SYNTHESIS OF TRITIUM LABELLED 1-(3,4-DICHLOROPHENYL)-3-(METHYLAMINO)PROPANOL HYDROCHLORIDE

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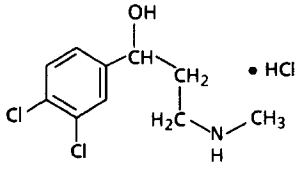
SUMMARY

1-(3,4-Dichlorophenyl)-3-(methylamino)propanol hydrochloride, 1, a potential antidepressant, was synthesized by a two-step method in the [^{3}H]-labelled form with specific activity 12.5 mCi/mmol suitable for drug metabolism and disposition studies (1).

Key Words: 1-(3,4-Dichlorophenyl)-3-(methylamino)propanol, phenylpropylamine, tritium, Mannich, antidepressant.

INTRODUCTION

During a development program on a variety of substituted phenylpropylamines, the compound 1-(3,4-dichlorophenyl)-3-(methylamino)propanol hydrochloride, 1, was found to have interesting antidepressant properties in animal models (2).



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0362–4803/90/070811–08$05.00
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Received November 28, 1989
Revised February 13, 1990

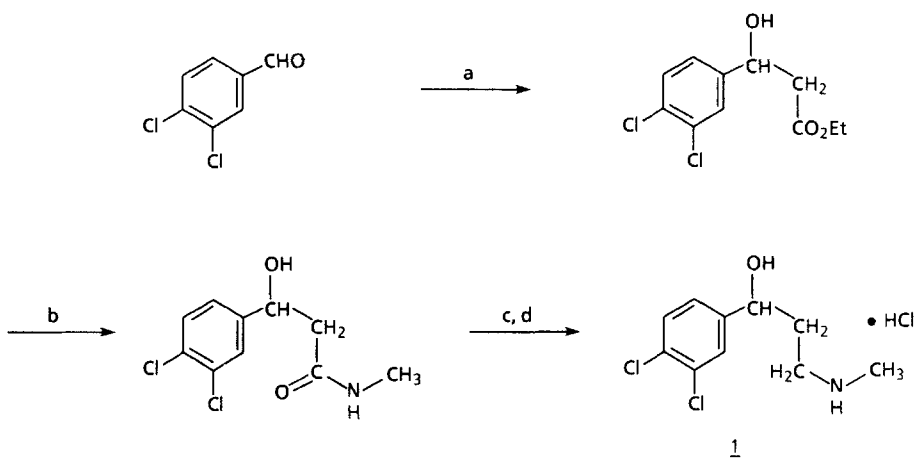
To facilitate metabolism and disposition studies in laboratory animals, a tritium labelled form of 1 was required. These studies required that the [^{3}H]-1 should be chemically stable, should be labelled at a position expected to be metabolically stable *in vivo*, should have a high chemical and radiochemical purity, and a minimum specific activity of 10 mCi/mmol.

This paper describes the preparation of [^{3}H]-labelled 1 with specific activity 12.5 mCi/mmol.

RESULTS AND DISCUSSION

The original synthesis of 1 was accomplished using the route outlined in Scheme I (3).

Scheme I



1

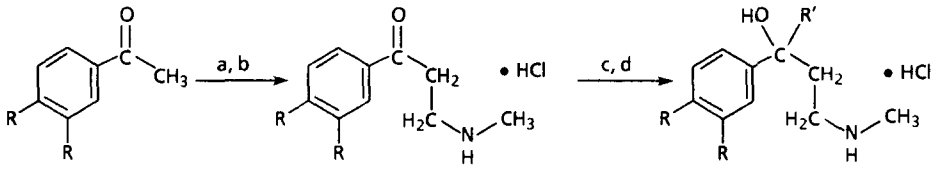
a) Zn, $BrCH_2CO_2Et$, C_6H_6, Et_2O
b) 40% aqueous $MeNH_2$
c) $LiAlH_4$, Et_2O
d) EtOH, HCl

Incorporation of tritium on C-3 by reduction of the penultimate amide using [^{3}H]-$LiAlH_4$ or [^{3}H]-BH_3 would appear to be relatively simple. Placement of the tritium label on either of the carbon atoms adjacent to the amine nitrogen was specifically precluded, however, because of metabolic considerations. Tritium on the *N*-methyl group would easily be lost by the action of demethylating enzymes. Both the demethylated compound and the parent 1 would very likely serve as substrates for monoamine oxidase (4), resulting in aldehyde formation at C-3 and, in the presence of aldehyde oxidase, complete oxidation at C-3 to a carboxylic acid. Either possibility would lead to loss of tritium from the C-3

position. The above synthetic route was therefore not suitable for the preparation of [^{3}H]-1 labelled as requested.

An alternative strategy for the efficient synthesis of [^{3}H]-1, labelled at the C-1 position, was successfully developed and is shown in Scheme II.

Scheme II



2 (R = Cl)
4 (R = H)

3 (R = Cl)
5 (R = H)

1 (R = Cl, R' = H)
6 (R = H, R' = H)
7 (R = Cl, R' = [^{3}H])

a) $(HCHO)_n$, $MeNH_2$.HCl, EtOH, HCl, reflux
b) H_2O, steam distillation, MeOH
c) $NaBH_4$ or [^{3}H]$NaBH_4$, 2-propanol/H_2O
d) MeOH, HCl; EtOH/Me_2CO

The key step in this synthesis is the Mannich aminomethylation reaction on 3',4'-dichloroacetophenone, 2, with paraformaldehyde and methylamine hydrochloride to produce, after salt formation, 3',4'-dichloro-3-(methylamino)propiophenone hydrochloride, 3.

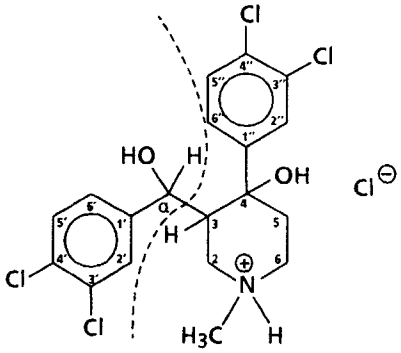
The corresponding synthesis of 3-(methylamino)propiophenone hydrochloride, 5, from acetophenone 4 had originally been reported by Mannich and Heilner (5), and the method had been modified by Satoda *et al.* (6).

A trial run through the literature method (6) for the synthesis of 5 from acetophenone 4 resulted in a 25.7% yield of 5 shown to be of good purity by NMR and m.p. The relatively modest yield was not unexpected (lit. (6) 25.1%) for the preparation of a secondary Mannich base using a primary amine (7,8).

When the method was adapted for the preparation of 3 from 2, the modified reaction was found to be slow and incomplete even under forcing conditions. Separation of 3 from the complex mixture was not trivial. After several attempts to effect this conversion, the method of choice required larger equivalent amounts of $MeNH_2$.HCl and $(HCHO)_n$, and a 65 hour reflux in ethanol, and provided 17.7% of a white crystalline solid shown to be the propiophenone 3 by NMR and elemental analysis. The same conversion was effected in 1,2-dimethoxyethane (9) but resulted in only 12.9% yield of 3.

The sodium borohydride reduction of the propiophenone 3 to the propanol 1 was expected to be straightforward, but during the early stages of development some anomalous results were obtained. The

literature reduction of 5 to 6 (10) employed 10 equivalents of $NaBH_4$, but this was considered to be an *impractical* excess in terms of [^{3}H]-$NaBH_4$. The initial attempt to reduce 3 involved the addition of 2 equivalents of $NaBH_4$ to a solution of 3 in EtOH/H_2O/NH_4OH at pH ~8 (pH paper). After 48 hours at 25°C, work-up, and recrystallization from EtOH/Et_2O, a 45.7% yield of white solid was obtained and shown to be 1 by TLC, m.p. and NMR. A second reaction performed under almost identical conditions for 90 hours, however, gave after recrystallization from EtOH/Et_2O and then from acetone, a 42% yield of a new product, subsequently identified as 3-(3,4-dichloro-α-hydroxybenzyl)-4-(3,4-dichlorophenyl)-1-methyl-4-piperidinol hydrochloride, 8 (*vide infra*). More accurate control of the pH of the reaction mixture would probably preclude these anomalous results.

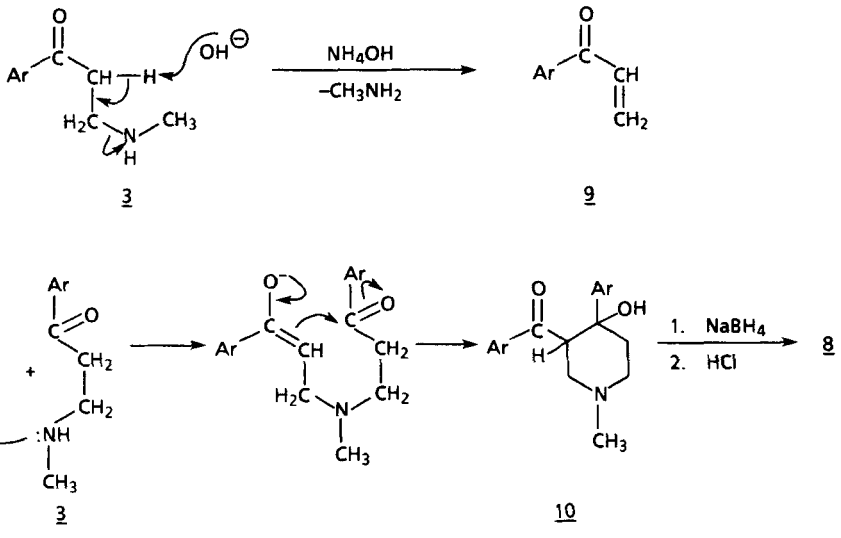


8

Determination of the structure 8 was made on the basis of elemental analysis, ^{1}H NMR, ^{13}C NMR and mass spectral data. Interpretation of the ^{1}H NMR spectrum was complicated by a large overlapping H_2O peak and by the fact that all the alicyclic proton peaks were broadened by fine splittings, but the proton assignments were confirmed by the use of D_2O exchange experiments and 300 MHz 2-dimensional COSY spectra. The ^{13}C NMR spectrum and the E. I. Mass Spectrum were both consistent with structure 8. In the mass spectrum, the appropriate chlorine isotopic cluster pattern and peaks at 433 (M^+), 175 and 258 support the major fragmentation shown above. Details of all the spectra are given in the Experimental section.

A plausible mechanism for the formation of 8 is shown in Scheme III. The addition of NH_4OH to pH ~8 apparently results in elimination of the amine function from the ß-aminoketone 3 to produce the vinylketone 9 which undergoes nucleophilic conjugate addition with another molecule of 3 in Michael fashion. Cyclization to form the piperidinol 10 is followed by $NaBH_4$ reduction of the ketone and acidification to give 8.

Scheme III



3 9 10 8

Production of 8 was prevented by using excess $NaBH_4$ as the neutralizing agent for the HCl salt, thereby negating the need for added base. Treatment of 3 with 6 equivalents of $NaBH_4$ in aqueous 2-propanol at 25°C routinely afforded crude 1 in greater than 88% yield. Although the product was of good purity by TLC and proton NMR, it was recrystallized from ethanol/acetone to give a white crystalline solid in 85.1% yield shown to be 1 by TLC, m.p. and ^1H NMR.

Tritium labelled 1 (7) was subsequently prepared by the latter method employing [^3H]-$NaBH_4$ in 2-propanol/H_2O. Recrystallization of the crude hydrochloride salt from ethanol/acetone gave the tritiated product 7 as a white crystalline solid in 86.4% yield from 3.

The radiochemical purity of 7 was found to be >99% by TLC, plate scanning and autoradiography. The specific activity was found to be 12.5 mCi/mmol.

EXPERIMENTAL

Sodium boro[^3H]hydride was obtained from DuPont NEN Products at a batch specific activity of 109.6 mCi/mmol. Sodium borohydride was purchased from MCB, Inc. 3',4'-Dichloroacetophenone was purchased from Aldrich Chemical Company. Acetophenone was purchased from Eastman Kodak Company. All other solvents and reagents were of reagent purity and were obtained from readily available commercial sources.

Thin layer chromatography (TLC) was performed on 5 x 20 cm glass plates pre-coated with 0.25 mm silica gel 60 (E. Merck), using as the mobile phase 2-propanol/H_2O/NH_4OH (16/3/1, v/v). Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were obtained in DMSO-d_6 with tetramethylsilane as internal standard using a Perkin-Elmer R-24B spectrometer (60 MHz), a Varian FT-80A spectrometer (80 MHz), a Varian XL-300 spectrometer (300 MHz) or a Varian VXR-300 spectrometer (300 MHz 2-D COSY and D_2O exchange experiments). The ^{13}C NMR spectrum was obtained in DMSO-d_6 with TMS as internal standard using a Varian CFT-20 spectrometer (20 MHz). The Electron Impact mass spectrum was recorded on a Varian MAT CH-5-DF instrument operating at 70 eV ionizing energy. Radiochemical purity was determined by autoradiography and by radiochromatogram scanning of a TLC plate using a Vangard VS940 Scanner. Specific activity was determined on an accurately weighed sample by liquid scintillation counting.

3-(Methylamino)propiophenone Hydrochloride 5

5 was prepared according to the method of Satoda *et al.* (6). From 60.0 g of acetophenone was obtained, after recrystallization from methanol/acetone, 25.6 g (25.7%) of white crystalline solid 5; m.p. 140.5-142°C [lit. (5) m.p. 139-141°C]; ^1H NMR (60 MHz): δ 2.6 (s, 3H, NCH_3), 3.45 (m, 4H, CH_2CH_2), 7.35-8.1 (m, 5H, ArH_5), 9.45 (bs, 2H, $^+NH_2$).

3',4'-Dichloro-3-(methylamino)propiophenone Hydrochloride 3

Hydrochloric acid (12*N*, 0.8 mL) was added to a stirred mixture of 3',4'-dichloroacetophenone (51.0 g), paraformaldehyde (13.5 g) and methylamine hydrochloride (30.0 g) in ethanol (500 mL) under nitrogen. The mixture was heated at reflux for 66 hours and then allowed to cool. After evaporation to dryness under reduced pressure, H_2O (300 mL) was added and the yellow mixture was steam distilled until no more oily material was observed in the distillate (~6 hours) [8.3 g of 2 was recovered from the distillate as white needles (16.3% recovery)]. The residual mixture was filtered hot and the yellow solid was discarded. The filtrate was evaporated to dryness to give 40.3 g of yellow crystalline solid. After two recrystallizations from methanol, 3 was obtained as a colourless crystalline solid (12.85 g; 17.7%); m.p. 180-181°C (dec.); TLC: single-spot material $R_f = 0.58$; ^1H NMR (60 MHz): δ 2.6 (s, 3H, NCH_3), 3.45 (m, 4H, CH_2CH_2), 7.6-8.3 (m, 3H, ArH_3), 9.4 (bs, 2H, $^+NH_2$). Anal. Calcd. for $C_{10}H_{11}Cl_2NO.HCl$: C, 44.72; H, 4.50; N, 5.22; Cl, 39.60%. Found: C, 44.57; H, 4.52; N, 5.20; Cl, 39.49%.

3-(3,4-Dichloro-α-hydroxybenzyl)-4-(3,4-dichlorophenyl)-1-methyl-4-piperidinol Hydrochloride 8

To a stirred mixture of 3 (200 mg), 95% ethanol (7 mL) and H_2O (2 mL) was added 2*N* NH_4OH (~0.6 mL) to pH ~8 (pH paper). After 10 min., a solution of $NaBH_4$ (14.1 mg) in 95% ethanol (7 mL) was added. The mixture was stirred at 25°C for 90 hours, then diluted with H_2O (50 mL) and Et_2O (50 mL), and acidified with 12*N* HCl (1 mL) in H_2O (10 mL). After 5 min., 1*N* NaOH was added to pH 10, the layers were separated, and the aqueous layer was extracted with Et_2O (80 mL). The combined organic extracts were dried and the solvent evaporated *in vacuo* to give a white solid which was dissolved in EtOH (25 mL) and treated with 12*N* HCl (0.15 mL). The solution was evaporated to dryness under reduced pressure and the residue (184.2 mg) crystallized from EtOH/Et_2O (3 mL / 11 mL), and recrystallized from MeOH/acetone (1 mL / 9 mL) to give 8 as a white crystalline solid (84.5 mg, 48.1%); m.p. 285-287°C (dec.); TLC: single-spot material $R_f = 0.70$; ^{1}H NMR (300 MHz, chemical shifts established by 2-D COSY and D_2O exchange experiments) δ 1.67 (d, 1H, H-5), 2.32 (m, 1H, H-5), 2.81 (s, 3H, N-CH_3), 2.99 (m, 1H, H-3), 3.11-3.34 (m, 4H, H_2-2 and H_2-6), 4.58 (m, 1H, H-α), 5.79 (s, 1H, 4-OH, D_2O exchangeable), 5.99 (m, 1H, α-OH, D_2O exchangeable), 7.06-7.53 (m, 6H, Ar-H), 10.77 (bs, 1H, N-H, D_2O exchangeable); ^{13}C NMR δ 37.2 (C-5), 42.1 (C-3), 46.7 (N-CH_3), 49.2 (C-6), 52.3 (C-2), 70.9 (α-C), 71.2 (C-4), 125.3 (Ar-CH), 126.3 (Ar-CH), 127.1 (Ar-CH), 128.1 (Ar-CH), 128.9 (Ar-CCl), 129.1 (Ar-CCl), 129.4 (Ar-CH), 129.6 (Ar-CH), 130.3 (Ar-CCl), 130.5 (Ar-CCl), 143.8 (Ar-CC), 147.4 (Ar-CC); mass spectrum, m/z (relative intensity) 433 (M^+, 4.9), 258 (3.1), 257 (5.8), 240 (23.3), 175 (11.1), 145 (4.7), 111 (11.6), 70 (20.2), 57 (24.2), 44 (100), 42 (36.5), 36 (13.5), 18 (11.8). Anal. Calcd. for $C_{19}H_{19}Cl_4NO_2$.HCl.0.3 H_2O: C, 47.84; H, 4.35; N, 2.94; Cl, 37.16%. Found: C, 47.73; H, 4.34; N, 2.88; Cl, 37.24%.

1-(3,4-Dichlorophenyl)-3-(methylamino)propanol Hydrochloride 1

To a stirred solution of the propiophenone 3 (400.6 mg) in 2-propanol (14 mL) and H_2O (3 mL) was added a solution of $NaBH_4$ (84.8 mg; 6 equiv.) in 2-propanol (14 mL) and H_2O (5 mL). After 40 hours at 25°C, the mixture was diluted with Et_2O (70 mL) and H_2O (70 mL), and acidified with 1.5*N* HCl (20 mL) for 5 minutes. 1*N* NaOH was added to pH 10, the layers were separated, and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic extracts were dried and the solvent evaporated *in vacuo* to give a colourless glass which was treated in MeOH (25 mL) with 12*N* HCl (0.3 mL). TLC showed almost entirely 1 with a trace impurity at the origin. 8 was not detected. Evaporation to dryness under reduced pressure was followed by recrystallization of the solid residue (356.0 mg) from EtOH-acetone (1 mL/18 mL) giving 1 as a white crystalline solid (343.0 mg; 85.1% yield); m.p. 156-157°C [lit. (3) m.p. 157-

158°C]; TLC: single-spot material $R_f = 0.40$; ^1H NMR (80 MHz): δ 1.96 (m, 2H, $CHCH_2$), 2.51 (s, 3H, NCH_3), 2.92 (t, 2H, $J = 8$ Hz, NCH_2), 4.75 (t, 1H, $J = 6.4$ Hz, CH), 7.34 (d of d, 1H, $J = 2.4$ Hz and 8 Hz, Ar-H-6), 7.57 (d, 1H, $J = 2.4$ Hz, Ar-H-2), 7.64 (d, 1H, $J = 8$ Hz, Ar-H-5). Anal. Calcd. for $C_{10}H_{13}Cl_2NO.HCl$: C, 44.39; H, 5.22; N, 5.18%. Found: C, 44.16; H, 5.17; N, 5.09%.

[1-^{3}H]-1-(3,4-Dichlorophenyl)-3-(methylamino)propanol Hydrochloride 7

The labelled synthesis was performed essentially as for 1, but employed 400.0 mg of 3, $NaBH_4$ (50.6 mg) and [^{3}H]-$NaBH_4$ (34.0 mg; 100 mCi at 109.6 mCi/mmol). The yield of white crystalline solid 7 was 348.2 mg (16.1 mCi; 86.4% yield) with specific activity 12.5 mCi/mmol; TLC: single-spot material $R_f = 0.40$ corresponding to authentic 1. No impurities were detected by radioactive scanning of the TLC plate or by autoradiography - thus the radiochemical purity was >99%.

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