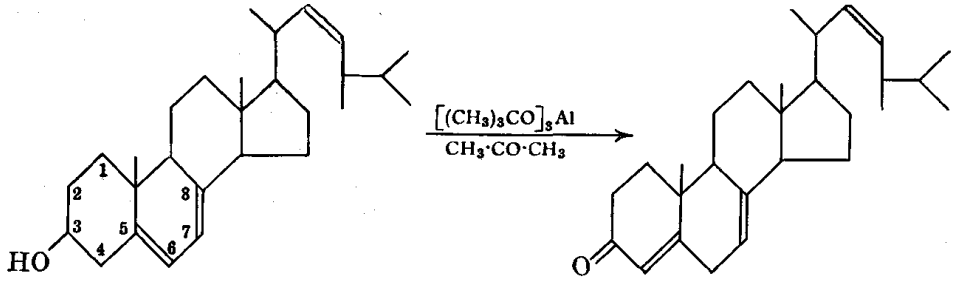
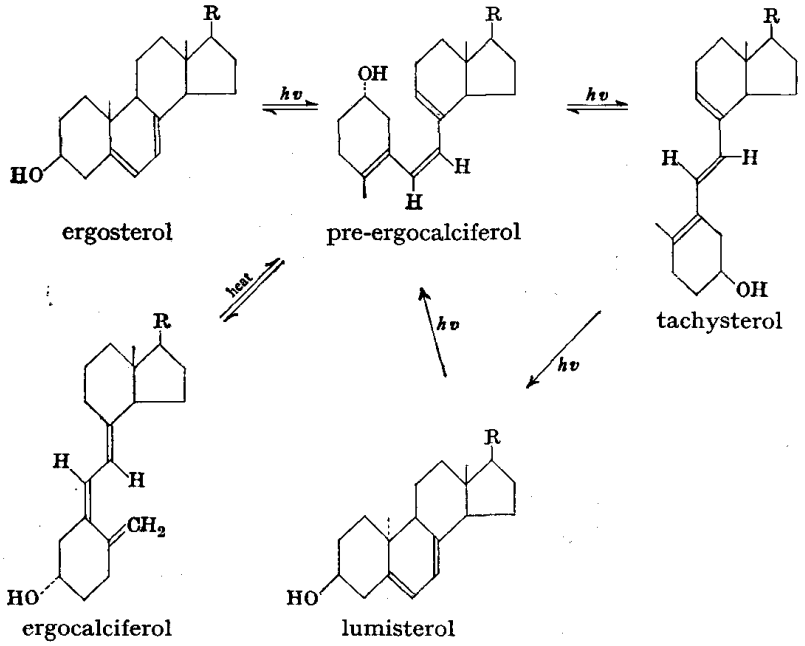


ergosterol

§6. Vitamin D. This vitamin is the antirachitic vitamin; it is essential for bone formation, its function being the control of calcium and phosphorus metabolism.

Steenbock *et al.* (1924) showed that when various foods were irradiated with ultraviolet light, they acquired antirachitic properties. This was then followed by the discovery that the active compound was in the unsaponifiable fraction (the sterol fraction). At first, it was believed that the precursor of the active compound was cholesterol, but subsequently the precursor was shown to be some " impurity " that was in the cholesterol fraction (*e.g.*, by Heilbron *et al.*, 1926). The ultraviolet absorption spectrum of this " impure cholesterol " indicated the presence of a small amount of some substance that was more unsaturated than cholesterol. This led to the suggestion that ergosterol was the provitamin D in the " impure cholesterol ", and the investigation of the effect of ultraviolet light on ergosterol resulted in the isolation from the irradiated product of a compound which had very strong antirachitic properties. This compound was named **calciferol** by the Medical Research Council (1931), and **vitamin D_1** by Windaus (1931). This potent crystalline compound, however, was subsequently shown to be a molecular compound of calciferol and lumisterol (one molecule of each). Windaus (1932) therefore renamed the pure potent compound as **vitamin D_2**, but the M.R.C. retained the original name calciferol. The *Chemical Society* (1951) has proposed the name **ergocalciferol** for this pure compound.

A detailed study of the irradiation of ergosterol with ultraviolet light has led to the proposal that the series of changes is as follows (R = C_9H_{17}):



Velluz *et al.* (1949) isolated the pre-ergocalciferol (P) by irradiation of ergosterol at 20°, and showed that it formed ergocalciferol (E) on heating (see also below). Velluz *et al.* (1955) and Havinga *et al.* (1955) showed that pre-ergocalciferol is the 6 : 7-*cis*-isomer of tachysterol (T), and the interconversion of these two compounds has been studied by Inhoffen *et al.* (1959) and Havinga *et al.* (1959). Lumisterol (L) is converted directly into pre-ergocalciferol (Rappoldt, 1960). It should be noted that tachysterol and lumisterol are formed in a side reaction from pre-ergocalciferol and are *not* directly involved in the formation of ergocalciferol as postulated in the original scheme of Windaus *et al.*, who carried out the irradiation in solution and allowed the temperature to rise to 50°:

$$\text{Ergosterol} \xrightarrow{h\nu} \text{L} \xrightarrow{h\nu} \text{T} \xrightarrow{h\nu} \text{E}$$

§6a. Ergocalciferol (calciferol, vitamin D_2) is an optically active crystalline solid, m.p. 115–117°. Its molecular formula is $C_{28}H_{44}O$, and since it forms esters, the oxygen is present as a hydroxyl group. Furthermore, since ergocalciferol gives a ketone on oxidation, this hydroxyl group is a secondary alcoholic group. Ozonolysis of ergocalciferol produces, among other products, methyl*iso*propylacetaldehyde. Thus the side-chain in ergocalciferol is the same as that in ergosterol. Catalytic hydrogenation converts ergocalciferol into the fully saturated compound octahydroergocalciferol, $C_{28}H_{52}O$. This shows that there are four double bonds present, and since one is in the side-chain, three are therefore in the nucleus. The parent hydrocarbon of ergocalciferol is $C_{28}H_{52}$, and since this corresponds to the general formula C_nH_{2n-4}, the molecule therefore is *tricyclic*. Furthermore, ergocalciferol does not give Diels' hydrocarbon when distilled with selenium. These facts indicate that ergocalciferol does not contain the four-ring system of ergosterol. The problem is thus to ascertain which of the rings in ergosterol has been opened in the formation of ergocalciferol. The following reactions of ergocalciferol are readily explained on the assumption that its structure is I. The absorption spectrum of the semicarbazone of II ($C_{21}H_{34}O$) was shown to be characteristic of $\alpha : \beta$-unsaturated aldehydes. The absence of the hydroxyl group and the carbon content of II indicate the *absence* of ring A. These facts suggest that in ergocalciferol " ring B " is open between C_9 and C_{10}, and that II arises by scission of the molecule at a double bond in position 5 : 6, and can be an $\alpha : \beta$-unsaturated aldehyde only if there is a double bond at 7 : 8 (these double bonds are also present in ergosterol). The isolation of the ketone III ($C_{19}H_{32}O$) confirms the presence of the double bond at 7 : 8 (Heilbron *et al.*, 1935).

The isolation of formaldehyde (IV) shows the presence of an exocyclic methylene group, and the presence of this group at C_{10} is in keeping with the opening of ring B at 9 : 10. The formation of V ($C_{13}H_{20}O_3$), a keto-acid, suggests that ring B is open at 9 : 10, and that there are two double bonds at 7 : 8 and 22 : 23. The position of the latter double bond is confirmed by the isolation of methyl*iso*propylacetaldehyde, VI (Heilbron *et al.*, 1936).

Structure I for ergocalciferol is also supported by the formation of VII, the structure of which is shown by the products VIII, IX, X and XI (Windaus *et al.*, 1936). The production of 2 : 3-dimethylnaphthalene (VIII) is in keeping with the fact that carboxyl groups sometimes give rise to methyl groups on selenium dehydrogenation (*cf.* §2 vii. X). Similarly, the formation of naphthalene, IX, and naphthalene-2-carboxylic acid, X, shows the presence of rings A and " B " in VII. Catalytic reduction of VII (to reduce the double bond in the *side-chain* only), followed by ozonolysis, gives XI. Thus the formation of these compounds VIII–XI establishes the structure of VII, and shows that the double bonds are at 5 : 6, 10 : 19 and 7 : 8.