# 69. *Partial Synthesis of Vitamins $D_2$ and $D_3$.*

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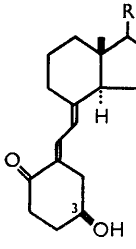
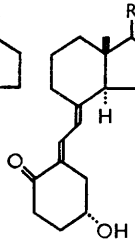
Syntheses of *epi*-vitamins $D_2$ and $D_3$ have been effected on the lines used before for the natural series. Harrison and Lythgoe's synthesis of vitamin $D_2$ rested on an unsuspected partial resolution by chromatography and led them to some erroneous identifications.

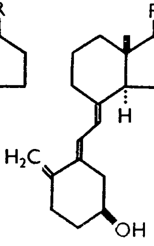
After preparation of 5 : 6-*trans*-vitamins $D_2$ and $D_3$ and their photoisomerisation to the natural (5 : 6-*cis*-)vitamins $D_2$ and $D_3$,[1-3] the remaining problem for partial synthesis of the natural vitamins was separation of the 3-hydroxy-epimers. For this we used the mixture[4] of the " dienolone " (I; $R = C_9H_{17}$) and its *epi*-isomer (II; $R = C_9H_{17}$), as well as the analogous mixture[5] (I + II; $R = C_8H_{17}$). Chromatography yielded, without difficulty, the two pairs of pure epimers; as expected each mixture was found to contain its epimers in a 1 : 1 ratio.



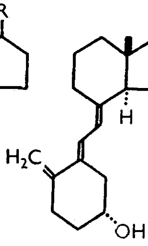
(I)



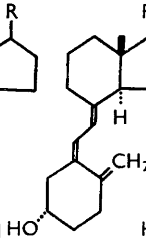
(II)



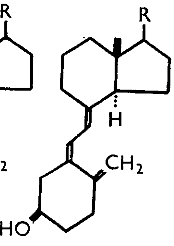
(III)



(IV)



(V)



(VI)

The Wittig reaction, with methylenetriphenylphosphorane, converted the four hydroxy-ketones into the four pure triene-alcohols, namely, (III; $R = C_9H_{17}$ and $C_8H_{17}$) and the *epi*-forms (IV; $R = C_9H_{17}$ and $C_8H_{17}$).

Of these, the former pair (III) were identical with normal 5 : 6-*trans*-vitamin $D_2$ and $D_3$ respectively.[3,6,7] Our photoisomerisation of this pair, by glass-filtered ultraviolet light, to the natural (5 : 6-*cis*-)vitamins $D_2$ and $D_3$ (V; $R = C_9H_{17}$ and $C_8H_{17}$ respectively) has already been described.[3] We have now similarly photoisomerised the pure *epi*-5 : 6-*trans*-trienes (IV; $R = C_9H_{17}$ and $C_8H_{17}$) to the (new) *epi*-vitamins $D_2$ and $D_3$ (VI; $R = C_9H_{17}$ and $C_8H_{17}$ respectively). These have not yet crystallised; moreover, their esters do not crystallise well and have unsharp melting points.

Harrison and Lythgoe[8] have also reported a partial synthesis of vitamin $D_2$. They photoisomerised our " dienolone " epimer mixture (I + II; $R = C_9H_{17}$), by our method, before introducing the methylene group by the Wittig procedure. Esterification of their mixed product gave the esters of natural (3β-)vitamin $D_2$ and *epi*(3α)-vitamin $D_2$ in a 1 : 3-ratio. However, in varying our procedure they chromatographed the dienolone *epimer* mixture (I + II): they discarded a fraction (15%) consisting of *epi*(3α)-rich dienolone

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[1] Inhoffen, Kath, Sticherling, and Brückner, *Angew. Chem.*, 1955, **67**, 276; Inhoffen, Quinkert, Hess, and Hirschfeld, *Naturwiss.*, 1957, **44**, 11.

[2] Inhoffen, Kath, Sticherling, and Brückner, *Annalen*, 1957, **603**, 25.

[3] Inhoffen, Quinkert, Hess, and Hirschfeld, *Chem. Ber.*, 1957, **90**, 2544.

[4] Inhoffen, Brückner, and Gründel, *ibid.*, 1954, **87**, 1.

[5] Inhoffen, Irmscher, Hirschfeld, Stache, and Kreutzer, *ibid.*, 1958, **91**, in the press.

[6] Inhoffen, Quinkert, Hess, and Erdmann, *Chem. Ber.*, 1956, **89**, 2273.

[7] Verloop, Koevoet, and Havinga, *Rec. Trav. chim.*, 1955, **74**, 1125.

[8] Harrison and Lythgoe, *Proc. Chem. Soc.*, 1957, 261; *J.*, 1958, 837.

thus producing unwittingly a mixture rich in normal (β-)form and so eventually the unequal proportions of esters which they recorded. In fact the epimeric esters cannot be separated by crystallisation as described if the original 1 : 1 ratio of the mixture (I + II) is maintained. (In the strict sense Harrison and Lythgoe's synthesis is thus not reproducible.) Harrison and Lythgoe's so-called *epi*-vitamin $D_2$ is, further, a 1 : 1 epimeric mixture. Our earlier sample of *trans*-vitamin $D_2$[2] is, as stated, a mixture (α : β = 87 : 13) and not " practically pure *epi*-vitamin $D_2$ " as Harrison and Lythgoe believed.

## EXPERIMENTAL

Rotations refer to benzene solutions unless otherwise stated. $\lambda_{max.}$ are for ether solutions. Light petroleum had b. p. 40—60°.

*Separation of Dienolones.*—(*a*) The dienolone epimer mixture[4] (I + II; R = $C_9H_{17}$) (2·9 g.) was chromatographed in 85 : 15 benzene–ether on alumina (580 g.; Woelm, neutral, grade 2). After rejection of two fractions (together 3·4 l.), fractions 3 and 4 (together 3 l.) yielded compound (I; R = $C_9H_{17}$), which after crystallisation from ether–light petroleum (yield, 0·71 g., 25%), had m. p. 142·5—144°, $[\alpha]_D$ 218°, $\lambda_{max.}$ 300 mμ (ε 25,200) (Found: C, 81·3; H, 10·4. Calc. for $C_{27}H_{42}O_2$: C, 81·4; H, 10·6%). After removal of intermediate fractions 5—8 (total 2 l.), fractions 9—23 (8 l.) afforded, after recrystallisation, the *epi*-form (0·69 g., 24%), m. p. 132—133·5°, $[\alpha]_D$ +106°, $\lambda_{max.}$ 300 mμ (ε 26,200).

(*b*) Similarly, the mixture (I + II; R = $C_8H_{17}$) {4 g.; m. p. 143—143·5°, $[\alpha]_D$ +143°, $\lambda_{max.}$ 301 mμ (ε 26,800) (Found: C, 80·9; H, 10·8. Calc. for $C_{26}H_{42}O_2$: C, 80·8; H, 10·95%)}, gave the compound (I; R = $C_8H_{17}$) (1·45 g.), m. p. 141—141·5°, $[\alpha]_D$ +200°, and the *epi*-form (II; R = $C_8H_{17}$) (1·53 g.), m. p. 125—126°, $[\alpha]_D$ +88°.

*Wittig Reactions.*—The pure dienolone (I; R = $C_9H_{17}$) (0·45 g.) and methylenetriphenylphosphorane (2·1 g.) in ether were boiled for 3 hr.; the product, isolated in the usual way, was chromatographed on alumina (45 g.) in 7 : 3 light petroleum–ether. The fraction with $\lambda_{max.}$ 272—273 mμ crystallised from a similar solvent mixture, giving a triene (III; R = $C_9H_{17}$) (0·2 g., 45%), m. p. 98·5—101°, $[\alpha]_D$ +216°, identical with 5 : 6-*trans*-vitamin $D_2$.[6,7]

Similarly, the epimeric dienolone (II; R = $C_9H_{17}$) (0·45 g.) gave the epi-*triene* (IV; R = $C_9H_{17}$) (0·19 g., 43%), m. p. 129·5—131·5°, $[\alpha]_D$ +52·5°, $\lambda_{max.}$ 272—273° mμ (ε 24,500) (Found: C, 85·0; H, 10·4. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%).

Also, in the $D_3$ series, where R = $C_8H_{17}$, the dienolone (I)[5] (0·45 g.) gave the triene (III) (0·16 g., 36%), m. p. 88—92°, $[\alpha]_D$ +212° (in ether), identical with 5 : 6-*trans*-vitamin $D_3$[3,7]; and the *epi*-compound (II) (0·75 g.) gave the *epi*-triene (IV) (0·22 g.), m. p. 114—116°, $[\alpha]_D$ +47°, $\lambda_{max.}$ 272—273 mμ (ε 25,800).

*Photoisomerisations.*—Irradiation, effected as before,[3] of the *epi*-triene (IV; R = $C_9H_{17}$) (0·94 g.) for 9 hr. and chromatography in 7 : 3 light petroleum–ether on alumina (150 g.) gave the (5 : 6-*cis*-)*epi*-vitamin $D_2$ (VI) as an oil (0·37 g.), $\lambda_{max.}$ 265 mμ (ε 14,800), whose 3 : 5-dinitrobenzoate (0·22 g.) had m. p. 97—100°, $[\alpha]_D$ +4°.

The *epi*-triene (IV; R = $C_8H_{17}$) (0·4 g.), on irradiation for 8·5 hr. and chromatography (on alumina, 75 g.), gave an oily (5 : 6-*cis*-)*epi*-vitamin $D_3$ (VI) (0·19 g.), $\lambda_{max.}$ 265 mμ (ε 14,000), whose 3 : 5-*dinitrobenzoate* (0·07 g.) had m. p. 96—100°, $[\alpha]_D$ −1° (Found: C, 70·5; H, 8·2; N, 4·9. $C_{34}H_{46}O_6N_2$ requires C, 70·6; H, 8·0; N, 4·8%).

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