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Synthesis and Characterisation of a Double Deuterium-Labelled Ferrochloroquine.

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Summary

Starting from the well known precursor *N,N*-dimethyl(ferrocenylmethyl)amine, the total synthesis of double deuterium labelled ferrochloroquine, a ferrocenic compound mimicking chloroquine, is reported. The labelled drug **1** has been fully characterised by ^{1}H, ^{2}H, ^{13}C NMR and MS MALDI TOF experiments.

Introduction

The most severe form of human malaria is caused by *Plasmodium falciparum*. An estimated 250 million people are infected every year and 1.7 to 2.7 million of them die[1]. The emergence of multi-drug resistant *P. falciparum* has become a major problem in both prophylaxis and treatment of malaria[1]. As chloroquine has been the most widely used drug, its

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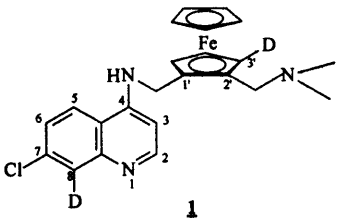
efficiency is now compromised by the spread of resistance to all parts of the world where malaria is endemic[1].

We have previously reported the synthesis and antimalarial activity *in Vitro* and *in Vivo* of a ferrocene-chloroquine analogue: ferrochloroquine (7-chloro-4-[(2-*N,N*-dimethylaminomethyl)ferrocenylmethylamino]quinoline)[2,3,4]. A deuterium labelled ferrochloroquine (**Chart 1**), both on the cyclopentadienyl ring and on the quinolin ring, was prepared. This isotopic compound could be useful for metabolic and pharmacological studies[5]. In fact, these could be used to examine the kinetics of accumulation and release by the parasite, as with chloroquine[6], to elucidate the formation of the metabolites and to study its interactions with malaria pigment.

This paper reports the synthesis and spectral characteristics of 8-deuterio-7-chloro-4-[(3-deuterio-2-*N,N*-dimethylaminomethyl)-*N*-ferrocenylmethylamino]quinoline.

Chart 1. 8-deuterio-7-chloro-4-[(3-deuterio-2-*N,N*-dimethylaminomethyl)-*N*-ferrocenylmethylamino]quinoline.



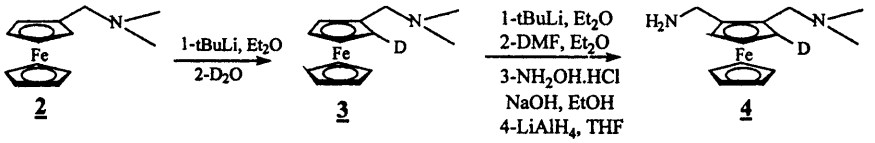
1

Results and Discussions

The precursor *N,N*-dimethyl(ferrocenylmethyl)amine **2** was metalated in the presence of *t*-butyllithium[7]. The resulting lithium derivative was then reacted with deuterium oxide giving, after workup, *N,N*-dimethyl(2-deuterioferrocenylmethyl)amine **3** which was used

without further purification. Next, compound **3** was converted to the 3-deuterio-2-(*N,N*-dimethylaminomethyl)ferrocenecarboxaldehyde following a reported procedure[7]. The latter was converted to the corresponding primary amine **4** (**Scheme 1**) via the oxime as previously described[2].

Scheme1 . Synthesis of [3-deuterio-2-(*N,N*-dimethylaminomethyl)ferrocenyl]methylamine.

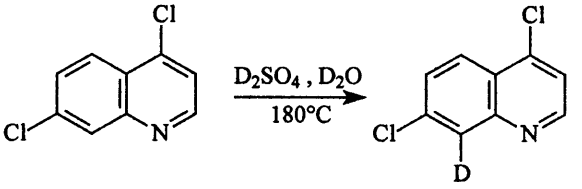


2 **3** **4**

The ^{1}H and ^{13}C NMR spectra are given in the Experimental Section. In the ^{1}H NMR spectra of **4**, two signals could be easily attributed to protons 4' and 5' at $\delta = 4.05$ ppm and $\delta = 4.13$ ppm with a small coupling $^{3}J_{4',5'} = 2.4$ Hz. The extent of deuterium incorporation was about 85%.

The deuterated dichloroquinoline **5** was easily synthesised as follows. The location of the deuterium was unambiguously deduced by comparing ^{1}H and ^{13}C NMR spectra, before and after heating.

Schema 2. Synthesis of 8-deuterio-4,7-dichloroquinoline.



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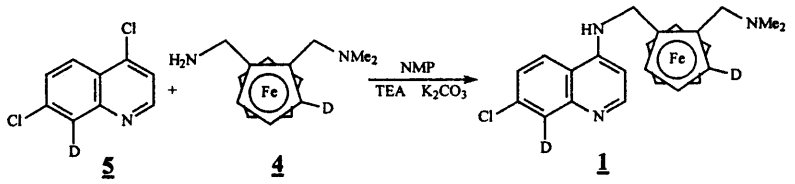
At 180°C, one hydrogen atom exchanged rapidly on treatment of 4,7-dichloroquinoline in deuterium oxide with deuteriosulfuric acid[8] (**Scheme 2**). After workup **5** was isolated in >98% yield.

Scheme 3. 8-deuterio-7-chloro-4-[(3-deuterio-2-*N,N*-dimethylaminomethyl)-*N*-ferrocenylmethylamino]-quinoline.



Finally, condensation of **4** with **5** in *N*-methyl-2-pyrrolidinone produced **1** which was isolated in a 44% yield after purification by column chromatography [2,9].

Fig. 1. $^{13}C\{^1H\}$NMR spectra of 7-chloro-4-[(2-*N,N*-dimethylaminomethyl)-*N*-ferrocenylmethylamino]quinoline (A) and 8-deuterio-7-chloro-4-[(3-deuterio-2-*N,N*-dimethylaminomethyl)-*N*-ferrocenylmethylamino]quinoline (B).

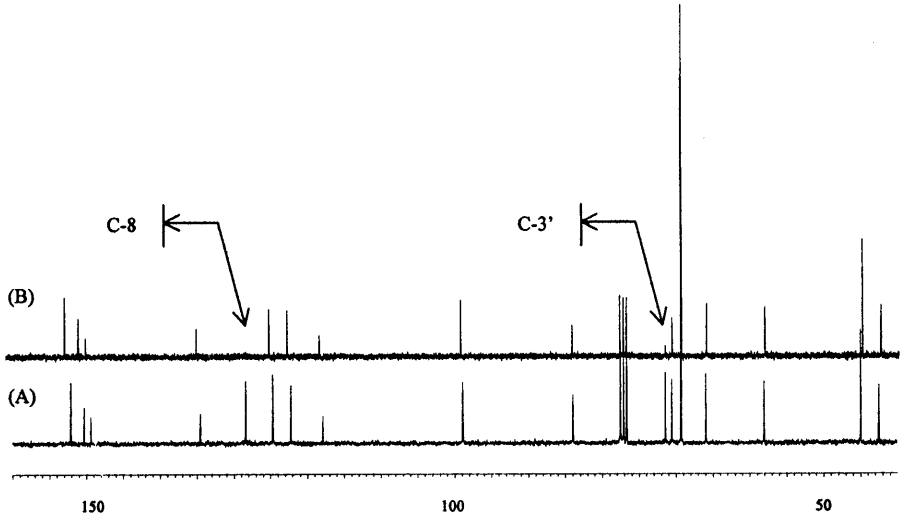


Figure 1 shows the $^{13}C\{^1H\}$NMR of the ferrochloroquine (A) and the labelled ferrochloroquine (B). The amount of deuteration can be deduced roughly from the measure of the intensity decrease of the residual CH signal of the partially deuterated carbon C-3' in the $^{13}C\{^1H\}$ NMR spectra[10,11]. The signals of ^2H compound are shifted to ^1H compound by 26.7 Hz (C-4') and 9.7 Hz (C-5'): replacement of the lighter isotope by the heavier isotope results in increasing shielding[12,13]. The spectrum of a mixture consisting of about 50% ferroquine and 50% labelled ferroquine confirmed these assignments.

The ^2H NMR spectrum showed two singlets at δ = 7.93 ppm and δ = 4.17 ppm. The relative intensities of these two signals were used to confirm the corresponding deuteration steps (C-8 : >98%, C-3' : 85%).

Conclusion

8-deuterio-7-chloro-4-[(3-deuterio-2-*N,N*-dimethylaminomethyl)-*N*-ferrocenylmethyl-amino]quinoline has been synthesised from *N,N*-dimethyl(ferrocenylmethyl)amine in 33% yield (5 steps).

Experimental Section

The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC 300 spectrometer using tetramethylsilane (TMS) as the internal standard and $CDCl_3$ as the solvent. The ^{2}H NMR spectra were recorded on a Bruker AC 400 in $CHCl_3$. MS MALDI TOF spectra were obtained using a Vision 2000 time-of-flight instrument (Finnigan MAT, Bremen, Germany) equipped with a nitrogen laser operating at wavelength of 337 nm. Between 20 and 30 single-shot spectra in either the reflector or linear mode were accumulated to obtain a good signal-to-noise ratio. The matrix used was trihydroxyacetophenone (thap). Melting points are uncorrected. Merck's Kieselgel 60 PF254 was used for the chromatography.

8-Deuterio-4,7-dichloroquinoline 5. Under nitrogen, a tube was charged with 4,7-dichloroquinoline (500 mg; 2.5 mmol) and deuteriosulfuric acid 90% (7 mL), sealed, and then heated at 180°C for 4h. After cooling to room temperature, the base was recovered and isolated by treatment with an excess of sodium hydroxide and extraction with portions of CH_2Cl_2 (2 × 50 mL). The combined extracts were dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give **5** as white needles (495 mg; 98%): mp 84-86°C; ^{1}HNMR ($CDCl_3$) δ 8.78 (d, H-2, J = 4.72 Hz), 8.16 (d, H-5, J = 8.98 Hz), 7.59 (d, H-6, J = 8.98 Hz), 7.48 (d, H-3, J = 4.73 Hz); ^{13}CNMR ($CDCl_3$) δ 150.9 (CH-2), 149.3 (C^{IV}-4), 142.6 (C^{IV}-10), 136.4 (C^{IV}-7), 128.6 (CH-6), 125.5 (CH-5),124.9 (C^{IV}-9), 121.4 (CH-3); MS MALDI TOF (thap) 203 $(MH^{37}Cl^{37}Cl)^{+}$, 201 $(MH^{37}Cl^{35}Cl)^{+}$, 199 $(MH^{35}Cl^{35}Cl)^{+}$, 191, 169. Anal ($C_9H_4DNCl_2$) C, H, N.

***N,N*-Dimethyl(2-deuterioferrocenylmethyl)amine 3.** Under nitrogen, a stirred solution of *N,N*-dimethyl(ferrocenylmethyl)amine (**2**; 2.43 g, 10 mmol) in 20 ml of anhydrous diethylether was treated with *t*-butyllithium in hexane (9 ml ; 15 mmol). Metalation was

completed in 1 hour, at room temperature. The crude solution was then reacted with deuterium oxide (0.4 ml ; 20 mmol) under nitrogen at room temperature. After 15 min., the compound was hydrolysed by addition of water (20 ml). The organic layer was separated and the remaining aqueous phase was washed with small portions of diethylether (2 × 20 ml). The Et_2O extracts were combined, dried over Na_2SO_4 and evaporated to dryness to give **3** as a red oil. We were unable to separate the ^2H and remaining ^1H compounds (90% yield). ^{1}HNMR ($CDCl_3$) δ 4.16 (m, 1H), 4.11 (s, 7H), 3.28 (s, 2H), 2.17 (s, 6H); ^{13}CNMR ($CDCl_3$) δ 83.2 (C^{IV}), 70.1 (CH), 68.5 (CH), 67.9 (CH), 59.1 (CH_2), 44.7 ($2CH_3$); MS MALDI TOF (thap) 244 M^+, 200 $(M - NMe_2)^+$.

3-Deuterio-2-(*N,N*-dimethylaminomethyl)ferrocenecarboxaldehyde. The preparation is analogous to the preparation of 2-(*N,N*-dimethylaminomethyl)ferrocenecarboxaldehyde[3] (87% yield). ^{1}HNMR ($CDCl_3$) δ 10.10 (s,1H), 4.78 (m, 1H), 4.56 (m, 1H), 4.22 (s,5H), 3.83 (d, 1H, J = 12.97Hz), 3.34 (d, 1H, J = 12.96 Hz), 2.21 (s, 6H); ^{13}CNMR ($CDCl_3$) δ 193.3 (CH), 86.5 (C^{IV}), 77.7 (C^{IV}), 75.8 (C^{IV}), 71.8 (CH), 70.3 (CH), 70.2 (5CH), 56.5 (CH_2), 44.8 ($2CH_3$); MS MALDI TOF (thap) 272 M^+, 243 $(M - CHO)^+$, 228 $(M - NMe_2)^+$.

3-Deuterio-2-(*N,N*-dimethylaminomethyl)ferrocenecarboxaldehyde-oxime. The preparation is analogous to the preparation of 2-(*N,N*-dimethylaminomethyl)ferrocene-carboxaldehyde-oxime[3] (98% yield). ^{1}HNMR ($CDCl_3$) δ 8.02 (s, 1H), 4.53 (m, 1H), 4.30 (m, 1H), 4.14 (s, 5H), 3.95 (d, J = 12.84 Hz), 3.37 (d, 1H, J = 12.85 Hz), 2.29 (s, 6H); ^{13}CNMR ($CDCl_3$) δ 148.0 (CH), 81.6 (C^{IV}), 77.3 (C^{IV}), 69.9 (C^{IV}), 69.8 (5CH), 68.9 (CH), 67.7 (CH), 56.5 (CH_2), 44.2 (CH_3); MS MALDI TOF (thap) 287 M^+, 270 $(M - OH)^+$, 243 $(M - NMe_2)^+$, 226 $[M - (NMe_2 + OH)]^+$.

[3-Deuterio-2-(*N,N*-dimethylaminomethyl)ferrocenylmethyl]amine. The preparation of compound **4** is analogous to that of [2-(*N,N*-dimethylaminomethyl)ferrocenylmethyl]amine[3] (98% yield). ^{1}HNMR ($CDCl_3$) δ 4.13 (d, 1H, J = 2.37 Hz), 4.05 (s, 5H), 4.02 (d, 1H, J = 2.40 Hz), 3.70 (d, 1H, J = 14.15 Hz), 3.61 (d, 1H, J = 13.09 Hz), 3.45 (d, 1H, J = 13.96 Hz), 2.88 (d, 1H J = 12.54 Hz), 2.17 (s, 6H); ^{13}CNMR ($CDCl_3$) δ 83.1 (C^{IV}), 68.7 (5CH), 68.1 (CH),

65.6 (CH), 58.0 (CH_2), 44.9 (CH_3), 40.5 (CH_2); MS MALDI TOF (thap) 274 $(MH)^+$, 257 $(M - NH_3)^+$, 230 $(M - NMe_2)^+$.

8-Deuterio-7-chloro-4-[(3-deuterio-2-*N,N*-dimethylaminomethyl)-*N*-ferrocenylmethyl-amino]quinoline 1. A mixture of 8-deuterio-4,7-dichloroquinoline (0.48 g, 2.41mmol), [3-deuterio-2-(*N,N*-dimethylaminomethyl)ferrocenylmethyl]amine (0.13 g, 0.48 mmol), triethylamine (2 mL, 14.4 mmol) and K_2CO_3 (0.33g, 2.38 mmol) in *N*-methyl-2-pyrrolidinone (5 mL) was stirred under nitrogen at 135°C for 4h. After cooling to room temperature, the reaction mixture was diluted with Et_2O (50 mL), washed with brine (10 × 20 mL) and dried over Na_2SO_4. The organic phase was then reduced under vacuum, and the resulting oil was purified by TLC (silicagel, eluent: AcOMe/hexane/triethylamine, 45:50:5). 1 was isolated as yellow crystals (0.438 g, 44%): mp 198-200°C; ^{2}HNMR ($CHCl_3$) δ 7.93 (s, 1H), 4.17 (s, 0.85H), ^{1}HNMR ($CDCl_3$) δ 8.53 (d, H-2, J = 5.39 Hz), 7.61 (d, H-5, J = 8.96 Hz), 7.27 (d, H-6, J = 8.95 Hz), 6.46 (d, H-3, J = 5.36 Hz), 4.38 (d, 1H, J = 12.99 Hz), 4.27 (d, 1H, J = 2.33 Hz), 4.14 (m, 6H), 4.08 (d, 1H, J = 2.38 Hz), 3.78 (d, 1H, J = 12.57 Hz), 2.88 (d, 1H, J = 12.56 Hz), 2.22 (s, 6H); ^{13}CNMR ($CDCl_3$) δ 152.1(CH), 150.3 (C^{IV}), 149.3 (C^{IV}), 134.4 (C^{IV}), 124.7 (CH), 122.2 (CH), 117.9 (C^{IV}), 98.9 (CH), 83.9 ($2C^{IV}$), 71.4 (CH/CD), 70.5 (CH), 69.2 (5CH), 65.9 (CH), 58.0 (CH_2), 44.9 (CH_3), 42.5 (CH_2); MS MALDI TOF (thap) 438 $(MH^{37}Cl)^+$, 436 $(MH^{37}Cl)^+$, 392 $(M - NMe_2{}^{37}Cl)^+$, 390 $(M - NMe_2{}^{35}Cl)^+$, 257, 214, 199. Anal ($C_{23}H_{22}D_2N_3FeCl$) C, H, N.

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