[CONTRIBUTION FROM THE WYETH INSTITUTE OF APPLIED BIOCHEMISTRY]

The Leuckart Reaction: A Study of the Mechanism

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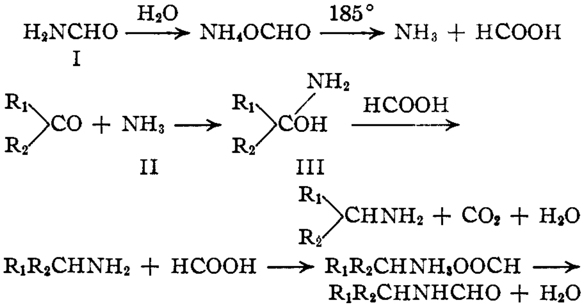
The preparation of N-benzhydryl formamide from benzophenone by the Leuckart reaction has been reported by Leuckart and Bach[2] using ammonium formate. The compound has been prepared in this laboratory by the general procedure of Ingersoll[3] with good results. Since Ingersoll[4] stated that somewhat higher yields might be expected in the Leuckart reaction if formamide itself were used rather than ammonium formate, benzophenone was refluxed with 99% formamide; after refluxing for four hours or more, much lower yields of the order of 40% N-benzhydryl formamide were obtained, accompanied by recovery of the benzophenone. This unexpected result led the authors to a study of some factors that influence the Leuckart reaction, in order to determine the conditions under which formamide can be used effectively in the reaction, and to elucidate the mechanism. Catalysis by a selected group of salts was found to be important in securing a good yield in this reaction.

Benzophenone is a good choice for a study of the reaction, as there are apparently no significant side reactions except the decomposition of formamide and the product is readily identified and purified. The reaction of benzophenone with formamide was carried out under a variety of conditions. Since the Leuckart reaction is concerned essentially with the formation of a formyl derivative, and not *per se* with the hydrolysis of the formyl compound to the amine, this formyl intermediate itself was isolated. It was found that one mole of benzophenone gave a homogeneous reaction mixture with six moles of formamide at 180–190°, but not with four moles; hence all the experiments were run using six moles of the reagent. The results of these experiments are summarized in Table I. For convenience, the amounts of reagents are referred to on the basis of one mole of benzophenone, although 0.467 mole was used in each case.

The procedure given in "Organic Syntheses" was followed, and a 92% yield of N-benzhydryl formamide was obtained (Table I, run 1). Schiedt,[5] using a very large excess of formamide, reported excellent yields. In order to test this with the 99% formamide, benzophenone was treated with 18 moles of this reagent for four hours. The amide was obtained in 87% yield, based on the benzophenone used (Table I, run 2). In contrast with this, the use of six moles of formamide gave less than 50% conversion (Runs 3-A and 4-A).

In testing the effect of the addition of various substances to the reaction mixture, all the runs numbered 3 were made in the same oil-bath at the same time and likewise for the runs numbered 4 in order to secure reaction conditions as comparable as possible. Runs 3-A and 4-A, with the same reagents, served as controls so that a comparison might be made between the two sets. The runs were made for four hours in each case. The results given in Table I show that the addition of a base, dimethyl aniline, or the "Zwitterion," pyridine-3-sulfonic acid to the reaction mixture had little effect on the amount of conversion (Runs 3-B and 4-C). The addition of the ammonium salts of sulfuric and formic acids, and of anhydrous magnesium chloride, an acid in the Lewis sense, increased the conversion by significant amounts (Runs 3-C, 4-B, and 4-C).

Mechanism.—The mechanism generally proposed for the reaction was advanced by Wallach[6] and reiterated by Crossley and Moore[7]

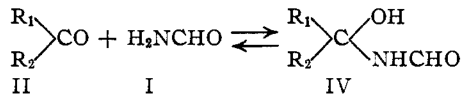


$$\underset{\text{I}}{H_2NCHO} \xrightarrow{H_2O} NH_4OCHO \xrightarrow{185°} NH_3 + HCOOH$$

$$\underset{\text{II}}{{}^{R_1}_{R_2}\!\!>\!CO} + NH_3 \longrightarrow \underset{\text{III}}{{}^{R_1}_{R_2}\!\!>\!C{<}^{NH_2}_{OH}} \xrightarrow{HCOOH} {}^{R_1}_{R_2}\!\!>\!CHNH_2 + CO_2 + H_2O$$

$$R_1R_2CHNH_2 + HCOOH \longrightarrow R_1R_2CHNH_3OOCH \longrightarrow R_1R_2CHNHCHO + H_2O$$

Doevre and Courtois[8] and Davies and Rogers[9] suggest that in the reaction between ketones and formamide, the first reaction is the addition of formamide to the carbonyl group



$$\underset{\text{II}}{{}^{R_1}_{R_2}\!\!>\!CO} + \underset{\text{I}}{H_2NCHO} \rightleftharpoons \underset{\text{IV}}{{}^{R_1}_{R_2}\!\!>\!C{<}^{OH}_{NHCHO}}$$

A compound of the same type as IV is reported by Shive and Shive[10]; they isolated α-hydroxy-α-formaminopropionic acid on mixing pyruvic acid with formamide at 40°. These investigators agree that the first step is the formation of a car-

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[2] Leuckart and Bach, *Ber.*, **19**, 2128 (1886).

[3] Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 503.

[4] Ingersoll, Brown, Kim, Beauchamp and Jennings, THIS JOURNAL, **58**, 1808 (1936).

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

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

[7] Crossley and Moore, *J. Org. Chem.*, **9**, 529 (1944).

[8] Doevre and Courtois, *Bull. soc. chim.*, **11**, 545 (1944).

[9] Davies and Rogers, *J. Chem. Soc.*, 126 (1944).

[10] Shive and Shive, THIS JOURNAL, **68**, 117 (1946); for the addition of amides to α-ketoacids, see also Shemin and Herbst, *ibid.*, **60**, 1954 (1938); Herbst and Martell, *J. Org. Chem.*, **6**, 878 (1941). For the addition of amides to aldehydes, see Pandya, *et al.*, *Proc. Indian Acad. Sci.*, **10A**, 282 (1939), and **7A**, 361 (1938) [*C. A.*, **34**, 1980^{9} (1940), and *C. A.*, **32**, 7434^{2} (1938)].

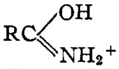
TABLE I

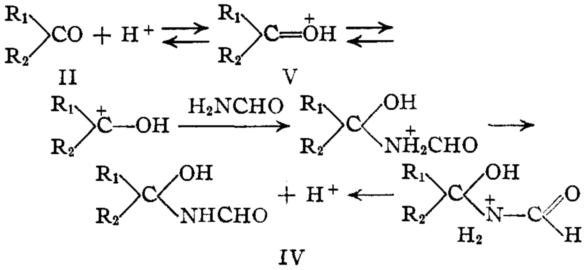
LEUCKART REACTIONS UNDER VARIOUS CONDITIONS WITH BENZOPHENONE (1 MOLE)

Run	Reagent	Temp. of reaction, °C.	Ketone[a] recovered, %	Amide obt., %	M. p. of distilled amide (cor.), °C.
1	("Org. Syn.") 6 moles HCO_2NH_4	180–190	2[b]	92	131–132
2	18 moles 99% $HCONH_2$	180–190	1	87	130–132
3-A	6 moles 99% $HCONH_2$	180–190	46	48	125–129
3-B	Same, plus 2.1 g. $Me_2NC_6H_5$	180–190	40	51	126–129
3-C	Same, plus 6.4 g. $(NH_4)_2SO_4$	180–190	12	80	123–126
4-A	Same as 3-A[c]	180–190	61.5	37.5	123–129
4-B	1 mole NH_4OOCH plus 5 moles 99% $HCONH_2$	170–176[d]	2	95.5	131–133
4-C	4-A plus 6.3 g. pyridine-3-sulfonic acid	180–190	67.5	30.5	124–130
4-D	4-A plus 6.3 g. $MgCl_2$	180–190	2	95.6	129.5–133

[a] These figures for benzophenone recovered on distillation are 1–2% too high; see experimental. [b] This ketone distilled over during the reaction. [c] To compare series 3 with series 4, run on different days. [d] The temperature is lower because of the lower boiling point of this mixture.

bon–nitrogen bond between the carbon atom of the carbonyl group, and the nitrogen atom of ammonia or formamide. This is then followed by the reduction of the alcohol thus formed by means of formic acid or formamide, respectively.

It is probable that the catalytic effects observed by us are due to an initial polarization of the carbonyl group of the ketone. The magnesium chloride, or its reaction product with formamide, $Mg(HNCHO)_2$, or magnesium ion could coördinate with the oxygen atom of the carbonyl group. The function of an ammonium salt as a catalyst for the reaction is probably to furnish a proton from a complex in equilibrium[11] with its dehydration product, the amide. It can be assumed that the formation of an amide from an ammonium salt involves stepwise loss of an hydroxyl ion and a proton from the intermediate, $R\text{-}C(OH)_2NH_2$, proposed by Noyes and Goebel[12]; Krieble and Holst[13] suggest that that the ion  $RC(OH)(NH_2^+)$ is also intermediate in this reaction; this ion can give up a proton to form the amide. A proton can also coördinate with the carbonyl group, increasing the effective positive charge on the carbon atom (making it more acidic), and facilitating the condensation with the relatively basic nitrogen atom of formamide



The reaction sequence in the case of magnesium chloride is similar; and if the reaction proceeds as suggested by Wallach, by the addition of ammonia, the catalysis could be explained on the same basis. The report of Crossley and Moore,[7] that the yield in the Leuckart reaction is lower at higher temperatures, may be due to lower concentrations of ammonium formate at these temperatures.

The Leuckart reaction using monoalkyl formamides[14,15] or dialkyl formamides[6,16,17] has not been investigated by the authors, but it is probable that they show the same catalysis. Wallach[6] found that when formic or acetic acid is added to a mixture of benzaldehyde and ammonium formate, only tribenzylamine was found in the product, whereas Leuckart[17] showed that the reaction without the addition of acid gave a mixture of N-benzyl formamide, N,N-dibenzyl formamide, and tribenzylamine. Nabenhauer[16] found that the addition of formic acid is essential when tertiary amines are prepared by the Leuckart reaction with dialkyl formamides. The mechanism of the reduction of the alcohol, III or IV, with formic acid or formamide is not known, but it may be related to the mechanism of the pyrolysis of alkyl formates to form the corresponding hydrocarbon derivative.[18]

The authors wish to acknowledge the benefit of discussions with Dr. R. T. Arnold in which possible mechanisms were critically examined.

Experimental

Decomposition of Formamide.—Refluxing formamide alone gave slow decomposition to ammonia and carbon monoxide: about one liter of carbon monoxide collected in an hour from 30 cc. of formamide. The formamide, meanwhile, turned black, both in the flask and in the reflux condenser. Replacing the air in the system with nitrogen prevented most of the tar formation. Novelli and Somaglino[19] conducted a current of carbon dioxide through the system, perhaps for the same reason. During the Leuckart reaction, the evolution of carbon dioxide

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[11] Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, London, 1942, p. 145.

[12] Noyes and Goebel, THIS JOURNAL, **44**, 2295 (1922).

[13] Krieble and Holst, *ibid.*, **60**, 2978 (1938).

[14] Novelli, *ibid.*, **61**, 520 (1939).

[15] Goodson, Wiegand and Splitter, *ibid.*, **68**, 2174 (1946).

[16] Nabenhauer, Abstracts of April, 1937, meeting of the American Chemical Society.

[17] Leuckart, *Ber.*, **18**, 2341 (1885).

[18] Bowden, Clark and Harris, *J. Chem. Soc.*, 874 (1940).

[19] Novelli and Somaglino, *Anal. Asoc. Quim. Argentina*, **31**, 150 (1943).

and ammonia protects the formamide from the air, and no trouble is encountered unless the heating is interrupted, or unless the heating is continued after the evolution of gases has ceased.

Standard Method of Carrying Out the Reaction.—Eighty-five grams of benzophenone (0.467 mole) and 110 cc. of 99% formamide (6 × 0.467 mole) (obtained from the Eastman Kodak Co.) together with any substances to be tested for catalytic effect, and a chip of porous plate were placed in a 200-cc. balloon flask equipped with an air-reflux-condenser. The air was displaced with nitrogen, and the flask immersed in an oil-bath kept at 190–200°. After boiling had started, the temperature in the flask was at 180–190°. A small quantity of ammonium carbonate sublimed into the reflux condenser, and ammonia and carbon dioxide were evolved. At exactly four hours after boiling started, the flask was removed from the oil-bath, allowed to cool to about 140°, and cautiously poured into about 200 cc. of cold water. (If it was cooled much below 130°, the formyl derivative crystallized, and removal from the flask was difficult.) The flask was washed out with a little water, and the mixture of benzophenone, N-benzhydryl formamide, and water soluble substances was cooled, seeded with a crystal of benzophenone, and the mixture of solids collected on a Buchner funnel, washed with a little water, and dried. The amount of benzophenone and of N-benzhydryl formamide in the mixture of solids was determined by distillation *in vacuo* without a column. Benzophenone boils at 114° at 1.2 mm., but was collected at 120–130° in order to speed up the distillation. When the benzophenone was all gone, the boiling point rose rapidly; at 160° the receiver was changed, and the remaining formyl derivative was distilled with strong enough heating to prevent crystallization in the side arm of the flask. The amide boils at 173° at 1.2 mm., but as before, it saved time to collect it at 185–190°. A small amount of tar (about a gram) remained in the Claisen flask. The amount of benzophenone determined by this method may be too great by one to two grams (estimated), as a small amount of formamide remains with the solids, and distills over with the first few drops of benzophenone.

All of the reaction mixtures were homogeneous, with the exception of 3-C; the ammonium sulfate added is not completely soluble in the reaction mixture. The results are shown in Table I. The melting point determined by Fischer block method was higher when the reaction was more complete. The value for the pure substance in the literature and in our hands is 132°.[2] In order to judge the purity of the amide, a solution of 2% benzophenone in molten N-benzhydryl formamide was made up and allowed to cool. This material melted at 126.5–130.5°, from which it is concluded that the maximum impurity in the amide samples in Table I is about 2 or 3%.

Summary

1. The Leuckart reaction with benzophenone and formamide has been run under various conditions; with pure formamide (99%) the yield is low unless a large amount of the reagent is used.

2. Ammonium formate, ammonium sulfate, and magnesium chloride have been shown to be effective catalysts for the reaction.

3. A partial mechanism is advanced for the reaction.

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Gelsemine

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Several recent papers[1a,2,3] deal with the structure of gelsemine, $C_{20}H_{22}O_2N_2$, the principal crystalline alkaloid of *Gelsemium sempervirens*, the American "yellow jasmine." Marion[2] isolated an indole derivative as the product of soda-lime or selenium treatment of gelsemine. This is the first major degradation product reported, and relates gelsemine to the indole alkaloids. Indole itself occurs in the oils from the enfleurage of jasmine flowers, where it is present in the form of an unknown complex.[4] Marion and other investigators,[1a,2] studying the degradation of gelsemine, report the presence of bases that were difficult to purify and obtainable only in very small yield.

By the use of a modified mild zinc dust distillation three degradation products have been obtained from gelsemine. Two of basic nature were separated by the difference in basicities. The stronger base is an oil with quinoline or isoquinoline odor, and yields a well-crystallized picrate. Analysis of the latter corresponds to an ethyl- or dimethyl- quinoline or -isoquinoline. It is clear from the data of Table I that gelsemine is such a strong tertiary base that the basic nitrogen atom can neither be attached to a benzene nucleus nor form part of an unreduced pyridine ring, as has been suggested already by Forsyth, Marrian and Stevens.[1a] A more weakly basic product, probably $C_{14}H_{11}N$, was obtained in the form of a picrate. According to the analytical data it might be a methylbenzquinoline (or -isoquinoline). Skatole was isolated as the main non-basic product of indolic nature in the form of the picrate.

TABLE I

*pK*a (negative logarithms of acidity constants of the hydrochlorides)

Quinoline	4.89[5]
Isoquinoline	5.36
Py-tetrahydroquinoline	5.03
Py-tetrahydroisoquinoline	9.41
Gelsemine	9.37[1a]

The dimethylindole reported by Marion[2] has not been observed in the present investigation. It should be pointed out, however, that the identification of alkyl indoles is often rendered difficult

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[1] Fellow of the Matthew T. Mellon Foundation.

[1a] Forsyth, Marrian and Stevens, *J. Chem. Soc.*, 579 (1945).

[2] Marion, *Can. J. Res.*, **21B**, 247 (1943).

[3] Chu and Chou, THIS JOURNAL, **62**, 1955 (1940); **63**, 827 (1941).

[4] Hesse, *Ber.*, **37**, 1457 (1904).

[5] Karrer and Schmid, *Helv. Chim. Acta*, **29**, 1858 (1946).