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156. Minoru Sekiya and Toshio Oishi : Reactions of Amide Homologs. II.[1] The Reaction among Azomethines, Aromatic Aldehydes, and Formamide.

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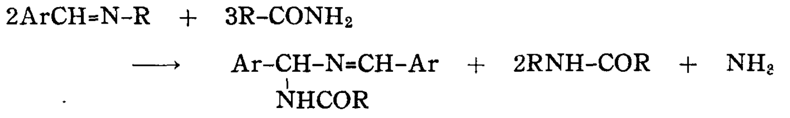
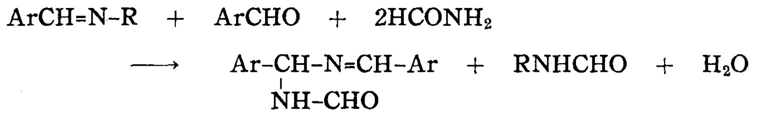
In the preceding paper,[1] it was shown with several examples that N-arylmethylenealkylamine reacts with amides to form N-arylmethylene-1-acylamino-1-arylmethylamine.



$$\begin{array}{l} 2\mathrm{ArCH{=}N{-}R} + 3\mathrm{R{-}CONH_2} \\ \longrightarrow \mathrm{Ar{-}}\underset{\mathrm{NHCOR}}{\mathrm{CH}}\mathrm{{-}N{=}CH{-}Ar} + 2\mathrm{RNH{-}COR} + \mathrm{NH_2} \end{array} \qquad (1)$$

The present work was undertaken to see if the reaction would take place in essentially the same way, when the aromatic aldehyde is used as a reactant instead of one-half the N-arylmethylenealkylamine in reaction (1). Several of the reaction were then attempted by heating together aromatic aldehyde, N-arylmethylenealkylamine, and formamide (molar ratio, 1:1:6), and it was found that the aromatic aldehyde took part in the reaction to give N-arylmethylene-1-acylamino-1-arylmethylamine acting as a substitute for a portion of N-arylmethylenealkylamine. The reaction equation would be represented as in the following :



$$\begin{array}{l} \mathrm{ArCH{=}N{-}R} + \mathrm{ArCHO} + 2\mathrm{HCONH_2} \\ \longrightarrow \mathrm{Ar{-}}\underset{\mathrm{NH{-}CHO}}{\mathrm{CH}}\mathrm{{-}N{=}CH{-}Ar} + \mathrm{RNHCHO} + \mathrm{H_2O} \end{array} \qquad (2)$$

The reaction was examined using benzaldehyde, *p*-chlorobenzaldehyde, or anisaldehyde as an aromatic aldehyde, together with the corresponding N-arylmethylenealkyl amine. A mixture of benzaldehyde, N-benzylidenemethylamine, and formamide was heated on a boiling water bath and gave N-benzylidene-α-formylamidobenzylamine. Its yield was 88% of the theoretical, which is much higher than that of the reaction[1] between N-benzylidenemethylamine and formamide in the same reaction period. This yield indicated that benzaldehyde took part in the reaction because if the yield was lower than 50%, it could not be deduced that benzaldehyde took part in the reaction. In the reaction among N-benzylideneëthylamine, benzaldehyde, and formamide, yield of N-benzylidene-α-formamidobenzylamine was 48%, but satisfactory amount of N-benzylideneëthylamine was recovered. The same reaction among *p*-chlorobenzaldehyde, N-(*p*-chlorobenzylidene)methylamine, and formamide occurred to afford N-(*p*-chlorobenzylidene)-α-formamido-*p*-chlorobenzylamine, whose yield was 72% of the theoretical. The reaction among anisaldehyde, N-(*p*-methoxybenzylidene)methylamine, and formamide

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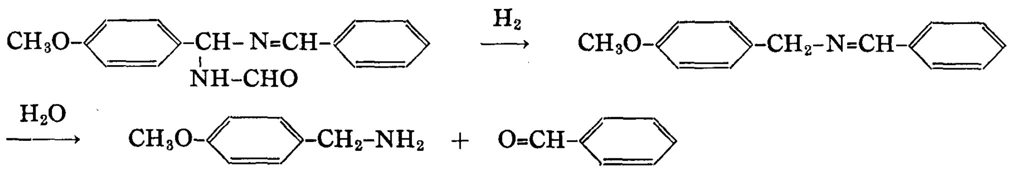
afforded N-(*p*-methoxybenzylidene)-α-formamido-*p*-methoxybenzylamine, but in this case, its yield was not more than 27% of the theoretical, so that anisaldehyde could not have taken part in the reaction.

In order to make further examination of this reaction, an attempt was made to prepare N-arylmethylene-1-formamidoarylmethylamine containing two different aryl groups. For this purpose, the reaction among benzaldehyde, N-(*p*-methoxybenzylidene)-methylamine, and formamide was examined. A product, m.p. 110∼111°, obtained by this reaction was analysed to give the empirical formula, $C_{16}H_{16}O_2N_2$, which corresponded to N-arylmethylene-1-formamido-1-arylmethylamine compound containing phenyl and *p*-methoxyphenyl as the two aryl groups, but the positions of the two groups, were not clear. The substance was reduced with hydrogen using palladium carbon as a catalyst. Immediately after absorption of one mole of hydrogen, resultant product was hydrolysed with 10% hydrochloric acid, and benzaldehyde and *p*-methoxybenzylamine were obtained as the product. From this fact, the above substance was identified as N-benzylidene-α-formamido-*p*-methoxybenzylamine.



The same reaction of a mixture of N-benzylidenemethylamine, anisaldehyde, and formamide did not produce the desirable product, N-(*p*-methoxybenzylidene)-α-formamidobenzylamine, but gave N-benzylidene-α-formamido-*p*-methoxybenzylamine, which was identical with the compound obtained by the foregoing reaction, N-(*p*-methoxybenzylidene)-α-formamido-*p*-methoxybenzylamine, and N,N′-bis(*p*-methoxybenzylidene)diformamide.

Considering the above findings, it could be concluded that aromatic aldehyde, N-arylmethylenealkylamine, and formamide reacted together to give N-arylmethylene-1-formamidoarylmethylamine. In most cases, N-alkylformamide was also isolated as a by-product, from which the reaction could be represented by the foregoing equation (2).

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Experimental

N-Benzylidene-α-formamidobenzylamine—a) A mixture of 6 g. (0.05 mole) of N-benzylidenemethylamine, 5.3 g. (0.05 mole) of benzaldehyde, and 13.5 g. (0.3 mole) of formamide was heated for 3 hr. on a boiling water bath and agitated from time to time. The resultant solution was concentrated on a water bath under a reduced pressure. The syrupy residue soon crystallized, the product was collected, washed with a small amount of EtOH, and dried. Yield, 10.6 g. (88%). Prisms (from EtOH), m.p. 123∼124°. No depression in m.p. was observed in admixture with an authentic sample prepared in the preceding work.

b) A mixture of 6.7 g. (0.05 mole) of N-benzylideneëthylamine, 5.3 g. (0.05 mole) of benzaldehyde, and 13.5 g. (0.3 mole) of formamide was treated as in a). In this case an initial oily layer of the reaction mixture did not disappear even at the termination of the reaction. N-Benzylidene-α-formamidobenzylamine was obtained in a yield of 5.8 g. (48%), and showed no depression in m.p. on admixture with an authentic sample. Even if the reaction time was extended to 10 hr., the yield did not increase markedly. An upper oily layer of the distillate obtained by distillation of the reaction mixture was separated, washed with formamide and water, dried, and purified by vacuum distillation. This was the recovery of N-benzylideneëthylamine; yield, 3.8 g.

N-(*p*-Chlorobenzylidene)-*α*-formamido-*p*-chlorobenzylamine—A mixture of 5 g. (0.033 mole) of N-*p*-chlorobenzylidenemethylamine, 4.6 g.(0.033 mole) of *p*-chlorobenzaldehyde, and 9 g. (0.2 mole) of formamide was heated for 3 hr. on a boiling water bath. Crystals deposited on cooling were collected by filtration and the same kind of crystals were obtained from the residue when the filtrate was concentrated *in vacuo*. Needles (from EtOH), m.p. 150°. Total yield, 7.3 g. (72%). No depression in m.p. was observed on admixture with an authentic sample.

N-(*p*-Methoxybenzylidene)-*α*-formamido-*p*-methoxybenzylamine—A mixture of 7.5 g (0.05 mole) of N-*p*-methoxybenzylidenemethylamine, 6.8 g. (0.05 mole) of anisaldehyde, and 13.5 g. (0.3 mole) of formamide was heated for 3 hr. on a boiling water bath. The solution was concentrated under a reduced pressure, the residue was chromatographed through alumina column, and developed with benzene. Plates, m.p. 151~154°, were obtained. Yield, 4.0 g. (27%). No depression in m.p. was observed on admixture with an authentic sample. The last eluate with EtOH gave needles, m.p. 169~170°, which were shown to be N,N′-bis(anisylidene)diformamide by their failure to depress the m.p. of an authentic sample.

N-Benzylidene-*α*-formamido-*p*-methoxybenzylamine—A mixture of 7.5 g. (0.05 mole) of N-(*p*-methoxybenzylidene)methylamine, 5.3 g. (0.05 mole) of benzaldehyde, and 13.5 g. (0.3 mole) of formamide was heated for 3 hr. on a boiling water bath. The solution was concentrated under a reduced pressure, the residue was dissolved in benzene, the benzene solution was passed through a column of alumina, and eluted with benzene. After evaporation the main fraction gave an oily substance which was treated with dry Et_2O. Crystals thereby separated were recrystallized from benzene-benzine, forming plates, m.p. 110~111°. Yield, 5.4 g. (40%). *Anal.* Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.62; H, 6.01; N, 10.44. Found : C, 71.76; H, 6.22; N, 10.40.

The last eluate with EtOH gave N,N′-bis(anisylidene)diformamide. Yield, 0.43 g.

b) A mixture of 6 g.(0.05 mole) of N-benzylidenemethylamine, 6.8 g.(0.05 mole) of anisaldehyde, and 13.5 g. (0.3 mole) of formamide was heated for 3 hr. on a boiling water bath. The solution was concentrated under a reduced pressure, the residue was chromatographed through alumina column, and developed with Et_2O:benzene (3:7). The eluted fraction was evaporated and the oily residue was treated with dry Et_2O, from which two kinds of crystals were separated; 1.71 g. (11%) of N-benzylidene-*α*-formamido-*p*-methoxybenzylamine, m.p. 105~115° (from AcOH), and 1.1 g. (16%) of N-(*p*-methoxybenzylidene)-*α*-formylamino-*p*-methoxybenzylamine, m.p. 128~135° (from AcOH). Both compounds were identified by their failures to depress the m.p. of authentic samples. The last eluate with EtOH gave 0.16 g. of N,N′-bis(*p*-methoxybenzylidene)diformamide.

Catalytic Reduction of N-Benzylidene-*α*-formamido-*p*-methoxybenzylamine—A solution of 3 g. of N-benzylidene-*α*-formamido-*p*-methoxybenzylamine dissolved in 20 cc. of EtOH was catalytically reduced with 0.6 g. of 10% Pd-C at a room temperature under an ordinary pressure until 1 mole of H_2 (240 cc.) was absorbed, taking about 13 min. After filtration of the catalyst, the solution was evaporated. The residue forming two layers was added with a suitable amount of water and extracted with benzene. By the usual treatment of the aqueous layer the presence of formamide was proved in it. The benzene layer was dried, evaporated, and the residual oily substance was hydrolysed by heating together with 12 cc. of 10% HCl. The separated oily layer was removed by steam distillation, which was shown to be benzaldehyde. The yield of its phenylhydrazone was 1.6 g. (74%). The crystalline residue obtained by steam distillation was recrystallized from EtOH forming crystals, m.p. 240~241°, which was shown to be *p*-methoxybenzylamine hydrochloride by its failure to depress the m.p. of an authentic sample. Yield, 1.3 g. (83%).

Summary

It was found that aromatic aldehyde, N-arylmethylenealkylamine, and formamide react together to give N-arylmethylene-1-formamido-1-arylmethylamine. Benzaldehyde and *p*-chlorobenzaldehyde were used as reactants with the corresponding N-arylmethylenealkylamine. By using benzaldehyde and N-(*p*-methoxybenzylidene)methylamine, N-(*p*-methoxybenzylidene)-*α*-formamidobenzylamines containing different aryl groups were obtained.

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