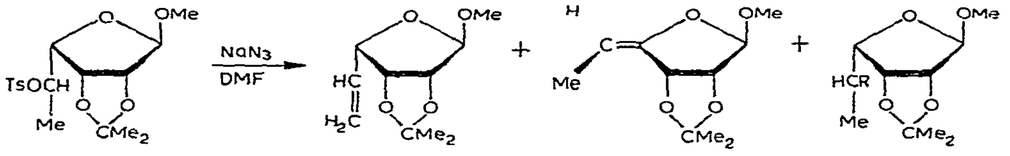
Carbohydrate Research, 31 (1973) 146–150

Note

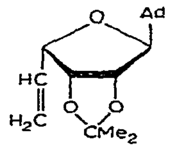
Nucleophilic displacement reactions in carbohydrates
Part XXI[1]. Displacements with methyl 2,3-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-L-rhamnofuranoside

John S Brimacombe, Jonathan Minshall, and Leslie C N Tucker
Chemistry Department, The University, Dundee DD1 4HN (Great Britain)
(Received June 12th, 1973, accepted for publication, July 2nd, 1973)

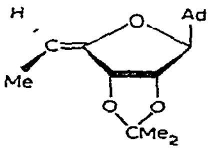
It is apparent that methyl 2,3-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-L-rhamnofuranoside (1) and related compounds do not readily undergo nucleophilic displacements For example, on treatment with fluoride ion (utilizing tetra-*n*-butylammonium fluoride), **1** afforded[2] the unsaturated derivatives methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hex-5-enofuranoside (2) and methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranoside (3) in yields totalling 83% From the physical constants of pure samples of **2** and **3** recovered from this reaction, it was concluded that both of these unsaturated sugars, rather than a single isomer, were probably obtained in earlier work[3 4] in which the sulphonate **1** was solvolyzed with aqueous, methanolic potassium hydroxide Recently, a benzoate displacement on 9-(2,3-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-L-rhamnofuranosyl)adenine has been shown[5] to yield the unsaturated sugar nucleosides **5** (minor) and **6** (major), without formation of significant amounts of the required benzoate By contrast, the reaction of sodium benzoate in *N*,*N*-dimethylformamide with the sulphonate **1**



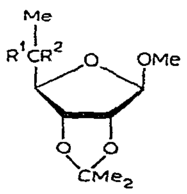
1 2 3
4 R = N_3
7 R = NH_2
8 R = OH



5



6



9 R^1 = OTs, R^2 = H
10 R^1 = H, R^2 = OTs

appeared to give[6] methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (no yield specified), as well as minor amounts (~10%) of an unsaturated sugar indicated to be **3**.

Our interest in the deamination of amino sugars led us to prepare methyl 5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**7**) by way of an azide displacement on the sulphonate **1** in *N*,*N*-dimethylformamide at 140° We now describe the results of this and related displacements

Careful chromatography of the products of the azide displacement gave **2** (21%)[*], **3** (19%), and the major product, methyl 5-azido-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**4**) (60%) The unsaturated sugars **2** and **3** have been thoroughly characterized[2] by Haines and Chaves O , and the physical properties and n m r and mass-spectral characteristics of our unsaturated compounds were in excellent agreement with reported data The structure assigned to the azide **4** was based on elemental analyses, n m r spectroscopy (see Experimental), and the appearance of a characteristic absorption at 2100 cm^{-1} (N_3) in the infrared spectrum The stereochemical requirements of this S_N2 displacement ensure that introduction of the azido group at C-5 is accompanied by inversion of configuration at this centre

It is clear that, even with such a highly nucleophilic, but weakly basic, species as azide ion, there is a tendency for the sulphonate **1** to undergo elimination reactions, although the amounts (40%) of elimination products are substantially less than those (83%) obtained[2] with the more-basic fluoride ion From these results, it would be expected that treatment of **1** with benzoate ion, which has a lower nucleophilicity and a higher basicity than azide ion, would also produce substantial proportions of elimination products Repetition of the original displacement[6] on **1** with benzoate ion in *N*,*N*-dimethylformamide showed this to be so, since, after debenzoylation, the proportions of products obtained were **2** (49 7%), **3** (35%), and methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside[6a] (**8**) (15 2%) In this experiment, identification of the products was achieved by g l c comparison with authentic materials The combined yield of unsaturated sugars is 84 7%, which is in keeping both with expectation and with the results of the benzoate displacement on related nucleoside derivatives[5] mentioned earlier.

Reduction of the azide **4** with lithium aluminium hydride in ether gave methyl 5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**7**), which was deaminated with sodium nitrite in 90% acetic acid solution. At least seven products were formed, but the major product (~49%) was identified as the terminal, unsaturated sugar **2**. Significantly, the internal olefin **3** was not formed, and we have noted[7] previously that both methyl 5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-α-L-talo- and -β-D-allo-furanosides yield exclusively the corresponding terminal olefin when deaminated Deaminative procedures thus offer useful, alternative means of preparing such terminal, unsaturated sugars as **2**

The behaviour of sulphonate **1** towards nucleophiles is in striking contrast to,

---

[*] The proportions of products were obtained by g.l c , using a Honeywell precision integrator

those of methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-β-D-allo- and -α-L-talofuranosides (**9** and **10**, respectively)[7,8], which predominantly undergo displacement reactions It seems that the disposition of the C-5 sulphonyloxy group in relation to the trioxabicyclo[3 3 0]octane ring-system (*i e* the configuration at C-4) is critical for a successful displacement reaction Presumably, the bicyclic ring-system of **1** imposes some form of steric constraint, either on the approach of nucleophiles to the sulphonyloxy group and/or to the departure of the sulphonyloxy anion in S_N2 or related processes*

EXPERIMENTAL

Thin-layer chromatography (t l c) was performed on Kieselgel G, and detection was effected with vanillin–sulphuric acid[9]. N m r spectra were obtained at 60 MHz with a Perkin–Elmer R-10 spectrometer, for deuteriochloroform solutions with tetramethylsilane as internal reference, infrared spectra were recorded on a Perkin–Elmer Infracord spectrometer Gas–liquid chromatography (g l c) was performed on a Pye 104 chromatograph, using a column of 25% silicone gum on Celite at 150° and an operating nitrogen pressure of 7 p s i Evaporations were performed *in vacuo* at ~40° Light petroleum refers to the fraction having b p 60–80°

*Treatment of methyl 2,3-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-L-rhamnofuranoside* (**1**) *with sodium azide* — A solution of the sulphonate[10] **1** (4 1 g) in dry *N*,*N*-dimethylformamide (40 ml) containing sodium azide (4 1 g) was heated for 5 h at 140°, after which time t l c (light petroleum–ether, 5.1) showed that no starting material remained Water (50 ml) was added, the aqueous solution was thoroughly extracted with chloroform (4 × 50 ml), and the combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent left an oil (2 8 g), which was shown by g l c to contain **2** (21%), **3** (19%), and **4** (60%), having retention times of 8 75, 10 0, and 27 0 min, respectively Chromatography on silica gel (elution with light petroleum–ether–chloroform, 17.1 1) gave sufficient of each component in a pure form to allow a positive identification Methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranoside (**3**, 0 33 g), b p 48–50°(bath)/1 mmHg, $[\alpha]_D$ +63 ±1° (*c* 0 95, chloroform), was eluted first; lit b p 70–74°(bath)/2 8 mmHg, $[\alpha]_D$ +65 3° (*c* 1 3, chloroform)[2], $[\alpha]_D$ +65 9° (chloroform)[11] The n m r and mass spectra and g l c properties of **3** were indistinguishable from those of an authentic material[2] Continued elution gave methyl 5-azido-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**4**, 0 67 g), b p. 70–72°(bath)/12 mmHg, $[\alpha]_D$ −78 ±1° (*c* 1 1, chloroform), ν_{max}^{film} 2100 cm^{-1} (N_3) (Found C, 49 3, H, 6 8, N, 16 8 $C_{10}H_{17}N_3O_4$ calc · C, 49 4, H, 7 0; N, 17 3%) N m r data τ 5 03 (*s*, H-1), 5 37 (*m*) and 6.15 (*m*) (H-2–H-5), 6 62 (*s*, OMe), 8 52 (*s*) and 8 69 (*s*) (CMe_2), and 8 70 (*d*, $J_{5,6}$ 6 Hz, CMe) Finally, methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hex-5-enofuranoside (**2**, 0 37 g),

---

*It is conceivable that an E2C-type of reaction, such as we have discussed[1] previously, may be operative in the formation of olefins with such highly nucleophilic species as azide ion b p 40–42°(bath)/12 mmHg, $[\alpha]_D$ −28 ±2° (*c* 0 7, chloroform), ν_{max}^{film} 3090 (olefin CH_2 stretch), 2820 (OMe), 1650 (C=C, weak), 1430 (olefin CH_2 deformation), and 990 cm^{-1} (olefin CH deformation), was eluted from the column The mass and n m r. spectra and g l c properties of **2** were indistinguishable from those of authentic material {lit [2] b p 76°(bath)/3 2 mmHg, $[\alpha]_D$ −23 5° (*c* 1 4, chloroform)} Unresolved mixtures of the components **3** and **4** (0 16 g) and **4** and **2** (0 47 g) were also recovered from the column

Treatment of sulphonate **1** *with sodium benzoate* — This experiment was carried out essentially as described in the literature[6]

Sodium benzoate (1 2 g) and **1** (0 6 g) in dry *N*,*N*-dimethylformamide (15 ml) were heated under reflux for 12 h Water (25 ml) was then added and the solution was extracted with ether (3×25 ml) The combined ether extracts were washed with aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$) Removal of the solvent left on oil (0 39 g), which was taken up in dry methanol (15 ml) containing M sodium methoxide (0 5 ml) and heated under reflux for 1 h to saponify the benzoate Work-up in the usual manner gave an oil (0 37 g) that was shown by g l c to contain methyl benzoate, **2** (49 7%), **3** (35%), and methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside[6a] (**8**, 15 2%), the identity of the products was established following co-injection with authentic materials A positive identification of **8** was also achieved by comparison (i r and n m r spectra) with authentic material[6a] following isolation by chromatography on silica gel (elution with light petroleum–ether, 5 1)

*Methyl 5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-β-*D*-gulofuranoside* (**7**) — The azide **4** (0 3 g) in dry ether (40 ml) containing lithium aluminium hydride (90 mg) was heated under reflux for 3 h, during which time the reduction was completed Work-up in the usual manner gave the amine **7** (0 26 g), b p 42–45°(bath)/1 5 mmHg, $[\alpha]_D$ −128 ±1° (*c* 0 8, chloroform) (Found C, 55 1; H, 8 5, N, 6 9 $C_{10}H_{19}NO_4$ calc C, 55 3, H, 8 7, N, 6 4%) N m r data: τ 5 09 (*s*, H-1), 5 37 (*m*) and 6 50 (*m*) (H-2–H-5), 6 67 (*s*, OMe), 8 12 (*s*, NH_2), 8 55 (*s*) and 8 69 (*s*) (CMe_2), and 8 82 (*d*, $J_{5\,6}$ 6 Hz, CMe)

Deamination of the amine **7** — A solution of **7** (0 24 g) in 90% acetic acid (4 ml) at 0° was treated during 30 min with a cold solution of sodium nitrite (0 24 g) in water (0 5 ml), whereafter the solution was set aside for 3 h at 0°. Water (8 ml) and chloroform (20 ml) were then added, and the separated organic layer was washed with cold, aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$) Removal of the solvent left a syrup (0 17 g), which g l c showed to contain at least seven components, the major component was identified as **2** (49%) following co-injection with an authentic sample A pure sample of **2** (37 mg), b p 40–45°/12 mmHg, $[\alpha]_D$ −24 ±1° (*c* 0 9, chloroform) {lit [2] b p 76°(bath)/3 2 mmHg, $[\alpha]_D$ −23 5° (*c* 1 4, chloroform)}, was obtained following chromatography on silica gel (elution with carbon tetrachloride–ether, 4 1) This material was identical in all respects with that previously isolated

ACKNOWLEDGMENTS

We thank Dr A H Haines, University of East Anglia, for copies of the n m r. spectra of the unsaturated sugars **2** and **3**, and for courteous exchange of information. One of us (J M) acknowledges a research scholarship from the University of Dundee

REFERENCES

1 Part XX A K. AL-RADHI, J S BRIMACOMBE, AND L C N TUCKER, *Carbohyd Res*, 22 (1972) 103
2 G CHAVES O AND A. H HAINES, *Carbohyd. Res*, 22 (1972) 205.
3 P A. LEVENE AND J COMPTON, *J Amer Chem Soc*, 57 (1935) 2306
4 I E MUSKAT, *J Amer Chem Soc*, 56 (1934) 2653.
5 L M LERNER, *J Org Chem*, 37 (1972) 477.
6 (*a*) H ARZOUMANIAN, E M ACTON, AND L GOODMAN, *J Amer Chem Soc*, 86 (1964) 74, (*b*) E J REIST, L GOODMAN, AND B R BAKER, *ibid*, 80 (1958) 5775
7 J S BRIMACOMBE and J MINSHALL, *Carbohyd Res*, 25 (1972) 267
8 J. S BRIMACOMBE AND J G H BRYAN, *J Chem Soc*, *C*, (1966) 1724, N K. KOCHETKOV, A I. USOV, AND K. S ADAMYANTS, *Tetrahedron*, 27 (1971) 549
9 E MERCK A. G , *Chromatography*, Darmstadt, 2nd edn , p 30.
10 A C FERGUSON AND A. H HAINES, *J Chem Soc*, *C*, (1969) 2372
11 K. J. RYAN, H ARZOUMANIAN, E M ACTON, AND L GOODMAN, *J Amer Chem Soc*, 86 (1964) 2503, see footnote 21.