NUCLEOPHILIC AROMATIC SUBSTITUTION OF A METHOXY GROUP BY AN ALKYLTHIO GROUP IN THE CASE OF 10-SUBSTITUED 2-METHOXY-9-THIOACRIDINONES

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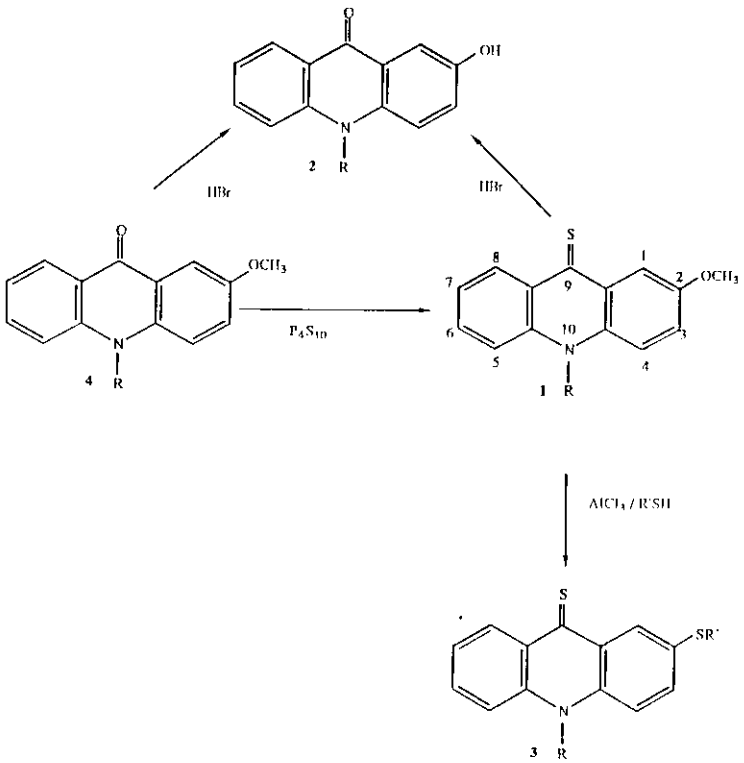
Abstract - The synthesis and nmr study (^{1}H and ^{13}C) of eleven acridine derivatives are reported. ^{13}C Chemical shifts are very sensitive to the oxygen or sulfur nature of the substituents at positions 2 (alkoxy vs thioalkoxy) and 9 (acridinones vs thioacridinones). The rather unusual replacement of an alkoxy group by a thioalkoxy group in thioacridinones, when treated by alkyl *mercaptans in the presence* of aluminium chloride, is described.

We became interested in the 2-hydroxy-10-methyl-9-thioacridinone as starting material for the preparation of bisacridine derivatives.[1-5] *The simplest way to obtain this product would* obviously be the demethylation of 2-methoxy-10-methyl-9-thioacridinone **1a**. However, use of hydrobromic acid, which gives excellent results in the case of methoxyacridinones,[6] led to the 2-hydroxy-10-methyl-9-acridinones **2**.[7-8] Hence to avoid the simultaneous hydrolysis of the thione group, two alternative methods were tried. The use of aluminium iodide in benzene[9] failed and the starting material was recovered. In constrast, aluminium chloride in ethanethiol [10-11] *afforded 2-ethylthio-10-methyl*-9-thioacridinones **3a**. The compound so obtained was somewhat unexpected because there is usually a demethylation under these experimental conditions.[10] Yet, substituted derivatives were obtained from methoxynaphthalene [11] but until now, this has never been mentioned in the field of heterocyclic chemistry.

The same reaction was observed when the substituent on the nitrogen is benzyl **1b** or ethyl **1c** - prepared by thiation of the 9-oxo analogs **4** *according to the method of Smolders*[12] - or when ethanethiol is replaced by propanethiol : compounds **3b-3e**. In contrast, the reaction failed with butanethiol, with 9-(10H)-thioacridinones, and with 2-methoxyacridinones (both NH and N-methyl). According to the opinion of Node,[11] this could be due to the decrease in the nucleophilic reactivity.

These results are schematized in the Figure and data about the compounds prepared are listed in Table 1.



Compounds	R	2-substituent
1a	CH_3	OCH_3
1b	$CH_2C_6H_5$	OCH_3
1c	C_2H_5	OCH_3
3a	CH_3	SC_2H_5
3b	$CH_2C_6H_5$	SC_2H_5
3c	C_2H_5	SC_2H_5
3d	CH_3	SC_3H_7
3e	C_2H_5	SC_3H_7
4a	CH_3	OCH_3
4b	$CH_2C_6H_5$	OCH_3
4c	C_2H_5	OCH_3

The ^{13}C chemical shifts gathered in Table II, prove that the SR group occupies the same position, C-2, that the methoxy leaving group. Actually, with a reference to 9-thioacridinone,[13] resonance peaks are shifted of about 33 ppm for C-2, 20 ppm for C-1, and 10 ppm for C-3 in the case of the 2-methoxy substitution, whilst resonance peaks are respectively shifted of only 8 ppm for C-2, and approximately 0.5 to 1.5 ppm for C 1 or C-3, in the case of compounds **3**. Added to this, ^{1}H nmr leads to the same conclusion. Indeed, protons 1 and 8 are deshielded (dd, δ = 9.1 ppm) when there are no substituents branched on the

9-thioacridinone nucleus. In the case of substitution with a methoxy group in position 2, there are two signals for the protons under discussion [H (1), δ = 9.1 ppm and H (8), δ = 8.6 ppm], whilst in the case of substitution with a thioethyl group, chemical shifts are 9.0 ppm for H (1) and 9.1 ppm for H (8). This is due to the deshielding effect of the thioether group.

Such a structure can be also deduced from mass spectra. Indeed with reference to the data presented in Table III, attention must be draw, on the one hand, on the parent-ion peaks at m/z 285, 351 and 299 for **3a**, **3b** and **3c**, and, on the other hand, on ion peaks at m/z 241 which correspond to the loss of all alkyl substituents for **3a**, **3b**, and **3c**, whilst ion peaks at m/z 270 is due to the loss of the benzyl group, for **3b**.

Thus, the mechanism involved corresponds to the SRNAr mechanism previously proposed by Node in the case of aromatic hydrocarbons,[11] with the possibility of a monoelectronic process.

Table III. Mass Spectra Data (m/z)

3a	285 (M^+) (100), 257 (45), 256 (30), 252 (24), 241 (23)
3b	361 (M^+) (38), 333 (1), 300 (1.5), 270 (50), 242 (7), 241 (8), 91 (100)
3c	299 (M^+) (100), 284 (12), 271 (33), 270 (25), 266 (16), 242 (13), 241 (15)

Table I. ^1H Nmr data

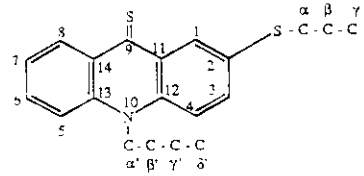
Compound	mp (°C)	Yield %	Analysis (%) Found C	H	N	S	Calc C	H	N	S	^1H - Nmr[a] ($CDCl_3$/TMS) δ (ppm), J (Hz)
1a (13)	175	87	70.59	5.10	5.49	12.55	70.71	5.29	5.52	12.50	9.2 (d, J = 8.5 Hz, 1H) ; 8.6 (s, 1H); 7.7 to 7.3 (m, 5H) ; 4.1 (s, 3H) ; 4.0 (s, 3H)
1b	184	76	76.13	5.16	4.23	9.63	76.26	5.23	4.34	9.63	9.3 (d, J = 8.5 Hz, 1H); 8.6 (s, 1H); 7.7 to 6.9 (m, 10H) ; 5.6 (s, 2H) ; 3.9 (s, 3H)
1c	149	85	71.38	5.58	5.20	11.90	71.46	5.77	5.35	11.79	9.2 (d, J = 8.5 Hz, 1H); 8.6 (s, 1H); 7.7 to 7.2 (m, 5H) ; 4.5 (q, J = 7 Hz, 2H); 3.9 (s, 3H); 1.5 (t, J = 7 Hz, 3H)
3a	152	92	67.37	5.26	4.91	22.45	67.39	5.20	4.69	22.60	9.0 (d, J = 7.5 Hz, 1H); 8.9 (s, 1H) ; 7.7 to 7.2 (m, 5H) ; 3.9 (s, 3H) ; 3.0 (q, J = 7 Hz, 2H) ; 1.4 (t, J = 7 Hz, 3H)
3b	163	84	73.13	5.26	3.88	17.73	73.14	5.33	3.83	17.90	9.3 (d, J = 7 Hz, 2H) ; 9.1 (s, 1H) ; 7.7 to 7.0 (m, 10H) ; 5.6 (s, 2H) ; 3.1 (q, J = 7 Hz, 2H) ; 1.4 (t, J = 7 Hz, 3H)
3c	129	83	68.23	5.69	4.68	21.40	68.37	5.76	4.52	21.20	9.2 (d, J = 7 Hz, 1H) ; 9.1 (s, 1H) ; 7.7 to 7.2 (m, 5H) ; 4.5 (q, J = 7 Hz, 2H); 3.9 (q, J =7 Hz, 2H) ; 1.7 to 1.3 (m, 6H)
3d	140	88	68.23	5.69	4.68	21.40	68.35	5.78	4.73	21.50	9.1 (d, J = 8 Hz, 1H) ; 9.0 (s, 1H) ; 7.6 to 7.2 (m, 5H) ; 3.9 (s, 3H) ; 2.9 (t, J = 7 Hz, 2H) ; 2.5 to 1.5 (m, 2H) 1.0 (t, J = 7 Hz, 3H)
3e	143	87	69.01	6.07	4.47	20.45	69.04	6.19	4.51	20.30	9.2 (d, J = 8 Hz, 1H) ; 9.1 (s, 1H) ; 7.7 to 7.2 (m, 5H) ; 4.5 (9, J = 7 Hz, 2H); 3.0 (t, J = 7.2 Hz, 2H) ; 1.9 to 1.5 (m, 5H) ; 1.1 (t, J = 7 Hz, 3H)
4a (14,15)	138	91	75.31	5.44	5.86		75.47	5.58	5.77		8.5 (d, J = 8 Hz, 1H) ; 7.9 (s, 1H) ; 7.6 to 7.2 (m, 5H) ; 3.9 (s, 3H) ; 3.8 (s, 3H)
4b (14,16)	148	56	80.00	5.40	4.44		80.05	5.53	4.57		8.6 (d, J = 8.5 Hz, 1H) ; 7.9 (s, 1H) ; 7.6 to 7.2 (m, 10H) ; 5.5 (s, 2H) ; 3.9 (s, 3H)
4c (14,17,18)	212	68	75.89	5.93	5.53		75.92	6.04	5.68		8.6 (d, J = 8 Hz, 1H) ; 8.0 (s, 1H) ; 7.8 to 7.3 (m, 5H) ; 4.5 (q, J = 7 Hz, 2H) ; 3.9 (s, 3H) ; 1.5 (t, J = 7 Hz, 3H)

a) Recorded with a Varian A 60 spectrometer.

Table II. ^{13}C Nmr chemical shifts δ (in ppm)

Carbons	COMPOUNDS											
	1a[a]	1b[a]	1c[a]	3a[a]	3b[a]	3c[a]	3d[a]	3e[a]	4a[a]	4b[c]	4c[b]	9-Thioacridinone[c]
1	110.53	110.86	110.89	131.56	131.91	132.26	131.77	132.29	105.9	103.76	107.12	129.9
2	155.83	156.16	155.86	131.18	131.59*	131.51*	131.42*	131.48*	153.8	159.88	154.38	122.6
3	125.36	125.56	125.73	133.62	134.08	134.02	133.76	134.00	123.7	134.19	124.30	132.8
4	115.36	115.79	115.05	115.51	115.95	115.17	115.49	115.16	117.9	121.09	114.25	120.2
5	117.14	117.62	116.87	116.17	116.64	115.86	116.12	115.81	115.8	119.17	116.20	120.2
6	133.42	133.75	133.67	134.71	135.27	135.29	134.92	135.26	133.5	139.90	133.48	132.8
7	122.68	123.00	122.74	122.78	123.23	122.96	122.91	122.95	120.7	126.49	120.71	122.6
8	131.97	132.09	132.44	130.10	130.53	130.85	130.18	130.73	126.5	130.71	127.81	129.9
9	198.12	199.43	198.01	198.89	200.41	199.20	199.24	199.23	175.9	169.46	177.21	192.9
11	132.00	132.60	131.64	131.91	132.44	132.00	132.32	132.30	120.6	119.53	123.22	129.0
12	132.61	132.33	132.20	135.67	135.94	134.94	135.82	134.89	137.0	141.10	136.29	138.0
13	137.09	137.23	136.11	137.14	137.43	136.36	137.30	136.36	141.8	143.72	141.00	138.0
14	130.81	131.04	130.91	131.18	131.65*	131.54*	131.36*	131.57*	122.3	128.32	121.74	129.0
α	55.79	55.83	55.83	27.95	28.05	28.05	35.98	36.01	55.4	57.43	55.71	–
β	–	–	–	14.20	14.26	14.24	22.47	22.48	–	–	–	–
γ	–	–	–	–	–	–	13.51	13.50	–	–	–	–
α'	34.82	51.86	42.16	34.65	51.76	42.07	34.72	42.05	33.6	54.91	40.90	–
β'	–	135.26	13.05	–	135.09	12.88	–	12.89	–	134.57	12.65	–
γ'	–	125.68	–	–	125.70	–	–	–	–	126.83	–	–
δ'	–	129.34	–	–	129.36	–	–	–	–	131.40	–	–
ε'	–	128.03	–	–	128.05	–	–	–	–	126.32	–	–

a) $CDCl_3$/TMS
b) TFA-d/TMS
c) $DMSO\text{-}d_6$/TMS
* These assignments may be reversed.



EXPERIMENTAL

10-Alkyl-2-methoxy-9-acridinones, **4** ; General Procedure : A stirred mixture of 2-methoxy-9(10H)-acridinone[20] (0.015 mol), alkylating agent (0.0375 mol), triethylbenzylammonium chloride (0.0075 mol), 50 % potassium hydroxide (75 ml) and toluene (150 ml) is heated for 5 days at 110°C. The toluene layer is separated, washed three times with water (about 50 ml each time), dried with sodium sulfate, and evaporated in vacuo. The crude is recrystallized from ethanol.

10-Alkyl-2-methoxy-9-thioacridinones, **1** ; General Procedure : A mixture of 10-alkyl-2-methoxy-9-acridinones **4** (0.010 mol), tetraphosphorus decasulfide (0.010 mol) and hexamethylphosphoramide (30 ml) is stirred at 100°C for 24 h. The solution is then poured out into 500 ml of cold water. The precipitate obtained is filtered out, washed with cold water and recrystallized from methanol.

10-Alkyl-2-alkylthio-9-thioacridinones, **3** ; General Procedure : Aluminium chloride (0.022 mol) is added to 10-alkyl-2-methoxy-9-thioacridinones **1** (0.004 mol). The use of any solvent is not necessary. The mixture is mildly heated for 10 min at 30°C, safe from moisture. Alkyl mercaptan (0.15 mol) is then added, and the mixture is stirred for a time which depends on the nature of the mercaptan (2 h with ethyl mercaptan, 7 h with propyl mercaptan), before the solution be poured out into water (500 ml). The red precipitate obtained is filtered out, washed with cold water and recrystallized from acetonitrile.

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