36. **Shigehiko Sugasawa and Makoto Kirisawa** : Oxidation of 3-Substituted 1-Alkylpyridinium Salt. III.1) Preparation of 1-Methyl-3-ethyl-6-pyridone and -piperidone.

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3-Ethylpyridine (II), which can be prepared from 3-acetylpyridine (I) by Huang-Minlon method, readily forms 1-alkyl (methyl used throughout this work)-pyridinium salt (III), which, when oxidized with alkaline potassium ferricyanide, gives 1-methyl-3-ethyl-2-pyridone (IV) as the only isolable product.2) Thus it appears impossible to prepare 1-methyl-3-ethyl-6-pyridone (X), which we need as the starting material for other synthetical work, by this oxidation method.

From the results1) hitherto obtained in our laboratories, it was shown that any cyclic substituent group in the 3-position of 1-alkylpyridinium salt directs the oxidation to occur at 6-position to give 3-substituted 1-alkyl-6-pyridone as the sole product. If so, the compound (VIa), which can be readily obtained from 3-acetylpyridine3) and ethyleneglycol by the usual procedure followed by quaternization, conforms to this requirement and, in case it would undergo smooth oxidation by means of alkaline ferricyanide, there should be produced 1-alkyl-3-(α-ethylenedioxyethyl)-6-pyridone (VIIa).

As was expected, the oxidation product, which was obtained in excellent yield, was proved to be 1-methyl-3-(α-ethylenedioxyethyl)-6-pyridone (VIIa),4) because the latter was converted into 1-methyl-3-carboxy-6-pyridone (IX) through hydrolysis (giving VIII) followed by haloform reaction. The compound (IX) was identified with an authentic sample.

Huang-Minlon reduction of (VIII) furnished 1-methyl-3-ethyl-6-pyridone (X), which gave the corresponding piperidone (XI) on being reduced with Raney nickel. On the other hand di(ethylthio) derivative (XII) of (VIII) was prepared and this was treated with Raney nickel according to Wolfrom *et al.*5) As a desulfurization product there was obtained a mixture of 1-methyl-3-ethyl-6-pyridone (X) and piperidone (XI), of which the latter formed the main product. The former gave the same picrate with the Huang-Minlon reduction product (X) of (VIII), thus the evidence for its constitution was provided. The identification of the latter will be discussed later.

Quaternization of 3-(α-ethylenedithioethyl)pyridine (Vb) proceeded smoothly, giving (VIb). On being oxidized, the latter yielded the pyridone (VIIb) as the only isolable product.6) This on being treated with Raney nickel gave mainly the piperidone (XI). So this is the simpler method of preparing (XI).

The compound (XI) forms a viscous oil, none of whose derivatives was obtained crystalline and its constitution was proved in the following manner. This compound was boiled with hydrochloric acid to cleave the lactam ring, giving an amino acid hydrochloride, which furnished a crystalline solid of m.p. 103~106° on being tosylated.

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1) Part II : This Bulletin, **3**, 187 (1955).

2) S. Sugasawa, Y. Ban : J. Pharm. Soc. Japan, **72**, 1336(1952).

3) Direct oxidation of 1-methy-3-acetylpyridinium salt with alkaline ferricyanide under a variety of conditions gave dark colored product, from which nothing definite was isolated.

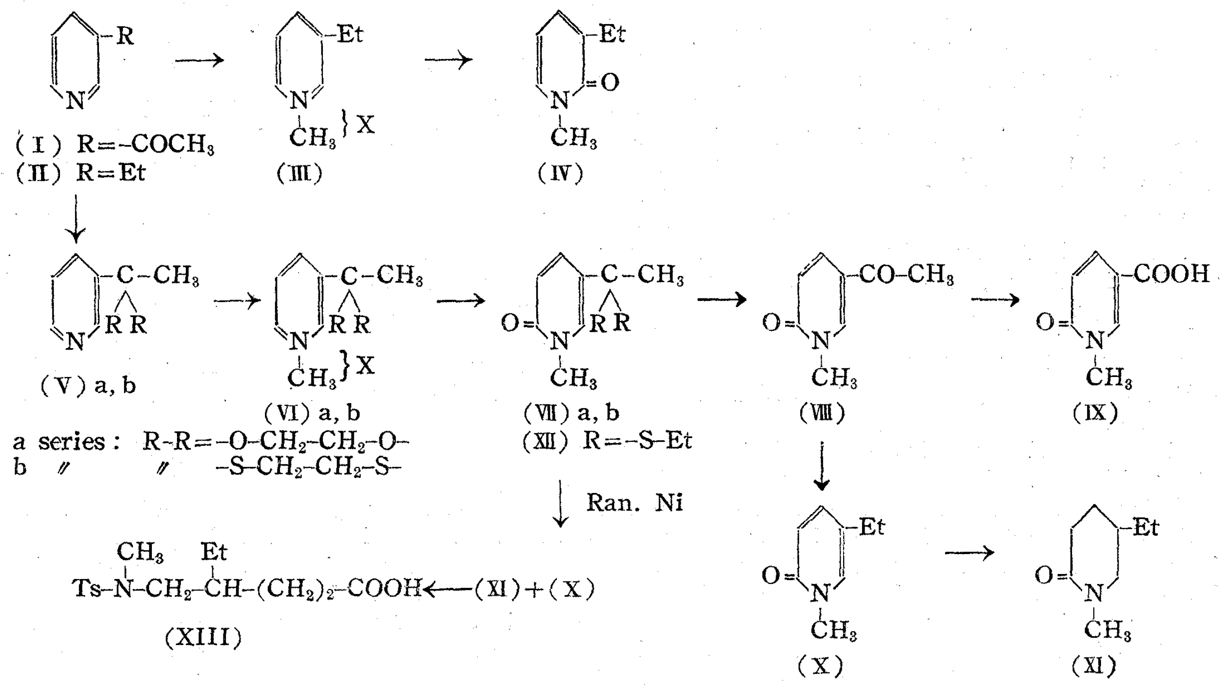
4) The oxidation of diethyl acetal corresponding to VI (R=OEt) also gave 6-pyridone, but in a somewhat inferior yield than (VI a)(by Mr. S. Ushioda).

5) Wolfrom, Karabinos : J. Am. Chem. Soc., **66**. 909(1944).

6) That alkaline ferricyanide does not oxidize the mercapto group was shown by an experiment, in which acetophenone ethylenethioketal was used as a model substance. This was recovered quantitatively after being treated with alkaline ferricyanide.

On the other hand, the authentic 1-methyl-3-ethyl-6-piperidone (XI), prepared from (X) by reduction, was hydrolyzed and the product was tosylated, giving the crystalline solid of m.p. 103~106° (XIII), which was proved to be identical with the one obtained above by direct comparison.

The scope of this reaction for the preparation of other 3-alkyl-6-pyridones will be investigated.



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Experimental

3-(α-Ethylenedioxyethyl)pyridine (Va)—3-Acetylpyridine (I: 4 g., 0.033 mole) in benzene (20 cc.) was added with ethyleneglycol (2.7 g., 0.044 mole) and *p*-toluenesulfonic acid (6.4 g., 0.037 mole) and the mixture was refluxed for 5 hrs. in an apparatus which removes water as it is formed. On cooling, the reaction mixture was poured into an excess of conc. K_2CO_3 soln., and the aq. layer was extracted with benzene, which was combined with the original benzene solution, washed, dried, and evaporated. The residue was distilled *in vacuo*, giving a viscous oily fraction of b.p$_6$ 101~103°, yield 5 g. or 92%. Characterized as yellow needle-shaped picrate of m.p. 140~141° from EtOH. *Anal.* Calcd. for $C_{15}H_{14}O_9N_4$: C, 45.7; H, 3.6; N, 14.2. Found: C, 45.5; H, 3.4; N, 13.8.

1-Methyl-3-(α-ethylenedioxyethyl)-6-pyridone (VIIa)—The foregoing compound (18.2 g., 0.11 mole) was added dropwise with freshly purified Me_2SO_4 (15.5 g., 0.12 mole), gradually separating a white crystalline solid with evolution of heat. The mixture was heated 1 hr. on a steam bath to complete the quaternization. The product (VIa), a white hygroscopic solid, in H_2O (100 cc.) was oxidized by adding dropwise an aq. solution of $K_3Fe(CN)_6$ (90 g., 0.27 mole) in H_2O (300 cc.) with stirring and ice-cooling. To this mixture was now added KOH pellets (50 g., 0.89 mole) during 20 mins., keeping the temp. at 5~10°. Benzene (100 cc.) was then introduced and the mixture was stirred for 1.5 hrs. The additional portions of oxidizing agents ($K_3Fe(CN)_6$ 45 g., 0.14 mole in 150 cc. of H_2O and KOH-pellets 30 g., 0.54 mole) were then added in a manner described above, but this time at a room temp., and the whole was left standing overnight. Filtered from the solid, the aq. filtrate was extracted with benzene, which was combined with the original benzene layer, dried, and evaporated, leaving a solid residue, m.p. 85~89°; yield, 18.6 g. or 86%. This was purified from hexane, forming colorless plates of m.p. 89~91°, soluble in H_2O and benzene, but sparingly so in ether and hexane. *Anal.* Calcd. for $C_{10}H_{13}O_3N$: C, 61.5; H, 6.7; N, 7.2. Found: C, 61.8; H, 6.4; N, 7.2.

Picrate: Yellow needles, m.p. 121~123°(from EtOH).

1-Methyl-3-acetyl-6-pyridone (VIII)—The foregoing compound (1.65 g., 0.0085 mole) was mixed with aq. HCl (10 cc. of 3.3%) and the mixture was heated on a steam bath for 1 hr. On cooling, the mixture was basified with KOH, separating needle-shaped crystals, which were taken up in BuOH, washed with sat. NaCl soln., dried, and evaporated, furnishing colorless needles of m.p. 145∼147°; yield, 1.17 g. Purified from benzene, it formed colorless needles of m.p. 146∼147°, which is soluble in H_2O, EtOH, but sparingly so in ether and benzene. *Anal.* Calcd. for $C_8H_9O_2N$: C, 63.6; H, 6.0; N, 9.3. Found : C, 63.8; H, 6.3; N, 9.2.

Phenylhydrazone : Faint yellow needles from aq. EtOH, m.p. 226∼228°(decomp.). *Anal.* Calcd. for $C_{14}H_{15}ON_3$: C, 69.7; H, 6.3; N, 17.4. Found : C, 70.2; H, 5.95; N, 17.85.

Semicarbazone : Colorless minute crystals from EtOH, m.p. 238∼239°(decomp.). *Anal.* Calcd. for $C_9H_{12}O_2N_4$: N, 26.9. Found : N, 27.1.

1-Methyl-3-carboxy-6-pyridone (IX)—The above-mentioned ketone was oxidized by means of alkaline NaBrO soln. as usual. The acid, obtained in 70% yield, was purified from hot water, forming colorless needles of m.p. 236∼238°, which was not depressed on admixture with an authentic 1-methyl-3-carboxy-6-pyridone of m.p. 236∼238°.

3-(α-Ethylenedithioethyl)pyridine (Vb) : 3-Acetylpyridine (3.9 g., 0.032 mole), ethanedithiol (3 g., 0.032 mole), and freshly fused $ZnCl_2$ (1.5 g.) were mixed and a stream of dry HCl-gas was passed through this mixture, first with cooling and then at room temp., giving a viscous syrupy mixture, in which $ZnCl_2$ remained undissolved on the bottom. After being left standing for a few days, the whole was poured into aq. KOH soln., containing crushed ice, and the product was extracted with $CHCl_3$. The $CHCl_3$ solution was washed, dried, and evaporated, leaving an oily residue, which distilled at 134∼135°/2 mm.; yield, 5.7 g. or 90% of an oil of disagreeable odor. Characterized as the picrate.

Picrate : Yellow needles of m.p. 146∼148° from EtOH. *Anal.* Calcd. for $C_{15}H_{14}O_7N_4S_2$: C, 42.25; H, 3.3; N, 13.1. Found : C, 42.6; H, 3.6; N, 13.5.

1-Methyl-3-(α-ethylenedithioethyl)-6-pyridone (VII b)—The foregoing compound (Vb : 3 g., 0.015 mole) was mixed with freshly purified Me_2SO_4 (2.1 g., 0.017 mole) with cooling and then the mixture was heated on a steam bath for 1 hr. to complete the quaternization, a white crystalline solid being obtained. The latter was dissolved in H_2O (15 cc.), which solution was once shaken with benzene, and the aq. layer was submitted to the oxidation in a similar manner described above; 20.5 g. of $K_3Fe(CN)_6$ (0.062 mole) and 12 g. of KOH pellets being used altogether. The oxidation product was obtained as a yellow viscous syrup, which solidified on standing (m.p. 69∼79°; yield, 3.1 g. or 89%). Purified from ligroine or hexane, forming colorless pillars of m.p. 80∼83°, which is soluble in benzene, EtOH, and ether. The picrate was prepared in ethereal solution and purified from EtOH, separating as yellow needles of m.p. 141∼143°. *Anal.* Calcd. for $C_{16}H_{16}O_8N_4S_2$: C, 42.1; H, 3.5; N, 12.3. Found : C, 42.1; H, 3.85; N, 12.6.

1-Methyl-3-ethyl-6-pyridone (X)—The compound (VIII : 1.5 g., 0.01 mole), $NH_2NH_2{\cdot}H_2O$ (1.2 g. of 85%, 0.02 mole), KOH (1.2 g., 0.02 mole), and 5 cc. of $(CH_2OH)_2$ were mixed together and the whole was heated at 115∼120° (bath temp.) for 2 hrs., with stirring; now the condenser was adjusted for distillation and the temp. was raised to 180° in 0.5 hr. and kept there for additional 2 hrs., the mixture being stirred all the time. The reaction product was diluted with H_2O and salted out by adding enough K_2CO_3 to allow an oily layer to separate. This oil was collected in benzene, dried, and evaporated, leaving an oily residue, which distilled at 120∼123° (6 mm); yield, 0.8 g. or 60%. Characterized as the picrate.

Picrate : Yellow minute crystals from MeOH, m.p. 121∼123°. *Anal.* Calcd. for $C_{14}H_{14}O_8N_4$: C, 45.9; H, 3.85; N, 15.3. Found : C, 45.5; H, 4.1; N, 15.2.

1-Methyl-3-ethyl-6-piperidone (XI)—i) The foregoing pyridone (X : 0.45 g., 0.0033 mole of the crude substance) in EtOH was reduced catalytically over Raney Ni (ca. 2 g.). Another 2-g. portion of the fresh catalyst was added during hydrogenation and thus 165 cc. of H_2 (corresponding roughly to 110% of the theoretical) was absorbed in 4 hrs. The reduction product was worked up as usual and the crude gelatine-like substance was dissolved in 10% aq. HCl, some insoluble material was removed by shaking with benzene, the aq. layer was basified, and the oil that separated was taken up in benzene, dried, and evaporated. The residue distilled at 90°/2 mm.; yield, 0.23 g. or 50%.

ii) To a mixture of anhyd. Na_2SO_4 (1 g.), freshly fused $ZnCl_2$ powder (1.5 g) and EtSH (4 cc., a large excess), 1-methyl-3-acetyl-6-pyridone (VIII : 1.5 g., 0.01 mole) was added with cooling and the latter gradually dissolved. The mixture was left standing at a room temp. for a few days and then extracted with $CHCl_3$, which solution was washed thoroughly with dil. NaOH soln., washed with H_2O, dried, and evaporated. The oily residue (crude XII) in 130 cc. of 70% EtOH was refluxed with Raney Ni (prepared from 40 g. Ni alloy according to Org. syntheses, **21**, 15, but heated 1 hr. only at the bath temperature of 50°.) for 3 hrs. The filtered Ni catalyst was repeatedly extracted with boiling EtOH and the combined EtOH soln. was concentrated to a small volume and diluted with water. The resultant aq. soln. was then salted out with K_2CO_3, the oily layer that separated was collected in $CHCl_3$, and worked up as usual. There was obtained a colorless oil of $b.p_7$ 110∼117° in

0.82 g. yield, which was separated into two components by treating with picric acid in ethereal soln. A crystalline picrate was obtained in 32% yleld, which, after being purified from EtOH, formed yellow needles of m.p. 121~123°, identical with the picrate of authentic 1-methyl-3-ethyl-6-pyridone (X) obtained above.

The remaining main portion, which did not form a picrate, was recovered and this was found to be the corresponding piperidone (XI).

iii) 1-Methyl-3-(α-ethylenedithioethyl)-6-pyridone (VII b) mentioned above was subjected to desulfurization reaction in a similar fashion and there was obtained a colorless oil of b.p$_2$ 96~97° (yield 84%), consisting predominantly, if not entirely, of the piperidone (XI), because no crystalline picrate was obtained from this oil.

δ-(N-Methyl-toluenesulfonamido)-γ-ethylvaleric acid (XIII)—The compound (XI: 0.23 g, 0.0016 mole) prepared from the authentic pyridone, which was obtained by the Huang-Minlon reduction of (VIII), was dissolved in 10 cc conc. HCl and refluxed for 20 hrs. The resultant soln. was diluted with H_2O, boiled with charcoal, and the filtrate was evaporated *in vacuo*, giving a hygroscopic white crystalline solid in a quantitative yield (0.32 g). Since the purification of this hydrochloride appeared dfficult owing to its deliquescent nature, it was tosylated as usual, furnishing a colorless crystalline solid of m.p. 90~100°, which was repeatedly purified from benzene-ligroine, forming colorless minute pillars of m.p. 103~106°. *Anal.* Calcd. for $C_{15}H_{23}O_4NS$: C, 57.5; H, 7.4; N, 4.5. Found: C, 58.00; H, 7.1; N, 4.9.

The oil of b.p$_2$ 96~97° obtained above under (iii) was treated in the same manner, yielding a compound of m.p. 103~106°, which was identified with the foregoing compound with the same m.p. by direct comparison.

Summary

1-Methyl-3-acetyl-6-pyridone (VIII) was prepared. Though quaternary metho-salt of 3-acetylpyridine did not undergo smooth oxidation with alkaline ferricyanide, the corresponding ethylene-ketal (VIa) was oxidized smoothly, giving 1-methyl-3-acetyl-6-pyridone ethylene-ketal (VIIa) in ca. 85% yield. The latter was hydrolyzed in dilute acid to give 3-acetyl compound (VIII) in quantitative yield. Huang-Minlon reduction converted the latter into 1-methyl-3-ethyl-6-pyridone (X) in a fair yield, from which the corresponding piperidone (XI) was obtained by catalytic hydrogenation over Raney nickel. Wolfrom and Karabinos method applied to di(ethylthio) compound (XII) of (VIII) gave a mixture of (X) and (XI), of which the latter was formed predominantly. For the direct synthesis of (XI), oxidation of ethylenedithio compound of 1-methyl-3-acetyl-pyridi nium salt (VIb) was preferred to furnish the corresponding 6-pyridone (VIIb), which was directly desulfurized according to the method of Wolfrom and Karabinos to yield (XI).

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