SYNTHESIS OF TRITIUM LABELLED (-)-3-PPP, A SELECTIVE DOPAMINE AUTORECEPTOR AGONIST

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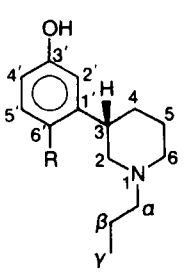
SUMMARY

^{3}H-(-)-3-PPP (11, (S)-3-(3-Hydroxyphenyl)-N-propyl-[3,4-^{3}H]piperidine) was prepared by hydrogenation of compound 3, with tritium gas followed by resolution of the racemic mixture. The incorporation of tritium was verified by tritium NMR spectroscopy. Also described is the synthesis and NMR interpretation of two isomeric unsaturated tetrahydropyridine derivatives i.e. compounds 8 and 10.

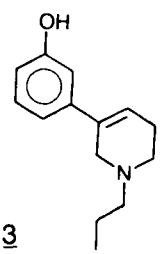
Key Words: (-)-3-PPP, dopamine autoreceptor agonist, tritium labelling, tritium NMR, tetrahydropyridines, NMR.

INTRODUCTION

The (-)-enantiomer of 3-(3-hydroxyphenyl)-N-propylpiperidine (3-PPP) 1 has been suggested as a selective agonist of dopamine autoreceptors (1). In order to further explore the possibilities for this compound as an antipsychotic agent, a radioactively labelled compound was required. The present paper describes the synthesis of tritium labelled (-)-3-PPP suited for the metabolic and pharmacokinetic evaluation of this drug.



1 R=H
2 R=^{3}H



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0362-4803/86/090925-08$05.00

Received January 28, 1986
Revised March 24, 1986

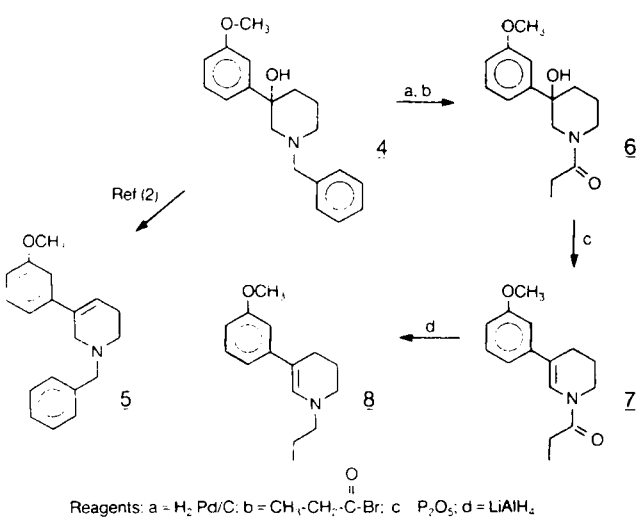
METHODS AND RESULTS

Since preliminary studies had shown that 3-PPP labelled with tritium in the aromatic ring i.e. compound 2 lost its label under the biological evaluation, we required a derivative labelled at a position expected to be metabolic stable. Consequently, we chose to use a precursor which would allow the introduction of tritium into the piperidine moiety.

In 1982, the synthesis of 3-(1-propyl-1,2,5,6-tetrahydro-3-pyridinyl)phenol 3 was reported in a French patent (2). The key step in the synthesis was the dehydration of the protonated amino alcohol 4 (Scheme 1) with P_2O_5, thus forming the tetrahydropyridine analogue 5 with the double bond in the 3,4-position. However, in our hands treatment of 4 afforded only a gum which did not react further to the dehydrated product. To circumvent this inhomogenity, the amine 4 was transformed into the soluble amide 6.

When treating compound 6 with P_2O_5 dehydration took readily place and subsequent $LiAlH_4$-reduction of the amide 7 furnished amine 8 which was characterized by ^1H and ^{13}C NMR spectroscopy.

Scheme 1



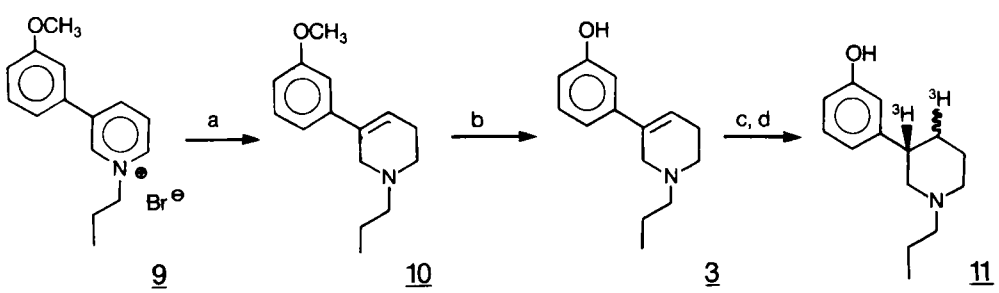
Reagents: a = H_2, Pd/C; b = CH_3-CH_2-C(=O)-Br; c P_2O_5; d = $LiAlH_4$

Somewhat unexpectedly the NMR spectrum indicated that the double bond had been introduced in 2,3-position of the piperidine ring. Since no spectroscopic data were presented in the French patent that supported the stated position of

the double bond in compound 10, we felt that a synthesis of this compound was needed to confirm our observation. Furthermore, reduction of the enamine 8 with tritium gas would give a compound with part of the label in the metabolically unstable position α to the nitrogen (3).

Analogous with partial $NaBH_4$-reduction of 1,4-disubstituted pyridinium salts (4), the reduction of 3-(3-methoxyphenyl)-1-propylpyridinium bromide 9 (Scheme 2) gave exclusively the desired 3,4-isomer 10 as deduced from ^{1}H and ^{13}C NMR. The assignment of the double bond in the 3,4- position is most easily achieved by a comparison of the 0-30 ppm region of the ^{13}C NMR spectra of compounds 8 and 10. The 3,4-isomer (10) gives rise to 3 signals (C_5, C_β and C_γ) in that region in contrast to the 2,3-isomer (8), which gives, as expected, 4 signals (C_4, C_5, C_β and C_γ). From the ^{1}H NMR interpretation the most obvious support for the location of the double bond in compound 8 is the sharp multiplet at 6.59 ppm emanating from the olefinic proton in position 2 influenced downfield by the adjacent nitrogen atom. In compound 10 the signal from the olefinic proton in position 4 appeared as a multiplet at 6.09 ppm. A complete interpretation of the ^{1}H and ^{13}C NMR spectra of compounds 8 and 10 is given in the Experimental (5). Demethylation with pyridinium chloride at 200°C furnished the phenol 3, which served as substrate for the tritium labelling.

Scheme 2



9 10 3 11

Reagents: a = $NaBH_4$; b = Pyridinium chloride; c = $^3H_2$ Rh/Al_2O_3; d = resolving agent, (+)-BNPPA

In order to find the most efficient conditions for the catalytic hydrogenation of 3 at atmospheric pressure, several runs on cold material were performed. When 5% rhodium on alumina was used as catalyst in DMF, 55% of 3-PPP was obtained after 5 h. The use of 5% Pt/C gave only about 10% of 3-PPP after 15 h. Wilkinson s catalyst gave an even more sluggish reaction. Consequent-

ly, compound 3 was reduced in presence of Rh/Al_2O_3 using 5 Ci of tritium gas. The racemic labelled 3-PPP, thus formed, was resolved according to the literature (6) by the use of the salt of (-)-3-PPP and (+)-(S)-2,2-(1,1-binaphtyl) phosphoric acid [(+)-BNPPA]. The specific activity of the formed salt was 1.6 Ci/mmol. Purification of the base on silica gel afforded tritium labelled (-)-3-PPP. The optical purity was 98% ee as determined by HPLC using a chiral α_1-acid glycoprotein column (7). Tritium NMR (Fig. 1) confirmed the exclusive incorporation of tritium in positions 3 and 4 in the piperidine ring. The presence of two major peaks at 1.56 and 2.40 ppm, indicate that mainly monotritiated species are present. However, a minor amount of ditritiated species might also be present since the expected doublets might be hidden in the broad bases of the two peaks. The excess of monotritiated species may be explained by scrambling in the reduction reaction or due to loss of the ditritiated material in the resolving procedure.

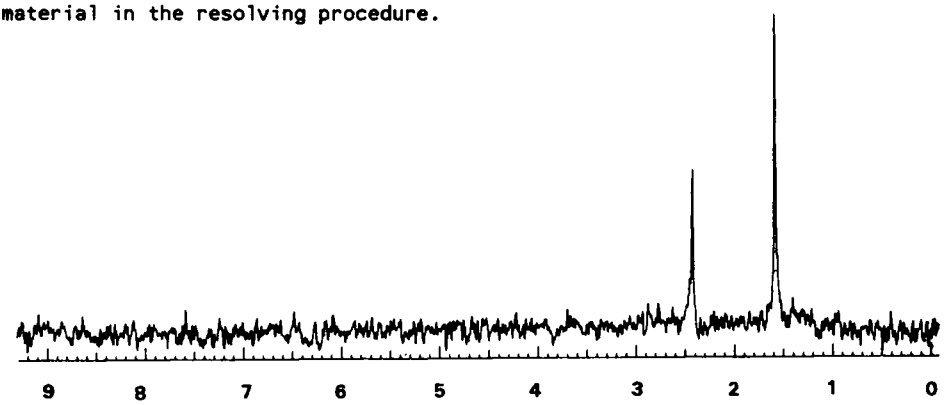


Fig. 1. Proton decoupled ^3H NMR spectra of ^3H-(-)-3-PPP (11, 30 mCi) obtained after 3000 scans at 212.8 MHz.

EXPERIMENTAL

Melting points were obtained on a Mettler FP 61 apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL FX 200 spectrometer in $CDCl_3$ using Me_4Si as internal standard. The ^3H NMR spectrum was recorded at 212.8 MHz using a JEOL FX 200 spectrometer in CD_3OD using Me_4Si as a ghost-reference (8). HPLC was performed on an LKB Enantiopac column eluted

(0.4 ml/min) with an 8 mM Na_2HPO_4/NaH_2PO_4 buffer (pH = 6.95) containing 0.1 m NaCl and 2% 2-propanol. Radiochemical purity was determined from TLC using a Berthold LB 283 Linear Analyzer. Radioactivity was measured with a Packard Tri-Carb 460 C liquid scintillation spectrometer. Tritium gas (98%) was purchased from Amersham International plc, England. (+)-BNPPA was purchased from Sigma, US.

3-Hydroxy-3-(3-methoxyphenyl)-1-propionyl-piperidine (6)

A solution of 1-benzyl-3-hydroxy-3-(3-methoxyphenyl)-piperidine hydrochloride (2) (14.5 g, 0.05 mol) in ethanol (300 ml) was hydrogenated at room temperature and atmospheric pressure with 5% Pd/C as catalyst. After 1 h the catalyst was filtered off and the solvent was evaporated. The debenzylated product was obtained as a colourless oil in a quantitative yield.

Propionylchloride (3.7 g, 0.04 mol) was dissolved in toluene (15 ml). The solution was added dropwise to a mixture of the 3-hydroxy-3-(3- methoxyphenyl)-piperidine (8.20 g, 0.04 mol) and triethylamine (4.0 g, 0.04 mol) in toluene (80 ml) at 0°C. Stirring was continued for one hour at room-temperature. After filtration and evaporation of the solvent the desired compound was obtained as a light yellow oil with a purity of 97% as determined by GC. Yield: 9.9 g (95%). ^{1}H-NMR δ 1.1 (t 3H); 1.5-2.0 (m, 4H); 2.3 (s, 2H); 2.4 (q, 2H); 3.3 D_2O exchangable (broad s, 1H); 3.9 (s, 3H); 7.3 (m, 4H).

3-(3-Methoxyphenyl)-1-propionyl-1,4,5,6-tetrahydropyridine (7)

To a solution of 3-hydroxy-3-(3-methoxyphenyl)-1-propionylpiperidine (6.7 g, 0.026 mol) in xylene (170 ml) was added phosphorous pentoxide (5.4 g, 0.038 mol) in portions with vigorous stirring. The mixture was heated at 140°C for 2 h. The clear solution was decanted from the smeary precipitate and after washing with brine and drying (Na_2SO_4) the solvent was evaporated. Distillation of the residual oil gave 2.1 g (35%) of the desired compound, bp: 141-143°C (0.007 mmHg). ^{1}H-NMR δ 1.2 (t, 3H); 2.0 (m, 2H); 2.5 (m, 4H); 3.8 (s, 3H); 6.7-7.3 (m, 4H); 7.1 (s, 1H).

3-(3-Methoxyphenyl)-1-propyl-1,4,5,6 tetrahydropyridine (8)

A solution of compound 7 (0.50 g, 2.0 mmol) in THF was added dropwise to a suspension of $LiAlH_4$ (0.20 g, 5.0 mmol) in THF (4 ml) at 0°C. Stirring was

continued for 2 hours at 25°C. Excess of hydride reagent was destroyed by adding a saturated aqueous solution of Na_2SO_4 dropwise to the mixture at 0°C. After filtration the organic layer was evaporated and the crude base was purified on a silica column using CH_2Cl_2 as eluent. Yield: 0.28 g (61%). ^{1}H NMR δ 0.89 (t, 3H) [γ]; 1.57 (m, 2H) [β]; 2.01 (m, 2H) [5]; 2,37 (m, 2H) [4]; 2.94 (m, 2H) [δ]; 3.03 (m, 2H) [6]; 3.79 (s, 3H) [methoxy]; 6.56 (m, 1H) [4']; 6.59 (sharp m, 1H) [2]; 6.76 (m, 1H) [2']; 6.85 (m, 1H) [6']; 7.14 (dd, 1H) [5'] ^{13}C NMR δ 11.37 [γ]; 21.47 [β]; 22.68 [5]; 23.29 [4]; δ 46.25 [6] 55.08 [methoxy]; 57.54 [α]; 104.39 [3]; 108.18 [4']; 108.34 [2'] 114.90 [6']; 129.03 [5']; 134.38 [2]; 143.65 [1'], 159.90 [3'].

3-(3-Methoxyphenyl)-1-propyl-1,2,5,6-tetrahydropyridine hydrochloride (10)

A solution of 3-(3-methoxyphenyl)-1-propyl-pyridiniumbromide (9) (9.24 g, 0.030 mol) 9 in aqueous methanol (70%, 50 ml) was cooled on ice. Sodium borohydride (11.36 g, 0.15 mol) was added in portions keeping the temperature below 10°C. Stirring was continued at 25°C for 16 h. The solvent was evaporated in vacuum and the residue was dissolved in 0.1-M HCL and washed with ether. The water-phase was made alkaline with 2-M NaOH and extracted with ether. The organic phase was dried (Na_2SO_4) and evaporated. The residual yellow oil 5.7 g (80%) was transformed to the hydrochloride salt and recrystallization from ethylacetate-2-propanol (10:1) gave the pure desired compound. Mp: 202-203°C. ^{1}H-NMR (liberated amine) δ 0.93 (t, 3H) [3]; 1.59 (m, 2H) [β]; 2.42 (m, 2H) [5]; 2.50 (m, 2H) [α]; 2.58 (m, 2H) [6]; 3.30 (m, 2H) [2]; 3.78 [methoxy]; 6.09 (m, 1H) [4] 6.79 (m, 1H) [4']; 6.87 (m, 1H) [2']; 6.95 (m, 1H) [6']; 7.20 (dd, 1H) [5'] ^{13}C-NMR (liberated amine) δ 12.00 [γ]; 20.34 [β]; 26.50 [5]; 49.58 [6]; 54.86 [2]; 55.11 [methoxy]; 60.58 [α]; 111.00 [4']; 112.17 [2']; 117.60 [6']; 122.73 [4]; 129.15 [5']; 135.50 [3]; 141.95 [1']; 159.63 [3'].

3-(3-Hydroxyphenyl)-1-propyl-1,2,5,6-tetrahydropyridine (3)

A mixture of compound 10 as the base (4.5 g, 0.019 mol) and pyridinium

hydrochloride (9.1 g, 0.076 mol) was heated at 200°C for 7 h under nitrogen. The reaction mixture was poured into ice-cooled brine. The clear solution was made alkaline with ammonia and was extracted with chloroform. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residual oil was purified on a silica column with chloroform-methanol (9:1) as eluent. Yield 2.1 g (51%) of the desired compound as the hydrochloride salt m.p. 205-206°C.

S(-)-3-(3-Hydroxyphenyl)-N-propyl-[3,4-^{3}H]piperidine (11)

A mixture of compound 3-HCl (7.0 mg, 32.3 μmol), 5% Rh/Al_2O_3 (9 mg), and DMF (0.5 ml) was stirred with 5 Ci of tritium gas for 72 h. The reaction mixture was then filtered and the solvent was evaporated. To remove labile tritium, the residue was treated twice with ethanol (1 ml) followed by evaporation to dryness. The crude product was dissolved in methanol (1.0 ml) and filtered through Celite. To this solution was added 60 mg of a salt of (-)-3-PPP and (+)-BNPPA, prepared according to reference (6). The salt was dissolved by heating and was allowed to crystallize. Recrystallization from hot methanol (1.0 ml) gave the tritium labelled salt of (-)-3-PPP and (+)-BNPPA with a specific activity of 1.6 Ci/mmol. The salt was dissolved in 2 M NH_3-solution (3 ml) and extracted with ethylacetate (3 x 2 ml). The organic phase was dried (Na_2SO_4) and evaporation of the solvent gave a crude product. Purification on a silica gel column, using ethyl acetate as the eluent, gave 30 mCi of the title compound. The radiochemical purity was 99% as determined by TLC (SiO_2, CH_3OH) and the optical purity was 98% as determined by HPLC. The retention times for 11 and its corresponding R(+)-isomer were 11.9 min and 20.6 min respectively.

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5. The complete assignment was achieved by the access of fully interpretated ^{1}H and ^{13}C NMR spectra of 3-PPP, which was based on 2-D ^{1}H - ^{1}H (COSY) and 2-D ^{13}C-^{1}H correlations. We thank Drs L. Kenne and H. Molin for helping us with these correlations which together with the complete assignment of 3-PPP will be reported elsewhere.

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