^{14}C-LABELED ANTIMALARIALS. I. SYNTHESIS OF dl-*erythro*- AND *threo*-α-(2-PIPERIDYL)-2,8-BIS(TRIFLUOROMETHYL)-4-QUINOLINEMETHANOL-α-^{14}C

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SUMMARY

Erythro- and threo- isomers of α-(2-piperidyl)-2,8-bis-(trifluoromethyl)-4-quinolinemethanol-α-^{14}C hydrochloride and methanesulfonate were prepared from labeled carbon dioxide for metabolic and pharmacological studies. Intermediates were 2,8-bis(trifluoromethyl)cinchoninic-carboxy-^{14}C acid and 2,8-bis(trifluoromethyl)-4-quinolyl 2-pyridyl ketone-^{14}C. The ratio of erythro to threo isomers formed on hydrogenation of the precursor ketone was 5.6. The diastereomers were separated by recrystallization and preparative tlc. Erythro-to-threo conversion was effected by isomerization of the acetylated erythro isomers and deacetylation.

Key Words: dl-*erythro*- and dl-*threo*-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol-α-^{14}C, Mefloquine-^{14}C, Antimalarial Agent.

dl-*erythro*-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)quinolinemethanol hydrochloride (5, Mefloquine, WR-142,490) is a potent antimalarial showing both curative action (1) and suppressive prophylaxis (2) against various drug-resistant strains of *Plasmodium falciparum* in humans. In addition, the drug is relatively non-toxic and non-phototoxic (1). Mefloquine and the corresponding threo compound (WR-177,602), labeled with ^{14}C in the methanol carbon, were prepared for metabolic (3) and pharmacological studies.

Mefloquine was first prepared by Ohnmacht, Patel, and Lutz (4) using previously published methods (5). The same route was used for the ^{14}C-synthesis.

2,8-Bis(trifluoromethyl)cinchoninic-carboxy-^{14}C acid (3) was obtained in an 82.6% yield by the carboxylation of 2,8-bis(trifluoromethyl)-4-lithioquinoline (2) with labeled carbon dioxide. The lithioquinoline was prepared by reaction of the corresponding bromide (1) and *n*-butyllithium. The labeled acid (3) was converted to 2,8-bis(trifluoromethyl)-4-quinolyl 2-pyridyl ketone-^{14}C (4) with 2-pyridyllithium which was generated from *n*-butyllithium and 2-bromopyridine. Hydrogenation of the ketone with platinum catalyst gave a mixture of erythro and threo isomers, (5) and (6). The dl-*erythro* pair (5) was separated from the dl-*threo* pair and purified by recrystallization. The corresponding dl-*threo*

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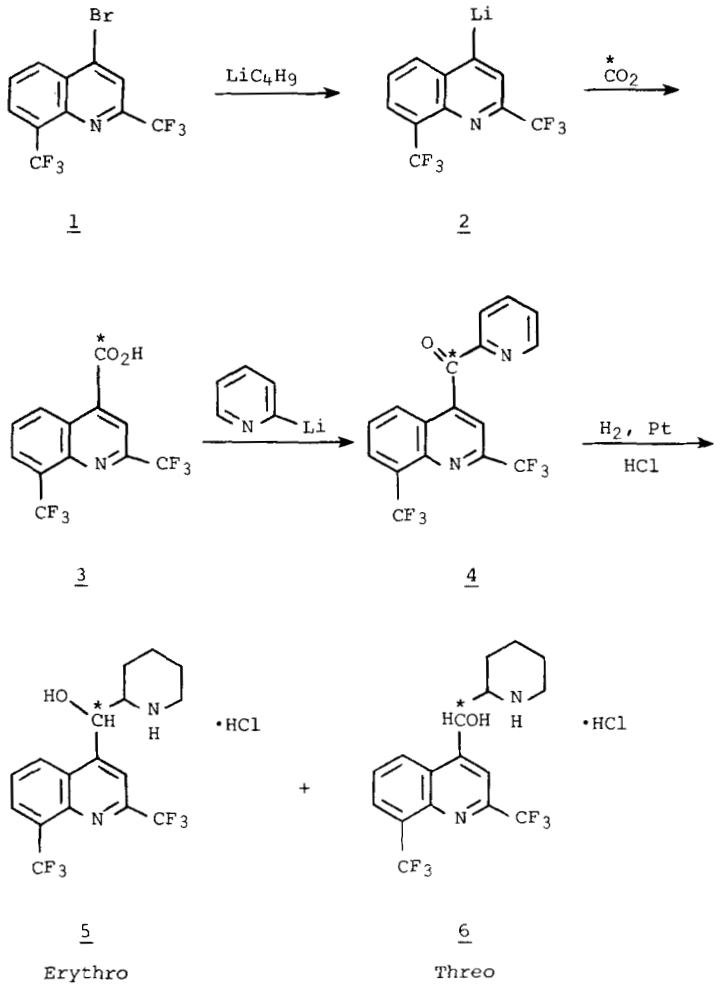

pair (6) was isolated from the recrystallization filtrates by preparative tlc. Methanesulfonate salts of the erythro (7) and threo (8) isomers were obtained by conversion of the corresponding hydrochlorides to the free bases and subsequent reactions with methanesulfonic acid.

The conversion of (5) to (6) by inversion at the carbinol carbon has been reported by Olsen (6) and Carroll and Blackwell (7). A modification of Olsen's method was used for this inversion. A mixture of 73.8% (5) and 13.1% (6) was obtained by the hydrogenation of the ketone (4). Treatment of a solution of this mixture in acetic anhydride at reflux with hydrogen chloride gave predominantly the acetylated threo isomers. Deacetylation and purification by recrystallization gave a 27.2% yield of pure (6) based on the ketone. A pilot run for this

conversion gave 41.7% pure (6), and the threo configuration was confirmed by pmr (dimethylsulfoxide-D_6-D_2O) (6, 7). The measured vicinal coupling constant (J) was 6.2 Hz, which was in agreement with a reference sample. The J value for (5) in the same system was 2.3 Hz.

EXPERIMENTAL

Radioactivity measurements were made with a Packard Tri Carb scintillation spectrometer, Model 3385. A Cary Model 11 spectrophotometer was used for uv measurements. Radiochemical purity was determined by tlc analyses with silica gel (Eastman Chromogram Nos. 6060 and 13181) and measurement of the sectioned strip. All R_f values of the prepared labeled compounds were in agreement with those from non-labeled reference samples.

2,8-Bis(trifluoromethyl)cinchoninic-carboxy-^{14}C Acid (3)

2,8-Bis(trifluoromethyl)-4-bromoquinoline, 1.1392 g (3.31 mmole), in 12 mL Et_2O, was added to 3.16 mmole *n*-butyllithium in 2.15 mL hexane and 10 mL Et_2O at -80° under argon. The lithio derivative was carboxylated with 35.08 mCi (3.00 mmole) $^{14}CO_2$ at -80°. The mixture was stirred 1 hr at -80° and warmed to 25°. The mixture was treated with 10 mL H_2O and the aqueous layer removed. The ether phase was extracted with 3 x 5 mL 0.8*N* NaOH and 3 x 2 mL H_2O. Acidification of the combined aqueous washings with 3.6 mL acetic acid precipitated the 2,8-bis(trifluoromethyl)cinchoninic-carboxy-^{14}C acid; 28.97 mCi, 11.69 mCi/mmole (82.6% radiochemical). The radiochemical purity was 99.6% as determined by tlc (EtOH), R_f 0.45. The acidification was done in a vacuum system, and 4.32 mCi (12.3%) $^{14}CO_2$ was recovered in aqueous alkali.

2,8-Bis(trifluoromethyl)-4-quinolyl 2-Pyridyl Ketone-^{14}C (4)

A solution of 1.6453 g (10.41 mmole) dry 2-bromopyridine in 3 mL dry Et_2O was added to a solution of 9.92 mmole *n*-butyllithium in 6.7 mL hexane and 15 mL Et_2O at -80° under argon. The mixture (-80°) was stirred 1 hr, and an 18 mL dry ether solution of 28.97 mCi (2.48 mmole) 2,8-bis(trifluoromethyl)cinchoninic-carboxy-^{14}C acid was added. The mixture was stirred and gradually warmed to -40° over 0.83 hr. Stirring was continued for 0.5 hr periods at -40°, -30°, -20°, and -10°. Water, 10 mL, was added. A black solid insoluble in both phases was

removed by filtration (0.95 mCi). The ether layer was removed, and the aqueous phase washed with 6 mL Et_2O. The ether phase was washed with 2 x 2 mL 0.5*N* NaOH and 2 x 2 mL H_2O. The combined aqueous phases contained 4.49 mCi of 2,8-bis(trifluoromethyl)cinchoninic-carboxy-^{14}C acid.

Evaporation of the Et_2O gave 20.15 mCi of crude ketone, a solid-oil mixture; radiochemical purity 95.9% (EtOH), R_f 0.60. The material contained a small amount of bromopyridine which was removed by evaporative chasing with 2 x 10 mL heptane. The resulting brown solid was washed with 2 x 25 mL hot heptane, and evaporation of the decanted heptane extracts gave 18.63 mCi crystalline ketone (53.1% overall; radiochemical purity 98.80%). The black solid, insoluble in hot heptane, contained 1.52 mCi.

dl-*erythro*-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol-α-^{14}C Hydrochloride (5)

2,8-Bis(trifluoromethyl)-4-quinolyl 2-pyridyl ketone-^{14}C, 18.63 mCi in 35 mL EtOH and 0.5 mL 12*N* HCl, was hydrogenated 3 hr with 0.1 g PtO_2 and 45.5 psig H_2. Theoretical amount of H_2 was absorbed in 1.25 hr. Analysis by tlc (EtOH) indicated 80.1% (5). After filtration and evaporation, recrystallization of the solid residue from 15 mL acetonitrile gave 7.80 mCi (5) (radiochemical purity 97.2%). Recrystallization from 9 mL acetonitrile, after decolorization with 0.1 g carbon in 25 mL MeOH, gave 5.85 mCi (0.2167 g) pure (5) (31.4% step, 16.7% overall); 11.20 mCi/mmole. Radiochemical purity and R_f values by tlc were: EtOH, 98.8%, 0.26; 95 EtOH:5 Et_3N, 98.6%, 0.41; MeOH, 98.3%, 0.36; 79 benzene:19 MeOH:2 NH_4OH, 98.2%, 0.40. Analysis by uv: λ_{max}^{EtOH} 282 nm (ε 5673), 304 (ε 3723), 317 (ε 2729).

A second crop of 0.96 mCi of the erythro isomers (5) (radiochemical purity 93.5%) was obtained from the first acetonitrile filtrate. This filtrate contained a mixture of (5), (6), and other materials. The threo isomers (6) and an additional quantity of (5) were isolated by preparative tlc.

dl-*erythro*-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol-α-^{14}C Methanesulfonate (7)

A portion of crude (5), 3.25 mCi (0.29 mmole, radiochemical purity 94.4%), was converted to the free base with 1 mL 2*N* NaOH. The free base was extracted

with 3 x 2 mL CH_2Cl_2 which was dried (Na_2SO_4). After evaporation, a solution of the free base in 2 mL MeOH was treated with 0.0396 g (0.41 mmole) anhydrous methanesulfonic acid. After evaporation, the residual solid was slurried with 5 mL Et_2O. Filtration gave 2.85 mCi crystalline (7) and 0.15 mCi ether solubles; radiochemical purity, 79 benzene:19 MeOH:2 NH_4OH, 96.10%. Recrystallization from 2 mL acetonitrile gave 1.61 mCi (7); radiochemical purity, 97.9% in the same solvent. An impurity, 0.44%, was observed at R_f 0.65, and the same impurity was present in the reference sample. Trituration of the 1.24 mCi filtrate residue with Et_2O gave 0.97 mCi solids. Recrystallization from 3 mL 2 Et_2O:tetrahydrofuran (THF) gave 0.78 mCi (7); radiochemical purity, 94.0%. A third fraction of (7), 0.66 mCi, was obtained from the preparative tlc separation of the free bases of (5) and (6). Recrystallization of the combined 3 crops of (7), 3.04 mCi, from 7 Et_2O:3 THF gave 2.79 mCi (0.1142 g) pure (7); 11.59 mCi/-mmole. Radiochemical purity and R_f values were: EtOH, 96.6%, 0.25; 79 benzene:19 MeOH:2 NH_4OH, 97.2%, 0.46; 8 hexane:HOAc:*n*-BuOH, 99.7%, 0.06. Analysis by uv: λ_{max}^{EtOH} 282 nm (ε 5689), 303 (ε 3541), 317 (ε 2664).

dl-*threo*-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol-α-^{14}C Methanesulfonate (8)

The residue from the first acetonitrile filtrate of (5), 7.43 mCi, was converted to the free base with 2.2 mL 1.5*N* NaOH. The free base consisted of 42.2% of the erythro and 31.8% of the threo diastereomers. The diastereomers were separated from a 5.66 mCi portion of the free base mixture with ten 20 x 20 x 0.1 cm silica gel GF plates (Analtech, Inc.) developed to 19 cm with EtOH which gave 3 zones: 1-2 cm, 3-3.5 cm, and 13-14.5 cm. The products were removed from the silica with MeOH. Zone 1 contained 2.08 mCi, 68.1% erythro (R_f 0.26, EtOH) and 31.0% unknown impurity R_f 0.6. Zone 2 contained 1.70 mCi, 85.7% threo (R_f 0.37, EtOH) and 9.4% unknown at R_f 0.61.

The 1.70 mCi of the threo free base isomers was converted to the methanesulfonate in 2 mL MeOH with 0.0207 g (0.22 mmole) methanesulfonic acid. After evaporation, washing the residue with 2 x 5 mL Et_2O gave 1.49 mCi (8). Recrystallization twice from 10 Et_2O:3 THF gave 1.10 mCi (0.0441 g); 11.86 mCi/mmole.

Radiochemical purity and R_f values were: EtOH, 94.5%, 0.38; 79 benzene:19 MeOH: 2 NH_4OH, 94.7%, 0.52; 8 hexane:HOAc:*n*-BuOH, 99.8%, 0.05. Analysis by uv: λ_{max}^{EtOH} 282 nm (ε 5358), 303 (ε 3558); 317 (ε 2585).

dl-*threo*-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol-^{14}C Hydrochloride (6)

2,8-Bis(trifluoromethyl)-4-quinolyl 2-pyridyl ketone-^{14}C, 27.30 mCi (2.03 mmole), in 40 mL EtOH and 0.6 mL 12*N* HCl, was hydrogenated 4 hr with 0.11 g PtO_2 and 50.0 psig H_2. Analysis by tlc (EtOH) indicated 73.8% (5), R_f 0.28, and 13.1% (6), R_f 0.37. After filtration, evaporation gave 26.34 mCi, 0.9979 g, tan crystals. A stream of hydrogen chloride was passed through a refluxing solution of the racemate mixture in 12.1 mL acetic anhydride over a 4 hr interval. After evaporation of the acetic anhydride and chasing with 3 x 10 mL Et_2O, trituration with 15 mL Et_2O gave 21.09 mCi (0.8249 g) ether insoluble acetylated threo isomers, a tan solid. The acetylated threo isomers were deacetylated by a 4 hr reflux in 8 mL EtOH and 8 mL 6*N* HCl. Evaporation gave 0.8341 g red-brown crystals. Trituration with 10 mL Et_2O and filtration gave 16.94 mCi (0.7173 g) crude (6), a tan solid. A radiometric tlc (EtOH) of the filtrate showed 76.3% (6).

A solution of 16.94 mCi (6) in 45 mL 44% EtOH 1.3*N* in HCl was treated with 0.1 g charcoal and stirred at 60°. Filtration, concentration of the solution to 15 mL, cooling at 0°, and filtration gave 8.69 mCi (0.2842 g) crude (6), a tan solid. A radiometric tlc analysis (silica/EtOH) showed 90.4% (6), R_f 0.34, and 5.5% (5), R_f 0.25. Retreatment with charcoal and recrystallization gave 7.43 mCi (0.2296 g) pure (6); 13.42 mCi/mmole. Radiochemical purity and R_f values were: EtOH, 96.9%, 0.34; MeOH, 97.0%, 0.41; 79 benzene:19 MeOH:2 NH_4OH, 98.6%, 0.50; 34 benzene:15 EtOH:NH_4OH, 98.5%, 0.54; HOAc, 99.1%, 0.45. Analysis by uv: λ_{max}^{EtOH} 282 nm (ε 5766), 304 (ε 3824), 317 (ε 2715).

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