Summary

Reductive desulfurization of phenyl 1-thio-β-cellobioside heptaacetate with Raney nickel has furnished 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol heptaacetate. The physical constants of this substance, as well as of the 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol obtained from it by deacetylation, conform quite closely with the constants which are recorded in the literature for the corresponding products obtained through the palladium catalyzed reduction of heptaacetyl-2-hydroxy-cellobial.

1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol and its heptaacetate have similarly been obtained through the reductive desulfurization of phenyl 1-thio-β-gentiobioside heptaacetate and found to possess physical constants in substantial agreement with those reported in the literature for the comparable substances arising through the palladium-catalyzed reduction of heptaacetyl-2-hydroxy-gentiobial.

1,5-Anhydro-D-galactitol and its tetraacetate have been prepared through the reductive desulfurization of 2′-naphthyl 1-thio-β-D-galactopyranoside tetraacetate. The physical constants of these two compounds depart markedly from those reported for the corresponding substances, derived through the palladium-catalyzed reduction of 2,3,4,6-tetraacetyl-2-hydroxy-D-galactal.

The behavior of 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol, 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol and 1,5-anhydro-D-galactitol toward sodium metaperiodate has been examined and found in each case to conform to the assigned structure.

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[Contribution from the Department of Chemistry of Stanford University]

The Deacetylation of Acetylated Carbohydrate Derivatives with Potassium Alkoxides

By William A. Bonner and Wayne L. Koehler

Fischer and Bergmann[1] were apparently the first to extend the catalytic deacylation of esters with sodium ethylate to the sugar acetates. In succeeding years Zemplén and his co-workers[2] gave a mechanistic interpretation to this reaction and extended it widely in the field of carbohydrates. Today the Zemplén–Pacsu deacylation, using a catalytic amount of sodium in methanol, is one of the standard tools employed by workers in this field.

One disadvantage inherent in deacylations with sodium methylate is the retention in solution of sodium ions. This is not serious where the deacylated product crystallizes directly from the methanol solvent and the sodium ion remains in the mother liquor. However it constitutes a source of non-removable impurity in cases where the deacylated product does not crystallize and must be isolated by distillation of the solvent and volatile constituents of the reaction mixture.

A procedure capable of obviating this difficulty is found in the use of barium methylate, a modification introduced by Weltzien and Singer[3] and subsequently extended by others.[4] In this technique the barium ion is quantitatively precipitated by addition of an equivalent amount of sulfuric acid. While excellent in principle, this method suffers from the colloidal nature of the precipitated barium sulfate and consequent added difficulties in its removal, as well as from the extra trouble involved in the preparation and standardizations of the solutions employed.

It became desirable to develop a simple and rapid procedure which would permit the isolation of sirupy deacetylation products in a substantially ash-free state. The procedure developed employs a potassium methylate or ethylate in place of the sodium or barium methylates used previously, followed by a quantitative precipitation of potassium ion as perchlorate on potentiometric titration with concentrated perchloric acid.

This procedure was tested by application to several known acetylated sugar derivatives. After deacetylation was complete and potassium was removed as perchlorate, the free sugar derivative was isolated from the filtrate by evaporation *in vacuo* of the volatile constituents. Physical constants and ash analyses were determined on the crude residues to determine their purity. The data obtained, tabulated in the Experimental Part, indicate that the method can be applied to instances where sirupy deacetylation products result with assurance that reasonably pure sirups will be obtained in substantially quantitative yield.

Although methanol has been the solvent commonly employed by previous workers, we have studied the efficacy of higher alcohols as solvents in deacetylations employing both sodium and potassium alkoxides as catalysts. Primary alcohols, whether straight-chained or branched, gave yields of deacetylated products very close to theoretical, but secondary and tertiary alcohols gave yields up to 55% high. This is apparently due to a decrease in the rate of deacetylation in these cases and, on grounds of steric hindrance, is in

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(1) Fischer and Bergmann, *Ber.*, **52**, 852 (1919).

(2) Zemplén and Kunz, *ibid.*, **56**, 1705 (1923); Zemplén, *ibid.*, **59**, 1258 (1926); **60**, 1555 (1927); Zemplén and Pacsu, *ibid.*, **62**, 1613 (1929).

(3) Weltzien and Singer, *Ann.*, **443**, 104 (1925).

(4) Brauns, This Journal, **48**, 2784 (1926); Mitchell, *ibid.*, **63**, 3534 (1941); Isbell, *Natl. Bur. Standards J. Res.*, **5**, 1185 (1930).

TABLE I

DEACETYLATION OF ACETYLATED SUGAR DERIVATIVES WITH POTASSIUM ALKOXIDES

			Deacetylated derivative				
			M. p., °C.		[α]D		
Acetate	Solvent	Yield, %	Obs.	Lit.	Obs.[a]	Lit.[b]	Ash, %
Phenyl tetraacetyl-β-D-glucoside	Methanol	101.3	172–172.5	171–172[5]	−63.3	−71.0[6] −65.5[5]	0.15
	Ethanol	98.6	171–172		−74.6		0.21
Methyl tetraacetyl-α-D-glucoside	Methanol	103.1	163–165	166[7]	151.5	158.9[7]	0.14[d]
	Ethanol	101.0[c]	163–165.5[c]		151.0[c]		0.23[c,d]
Phenyl tetraacetyl-β-D-thioglucoside	Methanol	99.3	129.5–130	133[8]	−68.3	−70.3[8]	0.13
	Ethanol	101.9	126–131		−67.1		2.75

[a] All rotations were taken in water at 23° at concentrations around 3%. [b] Rotations here were reported in water at 20°, with the exception of ref. 5 which was at 18°. [c] Deacetylation in ethanol gave rise to direct crystallization of about 75% of the methyl α-D-glucoside, The crystalline material, dried in the usual fashion, had m. p. 165.5–167° and $[\alpha]^{23}\text{D}$ 158.2° (*c*, 3.790; H_2O). The constants given in the table apply to the 25% of product remaining in the mother liquors. The yield is based on the total weight of both fractions. [d] It is interesting to calculate that, had the potassium not been removed in this case by precipitation, the quantities of inorganic impurity present would be about 6 to 7%, weighed as potassium alkoxide.

accord with the mechanism of deacetylation proposed by Zemplén.

It was believed possible to simplify the barium methylate deacetylation used previously[4] by a potentiometric titration of the barium ion with sulfuric acid. The method failed, however, since the *p*H required for complete precipitation of the barium was too low, and hydrolysis of the sugar derivatives occurred during subsequent processing. When *p*H values high enough to prevent hydrolysis were employed as an end-point in the titration, precipitation of barium was incomplete and the crude products contained excessive quantities of ash.

In applying the potassium methylate procedure to a typical deacetylation giving a sirupy product, we have deacetylated tetraacetyl-β-D-glucosylbenzene. β-D-Glucosylbenzene proved to be a clear, thick, non-reducing glass, isolable as an alcoholate. This substance, its tetrapropionate, and its tetrabenzoate are herein reported for the first time.

Experimental Part

Deacetylations with Potassium.—A sample of the acetylated sugar derivative (*ca.* 2 g.) was placed in a 50-ml. Erlenmeyer flask and methanol or ethanol added (10 ml. per gram of solute). A small chip of freshly cut potassium (20–35 mg.) was added, and the flask placed on the steam-bath for five minutes, removed, stoppered and permitted to stand at room temperature for about twenty-four hours. After this period the potassium was precipitated by titration with commercial 60% perchloric acid to a potentiometrically determined end-point using a Beckman *p*H meter. The *p*H value used for the end-point in methanol was 8.15 and in ethanol 7.55. These *p*H values were found in separate experiments when potassium perchlorate was permitted to stand with intermittent shaking for several hours in contact with these alcohols. Care must be taken in approaching the end-point, since it is easily passed when titrating with concentrated perchloric acid. Occasionally it was found expedient to titrate to one *p*H unit above the end-point with concentrated acid, and to approach the final end-point using perchloric acid diluted with solvent. It was found that the use of dilute perchloric acid during the entire titration led to a colloidal precipitate of potassium perchlorate which proved difficult to filter.

The precipitated potassium perchlorate was filtered and rinsed with a small amount of solvent, and the filtrate and washings placed in a small beaker. The beaker was placed under a micro bell jar and the latter evacuated with an aspirator. A fine stream of air, controlled by a pinch clamp, was directed onto the surface of the liquid through a capillary entering the top of the bell jar through a rubber stopper. The bell jar plate was warmed to 55° by controlled heating on a hot-plate. In this fashion the solvent and volatile products (methyl or ethyl acetates) were removed by vacuum evaporation under low heating.

The residual deacetylated sugar derivative was dried in a vacuum desiccator over phosphorus pentoxide for seventy-two hours, then in an oven at 60° for an additional twenty-eight hours. Melting points, rotations and ash analyses were taken on the resulting crude, dried, unrecrystallized products. Ash analyses were conducted by cautiously igniting 0.1 to 0.2 g. of the deacylated derivative in a platinum crucible.

Data on the known derivatives deacetylated in this manner are tabulated in Table I. The particular acetates employed were selected because preliminary experiments showed that their products would not precipitate directly from the solvent on deacetylation. This was desirable here, since the procedure was to be applied to acetates giving sirupy deacetylation products.

Deacetylations in Various Solvent Media.—Two sets of experiments were conducted, the first studying the completeness of deacetylations using sodium and potassium in three alcohols, and the second studying the completeness of deacetylation using potassium in ten alcohols.

In the first set approximately 2 g. of phenyl tetraacetyl-β-D-glucoside (weighed to mg.) was dissolved in 20 ml. of the solvent and a known weight (20–30 mg.) of freshly-cut sodium or potassium added. The solution was heated to 80–90° on the water-bath for five minutes, then allowed to stand for one day. The solvent was removed by vacuum evaporation, and the residue dried *in vacuo* over phosphorus pentoxide for seventy-two hours. The dried residue was weighed and the yield determined. The results are given in Table II; the yields are based on weights corrected for the amounts of metal alkoxides present in the residue.

TABLE II

DEACETYLATIONS WITH SODIUM AND POTASSIUM IN METHANOL, ETHANOL AND 2-PROPANOL

	Phenyl β-D-glucoside, % yield	
Solvent	Sodium	Potassium
Methanol	98.8	99.4
Ethanol	102.1	100.7
2-Propanol	103.1	111.6

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(5) Helferich, Bäuerlein and Wiegand, *Ann.*, **447**, 27 (1926).

(6) Fischer and Armstrong, *Ber.*, **34**, 2885 (1901).

(7) Riiber, *ibid.*, **57**, 1797 (1924).

(8) Purves, THIS JOURNAL, **51**, 3626 (1929).

In the second set of experiments a known weight of phenyl tetraacetyl-β-D-glucoside (weighed to mg.) was dissolved in the alcohol (10 ml. per gram of acetate). The solution was treated with a known weight of potassium, then permitted to react and processed exactly as above. The dried residue was weighed (mg.) and the yield determined, correcting for the quantity of potassium alkoxide remaining in the residue. The data for these experiments appear in Table III. It is seen that the yield of phenyl β-D-glucoside is close to the theoretical in the case of primary alcohols but far above the theoretical in the cases of secondary and tertiary alcohols, indicating incomplete deacetylation in these latter cases.

TABLE III

DEACYLATIONS WITH POTASSIUM IN VARIOUS ALCOHOLS

Alcohol	Type	Phenyl β-D-glucoside, % yield
Methyl	Primary	99.4
Ethyl		100.7
n-Propyl		98.0
n-Butyl		101.5
Isobutyl		100.2[a]
n-Amyl		105.4[a]
Isoamyl		98.2[a]
Isopropyl	Secondary	111.6
s-Butyl		153.3[a]
t-Amyl	Tertiary	154.9[a]

[a] In these experiments the product crystallized directly from the reaction mixture, confirming the expected decrease in solubility of the free glucoside in higher alcohols.

Attempted Deacetylations with Barium.—This describes the attempted extension of the potentiometric titration method to barium deacetylations. Samples of phenyl tetraacetyl-β-D-glucoside, methyl tetraacetyl-α-D-glucoside and phenyl tetraacetyl-β-D-thioglucoside were dissolved in methanol and ethanol. A small chip of barium metal (*ca.* 20 mg.) was added to each of the six solutions. These were then heated for five minutes and allowed to stand for twenty-four hours. They were next titrated with alcoholic sulfuric acid (*ca.* 1 *N*) with the aid of a *p*H meter. The *p*H found for pure barium sulfate in methanol was 2.00 and for ethanol 2.63. (The same barium sulfate gave a *p*H of 6.3 when shaken with water.) These values were used as end-points in the present titrations. On filtration of the barium sulfate and vacuum evaporation of the filtrate, each of the samples underwent marked decomposition.

When the end-point of one such titration was taken as *p*H 7.4 methyl α-D-glucoside was recovered in a yield of 106.3% from methanol. This crude product, however, proved to contain 7.8% ash.

β-D-Glucosylbenzene.—Crystalline tetraacetyl-β-D-glucosylbenzene[9] (5.925 g.) was dissolved in methanol (30 ml.) and a small chip of freshly-cut potassium added. The mixture was warmed on the steam-bath for five minutes and the resulting amber solution permitted to stand at 25° for twenty-four hours. It was then decolorized by filtration through a small bed of Norit over Supercel. The filtrate was potentiometrically titrated to the usual *p*H with 60% perchloric acid, and the solid filtered and rinsed with methanol. The product was isolated as before by vacuum evaporation, and was dried for several weeks *in vacuo* over phosphorus pentoxide. The product was a clear, non-reducing glass weighing 3.548 g. (89.9%). It proved to be an alcoholate, retaining one mole of methanol. Rotation: $[\alpha]^{23}\text{D}$ 18.25° (*c*, 2.740, H_2O). *Anal.* Calcd. for $C_{13}H_{20}O_6$: C, 57.35; H, 7.41. Found: C, 57.40, 57.15; H, 7.06, 7.64. When 0.228 g. of the product was ignited in a platinum crucible, there remained 0.2 mg. of residue; ash, 0.09%.

Tetrapropionyl-β-D-glucosylbenzene.—β-D-Glucosylbenzene methanolate (1.00 g.) was dissolved in pyridine (15 ml.) and propionic anhydride (15 ml.) added. The mixture stood for three days at room temperature with no color change. It was then poured into water (100 ml.) and allowed to stand for nine hours with intermittent shaking. A sirupy lower layer resulted. This was extracted into ether, and the extract washed with water, 4 *N* hydrochloric acid, water (twice), saturated sodium bicarbonate solution and finally water. The clear extract was dried over anhydrous sodium sulfate, filtered and the solvent distilled, last traces *in vacuo.* There resulted 1.76 g. (102%) of a clear, amber sirup which crystallized slowly on standing. This was recrystallized three times by dissolving in 2-propanol, adding water until faintly turbid and placing at 0°. The product, fine white needles, had m. p. 69.5° and $[\alpha]\text{D}^{25}$ −14.12° (*c*, 3.183; $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{32}O_9$: C, 62.08; H, 6.94. Found: C, 62.68; H, 7.11.

Tetrabenzyl-β-D-glucosylbenzene.—β-D-Glucosylbenzene methanolate (0.80 g.) was dissolved in pyridine (20 ml.) and benzoyl chloride (10 ml.) added. Considerable warming and darkening occurred, and a thin paste resulted. This stood for three days and was thrown into water. On standing for nine hours with occasional shaking an oily second phase resulted. The aqueous layer was decanted and the oil treated with ether. The oily product crystallized to give 1.91 g. (98.5%) of white solid, m. p. 181–182.5°. The residual ether was used to extract the aqueous layer, and the extract processed as above. Removal of the solvent after decolorization of the extract gave 3.54 g. of a thin, amber liquid. This had a negligible rotation and was not investigated. The white solid proved very insoluble in 2-propanol, and was purified by extracting with 2-propanol in a Soxhlet extractor for several hours. The undissolved residue had m. p. 184.5–185.5°. A small amount of material crystallized from the pot solvent, m. p. 183.5–185.5°. The purer sample had $[\alpha]^{25}\text{D}$ −22.93° (*c*, 0.960; $CHCl_3$). *Anal.* Calcd. for $C_{40}H_{32}O_9$: C, 73.20; H, 4.91. Found: C, 73.10, 73.30; H, 4.97, 5.10.

Summary

1. Potassium methylate and ethylate have been found useful for the catalytic deacetylation of acetylated sugar derivatives. After reaction the potassium is removed as perchlorate, permitting isolation of substantially ash-free products, even if the latter are sirups.

2. Such deacetylations have been studied using a wide variety of alcohols as solvent. Primary alcohols generally gave good results, but incomplete deacetylation was noted when secondary or tertiary alcohols were used under comparable conditions.

3. β-D-Glucosylbenzene methanolate, tetrapropionyl-β-D-glucosylbenzene, and tetrabenzoyl-β-D-glucosylbenzene are described.

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[9] Hurd and Bonner, THIS JOURNAL, 67, 1972 (1945).