Synthesis and ^{1}H NMR Characterization of Substituted 1-Amino-9-imino-4-nitro-9,10-dihydroacridines as Potential Antitumor Agents

Wieslaw M. Cholody* and Jerzy Konopa

Department of Pharmaceutical Technology and Biochemistry, Technical University of Gdansk,
80952 Gdansk, Poland

Ippolito Antonini and Sante Martelli*

Department of Chemical Sciences, University of Camerino,
62032 Camerino, Italy

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A convenient method for the synthesis of unsubstituted and substituted 1-amino-9-imino-4-nitro-9,10-dihydroacridines, **9** and **10**, respectively, is reported. Their ^{1}H nmr data are reported and discussed in order to confirm the imino tautomeric structure.

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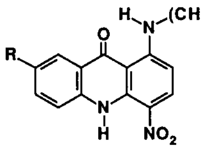
Introduction.

Recent reports from Warner-Lambert Company's laboratories, in the patent and journal literature, have detailed the synthesis and biological activity of two new groups of acridine antitumor agents, namely the substituted 1-amino-4-nitro-9(10*H*)-acridinones **1** and the 5-nitropyrazolo[3,4,5-*kl*]acridines **2** [1-5]. Both groups belong to the same broader class of chromophore modified acridine DNA-binders and seem to be very promising as solid tumor-selective anticancer agents. Particularly, the 9-methoxy derivatives of **2** were found to exhibit selectivity against solid and multidrug-resistant tumors [4,6].

Detailed structural requirements for the chromophore in this class are yet unknown. Basing on the hypothesis that modification of the acridine nucleus, while maintaining the C-9 oxo group and the polymethylenediamine side chain in the *peri* position, can result in biologically active compounds, we have obtained two additional groups of acridine antitumor agents, the imidazoacridinones **3** [7] and the triazoloacridinones **4** [8].



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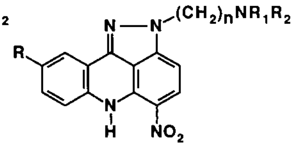

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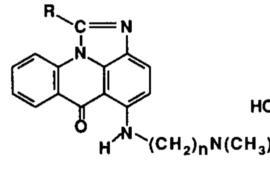

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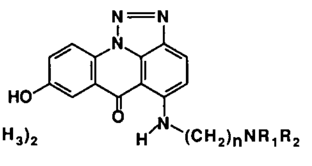

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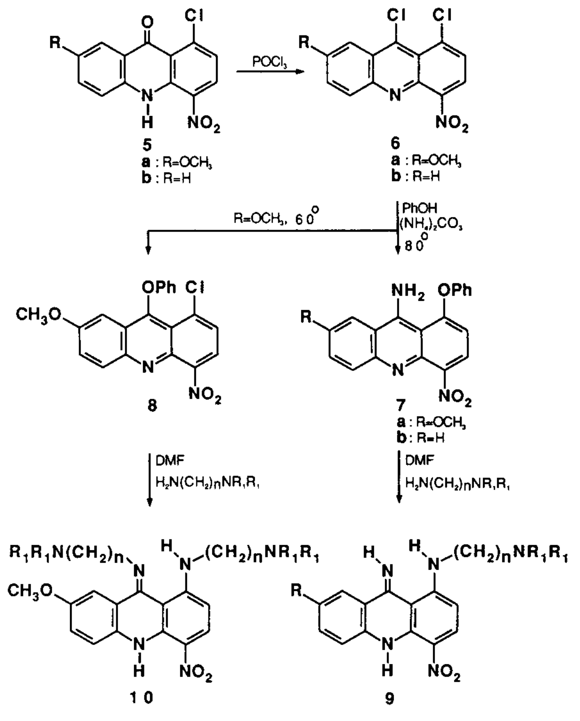
As a continuation of our search for additional acridine nucleus modifications, we synthesized some substituted 1-amino-9-imino-4-nitro-9,10-dihydroacridines **9** and **10** as a new class of potentially antineoplastic agents. These compounds, especially **9**, are structurally closely related to both **1** and **2**. We were interested to ascertain if the occurrence of the 9-oxo group is necessary for biological activity of **1** and, how "reduction" of the pyrazolo ring can modify the antitumor activity of **2**. The "open model" could give a contribution to a better understanding of the role played by the pyrazolo ring in biological activity of such new synthetic antitumor agents as anthrapyrazoles [9,10], 5-nitro-

Scheme 1



10
a : n=2;R$_1$=CH$_3$
b : n=2;R$_1$=CH$_2$CH$_3$
c : n=3;R$_1$=CH$_3$
d : n=3;R$_1$=CH$_2$CH$_3$

9
a : n=2;R=OCH$_3$;R$_1$=CH$_3$
b : n=2;R=OCH$_3$;R$_1$=CH$_2$CH$_3$
c : n=3;R=OCH$_3$;R$_1$=CH$_3$
d : n=3;R=OCH$_3$;R$_1$=CH$_2$CH$_3$
e : n=2;R=H;R$_1$=CH$_3$
f : n=2;R=H;R$_1$=CH$_2$CH$_3$
g : n=3;R=H;R$_1$=CH$_3$
h : n=3;R=H;R$_1$=CH$_2$CH$_3$

pyrazoloacridines [3] and benzothiopyranoindazoles [11]. Additionally, the "two armed" compounds **10** are particularly valuable for structure-activity-relationship studies in acridine anticancer agents as they constitute the first example of such disubstituted derivatives in this group.

We report in this paper the synthesis of a number of substituted 1-amino-9-imino-4-nitro-9,10-dihydroacridines in which the chromophore was additionally modified by a methoxy group at position 7. The utilized synthetic procedure is presented in Scheme 1.

Results and Discussion.

The starting acridinones **5** were obtained in a two step synthesis from 2,6-dichloro-3-nitrobenzoic acid [12], according to the methods given by Capps [1,2]. Refluxing of **5** with an excess of phosphorus oxychloride and catalytic amounts of *N,N*-dimethylformamide gave the 1,9-dichloro-4-nitroacridines **6**. In general, **6** are hard to work up because of their sensitivity to hydrolysis. They cannot be stored and must be utilized immediately.

Heating of **6** with phenol and ammonium carbonate gave 9-amino-4-nitro-1-phenoxyacridines **7** with good yields (65-80%) or, in the case of 7-methoxy derivative, 1-chloro-4-nitro-9-phenoxyacridine **8** with 92% yield. The formed product strongly depends on reaction temperature. Compound **8** was formed at temperature 55-60°. Positions of chloro and phenoxy substituents for **8** were deduced by comparison of its ^{1}H nmr spectrum with those of **6a** and **7a**. To confirm the assignments, compound **8** was hydrolized under acidic conditions to give starting acridinone **5a**, identified by mp and ^{1}H nmr data [13]. To obtain the derivatives **7** the reaction temperature was raised to 80°. At still higher temperature (*ca.* 100°) we observed formation of some side products (monitored by tlc on silica gel). In the case of the 7-methoxy derivative, the main side product was isolated and after crystallization from toluene, was identified on the basis of its mass spectrum and elemental analysis results as 1,9-diamino-7-methoxy-4-nitroacridine. Its ^{1}H nmr spectrum indicated that it exists as 1-amino-9-imino-7-methoxy-4-nitro-9,10-dihydroacridine tautomer **11**.

Compounds **7** are stable and served as intermediates for the synthesis of **9**. There is the possibility for occurrence of amino-imino tautomerism in the case of **7**. The ^{1}H nmr spectra proved that **7a** and **7b** exist in solution (dimethyl-d_6 sulfoxide) as 9-amino tautomers (well defined singlet of two 9-amino protons at 8.19 ppm for **7a** and at 8.40 ppm for **7b**). A crystal structure of **7b** confirmed the positions of substituents and revealed that also in the ground state it exists in the same tautomeric form. Unexpectedly, the 4-nitro group was not co-planar with the chromophore but was dramatically twisted [14].

Condensation of **7** with a 3-4 fold excess of a suitable amine, carried out in *N,N*-dimethylformamide at 100°, gave the target 1-amino-9-imino-4-nitro-9,10-dihydroacridines **9a-h** in excellent yields. Two general methods were used to isolate the products: (a) precipitation from reaction mixture after addition of 2*N* aqueous sodium hydroxide or (b) extractive method for compounds with side chain containing diethylamino moiety (see Experimental, example **9d**).

For preparation of disubstituted compounds **10** we used compound **8** as a convenient intermediate, *N,N*-dimethylformamide as the solvent and 6-8 equivalents of the corresponding amine. We have also obtained **10** directly from the dichloro derivative **6a** by heating with phenol and an excess of a suitable amine. However, **8** has the advantage of being more stable for a longer time and to give higher yields of **10**. In the reaction of **8** with 2-dimethylaminoethylamine some unidentified side products were formed (monitored by tlc on silica gel). To avoid formation of side products, in the case of 2-dimethylaminoethylamine the reaction was carried out without a solvent.

The structure of **9** and **10** was assigned on the basis of their ^{1}H nmr spectra. The ^{1}H nmr (300 MHz) data of some selected 1-amino-9-imino compounds are presented in Table I.

It can be seen from the data that, contrary to **7**, compounds **9** exist in solution as 9-imino tautomeric form. Three characteristic downfield, exchangeable signals issued from *N*-bonded protons are apparent for all derivatives **9**. This fact irrefragably argues for the existance of the imino tautomer. Additionally, the very high downfield shifts (triplet at *ca.* 14 ppm and singlet at about 12.2 ppm) suggest that in the molecule of **9** there are two intramolecular hydrogen bonds which stabilize molecule planarity. The triplet (in some cases a singlet) at 14 ppm corresponds to the proton of the 1-amino group which forms an hydrogen bond with the sp^2 nitrogen at position 9, as the triplet is coupled with quadruplet from methylene protons on the α-carbon. The signal at 12 ppm issues from N10-H involved in the hydrogen bond with the oxygen atom of the nitro group at position 4. This is confirmed by the fact that in case of disubstituted compounds **10**, the signal of the 9-imino proton (at *ca.* 10 ppm for all compounds **9**) disappeared and signals of the 1-amino proton and N10-H are shifted a little upfield (*ca.* 13.5 ppm and 11.8 ppm, respectively).

The ^{1}H nmr data for **10** showed significant differences in chemical shifts of protons for both side chains. The

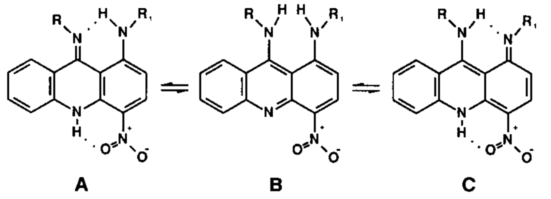


Table I

^{1}H NMR Data of Selected Target Compounds **9** and **10**

Compd.	^{1}H nmr (300 MHz) (∂ ppm, J in Hz) [a], [b]
9 a	14.15 (t, 1H, ex, -NH-CH$_2$-), 12.24 (s, 1H, ex, N10-**H**), 9.92 (s, 1H, ex, =N-**H**), 8.11 (d, 1H, J=10.0, C3-**H**), 7.77 (d, 1H, J=2.7, C8-**H**), 7.66 (d, 1H, J=8.9, C5-**H**), 7.23 (dd, 1H, J=8.9, J=2.7, C6-**H**), 6.48 (d, 1H, J=10.0, C2-**H**), 3.87 (s, 3H, -OCH$_3$), 3.50 (qu*, 2H, -NH-CH$_2$-CH$_2$-), 2.58 (t, 2H, -CH$_2$-CH$_2$-NMe$_2$), 2.23 (s, 6H, -N (CH$_3$)$_2$)
9 b	14.12 (t, 1H, ex, -NH-CH$_2$-), 12.26 (s, 1H, ex, N10-H), 9.90 (s, 1H, ex, =N-**H**), 8.10 (d, 1H, J=9.9, C3-**H**), 7.74 (d, 1H, J=2.4, C8-**H**), 7.64 (d, 1H, J=9.1, C5-**H**), 7.22 (dd, 1H, J=9.1, J=2.4, C6-**H**), 6.46 (d, 1H, J=10.0, C2-**H**), 3.87 (s, 3H, -OCH$_3$), 3.46 (qu*, 2H, -NH-CH$_2$-CH$_2$-), 2.71 (t, 2H, -CH$_2$-CH$_2$-NEt$_2$), 2.56 (qu, 4H, -N (CH$_2$-CH$_3$) $_2$), 1.00 (t, 6H, -N (CH$_2$-CH$_3$) $_2$)
9c	14.30 (s, 1H, ex, -NH-CH$_2$-), 12.28 (s, 1H, ex, N10-**H**), 9.92 (s, 1H, ex, =N-**H**), 8.11 (d, 1H, J=10.0, C3-**H**), 7.75 (d, 1H, J=2.7, C8-**H**), 7.68 (d, 1H, J=8.9, C5-**H**), 7.25 (dd, 1H, J=8.9, J=2.7, C6-**H**), 6.48 (d, 1H, J=10.1, C2-**H**), 3.87 (s, 3H, -OCH$_3$), 3.44 (t, 2H, -NH-CH$_2$-CH$_2$-), 2.37 (t, 2H, -CH$_2$-CH$_2$-NMe$_2$), 2.17 (s, 6H, -N (CH$_3$) $_2$), 1.81 (qt, 2H, -CH$_2$-CH$_2$-CH$_2$-)
9e	13.96 (t, 1H, ex, -NH-CH$_2$-), 12.18 (s, 1H, ex, N10-**H**), 10.08 (s, 1H, ex, =N-**H**), 8.29 (d, 1H, C8-**H**), 8.17 (d, 1H, J=10.1, C3-**H**), 7.68 (d, 1H, C5-**H**), 7.60 (t, 1H, C6-**H**), 7.31 (t ,1H, C7-**H**), 6.55 (d, 1H, J=10.0, C2-**H**), 3.52 (qu*, 2H, -NH-CH$_2$-CH$_2$-), 2.58 (t, 2H, -CH$_2$-CH$_2$-NMe$_2$), 2.23 (s, 6H, -N (CH$_3$) $_2$)
10a	13.26 (t, 1H, ex, -NH-CH$_2$-), 11.80 (s, 1H, ex, N10-**H**), 8.10 (d, 1H, J=9.8, C3-**H**), 7.62 (d, 1H, J=9.0, C5-**H**), 7.54 (d, 1H, J=2.5, C8-**H**), 7.22 (dd, 1H, J=9.0, J=2.7, C6-**H**), 6.47 (d, 1H, J=10.0, C2-**H**), 4.10 (I) (t, 2H, =N-CH$_2$-CH$_2$-), 3.82 (s, 3H, -OCH$_3$), 3.43 (A) (qu*, 2H, -NH-CH$_2$-CH$_2$-), 2.62 (I) (t, 2H, -CH$_2$-CH$_2$-NMe$_2$), 2.54 (A) (t, 2H, -CH$_2$-CH$_2$-), 2.23 (I or A) (s, 6H, -N (CH$_3$) $_2$), 2.22 (I or A) (s, 6H, -N (CH$_3$)$_2$
10b	13.58 (t, 1H, ex, -NH-CH$_2$-), 11.80 (s, 1H, ex, N10-**H**), 8.10 (d, 1H, J=9.9, C3-**H**), 7.62 (d, 1H, J=8.8, C5-**H**), 7.52 (d, 1H, J=2.7, C8-**H**), 7.23 (dd, 1H, J=8.8, J=2.5, C6-**H**), 6.48 (d, 1H, J=10.0, C2-**H**), 4.08 (I) (t, 2H, =N-CH$_2$- CH$_2$-), 3.82 (s, 3H, -OCH$_3$), 3.43 (A) (qu*, 2H, -NH-CH$_2$-CH$_2$-) , 2.76 (I) (t, 2H, -CH$_2$-CH$_2$-NEt$_2$), 2.67 (A) (t, 2H, -CH$_2$-CH$_2$-), 2.57 (I, A) (m, 8H, -N (CH$_2$-CH$_2$) $_3$), 0.98 (I, A) (m, 12H, -N (CH$_2$-CH$_3$) $_2$)
10c	13.58 (t, 1H, ex, -NH-CH$_2$-), 11.86 (s, 1H, ex, N10-**H**), 8.08 (d, 1H, J=9.8, C3-**H**), 7.60 (d, 1H, J=9.1, C5-**H**), 7.50 (d, 1H, J=2.7, C8-**H**), 7.23 (dd, 1H, J=9.0, J=2.6, C6-**H**), 6.45 (d, 1H, J=9.9, C2-**H**), 4.01(I) (t, 2H, =N-CH$_2$-CH$_2$-), 3.81 (s, 3H, -OCH$_3$), 3.38 (A) (qu*, 2H, -NH-CH$_2$-CH$_2$-), 2.34 (I, A) (m, 4H, -CH$_2$-CH$_2$-NMe$_2$), 2.15 (I or A) (s, 6H, -N (CH$_3$)$_2$), 2.13 (I or A) (s, 6H, -N (CH$_3$) $_2$), 1.84 (I, A) (m, 4H, -CH$_2$-CH$_2$-CH$_2$-)
10d	13.52 (br s, 1H, ex, -NH-CH$_2$-), 11.84 (s, 1H, ex, N10-**H**), 8.10 (d, 1H, J=9.9, C3-**H**), 7.58 (d,1H, J=9.0, C5-**H**), 7.52 (d, 1H, J=2.7, C8-**H**), 7.23 (dd, 1H, J=9.0, J=2.7, C6-**H**), 6.46 (d, 1H, J=9.9, C2-**H**), 4.05 (I) (t, 2H, =N-CH$_2$-CH$_2$-), 3.82 (s, 3H, -OCH$_3$), 3.40 (A) (t, 2H, -NH-CH$_2$-CH$_2$-), 2.51 (I, A) (m, 4H, -CH$_2$-CH$_2$-NEt$_2$), 2.47 (I, A) (t, 8H, -N (CH$_2$-CH$_3$) $_2$), 1.85 (I,A) (m, 4H, -CH$_2$-CH$_2$-CH$_2$-), 0.95 (I, A) (m, 12H, -N (CH$_2$-CH$_3$) $_2$)

[a] Solvent: hexadeuteriodimethyl sulfoxide. For abbreviations see EXPERIMENTAL.

[b] For compounds **10** the ∂ values related to amino side chain are labeled with (A) and those ones related to imino side chain with (I).

most striking is the difference of *ca.* 0.65 ppm for signals of the methylene protons on the carbons bonded to both proximal nitrogens (*e.g.* 4.08 ppm for 9-imino chain versus 3.43 ppm for 1-amino chain in case of compound **10b**). This fact once again confirms the imino structure of **10**. None the less, it is not sufficient for correct structure determination. In fact, one can imagine three tautomeric forms for compounds **9** and **10** (structures **A**, **B** and **C**).

The structure **B** must be rejected from consideration as, first, it seems the least stable (steric hindrance between positions 1 and 9) and, second, it does not fit the three observed signals at 14 ppm, 12 ppm and 10 ppm. For both structures **A** and **C** the chemical shifts related to the methylene protons and N-bounded protons could be the same. However, in the case of structure **C** the signal of the aromatic proton at position 2 should be shifted downfield in comparison with **A**. For all our compounds **9** and **10**, the chemical shifts of the proton at position 2 altered very slightly and were *ca.* 6.5 ppm. Similarly, the signals of the methylene protons on the α-carbon in the amino chain were in every case at *ca.* 3.5 ppm. This is in excellent accord with that ones found for the "imino-like" compounds **1** which constitute 9-oxo analogues of structure **A** (*e.g.* 6.59 ppm and 3.52 ppm, respectively, for compound **3** from ref [7] or 6.54 ppm and 3.49 ppm, respectively, for 1-[[2-(diethylamino)ethyl]amino]-7-methoxy-4-nitro-9(10*H*)-acridinone [15]), and finally point out the correctness of structure **A** for our compounds **9** and **10**.

In summary, we have reported a convenient method for the synthesis of the imino analogues of antitumor agents **1** and **2** as well as their ^{1}H nmr characterization. The results of antineoplastic activity of these compounds against murine L1210 leukemia *in vitro* and P388 leukemia *in vivo* will be reported in a separate paper.

EXPERIMENTAL

Melting points were taken on a Büchi 510 capillary melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Varian VXR-300 spectrometer operating at 300 MHz. Chemical shifts are reported as δ units in parts per million downfield from internal tetramethylsilane. The ^{1}H nmr abbreviations used are as follows: br (broad), s (singlet), d (doublet), t (triplet), qu (quartet), qt (quintet), m (multiplet), ex (exchangeable with deuterium oxide). Quartets that are transformed into triplets by addition of deuterium oxide are labeled with an asterisk (*). Single frequency decoupling was utilized to assign specific protons. Mass spectra were determined with a WG 7070 spectrometer using the direct insertion method and electron-impact at an ionizing voltage of 70 eV. Elemental analysis were performed by Laboratory of Elemental Analysis, Department of Chemical Sciences, University of Camerino and were within + 0.4% of the calculated values.

1,9-Dichloro-7-methoxy-4-nitroacridine (**6a**).

A mixture of 9.14 g (30 mmoles) of 1-chloro-7-methoxy-4-nitro-9(10*H*)-acridinone [2], 40 ml of phosphorus oxychloride and 0.2 ml of *N,N*-dimethylformamide was heated at reflux for 4 hours, then the solvent was evaporated. The obtained yellow solid was stirred with 50 ml of 1,4-dioxane, put into diluted ammonium hydroxide and crushed ice (about 200 g) and vigorously stirred for 5 minutes. The yellow crystals were collected by filtration, washed successively with water and acetone, dried *in vacuo* at room temperature and crystallized from toluene to give 8.52 g (88%) of analytically pure **6a**, mp 248-250° (reported [2] mp 243-246°); ^{1}H nmr (DMSO-d$_6$); δ 8.31 (d, 1H, J = 8.0, C3-**H**), 8.10 (d, 1H, J = 9.4, C5-**H**), 8.00 (d, 1H, J = 8.0, C2-**H**), 7.75 (dd, 1H, J = 9.4, J = 2.7, C6-**H**), 7.71 (d, 1H, J = 2.5, C8-**H**), 4.07 (s, 3H, -OC**H**$_3$).

Anal. Calcd. for $C_{14}H_8Cl_2N_2O_3$: C, 52.03; H, 2.49; N, 8.67. Found: C, 52.01; H, 2.45; N, 8.54.

1,9-Dichloro-4-nitroacridine (**6b**) was obtained in an analogous manner from 1-chloro-4-nitro-9(10*H*)-acridinone [2] in a yield of 74%, mp 208-210° (from toluene); ms: Calcd. Mass for $C_{13}H_6Cl_2N_2O_2$: 291.98063. Found: m/z 291.98008; ^{1}H nmr (DMSO-d$_6$): δ 8.57 (d, 1H), 8.32 (d, 1H, J = 8.1, C3-**H**), 8.15 (d, 1H), 8.05 (m, 1H), 8.00 (d, 1H, J = 8.1, C2-**H**), 7.90 (m, 1H).

Anal. Calcd. for $C_{13}H_6Cl_2N_2O_2$: C, 53.27; H, 2.06; N, 9.56. Found: C, 53.34; H, 2.10; N, 9.45.

9-Amino-7-methoxy-4-nitro-1-phenoxyacridine (**7a**).

A mixture of 94 g (1 mole) of freshly distilled phenol, 6.46 g (20 mmoles) of **6a** and 2.4 g (25 mmoles) of ammonium carbonate was gradually heated to 80° and stirred at this temperature for 2 hours. After cooling to 25°, 500 ml of 3*N* aqueous sodium hydroxide were added and stirred for 10 minutes. The precipitated product was collected by filtration and washed with water until neutral. The crude product was crystallized twice from acetone-water to give 5.78 g (80%) of **7a**, red crystals, mp 216-218°; ^{1}H nmr (DMSO-d$_6$): δ 8.19 (s, 2H, ex, -N**H**$_2$), 7.90 (d, 1H, J = 8.3, C3-**H**), 7.77 (d, 1H, J = 2.5, C8-**H**), 7.73 (d, 1H, J = 9.3, C5-**H**), 7.45 (dd, 1H, J = 9.3, J = 2.5, C6-**H**), 7.60-7.36 (m, 5**H**), 6.27 (d, 1H, J = 8.3, C2-**H**), 3.96 (s, 3H, -OC**H**$_3$).

Anal. Calcd. for $C_{20}H_{15}N_3O_4$: C, 66.47; H, 4.18; N, 11.63. Found: C, 66.67; H, 4.18; N, 11.56.

9-Amino-4-nitro-1-phenoxyacridine (**7b**) was obtained in an analogous manner from **6b**, in a yield of 65%, mp 200-201° (from acetone-water); ^{1}H nmr (DMSO-d$_6$): δ 8.51 (d, 1H, C8-**H**), 8.40 (s, 2H, ex, -N**H**$_2$), 7.96 (d, 1H, J = 8.3, C3-**H**), 7.76-7.38 (m, 8H), 6.26 (d, 1H, J = 8.3, C2-**H**).

Anal. Calcd. for $C_{19}H_{13}N_3O_3$: C, 68.87; H, 3.95; N, 12.68. Found: C, 68.80; H, 3.91; N, 12.60.

1-Chloro-7-methoxy-4-nitro-9-phenoxyacridine (**8**).

A mixture of 45 g of freshly distilled phenol, 6.46 g (20 mmoles) of **6a** and 1.5 g (15 mmoles) of ammonium carbonate was slowly heated to 60° and stirred at this temperature for 30 minutes. To the reaction mixture 50 ml of acetone were added. The solid was collected by filtration, washed with 100 ml of 10% aqueous potassium hydroxide, water and acetone. The product was dried *in vacuo* at a temperature of 30° and crystallized from toluene to give 7.0 g (92%) of **8** as yellow crystals, mp 268-270°; ^{1}H nmr (DMSO-d$_6$): δ 8.31 (d, 1H, J = 8.0, C3-**H**), 8.13 (d, 1H, J = 9.4, C5-**H**), 7.84 (d, 1H, J = 8.0, C2-**H**), 7.68 (dd, 1H, J = 9.4, J = 2.7, C6-**H**), 7.16 (d, 1H, J = 2.7, C8-**H**), 7.33, 7.09, 6.92 (dd, 2H; t, 1H; dd, 2H, respectively), 3.74 (s, 3H, -OC**H**$_3$).

Anal. Calcd. for $C_{20}H_{13}ClN_2O_4$: C, 63.08; H, 3.44; N, 7.36. Found: C, 63.34; H, 3.54; N, 7.12.

1-Amino-9-imino-7-methoxy-4-nitro-9,10-dihydroacridine (**11**).

A mixture of 4.5 g of phenol, 323 mg (1 mmole) of **6a** and 1.2 g (1.25 mmoles) of ammonium carbonate was stirred at 100° for 2 hours. After cooling to 25°, 50 ml of 3*N* aqueous sodium hydroxide was added and the mixture was stirred for 10 minutes. The precipitated solid was collected by filtration and washed with water. The solid was triturated with 50 ml of acetone and filtered. The orange residue was crystallized twice from toluene to give 98 mg (34%) of **11** as red crystals, mp 253-256° dec; ms: Calcd. Mass for $C_{14}H_{12}N_4O_3$: 284.09093. Found: m/z 284.09010; ^{1}H nmr (DMSO-d_6): δ 12.54 (s, 1H, ex), 12.00 (br s, 1H, ex), 10.00 (br s, 1H, ex), 8.56 (br s, 1H, ex), 8.06 (d, 1H, J = 9.7, C3-**H**), 7.75 (d, 1H, J = 2.7, C8-**H**), 7.65 (d, 1H, J = 9.0, C5-**H**), 7.23 (dd, 1H, J = 9.0, J = 2.7, C6-**H**), 6.40 (d, 1H, J = 9.7, C2-**H**), 3.86 (s, 3H, -OCH$_3$).

Anal. Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.26; N, 19.71. Found: C, 58.86; H, 4.19; N, 19.38.

1-[[3-(Dimethylamino)propyl]amino]-9-imino-7-methoxy-4-nitro-9,10-dihydroacridine (**9c**).

A mixture of 722 mg (2 mmoles) of **7a**, 3 ml of *N,N*-dimethylformamide and 820 mg (8 mmoles) of 3-dimethylamino-1-propylamine was heated for 2 hours at 100°. To the hot reaction mixture 25 ml of 2*N* aqueous sodium hydroxide were added and stirring was continued for 10 minutes. The precipitated solid was collected by filtration, washed with water and crystallized from acetone-water to give 680 mg (92%) of **9c**, orange crystals, mp 170-171°; ^{1}H nmr: (Table I).

Anal. Calcd. for $C_{19}H_{23}N_5O_3$: C, 61.77; H, 6.27; N, 18.96. Found: C, 61.86; H, 6.36; N, 18.82.

The following compounds were obtained in an analogous manner:

1-[[2-(Dimethylamino)ethyl]amino]-9-imino-7-methoxy-4-nitro-9,10-dihydroacridine (**9a**).

This compound was obtained in a yield of 84%, orange crystals, mp 186-188° (from acetone-water); ^{1}H nmr: (Table I).

Anal. Calcd. for $C_{18}H_{21}N_5O_3$: C, 60.83; H, 5.96; N, 19.71. Found: C, 60.56; H, 5.93; N, 19.45.

1-[[2-(Diethylamino)ethyl]amino]-9-imino-7-methoxy-4-nitro-9,10-dihydroacridine (**9b**).

This compound was obtained in a yield of 86%, orange-red crystals, mp 148-150° (from acetone-water); ^{1}H nmr: (Table I).

Anal. Calcd. for $C_{20}H_{25}N_5O_3$: C, 62.64; H, 6.57; N, 18.27. Found: C, 62.36; H, 6.53; N, 18.08.

1-[[2-(Dimethylamino)ethyl]amino]-9-imino-4-nitro-9,10-dihydroacridine (**9e**).

This compound was obtained in a yield of 92%, orange crystals, mp 206-207° (from dioxane-water); ^{1}H nmr: (Table I).

Anal. Calcd. for $C_{17}H_{19}N_5O_2$: C, 62.74; H, 5.88; N, 21.53. Found: C, 62.68; H, 5.94; N, 21.41.

1-[[3-(Dimethylamino)propyl]amino]-9-imino-4-nitro-9,10-dihydroacridine (**9g**).

This compound was obtained in a yield of 89%, orange crystals, mp 135-136° (from dioxane-water); ^{1}H nmr (DMSO-d_6): δ 14.10 (s, 1H, ex), 12.18 (s, 1H, ex), 10.02 (s, 1H, ex), 8.26 (d, 1H), 8.13 (d, 1H, J = 10.0, C3-**H**), 7.61 (m, 2H), 7.30 (m, 1H), 6.49 (d, 1H, J = 10.0, C2-**H**), 3.42 (t, 2H, -NH-C**H**$_2$-CH$_2$), 2.35 (t, 2H, -CH$_2$-C**H**$_2$-NMe$_2$), 2.16 (s, 6H, -N(C**H**$_3$)$_2$), 1.79 (qt, 2H, -CH$_2$-C**H**$_2$-CH$_2$-).

Anal. Calcd. for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N, 20.64. Found: C, 63.68; H, 6.25; N, 20.64.

1-[[3-(Diethylamino)propyl]amino]-9-imino-7-methoxy-4-nitro-9,10-dihydroacridine (**9d**).

A mixture of 722 mg (2 mmoles) of **7a**, 3 ml of *N,N*-dimethylformamide and 1.04 g (8 mmoles) of 3-diethylamino-1-propylamine was heated for 4 hours at 100°. After cooling, 100 ml of chloroform and 25 ml of 2*N* aqueous sodium hydroxide were added and the reaction mixture was vigorously shaken. To the separated chloroform layer 150 ml of water were added and acidified with L-lactic acid to *p*H 4. After shaking, the aqueous layer was separated and, after removal by evaporation of chloroform residue, was made basic with aqueous sodium hydroxide. The precipitated product was collected by filtration, washed with water and crystallized from acetone-water to give 640 mg (79%) of red crystals of **9d**, mp 120-121°; ^{1}H nmr (DMSO-d_6): δ 14.22 (s, 1H, ex), 12.22 (s, 1H, ex), 9.88 (s, 1H, ex), 8.06 (d, 1H, J = 10.0, C3-**H**), 7.66 (d, 1H, J = 2.7, C8-**H**), 7.55 (d, 1H, J = 8.9, C5-**H**), 7.19 (dd, 1H, J = 8.9, J = 2.7, C6-**H**), 6.40 (d, 1H, J = 10.0, C2-**H**), 3.84 (s, 3H, -OC**H**$_3$), 3.37 (t, 2H, -NH-C**H**$_2$-CH$_2$), 2.49 (t, 2H, -CH$_2$-C**H**$_2$-NEt$_2$), 2.44 (qu, 4H, -N(C**H**$_2$-CH$_3$)$_2$), 0.94 (t, 6H, -N(CH$_2$-C**H**$_3$)$_2$).

Anal. Calcd. for $C_{21}H_{27}N_5O_3$: C, 63.45; H, 6.85; N, 17.62. Found: C, 63.15; H, 6.81; N, 17.30.

The following compounds were obtained in an analogous manner:

1-[[2-(Diethylamino)ethyl]amino]-9-imino-4-nitro-9,10-dihydroacridine (**9f**).

This compound was obtained in a yield of 94%, mp 145-146° (from dioxane-water); ^{1}H nmr (DMSO-d_6): δ 13.90 (br s, 1H, ex), 12.12 (s, 1H, ex), 9.96 (s, 1H, ex), 8.25 (d, 1H), 8.13 (d, 1H, J = 10.0, C3-**H**), 7.60 (m, 2H), 7.29 (m, 1H), 6.49 (d, 1H, J = 10.0, C2-**H**), 3.50 (t, 2H, -NH-C**H**$_2$-CH$_2$), 2.72 (t, 2H, -CH$_2$-C**H**$_2$-NEt$_2$), 2.56 (qu, 4H, -N(C**H**$_2$-CH$_3$)$_2$), 1.00 (t, 6H, -N(CH$_2$-C**H**$_3$)$_2$).

Anal. Calcd. for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.80; H, 6.70; N, 20.01.

1-[[3-(Diethylamino)propyl]amino]-9-imino-4-nitro-9,10-dihydroacridine (**9h**).

This compound was obtained in a yield of 86%, mp 111-112° (from acetone-water); ^{1}H nmr (DMSO-d_6): δ 14.06 (t, 1H, ex), 12.12 (s, 1H, ex), 10.00 (s, 1H, ex), 8.26 (d, 1H), 8.13 (d, 1H, J = 10.0, C3-**H**), 7.64 (d, 1H), 7.58 (t, 1H), 7.29 (t, 1H), 6.48 (d, 1H, J = 10.0, C2-**H**), 3.42 (qu*, 2H, -NH-C**H**$_2$-CH$_2$), 2.50 (t, 2H, -CH$_2$-C**H**$_2$-NEt$_2$), 2.48 (qu, 4H, N(C**H**$_2$-CH$_3$)$_2$), 1.76 (qt, 2H, -CH$_2$-C**H**$_2$-CH$_2$), 0.95 (t, 6H, -N(CH$_2$-C**H**$_3$)$_2$).

Anal. Calcd. for $C_{20}H_{25}N_5O_2$: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.44; H, 6.87; N, 18.98.

1-[[2-(Dimethylamino)ethyl]amino]-9-[[2-(dimethylamino)ethyl]imino]-7-methoxy-4-nitro-9,10-dihydroacridine (**10a**).

To 2.2 g (25 mmoles) of 2-dimethylaminoethylamine vigorously stirred at 60°, 381 mg (1 mmole) of **8** was added and stirring was continued for 15 minutes. Then, 15 ml of methanol was added and the mixture was refluxed to complete dissolution of precipitate. The solution was left overnight at room temperature. Orange crystals were collected by filtration, washed with water and recrystallized from acetone-water to give 340 mg (80%) of **10a** as orange needles, mp 146-149°; ^{1}H nmr: (Table I).

Anal: Calcd. for $C_{22}H_{30}N_6O_3$: C, 61.95; H, 7.09; N, 19.71. Found: C, 62.16; H, 7.40; N, 19.54.

1-[[2-(Diethylamino)ethyl]amino]-9-[[2-(diethylamino)ethyl]imino]-7-methoxy-4-nitro-9,10-dihydroacridine (**10b**).

A mixture of 381 mg (1 mmole) of **8**, 2 ml of *N,N*-dimethylformamide and 700 mg (6 mmoles) of 2-diethylaminoethylamine was stirred for 45 minutes at 80°. After cooling to 25°, 20 ml of 2*N* aqueous sodium hydroxide was added and the mixture was stirred for 15 minutes. The precipitated product was collected by filtration and washed with water. Crystallization from acetone-water gave 404 mg (82%) of **10b** as red crystals, mp 117-118°; ^{1}H nmr: (Table I).

Anal. Calcd. for $C_{26}H_{38}N_6O_3$: C, 64.70; H, 7.94; N, 17.42. Found: C, 65.03; H, 8.12; N, 17.49.

The following compounds were obtained in an analogous manner:

1-[[3-(Dimethylamino)propyl]amino-9-[[3-(dimethylamino)propyl]-imino-7-methoxy-4-nitro-9,10-dihydroacridine (**10c**).

This compound was obtained in a yield of 76%, red crystals, mp 122-124° (from acetone-water); ^{1}H nmr: (Table I).

Anal. Calcd. for $C_{24}H_{34}N_6O_3$: C, 63.41; H, 7.54; N, 18.49. Found: C, 63.46; H, 7.56; N, 18.19.

1-[[3-(Diethylamino]propyl]amino]-9-[[3-(diethyamino)propyl)-imino]-7-methoxy-4-nitro-9,10-dihydroacridine (**10d**).

This compound was obtained in a yield of 73%, orange crystals, mp 77-78° (from acetone-water by condensation); ^{1}H nmr: (Table I).

Anal. Calcd. for $C_{28}H_{42}N_6O_3$: C, 65.85; H, 8.29; N, 16.46. Found: C, 65.96; H, 8.43; N, 16.45.

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