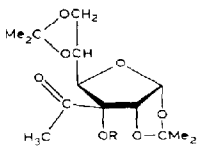
Carbohydrate Research, 123 (1983) 145–152
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

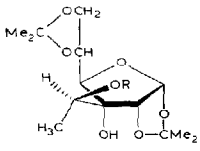
The crystal structure of 3-*C*-[(*R*)-(1-hydroxy-2-phthalimidoethyl)]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose and related studies*

JOHN S. BRIMACOMBE**, RODERICK HANNA, AND TIMOTHY J. R. WEAKLEY
Chemistry Department, Dundee University, Dundee DD1 4HN (Great Britain)
(Received April 11th, 1983; accepted for publication, June 1st, 1983)

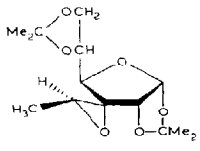
In connection with the synthesis of functionalised branched-chain sugars such as occur in antibiotics, we recently reported[2] the preparation of 3-*C*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**1**), which afforded a crystalline 3-*C*-(1-hydroxyethyl) derivative {m.p. 118–119°, $[\alpha]_D$ +25.5° (chloroform)} on reduction. In related work, Horton and co-workers[3] obtained a separable mixture of the latter compound and its 3^1-epimer {m.p. 97.5-98°, $[\alpha]_D$ +14.3° (chloroform)} by reduction of **2** with lithium aluminium hydride. Neither group attempted to establish the stereochemistry of these compounds at the new asymmetric centre (C-3^1). Based on the X-ray crystallographic analysis of a related compound, we are able to report that the higher-melting diastereoisomer has the *R* configuration (as depicted in formula **3**).



1 R = H
2 R = Ac



3 R = H
4 R = Ms
6 R = Bz



5

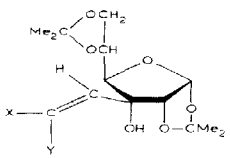
Although **3** and the derived methanesulphonate **4** and $3,3^1$-cyclic carbonate[3] are crystalline, they were not amenable to single-crystal X-ray analysis. In an effort to transform **3** into its crystalline 3^1-epimer[3], **4** was heated with sodium benzoate in

*Branched-chain Sugars, Part XV. For Part XIV, see ref. 1.
**To whom communications should be addressed.

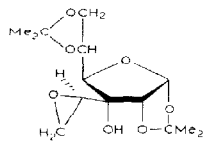
0008-6215/83/$ 03.00

N,N-dimethylformamide, and the resulting benzoate was debenzoylated by transesterification. The product from these reactions was readily identified as **3**, rather than its 3^1-epimer, by comparison with an authentic sample[2]. Presumably, **4** undergoes intramolecular displacement of the methanesulphonyloxy group to form the spiro-oxirane **5**, which, on ring-opening at C-3^1 with the benzoate anion, furnishes **6**. The configuration at C-3^1 is inverted twice in the sequence **4**→**5**→**6** and results in overall retention of the configuration at this centre. Since the intervention of **5** cannot be guaranteed in other nucleophilic displacements on **4**, the stereochemical outcome of these reactions will be uncertain. Therefore, this approach was abandoned.

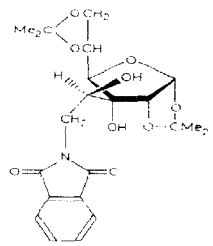
Our quest for a suitable derivative for X-ray crystallographic analysis then shifted to the oxirane **8**, which was obtained in 64% yield by oxidation of 1,2:5,6-di-*O*-isopropylidene-3-*C*-vinyl-α-D-allofuranose[3] (**7**) with *m*-chloroperoxybenzoic acid in 1,2-dichloroethane. Significantly, reduction of **8** with lithium aluminium hydride gave **3**, thereby establishing that these compounds have the same configuration at C-3^1. The crystalline 3-*C*-(1-hydroxy-2-phthalimidoethyl) derivative **9** (21%) was obtained by treatment of **8** with potassium phthalimide in hexamethylphosphoramide at 140°. No attempt was made to optimise the yield of **9**, and, doubtless, our work-up procedure could be improved. On completion of this work, we learned that Kakinuma and co-workers[4] had similarly prepared specifically deuteriated analogues of **9** (*e.g.*, from **10**), which glycol cleavage and oxidation transformed into chiral [2-^{2}H]glycine derivatives of assignable stereochemistry. By consideration of the route used to prepare these chiral glycine derivatives, they were able to deduce[4] that **8** and **9** have the *R* configuration at C-3^1. As can be seen from Fig. 1 and, more clearly, from Fig. 2, this assignment is confirmed by our X-ray crystallographic analysis of **9**. The interatomic distances and bond angles (see Table II) in **9** are unexceptional and require no comment.



7 X = Y = H
10 X = H, Y = ^{2}H



8



9

Since the stereochemical relationship between **9**, **8**, and **3** has been established, the latter compound is identified as 3-*C*-[(*R*)-(1-hydroxyethyl)]-1,2:5,6-di-

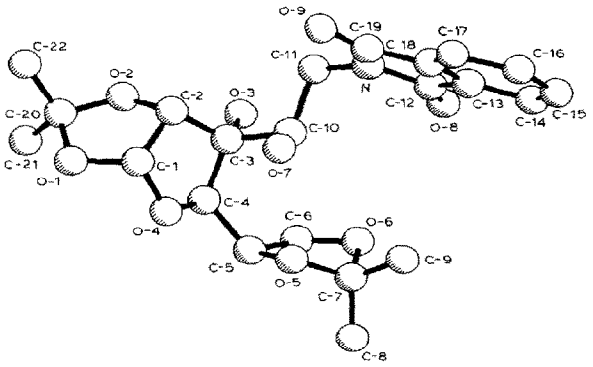


Fig. 1. Stereoview of 3-C-[(*R*)-(1-hydroxy-2-phthalimidoethyl)]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**9**), and the numbering scheme for the atoms.

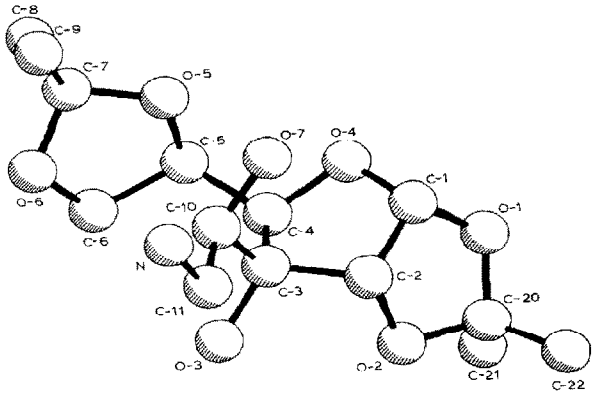


Fig. 2. A more conventional stereoview of **9**; most of the phthalimido group has been omitted, so that the stereochemistry at C-10 (≡C-3[1]) can be seen more clearly.

O-isopropylidene-α-D-allofuranose. The stereochemistry of other compounds[2,3] derived from, or related to, **3** can now be assigned.

EXPERIMENTAL AND RESULTS

General methods. — T.l.c. was performed on Kieselgel G, and detection was effected with 1% sulphuric acid. I.r. spectra were recorded for Nujol mulls with a Perkin–Elmer Infracord spectrometer, and p.m.r. spectra were recorded for solutions in deuteriochloroform (internal tetramethylsilane) by use of a Bruker Spectrospin (90 MHz) spectrometer. Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter. Melting points are uncorrected.

1,2:5,6-Di-O-isopropylidene-3-C-[(R)-1-methanesulphonyloxyethyl]-α-D-allofuranose (**4**). — A solution of **3**[1] (0.15 g, 0.49 mmol) in anhydrous pyridine (5 mL) containing methanesulphonyl chloride (0.327 g, 2.85 mmol) was set aside at room temperature for 3 h and then the excess of the reagent was destroyed by the addition of a few drops of water. The reaction mixture was poured into ice–water, the aqueous solution was extracted with chloroform, and the chloroform solution was processed in the usual way, to give **4** (0.18 g, 95.5%) as fine needles, m.p. 117–119° (from ethyl acetate–hexane), $[\alpha]_D$ +11° (*c* 1.4, chloroform) (Found: C, 46.8; H, 7.1; S, 8.7. $C_{15}H_{26}O_9S$ calc.: C, 47.1; H, 6.85; S, 8.4%). P.m.r. data: δ 5.77 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.27 (q, 1 H, $J_{3',Me}$ 6 Hz, H-3'), 4.56 (d, 1 H, H-2), 4.48–3.82 (4 H, H-4–H-6), 3.07 (s, 3 H, OMs), 1.64 (d, 3 H, Me-3'), and 1.62, 1.47, and 1.42 (3 s, 12 H, ratios 1:1:2, 2 CMe_2).

The benzoate-exchange reaction on the methanesulphonate **4**. — A solution of **4** (0.36 g, 0.94 mmol) in anhydrous *N*,*N*-dimethylformamide (8 mL) containing sodium benzoate (1.4 g, 9.7 mmol) was heated at 140° overnight, whereafter water (80 mL) was added to the cooled solution, and the aqueous solution was extracted with chloroform (3 × 50 mL). Concentration of the chloroform solution under reduced pressure and chromatography of the residue on silica gel (elution with dichloromethane–acetone, 10:1) gave 3-*C*-[(*R*)-(1-benzoyloxyethyl)]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**6**; 0.356 g, 93%), $[\alpha]_D$ −12 ±2° (*c* 1.5, chloroform), as a clear syrup. P.m.r. data: δ 7.78 (m, 5 H, Ph), 5.96 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.64 (q, 1 H, $J_{3',Me}$ 6 Hz, H-3'), 4.72 (d, 1 H, H-2), 4.18–3.78 (4 H, H-4–H-6), 1.51 (d, 3 H, Me-3'), and 1.62, 1.44, and 1.36 (3 s, 12 H, ratios 1:2:1:2 CMe_2).

To a solution of **6** (0.35 g, 0.86 mmol) in anhydrous methanol (10 mL) was added a small piece of sodium, and the mixture was set aside at room temperature for 2 h. Sodium ions were then removed with Amberlite IR-120 (H^+) resin and the solution was concentrated under reduced pressure. An ethereal solution of the residue was decolourised (charcoal) and concentrated under reduced pressure. The residue, which was contaminated with methyl benzoate, crystallised on standing. Recrystallisation from ether–hexane at −4° gave **3** (0.19 g, 73%), m.p. and mixture m.p. 118–119.5°, $[\alpha]_D$ +25° (*c* 1, chloroform), lit.[1] m.p. 118–119°, $[\alpha]_D$ +25.5° (*c* 1, chloroform).

1,2:5,6-Di-O-isopropylidene-3-C-[(R)-oxiran-2-yl]-α-D-allofuranose (**8**). — A solution of 1,2:5,6-di-*O*-isopropylidene-3-*C*-vinyl-α-D-allofuranose[3] (**7**; 2.5 g, 8.7 mmol) and *m*-chloroperoxybenzoic acid (85%; 5.25 g, 25.9 mmol) in 1,2-dichloroethane (87.5 mL) was stirred at room temperature for 70 h and then diluted with dichloromethane (250 mL). The organic solution was washed with 0.1M sodium hydroxide (3 × 300 mL) and water (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution with dichloromethane–acetone, 10:1) gave **8** (1.7 g, 64%), m.p. 92–94° (from hexane), $[\alpha]_D$ +20.5° (*c* 0.5, chloroform) (Found: C, 55.5; H, 7.6. $C_{14}H_{22}O_7$ calc.: C, 55.6; H, 7.3%). P.m.r. data: δ 5.85 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.48 (d, 1 H, H-2), 4.38–3.84 (4 H, H-4–H-6), 3.06 and 2.84 (m, 3 H, H-3^1,3^2), and 1.60, 1.43, and 1.36 (3 s, 12 H, ratios 1:1:2, 2 CMe_2).

3-C-[(R)-(1-Hydroxyethyl)]-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**3**). — A solution of **8** (0.1 g, 0.33 mmol) in anhydrous ether (5 mL) containing lithium aluminium hydride (0.2 g, ~5.3 mmol) was stirred at room temperature for 4 h and then the excess of the reagent was carefully destroyed with moist ethyl acetate. Solids were filtered off and washed thoroughly with ethyl acetate, and the combined filtrate and washings were washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave **3** (75 mg, 74.5%), m.p. 118.5–120° (from ether–hexane), $[\alpha]_D$ +25° (*c* 0.9, chloroform), which was indistinguishable from an authentic sample by the usual criteria; lit.[3] m.p. 118–119°, $[\alpha]_D$ +25.5° (*c* 1, chloroform).

3-C-[(R)-(1-hydroxy-2-phthalimidoethyl)]-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**9**). — A solution of **8** (0.302 g, 1 mmol) in hexamethylphosphoramide (10 mL) containing phthalimide (0.183 g, 1.24 mmol) and potassium phthalimide (0.053 g, 0.29 mmol) was heated at 140° for 23 h and, after cooling, poured into ice–water. The aqueous solution was extracted with chloroform, and the chloroform solution was dried ($MgSO_4$) and concentrated under reduced pressure. A solution of the residue in ether–light petroleum (b.p. 60–80°) (180 mL, 1:1) was washed with water and concentrated under reduced pressure. A solution of the residue in chloroform was washed with 3M sodium hydroxide and water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution with dichloromethane–acetone, 5:1) gave **9** (96.2 mg, 21%), m.p. 151–153° (from ether–hexane), $[\alpha]_D$ +49° (*c* 0.5, chloroform), ν_{max} 1780 and 1725 cm^{-1} (C=O) (Found: C, 58.9; H, 6.0; N, 3.4. $C_{22}H_{27}NO_9$ calc.: C, 58.8; H, 6.05; N, 3.1%); lit.[4] m.p. 150°. This material was used for the following single-crystal X-ray analysis.

(*a*) *Crystal data.* $C_{22}H_{27}NO_9$: M = 449.5, orthorhombic, space group $P2_12_12_1$, a = 24.89(3), b = 15.78(2), c = 5.650(5) Å, volume = 2219 $Å^3$, D_c = 1.35 $g.cm^{-3}$, Z = 4, $F(000)$ = 952, λ (CuKα) = 1.5418 Å, μ_λ (for CuKα) = 7.9 cm^{-1}.

(*b*) *Data collection.* Data were collected from prismatic crystals with prominent {110} faces. Equi-inclination, multi-film Weissenberg photographs (levels *h*0-4*l* and *hk*0-5) were scanned by using a microdensitometer (S.E.R.C. Micro-

densitometer Service, Daresbury Laboratory); because the intensities fell off markedly with increasing θ, only 1065 reflections (out of ~2400 scanned) were classified as statistically significant.

(*c*) *Structure analysis.* The structure was solved, with some difficulty, by direct methods after the inclusion of all unobserved reflections in the data set, with $|F| = 0.2\ |F_o|_{min}$. A molecular fragment containing 16 atoms was located in an *E*-map calculated from 360 reflections with $|E| > 1.4$. Subsequent cycles of tangent refinement located the remaining atoms and permitted the assignment (Table 1) of carbon, nitrogen, and oxygen atoms in the structure. Twelve of the hydrogen atoms were located near their expected positions in a difference Fourier synthesis; in the last cycles of refinement, hydrogen atoms were included at calculated positions (1.05 Å from carbon atoms with $U = U_c$). During full-matrix, least-squares

TABLE 1

FRACTIONAL ATOMIC CO-ORDINATES ($\times 10^4$) AND ISOTROPIC THERMAL PARAMETERS ($\times 10^3$) FOR **9**, WITH STANDARD DEVIATIONS IN PARENTHESES

Atom	x	y	z	*U*
O-1	3549(3)	4660(6)	4949(17)	45(2)
O-2	3961(3)	4942(6)	1442(17)	43(2)
O-3	4941(3)	4404(5)	382(14)	31(2)
O-4	4345(3)	4024(5)	6083(14)	30(2)
O-5	5397(3)	3362(5)	6707(14)	33(2)
O-6	5958(3)	2976(6)	3817(17)	42(2)
O-7	5268(3)	5255(5)	6141(15)	36(2)
O-8	6638(4)	5130(7)	2224(20)	63(3)
O-9	5597(3)	7213(6)	5283(17)	46(2)
N	6002(3)	6087(7)	3420(18)	29(2)
C-1	4098(4)	4784(9)	5485(21)	31(3)
C-2	4355(4)	5131(8)	3262(19)	25(3)
C-3	4840(4)	4564(7)	2838(20)	20(3)
C-4	4657(4)	3743(7)	4053(21)	27(3)
C-5	5050(4)	3065(8)	4861(22)	29(3)
C-6	5433(5)	2769(9)	2916(23)	36(3)
C-7	5899(6)	2979(11)	6333(30)	54(4)
C-8	5933(7)	2104(11)	7281(35)	76(5)
C-9	6328(6)	3523(11)	7386(33)	68(5)
C-10	5351(4)	4938(7)	3782(19)	23(2)
C-11	5547(4)	5695(8)	2310(21)	29(3)
C-12	6520(5)	5732(9)	3410(27)	45(4)
C-13	6838(5)	6214(10)	5102(27)	48(4)
C-14	7372(6)	6098(11)	5709(30)	62(5)
C-15	7565(7)	6674(12)	7441(35)	78(6)
C-16	7247(7)	7300(13)	8452(36)	79(6)
C-17	6702(6)	7380(11)	7725(28)	56(4)
C-18	6517(5)	6835(9)	6088(26)	43(4)
C-19	5986(5)	6762(8)	4951(24)	33(3)
C-20	3450(5)	4893(9)	2535(24)	39(3)
C-21	3175(7)	4141(13)	1501(37)	84(6)
C-22	3151(7)	5677(13)	2305(38)	85(6)

TABLE II

MOLECULAR DIMENSIONS FOR **9**, WITH STANDARD DEVIATIONS IN PARENTHESES

Bond lengths (Å)			
C-1–C-2	1.512(15)	C-20–C-22	1.450(22)
C-2–C-3	1.522(15)	C-1–O-1	1.413(14)
C-3–C-4	1.535(16)	C-1–O-4	1.388(14)
C-3–C-10	1.501(14)	C-2–O-2	1.450(13)
C-4–C-5	1.519(15)	C-3–O-3	1.433(14)
C-5–C-6	1.529(16)	C-4–O-4	1.455(13)
C-7–C-8	1.484(23)	C-5–O-5	1.434(14)
C-7–C-9	1.493(21)	C-6–O-6	1.439(14)
C-10–C-11	1.535(16)	C-7–O-5	1.404(16)
C-12–C-13	1.455(20)	C-7–O-6	1.429(18)
C-13–C-14	1.387(19)	C-10–O-7	1.438(13)
C-13–C-18	1.380(19)	C-12–O-8	1.198(16)
C-14–C-15	1.419(22)	C-19–O-9	1.215(14)
C-15–C-16	1.388(23)	C-20–O-1	1.434(16)
C-16–C-17	1.424(21)	C-20–O-2	1.417(14)
C-17–C-18	1.344(20)	C-11–N	1.435(14)
C-18–C-19	1.476(17)	C-12–N	1.406(15)
C-20–C-21	1.490(22)	C-19–N	1.374(16)
Bond angles (degrees)			
C-1–O-1–C-20	109.5(9)	C-9–C-7–O-5	109.2(13)
C-2–O-2–C-20	108.0(9)	C-9–C-7–O-6	109.0(14)
C-1–O-4–C-4	107.9(8)	C-8–C-7–C-9	110.5(14)
C-5–O-5–C-7	106.7(10)	C-3–C-10–O-7	110.1(9)
C-6–O-6–C-7	105.1(10)	C-11–C-10–O-7	106.1(9)
C-11–N–C-12	123.4(11)	C-3–C-10–C-11	112.5(9)
C-11–N–C-19	125.9(9)	C-10–C-11–N	110.4(9)
C-12–N–C-19	109.8(10)	O-8–C-12–N	122.9(13)
O-1–C-1–O-4	111.2(10)	C-13–C-12–O-8	130.4(13)
C-2–C-1–O-1	106.3(10)	C-13–C-12–N	106.7(12)
C-2–C-1–O-4	109.1(9)	C-12–C-13–C-14	128.0(15)
C-1–C-2–O-2	103.2(8)	C-12–C-13–C-18	108.8(12)
C-3–C-2–O-2	107.7(9)	C-14–C-13–C-18	123.2(15)
C-1–C-2–C-3	104.7(10)	C-13–C-14–C-15	114.3(16)
C-2–C-3–O-3	113.3(9)	C-14–C-15–C-16	123.2(18)
C-4–C-3–O-3	109.6(9)	C-15–C-16–C-17	119.2(18)
C-2–C-3–C-4	101.0(8)	C-16–C-17–C-18	117.9(16)
C-2–C-3–C-10	112.7(9)	C-13–C-18–C-17	122.3(13)
C-4–C-3–C-10	115.1(9)	C-13–C-18–C-19	106.7(12)
C-10–C-3–O-3	105.4(8)	C-17–C-18–C-19	131.0(13)
C-3–C-4–O-4	104.7(9)	O-9–C-19–N	125.1(11)
C-5–C-4–O-4	108.8(9)	C-18–C-19–O-9	127.0(12)
C-3–C-4–C-5	122.5(9)	C-18–C-19–N	107.9(10)
C-4–C-5–O-5	112.1(10)	O-1–C-20–O-2	105.9(9)
C-6–C-5–O-5	104.2(8)	C-21–C-20–O-1	104.4(13)
C-4–C-5–C-6	113.6(10)	C-21–C-20–O-2	106.7(12)
C-5–C-6–O-6	104.1(10)	C-21–C-20–C-22	114.1(13)
O-5–C-7–O-6	104.0(12)	C-22–C-20–O-1	113.1(13)
C-8–C-7–O-5	113.4(13)	C-22–C-20–O-2	112.0(13)
C-8–C-7–O-6	110.5(15)		

refinement, with isotropic thermal parameters for all atoms. R was reduced to 0.084 and R_w to 0.088 {1065 reflections, 129 parameters, and a weighting factor of $w = (1 + 0.00021 F^2)^{-1}$ in the last cycle}. The final difference map showed some evidence of anisotropic thermal motion, but was otherwise featureless. The assignment of anisotropic thermal parameters was precluded by the low ratio of data to parameters. All calculations were carried out on the Dundee University DEC 10 computer using the SHEL-X 76 program[5].

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

ACKNOWLEDGMENTS

We thank the S.E.R.C. Microdensitometer Service for microdensitometer measurements, and J. A. Chudek for recording the p.m.r. spectra.

REFERENCES

1 J. S. BRIMACOMBE, A. S. MENGECH, K. M. M. RAHMAN, AND L. C. N. TUCKER, *Carbohydr. Res.*, 110 (1982) 207–215.
2 J. S. BRIMACOMBE AND A. M. MATHER, *J. Chem. Soc., Perkin Trans. 1*, (1980) 269–272.
3 D. C. BAKER, D. K. BROWN, D. HORTON AND R. G. NICKOL, *Carbohydr. Res.*, 32 (1974) 299–319.
4 K. KAKINUMA, N. IMAMURA AND Y. SAWA, *Tetrahedron Lett.*, (1982) 1697–1700.
5 G. M. SHELDRICK, *SHEL-X 76 Program for Crystal Structure Determination*, Cambridge University, Great Britain, 1975.