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# Stereoselective Photochemical Cyclization of 3-O-Benzyl-6-deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose Derivatives

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Photoirradiation of a solution of 3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose in benzene for 92 h gave (6S)-3,6-anhydro-1,2-O-isopropylidene-5-C-methyl-6-C-phenyl-α-D-gluco- and -β-L-idofuranose in 54% and 11% yield, respectively. Related photocyclizations and solvent effects in the reactions were also described.

Photochemistry of simple ketones[1)] and α-alkoxyketones[2,3)] bearing γ-hydrogen atoms is well established; an oxygen atom of photoexcited carbonyl abstracts a γ-hydrogen atom to give a biradical species which undergoes mainly Norrish type II elimination producing a smaller ketone and an olefin or a carbonyl compound. Accompanying cyclization of the biradical producing a cyclobutanol or 3-oxetanol derivative is a less effective process. Thus, the photocyclization reaction of ketones and α-alkoxyketones has limited synthetic utilities.

Suitable stereochemical or stereoelectronic arrangements, however, can make the photocyclization more effective; methyl and benzyl 2-benzyloxyphenylglyoxylate underwent photocyclization in greater than 90% yields (δ-hydrogen abstraction forming dihydrofuran-rings),[4,5)] and the photolysis of methyl 4,6-O-benzylidene-2-O-methyl-α-D-ribo-hexopyranosid-3-ulose gave the photocyclization product, 3-oxetanol derivative, in 65% yield, while the photolysis of the corresponding 2-epimeric arabino-isomer gave the elimination products exclusively.[6)]

Recently we have found that a carbon radical at 6-position abstracts a hydrogen atom from 3-O-benzyl methylene carbon in the course of the $Bu_3SnH$ - AIBN induced radical reactions of 5-O-acetyl-3-O-benzyl-6-deoxy-6-iodo-1,2-O-isopropylidene-α-D-gluco- and -allofuranose.[7)] Therefore, photoexcited carbonyl oxygen in the similar stereochemical arrangement such as in 3-O-benzylhexofuranos-5-ulose derivatives could abstract a hydrogen atom from 3-O-benzyl methylene carbon (δ-hydrogen abstraction) rather than from carbon-2 (γ-hydrogen abstraction). Whether the resulting biradical undergoes decomposition or cyclization is an interesting problem to us, because the cyclization will provide a new synthetic method for bicyclic higher-carbon sugars such as griseolic acids.[8)]

Photoirradiation[9)] of a solution of 3-O-benzyl-6-deoxy-1,2-O-isopropylidene-

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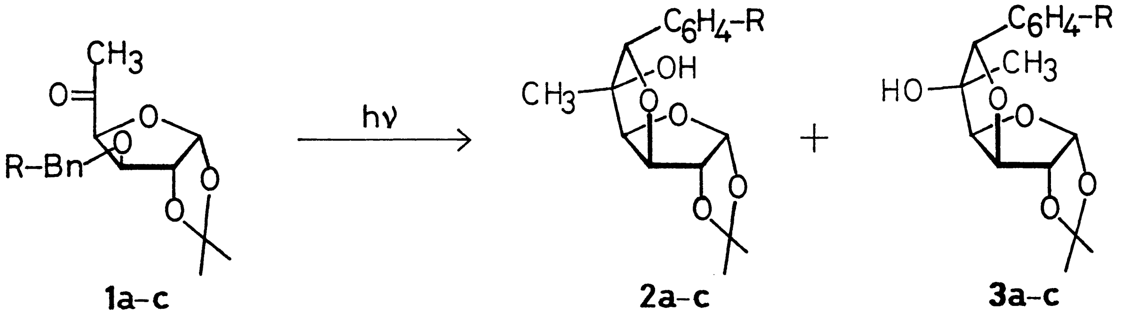
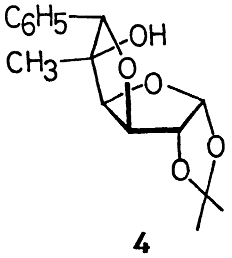
α-D-*xylo*-hexofuranos-5-ulose (**1a**)[10] in methanol for 28 h gave (6S)-3,6-anhydro-1,2-O-isopropylidene-5-C-methyl-6-C-phenyl-α-D-glucofuranose (**2a**)[11] (27% yield), (6S)-3,6-anhydro-1,2-O-isopropylidene-5-C-methyl-6-C-phenyl-β-L-idofuranose (**3a**)[11] (13% yield), and **1a** (36% recovery yield). The other two possible stereoisomers **4** and **5** were not isolated. Elongation of the irradiation time to 160 h brought about a moderate improvement; yields of **2a** and **3a** were up to 32% and 22%, respectively, and a recovery yield of **1a** was down to 5%. Benzene, acetonitrile, and acetic acid were also tested as reaction solvents. Among these solvents, benzene gave the best result both in yield and stereoselectivity. The elimination reaction or/and other decomposition reactions might occur as minor processes in the reactions from considerations of rather low material balance and tailings of the spots on TLC of the reaction mixture, but no decomposition product could be isolated. Thus the cyclization was shown to occur as a main process in these photochemical reactions.

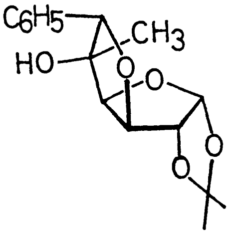


| **1** | | Solvent | Reaction time/h | Yield/% | | |
|---|---|---|---|---|---|---|
| | | | | 2 | 3 | 1 |
| **a** | R = H | MeOH | 28 | 27 | 13 | 36 |
| | | MeOH | 160 | 32 | 22 | 5 |
| | | $C_6H_6$ | 92 | 54 | 11 | traces |
| | | $CH_3CN$ | 122 | 39 | 10 | traces |
| | | HOAc | 110 | 40 | 14 | traces |
| **b** | R = 4-OMe | MeOH | 145 | 37 | 24 | 2 |
| | | $C_6H_6$ | 83 | 56 | 10 | 5 |
| | | HOAc | 157 | 12 | 7 | |
| **c** | R = 4-CN | MeOH | 102 | 45 | 20 | |
| | | $C_6H_6$ | 102 | 29 | 17 | |

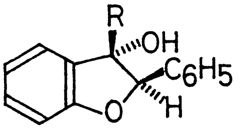
The stereochemical structures of **2a** and **3a** were determined on the bases of their $^1$H-NMR spectra[12] and polarities; a remarkable chemical shift difference between 5-C-$CH_3$ signals of **2a** and **3a** (**2a** : 1.42 ppm, **3a** : 0.98 ppm) and a large polarity difference between **2a** and **3a** (Rf values on silica gel TLC [hexane - AcOEt, 7 : 3], **2a** : 0.38, **3a** : 0.29) were observed. The chemical shift difference is most probably due to the anisotropic shielding effect of 6-C-phenyl ring on *cis*-$CH_3$ but not on *trans*-$CH_3$. Thus, the isomer with higher field signal of 5-C-$CH_3$ should be **3a** or **4**. The high polarity of this isomer ruled out the possibility of the structure **4**, because that the endo-OH in **4** is considered to be much less polar from the steric hindrance of the furanose ring and the hydrogen bonding effect with furanose ring oxygen. The observation of no NOEs on H-4 and on H-6 by the irradiation at 5-C-$CH_3$ agree well with the structure **3a**. In the other isomer with lower field signal of 5-C-$CH_3$, the hydroxyl group is in *cis*-relation to 6-C-phenyl (structure **2a** or **5**); thus it should resonate at higher field than that of **3a** in $^1$H-nmr by the shielding effect of the phenyl ring. The observed chemical shifts, however, were reversed (**2a** : 2.49 ppm, **3a** : 2.32 ppm). This fact is rationally explained by the effect of the hydrogen bond with ribofuranosyl ring oxygen in the structure **2a** ($\nu_{OH}$ in 0.03 mol $dm^{-3}$ solution in $CCl_4$, **2a** : 3550 $cm^{-1}$ and **3a** : 3610 $cm^{-1}$); the hydrogen bond strongly deshields the proton of OH and also fixes the proton at furthest distance from the benzene ring minimizing the shielding effect of the ring on the proton. And the observed NOEs on H-4 (3.5%) and on H-6 (3.5%) by the irradiation at 5-C-$CH_3$ in $C_6D_6$ agree well with the structure **2a**. Thus the structure of this isomer was decided to be **2a**. Similar shielding effects of benzene rings on *cis*-$COOCH_3$ protons and on a *cis*-OH proton and high polarities of less hindered hydroxyls were used as the stereochemical evidence for photocyclization product pairs of **6** and **7**,5) and **8** and **9**.13) For four membered cyclic compounds, cyclobutanols and 3-oxetanols, shielding effects of benzene rings on *cis*-$CH_3$ protons and on *cis*-OH protons and polarity differences of OH groups were also used as structural evidence.3)



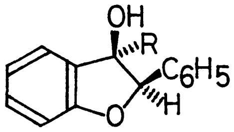
**4**



**5**



**6** R=$COOCH_3$
**8** R=H



**7** R=$COOCH_3$
**9** R=H

In order to know the electronic effects on the stereoselectivity of substituents on the benzene ring, reactions of 3-O-(4-methoxybenzyl) and 3-O-(4-cyanobenzyl) derivatives (**1b** and **1c**)10) were examined. Both compounds similarly underwent photocyclization to give **2b**11) and **3b**;11) and **2c**11) and **3c**,11) respectively. The stereoselectivities in the reactions of **1b** were nearly the same as those of **1a**, and that of **1c** in methanol was rather higher. On the other hand, the selectivity of the reaction of **1c** in benzene was low. From the consideration of the solvent effects in the reactions of **1a** and **1b** (the reactions in nonpolar solvent benzene most prefer the formations of less polar cyclization products **2a** and **2b**),14) the reaction of **1c** in benzene is expected to give **2c** more stereoselectively. The observed low stereoselectivity as well as the low material balance of the reaction of **1c** in benzene is probably due to much decomposition owing to the longer reaction time.

Thus the photocyclization of 3-O-benzylhexofuranos-5-ulose derivatives was shown to proceed effectively and to be used as a new synthetic method for bicyclic higher-carbon sugars.

## References

1) P. J. Wagner and G. S. Hammond, J. Am. Chem. Soc., 88, 1245 (1966); J. A. Barltrop and J. D. Coyle, ibid., 90, 6584 (1968); N. C. Yang and S. P. Elliott, ibid., 91, 7550 (1969); N. C. Yang, S. P. Elliott, and B. Kim, ibid., 91, 7551 (1969); P. J. Wagner, Acc. Chem. Res., 4, 168 (1971); H. Morrison, V. Tisdale, P. J. Wagner, and K.-C. Liu, J. Am. Chem. Soc., 97, 7189 (1975).

2) D. J. Coyle, R. V. Peterson, and J. Heicklen, J. Am. Chem. Soc., 86, 3850 (1964); P. Yates and A. G. Szabo, Tetrahedron Lett., 1965, 485; F. D. Lewis and N. J. Turro, J. Am. Chem. Soc., 92, 311 (1970).

3) R. B. LaCount and C. E. Griffin, Tetrahedron Lett., 1965, 1549.

4) S. P. Pappas, J. E. Alexander, and R. D. Zehr, Jr., J. Am. Chem. Soc., 92, 6927 (1970).

5) S. P. Pappas, B. C. Pappas, and J. E. Blackwell, Jr., J. Org. Chem., 32, 3066 (1967).

6) P. M. Collins, P. Gupta, and R. Iyer, J. Chem. Soc., Perkin Trans. 1, 1972, 1670.

7) Y. Araki, T. Endo, Y. Arai, M. Tanji, and Y. Ishido, Tetrahedron Lett., in press.

8) F. Nakagawa, T. Okazaki, A. Naito, Y. Iijima, and M. Yamazaki, J. Antibiot., 38, 823 (1985); S. Takahashi, F. Nakagawa, K.Kawazoe, Y. Furukawa, S. Saito, C. Tamura, and A. Naito, ibid., 38, 830 (1985).

9) Photoirradiations were conducted at room temperature using a water cooled 450 W high pressure mercury lamp with a pyrex glass filter under argon.

10) These hexofuranos-5-uloses were synthesized from the corresponding 3-*O*-benzyl- and 3-*O*-substitutedbenzyl-1,2;5,6-di-*O*-isopropylidene-α-*D*-glucofuranose by the sequence of the reactions; i) selective 5,6-de-*O*-isopropylidenation ($H_2O$ - HOAc, room temperature), ii) selective 6-*O*-tosylation (TsCl - $C_5H_5N$ / $CH_2Cl_2$, -65 °C), iii) reduction ($LiAlH_4$ / THF, room temperature and then reflux), and iv) oxidation (DMSO - TFA anhydride / $CH_2Cl_2$, -65 °C, and then $NEt_3$, -65 °C).

11) The structures of these compounds were confirmed by their ir and nmr spectra, and by their micro-elemental analyses.

12) $^1H$-NMR data of **2a** and **3a** (270 MHz, $CDCl_3$ - TMS); **2a**: $\delta$ 1.36, 1.56 (2×s, 2×3H, 2×isopropylidene-$CH_3$), 1.42 (s, 3H, 5-*C*-$CH_3$), 2.49 (s, 1H, OH), 4.57, 4.61 (2×s, 2H and 1H, respectively, H-3,4,6), 4.87 (d, 1H, $J_{1,2}$ 3.4 Hz, H-2), 6.06 (d, 1H, H-1), and 7.26 - 7.36 (m, 5H, $C_6H_5$); and **3a**: $\delta$ 0.98 (s, 3H, 5-*C*-$CH_3$), 1.37, 1.53 (2×s, 2×3H, 2×isopropylidene-$CH_3$), 2.32 (s, 1H, OH), 4.58, 4.74 (2×d, 2×1H, AB type $J$ 3.3 Hz, H-3,4), 4.85 (d, 1H, $J_{1,2}$ 3.6 Hz, H-2), 4.90 (s, 1H, H-6), 6.05 (d, 1H, H-1), and 7.20 - 7.34 (m, 5H, $C_6H_5$).

13) S. P. Pappas and J. E. Blackwell, Jr., Tetrahedron Lett., 1966, 1171.

14) Similar solvent effects as well as temperature effects (lower temperature also preferrs less polar products) in photocyclization reactions are known; see Ref. 5.

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