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Preliminary communication

A mild, photochemical process for the oxidation of nucleosides

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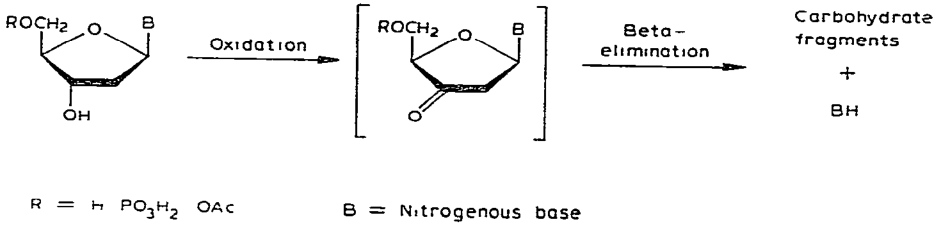
Several years ago, Pfitzner and Moffatt noted in their pioneering work on oxidation of nucleosides that a severe limitation existed to the successful synthesis of certain ketonucleosides* and ketonucleotides, particularly the 3′-keto compounds[1]. Oxidation of hydroxyl groups to carbonyl products, a logical process for obtaining keto derivatives, resulted in molecular decomposition of many compounds (such as thymidine 5′-phosphate, adenosine 5′-phosphate, uridine 5′-phosphate, 5′-*O*-acetylthymidine, and 5′-*O*-*p*-nitrobenzoylthymidine). To account for this instability, the reaction sequence shown in Scheme 1 was proposed[2]. [Subsequent research by Moffatt and coworkers showed that, in two examples where di-*O*-trityl derivatives could be formed (uridine[2] and *N*[4]-acetylcytidine[3]), oxidation produced keto compounds sufficiently stable for isolation.] It was clear that a significant need existed for an oxidation process sufficiently mild to permit general hydroxyl → carbonyl oxidation in nucleosides and their derivatives without further reaction. The research described here offers to meet this still-existing need with a recently developed, photochemical procedure[4].

Four nucleoside derivatives have been thus oxidized. Application of this process to 5′-*O*-tritylthymidine[5] (**1**) illustrates the procedure. A solution of 0.5 g (4.7 mmol) of pyruvoyl chloride[6] in benzene (5 ml) was added dropwise to a stirred solution of 0.5 g



Scheme I

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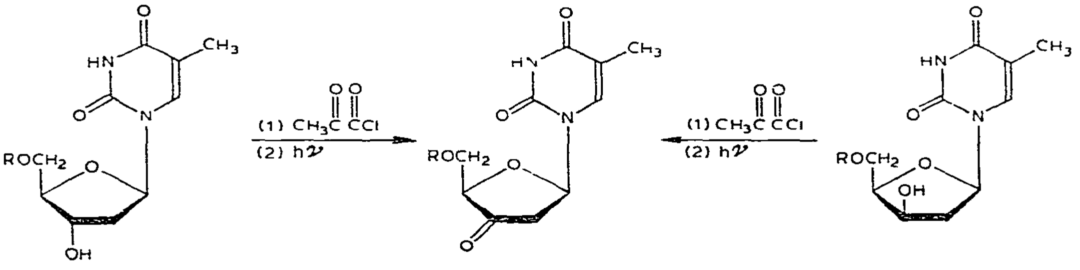
*Strictly *N*-[pentofuranosyl-2-(or 3-)ulose] derivatives.

(10 mmol) of **1** in 20 ml of anhydrous pyridine After 15 min, 50 ml of chloroform was added, the solution extracted with two 50-ml portions of water, and dried over anhydrous sodium sulfate Evaporation of the chloroform and pyridine *in vacuo* left a yellow oil that was dissolved in 350 ml of benzene, purged for one h with nitrogen, and irradiated for 1 5 h through a Pyrex filter with a 450-W Hanovia, medium-pressure mercury lamp The pale-yellow benzene suspension was filtered to remove a small amount of insoluble material, and the benzene was evaporated off *in vacuo* to leave a residue that was dissolved in 10 ml of chloroform After slow addition of 20 ml of carbon tetrachloride and keeping for 12 h, the photoproduct crystallized, m p 171–174°, ^{1}H n m r (60 MHz, $CDCl_3$) δ 8 55 (broad s, NH), 7 47–7 11 (m, aromatic and H-6), 6 55, 3 04, 2 85 (ABX pattern ($J_{1',2'}$ 7, $J_{1',2'}$ 8, $J_{2',2''}$ 9 5 Hz, H-1′,2′,2″), 4.14, 3 64, 3 36 (ABX pattern ($J_{4',5'} = J_{4',5''} = 3, J_{5',5''}$ 10 Hz, H-4′,5′,5″), and 1 52 (s, CH_3) Also, the photoproduct exhibited i r absorption at 1778 cm^{-1} (carbonyl group in a five-membered ring) The spectral evidence and the elemental analysis indicated the photoproduct to be 5′-*O*-trityl-3′-ketothymidine (**2**) This structure was confirmed by its reduction with sodium borohydride to yield exclusively 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine^7 (**3**) The yield of crystalline **2** from oxidation of **1** was 61%

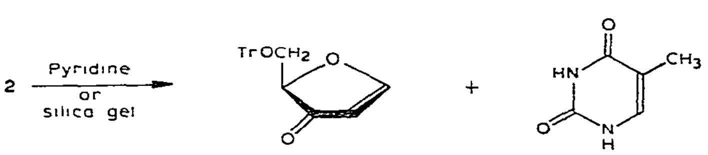
That the ketonucleoside **2** was unstable under certain, mild conditions was evidenced by the fact that dissolving **2** in pyridine at 25° or chromatographing it on silica gel resulted in quantitative formation of **7** and **8** The structure of **7** was determined from its elemental analysis, its ^{1}H n m r spectrum (C_5D_5N) δ 8 24 (d, $J_{1,2}$ 3 Hz, H-1), 7 50–6 76 (m, aromatic), 5 54 (d, H-2), 4 43 (t, $J_{4,5} = J_{4,5'} = 4$ Hz, H-4), and 3 33 (d, H-5,5′) and its independent synthesis by silica gel-catalyzed loss of methanol from methyl 2-deoxy-



1 2 3

4 5 6

1, 2 3 R = Tr , 4, 5 6 R = Bz



7 8

5-*O*-trityl-α-D-*glycero*-pentofuranos-3-ulose[8].

Three additional nucleoside derivatives have also been oxidized successfully by the photochemical oxidation procedure Compound **3** reacted to give **2** in 57% yield 5′-*O*-Benzoylthymidine[9] (**4**) was oxidized to a compound, m p. 87–92°, for which the structure 5′-*O*-benzoyl-3′-ketothymidine (**5**) was tentatively assigned on the basis of elemental and n m r analysis and analogy to the oxidation of compound **1**. The ^{1}H-n m r spectrum (60 MHz) of **5** showed absorptions at δ 8 94 (broad s, NH), 8.13–7 75 (m, *o*-aromatic), 7 65–7 11 (m, *m,p*-aromatic, H-6), 6 30, 3 04, 2 68 (ABX pattern $J_{1',2'}$ 7, $J_{1',2''}$ 6.5, $J_{2',2''}$ 10 Hz, H-1′,2′,2″), 5 03–4 24 (m, H-4′,5′,5″), and 1 62 (s, CH_3) The tentative assignment of structure **5** to the photochemical oxidation-product from **4** was confirmed by oxidation of 1-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine* (**6**) to the same product (**5**) under identical conditions The yields of **5** from **4** and **6** were 68 and 57%, respectively†

The successful oxidation of these four nucleoside derivatives demonstrates that the photochemical oxidation-technique is not only a mild process, but also one compatible with typical ester and ether protecting-groups The indications from this initial study are that photochemical oxidation should prove quite valuable for transforming nucleosides that cannot be oxidized successfully by existing techniques

ACKNOWLEDGMENT

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*Compound **6** was synthesized from 1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine[7] according to the procedure used by Baker and Neenan[9] to synthesize **4**

†The yields given are for material slightly contaminated with 5′-*O*-benzoylthymidine