mended for this purpose,[16] because of the resistance of the hemoglobin to the action of nitric acid. That it is applicable to fluids of much higher protein content than that found in plant saps is shown by the application of the method which has already been made in the analysis of hides.

COLD SPRING HARBOR, LONG ISLAND, NEW YORK

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE BECKMANN REARRANGEMENT

BY ARTHUR LACHMAN

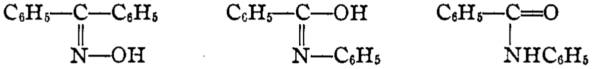
RECEIVED FEBRUARY 6, 1924

When benzophenone oxime is treated with reagents such as phosphorus chloride, concd. sulfuric acid, or a mixture of acetic acid, acetic anhydride and hydrochloric acid (Beckmann's mixture), and thereupon treated with water, it is converted into benzanilide:

$$(C_6H_5)_2C{=}NOH{=}C_6H_5CONHC_6H_5 \qquad (1)$$

A phenyl group has migrated from carbon to nitrogen. The mechanism of this rearrangement has been the subject of a discussion far too voluminous to be considered here in detail. It is sufficient to summarize briefly the two theories which rest more or less upon experimental support.

According to Beckmann,[1] the rearrangement is simply a direct interchange of radicals as shown in the following scheme.



$$\begin{array}{ccc} C_6H_5\text{—}C\text{—}C_6H_5 & C_6H_5\text{—}C\text{—}OH & C_6H_5\text{—}C{=}O \\ \| & \| & | \\ N\text{—}OH & N\text{—}C_6H_5 & NHC_6H_5 \end{array} \qquad (2)$$

The reagents are considered to be mere catalysts, and Beckmann has given no further account of how they catalyze. This view finds its strongest support in the behavior of stereo-isomeric oximes; for in the great majority of cases, the radical which wanders from carbon to nitrogen is the one which is spatially near the hydroxyl group.

Stieglitz has given a more detailed interpretation of the process, in a series of brilliant experimental and theoretical papers extending over a period of thirty years. These investigations group a variety of rearrangements of nitrogen compounds under one comprehensive viewpoint. Here we shall deal only with Stieglitz's explanation of the oxime rearrangement.[2]

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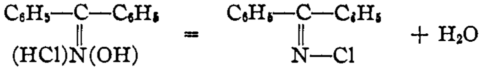
[16] After this was written, a paper by Van Slyke appeared [*J. Biol. Chem.*, **58**, 523 (1923)] in which he has suggested for blood essentially the same method which we have used for plant saps. We still feel that, because of reasons set forth above, the method is not to be recommended for general use in blood chemistry.

[1] Beckmann, *Ber.*, **27**, 300 (1894).

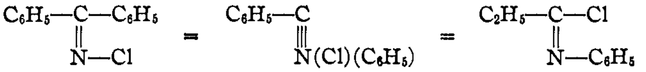
[2] Stieglitz's papers are too numerous to cite individually. He has given a summary of his theories recently, THIS JOURNAL, **44**, 1293 (1922). The details quoted here were taken from manuscript notes by him, communicated to Professor C. W. Porter, and incorporated in the latter's textbook (The Carbon Compounds) just issued (Ginn and Co., **1924**).

The first step, according to Stieglitz's view, is the formation of a salt, which is thereupon dehydrated by the action of the reagents.



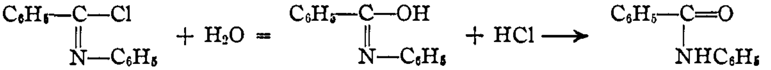
$$\begin{array}{c} C_6H_5{-}C{-}C_6H_5 \\ \| \\ (HCl)N(OH) \end{array} = \begin{array}{c} C_6H_5{-}C{-}C_6H_5 \\ \| \\ N{-}Cl \end{array} + H_2O \qquad (3)$$

The hydroxyl group of the salt is positive; and in the removal of water, it must capture two electrons from the nitrogen. The nitrogen, in turn, takes away two electrons from carbon; this leads to a rearrangement resulting in a more stable system.



$$\begin{array}{c} C_6H_5{-}C{-}C_6H_5 \\ \| \\ N{-}Cl \end{array} = \begin{array}{l} C_6H_5{-}C \\ \quad ||| \\ \quad N(Cl)(C_6H_5) \end{array} = \begin{array}{c} C_2H_5{-}C{-}Cl \\ \| \\ N{-}C_6H_5 \end{array} \qquad (4)$$

Finally, the chloro-acid-imide whose formation has just been indicated, and which can be actually isolated, is transformed upon treatment with water into benzanilide.



$$\begin{array}{c} C_6H_5{-}C{-}Cl \\ \| \\ N{-}C_6H_5 \end{array} + H_2O = \begin{array}{c} C_6H_5{-}C{-}OH \\ \| \\ N{-}C_6H_5 \end{array} + HCl \longrightarrow \begin{array}{c} C_6H_5{-}C{=}O \\ | \\ NHC_6H_5 \end{array} \qquad (5)$$

These two theories will be discussed below, in the light of additional experimental evidence.

The Action of Heat upon Benzophenone Oxime

Beckmann's explanation of the rearrangement carries the implicit assumption that under suitable conditions the oxime should change into benzanilide without the aid of any reagents whatever. Lehmann,[3] however, recently found that ultraviolet light was unable to effect this reaction.

The action of heat on the oxime was studied years ago by Beckmann, who noted decomposition into benzophenone and ammonia, and promised further details; but nothing more has been published. A very recent paper by Beckmann and Bark[4] contains no added information.

The heat decomposition of benzophenone oxime is a violent reaction which starts at about 185°, and rapidly goes to completion, but when air is excluded, it takes a perfectly definite course.[5] The reaction product is liquid when cold, and contains nearly equal molecular proportions of benzophenone and of iminodiphenylmethane, $(C_6H_5)_2C{=}NH$.

The reaction which has taken place is accurately given by the equation,

$$2(C_6H_5)_2C{=}NOH{=}(C_6H_5)_2CO + (C_6H_5)_2CNH + (NOH) \qquad (6)$$

except that the residue NOH does not appear as such, but goes over into nitrogen, oxides of nitrogen, and water. Almost exactly half of the nitrogen of the NOH residue appears as nitrogen gas; the oxides partly distil, and can be detected as such; and the water is taken up by iminodiphenylmethane, which hydrolyzes readily into benzophenone and ammonia.

$$(C_6H_5)_2CNH + H_2O = (C_6H_5)_2CO + NH_3 \qquad (7)$$

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[3] Lehmann, *Z. angew. Chem.*, **36**, 360 (1923).

[4] (a) Beckmann, *Ber.*, **19**, 991 (1886). (b) Beckmann and Bark, *J. prakt Chem.*, [2] **105**, 327 (1923).

[5] Hollemann [*Rec. trav. chim.*, **13**, 429 (1894)] showed that oxygen is taken up by the oxime, giving benzophenone and nitric acid. The data given by Hollemann are entirely correct; but it seems that a peroxide is first formed when oxygen is absorbed, without any substantial production of nitric acid; the acid develops later.

The amount of iminodiphenylmethane actually found is therefore a little less than 0.5 equivalent of the oxime taken, and the quantity of benzophenone a little more; and the difference between these quantities agrees closely with the amount of ammonia liberated during the reaction.

Iminodiphenylmethane, or benzophenone imide, has been described by Hantzsch and Kraft,[6] who obtained it by heating benzophenone chloride with a great excess of urethan. It can be prepared more cheaply and expeditiously by the new method described here (compare the Experimental Part, below).

In the small amount of tarry matter (about 3%) which appears in addition to the products already named, neither aniline nor benzoic acid could be found after hydrolyzing it with alkali. No benzanilide, therefore, is produced when benzophenone oxime is heated by itself.

The reaction is almost instantaneous at 185–190°, and the failure to yield benzanilide might have been due chiefly to a greater rapidity of this reaction, as compared with the rearrangement. As a matter of fact, the Beckmann reaction is also a very rapid process. To make sure that this possibility does not complicate the problem, the oxime was also heated in an evacuated tube for 72 hours, to 150° (a few degrees above its melting point). Even under these conditions, no benzanilide was formed; 60% was transformed into a mixture of ketone and imide, and the remainder was unchanged oxime.

The Action of Metallic Chlorides on Benzophenone Oxime

Beckmann and Bark[4b] have very recently reported some curious results upon heating benzophenone oxime with sodium and potassium chlorides. Potassium chloride, when heated with the oxime, at 160° gave a mixture of about equal parts of benzanilide and unchanged oxime; sodium chloride had no action at all, even when the temperature was increased to 250°, for the oxime was recovered unchanged.

These data are entirely out of accord with the work described here. They must be the result of some errors of observation or manipulation, for I have not been able to verify them. When mixtures of the oxime with sodium and with potassium chloride were heated side by side in the same bath, both behaved alike. There was a violent action at 185°; all of the oxime was converted into the mixture of ketone and imine already described, and no benzanilide was formed.

The Action of Hydrochloric Acid on Benzophenone Oxime

Lehmann[3] has recently shown that when the oxime is heated in a current of dry hydrogen chloride, or when the hydrochloric acid salt of the oxime is heated, complete rearrangement takes place at about 110–120°. These observations have been repeated, and found correct. Lehmann, however,

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[6] Hantzsch and Kraft, *Ber.*, **24**, 3516 (1891).

always employed at least one molecular equivalent of hydrochloric acid for each equivalent of oxime. It seemed worth while to test the action of smaller amounts.

Very small proportions of oxime salt suffice to bring about the conversion of oxime to benzanilide. When one molecular equivalent of salt was heated with five equivalents of oxime, six equivalents of benzanilide were produced. Similarly, heating one molecular equivalent of salt with ten equivalents of oxime, gave eleven equivalents of anilide; and when one molecular equivalent of salt was mixed with 25 equivalents of oxime, 18 equivalents of rearranged product were isolated.

As the proportion of oxime salt is reduced, somewhat higher temperatures are necessary to bring about reaction. Thus, two hours' heating of a mixture in the proportions of 1:10, gave practically no benzanilide at 125–130°; but when a second batch was heated to 135°, there was an energetic action after a few minutes, with complete conversion.

The ratio of 1:25 is probably the practical limit of catalytic efficiency, for but little rearrangement occurred when the ratio was decreased to 1:100. Even at 1:25, action is slow, so that heating to 160° for one hour was required to get a yield of 18. At these higher temperatures, however, ammonia and imide are also being formed, according to the reactions described above; and these substances, being much stronger bases than the oxime, capture and hold the hydrochloric acid. When all the hydrochloric acid is so combined, rearrangement ceases.

Discussion of Results

Neither the Beckmann nor the Stieglitz theory of the rearrangement of oximes is entirely adequate to account for the data reported above. Benzophenone oxime does not rearrange at all, *but its salts do*.[7] Dehydration of the oxime salt is not a *necessary* preliminary step in the rearrangement. If dehydration occurs in the sense conceived by Stieglitz, then we must further assume that the dehydrating agent, which is a trace of combined hydrochloric acid, immediately gives up its water again to the imide chloride (compare Equations 4 and 5), which therefore must have a greater affinity for water than the dehydrating agent itself.

The fundamental process of the Beckmann rearrangement would seem to be the direct conversion of the oxime salt into an acid amide and a free acid.

$$(C_6H_5)_2C{=}NOH.HCl{=}C_6H_5CO{-}NHC_6H_5 + HCl \qquad (8)$$

The acid liberated by this reaction re-enters the cycle with a fresh portion of oxime, and is thus strictly a catalytic agent. Dehydrating agents are not required; they merely help to furnish an anhydrous medium, which

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[7] Henrich and Ruppenthal [*Ber.*, **44**, 1533 (1911)] showed that only those oximes undergo the Beckmann rearrangement which are capable of forming hydrochlorides.

is a prerequisite to the formation of oxime salts. This is definitely shown when benzophenone oxime hydrochloride is heated with a small amount of water. A mixture of this salt with 10% of its weight of water (molecular ratio of salt to water = 1:1.5, approximately) was converted into benzanilide to the extent of 67%.

Experimental Part

Preparation of Benzophenone Oxime.—To a solution of 50 g. of benzophenone in 100 cc. of warm alcohol was added 30 g. of hydroxylamine hydrochloride dissolved in 30 cc. of hot water, in a flask provided with a funnel tube and connected to a reflux condenser. Through the funnel tube was added, very slowly at first, 70 cc. of a cold saturated solution of sodium hydroxide in water. The mixture boiled violently at the start. After it had quieted down, it was heated to gentle boiling on the water-bath, or a hot plate, for five minutes; 100 cc. of water was added and the mixture was heated again if not entirely homogeneous, and then cooled. The clear liquid was poured into 1 liter of water containing 150 cc. of concd. hydrochloric acid while the mixture was stirred. The precipitate was filtered off, washed with water, and dried in a vacuum. When desired, it was recrystallized by dissolving the substance in hot alcohol, and adding an equal volume of hot water; yield, 52–53 g.; time required, 30 minutes, not including drying or recrystallizing.

The melting point of pure benzophenone oxime has been found to be 143° in a capillary tube, instead of 140° as recorded in Beilstein..

Action of Heat on Benzophenone Oxime.—In an atmosphere of illuminating gas, 5 g. of oxime was carefully heated until action started at one point. It spread rapidly through the mass, brown fumes appearing momentarily. The apparatus was connected to a trap containing standard acid. After the reaction ceased, vacuum was applied to draw all possible ammonia into the trap; 15.0 cc. of 0.1 *N* solution was neutralized. The liquid contents of the reaction flask were then distilled; 4 g. of oil (b. p., 130–135° at 6 mm.) was obtained. The residue was hydrolyzed for several hours with hot sodium hydroxide solution, but neither aniline nor benzoic acid could be found. The oil was dissolved in ligroin, and treated with dry hydrogen chloride. The precipitated salt was dried in a vacuum and analyzed.

A solution of 0.2003 g. in cold water was allowed to stand for two hours. The precipitated benzophenone was dried in a vacuum; weight, 0.1611 g.; m. p., 48°. The filtrate was distilled with alkali into standard acid; 9.0 cc. of 0.1 *N* solution was used. The benzophenone calculated was 0.1673 g.; the ammonia calculated was 9.2 cc. The ratio of benzophenone to ammonia was 1:1.01.

To follow the reaction more accurately, 2.00 g. of oxime was spread along a slightly inclined tube, which had been blown out a little at the lower end to collect the liquid product. The air was displaced with carbon dioxide, and connection made with a nitrometer filled with potassium hydroxide solution. Heat was applied to but a small portion of oxime at a time; otherwise gas was formed too rapidly for collection; 65.2 cc. of gas (17°, 755 mm.) was obtained; of this, 2.4 cc. was absorbed by cuprous chloride, the remainder being nitrogen. The liquid reaction product was dissolved in cold ligroin; the insoluble residue weighed 0.06 g. (3%). The ligroin solution, treated with hydrochloric acid as described above, gave 0.95 g. of imine salt; the filtrate, on evaporation, left 1.00 g. of benzophenone which melted at 47–48° (not recrystallized). The ratio of imine to benzophenone found was 0.85:1.08, while that calculated was 1:1. The loss in imine corresponds to ammonia formation of 15%; in the previous experiment, ammonia equal to 17.7% had distilled.

The effect of slow heating was determined by heating 2.00 g. in a sealed, evacuated tube for 72 hours at 150°. The contents were then extracted with cold ligroin, which on evaporation left 1.13 g. of mixed imine and ketone. The residue insoluble in ligroin was completely soluble in cold 2% sodium hydroxide solution; this solution when acidified gave 0.78 g. of oxime, or 39%.

Benzanilide is insoluble in ligroin; benzophenone oxime is but slightly soluble. Cold weak alkali will not dissolve benzanilide; but a residue insoluble in this reagent may contain considerable oxime. Such residues must be dissolved in a little hot alcohol, precipitated with excess of water, and treated again with weak alkali. The solubility of benzophenone oxime in 0.5 *N* sodium hydroxide at 20° is 0.40 g. per 100 cc. of solution.

Preparation of Diphenylmethane-imine.—In a long bomb tube was loosely packed 25 g. of benzophenone oxime; the end of the tube was then drawn out to a length of about 15 cm. and a diameter of 6 to 8 mm. and bent at a right angle. This tube was supported in a nearly horizontal position, dipping slightly towards the closed end, and the bent, drawn-out end placed in a small flask. The air was pumped out and an oxygen-free gas admitted. The oxime was then heated with a free flame, beginning at the upper end and waiting for the reaction before heating a further portion; when the experiment was performed carefully, no material was carried out of the tube with the gases; the small flask served as a trap. When all of the oxime had been converted and collected at the bottom of the tube, it was heated strongly for a short time to complete the decomposition, allowed to cool, and distilled in a vacuum. A mixture of diphenylmethane-imine and benzophenone distilled within 5°. The distillate was dissolved in 200 cc. of ligroin or ether, and the imine salt precipitated with hydrogen chloride, which was dry; yield, 11–12 g. Benzophenone was recovered from the filtrate. The imine salt could be converted into the free base by the method of Hantzsch and Kraft (solution of the salt in chloroform and treatment with dry ammonia).

The salt sublimed without decomposition, slowly at 230°, very rapidly at 250°. It was preserved in a dry atmosphere; in moist air, it changed to a mixture of benzophenone and ammonium chloride. The free base, on standing in the air, smelled of ammonia and gradually deposited crystals of benzophenone.

Heating Benzophenone Oxime in the Presence of Alkali Chlorides.—Two g. each of oxime and of sodium chloride and separately of oxime and potassium chloride were finely ground in a mortar, and heated in tubes in a liquid bath. The initial temperature was 160°; this was increased at the rate of 1° per minute. After 25 minutes, when the temperature was 185°, there was a violent reaction in each tube. After five minutes, the tubes were cooled, and extracted with cold ligroin. The extracts, when evaporated, each left 1.7 g. of a mixture of imine and ketone. The ligroin residues were next extracted with water to remove the inorganic salts; 0.04 and 0.03 g., respectively, of residue were formed. These residues were combined and hydrolyzed, but no test for aniline was obtained with bromine water.

Action of Heat on Mixtures of Benzophenone Oxime and its Hydrochloride.—Solid benzophenone oxime readily absorbs hydrogen chloride, with the evolution of considerable heat. A number of experiments were made in which a small quantity of oxime was acted upon by the gas, the excess of gas pumped out, and more oxime then added; but it was found difficult to prepare mixtures of definite composition in this manner. For the results obtained below, oxime salt was prepared by precipitation from ether solution, and weighed quantities of this were taken. In all cases, the tubes were evacuated and sealed, and heated slowly in a liquid bath to permit observation. At the temperatures indicated in the table, the tube contents melted to a clear, colorless liquid; after a short time, and a rise of bath temperature of at most a few degrees, the liquid began to darken, and to boil. The reaction was then complete. The solidified contents of the tube were dissolved in a little boiling alcohol, and precipitated with a large excess of water; to this mixture enough sodium hydroxide solution was added to make about 300 cc. of 2% solution for each gram of oxime taken. The insoluble portion remaining after this treatment was recrystallized from hot alcohol by addition of water.

In each case, 2.00 g. of oxime (very nearly 0.01 molecule) was taken; the proportion of oxime salt was varied as shown in Table I.

TABLE I

CATALYTIC EFFECT OF BENZOPHENONE OXIME HYDROCHLORIDE IN THE BECKMANN REARRANGEMENT

Expt.	Wt. HCl salt	Ratio of salt to oxime	M. p. of mixture °C.	Benzanilid produced G.	Benzanilid produced Mols. per mol. of salt
1	0.45	1:5.2	123	2.20	5.8
2	.45	1:5.2	123	2.27	6.0
3	.22	1:10.5	not melted	0.20	1.0
4	.22	1:10.5	133	2.13	11.2
5	.095	1:25	135	1.45	18.2
6	See note	1:100	138	0.18	9.0

Notes on Table I. Expt. 3: The mixture was held between 125° and 128° for one hour. It darkened, and had shrunk noticeably, but did not melt.

Expt. 5: The temperature was slowly raised to 160°, and held there for one hour.

Expt. 6: As the handling of so small an amount of oxime salt involved risk of loss through atmospheric moisture, a thin-walled bulb containing 2.0 cc. of dry hydrogen chloride was sealed in with the oxime, and broken after the tube was evacuated. It was then heated in an air-bath to 160° for six hours.

Rearrangement of Benzophenone Oxime Hydrochloride in the Presence of Water.—In order to be sure of the composition of a mixture of water and of oxime salt, 3.7 g. of salt was weighed into a bomb tube (capacity 20 cc.), and a thin-walled bulb containing 0.37 g. of water was also sealed in. After evacuating, the bulb was broken, and the mass thoroughly mixed by shaking for 30 minutes. The tube was then carefully warmed[8] over a free flame; the contents melted to a clear colorless liquid, and after a very short time darkened and boiled vigorously. The tube after cooling contained gas at very high pressure. The contents were dissolved in hot alcohol and precipitated with water. This gave 1.6 g. of benzanilide, m. p. 160°. There was considerable hydrolysis of the anilide during the reaction; the mother liquor was made alkaline and then concentrated to remove alcohol; on acidifying, it gave 0.3 g. of benzoic acid. The combined weights of benzanilide and benzoic acid are equivalent to a rearrangement of 67%.

Summary

1. Benzophenone oxime does not give benzanilide on heating; instead, it is transformed into a mixture of benzophenone and diphenylmethane-imine.
2. A very small proportion of oxime salt will convert large amounts of oxime into anilide.
3. The reaction can even be carried out in the presence of water.
4. Improved methods of preparation of benzophenone oxime and of diphenylmethane-imine are given.

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[8] Benzophenone oxime hydrochloride melts at 120°; the reaction temperature in this experiment was below 125° as an upper limit.