ANALOGS OF PYRIMIDINE NUCLEOSIDES.

# 15.* SYNTHESIS OF 3'-HYDROXY- AND 4'-HYDROXYFTORAFUR

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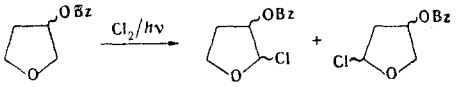
A method for the synthesis of ftorafur metabolites, viz., 3'-hydroxy- and 4'-hydroxyftorafur, from 3-benzoxytetrahydrofuran, which is chlorinated in the presence of UV irradiation, was developed. The resulting mixture of α-chloro ethers is alkylated by 2,4-bis(trimethylsilyl)-5-fluorouracil. The alkylation products are separated by fractional crystallization and column chromatography on silica gel, and the benzoyl protective group is removed. cis-4'-Hydroxyftorafur, trans-3'-hydroxyftorafur, and cis-3'-hydroxyftorafur, which were identified from the PMR spectra and by comparison with the literature data, were obtained.

The antitumorigenic preparation ftorafur [2] is widely used for the treatment of tumorous diseases of the gastrointestinal tract and the mammary gland [3]. A study of the metabolism of ftorafur in the human organism is of great value for an understanding of its antitumorigenic activity. Minor metabolites, viz., 3'-hydroxy-, 4'-hydroxy, and 3',4'-dehydroftorafur, in addition to the principal metabolite, viz., 5-fluorouracil, have recently been isolated from the urine of patients who have been treated with ftorafur and have been identified [4-6]. The formation of extremely unstable metabolic intermediates, viz., 2'-hydroxy- and 5'-hydroxyftorafur, is also proposed [4]. Some of these metabolites have been obtained by synthesis [7, 8].

We have found an original method for the synthesis of 3'-hydroxy- and 4'-hydroxyftorafur from 3-hydroxytetrahydrofuran. The hydroxy group is protected by benzoylation, and 3-benzoxytetrahydrofuran (I) is chlorinated at −5 to 10°C in $CCl_4$ to give a mixture of α-chloro ethers II and III in a ratio of 1:6 (according to PMR spectroscopic data). In view of the instability of II and III, the mixture obtained was subjected without separation to reaction with 2,4-bis(trimethylsilyl)-5-fluorouracil (IV). The reaction takes place in 4-5 h at room temperature. The reaction products were separated by fractional crystallization and column chromatography on silica gel, after which the benzoyl protective group was removed by the action of ammonia in methanol. The reaction products (VIIa, b and VIII) were identified on the basis of an analysis of the PMR spectra (Table 1) and comparison of them with the literature data [7, 8].




I II III

The principal alkylation products are the benzoyl derivatives of cis-4'-hydroxyftorafur [VI (40%)] and trans-3'-hydroxyftorafut [Vb (8%)]. Another compound, tentatively identified as the benzoyl derivative of cis-3'-hydroxyftorafur (Va), which was not isolated in individual form, is also formed in very small amounts. The benzoyl derivative of trans-4'-hydroxyftorafur was not detected. The characteristics of Vb, VI, VIIb, and VIII are presented in Table 2.

*See [1] for Communication 14.

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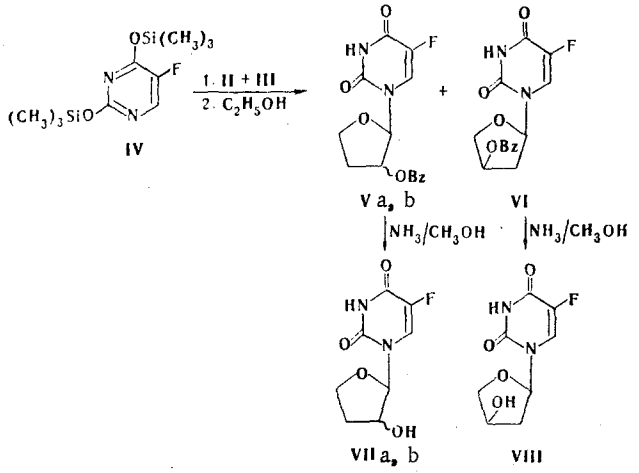
TABLE 1. PMR Spectra of V-VIII in $d_6$-DMSO

| Compound | Chemical shift, δ, ppm (J, Hz)* | | mp, °C |
|---|---|---|---|
| | 2'-H | 6-H (Ph) | |
| Va | 6,1 d ($J$=3,7) | (7,38—8,1) | — |
| Vb | 5,83 t ($J$=1,6) | (7,38—8,1) | 203—205 |
| VI | 6,01 dt ($J_d$=7,0) ($J_t$=2,0) | (7,26—8,06) | 189—191 |
| VIIa | 6,1 d ($J$=3,7) | 7,76 d ($J$=7,0) | — |
| VIIb | 5,5 t ($J$=1,6) | 7,71 d ($J$=7,0) | 214—216 |
| VIII | 6,01 dt ($J_d$=8,0) ($J_t$=2,0) | 8,1 d ($J$=7,1) | 205—207 |

*See [7]. 4'-Hydroxyftorafur: cis isomer (mp 204-205°C), δ, 6.05 (dt, 1H, 2'-H, $J_d$ = 8.0, $J_t$ = 2.0), 8.1 (d, 1H, 6-H, J = 7.0); trans isomer (mp 181-182°C), δ, 6.09 (td, 1H, 2'-H, $J_t$ = 7.0, $J_d$ = 2.0), 7.9 (d, 1H, 6-H, J = 7.0); 3'-hydroxyftorafur: cis isomer (mp 154-156°C), δ, 6.21 (d, 1H, 2'-H, J = 3.7), 7.62 (d, 1H, 6-H, J = 5.0); trans isomer (mp 214-216°C), δ, 5.58 (t, 1H, 2'-H, J = 1.5), 7.75 (d, 1H, 6-H, J = 7.0).

TABLE 2. Physicochemical Properties of 1-[3(4)-Benzoxytetrahydro-2-furyl]-5-fluorouracils (Vb, VI) and 1-[3(4)-Hydroxytetrahydro-2-furyl]-5-fluorouracils (VIIb, VIII)

| Compound | UV spectrum, $\lambda_{max}$, nm (ε · $10^{-3}$) | | | IR spectrum | Found, % | | | Empirical formula | Calculated, % | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | pH 2 | pH 7 | pH 12 | | C | H | N | | C | H | N |
| Vb | 270 (9,2) | 270 (9,0) | 269 (6,5) | — | 56,9 | 4,3 | 8,5 | $C_{15}H_{13}FN_2O_5$ | 56,3 | 4,1 | 8,7 |
| VI | 271 (9,2) | 271 (9,3) | 269 (7,8) | — | 57,1 | 4,1 | 8,6 | $C_{15}H_{13}FN_2O_5$ | 56,3 | 4,1 | 8,7 |
| VIIb | 270 (8,8) | 269 (8,7) | 269 (6,8) | 3460 | 44,9 | 4,1 | 12,7 | $C_8H_9FN_2O_4$ | 44,4 | 4,2 | 13,0 |
| VIII | 271 (9,0) | 270 (9,1) | 269 (7,0) | 3380 | 44,5 | 4,1 | 12,9 | $C_8H_9FN_2O_4$ | 44,4 | 4,2 | 13,0 |




V, VII a — cis isomer; b — trans isomer

## EXPERIMENTAL

The purity of the substances and the course of the reaction were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in a chloroform—ethanol system (9:1). Monitoring of the separation during column chromatography was carried out with a Uvikord II flow absorptiometer connected to a recorder (LKB, Sweden). The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with the compounds in $d_6$-DMSO were obtained with a Bruker WH-90 DS spectrometer with hexamethyldisiloxane as the internal standard. The melting points were determined with

a Boëtius microblock. The starting 3-hydroxytetrahydrofuran was synthesized by the method in [9].

3-Benzoxytetrahydrofuran (I). This compound was synthesized by acylation of 3-hydroxytetrahydrofuran with benzoyl chloride in pyridine and was purified by vacuum distillation [the fraction with bp 121-124°C (3 mm) was collected] to give a product with $n_D^{20}$ 1.525 in 76% yield. Found: C 67.9; H 5.9%. $C_{11}H_{12}O_3$. Calculated: C 68.7; H 6.3%.

2-Chloro-3-benzoxytetrahydrofuran (II) and 2-Chloro-4-benzoxytetrahydrofuran (III). A solution of 10.8 g (0.056 mole) of I in 100 ml of dry $CCl_4$ was placed in a quartz flask, the flask was cooled to −7°C and irradiated with a PRK-4 mercury lamp (with a power of 400 W at 30 to 40 cm from the flask), and a mixture of dry nitrogen and 4.8 g (0.068 mole) of chlorine was introduced in the course of 1 h. Irradiation was continued for 1 h, during which the reaction mixture was purged with nitrogen to remove the hydrogen chloride. The mixture was then stirred for another hour with NaA molecular sieves and filtered. The reaction yield was determined from the PMR spectrum. The reaction mixture contained 32% unchanged starting I (from the intensities of the signals of the 3-H–4-H and 2-H protons), 10% II, and 58% III.

1-(3-Hydroxytetrahydro-2-furyl)- and 1-(4-Hydroxytetrahydro-2-furyl)-5-fluorouracil (VIIa and VIIb, VIII). An 8.3-g (0.036 mole) sample of the mixture of α-chloro ethers II and III was added with stirring to 10 g (0.036 mole) of freshly distilled 2,4-bis(trimethylsilyl)-5-fluorouracil (IV), and condensation was carried out at a pressure of 30-40 mm in a nitrogen atmosphere with stirring at 20°C for 4 h. Ethanol (15 ml) was added, and the precipitate was separated and recrystallized from chloroform to give 3.58 g (31%) of VI with mp 189-191°C; evaporation of the chloroform gave an additional 1.0 g of VI for an overall yield of 40% (based on IV). The mother liquor was applied to a column filled with silica gel and eluted with chloroform–ethanol (9:1). The substances were eluted with two peaks. Evaporation of the eluate gave 0.88 g of Vb and 0.17 g of a mixture of Va and Vb. Compound Vb was obtained in 8% yield and Va was obtained in 1% yield.

The benzoyl protective group was removed by allowing 4.58 g of VI to stand in solution in 50 ml of methanol saturated with ammonia at 4°C for 24 h. The solvent was evaporated, and the residue was dried by azeotropic distillation with absolute ethanol (two 10-ml portions), and the precipitate was separated to give 3.0 g (95%, based on VI) of VIII with $R_f$ 0.24.

A 0.88-g sample of Vb yielded 0.46 g (78%, based on Vb) of VIIb with $R_f$ 0.28. A 0.17-g sample of the mixture of Va and Vb gave 0.09 g (79%, based on Va, b) of VIIa and VIIb with $R_f$ 0.31.

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