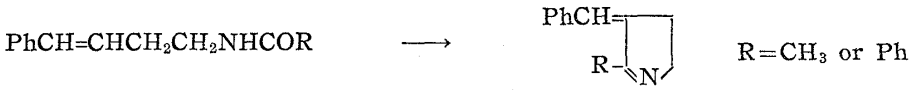
UDC 615.783.2

128. Tomishige Mizoguchi: A New Synthesis of *rac*-Nicotine*1,2

(*Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd.**3)

In their second communication[1] of "Extension of Bischler-Napieralski Reaction," Sugasawa and Ushioda reported a new synthesis of 2-substituted 3-benzylidene-1-pyrroline according to the following scheme :—

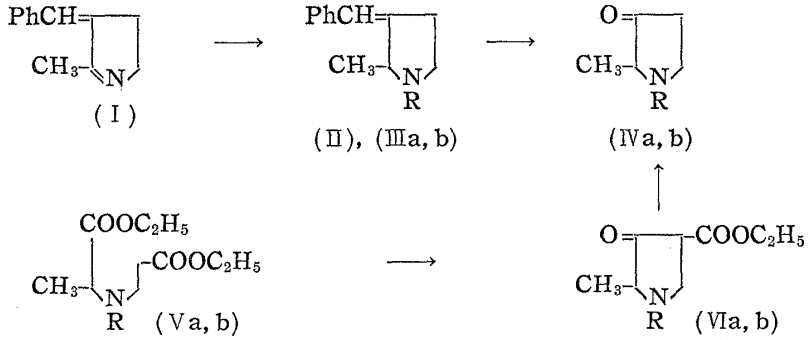


This appears to be a general method for building up various pyrrole derivatives with or without a substituent in 3-position.

The present writer thus elaborated to remove the 3-benzylidene group, which is inevitably present in pyrrolines prepared by this method.

Ozonization followed by mild hydrogenation was found to furnish 3-pyrrolidinone derivatives in a smooth reaction and the latter compounds may be worked up in various ways. As an example, a synthesis of *rac*-nicotine will be described.

First, the oxidative removal of the benzylidene group from 2-methyl-3-benzylidene-1-pyrroline (I) with potassium permanganate or ozone was examined, but without effect. After several fruitless attempts, it was found that the benzylidene group could be cleaved via the ozonide of 1-acyl-2-methyl-3-benzylidenepyrrolidine to yield the 3-pyrrolidinone derivative.



a : R=$COCH_3$; b : R=COPh; (II) : R=H

Chart 1.

Reduction of (I) with sodium borohydride in methanolic solution readily gave, 3-benzylidenepyrrolidine (II), whose crystalline derivatives, 1-acetyl (IIIa) and 1-benzoyl (IIIb) compounds, were dissolved in acetic acid and ozonized, the resulting ozonides were then decomposed reductively with zinc-dust to yield colorless liquids, (IVa), $b.p_{0.03}$ 96~98°(bath temp.), and (IVb) $b.p_3$ 165°(bath temp.), respectively. The ketonic nature of these substances was confirmed from their infrared spectra and also by preparing their 2,4-dinitrophenylhydrazones which gave satisfactory elemental analyses.

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*1 V. Communication of "Extension of Bischler-Napieralski Reaction" by S. Sugasawa. Part. IV: S. Sugasawa, T. Fujisawa : Tetrahedron, **7**, 185 (1959).

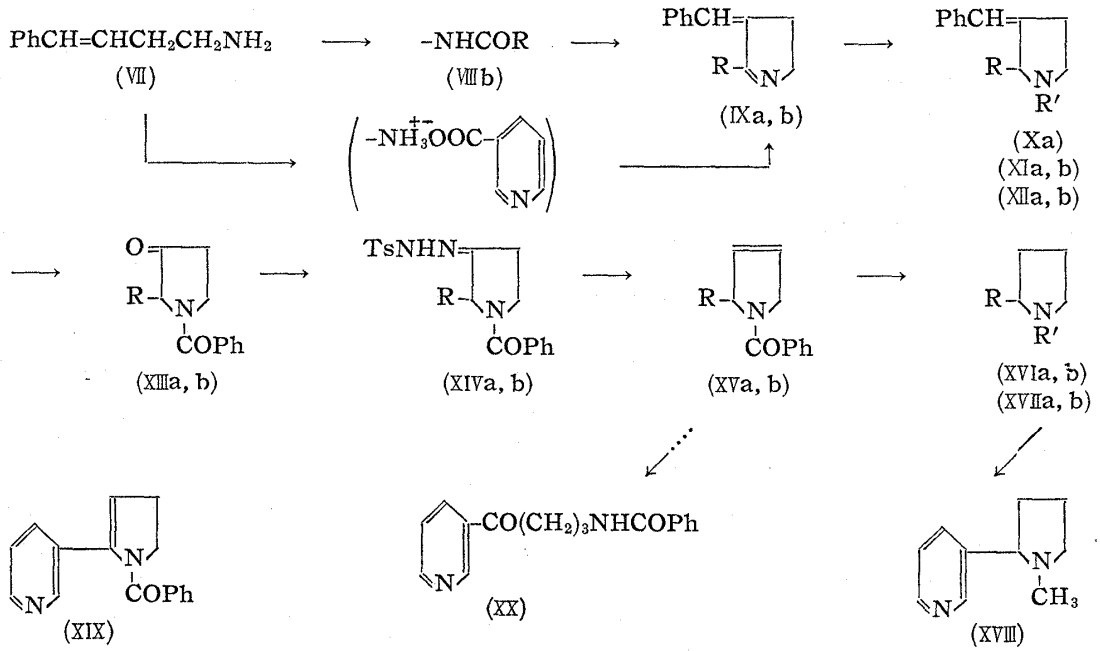
*2 A part of this work was represented at the Annual Local Meeting of the Pharmaceutical Society of Japan, October, 1959.

*3 Toda-machi, Kita-adachi-gun, Saitama-ken (溝口富茂).

1) S. Sugssawa, S. Ushioda : Tetrahedron, **5**, 48 (1959).

(IVa) and (IVb) were also identified with authentic specimens prepared by cyclization of N-acetyl- and N-benzoyl-N-(2-ethoxycarbonylethyl)-*dl*-alanine ester (Va and Vb) according to the method of McKinney, *et al.*[2] followed by acid hydrolysis.

Thus the exo-cyclic nature of the double bond as benzylidene substituent in the original base (I), which was hitherto deduced only from the ultraviolet absorption data[1] is now established chemically beyond doubt.



a : R=Ph; b : R=3-pyridyl.
(X) : R′=CH_3; (XI) : R′=H; (XII) : R′=COPh; (XVI) : R′=COPh; (XVII) : R′=H.

Chart 2.

Considering the synthesis of nicotine, the oxidative removal of the benzylidene group from 1-methyl-2-phenyl-3-benzylidenepyrrolidine (Xa), a reduction product of methiodide of (IXa), was variously attempted with potassium permanganate or ozone, but it again failed; ketonic substance was never traced in the reduction product, though a small amount of the starting material (m.p. 79~80.5°) was recovered under rather mild reaction conditions. The failure may probably be due to the lability of the starting material.

Therefore, as in the previous case, (IXa) was converted to 1-benzoyl-2-phenyl-3-benzylidenepyrrolidine (XIIa), which appeared in two crystalline forms of m.p. 104.5~106° and 117~118°, both of which gave correct analyses for (XIIa). Their infrared spectra, though not the same in Nujol mull, were identical in chloroform solution and moreover the former, when repeatedly recrystallized, was converted into the latter. Hence they are considered to be dimorphs.

They were ozonized separately in acetic acid solution and the resulting ozonides were reductively cleaved by hydrogen activated over palladium catalyst, and one and the same product was obtained from both as colorless needles, m.p. 105~106°, and was characterized as 1-benzoyl-2-phenyl-3-pyrrolidinone (XIIIa) from analyses. The ketonic nature of this compound was supported from the infrared data (1760 cm^{-1}), and also from the formation of 2,4-dinitrophenylhydrazone (m.p. 152~153°), hydrazone (m.p. 118~119° (decomp.)), piperonylidenehydrazone (m.p. 151.5~152.5°), and tosylhydrazone (m.p. 218° (decomp.)), all of which gave good analyses.

2) L.L. McKinney, F.H. Uhing, E.A. Selzkorn, J.C. Cowan : J. Am. Chem. Soc., **72**, 2599 (1950); **73**, 1641 (1951); **74**, 5183 (1952).

Conversion of (XIIIa) to the corresponding pyrrolidine derivative both by Wolff-Kischner method as well as by its Huang-Minlon modification met with failure; under usual working conditions no evolution of N_2 was observed, whereas under more drastic condition resinification ensued.

By heating cyclohexanone tosylhydrazone with sodium dissolved in an excess of ethylene glycol, Bamford, *et al.*[3] succeeded in obtaining cyclohexene in a quantitative yield. This procedure was now applied to the above mentioned tosylhydrazone (XIVa), and a similar reaction took place with the formation of a viscous yellow oil. A limited amount of sodium was found sufficient for this reaction, while Bamford, *et al.* used a large excess of the metal for their purpose. The infrared spectrum of this oil exhibits a strong band at 1620 cm^{-1}, suggesting the presence of C=C bond, which is probably located at 3-position based on the facts to be mentioned later.

The oil in ethanol was reduced over Adams platinum catalyst and yielded 1-benzoyl-2-phenylpyrrolidine (XVIa) as a viscous faint yellow oil, which was directly refluxed with 20% hydrochloric acid to furnish a colorless oily base, $b.p_{14}$ 122~125° (bath temp.). Its picrate and picrolonate were obtained in crystalline forms, whose m.p. 150.5~151.5° and 223~224° (decomp.) agreed respectively with those for 2-phenylpyrrolidine (XVIIa) mentioned in the literature.[4] They also gave good analyses.

The above synthesis of 2-phenylpyrrolidine was now extended to the preparation of nicotine. 4-Phenyl-3-butenylamine[1] (VII) was heated with ethyl nicotinate to yield the corresponding amide (VIIIb), whose hydrochloride was then cyclized by heating with phosphoryl chloride, forming 2-(3-pyridyl)-3-benzylidene-1-pyrroline (IXb). The latter was also prepared by treating the nicotinate of (VII) directly with phosphoryl chloride, which is the better method as regards overall yield of (IXb), though purification of the product was a little more tedious. The base (IXb) in methanol was then reduced with sodium borohydride in the presence of acetic acid, which was found essential to promote the reduction.

The product (XIb) was benzoylated to give (XIIb) and the latter was ozonized and decomposed as above to yield 1-benzoyl-2-(3-pyridyl)-3-pyrrolidinone (XIIIb), which could not be induced to crystallize. The ketonic nature of this compound was supported by the infrared absorption band at 1760 cm^{-1} and the chart was very similar to that of (XIIIa).

In conformity with its structure, this gave a crystalline tosylhydrazone (XIVb) as colorless needles, m.p. 196° (decomp.), which is also the key intermediate for further transformation.

(XIVb) was heated with sodium dissolved in an excess of ethylene glycol to yield a viscous yellow oil, whose infrared spectrum was similar to that of (XVa). This gave a crystalline picrate as yellow needles, m.p. 199~200°, and its analyses agreed for 1-benzoyl-2-(3-pyridyl)-3-pyrroline (XVb) picrate. The location of the ethylenic bond will be discussed later.

The above uusaturated base took up nearly 1 molar equivalent of hydrogen activated over Adams platinum to furnish a viscous faint yellow oil, whose infrared spectrum exhibited only a band at 1643 cm^{-1} corresponding to C_6H_5CO-.

The analyses for crystalline picrate of yellow needles, m.p. 172~173°, agreed with 1-benzoyl-2-(3-pyridyl)pyrrolidine (XVIb) picrate. Debenzoylation of (XVIb) was effected smoothly by boiling with 20% hydrochloric acid and the resulting base, *rac*-nornicotine (XVIIb) (m.p. 192~193° of its dipicrate was the same as that mentioned in the literature[5]) was methylated with formaldehyde-formic acid as uaual.

3) W.R. Bamford, T.S. Stevens : J. Chem. Soc., **1952**, 4738.
4) H.P.L. Gilsels, J.P. Wibaut : Rec. trav. chim., **59**, 1093 (1940).
5) P.G. Haines, A. Eisner, C.F. Woodward : J. Am. Chem. Soc., **67**, 1257 (1945).

rac-Nicotine[6] (XVIII) thus obtained was a colorless mobile oil, b.$p_{5.5}$ 98~100° (bath temp.), whose dipicrate, m.p. 224~225°, and dipicrolonate, m.p. 238° (decomp.), were identified with specimens prepared from authentic *rac*-nicotine[7] obtained by racemization of the levorotatory-base. The identity was also proved from their infrared spectra.

As for the location of the double bond in (XVb), its ultraviolet absorption spectrum was taken, which was similar to that of the reduced base (XVIb), but different from that of benzoylmyosmine (XIX) reported by Swain, *et al.*[8] (Fig. 1).

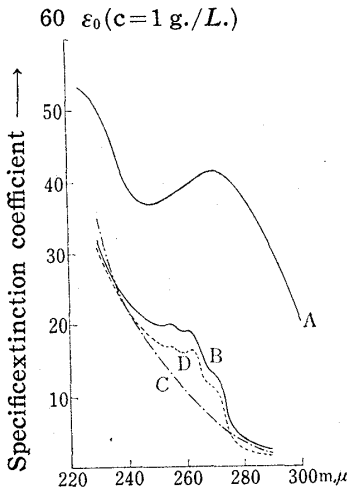


Fig. 1. Ultraviolet Spectra

A : (XIX) in 95% EtOH[8]
B : (XVb) in EtOH
C : (XVa) in EtOH
D : (XVIb) in EtOH

When (XVb) picrate was acidified with 6*N* hydrochloric acid, then basified with sodium hydroxide, only the original base (XVb) was recovered, whereas according to Haines, *et al.*[5] the picrate of (XIX) was cleaved to give N-(3-nicotinolypropyl)benzamide (XX, picrate, m.p. 151~152°) by the same procedure and Δ^3-structure was thus given to (XVb).

The product (XVa) showed infrared and ultraviolet spectra similar to that of (XVb) and Δ^3-structure may also be tenable to (XVa).

Experimental*4

2-Methyl-3-benzylidenepyrrolidine (II)——To a MeOH (30 cc.) solution of hydrochloride of 2-methyl-3-benzylidene-1-pyrroline (I) (3 g.) $NaBH_4$ (0.6 g.) was added in small portions during 30 min. with ice-water cooling and stirring, and stirring was continued for additional 1 hr. at room temperature. MeOH was evaporated *in vacuo*, 2% NaOH solution was added to the residue, and extracted with benzene. The benzene solution was washed with H_2O, dried, and evaporated leaving an oily product, which on distillation gave a colorless oil, b.p_3 109~110° (2.1 g., 84%). $IR_{(b)}$ $\nu_{max}^{capil.}$ cm^{-1} : 3320 (NH), 1663 (C=C).

Hydrochloride : Colorless needles (from EtOH-Et_2O), m.p. 204~205°. *Anal.* Calcd. for $C_{12}H_{16}NCl$: C, 68.72; H, 7.69; N, 6.68. Found : C, 68.45; H, 8.01; N, 6.70.

Picrate : Yellow prisms (from MeOH-iso-Pr_2O), m.p. 154~155°. *Anal.* Calcd. for $C_{18}H_{18}O_7N_4$: C, 53.73; H, 4.51; N, 13.93. Found : C, 53.64; H, 4.29; N, 13.69.

1-Acetyl derivative (IIIa) : Obtained by acetylation of (II) (1.05 g.) with Ac_2O (1.2 cc.) and pyridine (3 drops) by the usual method. Yield, 0.94 g. (72%). Colorless needles (from iso-Pr_2O), m.p. 67~68°. *Anal.* Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51. Found : C, 78.08; H, 8.20; N, 6.71. $IR_{(b)}$ ν_{max}^{Nujol} cm^{-1} : 1670 (C=C), 1620 (=$NCOCH_3$). UV λ_{max}^{EtOH} mμ (log ε) : 252 (4.51), 284 (shoulder) (3.07), 291 (shoulder) (2.75).

*4 Infrared spectrophotometers used in this experimental part were Nippon Bunko Model IR-S ($IR_{(a)}$), Koken Model DS-301 ($IR_{(b)}$), and Perkin-Elmer Model 21 ($IR_{(c)}$).

6) L. Marion : "The Alkaloids," **1**, 240 (1950); S. Sugasawa, T. Tatsuno, T. Kamiya : This Bulletin, **2**, 39 (1954); F. Zymalkowski, B. Trentrog : Arch. Pharm., **292**, 9 (1959); *idem.* : Angew. Chem., **71**, 199 (1959).
7) E. Späth, H. Bredtschneider : Ber., **61**, 327 (1928); A. Pictet, A. Rotschy : *ibid.*, **33**, 2357 (1900).
8) M. L. Swain, A. Eisner, C. F. Woodward, B. A. Brice : J. Am. Chem. Soc., **71**, 1341 (1949).

1-Benzoyl derivative (IIIb) : Obtained by benzoylation of (II) (0.62 g.) with BzCl (0.6 g.) and pyridine (0.5 cc.) by the usual method. Yield, 0.77 g. (77.5%). Colorless prisms (from iso-Pr_2O), m.p. 88~90°. *Anal.* Calcd. for $C_{19}H_{19}ON$: C, 82.38; H, 6.91; N, 5.06. Found : C, 82.11; H, 6.77; N, 5.15. $IR_{(c)}$ $\nu_{max}^{CHCl_3}$ cm^{-1} : 1622 (=NCORh). UV λ_{max}^{MeOH} mμ (log ε) : 249 (4.46).

1-Acetyl-2-methyl-3-pyrrolidinone (IVa)——Stream of O_2 (75 cc./min.) containing O_3 (2% by wt.) was bubbled through a solution of the above acetylpyrrolidine (IIIa) (0.5 g.) in AcOH (5 cc.) during 1.5 hr. with ice-water cooling, then Et_2O (10 cc.), H_2O (0.5 cc.) and Zn dust (0.5 g.) were added and resulting mixture was stirred until KI-starch paper test was negative. After filtration, the filtrate was evaporated *in vacuo*, H_2O was added to the residue, and extracted with benzene. The H_2O layer was evaporated *in vacuo*, the residue was taken up in benzene-Et_2O (1:1) mixture and the small amount of insoluble substance was filtered off. The solvent was removed and the residue thus obtained was distilled to give a colorless oil, $b.p_4$ 103~140° (bath temp.) (0.21 g., 63.1%), which was redistilled to $b.p_{0.03}$ 96~98° (bath temp.). $IR_{(b)}$ $\nu_{max}^{capil.}$ cm^{-1} : 1760 (5-membered ring C=O), 1640 (=$NCOCH_3$).

2,4-Dinitrophenylhdyrazone : Yellow prisms (from EtOH), m.p. 188° (decomp.). *Anal.* Calcd. for $C_{13}H_{14}O_5N_5$: C, 48.75; H, 4.38; N, 21.90. Found : C, 48.64; H, 4.44; N, 21.59.

1-Benzoyl-2-methyl-3-pyrrolidinone (IVb)——A solution of the above benzoylpyrrolidine (IIIb) (0.3 g.) in AcOH (5 cc.) was ozonized and worked up as above for (IVa), yielding an oily product from the benzene-soluble fraction, which was distilled to furnish a colorless oil (0.11 g., 49%), $b.p_3$ 165° (bath temp.), which gradually changed to brown on standing. $IR_{(b)}$ $\nu_{max}^{capil.}$ cm^{-1} : 1760 (5-membered ring C=O), 1630 (=NCOPh).

2,4-Dinitrophenylhydrazone : Orange yellow prisms (from EtOH), m.p. 176~177°. *Anal.* Calcd. for $C_{18}H_{17}O_5N_5$: C, 56.39; H, 4.47; N, 18.27. Found : C, 56.50; H, 4.33; N, 18.19.

Ethyl 1-Acetyl-4-oxo-5-methyl-3-pyrrolidinecarboxylate (VIa)——A mixture of the acetyl-diester (Va) (14 g.), dehyd. xylene (40 cc.), and freshly prepared Na powder (1.25 g.) was refluxed for 3 hr. and orange Na-compound of the cyclization product separated. The supernatant layer was decanted, to which another portion of Na powder (0.2 g.) was added and the mixture was refluxed for 2 hr. to separate a small amount of solid substance. The precipitates thus obtained were combined and decomposed cautiously by adding AcOH (5 cc.) and H_2O (1 cc.), and repeatedly extracted with benzene. The benzene solution was washed with satd. NaCl solution, dried, evaporated and the residue was distilled to afford a colorless oil, $b.p_3$ 137~138° (7.7 g., 67%), which was easily soluble in H_2O and gave a reddish violet colorlation with $FeCl_3$. By treating with a little H_2O, this oil solidified and was recrystallized from Me_2CO-hexane to (VIa)-monohydrate as colorless prisms, m.p. 71~73°. *Anal.* Calcd. for $C_{10}H_{15}O_4N \cdot H_2O$: C, 51.94; H, 7.14; N, 6.06. Found : C, 51.70; H, 7.09; N, 6.21.

Ethyl 1-Benzoyl-4-oxo-5-methyl-3-pyrrolidinecarboxylate (VIb)——A mixture of the benzoyl-diester (Vb) (15.5 g.), dehyd. xylene (40 cc.), and freshly prepared Na powder (1.1 g., and additional 0.3 g.) was refluxed similarly as above. The precipitated Na-compound was decomposed with AcOH (40 cc.) and H_2O (40 cc.), and worked up as above. The viscous red oily product (12.5 g.) thus obtained was insoluble in H_2O and it also gave a reddish violet color to $FeCl_3$ test (EtOH). This oil was directly used for the next hydrolysis because of its partial decomposition on distillation.

1-Acetyl-2-methyl-3-pyrrolidinone (IVa)——A solution of the foregoing keto-ester (VIa) (3.7 g.) in 1% HCl (20 cc.) was refluxed for 45 min. until the evolution of CO_2 had ceased. The solution was evaporated *in vacuo*, the residue was dissolved in EtOH, and passed through Amberlite IR-45 resin column (25 cc.) three times to remove HCl. EtOH was then evaporated, leaving an oily product, which on distillation yielded colorless oil, $b.p_3$ 85~102° (0.8 g., 32%), and redistilled to $b.p_{0.03}$ 92~105° (bath temp.). This was easily soluble in H_2O and slowly changed to red on standing. $IR_{(b)}$ $\nu_{max}^{capil.}$ cm^{-1} : 1760 (5-membered ring C=O), 1640 (=$NCOCH_3$).

2,4-Dinitrophenylhydrazone : Yellow prisms (from EtOH), m.p. 188° (decomp.). *Anal.* Calcd. for $C_{13}H_{14}O_5N_5$: C, 48.75; H, 4.38; N, 21.90. Found : C, 48.67; H, 4.72; N, 21.61. This was identified with the specimen prepared from the ozone oxidation product (IVa) described above by mixed melting point test and $IR_{(c)}$ spectra ($CHCl_3$).

1-Benzoyl-2-methyl-3-pyrrolidininone (IVb)——A solution of the foregoing oil (VIb) (5.4 g.) in AcOH (15 cc.) and 5% HCl (15 cc.) was refluxed for 1.5 hr. and the solvent was evaporated *in vacuo*, leaving an oily residue, which was taken up in benzene. The benzene solution was washed successively with H_2O, $KHCO_3$ solution, and satd. NaCl solution, dried, and evaporated to leave a brown oil, which on distillation gave a colorless oil, $b.p_{0.25}$ 143° (1.4 g., 36%). This was insoluble in H_2O and slowly changed to brown on standing. $IR_{(b)}$ $\nu_{max}^{capil.}$ cm^{-1} : 1760 (5-membered ring C=O), 1630 (=NCOPh).

2,4-Dinitrophenylhydrazone : Orange yellow prisms (from EtOH), m.p. 176~177°. *Anal.* Calcd. for $C_{18}H_{17}O_5N_5$: C, 56.39; H, 4.47; N, 18.27. Found : C, 56.14; H, 4.25; N, 18.65.

This was identified with the specimen prepared from the ozone oxidation product (IVb) described above by mixed melting point test and $IR_{(c)}$ spectra ($CHCl_3$).

1-Methyl-2-phenyl-3-benzylidenepyrrolidine (Xa)——The crude methiodide of pyrroline[1] (IXa) (9.5

g.) dissolved in MeOH (40 cc.) was reduced with $NaBH_4$ (1 g.) and worked up as above for (II) to yield a crystalline product, which was dissolved in hexane, treated with charcoal, and filtered. The product (Xa) (5.8 g., 92%) was recovered from the filtrate as colorless plates, m.p. 79~80.5°, but was very unstable and changed to a substance insoluble in hexane. *Anal.* Calcd. for $C_{18}H_{19}N$: N, 5.62. Found: N, 5.45.

Picrate: Yellow needles (from MeOH), m.p. 208~209° (decomp). *Anal.* Calcd. for $C_{24}H_{22}O_7N_4$: C, 60.25; H, 4.64; N, 11.71. Found: C, 60.27; H, 4.61; N, 11.98.

Methiodide: Its m.p. 225~226°(decomp.) agreed with the one previously reported.[1]

2-Phenyl-3-benzylidenepyrrolidine (XIa)——A solution of the pyrroline (IXa) (10.5 g.) in MeOH (105 cc.) was acidified with conc. HCl (3.5 cc.), treated with $NaBH_4$ (3 g.), and worked up similarly as above for (Xa) to yield (XIa) as colorless needles (from hexane), m.p. 82~83°(8.5 g., 80%). On further purification, the melting point was raised to 84~85°. *Anal.* Calcd. for $C_{17}H_{17}N$: C, 86.76; H, 7.28; N, 5.95. Found: C, 86.77; H, 7.24; N, 5.65. $IR_{(c)}$: ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 824 (-CH=C<). UV λ_{max}^{EtOH} mμ (log ε): 258 (4.37).

Hydrochloride: Colorless needles (from EtOH-Et_2O), m.p. 225~226°(decomp.). *Anal.* Calcd. for $C_{17}H_{18}NCl$: C, 75.12; H, 6.67; N, 5.15; Cl, 13.05. Found: C, 74.72; H, 6.52; N, 4.88; Cl, 12.86.

1-Benzoyl-2-phenyl-3-benzylidenepyrrolidine (XIIa)——a) Benzoylation of the foregoing pyrrolidine (XIa) (8.0 g.) with BzCl (8.0 g.) and pyridine (20 cc.) by the usual method afforded colorless fine needles (from benzene-hexane), m.p. 117~118°(9.5 g., 82.3%). *Anal.* Calcd. for $C_{24}H_{21}ON$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.95; H, 6.29; N, 4.06. $IR_{(c)}$ ν_{max}^{Nujol} cm^{-1}: 1635 (=NCOPh). UV λ_{max}^{EtOH} mμ (log ε): 253.5 (4.37).

b) Above-mentioned (XIa) (8.0 g.) was benzoylated with BzCl (5.3 g.) and 3.3% NaOH solution by the usual method, and the product was crystallized once from benzene-hexane to afford (XIIa) as colorless prisms, m.p. 104.5~106°(10 g., 86.7%). *Anal.* Calcd. for $C_{24}H_{21}ON$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.77; H, 6.07; N, 3.93. $IR_{(a)}$ ν_{max}^{Nujol} cm^{-1}: 1635 (=NCOPh).

A considerable difference was noted in the IR spectra between (a) and (b) in Nujol, but they were identical in $CHCl_3$ solution. The melting point of the product from method (b) was raised to 117~118° after repeated recrystallizations from the same solvents and was unchanged when admixed with the specimen prepared by (a).

1-Benzoyl-2-phenyl-3-pyrrolidinone (XIIIa)——a) A partial suspension of the foregoing benzoylpyrrolidine (XIIa), m.p. 117~118°(2.0 g.), in AcOH (25 cc.) was treated with O_2 stream (75 cc./min.) containing O_3 (6% by wt.) during 65 min. as above for (IVa), then EtOH (25 cc.) was added, and the product was reduced over 10% Pd-C (0.1 g.), absorbing 237.4 cc. of H_2 in 70 min. at room temperature. The catalyst was filtered off and the filtrate was evaporated *in vacuo* below 65° to leave an oily residue, which was dissolved in EtOH. AcOH was removed together with EtOH by evaporation and the residue obtained was dissolved in boiling iso-Pr_2O (80 cc.), leaving a small amount of insoluble matter. Charcoal was added to the above solution and was filtered off together with undissolved substance while hot. From the filtrate, (XIIIa) separated as colorless needles, m.p. 104~106°(1.08 g., 69%), which was raised to m.p. 105~106° by further purification. *Anal.* Calcd. for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.99; H, 5.74; N, 5.20. $IR_{(c)}$ ν_{max}^{Nujol} cm^{-1}: 1760 (5-membered ring C=O), 1635 (=NCOPh). UV (EtOH): No absorption maximum in 220~300 mμ region.

b) A solution of benzoylpyrrolidine (XIIa), m.p. 104.5~106°(3.6 g.), in AcOH (40 cc.) was ozonized, then reductively cleaved as in method (a) to give 1.88 g. (66.7%) of colorless needles, m.p. 104~106°, which were found to be identical with the one obtained by method (a) by mixed melting point test.

2,4-Dinitrophenylhydrazone: Yellow needles (from EtOH), m.p. 152~153°. *Anal.* Calcd. for $C_{23}H_{19}O_5N_5$: C, 62.02; H, 4.30; N, 15.73. Found: C, 61.72; H, 4.28; N, 15.74.

Hydrazone: This was obtained by refluxing a mixture of the above pyrrolidinone (XIIIa) and 100% hydrazine hydrate in EtOH for 20 hr., as colorless needles (from benzene-hexane), m.p. 118~119° (decomp.). *Anal.* Calcd. for $C_{17}H_{17}ON_3$: C, 73.09; H, 6.14; N, 15.04. Found: C, 72.84; H, 5.90; N, 14.88. $IR_{(a)}$ ν_{max}^{Nujol} cm^{-1}: 3400, 3220 (NH), 1615 (=NCOPh).

Piperonylidenehydrazone: Faint yellow needles (from EtOH), m.p. 151.5~152.5°. *Anal.* Calcd. for $C_{25}H_{21}O_3N_3$: C, 72.98; H, 5.15; N, 10.21. Found: C, 73.10; H, 5.37; N, 10.39. IR ν_{max}^{Nujol} cm^{-1}: 1650 (C=N), 1625 (=NCOPh), 1260 (methylenedioxy).

Tosylhydrazone (XIVa)——a) Tosylation of the above hydrazone (64 mg.) with tosyl chloride (57 mg.) and pyridine (0.1 cc.) gave 61 mg. (61%) of crude (XIVa), which was crystallized once from ethylene glycol to colorless fine needles, m.p. 218°(decomp.). *Anal.* Calcd. for $C_{24}H_{23}O_3N_3S$: C, 66.49; H, 5.35; N, 9.69; S, 7.40. Found: C, 66.86; H, 5.46; N, 9.74; S, 6.93. $IR_{(a)}$ ν_{max}^{Nujol} cm^{-1}: 3220 (NH), 1620 (=NCOPh), 1340, 1175 (S-O).

b) A solution of the above pyrrolidinone (XIIIa) (100 mg.) and tosylhydrazide (80 mg.) in EtOH was refluxed for 3 hr. The product (XIVa) separated out from the solution as colorless needles, m.p. 218° (decomp.) (120 mg., 73.4%), whose IR spectrum was identical with that for the one described above.

1-Benzoyl-2-phenyl-3-pyrroline (XVa)——The foregoing tosylhydrazone (XIVa) (1.35 g.) was mixed

with Na (0.083 g.) dissolved in ethylene glycol (13.3 cc.) and the whole was heated in oil bath at 128～138° for 45 min., until the evolution of N_2 almost ceased. After cool H_2O was added to the resulting reddish solution and repeatedly extracted with benzene. The benzene solution was washed with H_2O, dried, and evaporated leaving a red oily residue, which was dissolved in iso-Pr_2O, passed through Al_2O_3 column, and the solvent was removed from the effluent. A viscous yellow oily product (0.6 g.) thus obtained was directly used for the next hydrogenation. IR$_{(a)}$ $\nu_{max}^{capil.}$ cm^{-1} : 1650 (=NCOPh), 1620 (C=C). UV (EtOH) : No absorption maximum in 220～300 mμ region (Fig. 1).

1-Benzoyl-2-phenylpyrrolidine (XVIa)——A solution of the above-mentioned oil (XVa) (0.6 g.) in EtOH (35 cc.) was reduced over Adams Pt catalyst (0.16 g.), absorbing 62.4 cc. (105% of the theo. amt.) of H_2 at 27.2～28.5° in 80 min. The catalyst was removed by filtration and the filtrate was evaporated, leaving an oily residue, which was dissolved in warm hexane (70 cc.). A small amount of orange insoluble matter was filtered off, the filtrate was passed through Al_2O_3 column, and the solvent was removed from the effluent to afford a viscous faint yellow oil (0.56 g.), which did not crystallize and was used directly for the next reaction. IR$_{(a)}$ $\nu_{max}^{capil.}$ cm^{-1} : 1640 (=NCOPh).

2-Phenylpyrrolidine (XVIIa)——A suspension of the foregoing oil (XVIa) (0.405 g.) in 20% HCl (12cc.) was refluxed until a reddish violet homogeneous solution resulted (about 10 hr.) and the cooled solution was extracted once with Et_2O. The HCl solution was treated with charcoal, filtered, and the filtrate was evaporated *in vacuo*. The yellow residue was treated with 33% NaOH solution and the oil that separated was extracted with Et_2O. The Et_2O solution was washed with a small volume of satd. NaCl solution, dried over dehyd. Na_2SO_4, and Et_2O was evaporated to leave an oil, which on distillation yielded a colorless oil, b.p$_{14}$ 122～125° (bath temp.) (0.14 g., 42.2% from XIVa).
Picrate : Yellow pillars (from EtOH–iso-Pr_2O), m.p. 150.5～151.5°, which agreed with the one reported.[4] *Anal.* Calcd. for $C_{16}H_{16}O_7N_4$: C, 51.06; H, 4.29; N, 14.89. Found : C, 51.09; H, 4.23; N, 14.77.
Picrolonate : Yellow fine needles (from EtOH), m.p. 223～224° (decomp.), also agreed with the one reported.[4] *Anal.* Calcd. for $C_{20}H_{21}O_5N_5$: C, 58.38; H, 5.15, N, 17.03. Found : C, 58.60; H, 4.89; N, 17.21.

N-(4-Phenyl-3-butenyl)nicotinamide (VIIIb)——A mixture of 4-phenyl-3-butenylamine (VII) carbonate (9.4 g.) and ethyl nicotinate (7 g.) was heated in an oil bath at 190～200° for 15 hr. After cool, the product was converted into its hydrochloride and recrystallized three times from EtOH to (VIIIb) hydrochloride as colorless needles, m.p. 203～204° (6.3 g., 48.6%), which was raised to m.p. 204～205° by further purification. *Anal.* Calcd. for $C_{16}H_{17}ON_2Cl$: C, 66.54; H, 5.94; N, 9.70. Found : C, 66.47; H, 6.25; N, 9.79.
Picrate : Yellow needles (from MeOH), m.p. 158～159°. *Anal.* Calcd. for $C_{22}H_{19}O_8N_5$: C, 54.93; H, 3.99; N, 14.56. Found : C, 54.92; H, 4.35; N, 14.74.

The free base was recovered from its hydrochloride as colorless scales (from benzene-hexane), m.p. 110～111°. *Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 76.16; H, 6.38; N, 11.11. Found : C, 76.32; H, 6.21; N, 10.84. IR$_{(c)}$ ν_{max}^{Nujol} cm^{-1} : 3270, 1640, 1545 (amide), 967 (*trans* C=C), 707 (3-pyridyl). UV λ_{max}^{MeOH} mμ (log ε) : 253 (4.36), 284 (3.33), 293 (3.13).

2-(3-Pyridyl)-3-benzylidene-1-pyrroline (IXb)——a) The hydrochloride of finely powdered above amide (VIIIb) (2 g.) was mixed with $POCl_3$ (15 cc.) and the mixture was refluxed for 75 min. in an oil bath. Hexane was added to the cooled solution and the mixture was allowed to stand for several hours. The supernatant hexane layer was decanted and the residue was dissolved in ice-water and dil. HCl solution. After having been extracted once with benzene, HCl solution was basified with solid Na_2CO_3, the base liberated was extracted with benzene, the benzene layer was dried, and evaporated. The residue was again dissolved in benzene and the solution was purified by filtration through Al_2O_3, column. The product (IXb) was recovered from the filtrate as colorless pillars, m.p. 134～135° (1.1 g., 68%), the melting point of which was uneffected by purification from iso-Pr_2O. *Anal.* Calcd. for $C_{16}H_{14}N_2$: C, 82.12; H, 6.03; N, 11.97. Found : C, 82.04; H, 6.35; N, 11.68. IR$_{(c)}$ ν_{max}^{Nujol} cm^{-1} : 808 (-C=C<), 710 (3-pyridyl). UV λ_{max}^{MeOH} mμ (log ε) : 225 (4.09), 232 (4.09), 295 (4.40).
Dipicrate : Yellow needles (from 60% EtOH), m.p. 188～189° (decomp.). *Anal.* Calcd. for $C_{28}H_{20}O_{14}N_8$: C, 48.56; H, 2.91; N, 16.18. Found : C, 48.85; H, 3.30; N, 16.03.

b) The amine (VII) (2.7 g.) and nicotinic acid (2.26 g.) were dissolved in EtOH (20 cc.) by warming in steam bath, benzene was added to the solution, and EtOH was removed together with benzene by evaporation. The remaining crude amine nicotinate was mixed with $POCl_3$ (27 cc.) and the whole was refluxed for 1.75 hr. The cooled solution was worked up as in above (a) and the product was repeatedly recrystallized from iso-Pr_2O to (IXb) as colorless pillars, m.p. 134～135° (1.8 g., 41.8%), which was identified by mixed melting point test with the one obtained by method (a).

2-(3-Pyridyl)-3-benzylidenepyrrolidine (XIb)——A solution of the above pyrroline (IXb) (2.0 g.) in MeOH (30 cc.) acidified with AcOH (0.8 cc.), was reduced with $NaBH_4$ (1.2 g.) as above for (II) (2 hr. at room temp., then 1 hr. at 50°), and then worked up as the corresponding 2-phenyl derivative (XIa) to yield (XIb) as colorless needles, (from iso-Pr_2O), m.p. 89～90.5° (1.3 g., 64.5%), which was raised to m.p. 91～92° by further purification. *Anal.* Calcd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83; N, 11.86. Found:

C, 81.32; H, 6.83; N, 11.86. Found : C, 81.42; H, 7.01; N, 11.65. IR$_{(a)}$ ν_{max}^{Nujol} cm^{-1} : 3300 (NH), 1660 (C=C). UV λ_{max}^{MeOH} mμ (log ε) : 256 (4.40).

Hydrochloride : Colorless needles (from EtOH-Et$_2$O), m.p. 206.5~208°(decomp.). *Anal.* Calcd. for $C_{16}H_{18}N_2Cl_2 \cdot \frac{1}{4}H_2O$: C, 61.25; H, 5.94; N, 8.93. Found : C, 61.36; H, 6.06; N, 8.73.

1-Benzoyl derivative (XIIb) : The foregoing pyrrolidine (XIb) hydrochloride (5.4 g.) was benzoylated with BzCl (2.8 g.) and 4.8% NaOH solution by the usual method and yielded (XIIb) as colorless needles (from benzene-hexane), m.p. 106.5~108°(5.25 g., 89.6%), which melted at 106.5~107.5° after further recrystallization. *Anal.* Colcd. for $C_{23}H_{20}ON_2$: C, 81.52; H, 5.92; N, 8.23. Found : C, 81.21; H, 6.09; N, 8.19. IR$_{(a)}$ ν_{max}^{Nujol} cm^{-1} : 1630 (=NCOPh). UV λ_{max}^{MeOH} mμ (log ε) : 252 (4.47).

Ozone oxidation of (XIIb)——A solution of the above benzoylpyrrolidine (XIIb) (2.5 g.) in AcOH (60 cc. (was treated with O_2 stream (75 cc./min.) containing O_3 (5.46% by wt.), for 70 min., as above for (XIIIa), and the ozonized solution was reduced over 10% Pd-C (0.15 g.), absorbing 165 cc. of H_2 at 28° in 1 hr. On working up as above, a viscous yellow oily substance (1.8 g.) was obtained. IR$^{(a)}$ $\nu_{max}^{capil.}$ cm^{-1} : 1760 (5-membered ring C=O), 1635 (=NCOPh). This could not be obtained in a crystalline form, and was characterized as its tosylhydrazone (XIVb), of colorless needles (from ethylene glycol), m.p. 196°(decomp.). Yield, 1.45 g. (45.4% from XIIb). *Anal.* Calcd. for $C_{23}H_{22}O_3N_4S$: C, 63.57; H, 5.10; N, 12.90; S, 7.38. Found: C, 63.16; H, 5·30; N, 12.71; S, 7.39. IR$_{(a)}$ ν_{max}^{Nujol} cm^{-1} : 3210 (NH), 1622 (=NCOPh), 1340, 1168 (S-O).

1-Benzoyl-2-(3-pyridyl)-3-pyrroline (XVb)——The above-mentioned tosylhydrazone (XIVb) (2.5 g.) was mixed with Na (0.15 g.) dissolved in ethylene glycol (18 cc.) and the whole was heated at 130~140° for 45 min. The product was worked up as (XVa) and yielded a viscous yellow oily product (1.28 g.), which could not be induced to crystallize and was directly used for the next hydrogenation. IR$_{(\cdot)}$ $\nu_{max}^{capil.}$ cm^{-1} : 1645 (=NCOPh), 1620 (C=C). UV λ_{max}^{EtOH} mμ (ε_0)*5 : 255 (20.0), 261 (19.0), 268 (shoulder) (14.5) (Fig. 1).

Picrate : Yellow needles (from H_2O or MeOH), m.p. 199~200°. *Anal.* Calcd. for $C_{22}H_{17}O_8N_5$: C, 55.11; H, 3.57; N, 14.61. Found : C, 54.99; H, 3.88; N, 14.81.

This picrate (110 mg.) was decomposed by shaking vigorously with 6 *N* HCl (4 cc.) and the liberated picric acid was removed by extracting with Et$_2$O. When the HCl solution was basified, a viscous oil (51 mg.) was recovered, which proved to be the starting material by the IR spectrum and mixed melting point test of the picrate (m.p. 199~200°). N-(3-Nicotinoylpropyl)benzamide (XX) was not traced in the recovered substance.

1-Benzoyl-2-(3-pyridyl)pyrrolidine (XVIb)——The foregoing oil (XVb) (1.18 g.) in EtOH (20 cc.) was reduced over Adams Pt catalyst (0.07 g.), absorbing 110.6 cc. (95% of theo. amt.) of H_2 at 27~27.5° in 1.5 hr. On working up as for (XVIa), a viscous yellow oily product was obtained, which was dissolved in benzene and purified by filtration through Al_2O_3 column to give a viscous faint yellow oil (1.05 g.). IR$_{(a)}$ $\nu_{max}^{CCl_4}$ cm^{-1} : 1643 (=NCOPh). UV λ_{max}^{EtOH} mμ (ε_0)*5 : 252 (17.1), 262 (16.3), 268 (shoulder) (12.1) (Fig.1).

This oil could not be obtained in a crystalline form and was directly used for next debenzoylation.

Dipicrate : Yellow needles (from H_2O), m.p. 172~173°. *Anal.* Calcd. for $C_{22}H_{19}O_8N_5$: C, 54.88; H, 3.98; N, 14.55. Found : C, 55.31; H, 3.97; N, 14.32.

***rac*-Nornicotine (XVIIb)**——A solution of the above oil (XVIb) (1.0 g.) in 20% HCl (30 cc.) was refluxed for 6 hr. and worked up as above for (XVIIa) to yield (XVIIb) as a faint yellow oil, b.p$_3$ 105~107° (bath temp.) (0.43 g., 58% from XIVb). IR$_{(a)}$ $\nu_{max}^{CCl_4}$ cm^{-1} : 3300~3360 (NH), 716 (3-pyridyl).

Dipicrate : Yellow needles (from H_2O), m.p. 192~193°. *Anal.* Calcd. for $C_{21}H_{18}O_{14}N_8$: C, 41.59; H, 2.99; N, 18.48. Found : C, 41.63; H, 3.14; N, 18.45.

***rac*-Nicotine (XVIII)**——The above mentioned oil (XVIIb) (214 mg.) was dissolved in 80% formic acid (1 cc.) and 37% HCHO solution (0.16 cc.), and the solution was warmed at 75° for 10 min.; evolution of gas was observed. The temperature was then raised to 100~110° and maintained there for 3 hr. After cool, the excess of formic acid and HCHO solution was evaporated *in vacuo* and the residue was worked up as above for (XVIIb) to yield a colorless oil, b.p$_{5.5}$ 98~100°(bath temp.) (192 mg., 82%). IR$_{(a)}$ $\nu_{max}^{CCl_4}$ cm^{-1} : 2805 (=NCH$_3$), 717 (3-pyridyl).

Dipicrate : Long yellow needles (from H_2O), m.p. 224~225°. *Anal.* Calcd. for $C_{22}H_{20}O_{14}N_8$: C, 42.59; H, 3.25; N, 18.06. Found : C, 42.45; H, 3.16; N, 18.13.

This was proved to be identical with *rac*-nicotine dipicrate prepared by racemization of natural levorotatory-base by mixed melting point test.

Dipicrolonate : Yellow needles (from H_2O), m.p. 238°(decomp.). *Anal.* Calcd. for $C_{30}H_{30}O_{10}N_{10}$: C, 52.17; H, 4.38; N, 20.28. Found : C, 52.21; H, 4.20; N, 20.09.

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*5 ε_0 is the spectral density of a solution of 1 cm. thickness and concentration of g./L.

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Summary

A new synthesis of *rac*-nicotine was described. For this end the removal of the benzylidene group of 2-substituted 3-benzylidene-1-pyrroline prepared by Sugasawa and Ushioda was first examined. For the best effect, the starting materials ((I) : 2-methyl; (IXa) : 2-phenyl) were reduced by sodium borohydride and the reduction products were acylated to yield ((IIIa) : 1-acetyl-2-methyl; (IIIb) : 1-benzoyl-2-methyl; (XIIa) : 1-benzoyl-2-phenyl). These were cleaved via the corresponding ozonides to yield 3-pyrrolidinones, which were characterized appropriately.

This method was successfully extended to 2-(3-pyridyl)-3-benzylidene-1-pyrroline to afford 1-benzoyl-2-(3-pyridyl)-3-pyrrolidinone, whose tosylhydrazone was converted into 1-benzoyl-2-(3-pyridyl)-3-pyrroline according to the method of Bamford and Stevens.

The latter was reduced catalytically to *rac*-nornicotine, from which *rac*-nicotine was obtained smoothly by Eschweiler-Clark's method.

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129. Toshio Miyazaki : Studies on Fungal Polysaccharides. II.[*1] On the Componental Sugars and Partial Hydrolysis of the Capsular Polysaccharide from *Cryptococcus neoformans*.

(*Tokyo College of Pharmacy*[*2])

The preceding paper described some properties of the capsular polysaccharide isolated from *Cryptococcus neoformans* CRD-1 (Duke). In this paper, results on further investigations on the kinds of componental sugars, their molecular ratio, and partial hydrolysis of the capsular polysaccharide are described.

Table I. Rf values of the Componental Sugars

Substance \ Solvent system	(1)	(2)
D-Xylose	0.26	0.28
D-Mannose	0.17	0.20
D-Galactose	0.15	0.17
D-Glucuronic acid	0.12	0.14
Monosaccharide from Hydrolysate	0.26	0.28
	0.17	0.20
	0.12	0.14

Solvent system : (1) AcOEt-AcOH-H_2O (3:1:3).
(2) BuOH-AcOH-H_2O (4:1:5).
Detection by 3% *p*-anisidine-hydrochloride (BuOH) spray.

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*2 Kashiwagi 4-chome, Shinjuku-ku, Tokyo (宮崎利夫).