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Reaction of sugars with Meldrum's acid: a route to 3,6-anhydro-2-deoxyaldono-1,4-lactones

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ABSTRACT

Reactions between Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) and D-xylose, D-glucose, and D-galactose gave mainly 3,6-anhydro-1,4-lactones together with α,β-unsaturated-1,4-lactones. The preparation of 3,6-anhydro-1,4-lactones having the D-*xylo*, D-*gluco*, and D-*galacto* configurations is described.

INTRODUCTION

We have described the reaction of barbituric and 1,3-dimethylbarbituric acids with monosaccharides[1-2], to give the *C*-glycosylbarbiturates (**1**) in good yields, and now report on reactions with Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione[3,4] (pK_a 4.97), the acidity of which is similar to that of the barbituric acids.

RESULTS AND DISCUSSION

The reaction between D-xylose and Meldrum's acid, under the conditions (aqueous solution, pH 7, 80°) used[2] in the preparation of **1**, gave a complex mixture instead of the expected product **2**. When the reaction was carried out in *N,N*-dimethylformamide–triethylamine, column chromatography of the products gave **3** (57%) and **4** (4%).

The structure of **3** was assigned on the basis of its elemental analysis and spectral data, and those of its diacetate **5**. Thus, both **3** and **5** had i.r. absorption at 1770 cm^{-1} characteristic of γ-lactones. The 200-MHz ^{1}H-n.m.r. spectrum of **5** could be assigned completely (Tables I and II) and confirmed the structure proposed, as did the ^{13}C-n.m.r. data (Table III). The ^{1}H-n.m.r. spectra of the unsaturated lactone **4** and its triacetate **6** also indicated their structures. Thus, **4** had resonances (dd) for olefinic protons at 6.15 and 7.77 p.p.m. The spectrum of **6** indicated the presence of three acetyl protons, and the structure of the acyclic moiety chain could be established completely from the signals for H-5/7.

The reaction of Meldrum's acid with D-glucose and D-galactose gave, as the main products, the 3,6-anhydro-1,4-lactones **7** and **10**, respectively. The reaction with D-glucose also yielded a small proportion of the unsaturated lactone **8**, and that with

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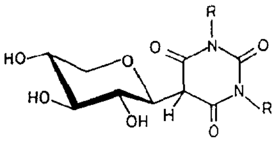
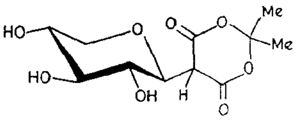


1
R = H,Me



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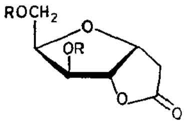
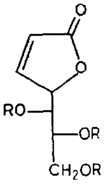
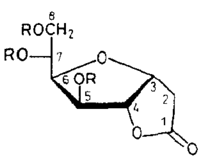


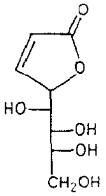
3 R = H
5 R = Ac



4 R = H
6 R = Ac



7 R = H
9 R = Ac



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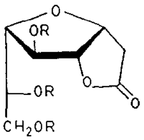
D-galactose also gave the bicyclic-1,4-lactone **12**. These structures were assigned on the basis of their ^{1}H- and ^{13}C-n.m.r. spectra, and those of the respective triacetates (**9**, **11**, and **13**). Thus, **10** and **12** gave signals for HO-5 (d), HO-7 (d), and HO-8 (t) that were assigned unequivocally by spin–spin decoupling experiments. The *cis* configurations of the D-*glycero*-D-*ido* (**7** and **9**) and D-*glycero*-L-*gluco* (**10** and **11**) compounds are indicated by their $J_{4,5}$ values (0 Hz), which accord[5-7] with a *trans* arrangement of H-4,5. The *cis*-D-*glycero*-L-*altro* configurations assigned to **12** and **13** were based on the $J_{4,5}$ values (4.6 and 4.7 Hz, respectively), which accord with a *cis* arrangement of H-4,5[6,8,9].

An attempt was made to confirm the structure of **12** on the basis of the n.m.r. spectra of the tetra-acetates **15** and **17** of the amides **14** and **16**, obtained by ammonolysis of **10** and **12**, respectively, followed by acetylation. The ^{1}H-n.m.r. spectra of **15** and **17** could be assigned fully (Tables I and II). The signal for H-3 of **15** appeared at higher field (4.50 p.p.m.) than the corresponding signal of **17** (4.60 p.p.m.). A *trans*-[3.3.0]-bicyclic structure for **12** would lead to an amide similar to **15** but with different "anomeric" configuration at C-3, and the signal for H-3 would appear at higher field[10] than that for **15**.

The formation of **3** and **7** can be explained by the initial formation from D-xylose and D-glucose of **18**, which could react via **19** to give the unsaturated lactones **4** and **8** followed by a Michael-type addition to yield **3** and **7**. This type of cyclization has been observed in the reaction of sugars with oxalacetaldehyde[11] and from the products of other condensation reactions with Meldrum's acid[12,13]. Likewise, **10** can be formed from D-galactose and **12** via an intermediate lactone with the configuration at C-4 inverted.

Kochetkov and Dmitriev[14] reported the formation of **20** as the main product of the reaction of D-galactose with ethoxycarbonylmethylenetriphenylphosphorane. However, when we performed the reaction using methoxycarbonylmethylenetriphenylphosphorane, the major product was **10**, and **12** and **21** were minor products. The structure of **21** was indicated by its spectral data and those of its tetra-acetate **22**. (Tables I–III). This compound may arise by the addition of HO-6 to the olefinic double-bond of



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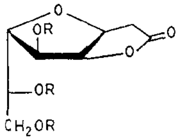
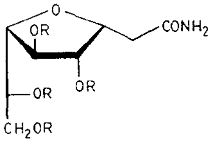
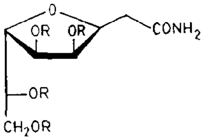
11 R = Ac



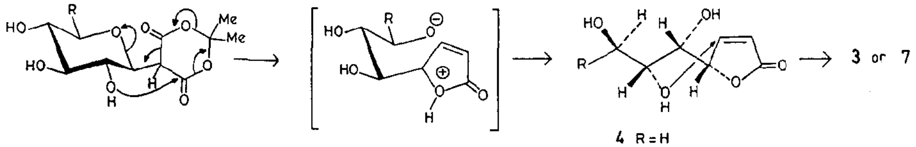
12 R = H
13 R = Ac



14 R = H
15 R = Ac



16 R = H
17 R = Ac

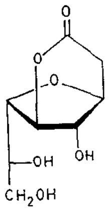


18 **19** **4** R = H
8 R = CH_2OH

23. The anomeric configurations of **21** and **22** are assigned tentatively on the basis of the similarity of the ^{1}H-n.m.r. data of **22** and **15**. Compounds **20** and **23**, reported by Kochetkov and Dmitriev[14], were not isolated.

EXPERIMENTAL

General. — Solutions were concentrated *in vacuo* at $<40°$. Melting points were determinated with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured at 18° with a Perkin–Elmer 141 polarimeter (10-cm cell). T.l.c. (analytical and preparative) was performed on Silica Gel 60 F_{254} (Merck) with detection by u.v. light or charring with sulfuric acid. Column chromatography was performed in the "flash" mode[15]. I.r. spectra (KBr discs or solutions in chloroform) were recorded with a Perkin–Elmer 1310 spectrometer. ^{1}H-N.m.r. spectra (Tables I and II) were recorded with a Bruker WP-80-SY (80.13 MHz), AC-200-E, or Varian XL-200 (200 MHz) instrument, and ^{13}C-n.m.r. spectra (Table III) with a Bruker WP-80-SY (20.15 MHz) spectrometer.



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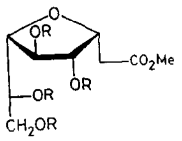

21 R = H
22 R = Ac

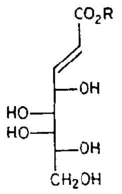

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TABLE I

^{1}H-N.m.r. chemical shift data (p.p.m.) for **4–6**, **8–13**, **15**, **17**, and **26**

Compound	*H-2*	*H-2'*	*H-3*	*H-4*	*H-5*	*H-6*	*H-7*	*H-7'*	*H-8*	*H-8'*	*Others*
4^{a}	6.15 dd		7.77 dd	5.21 dt	← 4.00–3.40 m →						
5^{b}	2.67 dd	2.52 dd	4.85 td	4.77 bd	5.31 bd	4.24 m	4.09 dd	4.00 dd			1.92 s (OAc) 1.97 s (OAc)
6^{b}	6.16 dd		7.35 dd	5.07 dt	5.16 dd	5.33 td	4.23 dd	3.98 dd			1.99 s (OAc) 2.07 s (OAc) 2.08 s (OAc)
8^{c}	6.19 dd		7.83 dd	5.09 dt	← 4.20–3.00 m →						
9^{b}	2.78 dd	2.67 dd	4.99 td	4.84 d	5.60 d	4.28 dd	5.18 ddd		4.56 dd	4.06 dd	2.01 s (OAc) 2.07 s (OAc) 2.09 s (OAc)
10^{d}	2.80 dd	2.45 d	4.59 t	4.71 d	4.16t	3.65 dd	3.47 m		← 3.39 m →		4.66 t (OH-8) 4.76 d (OH-7) 4.58 d (OH-5)
11^{b}	2.80 m	2.73 d	4.92 s	4.92 s	5.15 d	4.20 t	5.36 ddd		4.24 dd	4.16 dd	2.05 s (OAc) 2.11 s (OAc) 2.13 s (OAc)
12^{d}	2.86 dd	2.43 dd	4.67 t	4.88 t	4.20 ddd	3.70 dd	3.93 m		← 3.93 m →		4.60 t (OH-8) 4.61 d (OH-7) 5.37 d (OH-5)
13^{b}	2.83 dd	2.70 dd	4.94 ddd	5.17 t	4.93 dd	4.22 dd	5.21 ddd		4.28 dd	4.18 dd	2.06 s (OAc) 2.08 s (OAc) 2.14 s (OAc)

15[b]	2.57 dd	2.48 dd	4.50 ddd	5.29 dd	5.07 dd	3.99 dd	5.36 ddd		4.38 dd	4.14 dd	2.06 s (OAc) 2.10 s (OAc) 2.12 s (OAc) 2.14 s (OAc) 6.27 bs (NH_2)
17[b]	2.61 dd	2.47 dd	4.60 ddd	5.52 t	5.27 dd	4.21 dd	5.18 ddd		4.32 dd	4.17 dd	2.04 s (OAc) 2.07 s (OAc) 2.13 s (OAc) 2.14 s (OAc) 6.35 bs (NH_2)
22[b]	2.74 d	2.70 d	4.46 ddd	5.10 dd	5.16 dd	4.14 dd	5.34 ddd		4.34 dd	4.16 dd	2.05 s (OAc) 2.10 s (OAc) 2.11 s (OAc) 2.14 s (OAc) 3.70 s (OMe)

[a] D_2O at 80.13 MHz. [b] $CDCl_3$ at 200 MHz. [c] $(CD_3)_2SO$ at 80.13 MHz. [d] $(CD_3)_2SO$ at 200 MHz.

TABLE II

^{1}H-coupling constants (Hz) for **4–6, 8–13, 15, 17, and 22**

Compound	$J_{2,2'}$	$J_{2,3}$	$J_{2',3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{6,7'}$	$J_{7,7'}$	$J_{7,8}$	$J_{7,8'}$	$J_{8,8'}$
4[a]		5.8		1.9	1.5	5.4							
5[b]	−18.9	5.5	1.5		4.6	0.8	3.7	4.7	7.0	−11.7			
6[b]		5.8		1.9	1.5	6.7	3.1	6.0	6.2	−11.5			
8[c]		5.7		1.9	1.5	6.8							
9[b]	−18.6	5.1	2.2		4.6	0.0	3.2	9.4			2.4	5.1	−12.2
10[d]	−18.2	5.9	0.0		5.9	0.0	6.0	3.2					
11[b]	−18.5		0.0			0.0	3.5	3.5			4.9	7.0	−11.6
12[d]	−18.3	5.8	1.4		4.6	4.6	8.1	1.6					
13[b]	−18.9	6.4	1.8		4.7	4.7	8.1	3.3			5.2	6.7	−11.9
15[b]	−15.2	7.3	5.1		4.0	1.3	3.6	5.9			3.9	7.1	−12.2
17[b]	−15.6	8.1	5.2		3.8	4.7	7.6	3.4			4.8	6.7	−12.0
22[b]		7.4	6.0		4.4	2.4	3.7	4.8			4.2	7.0	−12.1

[a] D_2O at 80.13 MHz. [b] $CDCl_3$ at 200 MHz. [c] $(CD_3)_2SO$ at 80.13 MHz. [d] $(CD_3)_2SO$ at 200 MHz.

TABLE III

^{13}C-N.m.r. data[a] for **3, 5, 7, 9–13, 15, 17, 21, and 22**

Compound	*C-1*	*C-2*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	*C-7*	*C-8*	Me-*COO*-	*Me*-COO-	-*COO*-Me
3[b]	180.2	36.7	77.9	89.8	74.5	82.0	60.6				
5[c]	174.2	35.5	77.4	85.5	77.0	75.2	61.3		20.3 20.4	169.1 170.2	
7[d]	177.1	36.1	77.1	88.1	73.1	80.8	69.1	63.9			

9^c	174.0	35.7	77.6	85.1	77.6	73.9	67.7	63.1	20.5	169.0 169.5 170.4	
10^d	175.8	35.7	76.8	90.6	75.5	85.8	70.1	62.8			
11^c	174.1	35.7	77.5	86.3	78.2	83.7	69.1	62.2	20.2	169.3 170.1	
12^d	176.5	37.1	76.3	83.8	71.3	80.5	69.8	62.8			
13^c	174.3	36.3	77.9	80.3	77.1	72.9	69.5	62.4	20.3 20.5 20.6	169.9 170.3	
15^c	172.3	35.3	81.6	77.1	76.9	77.8	70.0	62.5	20.3 20.5	169.3 170.0 170.3	
17^c	172.2	36.0	77.7	76.1	72.1	71.6	69.7	62.2	20.0 20.3	169.2 169.3 169.8 170.2	
21^d	171.6	38.2	82.9	79.7	77.2	80.2	71.3	62.6			51.1
22^c	170.3	37.9	81.2	79.7	78.5	80.6	70.0	62.6	20.6	169.9	51.7

[a] At 20.15 MHz, in p.p.m. from Me_4Si; assignments marked* may have to be interchanged.
[b] In D_2O. [c] In $CDCl_3$. [d] In $(CD_3)_2SO$.

*3,6-Anhydro-2-deoxy-*D-ido-*heptono-1,4-lactone* (**3**) *and 2,3-dideoxy-*D-xylo-*hept-2-enono-1,4-lactone* (**4**). — A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (0.36 g, 2.5 mmol), D-xylose (0.37 g, 2.5 mmol), and triethylamine (0.35 mL, 2.5 mmol) in *N,N*-dimethylformamide (3 mL) was heated for 7 days at 46°, then concentrated under diminished pressure. Column chromatography (6:1 chloroform–methanol) of the residue gave, first, **3** (0.24 g, 57%), isolated as a syrup, $[\alpha]_D$ +23°, $[\alpha]_{578}$ +27°, $[\alpha]_{546}$ +27°, $[\alpha]_{436}$ +48° (*c* 0.5, water), R_F 0.46; ν_{max} 3600–3200 (OH) and 1770 cm^{-1} (C=O).

Anal. Calc. for $C_7H_{10}O_5$: C, 48.27; H, 5.78. Found: C, 47.73; H, 5.72.

The diacetate **5** had m.p. 61–62° (from ethanol), $[\alpha]_D$ +59°, $[\alpha]_{578}$ +63°, $[\alpha]_{546}$ +72°, $[\alpha]_{436}$ +122° (*c* 0.5, chloroform); ν_{max} 1770 and 1720 cm^{-1} (C=O).

Anal. Calc. for $C_{11}H_{14}O_7$: C, 51.16; H, 5.46. Found: C, 51.36; H, 5.45.

Eluted second was **4** (0.018 g, 4%), m.p. 126–127° (from ethanol), $[\alpha]_D$ −167°, $[\alpha]_{578}$ −171°, $[\alpha]_{546}$ −193°, $[\alpha]_{436}$ −322° (*c* 0.5, water), R_F 0.24; ν_{max} 3440–3250 (OH), 1730 (C=O), and 1590 cm^{-1} (C=C).

Anal. Calc. for $C_7H_{10}O_5$: C, 48.27; H, 5.78. Found: C, 48.04; H, 5.80.

The triacetate **6** had m.p. 157–158° (from ethanol); ν_{max} 1790, 1780, and 1740 cm^{-1} (C=O).

Anal. Calc. for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 51.86; H, 5.41.

*3,6-Anhydro-2-deoxy-*D-glycero-D-ido-*octono-1,4-lactone* (**7**) *and 2,3-dideoxy-*D-gluco-*oct-2-enono-1,4-lactone* (**8**). — Treatment of D-glucose (0.45 g, 2.5 mmol) as described for D-xylose gave, first, **7** (0.20 g, 40%), m.p. 113–114° (from ethanol), $[\alpha]_D$ +29°, $[\alpha]_{578}$ +29°, $[\alpha]_{546}$ +32°, $[\alpha]_{436}$ +56° (*c* 0.5, water), R_F 0.45; ν_{max} 3500–3300 (OH) and 1780 cm^{-1} (C=O).

Anal. Calc. for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 47.15; H, 6.00.

The triacetate **9** had m.p. 112–113° (from ethanol), $[\alpha]_D$ +75°, $[\alpha]_{578}$ +77°, $[\alpha]_{546}$ +86°, $[\alpha]_{436}$ +149° (*c* 0.5, chloroform); ν_{max} 1790, 1770, 1740, and 1725 cm^{-1} (C=O).

Anal. Calc. for $C_{14}H_{18}O_9$: C, 50.91; H, 5.49. Found: C, 50.89; H, 5.50.

Eluted second was **8** (0.02 g, 4%), m.p. 143–145° (from ethanol), R_F 0.25; ν_{max} 3350–3240 (OH), 1790, 1750 (C=O), and 1595 cm^{-1} (C=C).

Anal. Calc. for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 47.26; H, 6.00.

*3,6-Anhydro-2-deoxy-*D-glycero-L-gluco-*octono-1,4-lactone* (**10**) *and 3,6-anhydro-2-deoxy-*D-glycero-L-altro-*octono-1,4-lactone* (**12**). — Treatment of D-galactose (1.35 g) as described for D-xylose gave, first, **10** (0.7 g, 45%), m.p. 93–94° (from ethanol), $[\alpha]_D$ +27°, $[\alpha]_{578}$ +28°, $[\alpha]_{546}$ +32°, $[\alpha]_{436}$ +54° (*c* 1, water), R_F 0.30; ν_{max} 3500–3200 (OH) and 1755 cm^{-1} (C=O).

Anal. Calc. for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 46.68; H, 5.89.

The triacetate **11** had m.p. 66–67° (from ethanol), $[\alpha]_D$ +77° (*c* 1, chloroform); ν_{max} 1790 and 1730 cm^{-1} (C=O).

Anal. Calc. for $C_{14}H_{18}O_9$: C, 50.91; H, 5.49. Found: C, 50.49; H, 5.27.

Eluted second was **12** (0.10 g, 7%), m.p. 129° (from ethanol), $[\alpha]_D$ −122°, $[\alpha]_{578}$ −126°, $[\alpha]_{546}$ −143°, $[\alpha]_{436}$ −239° (*c* 0.5, water), R_F 0.24; ν_{max} 3600–3200 (OH) and 1775 cm^{-1} (C=O).

Anal. Calc. for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 47.27; H, 5.99.

Triacetate **13**, isolated as a colorless syrup, had $[\alpha]_D$ $-185°$ (c 1, chloroform); ν_{max} 1775 and 1735 cm^{-1} (C=O).

Anal. Calc. for $C_{14}H_{18}O_9$: C, 50.91; H, 5.49. Found: C, 51.00; H, 5.45.

Ammonolysis of **10** *and* **12**. — Ammonia was bubbled for 0.5 h through a methanolic solution containing **10** or **12** (60 mg) at 0°. The solution was kept at 0° for 2 d and then concentrated to a syrup that was acetylated conventionally with acetic anhydride–pyridine to give 4,5,7,8-tetra-*O*-acetyl-3,6-anhydro-2-deoxy-D-*glycero*-L-*gluco*-octonamide (**15**) or 4,5,7,8-tetra-*O*-acetyl-3,6-anhydro-2-deoxy-D-*glycero*-L-*altro*-octonamide (**17**) in quantitative yields as colorless syrups. The ^1H- and ^{13}C-n.m.r. data are given in Tables I–III.

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REFERENCES

1 J. A. Galbis Perez, M. Avalos Gonzalez, J. L. Jimenez Requejo, and J. C. Palacios Albarran, *Carbohydr. Res.*, 124 (1983) c15–c17.
2 M. Avalos Gonzalez, J. L. Jimenez Requejo, J. C. Palacios Albarran, and J. A. Galbis Perez, *Carbohydr. Res.*, 158 (1986) 53–66.
3 A. N. Meldrum, *J. Chem. Soc.*, 93 (1908) 598–601.
4 D. Davidson and S. A. Bernhard, *J. Am. Chem. Soc.*, 70 (1948) 3426–3428.
5 J. A. Galbis Perez, F. Zamora Mata, and P. Turmo Fernandez, *Carbohydr. Res.*, 163 (1987) 132–135.
6 J. A. Galbis Perez, J. C. Palacios Albarran, J. L. Jimenez Requejo, and M. Avalos Gonzalez, *Carbohydr. Res.*, 131 (1984) 71–82.
7 R. M. Davidson, E. White V, S. A. Margolis, and B. Coxon, *Carbohydr. Res.*, 116 (1983) 239–254.
8 H. Fritz, C. Morel, and O. Wacker, *Helv. Chim. Acta*, 51 (1968) 569–576.
9 J. C. Jochims, A. Seeliger, and G. Taigel, *Chem. Ber.*, 100 (1967) 845–854.
10 J. A. Montgomery, *Carbohydr. Res.*, 33 (1974) 184–187.
11 D. Charon and L. Szabo, *J. Chem. Soc., Perkin Trans. 1*, (1973) 1175–1179.
12 P. Jouin, D. Nisato, and B. Castro, Fr. Pat. 2,584,399 (1987); *Chem. Abstr.*, 107 (1987) 78252f.
13 Y. Yamamoto, Y. Morita, and K. Minami, *Chem. Pharm. Bull.*, 34 (1986) 1980–1986.
14 N. K. Kochetkov and B. A. Dmitriev, *Tetrahedron*, 21 (1965) 803–815.
15 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 43 (1978) 2923–2925.