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Preparation of 3,3'-linked bis(acridinones), 9,9'-linked bis(thioacridines) and 3-3', 9-9' bi-linked bis(thioacridinones)

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Introduction

Acridine derivatives act as intercalating agents [1]. It has been shown that biological properties and mainly antitumoral activity of bifunctional intercalators could be related to their high DNA binding affinity [2, 3]. With reference to this, some novel bis[9(10 H)-acridinones] and bis[9(10 H)-thioacridinones] were prepared with a view to being investigated as anticancer drugs. The starting compound used was 3-amino-9-(10 H)-thioacridinone, **4**. This compound was prepared by thiation [4] of the 9-oxo homologue, **2**, obtained from the 3-nitro-9(10 H)-acridinone **1** [5].

On the one hand, alkylation of **4** under the well-known phase-transfer catalysis conditions [6–9] led to the 9,9'-(α'',ω''-dithioalkyl)-bis(3-amino-acridine), **5**, although the yield was quite surprisingly enhanced where no catalyst was used!

On the other hand, acylation of **2** was achieved in acetone under warm conditions: about 40°C for 1 h.

Finally, twice-linked bis(acridinic) heterocycles were prepared by using bis[9,9'-(dithioalkyl)-3-amino-acridines], **5**, as starting materials, sodium amide as reagent and either anhydrous pyridine or dimethyl formamide as solvent. In so doing, the bis[9,9'-(α'',ω''-dithioalkyl)-3,3'-(α'',ω''-diaminoacyl)-acridines], **6**, were obtained.

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Synthetic pathways are portrayed in the scheme. Data about the compounds prepared are mentioned in table I.

Some of the bis(acridinic) derivatives prepared were preliminarily tested against P-388 lymphocytic leukemia. Results are presented in table II. During the assay, activities observed were not significant.

Experimental protocols

3-Amino-9(10 H)-acridinone ***2***

The 3-nitro-9(10 H)-acridinone, **1**, prepared according to Goldberg and Kelly [5], was reduced to the corresponding 3-amino-9(10H)-acridinone, **2**, by using metallic iron powder in hydrochloric acid. Yield, 85%; mp, 290°C; ^{13}C NMR (Me_2SO–d_6), 132.13 (C-1), 111.32 (C-2), 153.59 (C-3), 95.66 (C-4), 111.97 (C-5), 127.54 (C-6), 116.40 (C-7), 125.77 (C-8), 175.09 (C-9), 119.99 (C-11), 143.31 (C-12), 140.90 (C-13), 120.58 (C-14).

*Acylation (**3a-3d**)*

The acridinic monomer, **2** (10 mmol) was dissolved in 150 ml of acetone. Acyldichloride (5 mmol) was added gradually. The reaction was continued with agitation for 1 h at room temperature.

The mixture was poured into 200 ml of 5 N hydrochloric acid. The hydrochloride obtained as a precipitate, was filtered off and washed with ethanol–water (50/50, v/v) mixture.

Table I. Chemical data.

Compd	R	R_1	R_2	Yield %	mp, °C	mol formula	^{1}H NMR (TFAA-d/$(CH_3)_4Si_{int}$)[a] δ, ppm
1	-	-	-	64	> 360	$C_{13}H_8N_2O_3$ (240)	8.8(d,1H) ; 8.7(s,1H) ; 8.5(d,1H) ; 8.2(d,1H) 8.0(t,1H) ; 7.9(d,1H) ; 7.65(t,1H)
2	-	-	-	85	290	$C_{13}H_{10}N_2O$ (210)	8.9(t,3H) ; 8.35(d,1H) ; 8.2(d,1H) ; 8.0(t,2H)
3a	$(CH_2)_2$	-	-	42	> 360	$C_{30}H_{24}N_4O_4Cl_2$ (575)	9.2(s,2H) ; 8.3(m,7H) ; 8.0(m,5H) ; 3.4(s,4H)
3b	$(CH_2)_3$	-	-	44	> 360	$C_{31}H_{26}N_4O_4Cl_2$ (589)	8.9(d,2H) ; 8.7(t,4H) ; 8.1(m,4H) ; 7.8(m,4H) 2.9(s,4H) ; 2.5(s,2H)
3c	$(CH_2)_4$	-	-	46	> 360	$C_{32}H_{28}N_4O_4Cl_2$ (603)	9.2(s,2H) ; 8.7(d,2H) ; 8.3(m,3H) ; 8.2(m,2H) 8.1(m,2H) ; 8.0(t,3H) ; 2.9(s,4H) ; 2.1(s,4H)
3d	$(CH_2)_7$	-	-	59	> 360	$C_{35}H_{34}N_4O_4Cl_2$ (645)	9.2(s,2H) ; 8.3(t,8H) ; 8.0(m,4H) ; 2.8(s,4H) 2.0(s,4H) ; 1.6(s,6H)
4	-	-	-	77	235	$C_{13}H_{10}N_2S$ (225)	8.9(t,1H) ; 8.5(m,3H) ; 8.1(m,3H)
5a	-	$(CH_2)_2$	-	67	280	$C_{28}H_{22}N_4S_2$ (478)	8.7(t,4H) ; 8.1(m,6H) ; 7.7(t,2H) ; 7.4(d,2H) 3.4(s,4H)
5b	-	$(CH_2)_4$	-	72	255	$C_{30}H_{26}N_4S_2$ (506)	9.1(m,4H) ; 8.3(m,4H) ; 8.0(m,4H) ; 3.3(s,4H) 1.9(s,4H)
5c	-	$(CH_2)_6$	-	80	247	$C_{32}H_{30}N_4S_2$ (534)	9.1(m,4H) ;8.3(m,4H) ; 7.9(m,6H) ; 3.4(s,4H) 1.65(s,4H) ; 1.4(s,4H)
5d	-	$(CH_2)_8$	-	75	186	$C_{34}H_{34}N_4S_2$ (562)	9.6(m,4H) ; 8.7(m,4H) ; 8.4(m,6H) ; 3.9(t,4H) 2.2(t,4H) ; 1.8(d,8H)
6a	-	$(CH_2)_4$	$(CH_2)_2$	74	212	$C_{34}H_{28}N_4O_2S_2$ (588)	9.1(m,6H) ; 8.3(d,4H) ; 8.0(m,4H) ; 3.5(d,4H) 3.3(s,4H) ; 1.9(s,4H)
6b	-	$(CH_2)_6$	$(CH_2)_5$	49	285	$C_{39}H_{38}N_4O_2S_2$ (658)	9.1(d,6H) ; 8.25(s,4H) ; 7.95(m,4H) ; 3.4(d,4H) 2.8(s,2H) ; 2.1(m,6H) ; 1.8(s,6H) ; 1.5(s,4H)
6c	-	$(CH_2)_8$	$(CH_2)_5$	72	170	$C_{41}H_{42}N_4O_2S_2$ (686)	9.1(d,6H) ; 8.25(s,4H) ; 7.95(m,4H) ; 3.7(t,4H) 2.8(s,4H) ; 2.0(m,4H) ; 1.7(s,6H) ; 1.35(m,8H)

[a]Recorded with a Bruker AM 200 spectrometer

*3-Amino-9(10 H)-thioacridinone, **4***

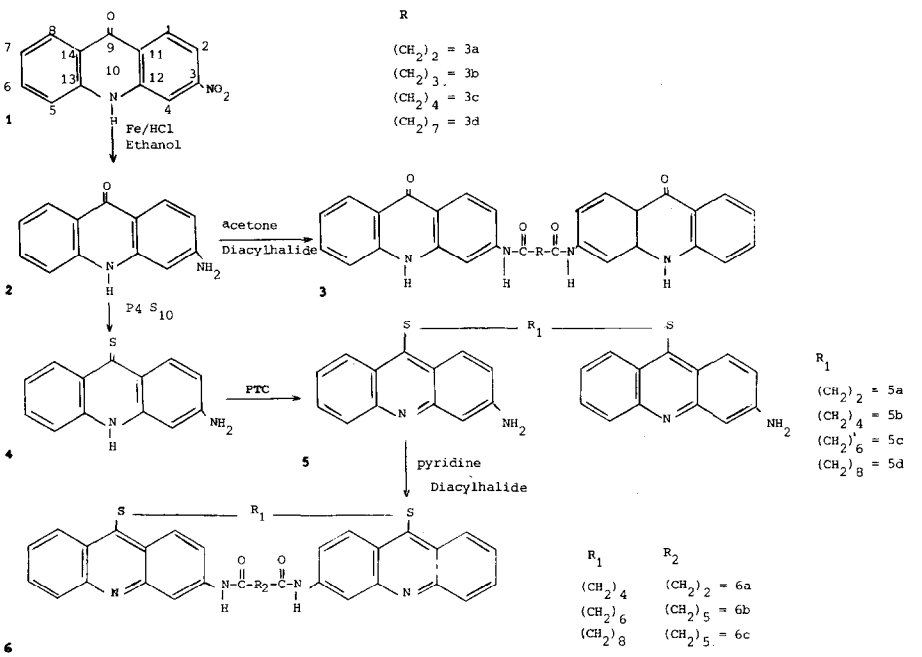
A stirred mixture of 3-amino-9(10 H)-acridinone, **2** (10 mmol), phosphorus pentasulfide (10 mmol) and hexamethylphosphoric triamide (30 ml) was refluxed for about 2 h. The reaction mixture was then poured into 500 ml of water and the reddish precipitate filtered off. The latter was dissolved in methanol before being precipitated by the addition of water.
Yield, 77%; mp, 235°C; ^{13}C NMR (Me_2SO–d_6), 132.18 (C-1), 114.91 (C-2), 154.38 (C-3), 94.34 (C-4), 117.22 (C-5), 131.92 (C-6), 121.59 (C-7), 130.03 (C-8), 192.50 (C-9), 122.86 (C-11), 139.07 (C-12), 136.07 (C-13), 127.47 (C-14).

*Alkylation (**5a-5d**)*

A mixture of 10 mmol of the acridinic monomer, **4**, 6 mmol of alkyldibromide, 50 ml of 50% aqueous potassium hydroxide, and 150 ml of toluene, was refluxed for 2 h. The toluene phase was separated, dried with calcium sulfate and evaporated *in vacuo*. The residual product was triturated with ethanol. A precipitate was obtained after the addition of water and a few potassium hydroxide pellets. The latter was filtered off, dried and crystallized from ethanol or acetone. Butanone can be used as a solvent instead of toluene. Under these conditions, the mixture was filtered after refluxing and the filtrate was poured into 500 ml of boiling water. Precipitation occurred upon cooling. The solid was recrystallized from ethanol or dissolved in acetone before being precipitated by the addition of water. Finally, the compound obtained was washed with petroleum ether.

*Twice-linkage heterocycles, **6***

Bis[9,9'-dithioalkyl)-3-amino-acridine] (5 mmol), **5**, was dissolved in 25 ml of either anhydrous pyridine freshly distilled



Scheme 1.

with soda or dimethyl formamide, also adding sodium amide (10 mmol) as a catalyst.

Acyldichloride (5.5 mmol) was added gradually. The reaction was continued with agitation overnight, at room temperature. The mixture was filtered and the filtrate poured into 300 ml of water. The precipitate obtained was filtered and washed with petroleum ether.

Biological assay

Six female mice CDF1 were inoculated with 0.1 ml of diluted ascite solution, containing 10^6 tumor cells of P-388 lymphocytic leukemia. Treatment began after 24 h inoculation. Three different doses of the hydrochloride as a drug, were administered daily for 5 d.

Results are given in percentage of average survival time, with reference to untreated mice (T/C). To be selected for further investigations, T/C must be more than 125%.

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Table II. Results of the leukemia screening test.

Compounds[a]	*Dose tested (mg/kg)*	*T/C (%)*
3b	200	100
	100	104
	50	98
3c	200	104
	100	104
	50	99
3d	200	92
	100	110
	50	103
5a	240	TOX
	120	100
	60	97
5b	240	TOX
	120	100
	60	106
5c	240	104
	120	101
	60	100
5d	240	TOX
	120	106
	60	106

[a]Hydrochlorides