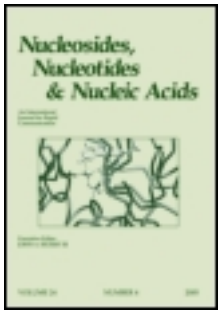


Nucleosides and Nucleotides
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn19

Selective Synthesis of 6-Ribo- (and Xylo) Pyrano and Furano Aminopyrimidines[1]. Anticancer and Anti-AIDS Activities

M. Nogueras [a], J. Cobo [a], M. L. Quijano [a], M. Melguizo [a], A. Sánchez [a] & M. Melgarejo [b]

[a] Dpto. Química Orgánica, Facultad de Ciencias Experimentales, Universidad de Jaén, 23071, JAEN, SPAIN

[b] Dpto. Química Orgánica, Facultad de Farmacia, Universidad de Granada, 18071, GRANADA, SPAIN

Published online: 23 Sep 2006.

To cite this article: M. Nogueras, J. Cobo, M. L. Quijano, M. Melguizo, A. Sánchez & M. Melgarejo (1994) Selective Synthesis of 6-Ribo- (and Xylo) Pyrano and Furano Aminopyrimidines[1]. Anticancer and Anti-AIDS Activities, Nucleosides and Nucleotides, 13:1-3, 447-457, DOI: 10.1080/15257779408013254

To link to this article: http://dx.doi.org/10.1080/15257779408013254

NUCLEOSIDES & NUCLEOTIDES, 13(1-3), 447-457 (1994)

SELECTIVE SYNTHESIS OF 6-RIBO- (AND XYLO) PYRANO AND FURANO AMINOPYRIMIDINES.[1] ANTICANCER AND ANTI-AIDS ACTIVITIES.[#]

M. Nogueras[*,a], J. Cobo[a], M.L. Quijano[a], M. Melguizo[a],
A. Sánchez[a] and M. Melgarejo[b].

[a]Dpto. Química Orgánica, Facultad de Ciencias Experimentales. Universidad de Jaén. 23071 JAEN. SPAIN.
[b]Dpto. Química Orgánica, Facultad de Farmacia. Universidad de Granada. 18071. GRANADA. SPAIN

Abstract: The synthesis and the anticancer and anti-AIDS activity of some 6-ribo (and xylo) pyrano and furano aminopyrimidines have been carried out. Isomerization to ribopyranose has been observed when per-O-acyl ribofuranoses were deprotected under basic medium.

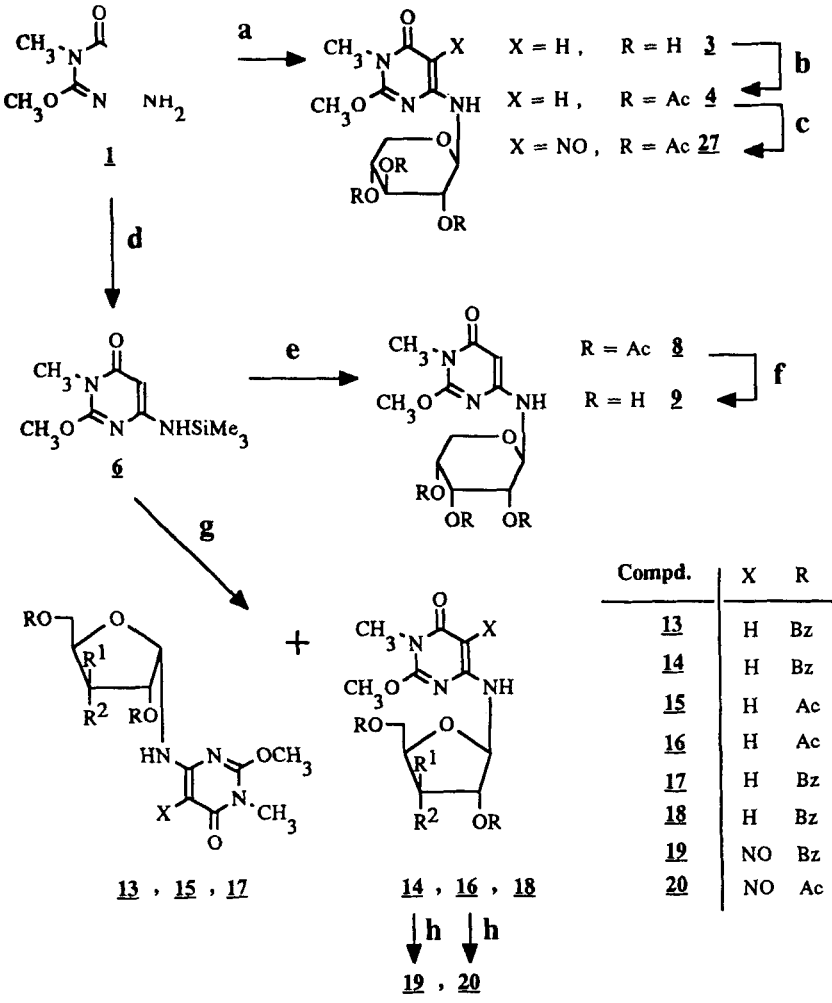
In previous papers, we have described glycosidation of several 6-aminopyrimidines.[2] In all these reactions only β-D-glycopyranosides were obtained. Such glycopyranosyl derivatives showed to be appropriate intermediates in the synthesis of other nucleoside analogues and they were tested against HIV and several tumours.[3]

As part of our programme of research on the synthesis and biological activity of these types of compounds, we became interested in the synthesis of the corresponding glycofuranosyl nucleosides analogues to the above glycopyranosides in order to study their anticancer and anti-HIV activities.

Reaction of the 6-aminopyrimidine **1** with molar amount of D-xylose, **2**, and acetic acid in ethanol gave 2-methoxy-3-methyl-6-β-D-xylopyranosylamino pyrimidin-4(3H)one **3** (49%). The configuration of **3** was evidenced from the ^{1}H-NMR spectrum[4] and studying some of its derivatives such as **4**[2,5] (Scheme I) (Tables I and II). The β-anomeric configuration shown for the pyranoside **3** was readily deduced from the trans-diaxial coupling (>8 Hz) observed between H-1' and H-2' in the ^{1}H-NMR spectra.

Under the same conditions, reaction of **1** with D-ribose, **5**, led to a mixture, probably of 6-β and 6-α-D-ribopyranosides and 6-β and 6-α-D-ribofuranosides. Due to its complexity, this mixture was unable to be resolved.

[#]Dedicated to the memory of Professor R.K. Robins, U.S.A



Compd.	X	R	R^1	R^2
13	H	Bz	H	OBz
14	H	Bz	H	OBz
15	H	Ac	H	OAc
16	H	Ac	H	OAc
17	H	Bz	OBz	H
18	H	Bz	OBz	H
19	NO	Bz	H	OBz
20	NO	Ac	H	OAc

a: D-xylose (2), EtOH/AcOH, reflux; **b**: Ac_2O/Pyridine, r.t.; **c**:$NaNO_2$/AcOH; **d**: HMDS, $(NH_4)_2SO_4$, reflux; **e**: Per-O-acetylribopyranose (7), CH_3CN, $SnCl_4$ (1.5 eq.), r.t.; **f**: NH_3/MeOH, r.t.; **g**: 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose (10), or 1,2,3,5-tetra-O-acetyl-ß-D-ribofuranose (11), or 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-ribofuranose (12), CH_3CN, $SnCl_4$ (1.5 eq.), r.t.; **h**: $NaNO_2$/AcOH.

SCHEME I

Table I.- Analytical and UV spectroscopic data.

Comp.	Yield (%)	MP (°C)	$[\alpha]_D^{20}$ (c=1) Solvent	Molecular Formula[a]	UV λ_{max} (ϵ) Solvent
3	49	238-9(d)	-20° H_2O	$C_{11}H_{17}N_3O_6$	266 (15600) 212 (25100) H_2O
6	92	133-5	---	$C_9H_{17}N_3O_2Si$	268 $CHCl_3$
8	29	201-2	+45.6° $CHCl_3$	$C_{17}H_{23}N_3O_9$	264 (13600) 221 (12800) MeOH
9	80	110-2	-10.7° H_2O	$C_{11}H_{17}N_3O_6 \cdot 2H_2O$	269 (15500) 216 (27800) H_2O
14	80	174-6	-26° $CHCl_3$	$C_{32}H_{28}N_3O_9$	266 (13000) 228 (33700) MeOH
16	49	121	-37.1° $CHCl_3$	$C_{17}H_{23}N_3O_9$	266 (11800) 222 (11800) MeOH
24	34	232-4(d)	-18.4° H_2O	$C_{11}H_{17}N_7O_6$	261 (12400) 213 (24900) H_2O
27	83	148-50(d)	+0.0° DMSO	$C_{17}H_{22}N_4O_{10}$	603 (59) 336 (12800) 302 Sh 229 (18200) MeOH

[a]Satisfactory analytical data for C, H and N were obtained for all the new crystalline solids.

The ribopyranoside analogue to **3** was prepared under the Vorbruggen's conditions[6], by treatment of **1** with hexamethyldisilazane (HMDS) and $(NH_4)_2SO_4$ affording **6** as a crystalline solid, and subsequent reaction of this derivative with per-O-acetylribopyranose, **7**. Deacetylation of intermediate **8** with NH_3/MeOH led to **9** in 80% yield (Scheme I) (Tables I and II).

Preparation of furanoside analogues of 3 and 9 was carried out under the same conditions by reaction of **6** with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose **10**, 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose **11** and 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-ribofuranose **12**.[7] In all these cases, mixtures of α and β anomers were obtained (Scheme I, Table I). Use of various quantities of catalyst[8] or change of solvent ($ClCH_2CH_2Cl$ instead of CH_3CN) did not produce improvement of these results.

Table II.- ^{1}H- and ^{13}C-NMR data.

Comp.	Solvent	$\delta_{H\text{-}1'}$[a]	$J_{1',2'}$(Hz)	δ_{NH}[b]	$J_{NH,1'}$(Hz)	$\delta_{C\text{-}1'}$
3	DMSO-d_6 D_2O	4.60, m 5.05, d	--- 9.0	7.25, d ---	9.0 ---	--- ---
4	$CDCl_3$	5.35, m	---	5.95, d	9.0	81.1
6	$CDCl_3$ DMSO-d_6	--- ---	--- ---	4.35, s 6.54, s	--- ---	--- ---
8	DMSO-d_6	5.40, m	8.9	7.65, d	8.9	--- 78.7($CDCl_3$)
9	DMSO-d_6	4.90, pst	8.2	7.15, d	8.5	79.1 81.0 (D_2O)
13	$CDCl_3$	6.30, dd	4.8	5.60, d	9.0	---
14	$CDCl_3$ DMSO-d_6	5.75, m 5.90, t	--- ---	5.75, m 8.05, d	--- 9.0	82.5 ---
15	$CDCl_3$	5.95, m	---	5.55	---	---
16	$CDCl_3$ DMSO-d_6	5.10-5.45,m 5.65, dd	5.5 4.8	5.10-5.45,m 7.80, d	--- 8.9	82.5 ---
17	$CDCl_3$	6.00. m	---	6.00, m	---	---
18	$CDCl_3$	5.70-5.90,m	---	5.70, m	---	---
19	$CDCl_3$	6.20, d	0.0	12.90, d	8.3	---
20	$CDCl_3$	5.95, dd	2.8	12.50, d	7.1	84.4
23	DMSO-d_6	5.50, dd	2.1	12.10, d	8.2	---
24	DMSO-d_6	5.00, m	---	7.30, d	9.5	79.2
25	$CDCl_3$	5.30-5.95,m	---	5.80, d	6.0	---
26	$CDCl_3$	5.70,dd	5.5	12.70, d	8.2	---
27	DMSO-d_6 $CDCl_3$	5.80, pst 5.90, m	8.2 8.2	12.70, d 12.30, d	8.2 8.2	--- 77.9

[a] Collapsing to doublet (3, 8, 9, 13, 16, 20, 23, 26 and 27) or singlet (19) on exchange with deuterium oxide

[b] Exchangeable with deuterium oxide, coupled with H-1'. s, singlet; d, doublet; dd, double doublet; t, triplet; pst, pseudotriplet; m, multiplet.

All the nitroso derivatives (19, 20, 23, 26 and 27) showed a six member intramolecular hydrogen bond between the O atom of the NO group and the H atom of the C_6-NH group that are not depicted in some cases in the schemes. This fact was evidenced by the downshifting of the doublet corresponding to the resonance of the C_6-NH proton.

Formation of α anomers in this type of glycosidation could be explained considering a previous formation of an intermediate 4-O-glycofuranoside with β configuration, as it has been described in similar situations.[9] This kinetically controlled compound could undergo evolution to the thermodynamically more stable product, 6-N-glycoside. As consequence, an anomeric mixture is obtained.

Configuration of these compounds were assigned on the basis of the coupling constants $J_{1',2'}$ values, comparing with compounds **4** and **8**, and by detailed examination of their ^{13}C-NMR spectra[10] (Table II). In furanoid rings the coupling constants vary from 3 to 8 Hz for neighbouring cis-protons and from 0 to 8 Hz for neighbouring trans-proton; Thus, only when the coupling constants are less than 3 Hz can assignments be made.

Nevertheless, the $J_{1',2'}$ values of compounds **14**, **15**, **17** and **18** were not measurable since the corresponding signals appear together with other sugar protons. For this reason, configurations at their anomeric centres were assigned, according to Nishimura and Shimizu[11], on the basis of $\delta_{H\text{-}1'}$ values (for α-anomer appears downshifted with regard to the corresponding β-anomer) (Table II). To confirm these assignments, compounds **14** and **16** were nitrosated with sodium nitrite and acetic acid leading to the corresponding 5-nitroso derivatives as unique compounds, **19** and **20**, showing unambiguous $J_{1',2'}$ values for β-furanosides (**19**, $J_{1',2'}$= 0.0 Hz; and **20**, $J_{1',2'}$= 2.8 Hz) (Scheme I, Table II).

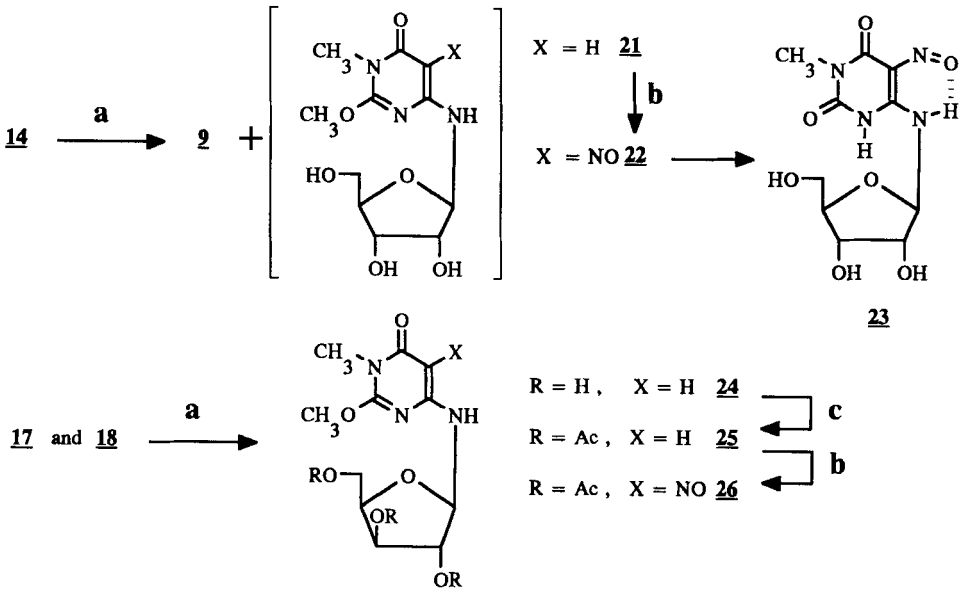
In the reaction between **6** and per-O-acetylribopyranose **7**, presence of low quantity of α-anomer was detected by t.l.c., even though the isolation of this isomer was not feasible.

Deprotection of **14** by treatment with NaOMe/MeOH led to **9** in 52% yield and from the mother liquors of this reaction, after nitrosation, 42% of the red derivative **23** ($J_{1',2'}$=2.10Hz;$\delta_{H\text{-}1'}$= 5.50ppm, DMSO-d_6) was isolated. This compound, **23**, may be originated from **21**; in aqueous medium the blue 5-nitroso derivative **22** may undergo CH_3O hydrolysis[13] (Scheme II).

The isomerization furanose-pyranose, could be caused by the basic medium generating a resonance stabilized anion by abstraction of the C_6-NH proton. This process causes the furanose ring opening and the pyranose ring is formed by attack of hydroxyl group at C-5' to the anomeric carbon; under acidic conditions such isomerization has been also observed.[12] Even if several products may be formed , only the β-pyranose and β-furanose derivatives, thermodynamically favoured, were able to be isolated.

When deprotection of a mixture of **17** and **18** was carried out only β-furanoside **24** ($\delta_{H\text{-}1'}$= 5.00ppm) was possible to isolate (Scheme II). As $J_{1',2'}$ could not be measure for **24** and because only one anomer was isolated, this compound was converted in its 5-nitroso-tri-O-acetyl derivative **26** and compared with the 5-nitroso-tri-O-acetylxylopyra-nosyl derivative, **27**, obtained by nitrosation of **4** (Table II, Schemes I and II).[14]

The screening for activities "in vitro" of compounds **3**, **9** and **24** against HIV and several tumours has been performed in the N.C.I. (according to standard methods), and none of them have shown significant anticancer or anti-AIDS activity.[15]



a: NaOMe/MeOH, r.t.; b: $NaNO_2$/AcOH; c: Ac_2O/DMAP.

SCHEME II

EXPERIMENTAL

Proton nuclear magnetic resonance spectra were recorded with a Hitachi Perkin-Elmer R-600 spectrometer (60 MHz). 13-Carbon nuclear magnetic resonance spectra were recorded with a Bruker AM-300 spectrometer from "Servicios Técnicos de la Universidad de Granada" (STUGRA). TMS served as the internal reference. Mass spectra were recorded with a Hewlett-Packard HP-5988-A spectrometer from STUGRA at an ionizing potential of 70 ev. Elemental analyses were obtained in a Perkin Elmer 240C from STUGRA. Ultraviolet and visible spectra were recorded on a Bausch & Lomb Spectronic 2000 spectrophotometer. Infrared spectra were recorded using a Beckman 4250 spectrophotometer (potassium bromide disk). Melting points are uncorrected and were determined on a Gallemkamp Melting Point Apparatus. Specific rotation values were determined with a Perkin-Elmer 241 polarimeter. Reaction progress and product purity were monitored by thin-layer chromatography (tlc) on Merck silicagel 60 F_{254}(0.2 mm) aluminium sheets with fluorescent indicator, the spots were visualized by ultraviolet irradiation and by spraying with 4% sulphuric acid/methanol solution and subsequent heating. Preparative tlc was performed on Merck Kiesegel 60 F_{254} (2mm, 20x20 cm). Column chromatography was done on Merck silicagel 60 (70-230 mesh).

2-methoxy-3-methyl-6-β-D-xylopyranosylaminopyrimidin-4-(3H)-one, 3.
This compound was prepared by a previously published procedure.[2]

2-methoxy-3-methyl-6-(2,3,4-tri-O-acetyl-β-D-xylopyranosylamino)pyrimidin-4-(3H)-one, 4.

This compound was prepared by a previously published procedure.[2]

2-methoxy-3-methyl-6-trimethylsilylaminopyrimidin-4-(3H)-one, 6.

To a mixture of 3.1 g (20 mmol) of dry 6-amino-2-methoxy-3-methyl pyrimidin-4(3H)-one 1 and 5 mg of dry $(NH_4)_2SO_4$, 60 ml of HMDS were added. The mixture was stirred at reflux, under nitrogen atmosphere, with the exclusion of mixture for 24 h. At this time, the obtained solution was concentred at reduced pressure to approximately 30 ml and kept overnight in fridge. The crystalline solid which appeared was filtered off and dried over P_2O_5 in vacuo. 4.20 g. Rf: 0.39 CH_2Cl_2/MeOH (5:0.3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 164.0, 163.1, 156.5 (C-2, C-4, C-6), 84.0 (C-5), 55.5 (CH_3O), 27.1 (CH_3N), 0.12 (CH_3Si). IR (KBr) ν_{max}(cm^{-1}): 3240 m, 2940 m, 1645 s, 1595 s, 1540 s, 1445 m, 1380 s, 1350 m, 1205 s, 1165 m, 925 m, 860 s, 835 s, 800 s. MS m/z (abundance %): 227 (M^+, 24), 212 (33), 197 (1), 182 (1), 155 (100), 140 (25), 125 (23), 68 (27).

2-methoxy-3-methyl-6-(2,3,4-tri-O-acetyl-β-D-ribopyranosylamino)pyrimidin-4-(3H)-one, 8.

To a cooled suspension of 1.13 g (5mmol, 1 eq) of the silyl derivative 6 and 1.59 g (5 mmol, 1 eq) of 1,2,3,4-tetra-O-acetyl-β-D-ribopyranose, 7, in 17.5 ml of dry CH_3CN, a cold solution of 0.88 ml (17.5 mmol, 1.5 eq) of freshly distilled $SnCl_4$ in 17.5 ml of dry CH_3CN was added. After stirring at room temperature for 28 h with exclusion of mixture, the obtained solution was evaporated under reduced pressure (temperature below 40°C) and the syrupy residue was dissolved in CH_2Cl_2 and neutralized with a saturated solution of $NaHCO_3$. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). The combined CH_2Cl_2 solutions were washed with water (2x10 ml), dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The residue was crystallized from ethyl alcohol. 0.6 g. Rf 0.39, CH_2Cl_2/MeOH (5:0.4). ^{13}C-NMR ($CDCl_3$) δ (ppm): 170.4, 169.9, 169.5 (COO), 164.0, 160.0, 156.8 (C-2, C-4, C-6), 82.3 (C-5), 78.7 (C-1'), 68.4, 68.3, 66.4 (C-2', C-3', C-4'), 62.3 (C-5'), 55.6 (CH_3O), 27.3 (CH_3N), 20.7, 20.6 ($\underline{C}H_3CO$). IR (KBr) ν_{max}(cm^{-1}): 3240 m, 3060 w, 1735 m, 1645 s, 1600 w, 1545 s, 1470 w, 1440 w, 1370 s, 1290 m, 1245 s, 1220 s, 1155 m, 1105 m, 1065 s, 1040 m, 995 m, 870 m, 800 m, 780 m, 745 m. MS m/z (abundance %): 413 (M^+, 3), 354 (5), 294 (3), 234 (7), 184 (69), 156 (40), 97 (15), 43 (100).

2-methoxy-3-methyl-6-ß-D-ribopyranosylaminopyrimidin-4-(3H)-one, 9.

A mixture of 8 (0.20g, 0.49 mmol) and methanolic ammonia (saturated at 0°C, 15 ml) was kept in a pressure bottle at room temperature for three days. The solvent was removed and the residue crystallized from MeOH/Diethyl ether at -20°C. 0.11 g. ^{13}C-NMR (DMSO-d_6) δ (ppm): 162.4, 161.0, 156.4 (C-2, C-4, C-6), 79.9 (C-5), 79.1 (C-1'), 70.6, 69.4, 67.1 (C-2', C-3', C-4'), 63.8 (C-5'), 55.2 (CH_3O), 26.5 (CH_3N). ^{13}C-NMR (D_2O) δ (ppm): 168.9, 164.8, 160.0 (C-2, C-4, C-6), 84.1 (C-5), 81.0 (C-1'), 72.9, 71.7, 69.0 (C-2', C-3', C-4'), 65.9 (C-5'), 58.5 (CH_3O), 30.1 (CH_3N). IR (KBr) ν_{max}(cm^{-1}): 3400-3120 s broad, 2920 m, 1635 s, 1555 s, 1535 s, 1415 m, 1365 m, 1280 m, 1250 m, 1210 s, 1165 m, 1135 m, 1105 m, 1055 s, 1030 s, 955 s, 800 m, 780 m. MS m/z (abundance %): 287 (M^+, 5), 256 (1), 198 (8), 184 (32), 156 (100), 125 (11), 72 (48), 60 (26).

Reaction between 6 and 1-O-acetyl-2,3-5-tri-O-benzoyl-β-D-ribofuranose, 10.

Reaction between 6 (3.41 g, 15 mmol, 1 eq), 10 (7.56 g, 15 mmol, 1 eq) and $SnCl_4$ (2.65 ml, 22.5 mmol, 1.5 eq in 50 ml of CH_3CN) was carried out in absolute CH_3CN (50 ml) as described above for compound 8. After evaporation the syrupy residue in tlc (CH_2Cl_2/petroleum ether/ethanol, 3.8:0.9:0.1) showed to be a mixture of two products. By crystallization from EtOH (300 ml), 7.2 g of **2-methoxy-3-methyl-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosylamino)pyrimidin-4-(3H)-one, 14**, were obtained. The compound was recrystallized from ethanol. Rf 0.34, CH_2Cl_2/EtOH (5:0.3). ^{13}C-NMR ($CDCl_3$) δ (ppm): 166.2, 165.5, 165.4 (COO), 163.9, 159.7, 156.8 (C-2, C-4, C-6), 133.6, 133.5, 133.2, 129.9, 129.8, 129.5, 128.9, 128.8, 128.5 (aromatic carbon atoms), 85.0 (C-5), 82.5 (C-1'), 79.0, 74.3, 71.1 (C-2', C-3', C-4'), 64.2 (C-5'), 55.5 (CH_3O), 27.3 (CH_3N). IR (KBr) ν_{max}(cm^{-1}): 3275 s, 3060 m, 3010 w, 2950 m, 2900 m, 1735 s, 1650 s, 1605 m, 1585 w, 1555 s broad, 1450 m, 1415 m, 1380 m, 1320 m,

1275 s, 1215 m, 1180 m, 1130 s, 1070 m, 1025 m, 1000 m, 965 m, 930 m, 880 w, 815 m, 800 w, 780 m, 710 s, 680 m, 640 m, 656 m. MS, m/z (abundance %): 599 (M^+, 1), 478 (1), 445 (1), 356 (1), 235 (2), 153 (1), 122 (1), 105 (100), 77 (19).

After compound **14** was filtered off, 0.37 g of the residue resulting from the evaporation of the mother liquors yielded 20 mg (11%) of the second product by preparative tlc (CH_2Cl_2/petroleum ether/ethanol, 11.4:4:0.1). Such compound was identified by ^{1}H-NMR as: **2-methoxy-3-methyl-6-(2,3,5-tri-O-benzoyl-α-D-ribofuranosylamino) pyrimidin-4-(3H)-one, 13**. ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.30 (3H, s, CH_3N), 3.95 (3H, s, CH_3O), 4.65 (3H, s, C(5')-H_2 and H-4'), 5.35 (1H, s, H-5) 5.60 (1H, d, C(6)-NH), 6.30 (1H, dd, H-1'), 7.20-8.10 (15H, m, Bz).

To a solution of 1.798 g (3 mmol) of **14** in 5 ml of acetic acid, 0.23 g (3.3 mmol) of $NaNO_2$ were added. The mixture was stirred at room temperature for 15 minutes and then 50 ml of water were added. After neutralization with a saturated solution of $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (4x10 ml) and the organic layer washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness at reduced pressure. The blue residue was not possible to recrystallize, However, since tlc showed enough purity, according to its ^{1}H-NMR spectrum this compound was assigned to **2-methoxy-3-methyl-5-nitroso-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosylamino)pyrimidin-4-(3H)-one, 19**. Rf 0.73, CH_2Cl_2/EtOH (5:0.2). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.40 (3H, s, CH_3N), 4.00 (3H, s, CH_3O), 4.70 (3H, s, C(5')-H_2 and H-4'), 5.80 (2H, m, H-2' and H-3'), 6.20 (1H, d, H-1'), 7.00-8.40 (15H, m, Bz), 12.90 (1H,d, C(6)-NH).

Reaction between 6 and 1,2,3-5-tetra-O-acetyl-β-D-ribofuranose, 11.

Reaction between **6** (2.27 g, 10 mmol, 1 eq), **11** (3.18 g, 10 mmol, 1 eq) in 40 ml of dry CH_3CN and freshly distilled $SnCl_4$ (1.76 ml, 15 mmol, 1.5 eq, in 40 ml of dry CH_3CN) was carried out as described above for compound **8**. After evaporation, the syrupy residue showed two product in tlc (diethyl ether/isopropanol, 9.5:0.5). By silica gel column chromatography using diethyl ether/isopropanol (97:3) as eluent, 2.02 g of **2-methoxy-3-methyl-6-(2,3,5-tri-O-acetyl-β-D-ribofuranosylamino)pyrimidin-4-(3H)-one, 16**, were obtained. The compound was crystallized from ethanol/diethyl ether/petroleum ether. Rf 0.51, diethyl ether/isopropanol (9.5:0.5). IR (KBr) ν_{max}(cm^{-1}): 3280 s, 3050 w, 2940 m, 1745 s, 1645 s, 1600 m, 1535 s, 1460 w, 1375 s, 1280 w, 1235 s, 1140 m, 1100 m, 1060 m, 1040 m, 1010 m, 925 m, 890 m, 800 m, 775 m, 745 m, 625 m. MS, m/z (abundance %): 413 (M^+, 9), 354 (8), 294 (7), 259 (4), 234 (25), 184 (96), 156 (51), 139 (33), 97 (20), 43 (100).

The second product (Rf:0.36, diethyl ether/isopropanol, 9.5:0.5) could not be isolated. By comparing between the ^{1}H-NMR spectrum of **16** and the ^{1}H-NMR of the residue resulting from the evaporation of the mother liquors of the reaction, this compound could be identified as: **2-methoxy-3-methyl-6-(2,3,5-tri-O-acetyl-α-D-ribofuranosylamino) pyrimidin-4-(3H)-one, 15**, (Table II).

Reaction between 6 and 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-xylofuranose, 12.

Reaction between **6** (1.13 g, 5 mmol, 1 eq), **12**[7] (2.52 g, 5 mmol, 1 eq) in 17.5 ml of dry CH_3CN and freshly distilled $SnCl_4$ (0.88 ml, 7.5 mmol, 1.5 eq in 17.5 ml of dry CH_3CN) was carried out as described above for compound **8**. After evaporation, the syrupy residue showed two products in tlc (CH_2Cl_2/petroleum ether/EtOH, 3.8:0.9:0.1). By preparative tlc (CH_2Cl_2/petroleum ether/EtOH, 12:3:0.3) 0.153 g of the residue yielded 0.037 g (24 %) of the product with lower Rf identifiedas:**2-methoxy-3-methyl-6-(2,3,5-tri-O-benzoyl-β-D-xylofuranosylamino)pyrimidin-4-(3H)-one, 18**, and 0.026 g (17%) of compound with the highest Rf identified as: **2-methoxy-3-methyl-6-(2,3,5-tri-O-benzoyl-α-D-xylofuranosylamino)pyrimidin-4-(3H)-one, 17**.

Both of them were identified by ^{1}H-NMR:

Compound **17**: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.30 (3H, s, CH_3N), 3.95 (3H, s, CH_3O), 4.70 (2H, m, C(5')-H_2), 4.85 (1H, st, H-4'), 5.55 (2H, m, H-5 and H-3'), 6.00 (3H, m, C(6)-NH, H-1' and H-2'), 7.10-8.30 (15H, m, Bz).

Compound **18**: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.30 (3H, s, CH_3N), 3.90 (3H, s, CH_3O), 4.70 (3H, m, C(5')-H_2 and H-4'), 5.30 (2H, m, H-5 and H-3'), 5.70-5.90 (3H, m, C(6)-NH, H-2'and H-1'), 7.10-8.30 (15H, m, Bz).

2-methoxy-3-methyl-5-nitroso-6-(2,3,5-tri-O-acetyl-β-D-ribofuranosylamino)pyrimidin-4-(3H)-one, 20.

Reaction between **16** (0.62 g, 1.5 mmol) in 1 ml of acetic acid and $NaNO_2$(0.21 g, 3 mmol) was carried out as described above for compound **14**. The blue residue was crystallized from ethanol. 0.33 g (60%). M.p.: 115°C. $[\alpha]_D^{20}$= -34.1° (c 1, $CHCl_3$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 171.02, 167.5, 169.2 (COO), 161.1, 158.9, 146.3 (C-2, C-4, C-6), 141.7 (C-5), 84.4 (C-1'), 79.3, 74.7, 70.1 (C-2', C-3', C-4'), 62.3 (C-5'), 57.2 (CH_3O), 28.0 (CH_3N), 21.0, 20.5 (CH_3CO).

Deprotection of compound 14.

To a suspension of 2.99 g (5 mmol) of **14** in 20 ml of MeOH, 5 ml (5 mmol) of 1M solution of NaOMe were added. The obtained mixture was stirred for 4 hours at room temperature and then neutralized with acetic acid and evaporated under reduced pressure. The residue was dissolved in 30 ml of water and extracted with CH_2Cl_2 (6x5 ml). The aqueous layer was evaporated and the residue crystallized from H_2O/MeOH (20 ml, 50%) yielding 0.75 g (52%) of compound **9**.

To the mother liquors 0.4 g (5.8 mmol) of $NaNO_2$ and 0.4 ml of acetic acid were added. Immediately, the solution became blue in colour turning red after several days. Then such mixture was evaporated to dryness at reduced pressure, the residue crystallized from EtOH/H_2O (9:1, v/v) and identified as **3-methyl-5-nitroso-6-(β-D-ribofuranosylamino)pyrimidin-2,4(1H,3H)-dione, 23**. 0.3 g. M.p.: 160°C (d). ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.20 (3H, s, CH_3N), 3.30-4.40 (8H, m, sugar protons and OH), 5.50 (1H, dd, H-1'), 12.10 (1H, d, C(6)-NH).

2-methoxy-3-methyl-6-β-D-xylofuranosylaminopyrimidin-4-(3H)-one, 24.

This compound was obtained when the syrupy residue obtained in the reaction between **6** and **12**, previously described, was disolved in MeOH (10 ml) and treated with NaOMe 1M (5 ml). After stirring at room temperature for 3 hours, the solution was neutralized with AcOH and kept at -20°C. The solid which appeared was filtered off and washed with cold MeOH and diethyl ether and recrystallized from MeOH. 0.49 g (34%). IR (KBr) ν_{max}(cm^{-1}): 3340 m, 3310 s, 2960 m, 2860 m, 1640 s, 1605 w, 1570 s, 1545 s, 1470 m, 1420 m, 1380 m, 1335 m, 1290 m, 1260 m, 1215 s, 1150 m, 1100 s, 1080 s, 1055 s, 1020 m, 970 m, 930 m, 800 m, 780 m. ^{13}C-NMR (DMSO-d_6) δ (ppm): 162.3, 160.5, 156.3 (C-2, C-4, C-6), 83.0 (C-5), 79.2 (C-1'), 77.4, 72.0, 69.7 (C-2', C-3', C-4'), 66.7 (C-5'), 55.2 (CH_3O), 26.5 (CH_3N). MS, m/z (abundance %): 287 (M^+, 4), 227 (2), 197 (6), 184 (30), 156 (92), 140 (20), 112 (16), 72 (100), 60 (69), 43 (87).

0.15 g of **24** were added to a mixture of 25 mg of dimethylaminopyridine (DMAP) in 10 ml of Ac_2O and stirred at room temperature for 3 days. The solution was evaporated to dryness under reduced pressure (temperature below 40°C) and coevaporated several times with MeOH. The residue was purified by preparative tlc (CH_2Cl_2/MeOH, 5:0.25) and according with its ^{1}H-NMR spectrum the obtained compound was assigned to **2-methoxy-3-methyl-6-(2,3,5-tri-O-acetyl-β-D-xylofuranosylamino)pyrimidin-4-(3H)-one, 25**. 0.15 g (70%). Rf 0.61 (CH_2Cl_2/MeOH, 5:0.3). ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.05 (6H, s, CH_3COO), 2.30 (3H, s, CH_3COO), 3.30 (3H, s, CH_3N), 3.95 (3H, s, CH_3O), 5.25 (1H, s, H-5), 5.30-5.95 (2H, m, C(6)-NH and H-1').

0.1 g of **24** were dissolved in AcOH (0.5 ml) and then 0.1 g of $NaNO_2$ were added. After stirring at room temperature for 15 minutes, 10 ml of water were added and the solution extracted with CH_2Cl_2 (3x5 ml). The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness. The blue residue could not be purified by the usual procedures nevertheless, since tlc showed enough purity, according with its ^{1}H-NMR spectrum was possible to infer that such compound is **2-methoxy-3-methyl-5-nitroso-6-(2,3,5-tri-O-acetyl-β-D-xylofuranosylamino)pyrimidin-4-(3H)-one, 26**. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.05 (6H, s, CH_3COO), 2.30 (3H, s, CH_3COO), 3.50 (3H, s, CH_3N), 4.10 (3H, s, CH_3O), 5.10 (3H, m, sugar protons), 5.70 (1H, dd, H-1'), 12.70 (1H, d, C(6)-NH).

2-methoxy-3-methyl-5-nitroso-6-(2,3,5-tri-O-acetyl-β-D-xylopyranosylamino)pyrimidin-4-(3H)-one, 27.

This compound was prepared by a previously published procedure.[14]

ACKNOWLEDGEMENTS

The anticancer and antiviral data are the results of the screening performed under the auspices of the Developmental Therapeutics Program, Division of Cancer Treatment NCI Bethesda, Maryland. This work was supported by the Spanish CICYT (FAR 89-414).

REFERENCES

1. Presented in part at the Tenth International Round Table. Nucleosides & Nucleotides and their Biological Applications. Park City. Utah (USA). September 16-20, 1992.
2. R. Asenjo, M. Melgarejo, C. Rodríguez, M. Nogueras and A. Sánchez, An. Quim.,1983, 79C, 417 (1983).
3. M. Melguizo, M. Nogueras and A. Sánchez, J. Org. Chem., 57, 559 (1992).
M. Melguizo, M. Nogueras and A. Sánchez, Synthesis, 5, 491 (1992).
M.L. Quijano, M. Nogueras, M. Melgarejo and A. Sánchez, Monatsh. Chem., 122, 255 (1991).
A. Sánchez, M.L. Quijano, M. Melguizo and M. Nogueras, Monatsh. Chem., 120, 1119 (1989).
M.L. Quijano, M. Nogueras, M. Melguizo, G. Alvarez de Cienfuegos, M. Melgarejo and A. Sánchez, Nucleosides & Nucleotides, 8(8), 1519 (1989).
R. Asenjo, M. Melgarejo, M. Nogueras, M. Rodríguez, C. Rodríguez and A. Sánchez, Nucleosides & Nucleotides, 3(2), 207 (1984).
4. L.B. Townsend, "Synthetic Procedures in Nucleic Acid Chemistry" vol.2, p. 331, Wiley-Interscience, New York, 1973.
5. M. Nogueras, A. Sánchez, R. Asenjo, M. Melgarejo, M. Rodríguez and C. Rodríguez, An. Quim., 80C, 234 (1984).
6. V. Niedballa and H. Vorbruggen, J. Org. Chem., 41, 2084 (1976).
Ibid., 39, 3672 (1974).
H. Vorbruggen, K. Krolikiewick and V. Niedballa, "Chemistry, Biology and Clinical Uses of Nucleoside Analogs", A. Block Ed., Annual of the New York Academic of Science, New York, p. 82, 1975.
7. G. Gosselin, PhD Thesis, Montpellier University, 1982. C. Nakayama and M. Saneyoshi, Nucleosides & Nucleotides, 1, 139 (1982).
8. A.J. Brink and A. Jordan, Carbohydr. Res., 41, 355 (1975).
9. F. Seela and V. Bindig, Liebigs Ann. Chem., 895 (1989).
P. Goya, A. Martinez, C. Ochoa and M.L. Jimeno, Nucleosides & Nucleotides, 6, 631 (1987).
P. Goya, A. Martinez, M.L. Jimeno and W. Pfleiderer, Liebigs Ann. Chem., 1872 (1986).
W. Pfleiderer, G. Ritzmann, K. Harzer and J.C. Jockims, Chem. Ber., 106, 2982 (1973).
10. E. Breitmaier and W. Voelter, "^{13}C-NMR Spectroscopy. Methods and applications in Organic Chemistry" 2nd Ed., Monographs in Modern Chemistry vol. 5, Verlag chemie, New York, 1978.
11. T. Nishimura and B. Shimizu, Chem, Pharm. Bull., 13, 803 (1965).
B. Rayner, C. Tapiero and J.L. Imbach, in "Chemistry and Biology of Nucleosides and Nucleotides", R.E. Harmon, R.K. Robins, L.B. Townsend eds., Academic Press New York, p. 229, 1978.
P.D. Cook, R.J. Rousseau, A.M. Mian, P. Dea, R.B. Meyer Jr. and R.K. Robins, J. Am. Chem. Soc., 98, 1492 (1976).
M.J. Robins and M. Maccoss, in "Chemistry and Biology of Nucleosides and Nucleotides", R.E. Harmon, R.K. Robins, L.B. Townsend eds., Academic Press New York, p. 311, 1978.

12. J.A. Montgomery and H.J. Thomas, Chem. Comm., 265 (1970).
Ibid, J. Org. Chem., 36, 1962 (1971).
ibid, Jerusalem Symp. Quantum Chem. Biochem., 4, 446 (1972).
ibid., J. Chem. Soc., Chem. Commun., 265 (1970).
13. M. Nogueras, M.L. Quijano, M. Melgarejo and A. Sánchez, Nucleoside & Nucleotides, 5, 301 (1986).
M. Nogueras, M.L. Quijano, A. Sánchez and M. Melgarejo, Nucleoside & Nucleotides, 8, 117 (1989).
M.L. Quijano, M. Nogueras, M. Melguizo, G. Alvarez de Cienfuegos, M. Melgarejo and A. Sánchez, Nucleoside & Nucleotides, 8, 1519 (1989).
M. Nogueras, M.L. Quijano, A. Sánchez and M. Melgarejo, Proceedings of the VIIth International Round Table, Nucleoside & Nucleotides, 6, 373 (1987).
14. M. Nogueras, R. López, M.D. Gutierrez and A. Sánchez, Journal of Thermal Analysis, 34, 1335 (1988).
15. O.W. Weislow, R. Kiser, D. Fine, J. Bader, R.H. Shoemaker, M.R. Boyd, "New soluble-formazan assay for HIV-1 cytophatic effects: application to high-flux screening of synthetic and natural products for AIDS-antiviral activity. J. Natl. Cancer Inst. 81:577-586, 1989.
M.R. Boyd, "Status of the NCI Preclinical Antitumor Drug Discovery Screen" in "Principles & Practice of Oncology" 3rd edition, 3(10), V.T. DeVita Jr., S. Hellman and S.A. Rosenberg, 1989.

Received 5/24/93
Accepted 10/12/93