AN IMPROVED SYNTHESIS OF DIDEUTERATED THIORIDAZINE WITH THE LABEL IN THE PIPERIDINE RING

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SUMMARY

2-(2-Hydroxyethyl)-1-methyl[6,6-$^2H_2$]piperidine was obtained by a new route from 2-(2-hydroxyethyl)-piperidine. This enabled dideuterated (±)-thioridazine to be obtained by an improved approach. The key steps involved ruthenium tetroxide oxidation of the N,O-diacetylated starting material and subsequent lithium aluminum deuteride reduction of O-acetylated 2-(2-hydroxyethyl)-6-piperidinone.

Key Words: Antipsychotic, thioridazine, deuterium labelling, piperidine ring.

INTRODUCTION

Thioridazine is a phenothiazine type of antipsychotic agent. The syntheses of its isotopomers which were required especially for use in metabolic and pharmacokinetic studies have been previously reported from these laboratories (1-3). In these reports the 2-(1-methyl-2-piperidinyl)ethyl side chain attached to the N-10 position of the phenothiazine ring has been labelled with two or four deuterium atoms. The synthesis of thioridazine with two deuterium atoms in the 6-position of the piperidine ring involved eleven steps in which the first two steps could only be handled in the laboratory on a relatively small scale (3). A more convenient synthesis to this piperidine ring labelled compound was sought which involved less steps and where potentially each step could be handled on a large scale. Also such a scheme would likely be more suitable than the published one (3) to adapt to the first synthesis of the piperidinone metabolites of piperidine type phenothiazine antipsychotic agents (4). In this paper a seven step scheme to dideuterated (±)-thioridazine via a new convenient synthesis of 2-(2-hydroxyethyl)-1-methyl[6,6-$^2H_2$]piperidine is reported (Scheme).

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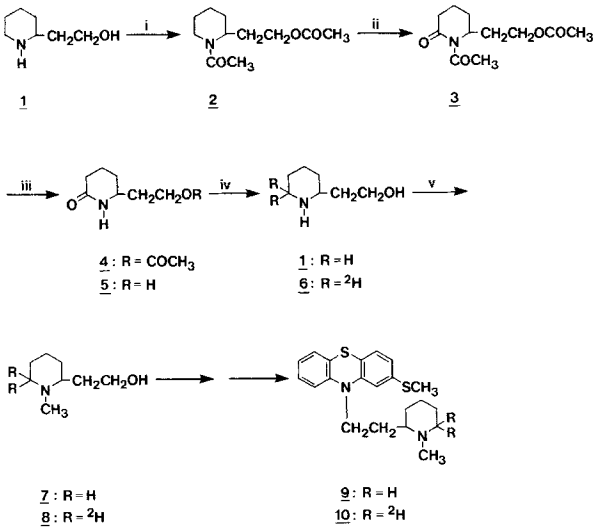
DISCUSSION

The key steps in the previously published scheme to the synthesis of piperidine ring labelled dideuterated thioridazine 10 involved ruthenium tetroxide

Scheme: Synthesis of deuterium labelled thioridazine



Reagents: i) $(CH_3CO)_2O$, C_5H_5N
ii) $RuO_2 \cdot xH_2O$, $NaIO_4$, $CH_3CO_2C_2H_5$-H_2O
iii) Al_2O_3, C_6H_{14}-$CH_3CO_2C_2H_5$
iv) $LiAlH_4$ or $LiAl^2H_4$, THF-$(C_2H_5)_2O$
v) HCHO, HCO_2H

(RuO_4) oxidation of N-protected methyl 2-piperidinylacetate and subsequent lithium aluminum deuteride (LAD) reduction of 2-(2-hydroxyethyl)-1-methyl-6-piperidinone (3). This approach necessitated three steps to obtain N-protected methyl 2-piperidinylacetate from commercially available ethyl 2-pyridinylacetate and the need for selective reduction of the side chain ester prior to LAD reduction of the piperidinone. Consequently it appeared that an alternative scheme to the desired labelled compound 10 could be developed which involved minimal synthetic steps. In this proposed alternative approach, the use of commercially available and inexpensive 2-hydroxyethylpiperidine as starting material allowed RuO_4 oxidation of the piperidine ring to be performed in the second step and the necessity for selective reduction was obviated.

In the first step of the new scheme to the synthesis of thioridazine (9), the aminoalcohol 1 was reacted with acetic anhydride in pyridine to produce the

N,O-diacetyl derivative 2. Subsequent RuO_4 oxidation of 2 with a catalytic amount of ruthenium oxide (RuO_2) and an excess of 10% $NaIO_4$ in a two-phase system of ethyl acetate-water (5) furnished the piperidinone 3. Under the controlled treatment of 3 with Al_2O_3 in n-hexane-ethyl acetate the N-acetyl group was removed selectively to afford 4 in high yield, although the N,O-dideacetylated compound 5 was obtained in low yield. Our first attempted strategy to convert 4 to the alcohol 7 was through initial N-methylation followed by lithium aluminum hydride (LAH) reduction. Difficulties were experienced, however, in the methylation of 4 in that reaction conditions such as NaH in DMF and CH_3I, gave at least three products. Therefore, in order to convert 4 to 7 an alternate strategy was utilised, where the piperidinone 4 was treated with LAH to give the aminoalcohol 1 which on Eschweiler-Clarke reaction (6) with a modified work up procedure afforded the desired alcohol 7. The conversion of 7 to thioridazine (9) in one (7) or two steps (2,3) has been reported previously.

By substitution of LAD for LAH in the reduction step the piperidinone 4 was converted in two steps to the dideuterated alcohol 8. The conversion of 8 to 6,6-$^2H_2$ labelled thioridazine (10) is detailed in a previous publication (3). Briefly, treatment of 8 with thionyl chloride gave 2-(2-chloroethyl)-1-methyl[6,6-$^2H_2$]piperidine which on N-10 alkylation of 2-methylthio-10H-phenothiazine yielded 10. For each of the seven steps in the conversion of 1 to 10 the yield was at least 76%.

EXPERIMENTAL

A previous paper (3) gives the general experimental techniques used in the present work.

1-Acetyl-2-[2-(acetyloxy)ethyl]piperidine (2): Acetic anhydride (40 ml) was added dropwise to a stirred solution of the aminoalcohol 1 (10.32 g, 0.08 mol) in dry pyridine (40 ml). After the addition was complete, the resultant yellow solution was further stirred at ambient temperature for 24 h. The solution was concentrated on a rotavapor and the obtained liquid was distilled in vacuo to give the diacetyl derivative 2 as a colorless oil (16.35 g, 96%), bp 111-113°C/0.15 mmHg [lit. (8) bp 135-137°C/2 mmHg]; IR: 1745(ester C=O), 1645 cm^{-1}(amide C=O); ^1H NMR(60 MHz): 1.07-2.00(m,8H,C_3-H_2,C_4-H_2,C_5-H_2,CH_2CH_2O), 2.07(s,3H,$COCH_3$), 2.10(s,3H,$COCH_3$), 2.30-3.87(m,2H,C_6-H_2), 4.07(m,2H,CH_2O),

4.33-5.17(m,1H,C_2-H); EIMS:m/z 213(5,$M^{+\cdot}$), 170(3), 127(5), 126(39), 98(3), 84(100), 56(7), 43(24). Anal. Calcd. for $C_{11}H_{19}NO_3$: C,61.95; H,8.98; N,6.56. Found: C,62.07; H,8.99; N,6.48.

1-Acetyl-2-[2-(acetyloxy)ethyl]-6-piperidinone (3): To a vigorously agitated mixture of $RuO_2.xH_2O$ (1.065 g) in 10% $NaIO_4$ (530 ml) at room temperature, a solution of the diacetyl compound 2 (10.65 g, 0.05 mol) in ethyl acetate (160 ml) (previously washed with water) was added slowly. After stirring the reaction mixture for 4 h, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were treated with isopropyl alcohol (10 ml) for 2 - 3 h to destroy the RuO_4 oxidant. The precipitated black RuO_2 was filtered on a celite pad and the filtrate was washed with water and dried. The solvent was removed on a rotavapor and the residual oil was distilled in vacuo to furnish the piperidinone 3 as a pale yellow liquid (9.87 g, 87%), bp 120-122°C/0.02 mmHg; IR: 1745(ester C=O), 1700 cm^{-1}(imide C=O);^{1}H NMR(60 MHz): 1.50-2.13(m containing $OCOCH_3$ spike at 2.03,9H,$OCOCH_3$,C_3-H_2,C_4-H_2,CH_2CH_2O), 2.30-2.83(m containing $NCOCH_3$ spike at 2.43,5H,$NCOCH_3$,C_5-H_2), 4.10(app.t,J=7Hz,2H,CH_2O), 4.43-4.93 (m,1H,C_2-H); EIMS:m/z 227(0.2,$M^{+\cdot}$), 186(3), 185(24), 142(4), 140(5), 125(9), 98(100), 70(4), 43(43), 42(6), 41(5). Anal. Calcd. for $C_{11}H_{17}NO_4$: C,58.13; H,7.54; N,6.16. Found: C,58.19; H,7.75; N,6.18.

2-[2-(Acetyloxy)ethyl]-6-piperidinone (4): A solution of the piperidinone 3 (2.27 g, 10 mmol) in n-hexane-ethyl acetate (1:2, 300 ml) was stirred with Al_2O_3 (62.5 g) for 15 h. The reaction mixture was filtered through a celite pad and the residual Al_2O_3 was washed with a mixture of methanol in chloroform. The combined filtrates were evaporated on a rotavapor and the crude product was purified by column chromatography over silica gel using 2% CH_3OH in $CHCl_3$ as eluent. Crystallization from ether afforded the piperidinone 4 as a white solid (1.41 g, 76%), mp 77-78°C; IR: 3200, 3080(N-H), 1735(ester C=O), 1670 cm^{-1} (lactam C=O); ^{1}H NMR(60 MHz): 1.33-2.00(m,6H,C_3-H_2,C_4-H_2,CH_2CH_2O), 2.10(s,3H, $COCH_3$), 2.20-2.53(m,2H,C_5-H_2), 3.53(m,1H,C_2-H), 4.20(app.t,J=7Hz,2H,CH_2O), 6.93(br s,1H,NH,D_2O exchangeable); EIMS:m/z 185(14,$M^{+\cdot}$), 157(9), 129(7), 125(8), 112(9), 98(100), 70(9), 56(14), 55(62), 43(37), 42(11), 41(10). Anal. Calcd. for $C_9H_{15}NO_3$: C,58.36; H,8.16; N,7.56. Found: C,58.50; H,8.19; N,7.67.

2-(2-Hydroxyethyl)-6-piperidinone (5): This was obtained from the above

reaction in ~ 5% yield and was crystallized from ether as an off-white solid, mp 67-68°C; IR: 3380(O-H), 3200, 3050(N-H), 1645 cm^{-1}(lactam C=O); ^{1}H NMR(60 MHz): 1.18-2.05(m,6H,C_3-H_2,C_4-H_2,$C\underline{H}_2CH_2OH$), 2.12-2.52(m,2H,C_5-H_2), 3.50-4.08(m,3H, C_2-H,$C\underline{H}_2OH$), 4.72(m,1H,$O\underline{H}$,D_2O exchangeable), 7.42(br s,1H,$N\underline{H}$,D_2O exchangeable); EIMS:m/z 143(5,$M^{+\cdot}$), 115(3), 98(100), 70(6), 56(5), 55(46), 43(5), 42(9), 41(8). Anal. Calcd. for $C_7H_{13}NO_2$: C,58.72; H,9.15; N,9.78. Found: C,58.89; H,8.97; N,10.08.

2-(2-Hydroxyethyl)piperidine (1): To a stirred suspension of LAH (76 mg, 2 mmol) in dry ether (10 ml) at 0°C was added a solution of the piperidinone 4 (0.185 g, 1 mmol) in dry THF (3 ml). After the addition was complete, the reaction mixture was refluxed for 7 h. Excess LAH was decomposed cautiously with moist ether, followed by the addition of 20% aqueous NaOH. The solvents were decanted off and the residual white cake was extracted with ether under reflux. The combined organic extracts were dried and evaporated on a rotavapor to leave the aminoalcohol 1 (0.116 g, 90%) in a pure enough form for use in the next step of the reaction sequence, mp 36-38°C; IR: 3340 cm^{-1}(O-H,N-H); ^{1}H NMR(60 MHz): 1.0-2.0(m,8H,C_3-H_2,C_4-H_2,C_5-H_2,$C\underline{H}_2CH_2OH$), 2.23-3.23(m,3H,C_2-H,C_6-H_2), 3.42(br s, 2H,$O\underline{H}$,$N\underline{H}$,D_2O exchangeable), 3.73(app.t,J=6Hz,2H,$C\underline{H}_2OH$); EIMS:m/z 129(5,$M^{+\cdot}$), 128(5), 110(3), 98(18), 85(20), 84(100), 70(11), 56(53), 55(24).

2-(2-Hydroxyethyl)[6,6-$^2H_2$]piperidine (6): This was prepared from the piperidinone 4 by use of LAD in the method described for 1, TLC and co-TLC as for 1. On refrigeration, the viscous oil solidified as a white solid, mp 36-38°C; IR: 3320 cm^{-1}(O-H,N-H); ^{1}H NMR(60 MHz): 1.13-1.97(m,8H,C_3-H_2,C_4-H_2, C_5-H_2,$C\underline{H}_2CH_2OH$), 2.70(m,1H,C_2-H), 3.23(br s,2H,$O\underline{H}$,$N\underline{H}$, D_2O exchangeable), 3.73(app.t,J=6Hz,2H,$C\underline{H}_2OH$); EIMS:m/z 131(3,$M^{+\cdot}$), 130(3), 112(2), 100(3), 86(100), 72(15), 58(23), 57(15).

2-(2-Hydroxyethyl)-1-methylpiperidine (7): The aminoalcohol 1 (5.16 g, 40 mmol) was added slowly to a stirred mixture of 36-38% formaldehyde (1.80 g, 60 mmol) and 98% formic acid (9.20 g, 0.20 mol) while cooling the reaction flask in an ice bath. The reaction mixture was slowly brought to room temperature after which the resultant yellow solution was refluxed gently (bath temperature ~ 125°C) for 12 h. The reaction mixture was cooled to room temperature, basified with NaOH and extracted with CH_2Cl_2 under reflux. The combined organic extracts were dried and evaporated on a rotavapor to leave the alcohol 7, which distilled

in vacuo as a colourless oil (5.03 g, 88%), bp 62-63°C/0.6 mmHg [lit. (9) bp 80°C/2 mmHg]; IR: 3360 cm^{-1}(O-H); ^{1}H NMR(60 MHz): 1.23-2.23(m,10H,C_3-H_2,C_4-H_2, C_5-H_2,C_6-H_2,CH_2CH_2OH), 2.30(s,3H,NCH_3), 2.83(m,1H,C_2-H), 3.73(m,2H,CH_2OH), 4.70(s,1H,OH,D_2O exchangeable); EIMS:m/z 143(2,$M^{+\cdot}$), 99(7), 98(100), 70(11), 55(3), 44(7), 42(10), 41(3).

2-(2-Hydroxyethyl)-1-methyl[6,6-$^2H_2$]piperidine (8): This was prepared from the aminoalcohol 6 using the procedure described for 7, TLC and co-TLC as for 7; IR: 3360 cm^{-1}(O-H); ^{1}H NMR(60MHz): 1.07-2.23(m,9H,C_2-H,C_3-H_2,C_4-H_2,C_5-H_2,CH_2CH_2OH), 2.30(s,3H,NCH_3), 3.73(m,2H,CH_2OH), 4.50(s,1H,OH,D_2O exchangeable); EIMS:m/z 145(1,$M^{+\cdot}$), 101(8), 100(100), 72(13), 57(3), 46(7), 44(5), 43(7), 42(14), 41(4).

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