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STUDIES ON VITAMIN D AND RELATED COMPOUNDS XXIV[1,2]
NEW IRRADIATION PRODUCTS OF PREVITAMIN D_3. TOXISTEROLS.

F. Boomsma, H.J.C. Jacobs, E. Havinga, and A. van der Gen

Gorlaeus Laboratories, Department of Organic Chemistry,
P.O. Box 75, University of Leiden, The Netherlands.

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In continuation of our investigations into the photoreactions and products originating from vitamin D_3[3,4] and from provitamin D_3 (7-dehydrocholesterol)[3,5] we wish to report on several products,- other than the known tachysterol$_3$, lumisterol$_3$ and 7-dehydrocholesterol -, formed upon irradiation of previtamin D_3. The presence of further compounds in the irradiation mixture has been described (e.g. toxisterol A[6], an isomer of previtamin D[7], and toxisterol B, an alcohol addition product[7]), but their structures have not been elucidated. Until now we have isolated and identified 6 compounds amongst which the product reported as toxisterol A and two others that resemble toxisterol B in being alcohol adducts.

In a typical experiment a solution of 1.5 g 7-dehydrocholesterol in 225 ml solvent was irradiated for 48 hrs (HP Hg arc, Pyrex apparatus). The temperature was carefully kept below 5°C to prevent the thermal conversion of previtamin D into vitamin D and subsequent photoreactions to suprasterols. The reaction mixture showed strong absorption at 244, 250 and 260 nm when the irradiation was carried out in alcoholic solvents (MeOH, EtOH, n-PrOH); irradiation of solutions in ether resulted in mixtures showing no well-defined UV-absorption maxima. Components were isolated and purified by repeated short-column chromatography (Kieselgel G, Merck).

The major component, C_1, of the irradiation mixtures (both in ether and in alcohol) is a bicyclo[3.1.0] hexene derivative: mp. 112°; R_F(benzene/acetone 9/1, silicagel) 0.63; MS:M^+ 384, base peak 351 (M - H_2O - CH_3); $[\alpha]_D^{22^\circ}$ ($CHCl_3$) + 141°; UV (EtOH) λ_{max} 227 nm (ε=6600); NMR (100 MHz, δ, $CDCl_3$): 0.57 (s, CH_3-18), 0.82 (s, CH_3-19), 3.50 (m, 3α-H), 5.01 (d, J=1.5, 7-H). The formation of the bicyclo[3.1.0] hexene skeleton can be rationalised as a cycloaddition starting from an excited 'tZc' conformer[3].

The stereochemistry of C_1 is of special interest. Owing to its substitution pattern the configuration of this product -an X-ray analysis of which is in progress- may be expected to yield more information on the mechanism of formation of the bicyclo[3.1.0] system, which may proceed by a symmetry-allowed and stereochemically feasible $\pi_s 4 + \pi_a 2$ process[8] or by a two-step reaction as described by Dauben et al[9]. There are indications that still another bicyclo[3.1.0] hexene derivative is present in the irradiation mixture.

The two irradiation products largely responsible for the absorption at 244, 250 and 260 nm are formed in alcoholic solution but not in ether. The two products are alcohol adducts (MS, NMR) similar to but not identical with the toxisterol B described by Westerhof[6]. They are assigned structures B_1 and B_2 on the basis of the following characteristics: UV λ_{max} 244, 250, 260 nm (similar to dihydrotachysterol[10]), ε_{250}= 33.10^3 (B_1), 25.10^3 (B_2); R_F(benzene/

acetone 9/1, silicagel) 0.42 (B_1), 0.46 (B_2); MS:M^+ 430; NMR (B_1-acetate): 0.56 (s,CH_3-18), 1.19 (t,J=7, $OCH_2\underline{CH_3}$), 1.49 (s, CH_3-19), 2.05 (s, 3-OAc),2.50-3.40 (m, 5 protons, $O\underline{CH_2}CH_3$, CH_2-4, 9β-H), 4.80 (m, 3-H), 6.20 and 6.34 (both d,J=11, 6-H and 7-H); NMR (B_2-acetate): 0.56 (s, CH_3-18), 1.17 (t,J=7,$OCH_2\underline{CH_3}$), 1.31 (s,CH_3-19), 2.05 (s, 3-OAc), 2.50-3.40 (m,5 protons, $O\underline{CH_2}CH_3$, CH_2-4, 9β-H), 4.58 (m, 3-H), 5.87 and 6.35 (both d,J=11,6-H and 7-H).

The choice between formulas B_1 and B_2 for the two adducts is mainly based on the chemical shifts of the CH_3-19 groups. In structure $B_1$$CH_3$-19 is situated in the deshielding region of the 5-6 double bond and should consequently resonate at lower field.

The formation of B_1 and B_2 can be visualized as resulting from 1,6-addition of alcohol to the excited triene system of previtamin D and/or tachysterol.

Two compounds were isolated with a relatively low retention volume. One was identified as toxisterol A by comparison of its IR and NMR data with those of a sample isolated in earlier investigations by Stiefelhagen[7], which had been checked against an authentic sample provided by Westerhof[6].

Although the UV-spectrum of this compound - henceforth called toxisterol A_1 -strongly resembles that of 'cis-isotachysterol'[11], an 8 (14)-previtamin D-isomer, no double bond isomerization could be observed upon treatment with $I_2/h\nu$.

A_1 and A_2 show very similar spectral properties, such as a characteristic doublet of triplets for the C-3-proton, as results from coupling with one equatorial and two axial protons. The allylic CH_3-19 protons are coupled with the (axial) proton at C-4. The coupling pattern of the vinylic protons (A_2) and the position of the UV-maxima indicate the presence of one of the conjugated double bonds in a 5-membered ring. ^{13}C-NMR reveals the presence of a new quaternary centre (C-8).

We feel that these characteristics are best accomodated by assuming a spiro structure as depicted in $A_{1,2}$ for both compounds, the differences between A_1 and A_2 resulting from the position of the A/B part relative to the C/D part of the molecule. The assignment of configuration at C-8 awaits further spectral information.

Some characteristic data are:

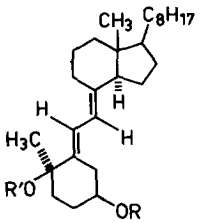
Toxisterol A_1. mp 94.5° - 96.5°C ; R_F(benzene, silicagel) 0.57; UV λ_{max} 251 nm, ε=14.2 x 10^3; MS M^+ 384, NMR. 0.89 (s, CH_3-18), 1.67 (d, J=1 5, CH_3-19), 2.51 (d, J=11,4-H), 3.85 (d of t, J=3.5 and J=11,3-H), 6.27 (s,6-H and 7-H), double resonance irradiation at 2.51 changes the signal at 3.85 into a d of d (J=3 5 and J=11) and the signal at 1 67 into a s, while irradiation at 3.85 results in a broad s at 2.51. ^{13}C-NMR shows two quaternary sp_3-atoms and four sp_2-atoms, two of which carry one, and two other no hydrogen atom.

Toxisterol A_2. R_F (benzene, silicagel) 0 31, UV λ_{max} 251 nm, ε= 13.3 x 10^3; MS M^+ 384; NMR. 0.90 (s, CH_3-18), 1.67 (d,J=1.5, CH_3-19), 3.81 (d of t, J=3.5 and J=11, 3-H), 6.06 and 6.33 (both d, J=5,6-H and 7-H). On 3,5-dinitrobenzoylation the 4-H signal appears at 2.70 (d,J=11) and the CH_3-18 shifts to 0.69.

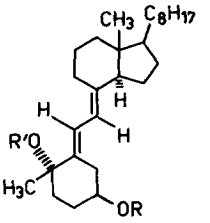
A fourth category of irradiation products (D-series) arises from shifts and Z-E isomerizations of double bonds. One isomer (D_1) has been completely characterized so far[12] Relevant data are R_F (benzene/acetone 9/1, silicagel) 0 71, MS M^+ 384; UV (EtOH) shoulder at 217 nm (ε=7000)[13], NMR 0.67 (s, CH_3-18), 2 83 (CH_2-7), 3 92 (m, 3α-H), 4.73 and 4 93

(both d, J=3, CH_2-19), 5.20 (m, 9-H), 5.34 (t, J=8,5-H); IR: 3075, 1640, 900 cm^{-1} (=CH_2); mp. (3,5-dinitrobenzoate): 108.5°- 109.5°C.

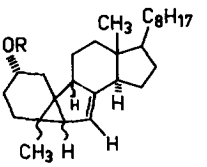
D_1 is most probably formed by a symmetry-allowed photochemical antarefacial [1,5] - H shift. This nicely complements the smooth thermal [1,7] shift towards vitamin D that must occur in an antarafacial manner.



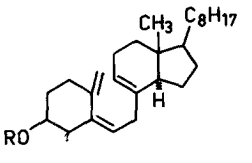
B_1



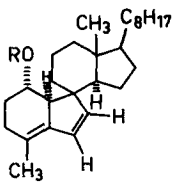
B_2



C_1



D_1



$A_{1,2}$

R=H, R'=C_2H_5

On the basis of results with simple model systems[14] and the chemical reactivity of some products obtained by irradiation in ether, we expect cyclobutene and bicyclobutane derivatives also to occur in the irradiation mixtures of previtamin D.

Possibly with previtamin D we have the interesting situation of a compound that in the groundstate occurs essentially in one form, strongly librating about the bonds 5/6 and 7/8. Upon light absorption it gives rise to two distinct excited species, corresponding to a 'cZc' and 'tZc' conformation. Each of these species may relax to form various products, some of which undergo further (photo)isomerisation.

The present investigation reveals the importance of cycloaddition to form bicyclo[3.1.0]hexene derivatives (toxisterols C), besides the reactions leading to the three classical photoproducts of previtamin D. Furthermore we are able to account now for the occurrence of UV absorption around 250 nm, repeatedly reported in literature, and ascribed to the formation of toxisterols. These are due to cyclopentano-spiro compounds (toxisterols A, absorption maximum at 251 nm) and alcohol adducts (toxisterols B, three-top spectra in the 240-260 nm region) Finally there exists a category of photoproducts (toxisterols D) consisting of isomers with a conjugated or deconjugated triene system. Thus a major gap that was remaining in the pattern of (pre) vitamin D photochemistry[3] is rapidly being filled.

Notes and references.

1. Previous communication: ref. 5.
2. A detailed report will be given in: F. Boomsma, thesis, Leiden, to be published.
3. For a review see: E. Havinga, Experientia 29, 1181 (1973).
4. S.A. Bakker, J. Lugtenburg, E. Havinga, Rec.Trav.Chim. 91, 1459 (1972).
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7. G.M. Sanders, J. Pot, E. Havinga, Progress Chem.Org.Nat.Products XXVII, 131 (1969).
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11. A. Verloop, G.J.B. Corts, E. Havinga, Rec.Trav.Chim, 79, 164 (1960).
12. Recently obtained data indicate the presence of a second compound of this series in the irradiation mixture, having a conjugated triene system with λ_{max} 288 nm.
13. Cf. 1,2-dimethylenecyclohexane. λ_{max} 220 nm, ε=5500.
14. P.J. Vroegop, J. Lugtenburg, E. Havinga, Tetrahedron, 29, 1393 (1973).