DEHYDROHALOGENATION OF GLYCOSYL HALIDES WITH 1,5-DIAZABICYCLO[5.4.0]UNDEC-5-ENE*

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(Received November 8th, 1971; accepted January 5th, 1972)

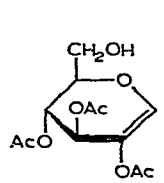
ABSTRACT

The 2-hydroxyglycals derived from D-glucose, D-galactose, cellobiose, and lactose, as well as 2,3,4-tri-*O*-benzoyl-2-hydroxy-D-xylal and 2,3,5-tri-*O*-benzoyl-2-hydroxy-D-ribal were prepared by the use of 1,5-diazabicyclo[5.4.0]undec-5-ene (**2**) in *N*,*N*-dimethylformamide. The reagent, 1,5-diazabicyclo[4.3.0]non-5-ene, was found to be a suitable substitute for **2**.

INTRODUCTION

2-Hydroxyglycals are obtained in a stable form only when the hydroxyl groups are blocked, generally as the acetate or benzoate esters[1], *e.g.* 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal (2,3,4,6-tetra-*O*-acetyl-1-deoxy-D-*xylo*-hex-1-enopyranose, **1**). The methods of synthesis of 2-hydroxyglycals, such as **1**, have been based upon the reaction of diethylamine with polyacylglycosyl halides in benzene or chloroform for 1–10 days[1]. This procedure was originally intended for the synthesis of glycosylamines, but diethylamine, in contrast to some other secondary and tertiary amines, tends to favor elimination rather than substitution[2,3]. The yields of 2-hydroxylgycals obtained with this procedure are generally low (see Table I). During a study of the mechanism of dehydrobromination of tetra-*O*-acetyl-α-D-glucopyranosyl bromide, Lemieux and Lineback[4] reported the synthesis of **1** in yields as high as 90% when the reaction was performed in acetonitrile with tetrabutylammonium bromide. However, application of these improved reaction conditions to the preparation of other 2-hydroxyglycals was not successful[5]. Instead, Ferrier and Sankey[6] treated the glycosyl bromide for a short time with sodium iodide in acetone, and then directly with diethylamine (Table I). Oedinger and Moller[7] introduced 1,5-diazabicyclo[5.4.0]undec-5-ene (**2**) for dehydrohalogenation reactions and reported that it was superior to the related 1,5-diazabicyclo[4.3.0]non-5-ene (**3**) for this purpose. When solutions of bromoalkanes in dimethyl sulfoxide were treated with **2** at 80–90°, the yields of alkenes obtained were 80–90%. Hanessian and coworkers[8] have applied both **2** and **3** to elimination reactions in carbohydrate derivatives, *e.g.* the elimination of the methylsulfonyl group at C-2 and C-3 of some glycosides, under conditions very similar to those

*A preliminary communication has been published[1].



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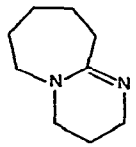

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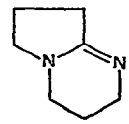

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originally used by Oedinger and Moller[7]. The synthesis of 2-hydroxyglycals by dehydrohalogenation with **2** is the subject of this report.

RESULTS AND DISCUSSION

The results of our application of **2** to the preparation of 2-hydroxyglycals are summarized in Table I. *N,N*-Dimethylformamide was used as a solvent in place of dimethyl sulfoxide because it is similar to the latter in many respects, but is easier to

TABLE I

COMPARISON OF YIELDS[a] OBTAINED IN THE PREPARATION OF 2-HYDROXYGLYCALS

Compound	*Reagent*		
	2	*Iodide*[b]	*Diethylamine*
1	85	60	51[c]
4	85	32	12.5[i]
5	78		58[e]
6	48 (49)[f]	54	23[g]; 11[h]
7	18		
8	76 (79)[f]	77	44[e]

[a]In per cent. [b]Ref. 6. [c]Ref. 2. [d]Ref. 3. [e]Ref. 9. [f]In parentheses, reagent 3. [g]Ref. 13. [h]Ref. 12.

remove during workup. The reaction of **2** with a glycosyl bromide without a solvent resulted in extensive decomposition within minutes. The choice of reaction conditions was such that four of the 2-hydroxyglycal derivatives prepared crystallized readily upon dilution of the reaction mixtures with water. The yields of 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-galactal (2,3,4,6-tetra-*O*-acetyl-1-deoxy-D-*lyxo*-hex-1-enopyranose, **4**) and 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-2-hydroxycellobial (**5**) were drastically improved over previous procedures[3,9]. Moreover, in all cases thus far studied, this reaction offered the advantage of simplicity over other methods and a reaction time (1–24 h) shorter than that generally required by the diethylamine–benzene procedure[2,3]. Furthermore, only a stoichiometric amount of **2** is required in comparison to the 2–10 fold excess of amines used with other procedures. When the temperature of the reaction mixtures was raised to that used earlier for dehydrohalogenation of bromo-

alkanes[7] (80–90°) in an attempt to shorten the reaction time, decomposition was observed, the 2-hydroxyglycals did not crystallize directly upon addition of water, and the more laborious workup required resulted in a substantial decrease of the yield. The reaction conditions employed did not give theoretical yields in every case, *e.g.* in the syntheses of 2,3,4-tri-*O*-benzoyl-2-hydroxy-D-xylal (2,3,4-tri-*O*-benzoyl-1-deoxy-D-*threo*-pent-1-enopyranose, **6**) and 2,3,5-tri-*O*-benzoyl-2-hydroxy-D-ribal (2,3,5-tri-*O*-benzoyl-1-deoxy-D-*erythro*-pent-1-enofuranose, **7**) which required column chromatography for their isolation. A small amount of a compound thought to be **7** had been originally isolated after reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride with the mercury salt of 4-benzyloxy-6(1*H*)-pyrimidone[10]. The synthesis of **7** from 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide by the use of **2** in *N*,*N*-dimethylformamide constituted a further proof of the identity of the previously isolated substance and demonstrated the preparation of the furanose form of 2-hydroxyglycals with **2**.

For comparison, two of the reactions were performed with **3** in place of **2**. The yields of **6** and 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-2-hydroxylactal (**8**) were approximately the same as those obtained with **2**, which suggests that **3** can be readily substituted for **2** in 2-hydroxyglycal synthesis. It is noteworthy that another strongly basic amine, 1,4-diazabicyclo[2.2.2]octane, was reported to give compound **1** in 90% yield[4], but its application to the preparation of other 2-hydroxyglycals was not investigated.

Reagent **2** did not dehydrobrominate tetra-*O*-acetyl-α-D-mannopyranosyl bromide and tri-*O*-acetyl-α-D-rhamnopyranosyl bromide, a fact that supported an E2 mechanism, which would require that the hydrogen at C-2 be oriented *trans* to the halogen at C-1. When some of the reactions were repeated in benzene, the solvent most often utilized in the diethylamine reaction, the yields dropped considerably; for example, the yield of **1** was reduced to about 70%. It was also important that the solvent and reaction mixture be kept dry. It had been shown[4] that sensitivity to water was dependent upon the nature of the amine used and that, in some cases, an 1,2-acetoxonium intermediate, which is an excellent water scavenger, is formed. When tri-*O*-benzoyl-D-xylopyranosyl bromide was treated with **2** in *N*,*N*-dimethylformamide which had not been dried prior to the reaction, a nearly quantitative yield of 2,3,4-tri-*O*-benzoyl-D-xylose (**9**) was obtained.

Glycosyl chlorides were not reactive enough with the reagent, and in most cases little or no product could be isolated. Tetra-*O*-acetyl-α-D-glucopyranosyl chloride gave only a 10% yield of **1**. Penta-*O*-acetyl-D-galactose decomposed extensively within minutes under the same reaction conditions and no 2-hydroxyglycal was detected.

The simple synthetic procedure reported herein should make available large quantities of 2-hydroxyglycal derivatives. A recent interesting application of these derivatives has been made in the synthesis of unsaturated nucleosides[11].

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler hot stage and correspond to corrected values. Optical rotations were determined with a Rudolph

polarimeter. Evaporations were performed *in vacuo* in a rotary evaporator at a bath temperature of 40°. Dry benzene was stored over sodium wire and dry *N,N*-dimethylformamide was stored over molecular sieves 3A. The reactions of glycosyl halides with **2** was followed by t.l.c., on 7.5-cm long microscope slides which were coated with Silica Gel G (E. Merck AG, Darmstadt) in 9:1 chloroform–methanol. The spots were located by charring with sulfuric acid.

2,3,4,6-Tetra-O-*acetyl-2-hydroxy*-D-*galactal* (**4**). — To an ice-cold solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (4.1 g, 10 mmoles) in dry *N,N*-dimethylformamide (3 ml) was added **2** (1.67 g, 11 moles), dropwise. The solution was stored at room temperature for 3 h and then diluted with ice–water (15 ml). The gum which separated was rubbed with a rod until it became crystalline, to give 2.8 g (85%) of pale-yellow crystals, m.p. 108–110°; after recrystallization from ethanol m.p. 112–113.5°; $[\alpha]_D^{24}$ +4.7° (*c* 1, ethanol); lit.[3]: m.p. 110–111°, $[\alpha]_D^{21}$ +4.7° (*c* 1.3, ethanol).

2,3,4,6-Tetra-O-*acetyl-2-hydroxy*-D-*glucal* (**1**). — *Method A.* The reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with **2** was carried out as described for **4** with 5 ml of *N,N*-dimethylformamide and a reaction time of 6 h. A white solid (2.8 g, 85%), which formed after treatment with water, was recrystallized from hot water; m.p. 64–65°; $[\alpha]_D^{24}$ −20° (*c* 1, ethanol); lit.[3]: m.p. 65–66°; $[\alpha]_D$ −20.4° (ethanol).

Method B. To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.7 g) in dry benzene (7 ml) was added **2** (0.3 g). Within several min., a white precipitate appeared. The mixture was kept overnight at room temperature, and the solid was filtered off and washed with benzene. The benzene solution was washed three times with 10-ml portions of water and dried with anhyd. magnesium sulfate. Evaporation gave a syrup which crystallized upon trituration with water. The crystals (0.38 g, 68%) were identical with those prepared by Method A.

2,3,6,2',3',4',6',-Hepta-O-*acetyl-2-hydroxycellobial* (**5**). — A solution of 2,3,6,2',3',4',6'-hepta-*O*-acetylcellobiosyl bromide (7 g, 10 mmoles) in *N,N*-dimethylformamide (20 ml) was chilled in an ice-bath and **2** (1.84 g, 12 mmoles) was added, dropwise. The reaction mixture was kept for 4 h at room temperature, and then diluted with ice–water (80 ml). A crystalline solid separated (m.p. 124–127°) which was recrystallized from aq. ethanol to give 4.8 g (78%) of **5**, m.p. 131–132°; $[\alpha]_D^{24}$ −23.2° (*c* 2.2, chloroform); lit.[9]: m.p. 125–126°; $[\alpha]_D^{20}$ −21.5° (chloroform). Because of the similarity of these data to those of 3,6,2',3',4',6'-hexa-*O*-acetylcellobial, a mixed m.p. with an authentic sample of the latter compound was determined and found to be depressed.

2,3,4-Tri-O-*benzoyl-2-hydroxy*-D-*xylal* (**6**). — *Method A.* To a solution of 2,3,4-tri-*O*-benzoyl-D-xylopyranosyl bromide (0.45 g) in *N,N*-dimethylformamide (1.2 ml) was added **2** (0.15 g), and the mixture was kept for 14 h in the refrigerator. Addition of water precipitated a brown solid which was filtered off. The solid was dissolved in benzene and chromatographed on a column of neutral alumina to afford 0.18 g (48%) of white crystals, m.p. 131–132°; $[\alpha]_D^{27}$ −270° (*c* 2.2, chloroform); lit.: m.p.

126–128°; $[\alpha]_D^{20}$ −280° (*c* 0.5, chloroform)[12]; m.p. 129–130°, $[\alpha]_D^{20}$ −285° (chloroform)[13].

Method B. To an ice-cold solution of 2,3,4-tri-*O*-benzoyl-D-xylopyranosyl bromide (2.9 g, 5.5 mmoles) in *N,N*-dimethylformamide (8 ml) was added **3** (0.75 g, 6 mmoles), dropwise. The mixture was kept for 23 h in the refrigerator, water was added, and an isolation procedure similar to that described under A gave a 49% yield of **6**.

*2,3,5-Tri-*O*-benzoyl-2-hydroxy-*D*-ribal* (**7**). — 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide[14] was prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (1 g) and was immediately dissolved in *N,N*-dimethylformamide (4 ml). The solution was chilled, and **2** (0.33 g) was added dropwise. The mixture was kept for 18 h in the refrigerator, and then diluted with ice–water (20 ml). A syrup separated, which was dissolved in chloroform, washed with water, and dried with anhyd. magnesium sulfate. The solvent was evaporated and the syrup was chromatographed on a column of neutral alumina with 8:1 benzene–ethyl acetate. The first band gave a syrup which crystallized to afford 160 mg (18%) of **7**; after recrystallization from ether: m.p. 124–124.5°: $[\alpha]_D^{27}$ +14.2° (*c* 1.5, chloroform); lit.[10]: m.p. 120–122°; $[\alpha]_D^{25}$ +14.4° (*c* 0.5, chloroform).

*2,3,6,2',3',4',6'-Hepta-*O*-acetyl-2-hydroxylactal* (**8**). — *Method A.* The reaction was performed on the peracetylated lactosyl bromide as described for the preparation of **5**, except that only 7 ml of *N,N*-dimethylformamide was used and a reaction time of 1 h was required. The reaction mixture was diluted with ice–water (28 ml), whereupon a syrup separated. The aqueous solution was decanted, and the syrup was triturated with a few ml of cold water, and then again with cold methanol. A white solid formed to give 4.7 g (76%) of **8**, m.p. 169–170°; after recrystallization from methanol: m.p. 172–173°; $[\alpha]_D^{24}$ −20.1° (*c* 1.7, chloroform); lit.[9]: m.p. 166–167°; $[\alpha]_D^{21}$ −17.1° (chloroform).

Method B. A solution containing the peracetylated lactosyl bromide (3.5 g, 5 mmoles) in *N,N*-dimethylformamide (3.5 ml) was chilled in an ice-bath, and **3** (0.73 g, 5.9 mmoles) was added dropwise. The reaction mixture was kept for 1 h at room temperature, and then diluted with ice–water (14 ml). The aqueous solution was decanted from a syrup, which was crystallized from methanol to afford 2.45 g (79%) of product.

*2,3,4-Tri-*O*-benzoyl-*D*-xylose* (**9**). — 2,3,4-Tri-*O*-benzoyl-α-D-xylopyranosyl bromide (2.9 g) was dissolved in *N,N*-dimethylformamide (15 ml) that had not been dried prior to being used. The solution was chilled in an ice-bath and **2** (0.83 g) was added, dropwise. The reaction mixture was kept for 5 h at room temperature, and then diluted with water (40 ml). A syrup settled out and the aqueous solution was decanted. The syrup was triturated with cold methanol until it crystallized to yield 2.54 g (99%), m.p. 180–182°; after recrystallization from ethanol: m.p. 183–184.5°, $[\alpha]_D^{27}$ +30° (*c* 1.76, chloroform); lit.[15]: m.p. 183–184°; $[\alpha]_D^{19}$ +25.5° (*c* 2, chloroform).

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