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Note

Preparation of lactams and lactones using pyridinium dichromate

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Several methods are known for the conversion of diols into lactones. Dehydrogenation of diols with catalysts such as copper chromite[1] and Raney nickel[2] gives lactones. Also, direct oxidation of diols with dichromate–acetic acid[3], manganese dioxide[4,5], the chromium trioxide–pyridine complex[6–8], and silver carbonate-on-Celite[9,10] provides lactones. Despite the availability of these methods, there still exists a need for new methods, especially for complex or sensitive compounds. For example, the chromium trioxide–pyridine complex, which has been the most widely used reagent for this purpose, could not successfully oxidize an androstanetriol[4]. In addition, the possibility of pyrophoric reactions exists during preparation of the reagent[11]. The relatively new reagent, silver carbonate-on-Celite, oxidizes preferentially secondary hydroxyl groups in some diols to give hydroxy ketones[10], and this oxidation requires a large excess of the oxidizing agent.

A project in this laboratory is concerned with syntheses of derivatives and analogs of L-ascorbic acid[12]. During the course of these studies, it was necessary to prepare 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranurono-6,3-lactam (**2**). Compound **2** is a nitrogen analog of 1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranurono-6,3-lactone (**4**) that can be converted into L-ascorbic acid by hydrolysis and subsequent reduction[13,14]. Compound **4** has been synthesized directly from 1,2-*O*-isopropylidene-α-D-glucofuranose (**3**) by catalytic oxidation under slightly acidic conditions[13] and from 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone[14,15] (**5**) by oxidation with manganese dioxide[14,16] or chromium trioxide[17]. In the last two studies, **5** was not derived from **3**. The formation of **5** from **3**, by chromic acid oxidation, has been observed; however, the yield was so low that the method is not useful[18]. The procedure employed in the first study, namely catalytic oxidation, is not always satisfactory and reproducible, because the reaction is too sensitive to the activity of the catalyst and to the pH of the reaction medium. Indeed, the catalytic oxidation of 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) was attempted in the present study under various pH conditions; however, only the inter-

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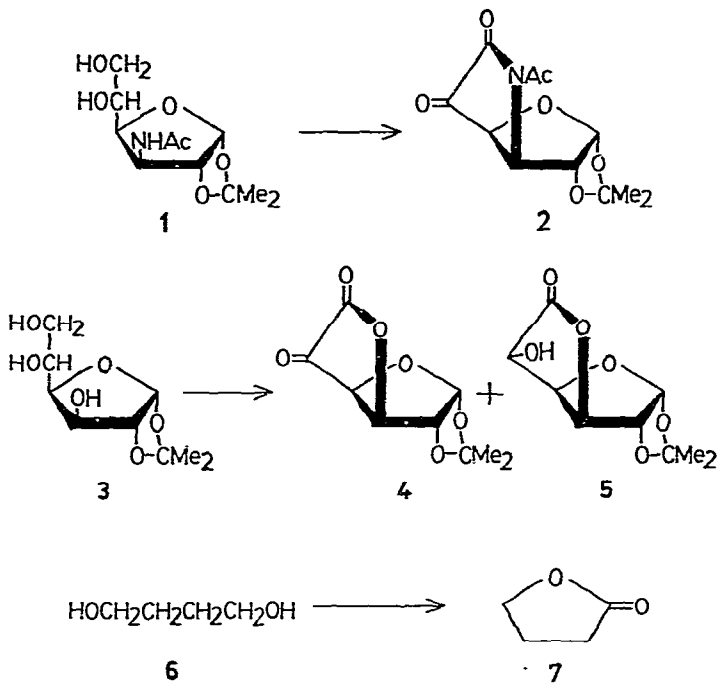


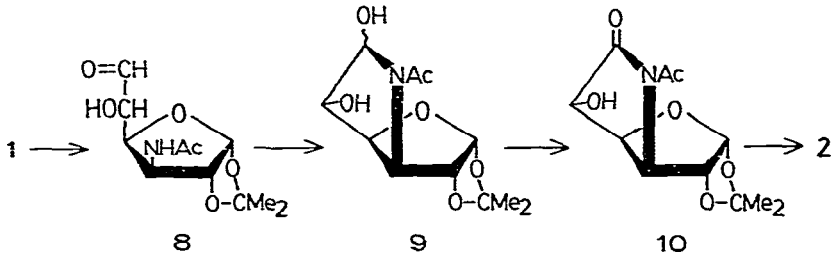
mediate product, 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactam (**10**) could be obtained in 6% yield.

Corey and Schmidt[19] showed that pyridinium dichromate in *N*,*N*-dimethylformamide easily oxidized primary alcohols to carboxylic acids in good yield through the intermediacy of the corresponding aldehydes. The reagent was considered to be useful for the preparation of **2**; the ease of preparation, unusual stability, and nearly neutral character of the reagent were particularly attractive features.

In this note, we report the preparations of **2** and **4**, from **1** and **3**, respectively, by use of pyridinium dichromate. In addition, we show the successful conversion of 1,4-butanediol (**6**) into 1,4-butyrolactone (**7**) in order to demonstrate that pyridinium dichromate can be generally used for the synthesis of lactones from diols. The procedure employed was essentially the same as that of Corey and Schmidt[19], except as regards the processing of the reaction mixtures in the cases of **2** and **4**. Extraction with ether in the processing procedure was not very satisfactory, because **2** and **4** are not very soluble in ether and are slightly soluble in water. Instead, ethyl acetate was employed, which, however, extracted more chromium salt than did ether. The concentrated ethyl acetate solution was diluted with ether, and the solution was filtered through silica gel to remove a trace of chromium salt.

Oxidation of **1** with pyridinium dichromate in *N*,*N*-dimethylformamide proceeded smoothly to afford crystalline **2** in 68% yield. The reaction was monitored by t.l.c. in order that the intermediates 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hexodialdo-1,4;6,3-difuranose (**9**) and **10** could be detected and isolated by

quenching the reaction at an appropriate time. The intermediates were identified by comparison with authentic samples that were synthesized by other routes. Thus, compound **10** could be obtained by catalytic oxidation of **1**, although the yield was low as mentioned earlier. Jones oxidation of **1** in water-saturated butanone provided **9** and **10** which were separated by fractional crystallization. The isolated intermediate **10** could be further oxidized to **2** by use of manganese dioxide. Examination of its ^{1}H-n.m.r. and i.r. spectra clearly indicated that the initial intermediate existed solely as the bicyclic form **9** and not as the monocyclic form **8**. On the basis of the above-mentioned results, the mechanism of the oxidation of **1** by pyridinium dichromate is



Scheme 1

suggested to be as illustrated in Scheme 1; this mechanism is similar to that assumed for the oxidation of diols to lactones by use of the chromium trioxide–pyridine complex[6,8]. The first step is the oxidation of the primary hydroxyl group in **1** to an aldehyde group. The aldehyde **8** enters quickly into equilibrium with the bicyclic form **9**, and the latter is oxidized to the lactam **10**; finally, the secondary hydroxyl group in **10** is oxidized to afford **2**. Oxidation of triol **3** with pyridinium dichromate was not as successful as that of **1**. The proportion of **4** formed early disappeared upon prolonged reaction. For a maximum yield of **4**, the reaction has to be terminated after 5–6 h when, however, the intermediate 1,2-*O*-isopropylidene-α-D-*gluco*-furanurono-6,3-lactone (**5**) has not yet been completely transformed into **4**. Finally, **6** was smoothly transformed into **7** in 70% yield.

The results obtained in this study indicate that pyridinium dichromate is a useful reagent, not only for the simple oxidation of alcohols to carbonyl compounds, but also for the synthesis of lactones and lactams.

EXPERIMENTAL

General. — Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter at 23 ±2°. I.r. spectra were recorded with a Beckman Acculab 6 or a Unicam SP 1000 spectrophotometer. ^{1}H-N.m.r. spectra were recorded

at 60 MHz with tetramethylsilane as the internal standard. T.l.c. was performed with Silica Gel G as the adsorbent, and 1 : 1 (v/v) toluene–acetone as the developing solvent. The developed plates were air-dried, and compounds located by heating the plates at ~150° after they had been sprayed with 10% aqueous sulfuric acid containing 1% of cerium sulfate and 1.5% of molybdic acid. Column chromatography was performed on silica gel (70–230 mesh). Pyridinium dichromate was prepared from pyridine and chromium trioxide according to the procedure of Corey and Schmidt[19]. An eight-step synthesis[20] from D-glucose provided **1**. Compound **3** could be prepared easily from D-glucose by a standard procedure[21].

Oxidation of 3-acetamido-3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**1**) *with pyridinium dichromate.* — To a solution of **1** (0.2 g) in dry *N*,*N*-dimethylformamide (5 mL), stirred at room temperature, was added pyridinium dichromate (2.3 g); stirring was continued for 24 h. The reaction mixture was poured into water (25 mL), and the aqueous solution was extracted exhaustively with ethyl acetate. The dried ($MgSO_4$) ethyl acetate solution was filtered, and the solvent was evaporated under reduced pressure <30°; a trace of *N*,*N*-dimethylformamide was removed under high vacuum. The residue was dissolved in ethyl acetate, and the solution was diluted with ether and filtered through a small amount of silica gel. T.l.c. indicated that the solution contained only one major component (R_F 0.51). The crystals which formed were recrystallized from toluene–petroleum ether (b.p. 60–80°) to afford white 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranurono-6,3-lactam (**2**) as a dihydrate (0.15 g, 68%), m.p. 84–85°; $[\alpha]_D^{23}$ −76.9° (*c* 0.08, ethanol); R_F 0.51; ν_{max}^{Nujol} 3550, 3480, 3340, 3210, 1760, 1680, and 1640 cm^{-1}; ^{1}H-n.m.r. (acetone-d_6): δ 5.85 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.89 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-2), 4.59–4.33 (m, 2 H, H-3 and -4), 2.46 (s, 3 H, NAc), 1.51 and 1.32 (6 H, CMe_2).

Anal. Calc. for $C_{11}H_{13}NO_6 \cdot 2\ H_2O$: C, 45.4; H, 5.9; N, 4.8. Found: C, 45.8; H, 5.7; N, 4.7.

Catalytic oxidation of **1**. — Compound **1** (0.5 g) was dissolved in water (70 mL), and the pH was adjusted to 3.5 with M hydrochloric acid. The solution was poured into a 250-mL, three-necked flask equipped with a mechanical stirrer; a pH probe was placed into one neck of the flask. The temperature was maintained at 60° (water bath). After platinum-on-carbon catalyst (~13%, 0.2 g, prepared[22] from chloroplatinic acid and Darco G-60 activated carbon) had been introduced, the mixture was vigorously stirred, and oxygen was forced into the reaction mixture through an inlet tube. During the course of the reaction, no significant change in pH was observed. After 20 h, t.l.c. indicated that the reaction was complete. The catalyst was removed by filtration, and the aqueous solution was extracted exhaustively with dichloromethane. The combined dichloromethane extracts were washed with cold water, dried ($MgSO_4$), and evaporated to give a syrup. Small amounts of slower-moving (t.l.c.) impurity and starting material were removed by passage through a short, silica gel column with 3:2 (v/v) toluene–acetone as eluent. Crystallization of the product from toluene or ethanol–petroleum ether (b.p. 60–80°) afforded white crystals of 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lac-

tam (**9**) (0.03 g, 6%), m.p. 178–180° (slight decomposition), $[\alpha]_D^{23}$ −83.8° (*c* 0.17, ethanol); R_F 0.57; ν_{max}^{Nujol} 3450, 1740, and 1700 cm^{-1}; ^{1}H-n.m.r. (acetone-d_6): δ 5.78 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.83 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-2), 4.71–4.34 (m, 3 H, H-3, -4, and -5), 2.35 (s, 3 H, NAc), 1.43 and 1.23 (6 H, CMe_2).

Anal. Calc. for $C_{11}H_{15}NO_6$: C, 51.4; H, 5.9; N, 5.4. Found: C, 51.5; H, 5.7; N, 5.4.

Jones oxidation of **1**. — To a stirred solution of **1** in water-saturated 2-butanone (15 mL) was added a solution of potassium dichromate (0.94 g) in aqueous sulfuric acid (4.1 mL of water and 0.4 mL of concentrated sulfuric acid) dropwise over a period of 30 min; stirring was continued for a further 1.5 h at room temperature. Insoluble material was removed by filtration, and the residue was washed with 2-butanone. The filtrate and washings were combined, and the aqueous layer was extracted with 2-butanone. The organic solution was made neutral with powdered barium carbonate, and the mixture was filtered. Evaporation of the dried ($MgSO_4$) filtrate gave a yellow syrup which afforded crystals upon addition of toluene. Recrystallization from ethanol–petroleum ether (b.p. 60–80°) gave pure **10** (0.23 g, 23%). The original mother liquor was evaporated to give a syrup that eventually, partially crystallized; toluene was added and the mixture was cooled in an ice bath. The crystals were collected and washed with toluene–acetone to afford white crystals of 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-1,4:6,3-difuranose (**9**) (0.16 g, 16%) which reduced Fehling's solution; m.p. 186–189°, $[\alpha]_D^{23}$ −75.3° (*c* 0.19, ethanol); R_F 0.19; ν_{max}^{Nujol} 3430, 3350, and 1620 cm^{-1}; ^{1}H-n.m.r. (Me_2SO-d_6): δ 5.76 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 5.09 (d, 1 H, $J_{5,6}$ 5.0 Hz, H-6), 4.67–3.73 (m, 4 H, H-2, -3, -4, and -5), 2.07 (s, 3 H, NAc), 1.42 and 1.26 (6 H, CMe_2).

Anal. Calc. for $C_{11}H_{17}NO_6$: C, 50.9; H, 6.6; N, 5.4. Found: C, 50.6; H, 7.0; N, 5.3.

*Oxidation of 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactam* (**10**) *with manganese dioxide.* — To a stirred solution of **10** (0.25 g) in acetone (7 mL), cooled in an ice-water bath, was added active manganese dioxide[23] (1 g); stirring was continued for 24 h at 5–10°. The insoluble material was removed by filtration, and the pale-brown filtrate was evaporated to give a syrup. The syrup was dissolved in acetone, and evaporation of solvent afforded a brownish, crystalline material. Recrystallization from toluene–petroleum ether (b.p. 60–80°) gave pure **2** as a dihydrate (0.22 g, 76%).

*Oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose* (**3**) *with potassium dichromate.* — To a stirred solution of **3** (0.6 g) in dry *N,N*-dimethylformamide (15 mL) at room temperature was added potassium dichromate (7.5 g); stirring was continued for 6 h at room temperature. The mixture was poured into water (70 mL), and the aqueous solution was extracted with ethyl acetate. The dried ($MgSO_4$) ethyl acetate solution was evaporated under reduced pressure, and a trace of *N,N*-dimethylformamide was removed under high vacuum. The residue was dissolved in ethyl acetate–ether, and the solution was passed through a small amount of silica gel. Two major components, having R_F 0.62 and 0.57 (t.l.c.), were separated by column chromato-

graphy on silica gel with 3:1 (v/v) toluene–acetone as eluent. The faster-moving component was identified as being 1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranurono-6,3-lactone (**4**) (0.32 g, 51%), m.p. 129–130°; lit.[13,17] m.p. 128–130°. The slower-moving component was 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**5**) (0.13 g, 22%), m.p. 140–142°; lit.[14] m.p. 140–142°.

Oxidation of 1,4-butanediol (**6**) *with potassium dichromate.* — To a stirred solution of **6** (0.4 g) in *N*,*N*-dimethylformamide (15 mL) was added potassium dichromate (6.6 g); stirring was continued for 20 h at room temperature. The mixture was poured into water (70 mL), and the aqueous solution was extracted with ether a few times; the combined ether extracts were washed with water. The dried ($MgSO_4$) ether solution was passed through a small amount of silica gel, and evaporation of the ether gave a mixture of *N*,*N*-dimethylformamide and 1,4-butyrolactone (**7**) that were separated by fractional distillation; compound **7** distilled at 78–82°/1.3 kPa (0.25 g, 70%).

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