

On the Formation of Benzonitrile from Benzaldehyde and Ammonia. II.¹⁾ Iodine as an Oxidant

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(Received May 22, 1967)

The present authors previously reported a method of synthesizing nitriles from aldehydes by using iodine as an oxidant (*Bull. Chem. Soc. Japan*, **39**, 854 (1966)). The possible route and detailed conditions of this reaction have now been investigated in the case of benzaldehyde; the results will be described in this paper. Benzaldehyde, ammonia, and iodine in methanol react to form benzonitrile and methyl benzoate as the main products. A possible reaction mechanism is suggested by a consideration of the effect of the temperature and of the concentrations of the reactants, and of the effect of the addition of ammonium iodide and water, as well as by a consideration of the results of the reaction starting from hydrobenzamide. The mechanism may be as follows. Iodamine, which is in equilibrium with iodine and ammonia, oxidizes benzilideneimine, which arises from the reaction between benzaldehyde and ammonia to give hydrobenzamide, to produce benzonitrile. Methyl benzoate is produced by the oxidation of the hemiacetal which arises from the reaction between benzaldehyde and methanol. Cyaphenin (2, 4, 6-triphenyl-1, 3, 5-triazine) is found as a by-product, but it is shown not to be produced by the trimerization of benzonitrile.

Several papers have been published describing one-step syntheses of nitriles from the corresponding aldehydes in the liquid phase. Brackman *et al.*²⁾ oxidized aldehydes to nitriles with oxygen in the presence of ammonia and using a certain copper salt as the catalyst. As for the mechanism of this reaction, investigations were made by Fischer³⁾ and the present authors.¹⁾ Benzilideneimine was recognized as an important intermediate, which was further oxidized to a nitrile. On the other hand, similar oxidation reactions have been performed with conventional oxidizing reagents. Parameswaran *et al.*⁴⁾ used lead tetraacetate, Nakagawa *et al.*⁵⁾ used nickel peroxide, and the present authors have been investigating the use of potassium permanganate, manganese dioxide, and so on.⁶⁾ In all the above cases, benzilideneimine is considered to be the important intermediate during the oxidation process. However, no detailed investigations have yet been carried out. The present authors have studied the reaction with iodine as the oxidant; the results will be described in this paper.

Benzaldehyde, ammonia, and iodine in methanol

reacted rapidly to form benzonitrile and methyl benzoate as the main products under moderate reaction conditions. Hydrobenzamide and cyaphenin (2, 4, 6-triphenyl-1, 3, 5-triazine) were also produced. This reaction is expected to be a useful method of synthesizing nitriles from aldehydes.

Results and Discussion

This reaction was carried out in methanol as the solvent. First, however, some other solvents were studied. In ethyl ether more amounts of by-products in the solid form were produced than in methanol. Benzene was not a good solvent because of the slow rate of the reaction. 1-Butanol was also unsuitable because of the low solubility of iodine in it. Strain⁷⁾ investigated the reaction of benzilideneimine with iodine in liquid ammonia. He obtained large amounts of cyaphenin with little benzonitrile. Methanol was thus found to be the most suitable solvent among those investigated.

The yields after distillation and the detailed conditions are described in the Experimental Section. Benzonitrile and methyl benzoate could each be formed and isolated in high yields under suitable reaction conditions. For example, benzonitrile was obtained in a yield of 82% at a higher temperature and at a high concentration of ammonia, while methyl benzoate was obtained in a yield of 72% at 0°C.

1) Part I: A. Misono, T. Osa and S. Koda, *This Bulletin*, **40**, 912 (1967).

2) W. Brackman and P. J. Smit, *Rec. Trav. Chim.*, **82**, 757 (1963).

3) E. Fischer, *J. Prakt. Chem.*, **29**, 199 (1965).

4) K. N. Parameswaran and O. M. Friedman, *Chem. & Ind.*, **1965**, 988.

5) K. Nakagawa, H. Onoe and K. Minami, Reprints for the 19th Annual Meeting of the Chemical Society of Japan (April, 1966), 3N221.

6) A. Misono, T. Osa, S. Koda and Y. Sato, *This Bulletin*, **40**, 1553 (1967).

7) H. H. Strain, *J. Am. Chem. Soc.*, **49**, 1558 (1927).

The yields of benzonitrile and methyl benzoate, as well as the amount of benzaldehyde unconsumed, were determined under various conditions by means of gas chromatography, with the intention of obtaining information about the possible reaction route. The analysis by gas chromatography showed the peaks of the unreacted benzaldehyde, benzonitrile, and methyl benzoate produced. No other peaks were found. Hydrobenzamide, which was found by isolation to be one of the main by-products, showed no peaks on the gas chromatogram. Benzoic acid and benzamide were produced in very small yields, if at all.

TABLE 1. THE EFFECT OF THE CONCENTRATION OF AMMONIA

Initial conditions: 10 ml of ammoniacal methanol (2.56–0 N), 3.21 mmol of iodine, 5 mmol of benzaldehyde, at 0°C

Concn. of ammonia		2.56 N	1.28 N	0.77 N	0.00 N
Reaction time					
30 min	BA	2.84 mmol	3.90	4.30	—
	BN	0.70 mmol	0.25	trace	0.00
	MB	0.24 mmol	0.36	0.24	0.00
	BN	2.9	0.7	—	—
	MB				
60 min	BA	2.12 mmol	3.37	4.03	—
	BN	1.08 mmol	0.33	0.05	0.00
	MB	0.28 mmol	0.39	0.32	0.00
	BN	3.9	0.8	0.2	—
	MB				

BA: benzaldehyde unreacted
BN: benzonitrile formed
MB: methyl benzoate formed

TABLE 2. THE EFFECT OF THE CONCENTRATION OF IODINE

Initial conditions: 10 ml of 2.56 N ammoniacal methanol, 1.62–6.40 mmol of iodine, 5 mmol of benzaldehyde, at 0°C

Amount of iodine		1.62 mmol	3.21	6.40*
Reaction time				
30 min	BA	3.16 mmol	2.84	2.20
	BN	0.41 mmol	0.70	0.90
	MB	0.14 mmol	0.24	0.29
	BN	2.9	2.9	3.1
	MB			
60 min	BA	2.28 mmol	2.12	1.14
	BN	0.71 mmol	1.08	1.54
	MB	0.19 mmol	0.28	0.37
	BN	3.7	3.9	4.2
	MB			

* Not perfectly dissolved at the beginning
BA: benzaldehyde unreacted
BN: benzonitrile formed
MB: methyl benzoate formed

The effects of the concentrations of ammonia, iodine and benzaldehyde were also studied; the data are shown in Tables 1–3. The effects of the addition of ammonium iodide, water, and

TABLE 3. THE EFFECT OF THE CONCENTRATION OF BENZALDEHYDE

Initial conditions: 10 ml of 2.56 N ammoniacal methanol, 3.21 mmol of iodine, 3–10 mmol of benzaldehyde, at 0°C

Amount of benzaldehyde		10 mmol	5	3
Reaction time				
30 min	BA	5.2 mmol	2.84	1.55
	BN	0.66 mmol	0.70	0.63
	MB	0.22 mmol	0.24	0.19
	BN	3.6	2.9	3.3
	MB			
60 min	BA	3.5 mmol	2.12	0.84
	BN	1.26 mmol	1.08	0.98
	MB	0.40 mmol	0.28	0.24
	BN	3.7	3.9	4.1
	MB			

BA: benzaldehyde unreacted
BN: benzaldehyde formed
MB: methyl benzoate formed

TABLE 4. THE EFFECT OF AMMONIUM IODIDE ADDED

Initial conditions: 10 ml of 2.14 N ammoniacal methanol, 3.21 ± 0.02 mmol of iodine, 10 mmol of benzaldehyde, 0–10.0 mmol of ammonium iodide, reaction time, 1.5 hr, at 0°C

NH ₄ I mmol	BA mmol	BN mmol	MB mmol	BN/MB
0	2.56	1.01	0.57	1.8
1.03	2.06	0.80	0.44	1.8
3.02	1.86	0.48	0.33	1.5
10.0	1.60	trace	trace	—

BA: benzaldehyde unreacted
BN: benzonitrile formed
MB: methyl benzoate formed

TABLE 5. THE EFFECT OF WATER ADDED

Initial conditions: 10 ml of 2.14 N ammoniacal methanol, 3.20 ± 0.01 mmol of iodine, 10 mmol of benzaldehyde, reaction time, 1.5 hr, at 0°C

H ₂ O mmol	BA mmol	BN mmol	MB mmol	BN/MB
0	2.56	1.01	0.57	1.8
5.6	2.74	1.03	0.59	1.7
10.1	3.01	0.89	0.48	1.8 ₃
20.8	3.10	1.34	0.75	1.8
40.6	2.26	0.95	0.58	1.6 ₃

BA: benzaldehyde unreacted
BN: benzonitrile formed
MB: methyl benzoate formed

TABLE 6. THE EFFECT OF SODIUM HYDROXIDE ADDED
Initial conditions: 10 ml of 2.14 N ammoniacal methanol, 9.8 ± 0.05 mmol of iodine, 10 mmol of benzaldehyde, 0 or 10.1 mmol of sodium hydroxide, reaction time, 2 or 3 hr, at 0°C

Reaction time		NaOH	
		0 mmol	10.1 mmol
2 hr	BA	1.30 mmol	1.96
	BN	1.81 mmol	0.00
	MB	0.90 mmol	4.10
3 hr	BA	1.26 mmol	2.04
	BN	2.14 mmol	trace
	MB	1.03 mmol	5.33

BA: benzaldehyde unreacted

BN: benzonitrile formed

MB: methyl benzoate formed

sodium hydroxide were also studied (*cf.* Tables 4–6).

Ammonium iodide considerably lowered the yields of both benzonitrile and methyl benzoate, while the addition of water had little effect on the yields of either methyl benzoate or benzonitrile, as is shown in Table 5. The changes in the concentrations of iodine, benzaldehyde, ammonium iodide, and water had little influence on the ratio of benzonitrile to methyl benzoate. On the other hand, an increase in the concentration of ammonia resulted in an increase in the ratio of benzonitrile to methyl benzoate. The effect of the addition of sodium hydroxide was also remarkable. When a small amount of sodium hydroxide was added, methyl benzoate was the predominant product. Moreover, it was found that methyl benzoate was produced from the reaction of benzaldehyde, methanol, and iodine with sodium hydroxide, without ammonia. However, concerning this oxidant, iodine with sodium hydroxide, no detailed discussions will be given in this paper. The ratio of benzonitrile to methyl benzoate increased with the reaction time. This can be seen in Tables 1–3.

The rate of the consumption of benzaldehyde increased with the reaction temperature (Table 7). Moreover, the reaction temperature had a striking effect on the ratio of the two main products. The yield of methyl benzoate decreased with the temperature. On the other hand, the yield of benzonitrile increased with the temperature until a definite point. The fall of the yields of both products at higher temperatures might be caused by the escape of ammonia from the liquid phase and/or by the pronounced formation of hydrobenzamide or some other undetected products.

When benzaldehyde was dissolved in ammoniacal methanol, it was found that benzaldehyde was consumed because of the reaction which led to

TABLE 7. THE EFFECT OF THE REACTION TEMPERATURE

Initial conditions: 10 ml of 2.14 N ammoniacal methanol, 10.1 mmol of sodium hydroxide, 9.8 ± 0.1 mmol of iodine, 10 mmol of benzaldehyde, reaction time, 1 hr

Reaction temp., °C	BA	BN	MB	BN/MB
0	2.64	0.00	4.37	0.0
19.5	1.25	0.54	1.84	0.29
29.5	1.70	1.78	0.50	3.8
39.5	0.83	0.79	0.12	6.6
50.0	1.20	0.85	0.00	—

BA: benzaldehyde unreacted

BN: benzonitrile formed

MB: methyl benzoate formed

hydrobenzamide. This reaction has been investigated kinetically by Ogata *et al.*⁸⁾ They found that this reaction was first-order in benzaldehyde and ammonia and concluded that the rate-determining step might be the formation of benzilideneimine (or α -aminobenzyl alcohol), which might then rapidly react through some unknown processes to yield hydrobenzamide.

When iodine was added to the mixture of benzaldehyde and ammonia in methanol, the consumption of benzaldehyde was hastened remarkably. These results are shown in Fig. 1. Besides, it was found that the presence of ammonium iodide in the mixture considerably hastened the consumption of benzaldehyde (Fig. 2). This effect of ammonium iodide could be expected, as Ogata *et al.*⁸⁾ had reported that the reaction between benzaldehyde and ammonia was an acid-catalyzed one

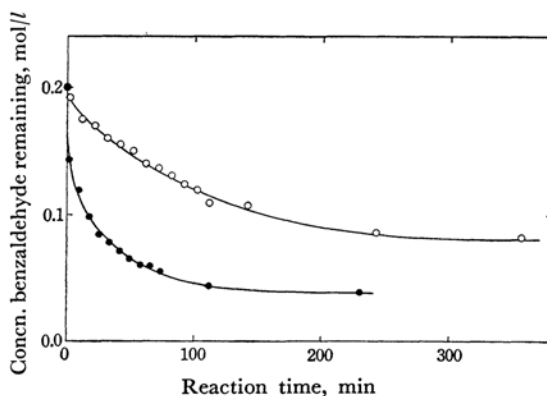


Fig. 1. Consumption of benzaldehyde accelerated by the addition of iodine.

Initial conditions: 10 ml of 0.849 N ammoniacal methanol, 2.0 mmol of benzaldehyde, *ca.* 0.085 g of 1-heptanol (as an internal standard for gas chromatographic analysis), 0.0 mmol (—○—), 1.97 mmol (—●—) of iodine, at 15°C.

8) Y. Ogata, A. Kawasaki and N. Okumura, *J. Org. Chem.*, **29**, 1985 (1964).

and was retarded by the addition of potassium hydroxide.

Some investigations were made of the formation

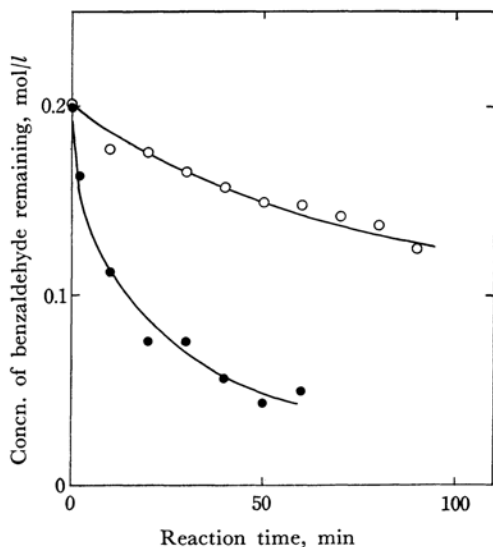
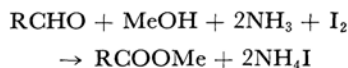


Fig. 2. Consumption of benzaldehyde accelerated by the addition of ammonium iodide.

Initial condition: 10 ml of 2.56 N ammoniacal methanol, 2.0 mmol of benzaldehyde, ca. 0.08 g of 1-heptanol (as an internal standard for gas chromatographic analysis), 0.0 mmol (—○—), 4.92 mmol (—●—) of ammonium iodide, at 0°C

of methyl benzoate. Moreover, the effect of ammonium iodide on the yield of methyl benzoate was again investigated (Fig. 3). The rate of the formation of methyl benzoate was related linearly to the reciprocal of the amount of ammonium iodide present in the reaction mixture, which was estimated as the sum of the ammonium iodide present in the beginning and of that produced during the reaction, according to the following assumed equation:



This relation is shown in Fig. 4.

The dependence of the reaction rate on the concentration of benzaldehyde is shown in Fig. 5. The values of the rates of the reaction were compared with the concentration of the aldehydes at a given reaction point. The reaction was found to be almost first-order in the concentration of the aldehyde.

It is known that one mole of an aldehyde reacts with one mole of an alcohol to yield one mole of the corresponding hemiacetal, which then reacts further with one mole of an alcohol to yield one mole of the corresponding acetal and one mole of water. The formation of hemiacetals is catalyzed by both an acid and a base,⁹⁾ but the formation of acetals is not catalyzed by a base. Based on the fact that ammonium chloride catalyzed the reaction of aldehydes with alcohols to acetals,¹⁰⁾ ammonium

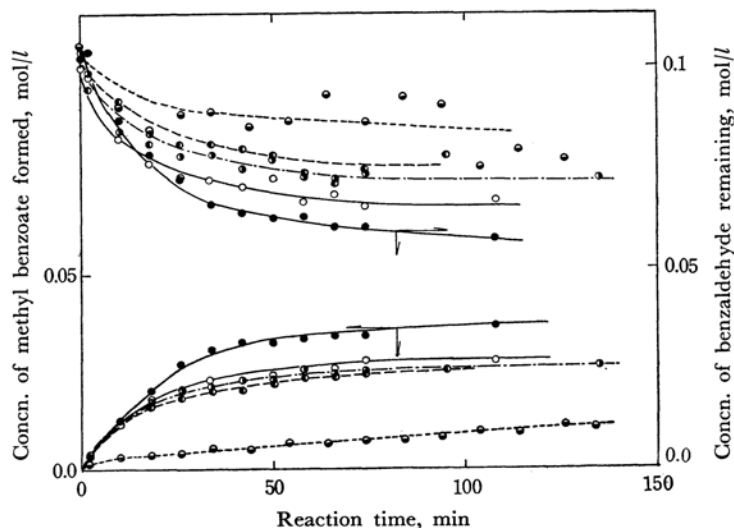


Fig. 3. The effect of ammonium iodide added.

Initial conditions: 10 ml of 0.304 N ammoniacal methanol, 1.00 ± 0.01 mmol of iodine, 1.03 ± 0.03 mmol (0.106–0.112 g) of benzaldehyde, ca. 0.06 g of 1-heptanol (as an internal standard for gas chromatographic analysis), 0 mmol (—●—), 0.31 mmol (—○—), 0.39 mmol (—●—), 0.48 mmol (—○—), 1.20 mmol (---●---) of ammonium iodide, at 0°C

9) W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 63 (1964).

10) R. D. Haworth and A. Lapworth, *J. Chem. Soc.*, **1922**, 76.

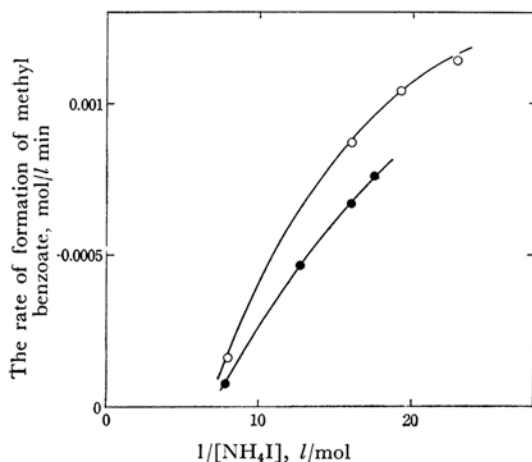


Fig. 4. The dependence of the reaction rate on the reciprocal of the amount of ammonium iodide present.

(From the slopes of the curves in Fig. 3)

—○—: at the point when 0.094 mmol (0.01 g) of benzaldehyde is consumed.

—●—: at the point when 0.189 mmol (0.02 g) of benzaldehyde is consumed.

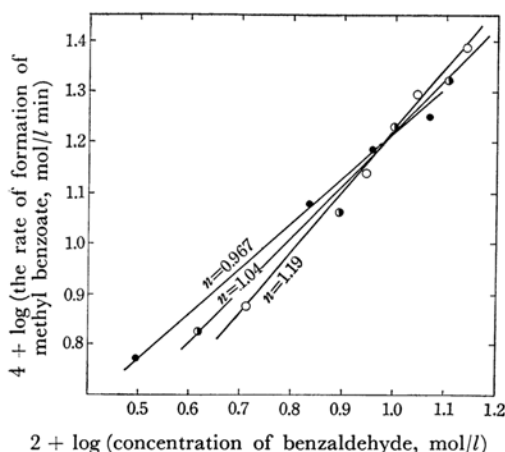


Fig. 5. The dependence of the reaction rate on the amount of benzaldehyde.

Initial conditions: 10 ml of 0.463 N ammoniacal methanol, 1.50 ± 0.01 mmol of iodine, 0.67–1.49 mmol (0.071–0.158 g) of benzaldehyde, ca. 0.07 g of 1-heptanol (as an internal standard for gas chromatographic analysis), at 0°C

—○—: at the point when 0.02 g of benzaldehyde is consumed.

—◐—: at the point when 0.03 g of benzaldehyde is consumed.

—●—: at the point when 0.04 g of benzaldehyde is consumed.

iodide was expected to have a similar effect on the conversion of benzaldehyde to the corresponding acetal. It was found, however, that very little acetal was produced from benzaldehyde and methanol under reaction conditions similar to

those adopted for the formation of the nitrile, especially when some ammonia was present in the mixture at 0°C.

The concentration of the hemiacetal produced from benzaldehyde and methanol in the reaction mixture would not be very large, but the rate of the formation of the hemiacetal would be rather large. As for the equilibrium of aldehydes and alcohols to hemiacetals, several reports have been published. Forrester¹¹⁾ studied the formation of the hemiacetal from a C_8 aldehyde and a C_8 alcohol by means of ultraviolet spectroscopy, and observed that the equilibrium constant decreased with the elevation of the temperature ($\Delta H = -1.8$ kcal/mol). Besides, Bell *et al.*¹²⁾ reported that the degree of the hydration of acetaldehyde became smaller at higher temperatures. On the basis of these reports, it seemed plausible that the amount of the methyl hemiacetal of benzaldehyde was smaller at higher temperatures in this reaction.

There have been quite a few reports on the oxidation of hemiacetals. Mosher *et al.*¹³⁾ studied the oxidation of cyclic hemiacetals with chromic acid. In general, this step is involved in the formation of the esters from alcohols. The conversion of 1-butanol to butyl butyrate is one example.¹⁴⁾

These foregoing investigations may justify the assumption that methyl benzoate is formed from the oxidation of the hemiacetal.

The following observations were made with the purpose of obtaining information concerning the identity of the actual oxidant.

Neither methyl benzoate nor benzonitrile was produced within 1 hr at 27°C from 1 ml of benzaldehyde and 0.4 g of sodium hydroxide (or 0.5 g of sodium) in 10 ml of 2.4 N ammoniacal methanol. No methyl benzoate was found to be formed at room temperature within two days from 0.5 ml of benzaldehyde, 1 ml of triethylamine, and 0.8 g of iodine in 10 ml of methanol.

These observations suggest that the actual oxidant for the formation of methyl benzoate is not iodine, but some other reaction products of iodine and ammonia. Moreover, the charge-transfer complex between ammonia and iodine, which might be expected to exist in the reaction mixture, might not be the actual oxidant, for iodine with triethylamine could not oxidize benzaldehyde to methyl benzoate, as has been stated above, and the charge-transfer complex of iodine and triethylamine may be expected to be similar to that of iodine and ammonia.¹⁵⁾

11) J. S. Forrester, *Anal. Chem.*, **32**, 1668 (1960).

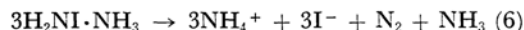
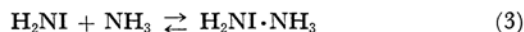
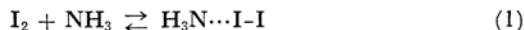
12) R. P. Bell and J. C. Clunie, *Trans. Faraday Soc.*, **48**, 439 (1952).

13) W. A. Mosher and D. M. Preiss, *J. Am. Chem. Soc.*, **75**, 5605 (1953).

14) G. R. Robertson, "Organic Syntheses," Coll. Vol. I, p. 138 (1941).

15) H. Yada, J. Tanaka and S. Nagakura, *This Bulletin*, **33**, 1660 (1960).

There have been several reports on the reaction between iodine and ammonia. Nagakura *et al.*¹⁵⁾ observed the formation of a charge-transfer complex between iodine and ammonia in heptane. In polar solvents, however, the charge-transfer complex would be unstable and would readily react further. Jander *et al.*¹⁶⁾ have studied the reaction of iodine with ammonia and suggested the following reaction steps:



They observed the precipitation of $\text{NI}_3\cdot\text{NH}_3$ when water was added to an ethanolic solution of iodine and ammonia. They also isolated iodamine at very low temperatures.¹⁷⁾

The present authors have found that the brown color of iodine faded immediately after the iodine was mixed with ammoniacal methanol, but the extent of fading was controlled by the amount of ammonium iodide added. The more ammonium iodide added, the deeper was the color of the iodine remaining (Fig. 6). This finding agreed with the description of Jander *et al.*¹⁶⁾ It seems probable that iodine and ammonia react to produce iodamine, the concentration of which is smaller when an additional amount of ammonium iodide is present. McAlpine¹⁸⁾ investigated by means

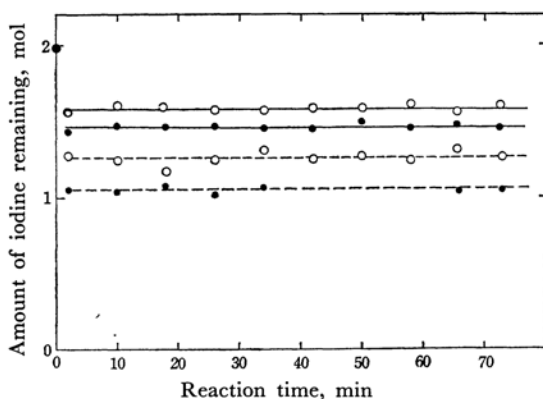


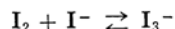
Fig. 6. Fading of the color of the mixture of iodine and ammonia in methanol.

Initial conditions: 10 ml of 0.849 N ammoniacal methanol, 1.98 ± 0.005 mmol of iodine, mmol (—●—), 0.66 mmol (---○---), 1.69 mmol (—●—), 2.46 mmol (---○---) of ammonium iodide, at 27°C

of colorimetry the fading of the color of iodine in water caused by the addition of ammonia; he concluded that the fading could be explained quantitatively by assuming the following reaction:

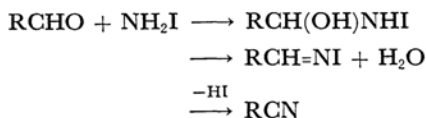


The finding that the addition of ammonium iodide caused a decrease in the rate of the formation of methyl benzoate as well as benzonitrile (Table 4, Figs. 3—4) suggests that the actual oxidant is not iodine but iodamine. In fact, the rate of the formation is related linearly to the reciprocal of the amount of ammonium iodide in the reaction mixture. There were still many ambiguous points regarding the real concentration of iodamine in the mixture. Of course, the iodide anion combines with iodine according to the following equation:



This fact does not, however, affect the conclusion that the concentration of iodamine decreases with an increase in the amount of ammonium iodide added. It was very difficult to analyse the reaction mechanism quantitatively, but it seems probable that the reaction of formation of methyl benzoate is first order in the concentration of iodamine.

As for the formation of benzonitrile, several possible reaction routes might be assumed. It is possible that the formation of benzonitrile proceeds through the addition of iodamine to the aldehyde as follows:



In fact, it is known that monochloramine adds to aldehydes to produce chloramines, which readily lose hydrogen chloride to yield nitriles under alkaline conditions.¹⁹⁾ This reaction route, however, could not explain the effect of the concentration of ammonia, the increase in the ratio of benzonitrile to methyl benzoate with the reaction time, and so on. Thus, most of the benzonitrile is probably produced through some other reaction processes.

It is possible that α -aminobenzyl alcohol from benzaldehyde and ammonia is oxidized by a certain oxidant. However, its oxidation would lead to benzamide instead of benzonitrile.

It is probable that benzilideneimine formed from α -aminobenzyl alcohol through dehydration is oxidized by iodamine to yield benzonitrile. The oxidant might not be iodine, judging from the effect of ammonium iodide.

As has previously been stated, benzaldehyde

16) J. Jander and U. Engelhardt, *Z. Anorg. Allgem. Chem.*, **B339**, 225 (1965).

17) *Ibid.*, **B341**, 146 (1965).

18) R. K. McAlpine, *J. Am. Chem. Soc.*, **74**, 725 (1952).

19) C. R. Hauser and A. G. Gillaspie, *ibid.*, **52**, 4517 (1930).

TABLE 8. THE REACTION STARTING FROM HYDROBENZAMIDE

Initial conditions: 10 ml of 2.14 N ammoniacal methanol, 3.20 ± 0.01 mmol of iodine, 3.34 mmol of hydrobenzamide, 10.7 or 43.0 mmol of water, at 0°C

H ₂ O		10.7 mmol	43.0
Reaction time			
0.5 hr	BA	0.84 mmol	0.90
	BN	1.48	1.39
	MB	0.0	0.0
1.0 hr	BA	0.97	0.51
	BN	1.48	1.52
	MB	0.0	0.0

BA: benzaldehyde unreacted

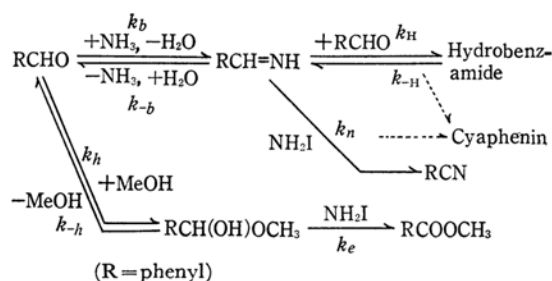
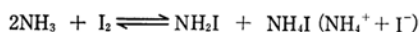
BN: benzonitrile formed

MB: methyl benzoate formed

and ammonia react to form the corresponding benzilideneimine, which then reacts further to yield hydrobenzamide. The fact that the existence of water had little effect on the yield of benzonitrile (Table 5) suggests that the oxidation step of benzilideneimine is so rapid that the reverse reaction of benzilideneimine with water to benzaldehyde and ammonia can be neglected, as compared to the oxidation step. The reaction of benzilideneimine to yield hydrobenzamide, though the detailed mechanism is not clear, is very rapid and would be a competitive reaction to the oxidation of benzilideneimine. Benzilideneimine could be produced from hydrobenzamide also, and, in fact, some benzonitrile and a very little methyl benzoate are formed from hydrobenzamide and water under reaction conditions similar to those adopted for the reaction starting from benzaldehyde (Table 8). Besides, the fact that very little methyl benzoate is produced justifies the assumption that benzonitrile is produced from benzilideneimine, while methyl benzoate is produced from the hemiacetal formed from benzaldehyde. Besides, the possibility of the formation of benzonitrile from hydrobenzamide might be one reason for the increase in the ratio of benzonitrile to methyl benzoate with the reaction time.

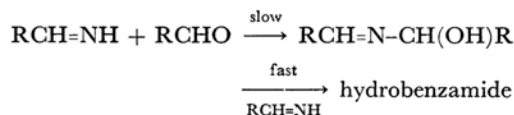
Cyaphenin was obtained in a small yield when the reaction was carried out for a long time. The possibility that cyaphenin is formed through the trimerization of benzonitrile was eliminated by the following qualitative observations. Hydrobenzamide with water produces cyaphenin in a small yield in methanol containing ammonia and iodine, but benzonitrile under similar conditions does not produce it even in traces.

On the basis of these discussions, the mechanistic scheme may be suggested.



Scheme. The reaction route.

Provided that the differential of the concentration of benzilideneimine to time, and that of the methyl hemiacetal of benzaldehyde, can be estimated to be zero, the following equations can be deduced. The reaction rate of benzilideneimine to hydrobenzamide was presumed for convenience to be first-order in the concentrations of benzilideneimine and benzaldehyde, as the mechanism of this step had not been made clear. This assumption corresponded to the following reaction route:



The reverse reaction was assumed to proceed according to the equation:

$$\frac{d[\text{benzilideneimine}]}{dt} = k_{-H}[\text{hydrobenzamide}]^p$$

("p" is an undetermined power, larger than zero)

$$-d[\text{BA}]/dt = [\text{BA}](k_b[\text{NH}_3] + k_e k_h [\text{MeOH}][\text{NH}_2\text{I}]/(k_{-h} + k_e[\text{NH}_2\text{I}])) \quad (1)$$

$$\begin{aligned} \frac{d[\text{BN}]}{dt} &= k_n[\text{NH}_2\text{I}](k_b[\text{BA}][\text{NH}_3] \\ &\quad + k_{-H}[\text{HB}]^p)/(k_n[\text{NH}_2\text{I}] + k_H[\text{BA}]) \end{aligned} \quad (2)$$

$$\begin{aligned} \frac{d[\text{MB}]}{dt} &= k_e k_h [\text{MeOH}][\text{BA}][\text{NH}_2\text{I}]/ \\ &\quad (k_{-h} + k_e[\text{NH}_2\text{I}]) \end{aligned} \quad (3)$$

$$\begin{aligned} \frac{d[\text{BN}]}{d[\text{MB}]} &= k_n(k_b[\text{BA}][\text{NH}_3] \\ &\quad + k_{-H}[\text{HB}]^p)(k_{-h} + k_e[\text{NH}_2\text{I}])/ \\ &\quad k_e k_h [\text{MeOH}][\text{BA}](k_n[\text{NH}_2\text{I}] + k_H[\text{BA}]) \end{aligned} \quad (4)$$

$$\begin{aligned} \frac{d[\text{HB}]}{dt} &= k_H[\text{BA}](k_b[\text{BA}][\text{NH}_3] \\ &\quad + k_{-H}[\text{HB}]^p)/(k_n[\text{NH}_2\text{I}] + k_H[\text{BA}]) \\ &\quad - k_{-H}[\text{HB}]^p \end{aligned} \quad (5)$$

$$[\text{NH}_2\text{I}] \propto [\text{NH}_3]^2[\text{I}_2]/[\text{NH}_4\text{I}]^q \quad q=1-2$$

$$k_b, k_{-b} = \text{function } ([\text{NH}_4\text{I}], [\text{NaOH}], [\text{NH}_3])$$

$$k_h, k_{-h} = \text{function } ([\text{NH}_3], [\text{NaOH}], [\text{NH}_4\text{I}])$$

BA: benzaldehyde, BN: benzonitrile, MB: methyl benzoate, HB: hydrobenzamide

In the earlier steps of the reaction, that is, when the concentration of hydrobenzamide can be neglected, these equations can be simplified as follows:

$$d[\text{BN}]/dt = k_n k_b [\text{NH}_2\text{I}][\text{BA}][\text{NH}_3]/(k_n [\text{NH}_2\text{I}] + k_H [\text{BA}]) \quad (2')$$

$$d[\text{BN}]/d[\text{MB}] = k_n k_b [\text{NH}_3](k_{-h} + k_e [\text{NH}_2\text{I}])/k_e k_h [\text{MeOH}](k_n [\text{NH}_2\text{I}] + k_H [\text{BA}]) \quad (4')$$

$$d[\text{HB}]/dt = k_b k_H [\text{BA}]^2 [\text{NH}_3]/(k_n [\text{NH}_2\text{I}] + k_H [\text{BA}]) \quad (5')$$

These equations are compatible with all the experimental results, at least qualitatively.

For example, judging from Eq. (4), an increase in the concentration of ammonia may result in an increase in the ratio of benzonitrile to methyl benzoate. This prediction proved to be correct in Table 1. On the contrary, the variation in the concentrations of iodine and ammonium iodide may have little effect on the ratio, because the factor of the concentration of iodamine appears identically in both the numerator and the denominator of Eq. (4) (the changes in the constants of reaction rate due to the changes of the concentration of ammonium iodide may mostly cancel each other out (for example, k_b versus k_h)). The variation in the initial concentration of benzaldehyde may have little effect on the ratio, which should be observed at a reaction time when the reaction has considerably proceeded, because the larger concentration of hydrobenzamide (in the numerator of Eq. (4)) caused by the larger initial concentration of benzaldehyde may cancel the larger concentration of benzaldehyde at the time (in the denominator of Eq. (4)). The increase in the concentration of hydrobenzamide with the reaction time may result in an increase in the ratio with the reaction time. These predictions are proved to be correct in Tables 2, 3 and 4.

The effect of the reaction temperature was very complex. In order to explain this effect completely, it is necessary to find the values of the activation energies of the all rate constants and the equilibrium constants of the formation of iodamine and the formation of the hemiacetal. For example, a smaller value of $K_h (=k_h/k_{-h})$ at a higher temperature would result in a larger ratio of benzonitrile to methyl benzoate ((4), (4')).

Experimental

Materials. *Methanol.* Commercial methanol of a guaranteed reagent grade was used for the A series, and that of a reagent grade was used for the B series, without any further purification. (Notations such as A, B, A-1, A-2, and A-3 will be explained later.)

Benzaldehyde. For the A-2 series: Commercial benzaldehyde of a guaranteed reagent grade was distilled under reduced pressure in a nitrogen atmosphere just before use (bp 67°C/15 mmHg, n_D^{20} 1.327). Gas chromatographic analysis proved that there were no peaks other than that of the aldehyde (conditions: column, 10% carbowax on diasolid M 2 m; column temperature, 160°C; hydrogen flame detector). For

the A-3 and B series: Commercial benzaldehyde of a reagent grade, similarly treated, was used.

Ammonia. Ammonia obtained commercially in a bomb was freed from moisture through a packed column of potassium hydroxide grains. For the A series, it had previously been dissolved in methanol to a certain concentration, as analyzed by titration with 1 N hydrochloric acid (bromothymol blue indicator).

Iodine. Commercial iodine of a guaranteed reagent grade was used for the A-2 series, and that of a reagent grade was used for the A-1, A-3 and B series, without any further purification.

Hydrobenzamide. Hydrobenzamide was synthesized from benzaldehyde and ammonia (mp, 101–101.5°C, lit.⁸ 100–102°C).

Other Reagents. Sodium thiosulfate, ammonium iodide, and sodium hydroxide (for the A-2 series) were of a guaranteed reagent grade. Sodium hydroxide (for the B series), ether, and 1-heptanol were of a reagent grade. These reagents were commercially obtained and were used without any further purification. The water was purified by ion-exchange processes.

Experimental Method A-1 (The Reaction of Iodine with Ammonia). Into 10 ml of 0.849 N ammoniacal methanol were dissolved 0.503–0.504 g (ca. 1.98 mmol) of iodine and some ammonium iodide. At constant intervals 0.1-ml samples of the mixture were taken out, and the sampled portion was diluted with 20 ml of methanol. The absorbance of the solution was measured through a 540 mμ filter (Beckman B type) by using a colorimeter (Hirama Rika Kenkyujo Type KD-165). The amount of iodine was calculated with a calibration curve prepared under similar conditions. The effect of ammonium iodide itself on the coefficient of the absorbance was negligibly small over the region of the measured wavelength.

Experimental Method A-2 (Tables 1–8). *The Effect of the Concentration of Ammonia.* A stoppered test tube containing 10 ml of methanol with ammonia dissolved in it at a given concentration (0–2.56 N) was placed in an ice-water bath, and 0.816–0.819 g (ca. 3.21 mmol) of iodine was added to the solution. After 30 min, 0.5 ml (5 mmol) of benzaldehyde was added to start the reaction. After a certain length of time had passed, 1-ml samples of the mixture were taken out and added to 3 ml of an aqueous solution of sodium thiosulfate (15 g or 60 mmol of sodium thiosulfate and 100 ml of water). Five milliliters of diethyl ether were then added to extract the organic components of the mixture. The ethereal layer was separated, and to it there was added 1 ml of ether containing a certain amount of 1-heptanol as a standard material for gas chromatographic analysis. The ether was distilled off under atmospheric pressure, and the concentrated liquid was analyzed by means of gas chromatography. The conditions were: 10% glutaronitrile on diasolid L 2 m; column temperature, 110°C. The calibration curve was prepared similarly.

The Effect of the Concentration of Iodine. The procedure used was the same as that used in examining the effect of the concentration of ammonia, except that the concentration of ammonia was fixed at 2.56 N, while the amount of iodine varied from 1.62 mmol to 6.40 mmol.

The Effect of the Concentration of Benzaldehyde. The procedure used was the same as that used in examining

the effect of the concentration of ammonia, except that the concentration of ammonia was fixed at 2.56 N, the concentration of iodine was fixed at 3.21 mmol (0.816–0.820 g)/10 ml, and the amount of benzaldehyde varied from 10 mmol to 3 mmol.

The Effect of the Addition of Ammonium Iodide. The procedure used was the same as that used in examining the effect of the concentration of ammonia, except that the amounts of ammonia, benzaldehyde and iodine were fixed at 2.14 N, 10 mmol, and 3.21 mmol (0.815–0.822 g) respectively and the desired amounts of ammonium iodide (0–10.0 mmol) were added at the beginning.

The Effect of Water. The method used was the same as that used in examining the effect of ammonium iodide. A certain amount of water was added to the ammoniacal methanol at the beginning.

The Effect of Sodium Hydroxide. The procedure used was the same as that used in examining the effect of ammonium iodide, except that the amount of iodine used was 2.50 g (10 mmol) instead of 0.815 g (3.21 mmol) and there was no ammonium iodide. The amount of sodium hydroxide added was either 10.1 mmol or 0 mmol.

The Effect of the Reaction Temperature. A test tube was filled with 10 ml of 2.14 N ammoniacal methanol containing 0.404 g (10.1 mmol) of sodium hydroxide and placed in a thermostat controlled at a desired temperature within $\pm 0.1^\circ\text{C}$. The analytical procedure was the same as that used in examining the effect of ammonium iodide.

The Reaction of Hydrobenzamide. To 10 ml of 2.14 N ammoniacal methanol there were added some water and 0.815 g (3.21 mmol) of iodine at 0°C (in an ice-water bath). After 30 min, 0.95 g (3.3 mmol) of hydrobenzamide was added to the solution. The analytical procedure was the same as has been described above.

Experimental Method A-3 (Figs. 1–5). A test tube equipped with a stopper was filled with 10 ml of ammoniacal methanol (2.56 N, 0.849 N, 0.463 N or 0.304 N), iodine (1.0, 1.97 or 1.5 mmol), additives where needed, and a certain amount of 1-heptanol (*ca.* 0.06 g–0.08 g) as an internal standard for gas chromatographic analysis. The test tube was then placed in a thermostat. After 30 min, a certain amount of benzaldehyde was added to start the reaction. At constant intervals thereafter a portion was sampled out and introduced instantaneously into the inlet tube of the gas chromatograph (column: carbowax 4000 on diasolid M 2 m; column temperature, 160°C ; hydrogen flame detector). As the stationary liquid, carbowax 4000, could not distinguish the peaks of benzonitrile and methyl benzoate, the sum of the two products was quantitatively analysed. The calibration curve was prepared similarly. The relative sensitivity of benzonitrile was almost the same as that of methyl benzoate.

The effect of the presence of iodine (0 or 1.97 mmol) and ammonium iodide (0 or 4.92 mmol) on the rate of the consumption of benzaldehyde, the effect of the ammonium iodide added (0–1.20 mmol), and the dependence of the rate on the initial concentration of benzaldehyde were studied. In the experiments concerning the effect of the addition of ammonium iodide and the effect of the concentration of benzaldehyde, the peak assigned to the two products was considered

to nearly entirely consist of pure methyl benzoate, judging from the low concentration of ammonia in these experiments (*cf.* Tables 1–4).

The dependence of the reaction rate on the concentration of benzaldehyde was estimated by the following procedure. Several reactions were performed, the amounts of benzaldehyde being varied. The concentrations of all the reagents except benzaldehyde were kept constant. The concentrations of the product were then plotted against the time. The rate of the reaction at the point when a certain fixed amount of the aldehyde was consumed was calculated from the slope of the tangent drawn at this point on the curve obtained by plotting the concentrations of the products against the time. The values of the rates of reaction thus obtained were then compared with the concentration of the aldehyde at this point.

Experimental Method B. In this series, the rate of the bubbling of ammonia into the reaction mixture was not rigorously controlled. The rate was, however, roughly 2–5 l/hr unless otherwise stated.

B-1) Methyl Benzoate. Twenty-four grams (0.6 mol) of sodium hydroxide were dissolved in 400 ml of methanol in a 500-ml flask. The flask was then chilled in an ice-water bath to below 5°C , and to it 32.5 g (0.3 mol) of benzaldehyde were added at one time. After 10 min had passed, the introduction of ammonia and the addition of iodine were started. Iodine, 91.2 g (0.36 mol) in total, was added in small portions over a 30-min period. The temperature was kept between 0°C and 10°C during the addition. For 30 min after the completion of the addition of iodine, ammonia gas was further bubbled in. The mixture was kept at 0 – 10°C for 2.5 hr after the end of the introduction of ammonia gas. Then the volatile reactants were distilled out under reduced pressure, and the residual mixture was extracted with 500 ml of ether. The ethereal part was treated with a sodium thiosulfate solution (75 g or 0.3 mol of sodium thiosulfate in 300 ml of water) and 100 ml of a saturated sodium bisulfite solution, and washed with pure water. The ethereal solution was then distilled; after the evaporation of the ether, 30.3 g (73%) of methyl benzoate were obtained. n_D^{26} 1.516, bp 90 – $91^\circ\text{C}/20$ mmHg. The infrared spectrum agreed with that of an authentic sample.

B-2) Benzonitrile. Throughout this experiment, ammonia was rapidly bubbled in (more than 5 l/hr). To 400 ml of methanol containing 12 g (0.3 mol) of sodium hydroxide, ammonia was bubbled in for 2 hr, and then 31.8 g (0.3 mol) of benzaldehyde were added at one time. After 30 min had passed, iodine, 91.5 g (0.36 mol) in total, was added in small portions over a 30-min period. The temperature was kept between 40°C and 60°C during the addition of iodine. After the mixture had been kept at about 40°C for 4 hr, the introduction of ammonia gas was stopped and the reaction mixture was treated much as in B-1). The obtained ethereal solution was distilled, and, after the evaporation of the ether, 25.3 g (82%) of benzonitrile were obtained. n_D^{15} 1.532, bp 78 – $79^\circ\text{C}/18$ mmHg. The infrared spectrum agreed with that of an authentic sample.

B-3) Benzonitrile with a Little Methyl Benzoate. To 400 ml of methanol ammonia was rapidly bubbled in (more than 5 l/hr). After 10 min, 32 g (0.3 mol) of

benzaldehyde was added at one time and then 76 g (0.3 mol) of iodine was added in portions over a 30-min period. During this addition, the solution was kept between 30°C and 50°C. Ammonia gas was continuously bubbled in for 2 hr after the end of the addition at about 30°C, and then the solution was refluxed for an additional hour. Twenty grams of a liquid (72°C/20 mmHg) were obtained by a treatment similar to that in B-1) (ca. 65%). The liquid was identified by the infrared spectra as benzonitrile containing 3% of methyl benzoate.

B-4) Methyl Benzoate with a Little Benzonitrile. To 400 ml of methanol containing 13.8 g (0.6 mol) of sodium, ammonia gas was rapidly bubbled in (more than 5 l/hr) for 30 min or so. To the solution there were added 32.2 g (0.3 mol) of benzaldehyde at one time and 91.2 g (0.36 mol) of iodine in portions over a 35-min period. The temperature was controlled below 20°C. Then, ammonia was continuously bubbled in for 2 hr below 20°C. The volatile reactants were removed *in vacuo* below 20°C, and the residue was extracted with 500 ml of ether. The ethereal layer, when treated as in B-1), gave 32.4 g of a liquid (83.2°C/19 mmHg—81°C/17.5 mmHg). The liquid was identified by the infrared spectra as methyl benzoate containing 4% benzonitrile.

B-5) Cyaphenin from Benzaldehyde. To 300 ml of methanol 92 g (0.36 mol) of iodine were added. The solution was kept at 40±5°C, and 32 g (0.3 mol) of benzaldehyde were added while ammonia was being introduced. The reaction was then carried out for 4 hr at 40±5°C, with the bubbling in of ammonia gas. After the end of the introduction of ammonia, the reaction mixture was kept at room temperature for 70 hr. Then the volatile parts were distilled off, and the residue was extracted with 500 ml of ether. After treatment as before, 0.6 g of a solid material was obtained, as well as 16.1 g of a liquid product. The solid was recrystallized from toluene. Yield, 0.4 g, mp 234.5—235°C. The infrared spectrum completely agreed with that of authentic cyaphenin (mp 231°C²²). The distillation of the liquid yielded a mixture of 4.8 g of methyl benzoate and 9.2 g of benzonitrile, which were identified by means of the infrared spectra.

B-6) Hydrobenzamide. To 10 ml of 2.14 N ammoniacal methanol there were added 0.815 g (3.21 mmol) of iodine, 1.456 g (10 mmol) of ammonium iodide, and 1 ml (10 mmol) of benzaldehyde. The

mixture was then kept at 0°C for 135 min. Five milliliters of the reaction solution were then separated, concentrated to 1 ml, treated with a sodium thiosulfate solution, and extracted with ether. After the evaporation of the ether, there remained 144 mg (ca. a 32% yield) of a white solid (mp 97.4—99.9°C). The infrared spectrum of this solid agreed with that of authentic hydrobenzamide.

B-7) Benzamide and Benzoic Acid. In the infrared spectra of the materials from ether extracts or those from ether extracts of acidified aqueous solutions of the reaction mixtures in B-1—6), there were no distinct absorptions which could be assigned to benzamide and/or benzoic acid.

B-8) Cyaphenin from Hydrobenzamide. Two grams of benzonitrile were added to a mixture of 20 ml of 2.14 N ammoniacal methanol, 5 g of iodine, and 1 ml of water. The solution was kept at room temperature for 5 days and then concentrated; the concentrate was treated with a thiosulfate solution, and the organic components were extracted with ether. After the evaporation of the ether, 1 g of a liquid was obtained; its infrared spectrum was identical with that of benzonitrile. No cyaphenin was found.

When 1.9 g of hydrobenzamide were used in place of benzonitrile as the starting material, there were found 0.5 g of a mixture of benzonitrile, benzaldehyde, and methyl benzoate and about hundred mg of a solid. The solid thus obtained melted at 234°C after recrystallization from toluene, and its infrared spectrum was identical with that of authentic cyaphenin.

B-9) Reaction in Diethyl Ether. To 300 ml of ether 92 g (0.36 mol) of iodine were added, and ammonia gas was bubbled in under 10°C. Thirty-two grams (0.3 mol) of benzaldehyde were then added to the mixture over a 15-min period. Ammonia was bubbled in below 10°C for 4 hr, and then the mixture was kept at 0—10°C for one day. After treatment with a thiosulfate solution and the evaporation of the ether, 5.5 g of a liquid were obtained; this liquid gave 4.0 g (13%) of benzonitrile upon distillation (bp 189—190°C, n_D^{22} 1.529; the infrared spectrum was identical with that of an authentic sample). Besides, 14.5 g of a solid was obtained; this solid was hardly soluble in either ether or water. In this solid a small amount of cyaphenin was found; a part of it was isolated by means of fractional crystallization in ether and recrystallized from toluene, mp 234.9°C.