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^{1}H and ^{13}C NMR spectral studies of some 4H-3,1-benzoxazin-4-ones and their 2-acylaminobenzoic acid precursors

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Abstract

The ^{1}H and ^{13}C NMR spectra of twelve 4H-3, 1-benzoxazine-4-ones and of their acylaminobenzoic acid precursors are presented. Differentiation between these two series of compounds is best achieved through the characteristic J_{CH} coupling interactions in the high frequency carbonyl region. Some 4H-pyrido[2,3-d][1,3]oxazin-4-ones have also been studied and some earlier literature assignments revised.

1. Introduction

4H-3,1-benzoxazinones (**1**–**4**) are valuable intermediates in heterocyclic synthesis [1] and are also potent inhibitors of chymotrypsin and other serine proteases [2]. 2-Alkyl-4H-3,1-benzoxazine-4-ones (e.g. acetylanthranil, **1a**), may be synthesised from anthranilic acid (**5a**) and acetic anhydride either by a stepwise pathway (method A) through the intermediate 2-acetaminobenzoic acid (**6a**) [3] or directly (method B) with an excess of the reagent [4]. Aryl derivatives (e.g. benzoylanthranil, **3a**) are most conveniently obtained by a one-step reaction with the appropriate aroyl chloride (method C) in the presence of pyridine.[5] (see Scheme 1).

Reaction of the benzoxazinones (**1**–**4**) with primary amines provides a route to the corresponding 4(3H)-quinazolines [6] with sedative-hypnotic (neurotoxic) properties of which methaqualone (**8**), is the prototype [7].

Since the stepwise pathway (method A) can lead to either the alkylbenzoxazinone (**1/2**) or to the intermediate acylaminobenzoic acid precursor (**6/7**) dependent upon the reaction conditions employed, a reliable spectral technique for the identification of the isolated product is therefore essential. Moreover, as **1a** is a semiacid anhydride it may undergo many of the reactions of a true anhydride but at a slower rate [4]. Thus hydrolysis back to the acid precursor (**6a**) has been shown to occur readily either in aqueous base [8] in certain

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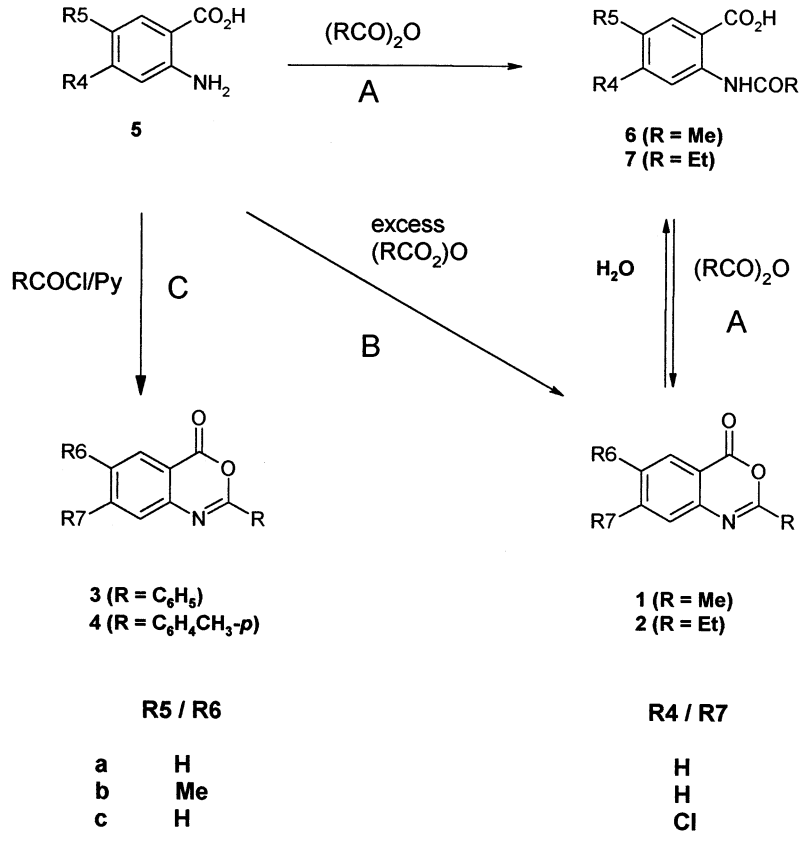
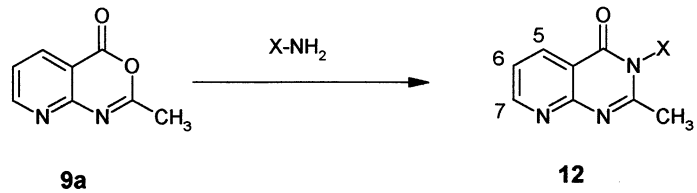
organic solvents [9] and even in the solid state [10] (see Scheme 1) all of which further serve to potentially confuse the situation.

NMR spectroscopy would appear to be the most suitable technique for sample differentiation, however, no such study with this specific objective has yet been reported. Investigations of the benzoxazines are particularly scarce, as far as we are aware no thorough systemmatic ^{1}H NMR study has yet been performed, the isolated examinations being restricted to individual compounds; initially [11] DMSO-d_6 and more recently [6,12–15] $CDCl_3$, have been used as solvent. ^{13}C NMR investigations are extremely limited with all examinations [16–18] being conducted in DMSO-d_6 which would not seem appropriate due to potential hydrolysis problems [9]. Indeed, the original study [16] of a sample of supposed **1a**, was later shown [18] to have actually been of the acetaminobenzoic acid **6a**, the confusion being exasperated since both compounds contain nine carbons comprising 1 methyl, 4 methine and 4 quaternary sites. Whether hydrolysis to **6a** had occurred during storage or during the course of spectral accumulation remains open to question.

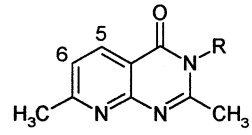
The aim of the present investigation was therefore to secure a spectral technique for the definitive and unequivocal differentiation between the two series of compounds by ^{1}H and ^{13}C NMR spectroscopy utilising solvent systems which were both dependable and appropriate. The work would also be extended to include certain 4H-pyrido[2,3-d][1,3]oxazin-4-ones (**9**) for which no spectral data is yet available, such compounds being obtained from 2-aminonicotinic acid (**10**).



Scheme 1. Synthesis of benzoxazinones.



9a 12



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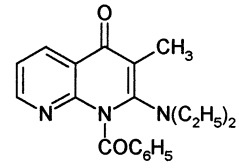
a R = CH_3

b R = $C_6H_4CH_3$-*o*



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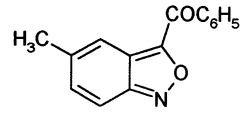

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Scheme 1. (*Continued*)

2. Experimental

^{1}H NMR spectra were recorded at 60 MHz (Jeol PMX60 at City University), 270 MHz (Jeol EX270 at University of Essex) and at 400 MHz (Bruker WH400, S.E.R.C. supported service at the University of Sheffield). ^{13}C NMR spectra were measured at 15 MHz (Jeol FX60 at City University) and at 68 MHz (Jeol EX270 at University of Essex). Chemical shifts are reported as p.p.m. (δ) to high frequency from internal TMS standard. The spectral results are shown in Tables 1–7.

2.1. Acylaminobenzoic acids (6/7)

The general procedure of Fitton and Smalley [3] was used. A solution of anthranilic acid **5a** (13.7 g, 0.1 mol) dissolved in excess acetic or propanoic anhydride (40 ml) was boiled under reflux for 1 h, and then poured into cold water (200 ml). The precipated product was filtered off, washed thor-

oughly with water, and recrystallised from an ethanol/water solvent pair. The products obtained are listed in Table 8.

2.2. Alkylbenzoxazinones (1|2)

2.2.1. Method A

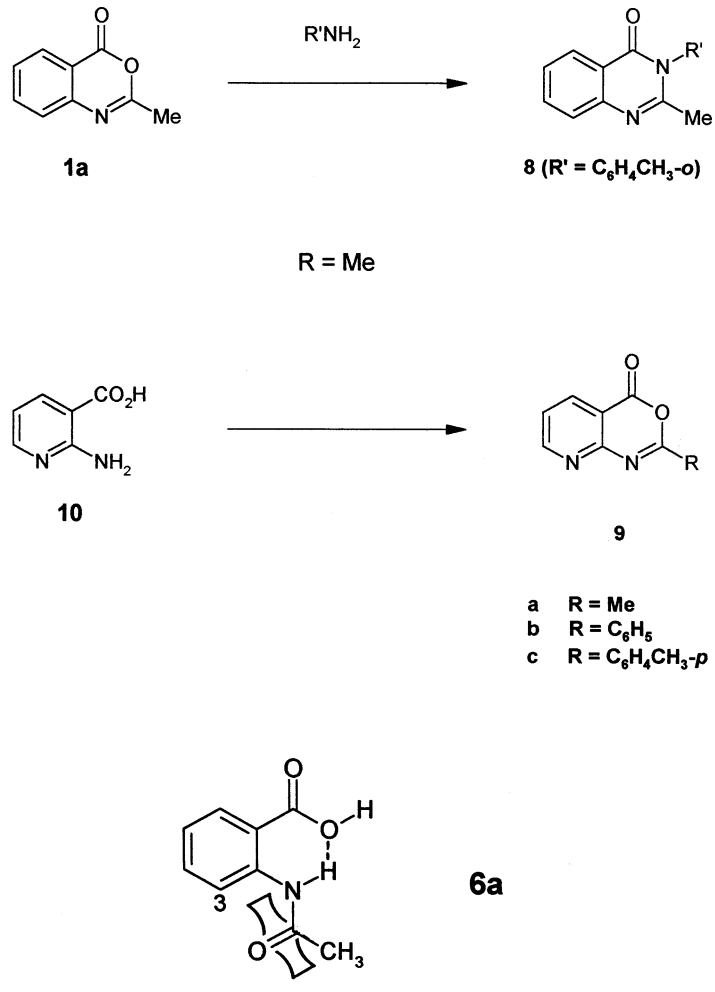
The general procedure of Fitton and Smalley [3] was used. A solution of 2-acetaminobenzoic acid **6a** (6.0 g, 0.03 mol) in excess acetic anhydride (40 ml) was boiled under gentle reflux for 1 h. Excess acetic anhydride was removed in vacuo, the dark brown residue then transferred to a Soxhlet apparatus and extracted with boiling heptane. 2-Methyl-4H-3,1-benzoxazin-4-one **1a** separated on cooling as colourless needles, see Table 9.

2.2.2. Method B

The general procedure of Errede [4] was used. A solution of anthranilic acid **5a** (13.7 g, 0.1 mol) dissolved in excess acetic or propanoic anhydride (50 ml) was boiled under reflux for 2 h. The products were isolated as described for method A and are listed in Table 9.

2.3. Arylbenzoxazinones (3|4) (Method C)

The general procedure of Bain and Smalley [5]



Scheme 1. (*Continued*)

Table 1
^{1}H NMR spectra of acylaminobenzoic acids in DMSO-d_6

Chemical shifts (δ, p.p.m.)

No.	H-3	H-4	H-5	H-6	NH	2-CH_2	2-CH_3
6a	8.53	7.60	7.15	8.03	11.12	-	2.15
6b	8.39	7.41	(2.30)	7.82	10.95	-	2.12
6c	8.61	-	7.20	8.00	11.21	-	2.17
7a	8.55	7.59	7.12	8.01	11.14	2.43	1.14
7b	8.45	7.43	(2.30)	7.83	11.02	2.41	1.13
7c	8.60	-	7.15	7.94	11.25	2.45	1.13
5a[b]	6.82	7.30	6.58	7.82			
Ac[c]	+1.71	+0.30	+0.57	+0.21			
Pr[d]	+1.73	+0.29	+0.54	+0.19			

Coupling constants (Hz)

No.	J_{34}	J_{35}	J_{45}	J_{46}	J_{56}	J_{alk}
6a	8.2	1.4	7.2	1.8	7.8	-
6b	8.4	-	-	2.2	-	-
6c	-	2.0	-	-	8.6	-
7a	8.4	1.4	7.2	1.8	7.8	7.5
7b	8.4	-	-	2.2	-	7.5
7c	-	2.0	-	-	8.4	7.5

a : CO_2H not observed

b : from lit.[34]

c : Ac = ($\delta_{6a} - \delta_{5a}$), p.p.m.

d : Pr = ($\delta_{7a} - \delta_{5a}$), p.p.m.

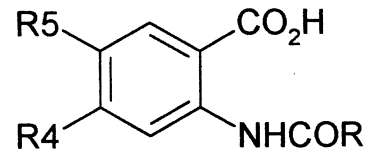


Table 2
^{1}H NMR spectra of benzoxazinones in $CDCl_3$

Compd.	*o*-Ph	H-5	H-6	H-7	H-8	2-CH_2 or *m*-Ph	2-CH_3 or *p*-Ph
Chemical shifts (δ, p.p.m.)							
1a		8.22	c	c	c		(2.47)
1a (b)		8.042	7.382	7.680	7.410		(2.355)
1b		8.00	(2.45)	7.65	7.48		(2.45)
1c		8.15	7.49	-	7.56		(2.42)
2a		8.21	c	c	c	(2.75)	(1.37)
2b		8.03	(2.48)	7.68	7.52	(2.75)	(1.37)
2c		8.16	7.50	-	7.62	(2.75)	(1.37)
3a	c	c	c	c	c	c	c
3a (b)	8.240	8.161	7.442	7.747	7.607	7.443	7.511
3b	8.24	7.98	(2.45)	c	c	c	c
3c	8.33	8.17	7.47	-	7.70	c	c
4a	8.18	8.23	c	c	c	7.30	(2.42)
4b	8.15	8.00	(2.47)	7.57	7.57	7.28	(2.42)
4c	8.19	8.18	7.45	-	7.68	7.33	(2.43)
Coupling constants (Hz)							
	J_{56}	J_{57}	J_{67}	J_{68}	J_{78}	Other	
1a (b)	7.9	1.6	7.3	1.2	8.1	-	
1b	-	2.0	-	-	8.4	-	
1c	8.0	-	-	1.8	-	-	
2a	f	f	f	f	f	7.6 (d)	
2b	-	2.0	-	-	8.2	7.6 (d)	
2c	8.4	-	-	1.8	-	7.6 (d)	

Table 2 Continued)

Compd.	*o*-Ph	H-5	H-6	H-7	H-8	2-CH_2 or *m*-Ph
3a (b)	7.9	1.5	7.3	1.2	8.1	-
3b	-	2.0	-	-	g	-
3c	8.2	-	-	1.8	-	-
4a	f	f	f	f	f	8.6 (e)
4b	-	2.0	-	-	h	8.6 (e)
4c	8.6	-	-	1.8	-	8.6 (e)

a : alkyl signals shown in parentheses

b : measured at 400 MHz

c : multiplet : **1a** - 3H, 7.35 - 7.98 ; **2a**, 3H, 7.35 - 7.97 ; **3a** - 3H, 8.18 - 8.47 (*ortho*-Ph, H-5) & 6H, 7.46 - 7.87 ; **3b** - 5H, 7.35 - 7.60 ; **3c** - 3H, 7.35 - 7.58 ; **4a** - 3H, 7.42 - 7.83.

d : J_{alkyl}

e : $J_{2'3'} + J_{2'5'}$

f : multiplet, not analysed

g : coupling obscured

h : signals accidentally equivalent

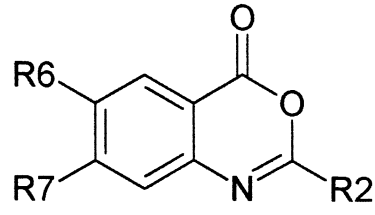


Table 3
^{1}H NMR spectra of 4H-pyrido[2,3-d][1,3]oxazin-4-ones in $CDCl_3$

Chemical shifts (δ, p.p.m.)							
No.	H-5	H-6	H-7	H-2′	H-3′	H-4′	CH_3
9a	8.531	7.495	8.991	–	–	–	2.566
9b	8.570	7.496	9.020	8.421	7.538	7.633	–
9c	8.560	7.480	9.010	8.312	7.348	–	2.462
Coupling constants (Hz)							
	J_{56}	J_{57}	J_{67}	Ar			
9a	7.8	2.0	4.7				
9b	7.5	2.0	4.8	m			
9c	7.9	2.0	4.8	8.3[a]			

[a] $J_{2'3'}+J_{2'5'}$.
m Multiplet.

was used. A solution of anthranilic acid **5a** (2.74 g, 0.02 mol) in pyridine (60 ml) containing benzoyl or para-toluoyl chloride (0.04 mol) was thoroughly agitated for 30 min and then stirred into cold water (400 ml). The precipated product was collected, washed with cold water and recrystallised from ethanol. The products obtained are listed in Table 9.

2.3.1. 2-Methyl-4H-pyrido[4,3-d][1,3]oxazin-4-one (**9*a***)

Method B was employed commencing from 2-aminonicotinic acid (13.8 g, 0.1 mol). The crude product from hexane was further purified by vacuum sublimation [29].

*2.3.2. 2-Aryl-4H-pyrido[4,3-d][1,3]oxazin-4-ones (**9b**/**9c**)*

A modified method C, as used by Hurd and Bethune [30] was employed. Due to the poor solubility of 2-aminonicotinic acid in pyridine, toluene (80 ml) was added and the reaction mixture instead boiled under reflux for 1 h. After removal of the solvent in vacuo, the mixture was poured into water. Product isolation was as described for method C; samples were recrystallised from petroleum ether (100–120°) and are listed in Table 9.

3. Results and discussion

3.1. Solvent selection

Previous ^{13}C NMR investigations [16–18,31] have used DMSO-d_6 as a common solvent for both series of compounds. Since most amides, such as **6/7**, readily dissolve in DMSO-d_6 but are only sparingly soluble in less polar solvents such as $CDCl_3$, use of the former solvent for these compounds is entirely appropriate.

In complete contrast, the alkylbenzoaxinones, **1/2**, are particularly susceptible to hydrolysis by water [23] which can also occur at significant rates in polar solvents such as DMSO-d_6 [9], hence the continued use of this medium for ^{13}C NMR studies appears somewhat fraught and is therefore not recommended. However, the rate of hydrolysis has been found to be slower in $CDCl_3$ [9], a solvent in which the heterocycles are readily soluble and which has been previously employed [12–15] for most ^{1}H NMR investigations. Moreover, since it has also been demonstrated that **1a** can even hydrolyse to **6a** in the solid state [10], then if the NMR investigation was conducted in $CDCl_3$ this would further ensure the absence of any insoluble **6a**, which may have been produced during storage.

Table 4
Corrected ^{1}H NMR spectral assignments for some 3H-pyrido[2,3-d]pyrimidin-4(3H)-ones in $CDCl_3$

	Chemical shifts (δ, p.p.m.)			Coupling Constants (Hz)		
No.	H-5[a] or H-7[b]	H-6[a]	H-7[a] or H-5[b]	J_{56}[a] or J_{67}[b]	J_{57}[a]	J_{67}[a] or J_{56}[b]
12a (c)	8.87	7.12-7.45[b,g]	8.55	4.5	2	8
12b (c)	8.85	7.24-7.44[b,h]	8.50	4.5	2	8
12c (c)	8.85	7.32	8.51	4.5	2	8
12d (c)	8.86	7.32	8.54	4.5	2	8
12e (c)	8.84	7.35	8.46	4.5	2	8
12f (d)	8.85	7.29-7.49[b,j]	8.50	4.5	2	8
12g (d)	8.81	7.31	8.41	4.5	2	8
12h (d)	8.92	7.34	8.54	4.5	2	8
13a (e)	-	7.23[b]	8.39[b]	-	-	4[b]
13b (e)	-	7.27[b]	8.43[b]	-	-	8[b]
11 (f)	8.60 (H-2)	7.25 (H-3)	7.64 (H-4)	5.5 (J_{23})	1.9 (J_{24})	7.6 (J_{34})

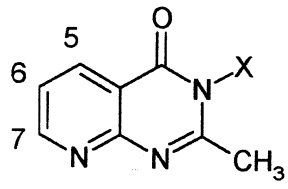


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Table 4 (Continued)

X	alk	R2	R3	R4
a	CH_2	MeO	H	H
b	CH_2	H	H	F
c	CH_2	H	MeO	MeO
d	CH_2	H	H	Me
e	CH_2		furan-2-yl	
f	CH_2CHMe	H	H	Cl
g	$(CH_2)_3$	Y	Y	Y
h	$(CH_2)_2$	Z	Z	Z

a : original literature assignments[41,42]

b : corrected assignments made in this work

c : data from ref. 41

d : data from ref. 42

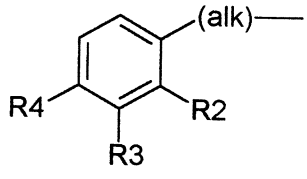
e : data from ref. 43

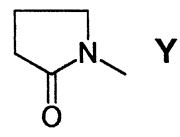
f : data from ref. 37

g : dd, 7.29 δ (b)

h : dd, 7.34 δ (b)

j : dd, 7.39 δ (b)





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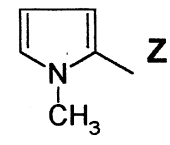

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Table 5
^{13}C NMR spectra of acylaminobenzoic acids in DMSO-d_6

Chemical shifts (δ, p.p.m.)

No.	C-1	C-2	C-3	C-4	C-5	C-6
6a	116.60	141.34	120.11	134.18	122.66	131.31
6b	116.67	138.67	120.24	134.34	131.77	131.19
6b calc[a]	116.50	138.24	120.01	134.88	131.86	132.01
6d	129.49	135.77	135.99	133.99	126.24	128.03
6d calc[a]	116.50	142.04	129.31	134.88	122.56	128.21
(diff.)	(+12.99)	(−6.27)	(+6.88)	(−0.89)	(+3.68)	(−0.18)
5a	110.13	151.75	116.60	133.98	114.91	131.51
5b	109.90	149.73	116.81	135.08	123.24	131.05
5b calc[a]	109.93	148.65	116.50	134.68	124.11	132.21

No.	C-7	C-8	C-9	CH_3
6a	169.92	168.75	25.06	–
6b	169.72	168.42	24.87	20.12
6b calc[a]	–	–	–	
6d	168.53	169.35	23.32	18.38
6d calc[a]	–	–	–	–
5a	169.98			
5b	169.99			19.93
5c calc[a]	–			

Coupling constants (Hz)

Coupling	**6a**	**6b**	**6d**	**5a**	**5b**
J_{13}	6.8	5.6	–	5.9	5.5
J_{15}	6.8	–	7.6	5.9	–
J_{24}	8.3	8.3	8.2	7.3	7.3
J_{26}	8.3	8.3	8.2	7.3	7.3
J_{33}	166.0	166.0	–	159.7	158.7
J_{35}	5.9	–	7.6	7.3	–
$J_{3.NH}$	5.9	3.9	∼0	–	–
J_{44}	162.0	159.2	160.2	158.2	156.2
J_{46}	8.6	6.8	8.2	8.8	7.9
J_{55}	165.2	–	162.4	165.1	–
J_{53}	8.8	8.1	–	7.8	6.2
J_{66}	163.1	162.0	162.9	161.7	157.4
J_{64}	8.6	7.0	8.2	7.3	5.5
J_{76}	4.5	4.6	4.4	3.9	4.2
J_{73}	1.5	1.6	–	[b]	1.2
$J_{8.NH}$	3.0	2.9	∼0[c]	–	–
J_{89}	5.9	5.9	6.1	–	–
J_{99}	127.9	127.9	127.5	–	–
$J_{2.Me}$	–	–	4.4	–	–
$J_{3.Me}$	–	–	6.5	–	–
$J_{4.Me-3}$	–	–	4.9	–	–
$J_{4.Me-5}$	–	4.9	–	–	4.9
$J_{5.Me}$	–	6.4	–	–	6.2
$J_{6.Me}$	–	4.9	–	–	5.5
J_{Me}	–	126.9	127.5	–	125.7
$J_{Me.4}$	–	4.0	4.9	–	4.3
$J_{Me.6}$	–	4.0	–	–	4.3

[a] Me S.C.S. values taken from [45].
[b] Not observed.
[c] $J_{8.NH} = 1.5$ Hz at 50°C.

Table 6
^{13}C NMR spectra of benzoxaxin-4-ones and pyridooxazinones in $CDCl_3$

Chemical shifts (δ, p.p.m.)

No.[a]	C-2	C-4	C-5	C-6	C-7	C-8
1a	160.48	159.91	128.62	128.42	136.76	126.63
1b	159.71	160.07	128.17	138.75	137.94	126.38
1c	161.95	159.18	130.00	129.02	143.23	126.58
2a	162.22	159.99	128.58	128.33	136.67	126.79
3a[c,d]	157.34	159.78	128.78	128.42	136.76	127.44
4a[c]	157.43	159.83	128.66	128.09	136.63	127.28
9a	164.18	159.18	137.74	123.74	157.43	–
9b[c]	160.92	159.67	138.14	123.86	157.92	–
9c[c]	160.72	159.51	137.82	123.34	157.52	–
No.	C-4a	C-8a	Alkyl			
1a	116.86	146.69	21.36			
1b	116.54	144.53	21.28 (2) 21.26 (6)			
1c	115.31	147.83	21.48			
2a	117.06	146.72	28.20 (CH_2) 10.25 (CH_3)			
3a[c,d]	117.19	147.21	–			
4a[c]	117.10	147.43	21.65			
9a	112.41	157.30	21.72			
9b[c]	113.07	158.20	–			
9c[c]	112.67	157.95	21.80			

Coupling constants (Hz)

No.	$J_{2.R}$	J_{45}	J_{55}	J_{57}	J_{66}	J_{68} (J_{67})[b]
1a	7.9[e]	4.3	167.3	7.3	164.8	7.3
1b	7.3[e]	3.0	163.0	5.5	–	6.4
1c	7.9[e]	3.6	168.5	–	170.3	5.5
2a	7.9[f] 5.5[e]	3.6	167.2	7.3	165.0	7.3
3a	4.2[g]	3.6	[h]	[h]	[h]	[h]
4a	4.2[g]	3.6	169.1	6.1	165.4	7.3
9a	8.0[e]	4.0	170.0	6.5	168.0	(8.9)
9b	3.9[g]	3.9	168.3	6.8	168.3	(7.8)
9c	3.9[g]	3.9	169.2	6.4	168.2	(7.8)

No.	J_{77}	J_{75}	J_{88} (J_a)[b]	J_{86} (J_{76})[b]	$J_{4a.6}$	$J_{4a.8}$
1a	162.0	8.9	164.8	7.3	7.9	5.5
1b	158.9	7.7	164.2	–	–	4.9
1c	–	12.2	169.9	4.6	7.3	6.2
2a	161.7	8.5	164.8	7.3	7.7	5.6
3a	162.1	8.6	165.1	7.3	7.3	5.5
4a	161.7	8.6	164.8	7.3	7.9	4.9
9a	181.9	7.9	(192.8)[i]	(3.0)	8.0	–
9b	180.9	7.8	(192.9)[i]	(3.9)	7.9	–
9c	180.9	7.8	(–)[j]	(2.9)	6.9	–

No.	$J_{8a.5}$	$J_{8a.7}$	J_{Me}	Other	
1a	7.3	7.3	130.0 (2)		
1b	7.3	7.3	130.0 (2) 127.2 (6)	$J_{Me.5}$ 4.3 $J_{5.Me}$ 5.5 $J_{7.Me}$ 4.9	$J_{Me.7}$ 4.3 $J_{6.Me}$ 6.4
1c	7.9	–	130.6 (2)	J_{76} 3.0	J_{78} 3.0

Table 6 (Continued)

Coupling constants (Hz)					
No.	$J_{89.5}$	$J_{89.7}$	J_{Me}	Other	
2a	7.3	7.3	128.8 (10)	J_{99} 128.8 $J_{10.9}$ 4.0	$J_{9.10}$ 4.3
3a	7.3	7.3	–	Ar, see Table 7	
4a	7.0	7.0	127.0 (4′)	Ar, see Table 7	
9a	6.0	12.9	131.2 (2)		
9b	5.9	12.7	–	Ar, see Table 7	
9c	5.9	12.7	127.2 (4′)	Ar, see Table 7	

[a] Measured at 15 MHz, **9a**–**9c** also at 68 MHz.
[b] Couplings in parentheses apply to compounds **9**.
[c] For aryl signals, see Table 7.
[d] For literature values see [47].
[e] $J_{2.Me}$.
[f] $J_{2.CH2}$.
[g] $J_{2.2'} = J_{2.6'}$.
[h] Peaks overlapped.
[i] $J_a = J_{77} + J_{75} + J_{76}$ (ABCX analysis at15 MHz).
[j] Not measured.

In order to demonstrate the suitability of $CDCl_3$ as a solvent medium for **1** and **2**, a solution of **1a** was prepared, with no special precautions taken, and the ^{13}C NMR spectrum measured. The solution was then allowed to mature in a sealed (with normal plastic cap only) NMR tube for 14 weeks. The ^{13}C NMR spectrum was then re-measured which indicated that the extent of hydrolysis to **6a** was only ca. 10% (Fig. 1).

Although the arylbenzoxazinones (**3/4**) may readily be hydrolysed by aqueous base at 85°C [5] Zentmyer and Wagner [23] noted that these compounds were much more resistant to hydrolysis at ambient temperatures, such that an aqueous work up could be employed for their isolation. In our hands a solution of **3a** in $CDCl_3$ showed no detectable deterioration after 12 weeks.

The alkylpyridooxazinone **9a** has been reported by Littell and Allen [32] to be rather unstable, such that it should be used immediately for conversion to the appropriate pyridodiazepine, and is best purified by vacuum sublimation [29]. This compound is readily soluble in $CDCl_3$, however, after the solution had been allowed to stand in a sealed NMR tube for 48–60 h a gel was formed, thus restricting the time available for the NMR study. The arylpyridooxazinones **9b** and **9c** were completely stable in $CDCl_3$ solution.

3.2. ^1H NMR spectral studies

3.2.1. Acylaminobenzoic acids

The results are shown in Table 1. The acetamino group is unusual such that it produces a downfield *ortho*-S.C.S. (Substituent Chemical Shift) effect but an upfield *para*-S.C.S. effect [33]. Rae [34] has noted that the extent of the downfield *ortho* shift at H-3 in **6a** was significantly enhanced. This effect, termed an 'acylation shift' occurred since intramolecular hydrogen bonding caused a considerably stronger anisotropic effect from the rigidly held carbonyl group.

By comparison with the chemical shifts of **5a**, 'acylation shifts' (Ac) for **6a** and 'propanoylation shifts' (Pr) for **7a** have been assessed (Table 1) the two series of shifts are quite similar and in accordance with the earlier results [34]. Thus, in all of the acylaminobenzoic acids (**6/7**) studied, H-3 showed a ca. 1.7 p.p.m. shift and appeared in the 8.4–8.6 δ region. The assignments were further confirmed from the unambiguous splitting pat-

Table 7
^{13}C NMR spectra of aryl signals

Chemical shifts (δ, p.p.m.)

No.	C-1'	C-2'	C-3'	C-4'	$\delta_o - \delta_m$	Δ[b]
3a[c]	130.45	128.50	128.94	132.81	-0.44	
4a	127.60	128.46	129.64	143.55	-1.18	0.74
9b	129.72	129.31	129.15	133.91	+0.16	
9c	126.57	129.02	129.63	144.65	-0.61	0.76

Coupling constants (Hz)

No.	$J_{1'3'}$	$J_{2'2'}$	$J_{2'4'}$	$J_{3'3'}$	$J_{3'5'}$	$J_{4'4'}$
3a	7.8	d	d	d	d	161.1
4a	7.6	163.3	6.1[e]	159.3	5.5	-
9b	7.8	163.4	6.9	163.4	6.9	161.4
9c	7.8	163.4	5.9[e]	160.4	4.9	-

No.	$J_{4'2'}$	$J_{3'.Me}$	$J_{4'.Me}$	$J_{Me.3'}$
3a	7.9	-	-	-
4a	7.6	5.5	7.6	4.3
9b	7.8	-	-	-
9c	6.8	4.9	6.8	4.9

a : For operating frequencies see Table 6

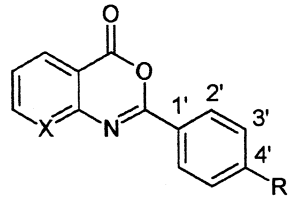
b : $\Delta = (\delta_o - \delta_m)_{4\text{-H}} - (\delta_o - \delta_m)_{4\text{-Me}}$

c : For literature values see [47]

d : peaks overlapped

e : $J_{2'6'}$

Table 7 (Continued)



X = CH or N

terns in the trisubstituted AMX spin systems, viz downfield *ortho*-doublet in **6b/7b** and *meta*-coupled fine doublet in **6c/7c**. The 'acylation shifts' at H-4, H-5, and H-6 were much smaller, consequently the next most deshielded aromatic proton was H-6, adjacent to the electron withdrawing carboxyl group. Thus for the acid precursors (**6/7**) two distinct aromatic signals may be discerned in the high frequency region (from 8 δ). The CO_2H peak was not observed in DMSO-d_6, whilst the NH signal at ca. 11 δ exchanged with D_2O which also collapsed the associated $J_{C.NH}$ interactions (Sections 3.4.1 and 3.4.2). The J_{HH} couplings have been assembled in Table 1, these were generally unremarkable.

Table 8
Synthesis of acylaminobenzoic acids

Compound	Yield (%)	m.p.	m.p. (lit.)
6a	85	185–6°	185° [19]
6b	93	180–1°	180–1° [20]
6c	84	213–4°	214° [21]
6d	85	206–7°	204–5° [20]
7a	80	120–1°	117° [22]
7b	90	125–6°	[a]
7c	77	192–3°	[b]

[a] Found: C, 63.94; H, 6.27; N, 6.70; Calc. for $C_{11}H_{13}NO_3$ C, 63.75; H, 6.32; N, 6.75%.

[b] Found: C, 52.66; H, 4.45; N, 6.06; Calc. for $C_{10}H_{10}ClNO_3$ C, 52.76; H, 4.42; N, 6.15%.

3.2.2. Benzoxazinones

Samples were examined in $CDCl_3$ solution, generally at 60 MHz, the results are shown in Table 2. All alkyl compounds (**1/2**) exhibited a low field signal for H-5 at ca. 8.0–8.2 δ, deshielded by an anisotropic effect of the *peri*-carbonyl, in accordance with earlier work [12–15].

This signal was thus intermediate between those for H-3 and H-6 in the acid precursors (**6/7**). A

Table 9
Synthesis of benzoxazines and pyridooxazines

Compound	Method	Yield (%)	m.p.	m.p. (lit.)
1a	A	76	81–2°	80–1° [23]
1a	B	74	81–2°	80–1° [23]
1b	B	86	122–3°	125–6° [24]
1c	B	81	149–51°	145° [25]
2a	B	78	84–5°	85–6° [23]
2b	B	76	102–3°	100° [26]
2c	B	71	81–2°	78° [26]
3a	C	90	123–4°	123° [5]
3b	C	93	145–6°	143–8° [27]
3c	C	93	192–3°	192° [25]
4a	C	89	154–5°	153–4° [8]
4b	C	91	193–4°	194° [28]
4c	C	91	183–4°	183° [28]
9a	B	53	178–82°[a]	176–80° [29]
9b	C	55	148–9°[b]	145–6° [30]
9c	C	91	201–2°[b]	[c]

[a] Purified by vacuum sublimation.

[b] Recrystallised from petroleum ether (100–120°).

[c] Found: C, 70.33; H, 4.28; N, 11.77, Calc. for $C_{14}H_{10}N_2O_2$ C, 70.58; H, 4.23; N, 11.76%.

high field (400 MHz) study was required for the analysis of the ABCD systems of **1a** and **3a**. At low field the 2-phenyl compound comprised two multiplets [13], the downfield 3H segment included the *ortho*-phenyl protons, which were subject to the diamagnetic anisotropy of the neighbouring heterocyclic ring and the electrostatic field effect of the nitrogen lone pair as experienced with 2-phenylpyridine [35]. The assignments were further supported by a study of the simpler AA′XX′ patterns for the *para*-tolyl compounds **4**. The carbocyclic ring couplings followed the established pattern [36] with J_{67} slightly reduced compared to J_{56} and J_{78} in accordance with the appropriate π-bond orders. Thus for a rapid distinction between the two series of compounds by low field ^{1}H NMR the high frequency aromatic region should be examined, the most deshielded signals being near 8.5 δ (acids, Table 1) or near 8.0 δ (heterocycles, Table 2).

3.2.3. Pyridooxazinones

4H-Pyrido[2,3-d][1,3]oxazin-4-ones **9**, prepared [29,30] from 2-nicotinic acid **10**, are valuable intermediates for the syntheses of therapeutic triazaheterocycles. The present work featured **9a**–**9c** examined at 270 MHz in $CDCl_3$ solution, the results are shown in Table 3.

Assignments for H-5, H-6 and H-7 were made by comparison with spectral data [37] for pyridine (**11**, see also Table 4). Thus in the **9** series H-7 resonated far downfield at ca. 9.0 δ compared

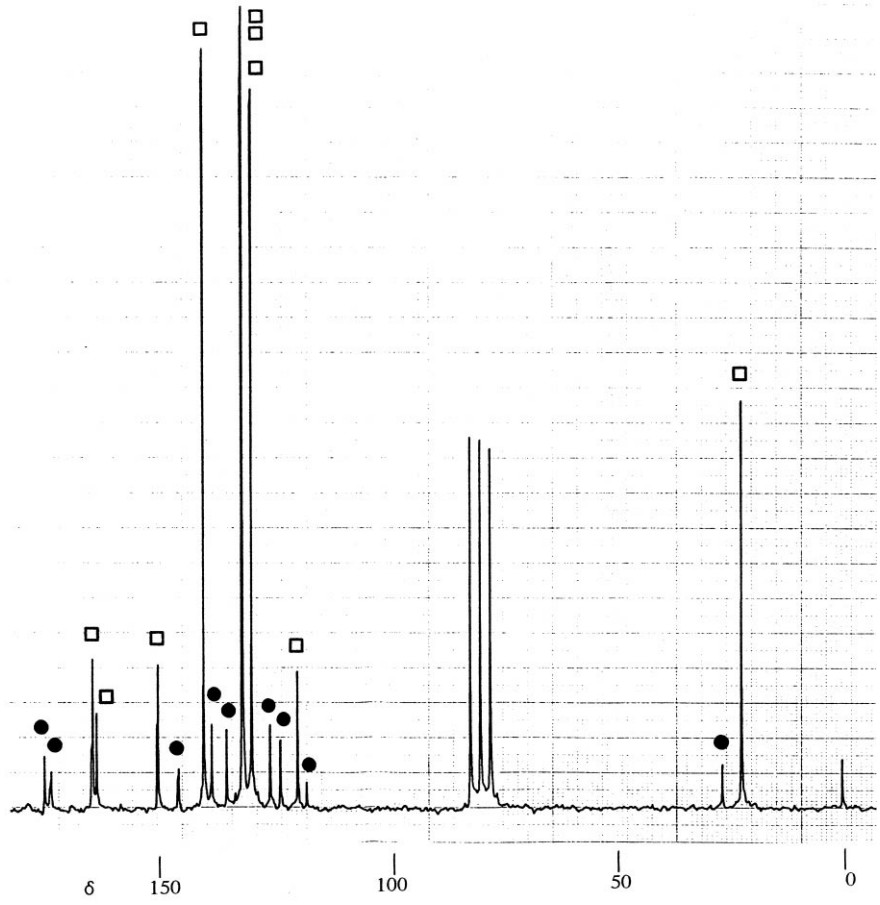


Fig. 1. ^{13}C NMR spectrum of **1a** in $CDCl_3$ after standing for 14 weeks. □, signals for **1a**; ●, signals for **6a**.

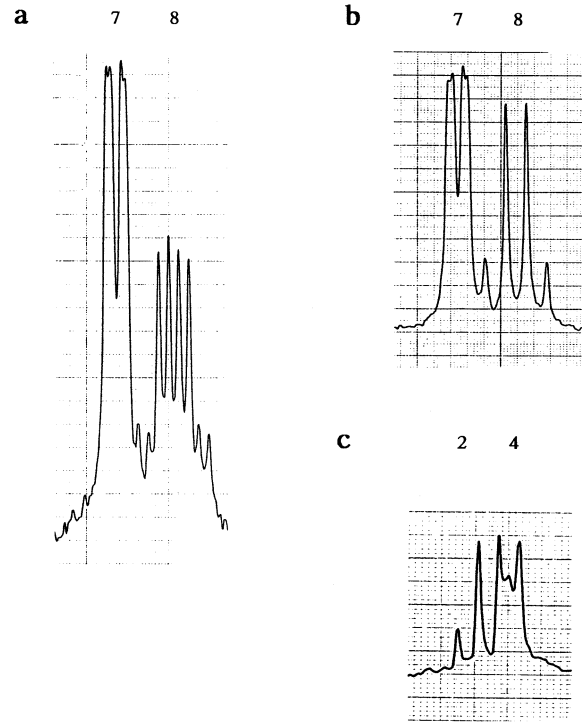
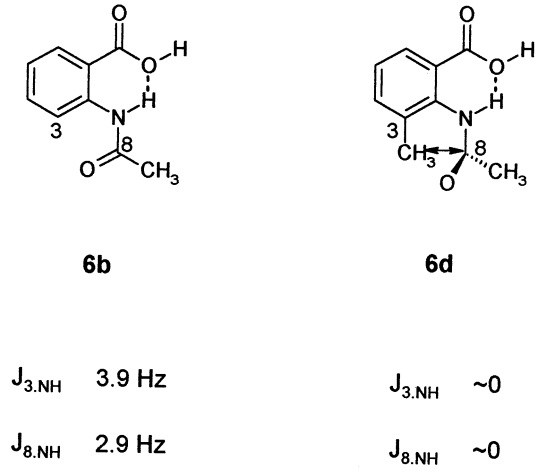


Fig. 2. ^{13}C proton coupled NMR spectra in high frequency region. a: **6a** in DMSO-d_6, C-7 is dd, C-8 is dq; b: **6a** in DMSO-d_6/D_2O, C-7 is dd, C-8 is q; c: **1a** in $CDCl_3$, C-2 is q, C-4 is overlapped narrow d.



Scheme 2. NH couplings in anthranilic acids.

with H-2 (8.60 δ) in **11**. The absorption of H-5, at ca. 8.6 δ, was somewhat downfield from H-4 (7.64 δ) of **11** due to the additional influence of an anisotropic effect from the *peri*-carbonyl, similar to that experienced by H-5 (8.13 δ) in 4-quinolone [38]. The assignments were supported by the characteristic heterocyclic ring splitting patterns, especially the diminished J_{23} coupling in **11** resulting from the electronegativity effect of the adjacent heterocyclic nitrogen [39]. The coupling correlations were very good, viz: J_{56} 7.8 Hz (**9a**) cf. 7.6 Hz (J_{34}, **11**) and J_{67} 4.7 Hz (**9a**) cf. 5.5 Hz (J_{23}, **11**). The aryl portions of **9b** and **9c** were similar to those of **3a** and **4a**. Thus the pyridooxazinones must be assigned by treating H-5 to H-7 as components of a 2,3-condensed pyridine rather than as an 8-substituted benzoxazinone. This assignment approach has highlighted certain errors in the literature which need to be addressed.

Herold [40–42] has investigated the condensation of **9a** with various substituted benzylamines [41] and phenylethylamines [40,42] to produce the corresponding 3-substituted 2-methyl-3H-pyrido-[2,3-d]pyrimidin-4(3H)-ones (**12**) for evaluation as potential antidepressant agents.

Although no spectral data was given for **9a**, low field (80 MHz, $CDCl_3$) ^1H NMR assignments were reported [41,42] for all of the 21 triazaproducts so obtained, selected data have been assembled in Table 4. It is now apparent that in all cases the assignments of H-5 and H-7 and of J_{56} and J_{67} must be exchanged. The revised assignments are then in agreement with the work of Andresen and Pedersen [43] on the synthesis of a range of pyrido[2,3-d]pyrimidin-4(3H)-ones including the 7-substituted compounds **13a** and **13b**, their results have also been included in Table 4. The absence of any signals at ca. 8.5–9.0 δ clearly supports our revised assignments for H-7 in **12a**–**12h**. The reported signals for **13a**/**13b** at ca. 7.2 δ and 8.4 δ may now be designated as H-6 and H-5, respectively. The variation in J_{56} coupling values [43] should be noted, that for **13a** appears suspect. Ming et al. [1] have described the application of a cyclisation extrusion reaction to **9b** to give the heterocondensed pyridine compound **14**.

However, their ^1H NMR assignments for H-5 and H-7 at 8.50 δ and 8.67 δ appear to require reversal since the reported *ortho*-couplings of 4.7 and 8.0 Hz are again more appropriately designated [37] as J_{67} and J_{56}, respectively.

3.3. ^{13}C NMR spectral studies

Although the ^{1}H chemical shift variations within the downfield portion of the acids (Table 1) and benzoxazinones (Table 2) should be sufficient to permit any required differentiation, a more definitive method was sought which would be universally applicable in all cases. Moreover, since some assignment errors in the condensed pyridoheterocycles **12**–**14** have been uncovered, further confirmation was sought to support the treatment of these compounds as 2,3-condensed pyridines. Accordingly a thorough study of the ^{13}C NMR spectra has been undertaken, including a survey of J_{CH} coupling interactions for which no reliable data are yet available.

3.3.1. ^{13}C Chemical shifts

3.3.1.1. Acylaminobenzoic acids. Samples were examined in DMSO-d_6 solution, the results are shown in Table 5, which also includes data for anthranilic acids **5a** and **5b**. Our assignments for **5a** were in good agreement with those previously reported for methyl anthranilate [44] and were further confirmed by the excellent agreement with the estimated shifts for **5b** obtained by addition of 5-Me Substituent Chemical Shift (S.C.S.) values [45]. Although O'Connor et al. [31] have presented a detailed study of 4-acetylaminobenzoic acid including a Dual Substituent Parameter (DSP) analysis, somewhat surprisingly no investigation of **6a** appears to have been reported to date. Our chemical shifts are in good agreement with those reported by Singh et al. [16] for their supposed **1a**, and also with the spectrum included in the recently published Aldrich catalogue [46] Initial assignments for **6a** were performed by direct comparison with those for the methyl ester given by Sopchik and Kingsbury [48] and further confirmed by excellent agreement with the estimated shifts obtained for **6b** (Table 5).

However, a similar calculation for **6d**, required as a coupling constant 'blocking' compound, gave a particularly poor correlation, partially the result of an *ortho*-proximity effect [49] but mainly caused by distortion of hydrogen bonding (Section 3.4.1).

Since both **5a** and **6a** are substituted benzoic acids the absorptions for C-4, C-6 and the carboxylic carbon C-7 were similar for each compound. In accordance with the respective NH_2/$NHCOCH_3$ S.C.S. values [45] reduced upfield shifts for C-3 and C-5 resulted such that their peak positions were reversed in **6a**, compared with **5a**, similar trends can be discerned in the respective methyl esters [44,48].

3.3.1.2. Benzoxazinones. Previously DMSO-d_6 had been used as solvent [16–18]. In this work, samples were examined in $CDCl_3$ solution which has been shown to be more suitable (Section 1) the results are shown in Table 6, aryl signals are given in Table 7. Assignments for **1a** and **3a** were in accordance with the work of Robinson and Spencer [18] the largest chemical shift difference caused by the DMSO-d_6/$CDCl_3$ solvent shift effect being 1.1 p.p.m. for C-8a of **3a**. The assignments were supported by the excellent correlations with estimated chemical shifts obtained for **1b**, **1c** and **4a** by addition of the appropriate S.C.S. values [45]. Variation of the 2-substituent (Me, Et, Ph) produced only small changes at C-2 and left the carbocyclic ring carbons essentially unaffected. The far downfield region of the benzoxazinones **1**–**4** features the C-2 and the 4-carbonyl signals which both appear at about 160 δ in contrast to the acylaminobenzoic acids **6/7** which exhibit two carbonyl signals near 170 δ; a useful preliminary means of differentiation.

During an investigation of the use of the solid N-haloimide, sodium dichlorocyanurate, as an alternate source of active chlorine, Staskun [50] obtained a product which was considered to be **3b**, however, the reported ^{13}C NMR spectrum included an inconsistent downfield signal at 181.34 δ; subsequently the structure of this product was revised [15] as 3-benzoyl-5-phenyl-2,1-benzisooxazole (**15**).

3.3.1.3. Pyridooxazinones. The ^{13}C NMR spectral study has been extended to include three pyridooxazinones, the results are included in Tables 6 and 7. Due to the loss of our 15 MHz ^{13}C instrument because of flood damage, this study

was conducted at 68 MHz. The oxazinone ring signals of **9a**–**9c** were similar to **1**–**4** with C-2 about 3–4 p.p.m. further downfield. The assignments for C-5 to C-7 were again made by treating these compounds as 2,3-condensed pyridines (Section 2.3) as shown by the following chemical shift comparison:

9a		**11** [from [51]]	
C-5	137.74 δ	C-4	136.03 δ
C-6	123.74 δ	C-3	123.83 δ
C-7	157.43 δ	C-2	149.57 δ

The aryl signals of both oxazinone series have been collected in Table 7. The locations of C-1′ and C-4′ readily followed from relaxation and integration considerations. Assignments for C-3′ in **4a** and **9c** were facilitated through coupling interactions with CH_3-4′. However, differentiation between C-2′ and C-3′ in **3a** initially proved difficult due to their close proximity such that the coupling patterns overlapped. However, a simple 2D HETCOR spectrum [52] established connectivities to the well separated H-2 and H-3 protons. Gobert et al. [53] have studied the spectra of a range of phenyl substituted polycyclic aromatic hydrocarbons and established some useful rules for the assignment of phenyl carbons. Thus for phenyls that occupy an unhindered site then $\delta_0 - \delta_m$ was negative, the rule has also been found to be applicable to arylheterocycles, such as 2-phenylpyridine [35]. In the present work, an extension of this basic phenyl rule has been applied so as to incorporate an additional 4-methyl substituent. Thus, the assignments for C-2′/C-3′ in the phenyl substituted compounds **3a** and **9b** were made such that similar positive values of Δ ($\delta_0 - \delta_m$/H → Me) were obtained for each pair of compounds (Table 7).

3.3.2. Carbon–proton coupling constants

No studies of J_{CH} coupling interactions of either the acid precursors or the heterocycles have yet appeared. Robinson and Spencer [18] have presented a 2D COLOC (Correlation of Long Range Couplings) [52] spectrum of 2-ethoxybenzoxazinone (1, R = OEt in place of Me) which illustrated certain coupling pathways.

Since the downfield quaternary signals have been found to be particularly suitable to readily distinguish between the two series of compounds (Section 3.3.1.2), a study of the J_{CH} coupling interactions at these carbons was expected to provide the required unequivocal evidence for definitive identification in cases of continued doubt. The discussion has accordingly been focused upon the high frequency region which includes these signals, the results are shown in Tables 5–7.

3.4. The high frequency region (150–200 δ)

3.4.1. Benzoic acids

The carboxylic carbon of anthranilic acid **5a** appeared as a doublet ($J_{76} = 3.9$ Hz), whilst for **5b** it was a doublet of doublets with an additional 1.2 Hz fine splitting present. For each of the 2-acetylamino compounds **6a** and **6b** a dd was again observed (see Fig. 2a). Since the fine splitting remained after deuterium exchange it cannot be $^3J_{7.NH}$ (see Fig. 2b) and was therefore most likely to be a ^4J interaction. Ihrig and Marshall [54] report $^3J_{72} = +4.08$ Hz and $^4J_{73} = +1.11$ Hz for methyl benzoate, however, in the 2-amino- and 2-acylaminobenzoic acids, where there are two possible ^4J coupling pathways only one interaction is actually observed. That this was $^4J_{73}$, across the 2-substituent was shown by the retention of the coupling in **6b** and lack of any fine splitting in **6d** where the interaction was especially 'blocked'. Such a lack of any $^4J_{75}$ coupling in the **5** and **6** series could result from the intramolecular hydrogen bonding present in these compounds and/or from another subtle substituent effect of the adjacent group.

In the **6** series the acylamino carbonyl (C-8) showed a quartet ^2J interaction to the adjacent methyl and a weaker doublet splitting to the NH, which collapsed after exchange with D_2O (see Fig. 2b). Such J_{CONH} couplings are known to be facilitated where intramolecular hydrogen bonding occurs since in such circumstances there is no fast proton exchange. However, for **6d**, used as a 'blocking' compound, C-8 appeared as a slightly broadened quartet at normal temperatures, whilst at 50°C a weakened ^2J interaction to the NH could just be detected. It would appear that the

3-methyl substituent is able to exert a sufficiently strong steric effect to influence the extent of NH-CO hydrogen bonding (see Scheme 2).

In order to relieve the steric strain it is probable that the $C_8 = 0$ bond would rotate to place the oxygen in a near orthogonal position to the ring plane. Some puckering could then result with consequent distortion of the hydrogen bond from planarity. At higher temperatures (e.g. 50°C) either restricted rotation or oscillation of the N–CO bond would be promoted giving rise to the observed weakened coupling. An alternative explanation could invoke exchange processes, caused by polar solvent interactions which would instead promote intermolecular hydrogen bonding, the consequent fast exchange effectively decoupling the splitting. A similar situation is likely also to influence the $^3J_{anti}$ coupling between C-3 and NH which was observed in the intramolecularly hydrogen bonded acids **6a** and **6b**, but not in the sterically hindered **6d**. Moreover, the correlation of observed and estimated chemical shifts for the aromatic carbons of **6d** was particularly poor (see Table 5). The excessively large deviation at C-1 ($+12.99$ p.p.m.) cannot be attributed to an *ortho*-proximity effect alone, since that for *ortho*-toluidine [49] is only -2.3 p.p.m., which further suggests a considerable degree of steric distortion.

Thus for those acetaminobenzoic acids unsubstituted at position-3 the high frequency coupled region comprises a doublet of doublets for C-7 and a quartet of doublets for C-8 (see Fig. 2a).

3.4.2. Benzoxazinones and pyridooxazinones

The high frequency region for these compounds comprises the quaternary C-2 carbon located between two heteroatoms and the C-4 carbonyl. As noted by Robinson and Spencer [18] C-2 couples only to the side chain protons, and hence produces splitting patterns characteristic of the particular 2-substituent, viz quartet (methyl, **1** and **9a**); triplet of quartets (ethyl, **2**) or triplet (aryl, **3**, **4**, **9b** and **9c**). (see Table 6) The C-4 carbonyl displays a characteristic reduced ^3J *peri*-coupling to H-5 [18] in all cases (see Fig. 2c).

Thus it is seen that the coupling patterns at the C-2 and C-4 carbons are clearly very different from those pertaining in the acid precursors which should permit an equivocal identification. Moreover, only the splitting patterns for the acids are modified by deuteration.

3.5. Other couplings

3.5.1. Benzoic acids

The aromatic ring couplings for **5** and **6** are shown in Table 5, these were generally unremarkable, the ^1J splittings were in the range 156–166 Hz, with J_{33} influenced by the adjacent substituent. The $^3J_{CH}$ *meta*-couplings were in the expected range [55] 6–9 Hz, comments regarding $^3J_{3.NH}$ have been given previously.

3.5.2. Benzoxazinones

The results are shown in Table 6, the aromatic ^1J couplings were in a narrower range between 162 and 169 Hz. Hansen [55] has noted that in aromatic polycyclic hydrocarbons the $^3J_{CH}$ *meta*-couplings at the β-carbons are generally stronger than those at the α-carbons, and it has been demonstrated that this trend also applies in 6-membered azaheterocycles [56].

However, the situation for oxygenated and other multi-functional heterocycles is less well defined. The benzoxazinones fall into the category [56] where the J_{75} coupling at β-carbon-7 is the strongest. Robinson and Spencer [18] established coupling correlations from C-8a to H-5 and H-7, and from C-4a to H-6 and H-8, which have been substantiated in the present work. The 'cross' ring coupling $J_{4a.6}$ is stronger than the 'through' ring $J_{4a.8}$ coupling in accordance with the work of Osborne and Hastings, in contrast, the couplings at C-8a are very similar, as expected for a bridgehead carbon adjacent to a heterocyclic nitrogen atom [57]. The aryl ring couplings are collected in Table 7, the additional quartet splittings to the methyl in **4a** and **9c** proved of great value for assignment purposes.

3.5.3. Pyridooxazinones

Inspection of Table 6, immediately indicates that the benzo- and pyrido-coupling interactions are quite different which confirms the need to treat these compounds as 2,3-fused pyridine derivatives. Thus, $^1J_{77}$ is enhanced due to the

adjacent heterocyclic nitrogen. (compare $J_{22} = 177.9$ Hz in **11**) [51]. Moreover, characteristic $^2J_{67}$ and $^2J_{76}$ interactions as found in pyridine derivatives are also observed, together with a very strong 'cross' ring coupling across the heterocyclic nitrogen atom. (compare $J_{26} = 11.08$ Hz in **11**) [51].

At 15 MHz the C-7 signals of **9a** and **9b** were doublets of multiplets, which have been treated as the X components of an ABCX spin system [58], such that only the sum of $J_{77} + J_{76} + J_{75}$ could be readily extracted [59]. At 68 MHz the C-7 signals of the **9** series compounds all appeared as widely spaced doublets of doublets of doublets, first order analysis then gave the individual couplings, the sums of which were in accordance with the low field ABCX analyses.

We have presented a thorough study of the ^1H and ^{13}C NMR spectra of some benzoxazinones and their acylaminobenzoic acid precursors and have highlighted several methods to distinguish between the two series of compounds. Moreover, with the introduction of such techniques as HMQC (for one bond interactions) and HMBC (for long range correlations) to quickly establish the coupling connectivities, definitive differentiation should now become routine within a reasonable time period.

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