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Studies on Tetrahydrofuryl-5-fluorouracils. IV.[1] Mode of Reaction of 5-Fluorouracil with 2-Acetoxytetrahydrofuran

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The mechanism of the condensation of 5-fluorouracil and 2-acetoxytetrahydrofuran (**3**), giving 1-(tetrahydro-2-furyl)-5-fluorouracil, was studied. An equilibrium between 2-acetoxytetrahydrofuran (**3**) and 2,3-dihydrofuran (**4**) was observed at 120—170 °C in dimethylformamide. It was found by the use of 1,3-dideuterio-5-fluorouracil that the condensation of 5-fluorouracil with **3** occurred both by direct substitution and by the formation of **4** from **3** followed by addition of the uracil to it. The contribution of the latter path increased with increase of the reaction temperature.

Keywords——5-fluorouracil; 1,3-dideuterio-5-fluorouracil; 2-acetoxytetrahydrofuran; 2,3-dihydrofuran; 1-(tetrahydro-2-furyl)-5-fluorouracil; tegafur; tetrahydrofuryl cation; mass spectra; isotopic effect

Numerous methods have been reported[2] recently for the preparation of 1-(tetrahydro-2-furyl)-5-fluorouracil (**1**, TFU), a widely used cancer therapeutic agent. We have already reported[3] that the reaction of 5-fluorouracil (**2**, 5-FU) with 2-acetoxytetrahydrofuran (**3**, 2-ATHF) proceeds smoothly in dimethylformamide without any catalyst to give tetrahydrofuryl-5-fluorouracils.

The present report describes the mechanism of this condensation reaction in detail. Similar condensation reactions utilizing certain purines and acetylated 2-deoxyriboses have been reported,[4,5] in which the sugar carbonium ion was postulated as an intermediate. Addition reactions of certain 6-substituted purines with glycals or 2,3-dihydrofuran (**4**, 2,3-DHF) have also been reported[5–7] to proceed with the formation of the tetrahydropyranyl or -furyl cation. On the other hand, thermal decomposition of 2-benzoyloxytetrahydrofuran[8] and aluminum chloride-catalyzed decomposition of 2-aryloxytetrahydrofurans[9] into **4** have been reported. It is possible that **2** reacts directly with **3** to form **1** or with **4** formed from **3** by prior elimination.

In the present work, we investigated the thermal decomposition of **3** and the mode of condensation of **2** and **3**, in part by the use of 1,3-dideuterio-5-fluorouracil (**5**).

Experimental

D_2O, dimethylsulfoxide-d_6 (DMSO-d_6), CH_3OD were obtained from Merck Co., Ltd. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-22 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a JEOL JMS-01 SG-2 or a JEOL JMS-D300 spectrometer. Elemental analyses were carried out with a Yanagimoto CHN corder MT-2 analyzer. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected.

Standard Condition for the Synthesis of 1-(Tetrahydro-2-furyl)-5-fluorouracil (1)——A mixture of 5-FU (**2**, 6.5 g, 0.05 mol) in dimethylformamide (DMF) (50 ml) and 2-ATHF (**3**, 7.8 g, 0.06 mol) was stirred for 2 h at 140 °C. The solvent was evaporated off and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated and the residue was crystallized from EtOH to give 5.3 g (53%) of **1**. mp 166—168.5 °C. *Anal.* Calcd for $C_8H_9FN_2O_3$: C, 48.00; H, 4.53; N, 14.00. Found: C, 47.68; H, 4.31; N, 13.80. The physical data, including NMR and MS of **1**, are

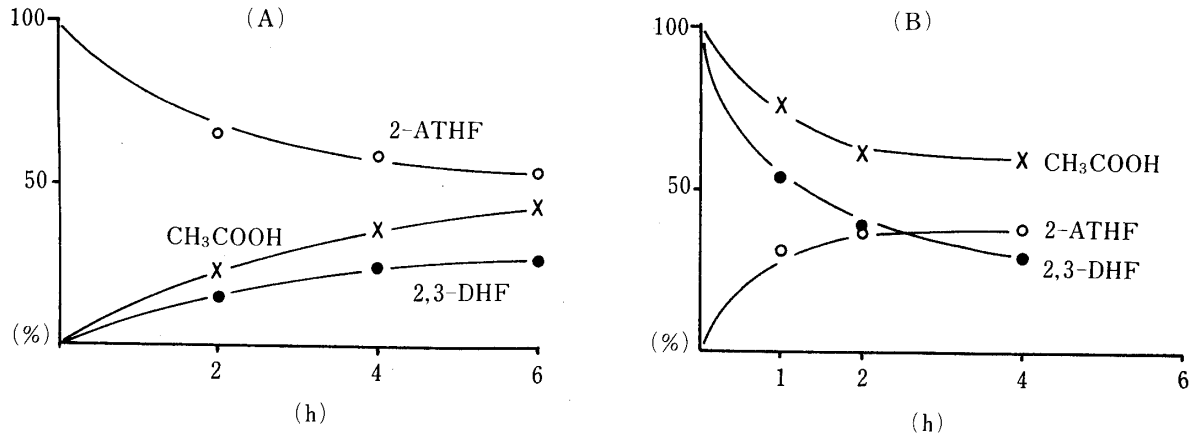

Fig. 1. Decomposition and Formation of 2-Acetoxytetrahydrofuran

(A) Decomposition of 2-acetoxytetrahydrofuran (2-ATHF, **3**) in DMF at 120 °C.
(B) Formation of 2-ATHF (**3**) from 2,3-dihydrofuran (2,3-DHF, **4**) and acetic acid in DMF at 120 °C.

identical with those of the compound prepared by the condensation of bistrimethylsilylated 5-fluorouracil and **3**.

Decomposition and Formation of 2-Acetoxytetrahydrofuran (3)——Decomposition of **3**: A solution of 2-ATHF (**3**, 7.8 g, 0.06 mol) in DMF (50 ml) was stirred at 120 °C in a 100 ml three-necked, round-bottomed flask, which was fitted with a reflux condenser, a thermometer and a $CaCl_2$ tube. Ice-water was used as cooling water. The reaction was monitored by gas chromatography as described below.

Formation of **3**: A mixture of acetic acid (3.6 g, 0.06 mol) and 2,3-DHF (**4**, 4.2 g, 0.06 mol) in DMF (50 ml) was stirred as described above and the reaction was monitored similarly.

Analytical Procedure: A Shimadzu GC-4CM gas chromatograph was used for the product analysis. The glass column (2 m) was packed with 20% polyethylene glycol on Chromosorb W AW (60—80 mesh, Gaschro Kogyo, Osaka, Japan). The temperature at the injection post and detector was set at 90 °C. Analyses were carried out with an initial column temperature of 70 °C and a temperature rise of 10 °C/min. One ml of the above reaction mixture was diluted to 5 ml with $CHCl_3$ and 1 or 2 μl of the solution was used for analysis. The results are shown in Fig. 1.

Synthesis of 1,3-Dideuterio-5-fluorouracil (1,3-dideuterio-5-FU, 5)——Monodeuteriomethanol (5 ml) was added to 2,4-*O*-bis(trimethylsilyl)-5-fluorouracil (2.7 g, 0.01 mol) and the mixture was stirred for 1 h at 50 °C. The separated crystalline precipitates were collected and recrystallized from a mixture of DMSO-d_6 (2—4 ml) and D_2O (12—14 ml). Relative isotopic abundances of the products were determined as 1,3-dideuterio-5-FU, 81.0%; 1- or 3-monodeuterio-5-FU, 17% and 5-FU, 2.0%, by mass spectral analysis. The mixture was used as **5** for the following experiment.

Reaction of 1,3-Dideuterio-5-fluorouracil (5) with 2-Acetoxytetrahydrofuran (3) or 2,3-Dihydrofuran (4)——A mixture of 1,3-dideuterio-5-FU (**5**, 197 mg, 1.5 mmol) and 1 to 2 equivalents of 2-ATHF (**3**) or 2,3-DHF (**4**) in DMF (3 ml) was stirred in a sealed glass tube under heating. The product analysis was carried out by high performance liquid chromatography (HPLC) and MS as described below.

Analytical Procedure: A Shimadzu–Du Pont LC-1 liquid chromatograph (Kyoto, Japan) equipped with a high-pressure injection valve (Model 513A, Gaschro Kogyo Co., Tokyo, Japan) was used.[10] A Du Pont Zorbax SIL chromatographic column (25 cm × 6.2 mm i.d.) was used for the separation, the mobile phase being 1,2-dichloroethane–EtOH (24 : 1) and the flow rate being 1.5 ml/min. The column was maintained at room temperature.

The reaction mixture (1 ml of the above reaction solution) was mixed with 0.01 N HCl (5 ml) and the mixture was extracted twice with $CHCl_3$ (30 ml, 15 ml). The combined $CHCl_3$ extracts were diluted to 50 ml with $CHCl_3$, then 2.5 ml of this solution was further diluted to 50 ml with 1,2-dichloroethane, and 20 μl of the solution was injected into the liquid chromatograph apparatus.

The rest of the reaction mixture was evaporated to dryness and the residue was purified by silica gel column chromatography ($CHCl_3$). The eluate containing the product was concentrated and the residue was subjected to mass spectrometry analysis to determine the relative isotopic abundance. The results are summarized in Fig. 2.

Thermal Stability of 1-(Tetrahydro-2-furyl)-5-fluorouracil (1)——A mixture of **1** (120 mg, 0.6 mmol) and 1,3-dideuterio-5-fluorouracil (**5**, 99 mg, 0.75 mmol) in DMF (3 ml) was stirred in a sealed glass tube for 5 h under heating at various temperatures and the reaction mixture was analyzed as described above. The results are summarized in Fig. 3.

Results and Discussion

When **3** was treated at 120 °C in DMF, the formation of **4** and acetic acid was observed,

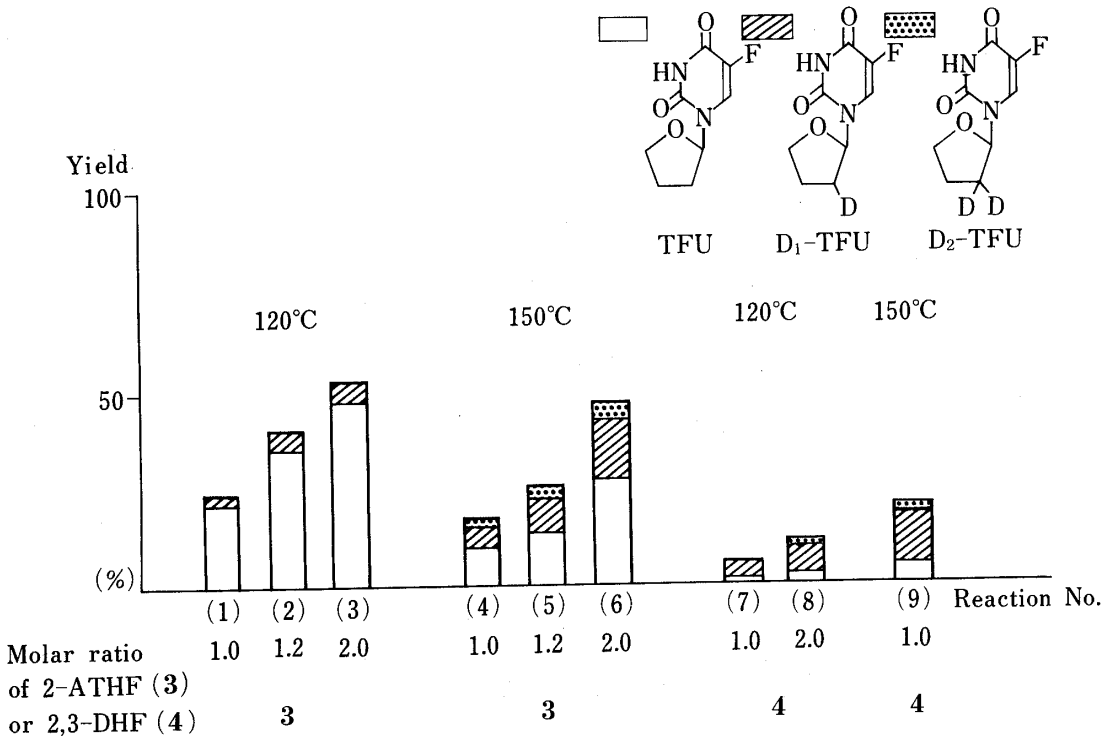

Fig. 2. Reaction of 1,3-Dideuterio-5-fluorouracil with 2-Acetoxytetrahydrofuran (2-ATHF) or 2,3-Dihydrofuran (2,3-DHF) to Give **1**

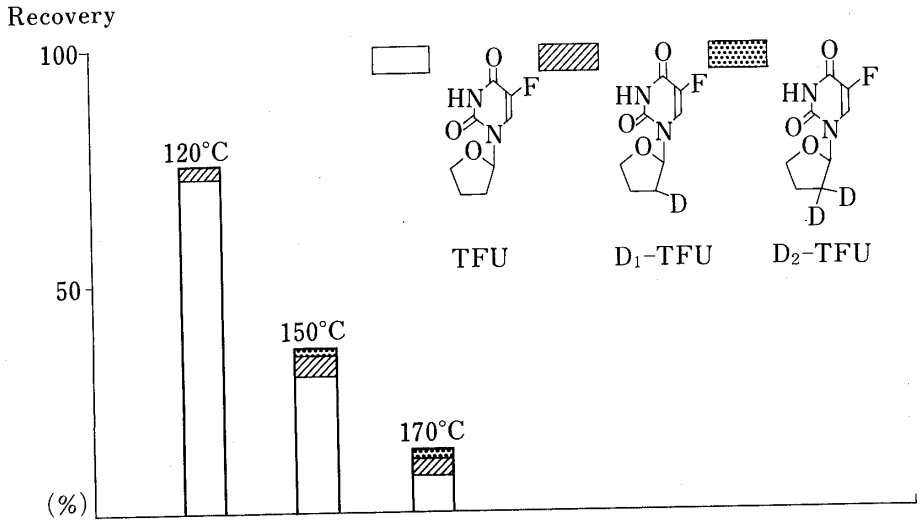

Fig. 3. Thermal Stability of TFU

TFU (**1**) in DMF was treated with 1.25 eq of 1,3-dideuterio-5-FU (**5**) at various temperatures.

with a gradual decrease of **3** (Fig. 1(A)). Treatment of an equimolar mixture of **4** and acetic acid under the same conditions resulted in the formation of **3** (Fig. 1(B)). These results clearly show the existence of an equilibrium between **3** and **4** (and acetic acid) under these conditions. This implies that, during the condensation of **2** with **3**, the participation of **4** formed from **3** is plausible.

To clarify this point, **5** (prepared by the solvolysis of 2,4-bis(trimethylsilyl)-5-fluorouracil by CH_3OD) was used in place of **2** in this reaction. The product **1** formed by the addition of **5**

to **4** should be deuterated at position 3 of the tetrahydrofuryl group of **1**. The yields of the products were determined by HPLC, and the distribution of non-, mono- and dideuterio products was determined by mass spectrometry.

From the results shown in Fig. 2, the following conclusions can be reached. a) The yield of **1** increased as the molar ratio of **3** was increased. b) At 120 °C, the main reaction path is the substitution of **3** with **5** by uni- or bimolecular reaction. However, there is a very minor path involving the prior elimination of **3** to **4**, since the formation of mono-deuterated **1** (D_1-TFU) was detected (Reaction Nos. 1—3). c) The formation of D_1-TFU increased with increase of the reaction temperature, as can be seen by comparison of the reactions at 120 and 150 °C. d) The above conclusion is further supported by the fact that the addition of **5** to **4** is very slow at lower temperature (Reaction Nos. 7 and 8). f) The formation of the dideuterio compound (D_2-TFU, Reaction Nos. 4—6) shows that the condensation reaction becomes reversible at

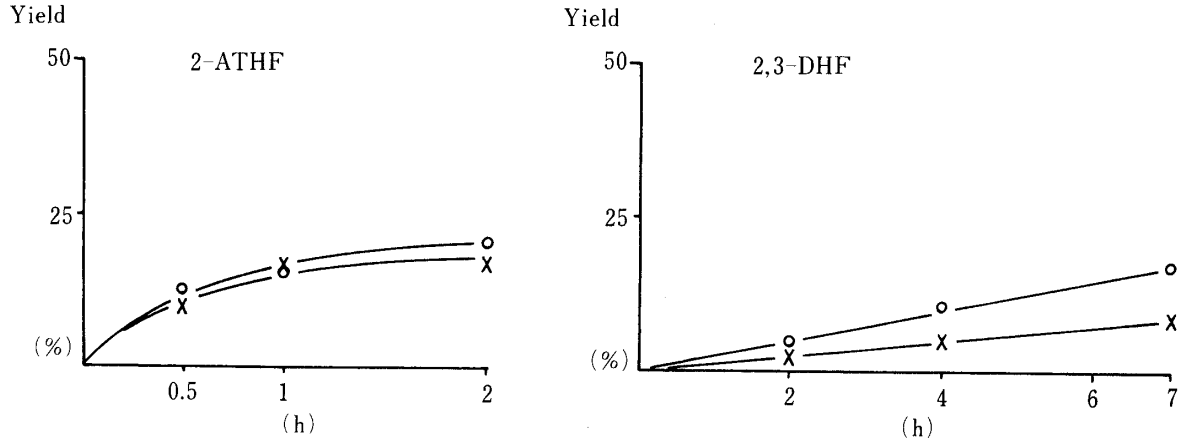

Fig. 4. Isotopic Effect

1,3-Dideuterio-5-FU (**5**, ×—×) or 5-FU (**2**, ○—○) and 1.2 eq of 2-ATHF (**3**) or 2,3-DHF (**4**) were heated in DMF at 120 °C.

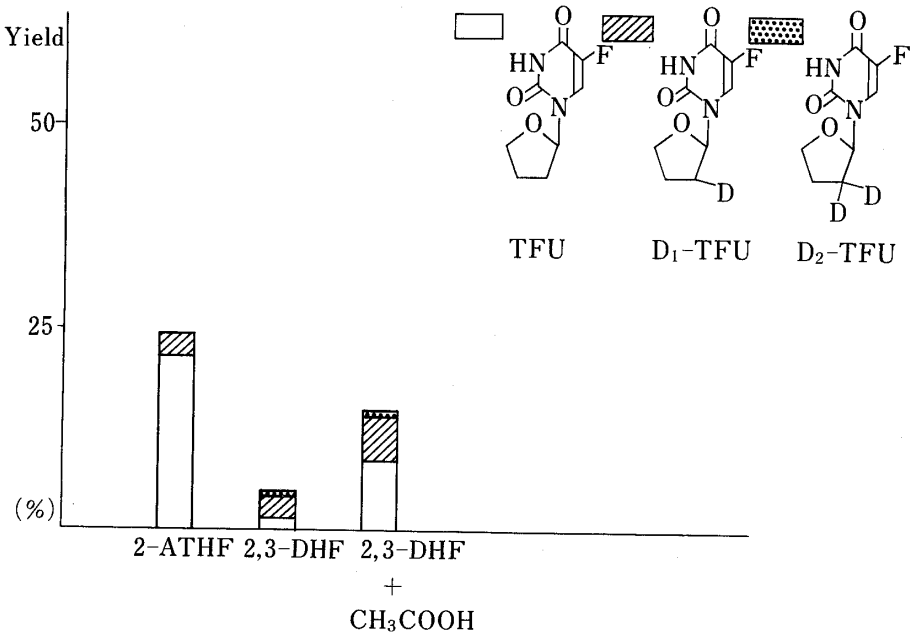

Fig. 5. Catalytic Effect of Acetic Acid in the Reaction of 1,3-Dideuterio-5-FU (**5**) and 2,3-DHF (**4**)

1,3-Dideuterio-5-FU and 2,3-DHF (1 eq) were heated in DMF at 120 °C with or without AcOH. The reaction of **5** with 2-ATHF is also shown for comparison.

higher temperature.

In fact, **1** (TFU) is thermally decomposed to **2** and **4**, and the latter reacts partially with added **5** to form D_1-TFU and D_2-TFU. In the reaction of **4** with **5**, an isotopic effect is observed, as shown in Fig. 4. While the substitution reaction of **3** with **2** or **5** proceeded at almost the same rate, the reactivity of **4** with **5** was lower than that with **2**. These results show that in the reaction of **4**, formation of the C-1 tetrahydrofuryl cation is rate-limiting. Therefore, it seems that the addition of an appropriate proton donor should be effective in the reaction of **4** with **5**. The results shown in Fig. 5 support this view.

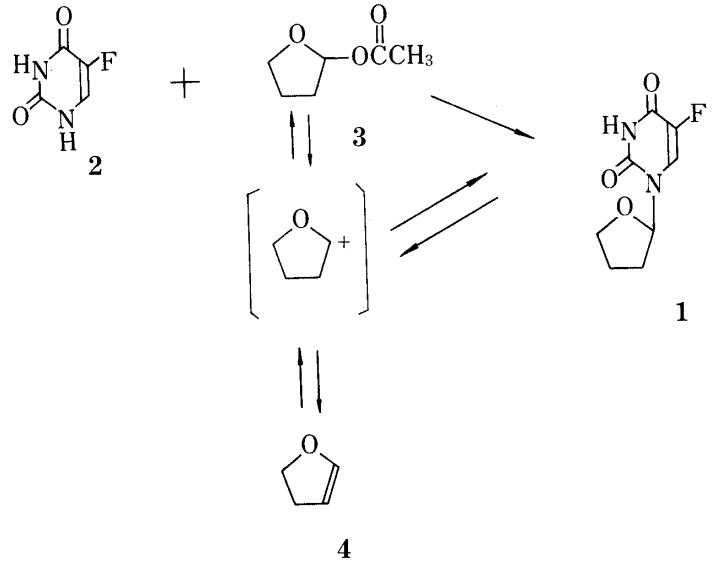

Chart 1

In conclusion, the overall scheme of the condensation of 5-fluorouracil (**2**) and 2-acetoxytetrahydrofuran (**3**) can be expressed as shown in Chart 1. At lower temperature, the formation of **1** is by substitution (S_N2 or S_N1) of the 2-acetoxy group of **3** with **2**. At higher temperature, elimination of **3** to **4** as well as **1** to **4** and **2** becomes significant and the generated **4** is also involved in the reaction through a tetrahydrofuryl cation.

It has been reported[2g] that condensation of **2** with **4** proceeded in pyridine only at higher temperature (170 °C). Although the present experiment was carried out in DMF as a solvent, similar results were also observed when pyridine was used in the condensation of **3** and **2**. Thus, 2-acetoxytetrahydrofuran is very reactive in the condensation, in pyridine as well as in DMF, and the reaction of **3** can be carried out at lower temperature than that required in the case of 2,3-dihydrofuran (**4**).

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