HETEROCYCLES, Vol. 31, No. 9, 1990

SYNTHESIS AND X-RAY ANALYSIS OF 1-BENZYL-6-CHLOROURACIL

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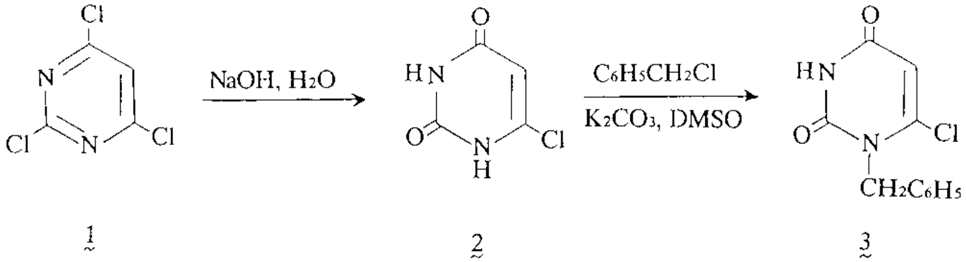
Abstract —— 1-Benzyl-6-chlorouracil (3) was prepared by benzylation of 6-chlorouracil (2) which was obtained by alkaline hydrolysis of 2,4,6-trichloropyrimidine (1).

1 (or 3)-Monosubstituted 6-chlorouracils[2,3] are useful as starting materials for the synthesis of pteridines, purines, xanthines, and fused uracils. Recentry, we prepared pyrido- and pyrrolo-[2,3-d]pyrimidines from 1-benzyl-6-chlorouracil (3) as a starting material.[2a] However, in our literature,[2] we did not report on the preparation of 3. Thus, in the present paper, we wish to report a synthesis of 3 along with the geometry thereof.



6-Chlorouracil (2) was synthesized from 2,4,6-trichloropyrimidine (1) by a modification of Davoll's[4] and Cresswell's[5] methods. Compound 3 was obtained in 74% yield by treatment of 2 with benzyl chloride using K_2CO_3 in DMSO, whereby the benzylation reaction proceeded regioselectively at N-1 of 2. Alkylation of 6-substituted uracils such as orotic acid usually take place on position 3.[6] To our knowledge, no reports dealing with direct 1-alkylation of 6-substituted uracils have appeared, yet.

The structure of 3 was elucidated by an X-ray crystallographic analysis.

X-Ray Analysis

Crystal Data : $C_{11}H_9N_2O_2Cl$, M 236.66, Monoclinic, space group $\underline{P}2_1/a$; $\underline{a}=24.745$ (9), $\underline{b}=7.956$ (2), $\underline{c}=5.629$ (2) Å, $\beta=107.10$ (3)° ; $\underline{D}x=1.484$ gcm^{-3}; $\underline{Z}=4$; $\mu(Cu\text{-}\underline{K}\alpha)=3.421$ cm^{-1}.

A single crystal with approximate dimensions of 0.4×0.3×0.3 mm was used. X-ray experiments were carried out on a Rigaku automated four-circle diffractometer (AFC-4) using graphite-monochromated Cu-$\underline{K}\alpha$ radiation ($\lambda=1.5479$ Å). Intensity data of the crystal with a range $2\theta<140°$ were collected by the 2θ-ω scan method at a rate of 8° min^{-1}. The data were corrected for Lorentz and polarization factors, but not for the absorption. The independent reflections (1810) were observed under the criterion $|F_o|>3\sigma(|F_o|)$ and were used in subsequent calculations.

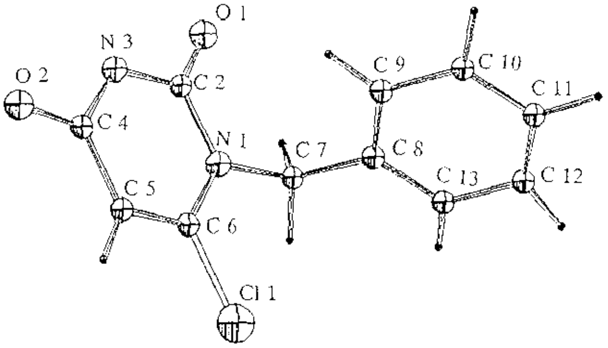


Figure 1. Perspective drawing of the molecule with the atomic numbering

Structure Solution and Refinement

The crystal structure was solved by a direct method using the program MULTAN 78.[7] Refinements of the structure were performed by block-diagonal least-squares calculations with anisotropic thermal parameters for non-hydrogen atoms. The hydrogen atoms were located on a difference map. The final refinement yielded an R value of 0.066. The atomic scattering factors used were those from the literature.[6]

Results and Discussion

The positional parameters of non-hydrogen atoms with their isotropic equivalent temperature factors are shown in Table Ⅰ. Atomic distances and bond angles are shown in Tables Ⅱ and Ⅲ. The perspective drawing of the compound and the numbering scheme of the atoms are shown in Figure 1. Bond lengths of O1-C2, O2-C4, N3-C4, and N3-C2 are 1.208 Å, 1.241 Å, 1.376 Å, and 1.401 Å, respectively (Table Ⅱ). These data suggested that O1-C2 and O2-C4 are double bonds and N3-C4 and N3-C2 are single bonds, respectively. In conclusion, the structure of **3** was confirmed by X-ray crystallographic analysis. We were able to develop a convenient synthesis of 1-monosubstituted 6-chlorouracil.

Table Ⅰ. The Positional Parameters and Equivalent Isotropic Thermal Parameters with Their Estimated Standard Deviations in Parentheses

Atom	$\underline{x}$ ($\times10^4$)	$\underline{y}$ ($\times10^4$)	$\underline{z}$ ($\times10^4$)	Beq (Å^2)
Cl 1	981(1)	4420(1)	493(3)	4.1
O 1	890(2)	10577(4)	725(8)	4.8
O 2	-40(2)	7788(4)	5350(8)	4.5
N 1	941(2)	7708(4)	768(8)	3.0
N 3	424(2)	9162(5)	3035(8)	3.4
C 2	760(2)	9242(6)	1422(10)	3.4
C 4	250(2)	7700(6)	3894(10)	3.3
C 5	434(2)	6170(6)	3074(10)	3.3
C 6	766(2)	6238(5)	1533(9)	2.9
C 7	1352(2)	7778(6)	-703(9)	3.4
C 8	1961(2)	7689(6)	928(9)	3.0
C 9	2140(2)	8423(7)	3230(9)	3.7
C 10	2712(2)	8412(8)	4612(10)	4.3
C 11	3106(2)	7654(7)	3624(12)	4.7
C 12	2925(2)	6939(7)	1256(12)	4.5
C 13	2355(2)	6935(6)	-62(11)	3.8

Table Ⅱ. Bond Lengths (Å)
(Standard deviations are in parentheses.)

Cl 1 — C 6	1.702(5)
O 2 — C 4	1.241(7)
O 1 — C 2	1.208(7)
N 1 — C 6	1.360(7)
N 1 — C 2	1.386(7)
N 1 — C 7	1.490(7)
N 3 — C 4	1.376(7)
N 3 — C 2	1.401(7)
C 6 — C 5	1.361(8)
C 5 — C 4	1.423(8)
C 7 — C 8	1.519(7)
C 8 — C 9	1.371(7)
C 8 — C 13	1.392(8)
C 9 — C 10	1.401(8)
C 10 — C 11	1.393(9)
C 11 — C 12	1.396(9)
C 12 — C 13	1.387(9)

Table Ⅲ. Bond Angles (°)
(Standard deviations are in parentheses.)

C 6 — N 1 — C 2	121.1(4)
C 6 — N 1 — C 7	122.7(4)
C 2 — N 1 — C 7	116.1(4)
C 4 — N 3 — C 2	124.9(5)
Cl 1 — C 6 — N 1	117.5(4)
Cl 1 — C 6 — C 5	119.6(4)
N 1 — C 6 — C 5	122.9(5)
C 6 — C 5 — C 4	118.9(5)
O 2 — C 4 — N 3	119.1(5)
O 2 — C 4 — C 5	124.3(5)
N 3 — C 4 — C 5	116.6(5)
O 1 — C 2 — N 1	123.4(5)
O 1 — C 2 — N 3	121.1(5)
N 1 — C 2 — N 3	115.5(5)
N 1 — C 7 — C 8	112.4(4)
C 7 — C 8 — C 9	122.6(5)
C 7 — C 8 — C 13	117.7(5)
C 9 — C 8 — C 13	119.5(5)
C 8 — C 9 — C 10	121.0(5)
C 9 — C 10 — C 11	119.5(6)
C 10 — C 11 — C 12	119.4(6)
C 11 — C 12 — C 13	120.1(6)
C 8 — C 13 — C 12	120.4(6)

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. Mass spectra (ms) were recorded on a JEOL D-100 instrument. ^{1}H-Nmr spectra were recorded on a Varian EM-390 nmr spectrometer with Me_4Si (TMS) as an internal standard in DMSO-*d*$_6$. Ultraviolet (uv) spectra were measured with a Hitachi 340 instrument. Microanalysis was performed by the staff in the Microanalytical Laboratory of this school.

6-Chlorouracil (2)[4,5]

A solution of 2,4,6-trichloropyrimidine[9] (**1**, 74.5 g, 0.41 mol) in water (650 ml) containing NaOH (65 g, 1.63 mol) was stirred under reflux for 1 h. The reaction mixture was adjusted to pH 2~3 with conc. aqueous HCl (*ca.* 160 ml). The resulting mixture was kept in a refrigerator, and the precipitate was collected by filtration. The solid was purified by recrystallization from H_2O to give 48.5 g (82%) of white needles (**2**), mp 292~293℃ (dec.) [lit.[5] mp 300℃ (dec.) and lit.[10] mp 294~295℃ (dec.)]. Ms: *m/z* 146 and 148 (M^+). ^{1}H-Nmr (DMSO-*d*$_6$) δ: 5.64 (1H, s, H-5), 11.21, 12.00 (1H each, br, NH). Uv $\lambda_{max}^{H_2O}$ nm (log ε): 259 (3.96). Uv $\lambda_{max}^{0.01\underline{N}\ NaOH}$ nm (log ε): 279 (4.16). *Anal.* Calcd for $C_4H_3N_2O_2Cl$: C, 32.78; H, 2.06; N, 19.11; Cl, 24.19. Found: C, 32.57; H, 2.20; N, 18.83; Cl, 23.91.

1-Benzyl-6-chlorouracil (3)

A mixture of **2** (29.2 g, 0.2 mol), benzyl chloride (38.1 g, 0.3 mol), and K_2CO_3 (13.8 g, 0.1 mol) in DMSO (200 ml) was stirred at 60~70℃ for 1 h. An aqueous NaOH solution (4%, w/v, 200 ml) was added to the hot reaction mixture with stirring. The reaction mixture was washed with benzene (2×100 ml), and the aqueous phase was adjusted to pH 2~3 with conc. aqueous HCl. The resulting aqueous mixture was kept in a refrigerator, and the precipitate was collected by filtration, washed with water, and dried. The solid was purified by recrystallization from MeOH to give 34.5 g (73%) of colorless needles (**3**), mp 149~150 ℃. Ms: *m/z* 236 and 238 (M^+). ^{1}H-Nmr (DMSO-*d*$_6$) δ: 5.16 (2H, s, $C\underline{H}_2C_6H_5$), 5.88 (1H, s, H-5), 7.14-7.46 (5H, m, $CH_2C_6\underline{H}_5$), 11.72 (1H, br, NH). Uv λ_{max}^{EtOH} nm (log ε): 266 (4.14). Uv $\lambda_{max}^{0.1\underline{N}\ NaOH\text{-}EtOH\ (1:10)}$ nm (log ε): 265 (4.05). *Anal.* Calcd for $C_{11}H_9N_2O_2Cl$: C, 55.81; H, 3.81; N, 11.84; Cl, 15.04. Found: C, 55.89; H, 3.66; N, 11.57; Cl, 14.80.

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1 The late assistant professor Tsuneo Itoh prepared this paper a few days before his untimely death on January 14th, 1990. The present co-workers gratefully acknowledge their indebtedness to his inspiration, enthusiasm, and leadership.

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Received, 14th June, 1990