Synthesis of 6-(10-hydroxy-[1-^{14}C]decyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone

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SUMMARY

6-(10-Hydroxy-[1-^{14}C]decyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIII) having a specific activity of 23.4 mCi/mmol was synthesized. 9-(2-Hydroxy-3,4-dimethoxy-6-methyl-[carbonyl-^{14}C]benzoyl)nonanol (VI) was obtained from the condensation of 3,4,5-trimethoxytoluene with 10-acetoxy-[1-^{14}C]decanoyl chloride (V) prepared from K^{14}CN (I). Reduction of VI with hydrogen in the presence of Pd-C provided 10-(2-hydroxy-3,4-dimethoxy-6-methylphenyl)-[1-^{14}C]decanol (VII). VII was oxidized with a Fremy's salt to give VIII in 21.5% radiochemical yield. 6-(10-Hydroxydecyl)-2-methoxy-3-[^{14}C]methoxy-5-methyl-1,4-benzoquinone (XI) was prepared in 34.6% radiochemical yield from the reaction of [^{14}C]dimethyl sulfate with 6-(10-hydroxydecyl)-3-hydroxy-2-methoxy-5-methyl-1,4-benzoquinone.

Key words: Synthesis, [^{14}C]CV-2619

6-(10-Hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (CV-2619) was synthesized[1,2] and shown to have a higher electron transfer activity than ubiquinone-10 in isolated mitochondria from bovine hearts.[3] It has also been shown that CV-2619 exerts improving effects on neurological symptoms and memory disturbance in

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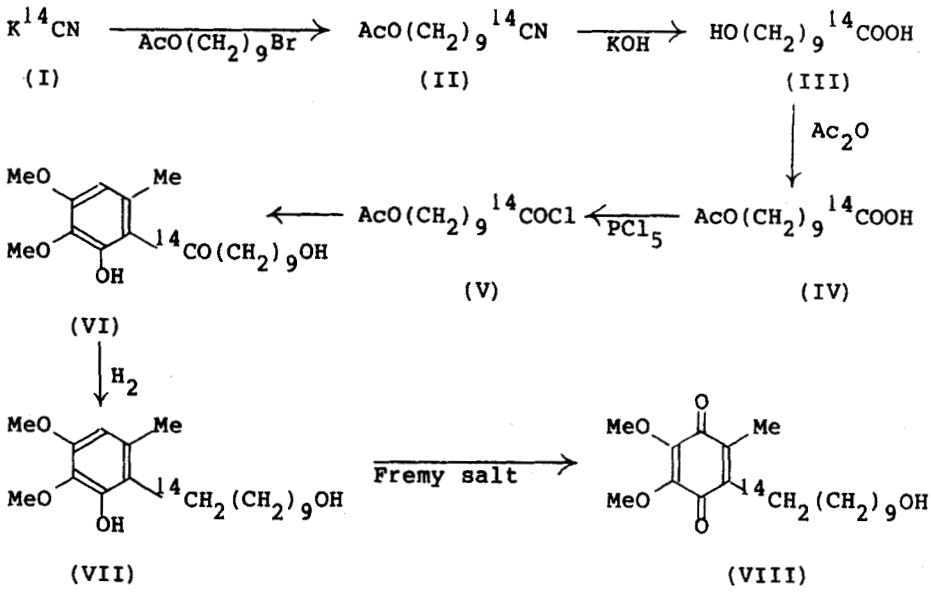
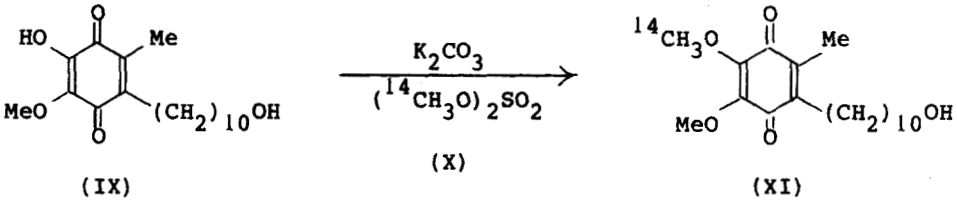
rats with cerebral ischemia.[4,5] This paper deals with the synthesis of CV-2619 labelled at [1-^{14}C]decyl and 3-[^{14}C] methoxy groups for the study of metabolic fate in animals. The synthetic route of 6-(10-hydroxy-[1-^{14}C]decyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIII) from K^{14}CN is shown in Scheme 1. 10-Hydroxy-[1-^{14}C]decanoic acid (III) was prepared in a quantitative yield by the hydrolysis of 9-acetoxynonane-[^{14}C]cyanide (II) which was synthesized from a reaction of K^{14}CN (I) with 9-acetoxynonane bromide, and subjected to the acetylation with Ac_2O to yield 10-acetoxy-[1-^{14}C]decanoic acid (IV) in 98.7% yield based on I. IV was converted to 10-acetoxy-[1-^{14}C]decanoyl chloride (V) by treating with PCl_5, and condensation of V with 3,4,5-trimethoxytoluene by a Friedel-Crafts ketone synthesis gave 9-(2-hydroxy-3,4-dimethoxy-6-methyl-[carbonyl-^{14}C]benzoyl)nonanol (VI) in 50.7% yield based on I. VI was reduced by shaking with hydrogen using palladium-carbon to provide 10-(2-hydroxy-3,4-dimethoxy-6-methylphenyl)-[1-^{14}C]decanol (VII) in 46.3% yield based on I. The conversion to VIII was effected by oxidation of VII with a Fremy's salt.[6] The overall chemical and radiochemical yield of VIII having a specific activity of 23.4 mCi/mmol were 22% and 21.5%, respectively. The purity of VIII was determined to be 100% by the radio thin-layer chromatography, the high performance liquid chromatography and the isotope dilution methods. On the other hand, 6-(10-hydroxydecyl)-2-methoxy-3-[^{14}C]methoxy-5-methyl-1,4-benzoquinone (XI) was obtained from the reaction of [^{14}C]dimethyl sulfate (X) with 6-(10-hydroxydecyl)-3-hydroxy-2-methoxy-5-methyl-1,4-benzoquinone (IX). The radiochemical yield of XI having a specific activity of 30.3 mCi/mmol was 34.6%. The purity was determined to be 100% by the radio thin-layer chromatography, the high performance liquid chromatography and the isotope dilution methods. The synthetic route of XI is shown in Scheme 2.

Scheme 1. Synthetic route of 6-(10-hydroxy-[1-^{14}C]decyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone



Scheme 2. The synthetic route of 6-(10-hydroxydecyl)-2-methoxy-3-[^{14}C]methoxy-5-methyl-1,4-benzoquinone



EXPERIMENTAL

9-Acetoxynonane-[^{14}C]cyanide (II)

A mixture of 2 mmole of 9-acetoxynonane bromide in 2.5 ml of dimethyl sulfoxide and 2 mmole (48 mCi) of K^{14}CN in a solution of 0.5 ml of water and 1 ml of dimethyl sulfoxide was heated at 80°C for 1.5 h with stirring, and then added to 20 ml of sat. NaCl. The mixture was extracted with ether. The ether layer was washed with sat. NaCl, dried over anhydrous Na_2SO_4 and evaporated to afford an oil residue as II.

10-Hydroxy-[1-^{14}C]decanoic acid (III)

II was dissolved in a mixture of 1 ml of EtOH and 2 ml of an aqueous solution containing 540 mg of KOH. The solution was refluxed for 20 h on an oil bath. After the addition of 20 ml of 3N HCl, the resulting solution was extracted with ether. The ether extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated to give crude crystals as III. The yield was 372 mg in 98.9% yield based on I.

10-Acetoxy-[1-^{14}C]decanoic acid (IV)

A mixture of 372 mg of III, 2.5 ml of Ac_2O and a small amount of p-toluene sulfonic acid was heated for 30 min at 60-70°C. After the reaction, the mixture was concentrated in vacuo to afford a residue. To the residue was added 5 ml of an aqueous solution containing 50 mg of $NaHCO_3$. The resulting mixture was stirred for 40 h at room temperature, acidified with 20 ml of 3N HCl and extracted with CH_2Cl_2. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated. The oil residue was passed through a column of 15 g of silica gel. The column was washed with $CHCl_3$ and then eluted with EtOH-$CHCl_3$ (5:95, v/v) to provide 454 mg of IV. The yield was 98.7% based on I.

10-Acetoxy-[1-^{14}C]decanoyl chloride (V)

A mixture of 454 mg of IV and 448 mg of PCl_5 in 10 ml of CH_2Cl_2 was refluxed for 30 min and then stirred for an additional 2 h at room temperature. Concentration under reduced pressure left an oil as V. V was used at next step without purification.

9-(2-Hydroxy-3,4-dimethoxy-6-methyl-[carbonyl-^{14}C]benzoyl)nonanol (VI)

To V in 6 ml of 1,2-dichloroethane was added 448 mg of anhydrous $AlCl_3$, followed by 360 mg of 3,4,5-trimethoxytoluene in 4 ml of 1,2-dichloroethane. After stirring for 4 days at room

temperature, 25 ml of 3N HCl was added to the mixture. The resulting mixture was extracted with CH_2Cl_2. The extract was washed with water, 5% $NaHCO_3$, then finally water and evaporated. The residue was dissolved in a mixture of 5 ml of 20% KOH and 8 ml of MeOH and stirring was continued for 1 h at room temperature. The solution was acidified with 30 ml of 3N HCl and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated to give a residue which was chromatographed on 14 g of silica gel column. The column was washed with CH_2Cl_2 and then eluted with MeOH-CH_2Cl_2 (1:99, v/v) to provide 343 mg of VI in 50.7% yield based on I.

10-(2-Hydroxy-3,4-dimethoxy-6-methylphenyl)-[1-^{14}C]decanol (VII)

A mixture of 343 mg of VI in 15 ml of AcOH, a drop of 60% $HClO_4$ and 150 mg of 5% Pd-C was treated with hydrogen until the calculated amount was absorbed. After the catalyst was removed and washed with AcOH, evaporation of the combined solution in vacuo left an oil which was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with water, 5% $NaHCO_3$, finally water and evaporated. A solution of the residue in a mixture of 7 ml of MeOH and 2 ml of 20% NaOH was stirred for 3 h at room temperature and then acidifed with 25 ml of 3N HCl. The resulting solution was extracted with AcOEt. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated to afford 300 mg of VII in 46.3% yield based on I.

6-(10-Hydroxy-[1-^{14}C]decyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIII)

A mixture of 300 mg of VII, 15 ml of DMF, 15 ml of water and 3 g of Fremy's salt was stirred at room temperature overnight. To the mixture was added 20 ml of water, and the resulting mixture was extracted with AcOEt. The AcOEt layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure.

The residue was chromatographed on a column of 14 g of silica gel and eluted with hexane-AcOEt (2:1, v/v) to give a crude product. Recrystallization from hexane-AcOEt gave 149 mg of VIII as needles, mp 53°C. The nature of the product was confirmed by the identity of its mixed mp, t.l.c. (Rf. 0.54) and HPLC (retention time, 29.0 min) with that of an authentic sample. The overall chemical and radiochemical yield of VIII having a specific activity of 23.4 mCi/mmol were 22% and 21.5%, respectively. The purity was determined to be 100% by the t.l.c., the HPLC and the isotope dilution methods.

6-(10-Hydroxydecyl)-2-methoxy-3-[^{14}C]methoxy-5-methyl-1,4-benzoquinone (XI)

A mixture of 0.46 mmole (28 mCi, 58 mg) of [^{14}C]dimethyl sulfate (X), 0.46 mmole (150 mg) of 6-(10-hydroxydecyl)-3-hydroxy-2-methoxy-5-methyl-1,4-benzoquinone and 0.92 mmole of K_2CO_3 in 8 ml of acetone was refluxed for 1.5 h with stirring. To the mixture was added 25 ml of water. The resulting mixture was acidified with 3N HCl, and extracted with AcOEt. The extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a column of 2 g of florisil (100-200 mesh). The column was washed with 20 ml of CH_2Cl_2 and then eluted with CH_2Cl_2-$CHCl_3$ (1:1, v/v) to give 135 mg of crude product. Recrystallization from hexane-AcOEt gave 108 mg of XI with a specific activity of 30.3 mCi/mmol. The overall chemical and radiochemical yield were 69.5% and 34.6%, respectively. The purity was determined to be 100% by the t.l.c., the HPLC and the isotope dilution methods.

Analytical procedure

The purities of VIII and XI were analyzed by the radio-thin-layer chromatography (t.l.c) on a precoated silica gel plate (60F-256, Merck) in AcOEt-benzene (2:3, v/v), the high performance

liquid chromatography (HPLC) and the isotope dilution methods. The instrument for radioscanning was used an Aloka radiochromatogram TLC-101. The instrument of HPLC used consisted of an UV-detector (254 nm) and a 4 x 150 mm column of Nucleosil 5C-18, and operated as follows: Temperature, room temperature. Pressure, 60 kg/cm^2. Mobile phase, MeOH-water (72:28, v/v). Flow rate, 0.3 ml/min.

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