The authors' thanks are due to Professor T. Isobe and Mr. K. Takahashi, the Institute, for their technical co-operation and discussion on NMR spectra; the Takasago Perfumery Co. for a supply of materials which made this investigation possible. The authors are also indebted to Mr. S. Aono for infrared spectral measurements and to Mr. S. Ohyama and Miss. Y. Endo for elemental analyses.

Summary

Reaction of difluoroboron compound of β-thujaplicin and bromine afforded 8-bromo compound, which gave β-dolabrin and 8-alkoxyhinokitiol by a treatment of base in alcohol.

(Received June 8, 1961)

UDC 547.457.1

143. Masuo Akagi, Setsuzo Tejima, and Masanobu Haga : A New Synthesis of 1,6-Anhydro-β-D-glucopyranose (Levoglucosan).

(*Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University*[*1])

Several methods for the preparation of 1,6-anhydro-β-D-hexoses (levoglycosans) have been reported. The pyrolysis of sugars and polysaccharides under reduced pressure have been well known to afford 1,6-anhydrides.[1]

Besides pyrolysis, 1,6-anhydro-β-D-glycopyranoses were also obtainable when aryl-β-D-glycopyranosides,[2] aryl-β-D-thioglucopyranoside,[3] 2,3,4,6-tetra-O-acetyl-β-D-glycopyranosyl trimethylammonium bromide,[4] 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl nitrate,[5] 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride[6] and 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide[6] were treated with hot alkali, respectively.

Moreover, it was reported that, by a treatment with alkaline reagents, the ester derivatives sterically hindered, stevioside[7] and 1-O-(2,4,6-trimethylbenzoyl)-β-D-glucopyranose[8,9] gave 1,6-anhydride.

In addition to the reaction with alkaline, the methods of preparing 1,6-anhydro-β-D-glucopyranose by treating 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose[10] and 6-O-trityl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose[11] with acidic reagents were reported.

The mechanism of 1,6-anhydro ring formation from phenyl-β-D-glucopyranoside

---

*1 Nishi-5-chome, Kita-12-jo, Sapporo, Hokkaido (赤木満洲雄, 手島節三, 羽賀正信).

1) A. Pictet, J. Sarasin : Helv. Chim. Acta., **1**, 87 (1918); J.C. Irvine, J.W.H. Oldham : J. Chem. Soc., **127**, 2729 (1925); R.J. Dimler : Advances in Carbohydrate Chemistry., **7**, 37 (1950) Academic Press Inc., New York.
2) *a*) C. Tanret : Compt. rend., **119**, 158 (1894); *b*) E.M. Montgomegy, N.K. Richtmyer, C.S. Hudson : J. Am. Chem. Soc., **65**, 3, 1483 (1942).
3) E.M. Montgomery, N.K. Richtmyer, C.S. Hudson, : J. Org. Chem., **10**, 194 (1945).
4) P. Karrer, A.P. Sminoff : Helv. Chim. Acta., **4**, 817 (1921); F. Micheel : Ber., **62**, 687 (1929).
5) E.K. Gladding, C.B. Purves : J. Am. Chem. Soc., **66**, 76 (1944).
6) F. Micheel, H. Wulff : Chem. Ber., **89**, 1521 (1956); F. Micheel, A. Klemer : *Ibid.*, **91**, 194 (1958).
7) H.B. Wood, Jr., R. Allerton, H.W. Diehl, H.G. Fletcher, Jr. : J, Org. Chem., **20**, 875 (1955).
8) H.B. Wood, Jr., H.G, Fletcher, Jr. : J. Am. Chem. Soc., **78**, 207 (1956).
9) F. Micheel, G. Baum : Chem. Ber., **88**, 2020 (1955).
10) R.U. Lemieux, C. Brice : Can. J. Chem., **30**, 295 (1952).
11) G. Hoschele : Angew. Chem., **65**, 267 (1953).

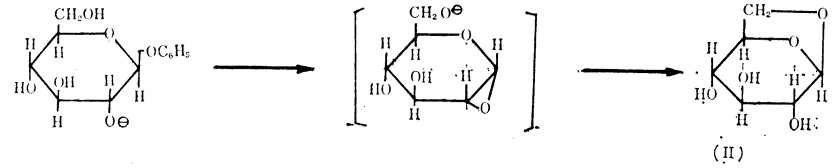


Chart 1.

with hot alkali was interpreted by McCloskey and Coleman,[12] with a formation of unstable intermediate of 1,2-anhydro ring (epoxide) to alkali-stable 1,6-anhydro ring.

Likewise, the reaction mechanism of 1,6-anhydro ring formation with acidic reagents was interpreted by Lemieux and Brice,[10] to form an unstable intermediate of 1,2-α-D-cyclic ion.

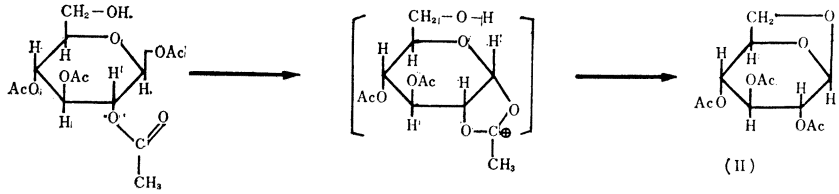


Chart 2.

Thus the reaction mechanism of 1,6-anhydro ring formation described above was accounted as a nucleophilic substitution of the groups situated at 1-position of the carbon by the hydroxyl group at 6.[9,13]

The present paper deals with the synthesis of 1,6-anhydro-β-D-glucopyranose from 6-O-*p*-toluenesulfonyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose by the reaction of cold sodium methoxide.

An elimination of the halogens, sulfonic ester groups, and to some extent, nitric ester groups from sugar derivatives in alkali is one of the main methods to provide anhydro sugars.[14]

For anhydro ring formation through the above procedure, the hydroxyl group participated in anhydro ring formation is required to be situated sterically so that the displacement of the hydroxyl group is capable to approach to the expelling group (i. e., *p*-toluenesulfonyl- or halogeno-group) from the rear side.[14]

According to the stereochemical criterion as discussed, the acetoxy groups located at 1-position of the carbon atom and 3 are capable to form anhydro rings (1,6- and 3,6-anhydro) when 6-O-*p*-toluenesulfonyl-1, 2, 3, 4-tetra-O-acetyl-β-D-glucopyranose (I) was treated with alkaline reagents.

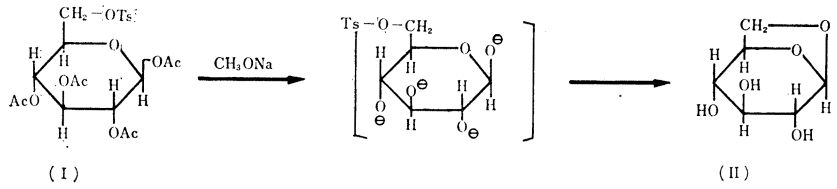


Chart 3.

12) C.M. McCloskey, G.H. Coleman : J. Org. Chem., **10**, 184 (1945).
13) R.U. Lemieux : "Advances in Carbohydrate Chemistry" **9**, 1 (1954); C.E. Ballou : *Ibid.*, **9**, 59 (1954) Academic Press Inc., New York.
14) P.S. Peat : *Ibid.*, **2**, 37 (1946).

As expected, by treatment of (I) with cold sodium methoxide, 1,6-anhydro-β-D-glucopyranose (II) was formed and isolated as triacetate in 60~70% yield. However, 3,6-anhydro-D-glucose (III) was failed to be isolated from this reaction mixture. For the reason of preferential formation of 1,6-anydro ring to 3,6-anhydro ring, the following two factors are suggested to be necessary for the formation; firstly, the hydroxyl group at 1-position of the carbon atom is hemiacetalic and would be more nucleophilic than the other hydroxyl groups; and secondly, there is no obstacles between the carbon atom at 1 and 5 (lactolic oxygen) by a comparison between the carbon atom at 3 and 5 (hydrogen and hydroxyl group at carbon atom 4) on the occasion of inversion from Cl to 1C conformation.[15]

On the other hand, however, the hydroxyl group situated at carbon atom 1 is unable to approach sterically at carbon atom 6 in the case of α-anomer, accordingly it would be also unable to expect the formation of (II) from this anomer.

Assumption cited above, by a similar treatment to 6-deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose (IV) with sodium methoxide, (II) was not obtained, but a syrup was obtained to give 3,6-anhydro-D-glucose phenylosazone in 60% yield.

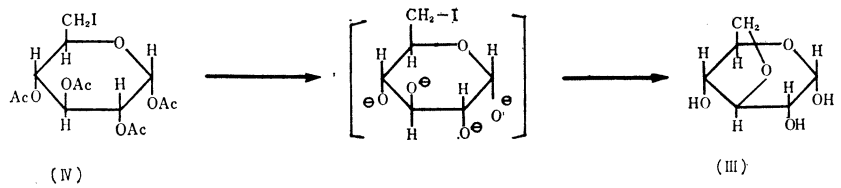


Chart 4.

For the estimation of anomeric configuration, the conductivity of sugars in boric acid solution,[16] molar refractive index,[17] infrared absorption spectrum,[18] and proton magnetic resonance spectrum[19] have been reported as physicochemical methods. As the chemical methods for determination of anomeric structure, the formation of 1,6-anhydride[20] and mercaptolysis of acetate[21] are also reported.

Evidently these results described above showed that the absolute configuration of α,β-anomers of glucopyranose derivatives agreed with the structural formula of present representation.[22]

Relating to D-galactose, however, 6-O-*p*-toluenesulfonyl-1,2,3,4-tetra-O-acetyl-β-D-galactopyranose (V) did not give an expected 1,6-anhydro-β-D-galactopyranose by treatment with sodium methoxide under the same conditions used for (I), but gave a syrup which reduced the Benedict's solution. As to the α-anomer of galactose derivative, 1,6-anhydride was not obtainable likewise to β-anomer.

The reason of this failure may be explained by a speculation of the following effects: D-galactose derivatives can be represented as Cl conformation and, on the other hand, 1,6-anhydrides exist in 1C conformation as appointed by Reeves.[15]

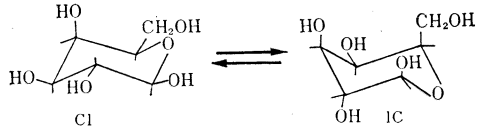
15) R.E. Reeves : J. Am. Chem. Soc., **72**, 1499 (1950).
16) R. Verschuur : Rec. trav. chim., **47**, 123 (1928).
17) C.N. Riiber : Kgl. Norske. Videnskab. Selskabs. Forh., **4**, 157 (1932).
18) S.A. Barker, E.J, Bourne, M. Stacey, D.H. Whiffen : J. Chem. Soc., 171 (1954).
19) R.U. Lemieux, R.K. Kullnig, H.J. Bernstein, W.G. Schneider : J. Am. Chem. Soc., **79**, 1005(1957); **80**, 6098 (1958).
20) See ref. 2*b*), 8), and 10).
21) R.U. Lemieux : Can. J. Chem., **29**, 1079 (1951).
22) C.S. Hudson : "Advances in Crabohydrate Chemistry" **3**, 1 (1948) Academic Press Inc., New York.

Cl lC

Chart 5.

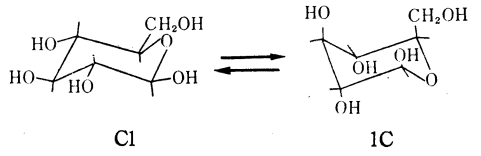
In the course of inversion of conformation from Cl to lC, the hydroxyl group located at 4-position must pass through with the hydroxyl group at carbon 3 and hydroxymethyl (carbon 6) group of carbon 5 in the configuration of galactopyranose. At low temperature, it would be concievable that this passing may give serious effect on the inversion of conformation of galactose derivatives. On the other hand, β-D-glucopyranose derivative (I) has no such effect at all, that it would give 1,6-anhydride (II) easily, being compared with galactose derivative (V).

6-O-*p*-Toluenesulfonyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (I) and 6-deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose (IV) were prepared after the method of Hardegger and Montavon,[23] and 1,6-anhydro-β-D-glucopyranose (II) was characterized through triacetate and tribenzoate. The anomeric 6-O-*p*-toluenesulfonyl-1,2,3,4-tetra-O-acetyl-D-galactopyranose were prepared according to Ohle and Thiel,[24] and a syrup obtained by alkali treatment has been investigating.



Cl lC

Conformational inversion of galactose



Cl lC

Conformational inversion of glucose

Chart 6.

Experimental

1, 6-Anhydro-2,3,4-tri-O-acetyl-β-D-glucopyranose——A solution of 16.2 g. of MeONa (6.9 g. of Na in 150 cc. of abs. MeOH) was cooled to 5~10° and to this 50 g. of 6-O-*p*-toluenesulfonyl-1,2,3,4-tetra-O-acetyl-β-D-glucose (I)[23] was added in small portions under stirring. After being kept overnight in refrigera tor, the mixture was neutralized with AcOH cautiously, and the solvent was removed under reduced pressure. The crystalline residues were acetylated with pyridine and Ac_2O as usual. In this case, sodium *p*-toluenesulfonate was deposited as crystals. The mixture was removed into ice-water and extracted with $CHCl_3$, which was washed with dil. H_2SO_4, $NaHCO_3$ solution, and water successively, and dried over Na_2SO_4. After a removal of the solvent, 20 g. of crude product was obtained in 70% of theory. Recrystallizations from Et_2O, the product melted at 109~110°; $[\alpha]_D^{20}$ −46°(c=2.5, EtOH), reported m.p. 108°,[25] 110°[26]; $[\alpha]_D$ −45.5° in EtOH.[25] *Anal.* Calcd. for $C_{12}H_{16}O_8$: C, 50.00; H, 5.60. Found: C, 49.93; H, 5.63.

1, 6-Anhydro-2,3,4-tri-O-benzoyl-β-D-glucopyranose——The alkali-treated mixture of 25 g. of (I), as described above, was treated with 30 g. of benzoyl chloride in 100 cc. of pyridine. After standing

23) F. Hardegger, R. Montavon: Helv. Chim. Acta., **29**, 1199 (1946).
24) H. Ohle, H. Thiel: Ber., **66**, 525 (1935).
25) See ref. 2) and 3).
26) E, Vongerichten, Fr. Mueller: Ber., **39**, 241 (1908).

overnight, the mixture was poured into ice-water, a syrupy product was produced, which was solidified on standing for several hours. This was filtered off and washed with water, and air dried; yielding was 14.1 g. in 60% of theory. After several recrystallizations from $CHCl_3$-EtOH, it melted at 201~202°; $[\alpha]_D^{20}$ −35.6°(c=0.92, $CHCl_3$), reported, m.p. 194°,[25] 199~200°,[26] 202~204°[8]; $[\alpha]_D$ −36.4°.[8] *Anal.* Calcd. for $C_{27}H_{22}O_8$: C, 68.35; H, 4.67. Found : C, 68.06; H, 4.66.

1,6-Anhydro-β-D-glucopyranose (II)——A solution of 5.6 g. of 1,6-anhydro-2,3,4-tri-O-acetyl-β-D-glucose in 50 cc. of 0.01*N* MeONa in MeOH was allowed to stand in refrigerator overnight. After a removal of the solvent, the residues were recrystallized from AcOEt to afford 2.8 g. of (II), m.p. 178°; $[\alpha]_D^{20}$ −66°(c=0.9, H_2O), reported,[25] m.p. 178° and $[\alpha]_D$ −66.5° in water. *Anal.* Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found : C, 44.52; H, 6.32.

Phenylosazone of 3,6-anhydro-D-glucose——10 g. of 6-deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose (IV)[23] was treated with 3.5 g, of MeONa (1.5 g. of Na in 30 cc. of MeOH) in the same manner described in (I). As compared with β-anomer, the reaction mixture was deepen in its color. After being kept standing overnight in refrigerator, the mixture was neutralized with AcOH and the solvent was removed under reduced pressure. The residues dissolved in water were passed through a column of Amberlite IR-120(H^+) and then a column of Amberlite IR-45(OH^-) successively. The effluent was treated with charcoal and concentrated under reduced pressure to slightly colored syrup, which reduced the Fehling's solution, yielding was 3 g. 1.0 g. of syrup, 2.0 g. of freshly distilled phenylhydrazine and 2 cc. of 50% AcOH were dissolved in 30 cc. of water and heated on a steam-bath for 30 min. After cooling, yellow precipitates were filtered off and washed with a small amount of cold water. Recrystallization from EtOH gave yellow needles, m.p. 190°(decomp.); $[\alpha]_D^{20}$ −84.4~−37.5°(after 24 hr.)(c=1.28, pyridine) reported[27] m.p. 187~188° and $[\alpha]_D$ −146° in MeOH. *Anal.* Calcd. for $C_{18}H_{20}O_3N_4$: C, 63.51; H, 16.46. Found : C, 63.66; H, 5.86; N, 16.55.

Thanks are expressed to Mr. K. Narita for performing microchemical analysis.

Summary

1,6-Anhydro-β-D-glucopyranose was synthesized from 6-O-*p*-toluenesulfonyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose by a treatment with sodium methoxide. Since 1,6-anhydro-β-D-glucose is not obtainable from 6-deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose, this procedure is applicable to distinguish α,β-anomers chemically.

Some conformational discussions are made.

(Received June 19, 1961)

27) H. El. Khadem, E. Schreier, G. Toehr, E. Hardegger : Helv. Chim. Acta., **35**, 232 (1952).

UDC 547.673.6:581.13

144. Mitiiti Fujita*1, Tsutomu Furuya*1, and Mitsuyoshi Matsuo*2 : Studies on the Metabolism of Naturally Occurring Anthraquinones. III.[1] The Metabolism of Alizarin Dimethyl Ether.

(*Faculty of Pharmaceutical Sciences, University of Tokyo**1)

The authors were interested in biological demethylation of anthraquinone derivatives, especially on the difference of behavior to demethylation between their 1-methoxyl and 2-methoxyl groups.

From this point of view, urinary metabolites of alizarin dimethyl ether were studied qualitatively and quantitatively in this paper. And as a reference, the metabolism of

*1 Hongo, Tokyo (藤田路一, 古谷 力).
*2 Present address:National Insutitute of Radiological Sciences, Kurosuna-cho, Chiba(松尾光芳).

1) Part II : This Bulletin, **9**, 967 (1961).