[Chem. Pharm. Bull. 15(6) 774~785 (1967)]

UDC 547.574.04 : 547.298.1.04

95. Minoru Sekiya, Akira Hara, Keiichi Ito, Jiro Suzuki, and Kozo Tanaka : Reaction of Amide Homologs. XVIII.[*1] Catalytic Hydrogenation of N-Arylmethylene-1-acylamino-1-arylmethylamines and Hydroamides in the Presence of Formamide and Related Studies.

(*Shizuoka College of Pharmacy*[*2])

Catalytic hydrogenations of both series of the compounds, N-arylmethylene-1-acylamino-1-arylmethylamines and hydroamides, over Raney nickel catalyst were examined under both conditions, in the presence of formamide and in the absence of it. While under the latter condition either of the hydrogenations proceeded to give secondary amine at least as one of the principal reduction products, under the former condition resulted in the predominant formation of N-formylated primary amine. In correlation with the previously reported azomethine-formamide hydrogenation the reaction paths for the hydrogenations influenced by formamide were revealed to be of involving intermediates, azomethine, aldimine, and N-arylmethylene-1-formamido-1-arylmethylamine (in the case with hydroamides).

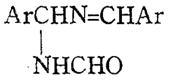
(Received August 6, 1966)

The catalytic hydrogenation of azomethine (Schiff's base) in the presence of formamide over Raney nickel catalyst under high hydrogen pressure at elevated temperature has been previously shown[1,2] to result in cleavage at the carbon-nitrogen double bond giving two N-formylated primary amines in excellent yield

$$\mathrm{ArCH{=}NR + H_2 + 2HCONH_2 \longrightarrow ArCH_2NHCHO + RNHCHO + NH_3} \quad (1)$$

and, in discussion of mechanism for the reaction, the reaction path involving the intermediate aldimine has been reached.[2]

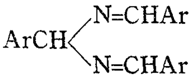
In continuation of our interest in these studies, attention was drawn to the surrounding compounds, N-arylmethylene-1-formamido-1-arylmethylamine (hereafter called AFA for short) and hydroamide (N,N′-diarylmethylene-1-arylmethylenediamine), which seemed likely also to have at least minor chance of forming as intermediates in the path of the foresaid azomethine-formamide hydrogenation, because the formation of the former is caused by the interaction[3] between azomethine and formamide and that of the latter by the self-conversion[4] of the intermediate aldimine. Both of the compounds still possess carbon-nitrogen double bond in their structures as azomethine has.



$$\begin{array}{l}\mathrm{ArCHN{=}CHAr}\\ \quad|\\ \mathrm{\ NHCHO}\end{array}$$

AFA

(N-Arylmethylene-1-formamido-1-arylmethylamine)



$$\mathrm{ArCH}\left\langle\begin{array}{l}\mathrm{N{=}CHAr}\\ \mathrm{N{=}CHAr}\end{array}\right.$$

Hydroamide

Hence, it seemed a problem how these compounds behave in the hydrogenation in the presence of formamide. As for hydroamide, there has been previously reported[1]

[*1] Part XVII. M. Sekiya, M. Tomie : This Bulletin, **15**, 238 (1967).

[*2] Oshika, Shizuoka (関屋 実, 原 明, 伊藤敬一, 鈴木次郎, 田中康三).

1) M. Sekiya, T. Fujita : Yakugaku Zasshi, **71**, 941 (1951).

2) M. Sekiya, A. Hara : This Bulletin, **11**, 895 (1963).

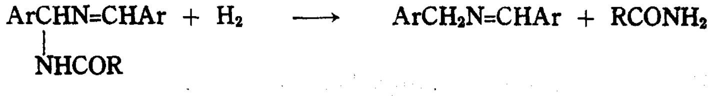
3) M. Sekiya, T. Oishi : *Ibid.*, **7**, 468 (1959).

4) M. Busch : Ber., **29**, 2137 (1896); H.H. Strain : J. Am. Chem. Soc., **49**, 1558 (1927).

only an example of the reaction with hydrobenzamide which resulted in the formation of N-benzylformamide nearly equivalent to three molar amount. Objective of the present paper was definitely to reveal behaviors of both series of the compounds, N-arylmethylene-1-acylamino-1-arylmethylamines (hereafter called AAA for short) and hydroamides, in the hydrogenation in the presence of formamide and to elucidate the mechanisms in correlation with the azomethine-formamide hydrogenation.

Influence of Formamide in Catalytic Hydrogenation of N-Arylmethylene-1-acylamino-1-arylmethylamine (AAA)

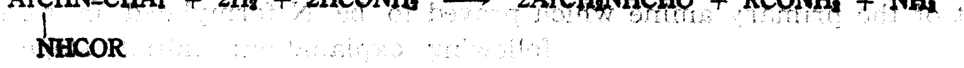
As to hydrogenation of the compound of this type, the hydrogenation over Raney nickel catalyst under high hydrogen pressure at elevated temperature and that over palladium-on-charcoal catalyst under ordinary hydrogen pressure at ordinary temperature have been previously demonstrated[5] with ethanolic solution of N-benzylidene-α-formamidobenzylamine. The former was reported to result in the formation of dibenzylamine (79% yield) and formamide, and the latter in the formation of N-benzylidenebenzylamine (84% yield) and formamide when hydrogen absorption was nearly stopped after uptake of one mole equivalent of hydrogen. Using palladium-on-charcoal catalyst, a selective hydrogenation similar to the latter has also been demonstrated[5] with N-benzylidene-α-formamido-4-methoxybenzylamine. In order to see whether under ordinary pressure at ordinary temparature Raney nickel catalyst could behave in the same fashion as palladium-on-charcoal catalyst does, a hydrogenation of the N-benzylidene-α-formamidobenzylamine over Raney nickel catalyst under the conditions was carried out. Very slow hydrogenation, taking uptake of one mole equivalent of hydrogen, resulted in the same formation of N-benzylidenebenzylamine and formamide. Thus, it becomes clear that major path of the hydrogenation of the representative AAA, N-benzylidene-α-formamidobenzylamine, over Raney nickel catalyst is initiated by the hydrogenolysis of the amide nitrogen-carbon single bond to give N-benzylidenebenzylamine and amide, and the complete hydrogenation under high hydrogen pressure transfers the former into dibenzylamine. Thus, the pathway would be realized by the following general sequence.



$$\underset{\displaystyle \text{NHCOR}}{\text{ArCH}}\text{N=CHAr} + \text{H}_2 \longrightarrow \text{ArCH}_2\text{N=CHAr} + \text{RCONH}_2 \qquad (2)$$

$$\text{ArCH}_2\text{N=CHAr} + \text{H}_2 \longrightarrow \text{ArCH}_2\text{NHCH}_2\text{Ar} \qquad (3)$$

As reported in earlier papers,[1,2] the catalytic hydrogenation of the mixture of azomethine and formamide over Raney nickel catalyst under high hydrogen pressure at elevated temperature has been known to result in the predominant formation of N-formylated primary amine, as illustrated by eq. 1. Therefore, when formamide was present in enough concentration in the high pressure hydrogenation of AAA, N-arylmethylene-1-arylmethylamine as the intermediate formed in the stage 2 was considered to undergo the reaction of eq. 1. Then, the hydrogenation of AAA in the presence of formamide was expected to result in the predominant formation of N-formylated primary amine, as could be written in the following equation obtained by summation of eq. 2 and 1 (R in eq. 1 is replaced by ArCH_2).



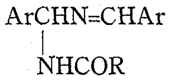
$$\underset{\displaystyle \text{NHCOR}}{\text{ArCH}}\text{N=CHAr} + 2\text{H}_2 + 2\text{HCONH}_2 \longrightarrow 2\text{ArCH}_2\text{NHCHO} + \text{RCONH}_2 + \text{NH}_3 \qquad (4)$$

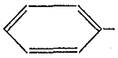
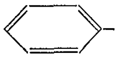
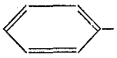
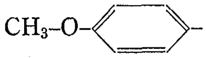
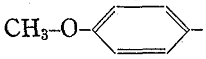
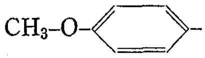
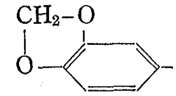
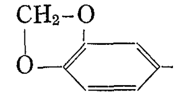
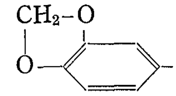
---

[5] M. Sekiya, T. Oishi: This Bulletin, 7, 855 (1959).

With this anticipation, a series of AAA were subjected to the catalytic hydrogenation in the presence of formamide and also in the absence of that for comparative studies. In brief, the general procedure was that the ethanolic solution was hydrogenated over Raney nickel catalyst under high hydrogen pressure at 130~135°. On carring out in the presence of formamide, one and a half fold as much as its theoretical amount based on eq. 4 was used in addition. Procedures and results of the experiments are summarized in Table I.

Table I. Influence of Formamide in Catalytic Hydrogenation[a] of N-Arylmethylene-1-acylamino-1-arylmethylamine under High Pressure

Substrate :

$$\underset{\displaystyle \mathrm{NHCOR}}{\mathrm{ArCH}}\mathrm{N{=}CHAr}$$

Substrate		Formamide	Product[b] (Mole equiv.[c])	
Ar.	R		$ArCH_2NH_2$	$(ArCH_2)_2NH$
	CH_3	absence	0.03	0.87
	CH_3	presence	1.78(N-Formyl)	trace(N-Formyl)
	H	absence	0.16 0.42(N-Formyl)	0.57
	H	presence	1.82	0.02[d]
	CH_3	absence	0.07	0.87
	CH_3	presence	1.58(N-Formyl)	0.13(N-Formyl)
	H	presence	1.60(N-Formyl)	0.11(N-Formyl)
	CH_3	absence	0	0.91
	CH_3	presence	1.73(N-Formyl)	0.06[d]
	H	presence	1.70(N-Formyl)	0.04[d]

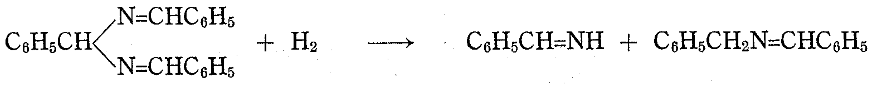
[a] General hydrogenation method and procedures are given in Experimental.
[b] N-Formyl : Product obtained as N-formylated compound.
[c] Mole equivalent of yield estimated from one mole of substrate.
[d] Products weighed as their hydrochloride by treatment with hydrochloric acid, as the direct products are little and impure. However, taking account of reactions between the amines and formamide, the high boiling or undistillable properties of the direct products are enough to assign them as N-formylated amines.

As can be seen, remarkable contrast between the hydrogenation in the presence of formamide and that in the absence was well demonstrated for each, as expected; the former resulted in the predominant formation of the N-formylated primary amine and the latter in that of the secondary amine.

As also seen in the product formation, the unmixed hydrogenation of the formamide analog, N-benzylidene-α-formamidobenzylamine, was somewhat distinguished from that of the acetamide analog, giving less amount of the secondary amine and more amount of the primary amine which proved to be N-formylated in part. This finding could be interpreted into the following explanation; initial stage of the hydrogenation, as anticipated in the foregoing, would give formamide and N-benzylidenebenzylamine according to eq. 2, and then both the compounds would in part react each other according to eq. 1, though the reacting formamide is deficient in amount to complete the reaction. In addition, we must again call attention to the previously reported hydrogenation$^{3)}$ of N-benzylidene-α-formamidobenzylamine under high hydrogen pressure, in which formation of the dibenzylamine in higher yield (79%) was reported. The reason for this result may be explained in that the applied conditions, in which the concentration of the reacting agents and the hydrogenation temperature were much lower than those presented herein, would be much less effective for the stage of eq. 1. Acetamide, as previously reported,$^{2)}$ is not so efficient as to effect the reaction 1 as formamide does. Though in a few runs the unmixed hydrogenation of acetamide analogs resulted in side formation of a very little amount of the primary amine, as indicated in Table I, the clear demonstrations to distinguish both unmixed and mixed hydrogenation could be best accomplished with these acetamide analogs.

Influence of Formamide in Catalytic Hydrogenation of Hydroamides

On survey of literature on catalytic hydrogenation of hydroamide a report$^{6)}$ has indicated that hydrogenation of hydrobenzamide (N,N′-dibenzylidenebenzylidenediamine) over Raney nickel catalyst under atmospheric hydrogen pressure at ordinary temperature proceeds to give N-benzylidenebenzylamine and benzylamine; the former exceeds the latter in molar amount. This phenomenon was also reaffirmed in this laboratory; the ethanolic solution was hydrogenated to give benzylamine and N-benzylidenebenzylamine in 1:1.7 molar proportion, when cease of hydrogen absorption was observed after uptake of the nearly equivalent of hydrogen. However, it has been also shown in another paper$^{7)}$ that under high hydrogen pressure at elevated temperature the hydrogenation over reduced nickel catalyst gave dibenzylamine and benzylamine in nearly 1:1 molar proportion. In this laboratory the almost same result was obtained in a similar hydrogenation procedure using Raney nickel catalyst. Pathway of the hydrogenation can be reasonably considered, also as mentioned in the foresaid publication,$^{6)}$ to be that the initial step is hydrogenolysis of the carbon-nitrogen single bond to give benzaldimine and N-benzylidenebenzylamine and then is followed by hydrogenation of both the intermediates, where the hydrogenation of the former precedes that of the latter which is resisted in the ordinary pressure hydrogenation.



$$C_6H_5CH\left\langle\begin{matrix}N=CHC_6H_5\\N=CHC_6H_5\end{matrix}\right. + H_2 \longrightarrow C_6H_5CH=NH + C_6H_5CH_2N=CHC_6H_5$$

$$C_6H_5CH=NH + H_2 \longrightarrow C_6H_5CH_2NH_2$$

$$C_6H_5CH_2N=CHC_6H_5 + H_2 \longrightarrow C_6H_5CH_2NHCH_2C_6H_5$$

The ascendant formation of N-benzylidenebenzylamine in the ordinary pressure hydrogenation can be interpreted into the following. In the course of the hydrogenation of benzaldimine to benzylamine, both the compounds could, in part, react each other to give N-benzylidenebenzylamine with liberation of ammonia ($C_6H_5CH=NH + C_6H_5CH_2NH_2 \rightarrow C_6H_5CH=NCH_2C_6H_5 + NH_3$) as like as the azomethine-amine exchange reaction reported previously,$^{8)}$ or, as indicated in the above-mentioned literature,$^{6)}$ benzaldimine could in part turn back to hydrobenzamide ($3\ C_6H_5CH=NH \rightarrow C_6H_5CH(N=CHC_6H_5)_2 + NH_3$) and then cycle the primary course. As the ordinary pressure hydrogenation was very slow, the above proposal appeared reasonable. In contrast, the high pressure hydrogenation was very rapid. Accordingly the side-paths could be retarded in this

---

6) G. Mignonac: Compt. rend., **171**, 1149 (1920).
7) C.F. Winaus, H. Adkins: J. Am. Chem. Soc., **54**, 306 (1932).
8) M. Sekiya, A. Hara, T. Masui: This Bulletin, **11**, 277 (1963).

case and on this account the formations of benzylamine and dibenzylamine in the nearly 1:1 molar proportion would be allowed.

3,4:3′,4′:3″,4″-Tris(methylenedioxy)hydrobenzamide, elected as another model hydroamide analog, was as well hydrogenated in the same fashion as hydrobenzamide, in the high pressure hydrogenation, to give 3,4-methylenedioxybenzylamine and 3,4:3,′4′-bis(methylenedioxy)dibenzylamine in nearly 1:1 molar proportion, though the ordinary pressure hydrogenation, very slow as it was, was impossible to be stopped before the hydrogenation of the likely intermediate, N-(3,4-methylenedioxybenzylidene)-3,4-methylenedioxybenzylamine, resulting in the formation of the same compounds in 1:9 molar proportion. The asendant formation of 3,4:3′,4′-bis(methylenedioxy)dibenzylamine, however, may be safely interpreted to proceed through the azomethine intermediate which is expected to be ascendant in formation, as described for N-benzylidenebenzylamine in the hydrogenation of hydrobenzamide. Therefore, the foresaid proposal for the hydrogenation path as to hydrobenzamide could not be excluded also for this case.

Thus, in general, the catalytic hydrogenation of hydroamide under high hydrogen pressure at elevated temperature can be realized to give primary and secondary amines in nearly 1:1 molar proportion and the reaction path can be said to be initiated by the hydrogenolysis of the carbon-nitrogen single bond.

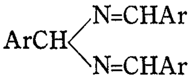
$$\mathrm{ArCH(N{=}CHAr)_2 + 3H_2 \longrightarrow ArCH_2NH_2 + ArCH_2NHCH_2Ar} \qquad (5)$$

In a previous paper,[1] hydrogenation of hydrobenzamide in the presence of formamide has been reported to result in the predominant formation of N-benzylformamide. In connection to our studies on azomethine-formamide hydrogenation, our attention was again called in mechanistic viewpoint to the influence of the presence of formamide in the hydrogenation of hydroamide.

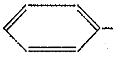
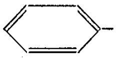
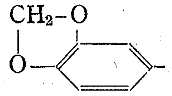
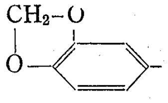
High pressure hydrogenation of the representative hydroamides, hydrobenzamide and 3,4:3′,4′:3″,4″-tris(methylenedioxy)hydrobenzamide, in the presence of formamide was examined in comparison to the unmixed hydrogenation described in the foregoing. The procedure for the unmixed hydrogenation was that ethanolic solution of each of

Table II. Influence of Formamide in Catalytic Hydrogenation[a] of Hydroamide under High Pressure

Substrate :



$$\mathrm{ArCH}\begin{matrix}\diagup \mathrm{N{=}CHAr}\\ \diagdown \mathrm{N{=}CHAr}\end{matrix}$$

Ar.	Formamide	Product[b] (Mole equiv.[c])	
		ArCH$_2$NH$_2$	(ArCH$_2$)$_2$NH
	absence	0.90	0.92
	presence	2.71 (N-Formyl)	0
	absence	0.91	0.98
	presence	2.83 (N-Formyl)	0

a) General method and procedures are given in Experimental.
b) N-Formyl : Product obtained as N-formylated compound.
c) Mole equivalent of yield estimated from one mole of substrate.

the hydroamides was hydrogenated over Raney nickel catalyst under conditions similar to those for the high pressure hydrogenation of AAA described in the foregoing section. For carring out the mixed hydrogenation, formamide (one and a half fold as much as the theoretical amount based on eq. 6) was added to the starting hydrogenation mixture. The comparative results of the experiments of the two hydrogenation methods for each hydroamide are summarized in Table II, and are shown to be markedly distinguished from each other. As realized in the foregoing, hydroamide alone was hydrogenated according to eq. 5 and, in contrast, in the mixed hydrogenation the predominant formation of N-formylated primary amine nearly equivalent to three molar amount was attained. Taking account of uptake of three mole equivalent of hydrogen in the hydrogenation, the reaction may safely be represented by the following general equation.

$$\mathrm{ArCH(N{=}CHAr)_2 + 3HCONH_2 + 3H_2 \longrightarrow 3ArCH_2NHCHO + 2NH_3} \quad (6)$$

The catalytic hydrogenation[1,2] of azomethine in the presence of formamide over Raney nickel catalyst under high hydrogen pressure at elevated temperature results in the predominant formation of N-formylated primary amine, as illustrated in eq. 1. Taking account of this phenomenon, a possible pathway for the mixed hydrogenation of hydroamide (eq. 6) can be safely explained as follows. Hydroamide first suffers by hydrogenolysis of its carbon-nitrogen single bond to give N-arylmethylene-1-arylmethylamine and aldimine, as explained early. Then the former reacts with existing formamide according to the azomethine-formamide hydrogenation (eq. 1 where R is replaced by $\mathrm{ArCH_2}$) to give N-formylated primary amine, and, on the other side, the latter is hydrogenated and then formylated with formamide to give the same N-formylated amine. The whole path can be generally illustrated as follows.

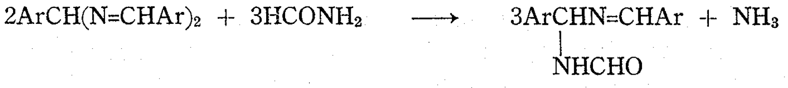
$$\mathrm{ArCH(N{=}CHAr)_2 + H_2 \longrightarrow ArCH_2N{=}CHAr + ArCH{=}NH} \quad (7)$$

$$\mathrm{ArCH_2N{=}CHAr + 2HCONH_2 + H_2 \longrightarrow 2ArCH_2NHCHO + NH_3} \quad (8)$$

$$\mathrm{ArCH{=}NH + H_2 \longrightarrow ArCH_2NH_2} \quad (9)$$

$$\mathrm{ArCH_2NH_2 + HCONH_2 \longrightarrow ArCH_2NHCHO + NH_3} \quad (10)$$

However, in addition to this pathway there was considered another pathway to be also possible for the mixed hydrogenation of hydroamide. In earlier papers[9,10] from this laboratory, has been reported facile conversion of hydroamide to AFA in good yields by heating with formamide at a boiling water bath temperature. This reaction has been actually demonstrated with hydrobenzamide[9] and 3,4:3′,4′:3″,4″-tris(methylenedioxy)hydrobenzamide.[10] These phenomena imply another pathway which proceeds through AFA as intermediate, since this compound is hydrogenated in the presence of formamide to give N-formylated amine, as described in eq. 4 of which the pathway was explained in the preceding section. On referring to the previous paper,[9] the conversion sequence from hydroamide to AFA could be represented as follows.



$$\mathrm{2ArCH(N{=}CHAr)_2 + 3HCONH_2 \longrightarrow 3Ar\underset{\displaystyle NHCHO}{\underset{|}{C}H}N{=}CHAr + NH_3}$$

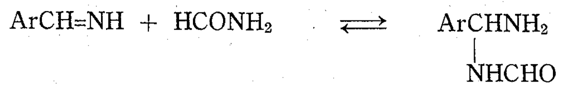
A pathway of this reaction was previously reported[9] to be led through intermediate, aldimine, being initiated by catalytic action of ammonia.

---

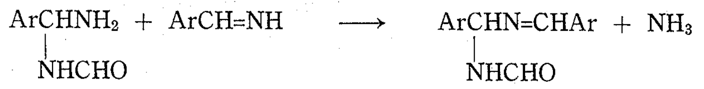
[9] M. Sekiya, A. Hara: This Bulletin, **11**, 901 (1963).

[10] M. Sekiya, K. Ito, M. Saito: *Ibid.*, **12**, 674 (1964).

$$\mathrm{ArCH(N{=}CHAr)_2 + NH_3 \rightleftarrows 3ArCH{=}NH} \qquad (11)$$

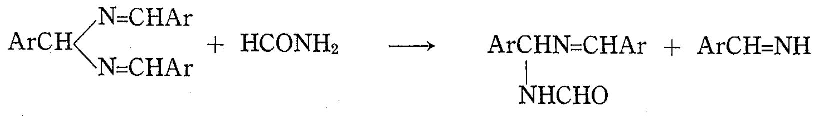


$$\mathrm{ArCH{=}NH + HCONH_2 \rightleftarrows \underset{\substack{|\\ NHCHO}}{ArCHNH_2}} \qquad (12)$$



$$\mathrm{\underset{\substack{|\\ NHCHO}}{ArCHNH_2} + ArCH{=}NH \longrightarrow \underset{\substack{|\\ NHCHO}}{ArCHN{=}CHAr} + NH_3} \qquad (13)$$

However, this pathway was lately considered not to be sufficient wholly to explain the reaction. Another possible pathway is to be initiated by direct attack of formamide as indicated in the following equation.



$$\mathrm{ArCH\!\left\langle\begin{matrix} N{=}CHAr \\ N{=}CHAr \end{matrix}\right. + HCONH_2 \longrightarrow \underset{\substack{|\\ NHCHO}}{ArCHN{=}CHAr} + ArCH{=}NH} \qquad (14)$$

The aldimine formed on the other side could move to eq. 12 followed by eq. 13 or to reverse direction of eq. 11 followed by eq. 14. The equation 14 could be accepted as like as the generalized initial stage ($\mathrm{ArCH{=}NR + HCONH_2 \rightarrow ArCH{=}NH + RNHCHO}$) of attack of formamide at carbon-nitrogen double bond which has been previously established[2] in the azomethine-formamide reaction, if the following involving steps would be allowed: $\mathrm{ArCH(N{=}CHAr)_2 + NH_3 \rightleftarrows \underset{\substack{|\\ N=CHAr}}{ArCHNH_2} + ArCH{=}NH; \underset{\substack{|\\ N=CHAr}}{ArCHNH_2} + HCONH_2 \longrightarrow \underset{\substack{|\\ N=CHAr}}{ArCHNHCHO} + NH_3}$. In the light of the above understanding as to pathways for the formation of AFA, the possible pathway for the mixed hydrogenation of hydroamide can be said to be that the reaction proceeds to give AFA possibly accompanied with aldimine, and then the former undergoes the reaction of eq. 4 to give N-formylated primary amine, and the latter is hydrogenated and then formylated with formamide to give the same N-formylated amine.

In a brief summay of the above discussion, there are considered two possible pathways for the hydrogenation of hydroamides in the presence of formamide, which are distinguishable by their initial stages. One is to be initiated by the hydrogenolysis of the carbon-nitrogen single bond to form the intermediates, N-arylmethylene-1-arylmethylamine and aldimine, and the other is to be initiated by direct action of formamide to form the intermediates, AFA and aldimine.

Conclusion and Related Discussion

After the earlier discussion together with the experimental results, the pathways for both the catalytic hydrogenations, in the presence of formamide or in the absence of it, as to AAA and hydroamide can be said rationally to be revealed as in the following. The high pressure hydrogenation of AAA with Raney nickel catalyst proceedes to begin with the hydrogenolysis at the amide nitrogen-carbon bond and the resulting N-arylmethylene-1-arylmethylamine is consecutively hydrogenated to the corresponding secondary amine, and, when formamide is present, undergoes the previously reported[1,2] azomethine-formamide hydrogenation to give N-formylated primary amine. The unmixed hydrogenation is represented by a combination of eq. 2 and 3, and the mixed one by a combination of eq. 2 and 1 (R in eq. 1 is replaced by $\mathrm{ArCH_2}$).

On the other hand, the high pressure hydrogenation of hydroamide is intiated by the hydrogenolysis of the carbon-nitrogen single bond to give N-arylmethylene-1-arylmethylamine and aldimine, and then the hydrogenations of both the intermediates are followed. When formamide is present, are considered two possible pathways; one is characterized by the course through the azomethine-formamide hydrogenation of the intermediate N-arylmethylene-1-arylmethylamine, being represented by a combination of eq. 7, 8, 9, and 10, and other is characterized by the course through the intermediate AFA formed by the direct attack of formamide on hydroamide.

Both hydroamide and AFA have close correlation with the previously reported azomethine-formamide hydrogenation.[1,2] The catalytic hydrogenation of azomethine in the presence of formamide over Raney nickel catalyst under high hydrogen pressure at elevated temperature has been known to proceed as indicated by eq. 1 and major reaction path of this reaction has also been established[2] as a combination of eq. 15, 9, and 10.

$$\mathrm{ArCH{=}NR + HCONH_2 \longrightarrow ArCH{=}NH + RNHCHO} \tag{15}$$

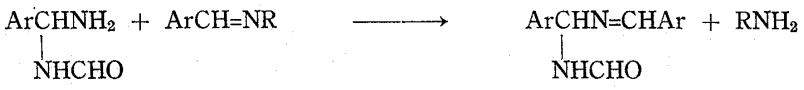
$$\mathrm{ArCH{=}NH + H_2 \longrightarrow ArCH_2NH_2} \tag{9}$$

$$\mathrm{ArCH_2NH_2 + HCONH_2 \longrightarrow ArCH_2NHCHO + NH_3} \tag{10}$$

However, without hydrogenation condition, the slower reaction has been known[3] to proceed with the mixture of azomethine and formamide on heating at boiling water bath temperature to give AFA.

$$\mathrm{2ArCH{=}NR + 3HCONH_2 \longrightarrow Ar\underset{\substack{|\\ NHCHO}}{C}HN{=}CHAr + 2RNHCHO + NH_3} \tag{16}$$

Formation path for this reaction has been explained[9] to be that the intermediate aldimine formed in eq. 15 suffers by eq. 12 and subsequently by eq. 13 or presumably by the following equation instead of eq. 13.



$$\mathrm{Ar\underset{\substack{|\\ NHCHO}}{C}HNH_2 + ArCH{=}NR \longrightarrow Ar\underset{\substack{|\\ NHCHO}}{C}HN{=}CHAr + RNH_2}$$

In addition, the intermediate aldimine is capable of facile self-conversion[4] to hydroamide shown by the reverse direction of eq. 11 and, on this account, a possible path through hydroamide is also considered for the reacton 16. As explained in the preceding section, this intermediate is conducted to the formation of AFA.

As explained in the above description, AFA is a product of the thermal reaction of azomethine-formamide mixture and also hydroamide is perceived to be a possible intermediate in its formation. Therefore, also in the azomethine-formamide hydrogenation indicated by the pathway of eq. 15, 9, and 10, though the hydrogenation was relatively rapid in general, AFA was considered to have at least minor possibility of forming, but the actual hydrogenation has been previously shown not to be contaminated by the production at all, resulting exclusively in the formation of N-formylated primary amine according to eq. 1. However, as realized by the results of the hydrogenation, in the presence of formamide, of AFA and of hydroamide, it is clearly revealed herein that fates of both compounds, even if they are formed in the azomethine-formamide hydrogenation, are conducted to the same formation of N-formylated primary amine.

In continuance from the previously reported paper,[2] all the major or minor possible reaction paths capable of existing in the azomethine-formamide hydrogenation have been described herein. With respect to representative N-benzylidene analogs, all the pathways are illustrated in Chart 1, where the arrows among the compounds enclosed by line, through the unstable intermediate aldimine or not, represent the actually demonstrated conversions. While the correlation among the compounds are complicated, it can be evidently said that the pathways are to be governed by the intermediate aldimine.

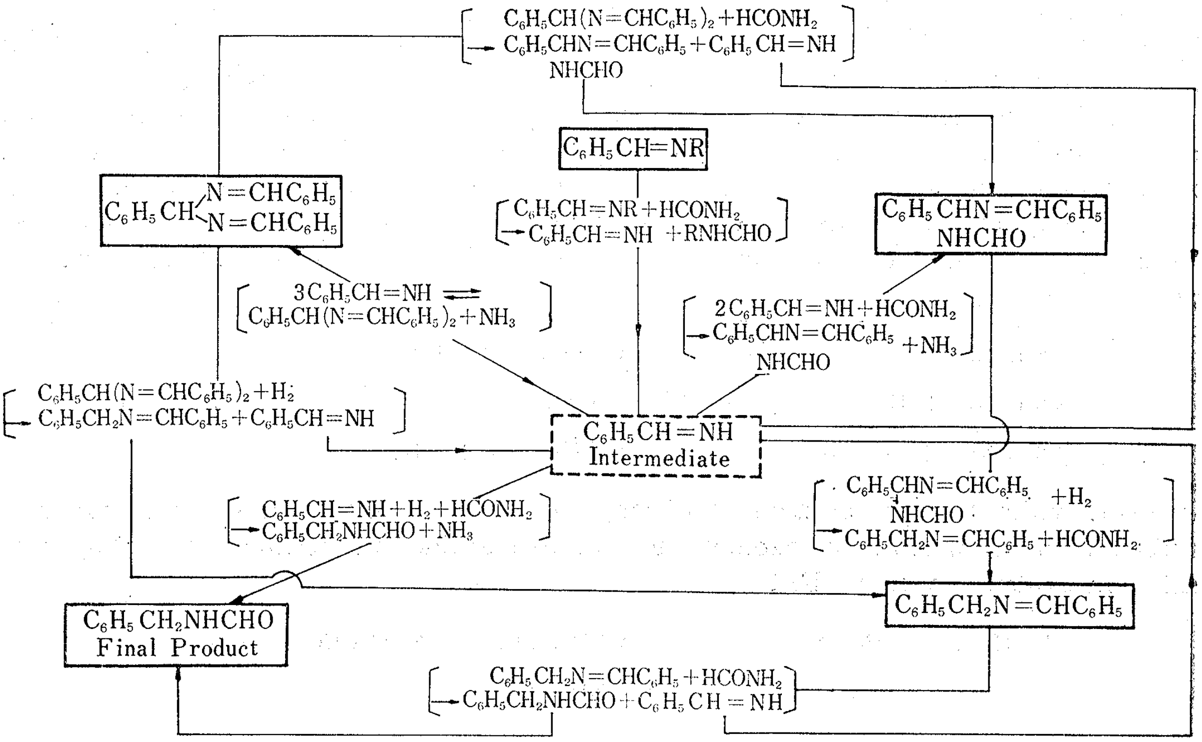


Chart 1. The Hydrogenation of a Variety of N-Benzylidene Compounds in the Presence of Formamide, leading to N-Benzylformamide

Experimental

Materials——The N-arylmethylene-1-acylamino-1-arylmethylamines were prepared according to the previously published papers and recrystallized to constant melting point: N-benzylidene-α-formamidobenzylamine,[9] m.p. 123～124°; N-benzylidene-α-acetamidobenzylamine,[9] m.p. 133～134°; N-(4-methoxybenzylidene)-α-acetamido-4-methoxybenzylamine,[9] m.p. 147～148°; N-(4-methoxybenzylidene)-α-formamido-4-methoxybenzylamine,[9] m.p. 154～155°; N-(3,4-methylenedioxybenzylidene)-α-acetamido-3,4-methylenedioxybenzylamine,[10] m.p. 142～143°; N-(3,4-methylenedioxybenzylidene)-α-formamido-3,4-methylenedioxybenzylamine,[10], m.p. 119～120°.

As hydroamides, hydrobenzamide, m.p. 101～103°, and 3,4:3′,4′:3″,4″-tris(methylenedioxy)hydrobenzamide, m.p. 170～171°, were used for the present studies. Both compounds were easily prepared by addition of the corresponding aldehydes to alcoholic NH_3, as well known.

Hydrogenation of N-Benzylidene-α-formamidobenzylamine under Ordinary Pressure——A solution of 7.1 g. (0.03 mole) of N-benzylidene-α-formamidobenzylamine dissolved in 100 ml. of EtOH was mixed with Raney nickel catalyst freshly prepared from 2 g. of 50% alloy and hydrogenated under ordinary pressure at ordinary temperature by usual method. Very slow absorption was nearly ceased after uptake of one mole equiv. of hydrogen in about 1330 min. After removal of catalyst by filtration and then, of EtOH by evaporation, the residual liquid was mixed with 15 ml. of H_2O and extracted with benzene. The benzene extract was dried over K_2CO_3 and, after evaporation of benzene, the residual liquid was distilled under reduced pressure to give a distillate, $b.p_3$ 135～142°, weighing 5.0 g., which proved to be N-benzylidenebenzylamine. Its IR spectrum was identical with that of an authentic sample, and comparison of the intensities of the characteristic absorption in its UV spectrum (UV: λ_{max}^{EtOH} 249 mμ (ε 20480), λ_{min}^{EtOH} 222 mμ (ε 6005)) with an authentic sample showed this material to be almost pure. Its derivative, dibromide, m.p. 139～140°, lit.,[11] m.p. 141～142°, which was obtained by treatment with Br_2 in dry ether, was also proved by its failure to depress the melting point of an authentic sample. *Anal.* Calcd. for $C_{14}H_{13}NBr_2$: C, 47.37; H, 3.69; N, 3.95. Found: C, 47.14; H, 3.68; N, 3.81. The foregoing aqueous layer was submitted to evaporation and

---

[11] M. A. Berg: Bull. soc. chim. France, **37**, 640 (1925).

then distillation under reduced pressure to give a liquid of b.p$_{17}$ 110∼111°, weighing 1.1 g., which proved to be formamide by comparison of its IR spectrum with an authentic sample.

Hydrogention of Hydrobenzamide under Ordinary Pressure——In the presence of Raney nickel catalyst prepared from 2 g. of 50% alloy a solution of 8.9 g. (0.03 mole) of hydrobenzamide dissolved in 230 ml. of EtOH was hydrogenated under ordinary hydrogen pressure at ordinary temperature. After uptake of less than two mole equiv. of hydrogen in about 450 min., hydrogen absorption was nearly ceased. After removal of the catalyst by filtration, EtOH was evaporated from the hydrogenation solution. The residual liquid was fractionally distilled under reduced pressure. The first distillate, b.p$_{21\sim22}$ 81∼83°, weighing 2.1 g., proved to be identical with benzylamine by comparison of its IR spectrum with an authentic sample. The hydrochloride, m.p. 253∼256°, was also confirmed by its failure to depress the melting point of an authentic sample. The second distillate, b.p$_5$ 149∼150°, weighing 6.6 g., proved to be almost pure N-benzylidenebenzylamine by comparison of its IR and UV spectrum with those of an authentic sample. The dibromide, m.p. 139∼140°, was identified by its failure to depress the melting point of an authentic sample.

Hydrogenation of 3,4:3′,4′:3″,4″-Tris(methylenedioxy)hydrobezamide——In the presence of Raney nickel catalyst prepared from 2 g. of 50% alloy a suspension of 12.9 g. (0.03 mole) of 3,4:3′,4′:3″,4″-tris-(methylenedioxy)hydrobenzamide in 400 ml. of EtOH was hydrogenated under ordinary pressure at ordinary temperature. Very slow and constant as the absorption was, it took 1055 min. until uptake of nearly three mole equiv. of hydrogen. After removal of the catalyst by filtration, the hydrogenation solution was concentrated under reduced pressure and crystals deposited were collected by filtration. This material, m.p. 108∼110°, weighing 9.4 g., proved to be identical with 3,4:3′,4′-bis(methylenedioxy)dibenzylamine. Recrystallization from EtOH gave an analytical sample, needles, m.p. 112∼114°, lit.,[12] m.p. 114°. *Anal.* Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91. Found : C, 67.61; H, 5.12; N, 4.74. Hydrochloride : m.p. 254∼256°, lit.,[13] m.p. 257°. *Anal.* Calcd. for $C_{16}H_{16}O_4NCl$: C, 59.72; H, 4.98; N, 4.35. Found : C, 59.61; H, 4.99; N, 4.47. The mother liquid was submitted to distillation under reduced pressure to give a liquid distillate, b.p$_4$ 115∼118°, weighing 0.7 g., of which IR spectrum was consistent with that of 3,4-methylenedioxybenzylamine. This was converted almost quantitatively to the hydrochloride, plates, m.p. 226∼227°, lit.,[14] m.p. 227°. *Anal.* Calcd. for $C_8H_{10}O_2NCl$: C, 51.25; H, 5.33; N, 7.47. Found : C, 51.15; H, 5.36; N, 7.64. The crystalline distillation residue was purified and proved to be identical with 3,4:3′,4′-bis-(methylenedioxy)dibenzylamine, weighing 2.2 g.

General Method for the Hydrogenation of N-Arylmethylene-1-acylamino-1-arylmethylamines under High Pressure

In an autoclave having a capacity of 175 ml. 0.05 mole each of the N-arylmethylene-1-acylamino-1-arylmethylamine, 15 ml. of EtOH and Raney nickel catalyst freshly prepared from 2 g. of 50% alloy, were placed. In the hydrogenations in the presence of formamide, 0.15 mole of formamide (1.5 fold in the theory) was added. Under 80 kg./cm^2 (at room temperature) of hydrogen, the whole was preheated and constant shaking was started at settled temperature of 130∼135°. Drop of hydrogen pressure was nearly ceased within a period of 10∼40 min. and then shaking and heating at this temperature were continued for further 30 min. The uptake of hydrogen was calculated nearly at three molar equiv. On cool, the hydrogenation mixture was taken out from the autoclave. Then, usually, catalyst was removed by filtration and the solvent, EtOH, was evaporated under reduced pressure. The residual mixture of the hydrogenation products was treated by the procedures described for each case in the following.

Procedures for Isolation of the Products

Hydrogention of N-Benzylidene-α-acetamidobenzylamine——a) In the absence of formamide : The residual mixture was fractionally distilled under reduced pressure. A first distillate, which, in part, solidified, was proved to be impure acetamide containing a little amount of benzylamine, which was isolated as its hydrochloride by means of extraction with benzene followed by treatment with HCl. The benzylamine hydrochloride, m.p. 252∼254°, weighed 0.2 g., which was identified by comparison of its IR spectrum with an authentic sample and mixed melting point test. Most of the residual liquid was distilled at 137∼141° under 3 mm. Hg. This material, weighing 8.6 g., proved to be dibenzylamine by comparison of its IR spectrum with an authentic sample and by mixed melting point test of its hydrochloride, m.p. 253∼256°.

b) In the presence of formamide : The residual mixture was fractionally distilled under reduced pressure. After an amide fraction was removed, a solid distillate, b.p$_3$ 142∼147° and m.p. 58∼60°, weighing 12.0 g., was obtained. This material proved to be N-benzylformamide by comparison of its IR spectrum with an authentic sample and mixed melting point test. Then, was obtained a little amount of a solid distillate, which was identified as N,N-dibenzylformamide by comparison of its IR spectrum with an authentic sample. Hydrolysis with 10% HCl gave dibenzylamine hydrochloride, m.p. 255∼257°, which was identified by mixed melting point test with an authentic sample.

---

12) J. Malan, R. Robinson : J. Chem. Soc., **1927**, 2653.
13) P. Pratesi, G. Castorina : C. A., **49**, 5468 (1955).
14) C. Mannich, R. Kuphal : Ber., **45**, 318 (1912).

Hydrogenation of N-Benzylidene-α-formamidobenzylamine——a) In the absence of formamide: The residual mixture was submitted to fractional distillation under reduced pressure. A little amout of the first distillate, b.p$_{13}$ 105～109°, proved to be impure benzylamine. This material was washed with 40% KOH and dissolved in benzene, and the clear benzene solution was concentrated and treated with HCl. Almost pure benzylamine hydrochloride, m.p. 250～253°, was obtained, weighing 1.2 g. Identification was made by comparison of its IR spectrum with an authentic sample and mixed melting point test. The second distillate, b.p$_4$ 136～139°, was regarded as a mixture of N-benzylformamide and dibenzylamine by the infrared spectroscopic measurement, where C=O stretching absorption band appeared at 1630 cm^{-1}. On cool, the distillate was added to 40 ml. of 10% aqueous HCl containing EtOH and the resulting precipitates were collected by filtration and washed with ether. This material, m.p. 250～254°, weighing 6.7 g., proved to be almost pure dibenzylamine hydrochloride by comparison of its IR spectrum and mixed melting point test. The above filtrate, after removal of ether, was refluxed for 30 min. and then concentrated to give crystals, m.p. 251～253°, weighing 3.0 g., which proved to be almost pure benzylamine hydrochloride by comparison of their IR spectra with an authentic sample and mixed melting point test.

b) In the presence of formamide: The residual mixture was fractionally distilled under reduced pressure. After removal of a formamide distillate, a solid distillate, b.p$_{0.02}$ 121～125°, m.p. 57～60°, weighing 12.2 g., was obtained. This material proved to be almost pure N-benzylformamide by comparison of its IR spectrum with an authentic sample and mixed melting point test. From a little amount of the last distillate 0.2 g. of dibenzylamine hydrochloride and 0.1 g. of benzylamine hydrochloride were isolated by hydrolysis with aqueous HCl and then by fractional crystallization.

Hydrogenation of N-(4-Methoxybenzylidene)-α-acetamido-4-methoxybenzylamine——a) In the absence of formamide: The residual mixture was submitted to fractional distillation under reduced pressure. The first distillate, which, in part, solidified, proved to be impure acetamide containing a little amount of 4-methoxybenzylamine, which was isolated as its hydrochloride by means of extraction with benzene followed by treatment with HCl. The hydrochloride, m.p. 226～229°, weighed 0.6 g. *Anal.* Calcd. for $C_8H_{12}ONCl$: C, 55.34; H, 6.97; N, 8.07. Found: C, 55.43; H, 6.86; N, 8.27. Most of the residue was distilled at 163～166° under 0.005 mm.Hg to give a solid distillate, m.p. 31～33°, weighing 11.2 g., which proved to be 4,4′-dimethoxydibenzylamine. Recrystallization from ether gave plates, m.p. 33～34°. *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.47; H, 7.51; N, 5.50.

b) In the presence of formamide: The residual mixture was submitted to distillation under reduced pressure. After removal of the amide fraction, a solid distillate, b.p$_{0.02}$ 150～152°, weighing 13.0 g., was obtained. This material proved to be N-(4-methoxybenzyl)formamide. Recrystallization from ether gave needles, m.p. 76～77°. *Anal.* Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.10; H, 6.53; N, 8.58. A little amount of the last distillate, b.p$_{0.01}$ 180～183°, weighing 1.8 g., proved to be N,N-(4,4′-dimethoxydibenzyl)formamide. Viscous liquid. *Anal.* Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.19; H, 6.58; N, 5.10.

Hydrogenation of N-(4-Methoxybenzylidene)-α-formamido-4-methoxybenzylamine——a) In the presence of formamide: The residual mixture was submitted to distillation under reduced pressure. After removal of a formamide distillate, was obtained a solid distillate, b.p$_{0.05}$ 154～158° and m.p. 73～75°, weighing 13.2 g., which proved to be almost pure N-4-methoxybenzylformamide by comparison of its IR spectrum with an authentic sample and mixed melting point test. The last distillate, b.p$_{0.03}$ 190～205°, weighing 1.6 g., proved to be almost pure N,N-(4,4′-dimethoxydibenzyl)formamide by comparison of its IR spectrum with an authentic sample.

Hydrogenation of N-(3,4-Methylenedioxybenzylidene)-α-acetamido-3,4-methylenedioxybenzylamine——a) In the absence of formamide: In this case crystals deposited in the hydrogenation mixture were dissolved on heating and then the catalyst was removed by filtration. After evaporation of EtOH, the residual mixture was submitted to distillation under reduced pressure. The first distillate which solidified was proved to be almost pure acetamide. Then, a solid distillate, b.p$_{0.02}$ 197～199°, and m.p. 96～98°, weighing 12.9 g., was obtained. This material proved to be 3,4:3′,4′-bis(methylenedioxy)dibenzylamine by comparison of its IR spectrum with an authentic sample and mixed melting point test.

b) In the presence of formamide: The residual mixture was submitted to distillation under reduced pressure. After removal of an amide fraction, was obtained a solid distillate, b.p$_{0.25}$ 180～184° and m.p. 91～93°, weighing 15.5 g. Recrystallization from MeOH gave an analytical sample, m.p. 96～97°, lit.,$^{15)}$ 106°, which proved to be N-(3,4-methylenedioxybenzyl)formamide. *Anal.* Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.22; H, 4.95; N, 8.03. Hydrolysis by refluxing with 10% HCl gave 3,4-methylenedioxybenzylamine hydrochloride, m.p. 225～227°, undepressed on admixture with an authentic sample. A little amount of the distillation residue was purified by extraction with benzene and then refluxed with 10% HCl. Concentration of the hydrolysis solution gave 1.0 g. of 3,4:3′,4′-bis(methylenedioxy)dibenzylamine hydrochloride, which was proved by comparison of its IR spectrum with an authentic sample and mixed melting point test.

---

15) P. Mastalgi, M. Métayer, G. de Bievre-Gallin: Bull. soc. chim. France, **1948**, 662.

Hydrogenation of N-(3,4-Methylenedioxybenzylidene)-α-formamido-3,4-methylenedioxybenzylamine——a) In the presence of formamide: The residual mixture was submitted to distillation under reduced pressure. After removal of a formamide distillate, a solid distillate, b.p$_{0.015}$ 167~170° and m.p. 92~95°, weighing 15.2 g., was obtained. This material proved to be identical with N-(3,4-methylenedioxybenzyl)formamide by comparison of its IR spectrum with an authentic sample and mixed melting point test. A little amount of the distillation residue was refluxed with 10% HCl. By concentration of the hydrolysis solution was obtained 3,4:3′,4′-bis(methylenedioxy)dibenzylamine hydrochloride, weighing 0.6 g., which was identified by comparison of its IR spectrum with an authentic sample and mixed melting point test.

General Method for the Hydrogenation of Hydroamides under High Pressure

The procedures of the hydrogenation operations were much the same as for those of N-arylmethylene-1-acylamino-1-arylmethylamines. Materials were 0.05 mole each of the hydroamides, 10 ml. of EtOH, and Raney nickel prepared from 2 g. of 50% alloy. In the hydrogenation in the presence of formamide, 0.225 mole of this was additionally used. Initial hydrogen pressure: 80 kg./cm^2 at room temperature. Settled hydrogenation temperature: 130~135°. Drop of hydrogen pressure was nearly ceased within a period of 5~10 min. The uptake of hydrogen was calculated nearly at two mole equiv. The content of the autoclave, usually, submitted to filtration to remove the catalyst and concentrated under reduced pressure to remove the solvent EtOH. The residual mixture of hydrogenation products was treated by the procedures described for each case in the following.

Procedures for Isolation of the Products

Hydrogenation of Hydrobenzamide——a) In the absence of formamide: The residual mixture was fractionally distilled under reduced pressure to give two kinds of distillates. The first distillate, b.p$_{35}$ 86~90°, weighing 4.8 g., had an identical IR spectrum with benzylamine. The hydrochloride, m.p. 251~253°, did not depress the melting point of an authentic sample with which it had an identical IR spectrum. The second distillate, b.p$_4$ 143~146°, weighing 9.1 g., had an identical IR spectrum with dibenzylamine. The hydrochloride, m.p. 253~255°, did not depress the melting point of an authentic sample which had an identical IR spectrum.

b) In the presence of formamide: The residual mixture was distilled under reduced pressure to give a solid distillate, b.p$_{0.1}$ 138~142°, m.p. 58~59°, weighing 18.3 g., which proved to be N-benzylformamide by comparison of its IR spectrum with an authentic sample and mixed melting point test.

Hydrogenation of 3,4:3′,4′:3″,4″-Tris(methylenedioxy)hydrobenzamide——a) In the absence of formamide: In this case were seen crystals deposited in the hydrogenation mixture which were dissolved on heating and then catalyst was removed by filtration. On cool, the crystals were collected by filtration, washed with EtOH, and weighed 10.3 g., which proved to be almost pure 3,4:3′,4′-bis(methylenedioxy)dibenzylamine by comparison of the IR spectrum with an authentic sample and mixed melting point test. The foregoing filtrate was concentrated and the residue was distilled under reduced pressure to give a distillate, b.p$_3$ 113~115°, weighing 6.9 g., which proved to be 3,4-methylenedioxybenzylamine. Melting point of its hydrochloride, m.p. 225~227°, was not depressed by admixture with an authentic sample. The residue, which remained undistilled, crystallized by washing with MeOH. Filtration gave crystals, m.p. 110~113°, weighing 3.6 g., which proved to be 3,4:3′,4′-bis(methylenedioxy)dibenzylamine by comparison of its IR spectrum with an authentic sample.

b) In the presence of formamide: In this case, crystals deposited in the hydrogenation mixture were dissolved on heating and then catalyst was removed by filtration. On cool, crystals were collected by filtration. The same crystals were further obtained by concentration of the filtrate. Total yield, 25.3 g. This material, m.p. 93~96°, proved to be N-(3,4-methylenedioxybenzyl)formamide by comparison of its IR spectrum with an authentic sample and mixed melting point test. Hydrolysis by refluxing with 10% HCl gave 3,4-methylenedioxybenzylamine hydrochloride, m.p. 225~227°, undepressed on admixture with an authentic sample.

The authors are indebted to Mr. K. Narita in this college for the elementary analyses.