PREPARATION OF METHADONE AND SOME CONGENERS LABELED WITH TRITIUM IN THE AROMATIC RINGS

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SUMMARY

[diphenyl-2,2'-$^{3}H_{2}$]Methadone with specific activity of 8-30 Ci/mmol was prepared by reductive dehalogenation of 6-dimethylamino-4,4-bis(2-chlorophenyl)-3-heptanone with carrier-free tritium gas. The labeled congeners (-)-α-acetylmethadol, (-)-α-acetyl-N-normethadol, and (-)-α-acetyl-N,N-dinormethadol were prepared from (+)-[diphenyl-2,2'-$^{3}H_{2}$]methadone.

Key Words: Tritium gas, Methadone, (-)-α-acetylmethadol, (-)-α-acetyl-N-normethadol, (-)-α-acetyl-N,N-dinormethadol

INTRODUCTION

Methadone (6-dimethylamino-4,4-diphenyl-3-heptanone, 8) is a synthetic drug thought at one time to be a non-addictive alternative to morphine.[1] A similar, synthetic analgesic, (-)-α-acetylmethadol [(3S,6S)-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane, 11] is now being studied as a replacement of methadone in the maintenance of opiate addicts. Metabolites of 11, (-)-α-acetyl-N-normethadol [(3S,6S)-6-methylamino-4,4-diphenyl-3-acetoxyheptane, 12] and (-)-α-acetyl-N,N-dinormethadol [(3S,6S)-6-amino-4,4-diphenyl-3-acetoxyheptane, 14] have been implicated as part of the analgesic activity of 11.[2,3]

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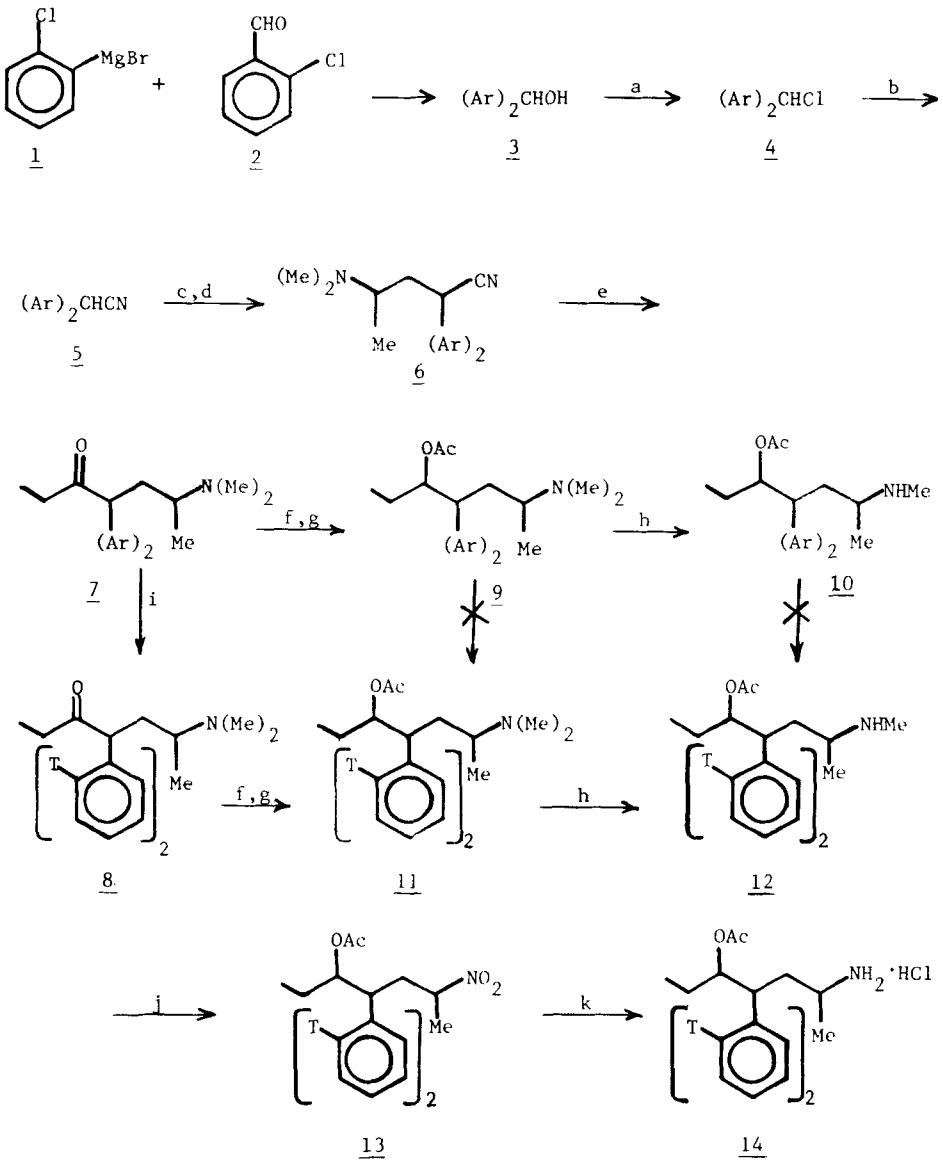
Radiolabeled samples of these drugs and metabolites were required for metabolic, pharmacokinetic, and other studies related to drug dependence. Consideration of the reported[4,5] metabolism of methadone and (-)-α-acetylmethadol discouraged labeling at carbon-1 and carbon-2 and the N-methyl groups since these carbons are lost during metabolism. In addition, methadone has been shown to undergo metabolic 4-hydroxylation of its aromatic rings. It was, therefore, decided to prepare the compounds specifically labeled with tritium at the 2-ring position.[6] The synthetic scheme is outlined in Chart 1.

Results and Discussion

Reaction of 2-chlorophenylmagnesium bromide with 2-chlorobenzaldehyde afforded bis(2-chlorophenyl)carbinol, 3, in 94% yield. Treatment of 3 with thionyl chloride allowed smooth conversion to the trichloro compound, 4, in 94% yield. Bis(2-chlorophenyl)acetonitrile, 5, was prepared in 80% yield by the reaction of 4 with potassium cyanide catalyzed by dibenzo-18-crown-6.

Base catalyzed reaction of compound 5 with 1-dimethylamino-2-chloropropane gave a 90% yield of a single isomer in contrast to the reported[7] 1:1 mixture of geometric isomers produced by reaction of diphenylacetonitrile with 1-dimethylamino-2-chloropropane. Mass spectral analysis of the product showed a base peak at m/z 72 (β cleavage of the amine) confirming that the product formed was the desired isomer, 2,2-bis(2-chlorophenyl)-4-dimethylaminovaleronitrile, 6, arising from attack of the anion at the least hindered position of the aziridinium intermediate. The desired common intermediate, 6-dimethylamino-4,4-bis(2-chlorophenyl)-3-heptanone, 7, was prepared from 6 by reaction with ethylmagnesium bromide.

Chart 1



Ar = 2-chlorophenyl

a. $SOCl_2$
b. KCN, dibenzo-18-crown-6
c. NaH
d. $CH_3CH(Cl)CH_2N(Me)_2$
e. EtMgBr
f. $LiAlH_4$
g. AcCl
h. EtOOCN=NCOOEt
i. $^3H_2$, $Pd(OH)_2/C$
j. m-chloroperbenzoic acid
k. H_2, Pd/C, C_6H_5Cl

It was our original intention to prepare the labeled compounds 11 and 12 by reduction of their respective dichloro analogues 9 and 10. Unfortunately, the increase in steric bulk provided by the 3-acetoxy group severely inhibited the reductive dehalogenation.[8] Consequently the synthesis of 11, 12, and 14 was carried out via reduction of optically resolved 7. Optically resolved 7 could not be prepared directly, but was prepared through resolution of the nitrile 6 and conversion of (S)-6 to (S)-7 via ethylmagnesium bromide.

The reduction of (S)-7 with tritium gas gave labeled (S)-methadone, 8. The optical purity of 8 was determined by isotopic dilution analysis. Crystallization of an aliquot of 8 with authentic (R)-methadone d-tartrate[9] to constant activity reduced the initial specific activity to only 0.1% of its original value, indicating that 8 was 99.9% optically pure. The reduction of 8 with $LiAlH_4$ followed by acetylation afforded labeled (-)-α-acetylmethadol, 11.

Labeled (-)-α-acetyl-N-normethadol, 12, was prepared from 11 by reaction with diethyl azodicarboxylate. Modification of the reported[10] procedure allowed the reaction to be carried out in a much shorter time and thereby greatly reduced the losses incurred by self radiolysis.

The preparation of labeled (-)-α-acetyl-N,N-dinormethadol hydrochloride, 14, was accomplished by the route reported[11] for the unlabeled compound. Thus, the oxidation of 12 with m-chloroperoxybenzoic acid (MCPBA) in chloroform provided 2-nitro-4,4-di(phenyl-2-^{3}H)-5-acetylheptanol (13) in 75% yield. Catalytic reduction of 13 gave 14 in 7.7% yield.

EXPERIMENTAL

Radioactive samples were counted in a Packard Tri-Carb 3375 liquid scintillation spectrometer using an Omnifluor-toluene (6 g/liter) cocktail. Developed TLC plates were scanned on a Varian Berthold Radioscanner fitted with a model LB 242 K ratemeter. ^{1}H NMR spectra were recorded on a Varian HA-100 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained on an AEI MS 902 instrument. Tritium gas was purchased from New England Nuclear, Boston, Massachusetts. Thin layer chromatography was done on E. Merck silica gel glass plates in the designated solvent systems.

Bis(2-chlorophenyl)carbinol (3). A two liter three-necked round bottom flask equipped with a stirrer, addition funnel, and condenser, containing 6.40 g (0.266 mol) of Mg turnings was flame dried under nitrogen. Dry ethyl ether (45 mL) was added and a solution of 50 g (0.261 mol) of 1-bromo-2-chlorobenzene in 200 mL of dry ethyl ether was added with heating and stirring over 1 h. The reaction was refluxed 1.3 h. A dry ethyl ether solution of 38.8 g (0.275 mol) of 2-chlorobenzaldehyde was added dropwise as rapidly as the reflux condenser would permit. The reaction mixture was refluxed 1 h after complete addition and stirred at 25°C overnight. The mixture was treated with 200 mL of 25% NH_4Cl and 100 mL of 3 N HCl. The phases were separated and the aqueous phase was extracted four times with 100 mL of ethyl ether. The combined ethyl ether extracts were washed with 250 mL of distilled water, 250 mL of 10% Na_2SO_3, and 250 mL of distilled water. The ethyl ether was dried (Na_2SO_4), filtered, and evaporated yielding 62.3 g (94.4% crude) of yellow oil. A portion of the oil was vacuum distilled giving the carbinol 3: bp 128°C (0.027 kPa): IR(CCl_4) 3600(O-H), 1470 and 1445 cm^{-1} (aromatic); NMR

($CDCl_3$) δ 2.78 (s, 1, OH), 6.48 (s, 1, 1-CH), 7.10-7.50 (m, 8, Ar-H); mass spectrum, m/z (rel intensity) 256 [2, $M(^{37}Cl_2)$], 254 [15, $M(^{35}Cl^{37}Cl)$], 252 [22, $M(^{35}Cl)_2$], 139 (100)

Anal. calc for $C_{13}H_{10}Cl_2O$: C 61.66, H 3.95, Cl 28.06

Found: C 61.96, H 3.86, Cl 27.91.

Bis-(2-chlorophenyl)chloromethane (4) To a solution of 62.3 g (0.246 mol) of 3 in 200 mL of dry benzene and 1 mL of pyridine was added dropwise under nitrogen, 29.3 g (0.246 mol) of thionyl chloride. After evolution of gas had ceased the reaction was refluxed 0.5 h. The mixture was quenched with 200 mL of water and was extracted three times with 200 mL of benzene. The benzene layers were combined, washed with 200 mL of saturated aqueous NaCl, dried (Na_2SO_4), and evaporated, yielding 63.1 g (94.5%) of orange-red oil which was 86% pure 4 by GC [2% OV-17 on Chromasorb W, 6', 200°C]. A portion of this material was recrystallized from benzene-hexane-methanol to give white crystalline 4: mp 56-57°C; IR (CH_2Cl_2) 1470 and 1443 (Aromatic), 1052, 1040, 627 cm^{-1}; NMR ($CDCl_3$) δ 6.86 (s, 1, ArCHCl), 7.18-7.60 (m, 8, Ar-H); mass spectrum, m/z (rel intensity) 276 [1, $M(^{37}Cl)_3$], 274 [5, $M(^{37}Cl_2{}^{35}Cl)$], 272 [15, $M(^{37}Cl^{35}Cl_2)$], 270 [16, $M(^{35}Cl)_3$], 239 (13), 237 (66), 235 (100), 165 (83).

Bis(2-chlorophenyl)acetonitrile (5). A solution of 10.2 g (0.04 mol) of 4 and 1.04 g of dibenzo-18-crown-6 in 100 mL of dry acetonitrile was stirred with 6.9 g (0.11 mol) of potassium cyanide for 104 h at 25°C. The solution was diluted to 1 L with ethyl ether and cooled to 0°C. The precipitate was filtered and washed with cold $CHCl_3$. The filtrates were evaporated and the residue was vacuum distilled affording 7.98 g (81%) of 5: bp 135°C (6.7 kPa); IR(CH_2Cl_2) 2245 (CN), 1465 and 1440 cm^{-1} (Aromatic); NMR ($CDCl_3$) δ 5.91 (s, 1, ArCHCN), 7.10-7.60 (m, 8,

Ar-H); mass spectrum m/z (rel. intensity) 265 [10, M($^{37}Cl)_2$)], 263 [61, M($^{37}Cl^{35}Cl$)], 261 [91, M($^{35}Cl)_2$], 228 (34), 226 (95), 190 (100).

2,2-Bis(2-chlorophenyl)-4-dimethylaminovaleronitrile (6) . A dry ethyl ether solution (300 mL) of 11.31 g (0.043 mol) of bis-(2-chlorophenyl)acetonitrile was added dropwise to 4.96 g (0.207 mol) of NaH suspended in 300 mL of dry ethyl ether. The suspension was stirred overnight under nitrogen. 2-Chloro-N,N-dimethylpropylamine hydrochloride (12.03 g, 0.076 mol) was added to this suspension in portions. The reaction was stirred for two days, added slowly to an equal volume of water, and the product was extracted with ethyl ether. The solvent was evaporated and the yellow solid was recrystallized from hexane-methylene chloride giving 10 g (65%) of the product 6: mp 147-148°C; IR ($CHCl_3$) 3060, 2970, 2940, 2865, 2830, 2790 (C-H), 2235 (-CN), 1590, 1470, 1435 (Aromatic), 1040 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (d, 3, J = 3Hz, 1-CH_3), 2.09 [s, 6, N($CH_3)_2$], 2.33-3.02 (m, 3), 7.02-7.58 (m, 6, Aromatic), 7.74-8.10 (m, 2, Aromatic); mass spectrum m/z (rel. intensity) 350 [1, M($^{37}Cl)_2$ - H], 348 [5, M($^{37}Cl^{35}Cl$) - H], 346 [8, M($^{35}Cl)_2$ - H], 331 (12), 72 [100, $CH_3CHN(CH_3)_2$].

Anal. calc for $C_{19}H_{20}Cl_2N_2$: C 65.71, H 5.76, Cl 20.46, N 8.07

Found: C 65.74, H 5.46, Cl 20.43, N 7.95

The (S)-isomer of 6 was obtained from repeated recrystallizations of the di-p-toluoyl-d-tartaric acid salt of 6 from acetone-water until constant optical rotations of $[\alpha]_D^{25}$ = 158° (C = 0.11) were obtained for consecutive crystallization products and their mother liquors. With this process 5.2 g of racemic 6 was used to give 470 mg of (S)-6. A solution of 14.9 mg (0.043 mmol) of S-6 in 3 mL of 95% ethanol and 6 μL (0.043 mmol) Et_3N was treated with 15 mg of 10% Pd/C under a hydrogen atmosphere for 41 h. The mixture was filtered. The filtrate residue

was purified by column chromatography [SiO_2; benzene-acetone (3:1)] yielding 2.7 mg (22%) of white crystalline (S)-2,2-diphenyl-4-dimethylaminovaleronitrile: mp 96-98°C; $[\alpha]_D^{25}$ = + 45.3°(C = 0.10, EtOH); [Lit[13] mp 101-102°C; $[\alpha]_D^{25}$ = + 49° (C = 1, EtOH)].

(S)-6-Dimethylamino-4,4-bis(2-chlorophenyl)-3-heptanone (7). A sample of 2.3 mL (7 mmol) of ethylmagnesium bromide (3 M in ethyl ether) was diluted with 40 mL of dry ethyl ether. A solution of 470 mg (1.36 mmol) of (S)-6 in 70 mL of dry toluene was added. The mixture was heated at 70-90°C for 5 h with evaporation of most of the ether. The mixture was quenched with 75 mL of 6 N HCl, heated 4.5 h at 90°C, and stirred at 25°C for 48 h. The mixture was basified with 100 mL of 25% NaOH and extracted five times with 150 mL of ethyl ether. The ether layers were combined, dried (Na_2SO_4), and evaporated yielding 468 mg of brown oil. The oil was purified by column chromatography [SiO_2; Gradient, 1% MeOH-$CHCl_3$ to 3% MeOH-$CHCl_3$] giving 118 mg of oil which was >90% pure 7 by GLC [2% OV-17 on Chromasorb W, 6', 240°C]. A 60 mg sample of the oil was dissolved in ethyl ether and converted to the hydrochloride salt with ethereal-HCl. The solvent was evaporated and the salt recrystallized from benzene-ethanol (9:1) giving 23.2 mg of (S)-7 hydrochloride: mp 227-230°C; IR ($CHCl_3$) 2965 (CH), 2700-2200 (NHR_3^+), 1714 (C=O), 1465, 1105, 1040 cm^{-1}; NMR ($CDCl_3$) δ 0.56 (t, 3, J = 6Hz, 1-CH_3), 0.90 (d, 3, J = 7Hz, 7-CH_3), 2.05 [s, 6, -$N(CH_3)_2$], 2.12-3.04 (m, 5, 2-CH_2, 5-CH_2, 6-CH), 7.22 (m ,6, Ar-H), 7.66 (m, 1, Ar-H), 8.24 (m, 1, Ar-H); mass spectrum, high resolution, found: 377.1308; calcd for $C_{21}H_{25}NOCl_2$, 377.1312; mass spectrum m/z (rel intensity) 381 [(0.2, $M(^{37}Cl)_2$], 379 [1, $M(^{37}Cl^{35}Cl)$], 377 [2, $M(^{35}Cl)_2$], 72 [100, $CH_3CHN(CH_3)_2^+$]; $[\alpha]_D^{28}$ = + 75° (C = 0.1).

(S)-6-Dimethylamino-4,4-di(phenyl-2-^{3}H)-3-heptanone (8). A solution of 9 mg (0.02 mmol) of 7 in 0.5 mL of THF and 50 µL of triethylamine was treated with 4.5 mg of 15% $Pd(OH)_2/C$ and 3 Ci (0.052 mmol) of tritium gas. The mixture was stirred 4 h. The mixture was filtered through Celite and the Celite was washed with 10 mL of CH_2Cl_2. The combined solvent was washed with 5% NaOH, dried (Na_2SO_4), and evaporated. The residue was purified by preparative TLC [MeOH-NH_4OH (100:0.1), R_f 0.4] yielding 243 mCi of 8 which was >98% radiochemical pure by radio-TLC (same system) and reverse isotopic dilution analysis. The specific activity was 12 Ci/mmol.[14]

The optical purity of 8 was determined by isotopic dilution analysis as follows: A sample of 8 was added to a solution of (R)-methadone d-tartrate. Removal of the solvent gave a residue with specific activity of 3.61 µCi/mg. Five recrystallization of this material from n-butanol-petroleum ether[9] gave crystals with specific activities of 1.47 µCi/mg, 0.099 µCi/mg, 0.018 µCi/mg, 0.005 µCi/mg and 0.0045 µCi/mg, indicating an optical purity of 99.9% for 8.

(3S,6S)-6-Dimethylamino-4,4-di(phenyl-2-^{3}H)-3-heptanol. A sample of 242 mCi (12 Ci/mmol) of 8 was isotopically diluted with 30.2 mg (0.10 mmol) of unlabeled 8. The sample was dissolved in 3 mL of dry ethyl ether and the solution was treated with 14 mg (0.37 mmol) of LAH. The mixture was stirred 10 minutes at 25°C then refluxed 1.5 h. Excess LAH was quenched with 10 mL of distilled water. The water was extracted four times with 20 mL of ethyl ether. The ether layers were combined, dried (Na_2SO_4), and filtered yielding 228 mCi (94%) of product which was >98% radiochemically pure by radio-TLC [MeOH-NH_4OH (100:1), R_f 0.5].

(3S,6S)-6-Dimethylamino-4,4-di(phenyl-2-^{3}H)-3-acetoxyheptane (11). A sample of 228 mCi (0.163 mmol) of (3S,6S)-dimethylamino-4,4-di(phenyl-2-^{3}H)-3-heptanol was dissolved in 0.7 mL of dry ethyl acetate in a 1 mL

Reactivial and treated with 30 μL (33 mg, 0.425mmol) of freshly distilled acetyl chloride. The reaction was heated at 70°C for 19 h. Radio-TLC [THF-NH_4OH (100:0.1); R_f 0.59, starting material; R_f 0.66, 11] showed the reaction was incomplete. A 30 μL sample of acetyl chloride was added and the mixture heated at 70°C for 24 h. Radio-TLC (same system) showed the reaction to be complete. A 4.7 mg (19 mCi) sample of white crystals were isolated from the yellow supernatant. The supernatant (163 mCi) was purified by preparative TLC [MeOH-NH_4OH (100:1), R_f 0.5] yielding 134 mCi of 11 which was >98% radiochemically pure by radio-TLC (both systems). The specific acitvity of 11 was 1.4 Ci/mmol (4.0 mCi/mg). Radiochemical yield was 67%.

(3S,6S)-6-Methylamino-4,4-di(phenyl-2-^{3}H)-3-acetoxyheptane (12). A sample of 25.4 mg (0.071 mmol, 100 mCi, 1.4 Ci/mmol) of 11 was treated with 20.0 mg (0.115 mmol) of diethyl azodicarboxylate in 1 mL of benzene. The solution was refluxed for 2.5 h.

Radio-TLC [EtOAc-hexanes-EtOH-NH_4OH (60:25:14:1)] showed the distribution of radioactivity as 6.6% 11 (R_f 0.69), 42.9% 12 (R_f 0.29), and 50.5% (R_f 0.59). The R_f 0.59 spot was presumed to be the azo intermediate which is hydrolyzed in the next step. The solvent was evaporated. The resulting yellow oil was dissolved in a mixture of 0.5 mL of ethanol and 0.5 mL of saturated aqueous NH_4Cl, and refluxed 1 h. The solution was cooled, filtered, and the filtrate was purified by preparative TLC (same system) giving 50 mCi of 12 which was 90% radiochemically pure. Repurification by TLC [EtOAc-AcOH-H_2O (6:3:1), R_f 0.64] afforded 27 mCi (27%) of 12 which was >98% radiochemically pure in both systems and had specific activity of 4.1 mCi/mg (1.4 Ci/mmol).

(3S,6S)-6-Nitro-4,4-di(phenyl-2-^{3}H)-3-acetoxyheptane (13). A sample of 23.8 mg (0.0684 mmol, 32.9 mCi, 0.48 Ci/mmol) of 12 and 75.6 mg (0.44 mmol) of m-chloroperoxybenzoic acid in 1 mL of $CHCl_3$ was refluxed 3 h. The mixture was purified by preparative TLC [$CHCl_3$-EtOH-NH_4OH (90:10:0.1)] yielding 24.8 mCi (18 mg) of 13 which was >98% radiochemically pure by TLC (same system).

(3S,6S)-6-Amino-4,4-di(phenyl-2-^{3}H)-3-acetoxyheptane Hydrochloride (14). A solution of 4.5 mg (43.3 mCi, 0.013 mmol) of 13 in 0.5 mL of 95% ethanol was treated with 10 mg of 10% Pd/C and 50 µL of chlorobenzene. The mixture was exposed to hydrogen at 40 psi at 40°C with stirring for 96 h. A sample of 40 mg (0.11 mmol) of unlabeled 14 was dissolved in the reaction mixture. The mixture was filtered through Celite, washed (MeOH), and the filtrate was evaporated yielding a white foam. Three crystallizations from CH_2Cl_2-Et_2O-H_2O did not yield material of suitable radiochemical purity. Purification by TLC [EtOAc-Hexanes-EtOH-NH_4OH (60:25:14:1)] and crystallization from CH_2Cl_2-Et_2O-H_2O yielded 12.9 mg (3.34 mCi) of 14 as the hydrochloride monohydrate salt with specific activity of 0.26 mCi/mg (94.3 mCi/mmol). Radio-TLC (same system) showed the sample was >98% radiochemically pure.

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14. This reductive tritiation was done several times on S-and racemic -7. The specific activity of the labeled 8 obtained from these reductions varied from 8-30 Ci/mmol. The usual specific activity obtained was 10-15 Ci/mmol. Attempts to improve the incorporation of tritium by changing the solvent, catalyst, or reaction time were not successful.