Formation and Molecular Structure of the Novel Acridine Substituted Uracil Derivatives

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The reaction of enamine between 9-chloroacridines and 6-aminouracil derivatives gives the novel acridine substituted uracils, the structure of which has been determined by X-ray crystallography.

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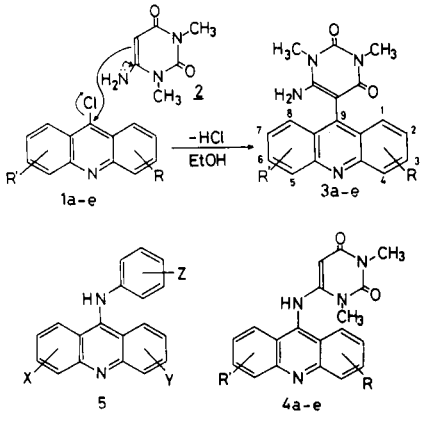
One of the important phenomenon of DNA is that of their reversible binding ability to accept planar molecules which can be inserted between the base pairs of the double helix [1-4]. Many of these intercalators are mutagens or compounds that have other significant biological and phisico-chemical properties [5-9]. It is thus of considerable interest to find the new type intercalators and understand the detailed manner in which the intercalator is found within the confines of a double helical structure. The recent synthesis and study of the 9-anilinoacridines **5** [10-19] which have antibacterial, antimalarial, mutagenic and carcinogenic properties by intercalating to DNA encouraged us to investigate the synthesis of the novel acridine derivatives and their molecular geometry. During this work the authors observed the reaction of enamine between 9-chloroacridines **1a-e** and 6-aminouracil derivative **2** to give the novel acridine substituted uracil **3a-e** instead of 9-aminouracilacridines **4a-e.**

Preparation of the novel acridine substituted uracils **3a-e** shown in Scheme 1 followed the general procedures described below; Jourdan-Ullmann condensation of an appropriate 2-chlorobenzoic acid and an aromatic amine formed an *N*-arylanthranilic acid. The acridine ring formation of *N*-arylanthranilic acid was carried out in many cases with phosphoryl chloride to provide 9-chloroacridines **1a-e** [20] directly, which were then coupled with the appropriate 6-aminouracil derivatives. When the ring formation with phosphoryl chloride was not desirable, this reaction was effected with either sulfuric acid, PPA, or PPE to give the 9(10*H*)-acridanones, which were then converted to the desired 9-chloroacridines (**1a-e**) with thionyl chloride/DMF [21].



Scheme 1. Substitutents R and R′ of products **3a-e** are described in Table 1. X, Y and Z of **5** are alkyl, alkoxy, amino, nitro and methanesulfonamide *etc* [15].

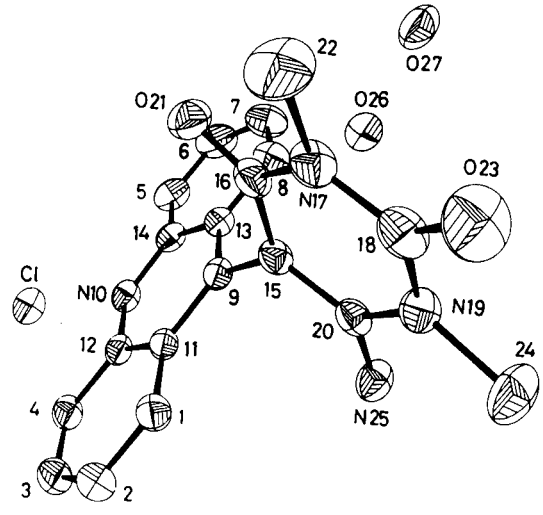


Figure 1. ORTEP drawing [23] of compound **3a** (including chloride ion and two water molecules) with thermal ellipsoids drawn at 50% probability level. Hydrogen atoms are omited for clarity.

A mixture of 9-chloroacridine (**1a**) (1.0 g, 0.0047 mole) and 6-amino-1,3-dimethyluracil (**2**) (0.73 g, 0.0047 mole) in 50 ml of ethanol was stirred at room temperature for 20 hours. At the end of this period the resulting red solid was filtered off and recrystallized from methanol-water (5:1 v/v) to give yellow crystals (**3a**) (1.33 g, 85%). mp > 300°; tlc (chloroform as an eluent) 0.09; ir (potassium bromide): 3500, 3170, 1690, 1640, 1580, 1500 cm^{-1}; pmr (200 MHz, DMSO): δ 3.24 (s, 3H), 3.46 (s, 3H), 6.65 (s, NH_2), 7.67-8.67 (m, 8H of acridine); ms: m/e (relative intensity): 332 (M^+, 31), 174 (31), 141 (31), 97 (41), 81 (81), 70 (98), 57 (100).

The structure of **3a** has also been confirmed by X-ray crystallography (Figure 1). Suitable crystals for X-ray investigation were obtained from the slow evaporation of an ethanol-water solution added a drop of concentrated hyd-

Table 1

Hydrochlorides of Compounds **3**	R	R'	PMR (200 MHz, DMSO) [1] δ CH_3 on uracil	NH_2	Acridine Protons	IR (Potassium Bromide) [2] cm^{-1}	mp °C	yield %
3a	H	H	3.24 3.46	6.65	7.67-8.67	3500, 3170, 1690 1640, 1580, 1500	> 300	85
b	2-CH_3O	H	3.25 3.46	6.60	7.45-8.63	3500, 3150, 1700 1630, 1600, 1500	> 300	80
c	2-CH_3	H	3.25 3.47	6.65	7.76-8.65	3400, 3170, 1690 1600, 1580, 1500	> 300	85
d	4-CH_3	6-Cl	3.20 3.41	6.30	7.38-8.24	3400, 3170 1690 1600, 1590, 1500	> 300	73
e	3-Cl	6-Cl	3.20 3.45	6.52	7.43-8.22	3360, 3180, 1690 1600, 1580, 1500	> 300	62

[1] The pmr spectra were determined in DMSO-d_6 with TMS as the internal standard on a JEOL FX-200 spectrometer. [2] The ir spectra were determined on a JASCO A-3 spectrometer.

rochloric acid at room temperature. Crystal data: $C_{19}H_{16}N_4O_2 \cdot HCl \cdot 2H_2O$, space group $P\bar{1}$, a = 8.763(3), b = 16.130(9), c = 7.620(2) Å, α = 117.51(4), β = 83.81(3), γ = 94.21(4)°, Z = 2, V = 949.3 Å^3, Dc = 1.16 gcm^{-3}, and μ = 5.3 cm^{-1}. Intensity data were collected at room temperature on Rigaku AFC diffractometer using Ni-filtered Cu Kα radiation (λ = 1.5418 Å) by the $\omega - 2\theta$ scan mode. A total of 3479 unique reflections were measured in the range $2\theta < 120°$; 2810 reflections had intensities greater than $3\sigma(I)$. Lorentz and polarization corrections were applied, but no absorption corrections were made. The structure was solved by direct methods using MULTAN[22] to calculate phases for the 300 |E| values greater than 1.50. The 2810 reflections were used for the block diagonal least-squares refinement of the structure, in which the function minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(F_o)$. The chloride ion and two water molecules were found on successive difference Fourier maps. All hydrogen atoms including those of the water molecules were located on the further difference Fourier maps. Refinement of non-hydrogen atoms with anisotropic temperature factors and hydrogen atoms with isotropic temperature factors was terminated at a conventional R of 0.057 and a weighted Rw of 0.079 ($Rw = (\Sigma w(|F_o| - |F_c|)^2 / \Sigma w|F_o|^2)^{1/2}$).

In a similar manner, the novel acridine substituted uracils **3b-e** were also prepared. For five compounds thus obtained **3a-e**, all the analytical and spectroscopic data are in accordance with the given structures (Table 1). Particularly informative are the pmr spectra measured at 200 MHz in dimethyl sulfoxide which correspond quite closely for each compounds **3a-e**. The two singlet lines at δ 3.2 and 3.4 were assigned to the methyl groups on the uracil ring, while the broad singlet signals of amino group were shown at δ 6.3-6.6. Furthermore, the pmr spectra of compounds **3a-e** indicate the characteristic signals at δ 7.3-8.6, all allocated to the acridine ring protons. The infrared spectra indicated a broad absorption band at 3400 cm^{-1} with a shoulder at 3170 cm^{-1}, very weak peaks at 2340 and 2300 cm^{-1}, and strong carbonyl absorption at 1690, 1600 and 1500 cm^{-1}. The mass spectra of the products **3a-e** exhibited a strong molecular ion M^+ corresponding to molecular weight.

The interesting physico-chemical and biological properties of these compounds are expected, such as antitumor activity and their binding characteristics to DNA and to synthetic polynucleotide. The application of this reaction to other 6-aminouracil derivatives and nucleotide bases makes us expect to find the potent biological active compounds as intercalators.

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Supplementary Material.

The atomic co-ordinates and the observed and calculated structure factors tables are available from the authors on request.

REFERENCES AND NOTES

[1] J. W. Drake, "The Molecular Basis of Mutation", Holdenday Inc., San Fransisco, p 134 (1970).

[2] S. Georghiou, *Photochem. Photobiol.*, **26**, 59 (1977).

[3] D. J. Patel, *Biopolymers*, **16**, 2739 (1977).

[4] F. S. Parker and J. L. Irvin, *J. Biol. Chem.*, **199**, 889 (1952).

[5] M. J. Waring, *Eur. J. Cancer*, **12**, 995 (1976).

[6] L. S. Lerman, *Proc. Nat. Acad. Sci. U. S. A.*, **49**, 94 (1963).

[7] M. J. Waring, *Chem. Ind.*, **1975**, 105.

[8] A. H. J. Wang, G. J. Quigley and A. Rich, *Nucl. Acids Res.*, **6**, 3879 (1979).

[9] W. D. Wilson and R. H. James in "Intercalation Chemistry", M. S. Whittingham and A. J. Jacobson, eds, Academic Press, New York, 1982.

[10] G. J. Atwell, B. F. Cain and W. A. Denny, *J. Med. Chem.*, **20**, 520

(1977).

[11] W. A. Denny, G. J. Atwell and B. F. Cain, *J. Med. Chem.*, **20**, 1242 (1977).

[12] W. A. Denny, G. J. Atwell and B. F. Cain, *J. Med. Chem.*, **21**, 5 (1978).

[13] W. A. Denny, G. J. Atwell and B. F. Cain, *J. Med. Chem.*, **22**, 1453 (1979).

[14] B. C. Baguley, W. A. Denny, G. J. Atwell and B. F. Cain, *J. Med. Chem.*, **24**, 520 (1981).

[15] W. A. Denny, B. F. Cain, G. J. Atwell, C. Hansch, A. Panthananickal and A. Leo, *J. Med. Chem.*, **25**, 276 (1982).

[16] W. A. Denny, G. J. Atwell and B. C. Baguley, *J. Med. Chem.*, **26**, 1619 (1983).

[17] G. J. Atwell, G. W. Rewcastle, W. A. Denny, B. F. Cain and B. C. Baguley, *J. Med. Chem.*, **27**, 367 (1984).

[18] G. W. Rewcastle, G. J. Atwell, B. C. Baguley and W. A Denny, *J. Med. Chem.*, **27**, 1053 (1984).

[19] G. J. Atwell, B. F. Cain, B. C. Baguley, G. J. Finaly and W. A. Denny, *J. Med. Chem.*, **27**, 1481 (1984).

[20] A. Albert, "The Acridines", 2nd Ed, Edward Arnold, London, 1966, p 403.

[21] B. F. Cain, R. N. Seelye and G. J. Atwell, *J. Med. Chem.*, **17**, 922 (1974).

[22] G. Germain, P. Main and M. M. Woolfson, *Acta Crystallogr.*, **A27**, 368 (1971).

[23] C. K. Johnson, ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Tennessee 1976.