510. *Photochemical Transformations. Part IV.* The Photochemistry of Prednisone Acetate.*

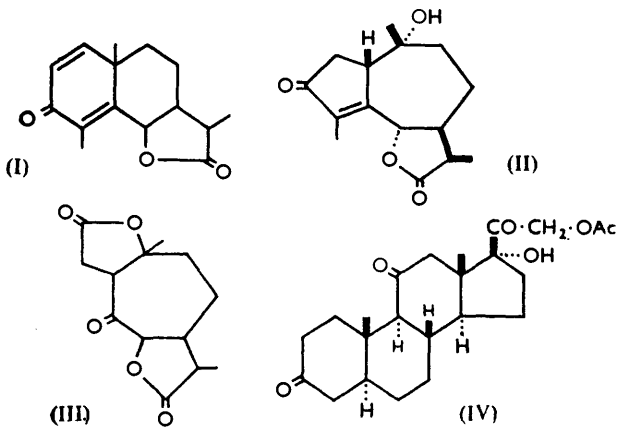
By D. H. R. Barton and W. C. Taylor.

Irradiation of prednisone acetate in aqueous acetic acid affords a product (VI) in which rings A and B have been changed into 5- and 7-membered respectively. Irradiation in ethanol at room temperature gives lumiprednisone acetate (VIII). In this compound ring A has become an umbellulone ring to which ring B is attached as a spiran. The chemistry of lumiprednisone acetate has been extensively explored. Irradiation in ethanol under more vigorous conditions furnishes a further isomer designated *neo*prednisone acetate (XXV). Irradiation in hot dioxan affords a "*para*" phenol.

The relation between lumiprednisone acetate and the other products formed by irradiation has been discussed and pertinent comparison made with the photochemistry of santonin.

Some of the results described in this paper have already been the subject of preliminary communications.[1]

The investigations described in this paper were initiated in parallel with our work on the photochemistry of santonin.[2,3,4] Some years ago we were led to suspect [5] that all *cyclo*hexadienones would prove to be readily capable of photochemical change. It was clearly desirable to examine, in particular, the effect of ultraviolet light on the medicinally important [6] prednisone acetate (V). Since it had been shown [2] that irradiation of santonin (I) in aqueous acetic acid afforded the lactone (II) our first experiments were concerned

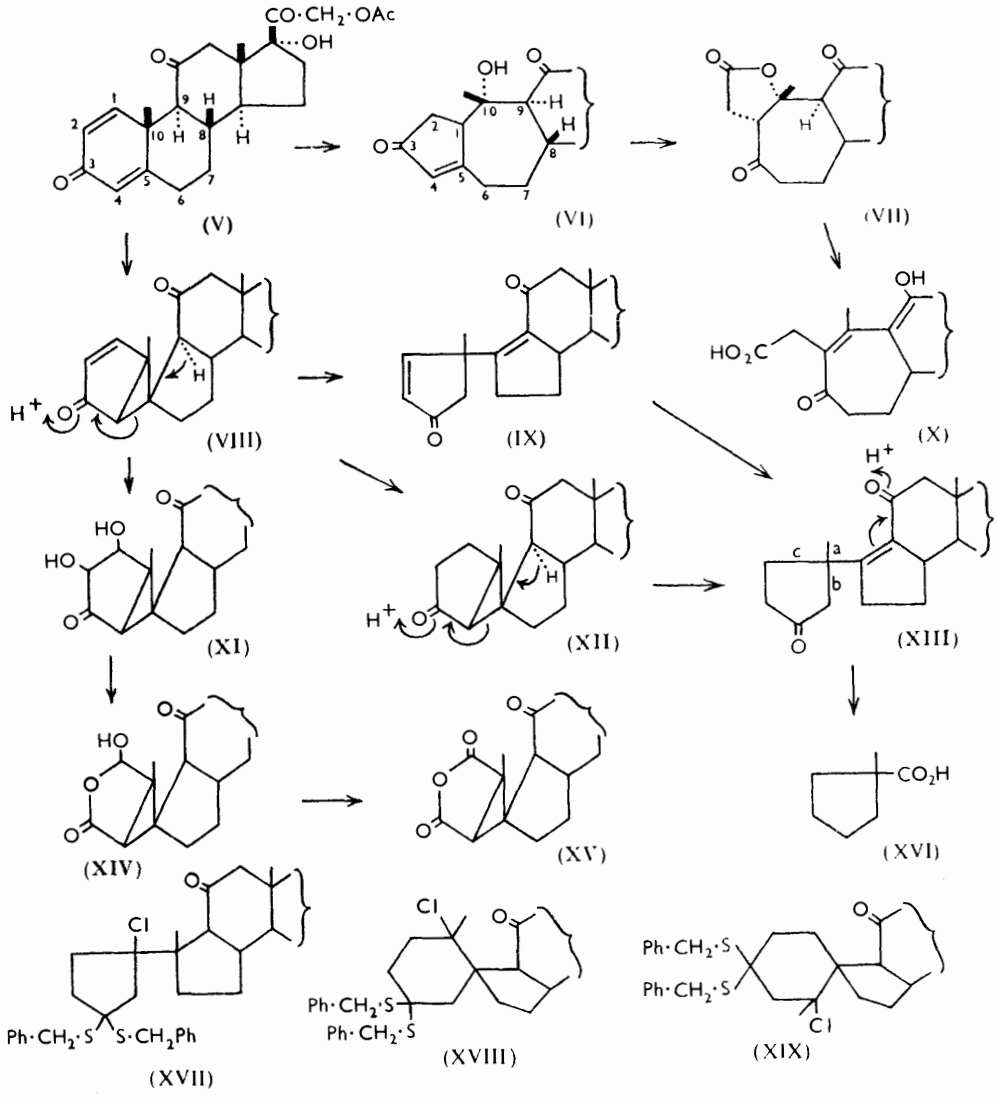


with the effect of these conditions on prednisone acetate (V). In this and subsequent photochemical experiments we showed that irradiation of 4 : 5α-dihydrocortisone acetate (IV) under the various conditions applied to prednisone acetate led to a fair recovery of unchanged material (IV). Any material not accounted for by recovery was shown to be an intractable mixture of products which could not be crystallised. We conclude that only ring A is involved in the photochemical reactions described in the sequel.

* Part III, *J.*, 1958, 688.

[1] Barton and Taylor, *Proc.*, 1957, 96, 147; *J. Amer. Chem. Soc.*, 1958, **80**, 244.
[2] Barton, de Mayo, and Shafiq, *J.*, 1957, 929.
[3] *Idem, Proc.*, 1957, 205; *J.*, 1958, 140.
[4] *Idem, Proc.*, 1957, 345; *J.*, 1958, in the press.
[5] Unpublished experiments in collaboration with Dr. E. L. Wheeler.
[6] Herzog, Payne, Jevnik, Gould, Shapiro, Oliveto, and Hershberg, *J. Amer. Chem. Soc.*, 1955, **77**, 4781; Nobile, Charney, Perlman, Herzog, Payne, Tully, Jevnik, and Hershberg, *ibid.*, p. 4184.

Irradiation of prednisone acetate (V) in refluxing aqueous acetic acid afforded a substance which is formulated as (VI) on the basis of analogy [2] and the following facts. The compound showed an ultraviolet maximum at 233 mμ (ε 15,500) characteristic of a *cyclo*pentenone (see below) with the degree of substitution indicated in formula (VI).[7] It gave infrared bands at 1740 (21-acetate), 1723 (20-ketone), 1685 (hydrogen-bonded



11-ketone and *cyclo*pentenone), and 1609 cm.$^{-1}$ (conjugated ethylenic linkage), and afforded a *cyclo*pentenone-derived mono-2 : 4-dinitrophenylhydrazone. It will be recalled that ozonolysis of the lactone (II) gave [2] the lactone (III). Similar ozonolysis of the irradiation product (VI) afforded a γ-lactone formulated as (VII). This derivative had bands in the infrared region at 1768 (γ-lactone), 1740 (21-acetate), and 1712 cm.$^{-1}$ (superimposed 11- and 20-ketones and the *cyclo*heptanone). It showed only low-intensity ketone absorption at 291 mμ in neutral solution, but in 0·1N-sodium hydroxide at room temperature it

[7] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76; Gillam and West, *J.*, 1942, 486.

at once gave a strong band at 440 mμ due to the anion of the acid (X). The compounds (IV), (V), and (VI) give no comparable band under the same conditions.

It has been shown [8] that the lactone (II) has the stereochemistry depicted. If, as already indicated, compound (VI) be assigned comparable stereochemistry, then it can be seen from models that the 11-ketone should be hydrogen-bonded with the tertiary 10-hydroxy group. The infrared evidence for this has been mentioned above.

Irradiation of prednisone acetate (V) in ethanol at room temperature under controlled conditions afforded an isomer which we call lumiprednisone acetate. This compound is sensitive to acid and base and cannot be chromatographed conveniently. It is formulated as (VIII) on the basis of the following evidence. The compound showed ultraviolet absorption at 218 and 265 mμ of a type characteristic of an umbellulone.[9] It showed infrared bands at 1735 (21-acetate), 1708 (superimposed 11- and 20-ketones), 1690 (ketone of umbellulone ring), and 1575 cm.$^{-1}$ (conjugated ethylenic linkage). Lumiprednisone acetate was readily hydrogenated to a dihydro-derivative (XII). This showed $\lambda_{max.}$ 207 mμ (ε 8100) indicative of a *cyclo*propane ring conjugated with a ketone.[9] It gave infrared bands at 1735 (21-acetate) and 1709 cm.$^{-1}$ (broad band representing superimposed 11- and 20-ketones and dihydroumbellulone ketone) and was stable to ozone. From these facts and from its composition this dihydro-derivative must contain an " extra " alicyclic ring indicated spectroscopically (see above) to be *cyclo*propane in conjugation with a ketone group. Lumiprednisone acetate contained 3 *C*-Me groups, one from the 21-acetate residue. The angular methyl group at $C_{(10)}$ must, therefore, be retained in the lumi-isomer.

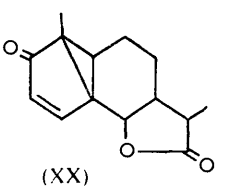
On brief treatment with acetic–perchloric acid or with Grade III alumina lumiprednisone acetate was converted into *iso*lumiprednisone acetate. This is formulated as (IX) for the following reasons. It showed an ultraviolet maximum at 241 mμ consistent with the presence (see further below) of two conjugated ketone functions and had infrared bands at 1735 (21-acetate), 1710 (superimposed 20-ketone and *cyclo*pentenone), 1675 (αβ-unsaturated 11-ketone), and 1585 cm.$^{-1}$ (conjugated ethylenic linkage). On catalytic hydrogenation it gave dihydro*iso*lumiprednisone acetate (XIII). In agreement with its formulation the latter showed an ultraviolet maximum at 251 mμ and had infrared bands at 1735 (superimposed 21-acetate and *cyclo*pentanone), 1673 (αβ-unsaturated 11-ketone) and 1595 cm.$^{-1}$ (conjugated ethylenic linkage). A subtraction curve of the ultraviolet absorption spectrum of this compound from that of its precursor (IX) gave $\lambda_{max.}$ 219 mμ (ε 7300). This is exactly the spectrum that would be expected [7] for a *cyclo*pentenone of the degree of substitution indicated in (IX). The dihydro*iso*lumiprednisone acetate (XIII) was also obtained by isomerisation of dihydrolumiprednisone acetate (XII) over alumina. These isomerisations under mild conditions are confirmatory for the presence of the *cyclo*propane ring in (VIII) and (XII). The mechanism of the rearrangements [see arrows in (VIII) and (XII)] is important in that it shows the relation between the 3- and the 11-ketone group and the *cyclo*propane ring.

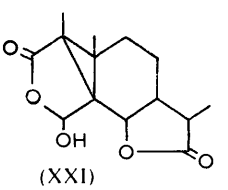
Reduction of the diketone (XIII) by the Wolff–Kishner method, followed by chromic acid oxidation in a current of steam,[10] gave acetic acid and, in small yield, 1-methyl*cyclo*pentanecarboxylic acid (XVI). The latter was identified by paper chromatography in three different systems (see p. 2508). That this represented part of the dihydro*iso*lumiprednisone acetate (XIII) molecule was confirmed by a control determination with 4 : 5α-dihydrocortisone acetate which gave only acetic acid, and by the following experiments. Dihydro*iso*lumiprednisone acetate (XIII) was treated with toluene-ω-thiol in the presence of dry hydrogen chloride to furnish in high yield a nicely crystalline product. This showed only benzylthio-absorption at 210 mμ (equivalent to two residues) and had infrared

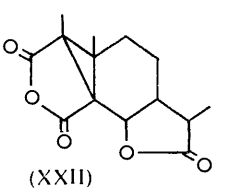
[8] Barton, *Proc.*, 1958, 61; Djerassi, Osiecki, and Herz, *J. Org. Chem.*, 1957, **22**, 1361.
[9] Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 4115, and references there cited.
[10] Pregl, " Quantitative Organic Microanalysis," ed. J. Grant, J. and A. Churchill Ltd., London, 5th edn., 1951, p. 206.

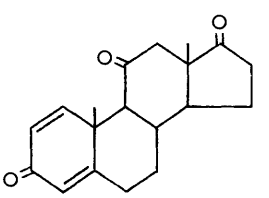
bands (in Nujol) at 1725 (21-acetate) and 1710 cm.$^{-1}$ (superimposed 11- and 20-ketones). In composition this substance represented the conversion of the *cyclo*pentanone of (XIII) into the thioketal (confirmed by a negative Zimmermann test and by the diminution of the intensity of the infrared band at about 1730 cm.$^{-1}$) with addition of one mol. of hydrogen chloride. The loss of the αβ-unsaturated 11-ketone and the addition of chloride could be explained as in (XIII; see arrows). However, the dithioketal did not give an αβ-unsaturated ketone with hot pyridine and therefore cannot be a β-chloro-ketone (with α-hydrogen). The formation of this compound is best explained by migration of bonds (a), (b), or (c) in (XIII) to give respectively the compounds (XVII), (XVIII), and (XIX), one of which formulæ must represent our product. Removal of the dithioketal grouping with Raney nickel (spectrophotometric control), followed by chromic acid oxidation, gave no trace of 1-methyl*cyclo*pentanecarboxylic acid.

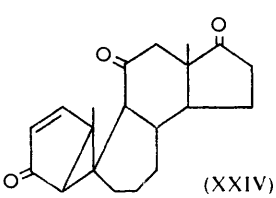
During the work [3,11] on lumisantonin (XX) the umbellulone ring was hydroxylated with osmium tetroxide and the product cleaved with periodic acid to furnish the neutral lactol (XXI). On further oxidation with chromic acid this gave [3] the anhydride (XXII), showing infrared bands at 1830 and 1770 cm.$^{-1}$. Treatment of lumiprednisone acetate in the same way gave the glycol (XI) showing ultraviolet absorption at 210 mμ (conjugated ketone and *cyclo*propane ring; cf. above) and infrared bands (in Nujol) at 1739 (21-acetate) and 1712 cm.$^{-1}$ (superimposed 11- and 20-ketones and dihydroumbellulone ketone). This was cleaved by periodic acid to afford the neutral lactol (XIV). This had no ultraviolet absorption but showed infrared bands (in Nujol) at 1767 (γ-lactol), 1748 (21-acetate), 1727 (20-ketone), and 1716 cm.$^{-1}$ (11-ketone). The lactol rapidly consumed one " atom " of oxygen on chromic acid oxidation under conditions where 4 : 5α-dihydrocortisone acetate (IV) showed no significant uptake. Although the product did not crystallise it was clearly the anhydride (XV), as shown by infrared bands at 1853 and 1773 [see bands for (XXII) mentioned above], 1745 (21-acetate), and 1718 cm.$^{-1}$ (superimposed 11- and 20-ketones).


(XX)


(XXI)


(XXII)


(XXIII)


(XXIV)

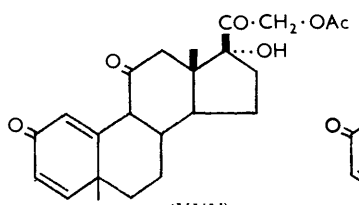
The photochemical isomerisation of prednisone acetate (V) to the lumi-isomer (VIII) is probably a general reaction of 11-keto-steroids with the dienone system in ring A. Thus androsta-1 : 4-diene-3 : 11 : 17-trione (XXIII), prepared by oxidation of prednisone with sodium bismuthate,[12,13] was isomerised readily to a lumi-isomer which we formulate, on the basis of its spectroscopic properties and optical rotation, as (XXIV).

Chromatography of the mother-liquors remaining after removal of lumiprednisone acetate afforded, besides unchanged prednisone acetate, a further isomer which we call *neo*prednisone acetate. This was obtained in only minute yield, but irradiation of

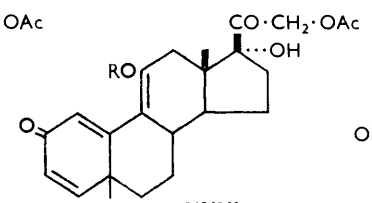
[11] Arigoni, Bosshard, Bruderer, Büchi, Jeger, and Krebaum, *Helv. Chim. Acta*, 1957 **40** 1732; see also Cocker, Crowley, Edward, McMurry, and Stuart, *J.*, 1957, 3416.
[12] Rigby, *J.*, 1950, 1907.
[13] Brooks and Norymberski, *Biochem. J.*, 1953, **55**, 371.

prednisone acetate in refluxing ethanol under controlled conditions improved the ease of preparation and gave sufficient material for our purposes. The compound had an ultraviolet absorption spectrum essentially the same as that of prednisone acetate. The infrared bands in the carbonyl (and hydroxy) region were superimposable upon those of prednisone acetate. Clearly *neo*prednisone acetate is a homoannular *cyclo*hexadienone. We formulate it as (XXV) on the basis of this and the following evidence. The ultraviolet spectrum of prednisone acetate is the same in ethanol and in 0·1N-ethanolic sodium hydroxide. *neo*Prednisone acetate gives an immediate red-brown colour on dissolution in this 0·1N-base and shows a strong band at 468 mμ which we assign to the anion of the enol (XXVI; R = H). On acidification this band shifts reversibly to 340 mμ, which is the position to be expected for the enol (XXVI; R = H). By very brief treatment with 0·1N-methanolic sodium hydroxide followed by acidification it was possible to isolate the enol in crystalline form. It showed the same spectroscopic behaviour as detailed above and showed infrared bands at 1735 (21-acetate), 1720 (20-ketone), 1660 (3-ketone), and 1605 cm.$^{-1}$ (conjugated ethylenic linkage). The saturated 11-ketone band of the diketone (XXV) had thus been destroyed by enolisation, as already formulated in (XXVI). Acetylation of the enol with pyridine–acetic anhydride gave the expected enol acetate (XXVI; R = Ac). This had ultraviolet absorption at 242 and 288 mμ in agreement with this formulation and showed infrared bands at 1749 (11-enol acetate), 1733 (21-acetate), 1662 (3-ketone), and 1621 and 1605 cm.$^{-1}$ (conjugated ethylenic linkages).

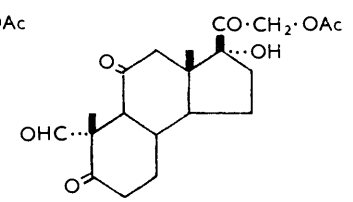
During the examination of *neo*prednisone acetate we had occasion to ozonise prednisone acetate in ethyl acetate at low temperature under spectroscopic control. This gave in



(XXV)



(XXVI)



(XXVII)

satisfactory yield the aldehyde (XXVII), which had infrared bands at 2725 (aldehyde-hydrogen), 1733 (superimposed aldehyde and 21-acetate), and 1701 cm.$^{-1}$ (superimposed 5- and 11-ketones), in agreement with the assigned constitution.

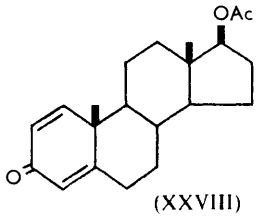
The photochemical conversion of a dienone into a phenol was first effected by Staudinger and Bereza.[14] During our work on the photochemistry of prednisone acetate there appeared a paper by Dutler, Bosshard, and Jeger[15] which reported the conversion of 1-dehydrotestosterone acetate (XXVIII) into the phenol (XXIX) by irradiation in dioxan. The application of these conditions to prednisone acetate gave us a phenol which we formulate as (XXX; R = X = H) or (XXXI; R = X = H) on the basis of the following evidence. Acetylation with pyridine–acetic anhydride gave a monoacetate (XXX or XXXI; R = Ac, X = H). The phenol and its acetate had the expected spectroscopic properties (see p. 2509). On bromination in aqueous dioxan in the presence of calcium carbonate with excess of bromine the phenol gave only a monobromo-derivative (XXX or XXXI; R = H, X = Br). Under the same conditions the phenol (XXXII; R = X = H) * gave a dibromo-derivative (XXXII; R = H, X = Br) isolated, after treatment with pyridine–acetic anhydride, as the diacetate (XXXII; R = Ac, X = Br). These experiments suggest that the phenol from prednisone acetate is of the "*para*" type,

* This phenol was very kindly provided by Messrs. Glaxo Laboratories Ltd. It is our understanding that this substance and many of its derivatives will be described in a paper to be submitted shortly for publication in this *Journal*.

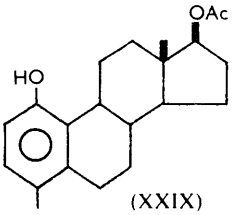
[14] Staudinger and Bereza, *Annalen*, 1911, **380**, 243.
[15] Dutler, Bosshard, and Jeger, *Helv. Chim. Acta*, 1957, **40**, 494.

as are (XXX) and (XXXI), and not of the "*meta*" type such as (XXXII). Inspection of infrared data (see p. 2509) confirmed this.

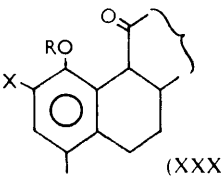
Lumiprednisone acetate probably occupies a special position in the photochemical transformation products of prednisone acetate. Thus (see XXXIII) further irradiation could well promote the migration of bond (a) or (b) to $C_{(10)}$ with re-formation of the *cyclo*hexadienone system. In the first case prednisone acetate is re-formed, in the second *neo*prednisone



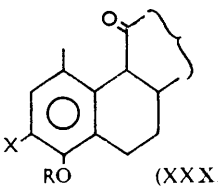
(XXVIII)



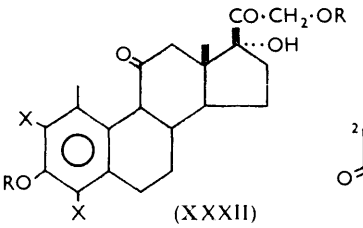
(XXIX)



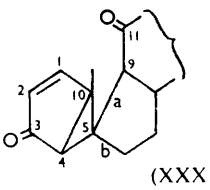
(XXX)



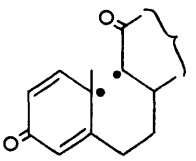
(XXXI)



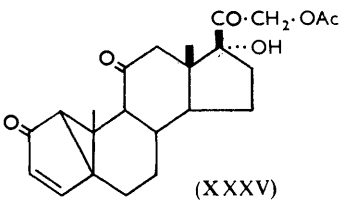
(XXXII)



(XXXIII)



(XXXIV)



(XXXV)

acetate results. Migration of bond (a), on the other hand, to $C_{(4)}$ would give the "*para*" phenol of type (XXX), whilst similar migration of bond (b) would give a "*para*" phenol of type (XXXI). We have confirmed that lumiprednisone acetate does not rearrange to a phenol when merely refluxed in dioxan, but does furnish the phenol (XXX or XXXI; R = X = H) mentioned above on irradiation in refluxing dioxan.

The compound "A4" of Dutler, Bosshard, and Jeger[15] may, on the basis of its ultraviolet absorption spectrum, have a structure comparable with that of our lumiprednisone acetate. However, the $[M]_D$ change for making "A4" is strongly positive, whereas the $[M]_D$ change for the conversion of prednisone into lumiprednisone acetate is strongly negative. If the compounds are indeed comparable then they may well differ in stereochemistry. We do not wish to imply any stereochemical assignments for the prednisone acetate derivatives described in the present paper.

The formation of substantially one product, lumiprednisone acetate, on irradiation of prednisone acetate in ethanol contrasts with the multiplicity of products reported by Dutler, Bosshard, and Jeger[15] from the irradiation of 1-dehydrotesterone acetate in dioxan. We believe that this is probably not a solvent effect but a consequence of the presence of the 11-keto-group in prednisone acetate. This must undoubtedly weaken the 9 : 10-bond because the diradical formed by homolytic rupture (see XXXIV) would be stabilised not only as a $C_{(10)}$ phenoxide radical but also by resonance of the $C_{(9)}$-radical with the 11-ketone. It is understandable therefore why lumiprednisone is formed by migration of the 9 : 10-bond rather than by internal rearrangement of the *cyclo*hexadienone ring (1 : 5-bond formation) such as happens preferentially in santonin[3,11] and (presumably) in 1-dehydrotestosterone acetate.

Lumiprednisone acetate is *not* the precursor of the *cyclo*pentenone (VI). Thus, whilst lumisantonin (XX) [3,11] is smoothly transformed into (II) in refluxing aqueous acetic acid,[3] lumiprednisone acetate is stable under these conditions. Indeed, the product (VI) could be derived from an isomer of prednisone acetate formulated as in (XXXV), which we have not isolated as a stable product, although there is probably a direct route to (VI) from (V) of the type encountered in santonin chemistry.[3]

Experimental

M. p.s were taken on the Kofler block. Ultraviolet absorption spectra were determined for EtOH solutions with the Unicam S.P. 500 Spectrophotometer. All rotations are in $CHCl_3$. Infrared spectra also refer to $CHCl_3$ solution unless stated otherwise. Light petroleum refers to the fraction of b. p. 60—80°.

Irradiation in Aqueous Acetic Acid.—Prednisone acetate (3·1 g.) in 45 : 55 acetic acid–water (250 ml.) was irradiated in a quartz flask under reflux with a bare mercury arc (125 w) lamp until the rotation fell to approx. 130° (about 1 hr.). Removal of the solvent under reduced pressure afforded a gum which was separated (sodium hydrogen carbonate) into neutral and acidic fractions. The neutral fraction (2·9 g.) was chromatographed over silica gel (150 g.): elution with chloroform (3 fractions) yielded starting material (0·45 g.); elution with acetone–chloroform (1 : 4) afforded the *acetate* (VI) (0·40 g.), prisms (from methanol), m. p. 240—243°, $[\alpha]_D$ +134° (*c* 0·51), $\lambda_{max.}$ 233 mμ (ε 15,500), $\nu_{max.}$ 1740, 1723, 1685, and 1609 cm.$^{-1}$ (Found: C, 66·0; H, 7·4; Ac, 10·7. $C_{23}H_{30}O_7$ requires C, 66·0; H, 7·25; 1Ac, 10·4%). The 2 : 4-*dinitrophenylhydrazone* (from chloroform–ethanol) had m. p. 270—275° (decomp.), $\lambda_{max.}$ 390—392 mμ (ε 29,500) (Found: C, 58·0; H, 6·0; N, 9·4. $C_{29}H_{34}O_{10}N_4$ requires C, 58·2; H, 5·7; N, 9·35%).

Ozonolysis of the Acetate (VI).—The acetate (40 mg.) in chloroform (15 ml.) was ozonised at −70° for 18 min. (disappearance of ultraviolet max. at 233 mμ). The ozonide was decomposed by evaporation of the solvent on the steam-bath in the presence of water (2 ml.); separation of the mixture through sodium hydrogen carbonate yielded a neutral fraction (20 mg.) which was crystallised from methanol (plates) to give the *lactone* (VII), m. p. 143—145°, $[\alpha]_D$ +128° (*c* 0·66), $\lambda_{max.}$ 291 mμ (ε 200), $\lambda_{max.}$ (in 0·1N-NaOH) 439—442 mμ (ε 8000), $\nu_{max.}$ 3420, 1768, 1740, and 1712 cm.$^{-1}$ (Found: C, 62·6; H, 6·6. $C_{22}H_{28}O_8$ requires C, 62·8; H, 6·7%).

Irradiation of 4 : 5α-*Dihydrocortisone Acetate.*—(*a*) 4 : 5α-Dihydrocortisone acetate (880 mg.) in 45 : 55 acetic acid–water (200 ml.) (initial $[\alpha]_D$ +110°) was irradiated as described above for 3 hr. (final $[\alpha]_D$ +65°). Separation of the product through sodium hydrogen carbonate yielded a neutral fraction (540 mg.), which was chromatographed on alumina (Grade V; 100 g.) (elution with benzene and 8 : 1-benzene–ethyl acetate) to yield starting material (490 mg.) (m. p. and mixed m. p., $[\alpha]_D$, and infrared spectrum) as the only isolable product. The acidic fraction (330 mg.) was a dark gum which did not afford any crystalline material on chromatography over silica gel.

(*b*) 4 : 5α-Dihydrocortisone acetate (860 mg.) in ethanol (200 ml.) (initial $[\alpha]_D$ +110°) was irradiated under reflux for 1 hr. (final $[\alpha]_D$ +92°). Starting material (553 mg.) (m. p. and mixed m. p., $[\alpha]_D$, and infrared spectrum) was recovered by crystallisation; the remaining material was a non-crystallisable syrup.

(*c*) 4 : 5α-Dihydrocortisone acetate (730 mg.) in dioxan (100 ml.) was irradiated under reflux for 1 hr. ($[\alpha]_D$ changed from +110° to +81°). Chromatography of the product over alumina afforded starting material (480 mg.) (m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum).

(*d*) 4 : 5α-Dihydrocortisone acetate (867 mg.) in dioxan (50 ml.) diluted with ethanol (300 ml.) was irradiated at room temperature for 30 hr. (rotation changed from +110° to +100°). Chromatography of the product on alumina afforded starting material (735 mg.) (m. p. and mixed m. p., $[\alpha]_D$, and infrared spectrum).

Lumiprednisone Acetate.—Prednisone acetate (3·4 g.) in ethanol (350 ml.) was irradiated in a quartz flask at room temperature (air cooling) until the rotation fell to approx. 0° (about 20 hr.). Removal of the solvent under reduced pressure afforded a yellow gum which was fractionally crystallised from ethyl acetate–light petroleum to constant rotation, giving as the less soluble product, *lumiprednisone acetate* (VIII) (0·8 g.), plates (from methanol), m. p. 224—226°, $[\alpha]_D$ −84° (*c* 0·80), $\lambda_{max.}$ 218 and 265 mμ (ε 5900 and 2300 respectively), $\nu_{max.}$ 1735, 1708, 1690, and 1575 cm.$^{-1}$ [Found: C, 68·95; H, 7·05; *C*-Me, 9·5. $C_{22}H_{28}O_6$ requires C, 69·0;

H, 7·05; 3*C*-Me (1 from 21-acetate), 11·3%]. Starting material (540 mg.) was obtained as the more soluble fraction. Chromatography of the mother-liquors over silica gel (100 g.) and elution with benzene–chloroform (1 : 1) gave a fraction which was chromatographed on alumina (Grade V; 20 g.) to give, after elution with benzene–chloroform (4 : 1), *neo*prednisone acetate (7 mg.).

Dihydrolumiprednisone Acetate.—Lumiprednisone acetate in ethanol was hydrogenated over palladium–charcoal (10%) (rapid uptake of 1 mol.). The *dihydro*-derivative (XII), prisms or needles (from ethyl acetate–light petroleum), had m. p. 200—203°, $[\alpha]_D$ +95° (*c* 1·15), $\lambda_{max.}$ 207 mμ (ε 8100), $\nu_{max.}$ 1735 and 1709 (broad) cm.$^{-1}$ (Found: C, 68·8; H, 7·65. $C_{23}H_{30}O_6$ requires C, 68·6; H, 7·5%). The compound was recovered unchanged (m. p. and mixed m. p.) after treatment for 30 min. at −70° with 3 molar equivalents of ozone.

iso*Lumiprednisone Acetate.*—(*a*) Lumiprednisone acetate (300 mg.) in acetic acid (25 ml.) and 70% perchloric acid (0·05 ml.) was heated at 85° for 20 min. The solution was then concentrated *in vacuo* to about 5 ml., diluted with ethyl acetate, and worked up the usual way, to yield iso*lumiprednisone acetate* (IX) (211 mg.), blades (from ethyl acetate–light petroleum), m. p. 202—204° (after loss of solvent at 140°), $[\alpha]_D$ −103° (*c* 0·50), $\lambda_{max.}$ 210 and 241 mμ (ε 8000 and 10,600 respectively), $\nu_{max.}$ 1735, 1710, 1675, and 1585 cm.$^{-1}$ [Found: C, 68·8; H, 6·85; *C*-Me, 11·9. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·05; 3*C*-Me (1 from 21-acetate), 11·3%].

(*b*) Lumiprednisone acetate (42 mg.) in benzene–chloroform (7 : 3) (30 ml.) was shaken with alumina (Grade III; 90 mg.) for 1 hr. The mixture was filtered, the alumina was washed 3 times with warm methanol, and the combined filtrates were evaporated to yield *iso*lumiprednisone acetate (9 mg.).

(*c*) Lumiprednisone acetate was recovered unchanged (m. p., mixed m. p., and $[\alpha]_D$) after 12 hours' refluxing in acetic acid–water (45 : 55).

*Dihydro*iso*lumiprednisone Acetate.*—*iso*Lumiprednisone acetate in ethanol was hydrogenated on palladium–charcoal (10%) (rapid uptake of 1 mol.). The *dihydro*-derivative (XIII) formed needles (from ethyl acetate–ether–light petroleum), m. p. 192—195°, $[\alpha]_D$ +127° (*c* 0·50), $\lambda_{max.}$ 251 mμ (ε 8700), $\nu_{max.}$ 1735, 1673, and 1595 cm.$^{-1}$ (Found: C, 68·6; H, 7·35. $C_{23}H_{30}O_6$ requires C, 68·6; H, 7·5%). The *monosemicarbazone*, prepared in aqueous ethanol at room temperature, had m. p. 253—256°, $\lambda_{max.}$ 236 mμ (ε 15,200), $\nu_{max.}$ 1740, 1720, 1690, 1655, and 1577 cm.$^{-1}$ (Found: N, 8·85. $C_{24}H_{33}O_6N_3$ requires N, 9·15%). The compound gave a negative Zimmermann test in agreement with the disappearance of the *cyclo*pentanone carbonyl absorption from the infrared spectrum.

Isolation and Characterisation of 1-*Methyl*cyclo*pentanecarboxylic Acid.*[16]—Dihydro*iso*lumiprednisone acetate (330 mg.) and hydrazine hydrate (0·2 ml.) were refluxed in ethanol (2 ml.) for 2 hr.; sodium (0·3 g.) in ethanol (5 ml.) was added, and the mixture heated at 150° for 7 hr. The crude product obtained after being worked up in the usual way gave a negative Zimmermann test; in the infrared spectrum, the comparative weakness of the carbonyl bands (1690, 1663 cm.$^{-1}$) suggested that considerable reduction had occurred also at the 11- and the 20-carbonyl position. This was not overcome by reduction of the semicarbazone under rigidly anhydrous conditions, the product being essentially the parent ketone (infrared spectrum and positive Zimmermann test).

Oxidation of the Wolff–Kishner reduction product was conducted under similar conditions to those described by Pregl [10] for the determination of *C*-methyl. The crude reduction product (*ca.* 100 mg.) was introduced into the reaction flask containing chromic acid reagent (10 ml.) (containing 10 times the concentration of chromium trioxide detailed in ref. 10) and concentrated sulphuric acid (2 ml.); the mixture was brought rapidly to the boil and water slowly distilled off, water being introduced at an equivalent rate to maintain a constant volume in the flask. Distillation was continued until production of volatile acid ceased (titration of distillates). The alkaline distillates were evaporated to dryness and acidified with the minimum volume of 6N-sulphuric acid, and the solution was extracted with ether (5 × 3 ml.). The combined ether extracts were dried (Na_2SO_4) and then carefully evaporated to dryness; the residue was subjected to partition chromatography on aqueous silica gel, with chloroform–butanol as the mobile phase,[17] the eluates being titrimetrically estimated for acids with 0·05N-sodium hydroxide and thymol-blue as indicator. Control experiments showed that 1-methyl*cyclo*pentanecarboxylic was quantitatively recovered under the conditions of oxidation and that it could

[16] Meerwein, *Annalen*, 1918, **417**, 255.
[17] Elsdon, *Biochem. J.*, 1946, **40**, 252.

be quantitatively separated from acetic acid by the partition chromatography, being eluted with water-saturated chloroform containing 1% (v/v) of butan-1-ol (CB1); acetic acid was eluted (94% recovery) with 20% butan-1-ol–chloroform (CB20). In a typical oxidation 99·4 mg. of crude reduction product afforded volatile acid equivalent to 11·82 ml. of 0·05N-alkali (2 mol. of acid require approx. 14 ml.). The concentrated volatile acid fraction, which gave spots on paper chromatograms with R_F values (in butan-1-ol–1·5N-ammonia) of 0·06 (acetic acid) and 0·43, was partitioned on a silica gel column (7 g.). Elution with CB1 (10 ml.) gave a fraction which consumed 0·098 ml. of 0·05N-alkali; isolation of the acidic material afforded a concentrate containing 1-methyl*cyclo*pentanecarboxylic acid, identified by paper chromatography in 3 solvent systems:

	R_F values		
	Oxidation product	1-Methyl*cyclo*pentanecarboxylic acid	1-Methyl*cyclo*hexanecarboxylic acid
*iso*Propanol–0·15N-ammonia	0·89	0·89	—
Butan-1-ol–1·5N-ammonia	0·43	0·43	0·52
Ethanol (95%)–1% ammonia	0·63	0·63	—

Elution with CB20 yielded acetic acid (R_F 0·06) equivalent to 10·32 ml. of 0·05N-alkali.

4 : 5α-Dihydrocortisone acetate (93 mg.), oxidised in a similar fashion, yielded acetic acid as the only detectable volatile acid.

*Reaction of Dihydroiso*lumiprednisone *Acetate with Toluene-ω-thiol.*—Dihydro*iso*lumiprednisone acetate (267 mg.) in acetic acid (3 ml.) saturated with hydrogen chloride was treated at 0° with toluene-ω-thiol (0·16 ml., 1 mol.); separation of crystalline product commenced after 30 min. After 2 hr. the mixture was carefully neutralised with sodium hydrogen carbonate, and extracted with chloroform to give the derivative [(XVII), (XVIII), or (XIX)], plates (from methanol), m. p. 172—173°, $\lambda_{max.}$ 210 mμ (ε 24,000), $\nu_{max.}$ (Nujol) 1725 and 1710 cm.$^{-1}$ (Found: C, 66·4; H, 6·7; Cl, 5·25; S, 9·55. $C_{37}H_{45}O_5S_2Cl$ requires C, 66·4; H, 6·8; Cl, 5·3; S, 9·6%). The compound gave a positive Beilstein test for halogen and a negative Zimmermann test; there was no αβ-unsaturated ketone chromophore (ultraviolet spectrum) after treatment with pyridine at 100°. The mercaptal (230 mg.) in dioxan (5 ml.) was refluxed with Raney nickel for 12 hr. (disappearance of ultraviolet max. at 215 mμ). Oxidation of the crude product yielded no 1-methyl*cyclo*pentanecarboxylic acid (paper chromatography).

Hydroxylation of Lumiprednisone Acetate.—Reaction of lumiprednisone acetate (36·4 mg.) with osmium tetroxide (23 mg.) for 48 hr. and decomposition of the osmate ester with hydrogen sulphide afforded the *glycol* (XI), prisms (from ethyl acetate–light petroleum), m. p. 225—228°, $[\alpha]_D$ +120° (*c* 0·70), $\lambda_{max.}$ 210 mμ (ε 7300), $\nu_{max.}$ (Nujol) 1739 and 1712 cm.$^{-1}$ (Found: C, 63·6; H, 7·05. $C_{23}H_{30}O_8$ requires C, 63·6; H, 6·95%).

The glycol (in aqueous ethanol) was cleaved by sodium metaperiodate (rapid uptake of 2 mol.) to furnish the *lactol* (XIV), leaflets from ethyl acetate–methanol–light petroleum, m. p. 211—214°, $[\alpha]_D$ +136° (*c* 0·50), high-intensity ultraviolet maximum, and bands in the infrared (Nujol) at 1767, 1748, 1727, and 1716 cm.$^{-1}$ (Found: C, 62·65; H, 6·7. $C_{22}H_{28}O_8$ requires C, 62·8; H, 6·7%).

Oxidation of the Lactol (XIV).—The lactol was oxidised rapidly with the chromic acid–acetone reagent [18] to give a product which did not crystallise; a purified fraction obtained by chromatography on silica gel (elution with 4 : 1 benzene–ethyl acetate) had strong infrared bands at 1853 and 1773 (5-membered unsaturated anhydride), 1745 (21-acetate), and 1718 cm.$^{-1}$ (11- and 20-ketones). The lactol had consumed 0·75 equivalent of oxygen after 24 hr. in acetic acid–sodium dichromate; a control experiment showed that 4 : 5α-dihydrocortisone acetate consumed 0·09 equivalent of oxygen in the same period.

Isomerisation of Dihydrolumiprednisone Acetate.—Dihydrolumiprednisone acetate (40 mg.) was chromatographed on alumina (Grade III; 6 g.) (larger quantities of alumina gave poor recovery of material); elution with benzene–ethyl acetate (85 : 15 and 80 : 20; 8 × 50 ml. fractions) gave material enriched in dihydro*iso*lumiprednisone acetate ($\varepsilon_{251}/\varepsilon_{210}$ ~1—1·5; cf. 2·9 for the pure compound). These fractions were combined (15 mg.) and rechromatographed on alumina (Grade III; 5·5 g.); material eluted with benzene–ethyl acetate (88 : 12, 2 fractions; and 86 : 14, 2 fractions) was recrystallised 3 times from ethyl acetate–light petroleum, to give dihydro*iso*lumiprednisone acetate (3·5 mg.), m. p. and mixed m. p. 193—195°,

[18] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.

$\lambda_{max.}$ 251 mμ (ε 8700). The semicarbazone had m. p. 253—255°, undepressed on admixture with dihydro*iso*lumiprednisone acetate semicarbazone.

Irradiation of Prednisone Acetate in Dioxan.—Prednisone acetate (1·4 g.) in dioxan (100 ml.) was irradiated in a quartz flask under reflux until the rotation fell to approx. 100° (about 1·3 hr.). Chromatography of the product on silica gel (20 g.) and elution with benzene–chloroform (70 : 30) yielded a fraction (530 mg.) from which were separated by chromatography on alumina (Grade V, 30 g.) starting material (120 mg.) and *iso*lumiprednisone acetate (25 mg.); elution with benzene–chloroform (6 : 4) afforded the *phenol* (XXX or XXXI; R = X = H) (200 mg.), needles (from methanol), m. p. 258—265° (decomp.), $[\alpha]_D$ +294° (*c* 1·20 in dioxan), $\lambda_{max.}$ 210 and 286 mμ (ε 21,600 and 3300 respectively), $\lambda_{max.}$ in 0·1N-NaOH 220, 246, and 302 mμ (ε 33,500, 11,500, and 4200 respectively) (Found: C, 69·3; H, 6·65. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·05%). The *acetate*, prepared in acetic anhydride–pyridine overnight, had m. p. 223—227° (from methanol), $[\alpha]_D$ +296° (*c* 1·05 in dioxan), $\lambda_{max.}$ 220 and 268 mμ (ε 7300 and 520 respectively) (Found: C, 68·2; H, 6·9; Ac, 19·0. $C_{25}H_{30}O_7$ requires C, 67·85; H, 6·8; 2Ac, 19·45%).

The *bromo-derivative* was prepared in aqueous dioxan (1 : 8) in the presence of calcium carbonate (uptake of 1 mol.); it had m. p. 235—238° (from ethyl acetate–light petroleum), $\nu_{max.}$ 3521, 3460 (hydrogen-bonded phenolic hydroxyl), 3401 (hydroxyl), 865 cm.$^{-1}$ (Found: C, 57·2; H, 5·95; Br, 16·9. $C_{23}H_{27}O_6Br$ requires C, 57·6; H, 5·7; Br, 16·7%).

A solution of the phenol (XXXII; R = X = H) (27·2 mg.) in dioxan (3 ml.) and water (0·1 ml.) was titrated in presence of calcium carbonate (500 mg.) with bromine in dioxan (2 mol. uptake). Inorganic material was removed and the filtrate diluted with water (8 ml.) and worked up in the usual way with ethyl acetate. Acetylation of the crude product in pyridine–acetic anhydride overnight afforded the *acetate* (XXXII; R = Ac; X = Br) (11 mg.), m. p. 215—217° (from ethyl acetate–light petroleum), with no strong bands in the infrared spectrum (Nujol) in the 800—900 cm.$^{-1}$ region (Found: Br, 26·9. $C_{25}H_{28}O_7Br_2$ requires Br, 26·6%). Under similar conditions of bromination, 4 : 5α-dihydrocortisone acetate was recovered unchanged.

Infrared Spectra of the Phenols and Derivatives in the 800—900 *cm.*$^{-1}$ *Region of the Spectrum.*—All spectra were taken (for solubility reasons) in Nujol with the results summarised in the annexed Table.

Compound	Intense band (cm.$^{-1}$)	Substitution assignment.[19,20]
(XXX or XXXI; R = X = H)	809	1 : 2 : 3 : 4-
(XXX or XXXI; R = Ac, X = H)	817	1 : 2 : 3 : 4-
(XXX or XXXI; R = Ac, X = Br)	865	1 : 2 : 3 : 4 : 5-
(XXXII; R = Ac, X = H and Ac at 17)	865	1 : 2 : 3 : 5-
(XXXII; R = Ac, X = Br)	None	1 : 2 : 3 : 4 : 5 : 6-

All compounds showed, in addition, a weak band at 844—847 cm.$^{-1}$ which was independent of the substitution pattern.

Irradiation of Lumiprednisone Acetate.—Lumiprednisone acetate (80 mg.) in dioxan (10 ml.) was irradiated in a quartz tube under reflux until the rotation rose to approx. +150° (7 min.). Starting material (10 mg.) and oil were separated (more soluble fraction) by crystallisation of the product from ethyl acetate; the remaining material was chromatographed on silica gel (20 g.). The material eluted with benzene–ethyl acetate (92 : 8) (7 fractions) was crystallised twice from methanol, to give the phenol (XXX or XXXI; R = X = H) (20 mg.) (m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum) characterised as the acetate (m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum). Lumiprednisone acetate (26 mg.) in dioxan (7 ml.) was refluxed for 1 hr., during which no change in rotation occurred. Starting material (m. p., and mixed m. p.) was recovered from the solution.

Androsta-1 : 4-*diene*-3 : 11 : 17-*trione* (XXIII).—Prednisone (2·12 g.) in acetic acid (60 ml.) and water (60 ml.) was treated with sodium bismuthate (25 g.) with stirring. After 35 min., 75% of the acetic acid was neutralised by addition of potassium hydroxide (45 g.) in water (300 ml.); the mixture was filtered, the residue was washed with chloroform, and the combined filtrates were extracted with chloroform in the usual way. The crude product, in benzene, was filtered through alumina (Grade V; 15 g.), to give *androsta*-1 : 4-*diene*-3 : 11 : 17-*trione* (XXIII) (1·45 g.),

[19] Bellamy, " Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 64.
[20] Randle and Whiffen, Conference on Molecular Spectroscopy (Institute of Petroleum), Oct. 1954, Paper 12.

prisms (from benzene–light petroleum), m. p. 196—199°, $[\alpha]_D$ +248° (*c* 1·17), $\lambda_{max.}$ 238 mμ (ε 13,800), $\nu_{max.}$ (Nujol) 1750 (*cyclo*pentanone), 1712 (11-ketone), 1670 (conjugated ketone), and 1630 and 1606 cm.$^{-1}$ (conjugated ethylenic linkages) (Found: C, 76·3; H, 7·65. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·45%). This trione (XXIII) (925 mg.) in dioxan (100 ml.) was irradiated with ultraviolet light under reflux until the rotation had fallen to +141° (19 min.). Chromatography of the product on silica gel (70 g.) and elution with benzene–ether (1 : 2) yielded the *lumi-compound* (XXIV) (20 mg.), prisms (from ethyl acetate–light petroleum), m. p. 179—181°, $[\alpha]_D$ −103° (*c* 0·46), $\lambda_{max.}$ 219, 264 mμ (ε 5500 and 2000 respectively), $\nu_{max.}$ 1746, 1720, 1696, and 1576 cm.$^{-1}$ (Found: C, 76·5; H, 7·75. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·45%).

neo*Prednisone Acetate and Derivatives*.—Prednisone acetate (3 g.) in ethanol (400 ml.) was irradiated in a quartz flask at the b. p. until the rotation had fallen to approx. 0° (about 1 hr.). The products of two such experiments were combined and chromatographed over silica gel (200 g.); after elution with benzene (1·7 l.) to remove the bulk of yellow oily material [chromatography of this fraction over alumina (60 g.) and elution with benzene–chloroform (9 : 1) gave *iso*lumiprednisone acetate (107 mg.), and with benzene–chloroform (6 : 1) gave starting material (1·2 g.)], the column was stripped with acetone and the recovered material rechromatographed over silica gel (200 g.). Six fractions eluted with benzene–chloroform (3 : 2 and 1 : 1) were combined and crystallised, to give neo*prednisone acetate* (XXV) (130 mg.), needles (from methanol), m. p. 230—233°, $[\alpha]_D$ −173° (*c* 0·51), $\lambda_{max.}$ 242 mμ (ε 12,700), in 0·1N-NaOH, $\lambda_{max.}$ 238, 468 mμ (ε 10,700 and 7900 respectively), changing on acidification to $\lambda_{max.}$ 240 and 340 mμ (ε 13,000 and 4200 respectively), $\nu_{max.}$ 1735, 1710, 1658, and 1618 cm.$^{-1}$ (Found: C, 68·85; H, 6·8. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·05%).

*neo*Prednisone acetate (50 mg.) in methanol (4 ml.) was treated with 0·1N-sodium hydroxide (1·4 ml.), and the red solution immediately acidified with 0·1N-sulphuric acid (2 ml.), after which the mixture was diluted with water (10 ml.) and extracted with ethyl acetate (3 × 20 ml.). The material thus obtained was essentially the enol; to complete the conversion, a solution in methanol (0·5 ml.) was re-treated with alkali and then acid as above, and the material precipitated on dilution with water (4 ml.) collected by centrifugation after good washing with water. The enol formed rosettes (from ethyl acetate–light petroleum), m. p. 228—230°, $\lambda_{max.}$ 242, 340 mμ (ε 11,700 and 3600 respectively), changing in 0·1N-NaOH to 238, 468 mμ (ε 9700 and 7900 respectively), $\nu_{max.}$ (Nujol) 1735 and 1720 (21-acetate and 20-ketone respectively), 1660 (conjugated ketone) and 1605 cm.$^{-1}$ (conjugated ethylenic linkage).

The enol was acetylated in pyridine–acetic anhydride (24 hr.) and worked up in the usual way. Chromatography of the product on alumina (Grade V; 4 g.) and elution with benzene–ethyl acetate (96 : 4) yielded the *enol acetate* (XXVI; R = Ac), needles (from ethyl acetate–light petroleum), m. p. 192—193°, $[\alpha]_D$ +147° (*c* 0·32), $\lambda_{max.}$ 242 and 288 mμ (ε 11,700 and 6800 respectively) changing after 30 min. in 0·1N-NaOH to $\lambda_{max.}$ 238 and 468 mμ (ε 11,600 and 6700 respectively), $\nu_{max.}$ 1749, 1733, 1662, 1621, 1605 cm.$^{-1}$ (Found: C, 67·7; H, 7·0; Ac. 19·45. $C_{25}H_{30}O_7$ requires C, 67·85; H, 6·85; 2Ac, 19·55%).

Ozonolysis of Prednisone Acetate.—Prednisone acetate (200 mg.) in ethyl acetate (20 ml.) was ozonised at −70° for 15 min.; the deep blue solution was kept at −70° until the ultraviolet max. at 240 mμ had disappeared (about 30 min.; in test solutions, the ratio, optical density at 210 mμ : that at 240 mμ, > 4 is desirable). The ozonide was decomposed by evaporation of the solvent under reduced pressure in the presence of water (2 ml.); the residue, in ethyl acetate, was separated through aqueous sodium hydrogen carbonate, to give a neutral fraction (140 mg.) which crystallised readily from ethyl acetate–light petroleum (prisms) to give the *aldehydo-ketone* (XXVII), m. p. 197—199°, $[\alpha]_D$ +105° (*c* 1·12), $\nu_{max.}$ 2725, 1733, and 1701 cm.$^{-1}$ (Found: C, 63·4; H, 7·0. $C_{20}H_{26}O_7$ requires C, 63·5; H, 6·95%).

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