p-Hydroxymethadone: Synthesis, Crystal Structure and CD Properties

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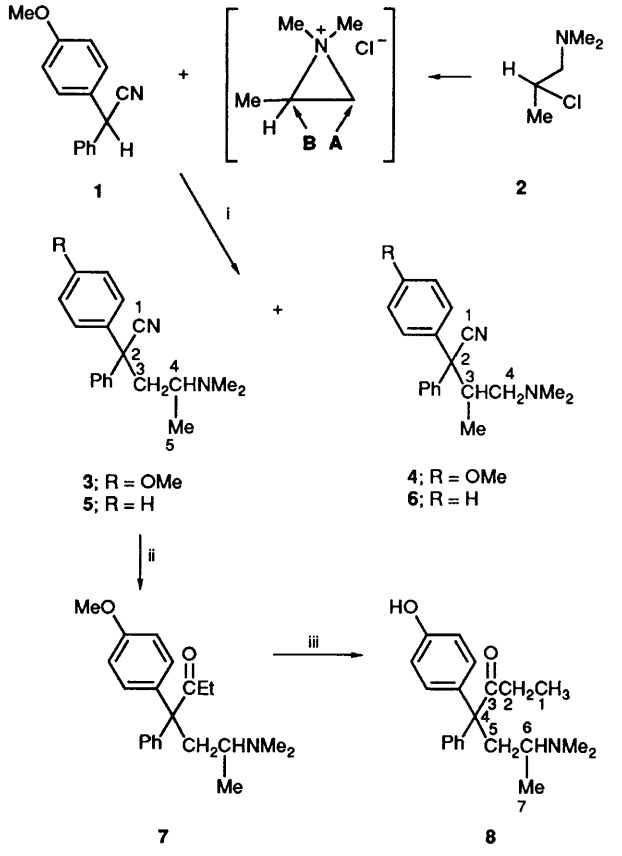
Alkylation of 2-chloro-*N*,*N*-dimethylpropylamine **2** with the lithium salt derived from 2-(*p*-methoxyphenyl)-2-phenylacetonitrile **1** afforded a mixture of *p*-methoxymethadone nitrile **3** and *p*-methoxyisomethadone nitrile **4**. The nitriles were separated chromatographically and the amino nitrile **3** was converted subsequently into the diastereoisomeric *p*-hydroxymethadone **8** hydrochlorides. Careful recrystallization afforded a separation of the (4*RS*,6*RS*)- and (4*RS*,6*SR*)-*p*-hydroxymethadone hydrochlorides. Repetition of the synthesis using (*R*)-2-chloro-*N*,*N*-dimethylpropylamine, derived in three steps from (*S*)-dilactide **9**, yielded the (4*S*,6*S*)- and (4*R*,6*S*)-*p*-hydroxymethadone hydrochlorides, which were also separated by fractional crystallization. The absolute configuration of the products was verified by X-ray crystallography. The (4*R*,6*S*)) salt exhibited a more intense Cotton effect than (*S*)-methadone hydrochloride while the (4*S*,6*S*) salt showed a less intense Cotton effect and less fine structure in the λ 260–275 nm range.

The continued use of methadone (6-dimethylamino-4,4-diphenylheptan-3-one) as a treatment drug for the maintenance of opiate addicts has stimulated an ongoing interest in its metabolism, especially in addicts undergoing prolonged treatment. As a result, the metabolic pathways involving *C*-hydroxylation on the aromatic carbons of methadone have received increased attention. One such pathway results in the production and excretion of *p*-hydroxymethadone **8**.[1] However, both the C-4 stereochemistry generated by the hydroxylation reaction and the optical properties of the metabolite are unknown. As samples of known stereochemistry are required to answer these questions, we have undertaken the preparation of the necessary optical isomers. In this paper we describe an efficient synthesis of (4*S*,6*S*)-**8** and (4*R*,6*S*)-**8**. In addition, we present the X-ray crystallographic analysis of the (4*S*,6*S*) isomer and the CD spectra of both optical isomers.

Synthesis

Prior to undertaking the preparation of the optical isomers, we developed an efficient synthesis of the diastereoisomeric *p*-hydroxymethadones **8**. The initial target compounds were the corresponding *p*-methoxymethadones **7**,[1–3] which we prepared by the route shown in Scheme 1. Thus, alkylation of 2-chloro-*N*,*N*-dimethylpropylamine **2** with the lithium salt derived from 2-(*p*-methoxyphenyl)-2-phenylacetonitrile **1**[4] afforded a mixture (*ca.* 2:1) of the amino nitriles **3** and **4**. The formation of **3** and **4** was due to anionic attack on the aziridinium ion intermediate[5] along pathways **A** and **B**, respectively. The aminonitriles **3** and **4** were separated by careful chromatography on silica gel and definitively identified by comparing their ^{1}H and ^{13}C NMR spectra with those of 4-dimethylamino-2,2-diphenylpentanenitrile **5**[6] and the isomeric 4-dimethylamino-3-methyl-2,2-diphenylbutanenitrile **6**,[6,†] (*cf.* Table 1). Subsequent treatment of the amino nitrile **3** with the Grignard reagent afforded the diastereoisomeric *p*-methoxymethadones **7**, the hydrochloride salts of which had m.p. 158–220 °C. Although the broad melting point was attributable to a diastereoisomeric mixture, it was considerably different from the data reported by Shapiro.[2] In the Shapiro synthesis, treatment of a mixture of *p*-methoxymethadone **7** and *p*-methoxyisomethadone with 0.5 equiv. of hydrochloric acid gave, in unspecified yield, **8** hydrochloride having m.p. 162–163 °C.[2] Possibly Shapiro observed selective crystallization of just one enantiomeric pair.

With the diastereoisomeric *p*-methoxymethadones **7** in hand, the conversion into the corresponding *p*-hydroxymethadones **8** was accomplished by boron tribromide[7] *O*-demethylation. We



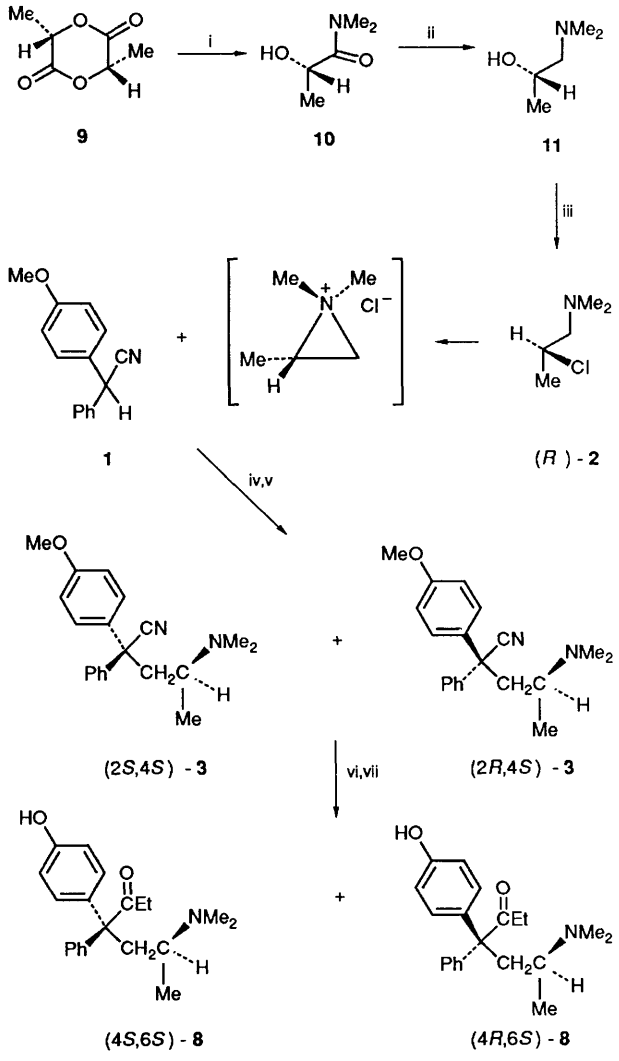
Scheme 1 *Reagents:* i, $LiNPr^i_2$; ii, EtMgBr; iii, BBr_3

† A reference sample of **5** was supplied by Regis Chemical Co., Morton Grove, IL. A reference sample of **6** was prepared as described in the literature.[6]

Table 1 Pertinent ^{13}C NMR data on compounds **3** and **4**[a]

Carbon	δ (3)	δ (5)	δ (4)	δ (6)
CMe	13.18	12.84	15.37	15.37
	12.98			
*C*H	55.13	55.16	38.05	38.00
*C*H$_2$	43.07	43.07	62.43	62.38
	42.87			
C	48.73	49.41	56.33	55.16
NMe	39.66	39.70	45.80	45.80

[a] The spectra were run in $CDCl_3$ solution on the free bases.



Scheme 2 *Reagents:* i, Me_2NH; ii, LAH; iii, $SOCl_2$; iv, $LiNPr^i_2$; v, chromatography; vi, EtMgBr; vii, BBr_3

used boron tribomide rather than refluxing hydrobromic acid [1] because we preferred the milder reaction conditions possible with boron tribromide. The *p*-hydroxymethadones **8** were purified as the hydrochloride salts. Careful fractionation of the salts resulted in a separation of the (4*RS*,6*RS*)-**8** hydrochloride and the (4*RS*,6*SR*)-**8** hydrochloride. The less soluble salt had m.p. 242–243 °C (decomp.) and showed a δ_H doublet at 0.54 for the C-7 methyl group. The corresponding data for the more soluble salt were m.p. 134–136 °C and a doublet at δ_H 0.50.

Having achieved an improved synthesis of racemic material, we undertook the preparation of the 6*S* optical isomers of *p*-hydroxymethadone **8**. Our approach was based on the reported preparation of (*S*)-4-dimethylamino-2,2-diphenylpentanenitrile by alkylation of (*R*)-2-chloro-*N*,*N*-dimethylpropylamine with

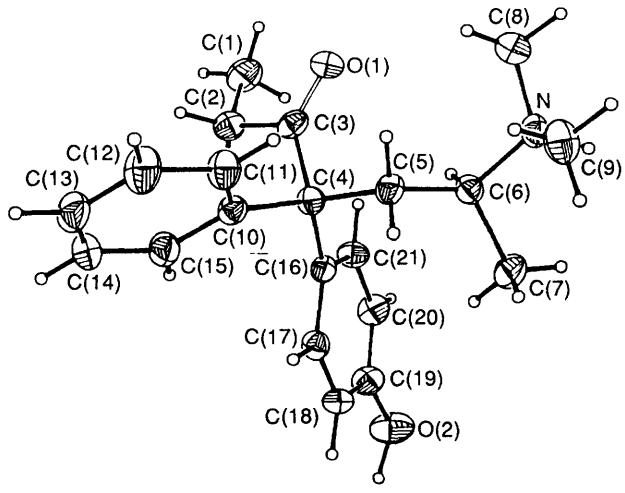


Fig. 1 ORTEP drawing of (4*S*,6*S*)-*p*-hydroxymethadone hydrobromide

sodium diphenylacetonitrile.[8] Thus, commercially available (*S*)-dilactide **9** was converted into the requisite (*R*)-chloroamine **2** in three steps as shown in Scheme 2. Subsequent alkylation of this amine followed by chromatography yielded the diastereoisomeric amino nitriles (2*S*,4*S*)-**3** and (2*R*,4*S*)-**3**. The key feature of this sequence was the double inversion of configuration which occurred during the transformation of (*S*)-1-dimethylaminopropan-2-ol **11** to the optically active aziridinium ion intermediate.[8] Subsequent anionic attack on this aziridinium ion to produce the desired product (*cf.* Scheme 1, pathway **A**) had no effect on the chiral centre.

The conversion of the amino nitriles (2*S*,4*S*)-**3** and (2*R*,4*S*)-**3** to (4*S*,6*S*)-**8** and (4*R*,6*S*)-**8** was accomplished by the same procedures developed for the synthesis of the racemic compounds. As expected on the basis of our earlier results, the hydrochloride salts of the diastereoisomeric *p*-hydroxymethadones **8** were separable by fractional crystallization. After the initial separation, each salt was recrystallized until its optical rotation was constant. Afterwards, the less soluble isomer had m.p. 234–235 °C and a δ_H doublet at 0.54 for the C-7 methyl group. Consequently, it clearly corresponded to the less soluble enantiomeric pair obtained from our racemic synthesis. Likewise, the more soluble isomer, which had m.p. 194–195 °C and a doublet at δ_H 0.50, corresponded to the other enantiomeric pair isolated in pure form. A portion of the less soluble isomer was converted into the hydrobromide salt, m.p. 223–225 °C, for X-ray analysis.

Crystallography.—The X-ray analysis was carried out on the hydrobromide salt prepared from the less soluble hydrochloride salt. A comparison of the cell dimensions and space group of the *p*-hydroxymethadone **8** hydrobromide crystal with those of (*S*)-methadone hydrobromide [9] suggested that the two crystals were isomorphous, a finding which helped in solving the crystal structure (*cf.* Experimental section). An ORTEP drawing of the crystal structure of the hydrobromide salt, presented in Fig. 1, shows that it has the (4*S*,6*S*) absolute configuration (*cf.* Table 2 for structural parameters). Therefore, the less soluble hydrochloride salt is the (4*S*,6*S*) isomer and the more soluble hydrochloride salt is the (4*R*,6*S*) isomer. In addition, the less soluble and more soluble forms of racemic *p*-hydroxymethadone **8** hydrochloride are the (4*RS*,6*RS*)- and (4*RS*,6*SR*)-isomers, respectively.

Circular Dichroism.—The CD spectra of (4*S*,6*S*)-**8** hydrochloride, (4*R*,6*S*)-**8** hydrochloride and (*S*)-methadone hydro-

Table 2 Atomic coordinates ($\times 10^4$)

Atom	x	y	z
Br	9 301(1)	12 500	1 010(1)
O(1)	5 810(3)	3 961(4)	846(2)
O(2)	10 177(3)	5 737(4)	6 380(3)
N	7 984(3)	7 076(4)	−40(3)
C(1)	5 980(5)	1 216(6)	2 250(5)
C(2)	5 541(3)	2 715(5)	2 759(3)
C(3)	5 838(4)	4 087(5)	1 972(4)
C(4)	6 059(3)	5 682(4)	2 612(3)
C(5)	6 485(3)	6 845(5)	1 643(3)
C(6)	7 862(3)	6 688(5)	1 323(3)
C(7)	8 802(3)	7 698(7)	2 105(3)
C(8)	7 494(4)	5 842(6)	−898(4)
C(9)	7 494(4)	8 604(5)	−437(4)
C(10)	4 720(3)	6 080(4)	2 970(3)
C(11)	3 838(3)	6 781(5)	2 116(4)
C(12)	2 587(4)	6 992(6)	2 391(4)
C(13)	2 216(4)	6 518(5)	3 511(4)
C(14)	3 067(4)	5 825(5)	4 373(4)
C(15)	4 309(4)	5 613(5)	4 102(4)
C(16)	7 055(3)	5 600(4)	3 733(3)
C(17)	7 127(3)	6 709(4)	4 659(3)
C(18)	8 142(4)	6 776(5)	5 580(3)
C(19)	9 113(4)	5 718(5)	5 559(4)
C(20)	9 049(3)	4 588(5)	4 658(4)
C(21)	8 035(3)	4 535(4)	3 751(3)

chloride[10] were obtained in methanol at 0.13 to 0.26 mg cm^{-3} concentrations. As expected, all three curves had the same sign. However, compared to (*S*)-methadone hydrochloride, the (4*R*,6*S*) salt had a more intense Cotton effect and had the maxima shifted to a slightly higher wavelength. In contrast, the (4*S*,6*S*) salt was similar to (*S*)-methadone hydrochloride except for a reduced intensity in the λ 290–300 nm range and less fine structure in the λ 260–275 nm range. From these data it was apparent that the diastereoisomeric *p*-hydroxymethadone 6*S* isomers were readily distinguishable by their CD spectra.

Discussion

p-Hydroxymethadone **8** was postulated as a urinary metabolite in man on the basis of GC–MS evidence obtained during early studies on methadone maintenance subjects.[11,12] That aromatic hydroxylation had occurred was deduced by mass spectral analysis of the *O*-methyl derivative of the metabolite while the position of hydroxylation was presumed by analogy with other microsomal hydroxylation reactions. During the same time period Misra and Mule[13] presented TLC–radioscan evidence for the formation of a *p*-hydroxyphenyl metabolite of (+)-methadone in rat brain. A possible hydroxymethadone metabolite was detected in a study on the fecal excretion of methadone and unconjugated metabolites by maintenance patients with chronic liver disease.[14] However, the hydroxymethadone metabolite was not clearly differentiated from another possible metabolite.

The preparation of racemic *p*-hydroxymethadone **8** made metabolite identification and quantitation possible. An HPLC study of the pharmacokinetics and disposition of methadone and its metabolites in the dog revealed that **8** was among the minor metabolites.[15] In a more recent study,[1] **8** in the urine and bile of the rat represented 1.82 and 38.03%, respectively, of the administered dose of methadone. More importantly, the definitive identification of *p*-hydroxymethadone **8** in the dog and the rat provided additional support for its presence as a methadone metabolite in man.

The aromatic hydroxylation of methadone will produce a second asymmetric centre assuming that only one aromatic ring is hydroxylated. In studies with either (*R*)-(−)-methadone or (*S*)-(+)-methadone, it is of interest to determine the stereochemistry of the aromatic hydroxylation reaction. We expect that the (4*S*,6*S*)- and (4*R*,6*S*)-isomers of *p*-hydroxymethadone **8** described in this paper will be valuable reference compounds for this purpose.

Experimental

M.p.s were determined on a Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 467 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian HA-100 spectrometer. All chemical shifts are reported in δ values relative to a tetramethylsilane standard. ^{13}C NMR spectra were determined at 25.03 MHz on a JEOL-JNM-PS-100 FT–NMR spectrometer interfaced with a Nicolet 1085 Fourier-transform computer system under conditions previously described.[16] Mass spectra were run at 70 eV on an AEI MS-902 mass spectrometer. Optical rotations were determined at the sodium D line on a Perkin-Elmer Model 141 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Circular dichroism (CD) measurements were made at ambient temperature with a Durrum-Jasco Model-20 ORD-CD spectropolarimeter calibrated with d-10-camphorsulphonic acid. Analyses were performed by Integral Microanalytical Laboratories, Inc., Raleigh, NC and by Micro-Tech Laboratories, Inc., Skokie, IL, USA.

p-*Methoxybenzhydryl Alcohol.*—Solid $NaBH_4$ (2.25 g, 0.059 mol) was added in one batch to a solution of *p*-methoxybenzophenone (25.01 g, 0.118 mol) in MeOH (150 cm^3). After the exothermic reaction had subsided, the mixture was stirred for a further 1.5 h. The solvent was then evaporated, and the white residue was partitioned between water and CH_2Cl_2 (100 cm^3 each). The aqueous layer was extracted with two additional portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated to give the *alcohol* (25.24 g, 100%) as an off-white solid, m.p. 65–66.5 °C; $\delta_H(CDCl_3)$ 5.6 (1 H, s) (Found: C, 78.75; H, 6.6. $C_{14}H_{14}O_2$ requires C, 78.48; H, 6.59%).

p-*Methoxybenzhydryl Chloride.*—A stirred suspension of the above alcohol (25.24 g, 0.118 mol) and powdered $CaCl_2$ (38.00 g, 0.34 mol) in C_6H_6 (400 cm^3) was bubbled with HCl gas for 45 min. The mixture was stirred for an additional 30 min and then filtered. The filtrate was evaporated to give the chloride (27.26 g, 99%) as a tan solid, m.p. 59–63 °C (lit., 61 °C;[4] 64 °C[17]); $\delta_H(CDCl_3)$ 6.0 (1 H, s).

2-(p-*Methoxyphenyl*)-2-*phenylacetonitrile* **1**.—Oven-dried glassware was used in this experiment, and MeCN used had been freshly distilled from CaH_2. To a solution of the above chloride (27.00 g, 116 mmol) in dry MeCN (150 cm^3) was added dibenzo-18-crown-6[18] (2.10 g, 6 mmol) followed by dry KCN (7.75 g, 119 mmol). The resultant mixture was refluxed for 54 h and then filtered and the solid washed with CH_2Cl_2. The combined filtrate and washings were evaporated to brown solid. This was redissolved in CH_2Cl_2 and flushed through a silica gel column (60 g). The CH_2Cl_2 eluent was concentrated almost to dryness, then diluted with heptane to precipitate the product. The solid was collected, washed with heptane and vacuum dried. Afterwards, the pale yellow solid (19.50 g, 75%) had m.p. 123–128 °C; $\delta_H(CDCl_3)$ 5.0 (1 H, s). A sample recrystallized from CH_2Cl_2–heptane had m.p. 130–131 °C (lit.,[4] 130 °C). In spite of the low melting point, the precipitated material was sufficiently pure for use in the alkylation reaction.

4-*Dimethylamino*-2-(p-*methoxyphenyl*)-2-*phenylpentanenitrile* **3** *and* 4-*Dimethylamino*-2-(p-*methoxyphenyl*)-3-*methyl*-

2-phenylbutanenitrile **4**.—The THF used in this experiment was freshly distilled from LAH, and the glassware was oven-dried. Into a 2 dm^3 Parr flask flushed with nitrogen were introduced dry THF (100 cm^3) and BuLi (1.8 mol dm^{-3}; 36 cm^3, 65 mmol). A solution of diisopropylamine (6.55 g, 65 mmol) in THF (25 cm^3) was added, and the resultant mixture was stirred for 15 min. A solution of compound **1** (14.45 g, 65 mmol) in THF (300 cm^3) was added, and the resultant mixture was stirred for a further 15 min. A solution of 2-chloro-1-*N*,*N*-dimethylpropylamine **2** (16.30 g, 134 mmol) in THF (50 cm^3) was then added. The flask was sealed and maintained at 60 °C for 24 h. Afterwards, the mixture was evaporated to dryness and the residue was partitioned between Et_2O and water (300 cm^3 each). The Et_2O layer was extracted with water and saturated brine (300 cm^3 each), dried (Na_2SO_4) and evaporated to give a black viscous oil (19.23 g). This was chromatographed on silica gel (1500 g) using an acetone–$CHCl_3$ gradient. Beginning with 1% acetone–$CHCl_3$, the gradient was increased by 1% increments to 5% acetone–$CHCl_3$, then by 5% increments to 20% acetone–$CHCl_3$. If the switch to 10% acetone–$CHCl_3$ was made before compound **3** began to be eluted, the separation of compounds **4** and **3** was considerably poorer. The chromatography afforded unchanged compound **1** (1.96 g, 13.5% recovery), compound **4** (4.83 g, 28% corrected), 0.44 g of product mixture and compound **3** (9.18 g, 53% corrected).

The amino nitrile **3** was obtained as a chromatographically pure yellow oil; $\delta_H(CDCl_3)$ 0.93 (3 H, overlapping d, CMe), 2.12 (6 H, s, NMe). The $\delta_H(CDCl_3)$ of **5** showed 0.91 (3 H, d, CMe) and 2.11 (6 H, s, NMe). The amino nitrile **3** was normally used in the next reaction without further purification. However, in one experiment, a solution of **3** (200 mg, 0.65 mmol) in acetone (20 cm^3) was treated with oxalic acid dihydrate (90 mg, 0.71 mmol), and the mixture was diluted to 125 cm^3 with Et_2O. After storage for 4 d at room temperature, the white solid was filtered off, washed with Et_2O and vacuum dried to give **3**•*oxalate* (60 mg), m.p. 140–144 °C (Found: C, 65.6; H, 6.6; N, 6.75. $C_{22}H_{26}N_2O_5$•$0.25H_2O$ requires C, 65.57; H, 6.63; N, 6.95%).

The amino nitrile **4** was obtained as a chromatographically pure yellow oil; $\delta_H(CDCl_3)$ 1.12, 1.19 (3 H, two d, CMe), 2.70–3.10 (1 H, m, C*H*), 2.17 and 2.19 (6 H, two s, NMe). The $\delta_H(CDCl_3)$ of **6** showed 1.14 (3 H, d, CMe), 2.70–3.10 (1 H, m, C*H*), 2.17 (6 H, s, NMe). An oxalate salt was prepared by adding oxalic acid dihydrate (2.90 g, 0.023 mol) to a solution of compound **4** (7.07 g, 0.023 mol) in a minimum volume of MeOH. Subsequent addition of Et_2O precipitated the salt as a white solid. Two crops totalling 6.03 g were collected and were recrystallized from MeOH–Et_2O. From the recrystallization were obtained **4**•*oxalate* as a white solid (5.20 g), m.p. 105–120 °C (Found: C, 64.65; H, 6.55; N, 6.65. $C_{22}H_{26}N_2O_5$•$0.5H_2O$ requires C, 64.85; H, 6.68; N, 6.87%).

6-Dimethylamino-4-(p-*methoxyphenyl*)-4-*phenylheptan*-3-*one* (p-*Methoxymethadone* **7**).—Under nitrogen an oven-dried flask was charged with ethylmagnesium bromide in Et_2O (2.94 mol dm^{-3}; 5.15 cm^3, 15 mmol). Next a solution of **3** (1.55 g, 5 mmol) in dry toluene (25 cm^3) was added dropwise, and the resultant mixture was refluxed gently for 5 h. Then HCl (6 mol dm^{-3}; 10 cm^3) was carefully added, and the solution was refluxed for 2 h. The layers were separated, and the organic phase was extracted with HCl (6 mol dm^{-3} × 2) and water. The combined aqueous layers were basified (pH 9) with concentrated NH_4OH (cooling) and extracted with CH_2Cl_2 (×2). After drying (Na_2SO_4), the combined organic extracts were evaporated to yield compound **7** (1.56 g, 91%) as a yellow oil; $\nu(CH_2Cl_2)/cm^{-1}$ 1700. That portion of compound **7** required for the next reaction was used without further purification.

The hydrochloride salt was prepared by dissolving compound **7** (5.37 g, 150 mmol) in a minimum volume of Pr^iOH and adding HCl (12 mol dm^{-3}; 1.35 cm^3). The salt was precipitated by adding Et_2O to the cloud point and chilling in the freezer. Two crops totalling 4.90 g were collected. Recrystallization from EtOAc–MeOH gave **7** *hydrochloride* (3.26 g, 54%) as a white solid, m.p. 158–220 °C; $\delta_H([^2H_6]$-DMSO) 0.54 (3 H, m), 0.74 (3 H, t), 2.60 (6 H, s), 3.80 (3 H, 2) and 6.86–7.60 (9 H, m). A sample was dried at 110 °C for analysis (Found: C, 69.25; H, 7.9; N, 3.6. $C_{22}H_{30}ClNO_2$•$0.25H_2O$ requires C, 69.46; H, 8.08; N, 3.68%).

6-Dimethylamino-4-(p-*hydroxyphenyl*)-4-*phenylheptan*-3-*one* (p-*Hydroxymethadone* **8**).—A solution of compound **7** (3.19 g, 9 mmol) in dry CH_2Cl_2 (60 cm^3) was cooled in a dry ice–acetone bath. A solution of BBr_3 in CH_2Cl_2 (1 g cm^{-3}, 7.10 cm^3) was added dropwise. The resultant mixture was stirred for 30 min at low temperature and then overnight after removal of the cooling bath. The CH_2Cl_2 was evaporated, the residue was diluted with MeOH (50 cm^3), and the resultant solution was concentrated to dryness. The MeOH dilution and evaporation process was repeated five times. Afterwards, the dark residue was partitioned between HCl (4 mol dm^{-3}; 150 cm^3) and Et_2O (100 cm^3). The layers were separated, and the aqueous phase was washed with two additional portions of Et_2O, basified (pH 9) using concentrated NH_4OH, and extracted with Et_2O (×3). The latter extracts were dried (Na_2SO_4) and evaporated to obtain compound **8** (2.63 g, 86%) as a tan foam; $\nu(CH_2Cl_2)/cm^{-1}$ 3550, 1690, 1500 and 1170; $\delta_H(CDCl_3)$ 0.60 (3 H, m), 0.78 (3 H, t), 2.12, 2.16 (6 H, 2 s), 2.00–2.88 (5 H, m), 5.54 (1 H, br s) and 6.52–7.40 (9 H, m); *m/z* 325 (M^+), 310, 239 and 72.

The hydrochloride salt was prepared by dissolving compound **8** (2.53 g, 7.8 mmol) in Pr^iOH–Et_2O and adding HCl (12 mol dm^{-3}; 0.70 cm^3). After chilling in the freezer, 2.52 g (89%) of compound **8** hydrochloride were obtained as a greenish solid. Material from several experiments (total: 4.89 g) was dissolved in hot EtOAc containing a small amount of MeOH. The solution was decolourized using Norit, filtered, concentrated and allowed to cool slowly. Three crops of *white needles* were collected. The first crop weighed 1.76 g, and had m.p. 242–243 °C (decomp.); $\delta_H([^2H_6]$-DMSO) 0.54 (d, 7-Me) (Found: C, 69.0; H, 7.9; N, 3.7. $C_{21}H_{28}ClNO_2$•$0.25H_2O$ requires C, 68.84; H, 7.84; N, 3.82%). The stereochemistry of this material was later determined to be (4*RS*,6*RS*).

The second crop (1.12 g) had m.p. 162–208 °C; $\delta_H([^2H_6]$-DMSO) 0.56, 0.50 (overlapping d, 7-Me) (Found: C, 67.3; H, 8.1; N, 3.7. $C_{21}H_{28}ClNO_2$•0.75•H_2O requires C, 67.19; H, 7.92; N, 3.73).

The third crop (0.83 g) had m.p. 140–160 °C; $\delta_H([^2H_6]$-DMSO) 0.50 (d, 7-Me). The spectrum also showed a very small doublet at 0.56. A sample (200 mg) was recrystallized once from EtOAc–MeOH and twice from EtOAc to give white needles (50 mg), m.p. 134–136 °C $\delta_H([^2H_6]$-DMSO) 0.50 (Found: C, 66.3; H, 7.7; N, 3.55. $C_{21}H_{28}ClNO_2$•H_2O requires C, 66.39; H, 7.96; N, 3.69%). The stereochemistry of this material was later determined to be (4*RS*,6*SR*).

The three crops represented at 56% yield from **7**. The overall yield of *p*-hydroxymethadone **8** hydrochloride from *p*-methoxybenzophenone was 20%.

(S)-2-*Hydroxy*-N,N-*dimethylpropionamide* **10**.—A mixture of (*S*)-dilactide **9** (100 g, 0.69 mol) and dimethylamine (100 g, 2.22 mol) in a sealed 1 dm^3 Parr flask was heated at 40 °C for 1 h, then cooled overnight. Evaporation of the excess of dimethylamine gave a pale yellow liquid (161.41 g). Material from two preparations was combined and vacuum distilled at 0.50 mmHg. Collection of the fraction boiling at 60–70 °C gave compound **10** (251.93 g, 77.5%) as a water white liquid, $\eta^{20}D$ 1.4591 (lit.,[19] $\eta^{20}D$ 1.4558); $[\alpha]_D^{25}$ +1.85 (*c* 2.17, $CHCl_3$).

(S)-1-*Dimethylaminopropan*-2-*ol* **11**.—To a stirred suspension of LAH (16.50 g, 0.435 mol) in dry THF (400 cm^3, freshly distilled from LAH) in an oven-dried flask was added a solution of compound **10** (49.49 g, 0.422 mol) in dry THF (250 cm^3) at such a rate as to maintain a gentle reflux. After addition was complete, the mixture was refluxed an additional 2 h and then cooled to room temperature. The residual hydride was destroyed by careful addition of water (16.5 cm^3), followed by NaOH (15%; 16.5 cm^3) and then by more water (49 cm^{-3}). The resultant white precipitate was filtered off and washed with THF. The THF filtrates and washings from six runs were combined and evaporated to give a yellow liquid (161.50 g). Addition of KOH pellets caused separation of a brown organic liquid (129.59 g). Subsequent distillation with collection of the fraction boiling at 105–127 °C gave compound **11** (84.07 g, 32%) as a water white liquid, $[\alpha]_D^{25}$ +22.4 (*c* 2.54, 95% EtOH) (lit.,[8] +24, *c* 2.17).

(R)-2-*Chloro*-N,N-*dimethylpropylamine* **2** *Hydrochloride*.—The conversion of compound **11** into the chloramine hydrochloride was carried out in 75% yield using the literature procedure,[8] and the reaction was easily scaled up. The product had $[\alpha]_D^{25}$ −65.5 (*c* 2.29, H_2O) (lit.,[8] −65, *c* 2.01).

(4S,6S)- *and* (4R,6S)-p-*Hydroxymethadone* **8** *Hydrochlorides*.—(*a*) The optically active chloroamine hydrochloride (50.00 g, 320 mmol) was converted into the free base in 92% yield by neutralization with NH_4OH solution followed by extraction with Et_2O. Alkylation of the liberated (*R*)-2-chloro-*N*,*N*-dimethylaminopropylamine **2** with the anion derived from compound **1** (15.00 g, 67 mmol) was accomplished using the procedure described for the racemic compound. The resultant mixtures of geometric isomers from two alkylations were separated on a Waters Prep LC/System 500 instrument using a silica gel column and a 5% acetone–$CHCl_3$ mobile phase. Chromatography afforded a mixture of the intermediate amino nitriles (2*S*,4*S*)-**3** and (2*R*,4*S*)-**3** (20.37 g, 52% corrected).

(*b*) The amino nitrile mixture (20.37 g) was divided into two batches, and each batch was treated with the Grignard reagent after the above procedure. Each reaction afforded a mixture (>100%) of the crude (4*S*,6*S*)- and (4*R*,6*S*)-*p*-methoxymethadones. Each mixture was used without further purification.

(*c*) *O*-Demethylation of the *p*-methoxymethadone mixtures with boron tribromide provided a mixture of (4*S*,6*S*)- and (4*R*,6*S*)-*p*-hydroxymethadone free bases (21.38 g, >100%, crude) as a brown foam. This was taken up in Pr^iOH (125 cm^3) and HCl (12 mol dm^{-3}; 5.5 cm^3) was added. The solution was treated with Norit, filtered and diluted to the cloud point with Et_2O. After 13 d of refrigeration, filtration afforded the crude (4*S*,6*S*) hydrochloride as a tan solid (7.00 g), m.p. 220–230 °C (decomp.); $[\alpha]_D^{25}$ +140.8 (*c* 1, MeOH).

The filtrate was evaporated, and the resultant yellow foam was dissolved in MeOH–EtOAc. The solution was again treated with Norit, filtered and diluted to the cloud point with Et_2O. After 2 d of refrigeration, filtration afforded the crude (4*R*,6*S*) hydrochloride as tan crystals (5.96 g), m.p. 192–195 °C; $[\alpha]_D^{25}$ +189.7 (*c* 1.03, MeOH). No addition material of interest was obtained from the filtrate.

(*d*) The crude (4*S*,6*S*)-*p*-hydroxymethadone hydrochloride was recrystallized four times from MeOH–EtOAc after which its optical rotation was constant. The purified salt (3.66 g) was obtained as white crystals, m.p. 234–235 °C; $[\alpha]_D^{25}$ +142 (*c* 1.02, MeOH); $\delta_H([^2H_6]$-DMSO) 0.54 (d, 7-Me); CD (*c* 0.26, MeOH) $[\Theta]_{332}$ 0, $[\Theta]_{324}$ 1100, $[\Theta]_{316}$ 7800, $[\Theta]_{308}$ 20 700, $[\Theta]_{300}$ 31 900, $[\Theta]_{296}$ 33 600, $[\Theta]_{292}$ 32 800, $[\Theta]_{288}$ 30 500, $[\Theta]_{284}$ 28 700, $[\Theta]_{280}$ 26 400, $[\Theta]_{276}$ 22 400, $[\Theta]_{268}$ 13 500, $[\Theta]_{260}$ 5200, $[\Theta]_{252}$ 2600 and $[\Theta]_{244}$ 0 (Found: C, 69.55; H, 7.85; N, 3.55. $C_{21}H_{28}ClNO_2$ requires C, 69.69; H, 7.80; N, 3.87%). The overall yield from **1** of pure (4*S*,6*S*)-**8** hydrochloride was 7.5%.

A sample of the above hydrochloride (202 mg, 0.558 mmol) was converted into the free base using concentrated NH_4OH followed by extraction with $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to give the free base as a clear viscous oil. A solution of the base in MeOH (25 cm^3) was acidified using 48% HBr. Evaporation of the solvent afforded 231 mg of off-white solid. Two recrystallizations from EtOAc–MeOH provided (4*S*,6*S*)-p-*hydroxymethadone hydrobromide* as colourless crystals (191 mg), m.p. 223–225 °C (Found: C, 62.45; H, 6.75; Br, 19.55; N, 3.25. $C_{21}H_{28}BrNO_2$ requires C, 62.07; H, 6.95; Br, 19.66; N, 3.45%).

(*e*) The crude (4*R*,6*S*)-*p*-hydroxymethadone hydrochloride was recrystallized twice from MeOH–EtOAc, once from MeOH–EtOAc–Et_2O, and twice from MeOH–Et_2O to give material of constant optical rotation. Afterwards, the purified salt (2.00 g) was obtained as white needles, m.p. 194–195 °C; $[\alpha]_D^{25}$ +192 (*c* 1.02, MeOH); $\delta_H([^2H_6]$-DMSO) 0.50 (d, 7-Me); CD (*c* 0.13, MeOH) $[\Theta]_{332}$ 0, $[\Theta]_{328}$ 1200, $[\Theta]_{320}$ 11 200, $[\Theta]_{312}$ 38 400, $[\Theta]_{308}$ 50 700, $[\Theta]_{304}$ 62 600, $[\Theta]_{300}$ 69 600, $[\Theta]_{298}$ 70 200, $[\Theta]_{296}$ 69 600, $[\Theta]_{292}$ 62 600, $[\Theta]_{288}$ 45 400, $[\Theta]_{284}$ 24 800, $[\Theta]_{280}$ 6500 and $[\Theta]_{278.5}$ 0 (Found: C, 69.45; H, 7.65; N, 3.85. $C_{21}H_{28}ClNO_2$ requires C, 69.69; H, 7.80; N, 3.87%). The overall yield from **1** was 4%.

X-Ray Crystallographic Analysis of (4S,6S)-p-*Hydroxymethadone* **8** *Hydrobromide*.—*Crystal data*. $C_{21}H_{28}BrNO_2$, M = 406.37. Monoclinic, a = 10.620(5), b = 8.724(4), c = 10.751(6) Å, β = 95.25°, space group $P2_1$, Z = 2, calculated density 1.36 g cm^3. Clear. Crystal dimensions 0.40 × 0.33 × 0.27 mm^3.

Data collection and Processing. Intensity data for 2437 unique reflections were measured on a Nicolet R3m/μ four-circle automatic diffractometer using M-Kα radiation (graphite crystal monochromator) by the $\Theta/2\Theta$ scan technique up to 55° in 2Θ at variable scan speeds between 4 and 29.3° min^{-1}, depending on intensity. The usual corrections were applied to the intensity data including an empirical absorption correction by the Ψ-scan method (μ = 20.7 cm^{-1}, maximum and minimum transmission factors were 0.84 and 0.71, respectively).

Structure Analysis and Refinement.—The *p*-hydroxymethadone hydrobromide crystal was isomorphous with a reported[9] (*S*)-methadone hydrobromide crystal (crystals of the hydrochloride salt of *p*-hydroxymethadone are also isomorphous). Thus, the atomic coordinates for the present crystal were taken from ref. 9 except for those for the oxygen atom of the *para* hydroxy group, which were obtained from an electron density difference map. The structure was refined by the blocked-cascade least-squares method[20] using 2086 data with intensities $I \geq 2.5\sigma(I)$. The hydrogen atoms were placed in calculated positions and refined in the riding mode except for the OH and NH hydrogens, which were obtained from an electron density map and not refined. The absolute configuration was obtained by the method of Rogers,[21] the refined value of the variable multiplying $\Delta f''$ being +0.99(2) which indicates that the coordinates given in Table 2 represent the correct absolute configuration. Final *R*-factors were R = 0.0329 and R_w = 0.0404 for 239 variable parameters. All computations were made on a Data General micro-eclipse computer with the program package SHELXTL.[22]

Supplementary material. Tables of bond lengths, bond angles, anisotropic thermal parameters, H-atom coordinates and

isotropic thermal parameters) have been deposited at the Cambridge Crystallographic Data Centre.*

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* For details of the CCDC deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1991, Issue 1.

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