Stereochemistry of Nucleophilic Addition Reactions. 6. Synthesis of Isoxazoline *N*-Oxide Derivatives from Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-*α*-D-*erythro*-hex-2-enopyranoside with Some *S*-Ylides[1)]

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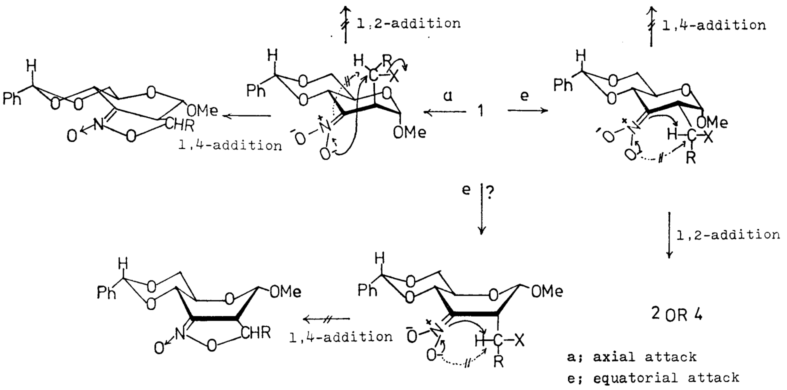
In the reactions of dimethyloxosulfonium methylide, dimethylsulfonium ethoxycarbonylmethylide, and dimethylsulfonium phenacylide with the title compound, axial attack predominates over equatorial attack, particularly in the case of dimethylsulfonium phenacylide equatorial attack being no longer observed. Axial attack afforded exclusively 1,4-addition products (isoxazoline *N*-oxide derivatives), whereas equatorial attack gave only 1,2-addition products (cyclopropane and stabilized ylide, respectively). Discussion is given on such high selectivities.

In a previous paper[2)] a report was given on the reactions of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3 nitro-*β*-D-*erythro*-hex-2-enopyranoside with some *S*-ylides, where equatorial attack occurs selectively to give cyclopropane derivatives or new stabilized ylides depending on the ylide used. In order to obtain information on the stereochemistry of Michael type reaction of α-glycoside series,[3)] we have carried out the reaction of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (**1**) with *S*-ylides and have found that axial attack predominates over equatorial attack, the former affording 1,4-addition product and the latter 1,2-addition product, exclusively.

Results and Discussion

Treatment of **1** with dimethyloxosulfonium methylide in DMSO at room temperature for 1.5 h afforded a mixture of methyl (2*R*,3*R*)-4,6-*O*-benzylidene-2,3-dideoxy-2,3-*C*-methylene-3-nitro-α-D-*erythro*-hexopyranoside (**2**) and (methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranosido)[3,2-*c*]isoxazoline *N*-oxide (**3**) in a 1 : 3.5 ratio as determined by NMR spectroscopy. After separation of **2** by crystallization, compound **3** was isolated by column chromatography on silica gel. The results of elemental analysis of both compounds correspond to the formula $C_{15}H_{17}NO_6$. The cyclopropane structure for **2** was determined from its IR (presence of NO_2 but absence of C=N absorption band) and NMR spectra (presence of cyclopropane ring protons at δ 2.61, 2.18, and 1.98). The configuration of **2** was determined from the value $J_{1,2}=6.2$ Hz[4)] and long range coupling ($J_{4,\mathrm{exo}}=1.0$ Hz) owing to "W-orientation." The IR spectrum of **3** revealed no absorption band for a nitro but a C=N group (1640 cm^{-1}). The complicated NMR spectrum of **3** due to overlap of ring protons was not completely assigned. However, the structure of **3** was deduced by comparison of its IR and NMR spectra with those of **5** and supported by conversion into hydroxyimino derivative **9**.

Reaction of **1** with dimethylsulfonium ethoxycarbonylmethylide in THF at 0 °C gave a mixture of the stabilized ylide **4** (*ca.* 22%) and isoxazoline *N*-oxide **5** (55%). After separation of crystalline compound **5**, stabilized ylide **4** was separated as a syrup by means of column chromatography on silica gel. Although **4** was not completely purified, the ylide structure for **4** was determined from its IR (the characteristic absorption band of an ester carbonyl group of the ylide species at 1630 cm^{-1} and that of a nitro group at 1560 cm^{-1}) and NMR spectra (two methyl signals for SMe_2 at δ 2.76 and 2.65).[2)] Assignment of the *gluco* configuration to **4** was based on the values $J_{1,2}=3.5$, $J_{2,3}=12.5$, and $J_{3,4}=10$ Hz. The structure of **4** was confirmed by desulfurization into methyl 4,6-*O*-benzylidene-2-*C*-(ethoxycarbonylmethyl)-2,3-dideoxy-3-nitro-α-D-glucopyranoside (**6**); $J_{1,2}=3.1$ and $J_{2,3}=J_{3,4}=11.1$ Hz. The structure of **5** was determined on the basis of its elemental analysis (molecular formula $C_{18}H_{21}NO_8$) and IR spectra (absence of NO_2 but presence of COOEt and C=N absorption bands at 1720 and 1645 cm^{-1}, respectively). The isoxazoline *N*-oxide structure was supported by the fact that treatment of **5** with triphenylphosphine in boiling benzene for 15 h afforded isoxazoline **7** in 91% yield. Thus with the isoxazoline ring fused at C-2 and C-3, compound **5** should have the *arabino* configuration existing in a boat form or the *ribo* configuration existing in a chair form. The signals of H-1 and H-7 (the ring proton of the isoxazoline nucleus), which overlap, were clearly resolved into two doublets having spacings 6.0 and 7.0 Hz by addition of shift reagent, $Eu(DPM)_3$. The reagent probably undergoes complexation with the *N*-oxide group or the ethoxycarbonyl group, resulting in displacement of the H-7 signal to much lower field than that of the H-1 signal. The value of $J_{1,2}=6.0$ Hz suggests that **5** has the *arabino* configuration existing in a boat form. This was confirmed chemically. Catalytic hydrogenation of **5** over Raney nickel afforded a mixture of two products at least in an approximately 3 : 1 ratio as determined by NMR spectroscopy, from which the major product **8** was isolated in 35% yield. The IR spectrum revealed the presence of a hydroxyl (3380), an amino (3310), and an ester carbonyl group (1735 and 1700 cm^{-1}). The *altro* configuration of **8** was determined from its coupling-constant data ($J_{1,2}=0$, $J_{2,3}=1.3$, and $J_{3,4}=3.8$ Hz), the values being confirmed with the aid of spin decoupling; irradiation at δ 2.41 (H-2) and at δ 3.49 (H-3).



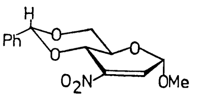
Hydrogenation of **3** and **5** over 10% Pd/C afforded hydroxyimino derivative **9** and **10**, respectively. The results of elemental analysis and IR and NMR spectra fit the hydroxyimino structures.

A similar reaction of **1** with dimethylsulfonium phenacylide in THF at room temperature afforded 5-benzoyl-(methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranosido)[3,2-*c*]isoxazoline *N*-oxide (**11**) in 89.9% yield, no evidence being detected for formation of stabilized ylide corresponding to **4**.[2] The structure of **11** was deduced by comparison of spectral data with those of **5**. When this reaction was carried out on a larger scale, another product was formed.

The ratio of axial attack, which affords the isoxazoline *N*-oxide **3**, **5**, and **11**, increased according to the sequence $Me_2SOCH_2 < Me_2SCHCOOEt < Me_2SCHCOPh$. The ratios of **5** to **4** were 1.6: 1 in THF at room temperature, 3.2: 1 in THF at 0 °C, and 5.3: 1 in DMSO at 0 °C. The results could be attributed to steric hindrance between incoming ylide and the glycosidic methoxyl group.

In general, conjugate addition of *S*-ylide with carbon-carbon double bond activated by electron-withdrawing substituent(s) gives preferentially a three-membered ring product. However, exceptions are reported, in which an unfavorable five-membered ring product predominates. This is explained in terms of formation of unusually stable cisoid intermediate.[5] However, the intermediary nitronate has no such cis or trans form. Thus, the explanation can not be applied to the observed high selectivity, *i.e.*, axial attack gave the 1,4-addition products, equatorial attack the 1,2-addition products. The following rationalization seems to be likely. If the ylide approaches from the axial side, an intermediary nitronate should have a chairlike transition state in which the carbon atoms at C-3 and C-2 move up and down, respectively, to afford a product. Molecular models indicate that, during this movement interaction between the oxygen atom of the nitro group and the carbon atom (C-7) bearing the sulfur atom is more efficient than that between the C-3 and C-7 carbon atom to give the isoxazoline derivative. On the other hand, when the ylide comes from the equatorial side, the orginal half-chair conformation changes into a boatlike transition state, where the incoming ylide approaches from the stereoelectronically acceptable axial direction. Although the alternative chairlike transition state is unfavorable for stereoelectronic control[6] and $A^{1,3}$ strain,[7] the transition state also seems to be possible because of the favorable anomeric effect.[8] The relationship between C-3 and C-7 in the boatlike transition state resembles that in the chairlike transition state derived by axial attack, indicating the preferred formation of 1,4-adduct. However, experimental results show selective formation of 1,2-addition products. Thus the chairlike transition state even in the case of equatorial attack is more likely, in which the favorable interaction between C-3 and C-7 carbon atoms is predicted by molecular models.

It is noteworthy that epoxidation of **1** with hydrogen peroxide in a weakly alkaline medium exclusively afforded 1,2-addition product, *i.e.*, methyl 2,3-anhydro-4,6-*O*-benzylidene-3-*C*-nitro-α-D-mannopyranoside.[3d] Though in this reaction intermediary nitronate should have a similar structure derived by axial attack of the ylides, molecular models suggest that the C-3 carbon atom is orientated in a more suitable position than the oxygen atom of the nitro group to make the displacement of hydroxide ion take place. Such a difference can be attributed to the shorter bond length of the C–O as compared with the C–C bond.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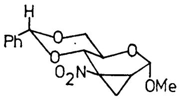
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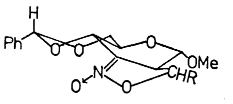
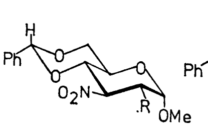
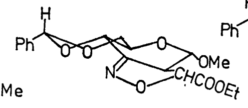

3: R=H
5: R=COOEt
11: R=COPh


4: $R = \bar{C}(COOEt)\overset{+}{S}Me_2$
6: $R = CH_2COOEt$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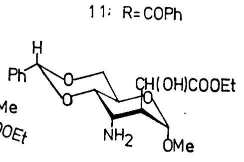
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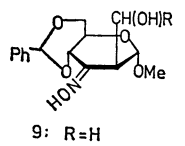
9: R=H
10: R=COOEt

Experimental

Melting points were determined in capillaries and are uncorrected. IR spectra were recorded by use of KBr discs and NMR spectra were determined with solutions in chloroform-*d* (tetramethylsilane as internal standard) with a JNM-4H-100 (JEOL) spectrometer. Solutions were evaporated under reduced pressure. Column chromatography was performed on silica gel (C-300, Wakogel, Japan).

*Treatment of **1** with Dimethyloxosulfonium Methylide.* To a solutions of dimethyloxosulfonium methylide, prepared from trimethyloxosulfonium iodide (770 mg) and sodium hydride (over 55% purity, 154 mg) in DMSO (7 ml), was added 6 ml of DMSO solution of **1**[9] (1.03 g, 3.5 mmol) at 0 °C. The mixture was kept at 0 °C for 30 min and for 1 h at room temperature and then poured into 70 ml of water. The precipitate was collected and washed with water. Its NMR spectrum revealed that it is a mixture consisting of **2** and **3** in the ratio 1: 3.5. Recrystallization from ethanol-diisopropyl ether gave 150 mg of **2**: Mp 131—132 °C; $[\alpha]_D^{20}+35.0°$ (c 1, $CHCl_3$); IR 1550 cm^{-1} (NO_2); NMR $\delta=5.81$ (s, 1, PhCH), 5.04 (d, 1, H-1, $J_{1,2}=6.3$ Hz), 4.92 (d, 1, H-4, $J_{4,5}=9.4$, $J_{4,\mathrm{exo}}=1.0$ Hz), 4.28 (q, 1, H-6e, $J_{5,6e}=5.0$, $J_{5,6a}=10$ Hz), 3.37 (six, 1, H-5), 3.37 (s, 3, OMe), 2.61 (oct, 1, H-2, $J_{2,\mathrm{exo}}=11.3$, $J_{2,\mathrm{endo}}=8.1$ Hz), 2.18 (oct, 1, H_{exo}, $J_{\mathrm{exo,\,endo}}=6.3$ Hz), and 1.98 (q, 1, H_{endo}).

Found: C, 58.60; H, 5.61; N, 4.44%. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56%.

The combined mother liquors were evaporated and chromatographed with benzene as eluent. The fast running fraction was **2** (28 mg, total yield 16.5%) and the slow running fraction was **3**, which was recrystallized from ethanol–diisopropyl ether to give 607 mg (56.2%) of **3**: Mp 178.5—179.5 °C; $[\alpha]_D^{20}-139.2°$ (c 1, $CHCl_3$); IR 1640 cm^{-1} (C=N); NMR $\delta=5.69$ (s, 1, PhCH), 4.73 (d, 1, H-1, $J_{1,2}=6.0$ Hz), 3.41 (s, 3, OMe), and 4.8—3.8 (7-H).

Found: C, 58.57; H, 5.65; N, 4.57%. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56%.

*Treatment of **1** with Dimethylsulfonium Ethoxycarbonylmethylide.* To a solution of **1** (293 mg, 1 mmol) in THF (7 ml) was added the ylide (163 mg, 1.1 mmol) at 0 °C. The mixture was kept at 0 °C for 30 min and then at room temperature for 16 h and evaporated. The residue crystallized from ethanol to give 138 mg of **5**: Mp 151.5—152 °C; $[\alpha]_D^{20}-121°$ (c 1, $CHCl_3$); IR 1720 (COOEt) and 1645 (C=N) cm^{-1}; NMR $\delta=5.72$ (s, 1, PhCH), 4.95 (d, 1, H-7, $J_{2,7}=7.0$ Hz), 4.89 (d, 1, H-1, $J_{1,2}=6.0$ Hz), 3.45 (s, 3, OMe), 1.31 (t, 3, OEt), and 4.55—3.85 (7-H).

Found: C, 57.32; H, 5.65; N, 3.64%. Calcd for $C_{18}H_{21}NO_8$: C, 56.99; H, 5.58; N, 3.65%.

The mother liquor was evaporated and chromatographed on a column with benzene–ethanol (20: 1, v/v) as eluent. The fast running fraction was **5** (70 mg, total yield 55%) and the slow running fraction was a light yellow syrup of **4** (80 mg). Attempts for purification by preparative TLC were unsuccessful. The syrup was hydrogenated without further purification. The syrup (143 mg) was dissolved in methanol and hydrogenated over 10% Pd/C (200 mg). After 2 days the catalyst was removed by filtration. The filtrate was evaporated to give a syrup, which crystallized from ethanol to afford 100 mg (81%) of **6**: Mp 91.5—92.0 °C; $[\alpha]_D^{20}+72°$ (c 1, $CHCl_3$); IR 1720 (COOEt) and 1550 (NO_2) cm^{-1}; NMR $\delta=5.55$ (s, 1, PhCH), 4.93 (d, 1, H-1, $J_{1,2}=3.1$ Hz), 4.78 (t, 1, H-3, $J_{2,3}=J_{3,4}=11.3$ Hz), 3.35 (s, 3, OMe), and 1.23 (t, 3, OEt).

Found: C, 56.55; H, 6.01; N, 3.94%. Calcd for $C_{18}H_{23}NO_8$: C, 56.68; H, 6.08; N, 3.67%.

A similar treatment in THF at room temperature or in DMSO (5 ml) at 0 °C for 30 min and then 1 h at room temperature afforded a mixture consisting of **5** and **4** in the ratios 1.6: 1 and 5.3: 1, respectively, as determined by NMR spectroscopy.

*5-Ethoxycarbonyl-(methyl 4,6-O-benzylidene-2,3-dideoxy-α-D-erythro-hexopyranosido)[3,2-c]isoxazoline (**7**).* To a solution of **5** (57 mg, 0.15 mmol) was added triphenylphosphine (39.3 mg, 0.15 mmol). The mixture was heated under reflux for 15 h and evaporated to give a syrup, which was chromatographed on a column with carbon tetrachloride–ethyl acetate (10: 1, v/v) to afford 51 mg of **7**. Recrystallization from ethanol gave 44 mg (81%) of **7**: Mp 159—160 °C; $[\alpha]_D^{20}-120°$ (c 0.5, $CHCl_3$); IR 1758 (COOEt) and 1620 (C=N) cm^{-1}; NMR $\delta=5.66$ (s, 1, PhCH), 4.8—4.7 (q, 2. H-1 and H-7, overlap), 3.82 (t, 1, H-6a, $J_{5,6a}=J_{6a,6e}=10$ Hz), 3.42 (s, 3, OMe), and 1.31 (t, 3, OEt).

Found: C, 59.77; H, 5.94; N, 3.98%. Calcd for $C_{18}H_{21}NO_7$: C, 59.49; H, 5.83; N, 3.86%.

*Methyl 3-Amino-4,6-O-benzylidene-2-C-[(ethoxycarbonyl)hydroxymethyl]-2,3-dideoxy-α-D-altropyranoside (**8**).* A solution of **5** (64 mg, 0.17 mmol) in ethyl acetate (10 ml) was hydrogenated in the presence of Raney nickel (80 mg) at room temperature. After 7 days the catalyst was filtered off and washed thoroughly with chloroform. The filtrate was evaporated to give a solid, the NMR spectrum of which showed the presence of two compounds. Recrystallization from acetone afforded 21.7 mg (35%) of **8**. The signals of its NMR spectrum corresponded to those of the major product: Mp 167—168 °C; $[\alpha]_D^{20}+64.2°$ (c 1, $CHCl_3$); IR 3380 (OH), 3310 (NH), and 1735 and 1700 (COOEt) cm^{-1}; NMR $\delta=5.62$ (s, 1, PhCH), 4.73 (s, 1, H-1), 4.24 (q, 2, OEt), 4.22 (d, 1, H-7, $J_{2,7}=7.5$ Hz), 3.49 (broad s, 1, H-3, $J_{2,3}=1.3$, $J_{3,4}=3.8$ Hz), 3.36 (s, 3, OMe), 2.41 (broad d, 1, H-2), and 1.30 (t, 3, OEt).

Found: C, 58.75; H, 6.85; N, 3.76%. Calcd for $C_{18}H_{25}NO_7$: C, 58.84; H, 6.86; N, 3.81%.

*Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-C-hydroxymethyl-3-hydroxyimino-α-D-arabinohexopyranoside (**9**).* A solution of **3** (240 mg, 0.78 mmol) in THF (10 ml) was hydrogenated in the presence of 10% Pd/C (200 mg) at room temperature. After 20 h the catalyst was removed by filtration and the filtrate was evaporated to give a white powder. Recrystallization from ethanol gave 176 mg (73%) of **9**: Mp 170.5—171.5 °C; $[\alpha]_D^{20}-68.6°$ (c 1, $CHCl_3$); IR 3450 and 3250 (OH) cm^{-1}; NMR $\delta=5.62$ (s, 1, PhCH), 4.73 (d, 1, H-1, $J_{1,2}=4.7$ Hz), 4.52 (q, 1, H-4, $J_{2,4}=1.0$, $J_{4,5}=9.4$ Hz), 3.38 (s, 3, OMe), and 2.90 (m, 1, H-2).

Found: C, 58.34; H, 6.24; N, 4.47%. Calcd for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19; N, 4.53%.

*Methyl 4,6-O-Benzylidene-2-C-[(ethoxycarbonyl)hydroxymethyl]-2,3-dideoxy-3-hydroxyimino-α-D-arabinohexopyranoside (**10**).* A similar treatment of **5** (139 mg, 0.37 mmol) with 10% Pd/C (100 mg) in THF (10 ml) afforded **10**. Recrystallization from ethanol gave 113 mg (81%) of **10**: Mp 163.5—164.5 °C; $[\alpha]_D^{20}-68.4°$ (c 1, $CHCl_3$); IR 3400 (OH) and 1720 (COOEt) cm^{-1}; NMR $\delta=5.58$ (s, 1, PhCH), 4.92 (d, 1, H-1 or H-7, $J_{1,2}=5.6$ or $J_{2,7}=5.6$ Hz), 4.49 (d, 1, H-4, $J_{4,5}=8.8$ Hz), 4.35 (d, 1, H-7 or H-1, $J_{2,7}=3.1$ or $J_{1,2}=3.1$ Hz), 3.75 (t, 1, H-6a, $J_{5,6a}=J_{6a,6e}=9.4$ Hz), 3.40 (s, 3, OMe), 3.34 (q, 1, H-2), and 1.21 (t, 3, OEt).

Found: C, 57.06; H, 6.23; N, 3.55%. Calcd for $C_{18}H_{23}NO_8$: C, 56.68; H, 6.08; 3.67%.

*5-Benzoyl-(methyl 4,6-O-benzylidene-2,3-dideoxy-α-D-erythro-hexopyranosido)[3,2-c]isoxazoline N-Oxide (**11**).* To a solution of **1** (58.6 mg, 0.2 mmol) in THF (3 ml) was added dimethylsulfonium phenacylide (45 mg, 0.25 mmol) at room temperature. The mixture was stirred for 3 h and then poured into ice-water. Extractien with chloroform and evaporation of the solvent afforded a NMR-spectroscopically pure solid (74 mg, 89.9%). Analytical sample was prepared by recrystallization from ethanol: Mp 162.5—163.0 °C; $[\alpha]_D^{20}-227°$ (c 1, $CHCl_3$); IR 1705 (COPh) and 1638 (C=N) cm^{-1}; NMR

δ=5.59 (s, 1, PhCH), 5.58 (d, 1, $J_{2,7}$=6.3 Hz), 4.88 (d, 1, H-1, $J_{1,2}$=6.0 Hz), and 3.37 (s, 3, OMe).

Found: C, 64.14; H, 5.21; N, 3.32%. Calcd for $C_{22}H_{21}NO_7$: C, 64.22; H, 5.15; N, 3.40%.

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