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]

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*2])

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)

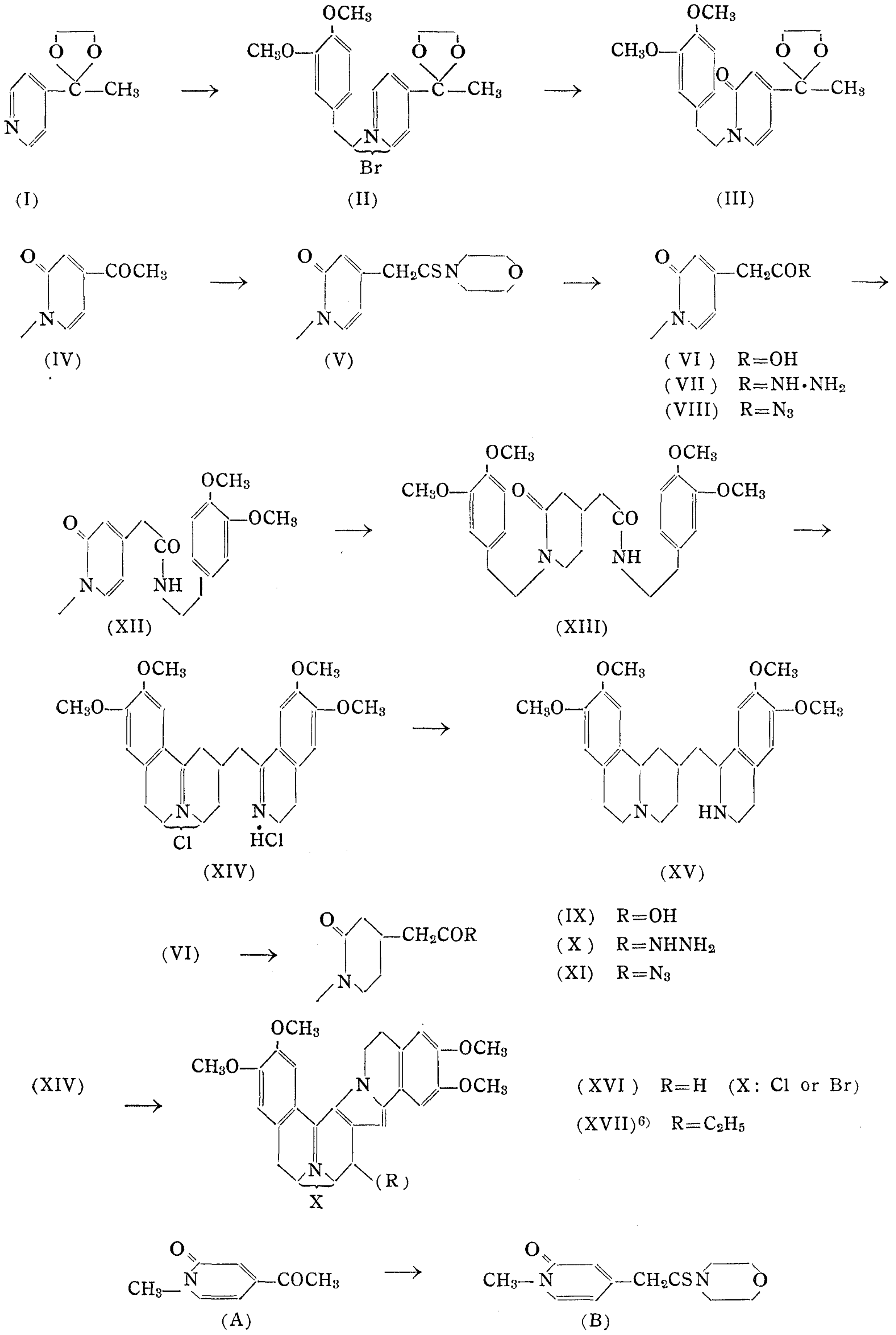
(I)
(II)
(III)
(IV)
(V)
(VI) R=OH
(VII) R=NH·NH2
(VIII) R=N3
(XII)
(XIII)
(XIV)
(XV)
(VI)
(IX) R=OH
(X) R=NHNH2
(XI) R=N3
(XIV)
(XVI) R=H (X: Cl or Br)
(XVII)6) R=C2H5
(A)
(B)

Chart 1.

ethoxyphenethyl)-4-acetyl-2(1*H*)-pyridone (IV) was obtained in a good yield and in this paper a synthesis of *rac*-c-bisnoremetine (XV), whose synthesis has already been recorded by several workers,[4] is described starting from this ketonic pyridone (IV).

The conversion of (IV) into the corresponding acetic acid (VI) constituted the first step of the synthesis and for this purpose a recourse was had to the Willgerodt's method. Since there seemed to be no precedent of this reaction executed with a lactam ketone, a model experiment was carried out with 1-methyl-4-acetyl-2(1*H*)-pyridone (A),[3] when 1-methyl-4-morpholinothiocarbonylmethyl-2(1*H*)-pyridone (B) was obtained in a fair yield. This method was also found successful with (IV) to yield the acetic acid (VI).

The key intermediate (XIII) for the synthesis of *rac*-c-bisnoremetine was now prepared by four different ways from this acid.

i) The acetic acid (VI) was converted to the corresponding azide (VIII), via the ester and the hydrazide (VII) as usual, which was condensed with homoveratrylamine to yield the amide (XII),[5] from which (XIII) was prepared by catalytic hydrogenation.

ii) The acid (VI) was first reduced to the corresponding piperidoneacetic acid (IX), whose azide (XI) prepared as usual was condensed with homoveratrylamine to yield the amide (XIII).

iii) The ester of piperidoneacetic acid (IX) was directly heated with homoveratrylamine to furnish the amide (XIII).

iv) The ester of pyridoneacetic acid (VI) was directly heated with homoveratrylamine to furnish the amide (XII), which was reduced to (XIII).

Of these the last-mentioned route was the simplest and gave the best yield of the product.

The amide (XIII) was now subjected to double cyclization with phosphoryl chloride and the product (XIV) was then reduced catalytically to yield the ultimate product (XV).

For structural proof, (XIV) was dehydrogenated with mercuric acetate to yield a crystalline

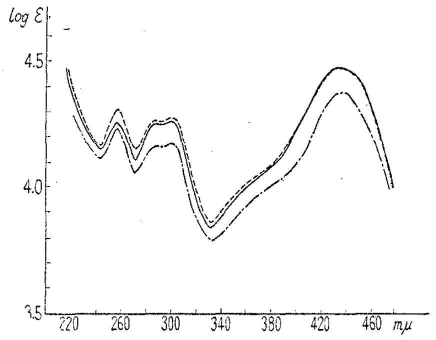

Fig. 1. Ultraviolet Absorption Spectra (in H_2O)

—— (XVI)
---- (XVII)[6]
—·— (XVI)[4c]

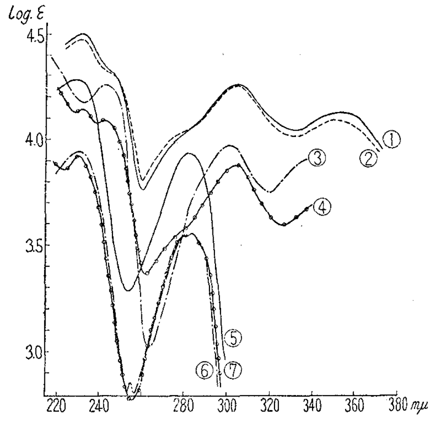

Fig. 2. Ultraviolet Absorption Spectra (in 95% EtOH)

① —— (XIV)
② ---- 1,2,3,4,6,7-Hexahydro-3-[2-(3,4-dihydro-6,7-dimethoxy-1-isoquinolyl)]ethyl-9,10-dimethoxybenzo[*a*]quinolizinium chloride hydrochloride[1]
③ —·— 1,2,3,4,6,7-Hexahydro-9,10-dimethoxybenzo[*a*]quinolizinium iodide[7]
④ -O-O- 3,4-Dihydro-1-propyl-6,7-dimethoxyisoquinoline hydrochloride[7]
⑤ —— (XV) dihydrobromide
⑥ —·— 1,2,3,4,6,7-Hexahydro-9,10-dimethoxy-11b*H*-benzo[*a*]quinolizine hydrochloride[7]
⑦ -O-O- 1,2,3,4-Tetrahydro-1-propyl-6,7-dimethoxyisoquinoline hydrochloride[7]

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4) a) M. Pailer, H. Strohmayer: Monatsh., **82**, 1125(1951); b) M. Pailer, K. Schneglberger, W. Reifschneider: *Ibid.*, **83**, 513(1952); c) M. Pailer, H. Strohmayer: *Ibid.*, **83**, 1198(1952); d) Y. Tomimatsu: Yakugaku Zasshi, **73**, 75(1953); e) S. Sugasawa, K. Oka: This Bulletin, **2**, 85(1954).

5) Besides a solid of m.p. 136~138° recorded by the previous authors (Footnote 4e), two other crystal modifications were obtained.

rubremetinium type of compound (XVI), whose ultraviolet spectrum (Fig. 1) was found to be quite similar to that of *d*-rubremetinium bromide (XVII)[6] and also identical with that recorded by Pailer, *et al.*[4c] for their compound (XVI).

Moreover, ultraviolet spectra of (XIV) and the similar compound ((IX) described in the previous paper[1]) (Fig. 2) were measured and no discrepancy was observed. As reference ultraviolet spectra of some other compounds[7] of similar structure were also recorded.

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. for elemental analyses. Author's thanks are due to Messrs. G. Chihara and K. Tanikawa for infrared spectral data and to Mr. H. Ohki for ultraviolet spectral data.

Experimental

4-(1,1-Ethylenedioxyethyl)-1-(3,4-dimethoxyphenethyl)pyridinium Bromide (II)—4-(1,1-Ethylenedioxyethyl)pyridine[3] (I) (24 g.), 3,4-dimethoxyphenethyl bromide (30 g.), and toluene (50 cc.) were heated on a steam bath to yield the crude quaternary bromide (II) in a yield of 45.3 g. (90%). This was a fairly hygroscopic salt melting around 164~167° and for characterization the picrate was prepared, which formed yellow needles of m.p. 168~169° from EtOH. *Anal.* Calcd. for $C_{25}H_{26}O_{11}N_4$: C, 53.8; H, 4.7; N, 10.0. Found: C, 53.9; H, 4.6; N, 10.2.

4-(1,1-Ethylenedioxyethyl)-1-(3,4-dimethoxyphenethyl)-2(1*H*)-pyridone (III)—The crude (II) (45.3 g.) in 250 cc. of H_2O, after being shaken once with benzene, was mixed with an aqueous solution of $K_3Fe(CN)_6$ (110 g.) in 450 cc. of H_2O. The mixture was stirred in an ice bath and added with KOH solution (65 g. of KOH dissolved in 130 cc. of H_2O) during 30 mins. During this period, 300 cc. of benzene was added at once and the whole was stirred for further 1 hr. in an ice bath and an additional 1 hr. at room temp. The reaction mixture was then allowed to stand overnight and the bottom layer was extracted with benzene, which was mixed with the original benzene layer, washed, dried, and the solvent was removed. A solid residue of m.p. 117~120° was obtained in a yield of 34.2 g. (90%) and was purified from benzene-hexane to form colorless needles of m.p. 120~121°. *Anal.* Calcd. for $C_{19}H_{23}O_5N$: C, 66.1; H, 6.7; N, 4.1. Found: C, 66.0; H, 6.6; N, 4.2.

1-(3,4-Dimethoxyphenethyl)-4-acetyl-2(1*H*)-pyridone (IV)—The foregoing crude (III) (34.2 g.) was refluxed on a steam bath with 60 cc. of 10% HCl and 175 cc. of EtOH. After 1.5 hrs.' heating, H_2O was added and EtOH was evaporated *in vacuo*. The residual aqueous solution was strongly basified with K_2CO_3, separating a large amount of oil, which soon solidified. This was collected in $CHCl_3$ and after evaporating the solvent there was obtained the crude (IV) of m.p. 97~100° in a yield of 29.8 g. (theoretical), which was purified from benzene, forming colorless prisms of m.p. 102~103.5°. *Anal.* Calcd. for $C_{17}H_{19}O_4N$: C, 67,8; H, 6.4; N, 4.65. Found: C, 67.75; H, 6.1; N, 4.3.

1-Methyl-4-morpholinothiocarbonylmethyl-2(1*H*)-pyridone (B)—1-Methyl-4-acetyl-2(1*H*)-pyridone[3] (A) (2.5 g.), morpholine (1.6 g.), and S (0.65 g.) were thoroughly mixed and the mixture was refluxed in an oil bath (150~160°) for 5.5 hrs. To this hot mixture 3 cc. of H_2o was added to give a dark solution, from which a solid substance began to separate immediately. This was collected on a filter, washed with a little H_2O (ca. 4 cc.), and there remaimed the crude (B) in a yield of 1.8 g. (43%) as faint brown needles of m.p 142~144°. From the benzene extract of the filtrate 0.9 g. of light brown needles of m.p. 120~130° was recovered which, when admixed with the sample of m.p. 142~144° obtained above, melted over a range of 130~138°. Since their identity was in doubt, the latter was not worked up further.

A prolonged heating (ca. 20 hrs.) of the starting materials did not give a better yield of the product. When purified from benzene, (B) formed light brown needles of m.p. 144~145°, while light brown prisms of the same m.p. separated from EtOH. *Anal.* Calcd. for $C_{12}H_{16}O_2N_2S$: C, 57.1; H, 6.4; N, 11.1; S, 12.7. Found: C, 57.2; H, 6.5; N, 10.8; S, 12.6.

1-(3,4-Dimethoxyphenethyl)-4-morpholinothiocarbonylmethyl-2(1*H*)-pyridone (V)—An intimate mixture of the compound (IV) (10.65 g.), morpholine (4.8 g.), and S (1.2 g.) was refluxed in an oil bath at 155° for 5 hrs. An excess of morpholine was distilled off *in vacuo* and the dark tarry residue was dissolved in 250 cc. of hot EtOH. The resultant solution was treated twice with charcoal to give a yellow filtrate (ca. 300 cc.), from which microneedles separated on standing. These were collected on a filter and washed with EtOH to give colorless minute needles of m.p. 158~160°, in a yield of 6.5 g. (46%).

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6) A. R. Battersby, H. T. Openshaw: J. Chem. Soc., **1949**, S67; Experientia, **6**, 387(1950); A. R. Battersby, H. T. Openshaw, H. C. S. Wood: J. Chem. Soc., **1953**, 2463.

7) Y. Ban, O. Yonemitsu: Paper presented at the Annual Meeting of the Pharmaceutical Society of Japan, April, 1958.

Some more crops (yellow needles of m.p. 152~156°, 0.57 g.) were obtained by concentrating the alcoholic filtrate and by extracting the spent decolorising charcoal with hot EtOH (light gray needles of m.p. 157~159°, 0.36 g.). Thus, the total yield of the crude (V) amounted to 7.43 g. (52%). This formed colorless needles of m.p. 160~161° from EtOH. *Anal.* Calcd. for $C_{21}H_{23}O_4N_2S$: C, 62.7; H, 6.5; N, 7.0. Found: C, 62.4; H, 6.6; N, 7.1.

By a prolonged heating with yellow HgO this was desulfurized to give 1-(3,4-dimethoxyphenethyl)-4-morpholinocarbonylmethyl-2(1*H*)-pyridone, which came in very faint brown needles of m.p. 121~123° from benzene-hexane. *Anal.* Calcd. for $C_{21}H_{26}O_5N_2$: C, 65.3; H, 6.8; N, 7.25. Found: C, 65.5; H, 6.6; N, 7.2.

1-(3,4-Dimethoxyphenethyl)-2-oxo-1,2-dihydro-4-pyridineacetic Acid (VI)—The foregoing crude (V) (6.5 g.) was heated with 90 cc. of 10% KOH solution on a steam bath for 10 hrs. The reaction product was treated with charcoal and the faint yellow filtrate was acidified to Congo Red with HCl. The separated solid was collected on a filter, washed with H_2O, and dried. The crude acid (VI) of m.p. 157~158° (decomp.) thus obtained amounted to 4.8 g. (94%). When purified from EtOH this formed colorless plates of m.p. 159~160° (decomp.). *Anal.* Calcd. for $C_{17}H_{19}O_5N$: C, 64.3; H, 6.0; N, 4.4. Found: C, 64.45; H, 6.2; N, 4.3.

1-(3,4-Dimethoxyphenethyl)-2-oxo-1,2-dihydropyridineacetohydrazide (VII)—The crude ethyl ester (1.63 g.) of (VI), obtained in a quantitative yield from the acid and anhydr. EtOH in the presence of dry HCl by the conventional method, and hydrazine hydrate (1.3 g. of 80%) were heated on a steam bath to form a clear, yellowish, homogeneous solution. After 0.5 hr.'s heating, excess of hydrazine hydrate was removed *in vacuo*, leaving 1.46 g. of a viscous syrup, which solidified on cooling. This was purified from EtOH-hexane to form colorless needles of m.p. 107~110°, in a yield of 1.32 g. (81%). Pure hydrazide formed colorless needles of m.p. 110~112° from EtOH or H_2O. *Anal.* Calcd. for $C_{17}H_{21}O_4N_3 \cdot H_2O$: C, 58.4; H, 6.6; N, 12.0. Found (in the substance dried at 50° for 50 hrs. *in vacuo*): C, 58.65; H, 6.4; N. 12.1.

1-(3,4-Dimethoxyphenethyl)-2-oxo-4-piperidineacetic Acid (IX)—The above-mentioned acid (VI) (2.00 g.) was dissolved in 8 cc. of 10% Na_2CO_3 solution and the solution was diluted to 50 cc. by adding H_2O. This was reduced catalytically at 40~50° over Raney Ni (ca. 1 g.), 2 molar equivalents of H_2 being absorbed in 10 hrs. From the filtrate, 1.86 g. (92%) of (IX) was recovered, which formed colorless pillars of m.p. 146~148° from EtOH. *Anal.* Calcd. for $C_{17}H_{23}O_5N$: C, 63.5; H, 7.2; N, 4.4. Found: C, 63.4; H, 6,8; N, 4.7.

1-(3,4-Dimethoxyphenethyl)-2-oxo-4-piperidineacetohydrazide (X)—This was prepared in a good yield from the foregoing acid (IX) via its ester by the standard method. The pure hydrazide came in colorless needles of m.p. 122~124° from EtOH. *Anal.* Calcd. for $C_{17}H_{25}O_4N_3$: C, 60.9; H, 7.5; N, 12.5. Found: C, 60.8; H, 7.5; N, 12.7.

N,1-Bis(3,4-dimethoxyphenethyl)-2-oxo-1,2-dihydro-4-pyridoneacetamide (XII)—i) The ester (5.37 g.) of the acid (VI) and homoveratrylamine (5.5 g.) were heated in an atmosphere of N_2 in an oil bath kept at 185~190° for 5 hrs. After cool, the mixture was dissolved in $CHCl_3$ and the resultant solution was washed successively with 10% AcOH, H_2O, 5% Na_2CO_3, and H_2O, dried, and the solvent was evaporated to leave 7.1 g. of a brown syrup. This was dissolved in a small amount of AcOEt, from which crystalline solid separated on standing. This formed light brown crystals of m.p. 109~113° and the yield was 5.37 g. (72%). Further purification from the same solvent afforded colorless scales of m.p. 111~113°. *Anal.* Calcd. for $C_{27}H_{32}O_6N_2$: C, 67.5; H, 6.7; N, 5.8. Found: C, 67.7; H, 6.9; N, 5.8.

When kept long in AcOEt, the above-mentioned scales of m.p. 111~113° were converted into needles of m.p. 126~128°, which gave correct analyses for (XII). When the melts of these crystals were inoculated with the one of m.p. 136~138° obtained by Sugasawa and Oka[4e] there was obtained another needle-shaped modification of m.p. 134~136°, which also gave correct analyses for (XII). Though the infrared spectra of these three modifications are not quite identical in Nujol phases, they are completely superimposable when measured in $CHCl_3$ solution, showing that they are crystal-modifications.

ii) Aq. $NaNO_2$ solution (0.4 g. of $NaNO_2$ in 5 cc. of H_2O) was added dropwise into a solution of the hydrazide (VII) (1.30 g.) in 30 cc. of 2.3% HCl with cooling to around 0°, separating a brown syrupy azide (VIII). After the excess of HNO_2 was decomposed with urea, the azide was collected in $CHCl_3$, which was washed, dried, and then mixed with homoveratrylamine (1.4 g.) in the same solvent. After several hrs.' standing the resultant solution was washed successively with 10% HCl, H_2O, 5% $NaHCO_3$, and H_2O, dried, and the solvent was evaporated to leave 1.65 g. of a reddish brown syrup. This was purified from AcOEt to form light brown crystals of m.p. 110~113°, which was not depressed when admixed with the one obtained above. The yield of pure product was 1.15 g. (65%).

N,1-Bis(3,4-dimethoxyphenethyl)-2-oxo-4-piridineacetamide (XIII)—i) The foregoing amide (XII) (3.90 g.) of m.p. 111~113° was dissolved in 250 cc. of warm EtOH and reduced at 40~50° with activated H_2 over Adams' Pt (prepared from 0.1 g. of PtO_2), 2 molar equivalents of H_2 being absorbed in 3 hrs. On being worked up as usual there was obtained a colorless oil, which was dissolved in 40 cc. of hot AcOEt. On cooling there separated 3.55 g. (90%) of colorless needles of m.p. 117~119° and the second crop of 0.3 g. was recovered from the mother liquor. When purified from AcOEt this formed colorless needles of m.p. 118～119°.8) *Anal.* Calcd. for $C_{27}H_{36}O_6N_2$: C, 66.9; H, 7.5; N, 5.8. Found: C, 67.05; H, 7.3; N, 5.95.

ii) 1.25 g. of the ester of (IX) and 1.3 g. of homoveratrylamine were heated in an atmosphere of N_2 and then worked up as described above. The yield of the crude (XIII) of m.p. 115～118° was 0.55 g. (32%), which was identified with the specimen obtained above.

iii) The same amide (m.p. 116～119°) was obtained in 54% yield from the hydrazide (X) via the azide (XI) and homoveratrylamine as mentioned above.

2-(6,7-Dimethoxy-3,4-dihydro-1-isoquinolylmethyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]-quinolizinium Chloride Hydrochloride (XIV)—The foregoing amide (XIII) (1.05 g.) of m.p. 117～119° was cyclized by boiling with 6 cc. of $POCl_3$ for 1.5 hrs. and worked up as usual. The crude (XIV) was thus obtained as a light brown solid of m.p. 178～180° (decomp.), which amounted to 1.21 g. (94% calculated as tetrahydrate), and formed colorless plates from hydr. acetone. The latter began to sinter at 60°, but solidified again at about 110° when heated rather slowly and melted at 179～181° with decomposition. The specimen kept in a desiccator showed a single m.p. 179～181° (decomp.), which was tetrahydrate as shown by the analysis. *Anal.* Calcd. for $C_{27}H_{33}O_4N_2Cl \cdot HCl \cdot 4H_2O$: C, 54.6; H, 7.15; N, 4.7. Found (in the subst. dried at 60° for 40 hrs. *in vacuo*): C, 54.6; H, 7.2; N, 4.7.

Picrate: Yellow micro-plates of m.p. 180～182° (decomp.) from hydr. EtOH. *Anal.* Calcd. for $C_{27}H_{33}O_4N_2 \cdot C_6H_2O_7N_3 \cdot C_6H_3O_7N_3$: C, 51.7; H, 4.2; N, 12.4. Found: C, 51.3; H, 4.1; N, 12.4.

Picrolonate: Showed very indefinite m.p. A specimen which was purified from 80% hydr. EtOH and dried at 50° for 48 hrs. *in vacuo* began to sinter at 125°, slightly effervesced at 140°, fused at 180°, darkened at 210°, and decomposed at 225°.9) *Anal.* Calcd. for $C_{27}H_{33}O_4N_2 \cdot C_{10}H_7O_5N_4 \cdot C_{10}H_8O_5N_4 \cdot 3H_2O$: C, 54.75; H, 5.3; N, 13.6. Found: C, 54.9; H, 5.1; N, 13.9.

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) (XV)—The foregoing (XIV) (2.0 g.) in 50 cc. of H_2O was reduced catalytically over Adams' Pt (prepared from 0.2 g. of PtO_2), 2 molar equivalents of H_2 being absorbed in 15 mins. When the filtrate was evaporated to dryness *in vacuo*, there was obtained the dihydrochloride of (XV) as a faint yellow caramel-like solid in a yield of 2.0 g., which was characterized as its picrate. The latter formed yellow powder from hydr. EtOH and was dried at 40° for 72 hrs. *in vacuo*. This specimen melted at 148～153° to give a dark brown vitreous substance and decomposed at 190°.4d,4e) *Anal.* Calcd. for $C_{27}H_{36}O_4N_2 \cdot 2C_6H_3O_7N_3 \cdot H_2O$: C, 50.4; H, 4.8; N, 12.1. Found: C, 50.5; H, 4.6; N, 11.65.

Picrolonate: Purified from 80% AcOH and dried at 50° for 48 hrs. *in vacuo*. Yellow minute pillars of m.p. 241° (decomp.).4d, 4e) *Anal.* Calcd. for $C_{27}H_{36}O_4N_2 \cdot 2C_{10}H_8O_5N_4 \cdot 3H_2O$: C, 54.5; H, 5.65; N, 13.5. Found: C, 54.6; H, 5.8; N, 13.6.

Hydrobromide: Prepared through conversion of the hydrochloride with NaBr in a concentrated solution. Purified from H_2O, forming colorless needles, it melted at 215～220° and decomposed at about 270°. A specimen dried at 60° for 40 hrs. *in vacuo* was analysed. Calcd. for $C_{27}H_{36}O_4N_2 \cdot 2HBr \cdot 4H_2O$: C, 47.2; H, 6.75; N, 4.1. Found: C, 47.0; H, 6.35; N, 4.0.

All efforts to obtain the free base (XV) in crystalline condition ended fruitless.

***rac*-C-Bisnorrubremetinium Bromide (XVI)**—The compound (XIV) (0.75 g.) in 7.5 cc. of H_2O was mixed with 0.15 g. of AcOK and the solution was treated with 3.0 g. of $Hg(AcO)_2$ in 20 cc. of 5% AcOH according to the standard method6) and worked up as usual. A crude *rac*-C-bisnorrubremetinium chloride was obtained as reddish orange silky crystals of m.p. 210～213° (decomp.), in a yield of 0.54 g. The corresponding bromide was prepared from the chloride and NaBr, and was purified from hot H_2O to form reddish orange needles of m.p. 236～237° (decomp. at 240°), which was obtained as trihydrate when air-dried. *Anal.* Calcd. for $C_{27}H_{29}O_4N_2Br \cdot 3H_2O$: C, 56.0; H, 6.1; N. 4.8. Found: C, 56.5; H, 6.1; N. 4.7. Further analyses were executed with a specimen dried at 100° for 50 hrs. *in vacuo*. Calcd. for $C_{27}H_{29}O_4N_2Br \cdot H_2O$: C, 59.7; H, 5.75; N, 5.2. Found: C, 59.3; H, 5.4; N. 5.1.

Summary

A new synthesis of *rac*-C-bisnoremetine was described, in which 4-acetylpyridine was one of the starting materials. Ethyleneketal of this compound was quaternized with 3,4-dimethoxyphenethyl bromide and the product (II) was subjected to oxidation with alkaline potassium ferricyanide to furnish 1-(3,4-dimethoxyphenethyl)-4-acetyl-2(1*H*)-pyridone in a good yield after acid hydrolysis. The latter ketone (IV) underwent a smooth Willgerodt reaction to give the

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8) m.p. of 130～131° was recorded by previous authors.4e)

9) According to the literature, the monohydrate decomposes at 221～222°4d) and the trihydrate does so at 220～221°.4e)

corresponding acetic acid (VI) from which the key intermediate (XIII) was prepared by several different routes. The structure of the final product (XV) was proved by converting the penultimate compound (XIV) into a well defined crystalline *rac*-c-bisnorrubremetinium bromide (XVI).

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10. **Toshihiko Okamoto**: The Aconite Alkaloids. XIX.[1]

The Structure of Kobusine. (1).

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Kobusine was first isolated from *Aconitum sachalinense* FR. SCHMIDT by Suginome and F. Shimanouchi[2] and $C_{20}H_{27}O_2N$ was given as its molecular formula by the above workers. One oxygen was proved to be present as a hydroxyl group and the other was considered to be an ether oxygen.[3] Kobusine absorbed one mole of hydrogen on catalytic reduction and these workers concluded that this double bond may be attached to nitrogen.[2,3]

Previously, Ochiai and others reported the isolation of an alkaloid from the aconite roots, gathered in Shimokita Peninsula, Aomori Prefecture, which showed quite similar physical properties with kobusine.[4] Later, this sample was identified as kobusine by admixture.[5]

This paper describes some reduction and oxidation reactions of kobusine. Kobusine (I) crystallized from acetone as prisms, m.p. 267~267.5°, $[\alpha]_D^{12}+104.4°$ (MeOH), and gave a picrate, m.p. 282~284°(decomp.), perchlorate, m.p. 185~187°(decomp.), and also a methiodide, m.p. 286~287°(decomp.).[4,6]

Kobusine (I) showed the bands at 1648 and 888 cm^{-1} in its infrared spectrum and consumed one mole of hydrogen on hydrogenation over platinium oxide in acetic acid, so the existence of a terminal methylene group could be considered. As was previously reported, shimoburo base-I[7] and hypognavine[1] have an allyl alcohol group in their structure and gave rearranged ketones by hydrogenation over palladium-carbon. In the relation to these alkaloids, kobusine was hydrogenated by the use of palladized carbon as the catalyst in methanol, and three products were isolated by alumina chromatography. The first fraction showed m.p. 230~232° (needles from acetone), $C_{20}H_{27}O_2N$ (II), the second showed m.p. 240~241° (needles from chloroform), $C_{20}H_{27}O_2N$ (III), and the third fraction melted at 229~231° (needles from acetone), $C_{20}H_{29}O_2N$ (IV). In the infrared spectra, the first two products (II and III) showed a strong absorption band at 1705 cm^{-1} and were considered to be ketones of a six-membered ring, which are the rearranged products in the allyl alcohol part of kobusine. The third product of m.p. 229~231° (IV) showed no absorption band of ketone in the infrared spectrum and this should be the dihydro derivative. The

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[1] Part XVIII: S. Sakai: This Bulletin, **5**, 1(1957).

[2] H. Suginome, F. Shimanouchi: Ann., **545**, 220(1940).

[3] H. Suginome, F. Shimanouchi: J. Fac. Sci., Hokkaido Univ., IV (1942).

[4] E. Ochiai, *et al.*: Yakugaku Zasshi, **75**, 639 (1955).

[5] The author is grateful to Dr. H. Suginome and Dr. T. Amiya, Department of Chemistry, University of Hokkaido, for their kind help for the identification of the sample.

[6] H. Suginome reported the following physical properties for kobusine in reference of Footnote(2): m.p. 268°, $[\alpha]_D^{22}$ +83.61° ($CHCl_3$); picrate, m.p. 273°(decomp.): perchlorate, m.p. 220°; methiodide, m.p. 286~287°(decomp.).

[7] T. Sugasawa: This Bulletin, **4**, 6(1956).