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DERIVATIVES OF 5-DEOXY-5-SELENO-D-XYLOSE[1]

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Abstract—The synthesis of derivatives of 5-deoxy-5-seleno-D-xylose is described. These anhydro derivatives represent a new class of carbohydrates in which the usual anhydro oxygen is replaced by selenium.

A NUMBER of monosaccharides has been synthesized in which the ring oxygen is replaced by either a sulphur[3] or nitrogen[4] atom This work reports the preparation of 5-deoxy-5-seleno-D-xylose derivatives. 1,2-O-Isopropylidene-5-O-*p*-toluenesulphonyl-α-D-xylofuranose[5] was treated with potassium selenocyanate in alcohol to give a low yield of 5-*deoxy*-1,2-O-*isopropylidene-5-selenocyanate-α-D-xylofuranose.* Treatment of this compound with sodium methoxide in methanol gave a mixture of 5-*deoxy*-1,2,-O-*isopropylidene-5-seleno-α-D-xylofuranose* and the corresponding diselenide. The selenol, the presence of which can be shown by reaction with iodine or sodium nitroprusside, could not be isolated because it is easily oxidized to the diselenide. The selenol was formed more conveniently from the tosylate by treatment with benzyl selenoyl anion and reduction of the 5-*deoxy*-1,2-O-*isopropylidene-5-selenobenzyl-α-D-xylofuranose* with sodium in ammoniacal solution. However, the diselenide was again the product obtained after evaporation of the ammonia even in an atmosphere of nitrogen. In an attempt to prevent the formation of the diselenide, the ammonia was evaporated without destroying the sodium salt and the product acetylated, but at this point extensive decomposition with formation of selenium occurred. Since the selenol is so easily oxidized, it was treated with acidic methanol without isolation. Thus after reduction in liquid ammonia, the ammonia was allowed to evaporate from the sodium salt and the residue de-ionized in methanol. On addition of hydrogen chloride to the solution, a number of compounds were formed which were separated by chromatography. Of the three components which were present in major amounts, one was shown to be *bis(methyl 5-deoxy-D-xylofuranoside)*5,5-*diselenide*. The other two components are isomeric and have the molecular formula, $C_7H_{14}O_4Se$ and analyse for two OMe groups. The two isomers are in equilibrium, because a solution of either isomer in acidic methanol gives a mixture of the two isomers on standing. The absence of a selenol group in either isomer is shown by their slow reaction with aqueous iodine and 2,3,5-triphenyl-2H-tetrazolium chloride at room temperature, as well as their negative reaction with sodium nitroprusside. One of the isomers consumed approximately one mole of

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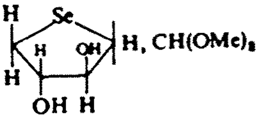
periodate indicating the presence of two adjacent OH groups. Assuming that these isomers are O–Me ethers of a methyl pyranoside or furanoside, the O–Me group could be at C_2, C_4 or C_5. A Se–Me group at C_5 was precluded as no methyl 5-deoxy-D-xylofuranoside was formed on removal[6] of selenium from either isomer.

It has been shown[7] that carbohydrates, e.g. 2-O-substituted sugars, which can give rise to malondialdehyde or its derivatives on oxidation with periodate, give a yellow colour with Schiff's reagent. When this test was applied to the isomers, a yellow colour was obtained within 40 min in each case. This result appears to indicate the presence of a C_2 OMe group in a pyranoside structure.

NMR spectra of the two isomers in deuterium oxide showed the presence of two OMe groups and at low field (5·20) one of the isomers showed a doublet (intensity 1, J 8·4 c/s). In the case of the other isomer this doublet was obscured by the water peak but when the spectrum was measured in deuterochloroform, the doublet (5·46, J 7·2 c/s) was clearly shown. The diacetates of the two isomers had very similar IR and NMR spectra. Their NMR spectra showed in addition to the presence of two MeO and Ac groups, a complex signal of intensity 2 at low field (4·5–4·7) and a doublet (intensity 1; 5·35, J 8·4 c/s; 5·39, J 8·4 c/s respectively). Also the fragmentation patterns shown in their mass spectra are similar, with the most noticable feature of a very intense peak of *m/e* 75. This peak, although not of the intensity observed, does occur in spectra of carbohydrate derivatives[8] and has been ascribed to $\mathrm{MeOCH{=}\overset{+}{O}Me}$. In addition the spectrum showed a molecular ion peak (*m/e* 326, selenium = 80) and an intense peak at *m/e* 132, ascribed to the selenophene cation.

When either isomer was treated with a warm solution of 2,4-dinitro-phenyl hydrazine, the 2,4-dinitro-phenylhydrazone of 2-formylselenophene was obtained. Both isomers, after brief hydrolysis, were treated with 2,4-dinitrophenylhydrazine. Two isomeric hydrazones were obtained, which had the molecular formula, $C_{11}H_{12}O_6N_4Se$ (only the two OMe groups had been lost). Both hydrazones showed UV absorption (λ_{max} 361 mμ), characteristic of an aliphatic aldehyde. When either of the hydrazones was warmed with dilute acid, the 2,4-dinitrophenylhydrazone of 2-formylselenophene was formed. On hydrolysis of either isomer the presence of an aldehyde was detected with Schiff's reagent. These facts suggest that both methoxyls are attached to the same carbon atom in a dimethyl acetal structure.

The spectral data are also not in keeping with a 2-O-methyl selenopyranoside structure. It is proposed that the two isomers are C_2 anomers of *D*-threo-3,4-dihydroxy-2,3,4,5-tetrahydroselenophene-2-dimethyl acetal. The intense peak (*m/e* 75) in the mass spectra of the acetates is ascribed to the dimethyl acetal side chain, giving rise to the ion $\mathrm{MeOCH{=}\overset{+}{O}Me}$. Also the positive test for a malondialdehyde



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derivative would be in agreement with the proposed structure because acid hydrolysis followed by periodate oxidation would give the malondialdehyde derivative OHC CH (Se CH_2CHO) CHO. A similar compound, namely the 4-nitrophenylhydrazone of D-threo-3,4-di-O-acetyl-2,3,4,5-tetrahydrofurfuraldehyde, was formed[9] when 2-deoxy-2-bromo-3,4-di-O-acetyl-D-xylose was treated with *p*-nitrophenylhydrazine. Lemieux[10] obtained the dimethyl acetal of chitose triacetate from methyl 2-deoxy-2-iodo-β-D-glucopyranoside triacetate on treatment with acetate ions and bromine followed by methanolysis. This is the first time that a 2,5-anhydro compound has been obtained from the methanolysis of 1,2-isopropylidene sugars. Further work on this reaction is in progress. Presumably the nucleophilic selenium at C_5 assisted by acid results in the displacement of the OH at C_2 to form the above 2,5-anhydro isomers.

EXPERIMENTAL

TLC was conducted on Merck Kieselgel-G with 15% MeOH in benzene as irrigant. A 10% soln of H_2SO_4 in EtOH was used as a spray reagent and plates were heated on a hot plate to develop colour.

M.ps were determined in an electrically heated copper block.

IR spectra were measured with a Perkin–Elmer, model 137 IR Spectrophotometer. NMR spectra were measured on a Varian A-60 spectrophotometer. Chemical shifts are given in τ units at 60 Mc/s downfield from TMS as internal standard. Mass spectra were determined on an A.E.I. MS9 mass spectrometer.

5-*Deoxy*-1,2-O-*isopropylidene-5-selenocyanate-α-*D*-xylofuranose*

A soln of 1,2-O-isopropylidene-5-O-*p*-toluene-sulphonyl-α-D-xylofuranose[9] (5 g) and potassium selenocyanate[11] (2·5 g) in EtOH (40 ml) was refluxed for 60 hr. The reaction mixture was evaporated to dryness and the residue extracted with Chf. The Chf extracts were washed with water and dried with Na_2SO_4. The Chf was evaporated to give a solid, which crystallized from AcOEt–hexane to give 1·5 g of compound, m.p. 171–172°; $[\alpha]_D^{26}$ −110 (*c*, 1·0 in MeOH). (Found: C, 38·6; H, 4·4; Se, 28·3. $C_9H_{13}O_4SeN$ requires: C, 38·8; H, 4·7; Se, 28·4%.)

5-*Deoxy*-1,2-O-*isopropylidene-5-seleno-α-*D*-xylofuranose*

A soln of the selenocyanate (1·65 g) in MeOH (30 ml) was treated with Na (0·27 g). The soln was allowed to stand overnight and gave an immediate colour with 2,3,5-triphenyl-2H-tetrazolium chloride. The diselenide (1 g) had separated and the filtrate was deionized and evaporated to give a further 0·4 g of the diselenide. The diselenide crystallized from AcOEt, m.p. 180°; $[\alpha]_D^{26}$ −109 (*c*, 1·5 in MeOH). (Found: C, 38·2; H, 5·0; Se, 31·6. $C_{16}H_{26}O_8Se_2$ requires: C, 38·0; H, 5·2; Se, 31·3%.)

Acetyl derivative. The diselenide (0·5 g) was dissolved in pyridine (2·5 ml) and Ac_2O (2·5 ml). The soln, after standing overnight, was poured into water. The solid (0·55 g) which separated, was crystallized from dilute alcohol, m.p. 101°; $[\alpha]_D^{26}$ −24 (*c*, 1·0 in MeOH). (Found: Se, 26·5. $C_{20}H_{30}O_{10}Se_2$ requires: Se, 26·8%.)

5-*Deoxy*-1,2-O-*isopropylidene-5-selenobenzyl-α-*D*-xylofuranose*

A soln of benzyl selenol[12] (20 g) in MeOH (100 ml) was treated with Na (2·7 g) in an atmosphere of N_2. The tosyl ester (20 g) was added and the soln refluxed for 6 hr. The soln was evaporated and

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the residue repeatedly extracted with Chf. The combined chf extracts were washed twice with dil NaOHaq, twice with ice-cold 0·1N HCl, sat $NaHCO_3$aq and finally dried over Na_2SO_4. The chf was evaporated and the residue crystallized from AcOEt on addition of hexane, 12·0 g, m.p. 106°; $[\alpha]_D^{25}$ −61 (*c*, 1·4 in MeOH). (Found: C, 52·6; H, 5·6; Se, 23·2. $C_{15}H_{20}O_4Se$ requires: C, 52·5; H, 5·8; Se, 23·0%.)

Reduction of the benzyl ether. To a soln of the benzyl ether (15 g) in liquid ammonia (250 ml) (under a blanket of N_2) small pieces of Na were added until the blue colour which developed was stable for 10 min. Enough NH_4Cl was added to discharge the blue colour and a further 25 g NH_4Cl was then added. The NH_3 was allowed to evaporate and the residue was extracted with chf. The chf soln contained the required selenol but evaporation and subsequent crystallization even under N_2 led to the isolation of diselenide (8·0 g), m.p. 180° (from AcOEt). Another reduction was done as above except that when the blue colour remained after addition of Na, the NH_3 was allowed to evaporate without the addition of NH_4Cl. The last traces of NH_3 were removed under reduced press. To the solid residue MeOH (150 ml) was added and the soln stirred with an excess of dry Amberlite IR 120 (H) until neutral. The methanolic soln was filtered and the resin repeatedly washed with MeOH (150 ml total). To the combined methanolic filtrate HCl (5 g) was added and the soln was allowed to stand at room temp for 2 days. During this period some selenium usually separated. All these operations were conducted under N_2. Paper chromatography of the reaction mixture, using a variety of developers, showed only an elongated spot. TLC revealed the presence of at least 8 components, R_f minor components, 0·16, 0·40, 0·55, 0·75, 0·94 and major components, 0·20, 0·26, 0·30. The methanolic soln was neutralized by passage through a column of Dowex 45 (OH^-) and the eluate evaporated. The syrupy residue (7·0 g) was applied to a column of silica gel (250 g) and eluated with a soln of 15% MeOH in benzene. The faster moving components were unstable syrups which were readily oxidized to selenium on esposure to air.

The compound (R_f 0·30, 1·5 g) crystallized on prolonged storage. Recrystallized from AcOEt–hexane, m.p. 59°; $[\alpha]_D^{25}$ +53 (*c*, 2·0 in MeOH or water). During periodate oxidation, it consumed 3·2 moles of oxidant in 6 hr and 5·0 moles in 10 hr. NMR ($CDCl_3$) 5·46 (one proton; doublet; J, 7·2 c/s); 6·55 and 6·62 (3 protons each; singlets two OMe). (Found: C, 34·8; H, 6·0; Se, 32·1; OMe, 25·5; Mol. wt. 242, mass spectrometry. $C_7H_{14}O_4Se$ requires: C, 34·9; H, 5·8; Se, 32·8; OMe, 25·6; Mol. wt. 242, Se = 80.) It formed a syrupy diacetate, $[\alpha]_D^{25}$ +40 (*c*, 2·9 in chf). (Found: Se, 24·2; Mol. wt., 326, mass spectrometry. $C_{11}H_{18}O_6Se$ requires: Se, 24·3; Mol. wt., 326, Se = 80.) NMR ($CDCl_3$) 4·40–4·70 (2 protons; complex; protons on C_3 and C_4); 5·39 (one proton; doublet; J, 8·4 c/s; C*H*$(OMe)_2$); 6·60 and 6·65 (6 protons; singlets; two OMe); 7·92 (6 protons; singlets; 2 OAc). Mass spectrum, 326 (M, 2·5%) 295 (M-31, 1·0%), 235 (M-31–60, 5·4%), 192 (5·3%), 132 (12·7%), 75 (100%).

The compound (1·2 g) R_f 0·26, crystallized from AcOEt, m.p. 121°; $[\alpha]_D^{25}$ −65 (*c*, 1·3 in MeOH or water). On periodate oxidation it consumed 1·0 mole in 7 hr and 1·2 mole in 24 hr. NMR (D_2O), 5·20 (one proton; doublet; J, 8·5 c/s); 6·53, 6·58 (singlets; 3 protons each; two OMe). (Found: C, 34·9; H, 5·8; Se, 32·3; OMe, 25·9; Mol. wt. 242, mass spectrometry. $C_7H_{14}O_4Se$ requires: C, 34·9; H, 5·8; Se, 32·8; OMe, 25·6; Mol wt. 242, Se = 80.) It formed a syrupy diacetate. $[\alpha]_D^{25}$ −83 (*c*, 0·8 in chf). (Found: Se, 24·1; Mol. wt., 326, mass spectrometry. $C_{11}H_{18}O_6Se$ requires: Se, 24·3; Mol. wt., 326, Se = 80.) NMR ($CDCl_3$) 4·55–4·66 (2 protons; complex; protons on C_3 and C_4); 5·35 (one proton; doublet; J, 8·5 c/s; C*H*$(OMe)_2$); 6·69, 6·63 (6 protons; singlets; 2 OMe); 7·88, 7·90 (6 protons; singlets; 2 OAc). Mass spectrum, 326 (M, 1·8%), 295 (M-31, 2·5%), 235 (M-31–60, 5·7%), 192 (8·1%), 132 (7·9%), 75 (100%).

The syrup (1·5 g), R_f 0·20 was chromatographed again. $[\alpha]_D^{25}$ −73·5 (*c*, 1·0 in MeOH). (Found: C, 32·3; H, 5·1; Se, 34·6; OMe, 13·7; Mol. wt., 448. $C_{12}H_{22}O_8Se_2$ requires: C, 31·9; H, 4·9; Se, 35·0; OMe, 13·7%; Mol. wt., 452.)

This compound was also prepared by treating the diselenide (100 mg) overnight at 25° with 1% HCl in MeOH (10 ml).

Methanolysis. Either of the crystalline isomers (100 mg) was dissolved in separate portions of MeOH (5 ml) containing 2% HCl. The solns were allowed to stand at 25° and examined periodically by TLC and polarimetry. After 5 hr both solns showed major components of R_f 0·26, 0·30, and minor components of R_f 0·16, 0·20, 0·55. The optical rotations of both fell to zero during the treatment.

Hydrolysis. A soln of either of the crystalline isomers (100 mg) in 0·2N HCl (5 ml) was allowed to stand at 25°. After one week both solns had the major components of R_f 0·20, 0·22, 0·26, 0·30 and minor component of R_f 0·55. A plate was also sprayed with sodium metaperiodate soln followed by Schiff's reagent as described,[7] yellow spots of identical R_f (0·30, very faint at 0·22) were obtained for both solns. The optical rotations were − 115° and +60° respectively after 0·5 hr and then gradually changed to nearly zero over a period of 12 days.

Hydrazones. Either of the crystalline isomers (100 mg) was treated with a warm soln of 2,4-dinitrophenylhydrazine in 30% perchloric acid (15 ml) and allowed to stand overnight. The red solid was crystallized from dilute pyridine, (yield 130 mg), m.p. 236–238°, the mixture m.p. with the 2,4-dinitrophenylhydrazone of 2-formylselenophene[13] was unchanged.

A soln of 20 mg of the isomer (m.p. 121°) in 0·2N HCl (5 ml) was allowed to stand at room temp for 15 min and a soln of 2,4-dinitrophenylhydrazine in 30% perchloric acid (15 ml) was added. The soln was allowed to stand a further 5 min the solid which separated, was crystallized from EtOH, m.p. 187–188°; $[\alpha]_D^{25}$ −214 (*c*, 0·7 in pyridine–EtOH 1:1 v/v) constant during 5 days. (Found: C, 35·1; H, 3·2; N, 14·8; Mol. wt., 376, mass spectrometry. $C_{11}H_{12}O_6N_4Se$ requires: C, 35·2; H, 3·2; N, 14·9%; Mol. wt., 376, Se = 80.)

The isomeric compound (m.p. 59°) gave 0·22 g of the 2,4-dinitrophenylhydrazone by the same procedure. The compound was crystallized from AcOEt–hexane, melting began at 129° but was sharp at 156–157°. This behaviour was not altered on repeated crystallization; $[\alpha]_D^{25}$ +198 (*c*, 1·3 in pyridine–EtOH 1:1 v/v) constant during 5 days. (Found: C, 35·0; H, 3·0 N, 14·7; Mol. wt., 376, mass spectrometry. $C_{11}H_{12}O_6N_4Se$ requires: C, 35·2; H, 3·2; N, 14·9%; Mol. wt., 376, Se = 80.)

The IR spectra of the above two hydrazones were similar over the range 4000–640 cm^{-1}. The hydrazone of the isomer, m.p. 121° showed two peaks at 872 and 851 cm^{-1} which were not present in the spectrum of the isomeric hydrazone. Both hydrazones were converted to the 2,4-dinitrophenylhydrazone of 2-formyl selenophene, on brief heating with 2N HCl.

Removal of selenium. A soln of either of the crystalline isomers (100 mg) in EtOH (5 ml) was refluxed for 5 hr with Raney Ni (2 g). The soln was filtered and the Raney Ni washed repeatedly with hot EtOH. The combined filtrate and washings were evaporated to give a syrup (70 mg). The major components have R_f of 0·29 and the minor components have R_f of 0·22, 0·39, 0·46, in either case. These components appeared on treatment with conc H_2SO_4 in the cold. The same treatment of the diselenide yielded a syrup with a major component of R_f 0·28 and minor components of R_f 0·16 and 0·21. These components appeared after prolonged treatment with conc H_2SO_4 at 100°.

Methyl 5-deoxy-D-xylofuranose. A soln of 5-deoxy-1,2,-O-isopropylidene-5-thio-D-xylofuranose[8] (1 g) in EtOH (25 ml) was refluxed for 3 hr with Raney Ni (10 g). The soln was filtered and the Raney Ni washed with hot EtOH. Evaporation of filtrate gave a syrupy residue which slowly solidified. It was crystallized from hexane, m.p. 69–70°; with the same constants reported by Levene[14] for 5-deoxy-1,2-O-isopropylidene-D-xylofuranose.

Methanolysis of the above compound gave a product, R_f 0·28 which was identical with the compound obtained above by the removal of the selenium from the diselenide.

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