158. *Modified Steroid Hormones. Part X.*[1] *Some New Œstradiol Derivatives.*

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Application is described of the "dienone–phenol" and the "heterophenol" rearrangement to some steroids having a chlorine atom or a methyl group in ring A.

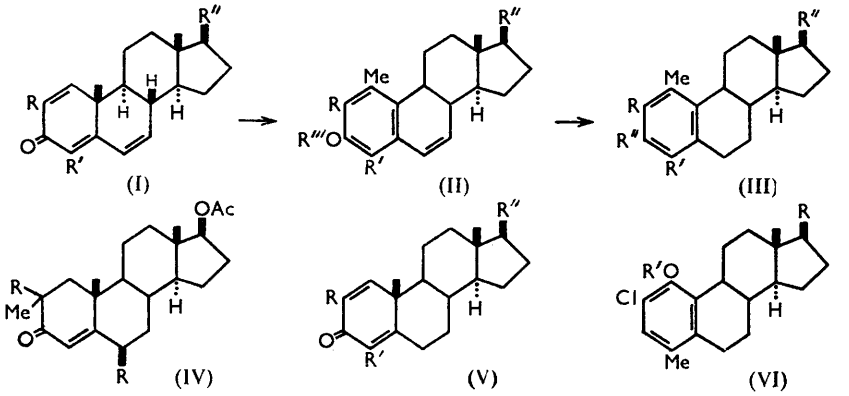
Part IX [1] described the preparation of some chloro-1 : 4-dien-3-ones and -1 : 4 : 6-trien-3-ones of the androstane and the cholestane series. Their conversion into aromatic structures is now reported.

2- (I; R = Cl, R′ = H, R″ = C_8H_{17}) and 4-Chlorocholesta-1 : 4 : 6-trien-3-one (I; R = H; R′ = Cl, R″ = C_8H_{17}) passed smoothly, albeit sluggishly, into 3-acetoxy-2-chloro- (II; R = Cl, R′ = H, R″ = C_8H_{17}, R‴ = Ac) and 3-acetoxy-4-chloro-1-methyl-19-norcholesta-1 : 3 : 5(10) : 6-tetraene (II; R = H, R′ = Cl, R″ = C_8H_{17}, R‴ = Ac) when heated with toluene-*p*-sulphonic acid and acetic anhydride at 100° or preferably at the boiling point. 2-Chlorocholesta-1 : 4-dien-3-one (V; R = Cl, R′ = H, R″ = C_8H_{17}) was similarly transformed into the "heterophenol," 1-acetoxy-2-chloro-4-methyl-19-norcholesta-1 : 3 : 5(10)-triene [2] (VI; R = C_8H_{17}, R′ = Ac). 4-Chlorocholesta-1 : 4-dien-3-one (V; R = H, R′ = Cl, R″ = C_8H_{17}), in contrast, proved resistant to the "heterophenol rearrangement," even under forcing conditions, a behaviour which accords well with the mechanism of the rearrangement proposed by Woodward and Singh.[3]

Aromatisation of 2- (I; R = Cl, R′ = H, R″ = O·COEt) and 4-chloro-17β-propionoxyandrosta-1 : 4 : 6-trien-3-one (I; R = H, R′ = Cl, R″ = O·COEt) was conveniently effected with toluene-*p*-sulphonic acid in boiling propionic anhydride. Transesterification at position 17 was thereby avoided and the somewhat slow reaction was accelerated. The resultant 6-dehydro-structures (II; R = Cl, R′ = H, R″ = O·COEt, R‴ = COEt; and R = H, R′ = Cl, etc.) were smoothly converted by catalytic hydrogenation into 2- (III;

[1] Part IX, Kirk and Petrow, *J.*, 1958, 1334.
[2] Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1948, **70**, 1911.
[3] Woodward and Singh, *ibid.*, 1950, **72**, 494.

R = Cl, R′ = H, R″ = O·COEt) and 4-chloro-1-methyl-3 : 17β-dipropionoxyœstra-1 : 3 : 5(10)-triene (III; R = H, R′ = Cl, R″ = O·COEt). 2-Chloro-17β-propionoxyandrosta-1 : 4-dien-3-one (V; R = Cl, R′ = H, R″ = O·COEt) yielded 2-chloro-4-methyl-1 : 17β-dipropionoxyœstra-1 : 3 : 5(10)-triene (VI; R = O·COEt. R′ = COEt) which differed from the product (cf. III; R = Cl, R′ = H, R″ = O·COEt) obtained by a normal rearrangement, thus confirming its " heterophenol " character.



Further we prepared 3 : 17β-diacetoxy-1 : 2-dimethylœstra-1 : 3 : 5(10)-triene (III; R = Me, R′ = H, R″ = OAc) from 2α-methyltestosterone acetate [4] (IV; R = H). Dibromination of the latter compound gave the 2β : 6β-dibromo-derivative (IV; R = Br). The β(axial)-configuration of the bromine atoms in this compound seems likely from its method of formation [5] and is supported by the ultraviolet absorption spectrum [$\lambda_{max.}$ (in EtOH) 253 mμ (ε 12,100),[5] (in *cyclo*hexane) 352 mμ (ε 16) [6]] and by the ease with which it passed into 17β-acetoxy-2-methylandrosta-1 : 4 : 6-trien-3-one (I; R = Me, R′ = H, R″ = OAc) on dehydrobromination. Dienone–phenol rearrangement of this trienone furnished the 6-dehydrophenol (II; R = Me, R′ = H, R″ = OAc, R‴ = Ac), which gave 3 : 17β-diacetoxy-1 : 2-dimethylœstra-1 : 3 : 5(10)-triene on catalytic hydrogenation.

The facility with which the foregoing 2-methylated triene undergoes the " dienone–phenol " rearrangement stands in marked contrast to the relative stability of its 2- and 4-chloro-analogues. The electron-attracting chloro-substituents presumably reduce the basicity of the carbonyl-oxygen atom, thus rendering the system less susceptible to attack by the acidic reagent. This is supported by the observed failure of 1 : 2-dichlorocholesta-1 : 4-dien-3-one to undergo the heterophenol rearrangement, even under forcing conditions.[1]

Experimental

Optical rotations refer to chloroform solutions. Ultraviolet absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc.

Dienone–Phenol Rearrangements.—(i) *Of 2-chlorocholesta-1 : 4-dien-3-one* (V; R = Cl, R′ = H, R″ = C_8H_{17}). A mixture of the 2-chlorodienone (1 g.) and toluene-*p*-sulphonic acid (300 mg.) in acetic anhydride (20 ml.) was heated under reflux for 8 hr., then shaken vigorously with water to destroy excess of acetic anhydride, and the steroid was extracted into ether which was washed with sodium hydrogen carbonate solution and water, dried, and evaporated. The resulting gum, dissolved in light petroleum (b. p. 40—60°), was chromatographed on alumina (20 g.). Elution with light petroleum–benzene, followed by crystallisation from methanol, gave *1-acetoxy-2-chloro-4-methyl-19-norcholesta-1 : 3 : 5(10)-triene* (VI; R = C_8H_{17}, R′ = Ac) in needles, m. p. 84—85°, $[\alpha]_D^{22}$ +164° (*c* 0·23), $\lambda_{max.}$ 273 (ε 436) and 281 mμ (ε 404) in ethanol (Found: C, 75·8; H, 9·3; Cl, 7·9. $C_{29}H_{43}O_2Cl$ requires C, 75·9; H, 9·4; Cl, 7·7%).

[4] Ringold and Rosenkranz, *J. Org. Chem.*, 1956, **21**, 1333.
[5] Ellis and Petrow, *J.*, 1956, 1179.
[6] Bird, Cookson, and Dandegaonker, *J.*, 1956, 3675.

(ii) *Of 2-chlorocholesta-1 : 4 : 6-trien-3-one* (I; R = Cl, R′ = H, R″ = C_8H_{17}). The 2-chlorotrienone (0·5 g.) and toluene-*p*-sulphonic acid (0·15 g.) in acetic anhydride (10 ml.) were heated under reflux for 2 hr. The product was isolated and purified as in the previous experiment, giving *3-acetoxy-2-chloro-1-methyl-19-norcholesta-1 : 3 : 5(10) : 6-tetraene* (II; R = Cl, R′ = H, R″ = C_8H_{17}, R‴ = Ac) (130 mg.) in needles, m. p. 80—82°, $[\alpha]_D^{22}$ −108° (*c* 0·19), $\lambda_{max.}$ 226 (ε 27,500), 232 (ε 23,100), 272 mμ (ε = 12,400) in ethanol (Found: C, 75·9; H, 8·9; Cl, 8·0. $C_{29}H_{41}O_2Cl$ requires C, 76·2; H, 8·9; Cl, 7·8%).

(iii) *Of 4-chlorocholesta-1 : 4 : 6-trien-3-one* (I; R = H, R′ = Cl, R″ = C_8H_{17}). A solution of the 4-chlorotrienone (600 mg.) and toluene-*p*-sulphonic acid (100 mg.) in acetic anhydride (15 ml.) was heated under reflux under nitrogen for 8 hr. *3-Acetoxy-4-chloro-1-methyl-19-norcholesta-1 : 3 : 5(10) : 6-tetraene* (II; R = H, R′ = Cl, R″ = C_8H_{17}, R‴ = Ac) separated from the solution on cooling in light brown crystals (540 mg.), m. p. 110—112°. Purified from ethanol it formed prisms, m. p. 119—121°, $[\alpha]_D^{22}$ −129° (*c* 0·31), $\lambda_{max.}$ 227 (ε 28,300), 270·5 mμ (ε = 9·470) in ethanol (Found: C, 76·4; H, 9·0; Cl, 7·5%).

(iv) *Of 2-chloro-17β-propionoxyandrosta-1 : 4-dien-3-one* (V; R = Cl, R′ = H, R″ = O·COEt). The 2-chlorodienone (250 mg.) and toluene-*p*-sulphonic acid (50 mg.) in propionic anhydride (5 ml.) were heated at 100° for 40 hr. The brown solution was then shaken with sodium hydrogen carbonate solution to hydrolyse the excess of anhydride, and the product extracted into ether. This solution was washed, dried, and evaporated, and the residue purified from hexane. *2-Chloro-4-methyl-1 : 17β-dipropionoxyœstra-1 : 3 : 5(10)-triene* (VI; R = O·COEt, R′ = COEt) formed needles, m. p. 114°, $[\alpha]_D^{22}$ +131° (*c* 1·35), $\lambda_{max.}$ 274 mμ (ε 485) in ethanol (Found: C, 69·0; H, 7·7; Cl, 8·1. $C_{25}H_{33}O_4Cl$ requires C, 69·4; H, 7·7; Cl, 8·2%).

(v) *Of 2-chloro-17β-propionoxyandrosta-1 : 4 : 6-trien-3-one* (I; R = Cl, R′ = H, R″ = O·COEt). A solution of the 2-chlorotrienone (1·5 g.) and toluene-*p*-sulphonic acid (300 mg.) in propionic anhydride (30 ml.) was heated under reflux for 2·5 hr. The product was isolated as in the previous experiment, and purified from methanol. *2-Chloro-1-methyl-3 : 17β-dipropionoxyœstra-1 : 3 : 5(10) : 6-tetraene* (II; R = Cl, R′ = H, R″ = O·COEt, R‴ = COEt) formed leaflets (440 mg.), m. p. 127—128°, $[\alpha]_D^{25}$ −131° (*c* 0·39), $\lambda_{max.}$ 226 (ε 29,450), 232 (ε 25,450), and 271 mμ (ε 12,700) in ethanol (Found: C, 70·0; H, 7·5; Cl, 8·1. $C_{25}H_{31}O_4Cl$ requires C, 69·7; H, 7·3; Cl, 8·2%).

The foregoing tetraene (400 mg.) in ethanol (40 ml.) was hydrogenated in the presence of 3% palladium–barium carbonate (10 mg.) at just over 1 atm. until 1 mol. of hydrogen had been absorbed. After filtration from the catalyst and removal of the solvent, purification of the product from methanol gave *2-chloro-1-methylœstradiol dipropionate* (III; R = Cl, R′ = H, R″ = O·COEt) (340 mg.) in needles, m. p. 128—130°, $[\alpha]_D^{21}$ +110° (*c* 0·21), $\lambda_{max.}$ 274 (ε 554) and 282 mμ (ε 550) in ethanol (Found: C, 69·4; H, 7·7; Cl, 8·2. $C_{25}H_{33}O_4Cl$ requires C, 69·3; H, 7·7; Cl, 8·2%).

(vi) *Of 4-chloro-17β-propionoxyandrosta-1 : 4 : 6-trien-3-one* (I; R = H, R′ = Cl, R″ = O·COEt). A solution of the trienone (5·5 g.) and toluene-*p*-sulphonic acid (1·5 g.) in propionic anhydride (50 ml.) was heated under reflux for 5 hr., and the product isolated as in previous examples. The crude brown material, in light petroleum–benzene (1 : 1), was percolated through alumina (110 g.), and the resulting colourless oil (3 g.) was purified from methanol. *4-Chloro-1-methyl-3 : 17β-dipropionoxyœstra-1 : 3 : 5(10) : 6-tetraene* (II; R = H, R′ = Cl, R″ = O·COEt, R‴ = COEt) formed needles (2·2 g.), m. p. 88—89°, $[\alpha]_D^{25}$ −146° (*c* 0·43), $\lambda_{max.}$ 227 (ε 30,800) and 269·5 mμ (ε 9900) in ethanol (Found: C, 69·4; H, 7·4; Cl, 8·6. $C_{25}H_{31}O_4Cl$ requires C, 69·7; H, 7·3; Cl, 8·2%).

4-Chloro-1-methylœstradiol dipropionate (III; R = H, R′ = Cl, R″ = O·CO·Et).—The 4-chlorotetraene (1 g.) in methanol (50 ml.) was hydrogenated as described for the 2-chlorotetraene. The *product* (450 mg.) separated from hexane in prisms, m. p. 124—125°, $[\alpha]_D^{23}$ +114° (*c* 0·49), $\lambda_{max.}$ 290 (ε 1940), $\lambda_{infl.}$ 285 mμ (ε 1875) in ethanol (Found: C, 69·6; H, 7·7; Cl, 8·0. $C_{25}H_{33}O_4Cl$ requires C, 69·3; H, 7·7; Cl, 8·2%).

17β-Acetoxy-2β : 6β-dibromo-2α-methylandrost-4-en-3-one (IV; R = Br).—2α-Methyltestosterone acetate (8 g.) in dry ether (500 ml.), cooled in ice, was treated dropwise with bromine in acetic acid (43 ml. of 1·09M-solution). After 15 min., when decolorisation was complete, the ether was removed *in vacuo* without heating. Dropwise addition of water to the residue caused crystallisation of a yellow product, which was purified from methylene chloride–methanol. *17β-Acetoxy-2β : 6β-dibromo-2α-methylandrost-4-en-3-one* formed flakes, m. p. 107—111° (decomp.), $[\alpha]_D^{18}$ −18° (*c* 0·29), $\lambda_{max.}$ 253 mμ (ε 12,100) in ethanol, $\lambda_{max.}$ 352 mμ (ε 16·1) in

*cyclo*hexane (Found: C, 53·2; H, 5·9; Br, 31·6. $C_{22}H_{30}O_3Br_2$ requires C, 52·6; H, 6·0; Br, 31·8%).

17β-*Acetoxy*-2-*methylandrosta*-1 : 4 : 6-*trien*-3-*one* (I; R = Me, R′ = H, R″ = OAc).—The 2β : 6β-dibromo-compound (8·5 g.) in collidine (60 ml.) was heated under reflux under carbon dioxide for 40 min., collidine hydrobromide (6·2 g., 1·84 mols.) separating. The resulting solution was diluted with ether and washed free from collidine with dilute sulphuric acid. The brown solid remaining after evaporation of the ether was percolated, in benzene, through alumina (30 g.), and purified from methanol. 17β-*Acetoxy*-2-*methylandrosta*-1 : 4 : 6-*trien*-3-*one* formed prisms, m. p. 159—160°, $[\alpha]_D^{19}$ −12° (*c* 0·35), $\lambda_{max.}$ below 220 mμ, 265·5 mμ (ε 11,900), and 300 mμ (ε 10,320) in ethanol (Found: C, 77·6; H, 8·2. $C_{22}H_{28}O_3$ requires C, 77·6; H, 8·3%).

3 : 17β-*Diacetoxy*-1 : 2-*dimethylœstra*-1 : 3 : 5(10) : 6-*tetraene* (II; R = Me, R′ = H, R″ = OAc, R‴ = Ac).—The 2-methyltrienone (1 g.) in acetic anhydride (20 ml.) containing toluene-*p*-sulphonic acid (300 mg.) was heated at 80° for 4 hr., then poured into water. After extraction with ether and purification from methanol, 3 : 17β-*diacetoxy*-1 : 2-*dimethylœstra*-1 : 3 : 5(10) : 6-*tetraene* formed plates, m. p. 144—146°, $[\alpha]_D^{20}$ −133° (*c* 0·27), $\lambda_{max.}$ 225 (ε 27,950), $\lambda_{infl.}$ 232 (ε 22,000), $\lambda_{max.}$ 268 mμ (ε 11,500) in ethanol (Found: C, 75·0; H, 7·9. $C_{24}H_{30}O_4$ requires C, 75·3; H, 7·9%).

3 : 17β-*Diacetoxy*-1 : 2-*dimethylœstra*-1 : 3 : 5(10)-*triene* (III; R = Me, R′ = H, R″ = Ac).—The 6-dehydro-compound (480 mg.) in ethanol (80 ml.) was hydrogenated in the presence of 2% palladium–barium carbonate (25 mg.) until 1 mol. proportion of hydrogen had been absorbed. 3 : 17β-*Diacetoxy*-1 : 2-*dimethylœstra*-1 : 3 : 5(10)-*triene* separated from methanol in flakes, m. p. 163—164°, $[\alpha]_D^{19}$ +112° (*c* 0·22), $\lambda_{max.}$ 272 (ε = 540) and 280 mμ (ε 530) in ethanol (Found: C, 75·2; H, 8·1. $C_{24}H_{32}O_4$ requires C, 75·0; H, 8·4%).

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