SYNTHESIS OF 1-ISOPROPYLAMINO-3-(PYRAZOLO[1,5-*a*]-PYRIDYLOXY)-2-PROPANOLS

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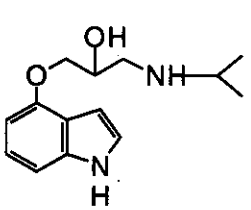
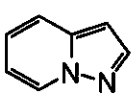
Abstract - Treatment of the 4-hydroxypyrazolo[1,5-*a*]pyridine with glycidyl tosylate in the presence of base, followed by reaction with isopropylamine gave 1-isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-4-yloxy)-2-propanol. In a similar manner, 1-isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-6- and 1-isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-3-yloxy)-2-propanol were also prepared.

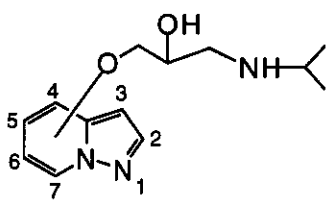
Pindolol (**1**),[1] 3-(4-indolyloxy)-1-isopropylamino-2-propanol, is an important member of 3-aryloxy-1-isopropylamino-2-propanol derivatives, which are known to possess a potent β-blocking activity. Pyrazolo[1,5-*a*]pyridine[2] is one of aza-analogue of indole but the chemical reactivity[3] and biological activity[4] of pyrazolo[1,5-*a*]pyridine derivatives are not well studied comparing with those of indoles.



1; Pindolol



Pyrazolo[1,5-*a*]pyridine



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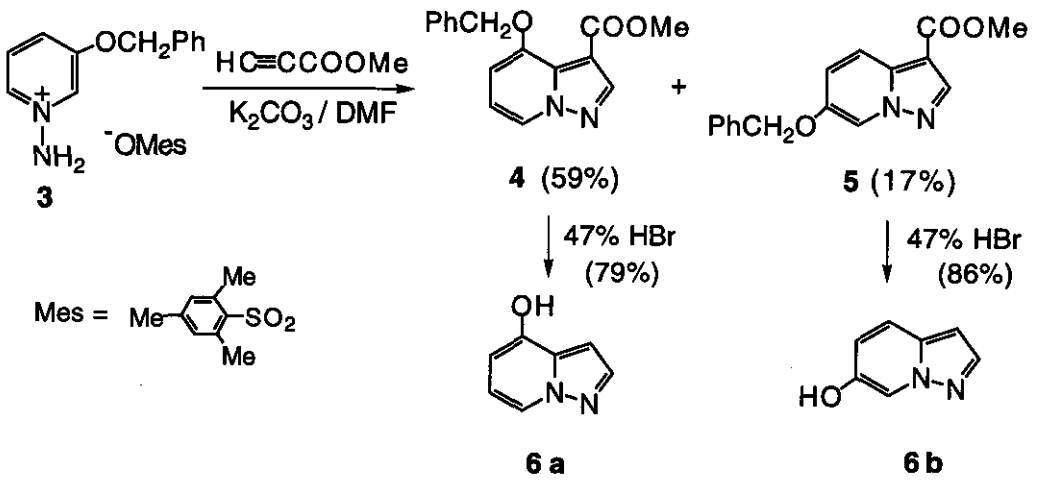
As our contribution to this relatively unexplored area, we have examined the synthesis of 1-isopropylamino-3-(pyrazolo[1,5-*a*]pyridyloxy)-2-propanols (**2**).

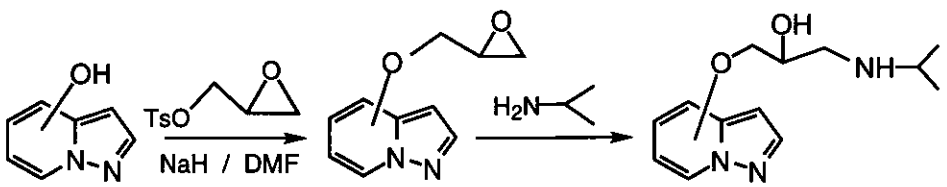
Reaction of 1-amino-3-benzyloxypyridinium mesitylenesulfonate (**3**), prepared from 3-benzyloxypyridine and *O*-mesitylenesulfonylhydroxylamine (MSH) in dichloromethane in 95% yield, with methyl propiolate in the presence of potassium carbonate in *N,N*-dimethylformamide at room temperature gave a mixture of methyl 4-benzyloxy- (**4**) and 6-benzyloxypyrazolo[1,5-*a*]-pyridine-3-carboxylate (**5**) in 59% and 17% yields, respectively. Treatment of **4** with refluxing 47% hydrobromic acid afforded 4-hydroxypyrazolo[1,5-*a*]pyridine (**6a**) in 79% yield. In a similar manner, **5** yielded 6-hydroxypyrazolo[1,5-*a*]pyridine (**6b**) in 86% yield (Scheme 1).

Scheme 1



Reaction of 4-hydroxypyrazolo[1,5-*a*]pyridine (**6a**) with glycidyl tosylate[5] in the presence of sodium hydride in *N,N*-dimethylformamide at room temperature afforded the epoxide (**7a**) (82%), which reacted with isopropylamine[5] to yield 1-isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-4-yloxy)-2-propanol (**8a**) in 76% yield. In a similar manner, 1-isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-6-yloxy)-2-propanol (**8b**) and 1-isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-3-yloxy)-2-propanol (**8c**) were prepared from the corresponding 6- (**6b**) and 3-hydroxypyrazolo[1,5-*a*]pyridines[6] (**6c**)(Scheme 2) (Table 1).

Scheme 2



6 7 8

a; 4-, b; 6-, c; 3-

Table 1

	yield(%)	
6	7	8
a	82	76
b	96	78
c	84	94

EXPERIMENTAL

All mps are uncorrected. The ^{1}H-nmr spectra were determined on a JEOL JNM-GSX270 spectrometer using tetramethylsilane as an internal standard. The ir spectra were recorded with a Hitachi EPI-G2 spectrophotometer.

3-Benzyloxypyridine

A mixture of 3-hydroxypyridine (76.0 g, 0.80 mol) and benzyl chloride (98.5 ml, 0.86 mol) in 40% sodium hydroxide (400 ml, 4.00 mol) and dichloromethane (400 ml) in the presence of Adogen 464 (5 ml) was stirred at room temperature for 60 h. The insoluble material was filtrated off and the reaction mixture was separated. The aqueous layer was extracted with dichloromethane three times. The organic layer and the combined extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by distillation under reduced pressure to give 3-benzyloxypyridine as a pale yellow oil (40.2 g, 27%) (bp$_4$ 121-123°C). ^{1}H-Nmr ($CDCl_3$) δ: 5.11 (2H, s, CH_2), 7.15-7.5 (7H, m, H-4, H-5, and Ph), 8.23 (1H, dd, *J*=4, 2 Hz, H-6), 8.39 (1H, dd, *J*=3, 0.5 Hz, H-2); HRms *m/z* (M^+) calcd for $C_{12}H_{11}NO$: 185.0841. Found: 185.0866.

1-Amino-3-benzyloxypyridinium Mesitylenesulfonate (3)

A solution of *O*-mesitylenesulfonylhydroxylamine (MSH)(27.64 g, 90 mmol, 70% assay) in dichloromethane (180 ml) was added to a solution of 3-benzyloxypyridine (16.65 g, 90 mmol) in dichloromethane (180 ml) under ice-cooling and the reaction mixture was stirred at 0°C for 1 h. Ether was added to the reaction mixture to give a white precipitate. The precipitate was collected and washed with ether to afford 1-amino-3-benzyloxypyridinium mesitylenesulfonate (**3**) (34.12 g, 95%), mp 105-108°C (from methanol-ethyl acetate). Ir (nujol): 3250, 3150 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.85-1.95 (2H, br s, NH_2), 2.20 (6H, s, CH_3x2), 2.67 (3H, s, CH_3), 5.12 (2H, s, $C\underline{H_2}Ph$), 6.83 (2H, s, Ph), 7.35 (5H, s, $CH_2\underline{Ph}$), 7.41 (1H, br d, *J*=9 Hz, H-4), 7.48 (1H, dd, *J*=9, 6 Hz, H-5), 8.67 (1H, br d, *J*=6 Hz, H-6), 8.97 (1H, br s, H-2); *Anal.* Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.99; H, 6.04; N, 7.00. Found: C, 62.85; H, 6.03; N, 6.71.

Methyl 4- (4) and 6-Benzyloxypyrazolo[1,5-*a*]pyridine-3-carboxylate (5)

To a solution of 1-amino-3-benzyloxypyridinium mesitylenesulfonate (**3**) (18.40 g, 46 mmol) in *N,N*-dimethylformamide (460 ml) was added potassium carbonate (7.62 g, 55 mmol) and the reaction mixture was stirred at 0°C for 10 min. Methyl propiolate (6.2 ml, 70 mmol) was added to the mixture and the reaction mixture was stirred overnight at room temperature. The insoluble material was filtered off and filtrate was evaporated off to give a residue, which was dissolved in dichloromethane. The insoluble solid was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (*n*-hexane : ethyl acetate = 5 : 1) to give methyl 4-benzyloxypyrazolo[1,5-*a*]pyridine-3-carboxylate (**4**) (7.64 g, 59%), and methyl 6-benzyloxypyrazolo[1,5-*a*]pyridine-3-carboxylate (**5**) (2.15 g, 17%).

4 ; mp 81-82°C (from methyl acetate-*n*-hexane). Ir (nujol): 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 3.73 (3H, s, CH_3), 5.25 (2H, s, CH_2), 6.71 (1H, dd, *J*=8, 1 Hz, H-5), 6.80 (1H, dd, *J*=8, 7 Hz, H-6), 7.3-7.45 (5H, m, Ph), 8.18 (1H, dd, *J*=7, 1 Hz, H-7), 8.37 (1H, s, H-2). *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.99; H, 4.99; N, 9.81.

5; mp 164-166°C (from methyl acetate). Ir (nujol): 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 3.90 (3H, s, CH_3), 5.08 (2H, s, CH_2), 7.27 (1H, dd, *J*=9.5, 2 Hz, H-5), 7.25-7.5 (5H, m, Ph), 8.05 (1H, dd, *J*=9.5, 0.5 Hz, H-4), 8.16 (1H, dd, *J*=2, 0.5 Hz, H-7), 8.30 (1H, s, H-7). *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.95; H, 5.03; N, 9.81.

4-Hydroxypyrazolo[1,5-*a*]pyridine (6a)

A mixture of methyl 4-benzyloxypyrazolo[1,5-*a*]pyridine-3-carboxylate (**4**) (1.69 g, 6 mmol) and 47% hydrobromic acid (60 ml) was refluxed for 10 min. The reaction mixture was evaporated off under reduced pressure to give a residue, which was neutralized with saturated sodium hydrogen carbonate solution. The solution was extracted with chloroform : methanol (10 : 1) and the extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was mixed with chloroform and the insoluble product was collected by filtration to afford 4-hydroxypyrazolo[1,5-*a*]pyridine (**6a**) (0.40 g, 50%). The filtrate was concentrated to give a residue, which was chromatographed on silica gel ($CHCl_3$: MeOH = 10 : 1) to give **6a** (0.23 g, 29%), mp 178-184°C (from ethyl acetate). Ir (nujol): 2625, 1555 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 3.1-3.3 (1H, br s, OH), 6.44 (1H, dd, *J*=7, 1 Hz, H-5), 6.61 (1H, dd, *J*=2.5, 1 Hz, H-3), 6.68 (1H, t, *J*=7 Hz, H-6), 7.84 (1H, d, *J*=2.5 Hz, H-2), 8.16 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.60; H, 4.77; N, 20.70.

6-Hydroxypyrazolo[1,5-*a*]pyridine (6b)

Using a procedure similar to that described for the preparation of **6a**, **6b** (86%) was obtained from **5**, mp 120-121°C (from *n*-hexane-ethyl acetate). Ir (nujol): 1645 cm^{-1}; ^{1}H-Nmr ($CDCl_3$) δ: 6.41 (1H, d, *J*=2.5 Hz, H-3), 6.88 (1H, dd, *J*=9, 2 Hz, H-5), 7.31 (1H, d, *J*=9 Hz, H-4), 7.78 (1H, d, *J*=2.5 Hz, H-2), 8.0-8.05 (1H, m, H-7). *Anal.* Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.85; H, 4.67; N, 20.70.

3-(Pyrazolo[1,5-*a*]pyrid-4-yloxy)-1,2-epoxypropane (7a)

To a suspension of sodium hydride (0.84 g, 21 mmol, 60% in oil) in dry *N,N*-dimethylformamide (75 ml) was added 4-hydroxypyrazolo[1,5-*a*]pyridine (**6a**) (2.01 g, 15 mmol) and the mixture was stirred at room temperature for 30 min under argon until an pale pinkish color was obtained. Glycidyl tosylate (4.10 g, 18 mmol) was added to the suspension and the mixture was stirred at room temperature overnight. The resulting brownish sludge was quenched with a saturated ammonium chloride solution, and the mixture was diluted with water and extracted with ether three times. The combined extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated to afford an oil. The oil was chromatographed on silica gel

(chloroform) to afford 3-(pyrazolo[1,5-*a*]pyrid-4-yloxy)-1,2-epoxypropane (**7a**) (2.33 g, 82%). ^{1}H-Nmr ($CDCl_3$) δ: 2.80 (1H, dd, *J*=5, 3 Hz, Hb), 2.95 (1H, dd, *J*=5, 4 Hz, Ha), 3.4-3.5 (1H, m, Hc), 4.08 (1H, dd, *J*=11, 6 Hz, one of CH_2), 4.38 (1H, dd, *J*=11, 3 Hz, one of CH_2), 6.38 (1H, d, *J*=7 Hz, H-5), 6.64 (1H, t, *J*=7 Hz, H-6), 6.65-6.7 (1H, m, H-3), 7.88 (1H, d, *J*= 2.5 Hz, H-2), 8.15 (1H, d, *J*=7 Hz, H-7); HRms *m/z* (M^+) calcd for $C_{10}H_{10}N_2O_2$: 190.0742. Found: 1190.0751.

3-(Pyrazolo[1,5-*a*]pyrid-6-yloxy)-1,2-epoxypropane (7b)

Using a procedure similar to that described for the preparation of **7a**, **7b** (96%) was obtained from **6b**. ^{1}H-Nmr ($CDCl_3$) δ: 2.79 (1H, dd, J=5, 3 Hz, Hb), 2.94 (1H, dd, J=5, 4 Hz, Ha), 3.35-3.45 (1H, m, Hc), 3.90 (1H, dd, J=11, 6 Hz, one of CH_2), 4.28 (1H, dd, J=11, 3 Hz, one of CH_2), 6.47 (1H, dd, *J*=2.5, 1.5 Hz, H-3), 6.97 (1H, dd, *J*=10, 2 Hz, H-5), 7.43 (1H, d, *J*=10 Hz, H-4), 7.85 (1H, d, *J*=2.5 Hz, H-2), 8.03 (1H, dd, *J*=2, 1 Hz, H-7); HRms *m/z* (M^+) calcd for $C_{10}H_{10}N_2O_2$: 190.0742. Found: 1190.0763.

3-(Pyrazolo[1,5-*a*]pyrid-3-yloxy)-1,2-epoxypropane (7c)

Using a procedure similar to that described for the preparation of **7a**, **7c** (84%) was obtained from **7**[6]. ^{1}H-Nmr ($CDCl_3$) δ: 2.80 (1H, dd, *J*=5, 3 Hz, Hb), 2.95 (1H, dd, *J*=5, 4 Hz, Ha) , 3.4-3.5 (1H, m, Hc), 4.08 (1H, dd, *J*=11, 6 Hz, one of CH_2), 4.38 (1H, dd, *J*=11, 3 Hz, one of CH_2), 6.38 (1H, d, *J*=7 Hz, H-5), 6.64 (1H, t, *J*=7 Hz, H-6), 6.66 (1H, dd, *J*=2.5, 1 Hz, H-3), 7.88 (1H, d, *J*= 2.5 Hz, H-2), 8.15 (1H, d, J=7 Hz, H-7); HRms *m/z* (M^+) calcd for $C_{10}H_{10}N_2O_2$: 190.0742. Found: 1190.0744.

1-Isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-4-yloxy)-2-propanol (8a)

A mixture of 3-(pyrazolo[1,5-*a*]pyrid-4-yloxy)-1,2-epoxypropane (**7a**) (2.09 g, 11 mmol) in isopropylamine (15 ml, 176 mmol) and water (1.5 ml) was refluxed for 1 h and the solvent was evaporated off to give a residue, which was dissolved in ether. The ether solution was dried over anhydrous sodium sulfate, and concentrated to afford a residue, which was purified by chromatography on silica gel (chloroform : methanol = 20 : 1) to afford 1-isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-4-yloxy)-2-propanol (**8a**)(2.08 g, 76%), mp 74-76°C. Ir (nujol): 3240 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.11 (6H, d, *J*=6 Hz, CH_3x2), 2.0-2.3 (2H, br s, NH and OH), 2.7-3.0 (3H, m,

-CH(OH)C*H*$_2$NHC*H*-), 4.0-4.2 (3H, m, -OC*H*$_2$C*H*(OH)-), 6.39 (1H, br d, *J*=7 Hz, H-5), 6.62 (1H, dd, *J*=2.5, 1 Hz, H-3), 6.64 (1H, t, *J*=7 Hz, H-6), 7.87 (1H, d, *J*= 2.5 Hz, H-2), 8.14 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.68; N, 16.86. Found: C, 62.76; H, 7.58; N, 16.73.

1-Isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-6-yloxy)-2-propanol (8b)

Using a procedure similar to that described for the preparation of **8a**, **8b** (78%) was obtained from **7b**, mp 122-123°C (from ethyl acetate). Ir (nujol): 3240 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.10 (6H, d, *J*=6 Hz, CH3x2), 2.1-2.35 (2H, br s, NH and OH), 2.7-2.95 (3H, m, -CH(OH)C*H*$_2$NHC*H*-), 3.95-4.1 (3H, m, -OC*H*$_2$C*H*(OH)-), 6.43 (1H, d, *J*=2.5 Hz, H-3), 6.96 (1H, dd, *J*=9.5, 2 Hz, H-5), 7.42 (1H, d, *J*=9.5 Hz, H-4), 7.85 (1H, d, *J*=2.5 Hz, H-2), 8.1-8.15 (1H, m, H-7). *Anal.* Calcd for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.68; N, 16.86. Found: C, 62.67; H, 7.62; N, 16.89.

1-Isopropylamino-3-(pyrazolo[1,5-*a*]pyrid-3-yloxy)-2-propanol (8c)

Using a procedure similar to that described for the preparation of **8a**, **8c** (94%) was obtained from **7c**, mp 66-68°C (from *n*-hexane). Ir (nujol): 3260 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.10 (6H, d, *J*=6 Hz, CH3x2), 2.0-2.3 (2H, br s, NH and OH), 2.75-3.0 (3H, m, -CH(OH)C*H*$_2$NHC*H*-), 4.05-4.2 (3H, m, -OC*H*$_2$C*H*(OH)-), 6.39 (1H, br d, *J*=7 Hz, H-5), 6.62 (1H, dd *J*=2.5, 1 Hz, H-3), 6.64 (1H, t, *J*=7 Hz, H-6), 7.87 (1H, d, *J*= 2.5 Hz, H-2), 8.15 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.68; N, 16.86. Found: C, 62.74; H, 7.66; N, 16.61.

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