Synthesis of New Bis(acridinic) Derivatives Monobridged in Positions 2,2′ or 9,9′ and Bibridged in Positions 2,2′ and 9,9′

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New bis(acridinic) compounds have been prepared as potential intercalating agents. These derivatives are quoted as 2,2′-(α'',ω''-diaminoacyl)bis(9-acridanones), 2,2′-(α'',ω''-diaminoacyl)bis(9-thioacridanones), 9,9′-(α'',ω''-dithioalkyl)bis(2-aminoacridines), and 9,9′-(α'',ω''-dithioalkyl)-2,2′-(α''',ω'''-diaminoacyl)bis(acridines).

In our researches devoted to the bisfunctionalization of acridine derivatives with a view to enhance the activity of the latter as anticancer drugs or antiparasitic drugs (*1-3*), a set of novel bis(9-acridanones) and bis(9-thioacridanones) have been prepared. Here we report the syntheses and the physicochemical data.

At first, 2-amino-9-acridanone, **1**, as well as 2-amino-10-methyl-9-acridanone, **2**, were selected as starting material. Acylation by the direct condensation (*4*), shown schematically in step I (Figure 1), was achieved in pyridine under refluxing conditions for 2 h. Dihydrochlorides **5** and **6** were subsequently isolated.

Similarly, acylation of 2-amino-9-thioacridanone, **3**, and that of 2-amino-10-methyl-9-thioacridanone, **4**, respectively prepared from **1** and **2** by means of phosphorus pentasulfide thiation (*5*),

Table I. Data on Bis(9-acridanone) Hydrochlorides 5 and 6, Bis(9-thioacridanone) Bases 7, 8, and 9, and Bibridged Bis(acridine) Bases, 10

compd	R_1	R_2	yield, %	mp, °C	mol formula[a]	^{1}H NMR (TFAA-d/$(CH_3)_4Si_{int}$)[b] δ, ppm
5a	$(CH_2)_2$		42	>360	$C_{30}H_{24}N_4O_4Cl_2$ (575)	9.3 (m, 2 H); 8.7 (m, 2 H); 8.1 (m, 8 H); 7.9 (m, 2 H); 3.3 (*c*, 4 H)
5b	$(CH_2)_3$		50	>360	$C_{31}H_{26}N_4O_4Cl_2$ (589)	9.3 (m, 2 H); 8.7 (m, 2 H); 8.1 (m, 8 H); 7.8_5 (m, 2 H); 2.9_5 (m, 4 H); 2.5 (*c*, 2 H)
5c	$(CH_2)_4$		49	>360	$C_{32}H_{28}N_4O_4Cl_2$ (603)	9.1_5 (m, 2 H); 8.6 (m, 2 H); 8.4_5 (m, 10 H); 8.1_5 (m, 2 H); 2.8_5 (m, 4 H); 2.1 (*c*, 4 H)
5d	$(CH_2)_7$		50	>360	$C_{35}H_{34}N_4O_4Cl_2$ (645)	9.1_5 (m, 2 H); 8.4_5 (m, 9 H); 8.1_5 (m, 3 H); 2.7_5 (m, 4 H); 1.9_5 (m, 4 H); 1.5 (*c*, 6 H)
5e	$(C_2H_5)_2C$		59	>360	$C_{33}H_{30}N_4O_4Cl_2$ (617)	9.3_5 (m, 2 H); 8.8 (m, 2 H); 8.2_5 (m, 8 H); 7.9 (m, 2 H); 2.4 (m, 4 H); 1.2 (m, 6 H)
6a	$(CH_2)_2$		30	264	$C_{32}H_{28}N_4O_4Cl_2$ (603)	9.1 (m, 2 H); 8.5_5 (m, 10 H); 8.1_5 (m, 2 H); 5.0 (s, 6 H); 3.3_5 (*c*, 4 H)
6b	$(CH_2)_3$		35	345	$C_{33}H_{30}N_4O_4Cl_2$ (617)	9.2 (m, 2 H); 8.5_5 (m, 10 H); 8.2 (m, 2 H); 5.0 (s, 6 H); 2.9_5 (m, 4 H); 2.4_5 (m, 2 H)
6c	$(CH_2)_4$		45	298	$C_{34}H_{32}N_4O_4Cl_2$ (631)	9.2 (m, 2 H); 8.5_5 (m, 10 H); 8.2 (m, 2 H); 5.0 (s, 6 H); 2.8 (*c*, 4 H); 2.0_5 (*c*, 4 H)
6d	$(CH_2)_7$		62	300	$C_{37}H_{38}N_4O_4Cl_2$ (673)	9.2 (m, 2 H); 8.6 (m, 10 H); 8.1_5 (m, 2 H); 5.0 (s, 6 H); 2.7 (m, 4 H); 1.9 (*c*, 4 H); 1.5 (*c*, 6 H)
6e	$(C_2H_5)_2C$		30	250	$C_{35}H_{34}N_4O_4Cl_2$ (645)	9.4 (m, 2 H); 8.9_5 (m, 2 H); 8.4_5 (m, 8 H); 7.9_5 (m, 2 H); 4.6_5 (s, 6 H); 2.5 (m, 4 H); 1.2_5 (m, 6 H)
7a	$(CH_2)_4$		74	355	$C_{32}H_{28}N_4S_2O_2$ (562)	9.5 (m, 2 H); 8.8 (m, 2 H); 8.4_5 (m, 6 H); 8.1 (m, 4 H); 2.8_5 (t, 4 H); 2.1 (*c*, 4 H)
8a	$(CH_2)_3$		67	225	$C_{33}H_{28}N_4S_2O_2$ (576)	9.4_5 (m, 2 H); 8.8 (m, 2 H); 8.5 (m, 8 H); 8.0_5 (m, 2 H); 4.8 (s, 6 H); 2.9_5 (t, 4 H); 2.5 (m, 2 H)
8b	$(CH_2)_4$		70	295	$C_{34}H_{30}N_4S_2O_2$ (590)	9.5_5 (m, 2 H); 8.9 (m, 2 H); 8.6_5 (m, 4 H); 8.5 (m, 4 H); 8.1_5 (m, 2 H); 5.0_5 (m, 6 H); 2.8_5 (t, 4 H); 2.1 (*c*, 4 H)
9a		$(CH_2)_5$	45	100	$C_{31}H_{23}N_4S_2$ (515)	9.7 (m, 2 H); 9.1 (m, 2 H); 8.3 (m, 8 H); 8.0 (m, 2 H); 3.4_5 (t, 4 H); 1.7 (*c*, 6 H)
9b		$(CH_2)_6$	30	102	$C_{32}H_{25}N_4S_2$ (529)	9.7 (m, 2 H); 9.1 (m, 2 H); 8.3 (m, 8 H); 8.0 (m, 2 H); 3.4_5 (t, 4 H); 1.7_5 (m, 4 H); 1.4_5 (*c*, 4 H)
9c		$(CH_2)_8$	75	194	$C_{34}H_{29}N_4S_2$ (557)	9.1 (m, 2 H); 8.9_5 (m, 2 H); 8.2 (m, 6 H); 7.9_5 (m, 2 H); 7.8 (m, 2 H); 3.4 (t, 4 H); 1.8 (m, 4 H); 1.5 (*c*, 4 H); 1.3_5 (*c*, 4 H)
9d		$(CH_2)_9$	65	162	$C_{35}H_{31}N_4S_2$ (571)	9.0_5 (m, 6 H); 8.2 (m, 4 H); 7.9 (m, 4 H); 3.4 (t, 4 H); 1.7 (m, 4 H); 1.4 (*c*, 4 H); 1.2 (*c*, 6 H)
9e		$(CH_2)_{12}$	62	223	$C_{38}H_{37}N_4S_2$ (613)	9.6_5 (m, 2 H); 9.0_5 (m, 2 H); 8.3 (m, 8 H); 7.9_5 (m, 2 H); 3.5 (t, 4 H); 1.7_5 (m, 4 H); 1.4_5 (*c*, 4 H); 1.2_5 (*c*, 12 H)
10a	$(CH_2)_4$	$(CH_2)_8$	72	132	$C_{40}H_{40}N_4O_2S_2$ (672)	9.8_5 (m, 2 H); 9.0_5 (m, 3 H); 8.2 (m, 6 H); 8.0 (m, 3 H); 3.4 (t, 4 H); 2.8 (m, 4 H); 2.1 (m, 2 H); 1.9_5 (m, 2 H); 1.7 (*c*, 4 H); 1.4 (*c*, 4 H); 1.2 (*c*, 4 H)
10b	$(CH_2)_7$	$(CH_2)_{12}$	65	112	$C_{47}H_{54}N_4O_2S_2$ (770)	9.7 (m, 2 H); 9.1 (m, 2 H); 8.2_5 (m, 8 H); 8.0 (m, 2 H); 3.5 (t, 4 H); 2.7_5 (m, 4 H); 1.9_5 (*c*, 4 H); 1.7_5 (m, 4 H); 1.5 (*c*, 10 H); 1.2 (*c*, 12 H)
10c	$(CH_2)_2$	$(CH_2)_{12}$	63	205	$C_{42}H_{44}N_4O_2S_2$ (700)	9.7_5 (m, 2 H); 9.1_5 (m, 2 H); 8.3_5 (m, 8 H); 8.0 (m, 2 H); 3.5 (t, 4 H); 1.7_5 (m, 4 H); 1.4_5 (*c*, 8 H); 1.2_5 (*c*, 12 H)
10d	$(CH_2)_7$	$(CH_2)_9$	70	120	$C_{44}H_{48}N_4O_2S_2$ (728)	9.0_5 (*c*, 6 H); 8.2_5 (*c*, 4 H); 7.9 (m, 4 H); 3.4 (t, 4 H); 2.7 (*c*, 4 H); 1.9_5 (*c*, 4 H); 1.8 (*c*, 4 H); 1.5 (*c*, 10 H); 1.2_5 (*c*, 6 H)

[a] The microanalyses, submitted for review, are in satisfactory agreement with the calculated values. [b] Recorded with a Bruker AM 200 spectrometer. [c] Unresolved signal.

0021-9568/86/1731-0374$01.50/0

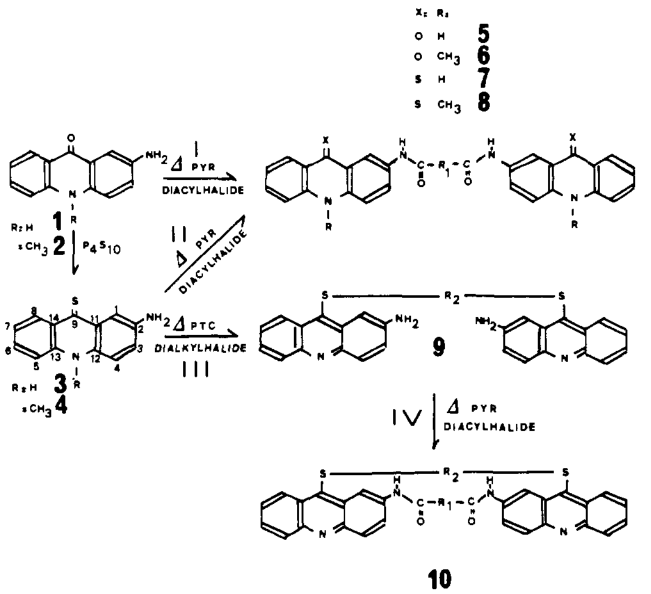

Figure 1.

were performed in the conditions mentioned above. Bis-thio derivatives **7** and **8** were so obtained. In contrast, alkylation of **3** under phase-transfer catalysis conditions leads to 9,9′-(α'',ω''-dithioalkyl)bis(2-aminoacridines), **9**. The synthetic pathway is shown schematically in step III (Figure 1).

Finally, some twice-bridged bis(acridinic)heterocycles were prepared according to step IV (Figure 1). In so doing, the 9,9′-(α'',ω''-dithioalkyl)-2,2′-(α''',ω'''-diaminoacyl)bis(acridines), **10**, were obtained.

Data on all the compounds prepared are collected in Table I.

Experimental Section

2-Amino-9-thioacridanone, 3. A stirred mixture of 2-amino-9-acridanone (10 mmol), **1** (*6*), phosphorus pentasulfide (10 mmol), and hexamethylphosphoric triamide (30 mL) is refluxed for 2.30 h. Solution is afterwards poured out into 450 mL of water. A scarlet precipitate is filtered off. The latter is recrystallized from methanol. Yield, 82%; mp, 242 °C; ^{13}C NMR (Me$_2$SO-d_6), 108.64 (C-1), 145.05 (C-2), 125.33 (C-3), 119.87 (C-4), 118.34 (C-5), 132.18 (C-6), 122.25 (C-7), 129.77 (C-8), 191.00 (C-9), 128.47 (C-11), 130.85 (C-12), 134.89 (C-13), 128.36 (C-14). The spectrum was recorded with a Bruker AM 200 spectrometer.

2-Amino-10-methyl-9-thioacridanone, 4. One works as in case of **3**, apart from the starting heterocyclic material which is now 2-amino-10-methyl-9-acridanone, **2** (*7*). Yield, 70%; mp, 194 °C (decomp.); ^{13}C NMR (Me$_2$SO-d_6), 110.02 (C-1), 144.66 (C-2), 124.84 (C-3), 117.57 (C-4), 116.44 (C-5), 132.66 (C-6), 121.77 (C-7), 130.59 (C-8), 194.16 (C-9), 129.35 (C-11), 131.74 (C-12), 136.38 (C-13), 129.89 (C-14), 34.58 (CH$_3$). The spectrum was recorded as above.

Acylation. The acridinic monomer (10 mmol) is dissolved in 25 mL of anhydrous pyridine freshly distilled with soda. Acyl dichloride (5 mmol) is gradually added. The mixture is then refluxed for 2.30 h before being poured out into 200 mL of either cold water (**7**, **8**) or 5 N hydrochloric acid (**5**, **6**). The precipitate obtained is filtered off and repeatedly washed with hot ethanol.

Alkylation. A stirred mixture of the acridinic monomer (10 mmol), alkyl dibromide (5 mmol), triethylbenzylammonium chloride (TEBAC) (5 mmol), aqueous 50% potassium hydroxide (75 mL), and toluene (150 mL) is refluxed for 3 h. The toluene layer is separated, washed 5 times with water (50 mL every time), dried with magnesium sulfate, and evaporated in vacuo. The residual product is dissolved in a small amount of hot ethanol. Large amount of water is added. A precipitate is filtered off and washed with butyl acetate before being recrystallized from acetone (**9a**, **9b**).

One must underscore that the yield is greatly increased when TEBAC is not used and butanone is used as solvent instead of toluene. In these conditions, the mixture is filtered after refluxing and solution is then poured out into 500 mL of boiling water. On cooling, there is a precipitation. Solid is recrystallized from acetone (**9c**, **9d**) or chloroform (**9e**).

Twice-Bridged Heterocycles. Bis(9-thioacridine), **9** (2 mmol), is dissolved in 25 mL of anhydrous pyridine freshly distilled with soda. Acyl dichloride (2.3 mmol) is gradually added. The mixture is refluxed for 24 h before being evaporated until a viscous residue is obtained. The latter is dissolved in a chloroform–methanol mixture (3:1). Insoluble impurities are filtered off and a large amount of hexane is added to the filtrate. The precipitate so obtained, is washed with warm hexane.

Registry No. **1**, 27918-14-5; **2**, 58658-03-0; **3**, 102724-56-1; **4**, 102724-57-2; **5a**, 102724-58-3; **5b**, 102724-59-4; **5c**, 102724-60-7; **5d**, 102724-61-8; **5e**, 102724-62-9; **6a**, 102724-63-0; **6b**, 102724-64-1; **6c**, 102724-65-2; **6d**, 102724-66-3; **6e**, 102724-67-4; **7a**, 102724-68-5; **8a**, 102724-69-6; **8b**, 102724-70-9; **9a**, 102724-71-0; **9b**, 102724-72-1; **9c**, 102724-73-2; **9d**, 102724-74-3; **9e**, 102724-75-4; **10a**, 102724-76-5; **10b**, 102724-77-6; **10c**, 102724-78-7; **10d**, 102724-79-8; ClCOCH$_2$CH$_2$COCl, 543-20-4; ClCOCH$_2$CH$_2$CH$_2$COCl, 2873-74-7; ClCO(CH$_2$)$_4$COCl, 111-50-2; ClCO(CH$_2$)$_7$COCl, 123-98-8; ClCOC(C$_2$H$_5$)$_2$COCl, 54505-72-5; Br(CH$_2$)$_5$Br, 111-24-0; Br(CH$_2$)$_6$Br, 629-03-8; Br(CH$_2$)$_8$Br, 4549-32-0; Br(CH$_2$)$_9$Br, 4549-33-1; Br(CH$_2$)$_{12}$Br, 3344-70-5.

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Received for review February 24, 1986. Accepted March 13, 1986. This work was partially supported by a grant from CNRS (AIP-PIRMED 1051).