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SYNTHESIS OF CARBON-14 LABELLED ROPIVACAINE, A LOCAL ANAESTHETIC AGENT

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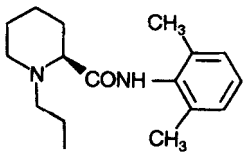
SUMMARY

Ropivacaine hydrochloride monohydrate (LEA 103) is a new local anaesthetic agent which currently is under preclinical and clinical investigation. The preparation of (S)-N-(2,6-[2-methyl-^{14}C]dimethylphenyl)-1-propylpiperidine-2-carboxamide hydrochloride monohydrate (6, [^{14}C]-LEA 103) with a specific activity of 12.44 mCi/mmol is described. The key step in the synthesis is a Pd(II)-mediated reaction of (S)-1-benzyloxycarbonyl-N-(2-methylphenyl)-piperidine-2-carboxamide (3) with [^{14}C]methyl iodide. Also described is the preparation of compound 3 from (S)-2-piperidinecarboxylic acid.

Key-words: ropivacaine, local anaesthetic agent, carbon-14 labelling, Pd(II)-mediated ortho-alkylation.

INTRODUCTION

The (S)-enantiomer of N-(2,6-dimethylphenyl)-1-propylpiperidine-2-carboxamide hydrochloride monohydrate (LEA 103, ropivacaine hydrochloride monohydrate) was chosen as a candidate in the search for a long acting local anaesthetic agent with low heart toxicity. In order to study the metabolism and pharmacokinetics of this drug a radioactively labelled compound was required. The present paper describes the synthesis of ^{14}C-labelled ropivacaine.



ROPIVACAINE

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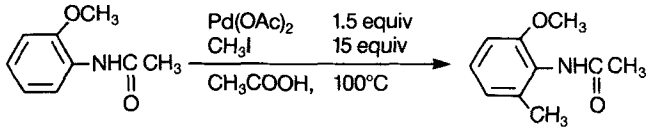
RESULTS AND DISCUSSION

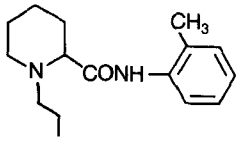
Tremont and Rahman recently reported (1) that acetanilides can be ortho-alkylated with reactive alkyl halides in the presence of $Pd(OAc)_2$. An example of this reaction is given in Scheme 1. Since, ropivacaine is a N-(2,6-dimethylphenyl)carboxamide derivative, we decided to apply this reaction type when introducing carbon-14 in ropivacaine. This would provide a compound containing the label in what would most probably be a metabolically stable position, which further supports the soundness of this synthetic strategy.



80%

Scheme 1

According to a preliminary experiment, when reacting 2-methyl-acetanilide with 1.2 equiv of CH_3I and 1.5 equiv of $Pd(OAc)_2$ in CH_3COOH at 60°C, the desired 2,6-dimethyl compound was formed in a yield of about 70%. This showed that the ortho-alkylation reaction is not dependent on the large excess of CH_3I (15 equiv) reported in reference 1. Since it is desirable to introduce carbon-14 as late as possible in the synthetic pathway, efforts were made to ortho-alkylate compound 1 as described above. However, as this failed, probably due to the presence of the free amino function in 1 , we decided to prepare a N-protected starting compound. (S)-Pipecolinic acid was reacted with benzyl chloroformate to give the carbamate 2, using standard methods. Compound 2 was coupled with ortho-toluidine, by the use of a method described by Arrieta et al (2).



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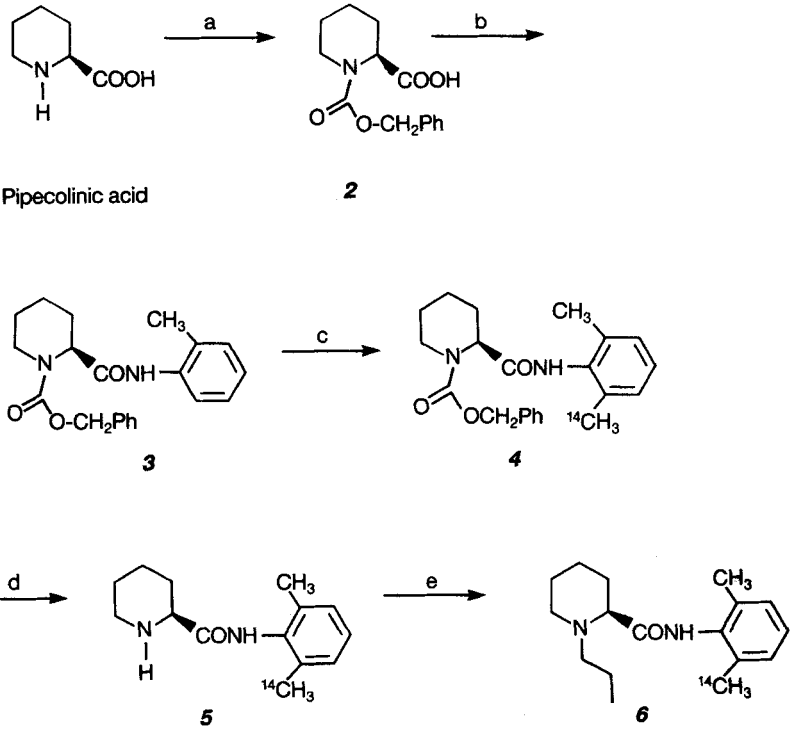
to give compound 3 (Scheme 2). Preliminary results using the racemic analogue of 3 in the Pd(II)-mediated reaction (1.2 equiv of CH_3I and 1.5 equiv of $Pd(OAc)_2$ at 80°C), indicated that the desired compound was formed in a yield of about 70%. Furthermore, applying the method on chiral material, i.e. 3, followed by depro-

tection (HBr/CH_3COOH) and alkylation with n-propyl iodide (cf. Scheme 2), no racemization in the formed ropivacaine was observed, as determined by HPLC using a chiral α_1-acid glycoprotein column (3). Application of the method using [^{14}C]methyl iodide gave the desired carbon-14 labelled LEA 103 in an overall yield of 37% (Scheme 2). The specific activity was, after addition of cold material, 12.44 mCi/mmol. The enantiomeric purity was 100±0.3%, as determined by HPLC.

Scheme 2



Reagents: a= $PhCH_2OCOCl$, NaOH; b= DMAP, $SOCl_2$ and $2\text{-}CH_3C_6H_4NH_2$, DMAP; c= $Pd(OAc)_2$, CH_3COOH, $^{14}CH_3I$; d= HBr, CH_3COOH; e= $n\text{-}C_3H_7I$, K_2CO_3.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Optical rotations were obtained on a AA-100 polarimeter from Optical Activity Ltd. ^{1}H and ^{13}C NMR spectra were recorded at 199.5 MHz and 50.1 MHz, respectively, on a JEOL FX 200 spectrometer using Me_4Si as the internal standard. Radiochemical purity was determined by scanning alumina-TLC plates

using a Berthold LB 283 TLC Linear Analyzer. Enantiomeric purity was determined by HPLC using a LKB EnantioPac column eluted (0.4ml/min) with 8 mM phosphate buffer (pH=7.2) containing 0.1 M NaCl and 6% 2-propanol. The column was connected to a Berthold LB504 radioactivity monitor and to a LDC/ Milton Roy UV-spectromonitor operating at 220 nm. Radioactivity was measured in a Packard Tri-Carb 460 C liquid scintillator spectrometer. [^{14}C]Methyl iodide was purchased from Amersham, U.K. (S)-Piperidinecarboxylic acid $[\alpha]_D^{20}$ -26.40°c=1, H_2O), was purchased from Jansen, Belgium.

(S)-1-Benzyloxycarbonyl-piperidine-2-carboxylic acid (2)

To a solution of (S)-piperidine-2-carboxylic acid (500 mg, 3.87 mmol) in 2M NaOH (1.9 ml, 3.8 mmol) at 4°C was added 0.660 ml (4.6 mmol) of benzyl chloroformate together with a simultaneous addition of 2.3 ml (4.6 mmol) of 2M NaOH. The ice-bath was then removed and the mixture was stirred at 20°C overnight, whereafter water (10 ml) was added. The mixture was washed with ether (2x15 ml) and acidified (pH 2) with 2M H_2SO_4. The acidic solution was extracted with ether (3x15 ml) and the combined extracts were dried (Na_2SO_4). Evaporation of the solvent gave 796 mg (78.3 %) of the title compound. Mp 108-109 °C. $[\alpha]_D^{22}$ -40.7° (c=1,CH_3OH). ^{1}NMR ($CDCl_3$) δ 1.28 - 1.46 (m, 2H), 1.61- 1.80 (m,3H), 2.18- 2.37 (m, 1H), 3.02 (q,1H), 4.09 (t, 1H), 4.94 (dd, 1H),7.32 (s, 2H), 7.35 (s, 3H), 8.65 (broad s, 1H). ^{13}C NMR (CD_3OD) δ 21.58, 25.66, 27.68, 42.89, 55.66, 68.33, 128.61, 128.95, 129.41, 137.92, 158.04, 174.51.

(S)-1-Benzyloxycarbonyl-N-(2-methylphenyl)-piperidine-2-carboxamide (3)

73 µl (1.0 mmol) of $SOCl_2$ was added to a solution of 4-dimethylaminopyridine (DMAP, 113 mg, 0.924 mmol) in CH_2Cl_2 (5 ml) at 20°C. The reaction mixture was stirred for 30 min and the acid 2 (222 mg, 0.84 mmol) in CH_2Cl_2 (2 ml) was added. The temperature was kept at -20°C and the stirring was continued for another 30 min. A solution of o-toluidine (90 µl, 0.84 mmol) and DMAP (113 mg, 0.924 mmol) in 2 ml of CH_2Cl_2 was slowly added at -20°C. The reaction mixture was stirred for another 18 h while the temperature slowly reached room temperature. After the addition of CH_2Cl_2 (10 ml), the organic phase was washed with 1M HCl, sat. Na_2CO_3 solution and finally water, dried over Na_2SO_4, and concentrated in vacuum. Purification on silica gel (eluent CH_2Cl_2/ EtOAc 9.5:0.5 v/v) followed by freeze drying afforded 130 mg (44%) of a white solid. M.p. 68-69

°C. $[\alpha]_D^{22}$ - 110.5° (*c*=0.344, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 1.40- 1.80 (m, 5H), 2.09 (s, 3H), 2.39 (d, 1H), 2.97 (t, 1H), 4.20 (broad d, 1H), 4.97 (s, 1H), 5.21 (s, 2H), 7.01- 7.20 (m, 4H), 7.35 (s, 5H), 7.88 (broad s, 1H). ^{13}C NMR (CD_3OD) δ 18.22, 21.19, 25.69, 28.34, 43.40, 56.48, 68.55, 127.17, 127.32, 127.54, 128.85, 129.09, 129.51, 131.52, 134.61, 136.66, 137.92, 158.06, 172.71.

(S)-1-Benzyloxycarbonyl-N-(2,6-[2-methyl-^{14}C]dimethylphenyl)-piperidine-2-carboxamide (4)

10 mCi (0.167 mmol) of $^{14}CH_3I$ was transfered, via a vacuum line, to a stirred mixture of compound 3 (58 mg, 0.167 mmol), Pd $(OAc)_2$ (56 mg, 0.25 mmol), and CH_3COOH (1 ml). After breaking the vacuum, the mixture was heated in a sealed tube at 90°C for 48 h. The solvent was evaporated and the residue partitioned between EtOAc (3 ml) and 2M NH_3 (3 ml). The organic phase was separated and the aqueous phase was extracted with EtOAc (2x3 ml). The combined extracts were dried (Na_2SO_4) and evaporation of the solvent gave crude 4. TLC (SiO_2, CH_2Cl_2/ EtOAc 9.5: 0.5 v/v) indicated that 61% of the radioactivity was present in the title compound.

(S)-N-(2,6-[2-Methyl-^{14}C]dimethylphenyl)-1-propylpiperidine-2-carboxamide hydrochloride monohydrate (6)

The crude product 4 obtained from the previous reaction was dissolved in CH_3COOH (1 ml) and treated with 30% HBr in CH_3COOH (0.5 ml) for 15 h at 20°C. The solvent was evaporated and the residue was dissolved in 2M HCl (2.5 ml). The acidic water phase was washed with ether/ EtOAc 1:1 v/v (2x2.5 ml) and basified with 45% NaOH. Extraction with EtOAc (3x3 ml), drying over Na_2SO_4, and evaporation of the solvent gave 35 mg of crude and uncharacterized 5.

To a solution of crude 5 (35 mg) in 2 ml of CH_3CN was added K_2CO_3 (25 mg, 0.18 mmol), and n-C_3H_7I (15 µl, 0.15 mmol). The mixture was stirred in a sealed tube for 18 h at 80°C. The solvent was evaporated and 2M NaOH (2.5 ml) was added to the reaction mixture, and this was extracted with EtOAc (3x2.5 ml). After drying (Na_2SO_4), the solvent was removed and the crude compound was purified on a short alumina column with ether/ hexane (1:1 v/v) as the eluent. The obtained base was converted to a HCl-salt by the addition of 4M HCl i ether (40 µl). Evaporation of the solvent gave 19 mg (37% overall yield from 3) of the hydrochloride analogue of 6. 50 mg of cold 6 was added and the combined salts were recrystallized from

acetone/ water (9:1 v/v) to give 48.2 mg of the title compound. The specific activity was 12.44 mCi/mmol and the overall radiochemical yield was 19%. The radiochemical purity was 98.7% as determined by TLC (Al_2O_3, ether/ hexane 1:1 v/v) and scanning. The radiochemical enantiomeric purity was 100% ee as determined by radio-HPLC. The enantiomeric purity was 100±0.3% ee as determined by HPLC using the UV-detector (the detection limit is 0.3% at a concentration of about 0.7 µmol/ ml). The retention times for 6 and its corresponding R-isomer were 28.9 min and 19.2 min, respectively.

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