SYNTHESIS OF LABELED ANTI-INFLAMMATORY AGENTS.*

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SUMMARY

The synthesis of the anti- inflammatory agents d-2-(6'-methoxy-2'-naphthyl)-propionic acid and l-2-(6'-methoxy-2'-naphthyl)-propanol labeled with ^{14}C and ^{3}H is described.

INTRODUCTION

d-2-(6'-Methoxy-2'-naphthyl)-propionic acid (Naproxen®) and l-2-(6'-methoxy-2'-naphthyl)-propanol (Naproxol®) have been shown[1,2] to be potent anti-inflammatory and analgetic agents. This communication describes the synthesis of these agents[3] labeled with ^{14}C and ^{3}H.

The following reaction sequence was used to incorporate ^{14}C into the side chain of the molecule:

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In order to obtain tritiated material of the required high specific activity, the catalyst was prepared with tritiated water which was made by oxidizing tritium gas in a vacuum system with platinum oxide. The specific activity of the tritiated product indicated a mean exchange of ca. 2 hydrogen atoms.

Parallel experiments with deuterated phosphoric acid catalyst permitted the assignment of the isotope to specific positions of the naphthalene nucleus. Thus, the nuclear magnetic resonance (NMR) spectrum of deuterated 2-(6'-methoxy-2'-naphtyl)-propionic acid indicated the presence of deuterium in the 1',4',7' and 3' positions, the ratio of deuterium incorporation being approximately 1:1:1:0.3. This was verified by mass spectroscopy (MS), the most abundant species being d_3 (48%), d_4 (28%) and d_2 (16%). The deuterium label was stable to treatment with boiling alkali.

The resolution of the racemic labeled Naproxen on the 0.1-1 mmole scale was achieved by multiple crystallizations of the d-1-amino-1-(1'-naphthyl)-ethane salt, followed by liberation of the optically pure acid with mineral acid. Finally, reduction of ^{3}H- and ^{14}C-Naproxen with diborane produced the corresponding alcohols in good yield.

No radiochemical impurities, detectable by thin layer chromatography (TLC) were formed when the labeled material was stored one year in benzene (up to 3 mCi/ml) in the dark at room temperature.

The specific activity of ^{14}C labeled Naproxol was verified by gas chromatography-mass spectroscopy (GC-MS),[7] which showed 44% of a molecular ion peak at 218 and 56% at 216.

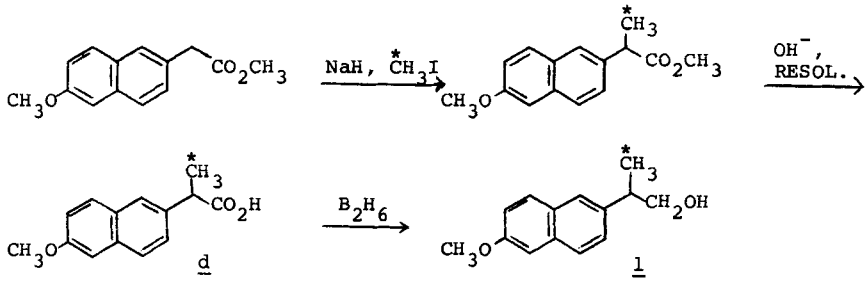

fig. 1

The synthesis of methyl 2-(6'-methoxy-2'-naphthyl)-propionate by alkylation of the α-carbanion of methyl 2-(6'-methoxy-2'-naphthyl)-acetate with methyl iodide has been described in an earlier publication.[1,4]

This procedure was modified for the ^{14}C synthesis in that two equivalents of the carbanion were used per equivalent of ^{14}C-methyl iodide. This resulted in an efficient utilization of the ^{14}C methyl iodide in the alkylation reaction, the radiochemical yield of the requisite propionic ester being 97%.[5] Alkaline hydrolysis then furnished the ^{14}C dl-acid.

For the tritium synthesis, the Jarvorsky[6] exchange technique utilizing a boron trifluoride ^{3}H-phosphoric acid complex was employed with dl-2-(6'-methoxy-2'-naphthyl)-propionic acid.

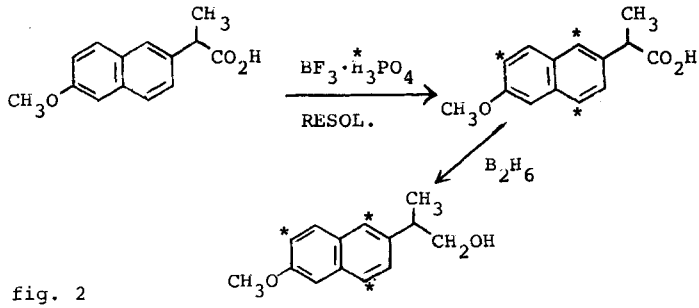

fig. 2

EXPERIMENTAL

a) d-3-^{14}C-2-(6'-Methoxy-2'-naphthyl)-propionic acid:

Methyl 2-(6'-methoxy-2'-naphthyl)-acetate (276 mg; 1.2 mmole) and 1.2 mmole sodium hydride in 2 ml dry tetrahydrofuran (THF) were stirred at room temperature in a vacuum system, until hydrogen evolution ceased. ^{14}C-Methyl iodide (85 mg=0.6 mmole, 15 mCi)* was condensed into the frozen, evacuated reaction mixture; after 2 hrs. stirring at 25°, no unreacted methyl iodide was detectable. The reaction product was diluted with ether, washed with water and purified by prep. TLC on three 20 x 20 x 0.2 cm silica gel plates with hexane-ethyl acetate 7:1 (4 developments). The band corresponding to methyl 3-^{14}C-2-(6'-methoxy-2'-naphthyl)-propionate was eluted with ethyl acetate and the solvent evaporated.

This resulting ester was refluxed 24 hrs. with 0.3 g NaOH in 1.2 ml water and 2 ml THF. Acidification with dil. HCl and ether extraction gave 142 mg (97% y. from CH_3I) dl-Naproxen.

To 59 mg of dl-acid in 0.5 ml boiling abs. ethanol-acetone 9:1 a solution of 46 mg d-1-amino-1-(1'-naphthyl)-ethane in 0.45 ml of the same solvent was added. The crude salt precipitated after seeding and slow cooling. It was purified by 2 recrystallizations from methanol acetone 9:1. The title compounds were obtained after acidification with dil. HCl, ether extraction, uptake into $NaHCO_3$ solution and reacification; 18 mg (y. of resolution=61%**); mp 154-155°;*** $[\alpha]_D$ (0.1% in $CHCl_3$) + 64.5°;

*Obtained from New England Nuclear Corporation, Boston.

**Additional material (19% radiochemical yield) of lower specific activity was obtained when carrier was added to the combined mother liquors and recrystallized to constant specific activity.

***Corrected.

radiochem. purity 99.5% by silica radio-TLC (3 times developed in hexane-ethyl acetate-formic acid 6:3:1).

b) l-3-^{14}C-2-(6'-Methoxy-2'-naphthyl)-propanol:

^{14}C-Naproxen (37 mg) was dissolved in 5 ml ether and stirred 4 hrs. at room temperature under nitrogen with 1.8 ml 1 m diborane in THF. The reaction mixture was quenched with acetone, diluted with ether, washed with water, dried with magnesium sulfate, evaporated and crystallized from 1 ml ethyl acetate-hexane 1:6; 28 mg (y=78% from Naproxen) ^{14}C-Naproxol were obtained; $[\alpha]_D$ (benzene) -29°; IR (1% in KBr) identical with unlabeled material; radiochem. purity 97% by silica radio-TLC (3 times developed in ethyl acetate-hexane 2:5); specific activity 25.6 mCi/mmole (liquid scintillation counting of an aliquot in dioxane-toluene-methanol counting solution,[8] with internal standardization); GC-MS: 44% 218 (^{14}C M^+), 56% 216 (M^+) = 27.5 mCi/mmole.

c) d-Naphthyl-^{3}H-2-(6'-methoxy-2'-naphthyl) propionic acid:

Tritium gas (ca. 17 Ci) was oxidized by stirring with 123 mg platinum oxide in 0.5 ml water in a vacuum system. The obtained tritiated water (spec. act. ca. 600 mCi/mmole) was transferred into 1.5 g phosphorus pentoxide, kept at -190° in one side of a two-arm stopcock flask. Excess boron trifluoride gas was condensed into the cooled exchange mixture and allowed to come to room temperature, while the vacuum line was purged with a slow boron trifluoride current.* The flask was disconnected from the vacuum system, 0.3 g dl-Naproxen was introduced from

*10 mCi ^{3}H were found after adsorption of an excess of boron trifluoride in dil. NaOH.

the other side arm, the viscous reaction mixture was homogenized with a magnetic stirrer and agitated 20 hrs. at room temperature. The exchange mixture was decomposed by distillation with water at the vacuum line and later at a rotory evaporator. The product was taken up in ether, washed with water and evaporated. It was 2 times redissolved in dil. NaOH and precipitated under reflux with dil. HCl to yield 0.25 g dl-^{3}H-Naproxen. After resolution as described under a), ^{3}H-Naproxen (70 mg) was obtained, which was stored at room temperature in 50 ml benzene; mp 152-154° (dil. HCl); $[\alpha]_D$ (0.1% in benzene) +59°; λ max 230,263,270 nm; radiochem. purity 97% [TLC as in a)]; specific activity 608±7 (σ)mCi/mmole (ε 5300, 263 nm).*

d) 1-Naphthyl-^{3}H-2-(6'-methoxy-2'-naphthyl)-propanol:

^{3}H-Naproxen was reduced as described under b) to give 11 mg ^{3}H-Naproxol, mp 87-89°; $[\alpha]_D$ (benzene) -28°, λ max 230,263,270 nm; radiochem. purity [as under b)] 99%, specific activity identical with c).

e) dl-1',4',7'-^{2}H-2-(6'-methoxy-2'-naphthyl)-propionic acid:

Phosphorus pentoxide (3.1 g) was allowed to adsorb in vacuum 1.3 ml deuterated water and the resulting mixture was saturated with boron trifluoride. dl-Naproxen [0.28 g] was added, the mixture was agitated until a homogenous solution formed and then allowed to stand 3 hrs. at room temperature. The product was poured onto ice, heated to boil, cooled and extracted with ether.

The residue obtained after evaporation of the ether was re-

*By UV mass determination, using given ε from reference samples and liquid scintillation counting of 5 replicates.

dissolved in dil. NaOH, heated briefly and acidified with dil. HCl to give 0.2 g dl-^{2}H-Naproxen, mp 152-154°; MS (corrected for naturally occurring isotopes) d_0=2%, d_1=3%, d_2=16%, d_3=48%, d_4=28%, d_5=3%; NMR (100 mc, d-chloroform, ppm downfield from internal tetramethylsilane) 1.57 (d, J=7, 3H) H3; 3.85 (q, 1H) H2; 3.88 (s, 3H) OCH_3-H; 7.10 (s, 1H) H5'; 7.40 (s, 0.7H) H3'; 7.67 (s, 1H) H8'.

No change of this spectrum was observed after the material was refluxed 1/2 hr. with 10% NaOH and acidified.

NMR of unlabeled reference material: 1.57 (d, J=7, 3H) H3; 3.85 (q, 1H) H2; 3.88 (s, 3H) OCH_3-H; 7.14 (d, J=2.5, 1H) H5'; 7.22 (dd, J=8.0, 2.5, 1H) H7'; 7.48 (dd, J=9, 1.5, 1H) H3'; 7.68 (m, 3H) H1',4',8'.

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