ANALOGS OF PYRIMIDINE NUCLEOSIDES

III. Derivatives of N_1-(α-Tetrahydrofuryl)-5, 6-dihydrouracil

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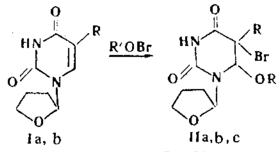
The reaction of alkoxy bromides with N_1-(α-tetrahydrofuryl) derivatives of pyrimidine bases has given a series of 6-alkoxy-5-bromo-1-(α-tetrahydrofuryl)-5, 6-dihydrouracils. The hydrogenation of the 1-(α-tetrahydrofuryl) derivatives of uracil and of 5-fluorouracil has been studied. It has been shown that in both cases 1-(α-tetrahydrofuryl)-5, 6-dihydrouracil is formed.

Two of us have previously [1] described 5-fluoro-1-(α-tetrafuryl)uracil (**Ia**), which proved to be 5–6 times less toxic than 5-fluorouracil (FU) while having a chemotherapeutic index twice as large (the substance is marketed under the trade name "Ftorafur"). In addition to this, according to Dushinsky et al. [2], 6-alkoxy-5-bromo derivatives of 5-fluoro-5, 6-dihydrodeoxyuridine are superior to 5-fluorodeoxyuridine (FUDR) in antileukemic activity, being, apparently, the transport form of the latter.

In this work we have made an attempt to synthesize derivatives of 5-fluoro-1-(α-tetrahydrofuryl)-5, 6-dihydrouracil both by the addition of alkoxy bromides to (**Ia**) and by its selective hydrogenation.

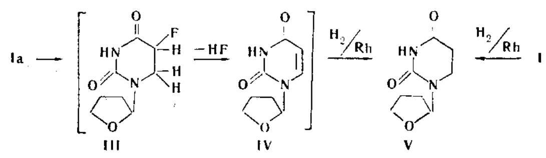
We obtained 6-alkoxy-5-bromo-5-fluoro-1-(α-tetrahydrofuryl)-5, 6-dihydrouracils (**IIa, b**) by the reaction of **Ia** with methyl and ethyl hypobromites. From **Ib** we have synthesized 5-bromo-6-methoxy-1-(α-tetrahydrofuryl)-5, 6-dihydrothymine (**IIc**).

It is known that the hydrogenation of FU in the presence of 5% of rhodium on Al_2O_3 leads to the formation of 5-fluoro-5, 6-dihydrouracil with a yield of 6.5% [3]. 5-Fluoro-5, 6-dihydro derivatives of uracil are unstable and readily split off HF [3, 4]. We performed the hydrogenation of the double bond in **Ia** with 5% of Rh on alumina in the presence of a phosphate buffer at pH 7 in order to obtain 5-fluoro-1-(α-tetrahydrofuryl)-5, 6-dihydrouracil (**III**). However, under these conditions we were able to obtain only 1-(α-tetrahydrofuryl)-5, 6-dihydrouracil (**V**).

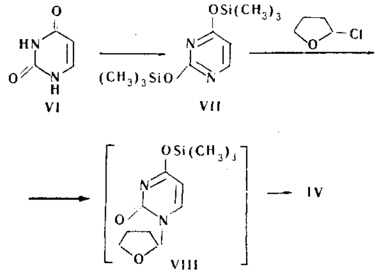


Ia R=F; Ib R=CH_3
IIa R=F, R'=CH_3;
IIb R=F, R'=C_2H_5;
IIc R=CH_3, R'=CH_3

In view of the absorption of two moles of hydrogen, it may be assumed that the mechanism of the reaction reduces to: 1) the saturation of the C_5—C_6 double bond in **Ia** with the formation of **III**; and 2) the splitting out of HF and the secondary saturation of the double bond in **IV** with the formation of **V**.



When **Ia** was hydrogenated in an unbuffered ethanolic medium, hydrolysis of the pseudoglycosidic bond and the formation of a mixture containing mainly FU, 5, 6-dihydrouracil, and **IV** took place. Compound **V** has also been obtained by independent synthesis through the hydrogenation of 1-(α-tetrahydrofuryl)uracil (**IV**), which we synthesized for the first time by the condensation of bis-O-(trimethylsilyl)uracil (**VII**) [5, 6] with 2-chlorotetrahydrofuran:



As was to be expected, in the hydrogenation of **IV** only one mole of hydrogen was absorbed, giving **V**, shown to be identical with the product obtained by the hydrogenation of **Ia**.

EXPERIMENTAL

Purity of the substances synthesized was checked by means of ascending chromatography on Filtrak FN-1 paper in the n-C_4H_9OH—CH_3COOH—H_2O (2 : 1 : 1) and ethanol–water (85 : 15) systems (systems 1 and 2, respectively). Compound **II** possesses residual absorption and was revealed in ultraviolet light. The **V** on the chromatograms was shown by means of 1 NaOH and subsequent treatment with Ehrlich's reagent [7]. The UV spectra were recorded on a UF-2 automatic spectrophotometer at pH 2 (0.01 N HCl), pH 7 (0.01 N H_3BO_3), and pH 12 (0.01 N KOH). The absence of an absorption maximum in the UV spectrum at 270 nm at pH 2 and pH 7, which is characteristic for **Ia**, and also the appearance of a new maximum at pH 12 shows the presence of a saturated 5, 6-bond. The IR spectra were taken on an IKS-14 spectrometer with suspensions of analytical samples of the substances in paraffin oil in the range of frequencies from 700 to 1800 cm^{-1} and in hexachlorobutadiene for the ranges 1300–1500 and 3000–3500 cm^{-1}.

1-(α-Tetrahydrofuryl)uracil (IV). A mixture of 5.6 g (0.05 mole) of uracil (**VI**), 25 ml of hexamethyldisilane (HMDS), and 0.5 ml of chlorotrimethylsilane was heated in an oil bath at 165° C for 2 hr. After the **VI** had dissolved, the excess of HMDS was distilled off in vacuum at a bath temperature not exceeding 55° C, the mixture was cooled to −20° C in a current of dry nitrogen, and 4.26 g (3.6 ml, 0.04 mole) of 2-chlorotetrahydrofuran was added; the mixture was kept at −10° C for 2 hr, left overnight at room temperature, treated with

10 ml of ethanol, and stirred for 2 hr, and the precipitate was filtered off with suction and extracted with 60 ml of chloroform. The insoluble part was **VI**: 2.9 g (52% of that used in the reaction). The chloroform extract after evaporation in vacuum yielded 3 g of **IV** (33%). Mp 102–104° C (ethanol). UV absorption spectrum: $\lambda_{max}^{pH\ 2}$ 262 nm (ε 11 300); $\lambda_{max}^{pH\ 7}$ 262 nm (ε 9700); $\lambda_{max}^{pH\ 12}$ 259 nm (ε 7300). IR spectrum in ν, cm^{-1}: 3149, 3107 (NH), 1709, 1680 (C=O), 1070 (—C—O—C). Found, %: C 52.18; H 5.59; N 15.72. Calculated for $C_8H_{10}N_2O_3$, %: C 52.74; H 5.53; N 15.38.

1-(α-Tetrahydrofuryl)-5,6-dihydrouracil (V). a) The hydrogenation of a solution of 0.6 g (2.5 mM) of **Ia** in 100 ml of phosphate buffer (pH 7) with the addition of 0.5 g of 5% of rhodium on alumina was carried out at room temperature and atmospheric pressure until the absorption of hydrogen ceased. The theoretical amount of hydrogen (5 mM) was absorbed in 1 hr. The catalyst was filtered off, the filtrate was evaporated in a rotary evaporator to dryness (bath temperature 60° C), the residue was treated with 40 ml of ethanol, and the mixture was filtered. The solvent was again evaporated to give an oily substance which crystallized at room temperature. It was washed with the minimum amount of ether and 0.4 g of **V** was obtained. Yield 87%, mp 108–111° C (ethyl acetate), R_f 0.75 (system 1), R_f 0.84 (system 2). UV absorption: $\lambda_{max}^{pH\ 12}$ 230 nm (ε 6590). IR spectrum in ν, cm^{-1}: 3200, 3082 (NH); 1710, 1680 (CO); doublet at 1054, 1035 (—C—O—C—). Found, %: C 52.59; H 6.62; N 15.37. Calculated for $C_8H_{12}N_2O_3$, %: C 52.17; H 6.57; N 15.21.

b) The hydrogenation of a solution of 0.5 g (2.75 mM) of **IV** in 100 ml of absolute methanol with the addition of 0.5 g of 5% of rhodium on alumina was carried out at room temperature and atmospheric pressure until the absorption of hydrogen ceased (~2.75 ml of hydrogen). The catalyst was filtered off, the filtrate was evaporated in vacuum to dryness, and the residue was recrystallized from ethyl acetate to give 0.34 g of **V** (yield 67%) in the form of a white crystalline substance. Compound **V** obtained by method (b) was identical with the compound obtained by method (a)

5-Bromo-5-fluoro-6-methoxy-1-(α-tetrahydrofuryl)-5,6-dihydrouracil (IIa). A solution of 1.4 ml of bromine in 100 ml of absolute methanol was cooled to −15° C, 17 g of Ag_2CO_3 was added, and the mixture was stirred at −10° to −15° C for an hour and filtered. A 70 ml quantity of the resulting solution of methyl hypobromite in methanol was added to 3 g of **Ia** suspended in 50 ml of absolute methanol, and the mixture was stirred at 0° C for 15 min and at room temperature for 1 hr. The solution was evaporated in a rotary evaporator at room temperature to dryness, and the residue was washed with the minimum amount of dry cold ether. It was recrystallized from ethyl acetate to give 2.46 g of **IIa** (yield 53%) and a white crystalline substance with mp 186° C, R_f 0.89 (system 1), R_f 0.95 (system 2). UV absorption, $\lambda_{max}^{pH\ 12}$ 243 nm (ε 6000) remaining unchanged for 24 hr; IR spectrum in ν, cm^{-1}: 3153, 3059 (NH); 1748, 1685 (CO); 1072, shoulder at 1051 (—C—O—C—). Found, %: C 34.42; H 4.02; N 8.58; Br 26.44; F 6.37. Calculated for $C_9H_{12}N_2O_4BrF$, %: C 34.74; H 3.89; N 9.00; Br 25.68; F 6.11.

5-Bromo-6-ethoxy-5-fluoro-1-(α-tetrahydrofuryl)-5,6-dihydrouracil (IIb). By the method described above, 5 g of **Ia** in 80 ml of absolute ethanol and 70 ml of a solution of ethyl hypobromite in absolute ethanol (2.6 ml of bromine, 100 ml of absolute ethanol, and 33.2 g of Ag_2CO_3) yielded 5.45 g of **IIb** (67%); after recrystallization from ethyl acetate, 3.4 g (42%). Mp 181–182° C. R_f 0.92 (system 1), R_f 0.96 (system 2); UV absorption $\lambda_{max}^{pH\ 12}$ 243 nm (ε 6100) (remaining unchanged for 24 hr); IR spectrum in ν, cm^{-1}: 3210, 3110 (NH); 1740, 1718 (CO); 1075, shoulder at 1060 (—C—O—C—). Found, %: C 36.53; H 4.47; N 8.48; Br 24.85; F 5.46. Calculated for $C_{10}H_{14}N_2O_4BrF$, %: C 36.94; H 4.34; N 8.62; Br 24.58; F 5.84.

5-Bromo-6-methoxy-1-(α-tetrahydrofuryl)-5,6-dihydrothymine (IIc). As for the preparation of **IIa**, 0.48 g of **Ia** in 50 ml of absolute methanol and 20 ml of a solution of methyl hypobromite in methanol gave 0.52 g of **IIc** (yield 71%). Mp 168° C (ethyl acetate), R_f 0.89 (system 1), R_f 0.94 (system 2); UV absorption $\lambda_{max}^{pH\ 12}$: 246 nm (ε 5500) (remaining unchanged for 24 hr); IR spectrum in ν, cm^{-1}: 3183, 3064 (NH); 1726, shoulder at 1693, 1676 (CO); doublet at 1087, 1073 (—C—O—C—). Found, %: C 38.61; H 4.86; N 8.79; Br 26.28. Calculated for $C_{10}H_{15}N_2O_4Br$, %: C 39.09; H 4.92; N 9.12; Br 26.01.

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