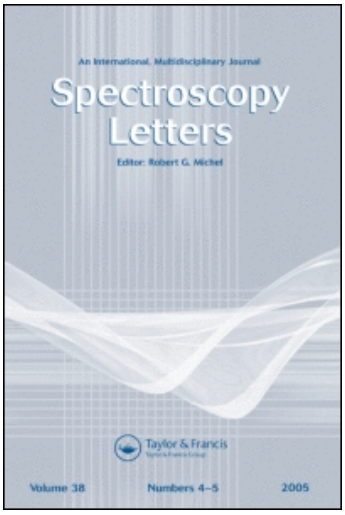

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^{1}H- AND ^{13}C-NMR STUDY OF SOME 6,7-DIHALOQUINOLONE NUCLEOSIDES AND THEIR DERIVATIVES

Key words: quinolone, nucleosides, ^{1}H- and ^{13}C-NMR, 2D-NMR (ROESY, HMBC, HMQC).

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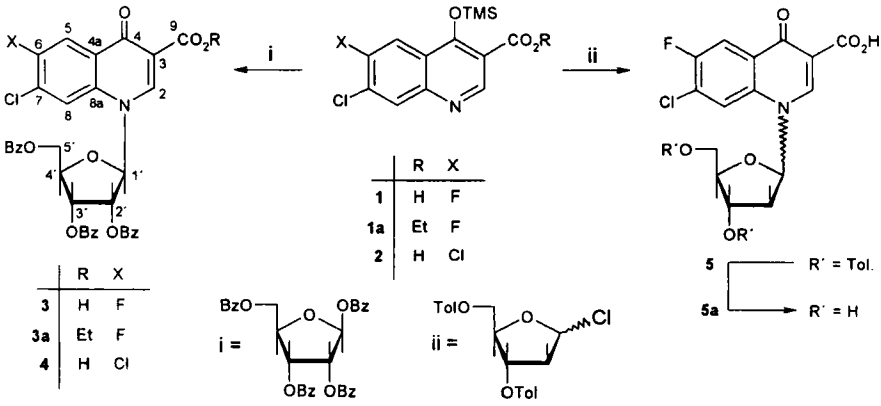
ABSTRACT: The ^{1}H- and ^{13}C-NMR spectra of 6,7-dihalo-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylic acids (**3**), (**4**), the ester (**3a**), 6-chloro-1-(2-deoxy-3,5-di-O-tolouyl-α- and β-D-*erythro*pentofuranosyl)-7-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (**5**), and its free α-nucleoside (**5a**) have been investigated. Resonance signals were assigned by homo- and heteronuclear two dimensional NMR methods (DQF-COSY, HMQC, and HMBC) for (**3**), (**4**), (**5**), and (**5a**). Ribosylation sites and anomeric configurations were identified from ROESY spectra.

INTRODUCTION

The interesting biological activities of the synthetic quinolines as antibacterial[1-3] and antiviral[4] agents or dehydrogenase inhibtors[5] urged many laboratories to construct numerous analogues of such compounds. In the present study, the spectral characteristics of some new dihaloquinolone nucleosides were investigated.[6-9]

RESULTS AND DISCUSSION

The N-nucleoside analogues 6,7-dihalo-1,4-dihydro-4-oxo-1-(2,3,4-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylic acids (**3**), (**4**), the ester (**3a**), and the 6-chloro-1-α-D-*erythro*pentofuranosyl-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**5a**) were prepared by ribosylation of the silylated quinolones 6,7-dihaloquinoloes (**1**, **1a**, and **2**) with ribose- and 2-deoxyribose derivatives *via* the Hilbert-Johnson Brikofer method [10].



The proton spin systems were identified form DQF-COSY[11] spectra, chemical shifts are listed in Table 1. Compounds **3** and **4** are discussed explicitely in the following, the assignments of **3a**, **5**, and **5a** were performed in the same way. The anomeric coupling constants of **3** and **4** are typical for β-configurated ribofuranoses (5.4 and 4.9 Hz, respectively). The rotating frame nuclear Overhauser effect (ROE)[12] between H-1′ and H-4′ is an additional proof for β-configuration. Ribosylation of **1** and **2** occurred at the N-site of the quinolone. This was also visible in the ROESY spectra where the anomeric protons of **3** and **4** showed cross signals to both H-2 and H-8 (*syn*- and *anti*- rotamers about the glycosidic bond), but not to H-5. (Fig.1).

Proton bearing carbons were detected in HMQC spectra[13]. Gradient selected HMBC spectra[14] allowed via $^{2}J_{C,H}$ and $^{3}J_{C,H}$ couplings the assignment of the residual

Table 1.

^{1}H- NMR chemical shifts [ppm] and coupling constans in $CDCl_3$ (600 MHz, 300 K).

	3[1])	3a	4	5 (α)	5 (β)	5a
H-1′	6.51	6.47	6.51	6.53	6.45	6.63
H-2′	5.91	[2])	[5])	3.19	3.01	2.85
H-2′′	--	--	--	2.60	2.75	2.11
H-3′	5.87	[2])	[5])	5.71	5.60	4.30
H-4′	4.98	4.95	4.97	5.18	4.79	4.56
H-5′	4.93	[3])	4.93	4.80	4.71	[6])
H-5′′	4.88	[3])	4.87	4.59	4.66	[6])
$J_{1',2'}$	5.4 Hz	5.0 Hz	4.9 Hz	6.2 Hz	4.2 Hz	6.5 Hz
heterocyclic ring						
H-2	9.23	8.95	9.21	9.19	9.14	9.06
H-5	8.21	8.90	8.54	8.20	7.70	8.23
$J_{5,F}$	8.4 Hz	8.9 Hz		9.0 Hz	9.1 Hz	9.1 Hz
H-8	8.02	7.88	8.02	7.87	7.68	8.36
$J_{8,F}$	5.5 Hz	5.6 Hz		6.0 Hz	6.2 Hz	7.9 Hz
H-9	14.08 (br)	[4])	(br)			

br = broad; [1]) ring couplings: $J_{2',3'}$ = 5.5 Hz, $J_{3',4'}$ = 4.3 Hz, $J_{4',5'}$ = 3.5, $J_{4',5''}$ = 3 Hz, $J_{5',5''}$ = 12.7 Hz; [2]) 5.89 ppm H-2′ and H-3′; [3]) 4.88 ppm H-5′and H-5′′; [4]) CO_2Et: 4.07 ppm (2H, q), 1.22 ppm (3H, t); [5]) 5.83 – 5.89 ppm H-2′ and H3′; [6]) 3.49 – 3.53 ppm (2H, m)

quaternery carbons (Fig. 2). The $^3J_{C,H}$ correlation of C-1′and H-2 is an additional proof for N-ribosylation in **4**. Carbons C-9 resonate at lowest field at δ_C 177.5 and 177.3 due to the deshielding nature around them. This is also visible for C-4 appearing at δ_C 165.3 and 165.1. The three carbonyls of the benzoate group resonate between δ_C 166.1 and 164.6. The olefinic carbons C-2 appear between δ 143.9 and 142.7. The presence of flourine at C-6 in compound **3** results in the appearance of a doublet with the large one-bond coupling constant of 253.6 Hz at δ_C 156.0. C-6 in **4** appeares as a singlet at higher field δ_C 131.8.The neighbouring carbons C-7 (δ_C 129.2) and C-5 (δ_C 113.6) in **3** show smaller two-bond couplings to fluorine of 20.8 Hz and 23.1 Hz, respectively. C-7 and C-5 in **4** resonate at lower field at δ_C 139.2 and δ_C 128.7, respectively.

The fused carbon C-4a of the quinoline system of the flourinated compound **3** resonates as a doublet at δ_C 126.6 with a small coupling ($J_{4a,F}$ = 6.4 Hz), carbons C-8a appear as singlets at δ_C 135.6 and 137.6, respectively. δ_C 125.7 and 137.6 were assigned to C-4a and C-8a of the dichloro compound **4**.

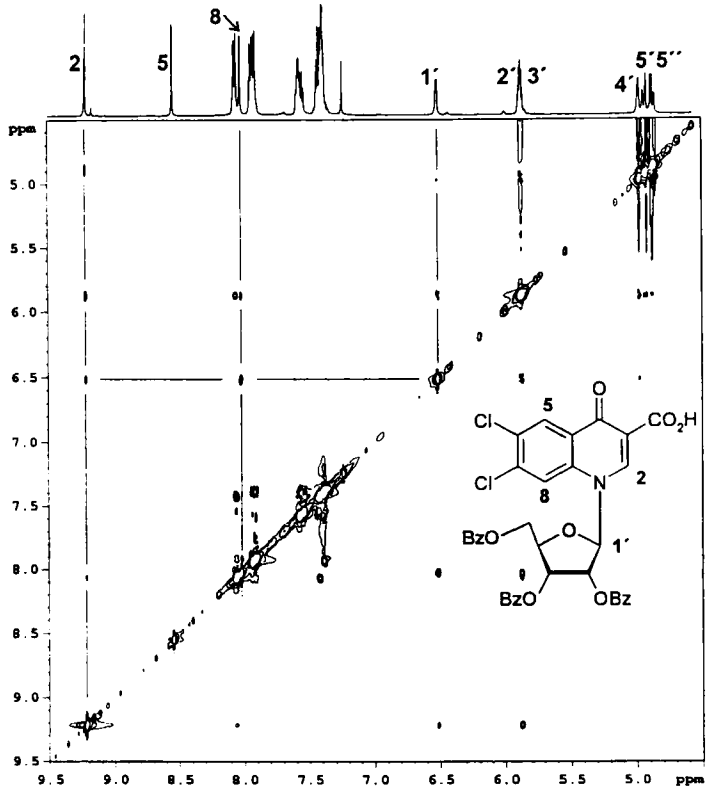


Fig. 1 2D ROESY spectrum of **4** in $CDCl_3$ (300 K, 600 MHz).

The para carbons of the aromatic rings of the benzoyl groups atoms resonate between δ_C 133.6 and 134.3, the ortho carbons were detected between δ_C 129.8 and 129.7, and the meta carbons between δ_C 128.8 and 128.6. The singlets between δ_C 128.9 and 127.6 were attributed to the quaternary carbon atoms of the aromatic groups. The resonances at δ_C 118.8 (**3**) and 118.1 (**4**) were assigned to C-8, while the signals at δ_C 113.6 (**3**, $J_{5,F}$ = 23.1 Hz) and 128.7 (**4**) were assigned to C-5. The C-3 were attributed to the signals at δ_C 109.7 and 110.3. The ^{13}C and ^{1}H chemical shifts of sugar moiety are very similar for **3** and **4**, the assignment was performed from the HMQC spectrum, the anomeric CH- groups appear separated at δ_C 91.1 (**3**) and δ_C 90.8 (**4**).

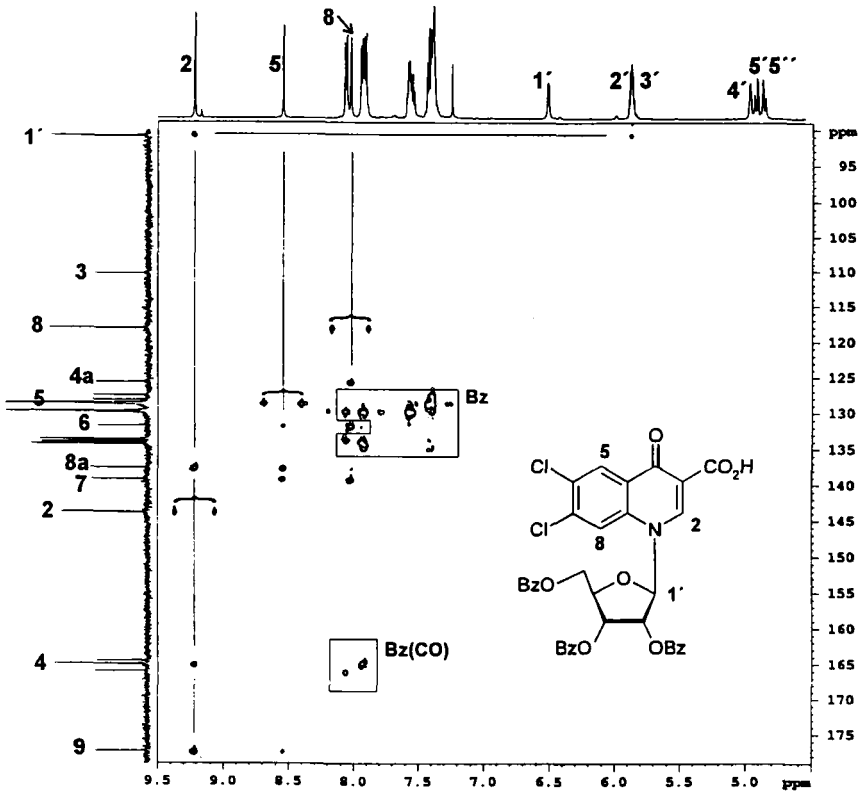


Fig. 2 2D Gradient selected HMBC spectrum of **4** in $CDCl_3$ (300 K, 600 MHz). Residual $^{1}J_{C,H}$ couplings are indicated by brackets.

Compound 5 was obtained as a mixture of α and β anomers. At 600 MHz the resonances are well separated to allow a complete assignment (Tab. 1). Deblocking of (5) with methanolic ammonia gave a mixture of α- and β-anomers of the free nucleosides, which on recrystallization from ethanol afforded mainly α-anomer (5a). The intense ROE between H-1′and H-2′^{proS} indicates the α-anomer. N-glycosylation was proven by the ROE between H-1′and H-8. The signal at δ_C 120.7 was assigned to C-8 as it has a cross peak to δ_H 8.36 of H-8 in the HMQC spectrum. The resonance at δ_C 118.8 was attributed to C-5, H-5 appears as doublet at δ_H 8.23. The olefinic C-2 at δ 144.4

Table 2

^{13}C- NMR chemical shifts [ppm] and $J_{C,F}$ coupling constans in $CDCl_3$ (600 MHz, 300 K)

	3	3a	4	5(α)	5(β)	5a
C-1′	91.1	89.8	90.8	90.5	89.3	91.6
C-2′	74.7	74.9	74.8	38.9	38.7	40.6
C-3′	71.0	71.3	71.0	74.1	74.2	70.3
C-4′	82.2	81.8	82.2	86.0	83.8	97.8
C-5′	63.0	63.7	63.0	63.6	63.4	61.5
heterocyclic ring						
C-2	143.7	142.8	143.9	143.4	142.9	144.4
C-3	109.7	111.9	110.3	108.3	108.5	106.7
C-4	165.3	165.2	165.1	166.1		165.7
C-4a	126.6,	126.5	125.7	127.5	126.3	126.2,
$J_{4a,F}$	6.4 Hz					6.0 Hz
C-5	113.6,	114.5,	128.7	113.8	113.4	118.8
$J_{5,F}$	23.1 Hz	29.0 Hz				
C-6	156.0,	155.6,	131.8	156.0,		156.0,
$J_{6,F}$	253.7 Hz	260 Hz		256 Hz		252 Hz
C-7	129.2,	128.8,	139.2	129.3		129.1
$J_{7,F}$	20.8 Hz	20.5 Hz				
C-8	118.8	117.7	118.1	118.5	118.8	120.7
C-8a	135.6	135.1	137.6	134.3	134.7	135.6
C-9	177.5	172.7	177.3	177.3	177.2	172.5
miscellaneous						
C=O (OBz)	166.1,	165.9	166.0	165.0		
	165.1	164.6	165.1	165.2		
	164.6	164.0	164.6	164.9		
Ortho carbons	129.8	129.8,	129.8	131.2		
(Ar)	129.8	127.7	129.7	131.1, 131.0		
		129.6				
Meta carbons	128.8	128.6	128.7	129.1		
(Ar)	128.7	128.5	128.6	129.0		
	128.6	128.4				
Para carbons	134.3	134.2	134.3	140.8		
(Ar)	134.0	133.9	134.0	140.6		
	133.7	133.6	133.6	140.3		
Quat carbons	128.9	128.7	128.8			
(Ar)	128.3	128.3	128.3			
	127.6	127.7	127.7			
Ar-CH_3				31.2		29.7

correlates with H-2 at δ_H 9.04. The ^{13}C and ^{1}H chemical shifts of the deoxyribose moiety were also identified in the HMQC spectrum with the anomeric carbon at δ_C 91.5 and the residual ring carbons are in regions expected for a deprotected deoxyribose (Table 2).

EXPERIMENTAL

NMR spectra were acquired with a Bruker DRX 600 spectrometer (^{1}H : 600.13 MHz, ^{13}C : 150.91 MHz). The chemical shifts are referenced to tetramethylsilane as internal standered. Spectra were acquired at 300 K in $CDCl_3$, except for **5a**, which was investigated in DMSO-d_6.

The quinolone bases 1-3 were prepared according to the references [7,15,16]. 7-Chloro-6-fluro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylic acid (**3**), ethyl 7-chloro-6-fluoro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) quinoline-3-carboxylic acid (**3a**), 6,7-dichloro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) quinoline-3-carboxylic acid (**4**), 6-chloro-1-(2-deoxy-3,5-di-O-toluoyl-α- and β-D-erythropentofuranosyl)-7-fluoro-1,4-dihydro-4-oxoquinolin-3-carboxylic acid (**5**) and 6-chloro-1-α-D-*erythro*pentofuranosyl-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**5a**), were prepared as reported earlier [9].

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