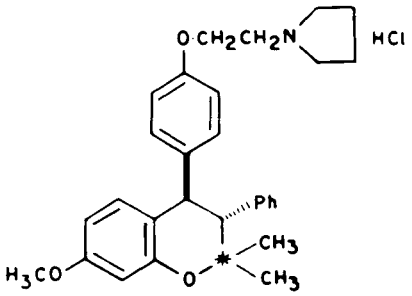
Synthesis of trans-2,2-Dimethyl-3-phenyl-4-(p-β-pyrrolidinoethoxy)phenyl-7-methoxy-[2-^{14}C]chroman*

SUMMARY

The synthesis of trans-2,2-dimethyl-3-phenyl-4-(p-β-pyrrolidinoethoxy) phenyl-7-methoxy-[2-^{14}C]chroman (Centchroman), a post-coital antifertility agent from [1-^{14}C]phenylacetic acid is reported.

INTRODUCTION

In a search for post-coital pregnancy inhibiting agents, trans-2,2-dimethyl-3-phenyl-4-(p-β-pyrrolidinoethoxy)phenyl-7-methoxychroman hydrochloride, (Centchroman)[1,2], was found to possess promising activity with a very favourable therapeutic index. This compound is presently under phase II clinical studies. As a part of the clinical studies, labelled Centchroman was required for pharmacokinetic and metabolism studies. This communication describes the preparation of [^{14}C]Centchroman (I).



I

The synthetic route for the preparation of [^{14}C]Centchroman is essentially the same as described earlier for the unlabelled compound[3].

EXPERIMENTAL

Characterisation and purification of the products were by TLC (silica gel) and high performance liquid chromatography (HPLC) comparison with authentic

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samples. HPLC was run on Waters Associates Liquid Chromatogram Model 440 using μ Porasil column. PMR was carried out in $CDCl_3$ using Perkin Elmer R-32 (90 MHz) instrument. Radioactivity was measured by liquid scintillation using a Packard Tricarb model 3330 spectrophotometer. [1-^{14}C]Phenylacetic acid was purchased from Bhabha Atomic Research Centre, Bombay, India.

3-Phenyl-4-(p-acetoxy)phenyl-7-methoxy-[2-^{14}C]coumarin (1)

A mixture of 2,4'-dihydroxy-4-methoxybenzophenone[4] (220mg, 0.9mmol), [1-^{14}C]phenylacetic acid (122.2mg, 0.9mmol; spec. act. 11.3mCi/mmol) acetic anhydride (0.4ml) and triethylamine (0.16ml) was refluxed under anhydrous condition for 8 hr. The reaction mixture was poured onto crushed ice (15g), the separated product was collected by filtration and recrystallised from benzene/hexane:yield: 304mg (spec. act. 6.5mCi/mmol).

2,2-Dimethyl-3-phenyl-4-(p-hydroxy)phenyl-7-methoxy-[2-^{14}C]- chromene (2)

A solution of 1 (300mg, 0.78mmol) and inactive 1 (300mg, 0.78mmol) in tetrahydrofuran (6ml) was gradually added to MeMgI [from 288mg (11.85mmol) of Mg and 2.2g (15.72mmol) of CH_3I] in dry ether (5ml). The mixture was heated under reflux for 4 hr. and poured into ice-water (25ml) containing NH_4Cl (1g) and 2 drops of HCl. The reaction mixture was extracted with ethyl acetate, the extract was washed with water to neutrality and dried (Na_2SO_4). The solvent was distilled off, the residue chromatographed over silica gel using benzene as eluant, and the product obtained crystallised from benzene/hexane:yield:350mg (spec. act. 3.29mCi/mmol).

cis-2,2-Dimethyl-3-phenyl-4-(p-hydroxy)phenyl-7-methoxy-[2-^{14}C]chroman (3)

Hydrogenation of 2 (250mg) in THF (150ml) in presence of Pd/C catalyst (0.3g of dry 5% Pd/C and 0.6g of 5% Pd/C wet (w/w 50/50) at 60°C and 100 psi of pressure gave 190mg of 3 (spec. act. 3.12mCi/mmol).

cis-2,2-Dimethyl-3-phenyl-4-(p-β-pyrrolidinoethoxy)phenyl-7-methoxy-[2-^{14}C]chroman (4)

N-(2-chloroethyl)pyrrolidinium chloride (115mg, 0.68mmol) was added to a warm solution of 3 (180mg, 0.5mmol) in NaOH (70mg, 1.75mmol), water (0.3ml), 2-propanol (1.1ml) and the mixture was heated at 50°C for 4 hr under vigorous stirring. The reaction mixture was cooled, diluted with cold water (2ml) and the solid which separated was collected by filtration, washed successively with 30% 2-propanol (0.1ml) and cold water (1ml), dried under vacuum and recrystallised from benzene-hexane; yield 200mg (spec. act. 2.95mCi/mmol).

trans-2,2-Dimethyl-3-phenyl-4-(p-β-pyrrolidinoethoxy)phenyl-7-methoxy-[2-^{14}C]chroman HCl (5)

n-BuLi in hexane (1.5ml of 19.85%) was added to a suspension of 4 (190mg, 0.415mmol) in anhydrous Me_2SO (4ml) at room temperature under nitrogen atmosphere and good stirring. The resulting red solution was stirred for a further 3 hr. and then decomposed with cold water (2ml). The reaction mixture was then poured into ice-water mixture (25ml) and extracted with ether. The organic layer was washed well with water and dried (Na_2SO_4), the solvent distilled off, and the residue converted into the hydrochloride and crystallised from ethanol-ether; yield 130mg (spec. act. 2.93mCi/mmol).

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