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On the synthesis of *C*-glycosyl compounds containing double bonds without the use of protecting groups

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Abstract

A new range of *C*-glycosyl compounds carrying double bonds have been synthesised as potential monomers for the preparation of polyvinylsaccharides. The syntheses were performed without the use of protecting groups and mostly in water as solvent. The starting material was the easily accessible 5-β-D-glucopyranosyl-1,3-dimethylbarbituric acid sodium salt (**3a**) (obtained from D-glucose and 1,3-dimethylbarbituric acid in water). The alkylation reaction of **3a** at C-5 of the barbiturate moiety was studied in detail. It works well with benzylic bromides in Me_2SO and with allylic or benzylic bromides by an ultrasound/phase transfer catalyst-promoted alkylation in water. The resulting 5,5-dialkylated barbiturates **5a–c** and **7a–c** undergo an unusually facile and specific cleavage of the barbituric ring, losing the C-2 carbonyl, to yield novel molecules with a diamide moiety.

1. Introduction

To further our work on the use of sugars as renewable resources in the preparation of polymers [1], we required methods for the synthesis of monomers having C–C bonds connecting the sugar and a polymerisable unit. In order to prepare these on a large scale, this should be possible in a cost-effective manner with a minimum of synthetic manipulations, cheap reagents, and no protecting groups during synthesis. We envisaged that these new types of monomer, composed entirely of C–C linkages, would yield polymers with enhanced stabilities and novel properties compared with polymers already known where the sugar is attached by an ester, ether, or amide linkage to the main chain [2].

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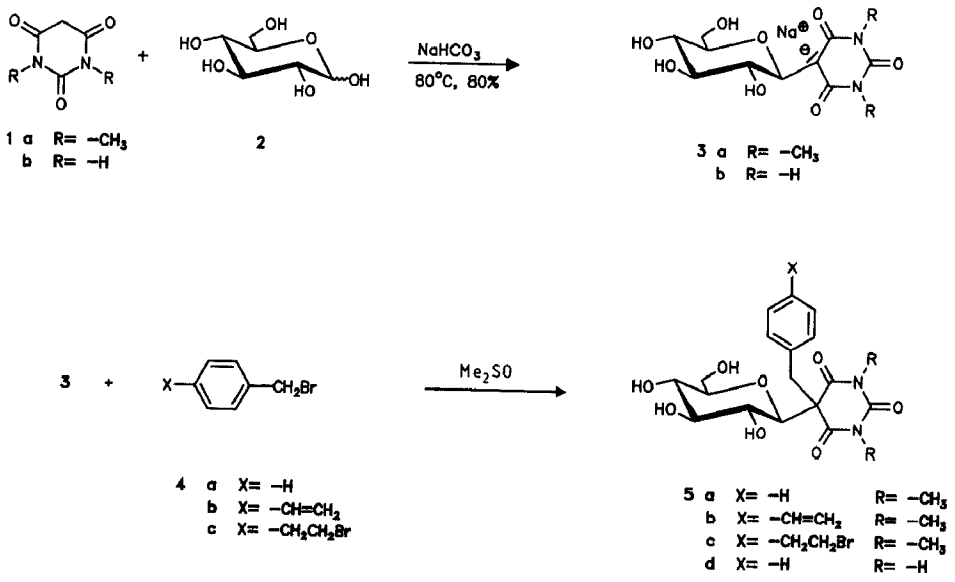
There have been several recent advances in C–C bond formation with unprotected sugars. These centre on reactions at the anomeric carbon with malonate-derived nucleophiles [3a–d] or Wittig reagents [3e,f], and Barbier-type reactions with allyl bromides promoted by tin [3g] and indium [3h].

Our work takes advantage of the condensation of 1,3-dimethylbarbituric acid (**1a**) with unprotected hexoses and pentoses to furnish the pyranosylbarbiturates, developed by Galbis Perez et al. [3a,b]. It was now planned to use the barbituric acid **1a** as a link between a monosaccharide, D-glucose being the most accessible, and a possible polymerisable group, to prepare *C*-glycosyl monomers and hence polymers with an all-carbon main chain and a C–C bond between the backbone and pendant sugar groups.

2. Results and discussion

The preparation of benzyl- and allyl-monomers.—The alkylation of barbituric acid derivatives is a well-known process [4] and is important in the production of a wide range of barbiturates with a variety of medicinal applications. The sodium salt **3a** [3b] was formed by the condensation of D-glucose (**2**) and 1,3-dimethylbarbituric acid (**1a**) in an aqueous solution of sodium hydrogencarbonate at 80°C in 80% yield. The salt was appreciably soluble only in water and sparingly soluble in dimethyl sulfoxide.

The alkylation of this easily accessible compound was systematically studied. Alkylation of a slurry of **3a** in Me_2SO with benzyl bromide (**4a**) proceeded well to



1 a R= –CH3
b R= –H

2

3 a R= –CH3
b R= –H

4 a X= –H
b X= –CH=CH2
c X= –CH2CH2Br

5 a X= –H R= –CH3
b X= –CH=CH2 R= –CH3
c X= –CH2CH2Br R= –CH3
d X= –H R= –H

Scheme 1.

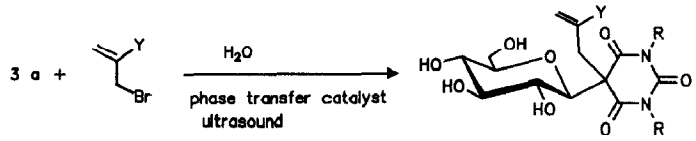
yield 5-benzyl-5-β-D-glucopyranosyl-1,3-dimethylbarbiturate (**5a**). The yield of 61% reflects the difficulty of extracting the highly water-soluble product from the aqueous workup medium and the chromatography required to remove persistent traces of Me_2SO. In a similar fashion, the benzyl bromides **4b** and **4c** reacted to give **5b** and **5c** in better isolated yields (67 and 75%, respectively), probably due to the larger alkyl groups aiding their extraction from the aqueous medium. Thus, the styrene monomer **5b** is accessible in two steps from D-glucose in an overall 54% yield. Compounds **5a–c** were white hygroscopic powders, with rather broad melting points, which were soluble in dichloromethane, ethyl acetate, alcohols, and water, and it was found beneficial to characterise them as their tetra-acetates (see later).

Reaction of **3a** with the allyl bromides **6a–c** under identical conditions to the benzylic bromides failed to yield the expected alkylated glycosylbarbiturates **7a–c**. By TLC, it was found that the starting material **3a** was consumed and several new spots appeared. Attempted extraction proved ineffective and removal of the Me_2SO at high vacuum left intractable gums. No pure product could be isolated from these and attempted acetylation with pyridine and acetic anhydride led to even more complex mixtures.

The problem with the reaction of the allylic bromides was circumvented by the discovery of novel alkylation conditions involving ultrasonication of an aqueous reaction mixture containing the sodium salt **3a**, the allyl bromide, and hexadecyltrimethylammonium bromide as a phase transfer catalyst. Both the phase transfer catalyst and sonication were necessary for the reaction to occur. Phase transfer catalysts with smaller alkyl groups like tetrabutylammonium bromide or benzyltriethylammonium bromide were ineffective, promoting only the hydrolysis of the allyl bromide. Addition of cosolvents such as ethanol, tetrahydrofuran, or dioxane considerably inhibited the reaction, causing longer reaction times and greatly reduced yields. The benefits of ultrasound [5] and phase transfer catalysis [6] in heterogeneous reaction systems are well documented. Phase transfer catalysis has been used in the *C*-alkylation of other barbituric acids [7] but, to our knowledge, this is the first time the combined advantages of both methods have been used.

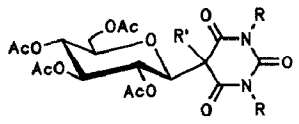
The benzylic bromides **4a** and **4c** also worked well under these alkylation conditions except for the bromomethylstyrene (**4b**), which could not be prevented from polymerising at the higher temperature (70°C) required for the reaction of the benzylic-type electrophiles.

The phase transfer catalyst could be recovered by cooling the aqueous reaction mixture to 4°C overnight and filtering off the precipitated catalyst (60% recovery). The remaining catalyst must be removed by chromatography. Both alkylation methods give yields of between 60 and 75% after chromatography, but the ultrasound reaction requires up to three equivalents of the alkyl bromide because of hydrolysis under the reaction conditions. Therefore, the preparation of **5a,b,c** is preferably done in Me_2SO, whereas the allyl compounds **7a,b,c** have to be prepared in water. **5b**, **5c**, and **7b** were crystalline, but the other compounds were isolated as white hygroscopic powders that required drying under high vaccum at



6 a Y= -H
b Y= $-C_6H_5$
c Y= $-CO_2CH_3$

7 a Y= -H
b Y= $-C_6H_5$
c Y= $-CO_2CH_3$



8 a R= $-CH_3$ R'= $-CH_2-C_6H_5$
b R= $-CH_3$ R'= $-CH_2-C_6H_4-CH=CH_2$
c R= $-CH_3$ R'= $-CH_2-C_6H_4-CH_2CH_2Br$
d R= -H R'= $-CH_2-C_6H_5$

9 a R= $-CH_3$ R'= $-CH_2-CH=CH_2$
b R= $-CH_3$ R'= $-CH_2-C(C_6H_5)=CH_2$
c R= $-CH_3$ R'= $-CH_2-C(COOCH_3)=CH_2$

10 R= $-CH_3$ R'= -H

Scheme 2.

10°C below their melting point in order to remove all traces of the last solvent with which the compounds were in contact. It seems to be a special property of these compounds that they bind firmly all types of solvents.

The characterisation of the newly prepared monomers.—The 300-MHz ^{1}H NMR spectra of the products were not very informative, as the signals for the glycosyl ring and the allylic or benzylic CH_2 were all overlapping. The products were therefore characterised as their tetra-acetates **8a–c** and **9a–c**. These were all crystalline, and signals for each hydrogen were well resolved and unequivocally assigned by H–H correlation spectroscopy (see Tables 1–3).

Values of ca. 10 Hz were recorded for vicinal coupling constants in the sugar ring, indicative of a pyranoid ring (where such protons exist in a trans-diaxial conformation [3b,8,9]). Also informative was the position of the resonance of the sugar H-5, being the most shielded ring proton of the tetra-acetates [3b]. Further evidence for a pyranoid ring stucture was gained from alkylation of the known 1,3-dimethyl-5-(tetra-*O*-acetyl-β-D-glucopyranosyl)barbituric acid (**10**) [3b] with the benzyl bromides **4a–c** or allylic bromides **6a–c**. This yielded compounds with

melting points and infrared and ^1H NMR spectra identical to those of the compounds formed by acetylation of the products from the alkylation of the sodium salt **3a**.

The alkylations of the sodium salt **3a** (either in Me_2SO or by the ultrasound method) and that of the tetra-acetate **10** were limited to allylic or benzylic bromides.

A coupling constant of $J_{1,2}$ 10 Hz in the sugar ring is also indicative of a β configuration of the alkyl barbiturate moiety at the former anomeric centre. The two *N*-methyl groups of all the products (except **3a**) are not magnetically equivalent. The signal for H-2 of the sugar ring in **8a,b,c** and **9a,b,c** is the most deshielded as was recorded for the tetra-acetate **10** [3b] and other similar compounds with a β-configuration [3c,10].

In the ^{13}C NMR spectrum, the signal for C-5 of the barbiturate ring at ca. 57 ppm is characteristic of 5,5-disubstituted barbiturates [11], as opposed to a value of ca. 95 ppm for an *O*-alkylated barbiturate [12] where it would form part of an enolic system.

A facile base-catalysed hydrolysis of the barbiturate moiety.—An interesting base-catalysed reaction was observed for the newly prepared alkyl barbiturates. When the disubstituted barbiturate **5a** was treated with two equivalents of sodium hydroxide at room temperature, the rapid disappearance of the starting material and the emergence of a new more polar spot was monitored by TLC, with complete consumption of the starting material after 10 min. Acidification with acetic acid caused effervescence (CO_2). The solvent was carefully evaporated at reduced pressure to yield a gum which gave only one compound after acetylation. This compound had absorptions in its IR spectrum characteristic of esters (1755 cm^{-1}) and secondary amides (3360, 3250, 1680, and 1535 cm^{-1}). An absorption at 755 cm^{-1}, interpreted as an out-of-plane vibration for the carbonyls of the barbituric ring [13] in the starting material, was absent. The ^1H NMR spectrum contained two low-field quartets for NH protons and two doublets for the *N*-methyl groups at a more upfield position than the two singlets for the *N*-methyl groups of **8a**. The signal for C-2 of the barbituric ring was also missing from the ^{13}C NMR spectrum of the compound. The compound was therefore formulated as the diamide **11a**. This specific hydrolysis was also realised for the other substituted barbiturates; **5b** gave **11b**, and **7a** and **7b** gave **12a** and **12b**, respectively. It was also possible to cleave the ring of **5c** to give **11c** without effecting the elimination of HBr.

Hydrolysis of the acrylate **7c** and acetylation gave the imide **14** instead of the expected diamide. Acidification of the hydrolysis mixture of **7c** after 10 min, with hydrochloric acid without acetylation, gave after evaporation a substance which showed ^1H NMR peaks at 2.70 and 2.67 ppm attributed to the *N*-methyl groups and no signal for the ester methoxyl *. The IR spectrum contained signals at 1650

* 90-MHz ^1H NMR in D_2O with 3-(trimethylsilyl)propanesulphonic acid sodium salt as internal standard.

Table 1
^{1}H NMR chemical shifts (ppm) of **8a–c** and **11a–c** recorded in $CDCl_3$

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	NMe	NH	Benzylic CH_aH_bAr [a]			x [b]	OAc [c]
8a	4.41	5.63	5.20	5.04	3.64	4.15	4.03	3.13		3.36	3.19	7.21 (3 H)		2.03, 2.01
								3.05				6.97 (2 H)		2.02, 1.99
8b	4.37	5.61	5.19	5.03	3.63	4.13	4.03	3.15		3.34	3.19	7.23 (2 H)	6.61, 5.69	2.03, 2.02
								3.07				7.61 (2 H)	5.24	2.01, 2.00
8c	4.39	5.62	5.19	5.03	3.63	4.13	4.03	3.14		3.34	3.18	7.05 (2 H)	3.50 (2 H)	2.03, 2.02
								3.06				6.92 (2 H)	3.08 (2 H)	2.01, 1.99
8d	4.39	5.63	5.22	5.06	3.68	4.16	4.09		8.89	3.33	3.24	7.22 (3 H)		2.04, 2.04
									8.76			7.09 (2 H)		2.01, 2.01
11a	4.65	5.01	5.28	5.04	3.87	4.46	4.16	2.89	9.25	3.28	3.18	7.21 (3 H)		2.12, 2.06
								2.57	7.06			7.00 (2 H)		1.96, 1.87
11b	4.64	5.01	5.23	5.08	3.87	4.46	4.16	2.89	9.28	3.27	3.16	7.26 (2 H)	6.65, 5.70	2.12, 2.06
								2.59	7.06			6.96 (2 H)	5.20	1.96, 1.87
11c	4.64	5.00	5.23	5.07	3.88	4.46	4.16	2.89	9.23	3.25	3.15	7.06 (2 H)	3.53 (2 H)	2.12, 2.06
								2.57	7.06			6.95 (2 H)	3.10 (2 H)	1.96, 1.87

[a] Values in parenthesis indicate the number of protons responsible for signal if more than one. [b] x = Substituents at the aromatic ring (see **5a–d**). [c] Each signal integrates for 3 protons.

Table 2
^{1}H NMR chemical shifts of **9a–c**, **12a,b**, and **14** recorded in $CDCl_3$

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	NMe	NH	Allylic CH_aH_b	Vinylic CH_aH_b	Y [a]	OAc
9a	4.21	5.48	5.15	4.99	3.59	4.12	3.99	3.30		2.79, 2.65	5.12, 5.08	5.43	2.03, 2.02
								3.29					2.01, 1.99
9b	4.32	5.53	5.15	4.99	3.59	4.14	4.01	2.92		3.31, 3.15	5.18, 5.07	7.28 (3 H)	2.02, 2.02
								2.85				7.11 (2 H)	2.00, 1.99
9c	4.26	5.40	5.16	5.01	3.61	4.17	4.01	3.26		3.07	6.19, 5.61	3.69 (3 H)	2.05, 2.03
								3.25					2.00, 1.99
12a	4.47	>—5.20–5.00— <			3.80	4.36	4.14	2.85	9.30	2.69	>—5.20–5.00— <	5.61	2.12, 2.05
								2.78	6.95				1.96, 1.93
12b	4.55	4.96	5.18	5.03	3.79	4.42	4.17	2.52	9.50	3.22, 3.11	5.17, 5.05	~ 7.26 (5 H)	2.14, 2.05
								2.40	6.77				1.94, 1.84
14	4.32	5.28	5.21	5.00	3.71	4.10	4.05	3.20		3.16, 3.06	6.33, 5.70		2.07, 2.02
								2.77	6.98				1.98, 1.97

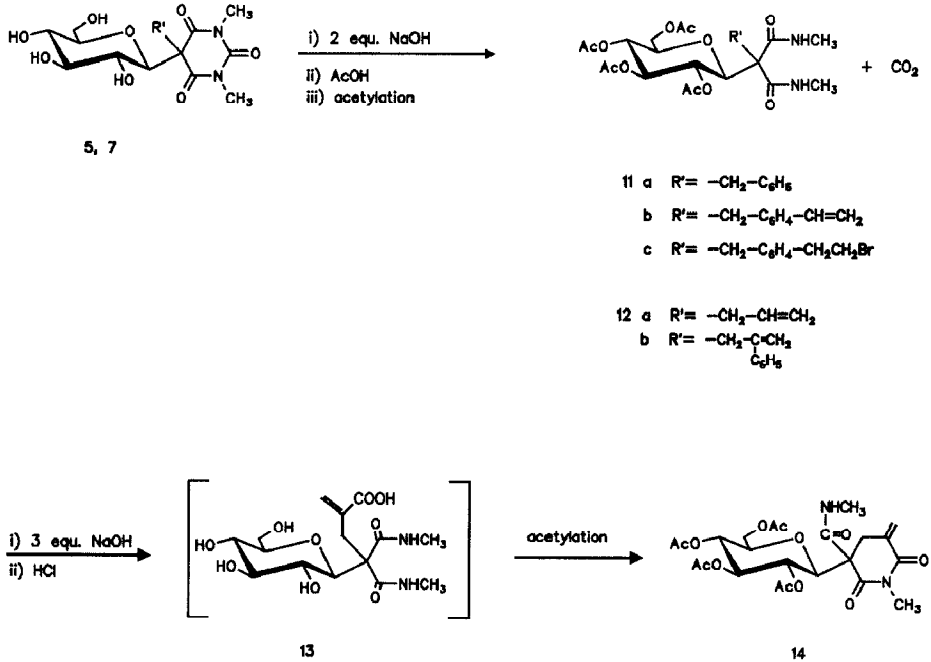
[a] Y = Substituent on the double bond (see **7a–c**).

Table 3
Coupling constants (Hz) of **8**, **9**, **11**, **12**, **14**

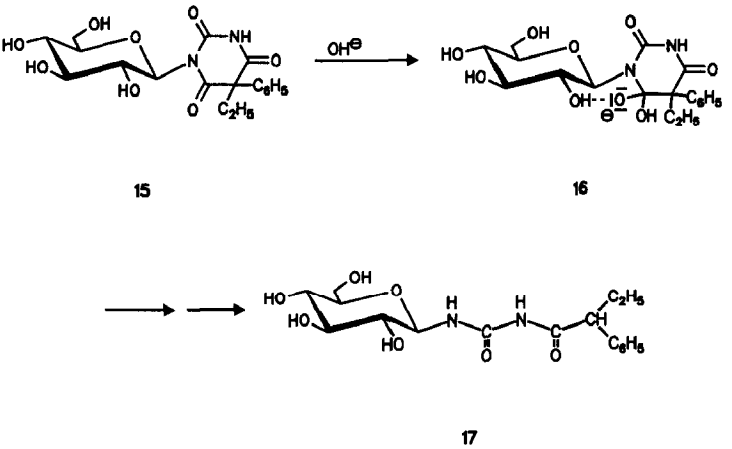
Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	Benzylic CH_2 [a] or allylic [a]	J_{NH,CH_3}
8a	10.0	9.0	9.5	10.0	2.5	5.3	−12.4	−12.6	
8b	9.9	8.9	9.5	10.0	2.4	5.3	−12.4	−12.6	
8c	9.9	8.9	9.5	9.9	2.5	5.2	−12.4	−12.6	
9a	9.9	8.9	9.5	9.9	2.4	5.3	−12.3	−12.8	
9b	10.0	9.3	9.6	9.9	2.4	5.4	−12.3	−13.2	
9c	9.9	9.0	9.4	9.9	2.4	5.5	−12.3	[b]	
11a	10.2	9.3	9.3	9.9	2.2	5.8	−12.4	−13.1	4.7
11b	10.2	9.3	9.3	10.0	2.1	5.7	−12.4	−13.0	4.6
11c	10.3	9.3	9.5	10.0	2.1	5.8	−12.4	−13.3	4.7
12a	10.2	[b]	[b]	10.0	2.2	5.3	−12.5	−13.5	4.7
12b	10.2	9.3	9.3	10.0	2.2	5.6	−12.4	−13.5	4.7
14	9.4	9.0	9.1	10.0	2.8	4.8	−12.5	−15.1 [c]	4.7

[a] Geminal coupling. [b] Not observed. [c] Geminal coupling of methylene group at C-4 of glutarimide.

and 1545 cm^{-1} for the secondary amide and 1710 cm^{-1} for an α,β-unsaturated acid. The hydrolysis of the ester seems to happen concurrently with the cleavage of the barbituric ring; the intermediate, presumably **13**, cyclised under the conditions of acetylation to yield **14**. Similar cyclisations of amide acid derivatives are well known [14]. No attempt was made to assign the configuration at the newly formed asymmetric centre at C-3 of the glutarimide.



Scheme 3.



Scheme 4.

This specific hydrolysis removing C-2 of 5,5-disubstituted 1,3-dimethylbarbiturates has been observed before for the 5,5-dimethyl and 5-ethyl-5-phenyl derivatives [15,16], but these were much slower and required 24 hours for completion. In our case, the sugar moiety seems to have a strong rate-enhancing effect. A very rapid hydrolysis has also been reported for the *N*-glycosylbarbiturate **15** by Soine et al. [17] to give **17**. From molecular model calculations, the authors postulated that the rapid hydrolysis is due to a stabilisation of the tetrahedral intermediate (produced by hydroxide attack on the C-6 carbonyl) by HO-2 of the glucopyranosyl moiety as depicted in **16**, which goes on to form **17**. In this case, C-6 of barbituric acid is removed.

In our systems, it is the C-2 carbonyl which is cleaved. It is also in a different relative position, with respect to the sugar moiety, to the one cleaved in **15**. It is also known that 5,5-disubstituted barbituric acids which are not alkylated at the NH are hydrolysed predominantly at the C-4/C-6 carbonyl [11]. Therefore, the NH derivative **5d** was synthesised to investigate its reactivity. 5-Benzyl-5-β-D-glucopyranosylbarbituric acid (**5d**) was synthesised in a similar way to **5a**, but in a lower yield. Alkylation of **3b** with benzyl bromide could only be achieved by the ultrasound method, to produce the desired compound **5d**. This was assumed to be in the β-*C*-glycopyranosyl configuration by comparison of the ^{1}H and ^{13}C NMR spectra of its tetra-acetate **8d** with that of the tetra-acetate of the 1,3-dimethyl compound **8a**. Attempted hydrolysis of **5d**, using the conditions effective for the *N*,*N*-dimethyl compounds, yielded only quantitative recovery of the starting material on acidification. Increasing the hydrolysis time to 48 h still produced only starting material on acidification. Therefore, the *N*-methyl derivatives are much more sensitive to this type of base hydrolysis. Compound **5d** is not hydrolysed at C-4/C-6 like other 5,5-disubstituted NH-barbituric acids. This might be due to hindrance from the rather bulky substituents. Other investigations have also found enhanced base-stability with barbituric acids disubstituted at the 5 position with bulky groups [11,17].

In conclusion, a new range of *C*-glycosyl compounds have been synthesised as potential monomers. The key alkylation step of the intermediate 1,3-dimethyl-5-(D-glucopyranosyl)barbituric acid sodium salt (**3a**) works well with benzylic bromides in Me_2SO or by an ultrasound/phase transfer catalyst-promoted alkylation in water utilising allylic or benzylic bromides. The products undergo a specific cleavage of the barbituric ring to yield novel molecules with a diamide moiety.

The results from the polymerisation of these monomers and further investigations into the hydrolysis will be published later.

3. Experimental

General methods.—Melting points were determined on a Büchi 510 apparatus. IR spectra (KBr discs) were recorded on a Perkin–Elmer 1420 spectrophotometer and mass spectra with a Varian MAT 311A instrument. NMR spectra were recorded on a Varian VXR-300 (300 MHz, ^1H; 75 MHz, ^{13}C) spectrometer. Ultrasonification was conducted in a Bandelin SONOREX RK 1028 H instrument. Elemental analyses were performed by the Institute of Pharmaceutical Chemistry, Heinrich-Heine-University of Düsseldorf. TLC was performed on Kieselgel 60 F_{254} (Merck), using 40 : 10 : 4 EtOAc–MeOH–water and detection with UV or charring with H_2SO_4 [19]. Kieselgel 60 (Merck) was used as adsorbent for column chromatography, with solvents as specified for each compound. Hexadecyltrimethylammonium bromide (Janssen), benzyl bromide (Merck), allyl bromide (Aldrich), Me_2SO (Roth), pyridine, Ac_2O, and 4-dimethylaminopyridine (Riedel-de Haen) were used as purchased. Methyl 2-(bromomethyl)acrylate [20], 4-(2-bromoethyl)benzyl bromide [21], 4-vinylbenzyl bromide [21], and 1-bromo-2-phenylprop-2-ene [22] were synthesised by literature procedures.

Alkylation in Me_2SO.—To a slurry of finely powdered sodium salt **3a** [3b] (3.4 g, 10 mmol) in Me_2SO (10 mL) was added the benzyl bromide **4a,b**, or **c** (13 mmol). The mixture was rapidly stirred for 12 h or till no more **3a** was detected by TLC ($R_f \sim 0.15$; product, ~ 0.75). The mixture was then poured into water (50 mL) and extracted with toluene (3×20 mL) to remove unreacted benzyl bromide. The toluene extracts were discarded and the aqueous mixture was extracted with EtOAc (3×20 mL). The EtOAc extracts were washed with water (2×20 mL) to remove Me_2SO and subjected to TLC. Visualisation with $KMnO_4$ solution shows up any residual Me_2SO as a brown spot ($R_f \sim 0.5$). The EtOAc extracts were washed until they were free of Me_2SO. The original aqueous reaction mixture was saturated with NaCl and again extracted with EtOAc (5×20 mL), and the EtOAc extracts were washed with water till free of Me_2SO. The water extracts collected from the washing of the EtOAc extracts were also saturated with NaCl and extracted with EtOAc (3×20 mL), which was then washed with water (2×10 mL) to remove Me_2SO. The combined EtOAc extracts were dried over $MgSO_4$ and filtered, and the solvent was removed at reduced pressure to yield a white foam. Column chromatography using an eluent gradient of 2 : 1 CH_2Cl_2–EtOAc to pure EtOAc gave a foam, free of the last traces of Me_2SO. The products could be

obtained as powders by dissolving the foam in the minimum amount of CH_2Cl_2 and precipitating into an excess of 1:1 diethyl ether–petroleum ether (40–60°C).

5-Benzyl-5-β-D-glucopyranosyl-1,3-dimethylbarbiturate (**5a**).—Obtained as a white powder (2.5 g, 61%); mp 114–120°C (dried at 90°C, 20 mmHg). ^{1}H NMR (Me_2SO): δ 5.31 (d, 1 H, *J* 5.8 Hz), 5.05 (d, 1 H, *J* 5.0 Hz), 4.96 (d, 1 H, *J* 5.6 Hz) [HO-2′, 3′, 4′]; 4.50 (t, 1 H, *J* 5.8 Hz, HO-6′); 3.83 (d, 1 H, *J* 9.8 Hz H-1); 3.75–3.00 (m, 8 H, H-2′,3′,4′,5′,6′a,6′b and benzylic CH_2); 2.97 and 2.92 (2 s, each 3 H, NMe); 7.21 (m, 3 H, aromatic), 6.92 (m, 2 H, aromatic). ^{13}C NMR (Me_2SO): δ 82.4, 82.1, 78.3, 71.2, 70.3 (5 C C-1′–C-5′); 61.4 (C-6′); 134.9 (C-1 aromatic); 128.9, 128.2, 127.2 (5 C, aromatic); 40.9 (1 C, benzylic); 169.6, 169.3 (2 C from C-4, C-6); 150.1 (1 C from C-2 barbit.); 59.7 (C-5); 27.8, 27.7 (2 C, NMe). IR: ν_{max} 3390, 1677, 758, 750, 703 cm^{-1}. MS (70 eV): *m/z* 408 (M^+), 244 (M − sugar), 91 (C_7H_7). Anal. Calcd for $C_{19}H_{24}N_2O_8$ (408.41): C, 55.88; H, 5.92; N, 6.86. Found: C, 56.16; H, 6.07; N, 6.82.

5-β-D-Glucopyranosyl-1,3-dimethyl-5-(4-vinylbenzyl)barbiturate (**5b**).—Obtained as a white powder (3.5 g, 69%) [4-*tert*-butylcatechol (50 mg) must be added to the reaction mixture to prevent polymerisation]; **5b** can be crystallised from a saturated aqueous solution, cooled to 4°C, as white needles; mp 110°C (polymerises as it melts). MS (70 eV): *m/z* 434 (M^+), 118 (C_9H_9). Anal. Calcd for $C_{21}H_{26}N_2O_8$ (434.45): C, 58.06; H, 6.03; N, 6.45. Found: C, 57.01; H, 6.19; N, 6.30.

5-[4-(2-Bromoethyl)benzyl]-5-β-D-glucopyranosyl-1,3-dimethylbarbiturate (**5c**).—Obtained as a white powder (3.9 g, 75%); **5c** can be recrystallised from a concentrated aqueous solution, cooled to 4°C, as white cubes; mp 116–118°C. MS (70 eV): *m/z* 516/514 (M^+), 199/197 ($C_9H_{10}Br$), 118 (C_9H_9). Anal. Calcd for $C_{21}H_{27}BrN_2O_8$ (515.35): C, 48.94; H, 5.28; N, 5.44. Found: C, 49.02; H, 5.41; N, 5.21.

Alkylations in water.—To a solution of the sodium salt **3a** (3.4 g, 10 mmol) and hexadecyltrimethylammonium bromide (200 mg) in water (25 mL) was added the allyl or benzyl bromide (13 mmol). For the allyl bromides **6a–c**, the mixture was sonicated at room temperature but the bath temperature gradually heats up with use to ca. 50°C after 6 h. For the benzyl bromides **4a–c**, the mixture was sonicated at 70°C. The reaction was monitored by TLC. When the consumption of starting material seemed to slow down, the mixture was neutralised by the addition of small portions of $NaHCO_3$ and a little more alkyl bromide was added to replace that lost through hydrolysis. This was continued till all **3a** was consumed. The mixture was then cooled to room temperature and extracted with toluene (3 × 10 mL) to remove excess of alkyl bromide and its hydrolysis products. The aqueous phase was cooled to 4°C for 24 h and the precipitate removed by filtration. The aqueous solution was then saturated with NaCl and extracted with EtOAc; **7a** with its small alkyl group requires up to 10 extractions for complete recovery from the aqueous phase. The combined EtOAc extracts were dried over $MgSO_4$ and filtered, and the solvent was removed at reduced pressure to give a foam. Column chromatography using an eluent gradient of 2:1 CH_2Cl_2–EtOAc to pure EtOAc gave the products as white foams free of traces of phase transfer catalyst. The products could be obtained as powders by precipitation of a saturated CH_2Cl_2

solution into 2:1 diethyl ether–petroleum ether (40–60°C). On scales larger than this, it is advisable also to employ stirring or the reaction rate is very slow.

5-β-D-Glucopyranosyl-1,3-dimethyl-5-(prop-2-enyl)barbiturate (**7a**).—Obtained as a white powder (2.8 g, 63%); mp 100–105°C (dried at 90°C, 20 mmHg). IR: ν_{max} 3370, 1675, 757 cm^{-1}. MS (70 eV): m/z 358 (M^+), 197 (M − sugar). Anal. Calcd for $C_{15}H_{22}N_2O_8$ (358.35): C, 50.28; H, 6.19; N, 7.82, Found: C, 50.16; H, 6.55; N, 7.67.

5-β-D-Glucopyranosyl-1,3-dimethyl-5-(2-phenylprop-2-enyl)barbiturate (**7b**).—Obtained as a white powder (3.3 g, 75%); **7b** can be crystallised from a saturated aqueous solution, cooled to 4°C, as white cubes; mp 134–136°C. IR: ν_{max} 3390, 1675, 755, 700 cm^{-1} MS (70 eV): m/z 434 (M^+), 272 (M − sugar), 118 (C_9H_{10}). Anal. Calcd for $C_{21}H_{26}N_2O_8$ (434.45): C, 58.06; H, 6.03; N, 6.45. Found: C, 58.24; H, 6.21; N, 6.43.

5-β-D-Glucopyranosyl-5-[2-(methoxycarbonyl)prop-2-enyl]-1,3-dimethylbarbiturate (**7c**).—Obtained as a white powder (2.8 g, 68%); mp 85–89°C (dried at 75°C, 20 mmHg). IR: ν_{max} 3370, 1720, 1675, 755 cm^{-1}. MS (70 eV): m/z 416 (M^+), 253 (M − sugar), 222 (253 − OMe). Anal. Calcd for $C_{17}H_{24}N_2O_{10}$ (416.38): C, 49.04; H, 5.81; N, 6.73, Found: C, 48.79; H, 5.83; N, 6.44.

5-Benzyl-5-β-D-glucopyranosyl-1,3-dimethylbarbiturate (**5a**; 2.8 g, 68%) and *5-[4-(2-bromoethyl)benzyl]-5-β-D-glucopyranosyl-1,3-dimethylbarbiturate* (**5c**; 4.2 g, 81%) were also synthesised in the manner above.

5-Benzyl-5-β-D-glucopyranosylbarbiturate (**5d**).—To a mixture of sodium 5-β-D-glucopyranosylbarbiturate [3b] (**3b**; 3.1 g, 10 mmol) and benzyl bromide (2.2 g, 13 mmol) in water (20 mL) was added hexadecylammonium bromide (200 mg), and the mixture was sonicated as described above. The reaction was cooled to room temperature and allowed to stand for 24 h. The precipitate was filtered off and washed with 2-propanol to remove the phase transfer catalyst. The precipitate was recrystallised twice from water cooled to 4°C (for 3 to 4 days), to give a white powder (1.4 g, 36%); mp 317°C. IR: ν_{max} 3500, 3410, 3040, 1718, 705 cm^{-1}. MS (70 eV): m/z 380 (M^+), 217 (M − sugar), 91 (C_7H_7). Anal. Calcd for $C_{17}H_{20}N_2O_8$ (380.35): C, 53.68; H, 5.30; N, 7.37. Found: C, 53.71; H, 5.37; N, 7.45.

Acetylations.—The alkylated barbiturate (2 g) was dissolved in pyridine (5 mL) and Ac_2O (5 mL), and 4-dimethylaminopyridine (50 mg) was added. The mixture was stirred for 24 h at room temperature, then poured into water (50 mL) and stirred for a further hour. The aqueous mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic extracts were washed with sat aq $NaHCO_3$ (3 × 20 mL) and 1 M HCl (3 × 20 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent removed at reduced pressure to give a foam. This was recrystallised from the solvent specified to give the tetra-acetates in 70–80% yield.

5-Benzyl-1,3-dimethyl-5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)barbiturate (**8a**).—Obtained as white flakes; mp 166–167°C (2-propanol). ^{13}C NMR ($CDCl_3$): δ 80.4, 76.4, 74.8, 69.6, 68.0 (5 C, C-1′–C-5′); 61.7 (C-6′); 170.4, 170.2, 169.4, 169.3, 168.9, 168.8 (6 C, C-4, C-6, and 4 CH_3CO); 150.0 (C-2); 60.3 (C-5); 28.3, 28.2 (2 MeN); 40.9 (benzylic); 133.6 (1 C, aromatic); 129.3 128.0 (5 C, aromatic); 20.7, 20.6, 20.5 (4 C, CH_3CO). IR: ν_{max} 1755, 1675, 756, 749, 702 cm^{-1} MS (70 eV): m/z 576

(M^+), 91 (C_7H_7). Anal. Calcd for $C_{27}H_{32}N_2O_{12}$ (576.56): C, 56.25; H, 5.59; N, 4.86. Found: C, 56.27; H, 5.56; N, 4.78.

*1,3-Dimethyl-5-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-5-(4-vinylbenzyl)barbiturate* (**8b**).—Obtained as white rhombs; mp 189–190°C (EtOH). MS (70 eV): *m/z* 602 (M^+), 117 (C_9H_9). Anal. Calcd for $C_{29}H_{34}N_2O_{12}$ (602.59): C, 57.80; H, 5.69; N, 4.65. Found: C, 57.31; H, 5.71; N, 4.54.

*5-[4-(2-Bromoethyl)benzyl]-1,3-dimethyl-5-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-barbiturate* (**8c**).—Obtained as white needles; mp 156°C (2-propanol). MS (70 eV): *m/z* 684/682 (M^+), 199/197 ($C_9H_{10}Br$). Anal. Calcd for $C_{29}H_{35}BrN_2O_{12}$ (683.50): C, 50.96; H, 5.16; N, 4.10. Found: C, 50.91; H, 5.19; N, 3.83.

*5-Benzyl-5-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)barbiturate* (**8d**).—Obtained as tiny white cubes; mp 210–212°C (EtOAc–diisopropyl ether). IR: ν_{max} 3500, 3230, 3080, 1755, 1725, 1700, 700 cm^{-1}. MS (70 eV): *m/z* 548 (M^+), 91 (C_7H_7). Anal. Calcd for $C_{25}H_{28}N_2O_{12}$ (548.50): C, 54.74; H, 5.15; N, 5.11. Found: C, 54.77; H, 5.34; N, 5.08.

*1,3-Dimethyl-5-(prop-2-enyl)-5-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)barbiturate* (**9a**).—Obtained as white needles; mp 145–146°C (EtOH). MS (70 eV): *m/z* 526 (M^+). Anal. Calcd for $C_{23}H_{30}N_2O_{12}$ (526.50): C, 52.47; H, 5.74; N, 5.32. Found: C, 52.63; H, 5.72; N, 5.39.

*1,3-Dimethyl-5-(2-phenylprop-2-enyl)-5-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)barbiturate* (**9b**).—Obtained as white cubes; mp 111–112°C (EtOH). MS (70 eV): *m/z* 602 (M^+), 118 (C_9H_{10}). Anal. Calcd for $C_{29}H_{34}N_2O_{12}$ (602.59): C, 57.80; H, 5.69; N, 4.65. Found: C, 57.76; H, 5.64; N, 4.76.

*5-[2-(methoxycarbonyl)prop-2-enyl]-1,3-dimethyl-5-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)barbiturate* (**9c**).—Obtained as white needles; mp 87–89°C (2-propanol). MS (70 eV): *m/z* 584 (M^+). Anal. Calcd for $C_{25}H_{32}N_2O_{14}$ (584.53): C, 51.37; H, 5.52; N, 4.79. Found: C, 51.31; H, 5.69; N, 4.70.

These compounds (**8a–d** and **9a–c**) could also be obtained by stirring a mixture of 1,3-dimethyl-5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)barbiturate [3b] (**10**; 2.5 g, 5 mmol) and acetone (50 mL) with the allyl bromides **6a–c** (7 mmol) and potassium carbonate (5 mmol) for 24 h at room temperature, or the benzyl bromides **4a–c** (7 mmol) at reflux for 12 h. The potassium salts were removed by filtration, and the acetone was evaporated at reduced pressure. The residue was crystallised twice from the solvent specified above to give compounds identical to those produced by the alkylation and acetylation of **3a** (70–85% yield).

Hydrolysis of barbiturate ring.—The alkyl-1,3-dimethyl-glucopyranosyl-barbiturate (2.5 mmol) was dissolved in water (5 mL), and 1 M NaOH (5 mL, 5 mmol) was added. The mixture was rapidly stirred till TLC showed complete disappearance of starting material and appearance of a new spot at $R_f \sim 0.35$ (ca. 10 min). The mixture was carefully acidified with glacial AcOH (0.35 mL, 6 mmol), when there was an evolution of gas. The solvent was removed on a rotary evaporator with the bath temperature at 35°C. The residue produced was treated with pyridine (2 mL), Ac_2O (2 mL), and 4-dimethylaminopyridine (20 mg) as described for the acetylations above. The compounds, isolated as foams, were

recrystallised from the solvents specified to give the tetra-*O*-acetyl-diamides in 50–75% yield.

2-Benzyl-N,N′-*dimethyl-2-(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)malonamide* (**11a**).—Obtained as white needles; mp 166–167°C (CH_2Cl_2–diisopropyl ether). ^{13}C NMR ($CDCl_3$): δ 79.6, 76.7, 74.2, 69.0, 68.5 (5 C, C-1′–C-5′); 62.1 (C-6′); 171.8, 170.9, 169.9, 169.6, 169.5, 169.0 (6 C, 4 CH_3COO, and C-1, C-3); 57.8 (C-2); 26.4, 25.8 (2 MeN); 42.7 (benzylic); 135.2 (1 C, arom.); 129.5, 128.1, 127.2 (5 C, arom.); 20.8, 20.6, 20.5, 20.3 (4 C CH_3CO). IR: ν_{max} 3360, 3250, 1755, 1680, 1645, 1535, 758, 702 cm^{-1}. Anal. Calcd for $C_{26}H_{34}N_2O_{11}$ (550.56): C, 56.72; H, 6.22; N, 5.09. Found: C, 57.05; H, 6.19; N, 5.09.

N,N′-*Dimethyl-2-(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-2-(4-vinylbenzyl)-malonamide* (**11b**).—Obtained as tiny white cubes; mp 169–171°C (2-propanol). IR: ν_{max} 3380, 3250, 1755, 1678, 1637, 1530 cm^{-1}. MS (70 eV): *m/z* 576 (M^+), 244 (M − sugar). Anal. Calcd for $C_{28}H_{36}N_2O_{11}$ (576.60): C, 58.33; H, 6.29; N, 4.86. Found: C, 58.18; H, 6.34; N, 4.75.

2-[4-(2-Bromoethyl)benzyl]-N,N′-*dimethyl-2-(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)malonamide* (**11c**).—The reaction was carried out as above, but the hydrolysis mixture was acidified with 1 M HCl (6 mL, 6 mmol) and the solvent removed on the rotary evaporator with the bath temperature at 35°C. The residue produced was dissolved in Ac_2O (4 mL) and a small drop of concentrated H_2SO_4 was added. The mixture was stirred for 48 h, then poured into water and stirred for a further hour. The mixture was extracted with EtOAc as described for the other acetylations. Evaporation of the solvent gave a white powder; mp 82–85°C; 50% yield. MS (70 eV): *m/z* 658/656 (M^+), 325/323 (M − sugar). Anal. Calcd for $C_{28}H_{37}BrN_2O_{11}$ (657.51): C, 51.14; H, 5.67; N, 4.26. Found: C, 51.16; H, 5.66; N, 4.06.

N,N′-*Dimethyl-2-(prop-2-enyl)-2-(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-malonamide* (**12a**).—Obtained as white cubes; mp 127–129°C (CH_2Cl_2–diisopropyl ether). MS (70 eV): *m/z* 500 (M^+), 169 (M − sugar). Anal. Calcd for $C_{22}H_{32}N_2O_{11}$ (500.50): C, 52.80; H, 6.44; N, 5.60. Found: C, 52.63; H, 6.45; N, 5.60.

N,N′-*Dimethyl-2-(2-phenylprop-2-enyl)-2-(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)malonamide* (**12b**).—Obtained as tiny white cubes; mp 173–175°C (EtOH). MS (70 eV): *m/z* 576 (M^+), 244 (M − sugar). Anal. Calcd for $C_{28}H_{36}N_2O_{11}$ (576.50): C, 58.33; H, 6.29; N, 4.86. Found: C, 57.82; H, 6.20; N, 4.72.

1-Methyl-3-(N-*methylcarbamoyl)-5-methylene-3-(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)glutarimide* (**14**).—The hydrolysis was carried out as above except with 7.5 mL of 1 M NaOH and acidification with 0.45 mL of glacial AcOH. Acetylation of the residue, presumably **13**, gave **14** as white needles; mp 184–185°C (EtOH). ^{13}C NMR ($CDCl_3$): δ 80.1, 76.4, 74.4, 69.2, 68.2 (5 C, C-1′–C-5′); 62.0 (C-6′); 171.4, 170.5, 169.4, 169.4, 169.2, 166.0, 165.0 (7 C, 4 CH_3CO, C-2, C-6, MeNH*C*O); 56.3 (C-3); 31.4 (C-4); 132.8 (C-5); 26.8 (*Me*NHCO); 126.5 (CH_2=); 27.6 (MeN=); 20.7, 20.6, 20.5 (4 C, CH_3CO). IR: ν_{max} 3370, 1750, 1680, 1640, 1540 cm^{-1}. MS (70 eV): *m/z* 526 (M^+), 195 (M − sugar). Anal. Calcd for $C_{23}H_{30}N_2O_{12}$ (526.50): C, 52.47; H, 5.74; N, 5.32. Found: C, 52.40; H, 5.86; N, 5.29.

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