The Synthesis of a New Polycyclic Heterocyclic Ring System: Pyrimido[5,6,1-*d,e*]acridine

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The synthesis of a new heterocylic ring system is reported. The condensation of 9,10-dihydro-9-oxo-4-acridine carboxamide (**7**) with diethoxymethyl acetate gave pyrimido[5,6,1-*d,e*]acridine-3,7-dione (**8**). The amide **7** reacts with ethyl chloroformate to afford 2*H*-pyrimido[5,6,1-*d,e*]acridine-1,3,7-trione (**9**).

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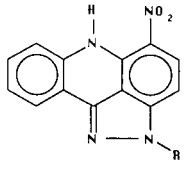
One of the most important classes of antitumor drugs, the DNA intercalating agents, usually possess a planar aromatic or heteroaromatic polycyclic system with one or two flexible cationic side chains in the appropriate position. Among them acridines represent one of the groups early and most thoroughly investigated [1-5].

The search of new chromophores was stimulated by the recent success in antitumor activity obtained with some acridine derivatives in which the chromophore moiety is the acridine ring condensed with an additional heterocyclic ring. So far, the most interesting results were obtained with pyrazoloacridines **1** [6,7], imidazoacridinones **2** [8], and triazoloacridinones **3** [9]. For acridine derivatives fused with six membered rings no data are available.

For these reasons we decided to investigate the synthesis of the new heterocyclic system pyrimido[5,6,1-*d,e*]-acridine (**4**) which appears to be an interesting chromophore for new potential antitumor compounds.



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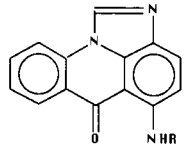

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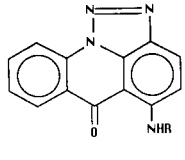

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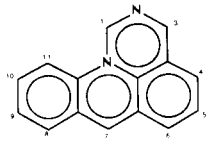

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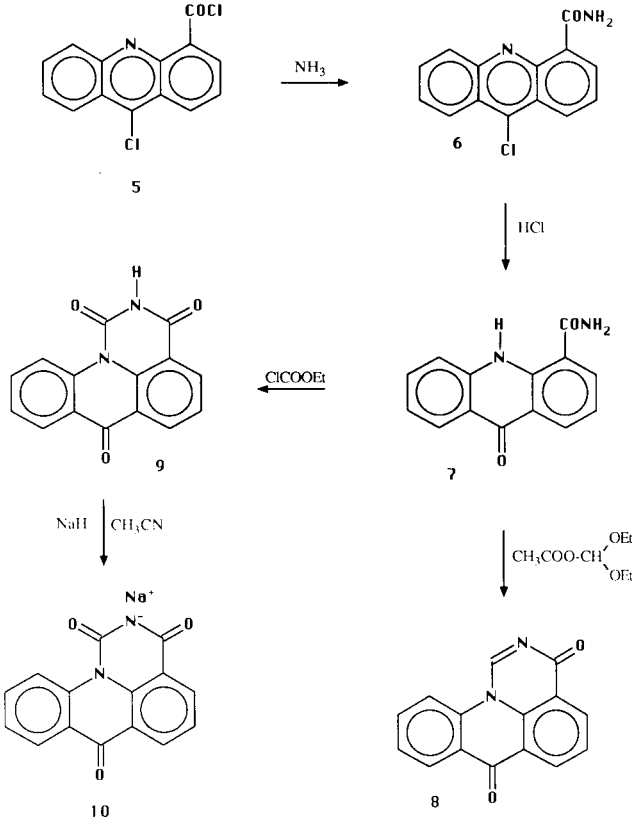
In this paper we report the synthesis of two derivatives of **4**, the pyrimido[5,6,1-*d,e*]acridine-3,7-dione (**8**) and the pyrimido[5,6,1-*d,e*]acridine-1,3,7-trione (**9**), according to the Scheme:

Scheme



The synthesis of 9,10-dihydro-9-oxo-4-acridinecarboxamide (**7**) has been previously described [10], but the method was complex and the total yield was poor. Thus we preferred to prepare the amide **7** starting from the 9-chloro-4-acridinecarbonyl chloride (**5**) [3]. By treatment with ammonia, under controlled conditions, **5** gave the 9-chloro-4-acridine carboxamide (**6**). Also this compound has been previously reported [11] but without information about the synthesis and the characterization. The reaction of **6** with hydrochloric acid afforded the desired derivative **7** in almost quantitative yields. The carboxamide **7** heated in diethoxymethyl acetate gave the pyrimido[5,6,1-*d,e*]-acridine-3,7-dione (**8**).

Attempts to cyclize **7** either with triethyl orthoformate or with formamidine acetate under various experimental conditions failed.

Condensation of **7** with ethyl chloroformate gave 2*H*-pyrimido[5,6,1-*d,e*]acridine-1,3,7-trione (**9**).

The structures of compounds **8** and **9** were confirmed by the ^{1}H- and ^{13}C-nmr spectra and by the elemental analyses. For the acridinetrione **9** proton assignment was also made on the basis of a COSY experiment [12].

All attempts to obtain *N*-alkyl derivatives of the chromophore **9** as potential antitumor drugs, performed under different experimental conditions, failed. In order to increase the reactivity the acridinetrione **9** was transformed into the corresponding sodium salt **10** by treatment with sodium hydride in acetonitrile. Unexpectedly, it was impossible to obtain **10** by using potassium carbonate or sodium hydroxide or sodium in ethanol. Furthermore efforts to alkylate **10** with dimethylaminoethyl chloride, under various experimental conditions, failed.

EXPERIMENTAL

Melting points were determined with a Büchi 510 capillary melting point apparatus and are uncorrected. Thin layer chromatography (tlc) was accomplished on plates pre-coated with silica gel 60 F-254 by Merck. The ir spectra were recorded on a Perkin Elmer 297 spectrophotometer. The ^{1}H and ^{13}C nmr spectra were recorded on a Varian VXR 300 spectrometer using deuteriodimethyl sulfoxide as the solvent. Chemical shifts are reported as δ units in part per million downfield from internal tetramethylsilane. The following abbreviations were used to designate the multiplicity of individual signals: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. Elemental analyses were performed by laboratory of Elemental Analyses, Department of Chemical Sciences, University of Camerino on a Elemental Analyzer Model 1106 by Carlo Erba Strumentazione and were within ± 0.4% of the calculated values.

9,10-Dihydro-9-oxo-4-acridinecarboxamide (**7**).

To a solution of 9-chloro-4-acridinecarbonyl chloride (**5**) [3] (1 g, 3.6 mmoles) in dichloromethane (10 ml), cooled at -5°, a saturated solution of dry ammonia in dichloromethane (20 ml) was added dropwise. The mixture was stirred at room temperature for 30 minutes, and the solid precipitated was filtered to yield the crude 9-chloro-4-acridine carboxamide (**6**) [11], Rf = 0.41 (ethyl acetate-benzene 1:1); ^{1}H nmr: δ 7.90 (m, 2H, aromatic protons), 8.05 (m, 1H, aromatic proton), 8.09 (s, 1H, amide proton, deuterium oxide exchangeable), 8.38 (m, 1H, aromatic proton), 8.49 (m, 1H, aromatic proton), 8.67 (m, 1H, aromatic proton), 8.78 (m, 1H, aromatic proton), 10.29 (s, 1H, amide proton, deuterium oxide exchangeable). A solution of 2*N* hydrochloric acid (10 ml) was added to the crude chlorocarboxamide **6** suspended in hot methanol (100 ml). The initial dissolution was followed by crystallization of a solid which was filtered and washed with methanol to afford the pure amidoacridinone **7** (0.8 g, 93%), mp 288-291° dec [lit 292-294° dec]; Rf = 0.26 (ethyl acetate-benzene 3:2); ^{1}H nmr: δ 7.33 (m, 2H, aromatic protons), 7.73 (m, 2H, aromatic protons), 7.91 (br s, 1H, amide proton, deuterium oxide exchangeable), 8.23 (m, 1H, aromatic proton), 8.31 (m, 1H, aromatic proton), 8.45 (m, 1H, aromatic proton), 8.51 (br s, 1H, amide proton, deuterium oxide exchangeable), 12.74 (s, 1H, 10-H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{10}N_2O_2 \cdot 0.5\ H_2O$: C, 67.95; H, 4.45; N, 11.33. Found: C, 68.25; H, 4.13; N, 11.18.

Pyrimido[5,6,1-*d,e*]acridine-3,7-dione (**8**).

The amide **7** (1 g, 4.2 mmoles) in diethoxy methyl acetate (50 ml) was heated at 120° for 5 hours, then the solvent was evaporated under reduced pressure. Dimethyl sulfoxide (10 ml) was added to the residue and the mixture was heated at about 120° and stirred for 10 minutes, then cooled at room temperature. The resulting solid was filtered and washed with methanol and then with diethyl ether to yield pure **8** (0.6 g, 58%), mp > 300°; Rf = 0.52 (ethyl acetate-benzene 1:1); ^{1}H nmr: δ 7.34 (m, 2H, aromatic protons), 7.77 (m, 2H, aromatic protons), 8.23 (d, 1H, aromatic proton), 8.35 (d, 1H, aromatic proton), 8.52 (d, 1H, aromatic proton), 9.35 (s, 1H, H-1); ^{13}C nmr: δ 117.057, 118.409, 119.995, 120.444, 121.416, 122.414, 125.740, 132.144, 134.181, 135.075, 139.918, 139.997, 164.144 (C-1), 169.014, 176.478.

Anal. Calcd. for $C_{15}H_8N_2O_2 \cdot 1.5\ H_2O$: C, 65.40; H, 4.00; N, 10.17. Found: C, 65.10; H, 3.97; N, 9.95.

2*H*-Pyrimido[5,6,1-*d,e*]acridine-1,3,7-trione (**9**).

The amide **7** (1 g, 4.2 mmoles) in ethyl chloroformate (10 ml) was refluxed for 2 days. After cooling a solid precipitated which was filtered, washed with methanol and then with diethyl ether to afford the pure acridinetrione **9** (0.98 g, 88%), mp 266-267° dec; Rf = 0.62 (benzene - ethyl acetate 7:3); ^{1}H nmr: δ 7.35 (m, 1H, H-9, aromatic proton), 7.38 (t, 1H, H-5, aromatic proton), 7.80 (m, 1H, H-10, aromatic proton), 8.01 (d, 1H, H-11, aromatic proton), 8.22 (m, 1H, H-8, aromatic proton), 8.25 (m, 1H, H-6 or H-4, aromatic proton), 8.53 (m, 1H, H-4 or H-6, aromatic proton), 11.58 (s, 1H, 2-H, imide proton, deuterium oxide exchangeable); ^{13}C nmr: δ 99.1839, 116.3829, 118.5021, 120.8424, 121.0393, 122.4967, 125.7443, 132.0704, 134.1015, 139.7334, 140.8492, 141.1325, 176.1184.

Anal. Calcd. for $C_{15}H_8N_2O_3 \cdot 2H_2O$: C, 60.00; H, 4.03; H, 9.33. Found: C, 60.32; H, 3.64; N, 9.63.

Sodium Salt of 2*H*-Pyrimido[5,6,1-*d,e*]acridine-1,3,7-trione (**10**).

To compound **9** (0.1 g, 0.38 mmole) in anhydrous acetonitrile (5 ml), 60% sodium hydride in mineral oil (0.028 g, 0.7 mmole) was added. The mixture was stirred at room temperature for 30 minutes, then filtered to obtain the sodium salt **10** (0.105 g, 97%); ^{1}H nmr: δ 6.97 (t, 1H, aromatic proton), 7.03 (m, 1H, aromatic proton), 7.52 (m, 1H, aromatic proton), 7.64 (d, 1H, aromatic proton), 7.94 (d, 1H, aromatic proton), 8.18 (m, 1H, aromatic proton), 8.41 (m, 1H, aromatic proton).

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