UDC 547.834.07

64. Torizo Takahashi and Akira Koshiro : Syntheses of Heterocyclic Compounds of Nitrogen. CXXVI. Syntheses of Oxazolopyridines and Related Compounds. (7).[1]

(*Faculty of Pharmacy, Kyoto University*[*1])

As a part of studies on the syntheses of oxazolopyridines, attempt was made to prepare 7-substituted oxazolo[4,5-*c*]pyridines using 3-amino-4-hydroxy-5-nitropyridine (II) and 3,5-diamino-4-hydroxypyridine as the starting materials.

Partial reduction of 3,5-dinitro-4-hydroxypyridine (I) was reported by Crowe,[2] but his description was a little indefinite. The hydrochloride of (II) was obtained in 65% yield by treatment of (I) with freshly prepared ammonium sulfide followed by extraction with hydrochloric acid. The hydrochloride of (II) immediately formed the free base by action of water or alcohol at room temperature and this free base could not be recrystallized from ordinary solvents because of its insolubility.

By heating (II) with acetic anhydride, 3-acetamido-4-hydroxy-5-nitropyridine (III) and 2-methyl-7-nitroxazolo[4,5-*c*]pyridine (IV) were obtained in 20.0% and 50.8% yield, respectively. Similar treatment of (II) with benzoic anhydride only gave 2-phenyl-7-nitroxazolo-[4,5-*c*]pyridine (V). Attempt to obtain 7-nitroxazolo[4,5-*c*]pyridine (VII) by heating 3-formamido-4-hydroxy-5-nitropyridine (VI), derived from (II) with formic acid, with acetic anhydride ended fruitless and the product was confirmed as (IV).

Catalytic reduction of (I) in methanol over palladium-carbon afforded 3,5-diamino-4-hydroxypyridine (VIII). On heating (VIII) with acetic anhydride, the corresponding diacetate

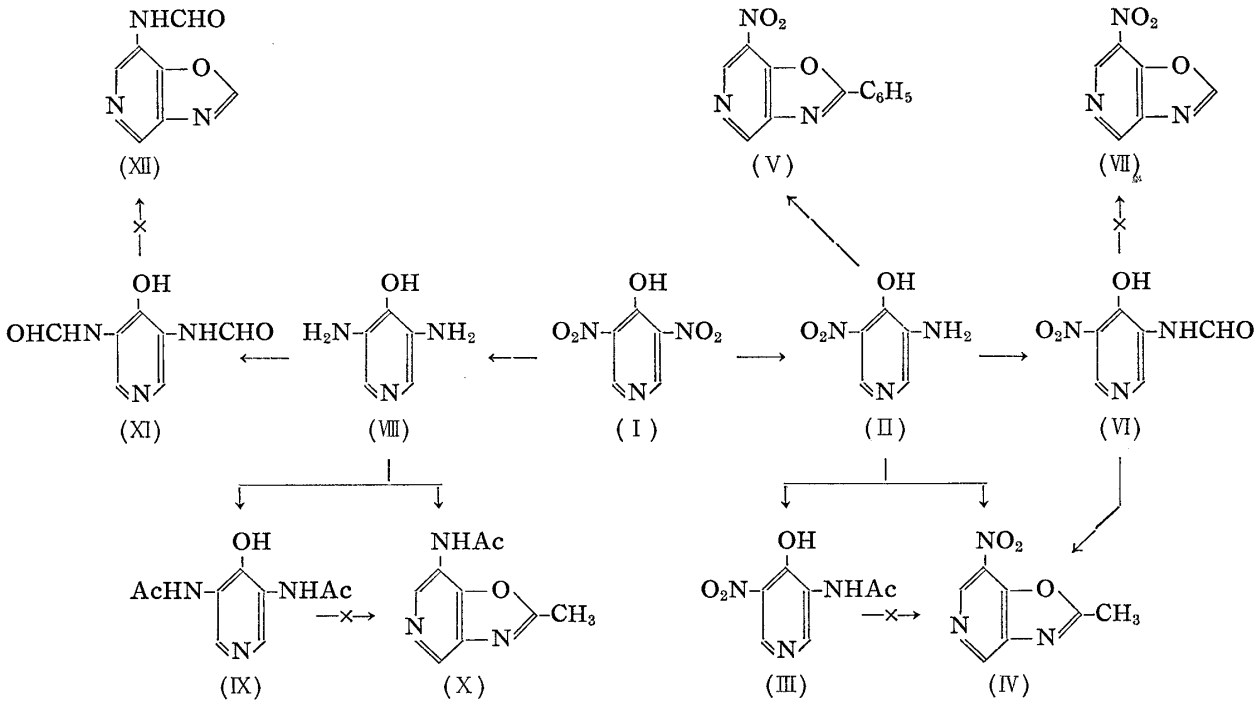

Chart 1.

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1) Paper presented at the Kinki Local Meeting of the Pharmaceutical Society of Japan, Osaka, October, 1959. Part CXXV : Yakugaku Zasshi, **80**, 895 (1960).

2) W. H. Crowe : J. Chem. Soc., **127**, 2028 (1925).

(IX) and oxazolopyridine (X) were obtained. Similar treatment of (VIII) with formic acid afforded 3,5-diformamido-4-hydroxypyridine (XI). Ring closure of (III), (IX), and (XI) by distillation was all unsuccessful owing to decomposition.

Treatment of (II) and (VIII) with ethyl chloroformate in alkaline medium afforded the corresponding urethans (XIII, XIV). However, N-ethoxycarbonyl compounds, as reported in part (3) of this series,[3] were not formed. (XIII) resolidified after it melted at 165° and melted again at 295°. On the other hand, when (XIII) was allowed to stand in ethanol for a long time, the resulting material melted at 295°, undepressed on admixture with (II). From these facts it was considered that (XIII) converted into (II) by the loss of carbon dioxide. All attempts to prepare the oxazolopyridinones (XV~XVIII) by treatment of (XIII) or (XIV) with carbonyl chloride or by distillation were unsuccessful.

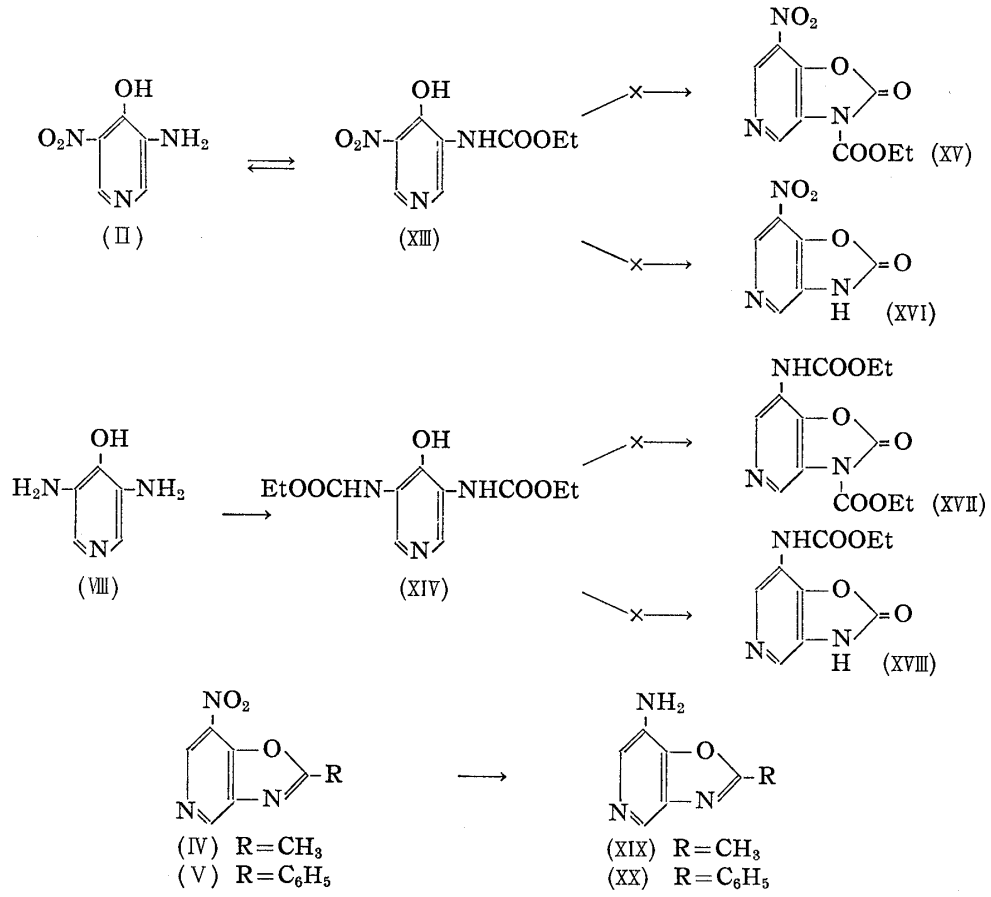

Chart 2.

The stability of oxazolopyridine system in acid or alkaline medium was reported in previous papers[4~6] and it is clear that oxazole ring is easily cleaved, especially in acid medium. To examine the stability of this ring system to catalytic reduction, hydrogenation of (IV) and (V) was carried out using palladium-carbon or Raney nickel under ordinary pressure and temperature, and judging from the volume of hydrogen absorbed and analytical values of the product, only the nitro groups were reduced to the corresponding amines (XIX and XX) and the oxazole ring was not cleaved.

Treatment of (IV) with an excess of methyl iodide afforded the corresponding mono-

3) T. Takahashi, A. Koshiro : Yakugaku Zasshi, **79**, 1123 (1959).
4) *Idem* : *Ibid.*, **76**, 1388 (1956).
5) *Idem* : This Bulletin, **7**, 720 (1959).
6) A. Koshiro : *Ibid.*, **7**, 725 (1959).

methiodide (XXII or XXII′). In spite of the presence of two basic nitrogen atoms, the product was a monomethiodide and it was questionable whether methyl iodide combined with nitrogen atom in the pyridine ring or that in the oxazole ring of oxazolopyridine system. In analogy with thiazolopyridine monomethiodides, it was previously reported that methyl iodide would combine with nitrogen atom of the oxazole ring in 2-alkyl-7-bromoxazolo-[4,5-*c*]pyridines.[7] In order to decide the correct structure, the following procedure was carried out.

2-Methyl-7-nitroxazolo[4,5-*c*]pyridine monomethiodide (XXII or XXII′) was very unstable and turned black rapidly in the air or by warming with hydrous methanol for a few minutes, forming a hydrolyzed product which had no iodine atom. Judging from its analytical values and analogous hydrolysis of benzoxazole methiodide[8] in aqueous solution, the product formed as above was considered to be 1-methyl-3-acetamido-5-nitro-4-pyridone (XXV) or 3-(N-acetyl-N-methylamino)-4-hydroxy-5-nitropyridine (XXV′). Its infrared absorption spectrum (in Nujol) showed N-H stretching vibration of an open-chain secondary amide at 3340 cm^{-1} and amide-II band of -NHCO- near 1520 cm^{-1}. This suggested the product to be (XXV) and to confirm this presumption, (XXV) was hydrolyzed to the corresponding amine (XXIX or XXIX′) by heating with hydrochloric acid. As the diazo reaction for aromatic primary amines of the amine obtained above was positive, it was clear that this amine was 1-methyl-3-amino-5-nitro-4-pyridone (XXIX). Accordingly, it was proved

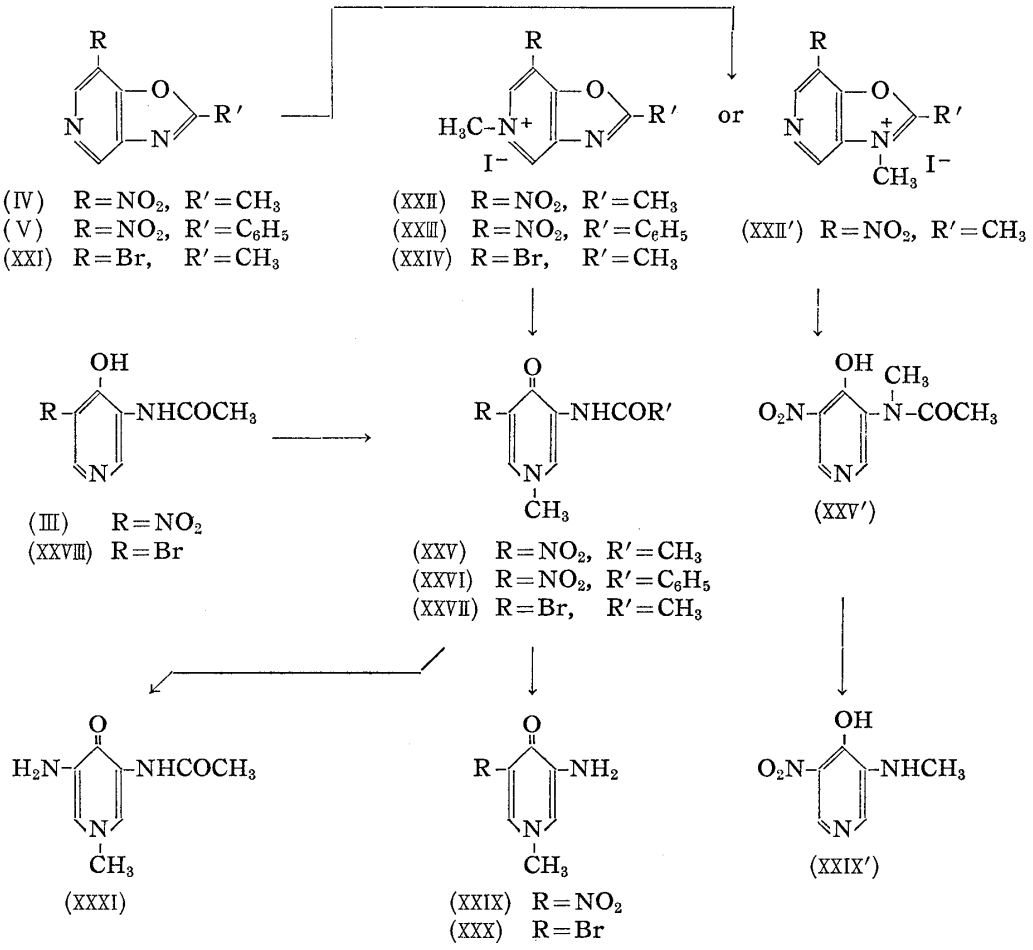

Chart 3.

7) T. Takahashi, A. Koshiro : Yakugaku Zasshi, **79**, 292 (1959).
8) L. M. Clark : J. Chem. Soc., **1926**, 282.

that methyl iodide had combined with the nitrogen atom in pyridine ring of the oxazolopyridine system. In analogy with the above result, 2-phenyl-7-nitroxazolo[4,5-*c*]pyridine monomethiodide must have the structure of (XXIII) which would be more stable than (XXII) and when allowed to stand in the air for a long time, no change could be recognized, but (XXIII) was easily hydrolyzed to 1-methyl-3-benzamido-5-nitro-4-pyridone (XXVI) in the same manner as (XXII).

Similarly, the structure of 2-methyl-7-bromoxazolo[4,5-*c*]pyridine monomethiodide was determined as (XXIV) by the same procedure as for (XXII). The structure of 2-alkyl-7-bromoxazolo[4,5-*c*]pyridine monomethiodides, which were reported in part (2)[7] of this series, is corrected as above.

(XXV) or (XXVII) was derived from 3-acetamido-4-hydroxy-5-nitropyridine (III) or 3-acetamido-4-hydroxy-5-bromopyridine (XXVIII) in a good yield by heating with methyl iodide in methanolic potassium hydroxide solution and (XXV) afforded 1-methyl-3-acetamido-5-amino-4-pyridone (XXXI) by catalytic reduction over palladium-carbon.

Similar procedure as above was carried out and it was also determined that 2-methyloxazolo[5,4-*b*]pyridine monomethiodide, reported in part (6)[6] of this series, had the structure of (XXXVI) as shown in Chart 4.

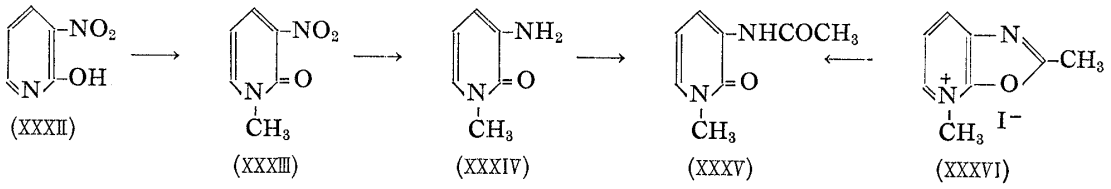

Chart 4.

Concerning the methylation of 2-hydroxy-3-nitropyridine (XXXII), several investigations[9,10] had been made and 1-methyl-3-nitro-2-pyridone (XXXIII) was prepared in 74% yield by heating the potassium salt of (XXXII) with methyl iodide in hydrous ethanol.

Ahmad and Hey[10] reported that (XXXIII) was reduced quantitatively to 1-methyl-3-amino-2-pyridone (XXXIV) by the action of ferric sulfate and ammonium hydroxide, and iron in sodium chloride solution was used as a reducing agent which was often effective in this series of experiments. However, in the present case, the yield of (XXXIV) was disappointing. Thus, (XXXIV) obtained was easily acetylated to 1-methyl-3-acetamido-2-pyridone (XXXV) by application of acetic anhydride.

On the other hand, the monomethiodide (XXXVI) was rapidly hydrolyzed to acylamido compound on leaving in potassium hydroxide solution at room temperature. The hydrolyzed product here obtained was confirmed as (XXXV) by mixed fusion with an authentic specimen prepared as above.

Experimental[*2]

3-Amino-4-hydroxy-5-nitropyridine (II) Hydrochloride——A mixture of 10 g. of 3,5-dinitro-4-pyridone (I) and 160 cc. of freshly prepared $(NH_4)_2S$ in 200 cc. of EtOH was boiled under reflux for 2.5 hr. The resulting mixture was evaporated to dryness *in vacuo* and the residue was extracted with 300 cc. of hot HCl. Separated S was filtered off and the filtrate was concentrated to about 100 cc. *in vacuo*. When cooled, separated crystals were recrystallized from HCl to colorless needles, m.p. 270° (decomp.). Yield, 6.5 g. *Anal.* Calcd. for $C_5H_5O_3N_3 \cdot HCl$: C, 31.33; H, 3.13. Found : C, 31.64; H, 3.40. The free base melted at 295°.

*2 All melting points are uncorrected.

9) W. Gruber : Can. J. Chem., **31**, 1181 (1953) (C. A., **49**, 314 (1955)).

10) Y. Ahmad, D. H. Hey : J. Chem. Soc., **1954**, 4516.

3-Acetamido-4-hydroxy-5-nitropyridine (III) and 2-Methyl-7-nitroxazolo[4,5-*c*]pyridine (IV)——A mixture of hydrochloride of (II) (1 g.) and Ac_2O (10 cc.) was refluxed for 4 hr., excess of the reagent was distilled off *in vacuo*, and the residue was extracted with Et_2O. Unextracted (III) was collected and recrystallized from MeOH to colorless needles, m.p. 239~240°. Yield, 0.2 g. *Anal.* Calcd. for $C_7H_7O_4N_3$: C, 45.19; H, 3.79. Found : C, 44.81; H, 3.58.

The above Et_2O extract was concentrated, cooled, and the separated product was recrystallized from Et_2O to colorless needles, m.p. 83°/95°. Yield, 0.5 g. *Anal.* Calcd. for $C_7H_5O_3N_3$: C, 46.93; H, 2.81. Found : C, 47.16; H, 2.81.

2-Phenyl-7-nitroxazolo[4,5-*c*]pyridine (V)——A mixture of (II) (1.2 g.) and Bz_2O (5.5 g.) was heated at 360~400° for 35 min., cooled, and the reaction mixture was washed with Et_2O and EtOH. The product was recrystallized from MeOH to colorless needles, m.p. 145°. Yield, 0.5 g. *Anal.* Calcd. for $C_{12}H_7O_3N_3$; C, 59.75; H, 2.93. Found : C, 59.64; H, 3.20.

3-Formamido-4-hydroxy-5-nitropyridine (VI)——A mixture of the hydrochloride of (II) (1 g.) and 80% HCOOH (15 cc.) was refluxed for 6 hr. After removal of the excess acid, the residue was washed with H_2O, dried, and recrystallized from 80% HCOOH to pale yellow needles, m.p. 298° (decomp.). Yield, 0.85 g. *Anal.* Calcd. for $C_6H_5O_4N_3$: C, 39.35; H, 2.75. Found : C, 39.28; H, 3.04.

Reaction of (VI) with Ac_2O——A mixture of (VI) (0.5 g.) and Ac_2O (10 cc.) was refluxed for 6 hr. After evaporation of Ac_2O, the residue was washed with Et_2O and recrystallized from Et_2O to colorless needles, m.p. 83°/95°. It was confirmed as (IV) by the elementary analysis and mixed fusion. *Anal.* Calcd. for $C_7H_5O_3N_3$: C, 46.93; H, 2.81. Found : C, 47.00; H, 3.15.

3,5-Diamino-4-hydroxypyridine (VIII)——A suspension of (I) (2 g.) in MeOH was hydrogenated over 5% Pd-C (0.3 g.). After the theoretical volume of H_2 (1559.2 cc. at 20°) was absorbed, the catalyst was filtered off and the filtrate was evaporated *in vacuo*. The obtained glutinous (VIII) (yield, ca. 1.4 g.) was immediately used in the next procedure because of its instability in the air. The hydrochloride of (VIII) was recrystallized from MeOH to pale yellow needles, m.p. 246°. *Anal.* Calcd. for $C_5H_7ON_3 \cdot HCl$: C, 37.12; H, 4.95. Found : C, 36.89; H, 5.12.

3,5-Diacetamido-4-hydroxypyridine (IX) and 2-Methyl-7-acetamidoxazolo[4,5-*c*]pyridine (X)——A mixture of (VIII) (1 g.) and Ac_2O (20 cc.) was refluxed for 9 hr. and treated in the same manner as for (III) and (IV). The Et_2O insoluble (IX) was recrystallized from MeOH to colorless leaflets, m.p. >312° (decomp.). Yield, 0.5 g. *Anal.* Calcd. for $C_9H_{11}O_3N_3$: C, 51.67; H, 5.30. Found : C, 51.39; H, 5.32.

The Et_2O extract was evaporated, the glutinous (X) was crystallized by treating with hot benzene, and recrystallized from Me_2CO to colorless needles, m.p. 240°. Yield, 0.2 g. *Anal.* Calcd. for $C_9H_9O_2N_3$: C, 56.54; H, 4.75. Found : C, 56.29; H, 4.83.

3,5-Diformamido-4-hydroxypyridine (XI)——A mixture of (VIII) (1 g.) and 80% HCOOH was treated in the same way as for (VI) and (XI) obtained was recrystallized from H_2O to colorless needles, m.p. 245°. Yield, 1.1 g. *Anal.* Calcd. for $C_7H_7O_3N_3$: C, 46.41; H, 3.90. Found : C, 46.22; H, 4.18.

(4-Hydroxy-5-nitro-3-pyridyl)urethan (XIII)——To a solution of (II) (1 g.) in 10% NaOH solution (100 cc.), Cl·COOEt (2 g.) was added dropwise with stirring at 4~6°, and continuously stirred for 1.5 hr. at the same temperature. Separated crystals were collected, washed with H_2O, and dried. Recrystallization from EtOH gave yellow leaflets, m.p. 165°/295°. Yield, 1.2 g. *Anal.* Calcd. for $C_8H_9O_5N_3$: C, 42.29; H, 3.99; N, 18.50. Found : C, 42.04; H, 3.99; N, 18.72.

3,5-Diethoxycarbamido-4-pyridone (XIV)——To a solution of (II) (1.2 g.) in $NaHCO_3$ solution (9 g. in 120 cc. H_2O), Cl·COOEt (5 g.) was added dropwise with stirring at 5~8°. After continuous stirring for 2 hr. at the same temperature, the mixture was kept standing overnight at room temperature. Separated crystals were treated as for (XIII) and recrystallized from MeOH to colorless needles, m.p. 215~216°. Yield, 1 g. *Anal.* Calcd. for $C_{11}H_{15}O_5N_3$: C, 49.07; H, 5.62; N, 15.61. Found : C, 49.15; H, 5.81; N, 15.89.

2-Methyl-7-aminoxazolo[4,5-*c*]pyridine (XIX)——(i) A suspension of (IV) (0.3 g.) in MeOH was hydrogenated over 5% Pd-C (0.2 g.). After theoretical volume of H_2 (121 cc. at 20°) was absorbed, the catalyst was filtered off, the filtrate was evaporated *in vacuo*, and the residue was recrystallized from EtOH to pale yellow needles, m.p. 156~157°. Yield, 0.2 g. *Anal.* Calcd. for $C_7H_7ON_3$: C, 56.37; H, 4.73. Found : C, 56.07; H, 4.97.

(ii) A suspension of (IV) (1.1 g.) in MeOH was hydrogenated over Raney Ni prepared from 1 g. of Ni-Al alloy (1:1). After absorption of theoretical volume of H_2 (443 cc. at 20°), the mixture was treated in a similar manner as above. The product melted at 156~157° which remained undepressed on admixture with (XIX) obtained as above.

2-Phenyl-7-aminoxazolo[4,5-*c*]pyridine (XX)——(V) (0.5 g.) was hydrogenated over 5% Pd-C (0.5 g.) to (XIX) (H_2 150 cc. at 20°). Recrystallization from MeOH gave colorless needles, turning red slowly in the air, m.p. 236°. Yield, 0.3 g. *Anal.* Calcd. for $C_{12}H_9ON_3$: C, 68.23; H, 4.30. Found : C, 68.00; H, 4.56.

2-Methyl-7-nitroxazolo[4,5-*c*]pyridine Monomethiodide (XXII)——A mixture of (IV) (0.5 g.) and MeI (2 g.) was heated at 100° in a sealed tube for 5 hr., the solidified reaction mixture was collected,

and washed with Et_2O. Recrystallization from dehyd. Me_2CO gave red prisms, m.p. 161~163° (decomp.). Yield, 0.7 g. *Anal.* Calcd. for $C_8H_8O_3N_3I$: C, 29.91; H, 2.49. Found : C, 30.18; H, 2.66.

2-Phenyl-7-nitroxazolo[4,5-*c*]pyridine Monomethiodide (XXIII)——A mixture of (V) (0.1 g.) and MeI (0.3 g.) was treated as for (XXII) and recrystallized from MeOH to red needles, m.p. 178°/244°. Yield, 0.1 g. *Anal.* Calcd. for $C_{13}H_{10}O_3N_3I$: C, 40.73; H, 2.61; N, 10.97. Found : C, 40.86; H, 2.90; N, 10.88.

1-Methyl-3-acetamido-5-nitro-4-pyridone (XXV)——(i) A solution of (XXII) in 90% MeOH (20 cc.) was heated on a water bath. After few min., red color of the solution faded and crystals appeared. The separated crystals were collected and recrystallized from MeOH to colorless needles, m.p. 323°. Yield, 0.2 g. *Anal.* Calcd. for $C_8H_9O_4N_3$: C, 45.50; H, 4.30; N, 19.90. Found : C, 45.80; H, 4.49; N, 20.01.

(ii) To a solution of (III) (0.2 g.) in KOH solution (0.05 g. in 10 cc. of 90% EtOH), MeI (0.2 g.) was added and the mixture was heated at 60~80° for 40 min. After cool, the separated crystals were recrystallized from MeOH to colorless needles, m.p. 323°. Yield, 0.2 g. It showed no depression of melting point on admixture with (XXV) obtained as above.

1-Methyl-3-benzamido-5-nitro-4-pyridone (XXVI)——A mixture of (XXIII) (0.1 g.) and 70% MeOH (10 cc.) was heated on a water bath for 30 min. When cool, separated crystals were recrystallized from MeOH to colorless needles, m.p. 244°. Yield, 0.07 g. *Anal.* Calcd. for $C_{13}H_{11}O_4N_3$: C, 57.14; H, 4.06. Found : C, 57.03; H, 4.18.

1-Methyl-3-acetamido-5-bromo-4-pyridone (XXVII)——(i) (XXIV)[7] (0.2 g.) was dissolved in KOH solution (0.04 g. in 4 cc. of H_2O). After 20 min., separated crystals were collected, washed with H_2O, and recrystallized from MeOH to colorless needles, m.p. 258~259°. Yield, 0.1 g. *Anal.* Calcd. for $C_8H_9O_2N_2Br$: C, 39.20; H, 3.70. Found : C, 39.27; H, 3.94. IR : ν_{N-H} 3280 cm^{-1}; $\nu_{C=O}$ 1699, 1630 cm^{-1}; δ_{N-H} 1530 cm^{-1} (Nujol).

(ii) To a solution of (XXVIII) (0.2 g.) in KOH solution (0.05 g. in 10 cc. of 50% EtOH), MeI (1 g.) was added and the mixture was heated at 60~80° for 30 min. The resulting mixture was chilled to 0°, separated crystals were collected, washed with H_2O, and recrystallized from MeOH to colorless needles, m.p. 258~259°. Yield, 0.2 g. The product was identified as (XXVII) by mixed fusion and infrared spectra.

1-Methyl-3-amino-5-nitro-4-pyridone (XXIX)——A solution of (XXV) (0.2 g.) in HCl (3 cc.) was heated on a water bath for 1 hr. and evaporated to dryness. The residue was recrystallized from MeOH to orange needles, m.p. 270° (decomp.).*3 Yield, 0.1 g. *Anal.* Calcd. for $C_6H_7O_3N_3$: C, 42.60; H, 4.17; N, 24.85. Found : C, 42.83; H, 4.38; N, 24.99.

1-Methyl-3-amino-5-bromo-4-pyridone (XXX)——A solution of (XXVII) (0.2 g.) in HCl (3 cc.) was treated as for (XXIX). Raw yield, 0.15 g. The picrate was recrystallized from EtOH to yellow needles, m.p. 195°. *Anal.* Calcd. for $C_6H_7ON_2 \cdot C_6H_3O_7N_3$: C, 33.35; H, 2.33. Found : C, 33.44; H, 2.56.

1-Methyl-3-acetamido-5-amino-4-pyridone (XXXI)——A suspension of (XXV) (0.1 g.) in MeOH was hydrogenated over 5% Pd-C (0.1 g.). After theoretical volume of H_2 (34 cc. at 20°) was absorbed, the reaction mixture was treated as usual. Recrystallization from EtOH gave pale yellow needles, m.p. 240~241° (decomp.). Yield, 0.06 g. *Anal.* Calcd. for $C_8H_{11}O_2N_3$: C, 40.98; H, 3.44. Found : C, 40.72; H, 3.62.

1-Methyl-3-nitro-2-pyridone (XXXIII)——To a solution of (XXXII) (1 g.) dissolved in KOH solution (0.5 g. in a mixture of 10 cc. EtOH and 25 cc. H_2O), MeI (2 g.) was added and the mixture was heated at 60~80° for 2 hr. Crystals that separated on cooling were collected and recrystallized from MeOH to pale yellow needles, m.p. 179~180°. Yield, 0.8 g. *Anal.* Calcd. for $C_6H_6O_3N_2$: C, 46.76; H, 3.92. Found : C, 47.01; H, 4.07.

1-Methyl-3-amino-2-pyridone (XXXIV)——To a suspension of (XXXIII) (0.8 g.) in NaCl solution (1 g. in 35 cc. of H_2O), Fe powder (3 g.) was added with stirring at 95~97° and the mixture was continuously stirred for 1.5 hr. at the same temperature. The reaction mixture was filtered rapidly and the filtrate was evaporated *in vacuo*. The residue was extracted with hot benzene (about 50 cc.) and the extract was evaporated. The resulting black oily residue (0.4 g.) was immediately used for the next procedure. The picrate was recrystallized from MeOH to yellow needles, m.p. 204° (decomp.). *Anal.* Calcd. for $C_8H_8O_2N_2 \cdot C_6H_3O_7N_3$: C, 40.80; H, 3.14. Found : C, 41.01; H, 3.24.

1-Methyl-3-acetamido-2-pyridone (XXXV)——0.3 g. of (XXXVI) was dissolved in KOH solution (0.02 g. in 5 cc. of H_2O) at room temperature. After few min., separated crystals were collected, washed with H_2O, and dried. Recrystallization from benzene gave colorless needles, m.p. 165~166°. Yield, 0.1 g. It showed no depression of melting point on admixture with a sample prepared by Ahmad's method.[10] *Anal.* Calcd. for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07. Found : C, 58.06; H, 6.36.

*3 Contrary to expectation, the product was not the hydrochloride but the free base. It seemed that HCl was lost during recrystallization from MeOH.

The authors are indebted to the members of the Analytical Center of the Kyoto University for the microanalyses and Miss I. Uchida for measurement of the infrared spectra. They are also grateful to Mr. H. Koyama for his technical assistance in this work.

Summary

1) 7-Substituted 2-methyl- or 2-phenyl-oxazolo[4,5-*c*]pyridines were prepared from 3,5-dinitro-4-hydroxypyridine and some of them were hydrogenated over palladium-carbon or Raney nickel.

2) By examination of the hydrolysis products of 2-methyl-7-nitro(or bromo)-oxazolo-[4,5-*c*]pyridine monomethiodide and 2-methyloxazolo[4,5-*b*]pyridine monomethiodide, it was confirmed that methyl iodide combined with nitrogen atom in the pyridine ring of oxazolo-pyridine system.

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65. Sadae Tsutsumi : Analytical Studies on Antileprous Drugs. IV.*2 On the Metabolic Substances of Human and Rabbit Urine after Administration of 4,4′-Diaminodiphenyl Sulfone and 4,4′-Diaminodiphenyl Sulfoxide, with Special Reference to Labile N-Conjugates.

(*National Institute for Leprosy Research**1)

In previous reports of this series,[1] electrophoretic method for the separation of 4,4′-diaminodiphenyl sulfone (DDS), 4,4′-diaminodiphenyl sulfoxide (DDSO) and 4,4′-diamino-diphenyl sulfide (DDSD) was reported. Applying this method, metabolites of DDSO excreted in human and rabbit urine were examined,[2] with special reference to intact N-acetyl conjugation of DDSO and unchangeability of DDSO to DDS or DDSD. As the second step, labile conjugates of DDS and DDSO were investigated in the present series of work. As reported by Bushby, *et al.*,[3] mono-N-glucuronide of DDS (DDSG) was detected in the urine of rabbit treated with DDS and also the mono-N-glucuronide of DDSO (DDSOG) in the urine of rabbit treated with DDSO. Both DDSG and DDSOG were also proved in human urine, but in this case, other metabolites of DDS and DDSO were found on the chromatogram.

In the case of DDS, the metabolite was found to be identical on chromatography with the synthesized potassium DDS mono-N-sulfamate (DDSS), while, in the case of DDSO, it was difficult to prove it, as the synthesis of mono-N-sulfamate of DDSO was not possible. However, it may be possible to consider that the mono-N-sulfamate of DDSO is metabolized in the same manner as DDS, because Rf value of the metabolite of DDSO is identical with that of DDSS and also there is no chromatographic difference between DDS and DDSO, DDSG and DDSOG, nor between the mono-N-acetylate of DDS and that of DDSO.[2]

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*2 Part III : La Lepro, **29**, 96 (1960).

1) S. Tsutsumi : *Ibid.*, **28**, 268 (1959).

2) *Idem* : *Ibid.*, **29**, 88 (1960).

3) S. R. M. Bushby, A. J. Woiwod : Biochem. J., **63**, 406 (1956).