SYNTHESIS OF PROPANOLAMINE SIDE CHAIN DEUTERATED PROPRANOLOL, PROPRANOLOL-DIOL AND 4-HYDROXYPROPRANOLOL

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SUMMARY

Syntheses of 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol-1,1,2,3,3-d5 (1), 3-(1-naphthyloxy)-1,2-propanediol-1,1,2,3,3-d5 (2) and 1-(isopropylamino)-3-(4-hydroxy-1-naphthyloxy)-2-propanol-1,1,2,3,3-d5 (3) from epichlorohydrin-d5 are described. Treatment of epichlorohydrin-d5 with 1-naphthol, in the presence of a catalytic amount of pyridine, afforded a mixture of 1-chloro-3-(1-naphthyloxy)-2-propanol-1,1,2,3,3-d5 (4) and 1,2-epoxy-(1-naphthyloxy)-propane-1,1,2,3,3-d5 which was converted to 4, with HCl or to 5 with 6N KOH. Reaction of 4 with isopropylamine afforded 1. Acid catalyzed hydrolysis of 5 afforded 2. A modification of the synthesis of 1 using 4-methoxy-1-naphthol, epichlorohydrin-d5 (1N NaOH) afforded epoxide 7, which was opened with isopropylamine. Ether cleavage with pyridine·HCl completed synthesis of 1-(isopropylamino)-3-(4-hydroxy-1-naphthyloxy)-2-propanol-1,1,2,3,3-d5 (3).

Key Words: Propranolol, Propranolol-diol, 4-Hydroxypropranolol, Beta-Adrenergic Antagonists.

INTRODUCTION

Propranolol [1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol] is an important member of a group of 3-aryloxy-1-alkylamino-2-propanol beta-adrenergic antagonists. It possesses therapeutically important properties in the treatment of cardiovascular disorders, valuable antihypertensive properties, and may be potentially useful in psychiatric disorders and in certain other conditions.[1] Propranolol is extensively metabolized in man, rats and dogs to a number of products including 4-hydroxypropranolol, propranolol-diol [3-(1-naphthyloxy)-1,2-propanediol], des-isopropylpropranol [1-amino-3-(1-naphthyloxy)-2-propanol], 3-(1-naphthyloxy)-lactic acid, 2-(1-naphthyloxy)-acetic acid, 4-hydroxypropranolol-diol, other ring hydroxylated propranolols and smaller fragments including isopropylamine, 1-naphthol and 1,4-naphthalenediol.[2-9] It has been suggested that several of the pharmacologically active metabolites may contribute to the therapeutically useful effects of propranolol.[3,4,10,11]

In order to undertake a mechanistic investigation of some of the

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processes which lead to these metabolites, we needed appropriate deuterated materials, including propranolol and some of its metabolites. Of particular importance to us was the need to locate the deuterium label at positions which are likely to remain intact in spite of the wide variety of metabolic processes. Propranolol-d_6 with deuterium atoms located in the methyl groups of the N-isopropyl substituent has been prepared,[11] but did not meet our requirements since this group is not retained in many of the metabolites. In this paper we report the synthesis of propranolol-d_5 (1) and two propranolol metabolites: propranolol-diol-d_5 (2) and 4-hydroxypropranolol-d_5 (3), each deuterated in the propanolamine side chain.

DISCUSSION

A synthesis of propranolol-d_5 was developed which requires no isolation of intermediates, yet affords the desired product in greater than 50% yield, based on 1-naphthol (Figure 1). 1-Naphthol was allowed to react with a two molar excess of epichlorohydrin-d_5 (Merck) forming a mixture of chlorohydrin 4 and epoxide 5, when the reaction was performed in the presence of a catalytic amount of pyridine. However, the mixture of the products was readily converted to either all chlorohydrin 4 or all epoxide 5 by appropriate treatment with acid or base. In the propranolol-d_5 synthesis, the mixture was converted to chlorohydrin 4 by shaking the crude mixture with conc. aqueous HCl for two

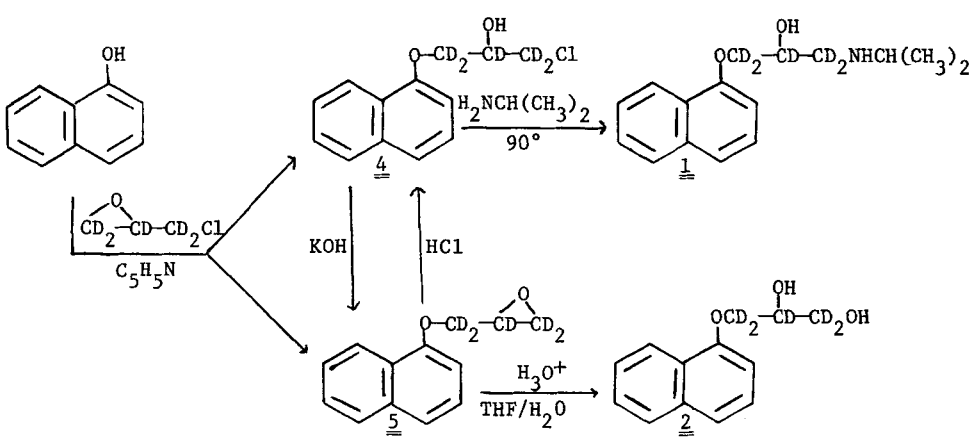

Figure 1. Synthesis of propranolol-d_5 and propranolol-diol-d_5

to three minutes. The nearly pure chlorohydrin (4) was then allowed to react with isopropylamine at 90° overnight. Workup and isolation afforded a 53% yield of propranolol-d5 (1), based on 1-naphthol.

Formation of propranolol-diol-d5 (2) (Figure 1) utilized the same mixture of chlorohydrin 4 and epoxide 5. The mixture was treated with 6N KOH for 10 minutes affording almost all epoxide 5, as shown by tlc. Hydrolysis was performed in THF-water with 1N H_2SO_4 affording a 45% yield of propranolol-diol-d_5 again without isolation of intermediates.

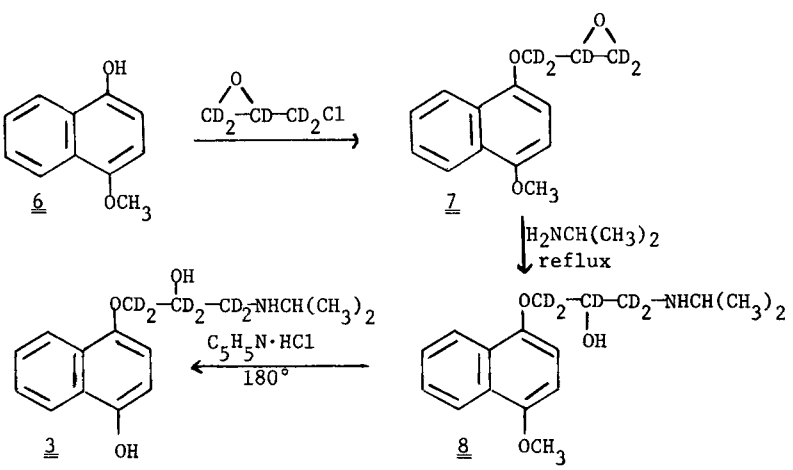

Figure 2. Synthesis of 4-hydroxypropranolol-d_5

The synthesis of 4-hydroxypropranolol required finding a facile method for obtaining 4-methoxy-1-naphthol. Although several methods are reported,[12,14] we found the easiest process to be reductive methylation of 1,4-naphthoquinone using stannous chloride in methanolic HCl. Subsequent steps are outlined in Figure 2. In contrast to the propranolol-d_5 synthesis, the most efficient conversion to epoxide 7 was treatment of 4-methoxy-1-naphthol (6), with one equivalent of epichlorohydrin-d5, in the presence of aqueous 1N NaOH. This process afforded the advantage of requiring only a single equivalent of epichlorohydrin-d5. The epoxide was opened in refluxing isopropylamine affording 4-methoxypropranolol-d5 (8). Carefully controlled conditions of heating 8·HCl with six equivalents of pyridine·HCl under nitrogen at 185-190° (2 hours) gave

4-hydroxypropranolol-d_5 HCl (3·HCl) without effecting substantial side chain cleavage. Other attempted methods to cleave the ether using boron tribromide,[15,16] hydrazine hydrate[17] or sodium propylmercaptide[18] were unsuccessful.

Synthesis of aryloxypropanolamines with pentadeuterated propanolamine side chains, based on the use of epichlorohydrin-d_5 and a phenol is likely to be sufficiently general that it could be applied to the preparation of many other beta-adrenergic antagonists and their metabolites.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary melting point apparatus, and are uncorrected. Nmr spectra were recorded on a Varian T-60 spectrometer using TMS as internal standard. Tlc plates used were silica gel-GF (Brinkmann). CI mass spectra were obtained on an SRI Biospect mass spectrometer (direct insertion probe) using methane as reagent gas.

1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol-1,1,2,3,3-d_5 (Propranol-d_5) (1) -- A mixture of 720 mg (5.0 mmol) of 1-naphthol, 1.46 g (15 mmol) of epichlorohydrin-d_5 (Merck, > 98% deuterium) and 3 drops of pyridine was heated at 90° for 5 hr. Tlc ($CHCl_3$) at 5 hr showed disappearance of the 1-naphthol (R_f 0.50) and appearance of epoxide 5 (R_f 0.85) and chlorohydrin 4 (R_f 0.57). Excess epichlorohydrin-d_5 was removed by rotary evaporation and the residue dissolved in 50 ml of $CHCl_3$ which was then washed with aqueous 5% NaOH and then with H_2O. The resulting $CHCl_3$ solution was shaken with 10 ml of conc. HCl (2 to 3 min) to convert epoxide 5 to chlorohydrin 4, as demonstrated by tlc. The $CHCl_3$ solution was washed with H_2O, dried ($MgSO_4$) and evaporated. To the crude chlorohydrin was added 20 ml of isopropylamine and the mixture heated in a reaction bomb at 95° overnight. The bomb was cooled, opened and the contents removed by rinsing with acetone and $CHCl_3$. After evaporation of solvents, the residue was partitioned between 100 ml of 4% aqueous HCl and 50 ml of ether. The aqueous layer was made alkaline by dropwise addition of 12N NaOH, with formation of a yellow precipitate which was removed by filtration and crystallized from cyclohexane (charcoal) affording 680 mg of

propranolol-d_5 (1), mp 96-97° (53% yield) (lit. mp 95-96°, nondeuterated).[19] M/e 265 (MH^+).

3-(1-Naphthyloxy)-1,2-propanediol-1,1,2,3,3-d_5 (Propranolol-diol-d_5) (2) -- A mixture of chlorohydrin 4 and epoxide 5 was prepared as described in the synthesis of propranolol-d_5 (1) from 5 mmol of 1-naphthol, 15 mmol of epichlorohydrin-d_5 and 3 drops of pyridine, by heating at 90°, 5 hr. To the crude mixture of 4 and 5 obtained after evaporation of excess epichlorohydrin-d_5 was added 10 ml of 6N KOH and the mixture stirred at 60° for 1 hr to convert chlorohydrin 4 to epoxide 5. The crude product was extracted into $CHCl_3$, washed with H_2O, with aqueous 3% HCl, with H_2O again, and dried ($MgSO_4$). After evaporation of the solvent, the crude epoxide in a mixture of 20 ml of THF and 10 ml of 1N H_2SO_4 was stirred at 70° overnight. One ml of conc. NH_3 was added and the THF evaporated. The residue was dissolved in $CHCl_3$, washed with water, evaporated and chromatographed on 30 g of silica gel (Merck), first using $CHCl_3$ as eluent. After 400 ml of $CHCl_3$ which removed a small amount of highly colored material, 400 ml of a mixture of $CHCl_3$-EtOAc, 70:30, was passed through the column followed by 400 ml of $CHCl_3$-ETOAc-MeOH, 45:45:10. The $CHCl_3$-EtOAc contained the product which was crystallized from benzene-hexane 3:1, affording 500 mg of propranolol-diol-d_5 (2) (45% yield), mp 95-96° (lit. 96-97°, nondeuterated material).[10] M/e 224 (MH^+).

4-Methoxy-1-naphthol (6) -- 1,4-Naphthoquinone (9.0 g, 77 mmol) and stannous chloride (14.0 g, 77 mmol) were dissolved in 45 ml of absolute methanol and heated at reflux for 30 min. An additional 45 ml of methanol which had previously been saturated with gaseous HCl was added and refluxing continued. After 1.5-2 hr the tlc spot corresponding to 1,4-dihydroxynaphthalene (R_f 0.32, $CHCl_3$-MeOH, 9:1) had nearly disappeared. The mixture was cooled to room temperature and 5 ml of H_2O was added. A small amount of precipitated 1,4-dimethoxynaphthalene was removed by filtration and discarded. Water (100 ml) was added and the mixture cooled to 0° and the precipitated crude product was removed by filtration, washed with H_2O and dried. Crude 6 was dissolved in

100 ml of $CHCl_3$, 1 g of activated charcoal was added and the mixture heated on a steam bath at reflux until the volume was reduced to 50 ml. The mixture was filtered and the charcoal residue washed with $CHCl_3$. On cooling the $CHCl_3$ solution afforded 3.50 g (38% yield) of 6 as white crystals, mp 128-129° (lit. 128°),[12] R_f 0.57.

1,2-Epoxy-3-(4-methoxy-1-naphthyloxy)-propane-1,1,2,3,3-d_5 (7) -- 4-Methoxy-1-naphthol (6), (1.55 g, 8.9 mmol), was dissolved in 4.0 ml 95% ethanol containing 1.09 g (8.9 mmol) epichlorohydrin-d_5. To the mixture was added 12 ml of 1N-NaOH. The mixture was stirred at room temperature under nitrogen for 12 hr. The precipitated solid was removed by filtration affording 1.29 g (63%) of crude epoxide 7. A 200 mg sample of the crude epoxide was purified by column chromatography on 50 g of silica gel using $CHCl_3$-petroleum ether, 7:1 as eluent, affording 70 mg of pure 7, mp 77-78° (lit. 80-81°, nondeuterated),[20] R_f 0.50 ($CHCl_3$), identical to the corresponding nondeuterated compound.

1-(Isopropylamino)-3-(4-methoxy-1-naphthyloxy)-2-propanol-1,1,2,3,3-d_5 HCl (4-Methoxypropranolol-d_5 HCl) (8·HCl) -- Deuterated epoxide 7, 1.09 g (45 mmol), in 10 ml of isopropylamine was heated at reflux for 48 hr. The isopropylamine was removed by rotary evaporation and the resulting oil crystallized from 25 ml cyclohexane, affording 1.10 g of the free base of 8. The free base was dissolved in ether at 0° and ethereal HCl was added until precipitation ceased. The solid was removed by filtration, washed with ether, and dried affording 1.09 g of 8·HCl (71% yield) mp 163-164° (lit. 168-170°, nondeuterated),[20] R_f 0.60 ($CHCl_3$-EtOAc-MeOH-NH_3, 30:15:5:0.5), identical with nondeuterated material. M/e 295 (MH^+).

1-(Isopropylamino)-3-(4-hydroxy-1-naphthyloxy)-2-propanol-1,1,2,3,3-d_5 HCl (4-Hydroxypropranolol-d_5 HCl) (3·HCl) -- A mixture of 8·HCl, 990 mg (3.0 mmol), and 2.08 g (18 mmol) of freshly prepared pyridine·HCl was heated under an atmosphere of nitrogen at 185-190° for 2 hr. The reaction mixture was cooled to room temperature and dissolved in 10 ml of H_2O with warming on a steam bath.

Sodium bisulfite, 300 mg, and a small amount of activated charcoal were added to the mixture, which was warmed for a few more minutes and then filtered. The charcoal was washed with 2.0 ml of H_2O. Sodium bicarbonate, 1.50 g, sodium chloride, 1.0 g and 1.0 ml of H_2O was added to the solution. The mixture was shaken until the salts dissolved and a mixture of 5 ml of ethyl acetate and 16.5 ml of ether was added to the mixture. The resulting two phase system was stirred in an ice bath for 1.5 hr and the resulting precipitate removed by filtration and dried (vacuum desicator). The crude free base (3) thus obtained, which contained a small amount of sodium bicarbonate, was mixed with 35 ml of hot ethyl acetate and the inorganic material removed by filtration. The filtrate was cooled to room temperature, filtered again and ethereal HCl added until precipitation ceased. The resulting oily precipitate was induced to crystallize using a glass rod while cooling on an ice bath affording white crystals which were removed by filtration, washed with ether and dried affording 470 mg of 3·HCl, mp 172-173° (50% yield) [lit. 174-176° (iPrOH-H_2O), nondeuterated material],[19] R_f 0.37 ($CHCl_3$-EtOAc-MeOH-NH_3, 30:15:15:0.5) identical with non-deuterated material. M/e 281 (MH^+).

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