

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

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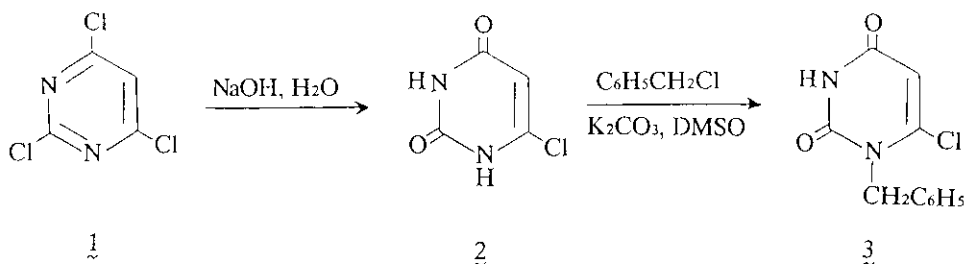
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Abstract — 1-Benzyl-6-chlorouracil (3) was prepared by benzylation of 6-chlorouracil (2) which was obtained by alkaline hydrolysis of 2,4,6-trichloropyrimidine (1).

1 (or 3)-Monosubstituted 6-chlorouracils^{2,3} are useful as starting materials for the synthesis of pteridines, purines, xanthines, and fused uracils. Recently, 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's⁴ and Cresswell's⁵ methods. Compound 3 was obtained in 74% yield by treatment of 2 with benzyl chloride using K₂CO₃ 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 : C₁₁H₉N₂O₂Cl, M 236.66, Monoclinic, space group P2₁/a; $a=24.745$ (9), $b=7.956$ (2), $c=5.629$ (2) Å, $\beta=107.10$ (3)°; $D_x=1.484$ gcm⁻³; $Z=4$; $\mu(\text{Cu-K}\alpha)=3.421$ 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-K α radiation ($\lambda=1.5479$ Å). Intensity data of the crystal with a range $2\theta < 140^\circ$ 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.

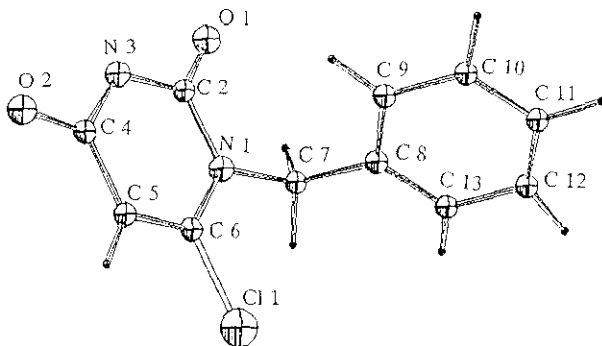


Figure 1. Perspective drawing of the molecule with the atomic numbering

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	\bar{x} ($\times 10^4$)	\bar{y} ($\times 10^4$)	\bar{z} ($\times 10^4$)	Beq (Å^2)
C 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.)

C1 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)
C1 1 — C 6 — N 1	117.5(4)
C1 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. $^1\text{H-Nmr}$ 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-trichloropyrimidine⁹ (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°C (dec.) [lit.⁵ mp 300°C (dec.) and lit.¹⁰ mp 294-295°C (dec.)]. Ms: m/z 146 and 148 (M^+). $^1\text{H-Nmr}$ (DMSO-d_6) δ : 5.64 (1H, s, H-5), 11.21, 12.00 (1H each, br, NH). Uv $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm (log ϵ): 259 (3.96). Uv $\lambda_{\text{max}}^{0.01\text{N NaOH}}$ nm (log ϵ): 279 (4.16). Anal. Calcd for $\text{C}_4\text{H}_3\text{N}_2\text{O}_2\text{Cl}$: 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°C 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 (2x100 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°C. Ms: m/z 236 and 238 (M^+). $^1\text{H-Nmr}$ (DMSO-d_6) δ : 5.16 (2H, s, $\text{CH}_2\text{C}_6\text{H}_5$), 5.88 (1H, s, H-5), 7.14-7.46 (5H, m, $\text{CH}_2\text{C}_6\text{H}_5$), 11.72 (1H, br, NH). Uv $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 266 (4.14). Uv $\lambda_{\text{max}}^{0.1\text{N NaOH-EtOH (1:10)}}$ nm (log ϵ): 265 (4.05). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{N}_2\text{O}_2\text{Cl}$: 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.

REFERENCES AND NOTES

- 1 The late assistant professor Tsuneco 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