yield was 1.5 g. It forms a yellow melt, indicating dissociation.

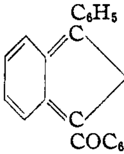
1,4,6,7-Tetraphenylnaphthalene-2,3-dicarboxylic Acid VIa.—A suspension of 1.5 g. of the previous anhydride (IX) in 150 cc. of dry methanol was saturated with hydrogen chloride, and then refluxed for four hours, while the current of hydrogen chloride was continued. The solvent was removed, and the pasty residue taken up in 200 cc. of ethanol. After the addition of 6 g. of sodium hydroxide in 50 cc. of water, and six hours of refluxing, it was acidified and extracted with chloroform. One gram of the acid crystallized. It melts at 310° with decomposition.

The anhydride VI was secured by a similar procedure from the thio analog IV, but using xylene as a solvent. It likewise melts at 310° with decomposition; there is no depression on admixture. While the acid is white, the anhydride has a slight yellow tint.

1,4-Diphenyl-6,7-dimethyl-2,3-dibenzoyl-1,4-oxido-1,2,3,4-tetrahydronaphthalene XI was produced on refluxing a mixture of 10 g. of 2,7-diphenyl-4,5-dimethylisobenzofuran,[2] 8 g. of *trans*-dibenzoylethylene and 500 cc. of ethanol for four hours; the yield was 17 g. after recrystallization from benzene. It was highly dissociated in boiling benzene: mol. wt., calcd., 534: found, 304, 316.

The Furan XII.—A solution of 5 g. of the above diketone XI in 100 cc. of boiling acetic acid was boiled for one minute after the addition of 10 g. of zinc dust. Upon cooling, 3.5 g. of deep orange-yellow crystals separated. In color and fluorescence this substance resembles the other isobenzofurans. It formed addition products with maleic anhydride and with *p*-benzoquinone XIV; the former is hydrolyzed to the acid XIII during the manipulation. The acid is soluble in aqueous sodium carbonate. Since XII is not formed by acetic acid or zinc acetate alone, some reduction must be involved; it is possible that an oxygen bond is attacked, but the structure is admittedly not proved.

In an earlier paper[10] an isobenzofuran ketone XV was described. We have since found that it resembles other isobenzofurans[5] in giving an addition product XVI with maleic anhydride. Thus, the benzoyl group does not have any unfavorable effect on this reaction.



XV

Summary

A sulfur-bridged substance has been obtained for the first time, making use of a new isobenzothiophene in the diene synthesis. The sulfur atom seems to be inactive and unable to participate in addition. The bridge is removed by alcoholic hydrogen chloride as hydrogen sulfide.

Some new isobenzofurans are described. They are strongly fluorescent.

Both series of products have been converted into derivatives of 1,4,6,7-tetraphenylnaphthalene.

[10] Allen and Gates, This Journal, **65**, 1230 (1943).

ROCHESTER, N. Y. RECEIVED MARCH 30, 1943

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

Steroids with Double Bonds between Quaternary Carbon Atoms. I. The Oxidation of α-Ergostenyl Acetate

BY HOMER E. STAVELY AND G. NORRIS BOLLENBACK

A number of natural and derived steroids are known which contain nuclear double bonds terminating at one of the bridgehead carbon atoms 8, 9 or 14, or lying between two of them. Thus four singly unsaturated cholesterol isomers, α-, β-, γ- and δ-cholestenol[1] and their C_{28} homologs α-, β- and γ-ergostenol[2] have been prepared. The double bond positions denoted by the Greek letters are α, $\Delta^{8,14}$; β, $\Delta^{14,15}$; γ, $\Delta^{7,8}$; δ, $\Delta^{8,9}$. Double bonds in the α, γ and δ positions cannot be hydrogenated catalytically, but in the presence of platinum or palladium catalyst and hydrogen, the 7,8 (γ) and 8,9 (δ) double bonds are shifted to the 8,14 (α) position.[1,2,3] Unequivocal proof for the position of the double bond has been obtained only in the case of β-ergostenol[4] and γ-cholestenol[1(a),5] but the structures of the α and δ compounds have been inferred from their chemical behavior with a high degree of probability. Nevertheless some confusion and contradiction exists in this field and better proof for the double bond position in some of these compounds is to be desired. Since the double bond present in a γ($\Delta^{7,8}$)- or δ($\Delta^{8,9}$)-stenol can be isomerized with hydrogen and palladium or platinum catalyst and the product (α-stenol) can in turn be isomerized by hydrochloric acid to a β-stenol of known structure ($\Delta^{14,15}$), it is logical to assign the 8,14 position to

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[1] (a) Schenck, Buchholz and Wiese, *Ber.*, **69**, 2696 (1936); (b) Windaus, Linsert and Eckhardt, *Ann.*, **534**, 22 (1938).

[2] Reindel, Walter and Rauch, *Ann.*, **402**, 74 (1927); Windaus and Langer, **506**, 105 (1933).

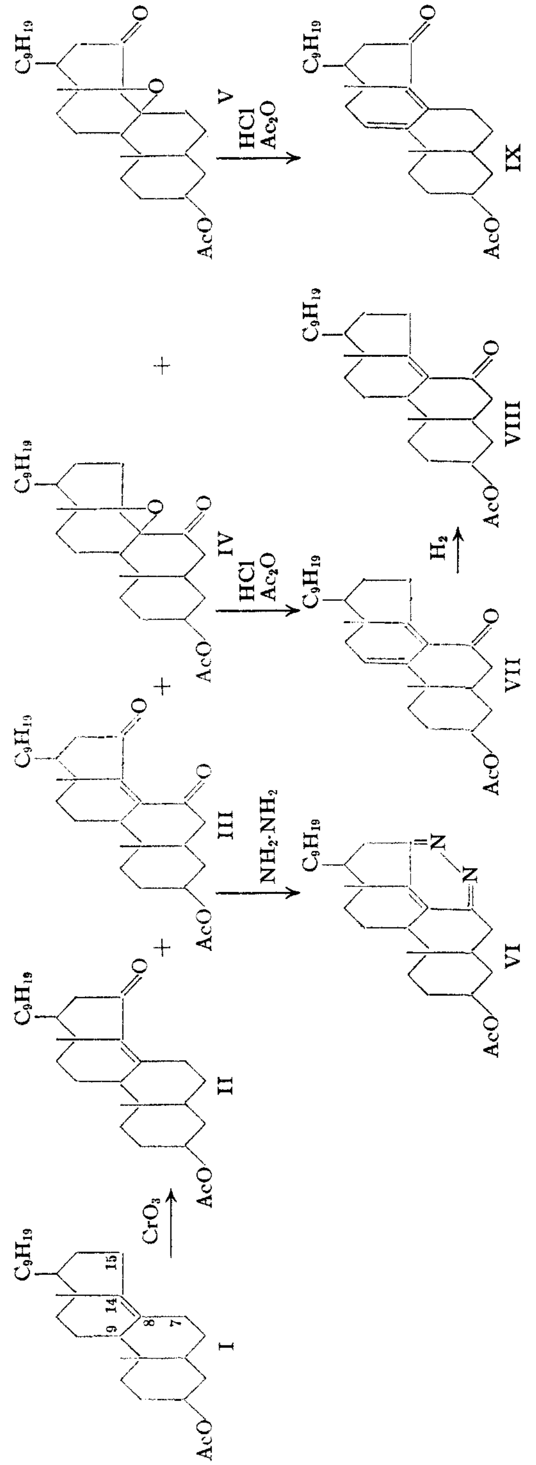
[3] Although a few investigators have attempted to carry out the double-bond isomerization by shaking with a hydrogenating catalyst in a nitrogen atmosphere, it is the opinion of the authors that hydrogen is essential for isomerization. This will be discussed in a later publication.

[4] (a) Achtermann, *Z. physiol. Chem.*, **225**, 141 (1934); (b) Laucht, *ibid.*, **237**, 236 (1935).

[5] Wintersteiner and Moore, This Journal, in press.

the double bond in the α-stenol, but precise proof has been lacking.

Reindel[6a] and Heilbron, *et al.*,[6b] have subjected α-ergostenol and its acetate to chromic acid oxidation. From the latter Heilbron obtained a monoketone and small amounts of two isomeric substances which contained two oxygen atoms more than the starting material. We have oxidized α-ergostenyl acetate (I) with chromic acid at room temperature and by careful chromatographic separations were able to isolate in pure form six neutral oxidation products. Three of them, II, IV and V, have melting points approximating the values given by Heilbron.[5,6b]



A diketone III was isolated which has an absorption maximum in the region characteristic for $\Delta^{2,3}$-1,4-diketones (Figure 1). The substance readily condensed with hydrazine to form a pyridazine derivative, also characteristic for 1,4-diketones. Noller[7] has pointed out that a product containing nitrogen which gives the correct analytical values for a pyridazine derivative may be a polymolecular condensation product. However, the crystalline pyridazine derived from the diketone III had a Rast molecular weight value[8] close to that of a normal pyridazine. Therefore a 1,4-diketone is clearly indicated. Assuming the 7,8, 8,9, 8,14 or 14,15 position for the double bond only two enedione structures are possible, namely, $\Delta^{8,9}$-7,11-dione or $\Delta^{8,14}$-7,15-dione. On stereochemical grounds only the latter could be expected to yield a normal pyridazine ring. Hence the diketone is probably $\Delta^{8,14}$-ergostenol-3-dione-7,15 acetate, and α-ergostenol is $\Delta^{8,14}$-ergostenol-3.

The isomeric products IV and V have the empirical formula $C_{30}H_{48}O_4$, and show no absorption maxima in the ultraviolet. On heating with mineral acid in ethanol, both substances lose the elements of water to form two different conjugated dienones each with distinct absorption characteristics (see Fig. 1). Such behavior would be expected from an α,β-ketoxide. Oxidation of an unsaturated substance to an α,β-ketoxide by means of chromic acid has been observed previously.[9] It is true that the dienones VII and IX could have been derived from β,γ- or γ,δ-unsaturated, α-tertiary-hydroxy ketones and IV and V could possess one of these structures, but if so an α,β-ketoxide must have been the immediate precursor. With the double bond in α-ergostenol fixed in the 8,14 position two ketoxide structures are possible, namely, a 7-keto-8,14 oxide and a

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(6) (a) Reindel, *Ann.*, **466**, 131 (1928); (b) Heilbron, Simpson and Wilkinson, *J. Chem. Soc.*, 1699 (1932).

(7) Noller, THIS JOURNAL, **61**, 2976 (1939).

(8) Decomposition permitted only a few temperature readings, but the determination clearly eliminated a polymolecular product.

(9) Rosenheim and King, *Nature*, **139**, 1015 (1937); Petrow, *J. Chem. Soc.*, 998 (1939).

15-keto-8,14-oxide. Hydrolytic cleavage of the epoxide ring in the ketoxide with the structure IV should yield a dienone with double bonds in the 8,9 and 14,15 positions. Such a cross conjugated system should absorb in the region 230–280 mμ. On the other hand, if the two olefinic double bonds both lie within the same ring the maximum should be located at longer wave lengths.[10] Since the dienone VII derived from IV has a maximum at 298 mμ, the alternative structure VII is to be preferred.

Conclusive proof for the structure of IV inferred from the spectrographic data has been obtained by Wintersteiner and Moore.[5] They oxidized α-cholestenyl acetate with chromic acid and obtained a series of homologous products corresponding in their properties (melting points, rotation trends, and absorption spectra) to II, IV and V. The ketoxide corresponding to IV was obtained also by an alternate route. $\gamma(\Delta^{7,8})$-Cholestenyl acetate was treated with perbenzoic acid. An intermediate 7-hydroxy-8,14-oxide was obtained which yielded the ketoxide homologous to IV on oxidation. Thus IV is a 7-keto-8,14-oxide. If the dienone IX ($\lambda_{\text{max.}}$ 307 mμ) derived from the ketoxide V were the $\Delta^{8,9;14,15}$ double bond isomer of VII ($\lambda_{\text{max.}}$ 298 mμ) the $\lambda_{\text{max.}}$ value of IX should be less than 280 mμ. Thus V must have the only alternative structure, that of a 15-keto-8,14-oxide.

When the dienone VII is hydrogenated in ethanol with palladium catalyst, one mole of hydrogen is utilized and the product is the α,β-unsaturated 7-ketone VIII, ($[\alpha]_D$ −62°) isomeric with the primary oxidation product II ($[\alpha]_D$ + 110°). According to the generalizations of Woodward[11] an α,β,β-substituted α,β-unsaturated ketone whose carbon–carbon double bond is exocyclic to two rings will have a $\lambda_{\text{max.}}$ value near 257 mμ, but if the carbon–carbon double bond is not exocyclic to any ring the most probable value will be 247 mμ. The ketones II and VIII have absorption maxima at 259 mμ and 262 mμ, respectively, and both clearly belong to the former class. They represent the only two such structures possible within the steroid ring system. Since the levorotatory ketone VIII was derived from the ketoxide IV which has been proved to be a 7-ketone, it must be $\Delta^{8,14}$-ergostenol-3-one-7 acetate, and the dextrorotatory ketone II must be assigned the only other possible structure, namely, that of $\Delta^{8,14}$-ergostenol-3-one-15 acetate. The alternative structure for VIII with the carbon–carbon double bond placed in the 8,9 position is excluded since such a substance would belong to the latter of the two classes of α,β,β-substituted ketones mentioned above and would absorb at lower wave lengths. A ketone of this type is described in paper II of this series.

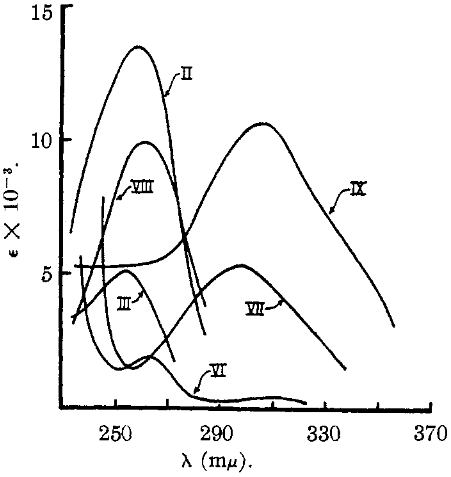

Fig. 1.—Absorption curves taken in ethanol of: II, $\Delta^{8,14}$-ergostenol-3-one-15 acetate; III, $\Delta^{8,14}$-ergostenol-3-dione-7,15 acetate; VI, pyridazine derivative of III; VII, $\Delta^{9,11;8,14}$-ergostadienol-3-one-7 acetate; VIII, $\Delta^{8,14}$-ergostenol-3-one-7 acetate; IX, $\Delta^{9,11;8,14}$-ergostadienol-3-one-15 acetate.

It seems probable that the ketone VIII, as well as the ketone II, is a primary oxidation product, even though only the latter can be isolated directly. During the oxidation VIII is presumably completely converted into the ketoxide IV, whereas only a small part of the ketone II undergoes oxidation to the ketoxide V. Thus it seems that a 7-keto group is able to activate carbon atoms 8 and 14 to a greater extent than a carbonyl group at 15. This is true also of hydrogenation, since the dienone VII can be reduced to a saturated ketone, whereas the ketone II either remains unchanged or is converted into α-ergostenyl acetate.[12]

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(10) Private communication from Dr. R. B. Woodward, Harvard University. Dr. Woodward has pointed out that the spectrographic data ($\lambda_{\text{max.}}$ 298) would fit either the structure given for VII or the $\Delta^{8,14;15,16}$-7-keto linear dienone. The latter structure is not excluded.

(11) Woodward, THIS JOURNAL, **64**, 76 (1942).

(12) When palladium black is used as the catalyst keto groups are ordinarily not reduced. However, in several instances we have found that the carbonyl oxygen was at least partially removed when α,β-unsaturated ketones containing diquaternary double bonds were shaken with hydrogen and palladium catalyst in glacial acetic acid, presumably by reduction of the keto group to an allylic alcohol followed by dehydration and reduction, or by hydrogenolysis of the allylic hydroxyl. The deoxygenated products can be easily removed by chromatographing.

Acknowledgment.—The authors wish to thank Dr. O. Wintersteiner for his interest and advice, Dr. N. H. Coy of the Squibb Vitamin Research Laboratory for the spectrographic measurements and Mr. J. F. Alicino of this Laboratory for the microanalyses.

Experimental

Oxidation of α-Ergostenyl Acetate (I) with Chromic Acid.—α-Ergostenyl acetate (8 g.) was placed with 600 cc. of acetic acid, and enough benzene was added to dissolve it at room temperature. A solution of 6.5 g. of chromic trioxide in 100 cc. of 90% acetic acid was added dropwise with stirring. After standing for twenty hours at room temperature, 25 cc. of ethanol was added and the solution was concentrated to a small volume *in vacuo*. Water was added and the mixture was thoroughly extracted with ether. Acid oxidation products and acetic acid were removed by washing the ether with water and 2 *N* sodium hydroxide. After washing out excess alkali with water and drying over sodium sulfate the ether was removed by distillation, yielding 7.0 g. of neutral oxidation product.

Chromatographic Separation of Neutral Oxidation Products.—The neutral residue was dissolved in hot ethanol and on cooling 2.0 g. of crystalline product was filtered off, m. p. 120–180°. It was dissolved in hexane and chromatographed on a column of alumina 2.1 × 25 cm. The column was eluted with successive portions of hexane, 20% benzene in hexane, benzene, 10% ether in benzene, 50% ether in benzene, ether, and finally with ether-ethanol mixtures. After passing through the column the eluant was collected in portions of 100 cc. and 35 fractions were thus obtained. The residue from each fraction was examined and combined with residues having a similar m. p. In the same way the non-crystalline portion of the neutral fraction was chromatographed. The combined residues of similar m. p. were recrystallized to a constant m. p. Thus four pure crystalline products were obtained, II, IV, V, and a substance with the formula $C_{30}H_{46}O_6$.

$\Delta^{8,14}$-Ergostenol-3-one-15 Acetate (II).—Recrystallized from 80% ethanol the m. p. was 170°[13]; $[\alpha]^{23}D$ 110 ± 3° (1.19% in chloroform); yield 7%.

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.60. Found: C, 78.91; H, 10.51.

The ketone exhibited maximum absorption at 259 mμ, ε 13,300.[14] When the substance was heated with semicarbazide acetate in ethanol for three hours only partial reaction occurred. On standing in alcohol for four days, however, a normal semicarbazone was formed, m. p. 199–200°.

Anal. Calcd. for $C_{31}H_{51}O_3N_3$: C, 72.48; H, 10.01; N, 8.18. Found: C, 72.80; H, 10.12; N, 7.86.

The compound formed an orange 2,4-dinitrophenylhydrazone, m. p. 220° (dec.).

Ergostanol-3-one-7-oxide-8,14 Acetate (IV).—Recrystallized from 80% ethanol the m. p. was 134°; $[\alpha]^{23}D$ −83 ± 3° (1.09% in chloroform); yield 18%.

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.10; H, 10.06.

No semicarbazone was formed when the substance stood for three days with semicarbazide acetate in pyridine-ethanol, a procedure[15] which yields cholestenone semicarbazone in a few hours. An orange 2,4-dinitrophenylhydrazone precipitated from acidified ethanol, perhaps only after the epoxide ring had been ruptured by the acidic reagent. The substance showed no absorption in the ultraviolet above 230 mμ.

Ergostanol-3-one-15-oxide-8,14 Acetate (V).—Recrystallized from 80% ethanol the m. p. was 208–210°; $[\alpha]^{23}D$ −6.0 ± 1.5° (0.985% in chloroform); yield 2%.

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.48; H, 10.40.

The compound surprisingly failed to yield a dinitrophenylhydrazone on standing with 2,4-dinitrophenylhydrazine for two days. It showed no absorption in the ultraviolet above 230 mμ.

The Compound $C_{30}H_{46}O_6$.—This substance was strongly adsorbed on the alumina column and was eluted with ether. The crude residues had a m. p. 185–200°. On recrystallization from 80% ethanol the m. p. was constant at 201–202°; $[\alpha]^{23}D$ −69 ± 2° (0.49% in chloroform).

Anal. Calcd. for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.24; H, 9.06.

The most probable structure is that of 3-acetoxy-ergostandiol-8,14-dione-7,15.

$\Delta^{8,14}$-Ergostenol-3-dione-7,15 Acetate (III).—It was evident from the chromatograms that the ketoxides IV and V interfered with the separation of other products in pure form. Therefore all chromatographic fractions except those yielding pure compound II, IV and V and the compound $C_{30}H_{46}O_6$ were combined with the mother liquor residues from these substances and dissolved in 100 cc. of ethanol. Concd. hydrochloric acid (5 cc.) was added, and the mixture was refluxed for two hours. The solution was poured into 400 cc. of water, and extracted with ether. The combined ether extracts were washed free of acid, dried over sodium sulfate, and the ether removed by distillation. The residue was refluxed with 5.0 g. of Girard ketone reagent T, 45 cc. of ethanol and 5.0 cc. of glacial acetic acid, and was separated into ketonic and non-ketonic fractions in the usual manner. Each fraction was acetylated in pyridine–acetic anhydride and chromatographed on a column of alumina 25 × 2.1 cm. From the non-ketonic moiety only one crystalline compound could be isolated, 100 mg. of a substance $C_{30}H_{48}O_2$, m. p. 138°, $[\alpha]^{23}D$ −29°, which appeared to be dehydroergostenol acetate.[16]

Anal. Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.90; H, 11.17.

This substance could have been derived from an 8,14 oxide or it might be a primary oxidation product.

Two crystalline substances were isolated from the ketonic fraction. The residues from the 50% benzene in hexane eluant yielded a compound, m. p. 177°, which was also prepared directly from the ketoxide IV as described below.

The residues from the 20% ether in benzene eluant yielded the diketone III, recrystallized from 80% ethanol,

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(13) All melting points are uncorrected.

(14) All absorption measurements were made in absolute ethanol.

(15) Dutcher and Wintersteiner, This Journal, **61**, 1992 (1939).

(16) Windaus and Lüttringhaus, *Ann.*, **481**, 119 (1930).

m. p. 149–151°; $[\alpha]^{24}\text{D}$ −24 ± 2° (0.64% in chloroform), yield 2%.

Anal. Calcd. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85. Found: C, 76.62; H, 9.85.

The substance exhibited maximum absorption at 255 mμ, ε 5000.

Pyridazine Derivative of III (VI).—Thirty mg. of the diketone III, 5 cc. of ethanol, and 0.1 cc. of 42% hydrazine hydrate were refluxed for six hours, the mixture was poured into 30 cc. of water and filtered. The precipitate was crystallized from 80% ethanol. The product was crystalline, m. p. 220–225° (dec.); molecular weight (Rast), 410.

Anal. Calcd. for $C_{30}H_{46}O_2N_2$: C, 77.20; H, 9.94; N, 6.00. Found: C, 76.92; H, 9.88; N, 6.29.

The pyridazine derivative showed selective absorption at 262 mμ, ε 1800.

Preparation of the Dienone VII from the Ketoxide IV.—Five hundred mg. of the ketoxide IV, 20 cc. of ethanol, and 1 cc. of concd. hydrochloric acid were refluxed for two and one-half hours, the mixture was poured into water and extracted with ether. The combined ether extracts were washed free of acid, dried over sodium sulfate and the ether was removed by distillation. The residue was acetylated overnight in pyridine–acetic anhydride and the resulting acetate was recrystallized from 80% ethanol to a constant m. p. 176–178°, $[\alpha]^{24}\text{D}$ −22 ± 2° (0.81% in chloroform).

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.36; H, 10.42.

The dienone exhibited maximum absorption at 298 mμ, ε 5100. It formed an orange 2,4-dinitrophenylhydrazone, m. p. 223° (dec.).

$\Delta^{8,14}$-Ergostenol-3-one-7 Acetate (VIII).—Palladium catalyst (30 mg.) in ethanol was saturated with hydrogen and a solution of 100 mg. of dienone VII in ethanol was added. Within fifteen minutes 5.4 cc. (1.1 moles) of hydrogen was taken up. The palladium was filtered off and the product precipitated by the addition of water. After 3 crystallizations from 80% ethanol the m. p. was constant at 155°, $[\alpha]^{22}\text{D}$ −62 ± 3° (0.56% in chloroform).

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.60. Found: 79.09; H, 10.30.

The ketone showed maximum absorption at 262 mμ, ε 9800.

Preparation of the Dienone IX from the Ketoxide V.—The ketoxide V (90 mg.), 10 cc. of ethanol, and 0.5 cc. of concd. hydrochloric acid were heated on the steam-bath for two hours and then poured into water and extracted with ether. The ether residue was reacetylated overnight in pyridine–acetic anhydride and chromatographed. A separation into two fractions was accomplished, the one a non-crystallizable oil (40%) and the other, recrystallized from 80% ethanol four times, had a constant m. p. of 155°.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 78.66; H, 9.66.

The low values for C and H were not unexpected in view of the fact that the substance was readily autoxidizable. The dienone exhibited maximum absorption at 307 mμ, ε 10,700.

Hydrogenation of the Ketone II.—With palladium in ethanol no reduction took place and the ketone was recovered unchanged. In glacial acetic acid 2.1 moles of hydrogen were taken up in eighty minutes. α-Ergostenyl acetate (80% yield) was the main product. The rest was starting material.

Summary

Mild oxidation of α-ergostenyl acetate yielded six neutral oxidation products. From chemical and spectrographic evidence it is concluded that the products are the $\Delta^{8,14}$-one-15; $\Delta^{8,14}$-dione-7,15; -one-7-oxide-8,14; -one-15-oxide-8,14; -dione-7,15-diol-8,14; and the $\Delta^{8,9;14,15}$-derivatives of ergostanyl acetate. Five of the products have keto groups in one or the other, or both, positions (7 and 15) α to the olefinic bond. They could only have been derived from a steroid having an 8,14 double bond and thus constitute proof for the previously inferred structure of α-ergostenol.

The two ketoxides were converted into conjugated dienones, one of which was partially reduced to $\Delta^{8,14}$-ergostenol-3-one-7 acetate. This substance was not found among the oxidation products presumably because it was completely converted into the more highly oxidized product ergostanol-3-one-7-oxide-8,14 acetate.

A $\Delta^{8,14}$-7-ketone and a $\Delta^{8,14}$-15-ketone are the only two possible representatives of the class of α,β,β-substituted, α,β-unsaturated steroid ketones with the carbon–carbon double bond exocyclic to two rings. The ultraviolet absorption maxima of $\Delta^{8,1}$-ergostenol-3-one-7 and $\Delta^{8,14}$-ergostenol-3-one-15 lie in the region predicted by Woodward[11] for ketones of this type. The latter substance is the first example of a 15-keto steroid to be reported.

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