THE PREPARATION OF TRITIUM LABELED METHADONE AND ITS METABOLITES

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SUMMARY

The synthesis and catalytic tritium reduction of 1,2-dehydro analogs of (-)-methadol, (-)-α-acetylmethadol, and (-)-α-acetyl-N-normethadol afforded the labeled compounds with high specific activity (44-60 Ci/ mmole). The use of the homogeneous catalyst $(\phi_3P)_3RhCl$ resulted in specific introduction of tritium without scrambling. (+)-Methadone-1-^{3}H (25 Ci/mmole) was obtained by oxidation of (-)-methadol-1,2-$^3H_2$ followed by sodium hydroxide exchange of the 2-^{3}H.

Key Words: methadone, (-)-methadol, (-)-α-acetylmethadol, (-)-α-acetyl-N-normethadol, homogeneous catalysis, tritium, deuterium

INTRODUCTION

The use of (+)-methadone and the interest in (-)-α-acetylmethadol for opiate addiction maintenance programs has created a need for sensitive assays such as radioimmunoassay, as well as for receptor site studies for these compounds and their metabolites. Both of these needs can be approached by methods that utilize high specific activity radiolabeled analogs of the above compounds. However, such analogs have not been available at sufficiently high activity (~30 Ci/mmole) to provide needed sensitivity for radioimmunoassays and receptor site studies, although the problem has been addressed.

The first route to tritium labeled methadone (la) and related compounds relied on catalytic dechlorination of o,o'-dichloro-(+)-methadone lb with carrier free tritium gas.[1] In principle, similar

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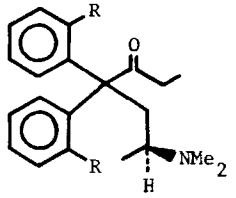
reduction of the corresponding chloro derivatives of (-)-methadol, (-)-α-acetylmethadol (LAAM), and (-)-α-acetyl-N-normethadol (nor-LAAM) would lead to their tritiated analogs; in practice, tritium reduction of o,o'-dichloromethadol was impractically slow and o,o'-dichloro-LAAM was inert.[1] These results were attributed to increased steric crowding about the ortho chlorine atoms resulting from conversion of the proximal trigonal carbonyl group of methadone to the sterically more demanding tetrahedral center of the methadols. Further, tritium reduction of 1b gave variable results, affording 1a with specific activities ranging from 1 to 24 Ci/mmole. While all the above tritium labeled methadols have been prepared from labeled methadone, these products were of a lower specific activity (15 to 0.14 Ci/mmole) due to the necessity of adding a carrier to provide sufficient material to accomplish these established transformations[2,3] without using unsafe amounts of labeled precursors.



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a: R = ^{3}H
b: R = Cl
c: R = H

In order to obtain high specific activity methadone, methadol and the related acetyl compounds we evaluated the synthesis and reduction of the dehydro analogs 3,6-8 (Figure 1). The unhindered monosubstituted double bond of these analogs was not expected to suffer the steric constraints that prevented tritiation of the o,o'-dichloro-acetylmethadols and permitted the use of the mild homogeneous catalyst $(\phi_3P)_3RhCl$ to

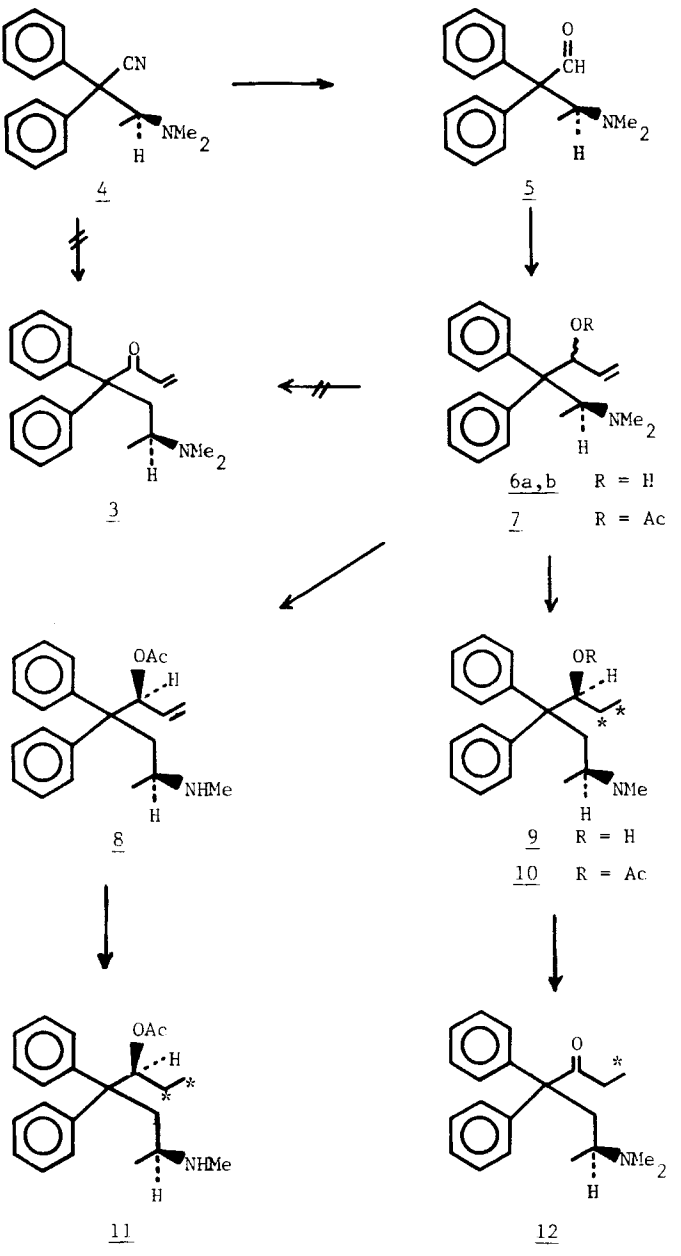
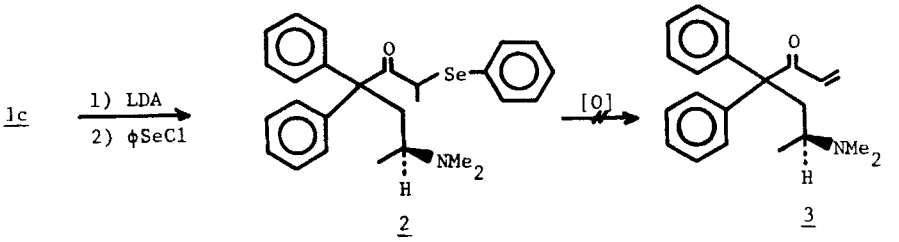

CN
NMe2
H
4
O
CH
NMe2
H
5
O
NMe2
H
3
OR
NMe2
H
6a,b R = H
7 R = Ac
OAc
H
NHMe
H
8
OR
H
*
*
NMe
H
9 R = H
10 R = Ac
OAc
H
*
*
NHMe
H
11
O
*
NMe2
H
12

Figure 1

introduce the carrier-free label regiospecifically in the last step of the syntheses without scrambling.[4]

Synthetic Methods and Results

The first approach to the dehydro analogs involved the attempted preparation of 1,2-dehydro-(+)-methadone (3) using the well established selenylation-selenoxide elimination method[5] of introduction of a double bond alfa to a carbonyl group. The subsequent dehydro compounds 6-8 would then be prepared from 3 by procedures established for the saturated molecules.[2,3] Treatment of (+)-methadone (1c) with lithium diisopropylamide in THF (-78°, 15 min), followed by addition of phenylselenium chloride and warming to room temperature (1 hr), afforded the selenide 2 in 36% yield. The next step, oxidation and *in situ* elimination of the intermediate selenoxide, proved to be impractical. Excess H_2O_2 gave evidence of over-oxidation, perhaps to the N-oxide, while the use of 1.1 equivalents gave only unchanged starting material. Sodium periodate oxidation gave a complex mixture and nmr analysis showed only small amounts of the desired enone 3.



2 3

The possibility of preparing the enone 3 via the addition of vinylmagnesium bromide to the optically pure nitrile 4 was then explored. However, reaction in either refluxing THF or refluxing toluene afforded no addition products, in contrast to the addition of ethylmagnesium

bromide to 4 which yields (+)-methadone.[6] This difficulty was apparently due to the lower reactivity of vinylmagnesium bromide and was circumvented by utilization of the more reactive aldehyde 5, prepared by reduction of the nitrile 4 with lithium triethoxyaluminum hydride[7] in 67% yield (Figure 1). Addition of excess vinylmagnesium bromide to 5 afforded a mixture of diastereomeric allylic alcohols 6a (26%) and 6b (32%) which were separated by chromatography. The lower R_f diastereomer (6a) proved to have the stereochemistry of (-)-α-methadol[8] (9) as shown by catalytic reduction [$(\phi_3P)_3RhCl$, benzene, $^2H_2$] to methadol and comparison with authentic 9 (tlc).

Dehydro-LAAM (7) was readily obtained in 71% yield by acetylation of 6a with acetic anhydride-pyridine at room temperature overnight. The preparation of dehydro nor-LAAM (8) was examined employing two methods reported[3] for the N-demethylation of LAAM. The first method, treatment of 7 with trichloroethyl chloroformate, yielded the intermediate carbamate (57%) but subsequent reduction with zinc gave only trace amounts of 8. The second method, treatment with diethyl azodicarboxylate in benzene (50°) overnight, afforded 8 in 68% yield after chromatography.

Attempts were made to prepare 1,2-dehydromethadone (3) by oxidation of 1,2-dehydromethadol (6). However, heterogeneous oxidation (MnO_2 or Pt/O_2) failed to affect any change and homogeneous oxidation (pyridinium chlorochromate) caused decomposition. The latter result contrasts with the successful oxidation of methadol using pyridinium chlorochromate. Labeled methadone was subsequently obtained via oxidation of labeled methadol (see below).

Catalytic deuterium reduction experiments were carried out to determine the extent and specificity of label incorporation. Hetero-

geneous reduction of 1,2-dehydro-β-methadol (PtO_2-$NaNO_2$, THF, 2 hr)[9] gave significant proportions of d_0, d_1, d_2, and d_3 labeled β-methadol while homogeneous reduction [$(\phi_3P)_3RhCl$, benzene, 18 hr] gave more specific label incorporation, affording predominently dideuterated β-methadol (Table 1). Similarly high d_2 incorporation was achieved on reduction of dehydro-α-methadol, dehydro-LAAM, and dehydro-nor-LAAM (Table 1). Oxidation of methadol to methadone resulted in retention of 93.7% d_1 after base exchange of the labile alfa deuterium. The position of the label in compounds 9-12 was determined by mass spectral analysis to be between 90 and 100% in the 1 and 2 positions (ethyl group) (Table 1), based on the deuterium content of the (M-ethyl) fragment.

(-)-Methadol-1,2-$^3H_2$ (47 Ci/mmole) (9), (-)-α-acetylmethadol-1,2-$^3H_2$ (60 Ci/mmole) (10) and (-)-α-acetyl-N-normethadol-1,2-$^3H_2$ (44 Ci/mmole) (11) were obtained in the last step of the reaction sequence by reduction of the 1,2-dehydro derivative with carrier free tritium gas (5Ci) in the presence of $(\phi_3P)_3RhCl$. (+)-Methadone-1-^3H (25 Ci/mmole) (12) was prepared by pyridinium chlorochromate oxidation of (-)-methadol-1,2-$^3H_2$ followed by treatment with aqueous sodium hydroxide to remove the labile 2-tritium.

EXPERIMENTAL PROCEDURES

NMR spectra were obtained using either a Varian HA-100 or EM-360 spectrometer using tetra-methylsilane as an internal standard. Infrared spectra were obtained using a Perkin-Elmer Model 467 spectrometer. Mass spectroscopic analyses were carried out using an AEI MS-902 mass spectrometer. Gas-liquid chromatographic analyses were performed using a Varian Model 1300 instrument with a column (152 cm x 1.59 mm) containing

Table 1

Deuterium Incorporation of Reduced Dehydromethadols and Analogs

#	Reduction Product	Catalyst	% d_0	d_1	d_2	d_3	d_4	d_5
-	β-methadol	PtO_2-$NaNO_2$	20.8	27.6	26.7	16.1	7.3	1.4
-	β-methadol	$(\phi_3P)_3RhCl$	0.0	0.0	88.1	7.5	4.4	0.0
9	(-)-α-methadol	$(\phi_3P)_3RhCl$	0.0	0.2	96.2	0.0	3.6	0.0
10	LAAM	$(\phi_3P)_3RhCl$	0.4	4.0	93.9	1.3	0.2	0.2
11	nor-LAAM	$(\phi_3P)_3RhCl$	1.8	11.6	77.6	7.3	1.4	0.2
12	(+)-methadone	$(\phi_3P)_3RhCl$	2.5	93.7	3.8	0.0	0.0	0.0
-	β-methadol minus ethyl	$(\phi_3P)_3RhCl$	99.8	0.0	0.2	0.0	0.0	0.0
-	9 minus ethyl	$(\phi_3P)_3RhCl$	98.5	1.6	0.0	0.0	0.0	0.0
-	12 minus ethyl	$(\phi_3P)_3RhCl$	97.6	0.0	2.4	0.0	0.0	0.0
-	10 minus ethyl	$(\phi_3P)_3RhCl$	92.7	0.6	4.2	0.3	1.2	1.0
-	11 minus ethyl	$(\phi_3P)_3RhCl$	89.8	3.4	1.3	3.3	2.2	0.0

2.0% OV-17 on Supelcoport. Radiopurity was determined using an Autochron LB-2722 radio scanner. Tritium was counted using a Packard Liquid Scintillation Counter Model 3003 with toluene/Omnifluor. Coated silica gel 60 F-254 (Merck) plates (iodine) were employed for TLC analysis. Elemental compositions of all compounds were determined by high resolution mass spectroscopy after verifying purity by TLC and GC analysis.

(+)-2,2-Diphenyl-4-dimethylaminovaleraldehyde (5). A 1.0 M solution of LAH in ether (20.0 mL, 0.020 mole) and 20 mL of Et_2O were cooled at 0°C under N_2, and ethyl acetate (1.7 g, 0.020 mol) in 20 mL of Et_2O was added over a 15 min period. After stirring for 15 min, (+)-2,2-diphenyl-aminovaleronitrile (5.0 g, 0.018 mol) in ether was added over a 20 min period at 0°C. The reaction was stirred for 2.0 hr and quenched with 40 mL of 5N H_2SO_4. The Et_2O was evaporated, the resulting aqueous solution was made basic with 50% aqueous NaOH, and the water evaporated *in vacuo*. The white residue was stirred overnight with methylene chloride, filtered, and the filtrate evaporated to afford 4.6 g of crude aldehyde. This material was chromatographed on 150 g of silica gel 60 (EtOAc-Hexanes-EtOH-NH_4OH 60:25:14:1) to afford 3.4 g (67%) of pure aldehyde as a semisolid. ^{1}H-NMR (chloroform-d_1) δ 9.21 (s, 1H, C<u>H</u>O), 7.3 (m, 10H, 2(ArH_5)], 2.29 [s, 6H, N-(C<u>H</u>$_3$)$_2$]; m/e 281.1777 ($C_{19}H_{23}N_1O_1$ requires 281.1774); $[\alpha]_D^{22}$ = +22.3° (CH_2Cl_4, c = 1.85).

1,2-Dehydromethadol (6a and 6b). To a 1.0 M solution of vinylmagnesium bromide in THF (36.3 ml, 36.3 mmole) and 10.0 mL of dry THF under N_2, a solution of 5 (3.4 g, 12 mmole) in THF was added dropwise over 5 min. The reaction was then refluxed for 1.5 hr and 6N HCl added. The THF was evaporated and the aqueous solution was made basic with 50% aqueous

NaOH. The resulting suspension was extracted with ether, and the ether extracts dried (Na_2SO_4) and evaporated, to afford 3.6 g of a crude mixture of the two anticipated diastereomers of 1,2-dehydromethadol. This separated by chromatography on a silica gel column (CCl_4-THF-NH_4OH 80:20:1) to afford 1.2 g (32%) of the higher R_f isomer and 960 mg (26%) of the lower R_f isomer as viscous oils. The higher R_f isomer was crystallized from CCl_4-hexanes to afford 531 mg (14%) of a colorless solid, mp 140-142°.

Higher R_f isomer (6b). ^{1}H-NMR (chloroform-d_1), δ 7.18 [m, 10H, 2(Ar$\underline{H}_5$)], 5.3-4.8 (m, 3H, $\underline{H}_2C{=}C\underline{H}$), 2.12 [s, 6H, N-($C\underline{H}_3$)$_2$]; m/e 309.2097 ($C_{21}H_{27}N_1O_1$ requires 309.2092); $[\alpha]_D^{22}$ = +139.2° (CH_2Cl_2, c = 3.3).

Lower R_f isomer (6a). ^{1}H-NMR (chloroform-d_1) δ 7.15 (m, 10H, 2(Ar$\underline{H}_5$)], 5.3-4.5 (m, 3H, $\underline{H}_2C{=}C\underline{H}$), 2.20 [s, 6H, N-($\underline{C}H_3$)$_2$]; m/e 309.2097 ($C_{21}H_{27}N_1O_1$ requires 309.2092) $[\alpha]_D^{22}$ = +16.5° (CH_2Cl_2, c = 3.0).

1,2-Dehydro-(-)-α-acetylmethadol (7). A solution of 6a (960 mg, 3.10 mmole), 2.5 mL of acetic anhydride and 3.2 mL of pyridine were allowed to stand overnight at room temperature. The reaction was poured into water and extracted with Et_2O. The ether extracts were dried (Na_2SO_4) and evaporated. Toluene was added to azeotrope the last traces of pyridine, to afford 770 mg (71%) of a viscous oil; ^{1}H-NMR (chloroform-d_1) δ 7.3-7.2 (m, 10H, 2Ar$\underline{H}_5$), 6.45 (d, 1H, AcO-C$\underline{H}$), 2.11 [s, 6H, (N-($C\underline{H}_3$)$_2$], 1.93 (s, 3H, $C\underline{H}_3CO$); m/e 351.2196 ($C_{23}H_{29}N_1O_2$ requires 351.2196); $[\alpha]_D^{22}$ = +0.28° (CH_2Cl_2, c = 2.16).

1,2-Dehydro-(-)-α-acetyl-N-normethadol (8). A solution of 7 (770 mg, 2.20 mmole) and diethyl azodicarboxylate (421 mg, 2.42 mmole) in 5.0 mL of benzene was stirred overnight at 50°C. The benzene was evaporated and 5.0 mL of ethanol and 10 mL of satd. NH_4Cl added and stirred under

reflux for 2 hr. The ethanol was removed in vacuo and the aqueous solution extracted with Et_2O, made alkaline with conc. NH_4OH, and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and evaporated to afford 1.1 g of crude solid. This material was chromatographed on a prepacked silica gel column (Merck, size B), eluting with $CHCl_3$-THF-NH_4OH (80:20:1), to afford 506 mg (68%) of the pure product as a viscous oil; ^{1}H-NMR (chloroform-d_1) δ 7.31-7.25 [m, 10H, 2(Ar$\underline{H}_5$)], 6.27 (m, 1H, AcO-C$\underline{H}$), 5.28 (m, 3H, $\underline{H}_2$C=C$\underline{H}$), 2.00 (s, 3H, N-CH_3), 1.98 (s, 3H, C$\underline{H}_3$CO); m/e 337.2046 ($C_{22}H_{27}N_1O_2$ requires 337.2040).

(-)-α-Methadol-1,2-$^2H_2$ (9). A solution of 6a (25 mg, 0.081 mg) and tris(triphenylphosphine)rhodium chloride (20 mg) in 1.0 mL of benzene was stirred under 1.0 atm of deuterium for 24 hr. The benzene was evaporated and the residue dissolved in 5.0 mL of 0.1N HCl and extracted with Et_2O. The aqueous solution was made basic with 25% aqueous NaOH and extracted with CH_2Cl_2. The latter was dried (Na_2SO_4) and evaporated to afford 23.5 mg of a crude residue, which was chromatographed on two 20 x 20 cm x 0.25 mm silica gel plates ($CHCl_3$-THF-NH_4OH 80:20:1) to afford 10 mg (40%) of the pure product as a semisolid; ^{1}H-NMR (chloroform-d_1) δ 7.70-7.10 [m, 10H, 2(Ar$\underline{H}_5$)], 3.80 (m, 1H, CHOH), 2.20 [s, 6H, N-(C$\underline{H}_3$)$_2$]; m/e 313 ($C_{21}H_{27}D_2N_1O_1$ requires 313); $[\alpha]_D^{22}$ = 1.43° (CH_2Cl_2, c = 0.35).

(+)-Methadol-1,2-$^2H_2$. A solution of 6b (25 mg, 0.081 mmole) and tris-triphenylphosphine)rhodium chloride (12 mg) in 1.0 mL of dry benzene was stirred overnight at room temperature under 1.0 atm of deuterium gas. The benzene was evaporated and the residue chromatographed on two 20 x 20 cm x 0.25 mm silica gel plates ($CHCl_3$-THF-NH_4OH 80:20:1) to afford 20.7 mg (82%) of the pure product as a semisolid; ^{1}H-NMR (chloroform-d_1) δ

7.49-7.15 [m, 10H, 2(Ar$\underline{H}_5$)], 4.11 (m, 1H, C$\underline{H}$OH), 2.15 [s, 6H, N-(C$\underline{H}_3$)$_2$]; m/e 313 ($C_{21}H_{27}D_2N_1O_1$ requires 313); $[\alpha]_D^{22}$ = +141.0° (CH_2Cl_2, c = 0.417).

(-)-α-Methadol-1',2'-$^3H_2$ (9). Following the above procedure, 6a (25 mg) was reduced with tritium (5 Ci) to afford 1.2 Ci (8.0 mg) of pure (-)-α-methadol-1,2-$^3H_2$, 47.0 Ci/mmole. The product was stored in a toluene-ethanol solution (9:1, 1000 mL) at 4°C.

The specific activity and yield were determined by quantitative GLC analysis using (+)-methadone as an internal standard.

(-)-α-Acetylmethadol-1,2-$^2H_2$ (10). A solution of 7 (25 mg, 0.071 mmole) and tris(triphenylphosphine)rhodium chloride (12 mg) in 1.0 mL of benzene was stirred overnight at room temperature under 1.0 atm of deuterium gas. The benzene was evaporated and the residue dissolved in 5 mL of 0.1N HCl and extracted with Et_2O. The aqueous solution was made basic with 25% NaOH and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and evaporated to afford 24.8 mg of the crude product. This material was chromatographed on two 20 x 20 cm x 0.25 mm silica gel plates ($CHCl_3$-THF-NH_4OH 90:10:1) to afford 16.3 mg (64%) of the pure product as a semisolid; ^{1}H-NMR (chloroform-d_1) δ 7.31-7.19 (m, 10H, ArH), 6.22 (m, 1H, AcO-C$\underline{H}$), 2.15 [(s, 6H, N-(C$\underline{H}_3$)$_2$], 1.95 (s, 3H, CH_3CO); m/e 355 ($C_{23}H_{29}D_2N_1O_2$ requires 355); $[\alpha]_D^{22}$ = -7.3° (CH_2Cl_2,c = 1.0)

(-)-α-Acetylmethadol-1,2-$^3H_2$ (10). A solution of 7 (28.8 mg, 0.0820 mmole) and tris(triphenylphosphine)rhodium chloride (14 mg) in 0.5 mL of dry benzene was stirred at room temperature under carrier free tritium gas (5.0 Ci). The benzene was evaporated under N_2 and the residue was dissolved as much as possible in 0.1 N HCl, extracted with Et_2O, made basic with 25% aqueous NaOH and extracted with CH_2Cl_2. The latter organic extracts were dried (Na_2SO_4) and evaporated. The residue was

chromatographed on two 20 x 20 cm x 0.25 mm silica gel plates (EtOAc-Hexanes-NH_4OH 60:25:14:1) to afford 649 mCi of the pure product.

The specific activity and yield were determined to be 60 Ci/mmole and 3.84 mg (13%), respectively, by quantitative GLC analysis of a toluene solution using (+)-methadone as an internal standard.

(-)-α-Acetyl-N-normethadol-1,2-$^2H_2$ (11). A solution of 8 (26 mg, 0.077 mmole) and tris(triphenylphosphine)rhodium chloride (12 mg) in 1.0 mL of dry benzene was stirred overnight at room temperature under 1 atm of deuterium gas. The benzene was evaporated and the residue was dissolved in 4.0 mL of 0.1 N HCl and extracted with Et_2O, made basic with 25% aqueous NaOH, and extracted with CH_2Cl_2. The latter organic extracts were dried (Na_2SO_4) and evaporated to afford 16.3 mg of a gum. This was chromatographed on two 20 x 20 x 0.25 mm silica gel plates ($CHCl_3$-THF-NH_4OH 80:20:1) to afford 12.5 mg (48%) of the pure product as a semisolid; ^{1}H-NMR (chloroform-d_1) δ 7.31 (m, 10H, ArH), 5.85 (m, 1H, AcO-CH), 2.00 (s, 3H, N-CH_3), 1.91 (s, 3H, CH_3CO); m/e 341 ($C_{22}H_{27}D_2N_1O_2$ requires 341); $[\alpha]_D^{22}$ = -47.0° (CH_2Cl_2, c = 1.0).

(-)-α-Acetyl-N-normethadol-1,2-$^3H_2$ (11). A solution of 8 (23.6 mg, 0.0700 mmole) and tris(triphenylphosphine)rhodium chloride (12.0 mg) in benzene (0.5 mL) was stirred under tritium gas (5 Ci) at room temperature for 48 hr. The mixture was diluted with ether and extracted with 0.1N HCl. The latter extract was made basic (pH 14) with aq NaOH and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), concentrated, and purified by PTLC on silica gel, to provide 971 mCi of the desired product.

The specific activity and yield were determined to be 44 Ci/mmole and 7.46 mg (31%), respectively, by quantitative GLC of a solution of the product in toluene-ethanol (9:1) using (+)-methadone as an internal standard.

(+)-Methadone-1-^{3}H (12). A mixture of 9 (4.0 mg, 0.013 mmole, 600 mCi) and pyridinium chlorochromate (5.5 mg, 0.025 mmole) in CH_2Cl_2 (2.5 mL) was stirred and refluxed for 1 hr, when TLC analysis showed the oxidation was complete. The solvent was evaporated and the residue was dissolved in 25% aq NaOH. This solution was extracted with ether, and the organic extracts were concentrated. The residue was purified by PTLC (SiO_2), to obtain 202 mCi (2.5 mg) of methadone-1-^{3}H, 25 Ci/mmole (GLC determination; internal standard (-)-α-methadol). The product was stored in 500 mL of toluene-ethanol (9:1) at 0°C.

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