

CHEMOTHERAPEUTIC POLYMERS. THE SYNTHESIS OF POLYMERS CONTAINING 5-FLUOROURACIL IN THE MAIN CHAIN*

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ABSTRACT

1,3-Dialkyl-5-fluorouracil compounds and polymers containing 5-fluorouracil in the main chain were synthesized by the reaction of 5-fluorouracil with alkylbromides and polymethylene bromides respectively. The structures of the new compounds and polymers were confirmed by IR and NMR spectra as well as elemental analyses.

The factors affecting the polycondensation, such as the temperature and time of the reaction were investigated. The anti-tumor activity of some of the 5-fluorouracil containing compounds and polymers were also measured.

INTRODUCTION

In recent years, there has been growing interest in the synthesis and in the preparation of pharmacologically active polymers. It is known that some of these polymers can serve as chemotherapeutic agent with desirable properties, i.e., prolongation of pharmacological activity, increase of the specificity and decrease of toxicity.

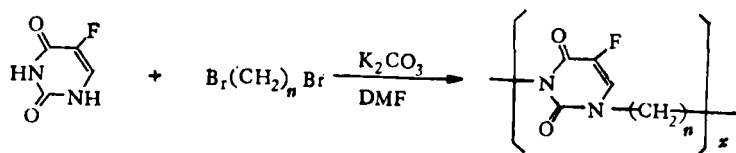
In view of the fact that 5-fluorouracil and some of its N-substituted derivatives are quite effective in treating several kinds of cancer, but are relatively toxic. The inclusion of 5-fluorouracil into polymer would probably enable it to show reduced toxic side effect and permit a longer duration of drug action. Much work has been done on chemotherapeutic polymers with pendant 5-fluorouracil groups^[1-4]. It is considered of interest to prepare new polymers which contain 5-fluorouracil groups in the polymer main chain.

In the present study, we synthesized a series of polymers with more than one carbon atom-one 5-fluorouracil backbone repeating unit. In order to compare and to obtain more detailed information on structure-property relations, we also synthesized a series of 1, 3-dialkyl-5-fluorouracil compounds, some of them have the same unit structure with the polymers.

Seven new polymers were obtained by the polycondensation of 5-fluorouracil with polymethylene bromides in the presence of anhydrous potassium carbonate as follows:

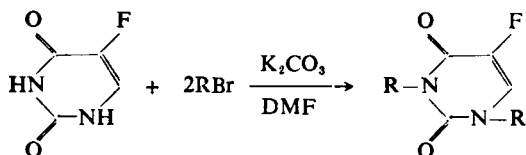
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Polymers were designated as P-II, $n=2$; P-III, $n=3$; P-IV, $n=4$; P-V, $n=5$; P-VI, $n=6$; P-VII, $n=7$; P-X, $n=10$.

In a similar way, ten new compounds of 1,3-dialkyl-5-fluorouracil were prepared in good yields by the condensation of 5-fluorouracil with n -alkyl bromides:



Compounds were designated as C-II, R=Ethyl; C-IV, R=Butyl; C-V, R=Amyl; C-VI, R=Hexyl; C-VII, R=Heptyl; C-VIII, R=Octyl; C-X, R=Decyl; C-XII, R=Dodecyl; C-XIV, R=Myristyl; C-XVI, R=Cetyl.

EXPERIMENTAL

Materials

All polymethylene bromides and alkyl bromides were reagent grade and used without further purification. 5-Fluorouracil was recrystallized from water to yield white crystals, m. p. 281°C, N,N-dimethylformamide (DMF) was dried over KOH and vacuum distilled. Anhydrous potassium carbonate was further dried by heating before use.

General preparation of 1,3-dialkyl-5-fluorouracils

A mixture of 0.05 mol. 5-fluorouracil (6.50 g), 0.15 mol. alkyl bromide, 0.10 mol. anhydrous potassium carbonate (13.82 g) and 150 ml DMF was stirred at 95–100°C for 25 hrs. After the reaction, the solid compounds were filtered off, and the solvent was removed at reduced pressure. The residue was distilled in vacuo or crystallized from ethanol to give the product. The yields, physical constants and elemental analyses are given in Table 1.

General procedure for the preparation of polymers

A mixture of 0.15 mol. 5-fluorouracil (19.51 g), 0.15 mol. polymethylene bromide, 0.3 mol. anhydrous potassium carbonate (41.46 g) and 300 ml DMF was heated with stirring. After the reaction time, the solid compounds were filtered off, the filtrate was concentrated under reduced pressure to a small volume (about 100–120 ml) and then slowly added to 1200 ml of vigorously stirred water. The polymer that collected was reprecipitated from DMF with methanol, dried at 50°C under vacuum to constant weight. The yields, physical data, and elemental analyses of the polymers are shown in Tables 2 and 3.

Table 1 Yields, physical constants and elemental analyses of 1,3-dialkyl-5-fluorouracils

Compd.	Yield (%)	B.p. (°C/mmHg)	M.p. (°C)	Analysis, $\frac{\text{Calcd.}}{\text{Found}}$			
				C (%)	H (%)	N (%)	F (%)
C-II	72	99—102/0.02	59—62	51.61	5.91	15.05	10.22
				51.62	6.49	14.83	9.60
C-IV	88	134—137/0.03	35—37	59.50	7.85	11.57	7.85
				59.51	8.02	11.34	7.55
C-V	74	164—168/0.56	36—38	62.22	8.52	10.37	7.04
				61.04	8.40	9.92	6.98
C-VI	84	186—189/0.75	39—42	64.43	9.06	9.40	6.38
				63.62	9.41	9.31	6.59
C-VII	87	182—185/0.04	41—43	66.26	9.51	8.59	5.83
				65.72	9.57	8.24	5.41
C-VIII*	84	169—171/0.02		67.80	9.89	7.91	5.37
				67.27	9.87	7.08	5.20
C-X	90	209—211/0.04	45—48	70.24	10.49	6.83	4.63
				69.63	10.63	6.82	4.67
C-XII	94		51—53	72.10	10.94	6.01	4.08
				70.90	10.83	6.08	3.78
C-XIV	96		57—60	73.56	11.30	5.36	3.64
				73.44	11.18	5.20	3.54
C-XVI	89		67—69	74.74	11.59	4.84	3.29
				73.00	10.56	4.54	3.29

* $n_D^{25}=1.4858$, $D_4^{20}=1.0195$.**Table 2** Yields and physical data of polymers

Polymer	Time (h)	Temp. (°C)	Yield (%)	$\overline{M}_n \cdot 10^{-3}$ **	$[\eta]$ ** (ml/g)	Soft. temp. (°C)
P-II	10	100	59.7	5.6	4.56	220
P-III	10	100	44.3	6.6	6.25	165
P-IV	10	100	65.1	8.2	8.97	160
P-V	10	100	62.0	8.7	9.15	115
P-VI	10	100	60.8	9.0	10.61	96
P-VII	10	100	66.2	9.4	11.86	82
P-X	10	100	87.7	11.0	12.96	48

* Number-average molecular weights were determined by dynamic osmometry^[5,6].

** Intrinsic viscosities were measured in DMF at 25°C with Ubbelohde viscometer.

Table 3 Elemental analyses of polymers

Polymer	Found (%)				Calcd. (%)*			
	C	H	N	F	C	H	N	F
P-II	44.83	4.36	17.68	9.30	45.04	3.17	17.35	11.77
P-III	47.38	3.84	15.31	9.57	48.40	4.08	15.95	10.82
P-IV	50.40	4.91	14.52	9.81	51.40	4.33	14.82	10.06
P-V	53.30	5.33	13.75	9.31	53.82	5.53	13.77	9.35
P-VI	55.82	5.87	12.24	8.36	55.87	6.10	12.85	8.72
P-VII	57.46	6.40	11.86	7.60	57.77	6.61	12.06	8.19
P-X	60.45	6.94	9.17	6.68	62.03	7.80	10.16	6.89

* Calculated values were based on molecular weights listed above.

RESULTS AND DISCUSSION

For a better understanding of the factors that influence the course of the polycondensation reaction, a series of experiments for the polycondensation of 5-fluorouracil with tetramethylene bromide were carried out by the variation of reaction conditions. The data are given in Table 4.

Table 4 Data of P-IV

P-IV No.	Time (h)	Temp. (°C)	Yield (%)	[η] (ml/g)
1	10	60	50.7	11.79
2	10	100	66.2	13.36
3	15	100	64.9	12.28
4	30	100	62.9	12.28
5	40	100	65.5	12.13
6	15	120	63.6	11.31
7	15	140	44.1	11.61

Table 4 shows a remarkable increase of the polymer yields with the increase of reaction temperature from 60°C to 100°C, but a further increase of 20°C from 120°C up to 140°C, leads to a substantial decrease of yields, and the polymer thus obtained was darkened in color (pale yellow). The prolongation of reaction time has no remarkable influence on the yields. The intrinsic viscosities of the polymers listed in Table 4, are somewhat higher than that of P-IV listed in Table 2. This was due to a slight modification of the resulting polymers from DMF with methanol instead of first adding the polymer solution into water.

It is interesting to note that when the number of carbon atoms in the polymer repeating unit reaches to 10, the values of the softening temperature of polymer P-X and the melting point of 1,3-didecyl-5-fluorouracil (C-X) are nearly the same.

As shown in Tables 1 and 3, the data of elemental analyses of 1,3-dialkyl-5-fluorouracil compounds and 5-fluorouracil containing polymers agreed well with the calculated values.

The structures of 1,3-dialkyl-5-fluorouracil compounds and 5-fluorouracil containing polymers were confirmed by IR and NMR spectra. In comparison with the IR spectrum of 5-FU, the IR spectra clearly show loss of N-H groups by the absence of the bands at 3130 cm^{-1} , 880 cm^{-1} and 813 cm^{-1} . The signals of ^1H NMR spectra also show loss of both $\text{N}_1\text{-H}$ (10.5 ppm) and $\text{N}_3\text{-H}$ (11.38 ppm), the existence of $\text{C}_6\text{-H}$ (8.1 ppm), and the appearance of expected alkyl or polymethylene groups in the 5-fluorouracil containing compounds and polymers.

These results indicate that all the 1,3-dialkyl-5-fluorouracil compounds and the polymers containing 5-fluorouracil in the main chain have the expected structures.

In comparison with 5-FU, we measured the antitumor effect of one of the compounds and two of the polymers which contain 5-FU. The antitumor activity and toxicity are shown in Table 5.

Table 5 Antitumor effect of agents against Sarcoma 180 on mice

Polymer or compd.	Dose mg/Kg/day	Route of administration	Survivors		Animal weight change (%)		Tumor weight (g)		Inhibition ratio (%)	P
			C.	T.	C.	T.	C.	T.		
5-FU	54	PO $\times$ 9	11/11	10/7	+15.50	-15.40	2.500	0.885	64.6	0.001
C-IV	80	IP $\times$ 7	12/12	10/10	+23.50	+23.07	2.170	1.706	21.4	
	130	IP $\times$ 7	11/11	11/11	+22.05	+12.17	1.827	1.412	22.7	
P-IV	130	IP $\times$ 7	11/11	11/11	+22.05	+5.79	1.827	1.298	28.0	
	130	IP $\times$ 10	12/12	11/9	+23.50	+8.80	2.170	1.620	25.3	
	154	IP $\times$ 7	11/11	10/8	+14.98	-2.90	2.064	0.862	58.2	
P-X	390	PO $\times$ 7	11/10	10/10	+6.8	-0.48	1.440	1.120	22.2	

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