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SYNTHESIS OF *N*-β-D-GLUCOPYRANOSYL DERIVATIVES OF BARBITAL, PHENOBARBITAL, METHARBITAL, AND MEPHOBARBITAL*

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ABSTRACT

The condensation of per(trimethyl)silylbarbital and -phenobarbital with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose in the presence of stannic chloride in dichloroethane gave moderate yields of the β-coupled barbiturate *N*-D-glucopyranosyl derivatives. Reaction of metharbital and mephobarbital under the same conditions was unsuccessful. The homologous *N*-methylglucosides were prepared by reaction of the barbital and phenobarbital *N*-glucosyl derivatives with diazomethane. The diastereomers of the phenobarbital and mephobarbital derivatives were resolved by use of C-18 reverse-phase h.p.l.c. ^{1}H- and ^{13}C-n.m.r. spectroscopy, and thermospray l.c.–m.s. proved to be the most useful methods for characterizing the barbiturate glucosides.

INTRODUCTION

It has been proposed that an additional and general pathway for metabolism of the barbiturate drugs is *via* *N*-D-glucosylation. This is based on the isolation and identification of the *N*-D-glucosyl derivatives of amobarbital and phenobarbital[1–3]. Coupling of D-glucose to N-1 or N-3 of these drugs confers an asymmetry at C-5 and generates two diastereomers. In man, amobarbital has been shown to form both *N*-glucosyl diastereomers but only one diastereomer is excreted in significant quantities in the urine[4]. Phenobarbital has been shown to form *N*-glucosyl derivatives in man[5–7], however, it is unknown whether both diastereomers are excreted in the urine. Therefore, to expand the studies on the structural requirements necessary for the formation or excretion (or both) of these novel D-glucose metabolites, it is necessary to have synthetic standards of the *N*-glucosyl derivatives of clinically useful barbiturate drugs. This report describes the use of the Hilbert–Johnson reaction using stannic chloride[8] for preparing the *N*-glucosyl derivatives of barbital (**1**), metharbital (**2**), phenobarbital (**3**), and mephobarbital (**4**).

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RESULTS AND DISCUSSION

The general approach used for the synthesis of these potential metabolites was to view the barbiturate as a pyrimidine compound and to use the reaction conditions optimized by Niedballa and Vorbruggen[8] for coupling pyrimidines with D-ribose or D-glucose. For the reaction to give an adequate yield with barbital (**1**) or phenobarbital (**3**), more than a catalytic amount of stannic chloride was required. This requirement had been previously observed for the reaction of per(trimethyl)silylated 5-substituted barbituric acids with 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose in which one equivalent or more of stannic chloride was required[9]. Attempts to obtain the metharbital (**2**) and mephobarbital (**4**) 2,3,4,6-tetra-*O*-acetyl-*N*-glucopyranosyl derivatives under the same reaction conditions were unsuccessful. Reaction of per(trimethyl)silylated metharbital gave only an O-coupled product **14**. Its identification was based on the ^{13}C-n.m.r. spectrum, in which the C-1′ absorbance was at δ 89.1. Also, acid hydrolysis of **14** gave metharbital as the major isolable product. Attempts to produce O-to-N migration by heating in the presence of stannic chloride led only to decomposition and recovery of metharbital[8] (**2**). The alternate approach for preparing the *N*-glycosyl-metharbital and -mephobarbital (**12, 13a,** and **13b**) was by treating the *N*-glycosyl-barbital and -phenobarbital **8, 9a,** or **9b** with diazomethane[1,10]. Treatment of these compounds with an ethereal alcoholic solution of diazomethane[11] led to extensive methylation of the D-glucose hydroxyl groups, and less than 20% of the desired product could be isolated. The methylation of the D-glucose hydroxyl groups could be minimized by dissolving the *N*-glucosylphenobarbital **9b** in methanol–water prior to addition of diazomethane. However, since *N*-glycosylimides are stable under strongly acidic conditions[12–15], treatment of the 2,3,4,6-tetra-*O*-acetyl-*N*-glucosyl-barbital **6** and -phenobarbital **7a** with diazomethane, followed by acid hydrolysis, was the preferred method for preparing the *N*-glycosyl-metharbital **12** and -mephobarbital **13a** compounds.

Although the synthesis of the 2,3,4,6-tetra-*O*-acetyl-*N*-glucosyl phenobarbital compound has been previously reported[2,3], the question of whether or not the sample obtained was a single diastereomer or a mixture of diastereomers was never addressed. In a previous report from this laboratory[3], we failed to recognize that a single *N*-glucosylphenobarbital **9a** had been isolated and characterized. In the present work, the second *N*-glucosylphenobarbital **9b** was purified by use of a C-18 reverse phase liquid chromatography (h.p.l.c.) system. Although the diastereomers have been isolated and characterized, the absolute configuration associated with C-5 of the barbiturate ring of the *N*-glucosylphenobarbital and mephobarbital compounds remains to be determined.

Interpretation of the ^{1}H- and ^{13}C-n.m.r. spectra of the glucosides in D_2O is complicated because two conformations can be observed in approximately a 3:1 ratio. This is due to hindered rotation around the glycosyl bond[16]. The barrier to rotation of a glycosyl residue linked to a planar, six-membered cyclic aglycon has

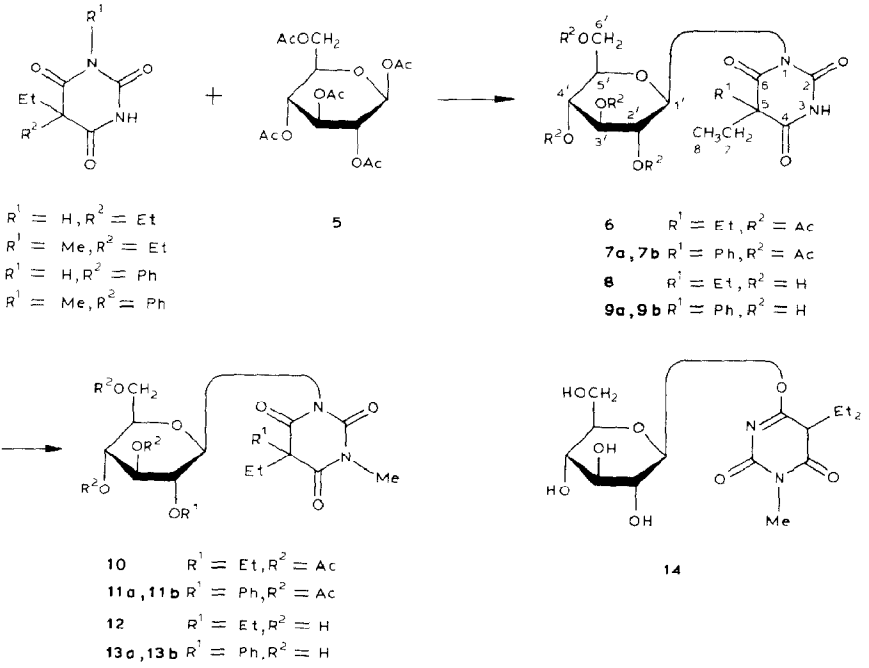
TABLE I

^{13}C-CHEMICAL SHIFTS OF 5,5-DISUBSTITUTED N-β-D-GLUCOPYRANOSYLBARBITURATES

Atom	**6**[a]	**7a**[a]	**8**[b]	**9a**[b]	**9b**[b]	**12**[b]	**13a**[b]	**13b**[b]	**14**[a]
2,4,6-(1H,3H,5H)Pyrimidinetrione residue									
C-2	147.6	147.3	150.1	149.6	149.5	150.4	150.2	150.2	150.2
C-4[c]	171.2	170.3	174.6	172.2	171.8	173.8	172.0	171.7	171.9
C-6[c]	172.7	170.6	174.1	173.1	173.1	173.5	172.5	172.4	172.7
C-5	58.3	61.8	58.6	61.3	61.6	58.9	58.9	62.0	58.3
(C-5)[d]			59.1	62.0		59.4			
N-Me						28.4	28.8	28.8	27.7
(N-Me)[d]						29.1	29.5	29.6	
Substituents at C-5 of pyrimidine residue									
C-7	31.7	30.0	31.8	29.9	29.7	32.3	30.8	30.4	32.5
(C-7)[d]	32.7		32.8	30.1		33.3 (31.8)		30.6	
C-8	9.3	9.9	8.7	9.0	9.1	8.8	8.8	9.3	9.5
ipso		137.1		137.4	137.4		137.7	137.7	
o		126.0		126.7	126.4		126.7	126.8	
(*o*)[d]					126.8			126.4	
m		129.2		129.6	129.5		129.6	129.6	
p		128.7		129.2	129.2		129.3	129.3	
Sugar residue									
C-1′	79.6	80.0	82.1	82.4	82.7	82.5	82.7	83.0	89.1
(C-1′)[d]	80.6		82.8	82.9	83.1	84.0	84.0	84.3	
C-2	74.7	74.8	77.3	77.3	77.2	77.3	77.2	77.2	69.9
(C-2′)[d]			77.7	77.7	77.6	77.9	77.4	77.7	
C-3′	73.8	73.6	79.5	79.5	79.4	79.6	79.6	79.5	69.9
C-4′	68.9	68.7	69.5	69.5	69.5	69.1	69.6	69.6	69.3
C-5′	68.1	67.9	69.0	69.0	69.3	69.7	69.0	69.6	68.0
C-6′	61.9	61.8	60.9	60.9	60.8	61.0	60.5	60.9	61.6
C=O	169.5, 170.2								168.8, 169.7
	170.6, 171.0								170.2, 170.6
CH_3	20.5, 20.6	20.5							20.4, 20.5
									20.6

[a]δ Values relative to the signal of tetramethylsilane as internal standard for solutions in $CDCl_3$. [b]δValues relative to the signal of ($^3H_4$)TPS; the solvent was D_2O containing 19% CH_3CN as internal standard δ_{CH_3} = 1.080 relative to δ_{TPS} determined in a separate experiment. [c]Signals may be reversed within each compound. [d]Additional carbon absorbances due to the minor conformational isomer.

been previously shown[17] to be ~65 J/mol, and it is expected that compounds **8, 9a, 9b, 12, 13a,** and **13b** would have a comparable barrier to rotation. The two different conformations were observed in the ^{1}H-n.m.r. spectra in which the H-1 signal appeared as two doublets. As shown in Table I, additional ^{13}C absorbances were usually observed for C-1′ and C-2′ of the D-glucosyl residue and for C-5 and N-CH_3 of the barbiturate residue. All the *N*-glucosyl compounds exhibited a *J* 9–10 Hz value for C-1′, which was expected for a β-D anomer[1]. Finally, ^{13}C-n.m.r. spectroscopy was extremely useful in verifying that N coupling had occurred. In this series of compounds and in a series of *N*-glucosyl derivatives of cyanuric acid and *N*-methylcyanuric acids[16], the chemical shift of C-1′ of the D-glucose unit occurs between δ 78 and 84.



It was anticipated that thermospray l.c.–m.s. would be a useful method for characterizing *N*-glucosylbarbiturates since this method has been successfully used to analyze nucleosides[18] and other carbohydrates[19,20]. The filament-on mode was necessary for good sensitivity, and under the conditions described, the only significant ions were the protonated or ammoniated ions of the intact *N*-glucosylbarbiturate. In all cases, the base ion corresponded to (M + NH_4^+) and the parent-ion intensity (M + H^+) ranged from 15 to 20%. No other common-ion fragments were consistently observed in this series of compounds. The use of thermospray l.c.–m.s. for detection of these compounds in biological samples has excellent potential.

In conclusion, the general synthetic approach of preparing the *N*-glucosylbarbiturates by condensing silylated barbiturates with 1,2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**5**) in the presence of stannic chloride was successful for simple barbiturates but failed for *N*-alkylbarbiturates. The n.m.r. and m.s. data for this series of compounds will facilitate the spectral identification of other *N*-glycosylated xenobiotics that have been detected in metabolism studies.

EXPERIMENTAL

General methods. — Melting points (uncorrected) were determined in an open capillary with a Thomas–Hoover Unimelt apparatus. Optical rotations were measured with a Perkin–Elmer 141 Polarimeter. I.r. spectra were recorded with a Nicolet 5ZDX F.t.–i.r. interferometer. N.m.r. spectra were recorded with a Jeol FX90Q spectrometer; for ^{1}H-n.m.r. spectra, tetramethylsilane was the internal standard in $CDCl_3$ and sodium 4,4-dimethyl-4-sila(2,3,-$^2H_4$)pentanoate[($^2H_4$)TPS] the internal standard in D_2O. Microanalyses were performed by Atlantic Microlab, Atlanta, GA.

Chromatographies. — L.c. separation was achieved on a C-18 reverse-phase column (analytical, 250 × 4 mm i.d., particle size 5 μm, Econosphere, Alltech; semi-preparative, 250 × 9 mm i.d., particle size 10 μm, Econosil, Alltech) with a C-18 guard column (20 × 2 mm i.d., particle size 30–40 μm, Perisorb RP-18, Upchurch), and u.v. detection with a LKB 2140 Rapid Spectral Detector or a Gilson Model HM/HPLC Holochrome variable-wavelength detector.

For the thermospray, l.c.–m.s., the h.p.l.c. system was a HP1090 liquid chromatograph with a 20-μL injection loop, and a C-18 reverse phase column (5 μm particle size) with a mobile phase of 15% acetonitrile–85% 0.1M sodium acetate buffer (v/v). The mass spectrometer was an HP 5998A l.c.–m.s. system, interfaced to the l.c. instrument with an HP thermospray interface, operated at a constant tip temperature (optimized) of 128° and a 1.2 mL/min flow from the l.c. instrument. For linear scanning, the mass spectrometer scanned between *m/z* 100 and 800, using 32 samples and an integration time of 100 m.s. The signal was generated with the positive-ion, filament-on mode, at a 1050 eV ionization energy. The ion source was at 320° and the detection threshold at 20 000 counts.

*5,5-Diethyl-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione* (**6**). — In a modification of the procedure of Niedballa and Vorbruggen[8], barbital [5,5-diethylbarbituric acid, 5,5-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, **1**; 15.3 g, 83.1 mmol] was suspended in hexamethyldisilazane (50 mL), trimethylchlorosilane (5 mL) was added, and the mixture was refluxed under an N_2 atmosphere until a clear solution was obtained (16 h). Excess trimethylsilylation reagent was removed under reduced pressure, and the remaining syrup was distilled at 95–112° under reduced pressure (~30 Pa) using a Kugelrohr apparatus to give a compound assumed to be 2,4-bis(trimethylsilyloxy)barbital (24.54 g, 74.8 mmol). In a separate flask (N_2 atmosphere) containing 1,2,3,4,6-penta-*O*-acetyl-β-

D-glucopyranose (**5**) (29.2 g, 74.8 mmol) in 1,2-dichloroethane (165 mL) was added the 2,4-bis(trimethylsilyloxy)barbital, and the solution was cooled to ice-bath temperature. To this solution was slowly added $SnCl_4$ (7.0 mL, 60 mmol) dissolved in 1,2-dichloroethane (40 mL). The mixture was kept overnight, and the reaction was stopped by dilution with 1,2-dichloromethane (200 mL), followed by shaking the mixture with a sufficient quantity of saturated $NaHCO_3$ solution such that the pH of the solution remained neutral to slightly basic. The emulsion was filtered over a layer of sand–Celite, and the organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure to give a gummy residue. This was taken up in a minimum volume of diethyl ether and kept for three days to give a white precipitate (9.8 g), which was recrystallized from acetone–diethyl ether azeotrope to give **6** (4.6 g, 9 mmol, 12% yield), m.p. 164–168°; ν_{max}^{KBr} 1753.6, 1724.9, 1369.6, and 1236.4 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.86 (br. t, 6 H, app. J 7.3 Hz, 2 H_3-8), 1.95, 2.02, 2.05 (s, 16 H, 4 $COCH_3$ and 2 H_2-7), 3.85 (br. m, 1 H, H-5′), 4.21 (br. m, 2 H, H_2-6′), 5.29 (br. m, 2 H, H-3′,4′), 4.98 (br. m, 2 H, H-1′,2′), and 8.70 (br. s, 1 H, NH).

Anal. Calc. for $C_{22}H_{30}N_2O_{12}$: C, 51.36; H, 5.88; N, 5.45. Found: C, 51.42; H, 5.92; N, 5.38.

5,5-Diethyl-1-β-D-glucopyranosyl-2,4,6-(1H,3H,5H)pyrimidinetrione (**8**). — In a minor modification of the procedure of Niedballa and Vorbruggen[8], **6** (1.0 g, 2 mmol) was dissolved in dry methanol (30 mL) and a 25% solution (w/v) of sodium methoxide in methanol (0.5 mL) was added. The reaction was monitored by t.l.c. (ether) and required ~2 h. The solution was passed over a column (20 × 1 cm) containing Dowex 50 (H^+, 3 g), and the eluate was concentrated to dryness under reduced pressure to give **8** (280 mg, 40% yield), a white amorphous solid, m.p. 169–171°, $[\alpha]_D^{24}$ −8.4° (*c* 0.62, methanol); ν_{max}^{KBr} 1720.2, 1701.8, 1443.6, 1390.5, 1329.8, and 1077.2 cm^{-1}; ^{1}H-n.m.r. (D_2O): δ 0.84 (br. t, 6 H, J 7.3 Hz, H_3-8), 2.00 (q, 4 H, J 7.3 Hz, 2 H_2-7), 3.55 (br. s, 2 H, H_2-6′), 3.87 (br. s, 2 H, H-3′,4′), 4.2–4.6 (br. m, 1 H, H-2′), 5.70 (d, 1 H, J 9.8 Hz, H-1′), and 5.66 (minor d, J 9.8 Hz, H-1′); m.s.: *m/z* (%), 347 (7) $(M + H)^+$ and 364 (100) $(M + NH_4)^+$.

Anal. Calc. for $C_{14}H_{22}N_2O_8$: C, 48.55; H, 6.40; N, 8.09; Found: C, 48.45; H, 6.44; N, 8.03.

5-Ethyl-1-β-D-glucopyranosyl-5-phenyl-2,4,6-(1H,3H,5H)pyrimidinetrione (**9a**). — Phenobarbital [5-ethyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)pyrimidinetrione, **3**] was condensed with **5** by the procedure previously reported[3]. After addition of ether to the reaction extract, a white precipitate was formed which, according to t.l.c., was ~95% of a single diastereomer (60% acetonitrile–water, detection at 220 nm). The major component was eluted at 5.96 min *vs.* 6.38 min for the other diastereomer. Repeated recrystallization of the tetra-*O*-acetyl intermediate **7a** from ether or methanol–water gave material that behaved as a single compound, 5-ethyl-5-phenyl-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,4,6(1*H*,3*H*,5*H*)pyrimidinetrione (**7a**).

Methanolysis of **7a** with sodium methoxide and crystallization from acetonitrile gave **9a** which showed a single peak on chromatography; this material was idential with the material initially reported[3]; $[\alpha]_D^{24}$ +42° (*c* 0.11, methanol); ν_{max}^{KBr} 1719.6, 1705.8, 1388.9, 1354.7, 1313.9, 1071.2, and 692.0 cm^{-1}; ^{1}H-n.m.r. (D_2O): δ 0.99 (br. t, 3 H, *J* 7.3 Hz, H_3-8), 2.51 (br. q, 2 H, *J* 7.3 Hz, H_2-7), 3.56, 3.40–3.70 (br. s, 3 H, H-3′,4′,5′), 3.70–3.95 (br. m, 2 H, H_2-6′), 4.20–4.55 (br. m, 1 H, H-2′), 5.75 (d, 1 H, *J* 9.3 Hz, H-1′), 7.72 (s, 5 H), and 5.70 (minor d, *J* 9.3 Hz, H-1); m.s.: *m/z* (%), 326 (10), 369 (8), 395 (21) $(M + H)^+$, and 412 (100) $(M + NH_4)^+$.

*5-Ethyl-1-β-*D*-glucopyranosyl-5-phenyl-2,4,6-(1*H*,3*H*,5*H*)pyrimidinetrione* (**9b**). — The diethyl ether mother liquor from **9b** was concentrated under reduced pressure to give a white solid. Methanolysis of this material (10.0 g), as previously described[3] gave after removal of the methanol under reduced pressure, a residue that was dissolved in M KH_2PO_4 (30 mL). The solution was washed four times with dichloromethane (5 mL), and then extracted four times with ethyl acetate (10 mL each). The extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a white powder (3.0 g). Purification of the diastereomers was achieved by semi-preparative l.c. (15% acetonitrile–85% 0.5M ammonium acetate; flow rate of 4.0 mL/min) using a 1.0-mL loop injector and a peak detection with a differential refractometer. Injection of 100 mg of the white powder dissolved in the mobile phase gave major peaks at 17.0 min (**9a**) and 18.0 min (**9b**). Fractions were collected from 18.0 to 21.0 min. After numerous injections, these fractions were pooled and evaporated to give an oil (650 mg) which was dissolved in an ethyl acetate–methanol–diisopropyl ether azeotrope to give a gel. This was dispersed in diisopropyl ether (35 mL) to form a white precipitate which was filtered off and dried under reduced pressure to give **9b** (150 mg), m.p. 108° (sint.), 178–180° (dec.), $[\alpha]_D^{24}$ −46° (*c* 0.78, methanol); ν_{max}^{KBr} 1717.9, 1700.8, 1399.5, 1354.9, 1078.1, and 694.4 cm^{-1}; ^{1}H-n.m.r. (D_2O): δ 1.00 (br. t, 3 H, *J* 7.1 Hz, H_3-8), 2.52 (br. q, 2 H, *J* 7.1 Hz, H_2-7), 3.57, 3.40–3.70 (br. s, 3 H, H-3′,4′,5′), 3.70–3.95 (br. m, 2 H, H_2-6′), 4.20–4.55 (br. m, 1 H, H-2′), 5.69 (d, 1 H, *J* 9.8, Hz, H-1′), 7.45 (s, 5 H), and 5.74 (minor d, *J* 9.5 Hz, H-1′); m.s.: *m/z* (%), 326 (6), 369 (8), 395 (16) $(M + H)^+$, and 412 (100) $(M + MH_4)^+$; h.p.l.c. (15% acetonitrile–85% 25mM sodium phosphate buffer, pH 6.5, flow rate of 1.4 mL/min) indicated a composition of 98% of **9b** and 2% of **9a**, based on peak area when monitoring at 198 nm.

Anal. Calc. for $C_{18}H_{22}N_2O_8 \cdot H_2O$: C, 52.42; H, 5.87; N, 6.79. Found: C, 52.29; H, 5.90; N, 6.73.

*5,5-Diethyl-1-β-*D*-glucopyranosyl-3-methyl-2,4,6-(1*H*,3*H*,5*H*)pyrimidinetrione* (**12**). — Compound **6** (1.3 g, 2.5 mmol) was dissolved in a freshly prepared ethereal alcoholic solution of diazomethane[11] (25 mL). Vigorous bubbling occurred, after which the mixture was stirred overnight, uncovered, under ventilation. The product failed to crystallize and it was dissolved in methanol (10 mL) and 0.5M H_2SO_4 (10 mL), and heated at 95°. A sample of the mixture (20 μL) was injected directly on-column to monitor the hydrolysis by l.c. (40% acetonitrile–

water, 1.2 mL/min; **6**, R_T 30.5 min; **12** R_T 3.0 min). The hydrolysis was complete after 2.5 h, and the mixture was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give an oil (0.89 g). This was dissolved in the mobile phase (4.0 mL), and 1.0-mL fractions were purified by semi-preparative l.c. The fractions eluted at 7.0 min (20% acetonitrile–water, 5 mL/min) were collected and lyophilized to yield **12** (480 mg, 53% yield), white powder, m.p. 68–76° (sint.) and 84–87°, $[\alpha]_D^{24}$ −5.2° (*c* 0.42, methanol); ν_{max}^{KBr} 1696.6, 1445.2, 1385.9, 1328.8, and 1075 cm^{-1}; ^{1}H-n.m.r. (D_2O): δ 0.803 (t, 6 H, *J* 7.3 Hz, 2 H_3-8), 2.03 (q, 4 H, *J* 7.1 Hz, 2 CH_2-7), 3.31 (s, 3 H, NCH_3), 3.58 (br. d, 2 H, H_2-6′), 3.85 (br. m, 2 H, H-3′,4′), 4.2–4.6 (br. m, 1 H, H-2′), 5.80 (d, 1 H, *J* 9.3 Hz, H-1′), 3.34 (minor, NCH_3), and 5.72 (minor, *J* 9.5 Hz, H-1′); m.s.: *m/z* (%), 361 (23), $(M + H)^+$, and 378 (100) $(M + NH_4)^+$.

Anal. Calc. for $C_{15}H_{24}N_2O_8 \cdot H_2O$: C, 47.61; H, 6.92; N, 7.40. Found: C, 47.42; H, 6.97; N, 7.30.

*5-Ethyl-1-β-*D*-glucopyranosyl-3-methyl-5-phenyl-2,4,6-(1*H*,3*H*,5*H*)pyrimidinetrione* (**13a**). — Compound **7a** (1.0 g, 1.8 mmol) was treated with diazomethane to give a white precipitate (930 mg) which was hydrolyzed and purified by l.c. as described for **12**. Purification of 0.18 g of the hydrolyzate by semipreparative l.c. (30% acetonitrile; 5 mL/ min) and lyophilization of the fractions eluted at 7.0 min yielded **13a** (137 mg, 67% yield), white powder, m.p. 84–94° (sint.), 114–140°, $[\alpha]_D^{25}$ +21.5° (*c* 0.28, methanol); ν_{max}^{KBr} 1700.6, 1435.4, 1382.6, 1363.6, and 1076 cm^{-1}; ^{1}H-n.m.r. (D_2O): δ 0.96 (t, 3 H, *J* 7.3 Hz, H_3-8), 2.55 (br. q, 2 H, *J* 7.3 Hz, H_2-7), 3.34 (br. s, 3 H, NCH_3), 3.55 (br. s, 2 H, H_2-6′), 3.73–4.00 (br. m, 2 H, H-3′,4′), 4.1–4.5 (br. m, 1 H, H-2′), 5.81 (d, 1 H, *J* 9.5 Hz, H-1′), 7.44 (s, 5 H, Ph), 3.37 (minor, NCH_3), 7.45 (minor, Ph), and 5.74 (minor d, *J* 9.5 Hz, H-1′); m.s.: *m/z* (%), 409 (19), $(M + H)^+$ and 426 (100) $(M + NH_4)^+$.

Anal. Calc. for $C_{19}H_{24}N_2O_8 \cdot H_2O$: C, 53.52; H, 6.15; N, 6.57. Found: C, 53.60; H, 6.13; N, 6.55.

*5-Ethyl-1-β-*D*-glucopyranosyl-3-methyl-5-phenyl-2,4,6-(1*H*,3*H*,5*H*)pyrimidinetrione* (**13b**). — Compound **9b** (400 mg, 1 mmol) was dissolved in methanol (3 mL) and water (0.2 mL), followed by dropwise addition of a 0.32mM solution of a freshly prepared ethereal alcoholic solution of diazomethane (~5.5 mL). The yellow solution was stirred for 15 more min, and then the reaction was stopped by addition of M HCl (2 drops) and the solution concentrated to an oil. This was dissolved in the mobile phase (1.5 mL), and 0.1-mL fractions were purified by semi-preparative l.c. The fractions eluting at 8.0 min (30% acetonitrile; 4 mL/min) were lyophilyzed to yield **13b** (154 mg, 38% yield), white powder, m.p. 92° (sint.), 109–124°, $[\alpha]_D^{24}$ −27.5° (*c* 0.29, methanol); ν_{max}^{KBr} 1696.4, 1437.9, 1384.0, 1363.1, and 1076.7 cm^{-1}; ^{1}H-n.m.r. (D_2O): δ 0.96 (t, 3 H, *J* 7.3 Hz, H_3-8), 2.51 (br. q, 2 H, *J* 7.6 Hz, H_2-7), 3.34 (br. s, 3 H, NCH_3), 3.57 (br. s, 2 H, H_2-6′), 3.70–4.03 (br. m, 2 H, H-3′,4′), 4.2–4.6 (br. m, 1 H, H-2′), 5.74 (d, 1 H, *J* 9.1 Hz, H-1′), 7.42 (s, 5 H, Ph), 0.99 (minor t, 3 H, *J* 7.3 Hz, H_3-8), 3.36 (minor, NCH_3), 7.45 (minor, Ph), and 5.78 (minor d, *J* 9.3 Hz, H-1′); m.s.: *m/z* (%), 409 (8), $(M + H)^+$, and 426 (100) $(M + NH_4)^+$.

Anal. Calc. for $C_{19}H_{24}N_2O_8 \cdot H_2O$: C, 53.52; H, 6.15; N, 6.57. Found: C, 53.55; H, 6.15; N, 6.54.

5,5-Diethyl-4-O-β-D-glucopyranosyl-1-methyl-2,6-(1H,5H)pyrimidinedione (**14**). — Metharbital [5,5-diethyl-1-methyl-2,4,6(1*H*,3*H*,5*H*)pyrimidinetrione, **2**; 10 g, 50 mmol] was condensed with **5** by use of the procedure described for **6**. The gummy residue obtained upon workup was dissolved in diethyl ether (50 mL) from which a white solid precipitated (10.94 g). This material crystallized from ether to give **14** (4.93 g), m.p. 105°, which was contaminated by a small proportion of metharbital detected by l.c. (40% acetonitrile–water, 1.2 mL/min); ^{1}H-n.m.r. ($CDCl_3$): δ 0.83 (t, 6 H, *J* 7.3 Hz, 2 H_3-8), 2.03 (br. s, 12 H, 4 Ac), 2.05 (q, 4 H, *J* 8.1 Hz, 2 H_2-7), 3.32 (s, 3 H, NCH_3), 3.95–4.40 (br. m, 2 H, H_2-6′), 4.95–5.70 (br. m, 3 H, H-2′,3′,4′), and 6.34 (d, 1 H, *J* 3.6 Hz, H-1′).

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