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Syntheses of 2-*n*-Alkylisothio-5-fluoro-4(1 or 3*H*)-pyrimidinone Derivatives

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The reactions of ethyl monofluoromalonaldehyde potassium enolate (**1**) and *S*-*n*-alkylisothiourea (**2a**—**e**) gave 2-*n*-alkylthio-5-fluoro-4(1 or 3*H*)-pyrimidinones (**3a**, **d**, **e**), 2-*n*-alkylthio-5-fluoro-6-monofluoromethyl-4(1 or 3*H*)-pyrimidinones (**4a**—**c**) and 2-*n*-alkylthio-6-*n*-alkylthiomethyl-5-fluoro-4(1 or 3*H*)-pyrimidinones (**5a**—**e**).

Keywords——2-*n*-alkylthio-5-fluoro-4(1 or 3*H*)-pyrimidinone; 2-*n*-alkylthio-5-fluoro-6-monofluoromethyl-4(1 or 3*H*)-pyrimidinone; 2-*n*-alkylthio-6-*n*-alkylthiomethyl-5-fluoro-4(1 or 3*H*)-pyrimidinone; ethyl monofluoromalonaldehyde potassium enolate; *S*-*n*-alkylisothiourea; ^{1}H-NMR; ^{13}C-NMR; UV

Since Heidelberger *et al.*[1] reported 5-fluorouracil to be a tumor-inhibitory compound, many 5-fluoropyrimidine derivatives have been synthesized in many laboratories. In the present paper, we report the syntheses of 2-*n*-alkylthio-5-fluoro-4(1 or 3*H*)-pyrimidinones as a part of our investigations[2] aimed at finding new antitumor agents.

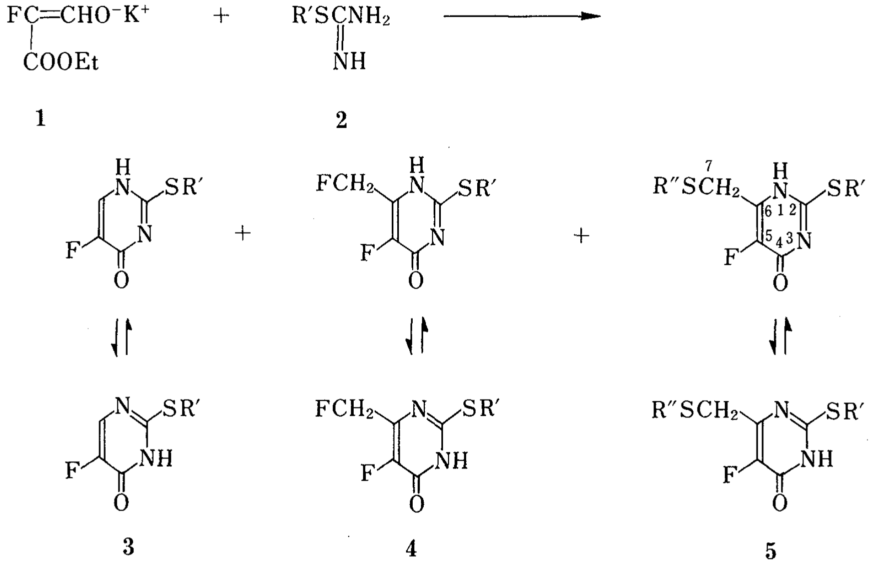
From ethyl monofluoromalonaldehyde potassium enolate (**1**) and *S*-methylisothiourea sulfate (**2a**), workers at Hoffmann-La Roche & Co.[3] synthesized 5-fluoro-2-methylthio-4(1*H*)-pyrimidinone (**3a**) by condensation in absolute methanol and sodium methoxide under reflux. We repeated this experiment and obtained three compounds, **3a**, **4a** and **5a** (Chart 1).

Compound **3a** was obtained as pale brown prisms from methanol, mp 230—233 °C (dec.) [lit. mp 230—237 °C (dec.)].[3] $C_5H_5FN_2OS$ (*m*/*z* 160, M$^+$). The infrared (IR) spectrum of **3a** showed the presence of a carbonyl group (1660 cm^{-1}). The ultraviolet (UV) spectrum of **3a** showed the coexistence of tautomers, a 4(1*H*)-pyrimidinone form and a 4(3*H*)-pyrimidinone form[4] (Table II). The proton nuclear magnetic resonance (^{1}H-NMR) spectrum and the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **3a** were consistent with the 5-fluoro-2-methylthio-4(1 or 3*H*)-pyrimidinone structure, as shown in Tables III and IV.

Compound **4a** was obtained as colorless prisms from hexane–benzene, mp 199—200 °C (dec.) [lit. mp 221—222 °C (dec.)].[5] $C_6H_6F_2N_2OS$ (*m*/*z* 192, M$^+$). The IR spectrum of **4a** showed the presence of a carbonyl group (1680 cm^{-1}). The UV spectrum of **4a** was similar to that of **3a** (Table II), so tautomers coexist in **4a**. The ^{1}H-NMR and ^{13}C-NMR spectra of **4a** indicated the presence of a methyl group substituted on the sulfur atom (δ: 2.50, 13.17), a methylene (δ: 5.31, 78.43) carrying a fluorine atom, and an aromatic ring. The C-6 carbon was coupled with two fluorines ($J=17.43$ and 12.77 Hz) in the ^{13}C-NMR spectrum (Tables III and IV). Thus, the structure of **4a** was concluded to be 5-fluoro-2-methylthio-6-monofluoromethyl-4(1 or 3*H*)-pyrimidinone. Duschinsky *et al.*[5] reported the synthesis of 5-fluoro-2-methylthio-6-monofluoromethyl-4(1*H*)-pyrimidinone from **2a** and ethyl 2,4-difluoro-3-hydroxy-2-butenoate.

Compound **5a** was obtained as pale brown needles from water, mp 168—170 °C. $C_7H_9FN_2OS_2$ (*m*/*z* 220, M$^+$). The IR spectrum of **5a** showed the presence of a carbonyl group

(1680 cm^{-1}). The UV spectrum of **5a** was similar to those of **3a** and **4a**, so the tautomers coexisted in **5a**, too (Table II). The ^{1}H-NMR and ^{13}C-NMR spectra of **5a** indicated the presence of two methyl groups substituted on sulfur (δ: 2.19, 16.04 and 2.57, 13.81), a



a : R'=R''=CH$_3$ **d** : R'=R''=n-C$_{12}$H$_{25$}
b : R'=R''=n-C$_6$H$_{13}$ **e** : R'=R''=n-C$_{16}$H$_{33}$
c : R'=R''=n-C$_8$H$_{17}$

Chart 1

TABLE I. Physical and Spectral Data for 5-Fluoro-4(1 or 3*H*)-pyrimidinones

Compd.	R	mp (°C) [lit. °C]	Formula	Analysis (%) Calcd (Found) C	H	F	N	S	IR (cm^{-1}) (KBr)	MS (m/z) M$^+$
3a	CH$_3$	230—233 (dec.)[a]	C$_5$H$_5$FN$_2$OS	37.49	3.15	11.86	17.49	20.02	1660	160
		[230—237 (dec.)[3]]		(37.53	3.24	11.57	17.52	20.28)		
3d	C$_{12}$H$_{25}$	98—99[b]	C$_{16}$H$_{27}$FN$_2$OS	61.11	8.65	6.04	8.91	10.20	1680	314
				(61.19	8.64	6.25	8.94	9.96)		
3e	C$_{16}$H$_{33}$	85—87[b]	C$_{20}$H$_{35}$FN$_2$OS	64.82	9.52	5.13	7.56	8.65	1665	370
				(64.84	9.59	5.37	7.40	8.91)		
4a	CH$_3$	199—200 (dec.)[c]	C$_6$H$_6$F$_2$N$_2$OS	37.50	3.15	19.77	14.58	16.68	1680	192
		[221—222 (dec.)[5]]		(37.71	3.20	19.47	14.69	16.87)		
4b	C$_6$H$_{13}$	106—109[b]	C$_{11}$H$_{16}$F$_2$N$_2$OS	50.37	6.15	14.48	10.68	12.22	1695	262
				(50.65	6.12	14.14	10.90	12.30)		
4c	C$_8$H$_{17}$	112—113[b]	C$_{13}$H$_{20}$F$_2$N$_2$OS	53.77	6.94	13.09	9.65	11.04	1695	290
				(54.05	6.95	13.16	9.67	11.19)		
5a	CH$_3$	168—170[d]	C$_7$H$_9$FN$_2$OS$_2$	38.17	4.12	8.62	12.72	29.11	1680	220
				(38.02	4.07	8.92	12.63	29.17)		
5b	C$_6$H$_{13}$	117—118.5[a]	C$_{17}$H$_{29}$FN$_2$OS$_2$	56.63	8.11	5.27	7.77	17.79	1680	360
				(56.71	8.16	5.40	7.79	17.90)	1655	
5c	C$_8$H$_{17}$	118—119[a]	C$_{21}$H$_{37}$FN$_2$OS$_2$	60.54	8.95	4.56	6.72	15.39	1690	416
				(60.40	8.95	4.63	6.71	15.56)	1658	
5d	C$_{12}$H$_{25}$	116—118[a]	C$_{29}$H$_{53}$FN$_2$OS$_2$	65.86	10.10	3.59	5.30	12.13	1680	528
				(65.88	10.09	3.42	5.25	11.85)	1655	
5e	C$_{16}$H$_{33}$	115—117[e]	C$_{37}$H$_{69}$FN$_2$OS$_2$	69.32	10.85	2.96	4.37	10.00	1690	641
				(69.06	10.86	2.33	4.43	9.81	1658	

a) From MeOH. *b*) From benzene. *c*) From hexane–benzene. *d*) From H$_2$O. *e*) From EtOH.

TABLE II. UV Spectral Data[a] for 5-Fluoro-4(1 or 3*H*)-pyrimidinones

Compd.	λ_{max} nm ($\log \varepsilon$)			
3a	209.0 (3.97)	219.0 (3.90)	239.0 (3.85)	289.0 (3.86)
3d	205.5 (3.96)	218.5 (3.91)	236.0 (3.85)	288.5 (3.87)
3e	207.5 (3.85)	219.5 (3.80)	238.0 (3.81)	290.0 (3.81)
4a	209.3 (3.77)	220.5 (3.77)	238.0 (3.78)	290.0 (3.80)
4b	208.3 (3.87)	220.0 (3.78)	240.5 (3.80)	294.0 (3.86)
4c	209.2 (3.79)	221.0 (3.69)	240.5 (3.75)	294.0 (3.79)
5a	208.5 (3.85)	221.5 (3.82)	242.5 (3.85)	288.5 (3.82)
5b	209.3 (3.83)	222.0 (3.80)	244.0 (3.84)	291.5 (3.84)
5c	208.0 (3.95)	221.5 (3.83)	243.5 (3.90)	290.0 (3.88)
5d	205.0 (4.12)	218.0 (3.95)	244.0 (3.93)	289.0 (3.88)
5e	205.0 (4.03)	217.0 (4.00)	243.0 (3.85)	288.5 (3.74)

a) In EtOH.

TABLE III. ^{1}H-NMR Chemical Shifts of 5-Fluoro-4(1 or 3*H*)-pyrimidinones

Compd.	H-1	H-6	H-7	H-$C_{1'}$	H-$C_{1''}$	Others		
3a[a]	9.48 (br s)	7.98 (d, $J''=3.0$)		2.50 (s)				
3d[b]	12.65 (br s)	7.83 (d, $J''=2.6$)		3.16 (t, $J'=7.0$)		0.86 (t, $J'=7.0$)	1.20 (br s)	
3e[b]	12.53 (br s)	7.83 (d, $J''=3.1$)		3.16 (t, $J'=7.0$)		0.87 (t, $J'=7.0$)	1.25 (br s)	1.70 (t, $J'=7.0$)
4a[c]	3.72 (br s)		5.31 (dd, $J''=46.8$, 2.9)	2.50 (s)				
4b[b]	12.54 (br s)		5.31 (dd, $J''=46.8$, 2.6)	3.20 (t, $J'=7.0$)		0.87 (t, $J'=7.0$)	1.30 (br s)	1.62 (t, $J'=7.0$)
4c[b]	12.37 (br s)		5.30 (dd, $J''=46.8$, 2.6)	3.20 (t, $J'=7.0$)		0.88 (t, $J'=7.0$)	1.29 (br s)	1.72 (t, $J'=7.0$)
5a[c]	12.92 (br s)		3.59 (d, $J''=3.1$)	2.57 (s)	2.19 (s)			
5b[b]	12.75 (br s)		3.59 (d, $J''=2.6$)	3.17 (t, $J'=7.0$)	2.60 (t, $J'=7.0$)	0.88 (m)	1.30 (m)	1.60 (m)
5c[b]	12.57 (br s)		3.58 (d, $J''=2.6$)	3.16 (t, $J'=6.6$)	2.59 (t, $J'=6.6$)	0.88 (m)	1.27 (m)	1.60 (m)
5d[b]	12.61 (br s)		3.58 (d, $J''=2.6$)	3.16 (t, $J'=7.0$)	2.60 (t, $J'=7.0$)	0.88 (m)	1.26 (m)	1.62 (m)
5e[b]	12.65 (br s)		3.59 (d, $J''=2.6$)	3.16 (t, $J'=7.0$)	2.60 (t, $J'=7.0$)	0.88 (m)	1.30 (m)	1.62 (m)

a) In pyridine-d_5. *b*) In $CDCl_3$. *c*) In dimethylsulfoxide-d_6. Chemical shifts: δ values. J': H–H coupling constant (Hz). J'': F–H coupling constant (Hz).

methylene (δ: 3.59, 32.51) linked to sulfur and an aromatic ring. The C-6 carbon was coupled with a fluorine ($J=12.20$ Hz) in the ^{13}C-NMR spectrum (Tables III and IV). Thus, the structure of **5a** was concluded to be 5-fluoro-2-methylthio-6-methylthiomethyl-4(1 or 3*H*)-pyrimidinone.

Compound **1** and the other *S*-*n*-alkylisothioureas (**2**) [*n*-hexyl (**2b**), *n*-octyl (**2c**), *n*-dodecyl (**2d**) and *n*-hexadecyl (**2e**)] also reacted in absolute ethanol and sodium ethoxide under reflux. The formation of **3**, **4**, **5** and dialkyl disulfide was recognized from the NMR spectra, but some of them were difficult to separate. In the present paper, only purified compounds are reported. No data on dialkyl disulfides are presented. The structures of **3d,e**, **4b,c** and **5b**—**e** were

Table IV. ^{13}C-NMR Chemical Shifts of 5-Fluoro-4(1 or 3*H*)-pyrimidinones

Compd.	C-2	C-4	C-5	C-6	C-7	Others
3a$^{a)}$	158.50 (d, 3.66)	157.20 (d, 23.19)	148.92 (d, 252.69)	137.32 (d, 20.75)		13.71
3d$^{b)}$	157.02 (d, 4.89)	157.99 (d, 24.41)	147.91 (d, 253.91)	137.94 (d, 20.75)		14.09, 22.70, 28.77, 28.93, 29.09, 29.37, 29.47, 29.64, 31.42, 31.97
3e$^{b)}$	156.99 (d, 4.88)	157.99 (d, 24.41)	147.86 (d, 253.91)	138.13 (d, 20.75)		14.09, 22.70, 28.77, 28.93, 29.09, 29.37, 29.47, 29.58, 31.37, 31.97
4a$^{c)}$	156.85 (d, 4.88)	155.66 (d, 24.41)	145.31 (d, 258.79)	141.95 (dd, 17.43, 12.77)	78.43 (d, 167.24)	13.17
4b$^{b)}$	156.58 (d, 4.88)	158.07 (d, 25.63)	145.20 (d, 257.57)	144.01 (dd, 16.48, 10.37)	78.15 (d, 172.12)	13.92, 22.43, 28.39, 28.82, 31.21, 31.42
4c$^{b)}$	156.47 (d, 4.89)	157.85 (d, 25.63)	145.39 (d, 257.57)	143.96 (dd, 15.87, 10.98)	78.16 (d, 172.12)	14.03, 22.65, 28.72, 28.88, 29.04, 31.48, 31.80
5a$^{c)}$	155.98 (d, 4.88)	157.77 (d, 24.41)	144.33 (d, 251.46)	148.97 (d, 12.20)	32.51	13.81, 16.04
5b$^{b)}$	155.72 (d, 4.89)	157.88 (d, 24.36)	144.73 (d, 253.91)	149.51 (d, 13.43)	32.52	13.98, 22.54, 28.44, 28.55, 28.99, 29.31, 30.50, 31.32, 31.42
5c$^{b)}$	155.55 (d, 4.89)	157.55 (d, 24.42)	144.23 (d, 251.47)	149.51 (d, 13.43)	32.56	14.03, 22.65, 28.82, 28.93, 29.15, 29.42, 30.50, 31.48, 31.86
5d$^{b)}$	155.55 (d, 4.86)	157.56 (d, 24.41)	144.23 (d, 251.47)	149.34 (d, 13.43)	32.56	14.03, 22.70, 28.82, 28.93, 29.04, 29.15, 29.31, 29.58, 30.50, 31.48, 31.97
5e$^{b)}$	155.44 (d, 4.87)	157.50 (d, 24.42)	144.28 (d, 251.42)	149.24 (d, 13.43)	32.56	14.03, 22.70, 28.82, 28.93, 29.09, 29.37, 29.69, 30.50, 31.53, 31.97

a) In Pyridine-d_5. *b*) In $CDCl_3$. *c*) In dimethylsulfoxide-d_6. Chemical shifts: δ values. J_{C-F} coupling constants (Hz) are shown in ( ).

confirmed by elemental analyses, the mass spectra (MS), and the IR, UV and NMR spectra in comparison with the data for **3a**, **4a** and **5a** (Tables I, II, III and IV).

Formation of **4** and **5** was not thought to be due to the direct condensation of **1** and **2**. Compound **4** might be formed by condensation of **2** and ethyl 2,4-difluoroacetoacetate, which would be produced from **1** under these reaction conditions, and **5** might be formed by replacement of the fluorine in the fluoromethyl group of **4** with an *n*-alkylthio group.

Compounds **3d,e**, **4b,c** and **5a—e** are novel substances. The biological activities of these compounds will be reported in the future.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. The IR spectra were recorded on a JASCO IRA-202 infrared spectrophotometer. The UV spectra were recorded on a Shimadzu UV-360 recording spectrophotometer. The NMR spectra were recorded on a JEOL JNM-FX 90Q FT NMR spectrometer (^{1}H-NMR 89.55 MHz; ^{13}C-NMR 22.5 MHz) with tetramethylsilane as an internal standard (δ value; s, singlet; d, doublet; t, triplet; q, quartet; br, broad). The MS were recorded on a JEOL JMS-OlSG-2 mass spectrometer. Silica gel 60 GF_{254} (Merck) was used for thin layer chromatography (TLC). Preparative thin layer chromatography (pTLC) was carried out on Silica gel 60 PF_{254} (Merck). For column chromatography, Silica gel 60 (Merck) was used.

Syntheses of *S*-*n*-Alkylisothiourea Hydrobromide (2b—e)——**2b—e** were synthesized from *n*-alkylbromide and thiourea by the method of Brooks *et al.*[6)]

Reaction of Ethyl Monofluoromalonaldehyde Potassium Enolate(1) and *S*-Methylisothiourea Sulfate (2a)——This reaction was done by the patented method.[3)] Compounds **1**[3)] (2.0 g) and **2a** (1.6 g) were added to an absolute MeOH solution (30 ml) of sodium methoxide (0.65 g). The mixture was refluxed with stirring for 2 h. After evaporation of the MeOH, the residue was dissolved in H_2O (40 ml) and the resulting solution was acidified to Congo red acidity with conc. HCl. White precipitates were filtered off and washed with H_2O. The filtrate and washing were combined and extracted with $CHCl_3$. The filtered precipitates were washed with $CHCl_3$. Recrystallization of the $CHCl_3$-insoluble precipitates from MeOH gave pale brown prisms (60 mg) of **3a**. Concentration of the mother liquor gave precipitates, and recrystallization of the precipitates from hexane–benzene gave colorless prisms (140 mg) of **4a**. The $CHCl_3$ extract and washing were combined and dried over Na_2SO_4. Silica gel column chromatography (solvent: $CHCl_3$) and recrystallization (from H_2O) of the $CHCl_3$-soluble fraction gave pale brown needles (310 mg) of **5a**.

Reaction of 1 and *S*-*n*-Hexylisothiourea Hydrobromide (2b)——Compounds **1** (2.0 g) and **2b** (2.6 g) were added to a solution of absolute EtOH (30 ml) and sodium ethoxide (0.76 g). The mixture was stirred under reflux for 2 h. After evaporation of the EtOH, H_2O (30 ml) was added to the residue. A small quantity of H_2O-insoluble solids was filtered off. The filtrate was acidified with conc. HCl to Congo red acidity, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4. After evaporation of the $CHCl_3$, the residue was chromatographed on a silica gel column (solvent: benzene–$CHCl_3$ gradient system). Dihexyl disulfide was eluted first. The second eluate was a mixture of **3b** and **4b**, and the third eluate was crude **5b**. Recrystallization of crude **5b** from MeOH gave colorless needles (450 mg) of **5b**. pTLC of the second eluate on silica gel (solvent; benzene : acetone = 4 : 1) and recrystallization from benzene gave colorless prisms (60 mg) of **4b**.

Reaction of 1 and *S*-*n*-Octylisothiourea (2c)——**1** (2.0 g) and **2c** (3.2 g) were reacted as described for the reaction of **1** and **2b** to give dioctyl disulfide, colorless prisms (80 mg) of **4c**, and colorless needles (190 mg) of **5c**.

Reaction of 1 and *S*-*n*-Dodecylisothiourea (2d)——**1** (1.5 g) and **2d** (2.6 g) were reacted as described for the reaction of **1** and **2b** to give didodecyl disulfide, colorless needles (40 mg) of **3d**, and colorless needles (210 mg) of **5d**.

Reaction of 1 and *S*-*n*-Hexadecylisothiourea (2e)——**1** (2.5 g) and **2e** (4.2 g) were reacted as described for the reaction of **1** and **2b** to give dihexadecyl disulfide, colorless prisms (320 mg) of **3e**, and colorless prisms (40 mg) of **5e**.

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