Analysis of the Tautomeric Structures of Auronols by ^{13}C N.m.r. and Comparison with the Isomeric Flavonols

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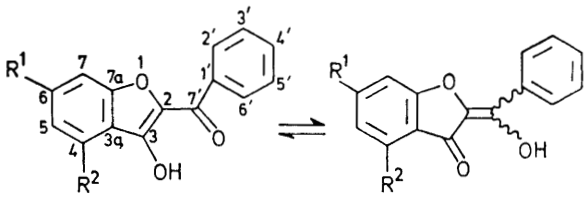
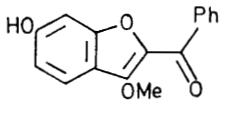
The ^{13}C n.m.r. spectra of a series of auronols and flavonols have been analysed in order to determine the tautomeric structures of the auronols and to distinguish between the two series. By using a specifically ^{13}C labelled auronol sample, together with coupling constants, changes on addition of D_2O, and solvent-shift data, it has been shown that auronol and 6-substituted auronols exist in solution as the 2-benzoyl-3-hydroxybenzofurans whereas 4,6 dihydroxyauronol exists as a mixture of the *E*- and *Z*-7′-hydroxyaurones.

In continuation of our earlier study of the ^{13}C n.m.r. spectra of flavonoids,[1-3] and as an aid to the structural elucidation of natural products and to the investigation of some rearrangements of auronols,[4] we have examined the ^{13}C n.m.r. spectra of a series of auronols (1)—(5) and flavonols (7)—(10). Some of the signals could be tentatively assigned by comparison with the spectra of simple aurones (11) and (12) and flavones (13) and (14) and on the basis of their off-resonance spectra. However in order to make rigorous assignments and to get information about the tautomeric structures of the auronols it was necessary to use a variety of other assignment techniques which are discussed below.



(a)		(b)
(1)	$R^1 = R^2 = H$	(1)
(2)	$R^1 = OH, R^2 = H$	(2)
(3)	$R^1 = OMe, R^2 = H$	(3)
(4)	$R^1 = OCOPh\ R^2 = H$	(4)
(5)	$R^1 = R^2 = OH$	(5)



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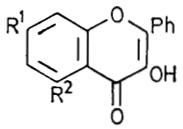
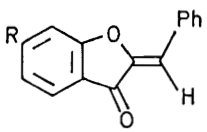
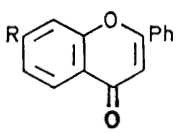


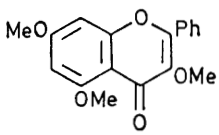
(7) $R^1 = R^2 = H$
(8) $R^1 = OH, R^2 = H$
(9) $R^1 = OMe, R^2 = H$
(10) $R^1 = R^2 = OMe$



(11) R = H
(12) R = OMe

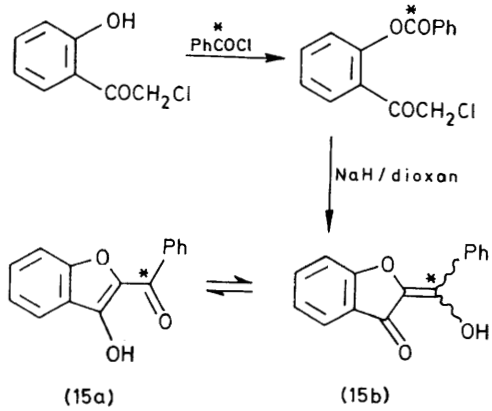


(13) R = H
(14) R = OMe



(16)

The spectra of the aurones and auronols are listed in Table 1. Auronol (1) and the 6-substituted auronols (2)—(4) give signals corresponding to exactly the number



(15a) (15b)

Scheme

of carbon atoms present indicating that they exist as only one of the three possible isomeric forms (1a) and *E*- and *Z*-(1b) in both $(CD_3)_2SO$ and $CDCl_3$ solution. In order to identify the signal due to C-7′ we prepared the specifically ^{13}C labelled auronol (15) in which C-7′ is derived from ^{13}C labelled benzoyl chloride (Scheme).[5] Examination of the ^{13}C spectrum of this compound (Table 2) shows conclusively that it is the signal at 182.54 which is enhanced and which can therefore be unequivocally assigned to C-7′. Furthermore the ^{13}C–^{13}C coupling constants of the other carbon atoms clearly identify the signals at 135.20 and 135.67 as due to C-1′ and C-2 since they are both strongly coupled to the labelled atom. However the spectrum of (15) alone does not permit a distinction between tautomers (15a) and (15b) since it is

not unknown for a ring enol carbon atom to appear at lower field than a carbonyl carbon atom.[6]

Examination of the undecoupled spectra of auronol (1) in $(CD_3)_2SO$ and $CDCl_3$ (Table 3) lends strong support to the signal assignments. For example it is possible to distinguish between the signals of C-2 and C-1′ since the former is seen as a singlet while the latter appears as a triplet due to long-range coupling to H-2′ and H-6′. Furthermore, the signals due to C-7a and C-3 can be identified since the former is present as a triplet coupled to H-4 and H-6 while the latter is present as a doublet coupled only to H-4. The appearance of C-3a as a double doublet rather than as a triplet is also in line with the observation that $^{13}C-^{1}H$ coupling through an oxygen substituted carbon atom (C-7a) is considerably reduced (1.7 Hz) as compared with the more normal value (8.7 Hz) for coupling to H-5.[7]

Two important changes were observed after addition of D_2O to the auronol solution. Firstly, there is a marked diminution in the signal assigned to C-3 in both $(CD_3)_2SO$ and in $CDCl_3$. This, by comparison with other compounds,[6,8] is taken to indicate that this carbon atom carries a hydroxy-group. Secondly, in $CDCl_3$ solution the signal due to C-3 experiences an upfield shift of 0.45 p.p.m. which is much larger than for any other carbon atom, although in $(CD_3)_2SO$ no such shift is observed. Such changes have been previously observed for other compounds [9] containing enolic hydroxy-groups and once again support the idea that C-3 carries a hydroxy-group which, at least in $CDCl_3$ solution, is involved in a weak intramolecular interaction with the carbonyl group at C-7′. This, therefore, defines the preferred tautomeric form of the auronol as the 2-benzoyl-3-hydroxybenzofuran (1a). Since the multiplicities of all the signals are unchanged after D_2O exchange it can be deduced that the rate of exchange of the enolic proton is not greatly reduced by hydrogen bonding which therefore rules out the possibility of a strong intramolecular interaction between the hydroxy and carbonyl groups.

Comparison of the spectra of auronol (1a) in $(CD_3)_2SO$ and $CDCl_3$ supports the assigned structure since the signal assigned to C-3 is shifted upfield by 7.17 p.p.m. on going from $CDCl_3$ to $(CD_3)_2SO$, while none of the other carbon atoms are shifted by more than 1.9 p.p.m. This large solvent shift presumably reflects the difference in solvation of the enolic hydroxy-group in the two solvents and may be diagnostic of a carbon atom bearing a hydroxy-group subject to differential solvation.

The ^{13}C n.m.r. spectrum of 4,6-dihydroxyauronol (5) is clearly different from those of the other aurones considered so far. Firstly, two tautomers/isomers are present since two sets of signals are observed. Secondly, the chemical shifts of the two oxygen-bearing carbon atoms of the β-diketone system are very different (in both isomers) from those of the other auronols. They are now found at 170.05/174.96 and 187.68/190.26 as compared, for example, to 157.65 and 176.87 in the case of compound (2) which only differs from (5) in lacking the 4-OH group. It would thus seem that compound (5) adopts the alternative tautomeric structure (5b), and also that both *Z*- and *E*-isomers are present. The preference in this case for the hydroxy-aurone form can be readily understood by the stabilisation of the 3-oxo-group due to hydrogen bonding to the 4-hydroxy-group. This point is being further investigated.

The enol ether (6) was obtained by treating compound (2) with diazomethane in ether. The close similarity between its ^{13}C spectrum and that of compounds (1)—(4),

TABLE 1

^{13}C N.m.r. spectra of aurones and auronols

Compd. no. / Carbon no.	(11) [a]	(12) [a]	(1) [b]	(2) [b]	(3) [b]	(4) [b]	(6) [b]	(5) [b]	$\Delta_{E/Z}$
1′	132.25	132.29	136.98	135.94	136.45	137.03	138.21	133.78/134.22	2.33
2′6′	131.47	131.13	129.08	128.76	128.81	128.95	128.75	128.67	
3′5′	128.82	128.66	128.37	128.38	128.33	128.30	128.07	128.23	
4′	119.81	129.40	132.49	132.11	132.19	132.39	131.92	129.58/131.91	0.44
7′	122.88	111.63	182.52	176.86	178.66	182.21	182.08	170.05/174.96	4.91
2	146.80	147.85	135.37	134.83	135.22	136.25	136.62	133.25/134.10	0.85
3	184.57	182.67	151.06	157.65	154.58	152.23	150.41	187.68/190.26	2.58
4	124.55	125.59	121.52	122.66	122.21	122.15	123.17	165.10/168.22	3.12
5	123.39	112.00	123.15	113.84	113.57	113.80	114.06	96.70/97.88	1.18
6	136.78	167.22	130.13	161.74	162.67	153.59	159.88	161.88/164.98	3.10
7	112.88	96.54	112.64	97.93	96.03	97.90	97.83	89.93/90.25	0.32
7a	166.03	168.33	153.57	157.42	156.38	161.73	155.22	156.31/158.32	2.01
3a	121.57	114.69	120.95	112.64	113.73	112.63	113.00	100.89/102.46	1.57
OMe		55.91			55.88		60.65		

[a] $CDCl_3$. [b] $(CD_3)_2SO$.

TABLE 2

^{13}C N.m.r. spectra of (15) and (1)

Carbon no.	δ($CDCl_3$)	$J(^{13}C-^{13}C)$	Intensity (15)	Intensity (1)
1′	135.20	58.4	52	44
2′6′	129.64	2.2	337	330
3′5′	128.60	3.8	321	326
4′	133.16		147	167
7′	182.54		3809	32
2	135.67	75.4	42	23
3	158.29	4.5	53	57
4	121.53		146	162
5	123.29		170	171
6	130.90		159	167
7	112.79		145	158
7a	155.01	3.4	46	26
3a	119.84	2.1	49	42

TABLE 3

Undecoupled spectra of auronol (1)

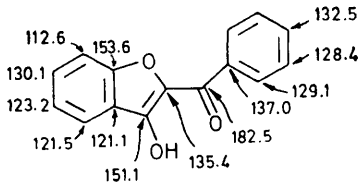
$(CD_3)_2SO$ Carbon no.		Mult.	^1J(C-H)	^3J(C-H)	$\Delta\delta(D_2O)$	Δ Intensity (%)	
1′	136.98	t	—	6.7	−0.12	17	
2′6′	129.08	dt	162.5	6.4	+0.03	−2	
3′5′	128.37	dd	163.8	6.8	+0.09	1	
4′	132.49	dt	161.5	7.7	+0.15	−2	
7′	182.52	t	—	3.4	+0.14	30	
2	135.37	s	—	—	−0.04	−18	
3	151.06	d	—	2.0	+0.06	−25	
4	121.52	dd	166.8	6.7	0.00	3	
5	123.15	dd	164.9	6.1	+0.12	−5	
6	130.13	dd	162.5	8.1	+0.17	−2	
7	112.64	dd	166.8	7.7	+0.03	3	
7a	153.57	t	—	7.2	+0.05	17	
3a	120.95	dd	—	8.7,1.7	−0.18	−6	
$CDCl_3$ Carbon no.							$\Delta\delta[(CD_3)_2SO \rightarrow CDCl_3]$
1′	135.10	t	—	6.6	−0.01	8	−1.88
2′6′	129.56	dm	166.0		−0.02	4	+0.48
3′5′	128.48	dm	159.4		−0.03	−3	+0.11
4′	133.06	dt	160.9	7.4	−0.02	2	+0.57
7′	182.19	t	—	3.7	+0.03	−4	−0.33
2	135.62	s	—	—	−0.09	−25	+0.25
3	158.23	d	—	2.8	−0.45	−46	+7.17
4	121.38	dd	165.7	7.4	−0.07	8	−0.14
5	123.17	dm	162.9		−0.02	3	+0.02
6	130.79	dd	161.7	8.2	−0.05	1	+0.66
7	112.66	dd	166.3	7.7	−0.03	−1	+0.02
7a	154.86	t	—	8.5	−0.10	7	+1.29
3a	119.72	m	—		−0.08	22	−1.23

TABLE 4

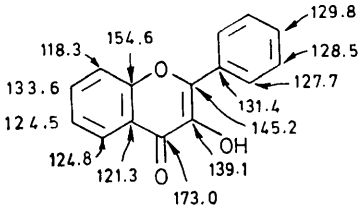
^{13}C N.m.r. spectra of flavones and flavonols

Compd. no. / Carbon no.	(13) [a]	(14) [a]	(7) [b]	(8) [b]	(9) [b]	(10) [b]	(16) [b]	(17) [b]
1′	131.5	131.6	131.35	131.49	131.42	131.20	130.68	121.7
2′6′	126.0	125.8	127.65	127.32	127.37	126.91	127.83	129.5
3′5′	128.8	128.7	128.46	128.40	128.40	128.42	128.52	115.4
4′	131.3	131.1	129.80	129.44	129.53	129.27	130.29	159.2
2	163.0	162.6	145.15	144.07	144.38	141.23	151.73	146.8
3	107.3	107.2	139.11	138.43	138.77	138.76	141.27	135.6
4	178.0	177.4	173.00	172.30	172.34	171.19	172.20	175.9
5	125.4	126.7	124.81	126.50	126.11	160.19	160.74	156.2
6	124.9	114.1	124.47	114.88	114.53	95.67	96.29	98.2
7	133.5	163.7	133.63	162.57	163.65	163.86	163.93	163.9
8	117.9	100.2	118.34	101.95	100.20	92.76	93.36	93.5
8a	156.0	157.7	154.61	156.56	156.53	158.20	158.39	160.7
4a	123.7	117.6	121.34	114.23	115.15	106.32	109.09	103.1
OMe	—	55.9	—	—	56.00	55.92	55.96	—
						56.15	56.30	
							59.50	

[a] $CDCl_3$. [b] $(CD_3)_2SO$.

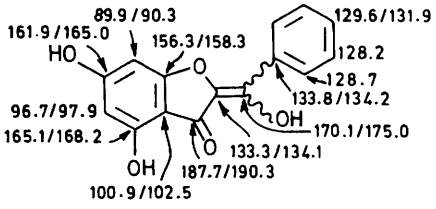


(1)



(7)

FIGURE 1



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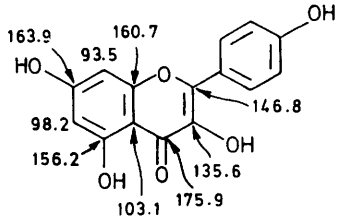

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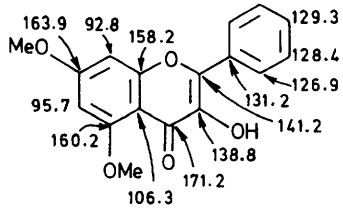

(10)

FIGURE 2 (* taken from ref. 10)

and its distinct difference from that of compounds (5) and (9) clearly shows that methylation has occurred at the 3-OH group of the tautomer (2a) without rearrangement to the flavonol form and that the compound has structure (6).

The spectra of the flavones and flavonols are listed in Table 4. It can be seen that C-2 and C-3 are both dramatically affected by the introduction of the 3-OH substituent into the flavone skeleton. Thus C-2 shifts upfield from 163.0 to 145.2 whereas C-3 moves downfield from 107.3 to 139.1 in going from flavone (13) to flavonol (7). Of greater interest in the context of the present paper is the comparison between flavonol (7) and the isomeric auronol (1). These differences are highlighted in Figure 1 from which it is clear that the chemical shifts of the central three carbon units are significantly different in the two series. Thus the carbonyl carbon atom gives a signal at 182.5 in the auronol but at 173.0 in the flavonol. The signal of the enol carbon atom (C-3) is at 151.1 in the auronol but at 145.2 in the flavonol, while C-2 is encountered at 135.4 in the auronol but at 139.1 in the flavonol. Not surprisingly C-1′ is also noticeably different in the two series (137.0 as opposed to 131.4) while minor differences are also evident in the chemical shifts of the A ring carbon atoms. In conclusion, the two series can be readily distinguished on the basis of their ^{13}C spectra and Figure 2 shows that these differences become even more pronounced when the auronol adopts the hydroxyaurone structure as in the case of compound (5).

EXPERIMENTAL

The ^{13}C n.m.r. spectra were determined using a Varian XL-100 instrument coupled to a 620L-100 computer. Chemical shifts are recorded as p.p.m. downfield from internal tetramethylsilane. Spectra were all run in $(CD_3)_2SO$ or $CDCl_3$ solution as indicated. The auronols and flavonols were prepared by standard methods which are fully described elsewhere.[5]

6-Hydroxyauronol Enol Methyl Ether (6).—6-Hydroxyauronol (0.2 g) was dissolved in ether and treated with an ethereal solution of diazomethane. The solution was left overnight after which the ether was evaporated. The residue was recrystallised from methanol to give fine yellow needles (0.1 g), m.p. 197—198 °C, $\nu_{max.}$ (KBr) 3 350br, 3 100, 2 855, and 1 630 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 346(4.35), and 254 nm (4.09); δ[$(CD_3)_2SO$ + D_2O] 4.13 (s, OMe), 6.80 (dd, *J* 2, 8 Hz, H-5), 6.93 (d, *J* 2 Hz, H-7), 7.60 (m, H-3′, -4′, -5′), 7.76 (d, *J* 8 Hz, H-4), and 7.83 (m, H-2′, -6′); *m/e* 268.0737 (M^+, 100%), 253.0501 (M − Me, 14%) 251.0708 (M − OH, 27%), 240.0787 (M − CO, 5%), 237.0552 (M − MeO, 6%), and 105.0230 ($PhCO^+$, 81%).

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