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PREPARATION OF 1-METHYL-4-[4-(7-CHLORO-4-QUINOLYL-[3-^{14}C]-AMINO)BENZOYL]PIPERAZINE

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SUMMARY

1-Methyl-4-[4-(7-chloro-4-quninolyl-[3-^{14}C]-amino)-benzoyl]piperazine (V) was prepared for pharmacokinetic and pharmacodynamic evaluation. The synthesis of V was accomplished first by a modified Claisen ester condensation reaction of diethyl-[2-^{14}C]-malonate, triethyl orthoformate, and acetic anhydride in the presence of $ZnCl_2$ to form ethyl ethoxymethylene-[2-^{14}C]-malonate (I), which was further condensed with m-chloroaniline to yield 7-chloro-4-hydroxy-3-[^{14}C]-quinoline-ethyl-carboxylate (II). Saponification of II yielded the corresponding carboxylic acid (III). Decarboxylation of the acid group upon heating and a substitution of the 4-OH group of compound III into chlorine atom with $POCl_3$ produced 4,7-dichloro-[3-^{14}C]-quinoline (IV), which then was reacted with 1-methyl-4-(p-amino-benzoyl)piperazine to form the title compound V. There were a total of five steps of reaction, with a overall yield of 34.3%. The specific activity was 1.74 mCi/mmol.

Key words: Claisen condensation, saponification, decarboxylation, chlorination, alkylation, C-14.

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INTRODUCTION

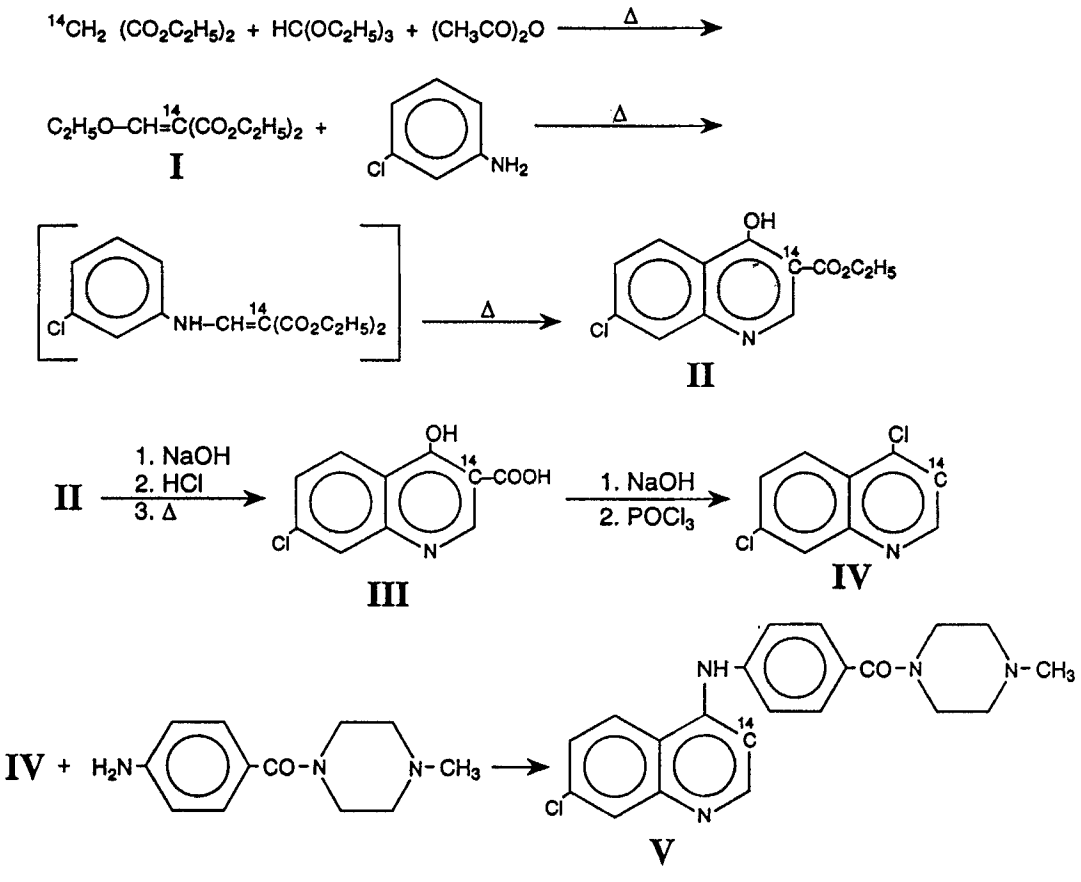
The antimalarial drug 1-methyl-4[4-(7-chloro-4-quinolyl-amino)benzoyl]piperazine, has been reported to possess antimalarial activity in mice infected with *plasmodium berghei* and *plasmodium geeenmium.* It has been also found to antagonize the cardiovascular and pulmonary actions of adrenergic receptors in experimental animals (1,2). The most serious toxic effect encountered in dogs was hypotension, which was brought about by blockade of both alpha and beta adrenergic receptors (3). Very recently, 1-methyl-4-[4-(7-chloro-4-quinolylamino)benzoyl]piperazine has been found to be an effective chemotherapeutic agent against Filariasis, acting to sterilize the reproductive system of female adult worms (4). Sterilization of the adult female filaria lowers blood microfilaraemia levels, interrupts the transmission cycle, and helps the host to assimilate the decycling dead worms at different intervals without a resultant anaphylactic reaction. Biological studies for this compound necessitates the radiolabeling of the quinoline ring system.

The synthesis of the key intermediate, 4,7-dichloro-4-^{14}C]-quinoline, was previously reported (5), starting with a carbonation of vinylmagnesium bromide with CO_2,[^{14}C]. A total of seven reaction-steps were required to yield 4,7-dichloro-[4-^{14}C]-quinoline, Attempts to obtain a higher overall yield and specific activity were unsuccessful. We therefore investigated an alternative route preperation of 4,7-dichloro-[3-^{14}C]-quinoline, starting with diethyl-[2-^{14}C]-malonate. A total of four steps of reaction are needed to produce this intermediate. The chemical reaction scheme is outlined in Scheme 1.

RESULTS AND DISCUSSION

Ethyl ethoxymethylene-[2-^{14}C]-malonate, (I) was prepared by heating triethyl orthoformate, diethyl-[2-^{14}C]-malonate,, and acetic

Scheme 1



anhydride in the presence of zinc chloride,a modification of the Claisen ester condensation reaction. The compound I was further condensed with m-chloroaniline to yield the cyclized compound, 7-chloro-4-hydroxy-[3-^{14}C]-qunoline-3-ethylcarboxylate (II). This was then saponified to convert the compound into the acid (III) A decarboxylation and a substitution of 4-hydroxy into chlorine with $POCl_3$ produced 4,7-dichloro-[3-^{14}C]-quinoline (IV), the key intermediate,which was then reacted with 1-methyl-4-(p-aminobenzoyl)piperazine to yield 1-methyl-4-[4-(7-chloro-4-qunolyl-[3-^{14}C]-amino)benzoyl]piperazine (V). The overall yield was 33.4%, and the specific activity was 1.74 mCi/mmol. The

radiochemical purity was >99%. These results indicate that the overall yield and specific activity of this preparation can be improved more than three times by these five steps of reaction compared with the eight steps for synthesis of the 7-chloro-[4-^{14}C]-quinoline-4-amino derivatives as previously reported.

EXPERIMENTAL

Melting points were obtained on a Fisher-Johns hot stage and were corrected. 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. Radiochromatograms were recorded on a Packard Radiochromatogram scanner, Model #7220. Radioactivity assays were assayed by a Liquid Scintillation Spectrometer, Model Delta 300, Tracer Analyticals.

Ethyl ethoxymethylene-[2-^{14}C]-malonate(I)

14 mg anhydrous zinc chloride, 4.45 g (30 mmol) freshly redistilled triethyl orthoformate, 4.57 g (45 mmol) freshly redistilled acetic anhydride, and 2.42 g (15 mmol, 26.5 mCi diethyl-[2-^{14}C]-malonate (6) were placed into a 50 mL three-nacked flask fitted with a gas-inlet tube, spiral condenser with Drierite drying tube, and glass stopper. Dry N_2 was bubbled through the reaction mixture at a rate of approximately 10 cubic centimeters per minutes. The mixture was heated to 105-115^{o}C and held at that temperature for 2 hrs, then at 120-127^{o}C for 7 hrs. The reaction mixture was cooled to room temperature and 3 mL each of triethyl orthoformate and acetic anhydride were added. The temperature was raised to 140-145^{o}C for 2 hrs. and finally to 165-175^{o}C for an additional 2 hrs. At the end of 13 hrs heating the mixture was cooled to room temperature and filtered. The filtrate was distilled in a one-piece Micro-Claisen distilling unit, under reduced pressure

(10 mm) until the temperature at the distill head reached 90-92^{o}C. The distillation was then continued under low pressure (0.20mm). The yield of product, b.p. 99.5-102^{o}C/0.2mm. (lit. b.p. 108-110^{o}C/0.25mm) (7) was 2.38 g (11.0 mmol, 19.0 mCi, 73%). The radiochemical purity was demonstrated by radiochromatogram to be >99%.

7-Chloro-4-hydroxy-quinoline-[3-^{14}C]-3-ethylcarboxylate (II)

Several boiling chips (carborundum) and 2.30 g (18 mmol) of freshly distilled 3-chloroaniline were added to compound I and heated at 101-105^{o}C for 1 hr to remove the ethanol formed in the condensation. The product was used directly in the next step of reaction.

The above product was added to 20 mL of diphenyl ether, and this solution heated at the boiling point (b.p.259^{o}C) for 1 hr, during which time a large proportion of the cyclization product crystallized out of the solution. The mixture was cooled, filtered, and washed with n-hexane to remove the major portion of colored impurities, and air-dried. The product was crystallized and recrystallized in EtOAc-MeOH. The yield of product was 2.39 g (9.48 mmol, 16.43 mCi.,86.5%), m.p. 292-294^{o}C (lit. m.p. 295-297^{o}C) (8).

7-Chloro-4-hydroxy-[3-^{14}C]-quinoline-3-carboxylic Acid (III)

Compound II was treated with 25 mL of 10N NaOH, and the mixture was refluxed vigorously until all the solid ester dissolved (about 1 hr). The saponification solution mixture was cooled, and the aqueous solution was treated with decolorizing charcoal and filtered. The filtrate was acidified with concentrated HCl. The product was filtered washed thoroughly with water, dried, crystallized and recrystallized from ethanol. The yield was 1.86 g (

8.34 mmol, 14.46 mCi, 88%). The melting point was 271-273°C (lit. 273-274°C) (8).

4,7-Dichloro-[3-^{14}C]-quinoline (IV)

Compound III was suspended in 30 mL in a flask equipped with a stirer and a reflux condenser. The mixture was boiled for 1 hr. under a stream of N_2 to assist in the removal of water. The clear, light-brown solution was cooled to room temperature, and 5 mL of phosphorous oxychloride was added. The temperature was raised to 135-140°C, and the mixture was stirred for 1 hr. The reaction mixture was cooled to room temperature. The product was extracted into 10% HCl. The combined acid extracts were cooled in ice and neutralized with 10% NaOH to precipitate the product. The solid was collected, washed thoroughly with water, and was purified by crystallization and recrystallization from 80% ethanol:water to yield 1.25 g (6.3 mmol,10.95 mCi., 75.7%) with a melting point of 83-85°C.(lit. 84-85°C) (8), (lit. 93°C) (9). The chemical purity was assayed by TLC-SG employing ethanol/water(95:5, v/v) as the developing solvent. The radiochromatogram scanning of the TLC plates also demonstrated a radiochemical purity >99%. The C-14 labeled product and the reference standard (8) were identical in their chromatographic behavior. The infrared spectra of the above samples were likewise esentially identical.

1-Methyl-4-[4-(7-chloro-4-quinolyl-[3-^{14}C]-amino)benzoyl]piperazine (V)

An ethanolic solution containing V, 792mg (4 mmol, 6.94 mCi) and 1-methyl-4-(p-aminobenzoyl]piperazine, 877 mg,(4 mmol), which was prepared according to Ida and Lorz (10),was acidified with concentrated HCl to pH 3.0. The mixture was refluxed for 2 hrs, cooled and the ethanol was evaporated *in vacuo.* The crude product was dissolved in water, decolorized with charcoal, and precipitated

with NH_4OH at pH 9.0. The product was collected by filtration, washed thoroughly with water and was then crystallized and recrystallized from benzene, melted at 190-192°C (lit.190°C) (11). Thin layer chromatography on Silica Gel G plates in methanol showed a single UV and radioactive spot. The radioactive spot was detected by radioautography. A yield of 1.23 g (3.22 mmol, 5.59 mCi, 80.6%) was obtained at a specific activity of 1.74 mCi/mmol.

The Ir (KBr) spectra: 1395 cm^{-1} (NH-), 2900 cm^{-1} (aliphatic C-H), and 1680 cm^{-1} (C=O of tertiary amidic). TLC (Rf=0.46), and mp data all agree with the authentic compound (11).

In conclusion, the title compound was prepared with an overall yield of 34.3%, and at a specific acitivy of 1.74 mc.mmol, and required five reaction-steps.

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