

33. Tetsuzo Kato and Fumiko Hamaguchi : Synthesis of Methylpyridine Derivatives. IX.¹⁾ Reduction of 4-Nitro-2,6-lutidine 1-Oxide and 4-Nitro-3-picoline 1-Oxide.

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Ochiai and his co-workers reported the reduction of 4-nitropyridine 1-oxide²⁾ and 4-nitro-2-picoline 1-oxide³⁾, and found a remarkable resistance of the N-oxide group to reduction as compared with the nitro group, which showed a tendency to undergo bimolecular reduction leading to the formation of azo and hydrazo derivatives.

The present paper describes a similar reduction of 4-nitro-2,6-lutidine 1-oxide (Ia) and 4-nitro-3-picoline 1-oxide (Ib), which were found to behave quite similarly as above.

Upon catalytic reduction with palladium-charcoal in neutral medium, both 4-nitro-2,6-lutidine 1-oxide (Ia) and 4-nitro-3-picoline 1-oxide (Ib) absorbed 3 moles of hydrogen and were reduced to the 4-amino 1-oxides (IIa, IIb), but no further. However, the absorption velocity of hydrogen was influenced by the quantity of palladium catalyst used and the temperature. In case a small amount of palladium-charcoal (10% or below of 50% Pd-C to the raw material) was used at room temperature, the reduction proceeded slowly and azo derivatives (Va, Vb) were obtained as by-products, but the use of a large amount of palladium catalyst (20~50% to the raw material) in aqueous solution effected the reduction smoothly and 4-amino 1-oxides (IIa, IIb) were obtained in a good yield. In methanolic solution, the reduction proceeded rapidly up to the point where 2 moles of hydrogen had been absorbed, and then became gradual, and an azo derivative (Va) was obtained as a by-product.

4-Amino-2,6-lutidine 1-oxide (IIa) is easily soluble in water and ethanol but insoluble in acetone, ether, benzene, and chloroform. Therefore, it was easily separated through recrystallization from the azo derivative (Va) and 4-amino-2,6-lutidine (IIIa), which are insoluble in water but soluble in acetone, benzene, and chloroform, so that this is a satisfactory method for the preparation of the 4-amino 1-oxides (IIa, IIb).

In 10% hydrochloric acid solution, the reduction proceeded smoothly up to a point where 2 moles of hydrogen had been absorbed, but after this point the absorption velocity slowed down. In this procedure, 4-amino-2,6-lutidine 1-oxide (IIa) and azo compound (Va) were formed, with the latter predominating. However, when the reduction was run in glacial acetic acid to which a small amount of acetic anhydride had been added, it proceeded smoothly until absorption of 3 moles of hydrogen, and then more slowly until another mole had been absorbed. When platinum oxide was added, the reduction proceeded smoothly at room temperature and the 4-amino derivatives (IIIa, IIIb) were obtained.

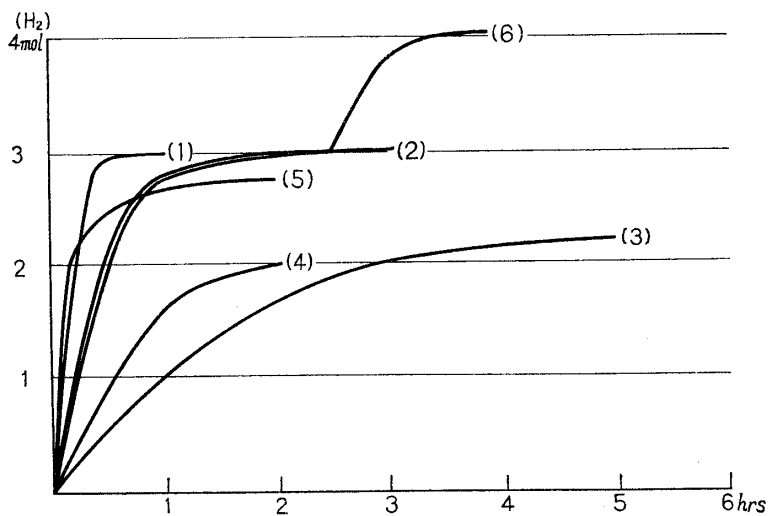
Treating with hydrogen sulfide, sodium nitrite, or zinc dust, 4-nitro 1-oxides (Ia, Ib) were reduced to azo or azoxy derivatives. That is, hydrogen sulfide was saturated in ethanolic ammonia solution of 4-nitro-2,6-lutidine 1-oxide (Ia) and

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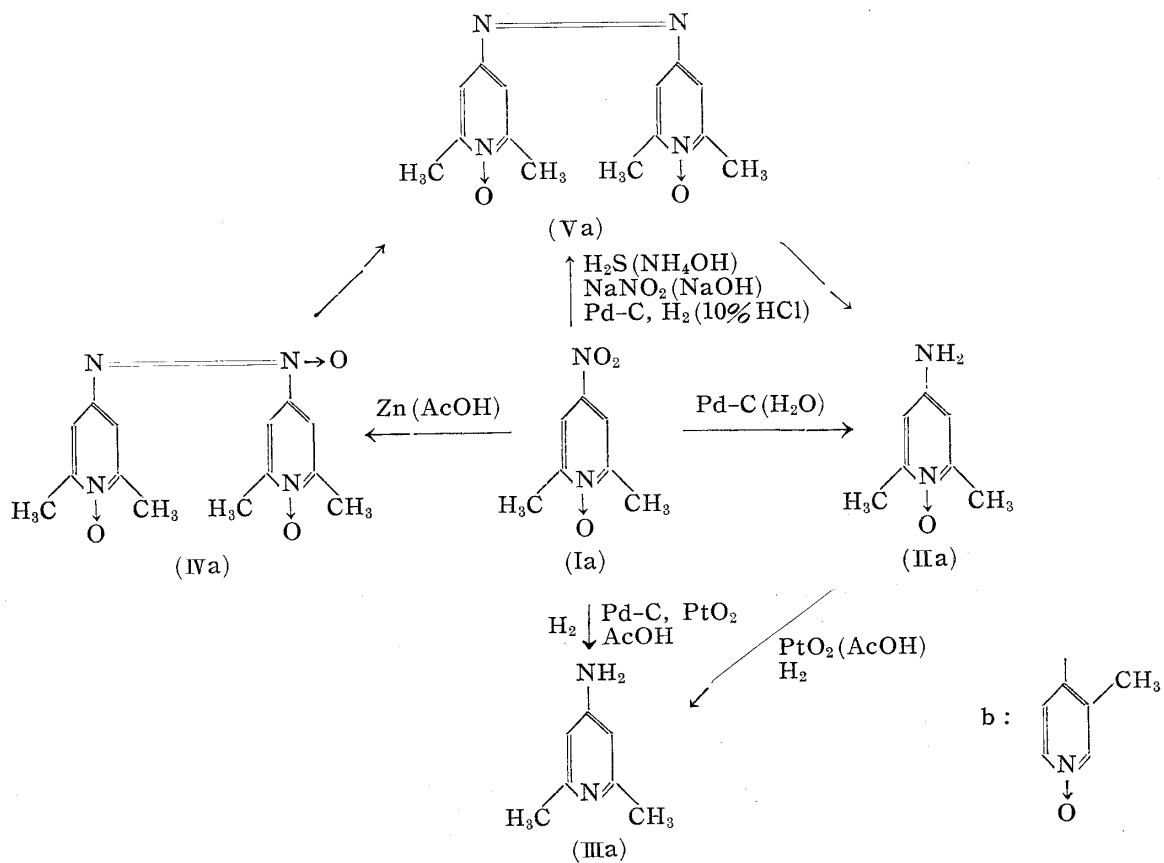
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2) E. Ochiai, M. Katada : *Ibid.*, **63**, 186(1943).

3) E. Ochiai, I. Suzuki : *Ibid.*, **67**, 158(1947).



Curve	Raw material (Ia) (g.)	Solvent (cc.)	50% Pd-C (g.)	Temp. (°C)	Yield (%)		
					(IIa)	(Va)	(IIIa)
(1)	0.5	H ₂ O, 30	0.3	26	quantitative	0	0
(2)	5.0	H ₂ O, 150	1.0	16	92	—	0
(3)	3.36	H ₂ O, 100	0.2	12	54	9	—
(4)	0.84	10% HCl, 25	0.5	13	7	80	—
(5)	0.5	MeOH, 30	0.3	24	65	3	0
(6)	1.68	AcOH, 50 (Ac ₂ O, 5)	1.0 (PtO ₂ , 0.2)	12	—	—	74



	Compound	m.p., °C	Method
(IIa)	4-Amino-2,6-lutidine 1-oxide	264~266(decomp.)	Pd-C, H ₂ (H ₂ O)
(IIb)	4-Amino-3-picoline 1-oxide	138	"
(IIIa)	4-Amino-2,6-lutidine	192	Pd-C(PtO ₂), AcOH(Ac ₂ O)
(IIIb)	4-Amino-3-picoline	107	"
(IVa)	4,4'-Azoxy-2,6-lutidine 1,1'-dioxide	233(decomp.)	Zn+AcOH
(IVb)	4,4'-Azoxy-3-picoline 1,1'-dioxide	258(decomp.)	"
(Va)	4,4'-Azo-2,6-lutidine 1,1'-dioxide	248(decomp.)	H ₂ S(NH ₄ OH), NaNO ₂ (NaOH) Pd-C, H ₂ (10% HCl)
(Vb)	4,4'-Azo-3-picoline 1,1'-dioxide	263(decomp.)	H ₂ S(NH ₄ OH), NaNO ₂ (NaOH)

4-nitro-3-picoline 1-oxide (Ib), and red needles of m.p. 248°(decomp.) and of m.p. 263°(decomp.) were obtained. These compounds were identified with 4,4'-azo-2,6-lutidine 1,1'-dioxide (Va) and 4,4'-azo-3-picoline 1,1'-dioxide (Vb). In this procedure a small amount of 4-amino-2,6-lutidine 1-oxide (IIa) was obtained from (Ia) as a by-product, but 4-amino-3-picoline 1-oxide (IIb) was not isolated from (Ib).

(Ia) was treated with sodium nitrite in sodium hydroxide solution and the azo compound (Va) was obtained in a poor yield, but no other reduction product was obtained.

(Ia) and (Ib) were treated with zinc dust in glacial acetic acid solution and from these solutions, orange needles of m.p. 233°(decomp.) and 243~246°(decomp.) were obtained. These compounds were taken to be 4,4'-azoxy-2,6-lutidine 1,1'-dioxide (IVa) and 4,4'-azoxy-3-picoline 1,1'-dioxide (IVb) from the result of analyses.

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Experimental

I. Catalytic Reduction—(i) Reduction in Aqueous Solution :

4-Amino-2,6-lutidine 1-Oxide (IIa)—A suspension of 5 g. (0.03 mole) of 4-nitro-2,6-lutidine 1-oxide (Ia) in 100 cc. of water was placed in a reduction vessel, 1 g. of 50% Pd-C was added, and the mixture was shaken in H₂ until 3 mol. equiv. (2150 cc. at 18°) had been absorbed. The time required was about 2 hrs. The catalyst was filtered off and water removed from the filtrate by evaporation under a reduced pressure, from which white crystalline residue was obtained. This was washed with ether and acetone, and crystallized from EtOH and acetone to 4 g. of a product melting at 230~255°(decomp.). 4-Amino-2,6-lutidine 1-oxide (IIa), recrystallized from EtOH and acetone, formed white needles of m.p. 264~266°(decomp.), giving positive diazo color test. *Anal.* Calcd. for C₇H₁₀ON₂(IIa) : C, 60.85; H, 7.30; N, 20.28. Found : C, 60.82; H, 6.80; N, 20.30. Picrate, recrystallized from MeOH to yellow needles, m.p. 214°(decomp.). *Anal.* Calcd. for C₇H₁₀ON₂·C₆H₃O₇N₃ (IIa picrate) : C, 42.51; H, 3.51; N, 19.07. Found : C, 41.95; H, 3.65; N, 19.32.

4-Amino-3-picoline 1-Oxide (IIb)—To a suspension of 2 g. of (Ib) in 50 cc. of water, 0.5 g. of 50% Pd-C was added and the mixture was shaken in H₂ until 933 cc. had been absorbed at 24°. The time required was about 0.5 hr. The mixture was treated in the same way as described above. 4-Amino-3-picoline 1-oxide (IIb) recrystallized from EtOH and acetone to white needles, m.p. 136~138° (somewhat hygroscopic), and in a long time yellow coloration appeared. Yield, 1.5 g. (94%). This was easily soluble in water and EtOH, but insoluble in ether, acetone, benzene, and CHCl₃. *Anal.* Calcd. for C₆H₈ON₂·H₂O (IIb-H₂O) : C, 50.69; H, 7.07. Found : C, 50.52; H, 7.07.

(ii) Reduction in Glacial AcOH Solution :

4-Amino-2,6-lutidine (IIIa)—To a solution of 1.68 g. (0.01 mole) of (Ia) in 50 cc. of AcOH and 5 cc. of Ac₂O, 1 g. of 50% Pd-C was added, and the mixture was shaken in H₂ until 3 mol. equiv. (700 cc. at 12°) had been absorbed, and then absorption velocity of H₂ gradually slowed down. To this mixture 0.2 g. of PtO₂ was added and again shaken until another mol. equiv. (230 cc.) had been absorbed. The catalyst was filtered off and the filtrate was concentrated. The residue was heated with 20 cc. of 10% HCl for about 0.5 hr., basified with NaOH, and the mixture was extracted with ether. From the ether extract a crystalline residue was obtained, which was crystallized from ligroine to colorless needles, m.p. 192°. Yield, 0.9 g. (74%). *Anal.* Calcd. for C₇H₁₀N₂ (IIIa) : C, 68.82; H, 8.25; N, 22.93. Found : C, 68.39; H, 8.30; N, 22.79.

4-Amino-3-picoline (IIIb)—1.5 g. of (Ib) was reduced by the same way as above. Colorless needles of m.p. 105~109° were obtained. Yield, 0.55 g. (50%). This was proved to be identical with the melting point in the literature.⁴⁾

II. Reduction with H₂S, NaNO₂, or Zn Dust

(i) **Reduction with H₂S: Reduction of (Ia)**—A mixture of 0.5 g. of (Ia), 1.2 g. of 25% NH₄OH, and 10 cc. of EtOH was saturated with H₂S without allowing the temperature to rise. The orange yellow coloration appeared along with a pale yellow precipitate. After allowing the mixture to stand over night, the reddish orange mixture was filtered and the precipitate was collected. The precipitate on the filter was washed with EtOH. The combined EtOH filtrate and washing was acidified with dil. HCl and was filtered again to remove a white precipitate of sulfur. The filtrate was concentrated under a reduced pressure. The acidic residue, after drying, was made alkaline with Na₂CO₃ solution, and the product was extracted with CHCl₃. The CHCl₃ solution was dried, filtered, and concentrated, leaving a reddish orange residue. This was crystallized from EtOH to reddish needles, m.p. 248°(decomp.). Yield, 0.19 g. (48%). *Anal.* Calcd. for C₁₄H₁₆O₂N₄ (Va): C, 61.75; H, 5.92; N, 20.58. Found: C, 61.80; H, 6.00; N, 20.20. The Na₂CO₃ solution, after extracting with CHCl₃, was evaporated to dryness and the residue was washed with EtOH. From the ethanolic washing, a small amount of 4-aminolutidine 1-oxide (IIa) was isolated as the picrate of m.p. 202°(decomp.).

Reduction of (Ib)—A solution of 0.5 g. of (Ib) dissolved in 10 cc. of MeOH, and added with 1.2 g. of 25% NH₄OH, was saturated with H₂S. A yellow precipitate separated, but this gradually dissolved into a reddish solution, and after a while, suddenly a yellow precipitate of sulfur separated. After removing sulfur by filtration, the filtrate was treated in the same way as above. Yield, 0.3 g. (75%). Red needles of m.p. 263°(decomp.) were obtained from EtOH. *Anal.* Calcd. for C₁₂H₁₂O₂N₄ (Vb): C, 59.01; H, 4.95; N, 22.95. Found: C, 58.83; H, 4.95; N, 22.55.

(ii) **Reduction with NaNO₂**—0.2 g. of (Ia) was added to 20 cc. of 10% NaOH solution and to this solution was added 2 g. of NaNO₂. The mixture was heated in a steam bath at 90° for about 20 mins., by which a reddish-brown coloration appeared and a precipitate separated out. After 2 hrs.' heating, the mixture was concentrated under a reduced pressure. The residue was extracted with CHCl₃, and from the CHCl₃ extract 0.04 g. of reddish orange crystals were obtained. Recrystallization from EtOH gave 0.01 g. of (Va), m.p. 245°(decomp.).

(iii) **Reduction with Zinc Dust: Reduction of (Ia)**—0.5 g. of (Ia) was dissolved in 12 cc. of glacial AcOH, added with 0.5 g. of Zn dust, and on shaking the mixture a yellow green coloration appeared. After being allowed to remain for 5 hrs. at 16°, the Zn dust was removed off by filtration. The orange filtrate was evaporated under a reduced pressure and made alkaline with NH₄OH. The alkaline solution was extracted with ether and CHCl₃. From the ether extract 0.07 g. of yellow crystals were obtained. This was identified with the raw material (Ia) by admixture. From the CHCl₃ solution an orange yellow crystals separated. This was recrystallized from EtOH to orange yellow needles, m.p. 233°(decomp.). Yield, 0.17 g. (47%). *Anal.* Calcd. for C₁₄H₁₆O₃N₄ (IVa): C, 58.33; H, 5.55; N, 19.44. Found: C, 58.39; H, 5.85; N, 19.27.

Reduction of (Ib)—A mixture of 0.3 g. of (Ib), 5 cc. of glacial AcOH, and 0.3 g. of Zn dust was treated in the same way as above, and the orange residue (0.18 g.) from the CHCl₃ extract was recrystallized from EtOH to orange needles, m.p. 243~246°(decomp.). After drying, the crystals melted at 258° with decomposition. Yield, 0.06 g. *Anal.* Calcd. for C₁₂H₁₂O₃N₄ (IVb): C, 55.38; H, 4.65; N, 21.53. Found: C, 55.78; H, 4.75; N, 21.80.

Summary

Reduction of 4-nitro-2,6-lutidine 1-oxide (Ia) and 4-nitro-3-picoline 1-oxide (Ib) under various conditions was examined. Upon catalytic reduction with palladium-charcoal in aqueous solution, (Ia) and (Ib) were respectively reduced to 4-amino-2,6-lutidine 1-oxide (IIa) and 4-amino-3-picoline 1-oxide (IIb). However, in methanolic solution or 10% hydrochloric acid solution, the reduction did not proceed smoothly and azo derivatives (Va, Vb) were obtained as a by-product. In glacial acetic acid, to which a small amount of acetic anhydride had been added, the reduction proceeded smoothly and 4-amino derivatives (IIIa, IIIb) were obtained. By the reduction of (Ia) and (Ib) with hydrogen sulfide or sodium nitrite, 4,4'-azo-2,6-lutidine 1,1'-dioxide (Va) and 4,4'-azo-3-picoline 1,1'-dioxide (Vb) were obtained. When zinc dust was used as a reducing agent 4,4'-azoxy 1,1'-dioxide compounds (IVa, IVb) were obtained.

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