Carbohydrate Research, 69 (1979) 47–54

THE CRYSTAL STRUCTURES OF METHYL 4,6-*O*-(*R*)-BENZYLIDENE-2,3-DI-*O*-METHYL-α-D-GLUCO- AND -β-D-GALACTO-PYRANOSIDE*

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(Received March 20th, 1978; accepted for publication, April 5th, 1978)

ABSTRACT

In the crystal structures of the thermodynamically less-stable (*R*)-diastereoisomers of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-gluco- and -β-D-galactopyranoside, the 2-phenyl-1,3-dioxane ring adopts a chair conformation having the phenyl group in axial orientation.

INTRODUCTION

Base-catalysed reaction of a methyl 2,3-di-*O*-methyl-D-aldohexopyranoside with benzylidene bromide furnishes two diastereoisomeric 4,6-*O*-benzylidene derivatives[2], one of which is also obtained[3,4] by acid-catalysed benzylidenation (*i.e.*, under conditions where thermodynamic control prevails). Depending on the configuration at C-4, the benzylidene acetals will resemble either the *trans*- or *cis*-decalin ring-system. The more-stable (*S*)-benzylidene acetal derived from methyl 2,3-di-*O*-methyl-α-D-glucopyranoside assumes a double-chair conformation **1** with an equatorial phenyl group[4], while that from methyl 2,3-di-*O*-methyl-β-D-galactopyranoside is generally regarded to adopt the "O-inside" conformation **2** with an equatorial phenyl group[4,5]. The conformations **1** and **2** are entirely acceptable when the principles of conformational analysis[6] are applied. It is not quite so obvious what conformation would be adopted by the 2-phenyl-1,3-dioxane ring of the thermodynamically less-stable diastereoisomers of **1** and **2**. Differences in the chemical shifts of the benzylic protons in **1** and **2** and the corresponding (*R*)-diastereoisomers suggested[2] that the 2-phenyl-1,3-dioxane rings in the latter might adopt boat conformations (see **3** and **4**) in chloroform-*d*, thereby reducing unfavourable *syn*-axial interactions associated with an axial phenyl group in a chair conformation. However, recent work by Eliel[7] has shown that the conformational free-energy of a phenyl group at position 2 of a 1,3-dioxane ring is only 3.1 kcal.mol^{-1}, compared with a destabilization of 5.7 kcal.mol^{-1} when a 1,3-dioxane ring adopts a twist-boat conformation[8], indicating that the phenyl group will favour an axial orientation on the chair con-

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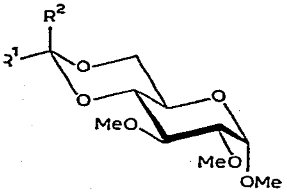
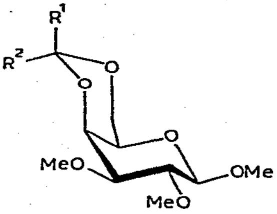
*Stereochemistry of Carbohydrate Derivatives: Part V. For Part IV, see Ref. 1.

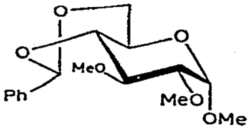
former. Since the conformational free-energies allow a clear-cut decision to be made in favour of the double-chair conformations **5** and **6**, determination of the crystal structures of methyl 4,6-*O*-(*R*)-benzylidene-2,3-di-*O*-methyl-α-D-gluco- and -β-D-galacto-pyranoside should provide evidence in support of these molecular conformations, unless they are unduly distorted by packing forces in the crystals.



1 R^1 = Ph, R^2 = H
5 R^1 = H, R^2 = Ph



2 R^1 = Ph, R^2 = H
6 R^1 = H, R^2 = Ph



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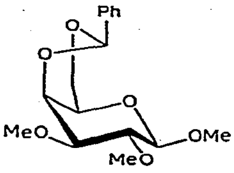

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TABLE I

ATOMIC CO-ORDINATES AND THERMAL PARAMETERS (ALL × 10^4) FOR 5, WITH STANDARD DEVIATIONS IN PARENTHESES

Atom	x/a	y/b	z/c	U/Å²
O-1	4313(9)	1281(5)	5620(18)	39(3)
O-2	3785(9)	2248(5)	7749(24)	65(4)
O-3	1604(9)	2298(5)	6864(19)	54(3)
O-4	903(8)	1360(4)	3908(17)	38(3)
O-5	2997(8)	822(4)	8067(17)	39(3)
O-6	807(10)	434(5)	3711(20)	56(3)
C-1	3765(12)	1260(6)	7951(27)	44(4)
C-2	3146(16)	1808(8)	8115(34)	58(6)
C-3	2219(13)	1840(7)	6070(29)	41(4)
C-4	1558(10)	1357(6)	6230(22)	28(3)
C-5	2290(12)	868(7)	5833(26)	38(4)
C-6	1559(15)	366(8)	5988(34)	57(5)
C-7	253(13)	898(9)	3781(29)	48(4)
C-8	−570(13)	916(8)	6149(29)	46(4)
C-9	−974(14)	401(8)	7001(37)	59(5)
C-10	−1800(15)	409(8)	8970(33)	63(5)
C-11	−2150(16)	924(9)	9953(36)	67(5)
C-12	−1716(21)	1382(11)	8883(46)	79(7)
C-13	−980(13)	1388(7)	7030(30)	47(4)
C-14	5061(20)	813(11)	5553(47)	102(7)
C-15	4574(18)	2310(11)	9961(42)	82(6)
C-16	1738(21)	2796(11)	5195(46)	97(8)

EXPERIMENTAL AND RESULTS

Methyl 4,6-O-(R)-benzylidene-2,3-di-O-methyl-α-D-glucopyranoside[2] (5). — (*a*) *Crystal data.* $C_{16}H_{22}O_6$, $M = 310$, orthorhombic, space group $P2_12_12_1$, $a = 12.78$, $b = 25.15$, $c = 4.95$ Å, $D_c = 1.29$ g.cm^{-3}, $Z = 4$, $F(000) = 664$, $\mu(\text{CuK}\alpha) = 7.3\,\text{cm}^{-1}$.

(*b*) *Data collection.* Data were collected from crystals of moderate quality which grew as needles extended in the *b* direction. Equi-inclination Weisenberg photographs (levels *h*0-2*l* and *hk*0-4) were scanned by using a microdensitometer (S.R.C. Service, Rutherford Laboratory), and 929 reflections were classified as above background.

TABLE II

MOLECULAR DIMENSIONS FOR 5, WITH STANDARD DEVIATIONS IN PARENTHESES

Bond lengths (Å)			
C-1–C-2	1.592(23)	C-1–O-5	1.476(17)
C-2–C-3	1.561(24)	C-1–O-1	1.350(16)
C-3–C-4	1.481(21)	C-2–O-2	1.387(22)
C-4–C-5	1.557(21)	C-3–O-3	1.450(19)
C-5–C-6	1.573(24)	C-4–O-4	1.422(14)
C-7–C-8	1.576(21)	C-5–O-5	1.433(16)
C-8–C-9	1.457(23)	C-6–O-6	1.491(21)
C-9–C-10	1.437(23)	C-7–O-4	1.429(21)
C-10–C-11	1.453(26)	C-7–O-6	1.366(20)
C-11–C-12	1.385(30)	C-14–O-1	1.516(27)
C-12–C-13	1.314(27)	C-15–O-2	1.496(24)
C-8–C-13	1.368(23)	C-16–O-3	1.510(25)
Bond angles (degrees)			
Pyranose ring		*1,3-Dioxane ring*	
O-5–C-1–C-2	108.2(1.2)	O-4–C-4–C-5	104.8(1.0)
C-1–C-2–C-3	112.9(1.4)	C-4–C-5–C-6	105.8(1.1)
C-2–C-3–C-4	110.9(1.3)	C-5–C-6–O-6	104.7(1.3)
C-3–C-4–C-5	107.3(1.1)	O-4–C-7–O-6	113.3(1.3)
C-4–C-5–O-5	110.2(1.1)	C-4–O-4–C-7	114.4(1.2)
C-1–O-5–C-5	109.2(1.1)	C-6–O-6–C-7	114.4(1.2)
Benzene ring		*Angles external to the rings*	
C-9–C-8–C-13	122.8(1.5)	O-1–C-1–C-2	105.5(1.2)
C-8–C-9–C-10	116.4(1.7)	O-5–C-1–O-1	114.0(1.2)
C-9–C-10–C-11	117.8(1.7)	C-1–C-2–O-2	113.1(1.4)
C-10–C-11–C-12	119.4(1.8)	O-2–C-2–C-3	108.7(1.4)
C-11–C-12–C-13	124.2(2.3)	O-3–C-3–C-4	109.1(1.2)
C-8–C-13–C-12	119.3(2.0)	C-2–C-3–O-3	106.1(1.2)
		C-3–C-4–O-4	106.8(1.0)
Methoxyl groups		O-5–C-5–C-6	105.8(1.2)
C-1–O-1–C-14	108.4(1.3)	O-4–C-7–C-8	109.4(1.4)
C-2–O-2–C-15	112.6(1.4)	O-6–C-7–C-8	112.9(1.5)
C-3–O-3–C-16	116.7(1.3)	C-7–C-8–C-9	115.3(1.6)
		C-7–C-8–C-13	121.2(1.7)

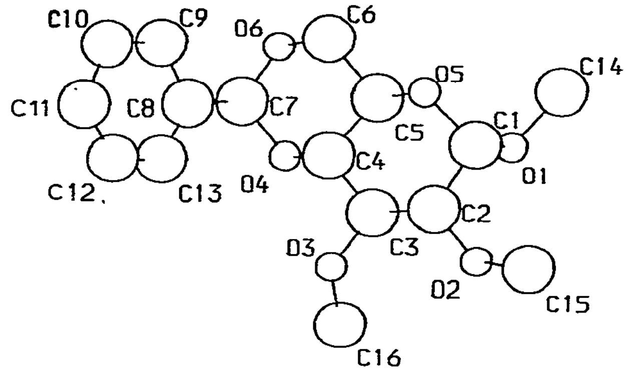

Fig. 1. Projection of methyl 4,6-*O*-(*R*)-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside (5) along the *c*-axis, and the numbering scheme for the atoms.

(*c*) *Structure analysis.* The structure was solved by direct methods after the inclusion of 500 unobserved reflections, which were assigned $F_o = \frac{1}{2}(F_o)_{min}$, in the data set. This revealed all the ring-carbon and ring-oxygen atoms. Successive Fourier syntheses revealed the remaining pendant atoms. During least-squares refinement, with isotropic thermal parameters for all atoms, *R* fell progressively to 0.18. Application of a correction for secondary extinction and the removal of 48 planes for which $|F_c/F_o| \geqslant 1.5$ allowed the refinement to converge at *R* 0.11. The introduction of hydrogen atoms at calculated positions did not improve *R*, while attempts at refinement with anisotropic thermal parameters produced many atoms having non-positive-definite coefficients. All calculations were carried out on the Dundee University DEC 10 computer, using the SHELX 76 program[9].

The numbering system used (see Fig. 1) is such that the carbon atoms of the parent hexose are numbered in the normal carbohydrate convention, and the remaining atoms are numbered arbitrarily.

*Methyl 4,6-*O*-(R)-benzylidene-2,3-di-*O*-methyl-β-D-galactopyranoside*[2] (6). — (*a*) *Crystal data.* $C_{16}H_{22}O_6$, *M* 310, orthorhombic, space group $P2_12_12_1$, $a = 23.17(2)$, $b = 14.26(1)$, $c = 4.819(4)$ Å, $D_c = 1.29$ g.cm^{-3}, $Z = 4$, $F(000) = 664$, $\mu(\text{Cu}K\alpha) = 7.3$ cm^{-1}.

(*b*) *Data collection.* Data were collected, as before, from two crystals, each measuring *ca.* 0.08 × 0.08 × 0.5 mm. The intensities fell off very sharply with increasing θ, and few reflections were apparent beyond $\theta = 40°$. The total number of reflections for measurement was *ca.* 1500, of which 629 were classified as above background.

(*c*) *Structure analysis.* The structure was solved by direct methods (multi-solution tangent formula, 512 initial phase combinations) after the inclusion of 374 unobserved reflections in the data set, and was refined (observed reflections only) by Fourier syntheses to *R* 0.33 and then by several rounds of full-matrix least-squares, with isotropic thermal parameters for all carbon and oxygen atoms, to *R* 0.124. A difference Fourier synthesis then showed a number of weak peaks near the positions

TABLE III

ATOMIC CO-ORDINATES AND THERMAL PARAMETERS (ALL × 10^4) FOR **6**, WITH STANDARD DEVIATIONS IN PARENTHESES

Atom	x/a	y/b	z/c	$U/Å^2$
O-1	159(6)	1780(10)	5186(33)	431(43)
O-2	290(6)	3647(10)	3068(33)	403(42)
O-3	1468(6)	4129(11)	2441(34)	459(46)
O-4	2029(5)	2576(9)	4256(30)	284(38)
O-5	1036(6)	1365(9)	3353(30)	349(38)
O-6	2242(5)	983(10)	4362(34)	372(44)
C-1	558(9)	2062(16)	2995(57)	467(72)
C-2	770(9)	2962(16)	3636(54)	394(63)
C-3	1267(8)	3253(13)	1578(48)	249(53)
C-4	1733(8)	2507(15)	1697(48)	256(53)
C-5	1469(8)	1522(13)	1302(44)	254(55)
C-6	1942(9)	827(15)	1797(50)	355(60)
C-7	2482(9)	1890(15)	4618(54)	427(66)
C-8	2979(9)	2076(17)	2618(51)	391(63)
C-9	3106(10)	2938(18)	1854(55)	484(71)
C-10	3590(10)	3102(20)	137(58)	652(80)
C-11	3907(11)	2341(17)	−931(59)	599(81)
C-12	3787(9)	1450(17)	−107(51)	441(66)
C-13	3299(8)	1244(16)	1674(48)	376(64)
C-14	−137(10)	913(18)	4508(62)	570(78)
C-15	−4(10)	3969(18)	5482(61)	623(82)
C-16	1757(11)	4654(20)	213(69)	710(89)

expected for hydrogen atoms; as these peaks were of similar intensity to the stronger "noise" peaks, hydrogen atoms were included at calculated positions in subsequent cycles of refinement (d_{C-H} 1.07 Å, U_H 0.06). Refinement was terminated at *R* 0.108. The final difference map showed no anomalies. The carbon and oxygen atoms of **6** are numbered in the same way as those of **5**.

DISCUSSION

It can be seen from the stereoviews of methyl 4,6-*O*-(*R*)-benzylidene-2,3-di-*O*-methyl-α-D-gluco- and -β-D-galacto-pyranoside in Figs. 1 and 3, respectively, that both derivatives adopt double-chair conformations which place the phenyl group attached to the 1,3-dioxane ring in an axial orientation. Using the accepted rules for conformation nomenclature[10], the saturated six-membered rings of the α-D-*gluco* derivative are designated as $^4C_1$ and $^{\alpha4}C_{\alpha1}$, while those of the β-D-*galacto* derivative are designated $^4C_1$ and $^{\alpha1}C_{\alpha4}$ (corresponding to the "O-inside" conformation). In both molecules, the plane of the aromatic ring is roughly parallel to one containing the C-4–H-4 and C-6–H-6ax bonds, so that non-bonded interactions between the ortho-hydrogen atoms on the aromatic ring and H-4 and H-6ax are minimized. The

TABLE IV

MOLECULAR DIMENSIONS FOR **6**, WITH STANDARD DEVIATIONS IN PARENTHESES

Bond lengths (Å)			
C-1–C-2	1.408(28)	C-1–O-5	1.497(24)
C-2–C-3	1.575(27)	C-1–O-1	1.460(27)
C-3–C-4	1.517(25)	C-2–O-2	1.505(24)
C-4–C-5	1.544(27)	C-3–O-3	1.396(22)
C-5–C-6	1.497(25)	C-4–O-4	1.415(25)
C-7–C-8	1.524(31)	C-5–O-5	1.426(22)
C-8–C-9	1.317(29)	C-6–O-6	1.436(27)
C-9–C-10	1.412(32)	C-7–O-4	1.445(24)
C-10–C-11	1.408(32)	C-7–O-6	1.414(24)
C-11–C-12	1.361(30)	C-14–O-1	1.452(26)
C-12–C-13	1.449(28)	C-15–O-2	1.424(28)
C-8–C-13	1.471(29)	C-16–O-3	1.471(31)
Bond angles (degrees)			
Pyranose ring		*1,3-Dioxane ring*	
O-5–C-1–C-2	108.9(1.8)	O-4–C-4–C-5	111.3(1.8)
C-1–C-2–C-3	110.9(2.0)	C-4–C-5–C-6	107.0(1.5)
C-2–C-3–C-4	108.2(1.7)	C-5–C-6–O-6	112.9(1.8)
C-3–C-4–C-5	110.6(1.5)	O-4–C-7–O-6	108.8(1.6)
C-4–C-5–O-5	109.7(1.6)	C-4–O-4–C-7	114.3(1.6)
C-1–O-5–C-5	109.6(1.6)	C-6–O-6–C-7	114.1(1.8)
Benzene ring		*Angles external to the rings*	
C-9–C-8–C-13	123.9(2.6)	O-1–C-1–C-2	108.2(2.1)
C-8–C-9–C-10	119.8(2.4)	O-5–C-1–O-1	101.6(1.7)
C-9–C-10–C-11	120.1(2.5)	C-1–C-2–O-2	107.1(1.7)
C-10–C-11–C-12	120.4(2.5)	O-2–C-2–C-3	104.8(1.7)
C-11–C-12–C-13	121.4(2.3)	O-3–C-3–C-4	112.2(1.5)
C-8–C-13–C-12	114.4(2.1)	C-2–C-3–O-3	107.0(1.7)
		C-3–C-4–O-4	109.3(1.8)
Methoxyl groups		O-5–C-5–C-6	107.5(1.7)
C-1–O-1–C-14	111.8(1.8)	O-4–C-7–C-8	110.8(1.8)
C-2–O-2–C-15	114.5(1.7)	O-6–C-7–C-8	113.7(2.0)
C-3–O-3–C-16	113.0(1.9)	C-7–C-8–C-9	120.6(2.2)
		C-7–C-8–C-13	115.9(2.0)

orientation of the aromatic ring in **5** and **6** can be seen in Figs. 2 and 3. Fig. 2 also shows how the molecules of **5** pack in the direction of the *c*-axis. The double-chair conformations **5** and **6** found for the benzylidene acetals bear out the expectation based on thermochemical data obtained with other 2-phenyl-1,3-dioxanes[7]. Interestingly, the conformational free-energy of a phenyl group at C-2 is only 3.1 kcal.mol^{-1} (*cf.* a $-\Delta G^0_{Ph}$ value of 3.0 kcal.mol^{-1} for a phenyl group on a cyclohexane ring[11]) and, somewhat surprisingly, is less than that[7,12] ($-\Delta G^0_{Me}$ 3.97 kcal.mol^{-1}) for a methyl group at C-2. The $-\Delta G^0_{Ph}$ value should be compared with a $\Delta G^0_{C\to TB}$ value of 5.7 kcal.mol^{-1} calculated[8] for the 1,3-dioxane ring. These figures indicate that the double-chair conformations **5** and **6** found in the crystals will persist in

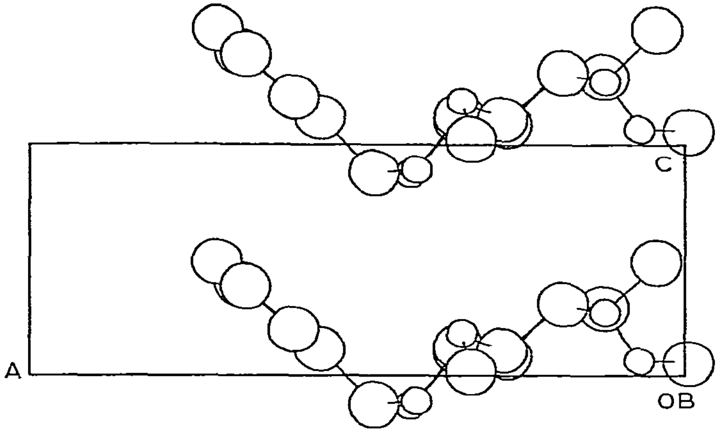

Fig. 2. Projection of methyl 4,6-*O*-(*R*)-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside (5) along the *b*-axis, showing the packing of the molecules in the direction of the *c*-axis.

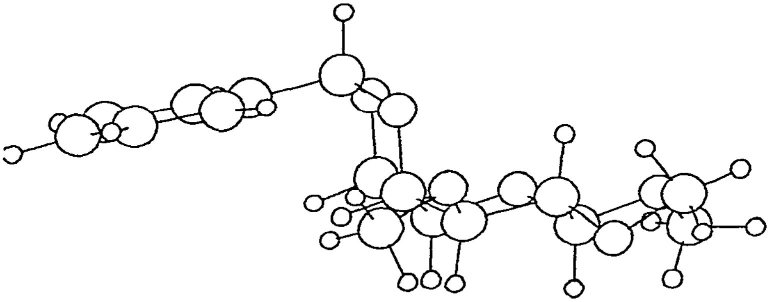

Fig. 3. Projection of methyl 4,6-*O*-(*R*)-benzylidene-2,3-di-*O*-methyl-β-D-galactopyranoside (6) along the *b*-axis; hydrogen atoms are included in calculated positions.

solution, so that the downfield chemical shift of the benzylic protons in the ^{1}H-n.m.r. spectra of the (*R*)-diastereoisomers[2] is associated with these protons moving from an axial position in **1** and **2** to an equatorial position in **5** and **6**, respectively.

ACKNOWLEDGMENTS

We thank the S.R.C. for microdensitometer measurements, and Rod Hanna for skilled experimental assistance.

REFERENCES

1 J. S. Brimacombe, J. Iball, and J. N. Low, *J. Chem. Soc. Perkin Trans. 2*, (1972) 937–942.
2 N. Baggett, J. M. Duxbury, A. B. Foster, and J. M. Webber, *Carbohydr. Res.*, 1 (1965) 22–30.
3 A. B. Foster, in W. Pigman and D. Horton (Eds.), *The Carbohydrates*, Vol. 1A, Academic Press, New York and London, 2nd edition, 1972, pp. 391–402.
4 J. F. Stoddart, *Stereochemistry of Carbohydrates*, Wiley–Interscience, New York, 1971, pp. 215–217.
5 N. Baggett, K. W. Buck, A. B. Foster, and J. M. Webber, *J. Chem. Soc.*, (1965) 3401–3407; J. A. Mills, *Adv. Carbohydr. Chem.*, 10 (1955) 1–53.

6 E. L. ELIEL, N. L. ALLINGER, S. J. ANGYAL, AND G. A. MORRISON, *Conformational Analysis*, Wiley, New York, 1965.
7 E. L. ELIEL, *Pure Appl. Chem.*, 25 (1971) 509–525.
8 K. PIHLAJA AND S. LUOMA, *Acta Chem. Scand.*, 22 (1968) 2401–2414.
9 G. M. SHELDRICK, SHELX 76 Program for Crystal Structure Determination, Cambridge University, 1975.
10 J. C. P. SCHWARZ, *J. Chem. Soc. Perkin Trans. 1*, (1973) 1912 ff.
11 J. A. HIRSCH, in E. L. ELIEL AND N. L. ALLINGER (Eds.), *Topics in Stereochemistry*, Vol. 1, Wiley–Interscience, New York, 1967, p. 199.
12 Ref. 4, p. 188.

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SOME APPLICATIONS OF THE KNOEVENAGEL REACTION IN THE CARBOHYDRATE FIELD

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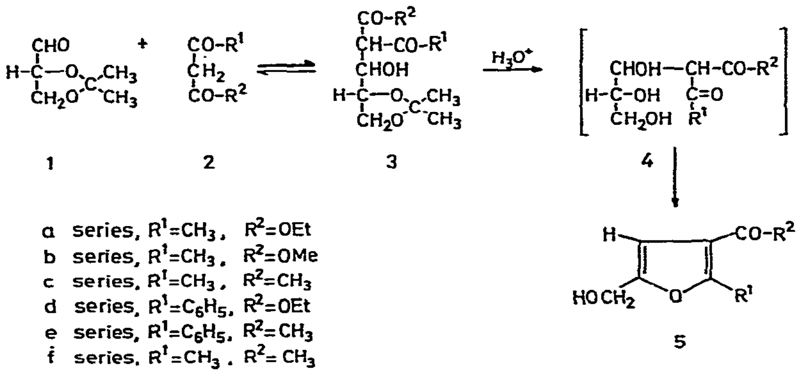
ABSTRACT

The reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**) with active methylene compounds in the absence of a catalyst involves facile and reversible addition to the formyl group. The adducts are readily transformed into furan derivatives by acid hydrolysis. When the reaction is catalysed with piperidine, unsaturated products are also formed, including α,β- and β,γ-unsaturated dicarbonyl compounds, which are transformed into furan derivatives *via* hydrolysis of the acetal group. A new type of unsaturated compound having a spiro-ketal structure is also produced as a result of intramolecular cyclisation.

INTRODUCTION

Application of the Knoevenagel reaction to aldehydo sugars was first described by Papadakis[1] and by Garcia Gonzalez and Lopez Aparicio[2]. The reaction provides a new route for the synthesis of modified sugars[3] and appears to be related to the synthesis of furan compounds from monosaccharides[4]. We now report on other aspects of this reaction.

Only for the reactions of 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**) with ethyl acetoacetate[2] (**2a**) and dibenzoylmethane[3] have the intermediate adducts been



a series, R^1=CH_3, R^2=OEt
b series, R^1=CH_3, R^2=OMe
c series, R^1=CH_3, R^2=CH_3
d series, R^1=C_6H_5, R^2=OEt
e series, R^1=C_6H_5, R^2=CH_3
f series, R^1=CH_3, R^2=CH_3

detected or isolated. In all other cases, either for **1** or for other aldehydo sugars, only α,β-unsaturated products of the type **6** have been described[3]. Some decarboxylation products were obtained when R^1 or R^2 was OH. The identification of **3a** presented a problem, because of the coincidence of its elemental composition with those of the reagents **1** and **2a**; the boiling point was also unexpectedly low.

The reaction of **1** with methyl acetoacetate (**2b**) was therefore studied. With piperidine catalysis, **3b** was formed; **3b** could be isolated and characterised, and its transformation into the furan derivative **5b** monitored by n.m.r. spectroscopy.

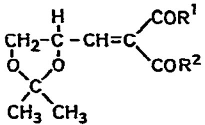
Under conditions of piperidine catalysis, unsaturated products also are always formed. In the reactions of **1** with pentane-2,4-dione (**2c**), ethyl benzoylacetate (**2d**), and benzoylacetone (**2e**), the respective adducts **3c**, **3d**, and **3e** could not be isolated free from contamination by the initial reagents. However, their formation was demonstrated on the basis of spectroscopic data. The failure to remove the contaminants suggested that the reactions were reversible during distillation of the products and that reaction can proceed without a catalyst. The catalyst or high temperature also promotes the dehydration of **3**, to yield such unsaturated compounds as **6** or its isomers. It was demonstrated that the reaction without a catalyst was exothermic and practically quantitative. The absence of the reagents in the mixture after a short reaction time at room temperature was demonstrated by i.r. and n.m.r. spectroscopy.

The transformation of **3a** into **5a** in the presence of pentane-2,4-dione (**2c**) indicated[2] that the formation of **3a** was an irreversible process. But when a mixture of **3b** and **2c** was heated and then hydrolysed with acid, a mixture of **5b** and **5c** was formed. Thus, the earlier conclusions would be explained if the relative velocity of the process **3** → **5** was much greater than that of the process **3** → **2**. A mixture of **5b** and **5c** was also obtained by condensing **3b** and **2c** in the vapour phase, *in vacuo*, and then hydrolysing the product.

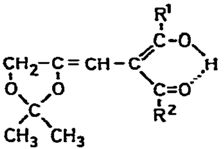
Although the Knoevenagel reaction of **1** with active methylene compounds of type **2** gave products having elemental analyses conforming to formula **6**, it was possible to identify or isolate up to four isomers (**6**–**9**) in various proportions. The complexity of these mixtures may be greater, since *E* and *Z* isomers are possible for some of the unsaturated products. In general, only the more stable isomers could be isolated pure, and the spiro-ketals **9** could be obtained by the action of heat or acid catalysis in an aprotic solvent on the isomers **6**–**8**.

In the reaction of **2c**, isomers **6c** and **7c** were formed, as shown by t.l.c. and spectroscopy. The isomer **8c** was not formed, probably because its stability is much lower than that of the corresponding enol **7c**. The isomerization **6c**→**7c** was accomplished by the action of a partially neutralised, acid resin. Since the spectrum of **7c** is known, that of **6c** could be deduced from a ~1:1 mixture of the compounds. The signals of vinyl protons [δ 6.6 (d, ^3J 6 Hz) for the α,β-unsaturated product **6c**, and 5.3 (t, ^4J 1.2 Hz) for the β,γ-unsaturated isomer **7c** (enol)] were important in the interpretation of the n.m.r. spectra of mixtures.

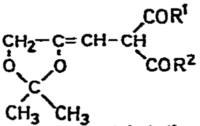
For the reaction of methyl malonate (**2f**), the situation in relation to the enol stability is the opposite of that noted for the enol **7c**. The β,γ-unsaturated diester **8f**



6 (a,b,c,f)

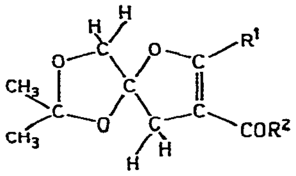


7 (a,b,c)



8 (a,b,f)

	R^1	R^2
a series	$R^1 = CH_3$	$R^2 = OEt$
b	CH_3	OCH_3
c	CH_3	CH_3
d	C_6H_5	OEt
e	C_6H_5	CH_3
f	OCH_3	OCH_3
g	CH_3	C_6H_5
h	CH_3	OH
i	CH_3	Cl
j	CH_3	NH_2
k	C_6H_5	OH

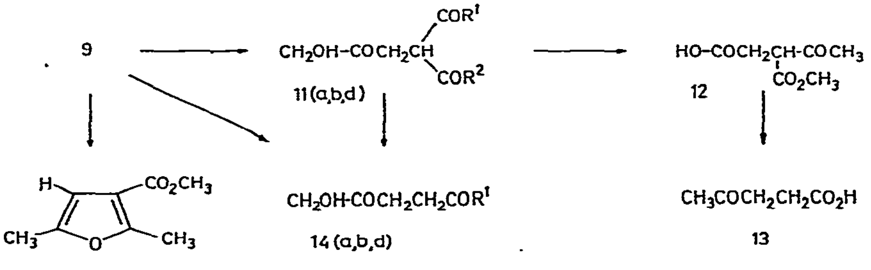


9 (a,b,c,d,e,g,h,i,j,k)

is the stable form and can be isolated. Once the spectrum of **8f** was known [δ 5.0 (dt, ^3J 10, ^4J 1 Hz, $=CH$)], it was possible to deduce that, under mild conditions, the α,β-unsaturated isomer was among the reaction products [δ 6.8 (d, $=CH$)] and must be formed first and then transformed into **7** and **8**.

The reactions of **1** with **2b** and **2a** appear to be intermediate between the above-mentioned cases, on the basis of the relative stability of isomers **7** and **8**. The reaction products were mixtures of four isomers, as shown by n.m.r. spectroscopy. The interpretation of these spectra could be accomplished (*a*) by subtraction of the signals for **9**, (*b*) by using the data for the **c** and **f** series of isomers, and (*c*) by correlating the intensities of sets of signals having the same proportions of components in a mixture. The most-prominent signals associated with this analysis were for Ac (*E*-**6**, δ 2.32–2.34; *Z*-**6**, 2.16–2.28; **8**, 2.13–2.19; **7**, 1.97–2.08) and -CH [**6**, δ 6.82–6.74 (*trans* to -COOR) and 6.70–6.60 (*trans* to Ac); **7** and **8**, 5.3–5.0].

The piperidine-catalysed reactions of **1** and ethyl benzoylacetate (**2d**) or benzoylacetone (**2e**) were exothermic, but the products, after distillation, contained only **9d** and **9e–g**, respectively. Thus, both Ac and Bz groups can participate in ring formation.



	R^1	R^2
a series,	$R^1 = CH_3$	$R^2 = OEt$
b	CH_3	OMe
d	C_6H_5	OEt