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SYNTHESIS OF TRITIATED CIPROFIBRATE

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Summary

A synthetic procedure for [^{3}H]ciprofibrate is described. The radiolabel was introduced by catalytic dehalogenation of bromo-ciprofibrate with tritium gas, as shown in the Scheme.

Key words

[^{3}H]Ciprofibrate, tritium gas

Introduction

Ciprofibrate (1), 2-[4-(2,2-dichlorocyclopropyl)phenoxy]-2-methylpropanoic acid, is a novel hypolipidemic agent.[1,2] As part of our drug development programme, *in vitro* studies required the preparation of tritium labelled drug. The susceptibility of the aromatic ring to electrophilic attack indicated ring bromination followed by catalytic dehalogenation with tritium gas as being a viable approach to labelled drug.

Discussion

The synthesis of [^{3}H]ciprofibrate (2-[2-^{3}H-4-(2,2-dichlorocyclopropyl)phenoxy]-2-methylpropanoic acid (4)) involved the reaction of a chloroform solution of ciprofibrate with bromine in the presence of ferric bromide by the method of Wisansky and Ansbacher.[3] The two

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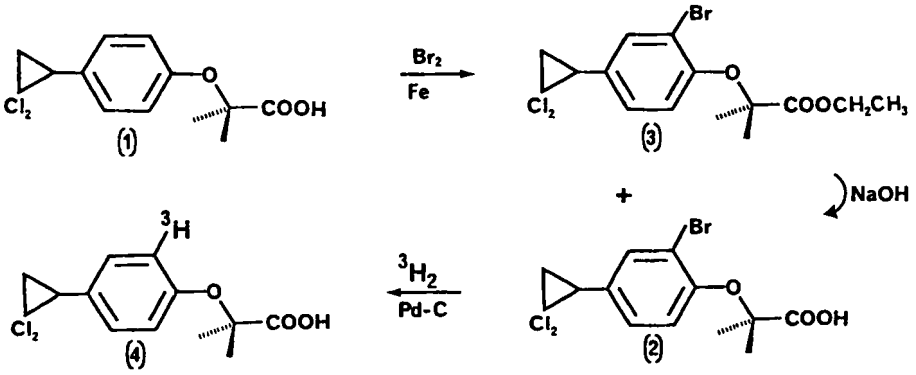
isolated products were the bromo acid (2) and the corresponding ethyl ester (3), the latter being readily hydrolysed to the former in ethanolic sodium hydroxide solution. The ester arose from the small amount of ethanol present in commercial chloroform as a stabilising agent. However, the stringent removal of ethanol from chloroform, rather than directing the reaction towards only the acid, gave the product as a multicomponent intractable tar.

The catalytic dehalogenation gave a product having a specific activity of 8.0 Ci/mmol (carried out by Amersham International plc). The radiochemical purity of the product was 93 - 95% as verified by TLC and UV spectroscopy by comparison with authentic ciprofibrate and suitable for further experimentation.



Scheme

Experimental

Infra-red spectra were recorded from dispersions in potassium bromide using a Perkin Elmer 177 spectrophotometer. Ultra-violet light absorption spectra were recorded using a Perkin Elmer 554 spectrophotometer. NMR spectra were obtained using a Bruker AC80 instrument for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were recorded on an AEI MS 9 mass spectrometer. The isotopic patterns were as expected (^{35}Cl, ^{79}Br quoted). Melting points (uncorrected) were obtained on a Buchi 510 instrument.

Ciprofibrate (1)

This compound was provided by Sterling Organics, a Division of Sterling-Winthrop Group Ltd., Dudley, Cramlington, Northumberland: mp 116.2 - 118.6°C, UV λ_{max} 233 (El% 450) nm, NMR spectrum (Partial) δ_H 11.16 (1H, OH), 7.14 (2H, d, J_{AB} 8.7 Hz), 6.89 (2H, d, J_{AB} 8.7 Hz) ppm; IR ν_{max} 1690 cm^{-1}; MS m/z 288 (M^+).

Bromociprofibrate (2)

Bromine (3.15 g; 20 mmol) in chloroform (20 ml) was added dropwise under a nitrogen atmosphere to a stirred suspension of iron filings (150 mg), ciprofibrate (2.89 g; 10 mmol) and a crystal of iodine in chloroform (10 ml) at 0 - 5°C. When addition was complete, cooling was removed, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was poured onto crushed ice (200 g) and the organic products removed by extraction with diethyl ether, dried ($MgSO_4$), and evaporated to give a viscous yellow oil (4.9 g).

A portion of the oil (3.6 g) was chromatographed on silica (Merck 60) using chloroform : n-hexane (50 : 50 by volume) as eluant. The ethyl ester (3) (0.91 g; 26%) was eluted first as a colourless oil (IR ν_{max} 1730 cm^{-1}; NMR spectrum (Partial) δ_H 7.42 (1H, d, J 2Hz), 7.06 (1H, dd, J 2.0, 8.5Hz), 6.81 (1H, d, J 8.5 Hz), 4.24 (2H, q, J 7Hz), 1.25 (3H, t, J 7Hz) ppm; MS m/z 394 (M^+)). Further elution afforded bromo acid (2) (1.78 g; 62%), which was recrystallised from cyclohexane to afford colourless crystals, mp 113.2 - 113.4°C (Elemental analysis: C, 42.33; H, 3.53%; $C_{13}H_{13}BrCl_2O_3$ requires: C, 42.42, H, 3.56%; UV λ_{max} 286 (El% 32) nm; IR ν_{max} 1705 cm^{-1}; NMR spectrum (Partial) δ_H 10.90 (1H, s, OH), 7.46 (1H, d, J 1.9 Hz), 7.13 (1H, dd, J 1.9, 8.7 Hz), 7.07 (1H, d, J 8.7 Hz) ppm; MS m/z 366 (M^+)).

Table: Carbon - 13 data (aromatic region only) δ/ppm

	C-1	C-2	C-3	C-4	C-5	C-6
Ciprofibrate(1)	154.3	120.1	129.8	129.3	129.8	120.1
Bromociprofibrate(2)	151.4	116.6	133.8	131.0	128.7	120.2

NOTE: Bromination at C-2 (ie. ortho to ether linkage) was confirmed by comparison of actual chemical shifts for (2) with predicted values for 2- and 3-substitution using the bromine substituent effect[4] and obtained ciprofibrate shifts (2-Br: C-1, 157.6; -2, 114.7; - 3, 133.1; -4, 131.5; -5, 128.8; -6, 122.3).

[^{3}H]Ciprofibrate (4)

Catalysed bromine-tritium replacement reaction was carried out on (2) (65 mg) in benzene (1 ml) and triethylamine (100 ul) using tritium gas (10 Ci, 370 GBq) over 10% palladium on charcoal catalyst (25 mg), which was subsequently removed by filtration. The solution was evaporated to dryness and an aliquot (50 mCi, 1.85 GBq) was taken up in ethanol (28.5 ml) to give a specific activity of 1.75 mCi/ml, and the solution was stored under nitrogen in a sealed tube. The compound identity was confirmed by TLC on silica gel $60F_{254}$, with the major spot corresponding to ciprofibrate. The radiochemical purity of the [^{3}H]ciprofibrate was found to be 95.0% and 92.6% in toluene : acetone : formic acid (78 : 20 : 2) (Rf 0.40) and n-butanol : ammonia (0.88) : water : ethanol (65 : 15 : 15 : 10) (Rf 0.44), respectively. (Note: After 3 years of storage in ethanol at -20°C, re-analysis in the former system gave a radiochemical purity of 84.0%). The ultra-violet light absorption spectrum of the sample solution compared favourably with that of a ciprofibrate reference, indicating a concentration of 0.063 mg/ml, hence a specific activity of 8.0 Ci/mmol.

Acknowledgements

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