

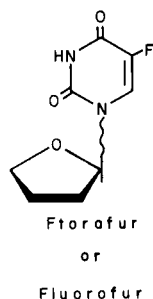
The Synthesis of 1-(Tetrahydro-2-furanyl)-5-fluorouracil (Ftorafur) via Direct Fluorination (1)

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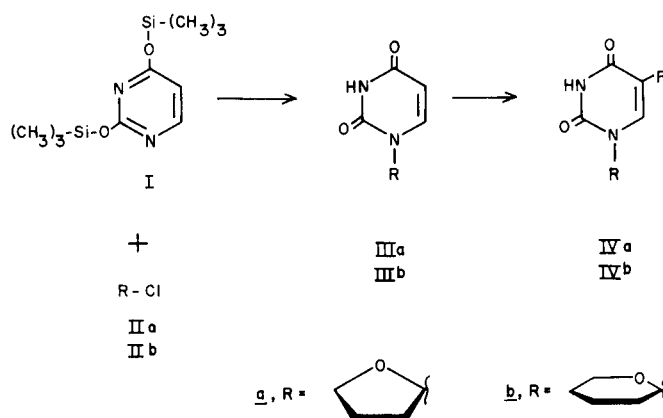
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Ftorafur [1-(tetrahydro-2-furanyl)-5-fluorouracil, IVa)] has been reported (2) to possess a high chemotherapeutic activity (twice that of 5-fluorouracil, 5-FU) and low toxicity (5-6 times less than 5-FU) toward cancer of the



breast and the gastrointestinal tract. This activity prompted the preparation of I in our laboratory for evaluation in the screening program of the National Cancer Institute of the National Institutes of Health. Ftorafur has been synthesized (3) by a condensation of the bistrimethylsilyl derivative of 5-fluorouracil and 2-chlorotetrahydrofuran. We now wish to report an alternate synthetic route to Ftorafur using the direct fluorination of 1-(tetrahydro-2-furanyl)uracil (4,5) as the terminal reaction.

In our initial experiments we used 1-(tetrahydro-2-pyranyl)uracil (6,7) since this compound could be synthesized from inexpensive commercially available starting materials. The low temperature reaction of anhydrous hydrogen chloride with an excess of dry 2,3-dihydropyran in methylene chloride provided 2-chlorotetrahydropyran (IIb) (8,9) as a colorless liquid (45%) which was stable for several days at -20° , if stored under strictly anhydrous conditions. The highly reactive nature of IIb was demonstrated by the fact that an ice-cold solution of IIb in methylene chloride was completely hydrolyzed when we attempted to wash the solution with cold (0°) water. Reaction of IIb with the bistrimethylsilyl derivative (I) of uracil in methylene chloride provided 1-(tetrahydro-2-pyranyl)uracil (IIIb) in 65% yield. We found that the use of a solvent in the reaction improved the yield of product in comparison to the same reaction without a solvent (7).



The fluorination (10) of IIIb was accomplished by passing a 60% excess of trifluoromethylhypofluorite into a stirred solution of IIIb in methylene chloride at -78° [until no uv absorbing material in the 250-340 nm range was detected in the reaction mixture]. It was found that even at this temperature (-78°) some of the trifluoromethylhypofluorite (b.p. -95°) was lost through the drying tube. We then added a liquid nitrogen cooled Dewar type condenser which allowed us to add a smaller excess of trifluoromethylhypofluorite while still achieving a complete reaction (11). Decomposition of the intermediate trifluoromethylhypofluorite adduct (colorless glass) was accomplished using a cold mixture of methanol-ammonium hydroxide. The use of ammonium hydroxide resulted in the formation of a salt-like by-product (presumably ammonium trifluoromethylate, $\text{NH}_4^+ \text{OCF}_3$) which was relatively insoluble in organic solvents of moderate polarity and facilitated the extraction of product from the inorganic salts using hot chloroform (12).

1-(Tetrahydro-2-pyranyl)-5-fluorouracil (IVb) was obtained in 44% yield. The pmr spectrum of IVb showed one doublet centered at δ 8.1 with a F-H coupling of 7.5 Hz which is in contrast to 1-(tetrahydro-2-pyranyl)uracil (IIIb) which displayed two doublets (centered at δ 7.73 and δ 5.67, $J_{5,6} = 8$ Hz) in the nmr spectrum. This appearance of a new downfield doublet with the con-

comitant disappearance of the original pair of doublets was strong evidence that fluorination had occurred. Other physical constants (m.p., ir, uv, etc.) observed for IVb prepared by direct fluorination were identical to those for an authentic sample (7) of 1-(tetrahydro-2-pyran-5-yl)-5-fluorouracil (IVb) and unequivocally established the structure of the compound prepared by direct fluorination.

We used the same general experimental conditions, *vide supra*, for the synthesis of Ftorafur. The 1-(tetrahydro-2-furanyl)derivative (IIIa) of uracil was synthesized by a condensation of 2-chlorotetrahydrofuran (IIa) with the bistrimethylsilyl derivative (1) of uracil using a slight modification of the reported procedure (5). Fluorination of IIIa with trifluoromethylhypofluorite gave a 60% yield of Ftorafur (IVa) with a melting point of 164-166° and other physical properties (ir, uv, nmr) identical with those of an authentic sample of Ftorafur prepared in our laboratory by the published procedure (3).

We feel that this experimentally simple preparation of Ftorafur, *via* direct fluorination, offers an attractive alternate route for its preparation.

EXPERIMENTAL

All melting points (Thomas-Hoover) are uncorrected. Pmr: Varian A-60 spectrometer (²H₆ dimethylsulfoxide as solvent and DSS as internal standard); uv: Beckman DK-2 spectrophotometer; ir (potassium bromide disks): Beckman IR-8 spectrophotometer. All glassware used for the reactions and distillations was dried in an oven at 120° for 1 hour or by the passage of a slow stream of dry nitrogen through the assembled apparatus for 1 hour. All concentrations *in vacuo* were carried out at 40°.

2-Chlorotetrahydropyran (IIb) and 2-Chlorotetrahydrofuran (IIa).

Dry methylene chloride (25 ml.) and freshly distilled 2,3-dihydropyran (13) (25.2 g., 0.3 mole) were placed in a 100 ml. round bottomed flask fitted with a gas inlet tube and containing a magnetic stirring bar. The solution was cooled (-78°, dry ice-acetone bath) and stirred while 0.28 mole of dry hydrogen chloride gas was introduced (measured with a gas flowmeter using a flowrate of 150 ml./min. for 41.7 minutes). The colorless solution was stored at -20° overnight and then the methylene chloride distilled off at atmospheric pressure. Fractional distillation under vacuum (water aspirator, 25 mm) yielded the product as a water-white liquid, 15.5 g. (46%) b.p. 73°/25 mm, $n_D^{25} = 1.466$ (Lit. (9) b.p. 55-56°/26 mm, $n_D^{25} = 1.4660$). The product thus obtained was stable (remaining colorless) for several days if stored at -20° under strictly anhydrous conditions. Attempts at washing methylene chloride solutions of 2-chlorotetrahydropyran with ice-cold water resulted in complete hydrolysis of the compound.

By substituting 2,3-dihydrofuran (14) for 2,3-dihydropyran in the above reaction, 2-chlorotetrahydrofuran (IIa) was obtained in 45% yield in the form of a water-white liquid, b.p. 53-56°/25 mm, $n_D^{25} = 1.460$ (Lit. (15) b.p. 28-31°/9 mm, $n_D^{20} = 1.4607$). The 2-chloro derivative of tetrahydrofuran was found to be less stable than the corresponding 2-chlorotetrahydropyran and darkened after standing for 1 hour at room temperature. A sample which was stored over molecular sieves (Linde, 4Å) at -20° for

18 hours turned very dark but gave good yields during condensation with the bistrimethylsilyl derivative (1) of uracil.

1-(Tetrahydro-2-pyran-5-yl)uracil, Hemihydrate (IIIb).

Uracil (5 g., 44.6 mmoles dried *in vacuo* at 25° for 1 hour), hexamethyldisilazane (HMDS, 25 ml.) and dry ammonium sulfate (20 mg.) were heated at 160° for 18 hours. Excess HMDS was distilled off *in vacuo* (25 mm, oilbath 70°), 10 ml. of dry xylene was added and then removed by distillation *in vacuo*. The residue (colorless liquid) was dissolved in 150 ml. of dry methylene chloride, the solution cooled to -78° and then 8.05 g. of 2-chlorotetrahydropyran (IIb, 66.3 mmoles) was added. The reaction mixture was tightly stoppered and allowed to stand at ambient temperature for 3.5 hours. Concentration of the solution *in vacuo* (aspirator and then oil pump) left an oily residue that was triturated with 50 ml. of cold (0°) ethyl ether-methanol (10:1) resulting in the separation of 6.83 g. of a white solid m.p. 183-188°. This solid was recrystallized from a minimum amount of 2-propanol to give 5.95 g. (65%) of IIIb, m.p. 185.5-187.5° (Lit. (6) m.p. 185-187°); uv spectral data were identical to those previously reported for this compound (6,7); pmr δ 11.32 (brs, (16), 1H, NH); δ 7.73 (d, J_{6,5} = 8 Hz, 1H, H₆); δ 5.67 (d, J_{5,6} = 8 Hz, 1H, H₅); δ 5.54 (m, 1H, H₁').

1-(Tetrahydro-2-furanyl)uracil (IIIa).

This compound was synthesized according to the published (5) procedure except that a solvent (methylene chloride) was used which resulted in a moderate improvement in yield. The ratio of 2-chlorofuran to uracil to solvent was 1.08 mmoles: 1 mmole:1 ml., respectively and the yield of pure IIIa was 45.5% (71% based on recovered uracil), m.p. 99-101° (ethyl acetate); uv and ir spectral data were consistent with literature values (4,5); pmr δ 11.3 (brs., 1H, NH); δ 7.64 (d, 1H, J_{5,6} = 8 Hz, H₆); δ 6.02 (m, 1H, H₁'); δ 5.64 (d, 1H, J_{5,6} = 8 Hz, H₅).

1-(Tetrahydro-2-pyran-5-yl)-5-fluorouracil (IVb).

Trifluoromethylhypofluorite (*ca.* 23.8 mmoles) was bubbled into a cold (-78°), magnetically stirred solution of 1-(tetrahydro-2-pyran-5-yl)uracil hemihydrate (IIIb, 3 g., 14.6 mmoles) in 100 ml. of AR grade methylene chloride for 35 minutes at a flow rate of 20 ml./min. (gas flowmeter). After 35 minutes the solution was clear and no uv absorbing material was observed in the 250-340 nm region. The solution was concentrated *in vacuo* to a colorless foam and then a cold (-20°) solution of concentrated ammonium hydroxide (9 ml.) in methanol (90 ml.) was added in one portion. The solution was allowed to stand for 18 hours at room temperature and then concentrated *in vacuo* to a white solid. Another portion of methanol was added (about 40 ml.) followed by *ca.* 4 g. of solid carbon dioxide. Concentration *in vacuo* gave a white solid that was extracted with hot chloroform (3 x 50 ml.). The chloroform was removed by distillation and the residue recrystallized from ethyl acetate (30 ml.) to give pure 1-(tetrahydro-2-pyran-5-yl)-5-fluorouracil (IVb), 1.36 g. (44%), m.p. 168-169°. The uv and pmr spectra of this material were identical to a sample prepared by another route (7) and there was no depression of m.p. on admixture with authentic material (7); pmr δ 11.92 (brs, 1H, NH); δ 8.1 (d, J_{F,H6} = 7.5 Hz, H₆); δ 5.4 (m, 1H, H₁').

1-(Tetrahydro-2-furanyl)-5-fluorouracil (IVa).

A 200 ml. round bottomed flask was fitted with a straight vacuum take off adaptor on top of which was placed a Dewar type condenser fitted with a drying tube. A solution of 1-(tetrahydro-2-furanyl)uracil (IIIa, 4.0 g., 22 mmoles) in AR grade methylene chloride (120 ml.) was placed in the flask along with a magnetic

stirring bar. The system was flushed with nitrogen while the flask was cooled to -78° (dry ice-acetone) and then liquid nitrogen was added to the Dewar condenser. Trifluoromethylhypofluorite (726 ml., 24.2 mmoles) was introduced above the surface of the stirred cold solution for 25 minutes (flow-rate ca. 30 ml./min.). A white solid separated from solution and after 25 minutes no uv absorbing material was observed in the 250-340 nm region. The solution was concentrated *in vacuo* to afford a white solid.

The reaction mixture was processed in the same manner as that used for IVb. The crude product was recrystallized from ethanol (12 ml.), 2.65 g. (60%), m.p. $164-166^{\circ}$ (Lit. (3), m.p. $164-166^{\circ}$). A second recrystallization from a minimum amount of ethanol (23 ml.) raised the m.p. to $168-169^{\circ}$. No depression in m.p. was observed on admixture of this material with an authentic sample prepared (3) by a different route. The ir, uv and pmr spectral data of this material were also identical to those of an authentic sample; pmr δ 11.17 (brs, 1H, NH); δ 7.81 (d, J_{F,6}, 7 Hz, 1H, H₆); δ 5.89 (m, 1H, H₁').

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