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Acridine Derivatives. I. Molecular Structure of the Novel Acridinyl-Substituted Uracil, 5-(9-Acridinyl)-6-amino-1,3-dimethyluracil

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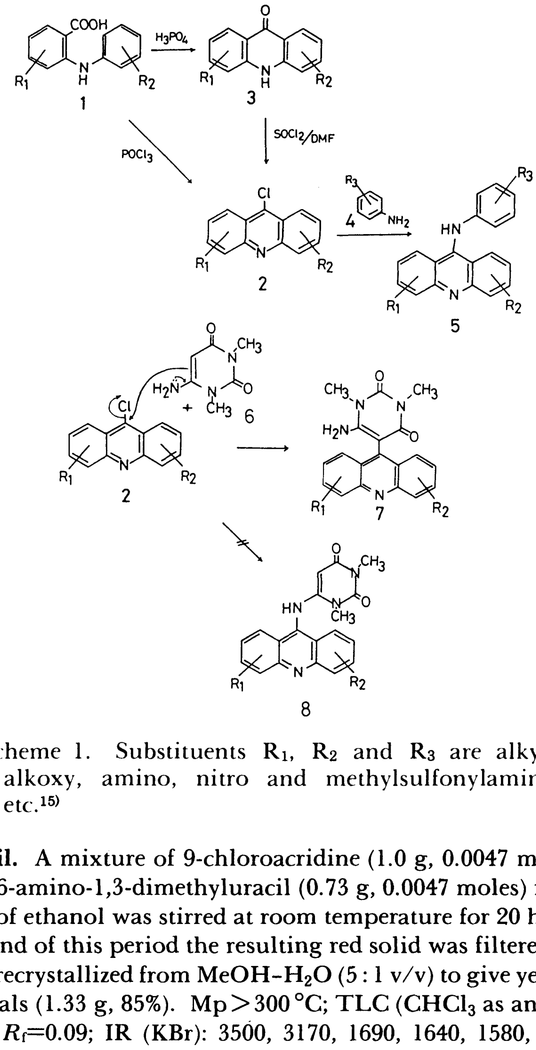
The reaction of enamine between 9-chloroacridines and 6-aminouracil derivatives give novel acridine substituted uracils, the structures of which have been determined by means of an X-ray analysis of 5-(acridin-9-yl)-6-amino-1,3-dimethyluracil hydrochloride dihydrate, $C_{19}H_{16}N_4O_2 \cdot HCl \cdot 2H_2O$. The crystal is triclinic with a space group $P\bar{1}$; also, 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, D_c=1.16 g cm^{-3}, and μ=5.30 cm^{-1} for Cu $K\alpha$. The structure was solved by a direct method and refined by a block-diagonal least-squares procedure: R=0.074 for 2810 reflections with $|F_o|>3\sigma(|F_o|)$. The crystal is composed of the title compound, chloride anion, and two molecules of water held together by hydrogen bonds (described in Table 4).

DNA has a reversible-binding ability for accepting planar molecules which can be inserted between the base pairs of a double helix.[1-4] Most intercalators are mutagens or compounds that have some significant biological and physicochemical properties.[5-9] It is thus of considerable interest to find new type intercalators and to understand the detailed manner of their binding modes within the confines of a double-helical structure. The recent synthesis and study of the 9-anilinoacridines (**5**) (Scheme 1)[10-19] which have antibacterial, antimalarial, mutagenic and carcinogenic properties by intercalating to DNA have encouraged us to investigate a synthesis of novel acridine derivatives and their molecular geometries. During this work the author observed the reaction of enamine between 9-chloroacridines (**2**) and 6-aminouracil derivative (**6**); this gives novel acridinyl-substituted uracils (**7**) instead of 6-(9-acridinylamino)uracils (**8**) corresponding to 9-anilinoacridines (**5**). In order to establish the structure of **7**, the title compound (R_1=R_2=H) was chosen for X-ray diffraction studies. The preparation of the novel acridinyl-substituted uracils, (**7**) shown in Scheme 1, followed general procedures: Jourdan-Ullmann condensation of an appropriate 2-chlorobenzoic acid and an aromatic amine formed an *N*-arylanthranilic acid (**1**). The acridine ring formation was carried out in many cases with $POCl_3$ in order to provide 9-chloroacridines (**2**)[20] directly; these were then coupled with the appropriate 6-aminouracil derivatives. When ring formation with $POCl_3$ was not desirable, this reaction was effected with either H_2SO_4, polyphosphoric acid (PPA), or polyphosphate ester (PPE) to give the 9(10*H*)-acridinones (**3**). These were then converted to the desired 9-chloroacridines (**2**) with $SOCl_2$/DMF.[21]

This paper is concerned about the molecular structure of 5-(9-acridinyl)-6-amino-1,3-dimethyluracil (**7**, R_1=R_2=H) obtained by means of an X-ray diffraction of its hydrochloride dihydrate.



Scheme 1. Substituents R_1, R_2 and R_3 are alkyl, alkoxy, amino, nitro and methylsulfonylamino etc.[15]

Experimental

Preparation of 5-(9-Acridinyl)-6-amino-1,3-dimethyluracil. A mixture of 9-chloroacridine (1.0 g, 0.0047 moles) and 6-amino-1,3-dimethyluracil (0.73 g, 0.0047 moles) in 50 cm^3 of ethanol was stirred at room temperature for 20 h. At the end of this period the resulting red solid was filtered off and recrystallized from $MeOH-H_2O$ (5 : 1 v/v) to give yellow crystals (1.33 g, 85%). Mp>300 °C; TLC ($CHCl_3$ as an eluent) R_f=0.09; IR (KBr): 3500, 3170, 1690, 1640, 1580, 1500 cm^{-1}; ^{1}H NMR (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/z* (rel intensity): 332 (M$^+$, 31), 174 (31), 141 (31), 97 (41), 81 (81), 70 (98), 57 (100).

Suitable crystals for X-ray investigation were obtained by a slow evaporation of an $EtOH-H_2O$ solution added a drop of concd HCl at room temperature.

Collection and Reduction of Data. The crystal used for the X-ray study had approximate dimensions of 0.20×0.25×0.20 mm. The unit cell parameters at room temperature were refined by least-squares using the Bragg angles (Cu *Kα*, λ=1.54178 Å) of 24 reflections (30°<2θ<40°). The crystal data are given in Table 1. Intensity data were collected at room temperature on a Rigaku AFC diffractometer utilizing nickel-filtered Cu *Kα* radiation. The θ—2θ scan mode was employed. The scan rate was 5° min^{-1} in θ, and the scan range in θ was varied by 1.2+0.15° tanθ. Background were counted for 7 s at both ends of the scan with an offset of 50% of the scan range from the calculated position of the *Kα* peak. A total of 3479 unique reflections of the type $\pm h$, $\pm k$, l were measured in the range 2θ<125°. The intensities of three standard reflections measured after every 57 reflections dropped by an average of a few percent over the period of data collection; however, no correction was applied for this fluctuation. Lorentz and polarization corrections were applied but no absorption correction was applied (μ=5.30 cm^{-1} for Cu *Kα*). Standard deviations in the intensities, $\sigma(|F_o|)$, were derived directly from counting statistics.

Solution and Refinement of the Structure. The structure was solved by direct methods using *MULTAN* 78[22] to calculate phases for the 300$|E|$ values with $|E|>1.50$. The E map computed from the phase set with the largest combined figure of merit (2.62) revealed all non-hydrogen atoms except for two oxygen atoms of water and one chlorine atom. The subsequent difference Fourier map readily gave the remaining atoms. Atomic parameters were refined by the block-diagonal least-squares procedure. The function minimized was $\sum w(|F_o|-|F_c|)^2$, where w was taken as $1/\sigma^2(F_o)$. All of the hydrogen atoms could be readily located from a difference Fourier map. During further refinement, anisotropic and isotropic thermal parameters were included for the non-hydrogen and hydrogen atoms, respectively. The refinement converged to a conventional $R=\sum||F_o|-|F_c||/\sum|F_o|$ of 0.057 and a weighted $R_w=\sum w((|F_o|-|F_c|)^2/\sum w|F_o|^2)^{1/2}$ of 0.079 with a GOF of 1.49 (Quality of fit=$[\sum w(|F_o|-|F_c|)^2/(N_{obsd}-N_{para})]^{1/2}$). The refinement was completed when the largest shift in any parameters among the non-hydrogen atoms was 0.05σ; the largest shift for hydrogen atoms was 0.08σ. The largest peak in the final difference map, 0.2 eÅ^{-3}, was located near the chlorine atom. Atomic scattering factors were taken from those of "International Tables for X-Ray Crystallography."[23] Mathematical and computational details are noted elsewhere.[24] Calculations were carried ouy by using the *UNICS*[25] program system on an ACOS 850 computer at the Crystallographic Research Center, Institute for Protein Research, Osaka University, and an ACOS 900 computer at Computation Center of Niigata University. The final positional parameters* of non-hydrogen and hydrogen atoms with equivalent isotropic and isotropic temperature factors are given in Table 2.

Table 1. Physical and Crystallographic Data

Formula unit	$C_{19}H_{16}N_4O_2\cdot HCl\cdot 2H_2O$
M	332.34
Crystal system	triclinic
Space group	$P\bar{1}$
a/Å	8.763(3)
b/Å	16.130(9)
c/Å	7.620(2)
α/°	117.51(4)
β/°	83.81(3)
γ/°	94.21(4)
V/Å^3	949.3
Z	2
D_x/g cm^{-3}	1.163
Radiation	Cu *Kα*
λ/Å	1.54178
No. of reflections measured	3479
Observed $[|F_o|>3\sigma(|F_o|)]$	2810
R	0.057

Discussion

The estimated structure of the title compound has shown the novel acridine derivative substituted by uracil, which is obtained by the interesting reaction of the enamine of 9-chloroacridine and biological important uracil. The molecular structure and the atom labeling are illustrated by an ORTEP drawing in Fig. 1.[31] The bond lengths and angles are given in Table 3,

Table 2. Final Atomic Positional and Thermal Parameters with Estimated Standard Deviations in Parentheses

Atoms	*x*	*y*	*z*	B_{eq} (or *B*)/Å	Atoms	*x*	*y*	*z*	B_{eq} (or *B*)/Å
C 1	1.2119(6)	0.1252(4)	0.5562(7)	3.15	C15	1.0078(5)	0.2829(3)	0.7257(7)	2.48
C 2	1.3054(6)	0.0498(4)	0.4780(8)	3.96	C16	0.9224(6)	0.3037(3)	0.9084(7)	2.94
C 3	1.2634(6)	−0.0346(4)	0.3124(8)	3.97	N17	0.9782(5)	0.3795(3)	1.0765(6)	3.19
C 4	1.1300(6)	−0.0433(4)	0.2290(7)	3.32	C18	1.1032(6)	0.4345(4)	1.0705(7)	3.43
C 5	0.6604(6)	0.0823(4)	0.2048(8)	4.05	N19	1.1737(5)	0.4162(3)	0.8855(6)	2.92
C 6	0.5638(6)	0.1553(5)	0.2691(9)	5.20	C20	1.1298(5)	0.3404(3)	0.7136(7)	2.63
C 7	0.5990(6)	0.2437(5)	0.4248(9)	4.95	O21	0.8061(4)	0.2602(3)	0.9292(5)	3.86
C 8	0.7300(6)	0.2585(4)	0.5189(8)	3.77	C22	0.9098(8)	0.3947(5)	1.2744(8)	5.26
C 9	0.9706(5)	0.1953(3)	0.5484(7)	2.50	O23	1.1505(5)	0.4984(3)	1.2211(6)	4.89
N10	0.8978(5)	0.0262(3)	0.2295(6)	2.84	C24	1.3138(7)	0.4717(4)	0.8806(9)	4.40
C11	1.0730(5)	0.1201(3)	0.4721(7)	2.44	N25	1.2087(5)	0.3261(3)	0.5433(6)	3.26
C12	1.0330(5)	0.0345(3)	0.3088(7)	2.70	O26	0.5221(7)	−0.3020(4)	0.0006(9)	9.30
C13	0.8341(5)	0.1845(3)	0.4576(7)	2.69	O27	0.6107(6)	−0.4369(4)	−0.3881(7)	7.30
C14	0.7979(5)	0.0969(4)	0.2959(7)	2.95	CL	0.8014(2)	−0.1731(1)	−0.0748(2)	4.04

$$B_{eq}=\frac{1}{3}(U_{11}+U_{22}+U_{33})\ \text{(where}\ U_{11}=\frac{B_{11}}{8\pi^2a^{*2}},\ \text{etc.).}$$

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* Tables of anisotropic thermal parameters, coordinates of hydrogen atoms, least-squares planes, and the observed and calculated structure factors are kept as Document No. 8717 at the Chemical Society of Japan.

Table 3. Bond Distances and Angles with Estimated Standard Deviations in Parentheses

(a) Bond distances for non-hydrogen atoms (*l*/Å)

C 1-C 2	1.371(7)	C 1-C11	1.416(6)	C 2-C 3	1.422(8)
C 3-C 4	1.358(7)	C 4-C12	1.417(7)	C 5-C 6	1.367(8)
C 5-C14	1.406(7)	C 6-C 7	1.410(9)	C 7-C 8	1.368(7)
C 8-C13	1.424(7)	C 9-C11	1.418(6)	C 9-C13	1.406(6)
C 9-C15	1.481(7)	N10-C12	1.358(6)	N10-C14	1.357(6)
C11-C12	1.419(7)	C13-C14	1.424(7)	C15-C16	1.411(7)
C15-C20	1.388(6)	C16-N17	1.406(6)	C16-O21	1.233(6)
N17-C18	1.370(6)	N17-C22	1.476(7)	C18-N19	1.383(7)
O18-O23	1.224(6)	N19-C20	1.385(6)	N19-C24	1.474(7)
C20-N25	1.330(6)				

(b) Bond angles (*ϕ*/°)

C11-C 1-C 2	120.4(5)	C 3-C 2-C 1	120.3(5)
C 4-C 3-C 2	121.4(5)	C12-C 4-C 3	118.6(5)
C14-C 5-C 6	118.7(5)	C 7-C 6-C 5	121.3(5)
C 8-C 7-C 6	120.8(5)	C13-C 8-C 7	120.0(5)
C15-C 9-C13	121.3(4)	C15-C 9-C11	119.2(4)
C13-C 9-C11	119.5(4)	C14-N10-C12	123.3(4)
C12-C11-C 9	119.1(4)	C12-C11-C 1	118.0(4)
C 9-C11-C 1	122.9(4)	C11-C12-N10	119.5(4)
C11-C12-C 4	121.3(4)	N10-C12-C 4	119.2(4)
C14-C13-C 9	119.4(4)	C14-C13-C 8	117.9(4)
C 9-C13-C 8	122.7(4)	C13-C14-N10	119.2(4)
C13-C14-C 5	121.2(4)	N10-C14-C 5	119.6(4)
C20-C15-C16	121.0(4)	C20-C15-C 9	120.2(4)
C16-C15-C 9	118.7(4)	O21-C16-N17	119.1(4)
O21-C16-C15	125.0(5)	N17-C16-C15	115.9(4)
C22-N17-C18	117.1(6)	C22-N17-C16	118.3(4)
C18-N17-C16	124.2(4)	O23-C18-N19	120.7(5)
O23-C18-N17	122.1(5)	N19-C18-N17	117.2(4)
C24-N19-C20	120.4(4)	C24-N19-C18	116.9(4)
C20-N19-C18	122.0(4)	N25-C20-N19	117.7(4)
N25-C20-C15	123.0(4)	N19-C20-C15	119.3(4)

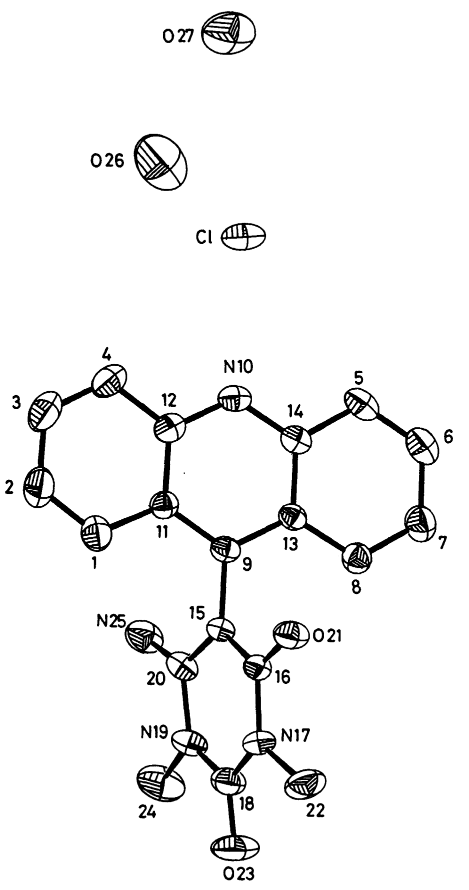

Fig. 1. An ORTEP[31] drawing of the title compound···Non-hydrogen atoms are drawn as thermal ellipsoids with 50% probability level.

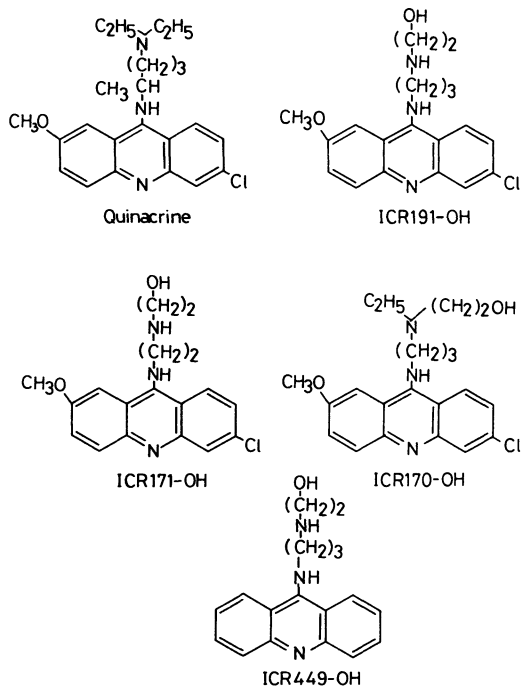

Fig. 2. Formulae of quinacrine and ICR series compounds.

together with estimated standard deviations. The average C-C distances of two benzene rings of acridine nucleus are 1.401 and 1.400 Å, respectively, while that of the C-N distances of the acridine nucleus is 1.358 Å. On the other hand, the uracil ring has average values of 1.386 Å in the C-N bond and 1.229 Å in the C=O bond. These values are normal, and the bond distances of the two benzene rings of acridine nucleus are exactly equivalent within experimental error. As shown in Fig. 1, the molecule consists of two planar portions. The derivatives from the least-squares planes through portions of the molecule are calculated and, the dihedral angle between the least-squares planes defined by the acridine ring and the uracil ring is 108.0°. The calculated dihedral angle is 2.5° between the best planes through the outer rings of the acridine ring system; these are compared with values of 8° for quinacrine,[26] 4.9° for ICR-191-OH,[27] 7.5° for ICR-171-OH,[28] 10.7°for ICR-170-OH,[29] and 12.5° for ICR-449-OH.[30] The formulate of the above ICR compounds are shown in Fig. 2. In these series of acridines, it seems that the more potent biological activities, such as antitumor and mutagenic activity,

Table 4. Hydrogen-Bond Distances (l/Å) and Angles (ϕ/°)

D-H···A	D-H	D···A	H···A	D-H···A
N10-HN10···Cl$^{a)}$	0.94(8)	3.093(4)	2.20(8)	157.7(6.6)
N25-H1N25···Cl$^{a)}$	0.84(6)	3.278(4)	2.47(6)	159.6(5.3)
N25-H2N25···O27$^{b)}$	0.83(6)	2.870(7)	2.09(6)	157.2(6.3)
O26-H1O26···Cl	0.93(9)	3.271(6)	2.38(9)	159.9(7.6)
O26-H2O26···O21$^{c)}$	1.11(7)	2.939(6)	1.83(7)	171.3(6.6)
O27-H2O27···O26	0.89(9)	2.813(9)	1.93(9)	167.4(7.7)
O27-H1O27···O23$^{d)}$	1.03(7)	3.005(6)	2.00(7)	163.1(6.0)

Symmetry code: a) $1-x, -y, -z$; b) $1+x, y, z$; c) $x, y, z-1$; d) $x-1, y, z-1$

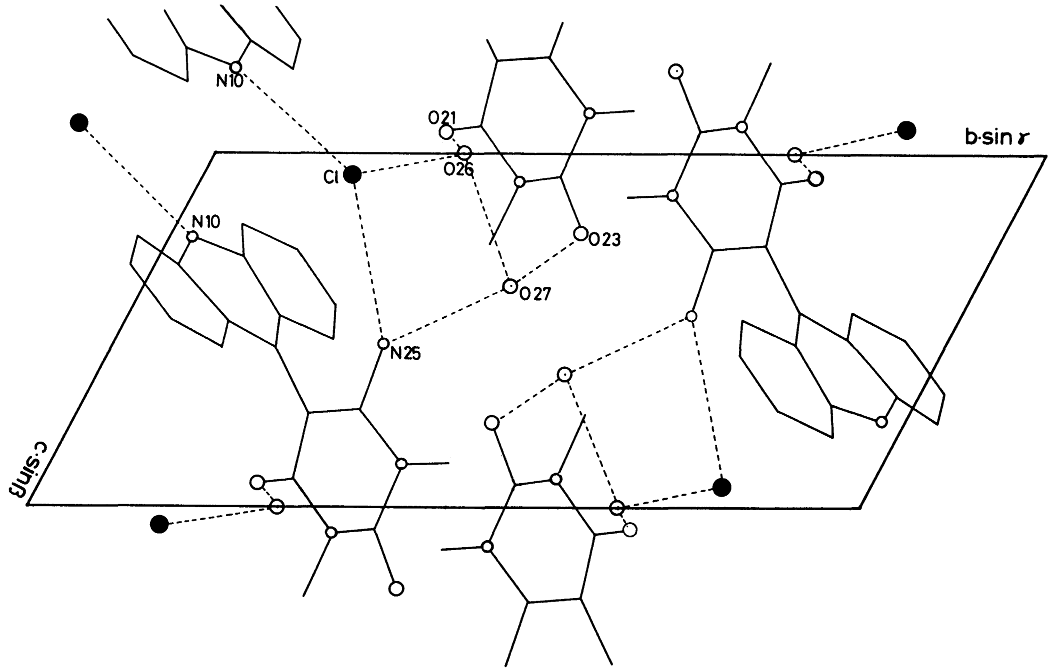

Fig. 3. Projection of the crystal structure along the a axis.

are caused by the flatter ring systems and better stacking ring systems as intercalators to DNA.

Hydrogen-bond distances and bond angles are given in Table 4. The molecules in the unit cell are connected by three-dimentional networks of hydrogen-bonds, composed of seven hydrogen atoms originating from atoms N25, O26, O27 and protonated N10, and corresponding hydrogen bonding acceptors (Fig. 3). That is, there are the hydrogen-bonds of 2.813 (9) Å between the water oxygen atom O27 and another water oxygen O26, and 2.939 (8) Å between the water oxygen atom O26 and the oxygen atom O21 of the uracil ring. Water oxygen atom O27 is also connected by oxygen O23 of the uracil ring and nitrogen atom N25 of the adjacent molecule by the hydrogen-bonds, 3.005 (8) and 2.870 (7) Å, respectively. On the other hand, the chloride anion has a hydrogen bonding interaction (3.093 (4) Å) with the protonated nitrogen atom N10 on which is also met a hydrogen atom (N10···H=0.94 (8) Å).

In a similar synthetic method, the novel acridinyl-substituted uracils related to the title compound were also prepared. For those compounds, all the analytical and spectroscopic data are in accordance with the given structures (Scheme 1). The interesting physicochemical 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 such that we can find potent biologically active compounds as intercalators. Studies concerning the above topics are now in progress and results will be published in due course.

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