Reaction of 4,5-Diamino, 5-Amino-4-glucosylamino and 4-Amino-5-glucosylaminopyrimidines with Nitrous Acid. Synthesis, Anticancer and Anti-AIDS Activities of 8-Azapurines [1]

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The reaction of the 4,5-diamino, 5-amino-4-glucosylamino and 4-amino-5-glucosylaminopyrimidines **3a**, **3b**, **3c** and **4** with nitrous acid is described. The 8-azapurines **7a**, **7c**, **8** and the *N*-nitrosoamino derivative **5** have been obtained. Some of these products were tested for anticancer and anti-AIDS activity.

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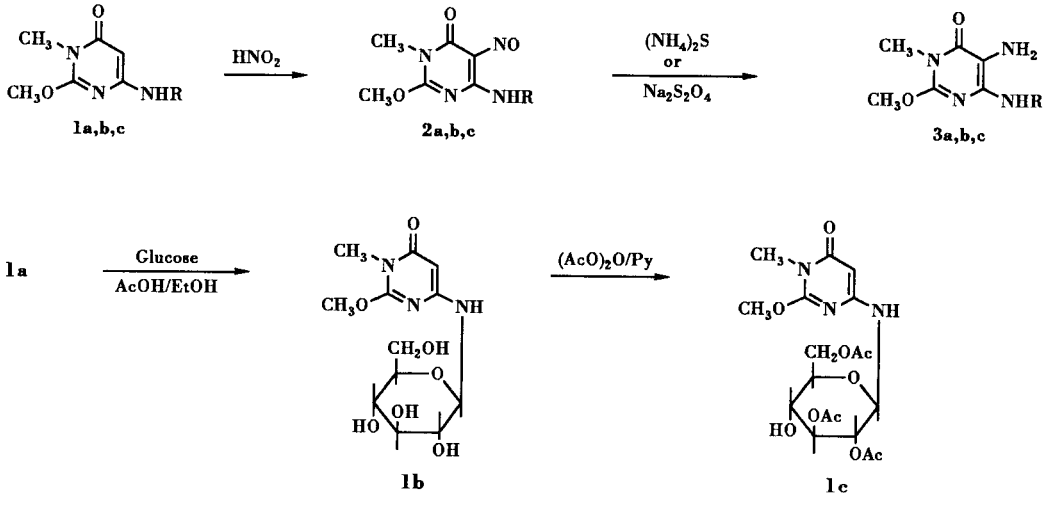
The 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (8-azapurines) [2] are natural products present in the fermentation products of a variety of "S albus" (vasocidine and patocidine) [3] and they are an important class of compounds, structurally and chemically related to naturally occurring nucleosides and some antibiotics [3,4]. The 8-azapurine nucleosides exhibit extraordinary biochemical and pharmacological activities [5]. They act as nucleoside antimetabolites in many biological systems. As they are isosteric with the purine nucleosides, their incorporation into DNA or RNA fragments is of interest.

Several methods have been described in the literature for the synthesis of 8-azapurine nucleosides [6]. In recent years, a number of 8-azaadenine D-ribofuranosyl [7], D-arabinofuranosyl [7,8] and other glycosyl derivatives [6,9] have been prepared. However, their synthesis was encompassed with difficulties as the additional *N*-atom at the position 8 caused problems of regioselectivity enlarging the number of glycosylation products. Recently, Seela and coworkers [10] have carried out regioselective and stereoselective synthesis of 8-azapurine nucleosides by using the nucleobase-anion glycosylation employing either the solid-liquid phase-transfer technique or the sodium hydride-mediated reaction.

During the last decade, our laboratory has developed a regiospecific synthesis of 5-amino-4-glycosylamino [11,12] and 4-amino-5-glycosylaminopyrimidines [13.14]. In this paper we describe the reaction of some of the above mentioned products with nitrous acid in view of testing the 8-azapurine nucleosides for anticancer and anti-AIDS activities.

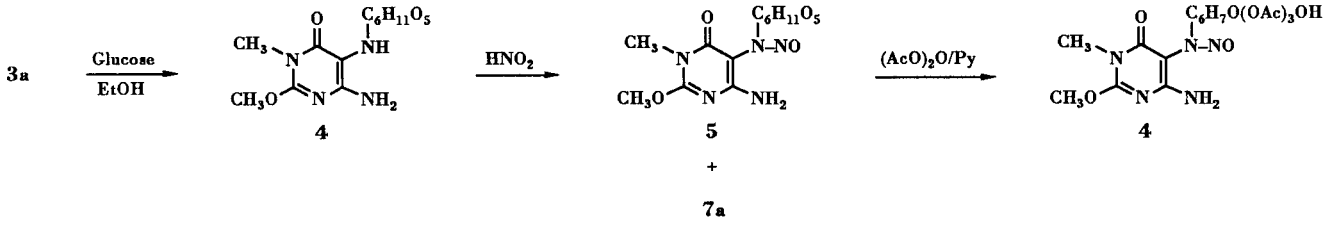
As we have previously reported [11], the reaction of the 4-aminopyrimidine **1a** with anhydrous D-glucose and glacial acetic acid in absolute ethanol stereoselectively led to the 4-β-D-glucopyranosylamino anomer **1b** (Scheme 1). On the other hand, the reaction of the 4,5-diaminopyrimidine **3a**, under the same conditions led, by and Amadori rearrangement [15], to the corresponding 7-polyhydroxyalkylpteridine [14]. However, when the reaction was carried out without catalytic acetic acid, the 5-*N*-glucoside **4** was obtained (Scheme 2). A study on the specific rotation values of compound **4** in several media

Scheme 1



a R = H
b R = β-D-glucopyranosyl
c R = β-D-(tetra-*O*-acetyl)glucopyranosyl

Scheme 2



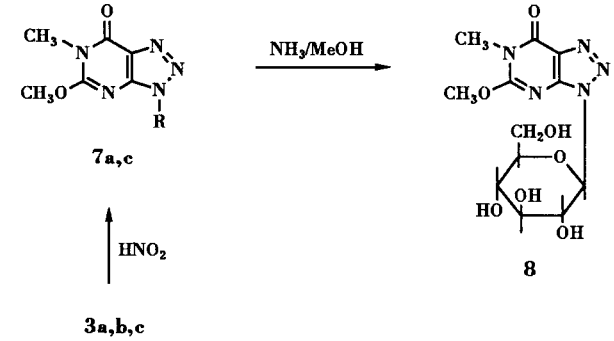
demonstrated that this product exists as a mixture of the α and β anomers together with the azomethine isomer as we have previously observed in other similar syntheses [13].

The treatment of the *N*-glucoside **4** with nitrous acid in water at room temperature afforded the *N*-nitroso-*N*-glucosyl-4-aminopyrimidine **5** and the 8-azapurine **7a** in 52% and 5.5% respectively. The separation of both products was easily accomplished due to the low solubility of **7a** in water. The structures of these two compounds were established by the usual analytical techniques and by the following observations: **7a** was identical to an authentic sample of 6,7-dihydro-6-methyl-5-methoxy-6-oxo-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine made by nitrosation of **1a** with aqueous nitrous acid, reduction of the corresponding 5-nitroso derivative **2a** with ammonium sulphide (10% aqueous solution) and cyclization of the 4,5-diamino derivative **3a** with aqueous nitrous acid (Scheme 1 and 3). The configuration of the sugar moiety in compound **5** has been shown to be β because the observed coupling constant between H-1′ and H-2′ protons in ^{1}H-nmr spectrum was 8.5 Hz.

The reaction of **5** with acetic anhydride and pyridine at room temperature provide selective acetylation of three of the four hydroxyl groups of the sugar moiety as can be shown by ^{1}H-nmr and ^{13}C-nmr (see Experimental). We think that the hydroxyl group which remains in compound **6** could be that at C(2′), because it is the nearest to the pyrimidine ring and in the ^{1}H-nmr spectrum it is observed as a doublet (J = 2.8 Hz). All the hydroxyl groups were acetylated in acetylation reactions of several samples similar to **5** in which the sole significant difference with regard to **5** was the absence of the *N*-nitroso group [16]. This fact points to some type of effect exerted by the *N*-nitroso group, which is able to establish a difference between the mentioned hydroxyl group and those others of the glycosyl moiety. The configuration of the sugar moiety in compound **6** has been shown to be β by the value of the coupling constant $J_{1',2'}$ = 9.2 Hz. Compound **6** was again obtained when **5** was treated with hot acetic anhydride and pyridine (80°), whereas the reaction in hot acetic anhydride or acetic anhydride/sulphuric acid led to decomposition and a complex mixture was obtained (tlc).

The synthesis of **8** has been carried out by two procedures (Scheme 1 and 3). In the first procedure, we started from the 4-glucosylaminopyrimidine **1b** [11], which was nitrosated with aqueous nitrous acid to give the blue 5-nitroso derivative **2b** [12]. This compound was reduced with 10% aqueous solution of ammonium sulphide [12] and the amino derivative **3b** obtained was then cyclized with aqueous nitrous acid. The 8-azapurine nucleoside was isolated as the completely acetylated derivatve **7c** because crystallization was not viable from this reaction [17]. The second procedure started from the 4-(tetra-*O*-acetyl)glucopyranosylaminopyrimidine **1c** obtained by acetic anhydride/pyridine acetylation of **1b** [11]. Compound **1c** was nitrosated with nitrous acid in water/ethanol mixture [18] to give the blue 5-nitrosoglucosylaminopyrimidine **2c**. Compound **2c** was reduced with sodium dithionite in a water/ethanol mixture and the 5-amino-4-glucosylaminopyrimidine **3c** obtained was cyclized with nitrous acid in a water/ethanol mixture. The 8-azapurine nucleoside **7c** obtained was then treated with methanolic ammonia to give the fully deprotected nucleoside **8** in excellent yield. Compounds **3b** and **3c** are unstable, particularly in solution, so, they must be immediately used after preparation. The configuration in compounds **7c** and **8** were β ($J_{1',2'}$ = 9 Hz for **7c** and 8.9 Hz for **8**).

Scheme 3



The above-mentioned results are consistent with the presence of a primary amino group in position five of the pyrimidine ring to obtain the desired 8-azapurines [19], across a diazonium salt intermediate. Compound **4** cannot form this salt and reacts to produce the corresponding *N*-nitroso derivative **5**.

Compounds **1b**, **2b** and **7a** have been tested in mice as inhibitors of the L-1210 Leukemia and none of them have shown significant anticancer activity. Furthermore, compounds **1b**, **2a**, **4** and **8** have been tested "in vitro" as inhibitors of the HIV virus. None of the compounds showed anti-AIDS activity. The tests were carried out at the National Cancer Institute (NCI) according to standard methods.

EXPERIMENTAL

Melting points were determined using a Gallenkamp Melting Point Apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded with a Hitachi Perkin-Elmer R-600 and a Bruker AM-300 spectrometers using tetramethylsilane as the internal standard. Chemical shifts were expressed in δ values. The following abbreviations were used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; dd, double doublet. Carbon-13 nuclear magnetic resonance spectra were determined with a Bruker AM-300 spectrometer. Carbon atoms have been assigned using the DEPT technique. Ultraviolet spectra were recorded with a Perkin-Elmer Lambda spectrophotometer. The following abbreviation was used: sh, shoulder. Infrared spectra were recorded using a Beckman 4250 spectrophotometer (potassium bromide). The following abbreviations were used: m, medium; st, strong; w, weak. The analysis for C, H and N have been performed in the "Servicios Técnicos de la Universidad de Granada" using a Perkin-Elmer 240C equipment. Mass spectra were recorded using a Hewlett-Packard HP-5988-A spectrometer. Specific rotation values were determined with a Perkin-Elmer 141 polarimeter. Thin layer chromatography (tlc) was performed on Merck pre-coated tlc aluminum sheets silica gel 60 F_{245}, visualization was accomplished by ultraviolet absorbance followed by carrying with a 4% sulphuric acid/methanol solution.

4-Amino-1,6-dihydro-5-glucosylamino-1-methyl-2-methoxy-6-oxopyrimidine **4**.

This compound was prepared by a previously published procedure [14]; ^{13}C-nmr (DMSO-d_6): 161.65, 158.08, 153.03 (C-4, C-2, C-6), 98.81 (C-5), 91.44 (C-1'), 78.02, 76.91, 72.22, 70.39 (C-2', C-3', C-4', C-5'), 61.55 (C-6'), 55.17 (CH_3O), 27.49 (CH_3N); ms: 332 (M^+).

4-Amino-5-(*N*-nitrosoglucopyranosylamino)-1-methyl-2-methoxy-6-oxopyrimidine **5**.

To a solution of 3.32 g (10 mmoles) of **4** in 40 ml of water, 0.76 g (11 mmoles) of sodium nitrite and 11 ml of 1*N* hydrochloric acid solution were added. The mixture was stirred at room temperature for 15 minutes and then evaporated in a rotary evaporator to half volume. The yellow solid which precipitated was filtered, washed with cold water and identified as **7a**, 0.1 g (5.5%). The mother liquors were kept in a refrigerator for 12 hours. The solid which appear was filtered and washed with cold water. Evaporation of mother liquors afforded new crops. The solid was recrystallized from water and identified as **5**, 1.88 g (52%), mp 185-186° dec; $[\alpha]_D^{20}$ = -72.6° (c 1, DMSO); ^{1}H-nmr (DMSO-d_6): 6.66 (2H, s, br, exchangeable with deuterium oxide, NH_2), 5.95 (1H, d, J = 8.5 Hz, C(1')-H), 5.50 (1H, d, J = 2.8 Hz, exchangeable with deuterium oxide, OH), 3.95 (3H, s, CH_3O), 3.20 (3H, s, CH_3N); ^{13}C-nmr (DMSO-d_6): 160.45, 159.31, 156.33 (C-4, C-2, C-6), 92.84 (C-1'), 87.48 (C-5), 79.90, 75.50, 70.34, 70.06 (C-2', C-3', C-4', C-5'), 61.82 (C-6'), 55.92 (CH_3O), 27.58 (CH_3N); ir: 3490 (m), 3370 (st), 3290 (m, br), 1615 (st), 1540 (st), 1505 (m), 1480 (m), 1375 (m), 1225 (m), 1080 (m), 1025 (m), 1005 (m), 900 (m), 820 (m); uv (water): λ max (nm) (ϵ) 211 (25500), 256 (12100).

Anal. Calcd. for $C_{12}H_{19}N_5O_8$: C, 39.89; H, 5.30; N, 19.38. Found: C, 40.29; H, 5.40; N, 19.28.

4-Amino-5-[*N*-nitroso-β-D-(3,4,6-tri-*O*-acetyl)glucopyranosylamino]-1-methyl-2-methoxy-6-oxopyrimidine **6**.

To a mixture of 10 ml of dry pyridine and 10 ml of acetic anhydride, 0.4 g (1.1 mmoles) of compound **5** was added. The mixture was stirred at room temperature for 7 hours. The solution obtained was poured on crushed ice and left for 24 hours. The precipitate was filtered off, washed with cold water and recrystallized from ethanol. It was possible to obtain a second crop of **6** from the mother liquors; thus, they were extracted with chloroform (3 x 10 ml), dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue obtained was dissolved in methanol and evaporated several time. 0.28 g (52%), mp 170-172°; $[\alpha]_D^{20}$ = -64.9° (c 1, chloroform); ^{1}H-nmr (deuteriochloroform): 6.30 (1H, d, J = 9.2 Hz, C(1')-H), 5.70 (1H, d, J = 2.8 Hz, exchangeable with deuterium oxide, OH), 5.30 (2H, s, br, exchangeable with deuterium oxide, NH_2), 4.00 (3H, s, CH_3O), 3.35 (3H, s, CH_3N), 2.05 (9H, s, CH_3 acetate groups). ^{13}C-nmr (deuteriochloroform): 170.77, 170.21, 169.86 (CO acetate groups), 161.50, 159.93, 157.18 (C-4, C-2, C-6), 93.25 (C-1'), 88.44 (C-5), 74.71, 74.07, 66.70, 66.33 (C-2', C-3', C-4', C-5'), 61.88 (C-6'), 56.32 (CH_3O), 28.29 (CH_3N), 20.87, 20.72 (CH_3 acetate groups); ir: 3450 (m), 3350 (st), 3250 (w), 3210 (w), 1755 (st), 1740 (st), 1620 (st, br), 1585 (m), 1535 (st, br), 1480 (m), 1370 (m), 1230 (st, br), 1070 (m), 1050 (m), 1030 (m), 1010 (m), 910 (m), 825 (m); uv (water): λ max (nm) (ϵ) 210 (15600), 256 (6200); ms: 458 (M^+).

Anal. Calcd. for $C_{18}H_{25}N_5O_{11}$: C, 44.35; H, 5.17; N, 14.37. Found: C, 44.73; H, 5.28; N, 14.73.

6,7-Dihydro-6-methyl-5-methoxy-6-oxo-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidine **7a**.

To a solution of 2.04 g (12 mmoles) of **3a** in 80 ml of hot water, 1.66 g (24 mmoles) of sodium nitrite and 1.44 g (24 mmoles) of acetic acid were added. The mixture was stirred at room temperature for 15 minutes. The solid which appeared was filtered, washed with cold water and recrystallized in water, 1.65 g (76%), mp 230°; ^{1}H-nmr (DMSO-d_6): 7.50 (1H, s, br, exchangeable with deuterium oxide, N(3)-H), 4.00 (3H, s, CH_3O), 3.30 (3H, s, CH_3N); ^{13}C-nmr (DMSO-d_6): 156.52, 155.30, 150.17 (C-3a, C-5, C-7), 124.64 (C-7a), 56.34 (CH_3O), 27.80 (CH_3N); ir: 3200 (w), 3130 (m, br), 1685 (st), 1610 (m, br), 1560 (st), 1520 (m), 1435 (m), 1355 (m), 1240 (m), 1200 (m), 805 (m), 780 (m); uv (water): λ max (nm) (ϵ) 207 (23800), 256 (7000).

Anal. Calcd. for $C_6H_7N_5O_2$: C, 39.78; H, 3.87; N, 38.66. Found: C, 39.91; H, 3.78; N, 38.54.

5-Amino-4-β-D-(tetra-*O*-acetyl)glucopyranosylamino-1-methyl-2-methoxy-6-oxopyrimidine **3c**.

To a suspension of 1.03 g (2 mmoles) of **2c** [18] in 20 ml of methanol, 20 ml of a sodium dithionite water solution (1 g/ml) was added. The mixture was stirred at room temperature until the blue colour disappeared. To the colourless solution, 30 ml of water was added and next washed with chloroform (5 x 10 ml). The chloroform solution was dried with sodium sulphate, filtered and the solvent removed in rotary evaporator, 0.70 g (70%), mp 162°; ^{1}H-nmr (deuteriochloroform): 5.90 (1H, d, J = 9 Hz, exchangeable with deuterium oxide, C(4)-NH), 4.80-6.00 (2H, s, br, exchangeable with deuterium oxide, NH_2), 4.00 (3H, s, CH_3O), 3.40 (3H, s, CH_3N), 2.00 (12H, s, CH_3 acetate groups); ir: 3390 (m,

br), 1755 (st), 1655 (st), 1635 (st), 1535 (st), 1480 (st), 1440 (m), 1370 (st), 1230 (st, br), 1090 (m), 1065 (st), 1030 (st, br); uv (methanol): λ max (nm) (ε) 255 (sh), 293 (9900).

6,7-Dihydro-6-methyl-5-methoxy-3-β-D-(tetra-*O*-acetyl)glucopyranosyl-7-oxo-1,2,3-triazolo[4,5-*d*]pyrimidine **7c**.

This compound was first prepared by a previously published method [17] and then by the following procedure:

To a solution of 1.5 g (3 mmoles) of **3c** in 30 ml of ethanol and 20 ml of water, 0.414 g (6 mmoles) of sodium nitrite and a solution of 0.36 g (6 mmoles) of acetic acid in 10 ml of water were added. The mixture was stirred at room temperature for 15 minutes and evaporated at reduced pressure until half volume. The solution was then washed with chloroform (5 x 10 ml) and the chloroform solution was dried with sodium sulphate, filtered and the solvent removed in rotary evaporator. The residue was crystallized from ethanol, 1 g (65%); ^{13}C-nmr (deuteriochloroform): 170.53, 170.18, 169.47, 168.70 (CO acetate groups), 157.83, 155.34, 147.98 (C-3a, C-5, C-7), 126.75 (C-7a), 84.18 (C-1'), 74.97, 73.57, 68.53, 67.74 (C-2', C-3', C-4', C-5'), 61.78 (C-6'), 57.19 (CH_3O), 28.45 (CH_3N), 20.72, 20.64, 20.37 (CH_3 acetate groups).

6,7-Dihydro-3-β-D-glucopyranosyl-6-methyl-5-methoxy-7-oxo-1,2,3-triazolo[4,5-*d*]pyrimidine **8**.

To a 20 ml of a saturated ammonia solution in methanol, 1.02 g (2 mmoles) of **7c** was added. The solution was left at 4° for 24 hours and next was evaporated at reduced pressure. The residue was crystallized from ethanol/water/ethyl ether mixture, 0.66 g (95%), mp 200°; $[\alpha]_D^{20}$ = -14.6° (C 1, water); ^{1}H-nmr (DMSO-d_6): 5.60 (1H, d, J = 8.9 Hz, C(1')-H), 4.10 (3H, s, CH_3O), 3.40 (3H, s, CH_3N); ^{13}C-nmr (DMSO-d_6): 157.48; 155.03, 147.80 (C-3a, C-5, C-7), 125.53 (C-7a), 84.89 (C-1'), 80.07, 76.96, 70.79, 69.70 (C-2', C-3', C-4', C-5'), 60.81 (C-6'), 56.77 (CH_3O), 28.01 (CH_3N); ir: 3470 (st), 3200 (m, br), 3150 (st), 1710 (st), 1570 (st), 1575 (m), 1445 (m), 1410 (m), 1380 (m), 1210 (st), 1115 (m), 1090 (st), 1060 (st), 1040 (st), 975 (st), 895 (st), 780 (m); uv (water): λ max (nm) (ε) 208 (16600), 255 (9400).

Anal. Calcd. for $C_{12}H_{17}N_5O_7$: C, 41.98; H, 4.99; N, 20.40. Found: C, 42.30; H, 5.03; N, 20.94.

Anticancer and Anti-AIDS Activity.

The "in vivo" antitumor activity against L-1210 Leukemia was determined by the NCI according to the standard protocol. The L-1210 Leukemia was implanted into CDF_1 mice and each mouse was inoculated one at various dose levels and observed for 20 days. The results were evaluated as %T/C = (median survival time (MST) treated/MST control) x 100, and compound is considered active if %T/C exceeds 125.

The "in vitro" anti-HIV activity was determined by the NCI against T4 lymphocytes (CEM cell line) exposed to HIV at a virus-to-cell ratio of approximately 0.05. Cultures were incubated at 37° in a 5% carbon dioxide atmosphere for 6 days. Individual wells were analyzed by addition of the tetrazolium salt and spectrophotometrycally studies were performed to quantitate formazan production. Drug-treated virus-infected cells were compared with drug-treated non-infected cells and with other appropriate controls (untreated infected and untreated non-infected cells, drug-containing wells without cells, *etc*) on the same plate. Approximate values for 50% effective concentration (EC_{50}), 50% inhibitory concentration (IC_{50}) and therapeutic Index (TI = IC_{50}/EC_{50}) were calculated for each test.

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