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Uracil Derivatives. V.[1] Syntheses and Growth-Inhibitory Activity against L-1210 Cells of 5-Substituted 2′-Deoxyuridines and Orotidine Derivatives

Jutaro Okada, Koichi Nakano,* and Hiroshi Miyake

Faculty of Pharmaceutical Sciences, Kyoto University, Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto 606, Japan

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5-Benzyloxymethyl-2′-deoxyuridine 3′,5′-di-*p*-toluate (III), a key intermediate in the preparation of 5-substituted 2′-deoxyuridines (VIa—d), was prepared in satisfactory yield. 5-(4-Substituted phenylthiomethyl)-2′-deoxyuridines (VIa—d) were synthesized in three steps from III. The reaction of silylated orotates (VIIa—e) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (VIII) gave the N_1,N_3-bisribosides (IXa—e) and the N_3-ribosides (Xa—e). The N_3-ribosides (Xa—e) were deprotected to give the N_3-nucleosides (XIa—e).

Compounds VIa—d and XIa—e were tested for ability to inhibit the growth of L-1210 cells *in vitro*.

Keywords——5-(4-substituted phenylthiomethyl)-2′-deoxyuridine; 5-(4-substituted phenylthiomethyl)-6-methoxycarbonyl-3-(*β*-D-ribofuranosyl)uracil; stannic chloride-catalyzed glycosylation; UV; L-1210 cell

We previously reported that 5-(4-substituted phenylthiomethyl)orotates and orotamides exhibited growth-inhibitory activity against L-1210 cells.[1-4] Because of the poor solubilities of these compounds in aqueous solution, however, the activity was apparently independent of concentration and was not much influenced by the substituent groups. Thus, we expected that active compounds would be obtained and the structure–activity relationships might become apparent if the water solubility could be improved. In this paper, the syntheses of the corresponding deoxyuridines and orotidine derivatives and the determination of their activities are reported.

First, 5-(4-substituted phenylthiomethyl)-2′-deoxyuridines (VIa—d) were prepared as shown in Chart 1. A key intermediate to VIa—d is 5-benzyloxymethyl-1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-*β*-D-ribofuranosyl)uracil (III). Though the benzyloxymethyl derivative (III) has been synthesized,[5,6] the yield, the reaction time and the purification were unsatisfactory. In the present study, the procedure of Niedballa and Vorbrüggen[7] was applied for the synthesis of III. Silylated 5-benzyloxymethyluracil (I)[6] and 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-ribofuranosyl chloride (II)[8] were dissolved in 1,2-dichloroethane. The solution was cooled and stannic chloride was added with exclusion of moisture. The reaction was complete after 2 h at room temperature. Work-up provided an anomeric mixture, and the *β*-anomer (III) was separated in satisfactory yield by fractional crystallization.

The intermediate (III), which could be readily synthesized in high yield and in a short time as described above, was treated in dioxane with dry hydrogen chloride to give the chloromethyl derivative (IV).[5] Treatment of IV with sodium thiolates in methanol gave the protected nucleosides (Va—d), which were deprotected with potassium carbonate to give 5-(4-substituted phenylthiomethyl)-2′-dioxyuridines (VIa—d).

The ultraviolet (UV) spectral data of VIa—d are listed in Table IV. The absorption maxima and molar absorptivities vary owing to the overlap of the absorption due to the uracil

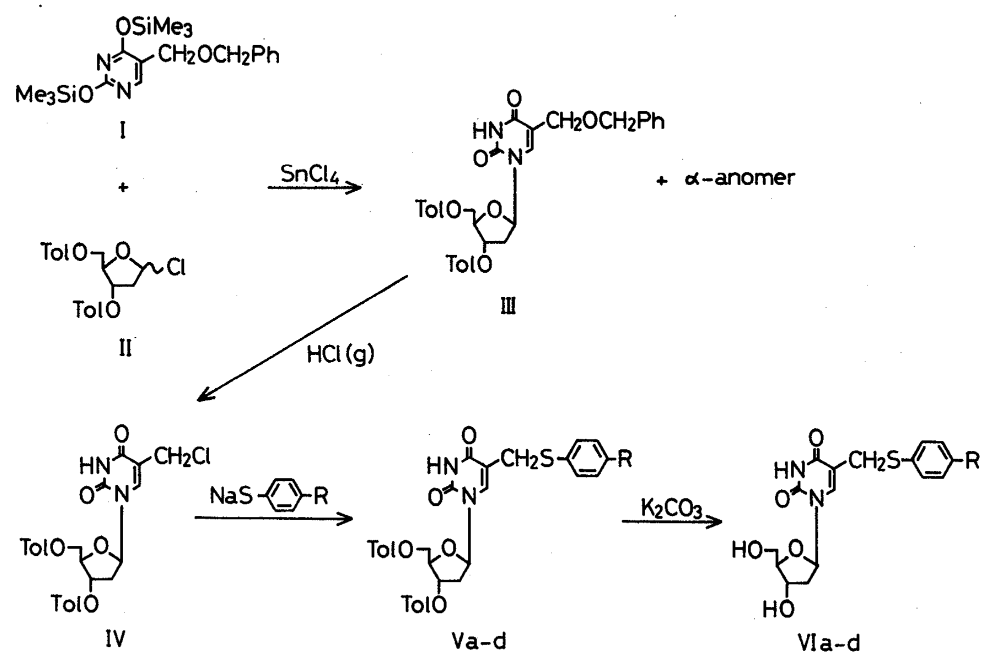


Chart 1

Table I. 5-(4-Substituted phenylthiomethyl)-1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-β-D-ribofuranosyl)uracils (Va—d)

Compd. No.	R	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
Va	Br	66.3	172—173	EtOH	$C_{32}H_{29}BrN_2O_7S$	57.75 (58.03	4.39 4.24	4.21 4.33)
Vb	OBu	60.8	146—147	EtOH	$C_{36}H_{38}N_2O_8S$	65.64 (65.77	5.81 5.79	4.25 4.13)
Vc	SMe	48.6	121—123	EtOH	$C_{33}H_{32}N_2O_7S_2$	62.64 (62.48	5.10 5.03	4.43 4.38)
Vd	NMe_2	26.1	107—111	EtOH	$C_{34}H_{35}N_3O_7S$	64.85 (64.81	5.60 5.40	6.67 6.59)

ring and the benzene ring.

Next, the ribosylation of 5-substituted orotates was carried out (Chart 2). Silylated orotates (VIIa—e) were allowed to react with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (VIII)[9] in acetonitrile in the presence of stannic chloride. After 3 h at 60 °C, the reaction mixture was worked up, then chromatographed on silica gel to give the N_1,N_3-bisribosides (IXa—e) and the N_3-ribosides (Xa—e). Removal of the blocking groups of Xa—e with sodium methoxide gave the N_3-nucleosides (XIa—e).

Their structures were determined as follows. The proton nuclear magnetic resonance (^{1}H-NMR) spectra of Xa—e showed a singlet ($J_{1',2'} < 1$ Hz) at δ 6.43—6.47 due to the anomeric proton (Table VIII), establishing the β-configuration.[10] The β-configuration is expected from the reaction mechanism.[7] The infrared (IR) spectra of the nucleosides (XIa—e) showed two carbonyl bands due to the uracil ring at 1740—1720 and 1660—1640 cm^{-1} (Table X). Thus, compounds XIa—e were identified as *N*-nucleosides, not *O*-nucleosides. The UV spectral data

Table II. Spectral Data for Va—d

Compd. No.	IR ν_{max}^{Nujol} cm^{-1} (C=O)	^{1}H-NMR (DMSO-d_6) δ			
		5-CH_2 (s)	1′-H (t, J=7 Hz)	NH (br s)	Other protons
Va	1730 1700 1680 (sh)	3.62	6.17	11.34	7.09 (2H, d, J=8 Hz, phenyl) 7.34 (2H, d, J=8 Hz, phenyl)
Vb	1720 1700 1690 (sh)	3.42	6.13	11.30	3.83 (2H, t, J=6 Hz, OCH_2)
Vc	1720 1700 1680 (sh)	3.56	6.15	11.31	2.39 (3H, s, SCH_3) 7.06 (4H, s, 5-phenyl)
Vd	1720 1700 1680 (sh)	3.35	6.14	11.29	2.82 (6H, s, $N(CH_3)_2$) 6.51 (2H, d, J=8 Hz, phenyl) 6.96 (2H, d, J=8 Hz, phenyl)

Table III. 5-(4-Substituted phenylthiomethyl)-2′-deoxyuridines (VIa—d)

Compd. No.	R	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
VIa	Br	73.3	182—183.5	EtOH–H_2O	$C_{16}H_{17}BrN_2O_5S$	44.77 (44.83	3.99 3.93	6.53 6.54)
VIb	OBu	63.0	155—156.5	EtOH–H_2O	$C_{20}H_{26}N_2O_6S \cdot 1/5H_2O$	56.38 (56.36	6.25 6.30	6.57 6.57)
VIc	SMe	50.4	153.5—155.5	EtOH–H_2O	$C_{17}H_{20}N_2O_5S_2$	51.50 (51.45	5.08 4.82	7.07 6.93)
VId	NMe_2	69.3	161 (dec.)	EtOH–H_2O	$C_{18}H_{23}N_3O_5S \cdot 1/2H_2O$	53.72 (53.65	6.01 5.97	10.44 10.41)

Table IV. Spectral Data for VIa—d

Compd. No.	IR ν_{max}^{Nujol} cm^{-1} (C=O)	^{1}H-NMR (DMSO-d_6) δ					UV	
		5-CH_2 (s)	1′-H (t, J=7 Hz)	Phenyl	6-H (s)	NH (br s)	$\lambda_{max}^{dioxane}$ nm (ε)	$\lambda_{max}^{0.1\,N\,NaOH}$ nm (ε)
VIa	1720 1660	3.73	6.00	7.14 (2H, d, J=8 Hz) 7.33 (2H, d, J=8 Hz)	7.56	11.17	263 (17000)	263 (11100)
VIb	1720 1660	3.59	5.99	6.76 (2H, d, J=8 Hz) 7.11 (2H, d, J=8 Hz)	7.27	11.13	259 (13700)	256 (10900)
VIc[a]	1730 1660	3.70	6.01	7.13 (4H, s)	7.45	11.19	271 (22100)	268 (20600)
VId[b]	1710 1655	3.39	6.04	6.57 (2H, d, J=8 Hz) 7.05 (2H, d, J=8 Hz)	7.09	11.13	271 (26000)	269 (21700)

[a] ^{1}H-NMR (DMSO-d_6): the signal due to SCH_3 appeared at δ2.43 (3H, s).

[b] ^{1}H-NMR (DMSO-d_6): the signal due to $N(CH_3)_2$ appeared at δ2.85 (6H, s).

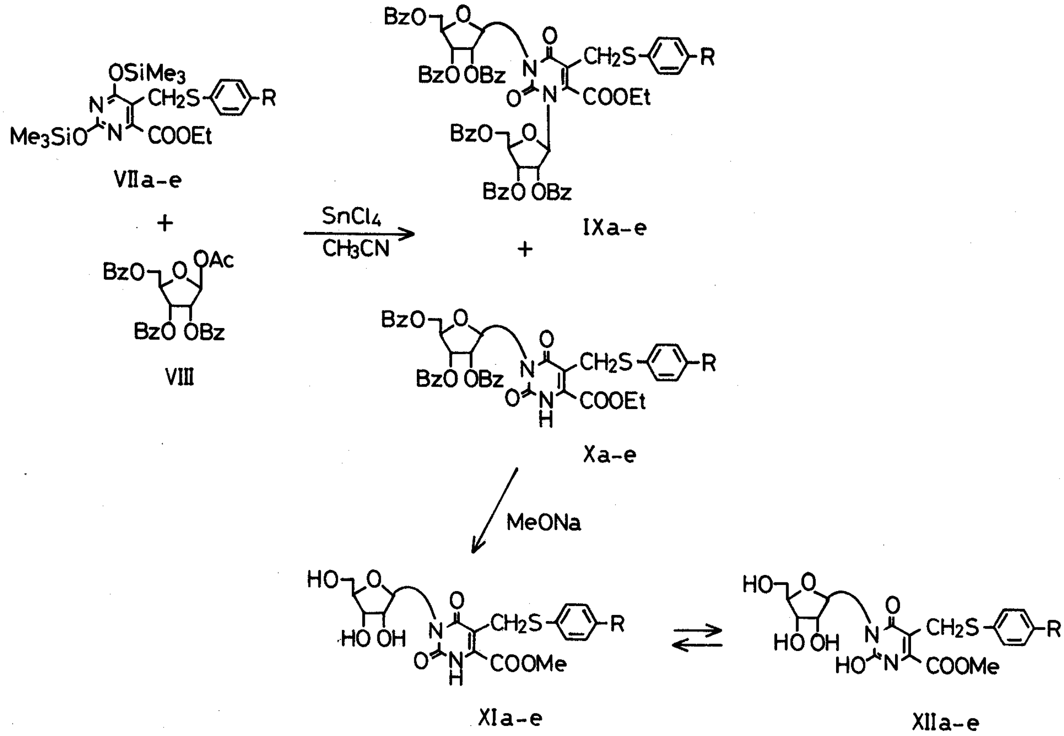


Chart 2

are listed in Table X. Similarly to deoxyuridines (VIa—d), the absorption due to the uracil ring overlapped with that due to the benzene ring. The absorption maximum due to the uracil ring, however, was assigned to *ca.* 296 nm in dioxane and *ca.* 303 nm in alkaline solution. This small but definite bathochromic shift and increase in the absorption are characteristic of N_3-nucleoside.[7] The absorption maximum (*ca.* 296 nm) in dioxane is shifted to a longer wavelength region compared with that of usual orotidine derivatives (*ca.* 280 nm).[11] Therefore the N_3-nucleosides (XIa—e) are assumed to take the enol form (XIIa—e) in dioxane (Chart 2).

On the basis of the data described above, compounds XIa—e were determined to be 5-(4-substituted phenylthiomethyl)-6-methoxycarbonyl-3-(β-D-ribofuranosyl)uracils.

The structures of N_1,N_3-bisribosides (IXa—e) were also determined in a similar manner. The ^{1}H-NMR spectra established the β-configuration at both anomeric centers (Table VI). The IR spectra of IXa—e resembled those of the N_3-ribosides (Xa—e). In the UV spectra, *O*-riboside is expected to exhibit an absorption maximum at *ca.* 296 nm, because the enol forms (XIIa—e) of the N_3-nucleosides showed absorption maxima at *ca.* 296 nm. The UV spectra of IXa—e failed to exhibit an absorption maximum at *ca.* 296 nm. Thus, compounds IXa—e were determined to be 5-(4-substituted phenylthiomethyl)-1,3-bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-ethoxycarbonyluracils.

The deoxyuridines (VIa—d) and N_3-nucleosides (XIa—e) were tested for ability to inhibit the growth of L-1210 cells *in vitro*. The method has been described previously.[3] The results are listed in Table XI. Both the deoxyuridines (VIa—d) and N_3-nucleosides (XIa—e) were synthesized in attempts to improve the water solubility of the original compounds, but their water solubility levels were still not sufficient for the activity to be dependent on concentration. Therefore the activity was evaluated at low concentrations (0.3 and 1 μg/ml).

Among the compounds synthesized in this study, no active compounds were found. However, when the activities were compared with those of the corresponding uracils (XIIIa—d) and orotates (XIVa—e) which had been prepared by us,[1-3] it was found that most of the

TABLE V. 5-(4-Substituted phenylthiomethyl)-1,3-bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-ethoxycarbonyluracils (IXa—e)

Compd. No.	R	Yield (%)	Appearance	Formula	Analysis (%) Calcd (Found) C	H	N
IXa	F	18.3	White foam	$C_{66}H_{53}FN_2O_{18}S$	65.34 (65.57	4.40 4.34	2.31 2.30)
IXb	Br	16.8	White foam	$C_{66}H_{53}BrN_2O_{18}S$	62.22 (62.27	4.19 4.11	2.20 2.09)
IXc	OBu	21.8	Slightly yellowish foam	$C_{70}H_{62}N_2O_{19}S$	66.34 (66.39	4.93 4.84	2.21 2.18)
IXd	SMe	21.4	Slightly yellowish foam	$C_{67}H_{56}N_2O_{18}S_2$	64.83 (65.09	4.55 4.52	2.26 2.20)
IXe	Bu-*tert*	27.0	Slightly yellowish foam	$C_{70}H_{62}N_2O_{18}S$	67.19 (67.11	4.99 4.95	2.24 2.02)

TABLE VI. Spectral Data for IXa—e

Compd. No.	IR ν_{max}^{Nujol} cm^{-1} (C=O)	^{1}H-NMR (CDCl$_3$) δ 5-CH$_2$ (s)	6-CH$_2$C$\underline{H}_3$ (t, J=7 Hz)	6-C$\underline{H}_2$CH$_3$ (q, J=7 Hz)	1′-H (N$_1$) (d, J=3 Hz)	1′-H (N$_3$) (s)	UV $\lambda_{max}^{CHCl_3}$ nm (ε)
IXa	1720 1680	3.78	1.22	4.18	5.65	6.44	281 (sh) (14700) 275 (16500) 268 (sh) (15400)
IXb	1720 1670	3.83	1.22	4.18	5.64	6.46	280 (sh) (15800) 273 (sh) (18400) 269 (18600)
IXc	1720 1670	3.80	1.22	4.18	5.66	6.47	280 (sh) (16100) 275 (18400) 268 (sh) (18300)
IXd[a]	1720 1670	3.82	1.22	4.18	5.67	6.47	281 (sh) (29000) 276 (31100)
IXe[b]	1720 1670	3.86	1.21	4.17	5.69	6.52	281 (sh) (15500) 274 (17800) 268 (sh) (17300)

a) ^{1}H-NMR (CDCl$_3$): the signal due to SCH$_3$ appeared at δ2.33 (3H, s).
b) ^{1}H-NMR (CDCl$_3$): the signal due to C(CH$_3$)$_3$ appeared at δ1.25 (9H, s).

deoxyuridines (VI) exhibited higher activity than the uracils (XIII). Thus, it seems that the 2′-deoxyribofuranosyl moiety at the 1 position of the uracil ring is essential for enhanced activity. The activity of the N_3-nucleosides (XI) was weaker than that of the orotates (XIV) except for XIe. It appears that introduction of the ribofuranosyl moiety at the 3 position results in low activity. From the above results, we consider that introduction of a 2′-deoxyribofuranosyl moiety at the 1 position of XIV should result in higher activity.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. 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

Table VII. 5-(4-Substituted phenylthiomethyl)-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-ethoxycarbonyluracils (Xa—e)

Compd. No.	R	Yield (%)	Appearance	Formula	Analysis (%) Calcd (Found)		
					C	H	N
Xa	F	17.4	Slightly yellowish foam	$C_{40}H_{33}FN_2O_{11}S$	62.49 (62.73	4.33 4.25	3.64 3.61)
Xb	Br	28.0	Slightly yellowish foam	$C_{40}H_{33}BrN_2O_{11}S$	57.91 (57.69	4.01 4.08	3.38 3.44)
Xc	OBu	14.6	Yellowish foam	$C_{44}H_{42}N_2O_{12}S$	64.22 (64.34	5.14 5.00	3.40 3.43)
Xd	SMe	22.2	Yellowish foam	$C_{41}H_{36}N_2O_{11}S_2$	61.80 (61.55	4.55 4.50	3.52 3.39)
Xe	Bu-*tert*	19.7	Slightly yellowish foam	$C_{44}H_{42}N_2O_{11}S$	65.50 (65.36	5.25 5.52	3.47 3.34)

Table VIII. Spectral Data for Xa—e

Compd. No.	IR ν_{max}^{Nujol} cm^{-1} (C=O)	^{1}H-NMR ($CDCl_3$) δ					
		5-CH_2 (s)	6-$CH_2C\underline{H}_3$ (t, J=7 Hz)	6-$C\underline{H}_2CH_3$ (q, J=7 Hz)	1′-H (s)	NH (s)	Other protons
Xa	1720 1660	4.15	1.26	4.16	6.45	8.55	
Xb	1720 1660	4.17	1.29	4.18	6.43	8.37	
Xc	1720 1660	4.09	1.26	4.08	6.47	8.37	3.81 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2$)
Xd	1720 1660	4.14	1.26	4.12	6.44	8.43	2.34 (3H, s, SCH_3)
Xe	1720 1660	4.12	1.25	4.08	6.46	8.30	1.24 (9H, s, $C(CH_3)_3$)

Table IX. 5-(4-Substituted phenylthiomethyl)-6-methoxycarbonyl-3-(β-D-ribofuranosyl)uracils (XIa—e)

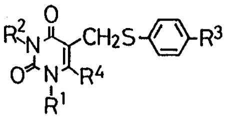
Compd. No.	R	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
XIa	F	87.6	161—166	H_2O	$C_{18}H_{19}FN_2O_8S$	48.87 (49.17	4.33 4.34	6.33 6.32)
XIb	Br	49.9	165—169	H_2O	$C_{18}H_{19}BrN_2O_8S$	42.95 (42.91	3.81 3.87	5.57 5.61)
XIc	OBu	71.3	187—189	EtOH–H_2O	$C_{22}H_{28}N_2O_9S$	53.22 (53.29	5.68 5.73	5.64 5.45)
XId	SMe	75.6	163—166	H_2O	$C_{19}H_{22}N_2O_8S_2$	48.50 (48.21	4.71 4.73	5.95 5.73)
XIe	Bu-*tert*	86.7	148 (dec.)	EtOH–H_2O	$C_{22}H_{28}N_2O_8S$	54.99 (54.85	5.87 5.90	5.83 5.71)

Table X. Spectral Data for XIa—e

Compd. No.	IR ν_{max}^{Nujol} cm^{-1} (C=O)	^{1}H-NMR (DMSO-d_6) δ 5-CH_2 (s)	$COOCH_3$ (s)	1′-H (d, $J=3$ Hz)	Phenyl	NH (br s)	UV $\lambda_{max}^{dioxane}$ nm (ε)	$\lambda_{max}^{0.1\,N\,NaOH}$ nm (ε)
XIa	1740 1710 1660	3.96	3.61	5.96	6.8—7.4 (4H, m)	11.01	298 (6710) 254 (5880)	304 (11100)
XIb	1735 1720 1650	3.98	3.62	5.96	7.16 (2H, d, $J=8$ Hz) 7.33 (2H, d, $J=8$ Hz)	11.05	294 (7460) 264 (10800)	302 (13100) 261 (11200)
XIc	1740 1700 1640	3.87	3.54	5.95	6.72 (2H, d, $J=8$ Hz) 7.09 (2H, d, $J=8$ Hz)	10.90	296 (7360) 257 (8890)	304 (11400)
XId[a]	1740 1700 1640	3.94	3.59	5.95	7.08 (4H, s)	10.98	295 (sh) (10500) 275 (19700)	295 (sh) (15800) 278 (17400)
XIe[b]	1720 1650 1640	3.96	3.57	5.95	7.13 (4H, s)	10.97	297 (7040) 257 (8870)	303 (12200) 255 (sh) (10100)

a) ^{1}H-NMR (DMSO-d_6): the signal due to SCH_3 appeared at δ 2.42 (3H, s).
b) ^{1}H-NMR (DMSO-d_6): the signal due to $C(CH_3)_3$ appeared at δ 1.25 (9H, s).

Table XI. Growth Inhibition of L-1210 Cells *in Vitro*, % Inhibition



Compd. No.	R^1	R^2	R^3	R^4	Concentration (μg/ml) 0.3	1	3	10
VIa	DR[a]	H	Br	H	31	15	6	−7
VIb	DR[a]	H	OBu	H	14	0	−12	55
VIc	DR[a]	H	SMe	H	21	13	13	−7
VId	DR[a]	H	NMe$_2$	H	3	22	10	−16
XIIIa	H	H	Br	H	0	−3	−3	−2
XIIIb	H	H	OBu	H	8	9	9	12
XIIIc	H	H	SMe	H	5	9	6	1
XIIId	H	H	NMe$_2$	H	10	7	10	17
XIa	H	RF[b]	F	COOMe	−1	−26	5	−8
XIb	H	RF[b]	Br	COOMe	−12	−1	−10	−11
XIc	H	RF[b]	OBu	COOMe	8	1	5	29
XId	H	RF[b]	SMe	COOMe	16	12	17	38
XIe	H	RF[b]	Bu-*tert*	COOMe	26	13	7	−1
XIVa	H	H	F	COOMe	15	21	18	−6
XIVb	H	H	Br	COOMe	17	27	23	3
XIVc	H	H	OBu	COOEt	27	23	22	28
XIVd	H	H	SMe	COOEt	16	12	6	7
XIVe	H	H	Bu-*tert*	COOEt	0	7	3	2
6-MPR[c]					66	78	84	91

a) DR = 2-deoxy-β-D-ribofuranosyl.
b) RF = β-D-ribofuranosyl.
c) 6-MPR = 6-mercaptopurine riboside.

δ (ppm) downfield from TMS. Mass spectra (MS) were measured with a JEOL JMS-01SG-2 mass spectrometer. UV spectra were recorded with a Shimadzu UV-240 spectrophotometer. Column chromatography was carried out with Kieselgel 60 (70—230 or 230—400 mesh, Merck).

The following compounds were prepared by the reported methods: 4-butoxybenzenethiol,[12] 4-methylthiobenzenethiol,[12] 4-dimethylaminobenzenethiol,[13] 4-*tert*-butylbenzenethiol,[13] 5-(4-fluorophenylthiomethyl)-6-ethoxycarbonyluracil,[3] 5-(4-bromophenylthiomethyl)-6-ethoxycarbonyluracil,[3] 5-(4-butoxyphenylthiomethyl)-6-ethoxycarbonyluracil,[1] and 5-(4-methylthiophenylthiomethyl)-6-ethoxycarbonyluracil.[1]

5-(4-*tert*-Butylphenylthiomethyl)-6-ethoxycarbonyluracil (XIVe) was prepared according to the method reported by us.[3] Yield: 53.0%. mp 227—231 °C. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1740, 1710, 1650 (C=O). NMR (dimethylsulfoxide (DMSO)-d_6) δ: 1.20 (3H, t, J=7 Hz, 6-CH$_3$), 1.24 (9H, s, C(CH$_3$)$_3$), 3.97 (2H, s, 5-CH$_2$), 4.04 (2H, q, J=7 Hz, 6-CH$_2$), 7.15 (4H, s, phenyl), 10.65, 11.27 (each 1H, br s, NH). MS m/z: 362 (M$^+$). *Anal.* Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.51; H, 6.09; N, 7.78.

5-Benzyloxymethyl-1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-β-D-ribofuranosyl)uracil (III)——Silylated 5-benzyloxymethyluracil (I)[6] derived from 15.0 g (64.7 mmol) of 5-benzyloxymethyluracil was mixed with 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-ribofuranosyl chloride (II)[8] (21.7 g, 55.8 mmol) in anhydrous 1,2-dichloroethane (400 ml). The solution was cooled with ice, and SnCl$_4$ (4 ml, 34.7 mmol) in anhydrous 1,2-dichloroethane (40 ml) was added with vigorous stirring and exclusion of moisture. The mixture was stirred for 2 h at room temperature, then diluted with 1,2-dichloroethane (170 ml) 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$_2$SO$_4$) and evaporated under reduced pressure to give a slightly yellowish oil. The β-anomer (III) was separated by fractional crystallization from MeOH to yield 15.0 g (46.0%) of III; mp 143—145 °C (lit.[5] 141—142 °C).

5-Chloromethyl-1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-β-D-ribofuranosyl)uracil (IV) was prepared from III according to the method reported by Brossmer and Rohm.[5]

General Procedure for the Preparation of 5-(4-Substituted phenylthiomethyl)-1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-β-D-ribofuranosyl)uracils (Va—d)——A Typical Example: 5-(4-Bromophenylthiomethyl) Derivative (Va): Sodium metal (70 mg, 3.0 mmol) was dissolved in MeOH (80 ml) and then 4-bromobenzenethiol (0.83 g, 4.4 mmol) was added. The solution was refluxed for 1 h. The 5-chloromethyl derivative (IV) (1.5 g, 2.9 mmol) was added to the solution after it had cooled, and the mixture was stirred at room temperature for 20 h. The solvent was evaporated off under reduced pressure and the residue was chromatographed on silica gel with CHCl$_3$–EtOAc (5 : 1). The main product was recrystallized from EtOH to give 1.28 g (66.3%) of Va.

Data for the compounds (Va—d) prepared as described above are listed in Tables I and II.

General Procedure for the Preparation of 5-(4-Substituted phenylthiomethyl)-2′-deoxyuridines (VIa—d)——A Typical Example: 5-(4-Bromophenylthiomethyl) Derivative (VIa): Compound Va (1.25 g, 1.9 mmol) and K$_2$CO$_3$ (0.21 g, 1.5 mmol) were added to MeOH (90 ml), and the solution was stirred at room temperature for 2 d. The resulting solution was neutralized with Amberlite IR-120 (H$^+$-form), the resin was removed by filtration and washed with hot MeOH. The combined filtrate and washing were evaporated under reduced pressure, and the residue was extracted with anhydrous ether to yield a white solid. The solid was recrystallized from EtOH–H$_2$O to give 0.58 g (73.3%) of VIa.

Data for VIa—d prepared as described above are listed in Tables III and IV.

Reaction of the Silylated Orotates (VIIa—d) with 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (VIII)——A Typical Example: Reaction of 5-(4-Fluorophenylthiomethyl) Derivative (VIIa) with VIII: 6-Ethoxycarbonyl-5-(4-fluorophenylthiomethyl)uracil[3] (8.3 g, 25.6 mmol) was heated under reflux in hexamethyldisilazane (HMDS) (100 ml) with a catalytic quantity of ammonium sulfate under anhydrous conditions. After 5 h, the solid had dissolved, and the excess HMDS was removed under reduced pressure. The slightly yellowish residue (VIIa) thus obtained was mixed with VIII (10.3 g, 20.4 mmol) in anhydrous CH$_3$CN (200 ml). The solution was cooled with ice, and SnCl$_4$ (3.5 ml, 30.4 mmol) in anhydrous CH$_3$CN (60 ml) was added with vigorous stirring and exclusion of moisture. The yellowish solution was heated at 60 °C for 3 h, then concentrated to 50 ml, diluted with 1,2-dichloroethane (250 ml) 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$_2$SO$_4$) and evaporated under reduced pressure. The brownish foam thus obtained a mixture containing N_1,N_3-bisriboside (IXa) and N_3-riboside (Xa) (2.73 g, 17.4%). Compound IXa was purified by rechromatography (silica gel, CHCl$_3$–benzene (5 : 1)) and obtained as a white foam: yield 2.27 g (18.3%).

Data for IXa—e and Xa—e prepared as described above are listed in Tables V, VI, VII and VIII.

General Procedure for the Preparation of 5-(4-Substituted phenylthiomethyl)-6-methoxycarbonyl-3-(β-D-ribofuranosyl)uracils (XIa—e)——A Typical Example: 5-(4-Fluorophenylthiomethyl) Derivative (XIa): Sodium metal (45 mg, 2.0 mmol) was dissolved in MeOH (70 ml) and then compound Xa (1.0 g, 1.3 mmol) was added. The solution was refluxed for 30 min and neutralized with Dowex 50 (H$^+$) after it had cooled. The resin was removed by filtration and washed with hot MeOH, and the combined filtrate and washing were evaporated under reduced pressure. The residue was triturated with CHCl$_3$–H$_2$O (1 : 2) to give 0.50 g (87.6%) of XIa.

Data for XIa—e prepared as described above are listed in Tables IX and X.

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