The Oppenauer Oxidation of Ergocalciferol.

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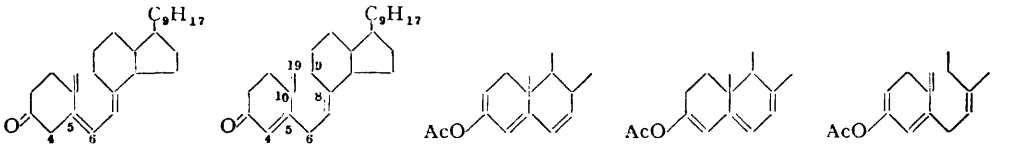
Oppenauer oxidation of ergocalciferol gave the crystalline conjugated ketone (II), which is reduced by lithium aluminium hydride or the Meerwein–Pondorf method without rearrangement. Attempts to convert the ketone into ergocalciferol *via* an enol acetate, or by treatment with *tert.*-butyl chloride followed by sodium borohydride, failed.

BY Oppenauer oxidation of ergocalciferol, Windaus and Buchholz (*Z. physiol. Chem.*, 1938, **256**, 273) obtained a non-crystalline ketone thought to have the structure (I) or (II), which had maximum light absorption in ethanol at 265 mμ and gave a semicarbazone with a maximum in chloroform at 293 mμ. They stated that Meerwein–Pondorf reduction of the ketone, purified by regeneration from its semicarbazone, gave ergocalciferol, isolated as the 3 : 5-dinitrobenzoate in 5·3% yield. Both the absolute value of the absorption maximum of the semicarbazone, and its difference from that of the ketone, suggest the αβ-unsaturated structure (II) rather than (I); if this were the case, the regeneration of ergocalciferol on reduction must be accompanied by a migration of the double bond from the 4 : 5 to the 5 : 6-position. Similar migrations have been recorded for steroids containing an intact ring B (for summary see Wilds, " Organic Reactions," J. Wiley & Son Inc., New York, 1944, Vol. II, p. 178), but this appears to be the sole example of a migration to an exocyclic position, so the original work was repeated.

Oppenauer oxidation of ergocalciferol, with acetone as the hydrogen acceptor, gave a crystalline ketone with maximum light absorption in ethanol at 272 mμ. The semicarbazone had $\lambda_{max.}$ 293 mμ in chloroform. The infra-red spectrum of the ketone showed bands at 1678 and 1590 cm.$^{-1}$ in " Nujol " suspension, as required by the conjugated ketone structure (II). The crude oxidation product gave the same semicarbazone and was free from absorption bands in the infra-red near 1720 cm.$^{-1}$, showing the absence of unrearranged ketone (I). According to Windaus and Buchholz (*loc. cit.*), the ketone (II) could be regenerated from its semicarbazone by the action of benzaldehyde in 80% ethanol under reflux,

but this was found to be possible only if benzaldehyde containing benzoic acid was used, and even then the product was difficult to purify. However, regeneration with pyruvic acid gave the original ketone in good yield. Meerwein–Pondorf or lithium aluminium hydride reduction of the ketone (II) gave a syrupy alcohol having maximum light absorption in ethanol at 235 mμ in agreement with the maximum at 237 mμ calculated for the alcohol derived from (II). The alcohol showed no selective light absorption at 265 mμ and this, and its failure to give a crystalline 3 : 5-dinitrobenzoate, shows that it contained no ergocalciferol.

Attempts were then made to convert the ketone (II) into ergocalciferol *via* the enol acetate (for the conversion of cholest-4-en-3-one into cholesterol *via* the enol acetate see Belleau and Gallagher, *J. Amer. Chem. Soc.*, 1951, **73**, 4458). Acetylation with acetic



anhydride and pyridine gave an enol acetate having maximum light absorption in ethanol at 306 mμ. Of the two enol acetates of cholest-4 : 6-dien-3-one, 3-acetoxy-cholesta-2 : 4 : 6-triene (III) has maximum light absorption in ethanol at 302 mμ and 3-acetoxycholest-3 : 5 : 7-triene (IV) at 316 mμ (Dauben, Eastham, and Micheli, *ibid.*, 1951, **73**, 4496); the enol acetate obtained from (II) is therefore formulated as the 3-acetoxy-2 : 4 : 7 : 10(19)-tetraene (V). In agreement with this, reduction with sodium borohydride gave no ergocalciferol. Acetylation of the ketone (II) under acidic conditions, *e.g.*, with acetyl chloride and acetic anhydride, caused migration of the exocyclic methylene double bond. Treatment of the ketone (II) with *tert.*-butylmagnesium chloride, followed by reduction with sodium borohydride, gave a product which, from its light absorption, contained no ergocalciferol.

Experimental

Oppenauer Oxidation of Ergocalciferol.—Ergocalciferol (4·2 g.) and aluminium *tert.*-butoxide (5 g.) were boiled in dry benzene (500 c.c.) and acetone (150 c.c.) under reflux in an atmosphere of nitrogen for 16 hr. After dilution with water, evaporation of the benzene layer gave a product containing much mesityl oxide. This was removed under reduced pressure and the residue crystallised from light petroleum (b. p. 40—60°) at −40° to give 9 : 10-seco*ergosta*-4 : 7 : 10(19) : 22-*tetraen*-3-*one*, m. p. 72—73°, $[\alpha]_D$ +37·5° (*c*, 2·6 in $CHCl_3$), $\lambda_{max.}$ 272 mμ (ε 14,600 in EtOH) (Found: C, 84·9; H, 10·9. $C_{28}H_{42}O$ requires C, 85·2; H, 10·7%). The semicarbazone, prepared from the crude oxidation product or from crystalline ketone, at room temperature or under reflux (cf. Windaus and Buchholz, *loc. cit.*), and crystallised from methanol–chloroform, had m. p. 217—218° (decomp.), $\lambda_{max.}$ 293 mμ (ε 31,300 in $CHCl_3$) (Found: N, 9·4. Calc. for $C_{29}H_{45}ON_3$: N, 9·3%).

The semicarbazone (0·62 g.) in acetic acid (10 c.c.) and water (2 c.c.) was heated on the steam-bath with pyruvic acid (2 c.c.) for 15 min. After addition of water, extraction with ether gave a product which crystallised from light petroleum (b. p. 40—60°) to give the ketone (II) (0·42 g.), m. p. and mixed m. p. 72—73°.

The ketone (II) (0·2 g.), when heated under reflux with pyridine (2 c.c.) and acetic anhydride (0·5 c.c.) for 3 hr., gave the *enol acetate* (V), b. p. 150° (bath-temp.)/10^{-4} mm., $\lambda_{max.}$ 306 mμ (ε 21,900 in EtOH), $\nu_{max.}$ 1751, 878 cm.$^{-1}$ (Found: C, 82·8; H, 10·5. $C_{30}H_{44}O_2$ requires C, 82·5; H, 10·2%).

Meerwein–Pondorf Reduction of the Ketone (II).—The ketone (0·31 g.) and aluminium *iso*propoxide (1 g.) were heated in dry *iso*propanol (100 c.c.) under reflux in an atmosphere of nitrogen for 9 hr. with continuous slow removal of *iso*propanol. After dilution with water, ether-extraction gave the *alcohol* as a colourless syrup, $\lambda_{max.}$ 235 mμ (ε 14,700 in EtOH), $\nu_{max.}$ 3300, 1608, 970, 880 cm.$^{-1}$ (Found: C, 84·8; H, 11·6. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%). From the absolute intensity of the light absorption of the alcohol at 265 mμ, there could not be more than 3% of ergocalciferol present, and the smooth shape of the curve at this point made

even this improbable. A similar reduction of the crude ketone, obtained by regeneration from the semicarbazone with pyruvic acid, again gave a product containing no ergocalciferol. This eliminated the possibility that a small amount of the unconjugated ketone (I) might have been formed during the regeneration.

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