Addition of Diazomethane and Sulfur Ylides to the Oxo-group in Derivatives of Ketoses and Aldoses. Part 2. Reactions of 1-Deoxy-3,4-*O*-isopropylidene-D-*glycero*-tetrulose and 1-Deoxy-3,4:5,6-di-*O*-isopropylidene-L-*arabino*-hexulose

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The reactions of diazomethane and dimethyloxosulfonium methylide with 1-deoxy-3,4-*O*-isopropylidene-D-*glycero*-tetrulose and 1-deoxy-3,4:5,6-di-*O*-isopropylidene-L-*arabino*-hexulose were studied. The sulfur ylide yielded two epimeric epoxides while diazomethane in addition furnished a homologous ketone. The relative yields of the three products in the reaction with diazomethane were determined with varying concentrations of methanol in the reaction medium, and the results were explained on the basis of a two-step reaction mechanism proposed earlier. Steric effects and complexation between the positive nitrogen and one of the ring oxygens were inferred to be important. Several new products were isolated and characterized.
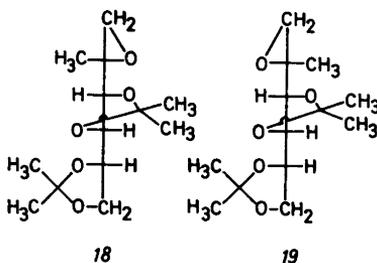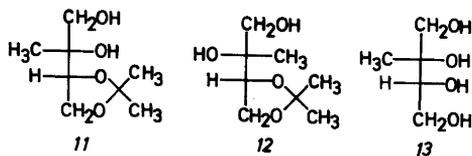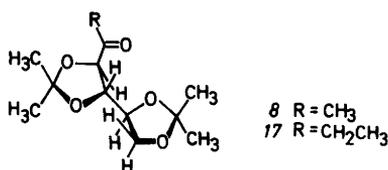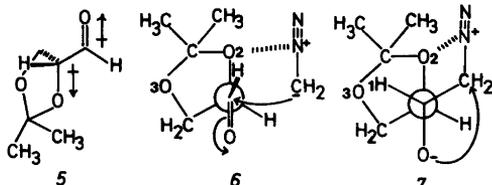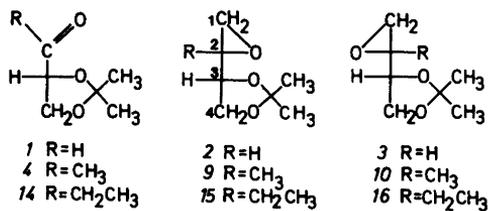
A recent communication[1] reported a study of the reactions of 2,3-*O*-isopropylidene-D-glyceraldehyde (*1*) with diazomethane[2] and sulfur ylides.[3] Dimethylsulfonium methylide and dimethyloxosulfonium methylide, both yielded epoxides *2* and *3* whose configurations were established by independent synthesis. Diazomethane yielded, in addition to *2* and *3*, 1-deoxy-3,4-*O*-isopropylidene-D-*glycero*-tetrulose (*4*), which reacted further when there was an excess of diazomethane.

For the reaction with diazomethane, a two-step mechanism was proposed upon a basis of experiments with reaction media of varying polarity. The initial step is a nucleophilic addition to the carbonyl group. Since *1* is chiral, this would give two intermediates in unequal amounts. Earlier observations[4] suggest that 2,3-*O*-isopropylidene-D-glyceraldehyde (*1*) prefers a conformation (*5*) in which the carbonyl group is pointing away from O-2. The best access for the attacking nucleophile would then be from the O-2 side as shown (*6*). Moreover, a coordination due to electrostatic forces between the positive nitrogen atom and O-2 would favour this attack, and lead mainly to the intermediate with the *erythro* configuration (*7*). In this intermediate, (*7*), there is an ideal arrangement for the formation of an epoxide, namely the *erythro*-epoxide *2*, with loss of nitrogen. In this arrangement the negatively charged oxygen atom is antiperiplanar with respect to the leaving N_2 group.

A more polar reaction medium, like methanol, should weaken the attraction between the ring oxygen and the positive nitrogen. The $CH_2 - N_2^+$ grouping would then be more free to rotate around the bond joining C-1 and the newly introduced CH_2 group, thus forming, among others, a conformation in which H-1 (the former aldehyde proton) is antiperiplanar relative to the N_2^+ group. This would favour a hydride shift, and hence a higher yield of the methyl ketone (*4*). Such an increase in the ratio of *4* to *2* as the amount of methanol in the reaction medium increases was observed, and shows that the *erythro* epoxide and the methyl ketone share a common intermediate.

Attack of diazomethane from the most hindered side would lead to the *threo* intermediate. Loss of nitrogen would then lead exclusively to the *threo*-epoxide *3*, in a low yield, independent of the

1 R=H
4 R=CH₃
14 R=CH₂CH₃

2 R=H
9 R=CH₃
15 R=CH₂CH₃

3 R=H
10 R=CH₃
16 R=CH₂CH₃

5   6   7

8 R = CH₃
17 R = CH₂CH₃

11   12   13

18   19

methanol concentration. An arrangement in which H-1 is antiperiplanar to the N_2^+ group is, in this case, unlikely for steric reasons.

A similar mechanism in which complexation plays an important role has been proposed previously[5] for the reaction between diazomethane and some hexopyranosid-3-uloses and may also explain the relative yields of products obtained with 3-epimeric 3-C-ethyl hexopyranosid-2-uloses.[6]

We have now undertaken a study of the reactions with 1-deoxy-3,4-O-isopropylidene-D-glycero- tetru-

lose (4)[1] and 1-deoxy-3,4:5,6-di-O-isopropylidene-L-arabino-hexulose (8).[7] The reaction of 4 with dimethyloxosulfonium methylide gave a mixture of the two epoxides 9 and 10 which in our hands was inseparable. ^{13}C NMR spectroscopy showed a ratio of 65:35 respectively. The resonances due to the respective C-1 carbons at δ 50.2 and 52.1 were particularly useful for determining this ratio. The latter peak was the larger and was shown to belong to the erythro-epoxide (9) as follows. Base hydrolysis of epoxides involves an SN_2 mechanism,[8] and since a primary carbon undergoes an SN_2 attack more readily than a more highly substituted carbon, the epoxides 9 and 10 should be attacked at C-1. The mixture of epoxides, when treated with base, gave a mixture of the diols 11 and 12, from which the dominating (11) crystallized (m.p. 100 °C), leaving an oil that was fairly pure 12. Acid-hydrolysis (10 % acetic acid) of 11 gave 2-C-methyl-D-erythritol (13) which had identical ^{1}H and ^{13}C NMR spectra and $[\alpha]_D$ with the natural compound isolated from Convolvulus glomeratus.[9,10]

The reactions of 4 with diazomethane were performed in diethyl ether containing varying amounts of methanol. The relative yields of the two epoxides 9 and 10 and the ethyl ketone 14 as a function of methanol concentration are given in Fig. 1. Since 14 reacts further, the amount of ethyl ketone here is the sum of the two epoxides 15 and 16. In the ^{13}C NMR spectrum resonances due to the four epoxides (9, 10, 15 and 16) are clearly
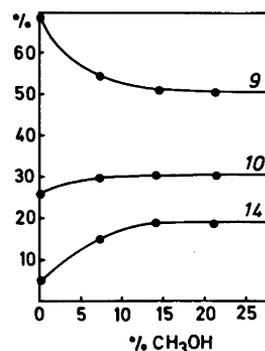

Fig. 1. The relative yields in per cent of the products 9, 10 and 14 at equilibrium when 1-deoxy-3,4-O-isopropylidene-D-glycero-tetrulose (4) reacts with diazomethane in diethyl ether solutions with varying concentrations of methanol. Since the ethyl ketone 14 reacts with another molecule of diazomethane to yield the epoxides 15 and 16, the amount of 14 here is the sum of 15 and 16.

visible, but there is no trace of the ethyl ketone 14. This ketone reacts further, to give the epoxides 15 and 16 at a rate similar to that of the reaction between 4 and diazomethane. The trend in Fig. 1 is the same as in the corresponding figure[1] for 2,3-O-isopropylidene-D-glyceraldehyde (1), but the magnitudes involved are markedly different. As in the aldehyde case, it seems that the erythro-epoxide (9) and the ethyl ketone (14) share a common intermediate. The initial ratio of the two intermediates without methanol in the reaction medium is 74:26. The corresponding ratio for the aldehyde 1 was 95:5,[1] which indicates a greater stereoselectivity in this case. The reason for this may be steric, but a more reasonable cause may be found in the fact that the rotational barrier around the C-1 — C-2 bond in an aldehyde is greater than in the corresponding methyl ketone.[4] This should favour conformation 5 for the aldehyde and hence greater stereoselectivity.

It is also noteworthy that the relative yield of methyl ketone from the aldehyde is much greater than the yield of ethyl ketone from the methyl ketone. The latter reaction requires a methyl shift, and this is less favoured than a hydride shift.

The reaction of 1-deoxy-3,4:5,6-di-O-isopropylidene-L-arabino-hexulose (8) with dimethyloxosulfonium methylide furnished a mixture of epoxides in the ratio 65:35. These were separable on a silica gel column under medium pressure, but it was not possible to decide which was erythro and which was threo. However, since 8 is related to both 1 and 4 it is likely that the stereochemistry of the reaction is also related. Thus the predominant epoxide formed should be related to the erythro-epoxide, i.e. 1,2-anhydro-2-C-methyl-3,4:5,6-di-O-isopropylidene-L-manno-hexitol (18) and the threo epoxide will be the corresponding L-gluco-hexitol (19).

The progress of the reaction of 8 with diazomethane was followed by GLC and ^{13}C NMR, as described for the tetrulose derivative 4. Along with the two epoxides was formed an ethyl ketone (17) which, unlike 14, did not react further.

Resonances due to the methyl carbons of 17, 18 and 19 were seen at δ 18.2, 16.4 and 7.2, respectively. The magnitudes must not all be taken as a valid measure of the relative amounts of 17, 18 and 19 because the methyl carbon of the ethyl group in 17 has a considerably longer relaxation time than the methyl carbon in 18 and 19. The reason for this is probably a shorter correlation time due to segmental motion.
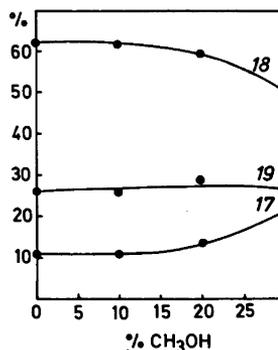
Fig. 2. The relative yields in per cent of the products 17, 18 and 19 at equilibrium when 1-deoxy-3,4:5,6-di-O-isopropylidene-L-arabino-hexulose (8) reacts with diazomethane in diethyl ether solutions with varying concentrations of methanol.

The ethyl ketone was separated from the epoxides and characterized spectroscopically. The relative yields of the three products in reaction media with varying methanol concentration are given in Fig. 2.

It is seen that the threo-epoxide (19) is formed in roughly the same amount as the threo-epoxide 10 (see Fig. 1) and it also shows a similar lack of dependence on solvent polarity. This strongly indicates that the condition for the initial addition must be similar. This is reasonable, because the immediate surroundings are almost identical. It is also seen that the erythro-epoxide (18) and the ethyl ketone (17) originate from a common intermediate. However, the effect of a rise in methanol concentration is different from that observed earlier. The rise in the ratio of 17 to 18 on addition of methanol was observed at a concentration higher than 15 %. The reason for this lag may be due to coordination of methanol molecules with other oxygen functions in the molecule.

EXPERIMENTAL

Chromatography. For GLC a Perkin Elmer F-11 instrument with Fl-detector was used. For the chromatography of 4 and products a 5′ × 1/8″ column at 90 °C packed with 5 % TCEP on Chromosorb W 80/100 was used. Chromatography of 8 and products was performed on a 3 m × 2.2 mm i.d. column at 130 °C, packed with 10 % OV 275 on Chromosorb W-AW-DMCS 80/100. N$_2$-pressures were 1.0 and 0.75 kg/cm^2, respectively.

TLC was performed on "Merck Fertigplatten" (0.25 mm Silica gel GF254); and preparative separations on "Merck Lobar Fertigsäulen" (silica gel 60 size B) under a pressure of $1.0-1.2$ kg/cm^2, equipped with Waters Ass. Model R 404 differential refractometer.

Spectroscopy. NMR spectra were recorded on Jeol FX-100, a Pulse-Fourier transform instrument, at 99.6 MHz for ^{1}H and 25.1 MHz for ^{13}C. The solvent was CDCl$_3$ containing 1 % TMS. Interpretations of both types of spectra were made by extensive use of double irradiation. Mass spectra were recorded with AEI MS 902 and optical rotations with a Perkin Elmer 241 polarimeter.

Model building. Extensive use was made of space-filling models of type "JUVO-Atommodelle", Karl Kurt Juchheim, Bernkastel-Kues, Germany.

*1-Deoxy-3,4:5,6-di-O-isopropylidene-*L-*arabino-hexulose (8)* was obtained from 3,4:5,6-di-O-isopropylidene-L-rhamnitol by ruthenium tetroxide oxidation,[11] yield 97 %, $[\alpha]_D^{18}$ $+5.7°$ (c 1.1, CHCl$_3$) lit.[7] $\sim 0°$. IR 1750 cm^{-1}, ^{1}H NMR: δ 1.31, 1.31, 1.40, 1.42 and 2.28 (all 3 H and s), 3.90−4.38 (5 H, m), ^{13}C NMR: δ 25.1, 26.2, 26.5, 26.7, 27.0 (all q, five CH$_3$ carbons), 66.5 (t, C-6), 76.3, 77.9 and 83.0 (all d, C-3, C-4 and C-5), 109.6 and 111.0 (both s, isopropylidene group), 206.9 (s, C-2).

Reaction of 4 and 8 with diazomethane. To freshly prepared solutions of 4 and 8 in diethyl ether with varying amounts of methanol (0−30 % of the total volume of the reaction mixture) were added etheral solutions of diazomethane (4× molar excess of diazomethane). The mixtures were left in the dark at room temperature and the reactions monitored by GLC for 4 days, at intervals beginning immediately after the reactions were initiated. Typical retention times (in min) under the conditions given were: 4 (5.5), 9 (11.2), 10 (11.8), 15 and 16 (13.7 and 16.7), 18 (9.4), 8 (10.4), 17 (11.1) and 19 (12.3). ^{13}C NMR spectra were also recorded from time to time as a double control. It was assumed that the relative intensities of the ^{13}C resonances gave an adequate measure for the relative amounts of the epoxides formed since the relaxation times of the carbons compared were probably of similar magnitude. An exception was the methyl carbon of the ethyl ketone 17 *(vide supra)*. Figs. 1 and 2 give the relative amounts of 9, 10 and 14, and of 17 18 and 19 for varying methanol concentrations after termination of the reactions. (5 h for the tetrulose 4 and 4 days for the hexulose 17).

Reaction of 4 and 8 with dimethyloxosulfonium methylide.[3] (The figures are taken from a reaction with 8). To a vigorously stirred mixture of DMSO (20 ml) and dimethyloxosulfonium methylide, prepared from trimethyloxosulfonium iodide (2.64 g, 0.012 mol) and sodium hydride (55 % dispersion in mineral oil, 0.58 g, 0.012 mol) was added at room temp., under nitrogen, the ketone 8 (2.44 g, 0.01 mol) in DMSO (5 ml). After stirring overnight and then at 50 °C for 1 h, the cooled reaction mixture was poured into cold water (400 ml) and extracted with ether (100 ml × 7). The combined extracts were washed with water (50 ml × 2), dried over sodium sulfate and concentrated under vacuum to yield a mixture of the epimeric epoxides 18 and 19, as an oil (2.4 g, 9.3 mmol, 93 %). A similar reaction with 4 (1.0 g) gave, after distillation (50 °C/10 mmHg), 0.4 g of the epimeric epoxides 9 and 10. Both reactions give epoxides in the ratio 65:35.

*2-C-Methyl-3,4-O-isopropylidene-*D-*erythritol (11) and 2-C-methyl-3,4-O-isopropylidene-*D-*threitol (12).* The epimeric mixture (0.5 g) of the epoxides 9 and 10 (which were inseparable), was suspended in M NaOH solution (50 ml) and heated at 80 °C for 2 h. After neutralization with HCl and saturation with ammonium chloride, the reaction mixture was extracted with ether and dried over sodium sulfate. Evaporation *in vacuo* gave a semicrystalline compound (0.3 g) which was crystallized from 5 % ether in hexane to yield 2-C-methyl-3,4-O-isopropylidene-D-erythritol (11) (254 mg), m.p. 100−101 °C. $[\alpha]_D^{20}$ $+5.14°$ (c 1.07, CHCl$_3$). MS: m/e 176 (absent, M), m/e 161 (24 %, M−15, obs. 161.081, as calc. for C$_7$H$_{13}$O$_4$), m/e 101 (49 %, C$_5$H$_9$O$_2$$^+$), m/e 43 (100 %, C$_2H_3O^+$). ^{1}H NMR: δ 1.16, 1.36 and 1.44 (all 3 H, and s), 2.87 (broad s, OH), 3.43 and 3.61 (AB system $J_{AB}=12.5$ Hz, H-1), 3.90−4.15 (3 H, m, H-3 and 2 H-4). ^{13}C NMR: δ 20.0 (C-2-Me), 24.8, 26.2 and 108.9 (isopropylidene group), 64.9 and 67.2 (C-1 and C-4), 72.3 (C-2) and 79.0 (C-3).

The mother liquor after removal of 11 was fairly pure 2-C-methyl-3,4-O-isopropylidene-D-threitol (12), (42 mg), $[\alpha]_D^{20}$ $+3.9°$ (c 1.05, CHCl$_3$). ^{1}H NMR: δ 1.07, 1.37 and 1.44 (all 3 H and s), 2.80 (broad s, OH), 3.43 and 3.65 (AB system $J_{AB}=11.2$ Hz, H-1), 3.90−4.10 (3 H, m, H-3 and 2H-4). ^{13}C NMR: δ 19.9 (C-2-Me), 25.4, 26.2 and 109.4 (isopropylidene group), 64.8 and 69.4 (C-1 and C-4), 70.7 (C-2) and 80.5 (C-3).

*2-C-Methyl-*D-*erythritol (13).* 2-C-Methyl-3,4-O-isopropylidene-D-erythritol (11) (100 mg) was dissolved in 10 % acetic acid (2 ml) and heated at 90 °C for 45 min. The reaction mixture was evaporated three times with benzene to give an oily product (70 mg), $[\alpha]_D^{20}$ $+15.7°$ (c 1.42, MeOH), lit.[9] $+21.4°$ (c 7.0, H$_2$O). This product had identical ^{1}H and ^{13}C NMR spectra with natural 2-C-methyl-D-erythritol isolated from *Convolvulus glomeratus.*[9,10]

*1,2-Anhydro-2-C-methyl-3,4:5,6-di-O-isopropylidene-*L-*)-manno-hexitol (18) and 1,2-anhydro-2-C-methyl-3,4:5,6-di-O-isopropylidene-*L-*gluco-hexitol (19).* The epimeric epoxide mixture (0.5 g) resulting from the reaction of 8 with dimethyloxosulfonium methylide was applied to a silica gel column and

eluted with 3 % acetone in hexane. Fractions (8 ml) were collected and identical and pure fractions were combined. Impure fractions were combined and rechromatographed using the same conditions. This procedure was repeated eight times. The combined pure fractions from all runs were concentrated *in vacuo* to yield (30 mg) *18* as an oil. $[\alpha]_D^{18}$ +25.6° (*c* 1.24, Et_2O). MS: *m/e* 258 (absent, M^+), *m/e* 243 (7 %, M−15, obs. 243.1236, calc. for $C_{12}H_{19}O_5$ 243.1233), *m/e* 149 (51 %), *m/e* 43 (100 %). ^1H NMR: δ 1.25, 1.36, 1.40, 1.43, 1.55 (all s, 5 Me), 2.64 and 2.83 (AB system J_{AB}=4.8 Hz), 3.4−4.2 (5 H, m). ^{13}C NMR: δ 18.2 (C-2-Me), 25.2, 26.4, 26.6, 27.2, 109.7 and 109.7 (2 isopropylidene groups), 61.6 (C-1), 55.6 (C-2), 67.4 (C-6), 77.1, 77.1 and 82.0 (C-3, C-4 and C-5).

The remaining mixture (0.42 g) was applied to the same column and eluted with 8 % ethyl acetate in hexane with the same pressure. The same procedure as described for the purification of *18* was carried out 11 times. The combined pure fractions from all runs were concentrated *in vacuo* to yield epoxide *19* as a thin oil (43 mg). $[\alpha]_D^{18}$ +17.9° (*c* 1.07, $CHCl_3$). MS: as given for *18*. ^1H NMR: δ 1.25, 1.34, 1.37, 1.40, 1.42 (all s, 5 Me), 2.64 and 2.88 (AB system J_{AB}=4.9 Hz), 3.6−4.2 (5H, m). ^{13}C NMR: δ 16.4 (C-2-Me), 25.2, 26.8, 26.9, 27.3, 109.7 and 110.2 (2 isopropylidene groups), 52.2 (C-1), 55.9 (C-2), 67.7 (C-6), 77.1, 78.8 and 83.9 (C-3, C-4 and C-5).

1,2-Dideoxy-4,5:6,7-di-O-isopropylidene-L-arabino-3-heptulose (17). The reaction mixture (0.7 g) resulting from the reaction of *8* with diazomethane was applied to a silica gel column and eluted with 25 % ether in hexane. Fractions (8 ml ×20) were collected and fraction 10 was shown (GLC) to be pure. It was concentrated in vacuum to yield the ethyl ketone *17* as a syrup (31 mg), $[\alpha]_D^{18}$ −4.6° (*c* 1.07, Et_2O). MS: *m/e* 258 (0.4 %, M^+, obs. 258.1461, calc. for $C_{13}H_{22}O_5$ 258.1467), *m/e* 243 (24 %, M−Me), *m/e* 201 (5 %, M−Et−CO), 157 (4 %, $C_8H_{13}O_3^+$), *m/e* 143 (35 %), *m/e* 101 (38 %, $C_5H_9O_2^+$) and *m/e* 43 (100 %). ^1H NMR: δ 1.09 and 2.69 (ethyl group), 2.38, 2.39, 2.43 and 2.48 (2 isopropylidene groups) 3.9−4.4 (5 H, m). ^{13}C NMR: δ 7.2 and 32.6 (ethyl carbons C-1 and C-2), 25.1, 26.2, 26.5, 27.0, 109.6 and 111.0 (2 isopropylidene groups), 66.5 (C-7), 76.4, 78.1 and 82.5 (C-4, C-5 and C-6). Repeated chromatography of fractions 11−13 yielded the epoxides *18* and *19*.

REFERENCES

1. Hagen, S., Anthonsen, T. and Kilaas, L. *Tetrahedron. 35* (1979) 2583.
2. Fieser, L. F. and Fieser, M. *Reagents for Organic Synthesis*, Wiley, New York 1967, Vol. 1, p. 191.
3. Corey, E. J. and Chaykovsky, M. *J. Am. Chem. Soc. 87* (1965) 1353.
4. Dale, J. *Stereochemistry and Conformational Analysis*, Universitetsforlaget, Oslo 1978, p. 80.
5. Sato, K. and Yoshimura, J. *Bull. Chem. Soc. Jpn. 51* (1978) 2116.
6. Inch, T. D., Lewis, G. J. and Peel, R. P. *Carbohydr. Res. 19* (1971) 29.
7. Inch, T. D., Ley, R. V. and Rich, P. *J. Chem. Soc. C* (1968) 1683.
8. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 2nd Ed., McGraw-Hill-Kogakusha, Tokyo 1977, p. 340.
9. Anthonsen, T., Hagen, S., Kazi, M. A., Shah, S. W. and Tagar, S. *Acta Chem. Scand. B 30* (1976) 91.
10. Shah, S. W., Brandänge, S., Behr, D., Dahmén, J., Hagen, S. and Anthonsen, T. *Acta Chem. Scand. B 30* (1976) 903.
11. Lawton, T., Szarek, W. A. and Jones, J. K. N. *Carbohydr. Res. 10* (1969) 456.