Studies in the Synthesis of Cortisone. Part IV. The Oxidation of Steroid 7 : 9-Dienes with Sodium Dichromate in Acetic Acid.*

By J. Elks, R. M. Evans, A. G. Long, and G. H. Thomas.

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Attempts are described at oxidizing steroid dienes of the ergosterol-D type (I) to compounds suitable for use in the synthesis of cortical hormones. With sodium dichromate in acetic acid at 80° the side-chain double bond was unattacked. Oxidation of the 5α-hydroxy-compound (I*d*) and isolation of the products left the hydroxyl group intact, but the 5α-acetoxy-group in the products from (I*c*) was eliminated during chromatography. Three types of nuclear oxidation could be discerned, leading severally to Δ^{9}-7-ketones (II), $\Delta^{8(9)}$-7-ketones (III) and $\Delta^{8(9)}$-7 : 11-diketones (IV); although means exist for utilising such compounds for the original ends, the low yields in the oxidations and the difficulties in separating such mixtures thwarted us.

Anomalies in the absorption spectra of the 5α-hydroxy-$\Delta^{8(9)}$-7 : 11-diketones (IV*c*) and (IV*d*), and the ultra-violet absorption due to the cross-conjugated $\Delta^{5:8(9)}$-7-keto-chromophores, are examined.

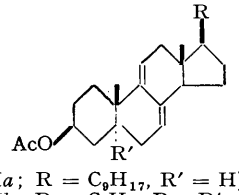
Oxidation of steroids of the ergosterol-D type (I), containing the 7 : 9-diene system, to $\Delta^{8(9)}$-7 : 11-dioxo-steroids has been suggested as a route to compounds of use in the synthesis of cortical hormones from relatively plentiful sources (cf. Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Chamberlin, Ruyle, Erickson,

* Part III, *J.*, 1953, 3864.

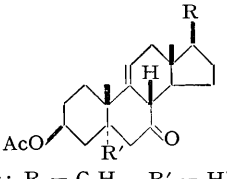
Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396). This communication describes attempts to achieve this oxidation in one step.

Previous work in the steroid and the lanosterol series (*inter al.*, Windaus, *Ber.*, 1906, **39**, 2249; Fieser, Herz, and Wei-Yuan Huang, *J. Amer. Chem. Soc.*, 1951, **73**, 2397; Fieser, Babcock, Herz, Wei-Yuan Huang, and Schneider, *ibid.*, p. 4053; Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892) suggested chromic acid as a suitable oxidant, and trials with it led us to adopt conditions of oxidation with sodium dichromate and acetic acid that resembled those developed in the later researches at Harvard (Fieser, Wei-Yuan Huang, and Babcock, *J. Amer. Chem. Soc.*, 1953, **75**, 116; Fieser and Herz, *ibid.*, p. 121). Scission of the ergosterol side chain, which would be a desirable adjunct to the nuclear oxidation in a proposed synthesis of cortisone, was negligible, acidic material, apparently with an intact steroid nucleus, accounting for only about 5% of the oxidation products. This experience confirms the impression given in the literature of the resistance of the 22 : 23-double bond to cleavage by chromic acid (cf. Burawoy, *J.*, 1937, 409; Heusser *et al.*, and Budziarek *et al.*, *locc. cit.*).

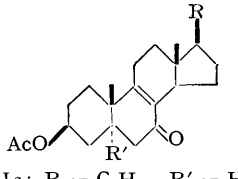
We studied the oxidation of four conjugated dienes : 3β-acetoxy-22 : 23-dibromo-ergosta-7 : 9-diene (I*b*), 3β-acetoxy- (I*a*), 3β : 5α-diacetoxy- (I*c*), and 3β-acetoxy-5α-hydroxy-ergosta-7 : 9 : 22-triene (I*d*). These reactions seemed consistently to beget three types of product, but it was not always possible to isolate each from the issue of one oxidation. The mixtures contained the unconjugated Δ^{9}-7-ketone (II), the conjugated $\Delta^{8(9)}$-7-ketone (III), and the $\Delta^{8(9)}$-7 : 11-diketone (IV), which were eluted in that order from an alumina column. All the products reacted slowly (as 7-keto-steroids) with Brady's reagent (cf. Barton, *J.*, 1953, 1027); the unreactive 11-monoketones (cf. Steiger and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 817; Barton, *loc. cit.*) were absent. Fieser *et al.* (*locc. cit.*) found compounds of the first and the last type among their oxidation products, and Budziarek *et al.* (*loc. cit.*) isolated the $\Delta^{(8)9}$-7-ketone (III*a*) after oxidation of ergosteryl-D acetate with chromic oxide. Our experience contrasts with these authors', for our main product from the last-mentioned oxidation was the Δ^{9}-7-ketone (II*a*); we attribute the difference to the nature of the alumina used in the separation of the products. We chose an adsorbent previously treated with acetic acid and reactivated, on which the unconjugated Δ^{9}-7-ketones survived, whereas on untreated alumina the double bond shifted into conjugation.



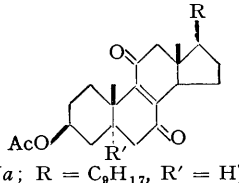
(I*a*; R = C_9H_{17}, R′ = H)
(I*b*; R = $C_9H_{17}Br_2$, R′ = H)
(I*c*; R = C_9H_{17}, R′ = OAc)
(I*d*; R = C_9H_{17}, R′ = OH)
(I*e*; R = C_9H_{19}, R′ = OH)



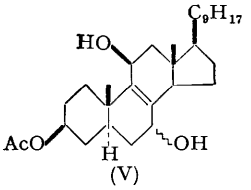
(II*a*; R = C_9H_{17}, R′ = H)
(II*b*; R = $C_9H_{17}Br_2$, R′ = H)
(II*c*; R = C_9H_{17}, R′ = OAc)
(II*d*; R = C_9H_{19}, R′ = H)
(II*e*; 8α-isomer of II*a*)



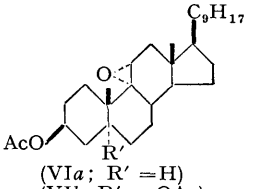
(III*a*; R = C_9H_{17}, R′ = H)
(III*b*; R = $C_9H_{17}Br_2$, R′ = H)
(III*c*; R = C_9H_{19}, R′ = H)



(IV*a*; R = C_9H_{17}, R′ = H)
(IV*b*; R = $C_9H_{17}Br_2$, R′ = H)
(IV*c*; R = C_9H_{17}, R′ = OH)
(IV*d*; R = C_9H_{19}, R′ = OH)



(V)



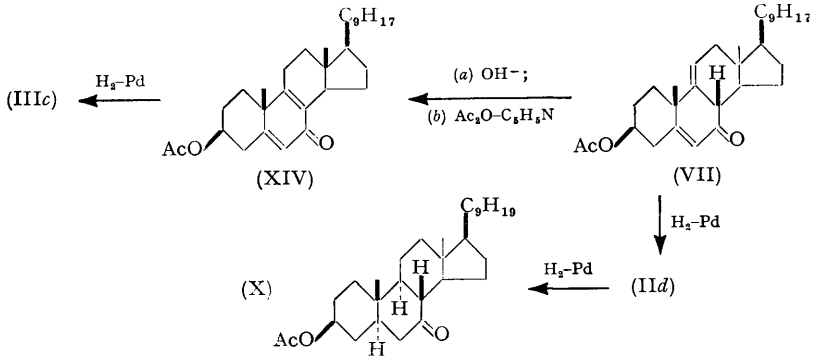
(VI*a*; R′ = H)
(VI*b*; R′ = OAc)

[C_9H_{17} = ·CHMe·CH:CH·CHMe·$CHMe_2$;
$C_9H_{17}Br_2$ = ·CHMe·CHBr·CHBr·CHMe·$CHMe_2$]

Ergosteryl-D acetate (I*a*) utilised 3O in 4 minutes from a solution of sodium dichromate in acetic acid at 80°; nevertheless the main product (*ca.* 20% yield) was the monoketone (II*a*), identical with a compound of this structure made by the alternative

method of Heusser, Anliker, Eichenberger, and Jeger (*Helv. Chim. Acta*, 1952, **35**, 936; cf. Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696). The absorption of the ketone in the infra-red and far ultra-violet supports the structure (II*a*). Only one of the fractions in this separation was dextrorotatory. It contained a yellow compound, believed to be the $\Delta^{8(9)}$-7 : 11-diketone (IV*a*), which Heusser *et al.* (*loc. cit.*, 1951) got by oxidation of the enediol (V), but we failed to purify our material.

Oxidation of the dibromo-diene (I*b*) gave three recognisable products: 3β-acetoxy-22 : 23-dibromoergost-9-en-7-one (II*b*), 3β-acetoxy-22 : 23-dibromoergost-8(9)-ene-7 : 11-dione (IV*b*), and a trace of 3β-acetoxy-22 : 23-dibromoergost-8(9)-en-7-one (III*b*). Their structures were assigned on the basis of their absorption spectra, and by analogy with other



compounds obtained in this work, and confirmed for (III*b*) and (IV*b*) by comparison with compounds obtained by Spring and his collaborators (*J.*, 1952, 3410, 4874).

The diacetoxy-triene (I*c*) yielded the oxidation products 3β-acetoxyergosta-5 : 9 : 22-trien-7-one (VII) and 3β-acetoxyergosta-5 : 8(9) : 22-triene-7 : 11-dione (VIII), these structures being established as described below. It seems that the 5α-acetoxy-group is eliminated during the chromatography, since Elks, Evans, Oughton, and Thomas (following paper) obtained 3β : 5α-diacetoxy-7-oxoergosta-9 : 22-diene (II*c*) by acid-catalysed rearrangement of 3β : 5α-diacetoxy-9α : 11α-epoxyergosta-7 : 22-diene (VI*b*) when they purified the product by chromatography on charcoal, whereas the Δ^5-compound (VII) issued from a column of alumina.

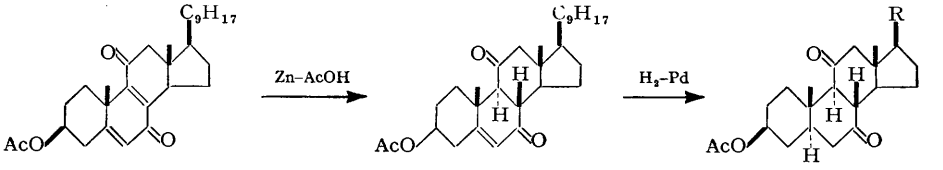
Hydrogenation of the trienone (VII) with a palladium–carbon catalyst in an acid medium gave 3β-acetoxyergost-9-en-7-one (II*d*), identical with the substance generated by hydrogenation of the dienone (II*a*). Therefore in these conditions the 5 : 6-double bond is hydrogenated on the α-face, engendering a *trans*-fusion of rings A and B (cf. Windaus, *et al.*, *Ber.*, 1920, **53**, 614; Marker and Rohrmann, *J. Amer. Chem. Soc.*, 1939, **61**, 3022; Reichstein and Lardon, *Helv. Chim. Acta*, 1941, **24**, 955; Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503). Prolonged hydrogenation of (VII) or (II*a*) in acetic acid or ethyl acetate saturated the 9 : 11-double bond and yielded the known 3β-acetoxyergostan-7-one (X) (Stavely and Bollenback, *ibid.*, 1943, **65**, 1285, 1290). The poor return from this hydrogenation is probably due to a shift of the 9 : 11-double bond into conjugation, with subsequent reduction to an allylic alcohol and hydrogenolysis (cf. McKenzie, Mattox, and Kendall, *J. Biol. Chem.*, 1948, **175**, 249).

The structure of the yellow enedione (VIII) was confirmed, not only by the infra-red and ultra-violet absorption, but also by hydrogenation. Zinc in acetic acid saturated the 8 : 9-double bond and gave 3β-acetoxyergosta-5 : 22-diene-7 : 11-dione (XI), which was then hydrogenated catalytically to 3β-acetoxyergostane-7 : 11-dione (XII*b*), identical with the product of hydrogenation of 3β-acetoxyergost-22-ene-7 : 11-dione (XII*a*) (Heusser *et al.*, *loc. cit.*, 1951).

The hydroxy-triene (I*d*) with sodium dichromate in acetic acid generated a complicated mixture, from which only one compound could be isolated. Its infra-red absorption supports the inference that it is 3β-acetoxy-5α-hydroxyergosta-8(9) : 22-diene-7 : 11-

dione (IV*c*), and its yellow colour denotes a *trans*-disposed enedione chromophore (cf. Conant and Lutz, *J. Amer. Chem. Soc.*, 1923, **45**, 1303). We had to forego a chemical study of (IV*c*), which arose from (I*d*) in less than 1% yield, but its structure would seem to be secure on the above foundations and by analogy with the products of similar oxidations in this series.

This contention was upheld by comparison of the properties of (IV*c*) with those of the analogous 3β-acetoxy-5α-hydroxyergost-8(9)-ene-7 : 11-dione (IV*d*), which was prepared



(VIII) (XI) (XII*a*; R = C_9H_{17}) (XII*b*; R = C_9H_{19}) (XII*c*; 8α-isomer of XII*a*)

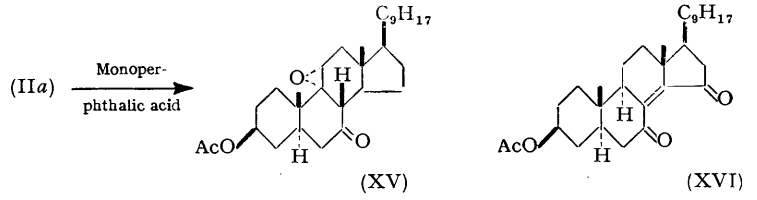
in the following alternative manner. 3β-Acetoxyergosta-7 : 9-dien-5α-ol (I*e*) (Bladon, Clayton, Greenhalgh, Henbest, Jones, Lovell, Silverstone, and Wood, *J.*, 1952, 4883) was treated with *N*-bromosuccinimide and aqueous *tert.*-butanol containing acetic acid (cf. Fieser, Schneider, and Wei-Yuan Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 124), producing a crude bromo-compound, which was hydrolysed with silver nitrate solution and finally oxidised with chromic oxide to the yellow enedione (IV*d*).

In view of the copious work of Kon and Linstead and their co-workers (cf. Baker, "Tautomerism," Routledge, London, 1934, p. 154; Alexander, "Principles of Organic Reactions," Wiley, New York, 1950, p. 281) on the relative stabilities of pairs of conjugated and unconjugated unsaturated ketones, we were interested in the properties of the Δ^9-7-keto-steroids. Partial conjugation in the ketones (II*a*) and (VII) occurred during their passage through a column of untreated alumina, and complete conjugation occurred in aqueous-alcoholic sodium hydroxide or in acetic acid containing perchloric acid. The ketone (III*a*), derived from (II*a*) (with subsequent acetylation, if necessary), was identified with a compound previously so described (Stavely and Bollenback, *locc. cit.*; Heusser *et al.*, *loc. cit.*, 1951; Budziarek *et al.*, *J.*, 1952, 3410, 4874). Isomerisation of (VII) in such conditions yielded the cross-conjugated ketone (XIV), whose structure was confirmed by hydrogenation in the presence of a platinum or nickel catalyst to the enone (III*c*), which was also obtained by the hydrogenation of (III*a*). The migrating double bond therefore settles in the 8 : 9- and not in the 8 : 14-position (cf. Stavely and Bollenback, *locc. cit.*).

The double bonds in the ketones (VII) and (XIV) could not be placed unequivocally on spectral evidence alone; however the supposed presence of the cross-conjugated system in (XIV) was proved during experiments designed to detect the precise juncture at which conjugation had occurred in the sequence of reactions arising from (VII). The possibility that the 9 : 11-double bond had shifted only during hydrogenation would allow (VII) and (XIV) to be represented as stereoisomers at $C_{(8)}$; but this was refuted by the inertness of (XIV) towards perphthalic acid, for double bonds conjugated with carbonyl groups are known to be immune to epoxidation in these circumstances, whereas the 9 : 11-double bond is active (Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corpn. New York, 1949, p. 227; Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278; Budziarek, Hamlet, and Spring, *J.*, 1953, 778). Moreover the present evidence is upheld by the absorption of 1 mol. of the oxidant by the Δ^9-7-ketone (VII), and by the reactivity of the nuclear double bonds in the crude mixture of stereoisomeric unsaturated alcohols obtained by sodium borohydride reduction of the ketone group in (XIV).

Although the structure of the lævorotatory unsaturated ketone (II*a*) is now well established, a dextrorotatory compound (II*e*) with a similar structure has been described by Budziarek *et al.* (*J.*, 1952, 2892), who prepared it by oxidising ergosteryl-D acetate (I*a*) with formic acid and hydrogen peroxide. Budziarek, Stevenson, and Spring (*J.*,

1952, 4874) have now attributed the difference to stereoisomerism about $C_{(8)}$. Unfortunately the migration of the double bond in enolizing conditions frustrates direct methods of testing the relative stabilities of the isomers of (II*a*) and (VII), and we therefore resorted to a study of the hydrogenation of (II*a*). It slowly absorbed 2 mols. of hydrogen and yielded the stable isomer (in aqueous-alcoholic sodium hydroxide) of 3β-acetoxyergostan-7-one (X). This evidence of the normal stereochemistry at $C_{(8)}$ in (II*a*) is not conclusive, however, since the hydrogenation may involve a prior shift of the double bond to the 8(9)- or 8(14)-position, as has been mentioned already, and accordingly a decision was sought by other means.



Perphthalic acid oxidised (II*a*) to 3β-acetoxy-9α : 11α-epoxyergost-22-en-7-one (XV), which Budziarek *et al.* (*J.*, 1952, 2892) and Anderson, Stevenson, and Spring (*J.*, 1952, 2901) prepared by oxidising their dextrorotatory isomer (II*e*) with per-acid. A normal structure (8β-hydrogen) for the epoxide (XV) is therefore indicated, but the evidence for the respective conformations of (II*a*) and its isomer (II*e*) is still indecisive. The molecular-rotation difference that accompanies the epoxidation of the 9 : 11-double bond is generally about −240° (cf. Heusser *et al.*, *loc. cit.*, 1952; Schoenewaldt *et al.*, *loc. cit.*); in the conversion of (II*e*) into the keto-oxide (XV) it is −470°, and in the present epoxidation of (II*a*) to (XV) it is −130°. The change that involves isomerisation at $C_{(8)}$ is therefore not unequivocally disclosed by these results, but, as the lævorotatory form (II*a*) survived in formic acid and in view of the trend of the optical evidence, we tentatively assign to it the normal conformation, and by analogy we presume that in (VII) also the hydrogen atom at $C_{(8)}$ has the β-configuration. Budziarek and Spring (*J.*, 1953, 956) have shown that the 8α-carbon–hydrogen bond in (XII*c*) is inverted in hot acetic acid; such unstable stereoisomers would not therefore be expected from the present oxidations, so that the assumptions made on the stereochemistry of (II*a*) and (VII) seem to be justified. The conformation of the 8α-steroids must include one boat-shaped ring, and their exceeding instability would undoubtedly be derived from the consequent strain.

The work of Barton, Holness, Overton, and Rosenfelder (*J.*, 1952, 3751), Barnes and Barton (*J.*, 1953, 1419), and Budziarek and Spring (*loc. cit.*) has shown that, although zinc dust reductions of conjugated unsaturated ketones probably involve initially *cis*-addition to the double bond, the abnormal configurations so generated in 7 : 11-diones of type (XII) invert in hot acetic acid to the *trans*-, and presumably normal, forms (with 8β- and 9α-hydrogen atoms). Further, alkaline isomerization of 3β-acetoxy-11α-hydroxyergosta-8(9) : 22-dien-7-one produces (XII*a*) (Budziarek *et al.*, *J.*, 1952, 2892; cf. Romo, Stork, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 2918). These seem good grounds for assuming that the zinc dust reduction of (VIII) in hot acetic acid yielded the normal form of (XI), which was then converted without inversion into (XII*a*). Although the molecular-rotation differences for *cis*- and *trans*-hydrogenations of (IV*a*) can be calculated from the data provided by Budziarek and Spring (*loc. cit.*) and by Heusser *et al.* (*loc. cit.*, 1951), the optical evidence for the steric course of the hydrogenation of the 8 : 9-double bond in (VIII) is ambiguous, presumably because of vicinal effects of the 5 : 6-double bond.

The ultra-violet absorption of the $\Delta^{8(9)}$-7 : 11-diketones (IV*c*) and (IV*d*) was exceptional; the maxima lay respectively at 263 and 265 mμ (ε 6550 and 6300), in contrast to those of other similarly disposed enediones of the steroid and lanosterol series, which occur at about 270 mμ (ε 7500—10,000) (see, *e.g.*, Heusser *et al.*, *loc. cit.*, 1951; Chamberlin *et al.*, Fieser *et al.*, Ruzicka *et al.*, Voser *et al.*, *locc. cit.*; Lahey and Strasser, *J.*, 1951, 873; Barton, Fawcett, and Thomas, *ibid.*, p. 3147; McGhie, Pradhan, and Ross, *J.*, 1953,

305). The simple *s-trans*-enedione, $\Delta^{9(10)}$-octalin-1 : 5-dione, also showed an absorption maximum at 263 mμ, but with an extinction coefficient of 12,000 (Campbell and Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 2721). The alternative explanation, that our products possess a $\Delta^{8(14)}$-7 : 15-diketo-chromophore, was dismissed because of the ultra-violet absorption ($\lambda_{max.}$ 253 mμ; ε 5000) and the whiteness of an archetype (XVI) of such a series (Stavely and Bollenback, *loc. cit.*; cf. Tschesche and Fugmann, *Chem. Ber.*, 1951, **84**, 810; Barton, Fawcett, and Thomas, *loc. cit.*).

We believe that the influence of the 5α-hydroxy-group in weakening the absorption of the enedione chromophore in (IV*c* and *d*) and in shifting the maxima to unusually low wave-lengths can be explained in terms of a steric interference that deforms the chromophore and increases the energy content of the contributing resonance forms (cf. Maccoll, *Quart. Reviews*, 1947, **1**, 16; Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890; Henbest and Woods, *J.*, 1952, 1150). Similar and probably cognate abnormalities have been observed by Henbest (*J.*, 1951, 1074) and Henbest, Jones, Wood, and Woods (*J.*, 1952, 4894) in the ultra-violet absorption of αβ-unsaturated ketones of the steroid and the β-ionone series, such compounds carrying an oxygen-containing substituent at the γ-position.

The 5α-hydroxy-groups in (IV*c* and *d*) also affect their infra-red spectra by shifting the carbonyl absorption towards the shorter wave-lengths that characterize the absorption of unconjugated ketones. Insofar as this evidence is reliable (since the spectra of Nujol mulls have to be studied for a complete comparison), it confirms the foregoing supposition that resonance in these chromophores is inhibited. Correspondingly the maxima in the ultra-violet and the infra-red spectra of the enediones (IV*a*), (IV*b*), and (VIII) fall at the longer wave-lengths that indicate uninhibited transitions in the vibrational states of the chromophores, and their absorptions are also more intense.

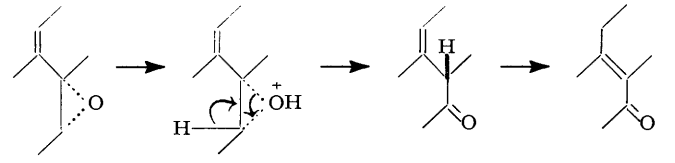
The molecular-rotation differences marking the oxidation of the hydroxy-dienes (I*e* and *d*) to the 5α-hydroxy-$\Delta^{8(9)}$-7 : 11-diketones (IV*d* and *c*) ($\Delta M_D = -470°$ and $-449°$ respectively) also show the influence of the 5α-hydroxy-group on the $\Delta^{8(9)}$-7 : 11-diketone system, since they contrast remarkably with the changes that accompany the oxidation of (I*a*) to (IV*a*) ($\Delta M_D + 29°$) and of (I*b*) to (IV*b*) ($\Delta M_D + 28°$), in which the effect is absent.

The ultra-violet absorption ($\lambda_{max.}$ 246 mμ) of the cross-conjugated dienone (XIV) represents a resultant between the effects of the Δ^5-7-keto- ($\lambda_{max.}$ 235 mμ) and the $\Delta^{8(9)}$-7-keto-chromophore ($\lambda_{max.}$ 253 mμ), and incidentally comes near to the predicted absorption ($\lambda_{max.}$ 244 mμ) for the Δ^5-7-keto-system (Fieser and Fieser, *op. cit.*, p. 191). However, apart from our experience with the ketones (VII) ($\lambda_{max.}$ 234·5 mμ) and (XI) ($\lambda_{max.}$ 233 mμ), enough other examples have been recorded (by, *e.g.*, Wintersteiner and Pfiffner *J. Biol. Chem.*, 1936, **116**, 291; Klyne, *J.*, 1951, 3449; Romo, Rosenkranz and Djerassi *J. Org. Chem.*, 1952, **17**, 1414; Ralls, *J. Amer. Chem. Soc.*, 1953, **75**, 2123) to show that in fact the absorption of the last chromophore is distinguished by a maximum at a lower wave-length than this. The absorption of the cross-conjugated $\Delta^{1:4}$-3-keto-steroids reproduces the behaviour of the Δ^4-3-keto-chromophore ($\lambda_{max.}$ 240 mμ), which absorbs more strongly and at a longer wave-length than the Δ^1-3-keto-system ($\lambda_{max.}$ 230 mμ) (cf. Inhoffen, Zühlsdorff and Huang-Minlon, *Ber.*, 1940, **73**, 451; Djerassi and Ryan, *J. Amer. Chem. Soc.*, 1949, **71**, 1000; Woodward and Singh, *ibid.*, 1950, **72**, 494). However, some examples in the santonin series (Clemo and Cocker, *J.*, 1946, 30; Clemo and McQuillin, *J.*, 1952, 3835, 3839) and in the lanosterol series (Barton and Thomas, *J.*, 1953, 1842), and our own findings with the steroid $\Delta^{5:8(9)}$-ketones (in which the $\Delta^{8(9)}$-7-keto-chromophore is the weaker), suggest that the absorption by the steroid $\Delta^{1:4}$-3-ketones does not typify the properties of cross-conjugated ketones, for, when the chromophoric component absorbing at the longer wave-length is the weaker, the single maximum in the absorption lies between the peaks that would distinguish the separate contributing chromophores.

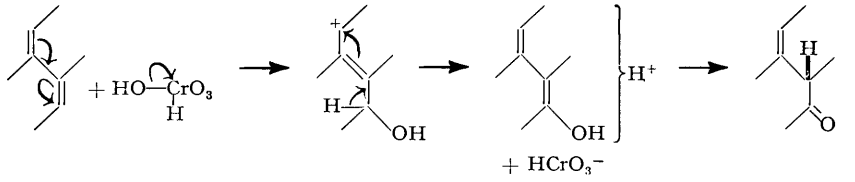
The low yields of recognizable products hinder attempts to explain the mechanism of these oxidations. Nevertheless it is significant that the unconjugated Δ^9-7-ketones frequently predominated and that compounds with the 11-keto-group have so far been found only as the $\Delta^{8(9)}$-7 : 11-diones. Hickinbottom and his co-workers (Byers and Hickin-

bottom, *J.*, 1948, 1334; Hickinbottom and Wood, *Nature*, 1951, **168**, 33; *J.*, 1953, 1906; cf. Fieser and Fieser, *op. cit.*, p. 227; " Heterocyclic Compounds," Vol. I, ed. Elderfield, Wiley, New York, 1950, p. 7; Dawson, Halsall, and Swayne *J.*, 1953, 590) have shown that chromic acid epoxidizes some olefins, and an explanation of this type in the present instance would presumably implicate the 7 : 8-oxides, since the 9α : 11α-epoxides have been found to behave differently in the conditions we used. Assuming that such oxides arise by a

(*a*)

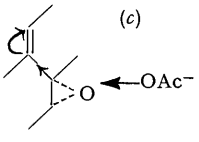


(*b*)



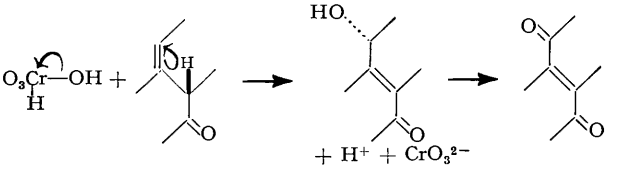
rearward attack by the hydroxylium ion (Fieser, *Experientia*, 1950, **6**, 312), we can propose a mechanism of type (*a*) for the formation of the Δ^9-7-ketones. Alternatively, in view of our present ignorance of the behaviour of such epoxides in these circumstances, we offer mechanism (*b*). The preponderance of unconjugated enones, and especially the scarcity of their conjugated isomers in the experiments of Fieser *et al.* (*locc. cit.*) and in our own experience, suggest that the $\Delta^{8(9)}$-ene-7 : 11-diones may spring from the Δ^9-7-ketones and not by " allylic " oxidation of the conjugated $\Delta^{8(9)}$-7-ketones. We also tentatively discard a proposed synthesis from the $\Delta^{8(9)}$-7 : 11-diols, which might arise by rearrangement of an intermediate epoxide (cf. Heusser *et al.*, *loc. cit.*, 1951; Schoenewaldt *et al.*, *loc. cit.*; Budziarek, Hamlet, and Spring, *loc. cit.*), because we were unable to isolate the products with the properties of the 8(9)-epoxy-7 : 11-diketones that might be expected to accompany the enediones (since oxidation of the 8 : 9-double bond would be expected in the diol only, and not in the fully conjugated enedione). Unconjugated Δ^9-7-ketones with a normal configuration (8β-hydrogen) would be expected to arise by mechanism (*a*). However, in view of the polarizability of the vinyl group, a sterically ambiguous sequence involving nucleophilic attack by the acetate ion at $C_{(8)}$, as represented in (*c*), cannot be entirely discounted.

(*c*)



The possibility that the oxidation of the unconjugated Δ^9-7-ketones yields $\Delta^{8(9)}$-7 : 11-diones recalls the oxidation of methyl 19-oxo-olean-13(18)-enolate acetate to methyl 12 : 19-dioxo-olean-13(18)-enolate acetate, for which Barton, Holness, Overton, and Rosenfelder (*loc. cit.*) proposed a mechanism that we have copied in (*d*) to explain the formation of the steroid $\Delta^{8(9)}$-7 : 11-diketones (cf. Djerassi, Mancera, Velasco, Stork, and Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 3321); the recent work of Fieser, Schneider, and Wei-Yuan Huang (*loc. cit.*) seems to corroborate such speculations. An explanation

(*d*)



of the synthesis of such diketones by the terminal oxidation of *s-trans*-dienes of the ergosterol-D type is probably inapt, since the other recognizable products seem to arise mostly from the expected attack on vicinal carbon atoms in the *transoid* diene.

Epoxidation of steroid Δ^9-7-ketones and subsequent hydrolysis has been used as a

practicable means of generating substituted 11-keto-steroids suitable for the synthesis of cortical hormones (cf. Fieser, Wei-Yuan Huang, and Babcock, *loc. cit.*, and the literature reviewed therein). Although these unconjugated enones were generally the most plentiful products of our oxidations, the yields were so low (less than 20%) as to nullify any advantage that might be gained, for example, by the use of the 5α-hydroxy-series of compounds in improving the synthesis of cortisone from *allo*steroids (cf. Bladon *et al.*, *J.*, 1952, 4883). Accordingly research on the present method of introducing oxygen-containing substituents into ring C was abandoned.

Experimental

In the sequel the phrase "working up in the usual manner" describes the following procedure. The acetic acid solution of oxidation products was poured into ice and water (5 vols.), and the precipitate filtered off or separated centrifugally. It was dissolved in ether or chloroform, washed twice with water, thrice with saturated sodium hydrogen carbonate solution, then with 0·5N-hydrochloric acid, and finally with water. The organic phase was dried ($MgSO_4$) and evaporated to dryness under reduced pressure, leaving the neutral fraction as the residue. The bicarbonate washings were acidified with hydrochloric acid, extracted with chloroform, and washed with water. Evaporation of the dried organic phase then gave the acidic fraction.

The adsorbent used for chromatography was prepared as follows, unless otherwise stated. Spence Grade O alumina was stirred five times with 2N-acetic acid, and then washed with water until the pH of the washings exceeded 4·5. After three further washings with methanol the alumina was air-dried, and then activated at 180°/16 mm. for 1 hr. or at 100°/16 mm. for 5 hr. It was graded on the Brockmann scale by Williams's method ("Introduction to Chromatography," Blackie, London, 1946, p. 13); the adsorbent used in this work was in Grade II, and when suspended in water it did not reduce the pH below 5. The chromatographic procedure copied the "Durchlaufmethode" described by Reichstein and Shoppee (*Discuss. Faraday Soc.*, 1949, **7**, 305).

M. p.s were determined on a hot stage. Unless otherwise stated, optical rotations were determined on chloroform solutions in a 0·5-dm. micro-tube, ultra-violet spectra on ethanolic solutions, and infra-red spectra on Nujol mulls. A model S3 infra-red spectrophotometer with sodium chloride optics, made by Sir Howard Grubb, Parsons & Co., was used, initially as a single-beam instrument and later modified for use as a double-beam instrument. The structural assignments were based on those reported by Jones, Humphries, and Dobriner (*J. Amer. Chem. Soc.*, 1950, **72**, 956). Ultra-violet absorption at less than 220 mμ was measured in the special conditions described by Bladon, Henbest, and Wood (*Chem. and Ind.*, 1951, 866; cf. Halsall, *ibid.*, p. 867).

The term "light petroleum" denotes the fractions of b. p. 40—60°.

Oxidation of Ergosteryl-D Acetate (I*a*).—The uptake of oxygen was followed titrimetrically: 3O were consumed within 4 min., 4O within 9 min., and a total of 5O in 113 min. The $[\alpha]_D^{20}$ of isolated steroid material dropped from an initial value of +21° to −18° after 9 minutes' oxidation, but did not change on further reaction.

Ergosteryl-D acetate (2 g.; $4·6 \times 10^{-3}$ mole) was dissolved in "AnalaR" acetic acid (30 ml.) and alcohol-free chloroform (10 ml.) at 80°, and added to a solution of sodium dichromate dihydrate (4·8 g.; $1·61 \times 10^{-2}$ mole) in acetic acid (30 ml.), also at 80°. The solution was kept at this temperature and stirred for 10 min.; methanol (3 ml.) was then added to reduce the remaining oxidant, and the solution was added to iced water (2 l.). The products from three more oxidations of this type were added to the same iced water, and the total solid was filtered off and worked up in the usual manner. Neutral (8·08 g.) and acidic fractions (0·182 g.) were obtained thereby. The latter was rejected.

The neutral fraction was chromatographed on alumina. Benzene–light petroleum eluted a fraction which, after three crystallisations from methanol, yielded prisms (403 mg.), m. p. 171—175° (subliming unchanged at 145—155°/10^{-5} mm.), $[\alpha]_D^{22}$ −55° (*c*, 0·47), $\lambda_{max.}$ 212 mμ (ε 1540; *c*, 0·042), of 3β-acetoxyergosta-9 : 22-dien-7-one (II*a*), $\nu_{max.}$ 1736 and 1236 (acetate), 1715 (ketone), 1642 and 970 (*trans*-1 : 2-disubstituted ethylene), and 815 cm.$^{-1}$ (trisubstituted ethylene) in CS_2 (Found: C, 79·5; H, 10·4. Calc. for $C_{30}H_{46}O_3$: C, 79·2; H, 10·2%). Heusser *et al.* (*loc. cit.*, 1952) give m. p. 176—177°, $[\alpha]_D^{20}$ −58°. The ketone (0·5 g.) was recovered quantitatively after being shaken in benzene (10 ml.) with formic acid (10 ml.) for 20 hr. No other distinct fraction could be discerned among the eluates from the alumina columns, of which

all except one (which was yellow) were lævorotatory, and several possessed absorption maxima in the ultra-violet between 253 and 262 mμ.

Oxidation of 3β-*Acetoxy*-22 : 23-*dibromoergosta*-7 : 9-*diene* (I*b*).—The dibromo-diene (2·0 g.) was dissolved in acetic acid (10 ml.) and chloroform (10 ml.), and the solution was added to sodium dichromate dihydrate (3·52 g.), dissolved in acetic acid (25 ml.) at 80°. The oxidation and working up were performed in the usual manner. The acid material (14 mg.) was rejected, and the neutral part (1·98 g.) resolved into fractions on alumina. The first fraction (133 mg.), eluted with benzene–light petroleum (3 : 7), crystallised from ethyl acetate as rhombs (44 mg.) of 3β-*acetoxy*-22 : 23-*dibromoergost*-9-*en*-7-*one* (II*b*), m. p. 235—236°, $[\alpha]_D^{21}$ −19° (*c*, 0·94), $\lambda_{max.}$ 206 mμ (ε 3620; *c*, 0·025), $\nu_{max.}$ 1735 and 1240 (acetate), and 1715 cm.$^{-1}$ (ketone) (Found : C, 58·3; H, 7·4; Br, 25·5. $C_{30}H_{46}O_3Br_2$ requires C, 58·6; H, 7·5; Br, 26·0%).

The second fraction (61 mg.) was eluted with benzene–light petroleum (3 : 1), and crystallised thrice from methanol and ethyl acetate as rhombs (15 mg.) of 3β-acetoxy-22 : 23-dibromoergost-8(9)-en-7-one (III*b*), m. p. 236—238°, $[\alpha]_D^{19}$ −24° (*c*, 0·86), $\lambda_{max.}$ 253 mμ (ε 9200), $\nu_{max.}$ 1735 and 1240 (acetate), and 1680 and 1590 cm.$^{-1}$ (αβ-unsaturated ketone). Budziarek, Johnson, and Spring (*loc. cit.*) give m. p. 241—242°, $[\alpha]_D$ −29°, $\lambda_{max.}$ 252 mμ (ε 10,000).

The third fraction (300 mg.), eluted with benzene, was crystallised thrice from ethyl acetate as yellow rhombs (155 mg.) of 3β-acetoxy-22 : 23-dibromoergost-8(9)-ene-7 : 11-dione (IV*b*), m. p. 248—252° (slight decomp.), $[\alpha]_D^{22}$ +25° (*c*, 0·84), $\lambda_{max.}$ 268 mμ (ε 8750), $\nu_{max.}$ 1735 and 1250 (acetate), 1685 and 1590 cm.$^{-1}$ (–CO·C:C·CO–) (the band at 1685 cm.$^{-1}$ had twice the usual intensity, indicating two keto-groups in conjugation with one double bond) (Found : C, 57·6; H, 7·2; Br, 25·25. Calc. for $C_{30}H_{44}O_4Br_2$: C, 57·3; H, 7·05; Br, 25·4%). Budziarek *et al.* (*locc. cit.*) have described this compound, with, for example, the following physical properties : m. p. 257—259°, $[\alpha]_D$ +30°, $\lambda_{max.}$ 270 mμ (ε 9600).

Oxidation of 3β : 5α-*Diacetoxyergosta*-7 : 9 : 22-*triene* (I*c*).—3β : 5α-Diacetoxyergosta-7 : 9 : 22-triene (5 g.; Bladon *et al.*, *J.*, 1952, 4883), dissolved in acetic acid (100 ml.), was added to sodium dichromate dihydrate (8·8 g.) in acetic acid (50 ml.) at 80°. Oxidation and working up were performed in the usual manner. The acidic fraction (120 mg.) was discarded, and the crude neutral part (4·94 g.) of the product was resolved into two components by chromatography on alumina. The first (760 mg.), eluted with benzene–light petroleum (4 : 6), occurred after the third crystallisation from methanol, as colourless prisms (249 mg.) of 3β-acetoxyergosta-5 : 9 : 22-trien-7-one * (VII), m. p. 169—172°, $[\alpha]_D^{22}$ −96° (*c*, 1·86), $\lambda_{max.}$ 234·5 (ε 12,800) and 212 mμ (ε 7400; *c*, 0·020), $\nu_{max.}$ 1740 and 1240 (acetate), 1680 (αβ-unsaturated ketone), 970 (*trans*-1 : 2-disubstituted ethylene), and 816 cm.$^{-1}$ (trisubstituted ethylene) in CS_2 (Found : C, 79·9; H, 9·8. Calc. for $C_{30}H_{44}O_3$: C, 79·6; H, 9·8%). This material gave an orange precipitate when treated with Brady's reagent.

The second fraction (889 mg.) was eluted with benzene–light petroleum (1 : 1), and crystallised three times from methanol. The final product was 3β-*acetoxyergosta*-5 : 8(9) : 22-*triene*-7 : 11-*dione* (VIII) (312 mg.), obtained as feathery yellow needles, m. p. 129°, $[\alpha]_D^{21}$ +51° (*c*, 0·98), $\lambda_{max.}$ 270 (ε 13,700) and 205 mμ (ε 16,700), $\nu_{max.}$ 1735 and 1240 (acetate), 1660, 1635, and 1585 (–CO·C:C·CO–) (the band at 1660 cm.$^{-1}$ had twice the usual intensity, indicating two keto-groups in conjugation with one double bond), and 969 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) (Found : C, 77·5; H, 9·1. $C_{30}H_{42}O_4$ requires C, 77·2; H, 9·1%). The compound gave an orange precipitate with Brady's reagent.

Oxidation of 3β-*Acetoxyergosta*-7 : 9 : 22-*trien*-5α-*ol* (I*d*).—The hydroxy-triene (2·27 g.; Bladon *et al.*, *J.*, 1952, 4883) was dissolved in " AnalaR " acetic acid (100 ml.), and sodium dichromate dihydrate (3·5 g.) was added during 10 min. The solution became olive-green, and the temperature rose, but was kept below 35°; thereafter the mixture was shaken at room temperature for 18 hr. and worked up in the usual manner. The acidic fraction (0·22 g.) was rejected, and the neutral part chromatographed on alumina. Benzene eluted material (23 mg.) that crystallised from methanol as colourless prisms (17 mg.), m. p. 121—122°, $[\alpha]_D^{22}$ +55° (*c*, 1·43), with no appreciable absorption between 220 and 350 mμ, $\lambda_{max.}$ 207 mμ ($E_{1\,cm.}^{1\%}$ 145). This appears to be impure 3β-acetoxy-5α-hydroxyergosta-9 : 22-dien-7-one.

The second distinct fraction (53 mg.), eluted mainly with ether, was crystallised four times from methanol, from which yellow prisms (13 mg.) of 3β-*acetoxy*-5α-*hydroxyergosta*-8(9) : 22-*diene*-7 : 11-*dione* (IV*c*) separated, having m. p. 185—195°, $[\alpha]_D^{24}$ −46° (*c*, 1·30), $\lambda_{max.}$ 263 mμ (ε 6560), $\nu_{max.}$ 3400 (hydroxyl), 1735 and 1240 (acetate), 1700, 1670, and 1600 (–CO·C:C·CO–), and 966 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) (Found : C, 74·1; H, 9·3. $C_{30}H_{44}O_5$ requires

* Burke, Turnbull, and Wilson (*J.*, 1953, 3237) give m. p. 171—172°, $[\alpha]_D$ −112°, $\lambda_{max.}$ 235 mμ (ε 13,300), $\nu_{max.}$ at 1726, 1668, and 1600 cm.$^{-1}$ (in $CHCl_3$).

C, 74·3; H, 9·15%). This material gave no colour with ferric chloride. After being treated for 8 hr. with Brady's reagent it yielded a red *dinitrophenylhydrazone* that crystallised from acetic acid as red needles, m. p. 222—224°, $\lambda_{max.}$ 415 mμ (ε 34,000 in $CHCl_3$), which we believe to be 7-(2 : 4-dinitrophenylhydrazono)ergosta-3 : 5 : 8(9) : 22-tetraen-11-one (Found : N, 9·7. $C_{34}H_{42}O_5N_4$ requires N, 9·55%).

No other purifiable material could be obtained by chromatography of the oxidation products.

When this oxidation was performed by Windaus's method (*loc. cit.*) the yield of acidic material was slightly greater; when the method used for the oxidation of ergosteryl-D acetate was employed, the yield of neutral products was slightly enhanced at the expense of the acid material. These acidic products could not be purified as their methyl esters (prepared by diazomethane) on alumina; samples of the eluate possessed no resolved absorption in the 250—260 mμ region, but gave red dinitrophenylhydrazones that separated slowly from Brady's reagent. The unesterified products were steam-distilled to remove aliphatic acids, and titration of the residues showed that the steroid skeleton had not been disrupted. Exploratory attempts to resolve this mixture by paper partition chromatography (cf. Gore, *Chem. and Ind.*, 1951, 479; Long, Quayle, and Stedman, *J.*, 1951, 2197) failed.

3β-*Acetoxy-5α-hydroxyergost-8(9)-ene-7 : 11-dione* (IV*d*) (with Dr. D. E. Hathway and Mr. L. Stephenson) (cf. Fieser, Schneider, and Wei-Yuan Huang, *loc. cit.*).—A solution of 3β-acetoxyergosta-7 : 9(11)-dien-5α-ol (I*e*) (0·912 g.; Bladon *et al.*, *J.*, 1952, 4883) in *tert.*-butanol (55 ml.) and water (5 ml.) was treated with recrystallised *N*-bromosuccinimide (0·960 g., 2·4 equivs.) and glacial acetic acid (0·5 ml.). After 16 hr. an aqueous solution of silver nitrate (0·94 g.) was added, and after 3 hours' digestion the precipitated silver bromide was filtered off, and the filtrate evaporated under nitrogen at reduced pressure. Carbon tetrachloride (100 ml.) was added, and the insoluble succinimide was filtered off. The filtrate was water-washed, dried ($MgSO_4$), filtered, and evaporated to dryness at reduced pressure. The residue, a pale yellow oil, was dissolved in chloroform–acetic acid (7 : 10; 8·5 ml.), and treated with " AnalaR " chromium trioxide (0·5 g.) in acetic acid (4·5 ml.), containing water (0·5 ml.). The mixture was left at room temperature for 16 hr., after which the solvents were removed under reduced pressure and the residue was triturated with water. The steroid was separated centrifugally from the wash-liquor, and after several triturations the clean dry precipitate (1 g.) was chromatographed on Grade O alumina. The ether–acetone (3 : 1) eluate afforded a residue (200 mg.), from which 3β-*acetoxy-5α-hydroxyergost-8(9)-ene-7 : 11-dione* (IV*d*) (95 mg.) was obtained as yellow needles, m. p. 175—176°, $[\alpha]_D^{25}$ −38° (*c*, 0·26), $\lambda_{max.}$ 265 mμ (ε 6300), $\nu_{max.}$ (single beam) 3600 (hydroxyl), 1725 and 1240 (acetate), 1700, and 1668 $cm.^{-1}$ (αβ-unsaturated ketone) in CS_2 (Found : C, 73·9; H, 9·65. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%). This compound afforded a red precipitate with Brady's reagent.

3β-*Acetoxyergost-9-en-7-one* (II*d*).—(*a*) 3β-Acetoxyergosta-5 : 9 : 22-trien-7-one (VII) (67 mg.) was hydrogenated at room temperature and pressure in the presence of prereduced 3% palladium–charcoal (30 mg.) in acetic acid (5 ml.). The hydrogen uptake corresponded to 2 mols. after 70 min., whereupon the catalyst was filtered off and the solvent removed under reduced pressure. The residue (55 mg.) crystallised from methanol as leaflets (34 mg.), m. p. 143—145°, $[\alpha]_D^{24}$ −19° (*c*, 1·34), identified by their infra-red spectrum and mixed m. p. with a sample of ketone (II*d*), as prepared in (*b*) below.

(*b*) 3β-Acetoxyergosta-9 : 22-dien-7-one (II*a*) (88 mg.) was hydrogenated as in (*a*) above. Hydrogen (1 mol.) was taken up in 70 min., and the previous isolation procedure yielded leaflets (40 mg.), m. p. 145—146°, $[\alpha]_D^{20}$ −17° (*c*, 1·24), λ_{max} 212 mμ (ε 1950; *c*, 0·044), of 3β-*acetoxyergost-9-en-7-one* (II*d*), $\nu_{max.}$ 1730 and 1235 (acetate), 1720 (ketone), and 813 $cm.^{-1}$ (trisubstituted ethylene) in CS_2 (Found : C, 79·1; H, 10·6. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

3β-*Acetoxyergostan-7-one* (X).—3β-Acetoxyergosta-9 : 22-dien-7-one (II*a*) (1 g.) was dissolved in ethyl acetate (35 ml.), and added to " AnalaR " acetic acid (10 ml.) in which reduced 4% palladium–charcoal (1 g.) was suspended. Hydrogenation at room temperature and pressure saturated one double bond in 20 min., but the uptake of another mol. took 8 hr. (There was then no sharp end of the hydrogenation.) The product (0·97 g.) was isolated as in the foregoing experiments, and crystallised from methanol as plates (0·39 g.), m. p. 168—171°. Two further crystallisations were required to raise their m. p. to 178—179°. This material is 3β-acetoxyergostan-7-one (X) (0·24 g.), $[\alpha]_D^{20}$ −36°, (*c*, 0·9), $\nu_{max.}$ 1734 and 1236 (acetate), and 1712 $cm.^{-1}$ (ketone) in CS_2 (Found : C, 78·35; H, 10·75. Calc. for $C_{30}H_{50}O_3$: C, 78·55; H, 11·0%). Stavely and Bollenback (*loc. cit.*) give m. p. 183—184°, $[\alpha]_D$ −36°. This material was recovered after alkaline treatment that isomerized (II*a*) to its conjugated isomer (III*a*).

3β-*Acetoxyergosta*-5 : 22-*diene*-7 : 11-*dione* (XI).—3β-Acetoxyergosta-5 : 8(9) : 22-triene-7 : 11-dione (VIII) (191 mg.) was dissolved in "AnalaR" acetic acid (20 ml.), the solution being refluxed with stirring while zinc dust (2 g.) was added portionwise during 1·5 hr. The solids were then filtered off, and the filtrate was diluted with ether (250 ml.). The ethereal solution was water-washed, dried ($MgSO_4$), filtered, and evaporated to a solid residue (162 mg.), which crystallised from methanol as prisms (145 mg.), m. p. 190°, $[\alpha]_D^{21}$ −82° (*c*, 1·10), $\lambda_{max.}$ 233 mμ (ε 10,300), of 3β-*acetoxyergosta*-5 : 22-*diene*-7 : 11-*dione* (XI), $\nu_{max.}$ 1735 and 1240 (acetate), 1720 (ketone), 1675 and 1600 (αβ-unsaturated ketone), and 1640 and 968 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) (Found : C, 77·0; H, 9·3. $C_{30}H_{44}O_4$ requires C, 76·9; H, 9·5%).

3β-*Acetoxyergostane*-7 : 11-*dione* (XII*b*).—(*a*) 3β-Acetoxyergosta-5 : 22-diene-7 : 11-dione (XI) (134 mg.) was hydrogenated at room temperature and pressure in acetic acid (10 ml.) in the presence of pre-reduced 3% palladium–charcoal (150 mg.). In 120 min. the hydrogen uptake (2 mols.) was complete. The filtered solution was evaporated to a solid residue (130 mg.), which crystallised from methanol in needles (105 mg.), m. p. 175—178°. Sublimation of these at 170°/10^{-6} mm. yielded colourless needles, m. p. 189—192°, $[\alpha]_D^{20}$ −9° (*c*, 2·5) of the diketone (XII*b*), identified by mixed m. p. determination and by its infra-red spectra in Nujol and CS_2 with the product obtained in the next experiment.

(*b*) A solution of 3β-acetoxyergost-22-ene-7 : 11-dione (XII*a*) (375 mg.; Heusser *et al.*, *loc. cit.*, 1951) in acetic acid (10 ml.) and ether (10 ml.) containing reduced 3% palladium–charcoal (300 mg.) was hydrogenated at room temperature and pressure. Hydrogen (1 mol.) was taken up in 70 min., and the material was worked up as in (*a*). Needles, m. p. 192—193°, $[\alpha]_D^{20}$ −8° (*c*, 3·0), $\lambda_{max.}$ 296 mμ (ε 695), of 3β-*acetoxyergostane*-7 : 11-*dione* (XII*b*) were obtained, unchanged by sublimation, with $\nu_{max.}$ (sublimed material) at 1735 and 1240 (acetate), and 1715 cm.$^{-1}$ (ketone) in CS_2 (Found : C, 76·1; H, 10·0. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·2%). This compound gave a yellow derivative with Johnson's dinitrophenylhydrazine reagent (*J. Amer. Chem. Soc.*, 1951, **73**, 5888). The dione (XII*a*) was recovered after alkaline treatment that isomerized (II*a*) to its conjugated ketone (III*a*).

Conjugation of the Double Bond in 3β-*Acetoxyergosta*-9 : 22-*dien*-7-*one* (II*a*). 3β-*Acetoxyergosta*-8(9) : 22-*dien*-7-*one* (III*a*).—(*a*) To the above dienone (287 mg.) in "AnalaR" acetic acid (6·5 ml.) N-perchloric acid in acetic acid (6·5 ml.) was added. After 3·5 hr. in the dark a pink tint had developed, and an aqueous solution of potassium acetate was added, and then water. The precipitate (0·28 g.) was filtered off, and crystallised from methanol–chloroform as prisms (180 mg.) of 3β-acetoxyergosta-8(9) : 22-dien-7-one (III*a*), m. p. 209—213°, $[\alpha]_D^{18}$ −56° (*c*, 1·04), $\lambda_{max.}$ 253 mμ (ε 9400), $\nu_{max.}$ 1740 and 1237 (acetate), 1669 (αβ-unsaturated ketone), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) in CS_2. These data confirm the identity with known samples, for which Budziarek, Johnson, and Spring (*loc. cit.*) give m. p. 209—211°, $[\alpha]_D$ −56°, $\lambda_{max.}$ 252 mμ (ε 10,000). This compound has also been described by Stavely and Bollenback (*locc. cit.*), by Heusser *et al.* (*loc. cit.*, 1951), and by Anliker *et al.* (*loc. cit.*).

(*b*) A solution of the ketone (II*a*) (119 mg.) in alcohol (30 ml.), to which 10% sodium hydroxide solution (1 ml.) had been added, was kept under nitrogen for 8 hr., then acidified and diluted with water. The crude dry precipitate was acetylated overnight at room temperature with acetic anhydride (5 ml.) and pyridine (5 ml.), and the residue then obtained by evaporation yielded the enone (III*a*) (57 mg.), identical with the material described in (*a*).

(*c*) The ketone (II*a*) (1 g.) was chromatographed on Grade O alumina (50 g.). Benzene–light petroleum (1 : 3) eluted the unchanged ketone (II*a*) (0·6 g.). Subsequent elution with solvents richer in benzene eluted material (0·4 g.) that on crystallisation from methanol yielded the pure enone (III*a*) (0·23 g.), identified with the foregoing products.

Conjugation of the Double Bond in 3β-*Acetoxyergosta*-5 : 9 : 22-*trien*-7-*one* (VII). 3β-*Acetoxyergosta*-5 : 8(9) : 22-*trien*-7-*one* (XIV).—A solution of the trienone (VII) (100 mg.) in ethanol (20 ml.) was treated with 30% potassium hydroxide solution (0·3 ml.), and set aside at room temperature under nitrogen. During 1 hr. the optical rotation of the solution successively decreased and increased, and then stayed constant. Steroid material was isolated by acidifying the solution and extracting it with ether. Evaporation of the water-washed and dried ($MgSO_4$) ethereal solution left a residue, which was acetylated in acetic anhydride (5 ml.) and pure pyridine (5 ml.) for 15 hr. This solution was evaporated, and the residue separated from methanol as shapeless white crystals (65 mg.) of 3β-acetoxyergosta-5 : 8(9) : 22-trien-7-one * (XIV), m. p. 197—203°. Sublimation at 160—175°/10^{-5} mm. yielded an analytical sample (24 mg.),

* Burke, Turnbull, and Wilson (*loc. cit.*) give m. p. 193—194°, $[\alpha]_D$ −21°, $\lambda_{max.}$ 245 mμ (ε, 11,300) for this compound.

m. p. 199—204°, $[\alpha]_D^{23}$ −32° (*c*, 0·88), $\lambda_{max.}$ 245 mμ (ε 11,800), $\nu_{max.}$ at 1738 and 1235 (acetate), 1658 and 1628 (αβ-unsaturated ketone), and 967 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) in CS_2, and at 1670, 1635, and 1600 (·CO·C:C·CO·) and 1730 and 1240, and 966 cm.$^{-1}$ in Nujol (Found : C, 79·6; H, 9·95. $C_{39}H_{44}O_3$ requires C, 79·6; H, 9·8%). This compound readily gave a red precipitate with Brady's reagent, and a yellow colour with tetranitromethane.

This cross-conjugated ketone (XIV) was recovered quantitatively after treatment for 4 days at 0° with 0·24N-monoperphthalic acid (4 mols.). The crude mixture of stereoisomeric alcohols obtained by reduction of the ketone with sodium borohydride took up 0·75 mol. of active oxygen in such conditions. Chromic acid oxidation of the product yielded material lacking significant absorption in the ultra-violet between 220 and 350 mμ.

Hydrogenation of 3β-*Acetoxyergosta*-5 : 8(9) : 22-*trien*-7-*one* (XIV).—(a) 3β-*Acetoxyergostan*-7-*one* (X). A solution of the ketone (XIV) (1 g.) in ethyl acetate–acetic acid (4 : 1; 50 ml.) was shaken with reduced 4% palladium–charcoal (1 g.) under hydrogen. Hydrogenation ceased after an uptake of 3 mols. (90 min.). The product was crystallised from methanol, giving the saturated 7-ketone (X) (0·3 g.) as plates, m. p. 178—180°, $[\alpha]_D^{20}$ −36° (*c*, 1·0), identified by mixed m. p. determinations, and by a comparison of the infra-red spectra with those of specimens of this ketone obtained previously in this work.

(b) 3β-*Acetoxyergost*-8(9)-*en*-7-*one* (III*c*). (i) The trienone (XIV) (500 mg.) in ethyl acetate (100 ml.) was hydrogenated in the presence of Raney nickel (Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471; 1 ml.) until 2·2 mols. of hydrogen had been absorbed. Crystallisation of the product from methanol gave 3β-*acetoxyergost*-8(9)-*en*-7-*one* (III*c*) (120 mg.) as needles, m. p. 180—186°, $[\alpha]_D$ −43°, $\lambda_{max.}$ 254 mμ (ε 9400). Further purification was achieved by chromatography on charcoal (Sutcliffe and Speakman No. 5; 15 g.); elution with benzene–ether (3 : 1) and ether, and subsequent crystallisation from methanol, yielded the pure ketone as needles, m. p. 184—188°, $[\alpha]_D^{20}$ −41° (*c*, 1·0), $\lambda_{max.}$ 253 mμ (ε 10,000), $\nu_{max.}$ at 1735 and 1237 (acetate), and 1666 cm.$^{-1}$ (αβ-unsaturated ketone) in CS_2 (Found : C, 79·05; H, 10·5. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

The hydrogenation appeared to be less selective in the presence of 4% palladium–charcoal; on purification the enone (III*c*) was obtained in only 5% yield with m. p. 165—170°, $[\alpha]_D$ −42°, $\lambda_{max.}$ 254 mμ (ε 9100).

(ii) A solution of 3β-acetoxyergosta-8(9) : 22-dien-7-one (III*a*) (500 mg.) in ethyl acetate (50 ml.) was shaken with pre-reduced 4% palladium–charcoal (100 mg.) under hydrogen until 1 mol. was absorbed. Crystallisation of the product several times from methanol gave the ketone (III*c*) as needles, m. p. 189—190°, $[\alpha]_D^{20}$ −40° (*c*, 1·0), $\lambda_{max.}$ 254 mμ (ε 9100) (Found : C, 79·0; H, 10·55%). The compound was identified by mixed m. p. determination and infra-red spectroscopy with a specimen prepared as in (i).

3β-*Acetoxy*-9α : 11α-*epoxyergost*-22-*en*-7-*one* (XV).—3β-Acetoxyergosta-9 : 22-dien-7-one (II*a*) (0·415 g.), dissolved in chloroform (50 ml.), was treated with 0·263N-ethereal monoperphthalic acid (9 ml.; 1·3 equiv.) at 0°. After a day crystals of phthalic acid had separated, and the solution was decanted, washed with water, and dried ($MgSO_4$). The filtered solution was evaporated to a residue (0·42 g.) that separated from ethyl acetate as a gel, m. p. 216—218°; a solution of this material in ethyl acetate again yielded on cooling a gel (0·137 g.) of 3β-acetoxy-9α : 11α-epoxyergost-22-en-7-one (XV), m. p. 216—218°, $[\alpha]_D^{19}$ −81° (*c*, 1·04), with no strong absorption between 220 and 350 mμ, but with $\nu_{max.}$ at 1738 and 1240 (acetate), 1720 (ketone), 1294 and 896 (epoxide), and 968 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) (Found : C, 76·6; H, 9·7. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%). This compound was identified by mixed m. p. and comparison of the infra-red spectra with an authentic sample, prepared by the method of Budziarek *et al.* (*J.*, 1952, 2892), who give m. p. 220—223°, $[\alpha]_D$ −85°.

The same product was obtained by oxidation with 30% hydrogen peroxide (1 ml.) of the ketone (II*a*) (1 g.) in benzene (10 ml.) mixed with formic acid (10 ml.). The mixture was shaken for 20 hr., and yielded the keto-oxide (XV) (0·49 g.) on working up (cf. Budziarek *et al.*, *loc. cit.*).

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