105. *Photochemical Transformations. Part VII.* Stereospecificity in an Irradiation Process.*

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Irradiation of dehydrolumisteryl acetate affords a stereoisomer of photodehydroergosteryl acetate. By comparison of a model diene-dione from artemisin with the diene-dione obtained earlier from photodehydroergosterol it has been shown that the photochemical transformation of dehydroergosterol proceeds with inversion of configuration at the angular methyl group. A complete stereochemical representation of photodehydroergosterol is thus provided.

The solvolysis rates of tetrahydrophotohydroergosterol toluene-*p*-sulphonate and related compounds have been measured and the vinylcyclopropane ring thus shown to participate strongly in the reaction.

A preliminary account of this work has already been published.[1]

The conversion of dehydroergosteryl acetate (I) into its photo-isomer (II; R = Ac) was described in an earlier paper of this series.[2] The stereochemistry of the product (II) is

* Part VI, *J.*, 1960, 1.

[1] Barton and Klein, *Bull. Res. Council Israel*, 1958, **7** *A*, 94.

[2] Barton and Kende, *J.*, 1958, 688.

of some interest, in particular in its bearing upon the stereospecificity of the photochemical rearrangement. In principle the rearrangement could involve homolysis of the 9,10-bond. If this were so then irradiation of dehydrolumisteryl acetate (III) would be expected to furnish the same photo-compound as was obtained earlier from the isomer (I). In fact a new compound, photodehydrolumisteryl acetate resulted. Since it has the same peculiar ultraviolet spectrum as its analogue (II; R = Ac), it is regarded as its 10-epimer, a conclusion confirmed by further degradation (see below). The photochemical rearrangement is, therefore highly stereospecific.

Now the hydroxyl group of photodehydroergosterol (II; R = H) must be equatorial because Windaus *et al.*[3] recovered tetrahydrophotodehydroergosterol[1] (IV) unchanged after subjecting it to equilibrating conditions. Furthermore, the reduction of tetrahydrophotodehydroergosterone (V) with sodium borohydride to give back exclusively[2] the alcohol (IV) suggests also[4] that the hydroxyl of (IV) [and hence of (II; R = H)] is equatorial. In view of the failure to isomerise the hydroxyl group of ergosterol (equatorial) or of lumisterol (axial) by irradiation, it is most improbable that such a change could have taken place in the genesis of the alcohol (II; R = H). Indeed the hydroxyl group has no ultraviolet absorption band which would conceivably permit such a change. The hydroxyl group of (II; R = H) must therefore be α if the formula is written as in (IIB; R = H), β if written as in (IIA; R = H). If the cyclohexane ring is placed in chair conformation with the α-hydroxyl equatorial and we note that a cyclopropane ring (like an ethylene oxide ring) must with a high degree of probability be *cis*-fused to a six- or five-membered ring, then the stereochemistry (VI) or (VII) for the alcohol (IIA; R = H) follows. In (VI), the configuration of the 10-methyl group has been preserved, in (VII) it has been inverted.

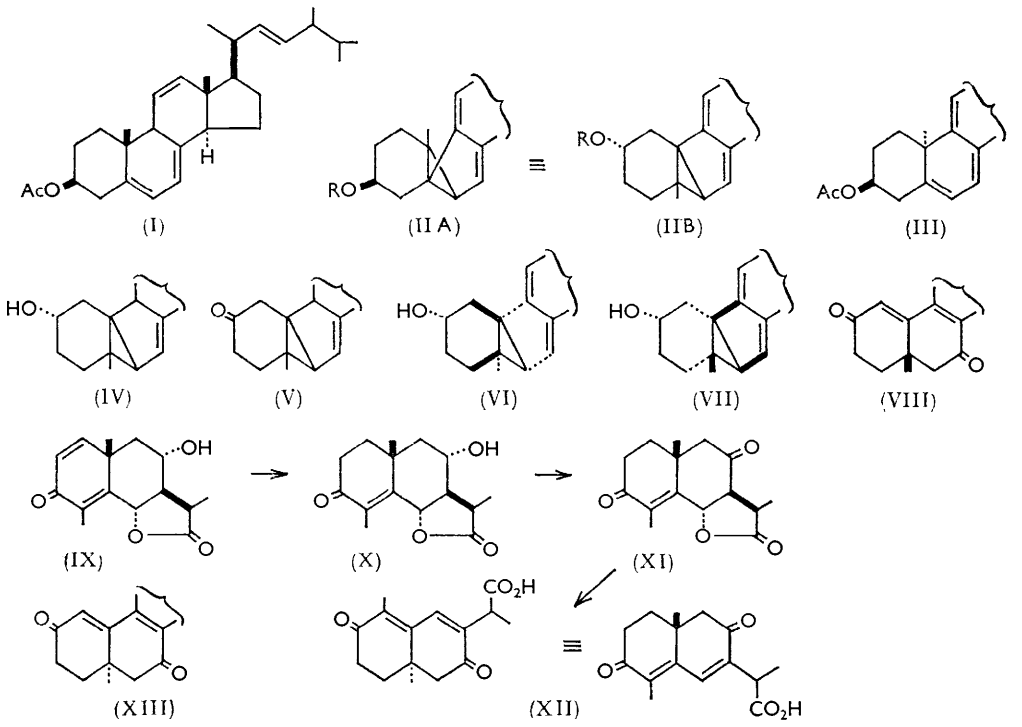
The configuration at position 10 was investigated by the method developed by Klyne[5] and applied successfully to problems very like the present one. The diene-dione (VIII) described in our earlier paper has a chromophore which can be closely approximated by starting with artemisin[6] (IX). Selective hydrogenation of this compound[7] gave dihydroartemisin (X) which, by controlled chromic acid oxidation to the diketone (XI) and treatment of this with mild base, afforded the model diene-dione (XII). The latter showed a very strongly positive $[\alpha]_D$ (+344°). In contrast the diene-dione described earlier[2] had a large negative $[\alpha]_D$ (−418°). One must conclude therefore[5] that the configurations of the angular methyl groups are opposite in the two cases. The correct configuration for the diene-dione is thus as already shown in (VIII), whilst photodehydroergosterol itself must be as represented in (VII). The implication is also that photodehydrolumisterol must be (VI), the initially axial hydroxyl of lumisterol[8] being thereby changed to an equatorial conformation. In agreement photodehydroergosterol acetate showed (in CS_2) a C–O stretching frequency at 1026 cm.$^{-1}$ and the dehydrolumisterol analogue a band at 1025 cm.$^{-1}$. These frequencies are characteristic of equatorial acetates.[9]

The assignment of stereochemistry to the angular methyl group of the dione (VIII) has been further confirmed by taking photodehydrolumisterol acetate through the series of reactions applied to photodehydroergosterol, thus obtaining a stereoisomeric diene-dione (XIII). This had $[\alpha]_D$ +134°, opposite in sign to the rotation of (VIII).

The solvolysis of toluene-*p*-sulphonates and related derivatives has been the subject of much investigation, particularly by Winstein and his collaborators.[10] It is well established that a suitably disposed βγ-ethylenic linkage causes marked participation in

[3] Windaus, Gaede, Köser, and Stein, *Annalen*, 1930, **483**, 17.
[4] Dauben, Fonken, and Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579.
[5] Klyne, *J.*, 1952, 2916; 1953, 3072.
[6] Sumi, *Proc. Japan Acad.*, 1956, **32**, 684; 1957, **33**, 153; *Pharm. Bull.*, 1957, **5**, 187.
[7] Cf. Banerji, Barton, and Cookson, *J.*, 1957, 5041.
[8] Cole, *J.*, 1952, 4969; Castells, Jones, and Williams, *Proc. Chem. Soc.*, 1958, 7.
[9] Page, *J.*, 1955, 2017.
[10] For example, Winstein, Morse, Grunwald, Jones, Corse, Trifan, and Marshall, *J. Amer. Chem. Soc.*, 1952, **74**, 1127.

the solvolytic process. From cholesteryl toluene-*p*-sulphonate cyclo-steroids are, of course, formed. The possible participation of a suitably disposed βγ-attached cyclopropane ring does not appear to have been examined hitherto.



The ready availability of photodehydroergosterol and its derivatives prompted us to measure the rates of solvolysis of appropriate toluene-*p*-sulphonates. The toluene-*p*-sulphonates of cholesterol (XIV) and 5,6-dihydroergosterol (XV) were used as models. Our results (see Table) on cholesteryl toluene-*p*-sulphonate are in good agreement with

	Mean first-order solvolysis constant at 56·1° (in min.$^{-1}$)		
Toluene-*p*-sulphonate of	In 99·5 : 0·5 w/w acetic acid–H_2O	In 90 : 10 v/v dioxan–H_2O	Relative rates
Cholesterol (XIV)	$1·9 \times 10^{-2}$	$1·1 \times 10^{-3}$	**126**
5,6-Dihydroergosterol (XV)	—	$8·7 \times 10^{-6}$	**1**
Tetrahydrophotodehydroergosterol (IV)	$2·3 \times 10^{-2}$ *	$1·0 \times 10^{-3}$	**115**
Photodehydroergosterol (VII)	—	$3·6 \times 10^{-3}$	**414**

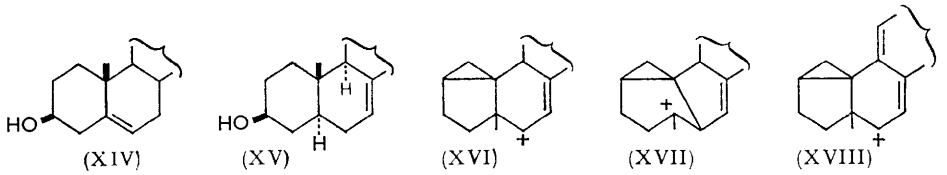
* $2·6 \times 10^{-2}$ in the presence of 0·1M-sodium acetate.

those recorded earlier for solvolysis in acetic acid [11] and for aqueous dioxan.[12] The rate for the toluene-*p*-sulphonate of (XV) is, so far as extrapolation is possible, in satisfactory agreement with the rate recorded [12,13] for cholestanyl toluene-*p*-sulphonate and indicates, as expected, no participation of the 7,8-ethylenic linkage. In contrast the toluene-*p*-sulphonate of tetrahydrophotodehydroergosterol (IV) showed strong participation, the rate constant being close to that found for cholesteryl toluene-*p*-sulphonate. The marked enhancement of rate over that for the toluene-*p*-sulphonate of the isomer (XV) can be

[11] Winstein and Adams, *ibid.*, 1948, **70**, 838.
[12] Sneen, *ibid.*, 1958, **80**, 3977.
[13] Stoll, *Z. physiol. Chem.*, 1937, **246**, 6.

explained by vinylcyclopropane participation. The toluene-*p*-sulphonate of the photo-alcohol (IV) does not react by an initial opening of the cyclopropane ring to give a $\beta\gamma$-unsaturated or other olefin followed by normal participation, for the corresponding acetate was completely stable in acetic acid containing sodium acetate or in dioxan with added toluene-*p*-sulphonic acid.

It will be noted that the initial product of the assisted solvolysis of the toluene-*p*-sulphonate of tetrahydrophotodehydroergosterol (IV) would be either the allylic carbonium ion (XVI) or the tertiary carbonium ion (XVII). The solvolysis of photodehydroergosteryl



(XIV) (XV) (XVI) (XVII) (XVIII)

toluene-*p*-sulphonate itself was even faster (by a factor of approx. 4) than that of its tetrahydro-analogue. This suggests that an even more stabilised intermediate is formed, suitably the allylic ion (XVIII).

Experimental

M. p.s were taken on the Kofler block. $[\alpha]_D$ refer to $CHCl_3$ solutions. Ultraviolet absorption spectra were determined for EtOH solutions on the Unicam S.P. 500 spectrophotometer. The alumina for chromatography was acid-washed, neutralised, and standardised according to Brockmann's method. Light petroleum refers to the fraction of b. p. 40—60°.

Photodehydrolumisteryl Acetate.—Dehydrolumisteryl acetate [14] was obtained in improved yield by the following procedure. Lumisteryl acetate (10 g.) in chloroform (150 ml.) was shaken at 0° under nitrogen with mercuric acetate (35 g.) in acetic acid (300 ml.) for 140 hr. (ultraviolet spectrophotometric control). The solution was worked up as in the earlier procedure,[14] and the product chromatographed over alumina (Grade III; 400 g.). Elution with 9 : 1 light petroleum–benzene afforded dehydrolumisteryl acetate (3 g.).

Dehydrolumisteryl acetate (400 mg.) in benzene (20 ml.) was irradiated under reflux with a bare-arc ultraviolet lamp in a nitrogen atmosphere. An ordinary Pyrex flask was employed. The reaction was followed spectrophotometrically. Removal of the solvent *in vacuo* and crystallisation of the residue from ethanol afforded *photodehydrolumisteryl acetate* (200 mg.), m. p. 100—102°. Chromatographed over alumina in light petroleum (b. p. 40—60°) and crystallised from the same solvent, this had m. p. 103°, $[\alpha]_D$ +25° (*c* 0·80), $\lambda_{max.}$ 261 mμ (ε 10,400) (Found: C, 82·4; H, 10·2. $C_{30}H_{44}O_2$ requires C, 82·5; H, 10·15%). There was a marked depression in m. p. on admixture with photodehydroergosteryl acetate.

Tetrahydrophotodehydrolumisterol and Derivatives.—Photodehydrolumisteryl acetate (1·0 g.) in ethyl acetate (80 ml.) and ethanol (100 ml.) was hydrogenated over palladised charcoal (2 mols. uptake). The product did not crystallise but it showed a broad band at 222 mμ (ε 5000) closely similar to that of tetrahydrophotohydroergosteryl acetate.[2] The oily tetrahydrophotodehydrolumisteryl acetate (1·0 g.) was saponified with 5% ethanolic sodium hydroxide (50 ml.) under reflux for 1 hr. The product again did not crystallise although it showed the correct ultraviolet absorption [$\lambda_{max.}$ 222 mμ (ε 5000)]. Tetrahydrophotodehydrolumisterol (1·2 g.) in 1 : 1 benzene–" AnalaR " pyridine (20 ml.) was added dropwise to the pyridine–chromium trioxide complex formed by adding chromium trioxide (1·5 g.) to " AnalaR " pyridine (20 ml.). After being shaken for 12 hr. the mixture was poured into water and extracted in the usual way. The oily product in ethanol (50 ml.) was treated with 5% ethanolic potassium hydroxide (2 drops). After 2 min. (ultraviolet absorption control of the appearance of the band at 305 mμ), the solution was acidified with acetic acid. Removal of the solvent *in vacuo* and chromatography over silica gel (60 g.) [elution with benzene ether (4 : 1)] gave the crystalline *diene-dione* [5α-methyl-19-norergosta-1(10),8,22-triene-2,7-dione] (XIII), m. p. (from ether–methanol) 193—195°, $[\alpha]_D$ +134° (*c* 0·75), $\lambda_{max.}$ 228 and 307 mμ (ε 7500 and 24,600 respectively), $\nu_{max.}$ (in CCl_4) 1675 (cyclohexenones) and 1581 (conjugated ethylenic linkages) $cm.^{-1}$ (Found: C, 81·55; H, 9·9. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·3%). We add the analysis

[14] Heilbron, Spring, and Stewart, *J.*, 1935, 1221.

for the corresponding diene-dione from photohydroergosterol which was inadvertently omitted from the earlier paper of Barton and Kende [2] (Found: C, 82·05; H, 10·3%).

On refluxing of the diene-dione (XIII) (12 mg.) with zinc dust (100 mg.) and acetic acid (5 ml.) the band at 307 mμ disappeared and a band at 254 mμ (ε 7000) took its place (cf. Barton and Kende [2]).

Dihydroartemisin and Derivatives.—Artemisin (5·2 g.) in ethanol (100 ml.) and benzene (100 ml.) was hydrogenated over Raney nickel until 1 mol. of hydrogen had been absorbed. Crystallisation from ethyl acetate afforded *dihydroartemisin* (X), m. p. 205—207°, $[\alpha]_D$ +96° (*c* 1·55), $\lambda_{max.}$ 244 mμ (ε 14,000) (Found: C, 68·45; H, 7·6. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·55%).

Dihydroartemisin (500 mg.) was oxidised as described for the oxidation of ψ-santonin.[15] Filtration of the product in benzene solution through silica gel and crystallisation from benzene or ethyl acetate gave the required *diketone* (XI), m. p. 156—158°, $\lambda_{max.}$ 240 mμ (ε 14,200) (Found: C, 69·05; H, 7·05. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

This diketone was treated under mildly basic conditions as detailed by Barton and de Mayo [15] for a closely analogous case. The course of the reaction was followed spectrophotometrically. Separation into acidic and neutral fractions afforded the required *diene-dione acid* (XII) (110 mg. from 200 mg. of starting diketone). Chromatography of this acid over silica gel and elution with 19 : 1 benzene–chloroform gave, on recrystallisation from benzene, the pure acid (XII), m. p. 183°, $[\alpha]_D$ +344° (*c* 0·53), $\lambda_{max.}$ 311 mμ (ε 20,500) (Found: C, 69·05; H, 7·15. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

5,6-*Dihydroergosteryl Toluene*-p-*sulphonate.*—5,6-Dihydroergosterol (2·0 g.), toluene-*p*-sulphonyl chloride (recrystallised; 2·1 g.), and pyridine (10 ml.) were left at room temperature for two days. Ethanol (2·0 ml.) was added and, after 15 min., the product was precipitated by the addition of water. Crystallisation from ether–acetone furnished the *toluene*-p-*sulphonate*, m. p. 170—172° decomp., $[\alpha]_D$ −26° (*c* 1·10) (Found: C, 76·1; H, 9·8. $C_{35}H_{52}O_3S$ requires C, 76·2; H, 9·45%). The toluene-*p*-sulphonates of cholesterol [16] and of tetrahydrophotodehydroergosterol [2] were prepared according to the literature cited.

Photodehydroergosteryl Toluene-p-*sulphonate.*—Photodehydroergosterol (IV) (300 mg.) in "AnalaR" pyridine (10 ml.) was treated with recrystallised toluene-*p*-sulphonyl chloride (500 mg.) for 18 hr. at room temperature. Crystallisation of the product from acetone furnished the *toluene*-p-*sulphonate*, m. p. 75—87° (decomp.), $[\alpha]_D$ +90° (*c* 1·03), $\lambda_{max.}$ 226 and 261 mμ (ε 16,500 and 12,500 respectively) (Found: C, 76·45; H, 9·1. $C_{35}H_{48}O_3S$ requires C, 76·6; H, 8·8%).

Tetrahydrophotodehydroergosterol Epoxide.—The alcohol (500 mg.) in dry ether was treated with perphthalic acid at 0° in the usual way (titrimetric control). After 1·1 ml. of per-acid had been consumed (constant) the solution was worked up. Crystallisation from ether–light petroleum gave *tetrahydrophotodehydroergosterol epoxide* (350 mg.), m. p. 137—139°, $[\alpha]_D$ −18° (*c* 1·00), no ultraviolet absorption (Found: C, 81·3; H, 11·2. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%).

Solvolysis of the Toluene-p-*sulphonates.*—Measurements were made at 56·1°.

(a) *In "AnalaR" acetic acid containing 0·5% of water.* Approximately 0·01M-solutions of the toluene-*p*-sulphonates were used. The course of solvolysis was determined by titration of aliquot parts with 0·5N-sodium acetate in "AnalaR" acetic acid with Crystal Violet as indicator.[17] When the acetolysis was run in the presence of sodium acetate the excess of acetate was titrated with 0·5N-toluene-*p*-sulphonic acid in "AnalaR" acetic acid.

(b) *In* 9 : 1 v/v *dioxan–water.* The determinations were made according to Sneen's method,[12] with 0·01M-solutions of the toluene-*p*-sulphonates made 0·02M with respect to sodium acetate. The stability of tetrahydrophotodehydroergosteryl acetate in this medium was checked as follows. The acetate (200 mg.) in 9 : 1 (v/v) dioxan–water (50 ml.) was heated with toluene-*p*-sulphonic acid (100 mg.) at 100° for 2 hr. The product was saponified with ethanolic sodium hydroxide and then crystallised from methanol to furnish tetrahydrophotodehydroergosterol (120 mg.), identified by m. p. and mixed m. p.

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[15] Barton and de Mayo, *J.*, 1957, 150.
[16] Wallis, Fernholz, and Gephart, *J. Amer. Chem. Soc.*, 1937, **59**, 137.
[17] Markunas and Riddick, *Analyt. Chem.*, 1951, **23**, 337.

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