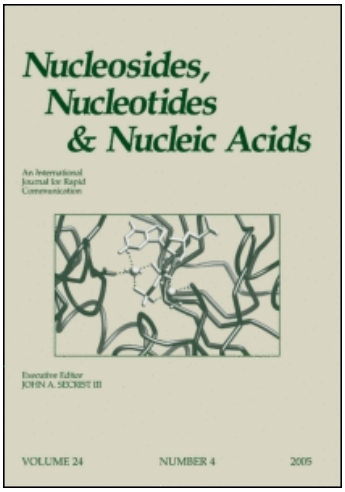


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Aminopyrimidines and Derivatives. 22[1]. Synthesis of 3-Glycopyrano-Syl-vic-Triazolo [4,5-d]Pyrimidines, 7-Glycopyranosyl-Pyrrolo [2,3-d]PY-Rimidines and 4-Glycopyranosylamino-Furo [2,3-d]Pyrimidines[2]

Manuel Nogueras[a]; M Luisa Quijano[a]; Adolfo Sanchez[a]; Miguel Melgarejo[b]
[a] Depto. Química Orgánica. Colegio Universitario de Jaén. Universidad de Granada, Jaén, Spain [b] Depto. Quimica Orgánica, Universidad de Granada, Granada, Spain

To cite this Article Nogueras, Manuel , Quijano, M Luisa , Sanchez, Adolfo and Melgarejo, Miguel(1989) 'Aminopyrimidines and Derivatives. 22[1]. Synthesis of 3-Glycopyrano-Syl-vic-Triazolo [4,5-d]Pyrimidines, 7-Glycopyranosyl-Pyrrolo [2,3-d]PY-Rimidines and 4-Glycopyranosylamino-Furo [2,3-d]Pyrimidines[2]', Nucleosides, Nucleotides and Nucleic Acids, 8: 1, 117 — 132
To link to this Article: DOI: 10.1080/07328318908054161
URL: http://dx.doi.org/10.1080/07328318908054161

NUCLEOSIDES & NUCLEOTIDES, 8(1), 117-132 (1989)

AMINOPYRIMIDINES AND DERIVATIVES. 22[1]. SYNTHESIS OF 3-GLYCOPYRANOSYL-vic-TRIAZOLO [4,5-d]PYRIMIDINES, 7-GLYCOPYRANOSYL-PYRROLO [2,3-d]PYRIMIDINES AND 4-GLYCOPYRANOSYLAMINO-FURO [2,3-d]PYRIMIDINES[2].

MANUEL NOGUERAS, Mª LUISA QUIJANO, ADOLFO SANCHEZ

Depto. Química Orgánica. Colegio Universitario de Jaén. Universidad de Granada. 23071 Jaén. Spain.

MIGUEL MELGAREJO

Depto. Química Orgánica. Universidad de Granada. 18071 Granada. Spain.

Abstract: Reaction between 4-β-D-(O-acetyl)glycopyranosylaminopyrimidines **1** and chloracetylchloride yields the corresponding 5-α-chloracetyl derivatives **2**, the hydrolysis products **3** and the corresponding 5-α-chloracetyl derivative of compounds **3**. The former compounds were cyclized to the corresponding 7- β-D-glycopyranosyl-pyrrolo[2,3-d]pyrimidines **5** (**2a** yields 5,6-dihydro-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-2-methoxy-5-oxo-furo[2,3-d]pyrimidine **6a**); the second ones to 3-β-D-(O-acetyl)glycopyranosyl-vic-triazolo[4,5-d]pyrimidines **10**, and the last one to 4-β-D-(O-acetyl)glycopyranosylamino-furo[2,3-d]pyrimidines **7**. The anticancer activity of some of these products is noticed.

In a previous work, we communicated the synthesis of one 7-glucopyranosyl-pyrrolo[2,3-d]pyrimidine and one 3-glucopyranosyl-vic-triazolo[4,5-d]pyrimidine[3]. The necessary intermediates were obtained by reaction between the corresponding 4-glucopyranosylamino pyrimidine and chloracetyl chloride. Herein we report the extension of this work to other 4-glycopyranosylaminopyrimidines. The compounds obtained in these reactions were cyclized to give the above heterocycles and

4-glycopyranosylamino-furo[2,3-d]pyrimidines. Likewise, we also report the results of anticarcinogenic in vivo tests against **L1210 Leukemia** of some of them.

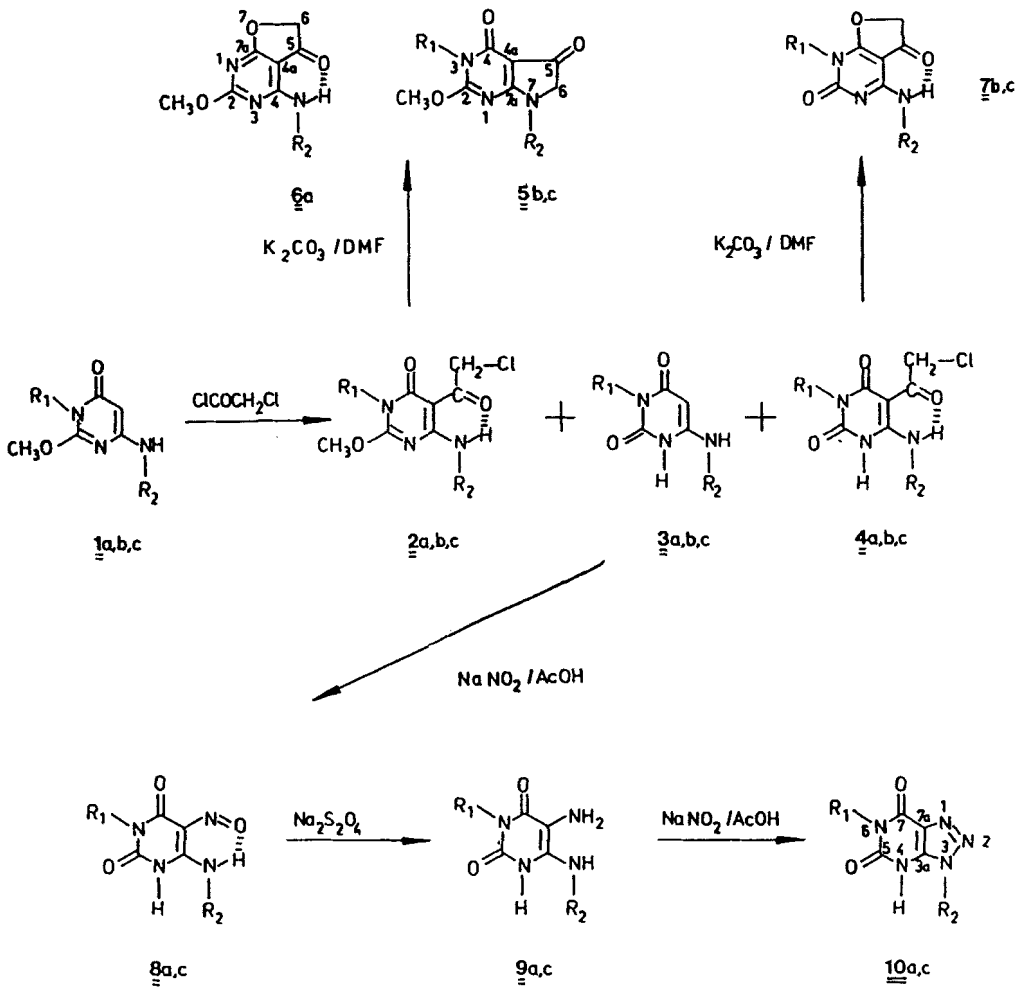
Furo[2,3-d]pyrimidines have been synthesized by acid catalyzed ring closure of 5-acetonylpyrimidin-4-ones[4-8], by heating 5-(CH_2-C≡C-R') pyridin-4-ones derivatives in the presence of small amount of zinc carbonate[9-10] or heating 5-(2-halovinyl)uracils in DMF/t-BuONa[11-12]. 4-aminofuro[2,3-d]pyrimidines are of potential pharmacological interest and several methods have been devised for the synthesis of this class of compounds. The most interesting being that in which the starting compounds are the corresponding 4-amino-6-hydroxy-pyrimidines and α-haloketones[13].

The reaction of **1** with freshly distilled $ClCOCH_2Cl$ leads to the three classes of compounds (Scheme 1) with variable yields depending on the solvent used. Thus, **1a** reacts in anhydrous ethyl acetate to give **2a**, **3a**, and **4a** in 9%, 60% and 21% yields, respectively, whereas when the solvent used is anhydrous chloroform (dried over aluminium oxide) respective yields of 52-60%, 15-23% and traces, are obtained. The reaction of **1b** gives 68% of **2b**, 6% of **3b**, and 14% of **4b** in chloroform. Although chloracetyl chloride amounts and reflux time were increased the said reaction did not take place completely in ethyl acetate. As it has been previously described[3], **1c** produces only **2c** and **4c** in ethyl acetate in yield of 42% and 43%, respectively. Reaction of **1c** in chloroform is similar to that of **1b** in ethyl acetate.

In the ^{1}H-NMR spectra of compounds **2**, the signal assigned to C_4-NH (which appears as a doublet due to the coupling with H-1', $J_{1',NH}$ = 8.2 Hz) appears downfield shifted (5 ppm) when compared to the corresponding signal in the ^{1}H-NMR spectrum of its precursor **1**. This shift is atributed to hydrogen bond between C_4-NH and C_5-$COCH_2Cl$ groups as shown in Scheme 1. This proton is exchangeable allowing to observe the anomeric protons signal as a doublet ($J_{1',2'}$ = 8.2 Hz).

Compounds **2** are formed by electrophilic aromatic substitution at C-5 of pyrimidine of **1**. The HCl molecule produced in this substitution is responsible for the formation of compounds **3**[3].

Upon prolonged heating of the reaction mixture in order to get complete disappearance of the starting product (2 mmol of $ClCOCH_2Cl$ per



Compd.	R_1	R_2
a	H	β-D-(tetra-O-acetyl)glucopyranosyl
b	CH_3	β-D-(tri-O-acetyl)xylopyranosyl
c	CH_3	β-D-(tetra-O-acetyl)glucopyranosyl

SCHEME 1

mol of **1**) the substitution of **3** at C-5 occurs to give compounds **4**, in low yields.

Compounds **4a** and **4c** can be directly prepared by treatment of **3a** and **3b** in ethyl acetate with an excess of $ClCOCH_2Cl$ (12 mmol per mmol of **3**) in yields 85-90% and 90-95%, respectively. This method enable us to prepare **4c** which is not formed by direct reaction. ^{1}H-NMR spectra of **4** show the same shifting as those of compounds **2** for C_4-NH signals (Scheme 1).

The treatment of **2b,c** intermediates in DMF with anhydrous K_2CO_3 at 80 - 90°C, leads to the 7-β-D-glycopyranosyl-pyrrolo[2,3-d]pyrimidines **5b** and **5c**[3]. When **2a** reacts under the same conditions the 4-β-D-glucopyranosylamino-furo[2,3-d]pyrimidine **6a** is obtained. This different behaviour is caused by aromatization which involves the cyclization of **2a** to **6a**.

In the ^{1}H-NMR spectra of **6a** the signal assigned to C_4-NH appears as a doublet at 8.1 ppm ($J_{1',NH}$= 8.2 Hz, in DMSO-d_6) whereas the said signal is not present in **5b** and **5c** spectra. The signal corresponding to the methylenic protons in C-6 disappears by adding D_2O in the case of compounds **5b** and **5c** due to the keto-enolic equilibrium. The doublet assigned to C_4-NH in the **6a** spectrum appears ($\Delta\delta$ 1.3 ppm) downfields shifted when compared to that of the same signal in **3a**, this might be caused by the hydrogen bonding, as shown in Scheme 1. This deshielding is lower than that of compounds **2** and **4**, and it could be the responsible for the smaller exchange rate of the methylenic C-6 proton in the presence of D_2O in the case of compound **6a** compared with **2b** and **2c**.

^{13}C-NMR spectra of compounds **5b**, **5c** and **6a** show differences in the resonance of C-6: 52.9 ppm in **5b**, 53.1 ppm in **5c** and 75.3 ppm in **6a**; and C-4: 173.4 ppm in **5b**, 169.3 in **5c** and 185.9 ppm in **6a** (C-7a). Both carbon atoms are downfields shifted in **6a** with regard to **5b** and **5c** (about 22 and 16 ppm, respectively).

The reaction of compounds **4** under the same conditions, as before mentioned for **2**, leads to 4-glycopyranosylamino furo[2,3-d] pyrimidines **7**, just as in the case of compound **2a**. The formation of a highly conjugated carbonyl system drives the reaction again towards furo[2,3-d] pyrimidines instead of the pyrrolo[2,3-d] pyrimidine. The purification of **7a** derivatives has not been possible.

The synthesis of 3-glycopyranosyl-vic-triazolo[4,5-d]pyrimidines **10** have been carried out by nitrosation of **3** in AcOH/$NaNO_2$, followed by the reduction of the resulting **8** with $Na_2S_2O_4$ in aqueous solution to give **9** and final cyclization of **9** with $NaNO_2$/AcOH. The synthesis of **10b** has not been carried out because we could not dispose of sufficent amounts of its precursor **3b**.

The ^{1}H-NMR spectra of derivatives **8** show the C_4-NH signal (doublet, $J_{1',NH}$= 9 Hz **8a** and $J_{1',NH}$= 8.9 Hz, **8c**) at lower field values than that of compounds **3**, due to hydrogen interaction between this group and the oxygen atom of C_5-NO[14] (Scheme 1). In the ^{13}C-NMR spectrum, the C-5 signal appears also at lower field values.

Purification of derivatives **8** by crystallization was impossible because of their extreme unstability in solution.

On the other hand, the optical rotation measurements indicated that compounds **8** undergo mutarotation as other glycosylaminopyrimidines[14].

The β-configuration of the sugar moieties in all compounds obtained has been confirmed by the values of the coupling constants $J_{1',2'}$ and by the chemical shifts of the anomeric proton and carbon. The α-anomers have not been detected in the crystalline products.

Compounds **2a**, **4a,b** ,**5b**, **6a** **10**, 5-α-chloracetyl-1,6-dihydro-4-β-D-glycopyranosylamino-1-methyl-2-methoxy-6-oxo-pyrimidine[3] **11** and 2,6-dioxo-4-β-D-glycopyranosylamino-1-methyl-1,2,3,6-tetrahydropyrimidine[3,15] **12**, 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 oscillated between 87 and 121, therefore none of those products shows anticancer activity.

EXPERIMENTAL

Melting points were determined in a Melting Point Apparatus Gallenkamp and are uncorrected. Proton nuclear magnetic resonance spectra were recorded with Hitachi Perking-Elmer R-600 and Bruker AM 300 Spectrometers, using tetramethylsilane as an internal standard. Carbon-13 nuclear magnetic resonance spectra were recorded with Bruker WP-805 and Bruker AM-300 spectrometers. Specific rotation values were determined with a Perkin-Elmer 141 polarimeter. Ultraviolet and visible spectra were recorded with a Model 25 Beckman spectrophotometer.

Infrared spectra were recorded with a Beckman 4250 spectrophotometer (KBr pellets). The analysis of C, H and N have been performed in "Instituto Nacional de Química Orgánica" in Madrid and with a Perkin-Elmer 240 C. Thin layer chromatography (TLC) was runned on silica gel Merck 60 G, using chloroform/hexane/ethanol (variable proportions) as eluent. Column chromatography was done on Kieselgel 60 Silica gel (70-230 mesh) using the solvent systems indicated in each case . Compounds **1** were prepared following the published method[16].

Reaction of **1a** with chloroacetyl chloride in ethyl acetate.

0.65 ml (8 mmol) of freshly distilled $ClCOCH_2Cl$ were added to a solution of 1.88 g (4 mmol) of **1a** in 25 ml of heated anhydrous ethyl acetate. A white solid precipitated after 15-20 minutes. The mixture was stirred under reflux for 5-6 h (at this time starting product was not detected in TLC, $CHCl_3$/EtOH, 100:3) and allowed to stand at room temperature for 12 h. The solid was filtered, washed with ethyl acetate and recrystallized from EtOH. This compound was identified as: 2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1,2,3,6-tetrahydropyrimidine, **3a**. 1.1 g (60%). m p: 298-306 °C (dec.). $[\alpha]_D^{20}$ = -1.5° (c 1, DMSO). UV (6.55×10^{-5} M, MeOH) λ_{max} (ε): 264 (18200) nm; IR $\nu_{max.}$ (cm^{-1}): 3270 w, 3100 w, 1760 s, 1730 s, 1600 s, 1240 s, 1220 s, 1050 s, 1030 s. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.0 (12 H, s, $COCH_3$), 4.8 (1H, s, C(5)-H), 5.3 (1H, m, with D_2O to d, $J_{1',2'}$ = 8.2 Hz, H-1'), 6.8 (1H, d, $J_{1',NH}$ = 8.2 Hz, with D_2O disappears, C(4)-NH), 10.1 (1H, s broad, N(1)-H), 10.5 (1H, s broad, N(3)-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.2, 20.3, 20.35 ($\underline{C}H_3CO$), 61.6 (C-6'), 67.9, 70.1, 71.6, 72.5 (C-2', C-3', C-4', C-5'), 75.9 (C-1'), 79.3 (C-5), 150.4 (C-4), 153.0 (C-2), 164.2 (C-6), 169.2, 169.3, 169.5, 169.9 ($CH_3-\underline{C}O$); Anal. Calcd. for $C_{18}H_{23}N_3O_{11}$: C, 47.26; H, 5.08; N, 9.19. Found: C, 47.57; H, 5.18; N, 8.95.

The mother liquors were neutralized with a satured $NaHCO_3$ aqueous solution, washed with water, dried over $CaCl_2$ and evaporated under reduced pressure. The solution of the syrupous residue in 1 ml of chloroform was applied on a chromatographic column, using $CHCl_3$-EtOH mixtures (0-2%) as eluent. Two products were obtained; the first one was recrystallized from EtOH-AcOEt (50%) and identified as: 5-α-chloracetyl-1,6-dihydro-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-2-methoxy-6-oxo-pyrimidine , **2a**. 0.2 g (9%). m p 219-220 °C. $[\alpha]_D^{20}$

= + 15.3° (c 1, $CHCl_3$). UV ($5.47x10^{-5}$ M, MeOH), λ_{max} (ε): 294 (11100) and 225 (31700) nm. IR ν_{max} (cm^{-1}): 3200 w, 1750 s, 1665 s, 1645 s, 1615 s, 1580 s, 1235 s, 1215 s, 1040 s. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.0 (12 H, s, $COCH_3$), 4.1 (3H, s, C(2)-OCH_3), 4.9 (2H, s, $COCH_2$), 5.6 (1H, m, with D_2O to d, $J_{1',2'}$ = 8.2 Hz, H-1'), 11.1 (1H, d, $J_{1',NH}$ = 8.2 Hz, with D_2O disappears C(4)-NH), 11.6 (1H, s broad, with D_2O disappears, N(1)-H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.45 ($\underline{C}H_3COO$), 51.2 ($CO-\underline{C}H_2$), 55.7 (OCH_3), 61.9 (C-6'), 68.4, 70.5, 73.1, 73.8 (C-2', C-3', C-4', C-5'), 78.7 (C-1'), 94.3 (C-5), 158.2 (C-4), 164.6 (C-2), 165.5 (C-6), 169.4, 170.2, 170.5 ($CH_3\underline{C}O$), 190.9 ($\underline{C}OCH_2$). Anal. Calcd. for $C_{21}H_{26}N_3O_{12}Cl$: C, 46.06; H, 4.78; N, 7.67. Found: C, 46.32; H, 5.09; N, 7.33.

The second collected fraction was crystallized from AcOEt-EtOH (80-20) and identified as: 5-α-chloracetyl-2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1,2,3,6-tetrahydro pyrimidine, **4a**. 0.45 g (21%). m p : 210-214 °C. $[\alpha]_D^{20}$ = - 9.9° (c 1, DMSO). UV ($4.87x10^{-5}$ M, MeOH) λ_{max} (ε): 283 (14000), 239 (9300), 222 (10700) nm.IR ν_{max} (cm^{-1}) : 3200 m, 1760 s, 1720 s, 1680 s, 1615 s, 1540 m, 1200-1240 s broad, 1070 s, 1045 s. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.0 (12H, s, $COCH_3$), 4.8 (2H, s, $COCH_2$), 5.5 (1H, m, with D_2O to d $J_{1',2'}$ = 8.2 Hz, H-1'), 11.1 (1H, s, with D_2O disappears, N(1)-H), 11.6 (1H, d, $J_{1',NH}$ = 8.2 Hz, with D_2O disappears, C(4)-NH). ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.05, 20.1, 20.2, 20.3, 20.6 ($\underline{C}H_3CO$), 50.6 ($CO\underline{C}H_2$), 61.5 (C-6'), 67.55, 70.01, 72.06, 72.1 (C-2', C-3', C-4', C-5'), 78.0 (C-1'), 89.7 (C-5), 148.7 (C-4), 158.1 (C-2), 162.5 (C-6), 169.1, 169.5, 169.9, 170.2 ($CH_3\underline{C}O$), 189.9 ($\underline{C}OCH_2$). Anal. Calcd. for $C_{20}H_{24}N_3O_{12}Cl$: C, 44.99; H, 4.53; N, 7.87. Found: C, 44.81; H, 4.66; N, 7.57.

Reaction of **1a** with chloracetyl chloride in chloroform.

1.88 g. (4 mmol) of **1a** were added to 25 ml of chloroform previously dried over active aluminium oxide. 0.65 ml (8 mmol) of freshly distilled $ClCOCH_2Cl$ were added to the resulting solution; a white solid precipitated after 1 h. The mixture was stirred under reflux for 5 h (at this time no starting product was detected by TLC , eluent $HCCl_3$-EtOH, 3-100) and next was allowed to stand at room temperature for 12 h. The solid was filtered, washed with chloroform and recrystallized from EtOH being identified as: 2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1,2,3,6-tetrahydro pyrimidine, **3a**. 0.27-0.42 g (15-23%). m p : 298-306 °C (dec.).

The mother liquors were neutralized with a saturated $NaHCO_3$ aqueous solution, washed with water, dried over $CaCl_2$ and evaporated under reduced pressure. The solution of the syrupous residue in 1 ml of chloroform was applied on a chromatography column, using a 0-2% $CHCl_3$-EtOH solution as eluent. Then a syrupous compound was obtained whose recrystallization from a EtOH-AcOEt mixture (50%) led to a solid which was identified as: 5- α-chloracetyl-1,6-dihydro-4- β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-2-methoxy-6-oxo pyrimidine, **2a**. 1.14- 1.32 g (52-60%). m p : 219- 220 °C.

By TLC a third hardly isolable product was detected and identified as: 5- α-chloracetyl-2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1,2,3,6-tetrathydro pyrimidine, **4a**.

Reaction of **1b** with chloracetyl chloride in chloroform.

0.216 ml (2.66 mmol) of freshly distilled $ClCOCH_2Cl$ were added to a solution formed by 0.82 g (2 mmol) of **1b** in 10 ml of anhydrous chloroform. The mixture was stirred under reflux for 4-6 h after which no starting product was detected by TLC (eluent EtOH-$CHCl_3$, 3:100). The said mixture was then neutralized with a 5% $NaHCO_3$ aqueous solution, washed with water, dried over $CaCl_2$ and evaporated under reduced pressure. The chloroform solution of the reaction mixture was applied on a chromatographic column, using a 0-2% $CHCl_3$-EtOH mixture as eluent. The highest Rf compound was recrystallized from AcOEt-EtOH (10-90) and identified as: 5-α-chloracetyl-1,6-dihydro-1-methyl-2 -methoxy-6-oxo-4-β-D-(2,3,4-tri-O-acetyl)xylopyranosylamino pyrimidine, **2b**. 0.66 g (68%). m p : 215-220 °C (dec.). $[\alpha]_D^{20}$ = -20° (c 1, $CHCl_3$). UV (4.89×10^{-5} M, MeOH) λ_{max} (ε): 294 (13000), 260 (4400), 266 (37000) nm. IR ν_{max} (cm^{-1}): 3200 w, 1755 s, 1680 s, 1640 s, 1590 s, 1560 s, 1240 s, 1220 s, 1070 s, 1040 s. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.0 (6H, s, $COCH_3$), 2.2 (3H, s, $COCH_3$), 3.3 (3H, s, N-CH_3), 4.1 (3H, s, OCH_3), 4.9 (2H, s, $COCH_2$), 5.8 (1H, st, with D_2O to d, $J_{1',2'}$ = 8.2 Hz, H-1'), 11.2 (1H, d, $J_{1',NH}$ = 8.2 Hz with D_2O disappears, C(4)-NH). ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.6 ($\underline{C}H_3CO$), 27.5 (N-CH_3), 51.5 ($CO\underline{C}H_2$), 62.6 (C-5'), 67.9, 69.4, 70.1 (C-2', C-3', C-4'), 78.3 (C-1'), 94.3 (C-5), 157.9 (C-4), 162.3 (C-2), 163.1 (C-6), 169.6, 169.8 ($CH_3\underline{C}O$), 191.4 ($\underline{C}OCH_2$). Anal. Calcd. for $C_{19}H_{24}N_3O_{10}Cl$: C, 46.58; H, 4.94; N, 8.58. Found: C, 46.74; H, 5.06; N, 8.54.

The second fraction was recrystallized from AcOEt-EtOH (50%) to give: 5-α-chloracetyl-2,6-dioxo-1-methyl-1,2,3,6-tetrahydro-4-β-D-(2,3,4-tri-O-acetyl)xylopyranosylamino pyrimidine, **4b**. 0.14 g (15%). m p : 245-248 °C (dec.). $[\alpha]_D^{20}$ = -18.5° (c 1, DMSO). UV (4.83×10^{-5} M, MeOH) λ_{max} (ε): 284 (14700), 242 (9000), 221 (14800) nm. IR ν_{max} (cm^{-1}): 3200 m, 1750 s, 1715 s, 1660 s, 1635 s, 1605 s, 1245 s, 1225 s, 1200 s, 1050 s, 1030 s. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.0 (9H, s, $COCH_3$), 3.1 (3H, s, N-CH_3), 4.9 (2H, s, $COCH_2$), 5.5 (1H, m, with D_2O to d, $J_{1',2'}$ = 8.2 Hz, H-1'), 11.6 (1H, d, $J_{1',NH}$ = 8.5 Hz, with D_2O disappears, C(4)-NH). ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.1, 20.2, 20.4 ($\underline{C}H_3CO$), 26.5 (N-CH_3), 50.99 ($CO\underline{C}H_2$), 62.6 (C-5'), 67.6, 69.7, 70.9 (C-2', C-3', C-4'), 78.1 (C-1'), 89.8 (C-5), 149.1 (C-4), 156.5 (C-2), 161.7 (C-6), 169.1, 169.3, 169.4 ($CH_3\underline{C}O$), 190.0 ($\underline{C}OCH_2$). Anal. Calcd. for $C_{18}H_{22}N_3O_{10}Cl$: C, 45.43; H, 4.66; N, 8.83. Found: C, 45.40; H, 4.68; N, 8.72.

Finally using TLC (eluent EtOH-$CHCl_3$ 3:100) a third product was detected with smaller Rf than the previously cited compounds. This product was occasionally isolated being identified as: 2,6-dioxo-1-methyl-1,2,3,6-tetrahydro-4- β-D-(2,3,4-tri-O-acetyl)xylopyranosylamino pyrimidine, **3b**. 0.05 g (6%). m p: 262 - 265 °C (dec.). $[\alpha]_D^{20}$ = +29.9° (c 1, DMSO). UV (9.28×10^{-5} M, MeOH) λ_{max} (ε): 264 (17400) nm. IR ν_{max} (cm^{-1}): 3280 m, 3125 m, 1750 s, 1720 m, 1680 m, 1600 s, 1580 s, 1250 s, 1230 s, 1080 s, 1035 s. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.0 (9H, s, $COCH_3$), 3.0 (3H, s, N-CH_3), 4.9 (1H, s, C(5)-H), 5.3 (1H, st, with D_2O to d, $J_{1',2'}$ = 8.2 Hz, H-1'), 6.7 (1H, d, $J_{1',NH}$ = 8.2 Hz with D_2O disappears, C(4)-NH), 10.3 (1H, s,with D_2O disappears, N(3)-H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.22, 20.25, 20.3 ($\underline{C}H_3CO$), 25.9 (N-CH_3), 62.7 (C-5'), 68.3, 70.1, 72.1 (C-2', C-3', C-4'), 75.5 (C-1'), 79.9 (C-5), 150.6 (C-4), 151.5 (C-2), 163.1 (C-6), 169.3, 169.4, 169.5 ($CH_3\underline{C}O$). Anal. Calcd. for $C_{16}H_{21}N_3O_9$: C, 48.12; H, 5.30; N, 10.52. Found: C, 48.05; H, 5.26; N, 10.12.

Reaction of **3** with chloracetyl chloride.

To a suspension of 1 mmol of **3** in 50 ml of anhydrous ethyl acetate, 0.97 ml (12 mmol) of freshly distilled $ClCOCH_2Cl$ were added. The mixture was stirred under reflux for 2 h. After this time the crude reaction was evaporated under reduced pressure. The excess of solvent was removed by dissolving in EtOH and by evaporating several times. The product obtained was recrystallized from AcOEt-EtOH (80-20) and identified as:

5-α-chloracetyl-2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl) glucopyranosylamino-1,2,3,6-tetrahydro pyrimidine, **4a**. Reaction time 2 h. 0.45-0.48 g (85-90%).

5-α-chloracetyl-2,6-dioxo-4- β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1-methyl-1,2,3,6-tetrahydro pyrimidine, **4c**.0.50-0.52 (92-95%). m p: 155-160 °C. $[\alpha]_D^{20}$ = -17.9° (c 1, DMSO). UV ($6.2x10^{-5}$ M, MeOH), λ_{max} (ε): 281 (12300), 241 (8000) and 220 (12500) nm. IR ν_{max} (cm^{-1}): 3340 m, 1755 s, 1735 s, 1635 s, 1605 s, 1548 m, 1230 s, 1220 s, 1200 s, 1035 s. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.0 (12H, s, $COCH_3$), 3.1 (3H, s, N-CH_3), 4.9 (2H, s, $COCH_2$), 5.5 (1H, st, with D_2O to d, $J_{1',2'}$ = 8.2 Hz, H-1'), 11.5 (1H, d, $J_{1',NH}$ = 8.5 Hz, with D_2O disappears, C(4)-NH), 11.7 (1H, s broad,with D_2O disappears, N(3)-H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.0, 20.1, 20.2, 20.3 ($\underline{C}H_3CO$), 26.5 (N-CH_3), 50.92 ($CO\underline{C}H_2$), 61.5 (C-6'), 67.6, 70.0, 72.1 (C-2', C-3', C-4', C-5'), 77.9 (C-1'), 89.8 (C-5), 149.1 (C-4), 156.6 (C-2), 161.7 (C-6), 169.1, 169.5, 169.9 ($CH_3\underline{C}O$), 190.2 ($\underline{C}OCH_2$). Anal. Calcd. for $C_{21}H_{26}N_3O_{12}Cl$: C, 46.03; H, 4.78; N, 7.67. Found: C, 46.30; H, 5.01; N, 7.40.

Cyclation of 5-α-chloracetyl derivatives **2** and **4**.

To 3 ml of DMF, 1 mmol of the corresponding 5-α -chloracetyl derivative (**2** or **4**) was added . To the resulting solution 0.14 g (1 mmol) of anhydrous K_2CO_3 were added. The reaction mixture was stirred at 80-90 °C for variable time. No starting product was then detected by TLC (eluent $CHCl_3$-hexane-EtOH, 6:1:0.25). DMF was eliminated using the following method: To the crude of the above reaction 3 g of silica gel and hexane were added; the mixture was then evaporated under reduced pressure and poured into a short chromatographic column and next eluted with hexane until DMF was eliminated. The compounds were eluted using $CHCl_3$-EtOH (0-25%) mixtures. The eluted fractions containing the compound were evaporated under reduced pressure and crystallized from EtOH and identified as:

5,6-dihydro-4- β -D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-2-methoxy-5-oxo furo[2,3-d]pyrimidine, **6a**. Reaction time: 30 m. 0.4 g (78%). m p 192 °C. $[\alpha]_D^{20}$ = - 14.2° (c 1, $CHCl_3$). UV ($4.69x10^{-5}$ M, MeOH) λ_{max} (ε): 281 (15800), 273 (15500), 264 (12500), 224 (34800) nm. IR ν_{max} (cm^{-1}): 3380 w, 1750 s, 1705 s, 1620 s, 1600 s, 1225 s, 1090 s, 1035 s. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.1 (12H, s, $COCH_3$), 4.1 (3H, s, OCH_3),

4.8 (2H, s,with D_2O disappears, $COCH_2$), 5.7 (1H, m, with D_2O to d, $J_{1',2'}$ = 9.6 Hz, H-1'), 7.3 (1H, d, $J_{1',NH}$ = 9 Hz with D_2O disappears, C(4)-NH). ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.0 (12H, s, $COCH_3$), 4.0 (3H, s, OCH_3), 4.8 (2H, s, $COCH_2$), 5.8 (1H, m, with D_2O to d, $J_{1',2'}$ = 8.2 Hz, H-1'), 8.1 (1H, d, $J_{1',NH}$ = 8.2 Hz, with D_2O disappears, C(4)-NH). ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.5, 20.6 ($\underline{C}H_3CO$), 55.8 (OCH_3), 61.6 (C-6'), 68.1, 70.5, 72.7, 73.6 (C-2', C-3', C-4', C-5'), 75.3 (C-6), 78.6 (C-1'), 91.8 (C-4a), 160.1 (C-4), 169.4 (C-2), 169.9, 170.1, 170.4, 170.5 ($CH_3\underline{C}O$), 185.9 (C-7a), 192.1 (C-5). Anal. Calcd. for $C_{21}H_{25}N_3O_{12}$: C, 49.32; H, 4.93; N, 8.22. Found: C, 49.05; H, 5.18; N, 8.34.

4,5-dioxo-3-methyl-2-methoxy-3,4,5,6-tetahydro-7-β-D-(2,3,4-tri-O-acetyl)xylopyranosyl pyrrolo[2,3-d]pyrimidine, **5b**. Reaction time: 40 minutes. 0.2 g (44%). m p: 198 °C (dec.). $[\alpha]_D^{20}$ = +2.6° (c 1, $CHCl_3$). UV (5.51×10^{-5} M, MeOH), λ_{max} (ε): 291 (8000), 262 (5700) and 230 (40600) nm. IR ν_{max} (cm^{-1}): 1755 s, 1735 s, 1670 s, 1580 s, 1530 s, 1260 s, 1233 s, 1215 s, 1070 s, 1040 s. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.0 (9H, s, CH_3CO), 3.3 (3H, s, N-CH_3), 4.2 (3H, s, OCH_3), 4.9 (2H, s, with D_2O disappears, $COCH_2$), 5.6 (1H, d, $J_{1',2'}$ = 9.6 Hz, H-1'). ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.4, 20.5 ($\underline{C}H_3CO$), 27.1 (N-CH_3), 52.9 ($CO\underline{C}H_2$), 56.9 (O-CH_3), 64.7 (C-5'), 68.5, 72.5 (C-2', C-3', C-4'), 80.0 (C-1'), 95.2 (C-4a), 156.2 (C-7a), 161.5 (C-2), 169.2, 169.6, 169.9 ($CH_3\underline{C}O$), 173.4 (C-4), 189.4 (C-5). Anal. Calcd. for $C_{19}H_{23}N_3O_{10}$: C, 50.33; H, 5.11; N, 9.27. Found: C, 49.99; H, 5.01; N, 9.54.

2,5-dioxo-1-methyl-1,2,5,6-tetrahydro-4-β-D-(2,3,4-tri-O-acetyl)xylopyranosylamino furo[2,3-d]pyrimidine, **7b**. Reaction time: 40 minutes. 0.28 g (63%). m p: 140 °C. $[\alpha]_D^{20}$ = - 51.8° (c 1, $CHCl_3$). UV (5.46×10^{-5} M, MeOH) λ_{max} (ε): 270 (17800), 228 (25300) nm. IR ν_{max} (cm^{-1}): 3650-3300 w broad, 1760 s, 1660 s, 1600 s, 1245 s, 1220 s, 1095 s, 1040 s. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.9 (3H, s, CH_3CO), 2.0 (6H, s, CH_3CO), 3.3 (3H, s, N-CH_3), 5.0 (2H, s, $COCH_2$), 5.7 (1H, st, with D_2O to d, $J_{1',2'}$ = 8.2 Hz, H-1'), 7.5 (1H, d, $J_{1',NH}$ = 8.2 Hz, with D_2O disappears, C(4)-NH). ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.2, 20.3, 20.4 ($\underline{C}H_3CO$), 27.7 (N-CH_3), 62.9 (C-5'), 68.2, 70.2, 71.7 (C-2', C-3', C-4'), 77.3 (C-1'), 77.9 (C-6), 87.7 (C-4a), 154.2 (C-4), 157.7 (C-2), 169.4, 169.5 ($CH_3\underline{C}O$), 177.2 (C-7a), 188.3 (C-5). Anal. Calcd. for $C_{18}H_{21}N_3O_{10}$: C, 49.20; H, 4.81; N, 9.56. Found: C, 48.97; H, 4.97; N, 9.55.

2,5-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1-methyl-1,2,5,6-tetrahydro furo[2,3-d] pyrimidine, **7c**. Reation time: 1 h. 0.3 g (58%). m p: 100-110 °C. $[\alpha]_D^{20}$ = -15.5° (c 1, $CHCl_3$). UV (6.06×10^{-5} M, MeOH) λ_{max} (ε): 269 (17400), 229 (25000) nm. IR ν_{max} (cm^{-1}): 3700-3300 m broad, 1760 s, 1680 s, 1595 s, 1250-1210 s broad, 1038 s. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.0 (12H, s, CH_3CO), 3.4 (3H, s, N-CH_3), 4.8 (2H, s, $COCH_2$), 5.7 (1H, st, with D_2O to d, $J_{1',2'}$ = 9.4 Hz, H-1'), 7.1 (1H, d, $J_{1',NH}$ = 9.4 Hz, with D_2O disappears, C(4)-NH). ^{13}C-NMR ($CDCl_3$) δ(ppm): 20.3, 20.5 ($\underline{C}H_3CO$), 28.1 (N-CH_3), 61.3 (C-6'), 67.8, 70.3, 72.5, 73.2 (C-2', C-3', C-4', C-5'), 77.5 (C-6), 77.6 (C-1'), 88.1 (C-4a), 154.7 (C-4), 158.2 (C-2), 169.3, 169.6, 170.0, 170.3 ($CH_3\underline{C}O$), 177.2 (C-7a), 187.3 (C-5). Anal. Calcd. for $C_{21}H_{25}N_3O_{12}$: C, 49.31; H, 4.93; N, 8.22. Found: C, 49.26; H, 4.94; N, 7.84.

General procedure for the synthesis of 5-nitroso uracil derivatives **8**.

0.21 g (3 mmol) of $NaNO_2$ were added to 6 ml of a solution of 2 mmol of **3** in hot acetic acid. The mixture was stirred at room temperature during 2-3 minutes and poured into 100 ml of water. The solution was neutralized with $NaHCO_3$ and allowed to stand in the fridge. In the course of time a crystalline compound precipitated being identified as the corresponding 5-nitroso derivatives **8**. The compounds proved to be pure.

2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-5-nitroso-1,2,3,6-tetrahidro pyrimidine, **8a**. 0.92-1.02 g (85-95%). m p: 210-215 °C (dec.). $[\alpha]_D^{20}$ = + 51° (c 1, DMSO). UV (4.44×10^{-5} M, MeOH) λ_{max} (ε): 322 (14000), 230 (7600) nm. Visible (5.36×10^{-3} M, MeOH) λ_{max} (ε): 510 (62) nm. IR ν_{max} (cm^{-1}). 3620-3200 m broad, 1750 s, 1705 m, 1665 s, 1550 s, 1275 s, 1230 s, 1065 s, 1035 s. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.0 (12H, s, CH_3CO), 5.8 (1H, st, with D_2O to d, $J_{1',2'}$ = 9 Hz, H-1'), 10.1 (1H, s, with D_2O disappears, N(3)-H), 12.2 (1H, d, $J_{1',NH}$= 9 Hz, with D_2O disappears, C(4)-NH). ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.1, 20.2, 20.3, 20.5 ($\underline{C}H_3CO$), 61.8 (C-6'), 66.1, 70.6, 72.3, 72.4 (C-2', C-3', C-4', C-5'), 76.6, (C-1'), 139.8 (C-5), 154.1 (C-4), 157.1 (C-2), 164.5 (C-6), 169.2, 169.3, 169.5, 170.1 ($CH_3\underline{C}O$). Anal. Calcd. for $C_{18}H_{22}N_4O_{12}.3H_2O$: C, 40.00; H, 5.22; N, 10.36. Found: C, 40.16; H, 5.32; N, 10.29.

2,6-dioxo-4- β -D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1-methyl-5-nitroso-1,2,3,6-tetrahydro pyrimidine, **8c**. 0.90-0.97 g (76-82%). m p: 190 °C (dec.). $[\alpha]_D^{20}$ = +67.0° (c 1, DMSO). UV (4.57 x 10^{-5} M, MeOH) λ_{max} (ε): 323 (11800), 231 (5800) nm. Visible (4.3 x 10^{-3} M, MeOH) λ_{max} (ε): 511 (58) nm. IR ν_{max} (cm^{-1}): 3650-3200 m broad, 1755 s, 1730 s, 1685 s, 1645 s, 1573 s, 1535 s, 1230 s, 1070 s, 1038 s. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.7 (3H, s, CH_3CO), 2.0 (9H, s, CH_3CO), 3.2 (3H, s, N-CH_3), 5.8 (1H, m, with D_2O to d, $J_{1',2'}$ = 8.2 Hz, H-1'), 12.2 (1H, d, $J_{1',NH}$ = 8.9 Hz with D_2O disappears, C(4)-NH). ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.1, 20.3, 20.4, 20.5 ($\underline{C}H_3CO$), 26.7 (N-CH_3), 61.8 (C-6'), 66.1, 70.6, 72.3, 72.4 (C-2', C-3', C-4', C-5'), 76.7 (C-1'), 140.1 (C-5), 152.3 (C-4), 156.7 (C-2), 164.1 (C-6), 169.2, 169.3, 169.5, 170.1 ($CH_3\underline{C}O$). Anal. Calcd. for $C_{19}H_{24}N_4O_{12}.5H_2O$: C, 38.64; H, 5.80; N, 9.49. Found: C, 38.60; H, 5.75; N, 9.48.

General procedure for the synthesis of 5-amino uracils derivatives **9**.

1 mmol of **8** was dissolved in 10 ml of water. A solution of 0.5 g (2.88 mmol) of $Na_2S_2O_4$ in 10 ml of water was then added. The mixture was stirred at room temperature during some seconds and the reduction happened at once. That was allowed to stand in the fridge appearing a precipitate after some minutes. The solid was filtered and identified as the corresponding 4,5-diamino uracil derivatives **9**. The recrystallization of them compounds were unable because the unstability of their solutions.

5-amino-2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1,2,3,6-tetrahydro pyrimidine, **9a**. 0.23-0.28 g (46-56%). m p: 156 °C (dec.). IR ν_{max} (cm^{-1}): 3650-3300 m broad, 1760 s, 1695 s, 1655 s, 1630-1615 s broad, 1233 s, 1210 s, 1065 s, 1033 s. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.0 (12H, s, CH_3CO), 4.0-6.0 (3H, m, C(5)-NH_2, H-1'), 6.6 (1H, d, $J_{1',NH}$ = 8.2 Hz, with D_2O disappears, C(4)-NH), 10.7 (1H, s broad, with D_2O disappears, N(3)-H), 11.3 (1H, s broad, with D_2O disappears, N(1)-H). ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.0 (12H, s, CH_3CO), 4.5-6.0 (3H, m, C(5)-NH_2 and H-1'), 5.3 (1H, d, $J_{1',NH}$ = 9.0 Hz, with D_2O disappears, C(4)-NH), 10.7 (1H, s broad, with D_2O disappears, N(1)-H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.2, 20.3, 20.36, 20.4 ($\underline{C}H_3CO$), 61.6 (C-6'), 67.8, 70.5, 71.6, 72.8 (C-2', C-3', C-4', C-5'), 79.7 (C-1'), 98.7 (C-5), 141.0 (C-4), 149.4 (C-2), 161.4 (C-6), 169.3, 169.4, 169.6, 169.9 ($CH_3\underline{C}O$).

5-amino-2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1-methyl-1,2,3,6-tetrahydro pyrimidine, **9c**. 0.16 g (34%). m p: 155-160 °C (dec). IR ν_{max} (cm^{-1}): 3650-3200 m broad, 1745 s, 1700 s, 1665 s, 1638 s, 1600 s, 1250 s, 1233 s, 1220 s, 1100 s, 1035 s. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.0 (12H, s, CH_3CO), 3.1 (3H, s, N-CH_3), 4.5-6.0 (3H, m, C(5)-NH_2 and H-1'), 5.3 (1H, d, $J_{1',NH}$ = 9.0 Hz, with D_2O disappears, C(4)-NH). ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.1, 20.2, 20.3, 20.4 ($\underline{C}H_3CO$), 26.7 (N-CH_3), 61.6 (C-6'), 67.8, 70.5, 71.5, 72.8 (C-2', C-3', C-4', C-5'), 79.7 (C-1'), 98.6 (C-5), 139.5 (C-4), 149.4 (C-2), 160.6 (C-6), 169.2, 169.3, 169.5, 169.9 ($CH_3\underline{C}O$).

Procedure for the synthesis of 8-azapurines **10**.

1 mmol of **9** was dissolved in 6 ml of acetic acid, then 0.14 g (2 mmol) of $NaNO_2$ were added. The mixture was stirred at room temperature to complete solution, when no more starting product was detected by TLC (eluent CH_2Cl_2-MeOH, 9:1), acetic acid was eliminated by adding methanol and evaporating several times. Finally a mixture formed by the residue, 1 g of silica gel and hexane was evaporated under reduced pressure, poured into a short chromatographic column and eluted using CH_2Cl_2-MeOH 0-5%. The compounds obtained were purified in hot ethanol and adding hexane.

5,7-dioxo-3-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosyl-4,5,6,7-tetrahydro-vic-triazolo[4,5-d]pyrimidine, **10a**. 0.29 g (60%). m p: 210-215°C (dec). $[\alpha]_D^{20}$ = -18.2° (c 1, DMSO). UV (7.03×10^{-5} M, MeOH) λ_{max} (ε) : 271 (3500), 231 (7300), 221 (8600) nm. IR ν_{max} (cm^{-1}): 3700-3200 m broad, 1745 s, 1700 s, 1665 s, 1638 s, 1600 s, 1250 s, 1233 s, 1100 s, 1035 s. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.75 (3H, s, CH_3CO), 2.0 (9H, s, CH_3CO), 5.9 (1H, d, $J_{1',2'}$ = 9 Hz, H-1'), 9.7 (2H, s broad, disappears with D_2O, N(1)-H, N(3)-H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 19.9, 20.2, 20.3, 20.4 ($\underline{C}H_3CO$), 61.6 (C-6'), 67.6, 68.9, 72.8, 72.9 (C-2', C-3', C-4', C-5'),79.6 (C-1'), 122.9 (C-7a), 155.0 (C-3a), 158.3 (C-5), 159.0 (C-7), 168.2, 169.2, 169.5, 169.9 ($CH_3\underline{C}O$). Anal. Calcd. for $C_{18}H_{21}N_5O_{11}$: C, 44.72; H, 4.38; N, 14.49. Found: C, 44.81; H, 4.25; N,14.45.

In vivo antitumor activity of **2a**, **4a**, **4b**, **5b**, **6a**, **10c**, **11** and **12** against the **L1210** Leukemia.

The tests have been done by the NCI according to the protocol described in the instruction 14. The **L1210** Leukemia has been implanted

into CDF_1 mice and each mouse was inoculated one with different doses and observed for 20 d. The tests evaluation is : %T/C= media survival time (MST) treated/MST control x100 and the survival systems indicate a degree of sucess when %T/C exceed 125.

Acknowledgement

The anticancer activity data are the results of the screening performed under the auspices of the Developmental Therapeutics Program. Division of Cancer Treatment, NCI, Bethesda, Maryland.

The autors thank the Consejeria de Educación y Ciencia, Junta de Andalucía, Spain, for the award of a fellowship of the Plan de Formación del Personal Investigador to one of them (M.L. Quijano).

REFERENCES

1. For Part 21 see: J. Negrillo, A. Sánchez, M. Nogueras and M. Melgarejo, **J. Chem. Pharm. Bull.**, in press.
2. This paper has been presented in part at the "VIIth International Round Table, Nucleosides, Nucleotides and their Biological Applications" (Konstanz,F.R.G., 1986).
3. M. Nogueras, Mª Luisa Quijano, M. Melgarejo and A. Sánchez, **Nucleosides, Nucleotides**,1986, 5, 301-312.
4. J.P. Marquet, J. Andre-Louisfert and E. Bisagni, **Bull. Soc. Chim. Fr.**, 1969, 4344.
5. E. Bisagni, J.P. Marquet and J. Andre-Louisfert, **Bull. Soc. Chim.Fr.**, 1969, 991.
6. H.J.E. Hess and T.H. Cronin, **Ger. Pat.**, 1 817 146 (1969). (**Chem. Abstr.**, 1970, 72, 31 834)
7. H. Wolfers, U. Kraatz and F. Korte, **Chem. Ber.**, 1973, 106, 874.
8. C.Fauran, G. Bourgery, G. Raynaud and N. Dorme, **Ger. Pat.**, 2 446 593 (1973). (**Chem. Abstr.**, 1975, 83, 97 351).
9. K.E. Shulte, J. Reisch, A. Mock and K.H. Kaucler, **Arch. Pharm.,Weinheim. Ger.**, 1963, 296, 235.
10. N. Kawahara and T. Nakajima, **Heterocycles**, 1984, 22, 2217.
11. R.C. Bleackley, A.S. Jones and R.T. Walker, **Tetrahedron**, 1976, 32, 2795.

12. F. Shatz, M. Skrobal, G. Werner and B. Rosenwirth, **Chemica Scripta**, 1986, 26, 67.
13. Y. Hamano and T. Nakamura, **Jpn. Kokai**, 78 12 888. (**Chem. Abstr.**, 1978, 89, 6341).
14. M. Melgarejo, C. Rodriguez y A. Sánchez, **An. Quím.**, 1981, 77C, 126.
15. Compounds **4c**, and **5c** have been sent to the National Cancer Institute of Brussels to study their activity as anticancer agents.
16. R. Asenjo, M. Melgarejo, C. Rodriguez, M. Nogueras y A. Sánchez, **An. Quím.**, 1982, 78C, 93.

Received January 20, 1988.