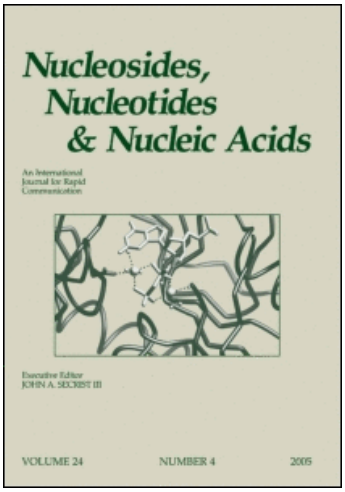

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STUDIES ON NUCLEOSIDES : PART XXVIII[1]. SYNTHESIS OF 4-AMINO (OR HYDROXY)-6-METHYLTHIO-1-(3'-DEOXY-β-D-RIBOFURANOSYL)-1-H-PYRAZOLO[3,4-d]PYRIMIDINES

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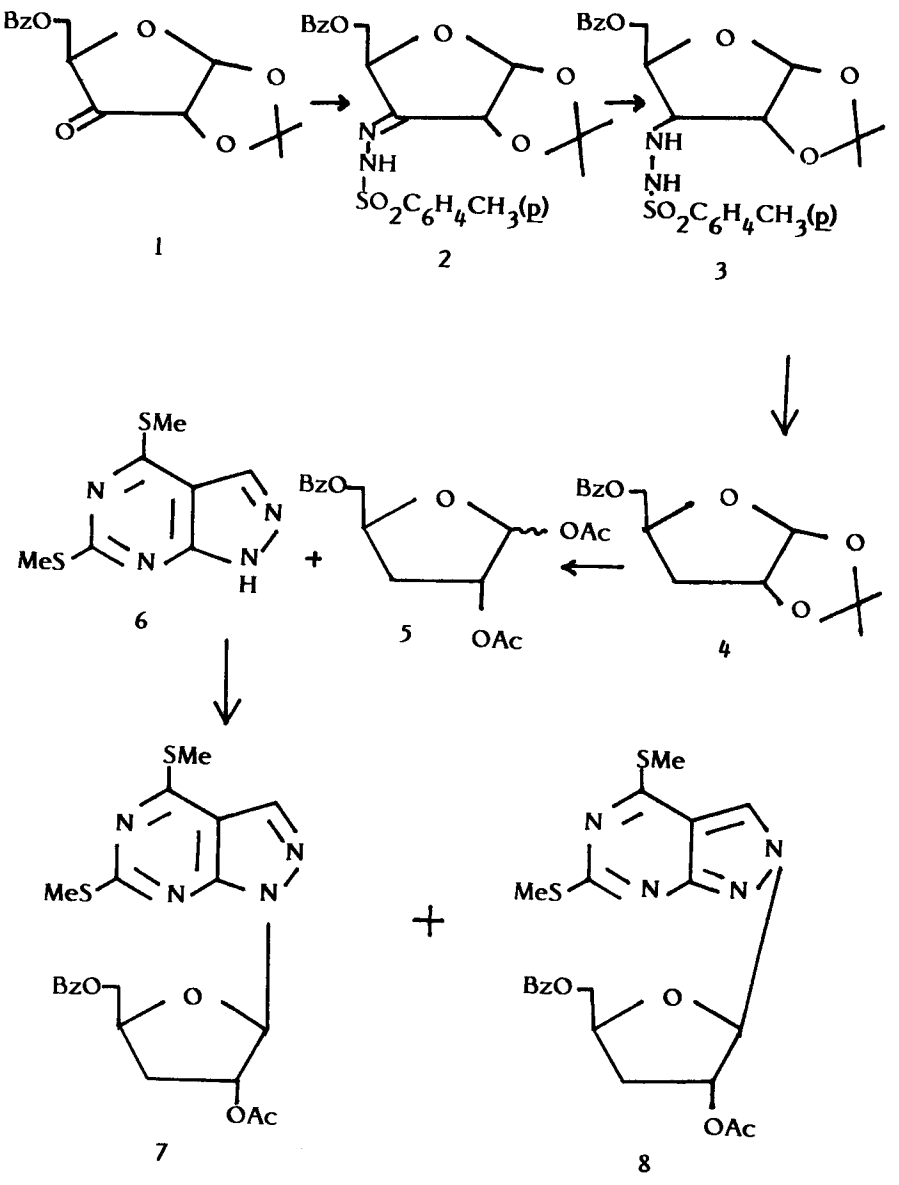
Abstract : *4-Amino-6-methylthio-1-(3'-deoxy-β-D-ribofuranosyl)-1H-pyrazolo-[3,4-d]pyrimidine (**11**) and 6-methylthio-4(5H)-oxo-1-(3'-deoxy-β-D-ribofuranosyl)-1H-pyrazolo[3,4-d]pyrimidine (**12**) have been synthesized from 1,2-di-O-acetyl-5-O-benzoyl-3-deoxyribofuranose (**5**) and 4,6-bis (methylthio)-1H-pyrazolo-[3,4-d]pyrimidine (**6**) in a convergent fashion. Structural proofs are based on MS, IR, ^{1}H NMR, ^{13}C NMR and elemental analyses.*

Derivatives of pyrazolo[3,4-d]pyrimidine, including the parent compound allopurinol (4-hydroxy-1H-pyrazolo[3,4-d]pyrimidine) have been intensively studied because they are metabolized in an unusual way by pathogenic parasitic protozoa of the genera Leishmania and Trypanosoma, which results in antiparasitic activity[2]. 4-Amino-1-β-D-ribofuranosyl- and 4(5H)-oxo-1-β-D-ribofuranosyl-, 1H-pyrazolo[3,4-d]pyrimidines have been found as promising candidates for the treatment of leishmaniasis and relevant literature has been reviewed recently[3]. While other pentofuranosides of pyrazolo[3,4-d]-pyrimidines like D-xylofuranosides[4], D-arabinofuranosides[4,5], 2'-deoxy-β-D-ribofuranosides[6] and 2',3'-dideoxy-D-ribofuranosides[7] have been synthesized as potential biologically active agents, 3'-deoxy-D-ribofuranosyl derivative of adenine (an isostere of pyrazolo[3,4-d]pyrimidine), a natural product (cordycepin) does show good antiparasitic activity[8] against Leishmania donovani along with other biological activities and has been synthesized several times[9] since its isolation. This observation and our interest in pyrazolo-[3,4-d]pyrimidines[10] as a source of biologically active substances[11] has prompted us to synthesize 4-amino(or hydroxy)-6-methylthio-1-(3'-deoxy-β-D-ribofuranosyl)-1H-pyrazolo[3,4-d]pyrimidines.

The starting material chosen for our synthetic plan was 4,6-bis (methylthio)-1H-pyrazolo[3,4-d]pyrimidine[12]. The 6-methylthio group of this base is comparable to 2-methylthio group of the corresponding isomeric purine derivatives and such 2-methylthio group has been known to contribute towards the biological activities in related nucleosides[13]. The other starting material 3-deoxy-1,2-O-isopropylidene-5-O-benzoyl-α-D-erythro-pentofuranose (**4**) was prepared following literature procedure. The procedure used for the synthesis of key sugar intermediate was similar to literature[14] except that benzoyl group instead of methoxycarbonyl group was used for the protection of primary hydroxyl function (SCHEME 1).

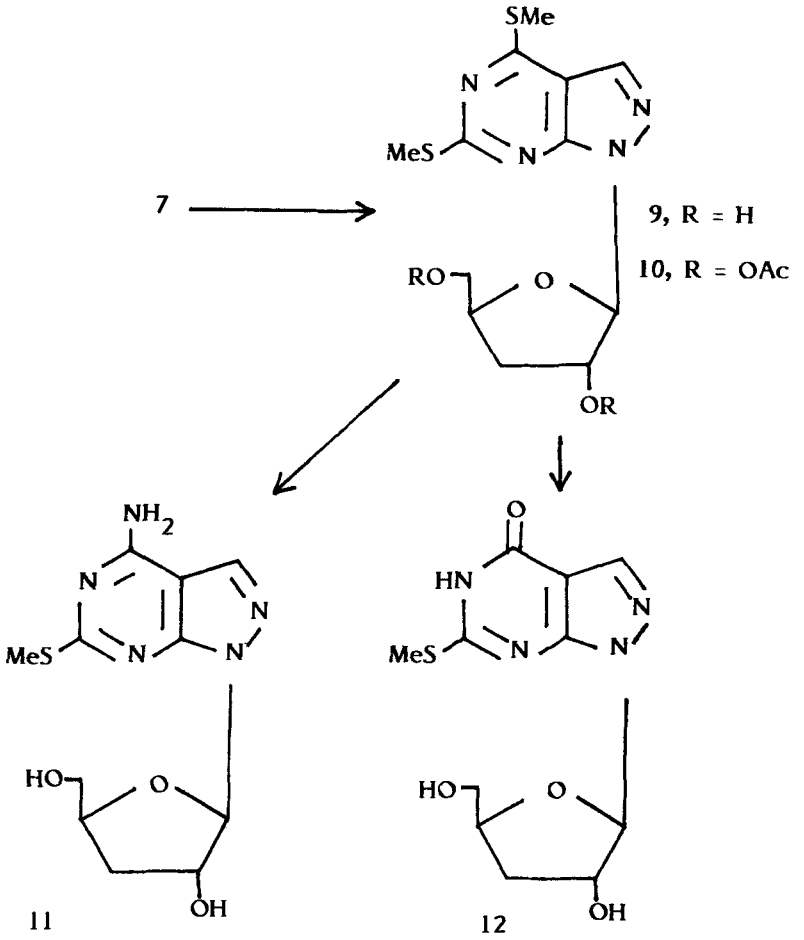
The starting ketone (**1**) was easily accessible by literature method[15] from D-xylose. The 3-deoxy-1,2-O-isopropylidene-5-O-benzoyl-α-D-erythro-pentofuranose (**4**) has been reported as an oil[16], while our product was a crystalline solid. The identity and purity of this compound was confirmed with the help of high resolution ^{1}H and ^{13}C NMR. Acetolysis under standard conditions provided an anomeric mixture of 1,2-di-O-acetate (**5**) having α : β ratio of 1:1 as determined by ^{1}H NMR. No effort was made to separate this mixture and it was used as such for subsequent glycosylation. Lewis acid catalysed[17] glycosylation of 4,6-bis(methylthio)-1H-pyrazolo)-[3,4-d]pyrimidine (**6**) with this sugar (**5**) gave a mixture of two nucleosides (N-1, **7** and N-2, **8**) in ratio of 30:1 (SCHEME 1). The site of glycosylation of the major product **7** was deduced to be N-1 on the basis of ^{13}C NMR data. It is well precedented that the site N-1/N-2 of glycosylation can be easily and unambiguously determined from the ^{13}C NMR spectra[10,11,18]. Since expected signal for C-3 in **7** was likely to be in the region of aromatic carbons of benzoyl group, **7** was hydrolysed to give **9**, in which the C-3 signal appeared at 133.0 ppm indicating **7** to be N-1-isomer. Diol **9** was further acetylated to give diacetate **10** in order to get a ^{13}C NMR spectrum which could be compared directly to the spectrum of **8** for unambiguous assignment of site of glycosylation.

Thus, C-3 signal in **10** appeared at 133.1 ppm, while corresponding carbon in the spectrum of **8** appeared at 123.6 ppm along with other expected differences for heterocyclic carbons. Configuration of the sugar moiety in the nucleosides was derived from the ^{1}H NMR analyses. It is well precedented[19] that in the spectra of α-nucleosides vicinal coupling constant (J) of anomeric proton is more than in the corresponding β-anomer. Since H-1'



SCHEME 1

in the spectra of both **7** and **8** appeared as singlets, they were assigned β-configuration. The target molecules **11** and **12** were synthesized using standard group manipulation as shown in SCHEME 2.



SCHEME 2

EXPERIMENTAL

All melting points were taken with a Buchi 530 melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on Perkin Elmer R-30 (90 MHz) or WM 400 MHz spectrometer, and are reported in parts per million from internal standard tetramethyl silane on the δ scale. ^{13}C NMR spectra were recorded on a WM 400 MHz NMR spectrometer at 100 MHz. Mass spectra were recorded on a Jeol JMS D300 spectrometer at an ionization energy of 70 ev. Infra-red spectra were taken on a Perkin Elmer 157 grating infracord and ultra-violet spectra were recorded on Perkin Elmer Lambda 15 uv/vis spectrophotometer (λ_{max} in nm).

Solvents and reagents were dried and purified prior to use when deemed necessary. Reactions requiring an inert atmosphere were run under a blanket of nitrogen. Analytical chromatography was performed with plates precoated with silica gel. Column chromatography was performed by using silica gel (60-120 mesh) and flash chromatography was performed with silica gel (250-400 mesh).

1,2-O-Isopropylidene-5-O-benzoyl-α-D-erythro-3-pentosulofuranose-p-toluenesulfonylhydrazone (2). 1,2-O-Isopropylidene-5-O-benzoyl-α-D-erythro-3-pentosulofuranose (10 g, 34.2 mmol) was taken in abs. ethanol (70 mL) and to it was added p-toluenesulfonhydrazide (7 g, 37.6 mmol). The reaction mixture was refluxed for 2 h and then cooled, when white crystalline needles of the hydrazone, **2** separated. It was filtered, washed with ether to give pure **2** (13.5 g, 90%), mp 174-175°C; MS (m/z): 460 (M^+); IR (Nujol): 3220 (NH), 1700 (C=O), 1620 (C=N); PMR ($CDCl_3$): δ 1.25 and 1.31 (2s, 6H, isopropylidene), 2.27 (s, 3H, Me-Ph), 4.2-5.0 (m, 4H, H-2, H-5 and H-5'), 5.9 (d, 1H, J = 5 Hz, H-1), 7-8 (m, 10H, Ar-H, NH).

Anal. Calcd. for $C_{22}H_{24}N_2O_7S$: C, 57.38; H, 5.25; N, 6.08.
Found : C, 57.50; H, 5.41; N, 6.22.

1,2-O-Isopropylidene-3-deoxy-3-(p-toluenesulfonylhydrazino)-5-O-benzoyl-α-D-ribofuranose (3). To a stirred solution of the **2** (10 g, 21.7 mmol) in a mixture of THF and MeOH (80 mL, 1:1) was added a trace of methyl orange (indicator) and sodium cyanoborohydride (0.63 g, 10 mmol). Methanolic HCl (saturated) was then added dropwise keeping the color of the solution at the red-yellow transition point. The mixture was stirred at room temp. for 1 h. A second portion of $NaCNBH_3$ (0.31 g, 5 mmol) was added followed by dropwise addition of methanolic HCl to maintain pH at ≃ 3.8. The mixture was stirred for 1 h at 25°C. A saturated solution of $NaHCO_3$ was then added (pH ≃ 7) and the mixture was concentrated at reduced pressure and room temp. Water (60 mL) was added and the solution extracted with CH_2Cl_2 (3 x 40 mL), washed with brine (3 x 30 mL), dried over Na_2SO_4 and then solvent removed at 40°C under reduced pressure to give **3** as a white solid (8.5 g, 85%), mp 150°C ($CHCl_3$-hexane); MS (m/z): 462 (M^+); IR (KBr): 1715 (C=O), 1610 (phenyl); PMR ($CDCl_3$, 90 MHz) : δ 1.30 and 1.45 (2s, 6H, isopropylidene), 2.25 (s, 3H, Me-Ph), 3.0-3.3 (m, 1H, H-3), 3.7-4.3 (m, 3H, H-4, H-5, H-5'), 4.55 (t, 1H, $J_{1,2} = J_{2,3}$ ◻ 4 Hz, H-2), 5.7 (d, 1H, J = 4 Hz, H-1), 7.1-8.0 (m, 9H, ArH).

Anal. Calcd. for $C_{22}H_{26}N_2O_7S$: C, 57.13; H, 5.67; N, 6.06.
Found : C, 57.32; H, 5.72; N, 6.10.

3-Deoxy-1,2-O-isopropylidene-5-O-benzoyl-α-D-erythro-pentofuranose (4). A mixture of **3** (5 g, 10.8 mmol) and sodium acetate trihydrate (5.9 g, 43.3 mmol) in abs. ethanol (140 mL) was refluxed for 1 h. Solvent was removed under vacuum, residue taken up in water (100 mL) and extracted with CH_2Cl_2 (3 x 60 mL). The organic layer was washed with water (1 x 30 mL), dried over Na_2SO_4 and solvent removed to give 4.0 g of yellow syrup. The crude product was purified by flash chromatography (hexane : EtOAc, 95:5) to give **4**, crystallized from a mixture of $CHCl_3$ and hexane (1.8 g, 60%), mp 61°C; MS (m/z) : 263 (M^+-15); IR (KBr) : 1720 (C=O), 1600 (phenyl); PMR ($CDCl_3$, 400 MHz) : δ 1.36 and 1.56 (2s, 6H, isopropylidene), 1.81 (m, 1H, H-3), 2.19 (dd, 1H, J = 4, 13.5 Hz, H-3), 4.33 (dd, 1H, J = 6, 12 Hz, H-5), 4.5-4.6 (m, 2H, H-5' and H-4), 4.79 (t, 1H, $J_{1,2} = J_{2,3}$ = 4 Hz, H-2), 5.89 (d, 1H, J = 4 Hz, H-1), 7.46 (t, 2H, J = 7.5 Hz, Ar-H), 7.58 (t, 1H, J = 7.5 Hz, Ar-H), 8.07 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) : 26.1, 26.7, 35.4, 65.2, 75.8, 80.2, 105.7, 111.3, 128.3, 129.7, 133.0, 166.2. Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52.
Found : C, 64.78; H, 6.80.

1,2-Di-O-acetyl-5-O-benzoyl-3-deoxy-D-ribofuranose (5). To a well stirred solution (0°C) of **4** (5.0 g, 18 mmol) in glacial acetic acid (68 mL) and acetic anhydride (6.8 mL) was added conc. H_2SO_4 (3.6 mL) dropwise. After storage at room temp. for three days, the solution was poured into vigorously stirred ice-water (100 mL) and the resulting solution was extracted with $CHCl_3$ (3 x 50 mL). The organic layer was washed with water (2 x 30 mL), aq. saturated $NaHCO_3$ (1 x 40 mL) and water (1 x40 mL) respectively, dried (Na_2SO_4) and concentrated to give the diacetate **5** (4.2 g, 73%) as viscous oil. MS (m/z) : 279 (M^+-Ac), 263 (M^+-AcOH); IR (film) : 1680 (C=O, benzoate), 1720 (C=O, acetates); PMR ($CDCl_3$, 90 MHz) : δ 2.03 (s, 3H, OAc), 1.8-2.3 (m, 2H, H-3), 5.15 (m, 1H, H-2), 4.0-4.7 (m, 3H, H-4, H-5, H-5'), 6.1 (s, 1/2H, H-1), 6.8 (d, 1/2H, J = 4 Hz, H-1), 7.2-7.5 (m, 3H, Ar-H), 7.8-8.1 (m, 2H, Ar-H).

4,6-Bis(methylthio)-1-(2'-O-acetyl-5'-O-benzoyl-3'-deoxy-β-D-ribofuranosyl)-1H-pyrazolo[3,4-d]pyrimidine and 4,6-bis(methylthio)-2-(2'-O-acetyl-5'-O-benzoyl-3'-deoxy-β-D-ribofuranosyl)-2H-pyrazolo[3,4-d]pyrimidine (7 and **8** respectively). A mixture of 4,6-bis(methylthio)-1H-pyrazolo[3,4-d]pyrimidine (3.6 g, 16.9 mmol) and **5** (5.0 g, 15.5 mmol) in dry acetonitrile (200 mL) was stirred at 70°C for 1 h. The reaction mixture was cooled to 50°C and freshly distilled borontrifluoride etherate (2.3 mL, 16.2 mmol) added

to it and reaction mixture refluxed for 2 h. The solvent was removed at reduced pressure, the residue taken up in EtOAc, washed with aq. $NaHCO_3$, water and dried over Na_2SO_4. The solvent was removed at reduced pressure and residue purified by column chromatography over silica gel. Elution with a mixture of EtOAc and $CHCl_3$ (4:96) gave a solid which was crystallized to give pure **7** (2.5 g, 60% based on recovered base), mp 68-70°C (hex-$CHCl_3$); MS (m/z) : 474 (M^+), IR (KBr) : 1720 ($COCH_3$); PMR ($CDCl_3$, 400 MHz) : δ 2.16 (s, 3H, OAc), 2.32 (dd, 1H, J = 6.0, 13 Hz, H-3'), 2.62 (s, 3H, SMe), 2.68 (s, 3H, SMe), 2.9-2.97 (m, 1H, H-3'), 4.42 (dd, 1H, J = 6.0, 12 Hz, H-5'), 4.56 (dd, 1H, J = 4, 12 Hz, H-5''), 4.74-4.82 (m, 1H, H-4'), 5.71 (d, 1H, J = 5.0 Hz, H-2'), 6.53 (s, 1H, H-1'), 7.41 (t, 2H, J = 7.5 Hz, Ar-H), 7.56 (t, 1H, J = 7.5 Hz, Ar-H), 7.87 (s, 1H, H-3), 8.0 (d, 2H, J = 7.5 Hz, Ar-H).

Anal. Calcd. for $C_{21}H_{22}N_4O_5S_2$: C, 53.15; H, 4.67; N, 11.81.
Found : C, 52.3; H, 4.45; N, 11.30.

Further elution gave compound **8** (80 mg, 2% based on recovered base) as an oil. MS (m/z) : 474 (M^+); PMR ($CDCl_3$, 400 MHz) : δ 2.18 (s, 3H, OAc), 2.30 (dd, 1H, J = 6.0, 14 Hz, H-3'), 2.65 (s, 3H, SMe), 2.66 (s, 3H, SMe), 2.72-2.82 (m, 1H, H-3''), 4.45 (dd, 1H, J = 5.5, 12 Hz, H-5'), 4.69 (dd, 1H, J = 3, 12 Hz, H-5''), 4.8-4.9 (m, 1H, H-4'), 5.85 (d, J = 5 Hz, H-2'), 6.02 (s, 1H, H-1'), 7.35 (t, 2H, J = 7.5 Hz, Ar-H), 7.52 (t, 1H, J = 7.5 Hz, Ar-H), 7.92 (d, 2H, J = 7.5 Hz, Ar-H), 8.15 (s, 1H, H-3) : ^{13}C NMR ($CDCl_3$) : δ 11.8, 14.2, 20.8, 32.4, 65.0, 78.7, 80.2, 94.8 (C-1'), 109.0, 123.6 (C-3), 128.3, 129.6, 133.0, 158.9, 166.2, 167.1, 169.2, 169.8.

Anal. Calcd. for $C_{21}H_{22}N_4O_5S_2$: C, 53.15; H, 4.67, N, 11.81.
Found : C, 52.38; H, 4.55; N, 12.11.

4,6-Bis(methylthio)-1-(3'-deoxy-β-D-ribofuranosyl)-1H-pyrazolo[3,4-d]-pyrimidine (9). The compound **7** (1 g, 2.1 mmol) was taken up in methanolic ammonia (75 ml, MeOH was saturated at 0°C with ammonia) and reaction mixture kept at room temperature for 12 h. The excess solvent was removed under reduced pressure and crude product was passed through a freshly generated (H^+ form) resin-column (Dowex X-50). The column was eluted with MeOH-$CHCl_3$ (2:98) to give **9** as a white solid (0.50 g, 72%), mp 120°C ($CHCl_3$-hexane); MS (m/z) : 328 (M^+); PMR (DMSO-d_6, 400 MHz) : δ 2.06-2.16 (m, 1H, H-3'), 2.66 (s, 3H, SMe), 2.71 (s, 3H, SMe), 2.6-2.74 (m, 1H, H-3''), 3.6-3.68 (m, 1H), 3.91-4.04 (m, 2H), 4.6-4.67 (m, 1H), 4.72 (br s, 1H), 4.95 (d, 1H, J = 4.5 Hz), 6.42 (s, 1H, H-1'), 7.96 (s, 1H, H-3);

^{13}C NMR (DMSO-d_6) : δ 11.6, 13.8, 36.1 (C-3'), 64.1, 74.5, 81.3, 90.8 (C-1'), 109.1, 133.0 (C-3), 152.0, 165.0, 168.4.

Anal. Calcd. for $C_{12}H_{16}N_4O_3S_2$: C, 43.89; H, 4.91; N, 17.06.
Found : C, 43.98; H, 4.82; N, 17.36.

4,6-Bis(methylthio)-1-(2',5'-di-O-acetyl-3'-deoxy-β-D-ribofuranosyl)-1H-pyrazolo[3,4-d]pyrimidine (10). The diacetate **10** was prepared using Ac_2O and pyridine by standard procedure. Yield 85%; PMR ($CDCl_3$, 400 MHz) : δ 1.97 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.18 (dd, 1H, J = 5.5, 14 Hz, H-3'), 2.54 (s, 3H, SMe), 2.60 (s, 3H, SMe), 2.65-2.75 (m, 1H, H-3"), 4.04 (dd, 1H, J = 7, 12 Hz, H-5'), 4.26 (dd, 1H, J = 3, 12 Hz, H-5'), 4.5-4.6 (m, 1H, H-4'), 5.58 (d, 1H, J ▫ 5 Hz, H-2'), 6.44 (s, 1H, H-1'), 7.88 (s, 1H, H-3): ^{13}C NMR ($CDCl_3$) : 11.7, 14.3, 20.7, 20.9, 34.0, 65.9, 78.1, 78.5, 88.6 (C-1'), 109.7, 133.1 (C-3), 152.6, 165.0, 169.6, 169.9, 170.6.

4-Amino-6-methylthio-1-(3'-deoxy-β-D-ribofuranosyl)-1H-pyrazolo[3,4-d]-pyrimidine (11). The compound **9** (0.32 g, 1 mmol) was heated with methanolic ammonia 40 mL) in a steel bomb at 120°C for 10 h. The excess solvent and ammonia were removed and residue crystallized to give pure **11** (0.14 g, 51%), mp 235°C (MeOH); MS (m/z): 328 (M^+); IR (KBr) : 3200 (NH_2), 3300 (OH); UV (MeOH) : 240, 272; PMR (DMSO-d_6, 90 MHz) : δ 2.0-2.8 (m, 2H, H-3'), 2.65 (s, 3H, SMe), 3.5-3.7 (m, 1H), 4.2-4.9 (m,3H), 5.64 (d, 1H, J = 4.5 Hz), 6.25 (s, 1H, H-1'), 7.9 (br s, 2H, NH_2), 8.2 (s, 1H, H-3).

Anal. Calcd. for $C_{11}H_{15}N_5O_3S$: C, 44.3; H, 5.08; N, 23.56.
Found : C, 44.6; H, 5.12; N, 23.72.

6-Methylthio-4(5H)-oxo-1-(3'-deoxy-β-D-ribofuranosyl)-1H-pyrazolo-[3,4-d]pyrimidine (12). A mixture of **9** (0.32 g, 10 mmol) and 1N NaOH (4 mL) in MeOH (15 mL) was refluxed for 3 h. The solvent was removed under reduced pressure and residue purified by chromatography over silica gel. Elution with MeOH-EtOAc (2:98) gave the title compound **12** (0.15 g, 55%), mp 212-15°C (MeOH); MS (m/z); 298 (M^+); IR (KBr) : 3350 (OH), 1700 (C=O); UV (MeOH): 263; PMR (DMSO-d_6, 90 MHz) : δ 1.9 -2.6 (m, 2H, H-3'), 2.5 (s, 3H, SMe), 3.2-4.8 (m), 6.0 (s, 1H, H-1'), 7.92 (s, 1H, H-3).

Anal. Calcd. for $C_{11}H_{14}N_4O_4S$: C, 44.43; H, 4.73; N, 18.78.
Found : C, 44.40; H, 4.75; N, 18.62.

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