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Reference Data

^{1}H and ^{13}C NMR spectra of 3-substituted 4-quinolones

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ABSTRACT: A series of 14 3-substituted 4-oxoquinolones with or without a substituent (methyl, ethyl) in position 1 were prepared. Literature and measured data were used to study the influence of the substituent on the shifts of carbon atoms of these compounds, which are model compounds for antibacterial drugs of the nalidixic acid type.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; 3-substituted quinolones; substituent effect; nalidixic acid-type drugs

INTRODUCTION

Many medicaments with antibacterial properties[1–3] or coccidiostatic[4] activity (e.g. cyproquinate, buquinolate, decoquinate, methylbenzoquate) have a 3-substituted 4-quinolone nucleus condensed on an additional (hetero)cyclic ring. These types of heterocyclic compounds have frequently been prepared by a modified Gould–Jacobs reaction[5] or alternative methods.[1] For the synthesis of compounds unsubstituted in the 3-position, the thermal cyclization of aminomethylene Meldrum's acid derivatives[6] may be used. 1-Methyl-4-quinolone is known as the alkaloid echinopsine isolated from the seeds of *Echinopsis rito* Linn,[7] and 1-methyl-4-quinolone-3-carboxylic acid is a degradation product of the alkaloids melicopine, melicopidine and melicopicine from *Melicope fareana* (Rutaceae).[8]

A search of the literature for model systems revealed that very little work has been carried out in this area with the help of ^{13}C NMR spectroscopy.[9–11] It therefore seemed of interest to study the influence of a fused 3-substituted 4-pyridone nucleus on the benzene ring in 3-substituted quinolones in the compounds with the formula illustrated.

We did not measure the ^{1}H and ^{13}C NMR spectra of **2a** and **3a** but we used literature data[9–11] for ^{13}C chemical shifts.

EXPERIMENTAL

Spectra

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 NMR spectrometer at ambient temperature in DMSO-d_6 solutions in 5 mm tubes at 299.9 and 75.0 MHz for proton and carbon, respectively. A spectral width of 4 kHz was chosen for ^{1}H with 32K data points, using a 45° pulse and repetition time of 3 s. ^{13}C NMR spectra were measured with a 16 kHz spectral width of 32K data points using a 45° pulse and WALTZ 16 decoupling sequence. Standard Varian pulse sequences and parameters were used for measurements of 1D APT and 2D HETCOR spectra. The chemical shifts were reference to the central peak of DMSO-d_6 solutions (2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C).

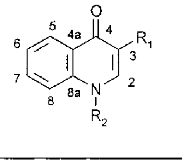
Materials

Compounds **1a–d**, **1f–h**, **2** and **3** were synthesized according to known procedures.[5,6,12] 3-Trifluoroacetyl-4-oxo-1,4-dihydroquinoline (**1e**) was prepared by a two-step procedure starting from ethyl ethoxymethylenetrifluoroacetoacetate[13] with aniline analogous to the Gould–Jacobs reaction.[5] Elemental analysis (calc./found): C 54.78/54.57, H 2.51/2.42, N 5.81/5.57%.

RESULTS AND DISCUSSION

Spectral analysis of ^{1}H NMR spectra was carried out by using a spin simulation and an iteration program based on LAOCOON.[14] In all simulated spectra the r.m.s. error was <0.003 Hz. ^{1}H NMR chemical shifts and coupling constants of the aromatic rings are given in Tables 1 and 2, respectively. Coupling constants of aromatic protons (Table 2) were in approximately the same range for all compounds (except **2b** and **3c**). From the assigned ^{1}H spectra the assignment of the ^{13}C chemical shifts was achieved by 2D HETCOR and 1D APT experiments. ^{13}C NMR data are given in Table 3.

The introduction of a substituent in the 3-position causes the strongest change of chemical shifts in compounds **1b–h** for H-2. This change is caused mainly by substituent effects of electron acceptor groups in the order $NO_2 > COCF_3 > CN > COOCH_3 > COCH_3 > COOC_2H_5$. Other aromatic hydrogens are also shifted to low field but not as much.



Compound	R$_1$	R$_2$	Compound	R$_1$	R$_2$
1a	H	H	**2a**	H	Me
1b	COOH	H	**2b**	COOH	Me
1c	COOMe	H	**2c**	COOMe	Me
1d	COOEt	H	**2d**	COOEt	Me
1e	$COCF_3$	H	**3a**	H	Et
1f	CN	H	**3b**	COOH	Et
1g	$COCH_3$	H	**3c**	COOMe	Et
1h	NO_2	H	**3d**	COOEt	Et

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Table 1. ^1H NMR chemical shifts of compounds **1–3** (in ppm)

Compound	H-5	H-6	H-7	H-8	H-2	$N\text{-}(CH_2)\text{-}CH_3/H$[c]	$O\text{-}(CH_2)\text{-}CH_3/R_1$
1a[a]	7.95	7.33	7.66	7.53	8.09	11.76 bs	—
1b[b]	8.25	7.59	7.83	7.76	8.86	13.40 bs	—
1c	8.15	7.43	7.70	7.61	8.58	12.18 bs	—
1d	8.19	7.40	7.68	7.60	8.46	11.94 bs	(4.25 q), 1.31 t
1e	8.21	7.48	7.76	7.66	8.96	12.86 bs	—
1f	8.25	7.47	7.77	7.63	8.71	12.35 bs	—
1g	8.23	7.44	7.70	7.62	8.51	12.50 bs	2.62 s
1h	8.28	7.50	7.82	7.74	9.20	12.60 bs	—
2b	8.39	7.69	8.00	7.98	9.06	4.11 s	—
2c	8.25	7.51	7.81	7.74	8.71	3.92 s	3.74 s
2d	8.23	7.48	7.78	7.70	8.65	3.93 s	(4.23 q), 1.33 t
3b	8.39	7.67	7.98	8.05	9.05	(4.59 q), 1.41 t	—
3c	8.24	7.47	7.79	7.79	8.71	(4.39 q), 1.35 t	3.73 s
3d	8.25	7.47	7.78	8.00	8.69	(4.40 q), 1.34 t	(4.21 q), 1.27 t

[a] δ (H-3) = 6.03, $^3J(2,3) = 7.42$ Hz.
[b] δ (COOH) = 15.34.
[c] bs, broad singlet; s, singlet; t, triplet; q, quartet.

Intramolecular hydrogen bonding influences the chemical shifts of **1b**, **2b** and **3b** (Table 1). We propose from the observed chemical shifts that the carboxylic acids have a hydrogen bond between the hydroxyl of the carboxyl group and the carbonyl of the pyridone nucleus. We could not measure the proton resonances of the carboxyl groups of these acids because of the low solubility of **2b** and **3b**.

In all cases an influence of the substituent in the 3-position was detected. Tables 4 and 5 give the substituent chemical shifts related to benzene (SCSB, $\delta = 128.5$ ppm) and to the corresponding quinolone (SCSQ[9–11]), respectively. The use of $CDCl_3$ for **1a** (Table 2) did not change the chemical shifts and it is possible to compare these data with shifts in DMSO solutions (SCSQ, Table 5).

Table 2. Absolute values of coupling constants of aromatic protons (in Hz)

Compound	$^3J(5,6)$	$^3J(6,7)$	$^3J(7,8)$	$^4J(5,7)$	$^4J(6,8)$
1a	8.15	7.65	8.41	1.40	1.10
1b	7.82	7.49	8.30	1.30	1.10
1c	8.67	6.07	7.38	1.73	0.68
1d	8.57	6.98	8.68	1.40	0.73
1e	7.47	7.00	8.34	1.36	0.90
1f	8.45	7.43	8.24	1.50	1.50
1g	8.10	6.97	7.54	1.43	1.00
1h	8.31	7.68	7.78	1.65	1.28
2b	8.88	6.41	2.45	1.48	1.57
2c	8.03	7.90	8.05	1.46	0.80
2d	7.84	7.25	8.30	1.50	0.50
3b	8.02	7.20	7.93	1.03	0.95
3c	7.79	—	—	—	—
3d	7.96	6.90	7.86	1.45	1.10

The change of $\delta(5)$ and $\delta(6)$ in **2a** and **3a** compound with **1a** is due to the introduction of the substituent in the 3-position. The substituent in the 3-position (R_1) had the strongest influence on carbon chemical shifts in the order C-3 > C-2 > C-4 (Tables 3 and 4), in agreement with the substituent effect of each substituent: it is in the range 93.6 ppm (for CN) to 131.0 ppm (for NO_2). The neighbouring C-2 signal also varied by 8.1 ppm (139.4–147.5 ppm). The intramolecular hydrogen bond between the hydroxyl of the carboxyl group and the carbonyl of the pyridone nucleus also has an influence on the chemical shifts of C-4 and the CO signals, which are shifted downfield by about 3–4 ppm.

The implementation of the substituent on nitrogen (R_2) changed the carbon chemical shift in the 2-position. The exchange of the substituent R_2 from methyl to ethyl caused a small (*ca.* 1 ppm) but observable change in the chemical shifts of C-2.

For all carbons of the benzene ring incremental chemical shifts elicited by the presence of the 3-substituted 4-quinolone ring were established (SCSB, Table 5). These, in combination with similar data pertinent to the fused triazole or pyrazine ring, allow the prediction of chemical shifts in various fused multi-ring systems.[15,16]

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Table 3. ^{13}C chemical shifts of compounds **1–3**

Compound[a]	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	R_1	N-R_2
1a[9]	139.5	108.8	177.2	125.9	125.0	123.1	131.5	118.3	140.1	—	—
1a	139.4	108.7	177.1	125.8	124.9	123.0	131.6	118.2	140.0	—	—
1b	145.1	107.6	178.3	124.4	125.0	126.1	133.9	119.6	139.9	166.4	—
1c	145.1	109.5	173.4	127.2	124.7	125.6	132.4	118.8	138.9	165.4 51.1	—
1d	143.7	109.9	172.8	126.9	123.9	125.2	131.6	118.1	138.6	164.3 58.9 13.7	—
1e	147.5	113.0	173.5	127.4	124.7	125.6	133.3	119.3	138.7	179.8 127.5	—
1f[b]	146.6	93.6	174.4	125.1	125.0	125.5	133.3	119.2	139.0	116.8	—
1g	144.2	117.7	175.3	127.8	125.0	125.8	132.6	118.9	139.1	196.4 31.2	—
1h	142.4	131.0	167.7	128.1	125.8	126.0	133.2	119.5	138.3	—	—
2a[10]	144.0	109.8	178.4	126.9	126.6	123.7	132.2	115.6	140.6	—	40.5
2b	150.2	107.3	177.8	125.2	126.4	125.6	134.2	118.3	140.3	166.2	41.7
2c	149.9	109.3	172.6	127.9	125.9	124.7	132.4	117.0	139.7	164.9 50.9	40.5
2d	150.4	109.6	172.9	128.0	126.1	124.9	132.6	117.3	139.8	164.9 59.6 14.3	40.8
3a[11]	143.8	108.8	176.1	126.6	125.7	122.9	131.9	116.3	139.2	—	46.7 14.2
3b	149.3	107.7	177.9	125.6	126.6	126.1	134.5	118.2	139.2	164.4	49.2 14.7
3c	149.4	109.8	173.3	128.4	126.7	125.2	133.1	117.4	138.7	165.4 51.5	48.3 14.5
3c[11]	148.9	110.0	172.7	128.3	126.4	124.7	132.6	117.0	138.5	164.6 59.6 14.3	47.8 14.3
3d	149.1	110.2	173.1	128.4	126.6	125.0	132.9	117.3	138.7	164.9 59.6 14.3	48.1 14.3

[a] Ref. 9, 9 : 1 DMSO-d_6–$CDCl_3$; Ref. 10, in $CDCl_3$; Ref. 11, in DMSO-d_6.
[b] ^1J(C,F) = 290 Hz, ^2J(C,F) = 36 Hz, ^3J(C,F) = 72 Hz.

Table 4. Substituent chemical shifts related to benzene (SCSB) of compounds **1–3**

Compound	C-4a	C-5	C-6	C-7	C-8	C-8a
1a	−2.7	−3.6	−5.5	3.1	−10.3	11.5
1b	−4.1	−3.5	−2.4	5.4	−8.9	11.4
1c	−1.3	−3.8	−2.9	3.9	−9.7	10.4
1d	−1.6	−4.6	−3.3	3.1	−10.4	10.1
1e	−1.1	−3.8	−2.9	4.8	−9.2	10.2
1f	−3.4	−3.5	−3.0	4.8	−9.3	10.5
1g	−0.7	−3.5	−2.7	4.1	−9.6	10.6
1h	−0.4	−2.7	−2.5	4.7	−9.0	9.8
2a	−1.6	−1.9	−4.8	3.7	−12.9	12.1
2b	−3.3	−2.1	−2.9	5.7	−10.2	11.8
2c	−0.6	−2.6	−3.8	3.9	−11.5	11.2
2d	−0.5	−2.4	−3.6	4.1	−11.2	11.3
3a	−1.9	−2.8	−5.6	3.4	−12.2	10.7
3b	−2.9	−1.9	−2.4	6.0	−10.3	10.7
3c	−0.1	−1.8	−3.3	4.6	−11.1	10.2
3d	−0.1	−1.9	−3.5	4.4	−11.2	10.2

Table 5. Substituent chemical shifts related to corresponding quinolones (**1a**, **2a**, **3a**) (SCSQO$^{9-11}$) of compounds **1**–**3**

Compound	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
1b	5.7	−1.1	1.2	−1.4	0.1	3.1	2.3	1.4	−0.1
1c	5.7	0.8	−3.7	1.4	−0.2	2.6	0.8	0.6	−1.1
1d	4.3	1.2	−4.3	1.1	−1.0	2.2	0	−0.1	−1.4
1e	8.1	4.3	−3.6	1.6	−0.2	2.6	1.7	1.1	−1.3
1f	7.2	−15.1	−2.7	−0.7	0.1	2.5	1.7	1.0	−1.0
1g	4.8	9.0	−1.8	2.0	0.1	2.8	1.0	0.7	−0.9
1h	−3.0	22.3	9.4	2.3	0.9	3.0	1.6	1.3	−1.7
2b	6.2	−2.5	−0.6	−1.7	−0.2	1.9	2.0	2.7	−0.3
2c	5.9	−0.5	−5.8	1.0	−0.7	1.0	0.2	1.4	−0.9
2d	6.4	−0.2	−5.5	1.1	−0.5	1.2	0.4	1.7	−0.8
3b	5.5	−1.1	1.8	−1.0	0.9	3.2	2.6	1.9	−0.5
3c	5.6	1.0	−2.8	1.8	1.0	2.3	1.2	1.1	−0.7
3d	5.3	1.4	−3.0	1.8	0.9	2.1	1.0	1.0	−0.5

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