Synthesis of 6-*C*-Substituted 9-Tetrahydrofuranylpurine Derivatives

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6-Dicyanomethylene-9-tetrahydrofuranylpurine (4), which was obtained by the reaction of 9*H*-1,6-dihydropurine-$\Delta^{6,\alpha}$-propanedinitrile (3) with 2,3-dihydrofuran, has been catalytically hydrogenated to the α-(aminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetonitrile (5) in good yield using *N*,*N*-dimethylformamide–benzene as a solvent over Pd–C under medium pressure. Substitution of 5 with amines gave the corresponding alkylaminomethylene purines (6 and 7). Reaction of 5 with hydrazine gave the pyrazole derivative (8).

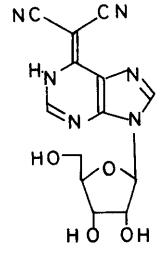
Keywords 9-(tetrahydrofuran-2-yl)-9*H*-1,6-dihydropurine-$\Delta^{6,\alpha}$-propanedinitrile; α-(aminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetonitrile; *N*-substituted α-(aminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetonitrile; pyrazole

6-*N*-Substituted purine derivatives and 9-alkylpurine derivatives exhibit a number of interesting biological[2] and antiviral activities.[3] Therefore, in recent years much attention has been focused on 6-*C*-substituted purine derivatives.

As part of our studies on the synthesis of 6-*C*-substituted purine derivatives, we have recently reported the reduction of 9*H*-1,6-dihydropurine-$\Delta^{6,\alpha}$-propanedinitrile (**3**) and 9-alkyl 1,6-dihydropurine-6-$\Delta^{6,\alpha}$-propanedinitrile to give 6-enaminonitrile purine derivatives.[4] Also, it was found that 9-β-D-ribofuranosyl-9*H*-1,6-dihydropurine-$\Delta^{6,\alpha}$-propanedinitrile (**1**) and α-(aminomethylene)-9-β-D-ribofuranosyl-9*H*-purine-6-acetonitrile (**2**) exhibited antitumor activity.[5] In this paper we describe the synthesis of α-(aminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetonitrile (**5**) *via* 6-dicyanomethylene-9-tetrahydrofuranylpurine (**4**) using catalytic hydrogenation in an *N*,*N*-dimethylformamide (DMF)–benzene solvent system, and synthesis of purine derivatives *via* **5**.

Reaction of **3** with 2,3-dihydrofuran in the presence of boron trifluoride etherate gave 9-(tetrahydrofuran-2-yl)-9*H*-1,6-dihydropurine-$\Delta^{6,\alpha}$-propanedinitrile (**4**) in 68% yield. The ultraviolet (UV) spectrum of **4** was identical with that of 9-(methoxymethyl)-9*H*-1,6-dihydropurine-$\Delta^{6,\alpha}$,-propanedinitrile prepared by the substitution of 6-chloro-9-(methoxymethyl)purine with malononitrile.[4] Therefore, the tetrahydrofuranyl group was concluded to be at position 9 of the purine ring. Hydrogenation of **4** over Pd–C in DMF–benzene (1 : 1) under medium pressure (4 atm) gave **5** in 62% yield. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **5** in deuteriodimethyl sulfoxide (DMSO-d_6) showed two sets of vinyl proton signals [δ 7.69 (*E*) and δ 9.32 (*Z*)] as a doublet of doublets which collapsed to a singlet with deuterium oxide. Generally, it is known that the signal of the vinyl proton of an enamine moiety appears at δ 7—8.[6] However, the downfield shift of the vinyl proton of the *Z*-form of **5** is due to the anisotropic effect of the purine ring. Therefore, the geometrical isomers (*E*/*Z*) of **5** exist in an enamino-nitrile tautomeric equilibrium rather than an imino-nitrile equilibrium. The ratio of geometrical isomers (*E*/*Z*) was found to be 15 : 85 by comparing the area of the vinyl proton signal of each isomer in the ^{1}H-NMR spectrum.

Substitution of **5** with furfurylamine under heating gave α-(*N*-furfurylaminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetonitrile (**6**) in 91% yield. The ^{1}H-NMR spectrum of **6** in DMSO-d_6 showed the presence of two sets of vinyl protons at δ 7.66 (*E*) and at δ 9.33 (*Z*). The ratio of geometrical isomers (*E*/*Z*) in DMSO-d_6 was 29 : 71. Substitution of **5** with piperidine gave (*Z*)-α-(piperidinomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetonitrile (**7**) in 88% yield. The ^{1}H-NMR spectrum of **7** showed the vinyl proton signal at δ 9.25 (1H, s). This indicates that the enamine moiety was in the *Z* form only. Reaction of **5** with hydrazine gave the pyrazole (**8**) in 70% yield.[7]



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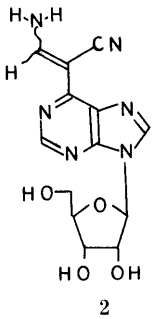

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Experimental

All melting points were determined on a Yamato capillary melting point apparatus, MP-21, and are uncorrected. Infrared (IR) spectra were taken on a JASCO A-102 spectrometer. UV spectra were measured using a Hitachi EPS-3T spectrometer. ^{1}H-NMR spectra were recorded on JEOL JNM-FX100 and JEOL GX spectrometers using tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a JEOL JMS-D300 spectrometer using a direct inlet system; ionizing potential, 70 eV. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; sh, shoulder; and dd, doublet of doublets.

9-(Tetrahydrofuran-2-yl)-9*H*-1,6-dihydropurine-$\Delta^{6,\alpha}$-propanedinitrile (4) A cold (0—5 °C) stirred solution of **3** (0.500 g, 2.7 mmol) and 2,3-dihydrofuran (3.80 g, 54 mmol) in dry DMF (10 ml) was treated with $BF_3O(C_2H_5)_2$ (0.08 ml), and the solution was stirred for 15 h at room temperature. The solution was adjusted to pH 7 with concentrated NH_4OH, and evaporated *in vacuo*. The residue was diluted with water (10 ml), and allowed to stand overnight in an ice-bath. The precipitate was collected by filtration, and recrystallized from DMF–ether to give **4** (0.469 g, 68%) as colorless microcrystals, mp 250—253 °C (dec.). IR (KBr): 3225 (NH), 2210 (CN), 2190 (CN) cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 236 (3.94), 335 (4.48). ^{1}H-NMR (DMSO-d_6) δ: 2.06—2.39 (4H, m), 3.90—4.19 (2H, m), 6.28 (1H, t, J=4.4 Hz, C_1-H), 8.24 (1H, s, C_2H), 8.46 (1H, s, C_8H). MS *m*/*z*: 254 (M^+), 184 (B+1). *Anal.* Calcd for $C_{12}H_{10}N_6$: C, 56.68; H, 3.96; N, 33.06. Found: C, 56.52; H, 3.85; N, 33.32.

α-(Aminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetonitrile (5) A solution of **4** (0.500 g, 1.9 mmol) and 5% (w/w) methanolic ammonia (5 ml) in DMF–benzene (1 : 1 (v/v), 240 ml) was hydrogenated over 5% Pd–C (250 mg) at room temperature for 40 h under 4 atm pressure. The catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on neutral alumina (20 g) with 3% MeOH in $CHCl_3$ as the eluent and the eluate was evaporated *in*

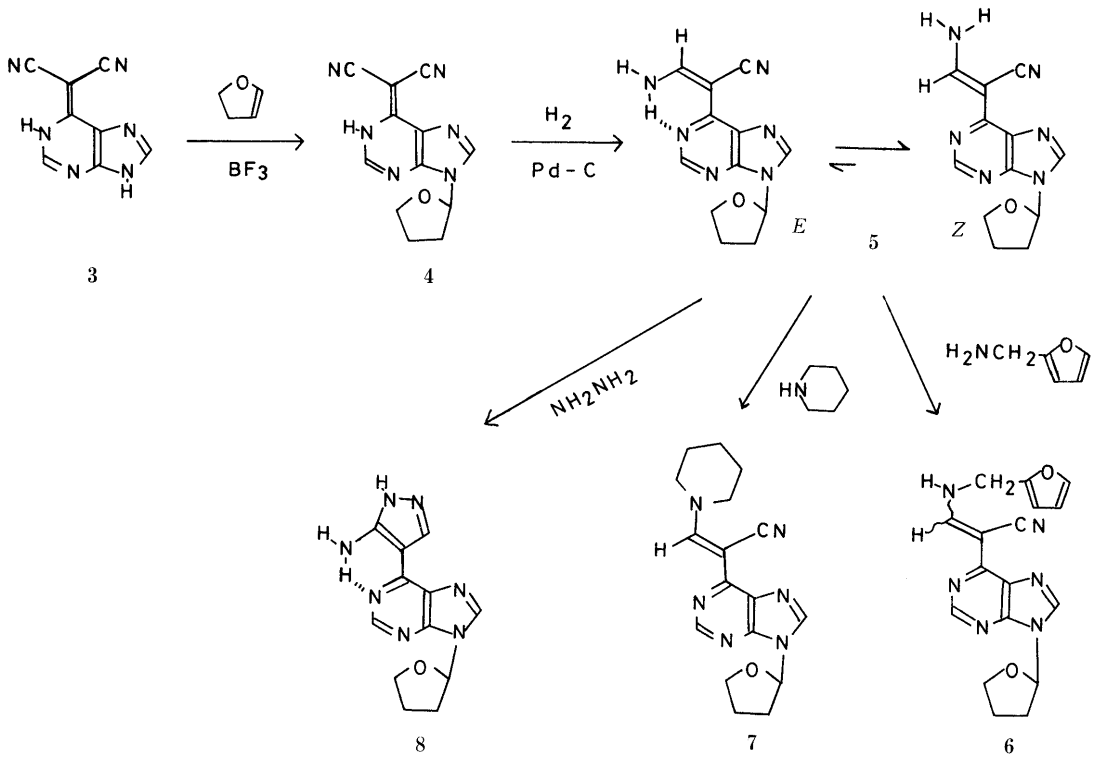

Chart 1

vacuo. The residue was recrystallized from MeOH–hexane to give **5** (313 mg, 62%) as slightly yellow needles, mp 180—183 °C (dec.). IR (KBr): 3253 (NH), 3175 (NH), 2200 (CN) cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 229 (4.21), 329 (4.44), 340 (4.38 sh). ^{1}H-NMR (DMSO-d_6) δ: 2.02—2.40 (4H, m), 3.82—4.29 (2H, m), 6.31 (1H, m, C_1·H), 7.69 (0.15H, dd, J=16, 8 Hz, C=CH, *E*), 7.97—8.42 (1.7H, m, NH, *Z*, exchangeable with D_2O), 8.51 (0.85H, s, C_8H, *Z*), 8.57 (0.15H, s, C_8H, *E*), 8.59 (0.85H, s, C_2H, *Z*), 8.68 (0.15H, s, C_2H, *E*), 9.32 (0.85H, dd, J=16, 8 Hz, C=CH, *Z*), 10.68 (0.15H, m, NH, *E*, exchangeable with D_2O). MS *m/z*: 256 (M^+), 186. *Anal.* Calcd for $C_{12}H_{12}N_6O$: C, 56.24; H, 4.72; N, 32.80. Found: C, 56.23; H, 4.81; N, 32.89.

α-(*N*-Furfurylaminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetonitrile (6) A solution of **5** (0.100 g, 0.39 mmol) and furfurylamine (0.114 g, 1.17 mmol) in EtOH (4 ml) was refluxed for 3.5 h, then allowed to cool. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (5 g) with CH_2Cl_2 as the eluent and the eluate was evaporated *in vacuo*. The residue was recrystallized from MeOH–hexane to give **6** (0.120 g, 91%) as colorless needles, mp 146—147 °C. IR (KBr): 3340 (NH), 2200 (CN), 1635 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 232 (4.23), 340 (4.49), 350 (4.48, sh), 376 (3.85). ^{1}H-NMR (DMSO-d_6) δ: 2.09—2.47 (4H, m), 3.83—4.29 (2H, m), 4.56—4.74 (2H, m, CH_2), 6.44 (2H, d, J=1.5 Hz, C_1·H), 7.66 (1H, br s), 7.91 (0.29H, d, J=14 Hz, C=CH, *E*), 8.51 (0.71H, s, C_8H, *Z*), 8.59 (1H, s, C_2H, *Z* and C_8H, *E*), 8.68 (0.29H, s, C_2H, *E*), 9.33 (0.71H, br s, C=CH, *Z*), 11.35 (0.29H, m, NH, *E*, exchangeable with D_2O). MS *m/z*: 336 (M^+), 266 (B+1). *Anal.* Calcd for $C_{17}H_{16}N_6O_2$: C, 60.70; H, 4.80; N, 24.99. Found: C, 60.51; H, 4.67; N, 25.18.

(*Z*)-α-(Piperidinomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetonitrile (7) A solution of **5** (0.100 g, 0.39 mmol) and piperidine (0.116 g, 1.17 mmol) in EtOH (3 ml) was refluxed for 2 h, then allowed to cool. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5 g) with 2% MeOH in $CHCl_3$ as the eluent and the eluate was evaporated *in vacuo*. The residue was recrystallized from $CHCl_3$–hexane to give **7** (0.110 g, 88%) as colorless needles, mp 164—165 °C. IR (KBr): 3105 (NH), 2200 (CN), 1617 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 237 (4.18), 260 (3.94), 270 (3.87, sh), 342 (4.56), 350 (4.55, sh). ^{1}H-NMR (DMSO-d_6) δ: 1.69 (6H, br s), 2.02—2.40 (4H, m), 3.40 (4H, m), 3.70—4.26 (2H, m), 6.34 (1H, t, J=5 Hz, C_1·H), 8.52 (1H, s, C_8H), 8.59 (1H, s, C_2H), 9.25 (1H, s, C=CH). MS *m/z*: 324 (M^+), 254 (B+1). *Anal.* Calcd for $C_{17}H_{20}N_6O$: C, 62.94; H, 6.21; N, 25.91. Found: C, 62.85; H, 6.23; N, 26.08.

6-(3-Aminopyrazol-4-yl)-9-(tetrahydrofuran-2-yl)-9*H*-purine (8) A solution of **5** (0.200 g, 0.78 mmol) and hydrazine hydrate (0.120 g, 2.34 mmol) in EtOH (8 ml) was refluxed for 5 h, then allowed to cool. The solution was evaporated *in vacuo*. The residue was purified by silica gel column chromatography on silica gel (10 g) with 2% MeOH in CH_2Cl_2 as eluent, and the eluate was evaporated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give **8** (0.15 g, 70%) as colorless needles, mp 133—136 °C (dec.). IR (KBr): 3380 (NH), 3255 (NH), 1590 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 220 (4.03, sh), 265 (3.57), 230 (4.09). ^{1}H-NMR (DMSO-d_6) δ: 2.09—2.32 (4H, m), 3.83—4.28 (2H, m), 6.35 (1H, t, J=5 Hz, C_1·H), 6.77 (2H, br s, NH_2, exchangeable with D_2O), 8.38 (1H, s, pyrazole-H), 8.53 (1H, s, C_8H), 8.67 (1H, s, C_2H), 12.38 (1H, br s, NH, exchangeable with D_2O). MS *m/z*: 271 (M^+). *Anal.* Calcd for $C_{12}H_{13}N_7O$: C, 53.13; H, 4.83; N, 36.15. Found: C, 53.55; H, 4.97; N, 36.38.

References and Notes

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