UDC 547.831.7 : 542.941.7

29. **Eisaku Hayashi, Hiroshi Yamanaka, and Takeo Higashino**: Catalytic Reduction of Heterocyclic Aromatic Amine Oxides with Raney Nickel. III.[2] Reduction of Hydroxamic Acid-type N-Oxides.

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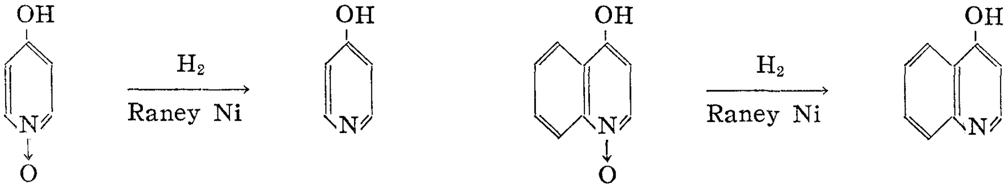
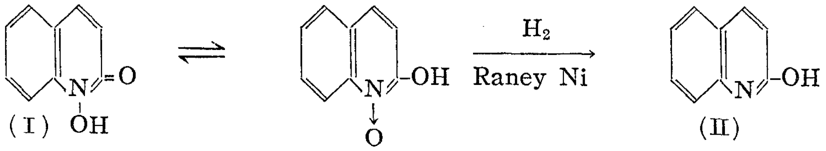
It has been found, as described in Parts I[1] and II[2] of this series, that 4-hydroxypyridine 1-oxide and 4-hydroxyquinoline 1-oxide, which greatly resist reduction over palladium-carbon catalyst at ordinary temperature and pressure, easily submit to reduction over Raney nickel catalyst and their N-oxide group is deoxygenated.



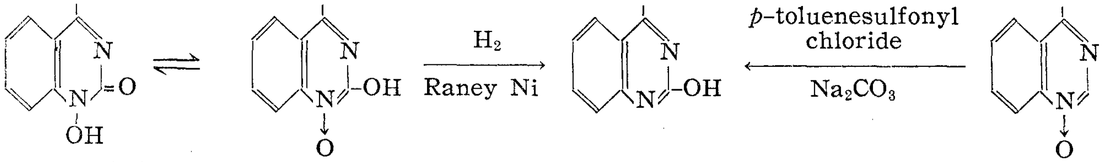
Based on the foregoing observations, the same reduction was carried out on several compounds possessing a hydroxyl adjacent to the N-oxide group. It is presumed that a hydrogen bonding occurs between the N-oxide and hydroxyl group adjacent to it, forming a cyclic hydroxamic acid-type structure, and that the N-oxide group in these compounds would be highly resistant to reduction over palladium-carbon catalyst, same as those compounds with hydroxyl *para* to the N-oxide group. Actually, 4-ethoxy-2-hydroxyquinazoline 1-oxide (IV) resisted catalytic reduction over palladium-carbon in methanol and the starting material was recovered almost wholly.

As a representative of compounds possessing a hydroxyl adjacent to N-oxide group, 2-hydroxyquinoline 1-oxide (I) was taken up. Its catalytic reduction over Raney nickel in methanol resulted in smooth taking up of 1 mole of hydrogen to form 2-hydroxyquinoline (II).



(I) (II)

The reaction progressed rapidly with 4-methoxy- (III) and 4-ethoxy-2-hydroxyquinazoline 1-oxide (IV) under the same conditions to respectively form 4-methoxy-2-hydroxyquinazoline (V) and 4-ethoxy-2-hydroxyquinazoline (VI). These reduction products were identified by admixture with authentic samples of (V) and (VI)[3] prepared by reacting the corresponding 4-alkoxyquinazoline 1-oxide and *p*-toluenesulfonyl chloride in chloroform and treating the product with alkali carbonate.



(III) $R=CH_3$ (V) $R=CH_3$

(IV) $R=C_2H_5$ (VI) $R=C_2H_5$

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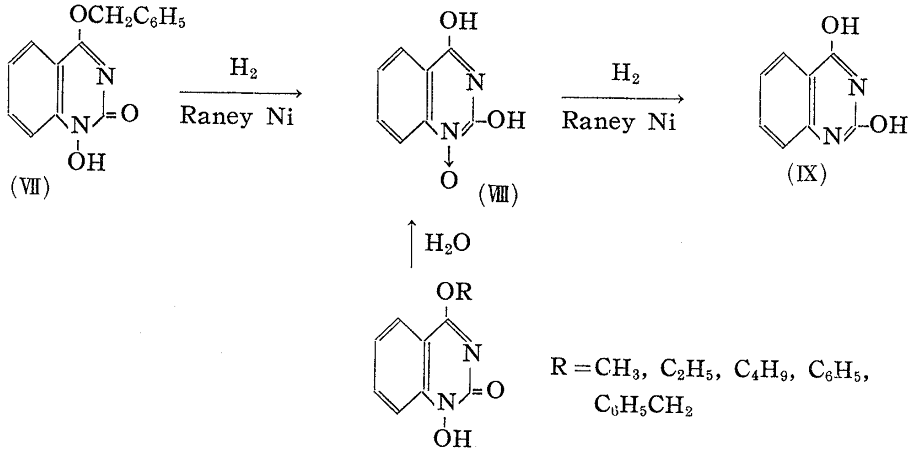
[1] Part I: This Bulletin, **7**, 141(1959).

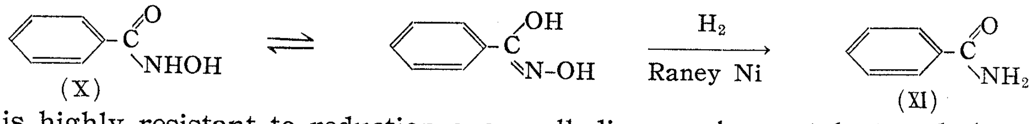
[2] Part II: *Ibid.*, **7**, 146(1959).

[3] T. Higashino: Paper presented at the 78th Meeting of the Pharmaceutical Society of Japan, Nagoya, April, 1958.

In the case of 4-benzyloxy-2-hydroxyquinazoline 1-oxide (VII), 2,4-dihydroxyquinazoline (IX) is formed via 2,4-dihydroxyquinazoline 1-oxide (VIII) and this has shown that the benzyloxyl group is more preferentially reduced than the N-oxide group taking part in the formation of a cyclic hydroxamic acid-type structure. (VIII) was identified with an authentic sample prepared by another route,[4] while (IX) was derived to 2,4-diethoxyquinazoline through its 2,4-dichloro compound by the method of Lange.[5]



Since the foregoing experiments have shown that the N-oxide group taking part in the formation of a hydroxamic acid-type structure is amenable to this reduction, the reaction was examined with hydroxamic acid. The reduction progressed rapidly in benzohydroxamic acid (X) and benzamide (XI) was obtained as the product.



(X) is highly resistant to reduction over palladium-carbon catalyst and the starting material is recovered almost completely.

The foregoing experiments have shown that Raney nickel catalyst is specifically active in severing the nitrogen-oxygen bond in hydroxamic acid and compounds containing such structure.

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Experimental

Catalytic Reduction of 2-Hydroxyquinoline 1-Oxide (I) with Raney Nickel—(I) was recrystallized from MeOH, with the use of activated carbon, as scaly crystals, m.p. 188~190°. A mixture of 0.2 g. of (I) and Raney Ni, prepared from Ni-Al alloy, in 20 cc. of MeOH was shaken in H_2 stream. Absorption of hydrogen was very rapid (at the rate of 10 cc./min.) and the desired 1 mole (28 cc.) was absorbed in ca. 3 mins. The catalyst was filtered off and evaporation of the filtrate afforded 0.18 g. of slightly orange needles, m.p. 160~180°. Recrystallization from MeOH gave white needles, m.p. 196~199°. Yield, 0.15 g.(83%). No depression of m.p. occurred on admixture with 2-hydroxyquinoline[6] (II), m.p. 199°, prepared by another route.

Catalytic Reduction of 4-Methoxy-2-hydroxyquinazoline 1-Oxide (III)—Raney Ni prepared from 0.3 g. of Ni-Al alloy was added to a solution of 0.3 g. of purified (III), m.p. 229~231°, dissolved in 30 cc. of MeOH and the mixture was shaken in H_2 stream. The reaction stopped after absorption of 1 mole of H_2. The catalyst was filtered off, the filtrate was evaporated, and crystalline residue

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4) H. Yamanaka : This Bulletin, **7**, 152(1959).
5) N. A. Lange, W. E. Roush, H. J. Asbeck : J. Am. Chem. Soc., **52**, 3696(1930).
6) E. Ochiai, T. Yokokawa : Yakugaku Zasshi, **75**, 213(1955).

was recrystallized from EtOH to 0.2 g.(74%) of 4-methoxy-2-hydroxyquinazoline (V) as white plates, m.p. 218~221°, undepressed on admixture with (V), m.p. 218~221°, prepared by another route.[3]

Catalytic Reduction of 4-Ethoxy-2-hydroxyquinazoline 1-Oxide (IV)—i) Over Raney Ni: Raney Ni prepared from 0.5 g. of Ni-Al alloy was added to 0.5 g. of (IV), m.p. 208~210°, dissolved in 30 cc. of EtOH and the mixture was shaken in H_2 stream. This was treated as in the case of (III) and 0.3 g.(65%) of crystals melting at 233° (as recrystallized from EtOH) was obtained. This showed no depression of m.p. on admixture with 4-ethoxy-2-hydroxyquinazoline (VI), m.p. 233°, prepared by another route.[3]

ii) Over Pd-C: A catalyst prepared from 1% HCl solution of $PdCl_2$ and 1.0 g. of activated carbon was added to a solution of 2.0 g. of (IV) dissolved in 150 cc. of EtOH, and the mixture was shaken in H_2 stream at ordinary temperature and pressure but, no absorption of H_2 occurred. After removal of the catalyst, the filtrate was evaporated and 1.8 g. of the starting compound (IV) was recovered.

Catalytic Reduction of 4-Benzyloxy-2-hydroxyquinazoline 1-Oxide (VII)—i) With Raney Ni: Raney Ni prepared from 0.5 g. of Ni-Al alloy was added to 0.5 g. of (VII) suspended in 70 cc. of MeOH and the mixture was shaken in H_2 stream, by which the crystals dissolved gradually and disappeared completely when ca. 1 mole of H_2 had been absorbed. The catalyst was filtered off and MeOH was evaporated from the filtrate, affording 0.26 g. (81%) of crystals melting at 283°, undepressed on admixture with 2,4-dihydroxyquinazoline 1-oxide (VIII), m.p. 287~289°, prepared by another route.[4] *Anal.* Calcd. for $C_8H_6O_3N_2$ (2,4-Dihydroxyquinazoline 1-oxide): C, 53.93; H, 3.40; N, 15.73. Found: C, 53.73; H, 3.66; N, 15.13.

ii) Raney Ni prepared from 0.5 g. of Ni-Al alloy was added to 0.5 g. of (VII) suspended in 50 cc. of MeOH and the mixture was shaken in H_2 stream. The reaction stopped completely when 2 moles of H_2 had been absorbed. The catalyst was filtered off, MeOH was evaporated to dryness, and the residue was suspended in 3% NaOH solution. This solution was filtered and the filtrate was acidified with AcOH, by which 0.21 g. (70%) of 2,4-dihydroxyquinazoline (IX), m.p. over 350°, was obtained.

Catalytic Reduction of Benzohydroxamic Acid (X)—i) With Raney Ni: Raney Ni, prepared from 1.0 g. of Ni-Al alloy, and 0.3 g. of (X) were added to 20 cc. of MeOH and the mixture was shaken in H_2 stream at ordinary temperature and pressure. The reaction stopped completely when 1 mole of H_2 was absorbed rapidly as in the case of (I). The catalyst was filtered off and MeOH was evaporated from the filtrate, affording 0.2 g. (74%) of white needle crystals which was recrystallized from benzene to prisms, m.p. 128°, undepressed on admixture with benzamide (XI).

ii) With Pd-C catalyst: The catalyst prepared from 15 cc. of 1% HCl solution of $PdCl_2$ and 0.7 g. of activated carbon was added to a solution of 1.0 g. of (X) dissolved in 50 cc. of MeOH and the mixture was shaken in H_2 stream at ordinary temperature and pressure. There was virtually no absorption of H_2 and 0.9 g. of the starting compound (X) was recovered.

Summary

In the catalytic reduction of hydroxamic acid and compounds possessing hydroxyl adjacent to the N-oxide group and forming a hydroxamic acid-type structure, Raney nickel catalyst was found to act specifically in severing the nitrogen-oxygen bond. 2-Hydroxyquinoline 1-oxide, 4-methoxy- and 4-ethoxy-2-hydroxyquinazoline 1-oxide, and benzohydroxamic acid were deoxygenated forming 2-hydroxyquinoline, 4-methoxy- and 4-ethoxy-2-hydroxyquinazoline, and benzamide. In 4-benzyloxy-2-hydroxyquinazoline 1-oxide, the reduction of benzyloxyl group preceded the reduction of N-oxide group and 2,4-dihydroxyquinazoline was formed via its 1-oxide compound.

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