# SYNTHESIS OF TRITIUM LABELED PHENYLEPHRINE

Lina Teng, Robert B. Bruce

Research Laboratories, A. H. Robins Company
1211 Sherwood Avenue. Richmond, Virginia 23220

Received October 26, 1977
Revised November 29, 1977

## SUMMARY

An improved method for small scale synthesis of phenylephrine hydrochloride is described. 5-[3-(phenylmethoxy)phenyl]-2-oxazolidinone was methylated with dimethylsulfate-methyl-$^3H_3$. The resulting compound was converted to phenylephrine hydrochloride by alkaline hydrolysis followed by hydrogenolysis. The radiochemical yield was over 50% based on dimethyl sulfate.

Key words: Phenylephrine Hydrochloride-methyl-$^3H_3$, Dimethyl Sulfate-methyl-$^3H_3$, Hydrolysis, Hydrogenolysis

## INTRODUCTION

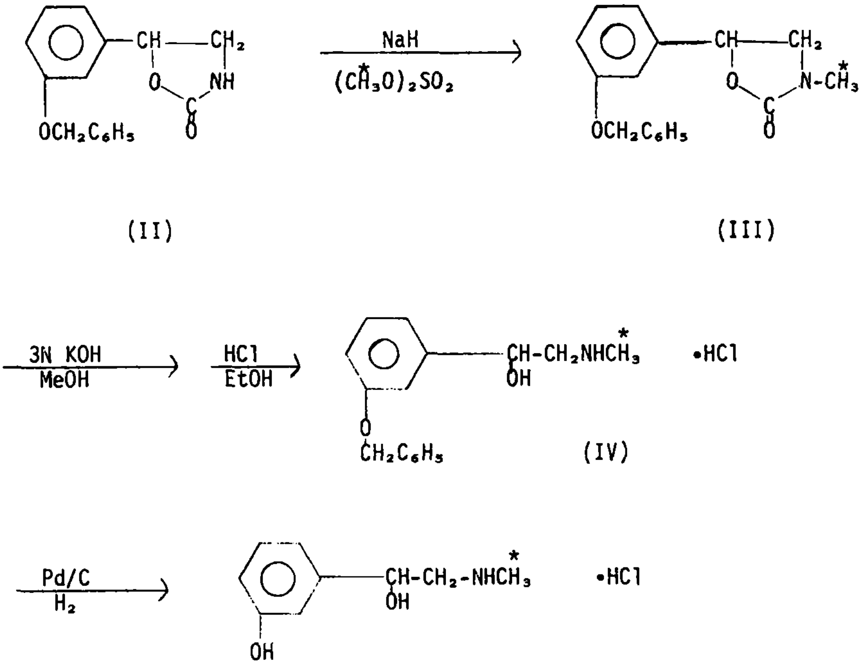
In conjunction with a program to study the pharmacokinetics of phenylephrine in humans, we were in need of a radioactive sample of phenylephrine hydrochloride (I). Although phenylephrine has long been used as a nasal decongestant, no synthetic method was available for small scale synthesis. We have devised the following synthetic scheme for our purpose.

The starting material, 5-[3-(phenylmethoxy)phenyl]-2-oxazolidinone (II) was obtained from m-hydroxybenzaldehyde in four steps following the method of Bergmann and Sulzbacher (1).

Methylation of the oxazolidinone was carried out with sodium hydride in toluene, followed by dimethylsulfate. This procedure was found more satisfactory than using sodium methoxide to prepare the anion, because it was not necessary to expel the solvent before adding dimethylsulfate. Bergmann and Sulzbacher (1) had reported that (III) was converted to (I) in 40% hydrochloric acid in a one step reaction.

0362-4803/78/0015-0321$01.00

Unfortunately, we were unable to repeat the experiment. In concentrated hydrochloric acid solution, (III) lost the benzyl group but the oxazolidinone ring remained intact. The ring-opening was effected in potassium hydroxide solution. The benzyl group was removed by hydrogenolysis. The overall yield was better than 50% based on tritium labeled dimethyl sulfate. The material obtained was satisfactory for our analytical purpose.



(II) (III)

(IV)

(I)

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on 250 micron precoated silica gel GF plates from Analtech, Newark, Delaware. Radioactivity was determined with a Packard Model 3385 liquid scintillation spectrometer. Dimethyl sulfate-methyl-$^3H_3$ was purchased from New England Nuclear, Boston, Mass. and was used directly. The structure of the compounds were confirmed by TLC and mass spectrometry.

3-Methyl-$^{3}H_{3}$-5-[3-(phenylmethoxy)phenyl]-2-oxazolidinone (III). Sodium hydride (50% in mineral oil, 363.2 mg, 7.27 mmoles) was washed with toluene several times to remove the mineral oil, then resuspended in toluene (20 ml). To the suspension, (II) (1.359 g, 5.05 mmoles) was added and the mixture was stirred until hydrogen evolution ceased. The mixture was cooled in an ice-bath, and tritium labeled dimethyl sulfate (0.8 mg, 22.7 mCi) in ether (1 ml) was added, stirred for 2-3 minutes, before non-radioactive dimethylsulfate (315 mg, 2.5 mmoles) was added. The mixture was refluxed for two hours, cooled, and the excess sodium hydride decomposed with water (10 ml). The toluene phase showed only one radioactive spot on TLC (2% MeOH in $CHCl_{3}$) corresponding to (III), total radioactivity: 14.9 mCi. The solvent was evaporated and the residue used directly for hydrolysis without further purification.

α-[(Methyl-$^{3}H_{3}$-amino)methyl]3-(phenylmethoxy)benzene methanol monohydrochloride (IV). To the residue obtained above, 15 ml each of 3N KOH and methanol were added. The mixture was refluxed for three hours to give a clear solution. The solution was cooled to room temperature and the methanol evaporated at reduced pressure. The resulting white solid was filtered, dried, and digested with absolute ethanol. The ethanol solution was then saturated with hydrogen chloride gas. After evaporation of the solvent, the solid residue was recrystallized from ethanol-ether to give (IV) as a white crystalline powder, m.p. 148-150° [lit. (2) 150-153°], 1.18 g, 13.8 mCi. TCL ($CHCl_{3}$:MeOH:con $NH_{4}OH$; 90:10:1) showed one spot corresponding to (IV).

Phenylephrine-Methyl-$^{3}H_{3}$ hydrochloride (I). (IV) (1.18 g) in 60 ml of methanol was hydrogenated in the presence of palladium-charcoal catalyst at room temperature for 90 minutes. The catalyst was filtered and the solvent evaporated. The residue was recrystallized twice from ethanol-ether to give a white crystalline powder, m.p. 142-143° [(lit. 140-145° (1); 143-145° (2)]. TLC showed one spot corresponding to authenic phenylephrine hydrochloride, wt.: 584.8 mg. Concentration of the mother liquor gave another 102.6 mg. Total radioactivity: 11.4 mCi, 50.2% based on radioactive dimethyl sulfate.

## Acknowledgment

The authors wish to thank Mr. S. Bearekman for his valuable technical assistance.

## References

1. Bergmann E. D. and Sulzbacher M. - J. Org. Chem. 16: 84 (1951).
2. Russell P. B. and Childress S. J. - J. Pharm. Sci. 50: 713 (1961).