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SOLVENT EFFECTS ON THE PHOTOCHEMICAL ADDITION OF ACETONE TO 3,4,6-TRI-*O*-ACETYL-D-GLUCAL*

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ABSTRACT

Irradiation of a solution of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) in various mixtures of acetone (**2**) and isopropyl alcohol was investigated to elucidate solvent effects on the photochemical addition of **2** to **1**. At high concentrations of acetone (**2**), 5,6,8-tri-*O*-acetyl-2,4:3,7-dianhydro-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (**3**) was obtained selectively. In mixtures containing less than 50% (v/v) of **2**, irradiation gave mainly 5,6,8-tri-*O*-acetyl-3,7-anhydro-1,4-dideoxy-2-*C*-methyl-D-*gluco*-octitol (**4**). The effects of ethanol and other solvents were examined and the mechanism of the reaction is discussed.

INTRODUCTION

The photochemical technique[2] has proved useful in the field of synthetic chemistry[3], and this report describes a continuation of work by the authors[4] on the photochemical addition of acetone (**2**) to 3,4,6-tri-*O*-acetyl-D-glucal (**1**).

Typical examples of the photochemical reactions of alkenes with carbonyl compounds are the Paterno–Buchi reaction[5], leading by photocycloaddition to oxetane derivatives, and the addition of ketone-derived radicals to alkenes[6] to afford tertiary alcohols (Scheme 1). Both reactions involve the $n \rightarrow \pi^*$ triplet state of the carbonyl compounds as the reaction intermediate. The oxetane appears to be formed by ring closure of a biradical arising by electrophilic addition of an excited, electron-deficient carbonyl oxygen-atom to the alkene, whereas the tertiary alcohol is produced by nucleophilic attack on the alkene by a radical, generated from the carbonyl compound by abstraction of a hydrogen atom from the solvent.

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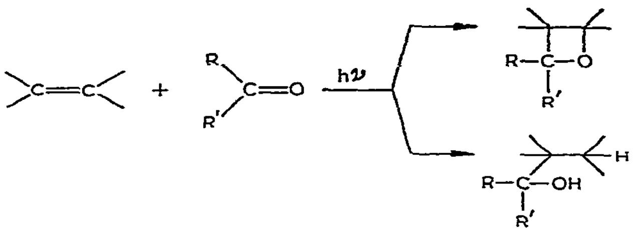
*Part VI of a series: Synthetic studies on Carbohydrate Derivatives by Photochemical Reactions. For Part V see Ref. 1.

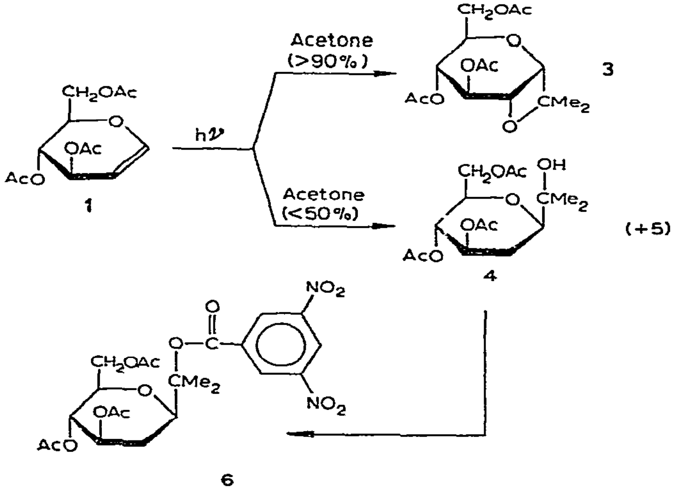


Sheme 1

RESULTS AND DISCUSSION

In a previous paper[4c], irradiation of a solution of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) in acetone (**2**) containing a small amount of isopropyl alcohol was shown to afford an oxetane derivative, earlier characterized by Ong and Whistler[7] as 5,6,8-tri-*O*-acetyl-2,4;3,7-dianhydro-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (**3**). This article describes an investigation on solvent effects in the photochemical addition of **2** to **1**.

Irradiating solutions of **1** in various mixtures of **2** and isopropyl alcohol, with a high-pressure mercury lamp (450 W) at room temperature under a nitrogen atmosphere, gave the results depicted in Scheme 2 and listed in Table I. The product ratios listed were determined by g.l.c. When the solvent contained 90% of **2**, the oxetane **3** was obtained selectively, whereas a tertiary alcohol, namely, 5,6,8-tri-*O*-acetyl-3,7-anhydro-1,4-dideoxy-2-*C*-methyl-D-*gluco*-octitol (**4**) was the major product when the solvent contained <50% of acetone (**2**). By comparing the results in runs 14



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and 15, it can be seen that **2** behaves also as a photosensitizer in this reaction. Furthermore, comparing the results of runs 1 and 2 indicates that the presence of isopropyl alcohol in **2** greatly facilitates formation of the oxetane **3**.

TABLE I

PHOTOCHEMICAL REACTION OF 3,4,6-TRI-*O*-ACETYL-D-GLUCAL (**1**) IN ACETONE–ISOPROPYL ALCOHOL

Run	*Solvent system*		*Product, relative content* (%)		
	Acetone (*ml*)	*Isopropyl alcohol* (*ml*)	**1**	**3**	**4**(+**5**)
1	10.0	0	86	14	0
2	10.0	0.008	4	96	0
3	10.0	0.038	3	97	0
4	9.5	0.5	1	99	trace
5	9.0	1.0	17	83	trace
6	8.0	2.0	19	67	14
7	6.5	3.5	4	64	32
8	5.0	5.0	30	0	70
9	3.5	6.5	23	0	77
10	2.0	8.0	1	0	99
11	1.0	9.0	0	0	100
12	0.5	9.5	8	0	92
13	0.037	10.0	1	0	99
14	0.007	10.0	1	0	99
15	0.0	10.0	57	0	43

Chromatography of the product from reaction in 9:1 (v/v) isopropyl alcohol–acetone afforded 86% of **4**, and 6% of **1** was recovered. Compound **4** was found by g.l.c. to be contaminated by a small proportion of a product (**5**) that gave a small shoulder on the g.l.c. peak of **4**; this product is possibly a structural isomer of **4**.

Use of ethanol in place of isopropyl alcohol gave substantially the same results (Table II). Again the oxetane **3** was selectively produced at high concentrations (>90%) of **2** and the tertiary alcohol **4** was produced in increasing proportion as the content of **2** in the solvent decreased .These results may provide an important clue to the mechanism of the reaction.

The best yield of **4** was obtained when the solvent contained 10% of acetone (**2**). Irridiation in various solvents containing 10% of **2** gave the results summarized in Table III. The tertiary alcohol **4** was the major product when primary and secondary alcohols (except methanol), ethers, and petroleum ether (b.p. 40–70°) were used; these solvents are susceptible to hydrogen-atom abstraction. In methanol the oxetane **3** was formed to a greater extent than **4**. Selective formation of **3** was observed in *tert*-butyl alcohol, acetonitrile, and acetic acid, but no reaction occurred in nitromethane, benzene, toluene, xylene, and pyridine. It was concluded that isopropyl alcohol is the best solvent both for the preparation of **3** and **4**.

TABLE II

PHOTOCHEMICAL REACTION OF 3,4,6-TRI-*O*-ACETYL-D-GLUCAL (**1**) IN ACETONE–ETHANOL

Run	*Solvent system*		*Relative ratios of products (%) after*					
	Acetone (ml)	*Ethanol (ml)*	*10 h*			*25 h*		
			1	**3**	**4**(+**5**)	**1**	**3**	**4**(+**5**)
1	10.0	0	93	7	0	84	16	0
2	10.0	0.006	48	52	0	19	81	0
3	10.0	0.029	41	59	0	14	86	0
4	9.9	0.12	52	47	1	34	66	trace
5	9.0	1.0	88	11	1	40	60	trace
6	5.0	5.0	85	12	3	54	37	9
7	2.0	8.0	76	5	19	31	13	56
8	1.0	9.0	78	0	22	40	0	60
9	0.15	9.9	92	0	8	73	0	27
10	0.037	10.0	98	0	2	89	0	11
11	0.007	10.0	100	0	0	100	0	0

TABLE III

PHOTOCHEMICAL REACTION OF 3,4,6-TRI-*O*-ACETYL-D-GLUCAL (**1**) IN SOLVENT SYSTEMS CONTAINING 10% OF ACETONE

Principal solvent[a]	*Relative ratios of products (%)*		
	1	**3**	**4**(+**5**)
Methanol	14	62	24
Ethanol	10	0	90
Propyl alcohol	2	0	98
Isopropyl alcohol	2	0	98
Isobutyl alcohol	50	0	50
tert-Butyl alcohol	2	98	0
n-Hexyl alcohol	96	0	4
Cyclopentanol	85	0	15
Cyclohexanol	77	0	23
Petroleum Ether (b.p. 40–70°)	20	10	70
Tetrahydrofuran	34	0	66
Tetrahydropyran	72	0	28
1,4-Dioxane	83	1	16
Acetonitrile	23	77	0
Acetic Acid	0	100	0
N,*N*-Dimethylformamide	77	3	20
Ethyl Acetate	80	2	18

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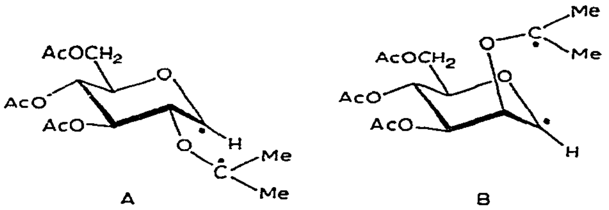
[a] The reactions in diethyl ether, cyclohexane, and *n*-hexane gave complicated products, impossible to analyze by g.l.c. No product was observed when nitromethane, benzene, toluene, xylene, or pyridine were used.

The tertiary alcohol **4** was converted into 5,6,8-tri-*O*-acetyl-3,7-anhydro-1,4-dideoxy-2-*O*-(3,5-dinitrobenzoyl)-2-*C*-methyl-D-*gluco*-octitol (**6**) by treating it with 3,5-dinitrobenzoyl chloride in pyridine, and the n.m.r. spectrum of **6** was analyzed (see Experimental). First-order analysis of the H-5 and H-6 signals could not be achieved as they gave a complicated, overlapping multiplet, but all signal assignments were verified by the double-resonance technique. The δ values of H-4a and H-4e are in good agreement with those reported for deoxy sugar derivatives[8]. Irradiation at H-4a collapsed the H-3 signal to a doublet ($J_{3,4e}$ 2.0 Hz), and irradiation at H-4e changed the H-3 signal to a doublet ($J_{3,4a}$ 11.5 Hz). The coupling constants of H-3 indicate that this proton is axial, and thus the 3,5-dinitrobenzoyloxyisopropyl group is equatorial, and the configuration at C-3 is concluded to be *R*. The values of $J_{5,6}$ (9.5 Hz) and $J_{6,7}$ (9.5 Hz) indicate that the pyranoid ring adopts the usual $^4C_1$ chair (D) conformation.

The mass spectra of **3** and **6** are shown in Figs. 1 and 2, respectively. Tentative fragmentation schemes are depicted, and these support the structures assigned to **3** and **6**.

The highly selective formation of the tertiary alcohol **4** in this photochemical reaction is of mechanistic interest, especially with regard to stereochemistry. In the previous paper[4c], the selective formation of **3** was explained by comparison of the relative stereochemical stabilities of biradical *A* and of biradical *B* (Scheme 3) that might arise by electrophilic attack of the electron-deficient carbonyl oxygen atom of acetone (in the $n \rightarrow \pi^*$ triplet state) on the electron-rich C-2 of **1**. The reaction leading to the alcohol **4** may be explained similarly by comparison of the stereochemical stabilities of potential intermediate radicals. This reaction is evidently initiated by nucleophilic attack of radical (**7**), produced from acetone (**2**) by abstraction of a hydrogen atom from a solvent molecule. It has generally been accepted that radicals such as **7** behave as electron donors in such reactions[9]. Consequently, **7** may attack on the electron-deficient C-1 of **1** to afford the intermediate radicals *C* and *D*. The highly selective formation of **4** can be rationalized stereochemically; radical *C* having the bulky hydroxyisopropyl substituent equatorial should be more stable than *D* where the group is axial. The minor product **5**, observed by g.l.c. as a small shoulder on the peak of **4**, may possibly arise from radical *D*. In solvent systems containing acetone (**2**), there is a noteworthy difference between isopropyl alcohol and other alcohols in



Scheme 3

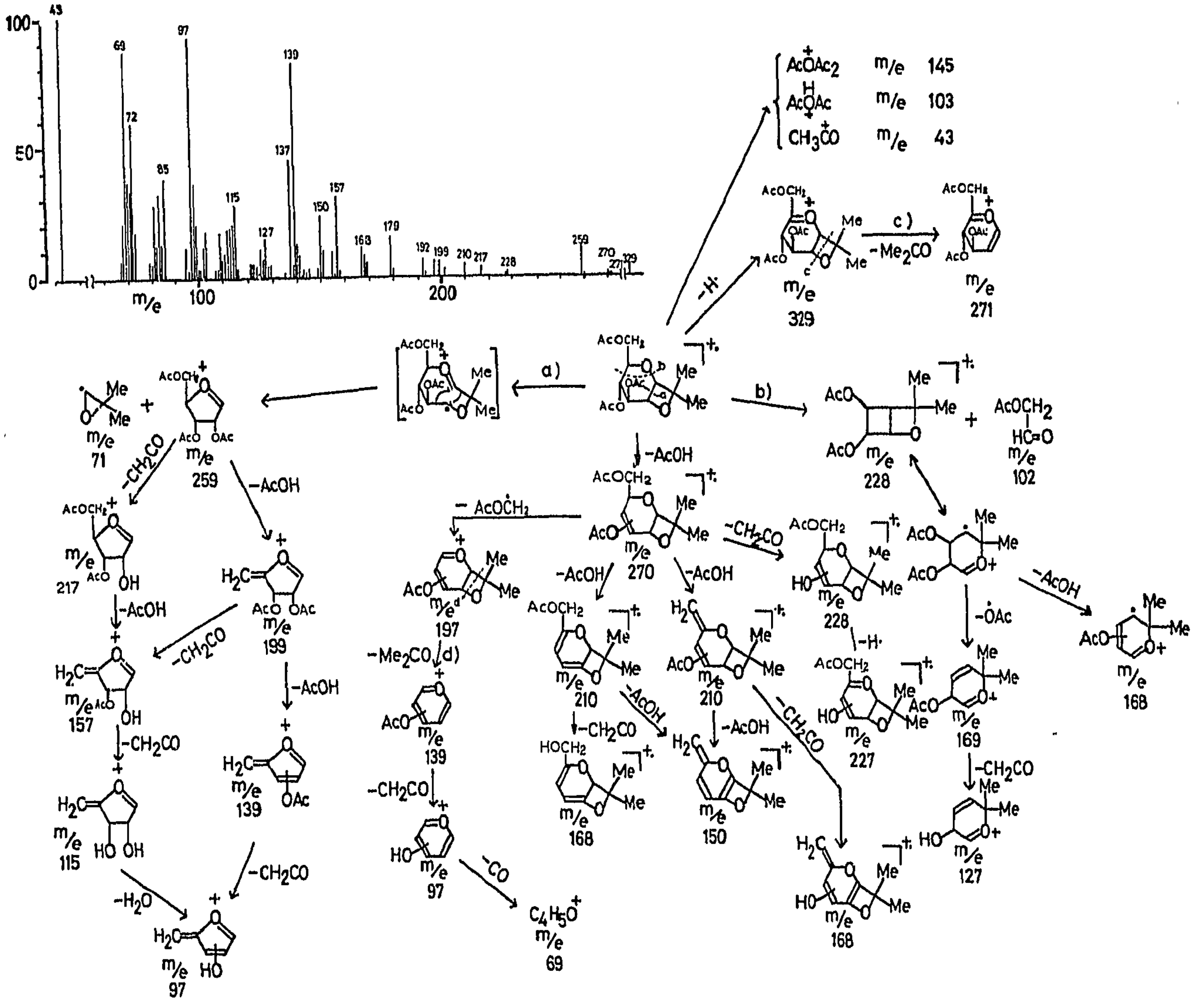


Fig. 1. Mass spectrum of 5,6,8-tri-*O*-acetyl-2,4:3,7-dianhydro-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (3), and a tentative scheme for its fragmentation.

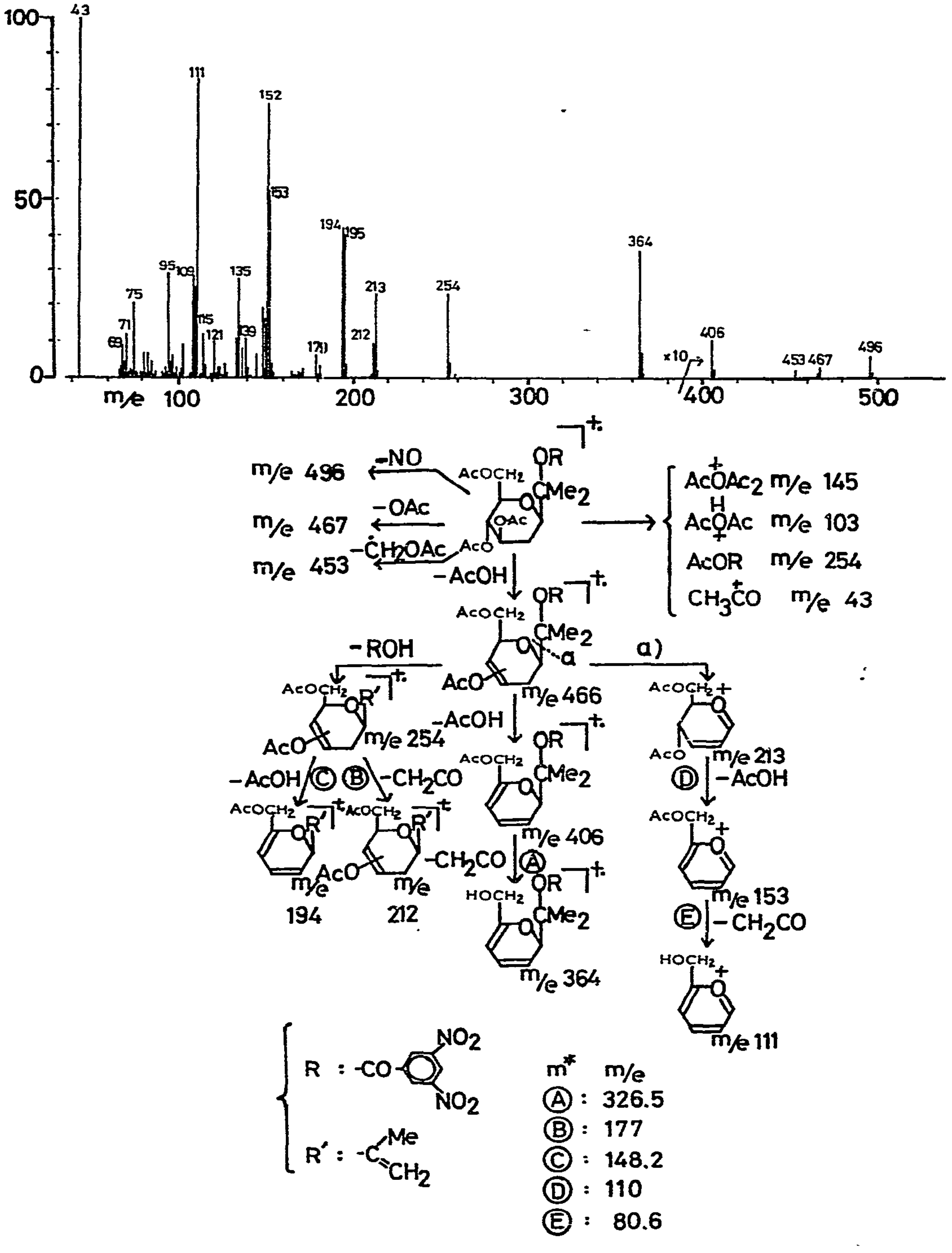
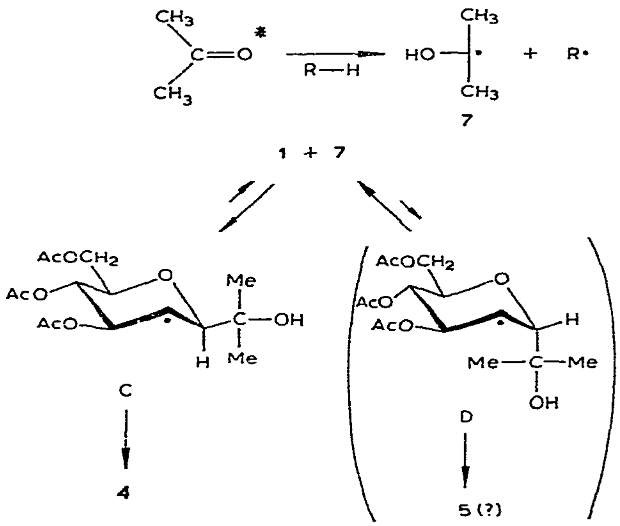


Fig. 2. Mass spectrum of 5,6,8-tri-*O*-acetyl-3,7-anhydro-1,4-dideoxy-2-*O*-(3,5-dinitrobenzoyl)-2-*C*-methyl-D-*gluco*-octitol (6), and a tentative scheme for its fragmentation.



Scheme 4

the reaction leading to the alcohol **4**. This may be ascribed to the following factors: (*a*) The correlation between the hydrogen-donating ability of solvents and the stability of the resultant radicals; and (*b*) in the case of isopropyl alcohol especially, the resultant radical from the alcohol is the same as that (**7**) produced from acetone (**2**), and it can thus also participate in the reaction. This assumption concerning the reaction mechanism is supported strongly by the observed utilization of butanone in place of **2** as the photosensitizer in the irradiation of **1** in isopropyl alcohol; no 1:1 adduct of **1** with butanone was obtained but alcohol **4** was obtained selectively in 80% yield. Also, irradiation of **1** in 1:9 butanone–isobutyl alcohol resulted in a quantitative recovery of **1**, whereas irradiation of **1** in 1:9 acetone–isobutyl alcohol afforded **1** and **4** in 50% yields, respectively (see Table III). Furthermore irradiation of **1** in isopropyl alcohol with a low-pressure mercury lamp gave **4** selectively in 58% yield, whereas, **1** was recovered quantitatively when other solvents were used.

EXPERIMENTAL

General. — Solvents were purified prior to use. Solvent ratios given are all v/v. Irradiations were conducted with a 450-W high-pressure mercury lamp (Ushio Electric Inc.) in a Pyrex-glass test tube at a distance of about 5 cm, or with a 7-W low-pressure mercury lamp (Ushio Electric Inc.) in a quartz test-tube. T.l.c. was performed on Wakogel B-5 with 9:1 benzene–methanol as developer. N.m.r. spectra were recorded with a Varian HA-100 instrument in deuteriochloroform with tetramethylsilane as the internal standard and benzene as the locking signal. G.l.c. was performed with a Hitachi Model K-53 instrument on a column of 10% SE-30 on Chromosorb-W (60–80 mesh) with nitrogen at 1.5 atm as carrier gas; oven temperature, 200° and injection temperature, 300°. Mass-spectral data were obtained with a Hitachi RMU-6E spectrometer.

Irradiation of 3,4,6-tri-O-acetyl-D-glucal (**1**) *in acetone* (**2**)*–isopropyl alcohol.* — Compound **1** (54 mg) in 10 ml of the solvent mixture was irradiated with the high-pressure mercury lamp for 30 h at room temperature under nitrogen. The resultant solutions were analyzed by g.l.c. and the results are summarized in Table I.

Irradiation of **1** *in acetone–ethanol.* — The foregoing procedure was repeated except that the reaction times were 10 and 25 h. The results are summarized in Table II.

Irradiation of **1** *in various solvents containing 10% of acetone.* — Irradiations by the foregoing procedure were conducted for 30 h, and the results are summarized in Table III.

*Isolation of 5,6,8-tri-O-acetyl-3,7-anhydro-1,4-dideoxy-2-C-methyl-D-*gluco*-octitol* (**4**). — A solution of **1** (1.000 g) in acetone (2.5 ml) and isopropyl alcohol (22.5 ml) was irradiated with the high-pressure mercury lamp for 70 h at room temperature under nitrogen, and then evaporated *in vacuo*. The residual syrup was chromatographed on a column of silica gel (Mallinckrodt Silica Gel, 100-mesh) 9:1 benzene–acetone as eluant. Compounds **1** (60 mg, 6% recovery) and **4** (1.04 g, 86% yield) were eluted in turn, and **4** was found by g.l.c. to contain <5% of a contaminant **5**. Retention volumes of **1**, **3**, **4**, and **5** by g.l.c. were 1, 2.4, 2.5, and 2.6, respectively.

Anal. Calc. for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 54.20; H, 7.34.

Irradiation of **1** *in isopropyl alcohol containing butanone as photosensitizer.* — A solution of **1** (1.000 g) in butanone (2.5 ml) and isopropyl alcohol (22.5 ml) was irradiated with a high-pressure mercury lamp for 70 h at room temperature under nitrogen and the resultant solution was treated as in the previous experiment to afford **1** (50 mg, 5% recovery) and **4**(+**5**) (970 mg, 80%).

When a solution of **1** (300 mg) in isopropyl alcohol (15 ml) was irradiated with a low-pressure mercury lamp for 190 h at room temperature under nitrogen there was obtained **1** (10 mg, 3% recovery) and **4** (214 mg, 58%).

*5,6,8-Tri-O-acetyl-3,7-anhydro-1,4-dideoxy-2-O-(3,5-dinitrobenzoyl)-2-C-methyl-D-*gluco*-octitol* (**6**). — To a solution at 0° of **4** (500 mg) in pyridine (8 ml), was added 3,5-dinitrobenzoyl chloride (1.0 g) and the mixture was kept at room temperature overnight. Chloroform (100 ml) was added and the solution was washed successively with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate solution, and water. After drying (sodium sulfate) the solution was concentrated *in vacuo* to a syrup, which was triturated with ethanol (3 ml). The resultant crystals were filtered off and recrystallized from ethanol to give **6** (120 mg, 15%), m.p. 190.5–191.0°, $[\alpha]_D^{20}$ +4.0° (*c* 0.67, acetone) (calc. by the Drude equation from $[\alpha]_{546}$ +0.020° and $[\alpha]_{578}$ +0.018°); mass spectrum, see Fig. 2; n.m.r.: δ 4.05 (1-proton quartet, $J_{3,4a}$ 11.5 and $J_{3,4e}$ 2.0 Hz, H-3), 1.71 (1-proton octet $J_{4a,4e}$ 11.5 Hz, H-4a), 2.21 (1-proton octet, H-4e), 4.9–5.2 (2-proton multiplet, $J_{4a,5}$ 11.5, $J_{4e,5}$ 4.0, and $J_{5,6}$ 9.5 Hz, H-5 and H-6), 3.62 (1-proton octet, $J_{6,7}$ 9.5, $J_{7,8}$ 1.8, and $J_{7,8'}$ 4.8 Hz, H-7), 4.06 (1-proton octet, $J_{8,8'}$ 11.7 Hz, H-8), 4.22 (1-proton octet, H-8'), 2.00 (3-proton singlet, OAc), 2.04 (3-proton singlet, OAc), 2.06 (3-proton singlet, OAc), 1.66 (3-proton singlet, C-Me), 1.68 (3-proton singlet, C-Me), and 9.0 (3-proton singlet, protons on the 3,5-dinitrobenzoyl group).

Anal. Calc. for $C_{22}H_{26}N_2O_{13}$: C, 50.18; H, 4.94; N, 5.32. Found: C, 50.24; H, 5.03; N, 5.09.

The filtrate and mother liquors were concentrated *in vacuo* to give syrupy **4** (410 mg, 82% recovery). G.l.c. analysis of this syrup showed that the relative content of the minor component **5** was increased in comparison with the syrup prior to acylation, indicating selective acylation of **4** in the syrupy mixture of **4** containing a little **5**.

ACKNOWLEDGMENT

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