SYNTHESIS OF CARBON C-14 LABELLED 2-PHENYL-4-alpha-ALKYLAMINOMETHYL-QUINOLINEMETHANOL: A POTENTIAL ANTI-LEISHMANIASIS AGENT

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SUMMARY

Using sodium acetate, [1-^{14}C] as a starting material, a total of seven steps were required to synthesize the title compound. This involved acylation of ortho-dichlorobenzene to form dichloroacetophenone, [2-^{14}C] (I). The 2-phenyl-4-quinoline carboxylic acid, [2-^{14}C] (II) was prepared by the Pfitzinger reaction from (I) and dichloroisatin. Compound II was converted to the acid chloride (III) by reaction with $SOCl_2$ in benzene. Grignard condensation reaction of (III) yielded 4-quinolylmethylketone, [2-^{14}C] (IV) which was then converted to the bromomethylketone (V). Compound V was reacted with $NaBH_4$ to form the ethylene oxide (VI). Alkylation of the oxide yielded the title compound (VII). The overall radiochemical yield was 10.1% and the specific activity was 3.0 mCi/mmol, with a radiochemical purity of >99.5%.

Key words: Quinolinemethanol, C-14, Antimalarial agent, anti-leishmaniasis agent, acylation, Pfitzinger reaction,Grignard, epoxidation, alkylation.

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CCC 0362–4803/95/070671–08

Received 19 December 1994
Revised 13 February 1995

INTRODUCTION

A group of 2-phenyl-4-quinolinemethanols structurally related to quinine was studied extensively as antimalarial compounds during World War II and the Viet-Nam war. Compounds of this type were found to have similar schizontocidal actions in animal and human *vivax* malaria as compared to Chloroquine, whereas *falciparum* malaria was found to respond better to 2-phenyl-4-quinoline-methanols than Chloroquine (1,2,3,4).

6,8-Dichloro-2-(3',4'-dichlorophenyl)-alpha-(di-n-butylaminoethyl)-4-quinolinemethanol (VII) (5) a 2-phenyl-quinolinemethanol derivative, has been reported to be active against *plasmodium bergei* in both animals and in man (6,7,8). However, it has also been reported to cause photosensitization in man (9,10,11,12).

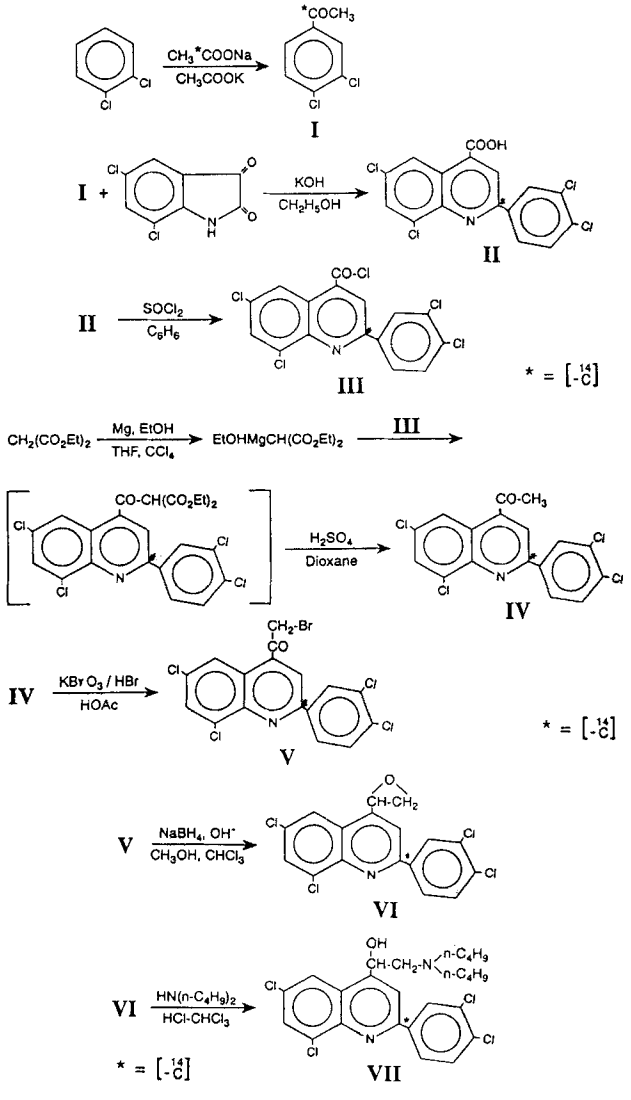
In recent studies, 6,-8-Dichloro-2-(3',4'-dichlorophenyl)-alpha-(di-n-butylaminoethyl)-4-quninolinemethanol was observed to possess anti-*Leishmaniasis major LV 39,* and *Leishmaniasis mexicana amazonensis LV 78* qualities both *in vitro* and *in vivo* (13,14). The pharmacokinetic and pharmacodynamic pathways of this compound are still not fully understood; thus a [C-14] labelled compound was prepared to study its mode of action *in vitro* and *in vivo*.

RESULTS

The synthesis of compound VII was begun with the acylation of 3,4-dichlorobenzene with sodium acetate,[1-^{14}C] to form 3,4-dichloroacetophenone, [2-^{14}C] (I), which was condensed with 5,7-dichloroisatin to form the corresponding quinolinic carboxylic acid, [^{14}C] (II). This was then converted to the acid chloride (III).

Reaction of (III) with a Grignard reagent yielded the 2-phenyl-4-quinlinolyl-methylketone, [2-^{14}C] derivative (IV). Bromination of (IV) with $KBrO_3$ in HBr yielded the bromomethylketone, [2-^{14}C] derivative (V), which was reacted with $NaBH_4$ to form the 2-phenyl-4-qunoline-ethylene oxide (VI). Ring opening of the oxide with di-n-butylamine yielded the final product (VII), with a overall radiochemical yield of 10.1%. The synthetic scheme is outlined in Scheme 1.

Scheme 1



EXPERIMENTAL

Melting points were obtained on a Fisher-Johns hot stage and were uncorrected. Ir spectra were recorded on a Perkin-Elmer 337 grating ir spectrophotometer. Type QIF silica gel plates from Quantum Industries were used for TLC development. Radio-chromatograms were recorded on a Packard Radiochromatogram scanner, Model #7220 Series. Radioactivity analyses were assayed by a Liquid Scintillation Spectrometer, TRI-CARB Model #1900CA, Packard Instrument Company.

3,4-Dichloroacetophenone,[2-^{14}C](I)

A mixture of sodium acetate, [1-^{14}C] (15), 82 mg (1.0 mmol, 60.0 mCi), potassium acetate 1.86 g (19 mmol), 11.75 g (80 mmol) of 3,4-dichlorobenzene and aluminum chloride 10 g was stirred and kept at 110°C overnight. The mixture was then decomposed by pouring it over crushed ice and adding concentrated HCl. The crude product was extracted with ether, washed with water and 2% KOH, and dried over anhydrous sodium sulfate. This product was subsequently distilled at 55-57°C/2mm.Hg., crystallized, and then recrystallized from ethanol-water (85:15,v/v). Thin layer radiochromatography using Silica Gel GF, developed in benzene:ethyl acetate (1:2,v/v) (Rf=0.66) revealed a pure product with a melting point of 72-74°C.(Lit. 72-74°C)(16), and a yield of 2.91 g (15.4 mmol, 46.3 mCi), (77%). The Ir (KBr) spectra: 1700-1650 cm^{-1} (Aryl ketone).

6,8-Dichloro-2-(3',4'-dichlorophenyl)-quinolinecarboxylic Acid,[2-^{14}C](II)

A mixture of 5,7-dichloroisatin, 3.45 g (16 mmol), compound (I), 2.91 g (15.4 mmol), KOH, 2.3 g (50 mmol) in 6 mL of water and 100 mL of ethanol was stirred and refluxed for 72 hrs. The solvent was evaporated and the residue was washed with benzene and then

with n-hexane by centrifugation. The product, potassium salt of 6,8-dichloro-2-(3',4'-dichlorophenyl)-quinoline carboxylic acid, [2-^{14}C], was then dissolved in warm methanol and the 6,8-dichloro-2-(3',4'-dichlorophenyl)-quinolinecarbocylic acid, [2-^{14}C] was precipitated by the addition of concentrated HCl. The product was filtered, crystallized and recrystallized from ethanol-acetone (2:3,v/v), and had a yield of 4.49 g (11.6 mmol, 34.73 mCi, 75%), with a melting point of 295-296^{o}C(d).(lit.295-296^{o}C)(d). The UV absorption of TLC and radiochromatographic scanning indicated a radiochemical pure compound.

6,8-Dichloro-2-(3',4'-dichlorophenyl)-quinoninyl chloride, [2^{14}C](III)

Compound II 4.49g (11.6 mmol), was refluxed overnight with 5 mL of $SOCl_2$ and 70 mL of benzene. The benzene and excess thionyl chloride were removed *in vacuo* , and the yellow crystalline product was stirred in hexane, collected by filtration, and dried. The product which was crystallized and recrystallized from benzene, melted at 195-198^{o}C. (lit.197-198^{o}C)(5). The yield of compound III was 2.35 g (5.8 mmol, 17.37 mCi, 50%).

6,8-Dichloro-2-(3',4'-dichlorophenyl)-4-quinolyl-alpha-methylketone,[2-^{14}C](IV)

A mixture of Mg, 150 mg (6.2 mmol), THF, 4.0 mL, CCl_4, 0.03 mL, and absolute ethanol, 0.03 mL was placed in a dry 3-necked flask, through which dry N_2 had been circulated. The mixture was stirred and heated to initiate the reaction. A solution of 993 mg (6.2 mmol) of diethyl malonate, 0.6 mL of absolute ethanol and 0.6 mL of THF, was added to the above stirring mixture slowly to maintain a gentle reflux .The mixture was refluxed until the Mg was consumed. Compound III 2.35 g (5.8 mmol) was added to this solution. The mixture was refluxed for 2 hrs. The mixture was then

decomposed by pouring it onto an ice-water sulfuric acid mixture. The yellow solids were filtered and washed with H_2O. The "diester" was then refluxed overnight in 5 mL of water, 10 mL of dioxane and 2 mL of sulfuric acid. The decarboxylation reaction mixture was poured onto ice-water, and treated with NaOH to adjust the pH to 8.0. The solids were collected by filtration, washed with water, and dried *in vacuo.* This product was purified by crystallization and recrystallization from acetone. The yield was 1.96 g (5.1 mmol, 15.29 mCi, 88%), and the melting point was 173-175°C.

6,8-Dichloro-2-(3',4'-dichlorophenyl)-4-quinolyl-alpha-bromomethylketone,[2-^{14}C](V)

300 mg of potassium bromate was added to a stirring solution of (IV), 1.96 g (5.1 mmol), glacial acetic acid 60 mL, and 4.5 mL of 48% HBr which had been preheated to reflux temperature. The mixture was refluxed for 1 hr and then poured onto ice-water. The crude product was filterted, crystallized and subsequently recrystallized from acetone-acetonitrile (1:1,v/v). A yield of 1.95 g (4.23 mmol, 12.69 mCi, 83%) was obtained, which melted at 164-166°C. (lit. 166-168°C)(5). TLC in acetic acid:methanol:acetone (1:4:5,v/v/v), showed a single UV spot. The radiochromatographic scanning also indicated it to be a pure compound.

6,8-Dichloro-2-(3',4'-dichlorophenyl)-4-quinolyl-alpha-ethyleneoxide,[2-^{14}C](VI)

Compound V 1.95 g (4.23 mmol) was suspended in 10 mL of methanol and 4 mL of chloroform, and cooled to 0°C. $NaBH_4$, 227 mg (6 mmol) was added slowly with stirring. The mixture was allowed to warm to ambient temperature and then refluxed for 1 hr. The mixture was then cooled in ice-water and the white solid collected and washed with acetone-ethyl acetate mixture (1:1,v/v) and dried *in vacuo.* The yield was 1.24g (3.2 mmol, 9.64 mCi, 76%), and the melting point was 215-218°C.(lit.218-219°C)(5,17).

6,8-Dichloro-2-(3',4'-dichlorophenyl)-alpha-(di-n-butylaminoethyl)-4-quinolinemethanol,[2-^{14}C].HCl(VII)

Compound VI, 1.24g (3.2 mmol), was stirred at 105°C for 16 hrs with di-n-butylamine, 1.29 g (10 mmol). The excess of di-n-butylamine was removed *in vacuo* , and the residue was dissolved in chloroform, and the hydrochloride salt was precipitated by adding concentrated HCl. The solution was cooled in ice-water, the solids were collected, crystallized and recrystallized from methanol and ether. The melting point was 207-209°C (lit.209-210°C) (5,16). A yield of 1.12 g (2.02 mmol, 6.06 mCi, 63%) of (VII) at a specific activity of 3.0 mCi/mmol was obtained. This represents an overall radiochemical yield of 10.1% based on sodium acetate, [1-^{14}C]. TLC-SG GF plates, developed in chlorform-ethylamine-methanol (10:1:3,v/v/v) showed a single UV and radioactive spot. The radiochemical purity was assayed by the radiochromatography scanner and was found to be greater than 99.5% The Ir (KBr) spectra: 1350-1250 $cm^{-1}$and 3500-3100 cm^{-1} (Secondary alcohol), 1675-1600 cm^{-1} (Subst. imine), and the synthetic product was essentially identical with that of the authentic compound (5).

In conclusion, the synthesis of the title compound was accomplished via a seven step scheme using conventional organic reactions to obtain an overall yield of 10.1%, and a specific activity 3.0 mCi/mmol.

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