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THE ABSOLUTE CONFIGURATION OF C-25 EPIMERS OF 25,26-DIHYDROXY-CHOLECALCIFEROL BY X-RAY DIFFRACTION ANALYSIS

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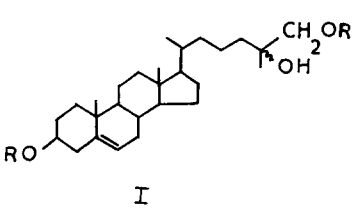
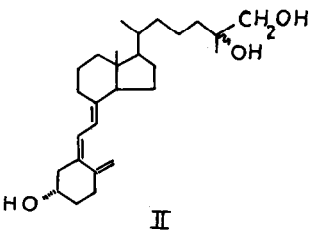
One of us has described[1] the synthesis of 25,26-dihydroxy-cholecalciferol (II), a metabolite of vitamin D_3. The poor stereoselectivity led to mixture of epimers at C-25. Recently, the resolution of epimers by HPLC at the intermediate stage of 25,26-dihydroxycholesterol 3β,26-diacetate (I, R = Ac) was reported [2]. As their configuration could not be elucidated by chiroptical methods, both epimers were characterized according to their polarity : the less polar - 25ξ[1] and the more polar - 25ξ[2]. They were then transformed[2] into 25ξ[1],26- and 25ξ[2],26-dihydroxycholecalciferol (II) respectively.

Their marked difference in biological activity[2] and the known[3] relation between C-24 chirality and biological response for 24-hydroxyvitamin D_3, rendered urgent the determination of the configuration at C-25 by X-ray studies.

The less polar epimer 25ξ[1](I, R = Ac) was saponified with methanolic KOH. That no epimerization occured was demonstrated by HPLC after reacetylation. The obtained 25,26-diol (I, R = H) was slowly recrystallized from methanol, Mp 199°.



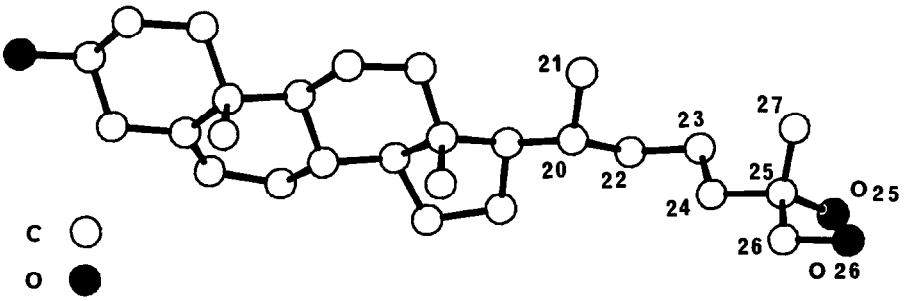
I



II

The crystals are monoclinic, space group $P2_1$. The cell parameters are a = 15.678, b = 6.055, c = 13.983 Å, β = 102.17° ; Z = 2. The diffraction data were collected with a 4-circle diffractometer, using θ/2θ scan technique and CuKα radiation. The crystal structure was solved using both direct methods (MULTAN[4]) which gave a translated part of the steroidal

skeleton, and Patterson-search method[5] which permitted the determination of the whole structure. The refinement was performed with the least-squares method to a R-value of 6.0% with 1189 observed reflexions[6].



The oxygen atoms 25 and 26 are in staggered position (64°) and no intramolecular H-bond can exist. Two intermolecular H-bonds link OH-25 to O-3 and O-26 to OH-3 of two different molecules, contributing to the crystal cohesion.

This X-ray determination gives the relative configuration of all chiral centers and thus the absolute configuration at C-25 is established through the known structure of the rest of the molecule.

We conclude that the 25ξ^1 epimer (I, R = H) has a 25 S-configuration and consequently 25ξ^1,26- and 25ξ^2,26-dihydroxycalciferol (II) are 25S,26- and 25R,26$(OH)_2D_3$ respectively.

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6. Atomic coordinates, thermal parameters and tables of bond lengths, bond angles and structure factors are available from one of the authors (M.C.).