MAGNETIC RESONANCE IN CHEMISTRY, VOL. 30, 1–5 (1992)

^{13}C NMR Study of *N*-Acyl- and *N*-Sulphonyl-isatins and their Ring-Opened Derivatives

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The complete assignments of the ^{13}C NMR resonances of 1-acetyl-, 1-benzoyl-, 1-benzenesulphonyl-, 1-methanesulphonyl- and 1-(2-nitrobenzenesulphonyl)-isatins and their ring-opened glyoxylic derivatives are reported. The ^{13}C assignments of acylisatins were derived from isatin as a model, while assignments of glyoxylic derivatives were made by complete assignment of compound 8b together with its use as a model.

KEY WORDS ^{13}C NMR 1-Acyl-2,3-dihydroindole-2,3-diones 2-Acylamidophenylglyoxylic acid derivatives

INTRODUCTION

1-Acyl-2,3-dihydroindole-2,3-diones (acylisatins) are an important class of compounds which behave as activated imides. They undergo ring-opening reactions with a variety of nucleophiles to yield 2-acylamidophenylglyoxylic acid derivatives.[1,2] These compounds have been used in the synthesis of quinoline and quinazoline derivatives.[3,4] Although ^{13}C NMR chemical shift assignments of isatins have been reported,[5] there is a scarcity of information regarding ^{13}C NMR chemical shifts of acylisatins and acylamidophenylglyoxylic acid derivatives. We now report the analyses of ^{13}C NMR spectra of a large number of acylisatins and their phenylglyoxylic acid derivatives.

EXPERIMENTAL

1-Acetyl-2,3-dihydroindole-2,3-dione was prepared by heating isatin with excess of acetic anhydride.[6] 1-Benzoyl-, 1-benzenesulphonyl-, 1-methanesulphonyl and 1-(2-nitrobenzenesulphonyl)-2,3-dihydroindole-2,3-diones were prepared from sodium isatide and corresponding acid chlorides by the method previously described for 1-benzoylisatin.[7] The *N*-acylamidophenylglyoxylic acid derivatives were prepared by the reaction of *N*-acylisatins with alcohols, water and amines.

^1H NMR spectra were recorded on a Bruker AM 500 spectrometer using $CDCl_3$ or $(CD_3)_2SO$ as solvent and internal deuterium lock. The chemical shifts were read from the solvent [$CHCl_3$, δ 7.26 pm; $(CD_3)_2SO$, δ 2.5 ppm]. The ^{13}C NMR spectra were recorded in the pulsed Fourier transform mode (16K data points for the FID) at 298 K on a Bruker AM 500 spectrometer (125.76 MHz) using $CDCl_3$ δ 77.00 ppm. All ^{13}C measurements were carried out using the DEPT heteronuclear multi-pulse program with a pulse repetition time of 3 s.

The acquisition parameters were AQ 0.297 s, $D_1 = 2$ s, $SI = 16K$, $S_2 = 18H$, $D_2 = 3.12$ μs, $PO = 45°$, 90°, 135°.

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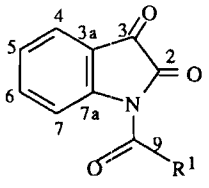
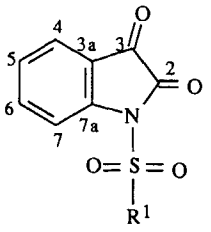
RESULTS AND DISCUSSION

The ^{13}C NMR spectral assignments of the parent acylisatins (**1** and **2**) and the parent sulphonamides (**3–5**) were easily made from the broad-band decoupled and DEPT spectra using isatin[5] as a model, and are presented in Table 1. The assignments of glyoxylic derivatives were made from the complete assignment of **8b**, which was subsequently used as the primary model system for the ^1H and ^{13}C NMR assignments. The 500 MHz ^1H NMR spectrum of derivative **8b** in $CDCl_3$ shows seven distinct resonances. Assignments of two upfield singlets (SO_2CH_3, OCH_3) and the slightly broadened downfield singlet (NH) were easily made on the basis of chemical shifts of the related acylisatin derivatives **6b** and **7b**. The four signals between 7.79 and 7.18 ppm were assigned on the basis of decoupling and NOE difference experiments. One doublet (7.79 ppm, H-7) and one triplet (7.18 ppm, H-5) were sharp whereas the other doublet (7.73 ppm, H-4) and triplet (7.66 ppm, H-6) appeared to be broadened. The broadening of the two signals is apparently due to unresolved *meta* coupling between protons H-4 and H-6. Their relative orientation was established by decoupling experiments. Irradiation at 7.18 ppm (H-5) caused the doublet at 7.73 ppm (H-4) to collapse to a singlet while the triplet at 7.66 ppm (H-6) collapsed to a doublet. Irradiation at 7.73 ppm (H-4) resulted in sharpening of the broadened triplet at 7.66 ppm (H-6) and the triplet at 7.18 ppm

0749–1581/92/010001–05 $05.00

Received 27 May 1991
Accepted (revised) 13 August 1991





	R^1
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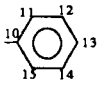
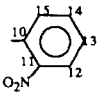
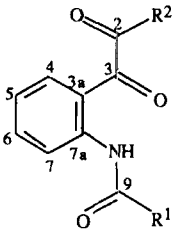
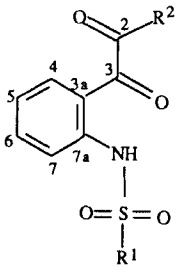
2	

	R^1
3	Me
4	
5	





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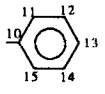
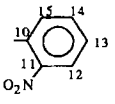
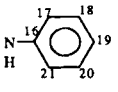
6	Me
7	

	R^1
8	Me
9	
10	

6 - 10	R^2
a	OH
b	OMe
c	
d	
e	NMe H
f	NMe_2
g	

(H-5) collapsed to a doublet. Irradiation of the doublet at 7.79 ppm (H-7) reduced the triplet at 7.66 ppm (H-6) to a doublet. The spectral orientation of protons H-4 and H-7 relative to the *ortho* substituent was established by a NOE difference experiment. Irradiation at 7.79 ppm (H-7) gave a NOE at 10.51 (NH) and 7.66 ppm (H-6), whereas irradiation at 7.73 ppm (H-4) gave a NOE at 7.18 (H-5).

The ^{13}C NMR broad-band decoupled and DEPT spectra of **8b** allowed the ready assignment of all carbons except C-4, C-5, C-6 and C-7. However, a $^{13}C/^{1}H$ heteronuclear correlation experiment allowed

Table 1. ^{13}C NMR chemical shifts[a] for isatin,[5] acylisatins (1 and 2) and sulphonylisatins (3–5) in DMSO

	Parent compound					
Carbon	1	2	3	4	5	Isatin
C-2	158.13	157.09	156.8	156.1	156.0	159.2
C-3	180.10	180.17	179.2	178.5	177.9	184.3
C-3a	119.70	119.89	119.7	120.0	120.0	117.8
C-4	125.49	125.23	125.5[b]	125.6[b]	125.9[b]	123.8
C-5	124.32	124.38	125.4[b]	125.3[b]	125.7[b]	122.7
C-6	137.77	137.38	138.2	138.2	138.1	138.3
C-7	117.16	116.06	114.5	114.5	115.1	112.5
C-7a	147.85	147.98	147.0	146.3	146.4	151.8
C-9	169.76	167.94				
C-10		133.68		137.7	130.1	
C-11		128.02[c]		129.9[c]	147.4	
C-12		129.58[c]		128.0[c]	125.3[b]	
C-13		132.96		135.3	136.9	
C-14		129.58[c]		128.0[c]	133.6	
C-15		128.02[c]		129.9[c]	132.5	
CH_3	25.88		41.7			

[a] In ppm from TMS at 0.0 ppm.
[b,c] Signals in any vertical column may be interchanged.

their assignment. The experiment clearly showed the ^{13}C signals at 137.2 (C-6), 134.2 (C-4), 122.7 (C-5) and 117.7 ppm (C-7) to be correlated with the ^{1}H NMR signals at 7.66 (H-6), 7.73 (H-4), 7.18 (H-5) and 7.79 ppm (H-7), respectively. This cumulative data allowed the complete ^{13}C NMR assignments for **8b**, which subsequently served as a primary model system for the assignments of compounds **6–10**, (Tables 2 and 3).

It can be noted that different chemical shifts are observed for C-16 and C-20 and also for C-17 and C-19 in the spectra of the morpholine and piperidine amide derivatives, resulting from slightly restricted rotation.

Table 2. ^{13}C NMR chemical shifts[a] for acids, methyl esters and anilides

	Acids[b]					Methyl esters[c]					Anilides			
Carbon	6a	7a	8a	9a	10a	6b	7b	8b	9b	10b	6c[b]	7c[b]	8c[c]	9c[c,f]
C-2	165.0	165.2[d]	165.6	165.4	165.2	163.7	163.7	163.4	163.2	163.4	162.1	162.5	160.2	159.7
C-3	189.4	190.8	191.5	190.8	191.0	190.1	190.5	189.7	189.6	189.1	190.3	191.7	190.9	190.7
C-3a	123.8	122.6	123.0	126.6	124.2	116.8	117.3	117.2	117.5	118.4	124.7	123.4	118.7	119.8
C-4	131.7	132.5[e]	133.3	132.4	133.3[d]	133.4	133.7	134.2	133.8[d]	134.0	131.6	132.7[d]	134.9	134.4
C-5	124.2	124.4	124.7	125.8	125.7[e]	122.4	122.7	122.7	122.8	123.4	124.6[d]	124.8[e]	122.6	123.0
C-6	135.0	135.8	136.4	135.3	136.0	137.0	137.4	137.2	136.7	136.8	134.2	135.2	136.5	135.9
C-7	122.3	122.4	121.2	123.0	121.8	120.5	120.7	117.7	118.4	118.3	122.0	122.3	117.9	119.6
C-7a	139.1	140.1	140.1	138.3[d]	137.9	142.5	143.0	141.9	141.2	140.2	138.4[e]	139.8	141.2	140.3
C-9	169.5	165.8[d]				169.5	165.9				169.2	165.9		
C-10		134.2		138.9[d]	130.9		134.2		138.7	132.2		134.2		138.3
C-11		127.7		129.7[e]	148.0		127.4		129.1	148.0		127.7		129.0[d]
C-12		129.2		127.3[e]	125.6[e]		128.8		127.0	125.6		129.1		126.8
C-13		132.6[e]		133.8	135.7		132.3		133.3[d]	134.6		132.6[d]		133.2
C-14		129.2		127.3[e]	133.2[d]		128.8		127.0	132.7		129.1		126.8
C-15		127.7		129.7[e]	131.1		127.4		129.1	131.2		127.7		129.0[d]
C-16											138.2[e]	138.1	136.4	136.3
C-17											120.4	120.4	120.1	120.0
C-18											129.1	129.1	128.9	128.8[d]
C-19											124.0[d]	124.3[e]	125.3	125.1
C-20											129.1	129.1	128.9	128.8[d]
C-21											120.4	120.4	120.1	120.0
CH_3	24.3		40.2			25.3		40.4			24.1		40.0	
OCH_3						52.8	53.0	53.1	52.9	53.1				

[a] In ppm from TMS at 0.0 ppm.
[b] DMSO as solvent.
[c] $CDCl_3$ as solvent.
[d,e] Signals in any vertical column may be interchanged.
[f] Values for the pairs C-11, C-15 and C-18, C-20 must be identical.

Table 3. ^{13}C NMR chemical shifts[a] for amide derivatives in $CDCl_3$

	Morpholine amide					*N*-Methyl amide					*N,N*-Dimethyl amide				Piperidine amide				
	6d	7d	8d	9d	10d	6e[c]	7e	8e	9e	10e	6f	7f	8f	9f	6g	7g	8g	9g	10g
C-2	163.9	164.3	163.9	163.7	163.7	164.5	163.8	163.3	163.0	162.6	165.8	166.0	165.3	165.1	163.8	164.0	163.5	163.5	163.6
C-3	194.7	195.5	194.5	194.6	194.0	191.8	192.6	191.6	191.4	190.6	195.6	196.3	195.2	195.3	195.5	196.2	195.3	195.5	194.9
C-3a	117.3	118.1	117.8	118.4	118.8	124.5	118.8	118.9	119.7	120.9	117.5	118.1	117.5	118.1	117.4	118.0	117.6	118.4	118.8
C-4	132.9	133.5	134.0	133.6[b]	133.9	131.9	134.7	135.1	134.5	134.4[b]	133.2	133.6	134.0	133.6	133.0	133.4	113.8	133.6[b]	133.9
C-5	122.2	122.8	122.7	123.1	123.4	123.8	122.7	122.7	122.9	123.6	122.5	122.9	122.6	123.1	122.2	122.7	122.5	123.0	123.3
C-6	136.4	137.1	137.0	136.6	136.6	134.3	136.7	136.5	135.9	136.0	136.5	137.0	136.8	136.3	136.2	136.7	136.6	136.2	136.4
C-7	120.0	120.7	117.4	118.9	117.9	121.9	120.6	117.8	119.1	119.0	120.3	120.6	117.2	118.6	120.0	120.4	117.1	118.7	117.8
C-7a	141.8	146.6	141.6	141.0	140.0	138.8	142.5	141.2	140.4	139.4	142.1	142.7	141.4	140.7	141.8	142.4	141.3	140.8	140.0
C-9	168.8	165.8				169.1	166.0				169.3	166.0			169.0	165.7			
C-10		134.1		139.0	132.0		134.4		138.6	132.2		134.2		138.8		134.0		139.0	132.2
C-11		127.3		129.1	147.8		127.4		129.0	147.9		127.4		129.0		127.1		129.0	147.9
C-12		128.7		127.0	125.4		128.8		126.9	125.5		128.8		126.8		128.6		126.7	125.4
C-13		132.2		133.2[b]	134.6		132.2		133.2	134.7[b]		132.2		133.2		132.0		133.1[b]	134.5
C-14		128.7		127.0	132.6		128.8		126.9	132.6		128.8		126.8		128.6		126.7	132.6
C-15		127.3		129.1	131.2		127.4		129.0	131.4		127.4		129.0		127.1		129.0	131.1
C-16	45.7	46.2	46.2	46.0	46.1										46.6	46.8	46.8	46.7	47.0
C-17	66.0[b]	66.4	66.4[b]	66.3	66.4[b]										25.6[b]	25.8[b]	25.7[b]	25.8[c]	25.9[b]
C-18															25.0[b]	25.1[b]	25.0[b]	25.0[c]	25.2[b]
C-19	65.9[b]	66.4	66.3[b]	66.3	66.3[b]										23.7	23.9	23.9	23.9	24.0
C-20	41.0	41.5	41.6	41.4	41.6										41.6	41.9	41.9	41.9	42.1
C-21																			
CH_3	24.9		40.4			24.3		40.1			25.2		40.2		24.9		40.1		
OCH_3																			
$NHCH_3$						25.8	26.2	26.1	25.9	26.2									
$N(CH_3)_2$											36.8	37.0	36.9	36.6					
											33.7	33.9	33.8	33.6					

[a] In ppm from TMS at 0.0 ppm.
[b,c] Signals in any vertical column may be interchanged.

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