

## Synthesis of $^{13}\text{C}$ -Bucindolol Hydrochloride

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### Summary

[Cyano- $^{13}\text{C}$ ] Bucindolol hydrochloride, 2-[2-hydroxy-3-[[2-(1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile-[cyano- $^{13}\text{C}$ ] hydrochloride, a novel beta-adrenergic antagonist, was synthesized in our laboratory for metabolic studies. The preparation of [cyano- $^{13}\text{C}$ ] bucindolol hydrochloride from 2-hydroxybenzonitrile-[cyano- $^{13}\text{C}$ ] utilizing  $^{13}\text{C}$ -copper(I) cyanide as an isotopic starting material is described.

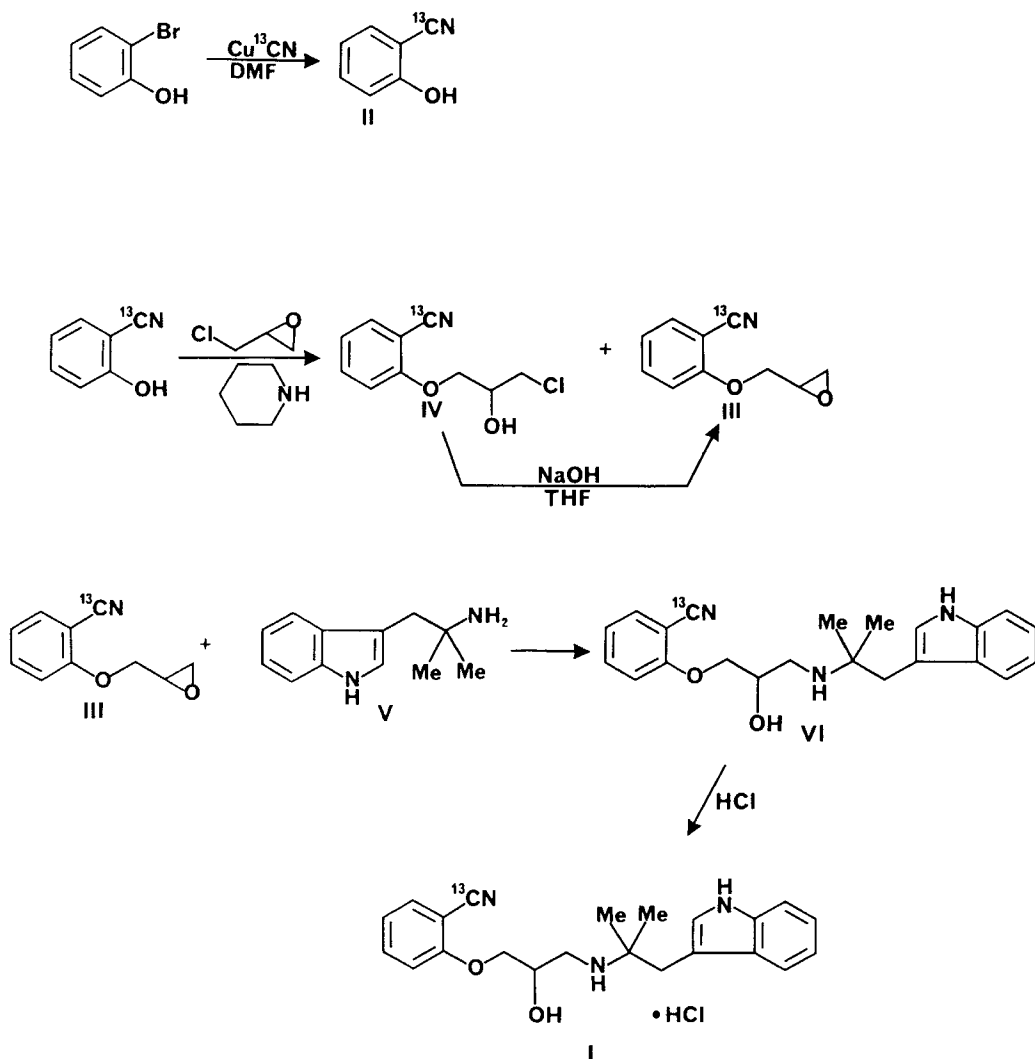
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### Introduction

Bucindolol hydrochloride, 2-[2-hydroxy-3-[[2-(1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile hydrochloride, is a novel antihypertensive agent currently under clinical investigation. In a variety of animal models, bucindolol hydrochloride has demonstrated vasodilator, beta-adrenergic antagonist and alpha-adrenergic antagonist properties.<sup>1,2</sup> In order to study the metabolic fate of bucindolol, a sample of [cyano- $^{13}\text{C}$ ] bucindolol hydrochloride (I) was required. The reaction sequence below describes the synthesis of I from 2-hydroxybenzonitrile-[cyano- $^{13}\text{C}$ ], a very versatile isotopically labelled starting material.

## Results and Discussion

The original preparation of bucindolol hydrochloride utilized 2-hydroxybenzonitrile as a starting material.<sup>1</sup> Since the corresponding 2-hydroxybenzonitrile-[cyano-<sup>13</sup>C] (II) was not readily available, it was synthesized from 2-bromophenol.



Treatment of 2-bromophenol with  $^{13}\text{C}$ -copper(I) cyanide in DMF afforded II in very good yield.<sup>3</sup> Heating II with a six-fold excess of epichlorohydrin in the presence of a catalytic amount of piperidine<sup>4</sup> gave a mixture of the desired 2-[(2,3-epoxy)propoxy]benzonitrile-[cyano- $^{13}\text{C}$ ] (III) and the corresponding chlorohydrin (IV). Treatment of the mixture of III and IV with dilute sodium hydroxide in aqueous THF<sup>4,5</sup> afforded III as a waxy solid in quantitative crude yield. Without further purification, III was stirred with 2-(3-indolyl)-1,1-dimethylethylamine (V)<sup>1</sup> in acetone affording 2-[2-hydroxy-3-[[2-(1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile-[cyano- $^{13}\text{C}$ ] (VI) in 43% yield after recrystallization from ethanol. The hydrochloride salt of VI was generated by treatment of a warm acetone solution of VI with concentrated hydrochloric acid. Clarification of the crude I with charcoal and crystallization from acetone and isopropanol gave 2-[2-hydroxy-3-[[2-(1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile-[cyano- $^{13}\text{C}$ ] hydrochloride (I) in 93% yield.

### Experimental

Proton magnetic resonance spectra were obtained on a Perkin-Elmer R-32 90 MHz spectrometer. All chemical shifts are reported as ppm from tetramethylsilane (TMS) used as an internal standard with  $\text{CDCl}_3$  or  $\text{DMSO-d}_6$  used as solvent. Infrared spectra were recorded on a Nicolet MX-1 using KBr pellets. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

#### 2-Hydroxybenzonitrile-[cyano- $^{13}\text{C}$ ], (II)

A mixture of 2-bromophenol (0.202 mol) and  $^{13}\text{C}$ -copper(I) cyanide<sup>6</sup> (0.202 mol) in DMF (200 mL) was heated at reflux for 19h. The resulting dark brown mixture was poured into a solution of iron(III) chloride hexahydrate (80 g) in concentrated hydrochloric acid (20 mL) and water (120 mL). The mixture was heated at 60-70°C for 30 min, cooled and extracted with ether (3 x 150 mL).

After drying over  $\text{MgSO}_4$ , the combined ether extracts were evaporated in vacuo. Chromatography of the residue on silica gel with chloroform-methanol (9:1) afforded 18.0 g of a tan solid (71% yield); mp 92-94°C; IR (KBr) 3290, 2180, 1590, 1505, 1460, 1360, 1300, 1235, 1165 and 745  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.55 (m, 2H), 7.01 (m, 2H) and 6.80 (s, 1H); 93%  $^{13}\text{C}$  enrichment<sup>7</sup>; Anal. ( $\text{C}_7\text{H}_5\text{NO}$ ) calc., C:70.59, H:4.24 and N:11.76; found, C:70.48, H:4.18 and N:11.75.

2-[(2,3-Epoxy)propoxy]benzonitrile-[cyano- $^{13}\text{C}$ ], (III)

A mixture of II (0.21 mol), epichlorohydrin (1.26 mol) and piperidine (10 drops) was heated at reflux for 2h. Excess epichlorohydrin was removed by distillation in vacuo. The residual oil was dissolved in THF (260 mL) and 1 N sodium hydroxide (260 mL) and heated at 40-50°C for 1 h. After cooling, the reaction mixture was extracted with methylene chloride (3 x 150 mL). The combined extracts were washed with water, dried over  $\text{MgSO}_4$  and evaporated in vacuo affording 36.7 g of a waxy solid (~100% yield);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.50(m, 2H), 7.00(m, 2H), 4.39 (dd,  $J = 5.0$  Hz and  $J = 11.5$  Hz, 1H), 4.05 (dd,  $J = 2.8$  Hz and  $J = 11.5$  Hz, 1H), 3.40(m, 1H) and 2.80(m, 2H); IR(KBr) 2220, 1600, 1495, 1290, 1260 and 750  $\text{cm}^{-1}$ . This material was used without further purification.

2-[2-Hydroxy-3-[[2-(1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile-[cyano- $^{13}\text{C}$ ], (VI)

A mixture of III (0.209 mol) and V (0.209 mol) in acetone (250 mL) was stirred at room temperature for 1 h. The acetone was removed by distillation at atmospheric pressure. The residual oil was heated at 95-100°C for 2 h, dissolved in ethanol (500 mL) and allowed to crystallize. A crude crystalline product (70 g) was collected by filtration and recrystallized from ethanol affording 35.1 g of a white crystalline solid (46% yield), mp 126-127°C; IR (KBr) 3420, 3250, 2950, 2910, 2170, 1580, 1480, 1440, 1290, 1260 and 735;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  11.08 (s, 1H), 7.75(m, 3H), 7.25(m, 6H), 5.04(s, 1H), 4.17(d,  $J = 3.5$  Hz, 2H), 3.90(s, 1H), 3.33(s, 1H), 2.75(s, 4H) and 1.00 (s, 6H); Anal. ( $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2$ ) calc., C:72.78, H:6.91 and N:11.53; found, C:72.38, H:6.96 and N:11.29; 93%  $^{13}\text{C}$  enrichment.<sup>7</sup>

2-[2-Hydroxy-3-[[2-(1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile-  
[cyano- $^{13}\text{C}$ ] Hydrochloride (I)

A solution of VI (0.096 mol) in acetone (400 mL) at 45°C was treated with concentrated hydrochloric acid (45 mL). Clarification with activated charcoal at 60°C for 20 min and filtration through celite gave a clear solution. Isopropanol (40 mL) was added to the filtrate, the mixture cooled, scratched and allowed to crystallize. Collection of the product by filtration afforded 36 g of a white crystalline solid (94% yield); mp 186-187°C. Anal. ( $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2 \cdot \text{HCl}$ ) calc., C:66.16, H:6.54 and N:10.48; found, C:65.94, H:6.59 anal N:10.50; 93%  $^{13}\text{C}$  enrichment.<sup>7</sup>

#### References

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6.  $^{13}\text{C}$ -Copper(I) cyanide was purchased from KOK Inc., Cat. No. C-434,  $^{13}\text{C}$  enrichment 93%.
7. Determined by mass spectral analysis.