PREPARATION OF [2-^{14}C]-2-(p-CHLOROPHENOXY) -2-METHYLPROPIONIC ACID AND ITS ETHYL ESTER, [^{14}C] CLOFIBRATE

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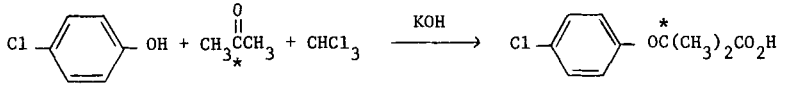
Ethyl 2-(p-chlorophenoxy)-2-methylpropionate (clofibrate) is an established and clinically useful antihyperlipidemic drug in man [1]. This note describes the synthesis of [^{14}C]clofibric acid 1 of high specific activity and the subsequent conversion of the labelled acid to [^{14}C]clofibrate 2.

Clofibric acid 1 was labelled by condensing [2-^{14}C]acetone and chloroform with p-chlorophenol according to the procedure of Julia et al [2]. The reaction was carried out on a micro scale and a specific activity of 19.5 mCi/mmole for the labelled acid was realized. Esterification of the acid with absolute ethanol gave [^{14}C]clofibrate in 84% (31% overall) yield.



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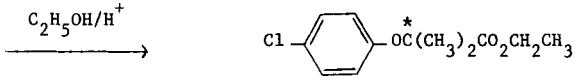

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[2-^{14}C]Acetone, 23.4 mg, sp.act. 19.2 mCi/mmole and 45.7 mg, sp.act. 10.4 mCi/mmole, were purchased from ICN Isotope and Nuclear Division, Irvine, California.

[2-^{14}C]-2-(p-Chlorophenoxy)-2-methylpropionic acid (1)

The [2-^{14}C]acetone (23.4 mg, 0.40 mmoles) in a break-seal vial was connected to a vacuum line and frozen with liquid nitrogen. A 25 ml three-necked reaction flask fitted with a dropping funnel, a dry nitrogen gas inlet (stopcock) and magnetic stirrer was also attached to the vacuum line. The reaction flask was charged with 130 mg powdered potassium hydroxide (KOH) and the whole system was evacuated to 0.2 mm of Hg pressure. Using liquid nitrogen, the [2-^{14}C]acetone was transferred to the flask under vacuum. A 3 ml N,N-dimethylformamide (DMF) solution containing p-chlorophenol (52 mg, 0.40 mmoles) and chloroform (0.07 ml, 0.88 mmoles) was added from the dropping funnel to the KOH, releasing the vacuum in the flask. The liquid nitrogen coolant was then replaced with an ice-water bath and the reaction mixture was stirred at 0^{o} for 3 hr and at room temperature for 18 hr. After dilution with water and crushed ice, the reaction mixture was acidified with concentrated hydrochloric acid and extracted with ether. The ethereal solution was then extracted with 5% sodium bicarbonate which, in turn, was acidified and extracted with chloroform. The final chloroform extract was washed with water, saturated saline solution, dried ($MgSO_4$) and concentrated. The crude acid was obtained as a crystalline solid (21 mg, 24% yield). In another reaction, using 45.7 mg [2-^{14}C]acetone (sp.act. 10.4 mCi/mmole) the acid was obtained in 37% yield. Recrystallization from hexane-benzene gave 9.1 mg of radiochemically pure (> 99%) [^{14}C]clofibric acid, sp.act. 19.5 ± 0.7 mCi/mmole. The purity of the compound was established by thin layer chromatography (TLC)-autoradiography in three solvent systems: methylcyclohexane-acetone-acetic acid 70:30:1; hexane-acetone-acetic acid 60:40:1; benzene-ethanol-acetic acid 80:12:5.

Ethyl [2-^{14}C]-2-(p-chlorophenoxy)-2-methylpropionate ([^{14}C]Clofibrate) (2)

The crude [^{14}C]clofibric acid (38 mg, sp.act. 10.4 mCi/mmole) and 100 mg unlabelled acid were dissolved in 10 ml anhydrous ethanol containing 0.2 ml concentrated sulfuric acid and refluxed for 18 hr. The cooled solution was then diluted with cold water and extracted with ether. The

ether extract was washed with ice-cold 5% sodium hydroxide solution, water, saturated saline solution, dried ($MgSO_4$) and concentrated. The crude ester (149 mg) contained two minor radioactive impurities as shown by TLC and autoradiography. The ester was twice purified by preparative TLC (Brinkman, 0.25 mm F-254 silica gel plates) using first hexane-ethyl acetate 95:5 then benzene as the developing solvent systems. An additional 100 mg unlabelled clofibrate was added before the second TLC purification step. The ester band was detected under short wave ultraviolet light, scraped from the plate and extracted from the silica gel with ethyl acetate. The [^{14}C]clofibrate (200 mg) was 98% radiochemically pure as shown by TLC-autoradiography in three solvent systems: benzene; hexane-ethyl acetate, 95:5; benzene-hexane, 9:1. The purified [^{14}C]clofibrate, specific activity 1.85 ± 0.01 mCi/mmole, was obtained in 84% yield from the acid.

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