(Ⅶ), whose identification by admixture with an authentic specimen proved the original compounds to be the 1-oxide. The structure of (Ⅳ) was also proved by its methylation followed by catalytic reduction to form 4-alkoxy-2-quinazolone (Ⅸ).

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31. Hiroshi Yamanaka : Catalytic Reduction of 4-Benzyloxy-6-methylpyrimidine and Related Compounds.

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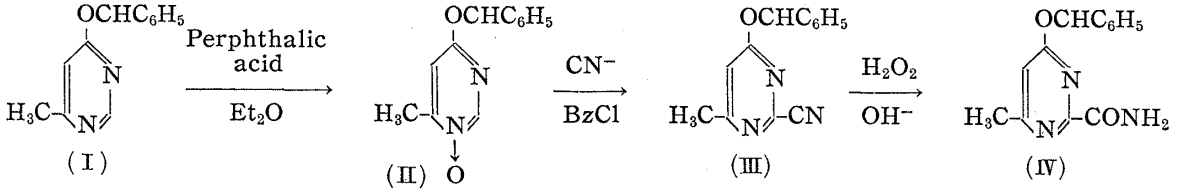
4-Benzyloxy-6-methylpyrimidine (Ⅰ) easily affords its 1-oxide (Ⅱ) when treated with perphthalic acid in ether or with 30% hydrogen peroxide in glacial acetic acid. Reissert reaction of (Ⅱ) gives (Ⅲ) which undergoes hydrolysis to form 4-benzyloxy-6-methylpyrimidine-2-carbonamide (Ⅳ).[1]



Catalytic reduction was carried out on (Ⅱ) and (Ⅳ) of this series and on a few of the related compounds in the present series of experiments.

Some time ago, Ochiai and Teshigawara[2] carried out catalytic reduction of 4-benzyloxypyridine 1-oxide over palladium-carbon catalyst in methanol at ordinary temperature and pressure, and found that the absorption of hydrogen stopped after absorption of one mole to afford 4-hydroxypyridine 1-oxide. In order to prepare 4-hydroxy compound of pyrimidine derivatives of this type by the same reaction, (Ⅱ) was submitted to catalytic reduction in methanol over palladium-carbon but unexpectedly, the compound absorbed two moles of hydrogen, forming 6-methyl-4-pyrimidinol (Ⅴ) alone, and the desired 4-hydroxy-6-methylpyrimidine 1-oxide (Ⅵ) was not obtained at all. The hydrogen absorption curve in this case is shown in Fig. 1 and it will be seen that the rate of hydrogen absorption differs markedly in the initial and latter stages.

For the sake of comparison, (Ⅳ), possessing only the benzyloxyl group that could be reduced, was submitted to catalytic reduction under the same conditions and one mole of hydrogen was absorbed to form 4-hydroxy-6-methylpyrimidine-2-carbonamide (Ⅶ), m.p. 285～286°(decomp.), in quantitative yield. The hydrogen absorption curve in this case was similar to that of (Ⅱ) during the first half period of reduction.

It follows, therefore, that the benzyloxyl group in 4-position of (Ⅱ) is first reduced and that of the N-oxide then follows, and it was assumed that stopping of the reduction after absorption of one mole of hydrogen would afford the desired (Ⅵ). This was found to be true and (Ⅵ), m.p. 198°(decomp.), was finally obtained, though in a somewhat unsatisfactory yield. Catalytic reduction of (Ⅵ) resulted in absorption of one mole of hydrogen to form (Ⅴ). The same was found to be true of 2,6-dimethyl-4-benzyloxypyrimidine 1-oxide (Ⅱ′).

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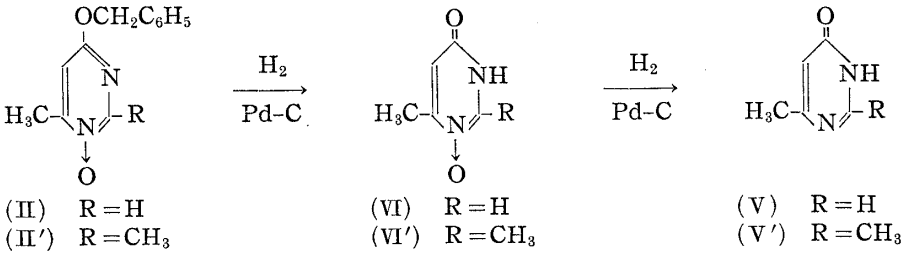
* Oshika, Shizuoka (山中 宏).

1) H. Yamanaka : This Bulletin, **6**, 633(1958).
2) E. Ochiai, T. Teshigawara : Yakugaku Zasshi, **65A**, 1(1945).



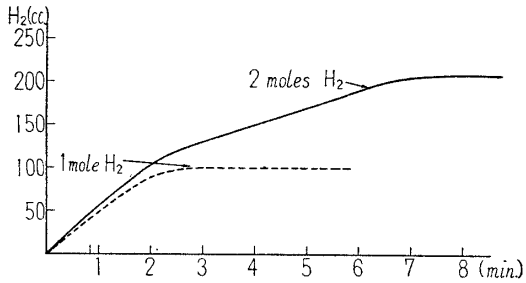
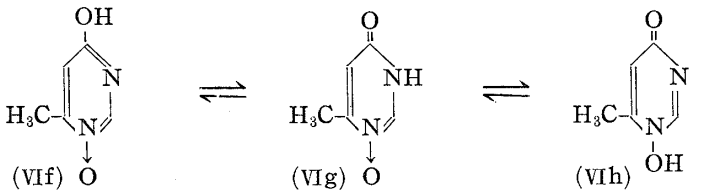


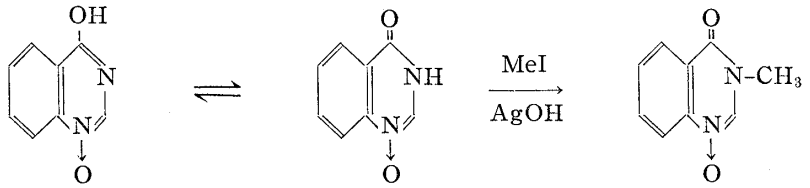
Fig. 1.
Absorption Curve of Hydrogen

—— 4-Benzyloxy-6-methylpyrimidine 1-oxide [II] (1 g.)
------ 4-Benzyloxy-6-methylpyrimidine-2-carbonamide [IV] (1 g.)

According to Ochiai and Hayashi,[3] 4-hydroxypyridine 1-oxide is highly resistant to catalytic reduction over palladium-carbon and it is very interesting that the reduction of the N-oxide group in the corresponding pyrimidine derivative (VI) occurs so easily. The reason for this marked difference is still not clear but it is assumed that the contribution of the structure (VIg), among the possible tautomers of (VI), is fairly great and there is no direct association between the N-oxide group in 1-position and hydroxyl in 4-position.



As shown in a previous report,[4] methylation of 4-hydroxyquinazoline 1-oxide affords the 3-methyl compound alone and this phenomenon can also be understood by similar consideration.



The reduction of (II) to (VI) progresses at a comparatively fast rate and it requires careful observations to stop the reaction at the stage of absorption of one mole of hydrogen, it being difficult to make a clear-cut separation of the reaction. This may be one of the reasons for the lowering of yield. In order to solve this problem and to obtain (VI) more easily, it was found necessary to use a reducing agent which would act only in severing the benzyloxyl group but not the N-oxide group. A few examinations made in this direction gave a rather interesting result, though it was contrary to the original idea.

The use of Raney nickel, prepared in the usual way, for catalytic reduction of (II) in methanol resulted in absorption of only one mole of hydrogen and 4-benzyloxy-6-methylpyrimidine (I) was obtained in a quantitative yield. This showed that Raney

3) E. Ochiai, E. Hayashi: Yakugaku Zasshi, **67**, 151(1947).
4) H. Yamanaka: This Bulletin, **7**, 152(1959).

nickel had a strong selectivity against the N-oxide group, in contrast to the palladium-carbon catalyst. The similar reduction of 4-methoxy-6-methylpyrimidine 1-oxide was also found to result in deoxygenation of the N-oxide group. The N-oxides of pyrimidines possess two ring-nitrogens and their properties are somewhat different from pyridine 1-oxides, not being the so-called typical aromatic tertiary amine oxides.

For the sake of comparison, the same reduction was carried out on 4-benzyloxypyridine 1-oxide[5] and the result was entirely the same. Absorption of hydrogen stopped after one mole and 4-benzyloxypyridine was obtained in quantitative yield, thereby confirming the action of Raney nickel toward the N-oxide group. These experiments on reduction of three kinds of N-oxide derivatives have shown that the use of Raney nickel as a catalyst is better than the reduction of N-oxide group with phosphorus trichloride, both in the way of procedures and yield, and the method is expected to play an important role in the reduction of N-oxides of various pyridine and quinoline derivatives.

The author expresses his deep gratitude to Prof. E. Ochiai of the University of Tokyo, to Dr. T. Ukai, the Dean of this College, and to Prof. E. Hayashi of this College for kind and continued guidance throughout the course of this work. He is indebted to Misses Y. Saito and N. Kamoto of this College for elemental analyses.

Experimental

Catalytic Reduction of 4-Benzyloxy-6-methylpyrimidine-2-carbonamide (IV) over Palladium-Carbon—Pd-C catalyst, prepared from 5 cc. of 1% $PdCl_2$ solution and 0.5 g. of activated carbon, was added to a solution of 3.0 g. of (IV) dissolved in 25 cc. of MeOH and the mixture was shaken in H_2 stream. The reduction stopped almost completely after rapid absorption of ca. 280 cc.(calcd., 276 cc.) of H_2. The catalyst was filtered off, this was extracted with a large quantity of hot MeOH, and the combined filtrate and extract was concentrated, affording 1.6 g.(85%) of white needles, m.p. 285~286°(decomp.). *Anal.* Calcd. for $C_6H_7O_2N_3$(4-Hydroxy-6-methylpyrimidine-2-carbonamide): C, 47.05; H, 4.61; N, 27.44. Found: C, 47.26; H, 4.48; N, 27.77.

Catalytic Reduction of 4-Benzyloxy-6-methylpyrimidine 1-Oxide (II) over Palladium-Carbon—i) Absorption of 2 moles of H_2: A mixture of a solution of 1 g. of (II) dissolved in 20 cc. of MeOH and Pd-C catalyst, prepared from 5 cc. of 1% $PdCl_2$ solution and 0.5 g. of activated carbon, was shaken in H_2 stream. The reduction stopped after rapid and later slower absorption of 200 cc. of H_2. The catalyst was filtered off, the filtrate was evaporated to dryness, and the white crystalline residue was recrystallized, after washing with ether, from benzene to 0.4 g.(80%) of white prisms, m.p. 148~149°, undepressed on admixture with 6-methyl-4-pyrimidinol, m.p. 149~150°.

ii) Absorption of 1 mole of H_2: Two grams of (II) was submitted to catalytic reduction by the same procedure as in above (i) and the reduction was terminated when 200 cc.(corresponding to 1 mole) of H_2 had been absorbed. The catalyst was filtered off and the catalyst was extracted with a large quantity of hot MeOH. The combined filtrate and extract was evaporated to dryness under a reduced pressure and the crystalline residue so obtained was recrystallized from MeOH to 0.75 g. (64%) of white needles, m.p. 198°(decomp.). *Anal.* Calcd. for $C_5H_6O_2N_2$ (4-Hydroxy-6-methylpyrimidine 1-oxide): C, 47.62; H, 4.80; N, 22.22. Found: C, 47.67; H, 4.85; N, 22.20.

Catalytic Reduction of 4-Hydroxy-6-methylpyrimidine 1-Oxide (VI) over Palladium-Carbon—Pd-C catalyst, prepared from 7 cc. of 1% $PdCl_2$ solution and 0.5 g. of activated carbon, was added to 1 g. of (VI) suspended in 30 cc. of MeOH and the mixture was shaken in H_2 stream. The reduction stopped after absorption of 1 mole (178 cc.) of H_2. The catalyst was filtered off, the filtrate was evaporated to dryness, and the white crystalline residue was recrystallized from benzene to 0.87 g.(80%) of white prisms, m.p. 148~150°, undepressed on admixture with (V), m.p. 149~150°.

Preparation of 2,6-Dimethyl-4-benzyloxypyrimidine (I′)—To a solution of 1.2 g. of metallic Na dissolved in 40 cc. of benzyl alcohol, 6 g. of 2,6-dimethyl-4-chloropyrimidine was added in small portions. The mixture was refluxed for 15 mins., benzyl alcohol was distilled off as much as possible under a reduced pressure, and 10 cc. of water was added to the residue. The oily substance that separated out was extracted with benzene, the extract was dried over anhyd. Na_2SO_4, and the solvent was evaporated. The residue was distilled under a reduced pressure and 7.2 g.(90%) of a fraction of $b.p_3$ 141~143° was obtained.

5) E. Hayashi, H. Yamanaka, K. Shimizu: This Bulletin, **7**, 141(1959).

Picrate : m.p. 142~143°(from MeOH). *Anal.* Calcd. for $C_{13}H_{14}ON_2 \cdot C_6H_3O_7N_3$(2,4-Dimethyl-4-benzyloxypyrimidine picrate) : C, 51.47; H, 3.87; N, 15.80. Found : C, 51.63; H, 3.74; N, 15.42.

Preparation of 2,6-Dimethyl-4-benzyloxypyrimidine 1-Oxide (II′)—To an ether solution of perphthalic acid containing 1.5 times the calculated amount of active oxygen, 7.0 g. of (I′) was added and the mixture was allowed to stand in a cool, dark place for 1 week. The crystals that separated out were decomposed with 20% K_2CO_3 solution and the mixture was extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4, $CHCl_3$ solution was passed through a short column of alumina to remove colored matter and the solvent was evaporated from the effluent. The residual oily substance solidified on cooling and the solid was recrystallized from a mixture of benzene and petr. ether to 6.1 g. (81%) of the N-oxide melting at 100~101.5°. *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$ (2,6-Dimethyl-4-benzyloxypyrimidine 1-oxide) : C, 67.81; H, 6.13; N, 12.17. Found : C, 67.73; H, 6.19; N, 11.97.

Catalytic Reduction of (II′) over Palladium-Carbon—i) Absorption of 2 moles of H_2 : One gram of (II′) was catalytically reduced as in the case of (II) and 0.45 g.(83%) of needles, m.p. 194°, as crystallized from acetone-MeOH, was obtained. No depression of m.p. occurred on admixture with 2,6-dimethyl-4-pyrimidinol, m.p. 194°.

ii) Termination of Reduction after 1 mole of H_2 Absorption : A mixture of Pd-C catalyst, prepared from 5 cc. of 1% $PdCl_2$ solution, and 2.0 g. of (II′) dissolved in 20 cc. of MeOH was shaken in H_2 stream. The reduction was stopped when 1 mole (195 cc.) of H_2 had been absorbed and the reaction mixture was treated as in the case of (II), from which 1 g.(78%) of prisms, m.p. 230°(decomp.), was obtained. *Anal.* Calcd. for $C_6H_8O_2N_2$ (2,6-Dimethyl-4-hydroxypyrimidine 1-oxide) : C, 51.40; H, 5.72; N, 20.00. Found : C, 51.38; H, 5.81; N, 19.41.

Catalytic Reduction of 2,6-Dimethyl-4-hydroxypyrimidine 1-Oxide (VI′) over Palladium-Carbon—Pd-C catalyst, prepared from 5 cc. of 1% $PdCl_2$ solution and 0.5 g. of activated carbon, was added to 1 g. of (VI′) suspended in 30 cc. of MeOH and the mixture was shaken in H_2 stream. The reaction mixture was treated as in the case of (VI) and 0.75 g. of needles (from acetone-MeOH), m.p. 194°, was obtained, showing no m.p. depression on admixture with 2,6-dimethyl-4-pyrimidinol, m.p. 194°.

Catalytic Reduction of 4-Benzyloxy-6-methylpyrimidine 1-Oxide (II) over Raney Nickel—Raney nickel catalyst prepared from 1 g. of Ni-Al (1:1) alloy and 30% NaOH solution was added to a solution of 1.0 g. of (II) dissolved in 20 cc. of MeOH and the mixture was shaken in H_2 stream at ordinary temperature and pressure. The reduction stopped after rapid absorption of 100 cc. of H_2 at the rate of ca. 40 cc./min. The catalyst was filtered off and MeOH was evaporated from the filtrate, affording 0.85 g.(92%) of colorless oil. Its picrate melted at 142~144°, showing no depression on admixture with the picrate, m.p. 142~144°, of (I).

Catalytic Reduction of 4-Methoxy-6-methylpyrimidine 1-Oxide over Raney Nickel—A mixture of 1 g. of 4-methoxy-6-methylpyrimidine 1-oxide and Raney Ni catalyst prepared from 0.5 g. of Ni-Al alloy in 20 cc. of MeOH was shaken in H_2 stream and the reduction stopped after rapid absorption (ca. 40 cc./min.) of 160 cc.(corresponding to 1 mole) of H_2. The catalyst was filtered off and MeOH was evaporated from the filtrate, leaving 0.8 g.(90%) of oily substance. This oil formed a picrate of m.p. 114~116°, undepressed on admixture with the picrate, m.p. 116~117°, of 4-methoxy-6-methylpyrimidine.

Summary

Catalytic reduction of 4-benzyloxy-6-methylpyrimidine 1-oxide in methanol over palladium-carbon resulted in the formation of 6-methyl-4-pyrimidinol via 4-hydroxy-6-methylpyrimidine 1-oxide. The use of Raney nickel as a catalyst in this case afforded 4-benzyloxy-6-methylpyrimidine and this is a new type of reaction not recorded in past literature.

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