UDC 547.456'314.07

77. Tadahiro Iwashige: Studies on Acetylenic Compounds. XVIII.[1] Total Synthesis of *dl*-Lyxose and *dl*-Xylose.

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It was reported in a previous paper[1] that *dl*-ribose (VIII) and *dl*-arabinose (IX) were finally obtained by the *cis*-hydroxylation of *dl-cis*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (IV), which was prepared by the catalytic hydrogenation of *dl*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-yn-2-ol (III). If it is possible to obtain *dl-trans*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol, it is expected that *dl*-lyxose and *dl*-xylose could be analogously obtained as the final product by the *cis*-hydroxylation of the *trans*-isomer or by the *trans*-hydroxylation of the *cis*-isomer (VI). Based on such assumption, *dl*-lyxose and *dl*-xylose were finally synthesized by the procedure shown in Chart 1.

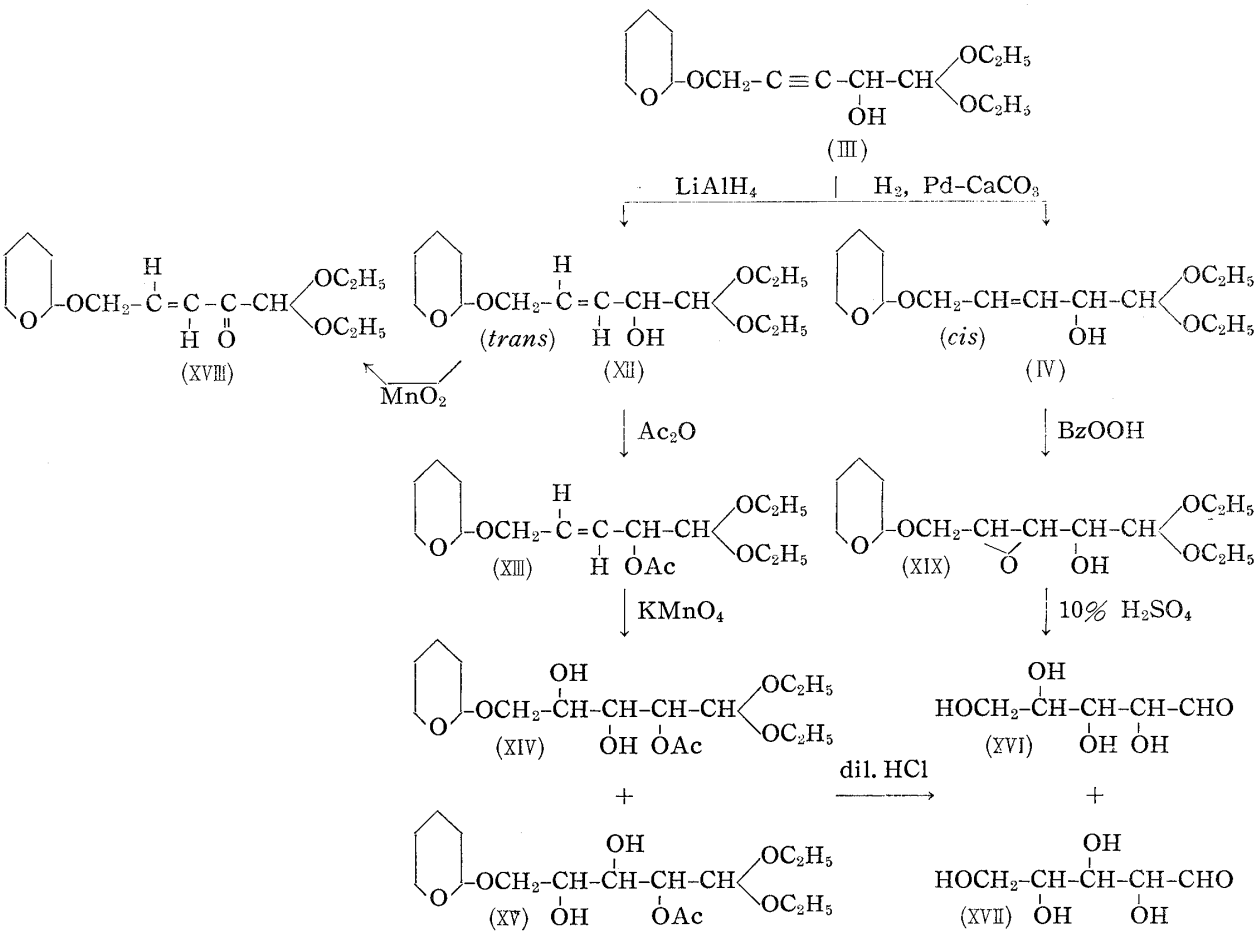

Chart 1.

It is known that reduction by alkali metal in liquid ammonia is a routine organic chemical procedure to obtain *trans*-ethylenes from acetylenes. However, a recently introduced reagent provides further selectivity of reduction of triple bonds.[2] It has been

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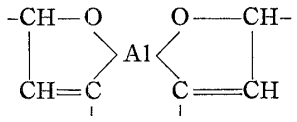
1) Part XVII. I. Iwai, T. Iwashige: This Bulletin, **9**, 316 (1961).

2) J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen, T. Walker: J. Chem. Soc., **1952**, 1094; R. Ahmad, F. Sondheimer, B.C.L. Weedon, R.J. Woods: *Ibid.*, **1952**, 4089.

shown that lithium aluminium hydride furnishes an excellent yield of *trans*-ethylene from acetylene if the triple bond of the latter is adjacent to a propargylic hydroxyl group. A plausible explanation of this selectivity involves the formation of an intermediate aluminium complex of the type (XX).



(XX)

Consequently, the reduction of *dl*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-yn-2-ol (III) with lithium aluminium hydride in dry ether was tried and *dl-trans*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (XII), b.$p_{0.3}$ 132~133°, was obtained in 60~70% yield. The infrared spectrum of this *trans*-ethylene did not show the absorption due to a double bond as in the case of *cis*-ethylene (IV) reported previously.[1] Therefore, in order to confirm the structure, *trans*-ethylene (XII) was oxidized with manganese dioxide, following the procedure described in the previous paper,[1] and it formed *trans*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-one (XVIII), b.$p_{5\times10^{-4}}$ 120~125°(bath temp.). The infrared spectrum of (XVIII) showed a strong absorption at 985 cm^{-1}, which was not observed in the *cis* compounds and seemed to be due to the C-H out-of-plane vibration of a double bond. The spectrum of the *trans* compound also showed absorptions at 1700(C=O) and 1630 cm^{-1}(-C=C-). The ultraviolet spectrum of (XVIII) showed a maximum absorption at 232 mμ. From these experimental results, it became apparent that the ethylenic alcohols (IV and XII) are *cis-trans* isomers and (XII) is the *trans* isomer. *dl-trans*-1,1-Diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (XII) was acetylated with acetic anhydride in pyridine to *dl-trans*-1,1-diethoxy-2-acetoxy-5-tetrahydropyran-2-yloxypent-3-ene (XIII), b.$p_{0.2}$ 132~135°, in a good yield. (XIII) was treated analogously, following the procedure described in the previous paper,[1] and the syrupy substance which appeared to be a mixture of *dl*-lyxose (XVI) and *dl*-xylose (XVII) was finally obtained. This substance showed only one spot (Rf 0.29) on paper chromatogram, while *d*-lyxose, and *d*-xylose, and their mixture, used as the control, all showed the same Rf value.*2 Therefore, it is assumed that these substances overlapped as one spot by one-dimensional chromatography. This mixture was chromatographed on a Dowex-1 column,[3] using aqueous potassium tetraborate solution as the eluting agent and two fractions showing positive orcinol test were obtained, as shown in Fig. 1.

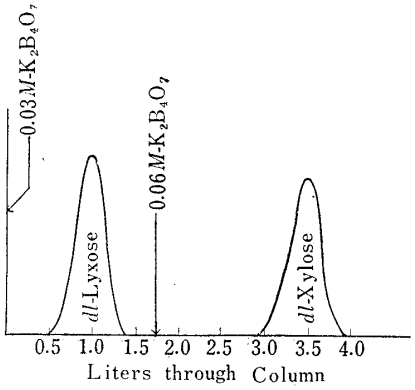


Fig. 1. Separation of a Mixture of *dl*-Lyxose and *dl*-Xylose

Exchanger, 9 $cm^2 \times 19$ cm. Dowex-1, borate form; Eluting agent, $K_2B_4O_7$, as shown at flow rate of 1.1 cc./min.

*2 Toyo Roshi No. 50. Solvent : BuOH-H_2O-AcOH (4:5:1). Temperature : 21°. Detection agent: Partridge reagent. Time : 16 hr. Product (Rf 0.29). Control (Rf) : Mixture of *d*-lyxose and *d*-xylose (0.29), *d*-lyxose (0.29), *d*-xylose (0.29).

3) J.X. Khym, L.P. Zill : J. Am. Chem. Soc., **74**, 2090 (1952); K. Mori, M. Nakamura : Nippon Nôgei-Kagaku Kaishi, **34**, No. 4, A5 (1960).

The residue obtained from the initial fraction was propionated, as described in the preceding paper[1] and the tetrapropionate formed, which gave identical infrared spectrum as that of *d*-lyxose tetrapropionate, as shown in Fig. 2. Thus, the residue obtained from the first fraction was confirmed as *dl*-lyxose.

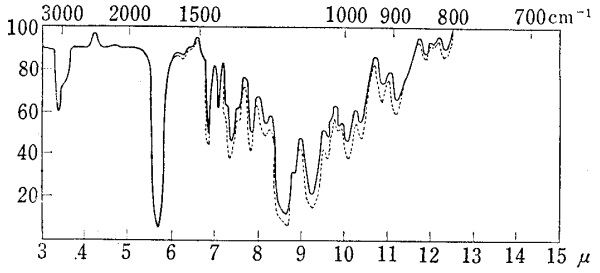


Fig. 2. Infrared Absorption Spectra of *dl*-Lyxose tetrapropionate and *d*-Lyxose tetrapropionate in $CHCl_3$ Solution
—— *dl*-Lyxose tetrapropionate
------ *d*-Lyxose tetrapropionate

The residue obtained from the second fraction was analogously propionated to a tetrapropionate which also gave infrared spectrum identical with that of *d*-xylose tetrapropionate, as shown in Fig. 3. Consequently, it became apparent, from these experimental results, that the reaction proceeded stereospecifically as was expected, and produced *dl*-lyxose and *dl*-xylose.

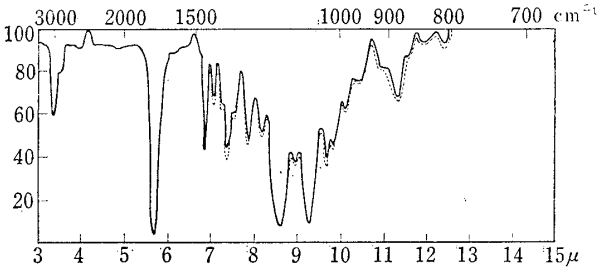


Fig. 3. Infrared Absorption Spectra of *dl*-Xylose tetrapropionate and *d*-Xylose tetrapropionate in $CHCl_3$ Solution
—— *dl*-Xylose tetrapropionate
------ *d*-Xylose tetrapropionate

The epoxidation of *dl-cis*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (IV) with perbenzoic acid was carried out and gave an oil (XIX), b.$p_{0.0005}$ 142~143°. (XIX) gave a negative tetranitromethane test, in contrast to the positive reaction of (IV), although there was no marked difference in the infrared spectrum between (XIX) and (IV). Therefore, it is considered that (XIX) is *dl-cis*-1,1-diethoxy-3,4-epoxy-5-tetrahydropyran-2-yloxypentan-2-ol from these experimental results and analytical data. (XIX) was heated with 10% sulfuric acid at 90° for 15 minutes, followed by deacidification with Amberlite IR-4B. The aqueous solution thus obtained was subjected to paper partition chromatography and the chromatogram showed only one spot (Rf 0.29) as before. Consequently, it is expected that *dl*-lyxose (XVI) and *dl*-xylose (XVII) would also be obtained by the *trans*-hydroxylation of *cis*-ethylenic isomer (IV).

Experimental

***dl-trans*-1,1-Diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (XII)**——To 2.92 g. of $LiAlH_4$ in 170 cc. of dehyd. Et_2O, a solution of 2.71 g. of *dl*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-yn-2-ol in 270 cc. of dehyd. Et_2O was added slowly with ice cooling and the mixture was refluxed for 3 hr. After cooling and adding AcOEt to decompose the excess $LiAlH_4$, the Li-Al complex of the reaction product was decomposed with cold saturated aqueous solution of NH_4Cl and the Et_2O layer was separated, dried over Na_2SO_4, and evaporated off. The residue was distilled *in vacuo* to leave 17 g. of a colorless viscous oil, b.$p_{0.3}$ 132~133°, n_D^{26} 1.4633, d_{25} 1.0532. *Anal.* Calcd. for $C_{14}H_{26}O_5$: C, 61.30; H, 9.49. Found : C, 61.34; H, 9.52. MR*3 Calcd. : 72.29. Found : 71.70. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400~3500 (OH), 900~1150 (C-O-C).

*3 MR (molecular refractivity) $=\left(\frac{n^2-1}{n^2+2}\right)\left(\frac{m}{d}\right)$.

***trans*-1,1-Diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-one (XVIII)**——To a solution of 1.56 g. of *dl-trans*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (XII) in 140 cc. of petr. ether, 13.8 g. of MnO_2 was added and the mixture was stirred at room temperature for 7 hr. MnO_2 was filtered off and washed several times with a small amount of petr. ether. The combined petr. ether solution was evaporated and the residue was distilled *in vacuo* to leave 0.8 g.of an oil, b.$p_{5\times10^{-4}}$ 120～125°(bath temp.), n_D^{23} 1.4652, d_{23} 1.0550. *Anal.* Calcd. for $C_{14}H_{24}O_5$: C, 61.80; H, 8.84. Found : C, 61.68; H, 8.99. MR Calcd. : 70.78. Found : 71.30. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1700(CO), 1630(-C=C-), 985(-CH=C-). UV : λ_{max}^{EtOH} 232 mμ(log ε 3.89).

***dl-trans*-1,1-Diethoxy-2-acetoxy-5-tetrahydropyran-2-yloxypent-3-ene (XIII)**——A solution of 8 g. of *dl-trans*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (XII) and 32 g. of Ac_2O dissolved in 80 cc. of dehyd pyridine was refluxed for 2.5 hr. After cool, excess pyridine and Ac_2O were removed in a reduced pressure on a steam bath and the residue was poured into ice-water. An oil that separated was extracted with Et_2O and the Et_2O solution was dried over Na_2SO_4 and evaporated. The residue was distilled *in vacuo* to leave 7.5 g. of a yellow viscous oil, b.$p_{0.2}$ 132～135°, n_D^{24} 1.4554, d_{27} 1.0594. *Anal.* Calcd. for $C_{16}H_{28}O_6$: C, 60.75; H, 8.86. Found : C, 60.73; H, 8.76. MR. Calcd.: 81.66. Found : 81.00. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1240, 1750 (OAc), 900～1150 (C-O-C).

2-O-Acetyl-5-O-tetrahydropyran-2-yl-*dl*-lyxose Diethylacetal (XIV) and 2-O-Acetyl-5-O-tetrahydropyran-2-yl-*dl*-xylose Diethylacetal (XV)——To 8.7 g. of *dl-trans*-1,1-diethoxy-2-acetoxy-5-tetrahydropyran-2-yloxypent-3-ene (XIII) suspended in 200 cc. of H_2O, a solution of 3.46 g. of $KMnO_4$ in 150 cc. of H_2O was added slowly during 1 hr. with stirring and ice-cooling. CO_2 gas was introduced into the reaction mixture and the temperature was controlled at 1～3° during the addition. After all $KMnO_4$ was added, the reaction mixture was left at room temperature for 30 min. to solidify the colloidal MnO_2, which was filtered, and washed with H_2O. The combined aqueous solution was passed through a column of Amberlite IRC-50 and the effluent was concentrated at room temperature in a reduced pressure to leave 6.7 g. of a red-brown syrup which gave a positive HIO_4-$AgNO_3$ test, showing the presence of α-glycol group, and a negative Benedict reaction.

***dl*-Lyxose (XVI) and *dl*-Xylose (XVII)**——A solution of 6.7 g. of a crude mixture of (XIV) and (XV) dissolved in 130 cc. of 4% HCl solution was left at room temperature for 4 days. The reaction mixture was passed through a column of Amberlite IR-4B for deacidification and the effluent was concentrated at room temperature in a reduced pressure to leave 1.27 g. of a syrup which gave a positive Benedict reaction showing the presence of a reducing aldehyde group. A solution of this syrup in 50 cc. of 0.18*M* $K_2B_4O_7$ was adsorbed on a column (9 cm^2 × 19 cm.) of Dowex-1 (200～400 mesh), converted to the borate form by the procedure described by Khym and Zill,[3] and the column was eluted with 0.03 *M* $K_2B_4O_7$.

After the first fraction showing a positive orcinol test was obtained, elution agent was changed to 0.06*M* $K_2B_4O_7$. The distribution of pentoses in the effluent is shown in Fig. 1. The first fraction showing a positive orcinol test was treated with Dowex-50 and concentrated *in vacuo* at room temperature. The residue was dissolved in 600 cc. of MeOH, concentrated *in vacuo* at room temperature to remove H_3BO_3 as volatile $(MeO)_3B$, and 0.42 g. of a syrupy residue was obtained.

This syrupy residue was treated with 2.1 g. of propionic anhydride and 2.9 g. of pyridine, following the procedure described in the preceding paper,[1] and 0.75 g. of a very viscous oil, b.$p_{5\times10^{-4}}$ 150～160°(bath temp.), was finally obtained. The infrared spectrum of this oil in $CHCl_3$ solution was identical with that of *d*-lyxose tetrapropionate prepared analogously from *d*-lyxose. *Anal.* Calcd. for $C_{17}H_{26}O_9$: C, 54.60; H, 6.95. Found : C, 54.36; H, 6.90.

The second fraction showing a positive orcinol test was treated likewise to give 0.25 g. of syrupy residue. This residue was similarly propionated with 1.2 g. of propionic anhydride and 1.7 g. of pyridine to yield 0.45 g. of an oil, b.$p_{5\times10^{-4}}$ 155～165°(bath temp.). The infrared spectrum of this oil in $CHCl_3$ solution was identical with that of *d*-xylose tetrapropionate analogously prepared form *d*-xylose. *Anal.* Calcd. for $C_{17}H_{26}O_9$: C, 54.60; H, 6.95. Found : C, 54.38; H, 6.86.

***dl*-1,1-Diethoxy-3,4-epoxy-5-tetrahydropyran-2-yloxypentan-2-ol (XIX)**——To a solution of 5 g. of *dl-cis*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (IV) in 25 cc. of $CHCl_3$, 55.4 cc. of $CHCl_3$ solution containing 2.8 g. of BzOOH[4] was added slowly, with chilling at −5° to −10°, and the mixture was left at room temperature for one day. The reaction mixture was washed successively with 10% Na_2CO_3 solution and H_2O, and evaporated after drying over Na_2SO_4. The residue was distilled *in vacuo* to give 2.5 g. of (XIX), b.$p_{5\times10^{-4}}$ 142～143°, n_D^{28} 1.4622, d_{25} 1.1043, with 1.0 g. of a low-boiling distillate. (XIX) gave a negative tetranitromethane test. *Anal.* Calcd. for $C_{14}H_{26}O_6$: C, 57.95; H, 8.98. Found : C, 57.99; H, 8.79. MR Calcd. : 72.20. Found : 72.22.

A mixture of 0.2 g. of (XIX) suspended in 10 cc. of 10% H_2SO_4 was heated at 90° for 15 min. The aqueous solution obtained by deacidification of this reaction mixture with Amberlite IR-4B gave a positive orcinol and Benedict tests, and showed a spot at Rf 0.29 on paper chromatogram.

4) G. Braun : Org. Syntheses, Coll. Vol. **I**, 431 (1941).

The author wishes to express his deep gratitude to Prof. K. Tsuda, The Institute of Applied Microbiology, University of Tokyo, Mr. M. Matsui, Director of this Laboratory, and Dr. I. Iwai for their kind guidance and encouragement throughout the course of this investigation. He is greatly indebted to Prof. C.D. Hurd, Northwestern University and Chicago Quaker Oats Co., for kindly supplying the valuable sample and to Drs. M. Nakamura and K. Mori, Agricultural Chemistry Department, University of Tokyo, for their kind advices, and to Mr. J. Ide of this Laboratory for his technical cooperation. The measurements of infrared and ultraviolet spectra were carried out by Messrs. O. Amakasu, H. Higuchi, and N. Higosaki and by Miss N. Sawamoto, and micro-analyses were made by Messrs. T. Onoe and H. Nagashima, and Misses C. Furukawa and H. Ohtsuka.

Summary

dl-Lyxose and *dl*-xylose were synthesized by the *cis*-hydroxylation of *dl-trans*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (XII) and it was anticipated that they would also be formed by the *trans*-hydroxylation of *dl-cis*-1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-en-2-ol (IV).

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78. Mitsuko Asai, Toru Masuda, and Satoru Kuwada : Application of Chromatography. XLII.*1 Formation of Riboflavin by Enzyme System from Leuco-type Strain of *Eremothecium ashbyii*.

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The mechanism[1] for synthesis of riboflavin by *Eremothecium ashbyii* presumed by the authors was further investigated biochemically by Katagiri, *et al.*[2] and the present authors,[3] and it was found that 6,7-dimethylribolumazine is an intermediate in the biosynthesis of riboflavin. Korte, *et al.*[4] and Maley, *et al.*[5] also duplicated the experiment using ^{14}C-labeled 6,7-dimethylribolumazine and confirmed the above result.

It was later reported[6] that the action of crude enzyme solutions prepared from yellow-type and leuco-type strain of *Er. ashbyii* on 4-ribitylamino-5-aminouracil and acetoin produced both 6,7-dimethylribolumazine and riboflavin, and Katagiri, *et al.*[7] also recognized the result using an enzyme solution prepared from yellow-type *Er. ashbyii*.

The above-mentioned leuco-type strain was produced in the course of successive cultivation of the yellow-type strain at the Fermentation Institute, Osaka, and it yielded only 200 γ/g. (wet mycelium) of riboflavin after 88 hours of culture, whereas the ordinary yellow-type strain produces about 8,800 γ/g. after 63 hours of culture, but no remarkable difference was found between the two strains in the amount of the mycelium produced.[8]

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*1 Part XLI : This Bulletin, **8**, 798 (1960).

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8) T. Masuda : This Bulletin, **4**, 382 (1956).