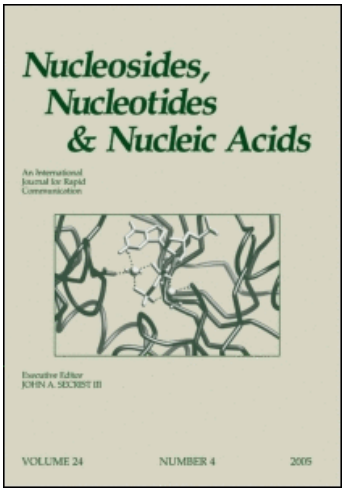

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Synthesis of Analogues of Ribosylbarbituric Acid

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SYNTHESIS OF ANALOGUES OF RIBOSYLBARBITURIC ACID

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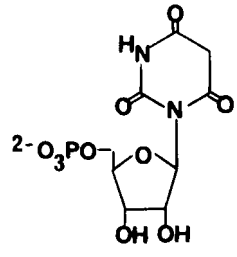
Abstract: Syntheses of 5-alkyl (5 b,c), 2'-deoxyribosyl (9, 10) and arabinofuranosyl (13) analogues of ribosylbarbituric acid (5a) are described. The compounds were prepared by condensation of persilylated barbituric acids with pentofuranosyl moieties. The 2'-tolylthio analogue (16) was obtained by an alternative procedure involving ring-opening of 6,2'-O-cyclouridine (15).

It has recently been reported that 1-(5'-phospho-β-D-ribofuranosyl) barbituric acid 1 is an exceptionally potent inhibitor (K_i 10^{-11}M) of



1

orotidylic acid decarboxylase, a key enzyme in pyrimidine nucleotide biosynthesis.[1] We have investigated 5-substituted and 2'-modified analogues of the corresponding ribosyl barbituric acid (5a, 6-hydroxyuridine). By analogy with other pyrimidine nucleosides, for example, 5-propyl-2'-deoxyuridine[2] and 1-(β-D-arabinofuranosyl)thymine,[3] it was thought that these compounds might be selectively phosphorylated by a herpes virus specified thymidine (cytidine) kinase and the

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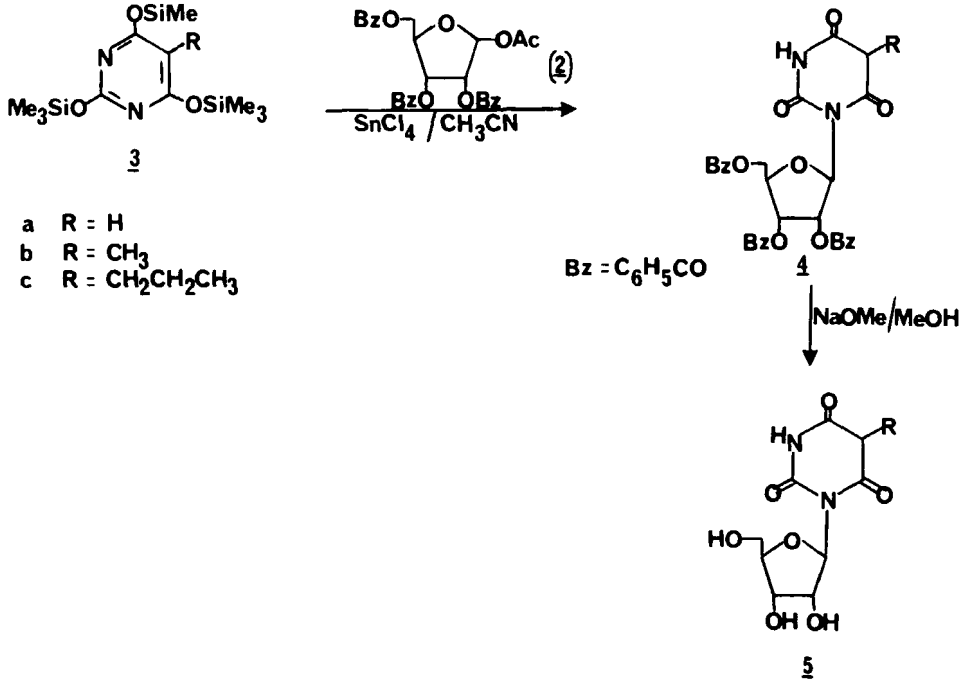
resultant analogues of the phosphate 1 might then inhibit nucleic acid biosynthesis in virally infected cells.

Barbituric acid riboside (5a) is most conveniently prepared by Lewis acid catalysed condensation of silylated barbituric acid (3a) with 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose (2).[1,4] The riboside and 2'-deoxyriboside have also been obtained from 5',6-cyclonucleosides prepared from 5-halouracil ribosides and 2'-deoxyribosides respectively,[5,6] but this route is not of such wide applicability. We have explored the condensation of silylated barbituric acids with suitable glycones as a route to various barbituric acid nucleosides.

The silylated barbituric acids 3b and 3c were readily prepared by refluxing the appropriate barbituric acid in 1,1,1,3,3,3-hexamethyldisilazane with chlorotrimethylsilane. In contrast to the reaction of



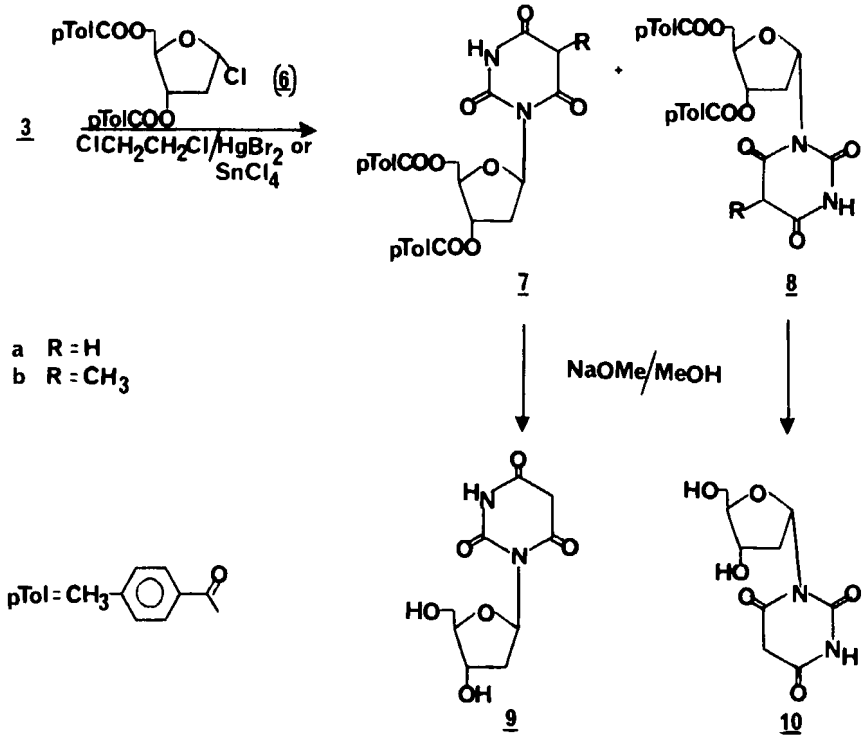
silylated barbituric acid (3a) with the ribose acetate 2, which proceeded with a catalytic quantity of stannic chloride, it was found that reaction with a 5-substituted barbituric acid such as 3b and 3c required at least one equivalent of the Lewis acid. This probably

reflects the increased basicity of the nitrogen atoms in 3b and 3c, which may lead to complexation and inactivation of one equivalent of stannic chloride. Reaction of 3b or 3c with 2 in the presence of 1.4-2.0 equivalents of stannic chloride in acetonitrile afforded the benzoylated barbituric acid nucleosides 4b and 4c in 25-30% yield. The benzoyl protecting groups were removed with sodium methoxide in methanol to give the 5-methyl and 5-propyl barbituric acid nucleosides, 5b and 5c respectively, in 75-80% yield.

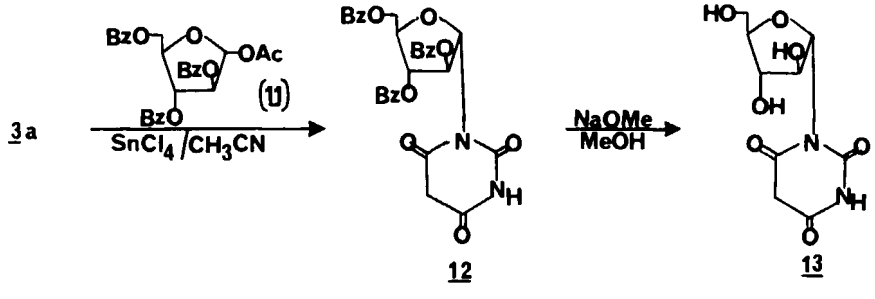
The condensation of silylated barbituric acid with a 2'-deoxyribose moiety has not been previously reported. We have found that silylated barbituric acids 3a and 3b react smoothly with 1-α-chloro-2-deoxy-3,5-di-O-p-toluoyl-D-erythropentofuranose (6) in the presence of mercuric bromide or stannic chloride in 1,2-dichloroethane. Thus, reaction of 3a with 6 for 1 hour in the presence of 1 mol % mercuric bromide in 1,2-dichloroethane gave the anomeric mixture 7a/8a in 62% yield after column chromatography. Recrystallisation from methanol afforded the β-anomer 7a (31% yield) and the α-anomer 8a was obtained from the mother liquor (9% yield). The toluoyl esters 7a and 8a were deprotected by treatment with sodium methoxide in methanol to give the 2'-deoxyriboside 9 and its α-anomer 10 in about 95 and 80 % yields, respectively.

Reaction of 3b with 6 in the presence of stannic chloride gave the anomers 7b and 8b in a ratio of 1:1. Using mercuric bromide (0.01 equiv) as the Lewis acid catalyst, the reaction was considerably slower than that of 3a. However, the required β-anomer 7b predominated with an anomeric ratio of about 2:1 and after 90 hours reaction the mixture of 7b and 8b was obtained in 68% yield after column chromatography. Attempts to separate these anomers by crystallisation or more extensive chromatography led to a rearranged product, possibly an O-nucleoside as has been postulated previously with a barbituric acid nucleotide,[7] and the individual anomers were not obtained from the mixture.

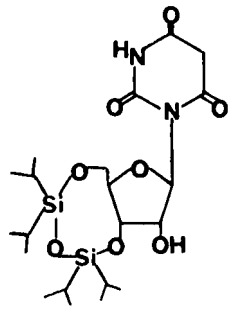
The preparation of an arabinofuranosyl barbituric acid by direct condensation was also achieved. Reaction of silylated barbituric acid 3a with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-arabinofuranose (11) in the presence of stannic chloride in acetonitrile for 16 hours gave the tribenzoyl barbituric acid nucleoside as the α-anomer 12 in 50% yield.



Deprotection of 12 with sodium methoxide in methanol afforded the α-arabinofuranosyl barbituric acid 13 in 90% yield.



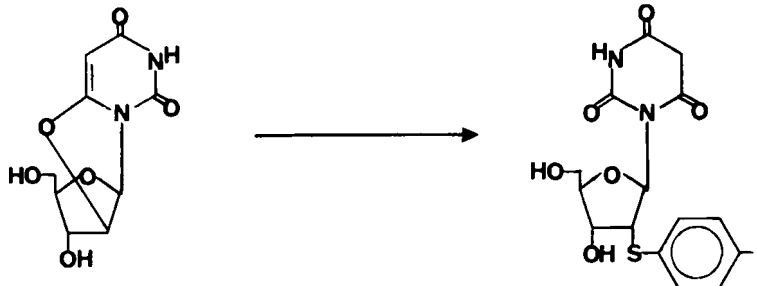
We have also explored stereocontrolled routes to 2'-modified barbituric acid nucleosides, such as the β-arabinofuranoside, using 2,2'- or 6,2'-cyclonucleosides. Treatment of 5a with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine afforded the 3',5'-protected nucleoside 14 in 78% crude yield.



14

However, modifications at the 2'-position of 14 could not be carried out because of the reactivity of the barbituric acid moiety with suitable reagents such as sulphonyl chlorides and diethyl azodicarboxylate/triphenylphosphine.

The readily prepared 6,2'-cyclonucleoside 15[8,9] provides a potential entry point to such 2'-modified barbituric acid nucleosides by ring opening at the C(6)-O-C(2') link. This cyclonucleoside is, however, quite stable to alkaline hydrolysis[9] (existing as the mono-anion) and is exceptionally stable to acidic conditions[9,10] (e.g. for 3 days at 70°C in 2N sulphuric acid) and ring opening to a barbituric acid nucleoside has not been reported. We have cleaved the C(2')-O bond of 15 with a thiolate nucleophile in a manner similar to that reported for 2,2'anhydrouridine.[11]



15 16

Reaction of 15 with a five-fold excess of toluene-4-thiol and triethylamine in refluxing methanol gave the 2'-functionalised barbituric acid nucleoside 16. The location of the tolylthio group at C(2') was confirmed by ^{13}C nmr (δ_C C(6) 152.9, C(2') 51.1).[11,12] Desulphurisation of 16 would afford an alternative route to the 2'-deoxyribosyl barbituric acid 9.

None of the barbituric acid nucleosides prepared showed antiviral activity against Herpes simplex virus type 1 (HFEM strain in Vero cells or SC16 strain in MRC-5 cells) or type 2 (MS strain in Vero cells) nor was cytotoxic for the cell monolayers at concentrations up to 30μg/ml.

EXPERIMENTAL

Melting points were determined with a Reichert hot-stage apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 580 spectrometer. Ultraviolet absorption spectra were taken on a Cary 219 spectrometer. ^{1}H nmr spectra were obtained at 90 MHz on a Varian DM390 spectrometer or at 80 MHz on a Bruker WP 80 DS spectrometer. ^{13}C nmr spectrum was recorded at 20.15 MHz on the latter spectrometer.

5-Methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)barbituric acid (4b)

5-Methylbarbituric acid (3.41g, 24mmol) and chlorotrimethylsilane (6ml) were heated under reflux in hexamethyldisilazane (70ml) until the solid had dissolved (about 0.5h). The solvent was removed and the residue taken up in dry acetonitrile (400ml). To this solution was added 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (10.09g, 20mmol) and tin (IV) chloride (4ml) and the solution was left for 90h. The solvent was removed and the residue partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was further washed with brine, dried (magnesium sulphate) and the solvent removed. Column chromatography on silica gel eluting with chloroform-methanol (100:1,50:1) afforded 5-methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)barbituric acid as a foam (3.1g, 26%); λmax (EtOH) 229 (ε 41,500) and 272 (ε 22,100) nm; νmax (KBr) 3260, 1730 and 1270 cm^{-1}; δ_H ($CDCl_3$) 1.56 (3H, d, J 7Hz, D_2O exchange leaves s, CH_3), 3.54 (1H, q, J 7Hz, D_2O exchangeable, 5-H), 4.5-4.85 (3H, m, 4'-H and 5'-H), 6.06 (2H, m, 2'-H and 3'-H), 6.39 (1H, s, 1'-H), 7.2-8.2 (15H, m, 3 x C_6H_5), and 8.77 (1H, br, D_2O exchangeable 3-H); (Found: C, 63.25; H, 4.47; N, 4.65%. $C_{31}H_{26}N_2O_{10}$ requires C, 63.48; H, 4.47; N, 4.78%).

5-Methyl-1-β-D-ribofuranosylbarbituric acid (5b)

To a solution of 5-methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) barbituric acid (2.3g, 3.9mmol) in methanol (88ml) was added sodium

methoxide (1M in methanol, 12ml) and the solution was stirred for 1h. The solution was neutralised with Amberlite IR 120 (H^+ form), filtered and the solvent removed. The residue was taken up in water (80ml) and extracted with chloroform (2 x 40ml). The aqueous solution was passed through a column of Amberlite IR 120 (H^+ form, 50ml) and the solvent removed to afford 5-methyl-1-β-D-ribofuranosylbarbituric acid (0.87g, 81%); λmax (H_2O) 272 (ε 15,800) nm; νmax (KBr) 3420, 1700 and 1380 cm^{-1}; δ_H [$(CD_3)_2SO$] 1.38 (3H, br.s, CH_3), 3.3-3.9 (4H, m, 4'-H, 5'-H and 5-H), 4.07 (1H, t, J 6Hz, 3'-H), 4.37 (1H, m, 2'-H), 4.85 (3H, br, D_2O exchangeable, 3 x OH), 5.92 (1H, d, J 3Hz, 1'-H), and 11.30 (1H, br.s, D_2O exchangeable, 3-H); (Found: C, 43.78; H, 5.43; N, 9.78%. $C_{10}H_{14}N_2O_7$ requires: C, 43.80; H, 5.15; N, 10.22%).

5-Propyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)barbituric acid (4c)

5-Propylbarbituric acid (0.85g, 5.0mmol) and chlorotrimethylsilane (2ml) were heated under reflux in hexamethyldisilazane (20ml) for about 2h. The solvent was removed and the residue was taken up in dry acetonitrile (100ml). 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (2.27g, 4.5mmol) and tin (IV) chloride (0.4ml) were added and the solution was stirred at room temperature. After 3h further tin (IV) chloride (0.8ml) was added and the solution was allowed to stand for 40h. The solvent was removed and the residue partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was further washed with brine, dried (magnesium sulphate) and the solvent removed. The residue was purified by column chromatography on silica gel eluting with chloroform-methanol mixtures (100:1, 50:1) to afford 5-propyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)barbituric acid as a colourless foam (0.80g, 29%); λmax (EtOH) 229 (ε 40,600) and 272 (ε 22,500) nm; νmax (KBr) 3260, 2960 and 1730 cm^{-1}; δ_H ($CDCl_3$) 0.87 (3H, 2 x t, J 7Hz, CH_3), 1.2-1.6 (2H, m, $CH_2CH_2CH_3$), 1.9-2.2 (2H, m, $CH_2CH_2CH_3$), 3.44 (1H, t, J 6Hz, D_2O exchangeable, 5-H), 4.5-4.8 (3H, m, 4'-H and 5'-H), 6.00 (2H, m, 2'-H and 3'-H), 6.34 (1H, s, 1'-H), 7.2-8.1 (15H, m, 3 x C_6H_5), and 8.70 (1H, s, D_2O exchangeable, 3-H); (Found: C, 64.26; H, 4.77; N, 4.50%. $C_{33}H_{30}N_2O_{10}$ requires: C, 64.49; H, 4.92; N, 4.50%).

5-Propyl-1-β-D-ribofuranosylbarbituric acid (5c)

To a solution of 5-propyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) barbituric acid (0.62g, 1.0mmol) in methanol (10ml) was added sodium

methoxide (1.0M in methanol, 3.3ml) and the solution was stirred for 40 min. The solution was neutralised by addition of Amberlite IR 120 (H^+ form), filtered and the solvent removed. The residue was taken up in water (20ml) and the solution was extracted with chloroform (2 x 10ml). The solvent was removed from the aqueous layer and the residue was purified by column chromatography on silica gel eluting with chloroform-methanol (3:1) to afford 5-propyl-1-β-D-ribofuranosylbarbituric acid (0.23g, 76%), m.p. >200° (dec); λmax (H_2O) 271 (ε 18,300) nm; νmax (KBr) 3400, 1690, 1630, and 1580 cm^{-1}; δ_H [$(CD_3)_2SO$] 0.80 (3H, t, J 7Hz, CH_3), 1.27 (2H, sextet, J 7Hz, $CH_2CH_2CH_3$), 2.03 (2H, t, J 7Hz, $CH_2CH_2CH_3$), 3.48 (2H, m, 5'-H), 3.63 (1H, m, 4'-H), 4.10 (1H, t, J 6Hz, 3'-H), 4.49 (1H, m, 2'-H), 5.0 (4H, br, D_2O exchangeable, 3 x OH and 5-H), 6.06 (1H, d, J 4Hz, 1'-H), and 9.3 (1H, br, D_2O exchangeable, 3-H); (Found: C, 38.82; H, 4.80; N, 6.90%. $C_{12}H_{18}N_2O_7 \cdot 0.8\ CHCl_3$ requires: C, 38.64; H, 4.76; N, 7.04%).

1-(2-Deoxy-3,5-di-O-p-toluoyl-β-D-erythropentofuranosyl)barbituric acid (7a) and 1-(2-Deoxy-3,5-di-O-p-toluoyl-α-D-erythropentofuranosyl) barbituric acid (8a)

Barbituric acid (0.54g, 4.2mmol) and chlorotrimethylsilane (1.2ml) were heated under reflux in hexamethyldisilazane (12ml) until the solid had dissolved (0.5h). The solvent was removed and the residue was taken up in dry 1,2-dichloroethane (4ml). This was added to a solution of 1-α-chloro-2-deoxy-3,5-di-O-p-toluoyl-D-erythropentofuranose (1.35g, 3.5mmol) and mercury (II) bromide (13mg) in 1,2-dichloroethane (40ml) and the reaction was stirred for 1h at room temperature. The solvent was removed and the residue was purified by column chromatography on silica gel eluting with chloroform followed by chloroform-methanol (40:1) to afford the anomeric mixture 7a/8a (1.04g, 62%). Recrystallisation from methanol afforded 1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythropentofuranosyl)barbituric acid as a white crystalline solid (0.52g, 31%); m.p. 146-149°; λmax (EtOH) 243 (ε 35,400) nm; νmax (KBr) 3250, 1720, 1615, and 1280 cm^{-1}; δ_H ($CDCl_3$) 2.33, 2.40 (6H, 2 x s, 2 x CH_3), 2.8-3.3 (2H, m, 2'-H), 3.58 (2H, s, D_2O exchangeable, 5-H), 4.53 (3H, m, 4'-H and 5'-H), 5.6-5.8 (1H, m, 3'-H), 6.62 (1H, dd, J 5Hz and 9Hz, 1'-H), 7.06-7.22 (4H, 2 x d, J 8Hz, Ar-H), 7.87 (4H, d, J 8Hz, Ar-H), and 8.95 (1H, s, D_2O exchangeable, 3-H); (Found: C, 62.34; H, 4.76; N, 5.59%. $C_{25}H_{24}N_2O_8$ requires: C, 62.50; H, 5.04; N, 5.83%).

The mother liquor afforded 1-(2-deoxy-3,5-di-O-p-toluoyl-α-D-erythropentofuranosyl)barbituric acid as a colourless foam (0.15g, 9%); νmax (KBr) 3240, 1720, 1615, and 1280 cm^{-1}; δ_H ($CDCl_3$) 2.36 (6H, s, 2 x CH_3), 2.5-3.1 (2H, m, 2'-H), 3.58 (2H, s, D_2O exchangeable, 5-H), 4.25-4.65 (2H, m, 5'-H), 4.90 (1H, dt, J_d 8Hz and J_t 4Hz, 4'-H), 5.42 (1H, q, J 8Hz, 3'-H), 6.56 (1H, t, J 7.5Hz, 1'-H), 7.06-7.22 (4H, 2 x d, J 8Hz, Ar-H), 7.80-7.93 (4H, 2 x d, J 8Hz, Ar-H), and 8.93 (1H, s, D_2O exchangeable, 3-H); (Found: C, 62.01; H, 4.76; N, 5.37%. $C_{25}H_{24}N_2O_8$ requires: C, 62.50; H, 5.04; N, 5.83%).

1-(2-Deoxy-β-D-erythropentofuranosyl)barbituric acid (9)

To a suspension of 1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythropentofuranosyl)barbituric acid (0.58g, 1.2mmol) in methanol (22.5ml) was added sodium methoxide (1M in methanol, 2.5ml). After 2.5h the solution was neutralised by addition of Amberlite IR 120 (H^+ form), filtered and the solvent removed. The residue was taken up in water (25ml) and the solution was extracted with chloroform (2 x 12ml). The aqueous solution was passed through a column of Amberlite IR 120 (H^+ form, 15ml) and on concentration 1-(2-deoxy-β-D-erythropentofuranosyl) barbituric acid crystallised (280mg, 96%); m.p. 104-107°; λmax (H_2O) 259 (ε 15,800) nm; νmax (KBr) 3440, 3100, 2890, 1695, and 1350 cm^{-1}; δ_H [$(CD_3)_2SO$] 1.75-2.15 (1H, m, 2'-H), 2.52-2.74 (1H, m, 2'-H), 3.30-3.75 (5H, m, 2H D_2O exchangeable, 4'-H, 5'-H and 5-H), 4.25 (1H, dt, J_d 7Hz and J_t 4.5Hz, 3'-H), 3.7-5.3 (very br., D_2O exchangeable, 3 x OH), 6.34 (1H, t, J 7Hz, 1'-H), and 11.27 (1H, s, D_2O exchangeable, 3-H); (Found: C, 43.84; H, 5.16; N, 11.14%. $C_9H_{12}N_2O_6$ requires: C, 44.27; H, 4.95; N, 11.47%).

1-(2-Deoxy-α-D-erythropentofuranosyl)barbituric acid (10)

To a solution of 1-(2-deoxy-3,5-di-O-p-toluoyl-α-D-erythropentofuranosyl)barbituric acid (97mg, 0.2mmol) in methanol (4.4.ml) was added sodium methoxide (1M in methanol, 0.6ml). After 2h the solution was neutralised by addition of Amberlite IR 120 (H^+ form), filtered and the solvent removed. The residue was taken up in water (5ml) and the solution was extracted with chloroform (2 x 5ml). The aqueous solution was passed through a column of Amberlite IR 120 (H^+ form) and the solvent removed to afford 1-(2-deoxy-α-D-erythropentofuranosyl) barbituric acid as a colourless foam (41mg, 84%); νmax (KBr) 3440,

3100, 2920, 1695, and 1350 cm^{-1}; δ_H [$(CD_3)_2SO$] 2.2-2.8 (4H, m, d_5-DMSO and 2'-H), 3.4-3.6 (2H, m, 5'-H), 3.66 (2H, s, D_2O exchangeable, 5-H), 4.04 (2H, m, 3'-H and 4'-H), 4.3 (1H, br, D_2O exchangeable, OH), 5.0 (1H, br, D_2O exchangeable, OH), 6.28 (1H, t, J 7.5Hz, 1'-H), and 11.28 (1H, s, D_2O exchangeable, 3-H); (Found: C, 44.26; H, 5.26; N, 10.60%. $C_9H_{12}N_2O_6$ requires: C, 44.27; H, 4.95; N, 11.47%).

1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)barbituric acid (12)

Barbituric acid (3.07g, 24mmol) and chlorotrimethylsilane (6.5ml) were heated under reflux in hexamethyldisilazane (65ml) until the solid had dissolved (about 0.5h). The solvent was removed and the residue taken up in dry acetonitrile (100ml). To this solution were added 1-O-acetyl-2,3,5-tri-O-benzoyl-D-arabinofuranose (10.1g, 20mmol) and tin (IV) chloride (1.6ml) and the solution was left overnight. The solvent was removed and the residue partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was washed with water, dried (magnesium sulphate) and the solvent removed. The residue was purified by column chromatography on silica gel eluting with chloroform-methanol mixtures (100:1 to 20:1) to afford 1-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)barbituric acid (5.77g, 50%) which could be crystallised from ethanol-water, m.p. 109-111°; λmax (EtOH) 229 (ε 40,800) and 260 (ε 23,100) nm; νmax (KBr) 1725 and 1275 cm^{-1}; δ_H ($CDCl_3$) 3.70 (2H, s, D_2O exchangeable, 5-H), 4.45-4.80 (2H, m, 5'-H), 5.02 (1H, dt, J_d 7.2Hz and J_t 3.6Hz, 4'-H), 6.05 (1H, dd, J 7.2Hz and 5.4Hz, 3'-H), 6.27 (1H, t, J 4.8Hz, 2'-H), 6.52 (1H, d, J 4.4Hz, 1'-H), 7.25-8.25 (15H, m, 3 x C_6H_5), and 8.77 (1H, s, D_2O exchangeable, 3-H); (Found: C, 62.66; H, 4.31; N, 4.81%. $C_{30}H_{24}N_2O_{10}$ requires: C, 62.94; H, 4.23; N, 4.89%).

1-(α-D-Arabinofuranosyl)barbituric acid (13)

To a solution of 1-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl) barbituric acid (2.98g, 5.2mmol) in methanol (80ml) was added sodium methoxide (1M in methanol, 16ml) and the solution was stirred for 40 min. The solution was neutralised with Amberlite IR 120 (H^+ form), filtered and the solvent removed. The residue was taken up in water (100ml) and extracted with chloroform (2 x 50ml). The aqueous solution was passed through a column of Amberlite IR 120 (H^+ form) and the solvent removed to afford 1-(α-D-arabinofuranosyl)barbituric acid as a crystalline

solid (1.22g, 90%), m.p. 208-210°; λmax (H_2O) 260 (ε 16,500) nm; νmax (KBr) 3470, 3230, 3040, 1700, 1410, and 1350 cm^{-1}; δ_H [$(CD_3)_2SO$] 3.2-3.5 (2H, m, 5'-H), 3.69 (2H, s, D_2O exchangeable, 5-H), 3.7-3.86 (1H, m, 3'-H), 3.9-4.1 (1H, m, 4'-H), 4.62 (1H, t, J 6.5Hz, 2'-H), 4.8 (3H, br, D_2O exchangeable, 3 x OH), 5.91 (1H, d, J 6Hz, 1'-H), and 11.36 (1H, s, D_2O exchangeable, 3-H); (Found: C, 41.57; H, 4.30; N, 10.55%. $C_9H_{12}N_2O_7$ requires: C, 41.54; H, 4.65; N, 10.77%).

1-(3,5-O-(Tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl)barbituric acid (14)

To a solution of 1-β-D-ribofuranosylbarbituric acid (1.19g, 4.5mmol) in dry pyridine (18ml) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.65ml, 4.95mmol) and the solution was stirred for 0.5h at room temperature. The solution was taken up in ethyl acetate and washed with dilute hydrochloric acid followed by aqueous sodium bicarbonate and dried (magnesium sulphate). The solvent was removed to afford substantially pure 1-(3,5-O-(tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl)barbituric acid (1.76g, 78%). Column chromatography on silica gel eluting with chloroform-methanol mixtures (25:1-15:1) considerably reduced the yield (0.61g, 27%); δ_H ($CDCl_3$) 1.1 (28H, m, 4 x $(CH_3)_2CH$), 3.28 (1H, s, D_2O exchangeable, 2'-OH), 3.62 (1H, s, D_2O exchangeable, 5-H), 3.7-4.0 (3H, m, 4'-H and 5'-H), 4.46 (1H, d, J 6Hz, 2'-H), 4.89 (1H, t, J 6Hz, 3'-H), 6.11 (1H, s, 1'-H), and 8.67 (1H, s, D_2O exchangeable, 3-H); (Found: C, 50.13; H, 8.03; N, 4.94%. $C_{21}H_{38}N_2O_8Si$ requires: C, 50.17; H, 7.62; N, 5.57%).

1-(2-(4-Tolylthio)-β-D-ribofuranosyl)barbituric acid (16)

A solution of 6,2'-O-cyclouridine (0.48g, 2.0mmol), toluene-4-thiol (1.20g, 10.0mmol) and triethylamine (1.4ml, 10.0mmol) in methanol (5ml) was heated under reflux for 24h. The solvent was then allowed to evaporate and the residue was purified by column chromatography on silica gel eluting with chloroform-methanol (4:1,3:2) to afford 1-(2-(4-tolylthio)-β-D-ribofuranosyl)barbituric acid as a white crystalline solid (210mg, 26%); m.p. >300° (dec); λmax (MeOH) 219 (ε 10,700) and 258 (ε 21,200) nm; νmax (KBr) 3400, 1690, and 1600 cm^{-1}; δ_H [$(CD_3)_2SO$] 2.22 (3H, s, CH_3), 3.4-3.9 (5H, m, 4'-H, 5'-H and 5-H), 4.22 (1H, m, (D_2O exchange gives d, J 6Hz), 3'-H), 4.71 (1H, dd, J 6Hz and 9Hz, 2'-H), 5.1 (1H, br, D_2O exchangeable, 5'-OH), 5.50 (1H, d, J 5Hz,

3'-OH), 6.38 (1H, d, J 9Hz, 1'-H), 6.95-7.19 (4H, m, C_6H_4), and 9.33 (1H, s, D_2O exchangeable, 3-H); δ_c [$(CD_3)_2SO$] 20.4 (CH_3), 51.1 (2'), 62.5 (5'), 72.5 (3'), 86.0 (1' and 4'), 129.3 (Ar), 130.0 (Ar), 132.0 (Ar), 135.4 (Ar), 152.9 (6), 163.7 (2), and 164.5 (4); (Found: C, 47.61; H, 4.40; N, 6.58%. $C_{16}H_{18}N_2O_6S$. $0.4CHCl_3$ requires: C, 47.56; H, 4.48; N, 6.76%).

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