[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

# THE ACTION OF AMMONIA ON BENZIL

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Interest in the action of ammonia on benzil dates back nearly a century to the observation of Zinin,<sup>1</sup> who found that the reaction in aqueous alcoholic medium at 70° yielded ethyl benzoate and a colorless, glistening, crystalline product which he named *Azobenzil*. Soon afterward, Laurent<sup>2</sup> made a more systematic study of the reaction in alcoholic solution, and isolated three substances termed by him *Imabenzil*, *Benzilimide*, and *Benzilam*. At the suggestion of Zincke,<sup>3</sup> Henius<sup>4</sup> reinvestigated the reaction. He identified Zinin's azobenzil with Laurent's benzilam, and found that in alcoholic solution at 130° imabenzil disappeared after one hour, and on continued heating the remaining benzilimide-benzilam mixture gave way to a mixture of benzilam and lophine.

In the meantime, Japp<sup>5</sup> had also attacked this problem and published the first reliable analyses of Laurent's products. He suggested the following structures for benzilimide (I) and benzilam (II); structures which



are presumably accepted at the present time. For imabenzil  $(C_{35}H_{28}N_2O_3)$  no structure was proposed by Japp, but he showed it to be converted by acids into one mole each of benzilimide, benzil, and ammonia. Somewhat later, Pinner<sup>6</sup> repeated part of Japp's work and proposed III as the structural formula for imabenzil.

<sup>1</sup> ZININ, Ann., 34, 190 (1840).

<sup>2</sup> LAURENT, J. prakt. Chem., 35, 461 (1845).

<sup>3</sup> ZINCKE, Ber., 16, 889 (1883).

<sup>4</sup> HENIUS, Ann. 228, 339 (1885).

<sup>5</sup> JAPP, J. Chem. Soc., **43**, 11 (1883); Ber., **15**, 2410 (1882); **16**, 2636 (1883); JAPP AND WYNNE, J. Chem. Soc., **49**, 473 (1886).

<sup>6</sup> PINNER, Ber., 35, 4131 (1902).



The present paper proposes a revision of the structure of benzilimide, suggests a more rational formula for imabenzil, offers a mechanism for the action of ammonia on benzil, and adds an improved procedure for the preparation of glyoxalines derived from benzil. It will be helpful first to review briefly the evidence for the structures of the products obtained from benzil by the action of ammonia, discussing these substances in the reverse order in which they appear in practice.

# LOPHINE

Although lophine (IV), m.p. 275°, has been obtained in many complex reactions, two methods of preparation are especially significant in structural discussions. The first is Radziszewski's<sup>7</sup> classic synthesis from benzil, benzaldehyde, and ammonia, while the second is Kulisch's<sup>8</sup> synthesis from benzoin and benzamidine. The latter particularly points to 2,4,5-triphenylglyoxaline as the structure for lophine.



### BENZILAM

Benzilam (II), m. p. 116°, occurs not only among the products of the action of ammonia on benzil; both imabenzil and benzilimide are converted into it by the action of sulfuric acid. It has also been reported as result-

<sup>8</sup> Kulisch, Monatsh., 17, 300 (1896). See FRANKLIN, Chem. Rev., 16, 315 (1935).

<sup>&</sup>lt;sup>7</sup> RADZISZEWSKI, *ibid.*, **15**, 1493 (1882).

ing from the action of fused ammonium acetate<sup>9</sup> or ammonium formate<sup>10</sup> on benzil, accompanied by a small amount of lophine. Japp<sup>5</sup> assigned an oxazole structure to benzilam, which he confirmed by a synthesis from benzoin and benzonitrile.<sup>11</sup>

#### BENZILIMIDE

Japp's structure for benzilimide (I) was based on its dehydration to benzilam (II). Since the latter is best represented as an oxazole, benzilimide was written as a hydrated oxazole, or, specifically, as 2-hydroxy-2, 4,5-triphenyloxazoline. Henius<sup>4</sup> described benzilimide as occurring in white, asbestos-like needles, melting at 137–139°. In 1913, McKenzie and Barrow<sup>12</sup> benzoylated desylamine and obtained a product consisting of rosettes of slender, colorless needles which melted at 139–140° and yielded benzilam (II) with concentrated sulfuric acid according to Robinson's method of producing oxazoles.<sup>13</sup> In the present work, the preparation of Laurent's benzilimide and of McKenzie and Barrow's benzodesylamide (N-desylbenzamide) (V) were repeated, and the products were

 $\begin{array}{c} C_6H_5CHNHCOC_6H_5\\ \downarrow\\ C_6H_5CO\\ V\end{array}$ 

found to be identical in crystalline form (rosettes of asbestos-like needles) melting point  $(141^{\circ})$ , and chemical behavior (conversion to cyclic bases by ammonia, aniline, or dehydration). Japp's formula for benzilimide, should, therefore, be superseded by N-desylbenzamide (V), the structure of which is established by the synthesis of McKenzie and Barrow. In harmony with this formulation benzilimide forms an oxime (m. p. 200°).

## THE MECHANISM OF THE ACTION OF AMMONIA ON BENZIL

To explain the formation of benzilimide or benzilam, Japp<sup>5</sup> assumed that one molecule of benzil is split by ammonia into benzaldehyde and benzoic acid. The latter fragment may appear as ethyl benzoate or benzamide depending on circumstances,<sup>14</sup> while the benzaldehyde reacts with

<sup>9</sup> JAPP AND WILSON, J. Chem. Soc., **49**, 825 (1886), recommended fused ammonium acetate as more convenient than alcoholic ammonia.

<sup>11</sup> JAPP AND MURRAY, J. Chem. Soc., 63, 469 (1893).

<sup>&</sup>lt;sup>10</sup> LEUCKART, J. prakt. Chem., [2], 41, 330 (1890).

<sup>&</sup>lt;sup>12</sup> MCKENZIE AND BARROW, *ibid.*, **103**, 1331 (1913).

<sup>&</sup>lt;sup>13</sup> ROBINSON, *ibid.*, **95**, 2167 (1909); ROBINSON AND LISTER, *ibid.*, **101**, 1297 (1912).

<sup>&</sup>lt;sup>14</sup> SCHÖNBERG, Ber., 54B, 242 (1921), obtained ammonium benzoate in aqueous ammonia at 120°.

a second molecule of benzil to form benzilimide or benzilam. As Japp recognized, the inherent weakness of this mechanism lies in the fact that, as Radziszewski<sup>7</sup> had shown, a mixture of benzaldehyde and benzil reacts with ammonia in alcohol at 40° to form lophine exclusively. Furthermore, benzil does not undergo the supposed scission when treated with derivatives of ammonia such as primary amines (Zincke<sup>3</sup>). It appears necessary, therefore, to devise a reaction scheme which does not involve benzaldehyde. What follows is proposed as a working hypothesis for the course of this reaction.

1. Benzil adds ammonia to form the hypothetical benzil-ammonia (VI).

2. Benzil-ammonia condenses with benzil to form another hypothetical intermediate, desylidenebenzil-ammonia (VII).

3. Such a structure (VII), it is proposed, possesses a particularly labile C-C bond between the azomethine carbon atom and the adjacent carbonyl group, which is subject to solvolysis (hydrolysis, alcoholysis, or ammonolysis). This results in the production of benzoic acid or a derivative (ethyl benzoate or benzamide) and a third hypothetical intermediate, benzylidenebenzil-ammonia (VIII).

4. Benzylidenebenzil-ammonia undergoes a form of internal Cannizzaro reaction leading to the benzoyl derivative of desylamine [N-desylbenzamide (V)].

5. Sufficiently activated molecules of V undergo spontaneous cyclodehydration to benzilam (II).



The recognition of benzilimide as *N*-desylbenzamide clarifies the action of ammonia on benzil by bringing to light the close analogy between this reaction of ammonia on an alpha-diketone and its action on alpha-ketoacids. Erlenmeyer, Jr.<sup>15</sup> found that acids of the type RCOCOOH were converted by ammonia to alpha-acylaminoacids of the type RCONH-CHRCOOH and carbon dioxide thus:

$$\begin{array}{c} \operatorname{RCO} \\ | \\ \operatorname{HOCO} \end{array} + \operatorname{NH}_3 + \begin{array}{c} \operatorname{COR} \\ | \\ \operatorname{COOH} \end{array} + \begin{array}{c} \operatorname{RCHNHCOR} \\ | \\ \operatorname{HOCO} \end{array} + \begin{array}{c} \operatorname{CO}_2 + \operatorname{H}_2 \operatorname{O} \end{array}$$

<sup>15</sup> ERLENMEYER, JR. AND KUNLIN, *ibid.*, **35**, 2438 (1902).

beside which may be written

$$\begin{array}{ccc} C_6H_5CO \\ | \\ C_6H_5CO \end{array} + \begin{array}{c} NH_3 \end{array} + \begin{array}{c} COC_6H_5 \\ | \\ COC_6H_5 \end{array} \rightarrow \begin{array}{c} C_6H_5CHNHCOC_6H_5 \\ | \\ C_6H_5CO \end{array} + \begin{array}{c} C_6H_5COOH \end{array}$$

In both reactions an active carbonyl group is converted to an acylated carbinamine group at the expense of a second molecule of the carbonyl compound. Erlenmeyer's mechanism for his reaction involved the intermediate IX. His concept is brought into line with that discussed above in the benzil case by considering this substance to dehydrate to X, which contains the azomethine grouping known to labilize the C—COOH bond and permit decarboxylation.<sup>16</sup> A subsequent rearrangement would yield the final aminoacid derivative.

RC(OH)NHC(OH)R		RC(OH)N:CR	
носо	COOH	HOCO	COOH
IX		X	

This picture of the mechanism of the action of ammonia on benzil accounts for the apparent (but not actual) scission of benzil. It remains to explain the formation of lophine when ammonia acts on a mixture of benzaldehyde and benzil in alcohol (Radziszewski<sup>7</sup>). Here it may be assumed that the reaction begins with the conversion of benzaldehyde to a diamine (XI), which condenses with benzil to form XII, which then undergoes a Cannizzaro reaction yielding lophine. The formation of the supposed intermediate XII is analogous to the formation of hydrobenzamide (XIII) by the action of ammonia on benzaldehyde alone.



The formation of lophine in Henius' experiments<sup>4</sup> mentioned above is to be traced to benzilimide, since it is known that such acylated aminoketones react with ammonia to yield glyoxalines.<sup>17</sup> This account for Henius' observation of the disappearance of benzilimide and the appearance of lophine as the action of ammonia was continued. In the present study it was found that benzilam was completely unaffected under conditions which converted benzilimide (*N*-desylbenzamide) quantitatively to lophine.

<sup>16</sup> LANGENBECK, Z. angew. Chem., 45, 97 (1932); Ber., 70B, 367 (1937).

<sup>17</sup> EVEREST AND MCCOMBIE, J. Chem. Soc., 99, 1746 (1911).

#### IMABENZIL

Another aspect of the reaction under discussion which requires clarification is the nature of imabenzil. Imabenzil, the first product to separate in the action of ammonia on benzil, gradually disappears as the action is continued. Hence, Henius considered it the primary product but both Henius and Japp were unable to assign it a structure. Pinner's formula (III) hardly explains the conversion of imabenzil to benzilimide and benzilam, and led Strain<sup>17</sup> to suggest two alternative formulas (XIV or XV). Since these structures were based on Japp's cyclic conception of



benzilimide, they also require revision. The essential facts that a structural formula for imabenzil must indicate are its composition  $(C_{35}H_{28}N_2O_3)$ and its scission by acid into benzilimide, benzil, and ammonia. In harmony with the mechanism of the action of ammonia on benzil presented above the simplest assumption to be made is that imabenzil is a condensation product of benzil-ammonia (VI) and benzilimide (V); namely, 1-benzoyl-5, 6-dihydroxy-2, 3, 5, 6-tetraphenyl-1, 2, 5, 6-tetrahydropyrazine (XVI).



GLACIAL ACETIC ACID AS A MEDIUM FOR THE ACTION OF AMMONIA ON BENZIL

The present paper is part of a research program including the study of the action of ammonia in glacial acetic acid on carbonyl compounds. This work was stimulated by the observation of Davidson<sup>18</sup> that glacial acetic acid is an excellent medium for the conversion of alloxantine to murexide

<sup>18</sup> DAVIDSON, J. Am. Chem. Soc., 58, 1821 (1936).

by ammonia.<sup>9</sup> When a gram of benzil is refluxed for an hour in 25 cc. of glacial acetic acid containing 5 g. of ammonium acetate, all the benzil reacts, forming over 90 per cent. of the theoretical yield of lophine together with a subordinate amount of benzilam.

Does this result indicate that the action of ammonia on benzil is essentially different in glacial acetic acid from that observed in aqueous or alcoholic medium where little (if any) lophine is formed in the same length of time, and benzilam is the principal final product? Such is apparently not the case. The principal difference between glacial acetic acid and other media is that it is particularly suitable for the conversion of acyl derivatives of desylamine, such as N-desylbenzamide (V) to glyoxalines by ammonia. This has been demonstrated by treating benzilimide with ammonium acetate in glacial acetic acid, thus effecting its smooth conversion to lophine. N-Desylacetamide behaves similarly. Under the same conditions benzilam is completely unchanged by the reagent. When aniline is employed in place of ammonia, the ring closures lead to Nphenyl glyoxalines.

It is worthy of note that at elevated temperatures, fused ammonium acetate<sup>9</sup> or formate<sup>10</sup> convert benzil mainly to benzilam. These results may be reconciled with that described just above by invoking postulate five of the mechanism proposed in an earlier section of this paper. In accordance with this idea, a larger proportion of labile molecules of benzilimide would be formed at the higher temperatures, and would undergo cyclodehydration to the oxazole before they could react with ammonia to form lophine.

## A MODIFIED RADZISZEWSKI SYNTHESIS OF GLYOXALINES

If an equimolecular mixture of benzaldehyde and benzil is refluxed for an hour in glacial acetic acid containing insufficient ammonium acetate to convert benzil alone to lophine, a quantitative yield of lophine is obtained. Hydrobenzamide may be substituted for the benzaldehyde. The advantage of the acetic acid medium over Radziszewski's alcoholic ammonia is seen clearly in the case of 4,5-diphenylglyoxaline. This compound was first prepared by Japp<sup>19</sup> by the action of alcoholic ammonia on a mixture of formaldehyde and benzil. Pinner<sup>6</sup> obtained very little of the desired product by Japp's method, the reaction yielding mainly the well-known products of the action of ammonia on benzil alone. Later, Pinner<sup>20</sup> somewhat improved the yield of 4,5-diphenylglyoxaline by working in the cold. This complication prompted Biltz<sup>21</sup> to study the indirect pro-

<sup>20</sup> PINNER, Ber., 38, 1536 (1905).

<sup>&</sup>lt;sup>19</sup> JAPP, J. Chem. Soc., **51**, 559 (1887).

<sup>&</sup>lt;sup>21</sup> Biltz, *ibid.*, 40, 2630 (1907); Biltz and Krebs, Ann., 391, 201, 203 (1912).

duction of this substance from 2-chloro and 2-mercapto derivatives. Pinner's difficulty disappears, however, when glacial acetic acid is employed and hexamethylenetetramine is utilized as a convenient source of formaldehyde, a quantitative yield of Japp's product being obtained. A similar result is experienced with a mixture of paraldehyde and benzil, which leads to 2-methyl-4,5-diphenylglyoxaline.<sup>5</sup>

#### EXPERIMENTAL

Preparation of Laurent's benzilimide.—Ammonia gas was passed into a solution of 25 g. of benzil in 500 cc. of ethanol at 30-40° until the gain in weight amounted to nine grams. Fine colorless needles of imabenzil soon appeared. After 24 hours the crop, amounting to 0.55 g., melting at 188° (corr.), was collected by filtration, and the filtrate was boiled down in vacuum in two stages to approximately 200 and 100 cc. respectively, further crops of imabenzil of 2.1 g., m. p. 208° (corr.), and 0.8 g., m.p. 193° (corr.), being obtained. The final liquor, on standing, deposited 9.2 g. of a mixture of benzilimide and benzilam melting at about 100°, from which 3 g. of benzilimide, m.p. 141° (corr.), was separated by fractional crystallization from ethanol. No depression of the melting point was observed when this material was mixed with the N-desylbenzamide prepared as described below.

N-Desylbenzamide from desylamine.—A suspension of 9.2 g. of desylamine stannochloride<sup>22</sup> in 100 cc. of water was covered with 200 cc. of benzene containing 4 cc. of benzoyl chloride. The mixture was stirred and maintained at 5-10° while 80 cc. of 10% sodium hydroxide was slowly dropped in. Stirring was then continued for thirty minutes at room temperature, the benzene layer was separated, the benzene removed, and the residue was crystallized from 60 cc. of ethanol. The yield was 5.0 g. (80% theoretical) of colorless, asbestos-like needles, melting at 141° (corr.). Like benzoin, this substance gives a yellow solution in alcoholic alkali, but, unlike benzoin, does not develop a deep purple color.

Benzilimide oxime.—This was obtained by refluxing 0.32 g. of benzilimide with 0.14 g. of hydroxylamine hydrochloride and 0.16 g. of sodium acetate in 10 cc. of ethanol for 16 hours or by refluxing the amide and hydroxylamine hydrochloride in 3 cc. of pyridine for two hours. In both cases the product was thrown out with water and crystallized from methanol, from which it was obtained in the form of needles, melting at 197-203° (corr.), depending on the rate of heating.

Anal. Calc'd for  $C_{21}H_{18}N_2O_2$ : C, 76.4; H, 5.5; N, 8.5.

Found: C, 75.9; H, 5.7; N, 8.9.

The mother liquors contained a much more soluble product  $(m.p. 140^\circ)$  which may be an isomeric oxime. Identical products were obtained from the N-desylbenzamide prepared from desylamine.

Action of ammonia in acetic acid on N-desylamides.—Lophine from N-desylbenzamide.—Benzilimide (0.32 g.) was refluxed for one hour with 1.5 g. of ammonium acetate in 10 cc. of acetic acid. Dilution of the hot solution with water yielded 0.28 g. (93% of theory) of colorless needles, melting at 270° (corr.). Recrystallization from a mixture of pyridine and water raised the melting point to 275° (corr.). Under the same conditions benzilam was recovered quantitatively and unchanged. Substitution of one cc. of aniline for the ammonium acetate yielded *tetraphenyl glyoxaline*,<sup>17</sup> melting at 221° (corr.) (from methanol). This has previously been reported as melting at 215°. Identical results were obtained from N-desylbenzamide prepared from from desylamine. Replacement of the N-desylbenzamide in the experiments de-

<sup>&</sup>lt;sup>22</sup> PSCHORR AND BRUGGEMANN, Ber., 35, 2740 (1902).

scribed above by N-desylacetamide, the preparation of which is reported below, yielded entirely similar results leading to 2-methyl-4,5-diphenylglyoxaline, m.p. 243° (corr.) and 2-methyl-1,4,5-triphenylglyoxaline, m.p. 197° (corr.).

N-Desylacetamide.—To a mixture of 20 cc. of dry pyridine and 4 cc. of acetic anhydride surrounded by an ice bath 9.1 g. of desylamine stannochloride was gradually added with stirring. The stirring was continued for an hour at room temperature and the mixture was then poured into chilled dilute hydrochloric acid. This precipitated an oil which soon solidified. Crystallization from methanol gave large, clear prisms, melting at 137° (corr.) in practically quantitative yield.

Anal. Calc'd for C16H15NO2: N, 5.5. Found: N, 5.6.

Action of ammonia on benzil in acetic acid.—A solution of 1.05 g. of benzil and 5.0 g. of ammonium acetate in 25 cc. of glacial acetic acid was refluxed for one hour. Twenty cc. of water was then added. This precipitated 0.05 g. (7% of theory) of benzilam, m.p. 110° (115° after crystallization from ethanol). Dilution of the original mother liquor to 250 cc. precipitated 0.70 g. (94% of theory) of crude lophine, m.p. 250°, which after solution in hot pyridine (10 cc.) and precipitation by addition of hot water (7.5 cc.) melted at 275° (corr.).

A modified glyoxaline synthesis.—Preparation of 4,5-diphenylglyoxaline.—A mixture of 1.05 g. of benzil, 0.13 g. of hexamethylenetetramine, 3.0 g. of ammonium acetate and 25 cc. of glacial acetic acid was refluxed for an hour and then diluted to 250 cc. A slight turbidity was removed by means of Darco and the glyoxaline was precipitated by adding ammonia; yield, 1.00 g. (91% of theory) of a product melting at 228° (corr.). Crystallization from 5 cc. of hot pyridine by addition of 5 cc. of boiling water yielded large, glistening needles, m.p. 232° (corr.).

Anal. Calc'd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>: N, 12.7. Found: N, 12.6.

Similar reactions in which the formaldehyde derivative was replaced (a) by paraldehyde (0.3 cc.) gave 2-methyl-4,5-diphenylglyoxaline, m.p. 244° (corr.) in 96% yield; or (b) by benzaldehyde (0.5 cc.) or by hydrobenzamide (0.5 g.) gave lophine, m. 272° in 90-95% yields.

#### SUMMARY

1. Laurent's benzilimide is identical with the benzodesylamide (N-desylbenzamide) of McKenzie and Barrow.

2. 1-Benzoyl-5, 6-dihydroxy-2, 3, 5, 6-tetraphenyl-1, 2, 5, 6-tetrahydropyrazine is suggested as the structure of Laurent's imabenzil.

3. A mechanism for the action of ammonia on benzil which avoids the scission of benzil as a step and relates the reaction to the formation of alpha-acylaminoacids by the action of ammonia on alpha-ketoacids is proposed.

4. N-Desyl derivatives of acid amides are converted smoothly into glyoxalines by the action of ammonia in acetic acid.

5. Ammonia in acetic acid converts benzil to lophine accompanied by a small amount of benzilam.

6. The preparation of glyoxalines from benzil, aldehydes, and ammonia is improved by the use of glacial acetic acid. Ammonia derivatives or reversible polymers of the aldehydes may be employed in place of the aldehydes themselves.