talline precipitate deposited. After cooling on ice, the precipitate was collected by suction and recrystallized from dioxane; yield, 0.21 g. of slightly greenish yellow prisms, m.p. 265° (decomp.).

*Anal. Calcd. for C_{13}H_{19}O_{3}N_{3}Br: N, 16.36. Found: N, 16.05.*

**Summary**

\(\beta-(5\text{-Nitro-2-furyl})-\alpha\text{-methylacrolein and } \beta-(5\text{-nitro-2-furyl})-\alpha\text{-ethy lacrolein were prepared by the condensation of } 2-(5\text{-nitro})furfural with propionaldehyde and butyraldehyde, respectively, in the presence of piperidinium acetate as a catalyst. Preparation of } \beta-(5\text{-nitro-2-furyl})-\alpha\text{-bromoacrolein was accomplished by bromination in the usual manner.}

These new compounds were used as an antibacterial group in the preparation of Schiff bases with semicarbazides, hydrazides, and amines, and then antibacterial screening of these bases was carried out.

From the screening results, \(\beta-(5\text{-nitro-2-furyl})-\alpha\text{-methylacrolein semicarbazone, } \beta-(5\text{-nitro-2-furyl})-\alpha\text{-methylacrolein oxime, and } 1-(\beta-(5\text{-nitro-2-furyl})-\alpha\text{-bromoacrylidene})-2\text{-isonicotinyldihydrazine were found to exert great activity against tubercle bacilli.}

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80. Sunao Furukawa: Reaction of 2,4-Lutidine 1-Oxide and 2,4-Dimethylquinoline 1-Oxide with Acetic Anhydride.

*(Pharmaceutical Faculty, University of Nagasaki*)

Previously, Boekelheide and Linn\(^1\) and Kobayashi and Furukawa\(^2\) succeeded independently in converting the active methyl group in the 2- or 4-position of pyridine ring into the hydroxymethyl group by rearrangement with acetic anhydride through their N-oxide compound. In this reaction, it is clear that the methyl group in 2-position is able to react more easily than that in 4-position from the yields of the hydroxymethyl compounds prepared by rearrangement of 2- and 4-picoline 1-oxide, quinaldine 1-oxide, and lepidine 1-oxide.\(^3\) Further, for the confirmation of these results, the present author experimented the rearrangement reaction with acetic anhydride of 2,4-lutidine 1-oxide and 2,4-dimethylquinoline 1-oxide, with active methyl groups in both 2- and 4-positions.

2,4-Lutidine 1-oxide was reacted with acetic anhydride, followed by hydrolysis with dilute hydrochloric acid, and three reaction products were isolated by repeated fractional distillation, (I) b.p. 100~107°, (II) b.p. 131~140°, and (III) b.p. 140~150°.

These three fractions, (I), (II), and (III), formed picrates melting at 156~158°, 155~157°, and 242~244°, respectively. Although the melting points of the picrates of (I) and (II) were similar, they depressed on admixture.

(I) and (II) were converted to the corresponding chloromethyl compounds with phosphorus trichloride. (I) was oxidized to 4-methylpicolinic acid and (II) to 2-methylisonicotinic acid by oxidation with calculated amount of potassium permanganate. Considering such results, it is certain that (I) is 4-methyl-2-hydroxy methylpyridine and (II) is 2-methyl-4-hydroxymethylpyridine. (III) colored red with

\* Showa-machi, Nagasaki (吉川 淑).
2) G. Kobayashi, S. Furukawa: This Bulletin, 1, 347(1953).
ferric chloride which suggests that it might be a phenolic base. An oily substance liberated from the purified picrate crystallized, showing m.p. 144–146°. Elemental analysis of this substance (C₆H₅ON), agreed with that of hydroxy-2,4-lutidine. Since it colored deep blue by Denis–Folin’s reagent, the hydroxyl group was considered to be present at the β-position of 2,4-lutidine. In order to determine whether the hydroxyl group exists in 3- or 5-position, Gibbs’ reagent which forms an indophenol-type blue dye when para-position to a phenolic hydroxyl group is vacant in aromatic ring was applied and the deep blue color produced suggested this substance to be 3-hydroxy-2,4-lutidine. Its ultraviolet absorption spectrum is shown in Fig. 1.

![Ultraviolet Absorption Spectra](image)

**Fig. 1. Ultraviolet Absorption Spectra**
*(in EtOH)*

(I) 3-Hydroxy-2,4-lutidine

(II) 3-Hydroxy-2,6-lutidine

The yield of 2-hydroxymethyl-4-methylpyridine, 4-hydroxymethyl-2-methylpyridine, and 3-hydroxy-2,4-lutidine was 30%, 6%, and 2%, respectively, and the formation ratio of 2-hydroxymethyl-4-methylpyridine and 2-methyl-4-hydroxy-methylpyridine was about 5:1.

In the case of 2,4-lutidine 1-oxide, an alcoholic substance was obtained in about 70% yield. This substance was proved to be 2-hydroxymethyllepidine by its oxidation with permanganate to lepidine-2-carboxylic acid. Besides this alcoholic substance, a phenolic base was obtained in an yield of 5%. The ultraviolet absorption spectrum of this phenolic base showed a curve similar to that of 3-hydroxylepidine which was obtained by the reaction of lepidine 1-oxide with acetic anhydride. This phenolic base was assumed to be 3-hydroxy-2,4-dimethylquinoline.

![Ultraviolet Absorption Spectra](image)

**Fig. 2. Ultraviolet Absorption Spectra**
*(in EtOH)*

(III) 3-Hydroxy-2,4-dimethylquinoline

(IV) 3-Hydroxylepidine

In the case of 2,4-dimethylquinoline 1-oxide, 4-hydroxymethylquininaldine was not obtained, differing from the reaction of 2,4-lutidine 1-oxide.

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**Experimental**

**Reaction of 2,4-Lutidine 1-Oxide with Acetic Anhydride**—Fifty g. of 2,4-lutidine 1-oxide was mixed with 60 cc. of Ac₂O and slowly warmed on a water bath, by which a violent reaction started and the reaction mixture turned dark brown. After the violent reaction subsided, further heating was continued for 1 hr. on a boiling water bath. After Ac₂O was distilled off under a diminished pressure, the residue was distilled in vacuum. The distillate of b.p. 100~150° weighed 48 g. The bases obtained were refluxed with 150 cc. of 10% HCl for 30 mins. The acidic solution was concentrated in vacuum, neutralized with K₂CO₃, and extracted with CHCl₃. The CHCl₃ residue was distilled in vacuum and the distillate of b.p. 100~150° weighed 33 g. These bases were separated into three fractions by repeated fractional distillation. (I) b.p. 100~107°; yield, 15 g. (II) b.p. 131~140°; yield, 3 g. b.p. 104~150°; yield, 1 g.


Picrate of (III): orange yellow columnar crystals, m.p. 242~243° (from MeOH). *Anal.* Calcd. for C₄H₆ON.C₂H₅O₂N₃ (2-Hydroxy-2,4-lutidine picrate): C, 44.33; H, 3.43; N, 15.75. Found: C, 44.21; H, 3.50; N, 15.42.

**Chlorination of (I) and (II) with PCl₅**—Into a solution of 0.2 g. of (I) in 5 cc. dry benzene 0.3 cc. PCl₅ was added, the mixture was warmed for 5 mins. on a water bath. After cooling, it was poured into ice water, neutralized withaq. NH₃, and extracted with benzene. The benzene residue was an oil with irritating odor. The picrate formed yellow prisms, m.p. 166~168° (from MeOH). *Anal.* Calcd. for C₅H₅NCl.C₂H₅O₂N₃ (2-Chloromethyl-4-methylpyridine): C, 42.13; H, 2.99; N, 15.07. Found: C, 42.24; H, 2.87; N, 14.94. 2) When 0.2 g. of (II) was treated in the same manner as in 1), an irritating oil was obtained. The picrate formed yellow needles, m.p. 146~148° (from MeOH). *Anal.* Calcd. for C₅H₅NCl.C₂H₅O₂N₃ (2-Methyl-4-chloromethylpyridine): C, 42.13; H, 2.99; N, 15.07. Found: C, 42.18; H, 2.87; N, 15.07.

**3-Hydroxy-2,4-lutidine**—When the oily base was liberated from the purified picrate, it crystallized into white needles (from benzene), m.p. 144~146°. *Anal.* Calcd. for C₄H₆ON: C, 68.29; H, 7.26; N, 11.38. Found: C, 67.92; H, 7.22; N, 11.27. 3-Hydroxy-2,4-lutidine colored deep blue with the Denis-Folin's reagent and deep blue with the Gibbs' reagent at pH 8.

**2,4-Dimethylquinoline 1-Oxide**—A mixture of 5 g. 2,4-dimethylquinoline, 3 cc. glacial AcOH, and 2 cc. 30% H₂O₂ was warmed for 8 hrs. on a water bath at 75~85°. AcOH was distilled off in vacuum, the residue was neutralized with K₂CO₃, and extracted with CHCl₃. The CHCl₃ residue was recrystallized from benzene to white prisms, m.p. 117~119°, yield, 3 g. *Anal.* Calcd. for C₁₀H₈ON: C, 76.32; H, 6.40; N, 8.09. Found: C, 76.29; H, 6.21; N, 7.80. The picrate formed yellow needles, m.p. 142~144° (from MeOH). *Anal.* Calcd. for C₁₀H₈ON.C₂H₅O₂N₃: C, 50.75; H, 3.50; N, 13.93. Found: C, 50.45; H, 3.78; N, 14.03.

**Reaction of 2,4-Dimethylquinoline 1-Oxide with Acetic Anhydride**—Five g. of 2,4-dimethylquinoline 1-oxide was mixed with 30 cc. Ac₂O and warmed for 2 hrs. on a water bath. The excess of Ac₂O was distilled off in vacuum and the residue was distilled under a diminished pressure, affording an oil, b.p. 110~145°. The oil was refluxed with 15 cc. of 10% HCl for 30 mins. After cooling, it was neutralized with 10% NaOH solution and extracted with ether. The ether solution was dried over anhyd. Na₂SO₄, and the ether was distilled off. The residue weighed 3.5 g. This oily residue crystallized slowly and was recrystallized from benzene to white prisms, m.p. 74~75°. *Anal.* Calcd. for C₁₀H₈ON.2(Hydroxymethylmepidine): C, 76.32; H, 6.40; N, 8.09. Found: C, 76.08; H, 6.13; N, 8.19. Picrate: Yellow needles, m.p. 161~163° (from MeOH). *Anal.* Calcd. for C₁₀H₈ON.C₂H₅O₂N₃: C, 50.75; H, 3.50; N, 13.93. Found: C, 50.56; H, 3.36; N, 13.89.

Into the NaOH solution left after extraction with ether, NH₄Cl was added, the precipitate of phenolic base formed was collected, and recrystallized from a mixture of MeOH and AcOEt to white columnar crystals, m.p. 200~202°. Yield, 0.25 g. *Anal.* Calcd. for C₁₀H₈ON (3-Hydroxymethylmepidine): C, 76.32; H, 6.40; N, 8.09. Found: C, 76.21; H, 6.27; N, 8.14.

**Reaction of 2-Hydroxymethylmepidine and Benzoic Anhydride**—A mixture of 0.2 g. of 2-hydroxymethylmepidine and 1.0 g. of BenzO was warmed for 30 mins. on a boiling water bath. After cooling, 10% HCl was added to the reaction mixture and the separated benzoic acid was filtered.
HCl solution was neutralized with NaOH, the base that precipitated was collected, and recrystallized from a mixture of benzene and petroleum ether to white columnar crystals, m.p. 80~82°. Anal. Calcd. for C₁₉H₁₈O₂N: C, 77.96; H, 5.45. Found: C, 77.67; H, 5.26.

Oxidation of 2-Hydroxymethyllepidine with KMnO₄—A solution of 0.5 g. of 2-hydroxymethyllepidine in 30 cc. acetone was oxidized with 0.3 g. KMnO₄ in the usual manner. The precipitated MnO₂ was filtered, MnO₂ was extracted several times with hot water, and the aqueous filtrate was evaporated in vacuum. The residue was dissolved in a small amount of water, weakly acidified with AcOH, and then precipitated with Pb(AcO)₂. The lead salt was suspended in hot water and decomposed with H₂S. The acidic substance obtained was recrystallized from MeOH, m.p. 152~153°, which agreed with reported m.p. of 4-methylquinoline-2-carboxylic acid.

Summary

2,4-Lutidine 1-oxide was converted to 2-hydroxymethyl-4-methylpyridine and 2-methyl-4-hydroxymethylpyridine by reaction with acetic anhydride, and its formation ratio was about 5:1. Besides these, 3-hydroxy-2,4-lutidine was obtained as a phenolic base. In the case of the reaction of 2,4-dimethylquinoline 1-oxide with acetic anhydride, 2-hydroxymethyllepidine and a small amount of 3-hydroxy-2,4-dimethylquinoline were obtained but not 4-hydroxymethylquinoline.

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