—SO_3Na produces substrates whose oxygen consumption is one atom per mole.

3. For those substrates in which both the 4- and 5- positions are substituted the oxygen consumption is one atom per mole.

4. It was shown that the —NO_2 group in the 3-position of the catechol ring produces a substrate which consumes two atoms of oxygen per mole, whereas the —SO_3Na group in this position produces a substance inert to tyrosinase.

5. Leaving the 4-position open and substituting in the 3- and 5-positions produces a substrate which consumes one atom of oxygen per mole.

6. Analysis of the literature shows that the oxidation of a monohydric phenol by tyrosinase fails when there is in the 2-position any group other than —OH.

7. Analysis of the literature shows that an *ortho*-directing group (except —OH) in the 3-position of phenol produces a substrate which consumes three atoms of oxygen, whereas if the group is *meta*-directing the substance is inert to tyrosinase.

8. When there is in the 4-position of the phenol ring an *ortho*-directing group the substance consumes three atoms of oxygen per mole. This was demonstrated with *p*-chlorophenol. When the group is *meta*-directing the substance is inert toward tyrosinase.

9. 4,5-Dimethylphenol was oxidized by tyrosinase with the consumption of two atoms of oxygen per mole.

10. Oxidation of catechol-type substrates enabled the enzyme to bring about the oxidation of hydroquinone.

NEW YORK, N. Y. RECEIVED NOVEMBER 15, 1947

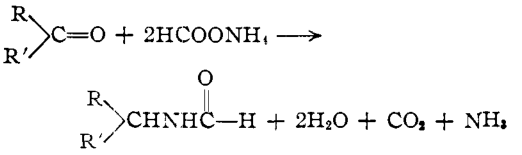
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Studies on the Mechanism of the Leuckart Reaction

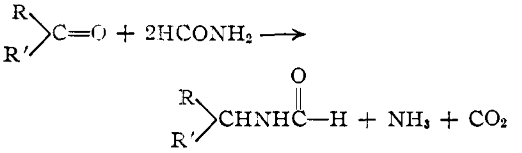
BY ELLIOT R. ALEXANDER AND RUTH BOWMAN WILDMAN

The conversion of carbonyl compounds into the corresponding amino derivatives by means of excess ammonium formate or formamide is usually called the Leuckart reaction. Recently this reaction has been used for the preparation of a rather large number of amines,[1] and the experimental conditions have been developed to the point where good yields can be obtained.

The mechanism of this reaction, however, is not definitely known. Superficially at least the equation may be written as in (1) or (2) in which either ammonium formate or formamide can be considered to be the essential reactant. It is quite interesting that both reagents have been used successfully, although ammonium formate appears to give somewhat better yields than formamide alone[1c,1d] or formamide in the presence of formic acid.[1b] These facts suggested that ammonium formate was the actual reactant, and it was therefore the object of this work to learn if there were conditions such that the reaction could be carried out with ammonium formate but not with formamide.



$$\begin{matrix}R\\R'\end{matrix}\!\!>C{=}O + 2HCOONH_4 \longrightarrow \begin{matrix}R\\R'\end{matrix}\!\!>CHNH\overset{\overset{O}{\|}}{C}{-}H + 2H_2O + CO_2 + NH_3 \qquad (1)$$

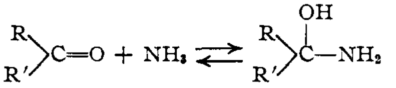


$$\begin{matrix}R\\R'\end{matrix}\!\!>C{=}O + 2HCONH_2 \longrightarrow \begin{matrix}R\\R'\end{matrix}\!\!>CHNH\overset{\overset{O}{\|}}{C}{-}H + NH_3 + CO_2 \qquad (2)$$

In Table I are summarized the important data from a number of reactions carried out under different conditions using acetophenone as the carbonyl component. In experiments 4 and 5 it will be observed that when the reaction was carried out in diethylene glycol solution at 120–130°, no reaction occurred with formamide even after as long as fifteen hours, while a yield of 10% was obtained with ammonium formate after four hours. Thus, although formamide is capable of reacting at temperatures greater than 165° (Experiments 1 and 2), at 120–130° ammonium formate appears to the reagent which is both necessary and sufficient for reaction.[2]

One mechanism for the reaction of a carbonyl compound with ammonium formate is the one originally proposed by Wallach[3] which is outlined in equations 3–5.

$$HCOONH_4 \rightleftharpoons HCOOH + NH_3 \qquad (3)$$



$$\begin{matrix}R\\R'\end{matrix}\!\!>C{=}O + NH_3 \rightleftharpoons \begin{matrix}R\\R'\end{matrix}\!\!>\overset{OH}{\overset{|}{C}}{-}NH_2 \qquad (4)$$

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[1] (a) Goodson, Wiegand and Splitter, THIS JOURNAL, **68**, 2174 (1946); (b) Crossley and Moore, *J. Org. Chem.*, **9**, 529 (1944); (c) Novelli, THIS JOURNAL, **61**, 520 (1939); (d) Johns and Burch, *ibid.*, **60**, 919 (1938); (e) Ingersoll, Brown, Kim, Beauchamp and Jennings, *ibid.*, **58**, 1808 (1936).

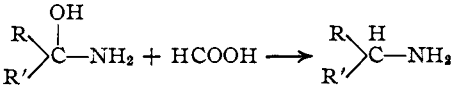
[2] At 165° there may exist an equilibrium between the systems.

$$HCONH_2 + O{=}\underset{|}{C}{-} \rightleftharpoons HCON{=}\underset{|}{C}{-} + H_2O$$

$$H_2O + HCONH_2 \rightleftharpoons [HCOO]^- + [NH_4]^+$$

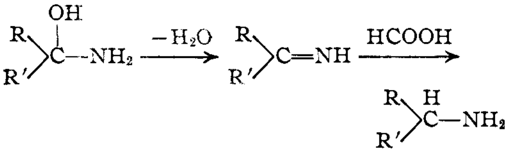
In support of this reaction series for the intermediate formation of ammonium formate, it will be observed that the yield was lowered from 30% to 17% by the introduction of anhydrous calcium sulfate into the reaction mixture (Experiments 1 and 2).

[3] Wallach, *Ann.*, **343**, 54 (1905).



$$\mathrm{RR'C(OH){-}NH_2} + \mathrm{HCOOH} \longrightarrow \mathrm{RR'CH{-}NH_2} \quad (5)$$

It has also been suggested that an alternative path for primary and secondary alkyl ammonium formates might involve the reduction of an imine formed by the loss of water from the carbonylammonia[1b] (6).



$$\mathrm{RR'C(OH){-}NH_2} \xrightarrow{-\mathrm{H_2O}} \mathrm{RR'C{=}NH} \xrightarrow{\mathrm{HCOOH}} \mathrm{RR'CH{-}NH_2} \quad (6)$$

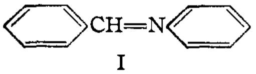
TABLE I

THE LEUCKART REACTION WITH ACETOPHENONE

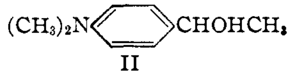
No.	Mole reactant/mole acetophenone[a] Formamide	Mole reactant/mole acetophenone[a] Ammonium formate	Solvent	Temp., °C.	Time, hr.	Yield, %
1	5.0			165–173	7.5	30[d]
2	5.0[b]			165–170	7.0	17[d]
3		5.2[c]		150–155	8.0	77[d]
4	2.3		Diethylene glycol[f]	120–130	15.0	0[e]
5		2.3	Diethylene glycol[f]	120–130[g]	4.0	10[e]

[a] Experiments 1–3 were carried out with 0.5 mole of acetophenone. Experiments 4 and 5 were carried out with 0.33 mole of acetophenone. [b] Anhydrous calcium sulfate (200 g.) was added to the reaction mixture. [c] Preheated at 160° until no more water came off. [d] Isolated as the formyl derivative of *dl*-α-phenylethylamine. [e] Isolated as *dl*-α-phenylethylamine. [f] 50 ml. [g] The reaction mixture became homogeneous at about 90°.

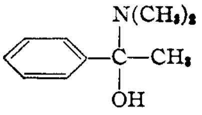
Except for the step involving the reduction of the carbonyl ammonia or imine by formic acid this reaction series seems most reasonable. However, no record of the reduction of a carbon–nitrogen double bond by formic acid could be found, and the reduction of a hydroxyl group by formic acid usually appears to require much more vigorous conditions than were employed in experiment 5. Thus, in a careful study of the minimum decomposition temperature of a number of formic esters, Bowden, Clarke and Harris[4] showed that methyl formate was stable at 440°, and that benzyl formate and benzhydryl formate began to decompose only at 320° and 206°, respectively.[5] Accordingly an investigation was undertaken to determine if intermediates such as those which are shown in equations 5 and 6 can be reduced with formic acid. As a model imine, benzalaniline (I) was chosen. Ketone ammonias, however, are well known to form only unstable addition compounds and for that reason *p*-dimethylaminophenylmethylcarbinol (II) was selected for study. *p*-Dimethylaminophenylmethylcarbinol, it will be observed, is a vinylog of the addition product of acetophenone and dimethylamine (III). Consequently, many of the electrical effects which might be conferred upon the α carbon atom as a result of the electron pair on the nitrogen atom in III would be expected to be relayed to the same atom by the electromeric mechanism shown in IV.



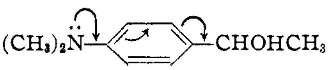
I



II



III



IV

Experiments showed that both benzalaniline and *p*-dimethylaminophenylmethylcarbinol produced resinous materials on boiling with 90% formic acid, but that when the acidity of the reaction mixture was reduced by employing triethylammonium formate, reduction occurred in both cases. Thus, on heating triethylammonium formate and the carbinol at 130–135° for twelve hours, a 6% yield of dimethylaminoethylbenzene was obtained (isolated as the methiodide). When benzalaniline was heated with the same reagent at 140–160° for two hours a 97% yield of N-benzylaniline hydrochloride was obtained. Although the yield in the case of the carbinol was very low, the fact that reduction occurred at all at 130° indicates that compounds of this type are much more susceptible to reduction with salts of formic acid than would normally be supposed.

Experimental[6]

The Leuckart Reaction with Acetophenone.—The procedure used for the runs given in Table I was a modification of the method described by Ingersoll.[7] The product was worked up by two methods. In one of them the formyl derivative of *dl*-α-phenylethylamine was hydrolyzed as described[7] and the product isolated was *dl*-α-phenylethylamine. In the other, the reaction mixture was poured into water and the resulting oil was extracted thoroughly with benzene. The benzene solution was then washed with water and dried over anhydrous magnesium sulfate. Distillation gave the formyl derivative as a thick yellow oil, b. p. 148–156° (4 mm.),[8] $n^{25}\mathrm{D}$ 1.5420–1.5448. The material showed no tendency to crystallize.

Reduction of *p*-Dimethylaminophenylmethylcarbinol with Triethylammonium Formate.—*p*-Dimethylaminophenylmethylcarbinol was prepared by the method of F. Sachs and L. Sachs.[9] After three recrystallizations from high-boiling petroleum ether the material melted at 59–60°.

Triethylammonium formate was prepared by neutralizing 50% formic acid with triethylamine and evaporating the resulting solution on a steam-bath for twelve hours at 20 mm. The crude triethylammonium formate was used without further purification. It was a light brown sirup.

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[4] Bowden, Clarke and Harris, *J. Chem. Soc.*, 874 (1940).

[5] Triphenylcarbinol, which forms no formate, can be reduced to triphenylmethane by boiling with formic acid; see Kauffmann and Pannwitz, *Ber.*, **45**, 767 (1912).

[6] All melting points and boiling points are uncorrected.

[7] A. W. Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 503.

[8] DeLeeuw, *Rec. trav. chim.*, **30**, 241 (1911).

[9] F. Sachs and L. Sachs, *Ber.*, **38**, 512 (1905).

The reaction was carried out by heating 5.0 g. (0.03 mole) of the carbinol with 22.0 g. (0.15 mole) of crude triethylammonium formate in a distilling flask which was equipped with a receiver and water-cooled condenser. The heating was carried out at a temperature of 120–125° for two hours; then it was raised to 130–135° and allowed to run overnight. During the heating period droplets of oil could be observed throughout the reaction mixture and the odor of triethylamine could be detected. A few drops of oil and water collected on the receiver.

On cooling and rinsing the entire apparatus with water into a beaker, a gummy mass separated. This mixture was extracted with ether, evaporated to dryness and stirred thoroughly with three small portions of low-boiling petroleum ether. This solution was again evaporated to dryness and the residue steam distilled. From the distillate a small amount of oil was obtained by extraction with ether and evaporation of the excess solvent. It was characterized by warming with excess methyl iodide and recrystallizing the yellow quaternary salt formed from a mixture of alcohol and ether. After three recrystallizations 0.6 g. (6%) of a very faintly yellow material was obtained, m. p. 219–220° (dec.).[10] A mixed melting point of this material showed no depression with the methiodide of a sample of *p*-dimethylaminoethylbenzene prepared by the high pressure reduction of *p*-dimethylaminophenylmethylcarbinol over Raney nickel.[11]

Reduction of Benzalaniline with Triethylammonium Formate.—Benzalaniline (5.0 g., 0.0276 mole) and triethylammonium formate (13.0 g., 0.0884 mole) were heated with a small flame until the temperature of the reaction mixture reached about 140°. At this point a mild exothermic reaction took place; triethylamine was evolved and the reaction proceeded without further heating. In a very short time the reaction subsided and heating was continued at 140–160° for two hours.

After cooling the reaction mixture was poured into water, an oil separated, and the aqueous layer extracted with two small portions of benzene. The oil and the benzene extracts were then combined and heated with 10 ml. of concentrated hydrochloric acid in such a way that the benzene was allowed to evaporate. The residual oil was hydrolyzed in about ten minutes and the resulting solution was completely homogeneous. On cooling, the hydrolysis mixture completely solidified. It was broken up with a spatula, sucked as dry as possible on a Büchner funnel and rinsed with ice water and ether. After drying thoroughly, 6.9 g. (97.5%) of benzylaniline hydrochloride, m. p. 214–215°[12] was obtained. A second recrystallization from water did not improve the melting point. On regeneration with alkali, the free amine gave a benzamide, m. p. 107–108°, and a benzenesulfonamide, m. p. 118–119°.[13]

Summary

At 120–130° in diethylene glycol solution, acetophenone has been found to undergo the Leuckart reaction with ammonium formate but not with formamide. This indicates that at this temperature ammonium formate and not formamide is the essential reactant for the transformation.

Benzalaniline and *p*-dimethylaminophenylmethylcarbinol were reduced to N-benzylaniline (97%) and *p*-dimethylaminoethylbenzene (6%) by heating with triethylammonium formate at temperatures ranging from 130 to 160°. These compounds are analogous to the intermediates which were postulated by Wallach and by Crossley and Moore for the Leuckart reaction.

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(10) Davies and Hulbert, *J. Soc. Chem. Ind.*, **57**, 349 (1938).

(11) The decomposition point of a quaternary salt depends somewhat upon the rate of heating. For the mixed melting point, therefore, samples of the material prepared in each way were included in the heating bath to serve as controls.

(12) Brand, *Ber.*, **42**, 3462 (1909).

(13) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 195.

URBANA, ILLINOIS

RECEIVED AUGUST 2, 1947

[CONTRIBUTION FROM THE GROSVENOR LABORATORY]

Preparation of Acetonechloroform and its Homologs

BY CH. WEIZMANN, E. BERGMANN AND M. SULZBACHER

For an investigation which is reported in the preceding paper, acetonechloroform ((trichloromethyl)-dimethylcarbinol) was needed in considerable quantities. Fishburn and Watson[1] concluded from a systematic investigation that the best method for its preparation was the condensation of acetone and chloroform by means of potassium hydroxide in excess acetone as solvent, and reported a yield of 25% under these conditions. Sodamide in anhydrous ether gives a yield of about 75%[2] but it has to be used in 50% excess and under strictly anhydrous conditions.

It has now been found that chloroform will condense with acetone and certain other ketones (see Experimental Part) in solutions of acetals containing potassium hydroxide to yield trichloromethyl carbinols. The yields are quite satisfactory, although some of the chloroform and/or the trichloromethyl carbinol formed reacts with the alkali to give potassium chloride, a side reaction which is the more pronounced the higher the water content of the potassium hydroxide used. The extent to which this side reaction occurs can be further reduced if one does not allow the reaction to go quite to the end.

The reaction can be extended to aldehydes, but only to those which are branched in α-position to the carbonyl group such as 2-ethylhexanal and isobutyraldehyde; straight-chain aldehydes undergo self-condensation more readily than condensation with chloroform. Benzaldehyde condenses with chloroform,[3] benzophenone does not.

While chloroform and bromoform condensed with the carbonyl compounds specified, methylene chloride failed to react at all, and 1,1,1,2,2,3,3-heptachloropropane was simply dehydrohalogenated to hexachloropropylene, even at low tem-

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(1) Fishburn and Watson, *J. Am. Pharm. Assoc.*, **28**, 491 (1939); see Taffe, *Chem. Zentr.*, **95**, II, 304 (1924).

(2) Schwyzer, "Fabrikation pharmazeutischer und chemisch-technischer Produkte," Berlin, 1931, p. 112.

(3) Rapson and co-workers, *J. Chem. Soc.*, **74** (1944).