SYNTHESIS OF 5-FLUORO-3-(2-TETRAHYDROFURYL)-6-VINYLURACIL. DESIGN OF A 5-FU-DERIVATIVE WITH EXTENDED CONJUGATION

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Abstract - Synthesis of a 6-vinyl-5-fluorouracil dervative is described.

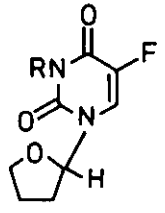
Thymidylate synthase is a target enzyme for cancer chemotherapy because it catalyzes the formation of deoxythymidine monophosphate (dTMP), which is a key building block for DNA bio-synthesis. In this connection, much interest has centred around the development of pyrimidine derivatives as inhibitors of dTMP synthase. One approach to evolving cytostatics with lower toxicity is via the study of prodrugs of known dTMP synthase inhibitors. With this objective we have synthesized and examined several potential prodrugs of 5-fluorouracil[1-3]. Another rational approach to selectivity of action (of inhibitors) consists in designing inhibitor molecules, which would be expected to exploit subtle structural differences between the enzymes from the malign and the normal cells. Since the two enzymes catalyze the same reaction, it has been suggested[4] that their differences cannot lie in a structural variation at the catalytic active site. From this reasoning it follows that selectively acting cytostatics may be developed by the introduction of reactive groups in a suitable region of the cytostatic molecule which would allow reaction with functional moieties of the protein, located outside the active site.

It is now accepted that during the process of dTMP synthase inhibition by FdUMP, the electrophilic 5,6-double bond of FdUMP is attacked by a thiol function of the enzyme. In order to prepare an analogue in which this reaction could take place with nucleophilic groups outside the active site, it was proposed to extend the electrophilic system with one or more conjugated double bonds. This communication describes the synthesis of 5-fluoro-6-vinyluracil derivatives[5].

Ftorafur 1c (FT-207) was used as the starting material. The N(3) of 1c was protected by either methylation (1a, mp 109 - 111° C) or derivatization by introduction of a tetrahydrofuryl group (1b, mixture of diastereomers[6]). Treatment of 1a with lithium diisopropylamide[7] and excess of acetaldehyde at -35° C, followed by acidification and column-chromatography yielded 2a[8] in 45% yield. Quenching the reaction mixture with tosyl chloride produced 3a in one practical step. In both cases the N(1) tetrahydrofuryl group was lost during the acid workup and chromatography. Treatment of 2a with methyl triphenoxyphosphonium iodide[9] in DMF at room temperature, gave the corresponding iodide (4)[10] in 80% yield.

Reaction of 1b with 1.5 eq. LDA and acetaldehyde at -50° C, followed by quenching with tosyl chloride produced 3b[11] in 75% yield. The NMR spectrum of 3b shows a signal at δ = 6.4 - 6.8 (m, H(1'), which indicates that in this reaction also the tetrahydrofuryl group was selectively removed from N(1)[6].

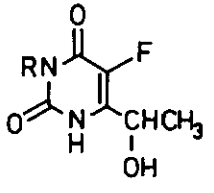
Base catalyzed elimination reactions of 3a,b and 4 were examined with the objective of preparing the vinyl derivatives 5a and 5b. Under a variety of conditions complex reaction mixtures were obtained in which the vinyl compounds could be spectroscopically identified (UV λ 298 nm). When 3b was treated with potassium t-butoxide and t-butanol, two crystalline products were obtained from



1a R = CH_3

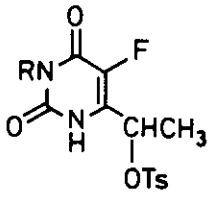
1b R = 

1c R = H

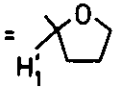


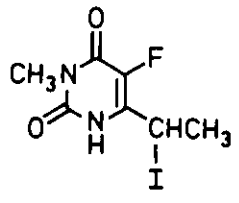
2a R = CH_3

2b R = 



3a R = CH_3

3b R = 



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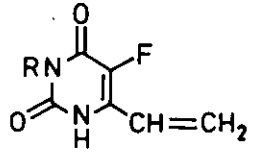
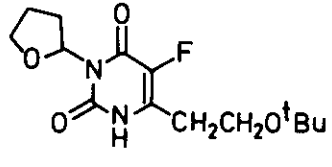


5a R = CH_3

5b R = 



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the reaction mixture. While the desired 6-vinyl derivative 5b[12] was formed in 10% yield, the major product was identified as the t-butyl ether 6[13]. It is obvious that the elimination reaction involving loss of p-TsOH from 3b is followed by addition of t-butanol to the vinyl group of 5b. This despite the steric bulk of the alcohol molecule. The occurrence of this reaction emphasizes the high electrophilic character of the vinyl function. In view of the susceptibility of 5b to nucleophilic attack, the hydrolytic removal of the N(3)-tetrahydrofuryl (protecting) group was frustrated. Studies directed to the use of suitable N(3)-protection are in progress.

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8. 2a: mp 151-160° C. IR(KBr): 3400, 1720, 1660, 1220, 1140. ^{1}H NMR: (DMSO/$CDCl_3$ 2:1) 1.44(d, 3H, CH_3), UV: 270 nm.
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10. 4a: IR ($CHCl_3$): 3400, 1720, 1655. ^{1}H NMR ($CDCl_3$): 2.15(d, 3H, CH_3); 3.41(s, 3H, CH_3), 5.35(q, 1H, CHI), 9-10(1H, NH).
11. 3b: mp 154-157° C. IR ($CHCl_3$): 3400, 1675, 1375, 1180. ^{1}H NMR: ($CDCl_3$): 1.67 (d,3H,CH_3), 1.8-2.8 (m,4H,CH_2CH_2), 2.45(s,3H,CH_3), 3.8-4.6 (m,2H,CH_2O), 5.4-5.9(dq, 1H, CH-methyl), 6.4-6.8 (m,1H,N-CH-O), 7.4, 7.75(AB, J=7, 4H, Ar-H), 9.87(s, 1H, NH). UV: 270 nm.
12. 5b: mp 155-157° C. IR (KBr): 1725, 1660, 1600, 1260, 1080. ^{1}H NMR ($CDCl_3$): 1.8-2.65 (m, 4H, CH_2CH_2), 3.8-4.4 (m,2H,CH_2O), 5.75 (d, 1H, J=18, C=CH), 6.1 (d, 1H, J=11.5, C=C-H), 6.6 (t, 1H, N-CH-O), 6.7 (ddd, 1H, J=18, J= 11.5, J= 0.7, C=CH-C), 9.8 (s, 1H, NH). Mass: 226.074210, $C_{10}H_{11}FN_2O_3$ requires 226.0754. UV: 298 nm.
13. 6b: IR ($CHCl_3$): 1720, 1660, 1250, 1160. ^{1}H NMR ($CDCl_3$): 1.2 - 1.3 (s,9H, t-butyl), 1.8-2.6 (m, 4H, CH_2CH_2), 2.75 (d x t, 2H, J=3, J=8, CH_2-C=C), 3.65 (t, 2H, J=8, CH_2-O-t-butyl), 3.8-4.0 (m, 1H, CH-O), 4.15-4.35 (m, 1H, CH-O), 6.57(t, 1H, N-CH-O), 8.85(s, 1H, N-H).

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