SYNTHESIS OF TRITIUM LABELLED MOMETASONE FUROATE

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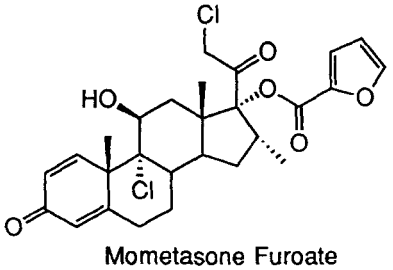
Summary

^{3}H-mometasone furoate was synthesized by a six step procedure. The label was introduced via the reduction and re-oxidation of the 1,2 double bond in the A ring. The remaining 4 steps were accomplished with on overall radiochemical yield of 28%. Analysis by ^{3}H nmr indicated that most of the label (≈95%) was located in the 2-position and the remainder in the 1-position.

Introduction

Mometasone furoate is a topical steroid used for treatment of corticosteroid responsive dermatoses, such as psoriasis.[1] It is also currently under development as a treatment for allergic rhinitis and asthma.



Mometasone Furoate

In order to support the development programme, large amounts of high specific activity material (>0.5Ci/mmole) was required. Hence, tritium labelled mometsone furoate was synthesized and subsequently analysed by ^{3}H nmr to confirm the sites of tritium labelling.

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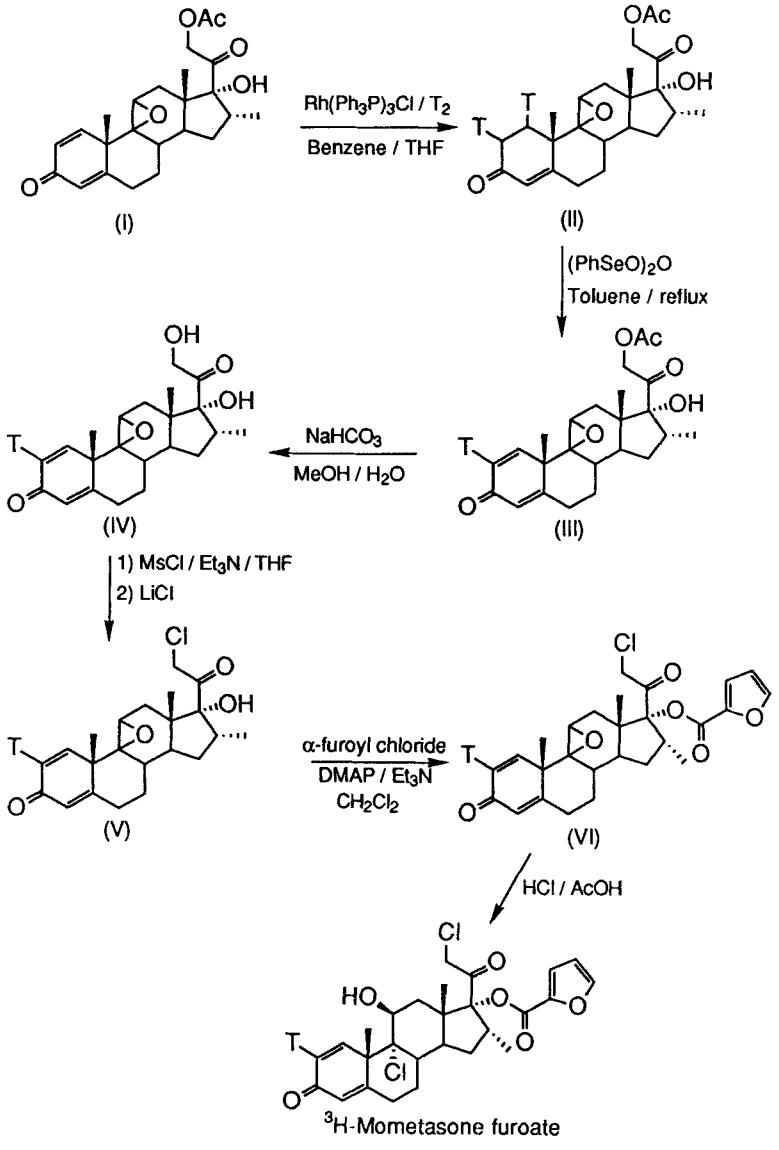
Synthesis

[^{3}H]-Mometasone furoate is prepared via a six step procedure from Compound (I) (synthesized by Schering-Plough Chemical Development):-



Initial effforts had focused on incorporating the label at a later stage of the synthesis, but were unsuccesful. Hence the 21-acetate was labelled with tritium via the reduction and re-oxidation of the

Δ^1 bond in the A ring. The remaining steps were then based on a Schering-Plough Research Institute synthesis.[2]

The reduction of (I) was carried out using Wilkinson's catalyst and 30Ci of tritium gas, using benzene and THF as solvents. A total of 14.5Ci of (II) was produced, after tlc purification. Re-oxidation of (II) back to (III), with regeneration of the Δ^1 bond, was accomplished by refluxing (II) with benzeneselenic anhydride to yield 2.4Ci of (III).

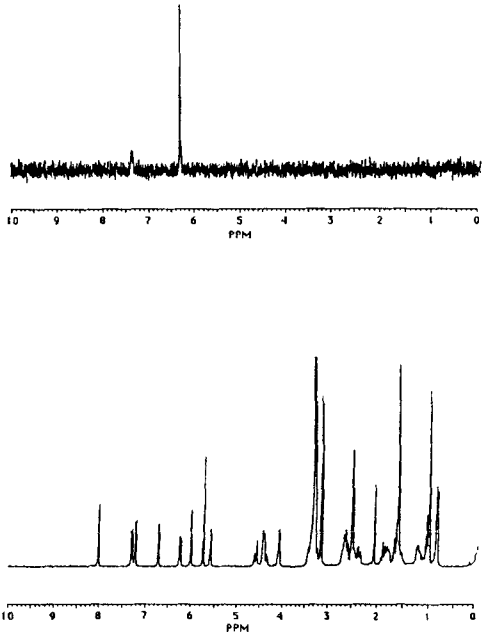
500mCi of (III) was diluted with unlabelled mometasone furoate and then taken through the remainder of the synthesis. Hydrolysis of the 21-acetate to (IV) was accomplished by stirring a methanolic solution of (III) with one equivalent of aqueous sodium bicarbonate solution, overnight. It was found that although the reaction with bicarbonate was slower, the use of stronger bases such as potassium carbonate or hydroxide gave rise to more impurities.

Crude (IV) (91% RCP) was next stirred with mesyl chloride and triethylamine in THF until the mesylation was complete by tlc(≈2hrs). The mesylate was then stirred overnight with lithium chloride to generate chloride (V) at 85% RCP. Crude (V) was then furoylated by treatment with α-furoyl chloride and dimethylaminopyridine (DMAP). The α-furoyl chloride DMAP complex was first generated as a suspension in methylene chloride, and then was added to a methylene chloride solution of (V) with triethylamine. The reaction was complete by hplc in ≈2hrs, with 74% of the activity corresponding to furoate (VI).

Finally crude (VI) was treated with HCl saturated acetic acid solution, which yielded 315mCi of ≈60% RCP mometasone furoate after work up. This was partially purified by gravity silica gel chromatography, followed by preparative hplc on silica, which raised the radiochemical purity to 95%.Finally the material was recrystallised from glyme and hexane to yield 140mCi of purified mometasone furoate (28% radiochemical yield from (III).

Analysis

The bulk drug was analysed by radio hplc on a C8 column, using a methanol: water mobile phase, and on PVA-silica using methylene chloride: *t*-butyl methyl ether. A radiochemical purity of >99% and a specific radioactivity of 652mCi/mmole were obtained. The analysis was completed with a 320MHz ^{3}H nmr, obtained at the University of Surrey, which indicated as expected, that 95% of the tritium was present in the 2-position in the A ring, with the remainder in the adjacent 1-position.



^{1}H and ^{3}H NMR of ^{3}H mometasone furoate

References

1. R.S Medansky *et al., Semin. Dermatol.*, **6**, 94 (1987).
2. E.L. Shapiro *et al., J. Med. Chem.*, **30**, 1581 (1987).