

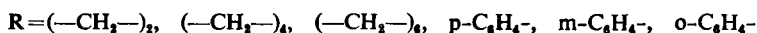
SYNTHESIS OF OLIGOMERS CONTAINING 5-FLUOROURACIL

PIAO Aichih (朴爱植) and SUN Shumen (孙树门)

(*Institute of Chemistry, Academia Sinica, Beijing*)

ABSTRACT

The condensation oligomers of 5-fluorouracil were prepared by reaction of 2,4-bis-(trimethylsilyloxy)-5-fluoropyrimidine) with various dicarboxylic chlorides, e.g.

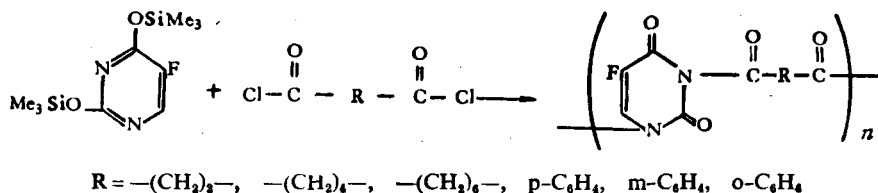


The structures of obtained oligomers were characterized by IR and the oligomers were then hydrolyzed in acid, alkaline and neutral media at room temperature respectively. The amount of 5-fluorouracil released was quantitated by measuring its UV absorbance at 265.5nm. However in the case of oligomers containing phenylene moiety, 5-fluorouracil was not detected when the hydrolysis was conducted in acid or neutral medium, while in the case of oligomers containing methylene moiety, hydrolysis proceeded easily in acid, alkaline and neutral media.

5-Fluorouracil (5Fu) is a well known drug in cancer chemotherapy. It is effective for the treatment of cancers such as lung cancer, mammary cancer, intestinal tumors, etc.

Although 5Fu has aforesaid therapeutic value, but it exhibits some toxic effects when it is used clinically nausea, vomiting, diarrhea, leukopenia are the most common toxic effects. One of the most serious shortcomings of the 5Fu is the fact that 5Fu is not only active against tumor cells but also against normal cells especially rapidly growing ones. In order to alleviate this shortcoming, antitumor drugs are chemically combined with low molecular weight substances, e.g. hormones, or sulfonamides, which are known to accumulate in certain tissues. This approach has gained little success so far^[1]. Thus the role of drug delivery system in cancer chemotherapy to increase the tumor cell specificity has become of increasing interest in recent years. Attempts have been made to introduce natural and synthetic polymers as carriers and have already been investigated by many authors^[2]. To take advantage of a polymeric carrier, which might be taken up by tumor cells due to their higher rate of endocytosis^[3] and thus enhances the concentration of the drug in tumor cells, the active metabolites of drugs have to be fixed.

This study was carried out to synthesize oligomers of 5Fu with organic diacids as carrier via the following reaction.



Phthaloyl chlorides react smoothly with silanated derivative of 5-fluorouracil, 2,4-bis-(trimethylsilyloxy)-5-fluoropyrimidine in the absence of solvent, resulting in the formation of condensation oligomers of 5-fluorouracil and phthalic acid via covalent C—N linkage, while in the case of aliphatic diacid chlorides, the above reaction proceeds only in the presence of solvent. These oligomers are expected to be hydrolyzed in vivo and antitumor component-5-fluorouracil will be released slowly under physiological conditions. This gives the possibility to reduce the side effects of a well established drug by combining it with an oligomer.

EXPERIMENTAL

2,4-bis-(trimethylsilyloxy)-fluoropyrimidine was prepared according to the method of Duschinsky^[4].

Preparation of poly(1,3(terephthaloyl)-5-fluorouracil)

2.7 g 2,4-bis-(trimethylsilyloxy)-5-fluoropyrimidine (0.01 mole) and 2.00 g terephthaloyl chloride (0.01 mol) were allowed to reflux for 4 hours. Precautions must be taken to exclude moisture from the system. The reaction mixture was evaporated and the residue was dissolved in 10 ml of dry acetone. The above solution was slowly added with vigorous stirring to 100 ml hexane. The white precipitate thus obtained was collected by filtration, and dried under vacuum. The crude polymer was redissolved in 15 ml of dry acetone. After removal of insoluble material by filtration, the product was reprecipitated in 100 ml hexane. The yield of polymer was 2.3 g (79.3%). The molecular weights of the p-, o-, m- oligomers were found to be 977, 655 and 683 respectively by ebulliometry.

Preparation of poly(1,3(succinyl)-5-fluorouracil)

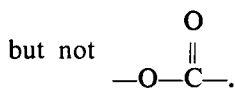
1.37 g (0.005 mole) 2,4-bis-(trimethylsilyloxy)-5-fluoropyrimidine was placed in a 25 ml three-necked flask. The system was flushed with pure N₂ to exclude moisture. To this stirred liquid, a solution of 0.8 g (0.005 mole) succinyldichloride in 10 ml dry acetonitrile was added slowly within 50 min and stirring was continued for 3 hours. The reaction mixture became brownish yellow. Acetonitrile and trimethylsilylchloride were removed under reduced pressure. A brownish yellow precipitate was obtained. The product was first dissolved in 5 ml dry acetone and then poured into 100 ml *n*-hexane. A yellow precipitate thus formed was filtered, dried under vacuum, redissolved and reprecipitated once more to give 1.08 g of oligomer in 93% yield.

RESULTS AND DISCUSSION

The IR spectra of 5-fluorouracil show the carbonyl absorption at 1689 cm⁻¹, but after silylation of 5-fluorouracil, this absorption band disappears and a new strong absorption band of N=C appears at 1590 cm⁻¹. Thus the structure of silylated 5-fluorouracil should be assigned as 2,4-bis-(trimethylsilyloxy)-5-fluoropyrimidine. When it is reacted with diacid chloride, the N=C stretching vibration (3000 cm⁻¹), Si—O stretching vibration (1040 cm⁻¹), Si—CH₃ stretching vibration (3000 cm⁻¹) bands of the obtained polymer are all disappeared.

Thus it is confirmed that the linkage between 5-fluorouracil and diacid must be

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{—N—C—} \end{array}$$



The oligomer gives the proton chemical shifts as follows:

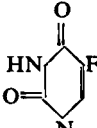
^1H NMR ($\text{DMSO}-d_6$, 250 MHz)

5-fluorouracil: $\delta 7.66$ (t, 1H, 6H); 10.58 (s, 1H, N_1H); 11.36 (s, 1H, N_3H);

Poly(1,3(phthaloyl)-5-fluorouracil): $\delta 8.00$ (m, 1H, 6H, 4H-); 11.40 (s, 1H, N_3H); 13.40 (br, 1H, COOH);

Poly(1,3(succinyl)-5-fluorouracil): $\delta 2.42$ (s, 4H, $-\text{CH}_2\text{CH}_2-$); 8.25 (t, 1H, 6H); 12.00 (s, 1H, N_3H).

From the above results, it shows that the signal N_1H in the oligomer disappears and signal N_3H still exists and at the same time a new broad COOH signal appears. Therefore

we can conclude that the end groups of the homopolymer should be  and

COOH. The degree of polycondensation calculated from the peak area of ^1H NMR of poly(1,3(p-phthaloyl)-5-fluorouracil) is 2.8 which agrees with the value 2.7 obtained from the number average mol. wt. 720.

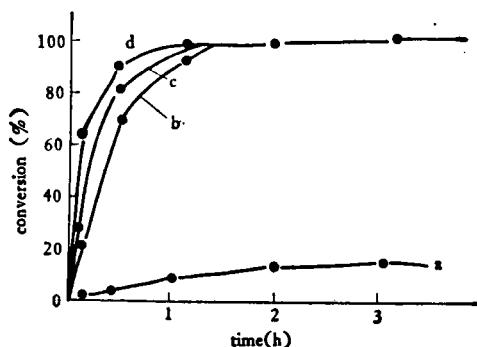


Fig. 1 Hydrolysis of oligomers containing phenylene moiety in alkaline medium
a) pH=10; b) pH=12; c) pH=12.3; d) pH=12.6.

The oligomers are hydrolyzed in different acidic and alkaline media, the amount of 5-fluorouracil released is determined by measuring its UV absorbance at 265.5 nm. Figure 1 shows that for the oligomer containing phenylene moiety, 5-fluorouracil is not detected when the hydrolysis was conducted in acid or neutral medium.

The pH value of human intestinal fluid is about 8, so we expect it may be useful for the treatment of intestinal cancer, while in the case of oligomers containing methylene moiety, hydrolysis proceeds easily in acid, alkaline and neutral media, thus it may be possible for the treatment of tumor in stomach, which has a relatively acidic medium (pH 1–2.5).

All of these speculations should be justified by the tests of antitumor activity in the near future.

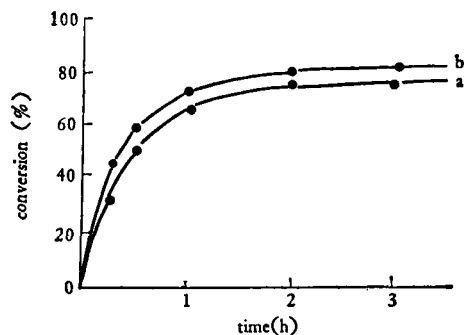


Fig. 2 Hydrolysis of oligomer containing methylene moiety in NaCl and acidic medium
a) 0.5 M NaCl; b) pH=1.3.

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