PREPARATION OF NEW 4,4'-LINKED BIS-ACRIDINES, 9,9'-LINKED BIS-ACRIDINES AND 4,4'-9,9' BI-LINKED BIS-ACRIDINES

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Abstract - New bis-derivatives belonging to the acridine series have been prepared. These compounds are bis(4-amino-9-acridanones) and bis(4-amino-9-thioacridanones) linked in positions 4,4' or 9,9'. There are also some 4,4'-diaminoacyl-9,9'-dithioalkyl bi-linked bis-acridines. In any case, chemical structures are discussed with reference to the ^{13}C NMR chemical shifts, as well as to the HSAB concept.

Until up to now, only 9,9'-bis(9-aminoacridines)[1-21] or, but in unusual instances, 10,10'-bis(9-acridanones)[13,22] have been prepared as acridinic bis-intercalators, although biological activities of intercalating agents seems to be widely enhanced by bis-functionalization[23-28]. With this in mind, several new bis(4-amino-9-acridanones) and bis(4-amino-9-thioacridanones) with an acyl or an alkyl linker chain, were prepared.

At first, we were interested in the 10-methyl substituted heterocycles 1 and 2 as substrates, because in the latter the extra amino group is the sole site for the linkage. Acylation can be then performed by using one or the other of the following classical methods:

a) direct condensation of an amine with an acyl halide in a basic medium[29].

b) preparation of an amide ion by means of a metal hydride, before reaction with an acyl halide[30].

The earlier method has been selected because solubility of the starting material - e.g. N-methyl-4-amino-9-acridanone - is greater in pyridine, which is the usual solvent for process a, than in dioxane or tetrahydrofuran, which are usual solvents for process b. Condensation has been successively achieved at 0°C, ambient temperature and 120°C but 4,4'-(α",ω"-diaminoacyl)bis(10-methyl-9-acridanones) 3 and 4,4'-(α",ω"-diaminoacyl)bis(10-methyl-9-thioacridanones) 4 have only been obtained *after 2 h under refluxing conditions (120°C) according to the synthetic pathway* schematized in Figure 1.

Compounds so prepared, are gathered in Tables I and II.

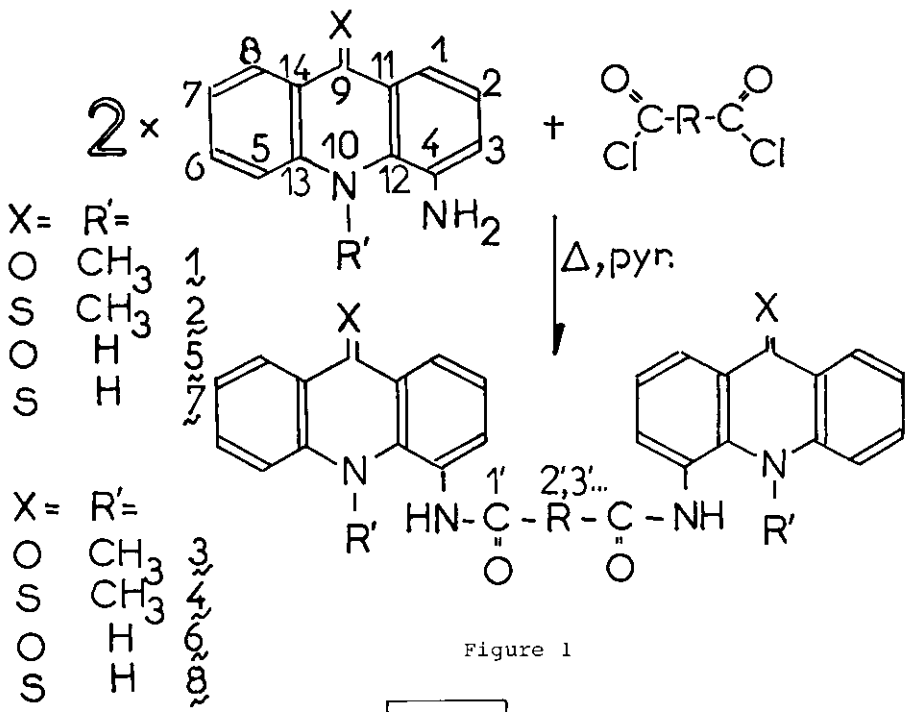
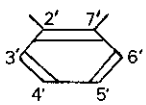


Figure 1

Table I

Compound	R	Mp	Yield	^{13}C NMR Spectra (TFAA-d) C(1);C(2);C(3);C(4);C(5);C(6);C(7);C(8);C(9);C(10); C(11);C(12);C(13);C(14);C(1');C(2');C(3');C(4');C(5'); C(6');C(7');C(8');C(9');C(10')
3a	$(CH_2)_2$	>260°C	54%	128.36*; 128.89*;141.85;127.85;119.51;141.49;126.96; 127.84;172.50;43.54;120.98;143.45;147.68;118.29; 177.36;32.40;32.40;177.36
3b	$(CH_2)_3$	>260°C	49%	128.30*;128.85*;141.86;127.73;119.47;141.06;126.90; 127.70;172.43;43.41;120.83;143.38;147.54;118.10; 178.26;36.92;22.84;36.92;178.26
3c	$(CH_2)_4$	>260°C	52%	128.44*;129.00*;142.00;127.86;119.64;141.32;127.05; 127.85;172.60;43.47;121.00;143.60;147.71;118.03; 179.21;37.66;26.86;26.86;37.66;179.21
3d	$(CH_2)_8$	>260°C	49%	128.38*;128.90*;141.87;128.01;119.52;141.24;126.91; 127.69;172.51;43.32;120.93;143.60;147.64;118.25; 180.42;38.25;27.44;31.02;30.68;30.68;31.02;27.44; 38.25;180.42
3e		>260°C	50%	128.40*;128.92*;141.89;122.98;119.87;141.12;126.92; 127.90;171.89;43.46;120.67;142.35;145.36;118.17; 173.41;132.67;127.45;139.23;139.23;127.45;132.67; 173.41

*These assigments may be inverted in a same compound

Table II

Compound	R	Mp	Yield	^{13}C NMR Spectra (TFAA-d)[a] C(1);C(2);C(3);C(4);C(5);C(6);C(7);C(8);C(9);C(10); C(11);C(12);C(13);C(14);C(1');C(2');C(3');C(4');C(5'); C(6')
4a	$(CH_2)_2$	210°C	42%	130.93*;130.98*;142.70; - ;120.07;142.92;129.72; 129.26;168.20;44.08; - ; - ; - ; - ;181.49;30.35; 30.35;181.49
4b	$(CH_2)_3$	218°C	44%	131.42*;131.26*;143.12; - ;120.10;143.21;129.76; 129.40;168.42;44.56; - ; - ; - ; - ;181.63;30.52; 23.46;30.52;181.63
4c	$(CH_2)_4$	220°C	44%	131.26*;130.95*;142.72; - ; 120.09;143.12;129.70; 129.11;168.44;44.70; - ; - ; - ; - ;181.52;30.48; 25.87;25.87;30.48;181.52

* These assigments may be inverted in a same compound

[a] Signals of quaternary carbons are unobserved due to the low solubility of compounds

Later, 4-amino-9-acridanone 5 has been used as starting material. With the latter, an equilibrium between the three canonical structures portrayed in Figure 2, can be fairly supposed in a basic medium with reference to previous results concerning substituted 9-acridanones[31].

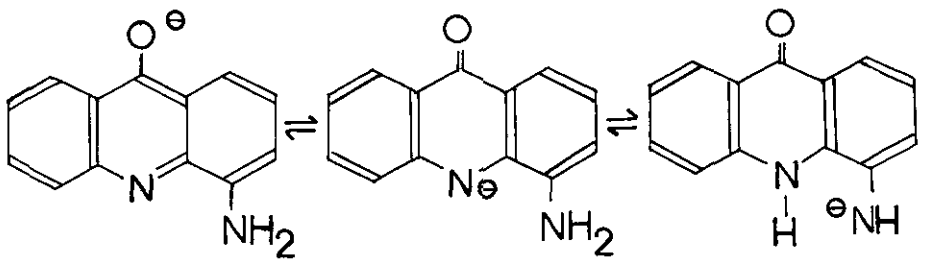


Figure 2

Because of these canonical structures, there are three nucleophilic sites in the substrate. Consequently, heterocycles can be linked by themselves either in positions 4,4' or 9,9' as well as in positions 10,10'.

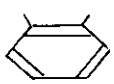
As previously, acylation has been achieved in pyridine at 0°C, ambient temperature and 120°C. However, reaction only succeeded in preparing bis-derivatives after refluxing for 2 h at 120°C. In this way, 4,4'-(α",ω"-diaminoacyl)bis(9-acridanones) 6 were isolated according to the Figure 1.

This is clearly shown by ^{13}C NMR spectrum. Indeed, the C(4) chemical shifts in compounds 6 are quite similar to the C(4) chemical shifts in compounds 3. On the

other hand, chemical shifts of C(9) are close to 172 ppm in compounds 3 and 6, while chemical shifts of C(9) are only close to 160 ppm in case of O-substituted derivatives[32]. According to that, it can be concluded that acyldichlorides run at the amino group branched on C(4). Yet, hardness of nucleophilic sites in 5 decreases in the following sequence O > N(4) > N(10)[22,33]. Moreover, chloro-substituted carbons in acyldichlorides are hard electrophilic sites because of the sp_2 hybridization[34], so that linkage would have had to occur only in the 9,9' positions or, but in a less extent, in the 4,4' positions with reference to the Pearson's concept[35,36]. As 4,4'-linked bis-heterocycles 6 have solely been obtained, thermodynamics seems to widely prevail over kinetics. No wonder owing to the well known more satisfactory use of HSAB concept for alkylation than for acylation. Bis-acridinic compounds 6 are collected in Table III.

Table III

^{13}C NMR Spectra (TFAA-d)

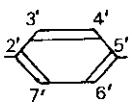
Compound	R	Mp	Yield	C(1);C(2);C(3);C(4);C(5);C(6);C(7);C(8);C(9);C(11);C(12);C(13);C(14);C(1');C(2');C(3');C(4');C(5');C(6');C(7');C(8');C(9');C(10')
6a	$(CH_2)_0$	>260°C	67%	128.12*;128.00*;141.70;121.35;119.20;140.37;125.90;127.55;172.35;118.10;140.84;146.20;117.89;176.85;176.85
6b	$(CH_2)_2$	>260°C	47%	128.89*;128.86*;141.85;127.85;119.52;141.49;126.96;127.84;172.50;120.98;143.45;147.68;118.29;177.36;32.40;32.40;177.36
6c	$(CH_2)_3$	>260°C	54%	128.93*;127.27*;140.10;127.50;120.51;139.40;125.98;127.99;172.08;118.14;139.70;142.15;116.79;181.51;37.67;22.21;37.67;181.51
6d	$(CH_2)_8$	>260°C	58%	128.43*;128.07*;141.92;127.66;120.95;141.27;126.82;128.84;172.41;120.93;143.60;147.23;118.09;180.40;38.28;27.45;31.20;30.59;30.59;31.20;27.45;38.28;180.40
6e		>260°C	58%	129.30*;129.02*;141.79;122.78;120.88;140.99;126.13;127.90;171.97;118.78;140.08;143.48;117.53;172.99;133.27;127.10;138.47;138.47;127.10;133.27;172.99

* These assigments may be inverted in a same compound

As regards 4-amino-9-thioacridanone 7, bis-functionalization leads to 4,4'-(α",ω"-diaminoacyl)bis(9-thioacridanones) 8 in accordance with the Scheme 1. As previously, this is demonstrated by ^{13}C NMR spectra. Chemical shifts of C (9) are quite similar in compounds 7 and 8, while there is a shielding in case of S-substituted derivatives[37]. Conversely, chemical shifts of C(4) are quite different in compounds 7 and 8. This is due to the N-substitution in case of 8. These results are in agreement with the Pearson's concept because the amino

nitrogen N(4) is harder than the sulfur atom as nucleophilic site[22]. Compounds 8 are gathered in Table IV.

Table IV

Compound	R	Mp	Yield	^{13}C NMR Spectra (TFAA-d) C(1);C(2);C(3);C(4);C(5);C(6);C(7);C(8);C(9);C(11);C(12);C(13);C(14);C(1');C(2');C(3');C(4');C(5');C(6');C(7');C(8')
8a	$(CH_2)_2$	>260°C	42%	128.90*;121.68;127.80*;125.81;117.65;132.77;122.61;130.81;197.82;128.32;131.82;134.71;129.31;172.85;30.38;30.38;172.85
8b	$(CH_2)_3$	>260°C	43%	128.89*;122.12;128.03*;126.00;118.24;133.14;121.84;131.22;197.80;128.36;132.03;135.23;129.30;172.94;32.08;23.41;32.08;172.94
8c	$(CH_2)_4$	>260°C	47%	128.43*;122.08;127.96*;125.84;118.12;133.09;121.96;130.87;196.84;128.16;131.74;135.03;129.36;172.84;32.87;26.80;26.80;32.87;172.84
8d		>260°C	45%	129.23*;123.26;129.02*;120.86;118.23;132.97;121.12;130.46;195.44;126.10;131.00;135.22;128.16;167.80;134.22;128.41;128.41;134.22;128.41;128.41;167.80

*These assigments may be inverted in a same compound

On the other hand, alkylation of 7 under phase transfer catalysis conditions leads to 9,9'-(α",ω"-dithioalkyl)bis(4-aminoacridines) 9. The synthetic pathway is schematized in Figure 3.

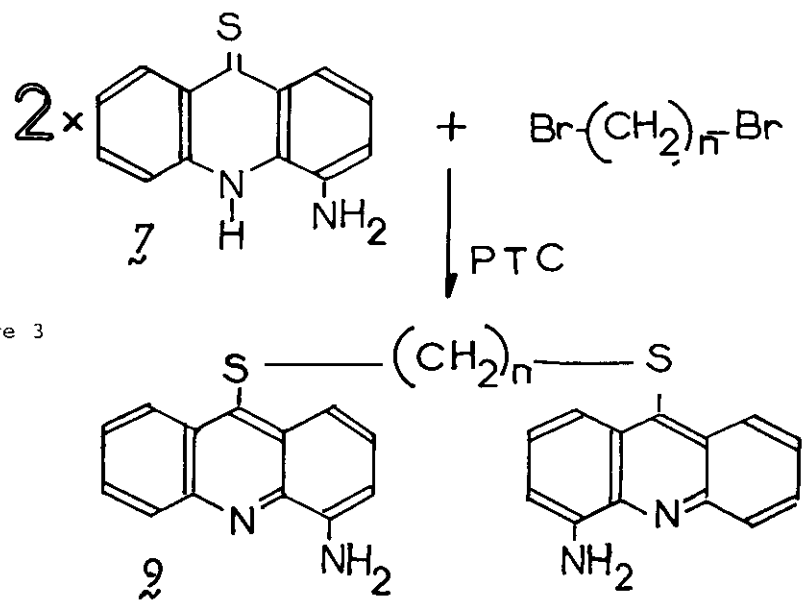


Figure 3

Chemical nature of compounds obtained, is unambiguously shown by ^{13}C NMR spectra with reference to the similarity noted between the C(9) chemical shifts in compounds 9 and the C(9) chemical shifts in substituted 9-thioacridines[38]. Bis(9-thioacridines) 9 are presented in Table V.

Table V

^{13}C NMR Spectra

Compound	n	Mp	Yield	C(1);C(2);C(3);C(4);C(5);C(6);C(7);C(8);C(9);C(11);C(12);C(13);C(14);C(1');C(2');C(3');C(4');C(5');C(6')
9a[a]	4	126°C	58%	111.65;125.34*;107.42;144.30;128.70;129.56;126.54*;128.32;140.95;127.74;125.42;139.52;129.43;37.08;27.90;27.90;37.08
9b[a]	5	128°C	63%	111.68;125.84*; 106.34;145.23;128.92;129.78;126.43*;128.21;140.58;128.90;125.80;139.25;129.78;36.24;28.62;26.52;28.62;36.24
9c[b]	6	132°C	55%	130.99*;131.16*;138.70;129.38;121.91;141.55;130.31;131.36;170.11;131.76;135.45;142.13;132.26;42.88;32.28;29.72;29.72;32.28;42.88

[a] In DMSO-d_6 as solvent

[b] In TFAA-d as solvent

* These assigments may be inverted in a same compound

Finally, some twice-linked bis-acridinic heterocycles have been prepared according to the Figure 4, by using bis(9-thioacridines) 9 as starting materials, acyldihalides as reagents and pyridine as solvent. The 9,9'(α",ω"-dithioalkyl)-4,4'-(α"',ω"'-diaminoacyl)bis-acridines 10 so obtained, are collected in Table VI.

Table VI

^{13}C NMR Spectra (TFAA-d)

Compound	n	m	Mp	Yield	C(1);C(2);C(3);C(4);C(5);C(6);C(7);C(8);C(9);C(11);C(12);C(13);C(14);C(1');C(2');C(3');C(4');C(5');C(6');C(1");C(2");C(3");C(4");C(5");C(6")
10a	5	3	116°C	67%	130.24*;130.66*;138.64;128.72;123.25;142.08;.130.34$^{\Delta}$;131.65$^{\Delta}$;169.34;131.98;136.07;140.72;131.96;42.86;36.02;27.31;36.02;42.86; - ;182.07;39.41;31.11;39.41;182.07
10b	6	4	120°C	69%	130.38*;130.70*;138.18;128.97;122.49;141.57;130.70$^{\Delta}$;131.63$^{\Delta}$;169.69;131.38;136.40;140.74;131.76;43.14;35.25;26.97;26.97;35.25;43.14;181.32;38.26;30.16;30.16;38.26;181.32

*,$^{\Delta}$ These assigments may be inverted in a same compound

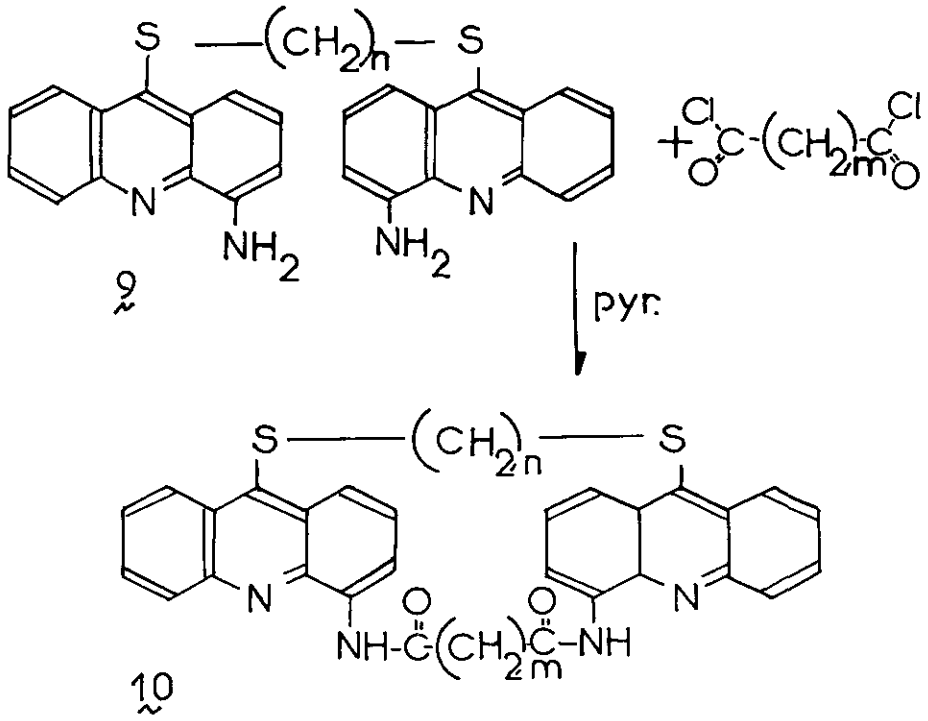


Figure 4

EXPERIMENTAL

4-Amino-9-thioacridanone, 7

The following mixture of 10 mmol of 4-amino-9-acridanone[39,40], 5, 10 mmol of phosphorous pentasulfide, and 20 ml of phosphorohexamethyltriamide is refluxed with stirring for 3 h. The red solution is poured out in 400 ml of hydrochloric acid (pH = 5). A scarlet precipitate is filtered. The latter is recrystallized from methanol. Yield, 71%; Mp, 244-248°C; ^{1}H NMR (DMSO-d_6), 8.95(d,2H);8.55(d, 2H);7.65(m,3H)

10-Methyl-4-amino-9-thioacridanone, 2

The following mixture of 5 mmol of 10-methyl-4-aminoacridanone[41], 1, 2.5 mmol of Lawesson's reagent[42], and 30 ml of benzene is refluxed with stirring for 2 h. After evaporation of benzene, the residual part is recrystallized from a water-acetonitrile mixture. Yield, 84%; Mp, 144-148°C; ^{1}H NMR (DMSO-d_6), 9.0(d,2H); 8.6(d,2H);7.8(m,3H);4.0(s,3H)

Acylation: general procedure

Heterocyclic compound (5 mmol) is dissolved in 25 ml of anhydrous pyridine freshly distilled with soda. Acyldichloride (3 mmol) is added in small amounts within 30 min. The mixture is then refluxed for 2.3 h. The precipitate obtained is filtered and recrystallized from a TFAA-water mixture.

Alkylation: general procedure

The following mixture of 5 mmol of heterocyclic compound, 3 mmol of alkyldibromide, 2 mmol of triethylbenzylammonium chloride (TEBAC), 50 ml of 30% aqueous potassium hydroxide, and 100 ml of toluene is refluxed with stirring for 3.3 h. The toluene phase is separated, dried with magnesium sulfate and evaporated in vacuo. The residual product is triturated with ethanol, before recrystallization from a 1,2-dichloroethane-hexane mixture.

Twice-linkage: general procedure

Bis(9-thioacridine) 9 (1.5 mmol) is dissolved in 25 ml of anhydrous pyridine freshly distilled with soda. Acyldichloride (1.5 mmol) is gradually added within 1 h. After stirring for 15 min, the mixture is filtered and filtrate is poured out in 400 ml of cold water. An orange precipitate is then obtained, filtered and washed with warm hexane.

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