ALKYLATION AND ACYLATION OF 2- HYDROXY- 9(10H)-ACRIDINONE AND 2- HYDROXY-9(10H)-THIOACRIDINONE

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Abstract - New compounds, mostly referred as bis(10H)-acridinones and bis-(10H)-thioacridinones, have been prepared from 2-hydroxy-9(10H)-acridinone and 2-hydroxy-9(10H)-thioacridinone. The alkyl-linked derivatives have been prepared under phase transfer catalysis conditions, while the acyl-linked derivatives have been prepared in pyridine by way of the corresponding acridinyl thallous salts. Some bis-acridines bilinked have been also prepared.

Reactivity of ambident molecules like 2-hydroxy-9(10H)-acridinone (1)[1,2] and 2-hydroxy-9(10H)-thioacridinone (2) must be accurately evaluated. This is due to the fact that these compounds can be acylated or alkylated on oxygen atom or nitrogen atom, as well as in position 10[3,4]. Moreover, the alkyl- and the acyl- derivatives obtained are of interest from a biological point of view, particularly in the case of dimers [5-7].

At first, we were interested in the 2-hydroxy-10-methyl-9(10H)-acridinone (3)[8] because there is only one site for the substitution in the latter.

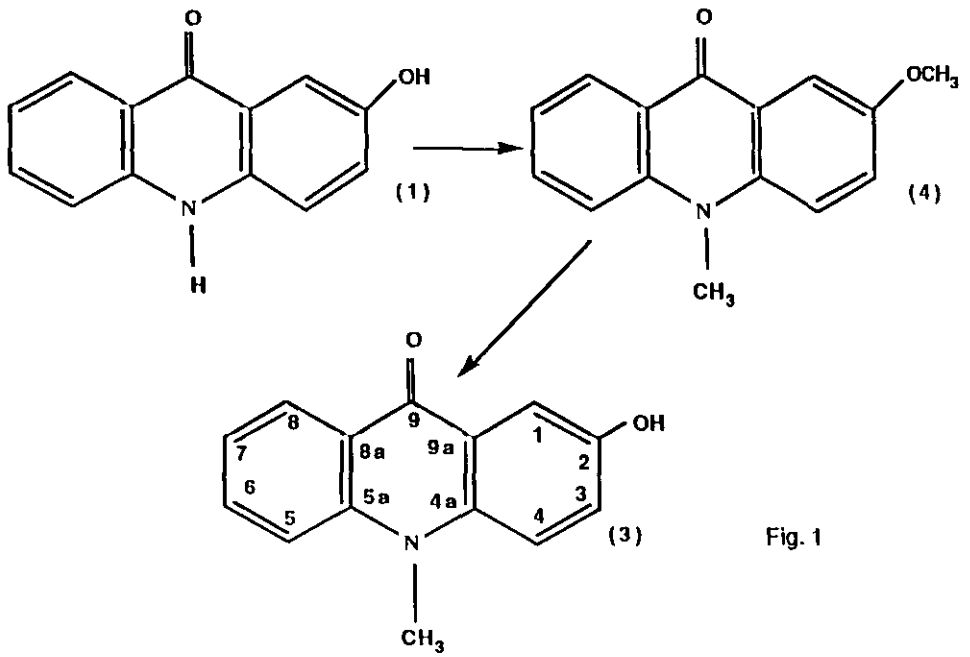


Fig. 1

Acylation of compound (3) either under phase transfer catalysis conditions in toluene or dioxane, or in pyridine at various temperatures, did never succeed. Conversely, the bisacridinone diesters (5) were obtained by acylating in pyridine in the stoichiometric concentrations, the thallous salts prepared from (3), by way of thallous ethoxide [9] as presented in figure 2.

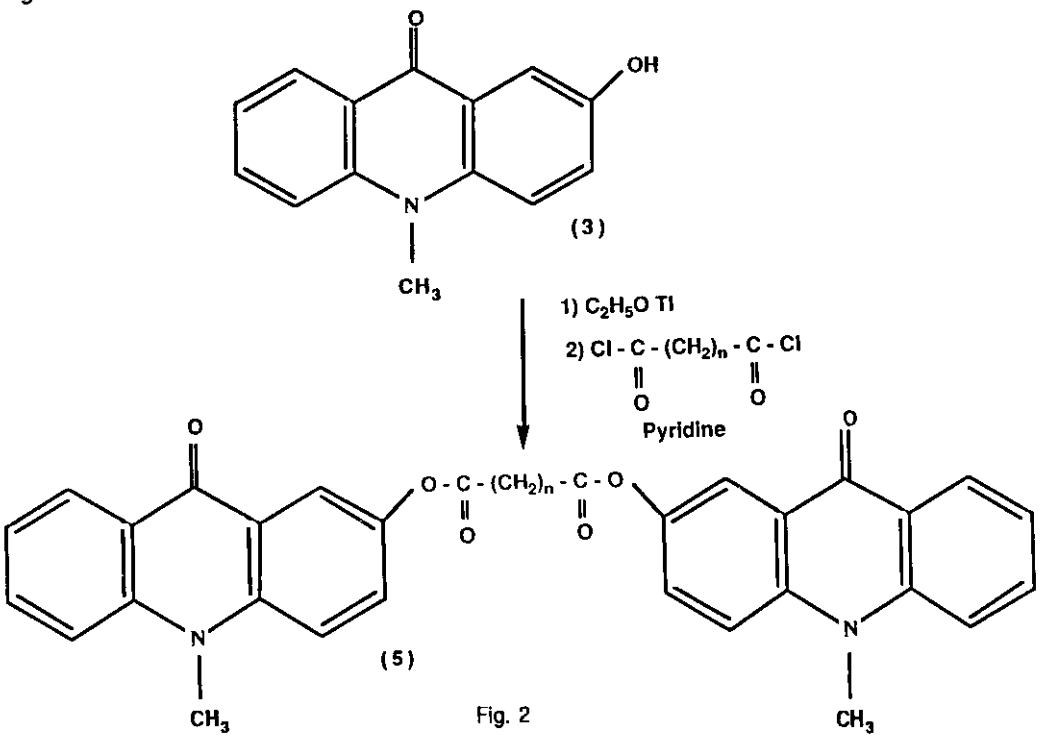


Fig. 2

Chemical data, ^{1}H and ^{13}C nmr data of compounds (5), are gathered in Tables 1 and 2.

Table 1.

Compound	n	Yield	mp	^{1}H - Nmr (TFA-d - δ /TMS)[a]
(5a)	4	33 %	194°C	8.7 (d,J = 8Hz,2H); 8.5 (dd,J =8.5 and 1.5 Hz, 2H); 8.4 to 7.7 (m,10H); 4.7 (s,6H); 2.9 (m,4H); 2.1 (m,4H)
(5b)	5	23%	212°C	8.8 (d,J = 8.1 Hz, 2H); 8.6 (dd, J = 7.6 and 1.7 Hz, 2H); 8.5 to 7.8 (m,10H); 4.6 (s,6H); 2.9 (m,4H); 1.9 (m,6H)
(5c)	6	28%	236°C	8.8 (d,J = 8 Hz, 2H); 8.6 (dd, J = 7.5 and 1.5 Hz, 2H); 8.5 to 7.8 (m,10H); 4.6 (s,6H); 2.9 (m,4H); 1.8 (m,8H)

a : Recorded with a Varian AM 60 spectrometer.

Table 2. ^{13}C Chemical shifts [a](ppm)

Compound	Solvent	C-1	C-2	C-3	C-4	C-5
(5a)	TFA*	121.22	150.06	135.49	119.02	118.41
(5b)	TFA	121.20	150.10	135.63	119.24	118.31
(5c)	TFA	121.30	150.19	135.58	119.13	118.35

C-6	C-7	C-8	C-9	C-4a	C-5a	C-8a	C-9a
141.31	127.12	128.90	171.47	143.20	145.28	118.78	b
141.33	127.01	128.90	171.28	143.23	145.25	b	b
141.34	127.02	128.99	171.20	143.19	145.29	b	b

5a : CH_2 (α), 35.72 ; CH_2 (β), 25.83 ; CH_3, 37.94 ; C = O, 177.61

5b : CH_2 (α), 37.71 ; CH_2 (β), 35.88 ; CH_2 (γ), 26.05 ; CH_3, 37.93 ; C = O, 178.00

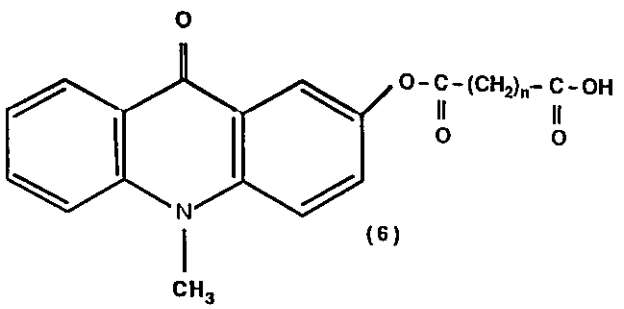
5c : CH_2 (α), 36.19 ; CH_2 (β), 30.43 ; CH_2 (γ), 26.35 ; CH_3, 38.00 ; C = O, 178.53

*: Lock, internal from CD_3COCD_3 placed in a capillary tube for trifluoroacetic acid solution.

a : Recorded with a Brucker AM 200 spectrometer.

b : Unobserved signal.

However, the acridinone monoesters (6) were isolated with a better yield when the same molar concentration of reagents as well as when a large excess of diacyl dihalide were used. These compounds are characterized in Tables 3 and 4.



(6)

Table 3

Compound	n	Yield	Mp	^{1}H - NMR (TFA-d - δ/TMS)
(6a)	4	40%	135°C	8.8 to 7.8 (m,7H) ; 4.6 (s,3H) ; 2.7 (m,4H) ; 2.0 (m,4H)
(6b)	6	39%	129°C	9.0 to 7.8 (m,7H) ; 4.6 (s,3H) ; 2.7 (m,4H) ; 1.7 (m,8H)

Table 4. ^{13}C Chemical shifts(ppm)

Compound	n	Solvent	C-1	C-2	C-3	C-4	C-5
(6a)	4	DMSO-d_6	121.17	140.02	128.08	117.64	117.80
(6b)	6	DMSO-d_6	121.17	140.06	128.10	117.63	117.85

C-6	C-7	C-8	C-9	C-4a	C-5a	C-8a	C-9a
133.99	121.17	126.38	175.99	142.17	144.59	121.90	121.90
134.00	121.20	126.45	176.02	142.23	144.59	121.98	121.98

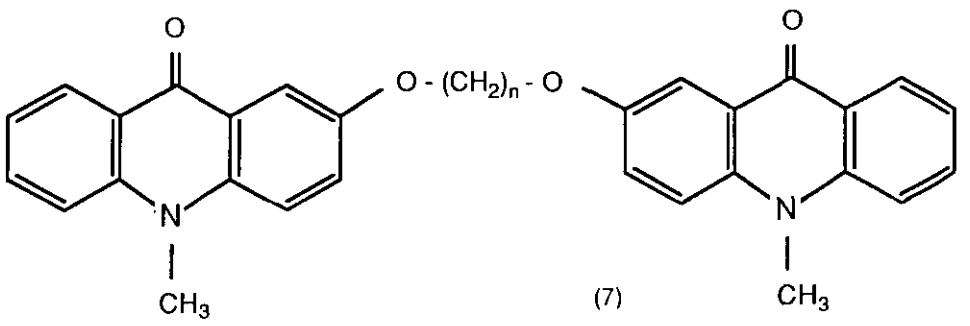
6a : CH_2 (α), 33.17 ; CH_2 (β), 23.83 ; CH_2 (γ), 23.83 ; CH_2 (δ), 33.27 ; CH_3, 33.83 ; C = O (1'), 171.74 ; C = O (6'), 174.08

6b : CH_2 (α), 33.47 ; CH_2 (β), 24.17* ; CH_2 (γ), 28.18 ; CH_2 (δ), 28.18 ; CH_2 (ε), 24.34* ; CH_2 (φ), 33.66 ; CH_3, 33.85 ; C = O (1'), 171.89 ; C = O (8'), 174.28

* These assignments may be inverted.

Structure of the latter was unambiguously demonstrated by ^{13}C nmr. Indeed, molecular asymmetry implies different carbonyl groups. Consequently, there are three different chemical shifts for these CO groups. In addition, the signals of the methylene groups of the bridge can be accurately identified by the DEPT technique.

On the other hand, alkylation of (3) under phase transfer catalysis conditions led to the bisacridine diethers (7). Data about these compounds are collected in Tables 5 and 6.



(7)

Table 5. Compounds (7)

Compound	n	Yield	Mp	^{1}H - NMR (TFAA-d - δ/TMS)
(7a)	4	86%	>260°C	8.9 (d,J = 8 Hz, 2H) ; 8.8 (s,2H) ; 7.8 to 8.5 (m, 10H) ;4.6 (s,6H) ; 4.5 (m,4H) ; 2.3 (m,4H)
(7b)	5	92%	>260°C	8.8 (d,J = 8.1 Hz, 2H) ; 8.7 (s,2H) ; 7.8 to 8.6 (m,10H) ; 4.6 (s,6H) ; 4.5 (m,4H) ; 2.1 (m,6H)
(7c)	6	95%	>260°C	8.8 (d,J = 8.1 Hz, 2H) ; 8.6 (s, 2H) ; 7.7 to 8.4 (m,10H); 4.6 (s,6H) ; 4.3 (m,4H) ; 1.9 (m,8H)
(7d)	8	90%	>260°C	8.8 (d,J = 8 Hz, 2H) ; 8.7 (s,2H) ; 7.8 to 8.5 (m,10H) ; 4.6 (s,6H) ; 4.4 (m,4H) ; 2.1 (m,4H) ; 1.6 (m,8H)
(7e)	$(CH_2)_2$-O-$(CH_2)_2$	45%	>260°C	8.9 to 7.7 (m,14H) ; 4.7 to 4.3 (m,14H)

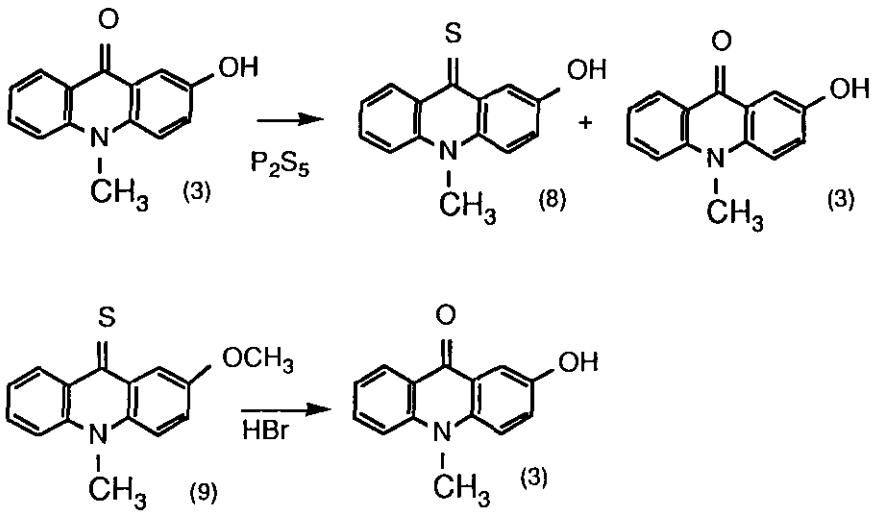
Table 6. ^{13}C Chemical shifts(ppm)

Compound	Solvent	C-1	C-2	C-3	C-4	C-5
(7a)	TFA	104.29	159.16	134.12	120.57	118.66
(7b)	TFA	104.33	159.52	134.48	120.63	118.80
(7c)	TFA	104.31	159.54	134.38	120.53	118.73
(7d)	TFA	104.38	159.49	134.36	120.50	118.73
(7e)	TFA	104.61	158.69	133.95	121.06	118.87

C-6	C-7	C-8	C-9	C-4a	C-5a	C-8a	C-9a
139.54	126.27	128.10	168.64	140.95	143.52	117.83	119.38
139.79	126.30	128.39	168.78	141.16	143.72	a	a
139.75	126.28	128.34	168.65	141.14	143.71	117.93	a
139.69	126.24	128.30	168.85	141.07	143.64	117.91	a
140.08	126.49	128.56	169.05	141.42	143.99	118.11	119.42

Compound	
(7a)	CH_2 (α), 70.80 ; CH_2 (β), 27.15 ; CH_3 : 37.57
(7b)	CH_2 (α), 71.41 ; CH_2 (β), 30.35 ; CH_2 (γ), 24.31 ; CH_3 : 37.65
(7c)	CH_2 (α), 71.57 ; CH_2 (β), 31.70 ; CH_2 (γ), 27.38 ; CH_3 : 37.62
(7d)	CH_2 (α), 71.81 ; CH_2 (β), 30.84 ; CH_2 (γ), 27.49 ; CH_2 (δ), 30.51 ; CH_3 : 37.58
(7e)	CH_2 (α), 72.24 ; CH_2 (β), 69.77 ; CH_3 : 37.78
a	Unobserved signals

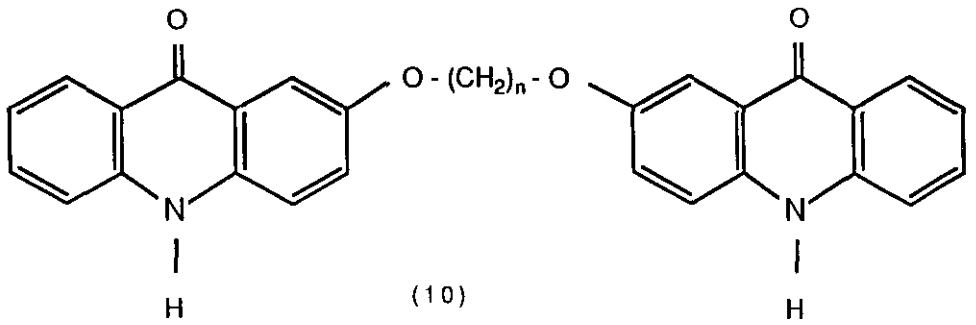
We were not able to investigate reactivity of the 10-methyl-2-hydroxy-9(10H)-thioacridinone (8) because thiation of (3) could not be achieved by the Lawesson reagent[10,11]. While a mixture of acridinone and thioacridinone was obtained when P_4S_{10} was used [12,13]. Added to this, 10-methyl-2-hydroxy-9(10H)-acridinone (3) was only obtained by demethylating 10-methyl-2-methoxy-9(10H)-thioacridinone (9)[14] with hydrobromic acid.



Acylation of 1 in pyridine at various temperatures as well as trans-esterification of this compound did never succeed, whilst thallous ethoxide led to a close mixture of isomers. This is clearly shown by the presence of several peaks for the same carbons in the ^{13}C nmr spectrum.

Alkylation of (1) with various dialkyl halides under phase transfer catalysis conditions for 48 hours, led to a mixture of isomers from which the 2,2'-bridged bis-acridine (10) was isolated by washing the crude product with hot ethanol. The branching of the bridge in positions 2 and 2' is shown by ^{13}C nmr. Indeed, there is a signal for the C(9) at 169 ppm. Hence, this carbon is included in a carbonyl group.

Moreover, the chemical shift of the two far methylene groups of the chain (70-72 ppm) infers a O-substitution instead of a N-substitution. Data about compounds (10) are gathered in Tables 7 and 8.



(10)

Table 7. Compounds 10

Compound	n	Yield	mp	^{1}H -Nmr (TFAd - δ/TMS)
(10a)	4	64%	>260°C	8.8 (d,J = 8 Hz, 2H) ; 8.7 (s,2H) ; 7.6 to 8.6 (m,10H) ; 4.5 (m,4H) ; 2.4 (m,4H)
(10b)	5	84%	>260°C	8.8 (d,J = 8.1 Hz, 2H) ; 8.6 (s,2H) ; 7.7 to 8.5 (m,10H) ; 4.4 (m,4H) ; 2.1 (m,6H)
(10c)	$(CH_2)_2$-O-$(CH_2)_2$	41%	>260°C	8.8 (d,J = 8.1 Hz, 2H) ; 8.6 (s,2H); 7.7 to 8.5 (m,10H); 4.6 (m,8H)
(10d)	$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$	28%	172°C	8.8 (d,J = 8 Hz, 2H) ; 8.7 (s,2H) ; 7.6 to 8.5 (m,10H) ; 4.3 (m,12H)

Table 8. ^{13}C Chemical Shifts (ppm)

Compound	Solvent	C-1	C-2	C-3	C-4	C-5
(10a)	TFA	103.10	159.68	134.03	122.30	120.58
(10b)	TFA	102.05	159.75	133.14	121.29	120.59
(10c)	TFA	103.46	159.13	133.72	122.73	120.72
(10d)	TFA	103.15	159.05	133.69	122.68	120.66

C-6	C-7	C-8	C-9	C-4a	C-5a	C-8a	C-9a
138.79	125.04	128.63	168.92	139.34	141.80	117.02	118.55
138.78	124.10	128.53	168.88	138.33	141.77	116.01	118.54
139.62	125.15	128.92	169.28	139.62	142.13	117.26	118.46
139.08	125.18	128.83	169.14	139.51	141.98	117.10	118.31

Compound	
(10a)	CH_2 (α), 70.88 ; CH_2 (β), 27.23
(10b)	CH_2 (α), 70.28 ; CH_2 (β), 29.18 ; CH_2 (γ), 23.17
(10c)	CH_2 (α), 72.25 ; CH_2 (β), 69.81
(10d)	CH_2 (α), 72.42 ; CH_2 (β), 69.74 ; CH_2 (γ), 71.18

Acylation of (2) [15,16] in pyridine did never succeed whilst alkylation of the latter led to the 9,9'-bridged bis-acridine derivatives (11).
As previously, structure is portrayed by the ^{13}C nmr spectra. Indeed, the signal of the C(9) is shifted from 194-195 ppm (thione) to 135.5 ppm (thioether).
Moreover, chemical shifts of the two far methylene groups of the chain (about 36 ppm) are just in agreement with the S-substitution.

Data about compounds (11) are listed in Tables 9 and 10.

As depicted in figure 3, syntheses of compounds (11) can be performed according to two possible pathways. In each case, yields are quite similar. Data about compounds (13) are collected in Tables 11 and 12.
Finally, the bi-bridged compounds (14) could be prepared by acylation of alkyl derivatives (11) in pyridine for 6 hours. The bi-bridged bisacridines prepared are listed in Tables 13 and 14.

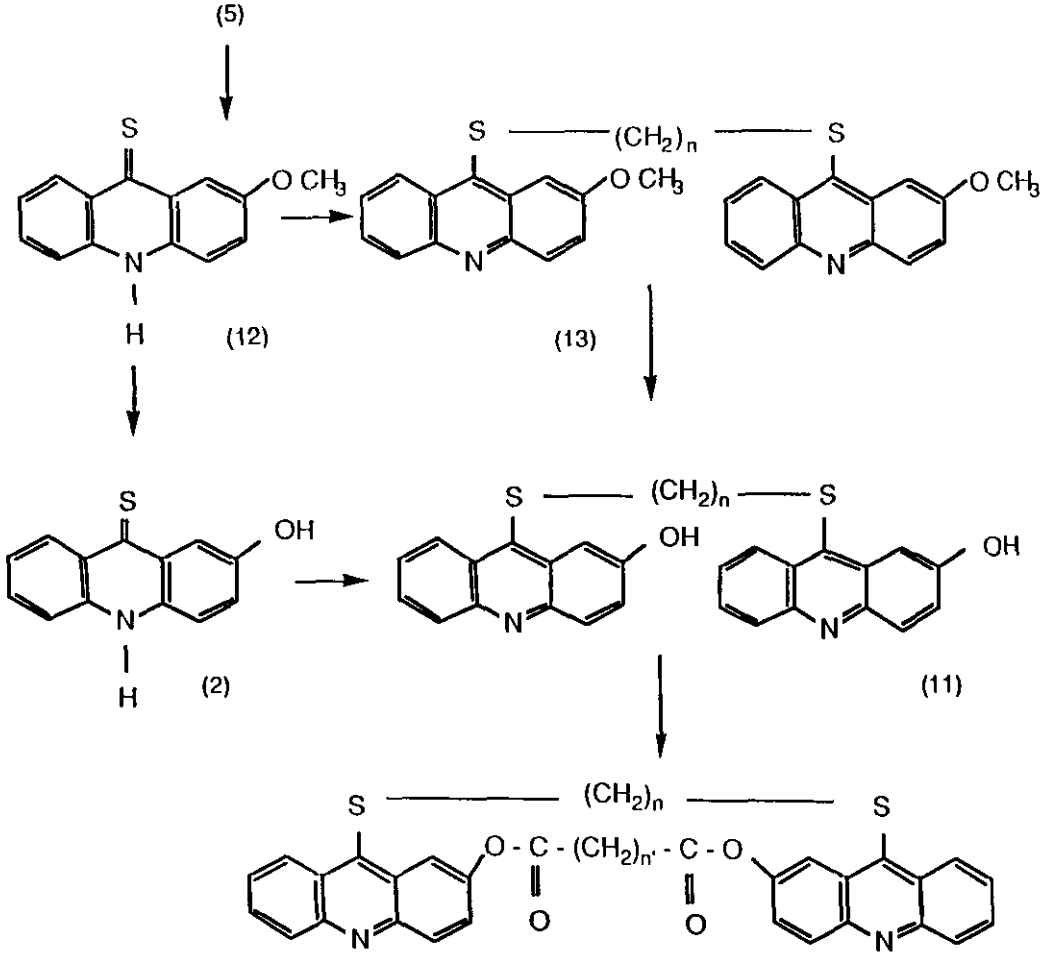


Fig.3

Table 9. Compounds (11)

Compound	n	Yield		mp	^{1}H - Nmr (TFA-d - δ/TMS) δ[a]
		b	c		
(11a)	5	66%		122 °C	8.6 to 7.4 (m,14H) ; 2.8 (m,4H) ; 1.4 (m,6H)
(11b)	6	69%	51%	135°C	9.1 to 7.8 (m,14H) ; 3.3 (m,4H) ; 1.6 (m,8H)
(11c)	7	62%		114°C	9.1 to 7.9 (m,14H) ; 3.3 (m,4H) ; 1.5 (m,10H)
(11d)	8	64%	49%	154°C	9.0 to 7.8 (m,14H) ; 3.3 (m,4H) ; 1.4 (m,12H)
(11e)	9		46%	138°C	9.1 to 7.8 (m,14H) ; 3.3 (m,4H) ; 1.4 (m,14H)

a (11a) Solvent = DMSO-d_6

b from demethylation of compounds (13)

c by linkage of 2-hydroxy-9(10H)-thioacridinone

Table 10. ^{13}C Chemical shifts (ppm)

Compound	Solvent	C-1	C-2	C-3	C-4	C-5
(11a)	TFA	110.83	158.07	133.59	123.78	121.74
(11b)	TFA	110.63	157.90	133.39	123.57	121.54
(11c)	DMSO-d_6	105.06	156.11	128.50	125.82	125.32
(11d)	TFA	111.10	157.93	133.53	123.72	121.66
(11e)	DMSO-d_6	105.14	156.15	128.52	125.38	125.87

C-6	C-7	C-8	C-9	C-4a	C-5a	C-8a	C-9a
139.27	129.77	130.91	a	136.49	a	a	a
138.91	129.61	130.68	a	136.29	138.99	130.88	132.49
131.82	126.71	130.00	137.45	144.77	146.20	128.63	130.14
139.22	129.98	130.84	a	136.54	a	131.22	a
131.79	126.69	129.97	a	144.74	146.16	128.65	130.19

Compound	
(11a)	CH_2 (α), 41.15 ; CH_2 (β), 32.16 ; CH_2 (γ), 31.78
(11b)	CH_2 (α), 41.27 ; CH_2 (β), 31.90 ; CH_2 (γ), 29.48
(11c)	CH_2 (α), 36.18 ; CH_2 (β), 29.31 ; CH_2 (γ), 27.60 ; CH_2 (δ), 27.68
(11d)	CH_2 (α), 41.85 ; CH_2 (β), 32.52 ; CH_2 (γ), 27.68 ; CH_2 (δ), 30.46
(11e)	CH_2 (α), 36.23 ; CH_2 (β), 29.46 ; CH_2 (γ), 27.75 ; CH_2 (δ), 28.11 ; CH_2 (ε), 28.36

a Unobserved signals

Table 11. Compounds (13)

Compound	n	Yield	mp	^{1}H - Nmr (TFA-d - δ/TMS)
(13a)	5	70%	128°C	9.1 to 7.8 (m,14H) ; 4.2 (s,6H) ; 3.3 (m,4H) ; 1.7 (m,6H)
(13b)	6	73%	151°C	9.1 to 7.9 (m,14H) ; 4.1 (s,6H) ; 3.3 (m,4H) ; 1.5 (m,8H)
(13c)	7	69%	122°C	9.1 to 7.8 (m,14H) ; 4.1 (s,6H) ; 3.3 (m,4H) ; 1.5 (m,10H)
(13d)	8	71%	148°C	9.0 to 7.8 (m,14H) ; 4.1 (s,6H) ; 3.3 (m,4H) ; 1.5 (m,12H)

Table 12. ^{13}C Chemical shifts (ppm) for Compounds (13)

Compound	Solvent	C-1	C-2	C-3	C-4	C-5
(13a)	TFA	106.21	162.17	135.02	123.39	121.81
(13b)	TFA	106.19	162.42	134.99	123.29	121.71
(13c)	TFA	106.39	162.21	134.78	123.29	121.70
(13d)	TFA	103.42	162.31	137.15	123.30	121.71

C-6	C-7	C-8	C-9	C-4a	C-5a	C-8a	C-9a
138.85	129.71	131.02	161.50	137.20	138.98	131.16	132.95
138.84	129.83	130.95	162.03	137.15	138.88	130.95	132.93
138.88	129.79	130.82	162.03	137.04	138.87	131.11	132.88
138.82	129.93	130.90	162.07	137.15	138.90	131.20	132.99

Compound	
(13a)	CH_2 (α), 40.81 ; CH_2 (β), 31.90 ; CH_2 (γ), 29.47 ; CH_3 : 57.52
(13b)	CH_2 (α), 41.12 ; CH_2 (β), 32.33 ; CH_2 (γ), 29.85 ; CH_3 : 57.52
(13c)	CH_2 (α), 41.31 ; CH_2 (β), 32.18 ; CH_2 (γ), 30.06 ; CH_2 (δ), 30.06 ; CH_3 : 57.51
(13d)	CH_2 (α), 41.45 ; CH_2 (β), 32.32 ; CH_2 (γ), 30.23 ; CH_2 (δ), 30.57 ; CH_3 : 57.52

Table 13. Compounds (14)

Compound	n	n'	Yield	Mp	^1H - nmr (TFA-d - d/TMS)a
(14a)	6	4	30%	126°C	9.0 to 7.8 (m,14H) ; 3.4 (m,4H) ; 3.0 (m,4H) ; 2.1 (m,4H) ; 1.6 (m,8H)
(14b)	8	6	26%	115°C	9.1 to 7,9 (m,14H) ; 3.4 (m,4H) ; 2.8 (m,4H) ; 1.5 (m,20H)

Table 14. ^{13}C Chemical shifts (ppm)

Compound	Solvent	C-1	C-2	C-3	C-4	C-5
(14a)	TFA	121.94	152.07	135.60	120.97	119.20
(14b)	TFA	122.01	152.10	135.66	120.99	119.22

C-6	C-7	C-8	C-9	C-4a	C-5a	C-8a	C-9a
140.82	130.15	131.36	b	138.50	139.64	129.37	133.60
141.03	130.18	131.40	b	138.52	139.53	129.72	133.66

Compound	
(16a)	CH_2 (α), 42.47 ; CH_2 (β), 32.14 ; CH_2 (γ), 29.57 CH_2 (α'), 35.62 ; CH_2 (β'), 25.85 ; C = O, b
(16b)	CH_2 (α), 42.82 ; CH_2 (β), 32.91 ; CH_2 (γ), 30.60 ; CH_2 (δ), 30.20 CH_2 (α'), 36.68 ; CH_2 (β'), 30.08 ; CH_2 (γ'), 26.30 ; C = O, b

b : unobserved signals

EXPERIMENTAL

2-Hydroxy-9-thioacridine (2).

The following mixture of 10 mmol of 2-methoxy-9(10H)-thioacridinone, 10 ml of acetic anhydride, and 10 ml of hydrobromic acid (d = 1.39) was refluxed with stirring for 48 h. The solution was poured out in cold water. The brown precipitate was filtered, washed with cold water before to be recrystallized from methanol. Yield : 85 % ; mp > 260°C ;

^1H nmr (DMSO-d_6): δ 9.0 [m, 1H] ; 8.4 [m,1H]; 7.6 [m,1H] ; 7.3 [m,4H].

^{13}C nmr (DMSO-d_6) : δ C-1 : 111.5 ; C-2 : 153.7 ; C-3 : 125.9 ; C-4 : 120.3 ; C-5 : 118.4 ; C-6 : 132.8 ; C-7 : 122.5 ; C-8 : 129.8 ; C-9 : 194.5 ; C-4a : 130.0 ; C-5a : 135.4 ; C-8a : 129.5 ; C-9a : 128.5.

Acylation : general procedure.

The 2-hydroxy-10-methyl-9(10H)-acridinone (3) (7.1 mmol) was dissolved in 300 ml of absolute ethanol. Thallous ethoxide (7.1 mmol) was added under stirring at ambient temperature. The mixture was stirred for 1 h. A red precipitate was filtered and washed with hot ethanol. About 4 mmol of the thallous salt of (3) was so obtained. The latter was then dissolved in 80 ml of anhydrous pyridine freshly distilled with sodium hydroxide. Acyl dichloride (2 mmol for (5) ; 5 mmol for (6)) was added in small amounts. Stirring was continued for 4 h. The precipitate obtained was filtered, dried, and recrystallized from ethanol.

Alkylation : general procedure.

The following mixture of heterocyclic compound (10 mmol), alkyl bromide (6 mmol), 100 ml of toluene, and 50 ml of 50 % aqueous potassium hydroxide was refluxed with stirring for 4 h. The toluene phase was separated, dried with magnesium sulfate and evaporated in vacuo. The residual product was recrystallized from ethanol.

Bi-bridged bisacridines (14).

Thallous ethoxide (3 mmol) was added to a solution of 9,9'-[bis-(2-hydroxy)acridinyl-1",6"]-dithioalkane in absolute ethanol (200 ml). Acyl chloride (1 mmol) in anhydrous pyridine (250 ml) was added in small amounts to the thallous salt (1 mmol). Stirring was continued for 6 h. The precipitate obtained is filtered, dried and recrystallized in ethanol.

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