Reference Data

^{1}H and ^{13}C Chemical Shifts of some Tetracyclic Acridinone Derivatives

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The ^{1}H and ^{13}C NMR resonances of 19 tetracyclic acridinone derivatives were completely and unambiguously assigned by a combination of ^{1}H-detected one-bond HMQC and long-range (two and three bonds) HMBC correlation experiments. ^{1}H and ^{13}C chemical shifts are also reported for the respective *N*-aryl benzoheterocyclic precursors.

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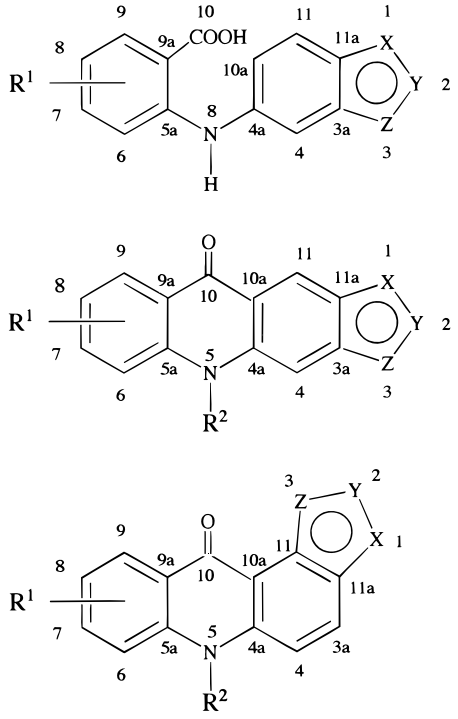
INTRODUCTION

The use of acridine derivatives as therapeutic agents has been the subject of numerous studies.[1] Therefore, the synthesis of new tetracyclic acridine compounds has increased rapidly in the last few years.[2] The potential biological activity of these novel ring systems renders them particularly attractive as candidates for pharmacological evaluation. In this respect, we have recently described the preparation of and NMR spectral data for, e.g., pyrazolo[*a*],[3,4] thiazolo[4,5-*a*],[5,6] thiazolo[5,4-*a*],[5,6] pyrrolo[2,3-*b*][7] and pyrrolo[3,2-*a*]acridinones.[7]

In this paper, we report the complete ^{1}H and ^{13}C NMR chemical shift assignments obtained from one- and two-dimensional NMR techniques for the following new classes of fused acridinones: 2,3-dihydro-1-cyclopent[*b*]acridin-10(5*H*)-one (**1b–5b**), 2,3-dihydro-1-cyclopent[*a*]acridin-11(6*H*)-one (**1c–5c**), 1,3-dioxolo[2,3-*b*]acridin-10(5*H*)-one (**6b**), 2,3-dihydro-1,4-dioxino[2,3-*b*]acridin-10(6*H*)-one (**7b–9b**), 2,3-dihydro-1,4-dioxino[2,3-*a*]acridin-12(7*H*)-one (**7c–9c**), 1,3-dihydroimidazo[4,5-*b*]acridin-2,10(5*H*)-dione (**10b**, **11b**) and 1,3-dihydroimidazo[4,5-*a*]acridin-2,11(5*H*)-dione (**10c**, **11c**) (Fig. 1).



	X	Y	Z	R^1	R^2
1	CH_2	CH_2	CH_2	H	H
2	CH_2	CH_2	CH_2	6-NO_2	H
3	CH_2	CH_2	CH_2	7-NO_2	H
4	CH_2	CH_2	CH_2	8-NO_2	H
5	CH_2	CH_2	CH_2	8-OCH_3	H
6	O	CH_2	O	H	H
7	O	2 2′ X-CH_2-CH_2-Z	O	H	H
8	O	2 2′ X-CH_2-CH_2-Z	O	H	CH_3
9	O	2 2′ X-CH_2-CH_2-Z	O	H	12 13 14 CH_2-CH_2-$N(CH_3)_2$
10	NH	CO	NH	H	H
11	NCH_3	CO	NCH_3	H	CH_3

Figure 1. Structures of the compounds studied (the numbering of the carbons is arbitrary).

EXPERIMENTAL

The compounds were prepared and purified as described previously.[8] All spectra were recorded on a Bruker AMX 400 spectrometer in DMSO-d_6 solutions. The ^{1}H and ^{13}C chemical shifts of the solvent were used as a secondary reference and referred to the TMS signal from the usual relationships.[9]

The ^{1}H-detected one-bond HMQC[10] spectra were obtained using a pulse sequence (INVBTP in the operating Bruker software) which includes the BIRD pulse[11] to invert the magnetization of the protons not coupled to ^{13}C. These spectra were collected with 2K × 256 data points, a data acquisition of 32 scans × 256 increments in the t_1 domain. Spectral widths of 3000 and 8000 Hz were employed in the F_2 (^{1}H) and F_1 (^{13}C) domains, respectively. Data were processed using sine-bell functions for weighting in both dimensions; the delay Δ_1 was set to 3.0 ms and Δ_2 was empirically optimized as 400 ms.

The long-range HMBC spectra[12] were obtained using the standard pulse sequence (the INV4LPRND microprogram in the Bruker software). The spectral widths were 3 kHz (F_2) and 10 kHz (F_1), and the delays Δ_1 and Δ_2 were set to 3.0 and 60 ms, respectively.

RESULTS AND DISCUSSION

The results are given in Tables 1–7. The structural determination of the fused tetracyclic acridinones **b** and **c** follows from the multiplet pattern analysis of C-ring protons; thus, H-3a (or H-11) and H-4 would be expected to resonate as two singlets in the case of linear isomer **b** and two doublets in the case of bent isomer **c**. Such an approach has been already used for the structural elucidation of pyrazolo[*a*]-9(10*H*)-acridinones[4] and pyrazolo[*b*]- and pyrazolo[*c*]phenothiazines.[13]

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Table 1. ^{1}H chemical shifts of *N*-aryl compounds 1a–7a and 10a[a]

Atom	1a	2a	3a	4a	5a[b]	6a	7a	10a
H-1	2.83	2.76	2.85	2.84	2.79	—	—	10.58
H-2/2′	2.00	1.97	2.07	2.02	1.99	6.01	4.22/4.22	—
H-3	2.83	2.76	2.85	2.84	2.79	—	—	10.58
H-4	7.08	6.78	7.14	7.14	7.04	6.86	6.72	6.80
H-10a	6.95	6.66	7.06	7.04	6.91	6.69	6.72	6.79
H-11	7.17	7.06	7.26	7.26	7.15	6.89	6.84	6.90
H-5	9.59	9.90	9.80	10.29	9.11	9.40	—	10.58
H-6	7.10	—	7.70	6.99	7.15	6.96	6.99	6.96
H-7	7.32	8.17	—	8.09	7.06	7.33	7.32	7.29
H-8	6.69	7.02	7.43	—	—	6.69	6.67	6.66
H-9	7.87	8.03	8.07	8.66	7.37	7.85	7.85	7.84

[a] In ppm from TMS; DMSO-d_6 as solvent.
[b] $\delta OCH_3 = 3.70$ ppm.

Table 2. ^{13}C chemical shifts of *N*-aryl compounds 1a–7a and 10[a]

Atom	1a	2a	3a	4a	5a[c]	6a	7a	10a
C-1	31.74	31.68	31.85	32.03	31.77	—	—	—
C-2/2′	25.19	25.08	25.18	25.34	25.32	101.24	63.96/64.18	155.45
C-3	32.74	32.36	32.40	32.50	32.51	—	—	—
C-3a	145.10	144.79	145.57	145.66	145.09	148.54	143.75	130.51
C-4	118.35	116.40	119.48	120.48	118.94	105.28	111.94	104.39
C-4a	138.93	139.30[b]	140.62	141.78	139.75	134.38	133.71	133.55
C-10a	120.36	118.00	121.32	122.43	121.88	116.39	116.34	116.13
C-11	124.83	124.57	125.15	125.33	124.85	108.61	117.59	108.98
C-11a	138.44	138.87	137.08	136.21	137.84	143.93	140.10	126.54
C-5a	147.99	139.59[b]	148.72	153.02	141.87	147.98	148.33	148.79
C-6	113.32	139.42[b]	107.18	113.07	114.46	113.17	113.14	112.96
C-7	134.01	130.93	150.79	129.29	116.84	134.19	134.12	133.76
C-8	116.62	114.61	109.91	136.21	150.62	116.56	116.51	116.21
C-9	131.84	136.68	133.54	128.61	116.16	131.80	131.80	131.69
C-9a	112.02	119.52	116.80	110.53	113.17	111.56	111.70	111.97
C-10	169.85	168.75	168.64	168.86	169.66	170.00	170.06	170.07

[a] In ppm from TMS; DMSO-d_6 as solvent.
[b] Assignments may be reversed.
[c] $\delta OCH_3 = 55.38$ ppm.

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Table 3. ^{1}H chemical shifts of tetracyclic derivatives of acridinone (linear isomer b)[a]

Atom	1b	2b[b]	5b[c]	6b	7b	8b[b,d]	9b[e]	10b	11b[b,g]
H-1	2.95	2.99	2.96	—	—	—	—	11.01[f]	—
H-2	2.05	2.12	2.05	6.13	4.30	4.28	4.33	—	—
H-2′	—	—	—	—	4.37	4.36	4.41	—	—
H-3	2.95	2.99	2.96	—	—	—	—	10.79[f]	—
H-4	7.46	7.30	7.33	6.95	6.93	6.90	7.16	7.02	6.78
H-5	12.13	11.20	11.56	11.71	11.46	—	—	11.97	—
H-6	7.58	—	7.48	7.47	7.44	7.40	7.66	7.53	7.42
H-7	7.66	8.68	7.34	7.65	7.65	7.63	7.76	7.64	7.65
H-8	7.18	7.29	—	7.21	7.18	7.20	7.26	7.16	7.24
H-9	8.18	8.86	7.60	8.17	8.17	8.48	8.27	8.18	8.51
H-11	8.02	8.24	8.03	8.50	7.59	7.97	7.69	7.64	7.98

[a] In ppm from TMS; DMSO-d_6 as solvent.
[b] $CDCl_3$ as solvent.
[c] $\delta OCH_3 = 3.83$ ppm.
[d] $\delta NCH_3 = 3.74$ ppm.
[e] δH-12 = 4.45 ppm; δH-13 = 2.61 ppm; δH-14 = 2.27 ppm.
[f] These assignments may be reversed (broad signals).
[g] $\delta N_1CH_3 = \delta N_3CH_3 = 3.44$ ppm; $\delta N_5CH_3 = 3.83$ ppm.

Table 4. ^{13}C chemical shifts of tetracyclic derivatives of acridinone (linear isomer b)[a]

Atom	1b	2b[b]	5b[c]	6b	7b	8b[b,d]	9b[f]	10b	11b[b,g]
C-1	31.41	32.15	31.42	—	—	—	—	—	—
C-2	25.36	25.80	25.46	101.95	63.91	63.99	63.86	155.81	155.19
C-2′	—	—	—	—	64.95	65.06	64.90	—	—
C-3	32.61	33.46	32.63	—	—	—	—	—	—
C-3a	150.74	153.36	150.56	152.57	149.46	149.50	149.65	136.06	136.20
C-4	112.10	113.10	111.93	95.71	102.95	102.00	102.59	94.58	92.26
C-4a	140.77	141.22	141.22	138.43	136.87	138.69	137.54	137.37	139.82
C-5a	140.21	134.22	139.76	140.19	140.91	142.38	141.47	140.40	142.13
C-6	117.16	135.83	118.92	117.01	117.05	114.33[e]	115.43	116.78	114.59
C-7	132.73	131.38	123.80	132.48	132.91	133.13	133.64	132.23	133.28
C-8	120.40	119.45	153.62	120.91	120.53	120.65	120.76	120.03	121.12
C-9	125.83	136.68	104.88	125.70	125.98	127.60	126.55	125.68	127.71
C-9a	120.17	124.17	120.68	119.91	119.58	121.69	120.76	119.37	121.81
C-10	176.40	176.86	175.76	174.97	176.18	176.73	175.01	175.71	177.25
C-10a	119.41	120.79	120.68	115.33	115.61	117.56	116.53	115.35	117.73
C-11	120.27	121.96	120.22	102.02	111.78	114.27[e]	112.55	102.76	104.45
C-11a	137.43	138.78	137.36	143.68	139.81	139.56	139.60	126.58	126.44

[a] In ppm from TMS; DMSO-d_6 as solvent.
[b] $CDCl_3$ as solvent.
[c] $\delta OCH_3 = 55.29$ ppm.
[d] $\delta NH_3 = 33.66$ ppm.
[e] Assignments may be reversed.
[f] δC-12 = 55.65 ppm; δC-13 = 44.31 ppm; δC-14 = 45.70 ppm.
[g] $\delta N_1CH_3 = \delta N_3CH_3 = 27.58$ ppm; $\delta N_5CH_3 = 34.39$ ppm.

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Table 5. ^{1}H chemical shifts of tetracyclic derivatives of acridinone (bent isomer c)[a]

Atom	1c	2c[b]	3c	4c	5c[c]	7c	8c[b,d]	9c[e]	10c	11c[b,g]
H-1	2.87	2.96	2.86	2.88	2.86	—	—	—	10.72[f]	—
H-2	2.07	2.18	2.08	2.08	2.07	4.33	4.48	4.45	—	—
H-2′	—	—	—	—	—	4.26	4.32	4.31	—	—
H-3	3.53	3.62	3.50	3.48	3.55	—	—	—	10.85[f]	—
H-3a	7.55	7.56	7.61	7.60	7.52	7.25	7.25	7.34	7.40	7.29
H-4	7.31	7.21	7.31	7.32	7.29	7.11	6.96	7.17	7.13	7.17
H-5	11.51	11.16	11.95	12.09	11.50	11.99	—	—	11.67	—
H-6	7.45	—	8.29	7.54	7.45	7.53	7.40	7.66	7.50	7.43
H-7	7.65	8.65	—	8.35	7.34	7.61	7.64	7.75	7.69	7.67
H-8	7.17	7.25	7.85	—	—	7.14	7.22	7.23	7.21	7.24
H-9	8.14	8.77	8.32	8.85	7.58	8.11	8.48	8.19	8.19	8.40

[a] In ppm from TMS; DMSO-d_6 as solvent.
[b] $CDCl_3$ as solvent.
[c] $\delta OCH_3 = 3.83$ ppm.
[d] $\delta NCH_3 = 3.60$ ppm.
[e] δH-12 = 4.31 ppm; δH-13 = 2.65 ppm; δH-14 = 2.29 ppm.
[f] These assignments may be reversed (broad signals).
[g] $\delta N_1CH_3 = 3.45$ ppm; $\delta N_3CH_3 = 3.87$ ppm; $\delta N_5CH_3 = 3.84$ ppm.

Table 6. ^{13}C chemical shifts of tetracyclic derivatives of acridinone (bent isomer c)[a]

Atom	1c	2c[b]	3c	4c	5c[c]	7c	8c[b,d]	9c[e]	10c	11c[b,f]
C-1	31.37	32.10	31.22	31.40	31.46	—	—	—	—	—
C-2	24.73	25.32	24.78	24.69	24.73	64.37	64.95	64.35	155.03	156.26
C-2′	—	—	—	—	—	63.40	63.69	63.37	—	—
C-3	34.37	34.76	34.53	34.23	34.48	—	—	—	—	—
C-3a	129.50	130.84	129.89	130.48	129.21	123.90	123.30	123.64	115.62	113.01
C-4	115.45	116.17	115.90	116.17	115.53	109.11	106.72	107.26	108.14	107.13
C-4a	140.62	140.67	140.62	140.09	140.32	137.71	139.40	138.01	136.26	139.74
C-5a	140.62	134.05	139.21	144.54	135.48	140.12	141.82	140.82	140.88	142.21
C-6	116.90	135.96	111.76	118.42	116.72	116.76	114.07	115.17	117.22	114.54
C-7	132.95	131.34	151.32	127.05	123.76	132.74	133.12	133.57	133.21	133.51
C-8	120.41	119.32	115.28	140.26	153.64	120.46	120.85	120.81	120.39	120.92
C-9	125.96	136.53	126.11	123.16	105.02	125.99	127.79	126.65	125.46	127.36
C-9a	121.28	125.05	120.19	119.78	121.78	121.16	123.64	122.68	119.80	123.31
C-10	177.98	178.11	177.70	177.47	177.31	176.18	177.81	175.83	177.09	177.50
C-10a	117.77	118.99	117.21	117.95	117.00	111.82	113.88	113.08	106.68	110.23
C-11	144.06	146.66	143.92	144.25	143.76	142.82	144.06	143.57	126.86	129.27
C-11a	136.39	136.53	137.21	138.73	135.98	136.09	137.05	136.71	122.26	125.06

[a] In ppm from TMS; DMSO-d_6 as solvent.
[b] $CDCl_3$ as solvent.
[c] $\delta OCH_3 = 55.26$ ppm.
[d] $\delta NH_3 = 33.44$ ppm.
[e] δC-12 = 55.69 ppm; δC-13 = 44.75 ppm; δC-14 = 45.58 ppm.
[f] $\delta N_1CH_3 = 27.48$ ppm; $\delta N_3CH_3 = 35.19$ ppm; $\delta N_5CH_3 = 34.75$ ppm.

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Table 7. Long-range proton–carbon couplings found in the HMBC spectra of 2,3-dihydro-1,4-dioxino[2,3-*b*]acridine-10(6*H*)-one (7b) and 2,3-dihydro-1,4-dioxino[2,3*a*]acridin-12(7*H*)-one (7c)

Carbon	Protons showing HMBC correlation (^3J couplings) 7b	7c
3a	H-11; H-2′	—
4	H-5	H-5
4a	H-11	H-3a
5a	H-7; H-9	H-7; H-9
6	H-5; H-8	H-5; H-8
7	H-9	H-9
8	H-6	H-6
9	H-7	H-7
9a	H-5; H-6; H-8	H-5; H-6; H-8
10	H-9	H-9
10a	H-4; H-5	H-4; H-5
11	—	H-2′; H-3a
11a	H-2; H-4	H-2; H-4

Although some of the remaining ^{1}H resonances can be assigned on the basis of the appearance of their multiplet patterns and the magnitude of the splittings, complete ^{1}H assignment cannot be obtained from the one-dimensional spectra. Therefore, assignment of the other ^{1}H and ^{13}C resonances of compounds **a**–**c** was deduced from the concerted application of both direct and long-range heteronuclear chemical shift correlation experiments. One-bond proton–carbon chemical shift correlations were established using the HMQC sequence and the $(CH)_n$ groups were unambiguously characterized from the analysis of long-range correlation responses over two and three bonds (^2J or ^3J couplings) using the HMBC technique. This procedure was exemplified for the 2,3-dihydro-1,4-dioxino[2,3-*b*]acridin-10(6*H*)-one **7b** and the 2,3-dihydro-1,4-dioxino[2,3-*a*]acridin-12(7*H*)-one **7c**, for which all the connectivities observed in the HMBC diagram are given in Table 7. For the assignment of the methylene groups CH_2-2 and CH_2-2′, the starting point were the C-4 and C-11 resonances for the linear isomer **b** and the C-3a and C-4 signals for the bent isomer **c**. These carbons, which can be ascribed in a straightforward manner from the HMQC spectra, show correlated peaks to either one of the two methylene protons CH_2-2 and CH_2-2′. The complete ^{1}H and ^{13}C NMR spectral data for tetracyclic heterofused acridinones are presented in tables **3**–**6** and assignments for *N*-aryl compounds are given in Tables 1 and 2.

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