Studies in the Synthesis of Cortisone. Part VI. Conjugated Trienones derived from Ergosterol.*

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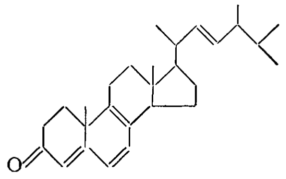
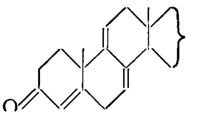
Ergosta-4 : 6 : 8(9) : 22-tetraen-3-one (I) has been prepared by hydrolysis of 3-acetoxyergosta-3 : 5 : 7 : 9(11) : 22-pentaene with acid. The isomeric ergosta-4 : 6 : 8(14) : 22-tetraen-3-one (IV) resulted when ergosterol was treated with aluminium *tert.*-butoxide and *p*-benzoquinone.

DURING an investigation into methods of preparing 11-keto-steroids from ergosterol, the preparation of ergosta-4 : 6 : 8(9) : 22-tetraen-3-one (I) was attempted. Treatment of ergosta-4 : 7 : 9(11) : 22-tetraen-3-one (II) (Heilbron, Kennedy, Spring, and Swain, *J.*, 1938, 869) with the boron trifluoride–ether complex in benzene, or with hydrogen chloride in chloroform, apparently caused rearrangement to (I), for in each instance a maximum appeared in the ultra-violet spectrum at 388 mμ. However, neither method was very satisfactory; boron trifluoride apparently allowed further reaction, as shown by the gradual disappearance of this peak, and its intensity in the spectrum of the crude product of the hydrogen chloride-catalysed rearrangement was rather low ($E^{1\%}_{1\,\mathrm{cm.}}$ 160—180). Compound (I) was finally obtained by hydrolysis of 3-acetoxyergosta-3 : 5 : 7 : 9(11) : 22-pentaene (III) (*idem, loc. cit.*) with aqueous hydrochloric acid in a mixture of chloroform and ethanol (cf. Yashin, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 4654). Although the rotation and the ultra-violet absorption of the crude product both indicated the presence of a high proportion of (I), the yield, after crystallisation, was poor; thus little material was available, and the purity of the compound cannot be guaranteed. However, the high rotation (+749°) and the ultra-violet spectrum (ε 16,700 at 245·5 mμ and 9300 at 390 mμ) are of the same order as those quoted by Yashin *et al.* (*loc. cit.*) for the analogous 22*a*-spirosta-4 : 6 : 8(9)-trien-3-one ($[\alpha]_D$ +627°; ε 17,800 at 244 mμ, and 12,300 at 388 mμ) and by Fried and Sabo (*J. Amer. Chem. Soc.*, 1953, **75**, 2273) for 21-acetoxy-17α-hydroxypregna-4 : 6 : 8(9)-triene-3 : 20-dione ($[\alpha]_D$ +531°; ε 14,300 at 244 mμ and 6700 at 385 mμ).

Wettstein (*Helv. Chim. Acta*, 1940, **23**, 388; Swiss P. 236,309; cf. Dauben, Eastham, Micheli, Takemura, Mandell, and Chemerda, *J. Amer. Chem. Soc.*, 1953, **75**, 3255) has reported that 3-hydroxy-Δ^{5}-steroids are converted into the 3-keto-$\Delta^{4:6}$-compounds by treatment with *p*-benzoquinone and aluminium *tert.*-butoxide; it seemed possible that this reaction might be extended to a 3-hydroxy-$\Delta^{5:7}$-compound with production of a conjugated trienone such as (I). When ergosterol was oxidised under these conditions the product yielded by chromatography a small quantity of a deep red solid and, in 12—16% yield, a very pale yellow solid isomeric with (I). The ultra-violet spectrum ($\lambda_{\max.}$ 350 mμ) suggested that the compound was ergosta-4 : 6 : 8(14) : 22-tetraen-3-one (IV) [the displacement of the absorption to a higher wave-length in (I) is related to the homo-annular diene system in that compound]; this was subsequently confirmed by Barton and Bruun's description (*J.*, 1951, 2728) of a compound with identical physical properties, which they had obtained by Oppenauer oxidation of ergosta-5 : 7 : 14 : 22-tetraen-3β-ol and formulated as (IV). A direct comparison of our ketone and of its 2 : 4-dinitrophenyl-hydrazone with samples kindly provided by Professor Barton proved the identity of the two


(I)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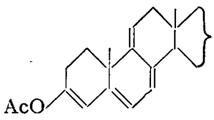
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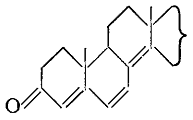
(IV)

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* Part V, preceding paper.

compounds. Compound (IV) was unchanged after treatment, in chloroform solution, with hydrogen chloride.

EXPERIMENTAL

Ergosta-4 : 6 : 8(9) : 22-*tetraen*-3-*one*.—3-Acetoxyergosta-3 : 5 : 7 : 9(11) : 22-pentaene (Heilbron *et al.*, *loc. cit.*) (0·7 g.) in a mixture of chloroform (30 ml.) and ethanol (70 ml.) was treated with concentrated hydrochloric acid (5 ml.) and left for 24 hr. at room temperature. The solution then had $[\alpha]_D$ +650° and showed a maximum at 380 mμ ($E_{1\,\text{cm.}}^{1\%}$ 198). The solution was diluted with chloroform and washed successively with water, aqueous sodium hydrogen carbonate, and water. The chloroform solution was evaporated to dryness under reduced pressure and the residue was dissolved in acetone. On being cooled to *ca.* −40°, the solution deposited a yellow solid (160 mg.), m. p. 142—145°, $\lambda_{\text{max.}}$ 388 mμ (ε 8900) in EtOH. Crystallisation from methanol yielded the unsaturated *ketone* as pale yellow plates, m. p. 151—153°, $[\alpha]_D$ +749° (*c*, 0·465 in $CHCl_3$) (Found: C, 85·4; H, 10·3. $C_{28}H_{40}O$ requires C, 85·6; H, 10·3%), $\lambda_{\text{max.}}$ 245·5 (ε 16,700) and 390 mμ (ε 9300) in EtOH, $\nu_{\text{max.}}$ 1661, 1634, 1594, 1573, (·CO·C:C·C:C·C:C·), 965 (*trans*-1 : 2-disubstituted ethylene), and 870 cm.$^{-1}$ (3-keto-Δ^4-) (in CCl_4) (C.S. no. 70).* The last band has been observed in known 3-keto-Δ^4-steroids and is believed to be characteristic of the group (this will be discussed more fully in a forthcoming publication).

The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate as very deep red needles, melting at 230—235° (Found: N, 10·0. $C_{34}H_{44}O_4N_4$ requires N, 9·8%), $\lambda_{\text{max.}}$ 437·5 mμ (ε 34,500) in $CHCl_3$.

Ergosta-4 : 6 : 8(14) : 22-*tetraen*-3-*one*.—A solution of ergosterol (10 g.) and *p*-benzoquinone (20 g.) in toluene (sodium-dried; 220 ml.) was evaporated under reduced pressure until about 20 ml. of distillate had been collected. Aluminium *tert.*-butoxide (10 g.) was added and the mixture was boiled under reflux for 1 hr. After being cooled, the solution was filtered and the dark solid washed with warm benzene. The combined filtrate and washings were extracted with dilute aqueous sodium hydroxide; persistent emulsions were formed and the layers could be separated only by centrifugation. The benzene solution was washed with water, dried ($CaCl_2$), and evaporated to dryness under reduced pressure. The residual red gum (4·36 g.), in benzene solution, was chromatographed on alumina (Peter Spence Grade 0; 200 g.). The first benzene eluates were red, and gave a deep red solid on evaporation. Subsequent benzene eluates were yellow and gave yellow gums, which crystallised readily. Elution of this material was completed with benzene–ether (1 : 1). Crystallisation of this yellow solid from light petroleum (b. p. 40—60°) gave the unsaturated ketone as yellow plates (1·59 g., 16%), m. p. 112—114°. After further chromatography on alumina and crystallisation from methanol the ketone melted at 113—114° and had $[\alpha]_D$ +588° (*c*, 0·98 in $CHCl_3$) (Found: C, 85·6; H, 10·4. Calc. for $C_{28}H_{40}O$: C, 85·6; H, 10·3%), $\lambda_{\text{max.}}$ 237 (ε 4700), 282 (ε 7100), and 350 mμ (ε 27,100) in EtOH, $\nu_{\text{max.}}$ 1666, 1644, 1588, and 1550 (·CO·C:C·C:C·C:C·), 970 (*trans*-1 : 2-disubstituted ethylene), and 874 cm.$^{-1}$ (3-keto-Δ^4-) in CCl_4 (C.S. no. 71).* Barton and Bruun (*loc. cit.*) give m. p. 114—115°, $[\alpha]_D$ +590° ($CHCl_3$), $\lambda_{\text{max.}}$ 348 mμ (ε 26,500) in EtOH. The infra-red spectrum of a specimen of (IV) made by the above method was identical with that of a sample provided by Professor Barton. There was no depression of the m. p. on mixing of the samples.

The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate in deep red needles, m. p. 231—234° (decomp.). It did not depress the m. p. of a sample provided by Professor Barton (Found: C, 71·4; H, 8·15; N, 10·1. Calc. for $C_{34}H_{44}O_4N_4$: C, 71·3; H, 7·7; N, 9·8%), $\lambda_{\text{max.}}$ 427 mμ (ε 43,200) in $CHCl_3$. Barton and Bruun (*loc. cit.*) give m. p. 236—237° (decomp.), and $\lambda_{\text{max.}}$ 427 mμ (ε 41,000) in $CHCl_3$.

The *semicarbazone*, an amorphous yellow solid, melted at *ca.* 215° (Found: N, 9·5. $C_{29}H_{43}ON_3$ requires N, 9·35%), $\lambda_{\text{max.}}$ 338 (ε 50,400) and 352 mμ (ε 47,100) in EtOH.

The red solid obtained from the first benzene eluates weighed 340 mg. After further purification on alumina and crystallisation from ethanol it was obtained as red needles, m. p. 157—159° (Found: C, 84·0; H, 8·3%), $\lambda_{\text{max.}}$ 236 ($E_{1\,\text{cm.}}^{1\%}$ 563) and 330 mμ ($E_{1\,\text{cm.}}^{1\%}$ 434) in EtOH.

The author is indebted to Professor E. R. H. Jones, F.R.S., for suggesting this problem and for providing accommodation and facilities in his laboratories at the University of Manchester, where part of this work was carried out.

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* Spectra thus marked have been deposited with the Society. Photocopies may be obtained from the General Secretary, price 3*s.* 0*d.* each; the C.S. numbers must be quoted in all applications.