Notes

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Aminopyrimidines and Derivatives. XXI.[1] Synthesis of 5-Acyl-(4-β-D-glycopyranosylamino)pyrimidine Derivatives as Potential Anticancer Agents

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Acetylation of 4-(*O*-acetyl-β-D-glycopyranosylamino)-6-oxo-pyrimidines (**2a**, **d**, **e**) with Ac_2O/pyridine at 80 °C gave the 6-acetoxy derivatives **3a**, **d**, **e**. Although these were also obtained by treatment with Ac_2O/H_2SO_4, prolonged reactions of **2a**—**c**, **e**—**f** gave the 5-acetyl derivatives **4a**—**c**, **e**—**f**. The Vilsmeier reaction of **2b**—**g** produced the 5-formyl derivatives **5b**—**g**, whereas **2a** gave the uracil derivative **9** under similar conditions.

Keywords——4-β-D-glycopyranosylaminopyrimidine; O-acetylation; C-acetylation; C-formylation; acyl migration; anticancer activity

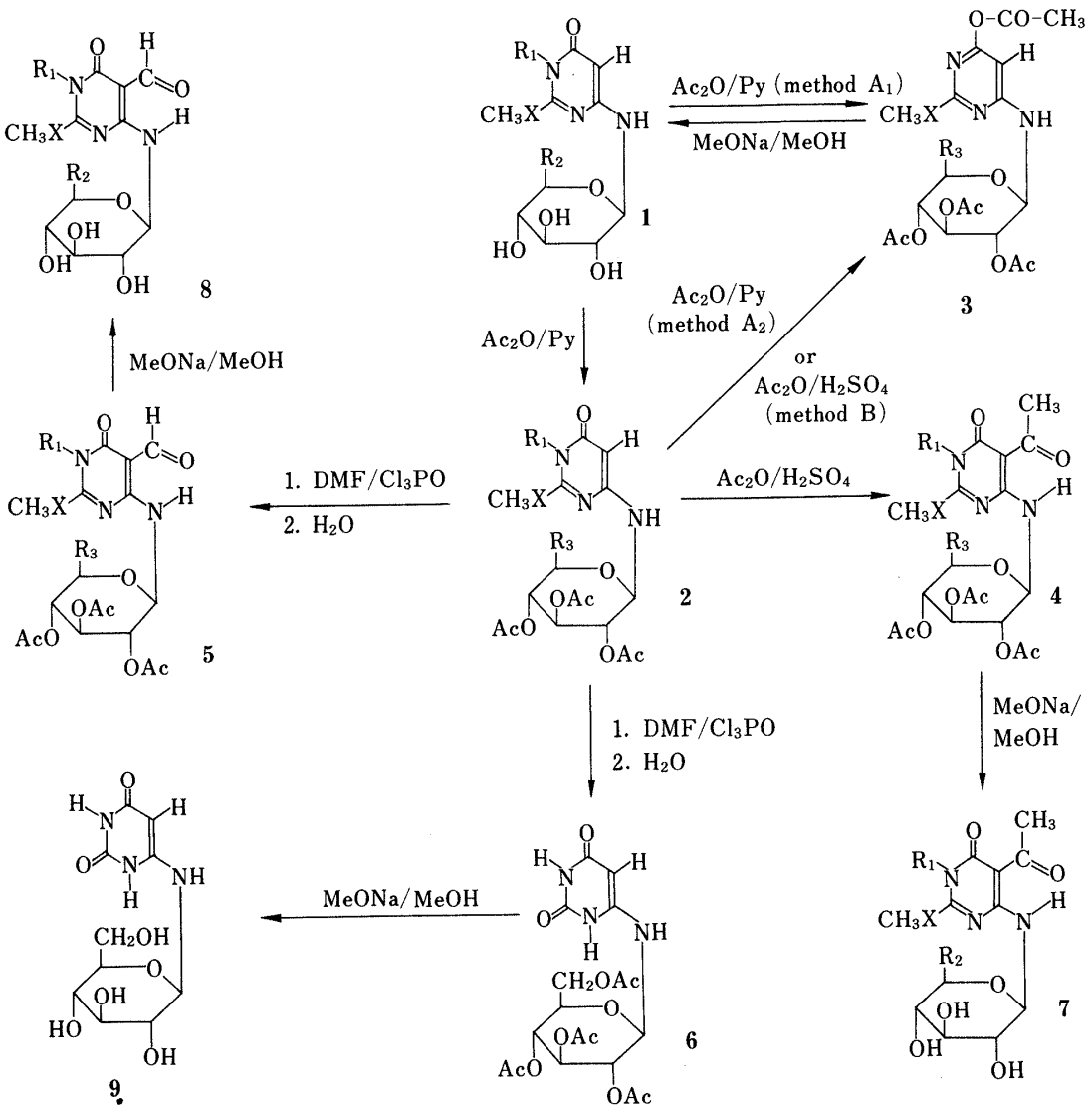
5-Substituted 4-(β-D-glycopyranosylamino)pyrimidines are of interest because of their potential biological activities[2-5] and as intermediates for the synthesis of condensed pyrimidines.[6-9] That is why we have initiated systematic investigations of the electrophilic substitution reactions at the 5-position of some 4-(β-D-glycopyranosylamino)pyrimidines, such as halogenation,[10] nitrosation,[11] acylation,[12-14] *etc.*

There have been several studies on acylation at the 1- and/or at the 3-position of uracil derivatives[15] and at the 5-position and/or at the exo amino group of 4-aminouracil derivatives[16-18]; likewise, some work has been done on the synthesis of 6-acylpyrimidine derivatives,[19] but so far, the approach *via* acylation of the enolic hydroxyl at the 6-position of 1,6-dihydro-6-oxopyrimidines derivatives has not been tried. In the present paper we report the synthesis of 6-acetoxy-4-(*O*-acetyl-β-D-glycopyranosylamino)pyrimidines (**3a**, **d**, **e**), 5-acetyl-4-(*O*-acetyl-β-D-glycopyranosylamino)pyrimidines (**4a**—**c** and **4e**—**g**), 5-formyl-4-(*O*-acetyl-β-D-glycopyranosylamino)pyrimidines (**5b**—**g**), 5-acetyl-4-(β-D-glycopyranosylamino)-pyrimidines (**7a**—**c** and **7e**—**g**), and 5-formyl-4-(β-D-glycopyranosylamino)pyrimidines (**8b**—**g**).

Results and Discussion

We have reported already that treatment of 4-β-D-glycopyranosylaminopyrimidines (**1a**—**g**) with acetic anhydride/pyridine at 25 °C gave *O*-acetyl-4-β-D-glycopyranosylamino-pyrimidines (**2a**—**g**).[20] When the reaction temperature was increased to 80 °C (method A_1), **1a**, **d**, **e** yielded **3a**, **d**, **e**. Compounds **3** were also obtained by reaction of **2a**, **d**, **e** with acetic anhydride/pyridine at 80 °C (method A_2).

The structures **3** are supported by the infrared (IR) absorption bands at 3190—3020 cm^{-1} corresponding to the C(5)-H and disappearance of the band at 1660—1650 cm^{-1}



	X	R_1	R_2	R_3		X	R_1	R_2	R_3
a	O	H	CH_2OH	CH_2OAc	**e**	S	H	CH_2OH	CH_2OAc
b	O	CH_3	H	H	**f**	S	CH_3	H	H
c	O	CH_3	CH_2OH	CH_2OAc	**g**	S	CH_3	CH_2OH	CH_2OAc
d	S	H	H	H					

Chart 1

corresponding to the C(6)=O group. In the proton magnetic resonance (^{1}H-NMR) spectra, the signal due to the N(1)H proton of **2** is not observed and the C(6)$OCOCH_3$ protons of **3** appear at δ 2.25—2.30 ppm; furthermore, the C(4)NH and C(5)H protons of **3** are more deshielded than those of **2** (by 5.65—5.70; 5.10—5.30 ppm).[13]

Compound **3a** was found to be too unstable for recrystallization.

The treatment of **2b, c, f, g** with acetic anhydride/sulfuric acid at 80 °C produced **4b, c, f, g**, whereas that of **2a, d, e** led to two types of derivatives depending on the reaction time: when the reaction time was short (method B), **3** and some unreacted **2** were isolated; when the reaction time was long, **4a, e** (**2d** produced only products of acetolysis) were obtained. This suggests that **3** are kinetically controlled products and **4** are thermodynamically controlled ones. The IR spectra display a band at 1685—1655 cm^{-1}, which is not present in those of **2**,

TABLE I. Preparation of the 5-Substituted-4-Glycopyranosylaminopyrimidine Derivatives

Compd.	Method	Reaction time	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
3a	A_1	24 h	TLC[a]	$C_{21}H_{27}N_3O_{12}$			
	A_2	8 h	TLC[a]				
	B	30 min	9				
3d	A_1	7 h	47	$C_{18}H_{23}N_3O_9S$	47.26	5.07	9.19
	A_2	3 h	57		(47.55	5.21	9.20)
	B	1.50 h	6				
3e	A_1	6 h	66	$C_{21}H_{27}N_3O_{11}S$	47.63	5.21	7.94
	A_2	1 h	46		(47.81	5.14	7.87)
	B	2 h	15				
4a		8.50 h	32	$C_{21}H_{27}N_3O_{12}$	49.12	5.30	8.18
					(48.91	5.34	8.02)
4b		2.50 h	24	$C_{19}H_{25}N_3O_{10}$	50.10	5.53	9.23
					(50.41	5.75	9.12)
4c		2 h	60	$C_{22}H_{29}N_3O_{12}$	50.09	5.54	7.97
					(50.33	5.65	7.89)
4e		12 h	46	$C_{21}H_{27}N_3O_{11}S$	47.63	5.14	7.94
					(47.90	5.29	7.87)
4f		2 h	57	$C_{19}H_{25}N_3O_9S$	48.49	5.34	8.91
					(48.54	5.50	8.65)
4g		2 h	71	$C_{22}H_{29}N_3O_{11}S$	48.61	5.38	7.73
					(48.68	5.49	7.67)
5b		15 min	73	$C_{18}H_{23}N_3O_{10}$	48.98	5.25	9.52
					(49.02	5.32	9.47)
5c		30 min	93	$C_{21}H_{27}N_3O_{12}$	49.12	5.30	8.18
					(49.30	5.20	8.10)
5d		2 h	95	$C_{17}H_{21}N_3O_9S$	46.05	4.77	9.48
					(45.72	4.76	9.53)
5e		3 h	90	$C_{20}H_{25}N_3O_{11}S$	46.60	4.89	8.15
					(46.35	4.93	8.14)
5f		30 min	99	$C_{18}H_{23}N_3O_9S$	47.26	5.07	9.19
					(47.10	5.13	9.10)
5g		15 min	92	$C_{21}H_{27}N_3O_{11}S$	47.63	5.14	7.94
					(47.61	5.18	7.84)
6		18 h	46	$C_{18}H_{23}N_3O_{11}$	47.27	5.07	9.19
					(46.57	5.18	8.95)
7a		2 h[b]	74	$C_{13}H_{19}N_3O_8$	45.22	5.55	12.17
					(45.73	5.69	11.72)
7b		1 h[c]	79	$C_{13}H_{19}N_3O_7 \cdot H_2O$	44.96	6.09	12.10
					(45.25	5.66	11.87)
7c		1 h[c]	91	$C_{14}H_{21}N_3O_8$	46.80	5.89	11.69
					(46.50	5.97	11.27)
7e		2 h[c]	89	$C_{13}H_{19}N_3O_7S$	43.21	5.30	11.63
					(42.88	5.32	11.28)
7f		1 h[d]	98	$C_{13}H_{19}N_3O_6S \cdot 1/2\,H_2O$	44.06	5.69	11.86
					(44.92	5.93	12.38)
7g		2 h[d]	77	$C_{14}H_{21}N_3O_7S \cdot H_2O$	42.74	5.89	10.68
					(43.12	5.86	10.66)
8b		35 min[c]	63	$C_{12}H_{17}N_3O_7$	45.72	5.43	13.33
					(46.03	5.53	13.59)
8c		35 min[c]	85	$C_{13}H_{19}N_3O_8 \cdot H_2O$	42.97	5.82	11.56
					(42.56	5.42	11.15)
8d		30 min[b]	99	$C_{11}H_{15}N_3O_6S$	41.64	4.76	13.24
					(41.86	4.63	13.47)
8e		1 h[b]	94	$C_{12}H_{17}N_3O_7S \cdot 2H_2O$	37.59	5.52	10.96
					(37.43	5.65	11.03)
8f		15 min[d]	64	$C_{12}H_{17}N_3O_6S$	43.50	5.17	12.68
					(43.47	5.30	12.81)
8g		15 min[d]	70	$C_{13}H_{19}N_3O_7S \cdot 1/2\,H_2O$	42.16	5.44	11.35
					(42.23	5.94	11.39)
9		30 min[b]	70	$C_{10}H_{15}N_3O_7 \cdot H_2O$	39.09	5.58	13.68
					(39.30	5.61	13.75)

a) The compound was detected by TLC. *b*) The solution was neutralized with acetic acid and a precipitate appeared. *c*) The compound precipitated in the reaction mixture. *d*) The reaction occurred in suspension.

due to the C=O carbonyl group of the C(5)$COCH_3$ group of **4**. In the ^{1}H-NMR spectra, the signal corresponding to the C(5)H proton of **2** is not present and the C(5)$COCH_3$ protons of **4** resonate at δ 2.50 ppm; on the other hand, the hydrogen bond between the 4-NH and the carbonyl oxygen atom of the acetyl group at the 5-position produces a downfield shift of C(4)NH (2.70—3.40 ppm).

The treatment of **3** and **4** with sodium methoxide in methanol at 25 °C gave **1** and **7**, respectively.

Treatment of **2**, with formic acetic anhydride[21] led to a complex mixture of products, from which the formyl derivatives were isolated as minor products,[14] whereas the Vilsmeier–Haack reaction according to the Delia–Otteman procedure afforded **5b—g** (**2a** did not give the corresponding formyl derivative but gave 1,2,3,6-tetrahydro-2,6-dioxo-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylamino)pyrimidine **6**, in high yields without any formation of 6-Cl derivatives.[22] The structures of **5** were supported by the analytical and spectral data. The IR spectra show a band at 1695—1660 cm^{-1}, which does not appear in those of **2**, due to the C(5)CHO of **5**. The ^{1}H-NMR spectra do not show the signal corresponding to the C(5)H proton of **2** at δ 5.05—5.25 ppm, but display a signal at δ 9.80—10.00 ppm characteristic of formyl protons.

The treatment of **5** and **6** with sodium methoxide in methanol at 25 °C produced **8b—g** and 1,2,3,6-tetrahydro-2,6-dioxo-4-*β*-D-glucopyranosylaminopyrimidine (**9**), respectively.

Compounds **1**, **7**, **8** and **9** have been tested *in vivo* as inhibitors of the L1210 leukemia at the National Cancer Institute (NCI) according to standard methods. The *T*/*C* percent values ranged between 87 (**8e**) and 105 (**1a**, **b**, **f**) and none of the products showed significant anticancer activity.

Experimental

The melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. The elementary analyses were performed by the Microanalysis Service of the University of Extremadura. The specific optical rotation were measured on a Perkin–Elmer 141 polarimeter. The ultraviolet (UV) spectra were taken on a Beckman Visible-UV 25 spectrophotometer. The IR spectra were obtained using a Beckman IR 4250 spectrophotometer. The ^{1}H-NMR spectra were recorded on a Hitachi Perkin–Elmer R-600 spectrophotometer using tetramethylsilane as internal standard. Thin layer chromatography (TLC) was performed on Merck Silica gel 60 G using chloroform : petroleum ether : ethanol (16 : 2 : 1) as the developer.

General Procedure for the Synthesis of 3a, d, e——Method A: Compound **1**[20] (method A_1) or **2**[20] (method A_2) (2 mmol) was suspended in anhydrous pyridine (20 ml) and Ac_2O (50 ml) was added. The suspension was heated at 80 °C and stirred for an appropriate time (Table I). The solution obtained was poured on crushed ice and left for 24 h. The precipitate was filtered off and washed with cold H_2O. The product obtained was crystallized from EtOH to give the following products.

6-Acetoxy-2-methylthio-4-(2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosylamino)pyrimidine (**3d**): mp 185—186 °C. $[\alpha]_D^{20}$ +20.0° (*c* = 1, $CHCl_3$). UV λ_{max}^{MeOH} nm (*ε*): 220 (20900), 230 (24200), 253 (12900), 268 (8900), 279 (7700). IR ν_{max}^{KBr} cm^{-1}: 3180, 3120, 3080 (C–H), 1785, 1755, 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.00 (9H, s, $OCOCH_3$), 2.30 (3H, s, C(6)–$OCOCH_3$), 2.50 (3H, s, SCH_3), 5.20—5.75 (1H, m, $J_{1',2'}$ = 9.2 Hz, H-1'), 6.00 (1H, s, H-5), 6.30 (1H, d, *J* = 9.0 Hz, N–H).

6-Acetoxy-2-methylthio-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylamino)pyrimidine (**3e**): mp 158 °C. $[\alpha]_D^{20}$ −18.0° (*c* = 1, $CHCl_3$). UV λ_{max}^{MeOH} nm (*ε*): 220 (17400), 230 (18700), 253 (10900), 268 (7800), 279 (6000). IR ν_{max}^{KBr} cm^{-1}: 3190, 3100, 3020 (C–H), 1780, 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (12H, s, $OCOCH_3$), 2.30 (3H, s, C(6)–$OCOCH_3$), 2.50 (3H, s, SCH_3), 5.25—5.60 (1H, m, $J_{1',2'}$ = 9.2 Hz, H-1'), 5.90 (1H, d, *J* = 9.2 Hz, N–H), 6.00 (1H, s, H-5).

Method B: H_2SO_4 (1 drop) was added to Ac_2O (10 ml) and the solution was heated at 80 °C. Then 2 mmol of **2a**, **d**, **e** was added and the suspension was stirred for an appropriate time (Table I). The solution obtained was poured on crushed ice and left for 24 h. The precipitate was filtered off and washed with cold H_2O. The product obtained was crystallized from EtOH (except **3a**).

6-Acetoxy-2-methoxy-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylamino)pyrimidine (**3a**): mp 118 °C. IR ν_{max}^{KBr} cm^{-1}: 3190, 3120, 3100 (C–H), 1750 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.00 (12H, s, $OCOCH_3$), 2.25 (3H, s, C(6)–$OCOCH_3$), 3.90 (3H, s, OCH_3), 5.35—5.65 (1H, m, $J_{1',2'}$ = 9.2 Hz, H-1'), 5.90 (1H, d, *J* = 8.2 Hz, N–H), 5.95 (1H, s,

H-5).

De-*O*-acetylation of 3d and 3e——Compound **3** (1 mmol) was suspended in MeOH (12.5 ml), an equimolar amount of MeONa was added, and the suspension was stirred at 25 °C for an appropriate time (30 min for **3d**, 1 h for **3e**). The solution obtained was neutralized with Amberlite IR-120 (H^+) in methanol and the solvent was remove under reduced pressure. The residue was treated with boiling EtOH to give **1d** and **1e** in 79—80% yield.

General Procedure for the Synthesis of 4a—c and 4e—g——H_2SO_4 (1 drop) was added to Ac_2O (10 ml) and the solution was heated at 80 °C. Compound **2** (2 mmol) was added just after this and the suspension was stirred for an appropriate time (Table I). The solution obtained was poured on crushed ice and left for 24 h. The precipitate was filtered off and washed with cold H_2O. The product obtained was crystallized from EtOH to give the following compounds.

5-Acetyl-1,6-dihydro-2-methoxy-6-oxo-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)pyrimidine (**4a**): mp 186 °C. $[\alpha]_D^{20}$ −2.5° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 225 (35100), 261 (6200), 268 (6800), 291 (10300). IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O, $OCOCH_3$), 1655 (C=O, C(5)–$COCH_3$), 1630 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (12H, s, $OCOCH_3$), 2.50 (3H, s, C(5)–$COCH_3$), 4.00 (3H, s, OCH_3), 5.70—6.20 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 11.10 (1H, d, $J=8.2$ Hz, C(4)-NH), 12.50 (1H, s br, N(1)-H).

5-Acetyl-1,6-dihydro-1-methyl-2-methoxy-6-oxo-4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosylamino)pyrimidine (**4b**): mp 214 °C. $[\alpha]_D^{20}$ −5.5° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 226 (39000), 261 (7100), 269 (6900), 291 (11100). IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O, $OCOCH_3$), 1685 (C=O, C(5)–$COCH_3$), 1625 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (9H, s, $OCOCH_3$), 2.50 (3H, s, C(5)–$COCH_3$), 3.20 (3H, s, N(1)-CH_3), 4.10 (3H, s, OCH_3), 5.60—6.00 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 11.00 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Acetyl-1,6-dihydro-1-methyl-2-methoxy-6-oxo-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)pyrimidine (**4c**): mp 200 °C. $[\alpha]_D^{20}$ +2.5° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 226 (38500), 261 (7100), 269 (6900), 291 (11300). IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O, $OCOCH_3$), 1685 (C=O, C(5)–$COCH_3$), 1625 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (12H, s, $OCOCH_3$), 2.50 (3H, s, C(5)–$COCH_3$), 3.20 (3H, s, N(1)-CH_3), 4.10 (3H, s, OCH_3), 5.85—6.10 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 10.95 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Acetyl-1,6-dihydro-2-methylthio-6-oxo-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)pyrimidine (**4e**): mp 241 °C. $[\alpha]_D^{20}$ −11.3° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 227 (33500), 244 (13300), 268 (7900), 308 (14400). IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O, $OCOCH_3$), 1655 (C=O, C(5)–$COCH_3$), 1625 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (12H, s, $OCOCH_3$), 2.50 (3H, s, C(5)–$COCH_3$), 2.60 (3H, s, SCH_3), 5.70—6.10 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 11.00 (1H, d, $J=8.2$ Hz, C(4)-NH), 12.50 (1H, s br, N(1)-H).

5-Acetyl-1,6-dihydro-1-methyl-2-methylthio-6-oxo-4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosylamino)pyrimidine (**4f**): mp 235 °C. $[\alpha]_D^{20}$ +4.9° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 228 (30500), 245 (shoulder), 269 (7100), 309 (12800). IR ν_{max}^{KBr} cm^{-1}: 1760, 1740 (C=O, $OCOCH_3$), 1685 (C=O, C(5)–$COCH_3$), 1625 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (9H, s, $OCOCH_3$), 2.50 (3H, s, C(5)–$COCH_3$), 2.60 (3H, s, SCH_3), 3.20 (3H, s, N(1)-CH_3), 5.50—6.00 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 10.80 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Acetyl-1,6-dihydro-1-methyl-2-methylthio-6-oxo-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-pyrimidine (**4g**): mp 243 °C. $[\alpha]_D^{20}$ +18.0° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 228 (33700), 245 (shoulder), 269 (8600), 310 (14200). IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O, $OCOCH_3$), 1680 (C=O, C(5)–$COCH_3$), 1625 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (12H, s, $OCOCH_3$), 2.50 (3H, s, C(5)–$COCH_3$), 2.60 (3H, s, SCH_3), 3.20 (3H, s, N(1)-CH_3), 5.40—5.90 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 10.80 (1H, d, $J=8.2$ Hz, C(4)-NH).

General Procedure for the Synthesis of 7a—c and 7e—g——Compound **4** was treated in a manner similar to that described for 3 for an appropriate time (Table I). The crude product was crystallized from H_2O to give the following products.

5-Acetyl-1,6-dihydro-2-methoxy-6-oxo-4-(β-D-glucopyranosylamino)pyrimidine (**7a**): mp 280 °C (dec.). $[\alpha]_D^{20}$ +26.4° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 226 (35600), 289 (10700). IR ν_{max}^{KBr} cm^{-1}: 1685 (C=O, C(5)–$COCH_3$), 1670 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.50 (3H, s, C(5)–$COCH_3$), 4.00 (3H, s, OCH_3), 4.90—5.70 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 11.10 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Acetyl-1,6-dihidro-1-methyl-2-methoxy-6-oxo-4-(β-D-xylopyranosylamino)pyrimidine (**7b**): mp 206 °C. $[\alpha]_D^{20}$ +32.1° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 227 (38600), 289 (11400). IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O, C(5)–$COCH_3$), 1615 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.50 (3H, s, C(5)–$COCH_3$), 3.20 (3H, s, N(1)-CH_3), 4.00 (3H, s, OCH_3), 5.20—5.50 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 11.00 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Acetyl-1,6-dihydro-1-methyl-2-methoxy-6-oxo-4-(β-D-glucopyranosylamino)pyrimidine (**7c**): mp 227 °C. $[\alpha]_D^{20}$ +22.2° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 228 (41400), 289 (12300). IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O, C(5)–$COCH_3$), 1630 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.50 (3H, s, C(5)–$COCH_3$), 3.20 (3H, s, N(1)-CH_3), 4.00 (3H, s, OCH_3), 5.10—5.40 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 10.90 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Acetyl-1,6-dihydro-2-methylthio-6-oxo-4-(β-D-glucopyranosylamino)pyrimidine (**7e**): mp 288 °C. $[\alpha]_D^{20}$ +13.0° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 228 (26300), 244 (11000), 274 (5900), 307 (13600). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O, C(5)–$COCH_3$), 1610 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.50 (6H, s, C(5)–$COCH_3$, SCH_3), 4.90—5.50 (1H, m, $J_{1',2'}=8.2$ Hz, H-1′), 11.00 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Acetyl-1,6-dihydro-1-methyl-2-methylthio-6-oxo-4-(β-D-xylopyranosylamino)pyrimidine (**7f**): mp 235—

236 °C. $[\alpha]_D^{20}$ +24.0° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 229 (32400), 244 (shoulder), 279 (shuolder), 306 (16000). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O, C(5)–$COCH_3$), 1610 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.50 (3H, s, C(5)–$COCH_3$), 2.60 (3H, s, SCH_3), 3.30 (3H, s, N(1)-CH_3), 4.80—5.50 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 10.80 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Acetyl-1,6-dihydro-1-methyl-2-methylthio-6-oxo-4-(β-D-glucopyranosylamino)pyrimidine (**7g**): mp 272 °C. $[\alpha]_D^{20}$ +8.8° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 229 (31300), 244 (shoulder), 278 (shoulder), 304 (13300). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O, C(5)–$COCH_3$), 1610 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.50 (3H, s, C(5)–$COCH_3$), 2.60 (3H, s, SCH_3), 3.30 (3H, s, N(1)-CH_3), 4.80—5.50 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 10.80 (1H, d, $J=8.2$ Hz, C(4)-NH).

General Procedure for the Synthesis of 5b—g and 6——$POCl_3$ (1.25 ml) was dissolved in dry $HCONMe_2$ (2.5 ml) below 0 °C and the solution obtained was stirred for 15 min. Compound **2** (12 mmol) in dry $HCONMe_2$ (20 ml) was added and the mixture was stirred at 25 °C for an appropriate time (Table I). The solution obtained was poured on crushed ice and left for 24 h. The precipitate was filtered off and washed with cold H_2O. The product obtained was crystallized from EtOH to give the following products.

5-Formyl-1,6-dihydro-1-methyl-2-methoxy-6-oxo-4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosylamino)pyrimidine (**5b**): mp 208—212 °C. $[\alpha]_D^{20}$ +0.9° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 229 (35900), 262 (6000), 269 (4900), 299 (12100). IR ν_{max}^{KBr} cm^{-1}: 1755 (C=O, $OCOCH_3$), 1685 (C=O, C(5)–CHO), 1645 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00—2.10 (9H, s, $OCOCH_3$), 3.20 (3H, s, N(1)-CH_3), 4.10 (3H, s, OCH_3), 5.70—6.00 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 9.90 (1H, s, CHO), 10.00 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Formyl-1,6-dihydro-1-methyl-2-methoxy-6-oxo-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)pyrimidine (**5c**): mp 181—182 °C. $[\alpha]_D^{20}$ +13.2° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 228 (33200), 262 (5500), 267 (4500), 299 (10100). IR ν_{max}^{KBr} cm^{-1}: 1760, 1730 (C=O, $OCOCH_3$), 1695 (C=O, C(5)-CHO), 1640 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (12H, s, $OCOCH_3$), 3.20 (3H, s, N(1)-CH_3), 4.10 (3H, s, OCH_3), 5.70—6.10 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 9.90 (1H, s, CHO), 10.00 (1H, s, d, $J=8.2$ Hz, C(4)-NH).

5-Formyl-1,6-dihydro-2-methylthio-6-oxo-4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosylamino)pyrimidine (**5d**): mp 224—230 °C. $[\alpha]_D^{20}$ +5.2° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 230 (29000), 250 (9500), 269 (7100), 273 (shoulder), 317 (23500). IR ν_{max}^{KBr} cm^{-1}: 1755 (C=O, $OCOCH_3$), 1675 (C=O, C(5)-CHO), 1645 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00—2.10 (9H, s, $OCOCH_3$), 2.60 (3H, s, SCH_3), 5.60—6.10 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 9.90 (1H, s, CHO), 10.10 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Formyl-1,6-dihydro-2-methylthio-6-oxo-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)pyrimidine (**5e**): mp 235—242 °C (dec.). $[\alpha]_D^{20}$ −12.6° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 230 (32300), 250 (10600), 269 (8000), 273 (shoulder), 317 (15200). IR ν_{max}^{KBr} cm^{-1}: 1755 (C=O, $OCOCH_3$), 1660 (C=O, C(5)-CHO), 1650 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (12H, s, $OCOCH_3$), 2.60 (3H, s, SCH_3), 5.70—6.20 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 9.80 (1H, s, CHO), 10.00 (1H, d, $J=8.2$ Hz, C(4)-NH), 12.70 (1H, s br, N(1)-H).

5-Formyl-1,6-dihydro-1-methyl-2-methylthio-6-oxo-4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosylamino)pyrimidine (**5f**): mp 197—198 °C. $[\alpha]_D^{20}$ +17.4° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 230 (26300), 248 (9200), 269 (5600), 279 (6300), 319 (12100). IR ν_{max}^{KBr} cm^{-1}: 1765, 1745 (C=O, $OCOCH_3$), 1680 (C=O, C(5)-CHO), 1645 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00—2.10 (9H, s, $OCOCH_3$), 2.60 (3H, s, SCH_3), 3.30 (3H, s, N(1)-CH_3), 5.60—6.10 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 9.90 (1H, s, CHO), 9.90 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Formyl-1,6-dihydro-1-methyl-2-methylthio-6-oxo-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-pyrimidine (**5g**): mp 215—216 °C. $[\alpha]_D^{20}$ −7.30° ($c=1$, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 230 (28300), 248 (9700), 269 (6200), 278 (6700), 317 (13000). IR ν_{max}^{KBr} cm^{-1}: 1765, 1735 (C=O, $OCOCH_3$), 1685 (C=O, C(5)-CHO), 1650 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (12H, s, $OCOCH_3$), 2.70 (3H, s, SCH_3), 3.40 (3H, s, N(1)-CH_3), 5.80—6.30 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 9.90 (1H, d, $J=8.2$ Hz, C(4)-NH), 10.00 (1H, s, CHO).

1,2,3,6-Tetrahydro-2,6-dioxo-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)pyrimidine (**6**): mp 304 °C (dec.). $[\alpha]_D^{20}$ +21.7° ($c=1$, Me_2SO). UV λ_{max}^{MeOH} nm (ε): 263 (20700), 266 (shoulder). IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O, $OCOCH_3$), 1750 (C=O, C(2)=O), 1605 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.00 (12H, s, $OCOCH_3$), 5.05 (1H, s, H-5), 5.30—5.70 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 6.90 (1H, d, $J=8.2$ Hz, C(4)-NH), 10.10 (1H, s br, N(3)-H), 10.50 (1H, s br, N(1)-H).

General Procedure for the Synthesis of 8b—g and 9——Compound **5** or **6** (2 mmol) was treated in a manner similar to that described for **3** for an appropriate time (Table I). The crude product was crystallized from H_2O to give the following products.

5-Formyl-1,6-dihydro-1-methyl-2-methoxy-6-oxo-4-(β-D-xylopyranosylamino)pyrimidine (**8b**): mp 218—219 °C (dec.). $[\alpha]_D^{20}$ +31.5° ($c=1$, $CHCl_3$). UV $\lambda_{max}^{H_2O}$ nm (ε): 229 (34600), 266 (4400), 296 (11000). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O, C(5)-CHO), 1640 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 3.20 (3H, s, N(1)-CH_3), 4.10 (3H, s, OCH_3), 4.90—5.80 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 9.90 (1H, s, CHO), 10.10 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Formyl-1,6-dihydro-1-methyl-2-methoxy-6-oxo-4-(β-D-glucopyranosylamino)pyrimidine (**8c**): mp 195—197 °C. $[\alpha]_D^{20}$ +32.2° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 229 (36100), 266 (4600), 296 (11300). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O, C(5)–CHO, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 3.20 (3H, s, N(1)-CH_3), 4.10 (3H, s, OCH_3), 5.20—5.50 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 9.90 (1H, s, CHO), 10.00 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Formyl-1,6-dihydro-2-methylthio-6-oxo-4-(β-D-xylopyranosylamino)pyrimidine (**8d**): mp 270 °C (dec.). $[\alpha]_D^{20}$

+35.2° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 231 (26800), 249 (8700), 276 (7000), 314 (15200). IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O, C(5)-CHO), 1635 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.6 (3H, s, S-CH_3), 4.90—5.70 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 10.00 (1H, s, CHO), 10.20 (1H, d, $J=8.2$ Hz, C(4)-NH), 12.60 (1H, s br, N(1)-H).

5-Formyl-1,6-dihydro-2-methylthio-6-oxo-4-(β-D-glucopyranosylamino)pyrimidine (**8e**): mp 280 °C (dec.). $[\alpha]_D^{20}$ +20.7° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 231 (26400), 248 (8600), 276 (6900), 314 (14800). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O, C(5)-CHO), 1640 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.60 (3H, s, SCH_3), 5.30—5.60 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 10.00 (1H, s, CHO), 10.10 (1H, s, $J=8.2$ Hz, C(4)-NH), 12.60 (1H, s br, N(1)-H).

5-Formyl-1,6-dihydro-1-methyl-2-methylthio-6-oxo-4-(β-D-xylopyranosylamino)pyrimidine (**8f**): mp 267 °C (dec.). $[\alpha]_D^{20}$ +32.0° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 231 (26100), 249 (6600), 283 (6900), 312 (11300). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O, C(5)-CHO), 1640 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.60 (3H, s, SCH_3), 3.20 (3H, s, N(1)-CH_3), 5.00—5.60 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 10.00 (1H, s, CHO), 10.00 (1H, d, $J=8.2$ Hz, C(4)-NH).

5-Formyl-1,6-dihydro-1-methyl-2-methylthio-6-oxo-4-(β-D-glucopyranosylamino)pyrimidine (**8g**): mp 238—239 °C (dec.). $[\alpha]_D^{20}$ +19.7° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 231 (25700), 248 (7400), 282 (7000), 313 (12500). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O, C(5)-CHO, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 2.60 (3H, s, SCH_3), 3.20 (3H, s, N(1)-CH_3), 5.30—5.50 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 10.00 (1H, s, CHO), 10.00 (1H, d, $J=8.2$ Hz, C(4)-NH).

1,2,3,6-Tetrahydro-2,6-dioxo-4-(β-D-glucopyranosylamino)pyrimidine (**9**): mp 250 °C (dec.). $[\alpha]_D^{20}$ −52.3° ($c=1$, Me_2SO). UV $\lambda_{max}^{H_2O}$ nm (ε): 266 (20400). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O, C(2)=O), 1630 (C=O, C(6)=O). ^{1}H-NMR (Me_2SO-d_6) δ: 4.70 (1H, s, H-5), 4.80—5.50 (1H, m, $J_{1',2'}=8.2$ Hz, H-1'), 6.80 (1H, d, $J=8.2$ Hz, C(4)-NH), 10.00 (1H, s br, N(3)-H).

***In Vivo* Antitumor Activity of 1, 7, 8 and 9 against L1210 Leukemia**——The tests were done by the NCl according to the protocol described in instruction 14. The *L*1210 leukemia was implanted into CDF_1 mice and each mouse was inoculated once at various dose levels, and observed for 20 d. The result evaluated as $\%T/C$=(median survival time (MST) treated/MST control)×100, and a compound is considered active if $\%T/C$ exceed 125.

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References and Notes

1) Part XX: M. Rodriguez, C. Rodriguez, M. Melgarejo, R. Asenjo, M. Nogueras and A. Sánchez, *Nucleosides and Nucleotides*, in press.
2) T. K. Bradshaw and D. W. Hutchinson, *Chem. Soc. Rev.*, **6**, 43 (1977).
3) J. L. Rideout, D. W. Henry and L. M. Beachan (eds.), "Nucleosides, Nucleotides and Their Biological Applications," Academic Press, New York, 1983.
4) K. A. Watanabe, T. L. Su, K. W. Pankiewicz and K. Harada, *Heterocycles*, **21**, 289 (1984).
5) R. M. Ottenbrite and G. B. Butler (eds.), "Anticancer and Interferon Agents," Vol. 24, Dekker, New York, 1984.
6) J. Baddiley, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, **1943**, 551.
7) W. Pfleiderer and E. Bühler, *Chem. Ber.*, **99**, 3022 (1966).
8) M. Nogueras, "Thesis," University of Granada, Granada, 1983.
9) A. Sánchez, C. Rodriguez, M. Rodriguez, M. Nogueras, M. Melgarejo and R. Asenjo, Heterocycles, **22**, 1555 (1984).
10) R. Asenjo, M. Melgarejo, J. Negrillo, M. Nogueras, M. Rodriguez, C. Rodriguez and A. Sánchez, Abstrácts of Papers, XX Reunión Bienal de la Real Sociedad Española de Química, Castellón, September 1984, pp. 26—47.
11) M. Nogueras, A. Sánchez, R. Asenjo, M. Melgarejo and C. Rodriguez, *An. Quím.* (*C*), **80**, 234 (1984).
12) A. Sánchez, C. Rodriguez, M. Rodriguez, M. Nogueras, J. Negrillo, M. Melgarejo and R. Asenjo, Abstracts of Papers, XX. Reuniòn Bienal de la Real Sociedad Española de Química, Castellón, September 1984, pp. 26—46.
13) A. Sánchez, M. Nogueras, J. Colmenero, R. Asenjo and M. Melgarejo, *Heterocycles*, **23**, 1961 (1985).
14) A. Sánchez, M. Nogueras, J. Negrillo, L. Gonzalez, M. Melgarejo and C. Rodriguez, *Ars Pharmaceutica*, **XXVII**, 199 (1986).
15) K. A. Cruickshank, J. Jiricny and C. B. Reese, *Tetrahedron Lett.*, **25**, 681 (1984).
16) W. Pfleiderer and G. Strauss, *Ann.*, **612**, 173 (1958).
17) J. L. Bernier, A. Lefebvre, J. P. Henichart, R. Houssin and Ch. Lespagnol, *Bull. Soc. Chim. Fr.*, **3—4**, 619 (1976).
18) J. L. Bernier, J. P. Henichart, V. Marín, C. Trentesaux and J. C. Jardillier, *J. Med. Chem.*, **28**, 497 (1985).
19) E. Ziegler, A. Argyrides and W. Steiger, *Naturforsch.*, **27**, 1169 (1972).
20) R. Asenjo, M. Melgarejo, C. Rodriguez, M. Nogueras and A. Sánchez, *An. Quím.* (*C*), **79**, 417 (1983).

21) I. Muramatsu, M. Murakami, T. Yoneda and A. Hagitani, *Bull. Chem. Soc. Jpn.*, **38**, 244 (1965).
22) T. J. Delia and R. Otteman, *Heterocycles*, **20**, 1805 (1983).
23) R. O. C. Norman, "Principles of Organic Synthesis," 2nd ed., Chapman and Hall, London, 1978, pp. 397—398.
24) O. Meth-Cohn and B. Tarnowski, "Advances in Heterocycles Chemistry," Vol. 31, ed. by A. R. Katrizky, Academic Press, New York, 1982, p. 207.