THE SYNTHESIS OF [^{14}C]-LABELLED HALOPERIDOL AND [d_4]-AND [d_8] HALOPERIDOL

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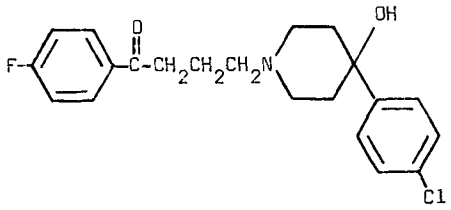
SUMMARY

The synthesis of [^{14}C] haloperidol for use in metabolism studies, and the synthesis of [d_4]-and [d_8] haloperidol for use in bioavailability studies, is described.

Key Words: Haloperidol, Carbon-14, Deuterium, Synthesis

INTRODUCTION

4-Fluoro-4'-[4-hydroxy-4-(4-chlorophenyl)-piperidino]-butyrophenone known as haloperidol (I) (Serenace (R); G.D. Searle & Co. Ltd) is the most important of a series of butyrophenone derivatives that are used clinically as neuroleptic agents.[1]



(I)

Studies of the disposition, metabolism and excretion of haloperidol in animals and man have used forms of haloperidol labelled with tritium, either generally labelled, or with the ^{3}H atom at a position meta to the F atom.[1] Haloperidol was found to be extensively metabolised, initially by an oxidative N-dealkylation process, and metabolites containing the fluorophenyl moiety

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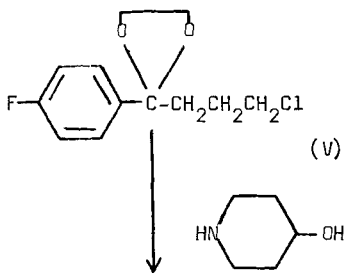
were isolated from the urine of rats.[2,3] Recently the synthesis of [Carboxyl-^{14}C] haloperidol has been reported.[4] In order to discover the metabolic fate of the chlorophenylpiperidinol moiety, haloperidol labelled with ^{14}C in the chlorophenyl ring or piperidine ring was required.

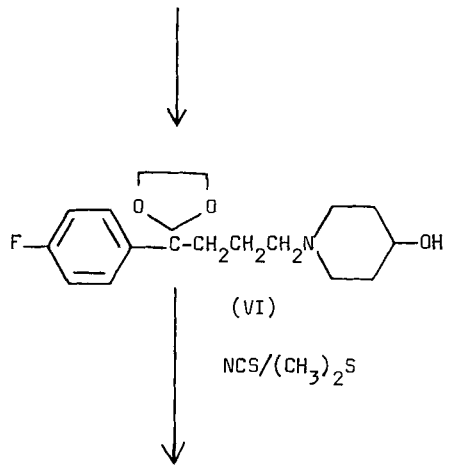
The plasma levels of [^{3}H] haloperidol after intramuscular dosage to man were found to be low[5], and this was confirmed in later studies with haloperidol in which a gas liquid chromatographic method was used.[6] The absolute availability of drugs has been determined using simultaneous oral and intravenous administration of unlabelled drug and a cold labelled analogue, whilst using a further labelled analogue as an internal standard.[7,8] A mass spectrometer is used to differentiate between the various isotopically labelled forms. This technique would require unlabelled haloperidol plus two labelled forms of haloperidol differing by 3-4 in mass units. [d_4] Haloperidol (III) and [d_8] haloperidol (IV) would be suitable.

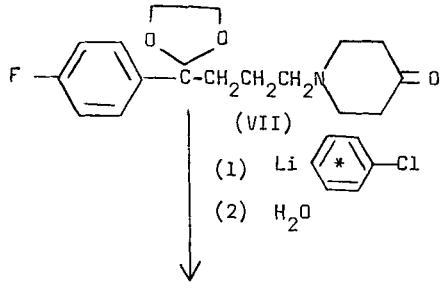
DISCUSSION

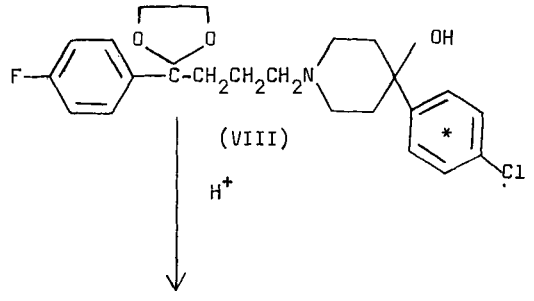
The synthetic route to ^{14}C-labelled haloperidol is shown in Scheme I and was designed to incorporate the radioactive label as late in the synthesis as possible. The ketone (VII) could not be made directly by condensing the ketal (V) with 4-piperidone as the latter compound is unstable. However, (V) reacted smoothly with 4-hydroxypiperidine to give (VI) which was oxidised to the desired compound (VII).

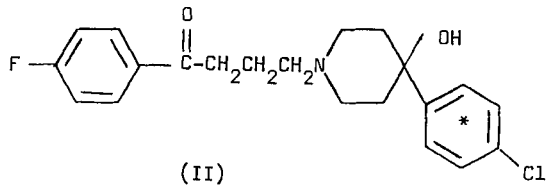
SCHEME 1











* Indicates the position of the ^{14}C label.

In order to retain the ketal group, the oxidation must be carried out under neutral or basic conditions. First chromium trioxide/pyridine was used but subsequent use of N-chlorosuccinimide/dimethyl sulphide led[9] to a cleaner product although it was found necessary to use an excess of the oxidising complex in order to obtain complete conversion of the alcohol (VI) to (VII). Both ethylene glycol and 2,2-dimethyl-1,3-propanediol were used to prepare the respective ketals of 4-chloro-1-(4-fluorophenyl)-1-butanone. Initially the ketal prepared using 2,2-dimethyl-1,3-propanediol seemed preferable since the product was a crystalline solid as opposed to an oil. However, when the corresponding ketal piperidinols and ketal piperidones were prepared the situation was reversed.

Trial experiments on coupling the p-chlorophenyl group to (VII) were not encouraging. Early experiments were carried out using the Grignard reagent derived from p-chloroiodobenzene but in order to obtain any significant amounts of haloperidol (5-10% based on p-chloroiodobenzene) it was found necessary to have a ten fold excess of the Grignard reagent present. No significant improvement in yield was found by adding either anhydrous magnesium bromide or a "bulky" Grignard reagent such as mesityl magnesium bromide. It had been hoped that these may have assisted by co-ordinating with the nitrogen atoms and consequently reducing the excess of Grignard reagent required. Some variation in yield using different solvents was noted; tetrahydrofuran and di-n-butyl ether being better than ether and toluene. However, when (VII) was reacted with four equivalents of p-chlorophenyllithium derived from p-chloroiodobenzene and t-butyllithium, 10-15% of haloperidol ketal was formed. At low temperatures (-70°C) the reaction of ether with t-butyllithium is sufficiently slow to enable the reaction to be carried out in ether and when lithium bromide (which is slightly soluble in ether) was added the yield of crude haloperidol ketal based on p-chloroiodobenzene increased to approximately 53%. These conditions were then used to convert p-chloroiodo [^{14}C]-benzene to haloperidol ketal (VIII).

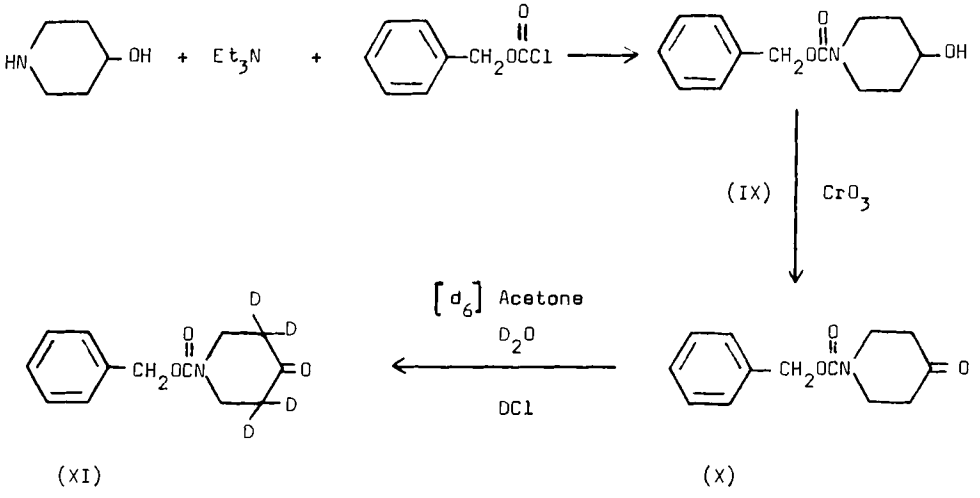
The haloperidol ketal (VIII) was purified by crystallisation and then converted to haloperidol using hydrochloric acid in aqueous acetone. The final product was purified by crystallisation, to give pure [^{14}C] haloperidol (II) as the free base in 44% yield based on p-chloroiodo [^{14}C] benzene.

Scheme 2 illustrates the synthetic route to both [d_4] haloperidol and [d_8] haloperidol. The compounds (XIII and XV) were used as key intermediates as they were also required for the absolute bioavailability study of haloperidol, and the coupling with 4-chloro-1-(4-fluorophenyl)-1-butanone is a known procedure.[10] Because p-dichloro [d_4]benzene was available commercially, the reaction of p-chlorophenyllithium with various N-protected-4-piperidones was investigated and proved unsuccessful. Subsequently it was found that p-chlorophenylmagnesium chloride in a 50% excess reacted to give a 60% yield of suitably N-protected 4-(4-chlorophenyl)-4-piperidinol.

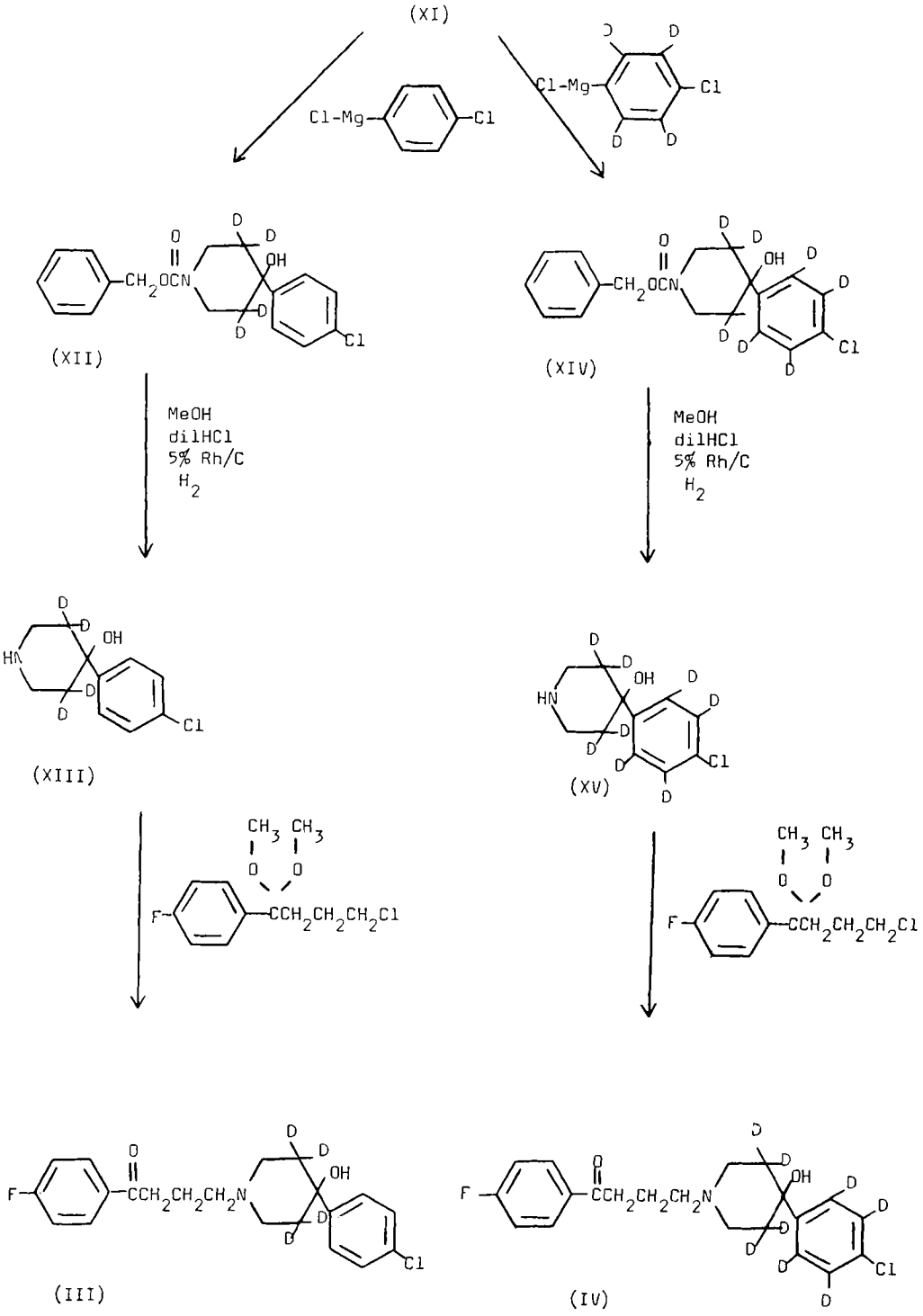
The N-protecting groups tried were methyl, ethoxycarbonyl, benzoyl, trifluoroacetyl and benzyloxycarbonyl. The first three protected piperidones underwent a Grignard reaction to form the corresponding N-protected 4-(4-chlorophenyl)-4-piperidinols, but the hydrolysis of these groups could not be accomplished under mild conditions. No product could be isolated using N-trifluoroacetyl-4-piperidone in the Grignard reaction. However, with N-benzyloxycarbonyl-4-piperidone (X) the reaction was successful and hydrogenolysis at atmospheric temperature and pressure removed the protecting group.

Four more deuterium atoms could be incorporated by exchanging the protons alpha to the carbonyl group in (X). This was initially attempted under basic conditions and although it was a fast reaction (ca 3 hours at room temperature), it caused an unacceptable level of decomposition.

SCHEME 2



(XI) (X)


(XI)
Cl-Mg
Cl
Cl-Mg
Cl
(XII)
(XIV)
MeOH
dilHCl
5% Rh/C
H2
MeOH
dilHCl
5% Rh/C
H2
(XIII)
(XV)
(III)
(IV)

Under acidic conditions (trifluoroacetic acid or deuterium chloride) a cleaner product was obtained after exchange at a higher temperature for a longer time (ca 70 hours at 70°C). When this reaction was performed twice a 99% isotopic exchange was affected and the product (XI) on reaction with p-chlorophenylmagnesium chloride gave (XII) as a white solid. Purification was achieved by column chromatography using florisil eluting with a benzene/ether mixture. The d_8 compound (XIV) was prepared by the same method using p-dichloro $[d_4]$ benzene. Hydrogenolysis of (XII) and (XIV) in methanol and dilute hydrochloric acid using 5% rhodium on charcoal as the catalyst, gave the corresponding labelled unprotected piperidinols (XIII) and (XV). These were condensed with the dimethyl ketal 4-chloro-1-(4-fluorophenyl)-1-butanone to give $[d_4]$ haloperidol (III) and $[d_8]$ haloperidol (VI) after an acidic work up.

Examination of the molecular ion regions in the mass spectra of (XIII), (XV), and for $[d_4]$-and $[d_8]$ haloperidol showed that a high degree of deuterium enrichment had been obtained, with negligible non-deuterated compound present in any of the samples. The enrichment factors for (XIII), (XV), $[d_4]$-and $[d_8]$ haloperidol were 99.6%, 99.1%, 99.3% and 99.0% respectively for the required fully deuterated compound.

EXPERIMENTAL

In general organic extracts were dried over sodium sulphate and solvents were removed on a rotary evaporator under vacuum. The products were characterised by their melting point or boiling point, spectral and chromatographic properties. Mass spectral analysis was performed on a Finnigan 3200E gas chromatograph mass spectrometer with a c.i. source using isobutane as the reactant gas at a source temperature of 150° and pressure of 0.35 Torr. (Finnigan Instruments, Sunnyvale, California). Data was analysed by an on-line Finnigan 6000 data system. N.M.R. spectra (60MHz) were recorded on a Varian EM.360. Thin Layer Chromatographic analysis was performed on Kieselgel 60F-254 Silica Gel precoated plates in the solvent system specified.

2-(3-Chloropropyl-2-(4-fluorophenyl)-1,3-dioxolane (V)

Ethylene glycol (62 g, 1 mol), p-toluene sulphonic acid, (8.0 g, 0.42 mol) and benzene (1 L), were heated under reflux, using a Dean and Stark separator. After 24 hours, 4-chloro-1-(4-fluorophenyl)-1-butanone (100 g, 0.5 mol) was added, and the reflux with removal of water continued for a further 25 hours. The mixture was allowed to cool and washed with saturated carbonate solution and water. Evaporation gave an oil (105 g, 86%) G.L.C. indicated a purity of 93%.

1-[3-[2-(4-Fluorophenyl)-1,3 dioxolan-2-yl] propyl]-4-piperidinol (VI)

A mixture of 4-hydroxypiperidine (20 g, 0.2 mol), a few crystals of potassium iodide, and the ketal (V) (27.5 g, 0.112 mol of 93% pure material ≡ 0.1 as pure ketal) was heated slowly to 120°C and held at this temperature for 20 minutes. The mix melted and two layers formed. The temperature was raised over 15 minutes to 150° and held at this temperature for a further 10 minutes. The reaction mixture was allowed to cool to room temperature and partitioned between water and chloroform. The aqueous phase was extracted with chloroform and the combined extracts washed with saturated sodium chloride solution, and evaporated to give a pale yellow oil. This was induced to crystallise by treatment with ether and hexane and purified by crystallisation from n-butyl bromide to give the product (11.4 g, 37%) as white needles, mp 82 - 84° (lit[11] mp 79 - 81°C).

1-[3-[2-(4-Fluorophenyl)-1,3 dioxolan-2-yl] propyl]-4-piperidone (VII)

Dry toluene (310 ml) was added to N-chlorosuccinimide (12.43 g, 93 mmol) and the mixture was stirred under nitrogen with cooling to 0°C. Dimethyl sulphide (9.3 ml, 127 mmol) was added dropwise and the mixture was stirred for 20 minutes at this temperature. After further cooling to -25°C, the piperidinol (VI) (11.1 g, 36 mmol) in dry toluene (46 ml) was added dropwise over 15 minutes. The reaction mixture was stirred at -25°C for 20 hours and the complex decomposed by the addition of 31 ml of a solution of triethylamine (3M) in toluene. Ether (310 ml) was added and the mixture was diluted with ether (310 ml) and water (250 ml). The combined organic extracts were washed with water and treated with a saturated solution of sodium bisulphite. A thick white precipitate of the bisulphite addition compound was filtered off and washed with ether and with ethyl acetate. It was reconverted to the

piperidone by suspending the solid in 2.5M sodium hydroxide solution and extracting with ether and ethyl acetate. The combined organic extracts were washed with water, and evaporated to give a pale straw coloured oil which rapidly solidified (8.15 g, 74%). This was crystallised from dichloromethane/cyclohexane to give the product as small white needles, mp 67 - 68° (lit[12] mp not quoted).

$[^{14}C]$ Haloperidol-ethylene ketal (VIII)

Finely ground lithium bromide (0.1125 g, 1.39 mmol) and the piperidone (VII) (0.221 g, 0.72 mmol), was placed in a 25 ml round bottom flask. To this was added p-chloroiodo $[^{14}C(U)]$benzene (Radiochemical Centre, Amersham, U.K.) (0.140 g, 0.59 mmol, 20 mCi, 34 mCi/mmol), which was washed into the flask with dry ether (20 ml). The mixture was stirred at room temperature for 30 minutes, then cooled, to -70°C in an acetone/solid carbon dioxide bath. t-Butyllithium solution (2.1 ml, 1.4M in pentane) was added rapidly using a syringe. After 2½ hours at -70°C the reaction was quenched by the addition of water (3 ml), the phases were separated and the aqueous phase extracted with ether. The combined organic extracts were washed with water and the solvent distilled off. The residue was crystallised from ether/pentane and then from n-butylbromide, and finally a crystallisation from cyclohexane gave a white solid (130 mg, 53%) mp 125 - 125.5°C.[13]

$[^{14}C]$ Haloperidol (II)

The ketal (VIII) was dissolved in a small volume of acetone and added to 2M hydrochloric acid (30 ml). The solution was left at room temperature for 5 minutes, made alkaline with 2.5M sodium hydroxide and extracted with ethyl acetate. The organic extract was washed with water and evaporation to dryness under a stream of nitrogen gave a white solid. Recrystallisation from ethyl acetate (4 ml) gave $[^{14}C]$ haloperidol (96.9 mg, 44%) as white needles mp 151.5 - 152.5°C (lit[10] mp 148 - 149.4°). Total activity 8.66 mCi at a specific activity of 33.7 mCi/mmol.

The radiochemical purity was 98.7% by dilution analysis, and 99% chemically pure by TLC in four systems. $CHCl_3$/MeOH 9:1; EtOAc/Toluene/Et_3N 5:4:1; $CHCl_3$/EtOAc/HCOOH 5:4:1; $CHCl_3$/MEK/Et_2NH 50:40:1.

1-Benzyloxycarbonyl-4-piperidone (X)

To a stirred solution of 4-hydroxypiperidine (65 g, 0.64 mol), triethylamine (100 ml, 0.72 mol) and chloroform (500 ml) at 0°C was cautiously added a solution of distilled benzylchloroformate (107.5 g, 0.65 mol) in chloroform (125 ml) and the mixture was stirred overnight at room temperature. The solution was washed with 2M HCl and saturated salt solution, and evaporated to give a brown oil. The oil was dissolved in ether and stirred while chromic acid solution[14] (375 ml) [sodium dichromate dihydrate (100 g, 0.33 mol) in water (300 ml) and conc. sulphuric acid (136 g, 1.34 mol) diluted to 500 ml with water] was cautiously added dropwise and the mixture was left stirring for three hours at room temperature. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with dilute sodium thiosulphate solution and sodium bicarbonate solution. Evaporation gave a light brown oil which was distilled to give a straw coloured oil bp 160 - 162°C at 0.2 mm (77.5 g, 51% (lit[15] bp 125 - 131° at 0.004 mm) NMR (CCl_4) δ 2.3 (4H,t), 3.65 (4H,t), 5.1 (2H,s), 7.3 (5H,s).

1-Benzyloxycarbonyl-4-[d_4]piperidone (XI)

Five sealed Carius tubes each containing the piperidone (X), (8 g), [d_6] acetone (40 ml) deuterium oxide (48 ml) and deuterium chloride (1.6 ml) were heated at 70°C for 3 days. The [d_6] acetone was removed by distillation and the aqueous solutions were extracted with dichloromethane. Evaporation of the combined organic extracts gave a light brown oil which on distillation gave a clear oil bp 160 - 162°C at 0.2 mm (38 g, 95%) NMR ($CDCl_3$) δ 3.65 (4H,s), 5.1 (2H,s), 7.3 (5H,s).

1-Benzyloxycarbonyl-4-(4-chlorophenyl)-4-[d_4] piperidinol (XII)

To p-chlorophenylmagnesium chloride, made from magnesium (3.3 g, 0.14 g atom) and p-dichlorobenzene (21 g, 0.15 mol) in tetrahydrofuran (130 ml), was added dropwise with stirring under nitrogen at room temperature, a solution of the labelled ketone (XI) (22 g, 90 mmol) in tetrahydrofuran (90 ml). After the reaction was stirred for one hour, saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic extract was washed with water and evaporation gave a light brown oil which was dissolved in benzene and purified by chromatography on

a florisil column. Gradient elution with benzene/ether was monitored by TLC (n-BuOAc). Evaporation of the selected fractions gave an oil which on trituration under pentane solidified to a white solid (19.3 g, 59%), mp 99 - 101°C. NMR ($CDCl_3$) δ 2.7 (1H,s), 3.6 (4H,dd), 5.1 (2H,s), 7.3 (9H,s).

1-Benzyloxycarbonyl-4-(4-chlorophenyl)-4-[d_8] piperidinol (XIV)

The method used was identical to the preparation of (XII) except p-dichloro[d_4] benzene was used. (Merck Sharp and Dohme). The product was isolated as a white solid in 47% yield, mp 100 - 102°C. NMR ($CDCl_3$) δ 2.25 (1H,s), 3.6 (4H,dd), 5.1 (2H,s), 7.3 (5H,s).

4-(4-Chlorophenyl)-4-[d_4] piperidinol (XIII)

The piperidinol (XII) (19.3 g, 55 mmol), methanol (560 ml), 2M hydrochloric acid (84 ml) and 5% rhodium on charcoal (3.5 g) was hydrogenated for 28 hours at room temperature and atmospheric pressure. The catalyst was filtered off through hyflo and the methanol was removed on a rotary evaporator. Further 2M hydrochloric acid (100 ml) was added to the solution which was washed with dichloromethane. The acidic solution was basified with ammonium hydroxide solution and extracted with chloroform. The organic extract gave a white solid on evaporation (6.8 g, 57%), mp 132 - 135° (lit[10] mp for the d_0 compound 134.4 - 136°). Mass spectral analysis m/e 216(78), 218(27),198(100), 200(32). (For the d_0 compound m/e 212(46), 214(16), 194(100), 196(32)). NMR ($CDCl_3/CD_3OD$) δ 3.0 (4H,q), 4.1 (2H,s), 7.3 (4H,t). (For the d_0 compound δ 1.8 (4H,m), 3.0 (4H,m), 4.0 (2H,s), 7.3 (4H,t).

4-(4-Chlorophenyl)-4-[d_8] piperidinol (XV)

The method was identical to that used in the preparation of compound (XIII) but using the piperidinol (XIV) (17 g, 48 mmol), methanol (525 ml), 2M hydrochloric acid (74 ml) and 5% rhodium on charcoal (3.1 g). The product was obtained as a white solid (6.8 g, 65%) mp 140 - 143°. Mass spectral analysis m/e 220 (28), 222(9), 202(100), 204(30). NMR ($CDCl_3/CD_3OD$) δ 3.0 (4H,q), 4.4 (2H,s).

[d_4] Haloperidol (III)

4-Chloro-1-(4-fluorophenyl)-1-butanone (4 g, 20 mmol), trimethylorthoformate (3.2 g, 30 mmol), methanol (2 ml) and conc. sulphuric acid (trace) were stirred

together for two hours at room temperature. After neutralisation with a little tetramethylguanidine evaporation gave an oil. To this oil was added the piperidinol (XIII) (4 g, 18 mmol), tetramethylguanidine (3.0 g), dimethylformamide (20 ml) and potassium iodide (3.2 g). The mixture was stirred at 75°C for 16 hours. After evaporation the residual oil was dissolved in a small quantity of methanol and a slight excess of 2M hydrochloric acid and a little toluene were added. The precipitate that formed was filtered off after 2 hours. The white solid obtained was dissolved in methanol and ammonium hydroxide solution was added to pH 8, at this point the solution was diluted with water when precipitation occurred. The product was obtained as a white solid, (4.8 g, 69%) mp 143 - 145°C. A sample was chromatographed on a silica column (Mallinckrodt CC4) using a gradient elution of chloroform/methanol/acetic acid to give a white solid, mp 149 - 151°C. Mass spectral analysis m/e 382 (34), 380 (100), 364 (32), 362 (83), 243 (8), 241 (23), 230 (2), 228 (7).

[d_8] Haloperidol (IV)

The method and quantities used were identical to the preparation of compound (III), except that the piperidinol (XV) was used and no column chromatography was employed. The compound was isolated as a white solid (2.7 g, 39%), mp 145 - 157°C. Mass spectral analysis m/e 386 (38), 384 (100), 368 (33), 366 (96), 247 (8), 245 (24), 234 (3), 232 (8).

A C K N O W L E D G M E N T

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