Mass Spectra of 5-Fluorouracil Derivatives. *N*-1-Substituted Sulfonyl Derivatives

Teruyoshi Marunaka

Research Laboratory, Taiho Pharmaceutical Co., Ltd., Kawauchi-cho, Tokushima, 771-01, Japan

Received January 15, 1981

The electron impact mass spectra of 1-sulfonyl substituted derivatives of 5-fluorouracil were investigated. The substituents were CH_3SO_2 (compound I), $CH_3(CH_2)_3SO_2$ (II), $C_6H_5SO_2$ (III) and p-$CH_3C_6H_4SO_2$ (IV).

J. Heterocyclic Chem., **18**, 1041 (1981).

Introduction.

5-Fluorouracil (FU) and its derivative 1-(tetrahydro-2-furanyl)-5-fluorouracil have been widely used as antitumor agents in cancer chemotherapy. Various derivatives of FU have been synthesized to develop more effective antitumor agents with fewer side-effects (1-3).

The field desorption, chemical ionization and electron impact (EI) mass spectra of the antitumor agents, FU, 1-and 3-(tetrahydro-2-furanyl)-5-fluorouracil and 1,3-bis-(tetrahydro-2-furanyl)-5-fluorouracil (4), and the EI mass spectra of various other *N*-substituted FU derivatives (5) have been reported previously. In the fragmentation pathways of the EI mass spectra of these compounds, the formation of characteristic fragment ions was observed. These ions were extremely useful for the determination of the position of the substituent on the FU skeleton.

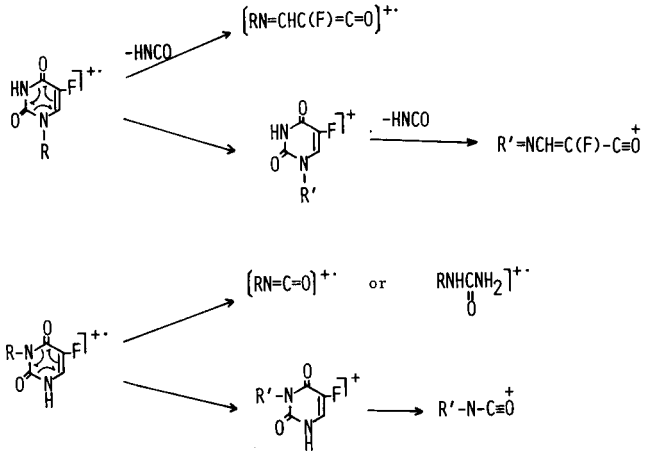
This paper described the EI mass spectra of 1-sulfonyl derivatives of FU, which are synthetic intermediates of 3-(tetrahydro-2-furanyl)-5-fluorouracil (2).

Results and Discussion.

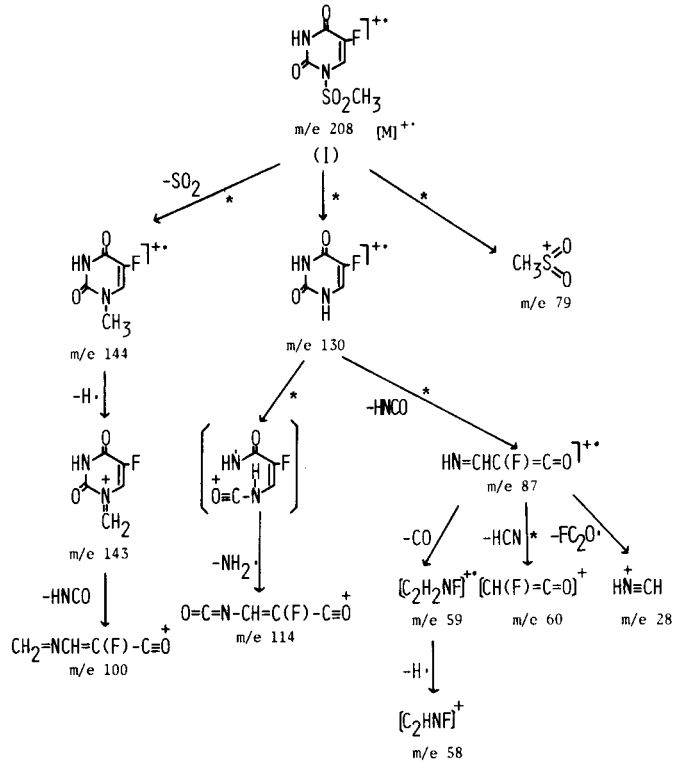
Verification of the position of the sulfonyl substituent in 1-methanesulfonyl-5-fluorouracil (I), 1-(*n*-butanesulfonyl)-5-fluorouracil (II), 1-benzenesulfonyl-5-fluorouracil (III) or 1-(*p*-toluenesulfonyl)-5-fluorouracil (IV) could not be estimated by the ultraviolet spectrophotometric method on the basis of the presence or absence of bathochromic shifts in alkaline solution, a method which has been used for determination of the position of a common substituent in pyrimidine derivatives (6), because the compounds I, II, III and IV decomposed to FU in alkaline solution (see Table 3).

As reported previously (4,5), it has been possible to determine the position of substituents on *N*-substituted FU derivatives by EI mass spectrometry. Characteristic fragment ions are produced by a retro Diels-Alder (RDA) decomposition of the molecular ion or the fragment ion formed directly from the molecular ion (Scheme 1).

Therefore, the EI mass spectra of 1-sulfonyl substituted derivatives of FU were studied, and the fragmentation pathways of these compounds were determined from the



Scheme 1



Scheme 2

0022-152X/81/051041-05$02.25

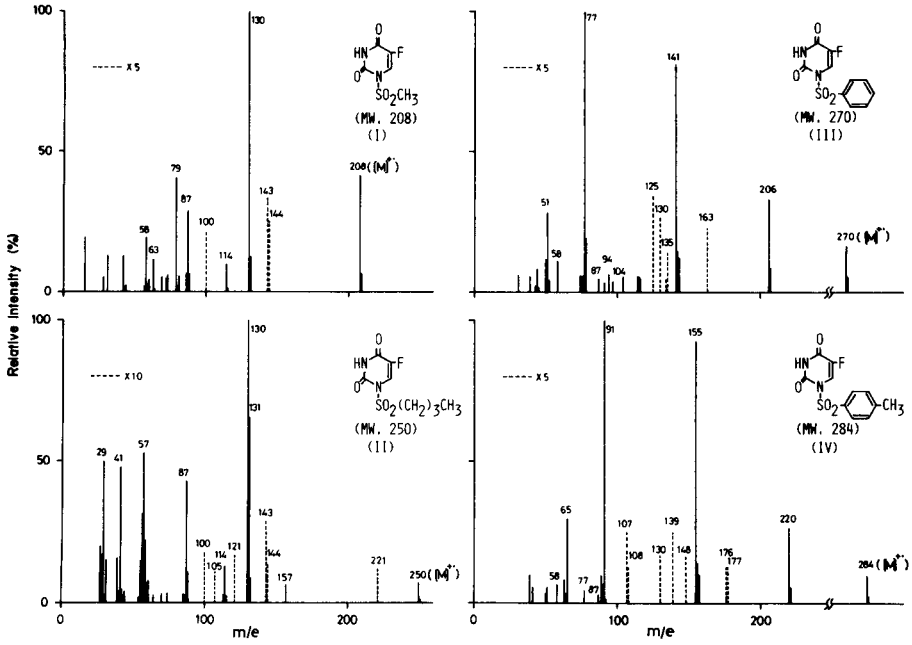


Figure 1. Mass spectra of (I) 1-methanesulfonyl-, (II) 1-(*n*-butanesulfonyl)-, (III) 1-benzenesulfonyl-, and (IV) 1-(*p*-toluenesulfonyl)-5-fluorouracil.

Table 1

Relative Intensities of EI mass Spectra and Elemental Composition of Fragment Ions according to High Resolution Mass Spectrometry

Compound	m/e	Relative Intensity %	Elemental Composition	Compound	m/e	Relative Intensity %	Elemental Composition
I	208	41.5	$C_5H_5N_2O_4SF$	III	270	16.5	$C_{10}H_7N_2O_4SF$
	144	5.0	$C_5H_5N_2O_2F$		206	33.0	$C_{10}H_7N_2O_2F$
	143	6.7	$C_5H_4N_2O_2F$		163	4.6	C_9H_6NOF
	130	100.0	$C_4H_3N_2O_2F$		141	81.0	$C_6H_5O_2S$
	114	10.0	C_4HNO_2F		135	4.5	C_8H_6NF
	100	4.3	C_4H_3NOF		134	1.0	C_8H_5NF
	87	28.7	C_3H_2NOF		130	5.8	$C_4H_3N_2O_2F$
	79	40.8	CH_3O_2S		125	6.9	C_6H_5OS
	63	11.5	CH_3OS		104	5.5	C_7H_6N
	60	6.3	C_2HOF		94	6.3	C_6H_6O
	59	5.0	C_2H_2NF		77	100.0	C_6H_5
	58	19.3	C_2HNF		51	28.4	C_4H_3
II	250	5.5	$C_8H_{11}N_2O_4SF$	IV	284	9.9	$C_{11}H_9N_2O_4SF$
	221	1.2	$C_6H_6N_2O_4SF$		220	26.4	$C_{11}H_9N_2O_2F$
	157	4.2	$C_6H_6N_2O_2F$		177	2.5	$C_{10}H_8NOF$
	143	2.9	$C_5H_4N_2O_2F$		176	2.5	$C_{10}H_7NOF$
	131	65.3	$C_4H_4N_2O_2F$		155	92.6	$C_7H_7O_2S$
	130	100.0	$C_4H_3N_2O_2F$		148	3.3	C_9H_7NF
	121	1.7	$C_4H_9O_2S$		139	5.0	C_7H_7OS
	114	11.8	C_4HNO_2F		130	3.3	$C_4H_3N_2O_2F$
	105	1.1	C_4H_9OS		108	2.5	C_7H_8O
	100	1.8	C_4H_3NOF		107	5.0	C_7H_7O
	57	53.8	C_4H_9		91	100.0	C_7H_7

Table 2

Metastable Ions of *N*-1-Substituted Sulfonyl-5-fluorouracil Derivatives

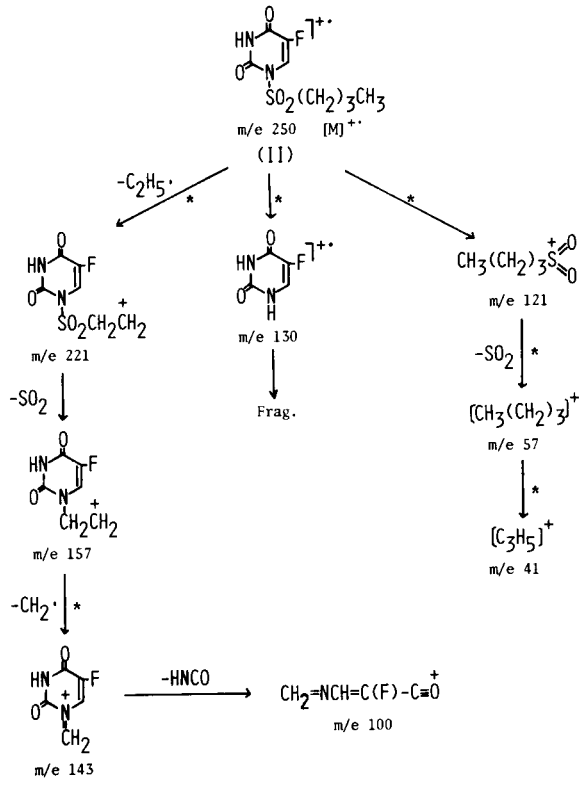
Compound	Transition: Initial Ion m/e		Resultant Ion m/e	Found m*	Calculated m*
I	208	→	144	99.5	99.7
	208	→	130	81.3	81.3
	208	→	79	30.1	30.0
	130	→	114	100.0	100.0
	130	→	87	58.3	58.2
	87	→	60	41.3	41.3
II	250	→	221	195.6	195.4
	250	→	130	67.6	67.6
	250	→	121	58.4	58.6
	157	→	143	130.1	130.2
	121	→	57	26.8	26.8
	57	→	41	29.5	29.5
III	270	→	206	157.1	157.2
	270	→	141	73.6	73.6
	270	→	94	32.8	32.7
	206	→	163	128.9	129.0
	163	→	135	111.6	111.8
	141	→	77	42.2	42.1
	77	→	51	33.8	33.8
IV	284	→	220	170.4	170.4
	284	→	155	84.6	84.6
	220	→	177	142.6	142.4
	155	→	91	53.4	53.4
	91	→	65	46.4	46.4

high resolution mass spectral data and metastable ions. The EI mass spectra of compounds I-IV are shown in Figure 1. Low and high resolution mass spectral data are given in Table 1, and their metastable ions are listed in Table 2.

The molecular ions $[M]^{+\cdot}$ were clearly observed in the EI mass spectra of all four derivatives. The base peaks composed a FU molecular ion of mass 130 ($C_4H_3N_2O_2F^{+\cdot}$) for compounds I and II, a phenyl ion of mass 77 ($C_6H_5^+$) for compound III and a tropylium ion of mass 91 ($C_7H_7^+$) for compound IV.

1-Methanesulfonyl-5-fluorouracil (I) showed the characteristic fragmentation pathway. The elements SO_2 were expelled from the molecular ion in the first step of fragmentation, and then a 1-methyl-5-fluorouracil ion of mass 144 ($C_5H_5N_2O_2F^{+\cdot}$) was formed after intramolecular rearrangemnt. This ion gave a fragment ion of mass 143 ($C_5H_4N_2O_2F^+$) by the elimination of a hydrogen radical ($H^\cdot$), and then produced a characteristic fragment ion of mass 100 ($C_4H_3NOF^+$) by the RDA decomposition involving expulsion of neutral HNCO (Scheme 2).

1-(*n*-Butanesulfonyl)-5-fluorouracil (II) produced a fragment ion of mass 221 ($C_6H_6N_2O_4SF^+$) from the molecular ion by β-cleavage of the *n*-butyl chain. An SO_2 fragment was then expelled from the $C_6H_6N_2O_4SF^+$ ion to form an ion of mass 157 ($C_6H_6N_2O_2F^+$). From the $C_6H_6N_2O_2F^+$ ion of mass 157, a fragment ion of mass 143 ($C_5H_4N_2O_2F^+$) was produced by loss of a methylene radical ($CH_2^\cdot$). The characteristic fragment ion of mass 100 ($C_4H_3NOF^+$) was formed from the ion of mass 143 by the RDA decomposition with expulsion of HNCO (Scheme 3).



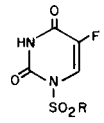
Scheme 3

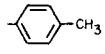
Thus, these fragmentation pathways confirm that the compounds I and II are *N*-1-substituted FU derivatives by analogy with previous reports (4,5).

A FU molecular ion of mass 130 ($C_4H_3N_2O_2F^{+\cdot}$) which was the base peak in the spectrum of compound I was formed from the molecular ion by cleavage of the N-S bond and the subsequent protonation. The $C_4H_3N_2O_2F^{+\cdot}$ ion at mass 130, like that of FU (4), released HNCO by the RDA decomposition to give a fragment ion of mass 87, $[HN{=}CHC(F){=}C{=}O]^{+\cdot}$. This ion at mass 87 decomposed to produce an ion of mass 59 ($C_2H_2NF^{+\cdot}$) by loss of carbon monoxide (CO). Subsequent removal of $H^\cdot$ gave a fragment ion of mass 58 (C_2HNF^+). The $C_3H_2NOF^{+\cdot}$ ion at mass 87 also decomposed by loss of a ketenyl radical ($FC_2O^\cdot$) or hydrogen cyanide (HCN) to form the protonated hydrogen cyanide ion of mass 28, $H\overset{+}{N}{\equiv}CH$, and the ketene ion of mass 60, $[CH(F){=}C{=}O]^{+\cdot}$, respectively. Furthermore, the FU molecular ion at mass 130 was subjected to ring opening between C-2 and N-3 with concomitant release of an amino radical ($NH_2^\cdot$) to yield a fragment ion of mass 114, $O{=}C{=}NCH{=}C(F)C{\equiv}\overset{+}{O}$. This ion at mass 114 was observed in the EI mass spectra of other

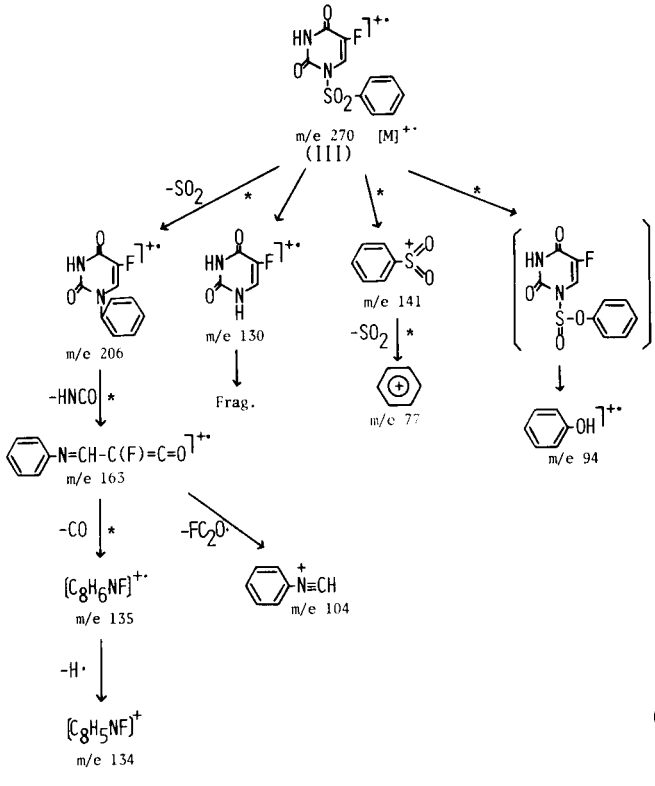
Table 3

Melting Points and Ultraviolet Spectral Data for *N*-1-Substituted Sulfonyl-5-fluorouracil Derivatives



Compound	R	Melting Point (a) (°C)	*p*H 2.0 λ max (nm)	*p*H 12.0 λ max (nm)
I	$-CH_3$	223-223.5 (b)	249.0	— (c)
II	$-(CH_2)_3CH_3$	139-140 (d)	253.0	—
III		255-256 (e)	250.0	—
IV		240.5-241.5 (f)	256.0	—

(a) All melting points are uncorrected. (b) Lit. (8) m.p. 234-224°. (c) Decomposition to FU. (d) Lit. (2) m.p. 139-140°. (e) Lit. (8) m.p. 256-257°.



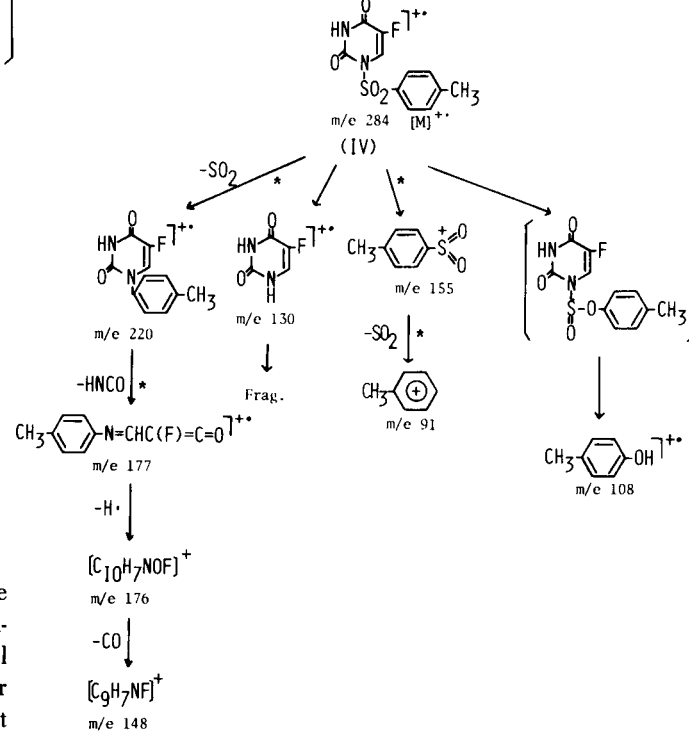
Scheme 4

N-substituted FU derivatives (4,5), but it could hardly be observed in the spectrum of FU because of its very low intensity of peak (4). On the other hand, a methanesulfonyl ion of mass 70 ($CH_3O_2S^+$) was produced from the molecular ion of compound I by cleavage of the N-S bond in the first fragmentation pathway (Scheme 2).

The formation of a FU molecular ion of mass 130 and the protonated FU ion at mass 131 from the molecular ion of compound II by cleavage of the N-S bond and the subsequent protonation were observed. The former ion at mass 130 was the base peak in the spectrum and showed the same fragmentation pathway as those of FU (4), compound I or other *N*-substituted FU derivatives (4,5). On the other hand, a *n*-butanesulfonyl ion of mass 121 ($C_4H_9O_2S^+$) was formed from the molecular ion of compound II by cleavage of the N-S bond. This ion of mass 121 produced a *n*-butyl ion of mass 57 ($C_4H_9^+$) by the expulsion of SO_2 (Scheme 3).

The first step in the fragmentation of 1-benzenesulfonyl-5-fluorouracil (III) was expulsion of SO_2 from the molecular ion resulting in the formation a 1-phenyl-5-fluorouracil ion of mass 206 ($C_{10}H_7N_2O_2F^{+\cdot}$). This ion of mass 206 gave the characteristic fragment ion of mass 163 ($C_9H_6NOF^{+\cdot}$) by the RDA decomposition with expulsion of HNCO. The $C_9H_6NOF^{+\cdot}$ ion lost CO to produce an ion of mass 135 ($C_8H_6NF^{+\cdot}$) which by removal of $H^\cdot$ yielded an ion of mass 134 ($C_8H_5NF^+$). The $C_9H_6NOF^{+\cdot}$ ion at mass 163 also disintegrated to an ion of mass 104 ($C_7H_6N^+$) by elimination of $FC_2O^\cdot$ (Scheme 4).

The expulsion of SO_2 from the molecular ion of 1-(*p*-toluenesulfonyl)-5-fluorouracil (IV) also occurred as the first fragmentation step. A 1-(*p*-tolyl)-5-fluorouracil ion of mass 220 ($C_{11}H_9N_2O_2F^{+\cdot}$) was produced in this way. The $C_{11}H_9N_2O_2F^{+\cdot}$ ion of mass 220 gave a characteristic frag-



Scheme 5

ment ion of mass 177 ($C_{10}H_8NOF^{+\cdot}$) by the RDA decomposition with expulsion of HNCO, followed by loss of $H^{\cdot}$ to produce an ion of mass 176 ($C_{10}H_7NOF^{+}$) and the subsequent removal of CO to form an ion of mass 148 ($C_9H_7NF^{+}$) (Scheme 5).

Compounds III and IV were thus confirmed to be *N*-1-substituted FU derivatives by their fragmentation processes.

Other major fragmentation pathways of compounds III consisted of the formation of a FU ion of mass 130 and a benzenesulfonyl ion of mass 141 ($C_6H_5O_2S^{+}$) from the molecular ion. The latter ion at mass 141 gave a phenyl ion of mass 77 ($C_6H_5^{+}$) which was the base peak in the spectrum of compound III by the expulsion of SO_2. The FU ion of mass 130 and a *p*-toluenesulfonyl ion of mass 155 ($C_7H_7O_2S^{+}$) were likewise observed from compound IV. The ion of mass 155 eliminated SO_2 to produce a tropylium ion of mass 91 ($C_7H_7^{+}$) which was the base peak in the spectrum. Furthermore, the migration of a phenyl group from sulfur to oxygen, which is commonly observed in the mass spectra of the aromatic sulfoxide and sulfonyl compounds (7), was observed in the spectra of compounds III and IV. A phenol molecular ion of mass 94 ($C_6H_6O^{+\cdot}$) was produced from the molecular ion of compound III, while a cresol molecular ion of mass 108 ($C_7H_8O^{+\cdot}$) was formed from compound IV (Schemes 4,5).

EXPERIMENTAL

For EI mass spectrometry, a JEOL JMS-01SG-2 mass spectrometer equipped with an electron impact ion source (Tokyo, Japan) was used. The EI mass spectra were measured under the following conditions: ion source temperature, 50-120°; ionization energy, 75 eV; ionization current, 200 μA and accelerating voltage, 10 kV. High resolution mass spectral data were determined from the photographic plates for calculation of the elemental composition of fragment ions. The metastable ions were obtained by the method of magnetic scan and high-voltage scan.

1-Methanesulfonyl-5-fluorouracil (I), 1-(*n*-butanesulfonyl)-5-fluorouracil (II), 1-benzenesulfonyl-5-fluorouracil (III) and 1-(*p*-toluenesulfonyl)-5-fluorouracil (IV) were synthesized and purified in my laboratory (2,8). The melting points and ultraviolet spectral data for these compounds are listed in Table 3.

Acknowledgement.

The author wishes to thank Professor Yuroku Yamamoto, Faculty of Science, Hiroshima University, for kind and helpful discussion and encouragement throughout the course of this work. The author is also grateful to Assistant Professor Mitsuru Nakayama, Faculty of Science, Hiroshima University, for his valuable advice and thoughtful suggestions and to Mr. Jun-ichi Yamashita, in my laboratory, for synthesis of *N*-1-substituted FU derivatives.

REFERENCES AND NOTES

(1) M. Yasumoto, I. Yamawaki, T. Marunaka and S. Hashimoto, *J. Med. Chem.*, **21**, 738 (1978).

(2) M. Yasumoto, J. Yamashita and S. Hashimoto, *Yakugaku Zasshi*, **98**, 1551 (1978).

(3) J. Yamashita, I. Yamawaki, S. Ueda, M. Yasumoto and S. Hashimoto, *J. Med. Chem.*, submitted for publication.

(4) T. Marunaka, Y. Umeno, Y. Minami and T. Shibata, *Biomed. Mass Spectrom.*, **7**, 331 (1980).

(5) T. Marunaka, *ibid.*, **8**, 105 (1981).

(6) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta.*, **9**, 199 (1952).

(7a) J. H. Bowie, B. H. Williams, S. O. Lawesson, J. O. Madson, C. Nolde and G. Schroll, *Tetrahedron*, **22**, 3515 (1966); (b) S. Meyerson, H. Drews and E. K. Fields, *Anal.* Chem., **36**, 1294 (1964).

(8) M. Tada, *Chemistry*, 129 (1975).