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SYNTHESIS OF CARBON-14 LABELED (±)-2-METHYL-3,3-DIPHENYL-3-PROPANOLAMINE (2-MDP)

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SUMMARY

The preparation of ^{14}C labeled (±)-2-methyl-3,3-diphenyl-3-propanolamine (3) from [^{14}C]-carbonyl-benzophenone is described.

Key words: 2-MDP, 2-Methyl-3,3-diphenyl-3-propanolamine, Dissociative Anesthetics, Carbon-14.

INTRODUCTION

(-)-2-Methyl-3,3-diphenyl-3-propanolamine (2-MDP, 3) (1) has been shown to have similar pharmacological activity to the dissociative anesthetic phencyclidine (PCP). In vivo it has been shown to substitute for PCP in discriminative stimulus tests in rat (2) and in pigeon (3). In vitro it has been shown to compete with ^{3}H-PCP for PCP receptor sites in CNS tissue homogenates (3). 2-MDP bears little structural resemblance to PCP, or to other molecules known to have PCP-like activity. Modest structural changes in the molecule which have been made, thus far, have resulted in a considerable loss in PCP-like activity (3). The PCP-like activity of the compound appears to be very dependent on a specific structure, unlike PCP itself, or other PCP-like compounds which can undergo considerable molecular modification and retain, or show increased PCP-like activity (4-5). The carbon-14 labelled 2-MDP would be of great use to investigators interested in studying the metabolism and pharmacokinetic properties of this remarkable compound.

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EXPERIMENTAL

Materials and Methods

Radioactivity determinations were carried out using a Packard Model 4000 liquid scintillation counter using Hydrofluor scintillation solvent and ^{14}C-toluene as an internal standard. Thin layer chromatography (TLC) plates were analyzed with a Berthold Model LB 2760 TLC scanner. ^{14}C-Benzophenone was purchased from Pathfinder Laboratories. Diethyl ether and tetrahydrofuran (THF) were dried over benzophenone ketyl and distilled. All synthetic and analytical operations were initially performed with unlabelled compounds, and the structures of unlabelled intermediates and products were confirmed spectroscopically.

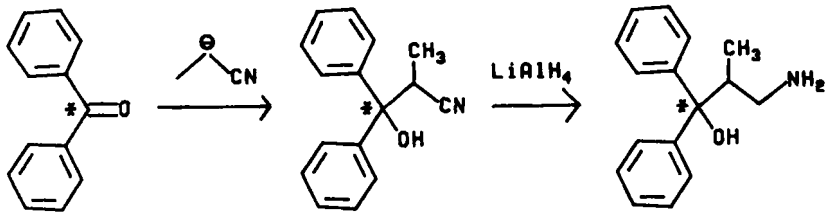
Synthesis

The synthetic pathway for preparing ^{14}C labeled 3 is shown in Scheme 1.

Scheme 1

Synthesis of Carbon-14 Labeled

(±)-2-Methyl-3,3-diphenyl-3-propanolamine (2-MDP)



1 2 3

Benzophenone-^{14}C (1) (6) was used as a starting material thereby placing the ^{14}C radiolabel at the quaternary carbon of 2-MDP. Compound 1 was condensed with the lithio anion of propionitrile to provide hydroxynitrile 2. Reduction of compound 2 with lithium aluminum hydride followed by basic workup led to the desired 3.

2-Methyl-3,3-diphenyl-3-hydroxypropionitrile (2). A standard solution of 2-lithiopropionitrile was prepared as follows. Diisopropylamine (253 mg, 350 µL, 2.5 mmol) and n-butyllithium solution (1.0 mL, 2.5 N in hexane) were added via syringe to cold (0 °C), dry diethyl ether (9.0 mL) contained in a 25 mL sidearm flask equipped with an argon inlet and rubber septum. Propionitrile (138 mg, 178 µL, 2.505 mmol) was then added dropwise via syringe over 2 min. After the addition was complete, the resulting solution was stirred for an additional 20 min. The ^{14}C-benzophenone (3.1 mg, 0.017 mmol, 14.9 mCi/mmol), contained in a one dram vial, was dissolved in dry ether (500 µL), the prepared, standard, 2-lithiopropionitrile solution (100 µL, 1.5 eq) was added, and the reaction was allowed to stand for 1 h. The reaction was quenched by the addition of water (500 µL). The resulting mixture was then extracted with diethyl ether (3 X 1 mL). The pooled ether extracts were filtered through a Pasteur pipette containing 1 g of anhydrous sodium sulfate (held between two small balls of glass wool) into a clean 1 dram vial. The solvent and the unreacted propionitrile were removed using a stream of argon. The resulting product appeared pure by TLC and showed Rf values and IR characteristics identical to those of cold 2. TLC Rf = 0.32 (30% EtOAc/hexane). IR (neat) 3500, 3390, 2990, 2195, 1640, 1600, 1450, 1365 cm^{-1}.

2-Methyl-3,3-diphenyl-3-propanolamine (3). Nitrile 2 (3.6 mg, 0.015 mmol) was dissolved in dry ether (2 mL). Powdered lithium aluminum hydride (15 mg, 0.395 mmol) was then added to this solution. The vial was then capped and allowed to stand for two days. The reaction was quenched by the addition of 40 µL of a 1.0 N NaOH solution. The resulting heterogeneous mixture was filtered through a small pad of celite held in a Pasteur pipette. The celite pad was then washed with an additional 2 mL of ether. The solvent was removed under a stream of argon and the product was purified by TLC on a silica gel plate (250 micron, 15 cm), using a solvent system of 1.5% methanol in chloroform containing 0.1% NH_4OH. The crude reaction mixture was applied to the plate in chloroform solution. A sample of cold 3 was applied at the edges of the plate to act as a

marker. After the plate was run, the separated products and the cold markers could be visualized under UV light. ^{14}C-2-MDP was obtained by removing the silica gel from the TLC plate in the region between the two cold markers and extracting the silica gel scrapings with chloroform/methanol/NH_4OH (80:18:2). The extract was concentrated under a stream of argon to give ^{14}C-2-MDP (50 µCi, 14.9 mCi/mmol, 20% overall yield). TLC Rf = 0.38 (5% methanol/chloroform/0.1% NH_4OH), identical to the cold material. The ^{14}C-2-MDP was shown to be >99% radiochemically pure using the Berthold TLC scanner.

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