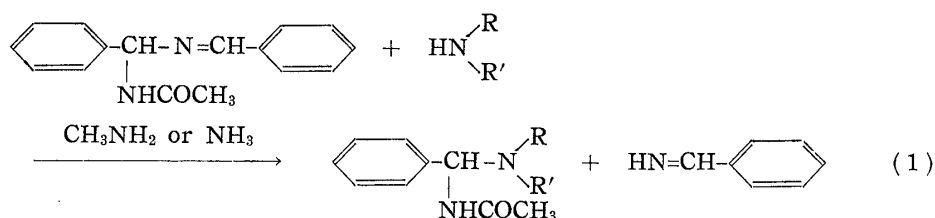


153. Minoru Sekiya and Keiichi Ito : Reaction of Amide Homologs. VII.
Formation of N-(α -Dialkylaminobenzyl)acetamides from
N-Benzylidene- α -acetamidobenzylamine.

(Shizuoka College of Pharmacy*1)

With N-benzylidene- α -acetamidobenzylamine, whose preparation was previously reported by Sekiya, *et al.*,¹⁾ a new reaction was found to occur, resulting in the formation of N-(α -dialkylaminobenzyl)acetamides. Such benzylidenediamine derivatives have not been reported previously, though the corresponding methylenediamine derivative, N-(dialkylaminomethyl)amide, is well known as N-Mannich base. The formation reaction and its mechanism are herein described.

A mixture of N-benzylidene- α -acetamidobenzylamine (BAB) dissolved in a considerable amount of secondary amine reactant was heated on a boiling water bath and methylamine or ammonia was passed through the reaction mixture.



As the secondary amine, piperidine, morpholine, dibenzylamine or N-methylbenzylamine was used for the reaction and the corresponding N-(α -dialkylaminobenzyl)acetamide was formed. For the separation of the product the reaction mixture was concentrated, the residue was washed with a saturated sulfur dioxide solution, and the crude product was separated from a considerable amount of impurities which were soluble in the solution. Yield of the reaction product was lower than 50%.

The product, N-(α -dialkylaminobenzyl)acetamide, was found to form benzaldehyde by hydrolysis with dil. sulfuric acid. Hydrolysis of N-(α -dibenzylaminobenzyl)acetamide resulted in the formation of benzaldehyde, dibenzylamine and ammonia. Infrared spectra exhibited the presence of N-monosubstituted amide group and other characteristic bands not corresponding with N-(α -dialkylaminobenzyl)acetamide were not recognized. Hydrogenolysis at the bond of the carbon connecting to nitrogen of the amide group was effected under high hydrogen pressure using Raney nickel, indicating the powerful interpretation of their formulations. Details of this hydrogenolysis will be published in the succeeding paper of this series.

Table I represents some data for the formation reaction.

TABLE I.

Secondary amine	Carrier	Product	m.p. (°C)	Yield (%)
Piperidine	Methylamine	N-(α -Piperidinobenzyl)acetamide	148~149	18
Piperidine	Ammonia	N-(α -Piperidinobenzyl)acetamide		7
Dibenzylamine	Methylamine	N-(α -Dibenzylaminobenzyl)acetamide	181~183	31
Dibenzylamine	Ammonia	N-(α -Dibenzylaminobenzyl)acetamide		15
Morpholine	Methylamine	N-(α -Morpholinobenzyl)acetamide	151~152	49
N-Methylbenzylamine	Methylamine	N-[α -(N'-Methylbenzylamino)benzyl]-acetamide	150~151	36

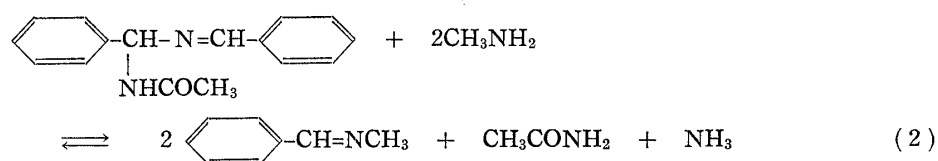
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1) M. Sekiya, T. Oishi : This Bulletin, 7, 471 (1959).

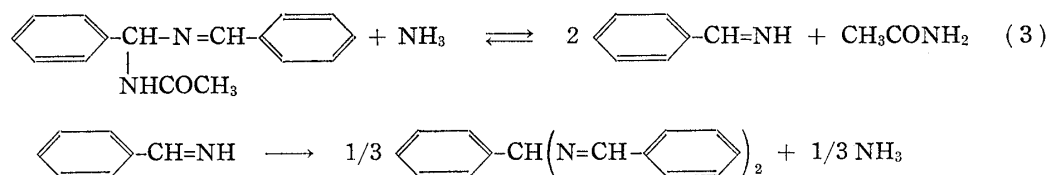
An attempt to use N-methylaniline as the secondary amine reactant for the reaction was unsuccessful. The use of the corresponding formamide homolog instead of BAB was also tested for the reaction, but the desired product was not obtained. This is considered to be due to the fact that formamide group is less stable than acetamide group.

In this formation reaction, methylamine or ammonia accelerates the reaction, because the reaction did not take place in their absence, and the former is more effective than the latter as shown in the case of piperidine and dibenzylamine in Table I.

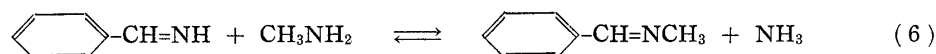
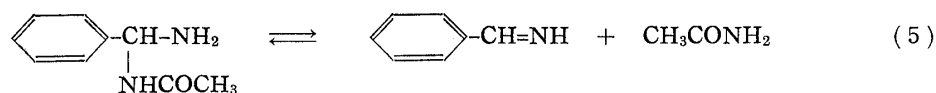
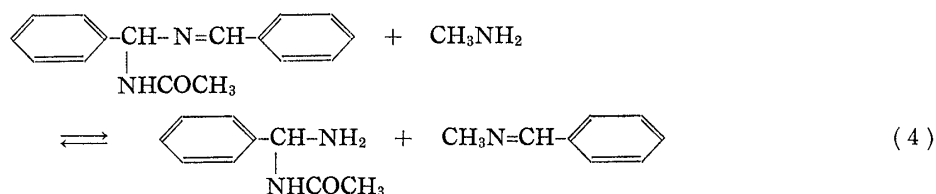
In order to pursue the essential step of this formation reaction, an experiment was undertaken to see whether or not the reaction between BAB and methylamine or ammonia will occur. When methylamine was passed through the solution of BAB in pyridine, the reaction was found to take place to a certain extent to give N-benzylidene-methylamine and acetamide. This reaction can be represented as follows :



The reaction with ammonia instead of methylamine in pyridine gave acetamide, the amount of which was less than that obtained from the reaction with methylamine. In consideration of the above reaction with methylamine, the following formula may be as well written for this reaction, though it failed to give an expected product, benzylideneimine or hydrobenzamide, because of difficulties in its separation.



Considering the pathway of reaction (2), the following scheme can be written reasonably for this reaction and the pathway of reaction (3) can be as well considered by the replacement of methylamine with ammonia.

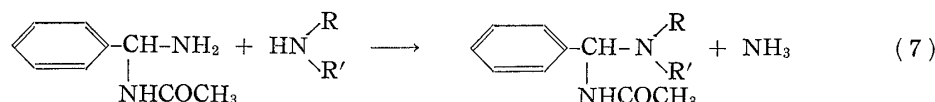


The stage (4) is the replacement reaction between azomethine and amine or ammonia, which type of the reaction has already been reported by Sekiya, *et al.*,²⁾ and in the stage (5), the decomposition of α -acetamidobenzylamine follows. As both stages (4) and (5) are equilibrium reactions, the equilibrium would not shift so far to the right.

2) M. Sekiya, A. Hara, T. Masui : This Bulletin, 11, 277 (1963).

In the reaction with methylamine, ammonia formed in stage (6) would escape from the equilibrium mixture and the reaction would be accelerated.

The mechanism of the reaction (1) will be discussed below. As mentioned in the foregoing, the reaction (1) did not take place in the absence of methylamine or ammonia. Therefore, it seems safe to say for the reaction (1) that the secondary amine in high concentration has an opportunity to attack the intermediate, α -acetamidobenzylamine formed in the stage (4), leading to the formation of N-(α -dialkylaminobenzyl)acetamide which is stable enough. This is represented as follows :



Thus, the mechanism for the reaction (1) would be explained by taking account of reactions (4) and (7).

It is considered that a large excess of secondary amine reactant used in the formation reaction (1) also serves as the basic environment which has an effect on promoting the reaction. This is thought by the fact that no reaction occurred in a test to carry out the essential reaction (2) in dioxane, though it took place in pyridine as mentioned in the foregoing. It was also found that the reaction (2) in N-methylaniline occurred to a certain extent, while the reaction (1) did not. Thus, the basic environment would be necessary for the reaction (2). The reason that the reaction (1) does not proceed in the case of N-methylaniline appears due to that the step (7) is retarded because of its weak basicity.

As a side reaction, formation of a considerable amount of N-acetylpiperidine was found in the use of piperidine as the amine in the reaction (1). This by-product is considered to be derived from piperidine by action of acetamide, liberated from BAB in the stage (5). Therefore, in the reaction with such a strong base, the formation of its N-acetylated amine must be expected as a by-product.

Experimental

Reaction of BAB with Methylamine—A solution of 5 g. of BAB in 10 cc. of pyridine was heated on a boiling water bath for 2 hr., while dry MeNH₂ was introduced. The reaction mixture was distilled under reduced pressure giving two kinds of distillates in addition to the solvent. The first distillate, b.p.₂₀ 78~82°, weighing 0.7 g., was N-benzylidenemethylamine, which was hydrolyzed with oxalic acid to methylammonium hydrogen oxalate and benzaldehyde, and the latter was converted into its phenylhydrazone. Melting point of both methylammonium hydrogen oxalate and benzaldehyde phenylhydrazone was not depressed by admixture with an authentic sample. The second distillate, b.p.₂ 60~69°, m.p. 72~75°, was identical with acetamide by admixture. Yield, 0.2 g.

Reaction of BAB with Ammonia—Except that dry NH₃ was used instead of MeNH₂, 5 g. of BAB was treated in the same manner as described in the foregoing experiment. By distillation, a fraction of b.p.₁ 55~67°, m.p. 71~73°, was obtained and this was identical with acetamide by admixture with an authentic sample. Yield, 0.1 g.

Reaction of BAB with Secondary Amine

1. N-(α -Piperidinobenzyl)acetamide—a) A mixture of 12.6 g. of BAB and 7.3 g. of piperidine was heated on a boiling water bath for 2 hr., while dry MeNH₂ was passed through the mixture. The reaction solution was concentrated under reduced pressure to give a distillate, b.p.₂₀ 73~115°, and a small amount of acetamide fraction. The residue was washed thoroughly with a saturated SO₂ solution, then with H₂O, and dried. Recrystallization from benzene afforded colorless needles, m.p. 148~149°, weighing 2.1 g. *Anal.* Calcd. for C₁₄H₂₀ON₂: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.31; H, 8.68; N, 11.92. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3276 (NH), 1635, 1525 (CONH).

The foregoing distillate was found to be mostly N-acetylpiperidine containing a certain amount of N-benzylidenemethylamine, as the hydrolysis of this distillate afforded piperidine, acetic acid, benzaldehyde and methylamine.

b) By the same procedure as in a) except that dry NH_3 was used instead of MeNH_2 , 0.8 g. of N -(α -piperidinobenzyl)acetamide was obtained from 12.6 g. of BAB.

2. N -(α -Dibenzylaminobenzyl)acetamide—a) A mixture of 16 g. of BAB and 19 g. of dibenzylamine was reacted in the same condition as in 1a) using MeNH_2 . Distillation of the reaction mixture afforded N -benzylidenemethylamine and acetamide in addition to unchanged dibenzylamine (because of its weak basicity, N -acetyldibenzylamine was not obtained). The residue was treated with a saturated SO_2 solution as in 1a). Recrystallization from benzene afforded white needles, m.p. $181\sim 183^\circ$, weighing 6.8 g. *Anal.* Calcd. for $\text{C}_{23}\text{H}_{24}\text{ON}_2$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.04; H, 6.89; N, 8.20. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3280 (NH), 1636, 1532 (CONH).

By hydrolysis with 5% H_2SO_4 , benzaldehyde was liberated in oily layer, which was collected by extraction with benzene and identified as its phenylhydrazone, m.p. $155\sim 156^\circ$, by admixture. The aqueous layer was basified with NaOH and distilled, when NH_3 was vaporized. By steam distillation dibenzylamine was obtained. After extraction with benzene this was identified as 1-phenyl-3,3-dibenzylthiourea, m.p. $144\sim 145^\circ$, by admixture.

b) By the same procedure as in a) except that dry NH_3 was used instead of MeNH_2 , 2.5 g. of N -(α -dibenzylaminobenzyl)acetamide was obtained from 12.6 g. of BAB.

3. N -(α -Morpholinobenzyl)acetamide—A mixture of 15 g. of BAB and 8 g. of morpholine was reacted in the same condition as in 1a) using MeNH_2 . The reaction mixture was concentrated under reduced pressure and the residue was washed with dry Et_2O and recrystallized from benzene to white needles, m.p. $151\sim 152^\circ$, weighing 6.9 g. *Anal.* Calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_2\text{N}_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.22; H, 7.66; N, 11.54. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3385 (NH); 1643, 1527 (CONH); 1120 (ether).

4. N -[α -(N' -Methylbenzylamino)benzyl]acetamide—A mixture of 10 g. of BAB and 7.2 g. of N -methylbenzylamine was reacted in the same condition as in 1a) using MeNH_2 . The reaction mixture was treated as in 3. Recrystallization from benzene afforded white needles, m.p. $150\sim 151^\circ$, weighing 3.8 g. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{20}\text{ON}_2$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.07; H, 7.37; N, 10.25. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3186 (NH), 1637, 1547 (CONH).

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Summary

N -Benzylidene- α -acetamidobenzylamine reacted with dialkylamines in the presence of methylamine or ammonia affording compounds of new benzylidenediamine type, N -(α -dialkylaminobenzyl)acetamides. By using piperidine, morpholine, dibenzylamine, and N -methylbenzylamine as the secondary amine reactant the corresponding products were obtained. A mechanism for this reaction was suggested.

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