SYNTHESIS OF CARBON-14 LABELLED CD 271 (6-[3-(1-ADAMANTYL)-4-METHOXYPHENYL]-2-NAPHTHOIC ACID) A POTENTIAL NEW AGENT FOR DERMATOLOGY

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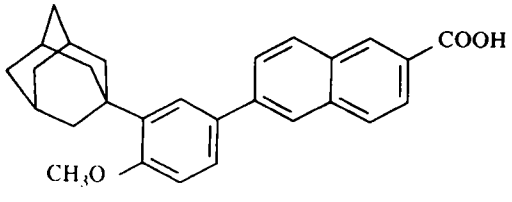
SUMMARY

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid (**1**), a promising new compound for the treatment of disorders of keratinization, has been synthesized in [^{14}C]-labelled form from barium [^{14}C]-carbonate via labelled benzene. Benzene-[U-^{14}C] was converted to 4-bromo-methoxybenzene-[phenyl-U-^{14}C] in six steps. Introduction of the adamantyl ring was carried out using 1-acetoxyadamantane under acid catalysis. 2-(1-Adamantyl)-4-bromo-methoxybenzene-[phenyl-U-^{14}C] (**2**) was converted to a zincate and coupled with methyl 6-bromo-2-naphthoate using a nickel catalyst. The product of the aryl coupling reaction (**3**) was then saponified to give 6-[3-(1-adamantyl)-4-methoxyphenyl-[phenyl-U-^{14}C]]-2-naphthoic acid.

Keywords : 4-bromo-1-methoxybenzene-[phenyl-U-^{14}C], biaryl synthesis, adamantylation, keratinization.



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(CD 271)

INTRODUCTION

Deregulation of the mechanisms of cellular proliferation is involved in many of the most frequently encountered diseases of the skin. Another feature of these diseases,

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which include acne and psoriasis, is abnormal maturation of the keratinocyte, the cell which constitutes the bulk of the epidermis. In normal skin, the keratinocyte migrates from the basal layer to the outermost layer (stratum corneum) undergoing a series of cellular differentiation steps which convert it into a terminally differentiated, flat, anucleated, keratin-containing, corneocyte. In acne and psoriasis, this process is interrupted, leading to incomplete keratinization. Retinoic acid, a natural metabolite of Vitamin A, occurs in most tissues of the body, including skin, where it plays a role in controlling protein synthesis, cell turnover and cellular differentiation. These effects of retinoic acid have been successfully exploited for the treatment of acne and may be keys to the treatment of other disorders of keratinization.

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid (CD 271) a product of our search for chemically stable structures possessing the essential biological activities of retinoic acid (1), is a potent inducer of cellular differentiation, is well tolerated after topical application and, as demonstrated in clinical studies (2), provides an effective topical treatment for acne. [^{14}C]-Labelled CD 271 was required for skin penetration and metabolism studies.

RESULTS AND DISCUSSION

Since aromatic carboxyl and methoxyl groups are often points of early metabolic attack, labelling of the benzene ring of 1 was judged to be more appropriate for our needs. The synthetic route, shown in Scheme 1, involves formation of a biaryl system as the key step, and in this way resembles the first synthesis of (unlabelled) CD 271 (3).

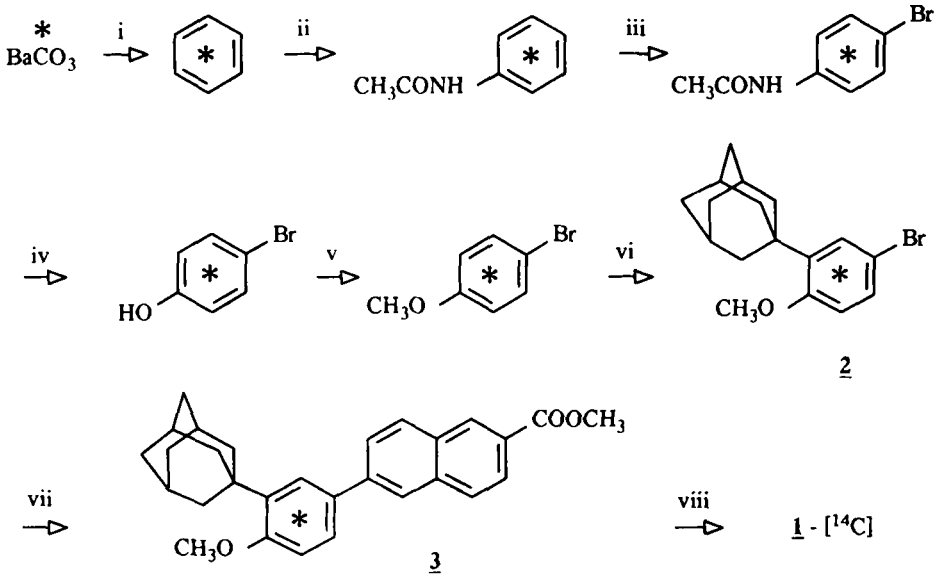
[^{14}C]-Labelled benzene was prepared from [^{14}C]-$BaCO_3$ (4) with a radiochemical yield of 77%. Nitration was effected in 91% yield using sodium nitrate in trifluoroacetic acid (5) and the resulting nitrobenzene was transformed directly to acetanilide-[phenyl-U-^{14}C] (90%) by hydrogenation in acetic anhydride as solvent (6). In contrast to the bromination of [^{14}C]-phenol (CS_2, <5°) which was attempted in exploratory work on an alternative route, bromination of [^{14}C]-labelled acetanilide was a clean reaction, yielding 96% of the *para* isomer.

In preliminary experiments thermolysis of (unlabelled) 4-bromobenzenediazonium sulfate in aqueous solution gave poor (<50%) yields of 4-bromophenol. A method using the fluoroborate salt in the presence of a high concentration of Cu^{2+} (7) was more promising, and indeed when applied to [^{14}C]-4-bromoaniline, gave [^{14}C]-4-bromophenol in 80% yield.

Selective introduction of the 1-adamantyl group at the C(2) position of 4-bromomethoxybenzene-[phenyl-U-^{14}C] was achieved using 1-acetoxyadamantane under acid catalysis in hexane (8). These conditions, established using unlabelled material, gave a higher yield than more conventional methods (9) and obviated the formation of di- or triaryladamantanes.

2-(1-Adamantyl)-4-bromomethoxybenzene-[phenyl-U-^{14}C] (2) was reacted with 2 equivalents of t-butyllithium and then zinc chloride; the resulting zincate was coupled with methyl 6-bromonaphthoate using bis-diphenylphosphinoethane nickel chelate as catalyst (10) to give the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl-[phenyl-U-^{14}C]]-2-naphthoic acid (3). Saponification of (3) provided the free acid form of CD 271-[phenyl-U-^{14}C] (1) in 6% overall radiochemical yield from [^{14}C]-$BaCO_3$.

Scheme 1



(i) a) Ca,Δ b) H_2O c) *Perlkatalysator Neu*, 200°C

(ii) a) $NaNO_3$ / CF_3COOH b) H_2 / Pd-C 10% / Ac_2O

(iii) Br_2 / CH_3COOH

(iv) a) H^+ b) $NaNO_2$ / H^+ c) HBF_4 / $Cu(NO_3)_2.3\ H_2O$ / Cu_2O

(v) $(CH_3)_2SO_4$ / OH^-

(vi) 1-Acetoxyadamantane / H^+ / hexane

(vii) a) t-BuLi / THF,-78°C

b) $ZnCl_2$

c) Methyl 6-bromo-2-naphthoate

d) $NiCl_2.Ph_2PCH_2CH_2PPh_2$

(viii) a) MeOH / OH^- b) HCl

EXPERIMENTAL

Instrumentation

Radioactivity determinations were carried out by liquid scintillation using a Beckman LS 2800 instrument with Picofluor 30 (Packard) as the scintillation cocktail. Radiochemical purities were determined by TLC on Merck 60F_{254} silica gel plates using a Berthold Automatic TLC Linear Analyser, and by HPLC on normal phase (DuPont Zorbax SIL) or reverse phase (DuPont Zorbax ODS) columns using an LDC Milton Roy instrument equipped with a Berthold LB 5034 splitter/mixer and a Berthold LB 503 monitor for liquid scintillation detection. Data acquisition and treatment were effected by a Berthold LB 510 system. UV spectra were recorded on a Beckman 25 spectrophotometer. Mass spectra were obtained using a Nermag R10-10C.

Chemicals

Barium [^{14}C]-carbonate (specific activity 59 mCi/mmole) was obtained from the CEA, Saclay, France. All solvents were dried before use; tetrahydrofuran was distilled from sodium-benzophenone ketyl. Commercial t-butyllithium solutions were titrated against 2-butanol using 1,10-phenanthroline as indicator. Reaction mixtures were worked up by solvent extraction; solutions of reaction products were dried over anhydrous magnesium sulfate. Silica gel (40-63 μm) was used for column chromatography (CC).

Benzene-[U-^{14}C]

An intimate mixture of $BaCO_3$ (11.7 g, 59 mmol), [^{14}C]-$BaCO_3$ (3.38 g, 17 mmol, 1 Ci) and granular (0.5-0.8 mm) calcium (30.6 g, 765 mmol) was placed in Pyrex tubes and the mixture in each tube was covered with a 5 mm layer of calcium. The tubes were purged with argon and then heated to incandescence with an oxy-butane torch. The calcium carbide thus formed was hydrolysed in water (250 ml) and the exit gases were passed through a cold water condenser and phosphorus pentoxide drying tube to a vacuum manifold. The labelled acetylene was condensed in a double glass coil cooled in liquid nitrogen.

On the same manifold, *Perlkatalysator Neu* (Kali Chemie AG, Hanover) was placed under vacuum (10^{-5} mm) and heated to 300°C for 12 hours, then cooled to room temperature and allowed to absorb the [$^{14}C_2$]-acetylene. The catalyst-bound acetylene was then heated at 200°C and evolved gases were drawn off on a vacuum line through a dry ice / acetone cooled double glass coil (to condense the evolved benzene-[U-^{14}C]) and then through a liquid nitrogen cooled coil to trap unreacted acetylene. After heating for 4 hours, 775 mCi of [^{14}C]-labelled benzene was obtained.

Nitrobenzene-[U-^{14}C]

Labelled benzene was introduced into a stirred suspension of sodium nitrate (0.76 g, 8.9 mmol) in trifluoroacetic acid (20 ml). After 16 hours at ambient temperature, the bulk of the trifluoroacetic acid was removed under vacuum at about 25°C and the residue was neutralized with 2N sodium hydroxide. Nitrobenzene-[U-^{14}C] (705 mCi) was obtained by extraction with diethyl ether. TLC: 40:60 acetone:hexane; rf 0.85.

Acetanilide-[phenyl-U-^{14}C]

Labelled nitrobenzene (580mCi) was dissolved in acetic anhydride (20 ml) and hydrogenated at atmospheric pressure using 10% Pd-C (100 mg) as catalyst. After purging with argon, the catalyst was removed by filtration. The filtrate was evaporated to dryness at about 25°C to give fine white crystals of acetanilide-[phenyl-U-^{14}C] (520 mCi). TLC: 40:60 hexane:acetone; rf 0.45.

4-Bromoacetanilide-[phenyl-U-^{14}C]

A solution of bromine (385 µl, 15 mmol) in acetic acid (2 ml) was added to an acetic acid (3 ml) solution of labelled acetanilide (520 mCi). Standard workup gave pure 4-bromoacetanilide-[phenyl-U-^{14}C] (502 mCi). TLC: 40:60 acetone:hexane; rf 0.5.

4-Bromophenol-[U-^{14}C]

Labelled 4-bromoacetanilide (502 mCi) in 6N sulfuric acid (25 ml) was heated at reflux for 6 hours. The solution was then taken to dryness and the residue dissolved in 2N sulfuric acid (20 ml) at 0°C. Sodium nitrite (0.52 g, 7.5 mmol) in water (3 ml) was added, followed 15 min. later with 8N tetrafluoroboric acid (1 ml). The suspension of 4-bromophenyldiazonium tetrafluoroborate obtained was poured into a solution of $Cu(NO_3)_2.3H_2O$ (120 g) in water (500 ml) containing Cu_2O (0.91 g, 6.4 mmol). Workup using dichloromethane for extraction and as eluant for CC gave pure [^{14}C]-4-bromophenol (401 mCi). TLC: dichloromethane; rf 0.5.

4-Bromo-1-methoxybenzene-[phenyl-U-^{14}C]

Labelled bromophenol (5.1 mmol, 401 mCi) was reacted with dimethylsulfate (640 µl, 6.8 mmol) in 2N sodium hydroxide (3.4 ml) at reflux for 45 min. Ether extraction followed by CC, using dichloromethane as eluent, of the evaporated residue gave pure 4-bromo-1-methoxybenzene-[phenyl-U-^{14}C] (330 mCi). TLC: hexane; rf 0.37.

2-(1-Adamantyl)-4-bromo-1-methoxybenzene-[phenyl-U-^{14}C] (2)

A solution of labelled 4-bromo-1-methoxybenzene (4.2 mmol, 330 mCi), 1-acetoxyadamantane (0.875 g, 4.5 mmol) and sulfuric acid (120 µl) in hexane (5 ml) was stirred at room temperature for 5 hours; additional sulfuric acid (200 µl) was added and stirring was continued for 16 hours. Water (20 ml) was added and the product was extracted with dichloromethane. After purification by CC (hexane), 2-(1-adamantyl)-4-bromo-methoxybenzene-[phenyl-U-^{14}C] (287 mCi) was obtained. TLC: hexane; rf 0.6.

Methyl 6-[3-(1-adamantyl)-4-methoxyphenyl-[phenyl-U-^{14}C]]-2-naphthoate (3)

Compound 2 (1.2 mmol, 100 mCi) dissolved in tetrahydrofuran (2 ml) was added to 1.7 M t-butyllithium (1.4 ml, 2.4 mmol) previously cooled to -78°C. After 15 minutes, anhydrous zinc chloride (185 mg, 1.3 mmol) was added. The temperature of the reaction mixture was then raised to 0°C and then powdered methyl 6-bromo-2-naphthoate (204 mg, 0.77 mmol) was added, followed by bis-diphenylphosphinoethane•$NiCl_2$ (11 mg). The solution was allowed to come to ambient temperature. After 1 hour, water (50 ml) was added. The crude product obtained by extraction with dichloromethane was purified by CC (1:1 dichloromethane:hexane) to give 3 (61 mCi). TLC: 1:1 dichloromethane:hexane ; rf0.6.

6-[3-(1-Adamantyl)-4-methoxyphenyl-[phenyl-U-^{14}C]]-2-naphthoic acid (1)
The methyl ester 3 (0.74 mmol, 61 mCi) was saponified by heating at reflux for 2 hours in a solution of methanol (30 ml), tetrahydrofuran (5 ml) and 5N sodium hydroxide (4.5 ml). Acidification gave pure 1 (55 mCi) which co-chromatographed with authentic material. TLC: diethyl ether; rf 0.65. HPLC: Spherisorb ODS2, 5μ; 430:360:210:0.2 acetonitrile:tetrahydrofuran:water:trifluoroacetic acid; 1.5 ml/min.; rt 6 min. The structure was confirmed by UV and mass spectroscopy. The specific activity of 1, as determined by UV, was 80 mCi/mmol.

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