A Convenient Synthesis of ^{14}C-Anthralin

Eine einfache Synthese für ^{14}C-Anthralin

Hsu-Shan Huang[+], Klaus K. Mayer, Klaus Müller, and Wolfgang Wiegrebe

Institut für Pharmazie, Pharmazeutische Chemie I, Universität Regensburg, D-93040 Regensburg, Germany

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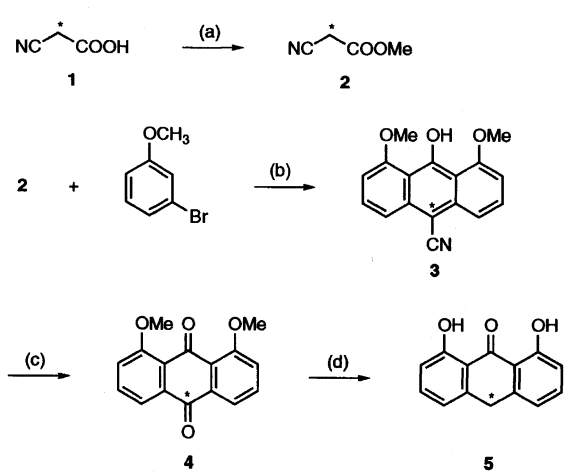
Anthralin [1,8-dihydroxy-9(10*H*)-anthracenone] is among the most widely used drugs in the topical treatment of psoriasis[1]. However, not much is known concerning its mode of action at the molecular level, although a variety of cellular targets have been implicated both in the main and side effects of anthralin[2]. In particular, the interaction of anthralin with proteins has long been recognized to occur[3,4] and there has been renewed interest in this topic, mostly directed toward the investigation whether enzyme inhibition by anthralin is related to oxygen radical-mediated damage of proteins[5]. In order to gain a more profound understanding of the interaction between this drug and cellular targets, anthralin labelled with a non-exchangeable radioisotope in a suitable position was highly desirable. Furthermore, this labelled compound might serve as a useful starting material for the synthesis of analogues labelled in the anthrone nucleus. Since structural modification of anthralin has provided compounds with improved biological activity[6,7], labelled compounds are required for studies on skin penetration and metabolism of these future drugs.

Although routes to ^{14}C-anthralin have already been described[8,9], each of these methods suffers from too many synthetic steps, or the use of hazardous ^{14}C-sources[1]. In this paper, we describe a short and efficient synthesis of 1,8-dihydroxy-[10-^{14}C]-9(10*H*)-anthracenone.



Scheme 1: Synthesis of ^{14}C-anthralin. Reagents: (a) CH_2N_2, ether; (b) LDA, THF; (c) 10% NaOH, 30% H_2O_2, ethanol; (d) $SnCl_2$, HCl, glacial acetic acid.

Chemistry

Scheme 1 shows the pathway for the synthesis of ^{14}C-anthralin, which is based on a procedure for the preparation of anthracenediones described by *Bhawal et al.*[11]. Accordingly, the commercially available ^{14}C-source [2-^{14}C]-cyanoacetic acid (**1**) was esterified with diazomethane to give the required methyl [2-^{14}C]-cyanoacetate (**2**). Ester **2**, upon reaction with the aryne obtained from 3-bromoanisole and lithium diisopropylamide (LDA), gave [10-^{14}C]-10-cyano-9-hydroxy-1,8-dimethoxyanthracene (**3**) directly. - The mechanism of this reaction has been suggested to consist of two pathways: a non-concerted [2 + 2] cycloaddition involving a tandem-addition rearrangement, and an aryne [4 + 2] cycloaddition[11]. - Oxidation of **3** with hydrogen peroxide in alkaline solution[11] gave [10-^{14}C]-1,8-dimethoxy-9,10-anthracenedione (**4**) in 80% yield. Final reduction of **4** with $SnCl_2$ in acetic acid/hydrochloric acid proceeded with concomitant ether cleavage and cleanly produced [10-^{14}C]-anthralin (**5**) in 86% yield.

Experimental Part

Melting points: Büchi 510 melting point apparatus, uncorrected.- EIMS: Varian MAT 311A (70 eV).- Analytical TLC: EM Science precoated TLC plates with silica gel F-254.- Tetrahydrofuran (THF) and diisopropylamine were distilled from $LiAlH_4$ and $CaCl_2$, respectively. All other organic reactants were distilled before use.- [2-^{14}C]-cyanoacetic acid: American Radiolabeled Chemicals Inc.- *n*-Butyllithium (*n*-BuLi) and Diazald: Aldrich Chemical Co.- 3-Bromanisole: Fluka Chemie AG.- All reactions were carried out in flame-dried flasks under N_2. Radioactivity was measured using LSC (Liquid Scintillation Counter) "Quantulus" 1220 (LKB Wallac).

Methyl [2-^{14}C]-cyanoacetate (**2**)

In a glove box (Atmos Bag, Aldrich) filled with N_2, [2-^{14}C]-cyanocetic acid (55 mCi/mmol ≈ 23.9 GBq/g) was dissolved in absol. ether and mixed with unlabelled cyanoacetic acid (0.85 g, 10 mmol) in 10 ml of absol. ether. The solution was cooled in an ice bath and a distilled ethereal solution of diazomethane was added in small portions. After stirring for 1 h, the mixture was dried over Na_2SO_4, distilled, and afforded 0.9 g (91%) of **2**, sufficiently pure for the next step.

[10-^{14}C]-10-Cyano-9-hydroxy-1,8-dimethoxyanthracene (**3**)

To a cooled (-78°C) solution of **2** (0.9 g, 9.1 mmol) in 10 ml of absol. THF, a cold solution of LDA (15 mmol in 30 ml in THF) was added over a period of 20 min, then the solution was stirred at -78°C for 15 min. Bromoanisole (3.8 g, 20 mmol) in 50 ml of absol. THF was added rapidly, the solution was warmed to -40°C, and a cooled (-40°C) solution of LDA (30 mmol in 50 ml of absol. THF) was added slowly (ca. 30 min). The solution was stirred for an additional 10 min, then allowed to warm to room temp.,

[+] On leave from the Institute of Pharmacy, National Defense Medical Center, Taipei, Taiwan, R.O.C.

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quenched with 20 ml of satd. NH_4Cl solution, and the solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (200 ml) and washed with dil. HCl (50 ml), then with a satd. aq. solution of NaCl, dried over Na_2SO_4, and concentrated (rotary evaporator) to afford a sufficiently pure labelled substance, homogeneous by TLC (CH_2Cl_2, Rf: 0.7). Yield 360 mg, mp. 261°C [lit.[11]: 261-262°C].- An experiment using a higher excess of aryne did not increase the incorporation rate of the label but triggered the formation of the pertinent trypticene derivative and non-identifed side products (tlc).

[10-^{14}C]-1,8-Dimethoxy-9,10-anthracenedione (**4**)

To a solution of **3** (360 mg, 1.3 mmol) in 50 ml of ethanol was added in one portion an aqueous solution containing 10% NaOH (10 ml) and 30% H_2O_2 (10 ml). The mixture was stirred for 5 h at 75°C and then at room temp. for 12 h. The mixture was cooled to 0°C, the precipitated anthracenedione was filtered, washed with water, and dried to give a pure product: 280 mg (80%), mp. 223°C (lit.[12]: 223-224°C).- EIMS (70 eV): m/z 268 (54), 253 (100), 251 (20), 152 (18), 139 (19).

[10-^{14}C]-1,8-Dihydroxy-9(10H)-anthracenone (**5**)

To a refluxing solution of **4** (250 mg, 0.93 mmol) in glacial acetic acid (20 ml) a solution of 40% $SnCl_2$ in 37% HCl (5.0 ml) was added dropwise over 3 h. The solution was poured into 10 ml of ice water, and the resulting yellow precipitate was collected by filtration. Recrystallization from acetic acid afforded **5**: 180 mg (86%), mp. 170°C (lit.[13]: 169-171°C). The activity conc. was determined using LSC "Quantulus" by measuring **5** (1.00 mg) dissolved in toluene (5 ml); the average activity conc. was 130 ± 20 kBq/g.- EIMS (70 eV): m/z 227 (15), 226 (100), 225 (5), 198 (11), 197 (13), 152 (9), 151 (8).

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