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50. Issei Iwai and Tadahiro Iwashige : Studies on Acetylenic Compounds. XVII. Total Synthesis of *dl*-Ribose and *dl*-Arabinose.

(*Takamine Research Laboratory, Sankyo Co., Ltd.*[*1])

With development of the chemistry of nucleic acids, much attention has recently been drawn to ribose, which is one of the typical pentoses. A number of organic preparations for ribose have been investigated, namely the degradation of higher sugar, build-up from lower sugars, or the fermentation by microörganisms. However, direct total synthesis from simpler compounds has not been previously described.

Synthesis of *dl*-ribose and *dl*-arabinose has now been accomplished, starting from a simple acetylenic compound. This has been done as a part of present series of studies on the acetylenic compounds.

Generally, the preparation of a sugar is classified into the following two groups on the basis of historical survey.[1]

(A) Formose and Related Compounds

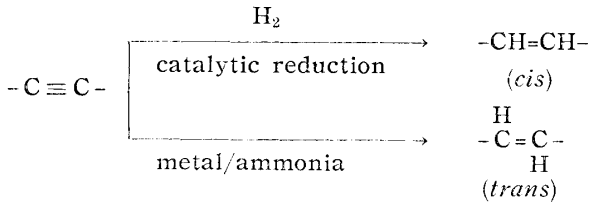
Formaldehyde undergoes aldol or acyloin condensation[2] in the presence of a weakly basic catalyst and the mixture of several kinds of polymerized polyhydroxyhydrocarbons, called formose, is obtained through such a condensation process. Fischer and Tafel[3] obtained a hexose and a ketohexose from acrolein dibromide in the presence of weak alkali, with glyceraldehyde as an intermediate, utilizing the mechanism mentioned above.

(B) Direct Total Synthesis by the Combination of Routine Chemical Reaction

Examination has recently started for the synthesis of this type and some sugar compounds have been synthesized from simple olefinic and acetylenic compounds. Lake, *et al.*[4] prepared *dl*-threose from 1,3-dichloro-2-propanol and 4-bromocrotonaldehyde, and Lespieau, *et al.*[5] synthesized alitol and galactitol from acetylene itself. Recently, Raphael, *et al.*[6a] synthesized *dl*-2-deoxyribose from 2-butyne-1,4-diol and also Weygand, *et al.*[6b] made it from 1-methoxy-1-buten-3-yne.

Only type (A) mentioned above has been known for the preparation of *dl*-ribose and *dl*-arabinose,[7] but it appears that the yield is quite poor. Direct total synthesis of these sugars is now described.

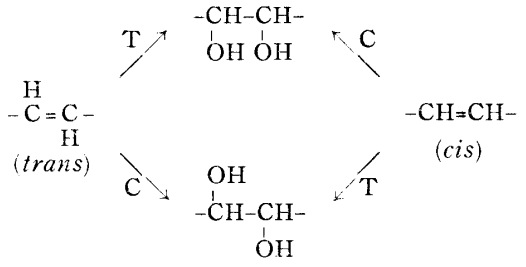
The following facts, as shown schematically, have been shown experimentally to be valuable for the reduction of triple bonds.[8]



*1 Nishi-Shinagawa, Shinagawa-ku, Tokyo (岩井一成, 岩重忠博).

1) W. Pigmann : "The Carbohydrate Chemistry, Biochemistry, Physiology," 103 (1957). Academic Press, New York.
2) A. Butlerow : Ann., **120**, 295 (1861).
3) E. Fischer, J. Tafel : Ber., **20**, 1088, 2566 (1887).
4) W. W. Lake, J. W. E. Glattfeld : J. Am. Chem. Soc., **66**, 1091 (1944).
5) R. Lespieau : "Advances in Carbohydrate Chemistry," **2**, 107 (1946).
6) *a*) M. M. Fraser, R. A. Raphael : J. Chem. Soc., **1955**, 4280; *b*) F. Weygand, H. Leube : Chem. Ber., **89**, 1914 (1956).
7) L. Hough, J. K. N. Jones : *Ibid.*, **1951**, 1122.
8) R. A. Raphael : "Acetylenic Compounds in Organic Synthesis," 93 (1955). Butterworths Scientific Publications, London.

Stereospecific oxidative hydroxylation of double bonds with various oxidation agents was examined and is summarized schematically in Chart 1.



T : *trans*-hydroxylation
peracid
iodine-silver benzoate complex
hypohalogenus acid
tungsten trioxide-hydrogenperoxide
C : *cis*-hydroxylation
alkaline permanganate
osmium tetroxide
osmium tetroxide-hydrogenperoxide

Chart 1.

The synthesis of *dl*-ribose and *dl*-arabinose was undertaken with the consideration that it would be possible to synthesize four kinds of pentose by combination of the stereospecific reduction and oxidative hydroxylation as summarized above. *dl*-Ribose and *dl*-arabinose were finally obtained by the processes shown in Chart 2.

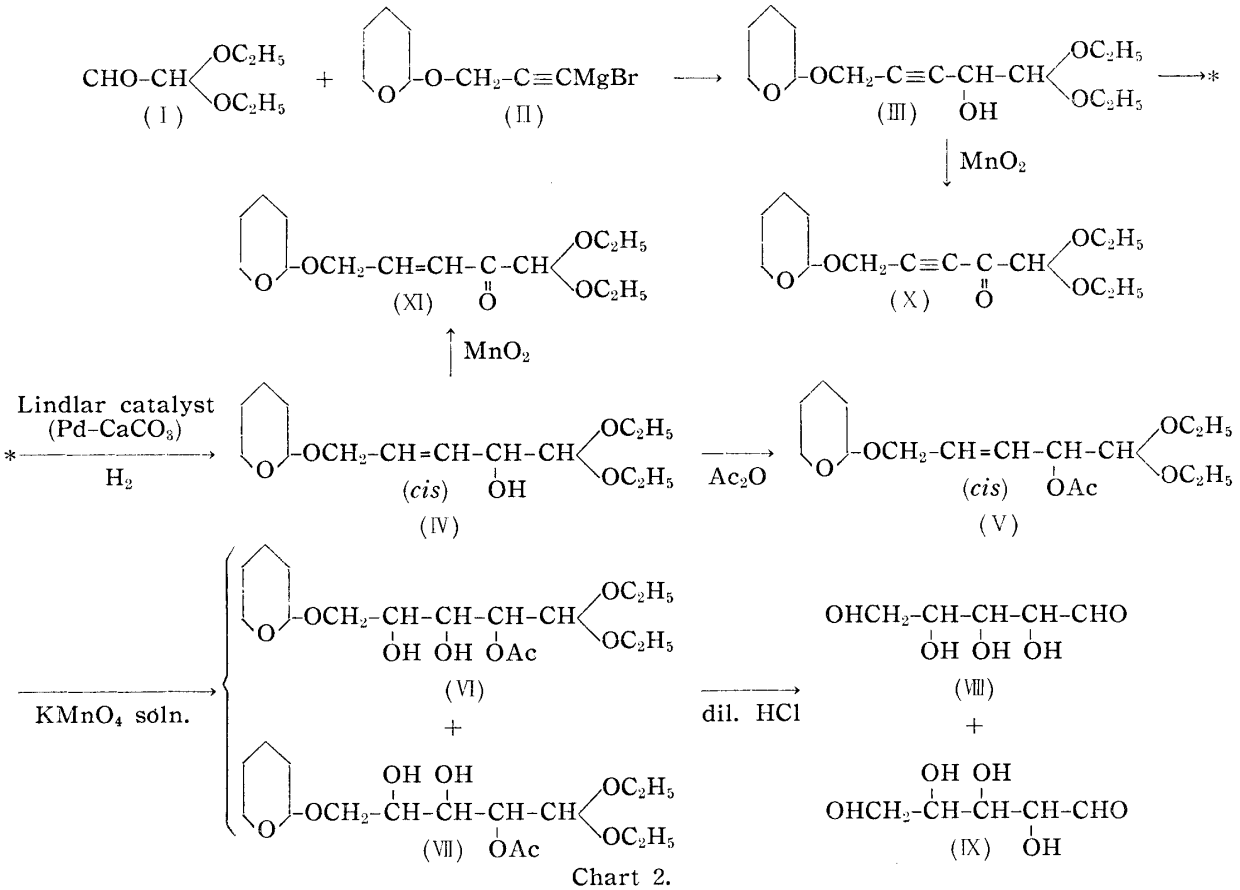


Chart 2.

Initially, glyoxal hemiacetal[9] (I), obtained by the lead tetraacetate oxidation of glyceraldehyde diethylacetal, was reacted with 3-(2-tetrahydropyranyloxy)-1-propynylmagnesium bromide[10] (II) in a mixture of dehyd. tetrahydrofuran and ether, and formed *dl*-1,1-diethoxy-5-(2-tetrahydropyranyloxy)-3-pentyn-2-ol (III) as a quite viscous oil, b.$p_{0.2}$ 140~141°. The actual yield of this reaction seems to be good (about 80%), considering the fact that an

9) H. O. L. Fischer, E. Baer : Helv. Chim. Acta, **18**, 514 (1935).
10) H. B. Henbest, E. R. H. Jones, I. M. S. Walls : J. Chem. Soc., **1950**, 3646; R. G. Jones, M. J. Mann: J. Am. Chem. Soc., **75**, 4048 (1953).

appreciable amount of 3-(2-tetrahydropyranyloxy)-1-propyne was recovered.*2 The infrared spectrum of (III) showed absorption bands at 3300~3500 cm^{-1} (-OH) and in the region of 900~1150 cm^{-1} (C-O-C), but the band due to -C≡C- stretching was not observed near 2200 cm^{-1}. Raphael[11] says that the band virtually disappears as the bond moves towards center of the molecule. Although it seems difficult to conclude whether this fact holds also in this case, there have been some other acetylenic derivatives which do not show absorption near 2200 cm^{-1}.*3

The compound (III) was oxidized in petroleum ether with active manganese dioxide[12] to give an oily product which agrees with the analysis for 1,1-diethoxy-5-(2-tetrahydropyranyloxy)-3-pentyn-2-one (X), b.$p_{0.08}$ 120~140° (bath temp.). The infrared spectrum of (X) shows absorption at 2210 cm^{-1} which is apparently due to -C≡C- stretching, besides those at 1695 cm^{-1} (-CO-) and 900~1500 cm^{-1} (C-O-C). Its ultraviolet spectrum shows a maximum at 224 mμ in ethanol. The structure of (III) was thus confirmed from these experimental results.

(III) was then hydrogenated in ethyl acetate, using the Lindlar catalyst,[13] and *dl-cis*-1,1-diethoxy-5-(2-tetrahydropyranyloxy)-3-penten-2-ol (IV) was obtained almost quantitatively by interrupting the reaction when the absorption suddenly slows down after 1 molar equivalent of hydrogen had been absorbed. Compound (III) was quite rapidly hydrogenated when 5% palladium-carbon was used instead of the Lindlar catalyst. However, the oil obtained by interrupting the reaction after absorption of 1 molar equivalent of hydrogen was observed to have almost the same purity as that obtained by the Lindlar catalyst, as determined by the refractive index value. This fact shows that the triple bond rather than the double bond was preferentially hydrogenated even by using 5% palladium-carbon. The infrared spectrum of (IV) did not show the absorption for a double bond as in the case of (III) and, therefore, it was oxidized with active manganese dioxide to give an oil, b.$p_{0.1}$ 130~150° (bath temp.), which agreed with the analytical values for 1,1-diethoxy-5-(2-tetrahydropyranyloxy)-3-penten-2-one (XI) and showed infrared absorptions at 1700 cm^{-1} (-CO-), 1630 cm^{-1} (-C=C-). Next, (IV) was acetylated as usual with acetic anhydride and pyridine to give *dl-cis*-1,1-diethoxy-2-acetoxy-5-(2-tetrahydropyranyloxy)-3-pentene (V), b.$p_{0.2}$ 123~126°, in a good yield. Osmium tetroxide and potassium permanganate are used as typical oxidation agents for the *cis*-hydroxylation of a double bond. By using the former, the osmium complex can be isolated as the oxidation intermediate and the *cis*-diol compound can be obtained in a pure state. However, the yield is not always good and osmium tetroxide is too expensive to use for practical purposes. Therefore, potassium permanganate was used for the *cis*-hydroxylation of (V).

Compound (V) was suspended in water and 10% excess of the calculated amount of potassium permanganate in aqueous solution was dropped slowly, with stirring at a low temperature (1~3°). The resultant precipitate of manganese dioxide was removed by filtration and the filtrate was passed through Amberlite IRC-50 to remove the potassium cation. The effluent was concentrated at room temperature in a reduced pressure to obtain a mixture of (VI) and (VII) as a rather hygroscopic syrupy residue. This residue gave a positive periodic acid-silver nitrate test, showing the presence of an α-glycol group and also a negative Benedict reaction, due to the retention of the aldehyde group as the acetal. This

*2 When only ether was employed as a solvent, (II) was sparingly soluble and the yield was quite poor.

*3 2-Pentyne-1,4-diol and 4-(*o*-benzyloxyphenyl)-2-butyn-4-ol do not show absorption due to -C≡C-. Unpublished work.

11) R. A. Raphael: "Acetylenic Compounds in Organic Synthesis," 209.

12) J. Attenburrow, *et al.*: J. Chem. Soc., **1952**, 1094; I. Iwai, Y. Okajima, T. Konotsune: Yakugaku Zasshi, **78**, 505 (1958).

13) H. Lindlar: Helv. Chim. Acta, **35**, 446 (1952).

residue was dissolved in dilute hydrochloric acid solution and left at room temperature for three days. This solution was filtered through Amberlite IR-4B for deacidification and concentrated at room temperature in a reduced pressure to obtain a red-brown syrupy residue which gave a strongly positive Benedict test showing the presence of a reducing aldehyde group. The residue was subjected to paper partition chromatography.*4 There are theoretically two possibilities in the *cis*-hydroxylation of (V), namely 2-OH/3-OH *cis* and 2-OH/3-OH *trans*, and the formation of *dl*-ribose from the former and *dl*-arabinose from the latter could be expected. The partition chromatogram of the reaction product actually showed 2 spots, at Rf 0.32 and 0.26, while *d*-ribose and *d*-arabinose employed as control showed Rf 0.32 and 0.26, respectively. Consequently, the formation of *dl*-ribose and *dl*-arabinose was confirmed qualitatively. The reaction product was chromatographed on cellulose powder at 60°,[14] using water-saturated butanol as the mobile phase, and three fractions were obtained: (i) The fraction showing one spot at Rf 0.32, (ii) the fraction showing two spots at Rf 0.26 and 0.32, and (iii) the fraction showing one spot at Rf 0.26. *dl*-Ribose was obtained from the first fraction. Hurd, *et al.*[15] obtained mono- and oligosaccharide polypropionates and found that they were distillable in a reduced pressure. Therefore, the syrupy residue obtained from the first fraction was treated with propionic anhydride and pyridine, following Hurd's process, and a very viscous oil, b.$p_{0.0003}$ 160~170°(bath temp.), which agreed with the theoretical analytical data for *dl*-ribose tetrapropionate, was obtained. The chloroform solution of this propionate showed a completely identical infrared spectrum as that of *d*-ribose tetrapropionate obtained analogously, as shown in Fig. 1. The syrupy residue obtained from the first fraction showing a spot at Rf 0.32 was thus confirmed as *dl*-ribose.

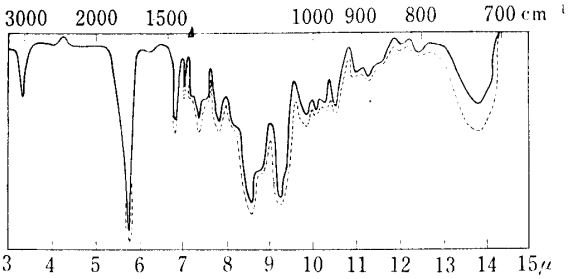


Fig. 1. Infrared Absorption Spectra of *dl*-Ribose Tetrapropionate and *d*-Ribose Tetrapropionate ($CHCl_3$ solution)
—— *d*-Ribose tetrapropionate
------ *dl*-Ribose tetrapropionate

The residue obtained from the third fraction showing a spot at Rf 0.26 was dissolved in methanol and refluxed with benzoylhydrazine. A benzoylhydrazone, m.p. 188~189° (decomp.), so obtained was recrystallized from methanol and agreed with the theoretical analytical data for the known *dl*-arabinose benzoylhydrazone. It did not show depression of the melting point with the authentic sample, m.p. 189~190°(decomp.), prepared from an

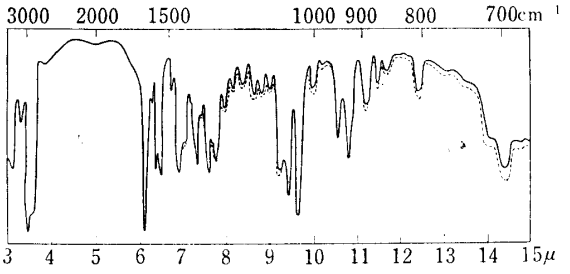


Fig. 2. Infrared Absorption Spectra of *dl*-Arabinose Benzoylhydrazones (Nujol mull)
—— Authentic sample prepared from an equimolecular mixture of *d*- and *l*-arabinose benzoylhydrazones
------ Synthetic *dl*-arabinose benzoylhydrazone

*4 Toyo Roshi No. 50. Solvent : BuOH-H_2O-AcOH (4:5:1). Temp. : 21°. Detection agent : Partridge reagent. Time : 15 hr.

14) L. Hough, J. K. N. Jones, *et al.* : J. Chem. Soc., **1949**, 2511.
15) C. D. Hurd, K. M. Gordon : J. Am. Chem. Soc., **63**, 2657 (1941).

equimolecular mixture of *d*- and *l*-arabinose benzoylhydrazone. The infrared spectrum of the benzoylhydrazone of the reaction product was completely identical with that of the authentic sample of *dl*-arabinose benzoylhydrazone, as shown in Fig. 2. The syrupy residue obtained from the third fraction, showing a spot at Rf 0.26, was thus confirmed to be *dl*-arabinose.

Consequently, it became apparent from these experimental results that the reaction proceeded stereospecifically as was expected, producing *dl*-ribose and *dl*-arabinose.

Experimental

***dl*-1,1-Diethoxy-5-(2-tetrahydropyranyloxy)-3-pentyn-2-ol (III)**——To EtMgBr solution prepared from 43.5 g. of EtBr and 8.75 g. of Mg in 190 cc. of dehyd. Et_2O, 130 cc. of dehyd. tetrahydrofuran was added. A solution of 46.2 g. of 3-(2-tetrahydropyranyloxy)-1-propyne in 35 cc. of dehyd. Et_2O was added dropwise over a period of 1 hr. to the above solution and vigorous evolution of ethane gas was observed during the addition. The mixture was stirred at room temperature for another 30 min., a solution of 36.5 g. of glyoxal hemiacetal in 100 cc. of dehyd. Et_2O was added during 40 min., and 10° rise in temperature was observed. The reaction mixture was stirred at room temperature for another 1 hr., left overnight, and decomposed with a cold saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous layer was further extracted with 200 cc. of Et_2O. The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was distilled *in vacuo* to give 43.0 g. of almost colorless viscous oil, $b.p_{0.2}$ 140~141°, n_D^{22} 1.4716, d_{18} 1.0756, and 20 g. of 3-(2-tetrahydropyranyloxy)-1-propyne was recovered. *Anal.* Calcd. for $C_{14}H_{24}O_5$: C, 61.75; H, 8.82. Found: C, 61.83; H, 8.80. M. R. Calcd : 70.80. Found : 70.70. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 3300~3500 (-OH), 900~1150 (C-O-C).

1,1-Diethoxy-5-(2-tetrahydropyranyloxy)-3-pentyn-2-one (X)——To a solution of 0.74 g. of *dl*-1,1-diethoxy-5-(2-tetrahydropyranyloxy)-3-pentyn-2-ol in 80 cc. of petr. ether, 8.0 g. of MnO_2 was added and stirred at room temperature for 7 hr. MnO_2 was filtered off and washed a few times with a small amount of petr. ether. The combined petr. ether solution was evaporated and the residue was distilled *in vacuo* to give 0.35 g. of an oil, $b.p_{0.08}$ 120~140° (bath temp.), n_D^{21} 1.4687. *Anal.* Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.15. Found : C, 62.21; H, 8.12. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 2210 (-C≡C-), 1695 (-CO-), 900~1150 (C-O-C). UV : λ_{max}^{EtOH} 224 mμ (log ε 3.622).

***dl-cis*-1,1-Diethoxy-5-(2-tetrahydropyranyloxy)-3-penten-2-ol (IV)**——A solution of 27.2 g. of 5-(2-tetrahydropyranyloxy)-3-pentyn-2-ol (III) in 500 cc. of AcOEt was hydrogenated in the presence of 9.5 g. of the Lindlar catalyst at atmospheric pressure and the reaction was stopped on sudden decrease in absorption with 1 mol. equiv. of H_2. The solution was filtered to remove the catalyst and the filtrate was evaporated. The residue was distilled *in vacuo* to give 24.2 g. of a viscous oil, $b.p_{0.08}$ 117~118°, n_D^{26} 1.4633, d_{25} 1.0496. *Anal.* Calcd. for $C_{14}H_{26}O_5$: C, 61.30; H, 9.49. Found : C, 61.36; H, 9.31. M. R. Calcd. : 72.29. Found : 72.03. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 3300~3500 (OH), 900~1150 (C-O-C).

1,1-Diethoxy-5-(2-tetrahydropyranyloxy)-3-penten-2-one (XI)——To a solution of 1.1 g. of *dl-cis*-1,1-diethoxy-5-(2-tetrahydropyranyloxy)-3-penten-2-ol (IV) in 100 cc. of petr. ether, 10 g. of MnO_2 was added and stirred at room temperature for 8 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 give 0.4 g. of an oil, $b.p_{0.1}$ 130~150° (bath temp.). *Anal.* Calcd. for $C_{14}H_{24}O_5$: C, 61.80; H, 8.84. Found : C, 61.68; H, 8.89. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1700 (CO), 1630 (C=C), 900~1150 (C-O-C).

***dl-cis*-1,1-Diethoxy-2-acetoxy-5-(2-tetrahydropyranyloxy)-3-pentene (V)**——A solution of 25.6 g. of *dl-cis*-1,1-diethoxy-5-(2-tetrahydropyranyloxy)-3-penten-2-ol (IV) and 102.3 g. of Ac_2O dissolved in 256 cc. of dehyd. pyridine was refluxed for 3 hr. When cool, excess Ac_2O and pyridine were removed on the steam bath under reduced pressure and the residue was poured into ice water. An oil that separated was extracted with Et_2O. The Et_2O layer was washed successively with water, 5% Na_2CO_3 solution, and water, dried over Na_2SO_4, and evaporated. The residue was distilled *in vacuo* to give 26.7 g. of viscous yellow oil, $b.p_{0.2}$ 123~126°, n_D^{18} 1.4566. *Anal.* Calcd. for $C_{16}H_{28}O_6$: C, 60.75; H, 8.86. Found : C, 60.89; H, 8.79. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1240, 1750 (OAc), 900~1150 (C-O-C).

5-O-(2-Tetrahydropyranyl)-2-O-acetyl-*dl*-ribose Diethylacetal (VI) and 5-O-(2-Tetrahydropyranyl)-2-O-acetyl-*dl*-arabinose Diethylacetal (VII)——To a stirred suspension of 11.7 g. of *dl-cis*-1,1-diethoxy-2-acetoxy-5-(2-tetrahydropyranyloxy)-3-pentene (V) in 175 cc. of water, a solution of 4.4 g. of $KMnO_4$ in 300 cc. of water was added dropwise within 1 hr. at 1~3° with ice-cooling. Then, the reaction mixture was left at room temperature for 30 min. to solidify colloidal MnO_2. The solidified MnO_2 was filtered off and washed several times with a small amount of water. The combined aque-

ous solution was passed through Amberlite IRC-50 and concentrated at room temperature in a reduced pressure to obtain 12.5 g. of hygroscopic syrupy residue which gave a positive HIO_4-$AgNO_3$ test, showing the presence of α-glycol group and a negative Benedict test.

***dl*-Ribose (VIII) and *dl*-Arabinose (IX)**——To a solution of 12.5 g. of a crude mixture of 5-O-(2-tetrahydropyranyl)-2-O-acetyl-*dl*-ribose diethylacetal (VI) and 5-O-(2-tetrahydropyranyl)-2-O-acetyl-*dl*-arabinose diethylacetal (VII) dissolved in 175 cc. of water, 30 cc. of conc. HCl was added and left at room temperature for 3 days. The reaction mixture, after passing through Amberlite IR-4B, was concentrated at room temperature in a reduced pressure to leave 6.0 g. of a red-brown syrup. This residue was chromatographed over a cellulose powder at 60°, using water-saturated BuOH as the mobile phase. Following three fractions were found by paper partition chromatography : (i) A fraction showing a spot at Rf 0.32 (0.5 g.), (ii) a fraction showing two spots at Rf 0.32 and 0.26 (1.6 g.), and (iii) a fraction showing a spot at Rf 0.26 (0.8 g.).

A solution of 0.12 g. of a syrupy residue obtained from the first fraction and 0.63 g. of propionic anhydride dissolved in 0.86 g. of pyridine was left at room temperature for 3 days. The reaction mixture was poured into ice water and a separated oil was extracted with Et_2O. The Et_2O layer was washed with 4*N* HCl and water, dried over Na_2SO_4, and evaporated. The residue was distilled *in vacuo* to give a colorless, very viscous oil, b.$p_{0.0003}$ 155~165° (bath temp.), which agreed with the analysis for ribose tetrapropionate. The infrared spectrum of this oil in $CHCl_3$ solution was identical with that of *d*-ribose tetrapropionate prepared analogously. *Anal.* Calcd. for $C_{17}H_{26}O_9$: C, 54.60; H, 6.95. Found : C, 54.71; H, 7.03.

A solution of 0.09 g. of a syrupy substance obtained from the second fraction and 0.08 g. of benzoylhydrazine dissolved in 3 cc. of MeOH was refluxed for 3 hr. The white solid that separated on concentration was recrystallized from MeOH to crystals of m.p. 188~189° (decomp.), which did not show depression with an authentic sample of *dl*-arabinose benzoylhydrazone, m.p. 189~190° (decomp.) (reported[16] m.p. 194~195°), prepared from an equimol. mixture of *d*- and *l*-arabinose benzoylhydrazones. The infrared spectrum of this sample was identical with that of the authentic sample. *Anal.* Calcd. for $C_{12}H_{16}O_5N_2$: C, 53.75; H, 5.97; N, 10.45. Found : C, 53,96; H, 6.13; N, 10.63.

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Summary

dl-Ribose and *dl*-arabinose were synthesized, starting from *dl*-1,1-diethoxy-5-(2-tetrahydropyranyloxy)-3-pentyn-2-ol which was prepared by the Grignard reaction of glyoxal hemiacetal with 3-(2-tetrahydropyranyloxy)-1-propionylmagnesium bromide.

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16) L. Hough, J. K. N. Jones : J. Chem. Soc., **1951**, 1125.