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 $C_{10}H_7O_5N_4Br$: N, 16.36. Found : N, 16.05.

Summary

β-(5-Nitro-2-furyl)-α-methylacrolein and β-(5-nitro-2-furyl)-α-ethylacrolein were prepared by the condensation of 2-(5-nitro)furfural with propionaldehyde and butyraldehyde, respectively, in the presence of piperidinium acetate as a catalyst. Preparation of β-(5-nitro-2-furyl)-α-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, β-(5-nitro-2-furyl)-α-methylacrolein semicarbazone, β-(5-nitro-2-furyl)-α-methylacrolein oxime, and 1-[β-(5-nitro-2-furyl)-α-bromoacrylidene]-2-isonicotinylhydrazine 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.

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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) $b.p_4$ 100~107°, (II) $b.p_4$ 131~140°, and (III) $b.p_4$ 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-hydroxymethylpyridine and (II) is 2-methyl-4-hydroxymethylpyridine. (III) colored red with

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1) V. Boekelheide, W. J. Linn : J. Am. Chem. Soc., **76**, 1286(1954).
2) G. Kobayashi, S. Furukawa : This Bulletin, **1**, 347(1953).
3) G. Kobayashi *et al.* : J. Pharm. Soc. Japan, **74**, 791(1954).

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 (C_7H_9ON), agreed with that of hydroxy-2,4-lutidine. Since it colored deep blue by Denis-Folin's reagent,[4] 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[5] 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.

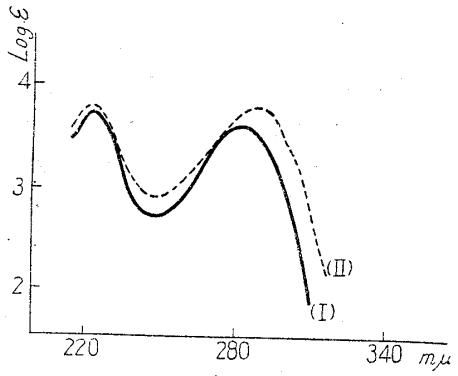

Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

(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-hydroxymethylpyridine 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.

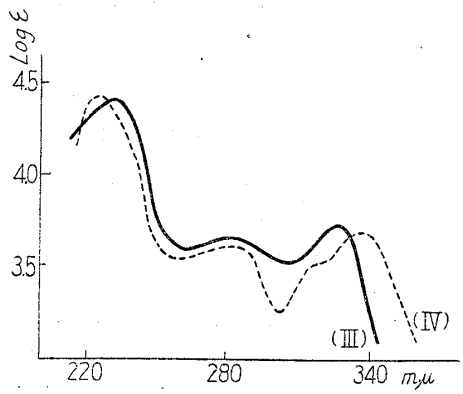

Fig. 2. Ultraviolet Absorption Spectra (in EtOH)

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

(IV) 3-Hydroxylepidine

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

4) O. Folin, W. Denis : J. Biol. Chem., **12**, 239(1912).
5) H. D. Gibbs : *Ibid.*, **72**, 653(1927).

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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 Ac_2O 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 Ac_2O was distilled off under a diminished pressure, the residue was distilled in vacuum. The distillate of $b.p_4$ 100~135° 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 K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ residue was distilled in vacuum and the distillate of $b.p_4$ 100~156° weighed 33 g. These bases were separated into three fractions by repeated fractional distillation. (I) $b.p_4$ 100~107°; yield, 15 g. (II) $b.p_4$ 131~140°; yield, 3 g. $b.p_4$ 104~150°; yield, 1 g.

Picrate of (I); yellow needles, m.p. 156~158°(from MeOH). *Anal.* Calcd. for $C_7H_9ON.C_6H_3O_7N_3$ (2-Hydroxymethyl-4-methylpyridine picrate) : C, 44.33; H, 3.43; N, 15.75. Found : C, 44.63; H, 3.78; N, 16.00.

Picrate of (II); yellow needles, m.p. 155~157°(from benzene-MeOH). *Anal.* Calcd. for $C_7H_9ON.C_6H_3O_7N_3$(2-Methyl-4-hydroxymethylpyridine picrate) : C, 44.33; H, 3.43; N, 15.75. Found : C, 44.39; H, 3.59; N, 16.09.

Picrate of (III); orange yellow columnar crystals, m.p. 242~243°(from MeOH). *Anal.* Calcd. for $C_7H_9ON.C_6H_3O_7N_3$(3-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 PCl_3—1) Into a solution of 0.2 g. of (I) in 5 cc. dry benzene 0.3 cc. PCl_3 was added, the mixture was warmed for 5 mins. on a water bath. After cooling, it was poured into ice water, neutralized with aq. NH_3, 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 $C_7H_3NCl.C_6H_3O_7N_3$(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 irritant oil was obtained. The picrate formed yellow needles, m.p. 146~148° (from MeOH). *Anal.* Calcd. for $C_7H_3NCl.C_6H_3O_7N_3$(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 C_7H_9ON : C, 68.29; H, 7.36; 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 17 cc. 30% H_2O_2 was warmed for 8 hrs. on a water bath at 75~85°. AcOH was distilled off in vacuum, the residue was neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ residue was recrystallized from benzene to white prisms, m.p. 117~119°, yield, 3 g. *Anal.* Calcd. for $C_{11}H_{11}ON$: 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 $C_{11}H_{11}ON.C_6H_3O_7N_3$: 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. Ac_2O and warmed for 2 hrs. on a water bath. The excess of Ac_2O was distilled off in vacuum and the residue was distilled under a diminished pressure, affording an oil, $b.p_2$ 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. Na_2SO_4, 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 $C_{11}H_{11}ON$(2-Hydroxymethyllepidine) : 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 $C_{11}H_{11}ON.C_6H_3O_7N_3$: 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, NH_4Cl 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 $C_{11}H_{11}ON$ (3-Hydroxy-2,4-dimethylquinoline) : C, 76.32; H, 6.40; N, 8.09. Found : C, 76.21; H, 6.27; N, 8.14.

Reaction of 2-Hydroxymethyllepidine and Benzoic Anhydride—A mixture of 0.2 g. of 2-hydroxymethyllepidine and 1.0 g. of Bz_2O 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 $C_{18}H_{15}O_2N$: C, 77.96; H, 5.45. Found : C, 77.67; H, 5.26.

Oxidation of 2-Hydroxymethyllepidine with $KMnO_4$—A solution of 0.5 g. of 2-hydroxymethyllepidine in 30 cc. acetone was oxidized with 0.3 g. $KMnO_4$ in the usual manner. The precipitated MnO_2 was filtered, MnO_2 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 suspensed in hot water and decomposed with H_2S. The acidic substance obtained was recrystallized from MeOH, m.p. 152~153°, which agreed with reported m.p.[6] 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 ahydride, 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-hydroxymethylquinaldine.

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6) W. Konig : Ber., **37**, 1327 (1904).