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REMARKS ON THE SPECIFICITIES OF THE PHOTOCHEMICAL AND THERMAL TRANSFORMATIONS IN THE VITAMIN D FIELD

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Abstract—A discussion is given of some mechanistic aspects of the photochemical and thermal isomerization reactions occurring in the vitamin D field. Possible explanations of the stereochemical specificities of these reactions are tentatively put forward.

IN a preceding publication the knowledge obtained thus far with regard to the main reaction paths and the stoichiometry of the—chiefly photoinduced—transformations in the vitamin D field were summarized (cf. Fig. 1).[1]

Whereas satisfactory completion of the investigations into these aspects was considered to be attainable within the near future, the remarks made at that time on

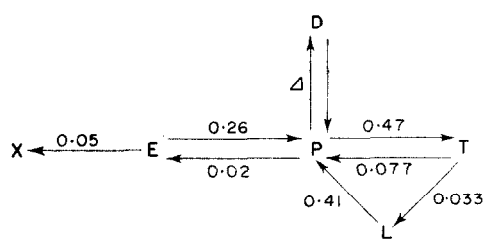

FIG. 1. The essential photochemical transformations of ergosterol and its isomers with quantum yields at 2537 Å and the thermal equilibrium between precalciferol and calciferol*.

the mechanisms of the reactions were still of a rather general nature. The only reaction for which a more detailed picture could be advanced was the *cis/trans* isomerization. A few crucial questions regarding the mechanism and the stereochemical specificity of the transformations were formulated. In this paper these questions are discussed and hypotheses are proposed which may constitute a basis for understanding the factors involved in determining the course of the reactions.

A. *The nature of the photochemical intermediates*

As has been reported earlier, experimental indications for the occurrence of a triplet state could not be obtained; no phosphorescence was detected during illumination of any of the compounds E, L, T or P in glasses at low temperatures. All compounds (except P) showed fluorescence spectra which can be attributed to transitions from the lowest excited singlet state to various levels of the ground state.

We wish to add another argument in favour of the idea that the first excited singlet states of the molecules function as the intermediates and that assumption of the occurrence of triplet states seems as yet unnecessary. The excited *cis*- and *trans*

[1] E. Havinga, R. J. de Kock and M. P. Rappoldt, *Tetrahedron* **11**, 276 (1960); more detailed information is given in R. J. de Kock, G. v. d. Kuip, A. Verloop and E. Havinga, *Rec. Trav. Chim.* **80**, 20 (1961); M. P. Rappoldt *Ibid.* **79**, 1012 (1960); and earlier papers published in *Rec. Trav. Chim.*

isomers P* and T* are different in that they undergo ring closure to different products, i.e. mainly to ergosterol and to lumisterol, respectively. If triplet states (that are known to be rather long lived; $\sim 10^{-6}$ sec to several seconds) were intermediates, one could expect the differences between the rotational isomers P* and T* to have levelled off in the early period of their existence. The P* and T* particles, thus having "forgotten" their configurationally different origin should give rise to the same products. The specificities observed seem to be more in line with the occurrence of a rather short lived intermediate as a molecule in the excited singlet state mostly is. On the other hand the lifetime of such a singlet state can still be sufficient (10^{-10}–10^{-7} sec) to permit the occurrence of structural and configurational changes. Further experimental evidence for the hypothesis that excited singlet rather than triplet states function as the intermediates in these photochemical reactions, is still required. A study of the influence of substituting deuterium for hydrogen in the chromophoric part of the molecules may provide additional information on this point.

B. *The photochemical ring closure of precalciferol and tachysterol*

One of the problems arising from the analytical studies on the photochemical transformations of the *cis/trans* isomers P and T concerns the question of why T upon irradiation undergoes ring closure to L and not to E whereas photoexcited P yields E.[2] According to the investigations of Castells *et al.*[3] L is configurationally the mirror image of E with regard to the atoms 9 and 10 between which bond formation occurs during ring closure. Inspection of the various conformations of the ground states and the excited states of T and P affords a way of understanding the observed specificities.

From Fig. 2 we see that the four (almost) planar conformations of T, that are interconvertible by rotation around the bonds (5,6) and (7,8), give rise to four different excited states. In the latter, rotation around the bond (6, 7) will be possible and rotation will be difficult around the bonds(5,6) and (7,8) which now have greater double bond character. It is clear that of those 4 stereoisomers only B*—upon rotation around (6,7)—will be able to transform into a cyclohexadiene derivative with a bond between C_9 and C_{10}. A* and B* may isomerize into the *cis* form, while C* and D* can only return to tachysterol in its ground state either with or without emittance of radiation.[4] Of course, the latter possibility is also open to A* and B*. The first tentative inference from these considerations could be that the quantum yields for the conversions T → P and T → ring closed isomer will not be high, the *trans* → *cis* isomerization probably having a larger probability than the cyclization. This is in harmony with the experimental data (Fig. 1). Upon looking more closely into the possibilities of ring closure for B* it becomes clear that the approach of atoms 9 and 10 effected by rotation around (6,7) is such that the anti-orientation of the C_{19} methyl group and the hydrogen atom at C_9 will necessarily result upon the formation of the bond between C(9) and C(10). Furthermore, examination of the two possibilities

* The following abbreviations will be used in this paper: D = vitamin D_2 (ergocalciferol); E = ergosterol; L = lumisterol$_2$; P = pre-ergocalciferol; T = tachysterol$_2$; X = "over-irradiation products".

[2] The efforts to trace lumisterol as a direct photoproduct of precalciferol gave negative indications thus far (cf. 1.c.1) but will be continued.

[3] J. Castells, E. R. H. Jones, R. W. J. Williams and G. D. Meakins, *Proc. Chem. Soc.* 7 (1958); *J. Chem. Soc.* 1159 (1959).

[4] For the moment we omit from the discussion the dimerization reactions and other transformations leading to what are commonly called overirradiation products[5]; cf. P. Westerhof, J. A. Keverling Buisman, *Rec. Trav. Chim.* **75**, 1243 (1956).

of approach for C(10) and C(9) teaches that the one resulting from rotation around (6, 7) in such a sense that C(10) attacks from above, will be sterically hindered, notably by the interaction of the two methylgroups (C(19) and C(18)). Rotation in the other sense and attack from below ('rear attack') does not encounter serious steric hindrance.

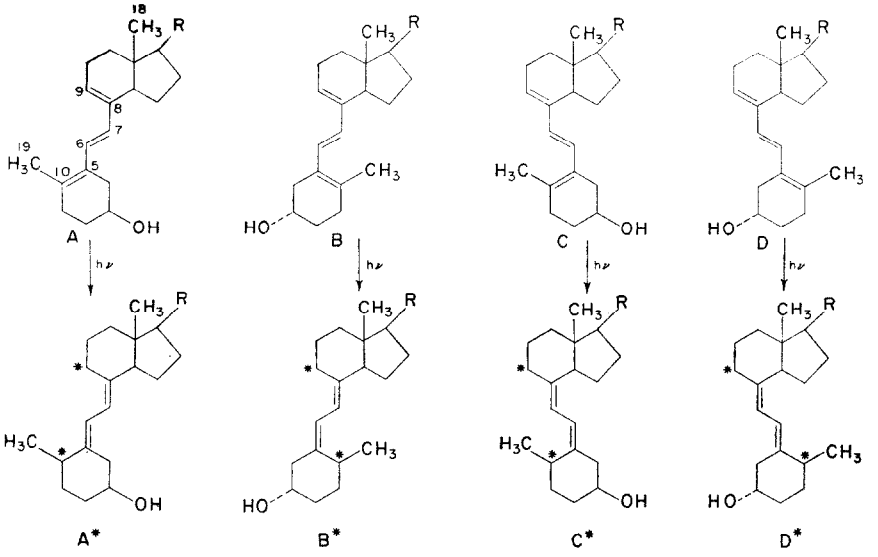

FIG. 2. Schematic representation of conformations of the ground state of the (6,7) *trans*-isomer tachysterol and of the corresponding excited states. A 'formal' bond that may be conceived in the excited states is indicated by marking the atoms 9 and 10 with an asterisk. The representation of single and double bonds in the excited states serves only to indicate possibilities of relatively easy and of more difficult rotation around these bonds.

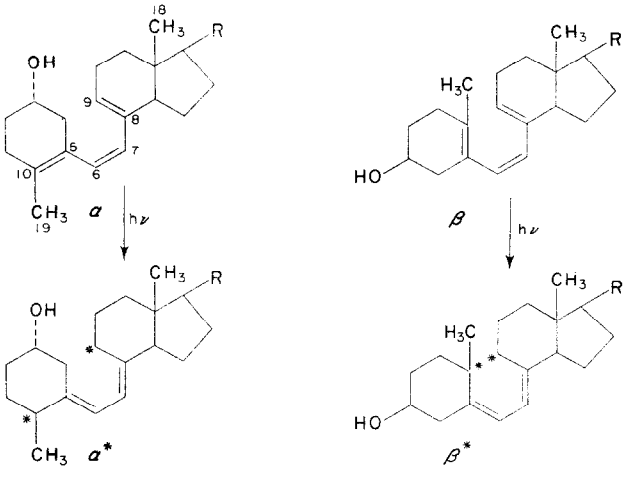

FIG. 3. Schematic representation of conformations of the (6,7) *cis* isomer precalciferol and of the corresponding excited states.

As the latter possibility leads to the formation of lumisterol, the—at first sight puzzling—preferential formation of this isomer from T* is to be expected.

The situation in the case of the precalciferol molecule is probably even more complex. In the ground state conformation α seems to be the relatively least hindered

one; β can exist only in a form deviating considerably from planarity. Conformations derivable from forms C and D of tachysterol (Fig. 2) by rotation around (6,7) will hardly play a role. Both forms α^* and β^* may—besides returning to unexcited P—transform into T upon rotation around (6,7). However, formation of a cyclohexadiene derivative is possible only to β^* that originates from conformation β, which is considered to be unfavourable on account of strong hindrance to planarity. The experimentally established small quantum yield for the ring closure reaction and the high quantum yield for the formation of T (Fig. 1) are therefore in accord with theoretical expectation. For the same reason as in the instance of the excited tachysterol, cyclization of β^* will result in a steroid having *anti* orientation of the methylgroup and the hydrogen atom at C(10) and C(9), respectively. However, the situation with β^* derived from P is more complicated than with B* resulting from excitation of T. One may speculate here on the existence of two variants of β (and of β^*) originating from ring opening of ergosterol and of lumisterol, respectively (see below). It is difficult to deduce which of those two 'enantiomeric' forms of β predominates normally in precalciferol or which of the corresponding β^* forms will be the most reactive in the cyclization reaction. Moreover, it has been argued[5,6] that a *cis* isomer like P—in contradistinction to the *trans* isomer T—upon taking up a quantum of light gives rise to a conformation of the excited state of relatively high energy content which makes predictions of the specificity of ring closure still more difficult. Experimental results point to formation of E from excited P. Attempts at theoretical deduction in this case lead to rather far fetched speculations and give no really pertinent indication why L could not also be formed. It is to be hoped that a careful analytical investigation into the formation or non-formation of L from P* will provide the factual basis necessary for a fruitful discussion of this remaining question.

C. *Photochemical transformation of ergosterol, lumisterol, pyrocalciferol and isopyrocalciferol*

As has been mentioned before there is no special difficulty in understanding the photo induced opening of ring B of ergosterol and lumisterol, this being a reaction

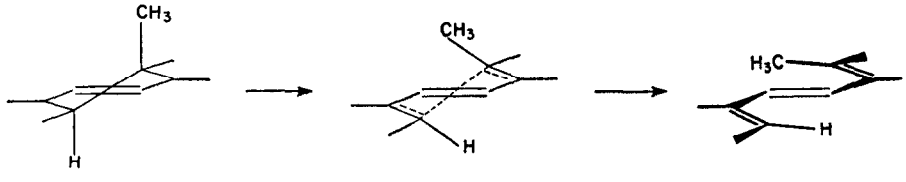

FIG. 4. Photochemical splitting of the 9,10 bond in ergosterol and comparable $\Delta^{1,3}$ cyclohexadiene derivatives.

commonly found with cyclohexadiene and cyclohexadiene derivatives (cf. l.c.1).[8–10,17]

The formation of the *cis* isomer precalciferol as the primary reaction product is to be expected according to the reaction path depicted in Fig. 4. Tachysterol is formed

[5] Cf. R. J. de Kock, G. van der Kuip, A. Verloop, and E. Havinga, *Rec. Trav. Chim.* **80**, 20 (1961).
[6] G. Riezebos and E. Havinga, *Rec. Trav. Chim.* **80**, (1961); **80**, 446 (1961); G. Riezebos, thesis, Leiden (1959).
[7] With simpler molecules such as cyclohexadiene itself only the *trans*-isomer was found as a product. The question whether in these cases, as with the formation of T from E or L, the *trans* compound is also a secondary product originating from the primarily formed *cis* hexatriene cannot yet be answered.[8]
[8] R. J. de Kock, N. G. Minnaard and E. Havinga, *Rec. Trav. Chim.* **79**, 922 (1960).
[9] D. H. R. Barton, *Helv. Chim. Acta* **42**, 2604 (1959).
[10] R. Srinivasan, *J. Amer. Chem. Soc.* **82**, 5063 (1960).

secondarily from precalciferol.[7] In relation to the discussion of the photocyclization of precalciferol (sub B) it is noteworthy that the ring opening of E and L should primarily yield two different conformations of P which might even prove to be relatively stable and non-interconvertible at low temperature.

The two isomers pyro- and isopyrocalciferol having syn arrangement of the methylgroup and the H-atom at 10 and 9, respectively,[3] are photochemically converted into products that according to Dauben and Fonken[11] possess bicyclohexene structures as indicated for the 9β, 10β (isopyro) series in Fig. 5.

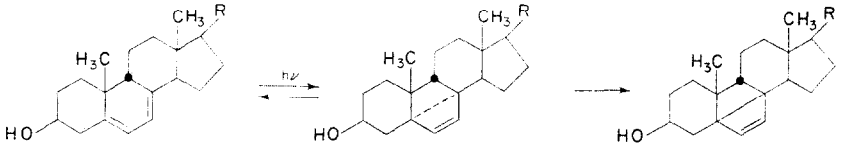

FIG. 5. Photochemical transformation of isopyrocalciferol into photoisopyrocalciferol according to Dauben and Fonken.[11]

Dauben and Fonken point out that formation of such a bicyclohexene derivative is difficult in the case of the *anti* isomers E and L. The following consideration may give some suggestion as to why these compounds do not also form hexatriene derivatives. The syn arranged methylgroup and hydrogen at 10 and 9 respectively, will sterically hinder a mechanism of ring opening that is natural to excited E and L and whereby the atoms 10 and 9 separate smoothly, the one moving to a position in front of the molecule and the other to the rear side. On the other hand, the *syn* arrangement at 9 and 10, together with the fact that bonds (5,10) and (8,9) form part of cyclohexane ring systems, will in the excited state favour relative movements of the atoms 5 and 8 and of the groups attached to these atoms in such a sense that e.g. in the isopyro series the 'rear sides' are oriented towards each other. The situation thus becomes favorable to the approach and bond formation between atoms 5 and 8, a process that is furthered by the symmetry characteristics of the orbital of the promoted electron in the butadiene system. Although it would seem rash to consider this qualitative reasoning as sufficient to explain the fact that photochemical ring opening does not occur to any detectable extent with pyro- and isopyrocalciferol[12], it may indicate the line along which a more rigorous treatment could clarify the preference for formation of the bicyclohexene systems in the case of these *syn* substituted cyclohexadiene derivatives.

D. *The specificity of the thermal reactions of (pre)calciferol*

It has previously been suggested that the formation of pyro- and isopyrocalciferol, brought about by heating (pre)calciferol in a neutral medium at 150–200°, starts from the precalciferol molecules (Fig. 6).[13] This assumption seems strengthened by the recent finding that in the case of a synthetic calciferol analog, where the P $\rightleftarrows$ D equilibrium proved to be strongly in favour of the precalciferol form (cf. sub E), the change in the spectra upon heating indicated a smooth thermal cyclization.[14] In order to understand why this thermal cyclization, in contradistinction to the photo induced ring closure leads specifically to the 9,10 *syn* compounds, one has to bear in mind

[11] W. G. Dauben and G. J. Fonken, *J. Amer. Chem. Soc.* **81**, 4060 (1959).
[12] R. van Moorselaar, Thesis Leiden (1961) to be published.
[13] A. Verloop, A. L. Koevoet and E. Havinga, *Rec. Trav. Chim.* **76**, 689 (1957).
[14] J. L. M. A. Schlatmann, Thesis Leiden (1961).

that here it is rotations around the bonds (5,6) and (7,8) that give rise to the conformations in which bond formation between 9 and 10 may directly originate. It is tempting to look for an explanation of the observed stereospecificity in considerations analogous to those that have been used for the Diels–Alder diene synthesis. If one

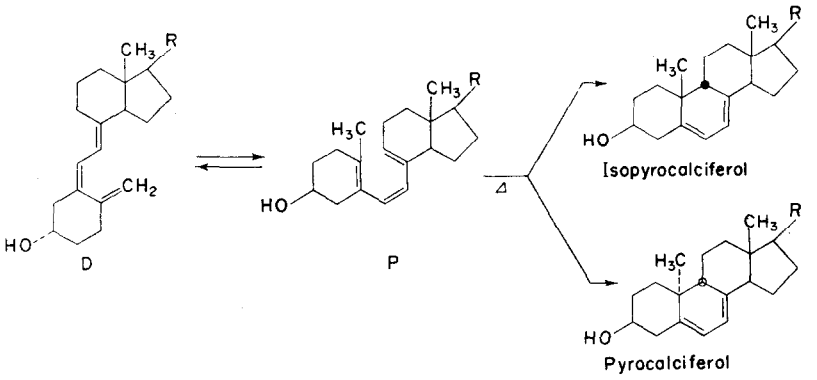

FIG. 6. Formation of pyro- and isopyrocalciferol by thermal cyclization of precalciferol.

postulates that the atoms 9 and 10 should approach each other in such a way that there is maximum overlap of the π electron clouds of the double bonds (10,5) and (8,9) it is seen (e.g. with the aid of molecular models) that only *syn* structures will result.

As Prof. Oosterhoff pointed out, another factor that possibly contributes to the stereochemical difference between the thermal and the photo induced ring closure may be found in the symmetry characteristics of the highest occupied π orbital of the conjugated hexatriene system. In the photo excited state this highest occupied orbital is antisymmetric with regard to the plane that is perpendicular to the bond 6,7 making '*syn*' approach less favourable.

E. *Some remarks on the previtamin D ⇄ vitamin D reaction*

To complete the survey of results and ideas bearing on the various isomerization reactions in the vitamin D field, it is of interest to summarize briefly some of the data obtained with the study of two calciferol analogs of the formula represented in Fig. 7.[14]

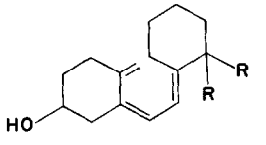

FIG. 7.

These synthetic compounds show the same remarkably smooth isomerization to the corresponding precalciferol analogs as is found with calciferol itself. A difference exists in that the equilibrium with the synthetic compounds lies farther to the precalciferol side; this may in part be due to the relatively greater entropy of the precalciferol analog. Furthermore, the features found with the calciferol ⇄ precalciferol

reaction could be corroborated and additional data were obtained. The reaction rate proved to be independent of the solvent, the presence of light, and the nature of the wall (glass or steel) of the vessel. It could not be influenced by acids or bases or a combination of acid and base nor could it be retarded by inhibitors that are known to affect free radical chain processes. From the variations with temperature of the rate constant of the first order reaction the energy of activation was calculated to be 18 Kcal/mol and the activation entropy ~ -20 e.u. Deuterium was not incorporated when a solution of calciferol acetate in a mixture of CH_3OD and benzene was kept at 70° for several hours. These data together with the fact that the isomerization is found

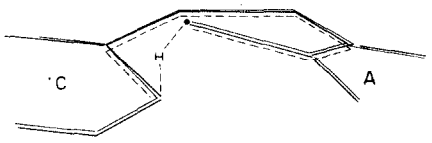

FIG. 8. Model for the transition state of the P ⇄ D reaction.

only with triene derivatives having *cis* configuration at the central double bond, point to an intramolecular reaction that occurs via a rigid cyclic transition state with simultaneous bond breaking and bond formation (Fig. 8). This mechanism is essentially the same as the one postulated tentatively in a former publication[15] and the one proposed by Legrand and Mathieu.[16] The reaction seems to occur normally with molecules containing a 6-methyl, $\Delta^{3,5}$ *cis*, hexatriene (1,3,5) system.[17]

It may be added that the analogs also seem to show the other reactions encountered with (pre)vitamin D. Upon irradiation of a solution containing a precalciferol analog with ultraviolet light the absorption spectrum changed into a three peak spectrum indicating isomerization to the tachysterol analog. Heating at 180° seemingly effected ring closure to an (iso)pyrocalciferol analog (cf. sub D) that in its turn could be photochemically converted into a non-absorbing product, probably the photo-(iso)pyrocalciferol analog.

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[15] A. Verloop, A. L. Koevoet, and E. Havinga, *Rec. Trav. Chim.* **76**, 689 (1957).
[16] M. Legrand and J. Mathieu, *C. R. Acad. Sci., Paris* **245**, 2502 (1957).
[17] R. L. Autrey, D. H. R. Barton and W. H. Reusch, *Proc. Chem. Soc.* 55 (1959).