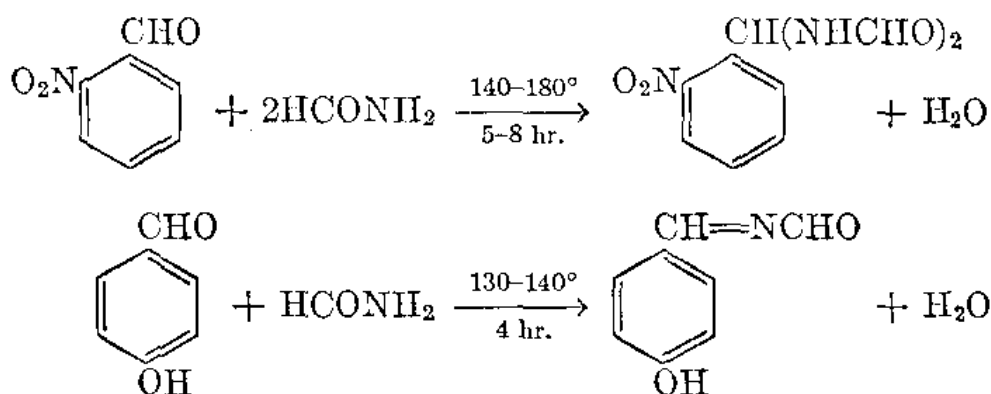
²¹ Emerson, Neumann, and Moundres, *J. Am. Chem. Soc.*, **63**, 972 (1941).

²² Forsee and Pollard, *J. Am. Chem. Soc.*, **57**, 1788 (1935).

Reactions of Aromatic and Heterocyclic Aldehydes

When benzaldehyde is heated with an excess of ammonium formate to a temperature of 180° for several hours, 35–40% of pure tribenzylamine is isolated, along with varying quantities of N,N-dibenzylformamide, dibenzylamine, N-benzylformamide, and benzylamine.¹ Dibenzylamine and its formyl derivative are obtained in 10–15% yields; only small amounts of the monobenzylamine and its formyl derivative are isolated. Although a portion of the benzaldehyde remains unchanged, as much as 20% is converted into polymerized products. When refluxed for five days with piperazine in formic acid, benzaldehyde gives an 84% yield of N,N'-dibenzylpiperazine.²²

Substitution in the ring of the aromatic aldehyde tends to reduce the reactivity toward the Leuckart reagents. Although the methoxybenzaldehydes give satisfactory yields of the formyl derivatives of the amines when treated with substituted ammonium formates,²³ it has been reported that some substituted benzaldehydes, such as piperonal, 6-nitropiperonal, and the hydroxy, nitro, and alkyl substituted benzaldehydes, are recovered unchanged from the reaction with formamide at 130 – 140° ; in the presence of a trace of pyridine, the nitro and alkyl substituted benzaldehydes condense to give 40–60% of the bisamides, and the hydroxybenzaldehydes give about 65% of the benzalamides.²⁴



A 65% yield of the bisamide²⁵ is obtained by bubbling dry hydrogen chloride through a suspension of 6-nitroveratraldehyde in formamide for one hour at 45 – 50° .

Furfural is reported to be converted to furfurylamine by reaction with formamide,²⁶ although the yield is not indicated and no mention is

²³ Wojahn and Erdelmeier, *Arch. Pharm.*, **280**, 215 (1942).

²⁴ Pandya and coworkers, *Proc. Indian Acad. Sci.*, **15A**, 6 (1942) [*C.A.*, **36**, 6144 (1942)]; references to earlier papers on this work are given.

²⁵ Fetscher and Bogert, *J. Org. Chem.*, **4**, 71 (1939).

²⁶ Nabenhauer, Abstract of a paper presented at the 93rd meeting of the American Chemical Society, Chapel Hill, North Carolina, April, 1937.

made of the presence of any of the corresponding secondary or tertiary amines. N-Methylfurfurylamine,²⁶ N,N-dimethyl-, and N,N-diethylfurfurylamine^{26,27} are prepared from N-methyl-, N,N-dimethyl-, and N,N-diethyl-formamide.

Reactions of Aliphatic Ketones

Acetone reacts with α -naphthylamine and methyl formate in an autoclave to produce isopropyl- α -naphthylamine.²⁸ Diethyl ketone⁴⁶ is reported to yield 3-aminopentane acetate by reaction with ammonium formate in the presence of acetic acid, and pinacolone reacts with excess formamide to produce the formyl derivative of methyl-*tert*-butylcarbinamine in a yield of 52%.⁶ The reaction has also been applied to a variety of methyl alkyl ketones (methyl propyl ketone,¹⁰ methyl butyl ketone,²⁹ methyl amyl ketone,^{10,29} methyl hexyl ketone,^{5,10,29} and methyl cyclohexyl ketone³⁰) to give the corresponding primary 2-aminoalkanes in yields of 30–60%. Dipropyl, dibutyl, and diheptyl ketones give yields of 40–80% of the primary amines.

Aliphatic ketones of certain types have been shown to be unsuitable for the reaction because of the formation of resinous by-products. Thus, minimum yields of primary amines are obtained from benzalacetone⁶ or acetylacetone.¹⁰ It appears that the method is unsuitable for application to α,β -unsaturated ketones.

Phenylacetone, substituted phenylacetones,^{31–38} and diphenylacetone³⁹ react to give primary amines in yields ranging from 20% to 70%. Secondary and tertiary amines are prepared in lower yields from these ketones in reactions with mono- or di-substituted amines and formic acid; the time necessary to complete such a reaction is longer.

²⁷ Weilmuenster and Jordon, *J. Am. Chem. Soc.*, **67**, 415 (1945).

²⁸ Speer, U. S. pat. 2,108,147 [*C.A.*, **32**, 2542 (1938)].

²⁹ Rohrman and Shonle, *J. Am. Chem. Soc.*, **66**, 1516 (1944).

³⁰ Blicke and Zienty, *J. Am. Chem. Soc.*, **61**, 93 (1939).

³¹ Johns and Burch, *J. Am. Chem. Soc.*, **60**, 919 (1938).

³² Novelli, *Anales asoc. quim. argentina*, **27**, 169 (1939) [*C.A.*, **34**, 1627 (1940)].

³³ Bobranskii and Drabik, *J. Applied Chem. U.S.S.R.*, **14**, 410 (1941) [*C.A.*, **36**, 2531 (1942)].

³⁴ Elks and Hey, *J. Chem. Soc.*, **1943**, 15.

³⁵ Suter and Weston, *J. Am. Chem. Soc.*, **63**, 602 (1941); **64**, 533 (1942).

³⁶ Sugawara, Kakemi, and Kazumi, *Ber.*, **73**, 782 (1940).

³⁷ Kakemi, *J. Pharm. Soc. Japan*, **60**, 11 (1940) [*C.A.*, **34**, 3748 (1940)].

³⁸ Nabenhauer, U. S. pat. 2,246,529 [*C.A.*, **35**, 6066 (1941)].

³⁹ Rajagopalan, *Proc. Indian Acad. Sci.*, **14A**, 126 (1941) [*C.A.*, **36**, 1603 (1942)].

Reactions of Aliphatic-Aromatic and Aliphatic-Heterocyclic Ketones

The Leuckart reaction has been applied successfully to many aliphatic-aromatic ketones, such as acetophenone,^{4g, 6, 10, 13, 31, 40, 41} propiophenone,^{10, 12} isobutyrophenone,¹⁰ caprophenone,¹² and lauorphenone,¹² with yields ranging from 50% to 85%. Acetophenones with a methyl group or halogen in the ring react as readily as the unsubstituted compound; the higher alkyl substituted and nitro derivatives appear to be less reactive, giving yields of 15–25% less even though the condensation time is longer.^{6, 12, 13, 31, 42} Hydroxyl substituted aryl derivatives polymerize so readily in formic acid that the results are unsatisfactory.

α -Acetothienone,⁴³ α -propiothienone,⁴³ β -acetonaphthone,⁶ *p*-phenylacetophenone,⁶ and *p*-phenoxyacetophenone⁶ readily undergo the reaction in 40–85% yields.

Secondary and tertiary amines can be readily prepared from the above aliphatic-aromatic ketones by the use of methyl-, ethyl-, butyl-, dimethyl-, or diethyl-amine, aniline, or naphthylamine in place of ammonia with the formic acid. Yields for the compounds of lower molecular weight are almost as good as with the primary amine, while compounds of higher molecular weight give slightly lower yields, and lauorphenone gives no product when heated with dimethylamine and formic acid at 160–180° for twenty-eight hours.¹²

β -Benzoylpropionic acid is reported not to give the corresponding amine.¹⁰

γ -Nitro- β -phenylbutyrophenone is converted to 2,2',4,4'-tetraphenylazadipyrromethine (I) in yields up to 33% by reaction with either ammonium formate or formamide.^{11, 44} The corresponding substituted azamethines can be prepared in comparable yields from γ -nitro- β -(dimethylamino-, hydroxy-, methylenedioxy-, methoxy-, and nitrophenyl)butyrophenones, γ -nitro- β -phenyl-*p*-methoxybutyrophenone, and γ -nitro- β -anisyl-*p*-methoxybutyrophenone. β -Benzoyl- α -phenylpropionitrile also reacts with ammonium formate to give 2,2',4,4'-tetraphenylazadipyrromethine along with a small amount of the formyl derivative of 5-amino-2,4-diphenylpyrrole; if formamide is used instead of ammonium formate the substituted pyrrole becomes the major product (59%), unless the reaction is run for a very long time (seventeen hours), in which event the azamethine again predominates. As might

⁴⁰ Ingersoll, *Org. Syntheses, Coll. Vol. 2*, 503 (1943).

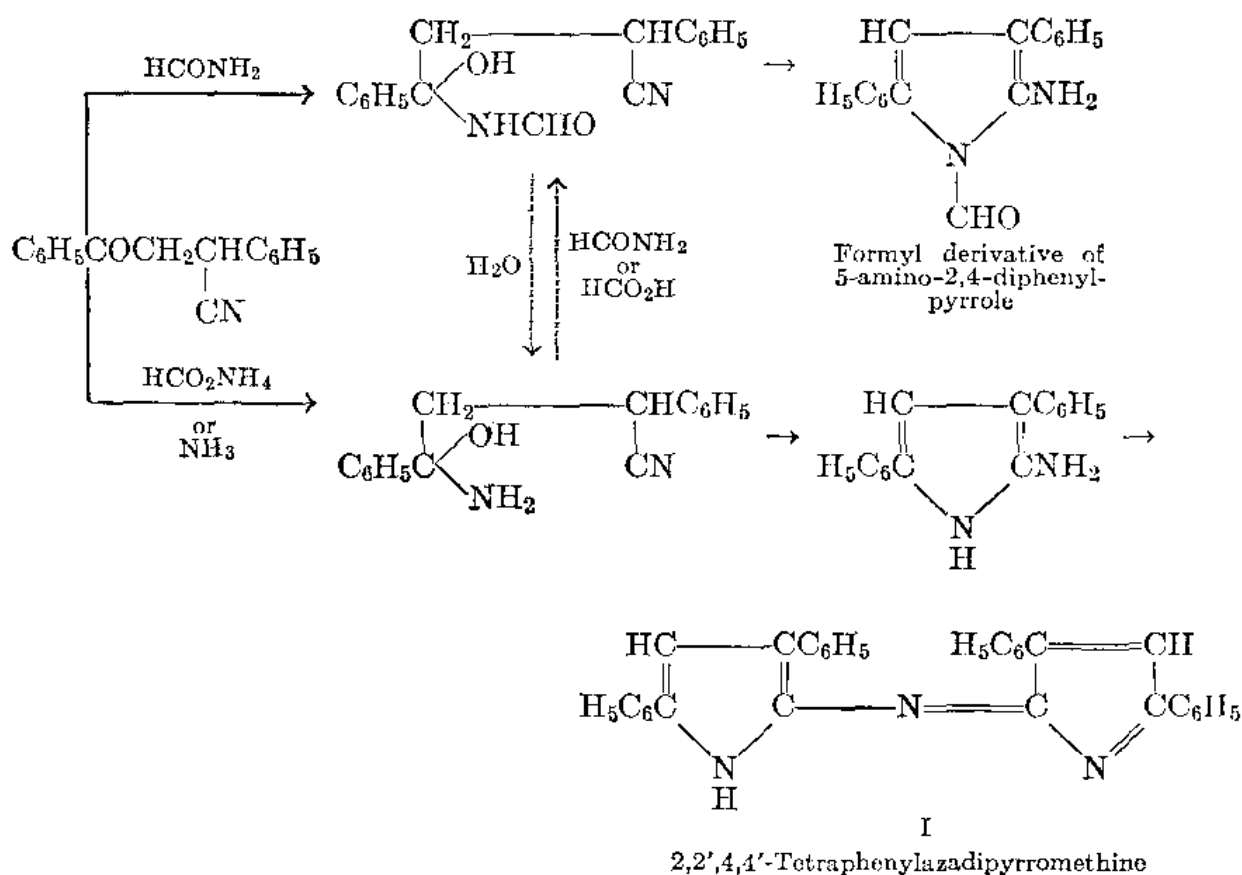
⁴¹ Ott, *Ann.*, **488**, 193 (1931).

⁴² Geigy A.-G., Swiss pat. 211,783 [*C.A.*, **36**, 4634 (1942)].

⁴³ Blicke und Burekhalter, *J. Am. Chem. Soc.*, **64**, 477 (1942).

⁴⁴ Rogers, *J. Chem. Soc.*, **1943**, 590.

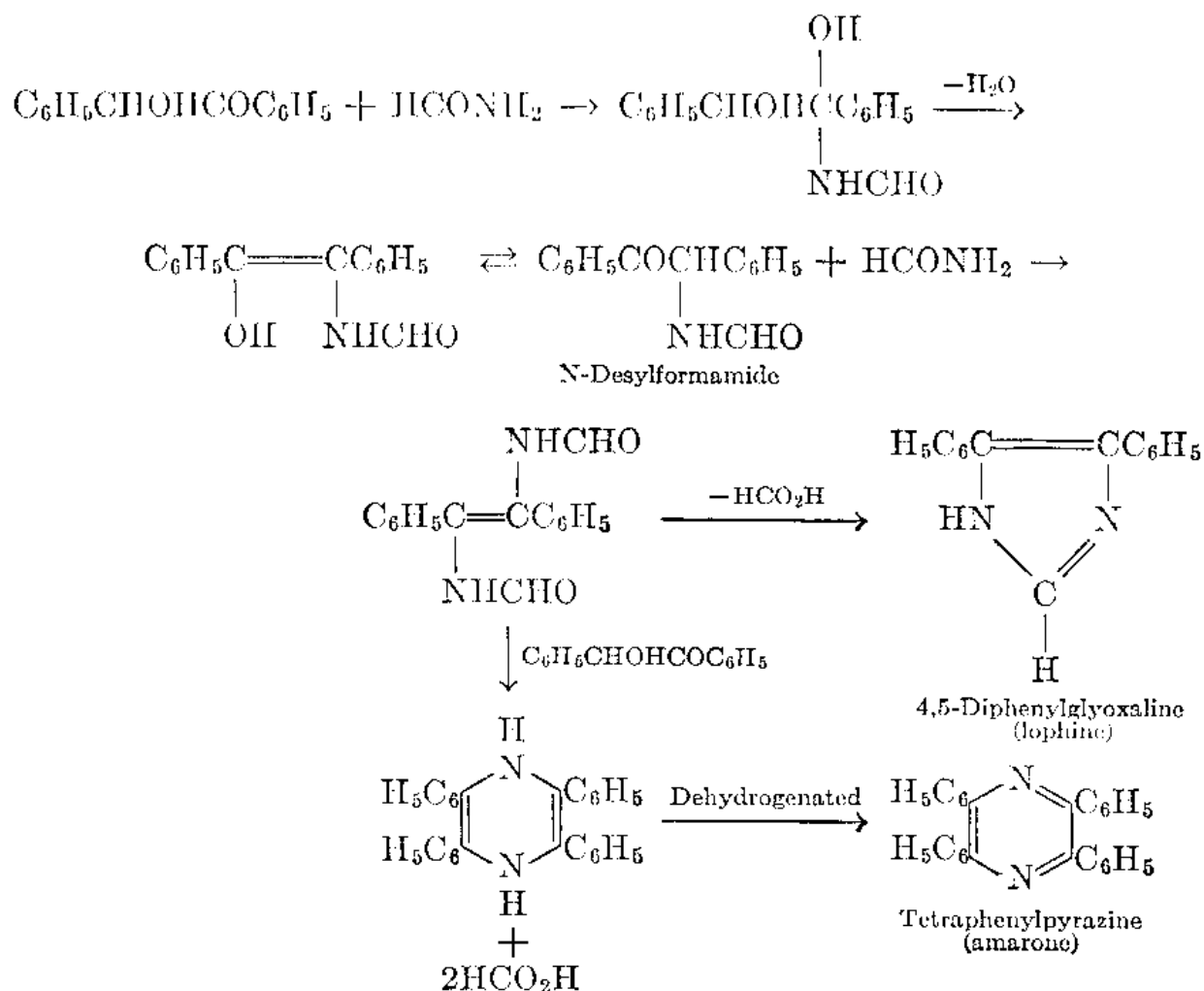
be expected from this observation, treatment of the isolated pyrrole with ammonium formate leads to the formation of the azamethine. A precursor of the pyrrole has been isolated, but, because of the ease with which it is converted into the pyrrole, it has not been identified with certainty. The mechanism of these remarkable reactions has not been elucidated, but the following equations have been suggested to account for the products obtained.



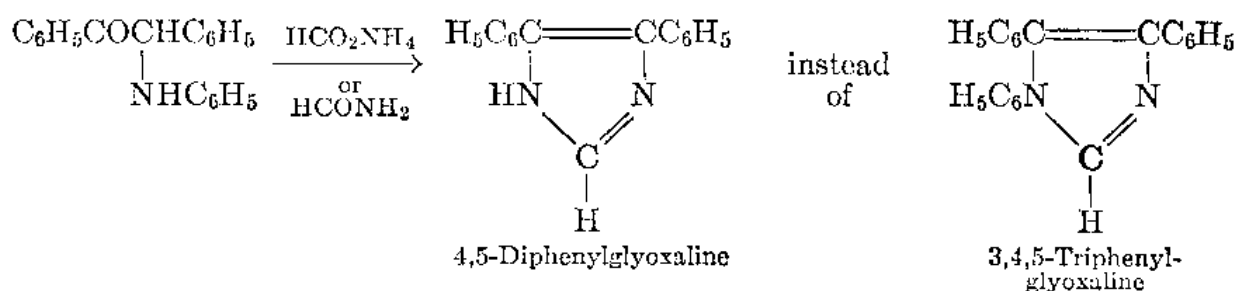
Benzoin behaves abnormally with the Leuckart reagent, giving chiefly glyoxalines along with lesser amounts of diazines. Benzoin reacts with ammonium formate⁴⁵ at 230° to give tetraphenylpyrazine (amarone) almost quantitatively along with a small amount of 2,4,5-triphenylglyoxaline (lophine). However, a 75% yield of 4,5-diphenylglyoxaline and a 10% yield of tetraphenylpyrazine result from heating the benzoin with formamide at 185–230°.⁴⁵ Similar products are obtained from anisoin, benzanisoin, and *p*-toluoin. The mechanism shown on p. 313 has been suggested to account for these products. The addition of acetic anhydride to a reaction mixture of benzoin and formamide leads to the formation of some *N*-desylformamide along with a 36% yield of 4,5-diphenylglyoxaline.⁴⁶ *N*-Desylaniline reacts with ammonium formate

⁴⁵ Novelli, *Anales asoc. quim. argentina*, **27**, 161 (1939) [*C.A.*, **34**, 1659 (1940)].

⁴⁶ Davidson, Weiss, and Jelling, *J. Org. Chem.*, **2**, 328 (1937).



to give a 40% yield of 4,5-diphenylglyoxaline instead of the expected 3,4,5-triphenylglyoxaline. N-Desyl-*p*-toluidine and N-(*p,p'*-dimethoxydesyl)aniline undergo similar reactions with formamide.⁴⁷



Reactions of Aromatic Ketones

Benzophenone reacts with 1.5 parts of solid ammonium formate, in a closed tube at 200–220° for four to five hours, to give an excellent yield of formylbenzohydrylamine, which may be hydrolyzed with ethanolic hydrochloric acid.¹ The reaction product is contaminated with some of the secondary amine, dibenzohydrylamine. With ammonia and

⁴⁷ Novelli and Somaglino, *Anales asoc. quim. argentina*, **31**, 147 (1943) [*C.A.*, **38**, 2957 (1944)].

formic acid, an 80% yield of the primary amine is obtained.^{12,48} Fluorenone and benzofluorenone⁴⁹ give the expected 9-aminofluorenes in yields of 65–75%. Benzoylbenzoic acid¹⁰ yields chiefly an unidentified solid.

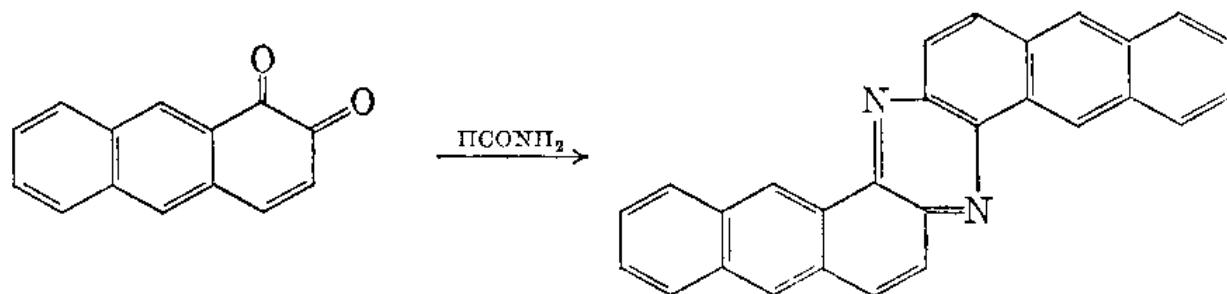
Reactions of Alicyclic Ketones

Cyclohexanone and its derivatives^{4,10,50} have been converted to the corresponding primary amines, accompanied by varying quantities of the secondary amines. With more complicated cyclic ketones, such as camphor,^{4,6,51,52} fenchone,^{4,6} menthones,^{4,10,53} carvomenthones,⁵³ and thujone,^{54,55} the reaction takes place less readily and requires a higher temperature or a longer time. No reaction occurs with menthone at 130° for three to four hours,⁴ whereas an 80% yield of menthylamines is obtained from the reaction at 180–190° for twenty-five hours¹⁰ or at 220–230° for five to six hours. A 20–35% conversion of carvomenthone to carvomenthylamines is obtained after forty-eight hours of refluxing at 130°.⁵³ Bornylamine is obtained in a yield of 55–65% from camphor.^{4,10} Carvone and α -bromocamphor are reported to be converted into neutral resins with only about 10% of the desired amines being isolated.¹⁰

Reactions of Quinones

p-Quinones also undergo the Leuckart reaction;⁴⁹ for example, the diformyl derivative of 9,10-diamino-9,10-dihydroanthracene is produced in the reaction of formamide with 9,10-anthraquinone. The free diamine can be obtained by hydrolysis with alcoholic potassium hydroxide.

o-Quinones, on the other hand, do not react normally but give the corresponding pyrazines. Thus, 1,2-anthraquinone is converted to *bis-ang*-dianthracenopyrazine (anthrazine). Acenaphthoquinone, substi-



⁴⁸ Mettler, Martin, Neracher, and Staub, U. S. pat. 2,270,587 [C.A., **36**, 4633 (1942)].

⁴⁹ Schiedt, *J. prakt. Chem.*, [2] **157**, 203 (1941).

⁵⁰ Wegler and Frank, *Ber.*, **70**, 1279 (1937).

⁵¹ Wegler and Ruber, *Ber.*, **68**, 1055 (1935).

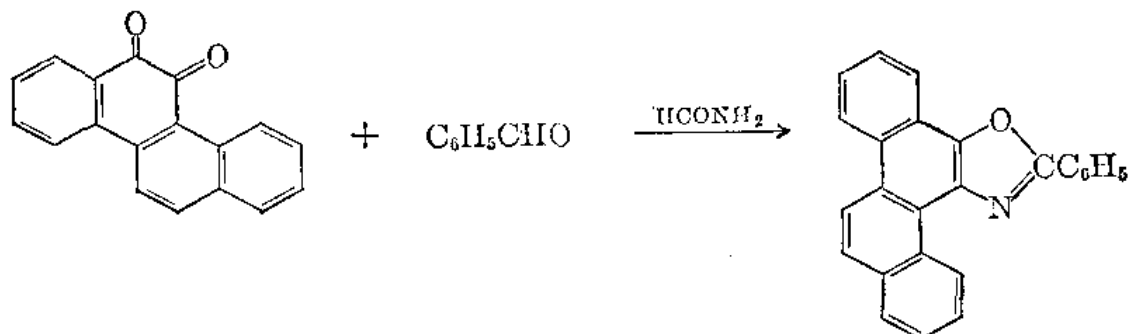
⁵² Tarbell and Paulson, *J. Am. Chem. Soc.*, **64**, 2842 (1942).

⁵³ Read et al., *J. Chem. Soc.*, **1926**, 2217; **1934**, 231.

⁵⁴ Short and Read, *J. Chem. Soc.*, **1938**, 2016.

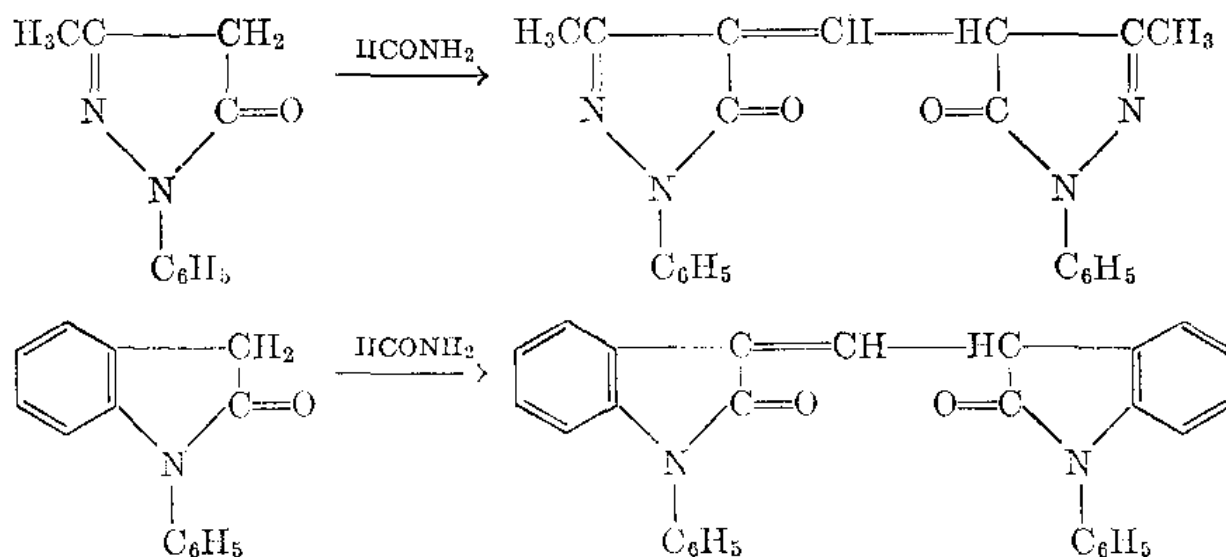
⁵⁵ Dickison and Ingersoll, *J. Am. Chem. Soc.*, **61**, 2477 (1939).

tuted acenaphthoquinones, phenanthraquinone, chrysenequinone, etc., undergo similar reactions with formamide. The addition of an aromatic aldehyde to a mixture of formamide with an *o*-quinone leads to the formation of an oxazole; for example, when chrysenequinone is treated with formamide in the presence of benzaldehyde, 2-phenylchrysene-oxazole is isolated.



Reactions of a Pyrazolone and an Oxindole

4,4'-Methyldyne-*bis*(1-phenyl-3-methyl-5-pyrazolone) results from the reaction of formamide with 1-phenyl-3-methyl-5-pyrazolone, while methyldyne-*bis*(*N*-phenyloxindole) is the product from *N*-phenyloxindole.⁴⁹



SIDE REACTIONS

The normal successive Leuckart reaction or reactions resulting in the formation of the secondary or the tertiary amine have been mentioned above as responsible for by-products in the preparation of primary and secondary amines. Under the influence of the bases present the carbonyl component of the reaction mixture may undergo condensations of the aldol type, some of the products of which may contain carbonyl groups

capable of undergoing the Leuckart reaction. Although such side reactions have not been extensively investigated it is likely that they are concerned in the formation of the resinous by-products sometimes obtained.

EXPERIMENTAL CONDITIONS

The Ammonium Formate or Formamide

Much has been written about the effective reagent in the Leuckart reaction, but no very specific conclusions can be reached. Dry solid ammonium formate was used by Leuckart,¹ and by Wallach in his first experiments,⁴ and the reaction mixture was heated at a temperature of 180–230° in a sealed tube. Later, Wallach obtained better yields by using a mixture of ammonia or substituted amine with formic acid. Formamide was used by Ott⁴¹ and Ingersoll¹⁰ in the preparation of α -phenethylamine from acetophenone. Anhydrous formamide alone is not a satisfactory reagent; the temperature required for the reaction is much higher, the yields are greatly decreased, and the sublimation of ammonium carbonate becomes troublesome. An ammonium formate-formamide reagent prepared by Ingersoll⁶ from commercial ammonium carbonate-carbamate and formic acid gave excellent results in his experiments.

In many instances,^{10,12} the most satisfactory reagent appears to be formamide or ammonium formate supplemented by the addition of sufficient 90% formic acid to maintain a slightly acidic medium and to serve as an active reducing agent. One to three equivalents of formic acid is generally required, and occasional distillation of accumulated water may be necessary to maintain a suitably high reaction temperature. The presence of formic acid appears to diminish the aldol-type side reactions and traps ammonia that otherwise would appear as such or as the carbonate.

Wallach⁴ used free formic or acetic acid with the intention of suppressing the formation of secondary and tertiary amines. The use of acetic acid with ammonium formate at 155° is reported to result in the formation of the acetate salt of the primary amine rather than the formyl derivative; acetophenone and ammonium formate give α -formylaminoethylbenzene, while the addition of acetic acid is stated to lead to the formation of α -aminoethylbenzene acetate.^{4g}

The ketone and ammonium formate or formamide are usually employed in a molecular ratio of 1:4 or 1:5. The excess of ammonium formate tends to diminish the formation of secondary or tertiary amines, but ratios higher than 1:4 or 1:5 appear to be of little advantage. In a

series of experiments with acetophenone the percentage yields of amine were 53, 62, 72, and 73, respectively, when the molar ratios of reagent to ketone were 1:3, 1:3.5, 1:4, and 1:5.⁶ Benzophenone and formamide in the ratio of 1:6 give 43% yields of N-benzohydrilformamide. Under the same conditions benzophenone and ammonium formate gave a 92% yield. The addition of ammonium formate or magnesium chloride to the benzophenone-formamide reaction mixture increased the yield of N-benzohydril formamide to 95%; the addition of ammonium sulfate was not so effective. With benzophenone and formamide in the absence of a catalyst the ratio of 1:18 was necessary in order to obtain a yield of 87%.^{12a}

Temperature

The Leuckart reaction should be carried out at the lowest temperature that will produce the desired product. With dry ammonium formate, it has been necessary to heat the reagents in a sealed tube at 210–240° for several hours. However, the use of an excess of formic acid or a mixed ammonium formate-formamide reagent has made it possible to carry out the reaction at a much lower temperature.⁶ With such a reagent, the reaction can be accomplished by refluxing at atmospheric pressure, usually at temperatures in the range 150–180°; however, temperatures of 175–190° for several hours are required for the conversion of hindered ketones of the terpenoid series. Most reaction periods have been in the range of six to twenty-five hours at 160–185°, but a few reactions with formamide have been carried out by refluxing the reagents for as long as thirty hours.³¹ The heating may be interrupted and resumed as desired.

In a comparative study of the condensation of α -methylphenylacetone with the reagent from ammonia and formic acid, the percentage yields of α,β -dimethyl- β -phenethylamine were 23, 47, and 50, respectively, when the reactions were run for fifteen hours at 190–200°, 170–180°, and 160–170°. Experiments in which the reaction mixture was heated for six hours at 190–200° and seven hours at 160–170° gave yields of 50%. With hindered ketones, such as menthone, camphor, and fenchone, it is advisable to heat at temperatures of 180–230°⁴ or at 175–190°⁶ for a period of twelve to twenty hours in order to obtain maximum yields.

Solvent

Most of the Leuckart reactions are carried out in the absence of any solvent other than the reagents themselves. Mixtures containing a considerable proportion of formamide usually dissolve the ketone o

aldehyde upon heating. However, nitrobenzene has been used as a solvent with a few ketones that were insoluble in the hot reaction mixture, and it has been used to increase the reflux temperature of reaction mixtures containing low-boiling ketones.^{6,10}

Hydrolysis

The formyl derivatives obtained as intermediates in the reaction may be hydrolyzed to the amines by refluxing with acid or alkali. The use of 100–200 ml. of concentrated or 1:1 hydrochloric acid for each mole of ketone appears to be generally satisfactory, and the reaction is usually complete in from thirty minutes to one and one-half hours.^{6,13} When the entire reaction mixture is subjected to hydrolysis it may sometimes be desirable to employ concentrated hydrochloric acid, whereas if the formyl derivative is isolated and purified a 10% solution of hydrochloric acid may give better results.¹² Hydrolysis with 30% aqueous sodium hydroxide usually requires from twelve to twenty hours of refluxing, and the yield of amine is not as good.⁴¹ In the alkaline hydrolysis of the material obtained by interaction of formamide and methyl α -phenyl-*n*-butyl ketone the yield of amine is only 5.3%, but when acid hydrolysis is employed the yield of amine is 86% based on the formyl derivative.³⁵ However, in the production of certain amines, such as thujylamine, it is desirable to hydrolyze the formyl derivative with alkali, inasmuch as acid solutions cause decomposition of the product.⁵⁵

Isolation

The method of isolation of the free amine directly or following the hydrolysis of the formyl derivative varies with the properties of the product and the procedure used in hydrolysis. After an alkaline hydrolysis, the reaction mixture is extracted with an inert solvent, such as ether or benzene, and the amine is isolated by distillation or by conversion to the hydrochloride. Following an acid hydrolysis, the reaction mixture is cooled and neutralized with alkali before extraction with the inert solvent. Amines of higher molecular weight sometimes separate as crystalline salts directly from the cooled acid hydrolysis mixture. When a salt of the amine, rather than the formyl derivative, is present in the reaction mixture it is only necessary to neutralize the cooled mixture with alkali before extraction with the inert solvent.

EXPERIMENTAL PROCEDURES

Tri-*n*-amylamine ⁴⁵

(Use of Ammonium Formate and Formic Acid)

A mixture of 20 g. of valeraldehyde, 30 g. of ammonium formate, and 10 ml. of formic acid is heated in a round-bottomed flask, equipped with a reflux condenser and suspended in a paraffin bath. The reaction begins at 90°, but the temperature is raised slowly to 130° and maintained there for three hours. The cooled residue is extracted with ether to remove the small quantity of non-basic material, and the base is liberated from the formate salt in the aqueous solution by neutralization with alkali. The base is separated, dried over solid potassium hydroxide, and distilled over sodium in a stream of hydrogen; it boils at 265–270°.

N,N-Dimethylfurfurylamine ^{27, 56}

(Use of Dimethylformamide and Formic Acid)

A mixture of 173 g. (2.5 moles) of dimethylformamide (b.p. 145–160°) and 54 g. (1 mole) of 85% formic acid is poured into a 1-l. distilling flask connected to a condenser. A dropping funnel is fitted into the neck of the flask so that its stem extends below the surface of the liquid. The flask is placed in an oil bath, the temperature of which is raised to 150–155°. Over a period of four to five hours, a mixture of 96 g. (1 mole) of redistilled furfural and 163 g. (3 moles) of 85% formic acid is added from the dropping funnel. The water and formic acid which distil are discarded. When all the furfural solution has been added, the receiver is changed and the temperature of the bath is gradually raised as long as distillation occurs. The distillate is made strongly acidic with dilute sulfuric acid, and the furfural and furfuryl alcohol are removed by steam distillation. The acid mixture is then made strongly alkaline by the cautious addition of sodium hydroxide solution; large amounts of dimethylamine are evolved. The alkaline mixture is steam-distilled to remove the tertiary amine. The N,N-dimethylfurfurylamine, which separates from the distillate upon the addition of 40% sodium hydroxide solution, is removed and the aqueous layer extracted twice with benzene. The base and benzene extracts are combined and dried over solid potassium hydroxide for twelve hours. The solvent is removed, and the residue is fractionated; the N,N-dimethylfurfuryl-

⁵⁶ Nabenhauer, private communication.

amine boils at 139–145°. Redistillation of the lower-boiling fractions yields more of the product. The pure base is obtained upon redistillation; b.p. 145–146°; yield 75 g. (60%).

α -(β -Naphthyl)ethylamine^{6,40}

(Preparation and Use of Formamide-Formic Acid Reagent from Ammonium Carbonate-Carbamate and Formic Acid)

A 1-l. flask, containing 215 g. (4 mole equivalents of ammonia) of commercial ammonium carbonate-carbamate, is fitted with a cork bearing a thermometer that extends nearly to the bottom of the flask, a small separatory funnel, and a wide, bent tube attached to a short, wide condenser set for distillation. There is then added cautiously 215–230 g. (4.1 moles) of commercial 85–90% formic acid. When the reaction moderates, the mixture is heated cautiously and then slowly distilled until the temperature is about 165°. (The same amount of reagent can be prepared by distillation of 250 g. of commercial solid ammonium formate.) To the hot mixture 173 g. (1 mole) of β -acetonaphthone is added, the bent tube is replaced by a 20- to 30-cm. distilling column, and the heating is continued with a small flame. Water, ammonia, carbon dioxide, and a small amount of ketone distil. Some of the solid ketone and ammonium carbonate collect in the upper part of the column. This material may be removed with the aid of a little concentrated formic acid and returned to the reaction mixture. The mixture gradually becomes homogeneous as the reaction proceeds.

The distillation of water practically ceases when the temperature reaches 175–185°; the temperature of the mixture is then maintained at 175–185° for three to five hours. Termination of the reaction is indicated when the deposition of ammonium carbonate in the condenser no longer occurs. The mixture is cooled and stirred thoroughly with twice its volume of water. The aqueous layer is separated; formamide may be recovered from it. The crude, water-insoluble material is refluxed for forty to fifty minutes with 100 ml. of concentrated hydrochloric acid. The small amount of material that does not dissolve in the acid is extracted with small portions of warm benzene and discarded. The amine hydrochloride crystallizes from the cooled acid solution. It is collected and recrystallized from boiling water; the yield is 174 g. (84%), m.p. 198–199°.

Methyl-*tert*-butylcarbinamine ^{6,10}

(Use of a Solvent, Nitrobenzene)

To a flask containing the Leuckart reagent, prepared as described in the first paragraph of the preceding section, is added 100 g. (1 mole) of pinacolone dissolved in 100-150 g. of nitrobenzene. The reaction is carried out as described above, except that a heating period of about eight hours is required and it is difficult to maintain the temperature at a level higher than about 150-160°. The nitrobenzene and ketone which distil are returned to the reaction mixture from time to time. The nitrobenzene and unchanged pinacolone are removed by steam distillation following the hydrolysis of the formyl derivatives. The acid solution is then neutralized with sodium hydroxide, and the amine is distilled with steam into an excess of hydrochloric acid solution. The acidic solution is evaporated almost to dryness, treated cautiously with saturated potassium hydroxide solution, and extracted with ether. The ether solution of the amine is dried with sodium hydroxide flakes and distilled. The product boils at 102-103°; the yield is 52 g. (52%).

o-*p*-Chlorophenethylamine ¹⁰

(Use of Formamide and Formic Acid)

A 1-l. round-bottomed flask, to which a narrow side tube has been attached for the insertion of a thermometer, is connected by a 19/38 or larger glass joint to an upright water-cooled condenser. The top of this condenser is joined by a wide, bent tube to a short condenser, arranged for downward distillation, and also is fitted with a small separatory funnel. The flask is charged with 310 g. (2 moles) of *p*-chloroacetophenone, 370 g. (about 8 moles) of 90-97% formamide, and 25 ml. of 90% formic acid. The flask is heated with a small flame; the mixture becomes homogeneous, and mild ebullition begins at about 160-165°. The temperature then rises somewhat, refluxing occurs, and a deposit of ammonium carbonate soon appears in the condenser. To prevent clogging and to maintain a slightly acidic reaction mixture, 20- to 25-ml. portions of 90% formic acid are added through the separatory funnel whenever ammonium carbonate is deposited or the odor of ammonia is detected.

The optimum reaction temperature is 175-180°; whenever it falls below about 165-170°, accumulated water is allowed to distil (by draining the reflux condenser) until the temperature rises again. Any ketone that distils with the water should be separated and returned. It is

necessary to add a total of 200–250 ml. (4.5–5.0 moles) of formic acid, and the reaction requires ten to fourteen hours, depending upon the average temperature that has been maintained. The process may be interrupted and resumed at any time. The reaction is considered complete when ammonium carbonate is deposited only very slowly in the condenser.

When the reaction is complete the mixture is cooled and extracted with 250–300 ml. of benzene in several portions. The insoluble portion, chiefly formamide, is retained for recovery or may be used without purification for the next run. The benzene extract is distilled to remove the benzene, and the residue is refluxed for about an hour with 200 ml. of concentrated hydrochloric acid (sp. gr. 1.18). The cold mixture is extracted with benzene in order to remove a small amount (10–12 g.) of oily, acid-insoluble material; the benzene extract is discarded.

The aqueous portion is made strongly alkaline with 20–30% sodium hydroxide solution and distilled with steam until practically no more water-insoluble distillate is obtained; about 2.5–3 l. of distillate usually is sufficient. About 18–20 g. of nonvolatile, basic residue, presumably higher amines, remains in the distillation vessel. The distilled amine is extracted with 200–300 ml. of benzene and is dried by distillation of the benzene. The amine is best distilled under reduced pressure; b.p. 103–104°/11 mm.; yield 254–270 g. (82–87%). A small residue of less volatile material remains in the distilling flask.

α -Aminododecylbenzene ¹²

(Use of Ammonia and Formic Acid)

One hundred and five grams (1.72 moles) of 28% aqueous ammonia and 88 g. (1.72 moles) of 90% formic acid are mixed carefully and poured into a 500-ml. three-necked flask, equipped with a dropping funnel, thermometer, and downward-directed condenser. The temperature is raised to 160° by distilling out water, and 89.5 g. (0.344 mole) of laurophenone is added in one portion. The temperature is maintained at 160–170° for twenty-two hours, and any ketone which distils is returned to the flask at intervals. The formyl derivative is hydrolyzed in the reaction mixture by refluxing for eight hours with 120 ml. of concentrated hydrochloric acid. After twelve hours at room temperature, 200 ml. of water is added and the compact crystalline mass of the hydrochloride is broken up with a glass rod and collected on a Büchner funnel. The α -aminododecylbenzene hydrochloride is washed three times with small portions of cold water and recrystallized from boiling water. The product weighs 76 g. (78%) and after recrystallization from boiling anhydrous ethanol melts at 115–116°.

α -(*o*-Chlorobenzyl)ethylamine ³¹

(Use of Formamide)

A mixture of 24 g. of *o*-chlorobenzyl methyl ketone and 50 g. of formamide in a 500-ml. flask is refluxed for thirty hours. The mixture is cooled, 100 ml. of 30% sodium hydroxide solution is added, and the alkaline mixture is refluxed for twelve hours to hydrolyze the formyl derivative of the amine. After cooling to room temperature, the reaction mixture is extracted with several portions of ether and the combined ether extract is shaken with 10% hydrochloric acid. Unchanged ketone may be recovered from the ether layer. The amine is recovered from the acid layer by the addition of sodium hydroxide and extraction with ether. The ether solution of the amine is dried over potassium hydroxide sticks and filtered. Dry hydrogen chloride gas is passed into the ether solution, and the precipitated hydrochloride of α -*o*-chlorobenzylethylamine is filtered and dried in a vacuum desiccator. The yield of amine hydrochloride is 15 g. (52%); m.p. 175–176°.

N,N-Dimethylbenzylamine ⁹

(Eschweiler-Clarke Procedure)

One hundred and seven grams (1 mole) of benzylamine is added, with cooling, to 255 g. (5 moles) of 90% formic acid. Then 188 g. (2.2 moles) of 35% formaldehyde solution is added, and the mixture is heated on the steam bath under reflux for two to four hours after evolution of gas has ceased (eight to twelve hours in all). About 85 ml. (slightly more than one mole) of concentrated hydrochloric acid is then added, and the formic acid and any excess formaldehyde are evaporated on a steam bath. The colorless residue is dissolved in water and made alkaline by the addition of 25% aqueous sodium hydroxide, and the mixture is steam-distilled. The distillate is saturated with potassium hydroxide; the oil is separated, dried by heating with solid potassium hydroxide, and distilled over sodium. About 108 g. (80%) of N,N-dimethylbenzylamine, b.p. 176–180°, is obtained.

TABULAR SURVEY OF THE LEUCKART REACTION

In the tables which follow, examples of the Leuckart reaction described in the literature through 1945 have been tabulated. It is probable that the list is incomplete because the reaction frequently has been used as one step in a synthesis without being indexed or referred to as a Leuckart

process. Since many of these reactions were carried out before the development of the modified procedures, it is likely that yields reported do not always represent the best that could be obtained. The arrangement of the carbonyl compounds in each table, or in groups of closely related compounds within a table, is alphabetical, and for each carbonyl compound the amines which react with it are also listed in alphabetical order.

TABLE III

LEUCKART REACTIONS WITH ALIPHATIC KETONES

Ketone	Reagent	Product	Yield %	Reference
Acetone	α -Naphthylamine + methyl formate	N-Isopropyl- α -naphthylamine	—	28
Diethyl ketone	Ammonium formate + acetic acid	3-Pentylamine	—	40
Di- <i>n</i> -heptyl ketone	Ammonia + formic acid	8-Nonadecylamine	40	12
Diisobutyl ketone	Formamide + formic acid	2,6-Dimethyl-4-heptylamine	77	10
Diisopropyl ketone	Formamide + formic acid	2,4-Dimethyl-3-pentylamine	64	10
Di- <i>n</i> -propyl ketone	Formamide + formic acid	4-Heptylamine	25	10
Methyl amyl ketone	Ammonium carbonate-carbamate + formic acid	2-Heptylamine	28	10
Methyl amyl ketone	Ammonium formate	2-Heptylamine	55	29
Methyl butyl ketone	Ammonium formate	2-Hexylamine	—	29
Methyl cyclohexyl ketone	Ammonium formate	α -Cyclohexylethylamine	—	30
Methyl hexyl ketone	Ammonium formate	2-Octylamine	—	5, 29
Methyl hexyl ketone	Formamide + formic acid	2-Octylamine	60	10
Methyl propyl ketone	Ammonium carbonate-carbamate + formic acid	2-Pentylamine	10-37	10
Methyl octadecyl ketone	Ethanolamine + methyl formate	N-Hydroxyethyl-2-eicosylamine	85	57
Pinacolone	Ammonium carbonate-carbamate + formic acid	3,3-Dimethyl-2-butylamine	52	6
<i>o</i> -Chlorophenylacetone	Formamide	β - <i>o</i> -Chlorophenylisopropylamine	52	31
Di-(bromoveratryl) ketone	Ammonium carbonate + formic acid	Di-(bromoveratryl)carbinamine	—	37
α,α -Dimethylphenylacetone	Formamide	β,β -Dimethyl- β -phenylisopropylamine	76	35
Diphenylacetone	Ammonium formate	Dibenzylcarbinamine	—	39
Diveratryl ketone	Ammonium carbonate + formic acid	Diveratrylcarbinamine	—	36
α -Ethylphenylacetone	Formamide	β -Ethyl- β -phenylisopropylamine	63	35
<i>p</i> -Fluorophenylacetone	Formamide	β - <i>p</i> -Fluorophenylisopropylamine	—	35
3,4-Methylenedioxyphenylacetone	Ammonia + formic acid	β -3,4-Methylenedioxyphenylisopropylamine	20	34
α -Methylphenylacetone	Ammonia + formic acid	β -Methyl- β -phenylisopropylamine	58	12
α -Methylphenylacetone	Butylamine + formic acid	N-Butyl- β -methyl- β -phenylisopropylamine	16	12
α -Methylphenylacetone	Formamide	β -Methyl- β -phenylisopropylamine	60	35
α -Methylphenylacetone	Methylamine + formic acid	N, β -Dimethyl- β -phenylisopropylamine	16, 41	12, 35
Phenylacetone	Ammonia + formic acid	β -Phenylisopropylamine	27	12, 32
Phenylacetone	Ammonium formate	β -Phenylisopropylamine	—	33
Phenylacetone	Amylamine + formic acid	N-Amyl- β -phenylisopropylamine	50-70	32
Phenylacetone	Butylamine + formic acid	N-Butyl- β -phenylisopropylamine	50-70	12, 32
Phenylacetone	Diethylamine + formic acid	N,N-Diethyl- β -phenylisopropylamine	50-70	32
Phenylacetone	Dimethylamine + formic acid	N,N-Dimethyl- β -phenylisopropylamine	50-70	32
Phenylacetone	Ethylamine + formic acid	N-Ethyl- β -phenylisopropylamine	50-70	32
Phenylacetone	Formamide	β -Phenylisopropylamine	50-60	31
Phenylacetone	Methylamine + formic acid	N-Methyl- β -phenylisopropylamine	50-70 (22)	12, 32, 35
α -Propylphenylacetone	Formamide	β -Propyl- β -phenylisopropylamine	68	35
<i>o</i> -Tolylacetone	Formamide	β - <i>o</i> -Tolylisopropylamine	—	38
<i>o</i> -Tolylacetone	Methylamine + formic acid	N-Methyl- β - <i>o</i> -tolylisopropylamine	—	38
<i>m</i> -Tolylacetone	Formamide	β - <i>m</i> -Tolylisopropylamine	—	38
<i>m</i> -Tolylacetone	Methylamine + formic acid	N-Methyl- β - <i>m</i> -tolylisopropylamine	—	38
<i>p</i> -Tolylacetone	Formamide	β - <i>p</i> -Tolylisopropylamine	—	38
<i>p</i> -Tolylacetone	Methylamine + formic acid	N-Methyl- β - <i>p</i> -tolylisopropylamine	—	38