Synthesis of (2S : 3R)-4-Dimethylamino-1, 2-diphenyl-3-methyl-2-propionoxybutane-1-^{14}C, d-Propoxyphene-1-^{14}C

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d-Propoxyphene, first synthesized by Pohland and Sullivan [1a], is a commonly used analgesic. Metabolism studies [2] on racemic N-methyl-^{14}C propoxyphene [3] established that the major metabolic product is the N-demethylated compound. Analytical and metabolic studies performed on d-propoxyphene in these laboratories required optically active radiolabeled drug in which the label would be metabolically secure. The availability of benzylchloride-7-^{14}C suggested the preparation of d-propoxyphene labeled at C-1. There is little likelihood that C-1 would be lost during the course of metabolic transformations. The previously reported [1] synthesis of d-propoxyphene was modified to permit efficient small scale preparation (Fig. 1).

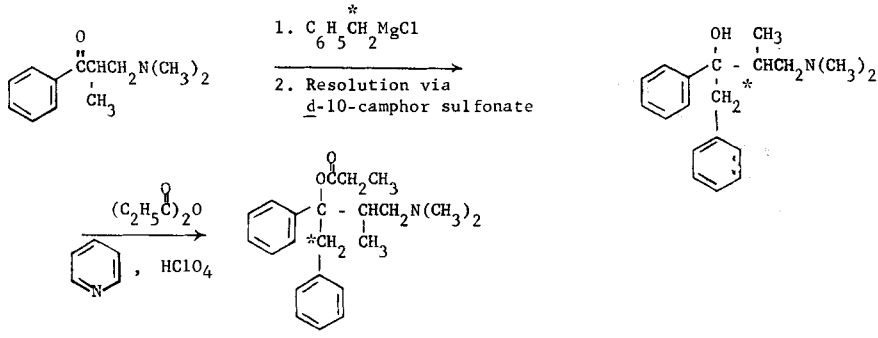

FIG. 1. Synthesis of d-Propoxyphene-1-^{14}C

EXPERIMENTAL.

(2S : 3R)-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride.

A solution of 215 mg (1.71 mmole, 1 mCi) of benzylchloride in 1.5 ml of anhydrous ether was added dropwise to 45 mg (1.85 mmole) of magnesium turnings. When the reaction was complete a solution of 179 mg (0.932 mmole) of β-dimethylaminoisobutyrophenone in 1.5 ml of anhydrous ether was added dropwise. After the addition was complete the mixture was refluxed for one hour. The excess Grignard reagent was decomposed with saturated ammonium

chloride solution, extracted with ether and dried (Na_2SO_4). Removal of the solvent followed by purification of the residue by preparative thin layer chromatography (silica gel H, acetone) afforded 170 mg (0.601 mmole, 64 %) of (2RS : 3RS)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol-1-^{14}C. d-10-Camphor sulfonic acid (139 mg, 0.60 mmole) and 170 mg of (2RS : 3RS)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol-1-^{14}C were dissolved in about 9 ml of hot ethanol and allowed to crystallize. The salt was crystallized three more times from a 7 : 3 ethanol-acetone mixture to give 110mg (0.214 mmole, 71 %) of (2S : 3R)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol-1-^{14}C. d-10-camphor sulfonate, $[\alpha]_D$ + 61.7° C; reported [1] $[\alpha]_D$ + 64.6° C. The salt was dissolved in water, treated with an excess of 10 % sodium hydroxide and the water solution extracted with ether. The ether solution was dried (Na_2SO_4) and treated with anhydrous ethereal hydrogen chloride to precipitate (2S : 3R)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol-1-^{14}C hydrochloride (65 mg, 0.204 mmole, 68 %).

(2S : 3R)-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane-1-^{14}C hydrochloride.

(2S : 3R)-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol-1-^{14}C hydrochloride (65 mg., 0.204 mmole) was dissolved in 5 ml. of pyridine, 1 ml of propionic anhydride and 2 drops of 70 % perchloric acid were added. The solution was heated for 15 min on the steam bath, cooled, diluted with ether and washed with 10 % sodium hydroxide. The organic layer was separated and dried (Na_2SO_4). Ethereal hydrogen chloride was added to the dried solution until precipitation was complete. Crystallization of the precipitate from toluene gave 39 mg (0.104 mmole, 51 %) of (2S : 3R)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane-1-^{14}C hydrochloride (d-propoxyphene-1-^{14}C hydrochloride). The specific activity was 0.9 μCi/mg.

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