Synthesis of N-[4-[2-(2,4-Dimethylphenoxy)phenyl]-2-thiazolyl]-hexahydro-2-pyrimidinimine, [^{14}C]BAY w 6341

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Summary

The title compound [^{14}C]BAY w 6341 was synthesized as part of a 4-step sequence. Starting from diethyl [2-^{14}C]malonate the final product (8) was obtained with a specific activity of 1.2 GBq/mmol (32.9 mCi/mmol) and a radiochemical purity of > 99 % in an overall yield of 19 %.

Key words

N-[4-[2-(2,4-Dimethylphenoxy)phenyl]-2-thiazolyl]-hexahydro-2-pyrimidinimine, [^{14}C]BAY w 6341

Introduction

N-[4-[2-(2,4-Dimethylphenoxy)phenyl]-2-thiazolyl]-hexahydro-2-pyrimidinimine, [^{14}C]BAY w 6341, 8) is a broadspectrum antimycotikum with supplementary action against grampositive bacteria. For studies of pharmacokinetics and biotransformation the carbon-14 labelled substance (8) was necessary. This paper describes the synthesis and the conditions suitable for labelling and for purification of [^{14}C]BAY w 6341.

Results and discussion

Starting from commercially available diethyl [2-^{14}C]malonate (2) (see scheme 1) and 2-bromobenzoyl chloride (1) labelled 2-bromoacetophenone (3) was prepared by condensation, saponification and decarboxylation in a total yield of 73 %. The formation of the diphenyl ether

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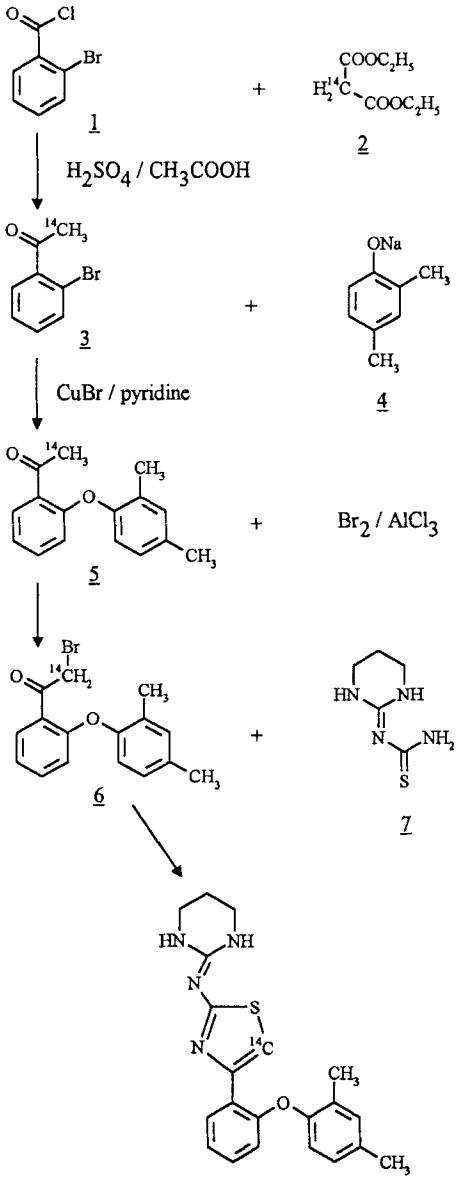
Scheme 1



[^{14}C]BAY w 6341 , 8

(5) was realized by reaction of (3) with sodium 2,4-dimethyl-phenolate (4) in the presence of copper(I) bromide in pyridine. A yield of 46 % was obtained although the non-radioactive preexperiments showed a yield of 66 %. The reason for this difference is not clear. For the bromination of the acetophenone (5) a literature procedure was used [1]. The main problem was to prevent the overbromination of the acetophenone (5). By optimizing the reaction

conditions e.g. solvent, catalyst and the rate of the addition of bromine, the monobromo compound (6) was obtained in a yield of 74 %. The best bromination conditions were acetonitrile as solvent, aluminium chloride as catalyst and slow addition of a solution of bromine and acetonitrile over 135 minutes.

The condensation of the phenacyl bromide (6) with 2-(N-thiocarbamoylimino)-hexahydro-pyrimidine (7) provided the final product (8) in a good yield of 84 %. 860 Mg [^{14}C]BAY w 6341 (8) was synthesized, equating to an overall radiochemical yield of 19 %.

Experimental

1. 2-Bromo[methyl-^{14}C]acetophenone (3)

To a mixture of 1.1 g (12.0 mmol) magnesium chloride in 7 ml dry acetonitrile a solution of 1.9 g (12.0 mmol) diethyl [2-^{14}C]malonate with a specific activity of 1307.3 MBq/mmol (35.3 mCi/mmol) purchased from NEN, Boston, USA, in 5 ml acetonitrile was added dropwise over 30 minutes at a temperature of 0 °C under a nitrogen stream. The radiochemical purity of the diethyl [2-^{14}C]malonate was only 84.5 % as determined by GC. The dropping funnel was rinsed with 3 ml dry acetonitrile and the reaction mixture was stirred for a further 20 minutes. 3.3 Ml (24.0 mmol) of triethylamine was added. After stirring for 30 minutes at 0 °C 2.9 g (13.2 mmol) 2-bromobenzoyl chloride dissolved in 3 ml dry acetonitrile were introduced into the reaction mixture over the course of 30 minutes. Stirring was continued for 2 hours at a temperature of 0 °C and 15 hours at room temperature. 20 Ml 2N hydrochloric acid was added whilst cooling with ice. The precipitated diethyl 2-bromobenzoyl[2-^{14}C]malonate was extracted three times with 10 ml diethyl ether. The extracts were combined and dried over anhydrous sodium sulfate. The solvent was distilled off under vacuum.

The residue was dissolved in a mixture of 18 ml glacial acetic acid and 12 ml 30 % sulfuric acid and refluxed for 7 hours. After addition of 20 ml water an oily residue separated overnight. The mixture was extracted three times with 20 ml hexane. The combined organic phases were washed with a solution of sodium hydrogencarbonate, dried over sodium sulfate and evaporated to dryness. Yield of (3): 1.7 g (8.8 mmol) = 73 %. The chemical and radiochemical purity was > 97 % as determined by GC.

2. 2-(2,4-Dimethylphenoxy)[methyl-^{14}C]acetophenone (5)

To a mixture of 1.7 g (8.8 mmol) (3) and 144 mg (1.0 mmol) copper(I) bromide 1.7 g (12.0 mmol) sodium 2,4-dimethylphenolate dissolved in 4 ml pyridine was added under a stream of nitrogen. After refluxing for 7 hours 5 ml pyridine and 20 ml water were added with intensive stirring. The solution was extracted three times with 17 ml hexane. The combined extracts were washed with 10 ml 2N hydrochloric acid, 10 ml water, dried over anhydrous sodium sulfate and evaporated to dryness.

The crude material was purified in two portions by chromatography under the following conditions:

column: Labor® RP8 Type B (Merck, FRG)
flow rate: 5.0 ml/minute
solvent: acetonitrile/water 3:1
detection: UV 254 nm

The fractions containing sufficiently pure (5) were combined, concentrated in the vacuum and exhaustively extracted with dichloromethane. The extracts were combined, dried over anhydrous sodium sulfate and evaporated to dryness. Yield of (5): 977 mg (4.1 mmol) = 46 %. The chemical and radiochemical purity was > 93 % as determined by GC.

3. *2-(2,4-Dimethylphenoxy)-1-bromo-[bromomethyl-^{14}C]acetophenone (6)*

To a mixture of 977 mg (4.1 mmol) (5) dissolved in 7 ml acetonitrile and 15 mg (0.1 mmol) anhydrous aluminium chloride a solution of 672 mg (4.2 mmol) bromine in 3.5 ml acetonitrile was added over the course of 135 minutes at room temperature. The reaction solution was stirred for a further 10 minutes. 3 Ml concentrated sodium hydrogensulfite solution and 17 ml water were added and the solution vigorously stirred. After extraction with hexane (4 x 11 ml) the combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated to dryness.

The residue was dissolved in 5 ml actonitrile and purified in two portions by chromatography using the following conditions:

column: Labor® RP8 Type B (Merck, FRG)
flow rate: 5.0 ml/minute
solvent: acetonitrile/water 7:3
detection: UV 254 nm

The fractions containing sufficiently pure (6) were combined, concentrated in the vacuum to remove the acetonitrile and extracted four times with 10 ml hexane. The combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness. Yield of (6): 959 mg (3.0 mmol) = 74 %. The chemical and radiochemical purity was > 97 % as determined by GC.

4. *Synthesis of N-[4-[2-(2,4-Dimethylphenoxy)phenyl]-2-thiazolyl]-hexahydro-2-pyrimidinimine, [^{14}C]BAY w 6341 (8)*

498 Mg (3.2 mmol) 2-(N-thiocarbamoylimino)-hexahydropyrimidine (7) and 959 mg (3.0 mmol) (6) dissolved in 9 ml acetone were refluxed for 2.5 hours. 8 Ml acetone and 15 ml diethyl ether were added to the precipitate formed overnight and the mixture vigorously stirred. The precipitate was filtered off and washed three times with 15 ml diethyl ether. The

residue was dried in a nitrogen stream and dissolved in a mixture of 18 ml methanol and 12 ml water at a temperature of 60 °C. After addition of 4 ml 1M sodium hydroxide solution the precipitate was filtered off, washed with a mixture of methanol/water 1:1 and dried over blue gel (dessiccant) in the vacuum. Yield of (8): 860 mg (2.3 mmol) = 75 %. The total radioactivity was found to be 2.7 GBq (73.4 mCi) corresponding to a specific activity of 1.2 GBq/mmol (32 mCi/mmol).
In total, starting with 15.7 GBq (424 mCi) diethyl [2-^{14}C]malonate (2), a radiochemical yield of 19 % was obtained.

5. *Determination of the chemical and radiochemical purity*

[^{14}C]BAY w 6341 (8) was analyzed by HPLC using the known reference standard of BAY w 6341, and a radioactivity and UV detector with the following conditions:

column: Nucleosil® C 18 AB, 5 µm, 250 x 4.6 mm (Macherey & Nagel, FRG)
flow rate: 1.5 ml/minute
solvent: A: 1.0 % perchloric acid, B: acetonitrile
gradient: 0 min 30 % B
25 min 80 % B
30 min 80 % B
detection: UV 270 nm
radioactivity: Ramona® 5 (Raytest GmbH, FRG)

Under these conditions the chemical and radiochemical purity was > 99 %.

In addition the radiochemical purity was determined by TLC under the following conditions:
Silica gel plate F 254 (Merck, FRG)
solvent: toluene/methanol / 25 % ammonia 45:15:1
R_F for (8): 0.54
The radioactivity was determined by a scanner (Berthold, FRG). The radiochemical purity of > 99 % was confirmed by this method.

References

[1] R.M. Cowper and L.H. Davidson, Org. Synth. 19, 24 (1939)