

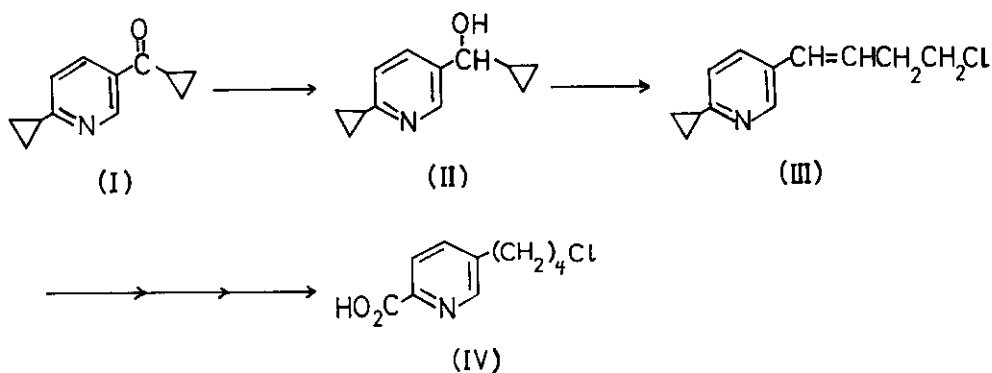
SYNTHESIS OF 5-(SUBSTITUTED ALKYL)PICOLINIC ACIDS, THE DOPAMINE
 β -HYDROXYLASE INHIBITORS. III

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Abstract - Several 5-alkylpicolinic acids, dopamine β -hydroxylase inhibitors were synthesized from 2-cyclopropyl-5-cyclopropylcarbonylpyridine (I) as a suitable starting material.

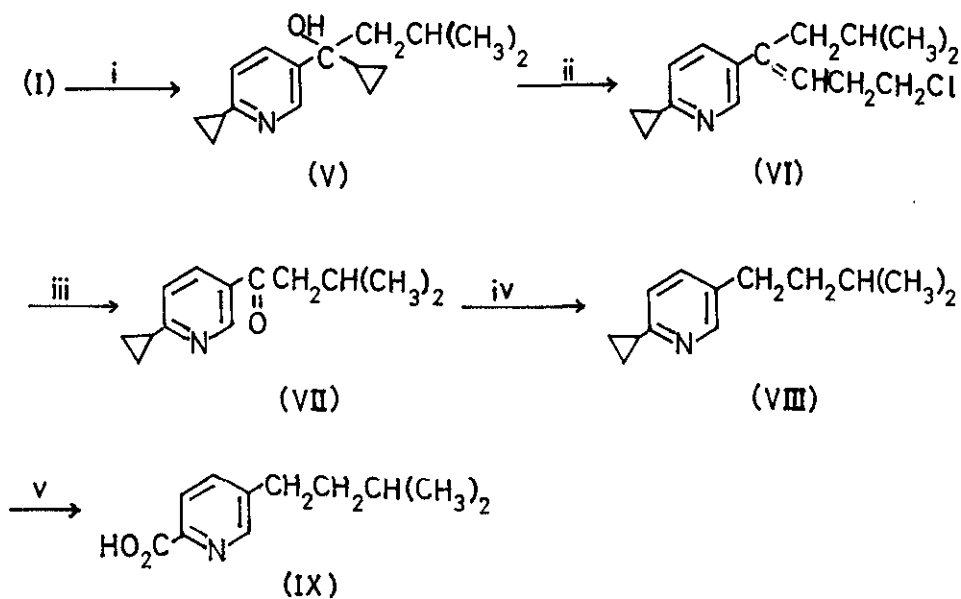
In the previous papers¹⁾, the synthesis of 5-(4-chlorobutyl)picolinic acid (IV), which was potent inhibitor of dopamine β -hydroxylase was described as shown in Scheme I.



Scheme I

Although fusaric acid and 5-haloalkylpicolinic acids have been synthesized by various methods as described in the previous papers¹⁾ and references²⁾, we tried to develop their general synthetic method. This paper deals with a general method of synthesis of 5-alkylpicolinic acids in which the starting material is 2-cyclopropyl-5-cyclopropylcarbonylpyridine (I). The synthesis of 5-isopentylpicolinic acid is illustrated in Scheme II.

2-Cyclopropyl-5-cyclopropylcarbonylpyridine (I) reacted with isobutyllithium in tetrahydrofuran (THF) at -20° to afford the alcohol (V, picrate, mp $171-172^{\circ}$) in



i: $i\text{-BuLi/THF}$, ii: conc. HCl, iii: $\text{KMnO}_4/\text{acetone}$,

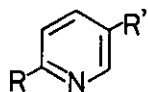
iv: $\text{H}_2\text{NNH}_2/\text{KOH/Diethyleneglycol}$, v: 70% HNO_3

Scheme II

85% yield³⁾. When I reacted with isobutylmagnesium bromide in THF at 0°, the main product was 2-cyclopropyl-5-(cyclopropylhydroxy)methylpyridine (II), and V was the minor product. The alcohol (V) was treated with concentrated hydrochloric acid at room temperature for 10 hr to give 2-cyclopropyl-5-(4-chloro-1-isobutyl-1-butenyl)pyridine (VI, picrate, mp 151-152°) in 96% yield⁴⁾, which was oxidized with potassium permanganate in acetone under reflux to give 2-cyclopropyl-5-isovalerylpyridine (VII, bp 125-127°/0.5 mmHg, styphnate, mp 134-135°) in 93% yield⁵⁾. The ketone (VII) was reduced by Huang-Minlon's method to give 2-cyclopropyl-5-isopentylpyridine (VIII, bp 72-75°/0.2 mmHg, picrate, mp 143-144°) in 89% yield⁶⁾, which was heated at 70° in 70% nitric acid containing the small amount of sodium nitrite for 5 hr to give 5-isopentylpicolinic acid (IX, mp 119-120°) in 65% yield. The melting point of this acid was not depressed by admixture with an authentic sample.^{1a)}

Similarly, 2-cyclopropyl-5-alkylpyridine and their oxidation products, 5-alkylpicolinic acids, were synthesized and listed in Table I. Oxidation of 2-cyclopropyl-5-

Table I 5-Alkyl-2-cyclopropylpyridines and 5-Alkylpicolinic Acids

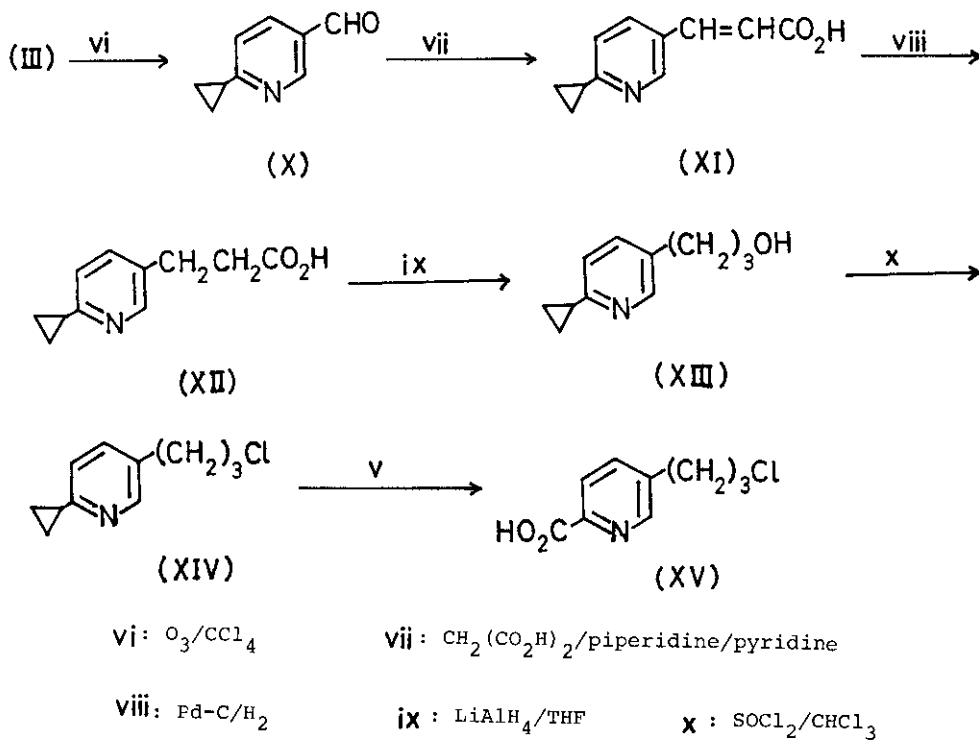


R	R'	Bp (mmHg)	MP	(Salt)
cyclopropyl	CH ₂ CH ₂ CH ₂ Cl	83-85° (0.3)	104-105°	(picrate)
"	CH ₂ CH(CH ₃) ₂	62-64° (0.3)	105-106°	(")
"	CH ₂ CH ₂ CH(CH ₃) ₂	72-74° (0.2)	143-144°	(")
"	(CH ₂) ₄ CH ₃	76-78° (0.2)	124-125°	(styphnate)
"	(CH ₂) ₅ CH ₃	93-100° (0.3)	96-97°	(")
"	CH ₂ C ₆ H ₅	113-115° (0.2)	123-124°	(picrate)
"	CH ₂ C ₆ H ₄ Cl (-p)	141-144° (0.2)	54-54.5°	(")
COOH	CH ₂ CH ₂ CH ₂ Cl	-	127-128°	
"	CH ₂ CH(CH ₃) ₂	-	127-128°	
"	CH ₂ CH ₂ CH(CH ₃) ₂	-	119-120°	
"	(CH ₂) ₄ CH ₃	-	104-105°	
"	(CH ₂) ₅ CH ₃	-	101-102°	
"	CH ₂ C ₆ H ₄ NO ₂ (-p)	-	181-182°	

benzylpyridine with nitric acid gave 5-(4-nitrobenzyl)picolinic acid.

In the synthesis of 2-cyclopropyl-5-(3-chloropropyl)pyridine (XIV), the alternative method was also applicable as shown in Scheme III.

2-Cyclopropyl-5-(4-chloro-1-buten-1-yl)pyridine (III) reacted with one equivalent of ozone in carbon tetrachloride at -40° to give 2-cyclopropylpyridine-5-carbaldehyde (X, bp 74-76°/1 mmHg, picrate, mp 107-108°) in 82% yield⁷⁾, which was treated with malonic acid in pyridine containing piperidine to give β-(2-cyclopropyl-5-pyridyl)-acrylic acid (XI, mp 105-106°) in 92% yield⁸⁾. The carboxylic acid (XI) was hydrogenated over Pd-charcoal in an autoclave (initial hydrogen pressure, 50 Kg/cm²) at room temperature to give β-(2-cyclopropyl-5-pyridyl)propionic acid (XII, mp 132-133°) in 89% yield⁹⁾. The carboxylic acid (XII) was reacted with lithium aluminum hydride in THF at room temperature to give 2-cyclopropyl-5-(3-hydroxypropyl)pyridine (XIII, bp 95-97°/0.4 mmHg, picrate, mp 111-112°) in 95% yield¹⁰⁾. The alcohol (XIII) was



Scheme III

treated with thionyl chloride in chloroform to give 2-cyclopropyl-5-(3-chloropropyl)pyridine (XIV, bp 83-85°/0.3 mmHg, picrate, mp 104-105°, yield 80%¹¹) which was oxidized as described in preparation of IX to give 5-(3-chloropropyl)picolinic acid (XV), mp 127-128°, undepressed by admixture with an authentic sample^{1a}).

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3. (V), NMR (CDCl₃); 0.25-0.60 (4H, m, (CH₂)₂CH-), 0.75-1.10 (10H, m, CH₃ x 2 and (CH₂)₂CH-), 1.15-1.40 (2H, m, (CH₂)₂CH- x 2), 1.60-2.00 (3H, m, CH₂ and CH), 4.5 (1H, s, OH), 7.10 (1H, d, J=8 Hz, β-H of pyridine ring), 7.70 (1H, dd, J=2 and 8 Hz, γ-H), 8.55 (1H, d, J=2 Hz, α'-H). MS: 245 (M⁺, trace), 188 (M⁺-C₄H₉, base peak).
4. (VI), NMR (CDCl₃); 0.67-1.10 (10H, m, CH₃ x 2 and (CH₂)₂CH-), 1.47 (1H, m, (CH₂)₂CH-), 1.96 (1H, m, -CH(CH₃)₂), 2.36 (2H, d, J=7 Hz, -CH₂CH(CH₃)₂), 2.70 (2H, sextet, J=7 and 7 Hz, =CHCH₂CH₂Cl), 3.55 (2H, t, J=7 Hz, -CH₂CH₂Cl), 5.53 (1H, t, J=7 Hz, =CHCH₂-), 6.98 (1H, d, J=8 Hz, β-H), 7.70 (1H, dd, J=2 and 8 Hz, γ-H), 8.38 (1H, d, J=2 Hz, α'-H), MS: 263 (M⁺, base peak), 265 (M⁺+ 2, isotope peak).
5. (VII), IR ν_{\max}^{Film} cm⁻¹: 1670 (C=O). NMR (CDCl₃), 0.76-1.40 (10H, m, CH₃ x 2 and (CH₂)₂CH-), 1.87-2.60 (2H, m, CH₂CH(CH₃)₂ and (CH₂)₂CH-), 2.80 (2H, d, J=7 Hz, -CH₂CH(CH₃)₂), 7.60 (1H, d, J=8 Hz, β-H), 8.07 (1H, dd, J=2 and 8 Hz, γ-H), 8.97 (1H, d, J=2 Hz, α'-H).
6. (VIII), NMR (CDCl₃); 0.83-1.07 (10H, m, CH₃ x 2 and (CH₂)₂CH-), 1.17-1.67 (3H, m, -CH₂CH(CH₃)₂ and (CH₂)₂CH-), 1.63-2.17 (1H, m, -CH(CH₃)₂), 2.15 (2H, t, J=7 Hz, PyCH₂CH₂-), 6.95 (1H, d, J=8 Hz, β-H), 7.30 (1H, dd, J=2 and 8 Hz, γ-H), 8.23 (1H, d, J=2 Hz, α'-H).
7. (X), NMR (CDCl₃), 1.00-1.16 (4H, m, (CH₂)₂CH-), 2.05 (1H, m, (CH₂)₂CH-), 7.19 (1H, d, J=8 Hz, β-H), 7.92 (1H, dd, J=2 and 8 Hz, γ-H), 8.27 (1H, d, J=2 Hz, α'-H), 9.94 (1H, s, -CHO), MS: 147 (M⁺), 118 (M-CHO, base peak).
8. (XI); IR ν_{\max}^{KBr} cm⁻¹ 3050, 2400, 1690 (COOH), 1935. NMR (CDCl₃); 1.00 (4H, m, (CH₂)₂CH-), 2.15 (1H, m, (CH₂)₂CH-), 6.55 (1H, d, J=16 Hz, -CH=CH-COOH),

- 7.31 (1H, d, J=8 Hz, β -H), 7.60 (1H, d, J=16 Hz, $-\underline{\text{C}}\text{H}=\text{C}\text{H}-\text{COOH}$), 8.00 (1H, dd, J=2 and 8 Hz, γ -H), 8.65 (1H, d, J=2 Hz, α' -H). MS: (methyl ester); 203 (M^+), 202 (base peak), 172 (M^+-OCH_3), 142 ($\text{M}^+-\text{COOCH}_3$).
9. (XII), IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$; 2500, 1700. NMR, (CDCl_3); 0.95-1.10 (4H, m, $(\underline{\text{C}}\text{H}_2)_2\text{CH-}$), 2.15 (1H, m, $(\text{C}\underline{\text{H}}_2)_2\text{-}$), 3.65 (2H, t, J=6 Hz, $-\underline{\text{C}}\text{H}_2\text{CH}_2\text{COOH}$), 4.25 (2H, t, J=6 Hz, $-\text{C}\underline{\text{H}}_2\text{CH}_2\text{COOH}$), 7.15 (1H, d, J=8 Hz, β -H), 7.63 (1H, dd, J=2 and 8 Hz, γ -H), 8.43 (1H, d, J=2 Hz, α' -H). MS: (methyl ester): 205 (M^+), 132 ($\text{M}^+-\text{CH}_2\text{CO}_2\text{CH}_3$, base peak).
10. (XIII), NMR (CDCl_3); 0.85-1.00 (4H, m, $(\underline{\text{C}}\text{H}_2)_2\text{CH-}$), 1.60-2.25 (3H, m, $(\text{C}\underline{\text{H}}_2)_2\text{-CH-}$ and $-\text{C}\underline{\text{H}}_2\text{CH}_2\text{CH}_2\text{OH}$), 2.65 (2H, t, J=6 Hz, $\text{PyC}\underline{\text{H}}_2\text{-}$), 3.66 (2H, t, J=6 Hz, $-\text{C}\underline{\text{H}}_2\text{CH}_2\text{OH}$), 3.55 (1H, br, s, -OH), 6.95 (1H, d, J=8 Hz, β -H), 7.35 (1H, dd, J=2 and 8 Hz, γ -H), 8.21 (1H, d, J=2 Hz, α' -H). MS: 177 (M^+), 132 ($\text{M}^+-\text{C}_2\text{H}_4\text{OH}$).
11. (XIV), NMR (CDCl_3); 0.70-1.10 (4H, m, $(\underline{\text{C}}\text{H}_2)_2\text{CH-}$), 1.45 (3H, m, $(\text{C}\underline{\text{H}}_2)_2\text{CH-}$ and $-\text{C}\underline{\text{H}}_2\text{CH}_2\text{CH}_2\text{Cl}$), 2.55 (2H, t, J=6 Hz, $-\text{C}\underline{\text{H}}_2\text{CH}_2\text{CH}_2\text{Cl}$), 3.50 (2H, t, J=6 Hz, $-\text{C}\underline{\text{H}}_2\text{CH}_2\text{CH}_2\text{Cl}$), 6.97 (1H, d, J=8 Hz, β -H), 7.30 (1H, dd, J=2 and 8 Hz, γ -H), 8.23 (1H, d, J=2 Hz, α' -H).
12. (XV), IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$ 3100, 1700. NMR (CDCl_3); 1.85-2.36 (2H, m, $-\text{C}\underline{\text{H}}_2\text{CH}_2\text{CH}_2\text{-Cl}$), 2.90 (2H, t, J=8 Hz, $-\text{C}\underline{\text{H}}_2\text{CH}_2\text{CH}_2\text{Cl}$), 3.50 (2H, t, J=8 Hz, $-\text{C}\underline{\text{H}}_2\text{CH}_2\text{CH}_2\text{Cl}$), 7.70 (1H, d, J=8 Hz, β -H), 8.10 (1H, dd, J=2 and 8 Hz, γ -H), 8.64 (1H, d, J=2 Hz, α' -H), 12.15 (1H, s, -COOH).

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