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154. **Minoru Sekiya and Keiichi Ito**: Reaction of Amide Homologs. VIII. Catalytic Hydrogenolysis of O- or N-Acylaminomethyl and N-α-Acylaminobenzyl Compounds.

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Though there are many reports concerning catalytic hydrogenolysis of variety of compounds, that of the derivatives of O- or N-acylaminomethyl and N-α-acylaminobenzyl compounds has remained unclarified. The present paper deals with the catalytic hydrogenolysis of some compounds classified as N-hydroxymethylamide, N-dialkylaminomethylamide, and N-(α-dialkylaminobenzyl)amide. With these compounds, there exist two possible modes of hydrogenolysis; *i.e.* hydrogenolysis of two bonds of the carbon atom connecting to nitrogen or oxygen. It appeared of interest to see how the hydrogenolysis actually follows.

There has been a report dealing with catalytic hydrogenolysis of N-hydroxymethylamides. According to this work,[1] the fission takes place at the position of carbon-oxygen bond, but the experiment dealt only with N-hydroxymethylacetamide, in which the hydrogenolysis was carried out under high pressure of hydrogen in aqueous solution with cobalt catalyst at elevated temperature, leading to the formation of N-methylacetamide.

In the present work, hydrogenolysis of N-hydroxymethylacetamide in dioxane solution was examined under high pressure of hydrogen using Raney nickel catalyst. Contrary to the above report, hydrogenolysis brought about fission at the cabon-nitrogen bond resulting in the formation of acetamide. Hydrogenolysis in aqueous solution could not be carried out, because N-hydroxymethylacetamide was hydrolyzed easily with water at elevated temperature forming acetamide.

In continuation, N-hydroxymethylbenzamide was hydrogenolyzed in alcohol in the same mode as in the above case giving benzamide.

Hydrogenolysis of some of the compounds of another type, such as N-(dialkylaminomethyl)benzamide and N-(α-dialkylaminobenzyl)acetamide, was examined in alcohol with Raney nickel catalyst and under high pressure of hydrogen. It was found in every case that the hydrogenolysis took place at the bond of the carbon connecting to nitrogen of amide group.

The above experimental data are summarized in Table I. As shown, hydrogenolysis proceeded almost quantitatively in every case.

TABLE I.

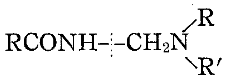
Material	Solvent	Reduction temp. (°C)	Hydrogenolysis (%)
N-Hydroxymethylacetamide	Dioxane	120～160	91
N-Hydroxymethylbenzamide[a]	Alcohol	80～ 90	90
N-(Dimethylaminomethyl)benzamide[b]	〃	80～ 92	98
N-(Piperidinomethyl)benzamide[a]	〃	80～ 85	98
N-(α-Piperidinobenzyl)acetamide[c]	〃	125～130	92
N-(α-Dibenzylaminobenzyl)acetamide[c]	〃	130～140	92
N-[α-(N′-Methylbenzylamino)benzyl]acetamide[c]	〃	100～105	90

a) A. Einhorn : Ann., **343**, 207 (1905).
b) H. Hellman, G. Haas : Chem. Ber., **90**, 52 (1957).
c) M. Sekiya, K. Ito : Part Ⅶ : This Bulletin, **11**, 888 (1963).

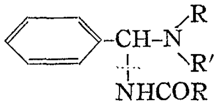
[*1] Oshika, Shizuoka (関屋 実, 伊藤敬一).
1) M. W. Farlow : U. S. Pat. 2,422,400 (1947).

Previously, hydrogenolysis of N-benzylidene-α-formamidobenzylamine2) and N-benzylidene-α-formamido-p-methoxybenzylamine3) has been reported, in which the bond adjacent to nitrogen of formamide group was attacked as in the case of N-(α-dialkylaminobenzyl)acetamide. From these facts, it is concluded that hydrogenolysis of O- or N-acylaminomethyl and N-α-acylaminobenzyl compounds takes place at the bond of the carbon connecting to nitrogen of amide group as shown in the following. Dotted lines show where hydrogenolyses occurred.

$RCONH\text{-}\vdots\text{-}CH_2OH$



$RCONH\text{-}\vdots\text{-}CH_2N\begin{smallmatrix}\nearrow R\\ \searrow R'\end{smallmatrix}$



With N-hydroxymethylamide, N-(dialkylaminomethyl)benzamide, and N-(α-dialkylaminobenzyl)acetamide the nucleophilic substitution has been known not to take place at the bond which is attacked in hydrogenolysis, but another bond of the carbon connecting to nitrogen or oxygen. This difference between the two reactions appears to be of interest.

Experimental

1. Preparation of N-Hydroxymethylacetamide[*2]

A mixture of 19 g. of acetamide, 24 cc. of 37% CH_2O, and a solution of 2 g. of K_2CO_3 was heated at 50° for a few min. After standing overnight at room temperature, the reaction mixture was neutralized with CO_2 and concentrated under reduced pressure below 50°. The residue was thoroughly dried in vacuum desiccator over P_2O_5. Yield, 23 g. Because of its impurity this was submitted to continuous extraction with anhyd. Et_2O at room temperature. By evaporation of a middle fraction of the extract, almost pure crystals, m.p. 49~52°, were obtained.

2. Catalytic Hydrogenolysis

a) **N-Hydroxymethylacetamide**——To a solution of 7 g. of N-hydroxymethylacetamide in 50 cc. of dioxane, Raney Ni catalyst (1 g. as 50% alloy) was added in an autoclave. Under 77 kg./cm^2 of initial H_2 pressure (at 18°), the mixture was heated and then constant shaking was started at 120°. Approximately calculated amount of H_2 was absorbed in about 4 hr., while the temperature was maintained at 120~160°. The reaction mixture was filtered and concentrated on an oil bath to remove majority of the solvent. The residue was distilled under reduced pressure to give a solid distillate, b.p$_{23}$ 118~123°, weighing 4.2 g. This was found to be identical with acetamide by admixture with an authentic sample.

b) **N-Hydroxymethylbenzamide**——A mixture of 10 g. of N-hydroxymethylbenzamide, 50 cc. of EtOH, and Raney Ni catalyst (1 g. as 50% alloy) was placed in an autoclave under initial H_2 pressure of 100 kg./cm^2 (at 20°) and hydrogenated at 80~90° in the same way as in a). Approximately calculated amount of H_2 was absorbed in about 1.5 hr. After removal of the catalyst and the solvent, the residue soon crystallized. The white crystals, m.p. 114~116°, weighing 7.2 g., was identical with benzamide by admixture.

c) **N-(Dimethylaminomethyl)benzamide**——A mixture of 9 g. of N-(dimethylaminomethyl)benzamide, 50 cc. of EtOH and Raney Ni (1 g. as 50% alloy) was placed in an autoclave under initial H_2 pressure of 70 kg./cm^2 (at 27°) and hydrogenated at 80~92° in the same way as in a). The absorption was nearly completed in about 1 hr. Excess H_2 pressure in the autoclave was drawn through alcoholic HCl solution and trimethylamine in H_2 was absorbed in it. After filtration, the reaction solution was concentrated and the vapor was also passed through alcoholic HCl solution through a condenser. Both alcoholic HCl solutions were combined and then concentrated to dryness, giving 4.7 g. of trimethylamine hydrochloride. This was identified as its picrate by admixture.

The foregoing residue was crystallized to 6.0 g. of benzamide, no depression of melting point being observed on admixture with an authentic sample.

d) **N-(Piperidinomethyl)benzamide**——A mixture of 11 g. of N-(piperidinomethyl)benzamide, 70 cc. of EtOH, and Raney Ni catalyst (1 g. as 50% alloy) was placed in an autoclave under initial H_2 pressure of 100 kg./cm^2 (at 26°) and hydrogenated at 80~85° in the same way as in a). The absorption was

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[*2] Pure substance was obtained by this modified method of A. Einhorn: Ann., **343**, 265 (1905).

2) M. Sekiya, T. Oishi: This Bulletin, **7**, 470 (1959).

3) *Idem*: *Ibid.*, **7**, 857 (1959).

nearly completed in about 2.5 hr. After filtration, the reaction solution was concentrated and its vapor was drawn through an alcoholic solution of picric acid through a condenser. By usual treatment of the alcoholic solution, 16.0 g. of a picrate, m.p. 208~211°, was obtained. This was identical with N-methyl piperidine picrate by admixture with an authentic sample.

The crystalline residue, weighing 6.0 g., was identical with benzamide by admixture.

e) **N-(α-Piperidinobenzyl)acetamide**——A mixture of 5.8 g. of N-(α-piperidinobenzyl)acetamide, 50 cc. of EtOH, and Raney Ni catalyst (0.5 g. as 50% alloy) was placed in an autoclave under initial H_2 pressure of 90 kg./cm^2 (at 25°) and hydrogenated at 125~130° in the same way as in a). The absorption was nearly completed in about 2 hr. After removal of the catalyst and the solvent, H_2O was added to the residue and this mixture was extracted with petr. ether. The petr. ether layer was dried and evaporated, and the residue was distilled under reduced pressure to give 3.9 g. of a distillate, b.p$_{20}$ 124~132°, which was identical with N-benzylpiperidine. Picrate, m.p. 175~178°, undepressed on admixture with an authentic sample. *Anal.* Calcd. for $C_{18}H_{20}O_7N_4$: C, 53.46; H, 4.99; N, 13.86. Found: C, 53.39; H, 5.10; N, 13.67.

By treatment of the foregoing aqueous layer, 1.4 g. of acetamide was obtained, which was identified by admixture.

f) **N-(α-Dibenzylaminobenzyl)acetamide**——A mixture of 6.5 g. of N-(α-dibenzylaminobenzyl)acetamide, 50 cc. of EtOH, and Raney Ni catalyst (0.5 g. as 50% alloy) was placed in an autoclave under initial H_2 pressure of 100 kg./cm^2 (at 20°) and hydrogenated at 130~140° in the same way as in a). The absorption was nearly completed in about 3.5 hr. After removal of the catalyst and the solvent, the residue was treated with H_2O and benzene in the same way as in e). By concentration of the benzene layer, 5.0 g. of tribenzylamine, m.p. 88~90°, was obtained. No depression in melting point was observed on admixture with an authentic sample.

By treatment of the foregoing aqueous layer, 1.0 g. of acetamide was obtained.

g) **N-[α-(N′-Methylbenzylamino)benzyl]acetamide**——A mixture of 6.0 g. of N-[α-(N′-methylbenzylamino)benzyl]acetamide, 50 cc. of EtOH, and Raney Ni catalyst (0.5 g. as 50% alloy) was placed in an autoclave under initial H_2 pressure of 100 kg./cm^2 (at 18°) and hydrogenated at 100~105° in same way as in a). The absorption of H_2 was nearly completed in about 2.5 hr. After removal of the catalyst and the solvent, the residue was treated with H_2O and benzene in the same way as in e). The benzene layer was concentrated and distilled under reduced pressure to give 4.2 g. of a distillate, b.p$_{15}$ 145~156°, which was identical with N-methyldibenzylamine by the analysis of its picrate, m.p. 105~106°. *Anal.* Calcd. for $C_{21}H_{20}O_7N_4$: C, 57.27; H, 4.58; N, 12.72. Found : C, 57.69; H, 4.52; N, 12.55.

By treatment of the foregoing aqueous layer, 1.2 g. of acetamide was obtained.

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Summary

The catalytic hydrogenolysis of some compounds that are classified as N-hydroxymethylamides, N-dialkylaminomethylamides, and N-(α-dialkylaminobenzyl) amides was carried out using Raney nickel catalyst under high pressure of hydrogen. It was found in every case that the hydrogenolysis took place at the carbon bond connecting to nitrogen in the amide group.

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