Cyclopropylcarbinyl–oxocarbonium † Ions. Part VII.[1] Orientational Effects

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The anomeric 2,3-dideoxy-2,3-*C*-methylene-D-allopyranosides (2α and β) along the with homoallyl iodide (6) comprise a configurationally related cyclopropylcarbinyl–homoallyl system; the 2,3-dideoxy-2,3-*C*-methylene-D-mannopyranosides (7α and β) along with the homoallyl iodide (11) comprise a second, different system. The three members of each system should undergo solvolysis through a common, highly stabilised cyclopropylcarbinyl–oxocarbonium ion [(3) or (8), respectively]. Evidence in support of this is the fact that compounds (2α and β) and (6) are hydrolysed to the same δ-hydroxy-cyclopropanecarbaldehyde (5), presumably formed *via* the related, cyclic hemiacetal (4). A study of the solvolysis of the cyclopropyl compounds (2α and β) and (7α and β) indicates that orientational effects are not important; however, in the case of the homoallyl iodides (6) and (11) an effect is observed.

THE cyclopropylcarbinyl–oxocarbonium ion (1) † has been of interest in this laboratory for the past few years.[2] The ion embodies two highly stabilised sub-units, oxocarbonium [3] and cyclopropylcarbinyl,[4] and a number of monosaccharide derivatives cognate with some of its many resonance contributors have been isolated.[1,5] The study has afforded a highly stereoselective route to α-linked disaccharides in which the conjugated diene (12) [6] is the key reactant.[7] The potential of the procedure has been exemplified with a synthesis of sucrose.[7,8]

(1)

The reactivity of cyclopropylcarbinyl systems is known to depend strongly on orientational factors: they are highly reactive in the bisected, but not in the perpendicular alignment.[9–11] In relation to this concept, compounds (2α), (2β), and (6) would be expected to act as precursors of the ion (3) (Scheme 1), whereas (7α), (7β), and (11) would yield the isomeric species (8) (Scheme 2).

In an attempt to ascertain whether these factors would play any recognisable role in the reactions of compounds (2), (6), (7), and (11), a number of solvolytic studies were carried out. Participation by the cyclopropyl group, the double bond, and the ring oxygen atom was assessed on the basis of (*a*) the products and (*b*) the relative rates of solvolysis, criteria which have been widely used in the study of other ionic systems.[12]

EXPERIMENTAL

M.p.s were determined with a Fischer-Johns apparatus. N.m.r. spectra were recorded with a Varian T-60, HA 100, or HR 220 spectrometer; unless otherwise specified the solvent was deuteriochloroform containing 1% tetramethylsilane as internal standard. I.r. spectra were determined

† In terms of I.U.P.A.C. nomenclature this species is more correctly referred to as cyclopropyl(oxy)methylium.

‡ The use of dotted lines for the two cyclopropane ring bonds of structure (1) is intended to imply that delocalisation of charge in both bonds is significant, although not necessarily equal (L. L. Birladeana, J. Hanafusa, B. Johnson, and S. Winstein, *J. Amer. Chem. Soc.*, 1966, **88**, 2316).

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[11] P. von R. Schleyer and G. W. van Dine, *J. Amer. Chem. Soc.*, 1969, **91**, 5880.

[12] R. Breslow in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1967, p. 261.

with a Beckman IR 5 spectrometer for solutions in chloroform (0.1 mm sodium chloride cells) or liquid films (silver chloride plates). Mass spectra were determined with a Hitachi RMU-6E spectrometer. T.l.c. was performed on glass plates coated (0.3 mm) with silica gel (HF-254; Merck). The chromatograms were viewed first under u.v. light, then exposed to iodine vapour, and finally sprayed with concentrated sulphuric acid. For column chromatography Merck silica gel (0.05—0.20 mm; 70—325 mesh) was used.

Compounds (2α and β),[5] (6),[1] (7α and β),[5] and (11) [1] were prepared as described previously.

Reactions of the Homoallyl Iodides (6) *and* (11).—4,6-O-*Benzylidene*-1,2,3-*trideoxy*-3-C-*iodomethyl*-D-ribo-*hex*-1-*enopyranose* (6).—(i) Compound (6) (0.2 g) was dissolved in dioxan (30 ml) and water (20 ml) and dry freshly prepared silver carbonate (0.5 g) was added, followed with stirring by aqueous silver nitrate (1.0 g in 10 ml). Silver iodide was filtered off and the filtrate was extracted with chloroform. Drying and evaporation of the extract gave 2-(5-*hydroxy*-2-*phenyldihydro*-1,3-*dioxin*-4-*yl*)*cyclopropanecarbaldehyde* (5), giving (0.135 g) a positive Schiff's test m.p. 142.5—144.5° [from benzene–light petroleum (b.p. 60—80°)] $[\alpha]_D^{23}$ −63.9° (*c* 3.10 in $CHCl_3$) (Found: C, 67.6; H, 6.45. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%); $\nu_{max.}$ 2 793, 2 703, and 1 701 cm^{-1}; τ 2.65 (5 H, m, Ph), 4.65 (1 H, s, PhC*H*), 0.38 (1 H, d, *J* 4.0 Hz, CHO), 7.89 [1 H, m, $J_{1.2}$ 9.0, $J_{1.3}$ (*cis*) 8.0, $J_{1.3}$ (*trans*) 5.5 Hz, H-1], 8.25 [1 H, m, $J_{2.4'}$ 9.0, $J_{2.3'}$ (*cis*) 8.0, $J_{2.3}$ (*trans*) 5.5 Hz, H-2], 8.67 (1 H, td, $J_{3.3}$ 5.5 Hz, H-3 *cis* to H-1), 8.44 (1 H, q, H-7 *trans* to H-1), 6.51 (1 H, q, $J_{4',5'}$ 9.5 Hz, H-4'), 6.31 (1 H, td, $J_{5',6'ax}$ 10.0, $J_{5',6'eq}$ 5.0 Hz, H-5), 6.48 (1 H, t, $J_{6',6'}$ 10.5, H-6*ax*), 5.77 (1 H, q, H-6*eq*), and 7.76br [1 H, s, exchangeable in D_2O; τ 5.37 in $(CD_3)_2SO$, OH]. Acetylation shifted the H-5' signal to τ 4.97.

(ii) Compound (6) (0.20 g) was dissolved in a 1 : 1 mixture of dioxan and pH 7.0 buffer and refluxed for 2 h; t.l.c. then indicated the disappearance of (6). Water (20 ml) was added and the solution was extracted with chloroform. The extract was dried and evaporated to give the cyclopropanecarbaldehyde (5) (0.135 g).

(iii) Compound (6) (0.9793 g, 2.74 mmol) was dissolved in dry methanol (75 ml), and silver carbonate (0.5 g) and saturated methanolic silver nitrate (10 ml) were added. Judging from the precipitation of silver iodide, the reaction was complete in seconds, but water (75 ml) was not added until 1 min later. The product was extracted with chloroform (3 × 50 ml). The extract was dried and evaporated to leave crystalline material (0.6851 g, 2.61 mmol, 96%). T.l.c. indicated two components, R_F 0.45 (2β) and 0.38 (2α) [4 : 1 light petroleum (b.p. 35—60°)–ethyl acetate as developing solvent]. The n.m.r. spectrum of the mixture showed that (2α) and (2β) [5] were present in equal amounts. Silica column chromatography with the above-mentioned solvent as eluant yielded compounds (2β) (0.2135 g, 29.8%) and (2α) (0.2632g, 37%).

4,6-O-*Benzylidene*-1,2,3-*trideoxy*-3-C-*iodomethyl*-D-*arabino*-*hex*-1-*enopyranose* (11). (i) Compound (11) (0.02 g) was treated with a solution of silver nitrate (1.0 g) in dioxan (5 ml) and water (5 ml) for 1 h at room temperature. Water was added and the mixture was extracted with chloroform. The extract was dried and evaporated. The n.m.r. spectrum of the product showed the presence of starting material (11), the aldehyde (10), and the previously described diene (12).[1] From the intensities of the olefinic, aldehyde, and PhC*H* signals, the three substances were judged to be present in the ratio 1 : 2 : 2. Compound (10) was not separated but the n.m.r. spectrum of the mixture in the cyclopropyl and aldehydic regions [compounds (11) and (12) do not absorb in these regions] was identical with the spectrum of syrupy (10) obtained from the hydrolysis of (7). Syrupy (10) showed *m/e* 248, $[\alpha]_D^{23}$ −46.1° (*c* 0.83 in $CHCl_3$); τ 2.60 (5 H, m, Ph), 4.53 (1 H, s, PhC*H*), 0.70 (1 H, d, *J* 5.0 Hz, CHO), 7.67—8.97 (4 H, m, H-1, H-2, and 2 × H-3), 6.00—6.70 (3 H, m, H-4', -5', and -6'*ax*), 5.73 (1 H, q, H-6'*eq*), and 7.13br (1 H, s, OH); $\nu_{max.}$ 2 816, 2 703, and 1 701 cm^{-1}.

(ii) Compound (11) (0.02 g), was dissolved in 1 : 1 dioxan–pH 7.0 buffer (10 ml) and refluxed for 20 h. Water was added and the solution was extracted with chloroform. The product was composed of starting material (11) (60%) and the diene (12) [1] (40%). Compound (10) was not detected (n.m.r.)

(iii) Compound (11) was dissolved in methanol (1 ml) and treated with saturated methanolic silver nitrate (10 ml) for 1 h at room temperature. Precipitate formation was much slower than in the case of compound (6). Water was added and the mixture was extracted with chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated to give compound (12) [1] as the only product.

Mixture of compounds (6) *and* (11). A mixture of compounds (6) and (11) (0.5 g; obtained from a Simmons–Smith reaction on methyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranoside) [5] was dissolved in dry methanol (50 ml). Silver carbonate (0.5 g) was added along with saturated methanolic silver nitrate (50 ml). After 1 min vigorous stirring, the reaction was stopped by adding saturated aqueous sodium hydrogen carbonate (50 ml). The precipitated silver salts were filtered off and the filtrate was extracted with chloroform. The extract was dried and evaporated under reduced pressure. The n.m.r. spectrum of the product did not show any evidence of compound (6). The mixture was put on a silica column (100 × 1.8 cm) and eluted with 4 : 1 light petroleum (b.p. 35—60°)–ethyl acetate to give compounds (11) (0.081 g), (2α) (0.013 g), and (2β) (0.091 g). No trace of the diene (12) was detected.

Reactions of 2,3-C-*Methyleneglycosides* (2) *and* (7).—The glycoside (0.2 g) was added to 1 : 1 dioxan–water (pH 6.2) (1 : 1) and refluxed for *ca.* 2 h in the case of (2α) and (2β) or *ca.* 2 min in the case of (7α) and (7β). After completion was verified by t.l.c., water (20 ml) was added and the solutions were extracted with chloroform. The extract was dried and evaporated to give crystalline aldehyde (5) (0.185 g) from (2), and syrupy aldehyde (10) (0.180 g) from (7).

DISCUSSION

Homoallyl Iodides.—In accordance with criterion (*a*) (see Introduction) the extent of double bond participation in the reactions of the homoallyl iodides (6) and (11) was inferred from the nature of the products of solvolysis. A precedent for this approach exists in the reactions of cholesteryl compounds: β-derivatives give rise to cyclopropyl products [13,14] whereas α-derivatives give rise to

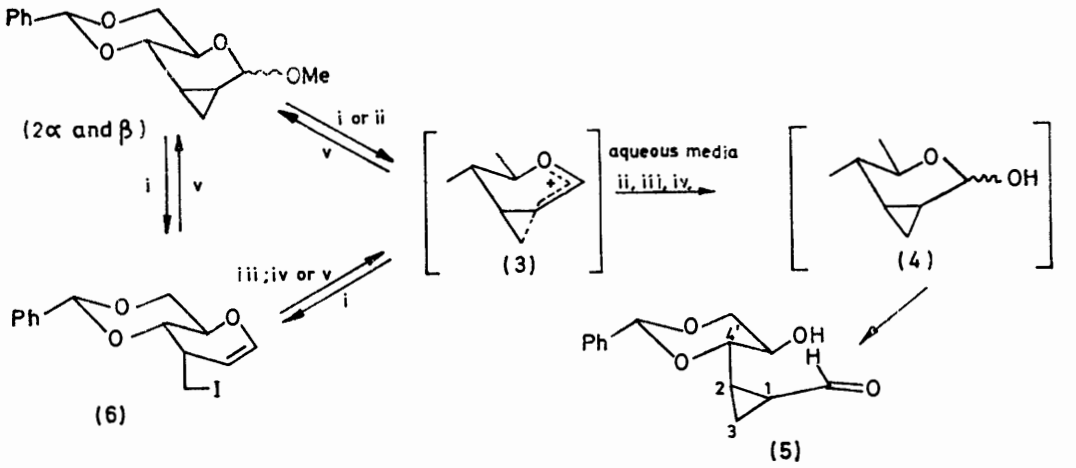
[13] R. H. Davies, S. Meecham, and C. W. Shoppee, *J. Chem. Soc.*, 1955, 629.

[14] S. Winstein and E. M. Kosower, *J. Amer. Chem. Soc.*, (*a*) 1956, **78**, 4347; (*b*) 1959, **81**, 4399.

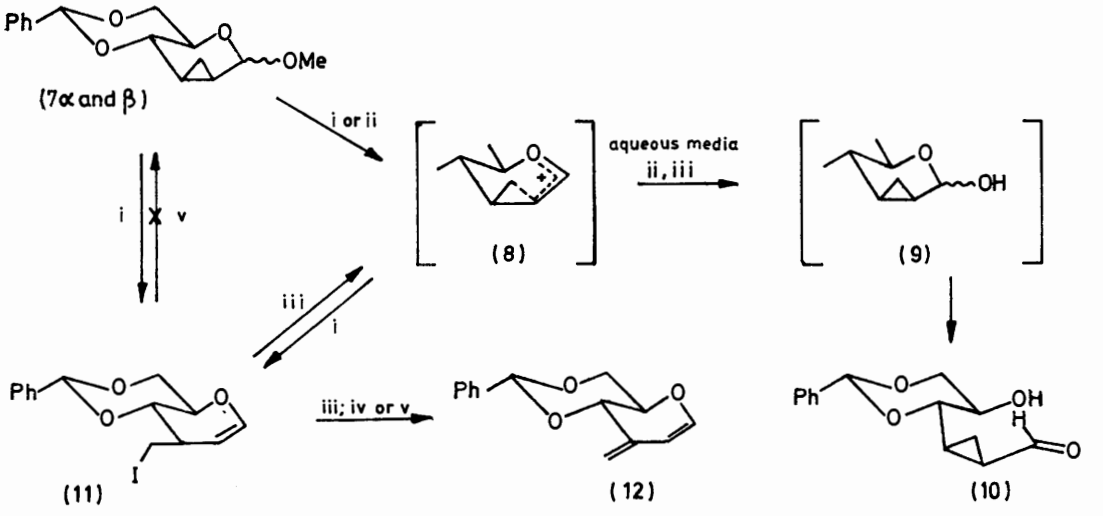
dienes.[15] The rationalisation for this is that in the former, the developing empty *p*-orbital points towards the double bond ($\sigma\pi$-participation), giving intermediates (and frequently products) which are cyclopropyl in character,[13] whereas in α-derivatives the axis of the developing empty *p*-orbital is parallel to the double-bond system ($\pi\pi$-interaction), leading to dienes only.

(10) and (12) (Scheme 2). These results show that the double bond in (6) participates more than the double bond in (11).

Isolation of the acetals (2α) and (2β) in the methanolysis of (6) supports the intermediacy of the hemiacetal (4) in the hydrolysis reactions. The hemiacetal (4) rearranges to the *aldehydo*-form presumably



SCHEME 1 i, Simmons–Smith conditions; ii, aqueous dioxan, reflux, 2 h; iii, aqueous dioxan, Ag^+, 1 min, room temp.; iv, aqueous dioxan (buffer, pH 7), reflux, 2 h; v, methanol, Ag, room temp., 1 min



SCHEME 2 i, Simmons–Smith conditions; ii, aqueous dioxan, reflux, 2 min; iii, aqueous dioxan, Ag^+, 1 h, room temp.; iv, aqueous dioxan (buffer pH 7), reflux, 20 h; v, methanol, Ag^+, room temp., 1 h

It is apparent from models and from analysis of the n.m.r. spectra [16] that (6) approximates to β-cholesteryl whereas (11) approximates to α-cholesteryl. Accordingly, with refluxing dioxan and aqueous pH 7.0 buffer (1 : 1), compound (6) gave cyclopropyl product (5) (Scheme 1), whereas compound (11) gave the diene (12) (Scheme 2). Silver-ion-assisted solvolyses of (6) gave cyclopropyl products (5) or (2) exclusively (Scheme 1), whereas (11) gave either diene (12) only, or a mixture of because of (i) the torsional strain inflicted upon the anomeric centre of this bicyclo[4.1.0]heptane system [17] and (ii) the stabilisation forthcoming from having the cyclopropyl and carbaldehyde groups in conjugation.[18,19]

In relation to criterion (*a*) (see Introduction), the products of the solvolyses imply greater double-bond participation in (6) than (11). In relation to criterion (*b*), the rates provide supporting evidence. Thus solvolyses of (6) were considerably faster than those of

[15] C. W. Shoppee and D. F. Williams, *J. Chem. Soc.*, 1955, 686.
[16] B. Fraser-Reid, B. J. Carthy, and B. Radatus, *Tetrahedron*, 1972, **28**, 2741.
[17] P. von R. Schleyer, *J. Amer. Chem. Soc.*, 1964, **86**, 1854.
[18] R. Hoffman, *Tetrahedron Letters*, 1965, 3819.
[19] R. Hoffman, *Tetrahedron Letters*, 1970, 2907.

(11); for example when a mixture of (6) and (11) was treated with silver ion in methanol for 1 min, only (6) reacted giving (2α and β), (11) being unchanged.

2,3-C-*Methyleneglycopyranosides*.—In the light of criterion (*a*) it is noteworthy that the products from hydrolyses of the 2,3-*C*-methylene glycosides (2) and (7) are all cyclopropanecarbaldehydes [(5) or (10), respectively], the formation of which is discussed above. The ions (3) and (8) therefore show no tendency for cyclopropylcarbinyl rearrangement under these solvolysis conditions.* The question therefore arises as to the extent of cyclopropyl influence in the reactions of (2) and (7). Significant influence is indicated by the ease of hydrolysis of the anomeric acetal group in these compounds as compared with a normal 2,3-dideoxyglycopyranoside, which requires mineral acid catalysis.[20]

General Comparison of Homoallyl Iodides and 2,3-C-*Methyleneglycosides*.—The formation of cyclopropanecarbaldehydes from glycosidic (acetal) as well as homoallylic precursors suggests that both classes of compounds are capable of reacting *via* the same cyclic intermediate ion [(3) or (8)]. Further evidence for the latter is found in the iodinolyses of the 2,3-*C*-methyleneglycosides (2α) and (7β) to homoallyl iodides (6) and (11), respectively.[1] The latter could be formed by iodinolysis of the glycosidic methoxy-group giving the glycosyl iodides, which under the reaction conditions (Simmons–Smith medium) would be expected to rearrange to the more stable homoallyl systems.[4b,†]

What is the nature of the ion (3)? In the first place it is a cyclic oxocarbonium ion (see above), and that it is also a cyclopropylcarbinyl system is indicated by the ease of its formation. The absence of cyclobutyl products implies that ions such as (13) cannot be making a significant contribution. Again, the fact that methanolysis of (6) gives equal amounts of (2α) and (2β) (see Experimental section) means that a bicyclobutane ion such as (14) cannot be involved, since the shielding of the α-face in (14) would preclude the formation of (2α). The formation of the latter by rearrangement of the less thermodynamically stable (2β)[22,23] can also be ruled out since the methanolysis is kinetically controlled. The results of the iodinolysis suggest that the ions (3) and (8) are unsymmetrical, since products cognate with the homoallyl ion (15) were never observed. The foregoing

(13) (14) (15)

results seem to justify our original description of the intermediates in these systems as cyclopropylcarbinyl–oxocarbonium ions.

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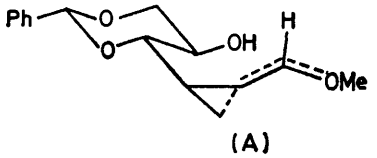
* Attempts to obtain reliable kinetic data were not fruitful owing to the wide variation in rate from one sample to the next. However, it was possible to conclude qualitatively that the *manno*-cyclopropyl compounds (7) were more reactive than the *allo*-analogues (2).

† Since the hydrolysis products of (2) and (7) are acyclic [(5) and (10), respectively], an acyclic intermediate such as (A) could be involved. However, ion (A) cannot be invoked for the interconversion of (2) and (6). Ion (3) has an advantage over (A) in that it can be invoked in the reactions of both cyclic [*e.g.* (2)] and acyclic [*e.g.* (6)] substrates. Furthermore, cyclic



(A)

oxocarbonium ions are currently favoured over acyclic systems as intermediates in the hydrolysis of glycopyranosides.[21]

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[21] J. N. BeMiller and E. R. Doyle, *Carbohydrate Res.*, 1971, **20**, 23.
[22] S. Wolfe, A. Rauk, L. M. Tel, and L. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136.
[23] R. U. Lemieux and N. J. Chu, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, 1958, P 31N.