STEREOCHEMICAL STUDIES

VI. REACTIONS OF 3β-HYDROXY-4-OXA-5α-ESTRANE AND 3α,17β-DIHYDROXY-4-OXA-5α-ESTRANE

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ABSTRACT

The configurations at the 3 positions of 3β-hydroxy-4-oxa-5α-estrane and of 3α,17β-dihydroxy-4-oxa-5α-estrane were assigned from a study of the anomerizations of these compounds in aqueous tetrahydrofuran. 3α-Chloro-4-oxa-5α-estrane solvolyzed in alkaline methanol to give a mixture of 3α- and 3β-methoxy-4-oxa-5α-estrane, the former predominating. The difference in the solvolytic behavior of 3α-chloro-4-oxa-5α-steroids and of α-glycosyl halides is discussed.

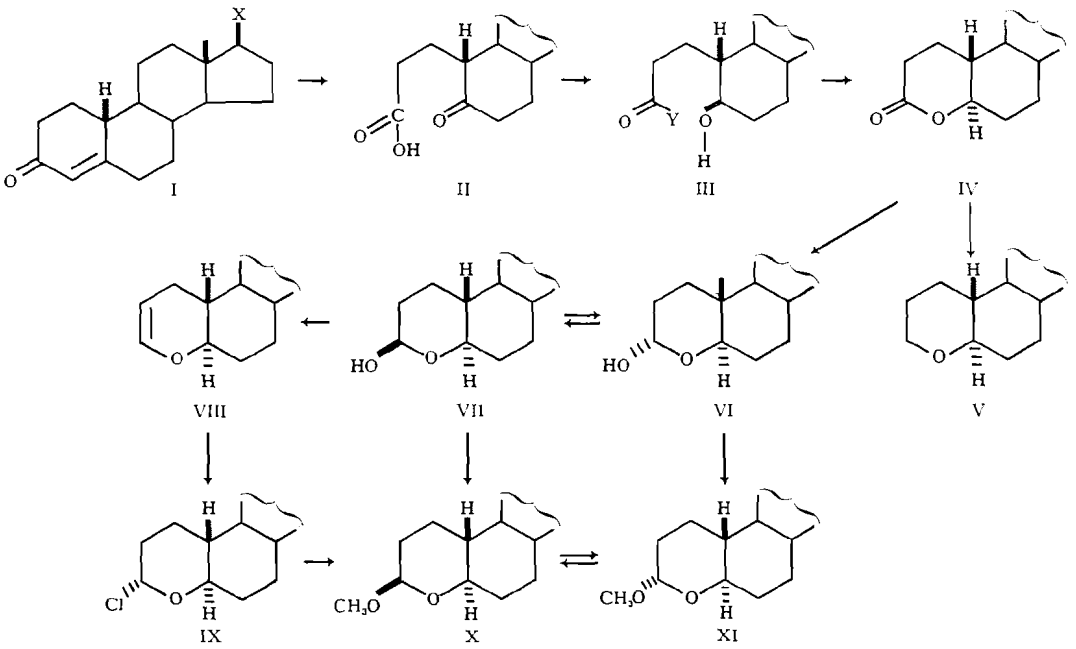
The solvolysis of 3α-chloro-4-oxa-5α-cholestane in buffered or alkaline alcohols gives 3-alkoxy derivatives with predominant retention of configuration (1). The solvolysis of acylglycosyl halides, on the contrary, generally gives a product of inverted configuration (2) if participation by neighboring groups is avoided (3, 4) and if there is not excessive hindrance to approach of the substituting molecule (5). A possible explanation for the behavior of the steroidal chloroether was considered to be the shielding of the β face of ring A by the angular methyl group (1). Although the shielding of this ring is believed to be less complete than the shielding of rings C and D (6), it has been invoked frequently to explain cases of preferential reaction of ring A on its α face; a recent example is the hydroboration of Δ^1-, Δ^2-, Δ^3-, and Δ^4-cholestenes (7).

To test this possibility, we have synthesized a chloroether (IX, X = H) lacking the angular methyl group, and have studied the stereochemistry of its solvolysis in methanol.

Synthetic Routes

The synthetic route to the desired chloroether IX (X = H) is outlined in Reaction Scheme 1. The three-stage preparation from estrone of the unsaturated ketone I (X = H) is described in the literature (8). Ozonolysis of this ketone gave the keto acid II (X = H), which was reduced with sodium borohydride to the hydroxy acid III (X = H, Y = OH). On acidification, the latter formed the lactone IV (X = H). The α configuration at the 5 position of the lactone was indicated by its nuclear magnetic resonance (n.m.r.) spectrum (discussed in ref. 9), and by the negative shift in molecular rotation (Table I) when it was hydrolyzed in alkaline solution (10, 11). Hydrogenation of the lactone over platinum in acetic acid containing a small amount of perchloric acid gave the ether V (X = H), whereas reduction with lithium aluminium hydride (cf. refs. 1 and 12) or diborane (cf. ref. 13) gave the cyclic hemiacetal VII (X = H). The evidence for the β configuration of the hydroxyl group of the crystalline hemiacetal is discussed below. An examination of the ultraviolet and infrared spectra of the hemiacetal in solution and in the solid state revealed no detectable amount of hydroxyaldehyde present (cf. ref. 1).

Dehydration of the hemiacetal with phosphorus oxychloride in pyridine yielded the dihydropyran VIII (X = H), which in ether solution added hydrogen chloride (cf. refs. 1 and 14) to give the reactive chloroether IX (X = H). This reaction is known to be reversible (1, 15), and the sample of chloroether sent for analysis lost hydrogen chloride completely when allowed to stand, and analyzed as the dihydropyran. However, the



REACTION SCHEME 1.

freshly prepared chloroether used in our experiments was free from the dihydropyran, as shown by the absence from its n.m.r. spectrum of characteristic peaks at 3.74 τ (doublet, J 6.0 c.p.s.) and 4.47 τ (triplet, J 6.0 c.p.s.) caused by the 3- and 2-hydrogen atoms, respectively, of VIII (X = H). Instead, the spectrum showed a single one-proton peak at 3.77 τ having a half-width of 6 c.p.s., diagnostic of an equatorial hydrogen (16, p. 154; 17). Furthermore, the infrared spectrum showed a band at 581 cm^{-1} characteristic of an axial chlorine atom (18), and no trace of the peaks at 3 058 and 1 652 cm^{-1} found in the spectrum of the dihydropyran.

The α configuration of the chlorine atom indicated by these spectral data was in accord with the molecular rotation of the compound. The 3β-chloroether should have about the same molecular rotation as the parent ether V (X = H), and the 3α-chloroether should have a more positive molecular rotation (1, 19, 20). The chloroether obtained in our work did indeed have a more positive molecular rotation (Table II), although much less than anticipated from the rotation of 3α-chloro-4-oxa-6α-cholestane (1). This may indicate a small deformation in ring A when the angular methyl group is present (cf. ref. 21); Brewster (19) has already drawn attention to this possibility.

TABLE I

Molecular rotation ($[M]_D$) values of lactones and of compounds derived from them

Lactone	$[M]_D$	Derived compound	$[M]_D$	$\Delta[M]_D$
IV, X = H*	+166°	III; X = H, Y = O⁻*	+70°	−96°
IV, X = OH*	+193°	III; X = OH, Y = O⁻*	+8°	−185°
IV, X = OH†	+200°	III; X = OH, Y = NH_2†	+56°	−154°

*In methanol–water (99:1 v/v).
†In methanol.

TABLE II

Molecular rotation ($[M]_D$) values of 3-substituted 4-oxa-5α-steroids

3-Substituent	Compound	$[M]_D$ (calcd.)	$[M]_D$ (obs.)	Solvent*
4-Oxa-5α-cholestanes (ref. 1)				
(Hydrogen)		(+190°)	+190°	THF
α-Hydroxy		+360°	+356°	THF–H_2O (9:1 v/v)
β-hydroxy		+160°	—	
α-Methoxy		+465°	+460°	THF–MeOH (1:1 v/v)
β-Methoxy		+75°	+73°	THF–MeOH (1:1 v/v)
4-Oxa-5α-estranes				
(Hydrogen)	V, X = H	(+94°)	+93°	$CHCl_3$
			+95°	THF
α-Hydroxy	VI, X = H	+264°	—	
β-Hydroxy	VII, X = H	+64°	+67°	THF–H_2O (9:1 v/v)
			+62°	$CHCl_3$
α-Methoxy	XI, X = H	+369°	+363°	THF–MeOH (1:1 v/v)
			+348°	$CHCl_3$
β-Methoxy	X, X = H	−21°	−24°	THF–MeOH (1:1 v/v)
			−23°	$CHCl_3$
α-Chloro	IX, X = H	> +94°	+210°	$CHCl_3$
17β-Hydroxy-4-oxa-5α-estranes				
(Hydrogen)	V, X = OH	(+111°)	+111°	$CHCl_3$
α-Hydroxy	VI, X = OH	+281°	+273°	Dioxane (26)
			+203°	THF–H_2O (9:1 v/v)
β-Hydroxy	VII, X = OH	+81°	—	

*THF = tetrahydrofuran.

This axial configuration of the chlorine atom was expected; the compound having equatorial chlorine would be less stable, because of the "anomeric effect" (1, 3, 15, 21–25), and would be expected to isomerize easily to the axial compound. For the same reason, glycosyl halides are generally more stable when the halogen is in an axial orientation (2, 3, 20, 24, 26), and frequently the equatorial halide is so unstable as to elude isolation. For compound IX (X = H), the data of Lemieux and Hayami (24) indicate that the 3β isomer, if in equilibrium with the 3α isomer, would be present to the extent of about 5%. Such an amount would be close to the limit of detection by our spectroscopic methods.

An attempt was made to synthesize 17β-acetoxy-3α-chloro-4-oxa-5α-estrane (IX, X = OAc) by a similar reaction sequence, starting with commercially available 19-nortestosterone acetate (I, X = OAc). This attempt succeeded as far as the hemiacetal VI (X = OH), but was frustrated by our failure to prepare a crystalline diacetate of this hemiacetal. The 5α configuration of the lactone IV (X = OH), and of the compounds derived from it, was indicated by its n.m.r. spectrum (9) and by the sign of the rotational shift when the lactone ring was opened to form the hydroxyamide (III; X = OH, Y = NH_2) or the sodium salt of the hydroxy acid (III; X = OH, Y = O^-) (Table I).

After most of this work was completed (27), Pettit *et al.* (28) described the synthesis of the lactone IV (X = OAc) by direct oxidation of 19-nortestosterone acetate with persulfuric acid, and its further conversion into the hemiacetal VI (X = OH). We had also used persulfuric acid to oxidize nortestosterone to the hydroxylactone IV (X = OH) in low yield (27). This reaction would be expected, on the basis of Pettit's mechanism (13) and of the known stereospecificity of the Baeyer–Villiger reaction (29), to yield a 5α-lactone, and hence may be construed as further evidence for the configurations shown in Reaction Scheme 1.

During the present work it was found that δ-lactones such as IV (X = H or OH) and others (see Experimental) were hydrogenolyzed over Adams' catalyst in acetic acid containing a small amount of perchloric acid to yield cyclic ethers.* The rate of the reaction varied greatly with different batches of catalyst. With any one batch it was strongly dependent on the concentration of perchloric acid, as shown in Table III. This unexpected

TABLE III

Effect of addition of differing volumes of 70% perchloric acid to the solvent acetic acid (5 ml) on the rate of absorption of hydrogen by 4-oxa-5α-cholestan-3-one*

Volume of perchloric acid (ml)	Initial rate (ml/min)
0	0.13
0.02	0.58
0.03	0.78
0.05	0.47
0.06	0.44
0.12	0.36

*Conditions: 20 mg lactone, 10 mg prereduced platinum oxide, magnetic stirring.

reaction accounts for the low yields of lactones sometimes obtained (e.g. refs. 11 and 31) from the hydrogenation of keto acids in acetic acid. Thus hydrogenation of II (X = OH) with 1 mole of hydrogen yielded a mixture of lactone IV (X = OH), ether V (X = OH), and starting material; hydrogenation with an excess of hydrogen gave the ether in good yield. The stereochemistry of this hydrogenation is discussed in ref. 9.

Solvolysis of 3α-Chloro-4-oxa-5α-estrane in Alkaline Methanol

Solvolysis of the chloroether IX (X = H) in alkaline methanol gave a mixture from which two isomeric methoxy compounds (X and XI; X = H) were isolated. The configurations of these methoxy compounds were shown by their differing n.m.r. spectra. For both compounds the peak at lowest field must be due to the anomeric 3-hydrogen atom, and numerous studies (17, 32) have shown that this peak is at higher field and has a greater width when the hydrogen atom is axial than when it is equatorial. Consequently, the isomer having this peak at 5.46 τ (half-width 4 c.p.s.) must be the 3α-methoxy derivative (XI, X = H), and the isomer having it at 5.83 τ (half-width 16 c.p.s.) must be the 3β-methoxy derivative (X, X = H). The latter peak was a poorly resolved quartet. These values of chemical shift and half-width agree closely with those found for the anomeric protons of 2-methoxy-4-methyltetrahydropyran (25).

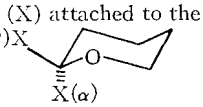
These configurations were also indicated by the molecular rotations of the compounds, which agreed well with the values calculated by Brewster's method (19) (Table II). The calculations made use of group parameters (Table IV) that were slightly altered from Brewster's parameters to give better agreement between the calculated and observed rotations of 4-oxa-5α-steroids,† including compounds from previous studies (1, 15).

The proportions of 3-methoxy anomers obtained from the solvolysis of the chloroether IX (X = H) were: 78% of the α anomer (XI, X = H) and 22% of the β anomer (X, X = H). These are almost the proportions in which the 3α- and 3β-benzyloxy derivatives

*A preliminary account of this reaction has been published (30).

†The superiority, for our purposes, of the revised parameters in Table IV may be explained by the particular solvents used in our studies. Brewster's calculations take no account of the effect of solvent, although obviously the extent to which a group is solvated will affect its torsional asymmetry and hence its effect on molecular rotation. The large effect of changing solvent is apparent from the data in Table I, ref. 1.

TABLE IV

Contributions to molecular rotation of groups (X) attached to the tetrahydropyran ring in the conformation: 

Group X	Brewster's parameters	Revised parameters
α-Hydroxyl	+100	+170
β-Hydroxyl	0	−30
α-Methoxyl	+205	+275
β-Methoxyl	−105	−115

were formed in the solvolysis of 3α-chloro-4-oxa-5α-cholestane in benzyl alcohol. The exact proportions of 3α- and 3β-methoxy derivatives formed from the solvolysis of the latter chloroether in methanol are not known, although the 3α-methoxy derivative clearly preponderated (1).

It thus becomes apparent that the angular methyl group at the 10 position has little or no effect on the stereochemistry of the displacement reactions of 3-chloro-4-oxa-5α-steroids. It would seem that the intermediate oxocarbonium ion (see ref. 1 for a detailed discussion of the mechanism) has an inherent tendency to react on its α rather than its β face. A similar tendency is shown by 19-nor-5α-steroids having a 3:4 double bond in adding diborane (33), although the absence of the angular methyl group makes the preference for reaction on the α face less complete (7). Various speculations based on stereoelectronic considerations may be advanced to explain this behavior (34), but discussion is best deferred until more experimental data have been accumulated.

If oxocarbonium ions derived from chlorotetrahydropyrans in the C1 conformation (35) have this tendency to react on their α face, the question arises: why do the ions derived from most α-glycosyl halides in this conformation react with alcohols on their β face? A possible explanation lies in the greater reactivity of the latter oxocarbonium ions, destabilized by many electron-withdrawing methoxy or acetoxy groups. For this reason these ions ("encumbered ions") will react with alcohol before the halide ion formed by rupture of the carbon–halogen bond has diffused away and while it is still blocking the α face.

Acid-Catalyzed Mutarotation of 3α- and 3β-Methoxy-4-oxa-5α-estrane

Although 3α- and 3β-methoxy-4-oxa-5α-estrane are stable in neutral or alkaline solution, in acidic methanol either one is rapidly converted into an equilibrium mixture, shown by its optical rotation to contain 67% of the 3α and 33% of the 3β compound (Fig. 1). About the same proportions (65% of 3α, 35% of 3β) were obtained by reaction of the hemiacetal VII (X = H) with methanol containing 3% hydrogen chloride, neutralization, and isolation of the products by chromatography. As expected (36), the 3β isomer, having the equatorial methoxyl group, was eluted more slowly than the 3α compound from the chromatographic column.

The proportions of the α and β anomers are about the same as those found from the equilibration of 3-alkoxy-4-oxa-5α-cholestanes (15).

Mutarotation of 3β-Hydroxy-4-oxa-5α-estrane and 3α,17β-Dihydroxy-4-oxa-5α-estrane

The optical rotation of 3β-hydroxy-4-oxa-5α-estrane (VII, X = H) dissolved in chloroform did not change when the solution was allowed to stand. However, in 90% (v/v) aqueous tetrahydrofuran the rotation increased, following a first-order rate equation (Fig. 2). This indicated a partial conversion into 3α-hydroxy-4-oxa-5α-estrane (VI,

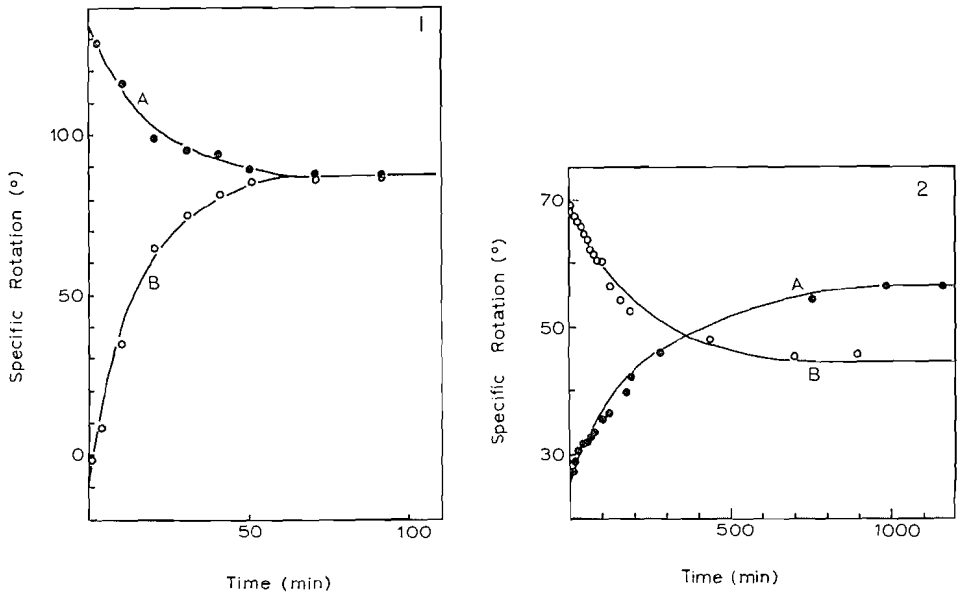


FIG. 1. Change in specific rotation of 3α- (A) and 3β-methoxy-4-oxa-5α-estrane (B) in methanol–tetrahydrofuran (1:1 v/v) containing 0.012 *M* hydrogen chloride at 24 ± 0.5°. Points: experimental; curves: theoretical for first-order reactions having $k = 0.063$ min^{-1}.

FIG. 2. Change in specific rotation of (A) 3β-hydroxy-4-oxa-5α-estrane and (B) 3α,17β-dihydroxy-4-oxa-5α-estrane in tetrahydrofuran–water (9:1 v/v) at 24 ± 0.5°. Points: experimental; curves: theoretical for first-order reactions having rate constants of (A) 0.0044 min^{-1} and (B) 0.0052 min^{-1}.

X = H), known from Hudson's rules of isorotation (37; cf. also ref. 19) to have a higher rotation. The molecular rotation of the 3α compound, estimated by Brewster's method (19) with the revised parameters of Table IV, is given in Table II. If this value is accepted, it may be calculated that the equilibrium mixture contains 41% of the 3α and 59% of the 3β isomer at equilibrium.

These results received a rough confirmation from n.m.r. analysis of equilibrated material isolated at a low temperature as quickly as possible (and so, it was hoped, with as little change in composition as possible during the isolation process). In pure, dry dimethyl sulfoxide this isolated material showed unresolved multiplets* at 3.83 and 4.26 τ caused by hydroxyl hydrogens, since they disappeared on treatment of the solution with deuterium oxide, and peaks at 5.00 and 5.56 τ caused by 3β and 3α protons. Pure 3β-hydroxy-4-oxa-5α-estrane showed only the peaks at 3.83 and 5.56 τ. The relative areas of peaks in the spectrum of the mixture indicated that it contained 38% of the 3α-hydroxy and 62% of the 3β-hydroxy anomers.

The chemical shifts of the anomeric hydroxyls are at higher field than the values for the anomeric hydroxyls of the common monosaccharides in dimethyl sulfoxide (39), as should be expected from the presence of many electron-withdrawing hydroxyl groups in the latter, but have the same order: axial hydroxyls absorb at higher field than equatorial hydroxyls. Thus, both n.m.r. data and optical rotation show the crystalline hemiacetal to have the 3β-hydroxy structure (VII, X = H). On the other hand, the crystalline hemiacetal isolated from the reduction of IV (X = OH) has the 3α-hydroxy structure (VI, X = OH). This is apparent from its molecular rotation (Table II), and from the

**The anomeric hydroxyl, perhaps because of its greater acidity, differs in this respect from the hydroxyl of secondary alcohols, which in dimethyl sulfoxide gives rise to a doublet (38).*

decrease in optical rotation of a solution in tetrahydrofuran–water (90:10 v/v) when it is allowed to stand (Fig. 2). If the calculated value shown in Table II for the molecular rotation of the 3β isomer is accepted, the final rotation indicates the equilibrium mixture to consist of 43% of the 3α and 57% of the 3β isomer.

The 3-hydroxy-4-oxa-5α-estranes thus differ from 3-hydroxy-4-oxa-5α-cholestane, in which the 3α isomer predominates at equilibrium (1). (If the revised molecular rotation for 3β-hydroxy-4-oxa-5α-cholestane given in Table II is accepted, the equilibrium mixture contains 61% of the 3α isomer, and not 55% as reported earlier (1).) However, the differences (in terms of free energy differences) are small, and may reflect slight changes in the shape of ring A brought about by the presence of the angular methyl group.

The predominance at equilibrium of the 3α-methoxy over the 3β-methoxy isomer is more decisive in both the 4-oxa-5α-cholestane and the 4-oxa-5α-estrane series. This predominance of the α isomer has also been noted in the mutarotation of methyl glycosides; in contrast, in the mutarotation of the parent sugars the β isomer may predominate (16, p. 411). It is apparent that in these equilibria the hydroxyl group behaves as a "larger" group than the methoxyl group, probably because of solvent interactions (25).

EXPERIMENTAL

Melting points were determined in a Gallenkamp apparatus and are corrected. Optical rotations were measured with a Carl Zeiss automatic polarimeter with chloroform as solvent. Infrared spectra were determined on a Perkin–Elmer 337 grating spectrophotometer with 1 mm sodium chloride cells and carbon tetrachloride as solvent. Nuclear magnetic resonance spectra were recorded on a Varian A-60 instrument with carbon tetrachloride as solvent. Woelm alumina was used for column chromatography, and Merck A.G. silica gel for thin- and thick-layer chromatography. Magnesium sulfate was used to dry all solvent extracts before concentration.

5-Oxo-3,5-seco-4-norestran-3-oic Acid (II, X = H)

A solution of 3-oxoestra-4-ene (I, X = H) (20 g (8)) in glacial acetic acid (300 ml) and ethyl acetate (300 ml) was cooled in an ice bath while being treated with oxygen containing ozone for 1.5 h. The solution was allowed to warm to room temperature, an aqueous 10% solution of hydrogen peroxide (60 ml) was added, and the mixture was left overnight. It was diluted with ether (2 l) and washed with water to remove acetic acid and hydrogen peroxide; the acidic product was then dissolved in 2% sodium hydroxide solution. Acidification of this solution gave an oil which was dissolved in ether and crystallized from hexane to give colorless crystals (13.9 g, 64%), m.p. 116–119°. After recrystallization several times from hexane – methylene chloride it melted at 117–119°, $[\alpha]_D^{20}$ −8.84° (*c*, 1.08).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.12; H, 9.20.

3-Oxo-4-oxa-5α-estrane (IV, X = H)

The keto acid II (X = H) (4.00 g) in ethanol (300 ml) – water (100 ml) was treated with sodium borohydride (2.00 g) in water (20 ml) for 3 h at room temperature. The reaction mixture was poured into ice water, acidified with concentrated hydrochloric acid, and extracted with ether. Evaporation of the ether gave a solid which was crystallized from methanol–water to give a first crop (2.01 g), m.p. 128–130°, and a second crop (0.52 g), m.p. 125–129°; total yield, 70%. Two more recrystallizations from methanol–water gave an analytical sample, m.p. 135–136°, $[\alpha]_D^{24}$ +92.3° (*c*, 0.72), ν_{max} 1 748 cm^{-1}.

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.74; H, 9.98.

4-Oxa-5α-estrane (V, X = H)

3-Oxo-4-oxa-5α-estrane (0.200 g) in acetic acid (15 ml) containing 70% perchloric acid (0.05 ml) was hydrogenated over platinum oxide (0.105 g) until there was no further uptake of hydrogen. The solution was filtered, diluted with ether, washed with 2% sodium hydroxide solution and with water, and dried. Evaporation of the ether left a solid which crystallized from methanol–ether as needles (0.162 g, 89% yield), m.p. 74–76°, $[\alpha]_D^{24}$ +37.5° (*c*, 1.08).

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 81.88; H, 10.86.

3β-Hydroxy-4-oxa-5α-estrane (VII, X = H)

(a) With Diborane

Diborane generated from sodium borohydride (5.00 g) and boron trifluoride etherate (27 ml) in diethylene glycol dimethyl ether (100 ml) was passed in a stream of nitrogen through dry tetrahydrofuran and then into a solution of lactone IV (X = H) (2.05 g) in dry tetrahydrofuran (100 ml). After 3 h the solution was poured

into ice water and extracted with ether. The oily residue from the extract was chromatographed on neutral alumina. Elution with benzene–ether (70:30 v/v) removed a solid (0.982 g, 49%) melting at 138–142°; on recrystallization from hexane – methylene chloride this solid melted at 143–144°, $[\alpha]_D^{24}$ +62.4° (*c*, 1.11), ν_{max} 3 610 cm^{-1}.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 76.96; H, 10.40.

(b) With Lithium Aluminium Hydride

Lithium aluminium hydride (58 mg) in anhydrous, peroxide-free tetrahydrofuran (50 ml) was added under nitrogen over a period of 5 min to a stirred solution of lactone IV (X = H) (2.00 g) in tetrahydrofuran (50 ml) cooled by an ice bath. The mixture was allowed to warm to room temperature and stirred for another 60 min. It was then poured into cold 1 *N* sulfuric acid (100 ml). A white solid precipitated and was removed by filtration, washed with water, and dissolved in ether. The ether solution was dried ($MgSO_4$) and evaporated, and the residue crystallized from hexane as a white solid (1.47 g, 74%), m.p. 139–142°. A recrystallized sample was shown by mixed melting point and infrared spectrum to be identical with the 3β-hydroxy-4-oxa-5α-estrane obtained above.

4-Oxa-5α-estra-2-ene (VIII, X = H)

A solution of 3β-hydroxy-4-oxa-5α-estrane (0.500 g) and phosphorus oxychloride (1.5 ml) in pyridine (5 ml) was refluxed for 1 h. The solution was cooled, diluted with water, and extracted with ether. The ethereal solution, on evaporation, gave an oily residue which crystallized from methanol–ether as plates (0.382 g, 81%), m.p. 59–62°. Recrystallization raised the melting point to 61–63°, $[\alpha]_D^{24}$ +125° (*c*, 0.66), ν_{max} 3 058 and 1 652 cm^{-1}, ϵ_{210} 5 000 (in cyclohexane; end absorption only).

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 83.13; H, 10.18.

3α-Chloro-4-oxa-5α-estrane (IX, X = H)

A solution of 4-oxa-5α-estra-2-ene (0.300 g) in anhydrous ether (20 ml) saturated with dry hydrogen chloride was kept under nitrogen for 2 h. Evaporation of the ether by a jet of dry nitrogen left crystals which sintered at 78°, m.p. 84–88°, $[\alpha]_D^{24}$ +74.0° (*c*, 1.00), ν_{max} 580 cm^{-1}. The compound contained chlorine, and was used immediately, without purification. A sample sent for analysis appeared to have decomposed to starting material.

3α- and 3β-Methoxy-4-oxa-5α-estrane (X and XI; X = H)

(a) From 3β-Hydroxy-4-oxa-5α-estrane

A solution of the hemiacetal VII (X = H) (0.360 g) in a mixture of anhydrous ether (15 ml) and anhydrous methanol (15 ml) containing 3% hydrogen chloride was refluxed for 30 min. To the cooled solution was added excess silver carbonate (40) (3 g), with stirring. The silver salts were removed by filtration and washed with anhydrous ether. The filtrate and washings, evaporated at reduced pressure, left an oil which was chromatographed on alumina (50 g, neutral, grade II). Elution with hexane removed 3α-methoxy-4-oxa-5α-estrane (XI, X = H) (0.234 g), m.p. 59–62°. This was purified by thick-layer chromatography to give a solid, m.p. 61–63°, $[\alpha]_D^{24}$ −8.2° (*c*, 0.75).

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.61; H, 10.42.

Elution with hexane–benzene (80:20 v/v) removed the 3β isomer (X, X = H) (0.116 g) which, after purification by thick-layer chromatography, melted at 79–81°, $[\alpha]_D^{24}$ +125° (*c*, 0.71).

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.97; H, 10.64.

(b) From 3α-Chloro-4-oxa-5α-estrane

Sodium (70 mg) was dissolved in absolute methanol (15 ml), and the 3α-chloro compound (IX, X = H) (0.250 g) was added. The solution was refluxed for 1 h, and the solvent then removed under reduced pressure. The residue was treated with water (15 ml) and ether (30 ml), and the ether layer was washed with water, dried, and evaporated. The oil thus obtained was chromatographed on alumina (50 g, neutral, grade II). Elution with hexane removed the 3α compound (XI, X = H) (0.179 g, 78%), m.p. 59–62°, identical (mixed melting point and infrared spectrum) with the 3α compound described above. Elution with hexane–benzene (80:20 v/v) removed the 3β compound (X, X = H) (0.050 g, 22%) as an oil. Thick-layer chromatography of this oil gave a solid which was identical (mixed melting point and infrared spectrum) with the 3β-methoxy compound described above.

17β-Hydroxy-5-oxo-3,5-seco-4-norestran-3-oic Acid (II, X = OH)

19-Nortestosterone acetate (I, X = OAc) (1.007 g) dissolved in ethyl acetate (60 ml) was treated with oxygen containing 6% ozone for 1 h at room temperature. Hydrogen peroxide (10%, 6 ml) and methanol (10 ml) were then added and the mixture was left overnight. It was concentrated to half volume, diluted with ether, and extracted with 2% sodium hydroxide. The alkaline extract, after standing for 12 h, was acidified and the keto acid dissolved in ether. Removal of the ether gave a crystalline solid (0.813 g, 95%), m.p. 85–92°. Two crystallizations from acetone–hexane gave the pure keto acid (II, X = OH), m.p. 108–109°, $[\alpha]_D^{24}$ +1.8° (*c*, 0.449), $\nu_{max}^{CHCl_3}$ 3 538 and 1 710 cm^{-1}.

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.27; H, 8.79.

17α-Acetoxy-5-oxo-3,5-seco-4-norestran-3-oic Acid (II, X = $OCOH_3$)

Potassium carbonate (0.28 g) in water (4 ml) was added, with vigorous stirring, to a solution of 19-nortestosterone acetate (0.500 g) in *t*-butanol–water azeotrope (30 ml), followed by 5 ml of a solution prepared from sodium metaperiodate (2 g) and water (25 ml), and then 0.5 ml of 0.8% aqueous potassium permanganate. The rest of the periodate was added at a rate of 5 ml/min for 2 min and then 2 ml/min for 5 min. Permanganate solution was added as necessary to maintain the purple color.

After 1 h excess permanganate was destroyed with sodium bisulfite. The solution was concentrated at reduced pressure to 30 ml, cooled to 4°, acidified with ice-cold 50% sulfuric acid, and extracted with ether. The ethereal extract was washed with sodium bisulfite until free from iodine, and then with water. Evaporation gave an oil (0.446 g) which was chromatographed on 3% deactivated silica gel. Elution with ether removed a crystalline fraction (0.068 g, 12%), m.p. 80–89°, which, after two recrystallizations from methanol–water, gave keto acid II (X = $OCOCH_3$), m.p. 114–115°, $[\alpha]_D^{24}$ −3.8° (*c*, 0.457), ν_{max} 1 708 and 1 733 cm^{-1} (lit. (41) m.p. 113–115°, $[\alpha]_D^{28}$ −4.08°).

Anal. Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.52; H, 8.33.

17β-Hydroxy-3-oxo-4-oxa-5α-estrane (IV, X = OH)

(a) With Sodium Borohydride

A mixture of keto acid II (X = OH) (1.00 g) in 25% aqueous ethanol (50 ml), and of sodium borohydride (1.00 g) in water (15 ml), was left overnight and then heated under reflux until decomposition of the borohydride was complete. The solution was acidified to pH 3, concentrated under reduced pressure to half volume, and diluted with ice-cold water. After 12 h a crystalline solid (0.404 g, 52%), m.p. 105–115°, was collected. Recrystallization from ethyl ether yielded pure 17β-hydroxy-3-oxo-4-oxa-5α-estrane, m.p. 131–132°, $[\alpha]_D^{24}$ +70.1° (*c*, 0.502), $\nu_{max}^{CHCl_3}$ 3 630 and 1 725 cm^{-1} (lit. (28) m.p. 132–134°, $[\alpha]_D^{20}$ +78.9°).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.31; H, 9.41. Found: C, 73.09; H, 9.13.

(b) With Lithium Aluminium Tri-t-butoxy Hydride

Keto acid II (X = OH) (0.972 g) dissolved in tetrahydrofuran (15 ml) was added to a suspension of lithium aluminium tri-*t*-butoxy hydride (4.0 g) in the same solvent (15 ml). The mixture was left at 0° for 30 min and at room temperature for 60 min, and then was poured into an excess of dilute hydrochloric acid. When allowed to stand overnight the solution deposited a solid (0.575 g, 61%) which, after recrystallization from ethyl ether, melted at 131–132°, $[\alpha]_D^{24}$ +70.1° (*c*, 0.504), $\nu_{max}^{CHCl_3}$ 3 630 and 1 725 cm^{-1}.

(c) With Potassium Persulfate

A solution of 19-nortestosterone acetate (0.999 g) in glacial acetic acid (22 ml) was treated with a mixture of potassium persulfate (1.3 g) and sulfuric acid (1.4 g) in acetic acid (22 ml) according to procedures already described (28). The product, after saponification with potassium hydroxide in aqueous dioxane, was obtained as an oil (0.158 g) which crystallized from ethyl ether, m.p. 131–132°, $[\alpha]_D^{24}$ +70.4° (*c*, 0.517), identical by mixed melting point and infrared spectrum with the product obtained in experiments *a* and *b* above.

5β,17β-Dihydroxy-3,5-seco-4-norestran 3-Carboxamide (III; X = OH, Y = NH_2)

A solution of 17β-hydroxy-3-oxo-4-oxa-5α-estrane (0.200 g) in methanol (20 ml) saturated with ammonia deposited needles of the hydroxyamide (III; X = OH, Y = NH_2) (0.165 g) which, after recrystallization from methanol, melted at 298–300°, $[\alpha]_D^{24}$ +18.8° (*c*, 0.461 in methanol); ν_{max}^{KBr} 3 465, 3 360, 3 180, 1 680, and 1 610 cm^{-1}.

Anal. Calcd. for $C_{17}H_{29}O_3N$: C, 69.11; H, 9.90; N, 4.74. Found: C, 69.31; H, 9.73; H, 4.91.

On treatment with dilute hydrochloric acid the amide regenerated the lactone (IV, X = OH), identified by melting point, mixed melting point, infrared spectrum, and optical rotation.

17β-Hydroxy-4-oxa-5α-estrane (V, X = OH)

(a) From Reduction of 17β-Hydroxy-3-oxo-4-oxa-5α-estrane with Lithium Aluminium Hydride – Boron Trifluoride

17β-Hydroxy-3-oxo-4-oxa-5α-estrane (0.262 g) dissolved in boron trifluoride – ether complex (0.840 g) was added to a suspension of lithium aluminium hydride (0.080 g) in ether (50 ml). The mixture was left at 0° for 1 h, refluxed for 2 h, and poured into an excess of dilute hydrochloric acid. The aqueous mixture was extracted with ether, and the extract washed with 2% sodium hydroxide and with water. Evaporation of the ether gave a crystalline solid (0.216 g, 86%), m.p. 166–168°, raised by two recrystallizations from ether to 173–175°, $[\alpha]_D^{24}$ +42.8° (*c*, 0.492) (lit. (26) m.p. 175–176°, $[\alpha]_D^{20}$ +28.8°).

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22: H, 10.67. Found: C, 77.15; H, 10.63.

(b) From Hydrogenation of 17β-Hydroxy-3-oxo-4-oxa-5α-estrane

17β-Hydroxy-3-oxo-4-oxa-5α-estrane (0.200 g) dissolved in glacial acetic acid (15 ml) was hydrogenated over Adams' catalyst (0.090 g) until no more hydrogen was absorbed (2 h). The catalyst was removed by filtration and the product, worked up as above, was obtained as a white crystalline solid (0.185 g, 90%), m.p. 173–175°, identical (mixed melting point, infrared spectrum, and optical rotation) with the product obtained above. The same compound was obtained in 87% yield by hydrogenation of the lactone in acetic acid (15 ml) containing 70% perchloric acid (0.1 ml), hydrogenation now being complete in 45 min.

(c) From Hydrogenation of 17β-Hydroxy-5-oxo-3,5-seco-4-norestran-3-oic Acid

Keto acid II (X = OH) (0.831 g) in glacial acetic acid (15 ml) was hydrogenated over Adams' catalyst (0.420 g) at room temperature and pressure. After 48 h, 3.7 moles of hydrogen/mole of keto acid had been absorbed. The catalyst was removed by filtration and the filtrate diluted with ether. The ether solution was washed with 2% aqueous sodium hydroxide and water. Evaporation gave colorless needles (0.545 g, 74%), m.p. 168–172°, raised by recrystallization from ether to 173–175°, $[\alpha]_D^{21}$ +42.6° (*c*, 0.496), $\nu_{max}^{CHCl_3}$ 1 103 and 1 093 cm^{-1}.

Hydrogenation of 17β-Hydroxy-5-oxo-3,5-seco-4-norestran-3-oic Acid with 1 Mole of Hydrogen

In the presence of Adams' catalyst (0.420 g), keto acid II (X = OH) (1.142 g) dissolved in glacial acetic acid (15 ml) absorbed the theoretical amount of hydrogen after 2½ h at room temperature and pressure. The catalyst was removed by filtration, and the filtrate diluted with ether and washed with 2% sodium hydroxide solution. The ether solution, on evaporation, gave an oil (0.142 g, 14%) that slowly crystallized and which, after recrystallization, was identified (melting point, mixed melting point, and infrared spectrum) as 17β-hydroxy-4-oxa-5α-estrane.

The sodium hydroxide solution was acidified and extracted with ether. The ether solution was washed with 5% sodium carbonate and with water, and dried. Evaporation of the ether gave an oil (0.487 g) which was chromatographed over activated silica gel. The fractions (0.287 g, 26%) eluted with benzene–ether (50:50 v/v) crystallized from ether to give 17β-hydroxy-3-oxo-4-oxa-5α-estrane, m.p. 125–129°, $[\alpha]_D^{21}$ +67.6° (*c*, 0.492), identified by mixed melting point, thin-layer chromatography, and infrared spectrum.

The sodium carbonate solution, after acidification, gave the starting keto acid II (X = OH) (0.456 g, 40%).

Preparation of Tetrahydropyrans by Hydrogenolysis of δ-Lactones

(a) 4-Oxa-5α-cholestane

3-Oxo-4-oxa-5α-cholestane (0.200 g) in acetic acid (15 ml) containing 70% perchloric acid (0.1 ml) was hydrogenated over Adams' catalyst (0.090 g) for 45 min. The product was obtained, after crystallization from methanol, as plates (0.187 g, 92%), m.p. 89–90°, $[\alpha]_D^{23}$ +43.4° (*c*, 0.577), identified as 4-oxa-5α-cholestane (12) by mixed melting point and infrared spectrum.

(b) 4-Oxa-5β-cholestane

Similar hydrogenation of 3-oxo-4-oxa-5β-cholestane (0.200 g) gave 4-oxa-5β-cholestane (0.175 g, 89%), m.p. 51–52°, $[\alpha]_D^{23}$ +3.5° (*c*, 0.629), identified by comparison (mixed melting point and infrared spectrum) with an authentic specimen (12).

(c) 1-Oxadecalin

2-Oxo-1-oxadecalin (42) (1.688 g), on hydrogenation, gave an oil (1.421 g, 80%), b.p. 184–185°, n_D^{27} 1.9686, ν_{max} 1 098 cm^{-1}.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.51; H, 11.23.

3α,17β-Dihydroxy-4-oxa-5α-estrane (VI, X = OH)

Lactone IV (X = OH) (2.2 g) was reduced with diborane according to Pettit *et al.* (28) to give the hemiacetal (0.8 g), m.p. 196–199°. After several recrystallizations from ether – ethyl acetate it had m.p. 202–205°, $[\alpha]_D^{21}$ +62° (*c*, 0.98) (lit. (28) m.p. 204–207°).

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