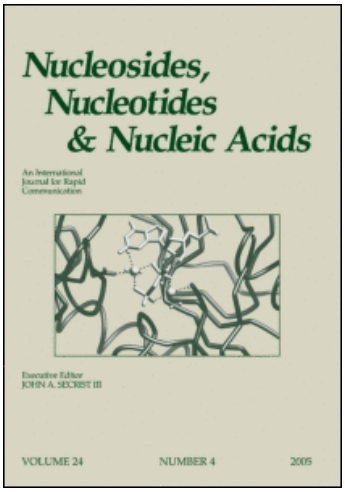

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Acyclic Nucleosides Containing Two Heterocyclic Bases

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ACYCLIC NUCLEOSIDES CONTAINING TWO HETEROCYCLIC BASES

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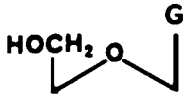
Abstract A new series of acyclic nucleoside derivatives is described which contain two purine or pyrimidine rings (or a combination) attached to glycerol. The analogues described have been tested for activity against herpesviruses and were found to be inactive.

Introduction.

As a result of the significant antiviral activity of two acyclic nucleosides acyclovir 1 (1) and 9-(1,3-dihydroxy-2-propoxymethyl)guanine 2 (2-5, BIOLF-62, DHPG or 2'-NDG), numerous acyclic nucleoside analogues have been developed and tested for antiviral activity. The majority of these analogues have been base-modified derivatives of acyclovir (6-8), or DHPG (9-16), or they have involved changes at the acyclic sidechain (17-23). We wish to describe in this report the synthesis of a new series of acyclic nucleosides



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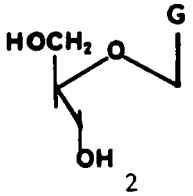

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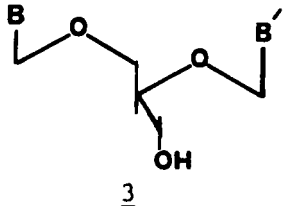

3

in which two heterocyclic bases are attached to a single sidechain (3).

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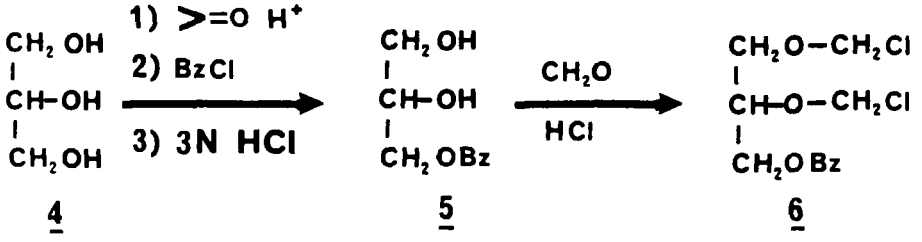
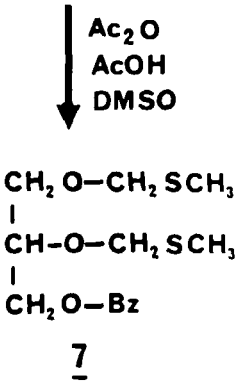
Results and Discussion

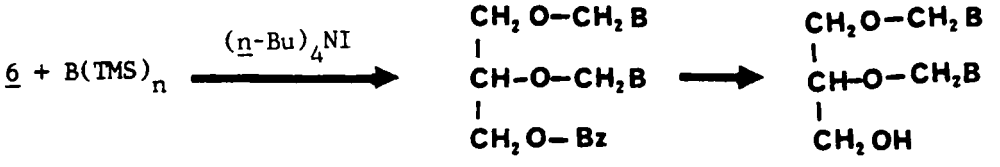
The key intermediate in the synthesis of compounds 3 is either the bischloromethyl ether 6 or the bisthiomethylether 7. Both of these intermediates were obtained directly from glycerol-1-benzoate 5 which was itself obtained from glycerol 4. The chloromethyl ether 6 was the more reactive intermediate and was very useful for preparing 3 where B=B'. The thiomethylether 7 proved useful in preparing mixed derivatives of 3 where B≠B'.





Cytosine, 6-chloroguanine, 6-chloropurine and thymine all coupled smoothly to 6 in the presence of tetrabutylammonium iodide to yield compounds 8a-d in 30-66% yield. Silylated N-acetylguanine did not give detectable amounts of product or reaction with 6 using either TBAI or DMF-triethylamine as catalysts. Attempts to convert 8b into the

bisguanine derivative failed. Treatment of 8b with sodium methoxide gave the expected (24) 6-methoxy derivative 9b in good yield.

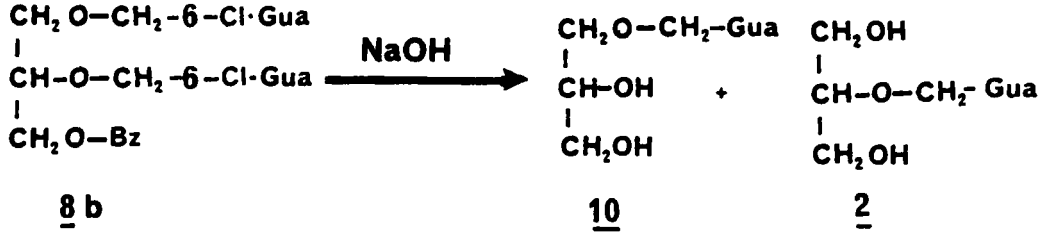


B=cytosine
6-chloroguanine
6-chloropurine
thymine

8 a, B = Cy
b, B = 6-Cl-Gu
c, B = 6-Cl-Pu
d, B = Th

9 a, B = Cy
b, B = 6-MeO-Gu
c, B = Ad
d, B = Th

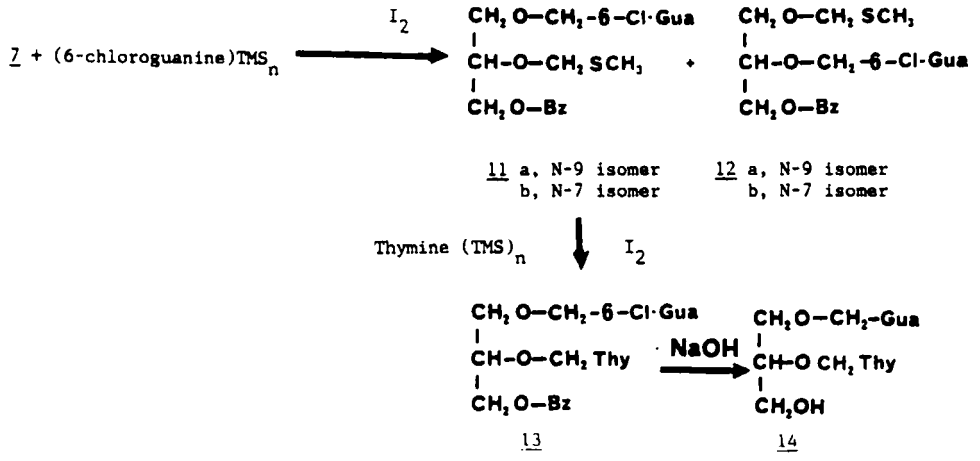
However treatment with sodium hydroxide led to cleavage of one methylether linkage producing a mixture of the known derivatives 2 and 10. In this latter reaction a small amount of a very polar material was always produced. This material was not characterized but was suspected to be the bisguanine derivative. Attempts to increase the quantity of this material by varying the concentrations failed. Compound 7 was condensed with 6-chloroguanine using iodine as a catalyst. Two sets of isomers 11 and 12 were obtained with 11 being the predominant product. The 9-isomer 11a was coupled with thymine to



8b 10 2

produce the mixed derivative 13. Compound 13 was easily converted to the guanine derivative 14 using sodium hydroxide.

The site of attachment to the heterocyclic base was determined from the UV spectra. Structural assignments were based on the NMR spectra.



Biological Activity: The compounds described in this manuscript were tested against HSV-1 and HSV-2 and found to be inactive.

Experimental

General Methods Thin-layer chromatography data R_f values) are recorded from Merck Kieselgel 60F, 254 analytical sheets. UV Spectra were recorded on a Cary 17 spectrometer. Nuclear Magnetic Resonance spectra were recorded using Varian XL-200 and T60A spectrometers. Elemental analyses were performed by Canadian Microanalytical Service.

Glycerol-1-benzoate

Glycerol (50g, 0.54mole) and a few milligrams of p-toluenesulfonic acid monohydrate were added to acetone (300ml) and the mixture was stirred at room temperature until the solution became clear (~30min). Anhydrous magnesium sulfate (10g) was added and the

stirring was continued for an additional 3h. Pyridine (2ml) was added and after 2min the solution was recovered by filtration and concentrated to a colorless syrup at reduced pressure.

The residue was dissolved in methylene chloride (11), the resulting solution was cooled in an ice bath and triethylamine (200ml) was added. After an additional 5min benzoyl chloride (90ml) was added dropwise. The solution was stirred for an additional 2h. Methanol (200ml) was slowly added and after 1h solvents were removed at reduced pressure to leave a solid residue. The solid was stirred vigorously in HCl (3N, 11) for 3h. The pH of the solution was maintained between 1 and 2. The solution was extracted with methylene chloride (4X150ml) and the combined extracts were washed with saturated sodium bicarbonate solution (2X200ml) and water (2X200ml) and then dried over magnesium sulfate. The solution was collected by filtration and the solvents were removed at reduced pressure to leave a dark syrup which contained two products (R_f0.14 and 0.8 in ethyl acetate:hexane (3:5)). The products were filtered through a silica gel column (5x19cm) using hexane (11), hexane:ethyl acetate (21) and hexane:ethyl acetate (1:1) as eluant. The desired product 5 was obtained in 47% yield (50g). The 200MHz PMR spectrum of 5 in $CDCl_3$ showed signals at δ(ppm): 8.02 (m, 2H, aromatic); 7.48 (m,3H,aromatic); 4.38 (m,2H, H-1); 4.02 (m,1H, H-2); 3.7 (m,2H,H-3); 2.88 (d, OH) and 2.42 (t, OH). This material was used directly in the coupling experiments.

The Bischloromethylether 6.

Compound 5 (6g, 30.6mmole) and paraformaldehyde (1.9g, 21.4mmole) were added to 1,2-dichloroethane (40ml) and the solution was cooled in

an ice-salt bath. HCl gas was passed through the solution for 2h. Calcium chloride (3g, anhydrous powder) was added and HCl was bubbled through for an additional 30min. The mixture was filtered and the solution was quickly evaporated to give a syrup (8g, 89%). Compound 6 is reasonably stable in dry solvents such as benzene and methylene chloride. It can also be stored under refrigeration for long periods as a syrup. The PMR spectrum of 6 in $CDCl_3$ showed signals at δ(ppm): 8.00 (m,2H,aromatic); 7.4 (m,3H,aromatic); 5.58 (s,2H,CH_2Cl); 5.48 (s,2H,CH_2Cl); 4.4 (m,3H,H-1&H-2) and 3.85 (m,2H,H-3).

The Bismethylthiomethylether 7.

Compound 5 (10g) was added to a solution containing DMSO (50ml), acetic anhydride (50ml) and acetic acid (100ml). The solution was stirred at room temperature for nine days whereupon the solvents were removed under high vacuum. The oily residue was chromatographed on silica gel (5x7cm) eluting first with hexane followed by increasing the ethyl acetate content by 1% every litre up to 5% ethyl acetate. Compound 7 (10g) was obtained in 62% yield. The 200MHz spectrum of 7 in $CDCl_3$ showed signals at δ(ppm): 8.04 (m,2H,aromatic); 7.48 (m, 3H,aromatic); 4.8 (s,2H,CH_2S); 4.69 (s,2H,CH_2S); 4.42 (m,2H,H-1); 4.26 (m,1H,H-2); 3.74 (d,2H,H-3); 2.14 (s,3H,CH_3S) and 2.12 (s,3H,CH_3S).

1-Benzoyl-2,3-bis[(cytosin-1-yl)methyl]glycerol (8a)

Cytosine (4.97g,17.8mmole), ammonium sulfate (0.5g) and HMDS (90ml) were heated at reflux with exclusion of moisture until the solution became clear. The solvent was removed at reduced pressure and the residue was dissolved in 1,2-dichloroethane (50ml). Tetrabutylammonium iodide (100mg) and compound 6 (2.6g, 8.87mmole)

were added. The mixture was heated at reflux for 2h whereupon water (10ml) and methanol (50ml) were added and after 2min the solvents were removed at reduced pressure. The desired product was obtained after silica gel chromatography using ethyl acetate:methanol (2:1) as eluant. Compound 8a (1.6g,41%) was precipitated from ethanol using ether, mp 155-158 °C, R_f 0.61 (iPrOH:NH_4OH:H_2O;7:1:2).

Compound 8a showed λmax in nm at pH 1: 275; at pH 7: 230,267 and at pH 13: 264. The 200MHz spectrum of 8a in DMSO-d_6 showed signals (δ,ppm) at 7.86(s,1H); 7.82(s,1H); 7.53(m,5H); 7.25(s,2H); 7.17(s,2H); 5.67(d,1H); 5.64(d,1H); 5.15(q,2H); 5.06(s,2H); 4.20 (m,3H) and 3.62 (m,2H).

Anal. Calc'd for $C_{20}H_{22}N_6O_6.H_2O$: C,52.17; H,5.25; N,18.25. Found: C,52.44; H,5.21; N,17.66.

1,2-Bis[(cytosin-1-yl)methyl]glycerol (9a)

Compound 8a (540mg,1.22mmole) was dissolved in 20ml of ammonium hydroxide:ethanol (1:1) and the solution was heated at 60°C for 10h. The solvents were removed at reduced pressure and the desired product 9a was obtained as a solid (mp 184-186°C,0.274g, 66%) on crystallization from ethanol (R_f0.39 in iPrOH:NH_4OH:H_2O,7:1:2).

Compound 9a showed λmax in nm (ϵ) at pH 1: 274 (24,700); pH7: 230sh,(15,300), 266 (14,500); pH 13: 267 (14,500). The PMR spectrum of 2 (DMSO-d_6) showed signals (δ,ppm) at 7.59(d,1H); 7.58(d,1H); 7.22(s,2H); 7.17(s,2H); 5.70(s,1H); 5.66(s,1H); 5.10(s,2H); 5.02(s,2H) and 3.40(m,5H).

Anal. Calc'd for $C_{13}H_{18}N_6O_5xH_2O$: C,43.82; H,5.65; N,23.59. Found: C,44.44; H,5.27; N,23.07.

1-Benzoyl-2,3-bis[(2-amino-6-chloropurin-9-yl)-methyl]glycerol (8b).

6-Chloroguanine (6g,35.4mmole) was treated as in the preparation of 8a above except that the condensation reaction was refluxed for 14h. The product was obtained by silica gel chromatography using chloroform:methanol (95:5) as eluant. Compound 8b was obtained as a solid (2.5g, 30%, mp196-197°C, R_f0.38 in $CHCl_3$:MeOH,9:1) after recrystallization from ethyl acetate:ethanol (3:1).

Compound 8b showed λmax in nm (ε) in ethanol at 220 (53,800) and 308 (14,000). The PMR spectrum of 8b in (DMSO-d_6) showed signals (δ,ppm) at 8.27 (s,1H), 8.25 (s,1H), 7.52 (m,5H), 5.53 (s,2H), 5.49 (s,2H), 4.20 (m,3H) and 3.68 (m,2H).

Anal. Calc'd for $C_{22}H_{20}N_{10}O_4Cl_2$: C,47.24; H.3.60; N,25.04. Found: C,47.04; H,3.60; N,24.97.

1,2-Bis[(2-amino-6-methoxypurin-9-yl)methyl]glycerol (9b).

Compound 8b (0.14g, 0.25mmole) was dissolved in 5ml of dioxane and 10ml of methanol containing 150mg of dissolved sodium. The solution was stirred at room temperature for 10min. Solvents were removed and the residue crystallized from water to give 9b(98mg,87%, mp 235-236°C, R_f0.18 in $CHCl_3$:MeOH,9:1).The conversion of 8b was also carried out using 160mg of sodium hydroxide dissolved in water (5ml) and methanol (15ml) at reflux for 1h. Compound 9b was obtained in 45% yield.

Compound 9b showed λmax in nm (ε) in ethanol at 245 (21,200) and 279 (17,900).The PMR spectrum of 8a in (DMSO-d_6) showed signals (δ,ppm) at 7.95 (s,1H), 7.94 (s,1H), 6.52 (s,2H), 6.49 (s,2H), 5.45 (s,2H), 5.35 (s,2H), 3.95 (s,6H) and 3.45 (m,5H).

Anal. Calc'd for $C_{17}H_{22}N_{10}O_5x1/2H_2O$: C,44.83; H,5.09; N,30.75. Found: C,44.60; H,5.03; N,30.30.

When compound 8b (0.2g, 0.36m mole) was heated in aqueous sodium hydroxide (eg 0.125M NaOH in dioxane:water(3:1, 20ml) at 60°C for 14h), a mixture of compound 2 and 9-[[2,3-dihydroxypropoxymethyl]-methyl]guanine (10) was always obtained. A small amount of a very polar material was obtained in these reactions. The PMR spectrum showed signals in DMSO-d_6 (δ,ppm) at 7.74(s,2H), 6.77(s,4H), 5.38(s,2H), 5.27(s,2H) and 3.50(m,5H) and max in ethanol occurred at 252 and 275nm. These values are consistent with those expected for 1,2-bis[(2-amino-6-hydroxypurin-9-yl]methyl]glycerol.

1-Benzoyl-2,3-Bis[(6-chloropurin-9-yl)methyl]glycerol 8c.

METHOD A

6-Chloropurine (3.15g,20.4mmole) was silylated and condensed with 7 as described for cytosine above. The product 9c was obtained through silica gel chromatography using ethyl acetate as eluant. Compound 8c crystallized from ethyl acetate (1.7g, 32%, mp 169-170°C, R_f0.45 in $CHCl_3$:MeOH, 9:1).

Compound 8b showed λmax in ethanol at nm (ϵ) : 231 (17,200 and 263 (14,600).The PMR spectrum of 8c (DMSO-d_6) showed signals (ppm) at 8.81(s,1H), 8.80(s,1H), 8.78(s,1H), 8.69(s,1H), 7.48(m,5H), 5.75(s,2H), 5.68(s,2H), 4.20(m,3H) and 3.74(m,2H).

Anal. Calc'd for $C_{22}H_{18}N_8O_4Cl_2$: C,49.92; H,3.43; N,21.17. Found: C,49.83; H,3.48; N,21.06.

METHOD B

6-Chloropurine (1.7g) was silylated in the standard manner and condensed with compound 7 (1.7g) and iodine (2.8g) in THF (100ml) at room temperature for 4 days. The solution was decolorized with sodium sulfite solution (saturated), solvents were concentrated at reduced pressure, and the desired product 8c was obtained in 36% yield (1.03g) from silica gel chromatography.

1,2-Bis[(adenin-9-yl)methyl]glycerol 9c.

Compound 8c(320mg, 0.6mmole) was dissolved in concentrated ammonium hydroxide:ethanol (1:1) and stirred at 55°C for 7h. The solvents were evaporated and the product isolated by silica gel chromatography using chloroform:ethanol,1:1. Compound 9c crystallized from ethanol:ethyl acetate (1:2) in 44% yield (105mg, mp 221-223°C, R_f0.71 in iPrOH:NH_4OH:H_2O,7:1:2).

Compound 9c showed λmax in nm (ϵ) at pH 1: 255 (27,100); pH 7: 255 (25,100); pH13: 255 (24,100). The PMR spectrum of 9c (DMSO-d_6) showed signals (δ,ppm) at 8.22 (s,1H), 8.21 (s,1H), 8.15(s,1H), 8.14(s,1H),7.30(s,4H), 5.57(s,2H), 5.46(s,2H) and 3.58(m,5H).

Anal. Calc'd for $C_{15}H_{18}N_{10}O_3xH_2O$: C,44.55; H,4.98; N,34.64. Found: C,45.16; H,4.73; N,34.06.

1-Benzoyl-2,3-Bis[(thym-1-yl)methyl]glycerol (8d).

Thymine (2.4g,19mmole) was silylated and condensed with 7 as described above for cytosine except that the condensation reaction was heated at reflux for 1h. The product was isolated by silica gel chromatography using ethyl acetate. Compound 8d was precipitated from ethyl acetate using ether and obtained in 66% yield (3g, mp 157-159°C, R_f0.41 in $CHCl_3$:MeOH,9:1).

Compound 8d showed max in nm at pH 1: 264, 232sh ; pH 7: 264,261sh; pH 14: 264.

Anal. Calc'd for $C_{22}H_{24}N_4O_8 x1/2H_2O$: C,54.88; H,5.23; N,11.64. Found: C,55.29; H,5.14; N,11.51.

1,2-Bis[(thym-1-yl)methyl]glycerol (9d).

The benzoyl group was removed from 8d(430mg) in the usual way and after chromatography on preparative TLC plates (silica, acetone), compound 9d was precipitated from ethanol with ether (236mg,71%, mp77-81°C, R_f0.23 in $CHCl_3$:MeOH,9:1). Compound 9d showed λmax in nm(ε) at pH 1: 262(19,400); pH 7: 262(17,500); pH 13: 264(12,000).

Anal. Calc'd for $C_{15}H_{20}N_4O_7 x1/2H_2O$: C,47.75; H,5.61; N,14.85. Found: C,47.49; H,5.48; N,14.28.

1-Benzoyl-2-methylthiomethyl-3-(2-amino-6-hydroxypurin-9-yl)glycerol (11) and 1-Benzoyl-2-(2-amino-6-hydroxypurin-9-yl)-3-methylthiomethylglycerol (12).

6-Chloroguanine (3g,17,7mmole), ammonium sulfate (300mg) and HMDS (60ml) were heated together at reflux until the solution became clear. The solvent was removed at reduced temperature and the residue was dissolved in dry THF (70ml). Compound 7(5.6g,17.7mmole) and iodine (4.46g,17.7mmole) were added and the solution was stirred overnight at room temperature. Solvents were removed at reduced pressure and the residue was dissolved in methylene chloride which was washed successively with sodium thiosulfate, sodium bicarbonate and water. The products were separated by silica gel chromatography using $CHCl_3$:MeOH,97:3. Compound 11a was the major product (1.25g,16%,mp143-144°C, R_f0.34 in $CHCl_3$:MeOH,95:5).

Compound 11a showed λmax (nm) in ethanol at 221(32,400) and 307(6000). The PMR spectrum of in $CDCl_3$ showed signals (δ,ppm) at 7.89(s,1H), 7.68(m,5H), 5.52(s,2H), 5.15(s,2H), 4.73(s,2H), 4.26(m,3H), 3.73(d,2H) and 2.10(s,3H).

Anal. Calc'd for $C_{18}H_{20}N_5O_4ClS$: C,49.37; H,4.60; N,15.94. Found: C,49.21; H,4.61; N,15.93.

The N-7 isomer (11b) was also obtained (350mg, mp 148-149°C, R_f0.20 in $CHCl_3$:MeOH,95:5). Compound had λmax(nm) in ethanol at 224(31,900) and 321(4,900). The PMR spectrum of ($CDCl_3$) showed signals (δ,ppm) at 8.10 (s,1H), 7.68 (m,5H), 5.71(s,2H), 5.11(s,2H), 4.72(s,2H), 4.25(m,3H), 3.68(m,2H) and 2.09(s,3H).

Anal. Calc'd for $C_{18}H_{20}N_5O_4ClS$: C,49.37; H,4.60; N,15.94. Found: C,49.26; H,4.63; N,15.96.

Compound 12a was obtained in 4% yield (300mg, mp 93-94°C, R_f0.38 in $CHCl_3$:MeOH,95:5). Compound 12a had λmax(nm) in ethanol at 221(33,000) and 307(6,900). The PMR spectrum of ($CDCl_3$) showed signals (,ppm) at 7.88 (s,1H), 7.55 (m,5H), 5.61(s,2H), 5.25(s,2H), 4.60(s,2H), 4.34(m,3H), 3.79(m,2H) and 2.08(s,3H).

Anal. Calc'd for $C_{18}H_{20}N_5O_4ClS$: C,49.37; H,4.60; N,15.94. Found: C,49.47; H,4.65; N,15.87.

The N-7 isomer 12b was also obtained (150mg, 2%, mp 122-123°C, R_f0.26 in $CHCl_3$:MeOH,95:5). Compound 12b had λmax(nm) in ethanol at 223(31,300) and 322(4,200). The PMR spectrum of (DMSO-d_6) showed signals (δ,ppm) at 8.12 (s,1H), 7.61 (m,5H), 5.83(s,2H), 5.16(s,2H), 4.60(s,2H), 3.99(m,5H) and 2.09(s,3H).

1-Benzoyl-2-(thym-1-yl)methyl-3-(2-amino-6-chloropurin-9-yl)methyl-glycerol. (13)

Compound 11a(1.87mmole), silylated thymine (5.6mmole) and iodine were stirred in THF at reflux for 14h. Solvents were removed at reduced temperature and the residue was washed with sodium thiosulfate solution and the products were extracted into chloroform. The product was purified by silica gel chromatography using chloroform:methanol (95:5,R_f0.15) as eluant. Compound 13 was obtained in 78% yield (mp105-106 °C).

Anal. Calc'd for $C_{22}H_{22}N_7O_6Cl x 1/2H_2O$: C,50.34; H,4.42; N,18.68. Found: C,50.71; H,4.43; N,18.29.

1-(2-Amino-6-hydroxypurin-9-yl)methyl-2-(thym-1-yl)-methylglycerol. (14)

Compound 13(390mg,0.76mmole) was heated at reflux in 0.75N NaOH for 2h. The product was isolated by preparative TLC plates developed in iPrOH:NH_4OH:H_2O (7:1:1; R_f0.53). The desired product 14 was eluted with ethanol:water(2:1) and crystallized from ethanol:ether (2:1) in 43% yield (128mg, mp158-160°C). The UV spectrum showed max(nm) in pH 1: 257(16,800); pH 7: 252(18,700) and 265sh(17,700); pH 13: 263(13,800). The PMR spectrum of (DMSO-d_6) showed signals (,ppm) at 7.78 (s,1H), 7.64 (m,5H), 7.05(s,1H), 5.54(s,2H), 5.48(s,2H), 5.21(q,2H), 4.30(m,3H), 3.71(m,2H) and 1.76(s,3H).

Anal. Calc'd for $C_{15}H_{19}N_7O_6 x 1/2H_2O$: C,42.86; H,5.27; N,23.32. Found: C,42.37; H,4.93; N,23.23.

Acknowledgement

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