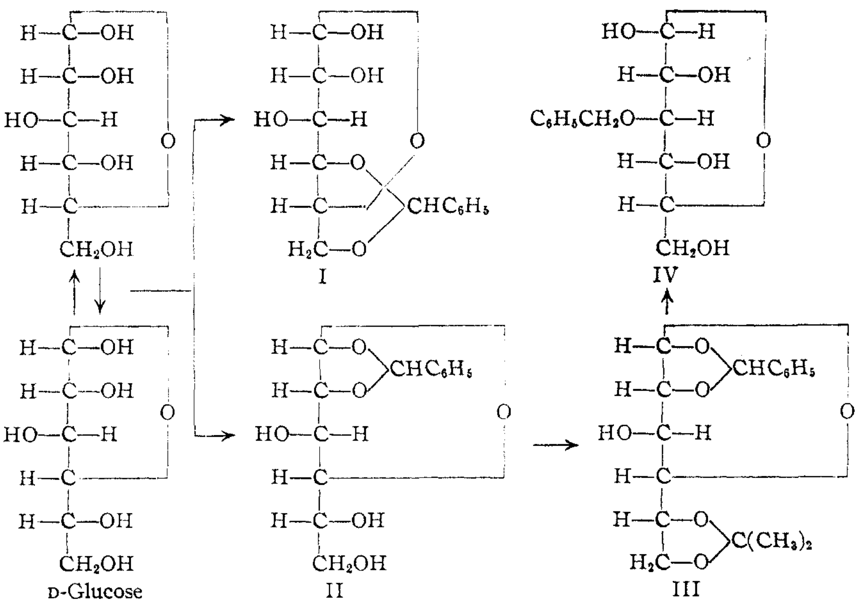
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

1,2-Benzylidene-D-glucofuranose[1]

BY JOHN C. SOWDEN AND DOROTHY J. KUENNE

The condensation of D-glucose with benzaldehyde in the presence of anhydrous zinc chloride results in a new monobenzylidene-D-glucose in addition to the previously known, isomeric 4,6-benzylidene-D-glucose. The new isomer does not reduce Fehling solution and has been shown, by oxidation with sodium metaperiodate and by the preparation from it of known derivatives of D-glucose, to be 1,2-benzylidene-D-glucofuranose. The substance has been characterized by the preparation of the following crystalline derivatives: 1,2-benzylidene-5,6-isopropylidene-D-glucose, 1,2-benzylidene-3-methyl-5,6-isopropylidene-D-glucose, 1,2-benzylidene-3-benzyl-5,6-isopropylidene-D-glucose, 1,2-hexahydrobenzylidene-D-glucofuranose and 1,2-benzylidene-3,5,6-tribenzoyl-D-glucose.

The first crystalline benzylidene-D-glucose was reported twenty years ago by Zervas.[2] By the condensation of D-glucose with benzaldehyde in the presence of zinc chloride he obtained, in moderate yield, a crude crystalline product from which, by repeated recrystallization, pure 4,6-benzylidene-D-glucopyranose (I) was isolated. In repeating the Zervas preparation, we have isolated a second crystalline, isomeric monobenzylidene-D-glucose from the same reaction mixture.[3] The structure of the new isomer has now been established as 1,2-benzylidene-D-glucofuranose, II.



D-Glucose I II III IV

Oxidation of II with aqueous sodium metaperiodate showed the consumption of one mole of oxidant with the production of formaldehyde. This indicated the presence of only one glycol grouping and limited its position to carbons five and six, thus limiting the position of hemiacetal ring closure to carbon four. No mutarotation was shown by II and it did not reduce Fehling solution, thus indicating that the benzylidene substituent involves carbon one. Combination of the above data limited the structure of the substance to 1,2- or 1,3-benzylidene-D-glucose. Acetonation of II under mild conditions, with acetone and cupric sulfate, produced 1,2-benzylidene-5,6-isopropylidene-D-glucose (III). The latter could be selectively hydrolyzed to II, showing that no migration of the benzylidene group had occurred during the acetonation. Methylation of III with dimethyl sulfate and sodium hydroxide gave a crystalline monomethyl derivative and hydrolysis of the benzylidene and isopropylidene groups from the latter then gave the known 3-methyl-D-glucose. In a parallel control experiment, 3-methyl-D-glucose also was prepared in similar fashion from the known 1,2:5,6-diisopropylidene-D-glucose. Table I compares the observed physical properties of the two preparations with the recorded values for 3-methyl-D-glucose as well as those for known 2-methyl-D-glucose.

Due to the similarity in properties of 2- and 3-methyl-D-glucose, further proof for the position of the unsubstituted hydroxyl group in III was desirable. Benzylation of III, by treatment with sodium naphthalene[4] followed by benzyl bromide,[5] gave a crystalline benzyl ether which, on hydrolysis of the acetal and ketal functions, yielded 3-benzyl-D-glucose. The physical properties of the latter, prepared both from III and from known 1,2:5,6-diisopropylidene-D-glucose, were in good agreement with the recorded values, as shown in Table I.

A complete structure proof for II would include determination of its configuration at the anomeric carbon atom. Although direct experimental evidence is lacking, steric considerations make it almost certain that the anomeric configuration is α-: Since two fused five-membered heterocyclic rings are present in the structure, it is geometrically improbable that they exist in other than a *cis* configuration.

Brigl and Grüner[6] employed a low-melting (172°) sample of "4,6-benzylidene-D-glucose," obtained by the method of Zervas,[2] to prepare 4,6-benzylidene-1,2,3-tribenzoyl-D-glucose. Their yield of the

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[1] Abstracted from the thesis of Dorothy J. Kuenne submitted in partial fulfillment of the requirements for the degree of Master of Arts at Washington University, June, 1950.

[2] L. Zervas, *Ber.*, **64**, 2289 (1931).

[3] J. C. Sowden, THIS JOURNAL, **72**, 808 (1950), footnote 12.

[4] N. D. Scott, J. F. Walker and V. L. Hansley, *ibid.*, **58**, 2442 (1936); J. F. Walker and N. D. Scott, *ibid.*, **60**, 951 (1938).

[5] J. C. Sowden and H. O. L. Fischer, *ibid.*, **63**, 3244 (1941).

[6] P. Brigl and H. Grüner, *Ber.*, **65**, 1428 (1932).

TABLE I

Compound	M.p., °C.	$[\alpha]_D^{25}$ in CH_3OH	 in C_2H_5OH	 in H_2O
4,6 Benzylidene D-glucose				
This work	187–188	10.9→−3.81° (2 hr.)	4.26→0.61° (150 min.)	
Zervas[2]	188	−3.85 (5 hr.)		
Brigl and Grüner[6]	172		39.6→4.3	
1,2-Benzylidene-D-glucofuranose	176–177	10.5		
3-Methyl-D-glucose				
From III	154–159			95.7→54.8
From diacetoneglucose	159–162			94.4→54.8
Irvine and Scott[7]	157–158			96.7→55.5
2-Methyl-D-glucose				
Oldham and Rutherford[8]	157–158			36.4→66.0
3-Benzyl-D-glucose				
From III	135–137			16.9→41.7
From diacetoneglucose	136–138			16.1→41.8
Adams, Reeves and Goebel[9]	138–141			20.3→41.9

latter was not recorded and the present work indicated the possibility of a different structure for their tribenzoate. Accordingly, the benzoylation of I as well as II was investigated. Benzoylation of 4,6-benzylidene-D-glucose with benzoyl chloride and pyridine[6] gives a mixture of the α- and β-tribenzoates. Either anomer may be crystallized in low yield from the mixture and our experiments indicate that Brigl and Grüner had obtained, indeed, the 4,6-benzylidene-1,2,3-tribenzoyl-β-D-glucose. Benzoylation of II leads to crystalline 1,2-benzylidene-3,5,6-tribenzoyl-D-glucose in high yield.

Experimental

4,6-Benzylidene-D-glucose (I) and 1,2-Benzylidene-D-glucofuranose (II).—A suspension of 130 g. of anhydrous D-glucose and 100 g. of powdered zinc chloride in 300 ml. of benzaldehyde was shaken for 20 hours at room temperature.[3] The resulting viscous mass was poured, with vigorous stirring, onto 400 ml. of ice and water. Filtration and washing with ether and ice-water yielded 17 g. of crude crystalline material showing vigorous reducing action toward Fehling solution. Several recrystallizations from water gave 4,6-benzylidene-D-glucose with the constants recorded in Table I.

The initial filtrate above was cooled to −20° and shaken vigorously, whereupon a second crystallization occurred. Filtration and washing with ether and ice-water yielded 10.9 g. of crystalline material showing negligible reduction of Fehling solution. Recrystallization from water and then from ethanol gave pure 1,2-benzylidene-D-glucofuranose showing the constants recorded in Table I. *Anal.* Calcd. for $C_{13}H_{16}O_6$: C, 58.2; H, 6.07. Found: C, 58.2; H, 6.18.

Oxidation of 1,2-benzylidene-D-glucofuranose with aqueous sodium metaperiodate showed the consumption of one mole equivalent of oxidant after one-half hour, and no further consumption after 23 hours. Distillation of an aliquot of the oxidation mixture at reduced pressure followed by treatment of the distillate with dimethyldihydroresorcinol produced 0.49 mole equivalent of formaldehyde dimedon, m.p. 184–186°.

1,2-Benzylidene-5,6-isopropylidene-D-glucose (III).—Ten grams of 1,2-benzylidene-D-glucofuranose and 25 g. of anhydrous cupric sulfate were shaken with 275 ml. of anhydrous acetone for 48 hours at room temperature. After filtration and washing, evaporation of the filtrate left a crystalline residue. Recrystallization from petroleum ether (b.p. 95–127°) gave 9.6 g. (83%) of product melting at 119–121°. Further recrystallization gave pure 1,2-benzylidene-5,6-isopropylidene-D-glucose, m.p. 120–121°; $[\alpha]^{25}D$ 3.5° in chloroform, *c* 2.8. *Anal.* Calcd. for $C_{16}H_{20}O_6$: C, 62.3; H, 6.54. Found: C, 62.5; H, 6.46.

Selective hydrolysis of 1,2-benzylidene-5,6-isopropylidene-D-glucose with nitric acid in ethyl acetate solution, according to the directions of Coles, Goodhue and Hixon[10] for the partial hydrolysis of diacetoneglucose, gave 60% of 1,2-benzylidene-D-glucofuranose, m.p., after recrystallization, 177–178°; $[\alpha]^{25}D$ 10.6° in methanol, *c* 1.

1,2-Benzylidene-3-methyl-5,6-isopropylidene-D-glucose.—Five grams of the above benzylideneacetoneglucose was methylated in acetone solution with dimethyl sulfate and sodium hydroxide according to the general directions of Haworth.[11] The crude product (5.2 g.) was recrystallized from acetone by the addition of water to give, in 96% yield, 1,2-benzylidene-3-methyl-5,6-isopropylidene-D-glucose, m.p. 101–102°; $[\alpha]^{25}D$ −22.9° in chloroform, *c* 1.35. *Anal.* Calcd. for $C_{17}H_{22}O_6$: C, 63.3; H, 6.88. Found: C, 63.3; H, 6.72.

3-Methyl-D-glucose.—One gram of the above methylated product (m.p. 101–102°) was refluxed with a solution containing 35 ml. of 0.1 *N* sulfuric acid and 15 ml. of ethanol for two hours. Following removal of the benzaldehyde by concentration at reduced pressure and of the sulfuric acid by ion-exchange, the solution was concentrated to dryness at reduced pressure to yield 0.55 g. (91%) of 3-methyl-D-glucose, m.p. 154–159°.

3-Methyl-D-glucose also was prepared from known diacetoneglucose by methylation and subsequent hydrolysis as described above for 1,2-benzylidene-5,6-isopropylidene-D-glucose. The observed physical constants for the two preparations are compared with the recorded values in Table I.

1,2-Benzylidene-3-benzyl-5,6-isopropylidene-D-glucose.—1,2-Benzylidene-5,6-isopropylidene-D-glucose was benzylated by treatment with sodium naphthalene followed by benzyl bromide according to the directions of Sowden and Fischer[5] for the benzylation of 1,2-isopropylideneglycerol. The crude benzyl ether was crystallized from 50% ethanol to give 50% of product melting at 89–91°. Recrystallization from 95% ethanol then gave the pure substance, m.p. 92–93°; $[\alpha]^{25}D$ −10.2° in chloroform, *c* 4. *Anal.* Calcd. for $C_{23}H_{26}O_6$: C, 69.3; H, 6.58. Found: C, 69.3; H, 6.31.

3-Benzyl-D-glucose (IV).—Hydrolysis of 1,2-benzylidene-3-benzyl-5,6-isopropylidene-D-glucose as described above for the corrresponding methyl ether, followed by crystallization from 95% ethanol, gave 54% of 3-benzyl-D-glucose, m.p. 135–137°.

3-Benzyl-D-glucose also was prepared from known diacetoneglucose by benzylation and hydrolysis as described above. The observed physical constants for the two preparations are compared with the recorded values in Table I.

1,2-Hexahydrobenzylidene-D-glucofuranose.—A sample of 0.5 g. of II in 25 ml. of glacial acetic acid was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 0.1 g. of platinum oxide (Adams catalyst). Hydrogenation was complete in one hour with the absorp-

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(7) J. I. Irvine and J. P. Scott, *J. Chem. Soc.*, 564 (1913).

(8) J. W. H. Oldham and J. K. Rutherford, THIS JOURNAL, **54**, 1086 (1932).

(9) M. H. Adams, R. E. Reeves and W. F. Goebel, *J. Biol. Chem.*, **140**, 653 (1941).

(10) H. W. Coles, L. D. Goodhue and R. M. Hixon, THIS JOURNAL, **51**, 519 (1929).

(11) W. N. Haworth, *J. Chem. Soc.*, **107**, 8 (1915).

tion of 3 mole equivalents of hydrogen. Filtration and evaporation of the solution then gave 88% of 1,2-hexahydrobenzylidene-D-glucofuranose, m.p., after recrystallization from water, 179–180°; $[\alpha]^{25}\text{D}$ 10.2 in pyridine, *c* 2. *Anal.* Calcd. for $C_{13}H_{22}O_6$: C, 56.9; H, 8.09. Found: C, 57.1; H, 8.07.

Hydrogenolysis of 1,2-Benzylidene-D-glucofuranose.—A sample of 0.2 g. of II in 25 ml. of absolute ethanol was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 0.2 g. of "S-palladium black."[12] Hydrogenolysis was complete in 1.5 hours with the absorption of 2.5 mole equivalents of hydrogen. After filtration, the solution showed $[\alpha]^{25}\text{D}$ 64°, calculated for D-glucose. For the equilibrium rotation of D-glucose in absolute ethanol, Rowley[13] reports $[\alpha]^{25}\text{D}$ 66.5°.

α- and β-Tribenzoates of 4,6-Benzylidene-D-glucose.—The benzoylation of I with benzoyl chloride and pyridine was carried out according to the directions of Brigl and Grüner,[6] to give 95% of crude, crystalline product. Fractional recrystallization from ethanol gave 1,2,3-tribenzoyl-4,6-benzylidene-β-D-glucose,[6] m.p. 193°; $[\alpha]^{30}\text{D}$ −10.6° in chloroform, *c* 1.3 and 1,2,3-tribenzoyl-4,6-benzylidene-α-D-glucose, m.p. 166–167°; $[\alpha]^{25}\text{D}$ 47.4° in chloroform, *c* 1.3. *Anal.* (α-anomer). Calcd. for $C_{34}H_{28}O_9$: C, 70.3; H, 4.86. Found: C, 70.5; H, 4.81.

The separation of the anomers by fractional crystallization was accompanied by considerable loss of material and it was not possible to estimate the relative proportions of the two products in the mixture.

1,2-Benzylidene-3,5,6-tribenzoyl-D-glucose.—The benzoylation of II with benzoyl chloride and pyridine at room temperature yielded 98% of the crystalline tribenzoate. Recrystallization from ethanol and then from acetone by the addition of water gave pure 1,2-benzylidene-3,5,6-tribenzoyl-D-glucose, m.p. 107–108°; $[\alpha]^{25}\text{D}$ −62.7° in chloroform, *c* 1.4. *Anal.* Calcd. for $C_{34}H_{28}O_9$: C, 70.3; H, 4.86. Found: C, 70.2; H, 4.58.

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[12] V. K. Kindler, E. Schärfe and P. Henrich, *Ann.*, **565**, 51 (1949).

[13] H. H. Rowley, THIS JOURNAL, **62**, 2563 (1940).

[CONTRIBUTION FROM THE ENZYME RESEARCH DIVISION, BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

Bitter Principles in Citrus. III. Some Reactions of Limonin[1]

BY OLIVER H. EMERSON

The hydrogenation of limonin ($C_{26}H_{30}O_8$) gives a mixture of tetrahydrolimonin ($C_{26}H_{34}O_8$) and hexahydrolimoninic acid ($C_{26}H_{36}O_8$). Limonin appears to be bicarbocyclic and has two ethylenic links, one of which forms an allylic system with the potential hydroxyl of a lactone group. The oxidation of limonin with alkaline hypoiodite gives limonilic acid ($C_{26}H_{30}O_8$). Tetrahydrolimonin and hexahydrolimoninic acid behave similarly. The reaction apparently involves the opening of a lactone ring and the formation of a new carbocyclic ring. One lactone ring is opened by hydrogenolysis and the other by oxidation. Treatment of limonin with hydriodic acid gives citrolin ($C_{26}H_{22}O_6$) which appears to be tricarbocyclic, and has four ethylenic links, one of which is conjugate with the carbonyl group, and one with a lactone group.

Previous investigations have shown that limonin, the bitter principle which occurs in Navel oranges and other Rutaceous plants[2] is a keto-dilactone of the composition $C_{26}H_{30}O_8$.[3–5] The two lactone groups are easily opened by alkali, and recyclized by acid, indicating they are γ-lactones. The three remaining oxygen atoms cannot be detected chemically and are presumed to be cyclic oxides. By fusion with potassium hydroxide, limonin yields acetone, and from the non-volatile residue, by selenium dehydrogenation, Koller and Czerny[3] reported the isolation of 1,2,5-trimethylnaphthalene, while by oxidizing limonin with manganese dioxide and sulfuric acid, they obtained benzenepentacarboxylic acid. By hydrogenation over palladium, they observed limonin to take up about three moles of hydrogen yielding a relatively small amount of a neutral tetrahydrolimonin and a larger amount of a substance which they called hexahydrolimoninic acid, whose analysis agreed with the composition $C_{26}H_{38}O_9$. However, the analysis of the methyl ester indicated the acid to be a very stable hydrate, which they were unable to dehydrate without further decomposition. The hydrogenation of limonin has been reinvestigated by Rosenfeld and Hofmann[6] who obtained similar results.

By oxidizing limonin in 6 *N* alkali with potassium manganate, Geissman and Tulagin[4] obtained limonilic acid which they believed to be $C_{25}H_{22}O_7$, while by treatment with hydriodic acid they obtained citrolin, $C_{26}H_{28-30}O_6$, and desoxylimonin, $C_{26}H_{30}O_7$. Unfortunately the yield of the latter substance was too small to permit further investigation. They noted that citrolin was very easily altered by alkali and gave acetone far more readily than limolin or limolinic acid, but no crystalline derivatives of citrolin could be obtained.

The purpose of this communication is to extend and correlate some of these observations. By refluxing limonin for 15 to 20 minutes with a moderate excess of 0.1 *N* methanolic potassium hydroxide, both lactone groups are opened quantitatively. By removing the methanol and titrating to the half-neutralization point of each acid group, the dissociation constants can be estimated. The substance is a very strong organic acid, *pK′* 2.7, *pK″* 4.7. The rate of recyclization of the two lactone groups depends on concentration of the hydrogen ion, and at *p*H 3.0, the stronger acid group cyclizes several times as fast as the weaker group.

By hydrogenation over palladium-on-charcoal, either in ethanol containing some HCl, as done by Koller and Czerny, or in acetic acid, limonin is hydrogenated readily, although rather slowly, yielding tetrahydrolimonin and hexahydrolimoninic acid which are both mixtures of epimers. Tetra-

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(1) Enzyme Research Division Contribution No. 138. Article not copyrighted.

(2) M. S. Schechter and H. L. Haller, THIS JOURNAL, **62**, 1307 (1940).

(3) (a) G. Koller and H. Czerny, *Monatsh.*, **67**, 248 (1936) *C. A.*, **30**, 3831 (1936). (b) G. Koller and H. Czerny, *Monatsh.*, **70**, 26 (1937) *C. A.*, **31**, 4334 (1937).

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(5) O. H. Emerson, THIS JOURNAL, **70**, 545 (1948).

(6) R. S. Rosenfeld and K. Hofmann, *ibid.*, **73**, 2491 (1951).