

## PREPARATION OF $\ell$ -[1-(p-n-BUTOXYBENZYL-1'-<sup>3</sup>H) HYOSCYAMINIUM BROMIDE ]

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[3 $\alpha$ -Hydroxy-8-(p-n-butoxybenzyl)-1 $\alpha$ H,5 $\alpha$ H-tropanium-(-) tropate] bromide ( $\ell$ -[1-(p-n-butoxybenzyl) hyoscyaminium] bromide, abbreviated as BHB) has been recognized to have an anticholinergic action<sup>(1)</sup>. For the purpose to know the metabolic fate of BHB in animals, we required radioactive BHB. This paper is concerned with the preparation of  $\ell$ -[1-(p-n-butoxybenzyl-1'-<sup>3</sup>H) hyoscyaminium bromide] (<sup>3</sup>H-BHB).

A solution of p-n-butoxybenzaldehyde (100 mg) in ethanol was reduced with tritium and then hydrogen gas in a presence of palladium on charcoal (5 %, 10 mg). After removal of solvent and labile tritium, p-n-butoxybenzyl alcohol-<sup>3</sup>H obtained had a specific radioactivity of 5.55 mCi/mg and showed a peak of radioactivity at the same position as the authentic p-n-butoxybenzyl alcohol (Rf : 0.37) on thin layer chromatogram of Kieselgel G developed with a solvent system of benzene/ethylacetate, 2/1. The labeling position of tritium in p-n-butoxybenzyl alcohol was confirmed as follows. A solution of 1.5 g of potassium permanganate in 50 ml of acetone and 5 ml of 3 % NaOH aqueous solution was added to an admixture of the tritium labeled compound ( $9.25 \times 10^7$  dpm) and 500 mg of p-n-butoxybenzyl alcohol at 4°C and then stood for 48 hours at room temperature under stirring. 50 ml of water was added to the residue obtained after evaporation and filtered. The filtrate was extracted with ethylether to remove the starting material. Following

acidified with 2 N  $\text{H}_2\text{SO}_4$ , the resultant solution was extracted with ethylether four times. 91 mg of crude product obtained by evaporation of ethereal extract showed monospot at the same position as the authentic p-n-butoxybenzoic acid<sup>(2)</sup> on thin layer chromatograms of Kieselgel GF<sub>254</sub> (250  $\mu$  in thickness), which was developed with two solvent systems of ethylacetate/methanol/5 N  $\text{NH}_4\text{OH}$ , 50/8/5 (Rf : 0.20) and n-hexane/dioxane/acetic acid, 20/5/1 (Rf : 0.75), under UV-lamp (2536 A). This crude product was repeatedly recrystallized from benzene. The fact that 32.1 mg of p-n-butoxybenzoic acid, of which specific radioactivity was 48 dpm/mg, was obtained indicates that p-n-butoxybenzyl alcohol was labeled with tritium at C-1 position alone.

To 106 mg of p-n-butoxybenzyl alcohol-1-<sup>3</sup>H (46 mCi) in 1 ml of benzene, 0.5 ml of 48 % hydrogen bromide was added dropwise on an ice-water bath under stirring. After standing for 1.5 hours, the reaction mixture was extracted three times with 25 ml of benzene. The benzene layer was washed with 7 % NaCl aqueous solution and dried on granulated  $\text{MgSO}_4$  unhydrous.

The residue, which was obtained following evaporation of benzene, was dissolved in 1.5 ml of acetone and added to a solution of 98 mg of 3- $\alpha$ -hydroxy-1 $\alpha$ H,5 $\alpha$ H-tropan-(-)tropate (*l*-hyoscyamine) in each 1 ml of acetone and ethanol. The mixture was stirred on ice-water bath for 1 hour. After removal of solvent from the reaction mixture at room temperature in vacuo, the residue was dissolved in 5 ml of acetone and stood at -20°C for 2 hours. <sup>3</sup>H-BHB obtained in a yield of 40 % was confirmed to be pure on thin layer chromatograms. Thin layer chromatography was carried out using Kieselgel GF<sub>254</sub> (250  $\mu$  in thickness)

with two solvent systems of acetic acid/n-butanol/water, 1/4/5 (upper layer) (Rf : 0.52) and ethylacetate/acetic acid/water, 9/2/2 (Rf : 0.35). The product showed a specific radioactivity of 146  $\mu$ Ci/mg and to be stable during storage for about 2 years at -20°C.

#### References

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