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NOTE

Synthesis of 2E, 4E, 8E - Nonatetraenoic acid-3, 7-dimethyl-1-[^{14}C]-9-(2', 6', 6'-trimethylcyclohex-1-enyl)-4-(N-acetamino) phenylester

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SUMMARY

The title compound 4-(N-acetylamino)phenyl-1-[^{14}C] retinoate (3) was synthesized by a 2-step sequence. Carboxyl-[^{14}C] vitamin A (1) was treated with ethylchloroformate to form the mixed anhydride (2). Treatment with acetamidophenol and heating with a catalytical amount of 4-dimethylaminopyridine produced 4-(N-acetylamino)phenyl-1-[^{14}C] retinoate (3) with a specific activity of 23.4 μCi/mg and a radiochemical purity of 97.2% in an overall yield of 42%.

KEY WORDS

2E, 4E, 8E-Nonatetraenoic acid-3, 7-dimethyl-1-[^{14}C]-9(2', 6', 6'-trimethyl-cyclohex-1-enyl)-4-(N-acetamino) phenylester, 4-(N-acetyl-amino)phenyl-1-[^{14}C] retinoate, retinoids.

INTRODUCTION

4-(N-acetylamino)phenyl retinoate is a novel retinoic acid derivative with significant efficacy in several retinoid responsive animal models. When 4-(N-acetylamino)phenyl retinoate is applied topically, it exhibits lower local irritation potential than tretinoin. It also shows

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little or no systemic hypervitaminosis, a related side effect in preclinical studies. Currently, 4-(N-acetylamino)phenyl retinoate is under development for the treatment of acne, psoriasis and photoaging via a topical application.

To investigate both metabolism and the extent of systemic absorption of 4-(N-acetylamino)phenyl retinoate after dermal application, a [^{14}C] labeled compound was needed. This report describes the details of the synthetic procedures of 4-(N-acetylamino)phenyl-1-[^{14}C] retinoate.

EXPERIMENTAL

[^{14}C] Carboxyl vitamin A was purchased from Amersham Corp. All other reagents were ACS grade or the highest quality commercially obtainable. NMR spectra were obtained on a Bruker Spectrospin 360 MHz instrument, using tetramethylsilane as an internal standard. All compounds gave NMR spectra consistent with their structure. Radioactivity was measured by a Beckman LS9000 liquid scintillator. TLC Plates: Silica gel, 250μ GF (Analtech). Method: Mobile phase, as indicated; visualization, UV 254 nm.

2E, 4E, 8E-Nonatetraenoic acid-3, 7-dimethyl-1-[^{14}C]-9-(2', 6', 6'-trimethylcyclohex-1-enyl)ethoxycarbonyl anhydride (2).

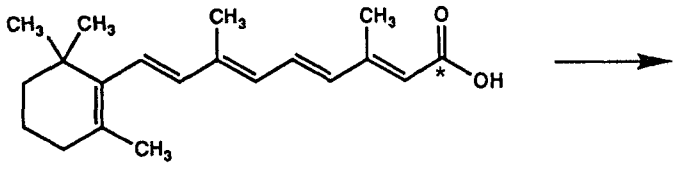
The reaction was run with artificial light. [^{14}C]-Carboxyl vitamin A (218 mg/0.73 mmole, 10 mCi, 13.7 mCi/mmole) and retinoic acid (73 mg, 0.26 mmole) were dissolved in anhydrous tetrahydrofuran (7.25 ml) and treated at room temperature with triethylamine (145 μl, 1.089 mmole). The solution was stirred for 5 minutes and ethylchloroformate (100 μl, 1.089 mmole) in tetrahydrofuran (1.7 ml) was added dropwise with stirring. After stirring for 2 hours at room temperature TLC (hexane 3-ether 10) showed one spot at Rf=0.8 (retinoic acid Rf=0.5). Hexane (10ml) was added and the triethylamine hydrochloride was collected by filtration. The filtrate was concentrated under nitrogen and dried *in vacuo* to a yellow oil (2). It was used without purification.

2E, 4E, 8E, Nonatetraenoic acid-3, 7-dimethyl-1-[^{14}C]-9(2', 6', 6'-trimethylcyclohex-1-enyl)-4-(N-acetamino)phenylester (3).

The reaction was run with artifical light. The mixed anhydride (2) was dissolved in acetonitrile (7.25 ml) and acetamidophenol (131.8 mg, 0.99 mmole) was added in one portion. The mixture was warmed to 30°C to

obtain a solution. Triethylamine (145 µl, 1.087 mmole) was added followed by 4-dimethylaminopyridine (9 mg as a catalyst). The reaction became exothermic and carbon dioxide evolved. It was stirred for 1 hour at 50°C (a yellow solid precipitated after 5 minutes) and after cooling to room temperature the yellow solid was removed by filtration, washed with acetonitrile (2 ml) and air dried. This was dissolved in boiling 100% ethanol (35 ml) filtered and the filtrate slowly cooled to room temperature then in an ice bath. The tan crystals were removed by filtration, washed with ethanol (1 ml) and dried in vacuo for 2 hours. This produced 183 mg of (3) having a radiochemical purity of 97.5% and specific activity of 23.4 µCi/mg.

SYNTHETIC PATHWAY



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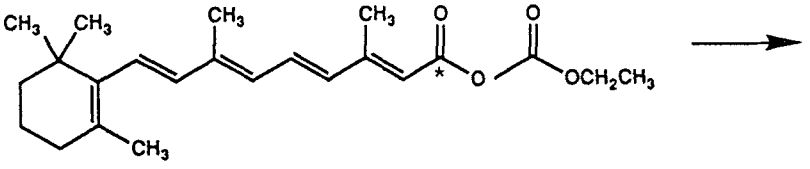

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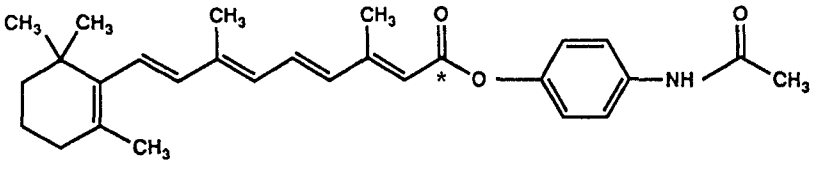

3

* = Position of radiolabel

RESULTS AND DISCUSSION

Synthesis of 4-(N-acetylamino)phenyl-1-[^{14}C] retinoate was achieved by preparing the carbonic anhydride of retinoic acid by treating carboxyl-[^{14}C] vitamin A with ethylchloroformate and triethylamine. After removing the triethylamine hydrochloride, the carbonic anhydride (2) was used without purification. This was then reacted with acetamidophenol and heated with a catalytical amount of 4-dimethylaminopyridine yielding crude 4-(N-acetylamino)phenyl-1-[^{14}C] retinoate (3). Purification by crystallization with boiling ethanol produced (3) as a crystalline solid having a radiochemical purity of 97.5% and a specific activity of 23.4 μCi/mg in an overall yield of 42%. The experimental conditions were optimized using nonradiolabeled materials.

REFERENCES

1. United States patent, Joev, et. al., Patent # 4,595,696, June 17, 1986.