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Synthesis of 5-(Substituted Alkyl)picolinic Acids. The Dopamine β-Hydroxylase Inhibitors.[1] II

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The improved synthesis of 5-(4-chlorobutyl)picolinic acid (II), the potent dopamine β-hydroxylase inhibitor, was reported. The key intermediate, 2-cyclopropyl-5-cyclopropylcarbonylpyridine (IV) was converted to 5-(4-chlorobutyl)-2-cyclopropylpyridine (VII), which was directly oxidized with nitric acid to give II. Similarly, fusaric acid (I) was synthesized from 2-cyclopropyl-5-(cyclopropylhydroxy)methylpyridine (V).

Keywords——dopamine β-hydroxylase inhibitor; hypotensive agent; fusaric acid; 5-(4-chlorobutyl)picolinic acid; methyl cyclopropyl ketone; 2-cyclopropyl-5-cyclopropylcarbonylpyridine; oxidation with nitric acid

As described in the previous papers, 5-haloalkyl- and 5-branched-alkylpicolinic acids which were the homologues of fusaric acid (5-*n*-butylpicolinic acid, I), dopamine β-hydroxylase (DBH) inhibitor, were prepared from 2-methyl-5-vinylpyridine[1] and were evaluated their enzyme-inhibiting activity[3] and their hypotensive activity.[4] As a result, it was found that 5-(4-chlorobutyl)picolinic acid (II) was the most potent inhibitor of DBH and was ascertained to have a marked and sustained hypotensive action in spontaneously hypertensive rats by a single administration and in conscious dogs by repeated administrations. It was required to prepare a large amount of II in order to investigate the further pharmacological and toxicological actions. However, it was difficult to apply the synthetic method described in a previous paper to the synthesis of II in a large scale preparation. Thus, it was tried to develop the alternative route which could be operated more easily and less expensively. The present work deals with the improved synthesis of II.

After several methods had been attempted, it necessarily followed that the formation of 2,5-disubstituted pyridine nucleus from the acyclic intermediate was the most favorable. There are a number of the investigations about the formation of 2,5-disubstituted pyridines. For example, Hardegger, *et al.* reported 2-chlorovinyl propyl ketone reacted with 2-aminovinyl propyl ketone to afford 5-butyryl-2-propylpyridine.[5] However, 5-chlorobutyryl-2-chloropropylpyridine could not be obtained by this method. On the other hand, Benary, *et al.* reported that the sodium salt of formylacetone reacted with ammonium acetate in acetic acid to give 5-acetyl-2-methylpyridine.[6] If the 5-acetyl group could be replaced with any four carbon unit such as the cyclopropylcarbonyl group, the synthesis would progress favorably. Mariella, *et al.* reported that the sodium salt of β-hydroxyvinyl cyclopropyl ketone (III) reacted with

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[1] Part I: K. Miyano, T. Koshigoe, T. Sakasai, and H. Hamano, *Chem. Pharm. Bull.* (Tokyo), **25**, 1465 (1978).

[2] Location: *3-31, Shimo, Kita-ku, Tokyo, 115, Japan.*

[3] H. Umezawa, T. Takeuchi, K. Miyano, T. Koshigoe, and H. Hamano, *J. Antibiot.* (Tokyo), Ser. A, **26**, 189 (1973).

[4] *a*) Y. Ishii, Y. Fujii, Ch. Mimura, and H. Umezawa, *Arzneim-Forsch.* (Drug Res.), **25**, 55 (1975); *b*) Y. Ishii, K. Natsugoe, and H. Umezawa, *ibid.*, **25**, 213 (1975); *c*) Y. Ishii, M. Homma, A. Yoshikawa, and H. Umezawa, *ibid.*, **25**, 383 (1975); *d*) Y. Ishii, M. Homma, and A. Yoshikawa, *Neuropharmacology*, **14**, 155 (1975).

[5] E. Hardegger and E. Nikles, *Helv. Chim. Acta*, **40**, 1016 (1957).

[6] E. Benary and H. Psille, *Chem. Ber.*, **57**, 828 (1924).

cyanoacetamide to afford 3-cyano-6-cyclopropylpyridone-2.[7] Therefore, it was assumed that 2-cyclopropyl-5-cyclopropylcarbonyl pyridine (IV) would be obtained by the reaction of III with ammonium acetate, and both the cyclopropyl groups would be cleaved readily with an acid.

This idea was put into practice as follows.

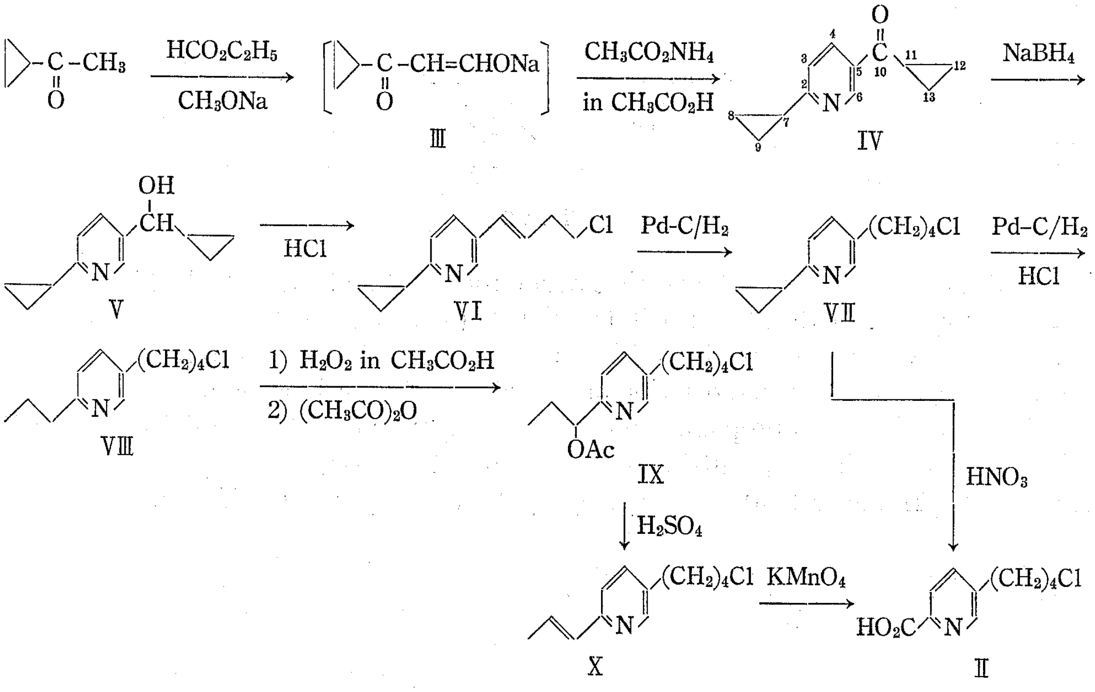

Chart 1

The sodium salt of III which was prepared by the reaction of methyl cyclopropyl ketone with ethyl formate in the presence of sodium methoxide reacted with ammonium acetate in acetic acid to give the key intermediate, 2-cyclopropyl-5-cyclopropylcarbonylpyridine (IV) in good yield. The structure of IV was confirmed on the basis of the infrared, mass, and ^{1}H- and ^{13}C-nuclear magnetic resonance spectral data. The ketone (IV) was reduced with sodium borohydride to give 2-cyclopropyl-5-(cyclopropyl-hydroxy)methylpyridine (V). The alcohol (V) was treated with concentrated hydrochloric acid at room temperature to afford 5-(4-chloro-1-buten-1-yl)-2-cyclopropylpyridine (VI), which was hydrogenated over palladium charcoal to afford 5-(4-chlorobutyl)-2-cyclopropylpyridine (VII). The cyclopropane ring of VII was not attacked with the Lewis acid or potassium permanganate, but was cleaved by hydrogenolysis over palladium charcoal to give 5-(4-chlorobutyl)-2-*n*-propylpyridine (VIII). The N-oxide prepared from VIII by oxidation with hydrogen peroxide was treated with acetic anhydride to yield 2-(α-acetoxypropyl)-5-(4-chlorobutyl)pyridine (IX), whcih was converted with concentrated sulfuric acid to 5-(4-chlorobutyl)-2-propenylpyridine (X). Although the olefin (X) was oxidized with potassium permanganate to yield the desired acid (II), this oxidative process seemed to be roundabout. The several experiments were tried in order to develop the more convenient method for the preparation of II from 2-cyclopropylpyridine derivative VII. It was found that VII was directly oxidized with nitric acid to afford II in good yield. This method could be applied to the synthesis of II in the large scale.

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[7] R.P. Mariella, L.F.A. Peterson, and R.C. Ferris, *J. Am. Chem. Soc.*, **70**, 1494 (1948).

Then we tried to synthesize fusaric acid (I) according to this method. Fusaric acid (I) was synthesized by the many workers,[5,8–14] but the new method in our hand gave more satisfactory result on the operation.

2-Cyclopropyl-5-(cyclopropyl-hydroxy)methylpyridine (V) was treated with hydrobromic acid at room temperature to yield 5-(4-bromo-1-buten-1-yl)-2-cyclopropylpyridine (XI). The olefin (XI) was hydrogenated over Raney nickel in a basic medium to afford 5-*n*-butyl-2-cyclopropylpyridine (XII), which was oxidized with nitric acid as described above to yield fusaric acid (I).

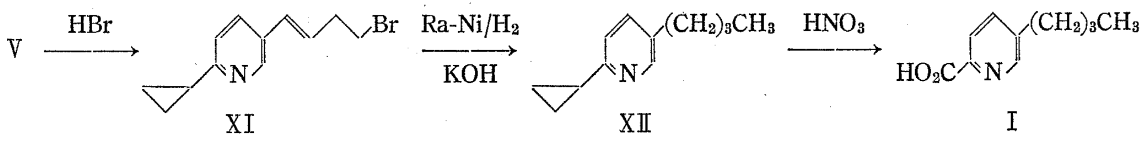

Chart 2

In the above study, it was shown that cyclopropylcarbinol was attacked by hydrochloric (or hydrobromic) acid to afford homoallylc chloride (or bromide), but the cyclopropane ring at the 2-position was not cleaved readily. This difference in the reactivity between the two cyclopropane rings shown by the reaction of 2-cyclopropyl-5-cyclopropylmethylpyridine(XIII) with nitric acid. The cyclopropane compound (XIII) prepared from IV by Huang-Minlon reduction reacted with 70% nitric acid at room temperature to give 2-cyclopropyl-5-carboxymethylpyridine (XIVa) and 2-cyclopropyl-5-carboxypyridine (XVa).

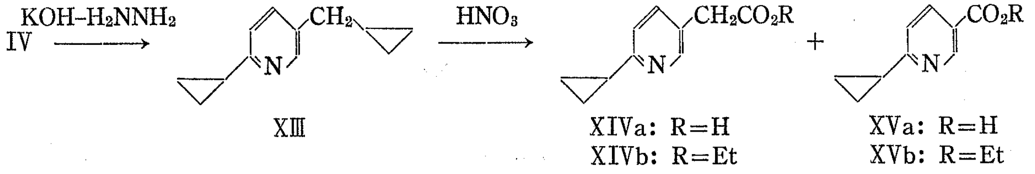

Chart 3

Experimental

All melting points were determined in a capillary and were uncorrected. Infrared (IR) spectra were recorded with JASCO IR-G spectrophotometer. Mass (MS) spectra were measured with Shimadzu-LKB 7000 spectrometer at 70 eV. Proton magnetic resonance (PMR) spectra were measured with Hitachi Perkin-Elmer R-20A spectrometer. Carbon magnetic resonance (CMR) spectra were measured with JEOL FX-60 spectrometer at 15.0 MHz in cubic tube. All signals were expressed by ppm downfield from tetramethylsilane used as an internal standard.

2-Cyclopropyl-5-cyclopropylcarbonylpyridine (IV)——To a suspension of sodium methoxide (62 g) in toluene (270 ml) was added dropwise a mixture of methyl cyclopropyl ketone[15] (84.1 g) and ethyl formate (77.6 g) at 25°. The reaction mixture was stirred at room temperature for 6 hr, and was added dropwise to a solution of ammonium acetate (250 g) in AcOH (300 ml) at 50°, and then was stirred at the same temperature for 20 hr. After cooling, the reaction mixture was poured into ice-water (1.5 l), and the aqueous solution

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8) Pl. A. Plattner, W. Keller, and A. Boller, *Helv. Chim. Acta*, **37**, 1379 (1954).

9) T. Nakashima, *Yakugaku Zasshi*, **75**, 1012 (1955); *Idem, ibid.*, **76**, 215 (1956).

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12) Yu. I. Chumakov and V.P. Sherstyuk, *Tetrahedron Lett.*, **1965**, 129.

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was basified with 6 N NaOH, and then the basic layer was extracted with ether. The ethereal solution was washed with H_2O, and dried over K_2CO_3. Ether was evaporated to give 72.6 g (77.8%) of crude IV as a solid. Recrystallization from light petroleum gave prisms, mp 51—52°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3100 (cyclopropane), 1660 (C=O), 1600 (Py[16]). MS *m/e*: 187 (M^+), 146 ($M^+ - C_3H_5$), 118 ($M^+ - CO - C_3H_5$). PMR ($CDCl_3$) δ: 0.90—1.55 (8H, m, $2 \times (C\underline{H}_2)_2CH-$), 2.00 (1H, m, $-COC\underline{H}(CH_2)_2$), 2.55 (1H, m, $(CH_2)_2C\underline{H}-Py$), 7.13 (1H, d, $J=8$ Hz, C_3-H), 8.00 (1H, dd, $J=2$ and 8 Hz, C_4-H), 8.95 (1H, d, $J=2$ Hz, C_6-H). CMR[17] ($CDCl_3$); 11.11 ($C_{12,13}$), 11.76 ($C_{8,9}$), 17.15 (C_{11}), 17.67 (C_7), 199.00 (C_{10}), 135.15 (C_4), 121.17 (C_3), 130.33 (C_5), 167.76 (C_2), 149.50 (C_6). *Anal.* Calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.66; H, 7.06; N, 7.40.

2-Cyclopropyl-5-(cyclopropyl-hydroxy)methylpyridine (V)——$NaBH_4$ (2.84 g) was added portionwise to a solution of IV (43.2 g) in isopropyl alcohol (iso-PrOH, 200 ml) containing 10 ml of MeOH at 60°. The stirring was continued at the same temperature for 3 hr. After the excess $NaBH_4$ was decomposed with AcOH (10 ml), iso-PrOH was evaporated under reduced pressure to give an oily residue, which was dissolved in H_2O and extracted with ether (100 ml × 3). The combined ethereal solution was treated as usual work to give an oily residue, which was distilled *in vacuo* to give V (42.0 g), $bp_{0.25}$ 113—115°. IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 3300 (OH), 3050 (cyclopropane), 1600 (Py). PMR ($CDCl_3$) δ: 0.3—0.7 (4H, m, $-CHOH-CH(C\underline{H}_2)_2$), 0.9—1.2 (5H, m, $-CHOH-C\underline{H}(CH_2)_2$ and $(C\underline{H}_2)_2CH-Py$), 1.8—2.25 (1H, m, $(CH_2)_2C\underline{H}-Py$), 3.30 (1H, br. s, $-OH$), 3.98 (1H, d, $J=8$ Hz, $-C\underline{H}OH$), 7.03 (1H, d, $J=8$ Hz, C_3-H), 7.61 (1H, dd, $J=2$ and 8 Hz, C_4-H), 8.38 (1H, d, $J=2$ Hz, C_6-H). CMR ($CDCl_3$) δ: 2.66 and 3.77 ($C_{12,13}$), 9.76 ($C_{8,9}$), 16.83 (C_{11}), 18.84 (C_7), 75.43 (C_{10}), 120.46 (C_4), 134.34 (C_3), 136.84 (C_5), 146.77 (C_2), 161.72 (C_6). *Anal.* Calcd. for $C_{18}H_{18}N_4O_8$: C, 51.68; H, 4.38; N, 13.39. Found: C, 51.96; H, 4.43; N, 13.70.

5-(4-Chloro-1-buten-1-yl)-2-cyclopropylpyridine (VI)——A solution of V (18.3 g) in toluene (40 ml) was added dropwise to 9 g of concentrated HCl at 20°. The reaction mixture was stirred at room temperature for 15 hr, and neutralized with 6 N NaOH at 15°. The organic layer was separated, and the aqueous solution was extracted with toluene (50 ml). The combined toluene solution was washed with H_2O, and dried (K_2CO_3). Toluene was evaporated under reduced pressure to give an oily residue (17.4 g). On distillation was obtained. VI (16.5 g), $bp_{0.2}$ 126—127°. IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 3100 (cyclopropane), 1665 (C=C), 1600 (Py) PMR ($CDCl_3$) δ: 0.77—1.10 (4H, m, $(C\underline{H}_2)_2CH-Py$), 1.75—2.10 (1H, m, $(CH_2)_2C\underline{H}-Py$), 2.61 (2H, sextet, $J=6$ and 7 Hz, $-CHC\underline{H}_2CH_2Cl$), 3.51 (2H, t, $J=7$ Hz, $-CH_2Cl$), 5.95 (1H, sextet, $J=6$ and 16 Hz, $-CH{=}C\underline{H}CH_2-$), 6.36 (1H, d, $J=16$ Hz, $Py-C\underline{H}{=}CH-$), 6.96 (1H, d, $J=8$ Hz, C_3-H), 7.43 (1H, dd, $J=2$ and 8 Hz, C_4-H), 8.33 (1H, d, $J=2$ Hz, C_6-H).

5-(4-Chlorobutyl)-2-cyclopropylpyridine (VII)——A solution of VI (15.3 g) in iso-PrOH (45 ml) was hydrogenated in an autoclave (initial H_2 pressure; 40 kg/cm^2 at 25°) over Raney-Ni (1 g) at 90—100° for 3 hr. The catalyst was filtered and iso-PrOH was evaporated under reduced pressure to give an oily residue, which was dissolved in ether (100 ml). The ethereal solution was washed with H_2O and dried (Na_2SO_4). Ether was evaporated to give crude VII, which was distilled *in vacuo* to give, $bp_{0.35}$ 105—107°. IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 3050 (cyclopropane), 1600 (Py). PMR ($CDCl_3$) δ: 0.8—1.10 (4H, m, $(C\underline{H}_2)_2CH-$), 1.40—2.10 (5H, m, $(CH_2)_2C\underline{H}-$ and $-CH_2CH_2-$), 2.55 (2H, t, $J=8$ Hz, $Py-CH_2-$), 3.50 (2H, t, $J=6$ Hz, $-CH_2Cl$), 6.97 (1H, d, $J=8$ Hz, C_3-H), 7.30 (1H, dd, $J=2$ and 8 Hz, C_4-H), 8.23 (1H, d, $J=2$ Hz, C_6-H). Picrate, mp 117—118°. *Anal.* Calcd. for $C_{18}H_{19}ClN_4O_7$: C, 49.26; H, 4.36; N, 12.77. Found: C, 49.10; H, 4.41; N, 12.77.

5-(4-Chlorobutyl)-2-propylpyridine (VIII)——A solution of VII (8.7 g) in EtOH (50 ml) containing 2.5 ml of concentrated HCl was hydrogenated in an autoclave (initial H_2 pressure: 50 kg/cm^2 at 25°) over 5% palladium charcoal (3 g) at 100° for 3 hr. After the usual work-up, an oily residue was distilled *in vacuo* to give VIII (6.96 g, 80%), $bp_{0.15}$ 90—92°. PMR ($CDCl_3$) δ: 1.90 (3H, t, $J=7$ Hz, $-CH_2C\underline{H}_3$), 1.37—1.96 (4H, m, $-CH_2CH_2-$), 1.65 (2H, m, $-C\underline{H}_2CH_3$), 2.32—2.77 (4H, m, $-C\underline{H}_2CH_2CH_3$, and $Py-C\underline{H}_2-$), 3.30 (2H, t, $J=6$ Hz, $-CH_2Cl$), 6.90 (1H, d, $J=8$ Hz, C_3-H), 7.26 (1H, dd, $J=2$ and 8 Hz, C_4-H), 8.27 (1H, d, $J=2$ Hz, C_6-H).

2-(α-Acetoxypropyl)-5-(4-chlorobutyl)pyridine (IX)——A solution of VIII (3.7 g) and 30% H_2O_2 (6 ml) in AcOH (20 ml) was heated with stirring at 70—80° for 3 hr, and furthermore, 3 ml of H_2O_2 was added. After the heating was continued at the same temperature for 9 hr, the solution was concentrated to one third of its original volume under reduced pressure. The residue was extracted with ether (30 ml × 3), and 10 g of anhydrous $CaCO_3$ was added to the extract to remove AcOH. Ether was evaporated to give a pale yellow oil (3.5 g). IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 1265 (N-oxide). This N-oxide was used to the next step without purification.

The above N-oxide was added dropwise to boiling acetic anhydride (40 ml). After the reaction mixture was refluxed for 20 min, acetic anhydride was evaporated under reduced pressure to give a dark brown oil, which was distilled *in vacuo* to give IX (3.6 g), $bp_{0.001}$ 121—122°. IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 1735 (ester C=O), 1230 (ester C–O–C). PMR ($CDCl_3$) δ: 0.89 (3H, t, $J=7$ Hz, $-CH_2C\underline{H}_3$), 1.6—2.15 (6H, m, $-C\underline{H}_2CH_3$ and $-C\underline{H}_2C\underline{H}_2-$), 2.06 (3H, s, $-OCOCH_3$), 2.55 (2H, t, $J=6$ Hz, $Py-CH_2-$), 3.45 (2H, t, $J=6$ Hz, $-CH_2Cl$), 5.60 (1H, t, $J=6$ Hz, $-CH_2CHOAc-$), 7.10 (1H, d, $J=8$ Hz, C_3-H), 7.36 (1H, dd, $J=2$ and 8 Hz, C_4-H), 8.25 (1H, d, $J=2$ Hz,

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16) Py: pyridyl radical. The numbering was shown in Chart 1.

17) All ^{13}C signals were assigned by means of single-frequency off-resonance decoupling techniques.

C_6–H). Styphnate, mp 95—96°. *Anal.* Calcd. for $C_{20}H_{25}ClN_4O_{10}$: C, 46.66; H, 4.50; N, 10.88. Found: C, 46.88; H, 4.59; N, 11.04.

5-(4-Chlorobutyl)-2-propenylpyridine (X)——To IX (24.8 g) was added dropwise concentrated H_2SO_4 (25 ml) with stirring at 15°. This mixture was stirred at 100° for 40 min, and then poured into ice-water (200 g). The aqueous solution was basified with aq. NH_3, and the basic substance was extracted with ether (50 ml × 3). The ethereal solution was treated as usual work to give V (15.4 g), $bp_{0.1}$ 115—117°. IR ν_{max}^{film} cm^{-1}: 1670 (C=C), 1600 (Py). PMR ($CDCl_3$) δ: 1.57—1.95 (4H, m, $-CH_2CH_2-$), 1.83 (3H, d, $J=5$ Hz, $-CHCH_3$), 2.55 (2H, t, $J=6$ Hz, Py–CH_2–), 3.43 (2H, t, $J=6$ Hz, $-CH_2Cl$), 6.32 (1H, d, $J=15$, $-C\underline{H}{=}CHCH_3$), 6.65 (1H, d of q, $J=5$ and 15 Hz, $-CH{=}C\underline{H}CH_3$), 7.00 (1H, d, $J=8$ Hz, C_3–H), 7.25 (1H, dd, $J=2$ and 8 H, C_4–H), 8.20 (1H, d, $J=2$ Hz, C_6–H).

5-(4-Chlorobutyl)picolinic Acid (II)——a) To a mixture of X (9.43 g) in H_2O (600 ml) was added dropwise a solution of $KMnO_4$ (19.0 g) in H_2O (600 ml) at 5—10° with vigorous stirring. The reaction mixture was stirred at the same temperature for 1 hr, and then at 50° for 30 min. The resulting MnO_2 was filtered, and washed with hot H_2O. The pH of the aqueous solution was adjusted to 5.2 with 2 N HCl, and the aqueous solution was concentrated under reduced pressure to give crude II as a solid. Recrystallization from ligroin gave II (5.76 g, 60%), mp 104—105°. The IR spectrum and TLC of II were identical with those of the authentic sample.

b) A solution of VII (34.0 g) in 70% HNO_3 ($d=1.42$, 175 ml) was added to 70% HNO_3 (87 ml) containing $NaNO_2$ (0.7 g) at 70° for 4 hr, and the stirring was continued at 80° for 15 hr. After cooling, the reaction mixture was poured into ice-water (200 ml). The pH of the aqueous solution was adjusted to 5.2 with 2 N HCl, and the aqueous solution was treated as described above to give crude II as a solid, which was recrystallized from ligroin to give II (28.1 g, 81%), mp 104—105°. The IR spectrum and TLC of II were identical with those of the authentic sample.

5-(4-Bromo-1-buten-1-yl)-2-cyclopropylpyridine (XI)——A solution of V (32.6 g) in toluene (40 ml) was added dropwise to 47% HBr (100 ml) with vigorous stirring at 20°. The reaction mixture was stirred at 20—30° for 3 hr to give the crystalline salt. The salt was filtered and the small amount of it was recrystallized from a mixture of ether and MeOH (3: 2) to give XI·HBr as prisms, mp 157—158°. *Anal.* Calcd. for $C_{12}H_{13}BrN$: C, 43.27; H, 4.54; N, 4.21. Found: C, 43.39; H, 4.51; N, 4.20.

The above salt was dissolved in 10% aq. NaOH at 20°, and the resulting base extracted with ether (100 ml × 3). The ethereal solution was treated as usual work to give oily XI (40.6 g, 93.7%). The crude XI was used to the next step without purification.

5-*n*-Butyl-2-cyclopropylpyridine (XII)——A mixture of XI (28.0 g), KOH (8 g), and Raney–Ni (prepared from 6 g of alloy) in EtOH (60 ml) was stirred at 80° under hydrogen atmosphere (20 kg/cm^2) for 1.5 hr. The reaction mixture was worked up as usual to give XII (18.9 g, 97%), bp_{17} 134—137°. PMR ($CDCl_3$) δ: 0.6—1.05 (7H, m, $-C\underline{H}_3$ and $-CH(C\underline{H}_2)_2$), 1.15—1.50 (4H, m, $-CH_2CH_2-$), 1.80 (1H, m, $-C\underline{H}(CH_2)_2$), 2.32 (2H, t, $J=6$ Hz, Py–CH_2–), 6.82 (1H, d, $J=8$ Hz, C_3–H), 7.10 (1H, dd, $J=2$ and 8 Hz, C_4–H), 8.12 (1H, d, $J=2$ Hz, C_6–H). Picrate, mp 111—112°. *Anal.* Calcd. for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99; N, 13.86. Found: C, 53.50; H, 4.97; N, 13.83.

5-*n*-Butylpicolinic Acid (I)——A solution of XII (17.5 g) in 70% HNO_3 (90 ml) was added dropwise to 70% HNO_3 (50 ml) at 70°. The reaction mixture was stirred at 80° for 18 hr, and treated in the same manner as described above to give I (14.2 g, 79%), mp 100—101°. The IR spectrum and TLC of I were identical with those of the authentic sample.

2-Cyclopropyl-5-cyclopropylmethylpyridine (XIII)——A solution of IV (13.5 g) in diethyleneglycol (150 ml) was heated at 125° with stirring for 2 hr. After adding potassium hydroxide pellets (14 g), the temperature was raised to 200° while the low-boiling material was azeotropically distilled off. The reaction mixture was stirred at the same temperature for 3 hr, and then was diluted with H_2O (200 ml). The above distillate was combined with the aqueous solution, and the organic layer was extracted with ether. The ethereal solution was treated as usual work to give colorless residue, which was distilled *in vacuo* to give XIII, bp_3 100—102°. PMR ($CDCl_3$) δ: 0.1—0.6 (4H, m, $CH_2CH(C\underline{H}_2)_2$), 0.8—1.0 (5H, m, $-CH_2C\underline{H}(CH_2)_2$ and $(C\underline{H}_2)_2CH$–Py), 1.85 (1H, m, $(CH_2)_2C\underline{H}$–Py), 2.35 (2H, d, $J=6$ Hz, Py–CH_2–), 6.90 (1H, d, $J=8$ Hz, C_3–H), 7.30 (1H, dd, $J=2$ and 8 Hz, C_4–H), 8.18 (1H, $J=2$ Hz, C_6–H). Picrate, mp 144—145°. *Anal.* Calcd. for $C_{18}H_{18}N_4O_7$: C, 53.55; H, 4.51; N, 13.93. Found: C, 53.91; H, 4.61; N, 14.01.

Oxidation of XIII with 70% HNO_3——A solution of XIII (2.173 g) in 20 ml of 70% HNO_3 was stirred at 25° for 72 hr. The reaction mixture was poured into ice-water (100 g). The pH of the aqueous solution was adjusted to 4.0, and the product was extracted with $CHCl_3$ (30 ml × 3). The $CHCl_3$ solution was treated as usual work to give a dark brown oil, which was dissolved in abs. EtOH saturated with gaseous HCl. The reaction mixture was allowed to stand at room temperature overnight, and was treated as usual work to give dark brown oil. IR ν_{max}^{film} cm^{-1}: 1735 and 1720 (ester, C=O). The crude ester was submitted to column chromatography on alumina. Elution with $CHCl_3$ gave XVb (0.585 g) and XIVb (0.189 g).

XVb: IR ν_{max}^{film} cm^{-1}: 1720 (ester C=O). PMR ($CDCl_3$) δ: 0.9—1.20 (4H, m, $(C\underline{H}_2)_2CH$–Py), 1.35 (3H, t, $J=7$ Hz, $-OCH_2C\underline{H}_3$), 2.03 (1H, m, $(CH_2)_2C\underline{H}$–Py), 4.30 (2H, q, $J=7$ Hz, $-C\underline{H}_2CH_3$), 7.10 (1H, d, $J=8$ Hz, C_3–H), 8.03 (1H, dd, $J=2$ and 8 Hz, C_4–H), 8.95 (1H, d, $J=2$ Hz, C_6–H). MS *m/e*: 191 (M^+), 190 (M^+-H), 162 ($M^+-C_2H_5$, base peak), 118 ($M^+-CO_2C_2H_5$). Picrate, mp 139—140°. *Anal.* Calcd. for $C_{17}H_{16}N_4O_9$: C, 48.57; H, 3.84; N, 13.33. Found: C, 48.68; H, 3.97; N, 13.40.

XIVb: IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1735 (ester, C=O). PMR ($CDCl_3$) δ: 0.9—1.15 (4H, m, $(C\underline{H}_2)_2CH$–Py). 1.20 (3H, t, $J=7$ Hz, $-OCH_2CH_3$), 2.0 (1H, m, $(CH_2)_2C\underline{H}$–Py), 3.47 (2H, s, Py–CH_2CO–), 4.07 (2H, q, $J=7$ Hz, $-OC\underline{H}_2CH_3$), 6.98 (1H, d, $J=8$ Hz, C_3–H), 7.40 (1H, dd, $J=2$ and 8, C_4–H), 8.25 (1H, d, $J=2$ Hz, C_6–H). MS *m/e*: 205 (M^+), 204 (M^+-H), 176 ($M^+-C_2H_5$), 132 ($M^+-CO_2C_2H_5$, base peak) Picrate, mp 124—125°. *Anal.* Calcd. for $C_{18}H_{18}N_4O_9$: C, 49.77; H, 4.18; N, 12.90. Found: 49.87; H, 4.20; N, 12.98.

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