that the initiating essential reaction between azomethine and formamide would be the reaction, $ArCH{=}NR+HCONH_2 \longrightarrow ArCH{=}NH+RNHCHO$ (NH_3 acts as a catalyst), which was demonstrated by using N-benzylidene-4-sulfonamidobenzylamine as azomethine. Based on this reaction, the whole pathway for the above hydrogenation reaction was proposed. Mechanism for hydrogenation reaction of nitriles, oximes, and ammonia-aldehyde mixtures in the presence of formamide was also suggested.

(Received February 13, 1962)

UDC 547.554'298.1

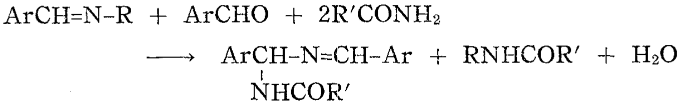
156. **Minoru Sekiya and Akira Hara**: Reaction of Amide Homologs. X. Mechanism of the Formation of N-Arylmethylene-1-acylamino-1-arylmethylamine.

(*Shizuoka College of Pharmacy*[*1])

In a previous paper of this series,[1] it has been shown with several examples that azomethines react with amides resulting in the formation of N-arylmethylene-1-acylamino-1-arylmethylamines, when heated together at a boiling water bath temperature.

$$2ArCH{=}N{-}R + 3R'CONH_2 \longrightarrow \underset{\displaystyle NHCOR'}{ArCH}{-}N{=}CH{-}Ar + 2RNHCOR' + NH_3 \quad (1)$$

Later,[2] this formation was found to occur when aromatic aldehyde is used as a reactant instead of a part of the azomethine in reaction (1). In this case, only formamide was used as an amide.



$$\begin{aligned}&ArCH{=}N{-}R + ArCHO + 2R'CONH_2\\&\qquad\longrightarrow \underset{\displaystyle NHCOR'}{ArCH}{-}N{=}CH{-}Ar + RNHCOR' + H_2O \qquad (2)\end{aligned}$$

However, the mechanisms of the above reactions have as yet remained unsolved.

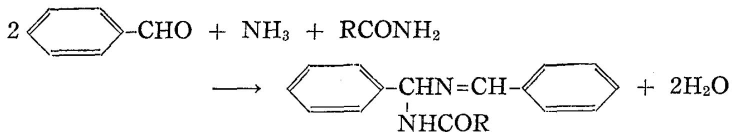
In some cases, N-arylmethylene-1-acylamino-1-arylmethylamine was formed when hydroamide or aromatic aldehyde-ammonia mixture was allowed to react with amides. In the light of this fact the mechanism comprehensive for the formation of N-arylmethylene-1-acylamino-1-arylmethylamine is proposed in the present paper.

Benzaldehyde-ammonia and anisaldehyde-ammonia as well as hydrobenzamide was employed for the reaction with amide, for which formamide and acetamide were used. In some experiments, ammonia was passed through a mixture of aldehyde and amide with heating, and in other case, a mixture of hydrobenzamide and amide was heated. All these reactions brought about the formation of corresponding N-arylmethylene-1-acylamino-1-arylmethylamine in a considerable yield. These methods appear to be most practicable for the preparation of the compound. The reaction formula when benzaldehyde-ammonia and hydrobenzamide were used can be represented as follows :

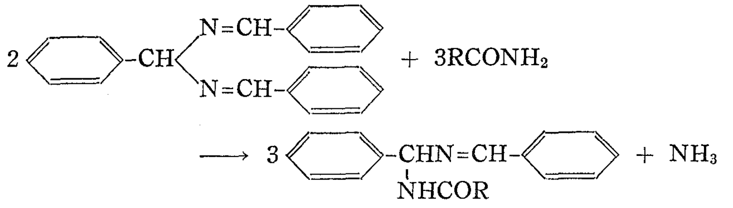
[*1] Oshika, Shizuoka (関屋 実, 原 明).

[1] M. Sekiya, T. Oishi : This Bulletin, **7**, 468 (1959).

[2] *Idem* : *Ibid.*, **7**, 855 (1959).

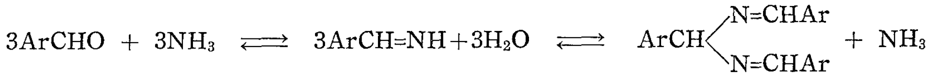


(3)



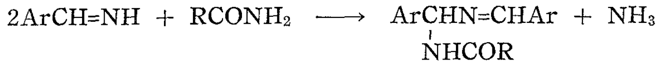
(4)

Between aromatic aldehyde-ammonia mixture and hydroamide, there exists the following equilibrium.



$$3ArCHO + 3NH_3 \rightleftarrows 3ArCH{=}NH + 3H_2O \rightleftarrows ArCH\begin{cases}N{=}CHAr\\N{=}CHAr\end{cases} + NH_3$$

Therefore, it is deduced that both the reactions (3) and (4) would proceed through a reaction of arylmethyleneimine and amide. This essential reaction would generally be written as in the following :



(5)

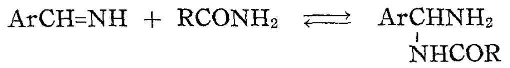
$$2ArCH{=}NH + RCONH_2 \longrightarrow \underset{\substack{|\\NHCOR}}{ArCHN}{=}CHAr + NH_3$$

Considering this reaction (5) as an stage, the pathway of the reaction (1) will also be explained reasonably. In a previous work of this series,[3] it was reported that the reaction between azomethine and amide is initiated by the following stage which leads to the formation of arylmethyleneimine.

$$ArCH{=}NR + R'CONH_2 \longrightarrow ArCH{=}NH + RNHCOR' \qquad (6)$$

Then, reaction (5) is supposed to be the subsequent reaction, which leads to the formation of N-arylmethylene-1-acylamino-1-arylmethylamine through the arylmethyleneimine.

The pathway of the reaction (5) can be written reasonably as in the following :



(7)

$$ArCH{=}NH + RCONH_2 \rightleftarrows \underset{\substack{|\\NHCOR}}{ArCHNH_2}$$

(8)

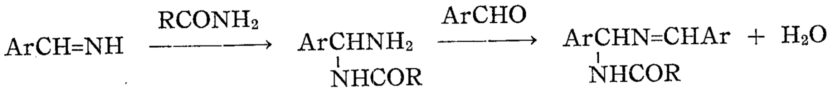
$$\underset{\substack{|\\NHCOR}}{ArCHNH_2} + ArCH{=}NH \longrightarrow \underset{\substack{|\\NHCOR}}{ArCHN}{=}CHAr + NH_3$$

Through equilibrium of an addition reaction followed by a condensation reaction, arylmethyleneimine would be led to N-arylmethylene-1-acylamino-1-arylmethylamine, which is probably stable enough to be formed.

As written by reaction (2), aromatic aldehyde is replaceable instead of a part of azomethine in the reaction (1). For reaction path of this, it can be deduced that aromatic aldehyde can take the part of arylmethyleneimine in the stage (7) or (8) in the pathway of the reaction (1). Therefore, the following two paths subsequent to the stage (6) can be written for the reaction (2), though it is difficult to determine which pathway would actually follow :

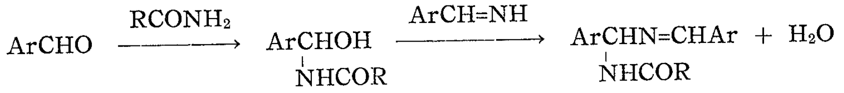
---

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



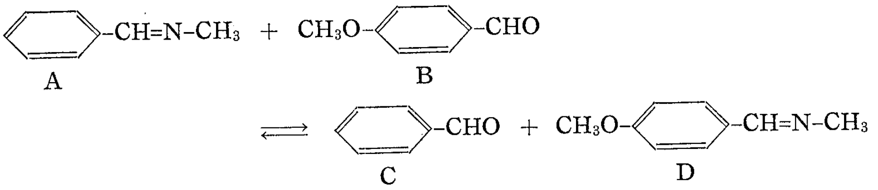
$$\mathrm{ArCH{=}NH} \xrightarrow{\mathrm{RCONH_2}} \underset{\mathrm{NHCOR}}{\mathrm{ArCHNH_2}} \xrightarrow{\mathrm{ArCHO}} \underset{\mathrm{NHCOR}}{\mathrm{ArCHN{=}CHAr}} + \mathrm{H_2O} \qquad (9)$$

or



$$\mathrm{ArCHO} \xrightarrow{\mathrm{RCONH_2}} \underset{\mathrm{NHCOR}}{\mathrm{ArCHOH}} \xrightarrow{\mathrm{ArCH{=}NH}} \underset{\mathrm{NHCOR}}{\mathrm{ArCHN{=}CHAr}} + \mathrm{H_2O} \qquad (10)$$

It was mentioned earlier[2] that either a N-(4-methoxybenzylidene)methylamine-benzaldehyde mixture or an anisaldehyde-N-benzylidenemethylamine mixture, when reacted with formamide, gave the same compound, N-benzylidene-α-formamido-4-methoxybenzylamine. However, it was found that an equilibrium exists between the aldehyde and the azomethine, which results in a replacement reaction. The reaction of this type was reported by Smith, *et al.*[4] in a reaction between methacrolein or crotonaldehyde and N-(1,3-dimethylbutylidene)-1,3-dimethylbutylamine. In the above case, the equilibrium is written as follows.



(11)

This equilibrium was determined by the means in which the equilibrium mixture was first fractionated into two kinds of mixtures, B–D and A–C, utilizing the difference between their boiling points, and azomethine content of each mixture was titrated in acetic acid with perchloric acid, following the method reported by Freeman.[5] At a boiling water bath temperature, the measurements of the equilibrium became constant over the reaction period of 4.5 hours and the equilibrium constant was found to be approximately 0.55. Either of an equimolar mixture of A–B or C–D leads to the equilibrium which is in the proportion of 57.4% in the left and 42.6% in the right in the reaction (11).

So, for the formation of N-benzylidene-α-formamido-4-methoxybenzylamine when formamide is allowed to react with the mixture, A–B or C–D, indicated on either side of the equilibrium, it seems obscure to decide which pathway, (9) or (10) in the foregoing mechanism, will follow. However, it has been shown[2] that the reaction with the mixture A–B results in a considerably lower yield than with the mixture A–B (11% in the former and 40% in the latter). As the time required for the reaction (11) to go from the one side to the another is fairly long, the latter mixture is considered to be effective for the reaction. Therefore, it may be concluded that the formation of N-benzylidene-α-formamido-4-methoxybenzylamine takes place by the pathway (9) which is brought about through the equation (6) between 4-methoxybenzylidenemethylamine and formamide. This is also supported by the fact[2] that the formation of a by-product, N-(4-methoxybenzylidene)-α-formamido-4-methoxybenzylamine, is resulted only in the reaction with the mixture C–D.

Experimental

1. Formation of N-Arylmethylene-1-acylamino-1-arylmethylamine

N-Benzylidene-α-formamidobenzylamine——a) A mixture of 6 g. of hydrobenzamide and 8.1 g. of formamide was heated for 3 hr. on a boiling water bath, agitated from time to time. Two layers

---

[4] C. W. Smith, D. G. Norton, S. A. Ballard : J. Am. Chem. Soc., **75**, 3316 (1953).

[5] S. K. Freeman : Anal. Chem., **25**, 1750 (1953).

which formed at the biginning disappeared at the termination of the reaction and NH$_3$ evolved during the reaction. The resultant solution was concentrated on a water bath under reduced pressure. The residue soon crystallized. The product was collected, washed with a small amount of EtOH, and recrystallized from EtOH to plates, m.p. 123～124°. Yield 5.8 g. (80%). No depression in the melting point was observed on admixture with an authentic sample.

b) Through a mixture of 10.6 g. of benzaldehyde and 13.5 g. of formamide, NH$_3$ was bubbled on a boiling water bath for 3 hr., during which an oily layer of benzaldehyde gradually disappeared. The resultant solution was concentrated on a water bath under reduced pressure. The residue crystallized and were recrystallized from EtOH. Yield, 9.6 g. (81%). No depression in the melting point was observed on admixture with an authentic sample.

N-Benzylidene-α-acetamidobenzylamine——a) A mixture of 9 g. of hydrobenzamide and 15.9 g. of acetamide was reacted for 3 hr. in the same way as above. After an excess of acetamide was removed from the reaction mixture, crystalline residue was recrystallized from EtOH to prisms, m.p. 132～134°. Yield, 7 g. (59%). No depression in the melting point was observed on admixture with an authentic sample.

b) NH$_3$ was bubbled through a mixture of 10.6 g. of benzaldehyde and 17.7 g. of acetamide on a boiling water bath for 3 hr. After an excess of acetamide was removed, the residue was recrystallized from EtOH. Yield 7.5 g. (50%). No depression in the melting point was observed on admixture with an authentic sample.

N-(4-Methoxybenzylidene)-α-formamido-4-methoxybenzylamine——A mixture of 13.6 g. of anisaldehyde and 17.5 g. of formamide was heated on a boiling water bath for 3 hr. with stirring, while NH$_3$ was introduced. The reaction mixture was allowed to stand overnight to deposit the crystals, which were washed with dry Et$_2$O and then with cold H$_2$O to remove unchanged anisaldehyde and formamide. Recrystallization of the crude crystals from MeOH gave plates, m.p. 154～155°, weighing 5.5 g. (37%). *Anal.* Calcd. for $C_{17}H_{18}O_3N_2$: C, 68.44; H, 6.08; N, 9.39. Found : C, 68.70; H, 6.00; N, 9.46.

In addition to the plate crystals, a small amount of needles, m.p. 124°, was obtained from the recrystallization filtrate. The needle crystals were analyzed to give the same molecular formula as that of the plate crystals obtained as above but were more soluble in MeOH or EtOH. *Anal.* Calcd. for $C_{17}H_{18}O_3N_2$: C, 68.44; H, 6.08; N, 9.39. Found : C, 68.62; H, 6.21; N, 9.58.

This substance seemed to exist two forms of crystals, but no effort was made to confirm the difference between them.

N-(4-Methoxybenzylidene)-α-acetamido-4-methoxybenzylamine——A mixture of 13.6 g. of anisaldehyde and 17.7 g. of acetamide was heated on a boilng water bath for 3 hr. with the introduction of NH$_3$. After removal of the unchanged anisaldehyde and acetamide by vaccum distillation, the residue was washed with dry Et$_2$O. The crude crystals were recrystallized from EtOH to prisms, m.p. 148°. Yield, 7.0 g. (45%). *Anal.* Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.21; H, 6.45; N, 8.97. Found : C, 69.42; H, 6.23; N, 9.18.

2. Replacement Reaction

Following compounds, which were carefully purified, were used : N-Benzylidenemethylamine (b.p. 184～185°), N-(4-methoxybenzylidene)methylamine (b.p. 236～237°), benzaldehyde (b.p. 178～179°), anisaldehyde (b.p. 246～248°).

An equimolar mixture of N-benzylidenemethylamine and anisaldehyde was heated on a boiling water bath. Immediately after being heated for a requisite period, the mixture was fractionated under reduced pressure at a water-bath temperature, when the mixture was satisfactorily separated into two kinds of distillates, b.p$_5$ 54～57° and b.p$_{1.5}$ 68～73°. A sample of each distillate in AcOH was titrated with 0.1*N* HClO$_4$ in AcOH using methyl violet as an indicator, following the method reported by Freeman.[5] Percentage of the conversion in this reaction was measured for the determination of the time taken to attain the equilibrium.

Time (hr.)	1	2	3	4	4.5	5	6
Conversion rate (%)	23.7	32.8	38.3	41.9	42.6	42.7	42.7

In was found that the percentage of the conversion is maintained constant in the reaction period of over 4.5 hr. and that the equilibrium is attained at the conversion of 42.7%.

An experiment to carry out the reverse reaction between N-(4-methoxybenzylidene)methylamine and benzaldehyde in the reaction period of 6 hr. was also in agreement with the above result giving the conversion rate of 57.5%.

Consequently, the approximate equilibrium constant is

$$K=\frac{[CH_3OC_6H_4CHO][C_6H_5CH=NCH_3]}{[CH_3OC_6H_4CH=NCH_3][C_6H_5CHO]}=0.55$$

The authors are grateful to Prof. Emeritus M. Ishidate of the Tokyo University and to Dr. T. Ukai, President of this college, for their kind encouragement during the course of this work. The authors are also indebted to Miss Y. Saito for the elementary analyses.

Summary

Formation of N-arylmethylene-1-acylamino-1-arylmethylamine resulted in some cases when aromatic aldehyde-ammonia mixture or hydrobenzamide was allowed to react with amide. In the light of this fact the mechanism comprehensive for all the reactions which lead to the formation of N-arylmethylene-1-acylamino-1-arylmetylamine was proposed.

(Received February 13, 1962)

UDC 547.292'172

157. Koji Yamakawa, Hisao Ochi, and Kiichi Arakawa : Organometallic Compounds. I. Some Transformation Reactions of 1,1'-Diacetylferrocene.

(*Tokyo Research Institute, Yawata Iron & Steel Co., Ltd.*[*1])

Since the discovery of ferrocene[1~3] in 1951 it has been found by numerous chemical confirmations that the compound undergoes facile aromatic substitution reactions.[4]

Some transformation reactions of 1,1'-diacetylferrocene has been investigated as described below.

Ferrocene (I) used in these reactions was prepared by the diethylamine method described by Wilkinson,[5] though a more convenient sodium alkoxide method was reported recently by Eisenthal *et al.*[6]

1,1'-Diacetylferrocene[7~9] is one of the important disubstituted ferrocene intermediates which was first synthesized by Woodward and his co-workers,[7] employing with aluminum chloride as catalyst in the Friedel-Crafts reaction. By the modified procedure of Woodward, oxidation of 1,1'-diacetylferrocene (II) with sodium hypochlorite gave yellow sodium salt of 1,1'-ferrocenedicarboxylic acid (III) in a good yield, which was hydrolyzed to the dicarboxylic acid III.

[*1] 1618 Ida, Kawasaki, Kanagawa-Ken (山川浩司, 越智久雄, 荒川基一).

1) T.J. Kealy, P.L. Pauson : Nature, **168**, 1039 (1951).

2) S.A. Miller, J.A. Tebboth, J.F. Tremaine : J. Chem. Soc., **1952**, 632.

3) In this and subsequent papers from this laboratory, the generic name "ferrocene" will be used instead of the more formal dicyclopentadienyliron (II) [cf. R.B. Woodward, M. Rosenblum, M.C, Whiting : J. Am. Chem. Soc., **74**, 3458 (1952)].

4) For a reviews of the aromatic reactions of ferrocene, see *a*) P.L. Pauson : Quart. Revs., **9**, 409 (1955); *b*) A.N. Nesmeyanov, E.G. Perealova : Uspekhi Khim., **27**, 3 (1955); *c*) M.D. Rausch, M. Vogel, H. Rosenberg : J. Chem. Educ., **34**, 268 (1957); *d*) S. Yamada, M. Kumada, S. Hagiwara, H. Yamazaki : Kagaku, **14**, 358 (1959); *e*) K. Arakawa, K. Yamakawa : Kagaku no Ryoiki, **14**, 632 (1960); *f*) K. Plesske : Angew. Chem., **74**, 301, 347 (1962).

5) G. Wilkinson : Organic Syntheses, **36**, 34 (1956).

6) W.F. Little, R.C. Koestler, R. Eisenthal : J. Org. Chem., **25**, 1435 (1960).

7) R.B. Woodward, M. Rosenblum, M.C. Whiting : J. Am. Chem. Soc., **74**, 3458 (1952).

8) R. Riemschneider, D. Helm : Chem. Ber., **89**, 155 (1956).

9) G.D. Broadhead, J.M. Osgerby, P.L. Pauson : J. Chem. Soc., **1958**, 650.