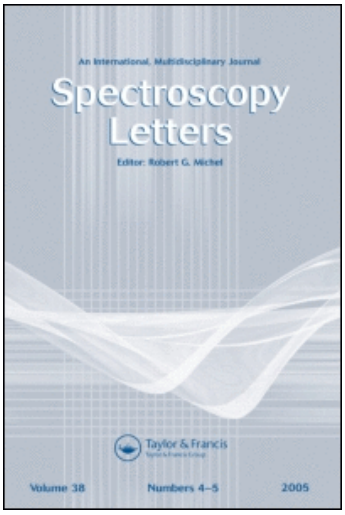

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Carbon-13 NMR Spectra of 7-Chloro-4(Substituted Amino) Quinolines Metabolites of Chloroquine

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CARBON-13 NMR SPECTRA OF 7-CHLORO-4(SUBSTITUTED AMINO) QUINOLINES METABOLITES OF CHLOROQUINE

Key Words : chloroquine metabolites, carbon-13 NMR

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ABSTRACT

Four 7-chloro-4-(substitutedamino) quinolines metabolites of chloroquine and 7-chloro-4-(2-methyl pyrrolidinyl) quinoline are studied by ^{13}C NMR spectroscopy. Assignments and chemical shifts are discussed.

INTRODUCTION

Previous studies[1-3] concluded that a series of degradation products is formed during the metabolism of chloroquine 1 (an antimalarial agent) in man. Four of these compounds have been identified as 7-chloro-4-(4-hydroxy 1-methylbutylamino) quinoline 2, 7-chloro-4-(4-N ethylamino 1-methylbutylamino) quinoline 3, 7-chloro-4 (4-amino 1-methylbutylamino) quinoline 4, and 7-chloro-4-amino quinoline 5. We report here ^{13}C NMR chemical shifts of these derivatives and also of 7-chloro-4-(2-methylpyrrolidinyl) quinoline 6, a secondary product of the synthesis of compounds 3 and 4.

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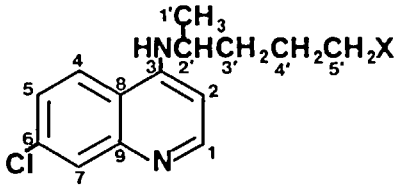

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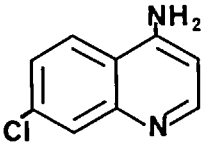
2 X=-OH

3 X=-NHC2H5

4 X=-NH2



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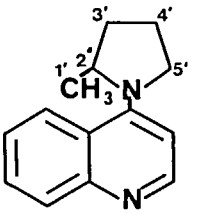

6

SCHEME

EXPERIMENTAL

Compounds

The chloroquine base 1 has been prepared by neutralization of chloroquine sulfate (Rhone-Poulenc) in aqueous solution and extraction with chloroform. Compound 5[4] was obtained also from Rhone-Poulenc . Metabolites 2 to 4, previously described by CARMACK et al.[5] have been prepared using their procedure with some modification. The hydroxylic compound 2 is obtained under the conditions foreseen by condensation of 4,7-dichloroquinoline (Aldrich Co.) on 4-amino 1-pentanol. We have synthesized this latest compound by reduction of 4-hydroxy-1-methylbutyl keton oxime with lithium aluminium hydride in diethyl ether[6]. Compound 3 normally obtained by substituting the hydroxyl group (via the bromo derivative), with N-ethylamine is purified by chromatography on silicagel : elution with chloroform supplies the secondary product 6 (oil, yield 40 %) and the following elution with methanol leads to the wished product obtained as an oil (yield 35 %). Compound 4 is prepared with the same procedure than for 3 but using liquid ammonia as nucleophile.

The crude product is a mixture of 6 and of the considered metabolite 4 separated by the same procedure than for 3. (4,oil, yield 15 %)

Purity of synthesized compounds has been controlled by elementary analysis (chlorhydrates of bases) and ^{1}H NMR spectroscopy [VARIAN EM 360 A instrument. δ ppm/TMS. Protons of aromatic rings are assigned by comparison with the corresponding spectra of chloroquine salts (7). s = singulet, d = doublet, t = triplet, q = quadruplet, m = multiplet. 1, solvent : $CDCl_3$+ CF_3CO_2H, H-1' : 1.43 (d) ; H-2' : 4.1 (m) ; H-3' : 1.78 (m) ; H-4' : 1.78 (m) ; H-5' : 3.56 (t) ; H-1 : 8.84 (m) ; H-2 : 6.83 (d) ; H-4 : 8.47 (m) ; H-5 7.57 (d) ; H-7 : 7.90 (wide). 2, solvent : $CDCl_3$, H-1' : 1.25 (d); H-2' : 3.57 (m) ; H-3' : 1.67 (m) ; H-4 : 1.67 (m) ; H-5': 2.83 (t) H-1 : 8.40 (d) ; H-2 : 6.30 (d) ; H-4 and H-5 : 7.62 to 7.92 (m) ; H-7 : 7.22 (s wide) ; CH_2 ($NHCH_2CH_3$) : 2.65 (q) ; ($NHCH_2CH_3$) : 1.10 (t) ; NH : 5.63 (wide). 3, solvent $CDCl_3$, H-1' : 1.25 (d) ; H-2' : 3.70 (m) ; H-3' : 1.63 (m) ; H-4' : 1.63 (m) ; H-5' : 2.67 (t) H-1 : 8.40 (d) ; H-2 : 6.30 (d) ; H-4 and H-5 : 7.60 to 8.10 (m) ; 7.12 (s wide). 4, solvent $CDCl_3$ + DMSO d_6 + CF_3CO_2H, H-1' : 1.46 (d); H-2' : 4.30 (m) ; H-3' : 1.8-1.9 (m) ; H-4' : 1.8-1.9 (m) ; H-5' : 3.65 (m) ; H-1 : in multiplet 7.9-8.8 ; H-2 : 6.55 (d) ; H-4 : in multiplet 7.9-8.8 ; H-5 : 7.40 (m) ; H-7 : 7.8 (s wide).]

Carbon - 13 NMR

Nucleus ^{13}C ; frequency : 20 MH_z ; instrument : VARIAN FT-80 A ; mode FT ; lock internal from the deutered solvent ; temperature : 30° C ; concentration : $\sim$0.1 mole l^{-1} ; tube size : 10 mm O.D. ; standard internal TMS or central pick of DMSO d_6 as 40.5 ppm TMS ; pulse conditions : pulse width : 8 μs ; flipangle : 45°; acquisition time : 0.8 s ; spectral width : 5 KH_z ; number of transients : 1000 to 33000 ; number of data points : 8 K.

RESULTS AND DISCUSSION

Carbon-13 chemical shifts of the cited compounds are reported on table 1. Assignments are made on signal multiplicities determined from off resonance decoupling spectra and comparison with the ^{13}C spectra of chloroquine salt in D_2O (8).

TABLE 1

^{13}C Chemical Shifts (ppm) from TMS

Compd.	C-1'	C-2'	C-3'	C-4'	C-5'	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	others
a)															
1	20.1	48.4	34.4	23.8	52.6	151.9	99.4	133.0	125.0	128.9	149.5	121.9	118.2	149.7	$N\underline{C}H_2CH_3$:47.0
															$NCH_2\underline{C}H_3$:11.2
b)															
2	20.8	48.5	33.1	30.2	61.7	152.7	99.6	134.3	124.6*	128.3	150.4*	125.2*	118.4	150.2*	
c)															
3	20.0	48.4	34.0	26.5	49.3	151.9	99.1	134.7	124.8	128.4	149.3	121.9	117.5	149.4	$N\underline{C}H_2CH_3$:44.2
															$NCH_2\underline{C}H_3$:15.2
c)															
4	19.9	47.9	33.9	26.0	49.4	151.3	98.6	134.8	124.4*	128.1	148.9*	120.5*	117.2	148.7*	
b)															
5						150.1	102.7	127.5	124.8	126.1	152.5*	124.1	116.8	149.8*	
c)															
6	18.8	55.6	34.3	25.2	55.0	150.7	104.9	134.3	128.3	126.7	153.0	123.9	121.0	-	

(*) : chemical shifts may be reversed

solvent: a) C_6D_6 + $CDCl_3$; b) DMSO d_6 ; c) $CDCl_3$

For metabolites 2, 3, 4 very weak variations are observed on the ring. Only with 6, chemical shifts of carbon atoms neighboured the 4-substituent are different from the corresponding atoms of the others compounds of the series because of the structural modification involved (the 4-substituent is here a cyclic pyrrolidin). We can also observe chemical shifts slightly differents on this substituent, in particular on C-2' C-5' and C-1'. On the other metabolites chemical shifts of the carbon chain are varying in accordance to the effect of the terminal substituent.

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