THE SYNTHESIS OF DEUTERIUM ENRICHED (+)-PROPOXYPHENE

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SUMMARY

(+)-Propoxyphene, benzyl-d_7 and (+)-propoxyphene, N,N-dimethyl-d_6 were prepared by literature methods for use to study the metabolism of deuterium enriched (+)-propoxyphene.

Key Words: (+)-Propoxyphene, deuterium

INTRODUCTION

(+)-Propoxyphene (1) is a widely accepted analgesic (1) whose metabolism has been extensively investigated (2). Studies to determine if any differences occur in the rate of metabolism or in the metabolic pathway of deuterium enriched 1 required the preparation of two labelled compounds. Based upon stability relative to metabolic changes and mass spectrometric fragmentation of 1 and its metabolites, the two deuterated compounds 1a and 1b were chosen for synthesis by the routes shown in Scheme I.

The Mannich ketone, (-)-3-dimethylamino-2-methylpropiophenone (2), when reacted with benzyl Grignard is known to yield mainly *threo*-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (3) (3). Propionylation of 3 provided 1. The reaction of 2 with benzyl-d_7 Grignard gave 3a and the formation of its propionate ester provided 1a.

Prior work (4) indicated that the stepwise conversion of 1 to 3 through the tosylate 4 proceeded without racemization.

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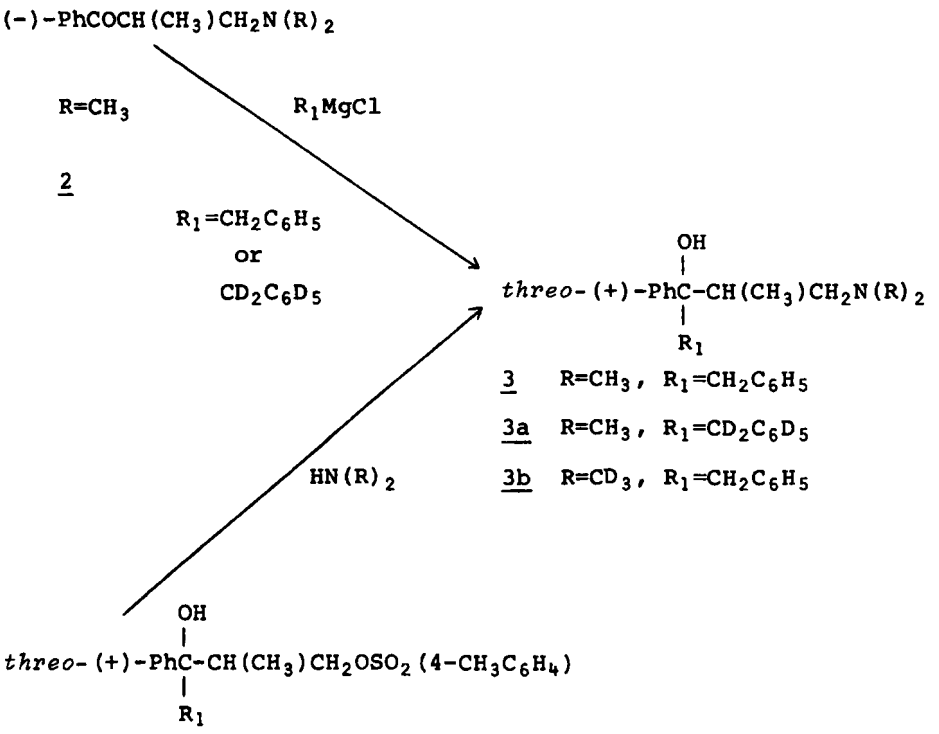
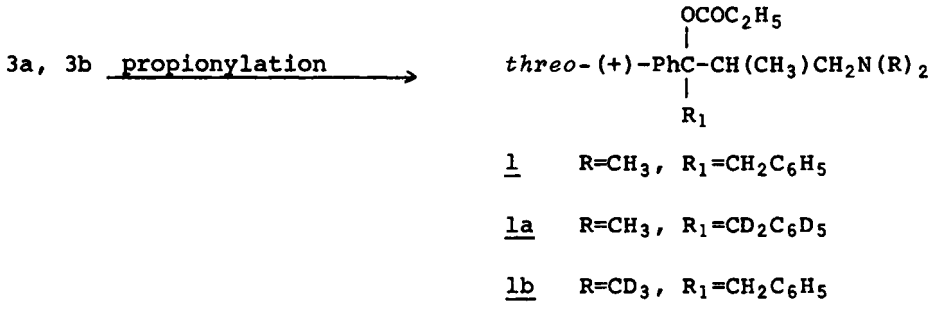

(-)-PhCOCH(CH3)CH2N(R)2
R=CH3
R1MgCl
2
R1=CH2C6H5
or
CD2C6D5
OH
threo-(+)-PhC-CH(CH3)CH2N(R)2
R1
3 R=CH3, R1=CH2C6H5
3a R=CH3, R1=CD2C6D5
3b R=CD3, R1=CH2C6H5
HN(R)2
OH
threo-(+)-PhC-CH(CH3)CH2OSO2(4-CH3C6H4)
R1
R1=CH2C6H5
4


3a, 3b propionylation
OCOC2H5
threo-(+)-PhC-CH(CH3)CH2N(R)2
R1
1 R=CH3, R1=CH2C6H5
1a R=CH3, R1=CD2C6D5
1b R=CD3, R1=CH2C6H5

SCHEME I

Displacement of the tosylate group of 4 with dimethyl-d_6 amine gave 3b. The esterification of 3b with the appropriate acid gave 1b. The metabolic results with compounds 1a and 1b will be discussed in later publications.

EXPERIMENTAL

Both deuterated reagents were purchased from Merck, Sharp and Dohme, Canada Ltd. The nmr spectra were taken on a Varian Associates T60 spectrometer in $CDCl_3$. Chemical shifts are in ppm downfield relative to TMS as an internal standard. Melting points are uncorrected.

threo-(+)-4-Dimethylamino-1-phenyl-d_5-2-phenyl-3-methyl-2-butanol-1,1-d_2 (3a). A solution containing (-)-3-dimethylamino-2-methylpropiophenone (2) (3) (26.8 g, 0.4 mol) in tetrahydrofuran (100 ml) was added to a stirred solution of benzyl-d_7-magnesium chloride prepared from benzyl-d_7-chloride (20 g, 0.15 mol), magnesium (3.65 g, 0.15 g-atoms) and tetrahydrofuran (100 ml). After complete addition of the ketone (2) the reaction mixture was refluxed for 2 hr. The reaction mixture was poured into an ice (200 g)-5*N* hydrochloric acid (200 ml) mixture. The acidic solution was extracted with ether and then made alkaline with excess ammonium hydroxide. The basic mixture was extracted with ether. The ether solution was washed with water. dried over anhydrous magnesium sulfate and evaporated to dryness *in vacuo* to yield 37 g (91%) of 3a as an oil; nmr 0.9 ($C\underline{H}_3C$,d), 2.0 ($C_2C\underline{H}C$,m), 2.1 ($CC\underline{H}_2N$,m), 2.3 [$(C\underline{H}_3)_2N$,s], 7.5 ($C_6\underline{H}_5$,m), 8.3 ($O\underline{H}$, broad s). The hydrochloride was prepared in ether and recrystallized from a methanol-ethyl acetate mixture to provide 33 g (72%) of 3a hydrochloride: mp 238-239°C.

threo-(+)-4-Dimethylamino-d_6-1,2-diphenyl-3-methyl-2-butanol (3b). A solution of *threo*-(+)-3-hydroxy-2-methyl-3,4-diphenyl-n-butyl-p-toluenesulfonate (4) (4) (4.26 g, 0.01 mol) and anhydrous dimethyl-d_6 amine in tetrahydrofuran (100 ml)

was prepared in a high-pressure reaction vessel and heated at 60° for 16 hr. The solvent was removed *in vacuo* and the residual oil was suspended in 5*N* hydrochloric acid (100 ml). The acidic mixture was extracted with ether and then made alkaline with excess ammonium hydroxide. The basic mixture was extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate and concentrated to dryness to yield 1 g (33%) of 3b as an oil: nmr 0.9 ($C\underline{H}_3C$,d), 1.9 ($C_2C\underline{H}C$,m), 2.0 ($CC\underline{H}_2N$,m), 3.2 ($ArC\underline{H}_2C$,s), 7.2 ($2C_6\underline{H}_5$,m), 8.3 ($O\underline{H}$, broad s).

threo-(+)-4-Dimethylamino-1-phenyl-d_5-2-phenyl-3-methyl-2-butanol-1,1-d_2 Propionate(1a), (Propoxyphene, benzyl-d_7). A mixture of propionic acid (10 ml) and trifluoroacetic anhydride (18.3 ml) was kept at room temperature for 1.5 hr and then diluted with toluene (100 ml). This solution was added dropwise to an ice bath cooled solution of 3a (23.2 g, 0.8 mol) and triethylamine (20.5 ml) in toluene (60 ml). The reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ether (200 ml) and was extracted with water. The aqueous extract was made alkaline with sodium bicarbonate and the basic mixture was extracted with ether. This ether extract was combined with the above ether solution. The combined ether solution was washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The ether solution was saturated with hydrogen chloride gas to give a precipitate which was recrystallized from a methanol-ethyl acetate mixture to yield 35 g (76%) of 1a hydrochloride: mp 164-165°C; $[\alpha]_D^{25}$ + 51.0° (c=1, H_2O); nmr 1.0 ($C\underline{H}_3CO_2$, t), 1.3 ($C\underline{H}_3C$,d), 2.2 ($CC\underline{H}_2CO_2$,q), 2.5 ($C_2C\underline{H}C$,m), 2.6 [$(C\underline{H}_3)_2N$,s], 2.9 ($\underline{H}Cl$, broad s), 3.0 ($C_2C\underline{H}_2N$,m), 7.3 ($C_6\underline{H}_5$,s). The molecular weight was confirmed by chemical ionization mass spectrometry.

threo-(+)-4-Dimethylamino-d_6-1,2-diphenyl-3-methyl-2-butanol Propionate(1b), (Propoxyphene,N,N-dimethyl-d_6.) By the same method as preparing 1a, the propionate ester of 3b (1 g,

3.5 mmol) gave 850 mg (75%) of 1b hydrochloride: mp 162-163°C from ethyl acetate-ether; $[\alpha]_D^{25}$ + 40.5° (c=0.1), (MeOH); nmr 1.0 ($C\underline{H}_3CO_2$,t), 1.3 ($C\underline{H}_3C$,d), 2.2 ($CC\underline{H}_2CO_2$,q), 2.4 ($\underline{H}Cl$, broad s), 2.5 ($C_2C\underline{H}C$,m), 3.0 ($C_2C\underline{H}_2N$,m), 2.8 ($ArC\underline{H}_2C$,s), 7.0 ($C_6\underline{H}_5CH_2C$,m), 7.2 ($C_6\underline{H}_5C$,s). The molecular weight was confirmed by chemical ionization mass spectrometry.

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