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

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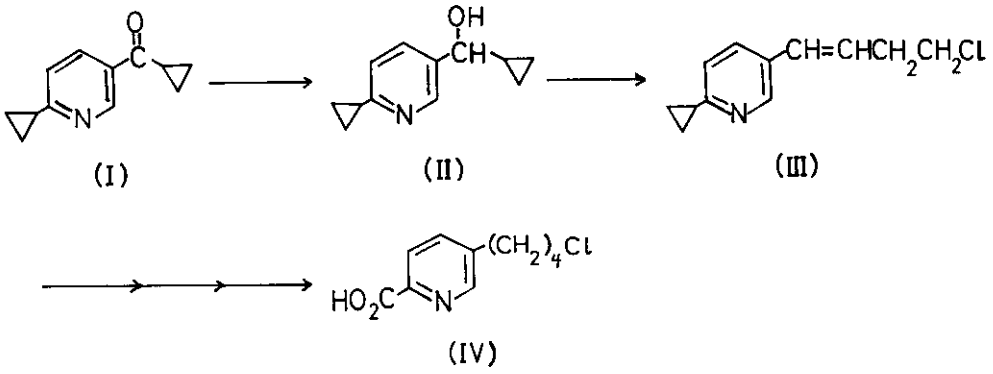
Abstract - Several 5-alkylpicolinic acids, dopamine β-hydroxylase inhibitors were synthesized from 2-cyclopropyl-5-cyclopropylcarbonylpyridine (I) as a suitable starting material.

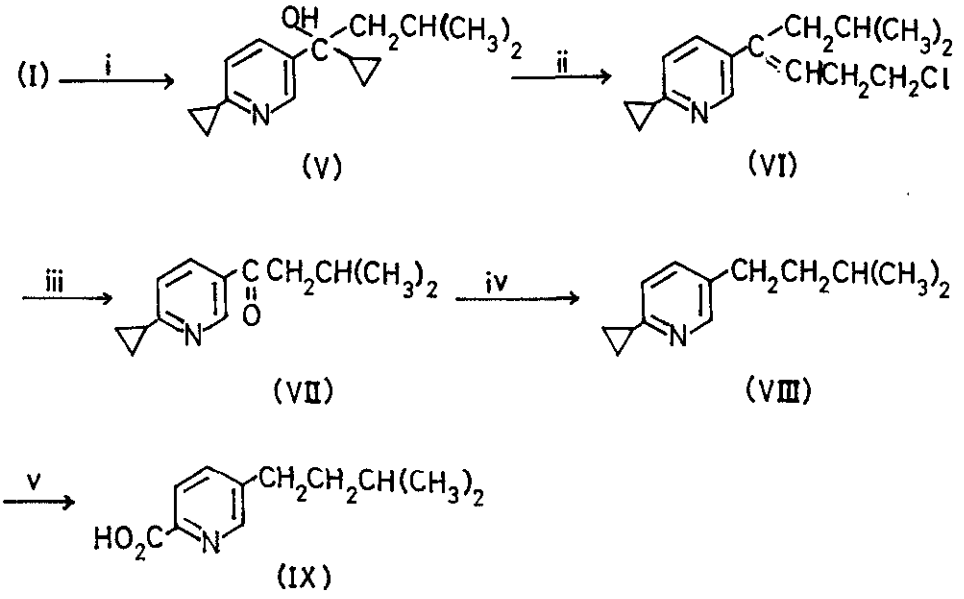
In the previous papers[1], the synthesis of 5-(4-chlorobutyl)picolinic acid (IV), which was potent inhibitor of dopamine β-hydroxylase was described as shown in Scheme I.



Scheme I

Although fusaric acid and 5-haloalkylpicolinic acids have been synthesized by various methods as described in the previous papers[1] and references[2], 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°) in



i : i-BuLi/THF, ii : conc. HCl, iii : $KMnO_4$/acetone,

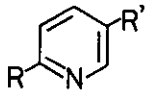
iv : H_2NNH_2/KOH/Diethyleneglycol, v : 70% HNO_3

Scheme II

85% yield[3]. 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% yield[4], 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% yield[5]. 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% yield[6], 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

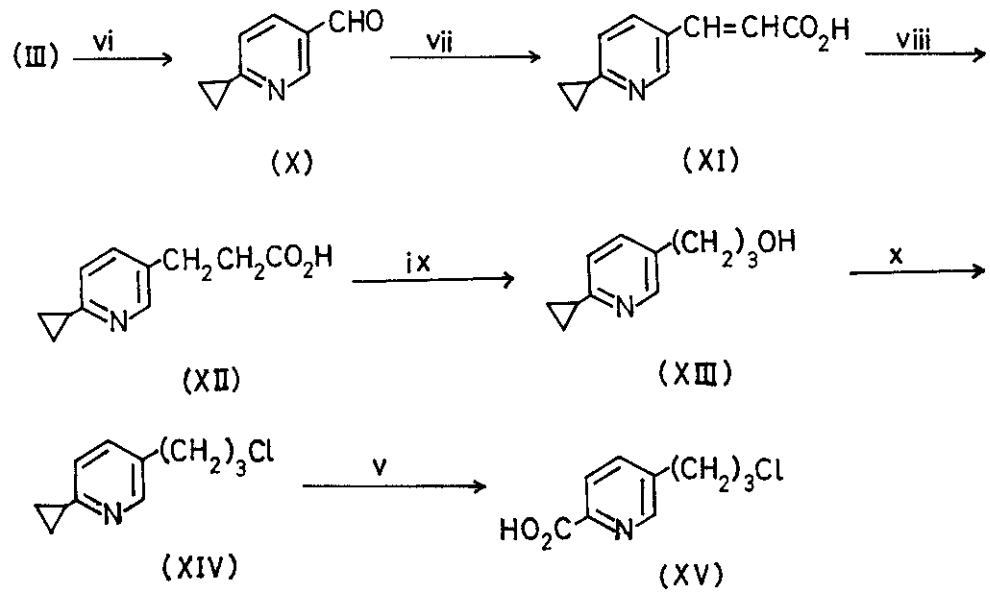


R	R'	Bp (mmHg)		MP	(Salt)
cyclopropyl	$CH_2CH_2CH_2Cl$	83-85°	(0.3)	104-105°	(picrate)
"	$CH_2CH(CH_3)_2$	62-64°	(0.3)	105-106°	(")
"	$CH_2CH_2CH(CH_3)_2$	72-74°	(0.2)	143-144°	(")
"	$(CH_2)_4CH_3$	76-78°	(0.2)	124-125°	(styphnate)
"	$(CH_2)_5CH_3$	93-100°	(0.3)	96-97°	(")
"	$CH_2C_6H_5$	113-115°	(0.2)	123-124°	(picrate)
"	$CH_2C_6H_4Cl$(-p)	141-144°	(0.2)	54-54.5°	(")
COOH	$CH_2CH_2CH_2Cl$	-		127-128°	
"	$CH_2CH(CH_3)_2$	-		127-128°	
"	$CH_2CH_2CH(CH_3)_2$	-		119-120°	
"	$(CH_2)_4CH_3$	-		104-105°	
"	$(CH_2)_5CH_3$	-		101-102°	
"	$CH_2C_6H_4NO_2$(-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-carboaldehyde (X, bp 74-76°/1 mmHg, picrate, mp 107-108°) in 82% yield[7], 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% yield[8]. The carboxylic acid (XI) was hydrogenated over Pd-charcoal in an autoclave (initial hydrogen pressure, 50 Kg/cm^2) at room temperature to give β-(2-cyclopropyl-5-pyridyl)propionic acid (XII, mp 132-133°) in 89% yield[9]. 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% yield[10]. The alcohol (XIII) was



vi: O_3/CCl_4 vii: $CH_2(CO_2H)_2$/piperidine/pyridine

viii: Pd-C/H_2 ix : $LiAlH_4$/THF x : $SOCl_2/CHCl_3$

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 ($CDCl_3$); 0.25-0.60 (4H, m, $(C\underline{H}_2)_2CH$-), 0.75-1.10 (10H, m, CH_3 x 2 and $(C\underline{H}_2)_2CH$-), 1.15-1.40 (2H, m, $(CH_2)_2C\underline{H}$- x 2), 1.60-2.00 (3H, m, CH_2 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 8Hz, γ-H), 8.55 (1H, d, J=2 Hz, α′-H). MS: 245 (M^+, trace), 188 ($M^+-C_4H_9$, base peak).

4. (VI), NMR ($CDCl_3$); 0.67-1.10 (10H, m, CH_3 x 2 and $(C\underline{H}_2)_2CH$-), 1.47 (1H, m, $(CH_2)_2C\underline{H}$-), 1.96 (1H, m, $-C\underline{H}(CH_3)_2$), 2.36 (2H, d, J=7 Hz, $-C\underline{H}_2CH(CH_3)_2$), 2.70 (2H, sextet, J=7 and 7 Hz, $=CHC\underline{H}_2CH_2Cl$), 3.55 (2H, t, J=7 Hz, $-CH_2C\underline{H}_2Cl$), 5.53 (1H, t, J=7 Hz, $=C\underline{H}CH_2$-), 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 ($CDCl_3$), 0.76-1.40 (10H, m, CH_3 x 2 and $(C\underline{H}_2)_2CH$-), 1.87-2.60 (2H, m, $CH_2C\underline{H}(CH_3)_2$ and $(CH_2)_2C\underline{H}$-), 2.80 (2H, d, J=7 Hz, $-C\underline{H}_2CH(CH_3)_2$), 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 ($CDCl_3$); 0.83-1.07 (10H, m, CH_3 x 2 and $(C\underline{H}_2)_2CH$-), 1.17-1.67 (3H, m, $-C\underline{H}_2CH(CH_3)_2$ and $(CH_2)_2C\underline{H}$-), 1.63-2.17 (1H, m, $-CH(CH_3)_2$), 2.15 (2H, t, J=7 Hz, $PyC\underline{H}_2CH_2$-), 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 ($CDCl_3$), 1.00-1.16(4H, m, $(C\underline{H}_2)_2CH$-), 2.05 (1H, m, $(CH_2)_2C\underline{H}$-), 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 ($CDCl_3$); 1.00 (4H, m, $(C\underline{H}_2)_2CH$-), 2.15 (1H, m, $(CH_2)_2C\underline{H}$-), 6.55 (1H, d, J=16 Hz, $-CH=C\underline{H}-COOH$),

7.31 (1H, d, J=8 Hz, β-H), 7.60 (1H, d, J=16 Hz, -CH=CH-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 ($M^+-COOCH_3$).

9. (XII), IR ν_{max}^{KBr} cm^{-1}; 2500, 1700. NMR, ($CDCl_3$); 0.95-1.10 (4H, m, $(CH_2)_2CH$-), 2.15 (1H, m, $(CH_2)_2CH$-), 3.65 (2H, t, J=6 Hz, $-CH_2CH_2COOH$), 4.25 (2H, t, J=6 Hz, $-CH_2CH_2COOH$), 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 ($M^+-CH_2CO_2CH_3$, base peak).

10. (XIII), NMR ($CDCl_3$); 0.85-1.00 (4H, m, $(CH_2)_2CH$-), 1.60-2.25 (3H, m, $(CH_2)_2$-CH- and $-CH_2CH_2CH_2OH$), 2.65 (2H, t, J=6 Hz, $PyCH_2$-), 3.66 (2H, t, J=6 Hz, $-CH_2CH_2OH$), 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 ($M^+-C_2H_4OH$).

11. (XIV), NMR ($CDCl_3$); 0.70-1.10 (4H, m, $(CH_2)_2CH$-), 1.45 (3H, m, $(CH_2)_2CH$- and $-CH_2CH_2CH_2Cl$), 2.55 (2H, t, J=6 Hz, $-CH_2CH_2CH_2Cl$), 3.50 (2H, t, J=6 Hz, $-CH_2CH_2CH_2Cl$), 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 ν_{max}^{KBr} cm^{-1} 3100, 1700. NMR ($CDCl_3$); 1.85-2.36 (2H, m, $-CH_2CH_2CH_2$-Cl), 2.90 (2H, t, J=8 Hz, $-CH_2CH_2CH_2Cl$), 3.50 (2H, t, J=8 Hz, $-CH_2CH_2CH_2Cl$) 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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