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Synthetic Studies of Carbohydrate Derivatives with Photochemical Reactions. X.[1] An Unusual Photo-induced Addition of Lactonitrile to Some Enoses

Kazuo Matsuura, Kazuo Senna, Younosuke Araki, and Yoshiharu Ishido

Department of Chemistry, Faculty of Science, Tokyo Institute of Technology,
O-okayama, Meguro-ku, Tokyo 152

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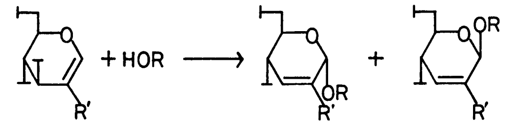
The photochemical addition of lactonitrile to 3,4,6-tri-*O*-acetyl-D-glucal, 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal, methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside, and methyl 5-deoxy-2,3-*O*-isorpopylidene-β-D-*erythro*-pent-4-enofuranoside afforded 1′-cyanoethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-(**6a**) and -β-D-*erythro*-hex-2-enopyranoside(**6b**), 1′-cyanoethyl 2,4,6-tri-*O*-acetyl-3-deoxy-α- and -β-D-*erythro*-hex-2-enopyranoside, **6a** and **6b**, and 1′-cyanoethyl [methyl (4*R*)-5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pentofuranosid]-4-uloside respectively, all in good yields. These facts can be explained by assuming the catalytic effect of a certain acidic species which might extricated from lactonitrile during the irradiation.

As part of this series of investigations, the photochemical addition of secondary alcohols to enoses has been reported briefly; in it the corresponding tertiary alcohols were obtained through the addition of α-*C*-radicals of secondary alcohols to enoses.[2] On the other hand, in contrast with the case of these secondary alcohols, the photochemical behavior of lactonitrile(**1**) was found to be unusual in such reaction; it gives the corresponding adducts, which have the 1′-cyanoethyl ether structure.[3] In this article, the detailed results of an investigation of the unusual photo-induced reaction of **1** with 3,4,6-tri-*O*-acetyl-D-glucal(**2**), 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal(**3**), methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside(**4**), and methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranoside(**5**) will be described.

Results and Discussion

The irradiation of a solution of **2** in **1** was carried out by the use of a low-pressure mercury lamp under a nitrogen atmosphere at room temperature. The resultant reaction mixture was, after concentration *in vacuo* to a sirup, subjected to chromatographic separation to afford 1′-cyanoethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside(**6a**) and the corresponding β-anomer(**6b**) in 37 and 47% yields[4] respectively. Moreover, 1′-cyanoethyl 2,4,6-tri-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranoside(**7a**) and its β-anomer(**7b**) were similarly obtained from **1** and **3** in 40 and 40% yields respectively. The structural assignment of these products was successfully accomplished by the use of the NMR and mass spectroscopic data (Table 1 and Fig. 1 respectively). The signals of the anomeric protons of 2,3-dideoxy- and 3-deoxy-α-D-*erythro*-hex-2-enopyranosides have been shown by Ferrier *et al.*[5,6]



2, R′=H
3, R′=OAC

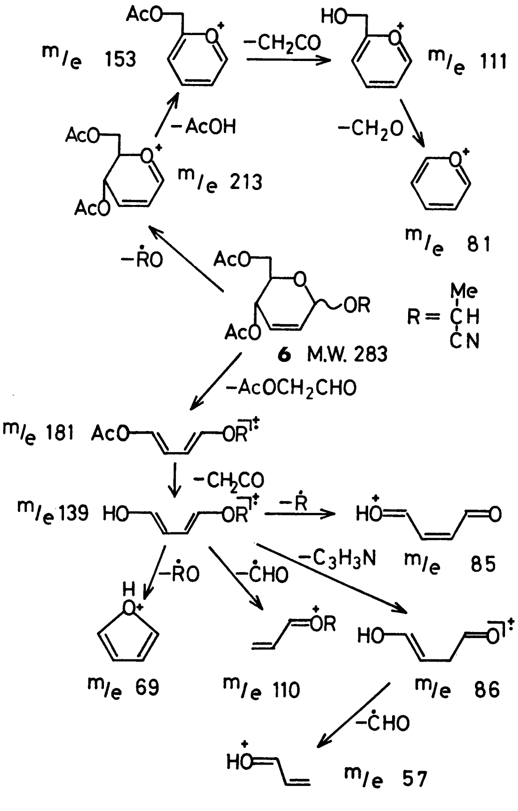
Me
R = CH
CN

$R = CH(Me)CN$

6a, R′=H
7a, R′=OAc

6b, R′=H
7b, R′=OAc

(⊢ =OAc)



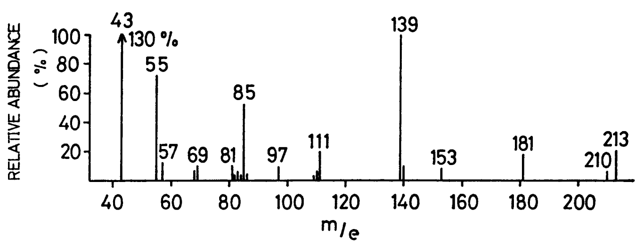


Fig. 1. Mass spectrum of **6**

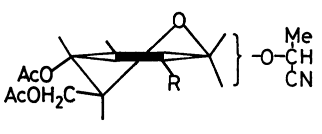


Fig. 2. **8** H1 conformation

Table 1. NMR data of **6a**, **6b**, **7a**, and **7b**

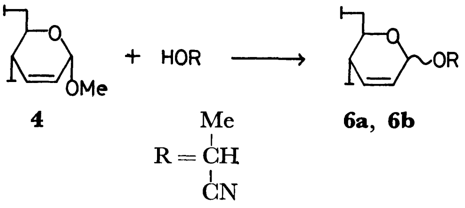
Protons	Chemical shifts			
	6a	**6b**	**7a**	**7b**
H-1′	4.47	4.72	4.47	4.68
H-1	5.23	5.34	5.30	5.34
H-2	6.06	6.05	—	—
H-3	5.85	5.89	5.87	5.89
H-4	5.44	5.40	5.57	5.55
H-5	4.23	4.09	4.23	4.16
H-6,6′	4.3—4.5	4.2—4.3	4.3—4.4	4.2—4.3
C-CH_3	1.63	1.64	1.66	1.66
O-$COCH_3$	2.13, 2.13	2.11, 2.11	2.13, 2.13, 2.19	2.12, 2.12, 2.24
Coupling constants				
H-1—H-2	$1>$	$0.5>$	—	—
H-1—H-3	2.5	$1>$		
H-2—H-3	10	10.5	—	—
H-2—H-4	$1>$	$1>$	—	—
H-3—H-4	1.5	2	2.3	2.0
H-4—H-5	9.5	9.5	9.5	10
H-5—H-6	2.5	2.2		$1>$
H-5—H-6′	3.5	3.5		3.5
H-1′—CH_3	7.0	7.0	7.0	7.0

All the chemical shifts in this table are expressed by δ value in ppm, and the coupling constants are expressed in Hz.

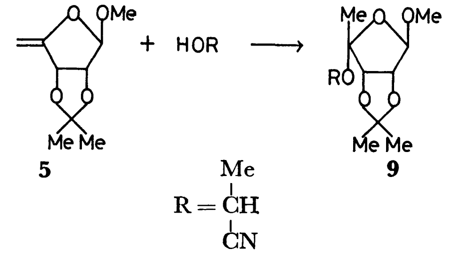
to appear at a field higher than those of the corresponding β-anomers. The signals of **6a**, **6b**, **7a**, and **7b** were observed at δ 5.23, 5.34, 5.30, and 5.34 ppm respectively; those products were thus concluded to occupy the α-, β-, α-, and β-anomeric configurations respectively. Incidentally, the chromatographic behavior of **6a** and **6b** in glc, tlc, and column chromatography was in full accordance with that of **7a** and **7b** respectively. A further comparison of their NMR data with those[5a] of 2-enopyranosides led us to the conclusion that all the D-*erythro*-hex-2-enopyranosides described herein adopted the H1 conformation(**8**) with the $J_{3,4}$ and $J_{4,5}$ values of *ca.* 2 and *ca.* 10 Hz respectively, indicative of the quasi-axial and axial protons at *C*-4 and *C*-5 respectively. Moreover, the mass spectra of **6a** and **6b** showed the same spectral pattern and supported the expected structures; such typical fragment peaks as *m/e* 213, 181, and 139 were apparently detected in their spectra, and were found to agree with the results of Ferrier *et al.*[7]

The present reaction was thus confirmed to afford neither sugar derivatives with the tertiary alcohol substituents, in contrast with the reactions of ordinary secondary alcohols to enoses,[2] nor those with an ether linkage at *C*-2, but the 2-enopyranosides.

The irradiation of a solution of **4** in **1**, followed by chromatographic separation, was subsequently carried out; it was found to involve a transglycosidation reaction giving **6a** and **6b** in 40 and 47% yields respectively.



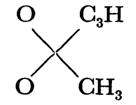
$R = \underset{CN}{\overset{Me}{CH}}$



$R = \underset{CN}{\overset{Me}{CH}}$

Subsequently, the addition of **1** to 4-enofuranosyl derivatives such as **5**, which have an exocyclic double bond, was studied in the expectation that their higher reactivity could be proved in comparison with those having an endocyclic double bond.[1] 1′-Cyanoethyl

Table 2. NMR data of **9**

Protons	H-1	H-2	H-3	H-1′	CH_3-1′	CH_3-4	O-CH_3	
Chemical shifts, δ	4.92	4.63	4.45	4.58	1.47	1.61	3.37	1.45 1.31
Coupling constants, Hz		H-1—H-2 0.5		H-2—H-3 6.0		H-1′—CH_3 7.0		

[methyl (4*R*)-5-deoxy-2,3-*O*-isopropylidene-*β*-D-*erythro*-pentofuranosid]-4-uloside(**9**) was afforded in a 60% yield by the irradiation of **5** in **1**, followed by chromatographic separation. The NMR evidence for its structural determination is presented in Table 2. Two new *C*-methyl signals appeared at *δ* 1.61 (Me-4) and 1.47 (doublet, J_{CH-CH_3}=7.0 Hz, Me-1′) ppm besides those of the isopropylidene group. Moreover, 12% of the NOE was observed in the *H*-3 signal (*δ* 4.45 ppm) on irradiation at the methyl signal at *δ* 1.61 ppm.[8] From these data, the chirality at *C*-4 was thus established to be *R*. In the mass spectrum of this product, the peaks of *m/e* 242 (M^+-CH_3) and 226 (M^+-OCH_3) were observed as well as that of *m/e* 54 ($NC-C^+H-CH_3$), although no molecular ion peak was observed.

In order to elucidate the mechanism of these unusual photochemical reactions, the following examinations were carried out by the use of **3** as the model compound of the enoses to **1**. Each 10 mg portion of **3** was dissolved in **1** (0.5 ml) and treated under the following conditions, after which it was analyzed by glc. The dark reaction of the solution afforded no product, but resulted in a quantitative recovery of **3**. However, the treatment of **3** under dark conditions in **1**, which had previously been irradiated with a low-pressure mercury lamp for 30 hr afforded **7a** and **7b**, whose peaks were apparently observed in the glc of this reaction mixture in the same ratio as has been presented before. The peak of neither **3** nor of any other product could be detected in the chromatogram. An examination of the separately-photoirradiated **1** by ESR proved it to involve no radical species; however, the dark reaction with **3** in this **1** still afforded **7a** and **7b**. It is of interest, on the other hand, that the addition of an appropriate amount of liquid hydrogen cyanide to the system of the dark reaction resulted in the same results as were obtained in the photoinduced reaction of **3** in **1**. In view of the results reported by Ferrier *et al.*,[5a,9] boron trifluoride was also used in the above dark reaction in place of liquid hydrogen cyanide. It was, however, found to be too effective to give a mixture of the above products and a considerable amount of by-products, in spite of a short reaction period such as within 10 min.[10] In any case, the photochemical process conceivably takes place in the process of liberating a certain acidic species such as hydrogen cyanide from **1**, in considering that **1** is known to be equilibrated with a system of acetaldehyde and hydrogen cyanide in an aqueous solution.[11] Therefore, these reactions can be explained as the acid-catalyzed reactions of the enoses with **1**. The acid-catalyzed reaction of **2** or **3** with alcohols has already been shown to give the corresponding 2-enopyranosides.[5a,9] Either the formations of **6a** and **6b** or of **7a** and **7b** are thus conceivably brought about by a similar reaction process, and **4** may be interpreted to give **6a** and **6b** in terms of an acid-catalyzed *trans*-glycosidation reaction. Moreover, **5** can also be explained to afford **9** by such an acid-catalyzed reaction selectively; the sole formation of **9** can be assumed to arise from the stereochemical requirement of the carbonium ion, which was produced by the protonation on *C*-5 of **5**, which has a slightly pyramidal conformation of its quasi-*ribo* structure because of the potential repulsion with the endo-methyl group of the isopropylidene ring.

Experimental

Irradiations were carried out with a low-pressure mercury lamp (30 W) of the Riko Kagaku Co., Ltd. in a quartz-glass test tube at a distance of about 5 cm. Tlc's were carried out by the use of Wakogel B-5 and the solvent system of benzene–methanol (9: 1 v/v) for the development. The NMR spectra were taken with a Varian XL-100 appratus in deuterochloroform, using tetramethylsilane (TMS) as the internal standard. Glc was carried out with a Hitachi K-53 apparatus; column: 10% SE-30 on Chromosorb W (60—80 mesh); carrier gas: nitrogen under 1.5 Atm unless otherwise noticed; oven temperature: 200 °C, and injection temperature: 300 °C. The mass spectra were taken with a Hitachi RMU-6E appratus. The ESR spectrum was taken with a JOEL JEP-1X EPR spectrometer.

*1′-Cyanoethyl 4,6-Di-*O*-acetyl-2,3-dideoxy-α-(***6a***) and -β-*D-ery*thro-hex-2-enopyranoside (***6b***).* *A*) A solution of 3,4,6-tri-*O*-acetyl-D-glucal (**2**) (1.00 g) in lactonitrile (**1**) (12 ml) was irradiated with the UV lamp under a nitrogen atmosphere at room temperature for 27 hr, after which the volatiles were evaporated *in vacuo*. The residue was subsequently chromatographed on a silica gel (Mallinckrodt Silica Gel, 100 mesh) column, using benzene–acetone (49: 1 v/v) as an eluting solvent system; **6b** (485 mg, 47%) and **6a** (380 mg, 37%) were in turn eluted out separately. The retention volumes of **2**, **6b**, and **6a** in glc were, respectively, 1 (=1.1 min), 1.7, and 2.1. Specific rotations: **6a**: $[\alpha]_D^{22}$ +49.4° (*c* 1.0, Me_2CO), **6b**: $[\alpha]_D^{22}$ +78.2° (*c* 1.0, Me_2CO). Found: C, 54.87 (**6a**) and 55.32 (**6b**); H, 5.81 (**6a**) and 6.18 (**6b**); N, 4.98 (**6a**) and 4.73 (**6b**) %. Calcd for $C_{13}H_{17}O_6N$: C, 55.12; H, 6.05; N, 4.95%. The NMR data of **6a** and **6b** are presented in Table 1. Their mass spectral data are presented in Fig 1.

B) A solution of methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**4**) (1.00 g) in **1** (12 ml) was irradiated with the UV lamp under the same conditions as have been described above for 27 hr; the resultant solution was treated as in the previous experiment to afford **4** (30 mg, 3% recovery), **6b** (560 mg, 47%) and **6a** (480 mg, 40%).

*1′-Cyanoethyl 2,4,6-Tri-*O*-acetyl-3-deoxy-α-(***7a***) and -β-*D-ery*thro-hex-2-enopyranoside (***7b***).* A solution of 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal (**3**) (500 mg) in **1** (12 ml) was irradiated with the UV lamp under the same conditions for 27 hr, and the resultant solution was evaporated *in vacuo*.

The residual sirup was subjected to chromatographic separation in the way described previously to afford **7b** (205 mg, 40%) and **7a** (205 mg, 40%). The retention volumes of **3**, **7b**, and **7a** in glc were, respectively, 2.1, 4.7, and 4.8. Specific rotations; **7a**: $[\alpha]_D^{22}$ +95.2° (*c* 1.0, Me_2CO) and **7b**: $[\alpha]_D^{22}$ +25.0° (*c* 1.0, Me_2CO). Found: C, 52.50 (**7a**) and 52.80 (**7b**); H, 5.91 (**7a**) and 5.40 (**7b**); N, 3.86 (**7a**) and 4.27 (**7b**) %. Calcd for $C_{15}H_{19}O_8N$: C, 52.78; H, 5.61; N, 4.10%.

The NMR spectral data of **7a** and **7b** are presented in Table 1.

*1′-Cyanoethyl [Methyl (4R)-5-Deoxy-2,3-*O*-isopropylidene-β-*D-*erythro-pentofuranosid]-4-uloside (***9***).* A solution of methyl 5-deoxy-2,3-*O*-isopropylidene-*β*-D-*erythro*-pent-4-enofuranoside (**5**) (1.00 g) in **1** (15 ml) was irradiated with the UV lamp under a nitrogen atmosphere at room temperature for 41 hr; the resultant solution was then subjected to column chromatography after its concentration *in vacuo* to give **9** (840 mg, 60%). Its retention volume in glc was 2.5 with reference to that of **5**

(1.0) under 0.8 Atm of nitrogen gas. $[\alpha]_D^{22}$ +24.0° (*c* 1.0, Me_2CO). Found: C, 55.55; H, 7.42; N, 5.29%. Calcd for $C_{12}H_{19}O_5N$: C, 56.02; H, 7.44; N, 5.44%. The NMR spectral data of this product are presented in Table 2. Mass spectral data of this product: *m/e* 242 (M^+–Me), 226 (M^+–OMe), 187 (M^+–OCH(Me)CN), 54 (C^+H(Me)CN), and so on.

Reactions of 2,3,4,6-Tetra-O-acetyl-2-hydroxy-D-glucal (3) with Lactonitrile (1) under Dark Conditions. *A*) A solution of **3** (10 mg) in **1** (0.5 ml) was allowed to stand for 100 hr at room temperature in the dark under a nitrogen atmosphere. In the gas chromatogram of the resultant mixture, there are no detectable peaks except that of **3**.

B) Lactonitrile (**1**) (0.5 ml) was irradiated with the UV lamp for 30 hr at room temperature under a nitrogen atmosphere, and then **3** (10 mg) was dissolved in this **1**. The solution was allowed to stand for 30 hr under the same conditions as in the previous Experiment A. In the gas chromatogram of the resultant mixture, there are two peaks of the **7a** and **7b** products, but no peak of **3**.

C) Lactonitrile (**1**) (5 ml) was irradiated with the UV lamp much as has been described in the previous Experiment B, and then the resultant **1** was examined by ESR spectrometry.

No radical species were detected in variable measurements, even with the sensitivity of 10^{13} molecules. After these examinations, **3** (10 mg) was added to 0.5 ml of the recovered **1** and the solution was allowed to stand for 30 hr under the same conditions as in Experiment A. The gas chromatogram of the resultant mixture has the same pattern as that of Experiment B.

D) A solution of **3** (10 mg) in **1** (0.5 ml) containing a drop of liquid hydrogen cyanide was allowed to stand for 10 hr under the same conditions as above. In the gas chromatogram of the resultant mixture, there are two peaks of **7a** and **7b**, and a small peak of **3**. In another experiment involving three drops of liquid hydrogen cyanide, its gas chromatogram has only the peaks of **7a** and **7b** in the same reaction time.

E) A solution of **3** (10 mg) in **1** (0.5 ml) containing a drop of trifluoroboron-diethyl etherate (BF_3: OEt_2) was allowed to stand for 10 min under the same conditions as above. In the gas chromatogram of the resultant mixture, there are two peaks of by-products, two peaks of **7a** and **7b**, and no peak of **3**. In a reaction time of 1 hr, only the peaks of the by-products were detected. The retention volumes of the by-products in glc were 1.1 and crossed soon after (*cf.* **3**=2.1, **7a**=4.8, and **7b**=4.7). The conversion of **7a** and **7b** into the by-products was also confirmed by adding a drop of BF_3: OEt_2 to the solution of **7a** and **7b** in **1** (those substances had been obtained in Experiment B) and by then allowing the mixture to stand for 1 hr under the same conditions.

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