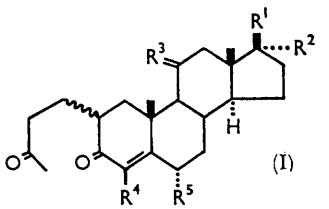
802. *Modified Steroid Hormones. Part XXIII.* Some Pentacyclic Types.*

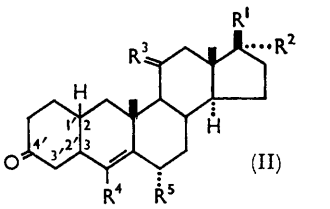
By G. Cooley, J. W. Ducker, B. Ellis, V. Petrow, and W. P. Scott.

Some pentacyclic structures have been prepared from the 2-hydroxymethylene derivatives of steroidal 3-ketones by condensation with methyl vinyl ketone. The products were without significant biological activity.

The discovery that 17β-hydroxy-17α-methylandrostano[3,2-*c*]pyrazole [1] possessed anabolic/androgenic activity focused attention upon pentacyclic systems of steroidal type. In consequence we have prepared, for biological study, some 4′-oxo-2β(H)-2,3-cyclohex-2′-eno-derivatives of testosterone, progesterone, and cortisone, employing the method of Urushibara and Inomata.[2] Since completion of our work some related experiments have been reported by Atwater,[3] who claims that his compounds have anti-inflammatory and progestational potency. In contrast the products described herein have been found by Dr. A. David and his colleagues (Biological Dept.) to be biologically virtually inactive (see Experimental section).

Reaction of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one [4] with methyl vinyl ketone in ethanol in the presence of triethylamine as catalyst furnished 17β-hydroxy-2ξ-3′-oxobutylandrost-4-en-3-one (I; $R^1 = OH$, $R^2 = R^4 = R^5 = H$, $R^3 = H_2$) which was cyclised by aqueous potassium hydroxide in dioxan to the required 17β-hydroxy-


(I)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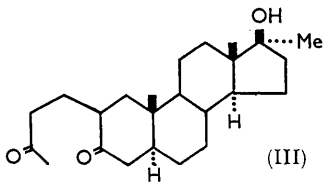
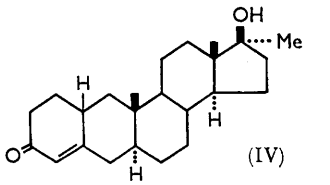

(III)


(IV)

2β(H)-2,3-cyclohex-2′-enoandrost-4-en-4′-one (II; $R^1 = OH$, $R^2 = R^4 = R^5 = H$, $R^3 = H_2$) in *ca.* 40% yield. From a study of models the β-configuration is tentatively assigned to the 2-hydrogen atom in this and analogous compounds.

The above reaction sequence was extended to the 2-hydroxymethylene derivatives of 17α-methyltestosterone (cf. I; $R^1 = OH$, $R^2 = Me$, $R^3 = H_2$, $R^4 = R^5 = H$), 4-methyltestosterone (cf. I; $R^1 = OH$, $R^2 = R^5 = H$, $R^3 = H_2$, $R^4 = Me$), progesterone (cf. I; $R^1 = Ac$, $R^2 = R^4 = R^5 = H$, $R^3 = H_2$), 17β-hydroxy-6α-methyl-17α-prop-1-ynylandrost-4-en-3-one (cf. I; $R^1 = OH$, $R^2 = C{\equiv}CMe$, $R^3 = H_2$, $R^4 = R^5 = H$), and the bismethylenedioxy-derivatives of cortisone and 17β-hydroxy-17α-methyl-5α-androstan-3-one (cf. III). In general, the crude hydroxymethylene derivatives could be successfully employed for

* Part XXII, *J.*, 1961, 2821.

[1] Clinton, Manson, Stonner, Beyler, Potts, and Arnold, *J. Amer. Chem. Soc.*, 1959, **81**, 1513; Arnold, Beyler, and Potts, *Proc. Soc. Exp. Biol. Med.*, 1959, **102**, 184.

[2] Urushibara and Inomata, *Bull. Chem. Soc. Japan*, 1959, **32**, 101.

[3] Atwater, U.S.P. 2,939,866.

[4] Ringold, Batres, Halpern, and Necochea, *J. Amer. Chem. Soc.*, 1959, **81**, 427.

condensation with methyl vinyl ketone. The resulting oxobutyl intermediates (I and III), however, required purification by chromatography before ring closure. Alternatively, the crude oxobutyl intermediates could be converted directly into the corresponding cyclohexeno-derivatives by prolonged adsorption on alumina. Hydrolysis of the bis-methylenedioxy-derivative of compound (II; $R^1 = CO{\cdot}CH_2{\cdot}OH$, $R^2 = OH$, $R^3 = O$, $R^4 = R^5 = H$) with 90% aqueous formic acid furnished the pentacyclic structure corresponding to cortisone.

The conversion of the unsaturated tetracyclic ketones into the cyclohexeno-derivatives is attended by a shift in molecular rotation, of +708° to +966° (in chloroform), as shown in the Table. In contrast, the corresponding shift in the case of the fully saturated 17β-hydroxy-17α-methyl-5α-androstan-3-one (cf. III) is −20°.

Molecular rotation differences.

Parent steroid	$[M]_D$ Unsubstituted	$[M]_D$ 4′-Oxocyclohex-2′-eno-derivative	ΔM_D
Testosterone	+314° [a]	+1022°	+708°
17-Methyltestosterone	+229 [a]	+1195	+966
4-Methyltestosterone	+405 [b]	+1237	+832
Progesterone	+635 [a]	+1598	+963
Cortisone	+754 [a]	+1655	+901
Cortisone B.M.D.	+330 [c]	+1273	+943
17α-Methylandrostanolone	+35 [d]	+15	−20

[a] Fieser and Fieser, "Steroids," Reinhold Publ. Corp., New York, 1959. [b] Sondheimer and Mazur, *J. Amer. Chem. Soc.*, 1957, **79**, 2906. [c] Beyler, Moriarty, Hoffman, and Sarett, *ibid.*, 1958, **80**, 1517. [d] Ruzicka, Meister, and Prelog, *Helv. Chim. Acta*, 1947, **30**, 867.

Experimental

Optical rotations were measured for chloroform solutions in a 1 dm. tube. Ultraviolet absorption spectra (in ethanol) were kindly determined by Mr. M. T. Davies, B.Sc., and Miss D. F. Dobson, B.Sc.

17β-*Hydroxy*-2ξ-3′-*oxobutylandrost*-4-*en*-3-*one* (I; $R' = OH$, $R^2 = R^4 = R^5 = H$, $R^3 = H_2$).—17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one [4] (15·8 g.) in ethanol (75 ml.) and ethyl acetate (75 ml.) was treated with triethylamine (14 g.) and redistilled methyl vinyl ketone (17 ml.). The mixture was left at 0° for 21 hr., then diluted with water, and the oily product isolated with ether. Chromatography on alumina, with benzene containing an increasing proportion of ether as eluant, gave a solid, m. p. 159—164°. Crystallisation from acetone–hexane gave 17β-*hydroxy*-2ξ-3′-*oxobutylandrost*-4-*en*-3-*one* as needles, m. p. 167—168°, $[\alpha]_D^{22}$ +83° (*c* 0·87), $\lambda_{max.}$ 240 mμ (log ε 4·19) (Atwater [3] gives m. p. about 176·5—177°) (Found: C, 76·7; H, 9·4. $C_{23}H_{34}O_3$ requires C, 77·1; H, 9·6%).

17β-*Hydroxy*-2β(H)-2,3-*cyclohex*-2′-*enoandrost*-4-*en*-4′-*one* (II; $R^1 = OH$, $R^2 = R^4 = R^5 = H$, $R^3 = H_2$).—The foregoing compound (4·0 g.) in dioxan (150 ml.) was treated with aqueous 0·5N-potassium hydroxide (100 ml.) and left at room temperature for 4 hr. The solid precipitated by addition of water was filtered off and extracted with acetone. Evaporation of the acetone extract gave a yellow gum which on crystallisation from acetone–light petroleum gave 17β-*hydroxy*-2β(H)-2,3-*cyclohex*-2′-*enoandrost*-4-*en*-4′-*one*, m. p. 210—211°, $[\alpha]_D^{24}$ +300° (*c* 0·35), $\lambda_{max.}$ 292—294 mμ (log ε 4·50) (Found: C, 81·3; H, 9·1. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%) (Atwater [3] gives m. p. about 212—214°). The compound has no anabolic/androgenic activity.

17β-*Hydroxy*-17α-*methyl*-2ξ-3′-*oxobutylandrost*-4-*en*-3-*one* (I; $R^1 = OH$, $R^2 = Me$, $R^4 = R^5 = H$, $R^3 = H_2$), prepared as indicated above, crystallised from ether–light petroleum as needles, m. p. 155—156°, $[\alpha]_D^{24}$ +57° (*c* 0·98), $\lambda_{max.}$ 241 mμ (log ε 4·18) (Found: C, 77·25; H, 9·5. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%).

17β-*Hydroxy*-17α-*methyl*-2β(H)-2,3-*cyclohex*-2′-*enoandrost*-4-*ene* (II; $R^1 = OH$, $R^2 = Me$, $R^4 = R^5 = H$, $R^3 = H_2$) formed plates (from acetone–hexane), m. p. 206—208°, $[\alpha]_D^{21}$ +337° (*c* 0·92), $\lambda_{max.}$ 294 mμ (log ε 4·49) (Found: C, 81·4; H, 9·55. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·7%). It was devoid of anabolic/androgenic activity.

17β-*Hydroxy*-4-*methyl*-2β(H)-2,3-*cyclohex*-2′-*enoandrost*-4-*en*-4′-*one* (II; $R^1 = OH$, $R^2 = R^5 = H$, $R^4 = Me$, $R^3 = H_2$), prepared without purification of the intermediates, crystallised

from aqueous methanol as needles, m. p. 120—121° or 155—157°, $[\alpha]_D^{24}$ +349° (*c* 1·01), $\lambda_{max.}$ 300 mμ (log ε 4·43) (Found: C, 77·1; H, 9·7. $C_{24}H_{34}O_2,2H_2O$ requires C, 77·4; H, 9·7%). The 17β-*propionate* formed needles (from acetone–hexane), m. p. 186—187°, $[\alpha]_D^{23}$ +310° (*c* 0·52), $\lambda_{max.}$ 300 mμ (log ε 4·46) (Found: C, 78·9; H, 9·1. $C_{27}H_{38}O_3$ requires C, 79·0; H, 9·3%). In one experiment, the intermediate 17β-hydroxy-4-methyl-2ξ-3′-oxobutylandrost-4-en-3-one was isolated as the 17β-*propionate*, needles (from aqueous methanol), m. p. 106—107°, $\lambda_{max.}$ 248·5 mμ (log ε 4·16) (Found: C, 75·8; H, 9·65. $C_{27}H_{40}O_4$ requires C, 75·7; H, 9·4%).

17β-*Hydroxy*-17α-*methyl*-2ξ-3′-*oxobutyl*-5α-*androstan*-3-*one* (III) formed needles (from ether–light petroleum), m. p. 129—130°, $[\alpha]_D^{24}$ −0·61° (*c* 0·16) (Found: C, 77·2; H, 10·0. $C_{24}H_{38}O_3$ requires C, 77·0; H, 10·2%).

17β-*Hydroxy*-17α-*methyl*-2β(H)-2,3-*cyclohex*-2′-*eno*-5α-*androstan*-4′-*one* (IV) formed plates (from aqueous acetone), m. p. 184—186°, $[\alpha]_D^{24}$ +4° (*c* 0·52), $\lambda_{max.}$ 241—242 mμ (log ε 4·16) (Found: C, 81·0; H, 10·3. $C_{24}H_{36}O_2$ requires C, 80·85; H, 10·2%). It was devoid of anabolic/androgenic activity.

17β-*Hydroxy*-6α-*methyl*-2ξ-3′-*oxobutyl*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one* (I; R^1 = OH, R^2 = C:CMe, R^4 = H, R^3 = H_2, R^5 = Me) formed needles (from ether–light petroleum), m. p. 151—153°, $[\alpha]_D^{25}$ −5° (*c* 0·50), $\lambda_{max.}$ 240 mμ (log ε 4·17) (Found: C, 79·4; H, 9·6. $C_{27}H_{38}O_3$ requires C, 79·0; H, 9·3%).

17β-Hydroxy-6α-methyl-17α-prop-1′-ynyl-2β(H)-2,3-cyclohex-2′-enoandrost-4-en-4′-one (II; R^1 = OH, R^2 = C:CMe, R^3 = H_2, R^4 = H, R^5 = Me) formed plates (from aqueous acetone), m. p. 229—230°. Paucity of material prevented complete characterisation. The infrared spectrum showed bands at 1200 and 900 cm.$^{-1}$.

2ξ-3′-*Oxobutylpregn*-4-*ene*-3,20-*dione* (I; R^1 = Ac, R^2 = R^4 = R^5 = H, R^3 = H_2) formed rods (from ether–light petroleum), m. p. 123—124°, $[\alpha]_D^{26}$ +183° (*c* 0·99), $\lambda_{max.}$ 240 mμ (log ε 4·11) (Found: C, 78·2; H, 9·3. $C_{25}H_{36}O_3$ requires C, 78·1; H, 9·4%).

2β-2,3-Cyclohex-2′-enopregn-4-ene-4′,20-dione (II; R^1 = Ac, R^2 = R^4 = R^5 = H, R^3 = H_2) formed prisms (from ether), m. p. 192—193°, $[\alpha]_D^{27}$ +436° (*c* 0·67), $\lambda_{max.}$ 293—294 mμ (log ε 4·48) (Found: C, 81·8; H, 9·1. Calc. for $C_{25}H_{34}O_2$: C, 81·9; H, 9·35%). Atwater [3] gives m. p. about 110·5—111·5°.

The 17,20,20,21-*bismethylenedioxy-derivative* of 2ξ-3′-oxobutylcortisone formed needles (from acetone–hexane), m. p. 213—217°, $[\alpha]_D^{26}$ +70° (*c* 1·03), $\lambda_{max.}$ 237 mμ (log ε 4·12) (Found: C, 68·7; H, 7·7. $C_{27}H_{36}O_7$ requires C, 68·6; H, 7·7%).

The 17,20,20,21-*bismethylenedioxy-derivative* of 2β(H)-2,3-cyclohex-2′-enopregn-4-ene-4′,11-dione formed prisms (from acetone–hexane), m. p. 281—286° (decomp.), $[\alpha]_D^{27}$ +280° (*c* 0·66), $\lambda_{max.}$ 291 mμ (log ε 4·49) (Found: C, 71·3; H, 7·3. $C_{27}H_{34}O_6$ requires C, 71·3; H, 7·5%).

17α,21-*Dihydroxy*-2β(H)-2,3-*cyclohex*-2′-*enopregn*-4-*ene*-4′,11,20-*trione* (II; R^1 = CO·CH_2·OH, R^2 = OH, R^4 = R^5 = H, R^3 = O).—The foregoing bismethylenedioxy-compound (3·0 g.) in 90% aqueous formic acid (30 ml.) was heated at 60° for 2 hr., and the mixture then poured into saturated sodium chloride solution (150 ml.). The precipitated solid was filtered off, washed with a little salt solution, then dissolved in methanol (250 ml.), and concentrated hydrochloric acid (5 ml.) was added. After 1½ hr. at room temperature the solution was concentrated somewhat *in vacuo* and then diluted with water. The filtered solid was washed until neutral, and crystallised from acetone and then from methanol to give the *cyclohexeno-compound* as the *monohydrate*, prisms, m. p. 193—198° (decomp.), $[\alpha]_D^{27}$ +401° (*c* 1·05), $\lambda_{max.}$ 292 mμ (log ε 4·46) (Found: C, 69·7; H, 8·0. $C_{25}H_{32}O_5,H_2O$ requires C, 69·7; H, 8·0%). The 21-*monoacetate* crystallised from acetone–hexane as needles, m. p. 222—223° (decomp.), $[\alpha]_D^{27}$ +407° (*c* 0·62), $\lambda_{max.}$ 292 mμ (log ε 4·46) (Found: C, 71·2; H, 7·5. $C_{27}H_{34}O_6$ requires C, 71·3; H, 7·5%). The compound had no anti-inflammatory activity in the turpentine agar-pellet assay.

CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1.

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