BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 40 2150—2154 (1967)

A Structural Study of Di-*O*-isopropyridene-pentitols by Conversion to the Corresponding Mono-*O*-benzyl Derivatives*[1]

Toshio NAKAGAWA, Hisao TOKUOKA, Kazuhiko SHINOTO,
Juji YOSHIMURA and Tetsuo SATO

Department of Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo

(Received February 23, 1967)

D-Arabinitol and xylitol were acetonated, benzylated and then hydrolyzed with a mineral acid to afford in good yields the corresponding 1-*O*-benzyl derivatives, which were identified by a periodate oxidation and a chemical identification. A preferential acetonation of the pentitols is discussed in a view of stereochemistry. Synthesis of 2-*O*-benzyl-D-arabinitol and 3-*O*-benzylxylitol are also described.

There are many variable factors in the formation of acetals and ketals of the alditols, and simple rules have been formulated to predict the courses of the acetal formation with a large measure of accuracy.[1,2] In the case of the ketal formation (for example acetonation), on the other hand, it is still not deviced comprehensive rules regarding the preferential formation· but it has been generally recognized that α- and αT-ring[3] are both permissible and that the former takes precedence over the latter.[1] These rules are explained by stereochemical stabilities of the rings formed (Fig. 1).

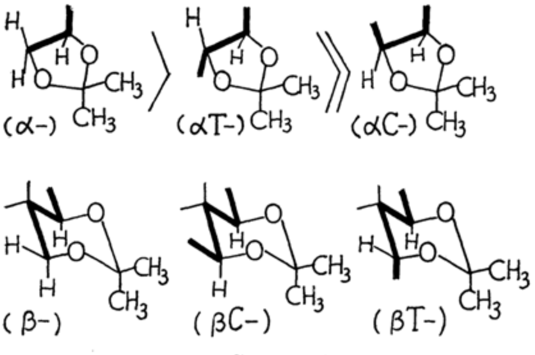


Fig. 1. Conformation of *O*-isopropylidene rings and order of their stabilities.

The α-ring has only a pair of eclipsed C–H/C–C bonds, whereas the αT-ring has two pairs. Therefore, the former takes precedence over the latter. In the case of the αC-ring two C–C bonds are eclipsed each other, which makes the formation of the ring much difficult. In the case of the six-membered β-, βC- and βT-ring, on the other hand, the formation of the ring would be strongly hindered by repulsions (or 1, 3-diaxial interaction) between the axial methyl group and the axial hydrogens or the axial carbon chain on the carbon atoms bearing the oxygens. Applying these rules to acetonation of pentitols, namely arabinitol (I), ribitol (II) and xylitol (III), one would expect a preferential formation of 1, 2 ; 4, 5-di-*O*-isopropylidene derivatives, but the case seems to be true only for II.[4,5]

A preferential formation of a 2, 3 ; 4, 5-di-*O*-isopropylidene derivative was described by Foster's school[5] in 1963 on acetonation of I (L-form) in the presence of concentrated sulfuric acid and anhydrous copper sulfate. In 1944 Hann *et al.*[6] reported a preferred formation of 2, 3 ; 4, 5-di-*O*-isopropylidenexylitol in acetonation of III. In 1965 Foster's school[7] has showed gas chromatographically that acetonation of III under various conditions afforded a mixture of 2, 3 ; 4, 5- and 1, 2 ; 4, 5-di-*O*-isopropylidene derivative, in which the former was always preferential to the latter in the ratio *ca.* 11 : 1—2.3 : 1, and the corresponding 1, 3 ; 4, 5-di-*O*-isopropylidene derivative reported

---

*1 A part of this paper was presented at the 18th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1965.

1) S. A. Barker and E. J. Bourne, "Advances in Carbohydrate Chemistry," Vol. 7, Academic Press Inc., New York (1952), p. 177.

2) R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 1909 (1944); A. T. Ness, R. M. Hann and C. S. Hudson, *ibid.*, **70**, 765 (1948).

3) According to Barker and Bourne[1] the Greek letters α and β will be used as in common practice to signify the relative positions, along the carbon chain of the polyhydroxy compound, of the two hydroxyl groups engaged in the cyclization, and C and T will indicate the relative configuration (cis or trans) of these two groups as they appear in the usual Fischer projection formula.

4) K. W. Buck, A. B. Foster, J. Lehmann, J. M. Webber and J. H. Westwood, *Chem.* & *Ind.*, **1964**, 1623.

5) M. A. Bukhari, A. B. Foster, J. Lehmann, J. M. Webber and J. H. Westwood, *J. Chem. Soc.*, **1963**, 2291.

6) R. M. Hann, A. T. Ness and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 73 (1944).

7) N. Baggett, K. W. Buck, A. B. Foster, R. Jefferis, B. H. Rees and J. M. Webber, *J. Chem. Soc.*, **1965**, 3382.

by Valentin and Tomkuljak[8] could not be found.

In this paper the preferential formation of 2, 3 ; 4, 5-di-*O*-isopropylidene derivatives in the case of I and III was confirmed by conversion to the corresponding mono-*O*-benzyl derivatives, and dis cussion was made on these results from stereochemical aspeacts.

Results and Discussion

I (D-form) was treated with a suspension of anhydrous copper sulfate in dry acetone containing sulfuric acid to give an oily di-*O*-isopropylidene derivative, which on benzylation and following acid hydrolysis yielded crystalline 1-*O*-benzyl-D-arabinitol (VI), mp 129—130°C, in a good yield. VI was also derived from 3, 4 ; 5, 6-di-*O*-isopropylidene-D-mannitol (VII) through successive lead tetraacetate oxidation, catalytic hydrogenation, benzylation and acid hydrolysis. The structure of VI was ascertained by periodate oxidation as shown in Fig. 2.

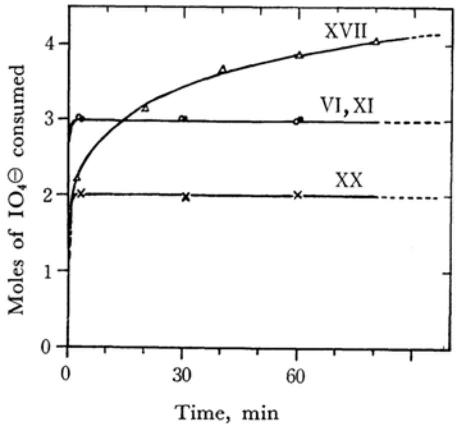


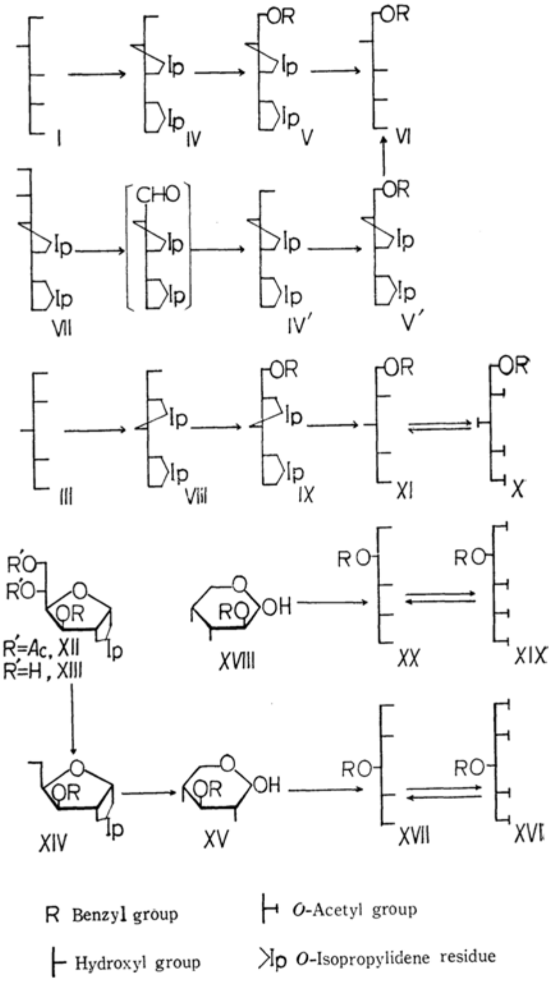
Fig. 2. Periodate oxidation of mono-*O*-benzyl-pentitols.

Similarly, III was acetonated, benzylated and then hydrolyzed to give a crude syrupy mono-*O*-benzylxylitol, which on acetylation gave a crystalline tetraacetate (X), mp 42—43°C, over a 65% yield. X was treated with a trace of sodium methylate in abs. methanol to give syrupy mono-*O*-benzylxylitol (XI). As XI consumes exactly 3.0 mol of periodate, X and XI must be the 1-*O*-benzyl derivatives. Thus, the 2, 3 ; 4, 5-di-*O*-isopropylidene derivative is preferentially formed in the case of acetonation of I and III. These results are consistent with those of Hann *et al.*[6] and of Foster's school[5,7].

2-*O*-Benzyl-D-arabinitol (XX) and 3-*O*-benzylxylitol (XVII) were prepared from 2-*O*-benzyl-D-arabinose (XVIII) and 3-*O*-benzyl-1, 2-*O*-isopropylidene-α-D-glucofuranose (XIII), respectively, and used as referential compounds for the periodate oxidation. XX consumed rapidly the theoretical amount (2.0 mol) of periodate, but XVII did extraordinarily as shown in Fig. 2, because benzyloxymalondialdehyde, the oxidation product of XVII, also consumed periodate.[9]

Against the general rules[1] the preferred products on acetonation of I and III were not 1, 2 ; 4, 5-but 2, 3 ; 4, 5-di-*O*-isopropylidene derivatives. Thus, the rules should be reconsidered on the basis of a stereochemical stability of not only individual ketal ring but also a whole molecule.

2, 3 ; 4, 5-Di-*O*-isopropylidene-D-arabinitol (IV) may take a number of conformations due to the free rotation of the single bond between C$_3$-C$_4$, however, conformational concepts[10] allow one to

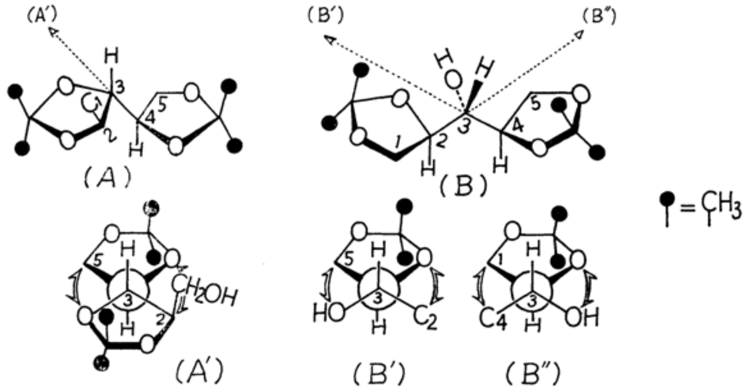


---

[8] F. Valentin and D. Tomkuljak, *Chem. Zvesti,* **3**, 146 (1949).

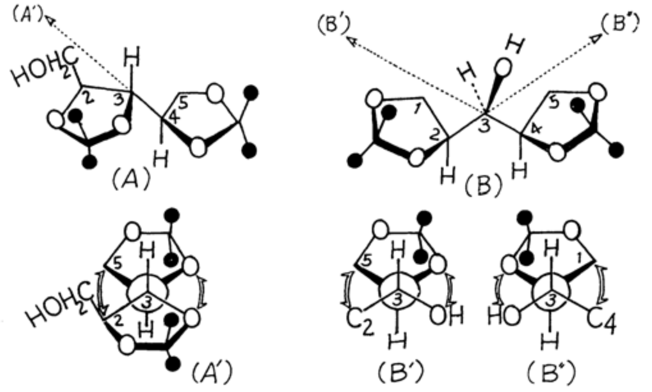
[9] J. C. P. Schwarz and M. MacDougall, *J. Chem. Soc.*, **1965**, 3065.

[10] W. G. Dauben and K. S. Pitzer, "Steric Effects on Organic Chemistry," ed. by M. S. Newman, John Wiley & Sons Inc., New York (1956), p. 4; E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill Book Co., Inc., New York (1962), p. 124.



		(A)	(B)
Gauche	C-C/C-C	—	1
	C-C/C-O	3	2
	C-O/C-O	—	1
Eclipsed pair	C-C/C-H	3	2
	C-H/C-H	1	2

Fig. 3. Conformations of di-*O*-isopropylidene-D-arabinitols.
(A) 2, 3; 4, 5-derivative (IV); (B) 1, 2; 4, 5-derivative (XXI)



		(A)	(B)
Gauche	C-C/C-C	1	2
	C-C/C-O	1	—
	C-O/C-O	1	2
Eclipsed pair	C-C/C-H	3	2
	C-H/C-H	1	2

Fig. 4. Conformations of di-*O*-isopropylidenexylitols.
(A) 2, 3; 4, 5-derivative (VIII); (B) 1, 2; 4, 5-derivative (XXII)

predict that the most stable conformer should be one as shown in Fig. 3A or 3A′ in which three pairs of C–C/C–H bonds and one pair of C–H/C–H bond on the five membered ring are eclipsed each other, and three pairs of C–C/C–O bonds are oriented in a gauche (or skew) type. On the other hand, 1, 2 ; 4, 5-di-*O*-isopropylidene-D-arabinitol would take the conformation as shown in Fig. 3B as the most stable one in which each two pairs of C–C/C–H and C–H/C–H bonds are eclipsed, and two pairs of C–C/C–O bonds and each one pair of C–O and C–C/C–C bond are in the gauche type. When it is postulated that the instability of a gauche C–C/C–C bond is the same as that of C–C/C–O bond, the comparable instability of IV to the latter structure will be presented by eclipsed (C–C/C–H – C–H/C–H) – gauche (C–O/C–O).

The difference between eclipsed C–C/C–H and C–H/C–H as an instability factor will be easily minimized by puckered motion of the five membered ring, but the gauche C–O/C–O bonds makes the molecule less stable especially on account of its electrostatic repulsion between the oxygen atoms.[10] The preferential formation of IV in acetonation of I will be rationally explained by the above comparison.

Similarly, in the case of 2, 3 ; 4, 5- and 1, 2 ; 4, 5-di-*O*-isopropylidenexylitol shown in Fig. 4A and 4B the circumstances are the same as above. The comparison of the free energy of each compound will offer more direct evidence on the above discussion.

Experimental

1-1) Isopropylidenation of D-Arabinitol. A mixture of D-arabinitol (12.2 g, 0.08 mol), anhydrous copper sulfate (20 g), concentrated sulfuric acid (0.7 m*l*) and dried acetone (250 m*l*) was stirred at room temperature for 20 hr and then filtered. The filtrate was neutralized with concentrated aqueous ammonia, insoluble material was filtered off, the organic solvent was almost distilled off *in vacuo*, and the resulting mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate and then concentrated. Distillation of the residue *in vacuo* gave an oily product. Yield 15.1 g (81%); bp 142—143°C/18 mmHg (lit.; 145—152°C/23 mmHg¹¹⁾; 74—80°C/0.05 mmHg¹²⁾); $n_D^{20}=1.4497$.

Found: C, 56.81; H, 8.84%. Calcd for $C_{11}H_{20}O_5$ (232.3): C, 56.88; H, 8.68%.

1-2) *O*-Benzyl-di-*O*-isopropylidene-D-arabinitol (V). A mixture of di-*O*-isopropylidene-D-arabinitol (14.5 g, 0.062 mol), obtained in 1-1), benzyl chloride (25 m*l*) and xylene (25 m*l*) was vigorously stirred with potassium hydroxide (30 g) at 100—110°C for 5 hr. The reaction mixture was cooled to room temperature, water (100 m*l*) was added to it, and the mixture was stirred until the residue dissolved. The aqueous layer was separated, extracted with benzene, and the benzene extract was combined with the nonaqueous layer. The combined solution was dried over anhydrous sodium sulfate, the benzene and the excess of benzyl chloride were removed by distillation under reduced pressure, and the residual oil was distilled *in vacuo* to afford syrup (17.6 g, 75%), bp 160—163°C/3 mmHg, $n_D^{20}=1.4890$.

Found: C, 67.22; H, 8.28%. Calcd for $C_{18}H_{26}O_5$ (322.4): C, 67.06; H, 8.13%.

1-3) 2, 3; 4, 5-Di-*O*-isopropylidene-D-arabinitol (IV′). A crude oily 2, 3; 4, 5-di-*O*-isopropylidene-*aldehydo*-D-arabinose, prepared by the method of Wiggins¹³⁾ from 17.0 g of 1, 2; 3, 4-di-*O*-isopropylidene-D-mannitol (VII), was dissolved in 90% ethanol (30 m*l*) and hydrogenated with platinum oxide (1.0 g) at room temperature overnight. The catalyst was filtered off, the filtrate was concentrated *in vacuo* to dryness, and the residue was distilled *in vacuo* to give an oily product. Yield, 9.2 g, bp 129—130°C/11 mmHg, $n_D^{20}=1.4515$.

Found: C, 56.83; H, 8.75%. Calcd for $C_{11}H_{20}O_5$ (232.3): C, 56.88; H, 8.68%.

1-4) 1-*O*-Benzyl-2, 3; 4, 5-di-*O*-isopropylidene-D-arabinitol (V′). The compound IV′ (7.5 g) was treated in the same manner as described in 1-2) to give syrup (7.7 g), bp 185—188°C/11 mmHg, $n_D^{20}=1.4989$.

Found: C, 67.15; H, 8.30%. Calcd for $C_{18}H_{26}O_5$ (322.4): C, 67.06; H, 8.13%.

1-5) 1-*O*-Benzyl-D-arabinitol (VI). *a) Hydrolysis of V.* A mixture of V (16.1 g), 1 N sulfuric acid acid (100 m*l*) and ethanol (100 m*l*) was refluxed for 4 hr and neutralized with barium carbonate. After a further reflux for 10 min the hot mixture was filtered, the precipitates were washed twice with hot ethanol, the filtrate was combined with the washings and concentrated at 40°C *in vacuo* to give crystalls which were recrystallized from ethanol. Yield, 8.7 g (72%), mp 129—130°C. The product consumed 3.0 mol of periodate.

Found: C, 59.80; H, 7.47%. Calcd for $C_{12}H_{18}O_5$ (242.3); C, 59.49; H, 7.49%.

b) Hydrolysis of V′. In the same manner as described in a), V′ (6.0 g) was hydrolyzed to give a product which was recrystallized from ethanol. Yield, 3.1 g, mp 129—130°C, not depressed by admixture with the product in a).

2-1) Isopropylidenation of Xylitol. A mixture of xylitol (50 g, 0.33 mol), anhydrous copper sulfate (80 g), concentrated sulfuric acid (3.0 m*l*) and dry acetone (1 *l*) was stirred at room temperature for 20 hr and then worked up essentially as in 1-1) to give an oily product (58 g, 76%), bp 160—162°C/25 mmHg (lit.⁵⁾: 102°C/0.3 mmHg), $n_D^{20}=1.4535$.

Found: C, 56.68; H, 9.07%. Calcd for $C_{11}H_{20}O_5$ (232.3): C, 56.88; H, 8.68%.

2-2) *O*-Benzyl-di-*O*-isopropylidenexylitol (IX). Di-*O*-isopropylidenexylitol (51.5 g), obtained in 2-1), was treated with benzyl chloride (90 m*l*) and potassium hydroxide (100 g) in xylene (90 m*l*) in the same manner as described in 1-2) to give syrup (50.8 g, 71%), bp 140—144°C/1 mmHg, $n_D^{20}=1.4906$.

Found: C, 67.23; H, 8.39%. Calcd for $C_{18}H_{26}O_5$ (322.4): C, 67.06; H, 8.13%.

2-3) Tetra-*O*-acetyl-1-*O*-benzylxylitol (X). A mixture of IX (50 g), 1 N sulfuric acid (250 m*l*) and ethanol (250 m*l*) was refluxed for 4 hr, neutralized with barium carbonate, filtered and the precipitates were washed twice with hot ethanol. The combined filtrate and washings were concentrated *in vacuo* to dryness and the residual syrup (29.7 g, 79%) was acetylated with acetic anhydride (50 m*l*) and pyridine (50 m*l*) overnight. The reaction mixture was then concentrated at 40—50°C *in vacuo* to dryness and the residue was recrystallized from ethanol-ether to give crystals melting at 42—43°C. Yield 33.2 g (66% on the basis of the crude deacetonated product).

Found: C, 58.50; H, 6.59%. Calcd for $C_{20}H_{26}O_9$ (410.4): C, 58.53; H, 6.39%.

2-4) 1-*O*-Benzylxylitol (XI). The compound X (20 g) dissolved in absolute methanol (50 m*l*) containing sodium methylate (2 mmol) and allowed to stand at room temperature overnight. The solution was deionized with IR-120 (H^+-form) and then concentrated *in vacuo* to dryness to yield a colorless viscous syrup, which failed to crystallize. This product showed no absorption of a carbonyl group in its infrared spectrum and consumed 3.0 mol of periodate.

3-1) Tetra-*O*-acetyl-2-*O*-benzyl-D-arabinitol (XIX). 2-*O*-Benzyl-D-arabinose⁹⁾ (5 g) was dissolved in water (50 m*l*), sodium borohydride (1 g) was added to it under stirring, and the mixture was allowed to stand at room temperature overnight. After addition of acetic acid (5 m*l*) it was concentrated *in vacuo* to dryness to give a colorless syrup, which was acetylated with acetic anhydride (30 m*l*) and a drop of 60% perchloric acid. After standing overnight at room temperature it was poured into ice-water and extracted with methylene

---

11) A. Seier, *Ber.*, **28**, 2531 (1895).
12) For the L-form: lit. 5.
13) L. F. Wiggins, *J. Chem. Soc.*, **1946**, 13.

chloride. The extract was washed with aqueous sodium bicarbonte and water, dried over anhydrous sodium sulfate and then concentrated *in vacuo* to dryness. Distillation of the residual syrup *in vacuo* gave viscous syrup (4.8 g) which failed to crystallize. Bp 183—186°C/0.015 mmHg.

Found: C, 58.19; H, 6.81. Calcd for $C_{20}H_{26}O_9$ (410.4): C, 58.53; H, 6.39%.

3-2) 2-*O*-Benzyl-D-arabinitol (XVIII). The compound XIX (4 g) was dissolved in absolute methanol (15 m*l*) containing sodium methylate (1 mmol) and allowed to stand at room temperature overnight. The solution was neutralized with IR-120(H^+-form) and then concentrated *in vacuo.* The residue was recrystallized from ethanol - petroleum ether. Yield 1.6 g, mp 66—68°C. The product consumed 2.0 mol of periodate.

Found: C, 59.37; H, 7.78%. Calcd for $C_{12}H_{18}O_5$ (242.3): C, 59.49; H, 7.49%.

4-1) 3-*O*-Benzyl-1,2-*O*-isopropylidene-*α*-D-xylofuranose (XIV). 5, 6-Di-*O*-acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-*α*-D-glucofuranose (XII)[14] (30 g) was dissolved in absolute. methanol (300 m*l*) containing sodium methylate (3 mmol). The mixture was allowed to stand at room temperature overnight and concentrated to dryness to give a viscous syrup, which showed no absorption of a carbonyl group in its infrared spectrum. The syrup was re-dissolved in 50% methanol (200 m*l*) and a solution of sodium periodate (19.5 g) in water (300 m*l*) was added into it under ice cooling and vigorous stirring in the period of 20 min. After further stirring for 3 hr at room temperature the reaction mixture was concentrated to about 300 m*l* at 40°C *in vacuo* and then extract was washed with aqueous sodium chloride, dried over anhydrous sodium sulfate and then concentrated to dryness at 40°C *in vacuo* to give a crude syrup. Without purification the product was allowed to treat with sodium borohydride (1 g) in methanol (20 m*l*) under ice cooling and then to stand at room temperature overnight. After acetone (3 m*l*) had been added the reaction mixture was concentrated *in vacuo* to dryness. The residual syrup was re-dissolved in absolute methanol (30 m*l*), the solvent was evaporated, and this process was repeated four times more. Distillation of the residual syrup gave syrup (12.5 g) which failed to crystallize. Bp 151—153°C/0.01 mmHg.

Found: C, 63.75; H, 7.58%. Calcd for $C_{15}H_{20}O_5$ (280.3): C, 64.27; H, 7.19%.

4-2) 3-*O*-Benzyl-D-xylose (XV). A mixture of XIV in 50% methanol (300 m*l*) containing concentrated sulfuric acid (7 g) was refluxed for 2 hr, cooled to room temperature, naturalized with aqueous sodium hydroxide and then extracted four times with ethyl acetate. The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give crystalls, which was recrystallized twice from methanol. Yield 7.9 g, mp 89—91°C.

Found: C, 59.71; H, 6.87%. Calcd for $C_{12}H_{16}O_5$ (240.3): C, 59.99; H, 6.71%.

4-3) Tetra-*O*-acetyl-3-*O*-benzylxylitol (XVI). In the same manner as described in 3-1), XV (9.0 g) was treated with sodium borohydride (1.5 g) and then acetylated to give a syrup which was purified by distillation. Bp 160—163°C/0.015 mmHg.

Found: C, 58.26; H, 6.65%. Calcd for $C_{20}H_{26}O_9$ (410.4): C, 58.53; H, 6.39%.

4-4) 3-*O*-Benzylxylitol (XVII). The compound XVI (2 g) was deacetylated in the same manner as described in 3-2) and the crude product was recrystallized from ethanol and then ethyl acetate. Mp 128—130°C.

Found: C, 59.37; H, 7.23%. Calcd for $C_{12}H_{18}O_5$ (242.2): C, 59.49; H, 7.49%.

The authors are indebted to Mr. Susumu Shimoyama for his assistance in the experiment.

---

[14] A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 152 (1946); K. Freudenberg, W. Durr and H. von Hochstetter *Ber.*, **61**, 1735 (1928).