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Note

Synthesis and conformational analysis of *C*-glycosylbarbiturates

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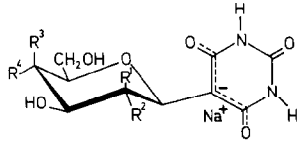
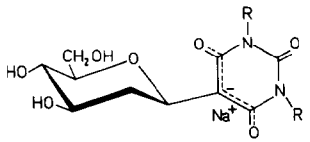
C-Nucleosides may have antibacterial, antiviral, and antitumor activity[1], and their syntheses usually involve C-1-functionalised sugar derivatives and a heterocyclic base, often as a metalated derivative. We have described[2] an efficient synthesis of *C*-nucleoside analogues of barbituric acid from unprotected sugars and now report further examples of this reaction.

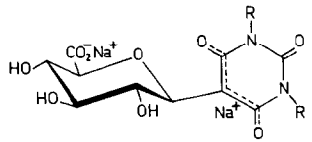
Thus, reaction of D-glucose, D-galactose, and D-mannose severally with barbituric acid, in hot water at pH 7, gave the 5-D-glycosylbarbiturates **1–3**, isolated as the sodium salts in good yields (73–80%). Likewise, 2-deoxy-D-*arabino*-hexose and D-glucuronic acid reacted severally with barbituric and 1,3-dimethylbarbituric acids to give **4–7** in good yields. The structures of **1–7** were assigned on the basis of u.v. and i.r. data (see Experimental) and the ^{13}C-n.m.r. spectra (Table I) which accorded with those of similar compounds[2]. Satisfactory conventional elemental analyses could not be



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



4 R = H
5 R = Me



6 R = H
7 R = Me

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TABLE I

^{13}C-N.m.r. Data[a] for 1–7

Compound	*Glycosyl ring*						*Barbituric ring*			
	C-1'	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	*C-2*	*C-4* *C-6*	*C-5*	*Me*
1	80.6	70.7	75.7*	70.7	79.3*	61.9	154.3	167.8	86.4	–
2	79.9	70.9	76.2*	68.6	76.5*	62.3	154.3	167.9	86.6	–
3	81.7	73.9	74.9	68.1	76.5	62.4	153.9	168.1	89.2	–
4	80.9	36.8	72.1*	72.1*	74.3*	62.2	154.1	167.4	89.6	–
5	80.9	36.8	73.4*	72.2*	74.4*	62.2	155.2	165.8	90.3	28.7
6	81.8	75.5	79.0	70.5*	73.6*	177.7	154.3	167.9	86.4	–
7	81.8	76.8	79.1	70.6*	73.5*	177.9	155.3	166.3	87.0	28.7

[a] In D_2O at 20.15 MHz; in p.p.m. from Me_4Si; assignments marked * may have to be interchanged.

obtained for these sodium salts, but sodium could be determined by atomic absorption spectroscopy.

C-Glucosyluronic acids have been identified as drug metabolites. Thus, in humans, sulfinpyrazone and phenylbutazone (derivatives of 1,2-diphenyl-3,5-dioxopyrazolidine) form *C*-glucosyluronic acid derivatives at C-4 of the pyrazolidine ring[3]. The facile formation of **6** and **7** under near-physiological conditions might explain the susceptibility of barbiturates with at least one hydrogen on C-5 to metabolic reaction with UDP-GlcA and the consequent lack of sedative and hypnotic properties.

The conformational equilibrium around the C-1'–C-5 glycosyl bond of the acetylated *C*-glycosylbarbituric acids **8–11** has been studied using molecular mechanics (MM) calculations (MM2 program[4]). The results, summarised in Table II, show that, for **8** and **9**, there is an equilibrium of the conformers **12** and **13** in similar proportions. The calculated *J* (averaged) values are close to the experimental data[2]. It is concluded that the configuration at C-2' is the determinant factor for this conformational equilibrium. Calculations for **10** and **11** also confirm that the barbituric ring is essentially planar and that the sugar ring is in the $^4C_1$ conformation.

EXPERIMENTAL

General methods. — Optical rotations were measured at 21 ±5° with a 10-cm, 0.5-mL cell and a Perkin–Elmer 241 polarimeter. I.r. spectra (KBr discs) were recorded with a Perkin–Elmer 1310 spectrophotometer and u.v. spectra (aqueous solutions) with a Spectronic 2000 instrument. Sodium was determined with a Perkin–Elmer 370 atomic absorption spectrophotometer. ^{13}C-N.m.r. spectra were recorded with a Bruker WP-80-SY spectrometer. MM calculations were performed on a Vax-11/785 computer.

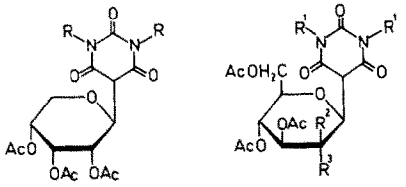
*Sodium 5-*D*-glycopyranosylbarbiturates.* — A solution of aldose (50 mmol) in water (100 mL) was treated with barbituric acid (50 mmol), neutralised with sodium carbonate, stored for 5 h at 80°, and concentrated under diminished pressure (to ~15 mL). Methanol was added, and the precipitated product was purified by re-

TABLE II

Conformational analysis around the C-1′ — C-5 bond for **8–11**

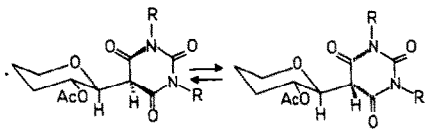
Compound	*Conformer*	$\varphi_{H,H}$ (°)	*Relative energy (kcal.mol^{-1})*	*Population*[a] *(%)*	J *(calc.)*[a] *(Hz)*	J *(averaged) (Hz)*	J *(exp)*[b] *(Hz)*
8						1.82	2.2
	1	−123.1	3.36	0.19	4.88		
	2	− 65.7	0.05	47.74	1.15		
	3	− 66.8	0.00	52.02	2.44		
	4	137.9	4.10	0.05	6.26		
9						1.79	2.2
	1	−123.0	3.36	0.18	4.88		
	2	− 65.8	0.05	47.65	1.13		
	3	66.8	0.00	52.12	2.34		
	4	138.8	4.09	0.05	6.26		
10						4.37	–
	1	− 97.9	1.48	6.53	1.03		
	2	− 58.3	1.09	12.54	2.03		
	3	50.6	0.00	79.90	4.93		
	4	163.1	2.57	1.03	10.31		
11						1.86	
	1	− 58.4	0.00	96.82	1.83		
	2	66.8	2.04	3.10	2.46		
	3	−150.5	4.15	0.08	8.57		

[a] Calculated by MM2; the proton–proton torsion angle ($\varphi_{H,H}$) is defined $-180° < \varphi \leqslant 180°$, being positive in the clockwise direction from H-5. [b] See ref. 2.



8 R = Me

9 R^1 = Me, R^2 = H, R^3 = OAc
10 R^1 = Me, R^2 = OAc, R^3 = H
11 R^1 = Me, R^2 = R^3 = H



12 13

precipitation from water–methanol. The following compounds were prepared in this way, and the ^{13}C-N.m.r. data are recorded in Table I.

Sodium 5-β-D-glucopyranosylbarbiturate (**1**, 80%), m.p. >170° (dec.), $[a]_D$ −13° (*c* 1, water); λ_{max} 256 nm (ε_{mM} 16.3); ν_{max} 3500–3200 (OH, NH) 1700 and 1590 cm^{-1} (C=O).

Anal. Calc. for $C_{10}H_{13}N_2NaO_8$: Na, 7.36. Found: Na, 7.02.

Sodium 5-β-D-galactopyranosylbarbiturate (**2**, 73%), m.p. >200° (dec.), $[a]_D$ −6°

(*c* 1, water); λ_{max} 260 nm (ε_{mM} 12.1); ν_{max} 3500–3100 (OH, NH), 1690 and 1590 cm^{-1} (C=O).

Anal. Calc. for $C_{10}H_{13}N_2NaO_8$: Na, 7.36. Found: Na, 6.94.

Sodium 5-β-D-mannopyranosylbarbiturate (**3**, 74%), m.p. >180° (dec.), $[\alpha]_D$ −21° (*c* 1, water); λ_{max} 257 nm (ε_{mM} 13.5); ν_{max} 3500–3100 (OH, NH), 1690 and 1590 cm^{-1} (C=O).

Anal. Calc. for $C_{10}H_{13}N_2NaO_8$: Na, 7.36. Found: Na, 7.00.

Sodium 5-(2-deoxy-β-D-*arabino*-hexopyranosyl)barbiturate (**4**, 80%), m.p. >180° (dec.), $[\alpha]_D$ −30° (*c* 1, water); λ_{max} 257 nm (ε_{mM} 16.9); ν_{max} 3500–3100 (OH, NH), 1700 and 1570 cm^{-1} (C=O).

Anal. Calc. for $C_{10}H_{13}N_2NaO_7$: Na, 7.76. Found: Na, 7.37.

*Sodium 5-(2-deoxy-β-*D-arabino-*hexopyranosyl-1,3-dimethyl*barbiturate (**5**). — Application of the general procedure to 2-deoxy-D-*arabino*-hexose and 1,3-dimethylbarbituric acid gave **5** (73%), m.p. >200° (dec.), $[\alpha]_D$ −15° (*c* 1, water); λ_{max} 259 nm (ε_{mM}16.4); ν_{max} 3460 and 3370 (OH), 1660 and 1585 cm^{-1} (C=O). For the ^{13}C-n.m.r. data, see Table I.

Anal. Calc. for $C_{12}H_{17}N_2NaO_7$: Na, 7.09. Found: Na, 7.42.

*Disodium 5-(β-*D-*glucopyranosyluronate)barbiturate* (**6**). — (*a*) A solution of D-glucurono-6,3-lactone (25 mmol) in water (50 mL) was treated with barbituric acid (25 mmol), then neutralised with sodium carbonate, stored at 40° for 12 h, and concentrated under diminished pressure (to ~10 mL). Compound **6** (73%), precipitated by the addition of methanol–ether (1:1) and purified by reprecipitation from water–methanol–ether, had m.p. >118° (dec.), $[\alpha]_D$ +12° (*c* 1, water); λ_{max} 256 nm (ε_{mM} 13.2); ν_{max} 3500–3100 (OH, NH), 1700–1590 cm^{-1} (C=O). For the ^{13}C-N.m.r. data, see Table I.

Anal. Calc. for $C_{10}H_{10}N_2Na_2O_9$: 13.21. Found Na, 13.00.

(*b*) Reaction as in (*a*), but with sodium D-glucuronate, gave 66% of **6**.

*Disodium 5-(β-*D-*glucopyranosyluronate)-1,3-dimethylbarbiturate* (**7**). — (*a*) Reaction of 1,3-dimethylbarbituric acid with D-glucurono-6,3-lactone, as described above for **6**, gave **7** (77%), m.p. >120° (dec.), $[\alpha]_D$ +22° (*c* 1, water); λ_{max} 257 nm (ε_{mM} 13.0); ν_{max} 3600–3100 (OH), 1680–1540 cm^{-1} (C=O). For the ^{13}C-n.m.r. data, see Table I.

Anal. Calc. for $C_{12}H_{14}N_2Na_2O_9$: Na, 12.22. Found: Na, 11.81.

(*b*) Reaction as in (*a*), but with sodium D-glucuronate, gave 64% of **7**.

ACKNOWLEDGMENTS

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