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Coriose and Related Compounds. VII.[1] Tautomerization of Crystalline α-Coriofuranose upon Trimethylsilylation[2]

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Crystalline coriose which forms α-furanose yielded a product (III) at the initial stage of the trimethylsilylation, and other two products (IV and V) upon prolonged trimethylsilylation. Increase of IV and V at the expense of III was observed in gas–liquid chromatography. These products were isolated by distillation and chromatography, and the structures of III, IV, and V were elucidated to be 1,2,4,5,7-pentakis-O-trimethylsilyl-α-coriofuranose, 1,2,3,4,5,7-hexakis-O-trimethylsilyl-α-coriofuranose, and 1,2,4,5,6,7-hexakis-O-trimethylsilylcoriose of keto-form, respectively.

It has generally been known that crystalline carbohydrates are trimethylsilylated retaining the original ring structures to exhibit a single peak by the gas–liquid chromatography (GLC), and that trimethylsilylated syrups show GLC peaks of the tautomers in the equilibrated mixtures.[4] However, crystalline coriose (D-*altro*-3-heptulose) (I), which was proved by the X-ray crystallography to form α-furanose (II),[5] was reported in a previous paper of this series to show a complicated pattern of the gas chromatogram of trimethylsilyl (TMS) derivatives.[6] The GLC peak which was almost a singlet for a short while decreased in the peak area on prolonged trimethylsilylation, and two new peaks appeared in the gas chromatogram, when trimethylsilylation was performed with pyridine solution of trimethylchlorosilane and hexamethyldisilazane. Increase of the new products at the expense of the initial product was observed by repeated GLC, until the final product of trimethylsilylation was shown by GLC to be composed wholly of the two new products. It has been reported that partially trimethylsilylated derivatives of carbohydrates are obtained by the trimethylsilylation for very short time[7] or by using a limited amount of the reagent.[8] However, the slow transformation in the gas chromatogram during the trimethylsilylation such as that observed with coriose has not been found with other sugars. The isolation and structure determination of trimethylsilylated derivatives from crystalline coriose are described in the present paper.

The gas chromatogram obtained on OV-17 column (Fig. 1) shows the initially formed trimethylsilyl derivative of coriose by the peak of R_{GLU} (Retention time relative to fully trimethylsilylated α-D-glucopyranose) 2.30 (III), and the other two products by the peaks of R_{GLU} 1.80 (IV) and R_{GLU} 2.37 (V). The ratio of the peak areas of the latter two products in the final product mixture was not always equal. It varied between 1:3 and 2:1 when the experiment was carried out repeatedly. It took about 5 hours at 20° to obtain the mixture

1) Part VI: T. Okuda, S. Saito, and K. Uobe, *Tetrahedron*, **30**, 1187 (1974).
2) A preliminary short communication: T. Okuda and K. Konishi, *Chem. Commun.*, **1969**, 1117.
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4) C.C. Sweeley, R. Bentley, M. Makita, and W.W. Wells, *J, Am. Chem. Soc.*, **85**, 2497 (1963).
5) T. Okuda, K. Osaki, and T. Taga, *Chem. Commun.*, **1969**, 851; T. Taga, K. Osaki, and T. Okuda, *Acta Cryst.*, **B26**, 991 (1970).
6) T. Okuda and K. Konishi, *Yakugaku Zasshi*, **89**, 1407 (1969).
7) C.C. Sweeley, *Bull. Soc. Chim. Biol.*, **47**, 1477 (1965).
8) L. Birkofer, R. Ritter, and F. Bentz, *Chem. Ber.*, **97**, 2196 (1964); S.M. Kim, R. Bentley, and C.C. Sweeley, *Carbohyd. Res.*, **5**, 373 (1967).

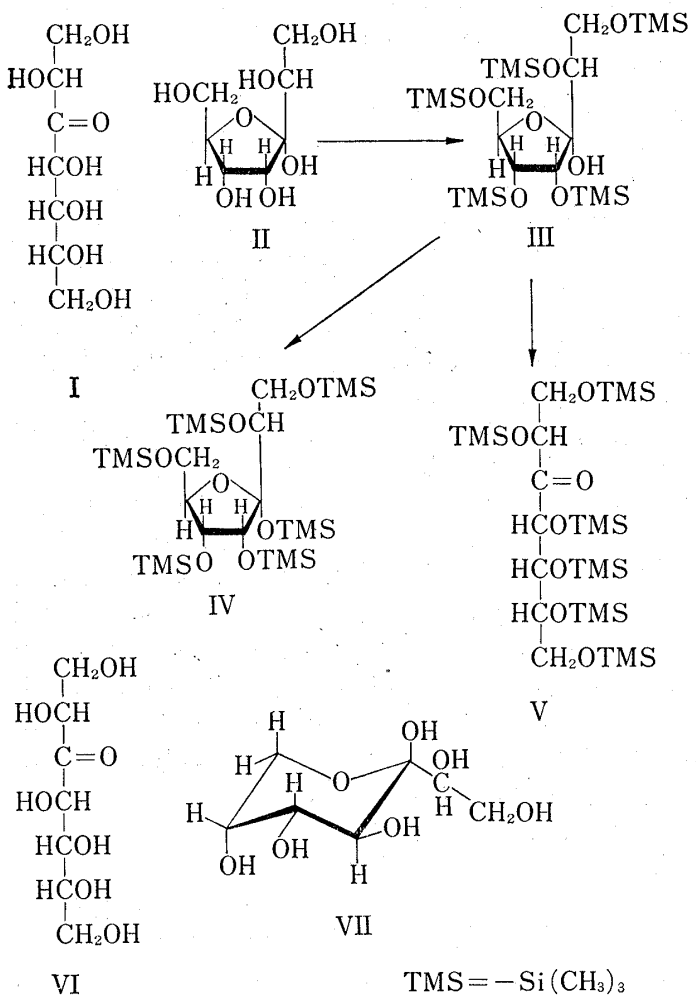

Chart 1

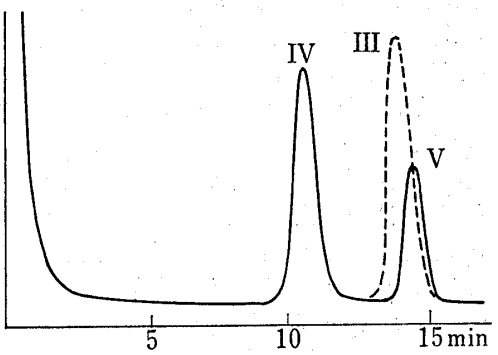

Fig. 1. GLC of Trimethylsilyl Derivatives of Coriose (OV–17)

which showed III and the average of IV and V to be equal in the peak area of the gas chromatogram. The production of the final product mixture was completed in 12 hours at the room temperature. The gas chromatograms obtained on non-polar and polar stationary phases such as SE-30[6] and NPGS also showed three peaks.

The initial trimethylsilyl derivative (III) was best prepared by the reaction under ice-cooling with a limited amount of the reagent. The GLC peak of III alone was exhibited for the period of almost one hour. As the trimethylsilyl derivatives of some carbohydrates are known to be purified by vacuum distillation,[9] III was distilled in vacuum, and the distillate was identified by thin-layer chromatography (TLC) and GLC with III in the reaction mixture. The distillate was also shown to be practically pure by GLC on the above shown stationary phases, by TLC, and by the singlet of hydroxyl proton in the nuclear magnetic resonance (NMR) spectrum in dimethyl sulfoxide (DMSO). It was analyzed as $C_{22}H_{54}O_7Si_5$, showed a hydroxyl absorption at 3400 cm^{-1} in the infrared (IR) spectrum, and *m/e* 552 (M-18) ion peak in the mass spectrum. Therefore, III is presumed to be pentakis-*O*-trimethylsilylcoriose in which the free hydroxyl group is at C-3. The furanoid structure of crystalline coriose would most probably be retained in this initial product because it is formed in a very short time as shown by the appearance of the GLC peak upon injection in 2 minutes after addition of the reagent to crystalline coriose. The mass spectrum of III also showed strong *m/e* 217 $(TMSO{=}CHCH{=}CHOTMS)^+$ peak and weak *m/e* 204 $(TMSO{-}CH{=}CH{-}OTMS)^{+\cdot}$ peak. As it has been approved that in the mass spectra of the derivatives of aldoses[10] and 2-ketoses,[11] $(RO{-}CH{=}CH{-}OR)^{+\cdot}$ (R=Me, *m/e* 88; R=TMS, *m/e* 204) ion peak is strong in the pyranoids,

9) E.J. Hedgley and W.G. Overend, *Chem. Ind.*, **1960**, 378.
10) N.K. Kochetkov and O.S. Chizov, "Advan. Carbohyd. Chem.," Vol. 21, ed. by M. Wolfrom, Academic Press, New York and London, 1966, pp. 39—93; O.S. Chizov, N.V. Molodtsov, and N.K. Kochetkov, *Carbohyd. Res.*, **4**, 273 (1967); D.C. DeJongh, T. Radford, J.D. Hribar, S. Hanessian, M. Bieber, G. Dawson, and C.C. Sweeley, *J. Am. Chem. Soc.*, **91**, 1728 (1969).
11) T. Okuda and K. Konishi, *Chem. Commun.*, **1969**, 796; H.-Ch. Curtius, M. Müller, and J.A. Völlmin, *J. Chromatog.*, **37**, 216 (1968); S. Karady and S.H. Pines, *Tetrahedron*, **26**, 4527 (1970).

while $(RO{=}CHCH{=}CH{-}OR)^+$ (R=Me, *m/e* 101; R=TMS, *m/e* 217) peak is strong in furanoids, III is presumed to be a furanoid if the assignment based on such ratio of the intensities of these fragment ion peaks is applicable to 3-heptuloses.

The final products of the trimethylsilylation, IV and V, were prepared as their mixture by the reaction with excess reagent at room temperature, and the two constituents in the mixture were isolated by preparative TLC or by column chromatography, upon which IV moved faster than V. One of the products, IV, $C_{25}H_{62}O_7Si_6$, obtained as a syrup, showed neither hydroxyl absorption in the IR spectrum, nor absorption of ketone in the UV, IR and optical rotatory dispersion (ORD) spectra. The mass spectrum showed *m/e* 627 (M−15) ion peak, and strong *m/e* 437 peak which is presumed to be produced by the loss of C-1—C-2 portion from the fully trimethylsilylated ring structure. Strong *m/e* 217 peak and weak *m/e* 204 peak, which are indicative of the furanoid structure, are also shown.

Another syrupy final product (V), $C_{25}H_{62}O_7Si_6$, also showed no IR absorption of hydroxyl group, but it exhibited a carbonyl absorption at 1722 cm^{-1}. The presence of ketone is shown by the UV absorption at 282 nm (ε=102), and by the negative cotton effect in the ORD spectrum $[\phi]^{20}_{316}$ −2680°, $[\phi]^{20}_{262}$ +3480°. The NMR spectrum showed downfield shift of two protons which are presumed to be on the carbons adjacent to the carbonyl group to δ 4.49 and 4.64. The mass spectrum showed *m/e* 642 (M^+) peak. Strong *m/e* 205 peak was shown and is regarded as characteristic of the keto-form as the TMS ethers of keto-form of some 2-ketoses are known to exhibit strong *m/e* 205 peak.[11] The product (V) is accordingly 1,2,4,5,6,7-hexakis-O-trimethylsilylcoriose of the keto-form. The production of IV and V *via* (III) gives an additional proof of the assignment of the structures, 1,2,4,5,7-pentakis-O-trimethylsilylcoriofuranose for III and 1,2,3,4,5,7-hexakis-O-trimethylsilylcoriofuranose for IV.

The anomeric configurations at C-3 of III and IV would be α- if crystalline α-coriofuranose (II) has been trimethylsilylated retaining the original anomeric configuration. Although structure II is regarded as being unstable on the basis of the conformational analysis,[5] this assumption is supported by the fact that the initial product (III) has been prepared by several reaction conditions including that under low-temperature with a limited amount of the reagent. This product as well as the two final products have always been found to show identical single peaks when analyzed by GLC on polar, non-polar, and weakly polar stationary phases. This assignment is also in accord with the velocity of the trimethylsilylation of carbohydrates in general, which has been regarded as being fast enough to leave the original anomeric configuration.[4]

However, III may be regarded as β-anomer produced by anomerization of α-furanose, when based on the lability of II in terms of the conformational analysis. The structure of IV would then also be regarded as β-furanose. This assumption is supported by the fact that the GLC peaks of III and IV in the trimethylsilylating reagent solution and those of the distilled syrup are shown as the same pair of singlets. It would be considered that the unstable structure such as III in α-form might be anomerized to β-furanose during the treatment such as vacuum distillation. But it is rather unusual that complete anomerization of α-furanose such as that of coriose occurred without leaving a trace of α-anomer.

The product (III) may also be presumed to be the equilibrium mixture of α- and β-anomer, if the retention time of α- and β-anomer happens to be almost equal. The peak of IV then would be regarded as due to the mixture of α- and β-anomer, or one of the anomers of IV is hidden in the peak of V. This may happen even if III is composed by α-anomer only, and this assumption may also be supported by the identical retention time of the products in the reagent solution and in the syrup. However, it is rather unlikely that the pair of anomers of both pentakis- and hexakis-O-TMS ether show almost identical retention time of GLC on several stationary phases of different polarity. The mass fragmentography[12] by multiple

12) C.C. Sweeley, W.H. Elliott, I. Fries, and R. Ryhage, *Anal. Chem.*, 38, 1549 (1966).

ion detector (MID) instrument monitored with *m/e* 204, 205 and 217 ion peaks showed that there is no furanoid of close retention time to that of V hidden in the GLC peak of the latter. It appears, therefore, to be more likely that the GLC peaks of III and IV represent α-anomers than otherwise.

Further analysis was performed with III, IV and V in the reagent solution, by combined gas chromatography-mass spectrometry (GC–MS), and each product represented by the GLC peaks showed identical mass spectrum with that of isolated syrup of III, IV and V.

When trimethylsilylation of α-coriofuranose was performed with a solution of trimethylsilylimidazole in pyridine, a mixture of IV and V, in which IV is markedly larger than V in the peak area of GLC, was produced in a few minutes, and only a trace of III was shown in GLC. This result would have been caused by rapid trimethylsilylation of α-coriofuranose by trimethylsilylimidazole, upon which a larger portion of α-coriofuranose than by the reagent mixture used above was fully trimethylsilylated retaining the original ring structure, and would be in accord with the assignment of α-furanoid structures to III and IV.

The tautomerization of α-coriofuranose to produce the open-chain form during the trimethylsilylation such as the one observed by the present study is the first example of tautomerization of carbohydrate to the carbonyl-form occurred during the trimethylsilylation. Such tautomerization of coriose may be due to the structure of 3-heptulose or 3-ketose in general regardless of the ring size, or otherwise may have been caused only by the sterically hindered structure of α-coriofuranose. The gas chromatogram of the trimethylsilylated derivative of D-*manno*-3-heptulose (VI)[6] shows that the former would be correct. This 3-heptulose has been found to form β-pyranose (VII) in the crystalline state,[13] which is considered to be stable in terms of the conformational analysis, and nevertheless showed a complicated pattern of gas chromatogram of the trimethylsilyl derivative, which somewhat resembles the gas chromatogram of trimethylsilylated coriose.

Experimental

GLC was carried out with Shimadzu 5A and 1C gas chromatograph equipped with hydrogen flame ionization detector (FID) using a glass column (2 m×3 mm i.d.) packed with 3% OV-17 on 80—100 mesh Chromosorb W treated with hexamethyldisilazane (HMDS), at column temperature 170°, or 1.5% SE-30 on 60—80 mesh Chromosorb W treated with HMDS, at column temperature 180°, and a glass column (1.2 m×3 mm i.d.) packed with 2% neopentyl glycol succinate (NPGS) on 80—100 mesh Gas-chrom S acid washed and treated with dimethyl dichlorosilane (DMCS), at column temperature 150°. Carrier gas: Nitrogen, 50 ml/min. R_{GLU} shows the retention time relative to fully trimethylsilylated α-D-glucose. TLC was performed on Silica gel G (Merck) and detection was effected with Tollens' reagent. Mallincrodt's silicic acid was used for column chromatography. Trimethylsilyl derivatives were prepared with trimethylchlorosilane–hexamethyldisilazane–pyridine (1:2:10, v/v/v), and trimethylsilylimidazole–pyridine (1:4 v/v) or Trisil-Z.[14] Optical rotations were measured with Yanaco OR-50, and ORD data were obtained on Jasco ORD/UV-5. IR spectra were recorded with Jasco IR-G, and NMR spectra were recorded with Varian A-60 at 60 MHz and Hitachi R-22 at 90 MHz with tetramethylsilane as the internal standard. Mass spectra of isolated TMS derivatives were obtained with Hitachi RMU-6D mass spectrometer with a 150° heated inlet system. Ion accelerating voltage 900 V, target current 40 μA. GC-MS and MID data were obtained with Shimadzu-LKB-9000 gas chromatograph-mass spectrometer equipped with MID. OV-17 column of the same type as that used for the GLC data was used as the introductory column. Temperature of ion source 250°, ion accelerating voltage 3.5 kV, ionizing potential 70 eV, trap current 60 μA.

1,2,4,5,7-Pentakis-O-trimethylsilyl-α-coriofuranose (III)——A solution of trimethylchlorosilane (0.1 ml) and hexamethyldisilazane (0.2 ml) in dry pyridine (1 ml) was added to finely powdered coriose (57.4 mg) under ice-cooling, and the cooled mixture was stirred for 25 min. GLC of the reaction mixture at this time showed almost a single peak of III. Petroleum benzine (20 ml) was added, and ppt was filtered through a layer of Celite. The filtrate was evaporated *in vacuo* at 30—35° and the residual syrup was warmed in a bath of 90—100° at 1.4 mmHg to remove the lower boiling fraction, and then the bath temperature was raised to 180° to distill colorless syrup of III. $[\alpha]_D^{20}$ +13.6° (*n*-hexane, c=0.44). ORD: $[\Phi]_{250}^{20}$=+502°, $[\Phi]_{590}^{20}$=

13) T. Taga and K. Osaki, *Tetrahedron Letters*, **1969**, 4433.
14) Produced by Pierce Chemical Company.

+102° (positive plain curve) (*n*-hexane, $c=0.44$). IR spectrum: ν_{max} 3360 cm^{-1} (OH). NMR ($CDCl_3$) δ: 0.1—0.23 ($Me_3Si\times5$), 4.22—4.42 ($H\times7$), 4.22—4.84 ($H\times1$), 4.58 ($OH\times1$). NMR (DMSO-d_6) δ: 5.01 (s, $OH\times1$). Mass Spectrum: *m/e* 552 (M—18), *m/e* 217 (87% of base peak), *m/e* 73 (base peak). R_{GLU}: 2.30 (OV-17), 2.43 (NPGS), 1.72 (SE-30). *Anal.* Calcd. for $C_{22}H_{54}O_7Si_5$: C, 46.26; H, 9.53. Found: C, 46.50; H, 9.33.

1,2,3,4,5,7-Hexakis-O-trimethylsilyl-α-coriofuranose (IV)——A solution of trimethylchlorosilane (0.5 ml) and hexamethyldisilazane (1 ml) in dry pyridine (5 ml) was added to finely powdered coriose (50 mg). The mixture was stirred for 1 hr, and then left stand overnight at room temperature. GLC performed at this time showed peaks of IV and V. Petroleum benzine was added, and ppt was filtered through a layer of Celite, and the filtrate was distilled *in vacuo*. The residual syrup was taken up in petroleum benzine, and chromatographed on a column of silicic acid (1.4×9 cm) which had been activated at 120° for 1 hr, developing with petroleum benzine. The fractions which showed the spot of IV were collected and solvent was distilled to give a syrupy residue. Isolation of IV from the mixture was also effected by preparative TLC on the plates of activated silicic acid (5×20×0.25 cm) developing with petroleum benzine–benzene (1: 1) and extracting the area of the faster spot with $CHCl_3$. $[\alpha]_D^{20}$ +51.72° (*n*-hexane, $c=0.41$). ORD: $[\Phi]_{250}^{20}=+17.6°\times10^2$, $[\Phi]_{589}^{20}=+119°$ (a positive plain curve) (*n*-hexane, $c=0.41$). NMR ($CDCl_3$): δ 0.10—0.18 ($Me_3Si\times6$), 3.38—4.07 ($H\times8$). Mass Spectrum: *m/e* 627 (M—15), *m/e* 437 (21.7% of base peak), *m/e* 217 (base peak). R_{GLU}: 1.80 (OV-17), 1.46 (NPGS), 2.04 (SE-30). *Anal.* Calcd. for $C_{25}H_{62}O_7Si_6$: C, 46.68; H, 9.72. Found: C, 46.90; H, 9.88.

1,2,4,5,6,7-Hexakis-O-trimethylsilylcoriose (V)——(a) The syrupy mixture of trimethylsilylated coriose, which was obtained by the above experiment, and showed GLC peaks of IV and V (196.2 mg), was developed on TLC plates of activated silicic acid (5×20×0.025 cm) with petroleum benzine–benzene (1: 1), and the area of the slower spot was extracted with $CHCl_3$. Upon evaporation of $CHCl_3$, a syrupy residue was obtained (13.5 mg). $[\alpha]_D^{20}$ −17.6° (*n*-hexane, $c=0.69$). ORD: $[\Phi]_{262}^{20}=+3480°$, $[\Phi]_{316}^{20}=-2680°$ (negative cotton effect) (*n*-hexane, $c=0.69$). IR spectrum: $\nu_{max}^{CHCl_3}$ 1722 cm^{-1} (>C=O). UV spectrum: λ_{max}^{hexane} 282 nm ($\varepsilon=102$, $c=0.007$). NMR ($CDCl_3$): δ 0.10—0.22 ($Me_3Si\times6$), 3.23—4.30 ($H\times6$), 4.49 ($H\times1$, dd, $J_1=7$ Hz, $J_2=4$ Hz, C_2-H), 4.64 ($H\times1$, d, $J=4$ Hz, C_4-H). Mass Spectrum: *m/e* 642 (M^+), *m/e* 627 (M—15), *m/e* 319 (95% of base peak), *m/e* 305 (58% of base peak), *m/e* 217 (57% of base peak), *m/e* 205 (95% of base peak), *m/e* 73 (base peak). R_{GLU}: 2.37 (OV-17), 2.04 (NPGS), 2.36 (SE-30). *Anal.* Calcd. for $C_{25}H_{62}O_7Si_6$: C, 46.68; H, 9.72. Found: C, 46.90; H, 9.65.

(b) The syrupy mixture (73.2 mg) of IV and V obtained in the same way as in (a) was chromatographed on a column of activated silicic acid (1.4×9.0 cm) developing with benzene–petroleum benzine (5: 95) for 1 hr. The developed column was cut into 9 pieces of equal size, and each piece was extracted with CH_2Cl_2. Evaporation of the solution from the piece second from the top of the column yielded syrupy residue which showed GLC peak of V.