Carbohydrate Research, 87 (1980) 219–226
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

ISOPROPYLIDENATION OF D-MANNITOL UNDER NEUTRAL CONDITIONS*

GORDON J. F. CHITTENDEN
Department of Exobiology, The University, Toernooiveld, 6525 ED Nijmegen (The Netherlands)
(Received April 21st, 1980; accepted for publication, May 12th, 1980)

ABSTRACT

Isopropylidenation of D-mannitol (**2**) under neutral conditions, by treatment with 2,2-dimethoxypropane in 1,2-dimethoxyethane, is described. 1,2:5,6-Di-*O*-isopropylidene-D-mannitol is the main equilibrium product, which does not undergo further substitution under the conditions used. 1,2:3,4:5,6-Tri-*O*-isopropylidene-D-mannitol, the other major product, was shown to be derived mainly from initial 3,4-substitution of **2**. The presence of a difunctional ether, of suitable geometry, is a necessary requirement for the reaction. Some mechanistic aspects of the reaction are discussed.

INTRODUCTION

Cyclic acetals of sugars and alditols are important synthetic intermediates: their preparation, chemistry, and physical properties have been comprehensively reviewed[1–4]. These compounds are generally prepared by the acid-catalysed condensation of carbonyl compounds with suitable hydroxylic substrates, and the nature of the final product is thermodynamically controlled. Acetal exchange, which is frequently used to acetalate carbohydrates[2,5], is considered to be under kinetic control and has led to products not always available by direct methods. The most commonly used reagent is 2,2-dimethoxypropane in *N*,*N*-dimethylformamide with toluene-*p*-sulphonic acid as catalyst. Acetonation under kinetic control may also be achieved by the use of 2-alkoxypropenes under similar conditions[6,7].

An improved synthesis[8] of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**) involved treatment of D-mannitol (**2**) with 2,2-dimethoxypropane in 1,2-dimethoxyethane containing a trace of tin(II) chloride as catalyst. The presence of tin(II) chloride seemed to be essential, but, apparently, it did not act as an ordinary Lewis-acid catalyst or as a source of hydrochloric acid (by reaction with hydroxyl groups), since the use of an identical amount of zinc chloride was unsuccessful.

Further investigations of this reaction have shown that no catalyst is required. Acetalation in the absence of an acid catalyst usually involves treatment of the reaction

*Acetalation Studies, Part II. For Part I, see ref. 8.

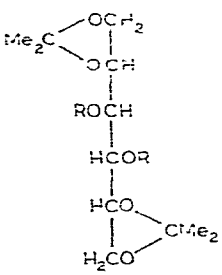
0008-6215/80/0000–0000/$ 02.25,

mixture with anhydrous cupric sulphate as a dehydrating agent[1,2]. It has been suggested[9] that, in such systems, complexing of the hydroxyl groups of a sugar with the cupric ion may release sufficient sulphuric acid to catalyse the reaction. Benzylidenation of D-xylose occurs in *tert*-butyl alcohol solution in the presence of anhydrous sodium sulphate as desiccant[10]. Irvine and Scott[11] found that the condensation of benzaldehyde with the methyl D-glucopyranosides proceeded in the absence of catalyst, provided that the temperature was sufficiently high to remove the water liberated. It is probable that both of these reactions were promoted[1] by the benzoic acid formed when benzaldehyde is exposed to air.

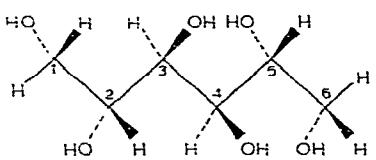
In the reactions described in this report, isopropylidenation occurs under completely neutral conditions, presumably by acetal exchange, so that the equilibrium of the reaction and the structure of the products are not influenced by acidic conditions.

RESULTS AND DISCUSSION

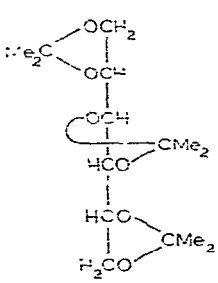
Treatment of D-mannitol (**2**) with a boiling mixture of 2,2-dimethoxypropane and 1,2-dimethoxyethane yielded a clear solution within 20–24 h. T.l.c. revealed two main components (R_F 0.75 and 0.49, in the ratio of ~1:2) and two minor



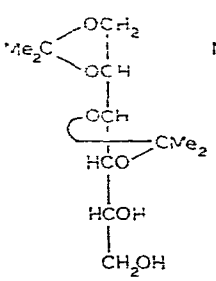
1 R = H
6 R = Ac



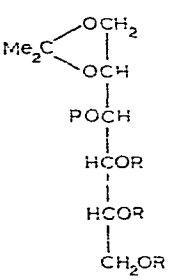
2



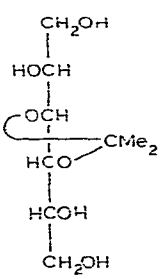
3



4



5 R = H
7 R = Ac



8

components (R_F 0.46 and 0.11). G.l.c. confirmed this result and showed further that the four components corresponded to 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (**3**), 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**), 1,2:3,4-di-*O*-isopropylidene-D-mannitol (**4**), and 1,2-*O*-isopropylidene-D-mannitol (**5**), which were present in the ratios 4:14:1:1. Compounds **4** and **5** were synthesised by previously described methods[12,13]. Allowing the reaction to proceed for a total of 10 days did not substantially alter these ratios of products, indicating that they probably represented the true equilibrium values of the system.

Recrystallisation of the crystalline, concentrated reaction-mixture gave **1** in 52% yield, and addition of ice–water to the concentrated mother liquors gave **3** in 19.5% yield. These yields could be increased to 63 and 29%, respectively, by using column chromatography; compound **4** was not isolated, but **5** was obtained in 2.3% yield. Compound **1** was characterised as the known diacetate **6**, and **5** gave the corresponding tetra-acetate **7**.

An almost identical result was obtained when the reaction solvent was bis(2-methoxyethyl) ether in place of 1,2-dimethoxyethane. No reaction was observed in the absence of these solvents. The use of a range of solvents also failed to yield products; in the presence of acetone, 1,1-dimethoxymethane, 1,4-dioxane, methanol, 2-methoxyethanol, *N*,*N*-dimethylformamide, and acetonitrile, **2** was recovered essentially unchanged after periods of up to 8 days at reflux temperature. When dibutyl ether was used as the reaction solvent, only partial acetalation occurred; after 5 days heating under reflux, 44% of **2** was recovered, and **1** was isolated from the solubilised fraction in 39% yield (based on reacted material). Addition of a small volume of methanol to the normal reaction mixture, equivalent to that which would be liberated by reaction of 2 mol of 2,2-dimethoxypropane with 1 mol of **2**, suppressed the acetalation. Unreacted **2** (58%) was recovered after treatment for 5 days: the monoacetal **5** was isolated in 9% yield, in addition to the diacetal **1** (26%).

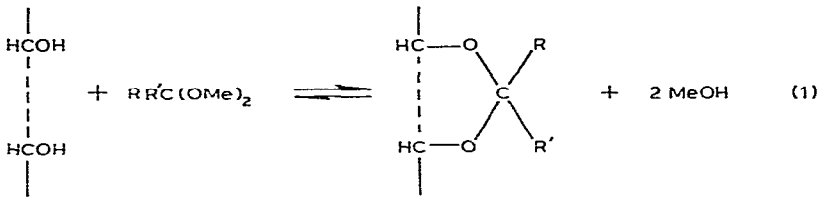
Removal of methanol from the system also severely inhibited transacetalation. This was achieved by allowing the reflux condensate to percolate through activated molecular-sieve contained in a Soxhlet extractor: after 11 days, 66% of **2** remained.

Treatment of compound **1** with boiling 2,2-dimethoxypropane in 1,2-dimethoxyethane for 48 h caused little further isopropylidenation; t.l.c. and g.l.c. revealed <7% of the triacetal **3**. When the diacetal **4** was treated under similar conditions, **3** was the major product. The reaction of 1,2-*O*-isopropylidene-D-mannitol (**5**) in a similar manner gave **1** in 70% yield, together with **3** and **4** in the ratio 3:1. The corresponding 3,4-*O*-isopropylidene-D-mannitol (**8**) gave **3** almost exclusively: t.l.c. revealed traces of **4** in the reaction mixture.

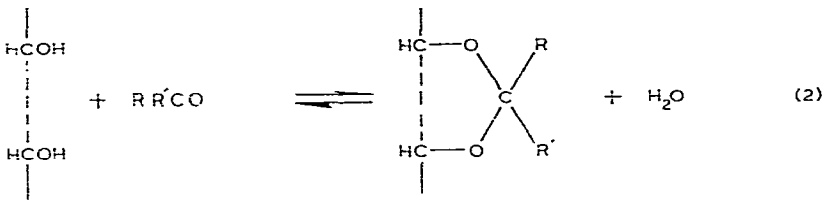
It was demonstrated that no acetal migration occurred between the derivatives under similar reaction conditions. Thus, when solutions of **1**, **4**, and a mixture of D-mannitol and **3** in 1,2-dimethoxyethane were heated separately under reflux for 48 h, only the original materials could be detected.

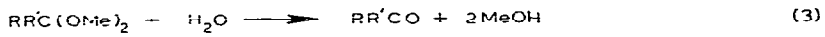
The presence of a difunctional ether appears to be essential for the acetal-exchange reactions observed under neutral conditions. The equilibrium involved in

acetal exchange under acidic conditions may be formulated[5] as shown in Equation *1*.



Hampton *et al.*[14] suggested that the diol and free carbonyl compound are the primary reactants, with the acetal acting as the desiccant (Equations *2* and *3*).





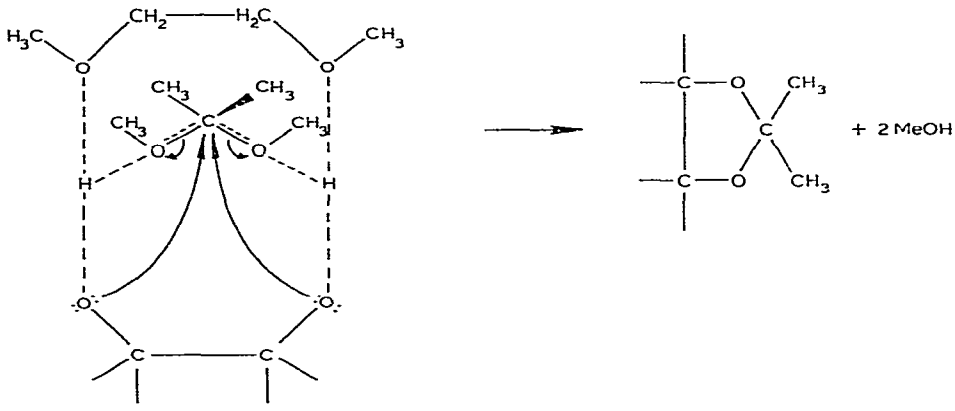
It seems unlikely that reactions *2* and *3* are operative in the systems described here, since there was no appreciable reaction between **2** and 2,2-dimethoxypropane alone or in the presence of acetone as solvent.

Furthermore, when the reaction was performed in methanol or when a small proportion of methanol was added to the normal reaction mixture, cyclic acetal formation was inhibited. This observation could be accounted for by reaction *1*, but is difficult to explain by reactions *2* and *3*. A similar situation presumably exists when the reaction is performed in the presence of 2-methoxyethanol. The equilibrium *1* seems to lie well to the right when certain difunctional ethers are used as reaction solvents, but not in the presence of hydroxylic solvents. The latter solvents either compete more effectively in the acetal exchange or affect the solvating action of the solvent. At present, it is difficult to explain the inhibitory effect of removing the methanol formed during the reaction, as this would be expected to displace the equilibrium to the right. In a similar reaction with D-glucitol, no inhibition was noted[15].

The kinetics of alkoxy exchange in acetals show[16] that the reaction is acid-catalysed, first-order with respect to acid and acetal, and independent of alcohol concentration, as required for a rate-determining formation of cation followed by rapid addition of alcohol. The equilibrium of acetal formation does depend on the structure of the alcohol, acetalation with ring formation being favoured, as deduced from hydrolysis studies[17,18].

It is proposed that, in the reactions described herein, 1,2-dimethoxyethane or bis(2-methoxyethyl) ether initially forms a co-ordinated complex with a diol group, which then enters into a multicentered transition-state with 2,2-dimethoxypropane.

Simultaneous attack of the slightly basic oxygen atoms of the diol group on the central carbon atom results in the elimination of two molecules of methanol with concomitant formation of the stable cyclic acetal, as shown below. The product does not subsequently rearrange under the neutral conditions.



An alternative route could be through a multi-stage process similar to the conventional mechanism for transacetalation reactions. Initial complexing of the ether with the diol group, with charge separation, yields the oxonium salt of the ether and the corresponding dianion of the diol group. The positive charges on the oxonium salt are then transferred successively, or simultaneously, to 2,2-dimethoxypropane, to give the corresponding carbonium ion, which undergoes attack by the oxygen atoms of the dianion, yielding the cyclic acetal with expulsion of methanol.

The latter mechanism could best explain the slow reaction and low yield observed when dibutyl ether was used as the solvent. In this reaction, each hydroxyl group of the diol would have to undergo separate complexing with the monofunctional ether, leading initially to a mixed-acetal intermediate, which would have to undergo further attack in a similar manner to yield the cyclic acetal. This process would be competitive with attack by the methanol that is released, to re-form the original intermediates.

There is nothing known about the acidity of alditols in non-aqueous solvents. A dissociation constant of 4.2×10^{-14} at 25° has been determined for **2** in aqueous solution[19]. This value is of the same order as the third dissociation constant of boric acid.

In the crystalline state, D-mannitol adopts[20] the planar zigzag conformation (**2**), with the terminal hydroxyl groups in the bent orientation. In solution, equilibration would be expected to occur, to give an approximately equal mixture of four rotamers having extended carbon-chains and extended or bent orientations for the terminal group. It seems that conformation **2** of D-mannitol is particularly well-suited to interact at the 1,2-, 3,4-, and 5,6-diol positions with 1,2-dimethoxyethane in the known[21] gauche conformation and with the similar bis(2-methoxyethyl) ether. The

absence of reaction in the presence of 1,1-dimethoxymethane and 1,4-dioxane is due to their unfavourable molecular geometry.

The central feature of the chemistry of ethers is their ability to act as bases and form co-ordination complexes with many molecules, including alcohols. The extent to which charge is transferred and the strength of the complex that is formed vary considerably. The basicity generally increases with increasing substitution. This trend is consistent with the inductive donation of electron density by the alkyl groups, which helps to stabilise the oxonium ion that is formed. 1,2-Dimethoxyethane has been shown[22] to be a useful solvent in acid-catalysed equilibria studies involving acetals; diethyl ether has been shown[23] to influence some acetalation reactions involving sugar derivatives.

The results show further that the triacetal **3** is derived mainly from initial substitution at the 3,4-position of **2**, to give **8** which then reacts further to give **3**. Initial attack on **2** probably occurs mainly at the 1,2-position, to give the monoacetal **5**, which is converted principally into **1**, which was shown not to undergo significant further substitution. A small proportion of **5** underwent reaction, to give the diacetal **4** and thence **3**. Consideration of molecular models indicates that the 3,4-diol group in **1** is hindered to an approach by a 1,2-dimethoxyethane molecule, mainly through H-2 and H-5, thus inhibiting the chelating effect of the solvent.

The acetonation of D-glucitol in the presence of zinc chloride has been investigated[24] recently by g.l.c. techniques. The starting material was rapidly converted into the 1,2:5,6-diacetal in a kinetically controlled reaction. This product then underwent simultaneous conversion into the expected triacetal and also to the isomeric, more stable, 2,3:5,6-diacetal by acetal migration. The acetalation of HO-3,4 was a sterically hindered process, and the 3,4-acetal was not prone to migration.

Preliminary results[15] show that, under the foregoing, neutral conditions, D-glucitol yields a mixture of three diacetals, and glycerol yields a relatively high proportion of 1,3-*O*-isopropylideneglycerol in addition to the expected 2,3-*O*-isopropylidene derivative. Studies of these and related systems are in progress.

EXPERIMENTAL

Kieselgel 60 (Merck) was used for column chromatography, and silica gel (Merck, DC Fertig-platten) for analytical t.l.c.; compounds were detected[24] by spraying with 0.1M $KMnO_4$–M sulphuric acid (1:1) followed by heating at 110°. G.l.c. was performed with a Varian 1400 Aerograph gas chromatograph, a glass column (2 m × 4 mm) packed with 5% of XE-60 on Gas-Chrom W/A.W./DMCS, a temperature range from 100 to 220° at 4°.min^{-1}, and helium as the carrier gas at 70 ml.min^{-1}. Where necessary, samples (10 mg) were acetylated by treatment with dry pyridine (0.5 ml) and acetic anhydride (0.5 ml) at 90° for 30 min prior to analysis. Compounds were identified by co-injection with authentic samples.

Reactions of 2,2-dimethoxypropane in 1,2-dimethoxyethane. — (*a*) *With* D-*mannitol.* D-Mannitol (10 g) was suspended with vigorous stirring in 1,2-dimethoxy-

ethane (60 ml), 2,2-dimethoxypropane (40 ml) was added, and the mixture was heated under reflux with continuous stirring until a clear solution was obtained (20–24 h). The cooled solution was concentrated *in vacuo* and the crystalline product was recrystallised from dibutyl ether (38 ml), to give 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**; 7.48 g, 52%), m.p. 119–121°; lit.[25] m.p. 122°. Treatment of the product with acetic anhydride–pyridine gave the 3,4-diacetate **6**, m.p. 121–122° (from benzene). $[\alpha]_D^{22}$ +26° (*c* 2.4, dichloromethane); lit.[13] m.p. 123°, $[\alpha]_D$ +26.7°.

The recrystallisation mother-liquor was evaporated and the residue was treated with ice–water (120 ml), to give a white, crystalline residue. Recrystallisation from light petroleum (b.p. 60–80°) gave **3** (3.24 g, 19.5%), m.p. 68°, $[\alpha]_D^{22}$ +12° (*c* 4.1, ethanol); lit.[26] m.p. 70°, $[\alpha]_D$ +12.5° (ethanol).

In another experiment, the crude, crystalline product obtained by treating **2** with 2,2-dimethoxypropane, as described above, was dissolved in cyclohexane and chromatographed on kieselgel (240 g). Elution with 1,2-dimethoxyethane–cyclohexane (1:1) gave compound **3** (4.8 g, 29%), m.p. 67–69°, followed by **1** (9.05 g, 63%), m.p. 117–119°. Elution with 1,2-dimethoxyethane then gave 1,2-*O*-isopropylidene-D-mannitol (**5**; 0.28 g, 2.3%), m.p. 164–166° (from ethanol); lit.[13] m.p. 167°. Treatment with acetic anhydride–pyridine, in the usual manner, gave the tetra-acetate **7**, m.p. 104–105° (from ethanol); lit.[13] m.p. 107°.

(*b*) *With 1,2:5,6-di-*O*-isopropylidene-*D*-mannitol* (**1**). Compound **1** (5 g) in 1,2-dimethoxyethane (25 ml) was treated with 2,2-dimethoxypropane (15 ml), and the mixture was boiled under reflux, with stirring, for 48 h. The solution was concentrated *in vacuo* and the crystalline product was recrystallised from dibutyl ether (20 ml), to give **1** (4.35 g, 87%), m.p. 118–120°.

(*c*) *With 1,2-*O*-isopropylidene-*D*-mannitol* (**5**). Compound **5**[13] (2.0 g) was treated as described in (*b*). The crystalline product was recrystallised from dibutyl ether, to give **1** (1.65 g, 70%), m.p. 117–119°.

(*d*) *With 3,4-*O*-isopropylidene-*D*-mannitol* (**8**). Compound **8**[28] (1.0 g) was treated as described in (*b*). The crystalline product was recrystallised from light petroleum (b.p. 60–80°), to give **3** (1.21 g, 89%), m.p. 67–69°.

(*e*) *With 1,2:3,4-di-*O*-isopropylidene-*D*-mannitol* (**4**). Compound **4**[12] (0.5 g) was treated as described in (*b*). The crystalline product was recrystallised from light petroleum (b.p. 60–80°), to give **3** (0.475 g, 82.5%), m.p. 68–70°.

Treatment of D-*mannitol* (**2**) *with 2,2-dimethoxypropane in dibutyl ether.* — A suspension of D-mannitol (5 g) in dibutyl ether (40 ml) and 2,2-dimethoxypropane (2.0 ml) was boiled under reflux, with continuous stirring, for 5 days. The hot mixture was then filtered, to give **2** (2.2 g, 44%), which was characterised as the known[27] hexa-acetate. The cooled filtrate, which contained crystalline material, was evaporated to dryness *in vacuo*, and the residue was recrystallised from dibutyl ether, to give **1** (1.57 g, 39%). T.l.c. indicated that the recrystallisation mother-liquor contained **3**, but no attempt was made to isolate this material.

Treatment of D-*mannitol* (**2**) *with 2,2-dimethoxypropane in 1,2-dimethoxyethane containing methanol.* — D-Mannitol (5 g) was boiled with a mixture of 2,2-dimethoxy-

propane (20 ml), 1,2-dimethoxyethane (30 ml), and methanol (4.4 ml) under reflux, with continuous stirring, for 5 days. The hot reaction mixture was then filtered to give **2** (2.9 g, 58%). The filtrate was evaporated *in vacuo*, and a solution of the residue in water (40 ml) was extracted with ethyl acetate (3 × 40 ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was recrystallised from a small volume of dibutyl ether, to give **1** (0.79 g, 26%), m.p. 116–119°.

The aqueous layer was exhaustively extracted with ethyl acetate for 48 h and the dried extract was concentrated *in vacuo*, to give a crystalline residue. Recrystallisation from ethanol gave **5** (0.23 g, 9%), m.p. 163–165°.

ACKNOWLEDGMENT

Martin Loef is thanked for valuable technical assistance.

REFERENCES

1 A. N. DE BELDER, *Adv. Carbohydr. Chem.*, 20 (1965) 219–302.
2 A. N. DE BELDER, *Adv. Carbohydr. Chem. Biochem.*, 34 (1977) 179–241.
3 A. B. FOSTER, in W. PIGMAN AND D. HORTON (Eds.), *The Carbohydrates: Chemistry and Biochemistry*, Vol. 1A, Academic Press, New York, 1972, pp. 391–402.
4 D. M. CLODE, *Chem. Rev.*, 79 (1979) 491–513.
5 M. E. EVANS, F. W. PARRISH, AND L. LONG, JR., *Carbohydr. Res.*, 3 (1967) 453–462; A. HASEGAWA AND M. KISO, *ibid.*, 63 (1978) 91–98 and earlier papers.
6 M. L. WOLFROM, A. B. DIWADKAR, J. GELAS, AND D. HORTON, *Carbohydr. Res.*, 35 (1974) 87–96; J. GELAS AND D. HORTON, *ibid.*, 67 (1978) 371–387; 71 (1979) 103–121.
7 E. FANTON, J. GELAS, AND D. HORTON, *Chem. Commun.*, (1980) 21–22.
8 G. J. F. CHITTENDEN, *Carbohydr. Res.*, 84 (1980) 348–350.
9 T. MAEDA, Y. MICHI, AND K. TOKUYAMA, *Bull., Chem. Soc. Jpn.*, 42 (1969) 2648–2655.
10 R. J. FERRIER AND L. R. HATTON, *Carbohydr. Res.*, 5 (1967) 132–139.
11 J. C. IRVINE AND J. P. SCOTT, *J. Chem. Soc.*, (1913) 575–581.
12 L. F. WIGGINS, *J. Chem. Soc.*, (1946) 13–14.
13 L. v. VARGHA, *Ber.*, 66 (1933) 1394–1399.
14 A. HAMPTON, J. C. FRATANTONI, P. M. CARROLL, AND SU-CHU WANG, *J. Am. Chem. Soc.*, 87 (1965) 5481–5487.
15 G. J. F. CHITTENDEN, unpublished results.
16 R. S. JUVET AND J. CHIU, *J. Am. Chem. Soc.*, 83 (1961) 1560–1563
17 A. SKRABAL AND M. ZLATEWA, *Z. Phys. Chem.*, 119 (1926) 305–318.
18 F. R. GALIANO, D. RANKIN, AND G. J. MANTELL, *J. Org. Chem.*, 29 (1964) 3424–3426.
19 P. TERECHOV, *Collect. Czech. Chem. Commun.*, 1 (1929) 551–559.
20 G. A. JEFFREY AND H. S. KIM, *Carbohydr. Res.*, 14 (1970) 207–216.
21 R. G. SNYDER AND G. ZERBI, *Spectrochim. Acta, Part A*, 23 (1967) 391–437.
22 S. W. SMITH AND M. S. NEWMAN, *J. Am. Chem. Soc.*, 90 (1968) 1249–1253.
23 D. M. HALL AND O. A. STAMM, *Carbohydr. Res.*, 12 (1970) 421–428.
24 J. KUSZMANN, P. SOHÁR, G. HORVÁTH, É. TOMORI, AND M. IDEI, *Carbohydr. Res.*, 79 (1980) 243–253.
25 E. BAER, *J. Am. Chem. Soc.*, 67 (1945) 338–339.
26 E. BAER AND H. O. L. FISCHER, *J. Biol. Chem.*, 128 (1939) 463–500.
27 T. S. PATTERSON AND A. R. TODD, *J. Chem., Soc.*, (1929) 2876–2889.
28 P. BRIGL AND H. GRÜNER, *Ber.*, 67 (1934) 1969–1973.