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New α,ω-Diamido and α,ω-Diamino Mono- and Bi-Bridged Acridine Dimers

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Abstract. A novel set of dimers derived from 9-amino acridine was prepared and characterized by ^1H and ^{13}C NMR. These derivatives are bridged at several different positions of the heterocyclic moieties, by the way of α,ω-diamido or α,ω-diamino side-chains. Additionally the preparation of some bi-bridged compounds was achieved.

Keywords. 9-Amino-acridine; Mono-bridged dimers; Bi-bridged dimers.

Neue α,ω-Diamido- und α,ω-Diamino-Mono- und Bi-überbrückte Acridin-Dimere

Zusammenfassung. Es wurde eine neue Reihe von Dimeren des 9-Aminoacridins hergestellt und mittels ^1H und ^{13}C-NMR charakterisiert. Diese Derivate sind an verschiedenen Positionen des Heterocyclus mit α,ω-Diamido- oder α,ω-Diamino–Seitenketten überbrückt. Zusätzlich wurden auch einige zweifachüberbrückte Verbindungen hergestellt.

Introduction

The amino acridines are important from the biological point of view and have give rise to numerous studies on the subject of biacridinic compounds [1–6]. Apart from a few of them [7] these biacridines, however, are exclusively bridged by position 9.

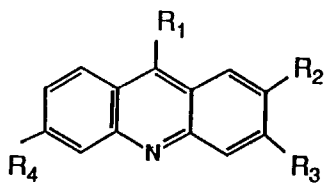
The biological importance of this position led us to synthesize some biacridines bridged in positions 2 or 3, and fulfilling an amino function, non-substituted in 9, so as to be able to compare them with some biacridines bridged in positions 9,9′ and including amino functions in 2 or 3.

In order to do this we concerned ourselves with acridines substituted by two amino functions, one in position 9 and the other in position 2 or 3. Moreover, these compounds show an interesting problem of reactivity [8], because, owing to the ambident character of the acridinic cycle, they possess three atoms of nitrogen capable for substitution.

Results and Discussion

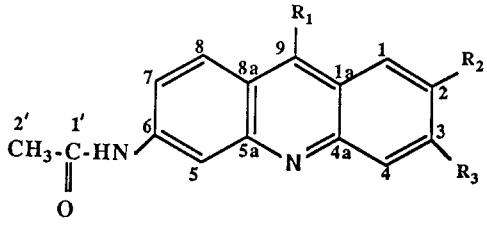
We have studied 2-ethoxy-6,9-diamino-acridine (**1**) (commercial), as well as 3,9-diamino-acridine (**2**) and 2,9-diamino-acridine (**3**) which we have prepared.

Table 1. Chemical and ^{1}H NMR data of compounds **5–8** (**5**, **7**, **8** in *TFAA-d*; **6** in *DMSO-d_6*)



Compound	R_1	R_2	R_3	R_4	M.p. (°C)	Yield (%)	M.w. or Ref.	^{1}H NMR
5	H	H	$NHCOCH_3$	NH_2	>260	83	[10, 13]	9.1–6.8 (m, 7H), 2.3–2 (s, 3H)
6	H	H	$NHCOCH_3$	$NHCOCH_3$	>260	43	[10]	9.7–7.7 (m, 7H), 2.8–2.4 (s, 6H)
7	NH_2	OC_2H_5	H	$NHCOCH_3$	>260	84	295	9.3–8 (m, 6H), 5.2–4.7 (qu, 2H), 3 (s, 3H), 2.5–2.1 (t, 3H)
8	$NHCOCH_3$	OC_2H_5	H	$NHCOCH_3$	>260	41	337	8.7–7.3 (m, 6H), 4.6–4.1 (qu, 2H), 2.5 (s, 3H), 2.2 (s, 3H), 1.9–1.3 (t, 3H)

Table 2. ^{13}CNMR Chemical shifts (in ppm) of compounds **5–7** in *DMSO-d_6*



Compound	**5**	**6**	**7**
R_1 =	H	H	NH_2
R_2 =	H	H	OCH_2–CH_3
R_3 =	NH_2	NH–$COCH_3$	H
C_1	128.91[a]	135.29	104.93
C_2	120.05[a]	123.87	157.92
C_3	140.71[b]	148.79	126.14
	140.30		
C_4	113.97[b]	107.39	121.34
	113.59		
C_5	102.80		110.12
C_6	150.93		145.11
C_7	117.92		122.50
C_8	129.37		131.51
C_9	134.78	149.78	158.58
C_{1a}	122.38	125.68	114.73
C_{4a}	149.77[b]	145.59	137.63
	149.45		
C_{5a}	151.29		142.08
C_{8a}	120.78		110.58
$C_{1'}$	169.05[b]	177.59	177.64
	168.84		
$C_{2'}$	24.21	24.87	24.33
$C_{1''}$			67.88
$C_{2''}$			14.87

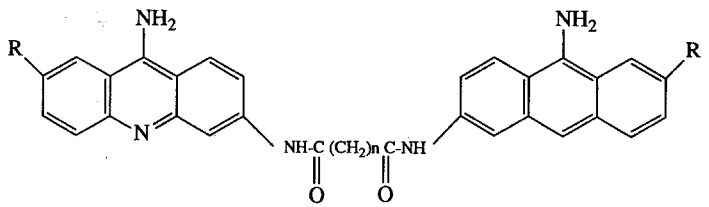
[a] May be inverted

[b] There are two signals because of *Z*/*E* isomers

Preliminary work had been performed to obtain some model molecules, indispensable to the spectrographic attribution for the interpretation of reactions.

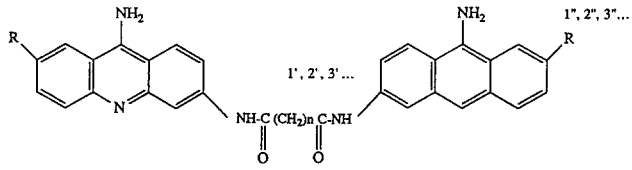
In addition to a certain number of compounds already prepared in our laboratory, we have acylated 3,6-diamino-acridine (**4**) to obtain 3-acetamido-6-amino-acridine (**5**) and 3,6-diacetamido-acridine (**6**). The monoacetylation was achieved by acetic anhydride with or without acetic acid [9, 10]. The diacetylation could not be

Table 3. Chemical and ^{1}H NMR data (in *TFAA-d*) of compounds **9**, **12**, and **19**



Compound	*R*	M.w.	M.p. (°C)	Yield (%)	^{1}H NMR
9a	OC_2H_5	602	>260	40	8.8–7.5 (m, 12H), 4.6–4 (qu, 4H), 3–2.5 (t, 4H), 2.5–2.1 (t, 2H), 1.4–1 (m, 6H)
9b	OC_2H_5	616	>260	48	8.7–7.4 (m, 12H), 4.6–4 (qu, 4H), 2.9–2.3 (t, 4H), 2.2–1.3 (m, 10H)
9c	OC_2H_5	644	>260	30	8.8–7.5 (m, 12H), 4.7–4.1 (qu, 4H), 3–2.3 (t, 4H), 2.2–1.2 (m, 14H)
9d	OC_2H_5	672	>260	40	9.3–7.5 (m, 12H), 4.7–4.1 (qu, 4H), 2.9–2.4 (m, 4H), 2.2–1.2 (m, 18H)
12a	H	556	>260	33	9–7.5 (m, 14H), 2.9–2.3 (t, 4H), 2.1–1.2 (m, 8H)
12b	H	570	>260	40	9–7.3 (m, 14H), 3–2.3 (t, 4H), 2.2–1.2 (m, 10H)
12c	H	580	>260	51	9.3–7.2 (m, 14H), 3–2.3 (t, 4H), 2.3–1.2 (m, 12H)
19a	H	528	>260	73	9.3–7.3 (m, 14H), 3.1–2.4 (m, 4H), 2.4–1.8 (m, 4H)
19b	H	556	>260	61	9.2–7.3 (m, 14H), 3–2.3 (m, 4H), 2.3–1.3 (m, 8H)
19c	H	570	>260	65	9.1–7.4 (m, 14H), 3–2.3 (m, 4H), 2.3–1.3 (m, 10H)

Table 4. ^{13}C-NMR Chemical shifts (in ppm) of compounds **9**, **12**, and **19** in *TFAA-d*



Compound	**9a**	**9c**	**9d**	**12a**	**12b**	**12c**	**19a**	**19b**	**19c**
$n=$	3	6	8	6	7	8	4	6	7
C_1	131.41	131.50	131.52	128.73	128.78	128.61	116.16	116.30	116.00
C_2	122.51	122.58	122.62	121.44	121.48	121.48	135.68	135.55	135.67
C_3	145.15	145.20	145.24	137.93	138.17	138.06	133.11	133.09	132.81
C_4	110.08	110.80	110.83	116.52	116.46	116.37	122.10	122.12	121.90
C_5	121.01	121.11	121.21	121.03	120.98	120.94	120.84	120.84	120.87
C_6	126.25	126.24	126.26	139.94	139.80	139.96	138.77	138.78	138.58
C_7	157.86	158.00	158.02	124.98	124.97	125.05	124.43	124.47	124.28
C_8	104.97	105.10	105.21	128.33	128.41	128.47	127.75	127.79	127.53
C_9	158.48	158.47	158.02	160.36	160.51	160.55	159.83	159.77	159.78
C_{1a}	110.53	110.57	110.63	107.95	108.17	108.11	113.56	113.52	113.57
C_{4a}	142.01	142.12	142.20	142.14	142.13	142.24	139.37	139.30	139.30
C_{5a}	137.60	137.70	137.75	141.76	141.78	141.73	141.35	141.30	141.30
C_{8a}	114.88	114.87	114.80	113.97	113.98	114.05	113.61	113.52	113.47
$C_{1'}$	182.58	182.41	181.00	181.09	181.05	180.98	178.69	179.76	179.77
$C_{2'}$	38.12	39.22	39.42	39.24	39.26	39.23	38.18	38.59	38.53
$C_{3'}$	22.36	30.71	30.72	30.14	30.16	30.19	26.59	30.30	30.20
$C_{4'}$		27.59	27.77	27.53	27.55	27.52		27.21	27.26
$C_{5'}$			30.55		30.28	30.38			30.40
$C_{1''}$	67.96	67.87	67.83						
$C_{2''}$	14.84	14.85	14.87						

successfully carried out in the presence of anhydrous sodium acetate as catalyst; the method recommended by Wilkinson [10] only leads to a monoacetylated product. Identical results were obtained using the same technique for 2-ethoxy-6,9-diamino-acridine (**1**). The compounds mentioned are described in Tables 1 and 2.

The acylation of **1** by an acid dichloride was performed in the presence of pyridine. This method [11] was chosen in preference to forming an intermediary amide by means of the action of a thallous salt [12], because of the satisfactory solubility of **1** in pyridine compared with dioxane or tetrahydrofuran. Manipulation is best done at ambient temperature (24 °C) avoiding differences in temperature during addition, rather than at 0 °C, even though the reaction is exothermic.

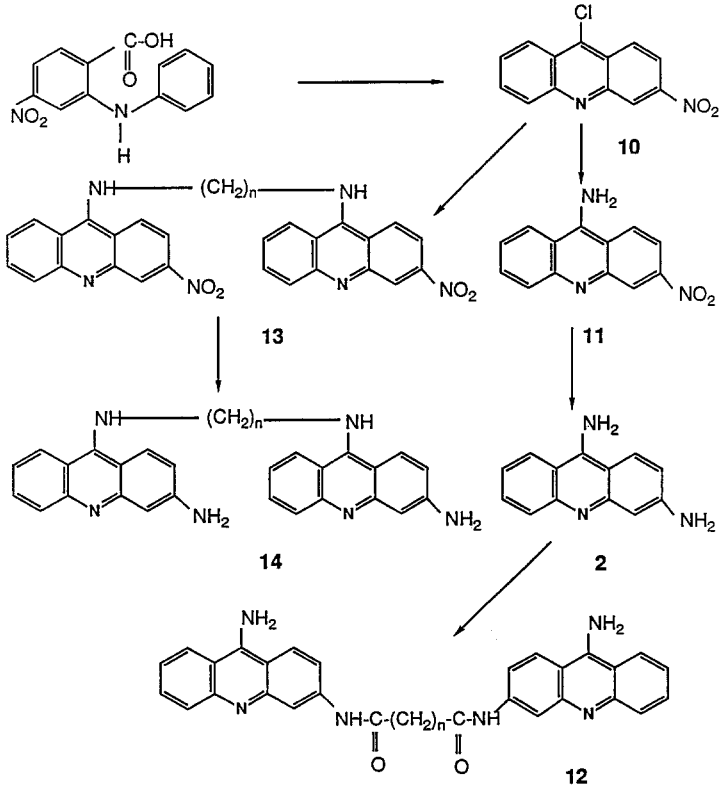
Four acylations were performed with four diacyl dichlorides comprising a variable number of CH_2 (from three to eight). Acylated biacridines **9** were obtained in position 6,6'. The characteristics of the compounds are presented in Tables 3 and 4.

The structures of all compounds were established by their physical properties as well as by their ^{1}H and ^{13}C NMR spectra.

One must first establish that they are indeed monobridged compounds. To demonstrate that substitution was occurring on the amino function in position 3, comparisons had to be made of the ^{13}C chemical shifts: (i) of carbon 3 substituted by an acetamido function in the 3-acetamido-6-amino-acridine; (ii) of carbon 9 of the 9-amino-acridine; (iii) of carbons 3 and 6 of the 3,6-diamino-acridine; and (iv) of carbons 6 and 9 of the monoacetylated product of the 2-ethoxy-6,9-diamino-acridine. Substitution took place in the first instance on the carbon 6 of the 2-ethoxy-6,9-diamino-acridine: the chemical shift of carbon 9 is at 159.1 ppm when it is substituted by an amino compound, and 151.9 ppm for an acylated substituent; the acetylated compounds in position 2 or 3 have an unchanged chemical shift of carbon 9 of 159 ppm.

In order to prove that acylation has really taken place, the chemical shift of CH_2 situated in α to CO may be observed; this shift is ca. 38 ppm, while its shift is 35 ppm when the free-acid form is present.

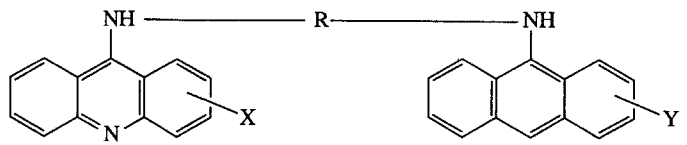
Our next interest concerned 3,9-diamino-acridine (**2**), prepared from 9-chloro-3-nitro acridine (**10**) via 9-amino-3-nitro-acridine (**11**) (Scheme 1).



Scheme 1

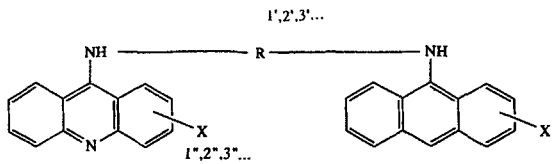
Two slightly different methods were used to synthesize this compound: see Refs [9] and [13]. For the last step of this synthesis, the reduction of the nitro function, a third technique, differing from those mentioned above, was employed, which is

Table 5. Chemical and ^{1}H NMR data (in *TFAA-d*) of compounds **13**, **14**, **20**, and **21**



Compound	*X*	*R*	M.w.	M.p. (°C)	Yield (%)	^{1}H NMR
13a	3-NO_2	$(CH_2)_6$	560	212	51	9.2–7 (m, 14H), 4.5–4.1 (t, 4H), 2.5–1.3 (m, 8H)
13b	3-NO_2	$(CH_2)_8$	588	191	80	9.7–6 (m, 14H), 4.6–4.1 (t, 4H), 2.5–1.3 (m, 12H)
13c	3-NO_2	$(CH_2)_{12}$	644	154	49	8.9–7.6 (m, 14H), 4.5–4.1 (t, 4H), 2.5–1.2 (m, 20H)
13d	3-NO_2	$(CH_2)_2NH(CH_2)_2$	547	182	42	9.2–7.3 (m, 14H), 5.2–4.1 (t, 4H), 4.4–3.7 (t, 4H)
14a	3-NH_2	$(CH_2)_6$	500	>260	64	9–7.4 (m, 14H), 4.5–4 (t, 4H), 2.5–1.4 (m, 8H)
14b	3-NH_2	$(CH_2)_8$	528	>260	72	8.9–7.5 (m, 14H), 4.5–4 (t, 4H), 2.3–1.3 (m, 12H)
14c	3-NH_2	$(CH_2)_{12}$	584	>260	65	9–7.4 (m, 14H), 4.6–3.8 (t, 4H), 2.5–1 (m, 18H)
14d	3-NH_2	$(CH_2)_2NH(CH_2)_2$	487	>260	62	9.1–7.3 (m, 14H), 5.1–4.3 (t, 4H), 4.2–3.5 (t, 4H)
20a	2-$NHCO_2C_2H_5$	$(CH_2)_6$	644	185	46	9–7.6 (m, 14H), 4.6–4 (m, 8H), 2.4–1.2 (m, 14H)
20b	2-$NHCO_2C_2H_5$	$(CH_2)_8$	672	193	50	9.1–7.4 (m, 14H), 4.7–4.1 (m, 8H), 2.4–1.3 (m, 18H)
20c	2-$NHCO_2C_2H_5$	$(CH_2)_{12}$	728	255	79	8.9–7.5 (m, 14H), 5.4–3.5 (m, 12H), 2.4–1.1 (m, 26H)
20d	2-$NHCO_2C_2H_5$	$(CH_2)_2NH(CH_2)_2$	631	234	90	9.4–7.2 (m, 14H), 5.4–3.5 (m, 12H), 1.9–1.1 (t, 6H)
21a	2-NH_2	$(CH_2)_6$	500	212	51	9.3–7.6 (m, 14H), 4.7–4.2 (m, 4H), 2.6–1.6 (m, 8H)
21b	2-NH_2	$(CH_2)_8$	528	152	72	9.2–7.5 (m, 14H), 4.6–4.1 (m, 4H), 2.4–1.3 (m, 12H)
21c	2-NH_2	$(CH_2)_{12}$	584	119	64	9.2–7.6 (m, 14H), 4.6–4.1 (m, 4H), 2.5–1.1 (m, 20H)
21d	2-NH_2	$(CH_2)_2NH(CH_2)_2$	487	196	65	9.3–7.6 (3, 14H), 5.3–4.6 (t, 2H), 4.4–3.8 (t, 2H)

Table 6. ^{13}C-NMR Chemical shifts (in ppm) of compounds **13**, **14**, **20**, and **21** in *TFAA-d*



Compound $R=$	**13a** $(CH_2)_6$	**13b** $(CH_2)_8$	**13c** $(CH_2)_{12}$	**13d** $(CH_2)_2$ NH $(CH_2)_2$	**14a** $(CH_2)_6$	**14b** $(CH_2)_8$	**14c** $(CH_2)_{12}$	**20a** $(CH_2)_6$	**20b** $(CH_2)_8$	**20c** $(CH_2)_{12}$	**20d** $(CH_2)_2$ NH $(CH_2)_2$	**21a** $(CH_2)_6$	**21b** $(CH_2)_8$	**21c** $(CH_2)_{12}$	**21d** $(CH_2)_2$ NH $(CH_2)_2$
C_1	127.86	128.71	128.01	128.44[a]	130.03	130.18	130.20	114.36	114.60	114.27	113.96	125.96	125.89	125.75	126.04
C_2	120.89	121.61	121.14	121.17	120.81	120.97	121.02	136.16	136.90	135.85	136.82	139.92	139.86	138.80	139.45
C_3	154.36	154.08	153.75	153.54	137.46	137.41	137.50	131.58	131.90	131.24	132.00	131.98	131.68	131.58	132.08
C_4	116.92	117.17	115.74	116.96	115.86	116.72	116.44	121.87	121.24	121.60	122.37	120.76	120.80	120.97	120.91
C_5	120.70	120.27	119.18	119.89	120.81	120.80	120.79	120.67	120.71	120.44	121.14	120.95	120.80	120.69	121.20
C_6	139.26	140.12	138.32	139.81	139.20	139.28	139.18	137.78	138.40	137.43	138.14	138.71	138.84	139.08	139.54
C_7	126.18	126.03	125.93	126.48	126.30	126.25	126.28	126.44	126.72	126.04	126.05	123.18	123.81	123.35	123.88
C_8	129.68	129.32	129.03	128.86[a]	127.88	127.72	127.64	126.84	127.21	126.23	127.57	127.64	127.72	127.40	127.51
C_9	161.51	161.42	161.42	161.48	160.71	160.88	160.78	159.02	159.86	159.32	158.77	160.28	160.40	160.40	161.30
C_{1a}	114.75	114.86	114.91	115.08	115.86	115.88	115.90	115.19	115.96	115.22	115.22	114.76	114.77	114.48	114.52
C_{4a}	144.76	143.92	114.21	143.31	142.24	142.25	142.21	138.50	139.19	138.11	138.86	142.11	142.23	142.55	141.39
C_{5a}	141.96	142.41	141.83	141.36	139.00	138.34	138.32	141.94	142.79	141.41	141.59	143.91	143.85	144.03	144.09
C_{8a}	116.52	116.83	117.02	117.71	114.85	114.86	115.07	113.99	113.77	113.90	114.90	113.13	113.26	113.37	113.40
$C_{1'}$	52.09	53.31	53.31	50.27	52.14	52.46	52.37	51.73	52.79	51.73	51.22	51.97	52.30	52.70	50.19
$C_{2'}$	31.01	32.53	33.39	47.92	31.59	31.83	31.72	31.65	32.79	31.60	48.07	31.45	31.66	31.67	47.67
$C_{3'}$	27.99	19.14	29.16		27.99	28.31	28.27	27.98	29.16	28.11		27.91	28.16	28.14	
$C_{4'}$		31.55	31.93			30.70	31.12		31.63	30.83			30.39	30.80	
$C_{5'}$			30.78				30.80[a]			30.55				30.31	
$C_{6'}$			30.08				30.12[a]			30.55				30.31	
$C_{1''}$								159.92	160.64	160.43	160.18				
$C_{2''}$								65.76	66.52	65.48	67.72				
$C_{3''}$								14.59	15.47	14.58	14.69				

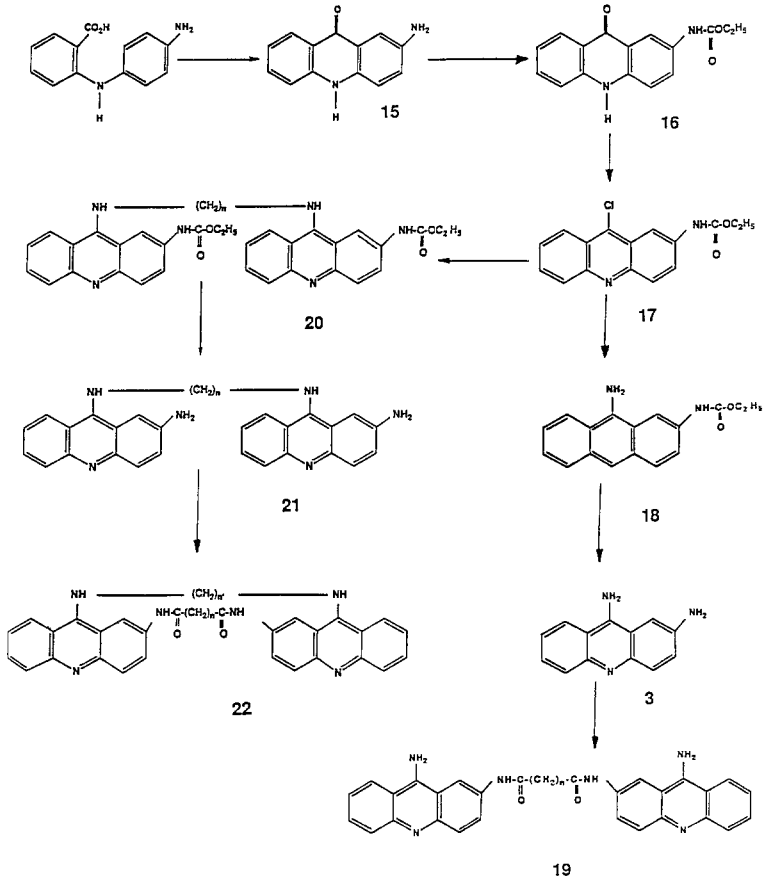
[a] May be inverted

superior to the use of ferrous sulphate mixture, calcium carbonate, or via the phenylhydrazone:

The reaction occurs in the presence of tin(II) chloride and hydrochloric acid to which 9-amino-3-nitro acridine is added in small quantities under vigorous stirring. This method represents an appreciable saving in time as well as an increase in yield, (from 10% to 50%). It should be mentioned that this technique already gave good results for the reduction of nitro acridinones in amino-acridinones [14].

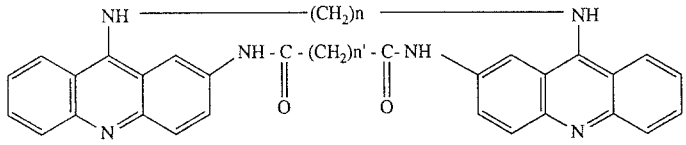
The acylation of **2** was carried out by different diacyl dichlorides in basic medium. The 10% soda solution is both base and solvent. This method is applicable both for 2-ethoxy-6,9-diamino-acridine and 3,9-diamino-acridine, since the amino functions are placed in the same positions. A substitution of amino function in position 3 is observed. This is proved by ^{13}C NMR. The carbon 9 substituted by an amido function, has a chemical shift of 159 ppm which one finds again unchanged in the compounds obtained by substitution reaction. In this case, as in the preceding ones, the chemical shifts of the cycle are not modified by the presence of the bridge.

For these molecules an inverted γ effect is noticeable at the level of the bridge: thus the carbon 3′ is observed to be more shielded than the carbon 4′. The reactivity of the chloro function in position 9 permitted the reaction of a diamine [15] and to obtain biacridines bridged in 9,9′ and having in 3 and 3′ nitro (**13**) or amino (**14**) functions. These compounds are described in Tables 5 and 6.



Scheme 2

Table 7. Chemical and ^{1}H NMR data (in *TFAA-d*) of compounds **22**



Compound	*n*	*n'*	M.w.	M.p.(°C)	Yield (%)	^{1}H NMR
22a	8	6	618	>260	31	9.3–7.4(m, 14H), 4.5–4(t, 4H), 3–2.4(t, 4H), 2.4–1.3(m, 20H)
22b	8	7	632	>260	45	9.4–7.4(m, 14H), 4.7–3.9(t, 4H), 3–2.4(t, 4H), 2.4–1.2(m, 22H)
22c	8	8	646	>260	37	9.4–7.3(m, 14H), 4.6–3.9(t, 4H), 3–2.5(t, 4H), 2.5–1.1(m, 24H)
22d	12	7	688	>260	45	9.3–7.4(m, 14H), 4.6–3.9(t, 4H), 3–2.3(t, 4H), 2.3–1.1(m, 30H)

The different molecules **12** obtained are presented together in Tables 3 and 4. 2,9-Diamino-acridine (**3**) may be prepared (Scheme 2) by a reaction sequence which, after having protected the amino function in 2, enables one to go from the 2-amino-9(10*H*)-acridinone (**15**) to the 2-urethano-9-amino-acridine (**18**) via the 2-urethano-9-chloro-acridine (**17**).

The acylation of **3** leads – for **2** – to the monobridged compound in a lateral position. Position 9 does not react. The physical constants and NMR spectra of the biacridinic compounds **19** are described in Tables 3 and 4.

The spectroscopic determination of their structure is done in the same way as for the compounds **12**. A further check verifies in a general manner that the 9-amino function does not react when there is another amino function and this no matter what the latter position may be.

The examination of the *pKa* of the different amino functions nevertheless might lead to the anticipation of a greater reactivity of the 9-amino function due to its greater basicity. Several reasons are generally presented to account for such phenomena:

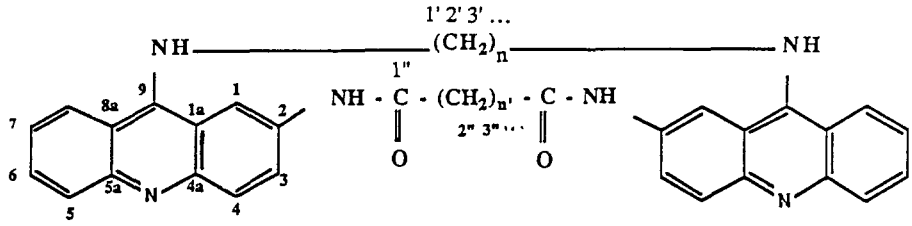
Protonation of the 9-amino might occur with difficulty, as the reaction takes place in basic medium. On the other hand, the choice becomes difficult between the other explanations put forward, namely steric effects, tautomerism, and thermodynamic equilibrium. Furthermore, and as in the case of position 2, the reactivity of chlorine in position 9 enables biacridinic compounds bridged in 9,9′ to be obtained, the amino function in position 3 protected by an urethano function (**20**) is then deprotected to give **21**. These compounds are described in Tables 5 and 6.

Finally, also bi-bridged biacridinic compounds, **22** were prepared, whose structure were determined by their ^{1}H and ^{13}C NMR spectra (Tables 7 and 8).

Experimental Part

Melting points are given uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 200 spectrometer using tetramethylsilane as internal standard (δ/ppm). Elemental analyses were

Table 8. ^{13}C-NMR Chemical shifts (in ppm) of compounds **22** in *TFAA-d*



Compound	**22a**	**22b**	**22c**	**22d**
$n =$	8	8	8	12
$n' =$	6	7	8	7
C_1	117.87	117.95	118.11	118.03
C_2	135.09	135.00	135.07	135.11
C_3	132.23	132.35	132.17	132.05
C_4	121.92	122.02	121.71	121.72
C_5	120.79	120.87	120.71	120.54
C_6	138.15	138.28	138.01	137.77
C_7	126.85	125.16	126.74	126.56
C_8	126.85	126.37	126.74	128.44
C_9	160.39	160.47	160.34	160.06
C_{1a}	114.35	114.00	114.23	114.12
C_{4a}	139.56	139.60	139.55	139.66
C_{5a}	142.07	142.06	142.00	141.95
C_{8a}	114.92	115.00	114.97	115.01
$C_{1'}$	52.17	52.19	58.18	52.03
$C_{2'}$	31.92	32.02	32.00	31.78
$C_{3'}$	27.45	28.24	27.84	27.51
$C_{4'}$	30.47	30.53	30.80	30.72
$C_{5'}$				27.81
$C_{6'}$				28.43
$C_{1''}$	180.00	180.29	180.29	180.50
$C_{2''}$	38.78	38.84	38.89	38.72
$C_{3''}$	30.95	30.53	28.99	31.01
$C_{4''}$	28.35	27.43	25.28	28.26
$C_{5''}$		30.23	30.27	30.34

performed on a Technicon CHN Autoanalyser. Analytical and spectroscopic data are given in the tables.

2-Ethoxy-6-acetamido-9-amino-acridine (7)

A mixture of 2-ethoxy-6,9-diamino-acridine lactate monohydrate (3.6 g, 10 mmol) and acetic acid (4 ml) was refluxed before acetic anhydride (1 ml) was added. The mixture was stirred for 10 min. The solution was then cooled and filtered off. The precipitate was washed with acetic acid (10 ml) and afterwards with aqueous 10% potassium hydroxide (10 ml). The compound was recrystallized from ethanol.

3,6-Diacetamido-acridine (**6**) *and 2-Ethoxy-6,9-diacetamido-acridine* (**8**)

A mixture of 3,6-diamino-acridine (1.05 g, 5 mmol), acetic anhydride (1.9 ml), and anhydrous sodium acetate (0.25 g, 3 mmol) was heated at 100 °C for 2 h with stirring. The solution was filtered off and brought to basic *pH*. Compound **6** was recrystallized from ethanol. The same process was used for **8** except that the starting material was 2-ethoxy-6,9-diamino-acridine (1.26 g, 5 mmol). Moreover, in this case, the mixture was cooled after heating, then acetone (10 ml) was added before filtration. The compound was recrystallized from ethanol.

α'',ω''-Diamidoalkyl-6,6'-bis-(2-ethoxy-9-amino-acridines) (**9**)

2-Ethoxy-6,9-diamino-acridine (1.12 g, 44 mmol) was dissolved in a small amount of anhydrous pyridine. The temperature was kept at 23 °C when acylchloride (4 mmol) was added dropwise. The mixture was allowed to cool to room temperature, then the solution was stirred for 3 days before it was filtered off. The precipitate was washed with methanol (10 ml).

α'',ω''-Diamidoalkyl-3,3'-bis-(9-amino-acridines) (**12**)

A mixture of 3,9-diamino-acridine (0.53 g, 25 mmol), aqueous 10% sodium hydroxide (2.5 ml), and acylchloride (16.8 mmol) was heated at 70–80 °C for 2 h. To the cooled solution water was added before the *pH* was brought to an acidic value. The precipitate was washed with methanol and the crude hydrochloride was then dissolved in water. Aqueous 10% sodium hydroxide was added for the precipitation of the free-base.

α'',ω''-Diaminoalkyl-9,9'-bis-(3-nitro-acridines) (**13**)

A mixture of 3-nitro-9-chloro-acridine (2 g, 77.4 mmol), phenol (8 g), and α,ω-diaminoalkane (50 mmol) was heated to 115–120 °C for 2 h with stirring. The solution was allowed to cool to room temperature before aqueous 10% sodium hydroxide was added. The precipitate was recrystallized from methanol.

α'',ω''-Diaminoalkyl-9,9'-bis-(3-amino-acridines) (**14**)

A solution of stannous chloride dihydrate (3 g) in concentrated hydrochloric acid (8 ml) was immersed in boiling water. Small amounts of **13** were added by fractions. The solution was stirred for 1 h before it was allowed to cool to room temperature. Aqueous 30% sodium hydroxide (25 ml) was then added. The precipitate obtained was dissolved in hot 20% acetic acid. The compound was finally isolated as free-base by adding aqueous 30% sodium hydroxide to the acetic solution.

α'',ω''-Diamidoalkyl-2,2'-bis-(9-amino-acridines) (**19**)

To a solution of 2,9-diamino-acridine (0.58 g, 30 mmol) in freshly distilled pyridine (150 ml) kept at room temperature, diacyldichloride (30 mmol) was added dropwise. The solution was stirred for 18 h. The precipitate obtained was filtered off and washed with acetone before it was dissolved in water. The free base was precipitated by aqueous sodium hydroxide and the compound recrystallized from methanol.

α'',ω''-Diamino 9,9'-bis-(9-urethano-acridines) (**20**)

A mixture of 9-chloro-2-urethano-acridine (2 g, 5 mmol), α',ω''-diamino-alkane (5 mmol), and *n*-pentanol (8 ml) was heated at 115–120 °C for 2 h with stirring. Ethyl ether was added after the solution was allowed to cool to room temperature. The precipitate obtained was separated and recrystallized from ethanol.

α″,ω″-Diaminoalkyl-9,9′-bis-(2-amino-acridines) (**21**)

A mixture of **20** (0.97 g, 15 mmol) and 47% hydrobromic acid (15 ml) was heated at 135 °C for 24 h with stirring. The solution, after cooling, was poured into water and aqueous 10% sodium hydroxide was added until neutral *pH*. The precipitate obtained was suitable for use without purification.

9,9′-(α″,ω″-Diaminoalkyl)-2,2′-(α‴,ω‴-diamidoalkyl)-bis-acridine (**22**)

Compound **21** (0.4 mmol) was dissolved in a mixture of dimethyl formamide (100 ml) and freshly distilled pyridine (100 ml). Diacyldichloride (1.1 mmol) was added dropwise at room temperature with stirring. The solution was stirred for 70 h. The precipitate obtained was filtered off and washed with water and then with aqueous 10% sodium hydroxide. The compound isolated was suitable for use without purification.

References

[1] Le Pecq, J. B., Le Bret, M., Barbet, J., Roques, B. (1975) Proc. Nat. Acad. Sci. USA **72**: 2915
[2] Chen, T. K., Fico, R., Canellakis, E. S. (1978) J. Med. Chem. **21**: 868
[3] McR. Wright, R. G., Wakelin, L. P. G., Fieldes, A., Acheson, R. M., Waring, M. J. (1980) Biochem. **19**: 5825
[4] Atwell, G. J., Stewart, G. M., Leupin, W., Denny, A. (1985) J. Am. Chem. Soc. **107**: 4335
[5] Zimmerman, S. C., Lamberson, C. R., Cory, M., Fairley, T. A. (1989) J. Am. Chem. Soc. **111**: 6805
[6] Takenaka, S., Jhara, T., Takagi, M. (1990) J. Chem. Soc., Chem. Commun. 1485
[7] Olomucki, M., Jerram, M., Parfait, R., Bollen, A., Gros, F. (1981) Bioorg. Chem. **10**: 455
[8] Galy, J. P., Vincent, E. J., Galy, A. M., Barbe, J., Elguero, J. (1981) Bull. Soc. Chim. Belges **90**: 947
[9] Albert, A., Linnell, W. H. (1936) J. Chem. Soc. 1614
[10] Wilkinson, J. H., Finar, I. L. (1946) J. Chem. Soc. **115**
[11] White, E. (1973) Org. Syntheses Coll. **5**: 336
[12] Vidal, R., Galy, J. P., Vincent, E. J., Barbe, J. (1988) Synthesis 148
[13] Albert, A., Gledhill, W. (1942) J. Soc. Chem. Ind. **61**: 159
[14] Buck, J. S., Ide, W. S. (1959) Org. Synthesis Coll. **2**: 130
[15] Dhar, M. L., Narang, K. S., Ray, J. N. (1938) J. Chem. Soc. 104

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