Synthesis of the 7-Deaza and 5-Aza-7-deaza Purine Analogs of the Antiherpes Agent 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine (DHPG)

Danny P. C. McGee*, John C. Martin and Julien P. H. Verheyden

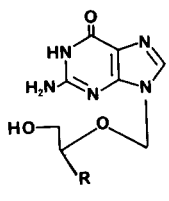
Syntex Research Contribution 210 from the Institute of Bio-Organic Chemistry, 3401 Hillview Ave., Palo Alto, California 94304

Received February 20, 1985

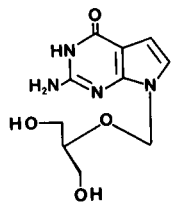
Synthesis of 2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-4-one (**3**) a 7-deaza purine analogue and 2-amino-8-[(1,3-dihydroxy-2-propoxy)methyl]imidazo[1,2-*a*]-*s*-triazin-4-one (**4**) a 5-aza-7-deaza purine analogue of DHPG (**2**) are reported.

J. Heterocyclic Chem., **22**, 1137 (1985).

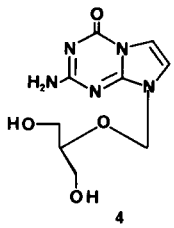
The appearance in the last few years of potent antiviral compounds, notably 9-(2-hydroxyethoxymethyl)guanine (acyclovir, **1**) [1] and 9-[(1,3-dihydroxy-2-propoxy)methyl]-guanine (DHPG, **2**) [2,3], has kindled an interest in the synthesis of related acyclic nucleoside analogues [4-7]. The natural occurrence of several 7-deaza nucleosides possessing biological activity [8] (*i.e.* tubercidin) prompted us to prepare 2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-4-one (**3**) and 2-amino-8-[(1,3-dihydroxy-2-propoxy)methyl]imidazo[1,2-*a*]-*s*-triazin-4-one (**4**) as analogues of DHPG (**2**), the most active lead in this series.



1 R = H
2 R = CH_2OH



3

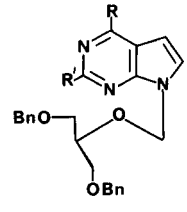


4

The synthesis of **3** (Scheme I) proceeds in a manner similar to that described by Seela for the synthesis of the acyclovir analogue [9]. Thus, the reaction of 2-amino-4-methoxy-pyrrolo[2,3-*d*]pyrimidine (**5a**) [10] with 1,3-dibenzyloxy-2-chloromethylglycerol (**6**) [2] under phase transfer conditions (50% sodium hydroxide/dichloromethane) gave in 27% yield the required adduct **7** whose uv spectrum compared favorably to that of the previously prepared acyclovir analogue [9]. Cleavage of the methyl ether with potassium *p*-thiocresolate in refluxing toluene/HMPA gave the 7-deaza guanine intermediate **8** which was cleanly debenzylated using boron tribromide in dichloromethane to give the desired 7-deaza analogue **3**. Attempted catalytic transfer hydrogenation of **8** (palladium hydroxide on carbon:cyclohexene) lead to the isolation of 2-amino-7-methylpyrrolo[2,3-*d*]pyrimidin-4-one.

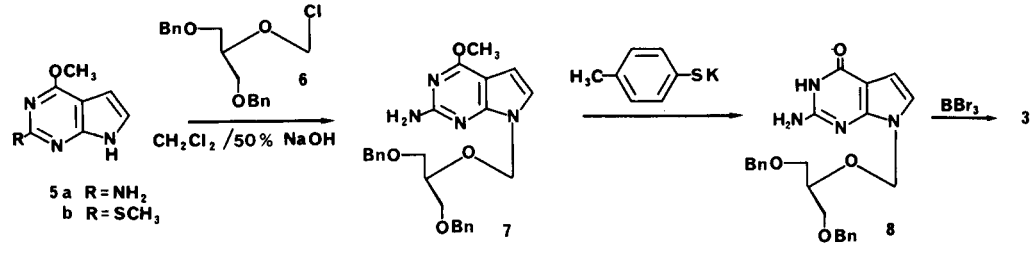
It is interesting to note that in our early attempts toward the synthesis of **3** we prepared adduct **9** which was a form of protected 7-deaza purine which had been successfully used by others [11,12] for the synthesis of glycosylated 7-deaza guanine derivatives. Attempts by us to displace the 2-methylthio group of **9** with acetamide lead exclusively to products resulting from displacement of methoxide at the 4-position of the heterocycle. In an attempt to salvage this approach **9** was oxidized to the sulfoxide **10** using *m*-chloroperoxybenzoic acid. Subsequent reaction of sulfoxide **10** with methanolic ammonia lead to a mixture of compounds which afforded the desired intermediate **7** in 12% yield.

Further efforts to encourage displacement at the 2-position involved demethylation of **9** with potassium thiocresolate to give methylthio derivative **11** which under forcing conditions with methanolic ammonia gave a clean conversion to the unexpected xanthine analogue **12**.

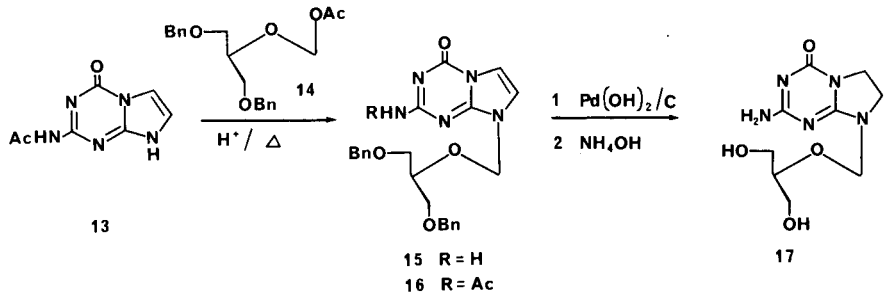


9 R = OCH_3, R′ = SCH_3
10 R = OCH_3, R′ = $SOCH_3$
11 R = OH, R′ = SCH_3
12 R = R′ = OH

Scheme I



Scheme II



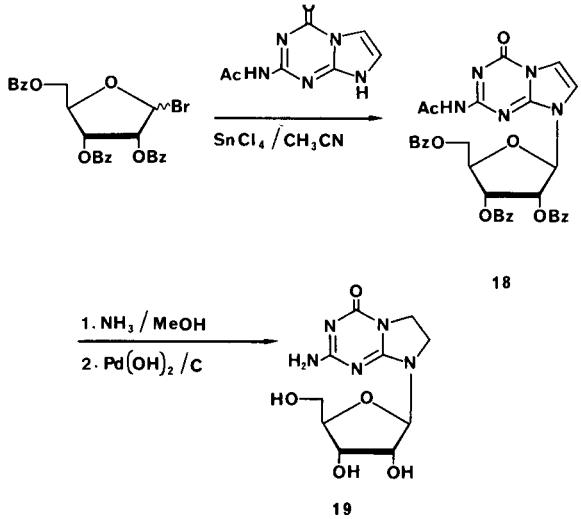
13

15 R = H
16 R = Ac

17

The synthesis of the 5-aza-7-deaza analogue **4** (Scheme II) was begun with the acid catalysed coupling of 2-acetamidoimidazo[1,2-*a*]-*s*-triazin-4-one (**13**) [13] and 1,3-dibenzyloxy-2-acetoxymethylglycerol (**14**) [2] to give the desired adduct **16** in 40% yield. Alternatively, we attempted to react **6** and pertrimethylsilyl 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one in acetonitrile using stannic chloride and obtained a 7% yield of two products arising from alkylation of N-1 and N-7. Catalytic transfer hydrogenation of **16** followed by deacylation with ammonium hydroxide lead to the isolation of **4** which was contaminated with 5-10% (^{1}H nmr) of the 6,7-dihydro compound **17**. Isolation of **4** from the above mixture was accomplished *via* a two step process involving first silylation (*t*-butyldimethylchlorosilane), purification of the silylated intermediate on silica and deprotection with acetic acid to give the requisite 5-aza-7-deaza analogue **4** in pure form. The structure of **4** and thus **16** was ascertained by the favorable comparison of the uv spectrum of **4** to that of the previously reported riboside [13]. The observation on the ease of over reduction of the 5-aza-7-deaza purine system was explored further when dibenzyl intermediate **15**, obtained by deacylation of **16**, was exhaustively hydrogenolysed to give the 6,7-dihydro product **17**.

Scheme III



18

19

Compounds **3** and **4** were inactive when assayed against herpes simplex virus types I (HSV-I) and II (HSV-II) in cell culture. Surprisingly **17** had moderate antiviral activity with a viral rating [14] of 0.9 and 0.6 against HSV-I and HSV-II respectively. The greater activity of the 6,7-dihydro compound **17** coupled with the reported antiviral activity of the 5-aza-7-deaza riboside [13] encouraged us to synthesize 2-amino-8-(β-D-ribofuranosyl)-6,7-dihydroimidazo[1,2-*a*]-*s*-triazin-4-one (**19**). Compound **19** was easily prepared from 2-acetamido-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-*s*-triazin-4-one (**18**) [13] by catalytic hydrogenation followed by deacylation with ammonium hydroxide. The 6,7-dihydro riboside **19** was inactive against both HSV-I and II in cell culture.

EXPERIMENTAL

The ^{1}H and ^{13}C nmr's [15] were recorded in dimethyl sulfoxide-d_6 on a Bruker WH-300 (^{1}H nmr 300 MHz, ^{13}C nmr 75.453 MHz) and are reported relative to internal tetramethylsilane. Ultraviolet spectra were recorded on a Hewlett Packard 8450A spectrophotometer. Spectroscopic data and elemental analyses were obtained by Syntex Analytical Research. All chromatographic separations were performed on silica gel. Melting points, reported in degrees Centigrade, were determined on a hot-stage microscope and are corrected.

2-Amino-4-methoxy-7-[(1,3-dibenzyloxy-2-propoxy)methyl]pyrrolo[2,3-*d*]-pyrimidine (**7**).

To an emulsion (Vibromixer) of 50% sodium hydroxide (30 ml), dichloromethane (30 ml), benzyltriethylammonium chloride (300 mg) and 7-deaza purine **5a** [9] (1.4 g, 8.52 mmoles) was slowly added (over 10 minutes) a dichloromethane solution (15 ml) of 1,3-dibenzyloxy-2-chloromethylglycerol [2] (9.9 mmoles). Mixing was continued for 15 minutes, then the layers were partitioned and the organic phase was washed with water (2 ×), dilute hydrochloric acid (1 ×), dried over magnesium sulfate and evaporated to a brown soil which was chromatographed (eluting first with dichloromethane (1 ℓ) then 2% methanol/dichloromethane. Evaporation of the correct fractions followed by crystallization from methanol afforded **7** (1.03 g, 27%), mp 80-82°; uv (methanol): λ max 259 (8990), 286 (6370); pmr: δ 7.27 (m, 10H, benzyl), 6.98 (d, 1H, J = 3.6 Hz, H-6), 6.24 (d, 1H, J = 3.6 Hz, H-5), 6.20 (broad s, 2H, NH_2), 5.50 (s, 2H, H-1'), 4.39 (s, 4H, benzyl CH_2), 3.99 (p, 1H, H-4'), 3.92 (s, 3H, CH_3), 3.47, 3.39 (ABX, 4H, J = 5, 11 Hz, H-3', H-5'); cmr: δ 162.94 (C-4), 159.69 (C-2), 154.49 (C-7a), 138.22, 128.07, 127.24 (benzyl), 122.57 (C-6), 98.83 (C-5), 97.05 (C-4a), 75.82 (C-4'), 72.48 (C-1'), 72.14 (benzyl CH_2), 69.61 (C-3', C-5'), 52.70 (OCH_3); ms: 448 (M^+), 193, 177, 164.

Anal. Calcd. for $C_{25}H_{28}N_4O_4$ (448.52): C, 66.95; H, 6.29; N, 12.49. Found: C, 66.82; H, 6.44; N, 12.56.

2-Amino-7-[(1,3-dibenzyloxy-2-propoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-4-one (**8**).

To a solution of *p*-thiocresol (386 mg, 3.1 mmoles) in toluene (25 ml) was added sodium hydride (150 mg 50% sodium hydride in oil, 3.1 mmoles) followed by hexamethylphosphoramide (1 ml) and **7** (930 mg, 2.07 mmoles). The above mixture was heated at 100-105°(18 hours) then partitioned with water (1 ×), dilute sodium bicarbonate (2 ×), the organic phase dried over magnesium sulfate and evaporated to a yellow oil which was chromatographed (3% methanol/dichloromethane). Evaporation of the correct fractions followed by crystallization from methanol gave **8** (500 mg, 55%) as light yellow crystals, mp 131-132.5°; uv (methanol): λ max 258 (13200), (shoulder) 284 (8000); pmr: δ 7.27 (m, 10H, benzyl), 6.80 (d, 1H, J = 3.6 Hz, H-6), 6.25 (d, 3H, J = 3.5 Hz, H-5, NH_2), 5.42 (s, 2H, H-1'), 4.41 (s, 4H, benzyl CH_2), 3.96 (p, 1H, H-4'), 3.44, 3.37 (ABX, 4H, J = 5, 10.3 Hz, H-3', H-5'); cmr: δ 158.60 (C-4), 152.64 (C-2), 150.73 (C-7a), 138.21, 128.10, 127.25 (benzyl), 120.18 (C-6), 102.00 (C-5), 100.09 (C-4a), 75.76 (C-4'), 72.64 (C-1'), 72.14 (benzyl CH_2), 69.58 (C-3', C-5'); ms: 434 (M^+), 165 (B + CH_2), 151 (B + H).

Anal. Calcd. for $C_{24}H_{26}N_4O_4$ (434.50): C, 66.34; H, 6.03; N, 12.89. Found: C, 66.35; H, 6.10; N, 12.85.

2-Amino-7-[(1,3-dihydroxy-2-propoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-4-one (**3**).

To a solution of **8** (217 mg, 0.49 mmole) in dichloromethane (2 ml) at −78° (dry ice/acetone) was added a boron tribromide solution (262 mg, 1.05 ml of 1 molar boron tribromide in dichloromethane). The resulting slurry was stirred at −78° for 25 minutes then quenched by the addition of methanol (10 ml), warmed to room temperature and evaporated to an oil. Chromatography (10% methanol/dichloromethane) of the oil and evaporation of the correct fractions gave a pink oil which crystallized from ethanol/ethyl acetate to give **3** (90 mg, 71%). An analytical sample was crystallized from ethanol, mp 234-235°; uv (hydrochloric acid): λ max 218 (19700), 259 (11600), (shoulder) 284 (7390); (sodium hydroxide): 217 (22300), 261 (11500), 277 (shoulder) (8960); pmr: δ 6.87 (d, 1H, J = 3.5 Hz, H-6), 6.30 (d, 1H, J = 3.4 Hz, H-5), 5.42 (s, 2H, H-1'), 4.54 (broad OH's), 3.48 (m, 1H, H-4'), 3.40, 3.29 (ABX, 4H, J = 5, 11 Hz, H-3', H-5'); cmr: δ 158.15 (C-4), 152.23 (C-2), 148.28 (C-7a), 120.57 (C-6), 102.00 (C-5), 100.15 (C-4a), 79.37 (C-4'), 72.86 (C-1'), 60.68 (C-3', C-5'); ms: 254 (M^+), 179 (B + CH_2O), 163 (B + CH_2), 150 (B + H).

Anal. Calcd. for $C_{10}H_{14}N_4O_4$ (254.24): C, 47.24; H, 5.55; N, 22.04. Found: C, 47.31; H, 5.57; N, 21.99.

2-Methylthio-4-methoxy-7-[(1,3-dibenzyloxy-2-propoxy)methyl]pyrrolo-[2,3-*d*]pyrimidine (**9**).

To an emulsion (Vibromixer) of 50% sodium hydroxide (30 ml), dichloromethane (30 ml), benzyltriethylammonium chloride (300 mg) and 7-deaza purine **5b** [10] (1.5 g, 7.68 mmoles) was slowly added (over 10 minutes) a dichloromethane solution (15 ml) of 1,3-dibenzyloxy-2-chloromethylglycerol [2] (9.17 mmoles). Mixing was continued for 20 minutes, the organic layer partitioned and washed with water (2 ×), dilute hydrochloric acid (1 ×), dried over magnesium sulfate and evaporated to a yellow oil. Chromatography of the yellow residue eluting with dichloromethane and evaporation of selected fractions yielded **9** (1.15 g, 31%) as an oil; uv (methanol): λ max 236 (15800), 281 (13600); pmr: δ 7.38 (d, 1H, J = 3.5 Hz, H-6), 7.27, 7.20 (m, 10H, benzyl), 6.47 (d, 1H, J = 3.5 Hz, H-5), 5.69 (s, 2H, H-1'), 4.39 (s, 4H, benzyl CH_2), 4.02 (s, 4H, CH_3, H-4'), 3.48, 3.41 (ABX, 4H, J = 5.7, 11 Hz, H-3', H-5'), 2.54 (s, 3H, CH_3); cmr: δ 162.89 (C-4), 161.78 (C-2), 152.65 (C-7a), 138.14, 128.04, 127.13 (benzyl), 125.81 (C-6), 101.50 (C-4a), 98.79 (C-5), 76.15 (C-4'), 72.69 (C-1'), 72.11 (benzyl CH_2), 69.56 (C-3', C-5'), 53.46 (OCH_3), 13.55 (SCH_3); ms: 480 (MH^+), 388, 271, 224, 196 (B + H).

Anal. Calcd. for $C_{26}H_{29}N_3O_4S$ (479.60): C, 65.11; H, 6.09; N, 8.76; S, 6.68. Found: C, 64.99; H, 6.38; N, 9.00; S, 6.54.

2-Methylsulfinyl-4-methoxy-7-[(1,3-dibenzyloxy-2-propoxy)methyl]pyrrolo-[2,3-*d*]pyrimidine (**10**).

A dichloromethane solution (10 ml) of **9** (900 mg, 1.87 mmoles) was treated at 0° (ice/water bath) with *m*-chloroperoxybenzoic acid (356 mg, 2.06 mmoles). The reaction was stirred 2 hours then partitioned with dilute sodium thiosulfate (1 ×), dilute sodium bicarbonate (1 ×), water (1 ×), then dried over magnesium sulfate and evaporated to a clear oil which was chromatographed eluting with 3% methanol/dichloromethane giving **10** (800 mg, 85%) as a clear oil; uv (methanol): λ max 265 (7480), 285 (8680); pmr: δ 7.27 (m, 11H, H-6, benzyl), 6.58 (d, 1H, J = 3.6 Hz, H-5), 5.83 (s, 2H, H-1'), 4.45 (s, 4H, benzyl CH_2), 4.18 (s, 3H, CH_3), 4.50 (p, 1H, H-4'), 3.50, 3.51 (ABX, 4H, H-3', H-5'), 2.88 (s, 3H, $SOCH_3$); cmr (deuteriochloroform): δ 164.84 (C-4), 163.52 (C-2), 152.21 (C-7a), 137.99, 128.31, 127.53 (benzyl), 127.41 (C-6), 105.94 (C-4a), 100.14 (C-5), 76.85 (C-4'), 73.66 (C-1'), 73.32 (benzyl CH_2), 70.05 (C-3', C-5'), 54.39 (OCH_3), 40.04 ($SOCH_3$); ir (potassium bromide): 2870, 1590, 1500, 1470, 1380, 1330, 1240, 1060 cm^{-1}; ms: 496 (MH^+), 480 (M - CH_3), 224 (B + CH_2), 212 (B + 2H), 196 (B + H - CH_3).

Anal. Calcd. for $C_{26}H_{29}N_3O_5S$ (495.59): C, 63.01; H, 5.90; N, 8.47; S, 6.47. Found: C, 62.81; H, 6.13; N, 8.70; S, 6.36.

2-Methylthio-7-[(1,3-dibenzyloxy-2-propoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-4-one (**11**).

To a mixture of thiocresol (1.45 g, 11.6 mmoles), sodium hydride (560 mg, 50% in oil, 11.6 mmoles), hexamethylphosphoramide (1 ml) in toluene (25 ml), was added **9** (2.8 g, 5.8 mmoles). The reaction was heated at reflux for 12 hours at which time additional thiocresol (600 mg, 4.8 mmoles) and sodium hydride (200 mg, 4.16 mmoles) was added and reflux was continued (48 hours). The reaction mixture was then partitioned with dilute sodium bicarbonate (2 ×) and the organic phase was dried over magnesium sulfate and evaporated. The resulting residue was chromatographed (3% methanol/dichloromethane) to give **11** (1.15 g, 42%), a sample of which was crystallized from ethyl ether, mp 92-93°; uv (methanol): λ max 268 (11900), 286 (11400); pmr: δ 12.27 (broad, 1H, NH), 7.26 (m, 10H, benzyl), 7.10 (d, 1H, J = 3.5 Hz, H-6), 6.41 (d, 1H, J = 3.5 Hz, H-5), 5.61 (s, 2H, H-1'), 4.40 (s, 4H, benzyl CH_2), 4.00 (p, 1H, H-4'), 3.48, 3.42 (ABX, 4H, J = 5, 11 Hz, H-3', H-5'), 2.48 (s, 3H, CH_3); cmr: δ 158.58 (C-4), 155.24 (C-2), 147.70 (C-7a), 138.17, 128.09, 127.17 (benzyl), 122.61 (C-6), 104.46 (C-4a), 102.28 (C-5), 76.04 (C-4'), 72.76 (C-1'), 72.16 (benzyl CH_2), 69.57 (C-3', C-5'), 12.73 (SCH_3); ms: 465 (M^+), 210, 194, 181.

Anal. Calcd. for $C_{25}H_{27}N_3O_4S$ (465.57): C, 64.50; H, 5.84; N, 9.02; S, 6.88. Found: C, 64.45; H, 5.75; N, 8.91; S, 6.70.

2-Hydroxy-7-[(1,3-dibenzyloxy-2-propoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-4-one (**12**).

A mixture of **11** (510 mg, 1.13 mmoles) and saturated methanolic ammonia (30 ml) was heated 72 hours at 110° in a pressure vessel, then evaporated and chromatographed (5% methanol/dichloromethane) to give the unexpected product **12** (310 mg, 63%) which crystallized from ethanol, mp 128-129°; uv (methanol): λ max 243 (8360), 272 (6160); pmr: δ 10.50, 9.60 (broad s, 2H, NH), 7.30 (m, 10H, benzyl), 6.80 (d, 1H, J = 3.5 Hz, H-6), 6.28 (d, 1H, J = 3.5 Hz, H-5), 5.47 (s, 2H, H-1'), 4.42 (s, 4H, benzyl CH_2), 3.90 (p, 1H, H-4'), 3.44, 3.49 (ABX, 4H, H-3', H-5').

Anal. Calcd. for $C_{24}H_{25}N_3O_5$ (435.48): C, 66.19; H, 5.79; N, 9.65. Found: C, 66.19; H, 5.83; N, 9.61.

2-Acetamido-8-[(1,3-dibenzyloxy-2-propoxy)methyl]imidazo[1,2-*a*]-*s*-triazin-4-one (**16**).

A slurry of 2-acetamidoimidazo[1,2-*a*]-*s*-triazin-4-one (**13**) (2 g, 10.35 mmoles), 1,3-dibenzyloxy-2-acetoxymethylglycerol (**14**) (15.53 mmoles), sulfolane (2 ml), bis(4-nitrophenyl)phosphate (100 mg) was first heated at 95° (12 hours) then 120° (16 hours) then left at room temperature (16 hours). The reaction mixture was filtered through a short silica gel column (10% methanol/dichloromethane), the uv absorbing fractions were pooled and evaporated to an oil which was chromatographed (3% methanol/dichloromethane) to give **16** as an oil (2.0 g, 40% yield); uv (methanol): λ max 225 (23900), 278 (9990); pmr: δ 10.36 (s, broad, 1H, NH), 7.65

(d, 1H, J = 2.6 Hz, H-6), 7.52 (d, 1H, J = 2.7 Hz, H-7), 7.30, 7.22 (m, 10H, benzyl), 5.55 (s, 2H, H-1'), 4.42 (s, 4H, benzyl CH_2), 4.16 (p, 1H, H-4'), 3.46, 3.48 (ABX, 4H, J = 5, 10.5 Hz, H-3', H-5'), 2.25 (s, 3H, acetyl); cmr: δ 170.12 ($COCH_3$), 161.01 (C-4), 149.99 (C-2, C-8a), 138.19, 128.21, 127.24 (benzyl), 119.27 (C-7), 108.45 (C-6), 77.53 (C-4'), 73.66 (C-1'), 72.20 (benzyl CH_2), 69.60 (C-3', C-5') 25.32 ($COCH_3$); as well as **15** (200 mg, 4%), mp 119-121° (ethyl acetate/hexanes); uv (methanol): λ max 258 (13070); pmr: δ 7.35, 7.38 (AX, 2H, J = 3 Hz, H-6, H-7), 7.30 (m, 10H, benzyl), 6.96 (broad s, 2H, NH_2), 5.42 (s, 2H, H-1'), 4.42 (s, 4H, benzyl CH_2), 4.07 (p, 1H, H-4'), 3.46, 3.44 (ABX, 4H, J = 5, 11 Hz, H-3', H-5'); cmr: δ 165.63 (C-4), 150.90, 150.19 (C-2, C-8a), 138.19, 128.24, 127.30 (benzyl), 117.42 (C-7), 107.86 (C-6), 77.30 (C-4'), 73.17 (C-1'), 72.23 (benzyl CH_2), 69.63 (C-5', C-3'); ir (potassium bromide): 3470, 1685, 1640, 1615, 1480, 1205 cm^{-1}; ms: 435 (M^+), 151 (B + H).

Anal. Calcd. for $C_{23}H_{25}N_5O_4$ (435.48): C, 63.43; H, 5.79; N, 16.08. Found: C, 63.67; H, 6.04; N, 16.37.

2-Amino-8-[(1,3-dihydroxy-2-propoxy)methyl]imidazo[1,2-*a*]-*s*-triazin-4-one (**4**).

A suspension of **16** (2 g, 4.19 mmoles), 20% palladium hydroxide on carbon (1.7 g), ethanol (100 ml), and cyclohexene (20 ml) was refluxed 24 hours, then filtered through Celite and evaporated to a clear oil. The oil was treated with concentrated ammonium hydroxide/methanol (1/1) for 16 hours at room temperature then evaporated. The residue was crystallized from hot ethanol giving **4** (530 mg, 49%) contaminated with 5-10% of **17**.

To a solution of the above mixture (344 mg) in dimethylformamide (2 ml) was added imidazole (459 mg, 6.68 mmoles) followed by *t*-butyldimethylsilyl chloride (468 mg, 3.10 mmoles). The reaction mixture was stirred at room temperature for 3 hours then partially evaporated. The residue was partitioned between dichloromethane and dilute sodium bicarbonate (1 ×) then dilute hydrochloric acid (1 ×). The organic phase was dried over magnesium sulfate and evaporated to a foam which was chromatographed (4% methanol/dichloromethane) giving a silylated intermediate (550 mg, 1.13 mmoles, 85%). Hydrolysis of this intermediate with 80% acetic acid (5 ml) at 70-75° for 6 hours followed by co-evaporation of the reaction mixture with ethanol (3 ×), trituration of the residue with acetone (1 ×) and crystallization from ethyl acetate afforded **4** (220 mg, 76%) in 2 crops, mp 199-201°; uv (hydrochloric acid): λ max (shoulder) 239 (8390), 265 (13700); (sodium hydroxide): λ max 216 (20100), 257 (15600); pmr: δ 7.35, 7.33 (AX, 2H, J = 7.3 Hz, H-6, H-7), 6.94 (s, broad, 2H, NH_2), 5.40 (s, 2H, H-1'), 4.63 (t broad, 2H, OH's), 3.57 (p, 1H, H-4'), 3.46, 3.32 (ABX, 4H, J = 5, 11 Hz, H-3', H-5'); cmr: δ 165.53 (C-4), 150.74, 150.23 (C-2, C-8a), 117.32 (C-7), 107.83 (C-6), 80.78 (C-4'), 72.91 (C-1'), 60.85 (C-3', C-5'); ir (potassium bromide): 3350 (OH), 1700, 1630, 1510, 1200, 1115 cm^{-1}; ms: 255 (M^+), 165, 151 (B + H).

Anal. Calcd. for $C_9H_{13}N_5O_4$ (255.23): C, 42.35; H, 5.13; N, 27.44. Found: C, 42.44; H, 5.15; N, 27.39.

2-Amino-8-[(1,3-dihydroxy-2-propoxy)methyl]-6,7-dihydroimidazo[1,2-*a*]-*s*-triazin-4-one (**17**).

A mixture of **15** (536 mg, 1.23 mmoles) and 20% palladium hydroxide on carbon (300 mg) in methanol (30 ml) was reacted in a Parr hydrogenator at 50 pounds per square inch of hydrogen gas for four days during which time additional catalyst (600 mg) was added, in equal portions over days 2, 3 and 4. The reaction was filtered through Celite and evaporated to a white solid. Crystallization from hot ethanol (charcoal) yielded **17** (123 mg, 39%), mp 235-237°; uv (hydrochloric acid): 217 (20700), 235 (9460); (sodium hydroxide): λ max 210 (12400), 235 (20900); pmr: δ 6.9 (broad, 2H, NH_2), 4.89 (s, 2H, H-1'), 4.63 (t broad, 2H, OH's), 3.82, 3.75 (ABXY, 4H, J = 3, 8 Hz, H-6, H-7), 3.45 (m, 3H, H-4', H-3'), 3.34 (m, 2H, H-5'); cmr: δ 167.78 (C-4), 159.84, 154.94 (C-8a, C-2), 80.03 (C-1'), 73.04 (C-4'), 60.95 (C-3', C-5'), 42.22 (C-7), 40.70 (C-6); ir (potassium bromide): 3400-3200 (OH), 1690, 1630, 1540, 1295, 1110 cm^{-1}; ms: 258 (MH^+), 227, 166 (B + CH_2), 152.

Anal. Calcd. for $C_9H_{15}N_5O_4$ (257.25): C, 42.02; H, 5.88; N, 27.22. Found: C, 42.03; H, 5.84; N, 27.18.

2-Amino-8-(β-D-ribofuranosyl)-6,7-dihydroimidazo[1,2-*a*]-*s*-triazin-4-one (**19**).

Compound **18** [13] (600 mg, 0.94 mmole) was stirred with saturated methanolic ammonia for 29 hours then evaporated to an oily residue, triturated with dichloromethane and the residue redissolved in 10% aqueous methanol, acidified with 2 drops of dilute hydrochloric acid and hydrogenolysed using 20% palladium hydroxide on carbon (200 mg) for 30 hours at 40-45 pounds per square inch of hydrogen gas on a Parr hydrogenator. Filtration through Celite, evaporation and crystallization of the residue from methanol/water afforded **19** (190 mg, 70%), mp 263-265°; uv (hydrochloric acid): λ max 210 (12100), 236 (20500); (sodium hydroxide): λ max 217 (21100), 236 (9470); pmr: δ 6.93 (broad s, 2H, NH_2), 5.52 (d, 1H, J = 6.2 Hz, H-1'), 5.22 (d, 1H, OH), 5.00 (d, 1H, OH), 4.81 (t, 1H, OH), 4.06 (dd, 1H, J = 11 Hz, H-2'), 3.86, 3.67 (m, 6H, H-6, H-7, H-4', H-3'), 3.47 (m, 2H, H-5').

Anal. Calcd. for $C_{10}H_{15}N_5O_5$ (285.26): C, 42.10; H, 5.30; N, 24.55. Found: C, 42.16; H, 5.31; N, 24.61.

REFERENCES AND NOTES

[1] H. J. Schaeffer, L. Beauchamp, P. De Miranda, G. B. Elion, D. J. Bauer and P. Collins, *Nature (London)*, **272**, 583 (1978).

[2] J. C. Martin, C. A. Dvorak, D. F. Smee, T. R. Matthews and J. P. H. Verheyden, *J. Med. Chem.*, **26**, 759 (1983).

[3a] W. T. Ashton, J. D. Karkas, A. K. Field and R. L. Tolman, *Biochem. Biophys. Res. Commun.*, **108**, 1716 (1982); [b] K. K. Ogilvie, U. O. Cheriyan, B. K. Radatus, K. O. Smith, K. S. Galloway and W. L. Kennell, *Can. J. Chem.*, **60**, 3005 (1982); [c] H. J. Schaeffer, Proc. 5th Intl. Round Table, "Nucleosides, Nucleotides and their Biological Applications", Academic Press Inc., New York, NY, 1983, p 1.

[4] M. J. Robins and P. W. Hatfield, *Can. J. Chem.*, **60**, 547 (1982).

[5] A. Parkin and M. R. Harnden, *J. Heterocyclic Chem.*, **19**, 33 (1982).

[6] J. C. Martin, G. A. Jeffrey, D. P. C. McGee, M. A. Tippie, D. F. Smee, T. R. Matthews and J. P. H. Verheyden, *J. Med. Chem.*, **28**, 358 (1985).

[7a] K. K. Ogilvie, Nghe Nguyen-Ba, M. F. Gillen, B. K. Radatus, U. O. Cheriyan, K. O. Smith and K. S. Galloway, *Can. J. Chem.*, **62**, 241 (1984); [b] K. K. Ogilvie, R. G. Hamilton, M. F. Gillen, B. K. Radatus, K. O. Smith and K. S. Galloway, *ibid.*, **62**, 16 (1984).

[8] D. E. Bergstrom, A. J. Brattesani, M. K. Ogawa, P. A. Reddy, M. J. Schweickert, J. Balzarini and E. De Clerq, *J. Med. Chem.*, **27**, 285 (1984).

[9] F. Seela, A. Kehne and H. D. Winkeler, *Ann. Chem.*, 137 (1983).

[10] J. Davoll, *J. Chem. Soc.*, 131 (1960).

[11] F. Seela and D. Hasselmann, *Chem. Ber.*, **114**, 3395 (1981).

[12] F. Seela, D. Hasselmann and H. D. Winkeler, *Ann. Chem.*, 499 (1982).

[13] S. H. Kim, D. G. Bartholomew, L. B. Allen, R. K. Robins and G. R. Revankar, *J. Med. Chem.*, **21**, 883 (1978).

[14] R. W. Sidwell and J. H. Huffman, *Appl. Microbiol.* **22**, 797 (1971).

[15] The acyclic compounds described are visualized as 2'-deoxynucleoside analogues and in keeping with this representation the terminal carbons of the glycerol portion are referred to as the 3' and 5' positions.