STEROIDAL OXAZOLIDONES

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Abstract—Isocyanates have been reacted with steroidal 17α -hydroxy-20-ketopregnenes to give oxazolidones.

STEROIDS with spiro ring systems at the C-17 position have produced compounds with interesting pharmacological properties.¹ Various workers have synthesized such compounds where the spiro ring is a substituted oxazolidone moiety.^{2.3} In these cases, the parent compound has been a 17β -hydroxy- 17α -ethynyl steroid. For comparison purposes in the present work, 3β , 17β -dihydroxy- 17α -ethynyl-androst-5ene 3-acetate (I) was treated with phenyl isocyanate to give the 17β -carbamate ester (IIa), which on treatment with sodium hydroxide gave the oxazolidone (IIIa). Acetylation gave the 3 acetate (IIIb). The ethyl analogue (IIIc) was similarly prepared.

The synthesis of the oxazolidone spiro system stereoisomeric at C-17 of the steroid nucleus, is now reported.

3 β , 17 α -Dihydroxy-pregn-5-en-20-one 3 formate (IV) was treated with an aryl isocyanate to produce the appropriate 17 α -carbamate ester (Va-e). Treatment of these esters with sodium hydroxide gave the required oxazolidones (VIa, d, c, g, f; R' = H) respectively, as high melting, crystalline solids with low solubility in most of the common organic solvents. Assignation of these structures was based on IR, NMR, and in some cases mass spectral results, together with analytical data. Selective acetylation produced the 3-acetates (VIa, d, c, g, f; R' = Ac), which were then treated with phosphorus oxychloride in pyridine, to produce the required exocyclic methylene oxazolidones (VIIa-d). Peculiarly, the *m*-tolyl derivative (VIf; R' = Ac) failed to react under these conditions. Comparison with the oxazolidones (IIIa, b) shows that although many of the expected similarities in the physical data exist, differences also occur, for example, the NMR signal for the C-13 Me group in (VIIa) is at 9.08 τ whereas in the stereoisomer (IIIb), the signal is at 8.93 τ . Although the reaction sequence worked quite well for some aryl isocyanates, *o*-chlorophenyl, *o*-tolyl and α -naphthyl isocyanates failed to react.

Reaction of the formate (IV) with aryl isocyanates in the presence of N-methylmorpholine gave the oxazolidones (VIa, b, c, e, f, g, i; $\mathbf{R}' = CHO$). Under these conditions the reaction was successful for all the aryl isocyanates used, except *p*chlorophenyl isocyanate, where the reaction product was the oxazolidone carbamate ester (VIII). The alternative structure (IX), is less likely as the spectral data, particularly the IR, are not in agreement with that expected of such a structure.² This would

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indicate that in this particular case, the oxazolidone was first formed and further reacted with the *p*-chlorophenyl isocyanate.

Reaction occurred between 17α -hydroxy pregn-4-ene-3,20-dione (XI) and phenyl, o, m, and p-chlorophenyl, and m-tolyl isocyanates, in the presence of N-methylmorpholine. No reaction was observed in the cases of o and p tolyl, and α -naphthyl isocyanates. The products in the successful reactions were the exocyclic methylene oxazolidones XIIa-e). The spectral data were as expected for such compounds.

Attention was then turned to alkyl isocyanates. Reaction of the formate (IV) with n-butyl and allyl isocyanates without base as catalyst, gave the oxazolidones (VIIf and g, respectively). Under these conditions, ethyl isocyanate failed to react. With the addition of N-methylmorpholine, ethyl isocyanate reacted to give the carbamate ester (Vf). Treatment with sodium hydroxide gave VIh (R' = H), which on acetylation



gave VIh (R' = Ac). Reaction with phosphorus oxychloride in pyridine gave the required exocyclic methylene oxazolidone (VIIe). As with the phenyl analogues, the NMR of this and of the hitherto known stereoisomeric system show characteristic differences. The NMR signal for the C-13 Me group in IIIc is at 9.02 τ and in VIIe, 9.14 τ . It can thus be seen that in both the phenyl and the ethyl examples, the C-13 Me group in the previously reported oxazolidone system, resonates at lower field.

Ethyl, n-butyl and allyl isocyanates failed to react with 17α -hydroxy-pregn-4ene-3,20-dione (XI) both with and without the addition of N-methylmorpholine.

All attempts to affect reaction between either the formate (IV) or the hydroxy diketone (XI), with phenyl isothiocyanate failed.

3 β -Acetoxy-17 α -cyano-androst-5-ene-17 β -ol⁴ (XIII) was treated with phenyl isocyanate, and the product was assigned structure XIV. The IR showed no CN absorption in the 2260–2240 cm⁻¹ region, but showed absorption at 3250 (==NH), 1550 (NH), and 1610 and 1505 (aromatic) cm⁻¹. The NMR showed aromatic resonance at 2.5–2.9 τ , corresponding to 5 protons. Resonance at 3.12 τ corresponded to one proton and this is possibly due to the presence of an ==NH group. The mass spectrum showed that the substance had a molecular ion at an *m/e* value of 476, that expected for structure XIV.

Some of these compounds have been submitted for investigation of their pharmacological properties.



EXPERIMENTAL

All m.ps were taken in open capillaries and are uncorrected. Where solubility permitted, UV spectra were determined in EtOH on a Cary 14 spectrophotometer. The IR spectra were recorded as Nujol mulls on a Perkin-Elmer Infracord. Optical rotations were recorded at 27° in pyridine. NMR spectra were determined with a Varian A 60 spectrometer, using TMS as internal reference. Unless otherwise stated, "parts" are by volume for liquids and by weight for solids.

3\u03b3-Acetoxy-17\u03a2-ethynyl-androst-5-ene-17\u03b3-ol phenyl carbamate ester (IIa)

A soln of 3β-acetoxy-17α-ethynyl-androst-5-ene-17β-ol (1 g) in phenyl isocyanate (3·5 ml) was heated at 100° for 4 hr, during which time a solid product separated. The mixture was cooled, filtered, and the product washed successively with hexane. Two crystallizations from CH₂Cl₂-MeOH gave the *phenyl carbamate* ester (600 mg) as spears, m.p. 260-261°; $[\alpha]_D - 90°$; λ_{max} 235 mµ, $10^{-3} \varepsilon = 15\cdot2$; ν_{max} 3310, 3190, 1740, 1705, 1605, 1540, 1500 cm⁻¹; τ (CDCl₃) 2·6-2·8, 3·35, 7·33, 7·96, 8·95, 9·08, relative areas 5:1:1:3:3:3. (Found: C, 75·54; H, 7·77; N, 3·19. C₃₀H₃₇NO₄, requires: C, 75·76; H, 7·84; N, 2·94%).

3\u00c3\u00e3-Acetoxy-17a-ethynyl-androst-5-ene-17\u00c3-ol ethyl carbamate ester (IIb)

A soln of 3 β -acetoxy-17 α -ethynyl-androst-5-ene-17 β -ol (500 mg) in ethyl isocyanate (3 ml) and Nmethylmorpholine (1 ml) was boiled under reflux for 50 hr. Evaporation of the solvents and chromatography of the residue on alumina (Grade V), elution with ether-pentane (1:4), and collection of the major fraction gave the required *ethyl carbamate ester* (300 mg) as spears, m.p. 191°; $[\alpha]_D - 97^\circ$; v_{max} 3400, 3250, 1740, 1520 cm⁻¹; τ (CDCl₃) 3:36, ca. 6:7, 7:95, 8:85 (tr, J = 7.0 c/s), 8:95, 9:12, relative areas 1:2:3:3:3:3. (Found : C, 73:33; H, 8:65; N, 3:23. C₂₆H₃₇NO₄ requires: C, 73:03; H, 8:72; N, 3:28%).

4'-Methylene-3'-phenylspiro[3B-hydroxy-androst-5-ene-17,5'(1'B)-oxazolidone]2'-one (IIIa)

A soln of NaOH (200 mg) in water (2 ml) was added to a soln of IIa (500 mg) in MeOH (15 ml). The mixture was boiled under reflux for 4 hr, cooled and poured into water. The ppt was collected and crystallized from CH₂Cl₂-MeOH to give the required *oxazolidone* (400 mg) as needles, m.p. 213°; $[\alpha]_D - 129^\circ$; λ_{max} 220 mµ, 10⁻³ $\varepsilon = 12\cdot3$; ν_{max} 3440, 1770, 1660, 1630, 1590, 1495 cm⁻¹; τ (CDCl₃) 2·5–2·7, 5·78 (AB pattern, $\Delta \tau = 10\cdot8$ c/s, $J_{AB} = 2\cdot5$ c/s), 8·94, relative areas 5:2:6. (Found: C, 77·70; H, 8·05; N, 3·32. C₂₈H₃₃NO₃ requires: C, 77·56; H, 8·14; N, 3·23%).

4'-Methylene-3'-phenylspiro[3B-acetoxy-androst-5-ene-17,5'(1'B)-oxazolidine]2'-one (IIIb)

A soln of the above product (130 mg) in pyridine (2 ml) and Ac₂O (0.5 ml) was heated at 100° for 1 hr, cooled, poured into water, and the ppt collected. Crystallization from CH₂Cl₂-MeOH gave the *acetate* (170 mg) as needles, m.p. 174°; $[\alpha]_D - 119^\circ$; λ_{max} 219 mµ, 10⁻³ $\varepsilon = 110$; ν_{max} 1770, 1730, 1655, 1590, 1490 cm⁻¹; τ (CDCl₃) 2.5–2.7, 5.76 (AB pattern, $\Delta \tau = 9.16$ c/s, $J_{AB} = 4$ c/s), 7.94, 8.92, relative areas 5:2:3:6; mol. wt. 475 (from the mass spectrum). (Found : C, 75.96; H, 7.93; N, 300. C₃₀H₃₇NO₄ requires: C, 75.76; H, 7.84; N, 2.95%).

4'-Methylene-3'-ethylspiro[3B-hydroxy-androst-5-ene-17,5'(1'B)-oxazolidine]2'-one (IIIc)

A soln of NaOH (200 mg) in water (2 ml) was added to a soln of IIb (400 mg) in MeOH (20 ml). The mixture was boiled under reflux for 7 hr, cooled, poured into water, and isolated with ether. Crystallization of the residue from acetone-hexane gave the *oxazolidone* (200 mg) as needles, m.p. 182°; $[\alpha]_D - 159^\circ$; $\lambda_{max} 224 \text{ mµ}$, $10^{-3} \varepsilon = 11.4$; $\nu_{max} 3450$, 1770, 1660 cm⁻¹; τ (CDCl₃) 5.80 (AB pattern, $\Delta \tau = 11.6 \text{ c/s}$, $J_{AB} = 3$ (c/s), ca. 6.5 (multiplet), 8.80 (trt, J = 70 c/s), 8.96, 9.01, relative areas 2:2:3:3:3. (Found: C, 74.66; H, 8.76; N, 3.67. C₂₄H₃₅NO₃ requires: C, 74.76, H, 9.15; N, 3.63%).

3B-Formoxy-17a-hydroxy-pregn-5-ene-20-one carbamate esters. General method of preparation

A soln of 3β , 17α -dihydroxy-pregn-5-ene-20-one 3-formate (2 parts) in aryl isocyanate (7 parts) was heated at 100° for 15 hr, during which time crystals separated. The mixture was cooled, filtered, and the crystals washed successively with hexane. Purification was achieved by crystallization from a suitable solvent system. Yields were in the region of 50-70%.

3β-Formoxy-17α-hydroxy-pregn-5-ene-20-one phenyl carbamate (Va), crystallized from MeOH in needles, m.p. 253-254°; $[\alpha]_D - 77°$; λ_{max} 228 mµ, $10^{-3} ε = 8.1$; v_{max} 3200, 1710, 1600, 1550, 1500 cm⁻¹; τ (CDCl₃) 1.92, 2.5-2.8, 3.1, 7.84, 8.95, 9.31, relative areas 1:5:1:3:3:3. (Found: C, 71.74; H, 7.88; N, 3.16. C₂₉H₃₇NO₅- $\frac{1}{2}$ MeOH requires: C, 71.5; H, 7.88; N, 2.83%).

3β-Formoxy-17α-hydroxy-pregn-5-ene-20-one p-chlorophenyl carbamate (Vb), crystallized from CH₂Cl₂-MeOH in needles, m.p. 248-249°; ν_{max} 3250, 1705, 1605, 1540, 1490 cm⁻¹; τ (CDCl₃) 1.92, 2.67-2.74, 3.07, 7.84, 8.95, 9.31, relative areas 1:4:1:3:3:3: (Found: C, 67.70; H, 6.95; N, 2.62; Cl, 7.2. C₂₉H₃₆NO₅Cl requires: C, 67.75; H, 7.06; N, 2.73; Cl, 6.92%).

3 β -Formoxy-17 α -hydroxy-pregn-5-ene-20-one p-tolyl carbamate (Vd), crystallized from CH₂Cl₂-MeOH in needles, m.p. 246°; $[\alpha]_p -92°$; $\lambda_{max} 236 \text{ m}\mu 10^{-3} \varepsilon = 15\cdot8$; $\nu_{max} 3300$, 1710, 1600, 1530 cm⁻¹; τ (CDCl₃) 1·91, 2·6-2·9, 3·14 (broad), 7·67, 7·82, 8·95, 9·31 relative areas 1:4:1:3:3:3:3. (Found: C, 72·89; H, 7·81; N, 3·16. C₃₀H₃₉NO₅ requires: C, 72·99; H, 7·96; N, 2·84%).

3β-Formoxy-17α-hydroxy-pregn-5-ene-20-one m-tolyl carbamate (Ve), crystallized from CH₂Cl₂-MeOH in needles, m.p. 256°; $[\alpha]_{D} = -107^{\circ}$; $\lambda_{max} 236 \text{ mμ}$, $10^{-3} \varepsilon = 11.85$; $\nu_{max} 3300$, 1720, 1700, 1620, 1600, 1545, 1490 (inflection) cm⁻¹; τ (CDCl₃) 1.90, 2:55–2:8, 3:14 (broad), 7:67, 7:82, 8:95, 9:31 relative areas 1:4:1:3:3:3:3:3. (Found: C, 73:13; H, 7:76; N, 2:80. C₃₀H₃₉NO₅ requires C, 72:99; H, 7:96; N, 2:84%).

3B-Formoxy-17a-hydroxy-pregn-5-ene-20-one m-chlorophenyl carbamate (Vc)

A soln of 3β , 17α -dihydroxy-pregn-5-ene-20-one 3 formate (500 mg) in *m*-chlorophenyl isocyanate (1 ml) and benzene (1 ml) was boiled under reflux for 40 hr, during which time a solid product separated. The mixture was cooled, filtered, and the product was washed successively with hexane. Two crystallizations from CH₂Cl₂-MeOH gave the m-chlorophenyl carbamate ester (637 mg) as needles, m.p. $247-248^{\circ}$; $[\alpha]_D - 71^{\circ}$; $\lambda_{max} 237 \text{ m}\mu$, $10^{-3} \varepsilon = 11\cdot25$; $\nu_{max} 3260$, 1720, 1595, 1530, 1475 (inflexion) cm⁻¹; τ (CDCl₃) 1-90, 2.7-2.85, 3.02, 7.82, 8.94, 9.31 relative intensities 1:4:1:3:3:3. (Found: C, 67-68; H, 6.80; N, 2.58; Cl, 7.1. C₂₉H₃₆NO₅Cl requires: C, 67.75; H, 706; N, 2.73; Cl, 6.92%).

3β-Formoxy-17α-hydroxy-pregn-5-ene-20-one ethyl carbamate (Vf)

A soln of 3β , 17α -dihydroxy-pregn-5-ene-20-one 3 formate (1 g) in ethyl isocyanate (3 ml) and N-methylmorpholine (1 ml) was boiled under reflux for 30 hr, during which time a solid product separated. The mixture was cooled, filtered, and the product was washed successively with hexane. Two crystallizations from CH₂Cl₂-MeOH gave the *ethyl carbamate ester* (650 mg) as prisms, m.p. 218-219°; $[\alpha]_D - 52°$; ν_{max} 3250, 1720, 1540 cm⁻¹; τ (CDCl₃) 1.93, ca. 6.7 (multiplet), 7.90, 8.81 (tr, J = c/s), 8.95, 9.34 relative areas 1:2:3:3:3:3. (Found: C, 69.76; H, 8-69; N, 3.38. C₂₅H₃₇NO₅ requires: C, 69.57; H, 8-64; N, 3.25%).

4'-Hydroxy, 4'-methyl-3'-arylspiro[3β-hydroxy-androst-5-ene-17,5'(1'α)oxazolidine]-2'-one

General method of preparation. A soln of NaOH (0-2 parts) in water (2 parts) was added to a soln of the steroidal 17α-carbamate ester (0-4 parts) in MeOH (10 parts). The mixture was boiled under reflux for 3 hr, cooled, poured into cold dil HCl, and filtered. The ppt was washed with water, dried, and purified by crystallization to give the required oxazolidone. Yields were in the region of 70-95%.

4'-Hydroxy,4'-methyl-3'-phenylspiro[3β-hydroxy-androst-5-ene-17,5'(1'α)oxazolidine]-2'-one (VIa; $\mathbf{R}' = \mathbf{H}$), crystallized from CH₂Cl₂-MeOH in needles, m.p. 255-256°; $[\alpha]_D - 71°$; $\lambda_{max} 222 \text{ mµ}$, $10^{-3} \varepsilon = 62$; $\nu_{max} 3230$, 1725, 1600, 1500 cm⁻¹; τ (pyridine) 8·32, 8·81, 8·92 relative areas 1:1:1. (Found: C, 74·46; H, 8·26; N, 3·22. C₂₈H₃₇NO₄ requires: C, 74·47; H, 8·26; N, 3·10%).

4'-Hydroxy,4'-methyl-3'-m-chlorophenylspiro[3β-hydroxy-androst-5-ene-17.5'(1'a)-oxazolidine]-2'-one (VIc; $\mathbf{R}' = \mathbf{H}$), crystallized from CH₂Cl₂-MeOH in plates, m.p. 263°; $[\alpha]_D - 66°$; $\lambda_{max} 227 \text{ m}\mu$; 10⁻³ $\varepsilon = 5.74$; $\nu^{max} 3230$, 1705, 1601, 1580, 1480 cm⁻¹; τ (pyridine) 8·31, 8·82, 8·93, relative areas 1:1:1. (Found: C, 68·02; H, 7·31. C₂₈H₃₆NO₄Cl- $\frac{1}{2}$ MeOH requires: C, 68·2; H, 7·58%).

4'-Hydroxy,4'-methyl-3'-p-chlorophenylspiro[3β-hydroxy-androst-5-ene-17,5'(1'α) oxazolidine]-2'-one (VId; R' = H), crystallized from CH₂Cl₂-MeOH in plates, m.p. 248°; $[\alpha]_D - 51^\circ$; $\lambda_{max} 224 \text{ mµ}$, 10⁻³ $\varepsilon = 6.8$; $\nu_{max} 3300$, 1715, 1603, 1500 cm⁻¹; τ (pyridine) 8.32, 8.82, 8.94 relative areas 1:1:1. (Found: C, 66.7; H, 7-6; N, 30. C₂₈H₃₆NO₄Cl. MeOH requires: C, 67.2; H, 7.7; N, 2.7%).

4'-Hydroxy,4'-methyl-3'-m-tolylspiro[3β-hydroxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one (VIf; R' = H), crystallized from CH₂Cl₂-MeOH in plates, m.p. 260-261°; $[\alpha]_D - 69°$; λ_{max} 223 mµ; ν_{max} 3250, 1715, 1615, 1585, 1490 cm⁻¹; τ (pyridine) 7-80, 8-30, 8-79, 8-92, relative dreas 1:1:1. (Found: C, 71-5; H, 8-5; N, 2-9, C₂₉H₃₉NO₄ + $\frac{1}{2}$ MeOH requires: C, 71-2; H, 8-65; N, 2-82%).

4'-Hydroxy,4'-methyl-3'-p-tolylspiro[3 β -hydroxy-androst-5-ene-17,5'(1' α)-oxazolidine]-2'-one (VIg; R' = H), crystallized from CH₂Cl₂-MeOH in plates, m.p. 225°; [α]_p -61°; λ_{max} 220 m μ , 10⁻³ ε = 6·98; ν_{max} (KBt disc) 3250, 1710, 1620, 1520 cm⁻¹; τ (pyridine) 7·76, 8·31, 8·80, 8·91, relative areas 1:1:1:1. (Found: C, 71·9; H, 8·3; N, 2·9. C₂₉H₃₉NO₄ · $\frac{1}{2}$ MeOH requires: C, 71·2; H, 8·65; N, 2·82%).

4'+ Hydroxy,4'-methyl-3'-ethylspiro[3β-hydroxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one (VIh;

R' = H) was similarly prepared and crystallized from CH₂Cl₂-MeOH in needles, m.p. 270–271°; [α]_D – 126°; v_{max} 3250, 1700 cm⁻¹; τ (pyridine) 6.55 (mt, probably a qu), 8.30, 8.78 (tr J = 7 c/s), 8.89, 8.99, relative areas 2:3:3:3:3. (Found: C, 68.7; H, 9.14; N, 3.52. C₂₄H₃₇NO₄·MeOH requires: C, 69.0; H, 9.27; N, 3.22%).

4'-Hydroxy,4'-methyl-3'-arylspiro[3β-acetoxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one

General method of preparation. A soln of the appropriate 3β -hydroxy steroid (1 part) in pyridine (10 parts) and Ac₂O (4 parts) was left at 27° for 15 hr. The soln was poured into water, and the ppt collected and washed with water. Purification was by crystallization to give the required 3β -acetates. Yields were in the region of 80–90%.

4'-Hydroxy,4'-methyl-3'-phenylspiro[3β-acetoxy-androst-5-ene-17,5'(1'a)-oxazolidine]-2'-one (VIa; R' = Ac), crystallized from CH₂Cl₂-MeOH in needles, m.p. 262°; λ_{max} 226 mµ; ν_{max} 3230, 1725, 1705, 1600, 1500 cm⁻¹; τ (CDCl₃) 7-94, 8-32, 8-82, 9-00 relative areas 1:1:1:1; mol. wt. 493 (from the mass spectrum). (Found: C, 73-15; H, 7-94; N, 3-09. C₃₀H₃₉NO₅ requires: C, 72-99; H, 7-96; N, 2-84%).

4'-Hydroxy,4'-methyl-3'-m-chlorophenylspiro[3β-acetoxy-androst-5-ene-17,5'(1'a)-oxazolidine]-2'-one (VIc; R' = Ac), crystallized from CH₂Cl₂-MeOH in needles, m.p. 276°; $[\alpha]_D - 69°$; ν_{max} 3200, 1740, 1700, 1595, 1570, 1480, cm⁻¹; τ (pyridine) 7-92, 8-32, 8-82, 8-99. (Found: C, 68-3; H, 7-0; N, 2-8. C₃₀H₃₈NO₅Cl requires: C, 68-25; H, 7-2; N, 2-65%).

4'-Hydroxy,4'-methyl-3'-p-chlorophenylspiro[3β-acetoxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one (VId; $\mathbf{R}' = \mathbf{Ac}$), crystallized from CH₂Cl₂-MeOH in plates, m.p. 268°; $[\alpha]_{p} - 60°$; λ_{max} 224 mµ; ν_{max} (KBr disc) 3200, 1730, 1705, 1599 (very weak), cm⁻¹; τ (pyridine) 7-93, 8-33, 8-82, 8-99 relative areas 1:1:1:1; mole wt. 527 (from the mass spectrum). (Found: C, 68-11; H, 7-16; N, 2-72. C₃₀H₃₈NO₅Cl requires: C, 68-23; H, 7-25; N, 2-65%).

4'-Hydroxy,4'-methyl-3'-m-tolylspiro[3β-acetoxy-androst-5-ene-17,5'(1'a)-oxazolidine]-2'-one (VIf; R' = Ac), crystallized from CH₂Cl₂-MeOH in plates, m.p. 275–276°; $[a]_0 - 73°$; λ_{max} 224 mµ; ν_{max} (KBr disc) 3250, 1730, 1710, 1615, 1600, 1490 cm⁻¹; τ (pyridine) 7-80, 7-92, 8-30, 8-80, 8-98 relative areas 1:1:1:1:1. (Found: C, 73-37; H, 7-83; N, 3-10. C₃₁H₄₁NO₅ requires: C, 73-34; H, 8-14; N, 2-76%).

4'-Hydroxy.4'-methyl-3'-p-tolylspiro[3 β -acetoxy-androst-5-ene-17,5'(1' α)-oxazolidine]-2'-one (VIg; R' = Ao), crystallized from CH₂Cl₂-MeOH in needles, m.p. 266°; [α]_D -61°; λ_{max} 227 mµ; ν_{max} 3310, 1725, 1715, 1610, 1520, 1480 (inflexion) cm⁻¹; τ (pyridine) 7.75, 793, 8.32, 8.81, 8.99, relative areas 1:1:1:1:1. (Found: C, 73.67; H, 8.02; N, 2.84. C₃₁H₄₁NO₅ requires: C, 73.34; H, 8.14; N, 2.76%).

4'-Hydroxy,4'-methyl-3'-ethylspiro[3 β -acetoxy-androst-5-ene-17,5'(1' α)-oxazolidine]-2'-one (VIh; R' = Ac), was similarly prepared and crystallized from CH₂Cl₂-MeOH in rhombs, m.p. 282°; [α]_D -124:5°; ν_{max} 3250, 1730, 1710 cm⁻¹; τ (pyridine) 7-97, 8-32, 8-78 (tr, J = 7 c/s), 8-89, 9-00 relative areas 1:1:1:1:1. (Found: C, 70-02; H, 8-89; N, 3-03. C₂₆H₃₉NO₅ requires: C, 70-08; H, 8-82; N, 3-14%).

4'-Methylene-3'-arylspiro[3B-acetoxy-androst-5-ene-17,5'(1'a)-oxazolidine]-2'-one

General method of preparation. A soln of the 4'-hydroxy,4'-methyl oxazolidone steroid (1 part) in pyridine (15 parts) and POCl₃ (2 parts) was left at 27° for 15 hr. The mixture was poured into ice/water and filtered. The ppt was washed with water, dried and purified by crystallization to give the required 4'-methylene compound. Yields were in the region of 80–90%.

4'-Methylene-3'-phenylspiro[3β-acetoxy-androst-5-ene-17,5'(1' α)-oxazolidine]-2'-one (VIIa), crystallized from CH₂Cl₂-MeOH in needles, m.p. 208°; [α]_D - 20°; λ_{max} 217 mµ, 10⁻³ ε = 15·7; ν_{max} 1775, 1725, 1680, 1650, 1590, 1490 cm⁻¹; τ (CDCl₃) 2·4-2·7, 5·74 (AB pattern, $\Delta \tau$ = 9·16 c/s, J_{AB} = 3 c/s) 7·96, 8·94, 9·09, relative areas 5:2:3:3:3; mol. wt. 475 (from the mass spectrum). (Found: C, 75·92; H, 7·63; N, 3·06. C₃₀H₃₇NO₄ requires: C, 75·76; H, 7·84; N, 2·95%).

4'-Methylene-3'-p-chlorophenylspiro[3β-acetoxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one (VIIb), crystallized from CH₂Cl₂-MeOH in spears, m.p. 285°; $[α]_D - 4°$; $\lambda_{max} 215 \text{ mµ}$; v_{max} (KBr disc) 1780, 1730, 1660, 1500 cm⁻¹; τ (CDCl₃) 2:60-2:80, 5:77 (AB pattern, $\Delta \tau = 8.5 \text{ c/s}$, $J_{AB} = 3 \text{ c/s}$) 7:96, 8:95, 9:10, relative areas 4:2:3:3:3: (Found: C, 70:31; H, 7:05; N, 2:96. C₃₀H₃₆NO₄ requires: C, 70:64; H, 7:11; N, 2:75%).

4'-Methylene-3'-p-tolylspiro[3β-acetoxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one (VIId), crystallized from CH₂Cl₂-MeOH in prisms, m.p. 282°; $[\alpha]_D + 0.6^\circ$; v_{max} 1775, 1740, 1650, 1520 cm⁻¹; τ (CDCl₃) 2·7-2·8, 5·77 (AB pattern, $\Delta \tau = 8\cdot1$ c/s, $J_{AB} = 2\cdot5$ c/s), 7·60, 7·95, 8·94, 9·10, relative areas 4:2:3:3:3:3. (Found: C, 75·93; H, 7·80; N, 2·99. C₃₁H₃₉NO₄ requires: C, 76·04; H, 8·03; N, 2·86%).

4-Methylene-3'-m-chlorophenylspiro[3 β -acetoxy-androst-5-ene-17,5'(1' α)-oxazolidine]-2'-one (VIIc). The crude product was chromtatographed on silica, and elution with benzene-chloroform (1:1), collection of the main band, evaporation of solvents, and crystallization of the residue from CH₂Cl₂-MeOH gave the

required *m*-chlorophenyl oxazolidone as needles, m.p. 184–185°; $[\alpha]_D - 15°$; $\lambda_{max} 214 \text{ mµ}$, $10^{-3} \varepsilon = 21.4$; $\nu_{max} 1800$, 1760, 1695, 1620, 1605, 1500 cm⁻¹; τ (CDCl₃) 2.63–2.73, 5.72 (AB pattern $\Delta \tau = 8.5$ c/s, $J_{AB} = 3$ c/s), 7.95, 8.94, 9.09, relative areas 4:2:3:3:3. (Found: C, 70.61; H, 7.04; N, 2.61; Cl, 6.85. C₃₀H₃₆NO₄Cl requires: C, 70.64; H, 7.11; N, 2.75; Cl, 6.95%).

4'-Methylene-3'-ethylspiro[3β-acetoxy-androst-5-ene-17,5'(1'a)-oxazolidine]-2'-one (VIIe), was similarly prepared and crystallized from CH₂Cl₂-MeOH in spears, m.p. 198-199°; $[\alpha]_D - 12.5^\circ$; $\lambda_{max} 222 \text{ m}\mu$, $10^{-3} \epsilon = 15.8$; $\nu_{max} 1770$, 1740, 1690, 1650 cm⁻¹; τ (CDCl₃) 5.78 (AB pattern, $\Delta \tau = 10 \text{ c/s}$, $J_{AB} = 2.5 \text{ c/s}$), 6.5 (mt), 7.94, 8.82, 8.96, 9.14 relative areas 2:2:3:3:3:3. (Found: C, 73.13; H, 8.62; N, 3.15. C₂₆H₃₇NO₄ requires : C, 73.03; H, 8.72; N, 3.28%).

4'-Hydroxy-4'-methyl-3'-arylspiro[3β-formoxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one

General method of preparation. A soln of 3β , 17α -dihydroxypregn-5-ene-20-one 3 formate (1 part) in aryl isocyanate (4 parts) and N-methylmorpholine (1 part) was heated to 100° for 3 hr, during which time crystals separated. The mixture was cooled and filtered. The solid product was washed with hexane and purified by crystallization to give the required oxazolidone. Yields were usually in the region of 60–90%.

4'-Hydroxy,4'-methyl-3'-phenylspiro[3β-formoxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one (VIa; R' = CHO), crystallized from CH₂Cl₂-MeOH in plates, m.p. 252°; $[α]_D - 78°$; $ν_{max}$ 3300, 1710, 1610, 1500 cm⁻¹; τ (pyridine) 8·39, 8·85, 9·02 relative areas 1:1:1. (Found: C, 72·25; H, 7·71; N, 2·74. C₂₉H₃₇NO₅ requires: C, 72·62; H, 7·78; N, 2·92%).

4'-Hydroxy,4'-methyl-3'-o-chlorophenylspiro[3β-formoxy-androst-5-ene-17,5'(1'a)-oxazolidine]-2'-one (VIb; R' = CHO), crystallized from CH₂Cl₂-MeOH in needles, m.p. 264°; $[\alpha]_D - 56^\circ$; ν_{max} 3200, 1740, 1600, 1500 cm⁻¹; τ (pyridine) 8·39, 8·82, 9·00 relative areas 1:1:1. (Found: C, 67·52; H, 6·90; N, 2·68; Cl, 7·24. C₂₉H₃₆NO₃Cl requires: C, 67·76; H, 7·06; N, 2·73; Cl, 6·90%).

4'-Hydroxy,4'-methyl-3'-m-chlorophenylspiro[3β-formoxy-androst-5-ene-17,5'-(1'a)-oxazolidine]2'-one (VIc; $\mathbf{R}' = CHO$), crystallized from CH₂Cl₂-MeOH in plates, m.p. 262-263°; $[\alpha]_D - 77^\circ$; λ_{max} 230 mµ; ν_{max} 3250, 1720, 1605, 1590, 1490 cm⁻¹; τ (pyridine) 8 31, 8 81, 9 02, relative areas 1:1:1. (Found: C, 67·18; H, 678; N, 2·71; Cl, 7·11. C₂₉H₃₆NO₅Cl requires: C, 67·76; H, 7·06; N, 2·73; Cl, 6·90%).

4'-Hydroxy,4'-methyl-3'-o-tolylspiro[3β-formoxy-androst-5-ene-17,5'(1α)-oxazolidine]-2'-one (VIe; R' = CHO), crystallized from CH₂Cl₂-MeOH in plates, m.p. 274-275°; [α]_D - 76°; ν _{max} 3200, 1730, 1605, 1590, 1500 cm⁻¹; τ (pyridine) 7.56, 8.46, 8.82, 9.01 relative areas 1:1:1:1:1. (Found : C, 72.90; H, 7.91; N, 2.74. C₃₀H₃₉NO₅ requires : C, 72.99; H, 7.96; N, 2.84%).

4'-Hydroxy,4'-methyl-3'-m-tolylspiro[3 β -formoxy-androst-5-ene-17,5'(1' α)-oxazolidine]-2'-one (VIf; $\mathbf{R}' \neq \mathbf{CHO}$), crystallized from $\mathbf{CH}_2\mathbf{Cl}_2$ -MeOH in needles, m.p. 267°; [α]_D -76°; λ_{max} 224 mµ; ν_{max} 3200, 1730, 1605, 1690, 1495 cm⁻¹; τ (pyridine) 7.80, 8.31, 8.81, 9.00 relative areas 1:1:1:1. (Found: C, 72.71; H, 7.75; N, 2.70. $\mathbf{C}_{30}\mathbf{H}_{39}\mathbf{NO}_{5}$ requires: C, 72.99; H, 7.96; N, 2.84%).

4'-Hydroxy,4'-methyl-3'-p-tolylspiro[3β-formoxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one (VIg; $\mathbf{R}' = \mathbf{CHO}$), crystallized from $\mathbf{CH}_2\mathbf{Cl}_2$ -MeOH in plates, m.p. 242-243°; $[\alpha]_D - 67.5°$; λ_{max} 219 mµ; ν_{max} 3200, 1720, 1690, 1600, 1505 cm⁻¹; τ (pyridine) 7.77, 8.32, 8.81, 9.01, relative areas 1:1:1:1. (Found: C, 73.16; N, 7.76; N, 3.07. C₃₀H₃₉NO₅ requires: C, 72.99; H, 7.96; N, 2.84%).

4'-Hydroxy,4'-methyl-3'- α -naphthylspiro[3B-formoxy-androst-5-ene-17,5'-(1' α)-oxazolidine]-2'-one (VI; R' = CHO), crystallized from CH₂Cl₂-MeOH in plates, m.p. 263°; [α]_D -68.5°; λ_{max} 222 (strong), 271, 280 (weak) m μ , $\lambda_{iaflerien}$ 290 m μ ; ν_{max} 3250, 1730, 1720, 1640, 1605 cm⁻¹; τ (pyridine 8.45, 8.80, 8.98 relative areas 1:1:1. (Found: C, 74.92; H, 7.22; N, 2.79. C₃₃H₃₉NO₅ requires: C, 74.83; H, 7.42; N, 2.64%).

4'-Hydroxy,4'-methyl-3'-p-chlorophenylspiro[3β-formoxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one 4'-pchlorophenyl carbamate (VIII)

A soln of 3 β ,17 α -dihydroxy-pregn-5-ene-20-one 3 formate (500 mg) in *p*-chlorophenyl isocyanate (2 ml) and N-methylmorpholine (0-5 ml) was heated at 100° for 5 hr, during which time crystals separated. The mixture was cooled, filtered, and the crystals washed with hexane. Three crystallizations from CH₂Cl₂-MeOH gave the *oxazolidone carbamate ester*, (300 mg) as needles, m.p. 232°; [α]_D -72°; ν _{max} 3200, 1740, 1720, 1605, 1540, 1500 cm⁻¹; τ (pyridine 7-69, 9-05, 9-38. τ (CDCl₃) 1-90, 2:39, 2:53-2:83, 7:85, 9-04, 9-44 relative areas 1:1:8:3:3:3; mol. wt. (from mass spectrum) 666. (Found: C, 64·12; H, 5·76; N, 4·04; Cl, 11·03. C₃₅H₄₀N₂O₆Cl₂ requires: C, 64·11; H, 6·15; N, 4·27; Cl, 10·82%).

4'-Methylene-3'-n-butylspiro[3β-formoxy-androst-5-ene-17,5'(1'α)-oxazolidine]-2'-one (VIIf)

A soln of 3β , 17α -dihydroxy-pregn-5-ene-20-one 3 formate (1 g) in n-butyl isocyanate (3 ml) was heated at

100° for 24 hr, cooled, and allowed to stand at 27° for 44 hr, during which time crystals separated. The mixture was filtered and the crystals washed with hexane. Two crystallizations from aqueous MeOH gave the exocyclic methylene oxazolidone (400 mg) as plates, m.p. 152–153°; $[\alpha]_D - 16°$; $\lambda_{max} 222 m\mu$, $10^{-3} e = 193$; $v_{max} 1775$, 1725, 1680, 1640 cm⁻¹; τ (CDCl₃) 193, 5·79 (AB pattern $\Delta \tau = 10$ c/s $J_{AB} = 2\cdot5$ c/s), 8·96, 9·15 relative areas 1:2:3:3. (Found: C, 73·23; H, 8·97; N, 3·30. C₂₇H₃₉NO₄ requires: C, 73·43; H, 8·90; N, 3·17%).

4'-Methylene-3'-allylspiro[3B-formoxy-androst-5-ene-17,5'(1'a)-oxazolidine]-2'-one (VIIg)

A soln of 3 β ,17 α -dihydroxy-pregn-5-ene-20-one 3 formate (1 g) in allyl isocyanate (7 ml) was boiled under reflux for 15 hr, cooled and poured into hexane. The resultant gum was washed by decantation, titurated with EtOH and the solid product collected by filtration. Three crystallizations from aqueous MeOH gave the *exocyclic methylene oxazolidone* (42 mg) as plates, m.p. 178°; $[\alpha]_D - 11^\circ$; α_{max} 220 mµ, $10^{-3} \epsilon = 12 \cdot 1$; ν_{max} 1770, 1725, 1690, 1655 cm⁻¹; τ (CDCl₃) 1.94, 5.80 (AB pattern $\Delta \tau = 10$ c/s, $J_{AB} = 3$ c/s) 8.96, 9.14 relative areas 1:2:3:3. (Found: C, 73.03; H, 8.25; N, 3.54. C₂₆H₃₅NO₄ requires: C. 73.38; H, 8.29; N, 3.29%).

4'-Methylene-3'-arylspiro[androst-4-ene-17,5'(1'a)-oxazolidine]-2',3-dione

General method of preparation. A soln of 17α -hydroxy-pregn-4-ene-3,20-dione (1 part) in aryl isocyanate (3 parts) and N-methylmorpholine (0.6 parts) was heated at 100° for 15 hr. The mixture was cooled, filtered, and the collected solid was washed with hexane to give the exocyclic methylene oxazolidone. Yields were in the region of 20-60%.

4'-Methylene-3'-phenylspiro androst-4-ene-17,5'(1' α)-oxazolidine-2',3-dione (XIIa), crystallized from CH₂Cl₂-MeOH in cubes, m.p. 308°; $[\alpha]_D$ + 153°; λ_{max} 233 m μ ; ν_{max} 1770, 1660, 1610, 1590, 1490 cm⁻¹; τ (CDCl₃) 2:5-2:7, 5:71 (AB pattern $\Delta \tau = 9.5$ c/s $J_{AB} = 3$ c/s), 8:77, 9:04 relative areas 5:2:3:3. (Found: C, 77:26; N, 7:62; N, 3:58. C₂₈H₃₃NO₃ requires: C, 77:92; H, 7:71; N, 3:25%).

4'-Methylene-3'-o-chlorophenylspiro[androst-4-ene-17,5'(1'a)-oxazolidine]-2',3-dione (XIIb), crystallized from CH₂Cl₂-MeOH in needles, m.p. 274°; $[\alpha]_D + 164°$; $\lambda_{max} 216$ mµ, $10^{-3} \varepsilon = 23\cdot65$, $\lambda_{max} 237$ mµ, $10^{-3} \varepsilon = 18\cdot7$; $\nu_{max} 1780$, 1675, 1640, 1605, 1490 cm⁻¹; τ (CDCl₃) 2·48-2·70, 5·78 (tr, J = 3 c/s), 6·00 (tr, J = 3 c/s), 8·78, 9·04 relative areas 4:1:1:3:3. (Found: C, 72·13; H, 6·71; N, 2·90; Cl, 7·44. C₂₈H₃₂CINO₃ requires: C, 72·16; H, 6·92; N, 3·00; Cl, 7·62%).

4'-Methylene-3'-m-chlorophenylspiro[androst-4-ene-17,5'(1'α)-oxazolidine]-2',3-dione (XIIc), crystallized from CH₂Cl₂-MeOH in cubes, m.p. 283–284°; [α]_D + 143°; λ_{max} 216, 234 mµ; ν_{max} 1770, 1675, 1630, 1600, 1490 cm⁻¹; τ (CDCl₃) 2·47–2·70, 5·65 (AB pattern $\Delta \tau$ = 9·5 c/s J_{AB} = 3 c/s), 8·77, 9·06 relative areas 4:2:3:3. (Found : C, 72·18; H, 6·85; N, 2·93; Cl, 7·73. C₂₈H₃₂ClNO₃ requires : C, 72·16; H, 6·92; N, 3·01; Cl, 7·61%).

4'-Methylene-3'-p-chlorophenylspiro[androst-4-ene-17,5'(1' α)-oxazolidine]-2',3-dione (XIId) was only obtained in a crude state τ (CDCl₃) 5.73 (AB pattern $\Delta \tau = 8 \text{ c/s } J_{AB} = 2.5 \text{ c/s}$), 8-80, 9-06 relative areas 4:3:3.

4'-Methylene-3'-m-tolylspiro[androst-4-ene-17,5'(1'a)-oxazolidine]-2',3-dione (XIIe), crystallized from CH₂Cl₂-MeOH in needles, m.p. 260-261°; $[\alpha]_D$ + 159°; λ_{max} 210 mµ, 10⁻³ ε = 17-6, 232 mµ, 10⁻³ ε = 18·2; ν_{max} 1770, 1675, 1620, 1600, 1495 cm⁻¹; τ (CDCl₃) 2·70-2·84, 5·76 (AB pattern $\Delta \tau$ = 8 c/s J_{AB} = 2·5 c/s) 7·58, 8·77, 9·05, relative areas 4:2:3:3:3. (Found: C, 77·4; H, 7·95; N, 3·28. C₂₉H₃₅NO₃ requires: C, 78·17; H, 7·82; N, 3·14%).

3B,17B-Dihydroxy-17a-cyano-androst-5-ene 3 acetate4 (XIII)

A soln of KCN (25 mg) in acetone cyanohydrin (7.5 ml) and water (1 drop) was added to a soln of $\beta\beta$ acetoxy-androst-5-ene-17-one (2.5 g) in EtOH (125 ml) at 0°. The mixture was stirred at 0° for 4 hr, poured into water and extracted with EtOAc. The organic phase was washed with water, dried and evaporated to a small volume. Addition of hexane caused crystallization, and the product was collected by filtration. NMR showed this product (1 g) to be the 17 β -hydroxy isomer. τ (CDCl₃) 7.94, 8.95, 9.11 relative areas 1:1:1. The product was left as such for the next stage. Evaporation of solvents gave a solid residue, shown by NMR to be a mixture of the 17 α and 17 β -hydroxy isomers.

4'-Imino-3'-phenylspiro[3B-acetoxy-androst-5-ene-17,5'(1'B)-oxazolidine]-2'-one (XIV)

A soln of 3β ,17 β -dihydroxy-17 α -cyano-androst-5-ene 3 acetate (500 mg) in phenyl isocyanate (2.5 ml) was heated at 100° for 15 hr. The mixture was cooled, poured into hexane, and filtered. The solid was washed with hexane and crystallized from aqueous MeOH to give the *imino oxazolidone* (630 mg) as needles, m.p. 208-209°; $[\alpha]_D = 157^\circ$; v_{max} 3250, 1740, 1720, 1630, 1610, 1550, 1505 cm⁻¹; τ (CDCl₃) 2.5-2.9, 3.13, 7.95,

8·95, 9·05 relative areas 5:1:3:3:3; mol. wt. 476 (from mass spectrum). (Found: C, 72·07; H, 7·20; N, 6·03. C₂₉H₃₆N₂O₄-½ MeOH requires: C, 71·9; H, 7·20; N, 5·70%).

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