DERIVATIVES OF β-ADRENERGIC ANTAGONISTS. PREPARATION OF PROPRANOLOL-3,3-$^{2}H_{2}$ AND PROPRANOLOL-^{18}O

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SUMMARY

Syntheses of 1-(isopropylamino)-3-(1-naphthoxy)-2-propanol-3,3-$^{2}H_{2}$ (propranolol-3,3-$^{2}H_{2}$) (1) and of 1-(isopropylamino)-3-(1-naphthoxy-^{18}O)-2-propanol (propranolol-^{18}O) (2) are described. Reaction of 1-naphthol (3) with glycerol-2,3-acetonide-1,1-$^{2}H_{2}$ tosylate (4) afforded, after hydrolysis, 3-(1-naphthoxy)propane-1,2-diol-3,3-$^{2}H_{2}$ (5). Tosylation afforded the primary tosylate (6) which was converted into 3-(1-naphthoxy)-1,2-epoxypropane-3,3-$^{2}H_{2}$ (7). Reaction of 7 with isopropylamine afforded 1 in 31% overall yield from 4. Reaction of 1-naphthol-^{18}O (8) with epichlorohydrin (pyridine) afforded a mixture of 1-chloro-3-(1-naphthoxy-^{18}O)-2-propanol (9) and 1,2-epoxy-3-(1-naphthoxy-^{18}O)propane (10), which was converted to chlorohydrin 9 with HCl. Reaction of 9 with isopropylamine afforded 2 in 60% overall yield from 1-naphthol-^{18}O.

Key Words: Propranolol, β-adrenergic antagonists.

INTRODUCTION

Propranolol [1-(isopropylamino)-3-(1-naphthoxy)-2-propanol] is an important β-adrenergic antagonist used extensively in the treatment of many cardiovascular diseases, including hypertension and angina pectoris, as well as in other disorders.[1-3] It is extensively metabolized in man and other species

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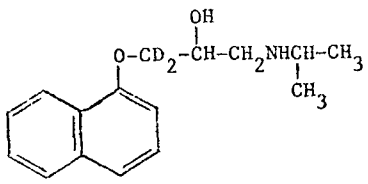
via several metabolic pathways, including oxidative N-dealkylation, aromatic hydroxylation, and glucuronidation.[4-11] Important metabolites formed include 4-, 5- and 7-hydroxypropranolol, propranolol glycol [3-(1-naphthoxy)-1,2-propanediol], desisopropylpropranolol [1-amino-3-(1-naphthoxy)-2-propanol], propranolol lactic acid [2-hydroxy-3-(1-naphthoxy)propionic acid], 2-(1-naphthoxy)acetic acid, and smaller fragments including 1-naphthol and 1,4-naphthalenediol, as well as glucuronide conjugates of the parent drug and some of the metabolites.[4-11] Evidence also exists for formation of additional minor metabolites.[12-16]

Metabolic studies have demonstrated substrate stereoselectivity in many of these metabolic transformations. In dogs and in man, significant differences in plasma levels of the enantiomers of the parent drug and of propranolol glucuronide have been observed.[17-20] Differences have been noted in the enantiomeric origin of metabolites formed via the N-dealkylation pathway, e.g., propranolol lactic acid and 2-(1-naphthoxy)acetic acid.[21] Similarly, enantiomeric differences have been observed in products formed via the hydroxylation pathways in rats[11,21,22] and in man.[23,24] These results, and evidence that the β-adrenergic antagonist properties are associated primarily with one enantiomer,[25,26] indicate the need for additional studies on stereochemical aspects of metabolism of propranolol.

Many previous studies on stereochemical aspects of propranolol metabolism have used pseudoracemic propranolol, in which one of the enantiomers is labelled with deuterium in the naphthalene ring or in the isopropylamine side chain, and the other enantiomer is not labelled.[19,21,22] These methods have limitations because the deuterium labels are not retained in certain metabolites. Incorporation of stable isotope label(s) at metabolically inert position(s) is needed to obviate the need for multiple pseudoracemic propranolols. In this manuscript, we report synthesis of propranolol-3,3-$^{2}H_{2}$ (1) and propranolol-^{18}O (2) which provide labelled metabolites resulting from all metabolic pathways in which the side chain is retained. In addition, propranolol-^{18}O (2) may provide a means for providing information on the enantiomeric origin of minor metabolites like 1-naphthol and 1,4-naphthalenediol.



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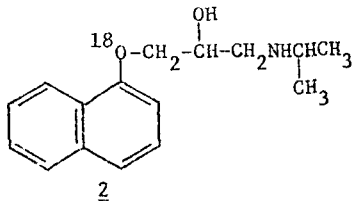

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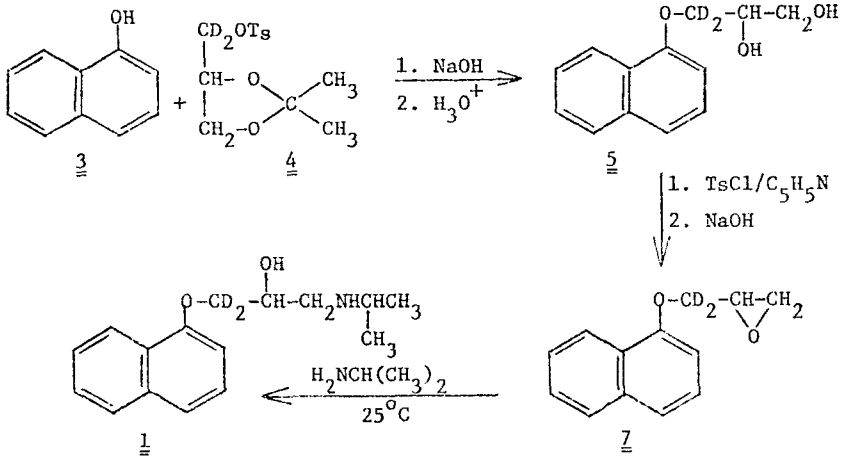
RESULTS AND DISCUSSION

Synthesis of propranolol-3,3-$^{2}H_2$ (1) provided deuterium atoms at a metabolically inert site in propranolol. Glycerol-1,2-acetonide-3,3-$^{2}H_2$, prepared from lithium aluminum deuteride (LAD) reduction of methyl glycerate-2,3-acetonide,[27] was converted to its tosylate (4), which was then allowed to react with 1-naphthol (3) using conditions previously developed to prepare single enantiomers of propranolol glycol and propranolol from chiral glycerol derivatives.[28] The reaction scheme is outlined in Figure 1. Propranolol glycol-3,3-$^{2}H_2$ (5) was converted to propranolol by monotosylation, ring closure to form the corresponding epoxide (7) and subsequent opening of the epoxide with isopropylamine afforded 1. The final steps occurred in 52% yield (based on 5), without isolation of intermediates.



3 4 5 7 1

Figure 1. Synthesis of propranolol-3,3-$^{2}H_2$ (1).

The synthesis of propranolol-^{18}O was accomplished directly from 1-naphthol-^{18}O (8), prepared from 1-naphthylmagnesium bromide and $^{18}O_2$.[29] Alkylation of 1-naphthol-^{18}O (8) with epichlorohydrin was accomplished by the

method of Walker and Nelson,[30] with slight modification (Figure 2). Subsequent steps afforded propranolol-^{18}O in 60% overall yield, without isolation of intermediates.

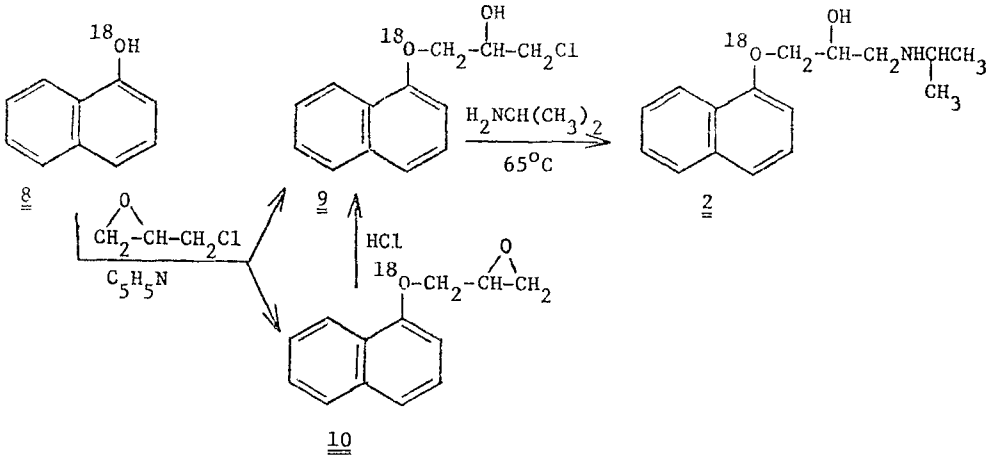


Figure 2. Synthesis of propranolol-^{18}O (2).

The availability of these two stable isotope labelled propranolols will facilitate additional work on stereochemical aspects of the metabolism of this important drug. Preparation of pseudoracemic mixtures of labelled and unlabelled enantiomers of propranolol depends only upon the separation of propranolol enantiomers by reported methods.[25,31,32] Compounds 1, 2 and 5 may also be useful mass spectral standards for quantitation of propranolol and its metabolites. 1-Naphthol-^{18}O could also be adapted to synthesis of several propranolol metabolites for this purpose.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus, and are uncorrected. Nmr spectra were recorded on a Varian 360-A and CFT-20 spectrometers using TMS as internal standard. Tlc plates used were silica gel-GF (Brinkmann). CI mass spectra were obtained on a VG-7070 mass spectrometer (direct insertion probe) using methane as reagent gas.

3-(1-Naphthoxy)-1,2-propanediol-3,3-$^2H_2$ (Propranolol glycol-3,3-$^2H_2$) (5)--To a solution of 21.4 g (0.16 mol) of glycerol-1,2-acetonide-3,3-$^2H_2$, prepared by the method of Kawakami, et al.[27] (90% $^2H_2$), in 90 ml pyridine at 0°C was added tosyl chloride (32.4 g, 0.17 mol). After standing at 5°C for 30 hrs, the resulting solution was warmed to room temperature, diluted to 250 ml with Et_2O, washed with 1N HCl (5 x 70 ml), H_2O (5 x 50 ml), dried ($MgSO_4$) and evaporated to yield 39.8 g (86%) of crude 4 as a white solid, mp 45-47°C (lit. mp 48.5-48.9°C)[27] which was used without further purification. A solution of 29.3 g (0.20 mol) of 1-naphthol (3) and 8.1 g (0.20 mol) NaOH in 80 ml EtOH and 20 ml H_2O was added to 39.8 g (0.14 mole) of crude 4 and the resulting mixture was refluxed for 17 hrs. Upon cooling to room temperature the solution was evaporated, 150 ml 5% aqueous NaOH added and the mixture extracted with Et_2O (3 x300 ml), dried ($MgSO_4$) and evaporated to yield 32.8 g (91%) of the crude acetonide of 5 as a tan oil. A mixture of the crude acetonide of 5, 250 ml 1N HCl and 700 ml acetone was heated at 70°C for 2 hrs. The solution was extracted with Et_2O (4 x 400 ml) and the combined Et_2O extracts washed with 5% aqueous K_2CO_3 (1 x 200 ml), H_2O (1 x 200 ml), dried ($MgSO_4$) and evaporated. Recrystallization afforded 17.9 g (65%) of 5, mp 94-95°C (benzene) (lit. mp 96-97°C, nondeuterated).[33] M/e 221 (MH^+) 90%, 219 (MH^+) 10%. Electron impact ions at m/e 220 and 218 were also observed.

1-(Isopropylamino)-3-(1-naphthoxy)-2-propranol-3,3-$^2H_2$ (Propranolol-3,3-$^2H_2$) (1)--A solution of 7.24 g (41 mmol) of tosyl chloride in 180 ml of benzene was added dropwise to a solution of 9.00 g (41 mmol) of 5 in 30 ml pyridine at 0°C and the mixture stirred at room temperature for 48 hrs. To the solution of tosylate 6 was added a solution of 10.0 g (0.18 mol) of KOH in 150 ml of MeOH and the mixture stirred an additional 30 min, and then filtered. The solution was dissolved in 1500 ml EtOAc, washed with 1N HCl (5 x 100 ml), H_2O (2 x 100 ml), dried ($MgSO_4$) and evaporated to yield crude epoxide 7 as an oil. This oil was allowed to stand in 100 ml of isopropylamine at room temperature for 96 hrs. Excess isopropylamine was evaporated and the resulting solid dissolved in 150 ml 1N HCl, washed with EtOAc, neutralized with 10% aqueous NaOH, and extracted into

EtOAc (2 x 50 ml). The combined EtOAc extracts were washed with H_2O, dried ($MgSO_4$) and evaporated. Crystallization from cyclohexane afforded 5.6 g (52%) of 1 as white needles, mp 90.5-91°C, (lit. mp 96°C, nondeuterated).[34] M/e 262 (MH^+) 90%, 260 (MH^+) 10%.

1-(Isopropylamino)-3-(1-naphthoxy-^{18}O)-2-propanol (Propranolol-^{18}O) (2)--A mixture of 1.46 g (10.0 mmol) of 1-naphthol-^{18}O (8) (Stable Isotope Resource Center, Los Alamos, New Mexico, >94% ^{18}O),[29] 2.80 g (30 mmol) of epichlorohydrin and 6 drops of pyridine in a sealed vial (N_2 blanket) was heated at 90°C for 5 hrs. Tlc ($CHCl_3$) at 5 hr showed disappearance of the 1-naphthol (R_f 0.45) and appearance of epoxide 10 (R_f 0.82) and chlorohydrin 9 (R_f 0.52). Excess epichlorohydrin was removed by rotary evaporation and the residue dissolved in 85 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 15 ml of conc. HCl (2 to 3 min) to convert epoxide 10 to chlorohydrin 9, as demonstrated by tlc. The $CHCl_3$ solution was washed with H_2O, dried ($MgSO_4$) and evaporated. To the crude chlorohydrin was added 40 ml of isopropylamine and the mixture placed in sealed vial and heated at 65°C. Samples were examined periodically by tlc ($CHCl_3$-EtOAc-MeOH-aqueous NH_3, 30:15:5:0.5) noting appearance of propranolol (Rf 0.40) and disappearance of chlorohydrin 9 (Rf 0.85). After 4 days, the reaction mixture was cooled and the contents were removed by rinsing with acetone. After evaporation of solvent, the residue was partitioned between 150 ml of 1N HCl and 75 ml of ether. The aqueous layer was made alkaline by addition of 10% aqueous NaOH and extracted with 2 x 75 ml of EtOAc. The combined EtOAc extracts were washed with H_2O, dried ($MgSO_4$) and evaporated. The crude propranolol-^{18}O was crystallized from cyclohexane (charcoal) affording 1.56 g of 2, mp 92-93°C (60% yield) (lit. mp 96°C, propranolol-^{16}O).[34] M/e 262 (MH^+).

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