

**NEW HETEROCYCLIC RING SYSTEMS : THE SYNTHESSES  
OF 2H,3H,7H-IMIDAZO[1',2':1,2]PYRIDO[4,3-b]INDOLES AND  
2H,3H,4H,8H-PYRIMIDO[1',2':1,2]PYRIDO[4,3-b]INDOLES**

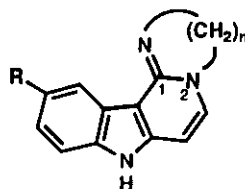
Kazuho Harada,\* Hitoshi Someya, and Shonosuke Zen

*School of Pharmaceutical Sciences, Kitasato University, Shirokane,  
Minato-ku, Tokyo 108, Japan*

**Abstract** - Heterocyclic [1,2]-annulated pyrido[4,3-*b*]indoles (**9** and **10**) were synthesized in five step sequences starting from 4-hydrazino-1*H*-pyrid-2-one (**1**).

Recent reports on antitumor and convulsant activities<sup>1,2</sup> for pyrido[4,3-*b*]indoles have focused our interest toward the synthesis of some structurally related compounds. A survey of the literature reveals that chemical study on pyrido[4,3-*b*]indole is poor compared to that on pyrido[3,4-*b*]indole and a few tetracyclic ring systems having a pyrido[4,3-*b*]indole moiety have been synthesized.<sup>3</sup> Especially, only two heterocyclic [1,2]-annulated pyrido[4,3-*b*]indoles, *i.e.*, pyrazino[1',2':1,2]pyrido[4,3-*b*]indole<sup>4</sup> and indolo[3,2-*a*]quinolizin-5-ium,<sup>5</sup> have been reported. In this paper we report the synthesis of new ring systems (general formula **A**), *i.e.*, imidazo[1',2':1,2]pyrido[4,3-*b*]indoles (**9**) and pyrimido[1',2':1,2]pyrido[4,3-*b*]indoles (**10**), which can be regarded as tetracyclic analogues of pyrido[4,3-*b*]indoles.

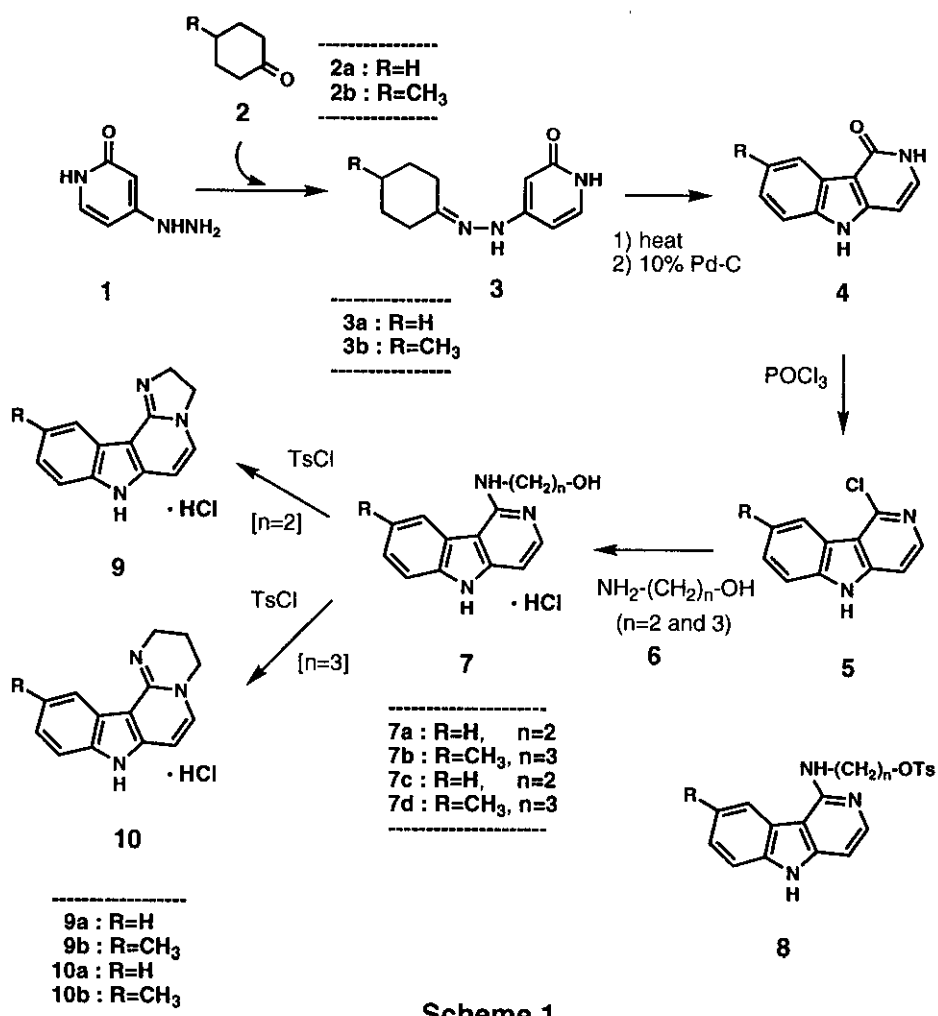
As shown in Scheme 1, the synthesis of **9** and **10** was achieved in five step sequences.



**A**

n=2 or 3  
R=H or CH<sub>3</sub>

1-Hydroxyalkylamino-5*H*-[4,3-*b*]indoles (7), the intermediates in this Scheme, were prepared by using a modification of the Bisagni's method.<sup>6</sup> Thus, condensation of cyclohexanone (2 **a**) with 4-hydrazino-1*H*-pyrid-2-one (1) in ethanol under reflux for 4 hours afforded the corresponding hydrazone (3**a**). Compounds (3**a**) was then heated at 280°C under nitrogen atmosphere in diphenyl ether followed by treatment with 10% Pd-C to give 2*H*,5*H*-pyrido[4,3-*b*]indol-1-ones (4 **a**)<sup>7</sup> in 87% yield. The chlorination of 4 **a** with phosphorus oxychloride under



Scheme 1

refluxing for 24 hours gave 1-chloro-5*H*-pyrido[4,3-*b*]indole (**5a**)<sup>8</sup> in 62% yield. The similar procedure was used to synthesize the 1-chloro-5*H*-pyrido[4,3-*b*]indole (**5b**) starting from **1** with 4-methylcyclohexanone (**2b**). The 1-chloro derivatives (**5a**, **5b**) were then refluxed with aminoethanol (**6a**) or aminopropanol (**6b**) to afford 1-hydroxyalkylamino derivatives (**7a**, **7b**, **7c**, and **7d**) as hydrochlorides in a range of 90-99% yields. The structure of **7** was confirmed by the following spectroscopic data. The ir spectra of these compounds showed peaks at 2800-3600 cm<sup>-1</sup> due to an amino and a hydroxy groups, and the <sup>1</sup>H-nmr spectra exhibited two or three multiplets ( $\delta$  1.89-3.80) due to the methylene protons at the C-1 substituent and also the corresponding ring protons. When **7d** was treated with tosyl chloride in pyridine at room temperature,<sup>9</sup> tosylate (**8d**) and the desired tetracyclic compound (**10b**) were isolated in 53% and 22% yield, respectively. On the other hand, heating a mixture of **7a-d** with tosyl chloride at 50°C in pyridine for 3 hours furnished the desired tetracyclic compounds (**9a**, **9b**, **10a**, and **10b**) in a range of 84-95% yield, without isolating the intermediate tosylates (**8**).

On the basis of elemental analysis, ir, ms, and <sup>1</sup>H-nmr spectral properties, each product was unambiguously determined as a new ring system, imidazo[1',2':1,2]pyrido[4,3-*b*]indole or pyrimido[1',2':1,2]pyrido[4,3-*b*]indole. Further evidence for supporting the structure determination of **9** and **10** was obtained from single crystal X-ray analyses of **9b** and **10b** as typical compounds. Perspective drawings of these compounds are shown in Figure 1, in which **9b** and **10b** are analysed as a hydrochloride and a *p*-toluenesulfonic acid salt, respectively. As shown in the ORTEP diagram of **9b**, the resultant imidazoline ring (C1-C2-N2-C13-N1) is fused with the pyridine ring (C13-N2-C3-C4-C5-C12) with the torsion angles (N2-C13-N1-C1 : 7.2° and C13-N2-C2-C1 : 10.1°). On the other hand, in the ORTEP diagram of **10b**, the resultant pyrimidine ring (C1-C2-C3-N2-C14), which adopts approximately a half-chair conformation, is fused with pyridine ring (C14-N2-C4-C5-C6-C13) with the torsion angles (N2-C14-N1-C1 : 3.9° and C14-N2-C3-C2 : 34.8°).

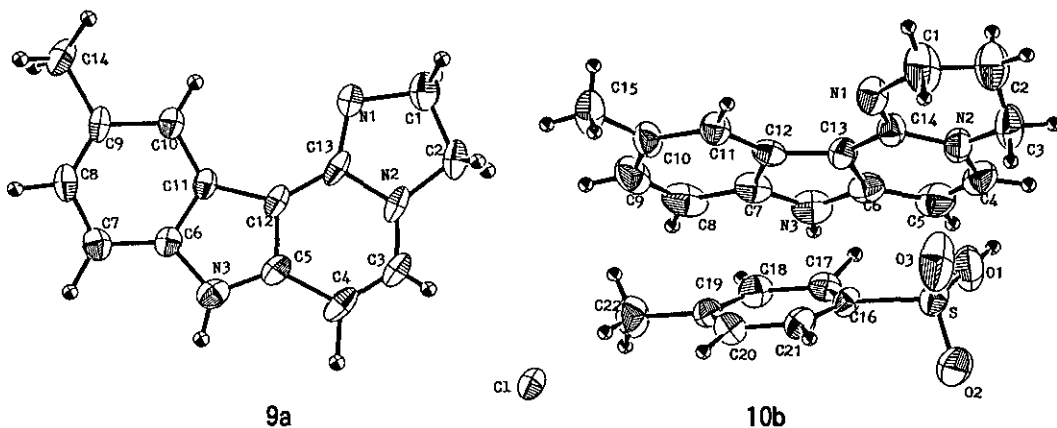


Figure 1 Perspective Drawings of Compounds (9a and 10b)

Table 1. Crystallographic Data for Compounds 9b and 10b

	9b	10b
Formula	$C_{14}H_{13}N_3O_3Cl$	$C_{22}H_{23}N_3O_2S$
$F_w$	306.73	393.50
Crystal dimensions (mm)	0.2x0.2x0.2	0.3x0.6x0.5
Crystal system	triclinic	monoclinic
Space group	$P\bar{1}$	$P2_1/n$
Lattice parameters		
$a/\text{\AA}$	9.068(3)	10.112(4)
$b/\text{\AA}$	9.874(2)	10.938(5)
$c/\text{\AA}$	7.516(1)	18.461(3)
$\alpha/\text{deg}$	101.45(1)	-----
$\beta/\text{deg}$	98.78(2)	101.56(7)
$\gamma/\text{deg}$	104.93(2)	-----
$V/\text{\AA}^3$	622.3(6)	2000(4)
Z	2	4
$D_c/\text{gcm}^{-3}$	1.637	1.306
$\mu(\text{Cu K}\alpha)/\text{cm}^{-1}$	28.90	15.75
$2\theta_{max}/\text{deg}$	140.3	140.2
No. of Reflections :total (unique)	2423 (2273)	4178 (3942)
No. of Observation ( $F_o > 3.50\sigma(F_o)$ )	1371	1901
No. of Variables	164	274
R	0.078	0.079

## EXPERIMENTAL

Melting points were measured with a Yamato MP-1 apparatus and are uncorrected. Spectral data were recorded on the following instruments : Jasco IRA-1(ir), JMS D-100(ms), and Varian EM-390(<sup>1</sup>H-nmr). Tetramethylsilane was used as an internal standard for nmr measurement in chloroform-d. Column chromatography was carried out on a silica gel(Kanto Kagaku Co. ; up to 100 mesh) column.

### Synthesis of *N*-(Substituted Cyclohexylidene)-*N'*-(1*H*-pyrid-2-one-4-yl)-hydrazines (3a,b) ——— General Procedure

A mixture of 4-hydrazino-1*H*-pyrid-2-one (1) (1.5 g, 12 mmol) and substituted cyclohexanone (2a, 2b) (12 mmol) in 30 ml of ethanol was refluxed for 4 h, and then cooled at 0°C. The product was collected by suction filtration, washed with ethanol previously cooled in ice-bath, then dried at reduced pressure to give *N*-(substituted cyclohexylidene)-*N'*-(1*H*-pyrid-2-one-4-yl)hydrazines (3a,b).

***N*-Cyclohexylidene-*N'*-(1*H*-pyrid-2-one-4-yl)hydrazine (3a) :** Yield 80 %. mp 271-276°C (decomp.). Ir ν (KBr)cm<sup>-1</sup> : 2800-3200(NH), 1650(C=O). Ms(m/z) : 205(M<sup>+</sup>). <sup>1</sup>H Nmr (DMSO-d<sub>6</sub>, δ, ppm) : 1.58-2.38(m, 10H, cyclohexane ring protons), 5.68(d, J<sub>3,5</sub>=2.0 Hz, 1H, H-3), 6.02(dd, J<sub>5,6</sub>=7.0 Hz, J<sub>3,5</sub>=2.0 Hz, 1H, H-5), 7.07(d, J<sub>5,6</sub>=7.0 Hz, 1H, H-6), 9.28(s, 1H, CO-NH), 10.49(s, 1H, N-NH). Anal. Calcd for C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O : C, 64.36; H, 7.37; N, 20.48. Found : C, 64.20; H, 7.43; N, 20.41.

### ***N*-(4-Methylcyclohexylidene)-*N'*-(1*H*-pyrid-2-one-4-yl)hydrazine (3b) :**

Yield 66 %. mp 290-295°C (decomp.). Ir ν (KBr)cm<sup>-1</sup> : 3200-2800(NH), 1650(C=O). Ms(m/z) : 219(M<sup>+</sup>). <sup>1</sup>H Nmr (DMSO-d<sub>6</sub>, δ, ppm) : 0.91-2.91(m, 12H, cyclohexane ring protons), 5.68(d, J<sub>3,5</sub>=2.0 Hz, 1H, H-3), 6.02(dd, J<sub>5,6</sub>=7.0 Hz, J<sub>3,5</sub>=2.0 Hz, 1H, H-5), 7.07(d, J<sub>5,6</sub>=7.0 Hz, 1H, H-6), 9.28(s, 1H, CO-NH), 10.49(s, 1H, N'H). Anal. Calcd for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O : C, 65.72; H, 7.81; N, 19.17.

Found : C, 65.47; H, 7.89; N, 19.17.

**Synthesis of 8-Substituted 2H,5H-Pyrido[4,3-b]indol-1-one (4) — General Procedure**

After a solution of **3** (3.91 mmol) in 30 ml of diphenyl ether was heated at 280°C under N<sub>2</sub> for 2.5 h, a suspension of 10% Pd-C (160 mg) in 5 ml of diphenyl ether was added dropwise to the solution and then the reaction mixture was further heated at 280°C under N<sub>2</sub> for 5.5 h. After cooling, the reaction mixture was suspended in 40 ml of hexane and filtered off. The unresolved materials were resolved in boiled acetic acid (80 ml) and filtered. The filtrate was concentrated to dryness *in vacuo* and the residue was recrystallized from ethanol to give 8-substituted 2H,5H-pyrido[4,3-b]indol-1-ones (**4**).

**2H,5H-Pyrido[4,3-b]indol-1-one (4a)** : Yield 87 %. mp 277-280°C (decomp.) (EtOH). (lit., 7)

**8-Methyl 2H,5H-Pyrido[4,3-b]indol-1-one (4b)** : Yield 96 %. mp > 300°C (EtOH).

Ir  $\nu$ (KBr)cm<sup>-1</sup> : 3300-2900(NH), 1630(C=O). Ms(m/z) : 198(M<sup>+</sup>). <sup>1</sup>H Nmr(DMSO-d<sub>6</sub>,  $\delta$ , ppm) : 2.43(s, 3H, CH<sub>3</sub>), 6.47(d, J<sub>3,4</sub>=7.0 Hz, 1H, H-4), 7.10(dd, J<sub>6,7</sub>=8.0 Hz, J<sub>7,9</sub>=0.8 Hz, 1H, H-7), 7.26(d, J<sub>3,4</sub>=7.0 Hz, 1H, H-3), 7.36(d, J<sub>6,7</sub>=8.0 Hz, 1H, H-6), 7.91(d, J<sub>7,9</sub>=0.8 Hz, 1H, H-9), 11.03(s, 1H, CO-NH) 11.57(s, 1H, NH). Anal. Calcd for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O · (1/4 · H<sub>2</sub>O) : C, 71.09; H, 5.22; N, 13.82. Found: C, 70.99; H, 5.05; N, 13.50.

**Synthesis of 8-Substituted 1-Chloro-5H-pyrido[4,3-b]indole (5) — General Procedure**

A solution of **4** (2.4 mmol) in 15 ml (160 mmol) of phosphorus oxychloride was refluxed for 24 h. After cooling, the reaction mixture was concentrated to dryness, and to the residue 50 ml of 3N HCl was added with ice cooling. The solution was refluxed for 2 h, and then filtrated. The filtrate was neutralized with 28% ammonia and the resulting precipitates were collected. The

crude materials were chromatographed with ethyl acetate-hexane (3:1) as an eluent to give 8-substituted 1-chloro-5*H*-pyrido[4,3-*b*]indoles (5).

**1-Chloro-5*H*-pyrido[4,3-*b*]indole (5a)** : Yield: 62 %. mp 270-271°C (EtOH) (lit., 8 : 269-270°C).

**1-Chloro-8-methyl-5*H*-pyrido[4,3-*b*]indole (5b)** : Yield 60 %. mp 274-275°C (EtOH).

Ir  $\nu$ (KBr) $\text{cm}^{-1}$ : 3250-2800(NH), 1610(C=N). Ms( $m/z$ ): 216( $M^+$ ).  $^1\text{H Nmr}$ (DMSO- $d_6$ ,  $\delta$ , ppm): 2.50(s, 3H,  $\text{CH}_3$ ), 7.37(dd,  $J_{6,7}=8.0$  Hz,  $J_{7,8}=1.0$  Hz, 1H, H-7), 7.49(d,  $J_{3,4}=5.5$  Hz, 1H, H-4), 7.52(d,  $J_{6,7}=8.0$  Hz, 1H, H-6), 8.16(d,  $J_{7,8}=1.0$  Hz, 1H, H-9), 8.19(d,  $J_{3,4}=5.5$  Hz, 1H, H-3), 12.02 (s, 1H, NH). *Anal.* Calcd for  $\text{C}_{12}\text{H}_9\text{N}_2\text{Cl}$ : C, 66.52; H, 4.19; N, 12.93; Cl, 16.36. Found: C, 66.16; H, 4.28; N, 12.86; Cl, 16.25.

### Synthesis of 1-Hydroxyalkylamino-5*H*-pyrido[4,3-*b*]indole Derivatives (7)

#### — General Procedure

A solution of 5 (1.0 mmol) in 4 ml (66 mmol) of aminoethanol (6;  $n=2$ ) or 4 ml (51.5 mmol) of aminopropanol (6;  $n=3$ ) was refluxed for 4~5 h, and then concentrated to dryness. The syrupy residue was chromatographed with ethyl acetate - methanol (1:1) as an eluent to give 1-hydroxyalkylamino-5*H*-pyrido[4,3-*b*]indoles (7).

**1-Hydroxyethylamino-5*H*-pyrido[4,3-*b*]indole (7a)** : Yield 98 %. mp 269.0°C (decomp.) (MeOH). Ir  $\nu$ (KBr) $\text{cm}^{-1}$ : 3600-2800(OH and NH), 1650(C=N). Ms( $m/z$ ): 227( $M^+$ ).

$^1\text{H-Nmr}$ (DMSO- $d_6$ ,  $\delta$ , ppm): 3.73(m, 2H,  $\beta\text{-CH}_2$ ), 3.80(m, 2H,  $\alpha\text{-CH}_2$ ), 7.16(d,  $J_{3,4}=7.0$  Hz, 1H, H-4), 7.39(dd,  $J_{6,7}=7.5$  Hz,  $J_{7,8}=7.5$  Hz, 1H, H-7), 7.52(dd,  $J_{7,8}=7.5$  Hz,  $J_{8,9}=7.5$  Hz, 1H, H-8), 7.69(d,  $J_{6,7}=7.5$  Hz, 1H, H-6), 7.82(d,  $J_{3,4}=7.0$  Hz, 1H, H-3), 8.05(m, 1H, NH), 8.57(d,  $J_{8,9}=7.5$  Hz, 1H, H-9), 12.85(s, 1H, indole NH). *Anal.* Calcd for  $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O} \cdot \text{HCl}$ : C, 59.16; H, 5.31; N, 15.93. Found: C, 59.01; H, 5.16; N, 15.77.

**1-Hydroxyethylamino-8-methyl-5*H*-pyrido[4,3-*b*]indole (7b)** : Yield 99 %. mp 282°C (decomp.) (MeOH). Ir  $\nu$ (KBr) $\text{cm}^{-1}$ : 3600-2800(OH and NH), 1650(C=N). MS( $m/z$ ): 241( $M^+$ ).

$^1\text{H-Nmr}$ (DMSO- $d_6$ ,  $\delta$ , ppm) : 2.51(s, 3H,  $\text{CH}_3$ ), 3.72-3.79(m, 4H,  $2\times\text{CH}_2$ ), 7.12(d,  $J_{3,4}=7.0$  Hz, 1H, H-4), 7.34(dd,  $J_{6,7}=8.5$  Hz,  $J_{7,9}=1.0$  Hz, 1H, H-7), 7.57(d,  $J_{6,7}=8.5$  Hz, 1H, H-6), 7.78(d,  $J_{3,4}=7.0$  Hz, 1H, H-3), 7.97(m, 1H, NH), 8.36(d,  $J_{7,9}=1.0$  Hz, 1H, H-9), 12.65(s, 1H, indole NH). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O} \cdot \text{HCl}$  : C, 60.54; H, 5.81; N, 15.13; Cl, 12.76. Found : C, 60.31; H, 5.81; N, 15.30; Cl, 12.92.

**1-Hydroxypropylamino-5H-pyrido[4,3-b]indole (7c)** : Yield 96 %. mp 225°C (decomp.) (MeOH).  $\text{Ir v(KBr)cm}^{-1}$  : 3600-2800(OH, NH), 1650(C=N). MS(m/z) : 241( $\text{M}^+$ ).  $^1\text{H-Nmr}$  (DMSO- $d_6$ ,  $\delta$ , ppm) : 1.89(m, 2H,  $\beta\text{-CH}_2$ ), 3.62(m, 2H,  $\gamma\text{-CH}_2$ ), 3.78(m, 2H,  $\alpha\text{-CH}_2$ ), 7.17(d,  $J_{3,4}=7.0$  Hz, 1H, H-4), 7.38(dd,  $J_{6,7}=7.5$  Hz,  $J_{7,9}=7.5$  Hz, 1H, H-7), 7.51(d,  $J_{6,9}=7.5$  Hz, 1H, H-8), 7.69(d,  $J_{6,7}=7.5$  Hz, 1H, H-6), 7.83(d,  $J_{3,4}=7.0$  Hz, 1H, H-3), 8.23(m, 1H, NH), 8.54(d,  $J_{8,9}=7.5$  Hz, 1H, H-9), 12.91(s, 1H, indole NH). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O} \cdot \text{HCl}$  : C, 60.54; H, 5.81; N, 15.13; Cl, 12.76. Found : C, 60.21; H, 5.66; N, 14.89; Cl, 12.37.

**1-Hydroxypropylamino-8-methyl-5H-pyrido[4,3-b]indole (7d)** : Yield 90 %. mp 237°C (decomp.) (MeOH).  $\text{Ir v(KBr)cm}^{-1}$  : 3600-2800(OH,NH), 1650(C=N). MS(m/z) : 255( $\text{M}^+$ ).  $^1\text{H-Nmr}$  (DMSO- $d_6$ ,  $\delta$ , ppm) : 1.89(m, 2H,  $\beta\text{-CH}_2$ ), 2.48(s, 3H, 8- $\text{CH}_3$ ), 3.64(m, 2H,  $\gamma\text{-CH}_2$ ), 3.78(m, 2H,  $\alpha\text{-CH}_2$ ), 7.13(d,  $J_{3,4}=7.0$  Hz, 1H, H-4), 7.34(dd,  $J_{6,7}=8.5$  Hz,  $J_{7,9}=1.0$  Hz, 1H, H-7), 7.55(d,  $J_{6,7}=8.5$  Hz, 1H, H-6), 7.74(d,  $J_{3,4}=7.0$  Hz, 1H, H-3), 8.17(d,  $J_{7,9}=1.0$  Hz, 1H, H-9), 8.34(s, 1H, NH), 12.67(s, 1H, indole NH). *Anal.* Calcd for  $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O} \cdot \text{HCl}$  : C, 61.17; H, 6.17; N, 14.41. Found : C, 61.33; H, 6.10; N, 14.32.

**Synthesis of 10-Substituted 2H,3H,7H-Imidazo[1',2':1,2]pyrido[4,3-b]indole (9) and 11-Substituted 2H,3H,4H,8H-Pyrimido[1',2':1,2]pyrido[4,3-b]indole (10)**

— General Procedure

A solution of **7** (0.36 mmol) and *p*-toluenesulfonyl chloride (84 mg, 0.44 mmol) in 2 ml of pyridine was stirred at 50°C for 3 h. The reaction mixture was concentrated to dryness and the residue was chromatographed with ethyl acetate - methanol (1:1) as an eluent to give



10-substituted *2H,3H,7H*-imidazo[1',2':1,2]pyrido[4,3-*b*]indoles (**9**) or 11-substituted *2H,3H,4H,8H*-pyrido[1',2':1,2]pyrido[4,3-*b*]indoles (**10**), respectively.

**2H,3H,7H-Imidazo[1',2':1,2]pyrido[4,3-*b*]indole (9a)** : Yield 95 %. mp 300°C (decomp.).

Ir  $\nu$ (KBr) $\text{cm}^{-1}$  : 3500-2800(NH), 1670(C=N). MS( $m/z$ ) : 209 ( $M^+$ ).  $^1\text{H-Nmr}$ (DMSO- $d_6$ ,  $\delta$ , ppm) : 4.07(m, 2H, 3- $\text{CH}_2$ ), 4.67(m, 2H, 2- $\text{CH}_2$ ), 7.12(d,  $J_{5,6}$ =7.0 Hz, 1H, H-6), 7.40(dd,  $J_{8,9}$ =8.0 Hz,  $J_{9,10}$ =8.0 Hz, 1H, H-9), 7.53(dd,  $J_{9,10}$ =8.0 Hz,  $J_{10,11}$ =8.0 Hz, 1H, H-10), 7.67(d,  $J_{8,9}$ =8.0 Hz, 1H, H-8), 8.02(d,  $J_{5,6}$ =7.0 Hz, 1H, H-5), 8.28(d,  $J_{10,11}$ =8.0 Hz, 1H, H-11), 10.00(s, 1H, NH). *Anal.* Calcd for  $\text{C}_{13}\text{H}_{11}\text{N}_3 \cdot \text{HCl}$  : C, 63.54; H, 4.89; N, 17.11; Cl, 14.46. Found : C, 63.22; H, 4.74; N, 17.36; Cl, 14.59.

Conversion of **9a**  $\cdot$  HCl into its free base was attempted by treating with aq. NaOH, however, **9a**  $\cdot$  HCl was recovered or several decomposed compounds were obtained, depending on the concentration of the aq. NaOH.

**10-Methyl-2H,3H,7H-imidazo[1',2':1,2]pyrido[4,3-*b*]indole (9b)** : Yield 89 %.

mp > 300°C (MeOH). Ir  $\nu$ (KBr) $\text{cm}^{-1}$  : 3300-2700(NH), 1660(C=N). MS( $m/z$ ) : 223 ( $M^+$ ).  $^1\text{H-Nmr}$ (DMSO- $d_6$ ,  $\delta$ , ppm) : 2.49(s, 3H,  $\text{CH}_3$ ), 4.08(m, 2H, 3- $\text{CH}_2$ ), 4.68(m, 2H, 2- $\text{CH}_2$ ), 7.11(d,  $J_{5,6}$ =7.0 Hz, 1H, H-6), 7.34(d,  $J_{8,9}$ =8.5 Hz, 1H, H-9), 7.56(d,  $J_{8,9}$ =8.5 Hz, H-1, H-8), 8.06(d,  $J_{5,6}$ =7.0 Hz, 1H, H-5), 8.21(s, 1H, H-11). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_3 \cdot \text{HCl}$  : C, 64.74; H, 5.43; N, 16.18; Cl, 13.65. Found : C, 64.57; H, 5.43; N, 15.82; Cl, 18.24.

**2H,3H,4H,8H-Pyrimido[1',2':1,2]pyrido[4,3-*b*]indole (10a)** : Yield 89 %. mp > 300°C.

Ir  $\nu$ (KBr) $\text{cm}^{-1}$  : 3300-2700(NH), 1650(C=N). MS( $m/z$ ) : 223 ( $M^+$ ).  $^1\text{H-Nmr}$ (DMSO- $d_6$ ,  $\delta$ , ppm) : 2.22(m, 2H, 3- $\text{CH}_2$ ), 3.64(m, 2H, 4- $\text{CH}_2$ ), 4.40(m, 2H, 2- $\text{CH}_2$ ), 7.14(d, 1H,  $J_{6,7}$ =7.0 Hz, 1H, H-7), 7.39(dd,  $J_{9,10}$ =7.5 Hz,  $J_{10,11}$ =7.5 Hz, 1H, H-10), 7.51(dd,  $J_{10,11}$ =7.5 Hz,  $J_{11,12}$ =7.5 Hz, 1H, H-11), 7.68(d,  $J_{9,10}$ =7.5 Hz, H-1, H-9), 7.87(d,  $J_{6,7}$ =7.0 Hz, 1H, H-6), 8.56(d,  $J_{11,12}$ =7.5 Hz, 1H, H-12), 12.80(s, 1H, NH). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_3 \cdot \text{HCl}$  : C, 64.74; H, 5.43; N, 16.18; Cl, 13.65. Found : C, 64.70; H, 5.45; N, 16.08; Cl, 13.48.

**11-Methyl-2H,3H,4H,8H-pyrimido[1',2':1,2]pyrido[4,3-*b*]indole (10b)** : Yield : 84 %.

mp > 300°C (MeOH).  $\nu(\text{KBr})\text{cm}^{-1}$ : 3400-2800(NH), 1650(C=N). MS(m/z): 237(M<sup>+</sup>).

<sup>1</sup>H-Nmr(DMSO-d<sub>6</sub>, δ, ppm): 2.22(m, 2H, 3-CH<sub>2</sub>), 2.28(s, 3H, CH<sub>3</sub>(*p*-toluenesulfonic acid)), 2.51(s, 3H, CH<sub>3</sub>), 3.64(m, 2H, 4-CH<sub>2</sub>), 4.39(m, 2H, 2-CH<sub>2</sub>), 7.11(d, J<sub>6,7</sub>=7.5 Hz, 1H, H-7), 7.11(d, J=8.0 Hz, 2H, aromatic protons of TsOH), 7.34(d, J<sub>9,10</sub>=8.5 Hz, 1H, H-10), 7.47(d, J=8.0 Hz, 2H, aromatic protons of TsOH), 7.56(d, J<sub>9,10</sub>=8.5 Hz, H-9), 7.83(d, J<sub>6,7</sub>=7.5 Hz, 1H, H-6), 8.31(s, 1H, H-12). *Anal.* Calcd for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub> · C<sub>7</sub>H<sub>8</sub>SO<sub>3</sub> · H<sub>2</sub>O: C, 61.80; H, 5.89; N, 9.83; S, 7.50. Found: C, 61.70; H, 5.55; N, 9.82; S, 7.29.

When the above reaction was carried out at room temperature for 24h, 3-(8-methyl-5*H*-pyrido[4,3-*b*]indolyl)amino-1-propyl *p*-toluenesulfonate (**8b**) (53%) and **10b** (22%) were isolated.

**8b**: mp 252°C (decomp.).  $\nu(\text{KBr})\text{cm}^{-1}$ : 3400-2800(NH), 1650(C=N), 1400(S-O). MS(m/z): 409 (M<sup>+</sup>). <sup>1</sup>H-Nmr(DMSO-d<sub>6</sub>, δ, ppm): 1.90(m, 2H, β-CH<sub>2</sub>), 2.28(s, 3H, Ts-CH<sub>3</sub>), 2.51(s, 3H, 8-CH<sub>3</sub>), 3.61-3.74(m, 4H, α-CH<sub>2</sub> and γ-CH<sub>2</sub>), 7.11(d, 2H, J=8.0 Hz, aromatic protons of Ts), 7.13(d, J<sub>3,4</sub>=7.0 Hz, 1H, H-4), 7.35(d, J<sub>6,7</sub>=8.0 Hz, 1H, H-7), 7.49(d, 2H, J=8.0 Hz, aromatic protons of Ts), 7.57(d, J<sub>6,7</sub>=8.0 Hz, 1H, H-6), 7.79(d, J<sub>3,4</sub>=7.0 Hz, 1H, H-3), 8.08(s, 1H, NH), 8.24(s, 1H, H-9), 12.52(s, 1H, indole NH). *Anal.* Calcd for C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>SO<sub>3</sub> · (5/4)H<sub>2</sub>O: C, 61.16; H, 5.72; N, 9.73; S, 7.42. Found: C, 61.11; H, 5.89; N, 9.73; S, 7.04.

### X-Ray Analyses of **9b** and **10b**

X-Ray structure analyses of **9b** and **10b** were carried out on a Rigaku AFC-5R diffractometer, and the cell parameters and the intensity data were measured with graphite monochromated Cu Kα(λ=1.54179 Å) radiation at 23°C. The crystal data are summarized in Table 1. The structures were solved by the direct method using the program MITHRIL (C. J. Gilmore: MITHRIL, an integrated direct method computer program, *J. Appl. Cryst.*, 1984, **17**, 42, Univ. of Glasgow, Scotland). The parameters of non-hydrogen atoms were refined by the full-matrix least-squares method with anisotropic temperature factors. The hydrogen atoms were located

from a difference Fourier synthesis, and refined only the temperature factors isotropically. The positional parameters for **9b** and **10b** are listed in Tables 2 and 3, respectively. The selected bond lengths, bond angles torsion angles for **9b** and **10b** are listed in Table 4.

Table 2 Positional Parameters and Their Estimated Standard Deviations for **9b**

Atom	x	y	z	$B_{eq}$
C1	0.2802(2)	0.1961(2)	0.5753(2)	3.79(7)
N1	1.0511(5)	0.2755(5)	0.8305(7)	3.6(2)
N2	0.8038(5)	0.2823(6)	0.7376(7)	3.7(2)
N3	0.9425(6)	0.6861(6)	0.6665(7)	3.8(2)
C1	0.9496(8)	0.1263(8)	0.806(1)	4.9(3)
C2	0.7848(7)	0.1392(7)	0.7741(9)	4.2(3)
C3	0.6882(7)	0.3377(8)	0.6805(9)	4.0(3)
C4	0.7192(7)	0.4671(8)	0.6470(9)	4.1(3)
C5	0.8809(6)	0.5537(7)	0.6870(8)	3.3(2)
C6	1.1057(7)	0.7228(7)	0.7195(8)	3.2(2)
C7	1.2164(8)	0.8514(7)	0.7170(8)	3.7(2)
C8	1.3709(8)	0.8561(7)	0.7792(9)	4.0(3)
C9	1.4164(6)	0.7466(7)	0.8353(8)	3.4(2)
C10	1.3024(7)	0.6177(7)	0.8321(8)	3.2(2)
C11	1.1457(6)	0.6084(6)	0.7725(7)	2.9(2)
C12	1.0006(6)	0.4949(7)	0.7503(8)	3.1(2)
C13	0.9599(6)	0.3592(7)	0.7758(8)	3.4(2)
C14	1.5882(7)	0.7594(8)	0.8991(9)	4.6(3)

Table 3 Positional Parameters and Their Estimated Standard Deviations for 10b

Atom	x	y	z	$B_{eq}$
S	0.1920(1)	0.3473(1)	0.8942(1)	4.97(7)
O1	0.2192(4)	0.2839(4)	0.8337(3)	7.9(3)
O2	0.1420(4)	0.2670(4)	0.9445(3)	7.5(2)
O3	0.3018(4)	0.4231(4)	0.9292(4)	10.6(3)
N1	0.2521(4)	0.5203(4)	0.6680(3)	5.3(2)
N2	0.2326(5)	0.3086(4)	0.6498(2)	5.1(2)
N3	- 0.1527(5)	0.3575(5)	0.5433(3)	5.7(2)
C1	0.3975(6)	0.5144(7)	0.7048(4)	8.5(4)
C2	0.4550(7)	0.3948(8)	0.6857(4)	8.2(4)
C3	0.3712(7)	0.2930(7)	0.6947(4)	6.9(3)
C4	0.1639(8)	0.2060(5)	0.6199(4)	6.0(3)
C5	0.0362(8)	0.2125(6)	0.5828(4)	6.5(4)
C6	- 0.0251(6)	0.3263(5)	0.5745(3)	4.8(3)
C7	- 0.1702(5)	0.4796(6)	0.5507(3)	4.6(3)
C8	- 0.2866(6)	0.5506(8)	0.5310(3)	6.7(4)
C9	- 0.2797(6)	0.6748(7)	0.5458(4)	6.3(3)
C10	- 0.1605(6)	0.7283(6)	0.5796(3)	5.3(3)
C11	- 0.0465(5)	0.6585(5)	0.6013(3)	4.5(2)
C12	- 0.0494(5)	0.5325(5)	0.5875(3)	4.1(2)
C13	0.0446(5)	0.4330(5)	0.6032(3)	4.2(2)
C14	0.1807(5)	0.4227(5)	0.6416(3)	4.4(3)
C15	- 0.1555(6)	0.8652(6)	0.5951(4)	7.1(3)
C16	0.0551(4)	0.4472(5)	0.8612(3)	3.8(2)
C17	- 0.0171(5)	0.4396(5)	0.7897(3)	4.4(2)
C18	- 0.1238(5)	0.5194(5)	0.7665(3)	5.0(3)
C19	- 0.1633(5)	0.6032(5)	0.8135(3)	4.5(2)
C20	- 0.0900(5)	0.6090(5)	0.8858(3)	4.4(3)
C21	0.0186(6)	0.5299(5)	0.9092(3)	4.5(3)
C22	- 0.2796(5)	0.6880(6)	0.7866(4)	6.8(3)

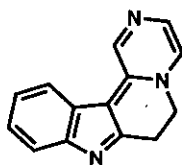
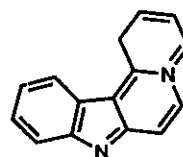
Table 4 Selected Bond Lengths, Bond Angles and Torsion Angles of 9b and 10b

	9b		10b	
Bond Length (Å)	N1-C1	1.481(8)	N1-C1	1.493(7)
	N2-C2	1.465(8)	N1-C14	1.326(6)
	N2-C3	1.354(8)	N2-C3	1.488(7)
	N2-C13	1.378(6)	N2-C14	1.351(6)
	C1-C2	1.520(9)	C1-C2	1.501(9)
	C3-C4	1.319(9)	C2-C3	1.429(9)
Bond Angle (°)	N1-C1-C2	104.2(6)	N1-C1-C2	108.8(6)
	N1-C13-N2	110.3(6)	N1-C14-N2	122.1(5)
	N2-C2-C1	104.1(5)	N2-C3-C2	111.1(5)
	N2-C13-C12	118.9(6)	N2-C14-C13	116.5(5)
	C1-N1-C13	109.1(5)	C1-N1-C14	123.2(5)
	C2-N2-C13	110.3(5)	C1-C2-C3	112.7(6)
	C3-N2-C13	122.9(6)	C3-N2-C14	118.1(5)
			C4-N2-C14	123.7(5)
Torsion Angle (°)	N1-C13-N2-C2	2.2(7)	N1-C1-C2-C3	- 47.4(8)
	N2-C13-N1-C1	7.2(7)	N2-C3-C2-C1	56.6(8)
	C1-C2-N2-C3	171.9(6)	N2-C14-N1-C1	3.9(8)
	C1-C2-N2-C13	- 10.1(6)	C1-N1-C14-C13	- 176.3(6)
	C12-C13-N1-C1	170.4(6)	C2-C3-N2-C4	146.1(6)
			C2-C3-N2-C14	- 34.8(8)

## REFERENCES AND NOTES

- 1) E. Bisagni, C.H. Nguyen, A. Pierre, O. Pepin, P. de Cointet, and P. Gros, *J. Med. Chem.*, 1988, **31**, 398 ; V. Pierson, A. Pierre, P. Cointet, C. H. Nguyen, E. Bisagni, and P. Gros, *Biochem. Pharmacol.*, 1989, **38**, 1395.

- 2) Y. Kanai, O. Wada, and S. Manabe, *J. Pharmacol. Exp. Ther.*, 1990, **252**, 1269.
- 3) Totally, twenty one ring systems for tetracyclic fused pyrido[4,3-*b*]indole have been reported including spiro type systems.
- 4) K. Bhandari, V. A. Murti, P. C. Jain, and N. Anang, *Indian J. Chem. Sect. B*, 1979, **17B**, 246.  
The ring structure is depicted below (**B<sub>1</sub>**).
- 5) R. K. Shakhatuni and F. R. Shiroyan, *Arm. Khim. Zh.*, 1983, **36**, 313. The ring structure is depicted below (**B<sub>2</sub>**).

**B<sub>1</sub>****B<sub>2</sub>**

- 6) C. H. Nguyen and E. Bisagni, *Tetrahedron*, 1986, **42**, 2303 ; C. H. Nguyen and E. Bisagni, *Tetrahedron*, 1987, **43**, 527.
- 7) C. H. Lee, T. Ohta, K. Shudo, and T. Okamoto, *Heterocycles*, 1981, **16**, 1981.
- 8) P. N. Namirski and J. Zieleniak, *Acta Polon. Pharm.*, 1977, **34**, 455.
- 9) A closely related reaction is reported in the following paper : J. P. Maffrand, D. Frehel, F. Eloy, D. Aubert, and J. C. Ferrand, *Eur. J. Med. Chem.*, 1975, **10**, 528.

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