Unsaturated Carbohydrates. Part XVII.[1] Synthesis of Branched-chain Sugar Derivatives by Application of the Claisen Rearrangement[2]

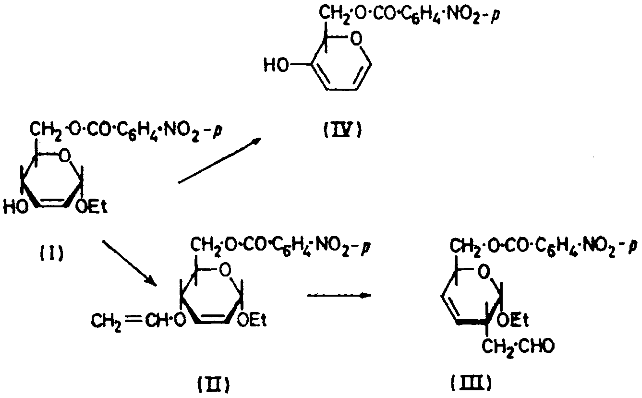
By **Robert J. Ferrier** *† and **Nadarajah Vethaviyasar**, Department of Chemistry, Birkbeck College, University of London, Malet St., London WC1E 7HX

2,3-Dideoxy-4-*O*-vinylhex-2-enopyranoside derivatives on heating to 180° undergo the Claisen rearrangement to give 2,3,4-trideoxy-2-*C*-(formylmethyl)hex-3-enopyranoside isomers. Suprafacial [3,3] sigmatropic processes are involved, so that stereochemical integrity is maintained at the allylic centres. The reaction represents a novel means whereby branch points can be introduced into carbohydrates.

Of the two general types of branched-chain sugars,[3] the ' deoxy ' class in which a hydroxy-group is replaced by a carbon-bonded group, and the ' dehydro ' class in which the carbon function replaces a hydrogen atom, the latter is the more accessible synthetically, usually by application of various addition reactions to carbonyl-containing derivatives.[4] Methods available for the preparation of members of the ' deoxy ' group include (*a*) reactions of sugar epoxides with nucleophilic carbon reagents,[5] (*b*) the Wittig reaction applied to ulose derivatives,[6] and (*c*) the ' oxo ' reaction[7] and other additions to unsaturated carbohydrate derivatives.[8] In addition, ring-contraction reactions which can be applied to certain pyranosyl compounds and which proceed by way of unstable carbonium ions can give furanoside derivatives belonging to the ' deoxy ' branched-chain class;[9] in these cases the generated branching function is the formyl group. Following our work on the isomerisation of allylic azides and thiocyanates in the carbohydrate series,[1] we now report the analogous application of the Claisen rearrangement[10] to the synthesis of ' deoxy ' branched-chain sugar derivatives. The formylmethyl group is the generated branching function, and in these reactions no alteration in ring size takes place. We believe them to be the first examples of the Claisen rearrangement in carbohydrate chemistry, but analogous applications have been described for introducing carbon-containing groups into the steroid nucleus.[11]

Controlled *p*-nitrobenzoylation of ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside afforded some diester but also a crystalline monoester (I) in 60% yield, shown by n.m.r. spectroscopy to have one free hydroxy-group and the C-6 protons deshielded by about 0·5 p.p.m. relative to those of the initial diol. Substitution therefore had taken place as expected at the primary hydroxy site in the same way as preferential benzoylation of methyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside occurs at position 6.[12]

Vinylation of the 6-*p*-nitrobenzoate (I) was effected by the transvinylation process:[13] the ester was treated with ethyl vinyl ether in the presence of mercuric acetate and the ethanol generated was continually removed by codistillation with pentane. A crystalline product was obtained in 30% yield (after chromatography) which had an n.m.r. spectrum indicative of the monovinyl ether structure (II). Heating this ether in nitrobenzene at 185° for 3·5 h caused its complete conversion into a chromatographically distinguishable product which, after isolation, was shown to have reducing



(IV) (I) (II) (III)

---

† *Present address:* Department of Chemistry, Victoria University of Wellington, New Zealand.

[1] Part XVI, R. J. Ferrier and N. Vethaviyasar, *J. Chem. Soc.* (*C*), 1971, 1907.

[2] Preliminary communication, R. J. Ferrier and N. Vethaviyasar, *Chem. Comm.*, 1970, 1385.

[3] F. Shafizadeh, *Adv. Carbohydrate Chem.*, 1956, **11**, 263; W. G. Overend, *Chem. and Ind.*, 1963, 342; J. S. Brimacombe, *Angew. Chem. Internat. Edn.*, 1969, **8**, 401; H. Grisebach and R. Schmid, *ibid.*, 1972, **11**, 159.

[4] R. F. Butterworth and S. Hanessian, *Synthesis*, 1971, 70.

[5] B. E. Davison, R. D. Guthrie, and A. T. McPhail, *Chem. Comm.*, 1968, 1273; M. Sharma and R. K. Brown, *Canad. J. Chem.*, 1968, **46**, 757; T. D. Inch and G. J. Lewis, *Carbohydrate Res.*, 1970, **15**, 1; N. R. Williams, *Chem. Comm.*, 1967, 1012.

[6] A. Rosenthal and P. Catsoulacos, *Canad. J. Chem.*, 1968, **46**, 2868; A. Rosenthal and M. Sprinzl, *ibid.*, 1969, **47**, 3941; A. Rosenthal and D. A. Baker, *Tetrahedron Letters*, 1969, 397; J. M. J. Tronchet and J. M. Bourgeois, *Helv. Chim. Acta*, 1970, **53**, 1463.

[7] A. Rosenthal and H. J. Koch, *J. Amer. Chem. Soc.*, 1968, **90**, 2181; A Rosenthal, *Adv. Carbohydrate Chem.*, 1968, **23**, 59.

[8] (*a*) R. J. Ferrier, *Adv. Carbohydrate Chem.*, 1969, **24**, 199; (*b*) R. F. Butterworth, W. G. Overend, and N. R. Williams, *Tetrahedron Letters*, 1968, 3239.

[9] P. W. Austin, J. G. Buchanan, and R. M. Saunders, *J. Chem. Soc.* (*C*), 1967, 372; E. J. Reist, D. F. Caldins, and L. Goodman, *J. Amer. Chem. Soc.*, 1968, **90**, 3852.

[10] (*a*) A. Jefferson and F. Scheinmann, *Quart. Rev.*, 1968, **22**, 391; (*b*) S. J. Rhoads in ' Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1963, p. 655.

[11] M. Torigoe and J. Fishman, *Tetrahedron Letters*, 1963, 1251.

[12] B. Fraser-Reid and B. Boctor, *Canad. J. Chem.*, 1969, **47**, 393.

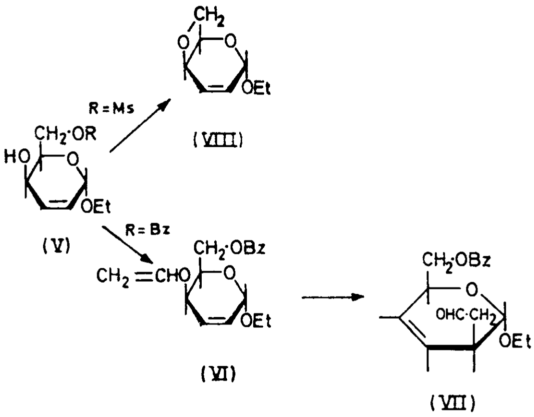
[13] W. H. Watanabe and L. E. Conlon, *J. Amer. Chem. Soc.*, 1957, **79**, 2828.

properties and a one-proton n.m.r. resonance at δ 9·8 characteristic of an aldehyde group. In addition the n.m.r. spectrum showed signals for only two vinylic protons (δ 5·76) and three protons resonating at high field (1 proton, δ 3·0; 2 protons, δ 2·6) which are assigned respectively to 2-H and the exocyclic methylene group attached to C-2 of compound (III). The anomeric proton resonated (δ 5·06) as a doublet ($J_{1,2}$ 3·7 Hz) which collapsed to a singlet on irradiation at δ 3·0. This is consistent with the assigned structure; in particular the coupling constant is diagnostic of a 3,4-unsaturated compound with the α-*erythro*-configuration.[1] Furthermore, the laevorotatory nature of the aldehyde is in agreement with this configuration;[1] indeed a suprafacial [3,3] sigmatropic shift would have been expected to give this product for theoretical reasons,[10a,14] and in view of findings during the application of the Claisen rearrangement to related cyclic systems.[15] From the syrupy aldehyde (III) a crystalline 2,4-dinitrophenylhydrazone was obtained.

In the mass spectrum of the vinyl ether (II) an ion was observed at m/e 140 $(M - \mathrm{OHC{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}C_6H_4{\cdot}NO_2})^{\cdot+}$ which arose by retrodienic cleavage of the hex-2-enopyranoside;[16] no ion at m/e 275 $(M - \mathrm{HCO_2Et})^{\cdot+}$ was observed as would have been expected for a 3-ene. In contrast, an ion with m/e 275 was apparent in the spectrum of the aldehyde (III) and there was no ion with m/e 140. This confirms that the isomerisation proceeded with rearrangement of the allylic system.

As well as compound (II), vinylation of the *p*-nitrobenzoate (I) gave a second crystalline product (20%), which was shown by n.m.r. spectroscopy to contain one *p*-nitrobenzoyl group, one exchangeable hydrogen atom, and no ethyl groups. Elemental analysis confirmed that this compound had been formed by elimination of ethanol from the starting material (I), and mass spectrometry indicated that no ring contraction of the kind that is prevalent with pyran derivatives [8a,17] had occurred. This by-product was identified as 3-hydroxy-2-(*p*-nitrobenzoyloxymethyl)-2*H*-pyran (IV). Splitting of the methylene n.m.r. resonance revealed the presence of a proton at C-2, and loss of the C-2 substituent to give an ion with m/e 97 indicative of a pyranol system suggests that no change in ring size had occurred. No peak at m/e 67 corresponding to a furan radical ion was observed.

A related sequence of reactions was carried out in the *threo*-series to establish a synthesis of compounds with the alternative configuration at the branch-point. Treatment of ethyl 2,3-dideoxy-6-*O*-methylsulphonyl-α-D-*threo*-hex-2-enopyranoside (obtained in the course of the work with azides and thiocyanates [1]) with sodium benzoate in *NN*-dimethylformamide gave the corresponding 6-benzoate (V; R = Bz). This ester was vinylated with n-butyl vinyl ether, which allows the transvinylation to be carried out at higher temperatures than can readily be used with the ethyl analogue, and the product (VI) was rearranged by heating in nitrobenzene at 180° for only 0·6 h. As with the azides and thiocyanates,[1] the *threo*-compound, which possesses a quasi-axial migrating group, proved to isomerise more rapidly than did the *erythro*-analogue; this is consistent with the reactions proceeding by way of cyclic transition states.[1] The crystalline product of rearrangement (VII), as is to be expected for a 3,4-unsaturated *threo*-compound,[1] is dextrorotatory, and its n.m.r. spectrum is entirely as expected: (*a*) aldehydic (δ 9·8), phenyl, vinylic (δ 5·87), anomeric proton (δ 4·78), and ethyl resonances were all clearly apparent as were the resonances for 5-H, 6-H, 6′-H, and the high-field signals for hydrogen and methylene groups attached to C-2 (δ 2·6, unresolved), (*b*) the 1-H signal appeared as a broadened singlet,[1] (*c*) 1-H resonated upfield of the corresponding resonance of the *erythro*-analogue,[1] (*d*) the vinylic proton signals appeared downfield of the equivalent resonances in compound (III),[1] and (*e*), the 2-H signal appeared upfield of the 2-H signal of the *erythro*-compound (III).[1]



The mass spectrum was consistent with the assigned 3,4-unsaturated structure: an ion m/e 230 $(M - \mathrm{HCO_2Et})^{\cdot+}$ was present in the spectrum whereas no ion m/e 140 $(M - \mathrm{OHC{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}C_6H_5})^{\cdot+}$ was detected.

During work in the *threo*-series ethyl 2,3-dideoxy-6-*O*-methylsulphonyl-α-D-*threo*-hex-2-enopyranoside (V; R = Ms) was treated with sodium hydride in anhydrous ether with the intention of generating the alkoxide derivative, which we expected could then be allylated. However, instead of the allyl ether being produced, an anhydride $[\alpha]_D$ −25°, believed to be ethyl 4,6-anhydro-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (VIII), was formed, presumably by an intramolecular nucleophilic displacement. Such 4,6-anhydrides are unusual but are not unknown;[18] oxetan rings are, however, more

---

[14] G. B. Gill, *Quart. Rev.*, 1968, **22**, 338.

[15] R. K. Hill and A. G. Edwards, *Tetrahedron Letters*, 1964, 3239.

[16] R. J. Ferrier, N. Vethaviyasar, O. S. Chizhov, V. I. Kadentsev, and B. M. Zolotarev, *Carbohydrate Res.*, 1970, **13**, 269.

[17] M. Katsuhara, S. Wakahara, and K. Tokuyama, *Bull. Chem. Soc. Japan*, 1968, **41**, 1208.

[18] G. Hanisch and G. Henseke, *Chem. Ber.*, 1968, **101**, 4170.

often encountered fused to furanoid systems.[19] The n.m.r. spectrum was consistent with the assigned structure and irradiation at the frequency of the vinylic protons (δ 6·14) caused collapse of the 1-H signal (δ 5·14, $J_{1,2}$ 3 Hz). The mass spectrum showed a molecular ion (*m/e* 156), a series of ions derived by initial loss of ·OEt, and a series derived from retrodienic ring opening which indicated that the double bond was at the assigned 2,3-position.

EXPERIMENTAL

N.m.r. spectra were measured for solutions in deuteriochloroform with tetramethylsilane as internal reference. Optical rotations were measured for solutions in chloroform (*c* 1 ± 0·5%). All reactions were monitored by t.l.c.

Ethyl 2,3-*Dideoxy*-6-O-p-*nitrobenzoyl*-α-D-erythro-*hex*-2-*enopyranoside* (I).—*p*-Nitrobenzoyl chloride (6·16 g, 0·58 mol. equiv.) in pyridine (100 ml) at 0° was added slowly to a solution of ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (10 g) in pyridine (15 ml). After 1 h the mixture was poured over ice to give a precipitate (2·9 g, 18%) of the 4,6-*diester*, m.p. 125°, $[\alpha]_D$ 169° (Found: C, 55·6; H, 4·4; N, 5·1. $C_{22}H_{20}N_2O_{10}$ requires C, 55·9; H, 4·2; N, 5·9%). The n.m.r. spectrum indicated the presence of two ester groups and the i.r. spectrum revealed the absence of hydroxy-groups.

After removal of the diester the solution was extracted with methylene dichloride. The organic phase was dried (Na_2SO_4) and evaporated to give a syrup which crystallised on trituration with ethanol. Recrystallisation from the same solvent gave the 6-*monoester* (6·7 g, 60%), m.p. 89—90°, $[\alpha]_D$ +7° (Found: C, 55·3; H, 5·2; N, 4·0. $C_{15}H_{17}NO_7$ requires C, 55·7; H, 5·3; N, 4·3%).

Ethyl 2,3-*Dideoxy*-6-O-p-*nitrobenzoyl*-4-O-*vinyl*-α-D-erythro-*hex*-2-*enopyranoside* (II).—The 6-nitrobenzoate (3·0 g) in dry ethyl vinyl ether (20 ml) was heated under reflux in the presence of mercuric acetate (0·5 g) for 24 h. At intervals of 8 h n-pentane (15 ml) was added and was removed (together with the ethanol azeotrope) by fractional distillation. The solvent was then removed and the residual syrupy mixture of starting material and products was fractionated on a column of silica gel. Recrystallisation of the main product from ethyl vinyl ether gave the 4-*vinyl ether* (0·95 g, 30%), m.p. 65—66°, $[\alpha]_D$ +100° (Found: C, 58·1; H, 5·5; N, 4·0. $C_{17}H_{19}NO_7$ requires C, 58·4; H, 5·4; N, 4·0%).

A second crystalline fraction obtained from the column gave 2-(*p-nitrobenzoyloxymethyl*)-2H-*pyran*-3-*ol* (IV) (0·48 g, 20%), m.p. 119° (from ethanol), $[\alpha]_D$ +7° (Found: C, 56·5; H, 4·2; N, 5·0. $C_{13}H_{11}NO_6$ requires C, 56·3; H, 4·0; N, 5·1%). $\nu_{max.}$ 3400 (OH) and 1750 (CO) cm^{-1}; δ 7·45 (6-H), 6·40 (4-H, 5-H), 5·18 (t, *J* 5 Hz, 2-H), and 4·7 (d, CH_2).

Ethyl 2,3,4-*Trideoxy*-2-C-(*formylmethyl*)-6-O-p-*nitrobenzoyl*-α-D-erythro-*hex*-3-*enopyranoside* 2,4-*Dinitrophenylhydrazone*.—Heating the vinyl ether (II) (0·2 g) in nitrobenzene (10 ml) at 185° for 3·5 h caused its conversion into a chromatographically less mobile product and darkening of the solution. The solvent was removed under reduced pressure and the residual dark syrup was purified on a column of silica gel to afford the pure (t.l.c.) *erythro*-branched-chain unsaturated glycoside (III) (0·15 g, 75%), $[\alpha]_D$ −17°, which reduced Fehling's solution and Tollens' reagent and gave an appropriate n.m.r. spectrum.

To the foregoing aldehyde (0·1 g) in ethanol (5 ml) was added 2,4-dinitrophenylhydrazine (0·06 g) in acetic acid (5 ml). Cooling and the addition of a small volume of water gave an orange precipitate which, on purification on a column of silica gel, gave the 2,4-*dinitrophenylhydrazone* (0·11 g, 67%), m.p. 125—126° (Found: C, 51·4; H, 4·6; N, 13·1. $C_{23}H_{23}N_5O_{10}$ requires C, 52·2; H, 4·4; N, 13·2%).

Ethyl 6-O-*Benzoyl*-2,3-*dideoxy*-α-D-threo-*hex*-2-*enopyranoside* (V; R = Bz).—Ethyl 2,3-dideoxy-6-*O*-methylsulphonyl-α-D-*threo*-hex-2-enopyranoside (2 g) was heated with stirring with sodium benzoate (0·5 g) in *NN*-dimethylformamide (20 ml) at 120° for 2 h. The mixture was poured over ice; crystallisation of the solid which separated gave the 6-*benzoate* (1·12 g, 51%), m.p. 115—116° (from ethanol), $[\alpha]_D$ −61° (Found: C, 64·4; H, 6·3. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%).

Ethyl 6-O-*Benzoyl*-2,3,4-*trideoxy*-2-C-(*formylmethyl*)-α-D-threo-*hex*-3-*enopyranoside* (VII).—The monobenzoate (1 g) was heated under reflux in n-butyl vinyl ether (15 ml) for 24 h in the presence of mercuric acetate (0·5 g). After removal of the solvent the products were fractionated on a column of silica gel and the fast-moving vinyl ether (VI) was isolated as a chromatographically pure syrup (0·32 g, 29%), $[\alpha]_D$ −122°, which gave an n.m.r. spectrum consistent with the allocated structure. The *threo*-vinyl ether (0·1 g) was heated in nitrobenzene (10 ml) at 180° for 0·6 h; the solvent was then removed and the residue was crystallised from n-butyl vinyl ether to give the threo-3,4-*unsaturated branched-chain glycoside* (0·07 g, 70%), m.p. 54—55°, $[\alpha]_D$ +50° (Found: C, 66·8; H, 6·5. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%). The product reduced Fehling's solution and gave an n.m.r. spectrum consistent with the assigned structure.

We thank Professor W. G. Overend for his encouragement.

[3/399 *Received*, 21*st February*, 1973]

---

[19] L. Hough and B. A. Otter, *Carbohydrate Res.*, 1967, **4**, 126.