New Photoisomerization of Provitamin D caused by Hydroxylation at C(1)

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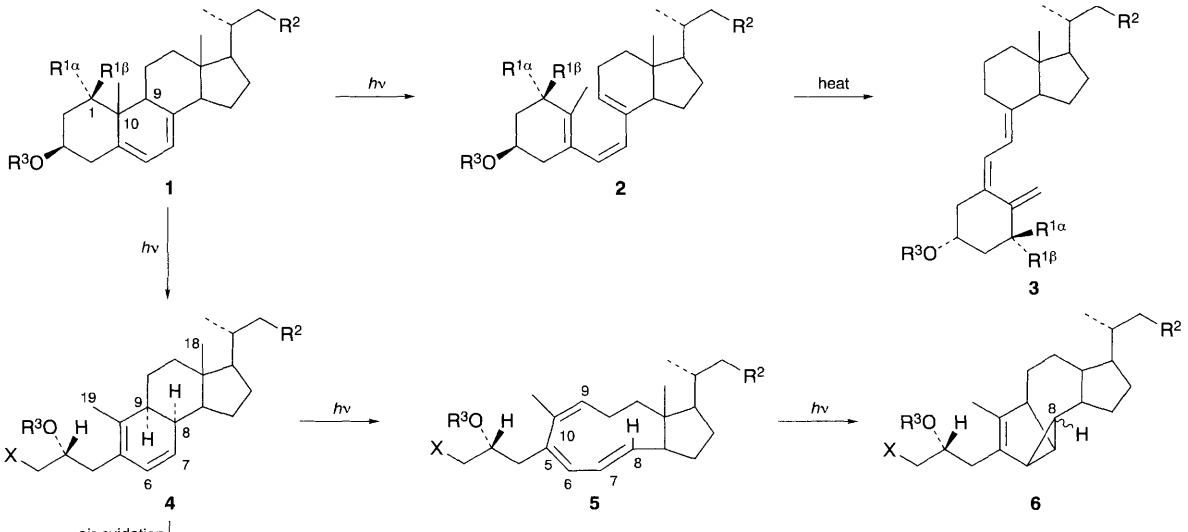
1α-Hydroxyprovitamin D is found to undergo a new photochemical isomerization cascade initiated by the 1,10-bond cleavage in addition to the normal electrocyclic B-ring opening and this new isomerization becomes the major pathway when a methyl group is present in the 1β-position.

The photochemical electrocyclic ring-opening[1] of a steroidal 5,7-diene is the key step in the synthesis of vitamin D (**3**) in the skin[2] as well as in laboratories. It has been known that 1α-hydroxylated provitamin D[3] undergoes the photoelectrocyclic reaction less efficiently than 7-dehydrocholesterol.[4] However, despite intensive studies on the photochemistry of provitamin D,[5] the related reaction of 1α-hydroxylated compounds has not been studied as much. We now disclose that the 1α-hydroxy group causes a series of new photochemical isomerizations of provitamin D.

The new isomerizations were first found in the photolysis of 1α-hydroxy-1β-methylprovitamins (**1a** and **1b**). Upon irradiation (medium-pressure lamp, in EtOH, THF, or THF–benzene, 0 °C), the provitamins (**1a** and **1b**) gave the expected previtamins (**2a** and **2b**) only in trace amounts (<5%) but furnished isomers **6a** and **6b**† in high yield (75–90%) (Scheme 1). When the irradiation of **1b** was terminated at an earlier stage, two additional photoproducts (**4b** and **5b**) could be isolated. More detailed studies showed that the primary photoproduct indeed is **4b** which upon further photolysis is converted to **5b** and then to **6b**. A significant NOE (10%) observed between CH_3(18) and H(7) suggested a *cis* BC-ring junction in **4b**. In **5b** a NOE (10%) between H(9) and CH_3(19) indicated the 9-*Z* geometry and that (7%) between H(8) and CH_3(18) the *s-cis* geometry of the 5,7-diene. It should be noted that each of the photoproducts **4**, **5** and **6** did not appreciably contain other stereoisomers as shown by HPLC analysis and ^{1}H and ^{13}C NMR spectra.

Similar photoisomerization was found to occur also with 1α-hydroxyprovitamin D (**1c**) itself. Thus, irradiation of **1c** under similar conditions gave a mixture of three new photoisomers (**4c**, **5c** and **6c**) in about 15% yield‡ in addition to the normal photoproducts (**2c** and its photoisomers, 70–80% yield‡). The structures of these photoisomers (**4c**, **5c** and **6c**) were determined after conversion to the alcohols, **4e**, **5e** and **6e**, to avoid hemiacetal formations. A 1β-hydroxy group did not cause such 1,10-bond cleavage: 1β-hydroxyprovitamin D (**1f**) gave exclusively the normal electrocyclic reaction products (90%)‡ upon photolysis. However the introduction of a 1α-methyl group caused 1,10-bond cleavage: irradiation (in THF–benzene) of 1β-hydroxy-1α-methylprovitamin (**1e**) gave 1,10- and 9,10-bond cleavage products in 41 and 45% yield,‡ respectively. The structures and the stereochemistries of the 1,10-bond cleavage products (**4b**, **5b** and **6b**) from **1e** were identical with those obtained from **1b**. The results indicate that H(8) in **4b** was derived not from the internal hydroxy group but from unavoidable moisture included in the solvent.

This new photoisomerization of 1α-hydroxy-1β-methylprovitamin D was completely inhibited upon protection of the hydroxy function showing that the 1,10-bond cleavage reaction requires a free hydroxy group at C(1). The irradiation of tris-MOM ether **1d** gave the previtamin D **2d** and its isomers as the



1–3a $R^{1\alpha}$ = OH, $R^{1\beta}$ = Me, R^2 = $CH_2CH_2CMe_2OH$, R^3 = H
b $R^{1\alpha}$ = R^2 = OH, $R^{1\beta}$ = Me, R^3 = H
c $R^{1\alpha}$ = R^2 = OH, $R^{1\beta}$ = R^3 = H
d $R^{1\alpha}$ = R^2 = OMOM, $R^{1\beta}$ = Me, R^3 = MOM
e $R^{1\alpha}$ = Me, $R^{1\beta}$ = R^2 = OH, R^3 = H
f $R^{1\alpha}$ = R^3 = H, $R^{1\beta}$ = R^2 = OH
4–7a X = COMe, R^2 = $CH_2CH_2CMe_2OH$, R^3 = H
b X = COMe, R^2 = OH, R^3 = H
c X = CHO, R^2 = OH, R^3 = H
d X = COMe, R^2 = OMOM, R^3 = MOM
e X = CH_2OH, R^2 = OH, R^3 = H

major products (about 50%) and none of the abnormal isomers (**4d**, **5d** and **6d**) have been detected. The rate of this photoreaction, however, was about 4 times slower than that of **1b**.

When **1c** was irradiated in the presence of D_2O (THF–benzene–D_2O, 10 : 24 : 0.05), one deuterium atom per molecule was incorporated into the 8-position in all photoisomers (**4c–6c**) as the MS and ^1H NMR spectra of **4e–6e** indicated.

The first step of this series of photoisomerizations is considered to be a photochemical variation of the β-hydroxy-olefin rearrangement.[6] The fact that both **1b** and **1e** gave the same photoisomer **4b** eliminates a mechanism involving intramolecular hydrogen shifts. This, together with the above deuterium incorporation experiment, suggests that this step proceeds through an ionic mechanism. A similar photochemical reaction in which 10,19 bond cleaves has been reported for 19-hydroxyprovitamin D.[7] The geometry of the AB-ring in the ground state§ as well as in the excited state¶ might play a role in determining which of the two pathways, 1,10- and 9,10-cleavage, predominates.

The subsequent isomerization of **4** to **5** is a 6π photochemical conrotatory electrocyclic reaction[1] and the stereochemical outcome supports the concerted mechanism. The isomerization of **5** to **6** is a typical intramolecular photochemical [π4s + π2a] cycloaddition.[1,10] Further mechanistic studies are in progress and the results will be reported in detail elsewhere.

Received, 21st November 1994; Com. 4/07098D

Footnotes

† Satisfactory analytical and spectral (^1H and ^{13}C NMR, IR, UV, mass and optical rotation) data were obtained for all new isolable compounds. The stereochemistries of the photoproducts were unequivocally determined as shown (Scheme 1) except for **6**.

‡ Yields based on the recovered starting material (20–30%).

§ In **1a** and **1b** the steric repulsion between the 1β-methyl group and $CH_2(11)$ changes the conformation of the provitamin D in favour of the 1,10-bond cleavage: the dihedral angles between the π lobe at C(5) and the 1,10- and 9,10-bonds in **1b** are calculated (MMX) to be 41 and 81°, respectively. Thus, according to the principle of least motion,[8] the 1,10-bond rather than 9,10-bond is predicted to be readily integrated into the π-bond system. This also explains the results of Paaren and Moriarty:[7] the 10,19-bond can be most readily integrated into the π system, since it is nearly parallel to the π lobe at C(5).

¶ The dihedral angles between the π lobe at C(5) and the 1,10- and 9,10-bonds do not explain the differences in the photochemical behaviours between **1c** and **1f**, and **1f** and **1e**, since in these provitamins those dihedral angles are not appreciably different from each other. The new mechanistic scenario proposed recently by Bernardi *et al.*[9a] for the photochemical transformation of provitamin D to previtamin D may explain these differences: MM-VB optimized geometry of the seco-B-ring at the conical intersection (a point where the excited and ground state energy surfaces are touching and where the photochemical reactions occurs) is twisted and the 1α-substituent is directed toward the CD ring. Therefore a bulky substituent at the 1α-position causes a steric congestion making the electrocyclic process less favourable.[9b]

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