Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.76; H, 4.65; N, 10.89.

Oxidation of Methyl (1-Benzylindol-3-yl)-3-propionate (49). A. In MeOH. To a solution of 146 mg (0.5 mmol) of **49** in 5 ml of MeOH, 227 mg (1 mmol) of DDQ in 2 ml of MeOH was added dropwise with stirring under argon at 20 °C. The stirring was continued for 1 h, and then the solvent was evaporated to dryness. The residue was extracted with CH_2Cl_2 and the extract was chromatographed on a silica gel column. Elution with CH_2Cl_2 gave two fractions.

The first fraction was 50 mg (34%) of **methyl 1-benzylindole-3-acrylate (50):** mp 106–108 °C (MeOH); ν (Nujol) 1700, 1620 cm^{-1}; λ (EtOH) 226, 274, 333 nm; *m/e* (rel intensity) 291 (M^+, 32), 91 (100).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.52; H, 5.77; N, 4.81.

The second fraction was 56 mg (36%) of **methyl 3-(1-benzylindol-3-yl)-3-oxopropionate (51):** mp 131–132 °C (MeOH); ν (Nujol) 1735, 1640 cm^{-1}; λ (EtOH) 245, 260 (sh), 304 nm; *m/e* (rel intensity) 307 (M^+, 25), 234 (46), 91 (100).

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.17; H, 5.45; N, 4.28.

B. In Anhydrous THF. To a solution of 146 mg (0.5 mmol) of **49** in 6 ml of anhydrous THF, 148 mg (0.65 mmol) of DDQ in 2 ml of anhydrous THF was added dropwise with stirring under argon at 20 °C. After being stirred for 45 min, the solvent was evaporated to dryness. The residue was purified by passing in Et_2O–hexane (1:1) through an alumina column to give 117 mg (80%) of **50.**

Registry No.—**1,** 942-01-8; **2,** 15128-52-6; **8,** 2047-91-8; **9,** 2047-89-4; **10,** 22793-63-1; **11,** 13357-61-4; **12,** 61364-20-3; **13,** 14961-03-6; **14,** 61364-21-4; **15,** 61364-22-5; **17,** 52751-32-3; **18,** 61364-23-6; **21,** 52850-96-1; **22,** 61364-24-7; **23,** 91-55-4; **24,** 5416-80-8; **25,** 5257-24-9; **26,** 35246-18-5; **27,** 22582-52-1; **28,** 21296-92-4; **29,** 61364-25-8; **30,** 1463-67-8; **31,** 17177-17-2; **32,** 51626-88-1; **35,** 83-34-1; **36,** 778-82-5; **37,** 40641-03-0; **38,** 5580-44-9; **39,** 771-51-7; **40,** 16108-06-8; **41,** 487-89-8; **42,** 51079-10-8; **43,** 52816-02-1; **44,** 61364-26-9; **45,** 942-24-5; **46,** 61364-27-0; **48,** 61364-28-1; **49,** 57901-09-4; **50,** 61364-29-2; **51,** 61364-30-5.

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A Mild Process for the Oxidation of Partially Protected Carbohydrates[1]

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A new process for selective hydroxyl to carbonyl oxidation in carbohydrate systems is described. This process consists of esterification of the alcohol to be oxidized using the acid chloride of pyruvic acid and subsequent photochemical reaction of the resulting pyruvate ester. Eight partially protected monosaccharides (**1–5** and **11–13**) were oxidized and found to give good yields of the corresponding carbonyl compounds. Of these eight the oxidation of three tetraacetates of D-glucopyranose (**11–13**) was of particular interest because of the sensitivity of the oxidation products to thermal and base-catalyzed elimination of the elements of acetic acid. The process described here is currently the only one known to allow oxidation of compounds **11–13** without causing further reaction.

Among the chemical transformations of carbohydrates, selective oxidation of hydroxyl groups to carbonyls is certainly one of the most useful.[2] For example, selective oxidation of a hydroxyl group to a carbonyl is often the first step in epimerization of a chiral center. When oxidation is followed by reaction with Grignard, Wittig, or other addition reagents, branched-chain carbohydrates result. If oxidation is combined with oximation and reduction, amino sugars are produced. Each of these three transformations is an essential process in carbohydrate chemistry, particularly in the synthesis of antibiotics, nucleosides, and nucleotides.

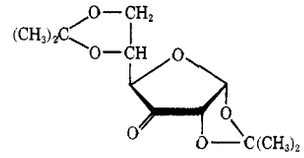
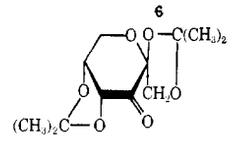
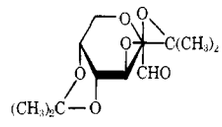
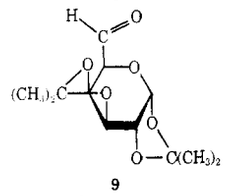
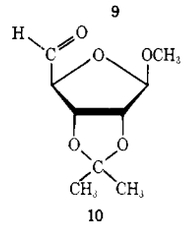
Considerable progress has been made in the past decade in the area of mild oxidation reactions of carbohydrates. The Pfitzner–Moffatt[3] and related, methyl sulfoxide based reagents have been shown to be extremely versatile.[4,5] Ruthenium tetroxide also has been found to be widely applicable to oxidation of carbohydrate systems.[6,7] Chromium trioxide in pyridine is another, mild oxidizing agent of considerable value.[8] Interest is increasing in indirect oxidation via formation and photochemical decomposition of azides.[9] A variety of additional methods and reagents (e.g., platinum and oxygen, electrochemical, and enzymic) have been used, although typically in somewhat specialized situations.

It is clear that considerable versatility currently exists in the chemist's ability to oxidize carbohydrates under relatively mild conditions; however, equally clear are the advantages of an even more versatile and mild oxidation process, that is, one which would oxidize primary and secondary hydroxyl groups with equal effectiveness and would not catalyze further reactions such as elimination of substituents adjacent to the newly formed carbonyl. In addition, this new process would be conducted at or below room temperature in a neutral, nonreactive solvent in the absence of catalytic or reactive materials (hydrogen or metal ions, powerful dehydrating agents, etc.). The research reported here describes an oxidation sequence which possesses all the characteristics mentioned above as desirable in a new oxidation process.

Results and Discussion

Initially selected for study were five alcohols whose oxidation to the corresponding carbonyl compounds by widely used oxidizing agents was well known. Oxidation of each of these

Table I. Oxidations of Partially Protected Carbohydrates

Alcohol	Oxidation products	Yields, %			
		Photochemical oxidation	Chromium trioxide/pyridine	Ruthenium tetroxide	Me_2SO-based reagents
1	 6	71[a] 74[b]	6[c] 0[k]	75–95[d]	45–65 (P_2O_5)[e] 0–70 (DCC)[f] 62 (Ac_2O)[g]
2	 7	53[h] 57[b]		55–75[i]	52–70 (Ac_2O)[j]
3	 8	62	53[k]	*m*	84 (DCC)[n]
4	 9	70	62[k]		46–83 (DCC)[o] Low (Ac_2O)[p]
5	 10	65	75[k]	Low[q]	48–80 (DCC)[r]

[a] 14% recovery of alcohol 1. [b] Reaction mixture subjected to reoxidation. [c] See ref 14. [d] See ref 6a, 7a, 15, 16, and 17. [e] See ref 18–20. [f] See ref 19 and 21. [g] See ref 22. [h] 13% recovery of alcohol 2. [i] See ref 23. [j] See ref 23–26. [k] See ref 8. [m] See ref 25. [n] See ref 27. [o] See ref 28–31. [p] See ref 32. [q] See ref 33. [r] See ref 19 and 33.

five, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[10] (1), 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose[11] (2), 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[11] (3), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[12] (4), and methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[13] (5), was conducted in the same manner. Pyruvoyl chloride was added to a benzene solution of the appropriate alcohol and pyridine, resulting in ester formation which was immediate and quantitative. The ester was subjected to Pyrex-filtered irradiation in benzene (0.01 M) under nitrogen using a 450-W Hanovia medium-pressure mercury lamp. (In initial syntheses, each ester was isolated and characterized; however, isolation was not essential to the oxidation process.) In general, a 60-min irradiation was sufficient for reaction of 1 g of ester. In each case, removal of benzene at 25 °C yielded a light yellow oil which was distilled (simple distillation) to give a colorless material. The distillates from oxidation of compounds **3**, **4**, and **5** were homogeneous and identified as aldehydes **8**, **9**, and **10**, respectively (Table I), initially by instrumental techniques (NMR and GC/MS) and ultimately by comparison with known samples. The distillates from reactions of alcohols **1** and **2** contained predominantly ketones **6** and **7**, respectively, with minor amounts of the corresponding reactant alcohols (**1** and **2**, Table I). The presence of these alcohols was reduced to a low level (2–4%) and yields of carbonyl compounds **6** and **7** slightly increased by subjecting the entire reaction mixtures again to the oxidation process (Table I). The yields reported in Table I are calculated from the amount of product isolated after distillation. NMR spectra of reaction mixtures before and after distillation showed only minor differences.

Study of compounds **1–5** demonstrated that photochemical oxidation is an effective means for oxidizing these alcohols. It is more versatile than chromium trioxide/pyridine or ruthenium tetroxide oxidations and it is more consistent than the Me_2SO-based reactions. Also, the undesirable competing reactions sometimes encountered in Me_2SO-based oxidations are avoided. Thus, photochemical oxidation compares favorably in product yield and versatility to the most widely used oxidizing agents in carbohydrate chemistry.

None of the five systems (**1–5**) considered thus far provided an adequate test of the ability of photochemical oxidation to function when extremely sensitive alcohols or carbonyl compounds are involved. Such a test was conducted by attempting the oxidation of three tetraacetates of D-glucopyranose [2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose[34] (**11**), 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose[35] (**12**), and 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose[36] (**13**)] to the corresponding carbonyl compounds. Previous attempts to oxidize these compounds apparently had been successful; however, oxidation was always accompanied by elimination of acetic acid to give unsaturated carbonyl compounds.[37,38]

The first of the tetraacetates to be studied was compound **11**.[39] Reaction of **11** with pyruvoyl chloride gave the ester **14** which then was subjected to Pyrex-filtered irradiation to

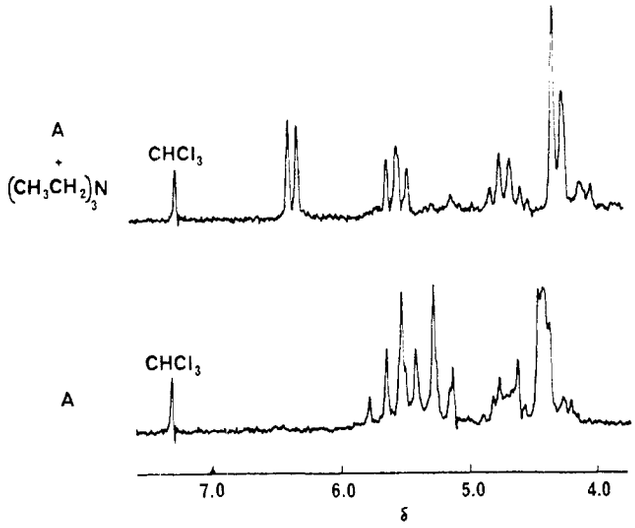
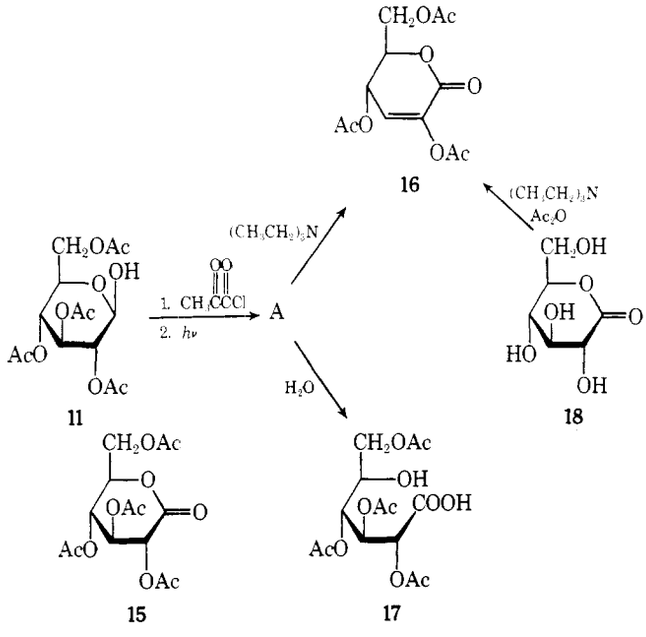


Figure 1. Partial ^1H NMR spectrum of A before and after treatment with triethylamine (60 MHz).

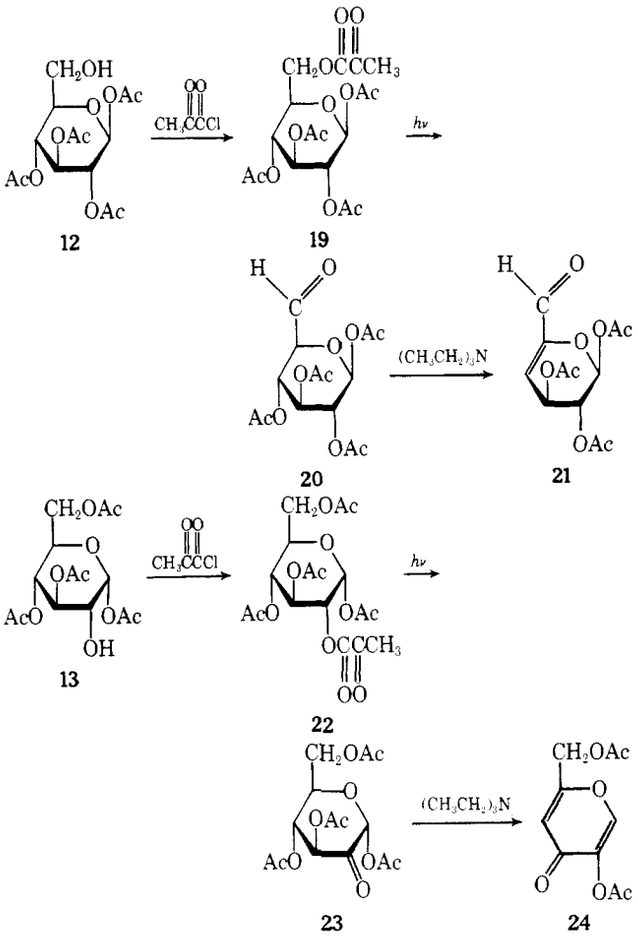
produce a homogeneous, colorless liquid. (One gram of **14** in 350 ml of benzene reacted totally in 1 h.) This material (designated A) was stable at 25 °C in the absence of atmospheric moisture but decomposed in the presence of chromatographic adsorbents or at temperatures above 100 °C. Molecular distillation of A was conducted without decomposition at 90 °C. The structure of A was first suggested by its ^1H NMR and mass spectra. The parent peak in the mass spectrum had a *m/e* value of 346. (The corresponding value for **11** was 348.) Although the ^1H NMR spectrum of A was complex (Figure 1), the signal for the anomeric proton, easily visible in compounds **11** and **14**, had disappeared; further, a 2:1 ratio of acetate protons to other protons in the molecule existed. This information indicated the most probable structure for A to be 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone (**15**). The indicated structure for A was confirmed by chemical transformation; that is, treatment of A with an equivalent amount of triethylamine at 25 °C resulted in instantaneous elimination of the elements of acetic acid to give 2,4,6-tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone[37] (**16**) (Figure 1). Degradation of A to **16** (Scheme I) established the structure

Scheme I. Chemical Reactions of the Product from Photochemical Oxidation of 2,3,4,6-Tetra-*o*-acetyl-β-D-glucopyranose (11)



of A except for the identity and configuration of the substituents at carbons 2 and 3. A reaction that determined the structure of A at the centers of uncertainty and, thus, conformed that A and **15** represented the same compound occurred when A was exposed to moist air at 25 °C for 3 days. These conditions resulted in hydrolysis of the lactone to 2,3,4,6-tetra-*O*-acetyl-D-gluconic acid[40] (**17**). Consistent with the behavior of **15** in the presence of base was the finding that acetylation of D-glucono-1,5-lactone (**18**) in acetic anhydride/triethylamine gave exclusively **16.**

Since the hydroxyl group being oxidized in **11** was anomeric and, thus, potentially unique in its reactivity, it was conceivable that oxidation of other tetraacetates of D-glucopyranose would not follow the same pathway or might produce even more unstable oxidation products. This possibility was investigated by oxidizing two additional tetraacetates, one with a primary hydroxyl (**12**) and the other a secondary hydroxyl (**13**). Irradiation of the pyruvate ester (**19**) derived from **12**



resulted in formation of a reaction mixture in which the major product (B) exhibited stability similar to **15.** Although B was unstable in the presence of chromatographic adsorbents, a stable minor product was isolated (5% yield) by chromatography on Florisil and identified as **12.** Compound B had a parent peak in its mass spectrum at *m/e* 346 and showed ^1H NMR absorptions at δ 9.53 (doublet, J = 2 Hz, aldehyde proton), 6.13–4.04 (complex absorption, five pyranose ring protons), and 2.14–1.90 (12 acetate protons); also, integration of the reaction mixture ^1H NMR spectrum indicated that it consisted of at least 90% aldehyde. The spectral evidence and the structure of the alcohol (**12**) being oxidized suggested that **20** and B were identical. Chemical degradation confirmed this suggestion. Treatment of B with triethylamine transformed it into 1,2,3-tri-*O*-acetyl-4-deoxy-6-aldehydo-α-L-*threo*-hex-4-enodialdo-1,5-pyranose (**21**).[37] The amount of **21** iso-

Table II. ^{1}H NMR Spectral Data of Pyruvate Esters of Alcohols 1–5 and 11–13

Pyruvate ester from alcohol	Pyranose ring protons	Chemical shift values, δ		
		Pyruvate protons	Isopropylidene protons	Acetate protons
1	5.80 (1, H, d, J = 4 Hz) 5.23 (1, H, d, J = 1 Hz) 4.12 (1 H, d, J = 4 Hz) 4.20–3.73 (4 H, m)	2.42 (3 H, s)	1.53–1.17 (12 H, m)	
2	5.05 (1 H, d, J = 7 Hz) 4.55–3.42 (6 H, m)	2.48 (3 H, s)	1.53 (3 H, s) 1.47 (3 H, s) 1.40 (3 H, s) 1.33 (3 H, s)	
3	4.87–3.47 (7 H, m)	2.48 (3 H, s)	1.53 (3 H, s) 1.47 (3 H, s) 1.43 (3 H, s) 1.33 (3 H, s)	
4	5.53 (1 H, d, J = 3 Hz) 4.80–3.97 (6 H, m)	2.48 (3 H, s)	1.55 (3 H, s) 1.48 (3 H, s) 1.37 (6 H, s)	
5	4.87–4.03 (6 H, m) 3.30 (3 H, s, methyl)	2.47 (3 H, s)	1.47 (3 H, s) 1.33 (3 H, s)	
11	5.87–5.67 (1 H, m) 5.33–4.93 (3 H, m) 4.47–3.67 (3 H, m)	2.42 (3 H, s)		2.10–1.90 (12 H, m)
12	5.90–5.67 (1 H, m) 5.40–4.90 (3 H, m) 4.67–3.73 (3 H, m)	2.45 (3 H, s)		2.20–1.98 (12 H, m)
13	6.52 (1 H, d, J = 3 Hz) 5.73–4.93 (3 H, m) 4.30–3.57 (3 H, m)	2.38 (3 H, s)		2.17 (3 H, s) 2.08 (3 H, s) 2.03 (3 H, s) 2.00 (3 H, s)

lated by chromatography of the photochemical reaction mixture after triethylamine treatment required at least an 85% yield of **20** from irradiation of **19**.

The final compound studied (**13**) was oxidized in the same manner as the previous seven. The major product (C) from the irradiation of the pyruvate ester (**22**) of **13** was even more unstable than **15** and **20**. (Attempted distillation at 90 °C caused reaction.) Identification of C was further complicated by formation of significant amounts of minor products which could not be removed without decomposition of C. These minor products were isolated by chromatography of the crude reaction mixture on Florisil and found to be **13** (15%) and a mixture of the α and β anomers of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (less than 5%). The only feature of the ^{1}H NMR spectrum of the crude reaction mixture of value in assignment of a structure to C was that the doublet at δ 6.40, assigned to the anomeric proton in **22**, had been replaced by a singlet at δ 6.16. This feature was consistent with the oxidation of **13** to 1,3,4,6-tetra-*O*-acetyl-α-D-*arabino*-hexopyranos-2-ulose (**23**). The assignment of the structure to C had to be based on the transformation of C either thermally at 80 °C or upon treatment with triethylamine into kojic acid diacetate[37,38] (**24**). The yield of **24** based on the amount of pyruvate ester (**22**) reacted was 70%. Kojic acid diacetate (**24**) is the product from oxidation of **13** with methyl sulfoxide/acetic anhydride, a reaction for which **23** is the proposed intermediate.[37,38] Also significant is the fact that the tetrabenzoyl analogue of **23** has been found to decompose to kojic acid dibenzoate under conditions causing C to be transformed into kojic acid diacetate (**24**).[41] On the basis of its conversion into **24** and by analogy to oxidation of the tetraacetates **11** and **12**, the structure **23** is assigned to C.

Although the lack of stability of the oxidation products **15**, **20**, and, particularly, **23** made their purification and identification difficult, the fact that they and compounds **6–10** were easily and conveniently formed in high yield by photochemical oxidation establishes this reaction sequence as not only being useful in general but most valuable where an extremely mild oxidation process is necessary. Further, photochemical oxidation satisfies well the criteria mentioned above for a desirable new oxidation process.

Experimental Section

General Procedures. The esterification and irradiation procedure used for oxidation of each of the alcohols **1–5** and **11–13** was the same. Also, isolation and identification of **6–10** were conducted in a similar manner. These procedures are described in a general form below. ^{1}H NMR spectra were obtained [$CDCl_3$, $(CH_3)_4Si$, δ 0 ppm] from a Varian T-60 spectrometer (coupling constants, J, are given in hertz; s, d, t, and m indicate singlet, doublet, triplet, and multiplet, respectively). Mass spectra were measured on a Finnigan 1015-D mass spectrometer using both electron impact (ionizing voltage of 70 eV) and chemical ionization with methane as the reagent gas at a pressure of 1.00 Torr and an ionizing voltage of 110 eV.

A. Esterification. The alcohol to be esterified (0.03 mol) and dry pyridine (0.033 mol) were dissolved in 100 ml of anhydrous benzene. Pyruvoyl chloride[42] (0.03 mol) in 50 ml of anhydrous benzene was added in a dropwise manner with stirring. Precipitation of pyridinium hydrochloride was immediate. Cooling with cold water was necessary to keep the reaction mixture below 10 °C. After stirring for 15 min, the pyridinium hydrochloride was removed by filtration and the benzene distilled in vacuo to yield the pyruvate ester contaminated with pyridinium hydrochloride. The contaminant could be removed by shaking the reaction mixture in 50 ml of carbon tetrachloride, allowing it to stand for a few hours, and filtering the insoluble material. When the carbon tetrachloride was evaporated from the filtrate, a quantitative yield of the appropriate ester remained.

The identity of each ester was established first by instrumental analysis [NMR (Varian T-60) and GC/MS (Finnigan 1015-D)] and then for esters from compounds **1–5** and **11** hydrolysis to the starting

alcohol and pyruvic acid. The ^1H NMR spectra of these esters (Table II) and their reconversion to the starting alcohol and pyruvic acid were sufficient to establish their structures. The principal value of the mass spectra was that the identity of the parent peaks confirmed that esterification had taken place without loss of other substituents. Three of the pyruvates were crystalline. Compound **14** crystallized from methylene chloride/carbon tetrachloride and melted at 139–140 °C, while **19** crystallized from carbon tetrachloride and melted at 118–120 °C. The pyruvate ester from **4** also crystallized from carbon tetrachloride and had a melting point of 82–86 °C.

B. Irradiation. The pyruvate ester (3.0 mmol) was dissolved in 350 ml of dry benzene and the solution purged with nitrogen for 1 h. The nitrogen purge was continued during Pyrex-filtered irradiation with a 450-W medium-pressure Hanovia mercury lamp. After 1 h, the irradiation was stopped, the reaction mixture analyzed by TLC, the benzene removed by distillation, and for compounds **1–5** the residual liquid distilled in vacuo using a Buchi/Brinkmann Micro Distillation Oven to give the products shown in Table I. Each product was compared by NMR and GC/MS with a known sample (see Table I).

Oxidation of 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranose (11). After irradiation and solvent removal, the residual oil from photolysis of **14** was analyzed by TLC on silica gel using ethyl ether and appeared to consist of a single product which slowly decomposed on the TLC plate. The electron impact mass spectrum had a parent peak at *m/e* 346. The chemical ionization mass spectrum exhibited the following important peaks (relative abundances in parentheses): *m/e* 347 (100), 287 (96), 227 (70), and 167 (46). There was a 12-proton NMR absorption at δ 2.18–2.10 assigned to the four methyl groups; in addition, there was the six-proton complex absorption, containing peaks at δ 5.77, 5.63, 5.53, 5.40, 5.30, 5.27, 5.17, 4.73, 4.58, 4.40, and 4.33, shown in Figure 1. Treatment of the photoproduct with an equivalent amount of triethylamine in methyl sulfoxide at 25 °C converted it in greater than 90% yield into 2,4,6-tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (**16**).[37] Allowing the photoproduct to stand at room temperature in an atmosphere saturated with water vapor resulted in gradual crystallization over a period of 3 days to yield 2,3,4,6-tetra-*O*-acetyl-D-gluconic acid[40] (**17**). The chemical and physical evidence allowed the identification of the photoproduct from irradiation of **14** as 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone (**15**) (see Results and Discussion).

Oxidation of 1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranose (12). Analysis of the reaction mixture after irradiation of **19** and subsequent solvent removal showed (TLC) a major (unstable) and a minor (stable) component. Chromatography of the reaction mixture on a 2.5 × 80 cm Florisil column packed in ethyl ether and eluted with 500 ml of ethyl ether and 500 ml of ethyl acetate resulted in the isolation of the minor product, which was identical with compound **12**, in the second 500-ml fraction. Attempted distillation of the reaction mixture or treatment with 1 equiv of triethylamine in methyl sulfoxide resulted in formation of 1,2,3-tri-*O*-acetyl-4-deoxy-6-aldehydo-α-L-*threo*-hex-4-enodialdo-1,5-pyranose[37] (**21**). Chromatography of the reaction mixture in the manner just described after treatment with triethylamine resulted in an 85% yield of **21** based on the amount of **12** oxidized. The electron impact mass spectrum of the major reaction product (containing a small amount of **12**) from irradiation of **19** showed a parent peak at *m/e* 346. The chemical ionization spectrum exhibited the following important peaks (relative abundances in parentheses): *m/e* 347 (100), 287 (64), 227 (27). The ^1H NMR spectrum (also containing a small amount of **12**) had absorptions at δ 9.53 (d, J = 2 Hz, aldehyde proton), 6.13–5.55 (1 H, m), 5.52–4.84 (2 H, m), 4.34–3.34 (2 H, m), and 2.14–1.90 (12 H, acetate protons). Chemical reactivity and spectral information (see Results and Discussion) allowed the assignment of structure **20** to the major product from oxidation of **12**.

Oxidation of 1,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranose (13). TLC analysis of the crude reaction mixture from irradiation of **22** showed a major but quite unstable product together with several minor products. Chromatography of the reaction mixture as described in the oxidation of **12** allowed the isolation of the stable minor products in the second 500-ml fraction. Compound **13** crystallized from this chromatography fraction. The remaining residue contained a small amount of material (less than 5% of the entire reaction mixture) which had the same chromatographic behavior (TLC on silica gel and GC on 10% OV-1 on 80–120 mesh Chromosorb W at 220 °C) as an anomeric mixture of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose. Attempted distillation of the crude reaction mixture or treatment with 1 equiv of triethylamine in chloroform or methyl sulfoxide resulted in a 70% yield of kojic acid diacetate[37,38] (**24**). The structure assigned to the major photoproduct from irradiation of **22** is **23** (see Results and Discussion).

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Registry No.—**1**, 582-52-5; 1 pyruvate, 61259-42-5; **2**, 25018-67-1; 2 pyruvate, 61259-43-6; **3**, 20880-92-6; 3 pyruvate, 61259-44-7; **4**, 4064-06-6; 4 pyruvate, 61259-45-8; **5**, 4099-85-8; 5 pyruvate, 61259-46-9; **6**, 2847-00-9; **7**, 18422-53-2; **8**, 32786-02-0; **9**, 4933-77-1; **10**, 33985-40-9; **11**, 3947-62-4; **12**, 13100-46-4; **13**, 7784-54-5; **14**, 61259-47-0; **15**, 61259-48-1; **16**, 22860-23-7; **17**, 61259-49-2; **19**, 61259-50-5; **20**, 61259-51-6; **21**, 38982-61-5; **22**, 61259-52-7; **23**, 61259-53-8; **24**, 26209-93-8; pyruvoyl chloride, 5704-66-5.

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D-Homoandrostanes. 2.[1] Preparation and Properties of Some Dioxygenated D-Homo-5α-androstanes

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The synthesis of D-homo-5α-androstane-2,17a-, -3,6-, -3-7-, -3,16-, -3-17-, and -3,17a-diones and their properties are described. Prolonged reaction time in the dehydrobromination of the 17,17-dibromo-17a ketone (12) resulted in 3β-acetoxy-D-homo-5α-androsta-14,16-dien-17a-one (14).

The first publication in this series[2] dealt with the synthesis of the four D-homo ring A ketoandrostanes and their derivatives, which like the difunctional compounds described here were required for microbiological experiments. Of equal importance are their use as spectroscopic standards, principally in NMR, as analysis of chemical shifts of the methyl groups of oxygenated steroids according to the method of Zurcher[3] enables the location and orientation of microbial hydroxylation to be determined with some precision.

Ring D expansion of 3β-hydroxy-5α-androstan-17-one yielded the hydroxy ketone mixture **1** and **2** which on oxidation gave the easily separable diketone mixture **3** and **4**. As in the reported 17-keto steroid expansions via cyanohydrin[4] or spirooxirane[5] formation, the 17a ketone predominated; consequently a route to the 3,17-dione **4** was developed as shown in the reaction scheme. No purification of the mixtures obtained in each stage was attempted until the removal of the 17a-acetoxy group (**8** → **9**) as the reaction sequence is well documented[2,6] and spectroscopic examination was sufficient to monitor the transformations.

Synthesis of D-homo-5α-androstane-3,16-dione (**19**) required the effective transfer of the oxygen substituent at C-17a to C-16, by treatment of the epoxy ketone **16** with hydrazine,[7] followed by oxidative–reductive manipulation. In the first stage, bromination of 3β-acetoxy-D-homo-5α-androstan-17a-one (**10**) resulted in a mixture of starting material (8%), monobromo (**11**, 53%), and dibromo ketones. After chromatographic separation the dibrominated material **12** was recycled by dehydrobromination and reduction (**12** → **13** → **10**). However, prolonged refluxing during dehydrobromination, 18 h instead of 2 h, led to dienone[8] (**14**, 83%), characterized by an IR absorption at 1660 cm^{-1}. The ease of reaction suggests a convenient route to aromatized 18-nor-D-homo steroids, or, as Japanese workers have ably demonstrated,[8] to 5α,14β-steroids, although by a more laborious route involving two brominations. Dienone **14** formation could be explained by a sequence of elimination, addition, and elimination of HBr, initiated by nucleophilic attack of bromide ion on the initially formed bromo enone **13** as depicted in the reaction scheme.

The hydroxy ketone mixture **1** and **2** also provided the starting material for preparing the 2,17a diketone **25**, in which PLC using silver nitrate impregnated silica gel was found necessary to purify the unsaturated ketone **21**. Hydrobromination with freshly prepared N-bromosuccinimide, careful chromatographic separation of the hydrobromide **22**, epoxide **23** formation, and subsequent reduction gave D-homo-5α-androstane-2β,17β-diol (**24**), which yielded the desired material **25** on oxidation.

Recent work by authors[9] interested in generating 3,6-dioxygenated 5α-androstanes has indicated several available routes. We found that treatment of D-homoandrost-5-en-3β-ol with diborane generated externally, rather than in situ, followed by alkaline hydrogen peroxide gave a complex mixture which contained the diol **26** as major component. Column chromatography gave the 3β,6α-diol (**26**, 42%), D-homo-5α-androstan-3β-ol[2] (9%), and a mixture of the 3β,6β-diols epimeric at C-5 which could only be separated as their diacetates by PLC. An authentic sample of D-homo-5α-androstane-3β,6β-diol was prepared by borohydride reduction of the dione **30** derived from the 3β,6α-diol **26**. Ease of synthesis could be accomplished by prolonged Jones oxidation of the total crude hydroboration product, when a mixture of only D-homo-5α-androstan-3-one[2] and the dione **30** was obtained. During preliminary work on this reaction, treatment with Jones reagent during 15 min gave, in addition to the ketonic products, 6α-hydroxy-D-homo-5α-androstan-3-one (**31**).

D-Homoandrost-5-en-3β-ol also provided a convenient starting point for synthesis of the 3,7-dione **37**. Oxidation of the derived acetate **32** yielded the desired acetoxy enone **34**, together with the acetoxy ketol **33** as minor product exhibiting on mass spectrometric examination the appropriate molecular ion and characteristic fragmentation of 6-oxo steroids,[10] together with IR absorptions at 3580 and 3400 cm^{-1}. Standard reactions (**34** → **37**) completed the synthesis.

Experimental Section

General directions have been described previously.[2] Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6h at 70 eV.

D-Homo-5α-androstane-3,17a- and -3,17-diones (3 and 4). Oxidation of a mixture of 3β-hydroxy-D-homo-5α-androstan-17a- and -17-ones (**1** and **2**) (198 mg) by Jones reagent, followed by extraction and separation by PLC, gave 128 mg of dione **3** recrystallized from ethyl acetate [mp 182–184 °C (lit.[4] 183–185 °C); ν_{max} 1700 cm^{-1}; NMR τ 8.96 (CH_3-19), 8.86 (CH_3-18)] and 16 mg of dione **4** recrystallized from ethyl acetate [mp 168 °C (lit.[4] 168–170 °C); ν_{max} 1700 cm^{-1}; NMR τ 9.16 (CH_3-18), 8.96 (CH_3-19)].