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Studies on Fluorinated Pyrimidines. V.[1] Preparation of optically Active (+)- and (−)-*t*-6-Butoxy-*r*-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracils

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Both optical isomers of *t*-6-butoxy-*r*-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil (**1**, TAC-278), a new candidate for use as a pro-drug of 5-fluorouracil (5-FU), have been prepared *via* the enantiomeric 6-(+)- and 6-(−)-α-methylbenzylamino derivatives (**4**).

Keywords——(+)- and (−)-TAC-278; (+)- and (−)-α-methylbenzyl alcohols; (+)- and (−)-α-methylbenzylamines; (±)-*t*-6-acetoxy-*r*-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil; diastereomer; enantiomer; X-ray analysis

t-6-Butoxy-*r*-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil (**1**, TAC-278), a new candidate for use as a pro-drug of 5-fluorouracil (5-FU), has been prepared[2] as shown in Chart 1, and is now under clinical investigation. It is a racemic mixture and the two enantiomers of **1** may differ in their antitumor activity as a result of the stereospecific action of enzymes that convert (+)- or (−)-**1** into 5-FU in the blood or tissues. Conversion of (±)-**1** into 5-FU *in vivo* by nonenzymatic hydrolysis followed by spontaneous decarboxylation and dealkoxylation may also occur since (±)-**1** gives 5-FU readily in chemical reactions.

The substituent at C-6 of (±)-*r*-5-alkoxycarbonyl-5-fluoro-*t*-6-substituted-5,6-dihydrouracils can be replaced easily with another nucleophile in the presence of an acid.[2] The *trans* (in connection with the stereochemistry of the 5-alkoxycarbonyl group and the 6-alkoxy group) isomer is produced predominantly and can be obtained in a pure state by recrystallizing the crude product.[1] Consequently, introduction of an optically active nucleophile, *i.e.*, a chiral alcohol or amine at C-6 of the 5,6-dihydrouracil skeleton, followed by separation of the resulting diastereomeric isomers, and reaction of the resolved products with butanol will give optically active (+)- and (−)-**1**.

First, we attempted the reaction of (±)-*t*-6-acetoxy-*r*-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil [(±)-**2b**] with (+)- or (−)-α-methylbenzyl alcohol. However, this resulted in a very complex mixture containing the (+)-*t*-6-(α-methylbenzyloxy) compound [(+)-**3**] or [(−)-**3**], its diastereomer, (±)-**2b**, and unidentified products. After purification of the crude product by repeated silica gel column chromatography, (+)-**3** was isolated as colorless prisms in only 9% yield [or (−)-**3** from the reaction mixture obtained with the (+)-alcohol in 8% yield] (Chart 1).

Reaction of (±)-**2b** with a chiral amine was then investigated. Reaction of (±)-**2b** and (+)- or (−)-α-methylbenzylamine gave the (−)- or (+)-6-(α-methylbenzylamino) derivative, (−)-**4** or (+)-**4**, respectively, as crystals. Each of the crude products was recrystallized from ethyl acetate, giving optically pure (−)-**4** or (+)-**4** (Chart 1). The purity of the enantiomers was checked by thin-layer chromatography (TLC) and by comparing optical rotation values.

Acid-catalyzed transformation of (+)- and (−)-**4** was achieved by heating each of them with butanol in the presence of methanesulfonic acid; this process gave (+)- and (−)-**1** in 73% and 70% yields, respectively. The proton magnetic resonance (PMR) spectra of (±)-**1**, (+)-**1**, and (−)-**1** were superimposable on each other. The melting point of (+)- and (−)-**1** were 20°C higher than that of (±)-**1**.

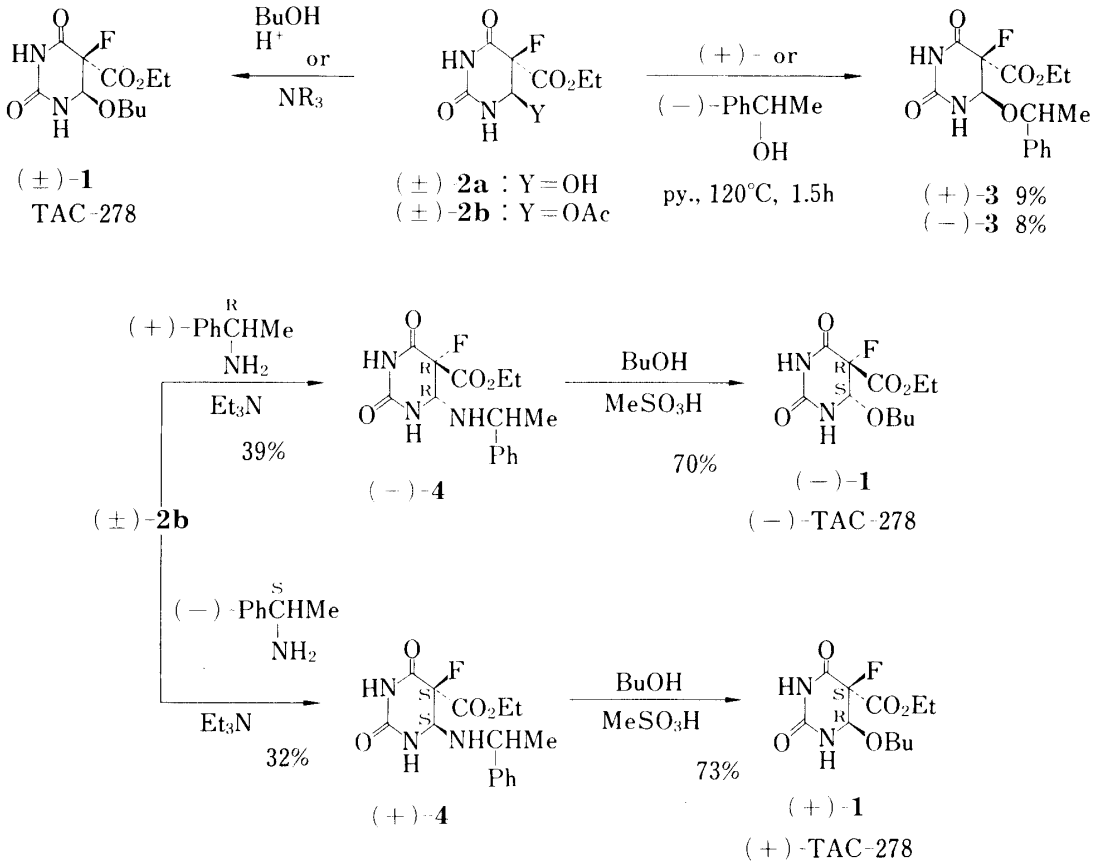

Chart 1

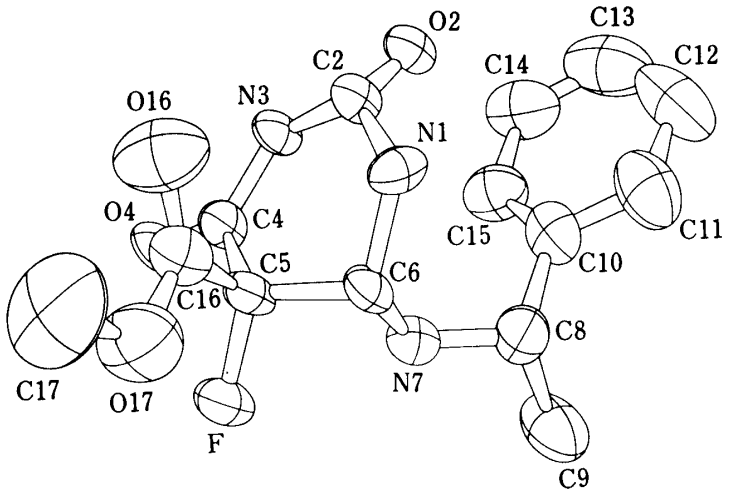

Fig. 1. Perspective View of (+)-5-Fluoro-*r*-5-methoxycarbonyl-*t*-6-(α-methylbenzylamino)-5,6-dihydrouracil

In order to confirm the absolute configuration of (+)-**1**, X-ray analysis of (+)-5-fluoro-*r*-5-methoxycarbonyl-*t*-6-(α-methylbenzylamino)-5,6-dihydrouracil[3] was carried out. It revealed the (5*S*, 6*R*) configuration for (+)-**1** in relation to the known configuration of (−)-α-methylbenzylamine[4] (Fig. 1).

X-Ray Analysis

A colorless plate of (+)-5-fluoro-*r*-5-methoxycarbonyl-*t*-6-(α-methylbenzylamino)-5,6-dihydrouracil[3] obtained from aqueous methanol solution was used for the analysis. The

Table I. Crystal Data for (+)-5-Fluoro-*r*-5-methoxycarbonyl-*t*-6-(α-methylbenzylamino)-5,6-dihydrouracil

Formula	$C_{14}H_{16}FN_3O_4$
Formula weight	303.3
Crystal system	Monoclinic
Cell dimensions	$a=22.790(9)$Å
	$b=6.883(2)$Å
	$c=10.514(4)$Å
	$\beta=109.42(5)$Å
Cell volume	1555(1)Å^3
Number of formulas in the unit cell	4
Calculated density	1.32 g cm^{-3}
Systematic absence	hkl, $h+k$ odd
Space group	$C2$

Table II. Fractional Coordinates ($\times 10^4$)

Atom	x	y	z
F	7935(2)	9789(8)	464(4)
N1	7620(3)	7900(10)	3379(6)
C2	7668(3)	9524(12)	4125(17)
O2	7385(3)	9504(8)	4738(5)
N3	7778(3)	11251(10)	3597(6)
C4	7945(3)	11419(12)	2448(7)
O4	8023(3)	12959(9)	1995(6)
C5	8042(4)	9463(13)	1828(7)
C6	7560(4)	8000(12)	1942(7)
N7	6950(3)	8680(11)	1107(6)
C8	6427(4)	7546(15)	1203(9)
C9	5873(5)	7811(24)	-145(10)
C10	6215(4)	8233(16)	2366(9)
C11	5966(5)	6822(19)	3027(12)
C12	5738(6)	7478(25)	4075(12)
C13	5792(5)	9465(28)	4441(11)
C14	6032(5)	10816(22)	3777(10)
C15	6230(4)	10165(17)	2719(10)
C16	8706(4)	8789(13)	2480(8)
O16	8976(3)	8933(13)	3638(7)
O17	8952(3)	8076(15)	1628(7)
C17	9606(5)	7438(28)	2193(16)

lattice parameters and intensities were measured on a Rigaku AFC-5 diffractometer with monochromated Mo$K\alpha$ radiation ($\lambda=0.7107$ Å). Crystal data are given in Table I. Among 1448 independent reflections measured in the range of $3°\leqq 2\theta \leqq 50°$, 1280 observed reflections ($F_o \geqq 3\sigma(F_o)$) were used for the calculations. The structure was solved by the direct method[5] and refined by the block-diagonal least-squares method,[6] applying anisotropic thermal parameters to nonhydrogen atoms (the final R value was 0.073). The final atomic parameters are given in Table II.

Experimental

Melting points are uncorrected. PMR data were recorded on a Varian EM-390 spectrometer using tetramethylsilane as an internal standard. Deuterated dimethylsulfoxide was used as the solvent. Chemical shifts were expressed in δ (ppm) values. Optical rotation was determined on a Perkin-Elmer Model 141 polarimeter using a 1% solution of the sample in methanol. TLC was performed on precoated Kieselgel 60F 254 sheets. Column chromatography was carried out using Kieselgel 60. All solutions were concentrated by evaporation *in vacuo*.

(+)-*r*-5-Ethoxycarbonyl-5-fluoro-*t*-6-(α-methylbenzyloxy)-5,6-dihydrouracil [(+)-3]——A mixture of (±)-**2b** (21.4 g, 82 mmol) and (−)-α-methylbenzyl alcohol (5.00 g, 41 mmol) in 10 ml of pyridine was heated at 120°C for 1 h. Then, 50 ml of H_2O was added and the mixture was heated at 120°C for 0.5 h in order to decompose excess (±)-**2b**. The reaction mixture was dissolved in 300 ml of EtOAc, and the resulting solution was washed with H_2O (100 ml×5) and dried (Na_2SO_4). Removal of the solvent by evaporation gave a yellow syrup. Crystallization of the crude product from EtOH–hexane gave 1.62 g (12%) of crude (+)-**3**. The crude (+)-**3** obtained from other runs was combined and purified further by silica gel chromatography and finally by recrystallization from EtOH–EtOAc–hexane (1/2/6 v/v), giving 11.00 g (9%) of (+)-**3** from 45.3 g of the (−)-alcohol. mp 228—229°C. PMR: 1.20 (3H, t, J=7.5 Hz), 1.38 (3H, d, J=6 Hz), 4.29 (2H, q, J=7.5 Hz), 4.87(1H, q, J=6 Hz), 4.98 (1H, dd, J_{HF}=2 Hz, J=5 Hz), 7.33 (5H, s), 8.8 (1H, br), 11.0 (1H, br). $[\alpha]_D^{20}$ +52.1°. *Anal.* Calcd for $C_{15}H_{17}FN_2O_5$: C, 55.55; H, 5.28; N, 8.64. Found: C, 55.64; H, 5.09; N, 8.78.

(−)-*r*-5-Ethoxycarbonyl-5-fluoro-*t*-6-(α-methylbenzyloxy)-5,6-dihydrouracil [(−)-3]——A mixture of (±)-**2b** (32.6 g, 124 mmol) and (+)-α-methylbenzyl alcohol (6.98 g, 57 mmol) in 9.5 ml of pyridine was heated at 120°C for 1.5 h. Then, the mixture was treated in a manner similar to the procedure described above, giving 22.2 g of crude (−)-**3** as a yellow syrup. It was crystallized from EtOH–hexane, giving 2.8 g (15%) of crude (−)-**3**. The crude (−)-**3** obtained from several runs was combined and recrystallized from EtOH–EtOAc–hexane, giving 9.55 g (8%) of (−)-**3** from 36.2 g of the (+)-alcohol. mp 228—230°C. PMR: 1.21 (3H, t, J=7.5 Hz), 1.39 (3H, d, J=6 Hz), 4.28 (2H, q, J=7.5 Hz), 4.85 (1H, q, J=6 Hz), 4.98 (1H, dd, J_{HF}=2 Hz, J=5 Hz), 7.32 (5H, s), 8.8 (1H, br), 11.0 (1H, br). $[\alpha]_D^{20}$ −50.4°. *Anal.* Calcd for $C_{15}H_{17}FN_2O_5$: C, 55.55; H, 5.28; N, 8.64. Found: C, 55.80; H, 5.19; N, 8.81.

(+)-*r*-5-Ethoxycarbonyl-5-fluoro-*t*-6-(α-methylbenzylamino)-5,6-dihydrouracil [(+)-4]——A mixture of (±)-**2b** (57.64 g, 0.22 mol), (−)-α-methylbenzylamine (20.87 g, 0.17 mol), and Et_3N (33 ml, 0.23 mol) in 250 ml of dioxane was allowed to stand at room temperature for 6 h. The solvent was removed, and the resulting syrup was dissolved in 700 ml of EtOAc. The resulting solution was washed with H_2O (300 ml×4) and dried (Na_2SO_4). Removal of the solvent gave a yellow semi-solid that was triturated with $CHCl_3$–hexane, giving 20.55 g of (+)-**4** as a white solid. The mother liquor was chromatographed on silica gel (400 g, solv.: $CHCl_3$ and $CHCl_3$/MeOH=100/1 v/v), giving a second crop of 2.17 g of (+)-**4** and 30.6 g of the diastereomer of (+)-**4** as a colorless glass which contained a small amount of $CHCl_3$. The total yield of (+)-**4** was 22.72 g (32%). mp 150—151°C (EtOAc). $[\alpha]_D^{24}$ +11.1°. PMR: 1.20 (3H, t, J=7 Hz), 1.24 (3H, d, J=7 Hz), 2.65 (1H, t, J=7 Hz), 3.98 (1H, m), 4.26 (2H, q, J=7 Hz), 4.56 (1H, ddd, J_{HF}=10 Hz, J=3 and 7 Hz), 7.32 (5H, s), 8.2 (1H, br), 10.8 (1H, br). *Anal.* Calcd for $C_{15}H_{18}FN_3O_4$: C, 55.72; H, 5.61; N, 13.00. Found: C, 55.56; H, 5.66; N, 13.27.

(−)-*r*-5-Ethoxycarbonyl-5-fluoro-*t*-6-(α-methylbenzylamino)-5,6-dihydrouracil [(−)-4]——The title compound was prepared similarly from the reaction of (±)-**2b** (62.00 g, 0.24 mol), (+)-α-methylbenzylamine (24.93 g, 0.21 mmol), and Et_3N (28 ml, 0.20 mol) in 250 ml of dioxane by allowing the mixture to stand at room temperature for 20 h, followed by work-up as described above. The total yield of (−)-**4** was 25.80 g (39%). mp 146—147°C (EtOAc). $[\alpha]_D^{24}$ −10.3°. PMR: 1.20 (3H, t, J=7 Hz), 1.24 (3H, d, J=7 Hz), 2.67 (1H, t, J=7 Hz), 3.98 (1H, m), 4.26 (2H, q, J=7 Hz), 4.55 (1H, ddd, J_{HF}=10 Hz, J=3 and 7 Hz), 7.32 (5H, s), 8.2 (1H, br), 10.8 (1H, br). *Anal.* Calcd for $C_{15}H_{18}FN_3O_4$: C, 55.72; H, 5.61; N, 13.00. Found: C, 55.71; H, 5.54; N, 13.04.

After chromatography on silica gel, 23.4 g of the diastereomer of (−)-**4** was isolated from the mother liquor as a colorless glass.

(−)-*t*-6-Butoxy-*r*-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil [(−)-1, (−)-TAC-278]——a) From (−)-**4**: A mixture of (−)-**4** (25.77 g, 79.8 mmol), BuOH (12.0 g, 0.16 mol), and $MeSO_3H$ (8.65 g, 90.1 mmol) in 200 ml of dioxane was heated at 100°C for 2 h. The solvent was removed by evaporation, giving a yellow-brown syrup. This was dissolved in 500 ml of EtOAc, and the solution was washed with H_2O (150 ml×4), an aq. $NaHCO_3$ solution and H_2O (100 ml×2), then dried (Na_2SO_4). Removal of the solvent gave a yellow solid, which was triturated with EtOAc–hexane, giving 15.35 g (70%) of crude (−)-**1** as a white powder. $[\alpha]_D^{23}$ −92.8°. Recrystallization of the crude (−)-**1** twice from $CHCl_3$ (70 ml each) gave 9.42 g of (−)-**1** as colorless flakes. $[\alpha]_D^{24}$ −100.2°.

b) From the Diastereomer of (+)-**4**: A mixture of the diastereomer of (+)-**4** (30.6 g, *ca.* 95 mmol, containing a small amount of $CHCl_3$), BuOH (20.0 ml, 0.22 mol), and $MeSO_3H$ (9.0 g, 94 mmol) in 300 ml of dioxane was heated at 100°C for 3 h. The reaction mixture was treated as above, giving crude (−)-**1**. The combined crops of crude (−)-**1** (12.36 g) were recrystallized from $CHCl_3$, giving 6.84 g of (−)-**1**. $[\alpha]_D^{24}$ −99.8°.

The crops of (−)-**1** obtained from procedures a) and b) were combined and recrystallized from EtOH–hexane, giving 10.13 g [9.7% from (+)- and (−)-α-methylbenzylamines] of optically pure (−)-**1** as colorless flakes. $[\alpha]_D^{23}$ −100.6°. mp 165—166°C. PMR: 0.86 (3H, m), 1.21 (3H, t, J=7 Hz), 1.4 (4H, m), 3.58 (2H, m), 4.29 (2H, q, J=7 Hz), 4.79 (1H, dd, J_{HF}=2 Hz, J=5 Hz), 8.9 (1H, br), 11.0 (1H, br). *Anal.* Calcd for $C_{11}H_{17}FN_2O_5$: C, 47.82; H, 6.20; N, 10.14. Found: C, 47.71; H, 6.22; N, 10.32.

(+)-*t*-6-Butoxy-*r*-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil [(+)-1, (+)-TAC-278]——a) From (+)-**4**: A mixture of (+)-**4** (22.64 g, 70.1 mmol), BuOH (10.5 g, 0.14 mol), and $MeSO_3H$ (7.70 g, 80.0 mmol) in 170 ml of dioxane was heated at 100°C for 2 h. Treatment of the reaction mixture in a manner similar to that

described above gave 14.18 g (73%) of crude (+)-**1** as a white solid. This was recrystallized three times from $CHCl_3$, giving 9.42 g of (+)-**1** as colorless flakes.

b) From the Diastereomer of (−)-**4**: A mixture of the diastereomer of (−)-**4** (23.4 g, *ca.* 72 mmol), BuOH (12.12 g, 0.16 mol), and $MeSO_3H$ (7.40 g, 77.1 mmol) in 170 ml of dioxane was heated at 100°C for 2 h. The reaction mixture was treated in a similar manner to that given above to yield 11.9 g of crude (+)-**1**, which was recrystallized from $CHCl_3$, giving 5.53 g of (+)-**1** as colorless flakes. The mother liquors from procedures a) and b) were combined and chromatographed on silica gel, giving 8.28 g of a yellow solid. It was combined with the flakes obtained from procedure a), and recrystallized from $CHCl_3$, giving 13.54 g of colorless flakes. The flakes (5.53 g and 13.54 g) were combined and recrystallized from EtOH–hexane, giving 13.86 g [13.3% from (+)- and (−)-α-methylbenzylamines used] of optically pure (+)-**1** as colorless prisms. $[\alpha]_D^{23}$ +100.5°. mp 165—166°C. PMR: 0.84 (3H, m), 1.20 (3H, t, J=7 Hz), 1.4 (4H, m), 3.56 (2H, m), 4.28 (2H, q, J=7 Hz), 4.78 (1H, dd, J_{HF}=2 Hz, J=5 Hz), 8.8 (1H, br), 11.0 (1H, br). *Anal.* Calcd for $C_{11}H_{17}FN_2O_5$: C, 47.82; H, 6.20; N, 10.14. Found: C, 47.73; H, 6.20; N, 10.06.

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References and Notes

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