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27. **Eisaku Hayashi, Hiroshi Yamanaka, and Kazuko Shimizu :** Catalytic Reduction of Heterocyclic Aromatic Amine Oxides with Raney Nickel. I. Reduction of 4-Substituted Pyridine 1-Oxide Derivatives.

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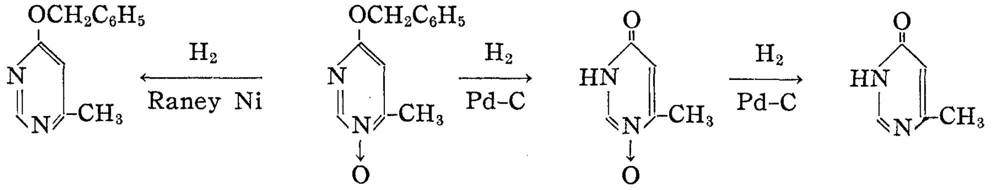
As will be shown in a later paper by Yamanaka,¹⁾ catalytic reduction of 4-benzyloxy-6-methylpyrimidine 1-oxide over palladium-carbon results in formation of 6-methyl-4-pyrimidinol through 4-hydroxy-6-methylpyridine 1-oxide. When Raney nickel is used as the catalyst, direction of the reaction becomes entirely different and the foregoing compound is reduced to 4-benzyloxy-6-methylpyrimidine. This is thought to suggest the fact that Raney nickel catalyst has an extremely specific selectivity in catalytic reduction of the N-oxide group.



This reduction reaction was examined in general and, in order to develop application of this reaction, various aromatic heterocyclic compounds possessing N-oxide group were submitted to this reduction. It was thereby found that this process is a very useful one for the reduction of N-oxide group, as was anticipated. A brief outline of this reaction was published as a Communication to the Editor in this Bulletin²⁾ and the present paper is a detailed report on the theory and application of this reaction.

Numerous reports have appeared in the past regarding the process for reduction of N-oxide group in nitrogen-containing heterocyclic compounds. The best among these for reducing the N-oxide group selectively without effect on other substituents is the process of Hamana³⁾ using phosphorus trichloride. Even this process required few improvements as a laboratory procedure because (i) it necessitated anhydrous condition, (ii) yield decreased when a substituent with active hydrogen, such as hydroxyl and amino, was present in the 4-position, (iii) after-treatment became rather complicated especially in the case of pyridine derivatives because many of the products were soluble in water, and (iv) some side reactions were inevitable. The use of Raney nickel as a catalyst is believed to have solved most of these problems as will be shown in the following description of this catalytic reduction with 4-substituted pyridine derivatives.

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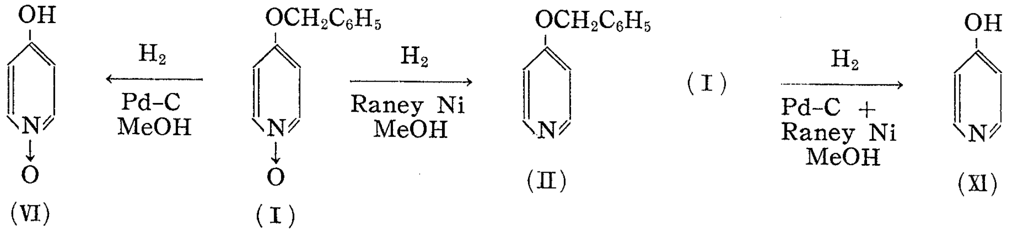
* Oshika, Shizuoka (林 英作, 山中 宏, 清水和子).
1) H. Yamanaka : This Bulletin, **7**, 158(1959).
2) E. Hayashi, H. Yamanaka, K. Shimizu : This Bulletin, **6**, 325(1958).
3) M. Hamana : Yakugaku Zasshi, **71**, 263(1951).

I. 4-Benzyloxypyridine 1-Oxide (I)

Catalytic reduction of (I) over palladium-carbon was carried out by Ochiai and Teshigawara,4) and they obtained 4-hydroxypyridine 1-oxide (VI) as the product. When (I) is reduced over Raney nickel catalyst, 4-benzyloxypyridine (II) is obtained quantitatively as in the case of pyrimidine.1) (II) is not reduced further under these conditions while catalytic reduction of (I) over a mixed catalyst of palladium-carbon and Raney nickel affords 4-pyridinol (XI) in one step.



II. Other 4-Alkoxypyridine 1-Oxides

Catalytic reduction of 4-methoxy- (III) and 4-ethoxypyridine 1-oxide (IV) in methanol, either over palladium-carbon or Raney nickel, results in the reduction of N-oxide group but the rate of reduction is much greater when Raney nickel is used. Palladium-carbon seems to be easily affected by catalyst poison and the reduction proceeds with difficulty when the starting material is not sufficiently purified but the reaction proceeds sufficiently with Raney nickel catalyst even if a slightly impure material is used.

The 4-substituted pyridines (I), (III), and (IV), can be prepared in a good yield by the application of corresponding sodium alkoxide to 4-nitropyridine 1-oxide5) and, therefore, this process is a very convenient method for laboratory preparation of 4-alkoxypyridines.

III. 4-Chloropyridine 1-Oxide (V)

Catalytic reduction of 4-chloropyridine 1-oxide6) (V) as in the foregoing cases results in rapid absorption of 1 mole of hydrogen and the reaction comes to a dead stop. Low-pressure distillation of the product affords 4-chloropyridine (X), b.p.$_{100}$ 85$\sim$87°, in a quantitative yield. The structure of (X) was confirmed through its derivation to 4-methoxypyridine and admixture of its picrate with an authentic sample. The compound (X) here odtained is of high purity and remained unchanged on storage over a long period.

The cessation of hydrogen absorption at one mole and failure of chlorine in 4-position to be reduced can be understood by considering the fact that hydrogen halide acts as a strong catalyst poison against Raney nickel.7) The present process is better for the preparation of (X) since the process generally employed for laboratory preparation of (X), i.e. the reaction of pyridine 1-oxide and acid chloride,8) results in concurrent formation of 2-chloropyridine, b.p. 170°, whose separation from (X), b.p. 148°, is very complicated.

IV. 4-Hydroxypyridine 1-Oxide (VI) and 4-Aminopyridine 1-Oxide (VII)

Catalytic reduction of (VI) and (VII) over palladium-carbon is difficult in neutral medium (methanol, etc.) and only in hydrochloric acidity, they are gradually reduced to (XI) or 4-aminopyridine (XII).9,10) Reduction with phosphorus trichloride gives a poor

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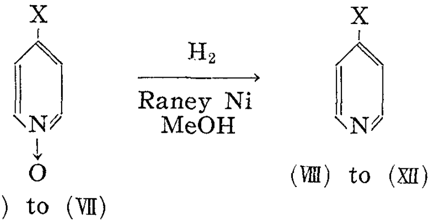
4) E. Ochiai, T. Teshigawara: *Ibid.*, **65A**, 1(1945).
5) E. Ochiai, M. Katada: *Ibid.*, **63**, 265(1943).
6) T. Itai: *Ibid.*, **65**, 70(1945).
7) Y. Urushibara, *et al.*: 'Jikken Kagaku Koza' (Textbook of Experimental Chemistry), Vol. 17 (b), 316, 322(1956), Maruzen Co., Tokyo.
8) B. Bobranski, *et al.*: Ber., **71**, 2385(1938).

yield.[3] On the other hand, reduction over Raney nickel, even in methanol, results in rapid reaction and the objective compounds, (XI) or (XII), are obtained quantitatively and in almost pure state, solely by evaporation of the solvent from a filtrate after removal of the catalyst. (VI) is prepared by catalytic reduction of (I) over palladium-carbon,[4] or by application of acetic anhydride to 4-nitropyridine 1-oxide, in the presence of dimethylaniline.[11] (VII) is prepared by catalytic reduction of 4-nitropyridine 1-oxide over palladium-carbon, in methanol.[10] As a process for laboratory preparation of (XI), the process described in the foregoing I of catalytic reduction over a mixed catalyst of palladium-carbon and Raney nickel is the most advantageous, while that of (XII) should follow the process to be described in the next section.



(VIII) to (XII)

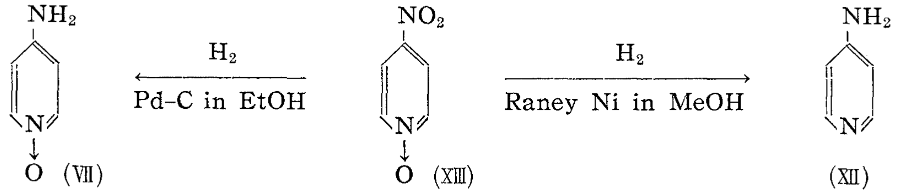
(III) to (VII)

X = OCH_3	(III)	X = OCH_3	(VIII)
OC_2H_5	(IV)	OC_2H_5	(IX)
Cl	(V)	Cl	(X)
OH	(VI)	OH	(XI)
NH_2	(VII)	NH_2	(XII)

V. 4-Nitropyridine 1-Oxide (XIII)

Reduction of (XIII) in neutral medium over palladium-carbon affords (VII) as a principle[10] but the reaction sometimes progresses in a different direction forming 4,4′-azopyridine 1,1′-dioxide and 4,4′-azoxypyridine 1,1′-dioxide.[12] The present process of reduction over Raney nickel always produces the reaction going in one direction and (XII) is invariably formed, irrespective of reaction conditions, although the reduction velocity is somewhat slower than in the foregoing four cases when the medium is neutral. In general, reduction of the nitro group is accelerated in an acid medium, but since hydrohalogen acid is a strong catalyst poison for Raney nickel, addition of a small amount of acetic acid will result in tremendous increase of the reduction velocity and hydrogen is absorbed with generation of heat. Removal of acetate ion with ion exchange resin and evaporation of the solvent will afford (XII) in quantitative yield. In the reduction of (XIII), there is no marked break in the hydrogen absorption curve, as shown in Fig. 1, and even if the reduction was stopped at some stage, 4-nitropyridine or (VII) was not isolated from the reaction system. Therefore, it may be assumed that, in this case, the reduction of N-oxide group does not occur preferentially but progresses with reduction of the nitro group.

Reduction of (XIII) to (XII) has been extensively studied by Hertog[13] who recommended the use of iron powder and acetic acid, but there is a great decrease in the yield when a large amount is submitted to experiment due to loss of (XII) with ferrous oxide formed by the reduction and a great solubility of (XII) in water. It is therefore thought that the present process of using Raney nickel is better as the method for laboratory preparation of (XII).



(VII) (XIII) (XII)

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[9] E. Ochiai, E. Hayashi : Yakugaku Zasshi, **67**, 23, 26(1947).
[10] E. Ochiai, M. Katada : *Ibid.*, **63**, 186(1943).
[11] E. Hayashi : *Ibid.*, **70**, 145(1950).
[12] *Idem.* : Unpublished data.
[13] H. J. Den Hertog, J. Overhoff : Rec. trav. chim., **69**, 472(1950).

Hydrogen absorption curves of compounds described in the foregoing I to V are indicated in Fig. 1.

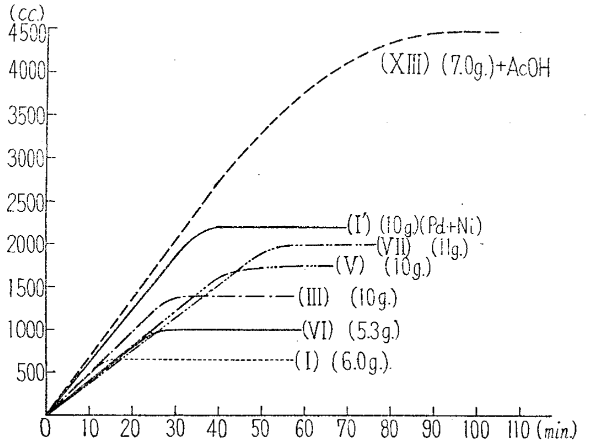

Fig. 1
Absorption Curves of H_2 on Raney Nickel Reduction

As shown above, catalytic reduction of the N-oxide group in methanol with Raney nickel as a catalyst is fundamentally different from the usual reduction using palladium catalyst and the N-oxide group is extremely easily reduced.[14] At the same time, this process has opened a way for a more advantageous route in the laboratory preparation of 4-substituted pyridine derivatives.

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Experimental

Reduction of 4-Benzyloxypyridine 1-Oxide (I)—(a) Raney Ni, prepared from 3 g. of Ni-Al alloy, was added to a solution of 6 g. of (I) dissolved in 30 cc. of MeOH and the mixture was shaken in H_2 stream at atmospheric pressure. Hydrogen absorption was rapid and reduction stopped when 660 cc. of H_2 had been absorbed. After removal of the catalyst by filtration, MeOH was evaporated from the filtrate and the colorless oily residue was taken up in Et_2O. After drying over anhyd. K_2CO_3, Et_2O was evaporated and 5.1 g.(92%) of needle crystals were obtained. Recrystallization from petr. ether afforded crystals of m.p. 57~58°, undepressed by admixture with 4-benzyloxypyridine, m.p. 57~58°, synthesized by a different route.[15]

(b) A mixture of Pd catalyst, prepared from 10 cc. of 1% $PdCl_2$ solution and 0.5 g. of activated carbon, and Raney Ni prepared from 5 g. of Ni-Al alloy, was added to a solution of 10 g. of (I) dissolved in 40 cc. of MeOH and the mixture was shaken in H_2 stream. After rapid absorption of 2200 cc. of H_2 (accompanied with generation of heat), the reduction stopped. The catalyst was filtered off, the filtrate was evaporated to dryness, and the residue was washed with Et_2O, affording 5.2 g. of 4-pyridone monohydrate, m.p. 66°, undepressed on admixture with an authentic sample. This substance is in a pure state and there is no need for further recrystallization.

Reduction of 4-Methoxypyridine 1-Oxide (III)—Raney Ni, prepared from 3 g. of Ni-Al alloy, was added to a solution of 10 g. of 4-methoxypyridine 1-oxide dihydrate dissolved in 40 cc. of MeOH and the mixture was shaken in H_2 stream. One mole of H_2 (1390 cc.) was absorbed at the rate of 50 cc./min. and the reduction stopped. The catalyst was filtered off, MeOH was evaporated from the filtrate, and the residue was dissolved in 30 cc. of Et_2O or benzene. After drying over anhyd. K_2CO_3, the solvent was evaporated and the liquid residue was distilled under a low pressure, affording 6.5 g.(85%) of 4-methoxypyridine, b.p$_{100}$ 125~126°.
Picrate: m.p. 170~172°, undepressed on admixture with an authentic sample.

Reduction of 4-Ethoxypyridine 1-Oxide (IV)—Ten grams of (IV) was reduced as in the case of (III) and purification through low-pressure distillation afforded 7.5 g.(86%) of 4-ethoxypyridine (IX), b.p$_{15}$ 96°.

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[14] A. R. Katritzky and A. M. Monroe (J. Chem. Soc., **1958**, 1263) also reported that the N-oxide group in 4-hydroxy- and 4-aminopyridine 1-oxides is reduced by catalytic reduction over Pd-C catalyst.

[15] E. Shaw: J. Am. Chem. Soc., **71**, 67(1949).

Reduction of 4-Chloropyridine 1-Oxide (V)—Raney Ni prepared from 5 g. of Al-Ni alloy was added to a solution of 10 g. of (V) dissolved in 30 cc. of MeOH and the mixture was submitted to reduction. One mole (1720 cc.) of H_2 was absorbed rapidly, at the rate of 40 cc./min., and the reduction stopped. The catalyst was filtered off, MeOH was evaporated from the filtrate, and the residue was dissolved in 30 cc. of Et_2O or benzene. After drying over anhyd. Na_2SO_4, the solvent was distilled off and the residue was purified by low-pressure distillation, affording 7.7 g. (88%) of 4-chloropyridine, b.p$_{100}$ 85~87°. This substance was derived to 4-methoxypyridine with MeONa by the usual method and its picrate, m.p. 170~172°, was identified by mixed fusion with an authentic specimen.

Reduction of 4-Hydroxypyridine 1-Oxide (VI)—Raney Ni prepared from 3 g. of Al-Ni alloy was added to 5.3 g. of (VI) suspended in 30 cc. of MeOH and the mixture was shaken in H_2 stream. The reduction stopped after rapid absorption of 1000 cc. of H_2 (at the rate of 40 cc./min.). The catalyst was filtered off and the filtrate was evaporated, affording 4.5 g. (98%) of 4-pyridone monohydrate of m.p. 66°, undepressed on admixture with an authentic sample.

Reduction of 4-Aminopyridine 1-Oxide (VII)—Raney Ni prepared from 5 g. of Ni-Al alloy was added to a solution of 11 g. of (VII) dissolved in 50 cc. of MeOH and the mixture was shaken in H_2 stream. After absorption of 2000 cc. of H_2 rapidly, the reduction stopped. The catalyst was filtered off and the filtrate was evaporated. The crystalline residue was dried in a vacuum desiccator and 9.2 g. (98%) of 4-aminopyridine, m.p. 155~158° (picrate, m.p. 215~216°), was obtained. This substance was almost pure in this state.

Reduction of 4-Nitropyridine 1-Oxide (XIII)—(a) Raney Ni, prepared from 3 g. of Ni-Al alloy, and 6 cc. of glacial AcOH were added to 7 g. of (XIII) suspended in 150 cc. of MeOH and the mixture was shaken in H_2 stream, when heat generated and 4450 cc. of H_2 was absorbed rapidly. The reaction ended after about 1.5 hrs., the catalyst was filtered off, and ion exchanger prepared as described below was added to the filtrate. After allowing this mixture to stand over night at room temperature, ion exchange resin was filtered off, the filtrate was evaporated to dryness, and the residue was extracted with benzene. After drying over anhyd. Na_2SO_4, benzene was distilled off and 4.7 g. (90%) of 4-aminopyridine, m.p. 154~157°, was obtained as the residue. No depression of m.p. occurred on admixture with an authentic sample.
Picrate: m.p. 215~216°.

Preparation of Ion Exchange Resin: A mixture of 100 cc. of Amberlite IRA-410 in 300 cc. of 4% NaOH solution was allowed to stand for 24 hrs., the resin was collected by filtration, and washed with water until the filtrate was no longer alkaline. This was finally washed with MeOH before use.

(b) Raney Ni prepared from 1 g. of Ni-Al alloy was added to a solution of 1 g. of (XIII) dissolved in a mixture of 20 cc. of MeOH and 20 cc. of Me_2CO, and the mixture was shaken in H_2 stream. When 160 cc. of H_2 was absorbed, the reaction was stopped, the catalyst was filtered off, and the filtrate was evaporated to dryness. The reddish-brown, viscous oily residue was dissolved in $CHCl_3$ and the $CHCl_3$ solution was passed through a column of 30 cc. of alumina. Elution with $CHCl_3$ afforded an initial fraction of 0.3 g. of yellow prisms, m.p. 160°, which showed no depression on admixture with the starting material (XIII). Further elution afforded 0.3 g. of yellowish orange crystals, m.p. 148~156°, which was not identified. The objective 4-nitropyridine was not obtained at all.

Summary

Catalytic reduction of various 4-substituted pyridine 1-oxides in neutral medium, with Raney nickel as a catalyst, was carried out at ordinary temperature and pressure. It was thereby found that N-oxide group in these compounds was selectively reduced, irrespective of the substituent in 4-position, and the products were obtained in a good yield of 85~98%. 4-Nitropyridine 1-oxide afforded 90% of 4-aminopyridine in acetic acid medium and 4-benzyloxypyridine 1-oxide afforded 93% of 4-hydroxypyridine in one step when reduced over a mixed catalyst of palladium-carbon and Raney nickel. It was considered that this process of reduction is the best method for laboratory preparation of 4-substituted pyridines.

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