Carbohydrate Research, 30 (1973) 381–385

Note

Derivatives of 5-seleno-D-ribose

JOSE JUAN RABELO AND THEODORUS VAN ES
Department of Biochemistry, Rutgers University, New Brunswick, N.J. 08903 (U. S. A.)
(Received February 12th, 1973; accepted for publication in revised form, March 19th, 1973)

The starting material for the preparation of 5-seleno-D-ribose derivatives was methyl 2,3-*O*-isopropylidene-D-ribofuranoside[1–3]. We found that the results described by Levene and Stiller[1] depended on the proportions of methanol and sulfuric acid, and variations in the reaction conditions were investigated in order to obtain the highest yield of **1** (see Table I).

TABLE I

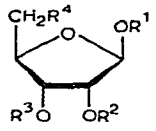
FORMATION OF METHYL 2,3-*O*-ISOPROPYLIDENE-β-D-RIBOFURANOSIDE (**1**) UNDER VARIOUS REACTION CONDITIONS

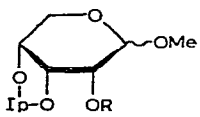
Conditions [a]	*Reaction time (h)*	1 (%)	2 (%)	3 (%)	4 (%)
A	20	91.9			
B	18	19.0	trace	81.0	
	42	78.6	0.4	21.0	
	66	95.6	1.9	2.5	
C	20	77.1	12.6	7.3	4.0
D	20	82.7	2.9	4.8	9.6
E	20	93.3	1.0	1.3	4.4
	2	27.4	47.0	trace[b]	1.3
F	20	95.6	0.4	1.2	2.8
G	20	94.0	0	3.4	2.6
H	10	91.9	3.8	0.2	4.1
I	20	95.5	3.2	1.2	

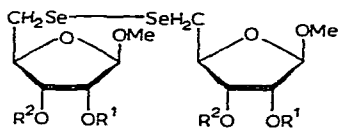
[a]The conditions were the following: (A) Methyl β-D-ribofuranoside[7] (2.4 g), acetone (20 ml), copper sulfate (2.0 g), and sulfuric acid (0.02 ml) were stirred at 37°. (B) Conditions as in A, except that no sulfuric acid was added. (C) D-Ribose (1.0 g), acetone (19 ml), methanol (1.0 ml), copper sulfate (4.0 g), and sulfuric acid (0.04 ml) were stirred at 37°. (D) Conditions as in C, except that the amount of methanol was 2.0 ml. (E) Conditions as in C, except that the amount of methanol was 5.0 ml. (F) Conditions as in C, except that the amount of methanol was 7.5 ml. (G) Conditions as in C, except that the amount of methanol was 10.0 ml. (H) Conditions as in E, except that the time of the reaction was 10 h. (I) Conditions as in E, except that the solution was heated under reflux. [b]A number of unidentified components were present.

The predominant reaction product was shown to be identical with compound **1** prepared from methyl 2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-ribofuranoside[1,4] (**5**) by displacement of the tosyloxy group with the acetate ion followed by de-acetylation. Thus, in agreement with Leonard[4] the product of the reaction was exclusively the

β-D anomer (**1**). Tosylation[1] of the crude reaction product gave the tosyl ester (**5**). Other products isolated were methyl 5-chloro-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**6**) and methyl 3,4-*O*-isopropylidene-2-*O*-tosyl-D-ribopyranoside (**7**).







1 R^1 = Me; R^2, R^3 = Ip; R^4 = OH
2 R^1 = H(α,β); R^2, R^3 = Ip; R^4 = OH
3 R^1 = Me; R^2, R^3 = H; R^4 = OH
5 R^1 = Me; R^2, R^3 = Ip; R^4 = OTs
6 R^1 = Me; R^2, R^3 = Ip; R^4 = Cl
8 R^1 = Me; R^2, R^3 = Ip; R^4 = SeCN
10 R^1 = Me; R^2, R^3 = Ip; R^4 = $SeCH_2Ph$

4 R = H
7 R = Ts

9 R^1, R^2 = Ip
11 R^1, R^2 = H
12 R^1, R^2 = Ac

Displacement of the tosyloxy group of **5** with potassium selenocyanate[5] in *N*,*N*-dimethylformamide gave methyl 5-deoxy-2,3-*O*-isopropylidene-5-selenocyanato-β-D-ribofuranoside (**8**). Treatment of this compound with sodium methoxide gave the diselenide, 5,5′-diselenobis(methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside) (**9**). This diselenide (**9**) was also obtained from the tosyl ester (**5**) by prolonged treatment with potassium selenocyanate in boiling methoxyethanol or by treatment with bis(methoxymagnesium) selenide[6]. The tosyloxy group was smoothly displaced by the benzyl selenolate ion to give methyl 5-*Se*-benzyl-2,3-*O*-isopropylidene-5-seleno-β-D-ribofuranoside (**10**). Compounds **9** and **10** were reduced with sodium in ammonia[5] to the selenol derivative. An attempt was made to introduce selenium in the ribopyranose ring by treatment of the selenol derivation with methanolic hydrogen chloride. The diselenide **9** was the main reaction product, the isopropylidene group having not been removed to any major extent. Methanolysis of reduced 5,5′-diselenobis(methyl 5-deoxy-D-ribofuranoside) (**11**) also led to the recovery of the starting compound. Hypophosphorous acid reduces diselenides to selenols in acidic solution[8], and the oxidation of the selenol derivatives to the diselenides **9** and **11** during the methanolysis was prevented by addition of hypophosphorous acid. Reduction to the selenol derivatives was shown by the disappearance of the characteristic yellow color of diselenides and by a positive 2,6-dichlorophenolindophenol test[8]. However, the only products isolated were the diselenides **9** and **11**.

EXPERIMENTAL

General methods. — Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Column chromatography was carried out on silica gel (60–200 mesh), G.l.c. was performed on a F and M, model 609, gas chromatograph specially modified for on-column injection, with a flame-ionization detector and a

560 × 2.2-mm stainless-steel column, packed with 3% JXR silicone on 100–200 mesh Gas-Chrom Q; the temperature was linearly programmed from 125 to 195° at a rate of 2.3° per min. The per(trimethylsilyl) derivatives of the mixtures analyzed were prepared with Tri-Sil Z before analysis. I.r. spectra were recorded on a Perkin–Elmer 700 spectrophotometer, and n.m.r. spectra with a Varian T-60 spectrometer. Chemical shifts are quoted in p.p.m. units, tetramethylsilane being the internal standard. Mass spectra were determined with a Hitachi Perkin–Elmer RMU7 mass spectrometer. Evaporations were conducted under diminished pressure at a bath temperature below 50°.

Methyl 2,3-O-isopropylidene-5-O-tosyl-β-D-ribofuranoside (**5**). — The crude reaction product (condition H, Table I, 2.04 g), was tosylated as described by Levene and Stiller[1]. The tosyl ester[1] (**5**), m.p. 83–84° (2.4 g, 67.5%) was obtained. The mother liquor was evaporated and the residue applied to a column of silica gel with 1:49 methanol–benzene as the eluant. A further amount of the tosyl ester (0.25 g, 7.0%) and methyl 5-chloro-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**6**) (0.37 g, 16.7%) were recovered.

The residue from another tosylation experiment was heated for 12 h under reflux with anhydrous sodium acetate (5.0 g) in methoxyethanol (20 ml). The solution was evaporated, and the residue extracted with chloroform and water. The chloroform extract was evaporated, and the residue applied to a column of silica gel with 1:49 methanol–benzene as the eluant. Methyl 3,4-*O*-isopropylidene-2-*O*-tosyl-D-ribopyranoside (**7**, 0.12 g, 3.4%) having the same constants as those described by Levene and Stiller[1] was isolated.

Methyl 5-chloro-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (**6**). — The tosyl ester (**5**, 1.0 g), lithium chloride (1.5 g), and *N,N*-dimethylformamide (15 ml) were heated for 4 h under reflux. The mixture was evaporated, and the residue extracted with chloroform and water. The chloroform extract was evaporated to a syrup (0.45 g) which was chromatographed on silica gel with 1:99 methanol–benzene as the eluant; $[\alpha]_D^{20}$ −91° (*c* 3.29, chloroform); n.m.r. data (chloroform-*d*): δ 1.42 (6-proton doublet, *J* 10 Hz, $C(Me_2)$, 3.37 (3-proton singlet, OMe), 3.60 (1-proton singlet), 3.90–4.45 (2-proton complex), 4.55–4.80 (2-proton complex), and 5.00 (1-proton singlet, H-1).

Anal. Calc. for $C_9H_{15}ClO_4$: C, 48.51; H, 6.74. Found: C, 48.56; H, 6.73.

Methyl 5-deoxy-2,3-O-isopropylidene-5-selenocyanato-β-D-ribofuranoside (**8**). — The tosyl ester (**5**, 5.0 g), potassium selenocyanate[5] and *N,N*-dimethylformamide (15 ml) were heated for 15 min under reflux. The solution was evaporated, and the residue extracted with chloroform and water. The chloroform extract was evaporated, and the residue crystallized from ethyl acetate–petroleum ether (40–60°) (3.0 g), m.p. 75–76°; $[\alpha]_D^{19}$ −21° (*c* 1.0, chloroform); i.r. datum: $\nu_{max}^{CHCl_3}$ 2100 cm^{-1} (SeCN); n.m.r. data (chloroform-*d*): δ 1.26 (6-proton doublet, *J* 10 Hz, $C(Me_2)$, 3.20–3.34 (2-proton complex), 3.42 (3-proton singlet, OMe), 4.38–4.51 (1-proton complex), 4.70 (2-proton singlet), and 5.01 (1-proton singlet, H-1); m.s. data: 278(276) ($M^+ - Me$), 261(259) ($M^+ - MeOH$).

Anal. Calc. for $C_{10}H_{15}NO_4Se$: C, 41.10; H, 5.14. Found: C, 41.02; H, 5.16.

5,5'-Diselenobis(methyl 5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside) (**9**). — The selenocyanate (**8**, 2.8 g) was dissolved in methanol (25 ml) containing sodium (0.27 g). The solution was kept overnight at room temperature, and then evaporated, and the residue extracted with chloroform and water. The chloroform extract was evaporated, and the residue crystallized from ethyl acetate–petroleum ether (40–60°), m.p. 62°; $[\alpha]_D^{18}$ −98° (*c* 2.14, chloroform); n.m.r. data (chloroform-*d*): δ 1.45 (6-proton doublet, *J* 9 Hz, CMe_2), 3.03–3.36 (2-proton complex), 3.40 (3-proton singlet, OMe), 4.37–4.75 (3-proton complex), and 5.02 (1-proton singlet, H-1).

Anal. Calc. for $C_{18}H_{30}O_8Se_2$: C, 40.61; H, 5.64. Found: C, 40.57; H, 5.62.

(*b*). The tosyl ester (**5**, 5.0 g), potassium selenocyanate (3.0 g), and methoxyethanol (50 ml) were heated for 6 h under reflux. The diselenide **9** (2.6 g) was isolated as just described.

(*c*) The tosyl ester (**5**, 5.0 g) was added to a boiling solution of bis(methoxy magnesium) selenide, prepared from magnesium (1.5 g), selenium (4.0 g), and methanol (125 ml) as described by Gunther[6]. The solution heated for 4 h at reflux under nitrogen, and then evaporated, and the residue extracted with chloroform and ice-cold, dilute hydrochloric acid. The chloroform extract was washed with sodium hydrogen carbonate solution and water, dried with sodium sulfate, and evaporated. The residue crystallized to give the diselenide **9** (2.8 g).

Methyl 5-Se-benzyl-2,3-O-isopropylidene-5-seleno-β-D-ribofuranoside (**10**). — Benzyl selenol[5] (7.5 g) and then the tosyl ester (**5**, 10.0 g) were added to methanol (50 ml) which contained sodium (0.98 g), and the solution was heated for 4 h at reflux. All operations were conducted under dry nitrogen. The solution was evaporated, and the residue extracted with chloroform and water. The chloroform extract was evaporated to a syrup which was dissolved in the minimum amount of warm ethanol. The solution was kept in a freezer, and the dibenzyl diselenide that separated was filtered off. The solution was evaporated to a syrup (8.5 g) which was sufficiently pure for subsequent reactions. A pure sample of the compound was obtained by chromatography on silica gel with 1:99 methanol–benzene as the eluant, $[\alpha]_D^{20}$ −96° (*c* 2.0, chloroform); n.m.r. data (chloroform-*d*): δ 1.37 (6-proton doublet, *J* 11 Hz, CMe_2), 2.50–2.68 (2-proton complex), 3.28 (3-proton singlet, OMe), 3.80 (2-proton singlet, $PhCH_2Se$), 4.03–4.37 (2-proton complex), 4.55 (2-proton singlet), 4.94 (1-proton singlet, H-1), 7.30 (5-proton singlet, Ph); m.s. data: 358(356) (M^+), 343(341) ($M^+ - Me$), 327(325) ($M^+ - MeO$), 312(310) ($M^+ - Me - MeO$).

Anal. Calc. for $C_{16}H_{22}O_4Se$: C, 53.61; H, 6.15. Found: C, 53.50; H, 6.16.

The selenobenzyl ether (**10**, 3.0 g) or the diselenide (**9**) was added to liquid ammonia (25 ml). All subsequent operations were performed under dry nitrogen. Sodium was added in small pieces until the blue color that developed was stable for 15 min. The ammonia was evaporated, and a suspension of Amberlite IR-120 (H^+) ion-exchange resin in methanol was added until the solution was neutral. The resin was removed, and 2% methanolic hydrogen chloride (50 ml) was added. In another experiment, hypophosphorous acid (50%, 1 ml) was also added. The solution was

kept overnight at room temperature (or heated for 2 h under reflux), and was then neutralised by passage over Dowex 45 (OH^-) ion-exchange resin. The eluate was evaporated to a syrup which consisted of a major migrating fast component on silica gel t.l.c. and a trace of a migrating component. The syrup was applied to a column of silica gel and eluted with 1:9 methanol–benzene to give the major compound (2.3 g), m.p. 62°, identical with the diselenide **9**.

5,5'-Diselenobis(methyl 5-deoxy 2,3-di-O-acetyl-β-D-ribofuranoside) (**12**). — Methyl 5-*O*-tosyl-β-D-ribofuranoside[7] (5.0 g), potassium selenocyanate (4.0 g), and methoxyethanol (50 ml) were heated for 6 h under reflux. The solution was evaporated and acetic anhydride (10 ml) and pyridine (10 ml) were added to the residue with cooling. The mixture was kept overnight at room temperature, and then diluted with water. Solid sodium hydrogen carbonate was added until the solution was neutral. The solution was extracted with chloroform, and the extracts were successively washed with ice-cold, dilute hydrochloric acid, sodium hydrogen carbonate solution, and water and dried with sodium sulfate. The chloroform was evaporated to a syrup (4.8 g). A portion of this syrup was purified by chromatography on silica gel with 1:99 methanol–benzene as eluant; $[\alpha]_D^{20}$ −44° (*c* 1.39, chloroform); i.r. datum: ν_{max}^{film} 1635 cm^{-1} (C=O); m.s. datum: 460(458) ($M^+ - 2 \times AcOH - CH_2CO$); the intensities of the isotopes peaks indicated 2 atoms of selenium per molecule of compound.

Anal. Calc. for $C_{20}H_{30}O_{12}Se_2$: C, 38.71; H, 4.84. Found: C, 38.65; H, 4.80.

Deacylation of **12** in methanol with a catalytic amount of sodium methoxide gave 5,5'-diselenobis(methyl 5-deoxy-β-D-ribofuranoside) (**11**), $[\alpha]_D^{20}$ −56° (*c* 1.5, chloroform); i.r. data: ν_{max}^{film} 3450 cm^{-1} (OH); m.s.: 422(420) ($M^+ - MeOH$), 390(388) ($M^+ - MeOH - MeOH$); the ratio of the isotope peaks showed the presence of two atoms of selenium per molecule of compound.

Anal. Calc. for $C_{12}H_{22}O_8Se_2$: C, 31.85; H, 4.23. Found: C, 31.82; H, 4.25.

The diselenide **12** (1.0 g) was reduced and methanolyzed as described for **9**. The diselenide **11** (0.70 g) was the only product isolated.

ACKNOWLEDGEMENT

One of us (J. R.) wishes to thank the University of Puerto Rico for financial support.

REFERENCES

1 P. A. Levene and E. T. Stiller, *J. Biol. Chem.*, 104 (1934) 299.
2 E. J. Reist, R. R. Spencer, M. E. Wain, I. G. Junga, L. Goodman, and B. R. Baker, *J. Org. Chem.*, 26 (1961) 2821.
3 J. A. Montgomery and K. Hewson, *J. Org. Chem.*, 29 (1964) 3436.
4 N. J. Leonard and K. L. Carraway, *J. Heterocycl. Chem.*, 3 (1966) 485.
5 T. van Es and R. L. Whistler, *Tetrahedron*, 23 (1967) 2849.
6 W. H. H. Gunther, *J. Org. Chem.*, 32 (1967) 3929.
7 B. Green and H. Rembold, *Chem. Ber.*, 99 (1966) 2162.
8 W. H. H. Gunther and H. G. Mautner, *J. Med. Chem.*, 8 (1965) 845.