19-HYDROXY STEROIDS. VI[1]. APPROACHES TO THE SYNTHESIS OF 7,19-DISUBSTITUTED ANDROGENS.

Peter Morand and A. Van Tongerloo

Department of Chemistry,

University of Ottawa,

Ottawa, Canada K1N 6N5

Received: 10/3/72

ABSTRACT

For the purpose of identification of 7-substituted Δ^5-steroids some compounds were prepared via stereospecific reactions and their molecular rotations and pertinent nuclear magnetic resonance data were correlated. Other approaches for the stereospecific introduction of 7-substituents into Δ^5-steroids were investigated.

In the preceding paper[1] the stereospecific synthesis of 3β,7α,19-trihydroxy-5-androsten-17-one 3,19-diacetate in good yield is reported. A number of other approaches for the preparation of 7α,19-disubstituted androgens and their related 7β-isomers have also

been investigated. In many of these reactions both 7α- and 7β-substituents are formed as products and these are often difficult[2,3,4] to separate. This paper describes some of the reactions involved in attempting to synthesize these compounds in good yield as well as a method that can be used to analyze products in order to determine the ratio of C-7 epimers formed in various reactions.

IDENTIFICATION OF 7α- AND 7β-SUBSTITUTED Δ^5-STEROIDS

The molecular rotations and relevant nuclear magnetic resonance data of a number 7α- and 7β-substituted Δ^5-steroids are given in Table 1. Synthesis of the Δ^5-7α-hydroxy compounds reported in this table was achieved by the method previously described[1]. The preparation of the 7β-hydroxy compounds from 3β-acetoxy-Δ^5-7-oxo steroids[9] is described in this paper. It is seen, as expected[10], in Table 1 that the 7α-substituted compounds are highly levorotatory while the 7β-substituted compounds are either dextrorotatory or only slightly levorotatory. Although it is possible to assign the configuration of a specific compound at C-7 with some confidence on the basis of the molecular rotation, this method cannot be used to analyze epimeric mixtures unless one of the epimers is available in the pure state.

Table 1. MOLECULAR ROTATIONS AND NUCLEAR MAGNETIC RESONANCE DATA OF SOME Δ^5-7-SUBSTITUTED STEROIDS.

COMPOUNDS	$[M]_D$	6-H(δ)	7-H(δ)	$J_{6,7}$
5-Cholestene-3β,7α-diol 3-acetate[1]	-388°[5]	5.60	3.75	5.4
5-Cholestene-3β,7β-diol 3-acetate (XII)	-89°[3]	5.30	3.81	2.0
5-Cholestene-3β,7α-diol diacetate (XIV)[1]	-846°[7,8]	5.59	4.97	5.0
5-Cholestene-3β,7β-diol diacetate (XIII)	+267°[3]	5.23	5.02	2.0
3β,7α-Dihydroxy-5-androsten-17-one 3-acetate[1]	-237°[1]	5.72	4.00	5.8
3β,7α-Dihydroxy-5-androsten-17-one diacetate[1]	-698°[6]	5.64	5.10	5.0
5-Androstene-3β,7α,17β-triol 3,17-diacetate (XXII)[1]	-454°[1]	5.61	3.80	5.0
5-Androstene-3β,7α,17β-triol triacetate (XXIII)[1]	-950°[1]	5.59	4.97	5.0
5-Cholestene-3β,7α,19-triol triacetate (XV)	-1120°	5.84	5.01	5.0
5-Cholestene-3β,7β,19-triol triacetate (XVI)	-44°	5.50	5.00	2.0

However, the nuclear magnetic resonance spectra of 7-substituted Δ^5-steroids are such that assignments of configuration as well as analysis of epimeric mixtures can be made on the basis of the chemical shift of the C-6 olefinic proton and of the coupling constant between the 6-H and the 7-H. Table 1 shows that

for 7α-substituted Δ^5-steroids the signal for the 6-H generally appears about 0.3 ppm more downfield[1,3] than in the case of 7β-substituted Δ^5-steroids. An examination of Dreiding models shows that the dihedral angle ($^{6\text{-H}}/_{7\text{-H}}$) is about 25° for 7α-substituted compounds and about 80° for 7β-substituted compounds which is consistent[3,11,12] with the observed coupling constants indicated in Table 1.

INTRODUCTION OF C-7 SUBSTITUENTS

Allylic oxidation of Δ^5-steroids.

One of the first approaches which we investigated for the introduction of a 7α-substituent in androgens involved the allylic oxidation of the appropriate Δ^5-steroid with t-butylperbenzoate. This reaction has been shown[13] to proceed without allylic rearrangement yielding the 7α- and 7β-benzoate derivatives. Stárka[4] has applied this reaction to Δ^5-steroids using acetic acid as the solvent and in his case was able to isolate a mixture of the 7α- and 7β-acetoxy derivatives in about 50% yield. However, column chromatography only partially separated the epimers and the 7α-epimer was shown to be the major product. Although it has been reported[14] that acetoxy derivatives obtained from the reaction of

olefins with t-butylperbenzoate in acetic acid are a result of ester interchange, it is possible that under these conditions a nucleophilic displacement of the benzoate group by acetic acid is involved.

In applying Stárka's method[4] to 19-oxygenated androgens it was decided to use the 19-acetates in order to prevent possible radical reactions at that position. Treatment of 3β,19-dihydroxy-5-androsten-17-one diacetate (I, FIGURE 1) with t-butylperbenzoate and

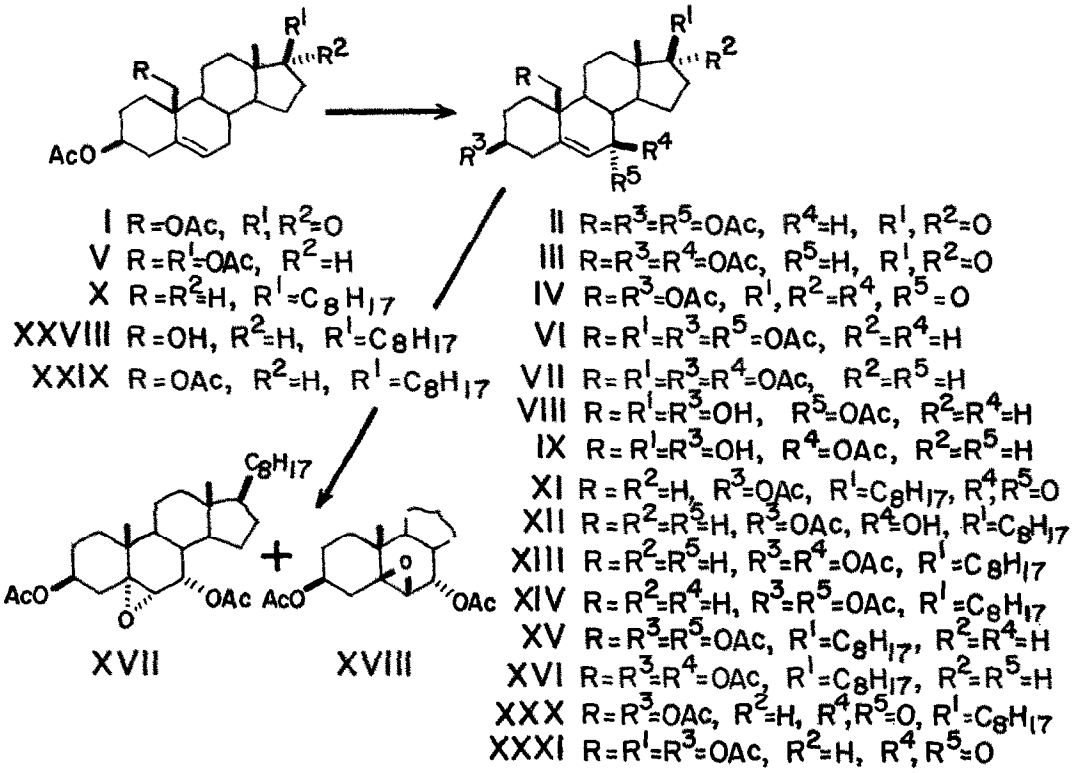

FIGURE 1

a catalytic amount of cuprous bromide in acetic acid led to the isolation of an oil consisting of the 7ξ- acetoxy derivatives in 40% yield. Nuclear magnetic resonance analysis indicated that the 7α- and 7β-acetates (II and III) were present in a 3:1 ratio. However all attempts to separate these epimers failed. A small amount of the corresponding 7-oxo compound (IV) was isolated and its structure was confirmed by comparison of its spectral data and by mixed melting point with 3β,19-dihydroxy-5-androstene-7,17-dione diacetate (IV) prepared by chromic acid oxidation[9] of 3β,19-dihydroxy-5-androsten-17-one diacetate (I).

When the t-butylperbenzoate reaction was performed on 5-androstene-3β,17β,19-triol triacetate(V),the product isolated in which substitution had occurred (40%) was also found to be a 3:1 mixture of the 7α- and 7β-epimers (VI and VII). Again it was not possible to separate these epimers on repeated column chromatography.

However, on treatment of the epimeric mixture with a methanolic solution of sodium carbonate at room temperature for 24 hrs., it was possible to selectively hydrolyze the 3β-,17β- and 19-acetoxy groups, leaving the 7ξ-acetoxy groups intact. This result is not unexpected since the 7-position is more sterically hindered than the other three positions[3,15]. When the resulting epimeric monoacetates (VIII and IX) were dissolved in chloroform

and left at 5°C for 24 hours, the 7α-monoacetate (VIII) crystallized preferentially and in this manner pure 5-androstene-3β, 7α,17β,19-tetraol 7-acetate(VIII) was obtained albeit in poor yield (14%). The epimeric 5-androstene-3β,7β,17β,19-tetraol 7-acetate (IX) was similarly prepared by selective hydrolysis of 5-androstene-3β,7β,17β,19-tetraol tetraacetate (VII).

The use of lead tetraacetate for the allylic oxidation of Δ^5-steroids has recently been reported[2] and it has been found that substitution also occurs non-stereospecifically giving epimeric mixtures of 7-acetoxy derivatives.

Attempts to functionalize Δ^5-7α-acetoxy steroids at C-19

One of the problems encountered early in our attempts to synthesize 7α,19-disubstituted androgens was the failure of 5α-hydroperoxy-19-substituted androgens to rearrange to give the desired product[1]. This problem might be avoided by rearranging the appropriate 5α-hydroperoxy androgen to the Δ^5-7α-substituted compound and subsequently functionalizing the latter at C-19.

It was hoped to achieve this functionalization at C-19 by preparation of the 5β,6β-epoxide of a Δ^5-7α-acetoxy androgen which could then be opened with HBr to give the appropriate system for making the 6β,19-oxide on reaction with lead tetraacetate[16].

In the epoxidation of allylic alcohols the hydroxyl group has been shown[17] to have a directing effect on the epoxide formed by virtue of an interaction between the peracid, the hydroxyl group and the double bond in the transition state. However, when an acetoxy group is involved, only a steric effect has been observed. Although the major product in the epoxidation of cholesterol with monoperphthalic acid is the 5α,6α-epoxide, a substantial amount[18] of the 5β,6β-epoxide is also formed. It was therefore expected that the presence of a 7α-acetoxy group would significantly increase the proportion of 5β,6β-epoxide.

When 5-cholestene-3β,7α-diol diacetate (XIV, FIGURE 1) was treated with monoperphthalic acid, two epoxides (XVII and XVIII) were isolated, after chromatography, in a ratio of 3:1. The nuclear magnetic resonance spectrum of the low-yield epoxide (XVIII) showed a doublet at δ3.1 with a coupling constant ($J_{6,7}$) of 3.6 Hz while the spectrum of the high-yield epoxide (XVII) showed a doublet at 3.35 with a coupling constant of 4.5 Hz. For C-7 unsubstituted 5,6-epoxides, Cross[19] has reported a larger coupling constant for the α-epoxide. He also observed that the signal for the 6-H occurs at higher field for the α-epoxide. In comparing our data with the above correlations we find that neither epoxide fits the pattern observed by Cross for the 7-unsubstituted 5,6-epoxides.

In 1936 Heilbron and co-workers[7] reported the isolation of only one epoxide after treating 5-cholestene-3β,7α-diol with peracid and acetylating the product. No configurational assignment was made for the epoxide group although it is clear from the foregoing discussion[17] that it must be the 5α,6α-isomer. Since our high-yield epoxide (XVII) has a melting point identical to that of Heilbron's compound and also exhibits an optical rotation which is significantly more levorotatory[19] than that of the low-yield epoxide (XVIII), we have assigned the structures shown in Figure 1 to these compounds. We therefore decided not to continue this approach in view of the low proportion of 5β,6β-epoxide obtained in this reaction.

Reactions with Δ^5-7-oxo steroids

The conventional methods[20] of reducing Δ^5-7-oxo steroids generally lead to the formation of epimeric C-7 alcohols although in some cases[3] (e.g. sodium borohydride) a great preponderance of the 7β-epimer has been obtained. Although our main objective was the synthesis of Δ^5-7α-substituted androgens we were also interested in the preparation of the 7β-isomers in order to investigate their behavior in biological systems. The 7β-substituted compounds (IX, XII, XVI) were easily obtained by sodium borohydride reduction[3] of the appropriate Δ^5-7-oxo steroids.

The application of an indirect method[21] has also been reported for the conversion of Δ^5-7-oxo steroids into either of the C-7 allylic alcohols. More recently Barton, McGhie and Batten[22] have used lead tetraacetate to convert the hydrazone of a 7-oxo B-ring saturated steroid into the corresponding 7α-acetoxy derivative (68%). It was decided to explore the scope of this reaction by using an α,β-unsaturated ketone. In a model experiment the hydrazone of 3β-hydroxy-5-cholesten-7-one acetate (XI) was treated with lead tetraacetate in methylene chloride at 5°C. Nuclear magnetic resonance analysis of the product indicated a 1:1 ratio of epimeric 7-acetates (XIII and XIV). In contrast to the results of Barton et al.[22] the non-stereospecificity of the reaction with our α,β-unsaturated hydrazone may be a consequence of a decrease in steric hindrance around the reaction centre due to the absence of the 6β-hydrogen atom. The C-5, C-6 double bond may also have a profound effect on the type of mechanism[22] involved in this reaction. It is interesting to note that the hydrazone of 3-oxo A-ring saturated steroids also yield epimeric 3-acetates upon reaction with lead tetraacetate[23]. In the latter case the non-stereospecificity of the raction may be attributed to the partial flexibility of the A-ring.

Reactions with Δ^6-5α-hydroxy steroids

As already mentioned[1], we had accumulated substantial amounts of Δ^6-5α-hydroxy steroids and we were interested in exploring how these compounds could be converted to the Δ^5-7α-hydroxy isomers. After failing to effect the allylic rearrangement of our compounds under various conditions in acid media[24], it was decided to attempt to obtain the desired Δ^5-7α-hydroxy derivatives by the sequence XIX → XX → XXI → XXII (FIGURE 2).

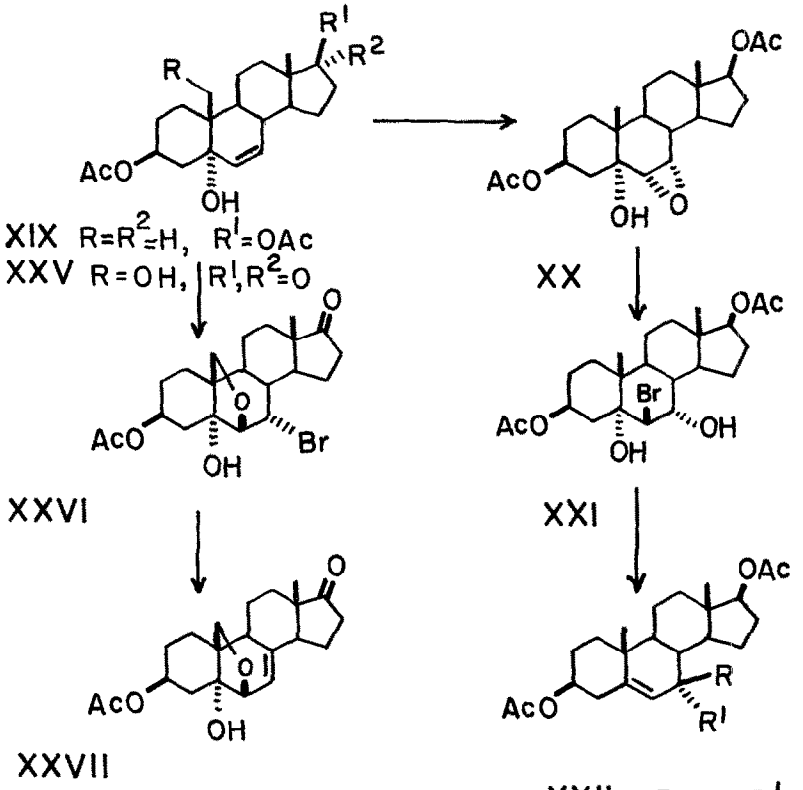

FIGURE 2.

When 5α-androst-6-ene-3β,5,17β-triol 3,17-diacetate (XIX) was treated with monoperphthalic acid, only one product was isolated in 80% yield. This substance was identified as 6α,7α-oxido-5α-androstane-3β,5,17β-triol 3,17-diacetate (XX) on the basis of its elemental analysis and nuclear magnetic resonance spectrum. The latter exhibited an unsymmetrical multiplet in the range δ 2.80-3.00. On the basis of the dihedral angles involved, a symmetrical multiplet would be expected[25] for the relevant protons of the isomeric 6β,7β-epoxide.

When the epoxide (XX) was opened with HBr in chloroform a single product was isolated in 56% yield. Assuming diaxial opening of the epoxide (XX) the product would be expected to be 6β-bromo-5α-androstane-3β,5,7α,17β-tetraol 3,17-diacetate (XXI). The elemental analysis of the latter compound was consistent with a bromohydrin and further evidence for the relative position and configuration of the substituents at C-6 and C-7 was obtained by the synthesis of XXVI for purposes of comparison. 3β,5,19-Trihydroxy-5α-androst-6-en-17-one 3-acetate (XXV) was treated with N-bromosuccinimide[34] in t-butanol and the assigned structure of the resulting bromooxide (XXVI) was confirmed by dehydrobromination with lithium carbonate and lithium chloride in N,N-dimethylformamide to give 3β,5-dihydroxy-6β,19-oxido-5α-androst-7-en-17-one 3-acetate (XXVII). The nuclear magnetic resonance spectrum of the latter compound (XXVII) indicated the presence of an olefinic proton (δ 5.66). Dehydrobromination could not have been achieved if the positions of the oxygen function and

the bromine atom had been reversed since this would have resulted in formation of a double bond at a bridgehead carbon. Furthermore a 7β,19-oxido structure implies a boat conformation for the B-ring. Comparison of the nuclear magnetic resonance spectra of the bromohydrin (XXI) and of the bromooxide (XXVI) (see experimental section) supports the assigned structure of the former compound.

When the bromohydrin (XXI) was reduced with zinc powder in refluxing 80% acetic acid, two products were isolated in a ratio of 9:1. The major product was identified as 5-androstene-3β,7α,17β-triol 3,17-diacetate (XXII). The minor product was shown by nuclear magnetic resonance to be a mixture of the corresponding 7-acetoxy compounds (XXIII and XXIV). It is not known whether the 7α-hydroxy compound (XXII) was formed directly on reduction of the bromohydrin (XXI) or whether it arose as a consequence of allylic rearrangement[1] of the 5α-hydroxy isomer (XIX) which may have been the initial reduction product.

EXPERIMENTAL[26]

5-Cholestene-3β,7β-diol 3-acetate (XII) and 5-cholestene-3β,7β-diol diacetate (XIII). To 5-cholesten-3β-yl acetate (X, 1.0 g, 2.3 mmoles) in glacial acetic acid (2 ml) at 51°C was added, with stirring, chromic anhydride (0.75 g, 7.5 mmoles). The temperature was maintained between 51° and 53° for two hours after which ethanol (10 ml) and water (50 ml) were added and the resulting solution extracted with ether. The ethereal solution was washed with a 10% $NaHCO_3$ solution and water then dried and evaporated. The crude product (800 mg) was crystallized twice from methanol yielding 3β-hydroxy-5-cholesten-7-one acetate (XI, 600 mg): mp 163-164° (lit[9] mp 164°).

To 3β-hydroxy-5-cholesten-7-one acetate (XI, 500 mg, 1.1 mmoles) in ethanol (25 ml) was added a solution of sodium borohydride (20 mg) in water (1.0 ml) and the mixture was stirred at room temperature for 16 hours. After the addition of water (25 ml) the mixture was filtered and the precipitate was dried in the air. The dry precipitate was crystallized from acetone yielding 5-cholestene-3β,7β-diol (XII, 400 mg): mp 109-112° (lit[27] mp 110-111°); nmr (60 Mc, $CDCl_3$) δ 0.70 (13-CH_3, s), 2.00 (3-OAc, s, 3H), 3.81 (7α-H, m, 1H), 4.60 (3α-H, m, 1H), 5.30 (6-H, d, 1H, J=2.0 Hz).

The latter product was acetylated with acetic anhydride in pyridine. The usual workup followed by crystallization of the product three times from methanol afforded 5-cholestene-3β,7β-diol diacetate (XIII): mp 109-110° (lit[28] mp 108-110°); nmr (100 Mc, $CDCl_3$) δ 0.64 (13-CH_3, s), 1.02 (10-CH_3, s), 1.99 (3, 7-OAc, s, 6H), 4.60 (3α-H, m, 1H), 5.02 (7α-H, d, 1H), 5.23 (6-H, d, 1H, J=2.0 Hz).

5-Cholestene-3β,7α,19-triol triacetate (XV) and 5-cholestene-3β,7β,19-triol triacetate (XVI). 5-Cholestene-3β,7α,19-triol 3-acetate[1] was acetylated with acetic anhydride in pyridine. The usual workup afforded as an oil 5-cholestene-3β,7α,19-triol triacetate (XV): $[\alpha]_D$ -206°; nmr (100 Mc, $CDCl_3$) δ 0.70 (13-CH_3, s), 2.03 (3,7,19-OAc, s, 9H), 3.89, 4.01, 4.54, 4.66 (10-CH_2-, q, 2H), 4.65 (3α-H, m, 1H), 5.01 (7β-H, t, 1H), 5.84 (6-H, d, 1H, J=5.0 Hz).

5-Cholestene-3β,19-diol 3-acetate[29] (XXVIII) was acetylated with acetic anhydride in pyridine and the usual workup afforded as an oil 5-cholestene-3β,19-diol diacetate (XXIX): $[\alpha]_D$ -54°; nmr (60 Mc, $CDCl_3$) δ 0.70 (13-CH_3, s), 2.01 (3, 19-OAc, s, 6H), 3.86, 4.06, 4.38, 4.58 (10-CH_2-, q, 2H), 4.62 (3α-H, m, 1H), 5.63 (6-H, d, 1H).

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.38; H, 10.28.

To the diacetate (XXIX, 500 mg, 1 mmole) in glacial acetic acid (4 ml) at 51°C was added, with stirring, chromic anhydride (0.38 g, 3.8 mmoles). The temperature was maintained between 51° and 53° for two hours. After the workup, as described earlier, the residue (386 mg) was chromatographed on SilicaR (10 g) with benzene as the eluent. The chromatography afforded as an oil 3β,19-dihydroxy-5-cholesten-7-one diacetate (XXX, 200 mg); ir ($CHCl_3$) ν_{max} 1680 (α,β-unsaturated carbonyl) 1730 cm^{-1} (ester carbonyl); nmr (100 Mc, $CDCl_3$) δ 0.72(13-CH_3, s, 3H), 2.00 (3, 19-OAc, s, 6H), 4.04, 4.17, 4.64, 4.76 (10-CH_2-, q, 2H), 4.62 (3α-H, m, 1H), 5.88 (6-H, s, 1H).

Anal. Calcd. for $C_{31}H_{48}O_5$: C, 74.38; H, 9.66. Found: C, 73.85; H, 9.60.

The above ketone (XXX, 160 mg) and lithium aluminum hydride (0.08 g) in anhydrous ether (30 ml) was stirred and refluxed for 2 hours. The excess hydride was destroyed by the addition of methanol and water and the mixture was filtered and the filtrate evaporated to dryness. The crude product was acetylated with acetic anhydride in pyridine and the usual workup afforded as an oil 5-cholestene-3β,7β,19-triol triacetate (XVI, 67 mg): $[\alpha]_D$ -8.2°; nmr (100 Mc, $CDCl_3$) δ 0.73 (13-CH_3, s, 3H), 2.02, 2.08 (3,7,19-OAc, s, s, 9H), 3.89, 4.01, 4.55, 4.67 (10-CH_2-, q, 2H), 4.62 (3α-H, m, 1H), 5.00 (7α-H, d, 1H), 5.50 (6-H, d, 1H, J=2.0 Hz).

Reaction of 3β,19-dihydroxy-5-androsten-17-one diacetate(I) with t-butylperbenzoate.- 3β,19-Dihydroxy-5-androsten-17-one diacetate[30](I, 800 mg, 2.0 mmoles) and cuprous bromide (0.25 g) in acetic acid (15 ml) were heated with stirring under a nitrogen atmosphere to reflux temperature. A solution of t-butylperbenzoate[31] (4.0 ml) in acetic acid (15 ml) was added dropwise over a period of 20 min and the mixture was maintained at reflux temperature for an additional 20 min. The mixture was then poured into benzene (50 ml) and the two phases were intimately mixed and then filtered. The benzene solution was separated and washed with a 5% Na_2CO_3 solution and water, then dried and evaporated. Chromatography of the residue (830 mg) on SilicaR (100 g) with ether-benzene (1:20) as the eluent afforded starting material (I, 250 mg). Further elution yielded an oil identified as an epimeric mixture of the 7-acetates (II and III, 360 mg): nmr (100 Mc, $CDCl_3$) δ 0.90 (13-CH_3, doublet due to mixture), 3.85, 3.97, 4.62, 4.74 (10-CH_2-, q), 4.69 (3α-H, m), 5.16 (7ξ-H, m), 5.52 (6-H, d, J=2.0 Hz), 5.87 (6-H, d, J=5.0 Hz). Further elution yielded a compound identified as 3β,19-dihydroxy-5-androstene-7,17-dione diacetate (61 mg): mp 160-161°; ir ($CHCl_3$) ν_{max} 1730 (ester carbonyl), 1670 cm^{-1} (α,β-unsaturated carbonyl); nmr (100 Mc, $CDCl_3$) δ 0.90 (13-CH_3, s, 3H), 2.02 (3,19-OAc, s, 6H), 4.02, 4.14, 4.72, 4.84 (10-CH_2-, q, 2H), 4.70 (3α-H, m, 1H), 5.92 (6-H, s, 1H). Mixed melting point with ketone (IV) prepared below: 160-161°.

Preparation of 3β,19-dihydroxy-5-androstene-7,17-dione diacetate (IV). To 3β,19-dihydroxy-5-androsten-17-one diacetate (I, 800 mg, 2.0 mmoles) in glacial acetic acid (4 ml) at 51°C was added chromic anhydride (0.60 g, 6 mmoles). The reaction was carried out as previously described and after the usual workup the residue (500 mg) was chromatographed on SilicaR (50 g) with ether-benzene (1:20) as the eluent. The chromatography afforded starting material (I, 110 mg) and 3β,19-dihydroxy-5-androstene-7,17-dione diacetate (IV, 340 mg): mp 160-161°; $[\alpha]_D$ -125°. The nmr spectrum of this compound was identical to that of the ketone isolated by reaction of I with t-butylperbenzoate (see above).

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68,63; H, 7.51. Found: C, 67.96; H, 7.64.

Reaction of 5-androstene-3β,17β,19-triol triacetate (V) with t-butylperbenzoate. 5-Androstene-3β,17β,19-triol triacetate[32] (V, 3.5 g, 8.0 mmoles) and cuprous bromide (1.0 g) in acetic acid (75 ml) were heated to reflux temperature with vigorous stirring under a nitrogen atmosphere. A solution of t-butylperbenzoate (20 ml) in acetic acid (80 ml) was added to the reaction mixture dropwise over a period of 45 min and reflux temperature was maintained for an additional 30 min. After the usual workup as described earlier, the crude product (3.0 g) was chromatographed on SilicaR (230 g) with ether-benzene (1:33) as the eluent. The chromatographic separation afforded starting material (V, 1.0 g) and an oil identified as an epimeric mixture of the 7-acetates (VI and VII, 1.39 g): nmr (100 Mc, $CDCl_3$) δ 0.80 (13-CH_3, s), 2.00 (3,7,17,19-OAc), 3.88, 4.00, 4.58, 4.70 (10-CH_2-, q), 4.68 (3α-,17α-H, m), 5.03 (7β-H, t), 5.18 (7α-H, d), 5.55 (6-H, d), 5.86 (6-H, d, J=5.0 Hz). The mixture was inseparable using SilicaR or alumina as adsorbants.

5-Androstene-3β,7α,17β,19-tetraol 7-acetate (VIII) and 5-androstene-3β,7β,17β,19-tetraol 7-acetate (IX). To an epimeric mixture of 5-androstene-3β,7ξ,17β,19-tetraol tetraacetate (VI and VII, 800 mg) in methanol (250 ml) was added a solution of Na_2CO_3 (500 mg) in water (5 ml) and this mixture was stirred at room temperature for 24 hours. The solution was neutralized by the addition of dilute acetic acid. Water (50 ml) was added and the solution was evaporated to half volume and extracted with ether (3 x 100 ml). After washing (H_2O) and drying the combined extracts the ether was evaporated and the residue was dissolved in hot chloroform and then allowed to stand at 4°C for 20 hours. The mixture was filtered and the precipitate was crystallized from chloroform yielding a single compound identified as 5-androstene-3β,7α,17β,19-tetraol 7-acetate (VIII, 88 mg): mp 165-167°; $[\alpha]_D$ -185°; ir(salts) ν_{max} 3450 (free-OH), 3340 (bonded-OH), 1720 cm^{-1} (ester carbonyl); nmr (60 Mc, $CDCl_3$ + DMSO) δ 0.80 (13-CH_3, s, 3H), 2.01 (7-OAc, s, 3H), 4.98 (7β-H, t, 1H), 5.78 (6-H, d, 1H, J=5.0 Hz).

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.20 H, 8.85. Found: C, 69.39; H, 8.84.

The above triol (VIII) was acetylated with acetic anhydride in pyridine yielding, after the usual workyp, 5-androstene-3β,7α,17β,19-tetraol tetraacetate (VI) as an oil: $[\alpha]_D$ -161°; nmr (100 Mc, $CDCl_3$), δ 0.80 (13-CH_3, s, 3H), 2.00 (3,7,17,19-OAc, s, 12H), 3.88, 4.00, 4.58, 4.70 (10-CH_2-, q, 2H), 4.68 (3α-,17α-H, m, 2H), 5.03 (7β-H, t, 1H), 5.86 (6-H, d, 1H, J-5.5 Hz).

To 5-androstene-3β,17β,19-triol triacetate (V, 1.0 g, 2.3 mmoles) in glacial acetic acid (5.5 ml) at 51°C was added chromic anhydride (0.75 g, 7.5 mmoles) over a period of 1 hour. The temperature of the mixture was maintained between 51° and 53° for 2 hours. After the usual workup the residue (600 mg) was chromatographed on SilicaR (50 g) with ether-benzene (1:14) as the eluent. Chromatography afforded, as an oil, a compound identified as 3β,17β,19-trihydroxy-5-androsten-7-one triacetate (XXXI), 400 mg): $[\alpha]_D$ -107°; ir ($CHCl_3$) ν_{max} 1730 (ester carbonyl), 1670 cm^{-1} (α,β-unsaturated carbonyl); nmr (60 Mc, $CDCl_3$) δ 0.80 (13-CH_3, s, 3H), 2.00 (3,17,19-OAc, s, 9H), 4.00, 4.20, 4.63, 4.83 (10-CH_2-, q, 2H), 5.90 (6-H, s, 1H).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.15; H, 7.67.

The above ketone (XXXI, 400 mg, 0.9 mmoles) in absolute ethanol (25 ml) and sodium borohydride (120 mg) were stirred at room temperature for 24 hours. Water (20 ml) was added and the mixture was extracted with chloroform. After drying and evaporating the chloroform the crude product was acetylated with acetic anhydride in pyridine. The usual workup afforded, as an oil, a compound identified as 5-androstene-3β,7β,17β,19-tetraol tetraacetate (VII, 220 mg): $[\alpha]_D$ -41°; nmr (60 Mc, $CDCl_3$) δ 0.95 (13-CH_3, s, 3H), 2.04 (3,7,17,19-OAc, 12H), 3.78, 3.98, 4.54, 4.74 (10-CH_2-, q, 2H), 4.60 (3α,17α-H, m, 2H), 5.00 (7α-H, d, 1H), 5.50 (6-H, d, 1H, J=2.0 Hz).

To the above tetraacetate (VII, 200 mg) in methanol (50 ml) was added a solution of Na_2CO_3 (100 mg) in water (1 ml) and the mixture was stirred at room temperature for 24 hours. The solution was neutralized with dilute acetic acid, and extracted with chloroform and the solution was evaporated to a volume of approximately 20 ml and allowed to stand at 4°C for 20 hours. The crystals which precipitated were collected by filtration and recrystallized twice from chloroform, affording a single material identified as 5-androstene-3β,7β,17β,19-tetraol 7-acetate (IX, 32 mg): mp 194-195°; $[\alpha]_D$ +65°; nmr (60 Mc, $CDCl_3$ + DMSO) δ 0.77 (13-CH_3, s, 3H), 1.99 (7-OAc, s, 3H), 4.90 (7α-H, d, 1H), 5.32 (6-H, d, 1H, J=2.0 Hz).

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.17; H, 8.74.

Reaction of 5-cholestene-3β,7α-diol diacetate (XIV) with monoperphthalic acid. 5-Cholestene-3β,7α-diol diacetate (XIV, 100 mg) was dissolved in a solution of monoperphthalic acid in ether (10 ml, 1.0 M) and the mixture was kept at 5°C for 24 hours. The acid was removed by passing the mixture through a Florisil column (50 g) with ether as the eluent. The phthalic acid-free product (100 mg) was then chromatographed on SilicaR (15 g) with benzene as the eluent. The first compound eluted was identified as starting material (XIV,

23 mg). Further elution yielded, as an oil, a compound identified as 5,6β-oxido-5β-cholestane-3β,7α-diol diacetate (XVIII, 15 mg): $[\alpha]_D$ +3°; nmr (60 Mc, $CDCl_3$) δ 2.01, 2.07 (3,7-OAc), 3.10 (6α-H, d, 1H, J=3.6 Hz), 4.74 (3α-H, m, 1H), 5.18 (7β-H, m, 1H). Further elution afforded a compound identified as 5,6α-oxido-5α-cholestane-3β,7α-diol diacetate (XVII, 50 mg): mp 203-204°; $[\alpha]_D$ -125°; nmr (60 Mc, $CDCl_3$) δ 2.02, 2.10 (3,7-OAc), 3.35 (6β-H, d, 1H, J=4.5 Hz), 5.0 (7β,3α-H, m, 2H).

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03; Found: C, 74.07; H, 10.12.

Reaction of the hydrazone of 3β-hydroxy-5-cholesten-7-one acetate (XI) with lead tetraacetate.- A mixture of 3β-hydroxy-5-cholesten-7-one acetate (XI, 1.0 g) and hydrazine hydrate (0.5 ml) in ethanol (25 ml) was refluxed for 2 hours. The solvent was evaporated and the crude hydrazone was dried in vacuo for 24 hours. A solution of lead tetraacetate (600 mg) in methylene chloride (20 ml) was cooled to 5°C and a solution of the crude hydrazone (650 mg) in methylene chloride (25 ml) was added dropwise over a period of 30 min. The mixture was allowed to warm to room temperature and water (20 ml) was added and the mixture filtered. The organic layer was separated and washed with $NaHCO_3$ solution and water, then dried and evaporated. The residue (650 mg) was chromatographed on SilicaR (100 g) with benzene as the eluent. The first fraction eluted was a mixture (60 mg) which was not identified. Further elution yielded a component (350 mg) identified as 1:1 mixture of the 7-acetoxy derivatives of 5-cholesten-3β-yl acetate (X): nmr(60 Mc, $CDCl_3$) δ 5.30(6-H, d, J=2.0 Hz), 5.62(6-H, d, J=5.0 Hz). Both signals had the same integral value. A third component eluted was identified as 3β-hydroxy-5-cholesten-7-one acetate (XI, 220 mg) which was part of the original crude hydrazone.

6α,7α-oxido-5α-androstane-3β,5,17β-triol 3,17-diacetate (XX). - 5α-Androst-6-ene-3β,5,17 -triol 3,17-diacetate (XIX, 1.0 g) was treated with a solution of monoperphthalic acid in ether (50 ml, 1.0 M) for 24 hours at room temperature. The mixture was poured onto a Florisil column (200 g) and the acid-free products were eluted with ether. After evaporation of the ether the crude material was crystallized from ether-petroleum ether (bp 30-60°) which afforded a compound identified as 6α,7α-oxido-5α-androstane-3β,5,17β-triol 3,17-diacetate (XX, 800 mg): mp 201.5-202°; $[\alpha]_D \simeq 0°$; nmr (60 Mc, $CDCl_3$) δ 0.82 (13-CH_3, s), 0.88 (10-CH_3, s), 2.02 (3, 17-OAc, s, 6H), 2.93 (6β-,7β-H, d, 2H), 3.01 (5-OH, b, 1H), 4.60 (17α-H, m, 1H), 5.20 (3α-H, m, 1H).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.07; H, 8.37.

6β-Bromo-5α-androstane-3β,5,7α,17β-tetraol 3,17-diacetate (XXI). The epoxide (XX, 300 mg) in chloroform (20 ml) and 50% HBr (9.0 ml) were vigorously stirred at room temperature for 5 hours. A solution of $NaHCO_3$ was added and the organic layer was separated, washed with water, then dried and evaporated. The residue was crystallized from ether-petroleum ether (bp 30-60°) affording a compound identified as 6β-bromo-5α-androstane-3β,5,7α,17β-tetraol 3,17-diacetate (XXI, 200mg) mp 167-171°; $[\alpha]_D$ -68°; nmr (60 Mc, $CDCl_3$) δ 3.60 (5-,7-OH, b, 2H), 4.03 (6α,7β-H, m, 2H), 4.62 (17α-H, m, 1H), 5.05 (3α-H, m, 1H).

Anal. Calcd. for $C_{23}H_{35}O_6Br$: C, 56.67; H, 7.23; Br, 16.80. Found: C, 56.12; H, 7.08; Br, 16.51.

Reaction of bromohydrin (XXI) with zinc in acedic acid[33]. - The bromohydrin (XXI, 150 mg) and zinc powder (2.0 g) in 80% acetic acid (10 ml) were heated to reflux for 3 hours. The mixture was filtered through celite and water (10 ml) was added to the filtrate. The filtrate was then extracted with ether and the ethereal solution was washed with a $NaHCO_3$ solution and water, then dried and evaporated. The residue (123 mg) was chromatographed on SilicaR (10g) with ether-benzene (1:9) as the eluent. The chromatography afforded a mixture (18 mg) of the 7-acetoxy derivatives of 5-androstene-3β,17β-diol diacetate (XXIII and XXIV) and 5-androstene-3β,7α,17β-triol 3,17-diacetate (XXII, 100 mg): mp 170-171°(lit[1] mp 170-171°).

7α- Bromo-3β,5-dihydroxy-6β,19-oxido-5α-androstan-17-one 3-acetate (XXVI) and 3β,5-dihydroxy-6β,19-oxido-5α-androst-7-en-17-one 3-acetate (XXVII). - 3β,5,19-Trihydroxy-5α-androst-6-en-17-one 3-acetate (XXV, 100 mg) and N-bromoacetamide[34] (160 mg) in t-butyl alcohol (5.0 ml) and water (2.0 ml) were stirred at room temperature for 5 min. After the addition of $NaHSO_3$ (0.1 g) and water (10 ml) the mixture was extracted with ether and the ethereal solution was dried and evaporated. Trituration of the residue with ether or acetone afforded crystals which were identified as 7α-bromo-3β,5-dihydroxy-6β,19-oxido-5α-androstan-17-one 3-acetate (XXVI, 80 mg): mp 208-209°; $[\alpha]_D$ -24°; ir ($CHCl_3$) ν_{max} 3540 (free-OH), 1720 cm^{-1} (ester carbonyl); nmr (60 Mc, $CDCl_3$) δ 0.95 (13-CH_3, s, 3H), 2.00 (3-OAc, s, 3H), 3.62, 3.80, 3.84, 4.02 (10-CH_2-, q, 2H), 3.90 (6α-H, 1H), 4.24 (7β-H, t, 1H), 5.02 (3α-H, m, 1H).

Anal. Calcd. for $C_{21}H_{29}O_5Br$: C, 57.13; H, 6.63; Br, 18.11. Found: C, 57.05; H, 6.64; Br, 17.86.

A mixture of the above bromooxide (XXVI, 50 mg), lithium carbonate (50 mg) and lithium chloride (25 mg) in N,N-dimethylformamide (5 ml) was refluxed for 3 hours. Water (10 ml) was added and the mixture was extracted with ether. The ethereal solution was dried and evaporated and the residue was triturated with ether affording a crystalline compound identified as 3β,5-dihydroxy-6β,19-oxido-5α-androst-7-en-17-one 3-acetate (XXVII, 30 mg): mp 212-214°;

$[\alpha]_D$ + 49.6°; nmr (60 Mc, $CDCl_3$) δ 0.92 (13-CH_3, s, 3H), 2.10 (3-OAc, s, 3H), 3.90 (6α-H, d, 1H), 4.02 (10-CH_2-, s, 2H), 5.06 (3α-H, m, 1H), 5.66 (7-H, d, 1H, J=5.5 Hz).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.04; H, 7.86.

ACKNOWLEDGEMENT

The authors are grateful to the National Research Council of Canada for financial support.

REFERENCES

1. For Part V, see preceding paper.
2. Stefanović, M., Jokić, A., Maksimović, Z., Lorenc, Lj. and Mihailović, M.Lj., HELV.CHIM.ACTA, 53, 1895 (1970).
3. Shoppee, C.W. and Newman, B.C., J.CHEM.SOC. (C), 981 (1968).
4. Stárka, L., COLL.CZECH.CHEM.COMM. 26, 2452 (1961).
5. Henbest, H.B., and Jones,E.R.H., J.CHEM.SOC.,1792 (1948).
6. Dodson, R.M., Nicholson, R.T. and Muir, R.D., J.AM.CHEM.SOC., 81, 6295 (1959).
7. Barr, T., Heilbron, I.M., Parry, E.G., and Spring, F.S., J.CHEM.SOC., 1437 (1936).
8. Lythgoe, B. and Trippett, S., J.CHEM.SOC., 471 (1959).
9. Fieser, L.F., Fieser, M. and Chakravarty, R.N., J.AM.CHEM. SOC., 71, 2226 (1949).
10. Fieser, L.F., and Fieser, M., STEROIDS, Reinhold Publishing Corp., New York, 1959, p. 161.
11. Karplus, M., J.CHEM.PHYS., 30, 11 (1959).
12. Morand, P. and Van Tongerloo, A., CHEM.COMM., 7, (1972).
13. Beckwith, A.L.J. and Evans, G.W., PROC.CHEM.SOC., 63 (1962).
14. Kharasch, M.S., Sosnovsky, G. and Yang, N.C., J.AM.CHEM. SOC., 81, 5819 (1959).
15. Loewenthal, H.J.E., TETRAHEDRON, 26, 269 (1959).
16. Wehrli, M., Heller, M.S., Schaffner, K. and Jeger, O., HELV. CHIM.ACTA , 44, 2162 (1961).
17. Henbest, H.B. and Wilson, R.A.L., J.CHEM.SOC., 1958 (1957).
18. Fieser, L.F. and Fieser, M., REAGENTS FOR ORGANIC SYNTHESIS, John Wiley and Sons, Inc., New York, 1967, p. 136.

19. Cross, A.D., J.AM.CHEM.SOC., 84. 3206 (1962).

20. See ref. 9, pp. 153-163.

21. Shoppee, C.W., Cremlyn, R.J.W., Evans, D.E. and Summers, G.H.R., J.CHEM.SOC., 4364 (1957).

22. Barton, D.H.R., McGhie, J.F., and Batten, P.L., J.CHEM.SOC. (C), 1033 (1970).

23. Debono, M. and Molloy, R.M., J.ORG.CHEM., 34, 1456 (1969).

24. Cf. Schenck, G.O., and Neumüller, O.A., ANN., 618, 194 (1958); de la Mare, P.B.D., MOLECULAR REARRANGEMENTS, Vol. 1, Editor P. de Mayo, Interscience Publishers, New York, 1963, pp. 30-86.

25. Tori, K., Komeno, T., and Nakagawa, T., J.ORG.CHEM., 29, 1136 (1964).

26. All melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-20 instrument with chloroform as the solvent. Nuclear magnetic resonance spectra were obtained from Varian H-4302-T-60 and Varian H-100 instruments with chloroform-d as the solvent and tetramethylsilane as the internal standard. Optical rotations were obtained on a Perkin-Elmer 141 automatic polarimeter with chloroform as the solvent. For column chromatography an L.K.B.-3400 fraction collector was used and SilicaR 200-325 mesh was the adsorbant. Microanalyses were done by Alfred Bernhardt, Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany, and by G. Daessle, Organic Microanalyses, Montreal, Canada.

27. Henbest, H.B. and Jones, E.R.H., J.CHEM.SOC., 1798 (1948).

28. Ruzicka, L., Prelog, V. and Tagman, E., HELV.CHIM.ACTA, 27, 1149 (1944).

29. Moriarty, R.M., and D'Silva, T.D.J., TETRAHEDRON, 21, 547 (1965).

30. Kalvoda, J., Heusler, K., Ueberwasser, H., Anner, G., and Wettstein, A., HELV.CHIM.ACTA, 46, 1361 (1963).

31. Milas, N.A. and Surgenor, D.M., J.AM.CHEM.SOC., 68, 642 (1946).

32. Bagli, J.F., U.S. Patent, 3,162,655. CA.,62, 16330d (1965).

33. The products of this experiment were identified by nuclear magnetic resonance and by comparison of their mobilities on thin layer chromatographic plates with authentic samples.

34. Cf. Bagli, J.F., Morand, P. and Gaudry, R., J.ORG.CHEM., 28, 1207 (1963).