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8. **Makoto Kirisawa**: A Synthesis of 3-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl) ethyl]-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (*rac*-c-Noremetine-Pyman).*

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In a previous paper[1] the present author with S. Sugasawa reported a syhthesis of 1-substituted 3-ethyl-6(1*H*)-pyridone,*1 in which the key intermediates were 1-alkyl-3-(1,1-ethylenedioxyethyl) pyridinium salt and its oxidation product, 1-alkyl-3-(1,1-ethylenedioxyethyl)-6(1*H*)-pyridone.*1 This technique will probably find a wide application to the preparation of various 1-substituted 3-alkyl-6(1*H*)-pyridones*1 and moreover the intermediate ketonic pyridones also will serve as starting materials of some further synthetic studies.

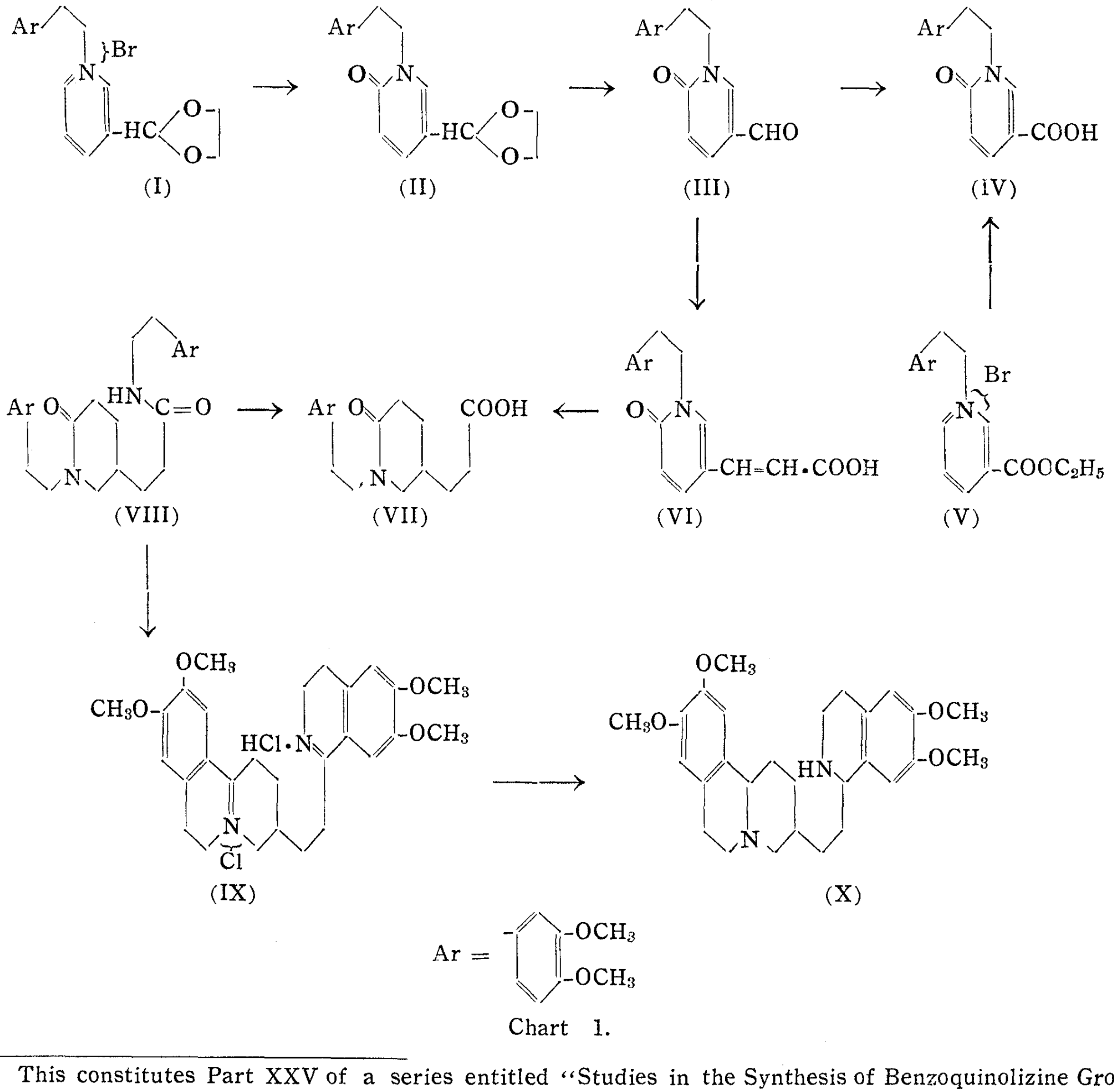

Chart 1.

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* This constitutes Part XXV of a series entitled "Studies in the Synthesis of Benzoquinolizine Group" by S. Sugasawa. Part XXIV. K. Mizukami: This Bulletin, **6**, 312 (1958).

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*1 This type of compound should be called 5-substituted 1-alkyl-2(1*H*)-pyridone, but in this paper another nomenclature was adopted to make the position clear which was involved in the oxidation reaction.

1) S. Sugasawa, M. Kirisawa: This Bulletin, **3**, 190(1955).

This oxidation technique was now extended to include 1-(3,4-dimethoxyphenethyl)-3-ethylenedioxymethylpyridinium salt (I) to furnish 1-substituted 3-ethylenedioxymethyl-6(1*H*)-pyridone[*1] (II), from which the corresponding aldehyde (III) was obtained by acid hydrolysis. For structural proof of (III) this was oxidized to the corresponding acid (IV),2) which was identified with an authentic specimen prepared by the standard method.

In this paper a synthesis of a benzoquinolizine derivative (X) mentioned in the title (*rac*-c-noremetine-Pyman3)) is described. The method of synthesis is self-explanatory from Chart 1.

The compound (X) has already been synthesized by Sugasawa, *et al.*3) via different routes. They recorded their compound as a solid substance which sintered from 45° and melted at 78~80° with effervescence, but the one obtained in the present study remained a viscous syrup, which could not be induced to solidify and was characterized as its solid picrate and picrolonate. Ultraviolet spectrum of (IX) is recorded in the succeeding paper.

The author wishes to express his gratitude to Prof. S. Sugasawa for his interest in this work. He is also thankful to members of the Analysis Room of this Faculty and of Tokyo Research Laboratories of Tanabe Seiyaku Co., Ltd.

Experimental

3-Ethylenedioxymethylpyridine (Nicotinaldehyde Ethyleneacetal)—Nicotinaldehyde4) (11.0 g.) in pure benzene (50 cc.), ethylene glycol (8 g.), and *p*-toluenesulfonic acid (19 g.) were mixed and the whole was heated in an oil bath kept at 130~140° for 3 hrs., the water being removed azeotropically with benzene, as it was formed. When cooled, the mixture was poured into an excess of 10% Na_2CO_3 solution to ensure basicity of the resultant mixture. The aqueous layer was extracted with benzene, which was combined with the original benzene layer, washed, dried, and the solvent was removed. The residual oil was distilled *in vacuo*, when a colorless liquid of b.p$_3$ 103~105° was obtained in a yield of 13.4 g. or 86%. This was characterized as picrate, which formed yellow needles of m.p. 155~156° from EtOH. *Anal.* Calcd. for $C_{14}H_{12}O_9N_4$: C, 44.2; H, 3.2; N, 14.7. Found: C, 44.3; H, 3.7; N, 14.65.

1-(3,4-Dimethoxyphenethyl)-3-ethylenedioxymethylpyridinium Bromide (I)—The foregoing acetal (8.7 g.), 3,4-dimethoxyphenethyl bromide (14.1 g.), and pure toluene (30 cc.) were heated on a steam bath for 6 hrs., separating a faint brownish viscous layer on the bottom. The supernatant toluene was decanted and the residue (11.7 g.) was washed with toluene, which was combined with the original toluene layer. Some of toluene was distilled off to leave about 30 cc. which was heated on a steam bath for additional 8 hrs., to give further 8.1 g. of the addition product (I). Additional 2.8 g. of (I) was obtaind by repeating the above-mentioned process twice more. Thus, the total yield of (I) amounted to 22.6 g., so nearly theoretical. (I) was hygroscopic and was characterized as its picrate, which was purified from EtOH to yellow prisms of m.p. 125~127°. *Anal.* Calcd. for $C_{24}H_{24}O_{11}N_4$: C, 52.9; H, 4.4; N, 10.3. Found: C, 52.9; H, 4.8; N, 10.5.

1-(3,4-Dimethoxyphenethyl)-3-ethylenedioxymethyl-6(1*H*)-pyridone[*2] (II)—A solution of the crude (I) (22.6 g.) in 120 cc. of H_2O, after being shaken once with benzene to remove the starting materials if present, was mixed with a solution of $K_3Fe(CN)_6$ (50 g.) in 200 cc. of H_2O with stirring and cooling in an ice bath. Benzene (150 cc.) was now added, followed by an addition of an aqueous solution of KOH (30 g. in 60 cc. of H_2O) during 40 mins. The whole was stirred for further 5 hrs. in an ice bath. The aqueous layer was extracted with benzene, which was combined with the original benzene layer, washed, dried, and the solvent was evaporated. The product (II) was obtained as a faint yellow oil in a yield of 16.4 g. or 87%, which did not form a picrate and was converted to the aldehyde (III) without being purified.

1-(3,4-Dimethoxyphenethyl)-3-formyl-6(1*H*)-pyridone[*3] (III)—The crude (II) (13.0 g.) was mixed with HCl (24 cc. of 10%) and EtOH (70 cc.), and the mixture was refluxed on a steam bath for 1.5 hrs. H_2O was then added and EtOH was evaporated, separating a faint brown oily layer. The whole was basified by adding K_2CO_3 and the oil was taken up in benzene, which was washed, dried, and the solvent was removed to yield the crude (III) as a faint brown solid of m.p. 109~115° in a yield of 10.6 g. or 94%. When purified from hydr. EtOH this formed colorless needles and melted over a range of 80~90°, but after being dried at 50° for 70 hrs. *in vacuo* it melted at 117~118°. *Anal.* Calcd. for $C_{16}H_{17}O_4N$: C, 66.9; H, 6.0; N, 4.9. Found: C, 67.2; H, 5.7; N, 4.9.

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2) R. H. Wiley, N. R. Smith, L. H. Knabeschuh: J. Am. Chem. Soc., **75**, 4482(1953).

3) S. Sugasawa, K. Sakurai: Yakugaku Zasshi, **62**, 82(1942); S. Sugasawa, H. Shigehara: *Ibid.* **65 B**, 369(1945).

4) L. Panizzon: Helv. Chim. Acta, **24**, 24E(1941).

[*2] 1-(3,4-Dimethoxyphenethyl)-5-(1,3-dioxolan-2-yl)-2(1*H*)-pyridone.

[*3] 1-(3,4-Dimethoxyphenethyl)-2-oxo-1,2-dihydro-3-pyridinecarboxaldehyde.

Semicarbazone: Colorless needles of m.p. 135～136°(decomp.) from hydr. MeOH. *Anal.* Calcd. for $C_{17}H_{20}O_4N_4 \cdot H_2O$: C, 56.3; H, 6.1; N, 15.5. Found (in the substance dried at 60° for 60 hrs. *in vacuo*): C, 56.7; H, 6.15; N, 15.4.

1-(3,4-Dimethoxyphenethyl)-3-carboxy-6(1*H*)-pyridone[*4] **(IV)**—a) Preparation of an authentic sample: An addition product (V) was prepared from ethyl nicotinate (4.5 g.) and 3,4-dimethoxyphenethyl bromide (10.6 g.) as usual. The crude (V) was obtained as a brownish solid in a yield of 10.6 g. (90%), 7.9 g. of which was oxidized with $K_3Fe(CN)_6$ (30 g.) and KOH (15 g.) by the conventional method. The reaction mixture was acidified with AcOH and extracted continuously with AcOEt. Faint yellow pillars of m.p. 204～206° were recovered from AcOEt solution in a yield of 2.9 g. or 48%, which was purified from EtOH(charcoal) to form colorless pillars (IV) of m.p. 204～206° (reported m.p. 207.5～209° (corr.)[2]). *Anal.* Calcd. for $C_{16}H_{17}O_5N$: C, 63.4; H, 5.6; N, 4.6. Found: C, 63.1; H, 6.0; N, 4.75.

b) The crude (III) (0.10 g.) was mixed with Ag_2O, prepared from $AgNO_3$ (0.13 g.) and aq. NaOH (0.08 g. in 1.5 cc. of H_2O), and the mixture was allowed to stand at room temp. with occasional shaking. The oxidation proceeded with a formation of silver mirror while all of (III) passed into solution after ca. 30 mins. After being kept standing overnight, the reaction mixture was filtered and the filtrate was acidified with HCl, separating colorless microcrystalline solid, which was collected on a filter, washed, and dried. The yield of the crude product of m.p. 198～203° was 0.095 g. or 90%. When purified from MeOH it melted at 204～206°, which remained the same on admixture with the authentic (IV).

1-(3,4-Dimethoxyphenethyl)-6-oxo-1,6-dihydro-3-pyridineacrylic Acid (VI)—The crude (III) (10.0 g.), malonic acid (5.0 g.), pyridine (20 cc.), and a few drops of piperidine were mixed, the whole was heated on a steam bath for 2 hrs., and then refluxed in an oil bath for an additional 1 hr. On cooling H_2O was added and pyridine was removed *in vacuo*, separating a faint brown solid, which was collected on a filter, washed, and was then dissolved in aq. $NaHCO_3$ solution. The solution was treated with charcoal, filtered, and the filtrate was acidified with HCl. The solid thus obtained was purified from MeOH to form colorless prisms (or needles) of m.p. 178～181° (yield, 6.5 g.).

From the mother liquor, further crop of 2.5 g., melting at 177～181°, was obtained. Thus, the total yield amounted to 9.0 g. or 81%. Sometimes this acid separated from hydr. MeOH in colorless needles of m.p. 155～157° but after a lapse of about 2 months, it melted over a range of 155～180°, which then formed colorless prisms of m.p. 179～181° when recrystallized from MeOH. This behavior is probably due to a dimorphism of (VI). *Anal.* Calcd. for $C_{18}H_{19}O_5N$: C, 65.6; H, 5.8; N, 4.25. Found (in prisms of m.p. 179～181°): C, 65.8; H, 5.6; N, 4.2. Found (in needles of m.p. 155～157°): C, 65.9; H, 6.3; N, 4.35.

1-(3,4-Dimethoxyphenethyl)-6-oxo-3-piperidinepropionic Acid (VII)—The compound (VI) of m.p. 179～181° (3.0 g.) was dissolved in warm EtOH(250 cc.) and was reduced catalytically over Adams' Pt-catalyst (prepared from 0.2 g. of PtO_2) at 40～50°. In ca. 10 hrs., 3 molar equivalents of H_2 was absorbed. On being worked up as usual a clear faint brown oil was obtained in a quantitative yield (3.0 g.), which was dissolved in dil. Na_2CO_3 solution, filtered, and the filtrate was acidified with HCl, separating an oily substance, which gradually solidified on standing. On being purified once again as above and air dried this formed colorless pillars of m.p. 58～59°, which contained 2 moles of water of crystallization, as was shown by analysis. *Anal.* Calcd. for $C_{18}H_{25}O_5N \cdot 2H_2O$: C, 58.2; H, 7.9; N, 3.8; H_2O, 9.7. Found: C, 57.7; H, 7.6; N, 3.9; H_2O, 9.4.

In a desiccator this crystal lost water of crystallization and changed to syrupy substance, which, when exposed to air, again solidified, forming the hydrate. When kept in a desiccator for a long time the syrup became a solid, which was probably anhydrated (VII), but this was so hygroscopic that its m.p. determination appeared impossible.

N,1-Bis(3,4-dimethoxyphenethyl)-6-oxo-3-piperidinepropionamide (VIII)—The anhydrous (VII) (2.1 g.) in 20 cc. of $CHCl_3$ was gently refluxed with $SOCl_2$ (2.1 g.) on a steam bath for 2 hrs. An excess of $SOCl_2$ and $CHCl_3$ were now removed *in vacuo* to leave reddish brown syrupy chloride of (VII), which was again dissolved in 30 cc. of $CHCl_3$ and reacted with 3,4-dimethoxyphenethylamine (4.2 g.) in 20 cc. of $CHCl_3$, with stirring and ice-cooling. The mixture was stirred for 1 hr. in the cold and then for an additional 1 hr. at room temp. The $CHCl_3$ solution was washed successively with 10% HCl, H_2O, 10% Na_2CO_3, and H_2O, dried, and the solvent was evaporated. The crude amide (VIII) formed a reddish orange viscous syrup, which could not be induced to crystallize and was directly used in the next step. The yield was nearly quantitative (3.1 g.).

3-[2-(6,7-Dimethoxy-3,4-dihydro-1-isoquinolyl)ethyl]-9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium Chloride Hydrochloride (IX)—A mixture of the foregoing crude amide (3.1 g.) and $POCl_3$ (18 cc.) was gently refluxed in an oil bath for 1.5 hrs. and an excess of $POCl_3$ was removed *in vacuo*, leaving a tarry residue, which was dissolved in ice water (ca. 70 cc.), treated with charcoal, and filtered. The clear reddish brown filtrate was concentrated to ca. 50 cc. and KI was now added in excess to this solution to cause a dark brownish tar to separate. The latter was taken up in $CHCl_3$, dried, and the solvent was evaporated, leaving a brown caramel-like iodide-hydriodide (ca. 4 g.), which was converted

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[*4] 1-(3,4-Dimethoxyphenethyl)-6-oxo-1,6-dihydro-3-pyridinecarboxylic Acid.

to the chloride-hydrochloride with AgCl as usual, thus yielding a reddish brown syrup in 2.7 g. yield. When a drop of H_2O was added to the latter, it solidified after some time and it was purified from hydr. acetone after being washed with the same solvent to form light brown grains of m.p. 134~137° (efferv. at 139°). *Anal.* Calcd. for $C_{23}H_{35}O_4N_2Cl \cdot HCl \cdot 5H_2O$: C, 53.8; H, 7.4; N, 4.5. Found (in the substance dried at 40° for 45 hrs. *in vacuo*): C, 53.8; H, 7.5; N, 4.6.

Picrate: Light brown plates of m.p. 220~222° (decomp.) (dried at 40° for 45 hrs. *in vacuo*) from EtOH. *Anal.* Calcd. for $C_{23}H_{35}O_4N_2 \cdot C_6H_2O_7N_3 \cdot C_6H_3O_7N_3$: C, 52.2; H, 4.4; N, 12.2. Found: C, 52.1; H, 4.3; N, 12.2.

Picrolonate: Yellow minute plates of m.p. 223° (decomp.) (dried at 40° for 45 hrs. *in vacuo*) from 80% EtOH. *Anal.* Calcd. for $C_{23}H_{35}O_4N_2 \cdot C_{10}H_7O_5N_4 \cdot C_{10}H_8O_5N_4 \cdot 3H_2O$: C, 55.2; H, 5.4; N, 13.4. Found: C, 54.9; H, 5.0; N, 13.2.

3-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl)ethyl]-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (rac-c-Noremetine-Pyman) (X)—The foregoing reddish brown syrupy (IX) (1.23 g.) in 60 cc. of H_2O was reduced catalytically over Adams' Pt, prepared from 0.15 g. of PtO_2 and 115 cc. of H_2 was taken up in 7 hrs. The filtrate from the catalyst was evaporated *in vacuo* to give a light brown vitreous hydrochloride of (X) in a yield of 1.2 g., which was hygroscopic and could not be obtained in solid state.

The dipicrate separated in indefinite plate-formed solid from 80% EtOH, which was probably the salt of a mixture of diastereoracemates of (X) as could be judged from its m.p. This sintered at 75° and fused gradually to give a clear melt, which effervesced at 110° and decomposed at 170°. When dried at 40° for 45 hrs. *in vacuo*, it sintered towords 100°, melted over a range of 115~130°, and decomposed at 170°. *Anal.* Calcd. for $C_{23}H_{33}O_4N_2 \cdot 2C_6H_3O_7N_3 \cdot H_2O$: C, 51.0; H, 4.9; N, 11.9. Found (in the substance dried at 40° for 45 hrs. *in vacuo*): C, 51.1; H, 5.35; N, 11.8.

The dipicrolonate of (X) formed yellow indefinite prismatic solid, which also did not show a sharp m.p. Thus this abruptly became thin at 160°, fused at 180°, and decomposed at 215°. After being dried at 40° for 48 hrs. *in vacuo*, there was observed no remarkable change in its melting behavior. *Anal.* Calcd. for $C_{23}H_{33}O_4N_2 \cdot 2C_{10}H_8O_5N_4 \cdot 3H_2O$: C, 54.95; H, 5.8; N, 13.35. Found: C, 55.3; H, 5.5; N, 12.95.

Summary

Ethyleneacetal of nicotinaldehyde was quaternized with 3,4-dimethoxyphenethyl bromide and the product (I) was oxidized with alkaline potassium ferricyanide, yielding 1-(3,4-dimethoxyphenethyl)-5-(1,3-dioxolan-2-yl)-2(1*H*)-pyridone (II) in a fair yield, from which the aldehyde (III) was recovered in an excellent yield. (III) will serve as a starting material for various syntheses and in this paper a synthesis of *rac*-c-noremetine-Pyman was described as such an example.

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9. Makoto Kirisawa: A Synthesis of 2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (*rac*-c-Bisnoremetine).[*1]

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The oxidation of ethyleneacetal derivatives of 3-formyl- and 3-acetylpyridinium salts to furnish the corresponding 3-formyl- and 3-acetyl-6(1*H*)-pyridones was described in the preceding[1] and earlier papers.[2] This oxidation technique was now successfully extended to the ethyleneacetal derivatives of 4-formyl- and 4-acetyl-pyridinium salts.[3] Thus 1-(3,4-di-

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[*1] This constitutes Part XXVI of a series entitled "Studies in the Synthesis of Benzoquinolizine Group" by S. Sugasawa.

[*2] Hongo, Tokyo (桐沢 誠).

1) Part XXV: M. Kirisawa: This Bulletin **7**, 35 (1959).

2) S. Sugasawa, M. Kirisawa: This Bulletin, **3**, 190 (1955).

3) *Idem.*: *Ibid.*, **6**, 615 (1958)