SYNTHESIS OF 1-(TETRAHYDROFURAN-2-YL)-5-FLUOROURACIL-2-^{14}C (FTORAFUR-2-^{14}C)

Steven J. Manning, Arthur M. Cohen and Leroy B. Townsend*
Division of Medicinal Chemistry and Division of Pharmacology,
Department of Biopharmaceutical Sciences, University of Utah,
Salt Lake City, Utah 84112
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SUMMARY

The synthesis of 1-(tetrahydrofuran-2-yl)-5-fluorouracil-2-^{14}C (Ftorafur-2-^{14}C) has been accomplished by the condensation of 5-fluorouracil-2-^{14}C and 2-chlorotetrahydrofuran using a procedure developed in our laboratory.

Key Words: 1-(Tetrahydrofuran-2-yl)-5-fluorouracil-2-^{14}C, Ftorafur-2-^{14}C, Condensation, 5-Fluorouracil-2-^{14}C, 2-Chlorotetrahydrofuran

INTRODUCTION AND DISCUSSION

Pharmacological studies in both experimental animals[1,2] and human cancer patients[3] have indicated that ftorafur [1, 1-(tetrahydrofuran-2-yl)-5-fluorouracil, F-5FU] is less toxic than 5-fluorouracil (5-FU) while retaining equal or greater antitumor activity. Recent studies have shown that ftorafur is active against the L-1210[4,5] murine leukemia. The principal clinical application of ftorafur, like that of 5-FU, is in the treatment of cancer of breast and gastrointestinal tract[6-8] and a clinical phase I study[9] has recently been completed.

The pharmacokinetics of ftorafur have been studied during the past several years, and, in general, the results indicate that ftorafur acts as a depot form of 5-FU.[10,11] Metabolic conversion of ftorafur to 5-FU appears to be a prerequisite for antitumor activity since it has been shown[10,12] that ftorafur itself possesses no inherent cytotoxic activity. We have synthesized ftorafur in our laboratory by the literature procedure[13] and by another route[14] which provides a better overall yield. We have also synthesized ftorafur by yet another route[15] which is amenable toward large scale preparations. We have been involved in some

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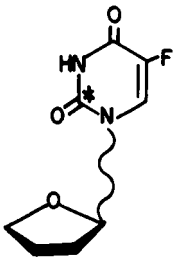

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pharmacological studies[11] which required the use of ftorafur-2-^{14}C, and this prompted us to synthesize ftorafur-2-^{14}C using 5-FU-2-^{14}C as our starting material. The procedure is described in the following experimental section.

EXPERIMENTAL[16]

5-Fluorouracil-2-^{14}C (38 mCi/mmol, 1.0 mCi)[17] was diluted with 1.0 g of dry 5-fluorouracil (5-FU, 7.69 mmol) and added to a four-necked round-bottomed flask. To this flask was added 4.6 ml of hexamethyldisilazane (HMDS) and one drop of trimethylchlorosilane as catalyst. The reaction mixture was then heated at reflux for 4 hr and protected from moisture with a drying tube containing Drierite (after 2 hr the solid 5-FU had completely dissolved). The excess HMDS was then removed by distillation in vacuo (60°/1 torr) leaving 2.10 g of the silyl derivative. A pmr spectrum of the residue (neat) indicated that complete conversion to the bis-silyl derivative had taken place. To the four-necked round-bottomed flask[18] was added a magnetic stirring bar, and the flask was fitted with a gas inlet and outlet tube, addition funnel with drying tube, and a low temperature thermometer. A slow stream of dry nitrogen was adjusted to flow through the assembled apparatus and this flow was continued throughout the reaction. An equal volume, or slight excess of dry methylene chloride was then added along with a small quantity of molecular sieves. With stirring, the internal temperature was cooled to -65° with a Dry Ice—acetone bath. Cold (-78°) 2-chlorotetrahydrofuran (colorless and freeflowing, 0.90 g, 8.45 mmol, 10% excess) previously mixed with an equal volume of dry, cold methylene chloride and stirred with

molecular sieves was added from a dropping funnel at such a rate that the internal temperature was kept below -65°. After the addition, the solution was stirred at room temperature for 1 hr or until there was no trace of 5-fluorouracil (checked by tlc - SilicAR 7GF, chloroform—acetone, 7:3, v/v, Rf 5-FU 0.2, Rf ftorafur 0.5). The solution was then cooled to -70° and poured into a precooled (-70°) solution of 30% aqueous ammonia (0.8 ml) and methanol (5 ml). The pH of the solution was kept below 7.5 (by the addition of more ammonium hydroxide if necessary) and the temperature was kept below -10°. The solution was then stirred for 1 hr at room temperature. The pH of the solution was then adjusted to 7.5 by the addition of small pieces of Dry Ice, followed by evaporation to dryness in vacuo. The residue was then triturated with ether (5 ml) and extracted with chloroform (5 × 5 ml). The combined extracts were evaporated to dryness under reduced pressure and the white solid was recrystallized from ethanol to give 1.23 g (80%) of chromatographically pure 1 as white needles; mp 169-170°; pmr δ 11.3 (brs, 1H, NH); δ 7.64 (d, 1H, $J_{5,6}$ = 8 Hz, H6); δ 6.02 (m, 1H, $H_{1'}$); δ 5.64 (d, 1H, $J_{5,6}$ = 8 Hz, H5).

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REFERENCES

1. I. Hrsak and S. Pavicic, Biomedicine, 21, 164 (1974).

2. R. S. Johnson, B. T. Garibjanian, D. P. Houchens, I. Kline, M. R. Gaston, A. B. Syrkin, and A. Goldin, Cancer Treatment Reports, 60, 1335 (1976).

3. M. Valdivieso, G. P. Bodey, J. A. Gottlieb, and E. J. Freireich, Cancer Research, 36, 1821 (1976).

4. B. Garibjanian, I. Kline, S. Vadlamudi, and A. Goldin, Proc. Am. Assoc. Canc. Res., 15, 100 (1974).

5. B. T. Garibjanian, R. K. Johnson, I. Kline, S. Vadlamudi, M. Gang, J. M. Venditti, and A. Goldin, Cancer Treatment Reports, 60, 1347 (1976).

6. N. G. Blokhina, E. K. Vozny, and A. M. Garin, Cancer, 30, 390 (1972).

7. N. I. Karev, Neoplasma, 19, 347 (1972).

8. A. Cichy, L. Jurga, and M. Klvana, Neoplasma, 21, 723 (1974).

9. C. R. Smart, L. B. Townsend, W. J. Rusho, H. J. Eyre, J. M. Quagliana, M. L. Wilson, C. B. Edwards, and S. J. Manning, Cancer, 36, 103 (1975).

10. A. Z. Smolyanskaya and O. A. Tugarinov, Neoplasma, 19, 341 (1972).

11. A. M. Cohen, Drug Metabolism and Disposition, 3, 303 (1975).

12. J. P. Horwitz, J. J. McCormick, K. D. Philips, V. M. Maher, J. R. Otto, D. Kessell, and J. Zemlicka, Cancer Research, 35, 1301 (1975).

13. S. A. Hiller, R. A. Zhuk, M. Yu. Lidak, and A. A. Zidermane, Brit. Pat. 1,168,391 (1969).

14. R. A. Earl and L. B. Townsend, J. Heterocyclic Chem., 9, 1141 (1972).

15. L. B. Townsend, R. A. Earl, and S. J. Manning, U.S. Pat. 3,960,864 (1 June 1976).

16. All glassware was dried in an oven (110°) prior to use. Proton magnetic resonance (pmr) spectra were obtained with a Varian A56/60 spectrometer in dimethylsulfoxide d_6 with chemical shift values being reported in δ, parts per million, relative to the internal standard (sodium 2,2-dimethyl-2-silapentane-5-sulfonate or tetramethylsilane).

17. Purchased from Cal Atomic, Los Angeles, California.

18. It is recommended that the silylation be carried out in a 4-necked flask so that the condensation reaction may be done without any transfers. Silyl derivatives are very moisture sensitive, and they should be stored under dry nitrogen.