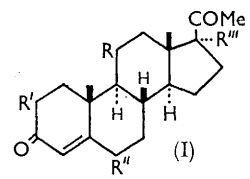
901. *Modified Steroid Hormones. Part XX.* The Dienone–Phenol Rearrangement of Some 11-Oxygenated $\Delta^{1,4,6}$-Steroidal 3-Ketones.*

By David N. Kirk and Vladimir Petrow.

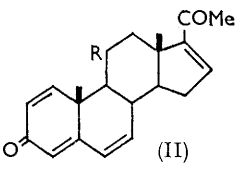
Successful extension of the dienone–phenol rearrangement to some 11-oxygenated structures is described.

In an earlier publication [1] we reported our failure to apply the dienone–phenol rearrangement to some $\Delta^{1,4}$- and $\Delta^{1,4,6}$-steroidal 3,11-diketones. We now describe some further experiments employing new 11-oxygenated structures which have been found to undergo the rearrangement.

Pregn-4-ene-3,11,20-trione [2] (I; R = :O, R′ = R″ = R‴ = H) was converted into the 2,6,17α-tribromo-derivative (I; R = :O, R′ = R″ = R‴ = Br) by reaction with 3-mol. of bromine in acetic acid. Treatment of the tribromo-compound with boiling collidine afforded pregna-1,4,6,16-tetraene-3,11,20-trione [3] (II; R = :O), which was characterised by its ultraviolet absorption ($\lambda_{max.}$ 230, 268, and 293 mμ; $\lambda_{infl.}$ 238 mμ). This compound failed to undergo the dienone–phenol rearrangement on treatment with toluene-*p*-sulphonic acid in acetic anhydride at 100° for 2 hr. When heating was prolonged for 12 hr., however, and the product saponified and purified by chromatography, a low yield of phenolic material was obtained which, on the basis of its spectral characteristics, appeared to be the required product (III; R = :O). There was insufficient material for complete purification. It is of interest that Elks *et al.*[4] have since reported an abnormal dienone–phenol rearrangement of prednisone acetate under somewhat unusual experimental conditions employing perchloric acid as catalyst.



(I)



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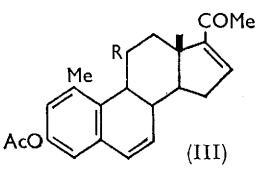

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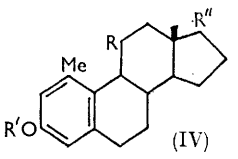

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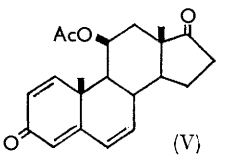

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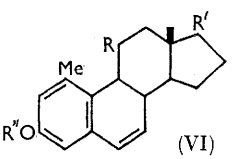

(VI)

We next turned our attention to 11α-acetoxypregna-1,4,6,16-tetraene-3,20-dione [3] (II; R = α-OAc) which was conveniently prepared from 11α-acetoxyprogesterone [2] (I; R = α-OAc, R′ = R″ = R‴ = H) by tribromination, followed by dehydrobromination with collidine. The tetraene (II; R = α-OAc), in contrast to its 11-oxo-analogue (II; R = :O) (above), smoothly underwent the dienone–phenol rearrangement to give 3,11α-diacetoxy-17-acetyl-1-methylœstra-1,3,5(10),6,16-pentaene (III; R = α-OAc) in

* Part XIX, preceding paper.

[1] Kirk, Patel, and Petrow, *J.*, 1957, 1046.
[2] Peterson, Murray, Eppstein, Reineke, Weintraub, Meister, and Leigh, *J. Amer. Chem. Soc.*, 1952, **74**, 5933.
[3] Cf. Djerassi, Rosenkranz, Iriarte, Berlin, and Romo, *J. Amer. Chem. Soc.*, 1951, **73**, 1523, for the preparation of the 11-deoxy-analogue.
[4] Elks, Oughton, and Stephenson, *Proc. Chem. Soc.*, 1959, 6.

excellent yield. The pentaene was reduced catalytically to 3,11α-diacetoxy-17β-acetyl-1-methylœstra-1,3,5(10)-triene (IV; R = α-OAc, R′ = Ac, R″ = β-Ac), which was converted by alkaline hydrolysis followed by methylation [5] into 17β-acetyl-3-methoxyœstra-1,3,5(10)-trien-11α-ol (IV; R = α-OH, R′ = Me, R″ = β-Ac). Oxidation of the last compound with chromium trioxide in pyridine [6] gave 17β-acetyl-3-methoxyœstra-1,3,5(10)-trien-11-one (IV; R = :O, R′ = Me, R″ = β-Ac).

11β-Hydroxyandrost-4-ene-3,17-dione [7] is readily prepared by degradation of hydrocortisone, and was therefore employed, as its 11β-acetoxy-derivative,[8] for the preparation of an 11β-hydroxylated aromatic structure. The 11-acetate was treated in very dilute ethereal solution with 2 mol. of bromine in acetic acid; the 2,6-dibromo-derivative was obtained. Bromination in more concentrated solution, in contrast, led to the separation of the sparingly soluble 6-bromo-diketone, which was identified by its dehydrobromination to 11β-acetoxyandrosta-4,6-diene-3,17-dione, $\lambda_{max.}$ 284 mμ.

Dehydrobromination of 11β-acetoxy-2,6-dibromoandrost-4-ene-3,17-dione furnished 11β-acetoxyandrosta-1,4,6-triene-3,17-dione (V) in rather low yield. Dienone–phenol rearrangement of the triene (V) proceeded normally, to give 3,11β-diacetoxy-1-methylœstra-1,3,5(10),6-tetraen-17-one (VI; R = β-OAc, R′ = :O, R″ = Ac), which was reduced catalytically to 3,11β-diacetoxy-1-methylœstra-1,3,5(10)-trien-17-one (IV; R = β-OAc, R′ = Ac, R″ = :O). As alkaline hydrolysis of the 11β-acetoxy-group was expected to offer difficulty,[9] the diacetoxy-ketone (IV; R = β-OAc, R′ = Ac, R″ = :O) was reduced with lithium aluminium hydride, giving 1-methylœstra-1,3,5(10)-triene-3,11β,17β-triol (IV; R = R″ = β-OH, R′ = H). We subsequently found that acylation of this compound with acetic anhydride–pyridine at 100° furnished the corresponding triacetate (IV; R = R″ = β-OAc, R′ = Ac), which was smoothly hydrolysed to the parent triol by ethanolic potassium hydroxide. There is, consequently, no steric hindrance to hydrolysis of 11β-acetoxy-groups in systems such as (IV; R = β-OAc).[10]

Experimental

Optical rotations were determined for $CHCl_3$ solutions in a 1 dm. tube. Ultraviolet (in EtOH) and infrared absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc. B.D.H. alumina (chromatography grade) was employed throughout.

Pregna-1,4,6,16-tetraene-3,11,20-trione (II; R = :O).—Pregn-4-ene-3,11,20-trione (10 g.) in dry ether (400 ml.) was cooled below 5° and treated with a drop of hydrogen bromide in acetic acid followed by bromine in acetic acid (90 ml. of 1·017M-solution; 3 mol.). After 1·5 hr., when decolorisation was complete, the solution was washed repeatedly with water. The crystalline material which separated in the ether phase was collected and washed with ether, to give crude *2,6,17α-tribromopregn-4-ene-3,11,20-trione* (13·7 g.), m. p. 150—153°. Purified from methylene chloride–acetone it formed needles, m. p. 150—153° (decomp.), $[\alpha]_D^{23}$ +41° (*c* 0·21), $\lambda_{max.}$ 246·5 mμ (ε 11,600) (Found: C, 44·7; H, 4·4; Br, 42·6. $C_{21}H_{25}O_3Br_3$ requires C, 44·6; H, 4·5; Br, 42·4%).

The tribromide (13 g. crude product above) in collidine (80 ml.) was heated under reflux in nitrogen for 2 hr. The mixture was cooled and filtered, giving collidine hydrobromide (10·24 g., 2·08 mol.). The filtrate was diluted with ether, and this solution washed with dilute sulphuric acid and water and dried, and the solvent removed. Chromatography of the product on alumina (100 g.), and elution with benzene–ether (4 : 1), gave products deficient in ethylenic linkages, as indicated by their ultraviolet absorption spectra. Elution with benzene–ether (1 : 1) and ether gave *pregna-1,4,6,16-tetraene-3,11,20-trione*, which was purified from ethyl

[5] Djerassi, Lippman, and Grossman, *J. Amer. Chem. Soc.*, 1956, **78**, 2479.
[6] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422; Herzog, Payne, Tully, and Hershberg, *ibid.*, p. 5751.
[7] Brooks and Norymberski, *Biochem. J.*, 1953, **55**, 371.
[8] Nussbaum, Brabazon, Oliveto, and Hershberg, *J. Org. Chem.*, 1957, **22**, 977.
[9] Callow and James, *J.*, 1956, 4739.
[10] Cf. Herzog, Joyner, Gentles, Hughes, Oliveto, Hershberg, and Barton, *J. Org. Chem.*, 1957, **22**, 1413, who reported a similar reactivity of the 11β-hydroxy-group in 18-nor-steroids.

acetate to give pale yellow flakes, m. p. 243—247°, $[\alpha]_D^{21}$ +345° (*c* 0·33), $\lambda_{max.}$ 230 (ε 17,650), 268 (ε 9550) and 293 mμ (ε 11,800), $\lambda_{infl.}$ 238 mμ (ε 16,700) (Found: C, 77·9; H, 6·8. $C_{21}H_{22}O_3$ requires C, 78·2; H, 6·9%).

Dienone–Phenol Rearrangement of Pregna-1,4,6,16-*tetraene*-3,11,20-*trione* (II; R = :O).—The tetraene (450 mg.), toluene-*p*-sulphonic acid (225 mg.), and acetic anhydride (12 ml.) were heated at 100° for 12 hr. The product was isolated with ether and formed a gum, $\lambda_{max.}$ 240 mμ ($E^{1\%}_{1\,cm.}$ 774), $\lambda_{infl.}$ 282 mμ ($E^{1\%}_{1\,cm.}$ 122). Hydrolysis of this material with potassium carbonate (250 mg.) in water (4 ml.) and methanol (12 ml.) at room temperature for 3 days, followed by dilution with water, acidification, and extraction with chloroform, gave non-crystalline material which was chromatographed on silica gel (30 g.; B.D.H. chromatography grade). Benzene–light petroleum (b. p. 40—60°) mixtures eluted 45 mg. of material which afforded a dark red 2,4-dinitrophenylhydrazone and was rejected. Benzene–ether eluates than gave 30 mg. of gum, $\lambda_{max.}$ 221—222 (ε 23,600), 253·5 (ε 15,400), 318 mμ (ε 3300) (ε values are based on an estimated molecular weight of 322, *i.e.*, $C_{21}H_{22}O_3$).

Acetylation with acetic anhydride (1 ml.) and pyridine (1 ml.) at 100° for 1·5 hr. gave an amorphous product, $\lambda_{max.}$ 250 (ε 13,500), $\lambda_{infl.}$ 284·5 (ε 2100), $\lambda_{max.}$ 313 mμ (ε 2900) (ε values are based on the formula $C_{23}H_{24}O_4$, *M*, 364), $\nu_{max.}$ (in CS_2) 1769 (" phenolic " OAc), 1738 (unexplained), 1710 (11-C:O), and 1675 cm.$^{-1}$ (Δ^{16}-20-C:O).

11α-*Acetoxypregna*-1,4,6,16-*tetraene*-3,20-*dione* (II; R = α-OAc).—A stirred suspension of 11α-acetoxyprogesterone (18·72 g.) in dry ether (500 ml.) at 5° was treated dropwise with bromine in acetic acid (148 ml. of 1·03M-solution; 3 mol.). Reaction occurred rapidly, and the solid dissolved. The ether was removed under reduced pressure without heating, and the residue diluted with water. The product was extracted with benzene which was washed, dried (Na_2SO_4), and evaporated under reduced pressure. The resulting crude tribromo-derivative in collidine (180 ml.) was heated under reflux in nitrogen for 2 hr. Extraction of the product as before, chromatography on alumina (200 g.), and elution with benzene gave low-melting materials. Elution with benzene–ether and ether furnished 11α-*acetoxypregna*-1,4,6,16-*tetraene*-3,20-*dione*. It was purified from acetone–hexane, forming fibrous crystals, m. p. 237—240°, $[\alpha]_D^{25}$ +77° (*c* 0·27), $\lambda_{max.}$ 233·5 (ε 17,800) and 295 mμ (ε 11,000) (Found: C, 74·9; H, 7·0. $C_{23}H_{26}O_4$ requires C, 75·4; H, 7·2%).

3,11α-*Diacetoxy*-17-*acetyl*-1-*methylœstra*-1,3,5(10),6,16-*pentaene* (III; R = α-OAc).—The foregoing tetraene (2·3 g.) and toluene-*p*-sulphonic acid (0·4 g.) in acetic anhydride (20 ml.) were heated at about 60° for 18 hr. The mixture was poured into water, and the product was isolated with benzene–ether and purified from acetone–hexane. The *pentaene* formed flakes, m. p. 185—187°, $[\alpha]_D^{25}$ −279° (*c* 0·53), $\lambda_{max.}$ 264—265 mμ (ε 8450).[11] $\nu_{max.}$ (in $CHCl_3$) 1762 (" phenolic " OAc), 1737 (OAc), 1660 and 1587 cm.$^{-1}$ (16-en-20-one) [12] (Found: C, 73·9; H, 7·0. $C_{25}H_{28}O_5$ requires C, 73·5; H, 6·9%).

3,11α-*Diacetoxy*-17β-*acetyl*-1-*methylœstra*-1,3,5(10)-*triene* (IV; R = α-OAc, R′ = Ac, R″ = β-Ac).—The foregoing pentaene (1·21 g.) in methanol (100 ml.) was hydrogenated on 2% palladium–barium carbonate (250 mg.). 2·05 Molar proportions of hydrogen were absorbed. The catalyst was removed and the solvent removed. The residue was purified from acetone–hexane, to give the 1,3,5(10)-*triene* as rods, m. p. 174—175°, $[\alpha]_D^{24}$ −72° (*c* 0·55), $\lambda_{max.}$ 266—267 mμ (ε 343) [11] (Found: C, 72·8; H, 7·7. $C_{25}H_{32}O_5$ requires C, 72·8; H, 7·8%).

17β-*Acetyl*-1-*methylœstra*-1,3,5(10)-*triene*-3,11α-*diol* (IV; R = α-OH, R′ = H, R″ = Ac).—The diacetate (500 mg.) in 90% methanol (25 ml.) containing potassium hydroxide (300 mg.) was heated under reflux for 2 hr. Dilution with water gave a clear solution, which was acidified, and the precipitated material was extracted with chloroform. Purification from aqueous methanol gave the 11α-*hydroxyphenol* as fibres, m. p. 106—112°, $[\alpha]_D^{22}$ −18° (*c* 0·19), $\lambda_{max.}$ 283·5 mμ (ε 1000) (Found: C, 74·9; H, 8·6. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·5%).

17β-*Acetyl*-3-*methoxy*-1-*methylœstra*-1,3,5(10)-*trien*-11α-*ol* (IV; R = α-OH, R′ = Me, R″ = Ac).—A solution of the above phenol (250 mg.) in ethanol (15 ml.) was stirred at 60° and treated alternately with four portions of dimethyl sulphate (2·5 ml. each) and of 60% aqueous sodium hydroxide (1·8 ml. each). After ½ hr. the mixture was diluted with water, and the product extracted with chloroform. After washing and evaporation of the solvent, the residue, in benzene, was percolated through alumina (3 g.; Brockmann grade IV). The eluted material

[11] Dorfmann, *Chem. Rev.*, 1953, **53**, 47.
[12] Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.

was purified from aqueous methanol, to give the 3-*methoxy-derivative* as granules, m. p. 125—126°, $[\alpha]_D^{25}$ −56° (*c* 0·07), $\lambda_{max.}$ 280 (ε 1020) and 283 mμ (ε 1060) (Found: C, 77·5; H, 9·1. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·8%).

17β-*Acetyl*-3-*methoxy*-1-*methylœstra*-1,3,5(10)-*trien*-11-*one* (IV; R = :O, R′ = Me, R″ = Ac).—The foregoing compound (100 mg.) in anhydrous pyridine (3 ml.) was added to chromium trioxide (100 mg.) in pyridine (2 ml.), and the mixture shaken intermittently for 24 hr. Extraction with benzene and purification from acetone–hexane gave the 11-*ketone* as needles, m. p. 187—189°, $[\alpha]_D^{24}$ +371° (*c* 0·06), $\lambda_{max.}$ 276 mμ (ε 1500), $\nu_{max.}$ (in CS_2) 1717 (11-C:O influenced by aromatic system), 1706 (20-C:O), and 1147 cm.$^{-1}$ (3-methoxy-aromatic system) [12] (Found: C, 76·9; H, 8·4. $C_{22}H_{28}O_3$ requires C, 76·6; H, 8·3%).

Bromination of 11β-*Acetoxyandrost*-4-*ene*-3,17-*dione*.—(*a*) 11β-Acetoxyandrost-4-ene-3,17-dione (1·15 g.), suspended in dry ether (100 ml.) at 0—5°, was treated dropwise with bromine in acetic acid (6·3 ml. of 1·08M-solution; 2 mol.). The material dissolved rapidly and was soon replaced by a fine precipitate which was collected and crystallised from methylene chloride–hexane, to give (crude) 11β-acetoxy-6-bromoandrost-4-ene-3,17-dione as needles, m. p. 162—164° (decomp.), $[\alpha]_D^{25}$ +86° (*c* 0·45), $\lambda_{max.}$ 234 mμ (ε 13,450) (Found: C, 58·7; H, 6·2; Br, 20·2. Calc. for $C_{21}H_{27}O_4Br$: C, 59·6; H, 6·4; Br, 18·9%).

Dehydrobromination of the crude 6-bromo-compound (500 mg.) in collidine (7 ml.) under reflux for 1 hr. gave 11β-*acetoxyandrosta*-4,6-*diene*-3,17-*dione*, needles (from acetone–hexane), m. p. 160—162° or 176—179°, $\lambda_{max.}$ 280 mμ (ε 25,000) (Found: C, 73·8; H, 7·6. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·7%).

(*b*) A repetition of the foregoing bromination, with 3·5 times the volume of ether, gave a clear solution which was concentrated under reduced pressure and diluted with hexane, to precipitate the crude 2,6-*dibromo-derivative*, m. p. 176—180°. After purification from acetone–hexane the compound was obtained as flakes, m. p. 186—189°, $[\alpha]_D^{24}$ +128° (*c* 0·52), $\lambda_{max.}$ 238—240 mμ (ε 10,700) (Found: C, 50·8; H, 5·3; Br, 30·8. $C_{21}H_{26}O_4Br_2$ requires C, 50·2; H, 5·3; Br, 31·8%).

11β-*Acetoxyandrosta*-1,4,6-*triene*-3,17-*dione* (V).—The 2,6-dibromo-derivative (7 g.) in collidine (50 ml.) was heated under reflux in nitrogen for 1 hr., giving the trienone, which separated from acetone–hexane in prisms, m. p. 196—200°, $[\alpha]_D^{25}$ +174° (*c* 0·22), $\lambda_{max.}$ 226 (ε 9800), 248 (ε 9600), and 296 mμ (ε 10,200) (Found: C, 73·8; H, 6·8. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·1%).

3,11β-*Diacetoxy*-1-*methylœstra*-1,3,5(10),6-*tetraen*-17-*one* (VI; R = β-OAc, R′ = :O, R″ = Ac).—11β-Acetoxyandrosta-1,4,6-triene-3,17-dione (1 g.) and toluene-*p*-sulphonic acid (300 mg.) in acetic anhydride (20 ml.) were heated on the steam-bath for 5 hr. The mixture was poured into water, and the product was isolated with benzene and purified from methanol. 3,11β-*Diacetoxy*-1-*methylœstra*-1,3,5(10),6-*tetraen*-17-*one* formed needles, m. p. 219—220°, $[\alpha]_D^{21}$ −25° (*c* 0·23), $\lambda_{max.}$ 266—267 mμ (ε 9800) [11] (Found: C, 71·8; H, 6·85. $C_{23}H_{26}O_5$ requires C, 72·2; H, 6·85%).

3,11β-*Diacetoxy*-1-*methylœstra*-1,3,5(10)-*trien*-17-*one* (IV; R = β-OAc, R′ = Ac, R″ = :O).—The foregoing tetraene (920 mg.) in methanol (150 ml.) was hydrogenated on 3% palladium–barium carbonate (200 mg.). One mol. of hydrogen was absorbed. The resulting triene, after purification from acetone–hexane, formed blades, m. p. 160—162°, $[\alpha]_D^{22}$ +168° (*c* 0·36), $\lambda_{max.}$ 270 mμ (ε 342) [11] (Found: C, 71·6; H, 7·4. $C_{23}H_{28}O_5$ requires C, 71·9; H, 7·3%).

1-*Methylœstra*-1,3,5(10)-*triene*-3,11β,17β-*triol* (IV; R = R″ = β-OH, R′ = H).—A solution of the foregoing diacetate (200 mg.) in anhydrous tetrahydrofuran (60 ml.) was treated with lithium aluminium hydride (500 mg.) in tetrahydrofuran (30 ml.), and the mixture heated under reflux for 5 hr. After destruction of excess of reagent by ethyl acetate (5 ml.) in ether (25 ml.), dilute sulphuric acid and chloroform were added. The chloroform layer was washed, dried (Na_2SO_4), and evaporated. The residual gum crystallised with difficulty from aqueous methanol. The 3,11β,17β-*trihydroxy-compound* was obtained in a solvated form, which was not completely freed from solvent by drying *in vacuo* at 100°. It formed flakes, m. p. 130—132° with frothing, $[\alpha]_D^{20}$ +10° (*c* 0·07), $\lambda_{max.}$ 283—287 mμ (ε 1460) (Found: C, 72·4; H, 8·7. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·7. $C_{19}H_{26}O_3,CH_3{\cdot}OH$ requires C, 71·8; H, 9·0%).

The 3,11,17-*triacetate*, prepared by treating the triol with acetic anhydride–pyridine on the steam-bath for 2 hr., separated from aqueous methanol in needles, m. p. 144—148°, $[\alpha]_D^{19}$ +78° (*c* 0·27), $\lambda_{max.}$ 268 mμ (ε 355), $\lambda_{max.}$ (in CCl_4) 1737 (OAc) and 1762 cm.$^{-1}$ (" phenolic " OAc) (Found: C, 69·8; H, 7·2. $C_{25}H_{32}O_6$ requires C, 70·1; H, 7·5%).

Alkaline Hydrolysis of 3,11β-*Diacetoxy*-1-*methylœstra*-1,3,5(10)-*trien*-17-*one* (IV; R = β-OAc, R′ = Ac, R″ = :O).—The diacetate (55 mg.) was treated with potassium hydroxide (100 mg.) in 90% aqueous methanol (6 ml.) under reflux for 2 hr. The solution was acidified with dilute sulphuric acid, and the product was extracted with chloroform and purified from acetone–hexane. 3,11β-*Dihydroxy*-1-*methylœstra*-1,3,5(10)-*trien*-17-*one* formed square prisms, m. p. 227—228°, $\lambda_{max.}$ 283 (ε 1500) and 287 mμ (ε 1530), $\nu_{max.}$ (in Nujol) 3508 and 3435 (OH) and 1700 cm.$^{-1}$ (C:O) (no OAc bands) (Found: C, 75·8; H, 8·1. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%).

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