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Synthesis of 5-Fluorouracil Derivatives Containing an Inhibitor of 5-Fluorouracil Degradation

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The reactivities of 5-fluorouracil (5-FUra) degradation inhibitors, 2,4- (2) and 2,6-dihydroxypyridines (3), were investigated. Acylation of 2 and 2,4-bis(trimethylsilyloxy)pyridines with equimolar amounts of acid chlorides preferentially occurred at the 4-OH and 2-OH positions, respectively, and the structure of monobenzoylated 5-chloro-2,4-dihydroxypyridine (2b) was determined as 4-benzoyloxy-5-chloro-2-pyridone (5b) by X-ray crystallographic analysis. Compounds 2 and 3, as well as the *N*-2-tetrahydrofuryl (11), *N*-alkyl (12), and *N*-carbamoyl (14) derivatives of 2, exhibit dynamic keto–enol tautomerism. The acyl derivatives of these pyridines are labile and are thought to be active esters. Monoacyl ester derivatives of these pyridines were combined with 5-FUra analogs to develop novel antitumor agents containing an inhibitor of 5-FUra degradation. One of them, 3-[3-(6-benzoyloxy-3-cyano-2-pyridyloxycarbonyl)benzoyl]-1-ethoxymethyl-5-fluorouracil (BOF-A2) (22b), was the most effective and is currently undergoing late phase-II clinical trials.

Keywords inhibitor; 5-fluorouracil degradation; 5-chloro-2,4-dihydroxypyridine; 3-cyano-2,6-dihydroxypyridine; X-ray analysis; antitumor agent

Since the preparation of 5-fluorouracil (5-FUra) (**1**),[2)] it has been regarded as a potential drug for the treatment of advanced cancer. However, 5-FUra is rapidly catabolized to α-fluoro-β-alanine through 5,6-dihydro-5-fluorouracil mainly in the liver,[3)] and is therefore not long-lasting. In order to improve the antitumor activity of 5-FUra, several masked compounds, *e.g.*, 1-(2-tetrahydrofuryl)-5-fluorouracil (Tegafur) (**20**),[4)] 1-hexylcarbamoyl-5-fluorouracil (Carmofur),[5)] and 5′-deoxy-5-fluorouridine (Doxifluridine),[6)] have been synthesized and used for the therapeutic purposes. On the other hand, Fujii *et al.* enhanced the antitumor activity of Tegafur by coadministration with uracil[7)] which is an inhibitor of 5-FUra degradation (IC_{50}: 18.0 μM[8a)]). This suggested that more potent inhibitors might increase the antitumor activity of 5-FUra and its masked derivatives.

Recently, our coworkers identified some new, potent inhibitors of 5-FUra degradation, namely 2,4- (**2**) and 2,6-dihydroxypyridines (**3**) (Chart 1).[8a)] They reported that these inhibitors remarkably enhanced the antitumor activity when coadministered with 5-FUra or its masked compound to mice or rats.[8b)]

We conjectured that a chemically bonded combination of the above inhibitors and 5-FUra masked forms might result in potent antitumor agents, and we considered that desirable compounds should be easily cleavable into the two components *in vivo*. Thus, an ester structure was selected to link the two components and to protect the hydroxy group in pyridines. However, there has been no report on the acylation of **2** and **3** so far. Accordingly, this paper describes the reactivities of derivatives of **2** and **3** and the synthesis of 5-FUra derivatives containing these inhibitors in the molecule.

Chemistry

Inhibitors of 5-FUra degradation, **2** and **3**, contain three acylatable positions[9)] and two of them can be acylated simultaneously. Thus, in order to combine them with 5-FUra derivatives, one functional group has to be blocked by a protecting group.

Synthesis of Pyridine Derivatives Acylation of **2** with equimolar (A) acid chloride, (B) acid anhydride, or (C) organic acid/dicyclohexylcarbodiimide (DCC) gave a major product, a minor product, and a trace amount of a third product. In the case of benzoylation of **2b**, the minor product was identified as 2,4-dibenzoyloxy-5-chloropyridine (**7a**) whose infrared (IR) spectrum showed ester carbonyl stretching bands at 1760 and 1748 cm^{-1} and no absorption at 1600—1700 cm^{-1}. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of this compound exhibited two singlet signals due to C_6-H and C_3-H on the pyridine ring at 8.72 and 7.77 ppm, respectively, and multiplet signals due to two phenyl groups at 8.22—8.13 and 7.83—7.55 ppm. The major and the trace products were assumed to be monobenzoyl ester derivatives from their IR and ^{1}H-NMR

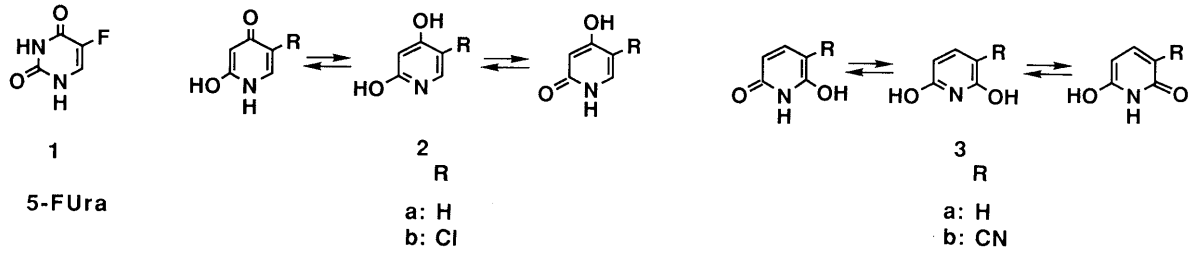


Chart 1

spectra. The IR spectrum of the major product showed strong bands at 1751 and 1661 cm^{-1}, and that of the trace product showed a strong absorption at 1742 and a medium band at 1675 cm^{-1}. Though IR data indicate that the major and the trace products have ester and α,β-unsaturated ketone groups, no significant spectral evidence allowing determination of the structures was obtained. However, the major product fortunately gave a good single crystal from EtOH, and this was subjected to X-ray analysis. A perspective view of the molecule is presented in Fig. 1. The C1–O1 distance of 1.245(5) Å is a typical double bond length (1.23(1) Å[10]). This indicates that the ring system is not 2-hydroxypyridine form (**5'b**), but 2-pyridone form (**5b**), that is, the structure of the major product was determined as 4-benzoyloxy-5-chloro-2-pyridone (**5b**). Consequently, the structure of the trace product was determined as 2-benzoyloxy-5-chloro-4-pyridone (**9b**) (Chart 2).

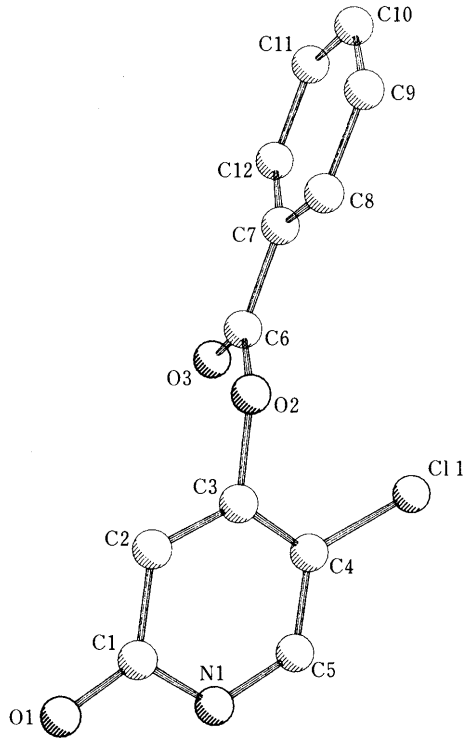


Fig. 1. A Perspective View of **5b**
Hydrogen atoms are omitted for clarity.

The silylation of **2** with hexamethyldisilazane gave the corresponding 2,4-bis(trimethylsilyloxy)pyridines (**10**) which were converted to **8** or **9** by reaction with an equimolar amount of acylating reagent, followed by hydrolysis.

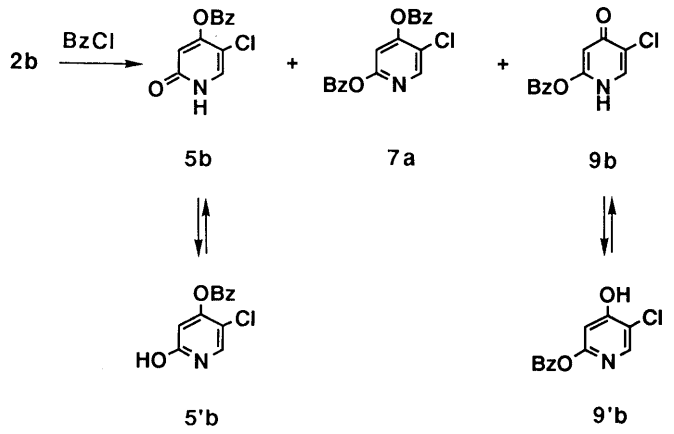


Chart 2

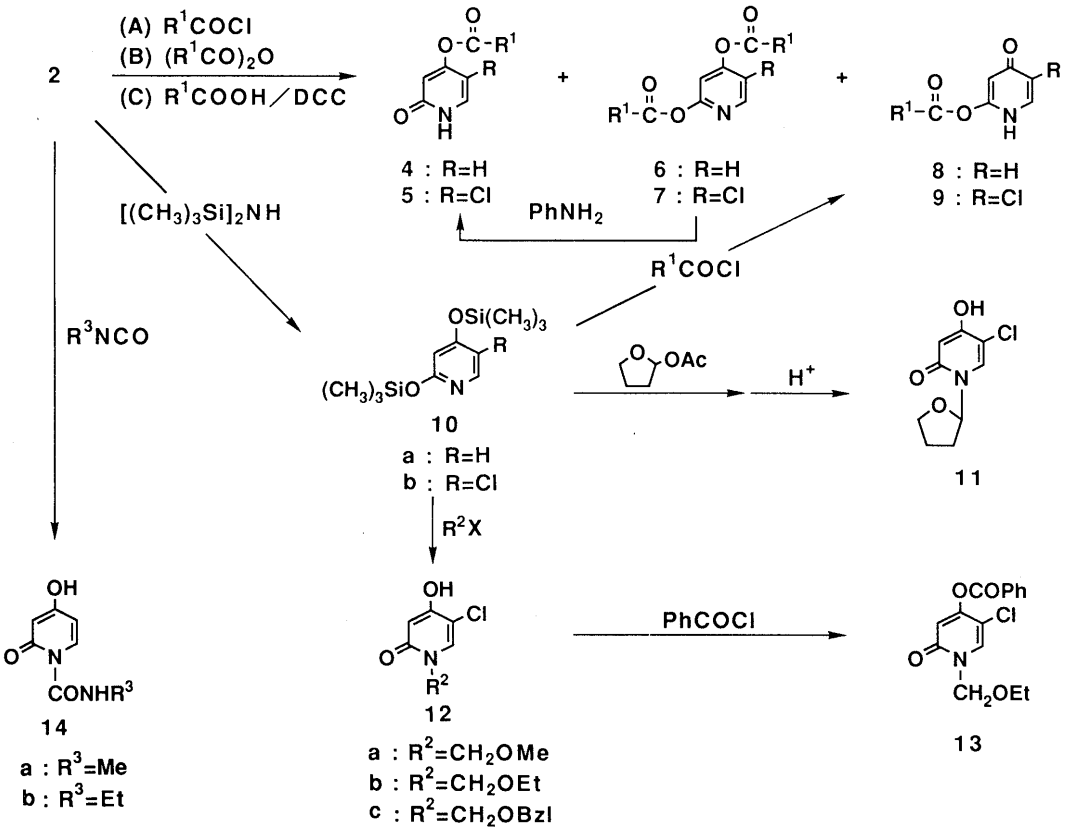


Chart 3

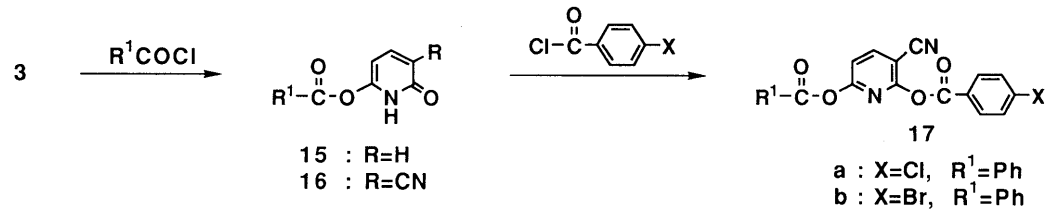


Chart 4

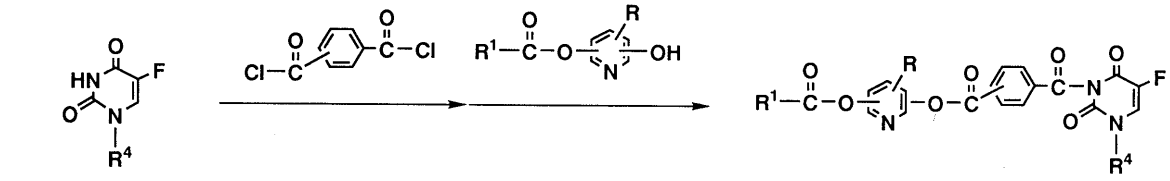


Chart 5

Compounds **8** and **9** prepared from **10** were identified as 2-acyloxy-4-pyridones from their spectral data, which were the same as those of the trace products prepared from **2** and acid chlorides as mentioned before. The monoesters **4**, **5**, **8** and **9** were rather labile, giving **2** in a protic solvent, and **6** or **7** reacted with aniline to afford **4** or **5**, respectively. Alkylation of **10b** with 2-acetoxytetrahydrofuran, followed by hydrolysis, afforded (±)5-chloro-4-hydroxyl-1-(2-tetrahydrofuryl)-2-pyridone (**11**). The 1-methoxymethyl- (**12a**), 1-ethoxymethyl- (**12b**), and 1-benzyloxymethyl-4-hydroxy-2-pyridones (**12c**) were also prepared by the reaction of **10b** and appropriate alkyloxymethyl chlorides. Benzoylation of **12b** gave 4-benzoyloxy-5-chloro-1-ethoxymethyl-2-pyridone (**13**) in good yield. The direct reaction of **2a** with alkyl isocyanates in pyridine gave 1-alkylcarbamoyl-4-hydroxy-2-pyridones (**14**) (Chart 3). All these derivatives of **2** were examined for stability *in vitro* and *in vivo*.

Compound **3b** was acylated with equimolar amount of benzoyl chloride to give a monobenzoyl derivative (**16a**). The IR spectrum showed strong bands at 1754 and 1654 cm^{-1}, suggesting that an ester and an amide bond are present in **16a**. However, the substituted position of the benzoyl group was not determined. Since **16a** did not give a suitable crystal for X-ray analysis, it was further acylated with 4-chlorobenzoyl chloride to afford a crystalline diacyl derivative (**17a**) (Chart 4), which was subjected to X-ray analysis. Its structure was determined as 6-benzoyloxy-2-(4-chlorobenzoyloxy)-3-cyanopyridine. The molecular structure of **17a** is illustrated in Fig. 2. Accordingly, the structure of **16a** was establsihed as 6-benzoyloxy-3-cyano-2-pyridone, which indicated that the 6-hydroxyl group of **3b** was preferentially acylated.

Combination of 5-FUra Masked Forms and Inhibitors

Several 1-substituted-5-fluorouracils, such as 1-ethoxy-

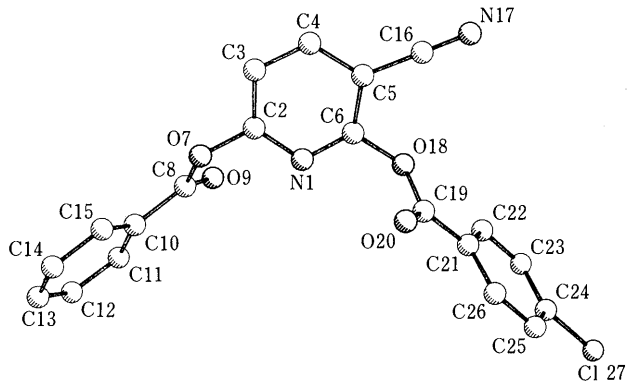


Fig. 2. A Perspective View of **17a**
Hydrogen atoms are omitted for clarity.

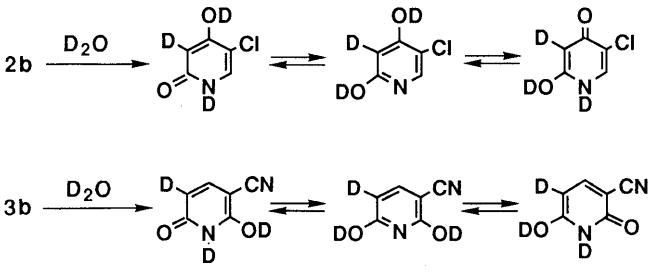


Chart 6

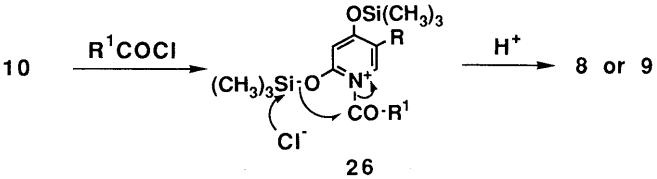


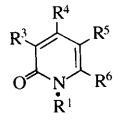
Chart 7

methyl-5-fluorouracil (**18**) (EMFU),[11] 1-benzyloxymethyl-5-fluorouracil (**19**),[12] tegafur (**20**),[4] and acetylated doxifluridine (**21**),[6b] were used as masked forms of 5-FUra, and **4**, **9** and **16** were used as derivatives of inhibitors. These two components were coupled by using bifunctional acyl chlorides such as isophthaloyl or terephthaloyl chloride in the presence of base in an anhydrous solvent to yield the desired compounds (**22**—**25**) (Chart 5). The two steps of the reaction were performed in one pot because the intermediates, the half acid chlorides, could not be effectively purified.

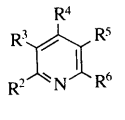
Discussion

The inhibitors, **2a**[13] and **2b**[14] were obtained in the manner described in the literature. Compound **3b** was prepared with 1,3-dimethyluracil, cyanoacetamide and sodium ethoxide in the molar ratio of 1 : 4 : 4 according to the literature.[15] However, **3b** thus prepared was contaminated with 4-amino-3-cyano-2,6-dihydroxypyridine, as determined by HPLC and TLC using an authentic sam-

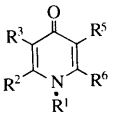
TABLE I. Physicochemical Properties of 2,4- and 2,6-Dihydroxypyridine Derivatives



4, 5, 12, 14—16



6, 7, 17



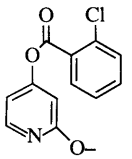
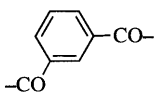
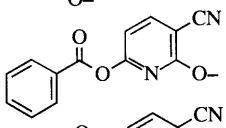
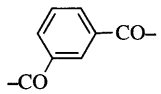
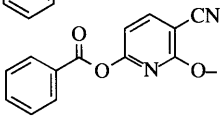
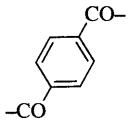
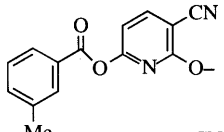
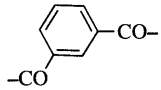
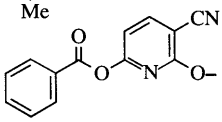
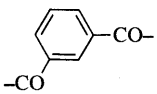
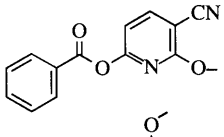
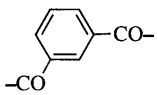
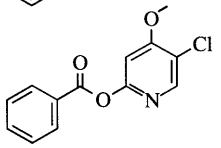
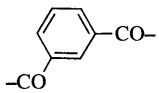
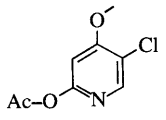
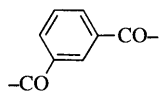
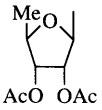
8, 9

	R^1	R^2	R^3	R^4	R^5	R^6	Method	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
4a	H	—	H	OAc	H	H	A	138—139	60	$C_7H_7NO_3$	54.90 (54.85	4.60 4.83	9.14 9.20)
4b	H	—	H	$OCOC_6H_5$	H	H	A	197—199	44	$C_{12}H_9NO_3$	66.97 (67.19	4.22 4.03	6.51 6.58)
4c	H	—	H	$OCOC_6H_4$(2-Cl)	H	H	A	144—145	68	$C_{12}H_8ClNO_3$	57.73 (57.76	3.23 3.02	5.61 5.56)
4d	H	—	H	$OCOC_6H_4$(3-O-*n*-pro)	H	H	A	180—181	81	$C_{15}H_{15}NO_4$	65.92 (65.74	5.53 5.65	5.13 5.13)
5a	H	—	H	OAc	Cl	H	A	160 (dec.)	52	$C_7H_6ClNO_3$	44.82 (44.71	3.22 3.21	7.46 7.49)
5b	H	—	H	$OCOC_6H_5$	Cl	H	A	196—197	47	$C_{12}H_8ClNO_3$	57.73 (57.98	3.23 3.08	5.61 5.67)
5c	H	—	H	$OCOC_6H_4$(4-Me)	Cl	H	A	187—189	36	$C_{13}H_{10}ClNO_3$	59.22 (59.39	3.82 3.80	5.31 5.31)
6	—	$OCOC_6H_4$(3-Cl)	H	$OCOC_6H_4$(3-Cl)	H	H	B	129—130	50	$C_{19}H_{11}Cl_2NO_4$	58.78 (58.70	2.85 2.55	3.60 3.60)
7a	—	$OCOC_6H_5$	H	$OCOC_6H_5$	Cl	H	B	124—125	87	$C_{19}H_{12}ClNO_4$	64.51 (64.81	3.42 3.17	3.96 4.04)
7b	—	$OCOC_6H_4$(4-Me)	H	$OCOC_6H_4$(4-Me)	Cl	H	B	146—148	97	$C_{12}H_{16}ClNO_4$	66.06 (65.99	4.22 4.04	3.67 3.76)
8a	H	$OCOC_6H_5$	H	—	H	H	C	124—127	30	$C_{12}H_9NO_3$	66.97 (67.16	4.22 4.08	6.51 6.50)
8b	H	$OCOC_6H_4$(2-Me)	H	—	H	H	C	116—119	44	$C_{13}H_{11}NO_3$	68.11 (68.15	4.84 4.94	6.11 6.17)
9a	H	OAc	H	—	Cl	H	C	270—272	64	$C_7H_6ClNO_3$	44.82 (44.59	3.22 3.13	7.46 7.36)
9b	H	$OCOC_6H_5$	H	—	Cl	H	C	184 (soften)	51	$C_{12}H_8ClNO_3$	57.73 (57.88	3.23 3.17	5.61 5.54)
12a	CH_2OMe	—	H	OH	Cl	H	D	216—217	49	$C_7H_8ClNO_3$	44.34 (44.26	4.25 4.43	7.38 7.10)
12b	CH_2OEt	—	H	OH	Cl	H	D	217—219	39	$C_8H_{10}ClNO_3$	47.18 (47.23	4.95 5.30	6.87 6.92)
12c	CH_2OBzl	—	H	OH	Cl	H	D	165—167	57	$C_{13}H_{12}ClNO_3$	58.77 (58.68	4.55 4.61	5.27 5.48)
14a	CONHMe	—	H	OH	H	H	E	268 (dec.)	30	$C_7H_8N_2O_3$	50.00 (50.27	4.80 5.07	16.66 16.36)
14b	CONHEt	—	H	OH	H	H	E	272 (dec.)	30	$C_8H_{10}N_2O_3$	52.74 (52.79	5.53 5.81	15.38 15.17)
15	H	—	H	H	H	$OCOC_6H_3$(2,4-Cl_2)	F	212—214	78	$C_{12}H_7Cl_2NO_3$	50.73 (50.72	2.48 2.18	4.93 4.89)
16a	H	—	CN	H	H	$OCOC_6H_5$	F	198—200 (dec.)	60	$C_{13}H_8N_2O_3$	65.00 (65.23	3.36 3.06	11.66 11.57)
16b	H	—	CN	H	H	$OCOC_6H_4$(2-Cl)	F	209—212 (dec.)	55	$C_{13}H_7ClN_2O_3$	56.85 (56.78	2.57 2.43	10.20 10.02)
16c	H	—	CN	H	H	$OCOC_6H_3$(2,4-Cl_2)	F	200—210 (dec.)	40	$C_{13}H_6Cl_2N_2O_3$	50.51 (50.78	1.96 1.77	9.06 8.84)
16d	H	—	CN	H	H	$OCOC_6H_4$(3-Me)	F	195—197 (dec.)	58	$C_{14}H_{10}N_2O_3$	66.14 (66.29	3.96 3.64	11.02 10.89)
16e	H	—	CN	H	H	O-(2-furoyl)	F	219—221 (dec.)	62	$C_{11}H_6N_2O_4$	57.40 (57.59	2.63 2.34	12.17 11.87)
16f	H	—	CN	H	H	O-(2-thenoyl)	F	196—203 (dec.)	43	$C_{11}H_6N_2O_4$	53.65 (53.72	2.46 2.31	11.38 11.33)
17a	—	$OCOC_6H_4$(4-Cl)	CN	H	H	$OCOC_6H_5$	H	157—160	82	$C_{20}H_{11}ClN_2O_4$	63.42 (62.96	2.93 2.54	7.40 7.19)
17b	—	$OCOC_6H_4$(4-Br)	CN	H	H	$OCOC_6H_5$	H	147—148	84	$C_{20}H_{11}BrN_2O_4$	56.76 (56.89	2.62 2.22	6.62 6.31)

TABLE II. ^{1}H-NMR Data for 2,4-, 2,6-Dihydroxypyridines and 5-FUra Derivatives

Compd.	^{1}H-NMR [**4**, **5**, **7**—**9**, **12**, **14**—**17** (DMSO-d_6) and **6**, **22**—**25** ($CDCl_3$)] δ ppm
4a	11.45 (1H, br s, NH), 7.43 (1H, d, J=8 Hz, C_6-H of pyridone), 6.10—6.04 (2H, m, $C_{3,5}$-H of pyridone), 2.24 (3H, s, $COCH_3$)
4b	11.72 (1H, br s, NH), 8.14—8.05 (2H, m, $C_{2,6}$-H of aroyl), 7.77—7.46 (4H, m, $C_{3,4,5}$-H of aroyl and C_6-H of pyridone), 6.29—6.21 (2H, m, $C_{3,5}$-H of pyridone)
4c	11.74 (1H, br s, NH), 8.12—7.62 (4H, m, aroyl), 7.51 (1H, d, J=8 Hz, C_6-H of pyridone), 6.29—6.20 (2H, m, $C_{3,5}$-H of pyridone)
4d	8.03 (2H, d, J=9 Hz, $C_{2,6}$-H of aroyl), 7.47 (1H, d, J=8 Hz, C_6-H of pyridone), 7.23 (2H, d, J=9 Hz, $C_{3,5}$-H of aroyl), 6.24—6.17 (2H, m, $C_{3,5}$-H of pyridone), 4.05 (2H, t, J=7 Hz, OCH_2), 1.88—1.65 (2H, m, $CH_2\underline{CH_2}CH_3$), 0.99 (3H, t, J=7 Hz, $CH_2CH_2\underline{CH_3}$)
5a	11.91 (1H, br s, NH), 7.81 (1H, s, C_6-H of pyridone), 6.35 (1H, s, C_3-H of pyridone), 2.32 (3H, s, $COCH_3$)
5b	12.01 (1H, br s, NH), 8.20—8.09 (2H, m, $C_{2,6}$-H of aroyl), 7.89 (1H, s, C_6-H of pyridone), 7.81—7.53 (3H, m, $C_{3,4,5}$-H of aroyl), 6.59 (1H, s, C_3-H of pyridone)
5c	11.97 (1H, br s, NH), 8.05 (1H, s, C_6-H of pyridone), 7.92 (2H, d, J=8 Hz, $C_{2,6}$-H of aroyl), 7.43 (2H, d, J=8 Hz, $C_{3,4}$-H of aroyl), 6.53 (1H, s, C_3-H of pyridone), 2.43 (3H, s, CH_3)
6	8.56 (1H, d, J=6 Hz, C_6-H of pyridine), 8.16—7.66 (8H, m, aroyl), 7.57—7.52 (2H, m, $C_{3,5}$-H of pyridine)
7a	8.72 (1H, s, C_6-H of pyridine), 8.23—8.13 (4H, m, $C_{2,6}$-H of aroyl × 2), 7.83—7.55 (7H, m, C_3-H of pyridine and $C_{3,4,5}$-H of aroyl × 2)
7b	8.70 (1H, s, C_6-H of pyridine), 8.06 (4H, dd, J=8, 2 Hz, $C_{2,6}$-H of aroyl × 2), 7.73 (1H, s, C_3-H of pyridine), 7.45 (4H, d, J=8 Hz, $C_{3,5}$-H of aroyl × 2), 2.45 (6H, s, CH_3 × 2)
8a	11.06 (1H, s, NH), 8.17—8.06 (3H, m, $C_{2,6}$-H of aroyl and C_6-H of pyridone), 7.77—7.59 (3H, m, $C_{3,4,5}$-H of aroyl), 6.80 (1H, dd, J=2, 6 Hz, C_5-H of pyridone), 6.65 (1H, d, J=2 Hz, C_3-H of pyridone)
8b	11.04 (1H, br s, NH), 8.11 (1H, d, J=6 Hz, C_6-H of pyridone), 8.04 (1H, d, J=9 Hz, C_6-H of aroyl), 7.60—7.36 (3H, m, $C_{3,4,5}$-H of aroyl), 6.79 (1H, dd, J=2, 6 Hz, C_5-H of pyridone), 6.64 (1H, s, J=2 Hz, C_3-H of pyridone), 2.58 (3H, s, CH_3)
9a	11.90 (1H, br s, NH), 8.20 (1H, s, C_6-H of pyridone), 6.69 (1H, s, C_3-H of pyridone), 2.27 (3H, s, $COCH_3$)
9b	8.27 (1H, S, C_6-H of pyridone), 8.16—8.07 (2H, m, $C_{2,6}$-H of aroyl), 7.78—7.51 (3H, m, $C_{3,4,5}$-H of aroyl), 6.91 (1H, s, C_3-H of pyridone)
12a	11.55 (1H, br s, OH), 7.87 (1H, s, C_6-H of pyridone), 5.76 (1H, s, C_3-H of pyridone), 5.12 (2H, s, NCH_2O), 3.24 (3H, s, OCH_3)
12b	11.63 (1H, br s, OH), 7.87 (1H, s, C_6-H of pyridone), 5.75 (1H, s, C_3-H of pyridone), 5.16 (2H, s, NCH_2O), 3.49 (2H, q, J=7 Hz, OCH_2), 1.09 (3H, t, J=7 Hz, CH_3)
12c	11.65 (1H, br s, OH), 7.92 (1H, s, C_6-H of pyridone), 7.31 (5H, s, aroyl), 5.77 (1H, s, C_3-H of pyridone), 5.27 (2H, s, NCH_2O), 4.55 (2H, s, OCH_2Ph)
14a	11.27 (1H, br s, OH), 10.36 (1H, br s, CONH), 8.23 (1H, d, J=8 Hz, C_6-H of pyridone), 6.13 (1H, dd, $J_{3,5}$=2 Hz, $J_{5,6}$=8 Hz, C_5-H of pyridone), 5.71 (1H, d, J=2 Hz, C_3-H of pyridone), 2.88 (3H, d, J=5 Hz, CH_3)
14b	11.05 (1H, br s, OH), 10.52 (1H, t, J=5 Hz, CONH), 8.25 (1H, d, J=8 Hz, C_6-H of pyridone), 6.15 (1H, dd, $J_{3,5}$=3 Hz, $J_{5,6}$=8 Hz, C_5-H of pyridone), 5.73 (1H, d, J=3 Hz, C_3-H of pyridone), 3.50—3.20 (2H, m, CH_2), 1.16 (3H, d, J=7 Hz, CH_3)
15	8.10 (1H, d, J=9 Hz, C_6-H of aroyl), 7.90—7.58 (3H, m, $C_{3,5}$-H of aroyl and C_4-H of pyridine), 6.78 (1H, d, J=8 Hz, C_5-H of pyridine), 6.64 (1H, d, J=8 Hz, C_3-H of pyridine)
16a	12.76 (1H, br s, NH), 8.33 (1H, d, J=8 Hz, C_4-H of pyridine), 8.17—8.07 (2H, m, $C_{2,6}$-H of aroyl), 7.94—7.58 (3H, m, $C_{3,4,5}$-H of aroyl), 6.95 (1H, d, J=8 Hz, C_5-H of pyridine)
16b	8.35 (1H, d, J=8 Hz, C_4-H of pyridine), 8.10 (1H, dd, J=7, 1 Hz, C_6-H of aroyl), 7.75—7.40 (3H, m, $C_{3,4,5}$-H of aroyl), 7.00 (1H, d, J=8 Hz, C_5-H of pyridine)
16c	8.29 (1H, d, J=8 Hz, C_4-H of pyridine), 8.17 (1H, d, J=8 Hz, C_6-H of aroyl), 7.74 (1H, d, J=2 Hz, C_3-H of aroyl), 7.61 (1H, dd, J=8, 2 Hz, C_5-H of aroyl), 7.01 (1H, d, J=8 Hz, C_5-H of pyridine)
16d	8.33 (1H, d, J=8 Hz, C_4-H of pyridine), 8.00—7.85 (2H, m, $C_{2,6}$-H of aroyl), 7.65—7.41 (2H, m, $C_{4,5}$-H of aroyl), 6.94 (1H, d, J=8 Hz, C_5-H of pyridine)
16e	8.32 (1H, d, J=8 Hz, C_4-H of pyridine), 8.14 (1H, dd, J=1, 2 Hz, C_5-H of furoyl), 7.63 (1H, dd, J=1, 4 Hz, C_3-H of furoyl), 6.95 (1H, d, J=8 Hz, C_5-H of pyridine), 6.82 (1H, dd, J=2, 4 Hz, C_4-H of furoyl)
16f	8.32 (1H, d, J=8 Hz, C_4-H of pyridine), 8.15 (1H, dd, J=1, 5 Hz, C_5-H of thenoyl), 8.06 (1H, dd, J=1, 4 Hz, C_3-H of thenoyl), 7.33 (1H, dd, J=4, 5 Hz, C_4-H of thenoyl), 6.96 (1H, d, J=8 Hz, C_5-H of pyridine)
17a	8.82 (1H, d, J=8 Hz, C_4-H of pyridine), 8.23—7.59 (10H, m, C_5-H of pyridine and aroyl)
17b	8.80 (1H, d, J=8 Hz, C_4-H of pyridine), 8.19—7.53 (10H, m, C_5-H of pyridine and aroyl)
22a	8.64—8.00 (5H, m, C_6-H of 2-chlorobenzoyl, $C_{2,4,6}$-H of phthaloyl and C_6-H of pyridine), 7.77—7.39 (5H, m, $C_{3,4,5}$-H of 2-chlorobenzoyl, C_5-H of phthaloyl and C_6-H), 7.34—7.25 (2H, m, $C_{3,5}$-H of pyridine), 5.14 (2H, s, NCH_2O), 3.61 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 1.20 (3H, t, J=7 Hz, $OCH_2C\underline{H_3}$)
22b	8.66—8.14 (6H, m, $C_{2,3}$-H of benzoyl, $C_{2,4,6}$-H of phthaloyl and C_4-H of pyridine), 7.82—7.33 (6H, m, C_6-H, $C_{3,4,5}$-H of benzoyl, C_5-H of phthaloyl and C_5-H of pyridine), 5.15 (2H, s, NCH_2O), 3.62 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 1.22 (3H, t, J=7 Hz, $OCH_2C\underline{H_3}$)
22c	8.39—8.02 (7H, m, $C_{2,6}$-H of benzoyl, $C_{2,3,5,6}$-H of terephthaloyl and C_4-H of pyridine), 7.67—7.39 (5H, m, $C_{3,4,5}$-H of benzoyl, C_6-H and C_5-H of pyridine), 5.14 (2H, s, NCH_2O), 3.61 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 1.22 (3H, t, J=7 Hz, $OCH_2C\underline{H_3}$)
22d	8.65—8.18 (4H, m, $C_{2,4,6}$-H of phthaloyl and C_4-H of pyridine), 8.01—7.96 (2H, m, $C_{2,6}$-H of 3-methylbenzoyl), 7.73 (1H, t, J=8 Hz, C_5-H of phthaloyl), 7.52—7.38 (4H, m, $C_{4,5}$-H of 3-methylbenzoyl, C_6-H, C_5-H of pyridine), 5.16 (2H, s, NCH_2O), 3.63 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 2.43 (3H, s, CH_3 of 3-methylbenzoyl), 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H_3}$)
23	8.66—8.14 (6H, m, $C_{2,6}$-H of benzoyl, $C_{2,4,6}$-H of phthaloyl and C_4-H of pyridine), 7.79—7.25 (11H, m, $C_{3,4,5}$-H of benzoyl, C_5-H of phthaloyl C_6-H, $C_{2,3,4,5,6}$-H of benzyl and C_5-H of pyridine), 5.21 (2H, s, NCH_2O), 4.63 (2H, s, OCH_2)
24a	8.69—8.12 (6H, m, $C_{2,6}$-H of benzoyl, $C_{2,4,6}$-H of phthaloyl and C_4-H of pyridine), 7.79—7.38 (6H, m, $C_{3,4,5}$-H of benzoyl, C_5-H of phthaloyl and C_5-H of pyridine), 5.96—5.87 (1H, m, $C_{1'}$-H), 4.30—3.80 (2H, m, $C_{4'}$-H), 2.50—1.85 (4H, m, $C_{2'}$-H and $C_{3'}$-H)
24b	8.69—8.16 (6H, m, $C_{2,6}$-H of benzoyl, $C_{2,4,6}$-H of phthaloyl and C_6-H of pyridine), 7.81—7.45 (5H, m, $C_{3,4,5}$-H of benzoyl, C_5-H of phthaloyl and C_6-H), 7.41 (1H, s, C_3-H of pyridine), 6.00—5.90 (1H, m, $C_{1'}$-H), 4.42—3.87 (2H, m, $C_{4'}$-H), 2.55—1.89 (4H, m, $C_{2',3'}$-H)
25	8.75—8.21 (4H, m, $C_{2,4,6}$-H of phthaloyl and C_6-H of pyridine), 7.73 (1H, t, J=8 Hz, C_5-H of phthaloyl), 7.48 (1H, d, J=6 Hz, C_6-H), 7.26 (1H, s, C_3-H of pyridine), 5.93 (1H, d, J=5 Hz, $C_{1'}$-H), 5.31 (1H, t, J=6 Hz, $C_{2'}$-H), 5.03 (1H, t, J=6 Hz, $C_{3'}$-H), 4.38—4.12 (1H, m, $C_{4'}$-H), 2.35 (3H, s, $COCH_3$ on pyridine), 2.10, 2.01 (each 3H, s, $COCH_3$), 1.46 (3H, d, J=6 Hz, $C_{5'}$-H)

TABLE III. Physicochemical Properties of 5-FUra Derivatives

No.	B	X	R^4	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
22a			$-CH_2OEt$	42	Powder	$C_{27}H_{19}ClFN_3O_8$	57.10 (56.89	3.37 3.45	7.40 7.10)
22b			$-CH_2OEt$	25	162—164	$C_{28}H_{19}FN_4O_8$	60.22 (60.28	3.43 3.29	10.03 9.79)
22c			$-CH_2OEt$	24	Powder	$C_{28}H_{19}FN_4O_8 \cdot 1/2H_2O$	59.26 (58.97	3.55 3.31	9.87 9.66)
22d			$-CH_2OEt$	34	155—157	$C_{29}H_{21}FN_4O_8$	60.84 (60.84	3.70 3.56	9.79 9.69)
23			$-CH_2OBzl$	26	Powder	$C_{21}H_{16}FN_3O_7 \cdot 3/2H_2O$	63.87 (63.75	3.43 3.42	9.03 8.75)
24a				22	Powder	$C_{29}H_{19}FN_4O_8 \cdot 1/2H_2O$	60.11 (60.38	3.48 3.08	9.67 9.27)
24b				31	Powder	$C_{28}H_{19}ClFN_3O_8$	57.99 (57.76	3.30 3.19	7.25 6.95)
25				19	Powder	$C_{28}H_{23}ClFN_3O_{12}$	51.90 (51.51	3.57 3.77	6.48 6.39)

ple[16] obtained from 2 mol of cyanoacetamide. For the synthesis of **3b**, an equimolar amount of cyanoacetamide to 1,3-dimethyluracil is sufficient. Thus, **3b** was obtained with 1,3-dimethyluracil, cyanoacetamide and sodium ethoxide at a molar ratio of 1 : 1 : 2.

The ^{1}H-NMR spectrum of **3b** in dimethylsulfoxide (DMSO)-d_6 gave two doublet signals at 7.83 and 5.71 ppm with $J = 8$ Hz, respectively. The signal at 5.71 ppm disappeared and the signal at 7.83 ppm became a singlet upon addition of D_2O. This shows that the proton at C_5 of **3b** is extremely labile, and there is a keto–enol tautomerism involving C_6-OH and C_5-H (Chart 6). Similar tautomerism was observed for the 2,4-dihydroxypyridines, **2a**, **2b**, **11**, **12** and **14**, at the C_3 proton. This finding is in agreement with the result of Robins and Currie for 3-deazauracil.[17] On the other hand, no exchange of C_3-H with D_2O was observed in **5b** or **9b**. Consequently, it appears that the tautomerism may occur in the case of 4-hydroxy-2-pyridone form.

Acylation of **2** using an equimolar amount of an acylating reagent provided mainly **4** or **5**, indicating that the tautomerism of compound **2** favors the keto form at the 2-position. On the other hand, acylation of **10** mainly yielded **8** or **9**, suggesting that **10** reacted with the acyl chloride to give the intermediate pyridinium salt of the acyl chloride (**26**), and then the acyl group was transferred to the oxygen of C_2(N→O) (Chart 7). The acylated pyridines, **6** and **7**, reacted with aniline to give benzanilide, indicating that these compounds are active esters.

The desired 5-FUra derivatives containing an inhibitor **3b** have potent antitumor activity in mice and rats.[18] Clinical trials of compound **22b** (BOF-A2) are in progress.

Experimental

Melting points were measured using a Yanagimoto apparatus and are not corrected. IR spectra were taken with KBr tablets on a Shimadzu

TABLE IV. Atomic Coordinates for Non-hydrogen Atoms of **5b** with Their Estimated Standard Deviations in Parentheses

Atom	x	y	z
Cl1	0.7716 (2)	0.43384 (9)	0.0805 (2)
O1	0.6258 (5)	0.7604 (2)	−0.1162 (5)
O2	0.7849 (4)	0.5101 (2)	−0.2662 (5)
O3	0.5590 (5)	0.4411 (2)	−0.3412 (5)
N1	0.6485 (5)	0.6574 (3)	0.0779 (6)
C1	0.6556 (6)	0.6890 (3)	−0.0839 (7)
C2	0.6999 (6)	0.6351 (3)	−0.2017 (7)
C3	0.7314 (6)	0.5590 (3)	−0.1542 (7)
C4	0.7228 (6)	0.5296 (3)	0.0135 (7)
C5	0.6798 (6)	0.5805 (3)	0.1241 (7)
C6	0.6905 (6)	0.4470 (3)	−0.3466 (6)
C7	0.7740 (6)	0.3916 (3)	−0.4311 (6)
C8	0.9303 (6)	0.4021 (3)	−0.4230 (7)
C9	1.0038 (7)	0.3459 (3)	−0.4994 (7)
C10	0.9197 (7)	0.2816 (4)	−0.5876 (7)
C11	0.7644 (7)	0.2713 (3)	−0.5950 (7)
C12	0.6902 (6)	0.3259 (3)	−0.5180 (6)

TABLE V. Bond Distances (Å) of **5b** for Non-hydrogen Atoms with Their Estimated Standard Deviations in Parentheses

Cl1–C4	1.714 (5)	C3–C4	1.417 (5)
O1–C1	1.245 (5)	C4–C5	1.351 (5)
O2–C3	1.385 (5)	C6–C7	1.471 (5)
O2–C6	1.383 (5)	C7–C8	1.391 (5)
O3–C6	1.193 (5)	C7–C12	1.391 (5)
N1–C1	1.384 (5)	C8–C9	1.387 (5)
N1–C5	1.353 (5)	C9–C10	1.377 (5)
C1–C2	1.429 (5)	C10–C11	1.383 (5)
C2–C3	1.342 (5)	C11–C12	1.373 (5)

TABLE VI. Bond Angles (°) of **5b** for Non-hydrogen Atoms with Their Estimated Standard Deviations in Parentheses

C3–O2–C6	117.5 (4)	N1–C5–C4	121.2 (5)
C1–N1–C5	123.2 (5)	O2–C6–O3	121.4 (5)
O1–C1–N1	119.3 (5)	O2–C6–C7	111.6 (4)
O1–C1–C2	125.0 (5)	O3–C6–C7	127.0 (5)
N1–C1–C2	115.7 (5)	C6–C7–C8	122.6 (5)
C1–C2–C3	120.7 (5)	C6–C7–C12	116.9 (4)
O2–C3–C2	118.8 (5)	C8–C7–C12	120.5 (5)
O2–C3–C4	119.6 (4)	C7–C8–C9	119.6 (5)
C2–C3–C4	121.4 (5)	C8–C9–C10	119.6 (5)
Cl1–C4–C3	121.9 (4)	C9–C10–C11	120.6 (6)
Cl1–C4–C5	120.2 (4)	C10–C11–C12	119.1 (5)
C3–C4–C5	117.9 (5)	C7–C12–C11	119.1 (5)

model IR-410 spectrometer. The ^{1}H-NMR spectra were obtained with a Hitachi (90 MHz) spectrometer. Chemical shifts are expressed downfield from tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed on a Yanaco CHN corder MT-3.

4-Benzoyloxy-5-chloro-2-pyridone (5b) (Method A) Benzoyl chloride (0.96 ml, 8.24 mmol) was added to a solution of **2b** (1.00 g, 6.87 mmol) in dry pyridine (50 ml) and the mixture was stirred at room temperature for 4 h. The solvent was evaporated and the residue was triturated with water. The resulting precipitate was collected on a filter and washed with EtOH to give 0.64 g (37%) of **5b**. IR (KBr): 1751 (C=O), 1661 (CONH) cm^{-1}. The EtOH wash was evaporated and the residue was purified by silica gel column chromatography ($CHCl_3$—2% MeOH–$CHCl_3$) to give 0.46 g (18.9%) of **7b** and more **5b** (0.17 g, 9.9%). Suitable crystals of **5b** for X-ray analysis were obtained by recrystallization from EtOH, and the structure of **5b** was determined by X-ray analysis as mentioned below. Compounds **4a—d** **5a**, and **5c** were synthesized by the same procedures employed in the preparation of **5b**. Physicochemical and ^{1}H-NMR spectral data of these compounds are given in Tables I and II, respectively.

X-Ray Analysis of 4-Benzoyloxy-5-chloro-2-pyridone (5b) $C_{12}H_8ClNO_3$, $M=249.7$, monoclinic, space group $P2_1/c$, $a=8.939(4)$ Å, $b=16.882(7)$ Å, $c=7.763(5)$ Å, $\beta=107.80(4)°$, $V=1115$ Å^3, $\mu(MoK_\alpha)=3.4$ cm^{-1}, $Z=4$, $D_x=1.49$ g/cm^3. The cell dimensions and intensities were measured on a Syntex R3 four-circle diffractometer with graphite-monochromated MoK_α radiation in the ω-scan mode for $2\theta<45°$. A total of 1465 independent reflections were collected, among which 1236 independent reflections [$I>1.96\ \sigma\ (I)$] were used for the structures analysis. The structure was solved by the direct method using MULTAN on a Syntex XTL crystallographic software package. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography.[19] Refinement was done by the block-diagonal least-squares method. Thermal parameters were refined anisotropically for non-hydrogen atoms and isotropically for hydrogen atoms. The final R value was 0.058. Atomic coordinates for non-hydrogen atoms, bond distances and bond angles are given in Tables IV, V and VI, respectively.

TABLE VII. Atomic Coordinates for Non-hydrogen Atoms of **17a** with Their Estimated Standard Deviations in Parentheses

Atom	x	y	z
N1	0.8673 (2)	0.8312 (5)	−0.0526 (3)
C2	0.8222 (2)	0.8865 (6)	−0.0951 (3)
C3	0.7692 (2)	0.9363 (5)	−0.0611 (3)
C4	0.7610 (2)	0.9238 (5)	0.0220 (3)
C5	0.8070 (2)	0.8649 (5)	0.0708 (3)
C6	0.8587 (2)	0.8232 (5)	0.0272 (3)
O7	0.8261 (2)	0.8852 (4)	−0.1789 (2)
C8	0.8790 (2)	0.9270 (5)	−0.2200 (4)
O9	0.9165 (2)	0.9918 (4)	−0.1829 (2)
C10	0.8798 (2)	0.8836 (5)	−0.3056 (3)
C11	0.9321 (3)	0.9150 (5)	−0.3524 (4)
C12	0.9337 (3)	0.8788 (7)	−0.4332 (4)
C13	0.8856 (3)	0.8140 (6)	−0.4686 (4)
C14	0.8356 (3)	0.7809 (6)	−0.4238 (4)
C15	0.8320 (2)	0.8164 (5)	−0.3416 (3)
C16	0.8021 (2)	0.8444 (5)	0.1571 (3)
N17	0.7974 (2)	0.8265 (4)	0.2263 (3)
O18	0.9082 (1)	0.7728 (3)	0.0732 (2)
C19	0.9168 (2)	0.6396 (5)	0.0711 (3)
O20	0.8798 (1)	0.5685 (3)	0.0410 (2)
C21	0.9759 (2)	0.6027 (5)	0.1103 (3)
C22	1.0165 (2)	0.6941 (5)	0.1413 (3)
C23	1.0724 (2)	0.6528 (5)	0.1749 (3)
C24	1.0854 (2)	0.5241 (5)	0.1779 (3)
C25	1.0457 (2)	0.4316 (5)	0.1491 (3)
C26	0.9904 (2)	0.4724 (5)	0.1153 (3)
Cl27	1.15602 (6)	0.4737 (2)	0.2197 (1)

TABLE VIII. Bond Distances (Å) of **17a** for Non-hydrogen Atoms with Their Estimated Standard Deviations in Parentheses

N1–C2	1.323 (7)	C12–C13	1.363 (10)
N1–C6	1.303 (7)	C13–C14	1.346 (9)
C2–C3	1.372 (7)	C14–C15	1.378 (8)
C2–O7	1.356 (6)	C16–N17	1.136 (6)
C3–C4	1.359 (8)	O18–C19	1.383 (6)
C4–C5	1.407 (7)	C19–O20	1.189 (6)
C5–C6	1.391 (7)	C19–C21	1.477 (7)
C5–C16	1.412 (7)	C21–C22	1.382 (6)
C6–O18	1.403 (6)	C21–C26	1.380 (7)
O7–C8	1.392 (6)	C22–C23	1.394 (6)
C8–O9	1.210 (6)	C23–C24	1.356 (7)
C8–C10	1.451 (8)	C24–C25	1.366 (7)
C10–C11	1.401 (8)	C24–Cl27	1.750 (5)
C10–C15	1.374 (7)	C25–C26	1.381 (7)
C11–C12	1.357 (9)		

2,4-Dibenzoyloxy-5-chloropyridine (7a) (Method B) Benzoyl chloride (1.76 ml, 15.1 mmol) was added to a solution of **2b** (1.00 g, 6.87 mmol) in dry pyridine (30 ml) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was dissolved in a mixture of AcOEt (60 ml) and H_2O (30 ml). The AcOEt layer was separated, dried

TABLE IX. Bond Angles (°) of **17a** for Non-hydrogen Atoms with Their Estimated Standard Deviations in Parentheses

C2–N1–C6	115.7 (5)	C11–C12–C13	121.1 (5)
N1–C2–C3	124.9 (5)	C12–C13–C14	121.0 (5)
N1–C2–O7	117.8 (5)	C13–C14–C15	119.8 (5)
C3–C2–O7	117.1 (5)	C10–C15–C14	119.7 (5)
C2–C3–C4	118.0 (5)	C5–C16–N17	178.9 (5)
C3–C4–C5	119.9 (5)	C6–O18–C19	117.1 (5)
C4–C5–C6	114.9 (5)	O18–C19–O20	122.0 (5)
C4–C5–C16	124.1 (5)	O18–C19–C21	111.1 (5)
C6–C5–C16	120.9 (5)	O20–C19–C21	126.9 (5)
N1–C6–C5	126.6 (5)	C19–C21–C22	122.1 (5)
N1–C6–O18	115.8 (5)	C19–C21–C26	118.2 (5)
C5–C6–O18	117.6 (5)	C22–C21–C26	119.7 (5)
C2–O7–C8	121.6 (5)	C21–C22–C23	119.1 (5)
O7–C8–O9	119.2 (5)	C22–C23–C24	119.5 (5)
O7–C8–C10	111.6 (5)	C23–C24–C25	122.6 (5)
O9–C8–C10	129.2 (5)	C23–C24–C127	119.0 (5)
C8–C10–C11	116.9 (5)	C25–C24–C127	118.4 (5)
C8–C10–C15	123.2 (5)	C24–C25–C26	117.9 (5)
C11–C10–C15	119.9 (5)	C21–C26–C25	121.1 (5)
C10–C11–C12	118.4 (5)		

over anhydrous $MgSO_4$ and evaporated. The resulting precipitate was washed with a small amount of EtOH to give 2.11 g (87%) of **7a**. IR (KBr): 1760 (C=O), 1748 (C=O) cm^{-1}. Compounds **6** and **7b** were synthesized by the same procedures employed in the preparation of **7a**. Physicochemical and ^{1}H-NMR spectral data of these compounds are given in Tables I and II, respectively.

2,4-Bis(trimethylsilyloxy)-5-chloropyridine (10b) A suspension of **2b** (9.6 g, 66 mmol) in hexamethyldisilazane (50 ml) was refluxed overnight. The solution was distilled to give 14.4 g (75%) of **10b**, bp 120 °C (7 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 7.97 (1H, s, C_6-H), 6.18 (1H, s, C_3-H), 0.33 (18H, $CH_3 \times 6$).

2-Benzoyloxy-5-chloro-4-pyridone (9b) (Method C) A suspension of **2b** (1.00 g, 6.87 mmol) in hexamethyldisilazane (10 ml, 47.7 mmol) was refluxed overnight. The excess silazane was removed by evaporation and the residue was dissolved in CH_2Cl_2 (30 ml). Benzoyl chloride (1.06 g, 7.54 mmol) and stannic chloride (0.10 ml, 0.87 mmol) were added and the mixture was stirred at room temperature for 5 h. The reaction mixture was neutralized with Et_3N and evaporated. The residue was triturated with MeOH and the resulting precipitate was collected on a filter and washed with H_2O to give 0.95 g (51%) of **9b**. IR (KBr): 1742 (C=O), 1675 (CONH) cm^{-1}. Compounds **8a**, **b** and **9a** were synthesized by the same procedures employed in the preparation of **9b**. Physicochemical and ^{1}H-NMR spectral data of these compounds are given in Tables I and II, respectively.

4-Benzoyloxy-5-chloro-2-pyridone (5b) (Aminolysis) Aniline (0.31 ml, 3.40 mmol) was added to a solution of **7b** (1.00 g, 2.83 mmol) in dioxane (30 ml) and the mixture was allowed to stand at 90—100 °C for 5 h. Aniline (0.51 ml, 1.65 mmol) was added again and the mixture was allowed to stand at the same temperature for another 2 h. The solvent was evaporated and the precipitate was purified by silica gel column chromatography (2% MeOH–$CHCl_3$) to give 0.26 g (37%) of **5b**. This was identical with the compound prepared by method A in terms of melting point and ^{1}H-NMR spectra.

(±)-5-Chloro-4-hydroxy-1-(2-tetrahydrofuryl)-2-pyridone (11) A suspension of **2b** (1.00 g, 6.87 mmol) and hexamethyldisilazane (10 ml, 47.7 mmol) was refluxed for 6 h. The solvent was evaporated and the oily residue was dissolved in CH_2Cl_2 (50 ml). To this solution, 2-acetoxytetrahydrofuran (1.00 g, 7.68 mmol) and stannic chloride (0.1 ml, 0.87 mmol) was added, and the mixture was allowed to stand at room temperature overnight. The mixture was neutralized with Et_3N and evaporated. The residue was triturated with MeOH and the mixture was evaporated again to give a crude product, which was purified by silica gel column chromatography (2% MeOH/$CHCl_3$) to give 1.07 g (73.5%) of **11**, mp 170—173 °C. IR (KBr): 1649 (CONH) cm^{-1}. *Anal.* Calcd for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67; N, 6.50. Found: C, 50.15; H, 4.81; N, 6.32 ^{1}H-NMR (DMSO-d_6) δ: 11.6 (1H, br s, OH), 7.59 (1H, s, C_6-H), 6.19—5.99 (1H, q, $C_{1'}$-H), 5.76 (1H, s, C_3-H), 4.39—3.73 (2H, m, $C_{4'}$-H), 2.42—1.82 (4H, m, $C_{2',3'}$-H).

5-Chloro-4-hydroxyl-1-methoxymethyl-2-pyridone (12a) (Method D) Chloromethyl methyl ether (0.66 g, 8.20 mmol) was added to a solution of **10b** (1.75 g, 6.04 mmol) in CH_3CN (20 ml) and the mixture was stirred at room temperature for 6 h. The mixture was neutralized with Et_3N and the solvent was evaporated. The residue was purified by silica gel column chromatography (2% MeOH–$CHCl_3$) to give 0.63 g (49%) of **12a**. IR (KBr): 1654 (CONH) cm^{-1}. Compounds **12b** and **12c** were synthesized by the same procedures employed in the preparation of **12a** physicochemical and ^{1}H-NMR spectral data of these compounds are given in Tables I and II, respectively.

4-Benzoyloxy-5-chloro-1-ethoxymethyl-2-pyridone (13) Benzoyl chloride (0.14 ml, 1.20 mmol) and Et_3N (0.68 ml, 4.91 mmol) were added to a solution of **12b** (0.20 g, 0.98 mmol) in dry dioxane (10 ml), and the mixture was refluxed for 6 h. The solvent was evaporated and the residue was washed with H_2O and a mixture of acetone–MeOH (1 : 1) to give 0.28 g (93%) of **13**, mp 119—120 °C. IR (KBr): 1746 (C=O), 1679 (CONH) cm^{-1}. *Anal.* Calcd for $C_{15}H_{14}ClNO_4$: C, 58.54; H, 4.58; N, 4.55. Found: C, 58.55; H, 4.63; N, 4.49. ^{1}H-NMR ($CDCl_3$) δ: 8.21—7.42 (6H, m, aroyl and C_6-H), 6.61 (1H, s, C_3-H), 5.35 (2H, s, NCH_2O), 3.65 (2H, q, $J=5$ Hz, OCH_2CH_3), 1.23 (3H, t, $J=5$ Hz, OCH_2CH_3).

4-Hydroxy-1-methylcarbamoyl-2-pyridone (14a) (Method E) Methyl isocyanate (0.64 g, 10.8 mmol) was added to a suspension of **2a** (1.00 g, 9.0 mmol) in pyridine (20 ml) and the mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was dissolved in AcOEt (50 ml). This solution was washed with H_2O (30 ml × 2). The organic layer was dried with anhydrous $MgSO_4$ and evaporated. The residue was recrystallized from EtOH–Et_2O to give 0.45 g (30%) of **14a**. IR (KBr): 1690 (CONH), 1655 (CONH) cm^{-1}. Compound **14b** was synthesized by the same procedures employed in the preparation of **14a**. Physicochemical and ^{1}H-NMR spectral data of these compounds are given in Tables I and II, respectively.

3-Cyano-2,6-dihydroxypyridine (3b)[15] 1,3-Dimethyluracil[20] (19.0 g, 0.136 mol) was added to a solution of sodium (6.50 g, 0.283 mol) in EtOH (400 ml), and the mixture was refluxed for 0.5 h. Then, cyanoacetamide (11.5 g, 0.137 mol) in EtOH (400 ml) was added dropwise over 0.5 h and the mixture was cooled. The resulting precipitate was collected on a filter and suspended in H_2O (500 ml). Concentrated hydrochloric acid was added to bring the pH to about 2. The precipitate was collected by filtration and dried over P_2O_5 to give 15.5 g (84%) of **3b**, mp colored from 165 °C and darkened at about 185 °C. IR (KBr): 2222 (CN), 1605, 1553 cm^{-1}. *Anal.* Calcd for $C_6H_4N_2O_2$: C, 52.95; H, 2.95; N, 20.58. Found: C, 53.13; H, 2.67; N, 20.31. ^{1}H-NMR (DMSO-d_6) δ: 11.04 (2H, br s, NH or OH × 2), 7.83 (1H, d, $J=8$ Hz, C_4-H), 5.71 (1H, d, $J=8$ Hz, C_5-H).

6-Benzoyloxy-3-cyano-2-pyridone (16a) (Method F) Et_3N (1.02 ml, 7.29 mmol) and benzoyl chloride (0.86 ml, 7.46 mmol) were added dropwise at room temperature to a solution of **3b** (1.00 g, 7.35 mmol) in *N*,*N*-dimethylacetamide (40 ml), and the reaction mixture was stirred for 1 h. The resulting precipitate was removed by filtration and the filtrate was evaporated. The residue was washed with $CHCl_3$ and H_2O to give 1.06 g (60%) of **16a**. IR (KBr): 2229 (CN), 1754 (C=O), 1654 (CONH), 1596, 699 cm^{-1}. Compounds **15** and **16b—f** were synthesized by the same procedures employed in the preparation of **16a**. Physicochemical and ^{1}H-NMR spectral data of these compounds are given in Tables I and II, respectively.

Method G Benzoic acid (1.83 g, 15.0 mmol) and DCC (3.10 g, 15.0 mmol) were added to an ice-cooled solution of **3b** (2.00 g, 14.7 mmol) in *N*,*N*-dimethylacetamide (40 ml), and the reaction mixture was stirred for 1 h, then at room temperature overnight. The resulting dicyclohexylurea was filtered off and the filtrate was evaporated. The residue was dissolved in a mixture of AcOEt (50 ml) and H_2O (50 ml) and the organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated and the resulting precipitate was washed with EtOH to give 1.39 g (39%) of **16a**. The product was identical with the compound prepared by method F in terms of ^{1}H-NMR and IR spectra.

6-Benzoyloxy-2-(4-chlorobenzoyloxy)-3-cyanopyridine (17a) (Method H) Et_3N (1.73 ml, 12.5 mmol) and 4-chlorobenzoyl chloride (0.72 g, 4.11 mmol) were added to a solution of **16a** (1.00 g, 4.16 mmol) in dioxane (50 ml), and the reaction mixture was stirred at room temperature for 1 h. The resulting precipitate was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$) to give 1.29 g (82%) of **17a**. Suitable crystals of **17a** for X-ray analysis were obtained by recrystallization from acetone. The structure of **17a** was determined by X-ray analysis as mentioned below. Compound **17b** was synthesized by the same procedures employed in the preparation of **17a**. Physicochemical and ^{1}H-NMR spectral data of these compounds are given in Tables I and II, respectively.

X-Ray Analysis of 6-Benzoyloxy-2-(4-chlorobenzoyloxy)-3-cyanopyridine (17a) $C_{20}H_{11}ClN_2O_4$, $M=378.8$, monoclinic, space group $C2c$, $a=$

21.668(8) Å, $b = 10.295(4)$ Å, $c = 16.133(11)$ Å, $\beta = 90.06(4)°$, $V = 3599$ Å^3, μ (MoK_α) $= 2.5$ cm^{-1}, $Z = 8$, $D_x = 1.40$ g/cm^3. Experimental conditions were the same as those for **5b**. The data were collected using the ω-scan mode for $2\theta < 40°$. A total of 1685 independent reflections were collected, among which 1269 independent reflections [$I > 1.96\sigma(I)$] were used for the structure analysis. The final R value was 0.053. Atomic coordinates for non-hydrogen atoms, bond distances and bond angles are given in Tables VII, VIII and IX, respectively.

3-[3-(6-Benzoyloxy-3-cyano-2-pyridyloxycarbonyl)benzoyl]-1-ethoxymethyl-5-fluorouracil (BOF-A2) (22b) (Method J) Isophthaloyl chloride (1.52 g, 7.49 mmol) and Et_3N (5.53 ml, 39.5 mmol) were added to a solution of 1-ethoxymethyl-5-fluorouracil (**18**)[11] (1.17 g, 6.22 mmol) in dry dioxane (50 ml) and the mixture was stirred at room temperature for 1 h. The resulting precipitate was removed by filtration and the filtrate was evaporated. The residue was dissolved in $CHCl_3$ (50 ml), then Et_3N (3.46 ml, 24.7 mmol) and **16a** (2.10 g, 8.74 mmol) were added. The reaction mixture was stirred at room temperature for 2 h and the resulting precipitate was removed by filtration. The filtrate was evaporated and the residue was purified by silica gel column chromatography ($CHCl_3$) to give 0.86 g (25%) of **22b**. IR (KBr): 2234 (CN), 1757 (C=O), 1714 (C=O), 1672 (CONH) cm^{-1}. Compounds **22a**, **c**, **d** and **23**—**25** were synthesized by the same procedures employed in the preparation of **22b**. Physicochemical and ^{1}H-NMR spectral data of these compounds are given in Tables III and II, respectively.

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