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Uracil Derivatives. IV.[1] Growth-Inhibitory Activity against L-1210 Cells of Orotic Acid Derivatives and Synthesis of 1-(β-D-Ribofuranosyl)furo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione

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5-(Substituted thiomethyl)-6-carbamoyluracils (IIIb—h) and 5-(substituted thiomethyl)-uracils (Va—h) were prepared and their ability to inhibit the growth of L-1210 cells *in vitro* was examined. The reaction of silylated furo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione (VI) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (VII) in acetonitrile in the presence of $SnCl_4$ gave 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione (VIII) in 81.0% yield. The protected nucleoside (VIII) was hydrolyzed by sodium methoxide to give the N_1-nucleoside (X).

Keywords——orotic acid (2,6-dioxo-1*H*,3*H*-pyrimidine-4-carboxylic acid) derivative; 5-substituted thiomethyluracil; L-1210 cell; stannic chloride; orotidine derivative; UV; ^{1}H-NMR

We previously reported the syntheses and biological activity of 5-(substituted methyl)-6-carbamoyluracils.[1-3] Among them, 5-(4-bromophenylthiomethyl)-6-carbamoyluracil (IIIa) or -6-ethoxycarbonyluracil (IIa) exhibited high growth-inhibitory activity against L-1210 cells.[2] Thus, we attempted to prepare more active compounds by structural modifications of IIa or IIIa.

5-(Substituted thiomethyl)-6-carbamoyluracils (IIIb—h) were prepared by the reaction of 5-chloromethyl-6-ethoxycarbonyluracil (I)[3] with sodium thiolates followed by treatment with ammonia water. In order to examine the effect of the carbonyl moiety at position 6 on the biological activity, 5-substituted phenylthiomethyluracils (Va—h) were prepared from 5-chloromethyluracil (IV)[4] (Chart 1).

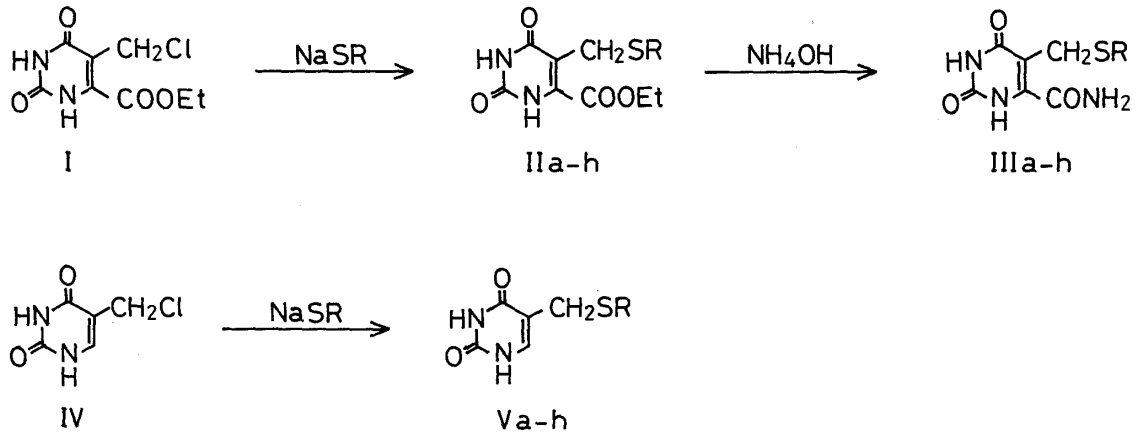
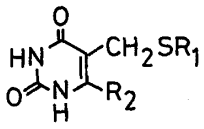


Chart 1

TABLE I. Growth Inhibition of L-1210 Cells *In Vitro*, % Inhibition



Compd. No.	R_1	R_2	Concentration (μg/ml)			
			0.3	1	3	10
IIa		COOEt	42		37	49
IIb		COOEt	27	23	22	28
IIc		COOEt	16	12	6	7
IId		COOEt	20	21	19	20
IIe		COOEt	16	15	17	16
IIf		COOEt	5	15	11	9
IIg		COOEt	14	22	16	11
IIh		COOEt	7	21	20	15
IIIa		$CONH_2$	30		33	65
IIIb		$CONH_2$	24	28	22	26
IIIc		$CONH_2$	16	19	23	19
IIId		$CONH_2$	26	23	23	22
IIIe		$CONH_2$	16	21	20	21
IIIf		$CONH_2$	14	20	11	17
IIIg		$CONH_2$	17	28	49	66
IIIh		$CONH_2$	21	18	18	17
Va		H	0	−3	−3	−2
Vb		H	3	11	12	14
Vc		H	3	13	15	9
Vd		H	8	9	9	12
Ve		H	5	9	6	1
Vf		H	8	6	11	9
Vg		H	10	7	11	17
Vh		H	8	7	10	17
6-MPR[a]			66	78	84	91

a) 6-MPR = 6-mercaptopurine riboside.

The orotic acid derivatives described above were tested for ability to inhibit the growth of L-1210 cells *in vitro*. The method has been described previously.[2] The results are listed in Table I. Since not all the compounds were sufficiently soluble, it seemed reasonable to evaluate the activity at lower concentrations. The activity of 5-substituted thiomethyluracils (Va—h) was weak compared with that of the corresponding esters (IIa—h) or amides (IIIa—h), and the esters (IIb—h) and amides (IIIb—h) exhibited lower activity than the parent compound IIa or IIIa.

However, differences of the substituent groups produced no significant difference in the activity. This seemed to be due to the poor solubility of the compounds. Thus, we tried to prepare the corresponding orotidine derivatives, which should have higher solubility.

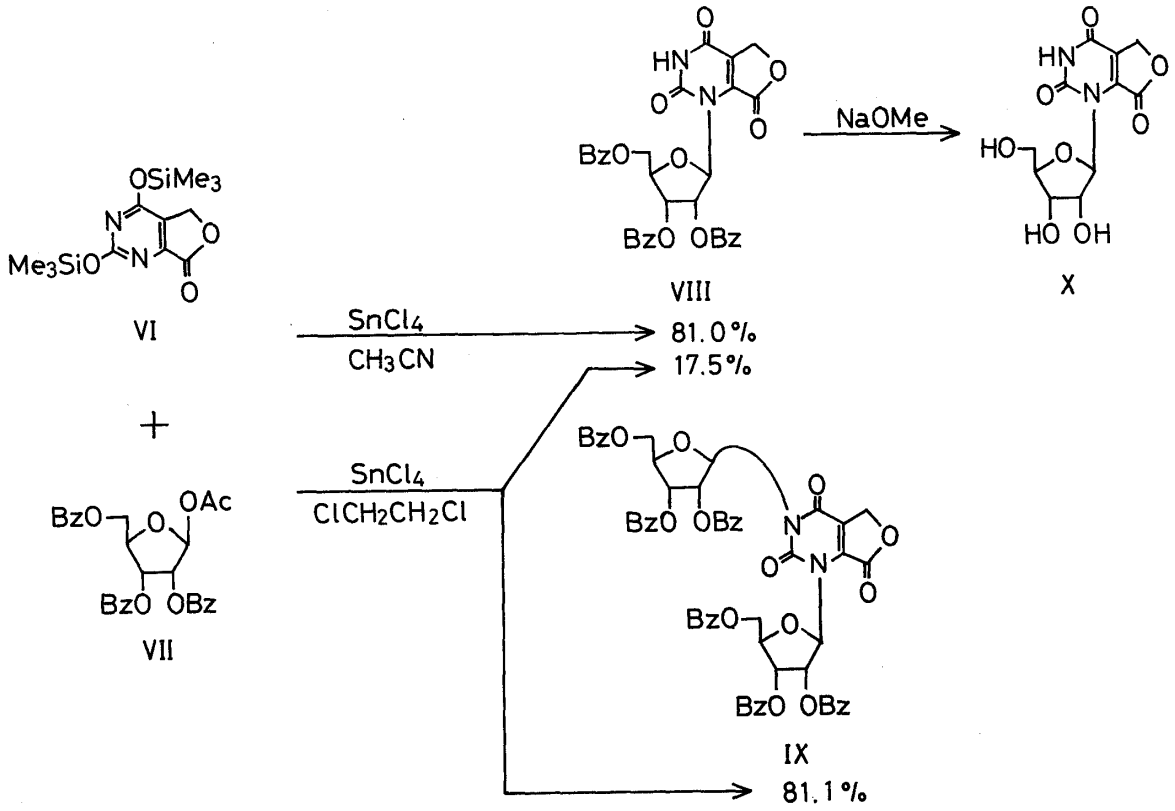


Chart 2

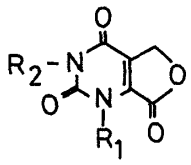
Previous workers have reported that, in the synthesis of 6-substituted pyrimidine nucleosides, the sterically favored N_3-riboside is formed and the reaction of silylated 5,6-dimethyluracil with protected ribose gives N_1-riboside and N_3-riboside.[5] Thus, we considered that N_3-product and N_1-product would be formed by the ribosylation of the silylated lactone (VI).

The reaction of the silylated lactone (VI) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (VII)[6] in 1,2-dichloroethane in the presence of $SnCl_4$ was therefore attempted according to the procedure of Niedballa and Vorbrüggen.[7] However, even after 5 h at room temperature, the N_3-riboside was not detected. The yield of the required N_1-riboside (VIII) was only 17.5% and N_1,N_3-bisriboside (IX) was obtained as the main product (81.1%). On the other hand, using the more polar acetonitrile as a solvent, the protected N_1-nucleoside (VIII) was obtained in 81.0% yield and the bisriboside and the N_3-riboside were not detected. Surprisingly, the reaction was complete within 0.5 h at 0—5 °C. Removal of the blocking groups of VIII with sodium methoxide in methanol gave the nucleoside (X) in 86.4% yield.

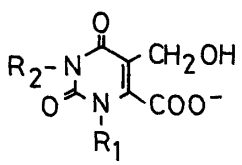
The structures of the orotidine derivatives described above were determined mainly on the basis of the ultraviolet (UV) and proton nuclear magnetic resonance (^{1}H-NMR) spectra. It is generally recognized that N_3-nucleosides show a bathochromic shift in alkaline media, and this has been employed for the identification of N_1-as well as N_3-nucleosides.[8] However, our preliminary investigation revealed that the prepared nucleoside (X) unexpectedly showed a hypthochromic shift. Therefore we investigated the UV spectra of the lactone derivatives (XI—XIV) in detail (Table II).

TABLE II. UV Data for Orotidine Derivatives

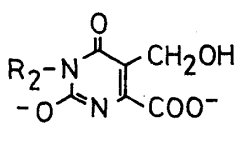
Compd. No.	$\lambda_{max}^{H_2O}$ nm (ε)	λ_{max}^{EtOH} nm (ε)	$\lambda_{max}^{0.1\,N\,NaOH}$ nm (ε)
XI	293	293	268
XII	293	293	270
XIII	281	322	287
XIV	282	322	287
X	285 (8700)	285 (7900)	265 (8100)
IX		282 (14800)	
		276 (14700)	
VIII		282 (11700)	
		276 (11600)	
VII		281 (2400)	
		274 (3000)	



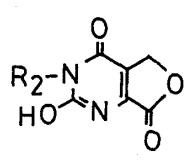
XI: R_1=Me, R_2=H
XII: R_1=Me, R_2=Me
XIII: R_1=H, R_2=Me
XIV: R_1=H, R_2=H



A



B



C

Chart 3

In neutral solution, the 1-methyllactone (XI), 1,3-dimethyllactone (XII),[9] 3-methyllactone (XIII)[10] and lactone (XIV)[10] each exhibited an absorption maximum at 293, 293, 281 and 282 nm, respectively. In alkaline solution, the absorptions of XI and XII appeared at 268 and 270 nm, respectively. This hypthochromic shift of *ca.* 25 nm is due to the cleavage of the lactone ring (structure A). In the case of XIII and XIV, there was a bathochromic shift of *ca.* 5 nm. This is due to both N_1-proton dissociation and cleavage of the lactone ring (structure B). Thus, the bathochromic shift induced by N_1-proton dissociation was assumed to be *ca.* 30 nm. This value is consistent with the reported data for uracils. For example, there is a bathochromic shift of 25 nm in 3-methyluracil in alkaline solution.[11] In alcoholic solution, the absorption appeared at 293 nm for XI and XII which have no N_1-proton, and there was no difference between the spectra in alcoholic solution and in neutral solution. In the case of XIII and XIV, possessing an N_1-proton, there was a bathochromic shift of *ca.* 40 nm. Therefore it is assumed that compounds XIII and XIV take the structure represented by C.

Compound X had a maximum at 285 nm in both neutral solution and alcoholic solution, and at 265 nm in alkaline solution. This observation showed compound X to be an N_1-nucleoside. The ^{1}H-NMR spectrum of the ester VIII showed a singlet ($J_{1',2'} < 1$ Hz) at δ 6.88 due to the anomeric proton, establishing the β-configuration.[12] The β-configuration also follows from the reaction mechanism.[7] Thus, the nucleoside X was determined to be 1-(β-D-ribofuranosyl)furo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione.

The UV spectra of compound IX and the protected N_1-nucleoside VIII could be measured only in ethanolic solution, and the maxima were observed at 276 and 282 nm. These absorption maxima were also observed in the benzoylated ribose VII. However, the absorption at 282 nm was due to the base moiety, because the molar absorptivity at 282 nm was greater than that at 276 nm in VIII and IX, compared with those of VII. If a compound is

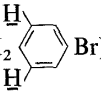
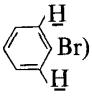
an *O*-riboside, a bathochromic shift is expected because of the lengthening of the conjugated system even in ethanolic solution as described above. Therefore compound IX was identified as the N_1,N_3-bisriboside. The ^{1}H-NMR spectrum of IX unequivocally indicates the β-configuration at both anomeric centers. Thus, compound IX was identified as 1,3-bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-RMX 60 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as δ (ppm) downfield from TMS. Mass spectra (MS) were measured with a JEOL JMS-01SG-2 mass spectrometer. UV spectra were recorded with a Hitachi 200-20 spectrophotometer. Column chromatography was carried out with Kieselgel 60 (70—230 mesh, Merck).

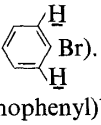
The following compounds were prepared as reported: 1,3-dimethylfuro[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione,[9] 3-methylfuro[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione,[10] furo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione,[10] 4-butoxybenzenethiol,[13] 4-methylthiobenzenethiol,[13] 4-butylthiobenzenethiol[13] and 4-dimethylaminobenzenethiol.[14]

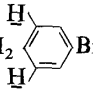
3-(4-Bromophenyl)-1-chloropropane (XV) was prepared from 4-(4-bromophenyl)butyric acid[15] according to the procedure of Kochi[16] in 33.2% yield, bp 115—118 °C (5 mmHg). IR ν_{max}^{film} cm^{-1}: 1490, 1075, 1015, 835, 800. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.4 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.71 (2H, t, J=7 Hz, $C\underline{H}_2$Ph), 3.46 (2H, t, J=6 Hz, $C\underline{H}_2$Cl), 7.02 (2H, d, J=8 Hz, CH_2  Br), 7.35 (2H, d, J=8 Hz, CH_2  Br). MS *m/z*: 236 (M^++4), 234 (M^++2), 232 (M^+).

4-(4-Bromophenyl)-1-bromobutane (XVI) was prepared by the reaction of 4-(4-bromophenyl)butan-1-ol[17] with 48% HBr and conc H_2SO_4 in 71.7% yield, bp 137.5—139 °C (4 mmHg). IR ν_{max}^{film} cm^{-1}: 1490, 1075, 1015, 835, 800. NMR ($CDCl_3$) δ: 1.4—2.2 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.52 (2H, t, J=7 Hz, $C\underline{H}_2$Ph), 3.33 (2H, t, J=6 Hz, $C\underline{H}_2$Br), 7.03 (2H, d, J=8 Hz, CH_2  Br), 7.37 (2H, d, J=8 Hz, CH_2  Br). MS *m/z*: 294 (M^++4), 292 (M^++2), 290 (M^+).

Thiols (XVII—XIX) were prepared from the corresponding halides according to the procedure of Kulka.[18]

2-(4-Bromophenyl)ethane-1-thiol (XVII) was prepared from 2-(4-bromophenyl)-1-bromoethane[19] in 47.0% yield, bp 121 °C (5 mmHg). IR ν_{max}^{film} cm^{-1}: 2560 (SH). NMR ($CDCl_3$) δ: 1.31 (1H, t, J=7.5 Hz, SH), 6.89 (2H, d, J=8 Hz, CH_2  Br), 7.23 (2H, d, J=8 Hz, CH_2  Br). MS *m/z*: 218 (M^++2), 216 (M^+).

3-(4-Bromophenyl)propane-1-thiol (XVIII) was prepared from XV in 67.4% yield, bp 120 °C (5 mmHg). IR ν_{max}^{film} cm^{-1}: 2560 (SH). NMR ($CDCl_3$) δ: 1.32 (1H, t, J=7.5 Hz, SH), 7.00 (2H, d, J=8 Hz, CH_2  Br), 7.34 (2H, d, J=8 Hz, CH_2  Br). MS *m/z*: 232 (M^++2), 230 (M^+).

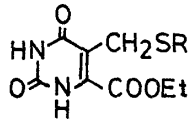
4-(4-Bromophenyl)butane-1-thiol (XIX) was prepared from XVI in 47.4% yield, bp 158 °C (5 mmHg). IR ν_{max}^{film} cm^{-1}: 2560 (SH). NMR ($CDCl_3$) δ: 1.30 (1H, t, J=7.5 Hz, SH), 6.96 (2H, d, J=8 Hz, CH_2  Br), 7.34 (2H, d, J=8 Hz, CH_2  Br). MS *m/z*: 246 (M^++2), 244 (M^+).

Compounds XV—XIX were identified by consideration of their IR, NMR and MS, and used for the next reactions.

1-Methylfuro[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione (XI)——A mixture of 1-methylorotic acid[20] (5.1 g, 30 mmol), 80% paraformaldehyde (3.6 g, 96 mmol of formaldehyde) and conc. HCl (100 ml) was heated with stirring at 70—80 °C for 5 h. The resulting yellowish solution was concentrated *in vacuo*. The precipitates were filtered off and recrystallized from EtOH to give 4.35 g (79.7%) of XI: mp 250 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1780 (lactone C=O). NMR (dimethyl sulfoxide (DMSO)-d_6) δ: 3.37 (3H, s, CH_3), 4.99 (2H, s, CH_2), 11.50 (1H, br s, NH). MS *m/z*: 182 (M^+). *Anal.* Calcd for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.19; H, 3.26; N, 15.50.

5-(Substituted thiomethyl)-6-ethoxycarbonyluracils (IIb—h) and -6-carbamoyluracils (IIIb—h) were prepared according to the method reported by us.[2] Data for the compounds are listed in Tables III, IV, V and VI.

TABLE III.

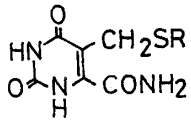


Compd. No.	R	Yield (%)	mp (°C)	Recryst. solv.	Formula	Analysis (%) Calcd (Found)		
						C	H	N
IIb		61.5	232—234	EtOH	$C_{18}H_{22}N_2O_5S$	57.13 (57.07	5.86 5.96	7.40 7.33)
IIc		68.1	240—242	EtOH	$C_{15}H_{16}N_2O_4S_2$	51.12 (50.83	4.58 4.59	7.95 7.83)
IId		66.1	224—226	EtOH	$C_{18}H_{22}N_2O_4S$	54.80 (54.75	5.62 5.45	7.10 6.95)
IIe		56.6	243—244	EtOH	$C_{16}H_{19}N_3O_4S$	55.00 (55.16	5.48 5.51	12.03 12.22)
IIf		25.8	201—203	EtOH	$C_{16}H_{17}BrN_2O_4S$	46.50 (46.52	4.15 4.05	6.78 6.75)
IIg		40.2	209—211	EtOH	$C_{17}H_{19}BrN_2O_4S$	47.78 (47.77	4.48 4.39	6.56 6.72)
IIh		44.3	187—189	EtOH	$C_{18}H_{21}BrN_2O_4S$	48.99 (49.24	4.80 4.81	6.35 6.51)

TABLE IV. Spectral Data for IIb—h

Compd. No.	MS m/z M^+	IR ν_{max}^{Nujol} (C=O)	^{1}H-NMR (DMSO-d_6) δ				
			5-CH_2 (s)	OCH_2CH_3 (t, J=7 Hz)	OCH_2CH_3 (q, J=7 Hz)	NH (br s)	Other protons
IIb	378	1740 1705 1660	3.86	1.18	3.96	10.68 11.30	6.72 (2H, d, J=8.5 Hz, phenyl) 7.09 (2H, d, J=8.5 Hz, phenyl)
IIc	352	1740 1705 1660	3.94	1.21	4.02	10.71 11.33	2.41 (3H, s, SCH_3) 7.14 (4H, s, phenyl)
IId	394	1735 1700 1660	3.97	1.21	4.05	10.73 11.34	2.89 (2H, t, J=7 Hz, SCH_2CH_2) 7.12 (4H, s, phenyl)
IIe	349	1740 1710 1670	3.81	1.16	3.92	10.54 11.27	2.86 (6H, s, $N(CH_3)_2$) 6.49 (2H, d, J=7 Hz, phenyl) 6.99 (2H, d, J=7 Hz, phenyl)
IIf	412	1735 1720 1670	3.60	1.28	4.22	10.81 11.35	2.71 (4H, s, SCH_2CH_2Ph) 7.03 (2H, d, J=8 Hz, phenyl) 7.30 (2H, d, J=8 Hz, phenyl)
IIg	426	1735 1720 1665	3.62	1.33	4.29	10.96 11.49	7.11 (2H, d, J=8 Hz, phenyl) 7.40 (2H, d, J=8 Hz, phenyl)
IIh	440	1735 1715 1665	3.59	1.31	4.28	10.94 11.48	7.11 (2H, d, J=8 Hz, phenyl) 7.40 (2H, d, J=8 Hz, phenyl)

TABLE V.

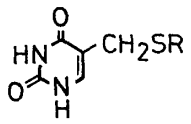


Compd. No.	R	Yield (%)	mp (°C)	Recryst. solv.	Formula	Analysis (%) Calcd (Found)		
						C	H	N
IIIb		70.4	225 (dec.)	MeOH–H_2O	$C_{16}H_{19}N_3O_4S$	55.00 (55.22	5.48 5.56	12.03 12.12)
IIIc		72.6	268 (dec.)	MeOH–H_2O	$C_{13}H_{13}N_3O_3S_2$	48.28 (48.33	4.05 3.92	12.99 12.81)
IIId		72.0	220 (dec.)	MeOH–H_2O	$C_{16}H_{19}N_3O_3S_2$	52.58 (52.37	5.24 5.22	11.50 11.41)
IIIe		81.8	252 (dec.)	MeOH–H_2O	$C_{14}H_{16}N_4O_3S$	52.49 (52.49	5.03 5.32	17.49 17.52)
IIIf		75.3	235 (dec.)	MeOH–H_2O	$C_{16}H_{14}BrN_3O_3S$	43.76 (43.55	3.67 3.47	10.94 10.92)
IIIg		71.5	216—218	MeOH–H_2O	$C_{17}H_{16}BrN_3O_3S$	45.23 (45.47	4.05 3.89	10.55 10.67)
IIIh		69.6	218 (dec.)	MeOH–H_2O	$C_{18}H_{18}BrN_3O_3S$	46.61 (46.49	4.40 4.45	10.19 9.93)

TABLE VI. Spectral Data for IIIb—h

Compd. No.	MS m/z M^+	IR ν_{max}^{Nujol} (C=O)	^{1}H-NMR (DMSO-d_6) δ			
			5-CH_2 (s)	$CONH_2$ (br s)	NH (br s)	Other protons
IIIb	349	1765 1700 1660	3.78	7.78 7.90	10.90 11.07	6.72 (2H, d, J=8.5 Hz, phenyl) 7.18 (2H, d, J=8.5 Hz, phenyl)
IIIc	323	1715 1670	3.84	7.83 7.97	10.98 11.13	2.40 (3H, s, SCH_3) 7.06 (2H, d, J=8 Hz, phenyl) 7.17 (2H, d, J=8 Hz, phenyl)
IIId	365	1755 1705 1665	3.84	7.81 7.96	9.97 10.12	2.87 (2H, t, J=7 Hz, SCH_2CH_2) 7.12 (4H, s, phenyl)
IIIe	320	1710 1670	3.70	7.83	10.87 11.05	2.83 (6H, s, $N(CH_3)_2$) 6.53 (2H, d, J=8.5 Hz, phenyl) 7.11 (2H, d, J=8.5 Hz, phenyl)
IIIf	383	1740 1680 1645	—	7.86 8.02	10.93 11.09	2.71 (4H, s, SCH_2CH_2Ph) 7.08 (2H, d, J=8 Hz, phenyl) 7.30 (2H, d, J=8 Hz, phenyl)
IIIg	397	1770 1685 1665	3.44	7.96 8.13	10.99 11.17	7.13 (2H, d, J=8 Hz, phenyl) 7.39 (2H, d, J=8 Hz, phenyl)
IIIh	411	1715 1685 1655	3.43	7.97 8.14	11.03 11.22	7.13 (2H, d, J=8 Hz, phenyl) 7.41 (2H, d, J=8 Hz, phenyl)

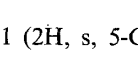
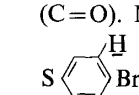
TABLE VII.



Compd. No.	R	Yield (%)	mp (°C)	Recryst. solv.	Formula	Analysis (%) Calcd (Found)		
						C	H	N
Vb		70.6	250—256 (dec.)	DMF–H_2O	$C_{11}H_9FN_2O_2S$	52.37 (52.12	3.60 3.47	11.11 11.13)
Vc		49.2	256 (dec.)	DMF–H_2O	$C_{12}H_{12}N_2O_3S$	54.43 (54.37	4.58 4.72	10.60 10.79)
Vd		70.6	253 (dec.)	DMF–H_2O	$C_{15}H_{18}N_2O_3S$	58.80 (58.53	5.92 5.71	9.14 9.08)
Ve		70.0	261—264	DMF–H_2O	$C_{12}H_{12}N_2O_2S_2$	51.41 (51.51	4.31 4.42	9.99 10.05)
Vf		83.2	239—242	DMF–H_2O	$C_{15}H_{18}N_2O_2S_2$	55.87 (56.13	5.63 5.89	8.69 8.77)
Vg		29.7	241—243.5	DMF–H_2O	$C_{13}H_{15}N_3O_2S$	56.30 (56.41	5.45 5.38	15.15 15.01)
Vh		61.3	213—216	EtOH	$C_{10}H_9N_3O_2S$	51.05 (51.01	3.89 3.96	17.87 17.65)

TABLE VIII. Spectral Data for Vb—h

Compd. No.	MS m/z M^+	IR ν_{max}^{Nujol} (C=O)	^{1}H-NMR (DMSO-d_6) δ			
			5-CH_2 (s)	1-NH (br s)	3-NH (br s)	Other protons
Vb	252	1755 1690	3.73	10.5	10.93	6.8—7.5 (5H, m, phenyl and 6-H)
Vc	264	1750 1685	3.59	10.4	10.88	3.68 (3H, s, OCH_3) 6.77 (2H, d, J=8.2 Hz, phenyl) 7.15 (2H, d, J=8.2 Hz, phenyl)
Vd	306	1760 1690	3.58	10.4	10.85	3.91 (2H, t, J=6 Hz, OCH_2) 6.75 (2H, d, J=8.2 Hz, phenyl) 7.14 (2H, d, J=8.2 Hz, phenyl)
Ve	280	1760 1690	3.69	10.5	10.93	2.42 (3H, s, SCH_3) 7.13 (4H, s, phenyl)
Vf	322	1760 1690	3.70	10.5	10.92	2.89 (2H, t, J=7 Hz, SCH_2CH_2) 7.13 (4H, s, phenyl)
Vg	277	1700 1665	3.48	10.4	10.88	2.83 (6H, s, $N(CH_3)_2$) 6.54 (2H, d, J=8.8 Hz, phenyl) 6.74 (1H, d, J=5 Hz, 6-H) 7.06 (2H, d, J=8.8 Hz, phenyl)
Vh	235	1725 1685	3.95	10.8 (2H)		

General Procedure for the Preparation of 5-(Substituted thiomethyl)uracils (Va—h)——A Typical Example: 5-(4-Bromophenylthiomethyl)uracil (Va): A solution of sodium (0.11 g, 4.8 mmol) and 4-bromobenzenethiol (0.95 g, 5.0 mmol) in ethanol (70 ml) was refluxed for 1 h. 5-Chloromethyluracil (IV)[4] was added to the solution after it had cooled, and the mixture was stirred for 5 h at room temperature. The product was filtered off and recrystallized from *N,N*-dimethylformamide (DMF)–H_2O to give 1.21 g (77.3%) of Va: mp 269 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1760, 1695 (C=O). NMR (DMSO-d_6) δ: 3.71 (2H, s, 5-CH_2), 7.13 (2H, d, J=8.2 Hz, S  Br), 7.31 (2H, d, J=8.2 Hz, S  Br), 10.5 (1H, br, 1-NH), 10.90 (1H, br s, 3-NH). MS m/z: 314 (M^++2), 312 (M^+). *Anal.* Calcd for $C_{11}H_9BrN_2O_2S$: C, 42.19; H, 2.90; N, 8.94. Found: C, 42.17; H, 3.04; N, 9..03.

Data for the compounds (Vb—h) prepared as described above are listed in Tables VII and VIII.

2,4-Bis(trimethylsilyloxy)furo[3,4-*d*]pyrimidine-7(5*H*)-one (VI)——Furo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione (XIV)[10] was heated under reflux in an excess of hexamethyldisilazane with a catalytic quantity of ammonium sulfate under anhydrous conditions. After 2 h, the solid had dissolved, and the excess of hexamethyldisilazane was removed under reduced pressure. The residual solid (VI) was used for the next reaction without purification.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)furo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione (VIII)——The silylated lactone (VI) derived from 0.5 g (3 mmol) of the lactone (XIV) was mixed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (VII)[6] (1.2 g, 2.4 mmol) in anhydrous acetonitrile (25 ml). The solution was cooled at 0—5 °C and stannic chloride (0.4 ml, 3.5 mmol) in anhydrous acetonitrile (5 ml) was added with vigorous stirring and exclusion of moisture. The slightly yellowish solution was stirred for 0.5 h at 0—5 °C, then concentrated to 10 ml, diluted with 20 ml of 1,2-dichloroethane and neutralized with sat. $NaHCO_3$. The resulting emulsion was filtered over a layer of Celite and the filter aid was washed with 1,2-dichloroethane. The organic phase was separated, dried (Na_2SO_4) and evaporated under reduced pressure. The slightly brownish foam thus obtained was chromatographed on silica gel with $CHCl_3$ to give 1.25 g (81.0%) of VIII as a colorless foam. IR ν_{max}^{Nujol} cm^{-1}: 1780 (lactone C=O). NMR (DMSO-d_6) δ: 5.07 (2H, s, 5-CH_2), 6.88 (1H, s, 1′-H), 12.12 (1H, s, NH). The NMR spectrum revealed the presence of $CHCl_3$. *Anal.* Calcd for $C_{32}H_{24}N_2O_{11}\cdot 0.3\ CHCl_3$: C, 59.84; H, 3.78; N, 4.32. Found: C, 59.93; H, 3.62; N, 4.23.

The analogous reaction in 1,2-dichloroethane (5 h at room temperature) afforded a brownish foam. The mixture was chromatographed on silica gel with $CHCl_3$–EtOAc (5 : 1). The N_1-nucleoside (VIII) was obtained as the less polar compound in 17.5% yield. 1,3-Bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione (IX) was obtained as the more polar compound in 81.8% yield, and recrystallized from ethanol, mp 118—120 °C. IR ν_{max}^{Nujol} cm^{-1}: 1780 (lactone C=O). NMR (CMSO-d_6) δ: 5.14 (2H, br s, 5-CH_2), 6.48 (1H, s, 1′-H(N_3)), 6.96 (1H, s, 1′-H(N_1)). *Anal.* Calcd for $C_{58}H_{44}N_2O_{18}$: C, 65.91; H, 4.20; N, 2.65. Found: C, 65.61; H, 4.14; N, 2.72.

1-(β-D-Ribofuranosyl)furo[3,4-*d*]pyrimidine-2,4,7-(1*H*,3*H*,5*H*)-trione (X)——VIII (0.2 g, 0.3 mmol) was added to a solution of sodium (9.2 mg, 0.4 mmol) in methanol (7 ml), and the solution was refluxed for 1 h. After cooling, the solution was filtered through a column of Dowex 50 (H^+) resin and the resin was washed with EtOH–H_2O. The eluate was concentrated and the residue was crystallized from $CHCl_3$–iso-PrOH. The white crystals obtained were recrystallized from iso-PrOH to give 80 mg (86.4%) of X: mp 188—191 °C. IR ν_{max}^{Nujol} cm^{-1}: 3480, 3395, 3280 (OH), 1780 (lactone C=O), 1715, 1695 (C=O). NMR (DMSO-d_6) δ: 5.00 (2H, s, 5-CH_2), 6.30 (1H, d, J=3.5 Hz, 1′-H), 11.65 (1H, s, NH). *Anal.* Calcd for $C_{11}H_{12}N_2O_8$: C, 44.01; H, 4.03; N, 9.33. Found: C, 44.30; H, 4.09; N, 9.32.

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