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SYNTHESIS OF ^{14}C-DILEVALOL

Timothy Duelfer, Raymond J. Duffin*, and Richard E. Youngstrom

Schering Corporation, Radiochemistry Section, 60 Orange Street,

Bloomfield, New Jersey 07003

SUMMARY

[1-^{14}C]-Dilevalol, (Figure 1), was synthesized from [1-^{14}C]-acetyl chloride. A key step in the synthesis, the coupling of a protected chiral amine with a bromoketone, was very sensitive to the choice of protecting group. The authors attribute this sensitivity to unexpected and severe radiolytic decomposition of the reaction product. The use of a simple benzyl protecting group rather than an α-methyl benzyl protecting group avoided most of the apparent autoradiolysis.

Key Words: Synthesis of ^{14}C-Dilevalol, radiolytic sensitivity, benzyl- and α-methylbenzyl- protected amines.

INTRODUCTION

Dilevalol, [(R)-1-hydroxy-2[((R)-1-methyl-3-phenylpropyl)amino]-ethyl]salicylamide (1) is an antihypertensive agent which acts through vasodilation and the blockade of β-adrenergic receptors[1,2]. Labetalol is a mixture of four stereoisomers of which Dilevalol is the R,R isomer. It has been shown that this R,R isomer has most of the β-blocking activity of the mixture and little α-blocking activity.[3,4] Dilevalol is expected to be more potent and have fewer side-effects than Labetalol. In order to more fully understand Dilevalol's absorption, distribution, metabolism and excretion, the ^{14}C-labelled compound was synthesized.

*Amersham International, Plc, Cardiff Laboratories, Forest Farm Whitchurch, Cardiff, Wales CF4 7YT

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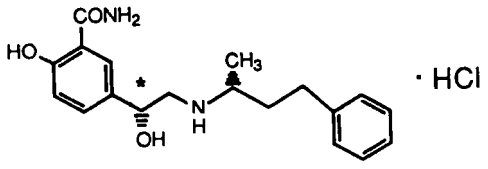


I , Dilevalol

Figure 1

DISCUSSION

The published syntheses[3,4,5,6] of unlabelled Dilevalol devote considerable effort to stereoselectivity and separation of isomers. We encountered a dramatic reduction in yield, probably due to autoradiolysis, in one of the steps, the alkylation of a protected chiral amine. The choice of amine protecting groups proved crucial to running the reaction at an acceptable yield, as described below.

Scheme 1 shows the reaction sequence that we employed. Friedel-Crafts acylation of salicylamide with [1-^{14}C]-acetyl chloride gave ketone (2). The hydroxy function was protected as the O-benzyl ether (3). (3) was reacted with elemental bromine to yield the α-bromo ketone (4). Two key steps in conferring stereoselectivity on the synthesis are the alkylation of the chiral amine (5) with the bromoketone (4)to give aminoketone (6) (reaction IV) and the subsequent stereoselective borohydride reduction of (6) to the amino-alcohol (7). There are two separate sets of reaction conditions which may be employed in reaction IV, depending on which chiral amine is used.

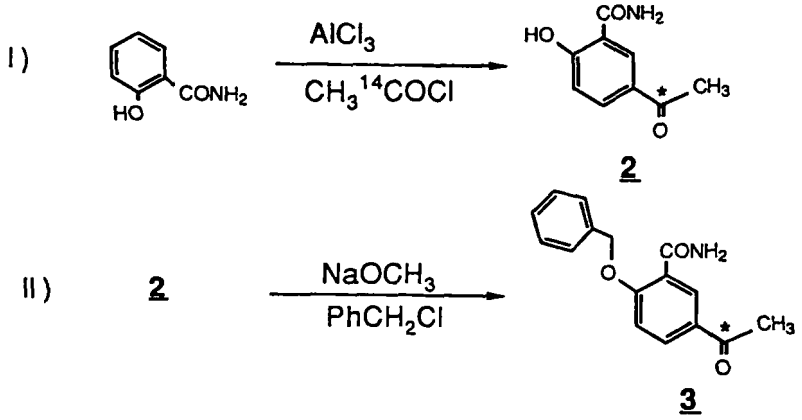
Using (5a), the (R)-α-methyl benzyl protected amine, propylene oxide was the HBr sink and DMF was the solvent. However, the resulting aminoketone is light-sensitive so it is never isolated during the cold synthesis of Dilevalol.

In reaction Vb, amine (5b) is treated with bromoketone (4) and K_2CO_3 in DMF. Aminoketone (6b) is not light sensitive and is isolated. It can be purified by column chromatography.

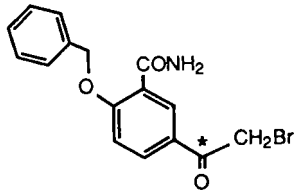
Compound (5a), the (R)-α-methyl benzyl protected amine, is the reactant of choice in the cold synthesis. Its chiral protecting group provided a 90:10 ratio of the desired to undesired diastereomer upon borohydride reduction of the ketone. The desired diastereomer is (R,R) rather than (S,R) at the carbinol and the (1-methyl)propylamine centers, respectively. The diastereomer ratio using (5b), the benzyl-protected amine, is 78:22. Using cold (4), reactions IVa and V, reliably give (7) in 75% overall yield. (Normally, (6a) is not isolated.) However, when [^{14}C]-(4) was used (17 mCi/mmol) (5a) was observed in only 12-15% yield by TLC plate scanning. The borohydride reduction, (reaction V) proceeded normally, but owing to the low yield from reaction IV, 15-20% [^{14}C]-(7) was observed by TLC scanning and 12% (based on (4)) was isolated. We attribute the failure of reaction IVa to autoradiolysis of (6a). We have supportive, but not conclusive, evidence for this inference. The reaction failed only at a relatively high specific activity. (6a) is a much less robust compound than (6b); it is labile to ambient laboratory light, chromatography on silica, and heat. It seems reasonable to attribute radiolytic instability to (6a) as well.

Catalytic reduction of (7) removes both benzyl protecting groups. Crystallization from the reduction medium with dibenzoyl tartaric acid (DBTA) resolved the diastereomers. Treatment of the (R,R) DBTA salt in isopropanol with HCl precipitated the HCl salt without racemization.

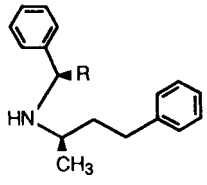
Scheme 1

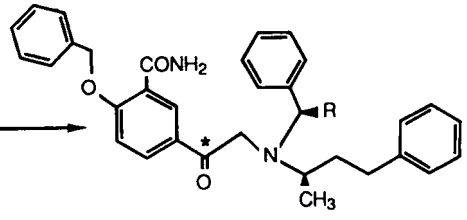


III) **3** $\xrightarrow{Br_2}$ **4**

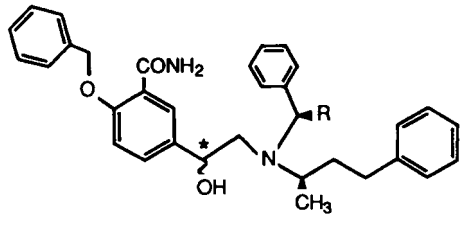


IV) **4** + **5a** R= CH_3, **5b** R= H → **6a** R= CH_3, **6b** R= H

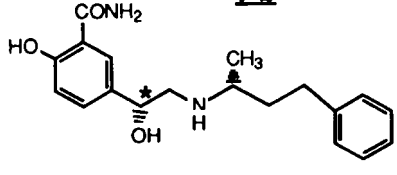




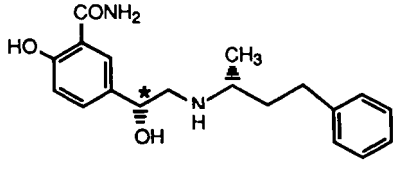
V) **6** $\xrightarrow{NaBH_4}$ **7a** R= CH_3, **7b** R= H



VI) **7** $\xrightarrow[2)\ DBTA\ Resolution]{1)\ H_2 \setminus Pd\text{-}C}$ **8** · DBTA



VII) **8** $\xrightarrow[iPrOH]{HCl}$ **1**, Dilevalol · HCl



MATERIALS AND METHODS

Radiochemical purity was measured by TLC using autoradiography and plate scanning. TLC used Merck 254-F plates or Whatman LK6DF plates. Both are fluorescent silica. Scanning of the plates was done with Amersham's proprietary 100 channel chromatogram analyzer or with a Bioscan 1000 linear analyzer.

The following TLC solvent systems were used:

System 1: EtOAc: hexane 3:2

System 2: $CHCl_3$: MeOH 96:4

System 3: EtOAc: CH_2Cl_2 10: 15

System 4: $CHCl_3$: EtOH: NH_3(Aq) 50:10:1

System 5: EtOAc: iPrOH: H_2O: NH_3(Aq) 100:60:32:8

System 6: $CHCl_3$: acetone: MeOH: HOAc:: 60:20:16:4

The radiochemical identity of products and intermediates was established by comparison of TLC characteristics with those of authentic unlabelled samples. Electron impact mass spectra, and melting points were also compared to authentic Dilevalol for the final product.

Melting points were determined on a Thomas Hoover apparatus and are reported uncorrected.

A Finnigan Mat CH5 mass spectrometer was used. Diastereomeric ratios were determined by gas chromatography on the butane boronic acid derivative of compound I on 5% OV-17 on Gas Chrom Q 325°C isothermal.

EXPERIMENTAL

5-[1-^{14}C]-Acetyl]Salicylamide (II)

A mixture of anhydrous nitrobenzene (30 mL) and salicylamide (2.52g, 18.4 mmol) was slowly treated with $AlCl_3$ (7.33g, 55 mmol). [1-^{14}C]Acetyl chloride (738 mg, 9.16 mmol, 535 mCi) was added slowly to the reaction mixture followed by cold acetyl chloride (7.95 mg, 9.5 mmol). The reaction mixture was stirred under an inert atmosphere for 90 min. Then an additional portion of acetyl chloride (100 μL) in nitrobenzene (500 μL) was added and stirring was continued for another 30 min.

The reaction was then slowly added to a mixture of conc. HCl (9 mL) in ice water (140 mL). The resulting slurry was heated slowly to 50° for 15 min. and then allowed to stand for 30 min. Product was collected by filtration, washed with 2N HCl (30 mL), then with water, and dried in a vacuum desiccator. The chemical yield was 1.65g, 9.30 mmol (51%). The radiochemical yield was 271.5 mCi (50.8%).

O-Benzyl-5[1-^{14}C]-Acetylsalicylamide (3)

5-[1-^{14}C]-Acetyl]salicylamide (1.65g, 9.30 mmol) was dissolved DMF (20 mL). Sodium methoxide (500 mg, 9.26 mmol) was added in small portions with cooling and stirring. A thick paste formed which was heated to 90°C. Benzyl chloride (1.20g, 9.50 mmol) was added dropwise and stirring was continued for 7 h. The mixture was then allowed to cool and was poured into ice water (100 mL) containing sodium carbonate (250 mg). A solid precipitated which was collected by filtration, washed with water and dried. Recrystallization from isopropanol gave 2.07g, 7.80 mmol, 225 mCi of product (83%). Radiochemical purity, as measured by TLC/plate scanning in two solvent systems was 98.5%. TLC Systems: 1 and 2.

4-Benzoxy-3-carboxamido-1-^{14}C,-2-bromoacetophenone (4)

^{14}C-3 (269 mg, 1.00 mmol, 29 mCi) and inactive 3 (179 mg, 0.66 mmol) were dissolved in a mixture of benzene (50 mL) and EtOH (1 mL). A solution of bromine (265 mg, 1.66 mmol) in benzene (5 mL) was added in a dropwise manner. After 2.5 h, a precipitate had formed and was collected by filtration. The filtrate was passed through a short plug of silica gel and then eluted with EtOAc. TLC (System 2) showed that both the precipitate and the EtOAc solution contained about 10% starting acetophenone. The two fractions were combined, EtOAc was added to form a solution, flash silica gel was added, then the solvent was removed. This material was applied to a flash column and purified using EtOAc: benzene (1:1). The purified product was recrystallized twice from isopropanol to give colorless crystals. Chemical yield: 463 mg, 75%. Radiochemical yield: 22.3 mCi, 70%. Radiochemical purity by TLC/plate scanning was 96%. (TLC System 2).

2-O-Benzyl-5[N-(R)-1-phenylethyl-N-(R)-1-methyl-3-phenylpropyl)[carbonyl-^{14}C]-glycyl]salicylamide

Aminoketone (6a) Via The α-Methylbenzyl Protected Amine (5a)

Bromoketone (4) (974 mg, 2.8 mmol, 52.7 mCi) was added to a dried flask along with propylene oxide (464 mg, 560 μl, 8 mmol), and dry DMF (4 mL). The flask was equipped with a stir bar, reflux, condenser, and drying tube. The reaction was shielded from light and stirred at 45-47°C for 24 h. The reaction mixture was worked up in the dark by extraction from water (25 mL) CH_2Cl_2 (3 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The product was analyzed by TLC/plate scanning. Because the aminoketone, VIa, is known to be unstable, it was used directly in the next reaction without further analysis or purification. The yield, measured by TLC/plate scanning of the reaction mixture, was 15%. TLC Systems 1 and 3.

Aminoketone (6b) Via The Benzyl-protected Amine (5b)

Bromoketone IV (1.80g, 5.17 mmol, 72.4 mCi) was added to a flask along with DMF (25 mL) and K_2CO_3 (1.94g, 14 mmol). The reaction mixture was stirred under N_2 as (R)-N-benzyl-1-methyl-3-propylamine (1.24g, 5.2 mmol) in DMF (1 mL) was added in one portion. Stirring was continued at room temperature overnight. TLC plate scanning showed a 58.8% radiochemical yield. The reaction mix was added to H_2O and extracted with benzene. After drying over Na_2SO_4, the benzene layer was evaporated under reduced pressure. The residue was purified on a silica column eluting with EtOAc/hexane to give a 47% isolated yield with a radiochemical purity of 97% by TLC/scanning in System 1.

Adding 5 mL of benzene to the reaction solvent raised the radiochemical yield to 74% as measured by TLC scanning of the reaction mixture. Also, the residue from evaporation of the dried benzene layer could be used directly in the next reaction without adversely affecting its yield.

2-O-Benzyl-5-[(R+S)-1-hydroxy-[1-^{14}C]-2-((R)-1-Methyl-3-phenylpropylbenzylamino)-ethyl] Salicylamide (7)

Compound 6b (45.2 mCi, 1.71g, 3.37 mmol) was dissolved in EtOH (100 mL) and cooled in an ice bath. $NaBH_4$ (126 mg, 3.3 mmol) was added in portions over 2 h. The mixture was stirred at 0°C for 3 h, then allowed to come to

room temperature overnight. Most of the EtOH was then removed in vacuo and H_2O was added. After heating the aqueous mixture (100 mL) to 90°C, it was cooled and extracted with toluene. The toluene solution was dried, concentrated in vacuo, and purified on a silica column. The column was eluted with benzene: EtOAc (3:1). The procedure gave 37 mCi, 1.32g, 2.6 mmol, of product which was 92% the desired R,R diastereomer and 5% S, R, by TLC. TLC System 4 distinguished the diastereomers. The radiochemical yield was 71%.

5-[(R)-[1-^{14}C]-2-1-Hydroxy-((R)-1-methyl-3-phenylpropylamino)-ethyl]-salicylamide, Dibenzoyl Tartrate (8)

Compound 7 (37 mCi, 1.32g, 2.6 mmol) was dissolved in EtOH (100 ml) and cooled in an ice bath under N_2. 150 mg on carbon 5% Pd was added. Hydrogenation was performed at one atmosphere and room temperature overnight. 76% of the theoretical volume of H_2 was consumed. Another 50 mg of catalyst was added. The reaction continued for 18 h while the total consumption of H_2 reached 100% of theory. TLC/plate scanning of this reaction mix indicated 93% 8 (TLC System 4). Filtration and charcoal treatment provided a colorless solution of (7) which was treated with dibenzoyl tartrate monohydrate (DBTA) (940 mg, 2.5 mmol) at 60°. This solution was cooled to room temperature, seeded, and stored at 0°C overnight. Crystals were collected and dried. Two more recrystallizations from 90% EtOH yielded a total of 22 mCi, 1.09g (1.6 mmol) of (7) mp. 182-183°C. Reference mp: 179-180°C radiochemical purity 97.5% by TLC/plate scanning. (60% radiochemical yield.)

5-[(R)-[1-^{14}C]-1-Hydroxy-2((R)-1-methyl-3-phenylpropylamino)ethyl]-salicylamide Hydrochloride, Dilelvalol, (1)

Ethanolic HCl was prepared by bubbling anhydrous HCl gas through a flask of EtOH. The concentration was determined immediately prior to use by titration with a standard NaOH solution using phenolphthalein as an indicator. (8) (980 mg, 1.43 mmol, 18.21 mCi) was slurred in 15 mL iPrOH at room temperature, under N_2 for 45 min. The ethanolic HCl (2.77 mL, 1.49 mmol) was added in one portion. A clear solution formed and precipitation began in 15 min. After 5.5 h of stirring at room temperature, the product was collected by filtration, washed with iPrOH, and vacuum dried. The yield was 344.6 mg, 0.944 mmol, 12.75 mCi, (70%). mp (product): 198.5-200°, mp (reference material):

199-200°. The radiochemical purity was 98% by TLC/plate scanning in Systems 4, 5, and 6. The electron impact mass spectrum of the product matched that of reference material except for peaks which are due to isotopic enrichment of the product.

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