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STEROIDS—LXXVIII

THE LEAD TETRAACETATE OXIDATION OF A 5-HYDROXY-B-NORSTEROID[1,2]

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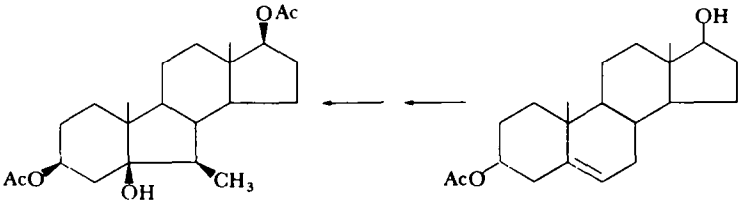
Abstract—The lead tetraacetate oxidation of the tertiary alcohol **1** gives rise to two products, **3a** and **4a**, which contain a transannular oxide bridge. These structures are determined by analytical and spectral properties and by two independent chemical interconversions. The stereochemistry can be deduced from these reactions. Two possible mechanisms for the formation of the products are presented.

ALTHOUGH the reaction of primary and secondary alcohols with lead tetraacetate has been studied extensively by numerous workers, there have been relatively few fundamental studies carried out which describe the scope and mechanism of the oxidation of tertiary alcohols with this reagent. We have recently carried out the oxidation of a steroidal tertiary alcohol with lead tetraacetate and wish to report on some unusual features of this reaction.

The compound on which we based our studies was the B-norsteroid 6β-methyl-B-nor-5β-androstane-3β,5β,17β-triol, 3,17-diacetate (**1**) which was prepared from 5-androstene-3β,17β-diol, 3-acetate (**2**) in 54% overall yield by a seven step synthesis.[4]



1 **2**

The oxidation of **1** was carried out in anhydrous benzene at reflux in the presence of calcium carbonate and a large excess of lead tetraacetate for 40 hr. Chromatography

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[2] Presented, in part, at the 151st meeting of the American Chemical Society, Pittsburgh, Pennsylvania, March, 1966. A preliminary account of some of this work appeared in the previous paper of this series, D. Rosenthal, C. F. Lefler and M. E. Wall, *Tetrahedron Letters* 3203 (1965).

[3] To whom inquiries should be directed.

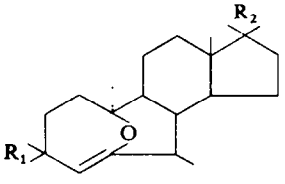
[4] [a] M. E. Wall and F. T. Ross, Abstracts of the Second International Congress on Hormonal Steroids, Milan, Italy, May, 1966, p. 229; [b] K. Tanabe and R. Takasaki, *Japanese Patent* 10,928; *Chem. Abstr.* **61**, 12063 (1964); [c] K. Tanabe, R. Hayashi and R. Takasaki, *Chem. Pharm. Bull. Tokyo*, **9**, 1, 7, 12 (1961).

of the reaction product on alumina yielded a small amount of benzyl acetate,[5] two principal products, **3a** and **4a**, and other more highly polar products not present prior to chromatography, which presumably arose by hydrolysis on the column.

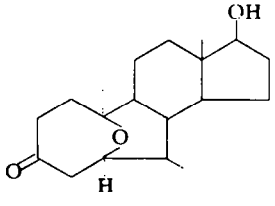
Compound **3a**, the first major product eluted, was obtained in 40% yield, and analyzed for $C_{23}H_{34}O_5$, a dehydro derivative of the starting material **1**. The IR spectrum was devoid of hydroxyl absorption and showed characteristic acetate bands at 1240 and 1730 cm^{-1}, as well as a strong double bond peak at 1675 cm^{-1}. These assignments were confirmed by the NMR spectrum which showed a 6 proton singlet at 7·95 τ (acetate methyl) and a sharp peak at 4·66 τ (one vinyl H) overlapping the C-3 proton multiplet.

Mild alkaline hydrolysis of **3a** yielded a *carbonyl free* diol **3b**, $C_{19}H_{30}O_3$, which could be reconverted to **3a** by acetylation. Four of the five oxygen atoms of **3a** were thereby accounted for as a diacetate. The fifth oxygen atom had to be contained in an ether linkage. In combination with the strong high frequency band at 1675 cm^{-1}, this suggested the presence of an enol ether grouping. One of the hydroxyl groups in **3b** was shown to be allylic to the double bond, since this compound was smoothly and selectively oxidized with manganese dioxide to a hydroxy α,β-unsaturated ketone **3c**. The conjugated ketone **3c** (λ_{max} 244 mμ, ε = 11,800) was readily hydrogenated to give the saturated dihydro product **5**. Further oxidation of **3c** with chromic acid-pyridine yielded the diketone **3d**. The latter could also be prepared directly from **3b** with chromium trioxide-pyridine.

Based on the reactions thus far presented we were able tentatively to formulate the structures **3a–d** as indicated below.[6]



3a R_1 = β-OAc, H R_2 = β-OAc, H
3b R_1 = βOH, H, R_2 = β-OH, H
3c R_1 = =O R_2 = β-OH, H
3d R_1 = =O R_2 = =O



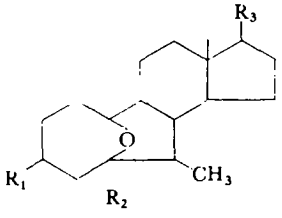
5

The second major and more polar component (compound **4a**) of the oxidation reaction mixture was obtained in 25% yield. Elemental analysis indicated the formula $C_{25}H_{38}O_7$, corresponding to **3a** plus the elements of acetic acid. Compound **4a** showed no hydroxyl band in the IR and contained no double bonds, as indicated by the IR and NMR spectra. The substance was shown to be a triacetate, since alkaline hydrolysis converted it to a triol $C_{19}H_{32}O_4$. This triol, **4b**, showed no carbonyl

[5] Benzyl acetate has been isolated previously [E. L. Fieser, R. C. Clapp and W. H. Daudt, *J. Am. Chem. Soc.* **64**, 2052 (1942)] in lead tetraacetate oxidations and its presence can be attributed to the attack of solvent benzene by the oxidant.

[6] In order to avoid duplication of figures, all structural formulas are drawn in full stereochemical detail in conformity with the conclusions and notational conventions which will be detailed and explained in the section *Stereochemistry*.

absorption in the IR, indicating that the seventh oxygen atom in **4a** was ether linked. Two hydroxyl groups of the triol **4b** were secondary while the third hydroxyl function was tertiary. This could be seen from the appropriate NMR bands in **4a**, **4b**, and in the diacetate **4c**, which was formed on overnight acetylation of **4b** at room temperature in acetic anhydride-pyridine. The tertiary acetate in **4a** was especially labile toward acid hydrolysis and could be converted selectively to a hydroxy-diacetate by heating at reflux with 0·02N sulfuric acid in acetone–water (70:30) at 56° for 5 hr. This product was identical with the diacetate **4c** prepared from triol **4b**.



4a $R_1 = R_2 = R_3 = OAc$
4b $R_1 = R_2 = R_3 = OH$
4c $R_1 = R_3 = OAc$
$R_2 = OH$
4d $R_1 = OH, R_2 = R_3 = OAc$
4e $R_1 = R_2 = OAc; R_3 = OH$
4f $R_1 = H, R_2 = OH, R_3 = OAc$

The lability of the tertiary acetoxy group in compound **4a** toward acid catalyzed solvolysis suggested its possible formulation as a hemiketal acetate. This formulation corresponds to the formal addition of acetic acid to the enol ether double bond of **3a**.

The NMR spectra of compounds **4a–c** supported the proposed formulation. The C-6 methyl doublet ($J = 6$) appeared at 9·06 τ in **4b** and **4c**. The acetate methyl groups in **4a** were distinct from one another at 7·90, 7·95 and 7·97 τ. In addition, a one proton signal was observed in **4a** at 6·45 τ as a clearly defined doublet of doublets with coupling constants of 6·5 and 17·5 c/s. This observation was confirmed in a 100 Mc/s spectrum. In the case of **4b** and **4c** this proton signal was shifted upfield to 7·56 and 7·50 τ, respectively. Although the exact assignment of this signal is not certain, we believe that it is attributable to the 4β-hydrogen which is deshielded strongly by the surrounding three oxygen atoms attached to the neighboring carbon atoms. The observed coupling constants are consistent with a vicinal coupling with the C-3 proton and with a geminal coupling.

Further confirmation of structure **4a** was obtained by comparison of the methyl resonances in the starting material **1** with the diacetate **4c**. These compounds differ only by the presence of an additional oxygen atom between positions 5 and 10 in **4c**. The C-19 and the 6β-methyl groups of **1** absorb at 9·10 and 9·06 τ respectively. In the oxide **4c** these absorptions occur at 8·84 and 9·04 τ. We see, then, that the C-19 methyl group is deshielded by 0·26 ppm while the 6β-methyl doublet is deshielded by only 0·02 ppm, which is consistent with the fact that the newly introduced oxide is one carbon atom farther removed from the 6β-methyl group than from C-19 methyl group. This evidence, along with the absence of any unaccounted for protons on carbon atoms bearing oxygen, precludes the presence of an ether bridge between C-5 and C-6 in **4c**.

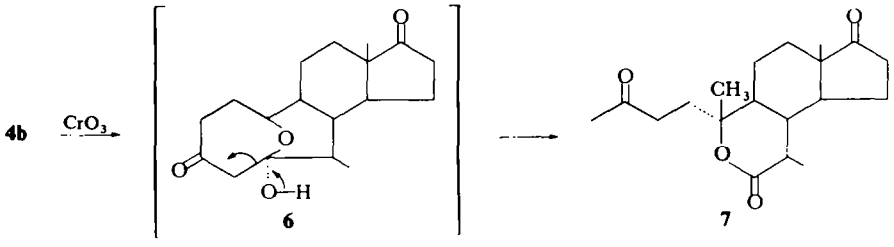
In view of the simple relationship proposed between the two major oxidation products **3a** and **4a**, we attempted their chemical interconversion. The direct elimination of the tertiary acetate to the olefin by pyrolysis of **4a** was tried first. Elimination occurred readily at 200°. However, the reaction invariably gave a complex mixture of

products. Since we could not achieve a definite identification of any of the products, we turned to other approaches, and eventually found two other methods to interrelate our two series.

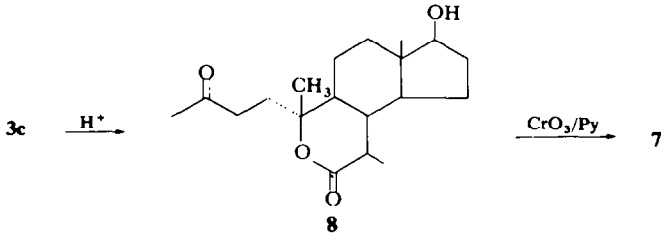
Since the acetate at C-5 in the triacetate **4a** did not spontaneously eliminate in the desired direction in good yield, it was hoped that this could be accomplished in the 3-keto series which would direct the elimination reaction towards the conjugated Δ^4 position. Careful saponification of **4a** with limited quantities of base in an attempt to synthesize the free 3β-ol, **4d**, did in fact allow the isolation in fair yield of a hydroxy diacetate; however, the NMR spectrum showed conclusively that the acetoxy group which had been removed selectively was at C-17, and our product was compound **4e**.

Oxidation of the triol **4b** with chromic acid-pyridine gave, in good yield, a new substance, $C_{19}H_{28}O_4$. This product showed no hydroxyl group in the IR but three carbonyl bands at 1722, 1727 and 1745 cm^{-1}. The compound was insoluble in aqueous base but dissolved on warming, suggesting the presence of a lactone. The compound also gave a positive iodoform reaction. Selective reduction of the ketone groups with lithium tri-t-butoxyaluminohydride gave a mixture of lactone alcohols absorbing at 1730 cm^{-1}.

These data can be interpreted as being due to methyl ketone, δ-lactone and cyclopentanone functions. The NMR spectrum confirmed these suppositions, showing a sharp peak at 7·83 τ ($\underline{CH_3}$—C(=O)—) as well as the expected pattern of two singlet (8·65, 9·06 τ) and one doublet (8·58 τ, $J = 7$) methyl groups. We therefore believe that the structure of the new compound is **7**, derived by the reverse aldol reaction on the unstable intermediate **6**.



To our satisfaction, we were able to obtain the identical diketolactone from our enol ether series. When the manganese dioxide oxidation product **3c** was hydrolyzed under mild acid conditons, the hydroxy-ketolactone **8** was formed, presumably by the hydration of the enol ether to the hemiketal, followed by an acid catalyzed reverse aldol reaction. The hydroxy-ketolactone, in our hands, did not crystallize and was

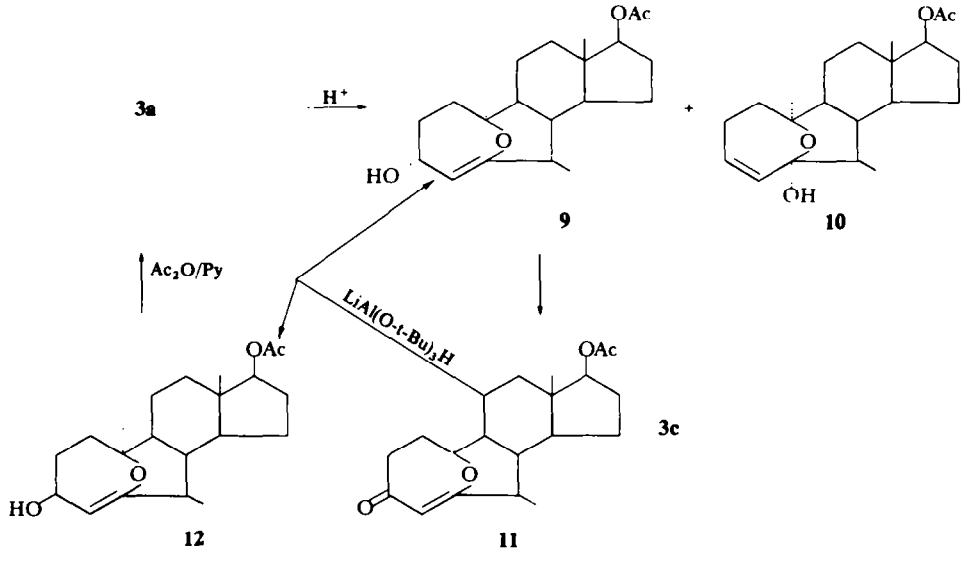


only characterized spectrally. However, when subjected to chromic acid-pyridine oxidation, it yielded the crystalline diketolactone, identical in all respects with the product **7** derived from the triacetate.

The second correlation of the two series arose from the study of the reaction of the enol ether with acid. When **3a** was treated with dilute sulfuric acid under the *identical conditions* used for the acid hydrolysis of the triacetate **4a**, two products **9** and **10** were isolated. These were isomeric hydroxy acetates, analyzing for $C_{21}H_{32}O_4$, which corresponds to the formal hydrolysis of one of the two acetate groups of **3a**. It was clear at once that neither of the two new compounds represented simple hydrolysis products of the starting material since reacetylation of **9** gave a diacetate different from the starting material **3a**, while **10** was unchanged on attempted acetylation, indicating the presence of a tertiary alcohol.

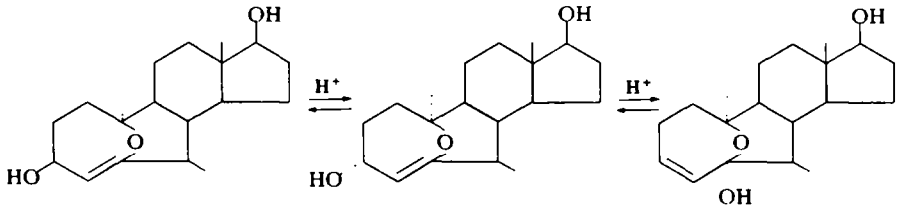
In an initial experiment we were able to show that the two products **9** and **10** were interconvertible under the reaction conditions, suggesting an equilibrium.

The structure of compound **9**, which was formed in lesser amount, was shown to be the 3α-hydroxy-17-acetate as follows: Oxidation of the alcohol **9** with chromium trioxide-pyridine gave a ketoacetate **11** which proved to be identical with the acetylation product of the ketoalcohol **3c** obtained previously from the manganese dioxide oxidation of diol **3b**. Reduction of ketoacetate **11** with lithium tri-t-butoxyaluminohydride gave two alcohols. The major product, formed in 80% yield, was a new compound which could only be the 3β-hydroxy acetate **12**, since it was converted, on acetylation, to **3a**. The other product, formed in 12% yield was identical in all respects with compound **9**.



The major acid hydrolysis product was shown to have structure **10** since it was unreactive toward acetylation, it gave evidence for the presence of vinyl hydrogens in the IR and NMR spectra, and its derived diol was involved as one component in the allylic rearrangement described below. The double bond of **10** was easily hydrogenated to form the saturated hemiketal **4f**.

We wished to study the reaction leading to the allylic rearrangement products in greater detail, and to estimate semiquantitatively the equilibrium concentrations of the components **9**, **10** and **12**. The reaction products could not be studied by vapor phase chromatography because of their instability at the temperatures needed for volatilization. We then looked to see if thin layer chromatography might provide an appropriate assay for our isomers. In the 17-acetate series just described, similar R_f values for compounds **10** and **12** made it difficult to distinguish them readily. In addition, long acid treatment gave rise to some hydrolysis at C-17. However, the 17-hydroxy series gave clear, distinct spots for all three isomers. The starting materials were prepared as follows. From the acid hydrolysis of the diol **3b**, the rearranged diol **13** was obtained in good yield. in addition, a small amount of the 3α-isomer **14** was isolated. Compound **14** was more easily obtained from the saponification of its 17-acetate **9**, which was formed as a minor component in the acid hydrolysis reaction

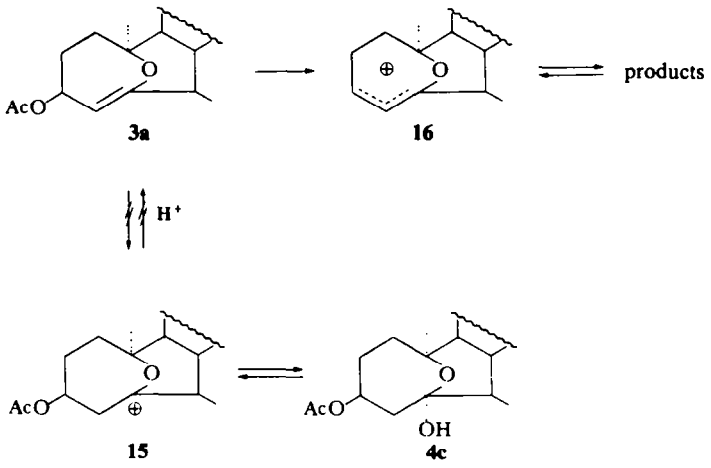


	3b	**14**	**13**
Fraction of isomer present at equilibrium:	< 1%	5 ± 2%	95 ± 2%

described previously. A 0·033M solution of each of the three isomers in acetone-water (2:1) which was 0·024N in sulfuric acid was individually heated under reflux. After 4·5 hr, each reaction showed the identical thin layer pattern and was unchanged by additional heating for 3 days. The equilibrium ratio of the products was determined by tlc comparison with known mixtures. By this method accuracy of ±2% in the observed range could be readily achieved. After total equilibration, this procedure showed the 3β-ol **3b** to be present in less than 1% (non-detectable), the 3α-isomer **14** in 5% and the rearranged product **13** in 95% ratios. The qualitatively observed very rapid disappearance of **3b**, as well as the moderate rate of reaction of **14** and the slow change in **13**, is in accord with this equilibrium distribution.

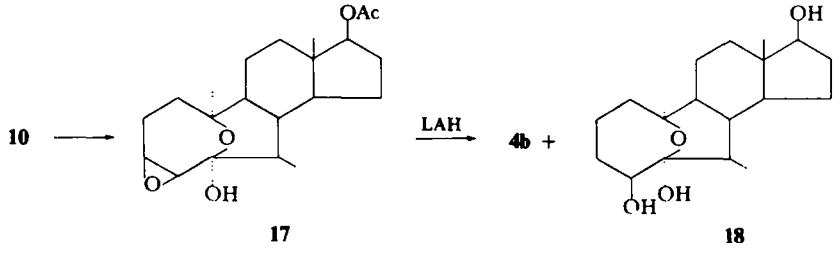
The initial purpose of carrying out the solvolysis of the enol ether **3a** in water was to achieve its hydration to the hemiketal **4c**, which is known to be stable to the reaction conditions. Since the simple hydration does not occur, we conclude that neither **4c**, nor the carbonium ion **15** which is its precursor can be included in the equilibrium involving **3a**. It then follows that the protonation of the 3-acetate group of **3a** followed by loss of acetic acid to form the intermediate carbonium ion **16** is a much more favored process than the protonation of **3a** at C-4, which would give intermediate **15**. This situation is reminiscent of the solvolysis of β-alkoxy allylic alcohols, in which the protonation on the hydroxyl oxygen is favoured over enol ether hydrolysis.[7]

[7] E. Wenkert and D. P. Strike, *J. Am. Chem. Soc.* **86**, 2044 (1964); M. Stiles and A. Longroy, *Tetrahedron Letters* 337 (1961).



The composition of the mixture resulting from the solvolysis of **3a** may be due to the special steric situation in this case. Compound **3a** exemplifies the smallest ring size, (S = 8) compatible with the violation of Bredt's rule.[8] The equilibrium distribution of products **13** and **14** may therefore be a reflection of the higher strain of the molecule with the bridgehead double bond. Similarly the preferential formation of ion **16** to ion **15** may be in part explained by the fact that the primary stabilization of **15** by overlap of the carbonium ion with the oxygen electrons can only occur with partial double bond formation at the bridgehead while in **16** forms containing bridgehead double bonds may only be minor contributors to the hybrid ion. Further comments on some aspects of this interesting allylic system will be made in the section Stereochemistry below.

The rearrangement of the enol ether system to a Δ^3-hemiketal suggested another approach to the chemical interrelation of the two products which arise from the lead tetraacetate oxidation. The rearranged unsaturated hemiketal **10**, obtained either directly from the acid hydrolysis of the enol ether **3a** or from the acetylation of the diol **13**, was epoxidized with m-chloroperbenzoic acid. The product, which formed smoothly and could be isolated in 92% yield, was the *single epoxide* **17**. This epoxide,

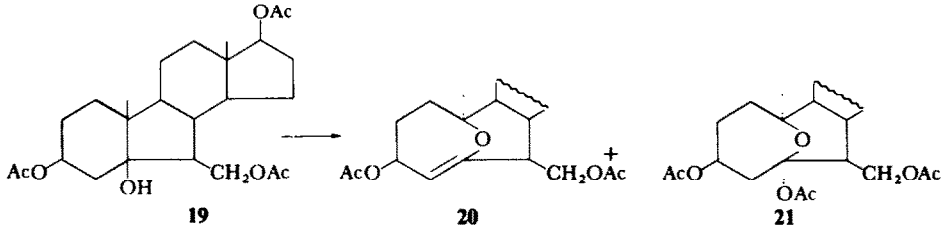


on reduction with lithium aluminum hydride, formed two isomeric diol hemiketals, one of which was *identical in all respects* with the triol **4b**, obtained by the saponification of the lead tetraacetate product **4a**. The other diol hemiketal isolated from the hydride reduction, is presumably the 4β-hydroxy isomer **18**.

[8] F. S. Fawcett, *Chem. Rev.* **47**, 219 (1950).

These data, we feel, offer convincing proof of the structural formulations of the two oxidation products **3a** and **4a**.

We do not yet know much about the scope of this novel lead tetraacetate oxidation. The effects of the substituents have not been studied. We did, however, carry out the oxidation on the hydroxy triacetate **19**, which is an intermediate in the synthesis of **1**. Two products were isolated, and based on their physical properties, and on analogy with **3a** and **4a** we formulate these compounds as **20** and **21**.

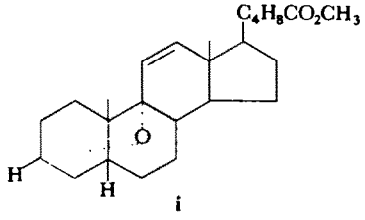


Stereochemistry

The stereochemistry of the two lead tetraacetate oxidation products can be derived from the facts presented above. The stereochemistry of the starting material **1** is secure and has been verified.[4b,c] We can safely assume that no change in the stereochemistry of the acetoxy groups at 3 and 17 occurred during the lead tetraacetate oxidation, and that these substituents are still in the β configuration in the products **3a** and **4a**. In addition, since the enol ether **3a** and the triacetate **4a** have been interrelated, it follows that they both have the same stereochemistry at C-10. It is the configuration at this atom as well as the asymmetric center at C-5[9] in **4a** which must be determined.

[9] At this point it seems appropriate to clarify some concepts in nomenclature which we have had to face in dealing with these oxides, and to define explicitly the words *cis* and *trans* as well as to explain the basis for the dotted and solid line conventions which we are using in this paper.

Chemists have for some time clearly distinguished between a conventional formula and the actual stereomodel from which it can be derived, and concluded that the formula does not necessarily reflect all the conformational nuances of the model. Indeed the formula is a *configurational definition only*, and need not have conformational significance. For example, in compound i the 3β-hydrogen atom



i

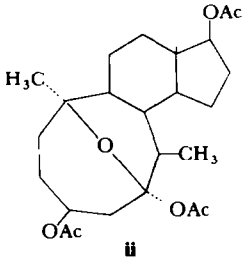
points straight down. These situations are normal and arise as a result of applying a standard distortion process which converts the space model into the structural formula to bring it into a standard form which is readily recognizable to the chemist.

For our system we must specifically define the standardization procedure so as to eliminate any confusion. We define the skeleton basic to our system as that of the nine-membered ring and all other groups attached to be substituents on this ring. For the purpose of the definition of the α and β positions, we further define a standard planar form for this ring containing *all convex angles* (*all internal angles*

The configuration at C-10 was determined by the study of the hydroxyl stretching frequencies of the epimeric alcohols **12** and **9**, formed during the hydride reduction of ketone **11**. When extrapolated to infinite dilution[10] the 3β epimer absorbed at 3555 cm^{-1} while the 3α epimer showed a sharp peak at 3610 cm^{-1}; the first epimer showed a moderately strong hydrogen bond, while the second did not.

The magnitude of the shift (>55 cm^{-1})[11] suggests that in the 3β epimer the hydrogen bond of the C-3 hydroxyl proton is to the ether oxygen and not to the double bond,[12] since allylic alcohols normally show a shift of only 11–18 cm^{-1}.[13] It is very clear from models that in order for the hydroxyl hydrogen to be sufficiently near to the ether oxygen to form a hydrogen bond the confirmational relationship between the 3-hydroxyl group and the oxygen attached to C-10 must be *cis*. Since the 3-OH group in the hydrogen bonded epimer **12** is in the β configuration, the carbon atom at C-10 of compound **12** and therefore also of compound **3a** must be of the indicated R configuration.

less than 180°) and to assign α and β in the usual manner from this form allowing for *no change* in the assignment by further rotation about single bonds. Thus, for example, compound **4a** could be written in the standard form, **ii**, which would be equivalent *by definition* with the other formulations in this paper.



ii

Cis and trans would have their usual significance based on the standard form. From this it follows that the isomer drawn is one of the two possible cis oxides. This kind of definition preserves the properties inherent in smaller rings in *all respects* save for those which relate to the concepts of the actual proximity of substituent groups. Definitions of cis and trans which are based on conformational properties of large rings may not always be general or consistent with the older definitions which were designed primarily for small ring compounds.

The conventions regarding the lactone **8** and its derivatives assume that the lactone ring is basic to the skeleton and planar. For this reason, cursory inspection of the structural formulas might seem to imply that inversion at C-10 occurred during the hydrolysis of compound **3c** to form **8**, where in fact no inversion is involved. For the purpose of naming the compounds, the unambiguous R and S designations are used throughout where needed.

Although these definitions may seem obvious, we wish to emphasize that there is presently no official IUPAC rule covering these points, so until such time that this matter is codified, we feel that authors should make their own definitions where necessary.

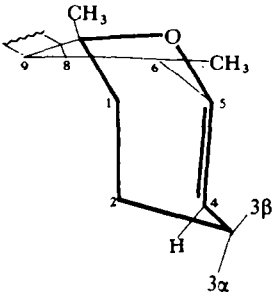
[10] Infrared spectra were determined in carbon disulfide solutions at various concentrations. From 1×10^{-2} M to 3×10^{-3} M there was no change in the hydroxyl band absorptions.

[11] Since the 3β-epimer **12** does not show a non-bonded hydroxyl band we do not know what its non-bonded frequency would be. The value of 3610 cm^{-1} is an estimate on the low side, making the estimated shift a minimum value.

[12] M. Tichý, *Adv. in Org. Chem.* **5**, 115 (1965).

[13] P. R. Schleyer, D. S. Trifan and R. Bacskai, *J Am. Chem. Soc.* **80**, 6691 (1958).

Because of the very high constraints which are placed on the seven-membered A ring of the epimeric acetoxy allylic alcohols **12** and **9** by the oxide bridge and the double bond, only two possible rigid conformers of this ring have reasonable stability. These are shown schematically as I and II. Because of the presence of a heteroatom and a double bond, as well as a bicyclic bridged system, it is difficult to predict *a priori* which of the two possible conformers I or II would predominate. In the hydrogen bonded 3β-hydroxy epimer **12** it may be assumed that the A ring of the molecule



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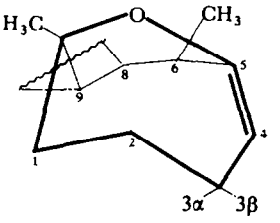


II

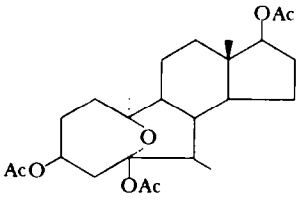
is in the chair conformation I, since hydrogen bonding is not possible in the boat conformation II. With epimer **12** in conformation I, models show that the dihedral angle between the vinyl proton at C-4 and the α-Hydrogen at C-3 is 15°. The coupling constant which corresponds to this angle using the modified Karplus equation[14] is 9·0 c/s. We observed a coupling of the C-4 proton in compound **12** of 6·5 c/s. The difference between these values may be attributed to the lowering influence of electronegative substituents on vicinal coupling constants.[14] The dihedral angles, determined from models, for the C-3 and C-4 protons in the 3α-epimer **9** are 135° for the chair form I and 110° for the boat form II. These angles would predict coupling constants of 7·5 and 1·5 c/s for the forms I and II, respectively, without any correction for the electronegativity factors. The observed coupling constant for the C-4 proton in the 3α-epimer **9** is 4 c/s. This value, after correction for the electronegativity factor, is in accord only with the chair conformer I, and not with the boat form II.

The observed coupling constants for the C-4 protons in the two diols **3b** and **14** are identical with those of their corresponding 17-acetates. We would therefore expect that these substances would also be in conformation I. This assumption would then explain the predominance of the 3α- to the 3β-isomer (at least 5:1) at equilibrium, since the 3α-isomer is equatorial, while the 3β-isomer is in the less stable axial position.

Having established that the oxide is attached β to the 9-membered ring at C-10, the remaining problem is the determination of configuration at C-5 in the triacetate **4a**.

[14] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry*, Chap. 3, Holden-Day, San Francisco (1964).

Derivatives of the parent system, 1,5-oxidocyclononane are known,[15] and it would be expected that these substances contain a cis oxide bridge since models show that the trans oxide is a highly strained molecule. In the trans isomer, one substituent on a carbon atom which bears the oxide bridge must occupy a crowded interannular position. In compound **4a** this substituent would have to be an acetoxy group and we believe that this requirement would impose an impossible strain on the molecule. Space filling models of compound **22**, which is the trans oxide corresponding to the C-5 epimer of **4a**, cannot be made and we believe that, at best, this would be a very highly strained molecule.



22

The equilibration of the enol ether **3a** gives rise to the rearranged alcohol **10** as the major product (95%). We have shown chemically that **10** and **4a** have their oxide bridge in the same configuration. It may be safely assumed from models that the cis oxide is more stable than the trans oxide. The major equilibrium product **10** and thus also **4a** must therefore be a cis oxide.

We can further distinguish between the cis and trans oxides **4a** and **22** based on the following experimental evidence. It has been shown by many groups that cyclic allylic alcohols give epoxides with peracids in a highly stereospecific manner. On treatment with peracid, 2-cyclohexen-1-ol forms exclusively the epoxide[16] which is cis[17] to the hydroxyl group. In 2-cyclohepten-1-ol[18] and 2-cycloocten-1-ol[19] increasing amounts of the trans oxide are formed, and in the latter case the trans oxide predominates.

These findings have been explained by assuming that the epoxide oxygen is introduced at a point which is proximate to the hydroxyl group in its particular conformation. In the seven- and eight-membered rings, the hydroxyl function becomes increasingly oriented to the trans face of the olefin by non-bonded interactions in the medium ring.[20]

In our case, the steric situation is such that the unsaturated tertiary allylic alcohol **10** gave rise to a single epoxide in 92% yield. A perspective drawing of the two possible structures for this alcohol is shown below.

[15] R. Criegee and H. Zogel, *Chem Ber.* **84**, 215 (1951).

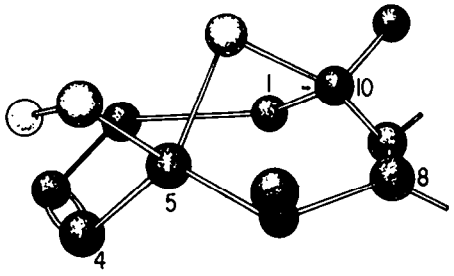
[16] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.* 1958 (1957).

[17] Cis and trans are here defined according to [9].

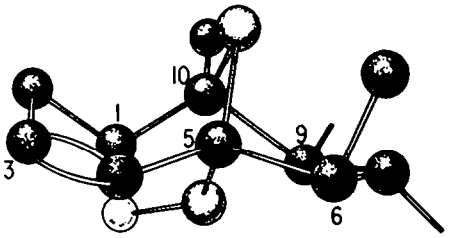
[18] A. C. Cope, T. A. Liss and G. W. Wood, *J. Am. Chem. Soc.* **79**, 6287 (1957).

[19] A. C. Cope, A. H. Keough, P. E. Peterson, H. E. Simmons, Jr. and G. W. Wood, *J. Am. Chem. Soc.* **79**, 3900 (1957).

[20] H. B. Henbest, B. Nicholls, W. R. Jackson, R. A. L. Wilson, N. S. Crossley, M. B. Meyers and R. S. McElhinney, *Bull. Soc. Chim. Fr.* 1365 (1960).



10



23

It will be noted that in the *cis* oxide **10** the 5α-hydroxy substituent is situated nearer to the β face of the double bond while in the C-5 epimeric *trans* oxide **23** the 5β-hydroxyl group is situated in a hindered portion of the α side of the molecule. We would therefore expect **10** to form a β-epoxide and the hypothetical **23** to form an α-epoxide. We know that in fact the epoxide **17** which is obtained is β; therefore **10** is the true representation of the rearranged alcohol. Since **10** has been converted to the triol **4b** without change in stereochemistry at C-5, it follows that the triacetate **4a** has the 10R, 5R configuration.

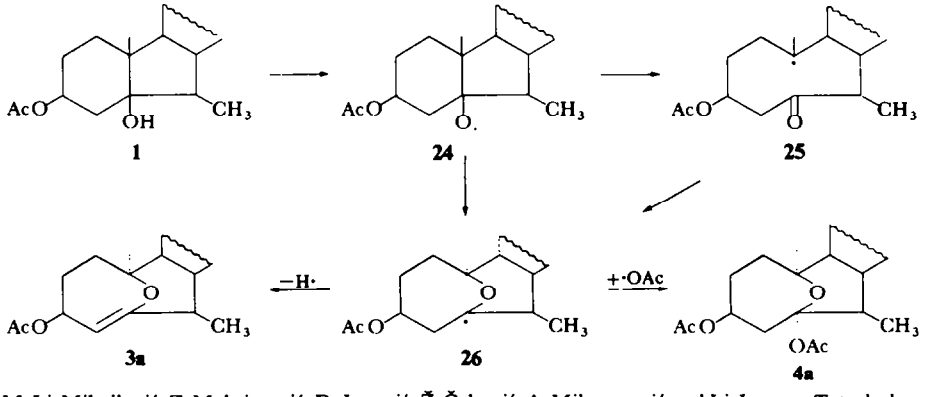
Mechanism

We presently have no clear understanding of the precise mechanism of this unusual lead tetraacetate oxidation. We do not know of any precedents for the formation of enol ethers or hemiketals from the lead tetraacetate oxidations of tertiary alcohols, and our case in that respect is unique.

It is generally agreed that in anhydrous benzene, the oxidation of alcohols with lead tetraacetate proceeds by way of a lead alkoxide salt which cleaves homolytically to form an alkoxy radical.[21]

$$ROH \xrightarrow{Pb(OAc)_4} ROPb(OAc)_3 + HOAc \longrightarrow RO\cdot + \cdot Pb(OAc)_3$$

Tertiary alkoxy radicals are known to cleave to form ketones and a new radical.[22] In our system this process would lead from the initial alkoxy radical **24** to a cleavage product of structure **25**.



[21] M. Lj. Mihailović, Z. Maksimović, D. Jeremić, Ž. Čeković, A. Milovanović and Lj. Lorenc, *Tetrahedron* **21**, 1395 (1965); K. Heusler and J. Kalvoda, *Angew. Chem., Inter. Ed.* **3**, 525 (1964).

[22] See for example F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith and P. M. Zanet, *J. Org. Chem.* **28**, 55 (1963).

Further reaction of this intermediate would give the radical **26** which could give the observed products **3a** and **4a** by the loss of a hydrogen atom or by reaction with an acetoxy radical.

We feel that there are a number of objections to this mechanism, and submit that radical **24** may rearrange directly to radical **26** by 1,2 migration. A more detailed discussion of this point will be published elsewhere.

EXPERIMENTAL

Thin layer chromatograms (tlc) were carried out on 25 × 75 mm microscope slides covered with Brinkmann Silica Gel G. The eluting solvent was 5–80% (v/v) ethyl acetate in chloroform. The spots were developed with phosphomolybdic acid. Unless otherwise indicated, chromatography was carried out on Woelm neutral alumina, activity III. NMR spectra were measured in deuteriochloroform and peaks are reported in τ units. Ultraviolet spectra were measured in 95% ethanol solution. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois.

Lead tetraacetate oxidation of 6β-*methyl-B-nor-androstane*-3β,5β,17β-*triol*,3,17-*diacetate*(**1**). A suspension of 14·6 g of calcium carbonate in 300 ml of dry benzene was heated at reflux for about 20 min. Then 11·85 g (26·8 mmole) of lead tetraacetate was introduced, followed by dropwise addition of 6·00 g (15·4 mmole) of 6β–methyl-B-nor-androstane-3β,5β,17β-triol, 3,17-diacetate (**1**), m.p. 90–92°, in 60 ml of benzene. The solution was heated at reflux with stirring for 18 hr at which time a starch-iodide test was negative. Additional 5·90 g (13·3 mmole) of lead tetraacetate was added, and the heating continued. Total time at reflux was 43 hr. The reaction mixture was filtered through celite, which was then rinsed with benzene. The organic phase was washed several times with 5% sodium bisulfite solution and the precipitated solids were removed. The organic phase was then washed successively with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated to yield 6·87 g of crude products. Chromatography of this mixture on 600 g of alumina using gradient elution from 3 l of benzene to 3 l of ether-benzene (1 : 19) and taking 100 ml fractions yielded, after evaporation, in fraction 2, 38 mg of a pure liquid whose NMR spectrum was identical in every respect with that of an authentic sample of benzyl benzoate; in fractions 4–11, 2·37 g (40%) of the enol ether **3a**. Two recrystallizations from hexane gave analytically pure (10*R*)-6β-*methyl*-5,10-*oxido-B-nor*-5,10-*seco*-4-*androstene*-3β,17β-*diol*, 3,17-*diacetate* (**3a**), m.p. 130–131°. (Found: C, 70·86; H, 8·86. $C_{23}H_{34}O_5$ requires: C, 70·74; H, 8·78%.) $[\alpha]_D$ − 225°. λ_{max} 213 (ε = 3,360). Tetranitromethane test (TNM): pos IR: 1675 cm^{-1} (enol ether). NMR: 4·85 (*m*, C-3 and C-4), 8·79 (19-CH_3) 8·90 (*d*, *J* = 7, C-6 —CH_3) 9·18 τ (18-CH_3). The second major component, triacetate **4a**, came over in fractions 24–57 and amounted to 1·70 g (25%). Recrystallization from methylene chloride-hexane and ether gave (5*R*, 10*R*)-6β-*methyl*-5,10-*oxido-B-nor*-5,10-*seco-androstane*-3β,5,17β-*triol*, 3,5,17-*triacetate* (**4a**), analytically pure, m.p. 161–171°. (Found: C, 66·70; H, 8·53. $C_{25}H_{38}O_7$ requires: C, 66·64; H, 8·50%.) $[\alpha]_D$ − 38·5°. TNM: neg. NMR: 4·95 (*m*, C-3), 5·29 (*m*, C-17), 6·47 (1 proton, *d-d*, *J* = 17·5, 6·5, C-4), 7·91, 7·95, 7·97 (—C(=O)—CH_3), 8·74 (19-CH_3), 9·12 (*d*, *J* = 6, C-6 —CH_3), 9·16 τ (18-CH_3).

Saponification of (10*R*)-6β-*methyl*-5,10-*oxido-B-nor*-5,10-*seco*-4-*androstene*-3β,17β-*diol*, 3,17-*diacetate* (**3a**). To a mixture of 50 ml of methanol and 5 ml of 5% potassium carbonate in water was added 500 mg of enol ether **3a**. The reaction proceeded at room temperature for 20 hr, then was diluted with 50 ml of water. The methanol was removed *in vacuo*, and the resulting crystals were collected, washed well with water, and dried *in vacuo* at 56°. One crystallization from acetone-hexane yielded 373 mg (90%) of analytically pure (10*R*)-6β-*methyl*-5,10-*oxido-B-nor*-5,10-*seco*-4-*androstene*-3β,17β-*diol* (**3b**), m.p. 169–171°. (Found: C, 74·65; H, 9·95. $C_{19}H_{30}O_3$ requires: C, 74·47; H, 9·87%.) $[\alpha]_D$ − 268°. TNM: pos. IR: 1670 cm^{-1} (enol ether). NMR: 4·59 (*d*, *J* = 6·5, C-4), 5·97 (*m*, C-3), 6·32 (*m*, C-17), 8·79 (19-CH_3), 8·95 (*d*, *J* = 7·0, C-6 —CH_3), 9·22 τ (18-CH_3).

This diol was also prepared by a room temperature reaction of the diacetate with lithium aluminum hydride.

Diol **3b** (11 mg) was acetylated by treatment with 0·1 ml of pyridine and 0·03 ml of acetic anhydride over-

night at room temperature. Evaporation *in vacuo*, elution through a short florisil column in chloroform, evaporation, and crystallization from hexane yielded 7·4 mg (56%) of crystals, m.p. 129·5–131°, which was identical with analytically pure **3a**, (m.p., m.m.p., 130–131°).

Oxidation of (10R)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-4-*androstene*-3β,17β-*diol* (**3b**) with *manganese dioxide*. The diol **3b** (4·20 g) was dissolved in 1·4 l of chloroform and shaken with 42 g of manganese dioxide for 60 hr. The solution was filtered through celite and evaporated to dryness. One crystallization from ether-hexane yielded 2·71 g (65%) of (10*R*)-3-*keto*-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-4-*androsten*-17β-*ol* (**3c**), m.p. 151–153° (dec). Recrystallization from ether-hexane gave analytical material, m.p. 154–154·5° (dec). (Found: C, 75·01; H, 9·06. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%.) $[\alpha]_D$ − 327°. λ_{max} 244 mμ (ε = 11,800), 308 mμ (ε = 92). IR: 3610, 1645 cm^{-1}. NMR: 4·38 (C-4), 6·32 (*m*, C-17), 8·67 (19-CH_3), 8·82 (*d*, *J* = 7·0, C-6 —CH_3), 9·21 τ (18-CH_3).

The keto-alcohol was acetylated exactly as in the case of the diol **3b** above, and gave a 74% yield of (10*R*)-3-*keto*-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-4-*androsten*-17β-*ol*, acetate (11), m.p. 106–108°, from hexane. (Found: C, 73·08; H, 8·91. $C_{21}H_{30}O_4$ requires: C, 72·80; H, 8·73%.) $[\alpha]_D$ − 297°. NMR: 4·38 (*s*, C-4), 5·39 (*m*, C-17), 7·96 (—$\overset{O}{\overset{\|}{C}}CH_3$), 8·69 (19-$CH_3$), 8·81 (*d*, *J* = 7, C-6 —CH_3), 9·17 τ (18-CH_3).

Preparation of diketone **3d** *by the chromic acid-pyridine oxidation of compound* **3c**. Chromium trioxide (2·92 g) was added, with stirring, to 40 ml of pyridine. Stirring was continued for 30 min. The mother liquors from the previous reaction, (1·29 g), which by NMR could be seen to contain mainly the 3-keto-17-ol **3c** but also contained some 3,17-diol **3b** and 3,17-diketone **3d** were dissolved in 8 ml of pyridine and added dropwise to the stirred chromic acid complex, and the stirring was continued overnight. The pyridine was then diluted with 50 ml of ethyl acetate, filtered through celite, and washed well with ethyl acetate. The organic phase was concentrated to a sludge containing 3–4 ml of pyridine, which was taken up in ethyl acetate and washed with 25 ml of cold 2N sulfuric acid. The organic phase was then washed successively with water, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. It was then dried over sodium sulfate, and evaporated. The residue was taken up in methylene chloride, passed through 5 g of alumina, and evaporated to dryness. Crystallization from ether-hexane yielded 658 mg (51%) of analytically pure (10*R*)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-4-*androstene*-3,17-*dione* (**3d**), m.p. 141–142°. (Found: C, 75·65; H, 8·79. $C_{19}H_{26}O_3$ requires: 75·46; H, 8·67%.) $[\alpha]_D$ − 255°. IR: 1745, 1665 cm^{-1}. NMR: 4·35 (C-4), 8·66 (19-CH_3), 8·73 (*d*, *J* = 7·0, C-6 —CH_3), 9·08 τ (18-CH_3). The overall yield of oxidation products **3d** and **3c** from diol **3b** amounted to 81%.

Diketone **3d** was also prepared by direct chromium trioxide-pyridine oxidation of the pure diol **3b**.

Hydrogenation of ketone **3c**. Ketone **3c** (76 mg, 0·25 mmole) was hydrogenated in 10 ml of ethyl acetate at atmospheric pressure, using 72 mg of 5% palladium on charcoal as catalyst. Hydrogen uptake was rapid, leveling off after 5 min with a 98% uptake. The catalyst was filtered off through celite, and the evaporated residue was taken up in chloroform and filtered through a short column of alumina. After evaporation, the crude produce weighed 67 mg (89%), m.p. 186·5–188° (dec). It was then crystallized from ethyl acetate to yield 47 mg of analytically pure (5*S*,10*R*)3-*keto*-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-*androstan*-17β-*ol* (**5**). (Found: C, 74·44; H, 10·05. $C_{19}H_{30}O_3$ requires: C, 74·47; H, 9·87%). IR: 3610, 1710 cm^{-1}. NMR: 6·31 (*m*, C-17 and C-5), 8·83 (*s*, 19-CH_3), 8·93 (*d*, *J* = 4, C-6 —CH_3), 9·21 τ (*s*, 18-CH_3).

Saponification of triacetate **4a**. To 4·79 ml of 5% (w/v) potassium hydroxide in 95% methanol was added 479 mg of the triacetate **4a**. The solution was heated under reflux for 30 min, then 0·27 ml of glacial acetic acid was added to the warm solution. The methanol was removed *in vacuo*, and the crystalline residue was extracted from the remaining water with chloroform. The organic phase was then washed successively with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated to yield 339 mg of crude triol. One crystallization from methylene chloride-hexane yielded 281 mg (82%) of **4b**, m.p. 153–157° (dec). The product was recrystallized from acetone-hexane to yield analytically pure (5*S*,10*R*)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-*androstane*-3β,5,17β-*triol* (**4b**), m.p. 156–158° (dec). (Found: C, 70·47; H, 10·11. $C_{19}H_{32}O_4$ requires: C, 70·33; H, 9·94%.) $[\alpha]_D$ − 25°. NMR: 5·85 (C-3), 6·32 (C-17), 7·56 (C-4, 1 proton, *d*-*d*, *J* = 16·5, 6·5), 8·82 (19-CH_3), 9·03 (*d*, *J* = 6, C-6 —CH_3), 9·21 τ (*s*, 18-CH_3).

Acetylation of triol (**4b**). Ten mg of triol **4b** was treated with 0·1 ml of pyridine and 0·03 ml of acetic anhydride overnight at room temperature. Solvent was removed *in vacuo* and the residue passed through a short florisil column in chloroform. Evaporation to dryness and crystallization from ether-hexane gave 6 mg (48%) of the diacetate **4c**, m.p. 171–172°. (Found: C, 67·63; H, 7·85. $C_{23}H_{36}O_6$ requires: C, 67·62; H,

8·88%.) $[\alpha]_D$ − 5°. IR: 3580, 1735, 1240 cm^{-1}. NMR: 4·81 (*m*, C-3), 5·32 (*m*, C-17), 7·91, 7·96 (*s*, O—C(=O)—CH_3), 8·82 (*s*, 19-CH_3), 9·03 (*d*, J = 6, C-6 —CH_3), 9·17 τ (*s*, 18-CH_3).

Acid hydrolysis of triacetate **4a**. Triacetate **4a** (201 mg, 0·45 mmole) was dissolved in 13·4 ml of acetone, and 6·7 ml of water was added, followed by 0·23 ml of 2N sulfuric acid. The solution was heated at reflux (56°) for 5 hr. Then 0·46 ml of saturated sodium bicarbonate solution was added and the acetone removed *in vacuo* to yield a crystalline product which was collected, washed well with water, and dried *in vacuo*. One crystallization from ether-hexane, followed by crystallization from ether gave pure (5*S*, 10*R*)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-*androstane*-3β,5,17β *triol*, 3,17-*diacetate*, (**4c**), m.p. 172–172·5°, undepressed when mixed with the acetylation product of triol **4b**.

The mother liquors from the first crystallization were combined and crystallized from ether to yield 75 mg of a second crop, m.p. 171–172·5°, and a third crop of 25 mg, m.p. 170–172°. The overall yield of crystalline diacetate **4b** was 72%.

Pyrolysis of triacetate **4a**. The pyrolysis of **4a** (56·8 mg) was carried out by heating the purified crystals under nitrogen in a small flask submerged in a Wood's metal bath at 200° for 4 min. The crude oil showed eight distinct spots on tlc. The total product was chromatographed on a 0·8-mm thick layer plate (20 × 20 cm) using Silica Gel HF as adsorbant. The elution solvent was 5% ethyl acetate in chloroform. The band corresponding to the enol ether **3a** was scraped from the plate and from this, 8·9 mg of oil was isolated. The IR spectrum of this oil was very similar to, but not totally identical with that of **3a**, probably due to the presence of some Δ^5 isomer.

Selective saponification of **4a**. To a solution of 200 mg of the triacetate **4a** in 20 ml of methanol was added 2·0 ml of 5% potassium carbonate solution. The solution was allowed to stand at room temperature for 9 hr, and then left overnight at 5°. Then 7 ml of water was added and the methanol was removed under vacuum. The product was collected by filtration and dried. Yield: 131·7 g of crude product. A 35·7 mg portion of this material was crystallized from acetone-hexane to give 21·0 mg of crystals, m.p. 166–173°. One further recrystallization yielded an analytical sample of (5*R*, 10*R*)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-*androstane*-3β,5,17β-*triol*,3,5-*diacetate*, **4e**, m.p. 167–169°. (Found: C, 68·12; H, 8·98. $C_{23}H_{36}O_6$ requires: C, 67·62; H, 8·88%.) IR: 3610, 1738 cm^{-1}. NMR: 4·93 (C-3), 6·32 (C-17), 8·72 (C-19), 9·14 (*d*, J = 8, C-6, —CH_3), 9·22 τ (C-18).

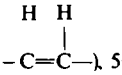
Preparation of (7*R*, 10*R*)-7-*methyl*-4,5-*seco*-5-*oxaandrostane*-3,6,17-*trione* (**7**). (*a*) *By chromic acid-pyridine oxidation of the triol* **4b**. Chromium trioxide (12·4 g) was added with stirring to 220 ml of pyridine, which had been cooled to 12°, and the suspension was stirred for 30 min and brought to room temperature. Then 5·7 g of triol **4b** in 34 ml of pyridine was added dropwise and the reaction stirred at room temperature overnight. The mixture was diluted with 200 ml of ethyl acetate and filtered through celite which was then washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo* to about 5 ml, taken up in ethyl acetate and washed with 100 ml of cold 2N sulfuric acid. The acid wash was extracted with a small amount of ethyl acetate. The combined organic phases were then washed successively with water, saturated sodium bicarbonate solution and water, dried over sodium sulfate, filtered, and evaporated to dryness, yielding a total crude product weighing 4·74 g. The crystalline solid was taken up in benzene and passed through a column of 120 g of alumina. Evaporation of the eluate to dryness and crystallization from acetone-hexane yielded 3·70 g of lactone **7**, m.p. 115·5–116°. Second crop 0·68 g, m.p. 108–114°. Total yield: 77%. The analytical sample of (7*R*, 10*R*)-7-*methyl*-4,5-*seco*-5-*oxaandrostane*-3,6,17-*trione* (**7**) melted at 116–116·5°. (Found: C, 71·16; H, 8·78. $C_{19}H_{28}O_4$ requires: C, 71·22; H, 8·81%.) $[\alpha]_D$ + 103°. λ_{max} 218 mμ (ε = 47·0), 288 (ε = 49·0). IR: 1722, 1727, 1745 cm^{-1}. NMR: 7·83 (CH_3—C(=O)—), 8·58 (*d*, J = 7, C-7, —CH_3), 8·65 (19-CH_3), 9·06 τ (18-CH_3).

Reduction of the δ-lactone **7** with lithium tri-t-butoxyaluminohydride yielded a crude mixture of hydroxy epimers which had a single ν_{max} at 1730 cm^{-1}.

(*b*) *From the hydroxy-ketone* **3c**. Compound (**3c**) (19·8 mg) was dissolved in 1·34 ml of acetone containing 0·66 ml of water and 0·024 ml of 2N sulfuric acid and heated at reflux for 5 days. To the cooled solution was added 0·12 ml of saturated sodium bicarbonate solution, and the acetone was removed *in vacuo*. The residue was taken up in ethyl acetate, washed twice with water, once with saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated to dryness. A portion (16·5 mg) of the crude hydroxy lactone was oxidized directly with 45 mg of chromium trioxide in 0·6 ml of pyridine. The reaction

was worked up as in the previous example and 12·3 mg (69% overall from **3c**) of the crystalline keto-lactone **7**, m.p. 113–115° was isolated. This compound was identical in all respects with the lactone prepared in the previous section.

Acid hydrolysis of enol ether **3a**. To 200 ml of acetone containing 3·45 ml of 2N sulfuric acid was added 3·00 mg of enol ether **3a**. The solution was heated at reflux for 45 min, then 15 ml of saturated sodium bicarbonate solution in 200 ml of water was added to the cooled solution. The acetone was removed *in vacuo*, and the resulting crystals were collected, washed well with water, and dried *in vacuo*, yielding 2·542 g of crude product which contained a major component and a more polar minor component. The total crude product was chromatographed on 80 g of alumina, and eluted with chloroform, taking 10 ml fractions. Fractions 1–4 contained a mixture of both components and, in fractions 5–7, 143 mg (5%) of pure minor component. Rechromatography of the first four fractions on 200 g of alumina, eluting with chloroform yielded (in fractions 6–13) 2·16 g (81%) of the rearranged alcohol **10** which, on crystallization from methylene chloridie-hexane, yielded 2·086 g of the purified product, m.p. 161–163°. Recrystallization from methylene chloride-hexane gave an analytical sample of (5*S*, 10*R*)-6β-*methyl*-5,10-*oxido*-B-*nor*-5,10-*seco*-3-*androstene*-5, 17β-*diol*, 17-*acetate* (**10**), m.p. 159–160·5°. (Found: C, 72·15; H, 9·01. $C_{21}H_{32}O_4$ requires:



C, 72·38; H, 9·26%.) $[\alpha]_D$ −116°. TNM: neg. NMR: 4·42 (−C=C—), 5·35 (*m*, C-17), 7·97 (—C—CH_3), 8·82 (19-CH_3), 8·97 (*d*, *J* = 12, C-6 —CH_3), 9·18 τ (18-CH_3). In the second chromatography, fractions 15–24 yielded an additional 0·121 g (4·5%) of the minor component, which was combined with the corresponding product from the original chromatography and crystallized from acetone-hexane to yield 186 mg (7%) of (10*R*)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-4-*androstene*-3α, 17β-*diol*, 17-*acetate* (**9**), m.p. 218–228° (dec). Recrystallization from acetone-hexane gave the analytical sample, m.p. 221–229° (dec). (Found: C, 72·28; H, 9·40. $C_{21}H_{32}O_4$ requires: C, 72·38; H, 9·26%.) $[\alpha]_D$ − 181°. NMR: 4·84 (*d*, *J* = 4·2, C-4),

5·00 (*m*, C-3), 5·35 (*m*, C-17), 7·95 (—C—$\underline{CH_3}$), 8·86 (19-CH_3), 8·95 (*d*, *J* = 7, C-6 —CH_3), 9·19 τ (18-CH_3). Acetic anhydride–pyridine gave the *acetate*, m.p. 131–132°. (Found: C, 69·93; H, 8·69. $C_{23}H_{34}O_5$ requires: C, 70·74; H, 8·78%.) The m.m.p. with the 3β-acetate (m.p. 130–131°) was 96–126°. NMR: 4·07 (*m*, C-3), 4·85 (*d*, *J* = 4·5, C-4), 5·37 (*m*, C-17), 7·95 ($\underline{CH_3}CO_2$—), 8·85 (C-19), 8·94 (*d*, *J* = 7, C-6 —CH_3), 9·18 τ (C-18).

Saponification of the 3α-*hydroxy*-17-*acetate* **9**. A reagent solution was prepared by dissolving 1 g of potassium hydroxide in 1 ml of water and diluting to 20 ml with methanol. A solution of 26 mg (0·0178 mmole) of the monoacetate **9** in 0·6 ml of reagent solution was heated at reflux for 15 min, then 0·6 ml of water containing 2 drops of acetic acid was added. The solution was concentrated *in vacuo* until all of the methanol had been removed, the solid residue was extracted with chloroform and the extract was washed successively with water, saturated sodium bicarbonate solution, water, saturated sodium chloride solution, dried over sodium sulfate, and evaporated to dryness, yielding 52 mg (95%) of a crystalline solid, m.p. 159·5–161°. One crystallization from ether-hexane yielded 46 mg of analytically pure (10*R*)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-4-*androstene*-3α, 17β-*diol* (**14**) m.p. 159–161°. (Found: C, 74·56; H, 9·93. $C_{19}H_{30}O_3$ requires: C, 74·47; H, 8·87%.) IR: 3620 cm^{-1}. NMR: 4·85 (*d*, *J* = 4, C-4), 5·05 (*m*, C-3), 6·34 (*m*, C-17), 8·86 (19-CH_3), 8·97 (*d*, *J* = 7, C-6 —CH_3), 9·24 τ (18-CH_3).

Oxidation of the 3α-*alcohol* **9**. Chromium trioxide (22 mg) was added to 0·39 ml of pyridine, and the mixture was swirled occasionally for 30 min. Then 9·8 mg (0·0282 mmole) of alcohol **9** in 0·2 ml of pyridine was added, and the mixture was allowed to stand overnight. The reaction mixture was diluted with ethyl acetate and filtered through celite. The organic phase was then washed with 4 ml of cold 2N sulfuric acid, water, saturated sodium bicarbonate solution, water, saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated to dryness. The residue, dissolved in benzene, was passed through a short alumina column, and after evaporation of the solvent the resulting crystals (8·8 mg, 89%) melted at 107–108°, which showed no depression when mixed with an authentic sample of compound **11**, m.p. 106–108°.

Hydride reduction of the conjugated ketone **11**. To 5·6 ml of dry tetrahydrofuran was added 397 mg of lithium tri-t-butoxyaluminohydride, followed by dropwise addition of a solution of 106 mg (0·307 mmole) of the ketone **11** in 0·5 ml of purified tetrahydrofuran. The solution was heated at reflux for 2 hr, then poured into 50 ml of ice water containing 0·2 ml of glacial acetic acid and concentrated on a rotary evaporator. The residue was extracted several times with methylene chloride, and the extract was washed

with water, saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated to dryness, yielding 98 mg of crude reduction products. The total reduction mixture was chromatographed on 10 g of alumina, and eluted with chloroform, taking 4 ml fractions. Fractions 4–5 yielded 85 mg (80%) of the analytically pure, crystalline, hydroxy-acetate, (10*R*)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-4-*androstene*-3β, 17β-*diol*, 17-*acetate* (**12**), m.p. 229–230°. (Found: C, 72·60; H, 9·30. $C_{21}H_{32}O_4$ requires: C, 72·38; H, 9·26%.) $[\alpha]_D$ −240°. IR: 3560, 1738, 1670, 1250 cm^{-1}. NMR: 4·58 (*d*, J = 6·5, C-4), 5·34 (C-17), 5·98 (*m*, C-3), 7·96 (—C(=O)—CH_3), 8·81 (19-CH_3), 8·94 (*d*, J = 7, C-6 —CH_3), 9·18 τ (18-CH_3). Acetylation of this compound gave the diacetate **3a**. The other epimer came over in fractions 6–8, and yielded 13 mg (12%) of crystals, m.p. 229–230° (dec). When mixed with an authentic sample of the 3α-alcohol **9**, m.p. 226–227°, it gave m.m.p. 229–230°. One further crystallization from acetone-hexane yielded 8 mg of a product whose IR spectrum was identical in every respect with the analytical sample of compound **9**.

Saponification of the hydroxy-acetate **10**. A reagent solution was prepared by dissolving 1 g of potassium hydroxide in 1 ml of water and diluting to 20 ml with methanol. A solution of 58 mg (0·0167 mmole) of monoacetate **10** in 0·6 ml of the reagent solution was heated at reflux for 15 min, then 0·6 ml of water containing 2 drops of glacial acetic acid was added. The solution was concentrated *in vacuo* until all of the methanol had been removed. The solid residue was extracted with chloroform and the extract washed successively with water, saturated sodium bicarbonate solution, water, saturated sodium chloride solution, dried over sodium sulfate, and evaporated to dryness. The crude product was crystallized from ether-hexane to yield 42 mg (82%) of crystals, m.p. 133–134° (with a transition at 90°). Two sublimations at 127° (0·005 mm) yielded the analytical sample, m.p. 134–135° (with no transition) of (5*S*, 10*R*)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-3-*androstene*-5,17β-*diol* (**13**). (Found: C, 74·22; H, 9·83. $C_{19}H_{30}O_3$ requires: C, 74·47; H, 9·87%.) NMR: 4·42 (*s*, C-3 and C-4), 6·34 (*m*, C-17), 8·81 (19-CH_3); 9·00 (*d*, J = 6, C-6 —CH_3), 9·22 τ (18-CH_3).

Hydrogenation of compound **10**. Compound **10** (252 mg, 0·72 mmole) was hydrogenated at atmospheric pressure in 10 ml of ethanol using 254 mg of 5% palladium on charcoal as catalyst. Hydrogen uptake was rapid and 1·07 equivalents was absorbed in 7 min. The catalyst was removed by filtration through celite and the solvent was evaporated. The crude product, which still contained some catalyst, was dissolved in chloroform and filtered through a short column of alumina. After evaporation of the eluate *in vacuo*, the residue was crystallized from hexane to yield 216 mg (85%) of (5*S*, 10*R*)-6β-*methyl*-5,10-*oxido*-*B*-*nor*-5,10-*seco*-*androstane*-5, 17β-*diol*, 17-*acetate* (**4f**), m.p. 103–104·5°. One additional crystallization from hexane gave the analytical sample, m.p. 104–105°. (Found: C, 72·00; H, 9·70. $C_{21}H_{34}O_4$ requires: C, 71·96; H, 9·78%.) NMR: 5·34 (*m*, C-17), 7·95 (—C(=O)—CH_3), 9·03 (*d*, J = 6, C-6 —CH_3), 9·17 τ (18-CH_3).

Acid hydrolysis of the enol ether diol **3b**. To 6·7 ml of acetone containing 3·3 ml of water was added 100 mg of diol **3b**, followed by 0·12 ml of 2N sulfuric acid. The solution was heated under reflux overnight, then 0·52 ml of saturated sodium bicarbonate solution was added, and the acetone was removed at reduced pressure. The residue was extracted with chloroform and the extract was washed with water until the washings were neutral, treated with saturated sodium chloride solution, then dried over sodium sulfate. After filtration and evaporation to dryness, the product, a mixture of two substances by tlc, was chromatographed on 10 g of alumina, taking 4 ml fractions and using a gradient from chloroform (100 ml) to isopropanol-chloroform (1:24, 100 ml). The major product came over in fractions 2–5. Sublimation at 124° (0·005 mm) yielded 92 mg (92%) of crystals, m.p. 133·5–135°. Identity with the diol **13** was established by m.m.p. and by acetylation to the monoacetate **10**.

The minor epimer came over in fractions 7–10. One crystallization from ether-hexane yielded 3·3 mg (3·3%) of diol **14**, m.p. 155–156·5. Comparison with an authentic sample prepared by the saponification of the 17-acetate (m.p. 159–161°), gave a m.m.p. of 157–159°.

Equilibrium study of the diols **3b**, **14** and **13**. Samples (10·0 mg) of each of the diols **3b**, **14** and **13** were dissolved in a mixture of 0·67 ml of acetone, 0·33 ml of water, and 0·012 ml of 2·0N sulfuric acid. The individual solutions were heated at reflux, and were checked periodically to determine the progress of the reaction, the tlc comparison with known samples. After 4½ hr all of the reaction solutions showed the identical tlc pattern. Heating at reflux for 3 days produced no further significant change (tlc). After equilibration was achieved, the ratio of the components was determined by comparison with synthetic mixtures,

and found to be 95:5: < 1 (13:14:3b). Mixtures which varied by as much as 2% from the determined values could be distinguished.

Equilibrium studies were also carried out at 0° and showed that a similar equilibrium composition was obtained, but that it was achieved about $\frac{1}{300}$ as fast.

Studies on the corresponding 17-acetates, **12**, **9** and **10**, when carried out over 24 hr, did not give rise to constant intensities of spots corresponding to an equilibrium, but developed new spots corresponding to the 17-ols, so equilibrium values for the acetates could not be determined.

Preparation of the oxide **17**. Compound **10**, (101 mg) was dissolved in 0·5 ml of benzene, and cooled to 4°. Then 205·0 mg of m-chloroperbenzoic acid in 3 ml of benzene was added. The reaction was maintained at 4° for 20 hr, then diluted with benzene and washed successively with two portions of saturated sodium bisulfite solution, 3 portions of saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. The organic phase was dried over sodium sulfate, filtered, and evaporated, and gave 101 mg of crude epoxide. The crude product was sublimed at 140° (0·005 mm) to yield 97 mg (92%) of pure **17**, m.p. 178–179° (dec). A portion of this product was passed through a short florisil column in methylene chloride and crystallized from ether-hexane to give an analytical sample of (5*R*, 10*R*)-6β-*methyl*-3β,4β; 5,10-*dioxido-B-nor*-5,10-*seco-androstane*-5,17β-*diol*, 17-*acetate* (**17**), m.p. 177–178·5° (dec). (Found: C, 69·48; H, 8·57. $C_{21}H_{32}O_5$ requires: C, 69·58; H, 8·34%.) NMR: 5·32 (*m*, C-17), 6·68 (*m*, C-3), 7·02 (*d*, J = 5, C-4), 7·95 (—C(=O)—$\underline{CH_3}$), 8·87 (19-CH_3), 8·92 (*d*, J = 5, C-6 —CH_3), 9·17 τ (18-CH_3).

Synthesis of **4b** *from epoxide* **17**. To 27 mg of lithium aluminum hydride in 2·1 ml of tetrahydrofuran (distilled from lithium aluminum hydride) was added 17·3 mg of epoxide **17** in 0·2 ml of tetrahydrofuran, and the reaction was heated at reflux for 20 hr. Three drops (ca. 4 equivalents) of water were cautiously added to the still refluxing solution, which turned from gray to white. The solution was then cooled and a small amount of solid anhydrous sodium sulfate was added. The reaction mixture was filtered, and the residue washed with ethyl acetate. The organic phase was evaporated to dryness; the crude reaction product was chromatographed on a silica Gel H plate, 20 × 20 cm, 0·8 mm thick, and eluted with ethyl acetate–chloroform (80:20). Two bands were obtained. Isolation of the more polar component gave 4·6 mg (30%) of a triol, m.p. 188–199° (dec), at least 90% pure (tlc).

This compound had the identical IR spectrum, and R_f value as the authentic triol **4b**.

The other, less polar product (6·9 mg, 45%) proved to be the isomeric triol. Crystallization from ether-hexane, followed by sublimation gave an analytical sample, m.p. 180–183°, of (5*R*, 10*R*)-6β-*methyl*-5,10-*oxido-B-nor*-5,10-*seco-androstane*-4β, 5, 17β-*triol* (**18**). (Found: C, 70·51; H, 9·94, $C_{19}H_{32}O_4$ requires: C, 70·33; H, 9·94%.) NMR: 6·36 (*m*, and C-4 and C-17), 8·87 (19-CH_3), 9·02 (*d*, J = 6, C-6 —CH_3), 9·21 τ (18-CH_3).

Lead tetraacetate oxidation of compound **19**. To 50 ml of refluxing benzene containing 2·27 g of calcium carbonate and 1·92 g of lead tetraacetate was added 1·0 g (2·23 mmoles) of the triacetate **19** in 10 ml of benzene. Additional lead tetraacetate (4·34 g) was added to the reaction mixture in two portions during the course of the reaction. After a total of 52 hr of reflux the reaction mixture was filtered through celite, washed with 2% potassium iodide solution and filtered again through celite. The excess iodine was then removed by washing the organic layer with 2% sodium thiosulfate solution containing a small amount of acetic acid. The organic phase was then washed with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution, dried over sodium sulfate, and evaporated to dryness, yielding 1·33 g of a total crude product which consisted of two major products (tlc). The total crude product was chromatographed on 150 g of silica gel (deactivated with 11% water) and eluted in 40 ml fractions with 3300 ml of a solvent system which was varied by gradient elution from benzene to benzene–ether (19:1). The first component which was eluted (fractions 47–49, 195 mg) did not crystallize, but was homogeneous by tlc and was identified as *compound* **20** by means of its IR and NMR spectra. IR: 1684, 1739 cm^{-1}. NMR: 4·83 (C-3), 4·73 (s, C-4), 5·36 (C-17), 6·00 (C-6 —$\underline{CH_2}$OAc), 8·82 (19-CH_3), 9·22 τ (18-CH_3). The second component (281 mg) was eluted in fractions 57–64. The product was crystallized from ether, yielding 74·6 mg of analytically pure (5*R*, 10*R*)-6β-*acetoxymethyl*-5,10-*oxido-B-nor*-5,10-*seco-androstane*-3β,5, 17β-*triol*, *triacetate* (**21**), m.p. 174–175°. (Found: C, 63·55; H, 8·31. $C_{27}H_{40}O_9$ requires: 63·76, 7·93%.) IR: 1737 cm^{-1}. NMR: 4·97 (C-3), 5·27 (C-17), 5·93 (C-6 —$\underline{CH_2}$OAc), 6·36 (1 proton, C-4, *d-d*, J = 6·5, 16·5), 8·73 (19-CH_3), 9·15 τ (18-CH_3).