Carbohydrate Research, 158 (1986) 53–66
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

FACILE PREPARATION OF *C*-GLYCOSYLBARBITURATES AND *C*-GLYCOSYLBARBITURIC ACIDS*

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(Received May 21st, 1986; accepted for publication, July 28th, 1986)

ABSTRACT

A general method for the synthesis of pyrimidine *C*-nucleosides involves a one-step reaction of aldohexoses and aldopentoses with barbituric acids. Thus, 2-amino-2-deoxy-D-glucose was converted into 5-(2-amino-2-deoxy-β-D-glucopyranosyl)barbituric and 5-(2-amino-2-deoxy-β-D-glucopyranosyl)-1,3-dimethylbarbituric acids. Likewise, D-glucose, D-galactose, D-mannose, D-xylose, D-ribose, and D-arabinose were transformed into sodium 5-D-glycopyranosyl-1,3-dimethylbarbiturates (**11**–**16**; average yields of 80%). The free acids **17** and **18**, with the α-D-arabinopyranosyl and β-D-galactopyranosyl structures, were also obtained. Acetylation of **11**–**18** gave *O*-acetylated 1,3-dimethyl-2,4,6-trioxo-1*H*,3*H*,5*H*-pyrimidin-5-ylidene-alditols, although some compounds with pyranoid structures were also obtained.

INTRODUCTION

C-Nucleosides may have antibacterial, antiviral, and antitumour activity[2], and they are resistant to hydrolysis[3]. Because of their structural analogy with *N*-nucleosides, they may serve as enzyme substrates or inhibitors[3,4], and considerable[5] effort has been directed towards the synthesis of such compounds.

Most syntheses involve C-1 functionalised sugar derivatives and/or a heterocyclic base, usually as a metalated derivative. These procedures are tedious and generally give low yields of products, and there have been some attempts to obtain *C*-nucleosides by condensation of an unprotected sugar and a heterocyclic base[6,7]. There has been only one report[8] of the direct condensation of barbituric acid with monosaccharides which involved treatment of the 2,3,4,5,6-penta-*O*-acetyl-*aldehydo* derivatives of D-glucose, D-galactose, and D-mannose with barbituric acid (**1**) in 10% acetic acid, which gave the products **2** after deacetylation.

*For a preliminary account, see ref. 1.

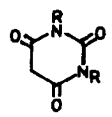
0008-6215/86/$ 03.50

When aqueous 50% ethanol was used as the reaction medium, the *C*-glycosides **3** were obtained. The sodium salt of 5-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)barbituric acid has been obtained by treatment of diethyl 2,3-*O*-isopropylidene-5-*O*-trityl-α,β-D-ribofuranosylmalonate with urea and sodium ethoxide in ethanol, but its transformation into the free *C*-nucleoside was not accomplished[9]. This procedure was proposed as a general way of synthesising *C*-glycosides of barbituric acids, and some *C*-glycosylmalonates have been prepared[10,11].

We now report a new one-step reaction with an overall yield averaging 80% for converting reducing monosaccharides into *C*-glycosylbarbiturates under nearly physiological conditions. Several drug metabolites have been described[12] with structures similar to that of the *C*-glycosylbarbiturates. Thus, sulfinpyrazone and phenylbutazone, both derivatives of 1,2-diphenyl-3,5-dioxopyrazolidine, are glucuronidated in humans at C-4 of the pyrazolidine ring. The facile formation of the *C*-glycosylbarbiturates might explain the lack of sedative and hypnotic properties of barbituric acids and 5-substituted barbituric acids.

RESULTS AND DISCUSSION

The reaction of barbituric acid (**1**) or 1,3-dimethylbarbituric acid (**4**) with 2-amino-2-deoxy-D-glucose hydrochloride and 1 equiv. of sodium carbonate in water at 50° afforded 5-(2-amino-2-deoxy-β-D-glucopyranosyl)barbituric acid (**5**) and 5-(2-amino-2-deoxy-β-D-glucopyranosyl)-1,3-dimethylbarbituric acid (**6**), respectively, in good yields, which had broad, strong i.r. bands between 3500 and 2500 cm^{-1}, and a weak band at 2080 cm^{-1}, characteristic of the NH_3^+ group, that was lacking in the i.r. spectra of their sodium salts (**7** and **8**). The ^{13}C-n.m.r. spectra are also in accordance with these structures (see below).



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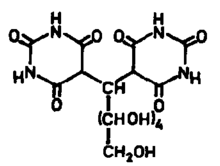
4 R = Me



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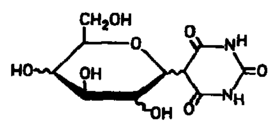

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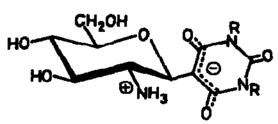

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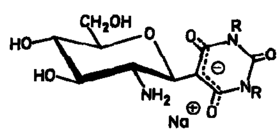
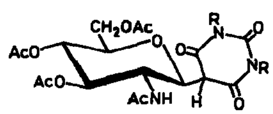


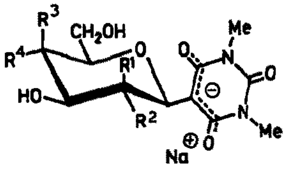
7 R = H
8 R = Me



9 R = H
10 R = Me

Compounds **5** and **6** were characterised as the tetra-acetates **9** and **10**, respectively. The application of Hudson's isorotation rules, using 2-amino-2-deoxy-α- and -β-D-glucose penta-acetate[13] for the determination of the ring contribution, gave negative values for C-1 in agreement with the β configuration which was confirmed by ^{1}H-n.m.r. data (see below). The structure of **9** has also been confirmed by X-ray crystallography[14].

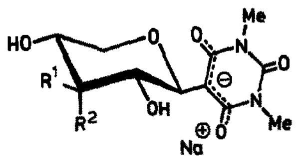
The reactions of 1,3-dimethylbarbituric acid with D-glucose, D-galactose, D-mannose, D-xylose, D-ribose, and D-arabinose were carried out in water at 80° and pH 7, and gave 75–93% of the sodium 5-D-glycosyl-1,3-dimethylbarbiturates **11–16**.



11 R^1=R^3=H, R^2=R^4=OH

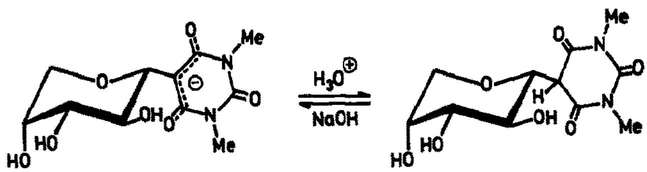
12 R^1=R^4=H, R^2=R^3=OH

13 R^2=R^3=H, R^1=R^4=OH

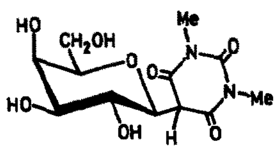


14 R^1=OH, R^2=H

15 R^1=H, R^2=OH



16 17



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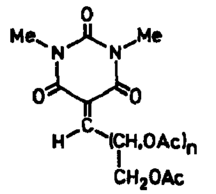
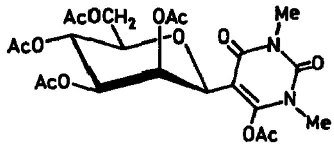
The ^{13}C-n.m.r. spectra for aqueous solutions showed **11–14** and **16–18** to be single isomers, but **15** gave a complex spectrum and was a mixture of furanoid and pyranoid structures in which the β-D-ribopyranosyl isomer preponderated.

On treatment of **11–16** with trifluoroacetic acid in order to obtain the corresponding free acids, only 5-α-D-arabinopyranosyl-1,3-dimethylbarbituric acid (**17**) and 5-β-D-galactopyranosyl-1,3-dimethylbarbituric acid (**18**) crystallised. The structure of **18** has been confirmed by X-ray crystallography[15]. The cyclic structure of the parent sodium salt (**12**) was confirmed because **13** was obtained by treatment of **18** with an excess of sodium hydroxide.

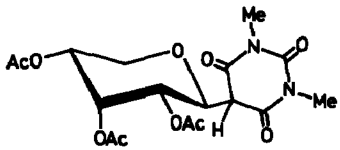
Treatment of **12**–**18** with acetic anhydride–anhydrous zinc chloride gave the *O*-acetylated 1,3-dimethyl-2,4,6-trioxo-1*H*,3*H*,5*H*-pyrimidin-5-ylidene derivatives **20**–**23**, although compounds having cyclic pyranoid structures were sometimes isolated. Thus, the acetylation of **13** gave **21**, but **24** was also obtained as a minor product. Likewise, acetylation of **15** gave a complex mixture of products from which **25** was isolated by flash chromatography. When **11** was acetylated in a similar manner, only **26** was obtained. In order to obtain **19** from **11**, a large excess of zinc chloride was necessary. On the other hand, **26** could be transformed into **19** by treatment with an excess of zinc chloride in acetic anhydride. These results suggest that the first-formed products must be the acetylated glycopyranosyl derivatives which are subsequently converted into the acyclic structures **19**–**23**.



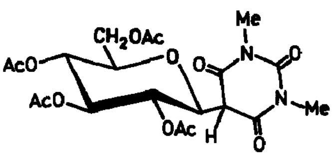
19 n=4 D- *gluco*
20 n=4 D- *galacto*
21 n=4 D- *manno*
22 n=3 D- *xylo*
23 n=3 D- *arabino*



24



25



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^{1}*H-N.m.r. spectra.* — The glycosidic protons (Table I) of cyclic (**9**, **10**, **24**–**26**) and acyclic (**19**–**23**) derivatives can be clearly differentiated on the basis of their chemical shifts. For the cyclic compounds, H-1′ resonates at high field (δ 5.00–4.30 p.p.m.) and H-5′ resonates at higher field (δ 3.81–3.35) than any other proton, which is indicative of a pyranoid structure. H-2′ and H-3′ are more deshielded for **24**–**26**, but the signal for H-2′ occurs at higher field (~1 p.p.m.) for **9** and **10**, in accordance with the substitution of the acetate by an acetamide group. The signal of the heterocyclic H-5 appears at δ 3.75–3.50 for **9, 10, 25**, and **26**, but it is not present in the spectrum of **24**, which shows a signal for vinyl acetate at δ 2.37. The J values (Table II) for **9, 10**, and **24–26** are indicative of a $^4C_1$(D) conformation, which was confirmed for **25** by the presence of a ^4J coupling between H-3′ and H-5′*e*.

The relative disposition of the heterocycle and sugar ring for **10, 25**, and **26** has been studied using $J_{1',5}$ values and the modified Karplus equations[16–17] (Table III). The Φ values obtained are indicative of a near perpendicular orientation between H-1′ and H-5 ($\Phi_{1',5}$ ~100°), closely related to that determined for **18** by X-ray crystallography[15].

The glycosidic protons of all the acyclic acetyl derivatives show the same chemical shift sequence (δH-1′ > δH-2′ > δH-3′ > δH-4′ > δH-5′ > δH-6′ > δH-6″ for **19–21** and δH-1′ > δH-2′ > δH-3′ > δH-4′ > δH-5′ > δH-5″ for **22** and **23**) as other polyacetoxyalkylheterocycles[18]. The deshielding of H-1′ (δ 7.40) accords with the ethylenic character of this proton.

The J values of **20, 21**, and **23** show that the favoured conformer has the planar zigzag structure. However, the small $J_{2,3}$ value indicates that **19** does not adopt such a conformation since this would require H-2′,3′ to be antiparallel and would generate a 1,3-parallel interaction between *O*-acetyl groups. Rotation about the C-2′–C-3′ bond to give the sickle conformer $_2G^-$ would explain the observed low value of $J_{2',3'}$. Likewise, the value (7.0 Hz) of $J_{3',4'}$ for **22** shows a tendency for the molecule to adopt a conformation having H-3′,4′ antiparallel. Such an arrangement would accord with the $_3G^+$ sickle conformation derived from the planar, extended conformation by counter-clockwise rotation about the C-3′–C-4′ bond. Similar results for other acyclic compounds have been found[19–21].

^{13}C-N.m.r. spectra. — The data in Table IV confirm the structures proposed for the *C*-glycopyranosyl compounds. Thus, all the salts (**5, 6**, and **11–16**) show a similar value for the signal of C-5, which is shifted upfield for the free acids (**17** and **18**) or for the acetyl derivatives (**9, 10, 25**, and **26**). This signal appeared as a triplet in the spectra of a solution of **17** or **18** in D_2O, because of the exchange of the H-5 deuterium. As could be expected, the *N*-methyl groups, which are equivalent for the salts, become non-equivalent for the acids and the acetyl derivatives which have a hydrogen on C-5. These groups are also non-equivalent for **25**, which also shows a large downfield displacement of the C-5 signal.

The assignments made for the glycopyranosyl rings accord with ^{13}C-n.m.r. data previously reported[22–24] for carbohydrates. Compounds **16** and **17** showed a range of chemical shifts and a sequence for C-2′,3′,4′ similar to those shown by other α-D-arabinopyranosides[24], but the signal of C-5′ was shifted downfield. The assignment of this signal was confirmed by experiments with a DEPT pulse sequence. However, this displacement downfield has also been observed for some *C*-glycopyranosyl heterocycles having α- and β-D-*lyxo* configurations[25]. A good correlation can also be observed for the spectra of compounds derived from homomorphous sugars, glucose–xylose (**11–14**) or galactose–arabinose (**12–16** and **17–18**), which confirms their respective structures.

TABLE I

^{1}H-N.M.R. CHEMICAL SHIFT DATA[a] FOR COMPOUNDS **9**, **10**, AND **19–26**

Proton	*Compound*											
	9[b,c]	**10**[c,d]	**10**[e,f]	**19**[d,g]	**20**[d,g]	**21**[d,g]	**22**[d,g]	**23**[d,g]	**24**[d,g]	**24**[e,g]	**25**[d,g]	**26**[d,g]
H-1′	4.37 m	4.49 m	4.71 dd	7.39 d	7.33 d	7.49 d	7.41 d	7.41 d	5.00 d	5.02 d	4.47 dd	4.30 dd
H-2′	4.37 m	4.49 m	4.44 dt	6.51 dd	6.37 dd	6.23 dd	6.48 dd	6.53 dd	5.42 dd	5.75 dd	5.27 dd	5.54 t
H-3′	5.15 t	5.29 t	5.49 t	5.58 m	5.64 dd	5.47 m	5.66 dd	5.70 dd	5.27 m	5.38 m	5.75 dd	5.17 t
H-4′	4.69 t	5.03 t	5.16 t	5.58 m	5.42 dd	5.47 m	5.40 m	5.36 m	5.27 m	5.38 m	4.95 m	5.01 t
H-5′	3.35 m	3.36 m	3.35 dq	5.25 m	5.32 m	5.14 m	4.38 dd	4.31 dd	3.79 m	3.33 m	3.81 qd	3.64 m
H-5″							4.12 dd	4.15 dd			3.56 t	
H-6′	4.05 dd	4.07 m	4.87 dd	4.40 dd	4.29 dd	4.25 dd			4.44 dd	4.49 dd		4.06 m
H-6″	3.96 dd	4.07 m	3.98 dd	4.40 dd	3.88 dd	4.12 dd			3.96 dd	3.82 dd		4.06 m
N-H	8.00 d	6.11 d	5.28 d									
OAc	1.95 s (6H) 1.90 s (3H) 1.73 s (3H)	2.05 s (3H) 2.03 s (3H) 2.02 s (3H) 1.96 s (3H)		2.17 s (3H) 2.09 s (3H) 2.06 s (3H) 2.04 s (3H) 2.01 s (3H)	2.15 s (3H) 2.12 s (3H) 2.02 s (9H)	2.11 s (3H) 2.05 s (3H) 2.02 s (6H) 1.98 s (3H)	2.17 s (3H) 2.09 s (6H) 2.04 s (3H)	2.14 s (3H) 2.13 s (3H) 2.06 s (3H) 2.04 s (3H)	2.12 s (3H) 2.08 s (3H) 2.04 s (3H) 1.96 s (3H)	1.82 s (3H) 1.80 s (3H) 1.72 s (6H)	2.16 s (3H) 2.01 s (3H) 1.97 s (3H)	2.04 s (3H) 2.00 s (9H)
H-5	3.67 m	3.69 m	3.29 d								3.55 d	3.56 d
N-CH_3		3.32 s (3H) 3.30 s (3H)		3.33 s (6H)	3.34 s (3H) 3.29 s (3H)	3.32 s (6H)	3.33 s (6H)	3.36 s (3H) 3.32 s (3H)	3.32 s (3H) 3.27 s (3H)	3.07 s (3H) 2.91 s (3H)	3.29 s (3H) 3.25 s (3H)	3.32 s (3H) 3.29 s (3H)
N-H[h]	11.29 s 11.20 s											
OAc[h]									2.37 s (3H)	1.96 s (3H)		

[a]In p.p.m. from Me_4Si by first-order analysis. [b]In $(CD_3)_2SO$. [c]At 360 MHz. [d]In $CDCl_3$. [e]In C_6D_6. [f]At 300 MHz. [g]At 90 MHz. [h]Barbituric ring.

TABLE II

^{1}H-N.M.R. SPIN-COUPLING DATA FOR COMPOUNDS **9**, **10**, AND **19–26**[a]

$J_{H,H}$	*Compound*											
	9[b,c]	**10**[c,d]	**10**[e,f]	**19**[d,g]	**20**[d,g]	**21**[d,g]	**22**[d,g]	**23**[d,g]	**24**[d,g]	**24**[e,g]	**25**[d,g]	**26**[d,g]
1′,2′				6.7	7.0	8.7	7.0	7.0	0.8	0.8	10.5	10.0
2′,3′	9.5	9.7	9.7	3.0	1.5	6.4	2.8	2.2	2.5	2.0	2.7	10.0
3′,4′	9.5	9.7	9.7		10.0		7.0	8.8			3.2	9.7
4′,5′	9.5	9.7	9.7		1.5		3.9	3.1		9.0	5.8	9.7
4′,5″							5.8	4.5			8.6	
5′,5″							−12.3	−12.6			−10.6	
5′,6′	5.1		4.7	3.0	5.0	3.2			6.0	6.0		
5′,6″	1.8		2.4	6.3	7.3	4.8			2.0	2.0		
6′,6″	−12.2		−12.4	−12.7	−11.7	−12.5			−12.3	−12.3		
2′,NH	7.8	7.7	8.1									
1′,5			1.9								2.2	2.2
3′,5′											1.0	

[a]Conditions described in Table I.

TABLE III

VICINAL-PROTON TORSION ANGLES (°) FOR H-1′ AND H-5 FOR **10**, **25**, AND **26**[a]

Compound	$J_{1',5}$	$\Phi_{1',5}$	
		Eq. Coxon[b]	*Eq. Altona*[c]
10[d]	1.9	118 (59)	99 (45)
25[e]	2.2	120 (56)	102 (42)
26[e]	2.2	120 (56)	102 (42)

[a]As derived from the observed spacings. [b]Calculated by using the expression proposed by Coxon[16]. [c]Calculated by using the expression proposed by Altona *et al.*[17]. [d]In C_6D_6 solution at 300 MHz. [e]In $CDCl_3$ solution at 90 MHz.

Mechanism of formation of C-*glycosylbarbiturates*. — From the pK_a values[26] (~4) of **1** and **4**, these compounds should react with electrophiles even in the absence of a strong base. The initial adduct **27** undergoes a β-elimination of water to give the unsaturated intermediate **28**, which, as in similar reactions from non-carbohydrate aldehydes[27,28], can add another molecule of barbiturate to give bis-products (**2**), or they can be attacked by other nucleophiles. The bis-products were not detected in our experiments, and the only products isolated (**30**) are formed by the fast intramolecular nucleophilic addition of the alkoxide **29** formed by loss of the HO-5′ proton, to give **30**. Analogous mechanisms have been proposed[29–31] for the cyclisation of other sugar derivatives having electron-withdrawing groups linked to C-1′.

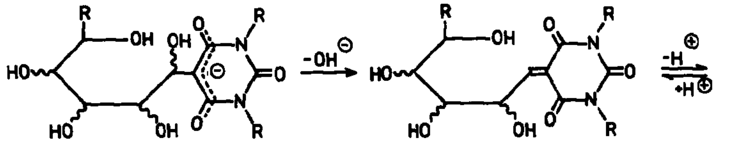
Although the intermediate **28** has never been isolated, analogous structures (**14–23**) have been obtained by acetylation of the *C*-glycosylbarbiturates **11–16**. In

TABLE IV

^{13}C-N.M.R. DATA[a,b] FOR COMPOUNDS **5**, **6**, **9–18**, AND **24–26**

Compound	*Glycosyl ring*						*Barbituric ring*						
	C-1'	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	*-CO-CH$_3$*	*-CO-CH$_3$*	*C-2*	*C-4 C-6*	*C-5*	*N-CH$_3$*	*-CO-CH$_3$*
5[c]	82.5	55.0	74.5	72.1	77.1	63.1			155.15	169.5	86.0		
6	81.0	53.7	74.2	71.0	75.6	61.9			155.3	166.3	84.8	28.7	
9[d]	77.4	50.6	73.4	68.5	74.7	61.5	169.8	22.6	150.6	169.3	48.3		
							169.5	20.3		167.2			
							169.4						
							169.3						
10[e]	78.7	51.8	73.5	68.4	75.9	62.0	171.0	23.2	151.4	167.3	49.6	28.7	
							170.7	20.6		163.3		28.4	
							170.3	20.5					
							169.3						
11	80.6	70.7	77.1	70.7	79.4	61.9			155.3	166.2	87.1	28.7	
12	79.7	70.9	76.2	68.6	77.7	62.2			155.3	166.3	87.2	28.7	
13	81.7	74.1	75.8	67.9	76.5	62.2			154.7	166.3	87.2	28.7	
14	79.5	70.8	77.8	70.6	70.1				155.2	166.0	87.0	28.6	
15	72.0	72.0	67.9[f]	67.6[f]	65.8				155.3	166.2	86.8	28.6	
16	78.0	70.7	75.7	68.6	71.0				155.2	166.2	87.2	28.6	
17	84.8	71.6	76.2	69.8	73.5				155.5	172.9	50.2	31.1	
										170.3		30.9	
18[c]	84.1	71.6	76.7	69.9	82.0	63.6			155.6	172.9	52.3	31.1	
										170.4		30.9	
24	75.2	68.0	69.7	64.4	72.0	60.7	168.2	18.5	148.4[f]	159.4	96.5	27.3	164.1
							167.8	18.4		150.4[f]		26.4	
							167.7	18.3					
							167.3	18.2					
25	73.8	65.5	64.1	65.9	62.2		167.8	18.7	149.5	165.7	47.1	26.8	
							167.2	18.5		163.3		26.5	
							166.6						
26	76.6	67.2	72.4	66.1	74.3	59.8	168.2	18.5	149.3	165.0	47.2	26.6	
							168.0	18.4		162.7		26.4	
							167.1	18.3					
							166.7						

[a]Chemical shifts in p.p.m. downfield from Me_4Si. [b]Recorded at 20.15 MHz in D_2O (external 1,4-dioxane) or in $CDCl_3$ (internal Me_4Si), unless otherwise indicated. [c]Recorded at 50.30 MHz in D_2O. [d]Recorded at 90.55 MHz in $(CD_3)_2SO$. [e]Recorded at 90.55 MHz in $CDCl_3$. [f]Assignments may have to be reversed.



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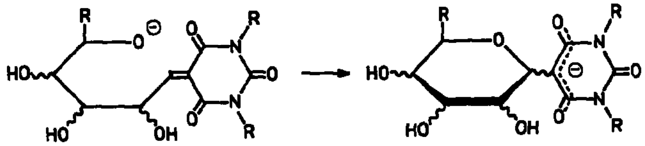

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addition, acetylation of **18** gives **20**, Zemplén deacetylation of which followed by addition of trifluoroacetic acid gives **18** again. This result supports the participation of such olefinic structures in the formation of the *C*-glycosylbarbiturates.

EXPERIMENTAL

General methods. — Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured at 22 ±5° with a Perkin-Elmer 141 polarimeter (10-cm, 5-mL cell). I.r. spectra (KBr discs) were recorded with a Perkin–Elmer 399 spectrophotometer, and u.v. spectra with a Beckman DB-6 or Spectronic 2000 instrument. P.c. was performed on Whatman No. 1 paper by the ascending technique using 1:1:1 1-butanol–pyridine–water and detection with silver nitrate–sodium hydroxide. T.l.c. was conducted on Silica Gel GF_{254} (Merck) with 3:1 ethyl acetate–ethanol or 3:1 benzene–ethanol, and detection with u.v. light or iodine vapour. Column chromatography was performed[32] on Silica Gel 60 (Merck) with 3:1 ethyl acetate–ethanol. Sodium was determined by flame emission with an atomic absorption spectrophotometer (Perkin–Elmer 370). N.m.r. spectra were recorded with Perkin–Elmer R-32, Varian XL-100, and Bruker 360 spectrometers (^{1}H), and a Bruker SP-80-WY spectrometer (^{13}C). Satisfactory elemental analyses could not be obtained for the sodium salts described below. However, the determination of sodium by atomic absorption gave the correct values.

5-(2-Amino-2-deoxy-β-D-glucopyranosyl)barbituric acid (**5**). — To a solution of 2-amino-2-deoxy-D-glucose hydrochloride (1.1 g, 5.0 mmol) in water (20 mL) were added sodium carbonate (0.27 g, 2.5 mmol) and barbituric acid (0.64 g, 5.0 mmol). The mixture was stirred at 50° until a solution was obtained, and then for 10 h more. The resulting crude product (1.08 g, 70%) was collected, washed with water, and recrystallised from water to give **5**, which gradually decomposed above 200° and had $[\alpha]_D$ −7° (*c* 0.7, M sodium hydroxide); $\lambda_{max}^{H_2O}$ 220 and 250 nm

(ε_{mM} 6.2 and 18.0); ν_{max} 3600–2500 (OH, NH_3^+), 1700, 1630, and 1600 cm^{-1} (C=O, NH_3^+). For the ^{13}C-n.m.r. data, see Table IV.

Anal. Calc. for $C_{10}H_{17}N_3O_8 \cdot H_2O$: C, 36.92; H, 5.88; N, 12.92. Found: C, 36.82; H, 5.55; N, 12.78.

5-(2-Amino-2-deoxy-β-D-glucopyranosyl)-1,3-dimethylbarbituric acid (**6**). — To a solution of 2-amino-2-deoxy-D-glucose hydrochloride (1.3 g, 6.0 mmol) in water (20 mL) were added sodium carbonate (0.32 g, 3.0 mmol) and 1,3-dimethylbarbituric acid (0.94 g, 6.0 mmol). The mixture was stirred at 50° until dissolution, and then for 10 h more. The solution was concentrated under diminished pressure to one-third volume, and **6** (1.75 g, 85%) was precipitated by addition of acetone and purified by precipitation from water–acetone. It gradually decomposed above 200° and had $[\alpha]_D$ −19° (*c* 0.6, water); $\lambda_{max}^{H_2O}$ 225 and 253 nm (ε_{mM} 6.5 and 17.0); ν_{max} 3600–2450 (OH, NH_3^+), 2080 (NH_3^+), 1720, 1610, and 1580 cm^{-1} (C=O, NH_3^+). For the ^{13}C-n.m.r. data, see Table IV.

Anal. Calc. for $C_{12}H_{21}N_3O_8$: C, 43.00; H, 6.31; N, 12.53. Found: C, 43.04; H, 6.47; N, 12.40.

Sodium 5-(2-amino-2-deoxy-β-D-glucopyranosyl)barbiturate (**7**). — To a solution of **5** (1.0 g, 3.1 mmol) in M sodium hydroxide (25 mL) was added methanol (100 mL) to give **7** (0.9 g, 86%), which was collected and washed with methanol. It gradually decomposed above 200° and had $[\alpha]_D$ −7° (*c* 0.7, M sodium hydroxide); $\lambda_{max}^{H_2O}$ 220 and 250 nm (ε_{mM} 6.2 and 18.0); ν_{max} 3600–2500 (OH, NH), 1700, 1630, and 1600 cm^{-1} (C=O, NH_2).

Sodium 5-(2-amino-2-deoxy-β-D-glucopyranosyl)-1,3-dimethylbarbiturate (**8**). — To a solution of **6** (2.0 g, 6.0 mmol) in M sodium hydroxide (10 mL) were added ethanol (35 mL) and acetone (250 mL), to give **8** (2.1 g, 99%), which was collected and washed with methanol. It gradually decomposed above 200° and had $[\alpha]_D$ −9° (*c* 0.6, water); $\lambda_{max}^{H_2O}$ 229 and 258 nm (ε_{mM} 5.8 and 20.1); ν_{max} 3600–2750 (OH, NH), 1680 and 1590 cm^{-1} (C=O, NH_2).

5-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)barbituric acid (**9**). — To a solution of freshly fused zinc chloride (1.0 g, 7.3 mmol) in acetic anhydride (10 mL, 106 mmol) was added **5** (1.0 g, 3.1 mmol). The mixture was stirred for 24 h, poured into ice–water, and extracted with chloroform (3 × 50 mL). The combined extracts were washed twice with water, dried, and concentrated to leave a syrup that crystallised from ethanol. Recrystallisation of the product (0.78 g, 55%) from methanol gave **9**, m.p. 170–171° (dec.), $[\alpha]_D$ −35° (*c* 0.6, methanol); λ_{max}^{MeOH} 253 nm (ε_{mM} 1.9); ν_{max} 3650–2700 (NH), 1735 (C=O ester), 1720 and 1705 (C=O heterocycle), and 1685 cm^{-1} (C=O amide). For the ^1H- and ^{13}C-n.m.r. data, see Tables I, II, and IV.

Anal. Calc. for $C_{18}H_{23}N_3O_{11}$: C, 47.26; H, 5.03; N, 9.19. Found: C, 47.24; H, 5.18; N, 9.37.

5-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-1,3-dimethylbarbituric acid (**10**). — Using the method described above, **6** was converted into **10** (63%), m.p. 178–179° (dec.), $[\alpha]_D$ −35.5° (*c* 0.4, methanol); λ_{max}^{MeOH} 224 and 255 nm

(ε_{mM} 4.7 and 2.2); ν_{max} 3600–3200 (NH), 1750 (C=O ester), 1710–1650 cm^{-1} (C=O heterocycle and amide). For the ^{1}H- and ^{13}C-n.m.r. data, see Tables I, II, and IV.

Anal. Calc. for $C_{20}H_{27}N_3O_{11}$: C, 49.48; H, 5.56; N, 8.66. Found: C, 49.21; H, 5.68; N, 8.45.

Sodium 5-D-glycopyranosyl-1,3-dimethylbarbiturates. — A solution of aldose (50 mmol) in water (100 mL) was treated with 1,3-dimethylbarbituric acid (50 mmol), then neutralised with sodium carbonate, stored at 80° for 5 h, and concentrated under diminished pressure to 15 mL. The hexose derivatives were precipitated from methanol and purified by re-precipitation from water–methanol (water–ethanol for the pentose derivatives). The following compounds were prepared in this way.

Sodium 5-β-D-glucopyranosyl-1,3-dimethylbarbiturate (**11**, 78%), m.p. 185–186° (dec.), $[\alpha]_D$ −13.5° (*c* 0.5, water); $\lambda_{max}^{H_2O}$ 225 and 253 nm (ε_{mM} 5.0 and 14.5); ν_{max} 3400–3300 (OH), 1665 and 1575 cm^{-1} (C=O). For the ^{13}C-n.m.r. data, see Table IV.

Sodium 5-β-D-galactopyranosyl-1,3-dimethylbarbiturate (**12**, 78%), m.p. 185–186° (dec.), $[\alpha]_D$ +17° (*c* 3, water); $\lambda_{max}^{H_2O}$ 225 and 255 nm (ε_{mM} 5.6 and 16.2); ν_{max} 3400–3300 (OH), 1670 and 1580 cm^{-1} (C=O). For the ^{13}C-n.m.r. data, see Table IV.

Sodium 5-β-D-mannopyranosyl-1,3-dimethylbarbiturate (**13**, 80%), which gradually decomposed above 200° and had $[\alpha]_D$ −34° (*c* 3, water); $\lambda_{max}^{H_2O}$ 225 and 256 nm (ε_{mM} 4.9 and 14.1); ν_{max} 3500–3300 (OH), 1630 and 1580 cm^{-1} (C=O). For the ^{13}C-n.m.r. data, see Table IV.

Sodium 1,3-dimethyl-5-β-D-xylopyranosylbarbiturate (**14**, 70%), which gradually decomposed above 200° and had $[\alpha]_D$ −24° (*c* 1.2, water); $\lambda_{max}^{H_2O}$ 259 nm (ε_{mM} 14.7); ν_{max} 3500–3100 (OH), 1670 and 1575 cm^{-1} (C=O). For the ^{13}C-n.m.r. data, see Table IV.

Application of the general procedure to D-ribose gave a mixture (77%) of several products in which sodium 1,3-dimethyl-5-β-D-ribopyranosylbarbiturate (**15**) preponderated, as demonstrated by the ^{13}C-n.m.r. spectrum (see Table IV).

Sodium 5-α-D-arabinopyranosyl-1,3-dimethylbarbiturate (**16**, 80%), which gradually decomposed above 200° and had $[\alpha]_D$ −34° (*c* 2, water); $\lambda_{max}^{H_2O}$ 259 nm (ε_{mM} 16.8); ν_{max} 3500–3300 (OH), 1655 and 1585 cm^{-1} (C=O). For the ^{13}C-n.m.r. data, see Table IV.

5-α-D-Arabinopyranosyl-1,3-dimethylbarbituric acid (**17**). — To a solution of **16** (2.0 g, 6.1 mmol) in the minimum volume of water was added trifluoroacetic acid (1 mL), to give **17** (1.45 g, 78%) which crystallised rapidly. Recrystallisation from water gave material with m.p. 110–111°, $[\alpha]_D$ −8° (*c* 0.3, water); $\lambda_{max}^{H_2O}$ 259 nm (ε_{mM} 13.8); ν_{max} 3550–3300 (OH), 1670 and 1650 cm^{-1} (C=O). For the ^{13}C-n.m.r. data, see Table IV.

Anal. Calc. for $C_{11}H_{18}N_2O_8$: C, 43.13; H, 5.88; N, 9.15. Found: C, 43.00; H, 6.03; N, 9.27.

5-β-D-Galactopyranosyl-1,3-dimethylbarbituric acid (**18**). — To a solution of

12 (2.0 g, 5.6 mmol) in the minimum volume of water was added trifluoroacetic acid (1 mL), and the mixture was kept for 1 h at 0° to give **18** (1.7 g, 93%). Recrystallisation from water gave material with m.p. 116–117°, $[\alpha]_D$ +11° (*c* 0.4, water); $\lambda_{max}^{H_2O}$ 225 and 255 nm (ε_{mM} 5.7 and 15.5); ν_{max} 3600–3100 (OH) and 1670 cm^{-1} (C=O). For the ^{13}C-n.m.r. data, see Table IV.

Anal. Calc. for $C_{12}H_{20}N_2O_9$: C, 42.85; H, 5.95; N, 8.33. Found: C, 42.93; H, 6.06; N, 8.39.

To methanolic 0.1M sodium methoxide (25 mL) was added **20** (1.0 g, 1.9 mmol). After 15 min at room temperature, t.l.c. showed that deacetylation was complete. The solvent was evaporated and to a solution of the dry solid residue in the minimum amount of water was added trifluoroacetic acid, to give **18** (0.13 g, 20%).

Acetylation procedure. — The carbohydrate derivative (1.0 g) was stirred for 10 h with a solution of freshly fused zinc chloride (1.0 g) in acetic anhydride (10 mL). The mixture was then poured into ice–water, and, unless otherwise stated, the crystalline product was collected and recrystallised. The following compounds were prepared in this way.

2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-(1,3-dimethyl-2,4,6-trioxo-1*H*,3*H*,5*H*-pyrimidin-5-ylidene)-D-glucitol (**19**, 78% from **11**), m.p. 130–131° (from ethanol), $[\alpha]_D$ +86° (*c* 1.5, chloroform); λ_{max}^{MeOH} 235 nm (ε_{mM} 15.4); ν_{max} 1740 (C=O ester), 1670 (C=O heterocycle), and 1220 cm^{-1} (C–O–C). For the ^{13}C-n.m.r. data, see Table IV.

Anal. Calc. for $C_{22}H_{28}N_2O_{13}$: C, 50.00; H, 5.30; N, 5.30. Found: C, 50.01; H, 5.20; N, 5.33.

To a solution of freshly fused zinc chloride (10.0 g, 73.0 mmol) in acetic anhydride (50 mL) was added **26** (1.0 g, 2.1 mmol). The mixture was kept for 24 h at room temperature and then it was poured on to ice–water, to give **19** (0.6 g, 55%).

2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-(1,3-dimethyl-2,4,6-trioxo-1*H*,3*H*,5*H*-pyrimidin-5-ylidene)-D-galactitol (**20**, 85% from **12**, 89% from **18**), m.p. 159–160° (from ethanol), $[\alpha]_D$ +47° (*c* 1.5, chloroform); λ_{max}^{MeOH} 235 nm (ε_{mM} 14.3); ν_{max} 1740 (C=O ester), 1670 (C=O heterocycle), and 1210 cm^{-1} (C–O–C). For the ^1H- and ^{13}C-n.m.r. data, see Tables I, II, and IV.

Anal. Calc. for $C_{22}H_{28}N_2O_{13}$: C, 50.00; H, 5.30; N, 5.30. Found: C, 49.98; H, 5.31; N, 5.45.

Fractional crystallisation (methanol–light petroleum) of the residual oil obtained by chloroform extraction of the product from **13** gave 4-acetoxy-1,3-dimethyl-2,6-dioxo-5-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-1*H*,3*H*-pyrimidine (**24**, 16%), m.p. 160–161° (from methanol), $[\alpha]_D$ −81° (*c* 1.6, chloroform); λ_{max}^{EtOH} 266 nm (ε_{mM} 11.6); ν_{max} 1790 (C=O vinyl ester), 1740 (C=O ester), 1700, 1660, and 1630 (C=O heterocycle), and 1235 cm^{-1} (C–O–C). For the ^1H- and ^{13}C-n.m.r. data, see Tables I, II, and IV.

Anal. Calc. for $C_{22}H_{28}N_2O_{13}$: C, 50.00; H, 5.30; N, 5.30. Found: C, 49.96; H, 5.15; N, 5.22.

Concentration of the mother liquors gave 2,3,4,5,6-penta-*O*-acetyl-1-deoxy-1-(1,3-dimethyl-2,4,6-trioxo-1*H*,3*H*,5*H*-pyrimidin-5-ylidene)-D-mannitol (**21**, 46%), m.p. 71–72° (from ethanol), $[\alpha]_D$ +39° (*c* 1.6, chloroform); λ_{max}^{EtOH} 238 nm (ε_{mM} 13.5); ν_{max} 1740 (C=O ester), 1670 (C=O heterocycle), and 1210 cm^{-1} (C–O–C). For the ^1H- and ^{13}C-n.m.r. data, see Tables I, II, and IV.

Anal. Calc. for $C_{22}H_{28}N_2O_{13}\cdot H_2O$: C, 48.35; H, 5.49; N, 5.13. Found: C, 48.28; H, 5.46; N, 5.07.

2,3,4,5-Tetra-*O*-acetyl-1-deoxy-1-(1,3-dimethyl-2,4,6-trioxo-1*H*,3*H*,5*H*-pyrimidin-5-ylidene)-D-xylitol (**22**, 75% from **14**), m.p. 136–137° (from ethanol), $[\alpha]_D$ +72° (*c* 3.7, chloroform); λ_{max}^{EtOH} 239 nm (ε_{mM} 12.7); ν_{max} 1740 (C=O ester), 1670 (C=O heterocycle), and 1205 cm^{-1} (C–O–C). For the ^1H- and ^{13}C-n.m.r. data, see Tables I, II, and IV.

Anal. Calc. for $C_{19}H_{24}N_2O_{11}$: C, 50.00; H, 5.26; N, 6.14. Found: C, 50.04; H, 5.43; N, 6.11.

2,3,4,5-Tetra-*O*-acetyl-1-deoxy-1-(1,3-dimethyl-2,4,6-trioxo-1*H*,3*H*,5*H*-pyrimidin-5-ylidene)-D-arabinitol (**23**, 93% from **16**, 88% from **17**), m.p. 154–155° (from ethanol), $[\alpha]_D$ ~0° (*c* 1.7, chloroform); λ_{max}^{MeOH} 239 nm (ε_{mM} 14.0); ν_{max} 1740 (C=O ester), 1665 (C=O heterocycle), and 1215 cm^{-1} (C–O–C). For the ^1H- and ^{13}C-n.m.r. data, see Tables I, II, and IV.

Anal. Calc. for $C_{19}H_{24}N_2O_{11}$: C, 50.00; H, 5.26; N, 6.14. Found: C, 49.78; H, 5.42; N, 6.07.

The crude product from the mixture of products from D-ribose and **4** was extracted with chloroform and subjected to column flash chromatography (Silica Gel 60, Merck; benzene–ethanol 3:1) to give 1,3-dimethyl-5-(2,3,4-tri-*O*-acetyl-β-D-ribopyranosyl)barbituric acid (**25**, 19%), m.p. 141–142° (from ethanol), $[\alpha]_D$ −27° (*c* 0.5, chloroform); λ_{max}^{MeOH} 259 and 226 nm (ε_{mM} 1.0 and 6.3); ν_{max} 1760 (C=O ester), 1695 and 1665 (C=O heterocycle), and 1220 cm^{-1} (C–O–C). For the ^1H- and ^{13}C-n.m.r. data, see Tables I, II, and IV.

Anal. Calc. for $C_{17}H_{22}N_2O_{10}$: C, 49.27; H, 5.35; N, 6.76. Found: C, 49.03; H, 5.27; N, 6.64.

1,3-Dimethyl-5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)barbituric acid (**26**, 80% from **11**), m.p. 177–178° (from ethanol), $[\alpha]_D$ −39° (*c* 1, chloroform); λ_{max}^{MeOH} 226 and 256 nm (ε_{mM} 8.5 and 4.5); ν_{max} 1740 (C=O ester), 1720 and 1675 (C=O heterocycle), and 1230 cm^{-1} (C–O–C). For the ^1H- and ^{13}C-n.m.r. data, see Tables I, II, and IV.

Anal. Calc. for $C_{20}H_{26}N_2O_{12}$: C, 49.38; H, 5.35; N, 5.76. Found: C, 49.03; H, 5.39. N, 5.87.

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