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Synthesis of the Enantiomers of [3-^{3}H]-2-[[4-[(7-Chloro-4-quinolinyl)-amino]pentyl]ethylamino]ethanol, [3-^{3}H]-Hydroxychloroquine

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SUMMARY

The enantiomers of [3-^{3}H]-2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol, [3-^{3}H]-hydroxychloroquine, **(R)-8** and **(S)-8**, have been prepared in two steps from the known precursors 4,7-dichloro-3-iodoquinoline, **4**, and the enantiomers of 2-[(4-aminopentyl)ethyl-amino]ethanol, **(R)-2** and **(S)-2**, by formation of the enantiomers of 2-[[4-[(7-chloro-3-iodo-4-quinolinyl)amino]pentyl]ethylamino]ethanol, **(R)-3** and **(S)-3**, and subsequent reductive deiodination with tritium gas over 10% palladium on charcoal.

Key Words: Plaquenil, Hydroxychloroquine, 2-[[4-[(Chloro-4-quinolinyl)amino]pentyl]ethyl-amino]ethanol, Enantiomers, Tritiation.

INTRODUCTION

2-[[4-[(7-Chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol, ***rac*-1**, also known as hydroxy-chloroquine, is an antimalarial[1] which has long been known to have value in the treatment of rheumatoid arthritis.[2-6] The drug is marketed as a racemate, Plaquenil™. A recent report[7] has indicated that the enantiomers, **(R)-1** and **(S)-1**, display different pharmacokinetics in man, and a further report[8] has indicated that there may be differences in absorption and distribution.

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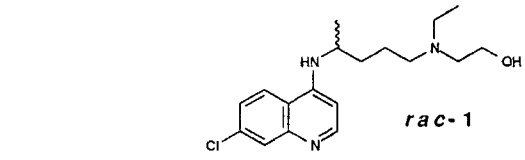
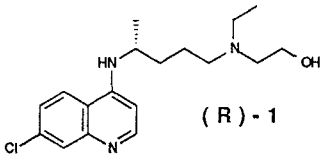
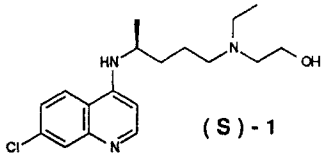


rac-1

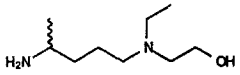


(R)-1

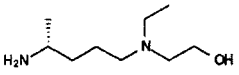


(S)-1

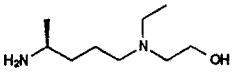
To enable a fuller evaluation of the pharmacological and toxicological activities of the enantiomers of hydroxychloroquine, we have elsewhere reported[9] their synthesis (with e.e. >98%) following resolution of the precursor amine 2-[(4-aminopentyl)ethylamino]ethanol, ***rac*-2**, to afford the enantiomers **(R)-2** and **(S)-2** (with e.e. >98%).



rac-2



(R)-2

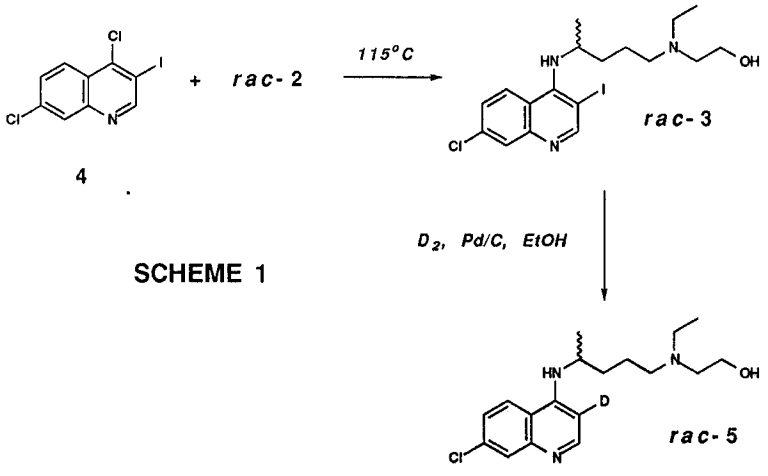


(S)-2

In the course of evaluation of these enantiomers it became necessary to develop a method of radiolabelling. Hydroxychloroquine is known[10] to be extensively metabolised in the alkyl chain and so it was decided that the label would be most appropriately placed in the aromatic nucleus to enable the resulting material to be most beneficially used in any in vivo studies required. It was therefore decided to introduce tritium at C-3, by reduction of an aryl iodide to maximise the likelihood of retaining the 7-chloro substituent.[11]

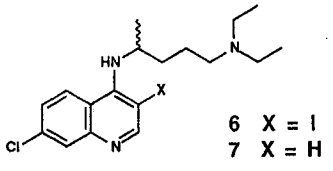
RESULTS AND DISCUSSION

In a preliminary study, 2-[[4-[(7-chloro-3-iodo-4-quinolinyl)amino]pentyl]ethylamino]ethanol, ***rac*-3**, was prepared in 61% yield by treatment of **4**,7-dichloro-3-iodoquinoline, **4**,[12] with 2-[(4-aminopentyl)ethylamino]ethanol, ***rac*-2**.[1] Reductive deiodination of ***rac*-3** at atmospheric pressure, using deuterium over 10% palladium on charcoal in ethanol, afforded the desired [3-^{2}H]-2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol, [3-^{2}H]-hydroxy-chloroquine, ***rac*-5**, in 68% yield. This sequence is outlined in Scheme 1. Mass Spectrometry showed the incorporation of deuterium to be 88%.



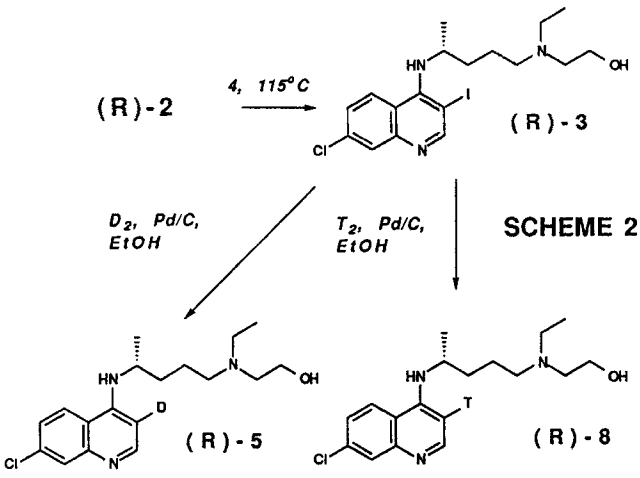
SCHEME 1

In a previously reported[13] synthesis of the related 3-iodochloroquine, **6**, a reaction analogous to the above synthesis of ***rac*-3** led only to formation of the deiodinated product, i.e. chloroquine, **7**, and the desired 3-iodochloroquine was only produced (30% yield) on heating these reactants under reflux in ethanol. However, in our experiment, only trace amounts of deiodinated material were observed.[14]



Using the enantiomers **(R)-2** and **(S)-2**, the displacements were carried out in diisopropylamine to afford **(R)-3** and **(S)-3**. The enantiomers **(R)-3** and **(S)-3** gave approximately equal and opposite optical rotations, indicating a lack of significant racemisation at this stage. No racemisation had been observed in the corresponding formation of **(R)-1** and **(S)-1** described in earlier unlabelled work.[9] Reaction of **(R)-3** with deuterium, as in the analogous synthesis of ***rac*-5** from ***rac*-3**, gave material, **(R)-5**, with rotation comparable with **(R)-1**. Additionally, ^{1}H NMR revealed no diminution of the signal due to the methine proton *gem* to the methyl group. From this we concluded that the conversion of **(R)-2** to **(R)-3** had been achieved without significant racemisation.

Reaction of each of **(R)-3** and **(S)-3** with tritium under similar conditions afforded the desired enantiomers, **(R)-8** and **(S)-8,** of [3-^{2}H]-2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]-ethanol, as outlined in Scheme 2 for the **(R)** enantiomer.[15] The specific activity of these materials were found to be 23.8 Ci/mmole for **(R)-8** and 28.7 Ci/mmole for **(S)-8**, with both chemical and radiochemical purities of >98% in each case as determined by chiral HPLC.[9]



EXPERIMENTAL

Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. N.m.r. spectra were recorded on a Bruker AC80 and are reported relative to internal tetramethylsilane. Mass spectra were obtained on a Finnigan TSQ-700 mass spectrometer.

2-[[4-[(7-Chloro-3-iodo-4-quinolinyl)amino]pentyl]ethylamino]ethanol, *rac*-3: A mixture of 4,7-dichloro-3-iodoquinoline, **4**, (3.94 g, 12.2 mmole) and 2-[(4-aminopentyl)ethylamino]-ethanol, ***rac*-2**, (10 ml) was heated to 115°C under an atmosphere of nitrogen. The reaction mixture was then poured into water and extracted with dichloromethane. The organic phase was dried over anhydrous magnesium sulphate and the solvent then removed under vacuum to leave a residue which was chromatographed on silica gel eluting with ethyl acetate : hexane : isopropylamine (4:16:1) to afford the desired 2-[[4-[(7-chloro-3-iodo-4-quinolinyl)-amino]pentyl]ethylamino]ethanol, ***rac*-3**, (3.44 g, 7.5 mmole, 61% yield) as an oil (Found: C, 46.86; H, 5.56; N, 9.09: $C_{18}H_{25}ClIN_3O$ requires C, 46.82; H, 5.46; N, 9.10%, NMR ($CDCl_3$) δ_H 0.99 (3H, t), 1.30 (3H, d), 1.55 (4H, m), 2.50 (6H, m), 2.80 (1H, br s), 3.50 (2H, t), 4.00 (1H, br m), 4.30 (1H, br d), 7.40 (1H, dd), 7.90 (1H, d), 7.97 (1H, d) and 8.86 (1H, s).

[3-^{2}H]-2-[[4-[(7-Chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol, [3-^{2}H]-hydroxy-chloroquine, *rac*-5: A solution of 2-[[4-[(7-chloro-3-iodo-4-quinolinyl)amino]pentyl]ethyl-amino]ethanol, ***rac*-3**, (120 mg, 0.26 mmole) in ethanol (5 ml), under an atmosphere of nitrogen, was treated with 10% palladium on charcoal (100 mg). The nitrogen was removed and replaced twice with deuterium. The reaction mixture was then left stirring overnight at room temperature. The catalyst was removed by filtration and the solvent then removed under vacuum to leave a residue which was chromatographed on silica gel eluting with ethyl acetate : methanol : isopropylamine (18:1:1) to afford [3-^{2}H]-2-[[4-[(7-chloro-4-quinolinyl)-amino]pentyl]ethylamino]ethanol, [3-^{2}H]-hydroxychloroquine, ***rac*-5**, (60 mg, 0.18 mmole,

68% yield) as a single component co-eluting with hydroxychloroquine, ***rac*-1**, (tlc, silica gel, ethyl acetate : methanol : isopropylamine (94:5:1)) and containing 88% deuterium isotope (mass spectrometry).

(S)-2-[[4-[(7-Chloro-3-iodo-4-quinolinyl)amino]pentyl]ethylamino]ethanol, (S)-3: A mixture of 4,7-dichloro-3-iodoquinoline, **4**, (462 mg, 1.42 mmole), (S)-2-[(4-aminopentyl)ethylamino]ethanol, **(S)-2**, (250 mg, 1.44 mmole) and diisopropylethylamine (250 µl, 1.44 mmole) were heated to 105°C overnight. The resulting crude reaction mixture was chromatographed on silica gel eluting with ethyl acetate : methanol : isopropylamine (94:5:1) to afford as an oil (S)-2-[[4-[(7-chloro-3-iodo-4-quinolinyl)amino]pentyl]ethylamino]ethanol, **(S)-3**, (150 mg, 23% yield) which co-eluted with ***rac*-3** and gave an $[\alpha]_D^{20}$(1M HCl) of +31.2.

(R)-2-[[4-[(7-Chloro-3-iodo-4-quinolinyl)amino]pentyl]ethylamino]ethanol, (R)-3: This compound was prepared by an identical method to that described for the (S)-enantiomer, **(S)-3**, but with (R)-2-[(4-aminopentyl)ethylamino]ethanol, **(R)-2**, used in place of **(S)-2**. The resulting (R)-2-[[4-[(7-chloro-3-iodo-4-quinolinyl)amino]pentyl]ethylamino]ethanol, **(R)-3**, gave an $[\alpha]_D^{20}$ (1M HCl) of -29.3.

(S)-[3-^{3}H]-2-[[4-[(7-Chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol, (S)-[3-^{3}H]-hydroxychloroquine, (S)-8: (S)-[3-^{3}H]-2-[[4-[(7-Chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol, [3-^{3}H]-hydroxychloroquine, **(S)-8**, (9.9 mCi, Specific Activity 28.7 Ci/mmole) was prepared from (S)-2-[[4-[(7-chloro-3-iodo-4-quinolinyl)amino]pentyl]ethylamino]ethanol, **(S)-3**, by the method described for the above synthesis of [3-^{2}H]-hydroxychloroquine, ***rac*-5**. The (S)-[3-^{3}H]-hydroxychloroquine was analysed by hplc[9] to have both a radiochemical and chemical purity of 98%.

(R)-[3-^{3}H]-2-[[4-[(7-Chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol, (R)-[3-^{3}H]-hydroxychloroquine, (R)-8: (R)-[3-^{3}H]-2-[[4-[(7-Chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol, [3-^{3}H]-hydroxychloroquine, **(R)-8**, (9.9 mCi, Specific Activity 23.8 Ci/mmole) was prepared from (R)-2-[[4-[(7-chloro-3-iodo-4-quinolinyl)amino]pentyl]ethylamino]ethanol, **(R)-3**, by the method described above for the synthesis of [3-^{2}H]-hydroxychloroquine, ***rac*-5**. The (R)-[3-^{3}H]-hydroxychloroquine was analysed by hplc[9] to have both a radiochemical and chemical purity of 98.5%.

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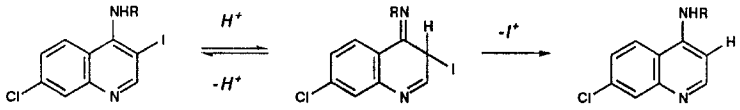
14. It is interesting to note that a similar displacement using pentylamine led only to deiodinated product, but that the iodine atom was retained when triethylamine was added to the reaction mixture. Furthermore, the iodine atom was lost from this product on heating under reflux with pentylamine hydrochloride in excess pentylamine (Smith D.I. and Thornton A.D., unpublished results). We speculate that, in these cases, the iodine atom is lost as an iodonium species after initial protonation at the 3-position of the 4-aminoquinoline nucleus as below;



15. Tritiations carried out at Cambridge Research Biochemicals, Billingham, Cleveland, U.K..