133. *Photochemical Transformations. Part III.* The Constitution of a Steroid Irradiation Product.*

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The chromophoric system of photodehydroergosterol has been shown to be a *cyclo*propane ring in conjugation with two ethylenic linkages. Hydrogenation affords tetrahydrophotodehydroergosterol which contains a vinyl*cyclo*propane residue. The relationship between the latter and the secondary hydroxyl group has been defined rigidly. On the basis of these and other observations a constitution has been proposed for photodehydroergosterol.

Although much attention has been devoted to the photochemical transformations of ergosterol, only preliminary work by Windaus and his collaborators [1, 2] has been recorded on the effect of ultraviolet light on the triene system of dehydroergosterol (I; R = H). We have confirmed the observation [1, 2] that irradiation of its acetate (I; R = Ac) affords in satisfactory yield a crystalline isomer, photodehydroergosteryl acetate. The experiments summarised in the sequel lead us to assign the constitution (V; R = Ac) to this compound.

The earlier workers [1, 2] had made the following pertinent observations. Photodehydroergosterol showed a high-intensity absorption maximum at 260 mμ. Its acetate, in contrast to the starting material (I; R = Ac), did not react with maleic anhydride. On hydrogenation in ethanol over platinum it gave tetrahydrophotodehydroergosteryl acetate, the side-chain and one of the nuclear ethylenic linkages being saturated. Hydrogenation over platinum in acetic acid furnished a non-crystalline product with uptake of four mols. of hydrogen.

We began our investigation with the knowledge that the absorption spectrum of the photo-compound acetate [$\lambda_{max.}$ 260 mμ (ε 11,300)] was very similar to that of "ergostatetraene" [3] (IV) which shows $\lambda_{max.}$ 261 mμ (ε 17,600). The conjugation between two ethylenic linkages and a *cyclo*propane ring suggested by this observation was confirmed by the spectrum of the tetrahydro-acetate. This had a broad maximum at 222 mμ (ε 6800) typical [4] of conjugated vinyl*cyclo*propanes.

We first excluded the possibility that the methyl group at position 10 was involved in the formation of a *cyclo*propane ring. Thus tetrahydrophotodehydroergosterol acetate gave no indication (in CCl_4) of the infrared band characteristic [5] of CH_2 in a *cyclo*propane ring. Also photodehydroergosterol afforded 3·8 *C*-Me groups on Kuhn–Roth oxidation. A simultaneous determination on 5 : 6-dihydroergosterol indicated 3·7 *C*-Me groups. These figures imply that the same number of *C*-Me groups must be present in both compounds.

There are three obvious formulæ, (II), (III), and (V; R = H), consistent with the spectroscopic data. Formula (II) could be excluded easily since oxidation of photodehydroergosterol with chromium trioxide in pyridine afforded a crystalline ketone (VI). This showed a carbonyl band at 1704 cm.$^{-1}$ indicative of a *cyclo*hexanone, not a *cyclo*pentanone as would be required for the ketone from (II).

Tetrahydrophotodehydroergosteryl acetate which, as will be shown in the sequel, must be formulated as (VIII; R = Ac), gave a crystalline epoxide (XII) with monoperphthalic acid, and a glycol (XIII) with osmium tetroxide. The latter was stable to ozone, thus confirming the assumption that one of the ethylenic linkages of the compound (I; R = Ac) had been converted into a ring during the photo-reaction. The uptake of 4 mols. of hydrogen on hydrogenation of the photo-product (V; R = Ac) in acetic acid is, of course,

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* Part II, *J.*, 1958, 140.

[1] Windaus and Linsert, *Annalen*, 1928, **465**, 148.

[2] Windaus, Gaede, Köser, and Stein, *ibid.*, 1930, **483**, 17.

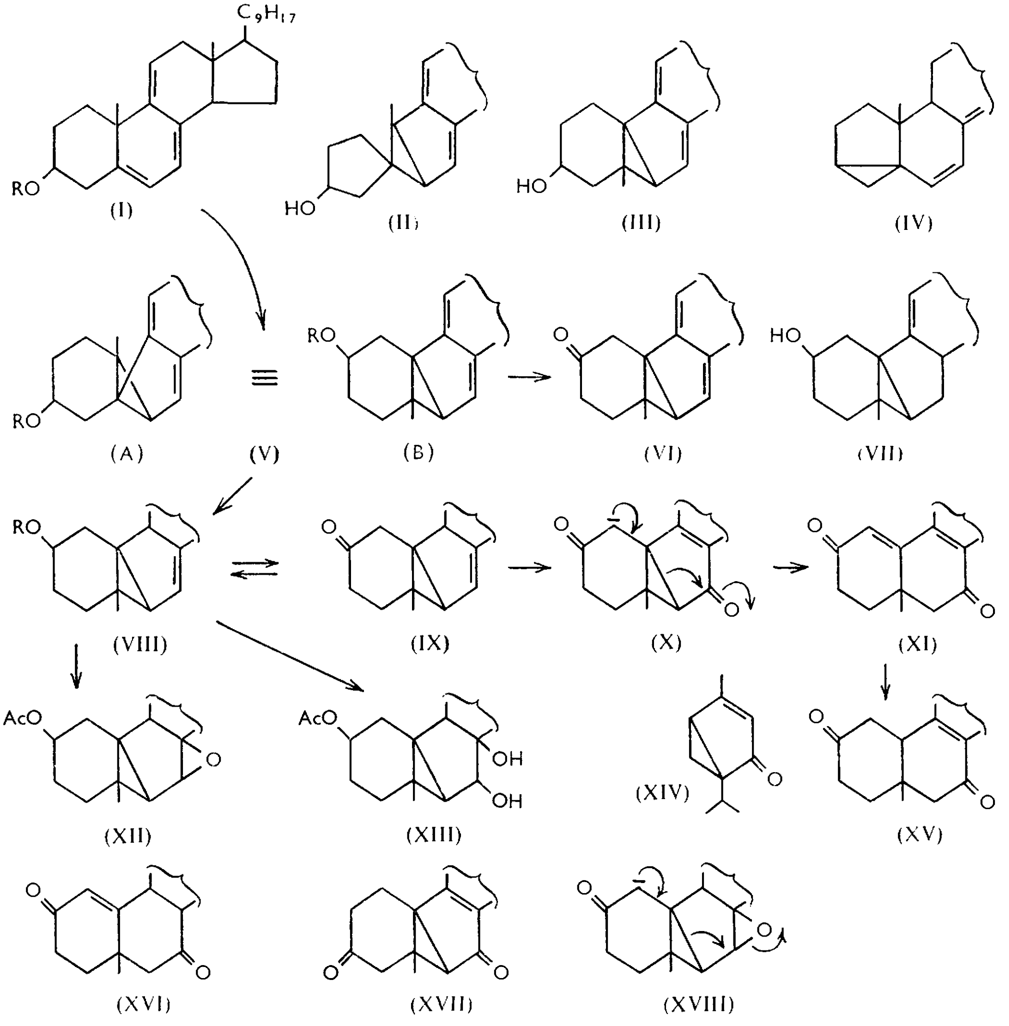
[3] Fieser, Rosen, and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5397.

[4] *Inter al.*, Zürcher, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1954, **37**, 2145; Rowe, Melera, Arigoni, Jeger, and Ruzicka, *ibid.*, 1957, **40**, 1.

[5] Cole, *J.*, 1954, 3807.

unexceptional if a *cyclo*propane ring be present. Neither the oxide (XII) nor the diol (XIII) showed double-bond absorption in the ultraviolet region, in agreement with the presence of a *cyclo*propane (or other carbon) ring.

Oxidation of tetrahydrophotodehydroergosterol (VIII; R = H) with chromium trioxide in pyridine–benzene gave, as main product, the expected ketone (IX), which exhibited a *cyclo*hexanone band at 1704 cm.$^{-1}$ in agreement with the assigned constitution. Further oxidation of this ketone with the same reagent, followed by chromatography over silica gel, furnished an αβ-unsaturated ketone with an ultraviolet absorption spectrum typical[6] of an umbellulone (as XIV). This is formulated as (X). Its formation suggests (*a*) that the residual ethylenic linkage of tetrahydrophotodehydroergosterol, as implied by an infrared band at 3030 cm.$^{-1}$ (in CCl_4), has at least one vinyl hydrogen atom and (*b*) that the *cyclo*propane ring and the residual ethylenic linkage are in the same six-membered ring. Alternative formulæ such as (VII) for tetrahydrophotodehydroergosterol are thus excluded. The umbellulone (X) showed infrared bands at 1704 (*cyclo*hexanone), 1673 (*cyclo*hexenone), and 1617 (conjugated C=C) cm.$^{-1}$ in agreement with the assigned constitution.



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[6] Gillam and West, *J.*, 1945, 98; Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 4115.

The ketone (X) was extremely sensitive to base, being thereby converted [see (X); arrows] into a diene-dione (XI), which had an intense ultraviolet band at 307 mμ consistent with the chromophore postulated.[7] In the infrared region, this dione (XI) showed bands at 1655 (1667 in CCl_4) (2-*cyclo*hexenones), 1587 and 1563 (conjugated C=C) cm.$^{-1}$ in agreement with the proposed formula. Reduction of it with zinc dust and acetic acid afforded an αβ-unsaturated ketone (XV). The ultraviolet absorption of this compound at 256 mμ implies a heavily substituted enone system and excludes the alternative (XVI) which would absorb at about 240 mμ.[8] Compound (XV) gave infrared maxima at 1702 (*cyclo*hexanone), 1650 (*cyclo*hexenone), and 1595 (conjugated C=C) cm.$^{-1}$ The ready reduction of its precursor (XI) provides chemical evidence [9] that it is a fully conjugated diene-dione of the type postulated.

The diene-dione (XI) was also obtained from the chromatography of the crude oxidation product of tetrahydrophotodehydroergosterol over alumina. The main oxidation product (IX) was stable to alumina, and clearly the diketone (X), formed in the oxidation, was thereby rearranged to (XI).

If photodehydroergosterol had, in fact, constitution (III), then the umbellulone analogous to (X) would have formula (XVII) and its rearrangement product could not be a fully conjugated diene-dione such as (XI). On these grounds formula (III) is excluded from further consideration.

From the mechanistic point of view it was of some interest that the epoxide (XVIII), prepared from the cyclene (IX) in the usual way, did not show the same remarkable sensitivity to base as (X) in spite of the possibility (XVIII; see arrows) of opening both three-membered rings simultaneously.

EXPERIMENTAL

M. p.s were taken on the Kofler block. $[\alpha]_D$ refer to $CHCl_3$ solutions. Ultraviolet absorption spectra were determined in EtOH on the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined, unless stated to the contrary, as Nujol mulls by Dr. G. Eglinton and his colleagues. The alumina for chromatography was acid-washed, neutralised, and standardised according to Brockmann and Schodder's method.[10] Microanalyses were carried out by Mr. J. M. L. Cameron and his associates.

Photodehydroergosterol (V; R = H).—Photodehydroergosteryl acetate was prepared essentially according to the method of Windaus and Linsert [1] but with "AnalaR" benzene as solvent instead of ethanol. It showed infrared bands at 1727 and 1242 (acetate) cm.$^{-1}$, gave a strong colour with tetranitromethane, and showed $\lambda_{max.}$ 260 mμ (ε 11,300). Hydrolysis with ethanolic sodium hydroxide afforded photodehydroergosterol with properties in agreement with those in literature.

Photodehydroergosterone (VI).—Photodehydroergosterol (250 mg.) in "AnalaR" benzene (3 ml.) was treated with chromium trioxide (250 mg.) in "AnalaR" pyridine (12 ml.) for 24 hr. at room temperature. The product, on chromatography over alumina (grade III) and elution with 15 : 1 benzene–ether, gave *photodehydroergosterone* (VI). Recrystallised from aqueous ethanol this had m. p. (needles) 111—113°, $\lambda_{max.}$ 259 mμ (ε 12,500) (Found: C, 85·6; H, 10·4. $C_{28}H_{40}O$ requires C, 85·6; H, 10·3%).

Tetrahydrophotodehydroergosterol (VIII; R = H) *and its Derivatives*.—The acetate was prepared by hydrogenation of photodehydroergosteryl acetate over platinum in ethanol–ethyl acetate essentially according to Windaus, Gaede, Köser, and Stein's directions.[2] Recrystallised from ethanol–ethyl acetate it had m. p. 104—105°, $[\alpha]_D$ +8° (*c* 1·90), $\lambda_{max.}$ 222 mμ (ε 6800), and infrared bands at 1733 and 1242 (acetate) cm.$^{-1}$ (Found: C, 81·6; H, 10·9. Calc. for $C_{30}H_{48}O_2$: C, 81·8; H, 11·0%). Hydrolysis with 5% ethanolic sodium hydroxide gave the known tetrahydrophotodehydroergosterol. The alcohol (130 mg.) in "AnalaR" pyridine (3 ml.) was treated with recrystallised toluene-*p*-sulphonyl chloride (170 mg.) for 18 hr. at room temperature.

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[7] Cf. Ruzicka, Nisoli, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 2017.

[8] Cf. Dorfman, *Chem. Rev.*, 1953, **53**, 47.

[9] *E.g.*, Dorée, McGhie, and Kurzer, *J.*, 1948, 988; 1949, 570.

[10] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

Crystallisation from ethanol afforded the *toluene*-p-*sulphonate* (74 mg.), m. p. (needles) 107—108°, $[\alpha]_D$ +31° (*c* 0·36), $\lambda_{max.}$ 224 mμ (ε 16,100) (Found: C, 76·2; H, 9·0. $C_{35}H_{52}O_3S$ requires C, 76·1; H, 9·5%).

Treatment of tetrahydrophotodehydroergosteryl acetate (165 mg.) in "AnalaR" benzene (19·5 ml.) with monoperphthalic acid (105 mg.; by titration) at 0° for 90 min. (uptake of 1·15 mols. of per-acid) gave the corresponding *epoxide*. Recrystallised from aqueous ethanol this (88 mg.) had m. p. (plates) 99—101°, $[\alpha]_D$ −21° (*c* 0·36), no ultraviolet absorption (Found: C, 78·8; H, 10·8. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

Reaction of Tetrahydrophotodehydroergosteryl Acetate with Osmium Tetroxide.—Tetrahydrophotodehydroergosteryl acetate (950 mg.) in dry "AnalaR" benzene (5 ml.) was added to osmium tetroxide (1·0 g.) and pyridine (0·1 ml.) in the same solvent (10 ml.) and left in the dark at room temperature for 13 days. Benzene (25 ml.) was added and the solution saturated with hydrogen sulphide. Filtration, evaporation *in vacuo*, and crystallisation from 90% aqueous ethanol (8 ml.) afforded the *triol monoacetate* (XIII). Recrystallised from the same solvent this had m. p. 122°, $[\alpha]_D$ −3° (*c* 6·00), no ultraviolet absorption down to 215 mμ (Found: C, 75·6; H, 10·8. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%).

The triol monoacetate (90 mg.) was refluxed in ethanol (10 ml.) with 4N-aqueous sodium hydroxide (0·5 ml.) for 5 min. The very insoluble crystalline *triol* which was precipitated (73 mg.) was filtered off and recrystallised from *iso*propyl alcohol. It had m. p. 230—235° (decomp.), no ultraviolet absorption (Found: C, 76·6, 76·9; H, 11·3, 11·0. $C_{28}H_{48}O_3,\frac{1}{2}C_3H_8O$ requires C, 76·6; H, 11·2%).

The triol monoacetate (47 mg.) in methylene dichloride (20 ml.) was ozonised at −20° for 20 min. Washing with water, removal of the methylene dichloride *in vacuo*, and hydrolysis with 0·5N-ethanolic potassium hydroxide (5 ml.) under reflux for 20 min. afforded the triol (70%), identified by m. p. and mixed m. p.

Tetrahydrophotodehydroergosterone (IX) *and Congeners.*—Tetrahydrophotodehydroergosterol (1·3 g.) in benzene–"AnalaR" pyridine (1 : 1; 10 ml.) was treated with chromium trioxide (1·5 g.) in "AnalaR" pyridine (25 ml.) at room temperature for 18 hr. The oily product (1·2 g.) was chromatographed over alumina (40 g.; grade III). Elution with benzene, and benzene containing 2% of ether, gave *tetrahydrophotodehydroergosterone* (IX) (385 mg.). Recrystallised from ethanol, this had m. p. 116—117°, $[\alpha]_D$ +29° (*c* 1·00), $\lambda_{max.}$ 220 mμ (ε 6500) (Found: C, 84·8; H, 11·7. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%). This ketone was stable to rechromatography over grade III alumina.

Continued elution of the column with 9 : 1 benzene–ether gave, on crystallisation from ether–methanol or from ethanol, the *diene-dione* (XI) (141 mg., crude), m. p. 189—191°, $[\alpha]_D$ −418° (*c* 0·52), $\lambda_{max.}$ 227 and 307 mμ (ε 6200 and 23,000 respectively). The use of pure pyridine, instead of benzene–pyridine, as solvent for the oxidation led to 37% of the ketone (IX) and 5% of the diene-dione (XI).

Tetrahydrophotodehydroergosterone (50 mg.) in "AnalaR" benzene (6 ml.) containing monoperphthalic acid (40 mg.) was left at room temperature for 4 hr. The product was chromatographed over alumina (5 g.; grade V). Elution with 9 : 1 benzene–ether gave the *epoxide* (XVIII) (18 mg.). Recrystallised from ethanol this had m. p. (needles) 132—134°, infrared bands at 1707 (*cyclo*hexanone) and 853 (epoxide) cm.$^{-1}$ and no high-intensity ultraviolet absorption (Found: C, 81·1; H, 11·4. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·8%).

Tetrahydrophotodehydroergosterone (50 mg.) in dioxan (distilled over sodium; 8 ml.) was treated with potassium borohydride (60 mg.) in water (1·5 ml.) for 1 hr. at room temperature. The product was acetylated with pyridine–acetic anhydride at 55° for 2 hr., to give, on crystallisation from aqueous ethanol, tetrahydrophotodehydroergosteryl acetate (20 mg.) identified by m. p. and mixed m. p.

Zinc-dust Reduction of the Diene-dione (XI).—The diene-dione (70 mg.) in "AnalaR" acetic acid (10 ml.) was refluxed with zinc dust (350 mg.) for 45 min. (spectrophotometric control by disappearance of band at 307 mμ). Crystallisation of the product from ethanol gave the *ene-dione* (XV) (21 mg.), m. p. (plates) 198—200°, $[\alpha]_D$ −51° (*c* 0·40), $\lambda_{max.}$ 256 mμ (ε 7900) (Found: C, 81·2; H, 10·5. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·8%).

Oxidation of Tetrahydrophotodehydroergosterone (IX) *with Chromium Trioxide in Benzene–Pyridine.*—The ketone (350 mg.) in "AnalaR" benzene (4 ml.) was treated with chromium trioxide (450 mg.) in "AnalaR" pyridine (8 ml.) at room temperature for 20 hr. The solution was poured into ice-water (150 ml.) and kept at 15° whilst being saturated with sulphur dioxide.

Cold 2N-sulphuric acid (100 ml.) was added and the solution extracted with 1 : 1 ether–benzene (3×50 ml.). The combined organic extracts were washed successively with 2N-sulphuric acid, water, saturated sodium hydrogen carbonate, and water, then dried ($MgSO_4$), and the solvent removed *in vacuo*. The product was chromatographed over silica gel (B.D.H.; 10 g.). Elution with 7 : 3 and 6 : 4 light petroleum (b. p. 40—60°)–benzene gave unchanged tetrahydrophotodehydroergosterone (58 mg.). Elution with 1 : 2 light petroleum (b. p. 40—60°)–benzene, with benzene and with 30 : 1 benzene–ether furnished the *umbellulone* (X) (70 mg.). Recrystallised from ether–methanol this had m. p. (needles) 163—165°, $[\alpha]_D$ +78° (*c* 0·75), $\lambda_{max.}$ (broad and flat) 225 and 283 mμ (ε 5200 and 3100) (Found: C, 81·7; H, 10·6. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·3%). This compound (21 mg.) in ethanol (3 ml.) was treated with 5% methanolic sodium hydroxide (2 drops) for 30 sec. 20% Aqueous acetic acid (2 drops) was added. Crystallisation of the product from ether–methanol gave the diene-dione (XI) (15 mg.) identified by m. p., mixed m. p., and ultraviolet absorption spectrum. The spectrum of the diene-dione is seen as soon as an ethanolic solution of the compound (X) s treated with a trace of base. The same spectrum is seen on warming the compound (X) on the steam-bath with 0·2N-ethanolic sulphuric acid.

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