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Synthesis of Tetrahydro-2-furyl Derivatives of 5-Substituted Uracils

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Addition of 5-fluorouracil (**1**) to the double bond of 2,3-dihydrofuran (**3**) without using any catalyst progressed smoothly at an elevated temperature and afforded an equilibrium mixture of 1-(tetrahydro-2-furyl)-5-fluorouracil (**5**) and 1,3-bis(tetrahydro-2-furyl)-5-fluorouracil (**7**). By choosing favourable reaction conditions, each of these compounds was obtained in high yield.

Thermal decomposition of **7** gave an equimolar mixture of **3** and **5**. At a higher temperature, **5** underwent thermal reaction to yield **1** and **3**.

Study of the present addition reaction was extended to other 5-substituted uracils (**8**, R=–H, $-CH_3$, –Cl, –Br, $-COOCH_3$, $-CONH_2$, –CN) which furnished the corresponding 1-(tetrahydro-2-furyl)- and 1,3-bis(tetrahydro-2-furyl)-derivatives (**9**—**15**, **18**—**23**) with high yields. A very small amount of 3-(tetrahydro-2-furyl)-5-substituted uracils (**6**, **16**, **17**) by-produced in the reactions was isolated and the structures unequivocally identified.

Keywords——anticancer drug; 1-(tetrahydro-2-furyl)-5-fluorouracil; tetrahydrofurylation; 5-substituted uracils; addition reaction; elimination reaction; 2,3-dihydrofuran

This report deals with a new and facile synthesis of 1-(tetrahydro-2-furyl)-5-fluorouracil (**5**), a cancer therapeutic agent which is widely used clinically, and its analogs, 3-(tetrahydro-2-furyl)-5-fluorouracil (**6**), 1,3-bis(tetrahydro-2-furyl)-5-fluorouracil (**7**), and the related tetrahydro-2-furyl derivatives of 5-substituted uracils (**9**—**23**).

Recently attention has been paid to the synthesis of 1-(tetrahydro-2-furyl)-5-fluorouracil, and a large number of reports dealing with the preparation have appeared in patent and academic literature.[2–9] The previously reported syntheses involve the reaction of 5-fluoro-

1) Location: *17–85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan.*
2) S.A. Hiller, R.A. Zhuk, and M. Yu. Lidak, *Dokl. Acad. Nauk.* (USSR), **176**, 332 (1967).
3) S.A. Hiller, R.A. Zhuk, M. Yu. Lidak, and A.A. Zidermane, British Patent 1168391 (1969).
4) C.W. Noell and C.C. Cheng, *J. Heter. Chem.*, **5**, 25 (1968).
5) S.A. Hiller, M.Y. Lidak, R.A. Zhuk, A.E. Berzinya, K.I. Pets, I.N. Getsova, and E.I. Bruk, *Chem. Heterocyclic Compounds* (USSR), **5**, 283 (1969).
6) S.A. Hiller, A.A. Lazdinsh, A.K. Veinberg, and A.B. Sidorov, Bergium Patent 830215 (1975).
7) R.A. Earl and L.B. Townsend, *J. Heter. Chem.*, **9**, 1141 (1972).
8) T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, O. Kusama, H. Sugi, and K. Kawasaki, *Heterocycles*, **6**, 529 (1977), and patent references cited; *a*) M. Yasumoto, I. Yamawaki, T. Muranaka, and S. Hashimoto, *J. Med. Chem.*, **21**, 738 (1978).
9) Recent patent publications listed below indicate that the tetrahydro-2-furylation of **1** can be achieved by treating O-bis(trimethylsilyl)-5-fluorouracil with **3** only when an acid catalyst, such as hydrogen chloride or *p*-toluenesulfonic acid is present.[9a–h] Relating to this, the foregoing information[7,10] clearly indicated that the formation of **4** (X=–Cl, $-OCOCH_3$) by treating an acid (HCl, CH_3COOH) with **3** occurred very smoothly under the mild conditions, usually at room temperature or below 0°. This was also confirmed in our hands by NMR analysis as described in the experimental section. Accordingly, the reaction in the presence of an acid catalyst can be considered to proceed by an initial addition of the catalyst to the double bond of **3** with the formation of intermediate **4**, which on the subsequent substitution with trimethylsilylated uracils yields the tetrahydro-2-furylated products of **1**. *a*) As. Latv. Org. Synth. Japan Kokai Pat. 51-127087 (1976) [*C.A.*, **85**, 192750 (1976)]; *b*) Fujikagaku Co., Japan Kokai Pat. 52-31079 (1977) [*C.A.*, **87**, 53375d (1977)]; *c*) Asahikasei Co., Japan Kokai Pat. 52-42887 (1977); *d*) Asahikasei Co., Japan Kokai Pat. 52-48677 (1977); *e*) Asahikasei Co., Japan Kokai Pat. 52-59174 (1977); *f*) Asahikasei Co., Japan Kokai Pat. 52-59175 (1977); *g*) Mitsuitoatsukagaku Co., Japan Kokai Pat. 52-89678 (1977) [*C.A.*, **87**, 135397b (1977)]; *h*) T. Toyama, Japan Kokai Pat. 52-71479 (1977).
10) M.H. Normant, *C. R. Acad. Sci.*, **228**, 102 (1949).

uracil (**1**) or its mercury salt or O-bis(trimethylsilyl)-5-fluorouracil (**2**) with a 2-substituted tetrahydrofuran (**4**, X=2-chloro-, 2-acetoxy- and 2-alkoxy-)[2-6,8,9] in the presence or absence of additives, or the fluorination of 1-(tetrahydro-2-furyl)uracil.[7]

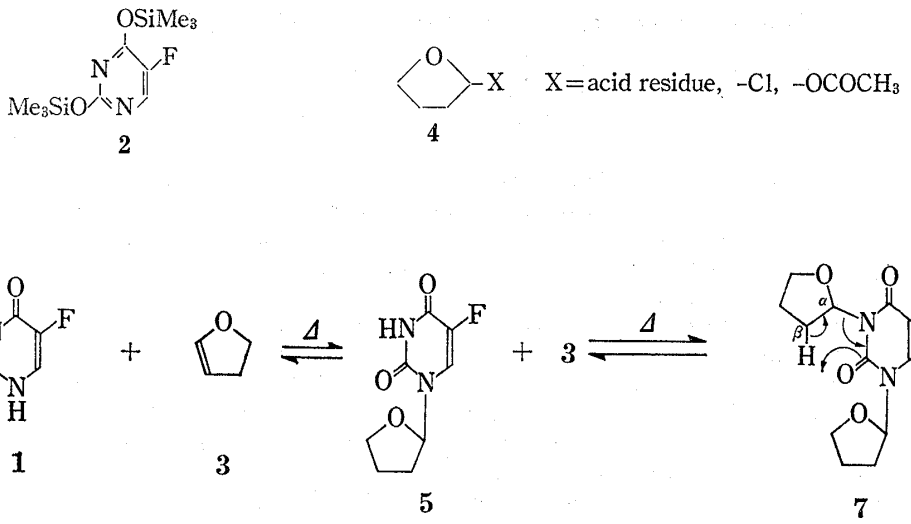


Chart 1

Tetrahydro-2-furylation of uracils by the direct addition to the double bond of 2,3-dihydrofuran (**3**) has not yet been reported. Hiller *et al.*[2] have reported that this reaction does not proceed in spite of their intensive trials. In contrast to this, we found that the direct addition of 5-fluorouracil (**1**) to 2,3-dihydrofuran (**3**) proceeded smoothly in an aprotic solvent at elevated temperatures and gave tetrahydro-2-furylated 5-fluorouracils in high yields.

It should be emphasized that the nucleophilic addition of **1** to the double bond of **3** took place successfully without any catalyst. The main products were 1-(tetrahydro-2-furyl)-5-fluorouracil (**5**) and 1,3-bis(tetrahydro-2-furyl)-5-fluorouracil (**7**) (Chart 1).

The proportion of **5** and **7** in the reaction mixture was dependent upon the molar concentrations and the molar ratio of **1** and **3** used. By using a low molar concentration of **3**, this reaction favoured the formation of **5**, for instance, when a mixture of 1 mol of **1** and 4 mol of **3** was dissolved in a large quantity of pyridine and allowed to react at about 180°, **5** was the main product. Under these conditions and at higher temperatures, the yield of **7** was prone to decrease, presumably due to the thermal decomposition of **7** to **5**.

The reaction with a large excess of **3**, which served both as the reagent and solvent, at about 160° gave **7** as the main product. In this case, the temperature appeared to have little effect on the proportion of **5** and **7** in the reaction mixture.

Careful examination of the reaction mixture revealed the presence of a small amount of 3-(tetrahydro-2-furyl)-5-fluorouracil (**6**) which was chromatographically isolated as colorless needles. The yield was always less than 2% despite repeated trials under different reaction conditions. This indicates that the main pathway is the initial introduction of a tetrahydro-2-furyl group at position 1 of **1** to yield **5**.

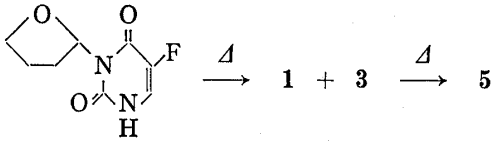
The structure of **5** was unequivocally confirmed to be identical with an authentic sample, prepared by a published procedure,[2] by direct comparison of the melting point, elemental analysis and spectral examination. The structure of **6** was determined by elemental analysis and the spectral data. The location of the tetrahydro-2-furyl group was assigned to position 3 due to the similarity of the ultraviolet (UV) absorption spectrum of **6** to those of 3-methyl-5-fluoro-[11] and 3-methyl-5-bromouracil,[12] and by the marked difference from those of **5** and **7**.

11) K.L. Wierzchowski, E. Litonska, and D. Shugar, *J. Am. Chem. Soc.*, **87**, 4621 (1965).
12) K. Berens and D. Shugar, *Acta Biochim. Poln.*, **10**, 25 (1963).

The tetrahydro-2-furyl group located at position 3 of **6** and **7** was more labile than that at position 1, and was readily cleaved on acid hydrolysis to generate **1** or a mixture of **1** and **5**, respectively. On hydrolysis under neutral conditions in water at a temperature of 20—70°, **7** was selectively converted to 1-(tetrahydro-2-furyl)-5-fluorouracil (**5**) in a quantitative yield.

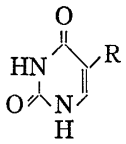
Thermal decomposition of the tetrahydro-2-furyl derivatives of **1** occurred smoothly at a temperature above their melting points resulting in the formation of **3** and **5** or **1**, depending upon the reaction conditions. In fact, heating of 1,3-bis(tetrahydro-2-furyl)-5-fluorouracil (**7**) at a temperature between 135 and 145° without any solvent gave an equimolar amount of **3** and **5**. Similarly, by refluxing the picoline solution, **7** underwent elimination reaction to give **3** and **5** in good yields, suggesting that the linkage between the tetrahydro-2-furyl group and the N_3-atom is more labile to heat than the corresponding linkage to the N_1-atom of **7**. The marked instability of the former is assumed to be due to the electronic effect of the neighboring carbonyl groups at positions 2 and 4 of the uracil ring which act as the base, internally abstracting the β-hydrogen atom of the tetrahydro-2-furyl ring (Chart 1).

Heating of **5** at 179° for 30 min under slightly reduced pressure led to the formation of **1** in quantitative yields. Thermolysis of **6**, performed in a sealed glass tube, yielded **5** together with small amounts of **1** and **7**. The formation of **5** can be accounted for by the thermal decomposition and the following recombination of intermediates **1** and **3** (Chart 2). These thermolyses, which represent the reverse of the reactions for the preparation of **5** and/or **7**, are shown in Chart 1.



6

Chart 2



8

R=–H, –CH_3, –Cl, –Br, –$COOCH_3$, –$CONH_2$, –CN

In connection with the preparation of tetrahydro-2-furyl derivatives of **1**, other uracil derivatives were also studied. Direct addition of uracil and several 5-substituted uracils (**8**, R=–H, –CH_3, –Cl, –Br, –$COOCH_3$, –$CONH_2$, –CN) to 2,3-dihydrofuran (**3**) under similar reaction conditions, proceeded smoothly to give the corresponding 1-(tetrahydro-2-furyl)- and 1,3-bis(tetrahydro-2-furyl)uracils in high yields. In all cases attempted, introduction of the first tetrahydro-2-furyl group into the N_1-atom of the uracil ring predominanted over the substitution at the N_3-atom of **8**.

The structure and physical properties of the tetrahydro-2-furyl uracils are shown in Table I. The location of the tetrahydro-2-furyl group was determined on the basis of the UV and nuclear magnetic resonance (NMR) spectra. Changes of the solution medium of the 3-(tetrahydro-2-furyl)-uracils (**16** and **17**) from neutral to alkaline produced characteristic 26—32 nm bathochromic shifts of the λ_{max} in the UV spectra, accompanied by appreciable increases in the extinction coefficient, while those of 1-(tetrahydro-2-furyl)- and 1,3-bis(tetrahydro-2-furyl)- derivatives of these uracils (**9**—**15** and **18**—**23**) did not show such a shift. The analogous relationship between the structure and UV spectra has been found for 1- and 3-methyluracils,[13] for 1- and 3-methyl-5-fluorouracils[11] and for 1- and 3-(tetrahydro-2-furyl)-5-fluorouracils. The NMR analysis gave additional support to the above discussion. The chemical shift of the C_2-methine proton of the 3-(tetrahydro-2-furyl) group appeared down field from that for the corresponding proton of the 1-(tetrahydro-2-furyl) group of the 5-substituted uracil derivatives.

13) D. Shugar and J.J. Fox, *Biochim. Biophys. Acta*, 9, 199 (1952).

Table I

No.	R	mp (°C)	UV: $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^{-3}$)[a] pH 1	pH 7	pH 12
		1-(Tetrahydro-2-furyl)-5-substituted uracils			
5	-F	168—169	270 (8.87)	270 (8.95)	270 (6.79)
9	-Cl	200—202	275 (8.9)	273 (7.9)	272 (6.36)
10	-Br	203—205	278 (8.52)	278 (8.45)	278 (6.40)
11	-H	105—106	265(10.8)	265(10.0)	225 (6.5)
12	$-CH_3$	182—183.5	269 (9.81)	269 (9.73)	269 (7.24)
13	-COOMe	191—193	278(13.5)	278(14.0)	278 (9.17)
14	$-CONH_2$	300	280(12.9)	280(12.9)	280 (9.85)
15	-CN	194—195	280(11.8)	280(12.1)	280(11.5)
		3-(Tetrahydro-2-furyl)-5-substituted uracils			
6	-F	128—129	271 (6.31)	271(6.25)	303.5 (9.3)
16	-H	137—139	263 (7.15)	263(7.21)	291.5(10.3)
17	$-CH_3$	145—146	269.5(6.94)	269(6.98)	298 (9.07)
		1,3-Bis(tetrahydro-2-furyl)-5-substituted uracils			
7	-F	98 — 99.5	275 (8.00)	275 (8.04)	272 (6.42)
18	-Cl	97.5— 99.5	283.5(8.62)	283.5(8.62)	283.5(5.15)
19	-Br	113 —115	285 (8.67)	285 (8.67)	285 (——)
20	-H	——	269 (8.33)	269 (8.37)	269 (8.33)
21	$-CH_3$	——	273.5(9.21)	273.5(9.33)	273.5(9.26)
22	$-CONH_2$	194 —195	280 (11.9)	280 (12.1)	282 (12.6)
23	-CN	141	283 (12.0)	283 (12.0)	283 (——)

a) Measurements of the tetrahydrofuryl uracils listed in the table were made in pH-controlled aqueous solutions, except for 1,3-bis(tetrahydro-2-furyl)uracils (**7**, **18**—**23**) which were determined in 10% EtOH–water solutions adjusted to the given pH values.

Since the linkage between the tetrahydro-2-furyl group and the uracil ring nitrogen of the products (**5**—**7**, **9**—**23**) is, in general, not very stable to acid, the present synthetic method which used no acid catalyst is preferable. With the elimination of (a) the trimethylsilylation of uracils and (b) the preparation of 2-substituted derivatives of tetrahydrofuran (**4**), which had been essential to previously known methods,[2-8] the present simple addition reaction of uracils to **3** provides a new and attractive synthetic method for preparing 1-(tetrahydro-2-furyl)-5-fluorouracil (**5**) and its related analogs.

Experimental

Melting points were determined with Yanagimoto melting point apparatus and were uncorrected. Unless otherwise noted, UV spectra were taken with Hitachi EPS-3T spectrophotometer; infrared (IR) spectrum with Hitachi EPI-S_2 spectrometer; and NMR with Varian T-60 using tetramethylsilane (TMS) as internal reference and chemical shifts are given in δ values.

1-(Tetrahydro-2-furyl)-5-fluorouracil (5)——a) A mixture of 5-fluorouracil (5.2 g, 0.04 mol), freshly prepared 2,3-dihydrofuran (9.6 g, 0.137 mol) and pyridine (120 ml) was placed in a sealed steel tube and kept at 180° for 6 hr under mechanical stirring. The reaction mixture gave four UV absorption zones, on thin-layer chromatography (TLC, silica gel plate, $CHCl_3$–EtOH, 19: 1), which corresponded to 1-(tetrahydro-2-furyl)-5-fluorouracil (5), 1,3-bis(tetrahydro-2-furyl)-5-fluorouracil (7), 3-(tetrahydro-2-furyl)-5-fluorouracil (6) and 5-fluorouracil (1). UV absorption measurement of each of the extract indicated that the reaction gave 83.5 mol % of 5, 6.9% of 7, 1.6% of 6 and 7.9% of 1.

The reaction mixture was evaporated to dryness leaving a pale yellow residue which was partitioned between $CHCl_3$ and water. After the $CHCl_3$ layer was collected and evaporated to dryness, a pale yellow residue was obtained. Crystallization from EtOH yielded 5.75 g (71.9%) of the desired product as colorless needles. No depression in melting point was observed in the admixture of this product with an authentic sample prepared by a known method.[2] The IR, UV, and NMR spectra were identical to those of an authentic sample. NMR (d_6-DMSO) 5.91 (1H, m, C_2'–H), 7.8 (1H, d, J=7.0 Hz, C_6–H), 11.7 (1H, s, –NH–). *Anal.* Calcd. for $C_8H_9FN_2O_3$: C, 48.00; H, 4.53; N, 14.00. Found: C, 47.85; H, 4.53; N, 13.82.

b) A mixture of 5-fluorouracil (1.04 g, 8 mmol), 2,3-dihydrofuran (3.36 g, 48 mmol) and pyridine (3.12 ml) was heated in a sealed tube at 180° for 3 hr. After evaporation of the reaction mixture the residue was dissolved in EtOH–H_2O (1: 4, 30 ml) and kept at 55° for 1.5 hr. The solution was evaporated to yield almost colorless powder which on crystallization from 90% EtOH gave the desired product as colorless needles (1.2 g, 75%). An additional crop of the crystalline product (0.23 g, 14.4%) was obtained from the mother liquor by evaporation, followed by crystallization from a small amount of 90% EtOH. The melting point and the spectral data were identical with those of an authentic specimen.

3-(Tetrahydro-2-furyl)-5-fluorouracil (6)——To a solution of 9.6 g (0.37 mol) of 2,3-dihydrofuran in 41 ml of pyridine was added 10.4 g (0.08 mol) of 5-fluorouracil. The mixture was stirred for 6 hr at 150° in a sealed steel tube. TLC on silica gel using $CHCl_3$–EtOH (19: 1) and the measurement of each UV-absorption zone on the plate showed that the reaction gave 1,3-bis(tetrahydro-2-furyl)-5-fluorouracil (7), 1-(tetrahydro-2-furyl)-5-fluorouracil (5), 3-(tetrahydro-2-furyl)-5-fluorouracil (6) and 5-fluorouracil (1) at the ratio of 41.6 mol %: 56%: 1.9%: 0.5%. Evaporation of the reaction mixture gave a pale yellow residue. Washing with a small amount of methanol resulted in the precipitation of colorless needles of 5 which was removed by filtration. The filtrate was evaporated to dryness leaving a slight yellow syrup.

Column chromatography on silica gel (4×20 cm) with $CHCl_3$ as eluent gave fractions containing 7. The subsequent elution with $CHCl_3$–EtOH (97: 3, 450 ml) resulted in two fractions which contained compound 5 and 6. Evaporation of the latter fraction and crystallization from EtOH (1 ml) yielded 50 mg of 6 as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1722 (s), 1660—1645 (vs), 1440, 1250 (s), 1050 (m). NMR (d_6-DMSO): 2.24 (4H, bs, $-CH_2-CH_2-$), 3.5—4.2 (2H, m, $-O-CH_2-$), 6.43 (1H, m, C_2'–H), 7.75 (1H, d, J=5 Hz, C_6–H). *Anal.* Calcd. for $C_8H_9FN_2O_3$: C, 48.00; H, 4.53; F, 9.49; N, 14.00. Found: C, 47.86; H, 4.48; F, 9.57; N, 13.68.

1,3-Bis(tetrahydro-2-furyl)-5-fluorouracil (7)——The mixture of 5-fluorouracil (5.2 g, 0.041 mol) and 2,3-dihydrofuran (25 g, 0.357 mol) was allowed to react in a sealed steel tube with stirring at 160° for 18 hr. After cooling, the reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed on a column of silica gel (3×20 cm) with $CHCl_3$ as the eluent. The eluate containing the desired product 7 was collected and evaporated to dryness. The residue was crystallized from petroleum ether to yield 9.9 g (90.0%) of 7 as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O), 1665 (C=O), 1469. NMR ($CDCl_3$): 5.93 (1H, m, N_1-C_2'–H), 6.57 (1H, t, J=3 Hz, N_3-C_2'–H), 7.34 (1H, d, J=6 Hz, C_6–H). *Anal.* Calcd. for $C_{12}H_{15}FN_2O_4$: C, 53.33; H, 5.59; N, 10.64. Found: C, 53.24; H, 5.67; N, 10.32.

Thermal Decomposition of 3-(Tetrahydro-2-furyl)-5-fluorouracil (6)——3-(Tetrahydro-2-furyl)-5-fluorouracil (10 mg) was loaded into a glass capillary of 1 mm diameter and sealed. The capillary was dipped in an oil bath and heated at 140° for 2 hr. TLC on silica gel using $CHCl_3$–EtOH (19: 1) as a solvent and the measurement of each UV-absorption zones on the plate showed that the reaction mixture was composed of 50.7% of 5, 30.5% of 1, 14.7% of 7 and 4.2% of the starting compound.

Thermal Decomposition of 1,3-Bis(tetrahydro-2-furyl)-5-fluorouracil (7)——a) Without Solvent: 1,3-Bis(tetrahydro-2-furyl)-5-fluorouracil (7, 3.0 g, 11.1 mmol) was placed in a round bottom flask connected to a cold trap. Heating 7 in an oil bath maintained at 135° brought about fusion. Upon continued heating for 12 hr under slightly reduced pressure (140 mmHg), the viscosity of the molten substance was greatly increased and solidified with evolution of the low boiling substance which was trapped in a cold trap cooled at −78°. TLC on silica gel and the measurement of the extract of each UV-absorption zones showed that the residue was composed of 75.5% of 5, 15% of 1 and 8% of the starting material 7. Working up according to the

method as described in the previous section gave 1.49 g of **5** as colorless needles. Melting point and TLC analysis were found to be identical with an authentic **5**. The oil separated in the trap was confirmed to be pure 2,3-dihydrofuran on the basis of NMR and GLC-Mass analysis. NMR (CCl_4): 6.73 (1H, q, J=2, 4 Hz, C_5–H), 4.98 (1H, q, J=2, 4 Hz, C_4–H), 4.33 (2H, t, J=10 Hz, C_2–H), 2.64 (2H, m, J=2, 10 Hz, C_3–H). Mass spectrum m/e: 70 (M^+).

b) In Solution: The picoline solution (10 ml) of 1,3-bis(tetrahydro-2-furyl)-5-fluorouracil (1 g) was refluxed for 8 hr. TLC and the measurement of the UV absorption zones on the silica gel plate showed that the reaction gave 1-(tetrahydro-2-furyl)-5-fluorouracil, 5-fluorouracil and the starting compound (**7**) in the mol ratio 89: 0.6: 10.4. Work-up with the reaction mixture, in the similar way described in the previous section, gave 0.6 g of **5** as colorless needles.

1-(Tetrahydro-2-furyl)uracil (11)——A mixture of uracil (0.615 g, 11 mmol), 2,3-dihydrofuran (7.7 g, 0.11 mol) and pyridine (2 ml) was maintained at 180° for 18 hr ir a stainless steel tube. The reaction mixture was evaporated to dryness, dissolved in $CHCl_3$ and filtered. After evaporation, the residue was dissolved in EtOH–H_2O (1: 1) containing a small amount of 1 N hydrochloric acid and kept at 60° for 45 min. The reaction mixture was evaporated to dryness giving a residue which, upon crystallization from 90% EtOH, yielded the desired product as colorless needles (0.63 g, 63.1%). The mother liquor, after evaporation, was chromatographed on a silica gel column. Elution with 1% MeOH–$CHCl_3$ gave fractions containing the desired product. After working up, additional crop was obtained as colorless needles. Yield 0.17 g (17.0%). IR ν_{max}^{KBr} cm^{-1}: 1723, 1710, 1678, 1660 (C=O). NMR (60 Mc, d_6-DMSO): 1.7—2.4 (4H, m, C_3'–H, C_4'–H), 3.6—4.5 (2H, m, C_5'–H), 5.54 (1H, d, J=8 Hz, C_5–H), 5.95 (1H, t, J=3 Hz, C_2'–H), 7.50 (1H, d, J=8.0 Hz, C_6–H), 11.2 (1H, brs, N_3–H). *Anal.* Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.59; H, 5.52; N, 15.60.

3-(Tetrahydro-2-furyl)uracil (16)——A mixture of uracil (672 mg), 2,3-dihydrofuran (2.1 g) and pyridine (50 ml) placed in a sealed tube was heated at 180° for 10 hr. The reaction mixture was evaporated to dryness and the residue was chromatographed on a silica gel column. Elution with $CHCl_3$ gave fractions containing compound **20**. Further elution with 1% MeOH–$CHCl_3$ and 3% MeOH–$CHCl_3$ gave the fractions containing 1-(tetrahydro-2-furyl)uracil and those containing 3-(tetrahydro-2-furyl)uracil, respectively. The final fractions were collected and evaporated to dryness. Recrystallization from benzene-*n*-hexane gave the product as colorless needles (70 mg). IR ν_{max}^{KBr} cm^{-1}: 1740, 1720 sh (C=O). NMR (d_6-DMSO): 5.54 (1H, d, J=7.5 Hz, C_5–H), 6.46 (1H, m, C_2'–H), 7.37 (1H, m, C_6–H), 10.97 (1H, brs, –NH–). *Anal.* Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.86; H, 5.34; N, 15.23.

1,3-Bis(tetrahydro-2-furyl)uracil (20)——A mixture of uracil (369 mg, 3.3 mmol), 2,3-dihydrofuran (4.62 g, 66 mmol) and pyridine (1.2 ml) placed in a sealed tube was kept at 180° for 20 hr. The reaction mixture was evaporated to dryness and the residue was chromatographed on a silica gel column with $CHCl_3$ as eluent. Fractions containing **20** was collected and evaporated. The residue, after being dissolved in petroleum ether and left standing, gave the desired product as a colorless paste (0.68 g, 82.1%). IR ν_{max}^{liq} cm^{-1}: 2980 (CH), 1720, 1664 (–C=O). NMR (CCl_4): 5.51 (1H, d, J=8.4 Hz, C_5–H), 5.83 (1H, m, N_1–C_2'–H), 6.42 (1H, m, N_3–C_2'–H), 7.23 (1H, d, J=8.4 Hz, C_6–H).

1-(Tetrahydro-2-furyl)thymine (12)——Thymine (757 mg, 6 mmol) was allowed to react with 2,3-dihydrofuran (5.0 g, 71.4 mmol) in pyridine (7.5 ml) at 180° for 8 hr. Working up in the similar procedure as described in the section for the compound **11**, gave **12**. Recrystallization from AcOEt gave colorless needles. Yield 1.06 g (89.9%). IR ν_{max}^{KBr} cm^{-1}: 1693, 1663 (C=O). NMR (d_6-DMSO): 1.82 (3H, s, CH_3), 5.98 (1H, m, C_2'–H), 7.38 (1H, s, C_6–H), 11.16 (1H, br. s, –NH–). *Anal.* Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.20; H, 6.03; N, 14.21.

3-(Tetrahydro-2-furyl)thymine (17)——A mixture of thymine (757 mg, 6 mmol), 2,3-dihydrofuran (2.1 g, 30 mmol) and pyridine (7.5 ml) was placed in a sealed tube and kept at 180° for 8 hr. Working up in the similar manner as described in the above section for **16** gave 0.55 g (34.6%) of **21**, 0.52 g (44%) of **12** and 45 mg of **17**. Recrystallization from benzene–*n*-hexane gave **17** as colorless needles (35 mg, 2.9%). IR ν_{max}^{KBr} cm^{-1}: 1722, 1640 (C=O). NMR (d_6-DMSO): 1.76 (3H, s, CH_3), 6.47 (1H, m, C_2'–H), 7.21 (1H, s, C_6–H), 10.70 (1H, brs, –NH–). *Anal.* Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.11; H, 6.10; N, 14.31.

1,3-Bis(tetrahydro-2-furyl)thymine (21)——A mixture of thymine (630 mg, 5.0 mmol), 2,3-dihydrofuran (7.0 g, 0.1 mol) and pyridine (2.5 ml) was heated in a sealed tube at 180° for 15 hr. After evaporation, the residue was chromatographed on a silica gel column with $CHCl_3$ as the eluent. Fractions containing **21** were collected and evaporated to dryness. The residue was dissolved in petroleum ether and left standing to yield **21**. Yield 1.23 g (91.9%). IR ν_{max}^{liq} cm^{-1}: 1703, 1661, 1645 (C=O). NMR (d_6-DMSO): 1.83 (3H, s, CH_3), 6.00 (1H, m, N_1–C_2'–H), 6.50 (1H, m, N_3–C_2'–H), 7.42 (1H, s, C_6–H).

1-(Tetrahydro-2-furyl)-5-chlorouracil (9)——A mixture of 5-chlorouracil (439.5 mg, 3.0 mmol), 2,3-dihydrofuran (735 mg, 10.5 mmol) and pyridine (1.6 ml) was enclosed in a stainless steel tube and kept at 150° for 6 hr. The reaction mixture was evaporated to dryness and the residue dissolved in EtOH–H_2O (1: 1, 15 ml). After being kept at 65° for 30 min, the solution was evaporated to dryness and the residue was chromatographed on a silica gel column. Elution was made first with $CHCl_3$, followed by EtOH–$CHCl_3$ (1: 49). The latter fractions were collected, followed by working up as usual gave the desired product as colorless needles. Yield 551.9 mg (85%). IR ν_{max}^{KBr} cm^{-1}: 1705, 1678, 1661 (C=O). NMR (d_6-DMSO):

1.7—2.4 (4H, m, C_3'–H, C_4'–H), 3.5—4.5 (2H, m, C_5'–H), 5.99 (1H, m, C_2'–H), 7.85 (1H, s, C_6–H). *Anal.* Calcd. for $C_8H_9ClN_2O_3$: C, 44.37; H, 4.19; Cl, 16.37; N, 12.93. Found: C, 43.90; H, 4.05; Cl, 16.48; N, 12.52.

1,3-Bis(tetrahydro-2-furyl)-5-chlorouracil (18)——A mixture of 5-chlorouracil (439 mg, 3 mmol) and 2,3-dihydrofuran (4.2 g, 60 mmol) was heated in a stainless steel tube at 150° for 15 hr. After evaporation, the residue was chromatographed on a silica gel column with $CHCl_3$ as the eluent. Fractions containing the desired compound were collected and evaporated to dryness. The residue was dissolved in petroleum ether and left standing to give the desired product as a colorless prisms. Yield 745 mg (86.6%). IR ν_{max}^{KBr} cm^{-1}: 2960, 2900 (CH), 1710, 1665 (C=O). NMR ($CDCl_3$): 6.0 (1H, q, N_1–C_2'–H), 6.70 (1H, t, N_3–C_2'–H), 7.57 (1H, s, C_6–H).

1-(Tetrahydro-2-furyl)-5-bromouracil (10)——A mixture of 5-bromouracil (764 mg, 4 mmol), 2,3-dihydrofuran (2.8 g, 40 mmol) and pyridine (3.0 ml) placed in a sealed tube was heated at 150° for 16 hr. The reaction mixture was evaporated to dryness to give a residue which was dissolved in EtOH–H_2O (1: 1, 15 ml) and maintained at 70° for 2 hr. After evaporation to dryness, the residue was crystallized from 90% EtOH to yield 10 as colorless needles (0.63 g, 60%). The mother liquor, after evaporation, was chromatographed on a silica gel column. Elution with 1% MeOH–$CHCl_3$ gave fractions containing the desired product. After working up in the usual way, an additional crop was obtained as a colorless crystalline powder (148 mg, 14.2%). IR ν_{max}^{KBr} cm^{-1}: 1700, 1665 (C=O). NMR (d_6-DMSO): 5.90 (1H, m, C_2'–H), 7.85 (1H, s, C_6–H), 11.69 (1H, br. s, –NH–). *Anal.* Calcd. for $C_8H_9BrN_2O_3$: C, 36.80; H, 3.48; Br, 30.61; N, 10.73. Found: C, 36.78; H, 3.40; Br, 30.68; N, 10.77.

1,3-Bis(tetrahydro-2-furyl)-5-bromouracil (19)——A mixture of 5-bromouracil (382 mg, 2 mmol), 2,3-dihydrofuran (9.0 g, 0.128 mol) and pyridine (3 ml) placed in a sealed tube was heated at 150° for 15 hr. After evaporation, the residue was chromatographed on a silica gel column with $CHCl_3$ as the eluent. Fractions containing 19 were collected and evaporated to dryness. The residue was dissolved in petroleum ether and left standing to yield the desired product as a colorless prisms. Yield 575 mg (86.8%). IR ν_{max}^{KBr} cm^{-1}: 2950, 2890 (CH), 1710, 1665 (C=O). NMR ($CDCl_3$): 6.0 (1H, q, J=6.0 Hz, N_1–C_2'–H), 6.68 (1H, t, J=6.0 Hz, N_3–C_2'–H), 7.65 (1H, s, C_6–H).

1,3-Bis(tetrahydro-2-furyl)-5-methoxycarbonyluracil (24)——A mixture of 5-methoxycarbonyluracil (340 mg, 2.0 mmol), 2,3-dihydrofuran (490 mg, 7.0 mmol) and pyridine (1.4 ml) placed in a sealed tube was kept heating at 140° for 6 hr. The reaction mixture was evaporated to dryness to give the residue. This was chromatographed on a silica gel column with $CHCl_3$ as the eluent. The eluate, after working up, gave 24 as a colorless powder (82 mg). NMR ($CDCl_3$): 1.7—2.8 (8H, m, $-CH_2CH_2-$), 3.5—4.5 (4H, m, C_5'–H), 3.89 (3H, s, CH_3–), 6.00 (1H, m, N_1–C_2'–H), 6.59 (1H, m, N_3–C_2'–H), 8.25 (1H, s, C_6–H).

1-(Tetrahydro-2-furyl)-5-methoxycarbonyluracil (13)——Further elution with 2.5% EtOH–$CHCl_3$ in the chromatography in the preceding section gave fractions containing 13. Working up as usual gave the desired compound as colorless needles (EtOH–$CHCl_3$). Yield 204 mg (42.5%). IR ν_{max}^{KBr} cm^{-1}: 1724, 1705, 1688 (C=O). NMR (d_6-DMSO): 1.5—2.3 (4H, m, C_3'–H, C_4'–H), 3.5—4.4 (2H, m, C_5'–H), 3.75 (3H, s, CH_3–), 5.88 (1H, m, C_2'–H), 8.20 (1H, s, C_6–H). *Anal.* Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.96; H, 5.06; N, 11.74.

1,3-Bis(tetrahydro-2-furyl)-5-carbamoyluracil (22)——A mixture of 5-carbamoyluracil (1.55 g, 10 mmol), 2,3-dihydrofuran (5 g) and pyridine (30 ml) placed in a sealed tube was kept heating at 150° for 8 hr and the reaction mixture was evaporated to dryness. The resulting residue was chromatographed in the usual manner. Elution with 1% EtOH-$CHCl_3$ gave fractions containing the desired product. After evaporation, the resulting concentrate was left standing to yield 22 as colorless needles (200 mg). IR ν_{max}^{KBr} cm^{-1}: 1724, 1690 (C=O), 1642 (-CONH$_2$). NMR (d_6-DMSO): 1.6—2.6 (8H, m, N_1– and N_3–C_3'–H, C_4'–H), 3.5—4.5 (4H, m, N_1–, N_3–C_5'–H), 5.92 (1H, m, N_1–C_2'–H), 6.49 (1H, m, N_3–C_2'–H), 7.42, 8.04 (each 1H, br. s, $-CONH_2$), 8.21 (1H, s, C_6–H). *Anal.* Calcd. for $C_{13}H_{17}N_3O_5$: C, 52.87; H, 5.80; N, 14.22. Found: C, 52.74; H, 5.72; N, 13.95.

1-(Tetrahydro-2-furyl)-5-carbamoyluracil (14)——Further elution with 20% EtOH–$CHCl_3$ in the chromatography described in the preceding section gave fractions containing the desired compound. Evaporation to a small volume yielded the desired product as colorless needles (510 mg). IR ν_{max}^{KBr} cm^{-1}: 1724 (sh), 1700 (C=O), 1655 (-CONH$_2$). NMR (d_6-DMSO): 1.5—2.4 (4H, m, C_3'–H, C_4'–H), 3.5—4.5 (2H, m, C_5'–H), 5.92 (1H, m, C_2'–H), 7.44, 8.13 (each 1H, br. s, $-CONH_2$), 8.26 (1H, s, C_6–H). *Anal.* Calcd. for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 47.57; H, 4.88; N, 18.35.

1-(Tetrahydro-2-furyl)-5-cyanouracil (15)——A mixture of 5-cyanouracil (822 mg, 6.0 mmol), 2,3-dihydrofuran (4.25 g, 60 mmol) and pyridine (4.0 ml) placed in a sealed tube was kept heating at 150° for 6 hr. Working up in the similar procedure as described in the section for 11 gave the desired product as colorless needles. Yield 810 mg (65.7%). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN), 1720, 1693 (CO). NMR (d_6-DMSO): 1.5—2.5 (4H, m, C_2'–H, C_3'–H), 3.5—4.7 (2H, m, C_5'–H), 5.90 (1H, m, C_2'–H), 8.41 (1H, s, C_6–H). *Anal.* Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.78; N, 20.28. Found: C, 51.89; H, 4.42; N, 19.98.

1,3-Bis(tetrahydro-2-furyl)-5-cyanouracil (23)——A mixture of 5-cyanouracil (411 mg, 3 mmol) and 2,3-dihydrofuran (4.2 g, 60 mmol) was heated in a sealed tube at 150° for 15 hr. After evaporation of the reaction mixture, the residue was chromatographed on a silica gel column with $CHCl_3$ as the eluent. Fractions containing 23 were collected and evaporated to dryness. The residue was crystallized from EtOH to yield

the desired product as colorless crystals. Yield 775 mg (93.2%). IR ν_{max}^{KBr} cm^{-1}: 2225 (CN), 1720, 1670 (CO). NMR (d_6-DMSO): 1.6—2.7 (8H, m, N_1– and N_3–C_3'–H, –C_4'–H), 3.8—4.5 (4H, m, N_1– and N_3–C_5'–H), 5.93 (1H, m, N_1–C_2'–H), 6.45 (1H, m, N_3–C_2'–H), 8.48 (1H, s, C_6–H). *Anal.* Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.28; H, 5.41; N, 15.09.

Addition of Acids to 2,3-Dihydrofuran——A rapid conversion of 2,3-dihydrofuran (3) into 2-substituted tetrahydrofuran, when an acid is present, is generally observed. For example, the following reactions proceeded to a completion within a few minutes to 3 hr at room temperature or even at much lower temperatures.

a) Trifluoroacetic Acid: To a CCl_4 solution (5 ml) of 3 (140 mg, 2 mmol), 228 mg (2 mmol) of CF_3COOH was added under ice-water cooling. Immediately, the NMR analysis of the resulting mixture was performed. The spectral pattern obtained was essentially the same with that of a pure 2-trifluoroacetoxtyetrahydrofuran: NMR (CCl_4): 2—2.3 (4H, m, C_4–H_2, C_5–H_2), 3.9—4.2 (2H, m, C_3–H_2), 6.45 (1H, bs, C_2–H).

b) Hydrogen Chloride: The reaction of HCl and 3 was performed in a similar manner as described in the previous papers.[7,10] Dry HCl gas was bubbled into a CH_2Cl_2 solution (15 ml) of 3 (3.5 g, 0.05 mol) at −78° until 1.75 g (0.048 mol) of HCl was absorbed in the solution. The mixture was allowed to stand at room temperature for several minutes and the NMR analysis was carried out. The spectral pattern showed the presence of 2-chlorotetrahydrofuran (4, X=Cl) as the main reaction product. No signal due to the protons of 3 was observed. NMR ($CDCl_3$): 2.0—2.7 (m, C_4–H_2, C_5–H_2), 3.8—4.6 (m, C_3–H_2), 6.20 (bs, C_2–H).

c) Methanesulfonic Acid: To a d_6-DMSO solution (1 ml) of 3 (70 mg, 1 mmol), anhydrous methanesulfonic acid (86 mg, 1 mmol) was added under ice-water cooling. The NMR analysis was performed within 15 min at room temperature after the addition. No detectable amount of 3 remained in the solution.

d) Acetic Acid: A mixture of an equimolar quantity of 3 and acetic acid was placed in a closed vessel. The mixture was allowed to stand at 27°. The NMR analysis showed that the conversion to 2-acetoxytetrahydrofuran (4, X=–$OCOCH_3$) reached 55% after 20 min and was almost complete after 3 hr at 27°. The reaction mixture was distilled *in vacuo* yielding the desired product as a colorless oil. bp $_{17}$ 72—77°. NMR ($CDCl_3$): 2.00 (7H, bs, CH_3COO–, C_3–H_2, C_4–H_2), 3.6—4.3 (4H, m, C_5–H_2), 6.30 (1H, t, J=2 Hz, C_2–H).

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