[Chem. Pharm. Bull.
15(6) 802~815 (1967)]

UDC 547.298.1.04 : 547.574.04

99. Minoru Sekiya, Keiichi Ito, Akira Hara, and Jiro Suzuki :

Reaction of Amide Homologs. XIX.[*1] Thermal Reactions of Azomethines with Formates and Formamide.

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

Thermal reactions of the representative azomethines of N-benzylidene type with the reagents, trimethylammonium formate given by $5HCO_2H\cdot 2N(CH_3)_3$, ammonium formate and formamide, were examined in order to elucidate distinctions among them. The reduction and oxidation courses as to the formate reaction and the formamide reaction were definitely distinguished from each other; in the former reaction saturation of the azomethine double bond is induced by oxidation of formic acid to carbon dioxide and in the latter reaction reductive cleavage at the double bond, induced by self-oxidation of the azomethine, leads to the formation of the cleaved N-formylated primary amines. Elucidation on the mechanistic paths as to both of the essential reactions was investigated. Particularly, the pathways of the very complicated formamide reaction were declared to be of involving aldimine, hydroamide, N-arylmethylene-1-formamido-1-arylmethylamine and N,N'-arylmethylenebisformamide as major or minor intermediates.

(Received August 26, 1966)

Scattered reports have indicated the reduction of certain azomethines (Schiff's bases) on heating with formate and formamide. The general reaction with formate is that leads to the reduction of the carbon-nitrogen double bond to form the saturated secondary amine. This has been exemplified by the reaction1) of N-benzylideneaniline with a mixture of formic acid and triethylamine and also by the reaction2) of certain azomethines, derived from ethylenediamines and aromatic aldehydes, with formic acid in the presence of sodium formate. Use of formic acid as to N-benzylidenebenzylamine and N-benzylidenemethylamine has been reported3) to cause the hydrolysis giving benzaldehyde. On the other hand, the reactions of N-benzylidenebenzylamine and N-benzylidenemethylamine with formamide were reported by Sekiya, *et al.*,4) to proceed at higher temperature resulting in reductive cleavage of the carbon-nitrogen double bond to give mixture of N-formylated amines. Then, there seems to exist essential differences between the reduction reactions with formate and formamide.

We began with comparative studies among reactions of representative N-benzylidene analogs of azomethine with such reagents as trimethylammonium formate nevig by $5HCO_2H\cdot 2N(CH_3)_3$ (hereafter called TMAF for short), ammonium formate, and formamide. TMAF was first employed by Sekiya, *et al.*,5) for the formic acid reduction of N-amidomethyl compounds with the definite advantages of being constant high boiling liquid, b.p$_{18}$ 91~93° and of being less effective for the hydrolysis of the starting material. We elected this reagent in expectation of pure formate reaction. Ammonium formate is expected to behave as both formate and formamide, because this reagent is led to the dehydration equilibrium at elevated temperature ($HCO_2NH_4 \rightleftarrows HCONH_2 + H_2O$). Our objectives in the present investigation was to define the distinctions between the reactions with formate and formamide, and in further studies to elucidate

---

[*1] Part XVIII : This Bulletin, **15**, 774 (1967).

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

1) E.R. Alexander, R.B. Wildman : J. Am. Chem. Soc., **70**, 1187 (1948).

2) Z. Eckstein, A. Lukasiewicz : C.A., **54**, 24679, 24680 (1960); *Ibid.*, **55**, 3501 (1961).

3) H.T. Clarke, H.B. Gillespie, S.Z. Weisshaus : J. Am. Chem. Soc., **55**, 4571 (1933).

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

5) M. Sekiya, K. Ito : This Bulletin, **12**, 677 (1964).

Table I. Reactions[a] of N-Benzylideneamine with TMAF, Ammonium Formate and Formamide

N-Benzylideneamine	Reaction		Amine Product and Yield (mole equiv.[b])				Conversion[c] (%)
	Temp. (°C)	Time (min.)	N-Formylated prim. amine		N-Formylated sec. amine	tert. Amine	
With TMAF($5HCO_2H \cdot 2N(CH_3)_3$)							
N-Benzylideneaniline	120~125	140			N-Benzylformanilide 0.97		97
N-Benzylidene-benzylamine	120~125	45	N-Benzylformamide 0.17		N,N-Dibenzylformamide 0.58	Tribenzylamine 0.20	97
N-Benzylidene-cyclohexylamine	120~125	40		N-Cyclohexyl-formamide 0.14	N-Benzyl-N-cyclo-hexylformamide 0.61	N-Cyclohexyl-dibenzylamine 0.16	93 91
With Ammonium Formate							
N-Benzylideneaniline	120~125	360	N-Benzylformamide 0.34	Formanilide 0.52	N-Benzylformanilide 0.30		64 82
N-Benzylidene-benzylamine	120~125	80	N-Benzylformamide 0.52		N,N-Dibenzylformamide 0.35	Tribenzylamine 0.16	85
N-Benzylidene-cyclohexylamine	120~125	90	N-Benzylformamide 0.28	N-Cyclohexyl-formamide 0.48	N-Benzyl-N-cyclo-hexylformamide 0.34	N-Cyclohexyl-dibenzylamine 0.10	82 92
With Formamide[d]							
N-Benzylideneaniline	165~170	600	N-Benzylformamide 0.28	Formanilide 0.56	N-Benzylformanilide 0.07		35 63
N-Benzylidene-benzylamine	165~170	600	N-Benzylformamide 1.16		N,N-Dibenzylformamide 0.07		65
N-Benzylidene-cyclohexylamine	165~170	600	N-Benzylformamide 0.37	N-Cyclohexyl-formamide 0.47	N-Benzyl-N-cyclo-hexylformamide 0.05		42 52

[a] In each run, 0.1 mole of N-benzylideneamine substrate was used. General method and procedures are given in Experimental.

[b] Tenfold molar amount of yield.

[c] Percentage of the reductive conversion summing up the yields of the reduction amine products. For both runs of N-benzylideneaniline and N-benzylidenecyclohexylamine, there are written two values in a space; the upper value is for the N-benzylidene part and the lower is for the amine part.

[d] Particularly, in every run of these formamide reactions, resinous material was obtained as by-product, from which lophine, amaron and cyaphenine were obtainable.

the mechanistic differences between them for reaction path and the reducing sourse.

Distinctions among the Thermal Reaction of Azomethines with Trimethylammonium Formate (TMAF), Ammonium Formate, and Formamide

Three model azomethines of N-benzylidene type, N-benzylideneanilne, N-benzylidenebenzylamine, and N-benzylidenecyclohexylamine, were elected and subjected to each of reactions with TMAF, ammonium formate and formamide. The experiments and the results are summarized in Table I.

All the reactions were carried out under the settled conditions in that 0.1 mole each of azomethines was heated with constant stirring along with each of the reagents, formates and formamide, of which 2 moles as formic acid were used. In all runs with TMAF and with ammonium formate, the temperature was maintained at 120~125°, while the reaction was indicated by considerable evolution of carbon dioxide in addition to that of trimethylamine or ammonia. In all runs with formamide, higher temperature (165~170°) and longer reaction period (10 hours) were necessary, and almost no evolution of carbon dioxide but that of ammonia was observed. First of all, by this observation the formamide reaction was distinguished from the formate reactions indicating certainly that the reduction is not caused by carbon dioxide-forming oxidation of formamide or any formic acid source derived from it. Treatment of the reaction mixture gave a variety of N-formylated amines and tertiary amine as reduction products, that were varied in each run of all as shown in Table I. In the TMAF reduction, no other product but these reduction amines was observed, however, in the formamide reaction, in addition to the distillable amine products of which total yields were lower than those for the formate reaction, considerable amount of undistillable resinous residue was generally obtained. In the ammonium formate reaction, which is in a position between the formate and formamide reactions because of the dehydration equilibrium, nearly negligible amount of that was observed. As distinguished by no carbon dioxide evolution in the course of the formamide reaction, formamide appeared not to participate as a reducing agent in the reaction, therefore, the resinous material characteristic in the formamide reaction would be regarded as material involving oxidation products of the starting azomethines. In each run of the formamide reactions chromatography of the resinous material soluble in chloroform (a little amount of chloroform-insoluble blackish material was also obtained) through silica gel column using chloroform as an eluent gave several components. All of the components crystallized or not crystallized show in their infrared spectra characteristic peaks of benzene ring which bear evidence that the products are of being derived from the starting N-benzylideneamine. The crystallized materials were identified as amaron (2,3,5,6-tetraphenylpyrazine) and lophine (2,4,5-triphenylimidazole). For varying reaction periods sampling experiments with N-benzylidenebenzylamine specially showed changes in the undistillable residue. In a reaction for 5 hr. cyaphenine (2,4,6-triphenyl-s-triazine) was obtained in addition to amaron and lophine, for 10 hr. cyaphenine faded away from the three components, as mentioned above, and for 30 hr. the blackish insoluble material was increased occupying most of the residue, amaron being faded away and lophine being decreased. The formation of such compounds, amaron, lophine, and cyaphenine, from N-benzylideneamines would straightforwardly indicate oxidation of divalent benzylidene to trivalent phenylmethylidyne. Though we describe further discussion on this oxidation course in the succeeding section, the formamide reaction probably appeared to be regarded as self-oxidation-reduction reaction of the azomethines.

As for the reduction amine products, of which the sorts can be divided into N-formylated primary amine, N-formylated secondary amine and tertiary amine, the proportion of them was varied in each series of the reactions with TMAF, ammonium formate and formamide as shown in Table I. Determination of the product compositions relatively complicated was carried out by careful separation operations as described in Experimental, which were established beforehand by preliminary test using authentic samples and to predict reasonable accuracy the run was repeated at least twice. Comparison of the product compositions of the reactions with three

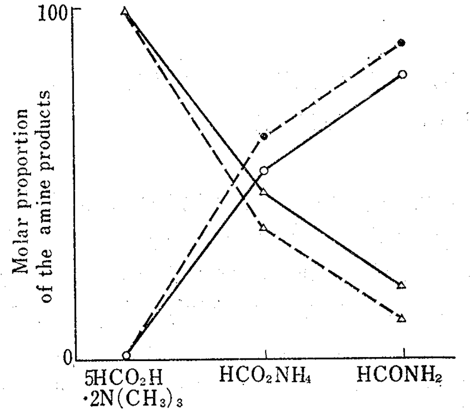


Fig. 1. Reactions of N-Benzylideneaniline (Comparison of Amine Product Compositions)

○ $C_6H_5CH_2NHCHO$
● C_6H_5NHCHO
△ $\genfrac{}{}{0pt}{}{C_6H_5CH_2}{C_6H_5}{>}NCHO$
benzylidene part ————
amine part - - - - - - - -

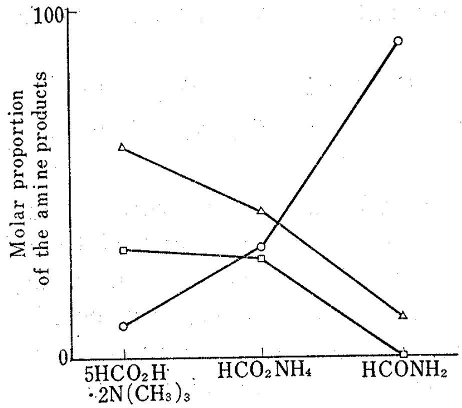


Fig. 2. Reactions of N-Benzylidenebenzylamine (Comparison of Amine Product Compositions)

○ $C_6H_5CH_2NHCHO$
△ $(C_6H_5CH_2)_2NCHO$
□ $(C_6H_5CH_2)_3N$

reagents would be helpful in rationalizing the different nature of the reactions. This comparison was shown in Fig. 1, 2, and 3, respectively as to the reactions of N-benzylideneaniline, N-benzylidenebenzylamine, and N-benzylidenecyclohexylamine, in which percentages of molar equivalent amount of the amine products with respect to each of benzylidene and amine fragments are plotted against each of the reactions with three reagents. As can obviously be seen from these figures, the reaction with TMAF was characterized by predominant formation of N-formylated secondary amine corresponding to the hydrogenated N-benzylideneamine and, in contrast, the reaction with formamide by predominant formation of N-formylated primary amine. The reaction with ammonium formate was obviously shown to result in the mixed formation of the products of both the reaction, indicating that ammonium formate behaves in a position between TMAF and formamide, because of attaining to the formate-formamide equilibrium at elevated temperature. Then, from viewpoint of the predominant amine formation, different behavior between formate and formamide is interpreted as in the following. TMAF, usually formate, affects saturation of azomethine double bond, induced by oxidation of formic acid to carbon dioxide, leading to the formation of N-formylated secondary amine

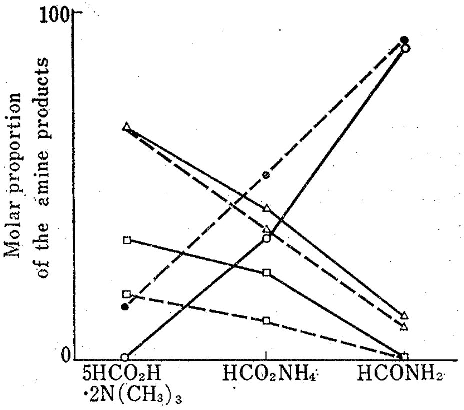
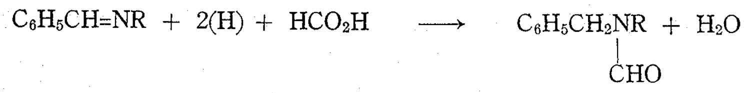


Fig. 3. Reactions of N-Benzylidenecyclohexylamine (Comparison of Amine Product Compositions)

○ $C_6H_5CH_2NHCHO$
● $C_6H_{11}NHCHO$
△ $\genfrac{}{}{0pt}{}{C_6H_5CH_2}{C_6H_{11}}{>}NCHO$
□ $(C_6H_5CH_2)NC_6H_{11}$
benzylidene part ————
amine part - - - - - - -



$$C_6H_5CH{=}NR + 2(H) + HCO_2H \longrightarrow C_6H_5CH_2\underset{\displaystyle CHO}{\underset{|}{N}}R + H_2O \qquad (1)$$

(Formic acid acts as hydrogen donor)

and formamide causes reductive cleavage at the double bond, induced by self-oxidation of the azomethine, leading to the cleaved N-formylated primary amines. The reaction equation can reasonably be written as follows.

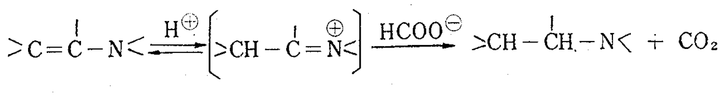
$$C_6H_5CH{=}NR + 2(H) + 2HCONH_2 \longrightarrow C_6H_5CH_2NHCHO + RNHCHO + NH_3 \qquad (2)$$

(Hydrogen is provided by self-oxidation of azomethine.)

As can be also seen from Table I or three Figures, the amine products, N-formylated secondary amine and N-formylated primary amine, respectively of the TMAF and formamide reactions were contaminated with much less amount of other amine products. This is reasonably considered to be attributed to participation of a little amount of water which appeared to come from the hygroscopicity and, at elevated temperature the decomposition, very slow as it is, of the two reagents. In the TMAF reaction water would affect hydrolysis of azomethine influenced by the acidic environment to give primary amine and aldehyde, and then, formylation of the former and a formate reaction of the latter with the parent azomethine would give respectively N-formylated primary amine and tertiary amine, both of which can be seen in Table I as by-products in the TMAF reactions of N-benzylidenebenzylamine and N-benzylidenecyclohexylamine. In the formamide reaction water would induce formamide to act in part as ammonium formate through hydrolysis. Then, the formation of N-formylated secondary amine in each run of the formamide reaction, as shown in Table I, would be explained as the same formation in the TMAF reaction.

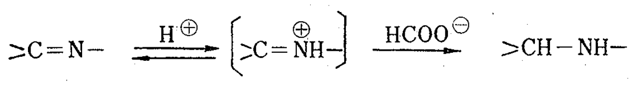
Mechanistic and Related Discussion for the Reaction Paths

In the foregoing section, we described the distinctions between both of the reactions of azomethine with formate and formamide in the composition of the reduction amine products and in the reducing source. The formate reaction, leading to saturation of the azomethine double bond as exemplified by the use of TMAF, was realized to be induced by oxidation of formic acid to carbon dioxide. Mechanism of this type of reaction has not been investigated, however, it may be appropriate to refer to the reaction as the reduction of enamine with formic acid. The mechanistic path of the facile conversion of enamine to tertiary amine by formic acid has been substantiated⁶⁾ by the use of deuterium labelled formic acid to involve intermediate



$$>C{=}\overset{|}{C}-N< \underset{}{\overset{H^{\oplus}}{\rightleftharpoons}} \left[>CH-\overset{|}{C}{=}\overset{\oplus}{N}<\right] \xrightarrow{HCOO^{\ominus}} >CH-\overset{|}{C}H-N< + CO_2$$

ternary iminium ion. On referring to this, a likely reaction path of the reduction of azomethine may involve protonation forming the nearly same intermediate. Further detailed studies for the mechanism are in investigation in this laboratory.



$$>C{=}N- \overset{H^{\oplus}}{\rightleftharpoons} \left[>C{=}\overset{\oplus}{N}H-\right] \xrightarrow{HCOO^{\ominus}} >CH-NH-$$

---

6) N. J. Leonard, R. R. Sauers: J. Am. Chem. Soc., **79**, 6210 (1957).

In contrast with the formate reaction, the formamide reaction is more complicated causing reductive cleavage at the azomethine double bond accompanied by the likely oxidation of the same azomethine. On referring to our current related studies on azomethine-amide chemistry, discussion and investigation for this reaction path and for its relation to some surrounding compounds are described in the following.

As the principal overall-reaction with formamide was represented by eq. 2 indicated in the earlier section, the similar reaction is referred to as the previously reported reaction,[4~7] which involves catalytic hydrogenation of azomethine in the presence of formamide at elevated temperature under high hydrogen pressure, the overall-reaction equation of which has been established as written in the following. Close resemblance

$$\mathrm{ArCH{=}NR + H_2 + 2HCONH_2 \longrightarrow ArCH_2NHCHO + RNHCHO + NH_3} \qquad (3)$$

between the reaction 2 and 3 is shown except for reducing sourse. In our investigation for the reaction path of 3, it has been well established[7] that, when azomethine is mixed with formamide at elevated temperature, the reaction is initiated by the following equation

$$\mathrm{ArCH{=}NR + HCONH_2 \longrightarrow ArCH{=}NH + RNHCHO} \qquad (4)$$

and to attain the reaction 3 aldimine formed in eq. 4 is hydrogenated to primary amine and then followed by formylation with formamide.

$$\mathrm{ArCH{=}NH + H_2 \longrightarrow ArCH_2NH_2} \qquad (5)$$

$$\mathrm{ArCH_2NH_2 + HCONH_2 \longrightarrow ArCH_2NHCHO + NH_3} \qquad (6)$$

On referring to this pathway, it may be safe to say that also in the reaction 2 the aldimine behaves in the same way except for that the hydrogenation is replaced by the reduction with a certain different source.

As described in the earlier section, formamide was not the reactant to behave as reducing agent and our search for the oxidation product, through the formation of which the reduction was induced, was focussed on the undistillable troublesome resinous mixture, which came from azomethine. From the material, the isolations of amaron, lophine and cyaphenine as its components appeared to give rationalization for the oxidation courses of azomethines. It seems likely and probable that the formation of three compounds is brought about through dehydrogenation of the intermediate aldimine formed in eq. 4, as shown in the following eq. 7, 8, and 9, though the reaction paths are obscure, and the formed hydrogen is donated to the aldimine to attain the above reduction step. In close relations to eq. 7, 8, and 9, in the literatures there have been known the conversions under relatively simple conditions from benzaldimine into lophine,[8] cyaphenine[8] and amarine[8] (2,4,5-triphenylimidazoline), from hydrobenzamide, which is obtainable by facile self-condensation[8,9] of benzaldimine, into lophine,[10] cyaphenine[11] and amarine,[8,12] from amarine into amaron[13] and lophine,[14] and from lophine into cyaphenine.[8] The observation of considerable evolution of ammonia during the course of every formamide reaction also appeared to bear evidence upon the ammonia formation eq. 7 and 8. Therefore,

---

[7] M. Sekiya, A. Hara: This Bulletin, **11**, 895 (1963).

[8] H.H. Strain: J. Am. Chem. Soc., **49**, 1563 (1927).

[9] M. Busch: Ber., **29**, 2137 (1896).

[10] F. Rochleder: Ann., **41**, 89 (1842); Laupent: J. prakt. Chem., **35**, 455 (1845); Ekmann: Ann., **112**, 163 (1853); Br. Radzieszewski: Ber., **10**, 70 (1877); H.M. Rau: *Ibid.*, **14**, 444 (1881).

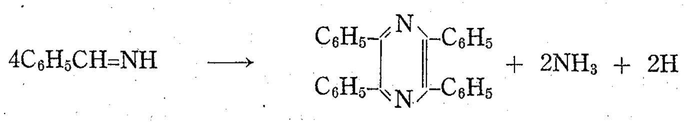
[11] M.M.J. Boucault, P. Robin: Compt. rend., **169**, 978 (1919).

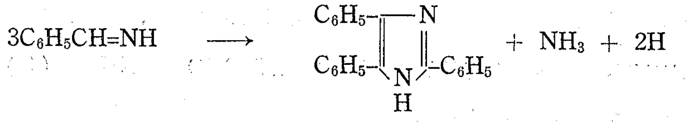
[12] G. Fownes: Ann., **54**, 364 (1845); C. Bertagnini: *Ibid.*, **88**, 127 (1853); R. Bohrmann: J. prakt. Chem., **27**, 296 (1883).

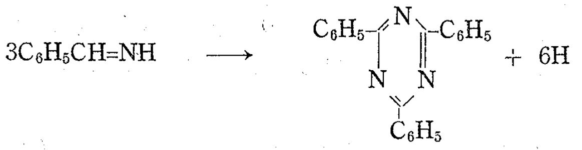
[13] S. Takaki, T. Ueda: Yakugaku Zasshi, **58**, 152 (1938).

[14] E. Fischer, H. Trosche: Ber., **13**, 706 (1880); H.H. Strain: J. Am. Chem. Soc., **52**, 1218 (1930).

the formamide reaction can be expressed just as self-oxidation-reduction reaction of the intermediate aldimine. Though another part of the resinous material, regarded still as a mixture of several compounds, remained not clarified, it should be expected that some other oxidation, components equivalent to the reduction amine products are contained in it.

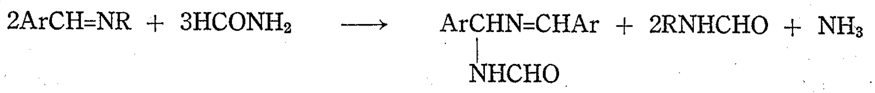

(7)


(8)


(9)

Thus, the pathways of the N-formylated amine formation along with the likely reducing source were explained, however, the pathways are considered to have more complication with the certain surrounding compounds, which are likely to have at least minor chance of forming in the reaction. In the following our investigation of behaviors of formamide in the reaction with such surrounding compounds is described in correlation with the foresaid paths.

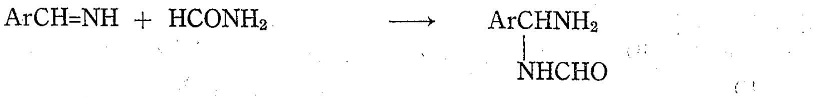
In an earlier paper[15] from this laboratory we reported another reaction between azomethine and amide at lower temperature (boiling water bath temperature), which resulted in the formation of N-arylmethylene-1-acylamino-1-arylmethylamine. Formamide gave the formamido analog, N-arylmethylene-1-formamido-1-arylmethylamine, as in the following. The pathway of this reaction has been explained[16] to involve the


(10)

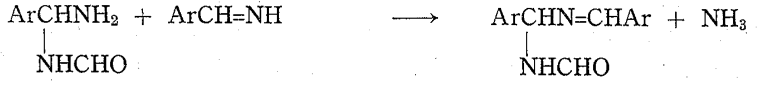
$$2ArCH{=}NR + 3HCONH_2 \longrightarrow \underset{\displaystyle NHCHO}{ArCHN{=}CHAr} + 2RNHCHO + NH_3 \quad (10)$$

intermediate aldimine, which is formed in eq. 4. The stage 4 is followed by the possible paths indicated in Chart 1, which have been explained mostly in two ways; one[16] through the intermediate 1-formamido-1-arylmethylamine and the lately considered other[17] through the intermediate hydroamide.

$$ArCH{=}NR + HCONH_2 \longrightarrow ArCH{=}NH + RNHCHO \quad (4)$$


(11)

$$ArCH{=}NH + HCONH_2 \longrightarrow \underset{\displaystyle NHCHO}{ArCHNH_2} \quad (11)$$

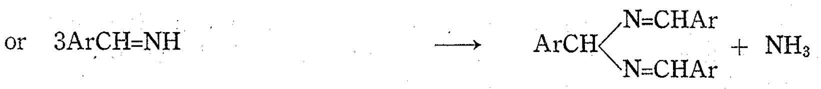

(12)

$$\underset{\displaystyle NHCHO}{ArCHNH_2} + ArCH{=}NH \longrightarrow \underset{\displaystyle NHCHO}{ArCHN{=}CHAr} + NH_3 \quad (12)$$


(13)

$$\text{or}\quad \underset{\displaystyle NHCHO}{ArCHNH_2} + ArCH{=}NR \longrightarrow \underset{\displaystyle NHCHO}{ArCHN{=}CHAr} + RNH_2{}^{a)} \quad (13)$$

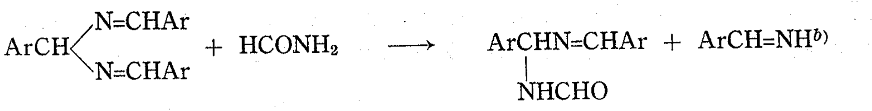
……………………………………


(14)

$$\text{or}\quad 3ArCH{=}NH \longrightarrow ArCH\begin{cases} N{=}CHAr \\ N{=}CHAr \end{cases} + NH_3 \quad (14)$$

---

[15] M. Sekiya, T. Oishi: This Bulletin, **7**, 468 (1959).
[16] M. Sekiya, A. Hara: *Ibid.*, **11**, 901 (1963).
[17] M. Sekiya, A. Hara, K. Ito, J. Suzuki, K. Tanaka: *Ibid.*, **15**, 774 (1967).



$$\mathrm{ArCH}\left<\begin{array}{l}\mathrm{N{=}CHAr}\\ \mathrm{N{=}CHAr}\end{array}\right. + \mathrm{HCONH_2} \longrightarrow \begin{array}{l}\mathrm{ArCHN{=}CHAr}\\ \;|\\ \mathrm{NHCHO}\end{array} + \mathrm{ArCH{=}NH}^{b)} \qquad (15)$$

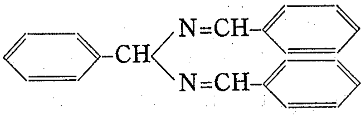
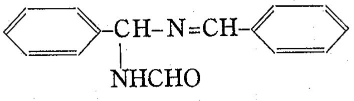
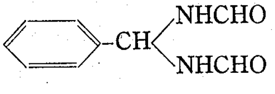
Chart 1.

a) This is followed by formylation with formamide ($\mathrm{RNH_2 + HCONH_2 \rightarrow RNHCHO + NH_3}$).
b) This cycles the earlier course 11 or 14.

It is considered that these pathways for the reaction 10 at lower temperature is not wholly excluded even for the said reaction at higher temperature, in that benzylidene analog of N-arylmethylene-1-formamido-1-arylmethylamine, N-benzylidene-α-formamidobenzylamine, would possess some opportunity of its formation. We took it in a problem how this compound and also the actual compound, hydroamide, which is considered as an intermediate in the formation of the former compound, react with formamide at higher temperature. N-Benzylidene-α-formamidobenzylamine still possesses carbon-nitrogen double bond in its structure, accordingly further reaction with formamide was expected. As for hydroamide, a reaction of hydrobenzamide with formamide at high temperature was reported in an earlier paper[4] to give products, N-benzylformamide as major product, N,N-dibenzylformamide, and tribenzylamine.

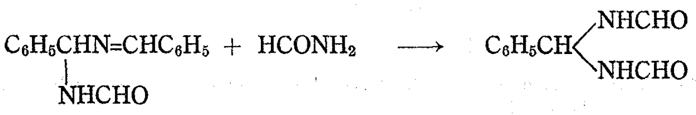
We examined the reaction of N-benzylidene-α-formamidobenzylamine with formamide and the above hydroamide reaction to predict reasonable accuracy at high temperature under the same conditions as in the reaction with the azomethines described in the earlier section. Both the reactions were shown to result, as written in Table II, in only the formations of N-benzylformamide as reduction product, which also showed an interest in resulting in nearly the same yield, and of a resinous mixture, from which amaron, lophine, and cyaphenine were isolated. The formation of these products is nearly in accord with that of those which come from benzylidene fragment of the azomethine in the reactions of the azomethines described in the preceding. In view of the above results, for the azomethine reaction at high temperature a pathway through N-benzylidene-α-formamidobenzylamine is also considered to be a quite possible one.

Table II. Formation of N-Benzylformamide in the Reactions[a] of N-Benzylidene Compounds with Formamide

N-Benzylidene Compound	Yield (%)[b] of N-Benzylformamide
	30 (3)
	27 (2)
	42 (1)

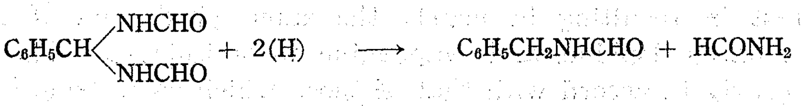
a) General reaction method and procedures are given in Experimental.
b) Theoretical mole of N-benzylformamide formed per mole of N-benzylidene compound is written in parenthesis, on which yield is based.
In every run, by-product was resinous material, from which cyaphenine, lophine, and amaron were obtainable.

Then, how formamide reacts with this compound at higher temperature to lead to N-benzylformamide comes into a problem. As a possible starting stage for the reaction, it would be quite likely that formamide attacks at the azomethine-like carbon-nitrogen double bond of N-benzylidene-α-formamidobenzylamine in accordance with eq. 4, as written in the following. If this eq. 16 would be an actual initial stage, the compounds



$$\underset{\text{NHCHO}}{\text{C}_6\text{H}_5\text{CHN=CHC}_6\text{H}_5} + \text{HCONH}_2 \longrightarrow \text{C}_6\text{H}_5\text{CH}\left\langle {\text{NHCHO} \atop \text{NHCHO}} \right. + \text{C}_6\text{H}_5\text{CH=NH} \qquad (16)$$

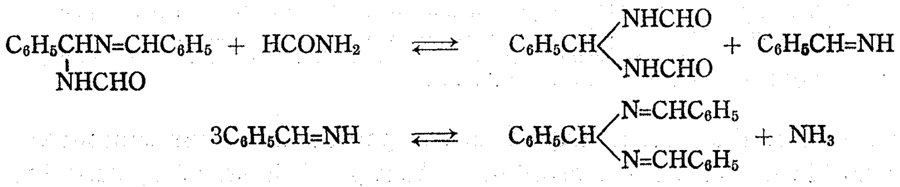
formed, N,N′-benzylidenebisformamide and benzaldimine, should be led to N-benzylformamide, by reacting further with formamide. The latter compound, to attain the formation of N-benzylformamide, can move in eq. 5 followed by 6, in the reaction of which the reduction with hydrogen is replaced by that with self-oxidation of azomethine, or in the equations shown in Chart 1, making a cycle to result in the formation of N-benzylidene-α-formamidobenzylamine followed by the former course (Ar in eq. 5, 6, and Chart 1 are replaced by C_6H_5). Whether the former compound would undergo the further reaction with formamide to give N-benzylformamide has not been learned, however, the formation of N-benzylformamide was actually demonstrated in the reaction with the N,N′-benzylidenebisformamide under the condition similar to that of the reaction of azomethine at high temperature. As the result is also indicated in Table II, the formations of N-benzylformamide and of a resinous oxidation material containing amaron, lophine, and cyaphenine are in accord with those in the reaction with azomethine. Thus, the reaction can be represented by the following equation, in which hydrogen is considered to be provided by self-oxidation of the starting N,N′-benzylidenebisformamide.



$$\text{C}_6\text{H}_5\text{CH}\left\langle {\text{NHCHO} \atop \text{NHCHO}} \right. + 2(\text{H}) \longrightarrow \text{C}_6\text{H}_5\text{CH}_2\text{NHCHO} + \text{HCONH}_2 \qquad (17)$$

Extensive and mechanistic studies on this type of the reaction will be reported in the succeeding paper of this series.

In addition, an attempt to demonstrate eq. 16 was successfully carried out, which gave great help for rationalization of the pathway through the intermediate, N,N′-benzylidenebisformamide. For this demonstration, a reaction of N-benzylidene-α-formamidobenzylamine with formamide at boling water bath temperature, though this compound resists considerably at this temperature, was carried out under the condition in that a solution of N-benzylidene-α-formamidobenzylamine in formamide was vigorously stirred along with an immiscible ligroin of boiling point above 105° for longer period (10 hr.). Benzaldimine formed by eq. 16 is known[8,9] to undergo facile self-condensation to give hydrobenzamide as illustrated by eq. 14. The formed hydrobenzamide, by the above means, was transferred into the ligroin layer as soon as it was formed, being kept out of the further reaction with formamide, which gives N-benzylidene-α-formamidobenzylamine as in eq. 15. Thus, hydrobenzamide was isolated by concentration of the ligrion layer. Also the other product, N,N′-benzylidenebisformamide, in eq. 16 was isolated by treatment of the formamide layer, accompanied by considerable amount of the starting N-benzylidene-α-formamidobenzylamine. Percentage of the conversion into the two compounds was roughly estimated at 12~15% in the theory for reaction period of 10 hr. The relatively good stability of



$$\underset{\text{NHCHO}}{\text{C}_6\text{H}_5\text{CHN=CHC}_6\text{H}_5} + \text{HCONH}_2 \rightleftarrows \text{C}_6\text{H}_5\text{CH}\left\langle {\text{NHCHO} \atop \text{NHCHO}} \right. + \text{C}_6\text{H}_5\text{CH=NH}$$

$$3\text{C}_6\text{H}_5\text{CH=NH} \rightleftarrows \text{C}_6\text{H}_5\text{CH}\left\langle {\text{N=CHC}_6\text{H}_5 \atop \text{N=CHC}_6\text{H}_5} \right. + \text{NH}_3$$

N-benzylidene-α-formamidobenzylamine at boiling water bath temperature is, of course, explained by higher yield of its formation in the previously reported reactions of hydrobenzamide[16,18] and of N-benzylideneamine[15] in formamide at the same temperature. It was also found that rate of the above conversion was increased by the use of acid catalyst. In the above reaction an addition of a little amount of formic acid increased the yield of N,N′-benzylidenebisformamide up to 29%, though that of the other product, hydrobenzamide, decreased, probably owing to its decomposition by the acid.

Supported by the above finding, the pathway through N,N′-benzylidenebisformamide, shown in eq. 16 and 17, was well rationalized for the formation of N-benzylformamide in the reaction of N-benzylidene-*α*-formamidobenzylamine with formamide.

All possible reaction paths for the formation of N-benzylformamide in the reaction of azomethine with formamide at high temperature are described up to here with the reasonable rationalizations. These pathways with respect to N-benzylidene analog are illustrated in Chart 2. In summary, the reaction would be initiated by the formation of unstable intermediate, benzaldimine, and then the reductive formylation of the benzaldimine to N-benzylformamide proceeds directly or *via* N-bezylidene-*α*-formamidobenzylamine and N,N′-benzylidenebisformamide; the former forms directly or *via* hydrobenzamide. It can be said that, though predominant pathway is not evident, all pathways appear to have certain possibilities of existing in the reaction. In Chart 2

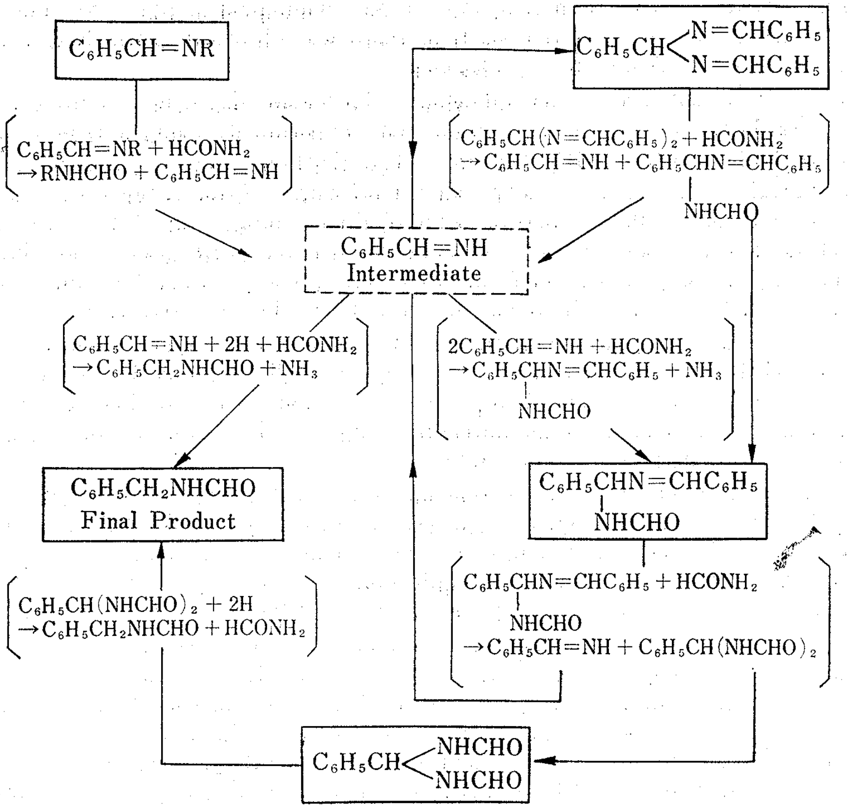


Chart 2. Pathways for the Formation of N-Benzylformamide in the Reactions of N-Benzylidene Compounds with Formamide

---

[18] M. Sekiya, K. Ito, M. Saito: This Bulletin, **12**, 676 (1964).

actual compounds are inclosed by line, and arrows joining these compounds each other represent the actually demonstrated conversions.

Experimental

Reactions of Azomethines with TMAF, Ammonium Formate, and Formamide

Materials——The starting azomethines were best prepared from benzaldehyde and the corresponding primary amines as follows. For every case, both equimolar benzene solutions were mixed, when the reaction set in without application of heat; to make escape of H_2O formed in the reaction K_2CO_3 was added. The solution was dried over K_2CO_3 and evaporated, and the residual liquid was carefully distilled under reduced pressure. The following pure materials were obtained: N-benzylideneaniline, m.p. 50~51°, which was obtained by recrystallization of the solid distillate from benzene; N-benzylidenebenzylamine, b.p$_{15}$ 181~182°; N-benzylidenecyclohexylamine, b.p$_{22}$ 154~155°.

TMAF is of constant boiling liquid salt b.p$_{18}$ 91~92° given by $5HCO_2H \cdot 2N(CH_3)_3$, which was prepared by the method reported previously.[5] Ammonium formate, m.p. 116°, was carefully prepared. Commercially available formamide was purified by distillation and the fraction, b.p$_{16}$ 109~111°, was used.

General Procedures——To 2 moles (as HCO_2H) of TMAF (139 g.), HCO_2NH_4 (126 g.), or $HCONH_2$ (90 g.) 0.1 mole each of the azomethine was added in a flask provided with a long air condenser tube. The mixture was warmed by immersing in a preheated silicon-oil bath and, during the course of the reaction, constantly stirred with magnetic stirrer. With the exception of the case of using HCO_2NH_4, the primary immiscible mixture turned to a homogeneous liquid on heating.

In every run with TMAF or HCO_2NH_4, the temperature was maintained at 120~125°. The reaction was indicated by considerable evolution of CO_2 in addition to that of $N(CH_3)_3$ or NH_3. There was passed a stream of air free from CO_2, transfer of CO_2 was assured by $Ba(OH)_2$ solution. The reaction was continued until the evolution was nearly subsided.

In every run with $HCONH_2$, the reaction temperature was maintained at 165~170°, and the reaction was continued for 10 hr. During the course of the reaction, there was observed gentle NH_3 evolution for any length of time, but almost no CO_2 evolution was checked.

The product isolations are described in the following. To obtain reasonable accuracy for product composition the isolation methods were established by preliminary experiments using authentic samples.

Reaction of N-Benzylideneaniline with TMAF——The reaction mixture from the general procedure (the reaction period: 140 min.) was distilled under reduced pressure. After removal of TMAF, most of the residue was distilled to give 20.5 g. (0.097 mole) of solid distillate, b.p$_{0.1}$ 138~142°, m.p. 45~48°. This material was identified as N-benzyl-N-phenylformamide by comparison of IR spectra and mixed melting point test with an authentic sample. Crystallization from ether-petr. ether gave crystals, m.p. 48~49°. *Anal.* Calcd. for $C_{14}H_{13}ON$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.52; H, 6.02; N, 6.63.

Reaction of N-Benzylidenebenzylamine with TMAF——In the reaction mixture from the general procedure (the reaction period: 45 min.), tribenzylamine was crystallized on cool, which was collected by filtration, weighed 5.2 g. (0.018 mole) and showed m.p. 90~92°. This was identified by comparison of IR spectra and mixed melting point test with an authentic sample. *Anal.* Calcd. for $C_{21}H_{21}N$: C, 87.76; H, 7.37; N, 4.87. Found: C, 87.68; H, 7.32; N, 4.87.

The foregoing filtrate was submitted to distillation under reduced pressure to remove TMAF and the residue was carefully fractionated under higher reduced pressure. The first distillate, b.p$_{0.2}$ 127~131°, weighing 2.3 g. (0.017 mole), solidified, showing m.p. 56~59°. This was identified as N-benzylformamide by comparison of IR and mixed melting point test. Crystallization from ether gave crystals, m.p. 60°. *Anal.* Calcd. for C_8H_9ON: C, 71.09; H, 6.71; N, 10.39. Found: C, 71.06; H, 6.72; N, 10.32.

The second distillate, b.p$_{0.2}$ 144~158°, was a mixture of N,N-dibenzylformamide and tribenzylamine. The successful separation was accomplished by the following procedure, of which the effectiveness was assured by preliminary test using authentic sample. The mixture was dissolved in benzene and dry HCl was passed through, whereupon tribenzylamine hydrochloride was precipitated, collected by filtration and weighed 0.6 g. (0.002 mole). The m.p. 213~221°, and the IR spectra agreed with those of an authentic sample. The filtrate was washed with $KHCO_3$ solution and dried over Na_2SO_4, and benzene was evaporated. The residue, weighing 13.1 g. (0.058 mole), solidified, showing m.p. 49~50°. This was identified as N,N-dibenzylformamide by comparison of the IR and the mixed melting point test with an authentic sample. Crystallization from ether gave crystals, m.p. 52°. *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.91; H, 6.69; N, 6.19.

Reaction of N-Benzylidenecyclohexylamine with TMAF——The reaction mixture from the general procedure (the reaction period: 40 min.) was submitted to distillation under reduced pressure, whereupon TMAF was first distilled off and then all the reaction products were distilled as a mixture continuously in a range from 104 to 166° under 3 mm. Hg pressure. The mixture weighing 20.3 g. was shown to contain N-formyl compounds, which were confirmed by checking amide carbonyl band in the IR spectra and by observation of CO evolution on treatment with H_2SO_4. Components of the mixture were successfully separated as amines after hydrolysis as in the following. The mixture was refluxed with 100 ml. of 10% HCl for 3 hr. In the hydrolysis solution solid KOH was dissolved until saturation and the separated oily layer was extracted with ether. The ethereal extract was dried over K_2CO_3 and evaporated. The oily residue was carefully fractionated. The first distillate, b.p. 115∼131°, weighing 1.4 g. (0.014 mole) was identified as cyclohexylamine by comparison of the IR spectra with an authentic sample. N-Cyclohexyl-N-phenylthiourea; m.p. 147∼148°. *Anal.* Calcd. for $C_{13}H_{18}NS$: C, 66.64; H, 7.74; N, 11.96; S, 13.66. Found: C, 66.44; H, 7.64; N, 11.97; S, 13.95. The second distillate, b.p.$_{14}$ 147∼149°, weighing 11.5 g. (0.061 mole) was identified as N-benzylcyclohexylamine. This was converted into its hydrochloride, m.p. 284∼285°. *Anal.* Calcd. for $C_{13}H_{20}NCl$: C, 69.15; H, 8.93; N, 6.20; Cl, 15.70. Found: C, 68.99; H, 8.96; N, 6.21; Cl, 15.79. The third distillate, b.p.$_3$ 161∼166°, m.p. 57∼59°, weighing 4.5 g. (0.016 mole) was identified as N-cyclohexyldibenzylamine. Crystallization from petr.-benzine gave prisms, m.p. 59∼60°. *Anal.* Calcd. for $C_{20}H_{25}N$: C, 85.97; H, 9.02; N, 5.01. Found: C, 85.77; H, 9.00; N, 4.94.

Reaction of N-Benzylideneaniline with Ammonium Formate——The reaction mixture from the general procedure (the reaction period: 360 min.) was distilled under reduced pressure. After removal of a mixture of H_2O, HCO_2NH_4, and $HCONH_2$, volatile reaction products were distilled as a mixture, weighing 15.5 g., in a range from 122 to 152° under 0.2 mm. Hg pressure and a resinous residue, weighing 2.1 g., remained. The distillate was shown to contain N-formyl compounds by checking amide bands in the IR spectra and by observation of CO evolution on treatment with H_2SO_4. Components of the distillate separated as amine hydrochloride after hydrolysis as follows. The distillate was refluxed with 95 ml. of 10% HCl for 3 hr. In the solution nearly pure N-benzylaniline hydrochloride was deposited on cool, collected by filtration and weighed 6.6 g. (0.03 mole). This was identified by comparison of the IR spectra and mixed melting point test with an authentic sample. Recrystallization from EtOH gave crystals, m.p. 211∼212°. *Anal.* Calcd. for $C_{13}H_{14}NCl$: C, 71.05; H, 5.96; N, 6.37. Found: C, 70.76; H, 6.32; N, 6.20. The filtrate was neutralized and saturated with solid KOH and an oily layer liberated was extracted with ether. To the ethereal extract H_2O was added, and CO_2 was bubbled through the mixture until saturation. The ethereal and aqueous layers were separately treated. The ethereal layer was dried over K_2CO_3, and dry HCl was introduced into the solution whereupon aniline hydrochloride precipitated and was collected by filtration. This showed m.p. 194∼197°, weighed 6.7 g. (0.052 mole) and was identified by comparison of the IR spectra and mixed melting point test with an authentic sample. The aqueous layer was acidified with HCl and evaporated to dryness, whereupon benzylamine hydrochloride, m.p. 240∼245°, was obtained, weighing 4.9 g. (0.034 mole). This was identified by comparison of the IR spectra and mixed melting point test with an authentic sample. Recrystallization from EtOH gave crystals, m.p. 255∼256°. *Anal.* Calcd. for $C_7H_{10}NCl$: C, 57.55; H, 7.02; N, 9.76. Found: C, 57.62; H, 7.09; N, 9.78.

Reaction of N-Benzylidenebenzylamine with Ammonium Formate——From the reaction mixture obtained from the general procedure (the reaction period: 80 min.), H_2O, HCO_2NH_4, and $HCONH_2$ were distilled off under reduced pressure, when a part of tribenzylamine weighing 0.2 g. (0.001 mole) also vaporized in the distillate as a suspending state. The residual liquid was carefully fractionated under higher reduced pressure. The fractions were similar to those of the experiment with TMAF (distillation residue 1.1 g.) and worked up by the same procedure giving the following products. N-Benzylformamide, m.p. 57∼59°, 7.0 g. (0.052 mole); tribenzylamine hydrochloride, m.p. 215∼223°, 4.8 g. (0.015 mole); N,N-dibenzylformamide, m.p. 47∼50°, 7.8 g. (0.035 mole).

Reaction of N-Benzylidenecyclohexylamine with Ammonium Formate——After removal of H_2O, HCO_2NH_4, and $HCONH_2$ from the reaction mixture obtained from the general procedure (the reaction period: 90 min.), the residual liquid, which was shown to contain N-formylamines, was followed by distillation (residue 0.5 g.), hydrolysis, and fractionation of free amine products in the same manner as in the experiment with TMAF giving the following products. Cyclohexylamine, b.p. 112∼131°, 4.7 g. (0.048 mole); benzylamine, b.p.$_{54}$ 81∼83°, 3.0 g. (0.028 mole); N-benzylcyclohexylamine, b.p.$_{13}$ 145∼150°, 6.4 g. (0.034 mole); N,N-dibenzylcyclohexylamine, b.p.$_3$ 162∼165°, m.p. 58∼59°, 2.7 g. (0.01 mole).

Reaction of N-Benzylideneaniline with Formamide——The reaction mixture obtained from the general procedure was distilled under reduced pressure. After removal of $HCONH_2$, the volatile reaction products were distilled as a mixture under 0.2 mm. Hg pressure. The distillate, weighing 13.1 g., was a mixture similar to that of the experiment with HCO_2NH_4 and worked up by the same procedure giving the following products. N-Benzylaniline hydrochloride, m.p. 199∼205°, 1.6 g. (0.007 mole); aniline hydrochloride, m.p. 194∼196°, 7.3 g. (0.056 mole); benzylamine hydrochloride, m.p. 241∼245°, 4.0 g. (0.028 mole). Most of the foregoing residue were soluble in $CHCl_3$, while a little amount of insoluble blackish charcoal-like material was contained in the residue. The $CHCl_3$-soluble material was chromatographed through silica gel and developed with $CHCl_3$. Amaron was obtained from the earlier eluated fraction and lophine from the later fraction, though the larger part remained not to crystallize. The former was recrystallized from $CHCl_3$ to needles, m.p. 244∼246°, weighing 0.5 g. *Anal.* Calcd. for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.12; H, 5.30; N, 7.30. The latter was recrystallized from EtOH to needles, m.p. 275∼277°, weighing 0.5 g. *Anal.* Calcd. for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.34; H, 5.75; N, 9.52.

Reaction of N-Benzylidenebenzylamine with Formamide——From the reaction mixture obtained from the general procedure $HCONH_2$ was distilled off under reduced pressure. The residual liquid was carefully fractionated under higher reduced pressure. The first distillate, b.p$_{0.2}$ 126~132°, weighing 15.7 g. (0.116 mole), solidified, showing m.p. 54~59°. This material was identical with an authentic N-benzylformamide by comparison of the IR spectra and mixed melting point test. The second distillate, b.p$_{0.2}$ 159~162°, weighing 1.6 g. (0.007 mole), solidified on cool, showing m.p. 48~50°. This was identical with an authentic N,N-dibenzylformamide by comparison of the IR spectra and mixed melting point test. The residue, which was similar to that obtained with N-benzylaniline, was chromatographed in the same manner. Amaron (0.5 g.) and lophine (0.4 g.) were separated as parts of the residue. These were identified by comparison of IR spectra and mixed melting point test.

For varing reaction periods the sampling reactions were carried out, when changes in the results were observed particularly in the distillation residue. In the run for 5 hr. 0.9 g. of cyaphenine, 0.3 g. of lophine, and 0.3 g. of amaron were isolated from the distillation residue, however in that for 10 hr. cyaphenine faded away as in the foregoing description. Cyaphenine: needles (from $CHCl_3$), m.p. 227~228°. *Anal.* Calcd. for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.36; H, 4.71; N, 13.83. In the run for 30 hr. blackish charcoal-like material was more increased, occupying most of the residue, and amaron faded away and lophine was decreased.

Reaction of N-Benzylidenecyclohexylamine with Formamide——After removal of $HCONH_2$ from the reaction mixture obtained from the general procedure, the residual liquid was distilled under higher reduced pressure to give a distillate (11.6 g.) containing N-formylated amine products. The distillate was followed by hydrolysis and fractionation of tree amine products in the same manner as in the experiment with TMAF or HCO_2NH_4 giving the following products. Cyclohexylamine, b.p. 113~132°, 4.6 g. (0.047 mole); benzylamine, b.p$_{88}$ 110~113°, 4.0 g. (0.037 mole); N-benzylcyclohexylamine, b.p$_5$ 110~113°, 0.9 g. (0.005 mole). The residue was chromatographed in the same manner as in the experiment with N-benzylideneaniline giving amaron (1.0 g.) and lophine (0.5 g.) as parts of the residue.

Reactions of Formamide with Hydrobenzamide, N-Benzylidene-*α*-formamidobenzylamine, and N,N′-Benzylidenebisformamide

Materials——Hydrobenzamide was obtained from benzaldehyde and 30% aqueous NH_3, and purified by recrystallization, m.p. 101~103°. N-Benzylidene-*α*-formamidobenzylamine, m.p. 123~124°, was prepared by condensation of hydrobenzamide with formamide according to the previous paper.[16] N,N′-Benzylidenebisformamide was obtained on referring to the literature[19] by heating a mixture of benzaldehyde and an excess of $HCONH_2$ on a boiling water bath for 24 hr. and purified by recrystallization from MeOH to crystals of m.p. 149~150°. Formamide of b.p$_{16}$ 109~111° was used.

General Procedures——In a flask provided with an air condenser tube 0.1 mole each of N-benzylidene compounds, *i.e.*, hydrobenzamide, N-benzylidene-*α*-formamidobenzylamine, and N,N′-benzylidenebisformamide, were placed and 2 moles of $HCONH_2$ was added. The mixture was warmed by immersing in a preheated silicon-oil bath and constantly stirred with magnetic stirrer. Temperature was maintained at 165~170° for a period of 10 hr. On warming the mixture became homogeneous and, during the course of the reaction gentle NH_3 evolution was observed for any length of time and almost no CO_2 evolution was checked to accompany.

After the reaction, $HCONH_2$ was distilled off from the reaction mixture under reduced pressure. The residual liquid was fractionally distilled under higher reduced pressure. N-Benzylformamide was obtained as a solid distillate, which showed b.p$_{0.4}$ 131~134° (as an instance) and m.p. in a range from 56 to 61°. The melting point was not depressed by admixture with an authentic sample. Comparison of its IR spectrum with that of a pure authentic sample showed it to be nearly pure, so yield was calculated from its weight. The yields for all runs are indicated in Table II.

The distillation residue, of which amount occupied roughly a range from 1/3 to 2/3 for the theoretical amount of product, was dark brown resinous material. By treatment with $CHCl_3$, this separated into two parts, a material soluble in $CHCl_3$ and a smaller amount of charcoal-like material insoluble in any solvent. The former was chromatographed through silica gel column using $CHCl_3$ as an eluent. Though larger part remained not to crystallize, cyaphenine (1.1 g.) in the run with hydrobenzamide, amaron (0.5 g.) in the run with N-benzylidene-*α*-formamidobenzylamine, and lophine (2.9 g.) and amaron (0.2 g.) in the run with N,N′-benzylidenebisformamide were isolated. These compounds were identified by comparison of their IR spectra with authentic samples and mixed melting point tests.

Reaction of N-Benzylidene-*α*-formamidobenzylamine with Formamide at Lower Temperature

a) To a solution of 12 g. (0.05 mole) of N-benzylidene-*α*-formamidobenzylamide, m.p. 123~124°, dissolved in 11 g. (0.25 mole) of $HCONH_2$, b.p$_{16}$ 109~110°, on heating, 50 ml. of ligroin fraction of boiling point above 105° was stratified. The immiscible mixture was vigorously stirred on a boiling water bath for 10 hr. Immediatiately after the reaction, the two layers were separated and on cooling most of unchanged N-benzylidene-*α*-formamidobenzylamine was crystallized in the $HCONH_2$ solution and much less in the ligroin solution.

---

[19] K. Bülow: Ber., **26**, 1972 (1893).

On evaporation of the $HCONH_2$ filtrate and the ligroin filtrate under reduced pressure, 1.3 g. (14.6%) of N,N′-benzylidenebisformamide, m.p. 139°, was obtained from the former and 0.6 g. (12.0%) of hydrobenzamide, m.p. 97°, from the latter. Both of the crystals were nearly pure and identical with authentic samples by comparison of the IR spectra and by admixture.

b) By the same procedure as in a) except that 0.2 ml. of 98% HCO_2H was added to the reaction mixture, 2.6 g. (29.0%) of N,N′-benzylidenebisformamide and 0.4 g. (8.2%) of hydrobenzamide were obtained. The yield of the former is higher than that in the method a).

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