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

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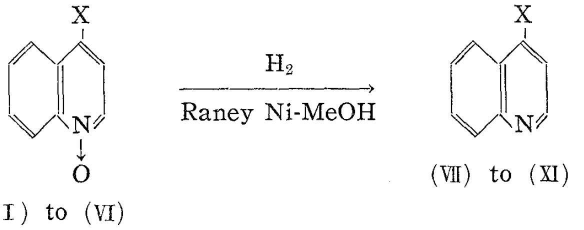
It was shown in the preceding paper[1] that catalytic reduction of 4-substituted pyridine 1-oxide derivatives with Raney nickel as a catalyst effected selective reduction of the N-oxide group and a process for laboratory preparation of 4-substituted pyridine derivatives via their 1-oxides was thereby established.

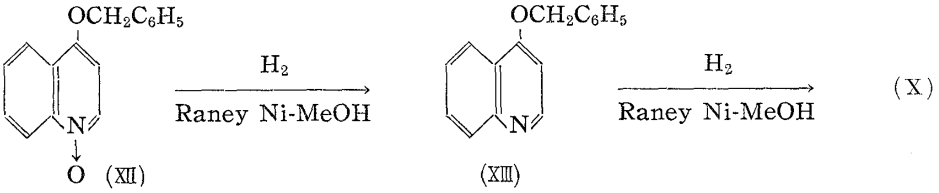
In the present series of work, the same catalytic reduction was attempted on the corresponding 4-substituted quinoline 1-oxide derivatives. The reactions were carried out according to those in the case of pyridine derivatives and the result was almost in parallel. Quinoline 1-oxide (I), 4-methoxyquinoline 1-oxide[2] (II), 4-chloroquinoline 1-oxide[3] (III), 4-hydroxyquinoline 1-oxide[4] (IV), and 4-aminoquinoline 1-oxide[5] (V) were respectively reduced in almost quantitative yield into quinoline (VII) and 4-methoxy- (VIII), 4-chloro- (IX), 4-hydroxy- (X), and 4-aminoqinolines (XI), while 4-nitroquinoline 1-oxide (VI) afforded (XI) in one step, also in quantitative yield.



(I) to (VI) (VII) to (XI)

X = H	(I)	X = H	(VII)
OCH$_3$	(II)	OCH$_3$	(VIII)
Cl	(III)	Cl	(IX)
OH	(IV)	OH	(X)
NH$_2$	(V)	NH$_2$	(XI)
NO$_2$	(VI)		

Only in the case of 4-benzyloxyquinoline 1-oxide[4] (XII), the first one mole of hydrogen is absorbed rapidly and 4-benzyloxyquinoline (XIII) is obtained. Subsequent absorption of hydrogen becomes very slow but continued reduction will result in absorption of one more mole of hydrogen to form (X). This is somewhat different from the corresponding 4-benzyloxypyridine 1-oxide whose N-oxide group is reduced readily.



(XII) (XIII)

Catalytic reduction of 4-benzyloxypyridine 1-oxide was attempted with Raney cobalt and Raney copper, prepared in a manner similar to that of Raney nickel, but absorption of hydrogen was almost nil in the former and entirely none in the case of the latter, recovering the starting material completely. This showed that these reduction reactions are entirely specific to nickel.

It was also found that the preparation of the catalyst could be effected by the simple process described at the beginning of the Experimental section in this paper

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

[2] Masao Ishikawa : Yakugaku Zasshi, **65A**, (3), 5(1945).

[3] T. Itai : *Ibid.*, **65B**, (8), 4(1945); E. Ochiai : J. Org. Chem., **18**, 534(1953).

[4] E. Ochiai, T. Naito : Yakugaku Zasshi, **65**, 444(1945).

[5] *Idem.* : *Ibid.*, **64**, 206(1944).

instead of that by the W-1 type as reported previously[6] and that the properties of the catalyst was the same.

The present and the preceding papers have shown that Raney nickel has an exceptionally specific action in reducing the N-oxide group. This reaction has made it extremely easy to prepare 4-substituted pyridines and quinolines from their N-oxide derivatives and also offers such advantages as (i) shortening of reaction time, (ii) reaction progresses in only a definite direction, there is no formation of by-products, and consequently the yield is quantitative, and (iii) after-treatment and other experimental procedures are easy.

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Experimental

Preparation of Raney Nickel—A solution of 10 g. of NaOH (purity, 80%) dissolved in 40 cc. of distilled water was placed in a 300-cc. beaker, chilled in ice, and 5 g. of Ni-Al alloy (1:1) was added in small portions. There is a great generation of heat and efficient cooling is required. The mixture was then heated at 100° for 2 hrs. with occasional stirring, 20 cc. of 20% NaOH solution was added, and the mixture was further heated at 100° for 1 hr. When the evolution of H_2 became no longer evident, the mixture was cooled and the whole was diluted to 200 cc. with water. The supernatant solution was decanted, water was added, the whole was stirred, and the supernatant was again decanted. The catalyst was washed six times in this manner, finally collected by suctional filtration, and washed with MeOH. This was used immediately.

Reduction of Quinoline 1-Oxide (I)—Raney Ni, prepared from 1 g. of Ni-Al alloy (1:1), and 3.0 g. of (I) were added to 30 cc. of MeOH and the mixture was shaken in H_2 stream, at ordinary temperature and pressure. The reduction stopped after absorption of 465 cc. of H_2. The catalyst was filtered off, MeOH was evaporated from the filtrate, and the residue was dissolved in benzene. After drying over anhyd. Na_2SO_4, benzene was evaporated and the residue was distilled under a reduced pressure, affording 2.2 g.(82.4%) of quinoline, b.p$_{10}$ 95~97°.

Picrate: m.p. 202~203°, undepressed on admixture with an authentic specimen.

Reduction of 4-Methoxyquinoline 1-Oxide (II)—Raney Ni prepared from 3 g. of Ni-Al alloy was added to a solution of 10 g. of (II) dissolved in 100 cc. of MeOH and the mixture was reduced at ordinary temperature and pressure. The reaction stopped after rapid absorption of H_2. The catalyst was filtered off, the filtrate was evaporated, and the crude 4-methoxyquinoline (VIII) so obtained was purified by low-pressure distillation, affording 8.3 g. (93%) of a fraction of b.p$_{12}$ 137°.

Picrate: m.p. 174~176°, undepressed on admixture with an authentic sample.

Reduction of 4-Chloroquinoline 1-Oxide (III)—Raney Ni prepared from 3 g. of Ni-Al alloy was added to a solution of 10 g. of (III) dissolved in 100 cc. of MeOH and the mixture was reduced at ordinary temperature and pressure. One mole (1300 cc.) of H_2 was absorbed. The catalyst was filtered off, MeOH was evaporated from the filtrate, and the oily residue so obtained was submitted to low-pressure distillation, from which 8.0 g. (90%) of 4-chloroquinoline (IX) was obtained as a fraction of b.p$_{15}$ 130°.

The oily residue (IX) was also reacted with MeONa in MeOH and derived to (VIII) which was identified as its picrate of m.p. 174~176° by admixture with an authentic specimen.

Reduction of 4-Hydroxyquinoline 1-Oxide (IV)—Raney Ni prepared from 4 g. of Ni-Al alloy was added to a solution of 10 g. of well-purified quarter hydrate of (IV) dissolved in 100 cc. of MeOH and the mixture was submitted to catalytic reduction at ordinary temperature and pressure. The reaction was stopped when ca. 1 mole (1300 cc.) of H_2 had been absorbed. The catalyst was filtered off, MeOH was evaporated from the filtrate, and the crystalline residue was recrystallized from EtOH to 7.2 g. (83%) of crystals melting at 201°, undepressed on admixture with authentic 4-quinolone (X).

Reduction of 4-Aminoquinoline 1-Oxide (V)—Raney Ni prepared from 1 g. of Ni-Al alloy was added to a solution of 1 g. of (V) in 30 cc. of MeOH and this mixture was reduced at ordinary temperature and pressure. The reaction was stopped when ca. 1 mole of H_2 had been absorbed. The catalyst was filtered off, the solvent was evaporated from the filtrate, and crude 4-aminoquinoline monohydrate (XI) so obtained was recrystallized from EtOH to 0.74 g. (74%) of crystals melting at 70°, undepressed on admixture with an authentic sample.

Reduction of 4-Nitroquinoline 1-Oxide (VI)—Raney Ni prepared from 4 g. of Ni-Al alloy was

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[6] E. Hayashi, H. Yamanaka, K. Shimizu: This Bulletin, **6**, 325(1958).

added to a solution of 5 g. of (VI) dissolved in 150 cc. of MeOH, 3 cc. of AcOH was added, and this mixture was reduced at ordinary temperature and pressure. The reaction stopped after rapid absorption of 2350 cc. of H_2. The catalyst was filtered off and the ion exchanger prepared as described in the preceding paper, Amberlite IRA-410 (OH type),[1] was added to the filtrate. After allowing to stand over night at room temperature, the ion exchanger was filtered off, the filtrate was evaporated to dryness, and residual 4-aminoquinoline monohydrate (XI) was dried in a vacuum desiccator. Yield, 3.3 g. (79%) of m.p. 70° (from EtOH). No depression of m.p. occurred on admixture with an authentic sample of (XI).

Reduction of 4-Benzyloxyquinoline 1-Oxide (XII)—i) Raney Ni prepared from 4 g. of Ni-Al alloy was added to a solution of 10 g. of (XII) dissolved in 150 cc. of MeOH and the mixture was reduced at ordinary temperature and pressure. The first 1 mole of H_2 was absorbed rapidly but the next mole was absorbed very slowly. The reaction was stopped when 2 moles of H_2 was absorbed, the catalyst was filtered off, and the filtrate was evaporated, affording 3.7 g. (69%) of (X), m.p. 201°(as recrystallized from EtOH), undepressed on admixture with an authentic specimen.

ii) Raney nickel prepared from 4 g. of Ni-Al alloy was added to a solution of 10 g. of (XII) dissolved in 150 cc. of MeOH and the mixture was submitted to catalytic reduction at ordinary temperature and pressure. The reaction was stopped when 1 mole of H_2 had been absorbed, the catalyst was filtered off, and the filtrate was evaporated, leaving 8.6 g. (81%) of 4-benzyloxyquinoline (XIII), b.p$_{10}$ 217~218°.
Picrate: m.p. 190~192°(decomp.). *Anal.* Calcd. for $C_{16}H_{13}ON \cdot C_6H_3O_7N_3$ (4-Benzyloxyquinoline picrate): N, 12.59. Found: N, 12.15.

Catalytic Reduction of 4-Benzyloxypyridine 1-Oxide with Raney Cobalt—Raney Co, prepared from 1 g. of Al-Co alloy as in the case of Raney Ni, and 0.5 g. of 4-benzyloxypyridine 1-oxide were added to 20 cc. of MeOH and the mixture was submitted to catalytic reduction in a usual manner. Hydrogen absorption was almost nil, there being only about 1 bubble during 10 mins. After shaking this mixture for ca. 5 hrs. the catalyst was filtered off and the filtrate was evaporated. The residual crystals (0.44 g.) were recrystallized from Me_2CO-MeOH mixture and the crystals melting at 173° thereby obtained were identified with the starting material.

Catalytic Reduction of 4-Benzyloxypyridine 1-Oxide with Raney Copper—A mixture of 0.5 g. of 4-benzyloxypyridine 1-oxide and Raney Cu, prepared from 1 g. of Al-Cu alloy similarly as Raney Ni, in 20 cc. of MeOH was catalytically reduced by the usual method. There was no absorption of H_2 and 0.45 g. of the starting material was recovered.

Summary

Quinoline 1-oxide and various 4-substituted quinoline 1-oxide derivatives were submitted to catalytic reduction over Raney nickel as a catalyst and results obtained were similar to the case of pyridine derivatives described in the preceding paper. In all cases, compounds were reduced smoothly and in a good yield. In the case of 4-benzyloxyquinoline 1-oxide, the first mole of hydrogen is absorbed rapidly while the next mole of hydrogen is absorbed very slowly, and 4-benzyloxyquinoline 1-oxide is reduced to (X) via 4-benzyloxyquinoline (XIII). This is somewhat different from the behavior of 4-benzyloxypyridine 1-oxide to catalytic reduction over Raney nickel.

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