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Catalytic Reduction of Heterocyclic Aromatic Amine N-Oxides with Raney Nickel. Ⅳ.[1] Reduction of 4,4'-Azopyridine 1,1'-Dioxide, 4,4'-Azoxypyridine 1,1'-Dioxide, and 2-Styrylpyridine 1-Oxide.

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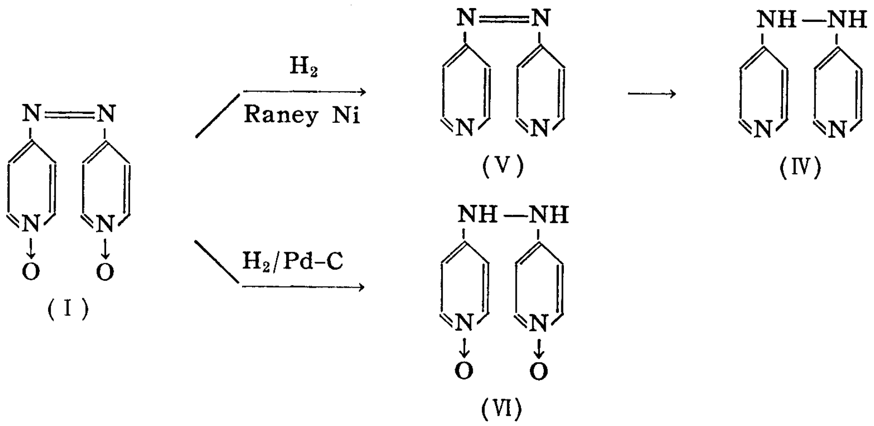
It was shown in Parts I and Ⅱ of this series[2] that catalytic reduction over Raney nickel at atmospheric temperature and pressure was a suitable method for reduction of N-oxide group. As was also reported earlier, the use of Raney nickel effects selective reduction of the N-oxide group alone even in the presence of chlorine or benzyloxyl group as a substituent which are easily reduced by the use of palladium-carbon as a catalyst. The present paper gives results of application of this reduction over Raney nickel to 4,4'-azopyridine 1,1'-dioxide (I), 4,4'-azoxypyridine 1,1'-dioxide (Ⅱ), and 2-styrylpyridine 1-oxide (Ⅲ) which have substituent and carbon-carbon double bond that are easily reduced.

Reduction of 4,4'-Azoxypyridine 1,1'-Dioxide (I)

Catalytic reduction of (I) in methanol, with Raney nickel as a catalyst, at atmospheric temperature and pressure, results in absorption of 3 moles of hydrogen and 4,4'-hydrazopyridine (Ⅳ) is obtained. In this case, uptake of the first two moles of hydrogen is comparatively rapid, absorption becomes gradually slow, and stops after absorption of 3 moles of hydrogen. If the reduction is stopped after absorption of one mole of hydrogen, 4,4'-azopyridine (V) is obtained together with recovery of one-half the quantity of (I). If the reduction is stopped after absorption of two moles of hydrogen, a mixture of (I), (Ⅳ), and (V) is obtained. Summarizing the above, it seems that the reduction of the N-oxide group precedes that of the azo to hydrazo group.

In this connection, catalytic reduction of (I) over palladium-carbon in methanol results in ceasure of the reaction after one mole of hydrogen has been absorbed and a substance assumed to be 4,4'-hydrazopyridine 1,1'-dioxide (Ⅵ) is obtained. This product comes as white microneedles, m.p. 200~200.5°(decomp.), and changes easily into (I) in solvents like methanol that its purification is difficult. Although elemental analysis of this product is yet to be made, it may be assumed as (Ⅳ) since it was formed by absorption of one



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[1] Part Ⅲ. E. Hayashi, H. Yamanaka, T. Higashino : This Bulletin, 7, 149(1959).

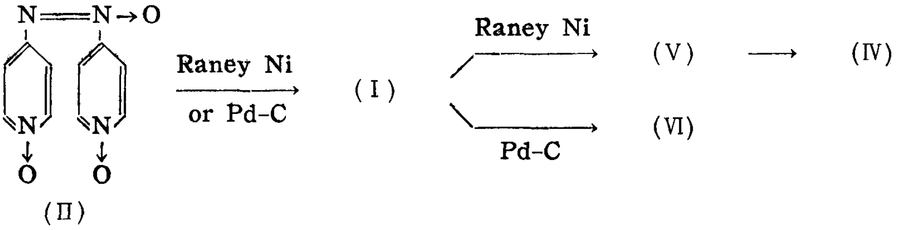
[2] E. Hayashi, H. Yamanaka, K. Shimizu ; *Ibid.*, 7, 141, 146(1959).

mole of hydrogen by (I) and shows a strong reductive action to the Fehling solution, as well as being easily changed to (I) by merely being left in a solution. Further reduction of the N-oxide group is difficult using this catalyst of palladium-carbon. This is comparable to the difficulty in reduction of N-oxide group in compounds like 4-amino- and 4-hydroxy-pyridine 1-oxides in which a substituent with active hydrogen is present in the position *para* to the N-oxide group.

Reduction of 4,4'-Azoxypyridine 1,1'-Dioxide (II)

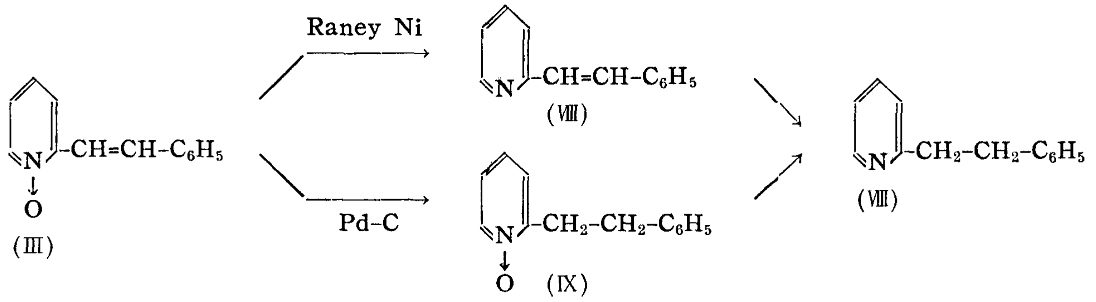
Reduction of (II) in methanol over Raney nickel in a similar manner results in absorption of four moles of hydrogen and 4,4'-hydrazopyridine (IV) is obtained. Termination of the reaction after absorption of one mole of hydrogen results in recovery of majority of (I) mixed with a small amount of 4,4'-azopyridine. This result indicates that the reduction of azoxy to azo group precedes that of N-oxide group.

The use of palladium-carbon in this case results in ceasure of reduction after absorption of two moles of hydrogen and 4,4'-hydrazopyridine 1,1'-dioxide (VI) is obtained. Thus, in the case of (II), the first step is the reduction of azoxy to azo group whether Raney nickel or palladium-carbon is used as the catalyst. Other points are the same as in the case of (I).



Reduction of 2-Styrylpyridine 1-Oxide (III)

Reduction of (III) over Raney nickel in methanol results in absorption of two moles of hydrogen and 2-phenethylpyridine (VII) is obtained. Ceasure of the reaction after absorption of one mole of hydrogen chiefly gives 2-styrylpyridine (VIII) with a small amount of (VII). These results suggest that the reduction of N-oxide group precedes that of carbon-carbon double bond. The use of palladium-carbon as a catalyst in this reduction is said to result in hydrogenation of the double bond to form 2-phenethylpyridine 1-oxide (IX) which is further reduced to (VII)[3] and this is rather in contrast to reduction with Raney nickel.



Experimental

Preparation of the Catalyst—i) Raney Ni: Prepared from 2 g. of Ni-Al alloy by the method previously described.[2]
ii) Pd-C: A mixture of 10 cc. of 1% $PdCl_2$ and 0.1 g. of activated carbon was shaken in H_2 stream

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[3] A. R. Katritzky, A. M. Monro: J. Chem. Soc., **1958**, 1263.

until the brown solution became colorless. The carbon was collected by filtration, washed thoroughly with water and MeOH, and used.

Catalytic Reduction of 4,4′-Azopyridine 1,1′-Dioxide[4] **(I) over Raney Nickel**—i) A solution of 1 g. of (I) dissolved in 150 cc. of MeOH, added with Raney Ni catalyst (prepared from 2 g. of Ni-Al alloy), was shaken in H_2 stream. Absorption of H_2 took 9 min. for the first 1 mole, 20 min. until the next 1 mole, and 70 min. until the third mole, after which the absorption ceased. The catalyst was filtered off and the solvent was evaporated to dryness under a reduced pressure. Recrystallization of the residue from MeOH gave white needles, m.p. 240°(decomp.). Yield : 0.80 g. *Anal.* Calcd. for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41. Found : C, 64.3; H, 5.3. This was identified with 4,4′-hydrazopyridine (IV).

ii) Similar reduction of 1 g. of (I) as in foregoing (i) was stopped after absorption of ca. 1 mole of H_2. The catalyst was filtered off, the filtrate was evaporated to dryness under a reduced pressure, and the residue was digested with petr. benzine (b.p. 60~80°). Benzine-soluble portion was recrystallized from petr. benzine to orange needles,[5] m.p. 107°. Yield, 0.15 g. *Anal.* Calcd. for $C_{10}H_8N_4$: C, 65.20; H, 4.38. Found : C, 65.1; H, 4.4. This was identified with 4,4′-azopyridine (V).

The residue left after digestion with petr. benzine was recrystallized from MeOH and afforded (I) as red needles, m.p. 242°(decomp.). Rate of recovery, 0.55 g.

iii) Similar reduction of (I) over Raney nickel as in (i) was stopped after absorption of ca. 2 moles of H_2. The catalyst was filtered off, the filtrate was evaporated to dryness under a reduced pressure, and the residue was digested with warm petr. benzine. From the portion soluble in benzine, 0.1 g. of (V) was obtained. The residue from petr. benzine digestion was digested with MeOH and the portion soluble in MeOH was recrystallized from MeOH, affording 0.1 g. of (IV). MeOH-digestion residue was recrystallized from MeOH and 0.35 g. of (I) was recovered.

Catalytic Reduction of (I) over Palladium-Carbon—A solution of 0.3 g. of (I) dissolved in 40 cc. of MeOH and added with Pd-C (prepared from 10 cc. of 1% $PdCl_2$) was submitted to reduction at atmospheric temperature and pressure. The reaction almost came to a stop after absorption of ca. 1 mole of H_2 during ca. 3 min., and the initial red color of the solution faded. The catalyst was filtered off, the filtrate was evaporated to dryness under a reduced pressure, when the colorless solution was again tinted with red, and the residue was dissolved in EtOH. Addition of benzene to this EtOH solution precipitated white microneedles, m.p. 200~200.5°(decomp.). Yield, 0.25 g. The solution of this substance dissolved in MeOH or EtOH gradually colors reddish and on standing, (I) is recovered from this solution. This substance strongly reduces the Fehling solution. Due to such easy oxidizability, this product was not analyzed but from its formation from (I) by absorption of 1 mole of H_2 and its strong reducing tendency, it was assumed to be 4,4′-hydrazopyridine 1,1′-dioxide[*2] (VI). (VI) forms a monopicrate of yellow needles (from MeOH), m.p. 216°(decomp.). *Anal.* Calcd. for $C_{10}H_{10}O_2N_4 \cdot C_6H_3O_7N_3$: C, 42.96; H, 2.92; N, 21.92. Found : C, 43.0; H, 2.9; N, 21.9.

Catalytic Reduction of 4,4′-Azopyridine 1,1′-Dioxide[4] **(II) over Raney Nickel**—i) A solution of 1 g. of (II) dissolved in 150 cc. of MeOH and added with Raney Ni catalyst (from 2 g. of Ni-Al alloy) was hydrogenated and the reaction stopped after absorption of ca. 4 moles of H_2. The catalyst was filtered off, the solvent was evaporated to dryness under a reduced pressure, and the residue was recrystallized from MeOH to (IV) as white needles, m.p. 240°(decomp.). Yield, 0.75 g.

ii) The same reduction of 1 g. of (II) as in (i) was stopped after absorption of ca. 1 mole of H_2. The catalyst was filtered off, the solvent was evaporated under a reduced pressure, and the residue was digested with warm petr. benzine. From the soluble portion, 0.7 g. of (V) was obtained and recrystallization of benzine digest residue from MeOH afforded 0.7 g. of recovered (I).

Catalytic Reduction of (II) over Palladium-Carbon—A solution of 0.1 g. of (II) dissolved in 20 cc. of MeOH, added with Pd-C as a catalyst, was shaken in H_2 stream and the reaction stopped after absorption of ca. 2 moles of H_2. The initial red color of the solution faded. The colorless solution was evaporated to dryness under a reduced pressure and the residue was dissolved in MeOH. Addition of benzene to this solution precipitated (VI) as white microneedles, m.p. 200~200.5°.

2-Styrylpyridine 1-Oxide (III)—To a solution of 18 g. of 2-styrylpyridine[6] (VIII) dissolved in 60 cc. of glacial AcOH, 15 cc. of H_2O_2 solution (0.23 g. H_2O_2/cc.) was added and the mixture was heated for 18 hr. at 65~75°(bath temp.). The solvent was evaporated under a reduced pressure, the residue was dissolved in water, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 10% K_2CO_3 solution and water, dried over Na_2SO_4, and the solvent was evaporated. The residue was recrystallized from benzene to pale yellow plates, m.p. 162~162.5.[7] Yield, 14.9 g.

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[4] E. Ochiai, M. Katada : Yakugaku Zasshi, **63**, 191(1943).

[5] H. J. den Hertog, *et al.* : Rec. trav. chim., **70**, 591(1951)(C. A., **46**, 8655(1952)).

[*2] E. Ochiai and M. Katada (*loc. cit.*) reported that the dipicrate of (VI) melted with decomposition at above 320°.

[6] B. D. Shaw, E. A. Wagstaff : J. Chem. Soc., **1933**, 77.

[7] A. R. Katritzky, A. M. Monro : *Ibid.*, **1958**, 151.

Catalytic Reduction of (III) over Raney Nickel—i) A solution of 1.35 g. of (III) dissolved in 30 cc. of MeOH and added with Raney Ni catalyst (from 2 g. of Ni-Al alloy) was shaken in H_2 stream and the reaction stopped after absorption of ca. 2 moles of H_2, requiring about 15 min. The catalyst was filtered off, the solvent was evaporated from the filtrate, and benzene solution of the residue was passed through a column of activated alumina for purification. The effluent afforded 0.9 g. of colorless liquid. The picrate of this oil was recrystallized from MeOH to yellow needles, m.p. 125~127°, identical with the picrate[3] of 2-phenethylpyridine (VII).

ii) A solution of 1 g. of (III) dissolved in 30 cc. of MeOH and added with Raney Ni catalyst (from 2 g. of Ni-Al alloy) was reduced and the reaction was stopped after absorption of ca. 1 mole of H_2, which required 4.5 min. The catalyst was filtered off, the solvent was removed from the filtrate, and the residue was purified by alumina chromatography as benzene solution. From the less adsorbed portion eluted with benzene, 2-styrylpyridine was obtained as white needles, m.p. 90~91°.

The portion with greater adsorptivity was eluted with MeOH and a small amount of colorless oil was obtained. Its picrate melted at 125~127°, identical with the picrate of (VII).

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Summary

Catalytic reduction of 4,4′-azopyridine 1,1′-dioxide (I) in methanol with Raney nickel catalyst at atmospheric temperature and pressure results in formation of 4,4′-hydrazopyridine (IV) via 4,4′-azopyridine (V). The same reduction with palladium-carbon as a catalyst affords 4,4′-hydrazopyridine 1,1′-dioxide (VI) and the reduction stops at this stage. This shows that the reduction of N-oxide group precedes that of azo to hydrazo group when using Raney nickel as a catalyst, but reduction of the azo to hydrazo group alone takes place when palladium-carbon is used as a catalyst.

In the case of 4,4′-azoxypyridine 1,1′-dioxide (II), the use of Raney nickel as a catalyst effects reduction of (II) to (IV) through (I) and (V), while the use of palladium-carbon produces (VI) through (I). In this case, reduction of azoxy to azo group is the first step and the rest is the same as in the case of (I).

In the case of 2-styrylpyridine 1-oxide (III), reduction of N-oxide group precedes that of the double bond and 2-phenethylpyridine (VII) is formed via 2-styrylpyridine (VIII). When palladium-carbon is used as the catalyst, reduction of the double bond is said to precede that of N-oxide group and (VII) is formed via 2-phenethylpyridine 1-oxide (IX). This is in contrast to the use of Raney nickel as a catalyst.

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