PREPARATION OF CARBON-14 AND TRITIUM LABELED *d*- AND *l*-1,1-DIPHENYL-2-METHYL-3- AMINOPROPANOL HYDROCHLORIDE

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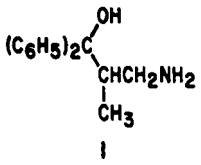
SUMMARY

1,1-Diphenyl-2-methyl-3-aminopropanol-1-^{14}C was prepared in a five-step sequence of reactions from $^{14}CO_2$ and resolved into its *d* and *l* isomers in an overall yield of 9.5% based on carbon-14. 1,1-Diphenyl-2-methyl-3-aminopropanol-3-^{3}H was prepared by reduction of an intermediate with lithium aluminum tritide and resolved into its *d* and *l* isomers in an overall yield of 7.3% based on tritium.

Key Words: Carbon-14, Tritium

INTRODUCTION

1,1-diphenyl-2-methyl-3-aminopropanol (I) is a CNS stimulant having a unique,



dose-related spectrum of pharmacologic activity (1,2). Resolution of I into its optical isomers permitted separate testing of the *d* and *l* forms of the drug. Although toxicity of both isomers was equivalent, the *l* isomer was markedly more active than the *d* isomer. Therefore, further efforts to develop I as a CNS agent involved its *l* isomer.

Planned metabolism studies required preparing the *l* form of I in a radioactive form. Because of the split in activity between the *d* and *l* forms, it was decided to label both isomers, and, in fact, to label each with tritium and carbon-14. This would permit studying the fate of each isomer, one labeled

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with tritium and the other with carbon-14 simultaneously. Metabolism studies with the *l* isomer of I have been reported (3).

EXPERIMENTAL

Radioactivity measurements

All counting was performed with a Model 314EX2A Packard Tricarb liquid scintillation spectrometer at -8° under conditions suitable for carbon-14 or tritium. Appropriate aliquots of samples were dissolved in 15 ml of scintillation solvent [toluene-dioxane-methanol (350:350:210 by volume) containing 73 g of naphthalene, 4.6 g of 2,5-diphenyloxazole, and 0.08 g of 1,4-bis [2-(5-phenyloxazolyl)] benzene per liter]. The absolute counting efficiency for each sample was determined by recounting following addition of an internal standard of carbon-14 or tritium-labeled toluene and results were then converted to mCi.

Paper and Thin-Layer Chromatography

Paper chromatography was carried out by the descending method on 57-cm strips of Whatman No. 1 paper in the (a) 1-butanol-acetic acid-H_2O (2:1:1 by volume) and (b) 1-butanol-piperidine-H_2O (81:2:17 by volume) systems. Thin-layer chromatography was carried out in the (c) $CHCl_3$-methanol-formic acid (95:4:1 by volume) and (d) acetone-methanol (4:1 by volume) systems on 0.25-mm films of silica gel G. The R_f value of I in the last system was 0.57. The UV absorption of standards and products was detected by viewing the dried paper and thin-layer chromatograms under short-wavelength UV light.

Paper chromatograms were scanned for radioactivity with a Model 880 Vanguard paper chromatogram scanner. Zones of radioactivity on thin-layer chromatograms were located by transferring sequential 0.5-cm segments of the developed chromatogram into individual vials and counting, using scintillation solvent containing 3% H_2O

Synthesis

Benzoic Acid-7-^{14}C (III) - A solution of phenylmagnesium bromide (5.2 mM) in 10 ml of ethyl ether was carbonated with the $^{14}CO_2$ (II) generated from 0.5 g (2.5 mM, 28 mCi) of $Ba^{14}CO_3$ using the method and apparatus described by Eberson (4). During its isolation the product was diluted with sufficient

nonradioactive benzoic acid to yield 2.62 g (22 mCi, 79%) of benzoic acid-7-^{14}C having a specific activity of 1.02 mCi/mM; m.p. 122° (capillary, uncorrected). The IR and UV spectra of the product were identical to those of authentic benzoic acid.

Benzophenone-1-^{14}C (V) - Benzoic acid-7-^{14}C (2.62g, 21.9 mCi) was converted to benzophenone-1-^{14}C (V) *via* benzoylchloride-7-^{14}C (IV) as described by Speer and Jeanes (5). The final product was purified by sublimation *in vacuo* and recrystallization from ethanol-water to yield 3.30 g (18.3 mCi, 84%) of benzophenone-1-^{14}C (V) having a specific activity of 1.01 mCi/mM. The IR and UV spectra of the product were identical to those of authentic benzophenone. Paper and thin-layer chromatography in systems (a), (b) and (c) revealed single UV-absorbing and radioactive zones corresponding to benzophenone. *Anal.* Calcd. for $C_{13}H_{10}O$: C, 85.7; H, 5.5. Found: C, 85.0; H, 5.8.

d,l-1,1-Diphenyl-2-methyl-3-aminopropanol-1-^{14}C (I) - Benzophenone-1-^{14}C (V) (3.26 g), having a specific activity of 1.01 mCi/mM, was condensed with propionitrile in the presence of $NaNH_2$ by the method of Moffett and Pickering (1) to obtain 1.652 g (39%) of *d,l*-1,1-diphenyl-2-methyl-3-aminopropanol-1-^{14}C (I) having a specific activity of 1.00 mCi/mM; m.p. 122.5-123.5° (capillary, uncorrected).

d,l-1,1-Diphenyl-2-methyl-3-aminopropanol-3-^{3}H (I) - A 1.35 g sample of 1,1-diphenyl-2-cyanopropanol (VI)* was reduced with 0.325 g of $LiAl^{3}H_4$ containing 75 mCi of tritium in a manner similar to that described by Moffett and Pickering (1) to obtain 1.051 g (77% chemical and 26% radiochemical yields) of *d,l*-1,1-diphenyl-2-methyl-3-aminopropanol-3-^{3}H (I) having a specific activity of 4.40 mCi/mM. Thin-layer chromatography in the acetone-methanol system revealed a single radioactive and UV-absorbing zone corresponding to authentic I. The UV absorption spectrum [(EtOH) shoulder 249 mμ (ε363), 253 mμ (ε428), 258 mμ (ε477), shoulder 264 mμ (ε373), shoulder 269 mμ (ε247)] corresponded to that of authentic I.

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*Supplied by Dr. R. B. Moffett.

l-1,1-Diphenyl-2-methyl-3-aminopropanol-1-^{14}C (I) Hydrochloride - The *d,l* form of carbon-14 labeled I (1.64 g) was treated with 1.017 g of *d*-tartaric acid, and the resulting *l*-base-*d*-tartrate salt was separated by fractional crystallization as described by Moffett and Pickering (1). The salt was decomposed with alkali to generate the free base which was crystallized as its hydrochloride salt to yield 0.337 g (36%) of *l*-1,1-diphenyl-2-methyl-3-aminopropanol-1-^{14}C (I) hydrochloride having a specific activity of 1.02 mCi/mM. Its UV and IR [(KBr) 3260, 3220, 3160, 3110 (OH); 2940, 2870, (C-H,-$\overset{+}{N}H_3$); 2780, 2660 (-$\overset{+}{N}H_3$); 1615, 1575, 1495, 1445 (C=C, -$\overset{+}{N}H_3$); 1465 (C-H); 1060, 1015, 1000 (C-O, C-N); 775, 765, 760, 715 and 700 cm^{-1} (aromatic C-H)] spectra and optical rotation, $[\alpha]_D^{25°}$ -42° in MeOH, corresponded to those of the hydrochloride salt of the *l* isomer of authentic I. Thin-layer chromatography in the acetone-methanol system revealed a single UV absorbing and radioactive zone corresponding to the hydrochloride of I. *Anal.* Calcd. for $C_{16}H_{19}NO \cdot HCl$: C, 69.2; H, 7.3. Found C, 69.2; H, 7.6.

d-1,1-Diphenyl-2-methyl-3-aminopropanol-1-^{14}C (I) Hydrochloride - The filtrates from fractional crystallization of the carbon-14 labeled *l*-base-*d*-tartrate were combined and worked up as described by Moffett and Pickering (1) for isolation of the *d* base. The *d* rich base (1.278 g) was treated with 0.795 g of *l*-tartaric acid, and the resulting *d*-base-*l*-tartrate salt was separated by fractional crystallization. The salt was decomposed with alkali to generate the free base which was crystallized as its hydrochloride salt to yield 0.346 g (37%) of *d*-1,1-diphenyl-2-methyl-3-aminopropanol-1-^{14}C (I) hydrochloride having a specific activity of 1.02 mCi/mM. Its UV and IR spectra and optical rotation, $[\alpha]_D^{25°}$ + 42° in MeOH, corresponded to those of the hydrochloride salt of the *d* isomer of authentic I. Thin-layer chromatography in the acetone-methanol system revealed a single UV absorbing and radioactive zone corresponding to the hydrochloride of I. *Anal.* Calc. for $C_{16}H_{19}NO \cdot HCl$: C, 69.2; H, 7.3. Found: C, 69.4; H,7.6.

l-1,1-Diphenyl-2-methyl-3-aminopropanol-3-^{3}H (I) Hydrochloride - The *d,l* form of tritium-labeled I (1.04 g) was treated with 0.651 g of *d*-tartaric acid

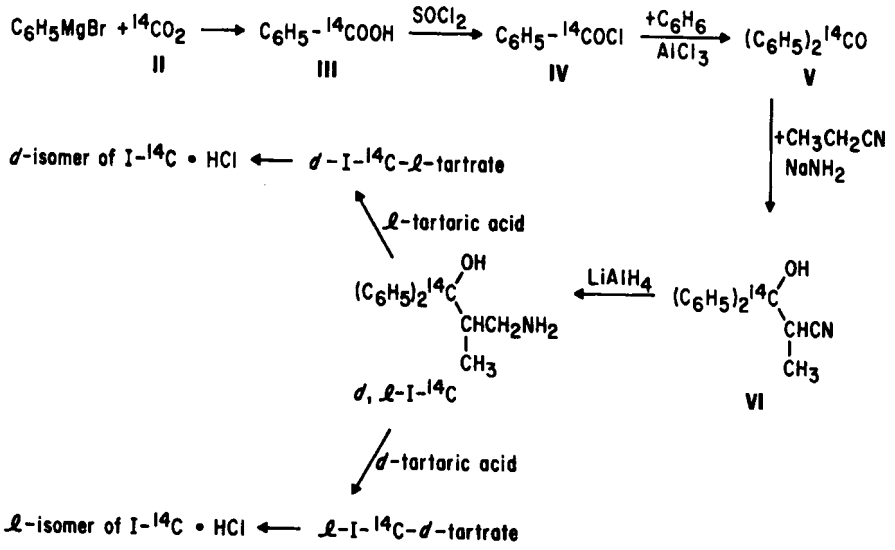
and the resulting *l*-base-*d*-tartrate salt was separated by fractional crystallization as previously described. The salt was decomposed with alkali to generate the free base which was crystallized as its hydrochloride salt to yield 0.186 g (31%) of *l*-1,1-diphenyl-2-methyl-3-aminopropanol-3-^{3}H (I) hydrochloride having a specific activity of 4.40 mCi/mM. Its UV spectrum and optical rotation, $[\alpha]_D^{25^\circ}$ -41° in MeOH, corresponded to those of the hydrochloride salt of the *l* isomer of authentic I. Thin-layer chromatography in the acetone-methanol system revealed a single UV absorbing and radioactive zone corresponding to the hydrochloride of I. *Anal.* Calcd. for $C_{16}H_{19}NO \cdot HCl$: C, 69.2; H, 7.3; N, 5.0. Found: C, 69.2; H, 7.1; N, 5.0.

d-1,1-Diphenyl-2-methyl-3-aminopropanol-3-^{3}H (I) Hydrochloride - The filtrates from fractional crystallization of the tritium-labeled *l*-base-*d*-tartrate were combined and worked up as previously described. The *d* rich base (0.807 g) was treated with 0.503 g of *l*-tartaric acid, and the resulting *d*-base-*l*-tartrate salt was separated by fractional crystallization. The salt was decomposed with alkali to generate the free base which was crystallized as its hydrochloride salt to yield 0.156 g (26%) of *d*-1,1-diphenyl-2-methyl-3-aminopropanol-3-^{3}H (I) hydrochloride having a specific activity of 4.40 mCi/mM. Its UV spectrum and optical rotation, $[\alpha]_D^{25^\circ}$ + 39° in MeOH, corresponded to those of the hydrochloride salt of the *d* isomer of authentic I. Thin-layer chromatography in the acetone-methanol system revealed a single UV absorbing and radioactive zone corresponding to the hydrochloride of I. Calcd. for $C_{16}H_{19}NO \cdot HCl$: C, 69.2; H, 7.3; N, 5.0. Found: C, 69.1; H, 7.5; N, 5.0.

RESULTS AND DISCUSSION

Carbon-14 labeled 1,1-diphenyl-2-methyl-3-aminopropanol (I) was prepared and resolved into its *d* and *l* isomers by the sequence of reactions shown in Scheme 1. The first three steps in the sequence, conversion of $^{14}CO_2$ into

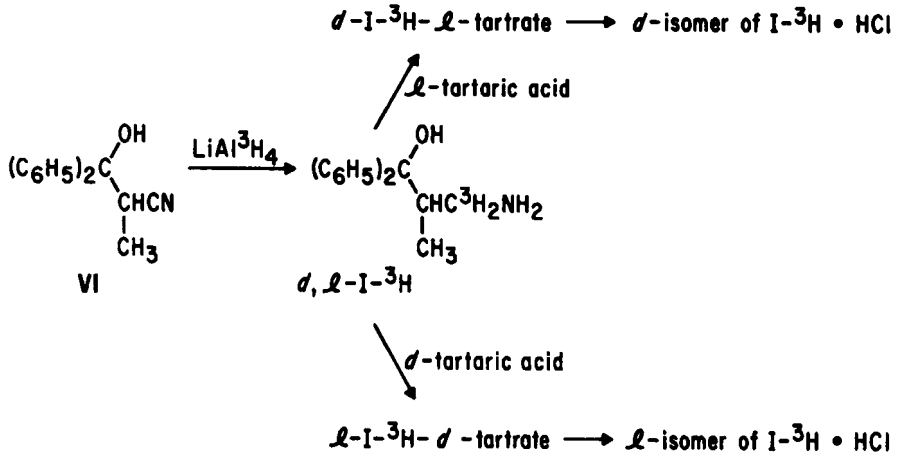
Scheme 1



benzophenone-1-^{14}C (V), were carried out in a yield of 66% by reactions well established in carbon-14 syntheses. The next two steps in the sequence, condensation of the benzophenone-1-^{14}C (V) with propionitrile and reduction of the resulting nitrile (VI) with lithium aluminum hydride, resulted in a 39% yield of the *d,l* form of carbon-14 labeled I. The last step, resolution of racemic I into its *d* and *l* isomers, was accomplished in 36% yield by fractional crystallization of its *d*-tartrate salt to give the *l* isomer of I and of its *l*-tartrate salt to give the *d* isomer of I. The overall yields of the separated *d* and *l* isomers of carbon-14 labeled I, based on $^{14}CO_2$, were 9.5%.

Tritium-labeled 1,1-diphenyl-2-methyl-3-aminopropanol (I) was prepared and resolved into its *d* and *l* isomers by the sequence of reactions shown in Scheme II. The first step, reduction of the nitrile intermediate (VI) with $LiAl^3H_4$,

Scheme 2



resulted in a 26% (radiochemical) yield of the *d,l* form of tritium-labeled I. In the final step, the tritium-labeled racemate was resolved into its *d* and *l* isomers in a yield of approximately 28%. The overall yields of the separated *d* and *l* isomers of tritium-labeled I, based on $LiAl^3H_4$, averaged 7.3%.

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