[Chem. Pharm. Bull. 17(4) 735—737 (1969)]

UDC 547.457.7.07

Coriose and Related Compounds.[1] III.[2] Synthesis of D-*altro*-3-Heptulose

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(Received August 22, 1968)

Coriose (D-*altro*-3-heptulose) (I) was synthesized by the lead tetraacetate oxidation of hydrolyzate of the mother liquor of 1,3:5,7-di-O-ethylidene-3-C-formyl-D-*glycero*-D-*talo*-heptitol-3 (1),6-pyranose (IV) which was derived from 2,4-O-ethylidene-D-erythrose (V) by the aldol condensation.

The isolation of coriose from *Coriaria japonica* A. Gray,[4] and the assignment of the structure D-*altro*-3-heptulose (I) to this sugar[2] were reported in previous papers of this series. The synthesis of this 3-heptulose *via* the product of the aldol condensation of 2,4-O-ethylidene-D-erythrose is described in the present paper.

D-*manno*-3-Heptulose (II) has been reported as the first synthetic 3-heptulose by Schaffer who prepared it by the lead tetraacetate oxidation of a branched-chain octose, 3-C-formyl-D-*glycero*-D-*talo*-heptitol (III) formed on the hydrolysis of its diethylidene derivative, 1,3:5,7-di-O-ethylidene-3-C-formyl-D-*glycero*-D-*talo*-heptitol-3 (1),6-pyranose (IV) which was obtained by the aldol condensation of 2,4-O-ethylidene-D-erythrose (V) as the only crystalline condensation product.[5] The crude product of the aldol condensation of V may possibly contain, besides IV, three stereoisomers of IV with regard to C-3 and C-4, *i.e.*, VI, VII and VIII, although the production of these isomers has not been reported. 3-C-Formyl-D-*glycero*-D-*manno*-heptitol (X) and 3-C-Formyl-D-*glycero*-D-*altro*-heptitol (XI) which would be formed on the hydrolysis of VII and VIII are presumed to yield D-*altro*-3-heptulose upon the oxidation with equimolar lead tetraacetate which is expected to cleave X and XI preferentially between C-3 and the potential formyl group in analogy to the production of II and to the lead tetraacetate oxidation of straight-chain aldoses.[6] The remaining possible condensation product VI, which would give 3-C-formyl-D-*glycero*-D-*ido*-heptitol (IX) on the hydrolysis, should yield D-*manno*-3-heptulose. Although the stereostructures of IV and its isomers in the all-chair conformations show that IV and VI which have 4-OH oriented equatorial would be more stable production of VII and VIII to a certain extent is presumable.

The sirupy crude product of the aldol condensation of 2,4-O-ethylidene-D-erythrose which was obtained as the crystalline dimer on the sodium metaperiodate oxidation of 4,6-O-ethylidene-D-glucose was left stand to deposit the crystals of IV from which D-*manno*-3-heptulose was produced by the lead tetraacetate oxidation according to the method of Schaffer.[5] The mother liquor which showed on thin-layer chromatography (TLC) more than three spots including that corresponding to V and a faint spot corresponding to IV was hydrolyzed and oxidized with about 0.7 molar equivalent of lead tetraacetate. After removal of the accompanying aldoses by the bromine oxidation followed by the treatment with ion-exchange resins, the crude product showed on paper-partition chromatography

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[1] This work was reported at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968. Preliminary communication, T. Okuda and K. Konishi, *Chem. Commun.*, **1968**, 671.

[2] Part II: T. Okuda and K. Konishi, *Tetrahedron*, **24**, 6907 (1968).

[3] Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*

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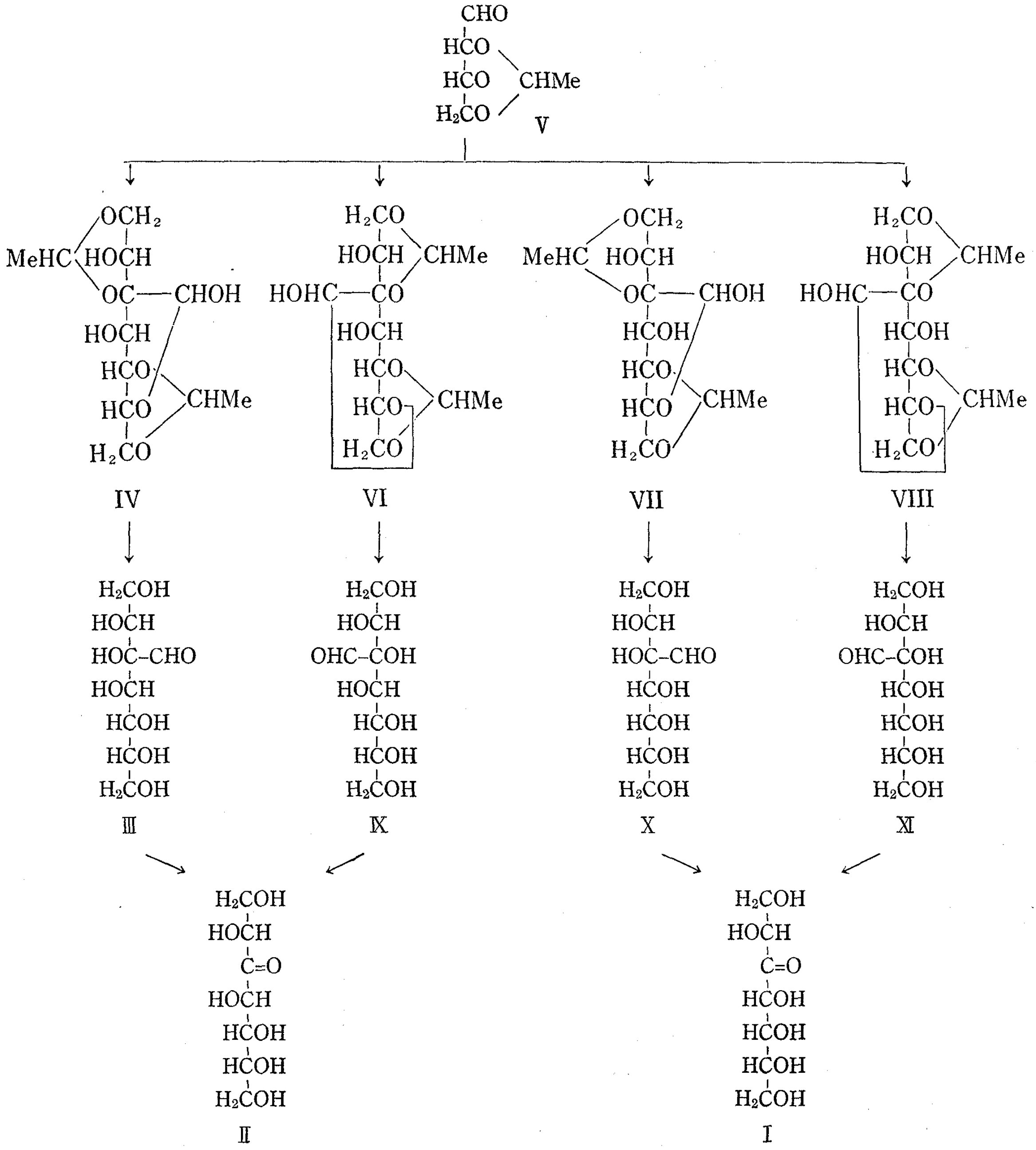
[5] R. Schaffer, *J. Am. Chem. Soc.*, **81**, 2838 (1959): *idem*, *J. Org. Chem.*, **29**, 1473 (1964).

[6] A.S. Perlin and C. Brice, *Can. J. Chem.*, **34**, 85, 541 (1956).



(PPC) two dark brown spots corresponding to D-*altro*-3-heptulose and D-*manno*-3-heptulose. The presence of these two 3-heptuloses was also exhibited by gas–liquid chromatography (GLC) of the trimethylsilyl ethers. The purification was done by the preparative PPC upon which the area of 3-heptuloses was cut out and extracted with methanol. The sirupy extract which again showed the spots of 3-heptuloses on PPC was seeded with I to yield crystals which were identified with coriose isolated from *Coriaria japonica.*

Experimental[7]

2,4-O-Ethylidene-D-erythrose (V)——The preparation of V was done by Schaffer's method starting with anhydrous D-glucose (10.3 g). The product was obtained as the crystalline dimer, bis(2,4-O-ethylidene-D-erythrose)-1,1′:1′,3-cyclic acetal (4.37 g) which showed a single spot on TLC. mp 150°. $[\alpha]_D^{25}$ −42.0°→−47.3° (2 hr, $c=1.1$, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3310, 1413, 1276, 1236, 1155, 1120, 1047, 998, 940, 885, 850. *Anal.* Calcd. for $C_{12}H_{20}O_8$: C, 49.31; H, 6.90. Found: C, 49.03; H, 6.96.

Aldol Condensation of 2,4-O-Ethylidene-D-erythrose——Dimeric 2,4-O-ethylidene-D-erythrose (7.5 g) was dissolved in 0.05N $Ca(OH)_2$ (1 liter) at 0°, and the solution was kept at room temperature for 4 hr. The solution was then cooled to 0° and passed through a column of mixture of IR–120 and IRA–410 (1:1), and then concentrated. EtOH was added and the mixture was left to stand overnight. Deposited crystals of IV which showed a single spot on TLC were filtered (734 mg), and recrystallized from EtOH. mp 228—229°. $[\alpha]_D^{20}$ +45.3 (c=5, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3300 (shoulder), 1407, 1253, 1178, 1145, 1110, 1085, 1040, 990, 902, 852. NMR $_{max}^{D_2O}$ τ: 8.73 (d, J=5 c/s), 8.65 (d, J=5 c/s) (-O-CH$\underline{\mathrm{Me}}$-O-×2); 4.20 (s, -O-C$\underline{\mathrm{H}}$OH–). *Anal.* Calcd. for $C_{12}H_{20}O_8$: C, 49.31; H, 6.90. Found: C, 49.47; H, 6.97.

Upon the hydrolysis with 0.1N H_2SO_4 under N_2 atmosphere followed by the oxidation with one mole of lead tetraacetate, and removal of aldoses by the bromine oxidation and the treatment with ion–exchange resins, IV yielded D-*manno*-3-heptulose which was recrystallized from EtOH. mp 80—82°. $[\alpha]_D^{28}$ −40° (c=0.2, equilibrium in water). *Rf* on PPC: 0.35. IR spectrum of this product was identical with that reported by Tipson and Isbell.[8] *Anal.* Calcd. for $C_7H_{14}O_7 \cdot H_2O$: C, 36.84; H, 7.07. Found: C, 36.77; H, 7.20.

D-*altro*-3-Heptulose (I)——The mother liquor from IV (2.2 g) was dissolved in 0.1N H_2SO_4 (20 ml), and was warmed under N_2 atmosphere for 15 min to distill acetaldehyde. The hydrolyzate was neutralized with IRA–410 (3 ml), freeze–dried and weighed (1.3 g). The lyophilizate was dissolved in H_2O (10 ml), and AcOH (200 ml) was added. To the stirred solution was added $Pb(OAc)_4$ (1.86 g, 0.7 molar equivalent). A solution of oxalic acid (0.5 g) in AcOH was added 15 min later, and stirring was continued for 30 min. The precipitate was filtered, and the filtrate was concentrated. The concentrate was hydrolyzed in 0.05N HCl (20 ml) for 30 min at 80°. The solution was diluted with water (80 ml), and $Ba(OBz)_2 \cdot 2H_2O$ (1.5 g) and Br_2 (0.31 ml) were added. The mixture was then kept dark at room temperature for 32 hr. After removal of excess Br_2 by aeration, 5N H_2SO_4 (1.4 ml) was added, and the filtrate was extracted with CH_2Cl_2. Ag_2CO_3 (3 g) was added to the aqueous layer and the filtrate was passed through columns of IR–120 (6 ml) and IRA–410 (10 ml), and then concentrated. The sirupy residue showed on PPC dark brown spots at *Rf* 0.40 and *Rf* 0.35, which correspond to I and II respectively. These two 3-heptuloses were also exhibited on GLC. The preparative PPC of this mixture was done with *n*-BuOH–EtOH–H_2O (4:1:1.2, v/v). After developing, 3-heptuloses were detected by pressing 4 pieces of Toyo Roshi No. 51 (20 mm×400 mm) paper *ca.* 8 cm apart from each other on both side of the wet developed chromatogram of No. 527 paper, and applying orcinol–Cl_3CCOOH and $AgNO_3$–NaOH–EtOH[9] as the coloring reagents. Two areas on the thick paper chromatogram, *Rf* 0.34—0.59 and *Rf* 0.17—0.34, where reducing sugars were detected on No. 51 papers, were cut out, and extracted with MeOH. The extract from the lower *Rf* region showed on PPC (BuOH–pyridine–H_2O) the presence of two 3-heptuloses. The sirupy residue obtained on evaporation of the solution from the lower *Rf* area was seeded with coriose. The crystals deposited in the sirup was filtered and recrystallized from EtOH–H_2O. mp 164—165°. The identification with coriose isolated from *Coriaria japonica* was done by PPC, mixed melting point, and also by the comparison of IR spectra.

GLC of Trimethylsilyl Ethers of D-*altro*-3-Heptulose (I) and D-*manno*-3-Heptulose (II)——Trimethylsilyl ethers of I, II and the sirup were prepared by adding the mixture of trimethylchlorosilane, hexamethyldisilazane and pyridine (1:2:10, v/v) under ice–cooling, and shaking the mixture vigorously. GLC was run within 5 min after the reagent mixture was added. Identifications were done by the major peaks of I and II, whose retention times relative to α-D-glucose were 1.72 and 1.61 respectively. Transformations of the TMS ethers of I and II on standing in the presence of excess reagents at room temperature were observed.

Acknowledgement The authors are indebted to Dr. T. Shingu for NMR measurement, and to the members of the Microanalytical Center of this university for elemental analysis.

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7) Specific rotations were recorded with a Rex Photoelectric Polarimeter. Concentrations of solutions were carried out *in vacuo* at temperatures not over 45°. PPC was run on Toyo Roshi No. 50 or No. 51 filter paper by the ascending method using *n*-BuOH–pyridine–H_2O (6:4:3, v/v) for the identification purpose, and No. 527 (400 mm×400 mm) thick paper for the preparative purpose. Silicic acid acc. to Stahl (E. Merck) was coated on the TLC plates (0.25 mm). TLC was developed with $CHCl_3$–MeOH (8:2 and 7:3, v/v), and spots were detected with iodine. GLC was run on Shimadzu GC–1C with hydrogen flame ionization detector, employed stainless steel column, 225×3 mm, packed with 1.5% SE–30 on Chromosorb W. column temp.: 190°. carrier gas: N_2 56 ml/min detector temp.: 210°. NMR spectrum was recorded with tetramethylsilane as an internal standard using a Varian A–60 spectrometer. Ion–exchange resins used were Amberlite IR–120 and IRA–410 (Rohm and Haas Co.).

8) R.S. Tipson and H.S. Isbell, *J. Res. Natl. Bur. Standards*, **66A**, 31 (1962).

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