Solution phase, solid state and computational structural studies of the 2-aryl-3-bromoquinolin-4(1*H*)-one derivatives[1]

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The structures of the potentially tautomeric 2-aryl-3-bromoquinolin-4(1*H*)-ones were studied using spectroscopic (NMR, IR and mass), X-ray crystallographic and quantum chemical calculations. These systems are found to exist in solution (^{1}H NMR, ^{13}C NMR, and PCM-B3LYP) and solid state (IR and X-ray) as the NH-4-oxo derivatives, and their carbonyl nature is also corroborated by comparison of their spectroscopic data with those of the corresponding *N*-methylated and *O*-methylated derivatives. The presence of the quinolinol (hydroxyquinoline) isomer in the gas phase is confirmed by low and high resolution mass spectrometry, and supported by B3LYP gas phase calculations.

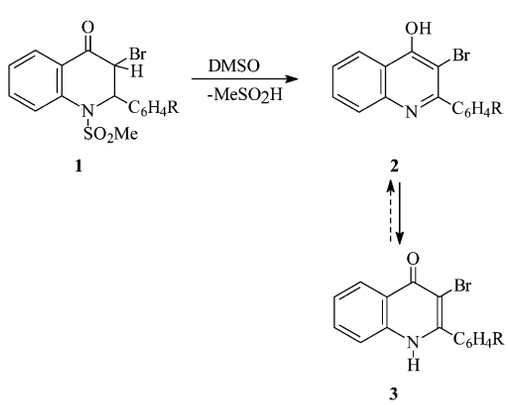
Introduction

The determination of the precise structure of heterocyclic molecules which are potentially tautomeric such as the quinolone *versus* quinolinol relationship has attracted considerable attention over the years because of the role of tautomerism in both chemical and biochemical processes.[2,3] The 4-hydroxy derivatives of the six-membered aromatic nitrogen heterocycles are known to exist in equilibrium with the NH-4-oxo form and the position of the tautomeric equilibrium is known to favour the keto isomer because of the marked acidity of the OH and basicity of nitrogen.[2,3] The enol form, on the other hand, has been found to be favoured by electron-withdrawing groups at the α-position (relative to N) or the presence of hydrogen bonding substituents such as the carboxy group at the β-position.[2] Most of the studies on the tautomerism of the 2-substituted quinolin-4-ols and the 2-substituted 4-quinolones are based largely on the UV, IR and NMR spectroscopic data and to a lesser extent on the semiempirical and *ab initio* methods.[2] The scarcity of information from X-ray crystallographic studies of the 2-substituted-4-quinolone or 2-substituted-quinolin-4-ol derivatives is probably due to the lack of suitable crystalline material for such analysis.[2]

Despite the existence of a large amount of data from NMR, UV and IR spectroscopic studies of the 4-quinolone derivatives, several researchers still continue to erroneously report the structures of the analogous systems as either the quinolinols[4] or the quinolone isomers.[5,6] The ability to accurately predict the position of the tautomeric equilibrium in such compounds is critical in order to design models for biochemical transformations and to gain a sound understanding of the structure–activity relationship. Our continued interest in the synthesis and structural property studies of quinolone derivatives,[7] prompted us to investigate the solution, gas and solid-state structural properties of the title compounds using spectroscopic (NMR, IR and mass), X-ray crystallographic and computational techniques. The results of the spectroscopic and X-ray crystallographic methods have been interpreted in combination with the results of computer modelling and by comparison with the corresponding *N*-methyl and *O*-methyl derivatives.

Results and discussion

Continued interest in the design and synthesis of analogues of the medicinally important quinolone derivatives with potential antibacterial activity stems from the alarming increase in bacterial infections that have become resistant to the most commonly used antibiotics.[8] Recently, we have reported the results of dimethyl sulfoxide-promoted dehydromethylsulfonylation of the 2-aryl-3-bromo-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones **1** to afford the 2-aryl-3-bromo-4-quinolones **3** as products, which have been characterized by means of NMR (^{1}H and ^{13}C), IR and mass spectroscopic techniques (Scheme 1).[9] The NH-4-oxo structures **3** of the products of Scheme 1 were assigned by comparison of their C-4 signals



1 **2** **3**

4'-R = H (**a**); F (**b**); Cl (**c**); Br (**d**) and OMe (**e**)

Scheme 1

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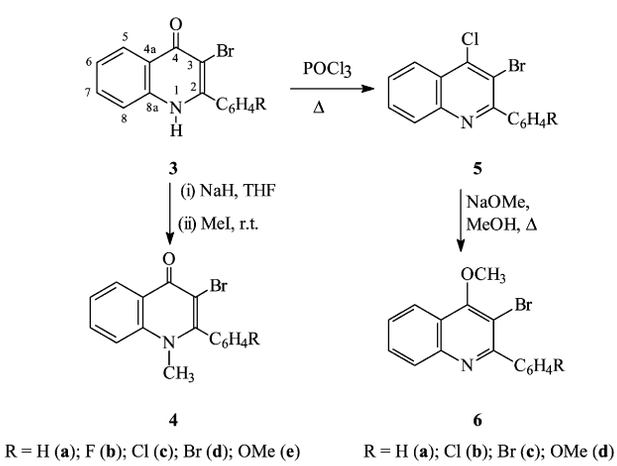
Table 1 ^{13}C NMR chemical shifts (ppm) of systems **3** (in DMSO-d_6, 75 MHz), **4** (in $CDCl_3$, 75 MHz) and **6** (in $CDCl_3$, 75 MHz), and the calculated ^{13}C NMR chemical shifts for **3a** and **2a**. For atom labeling see Scheme 2

Compound (R)	CH_3	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
3a (H)	—	149.9	105.3	171.7	122.9	124.0	125.3	132.2	118.5	139.0
3a (Calc.)[a]	—	148.9	105.7	180.6	125.9	124.5	124.6	134.3	120.3	141.6
2a (Calc.)[a]	—	156.4	108.0	151.0	120.4	125.5	127.8	128.3	133.3	146.1
3b (F)	—	149.3	105.9	172.1	123.3	124.5	125.7	132.6	118.9	139.3
3c (Cl)	—	148.7	105.4	171.7	123.0	124.1	125.3	132.2	118.5	139.0
3d (Br)	—	149.1	105.3	171.6	123.1	123.4	125.3	132.1	118.9	139.3
3e (OMe)	—	149.6	105.4	171.7	122.8	123.8	125.2	131.9	118.4	139.0
4a (H)	38.4	152.6	109.0	172.6	124.8	124.3	127.6	132.6	115.8	140.5
4b (F)	38.4	151.3	109.0	172.9	124.2	124.5	127.7	132.6	115.7	140.6
4c (Cl)	38.4	151.4	109.0	172.4	124.2	124.5	127.6	132.7	115.8	140.6
4d (Br)	38.4	151.4	109.1	172.5	124.4	124.5	127.6	132.7	115.8	140.6
4e (OMe)	38.4	152.6	109.5	172.6	124.8	124.2	127.5	132.5	115.8	140.5
6a (H)	61.8	148.1	110.1	160.2	123.6	121.8	127.1	129.7	130.3	140.3
6b (Cl)	61.9	148.1	110.0	158.9	123.7	121.9	127.3	129.7	130.5	139.0
6c (Br)	61.9	148.1	110.1	158.9	123.7	121.8	127.3	129.7	130.5	138.6
6d (OMe)	61.9	148.3	110.5	160.2	123.4	121.8	127.0	129.2	130.5	138.9

For the sake of clarity, the ^{13}C NMR chemical shifts of the aryl substituents (ring B) are not included. [a] Computed chemical shifts for quinolinol **2a** and quinolone **3a**.

(at δ *ca.* 172 ppm) with those of the analogous 2-methyl-3-bromo-4(1*H*)-oxo-8-(1-methylethyl)quinoline-5-carbaldehyde[10] and the *N*-alkylated quinolone derivatives[9] which resonate at $\delta_C \geq 170$ ppm.

Literature reports indicate that the enol tautomers of 4-hydroxypyridines predominate in systems bearing hydrogen bond-acceptors at the 3-position adjacent to the OH group, as for instance in hydroxyquinoline-3-carboxylic acid derivatives[2] or a strong electron-withdrawing group such as a chlorine atom at the 2-position in pyridones.[3] The keto form is also known to exist exclusively in polar solvents such as DMSO as well as in the solid state where efficient solvation and intermolecular hydrogen bonding are key stabilizing factors, respectively.[11] In order to obtain qualitative information on the tautomeric structure prevailing in solution and the solid state, we prepared the corresponding *N*-methyl and *O*-methyl derivatives of the products of Scheme 1 and compared their spectroscopic data. Regioselective *N*-methylation of systems **3** to afford the *N*-methylated derivatives **4** was achieved using NaH and MeI in THF (Scheme 2).[9] Methylation of the analogous 2-alkyl-4(1*H*)-



Scheme 2

quinolones using NaH and methyl iodide in DMF is reported to give the *O*-methylquinoline derivatives,[8] while on the other hand, MeI–K_2CO_3 mixture in DMF affords a mixture of the *O*-methylated and *N*-methylated derivatives.[4a,12] The isomeric *O*-methylquinolines **6** were synthesized in this work from the corresponding 2-aryl-3-bromo-4-chloroquinolines **5**, prepared in turn, from substrates **3** by refluxing in phosphoryl chloride (Scheme 2).[9]

The carbonyl nature of systems **3** in solution is also corroborated by comparison of their ^1H NMR and ^{13}C NMR spectroscopic data (Table 1) with those of the corresponding *N*-methylquinolone **4** and *O*-methylquinoline derivatives **6**. The ^1H NMR spectra of systems **4** are characterized by the intense singlet at δ *ca.* 3.57 ppm corresponding to the methyl group and a group of aromatic proton signals in the region δ 7.00–8.60 ppm. The significant downfield shift of the doublet corresponding to the 5-H nucleus to δ *ca.* 8.57 ppm reflects the *peri*-deshielding effect of the neighbouring carbonyl group.[13]

The ^{13}C NMR signals at δ 38.4 ppm and at δ 172.4 ppm corresponding to the N–CH_3 and C=O nuclei emphasize their carbonyl nature and rule out the possibility of the isomeric *O*-methylated derivatives **6** (Table 1). The ^{13}C=O chemical shift values (at δ *ca.* 172.4 ppm) of the *N*-methylated derivatives **4** compare well with those of the corresponding precursors **3** (at δ *ca.* 171.7 ppm). The methyl signals of the *O*-methylated derivatives **6**, on the other hand, resonate relatively downfield at δ_H *ca.* 4.13 ppm and δ_C *ca.* 61.9 ppm compared with those of the *N*-methylated isomers **4** (at δ_H *ca.* 3.57 ppm and δ_C *ca.* 38.4 ppm). The high-field shift of the C-4 signals to δ *ca.* 158.9 ppm, confirm the absence of the carbonyl group in systems **6**. The fact that the products adopt the NH-4-oxo structures **3** rather than the 4-hydroxy structures **2** is supported by the C-4 signals at δ *ca.* 172 ppm which are comparable to those of the corresponding *N*-alkylated derivatives (Table 1). The ^{13}C NMR chemical shifts of the geometrically optimized quinolinol **2** and the NH-4-oxo derivatives **3** were also computed using the ACD/CNMR Spectrum Generator from ACD/Labs™ which emulates operation of the actual spectrometer (operating frequency, solvent and concentration of solute) and can quantitate precisely intramolecular interactions.[14] The difference in chemical shift values for the C-4 nuclei of the products of Scheme 1 ($\delta_{C=O}$ *ca.* 172.0 ppm) and the computed values (also in DMSO-d_6) for the NH-4-oxo systems **3** ($\delta_{C=O}$ *ca.* 180.9 ppm) and the quinolinol tautomer **2** (δ_{C-OH} *ca.* 151.0 ppm) are $\Delta\delta_{C=O}$ *ca.* 8.0 ppm and $\Delta\delta_{C-OH}$ *ca.* 21.0 ppm, respectively. The experimentally determined chemical shifts of the products of Scheme 1 compare well with the computed chemical shift values for the NH-4-oxo derivatives and rule out the possibility of the quinolinol tautomers (see Table 1). The computed chemical shifts values of the quinolinol tautomers **2** are, in turn, comparable to those of the 4-methoxy derivatives **6**. Thus, in addition to the computed chemical shift data, a comparison of the measured ^1H NMR and ^{13}C NMR spectroscopic data of the *N*-methylated **4** and *O*-methylated derivatives **6** with those of the products of Scheme 1 allows an unequivocal retrospective assignment of the carbonyl functionality to systems **3**. The

Table 2 IR frequencies for compounds **3**, **4** and **6**

3, **4**, **6** (R)	ν_{max}/cm^{-1} (raw powder)
3a (H)	3366, 3061, 2906, 1686, 1627, 1572, 1541, 1500, 1492, 1469, 755, 696
3b (F)	3367, 3067, 2933, 1676, 1629, 1574, 1541, 1500, 1473, 838, 759, 699
3c (Cl)	3369, 3062, 2905, 1685, 1628, 1550, 1501, 1013, 876, 821, 759, 700
3d (Br)	3386, 3065, 2917, 1678, 1629, 1550, 1501, 1489, 1013, 821, 759, 700
3e (OMe)	3368, 3059, 2902, 1687, 1628, 1596, 1550, 1500, 876, 822, 759, 700
4a (H)	2924, 1615, 1593, 1491, 1462, 1400, 1220, 1157, 864, 806, 769
4b (F)	2923, 1616, 1594, 1511, 1457, 1346, 1153, 967, 876, 812, 759
4c (Cl)	2923, 2853, 1620, 1597, 1505, 1464, 1396, 1246, 1180, 770
4d (Br)	2918, 2849, 1617, 1593, 1526, 1482, 1157, 1081, 1008, 869, 771
4e (OMe)	2924, 1620, 1597, 1505, 1490, 1463, 1396, 1246, 1081, 859, 770
6a (H)	1578, 1487, 1367, 1087, 876, 850, 770, 593, 573
6b (Cl)	1572, 1489, 1366, 1260, 1113, 1084, 981, 823, 761
6c (Br)	1572, 1488, 1366, 1112, 1080, 981, 899, 822, 761
6d (OMe)	1577, 1486, 1368, 1351, 1086, 877, 824, 760

Table 3 Crystal data and details of the X-ray data collections and refinements for **3b**

Empirical formula	$C_{15}H_9BrFNO$
Formula weight	318.14
T/K	293(2)
Wavelength/Å	0.71073
Crystal system	Rhombohedral
Space group	$R\bar{3}$
Unit cell dimensions	
a/Å	19.117(3)
b/Å	19.117(3)
c/Å	18.364(5)
V/ Å^3	5812(2)
Z	18
D_c/g cm^{-3}	1.636
Absorption coefficient μ/mm^{-1}	3.184
F(000)	2844
Crystal size/mm	0.43 × 0.18 × 0.14
θ range for data collection	1.66–28.35°
Index ranges	$-25 \le h \le 20$
	$-25 \le k \le 24$
	$-24 \le l \le 24$
Reflections collected	13404
Independent reflections	3215 [R_{int} = 0.0853]
Completeness to θ	99.3% (to θ = 28.35°)
Absorption correction	Semiempirical from equivalents
Max. and min. transmission	0.6641 and 0.3413
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3215/0/176
Goodness-of-fit on F^2	0.964
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0338, wR_2 = 0.0793
R indices (all data)	R_1 = 0.0624, wR_2 = 0.0892
Largest diff. peak and hole/e Å^{-3}	0.658 and −0.261

carbonyl nature of the products of Scheme 1 was further confirmed in the solid state by IR spectroscopy. Their IR frequencies [ν_{max}/cm^{-1} *ca.* 1627 (strong) and 1680 (weak)] are comparable to those of the analogous C-3 unsubstituted 2-aryl-quinolin-4(1*H*)-ones described in the literature.[6,15] The presence of the carbonyl moiety in systems **4** (ν_{max} *ca.* 1618 cm^{-1})[16] and its absence in the 4-methoxyquinoline derivatives **6** was also confirmed by IR spectroscopy (Table 2). The failure for IR spectroscopy to easily distinguish between strongly coordinated O–H ··· N bond and O ··· H–N bond is known to limit its application in the determination of the tautomeric structures of certain strongly hydrogen-bonded compounds.[3]

Single X-ray crystal structure determination (see Table 3 and Experimental section)† was therefore carried out on the 4′-fluorophenyl derivative prepared in Scheme 1 and the compound is found to exist as the NH-4-oxo derivative **3b** instead of the quinolinol **2b**. In the crystal lattice (Fig. 1(a)) compounds **3** adopt a conformation in which the 2-aryl group lies at an angle (125°) to the plane of the C-ring thus deviating from co-planarity to relieve steric interaction between the 3-Br and 1-H atoms and phenyl hydrogen atoms (2′-H and 6′-H) (see Table 4 for torsion angles). This deviation from co-planarity is probably responsible for the facilitation of *N*-methylation of systems **3** described in Scheme 2. In the crystal lattice, systems **3** exhibit strong intermolecular hydrogen bonding with the O ··· H and N–H interatomic distances of 2.04 and 0.81 Å, respectively (Fig. 1(b)). This observation agrees with literature results for the simple 4-hydroxypyridine–pyridone system, in which the keto tautomer exists exclusively in the solid state as C=O ··· H–N intermolecularly hydrogen-bonded ribbons.[11]

† CCDC reference number 189746. See http://www.rsc.org/suppdata/p2/b2/b206657b/ for crystallographic files in .cif or other electronic format.

Table 4 Selected torsion angles (°) for compound **3b**

N(1)–C(1)–C(10)–C(11)	125.9(3)
C(2)–C(1)–C(10)–C(11)	−55.9(3)
N(1)–C(1)–C(10)–C(15)	−53.1(3)
C(2)–C(1)–C(10)–C(15)	125.1(3)
C(1)–C(10)–C(15)–C(14)	179.5(3)
C(9)–N(1)–C(1)–C(10)	179.3(2)
C(1)–N(1)–C(9)-C(8)	179.3(2)

Geometry optimizations of the quinolinols **2** and quinolones **3** were first accomplished using PM3 (Table 5). In all cases, the 2-aryl-3-bromoquinolin-4(1*H*)-ones **3** which adopt a geometry similar to that obtained from X-ray studies are essentially iso-energetic with **2** at this level of computation. The calculated dipole moments of the quinolones **3** are higher than those of the corresponding quinolinol isomers **2** thus predicting the greater stability for the keto forms in agreement with the solution phase and solid state results. The small energy differences between the corresponding tautomeric isomers (<0.5 kcal mol^{-1}) obtained using PM3 are supported by B3LYP/6-31G(d) computations also after ZPE corrections were added (Table 5). The large difference in dipole moments between quinolinols **2** and quinolones **3** remains at the B3LYP level. The latter compounds should therefore be preferentially stabilized in polar solvents. Indeed, PCM-B3LYP/6-31G(d) calculations, in which the action of a polar solvent with the same dielectric constant as DMSO is modeled, reveal that the quinolinones are more stable than the quinolinols by 4–5 kcal mol^{-1} (Table 5). Our results agree with the observation reported in literature[2,3,11] and support the formulation of the NH-4-oxo form which exists exclusively in this form in the solid state and in a polar solvent such as DMSO.

Although mass spectrometry does not allow detailed information to be obtained on the conformational properties of a given molecule, which are fundamental in the evaluation of the structure–activity relationship,[17] this technique is used to characterize organic compounds in the gas phase. The study of tautomerism in the gas phase by means of mass spectrometry is complicated by the problem of distinguishing between prototropic equilibria occurring before and after ionization.[2] Low and high-resolution mass spectroscopic data were obtained for compounds **3**, **4** and **6** and the experimentally determined

Table 5 Calculated energies (kcal mol^{-1} and a. u.) and dipole moments (D) for the enol **2** and keto **3** forms at PM3 and B3LYP/6-31G(d) levels

		PM3					B3LYP/6-31G(d)				
2/3	R	ΔH_f(**2**)	ΔH_f(**3**)	ΔH_f(**2** − **3**)	μ(**2**)	μ(**3**)	E_{abs}(**2**)[a]	E_{abs}(**3**)[a]	E_{rel}(**2**–**3**)[b]	μ(**2**)	μ(**3**)
a	H	39.4	38.9	0.5	2.35	5.34	−3279.31349	−3279.31563	1.3	0.81	6.91
							−3279.31611	*−3279.32503*	(0.4)		
									4.7		
b	F	−3.7	−4.4	0.7	2.84	4.74	−3378.54718	−3378.54852	0.8	2.06	6.24
							−3378.54753	*−3378.55600*	(0.0)		
									4.5		
c	Cl	32.6	32.4	0.2	3.44	4.93	−3738.90974	−3738.91062	0.6	2.80	6.01
							−3738.90983	*−3738.91764*	(−0.3)		
									4.1		
d	Br	47.1	47.0	0.1	3.76	4.82	−5850.41845	−5850.41919	0.5	2.69	6.05
							−5850.41888	*−5850.42655*	(−0.4)		
									3.9		
e	OMe	2.5	1.1	1.4	3.13	6.22	−3393.83703	−3393.83689	−0.1	1.80	7.06
							−3393.83917	*−3393.84833*	(−0.9)		
									4.9		

[a] Absolute energies in a.u. from B3LYP/6-31G(d) (normal print) and PCM-B3LYP/6-31G(d)//B3LYP/6-31G(d) (italics) calculations. [b] Relative energies in kcal mol^{-1} calculated with B3LYP/6-31G(d) (normal print), B3LYP/6-31G(d) + ZPE corrections from B3LYP/3-21G (normal print in parenthesis), and PCM-B3LYP/6-31G(d)//B3LYP/6-31G(d) ($\varepsilon = \varepsilon_{DMSO} = 46.7$) + ZPE corrections from B3LYP/3-21G (italics) .

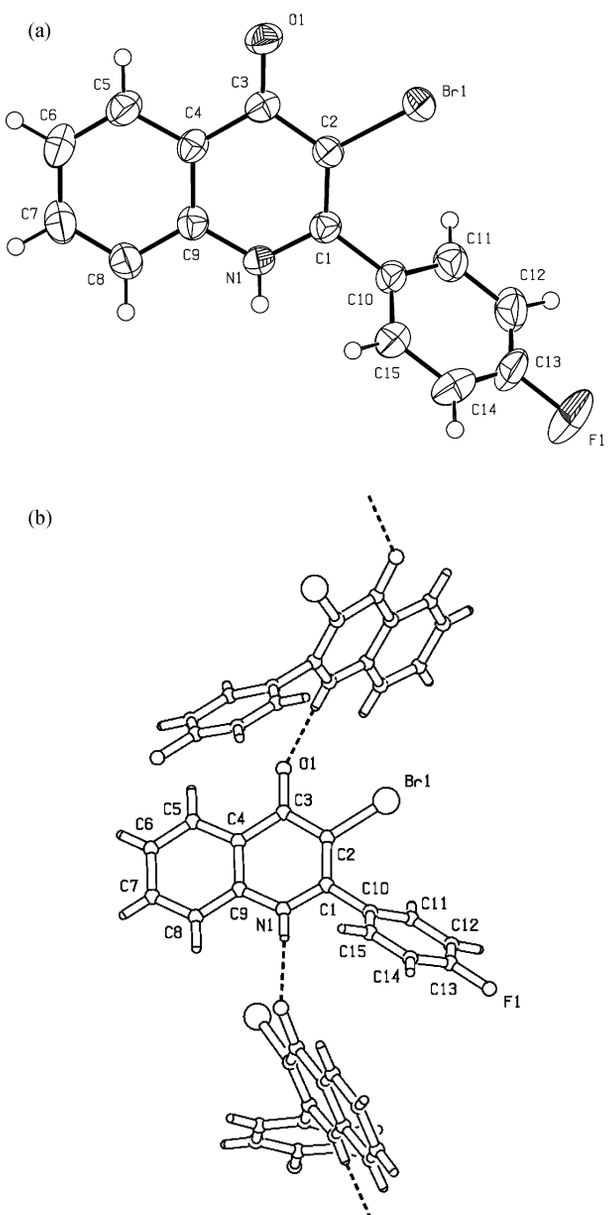


Fig. 1 (a) ORTEP diagram of **3b**, showing crystallographic labeling. Thermal ellipsoids are drawn at the 50% probability level. (b) X-Ray crystal structure for **3b**, showing the hydrogen-bonding pattern.

accurate *m*/*z* values, represent in each case, closest fit consistent with the assigned structures (Table 6).

The contraction of the C-ring of the molecular ion of systems **3** and their *N*-methyl derivatives **4** by the elimination of carbon monoxide affords radical cations in 4.5–9.3% and 22–33% relative abundance, respectively. The 4-methoxyquinolines **6**, on the other hand, undergo fragmentation patterns typical for ethers, which distinguish them from the isomeric *N*-methyl derivatives **4**. The molecular ion (M^+) in the spectra of the *N*-methyl derivatives **4** constitutes the base peak indicative of the high stability of these NCH_3-4-oxo derivatives. On the other hand, the base peak in the spectra of the potentially tautomeric systems **3** results from the extrusion of bromine from the molecular ion. The significantly low relative abundance of the [M – CO] fragments in the spectra of the products of Scheme 1 when compared to those of the corresponding *N*-methyl derivatives **4** may be due to some proportion of the quinolinol isomer **2** in the gas phase. This is further confirmed in the case of derivatives **2a**,**b** and **d** by the presence of the low abundance fragment (2.0–3.5%) formulated as $[C_{15}H_8N^{79}BrX]^+$ resulting from the extrusion of OH radical from the molecular ion (see Table 6). The negligible energy differences between tautomers **2** and **3** as determined by semiempirical and density functional computations (see Table 5) explain the coexistence of both tautomers in the gas phase as determined by mass spectrometric techniques.

Conclusion

A comparison of the ^{1}H NMR, ^{13}C NMR and IR spectroscopic data of systems **3** with those of the *N*-methylated **4**[9] and *O*-methylated derivatives **6** and the crystal lattice data from X-ray analysis all point to the exclusive NH-4-oxo nature of the products of Scheme 1. The 3-bromine atom in systems **3** which is inductively electron withdrawing and equidistant from the N-1 and O-4 atoms in terms of bonds does not affect the position of equilibrium. On the other hand, the resonance effect of the 2-aryl ring and remote factors such as the electron-withdrawing or -donating inductive effect of the *para* substituents on this ring also appear not to upset the position of the equilibrium. Thus the NH-4-oxo form exists exclusively in DMSO and in the solid state in agreement with DFT calculations using a polarizable continuum model and literature observations.[2,3,11] The results from gas phase quantum chemical calculations and the negligible relative abundance (< 10 %) of the [M – CO] fragments in the low and high-resolution mass spectra of the products of Scheme 1 implicate the quinolinol

Table 6 Selected mass fragments of systems **3**, **4**, and **6** with relative intensities in parentheses

Compound	Molecular formula	M^+ (%)	*m*/*z* (%)	*m*/*z* (%)
3a	$C_{15}H_{10}NO^{79}Br$	298.9941 (67.2)	270.999 (M − CO, 9.2) 281.992 (M − OH, 3.5)	220.076 (M − Br, 100)
3b	$C_{15}H_9NOF^{79}Br$	316.9838 (56.2)	288.991 (M − CO, 6.6) 299.945 (M − OH, 3.1)	238.067 (M − Br, 100)
3c	$C_{15}H_9NOF^{35}Cl^{79}Br$	332.9559 (55.6)	306.971 (M − CO, 7.9)	254.039 (M − Br, 100)
3d	$C_{15}H_9NO^{79}Br_2$	376.9029 (50.8)	348.901 (M − CO, 4.6) 359.902 (M − OH, 2.0)	219.066 (M − Br, 100)
3e	$C_{16}H_{12}NO_2{}^{79}Br$	329.0053 (87.7)	301.002 (M − CO, 5.5)	250.087 (M − Br, 100)
4a	$C_{16}H_{12}NO^{79}Br$	313.0108 (100)	285.015 (M − CO, 33.1)	234.093 (M − Br, 67.9)
4b	$C_{16}H_{11}NOF^{79}Br$	331.0009 (100)	303.005 (M − CO, 28.7)	252.083 (M − Br, 57.2)
4c	$C_{16}H_{11}NO^{35}Cl^{79}Br$	346.9727 (100)	318.977 (M − CO, 23.8)	268.053 (M − Br, 39.2)
4d	$C_{16}H_{11}NO^{79}Br_2$	390.9213 (100)	362.925 (M − CO, 25.4)	311.999 (M − Br, 19.2)
4e	$C_{17}H_{14}NO_2{}^{79}Br$	343.0211 (100)	315.024 (M − CO, 22.4)	264.102 (M − Br, 56.7)
6a	$C_{16}H_{12}NO^{79}Br$	313.0113 (100)	312.003 (72.8)	284.006 (48.6)
6b	$C_{16}H_{11}NO^{35}Cl^{79}Br$	348.9701 (100)	347.971 (82.2)	318.953 (47.8)
6c	$C_{16}H_{11}NO^{79}Br_2$	390.9207 (51.3)	389.914 (35.8)	361.918 (26.3)
6d	$C_{17}H_{14}NO_2{}^{79}Br$	343.0225 (100)	342.017 (65.7)	314.982 (39.3)

tautomers **2** in the vapour phase, which is also confirmed by the [M – OH] fragments. The results of this study serve to extend the existing prototropic tautomerism data for the *N*-containing heterocyclic compounds and also demonstrates the importance of X-ray crystallography and the use of fixed derivatives in resolving uncertainties on the 2-substituted-4-quinolone *versus* 2-substituted-quinolin-4-ol tautomeric equilibrium.

Experimental

Melting points were recorded on a Thermocouple digital melting point apparatus and are uncorrected. IR spectroscopic data were obtained as powder using Nicolet Nexus FT-IR spectrometer equipped with an OMNI Sampler. NMR spectra were obtained as DMSO-d_6 or $CDCl_3$ solutions using Varian Mercury 300 MHz or Varian Gemini 200 MHz NMR spectrometers and the chemical shifts are quoted relative to the solvent peaks. Low and high-resolution mass spectra were recorded at Cape Technikon Mass Spectrometry Unit using VG–70 SEQ MASPEC II[32] instrument. XRD data collection and solution were carried out at the Jan Boeyens Structural Chemistry Laboratory (University of the Witwatersrand). The synthesis and characterization of compounds **3**, **4a**,**c**–**e** and **5a**,**b** and **c** described in this investigation have recently been reported.[9] Analytical data for compounds **4b** and **5d**, which are new are as follows:

2-(4′-Fluorophenyl) derivative 4b. Solid (55%); mp 195–198 °C (EtOH); δ_H (300 MHz, $CDCl_3$) 3.56 (3H, s, NCH_3), 7.19–7.27 (3H, m, 2′-H, 6′-H and 6-H), 7.48 (1H, t, *J* 8.1 Hz, 7-H), 7.53 (1H, d, *J* 8.4 Hz, 8-H), 7.72 (2H, d, *J* 8.7 Hz, 3′-H and 5′-H) and 8.57 (1H, dd, *J* 1.5 and 9.0 Hz, 5-H).

2-(4′-Methoxyphenyl) derivative 5d. Solid (67%); mp 188–190 °C (EtOH); *m*/*z* (Found: M^+, 346.972. $C_{16}H_{11}NO^{79}Br^{35}Cl$ requires 346.971).

Synthesis of 2-aryl-3-bromo-4-methoxyquinolines 6

A stirred mixture of 2-aryl-3-bromo-4-chloroquinoline **5** (1 equiv.) and NaOMe (1.5 equiv.) in methanol (5 ml per mmol of **6**) was boiled under reflux for 18 h. The cooled reaction mixture was quenched with ice-cold water and the resulting precipitate was filtered and recrystallised to afford the 2-aryl-3-bromo-4-methoxyquinoline **6**.

2-Phenyl derivative 6a. Solid (65%); mp 175–178 °C (EtOH); δ_H (200 MHz, $CDCl_3$) 4.16 (3H, s, OCH_3), 7.48–7.81 (7H, m, C_6H_5, 6-H and 7-H), 8.14 (1H, d, *J* 8.4 Hz, 8-H) and 8.16 (1H, d, *J* 8.4 Hz, 5-H).

2-(4′-Chlorophenyl) derivative 6b. Solid (60%); mp 189–192 °C (EtOH); δ_H (300 MHz, $CDCl_3$) 4.13 (3H, OCH_3), 7.56–7.65 (6H, m, 7-H, 8-H and C_6H_4Cl), 7.76 (1H, dt, *J* 0.9 and 8.7 Hz, 6-H) and 8.11 (1H, d, *J* 8.1 Hz, 5-H).

2-(4′-Bromophenyl) derivative 6c. Solid (70%); mp 194–196 °C (EtOH); δ_H (300 MHz, $CDCl_3$) 4.13 (3H, s, OCH_3), 7.46 (2H, d, *J* 8.4 Hz, 3′-H and 5′-H), 7.57–7.68 (4H, m, 2′-H, 6′-H, 7-H and 8-H), 7.75 (1H, dt, *J* 1.5 and 7.9 Hz, 6-H) and 8.11 (1H, d, *J* 8.4 Hz, 5-H).

2-(4′-Methoxyphenyl) derivative 6d. Solid (60%); mp 178–180 °C (EtOH); δ_H (200 MHz, $CDCl_3$) 3.90 (3H, s, 4′-OCH_3), 4.16 (3H, s, 4-OCH_3), 7.05 (2H, dd, *J* 2.8 and 9.3 Hz, 3′-H and 5′-H), 7.45 (1H, t, *J* 8.3 Hz, 7-H), 7.73 (3H, dd, *J* 2.4 and 9.2 Hz, 2′-H, and 6′-H), 7.77 (1H, t, *J* 8.3 Hz, 6-H), 8.13 (1H, dd, *J* 0.8 and 9.8 Hz, 8-H) and 8.20 (1H, d, *J* 9.2 Hz, 5-H).

X-Ray crystallographic data collection and processing[18]

Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo–*K*α radiation (50 kV, 30 mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program SAINT+ [18a] and absorption corrections were made using the program SADABS. [18b] The crystal structure was solved by direct methods using SHELXTL.[18c] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculation based on F^2 using SHELXTL. With the exception of H1, atoms were located from the difference map then positioned geometrically and allowed to ride on their respective parent atoms. H1 was located from the difference map and refined isotropically without restraints. Diagrams and publication material were generated using SHELXTL and PLATON.[18d]

Quantum chemical calculations

Geometry optimizations were accomplished using PM3 with the MOPAC program as implemented in Alchemy 2000 software package from Tripos inc.[19] Density functional theory (DFT) calculations were carried out with the GAUSSIAN 98 program.[20] Full geometry optimizations have been carried out without symmetry constraints using the three-parameter hybrid DFT functional of Becke (B3LYP)[21] with the 6-31G(d) basis set. Frequency calculations were done at the B3LYP/3-21G level and indicate that all of the investigated forms are minima (no imaginary eigenvalues of the Hessian matrix). The zero-point vibrational energies were retrieved from the frequency calculations and used to correct the relative energies. Single-

point energy calculations in DMSO have been performed at the B3LYP/6-31G(d)//B3LYP/6-31G(d) level using the Polarized Continuum Model (PCM) of Tomasi and co-workers.[22]

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