Synthesis of 5-(Substituted Alkyl) Picolinic Acids, the Dopamine β -Hydroxylase Inhibitors. I¹⁾

KOICHI MIYANO, TAICHI KOSHIGOE, TAKEJI SAKASAI, and HIROAKI HAMANO

Research Laboratory, Pharmaceutical Division, Nippon Kayaku Co., Ltd.²⁾

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5-Haloalkyl or 5-branched alkyl picolinic acids, dopamine β -hydroxylase inhibitor were synthesized by the various methods. 2-Methyl-5-ethynyl pyridine (III) reacted with alkyl dihalide followed by hydrogenation to give 2-methyl-5-haloalkyl pyridine. III also reacted with ethylene oxide in the same manner to give 2-methyl-5-(4-hydroxybutyl)-pyridine, which was converted to halobutyl derivative. 2-Methylpyridine-5-aldehyde reacted with isoalkylidene phosphorane followed by hydrogenation to give 2-methyl-5-isoalkyl pyridines. These 2-methyl-5-(substituted alkyl)pyridines were oxidized *via* N-oxide and 2-acetoxymethyl compounds to 5-(substituted alkyl)picolinic acids.

Keywords—dopamine β -hydroxylase inhibitor; antihypertensive agents; N-oxide; C-acyloxylation; 5-isoalkylpicolinic acid; 5-(ω -haloalkyl)picolinic acids; fusaric acid

In 1969, Umezawa, *et al.* found that in the course of screening of fungus products, fusaric acid (I) inhibited dopamine β -hydroxylase (DBH), and showed the hypotensive effect in mice, rabbits, and dogs.³⁾ Moreover, it was reported by them that there was a correlation between the length of 5-alkyl group of picolinic acids and the activity inhibiting DBH.⁴⁾ Further modification of 5-alkyl group was of interest and carried out. In the previous paper, we reported the biological activity of 5-(substituted alkyl) picolinic acids *in vitro* (*cf.* Table I),⁵⁾ and Ishii, *et al.* reported that these acids decreased blood pressure in spontaneously hypertensive rats (SHR) and lowered endogeneous norepinephrine levels in the heart and brain of normotensive rats and SHR.⁶⁾ This paper deals with the synthesis of the 5-(substituted alkyl) picolinic acids.

(A) The Synthesis of 2-Methyl-5-haloalkyl- and 5-Isoalkyl Pyridines (V, VIIIb, d, XI, XIVb, XVIIb, XX)

Fusaric acid (I) and its homologues have the simple structure but the synthesis of them was not easy. Since I was first isolated by Yabuta,⁷⁾ the many synthetic methods were proposed,⁸⁾ but those methods could not be applied for the synthesis of 5-substituted alkyl

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TABLE I. Concentration of 5-(Substituted Alkyl)
Picolinic Acids for 50% Inhibition
of Dopamine β -Hydroxylase

	Alkyl chain	ID ₅₀ (M)
XXIIIa	-(CH ₂) ₄ Cl	4.3 × 10 ⁻⁹
XXIIIb	-(CH ₂) ₃ Cl	4.0 × 10 ⁻⁸
XXIIIc	-(CH ₂) ₅ Cl	4.6 × 10 ⁻⁹
XXIIId	-(CH ₂) ₆ Cl	1.35 × 10 ⁻⁸
XXIIIe	-(CH ₂) ₂ CHClCH ₃	6.9 × 10 ⁻⁹
XXIIIf	-(CH ₂) ₄ F	2.4 × 10 ⁻⁸
XXIIIg	-(CH ₂) ₅ F	1.5 × 10 ⁻⁸
XXIIIh	-CH ₂ CHMe ₂	1.29 × 10 ⁻⁸
XXIIIi	-(CH ₂) ₂ CHMe ₂	6.1 × 10 ⁻⁹
XXIIIj	-(CH ₂) ₃ Br	3.1 × 10 ⁻⁸
XXIIIk	-(CH ₂) ₄ Br	5.7 × 10 ⁻⁹
I	-(CH ₂) ₃ CH ₃	1.0 × 10 ⁻⁸

picolinic acids. 2-Methyl-5-vinylpyridine (II) is suitable for our purpose because it is commercially and inexpensively available. II was converted to more reactive 2-methyl-5-ethynylpyridine (III).⁹⁾ After III was treated with sodium amide in liquid ammonia, 1-bromo-3-chloropropane was added to a reaction mixture to give 2-methyl-5-(5-chloro pentyn-1-yl)-pyridine (IVa), which was hydrogenated over Raney-nickel to give 2-methyl-5-(5-chloro pentyl)pyridine (Va). Although 2-methyl-5-(6-chloro hexyl)pyridine (Vb) was obtained by treating above sodium acetylide (III-Na) with 1-bromo-4-chlorobutane followed by hydrogenation, the reaction of III-Na with 1-bromo-4-chloroethane did not give 2-methyl-5-(4-chloro butyn-1-yl)-pyridine (IVc). In the latter case it was supposed that the elimination reaction in 1-bromo-2-chloroethane might take preference to the substitution reaction. Then, it was tried to prepare 2-methyl-5-(4-chloro butyl)pyridine (VIIIb) in the alternative route. Sodium acetylide (III-Na) was treated with ethylene oxide in liquid ammonia followed by hydrogenation to give 2-methyl-5-(4-hydroxy butyl)pyridine (VII), which was converted to *p*-toluenesulfonyl ester and then was treated with lithium chloride in dimethylformamide (DMF) to give VIIIb. Similarly *p*-toluenesulfonyl ester of VII was treated with lithium bromide in DMF to give 2-methyl-5-(4-bromo butyl)pyridine (VIIIc). But the bromide (VIIIc) was unstable to decompose gradually at room temperature, and did not give the corresponding N-oxide in treatment with hydrogen peroxide in acetic acid (*vide infra*). Then, the alternative method was tried, *i.e.* mono *p*-toluenesulfonyl ester (Xa) of 2-hydroxymethyl-5-(4-hydroxy butyl)-pyridine (IX) prepared from N-oxide of VII was treated with lithium bromide in DMF to give 2-hydroxymethyl-5-(4-bromo butyl)pyridine (Xb) (*vide infra*). *p*-Toluenesulfonyl ester (VIIIa) reacted with potassium fluoride in diethyleneglycol to give 2-methyl-5-(4-fluoro butyl)pyridine (VIIIId). The chlorine atom of the alkyl side chain could be substituted by a fluorine atom. The chloride (Va) was heated with potassium fluoride in diethyleneglycol to give 2-methyl-5-(5-fluoro pentyl)pyridine (XI).

The elongation of the side chain in III was also achieved by the Grignard reaction. 5-(2-Methylpyridyl)ethynyl magnesium bromide (XII) prepared from III and ethylmagnesium bromide reacted with formaldehyde to give 2-methyl-5-(3-hydroxypropyn-1-yl)pyridine (XIII), which was hydrogenated to give 2-methyl-5-(3-hydroxypropyl)pyridine (XIVa). 2-Methyl-5-(3-chloro butyl)pyridine (XVIIb) was also obtained by the treatment of XII with acetaldehyde followed by hydrogenation and subsequent chlorination. 2-Hydroxymethyl-5-(3-

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Chart 1

Chart 2

bromo propylpyridine (XVb) was obtained from XIVa according to the procedure described for Xb.

Next, 2-methyl-5-isoalkyl pyridines were prepared. 2-Methylpyridine-5-aldehyde¹⁰⁾ prepared from II by ozonolysis reacted with isopropylidene phosphorane in dimethylsulfoxide (DMSO) followed by hydrogenation with palladium charcoal to give 2-methyl-5-isobutylpyridine (XXa). Similarly, 2-methyl-5-isopentylpyridine (XXb) was prepared.

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(B) The Synthesis of 5-(Substituted Alkyl) Picolinic Acids (XXIIIa–k)

It is known that picolinic acids are synthesized by the oxidation of 2-alkylpyridine with the various oxidizing methods.^{8,11)} We adopted the method of the oxidation of 2-hydroxymethyl-5-alkylpyridines prepared from 2-methyl-5-alkylpyridine N-oxides with potassium permanganate. Although this method was roundabout, the overall yield was relatively good and the operation of the reaction was suitable for the large scale. Thus, VIIb was oxidized with hydrogen peroxide in acetic acid at 80° to give 2-methyl-5-(4-chloro butyl)pyridine N-oxide (XXI, R=—C₄H₈Cl), which was added to boiling acetic anhydride to give 2-acetoxymethyl-5-(4-chloro butyl)pyridine (XXIIa, R=—C₄H₈Cl). After the acetate was hydrolyzed with hydrochloric acid, the resulting 2-hydroxymethyl compound (XXIIb, R=—C₄H₈Cl) was oxidized with potassium permanganate to give 5-(4-chloro butyl)picolinic acid (XXIIIa). The other 2-methyl compounds (XIVb, Va, Vb, XVIIb, XXa and XXb) were similarly oxidized to give the corresponding picolinic acids (XXIIIb–h, j, k). The acetoxymethyl group of the fluorinated alkyl compounds (XXIIa, R=—C₄H₈F, and —C₅H₁₀F) was hydrolyzed with base.

As described above, the bromide VIIc did not give the corresponding N-oxide. Then, we tried to convert 2-methyl group to the more oxidized state prior to bromination. 2-Methyl-

Chart 3

TABLE II. 5-(Substituted Alkyl) Picolinic Acids

Compd. No.	R	mp (°C)	Formula	Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
XXIIIa	—(CH ₂) ₄ Cl	104—105	C ₁₀ H ₁₂ ClNO ₂	56.21	5.66	6.56	56.37	5.71	6.57
XXIIIb	—(CH ₂) ₃ Cl	127—128	C ₉ H ₁₀ ClNO ₂	54.15	5.05	7.02	54.00	5.01	7.17
XXIIIc	—(CH ₂) ₅ Cl	113—114	C ₁₁ H ₁₄ ClNO ₂	58.03	6.02	6.15	58.21	6.23	6.19
XXIIId	—(CH ₂) ₆ Cl	103—104	C ₁₂ H ₁₆ ClNO ₂	59.63	6.67	5.80	59.55	6.58	6.02
XXIIIe	—(CH ₂) ₂ CHClCH ₃	114—115	C ₁₀ H ₁₂ ClNO ₂	56.21	5.60	6.56	56.09	5.63	6.72
XXIIIf	—(CH ₂) ₄ F	100—101	C ₁₀ H ₁₂ FNO ₂	60.90	6.13	7.10	60.67	6.11	7.34
XXIIIg	—(CH ₂) ₅ F	110—111	C ₁₁ H ₁₄ FNO ₂	62.54	6.68	6.63	62.66	6.59	6.58
XXIIIh	—CH ₂ CHMe ₂	127—128	C ₁₀ H ₁₃ NO ₂	67.02	7.31	7.82	67.32	7.37	8.14
XXIIIi	—(CH ₂) ₂ CHMe ₂	119—120	C ₁₁ H ₁₅ NO ₂	68.37	7.82	7.28	68.39	7.99	7.01
XXIIIj	—(CH ₂) ₃ Br	122—123	C ₉ H ₁₀ BrNO ₂	44.29	4.13	5.74	44.12	4.11	6.02
XXIIIk	—(CH ₂) ₄ Br	106—107	C ₁₀ H ₁₂ BrNO ₂	46.53	4.69	5.43	46.29	4.67	5.65

11) P.I. Pollak and M. Windholz, "Pyridine and its Derivatives," ed. by R.A. Abramovitch, John Wiley and Sons, Inc., New York, 1974, p. 268 and references therein.

5-(4-hydroxy butyl)pyridine N-oxide was treated with boiling acetic anhydride to give a mixture of 2-acetoxymethyl-5-(4-hydroxy butyl)pyridine and 2-acetoxymethyl-5-(4-acetoxybutyl)pyridine in a 1:1 ratio. 2-Hydroxymethyl-5-(4-hydroxy butyl)pyridine (IX) obtained from the above mixture was converted to the bromobutyl compound (Xa) as described above, which was oxidized cautiously with potassium permanganate to give 5-(4-bromobutyl)picolinic acid (XXIIIk). These 5-(substituted alkyl) picolinic acids are shown in Table II.

Experimental

All melting points were determined in a capillary and are uncorrected. Infrared (IR) spectra were recorded with JASCO IR-G spectrophotometer. Mass spectra were measured Shimadzu LKB 7000 Mass spectrometer (at 70 eV). Nuclear magnetic resonance (NMR) spectra were measured with JEOL C-60 HL spectrometer. All signals were expressed by the ppm downfield from tetramethylsilane used as an internal standard (value). Following abbreviations were used: singlet (s), doublet (d), double doublet (dd), triplet (t), multiplet (m), broad (br).

2-Methyl-5-(5-chloro pentyl)pyridine (Va)—Solution of Na (12.7 g) and $\text{Fe}(\text{NO}_3)_3$ (150 mg) in liquid NH_3 (600 ml) was added portionwise 2-methyl-5-ethynylpyridine (58.6 g, 0.5 mol) over a period of 30 min. After the reaction mixture was stirred for 3 hr, 1-bromo-3-chloropropane (157 g, 1.0 mol) was added dropwise. The reaction mixture was stirred for 4 hr, and then NH_3 was evaporated. The residue was treated with H_2O (500 ml), and acidified with 2N HCl. After the non-basic substance was extracted with ether, the aqueous layer was basified with aq. NH_3 . The base was extracted with ether (200 ml $\times$ 3) and dried over K_2CO_3 .¹² Ether was evaporated to give an oily residue (65 g), which was dissolved in MeOH (300 ml), and hydrogenated over Raney-Ni (W-7, 3 g) in an autoclave (H_2 pressure, 50 kg/cm²) at 30–50° for 2 hr. The catalyst was filtered and MeOH was evaporated under reduced pressure to give an oily residue. On distillation was, given 2-methyl-5-(5-chloro pentyl)pyridine (63 g, 65% based on III), bp_{0.5} 97–99°. MS m/e : 197 (M^+), 120 ($\text{M}^+ - (\text{CH}_2)_3\text{Cl}$), 106 ($\text{M}^+ - (\text{CH}_2)_4\text{Cl}$). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 2900, 1600, 1485 and 1025. NMR (CDCl_3) δ : 1.36–2.00 (6H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.48 (3H, s, $-\text{CH}_3$), 2.38–2.70 (2H, t, $J=6$ Hz, $\text{Py}-\text{CH}_2-$), 3.44 (2H, t, $J=6$ Hz, $-\text{CH}_2\text{Cl}$), 6.91 (1H, d, $J=8$ Hz, $\beta\text{-H}^{13}$), 7.27 (1H, dd, $J=2$ and 8 Hz, $\gamma\text{-H}$), 8.18 (1H, d, $J=2$ Hz, $\alpha'\text{-H}$). Picrate, mp 107–108°. Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{ClN}_4\text{O}_7$: C, 47.84; H, 4.49; N, 13.13. Found: C, 47.99; H, 4.46; N, 13.18.

2-Methyl-5-(6-chloro hexyl)pyridine (Vb)—a) III reacted with 1-chloro-4-bromobutane as described above for Va to give Vb (78%), bp_{0.09} 100–101°. Picrate, mp 110–111°. Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{ClN}_4\text{O}_7$: C, 49.04; H, 4.80; N, 12.71. Found: C, 48.86; H, 4.83; N, 12.99.

b) To wired Na (1.15 g) in dry tetrahydrofuran (THF, 10 ml) was added dropwise a solution of III (5.85 g) in THF (10 ml). The reaction mixture was refluxed for 5 hr, then 4-chlorobutanol *p*-toluenesulfonate (13 g) was added dropwise, and the reaction mixture was stirred under reflux for 2 hr, and poured in ice-water (50 ml). The organic layer was extracted with ether and treated as usual work to give Vb (57%), bp_{0.09} 101–105°.

2-Methyl-5-(4-hydroxybutyl)pyridine (VII)—a) To a mixture of $\text{Fe}(\text{NO}_3)_2$ (130 mg) and NaNH_2 (from 10.3 g of Na) in liquid NH_3 (500 ml) was added II (50 g). The reaction mixture was stirred for 2 hr, and well dried ethylene oxide (35 g) was introduced carefully, and then the reaction mixture was stirred for 20 hr. NH_4Cl (31 g) was added and NH_3 was evaporated. To a residue was added 200 ml of H_2O , and the organic layer was extracted with ether (100 ml $\times$ 3). The combined ethereal solution was washed with H_2O and dried (K_2CO_3). Ether was evaporated to afford an oil. This oil was dissolved in MeOH (40 ml) and hydrogenated over Ra-Ni (1.5 g) in an autoclave (H_2 pressure, 50 kg/cm²) at 30–50° for 2 hr, and the catalyst was filtered. MeOH was evaporated to give an oil. On distillation was given VII (28 g, 45%), bp_{0.08} 108–110°. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3250, 1600, 1485, 1060, 1030, 750. NMR (CDCl_3) δ : 1.40–1.95 (4H, m, $-\text{CH}_2\text{CH}_2-$), 2.35 (3H, s, $-\text{CH}_3$), 2.54 (2H, t, $J=6$ Hz, $\text{Py}-\text{CH}_2-$), 3.57 (2H, t, $J=6$ Hz, $-\text{CH}_2\text{OH}$), 4.60 (1H, br. s, $-\text{OH}$), 6.95 (1H, d, $J=8$ Hz, $\beta\text{-H}$), 7.35 (1H, dd, $J=2$ and 8 Hz, $\gamma\text{-H}$), 8.21 (1H, d, $J=2$ Hz, $\alpha'\text{-H}$). Styphnate, mp 113–114°. Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_9$: C, 46.83; H, 4.42; N, 13.65. Found: C, 46.59; H, 4.45; N, 13.33.

b) To a solution of $\text{C}_2\text{H}_5\text{MgBr}$ prepared from 5.28 g of ethyl bromide and 1.23 g Mg in 15 ml of ether was added dropwise a solution of III (5.15 g) in dry THF (50 ml). The reaction mixture was stirred at 50° for 4 hr, and cooled to -10° . Ethylene oxide (3.9 g) was introduced, and the reaction mixture was stirred at 0° for 4 hr, then allowed to stand at room temperature overnight. Usual work-up gave 0.4 g (6%) of VII.

2-Methyl-5-(4-chloro butyl)pyridine (VIIIb)—a) To a solution of *p*-toluenesulfonyl chloride (14 g) in pyridine (30 ml) was added dropwise VII (10 g) at -5 – 0° , and the reaction mixture was stirred at the same temperature for 3 hr, and poured into ice-water. The organic layer was extracted with CHCl_3 (30 ml $\times$ 4).

12) This procedure for extraction of base was generally used in the following experiments.

13) $\alpha'\text{-H}$, $\beta\text{-H}$, and $\gamma\text{-H}$ stand for the protons on the pyridine nucleus.

The chloroform solution was treated as usual work to afford brown oil. This oil and LiCl (7.7 g) were dissolved in DMF (80 ml), and the reaction mixture was stirred at 60° for 4 hr, and poured into ice-water (200 ml). The organic layer was extracted with ether. The ethereal solution was treated as usual work to afford the brown oil, which was distilled *in vacuo* to afford VIIIb as colorless oil (6.8 g, 67%) bp_{0.15} 80°. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 2850, 1600, 1485, 1025, 820. NMR (CDCl₃) δ : 1.45—1.95 (4H, m, -CH₂CH₂-), 2.46 (3H, s, -CH₃), 2.53 (2H, t, J =5 Hz, Py-CH₂-), 3.43 (2H, t, J =6 Hz, -CH₂Cl), 7.02 (1H, d, J =8 Hz, β -H), 7.35 (1H, dd, J =2 and 8 Hz, γ -H), 8.30 (1H, d, J =2 Hz, α' -H). Picrate, mp 114—115°. Anal. Calcd. for C₁₆H₁₇ClN₄O₇: C, 46.56; H, 4.15; N, 13.57. Found: C, 46.40; H, 4.18; N, 13.74.

b) To a solution of *p*-toluenesulfonyl chloride (14 g) in pyridine was added dropwise VII (10 g) at 0°, and the reaction mixture was stirred at room temperature for 60 hr. After the reaction mixture was treated as usual work, VIIIb (6.0 g) was isolated.

2-Methyl-5-(4-fluoro butyl)pyridine (VIIIId)—To a solution of *p*-toluenesulfonyl chloride (2.92 g) in dry pyridine (10 ml) was added dropwise (5 ml) with stirring at -15—-10°. The stirring was continued at the same temperature for 3 hr. The reaction mixture was poured into ice-water (30 ml), the product was extracted with ether (30 ml $\times$ 3), and the combined ethereal solution was treated as usual work to give rose-colored oil (3.44 g). In IR spectrum of this oil, the signal of hydroxyl group disappeared. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1335 and 1170. A mixture of above oil (3.3 g) and KF (3.2 g) in diethyleneglycol (20 g) was heated with stirring at 100° for 15 hr. After cooling, 30 ml of H₂O was added, and the product was extracted with ether (50 ml $\times$ 4). The ethereal solution was treated as usual work to afford an oil, which was distilled *in vacuo* to afford 1.07 g of VIIIId, bp_{0.85} 74°. Picrate, mp 122—123°. Anal. Calcd. for C₁₆H₁₇FN₄O₇: C, 48.48; H, 4.32; N, 14.14. Found: C, 48.22; H, 4.28; N, 14.39. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1600, 1475, 1050. NMR (CDCl₃) δ : 1.20—2.10 (4H, m, -CH₂CH₂-), 2.50 (3H, s, -CH₃), 2.63 (2H, t, J =8 Hz, Py-CH₂-), 4.02 (1H, t, J =6 Hz, -CH₂F), 4.83 (1H, t, J =6 Hz, -CH₂F), 7.04 (1H, d, J =8 Hz, β -H), 7.40 (1H, dd, J =2 and 8 Hz, γ -H), 8.37 (1H, d, J =2 Hz, α' -H).

2-Methyl-5-(5-fluoro pentyl)pyridine (XI)—A mixture of Va (6.64 g) and KF (3.0 g) in diethyleneglycol (25 ml) was heated at 130—135° with stirring for 25 hr, and treated as the same manner described for the preparation of VIIIId to give XI (2.38 g) as colorless oil, bp_{0.2} 68—70°. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1600, 1485, 1390, 1025. NMR (CDCl₃) δ : 1.21—2.15 (6H, m, -CH₂CH₂CH₂-), 2.50 (3H, s, -CH₃), 2.65 (2H, t, J =8 Hz, Py-CH₂-), 4.03 (1H, t, J =6 Hz, -CH₂F), 4.85 (1H, t, J =6 Hz, -CH₂F), 7.05 (1H, d, J =8 Hz, β -H), 7.40 (1H, dd, J =2 and 8 Hz, γ -H), 8.37 (1H, d, J =2 Hz, α' -H).

2-Methyl-5-(3-hydroxy butyl)pyridine (XVIIa)—To a solution of ethylmagnesium bromide prepared from ethyl bromide (6.24 g) and Mg (1.46 g) in dry THF (10 ml) was added dropwise a solution of III (6.10 g) in dry THF (45 ml) under ice-cooling. A solution of acetaldehyde which was depolymerized from paraldehyde (3.4 g) with *p*-toluenesulfonic acid (0.1 g), in dry THF (15 ml) was added dropwise to the above Grignard solution at -10—-15°, and was stirred at -5° for 1 hr. After the addition of the saturated solution of NH₄Cl (20 ml), the product was extracted with ether (50 ml $\times$ 3), the combined ethereal solution was treated as usual work. The resulting crude 2-methyl-5-(3-hydroxy butyl)pyridine (XVI, 7.5 g) was dissolved in 30 ml of MeOH, hydrogenated over Ra-Ni (1 g) at 50° in an autoclave (H₂ pressure: 50 kg/cm²) for 2 hr. The reaction mixture was worked up as usual to afford XVIIa (6.1 g), bp_{0.2} 101°. NMR (CDCl₃) δ : 1.22 (3H, d, J =6 Hz, -CH₃), 1.50—1.90 (2H, m, -CH₂CHOH), 2.48 (3H, s, CH₃-Py), 2.68 (2H, t, J =7 Hz, Py-CH₂-), 3.51 (1H, s, OH), 3.5—4.0 (1H, m, -CHOH-), 6.97 (1H, d, J =8 Hz, β -H), 7.34 (1H, dd, J =2 and 8 Hz, γ -H), 8.24 (1H, d, J =2 Hz, α' -H). Picrate, mp 148—149°. Anal. Calcd. for C₁₆H₁₈N₄O₈: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.39; H, 4.62; N, 14.53.

2-Methyl-5-(3-chloro butyl)pyridine (XVIIb)—A mixture of above oil (5.49 g) and *p*-toluenesulfonyl chloride (7.0 g) in dry pyridine (23 ml) was stirred at 40° for 10 hr, and then was worked up as usual manner to give red-brown oil. This oil was distilled *in vacuo* to give colorless XVIIb (3.6 g, 60%), bp_{0.2} 72—75°. NMR (CDCl₃) δ : 1.50 (3H, d, J =8 Hz, -CHCH₃), 1.80—2.10 (4H, m, -CH₂CH₂-), 2.49 (3H, s, CH₃-Py), 2.59 (2H, t, J =9 Hz, Py-CH₂-), 3.90 (1H, m, -CH₂CHCH₃), 6.90 (1H, d, J =8 Hz, β -H), 7.30 (1H, dd, J =2 and 8 Hz, γ -H), 8.25 (1H, d, J =2 Hz, α' -H). Picrate, mp 131—132°. Anal. Calcd. for C₁₆H₁₇ClN₄O₇: C, 46.56; H, 4.15; N, 13.57. Found: C, 46.36; H, 4.12; N, 13.83.

2-Methyl-5-(3-hydroxy propyl)pyridine (XIVa)—The reaction of III (11.7 g) with ethylmagnesium bromide followed by formaldehyde in the manner described for XVIIa gave a solid. Recrystallization from ether to give XIII, mp 92—93°. Anal. Calcd. for C₉H₉NO: C, 73.45; H, 7.53; N, 9.52. Found: C, 73.32; H, 7.50; N, 9.71.

This unsaturated compound was hydrogenated in the manner as described for XVIIa to give XIVa, bp_{0.25} 104—107°. Picrate, mp 127—128°. Anal. Calcd. for C₁₅H₁₆N₄O₈: C, 47.37; H, 4.24; N, 14.73. Found: C, 47.06; H, 4.11; N, 14.89.

2-Methyl-5-(3-chloro propyl)pyridine (XIVb)—XIVa (4.08 g) was reacted with *p*-toluenesulfonyl chloride (5.15 g) in dry pyridine (15 ml) as described for the synthesis of XVIIb gave XIVb (3.10 g), bp_{0.6} 84—87°. NMR (CDCl₃) δ : 2.07 (2H, m, -CH₂CH₂Cl), 2.50 (3H, s, -CH₃), 2.73 (2H, t, J =6 Hz, Py-CH₂-), 3.49 (2H, t, J =6 Hz, -CH₂Cl), 7.07 (1H, d, J =8 Hz, β -H), 7.36 (1H, dd, J =2 and 8 Hz, γ -H), 8.33 (1H, d, J =2 Hz, α' -H). Picrate, mp 137—138°. Anal. Calcd. for C₁₆H₁₅ClN₄O₇: C, 45.18; H, 3.79; N, 14.05. Found: C, 44.92; H, 3.69; N, 14.33.

2-Hydroxymethyl-5-(4-hydroxy butyl)pyridine (IX)—A mixture of VII (9.85 g) and 30% H_2O_2 (6 ml) in glacial acetic acid (36 ml) was heated at 70–80° with stirring for 3 hr, and the further H_2O_2 (36 ml) was added. The reaction mixture was heated at the same temperature for 9 hr, and was concentrated to one third of its original volume under reduced pressure. 70 ml of H_2O was added, and the solution was concentrated again to one third of its original volume under reduced pressure. The residue was extracted with CHCl_3 (50 ml $\times$ 3). To the CHCl_3 solution was added anhydrous K_2CO_3 (20 g) to remove AcOH , and CHCl_3 was evaporated under reduced pressure to give pale yellow viscous oil (10.35 g). GLC–Mass analysis showed the product was a mixture of 2-methyl-5-(4-hydroxy butyl)pyridine N-oxide and 2-methyl-5-(4-acetoxy-*n*-butyl)pyridine N-oxide (ratio was *ca.* 1:1). This mixture was dissolved in 10 ml of acetic anhydride. The solution was added dropwise to boiling acetic anhydride (15 ml), and the reaction mixture was refluxed for 20 min. Acetic anhydride was evaporated under reduced pressure to give dark brown oil. To a solution of this oil in MeOH (100 ml) was added 10% aq. NaOH and the reaction mixture was stirred at room temperature for 3 min. MeOH was evaporated under reduced pressure. The product was extracted with CHCl_3 (60 ml $\times$ 5). The CHCl_3 solution was treated as usual work to give crude IX as a solid. Analytical sample was recrystallized from acetone, mp 54–55°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3300, 1600, 1020. NMR (CDCl_3) δ : 1.35–1.75 (4H, m, $-\text{CH}_2\text{CH}_2-$), 2.52 (2H, t, $J=6$ Hz, $\text{Py}-\text{CH}_2-$), 3.52 (2H, t, $J=6$ Hz, $-\text{CH}_2\text{OH}$), 4.60 (2H, s, $-\text{CH}_2\text{OH}$), 4.77 (2H, s, $\text{OH} \times 2$), 7.17 (1H, d, $J=8$ Hz, β -H), 7.37 (1H, dd, $J=2$ and 8 Hz, γ -H), 8.12 (1H, $J=2$ Hz, α' -H). Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{NO}_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.13; H, 8.32; N, 8.01.

2-Hydroxymethyl-5-(4-bromo butyl)pyridine (Xb)—To a solution of *p*-toluenesulfonyl chloride (1.07 g) in dry pyridine (2 ml) was added a solution of XVa (0.92 g) in dry pyridine (2 ml) at -10° . The reaction mixture was stirred at the same temperature for 3 hr, and worked up as usual manner to give monotosylate (Xa, 1.06 g). A solution of this ester and LiBr (2.4 g) in DMF (10 ml) was stirred at 40° for 19 hr, and treated as usual manner to give XVb (0.46 g) as an oil. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3200, 1600, 1060. NMR (CDCl_3) δ : 1.60–2.15 (4H, m, $-\text{CH}_2\text{CH}_2-$), 2.63 (2H, t, $J=8$ Hz, $\text{Py}-\text{CH}_2-$), 3.36 (2H, t, $J=8$ Hz, $-\text{CH}_2\text{Br}$), 4.66 (2H, s, HOCH_2-Py), 4.48 (1H, s, $-\text{OH}$), 7.24 (1H, d, $J=8$ Hz, β -H), 7.47 (1H, dd, $J=2$ and 8 Hz, γ -H), 8.28 (1H, d, $J=2$ Hz, α' -H).

2-Hydroxymethyl-5-(3-bromo propyl)pyridine (XVb)—The title compound was prepared according to the procedure for the synthesis of Xb from XIVa as an oil. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3300, 1600, 1060. NMR (CDCl_3) δ : 2.05 (2H, m, $-\text{CH}_2-$), 2.70 (2H, t, $J=6$ Hz, $\text{Py}-\text{CH}_2-$), 3.53 (2H, t, $J=6$ Hz, $-\text{CH}_2\text{Br}$), 7.20 (1H, d, $J=8$ Hz, β -H), 7.40 (1H, dd, $J=2$ and 8 Hz, γ -H), 8.25 (1H, d, $J=2$ Hz, α' -H).

This compound was unstable and was used for the next step without purification.

2-Methyl-5-isobutylpyridine (XXa)—Triphenylisopropylidene phosphorane was prepared from NaH (0.6 g, in mineral oil, content, 50%) and isopropyltriphenyl phosphonium bromide (22.0 g) in DMSO (120 ml).¹⁴ To this solution was added dropwise a solution of 2-methylpyridine-5-aldehyde (6.0 g) in DMSO (15 ml) at 20–25°. The reaction mixture was stirred at 40° for 30 min, and the product was extracted with *n*-hexane (50 ml $\times$ 3). *n*-Hexane was evaporated, and the residue was distilled *in vacuo* to give XIXa (4.4 g), bp₂₀ 115°. GS–MS, m/e 147 (M^+). This base (3.0 g) was hydrogenated in MeOH (30 ml) containing AcOH (2 ml) over 5% Pd–C (1 g) in an autoclave (H_2 pressure, 20 kg/cm²) at 60–70° for 6 hr. Usual work-up gave XXa, bp₂₀ 105–107°. NMR (CDCl_3) δ : 0.89 (6H, d, $J=7$ Hz, $-\text{CH}(\text{CH}_3)_2$), 1.33–2.10 (1H, m, $-\text{CH}-$), 2.35 (2H, d, $J=6$ Hz, $-\text{CH}_2-$), 2.40 (3H, s, CH_3-Py), 6.77 (1H, d, $J=8$ Hz, β -H), 7.10 (1H, dd, $J=2$ and 8 Hz, γ -H), 8.05 (1H, d, $J=2$ Hz, α' -H).

2-Methyl-5-isopentylpyridine (XXb)—XVIII (3.63 g) reacted with triphenyl isobutylidene phosphorane prepared from 12 g of triphenylisobutylphosphonium bromide in DMSO (100 ml) followed by hydrogenation as described for the synthesis of XXa gave XXb (2.72 g, 60%), bp₁₅ 93–96°. NMR (CDCl_3) δ : 0.93 (6H, d, $J=5$ Hz, $-\text{CH}(\text{CH}_3)_2$), 1.30–1.60 (3H, m, $-\text{CH}_2\text{CH}-$), 2.38 (3H, s, CH_3-Py), 2.46 (2H, t, $J=7$ Hz $\text{Py}-\text{CH}_2-$), 6.83 (1H, d, $J=8$ Hz, β -H), 7.12 (1H, dd, $J=2$ and 8 Hz, γ -H), 8.05 (1H, d, $J=2$ Hz, α' -H).

5-(4-Chloro butyl)picolinic Acid (XXIIIa)—To a solution of VIIIb (8.2 g) in AcOH (40 ml) was added 12 ml of 30% H_2O_2 . The reaction mixture was heated with stirring at 70–80° for 3 hr, and further 5 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. Fifty ml of H_2O was added to the residue, and the solution was concentrated again to one third of its original volume under reduced pressure. The residue was extracted with ether (30 ml $\times$ 3), and 10 g of anhydrous CaCO_3 was added to the extract to remove AcOH. Ether was evaporated to give pale yellow oil (8.9 g). This N-oxide was used to the next step without purification.

A solution of the above N-oxide in AcOH (15 ml) 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 dark brown oil. This oil was refluxed with 50 ml of conc. HCl for 3 hr. The reaction mixture was concentrated under reduced pressure and basified with aq. NH_3 . The basic product was extracted with ether (50 ml $\times$ 3), and the ethereal solution was washed with H_2O and dried over K_2CO_3 . Ether was evaporated to give 2-hydroxymethyl-5-(4-chloro butyl)pyridine (XXIIb, 5.22 g, 58%). Picrate, mp 82–83°.

14) U.H.M. Fagerlund and D.R. Idler, *J. Am. Chem. Soc.*, **79**, 6473 (1957).

Anal. Calcd. for $C_{16}H_{17}ClN_4O_3$: C, 44.82; H, 4.00; N, 13.07. Found: C, 44.76; H, 4.02; N, 13.37. NMR (free base, $CDCl_3$) δ : 1.60–1.85 (4H, m, $-CH_2CH_2-$), 2.57 (2H, t, $J=6$ Hz, $Py-CH_2-$), 3.45 (2H, t, $-CH_2Cl$), 4.17 (1H, s, $-OH$), 4.62 (2H, s, $HOCH_2-Py$), 7.10 (1H, d, $J=8$ Hz, $\beta-H$), 7.42 (1H, dd, $J=2$ and 8 Hz, $\gamma-H$), 8.24 (1H, d, $J=2$ Hz, $\alpha'-H$).

To a solution of the above alcohol (2.22 g) in H_2O (30 ml) was added dropwise a solution of $KMnO_4$ (2.58 g) in H_2O (100 ml) at $5-10^\circ$ with vigorous stirring, then the reaction mixture was stirred at the same temperature for one hr, and at 50° for 30 min. MnO_2 was filtered, and washed with hot H_2O . The aqueous solution was concentrated under reduced pressure. The unreacted substance was removed by extraction with ether. pH of the aq. layer was adjusted to 5.2 with 2 N HCl, and the product was extracted with $CHCl_3$ (70 ml $\times$ 3). $CHCl_3$ was evaporated under reduced pressure to give crude XXIIIa as a solid. Recrystallization from ligroin gave XXIIIa (1.55 g, 65%), mp $104-105^\circ$. NMR ($CDCl_3$) δ : 1.67–2.02 (4H, m, $-CH_2-CH_2-$), 2.76 (2H, t, $J=6$ Hz, $Py-CH_2-$), 3.50 (2H, t, $J=6$ Hz, $-CH_2Cl$), 7.63 (1H, dd, $J=2$ and 8 Hz, $\beta-H$), 8.07 (1H, d, $J=8$ Hz, $\gamma-H$), 8.57 (1H, d, $J=2$ Hz, $\alpha'-H$), 11.97 (1H, s, $-COOH$). Methyl ester was prepared by the Fischer's method. MS m/e : M^+ was not observed, 197 (M^+-OCH_3), 169 ($M^+-COOCH_3$). *Anal.* Calcd. for $C_{16}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.37; H, 5.71; N, 6.57.

5-(4-Bromo butyl)picolinic Acid (XXIIIk)—To a solution of Xb (0.46 g) in H_2O (3 ml) was added a solution of $KMnO_4$ (0.70 g) in H_2O (25 ml) at 0° , and was treated as described for the synthesis of XXIIIa to give crude XXIIIk (0.21 g). Recrystallization of a mixture of *n*-hexane and ligroin gave a pure XXIIIk, mp $106-107^\circ$. *Anal.* Calcd. for $C_{10}H_{12}BrNO_2$: C, 46.53; H, 4.69; N, 5.43. Found: C, 46.29; H, 4.67; N, 5.65.

5-(5-Fluoro pentyl)picolinic Acid (XXIIIg)—XXIIa ($R=-(CH_2)_5F$, 2.03 g) prepared from XI (1.86 g) as described for the synthesis of XXIIIa was dissolved in MeOH (10 ml) containing 10% aq. NaOH (10 ml). The reaction mixture was allowed to stand at room temperature for 2 hr, and worked up as usual manner. The resulting XXIIb ($R=-(CH_2)_5F$, 1.75 g) was oxidized with $KMnO_4$ (1.95 g) as described for the synthesis of XXIIIa to give XXIIIg (1.35 g), mp $110-111^\circ$. *Anal.* Calcd. for $C_{11}H_{14}FNO_2$: C, 62.54; H, 6.68; N, 6.63. Found: C, 62.66; H, 6.59; N, 6.58.

The other picolinic acids prepared as described for the synthesis of XXIIIa, XXIIIg or XXIIIk are listed in Table II.

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