THE SYNTHESIS OF SOME 3β-HYDROXY-Δ^5 STEROIDS WHICH ARE POSSIBLE METABOLITES OF THE NEWBORN INFANT

by

Rodney W. Kelly

A Thesis presented for the Degree of Doctor of Philosophy

University of Edinburgh October, 1967

T O M Y P A R E N T S

Acknowledgements

The author would like to express his gratitude to Dr. P. J. Sykes for his constant advice and attention during this work, and to Professor Sir Edmund Hirst, C.B.E., F.R.S. for the provision of technical and library facilities.

Thanks are also due to Dr. D. N. Kirk of Westfield College for helpful discussion and advice, to Glaxo Ltd. (Montrose), for the generous gift of sapogenin derivative and to the Medical Research Council for financial assistance during the period of this work.

Summary

The purpose of this research has been to synthesise some new compounds which are useful standards in the identification of naturally occurring steroids of unknown structure.

The work has been divided into three parts, the synthesis of 11-oxygenated counterparts of the 3β-hydroxy-Δ^5 steroids which have already been found in the processed urine of newborn infants, the synthesis of 15,17-disubstituted 3β-hydroxy-Δ^5 steroids and the synthesis of 3β,18-dihydroxyandrost-5-en-17-one and 3β-hydroxy-18-nor-13α-androst-5-en-17-one.

The synthesis of the 11-oxygenated counterparts of the known 3β-hydroxy-Δ^5 steroids has involved the development of an efficient method for converting the 3-keto-Δ^4 structure into the 3β-hydroxy-Δ^5 system. This has been achieved by the reaction of the conjugated enone with strong base in dimethylsulphoxide and the quenching of this reaction mixture with aqueous methanolic borohydride solution. The preparation from adrenosterone of 3β, 16α-dihydroxyandrost-5-ene-11,17-dione and the corresponding 11β-alcohol is described.

The route to 3β-hydroxy-Δ^5 steroids from the sapogenin derivative 3β,12β-diacetoxy-25R,S-spirost-5-en-11-one has been used to synthesise 3β,16α-dihydroxypregn-5-ene-11,20-dione and 3β,21-diacetoxypregn-5-ene-11,20-dione.

In the synthesis of 15,17-disubstituted steroids suitably protected Δ^{14} compounds were prepared *via* the intermediate

Δ^{15}-17-ketone and the action of diborane on these compounds was investigated. 3β,15α,17β-Trihydroxyandrost-5-ene was prepared in a 1:1 mixture with 3β,15β,17β-trihydroxy-14β-androst-5-ene. 3β,15β,17β-Trihydroxyandrost-5-ene has been synthesised by way of the intermediate 15β-benzyloxy-17-keto compound.

The synthesis of 3β-hydroxy-Δ^5 steroids substituted at the C-18 position has been investigated. 3β-Acetoxy-18-hydroxypregn-5-en-20-one hemiacetal has been prepared from pregnenolone by the 'hypoiodite' reaction. This intermediate was used to synthesise 3β,18-dihydroxyandrost-5-en-17-one.

3β-Hydroxy-18-nor-13α-androst-5-en-17-one has been prepared by the sublimation of 3β,18-dihydroxyandrost-5-en-17-one at 230°. The 13α-configuration of the isolated product has been deduced by optical rotatory dispersion studies.

Nomenclature

In general, steroids are referred to by their full names, but for the more common compounds the following trivial names are used.

Adrenosterone	Androst-4-ene-3,11,17-trione
Androstenedione	Androst-4-ene-3,17-dione
Cortisol	11β,17α,21-trihydroxypregn-4-ene-3,20-dione
Cortisone	17α,21-dihydroxypregn-4-ene-3,11,20-trione
Cholesterol	3β-hydroxycholest-5-ene
Dehydroepiandrosterone	3β-hydroxyandrost-5-en-17-one
Oestrone	3-hydroxyestra-1,3,5(10)-trien-17-one
Pregnenolone	3β-hydroxypregn-5-en-20-one
Dehydropregnenolone	3β-hydroxypregna-5,16-dien-20-one
Progesterone	pregn-4-ene-3,20-dione
Testosterone	17β-hydroxyandrost-4-en-3-one
Etiocholanolone	3α-hydroxy-5β-androstan-17-one
Botogenin	3β-hydroxy-20α,22α,25R-spirost-5-en-12-one
Neobotogenin	3β-hydroxy-20α,22α,25S-spirost-5-en-12-one
Diosgenin	3β-hydroxy-20α,22α,25R-spirost-5-ene

Table of Contents

	Page
Summary	
Nomenclature	
1. Introduction	1
2. The Characterisation of 3β-Hydroxy- Δ^5 Compounds by Physical Methods	
a. Infrared Spectroscopy	5
b. Nuclear Magnetic Resonance Spectroscopy	5
c. Mass Spectrometry	6
d. Thin Layer Chromatography	7
e. Gas Liquid Chromatography	7
3. The Stability of the 3β-Hydroxy- Δ^5 system under various reaction conditions	9
4. The Availability of 3β-Hydroxy- Δ^5 Compounds for use as Starting Materials	13
5. Previous Partial Syntheses of 16 and 11 Substituted 3β-Hydroxy- Δ^5 Steroids which are Possible Metabolites of the Newborn Infant	15
6. The Partial Synthesis of new 16- and 11-Oxygenated 3β-Hydroxy- Δ^5 compounds and an improved synthesis of 3,11,17-Trisubstituted Androst-5-enes ..	
a. The Conversion of Adrenosterone to 3β-Hydroxy-androst-5-ene-11,17-dione	19
b. The Synthesis of 3β,11β,16α-Trihydroxyandrost-5-en-17-one and 3β,16α-Dihydroxyandrost-5-ene-11,17-dione	29
Experimental Section	32

Page

7. The Synthesis of 3β,16α-Dihydroxypregn-5-ene-11,20-dione and 3β,21-Diacetoxy pregn-5-ene-11,20-dione 49

Experimental Section 53

8. The Synthesis of New 15,17-Disubstituted 3β-Hydroxy-Δ^{5}-Androstanes 61

Experimental Section 74

9. The Synthesis of 3β,18-Dihydroxyandrost-5-en-17-one and 3β-Hydroxy-18-nor-13α-androst-5-en-17-one . 90

Experimental Section 96

10. Bibliography 102

Note on Publication 111

INTRODUCTION

The metabolism of steroids in the foetus and newborn infant has attracted much recent research[1] and of the many facts so far revealed, one of the most important is that in the foetus there is a relative deficiency of 3β-hydroxy steroid dehydrogenase.[2,3,4] This is the enzyme system which (possibly in conjunction with $\Delta^{4,5}$ isomerase) transforms the 3β-hydroxy-Δ^5 grouping into the Δ^4-3-keto system. This conversion to the enone in the A-ring is an essential step in the *in vivo* synthesis of the important steroidal hormones such as progesterone and cortisol, from cholesterol and pregnenolone. The low activity of this enzyme system means that many of the important steroidal metabolites of the foetus have the 3β-hydroxy Δ^5 system.

After birth, 3β-hydroxy-Δ^5 steroids continue to play an important role in the newborn infant's steroid metabolism. As well as the presence in relatively large quantities of steroids still having the 3β-hydroxy-Δ^5 structure, there is evidence for the continued presence of the enzyme system responsible for 16α-hydroxylation. These features of the newborn infant's metabolism are responsible for the relatively large proportion of 3β-hydroxy-Δ^5 steroids and 16α-hydroxylated steroids excreted by the infant for the first few days after birth.

Immediately after birth, changes in the infant's steroid metabolism occur and the pattern of excreted steroids changes markedly. In 1965 Eberlein[5] showed that the concentration of

3β-hydroxy- Δ^5 steroids in infant blood rose after birth to 200-600 ug./100 ml.; this high level was maintained for about six days and fell to a very low level by the fiftieth day of life. The activity of the 16α-hydroxylating enzyme is considerably reduced by the sixth month of life,[6] but for the first few weeks after birth the two most abundant steroids isolated from newborn infant's urine are 3β,16α-dihydroxyandrost-5-en-17-one and 3β,16α-dihydroxypregn-5-en-20-one.[7]

Although much has already been discovered about the metabolism of steroids in the newborn infant, the analysis of 3β-hydroxy- Δ^5 steroids in processed urine from newborn infants has shown the presence of steroids which cannot yet be identified. The identification of these steroids is difficult because of the small amounts of material which can conveniently be isolated. The main analytical techniques in use are as follows:

1. Thin layer chromatographic comparisons, usually associated with specific colour stains.
2. Gas-liquid chromatographic comparisons of both the free steroids and as methyl oxime and trimethylsilyl ether derivatives formed for protection of the steroids and for the greater resolution that these derivatives show during gas chromatography.
3. The mass spectrographic analysis of steroids and their derivatives which is frequently combined with prior gas chromatographic separation of the components of a mixture.
4. Infrared and ultraviolet spectroscopy of the steroids

isolated by thin layer and gas chromatography.

5. Various specific colour reactions for the indication of functional groupings.

For all of the above techniques standards are desirable and any positive identification of a steroid would be difficult and possibly uncertain without the independently synthesised standard.

From the use of the available techniques it is apparent that several of the unidentified steroids have the 3β-hydroxy-Δ^5 structure.[8] These steroids exhibit characteristic colour stains when the compounds separated by thin layer chromatography are sprayed with a saturated solution of antimony trichloride in chloroform on the thin layer plate.[9] The assignation of 3β-hydroxy-Δ^5 structure is also supported by mass spectral data and the lack of strong u.v. absorption by the unidentified steroids. A further difficulty encountered in the research into the steroid metabolism of newborn infants has been the limited availability of 3β-hydroxy-Δ^5 standards. The object of this thesis is to present the partial synthesis of some 3β-hydroxy-Δ^5 compounds which might be useful standards for this investigation. Routes to 3β-hydroxy-Δ^5 steroids from readily available 3-keto-Δ^4 compounds have been investigated, together with routes to 3β-hydroxy-Δ^5 steroids substituted at positions 11,15,16 or 18. The synthesis of 3β-hydroxy-18-nor-13α-androst-5-en-17-one is described; this steroid could occur as an artefact if 18-hydroxy dehydroepiandrosterone was present and was treated with base, as is the normal practice for the removal of phenolic steroids from the mixtures derived from urine. The occurrence of 18-nor oestrone as an

artefact in the identification of 18-hydroxy oestrone has previously been described.[10]

The interest in positions 18 and 15 has been aroused because of the detection of 18 and 15 hydroxylated oestrogens in human pregnancy urine.[10,11,12,13] Just as 16α-hydroxy dehydroepiandrosterone is probably the precursor of the large amount of oestriol generated during pregnancy,[1] it has been thought possible that 15-hydroxy and 18-hydroxy dehydroepiandrosterones might be precursors of the correspondingly substituted oestrogens. Recently it was suggested that 18-hydroxy dehydroepiandrosterone should be searched for in human cord blood.[12]

The Characterisation of 3β-Hydroxy-Δ^5 steroids by Physical Methods

Infrared Spectroscopy

Hirschman[14] has studied a large range of 3β-hydroxy-Δ^5 steroids paying particular attention to common features in their infrared spectra, which are notably twin peaks in the 800-807 $cm.^{-1}$ region. These twin peaks vary in relative intensity with substitution elsewhere in the molecule and have been assigned[14,15] to the out of plane deformation of the 6-hydrogen. The observed frequencies for the corresponding 3β-acetates lie in the range 800-812 $cm.^{-1}$ These sets of twin peaks have however limited diagnostic value due to their low intensities, but it is notable that in the infrared spectra of the three 3β-acetoxy-11-oxo-Δ^5 steroids whose preparation is described here, (3β-acetoxyandrost-5-ene-11,17-dione, 3β,17-diacetoxyandrost-5,16-dien-11-one and 3β-acetoxy-16α-bromoandrost-5-ene-11,17-dione), only one characteristic medium intensity peak in the region 817-820 $cm.^{-1}$ is observed, both for solution (CS_2) and nujol mull spectra.

Nuclear Magnetic Resonance Spectroscopy

The proton magnetic resonance spectra of 3β-hydroxy and 3β-acetoxy-Δ^5 steroids measured in deuteriochloroform exhibit characteristic multiplets due to the hydrogen at the 6 position; these multiplets are centred between τ 4.55 and 4.65. When the 5α,6β-dichloro derivative is made the multiplet is again observed, now due to the 6α-hydrogen atom, and is then characteristically

centred between τ 5.55 and 5.65. From examples presented later it has become apparent that the partial contribution for the transition 3β-acetoxy-Δ^5 to 3β-acetoxy-5α,6β-dichloro is 0.02∓0.02τ for the C-18-methyl and -0.35±0.02τ for the C-19-methyl group. This characteristic shift in the methyl frequencies on chlorination has proved to be useful in assigning the C-18 and C-19-methyl signals where a compound and its corresponding dichloride have been made.

For the polyhydroxylated steroids prepared in this work, deuteriochloroform was not suitable as a solvent due to the low solubility of the steroids. However, pyridine has proved a very useful solvent for studying the n.m.r. spectra of these polyhydroxylated steroids.

Mass Spectrographic analysis

Most information from the mass spectra of 3β-hydroxy-Δ^5 steroids can be obtained by converting the free alcohol into the corresponding trimethylsilyl ether. The 3β-trimethylsilyloxy compound has a characteristic fragmentation pattern with a strong peak at m/e 129,[16] this is frequently the strongest peak in the spectrum. This peak with mass/charge ratio 129 has recently been proved by Djerassi[17] to be due to a fragment derived from carbon atoms 1, 2 and 3 of the steroid skeleton together with the trimethylsiloxy group. Although it has been shown that the m/e 129 peak can arise from groups other than the Δ^5-3β-trimethylsilyloxy structure[17,18] the intense m/e 129 peak is characteristic of the 3β-hydroxy-Δ^5 derivative. The formation of a fully

trimethylsilanised derivative of a poly-alcohol also allows the number of hydroxyl groups in the molecule to be counted by observing the molecular weight shown by the mass peak, and by the presence of m-90, m-180 and m-270 peaks which for example would appear in the spectrum of a triol derivative.

Thin Layer Chromatography

The thin layer chromatography of 3β-hydroxy-Δ^5 steroids has been extensively studied by Lisboa.[19] Lisboa's systems were used throughout this work and the staining reagent used was a saturated solution of antimony trichloride in chloroform. With this reagent both 3β-hydroxy-Δ^5 steroids and their acetates give rise to bright pink spots on the thin layer plates. Where a 7α- or 7β-hydroxyl substituent is present a very intense blue-green colour appears without heating of the plate. When an 11β-hydroxyl or a 14α-hydroxyl group is present the normal pink colour is tinged with blue to an extent which varies with the nature of the substituent. The 5α,6β-dichloro group together with a 3β-hydroxyl gives rise to a bronze colour when the steroid is stained with antimony trichloride.

Gas Liquid Chromatography

The 3β-hydroxy-Δ^5 system is quite stable to the gas chromatographic conditions used in this work. The chromatography was carried out on a Perkin Elmer model 801; all glass columns packed with 2½% E301 on Chromosorb G were used, with a gas flow of 33 ml. of helium per minute. The injector temperature was 250°, the

column temperature 240° and the detector temperature 240°. On-column injections of solutions were made with a Hamilton syringe. A flame ionisation detector was used throughout. When the 5α,6β-dichloro grouping was used to protect the 5,6-double bond, the resulting intermediates could not be analysed by g.l.c. as the dichloride grouping is not stable to the high temperatures involved.

3β-Hydroxy-Δ^4 systems are unstable when chromatographed at 240°[20] but the diene peak which appears due to dehydration has been useful in determining some impurity concentrations in the work described later.

The Stability of the 3β-Hydroxy-Δ^5 system Towards Various Reaction Conditions

Oxidising Conditions. The hydroxyl function at C-3 in the 3β-hydroxy-Δ^5 system can be adequately protected through most oxidation reactions by the formation of the 3β-acetate, the 5,6-unsaturation has also to be protected against many oxidising agents. In particular, protection is required against per-acids,[21] chromic anhydride in acetic acid[22] and also against conditions where allylic oxidation at C-7 can occur.[23] Oxidation with lead tetraacetate is better effected with a protected 5,6-double bond,[24] but in the case of oxidation of a Δ^{16}-17-acetate by this reagent, the unwanted side reaction at Δ^5 does not appear to be serious.[24] For all the above oxidations, protection of the double bond with 5α and 6β-halogens has proved satisfactory. The 5α,6β-dichloro group has proved particularly stable and consequently particularly useful in this synthetic work, and the parent double bond can easily be regenerated by treatment of the dichloride with zinc powder in acetic acid.[21]

The 5α,6β-dichloro group can easily be introduced into the steroid nucleus by adding sulphuryl chloride to a cooled solution of a Δ^5 steroid in pyridine.[25] Sulphuryl chloride reacts with pyridine to give a sulphur dioxide-pyridine complex and chlorine; the chlorine thus generated can react with any unsaturation in the usual manner. The advantages of the sulphuryl chloride - pyridine chlorination over the straight chlorination with chlorine gas is firstly that a weighed amount of sulphuryl chloride and hence

a weighed amount of chlorine may be used. The second advantage is that the pyridine serves a second function of removing any hydrogen chloride which might be formed in the reaction. Should hydrogen chloride be present, it might catalyse chlorination of a methylene group alpha to a ketone.

One disadvantage of using pyridine, is that the formation of pyridinium salts with the steroid halide[26] and with chlorine[27] occur as side reactions. Previous workers[27] using chlorine and pyridine as a chlorinating agent have found that a pyridine : steroid ratio of 0.5 : 1 has given the best yields of addition product. However, in the work presented here the best conditions proved to be the use of a 10% solution of pyridine in benzene as the solvent, the sulphuryl chloride being added as an approximately 5% solution in dry benzene. This sulphuryl chloride solution was stable over a period of one day and could be prepared as a standard solution by using a weighed amount of sulphuryl chloride. The reaction was performed in the presence of solid benzene which allowed a constant low temperature to be maintained during the reaction.

The 5,6-dichlorides are much more convenient protecting groups than the 5,6-dibromides, which are difficult to crystallise[27] and have been reported to mutarotate;[28] moreover the dibromides are much less stable to heat[27] and to reducing and alkaline conditions.

Halogenation of the 5,6-double bond can be achieved in the presence of a conjugated enone elsewhere in the molecule. Previously such a selective reaction has been reported as a bromination to protect the 5,6-double bond through an allylic

bromination at C-15 in 3β-acetoxy-5α,6β-dibromopregn-16-en-20-one.[29]

Selective peroxidation of an unhindered double bond with an organic peracid in the presence of a 5,6-double bond is generally unsuccessful. The literature supports this contention both categorically[27] and tacitly;[24] in work described later in this thesis, attempts to selectively oxidise the 15,16-double bond in the presence of 5,6 unsaturation resulted in a Δ^{15}-5α,6α-oxide being the only separable product. Peroxidation of an enone with alkaline hydrogen peroxide may, on the other hand, be carried out in the presence of a 5,6-double bond,[30,31,32] this reaction has been used to prepare 16α-hydroxypregnenolone.[32] Selective hydroxylation of an enone with potassium permanganate may also be carried out in the presence of a 5,6-double bond.[33]

Introduction of a bromine atom in a position alpha to a 17-ketone may be achieved by brominating the corresponding enolacetate; this bromination proceeds so rapidly that when one equivalent of bromine is added very little of the bromine reacts with any 5,6-unsaturation.[34] Bromination alpha to a ketal is in some reaction sequences an alternative to the bromination of the ketone, in this work it was found that attempts to brominate alpha to a ketal using phenyltrimethylammonium bromide perbromide[35] and pyridinium hydrobromide perbromide brought about partial bromination at Δ^{5}. However, in this case as in other cases of unwanted bromination at C-5 and C-6 the 5,6-diaxial bromines can be removed by treatment with sodium iodide[36] followed by aqueous

sodium thiosulphate, this sequence leaves other isolated bromines untouched.

Reducing Conditions

The catalytic hydrogenation of the Δ^5 bond is reported to be difficult when a 3β-alcohol group is present,[37,38] although when the substituent atC-3 is an acetate, the reduction is easier.[37] Selective hydrogenations have been performed in the presence of the 5,6-double bond[39] and it has recently been reported[40] that when an homogeneous catalyst such as tris-(triphenylphosphine)-rhodium is used, the 5,6-unsaturation remains intact after two days.

When the 5,6-double bond is protected with a 5α,6β-dichloro group, greater care has to be taken over reducing agents. This trans diaxial group is reported to be stable to sodium borohydride,[24] but carbon-chlorine bonds in general are reported to be reduced by lithium aluminium hydride.[41] The 5α,6β-dichloro group is reported here to be unaffected by the conditions used for the internal generation of diborane, and this stability means that selective hydration of a double bond elsewhere in the molecule can be achieved.

Alkaline Conditions

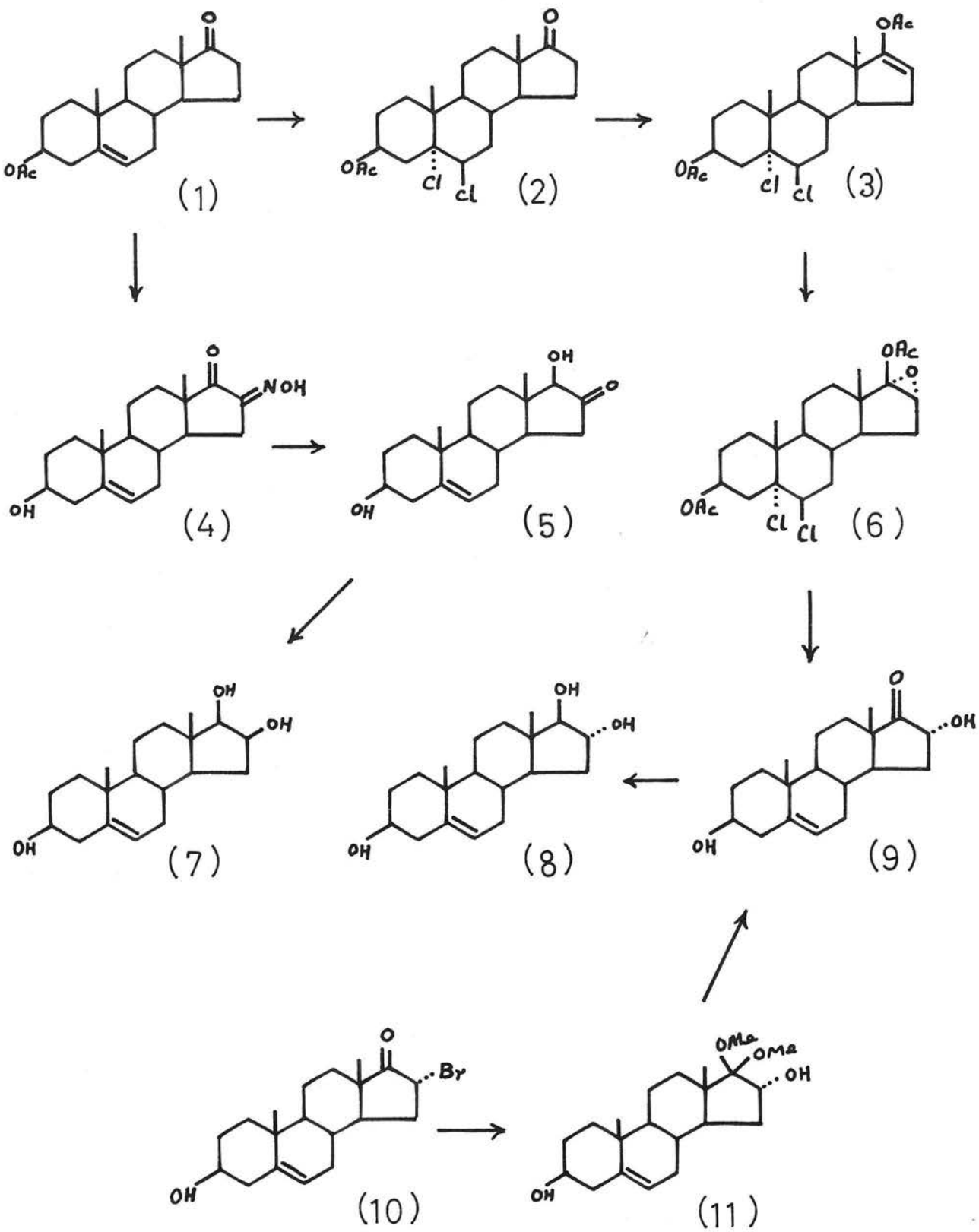
The 3β-hydroxy-Δ^5 system is found to be unaffected by very strong basic conditions, and the only danger of unwanted reaction occurring under basic conditions is when molecular oxygen is present, since this can give rise to allylic substitution at C-7.[23]

The Availability of 3β-hydroxy-Δ^5 Steroids for use as Starting Materials

The most common steroid found in animals is cholesterol, which occurs in brain and spinal cord in large amounts and is probably the metabolic precursor of pregnenolone. Cholesterol is cheap and commercially available from animal sources for the partial synthesis of compounds with the cholestane side chain. Most other 3β-hydroxy-Δ^5 steroids available in commercial quantities are obtained from vegetable sources. Diosgenin is a spirostane obtained from plants of the Dioscorea family and this compound is possibly the most important vegetable source of steroids. The sapogenin side chain can be degraded by techniques originally developed by Marker[42] to give dehydropregnenolone, which in turn can be easily transformed into dehydroepiandrosterone, pregnenolone or progesterone; progesterone is widely used as a substrate for microbiological hydroxylation at position 11 in modern syntheses of cortisone. Dehydroepiandrosterone, pregnenolone and dehydropregnenolone are all used for the synthesis of commercially useful steroids and as such they are cheaply and readily available; these steroids therefore represent the best starting materials for the synthesis of many 3β-hydroxy-Δ^5 steroids.

3β-Hydroxy-Δ^5 steroids oxygenated at C-11 are however not so readily available. Most 11-oxygenated steroids produced industrially incorporate the 11-oxygen by microbiological hydroxylation, and this is necessarily carried out with the 3-keto-Δ^4 structure in the molecule.

A convenient source of 3β-hydroxy-Δ^5 steroids substituted at position 11 is a mixture of botogenin and neobotogenin (3β-hydroxy-25R,S-spirost-5-en-12-one). The mixture of isomers at C-25 is normally used because of the difficulty of separation of the isomers and because this centre of asymmetry is lost when the side chain is degraded. The 12-ketone group can be transformed into an 11-ketone group by using standard methods used for cortisone synthesis. The sapogenin side chain can be removed by the procedure of Marker[42] to give 3β-hydroxypregna-5,16-diene-11,20-dione which is in turn a useful intermediate for the introduction of substituents at 16, 17 and 21. Although a good source of botogenin and neobotogenin has been reported[43] in Dioscorea spiculiflora, supplies of this material seem to be restricted. For the work described here a generous supply of 3β,12β-diacetoxy-25R,S-spirost-5-en-11-one was kindly donated by Glaxo Laboratories Ltd., Montrose. This material was obtained by Glaxo from a mixture of botogenin and neobotogenin.

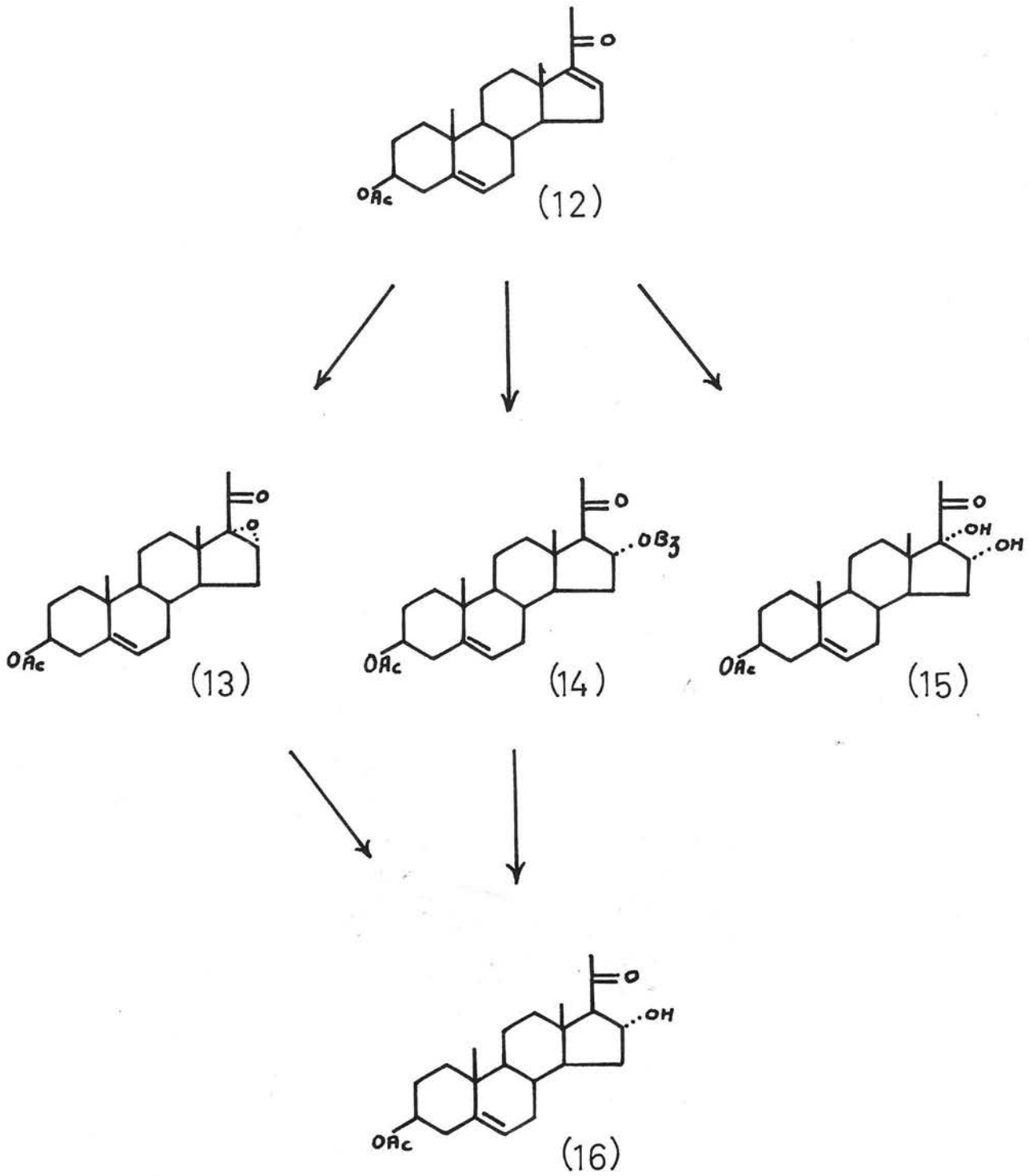


PREVIOUS SYNTHESES OF 3β,16α-DIHYDROXYANDROST-5-EN-17-ONE AND DERIVATIVES

Previous Partial Syntheses of 16 and 11-Substituted 3β-hydroxy-Δ^5 Steroids which are possible Metabolites of the Newborn Infant.

Many of the possible steroid metabolites of the newborn infant have been synthesised from 3β-hydroxyandrost-5-en-17-one and some of these compounds have been shown to be present in processed urine of infants.[1] 3β-Hydroxyandrost-5-en-17-one can be transformed into 3β,17β-dihydroxyandrost-5-en-16-one (5)[44] by the reaction with isoamyl nitrite in the presence of strong base to give the α-oximino ketone (4), which is reduced by zinc in acetic acid to the required ketol (5). This ketol has been detected in the processed urine of infants.[45] The ketol (5) may be reduced to the triol (7) with sodium borohydride.

3β,16α-Dihydroxyandrost-5-en-17-one (9) has been synthesised from 3β-acetoxyandrost-5-en-17-one (1)[24] by the chlorination of the 5,6-double bond followed by enolacetylation of the dichloride (2) to give a Δ^{16}-17-acetate (3). Oxidation of the enolacetate with peracid and subsequent acid catalysed rearrangement of the oxide (6) gives 3β,16α-diacetoxy-5α,6β-dichloroandrostan-17-one which can be hydrolysed and dechlorinated to give the required ketol (9). This ketol can be reduced to give 3β,16α,17β-trihydroxyandrost-5-ene (8). A newer synthesis of the ketol (9) has been reported by Hassner and Catsoulacos[46] proceeding *via* the 16α-bromo-17-ketone (10). This α-bromoketone is reacted with sodium methoxide in methanol to give 3β,16α-dihydroxy-17,17-dimethoxyandrost-5-ene (11) which can then be hydrolysed to give 3β,16α-dihydroxyandrost-5-en-17-one (9).

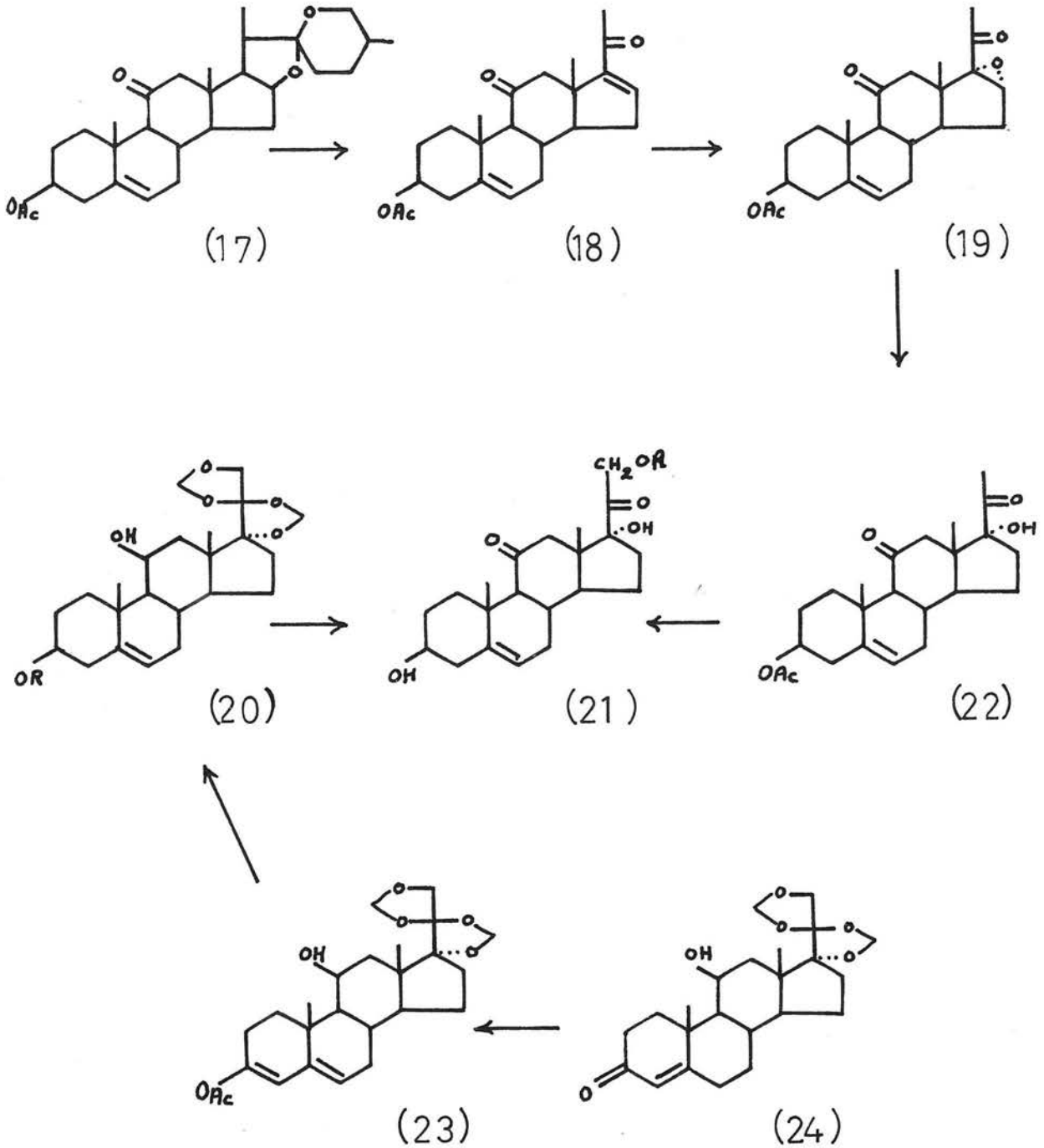


PREVIOUS SYNTHESES OF 16α-OXYGENATED DERIVATIVES OF

3β-HYDROXYPREGN-5-EN-20-ONE

16α-Hydroxypregnenolone acetate (16) has been synthesised from dehydropregnenolone (12) by selective formation of the 16α,17α-oxide (13) and reduction of this with chromous acetate.[32] A separate synthesis of the 16α-hydroxy-20-ketone proceeded *via* 3β-acetoxy-16α-benzyloxypregn-5-en-20-one (14),[47] this benzyloxy steroid is obtained by the base catalysed addition of benzyl alcohol across the enone in 3β-acetoxypregna-5,16-dien-20-one. The 16α-benzyloxy group may then be selectively hydrogenolysed using a palladium on charcoal catalyst, to give 16α-hydroxypregnenolone acetate. 3β,16α,17α-Trihydroxypregn-5-en-20-one (15) has been prepared by two different procedures. Dehydropregnenolone acetate (12) may be selectively hydroxylated at positions 16 and 17 by reaction with one mole of potassium permanganate.[33] Alternatively the 16α,17α-oxide of dehydropregnenolone (13) may be prepared and this reacted with hydrazine carbonic ester sulphate solution ($NH_2NH.CO_2Et/H_2SO_4$) to give 3β,16α,17α-trihydroxypregn-5-en-20-one (15).[48,49] This trihydroxy ketone may be converted into 16α-hydroxydehydroepiandrosterone (9)[33] by acetylation at C-16, reduction of the 20-ketone and cleavage of the glycol with periodic acid.

Most of the 11-oxygenated dehydroepiandrosterone derivatives have been prepared from botogenin. Rothman and Wall have reported the synthesis of 3β-acetoxyandrost-5-ene-11,17-dione (30),[50] which was obtained by the standard degradation of the side chain of botogenin followed by further side chain degradation *via* the 20-oxime (25). In the presence of unsaturation at 16 this oxime



PREVIOUS SYNTHESES OF 11-OXYGENATED DERIVATIVES OF

3β-HYDROXYPREGN-5-EN-20-ONE

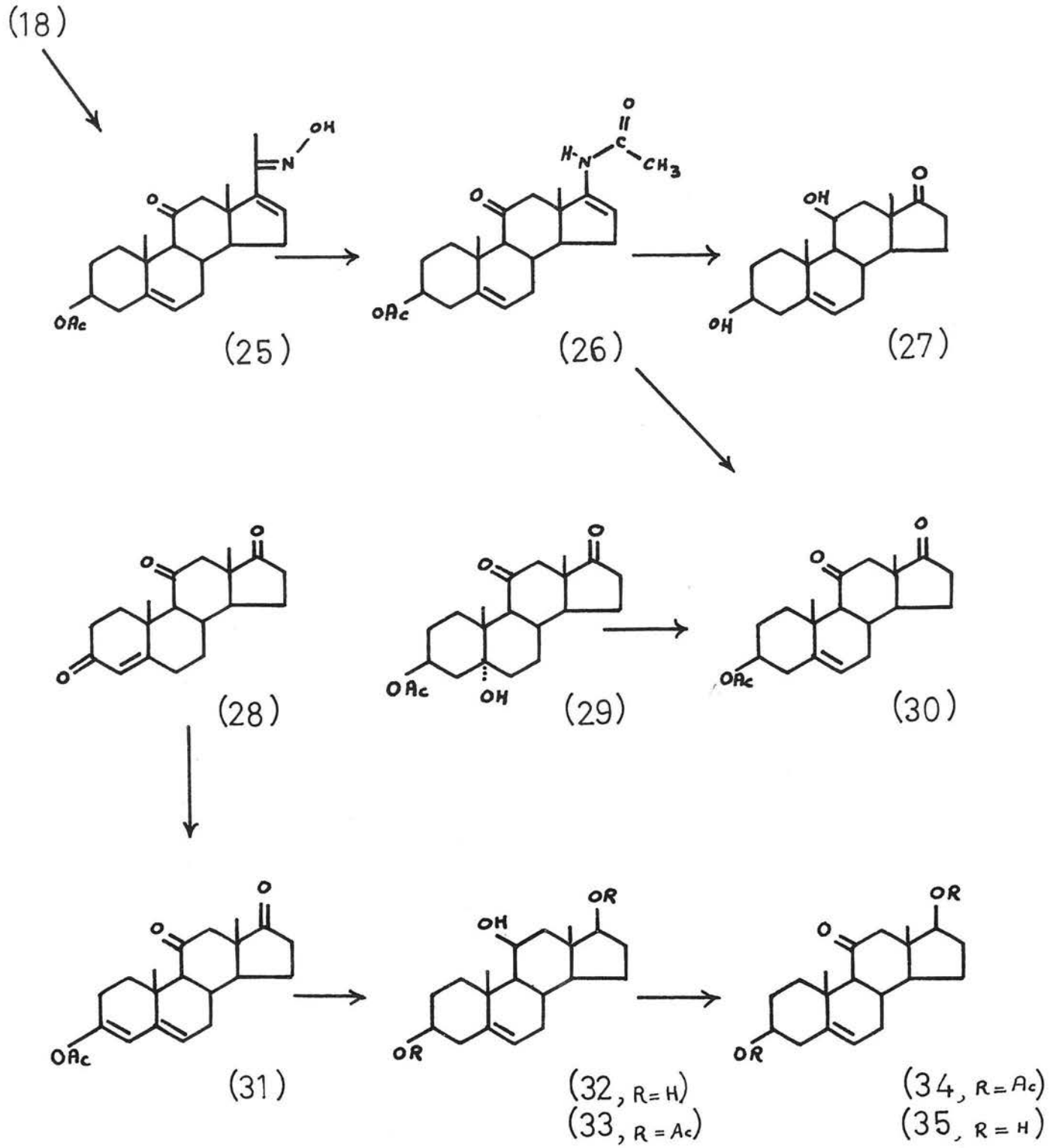
readily rearranges, and the product can be hydrolysed to give 3β-acetoxyandrost-5-ene-11,17-dione (30).

3β-Acetoxyandrost-5-ene-11,-17-dione was first reported by Martin-Smith[51] as a dehydration product of the corresponding 5α-hydroxy compound (29). The properties of the compound described by Martin-Smith agree with the properties of the compound derived from botogenin.

The rearranged oxime (26) serves as a good protecting group for the potential 17-ketone and the ketone at C-11 can be reduced in the presence of this unsaturated amide. Subsequent hydrolysis gives the 11β-hydroxy-17-ketone (27).

Rothman and Wall[30] and Djerassi[31] have published separate routes from botogenin to cortisone by elaborating in the standard ways the intermediates 3β-acetoxypregna-5,16-diene-11,20-dione (18) and 3β,11α-diacetoxypregna-5,16-dien-20-one which are obtained from the degradation of botogenin. The routes from botogenin to cortisone as published do not use 3β,17α,21-trihydroxypregn-5-ene-11,20-dione as an intermediate but in a patent to the U.S. Department of Agriculture,[52] Rothman and Wall report the preparation of 21-acetoxy-3β,17α-dihydroxypregn-5-ene-11,20-dione (21). This material is the 3β-hydroxy-Δ^5 analogue of cortisone acetate.

Interest in the preparation of cholesterol from cholest-4-en-3-one stimulated research into ways of converting 3-keto-Δ^4 compounds into the corresponding 3β-hydroxy-Δ^5 steroids. The conversion in the case of cholesterol was required in order to obtain cholesterol labelled at the 4 position. Cholest-4-en-3-one labelled at C-4 with ^{14}C can be prepared by cleaving the A-ring



PREVIOUS SYNTHESES OF 11-OXYGENATED DERIVATIVES OF

3β-HYDROXYANDROST-5-EN-17-ONE

and recyclising. Cholestenone was converted into cholesterol by Dauben and Eastham[53] who formed the dienol acetate of cholestenone and subjected this derivative to hydrolysis and *in situ* reduction with sodium borohydride in aqueous methanol. This deconjugation of the 3-keto- Δ^4 system has been used subsequently in the preparation of other 3β-hydroxy- Δ^5 steroids.

Adrenosterone (androst-4-ene-3,11,17-trione) (28) has been converted into 3β,11β,17β-trihydroxyandrost-5-ene[54] by the deconjugation and reduction route of Dauben and Eastham. This triol (32) can be selectively acetylated at positions 3 and 17, this allows subsequent oxidation at the 11 position to give the diacetoxy ketone (34).

The 3β-hydroxy-Δ^5 counterpart of cortisone (21) has been synthesised by Fukushima and Teller.[55] These workers prepared 3β-acetoxy-11β,17α,21-trihydroxypregna-3,5-dien-20-one bismethylenedioxy ketal (23) which was hydrolysed and reduced to the 3β, 11β-diol (20) with the sidechain still protected as the *bis*-methylenedioxy derivative. This molecule can be selectively acetylated at position 3, oxidised and fully hydrolysed to give the cortisone analogue (21) (R=H).

Pregnenolone with a ^{14}C at position 4 has been synthesised from the corresponding progesterone,[56] in this case the 20-ketone group was protected as the semicarbazone, which was introduced after the enone had been enolacetylated.

The Synthesis of 16 and 11 Oxygenated 3β-Hydroxy-Δ^5 Compounds

The most convenient source of 3β-hydroxy-11-oxo Δ^5 compounds is the mixture of botogenin (3β-hydroxy-20α,22α,25R-spirost-5-en-12-one) and neobotogenin (3β-hydroxy-20α,22α,25S-spirost-5-en-12-one) obtained together from Dioscorea spiculiflora. These 12-keto sapogenins can be readily converted to 3β-acetoxypregna-5,16-diene-11,20-dione (18),[50] an ideal intermediate for the preparation of most of the 11 and 16 disubstituted androstenes required. However, the limited availability of either the original sapogenins or any processed material stimulated research into the conversion of 3-keto-Δ^4 compounds into 3β-hydroxy-Δ^5 compounds. A generous gift of some 3β,12β-diacetoxy-25R,S-spirost-5-en-12-one (49) from Glaxo Laboratories Ltd., (Montrose), enabled some syntheses to be executed starting from the 11-keto dehydropregnenolone derivative. These syntheses were confined to the pregnenes because here the intermediate was most useful. The substituted androstenes were synthesised from adrenosterone.

The Conversion of Adrenosterone to 3β-Hydroxyandrost-5-ene-11,17-dione

The only previously successful method of converting 3-keto-Δ^4 compounds into their 3β-hydroxy-Δ^5 counterparts has depended on the hydrolysis and the in situ reduction of the 3,5-dienol acetate. In this combined reaction it is obviously the hydrolysis which under these conditions is the difficult stage, because the 3-keto-Δ^5 intermediate is readily reduced.[39] The result of a lengthy hydrolysis (about twenty-four hours at room temperature) is that

any other group in the molecule must be able to withstand the extended contact with the reducing agent. In most previous uses of this hydrolysis and reduction procedure there have not been other functional groups to reduce,[53,55,56] but where such other reduction was possible this has been allowed to proceed.[54]

Selective reductions have been achieved which leave an 11-ketone group intact,[39] but the 11-keto group is at least partly reduced after reaction with sodium borohydride for twenty-four hours with this reagent, whereas a 17-carbonyl group is quite quickly reduced. The problem therefore in the preparation of 3β-hydroxyandrost-5-ene-11,17-dione is the preservation of the 11- and 17-ketone functions through the reaction. For the 17-ketone, a ketal would suffice for protection but the 11-ketone group is very difficult to ketalise.[39]

The 17-ethyleneketal of adrenosterone was prepared (a discussion of this synthesis will follow later) and this ketal was subjected to the borohydride hydrolysis and reduction reaction of Dauben and Eastham.[53] The result of this reaction was that after twenty-four hours only 60% of the 11-ketone remained unreduced together with 11% of unreacted enolacetate. This route did not therefore appear promising and consequently an alternative reaction was sought which would allow rapid reduction of a Δ^5-3-ketone system and leave the 11-ketone untouched.

The possibility of hydrolysing another derivative of the Δ^4-3-ketone to give a 3β-hydroxy-Δ^5 compound was considered. The other derivatives of the conjugated enone which are formed with

an accompanying shift of the double bond to the B-ring are the enamines, the dienol ethers, and the ethyleneketal. Since the Δ^5-3-ketone is readily isomerised in the presence of acids,[57] only alkaline hydrolysis of these groups can be considered, and this means that the ethylene ketal derivative is of no further interest since this derivative is stable to base.

The only dienol ether which might be of use was the trimethylsilyl enol ether which would be expected to hydrolyse very readily. However, attempts to prepare this ether were unsuccessful. Bis-(trimethylsilyl)-acetamide being itself an enol ether is a very reactive silanising agent,[58] and it was thought that if triethylamine was used as a solvent, this might produce sufficient steroid enol to be transetherified. However, when a solution of testosterone in bis-(trimethylsilyl)acetamide and triethylamine was refluxed, only the 17β-trimethylsilyl ether of testosterone could be isolated from the reaction mixture.

The possibility of hydrolysing an enamine under mildly basic conditions seemed reasonable. Previous methods of obtaining Δ^5-3-ketones have subjected these compounds to aqueous ammonia during the work-up procedure;[59] therefore the isomerisation of Δ^4 to Δ^5 in the presence of this base is obviously slow. The enamine of adrenosterone was prepared and this compound was hydrolysed with aqueous ammonia to give a product which was indeed mainly the deconjugated enone androst-5-ene-3,11,17-trione. U.v. analysis of the crude semicrystalline mixture isolated from the hydrolysis reaction showed that there was approximately 70%

of the unconjugated and 30% of the conjugated isomeric enone present.

From the crude mixture of the conjugated and the deconjugated isomers, pure androst-5-ene-3,11,17-trione was isolated by column chromatography on Florisil. The yield of isolated deconjugated material was low due to the difficulty of separation and to further isomerisation taking place on the column. The deconjugated enone was reduced to give 3β,17β-dihydroxyandrost-5-en-11-one but selective reduction of the 3-ketone over the 17-ketone was found not to be possible. Selective acetylation of the 3β-hydroxyl over the 17-hydroxyl was also not possible and consequently no differentiation between the 3 and the 17 position could be achieved.

The logical next step was to apply the enamine deconjugation route to 17-ethylenedioxyandrost-4-ene-3,11-dione. Unfortunately, when the experiments were repeated using the identical conditions, the hydrolysis reaction appeared to be much slower for the 17-ketalised compound. After four hours of hydrolysis, original enamine remained and partial isomerisation to the conjugated enone had occurred as before, giving an approximately 1:1:1 mixture of original enamine, deconjugated ketone and conjugated ketone. This route was therefore not a promising one for the synthesis of 3β-hydroxyandrost-5-ene-11,17-trione. Experiments on the hydrolysis of testosterone enamine produced results similar to those with the ketal of adrenosterone. Thus it would appear that the speed of hydrolysis of these 3,5-dienamines depends largely on the nature of the other substituents in the molecule.

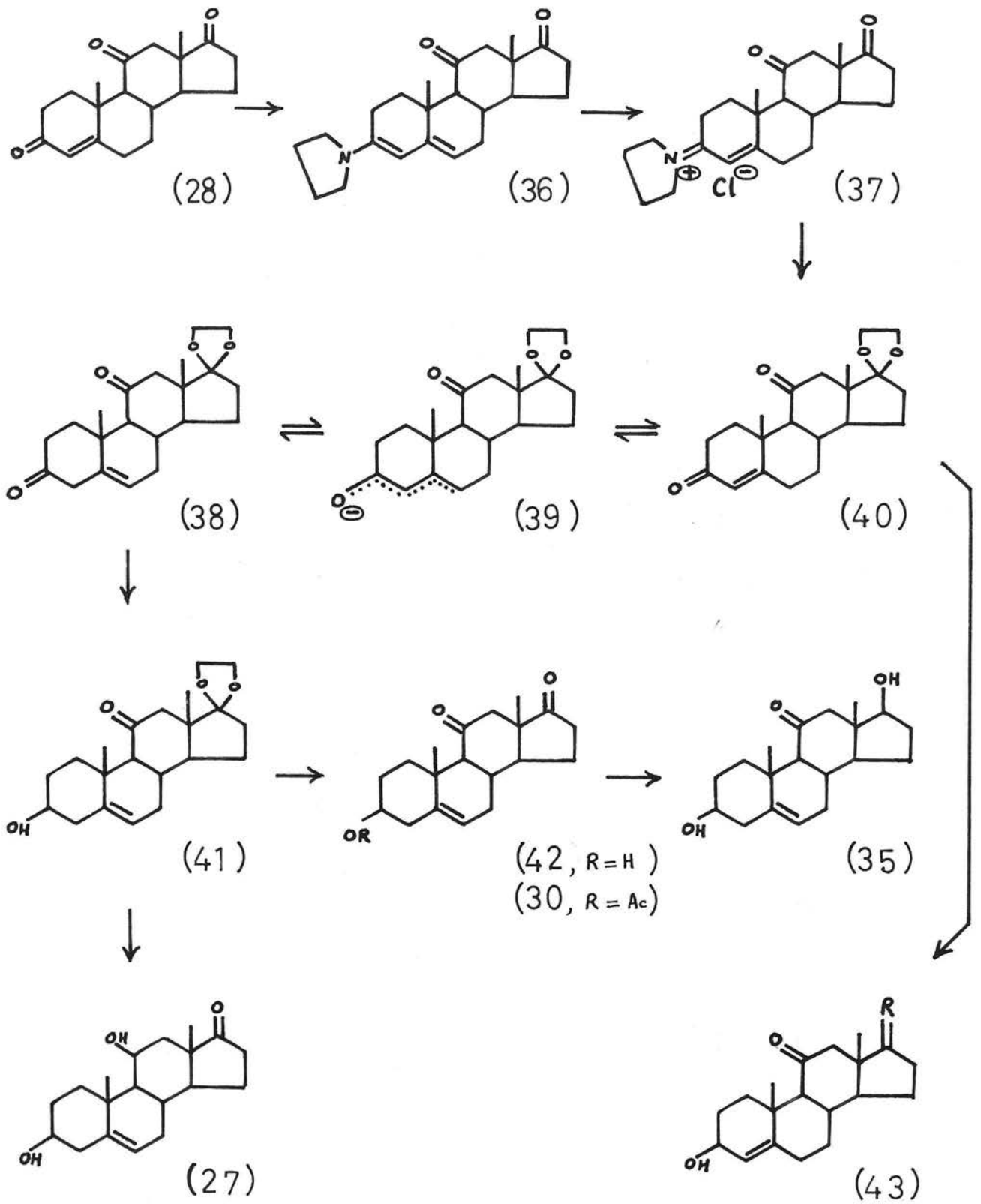
The dienamines of Δ^4-3-ketones are reduced to tertiary amines

by sodium borohydride[60] and therefore there is no possibility of effecting an hydrolysis in the presence of borohydride and reducing the deconjugated enone *in situ*.

No stable derivative of adrenosterone seemed suitable for the conversion to 3β-hydroxyandrost-5-ene-11,17-dione and therefore attention was focussed on the preparation of the 3-keto-Δ^5 system by direct deconjugation with strong base.

Previous preparations of the 3-keto-Δ^5 system have been reported which have used solutions of strong base to convert the enone to the thermodynamically favoured 3,5-dienolate anion. Ringold and Malhotra[61,62] have studied this enolisation and in a series of papers have reported high concentration of the 3,5-dienolate anion. In the preparation of 3-keto-Δ^5 compounds these authors quench the dienolate anion solution with acetic acid to give the deconjugated ketone by protonation at C-4.

In the deconjugation of $\Delta^{1,4}$-dien-3-ones, Shapiro *et al.*[63] have reported the preparation of $\Delta^{1,5}$dien-3-ones; these compounds have been isolated and reduced with aqueous borohydride solution. Shapiro and coworkers treated the cross conjugated dienone with strong bases in dimethylsulphoxide, however, they did not quench the reaction mixture with acetic acid but poured the mixture into iced water which consequently became alkaline due to addition of the base. The high concentration of trienolate anion produced during the deconjugation must therefore have been protonated by the aqueous alkaline solution during the quenching. However, this reaction is more likely than the alternative one in which a high concentration of deconjugated $\Delta^{1,5}$-ketone would have existed before



THE SYNTHESIS OF 11-OXYGENATED DERIVATIVES OF 3β-HYDROXYANDROST-5-EN-17-ONE

quenching, since this would have involved protonation of the trienolate anion by the aprotic alkaline solution used for this deconjugation.

The deconjugated $\Delta^{1,5}$-dienones of Shapiro are more stable than the Δ^{5}-3-ketones because the 3-ketone remains conjugated to Δ^{1} and this extra stability allows a better isolation of the $\Delta^{1,5}$-compound. This deconjugation of 1,4-dien-3-ones might represent a route to the 3β-hydroxyandrost-5-enes since the unsaturation at position 1 can be readily removed by homogeneous catalytic hydrogenation.[64] The starting material (androsta-1,4-diene-3,11,17-trione) is commercially available, however a more convenient route to 3β-hydroxyandrost-5-ene-11,17-dione was developed. Previous authors[61,63] have commented on the variable concentrations of the thermodynamically more stable anion and also on the variable amounts of the deconjugated ketones which are present after quenching. These variations seem to be dependant in some uncertain way on the other functional groups present in the molecules, and these observations seem to be born out in the following deconjugation experiments.

A solution of 17-ethylenedioxyandrost-4-ene-3,11-dione (40) in dry dimethylsulphoxide was treated with potassium tertiary butoxide under nitrogen to generate a large amount of the enolate anion (39). This solution was poured into a stirred solution of sodium borohydride in aqueous methanol. The Δ^{5}-ketone (38) which must have been produced initially was rapidly reduced to the 3β-hydroxy-Δ^{5} compound (41), however the reaction time (ten minutes) was such that the amount of reduction of the Δ^{4}-3-ketone present, was small

and that of the 11-ketone negligible. Gas liquid chromatographic analysis of the reaction product, isolated by an ether extraction, demonstrated the presence of 4% of 3β-hydroxy- Δ^4 compound (43, R = ). This reduced enone was analysed as its $\Delta^{3,5}$-diene derivative,[20] which is produced quantitatively during gas chromatography. Subsequent column chromatography of the product gave an 8% return of unreduced Δ^4-3-ketone (40); further column fractions contained 17-ethylenedioxy-3β-hydroxyandrost-5-en-11-one (41), which after crystallisation firstly from acetone-petrol and secondly from aqueous methanol represented a 70% yield of pure Δ^5-3β-alcohol.

In order to prove the position of the double bond in the reduced enone, the starting material, 17-ethylenedioxyandrost-4-ene-3,11-dione (40) was reduced with borohydride, the melting point of the 17-ethylenedioxy-3β-hydroxyandrost-4-en-11-one (43, R = ) produced, differed markedly from that of the deconjugated and reduced compound (41). Further evidence of the 3β-hydroxy- Δ^5 structure comes from the n.m.r. spectra (in pyridine) of the two isomers. The spectrum for the Δ^5-3β-hydroxy compound exhibits strong absorptions at τ 9.12, 8.64 and 6.19 which correspond to the C-18 and C-19 methyl groups and to the ethyleneketal protons respectively, there is also a characteristic multiplet centred at τ 4.61 due to the hydrogen on C-6. The spectrum of the Δ^4 isomer shows similar absorptions for the methyl and ketal protons, but the absorption at τ 4.61 has disappeared and two peaks at τ 4.25 and τ 4.36 are present; these absorptions are tentatively assigned to the (4-H) and the 3-hydroxy proton.

Further proof of the identity of the 3β-hydroxy-Δ^5 compound was obtained by the hydrolysis of the ketal and acetylation of the 3β-alcohol to give the known 3β-acetoxyandrost-5-ene-11,17-dione (30), the material obtained from the deconjugation route was identical in all respects with material obtained by an independent route.[65]

By the route outlined above, 3β-hydroxyandrost-5-ene-11,17-dione (42) may be synthesised from the readily available androst-4-ene-3,11,17-trione (28) in an overall yield of 45%. The intermediates in this route provide a convenient synthetic pathway not only to 3β-hydroxy-Δ^5 compounds but also to 3β-hydroxy-Δ^4 compounds which possess a ketone group at C-17. Such compounds have been made previously by indirect routes. Morreal[66] has recently published a route to 3β-hydroxyandrost-4-ene-11,17-dione (43R=o) which involves the selective acetylation of a 3,17-diol at position 3; this acetylation gives the desired monoacetate in only 9% yield and the overall yield to the required 11,17-dione is considerably lower. Fukushima[67] has published a synthesis of 3β,11β-dihydroxyandrost-4-en-17-one which starts from cortisol and introduces the 17-ketone by periodate oxidation of the side chain. The key intermediate in the work presented above which allows the conversion to 3β-hydroxy-Δ^4 structure and the ready reintroduction of the 17-ketone is the 17-monoketal of androst-4-ene-3,11,17-trione.

A previous synthesis[68] of the 17-monoketal of androst-4-ene-3,17-dione used one equivalent of ethyleneglycol and a limited amount of p-toluenesulphonic acid catalyst. This method required the chromatographic separation of the products and the best yield

of 17-monoketal was only 25% after crystallisation. Although the process could presumably be applied to androst-4-ene-3,11,17-trione a more efficient route was sought.

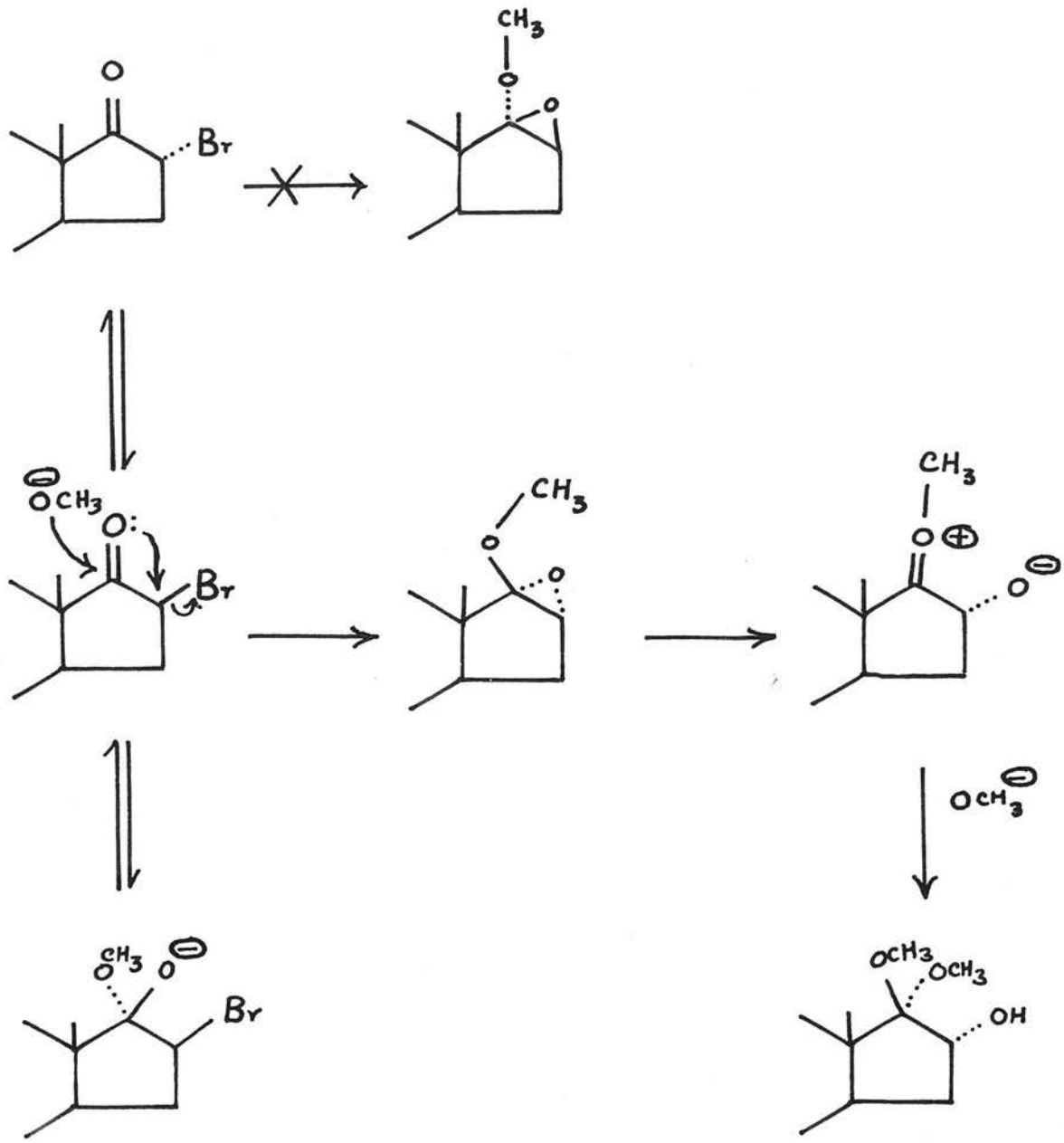
The Δ^4-3-ketone will readily form an enamine with pyrrolidine[69] and using one mole of the amine, reaction can be confined to the enone in the presence of other saturated ketones.[70] Enamines have previously been transformed to their iminium salts to protect them through lithium aluminium hydride reductions; since the iminium salts are necessarily formed in the presence of anhydrous strong acid, it would seem probable that they are stable to these conditions and it was thought that these salts might be a good protection of the enone group through a ketalisation at the 17 position.

The iminium salt of 3-(N-pyrrolidyl)-androsta-3,5-diene-11,17-dione (36) was prepared and because this was a salt, it was readily soluble in ethyleneglycol; this meant it was ideally suited to the ketalisation procedure of Campbell *et al.*[71] The salt was dissolved in ethyleneglycol and *p*-toluenesulphonic acid was added, the solvent was then distilled off very slowly at about 60° under high vacuum. Any water formed as a result of formation of ketal was quickly removed under these conditions and therefore formation of the ketal was favoured. When the ketalisation was complete (after about two hours) aqueous ammonia was added to regenerate the enamine and the steroid was isolated with an ether extraction. The regenerated enamine was unstable to the conditions of the work-up and the product that was isolated in 72% yield after crystallisation

was 17-ethylenedioxyandrost-4-ene-3,11-dione (40).

The synthesis of 17-ethylenedioxy-3β-hydroxyandrost-5-en-11-one has allowed an alternative synthesis of 3β,11β-dihydroxyandrost-5-en-17-one (27) which has been previously synthesised by Rothman and Wall from botogenin[50] and by Meystre from cortisone.[72] The latter synthesis is reported in a patent, but the physical constants of the 3β-hydroxy-Δ^5 compounds prepared by Dr. C. Meystre have been kindly supplied by Dr. R. Neher.[73]

In order to check on the general applicability of the base deconjugation procedure, the reaction was applied to other suitable Δ^4-3-ketones namely testosterone and adrenosterone. In both these cases the reaction did not proceed as well as in the case of the monoethyleneketal of adrenosterone and it was found necessary to acetylate the products from these reactions to simplify the isolation procedure, even so the yields of the corresponding Δ^5-3β-acetates were only moderate. In the case of testosterone the product isolated after acetylation was 3β,17β-diacetoxyandrost-5-ene in 46% yield and in the case of adrenosterone the isolated product was 3β,17β-diacetoxyandrost-5-en-11-one (34) obtained in 16% yield. In both these cases the amounts of Δ^4-3-ketones and Δ^4-3β-hydroxy compounds shown to be present were higher than in the case of the 17-ethylenedioxy compound (40). It seems likely in view of the previous evidence[61,63] on the variable concentrations of the 3,5-dienolate anion in base deconjugation mixtures that these lower yields of deconjugated ketones are indeed the result of lower concentrations of the corresponding



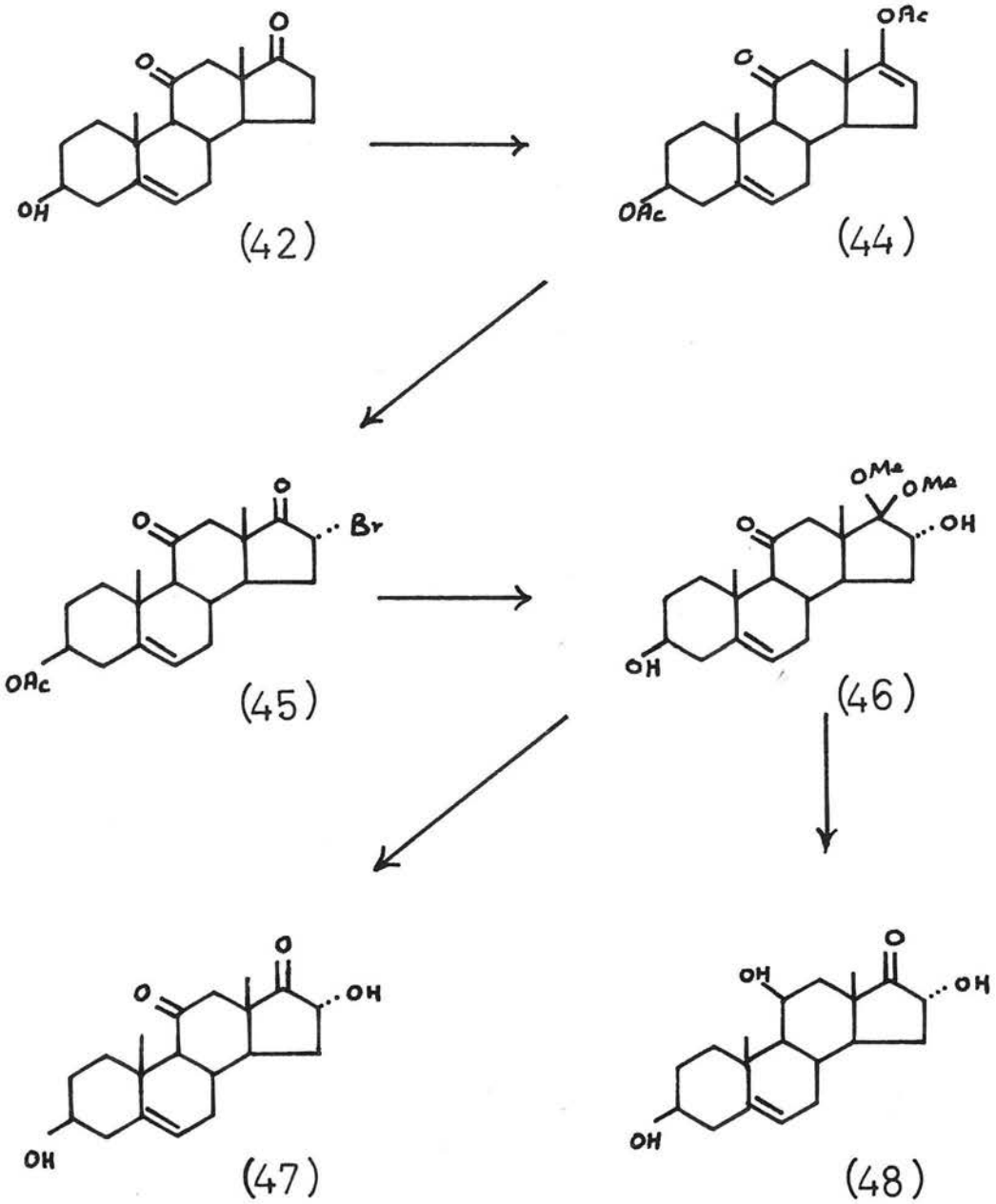
THE MECHANISM OF REACTION OF A 16α-BROMO-17-KETONE WITH SODIUM METHOXIDE PROPOSED BY A.HASSNER AND P.CATSOULACOS

dienolate anions in the basic deconjugating medium before the quenching and reduction.

The Synthesis of 3β,11β,16α-Trihydroxyandrost-5-en-17-one and 3β,16α-Dihydroxyandrost-5-ene-11,17-dione

The efficient synthesis of 3β-hydroxyandrost-5-ene-11,17-dione described above allowed the synthesis of 11,16 disubstituted androst-5-enes. As has already been described two methods exist for the preparation of the 16α-hydroxy-17-ketone structure; the first, a longer route,[24] involves the protection of the 5,6-double bond and subsequent oxidation of the enolacetate (3) formed from the 17-ketone. The second synthesis involves the preparation of the 16α-bromo-17-ketone, reaction of this with sodium methoxide in methanol to give a 16α-hydroxy-17-dimethylketal and hydrolysis of the ketal to give the required 16α-hydroxy-17-ketone. The mechanism of this unusual reaction has been studied by Hassner and Catsoulacos[46] and these authors have proposed the sequence illustrated. Their mechanism depends on an equilibrium between the 16α- and 16β-bromo ketones and they postulate β attack by the methoxy ion on the β-bromoketone. An oxide intermediate is formed and this opens prior to final attack by methoxide ion to give the stable hydroxy-ketal.

The α-bromo ketone route has several advantages; it involves less intermediates, it is likely to proceed in a higher overall yield and the most important is that it provides an intermediate where the 17-ketone group is protected against lithium aluminium hydride reduction. This protected intermediate allows the



THE SYNTHESIS OF 11-OXYGENATED DERIVATIVES OF

3β,16α-DIHYDROXYANDROST-5-EN-17-ONE

preparation of the corresponding 11β-hydroxy compound. The preparation of the 16α-bromo ketone, however, presented an initial problem; direct bromination with bromine would give 5,6-bromination apart from the fact that the bromination of the 17-ketone group does not proceed smoothly.[74] Bromination of a 17-ketone with cuprous bromide proceeds in moderate yield (50%) only.[75] Bromination of the enol acetate[76] gives a good yield (77%) of bromo ketone but this method requires the initial preparation of the enol-acetate.

The enol-acetate (44) was prepared using acid catalysed exchange with isopropenyl acetate. This method which is very mild gave a clean product which could be isolated in 80% yield. The bromination of this enol-acetate in carbon tetrachloride with one mole of bromine at -10^{o} was virtually instantaneous. The product could be isolated in 76% yield, this was an overall yield of bromoketone (45) of 61%, which was reasonable considering the other functional groups present in the molecule.

The bromo-ketone was reacted with sodium methoxide in methanol following the method of Hassner and Catsoulacos.[46] The yield of pure product (46) was 37%. The yield in this reaction was lower than expected since the literature records a 65% yield for the 11-desoxy analogue. The mother liquors from the crystallisation were analysed by column chromatography but this did not achieve a good separation of the mixture, however a small amount of 3β-hydroxy-androst-5-en-11,17-dione (42) was finally isolated. Although the amount of 3β-hydroxyandrost-5-ene-11,17-dione isolated represents

only a proportion of the amount present, its presence does not allow the explanation of the low yield of the product (46) from the reaction.

The hydroxy ketal (46) could be hydrolysed at 40° using p-toluene sulphonic acid in aqueous acetone, this method gave a good (80%) yield of the ketone (47). This milder hydrolysis gave a better yield than that obtained by Hassner and Catsoulacos on the 11-desoxy compound for the hydrolysis of which a 65% yield was quoted.

The dimethoxy ketal (46) was reduced with lithium aluminium hydride to give the 11β-alcohol, the acid hydrolysis of the work-up removed the ketal group to give 3β,11β,16α-trihydroxyandrost-5-en-17-one (48) in an overall yield of 36% from the ketal (46).

EXPERIMENTAL SECTION

Experimental Procedure.- Melting points were determined on a Kofler hot stage apparatus and are corrected.
Rotations were measured either on an E.T.L.-N.P.L. automatic polarimeter or on a Perkin Elmer polarimeter model 141, rotations were measured at 589 mμ in chloroform unless otherwise stated. Optical Rotatory Dispersion curves were measured in methanol on a Bendix-Ericsson Polarmatic 62. Infra red spectra were recorded on a Unicam S.P.200 or on a Perkin Elmer 237 instrument, spectra were usually for carbon disulphide solutions. Ultra-violet spectra were recorded on a Unicam S.P.800 using ethanol solutions. Nuclear Magnetic Resonance spectra were obtained from a Perkin Elmer R10 (60mc/s) spectrometer using tetramethyl-silane as an internal standard; deuteriochloroform solutions were used unless otherwise stated. Gas-liquid Chromatography was done on a Perkin Elmer model 801 using 6 ft. all glass columns of 1/16" internal diameter. The stationary phase was 2½% silicone gum rubber E301 on Cromosorb G. Injector, column and detector temperatures were 250,240 and 250° respectively. Relative retention times for both g.l.c. and t.l.c. are expressed relative to 3β-hydroxyandrost-5-en-17-one (dehydroepiandrosterone) and are written as R_D values. For thin layer chromatography Merck silica gel G was used throughout and the steroids were stained with saturated solutions of antimony trichloride in chloroform. The developing systems were those of Lisboa.[19]
Mass spectrometry was carried out on an L.K.B.9000 instrument by Dr. C. J. W. Brooks of Glasgow University. Trimethylsilyl

ethers were prepared by the method of Sweely *et al.*[136] using pyridine, hexamethyldisilazane and trimethylchlorosilane in the proportions 7:2:1, the steroid solutions were then injected directly into the gas chromatographic columns.

Alumina refers to Spence type H alumina of Brockman activity 2. Florisil refers to a synthetic magnesia-silica gel adsorbent. Petrol refers to petroleum ether with boiling range 60-80°. Microanalyses were determined either by Drs. Weiller and Strauss of Oxford or by Bairds Ltd. of Edinburgh.

3-(N-Pyrrolidyl)-androsta-3,5-diene-11,17-dione (36)

Pyrrolidine (1.90 g.) was added to a hot solution of androst-4-ene-3,11,17-trione (28) (7.17 g.) in methanol (220 ml.) under a nitrogen atmosphere. The solution was allowed to cool slowly to room temperature. The crystals which formed were filtered off, washed with cold methanol and dried. The crystals decomposed above 185° (lit.[70] dec. above 180°). ν_{max} 1735, 1701 and 1634 $cm.^{-1}$ Yield 7.6 g.

17-Ethylenedioxyandrost-4-ene-3,11-dione (40)

3-(N-Pyrrolidyl)-androsta-3,5-diene-11,17-dione (7.5 g.) was dissolved in ether (100 ml.) and chloroform (100 ml.) dry hydrogen chloride was passed through the solution for 15 minutes. The steroid was extracted into water (150 ml.) and the aqueous solution was washed twice with 100 ml. portions of ether. The aqueous solution was evaporated to dryness leaving a glass (7.6 g.) which did not crystallise. N.m.r. (D_2O) showed one olefinic proton at τ 3.58 and methyl resonances at τ 9.13 and τ 8.62. The non-crystalline imminium hydrochloride (37) (7.6 g.) and p-toluene sulphonic acid (500 mg.) were dissolved in ethylene glycol (150 ml.). The ethylene glycol solution was stirred and gently distilled at about 0.01 mm. pressure keeping the temperature between 60 and 70°. The distillation was continued for three hours after which time about 5 ml. of liquid remained. The residue was dissolved in water (200 ml.) and 80% ammonia (5 ml.) was added. The flocculent precipitate which formed was dissolved in ether (400 ml.) and the ethereal solution was washed with saturated salt solution, dried with

magnesium sulphate and evaporated to dryness. The crystalline residue was recrystallised from methanol to give 17-ethylenedioxyandrost-4-ene-3,11-dione (40) (5.7 g.) m.p. 149-151°; $[\alpha]_D$ =+198° (c 0.1); ν_{max} 1701 and 1673 $cm.^{-1}$ n.m.r. ($CDCl_3$) τ 9.15 (C-18 methyl), τ 8.54 (C-19 methyl) and τ 4.28 (4H). An analytical sample was recrystallised from methanol, m.p. 151-152°. (Found: C, 72.9; H, 8.1. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.2%).

3-Acetoxy-17-ethylenedioxyandrosta-3,5-dien-11-one.

17-Ethylenedioxyandrost-4-ene-3,11-dione (40) (1.3 g.) was dissolved in redistilled ethyl acetate (50 ml.) and a solution of acetic anhydride (10 ml.) and 70% perchloric acid (0.02 ml.) in ethyl acetate (40 ml.) was added. The solution was allowed to stand at room temperature for five minutes then it was poured into dilute sodium carbonate solution. The mixture was shaken until evolution of gas had ceased then ether (500 ml.) was added, the ethereal solution was washed with sodium carbonate and saturated salt solution. The solution was dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from aqueous methanol to give 3-acetoxy-17-ethylenedioxyandrosta-3,5-dien-11-one (0.9 g.) m.p. 153-156°; $[\alpha]_D$ -83° (c 0.1); ν_{max} 1747, 1700 $cm.^{-1}$ n.m.r. ($CDCl_3$) τ 9.15 (C-18 methyl), τ 8.80 (C-19 methyl), τ 7.88 (3-acetate) and τ 4.65, 4.32 multiplets, (6H, 4H). (Found: C, 71.4; H, 7.9. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%).

Hydrolysis and in situ reduction of 3-Acetoxy-17-ethylenedioxyandrosta-3,5-dien-11-one.

3-Acetoxy-17-ethylenedioxyandrosta-3,5-dien-11-one (180 mg.)

was dissolved in 90% aqueous methanol (110 ml.) and sodium borohydride (55 mg.) was added. The mixture was stirred until the borohydride had dissolved and then maintained at 25° for 24 hours. Water was added and the steroid was recovered by an ether extraction. The ethereal solution was dried and evaporated to dryness. The infrared spectrum showed there to be approximately 60% of the 11-ketone remaining (ν_{max} 1700 $cm.^{-1}$) and 10% of unreacted enolacetate, (ν_{max} 1747 $cm.^{-1}$).

Attempted Preparation of the Dienolsilyl ether of Testosterone.

17 β-Hydroxyandrost-4-en-3-one (0.5 g.) was dissolved in triethylamine (25 ml.) and freshly prepared[58] bis(trimethylsilyl)-acetamide (5 ml.) was added and the solution was refluxed for two hours with the rigorous exclusion of moisture. After two hours the reaction mixture was poured into water and the steroid was extracted with ether, the ethereal solution was washed with water and saturated salt solution, dried with magnesium sulphate and evaporated to dryness. Infrared analysis of the product showed there to be strong enone absorption, this indicated that there could only be a very small amount of the required dienolsilyl ether. No absorption at 1700 $cm.^{-1}$ was noticeable.

Androst-5-ene-3,11,17-trione

3-(N-Pyrrolidyl)-androsta-3,5-diene-11,17-dione (36) (800 mg.) was dissolved in acetone (120 ml.), ammonium chloride (1 g.) dissolved in 40% aqueous ammonia (20 ml.) was added. The suspension of ammonium chloride was stirred at room temperature for two

hours. Water (40 ml.) was added and the solution was evaporated to 40 ml. at room temperature, a crystalline precipitate formed and this was filtered off and dried. Yield 620 mg. The ultraviolet spectrum of this crude product had $\lambda_{max.}$ at 238 mμ (ϵ = 4500) indicating there to be 30% of the conjugated ketone remaining. The extinction coefficient for pure adrenosterone being 15,180 measured at 238 mμ. The crude mixture was chromatographed on Florisil (100 g.). Elution with ether gave androst-5-ene-3,11,17-trione (200 mg.), further elution with ether-chloroform (1:1) gave mixed fractions containing both androst-5-ene-3,11,17-trione and the original androst-4-ene-3,11,17-trione, these mixed fractions were not crystallisable. The deconjugated enone was recrystallised from ethanol to give 100 mg. of pure androst-5-ene-3,11,17-trione. An analytical sample was recrystallised from ether, m.p. 170-182°, (the large melting point range is due to the ready isomerisation of Δ^5 to Δ^4) $\nu_{max.}$ ($CHCl_3$) 1740 and 1710 $cm.^{-1}$; n.m.r. τ 9.11 (C18 methyl), τ 8.60 (C19 methyl), and τ 4.59 multiplet (6H). (Found: C, 76.2; H, 8.4. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.05%).

3β,17β-Dihydroxyandrost-5-en-11-one (35)

Androst-5-ene-3,11,17-trione (100 mg.) was added to a stirred solution of sodium borohydride (100 mg.) in methanol (22 ml.) and water (2.5 ml.). The steroid dissolved and the solution was stirred for 30 minutes. Excess water was added and the steroid was extracted into ether. The ethereal solution was washed with dilute hydrochloric acid, sodium carbonate and saturated salt solution and was evaporated to dryness to give a residue which was recrystallised

from aqueous methanol to give 3β,17β-dihydroxyandrost-5-en-11-one (35) (50 mg.), m.p. 222-224° (lit.,[73] m.p. 230-232°) $[\alpha]_D$ =-41° (c 0.1); n.m.r. (pyridine) τ 9.08 (C-18 methyl), τ 8.60 (C-19 methyl) and τ 4.55 multiplet (6H).

3-(N-Pyrrolidyl)-17-ethylenedioxyandrost-3,5-dien-11-one.

17-Ethylenedioxyandrost-4-ene-3,11-dione (1 g.) was dissolved in hot methanol (50 ml.) and pyrrolidine (0.5 ml.) was added. The solution was allowed to cool to room temperature and the enamine crystallised out. The crystals were filtered off and dried to give 3-(N-pyrrolidyl)-17-ethylenedioxyandrosta-3,5-dien-11-one (1 g., dec. above 175°), which was not further purified. The infrared spectrum of the enamine showed no enone absorption in the 1660 $cm.^{-1}$ region. ν_{max} 1699, 1635 $cm.^{-1}$

Mild Hydrolysis of 3-(N-Pyrrolidyl)-17-ethylenedioxyandrosta-3,5-dien-11-one.

3-(N-Pyrrolidyl)-17-ethylenedioxyandrosta-3,5-dien-11-one (300 mg.) was hydrolysed using the same reaction conditions as for the hydrolysis of adrenosterone enamine. The infrared spectrum of the hydrolysed product showed there to be approximately equal proportions of enamine $\nu_{max.}$ 1635 $cm.^{-1}$, conjugated ketone (40) 1675 $cm.^{-1}$ and deconjugated ketone (38) 1703 $cm.^{-1}$

Mild Hydrolysis of the Enamine of Testosterone.

17β-Hydroxy-3-(N-pyrrolidyl)-androsta-3,5-diene[69] (850 mg.) was hydrolysed in the manner already described, but increasing the reaction time from two hours to eight hours. The infrared spectrum

of the crude product showed it to contain approximately equal amounts of the original enamine (ν_{max} 1635 $cm.^{-1}$), conjugated ketone (testosterone, ν_{max} 1675 $cm.^{-1}$) and 17β-hydroxyandrost-5-en-3-one, (ν_{max} 1703 $cm.^{-1}$).

17-Ethylenedioxy-3β-hydroxyandrost-5-en-11-one (41)

17-Ethylenedioxyandrost-4-ene-3,11-dione (40) (4.2 g.) in dry dimethylsulphoxide (300 ml.) was stirred under nitrogen whilst potassium tert.-butoxide (12 g.) was added. The solution was stirred for two and a half hours then poured quickly into a stirred solution of sodium borohydride (1.9 g.) in methanol (270 ml.) and water (30 ml.). The reduction was allowed to continue for ten minutes then water (500 ml.) was added and the steroid was extracted into chloroform. The chloroform solution was washed with dilute hydrochloric acid, sodium carbonate solution, saturated salt solution and dried with magnesium sulphate. The chloroform solution on evaporation to dryness yielded a residue which was chromatographed on alumina (150 g.). Elution with ether gave unchanged 17-ethylenedioxyandrost-4-ene-3,11-dione (40) (0.5 g.) m.p. 150-151° (from methanol); further elution with ether-chloroform (9:1) gave crystalline material (3.2 g.), which on recrystallisation from acetone-petrol and again from aqueous methanol gave 17-ethylenedioxy-3β-hydroxyandrost-5-en-11-one (41) (2.9 g.) m.p. 150-151°. An analytical sample was recrystallised from methanol m.p. 150-151°; $[\alpha]_D$ -41° (c 0.1); $\nu_{max.}$ 1700 $cm.^{-1}$; n.m.r. (pyridine) τ 9.12 (C18 methyl), τ 8.64 (C19 methyl), τ 6.19 (ethyleneketal protons), τ 4.61 multiplet (6H); ($CDCl_3$) τ 9.18, 8.81, 6.13 and 4.65.

(Found: C, 72.4; H, 8.4. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%). Gas-liquid chromatography of the reaction product using helium carrier gas (column temperature 240°, flow rate 25 ml./min.) showed a peak with a relative retention time with respect to 5α-cholestane of 0.59 (17-ethylenedioxyandrosta-3,5-dien-11-one) and two further peaks not fully resolved of relative retention times 1.03 and 1.22 (17-ethylenedioxy-3β-hydroxyandrost-5-en-11-one and 17-ethylenedioxyandrost-4-ene-3,11-dione respectively). The area under the diene peak was 4% of the total area.

17-Ethylenedioxy-3β-hydroxyandrost-4-en-11-one (43, R = )

17-Ethylenedioxyandrost-4-ene-3,11-dione (40) (440 mg.) was dissolved in methanol (45 ml.) and water (5 ml.), sodium borohydride (200 mg.) was added and the mixture was stirred for 15 minutes. Dilute hydrochloric acid was then added and the steroid extracted into chloroform. After the usual work up, this solution was evaporated to yield a residue which was crystallised from acetone-petrol (b.p. 100-120°) to give 17-ethylenedioxy-3β-hydroxyandrost-4-en-11-one (240 mg.), m.p. 206-209°; $[\alpha]_D$ =+79° (c 0.1); ν_{max} ($CHCl_3$) 1702 $cm.^{-1}$; n.m.r. (pyridine) τ 9.11 (C18 methyl), τ 8.63 (C19 methyl) τ 6.20 (4 ethyleneketal protons), τ 5.55 multiplet (3αH), τ 4.36 and 4.25 (unassigned); ($CDCl_3$) τ 9.18, 8.74, 6.14 and 4.66 (4H). An analytical sample was recrystallised from methanol, m.p. 208-210°. (Found: C, 72.8; H, 9.0. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%).

3β-Hydroxyandrost-4-ene-11,17-dione (43, R=O)

17-Ethylenedioxy-3β-hydroxyandrost-4-ene-11-one (61 mg.) was dissolved in acetone (30 ml.) and water (10 ml.). p-Toluene-sulphonic acid (50 mg.) was added and the solution was kept at 40° for twelve hours. The solution was evaporated to half its volume in vacuo and the steroid was extracted into chloroform. The chloroform solution was washed with sodium carbonate solution, saturated salt solution and was dried with magnesium sulphate. The solution was evaporated to dryness and the residue was recrystallised from hexane to give 3β-hydroxyandrost-4-ene-11,17-dione (37 mg.) m.p. 167-170° (lit.[66] m.p. 172-173°) $[\alpha]_D$ = +15° (c 0.1) ν_{max} 1734 and 1704 $cm.^{-1}$; n.m.r. ($CDCl_3$) τ 9.13 (C-18 methyl), τ 8.83 (C-19 methyl) and τ 4.14 multiplet (4H).

3β-Hydroxyandrost-5-ene-11,17-dione (42)

17-Ethylenedioxy-3β-hydroxyandrost-5-ene-11,17-dione (5.2 g.) was dissolved in acetone (400 ml.) and p-toluene-sulphonic acid (3 g.) in water (70 ml.) was added. The solution was refluxed for four hours. Water (200 ml.) was added and the solution was evaporated to half its volume. The steroid was extracted into chloroform and this solution was washed with sodium carbonate and saturated salt solution. After drying with magnesium sulphate the chloroform solution was evaporated to give a residue which was recrystallised from aqueous acetone to give 3β-hydroxyandrost-5-ene-11,17-dione, (4.3 g.), m.p. 221-222°; $[\alpha]_D$ =+48° (c 0.1). (Lit.[73] m.p. 217-219°; $[\alpha]_D$ +57 ± 4° (c 0.805) dioxan). ν_{max} ($CHCl_3$) 1704 and 1734 $cm.^{-1}$, n.m.r. ($CDCl_3$) τ 9.14 (C-18 methyl), τ 8.78 (C-19 methyl) and τ 4.55 multiplet (6H).

3β,17β-Dihydroxyandrost-5-en-11-one (35) from 3β-hydroxyandrost-5-en-11,17-dione (42)

3β-Hydroxyandrost-5-ene-11,17-dione (200 mg.) was reduced with sodium borohydride in aqueous methanol to give a product identical to that from the borohydride reduction of androst-5-ene-3,11,17-trione described above.

3β-Acetoxyandrost-5-ene-11,17-dione (30)

3β-Hydroxyandrost-5-ene-11,17-dione was acetylated using acetic anhydride and pyridine. The product was recrystallised from methanol, m.p. 175-176°, $[\alpha]_D$ +34° (c 0.1) (lit.[50] m.p. 174-175°; lit.[51] m.p. 170-171.5°; $[\alpha]_D$ =+38° (c 2.1) dioxan). ν_{max} 1738, 1706, 1240 and 819 $cm.^{-1}$; ν_{max}(nujol) 1742, 1730, 1712, 1240 and 817 $cm.^{-1}$; n.m.r. ($CDCl_3$) τ 9.14 (C-18 methyl), τ 8.77 (C-19 methyl), τ 7.97 (acetate) and τ 4.56 multiplet (6H).

3β,11β-Dihydroxyandrost-5-en-17-one (27)

17-Ethylenedioxy-3β-hydroxyandrost-5-en-17-one (500 mg.) was dissolved in anhydrous ether (60 ml.) and lithium aluminium hydride (500 mg.) was added; the suspension was stirred for twelve hours at 20°. After a conventional work up the infrared spectrum of the crude product showed appreciable absorption at 1740 $cm.^{-1}$; the hydrolysis of the ketal was therefore completed by dissolving the residue in acetone (150 ml.) and water (50 ml.) and adding concentrated hydrochloric acid (5 ml.) and allowing the solution to stand for three hours. The steroid was recovered by chloroform extraction. Evaporation gave 3β,11β-dihydroxyandrost-5-en-17-one

which was recrystallised from methanol to give crystals (200 mg.) m.p. 191-193° (lit.[50] m.p. 190-192°).

Base Deconjugation of Adrenosterone and the in situ Reduction of the Deconjugated Enone.

Androst-4-ene-3,11,17-trione (2 g.) was deconjugated by base and then reduced using the procedure already described for the deconjugation and reduction of the 17-ethylene ketal of adrenosterone. The reaction product was chromatographed on alumina (150 g.). Elution with ether-chloroform (1:3) gave crystalline material (340 mg.) which on recrystallisation from petrol-acetone gave 17β-hydroxyandrost-4-ene-3,11-dione (250 mg.) m.p. 178-182° (lit.[131] m.p. 183-184°). Further elution with chloroform-methanol (98:2) gave material (1.1 g.) which did not crystallise well, this material was acetylated with acetic anhydride-pyridine. The acetylated material was recrystallised from acetone-petrol and again from ethanol to give crystals of 3β,17β-diacetoxyandrost-5-en-11-one (370 mg.) m.p. 166-169° (lit.,[72] m.p. 173-175°). The infrared spectrum of this material was identical with authentic material.[65] Gas liquid chromatography of the total product (column temperature 240°, helium flow rate 25 ml./min.) showed there to be 16% of 3β,17β-dihydroxyandrost-4-en-11-one, which was analysed as the corresponding 3,5-diene with relative retention time 0.41 that of 5α-cholestane.

Base Deconjugation and Reduction of Testosterone.

17β-Hydroxyandrost-4-en-3-one (4.5 g.) was deconjugated and reduced in the manner described above for adrenosterone. Infrared

analysis of the total reaction product showed there to be some conjugated ketone still present (ν_{max} 1673 $cm.^{-1}$). The product was chromatographed on alumina (200 g.); elution with ether-chloroform (4:1) gave crystalline material which on recrystallisation from acetone-petrol gave testosterone (650 mg.), m.p. and mixed m.p. 147-150°. Further elution with ether-chloroform (1:1) gave crystalline material which was acetylated with acetic anhydride pyridine and recrystallised from aqueous methanol to give 3β,17β-deacetoxyandrost-5-ene (2.2 g.) m.p. 157-158° (lit.,[132] 157-157.5°). Gas liquid chromatography of the total reaction product as above showed there to be 3% of 3β,17β-dihydroxyandrost-4-ene, analysed as 17β-hydroxyandrosta-3,5-diene with a relative retention time of 0.31 to 5α-cholestane.

3β,17-Diacetoxyandrosta-5,16-dien-11-one (44).- 3β-Hydroxyandrost-5-ene-11,17-dione (42) (2.5 g.) and p-toluenesulphonic acid (200 mg.) were dissolved in isopropenylacetate (30 ml.). The solution was refluxed through a short fractionating column so that the vapours were on the point of distilling over into a receiving condenser. With this arrangement any acetone formed was removed from the reaction flask. The constant slow distillation was continued for eight hours. The volume in the reaction flask was kept constant by the addition of fresh isopropenyl acetate; a total of 30 ml. of fresh isopropenyl acetate was added during the eight hours. When the reaction was complete the solution was evaporated to 15 ml. and poured into sodium carbonate solution; the steroid was extracted into ether. The ethereal solution was washed with

further sodium carbonate solution and with saturated salt solution. The ethereal solution was dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from ether-petrol to give 3β,17-diacetoxyandrosta-5,16-dien-11-one (2.25 g.) m.p. 155-161° $[\alpha]_D$ = -13° (c 0.1); ν_{max} 1757, 1734, 1706, 1245, 1204 and 822 $cm.^{-1}$; n.m.r. ($CDCl_3$) τ 9.13 (C-18 methyl), τ 8.78 (C-19 methyl), τ 7.98 (acetate), τ 7.85 (enolacetate), τ 4.57 multiplet (6H) and τ 4.42 multiplet (16H). An analytical sample was recrystallised from hexane m.p. 159-161° (Found: C, 71.1; H, 7.5. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%).

3β-Acetoxy-16α-bromoandrost-5-ene-11,17-dione (45).- 3β,17-Di-acetoxyandrosta-5,16-dien-11-one (44) (2.5 g.) was dissolved in dry carbon tetrachloride (100 ml.) and the solution was cooled to -10°. The solution was stirred while a solution of bromine (1.06 g., 1.02 eq.) in carbon tetrachloride (13 ml.) was added over two minutes. The solution was stirred for a further two minutes then an aqueous solution of sodium bisulphite was added. The steroid was extracted into chloroform (100 ml.) and the chloroform solution was washed with sodium carbonate and saturated salt solution. The solution was dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from ethanol to give 3β-acetoxy-16α-bromoandrost-5-ene-11,17-dione (2.1 g.) m.p. 182-185°; $[\alpha]_D$ +37°, (c 0.1); ν_{max} 1760, 1738, 1714, 1241 and 814 $cm.^{-1}$; n.m.r. ($CDCl_3$) τ 9.10 (C-18 methyl), τ 8.77 (C-19 methyl), τ 7.97 (acetate), τ 4.55 multiplet (6H), τ 5.37 multiplet (16βH). An analytical sample was recrystallised from ethanol, m.p. 183-185°. (Found: C, 60.1;

H, 6.0; Br, 18.1. $C_{21}H_{27}O_4$ Br requires C, 59.7; H, 6.4; Br, 18.9%).

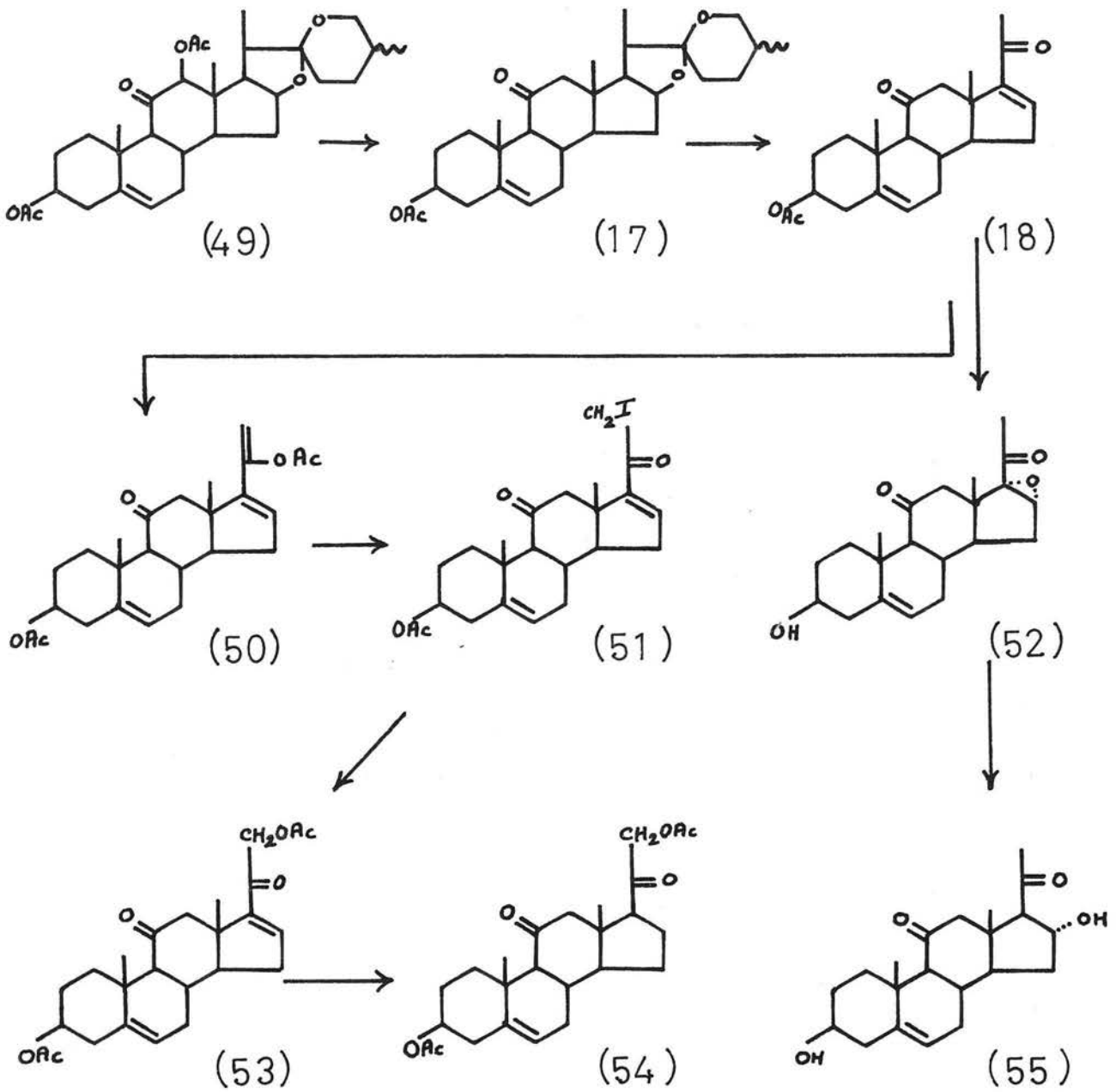
3β,16α-Dihydroxy-17,17-dimethoxyandrost-5-en-11-one (46).- 3β-Acetoxy-16α-bromoandrost-5-ene-11,17-dione (45) (1.9 g.) in hot methanol (80 ml.) was added to a solution of sodium methoxide in hot methanol (50 ml.) formed by the dissolution of sodium (2 g.) in the methanol. The solution was refluxed for one hour then poured into cold water (300 ml.). The steroid was extracted with ether and the ethereal solution was successively washed with dilute hydrochloric acid, sodium carbonate solution and saturated salt solution. The ethereal solution was dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from ether to give 3β,16α-dihydroxy-17,17-dimethoxyandrost-5-en-11-one (0.6 g.) m.p. 168-174°; $[\alpha]_D$ -68° (c 0.1); ν_{max} ($CHCl_3$) 1704, 1170, 1112 and 1055 $cm.^{-1}$; n.m.r. ($CDCl_3$) τ 9.26 (C-18 methyl), τ 8.81 (C-19 methyl), τ 6.65, 6.59 (methoxy protons) and τ 4.66 multiplet (6H). An analytical sample was recrystallised from ether m.p. 172-176°. (Found: C, 68.7; H, 9.14. $C_{21}H_{32}O_5$ requires C, 69.2; H, 8.9%). Chromatography of the mother liquors on alumina gave crystalline material which was recrystallised from ether to give 3β-hydroxyandrost-5-ene-11,17-dione (42) (45 mg.), identified by infrared and n.m.r. spectroscopy and an undepressed mixed melting point with authentic 3β-hydroxyandrost-5-ene-11,17-dione.

3β,16α-Dihydroxyandrost-5-ene-11,17-dione (47).- 3β,16α-Dihydroxy-17,17-dimethoxyandrost-5-en-11-one (46) (240 mg.) was dissolved in

acetone (50 ml.) and a solution of p-toluene-sulphonic acid (200 mg.) in water (5 ml.) was added. The solution was kept at 40° for twelve hours then water (10 ml.) was added and the solution evaporated in vacuo to a half its volume. The steroid was extracted with chloroform. The chloroform solution was washed with sodium carbonate solution and with saturated salt solution. The solution was dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from acetone-petrol to give 3β,16α-dihydroxyandrost-5-ene-11,17-dione (170 mg.) m.p. 204-210°. A further recrystallisation from aqueous acetone gave material m.p. 209-212° $[\alpha]_D$ +81°, (c 0.1) ν_{max} (nujol) 1755, and 1690 $cm.^{-1}$; n.m.r. (pyridine) τ 9.12 (C-18 methyl), τ 8.66 (C-19 methyl), τ 5.30 multiplet (16βH), τ 4.63 multiplet (6H). An analytical sample was recrystallised from aqueous acetone, m.p. 209-212°. (Found: C, 70.2; H, 8.3. $C_{19}H_{26}O_4 \cdot CH_3.CO.CH_3$, requires C, 70.2; H, 8.6%).

3β,11β,16α-Trihydroxyandrost-5-en-17-one (48).- 3β,16α-Dihydroxy-17,17-dimethoxyandrost-5-en-11-one (46) (320 mg.) was dissolved in ether (100 ml.) and lithium aluminium hydride (500 mg.) was added, the solution was refluxed for two hours. The excess lithium aluminium hydride was decomposed with ethyl acetate and then dilute hydrochloric acid was added. The acidified material was allowed to stand for two hours. Fresh ether (300 ml.) was added and the ethereal solution was washed with sodium carbonate solution followed by saturated salt solution. The solution was dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised

from acetone-petrol and again from aqueous acetone to give 3β,11β, 16α-trihydroxyandrost-5-en-17-one (48) (100 mg.) m.p. 209-212°; $[\alpha]_D$ +8° (c 0.1) $\nu_{max.}$ (nujol) 1745 cm^{-1}; n.m.r. (pyridine) τ 8.56 (C-18 methyl), τ 8.38 (C-19 methyl), broad multiplet τ 6.05 (3αH), τ 5.31 multiplet (16βH), τ 4.66 multiplet (6H), τ 4.5 doublet (11αH). An analytical sample was recrystallised from aqueous methanol m.p. 209-212°. (Found: C, 68.1; H, 9.1. $C_{19}H_{28}O_4 . CH_3OH$ requires C, 68.15; H, 9.15%).



THE SYNTHESIS OF SOME DERIVATIVES OF 11-KETO-PREGNENOLONE

The Synthesis of 3β,16α-Dihydroxypregn-5-ene-11,20-dione and 3β,21-Diacetoxypregn-5-ene-11,20-dione from Sapogenins

The starting material for these syntheses was 3β,12β-diacetoxy-25R,S-spirost-5-en-12-one (49), a gift from Glaxo Ltd., Montrose. This material was treated with calcium in liquid ammonia to remove the 12β-acetoxy group. The reductive cleavage of the 12β-acetoxy group is reportedly[77] accompanied by only small loss of the 3β-acetoxy group, though partial hydrolysis of this group occurs and reacetylation is necessary. This method was an adaption of that of Chapman et al.[77], altered to suit the solubility of the sapogenin. The 3β-acetoxy-25R,S-spirost-5-en-11-one was subjected to a modification of the Marker degradation[42] to remove the spirostane side chain. The best yields were obtained by omitting a crystallisation of the intermediate epimeric 3β-acetoxy-25R,S-spirost-5-en-11-one since it would not crystallise well. No attempts were made to isolate any of the intermediates in the degradation of the spirostane side chain. The crude side chain degradation product was then chromatographed on alumina. The removal of the side chain also removed the epimeric nature of the material and pure 3β-acetoxypregna-5,16-diene-11,20-dione (18) was obtained in 24% overall yield from the 12β-acetoxy sapogenin (49).

The methods of synthesising the 16α-hydroxy-20-ketone structure were investigated. A trial reaction involving the addition of benzyl alcohol across the eneone system was carried out on a small scale. Alumina chromatography of the product gave unchanged starting material but no other crystalline material

was obtainable. The hydrogenolysis of the benzyl group in the presence of the 20-ketone and the Δ^5 moiety was almost certain to prove difficult and consequently an alternative route was sought. The chromous ion has been reported to reduce the 16α,17α-oxido-20-ketone to the 16α-hydroxy-20-ketone in poor to moderate yield,[32] but the product having an extra hydroxyl group is easily separable by column chromatography. Unfortunately the 16α-hydroxy-20-ketone is sensitive to acids and the use of chromous chloride leads to considerable dehydration to the original enone. Chromous acetate is therefore used but since chromous acetate is rather insoluble in most organic solvents, long reaction times are essential.

3β-Hydroxy-16α,17α-oxidopregn-5-ene-11,20-dione(52) was prepared by increasing the time of the alkaline peroxidation of the Δ^{16} compound (18) to allow complete hydrolysis of the 3β-acetate. This oxide was reacted with freshly prepared chromous acetate in a sealed vessel for 16 hours. The product was chromatographed on Florisil and recrystallised to give a 16% yield of 3β,16α-dihydroxy-pregn-5-ene-11,20-dione (55). The identity of this material was confirmed by infrared spectroscopy, the absence of strong u.v. absorption, the increased polarity of the product and its n.m.r. spectrum. The n.m.r. spectrum in pyridine showed the disappearance of the oxide signal at τ6.19 and the appearance of a one hydrogen multiplet at τ5.0 due to the 16β-hydrogen.

Turning to the synthesis 3β,21-diacetoxypregn-5-ene-11,20-dione (54), a model reaction in the 11-desoxy series was the introduction of the 21-acetoxy group into dehydropregnenolone acetate.[79]

The only really satisfactory method for the introduction of the 21-acetate has been that of Djerassi,[79] and this method involving the 21-iodo compound has been followed here in the 11-keto series.

The dienol acetate (50) was prepared by the established method,[78] the perchloric acid catalysed reaction with acetic anhydride in ethyl acetate has been reported not to acetylate the Δ^{16}-20-ketone,[80] although results with the Δ^{4}-3-ketone are excellent. The enolacetate was treated with freshly prepared N-iodosuccinimide[81] in dioxan and the resulting iodo ketone (51) was not isolated but treated directly with potassium acetate in acetone. The resulting 21-acetoxy compound (53) was obtained in an overall yield of 51% from 3β,20-diacetoxypregna-5,16,20-trien-11-one (50).

The hydrogenation of the enone (53) produced an unexpected difficulty, when the enone was hydrogenated using a 10% palladium on charcoal catalyst one mole of hydrogen was rapidly taken up, but the steroid isolated was non crystalline and presumably a mixture of the 17α- and 17β-isomers. However, when the catalyst was changed to tris(triphenyl)phosphine rhodium,[40] the homogeneous catalytic hydrogenation proceeded over the space of 22 hours to give pure 3β,21-diacetoxypregn-5-ene-11,20-dione (54) in a 50% yield. The 17β configuration of the side chain is expected from consideration of the reaction involving the corresponding compound without 11 and 21 functional groups.[40] The 17β configuration is also supported by n.m.r. evidence, the frequencies of the methyl signals agree with those calculated from additive values,[82] the calculation below uses the values of Zurcher.

Contributing Structure	Contribution	
	19 Methyl	18 Methyl
5α,14α-androstane	τ 9.208	τ 9.308
3β-acetoxy	-0.017	0.000
Δ^5	-0.233	-0.042
11-keto	-0.217	+0.033
17β-CO.CH_2OAc	+0.008	+0.042
	τ 8.749	τ 9.341

The observed frequencies of absorption of the methyl groups in 3β,21-diacetoxy-pregn-5-ene-11,20-dione in $CDCl_3$ are:

τ 8.79 τ 9.34

EXPERIMENTAL SECTION

For general Experimental Procedure see page 32

3β-Acetoxy-25R,S-spirost-5-en-11-one (17).- 3β,12β-Diacetoxy-25R,S-spirost-5-en-11-one (49) (20 g.) was dissolved in toluene (150 ml.) and solvent (25 ml.) was distilled off at atmospheric pressure. Calcium granules (5.8 g.) were added to anhydrous liquid ammonia (1 litre) and the solution was stirred for five minutes to allow the metal to dissolve. The steroid solution in toluene was allowed to cool to room temperature and it was then added dropwise to the stirred solution of ammonia over a period of ten minutes. The solution was stirred for a further thirteen minutes then a solution of bromobenzene (4.8 ml.) in toluene (25 ml.) was added cautiously over four minutes, the solution was stirred until all calcium had disappeared. Water (180 ml.) was cautiously added over a period of 20 minutes and the excess ammonia was then evaporated off and the residue acidified with hydrochloric acid. The steroid was extracted into ether (1 litre) and the ethereal solution was washed with sodium carbonate solution and saturated salt solution. The ethereal solution was dried with magnesium sulphate and evaporated to dryness. The residue was dissolved in pyridine (50 ml.) and acetic anhydride (200 ml.) and this solution was allowed to stand for twelve hours. The excess reagent was evaporated off under reduced pressure and the residue was dissolved in ether, the ethereal solution was washed with dilute hydrochloric acid, sodium carbonate solution and saturated salt solution, dried with magnesium sulphate and evaporated to dryness. The crystalline residue was used directly in the side chain degradation procedure.

3β-Acetoxypregna-5,16-diene-11,20-dione (18).- Crude 3β-acetoxy-25R,S-spirost-5-en-11-one (17) (18 g. from the preceding experiment) was dissolved in acetic anhydride (100 ml.) and pyridine (50 ml.) at 80°, anhydrous methylamine hydrochloride (25 g.) was added and the mixture was refluxed for ten minutes. Solvent (about 10 ml.) was distilled off and the temperature of the reaction mixture rose to 155°, the solution was then refluxed at this temperature for four hours. The reaction mixture was cooled and poured into crushed ice (1 litre) and the ice was stirred periodically for one hour. The steroid was extracted into chloroform (1 litre), the chloroform solution was washed well with water and with saturated salt solution, dried with magnesium sulphate and evaporated in vacuo to remove the chloroform. The residue was dissolved in dichloromethane (400 ml.) and acetic acid (400 ml.), the solution was cooled to -5° in an ice-salt bath and was stirred while a solution of chromic anhydride (12.5 g.) in 90% aqueous acetic acid (400 ml.) was added, the temperature was kept below -2° during the addition. A solution of sodium bisulphite (30 g.) in water (200 ml.) was added with the temperature kept below 0°; water (1 litre) was added and the steroid was extracted into ether (2 litres). The ethereal solution was washed well with water and with saturated salt solution, dried with magnesium sulphate and the ether was evaporated off in vacuo. Acetic acid (500 ml.) was added to the residue and the solution was refluxed for eight hours. The acetic acid was removed in vacuo and the residue was dissolved in petrol and benzene (7:3), this solution was washed with sodium

carbonate and saturated salt solution and dried with magnesium sulphate. The petrol and benzene solution was placed on a column of alumina (400 g.), elution with ether gave non crystalline material, elution with ether/chloroform (19:1) gave crystalline material which was recrystallised from methanol to give 3β-acetoxypregna-5,16-diene-11,20-dione (18) (5.5 g.); m.p. 179-183°, (lit.[30] m.p. 183-186°).

3β-Hydroxy-16α,17α-oxidopregn-5-ene-11,20-dione (52).- 3β-Acetoxy-androsta-5,16-diene-11,20-dione (18) (1 g.) was dissolved in methanol (60 ml.) and chloroform (10 ml.) and the solution was cooled to -5°; 30% hydrogen peroxide (3 ml.) was added over a period of 5 minutes whilst maintaining the low temperature, this was followed by the addition of 2N.NaOH (3 ml.). After one hour the solution was allowed to warm to room temperature and was stirred at this temperature for twelve hours. Water (300 ml.) was added and the steroid was extracted into ether, the ether solution was washed with water then with ferrous sulphate until no further discoloration of the ferrous solution was noticed, the solution was then washed with water and saturated salt solution dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from aqueous acetone to give 3β-hydroxy-16α,17α-oxidoandrost-5-ene-11,20-dione (0.80 g.), m.p. 193-196°; $[\alpha]_D$ +17° (c, 0.1); $\nu_{max.}$ (nujol) 1693, 1050, 861 and 819 $cm.^{-1}$; n.m.r. τ 8.98 (C-18 methyl), τ 8.81 (C-19 methyl), τ 7.98 (C-21 methyl), τ 6.19 (16βH), τ 4.65 multiplet (6H). Found: C, 69.75; H, 8.6. $C_{21}H_{28}O_4;H_2O$ requires C, 69.6; H, 8.3%.

3β,16α-Dihydroxypregn-5-ene-11,20-dione (55).- 3β-Hydroxy-16α, 17α-oxidopregn-5-ene-11,20-dione (52), (.88 g.) and sodium acetate (200 mg.) were dissolved in acetic acid (30 ml.) and freshly prepared moist chromous acetate (4 g.) was added; a magnetic stirring bar was introduced into the flask, the air was displaced with nitrogen and the flask was firmly stoppered. The contents of the flask were vigorously stirred for 16 hours, the solution was then poured into water and the steroid was extracted by two extractions with 150 ml. chloroform. The chloroform solutions were combined and washed with water, sodium carbonate solution, water and saturated salt solution. The solution was dried with magnesium sulphate and evaporated to dryness. The residue was analysed by t.l.c. analysis (20% ethanol in benzene, system H of Lisboa[19]), this showed 2 spots, the more polar spot was the minor one and was of a polarity compatible with the 16α hydroxylated material the polarity of the major component showed that it was probably the original oxide (52). The crude material was chromatographed on Florisil (60 g.) deactivated with 5% w/w of water. Elution with ether gave crystalline material which infra-red evidence showed to be mainly original oxide but to contain some Δ^{16}-20-ketone (ν_{max} 1660 $cm.^{-1}$) estimated to be about 20% of the total product. Further elution with chloroform-methanol (9:1) (200 mg.) this was recrystallised from acetone-petrol to give 3β,16α-dihydroxypregn-5-ene-11,20-dione (55) (140 mg.); m.p. 211-213°; $[\alpha]_D$ +17° (c 0.1, dioxan); ν_{max} (nujol) 1700, 1210, 1169, 1062, 879 and 817 $cm.^{-1}$; n.m.r. (pyridine) τ 9.29 (C-18

methyl), τ 8.68 (C-19 methyl), τ 7.84 (C-21 methyl), τ 5.00 (16βH) and τ 4.60 (6H). Found: C, 72.8; H, 8.7. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%.

3β,20-Diacetoxypregna-5,16,20-trien-11-one (50).- 3β-Acetoxypregna-5,16-diene-11,20-dione (18) (2 g.) and p-toluenesulphonic acid (100 mg.) were dissolved in freshly distilled isopropenyl acetate (15 ml.) and the solution was refluxed for one hour. After this time gradual distillation was commenced with the temperature adjusted so that the solvent was on the point of being distilled from the reaction flask. This constant slow distillation was continued for ten hours. The solvent volume was maintained at 15 ml. by the addition of fresh isopropenyl acetate and a total of about 10 ml. of solvent was distilled off during the ten hours. The reaction mixture was cooled and poured into an aqueous sodium carbonate solution. The steroid was extracted into ether and the ethereal solution was washed with saturated salt solution, dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from ether to give 3β,20-diacetoxypregna-5,16,20-trien-11-one (1.0 g.) m.p. 140-146° an analytical sample was recrystallised from methanol, m.p. 145-150° $[\alpha]_D$ -26° (c, 0.1); $\nu_{max.}$ 1757, 1730, 1700, 1242, 1198, 1029, 959 and 817 $cm.^{-1}$; n.m.r., τ 9.06 (C-18 methyl), τ 8.76 (C-19 methyl), τ 7.97 (3-acetate methyl), τ 7.82 (20-acetate methyl), τ 5.77 and 4.99 doublets J=2 c.p.s. (21-protons), τ 4.56 (6H), and τ 4.11 (16H). Found: C, 72.7; H, 8.0. $C_{25}H_{32}O_5$ requires C, 72.8; H, 8.0%.

3β,21-Diacetoxypregna-5,16-diene-11,20-dione (53).- 3β,20-Diacetoxypregna-5,16,20-trien-11-one (50) (.94 g.), dry dioxan (2 ml.) and freshly prepared N-iodosuccinimide[81] (.63 g. m.p. 200-205°) were placed in a 50 ml. round bottomed flask, the air was displaced with nitrogen and the flask was sealed firmly. The sealed flask was warmed at 85° for one hour then hot methanol (5 ml.) and hot 10% aqueous potassium iodide solution (1 ml.) were added. This mixture was stirred for two minutes then 20% aqueous thiosulphate solution was slowly added until precipitation of steroid was complete, the crystalline material which had been precipitated was filtered off washed with water and dried. The crystalline product 3β-acetoxy-21-iodopregna-5,16-diene-11,20-dione (51) (810 mg., $\lambda_{max.}$ 243 mμ. ϵ 8,100) was not purified further but was used directly for the next stage in the reaction. This crude product (750 mg.) was dissolved in acetone (50 ml.). Potassium hydrogen carbonate (6 g.) and acetic acid (3.2 ml.) were ground together and the resulting paste was added to the solution of steroid in acetone. The slurry was stirred and refluxed for 16 hours. Water was added and the reaction mixture was evaporated in vacuo to remove most of the acetone. The crystals which formed during this evaporation were filtered off and recrystallised from aqueous acetone to give 3β,21-diacetoxypregna-5,16-diene-11,20-dione (460 mg.) m.p. 170-172°; $[\alpha]_D$ -25° (c, 0.1); $\lambda_{max.}$ 236 mμ ϵ 9020; $\nu_{max.}$ (nujol) 1761, 1729, 1700, 1682, 1592, 1240, 1220, 828 and 816 $cm.^{-1}$; n.m.r. τ 9.09 (C-18 methyl), τ 8.79 (C-19 methyl), τ 8.00 (3-acetate methyl), τ 7.86 (21-acetate methyl), τ 5.06 (21-methylene), τ 4.59 (6H),

τ 3.17 (16H). Found: C, 70.0; H, 7.7. $C_{25}H_{32}O_6$ requires C, 70.1; H, 7.5%.

Hydrogenation of 3β,21-Diacetoxypregna-5,16-diene-11,20-dione with 10% palladium on Charcoal.- 3β,21-Diacetoxypregna-5,16-diene-11,20-dione (53) (50 mg.) was hydrogenated in a Clauson-Kaas and Limborg[130] microhydrogenation apparatus using benzene as solvent (3 ml.). 10% Palladium on charcoal (5 mg.) was added to the benzene solvent and the catalyst was prehydrogenated, the steroid was then added to the system. 1.05 Equivalents of hydrogen were rapidly taken up and the hydrogen uptake ceased after 30 minutes. The solution was filtered and the filtrate was evaporated to dryness to give a non crystalline glass. Chromatography of the product on alumina (10 g.) produced no crystalline material. T.l.c. analysis showed one pink spot.

Hydrogenation with a homogeneous catalyst.- The above hydrogenation was repeated using tris(triphenylphosphine)rhodium (7 mg.) as the catalyst. The steroid (50 mg.) was hydrogenated for 30 hours after which time only very slow hydrogen uptake was noticeable. The solution was removed from the hydrogenation apparatus and was allowed to stand in an open vessel overnight, the solution was then passed down a column of alumina (20 g.) and the column was eluted with ether. The total eluate was evaporated to dryness in vacuo. The residue crystallised and was recrystallised from aqueous acetone to give 3β,21-diacetoxypregn-5-ene-11,20-dione (54) (25 mg.), m.p. 118-120°; $[\alpha]_D$ +30° (c, 0.1); $\nu_{max.}(CS_2)$ 1752, 1730, 1706, 1240,

1228, 1038 and 817 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl), τ 8.79 (C-19 methyl), τ 7.97 (3-acetate methyl), τ 7.84 (21-acetate methyl), τ 5.45 (21-methylene) and τ 4.64 multiplet (6H). Found: C, 69.4; H, 8.2. $C_{25}H_{34}O_6$ requires C, 69.7; H, 8.0%.

The Synthesis of 15,17-Disubstituted 3β-Hydroxyandrost-5-enes

The main aim of this work has been the preparation of the 15α- and 15β-hydroxy derivatives of 3β-hydroxyandrost-5-en-17-one (dehydroepiandrosterone) and 3β,17β-dihydroxyandrost-5-ene. In these preparations the difficulty lies not only in the preparation of the D-ring structure but also in carrying out the synthesis in the presence of the 3β-hydroxy- Δ^5 structure. However the main problem is the inaccessibility of the 15 position.

The chemical preparation of 15 substituted steroids fall into three important classes; transformations of naturally occurring 15 substituted material, transformations on the 14,15-double bond and reactions of Δ^{15}-17-ketones. The first class is severely restricted by the non-availability of the naturally occurring 15 substituted compounds. The only synthesis of interest is that of 15-keto progesterone from digitogenin.[96] The applicability of the reactions in the other two classes to the syntheses required here will be discussed in detail.

The transformations of the 14,15-double bond have been mainly concerned with cardiac aglycones. Most of these aglycones have a 14 substituent as well as the distinctive side chain, the 14 substituent (usually a β-hydroxyl group) lends itself to ready dehydration. The transformations of the 14,15-double bond in this series are not generally applicable to the androstanes. The most important discrepancy between the two series, is the configuration of the oxides obtained in peroxidation of the double bond; in general peroxidation with peracid is α in the cardanolides

and pregnanes[83,84,85] and β in the androstanes.[86] The preparation of Δ^{14} compounds in the androstane series has been difficult and consequently little chemistry has been done on these compounds.

There are two main ways of converting a saturated 17-keto compound into a Δ^{14} compound. The first is due to St. André et al.[22] who treated 3β-acetoxyandrost-5-en-17-one with bromine to protect the double bond, treated the dibromide with chromic anhydride in acetic acid and then removed the bromines with zinc. The product contained 25% of a polar 14-hydroxy compound, which has subsequently been identified[87] as 3β-acetoxy-14α-hydroxyandrost-5-en-17-one. This hydroxy compound has been reported to dehydrate with potassium bisulphate and acetic anhydride at 100° to give the 14,15-double bond.[22] This method has been used on several occasions[86,88] despite the low yields of the reaction. For the synthesis of Δ^{5} steroids a $\Delta^{5,14}$ diene is not desirable because selective reaction between these double bonds is not possible. The St. André method was an obvious possibility of getting to 3β-acetoxy-5α,6β-dichloroandrost-14-en-17-one. 3β-Acetoxy-5α,6β-dichloroandrostan-17-one was prepared by chlorinating the Δ^{5} compound with sulphuryl chloride and pyridine followed by an ether extraction and crystallisation; but when this compound was put through the chromic anhydride oxidation in acetic acid no reaction was observed. It had been noticed in previous brominations of 5,6-double bonds in the presence of a 17-ketone that hydrogen bromide was generated, presumably due to bromination at C-16. It was thought possible that in the reaction sequence of St. André, the

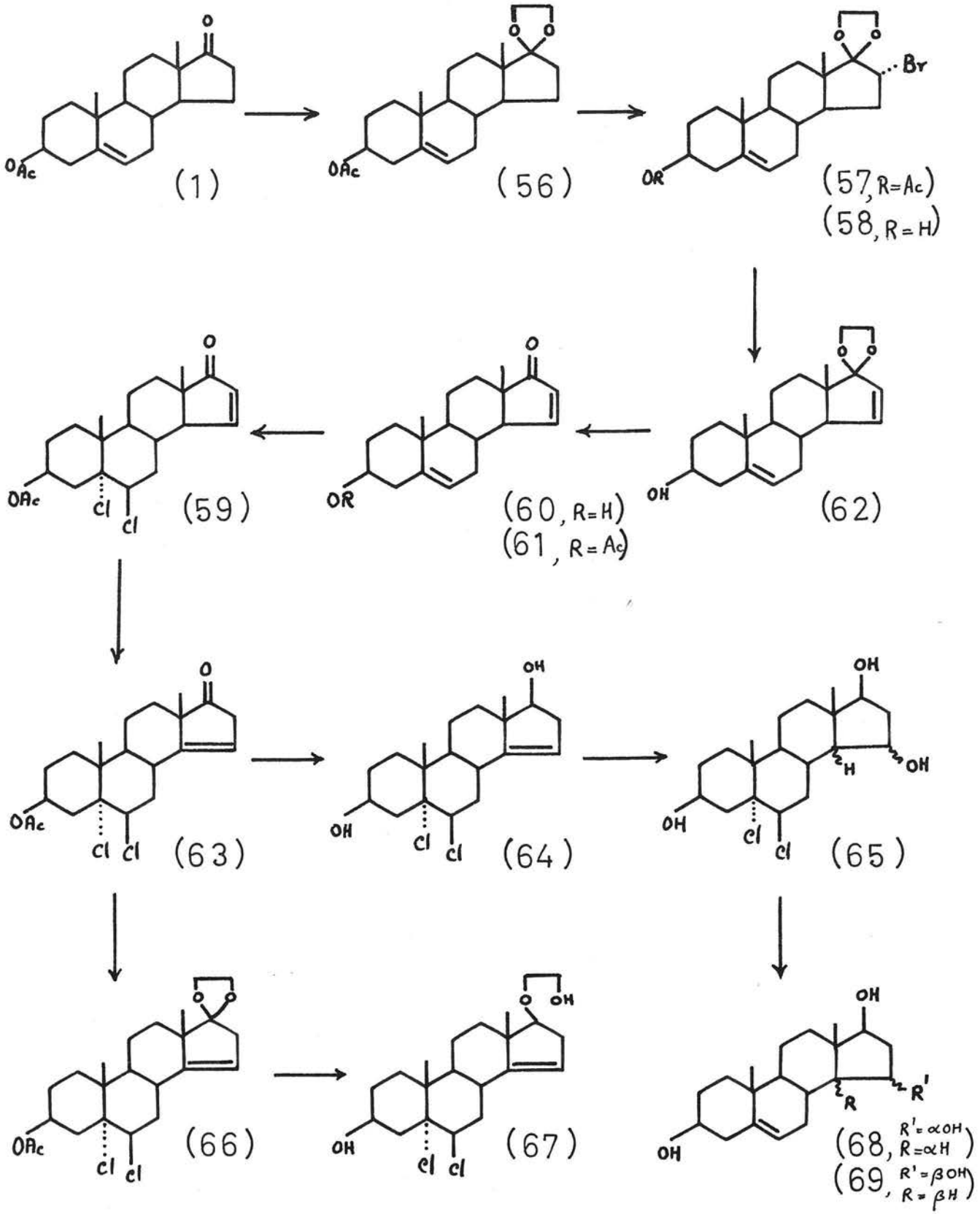
failure to isolate the dibromo compound meant that the oxidation reaction took place in the presence of strong acid, consequently the oxidation of the dichloro compound was repeated but this time with the addition of hydrogen bromide in acetic acid. In the presence of HBr the reaction observed by St. André et al. occurred and crystalline 3β-acetoxy-5α,6β-dichloro-14α-hydroxyandrostan-17-one was isolated. The yield in this reaction was lower than that of the previous workers and attempts to improve the yield by varying the concentration and nature of the acid failed. Performing the reaction at 100° gave lower yields. The 14α-hydroxy compound obtained was put through the dehydration procedure but no crystalline product could be obtained even after chromatography on alumina.

The second main preparation of Δ^{14} compounds proceeds through the Δ^{15}-17-ketone. This enone was first reported by Fajkos[89] who reacted the Δ^{16}-17-acetate with N-bromosuccinimide to give the 15β-bromo compound and the remaining enol acetate was treated with bromine to introduce a 16α-bromo group. The result was a trans diaxial dibromo compound which could easily be debrominated to give the Δ^{15}-17-ketone. This reaction has not been used to any extent since, although the yields reported were good. The first synthesis cleverly avoided the difficulty in the preparation of the Δ^{15}-17-ketones, namely that the very reactive nature of the enone group causes intermolecular additions in the presence of base[90] and therefore dehydrobromination of an α-bromo ketone is ruled out. Subsequent methods have depended on the

preparation of a 16α-bromo-17-ketal, dehydrobromination with strong base, then mild hydrolysis of the ketal.[91,92] In the first case reported the bromo ketone was ketalised, but recently bromination α to a ketal has been reported to occur in good yields and the best synthesis of the Δ^{15}-17-ketone follows the lines of Djerassi et al.[92] The Δ^{15}-17-ketone rearranges to a Δ^{14}-17-ketone in the presence of acid.[90]

The reactions of the 14,15-double bond in the androstane series have not been widely investigated. When a 17-ketone is present the peroxidation of this double bond with a peracid occurs from the β-face of the molecule to give the 14β,15β-oxide.[86] Moreover in a similar Δ^{14}-17-keto oestrane the hydrogenation of the Δ^{14} bond has been shown to produce the 14-iso compound[90] as a result of addition of hydrogen again from the β face of the molecule. However, the reaction of diborane on the Δ^{14}-17β-hydroxy compound has been reported to give the 15α hydroxy group.[88] In a recent paper[93] a synthetic oestrane type compound was hydrated with diborane to give the 14-iso-15β-hydroxy compound.

The use of a 14β,15β oxide to obtain a 15-hydroxy steroid with a 17-ketone appeared to be a very difficult route. The best way to protect the ketone would be as the ethylene ketal but this group would possibly not resist the acid conditions necessary for the rearrangement of the oxide to a 15-ketone. A 15,17-diketone would be of no use for no selective reaction would then be available for the differentiation of these two groups. Moreoever, it has been reported that a 14β,15β-oxide rearranges



THE REACTION OF DIBORANE ON SOME Δ^{14} COMPOUNDS

to a 15-keto-14α-cardanolide[94] but it has also been reported (in a patent)[95] that a 14α,15α-oxide in the pregnane series undergoes rearrangement to the 14α-pregnane as well. Because of the uncertainty of the oxide route the hydration of a 14-double bond with diborane was considered the most hopeful route and suitably protected Δ^{14} steroids were prepared via the Δ^{15}-17-ketone.

3β-Acetoxyandrost-5-en-17-one was ketalised using an adaptation of the method of Delepine;[97] the ketal (56) was prepared on the 100 g. scale in 93% yield using ethyleneglycol, triethylorthoformate and a p-toluene sulphonic acid catalyst. In this ketalisation the purpose of triethylorthoformate is effectively to remove water, water reacts with the triethylorthoformate to give ethyl formate and ethanol, these both have boiling points below 90° and can be distilled from the reaction mixture (all other reactants have boiling points above 120°). The water which is removed is that formed in the equilibrium between ethyleneglycol and steroid ketone and this removal of one of the products of the equilibrium ensures very efficient ketalisation. The removal of the ethanol and ethylformate are not essential if lower yields are to be accepted, and the reaction has been carried out at room temperature when the reaction time was extended to 48 hours.

The ketal (56) was brominated in tetrahydrofuran with either pyridiniumhydrobromide perbromide or trimethylammonium bromide perbromide.[98] Bromination occurred at 5,6 during this reaction but these bromines were subsequently removed by the addition of

solid sodium iodide to the tetrahydrofuran solution followed by the addition of aqueous sodium thiosulphate. The overall yield for the bromination of the ketal was 74%. The dehydrobromination of the ketal was best achieved in dimethylsulphoxide[99] and to make the ketal more soluble in this solvent the 3β-acetate was hydrolysed. The resulting 16α-bromo-17-ethylenedioxy-3β-hydroxyandrost-5-ene (58) was treated with resublimed potassium tertiary-butoxide in dry dimethylsulphoxide at 40° for twelve hours, the steroid was then recovered with an ether extraction. This method usually gave very good yields. The Δ^{15}-17-ketal could be readily hydrolysed to the enone (60) by reaction with p-toluenesulphonic acid in aqueous acetone at room temperature.

The Δ^{15}-17-ketone (60) may be rearranged to the Δ^{14}-isomer by refluxing with acid in toluene, but to avoid formation of a 5,14-diene with no possibility of a selective reaction, the 5,6-double bond was first protected. The 3β-hydroxy-eneone (60) was acetylated and the resulting acetate (61) was reacted with sulphuryl chloride and pyridine to give 3β-acetoxy-5α,6β-dichloro-androst-15-en-17-one (59). This enone was isomerised to the Δ^{14}-17-ketone (63) with p-toluenesulphonic acid in refluxing toluene.

The 17-ethylene ketal of the Δ^{14} compound could be prepared by using the ketalisation procedure described above with toluene as co-solvent to allow easier handling of the small amount of material; the reaction was continued until the slowly distilled vapour was at the temperature of boiling toluene. A further

protected Δ^{14} compound was prepared by reducing and hydrolysing the Δ^{14}-17-ketone (63) to give 5α,6β-dichloro-3β,17β-dihydroxy-androst-14-ene (64).

The hydration with diborane was tried on 5α,6β-dichloro-3β, 17β-dihydroxyandrost-14-ene (64). The diborane was generated *in situ* and the method of Sondheimer *et al.*[88] was followed closely except that sodium borohydride was substituted for lithium aluminium hydride as the generating agent, this was done to protect the chlorines which might have been reduced by the latter reagent.[41] The result of the hydration sequence was a mixture of products; thin layer chromatographic analysis showed five spots, these were bronze in colour indicating that the 5,6-dichloro grouping had remained intact and this was subsequently confirmed by n.m.r. spectroscopy. The polarities of the spots ranged from that of the original diol to considerably more polar material which might correspond to a 15α-hydroxy triol. The crude hydration mixture was chromatographed on alumina and the component corresponding to the most polar spot on t.l.c. was isolated. This material was dechlorinated with zinc and acetic acid to give a 3β-hydroxy-Δ^5 substance, which was evident from a n.m.r. spectrum in pyridine and the fact that it stained bright pink with antimony trichloride in chloroform. The material was semi-crystalline and could be recrystallised from methanol - benzene to give material with a melting point range 240-250°. This material was apparently homogeneous on t.l.c. and g.l.c., however when the trimethylsilyl ether derivative was prepared, this chromatographed on g.l.c. to give two equal area peaks of retention times 1.70 and 2.38 (relative

to 3β-hydroxyandrost-5-en-17-one). The mixture of ethers was further analysed by combined g.l.c. and mass spectrometry; the ethers were both tris(trimethylsilyl)ethers and the mass spectra of the two compounds were both indistinguishable from the mass spectrum of 3β,15β,17β-tris(trimethylsilyloxy)-androst-5-ene. The preparation of the 3β,15β,17β triol is described later.

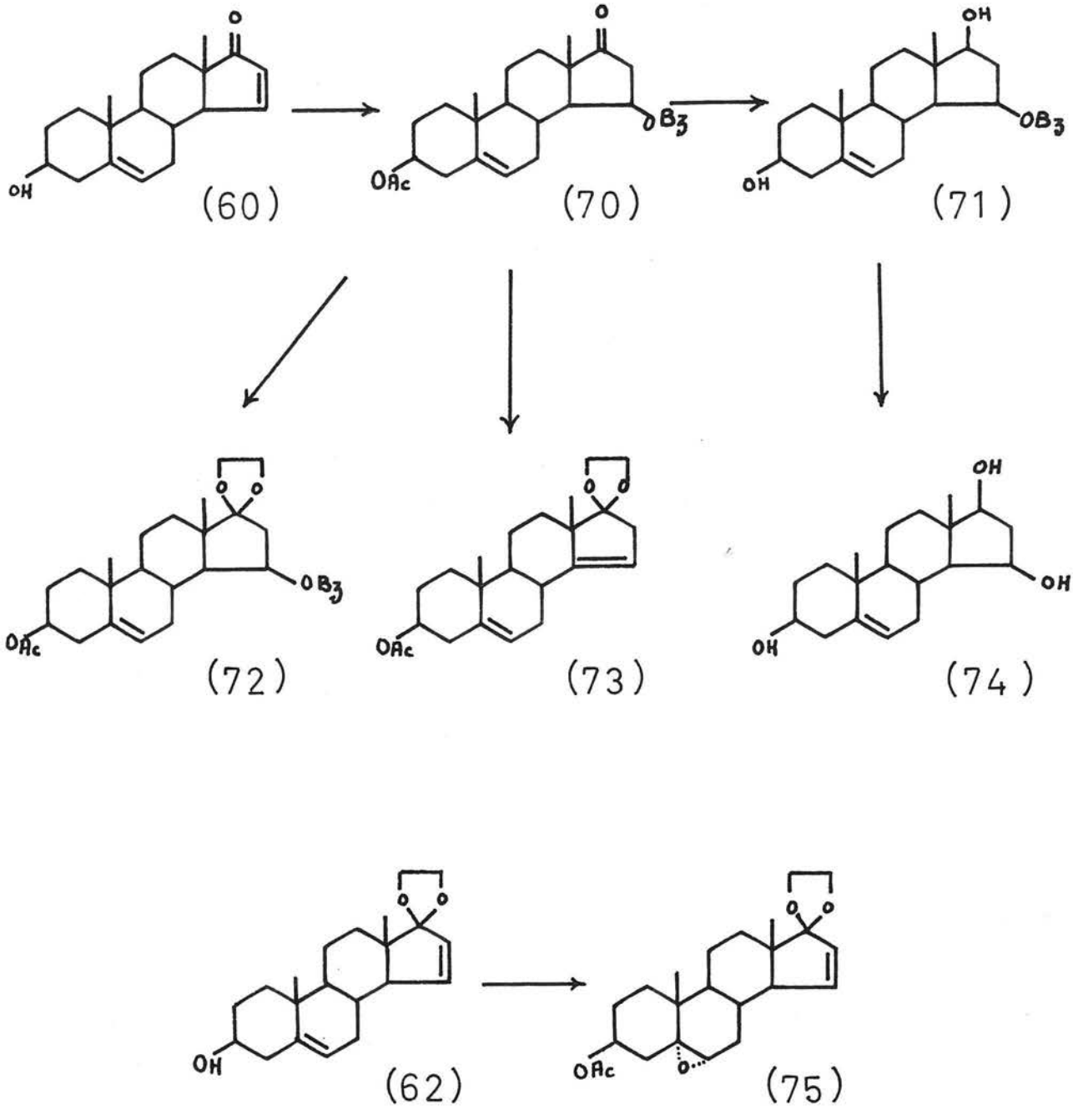
These results indicate that the diborane addition has not been selectively from the α face of the molecule, this may be partly due to the chlorines at 5 and 6. The preparation of the two triols of similar polarity, which appear to be 3β,15,17β-triols, can be explained if it is assumed that the attack of diborane is from both sides of the molecule. Since diborane would be expected to give a cis addition product, the two triols would be 3β,15α,17β-trihydroxyandrost-5-ene (68) and 3β,15β,17β-trihydroxy-14β-androst-5-ene (69). Although the 15α- and 15β-hydroxy groups confer different polarities on the molecules of the 14α-androstane series and are easily separable by column chromatography,[92] this does not hold if there is a change in configuration at C-14. It is therefore not unreasonable that these two triols should have very similar polarities, but in the gas liquid chromatography of tris(trimethylsilyl) ethers it is the molecular shape which is the main factor in the separation and in this respect the two derivatives are decidedly different.

A further attempt at the hydroboration of a Δ^{14} compound was made on 3β-acetoxy-5α,6β-dichloro-17-ethylenedioxyandrost-14-ene (66), here the 17-ethyleneketal presents a difficulty. The

ketal group and the acetate group are reported to be reduced by lithium aluminium hydride in the presence of a Lewis acid such as boron trifluoride.[88] In the diborane reaction used here the conditions were milder (borohydride was used) but when the ketal (66) was reacted with diborane generated internally, the product isolated was 5α,6β-dichloro-3β-hydroxy-17-(2-hydroxyethoxy)-androst-14-ene (67), the structure of which was proved by n.m.r. spectroscopy and the fact that it could not be hydrolysed by aqueous acidic acetone. Attempts at reaction of the 17-ethylenedioxy-Δ^{14} compound (66) with diborane generated externally failed to produce any reaction even though long reaction times were used.

Reactions of the Δ^{15}-17-ketones have been the most convenient source of 15 substituted steroids, one of the advantages of this route is that it need not involve a ketone at the 15 position and the consequent uncertainty of the configuration at the 14 position.

The generalisation of normal attack from the α-face of the steroid molecule does not hold in the D-ring. It has already been mentioned that attack on the 14,15-double bond has been reported to occur from different faces of the molecule depending on the substituent at C-17.[86,88,90,93] In the case of the Δ^{15}-17-ketone attack has consistently been from the β-face. Firstly the Δ^{15}-17-ketone has been peroxidised with alkaline peroxide to give a 15β, 16β-oxido ketone[92] and secondly both methanol and benzyl alcohol add 1,4 across the enone to give β substituents.[100] These reactions have meant that 15β substituents have been much easier to prepare than 15α ones. The first method of preparing a 15β-hydroxy-17-



THE SYNTHESIS OF 3β,15β,17β-TRIHYDROXYANDROST-5-ENE

keto compound was to add benzyl alcohol across the enone and to hydrogenolyse the 15β-benzyloxy group to a hydroxyl. This hydroxy ketone may subsequently be reduced to a 15β,17β-diol.[12] These preparations have been carried out in the oestrane and androstane[101] series, but no 15 substituted steroids in the androst-5-ene series have been reported. The interest in the oestranes has been mainly because of the isolation of 15β-hydroxyoestrone and 15β-hydroxy-17β-oestradiol.[12] A recent paper reported the synthesis of a 15β,17β-diol of the androstane series by the lithium aluminium hydride reduction of 15β,16β-oxidoandrostan-17-one.[101] Djerassi[92] has used this oxido ketone derivative for the synthesis of 15-monosubstituted androstanes.

The preparation of the enone (60) has already been described and this enone has been used in the syntheses of 15 substituted androst-5-enes. Benzyl alcohol was added across the enone and the product was acetylated to facilitate its isolation. The addition product was as expected a 15β compound (70); this was evident from its molecular rotation, n.m.r. spectrum and polarity. Attempts to hydrogenolyse this 15β-benzyloxy group resulted in partial loss of the 5,6-double bond although a previous successful hydrogenolysis of a 16α-benzyloxy group in the presence of a 5,6-double bond[47] has already been mentioned. Of the remaining reagents which would cleave the benzyloxy group only metal in ammonia (or sodium in alcohol) would be suitable; reagents of an acidic nature which have been reported to cleave an ether group (hydriodic acid[102] and boron trifluoride in acetic anhydride[103])

would not be suitable because both the resulting 15β-hydroxy and the original 15β-benzyloxy groups are unstable to acid. Unfortunately, the reagents which are suitable as regards the 5,6-double bond and the 15 substituent will reduce the 17-ketone, consequently for the preparation of the 3β,15β,17β-triol (74) the diol (71) was first prepared by reduction of the benzyloxy ketone with lithium aluminium hydride. The diol (71) reacted smoothly with calcium in liquid ammonia to give the required triol. The 15β-hydroxy-17-ketone could therefore be prepared if it was possible to obtain the 15β-benzyloxy-17-ethyleneketal (72) in reasonable yield. It was found however that this ketal could not be prepared by conventional ketalisation reactions since the acid catalyst caused the elimination of benzyl alcohol from the system at the high temperatures normally used. The conventional ketalisation was carried out on 3β-acetoxy-15β-benzyloxyandrost-5-en-17-one (70) and the sole product of the reaction was 3β-acetoxy-17-ethylenedioxyandrosta-5,14-diene (73). It seemed probable that the elimination of benzyl alcohol was due to the relatively high temperature of the ketalisation reaction and consequently the modification of the ketalisation reaction already described was carried out at room temperature on the 15β-benzyloxy-17-ketone (70). The result of this ketalisation was a low yield of the required ketal (72) which was identified by infrared and n.m.r. spectroscopy. As well as the required ketal considerable amounts of diene and unreacted starting material were obtained.

It has been shown[101] that a 15β,16β-oxido-17-ketone is reduced

with lithium aluminium hydride to a 15β,17β-diol and it is therefore possible that a 15β,16β-oxido-17-ethyleneketal would be reduced to a 15β-hydroxy-17-ketal which would be a useful intermediate for the synthesis of the required steroids. It was thought that the 15,16-bond in the Δ^{15} unsaturated ketal (62) might be easily peroxidised and consequently selectively peroxidised in the presence of a Δ^{5} double bond. However, an attempted peroxidation followed by an acetylation gave a mixture which was chromatographed on alumina to give 3β-acetoxy-17-ethylenedioxy-5α,6α-oxidoandrost-15-ene which was identified by its n.m.r. spectrum. This spectrum showed the characteristic quartet and doublet of the 15 and 16 protons as well as only one oxide proton. The α-configuration of the oxide is deduced from the 6βH,7βH coupling constant of 4.5 c.p.s., which is in the characteristic range for the α oxide.[104] If the oxide had been 5β,6β the coupling constants 6αH,7αH and 6αH,7βH would have been in the ranges 0-0.6 τ and 1.9 - 2.6τ respectively.

It has not been possible to synthesise 3β-acetoxy-5α,6β-dichloro-17-ethylenedioxyandrost-15-ene because there has been no chance of selectively forming the dichloro compound. It is unlikely that a 5α,6β-dichlorocompound will withstand the dehydrobromination conditions necessary to form the Δ^{15} bond and if the chlorines were not introduced at this stage in the sequence it would lead to a system of two olefinic bonds. Unfortunately when the enone is formed, although it now becomes possible to selectively chlorinate the 5,6-double bond in the manner already

described to give (59) it is not possible to reintroduce the ketal group because the necessary acid catalysis would probably rearrange the Δ^{15} bond to Δ^{14}.

No efficient synthesis of 15-hydroxy-17-ketones in the androst-5-ene series has been found and it is thought probable that the best method would be the microbiological introduction of a 15α substituent on a 3-keto-Δ^4 compound and the subsequent introduction of the Δ^5 bond by the deconjugation and reduction route already described.

EXPERIMENTAL SECTION

For general Experimental Procedure see page 32

3β-Acetoxy-5α,6β-dichloroandrostan-17-one.- 3β-Acetoxyandrost-5-en-17-one (9 g.) was dissolved in benzene (280 ml.) and pyridine (15 ml.), the solution was stirred at 0° while a solution of redistilled sulphuryl chloride (4.09 g., 1.1 eq.) in benzene (40 ml.) was added over a period of ten minutes. The solution was stirred for twenty minutes after the addition of the sulphuryl chloride, then water was added and the steroid was extracted into ether. The ethereal solution was washed with sodium carbonate solution and evaporated to dryness. The residue was recrystallised from methanol to give 3β-acetoxy-5α,6β-dichloroandrostan-17-one, (7.2 g.), m.p. 220-222°, (lit.[25], m.p. 217-218°).

The oxidation of 3β-acetoxy-5α,6β-dichloroandrostan-17-one with chromic anhydride in acetic acid catalysed with hydrobromic acid.- 3β-Acetoxy-5α,6β-dichloroandrostan-17-one (8.1 g.) was dissolved in benzene (60 ml.) and acetic acid (60 ml.). Chromic anhydride (40 g.) was pulverised and added to acetic acid (200 ml.) and commercial 60% HBr in glacial acetic acid (20 ml.); the mixture was cooled to 20°. The solution of steroid was then added and the mixture was stirred at 20° for thirty minutes. The mixture was poured into an aqueous solution of sodium bisulphite and the steroid was extracted with three 300 ml. portions of chloroform; the chloroform solutions were combined and washed three times with 10% aqueous potassium hydroxide then with water and with saturated salt solution. The chloroform solution was dried with magnesium sulphate and evaporated to dryness. The residue (7.6 g.) was chromatographed on alumina (20 g.). Elution with benzene-ether (50:50) gave crystalline material which was recrystallised from

methanol to give starting material (4.6 g.); elution with ether-chloroform (7:3) gave non-crystalline material (0.27 g.); elution with chloroform gave crystalline material which was recrystallised from methanol to give 3β-acetoxy-5α,6β-dichloro-14α-hydroxyandrostan-17-one (0.70 g.) m.p. 208-210°; $[\alpha]_D$ -19° (c 0.1); $\nu_{max.}$ ($CHBr_3$) 3580, 1730, 1250, 1034 and 902 $cm.^{-1}$; n.m.r. τ 8.96 (C-18 methyl), τ 8.58 (C-19 methyl), τ 7.97 (acetate methyl), τ 5.55 multiplet (6H). (Found: C, 59.8; H, 7.3. $C_{21}H_{30}O_4Cl_2$ requires C, 60.4; H, 7.2%).

This oxidation was carried out with the omission of the hydrobromic acid catalyst and t.l.c. analysis of the isolated product showed there to be no significant component other than the starting material. Substitution of borontrifluoride etherate (10 ml.) for the hydrobromic acid produced no 14α-hydroxy compound. When the reaction was performed using concentrated sulphuric acid (1 ml.) and 70% perchloric acid (0.5 ml.) as catalysts, a small amount of 14α-hydroxy steroid was obtained but never in more than 5% yield. When these two acids were used the total weight of recovered material was less than 4 g. The acidic material from this reaction which was recovered in the alkaline wash was not investigated further. The reaction was also performed at 100° using hydrobromic acid as the catalyst, the yield in this case was 10% of the 14α-hydroxy steroid.

Attempted dehydration of 3β-Acetoxy-5α,5β-dichloro-14α-hydroxy-androst-17-one.- 3β-Acetoxy-5α,6β-dichloro-14α-hydroxyandrost-17-one (500 mg.) was dissolved in acetic anhydride (5 ml.) and fused potassium hydrogen sulphate (500 mg.) was added; the solution was heated at 100° for fifteen minutes. The solution was cooled and poured into water, the steroid was recovered with an ether extraction, the product was a gum which was chromatographed on alumina

(50 g.). No crystalline product could be isolated from the mixture.

3β-Acetoxy-17-ethylenedioxyandrost-5-ene (56).- p-Toluenesulphonic acid (2 g.), 3β-acetoxyandrost-5-en-17-one (1) (105 g., 0.32 mole), ethyleneglycol (60 ml., 1 mole) and triethylorthoformate (150 ml., 1 mole) were stirred together at 90° in an apparatus fitted with a reflux condenser and provision for the exclusion of moisture. After one hour the solvent was gradually distilled off and the distillation was continued until the temperature of the reaction mixture reached 110°, at this stage all the ethanol and ethyl formate had been removed. The hot reaction mixture was poured with caution into hot methanol (1.2 l.) containing pyridine (15 ml.), water (300 ml.) was then added and the solution was allowed to cool slowly to room temperature. The crystals which formed were filtered off and dried to give 3β-acetoxy-17-ethylenedioxyandrost-5-ene (110 g.) m.p. 143-144°. (Lit.[133] m.p. 140-142°).

Room temperature ketalisation of 3β-acetoxyandrost-5-en-17-one.- p-Toluenesulphonic acid (2 g.) was dissolved in triethylorthoformate (260 ml.) and solvent (20 ml.) was distilled off; the solution was allowed to cool and then 3β-acetoxyandrost-5-en-17-one (80 g.) and ethyleneglycol (40 ml.) were added. The mixture was stirred at 20° for 48 hours, after 4 hours the reaction mixture was homogeneous. When the reaction was over, solvent (250 ml.) was evaporated off at 30° on a rotary evaporator. The solution which was largely free of benzene was poured into methanol (500 ml.) and the steroid precipitated out of solution. The precipitated material was filtered off and recrystallised from aqueous methanol to give 3β-acetoxy-17-ethylenedioxyandrost-5-ene, (60 g.), m.p. 143-144° (lit.,[133] m.p. 140-142°).

3β-Acetoxy-16α-bromo-17-ethylenedioxyandrost-5-ene (57)

3β-Acetoxy-17-ethylenedioxyandrost-5-ene (56) (50 g.) was dissolved in freshly distilled anhydrous tetrahydrofuran (150 ml.), pyridinium hydrobromide perbromide (100 g.) in tetrahydrofuran (150 ml.) was added and the resulting mixture was stirred for two hours, after which time pyridinium hydrobromide had precipitated and the remaining solution was pale orange. Sodium iodide (75 g.) was finely ground and added to the reaction mixture which was stirred for half an hour; during this time the solution became dark brown with liberated iodine. A solution of sodium thiosulphate (100 g.) in water (150 ml.) and pyridine (30 ml.) was added and the solution was stirred for two hours. The reaction mixture was diluted with water (300 ml.) and the tetrahydrofuran was evaporated under vacuum. The crystalline material which formed was filtered off, washed well with water, dried and then recrystallised from aqueous ethanol to give 3β-acetoxy-16α-bromo-17-ethylenedioxyandrost-5-ene (57) (45 g.) m.p. 189-191°. Concentration of the mother liquors from the crystallisation gave a second crop (5 g.) m.p. 185-189° which was sufficiently pure for the next stage of the reaction. An analytical sample was recrystallised again from methanol m.p. 190-192°; $[\alpha]_D$ -101° (c 0.1) ν_{max} 1740, 1363 and 1240 cm.$^{-1}$ (Found: C, 61.0; H, 7.5; Br, 17.4. $C_{23}H_{33}O_4Br$ requires C, 60.7; H, 7.3; Br 17.6%).

16α-Bromo-3β-hydroxy-17-ethylenedioxyandrost-5-ene (58)

3β-Acetoxy-16α-bromo-17-ethylenedioxyandrost-5-ene (57) (50 g.) was dissolved in hot benzene (200 ml.) and hot methanol (2 l.) was

added, the solution was refluxed and a solution of potassium hydroxide (40 g.) in water (300 ml.) was added. The solution was refluxed for three hours then 200 ml. of solvent was distilled off and the reaction mixture was allowed to cool slowly to room temperature. The crystals which formed were filtered off, washed with methanol and dried. The product was recrystallised from aqueous methanol to give 16α-bromo-3β-hydroxy-17-ethylenedioxyandrost-5-ene (58) (40 g.) m.p. 179-181°. $[\alpha]_D$ -91° (c 0.1); ν_{max} 3600, 1388, 1217, 1110 and 1040 cm^{-1} n.m.r. τ 9.10 (C-18 methyl), τ 9.00 (C-19 methyl), τ 5.3 to 6.2, multiplet (four ethylene ketal protons) and τ 4.66, multiplet (6H). An analytical sample was recrystallised from acetone, m.p. 179-181°. (Found: C, 61.6; H, 7.4; Br, 19.2. $C_{21}H_{31}O_3Br$ requires C, 61.2; H, 7.6; Br, 19.4%).

17-Ethylenedioxy-3β-hydroxyandrosta-5,15-diene (62)

16α-Bromo-17-ethylenedioxy-3β-hydroxyandrost-5-ene (58) (9.5 g.) was dissolved in dry dimethylsulphoxide (120 ml.) at 40°. Resublimed and freshly dried potassium tert.-butoxide (5.5 g.) was added to the steroid solution under nitrogen. The reaction flask was stoppered and left to stand at 40° for twelve hours. The solution was then poured into dry ether (1 l.) and the ether was shaken until any precipitated solid had been dissolved. Water was added and the ethereal solution was washed with water followed by saturated salt solution. The solution was dried with magnesium sulphate and evaporated to dryness. The crystalline residue was recrystallised from aqueous ethanol to give 17-ethylenedioxy-3β-hydroxyandrosta-5,15-diene (7.2 g.) m.p. 150-156°; $[\alpha]_D$ -176°

(c 0.1); ν_{max} 1381, 1348, 1200, 1110, and 1050 $cm.^{-1}$; n.m.r. τ 9.07 (C-18 methyl), τ 8.96 (C-19 methyl), τ 6.07 (four ethylene ketal protons), τ 4.63 multiplet (6H), τ 4.30 quartet (15H) and τ 3.87 doublet (16H). An analytical sample was recrystallised from acetone-hexane. M.p. 158-161°. (Found: C, 76.7; H, 9.2. $C_{21}H_{30}O_3$ requires C, 76.3; H, 9.15%).

3β-Hydroxyandrosta-5,15-dien-17-one (60)

17-Ethylenedioxy-3β-hydroxyandrosta-5,15-dien-17-one (62) (10 g.) was dissolved in absolute acetone (500 ml.), a solution of p-toluenesulphonic acid (500 mg.) in water (50 ml.) was added and the solution was kept at 15° for 16 hours. Water (150 ml.) was added to the solution, then the solution was evaporated to half its volume at 25°. Material which crystallised during evaporation was filtered off, washed well with water and dried in vacuo to give 3β-hydroxyandrosta-5,15-dien-17-one (8 g.) m.p. 185-190°. An analytical sample was recrystallised from ethyl acetate, m.p. 202-205°; $[\alpha]_D$ -150° (c 0.1); λ_{max} 231 mμ (ϵ=7,700) (ethanol); ν_{max} 3600, 1708, 1048 and 823 $cm.^{-1}$; n.m.r. τ 8.91 (C-18 and C-19 methyls), τ 4.55 multiplet (6H), τ 3.94 quartet, $J_{15,16}$ =6 c.p.s., $J_{14,15}$=2.8 c.p.s. (15H), τ 2.48 doublet $J_{15,16}$=6 c.p.s. (16H); (Found: C, 79.3; H, 9.2. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.15%).

3β-Acetoxyandrosta-5,15-dien-17-one (61)

3β-Hydroxyandrosta-5,15-dien-17-one (60) (8.0 g.) m.p. 185-190°) was dissolved in pyridine (50 ml.) and acetic anhydride (100 ml.). The solution was kept at 20° for three hours then poured

into stirred crushed ice. The mixture was allowed to warm up to room temperature, the crystals which had formed were filtered off, washed well with water and dried in vacuo at 100° to give 3β-acetoxyandrosta-5,15-dien-17-one m.p. 185-190°. An analytical sample was recrystallised from acetone-hexane, m.p. 193-196°; $[\alpha]_D$ -138° (c 0.1); ν_{max} 1730, 1710, 1245, 1037 and 827 $cm.^{-1}$; (Found: C, 76.5; H, 8.5. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%).

3β-Acetoxy-5α,6β-dichloroandrost-15-en-17-one (59)

A solution of 3β-acetoxyandrosta-5,15-dien-17-one (61) (8.5 g. m.p. 185-190°) in benzene (150 ml.) and pyridine (15 ml.) was cooled to 0°, solid benzene began to separate out and subsequent additions were carried out in the presence of solid benzene. Sulphuryl chloride (3.95 g., 1.12 mole) in dry benzene (72 ml.) was added slowly, keeping the temperature of the reaction below 2°. When the addition was complete the flask was allowed to warm to 15° and the steroid was extracted into ether. The ethereal solution was washed with water, sodium carbonate solution and saturated salt solution, dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from aqueous acetone to give 3β-acetoxy-5α,6β-dichloroandrost-15-en-17-one (5.6 g.) m.p. 189-191°. An analytical sample was recrystallised from acetone, m.p. 189-191°; $[\alpha]_D$ -110° (c 0.1); λ_{max} 231 mμ (ϵ=8840) (ethanol) $\nu_{max.}$ 1728, 1709, 1244, 1021, 826 and 658 $cm.^{-1}$ (Found: C, 63.4; H, 7.1; Cl, 17.6. $C_{21}H_{28}O_3Cl_2$ requires C, 63.0; H, 7.1; Cl, 17.7%).

3β-Acetoxy-5α,6β-dichloroandrost-14-en-17-one (63)

3β-Acetoxy-5α,6β-dichloroandrost-15-en-17-one (59) (2.1 g.) was dissolved in dry toluene (250 ml.) and p-toluenesulphonic acid (200 mg.) was added. The mixture was refluxed for two hours. The solution was then cooled and diluted with ether (500 ml.), washed with sodium carbonate solution and saturated salt solution and dried with magnesium sulphate. Evaporation gave a product which was recrystallised from aqueous methanol to give 3β-acetoxy-5α,6β-dichloroandrost-14-en-17-one (1.3 g.) m.p. 178-180°. An analytical sample was recrystallised from methanol, m.p. 178-179°; $[\alpha]_D$ +25° (c 0.1); ν_{max} 1737, 1244, 1044 and 664 $cm.^{-1}$; n.m.r. τ 8.86 (C-18 methyl), τ 8.59 (C-19 methyl), τ 7.97 (acetate methyl), τ 5.62 multiplet (6H), τ 4.46 multiplet (15H). (Found: C, 63.2; H, 7.4; Cl, 17.5. $C_{21}H_{28}O_3Cl_2$ requires C, 63.0; H, 7.1; Cl, 17.7%).

3β-Acetoxy-5α,6β-dichloro-17-ethylenedioxyandrost-14-ene (66)

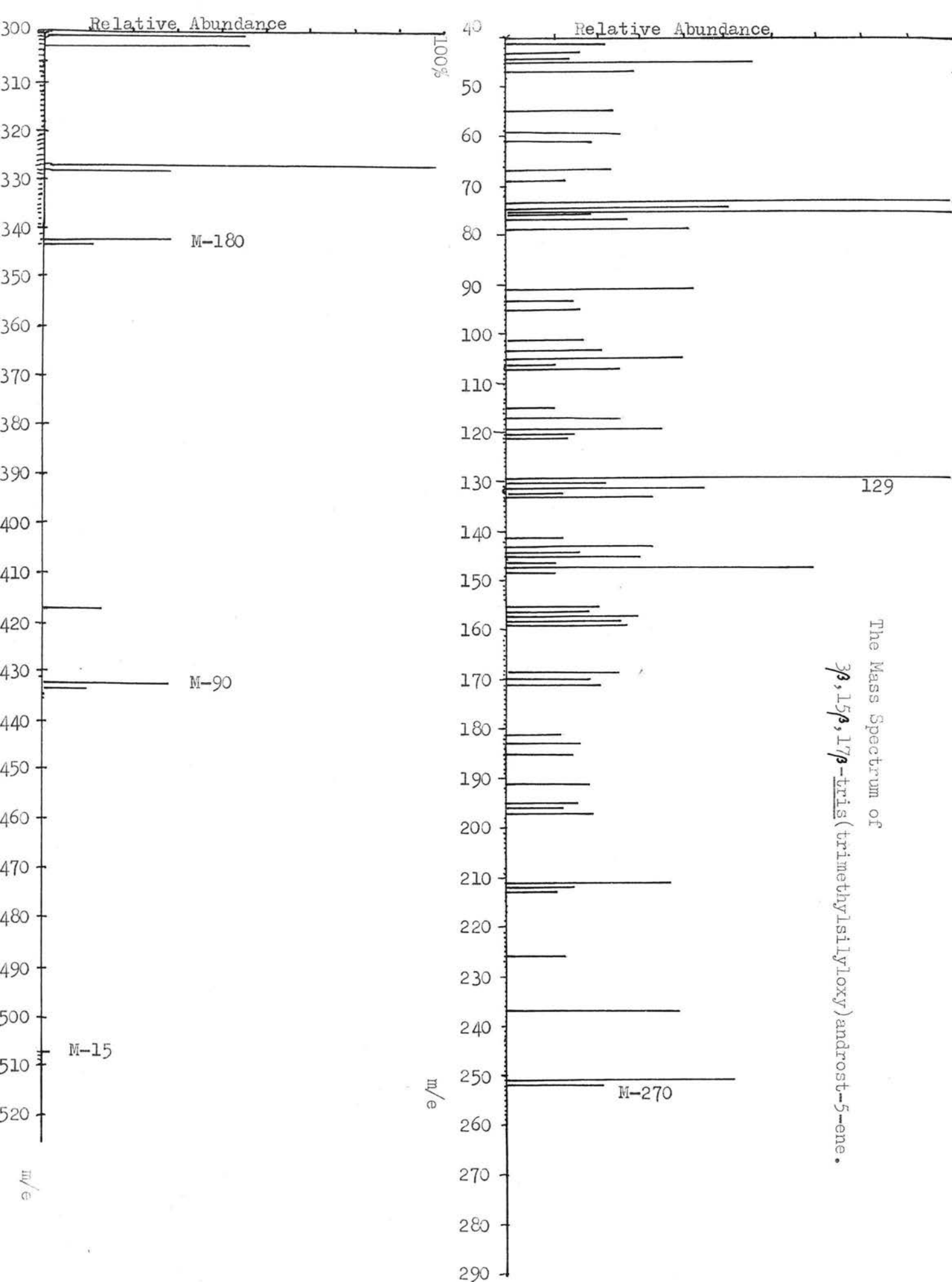
3β-Acetoxy-5α,6β-dichloroandrost-14-en-17-one (63) (330 mg.) was dissolved in dry toluene (15 ml.) and ethylene glycol (2 ml.), triethylorthoformate (4 ml.) and p-toluenesulphonic acid (40 mg.) were added. The solution was stirred and heated under reflux with an air condenser. The heating of the flask was adjusted so that the condensing vapours almost reached the top of the air condenser, this arrangement ensured that little toluene or triethylorthoformate was lost from the solution whilst any ethanol or ethyl formate formed during the reaction was removed from the system. After two hours of refluxing the flask was cooled and

pyridine (0.5 ml.) was added. The steroid was isolated by ether extraction. The reaction product was recrystallised from aqueous methanol to give 3β-acetoxy-5α,6β-dichloro-17-ethylenedioxyandrost-14-ene (106 mg.) m.p. 159-162°. An analytical sample was recrystallised from aqueous methanol. M.p. 162-163°; $[\alpha]_D$ -119° (c 0.1) ν_{max} 1734, 1245, 1035 and 655 $cm.^{-1}$; n.m.r. τ8.92 (C-18 methyl), τ 8.62 (C-19 methyl), τ 7.98 (acetate methyl), τ 6.09 (four ethylene ketal protons), τ 5.57 multiplet (6H) and τ 4.78 multiplet (15H). (Found: C, 62.2; H, 7.4; Cl, 16.3. $C_{23}H_{32}O_4Cl_2$ requires C, 62.2; H, 7.3; Cl, 16.0%).

5α,6β-Dichloro-3β,17β-dihydroxyandrost-14-ene (64)

3β-Acetoxy-5α,6β-dichloroandrost-14-en-17-one (63) (2.8 g.) was stirred with sodium borohydride (500 mg.) in 90% aqueous methanol (200 ml.) for 16 hours. Water was then added followed by dilute hydrochloric acid, the steroid was extracted into chloroform. The chloroform solution was washed with sodium carbonate solution and saturated salt solution, dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from benzene to give 5α,6β-dichloro-3β,17β-dihydroxyandrost-14-ene (2.1 g.), m.p. 160-168°. An analytical sample was purified by alumina chromatography and recrystallised from hexane. M.p. 166-169°; $[\alpha]_D$ -38° (c 0.1); ν_{max} ($CHCl_3$) 1068, 960 and 908 $cm.^{-1}$; n.m.r. (pyridine) τ 8.76 (C-18 methyl), τ 8.59 (C-19 methyl), τ 5.40 multiplet (16H) and τ 4.86 multiplet (15H). (Found: C, 66.5; H, 9.0. $C_{19}H_{28}O_2Cl_2$: C_6H_{14} requires C, 66.0; H, 9.2%).

The Reaction of Diborane on 5α,6β-Dichloro-3β-17β-dihydroxyandrost-14-ene.- 5α,6β-Dichloro-3β,17β-dihydroxyandrost-14-ene (64) (500 mg.) and sodium borohydride (2 g.) were dissolved in dry dioxan (10 ml.) and the solution was cooled to 10°. A solution of redistilled borontrifluoride etherate (3 ml.) in dioxan (10 ml.) was added dropwise over forty minutes with continuous stirring and cooling. The mixture was stirred for a further twelve hours at 18°. The reaction mixture was then poured into a solution of potassium hydroxide (1 g.) in water (10 ml.) and methanol (90 ml.) this mixture was stirred and cooled with ice for ten minutes. The stirring and cooling were continued while 30% hydrogen peroxide (30 ml.) was added slowly over twenty minutes. The mixture was stirred for a further ten minutes at room temperature. Water and chloroform were added and the chloroform solution was washed successively with water, ferrous sulphate solution, dilute hydrochloric acid, sodium carbonate solution and saturated salt solution. The solution was dried with magnesium sulphate and evaporated to dryness. The residue was analysed by thin layer chromatography using 10% ethanol in benzene as the solvent system (system K)[19] development of the plate with antimony trichloride in chloroform showed five bronze coloured spots which had R_D values 0.92, 0.86, 0.69, 0.63 and 0.54. The least polar spot had a polarity identical to that of 5α,6β-dichloro-3β,17β-dihydroxyandrost-14-ene. The total reaction product was chromatographed on alumina (100 g.), elution with methanol-chloroform (1:9) gave non-crystalline material (140 mg.) which showed one spot on thin layer chromatography, R_D 0.54. This polar material (90 mg.) was dissolved in



The Mass Spectrum of
3β,15β,17β-tris(trimethylsilyloxy)androst-5-ene.

acetic acid (30 ml.) and zinc dust (500 mg.) was added, the mixture was stirred at 100° for one hour. The reaction mixture was filtered and water was added to the filtrate, the steroid was extracted with chloroform. The residue from this extraction showed one major bright pink spot on thin layer chromatography, R_D 0.42. This crude material was semicrystalline and crystals could be obtained by recrystallisation from methanol-benzene; m.p. 240-250°. Gas chromatographic analysis of this crystalline material showed only one peak of relative retention time 1.82. The tris(trimethylsilyl) ether of this material was prepared using hexamethyldisilazane and trimethylchlorosilane in pyridine. Gas chromatographic analysis of this tri-ether showed two peaks of equal area (electronic integrator) and of relative retention times 1.70 and 2.38. The mass spectra of these two components were the same and both spectra were indistinguishable from the mass spectrum of pure 3β,15β,17β-trihydroxyandrost-5-ene tris(trimethylsilyl) ether. The n.m.r. (pyridine) spectrum of the mixed triols (68,69) had peaks at τ8.94, 8.90, 8.87 and 8.73. (Two C-18 methyl groups and two C-19 methyl groups; not assigned).

Attempted Hydroboration of 3β-Acetoxy-5α,6β-dichloro-17-ethylenedioxyandrost-14-ene.- 3β-Acetoxy-5α,6β-dichloro-17-ethylenedioxyandrost-14-ene (66) (300 mg.) was reacted with diborane generated internally using the same conditions and isolation procedure as for the reaction of compound (64) above. The residue was chromatographed on alumina (30 g.), activity III. Elution with ether gave crystalline material (180 mg.) which was

recrystallised from acetone-hexane to give 3β-hydroxy-5α,6β-dichloro-17-(2-hydroxyethoxy)-androst-14-ene (67) m.p. 82-85°; $[\alpha]_D$ -50° (c 0.1); ν_{max} 3550, 1136 and 656 $cm.^{-1}$; n.m.r. τ 9.00 (C-18 methyl), τ 8.65 (C-19 methyl), τ 6.38 multiplet (four ethylene ketal protons), τ 5.58 (6H) and τ 4.91 (15H). (Found: C, 61.7; H, 8.5. $C_{21}H_{34}O_3Cl_2$ requires C, 62.0; H, 8.45%). Further elution with chloroform-methanol (10:1) gave hydroxylated material (60 mg.) which contained no hydrolysable ethylene ketal group. The ethereal compounds obtained in this reaction showed no change when they were heated for four hours in refluxing aqueous acetone containing p-toluenesulphonic acid.

3β-Acetoxy-15β-benzyloxyandrost-5-en-17-one (70)

Androsta-5,15-dien-3β-ol-17-one (60) (9.5 g.) was stirred as a slurry with benzyl alcohol (15 ml.) and powdered sodium hydroxide (200 mg.) under nitrogen for twelve hours. The benzyl alcohol solution was added to acetic anhydride (100 ml.) and pyridine (30 ml.) and the mixture was stirred for three and a half hours at room temperature. The acetylation mixture was evaporated to 20 ml. in vacuo and the residue was taken up in ether (600 ml.). The ethereal solution was washed with sodium carbonate solution and with saturated salt solution and was dried with magnesium sulphate and evaporated to dryness. The residue was chromatographed on alumina (300 g.); elution with petrol-benzene (9:1) gave benzyl acetate. Further elution with ether gave crystalline material which was recrystallised from methanol to give pure 3β-acetoxy-15β-benzyloxyandrost-5-en-17-one (5.9 g.) m.p. 232-233°.

An analytical sample was recrystallised from methanol, m.p. 236-237°; $[\alpha]_D$ -47° (c 0.1); $\nu_{max.}$ 1737, 1242, 1030, 739 and 700 $cm.^{-1}$; n.m.r. τ 8.91 (C-18 methyl), τ 8.81 (C-19 methyl), τ 7.97 (acetate methyl) τ 5.81 triplet (15αH), τ 5.50 doublet (benzyl methylene) and τ 4.61 (6H). (Found: C, 77.05; H, 8.6. $C_{28}H_{36}O_4$ requires C, 77.0; H, 8.3%).

15β-Benzyloxy-3β,17β-dihydroxyandrost-5-ene (71)

3β-Acetoxy-15β-benzyloxyandrost-5-en-17-one (70) (2.2 g.) was dissolved in dry tetrahydrofuran (150 ml.) and lithium aluminium hydride (500 mg.) was added. The solution was refluxed for one hour and then was allowed to cool. Excess lithium aluminium hydride was destroyed with ethyl acetate followed by water. Dilute hydrochloric acid was then added and the steroid was isolated using a chloroform extraction. The chloroform solution was dried and evaporated to dryness and the residue was recrystallised from methanol and carbontetrachloride to give 15β-benzyloxy-3β,17β-dihydroxyandrost-5-ene (1.7 g.) m.p. 180-185°. An analytical sample, crystallised from aqueous methanol had a m.p. 183-187°; $[\alpha]_D$ -82° (c 0.05) (Found: C, 75.4; H, 8.9. $C_{26}H_{36}O_3 \cdot H_2O$ requires C, 75.3; H, 9.2%), $\nu_{max.}$ (nujol) 1058, 758, 735 and 695 $cm.^{-1}$

3β,15β,17β-Trihydroxyandrost-5-ene (74)

15β-Benzyloxy-3β,17β-dihydroxyandrost-5-ene (71) (1.5 g.) was dissolved in dry tetrahydrofuran (100 ml.) and this solution was added to a stirred solution of calcium (7.5 g.) in liquid

ammonia (1 litre). The mixture was stirred for twelve hours allowing the ammonia to evaporate. Chloroform and dilute hydrochloric acid were added to the residue and the chloroform solution was washed with water, sodium carbonate solution and saturated salt solution. The solution was dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from methanol-carbon tetrachloride to give 3β,15β,17β-trihydroxyandrost-5-ene (300 mg.) m.p. 244-248°. An analytical sample was recrystallised from aqueous methanol, had a m.p. 249-251°, $[\alpha]_D$ -72° (dioxan c 0.1), (Found: C, 70.0; H, 9.9. $C_{19}H_{30}O_3$ requires C, 70.3; H, 9.9%), n.m.r. (pyridine) τ 8.90 (C-18 methyl), τ 8.49 (C-19 methyl), τ 4.51 multiplet (6H).

3β-Acetoxy-17-ethylenedioxyandrosta-5,14-diene (73)

3β-Acetoxy-15β-benzyloxyandrost-5-en-17-one (70) (420 mg.) and p-toluenesulphonic acid (20 mg.) were dissolved in toluene (10 ml.), triethylorthoformate (5 ml.) and ethylene glycol (2 ml.). The reaction mixture was refluxed for three hours and then cooled. The steroid was extracted with ether and the ethereal solution was washed with sodium carbonate solution and saturated salt solution, dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from methanol to give 3β-acetoxy-17-ethylenedioxyandrosta-5,14-diene (250 mg.) m.p. 145-149°. An analytical sample was recrystallised from methanol, m.p. 147-149°, (Found: C, 74.3; H, 8.9. $C_{23}H_{32}O_4$ requires C, 74.2; H, 8.7%); $\nu_{max.}$ 1735, 1381, 1373, 1312, 1242 and 1034 $cm.^{-1}$; n.m.r. τ 8.96 (C-19 methyl), τ 8.92 (C-18 methyl), τ 7.96 (acetate methyl),

τ6.09 (four ethylene ketal protons), τ 4.78 multiplet (15H) and τ4.56 multiplet (6H).

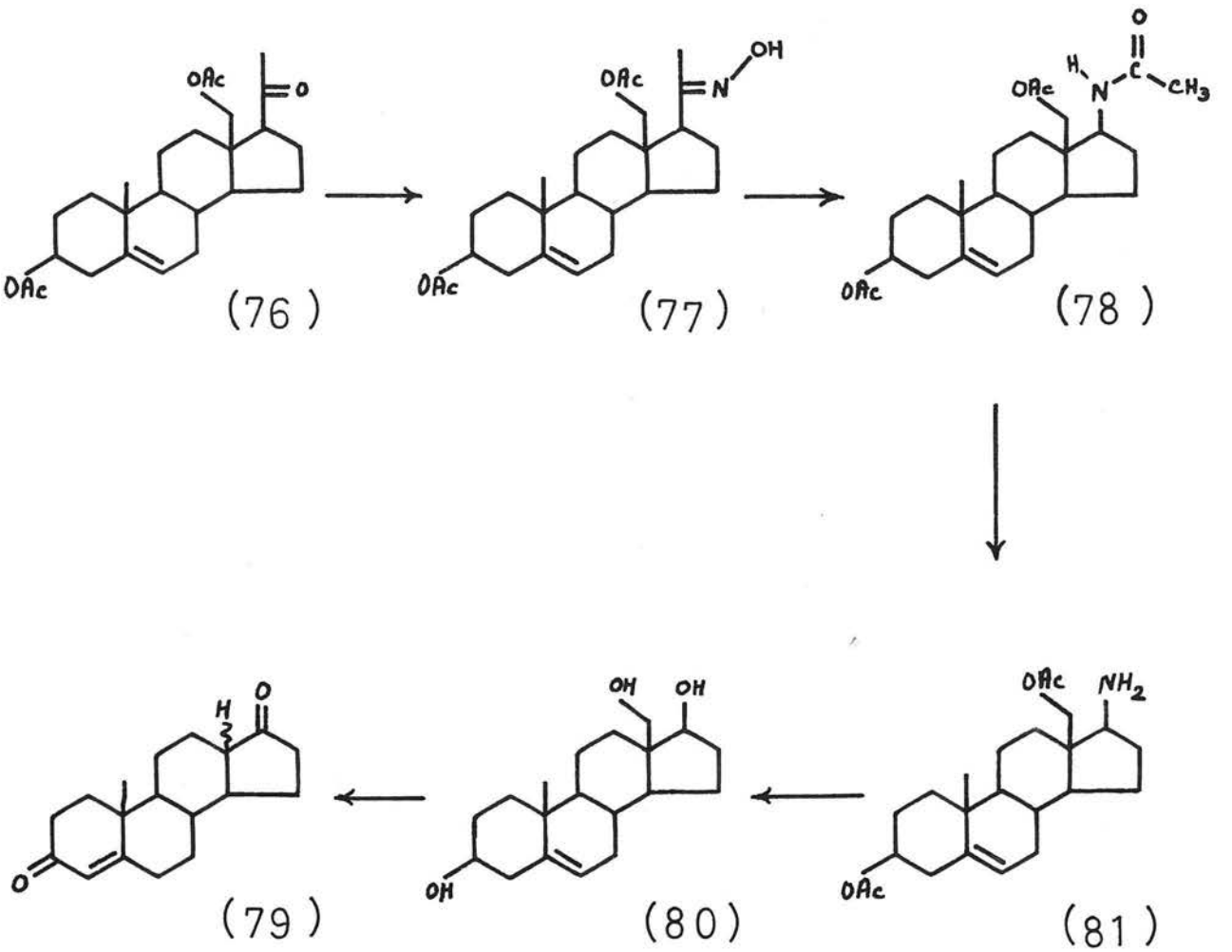
3β-Acetoxy-15β-benzyloxy-17-ethylenedioxyandrost-5-ene (72)

3β-Acetoxy-15β-benzyloxyandrost-5-en-17-one (70) (2.6 g.) was stirred with ethylene glycol (5.5 ml.), benzene (5 ml.), triethyl-orthoformate (15 ml.) and p-toluenesulphonic acid (0.2 g.) at 20°. After fifteen hours the reaction mixture was homogeneous, the stirring was continued for sixty hours. The steroid was extracted into ether. The ethereal solution was dried and evaporated to dryness, the residue was chromatographed on alumina (150 g.). Elution with petrol-ether (9:1) gave material (900 mg.) containing no benzyloxy group as shown by the absence of infrared absorption at 730 and 649 $cm.^{-1}$ Further elution with petrol-ether (6:4) gave 3β-acetoxy-15β-benzyloxy-17-ethylenedioxyandrost-5-ene (72) which was crystallised from methanol (350 mg.) m.p. 147-150°. An analytical sample was recrystallised from methanol, m.p. 149-151°; $[\alpha]_D$ -100° (c 0.1); $\nu_{max.}$ 1733, 1366, 1237, 1105, 1027, 730 and 694 $cm.^{-1}$; n.m.r. τ 8.95 (C-18 methyl), τ 8.88 (C-19 methyl), τ 7.98 (acetate methyl), τ 6.11 (four ethylene ketal protons) and τ 5.63 doublet, J = 9 c.p.s. (benzyl methylene protons). (Found: C, 74.9; H, 8.5. $C_{30}H_{40}O_5$ requires C, 75.0; H, 8.4%). Further elution with ether gave unchanged starting material (70) (1.2 g.).

3β-Acetoxy-17-ethylenedioxy-5α,6α-oxidoandrost-15-ene (75)

17-Ethylenedioxy-3β-hydroxyandrosta-5,15-diene (62) (16.8 g.) was dissolved in benzene (600 ml.) and the solution was cooled to

10° in ice. p-Nitroperoxybenzoic acid (18.1 g. of 55% peracid content, = 1.06 eq.) was added over ten minutes keeping the temperature below 15°. The solution was stirred for 20 minutes at 15° and then for twelve hours at room temperature. The benzene solution was washed thoroughly with sodium carbonate solution followed by water and saturated salt solution. The solution was dried with magnesium sulphate and evaporated to dryness. The residue was dissolved in pyridine (50 ml.) and acetic anhydride (100 ml.) and the solution was kept at 18° for three hours. This solution was then evaporated to dryness in vacuo and the residue was chromatographed on alumina (300 g.). Elution with ether-chloroform (98:2) gave crystalline material (7 g.) which was recrystallised from acetone-hexane to give 3β-acetoxy-17-ethylenedioxy-5α,6α-oxidoandrost-15-ene (5.5 g.) m.p. 196-199°. An analytical sample was recrystallised from acetone m.p. 199-200°; $[\alpha]_D$ -156° (c 0.1); $\nu_{max.}$ 1734, 1238, 1195, 1104, 1032 and 985 $cm.^{-1}$; n.m.r. τ 9.14 (C-18 methyl), τ 8.90 (C-19 methyl), τ 8.01 (acetate methyl), τ 7.08 doublet $J_{6\beta,7\beta}$ =4.5 c.p.s. (6H), τ 6.08 multiplet (four ethylene ketal protons), τ 4.29 quartet $J_{15,16}$ = 6 c.p.s. $J_{14,15}$ = 2.8 c.p.s. (15H), and τ 3.92 doublet, $J_{15,16}$ = 6 c.p.s. (16H). (Found: C, 70.85; H, 8.4. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%).

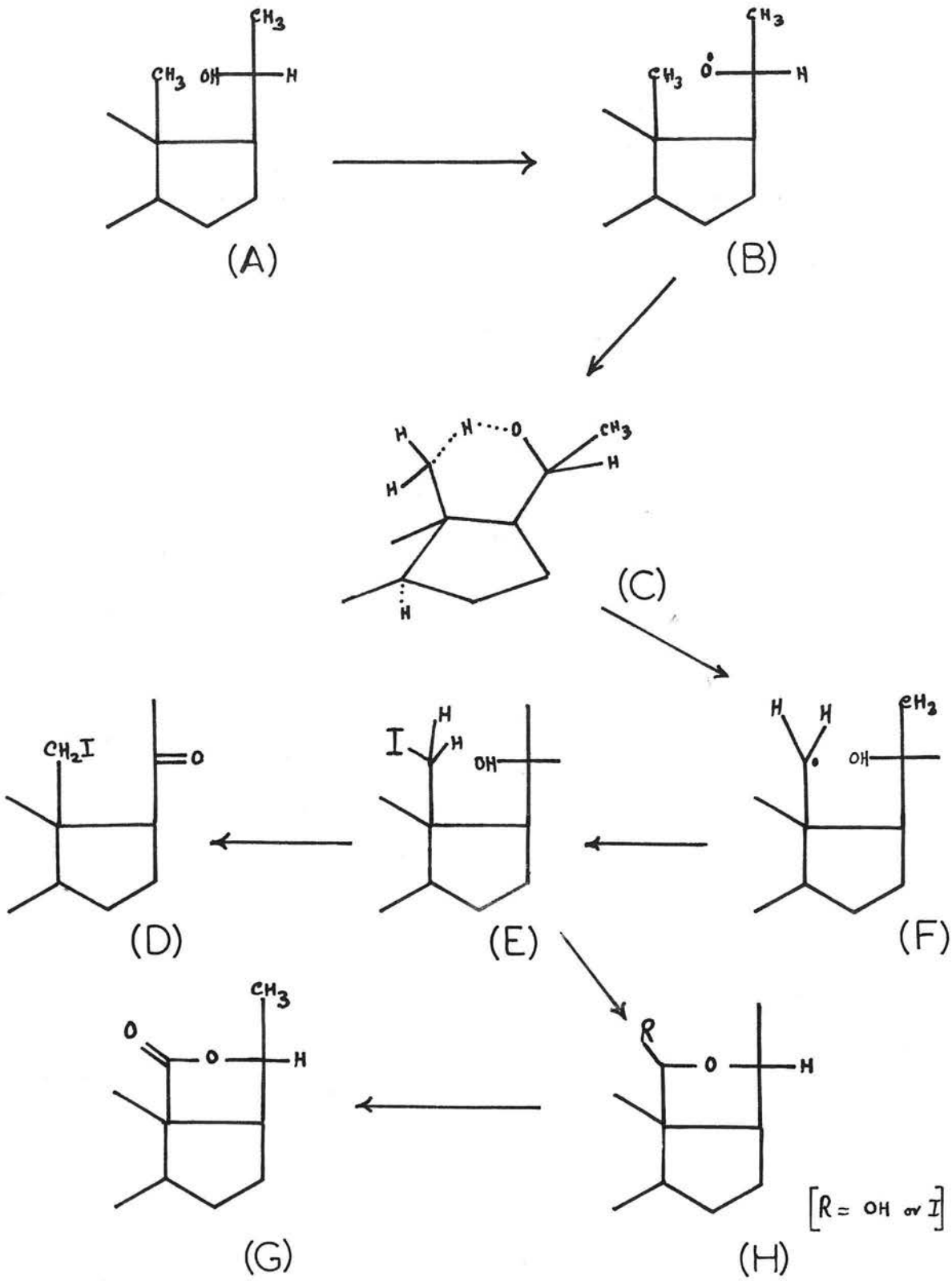


THE SYNTHESIS OF 18-NOR-13ξ-ANDROST-4-ENE-3,17-DIONE BY R.PAPPO

The Synthesis of 3β,18-Dihydroxyandrost-5-en-17-one and 3β-Hydroxy-18-nor-13α-Androst-5-en-17-one

Many 18-oxygenated steroids have been derived from pregnenolone and conessine (3β-dimethylaminocon-5-enine) and since both of these compounds have the 5,6-double bond and a 3β substituent it is not surprising that 18 substituted 3β-hydroxy-Δ^5 steroids have been made as intermediates in the syntheses of other steroids. Apart from the synthesis of the pregnenes,[105,106,107] Pappo has reported[108] the synthesis of 3β,17β,18-trihydroxyandrost-5-ene (80) as an intermediate in the synthesis of 18-nor-13β-androst-4-ene-3,17-dione (79). Early work on 18 substituted steroids was based on conessine which had been shown[109] to contain both an 18 substituent and a Δ^5 bond, the syntheses of steroids from conessine[105,110] involved the intermediate 21-hydroxy-3α,5-cyclo-5α-pregn-20-en-6-one which was eventually converted to a 3β-hydroxy-Δ^5-steroid. Most of the attention in the previous work however has been focussed on the pregnane type compounds and those with 3-keto-Δ^4 groups especially as intermediates in the synthesis of aldosterone.[111] No synthesis of 3β,18-dihydroxyandrost-5-en-17-one (90) has been reported in the literature.

The routes to 18 substituted steroids were examined to find the best preparation of a suitable intermediate. Attempts to introduce substituents at C-18 when a 17-ketone is present by the photolysis of a 11β-nitrite have led to D-homo compounds.[112] It has already been mentioned that the 17β-acetyl side chain is readily degraded to a 17-ketone if a Δ^{16} double bond or a 17α-hydroxy

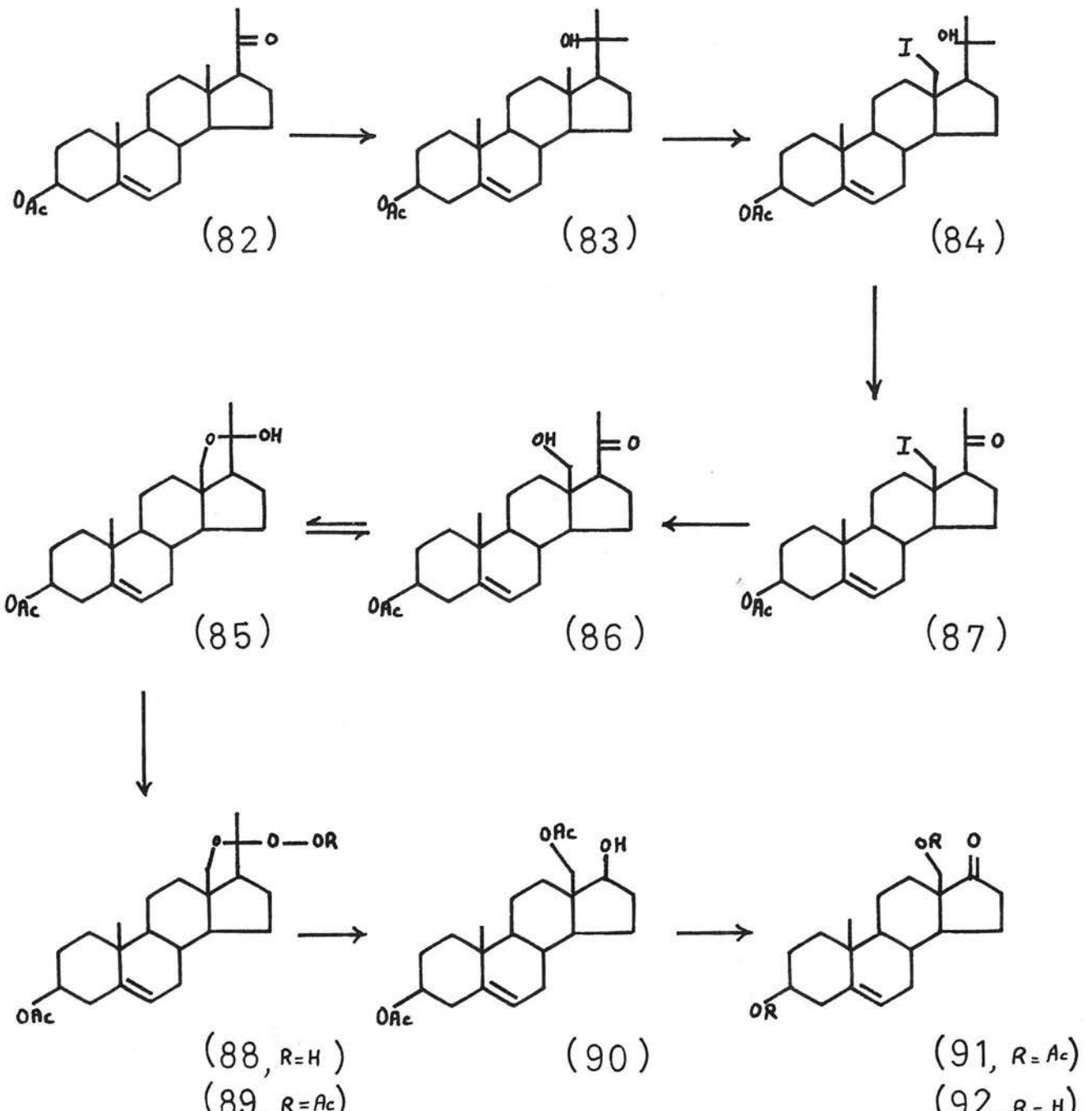


THE HYPOIODITE REACTION

group is also present in the molecule, however when an oxy-radical is generated at 20, the presence of these groups in the molecule present alternative breakdown paths for the radical and the result is a completely different reaction.[112] It was necessary therefore to form the usual derivative of 3β,20β-dihydroxypregn-5-ene [the hemiacetal (85)] and to use one of the side chain degradations developed by Pappo.[105,113,114]

Of the methods of getting the initial 18 substituent, the choice was between photolysis of nitrite esters,[112] the hypoiodite reaction,[115,116] oxidation of alcohols with lead tetraacetate[117] and the homolysis of N-chloramines[118] and hypochlorites.[119] Of these methods the best seemed to be the hypoiodite method which was originally developed by Wettstein and his coworkers, this reaction leads readily to an 18-hydroxy-20-ketone (hemiacetal) which lends itself to the side chain degradations. The method used was that described in the second main publication of the Swiss group[116] on the hypoiodite reaction; two of the main advantages of this method as of the hypoiodite reaction in general are that no reactive intermediates have to be isolated and that no special light source is required.

The hypoiodite reaction proceeds via the 20-alkoxy radical (B) as illustrated. The alkoxy radical is engaged in a six membered transition state (C) with a hydrogen from the 18-methyl group and this proton is exchanged to the 20-oxygen. The resulting alkyl radical at 18 (F) gains an iodine to give the 18-iodo-20-hydroxy-compound (E). If one mole of iodine is used the main product is



THE SYNTHESIS OF 3β,18-DIHYDROXYANDROST-5-EN-17-ONE

the 18-iodo-20-hydroxy compound, but a by-product is obtained by further attack by the 20-hydroxy group on the 18-methylene which leads to an iodo-oxide or a hemiacetal both of which give the lactone (G)[120] on oxidation with Jones reagent.[121] The iodo alcohol (84) was prepared and immediately oxidised to give the iodoketone (87) which was treated with freshly precipitated silver acetate in methanol to give the hemiketal (85). No evidence was found in this work of the 20-epimers of the hemiketal which were previously reported.[122] T.l.c. analysis of the intermediates consistently showed single spots. The yield of the hemiacetal (85) from 3β-acetoxy-20β-hydroxypregn-5-ene was 24%.

The method that Pappo[108] used to obtain 3β,17β,18-trihydroxyandrost-5-ene (80) is not readily applicable to the synthesis of the 17-ketone (92), because no opportunity for selective oxidation exists in the method as it is reported, although since the report is in the form of a patent not all the details are available. The side chain degradation of Pappo involves the rearrangement of the oxime (77) which in the absence of a 17-hydroxyl group or a Δ^{16} bond gives the 17-acetamido compound (78). The acetamido group is hydrolysed to give the amine (81) which is reacted with nitrous acid to give the triol (80) although the yield for this reaction is not quoted.

A more attractive method of removing the side chain was the modification of Pappo's hydroperoxide method used by Fukushima and Iseli[122] to prepare 18-hydroxyetiocholanolone. This method depends on the formation of the hydroperoxide of the hemiacetal

and this could be carried out in the presence of a 5,6-double bond by using 30% aqueous hydrogen peroxide. The hydroperoxide (88) was prepared and acetylated and this hydroperoxide acetate (89) was rearranged by refluxing with trimethylamine in aqueous dioxan to give as the main product 3β,18-diacetoxy-17β-hydroxyandrost-5-ene (90) which was purified by column chromatography on alumina and identified by its n.m.r. spectrum. The n.m.r. spectrum showed one sharp peak at τ 5.75 (18-methylene) which is exactly what was observed by the previous workers in the etiocholane series. The 17-hydroxy compound was oxidised to the 18-acetoxy-17-ketone (91) with Jones' reagent[121] and this was readily hydrolysed by aqueous acidic methanol to give 3β,18-dihydroxyandrost-5-en-17-one (92) in 24% overall yield from the hemiacetal (85).

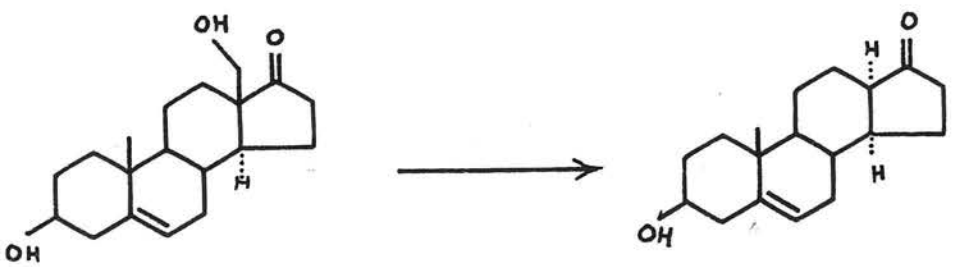
3β-Hydroxy-18-nor-13α-androst-5-en-17-one

Most of the common steroid hormones have been prepared in the 18-nor form, however the interest in these compounds has been short lived because it was soon found that they did not have any biological activity or at least greatly reduced biological activity. The following syntheses are reported; 18-nor-progesterone,[123] 18-nor-androst-4-ene-3,17-dione[108] (79), 18-nor-oestrone,[124] 18-nor-testosterone,[125] and 18-nor-cortisone.[126] The methods of synthesis have been varied but for the cortisone and progesterone anologues the D ring has been cleaved and recyclysed and the oestrone and testosterone derivatives have been obtained by total synthesis.

When Marrian first isolated 18-hydroxy-oestrone[10] he found that when this compound was treated with base, formaldehyde was liberated and this liberation of formaldehyde has become almost a standard test for the presence of the 18-hydroxy-17-ketone group in a molecule. In Marrian's proof of the structure of 18-hydroxy oestrone the oestrogen-like material which was left after formaldehyde was liberated was identified as 18-nor oestrone by comparison with an authentic sample totally synthesised.[124]

In the synthesis of 18-nor androstenedione (79), 3β,17β,18-trihydroxyandrost-5-ene was subjected to Oppenauer oxidation and under the conditions of the reaction formic acid was eliminated to give 18-nor-13ξ-androst-4-ene-3,17-dione (79) as a mixture of 13-epimers.

When 3β,18-dihydroxyandrost-5-en-17-one (92) was prepared and this compound was chromatographed on g.l.c. one peak was observed of a shorter retention time than that of 3β-hydroxyandrost-



(92) (93)

THE SYNTHESIS OF 3β-HYDROXY-18-NOR-13α-ANDROST-5-EN-17-ONE

5-en-17-one the shorter retention time indicated that part of the molecule had been lost and it was likely that formaldehyde had been eliminated. The sharpness of the peak indicated that the pyrolytic reaction had been almost instantaneous and the preparation of a sample of the product on a larger scale was attempted by sublimation of the 18-hydroxy-17-ketone under high vacuum. A sample of the 18-hydroxy compound (92) was sublimed under high vacuum to give a white crystalline product which could be recrystallised from methanol to give a crystalline material of m.p. 161-164°.

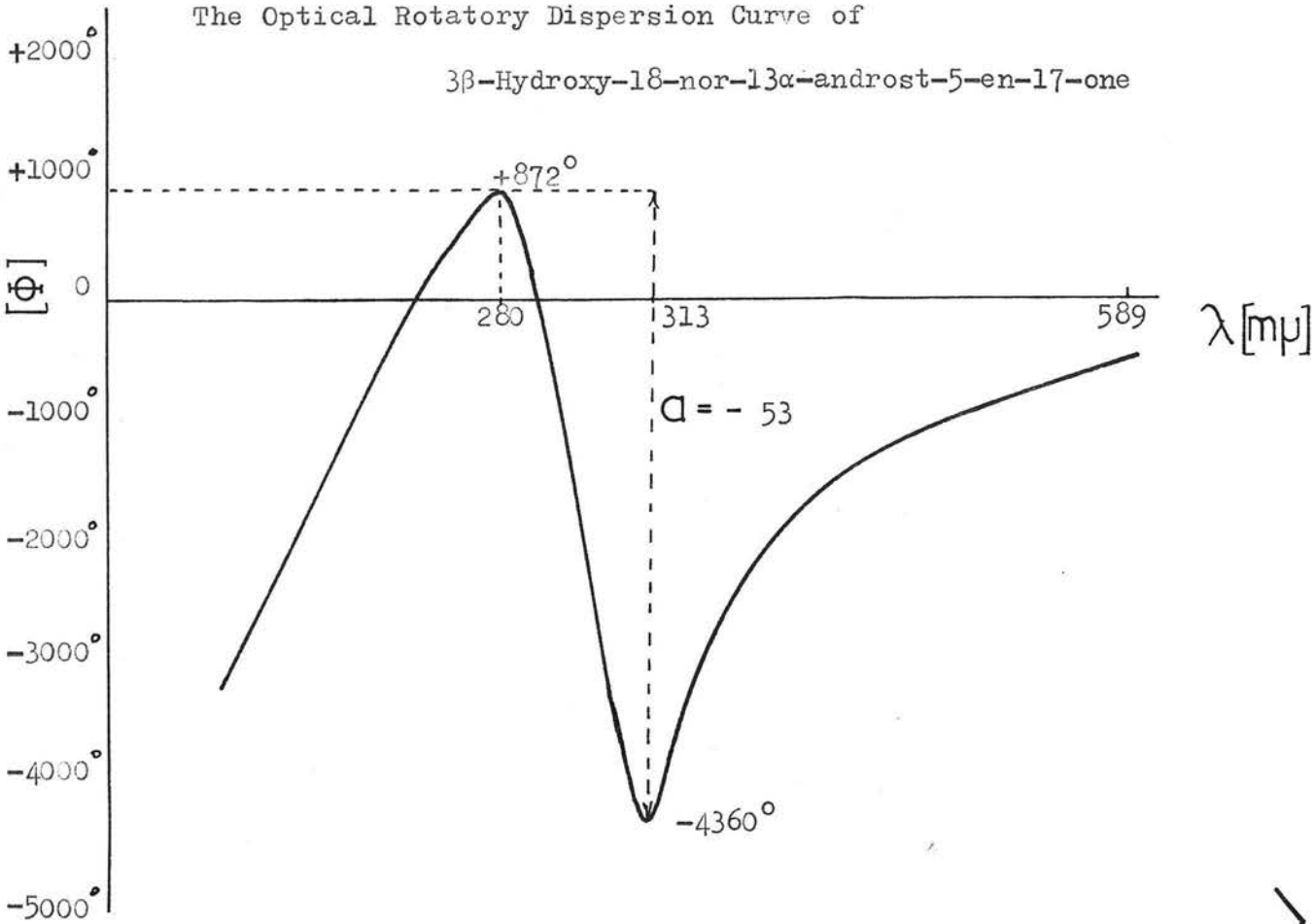
N.m.r. analysis of the material obtained from the vacuum sublimation showed the presence of only one methyl resonance at τ 9.15 and no signal in the region where the 18-methylene group originally absorbed. Elemental analysis of the product was compatible with the formula $C_{18}H_{26}O_2$ and it was clear therefore that an 18-nor compound had been formed. This pyrolysis product behaved on thin layer chromatographic analysis exactly as material obtained by the treatment of the 18-hydroxy-17-ketone (92) with base.

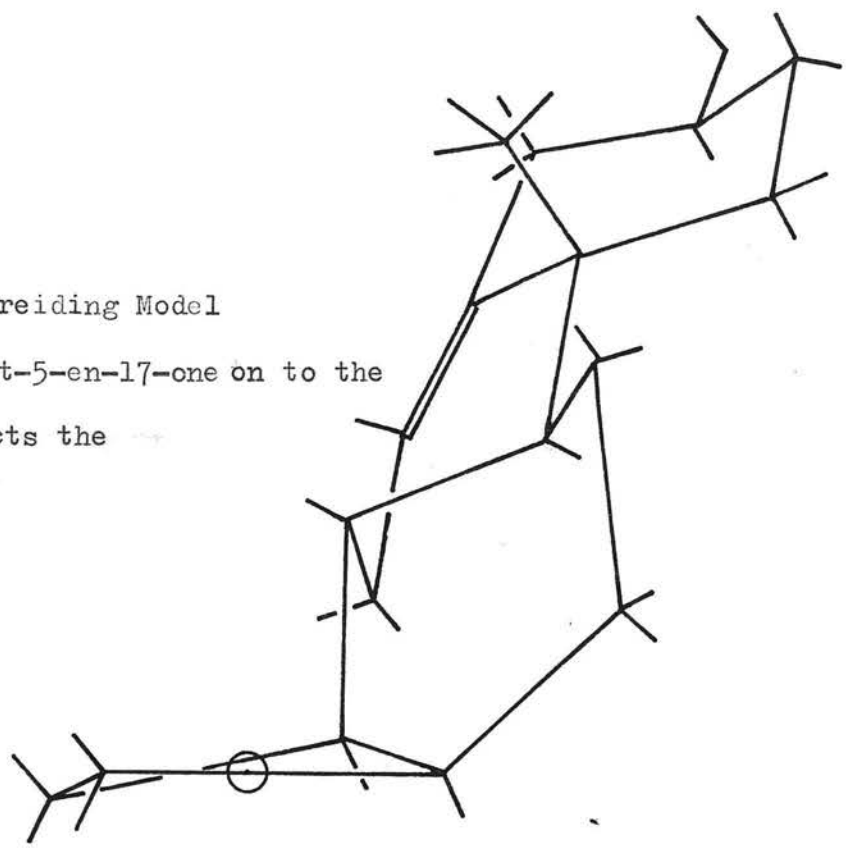
A parallel pyrolytic reaction has recently been reported by Menini *et al.*;[127] in this case 19-hydroxy-androstenedione eliminated formaldehyde on gas chromatography to give a mixture of 19-nor steroids.

It has been stated that for the junction between five and six membered rings the most stable configuration is cis,[128] and for a compound formed under pyrolytic conditions or under basic conditions the most stable configuration would be expected particularly when

The Optical Rotatory Dispersion Curve of

3β-Hydroxy-18-nor-13α-androst-5-en-17-one





The Projection of a Dreiding Model of 3β-Hydroxy-18-nor-13α-androst-5-en-17-one on to the plane which perpendicularly bisects the carbon-oxygen double bond

a ketone is present α to the ring junction. Therefore, it is likely that the 18-nor compound obtained here (93) has a C/D-cis ring junction and this has been supported by optical rotatory measurements.

The o.r.d. curves for a pair of 13-epimeric 17-ketones are published,[129] these epimers are 13β- and 13α-octanordammarane-3,17-dione and these exhibit positive and negative Cotton curves respectively although in this case the equilibrium of the two forms shows that the 13β is the more stable form. This however can be shown by the use of Dreiding models to be due to the effect of the 8β-methyl group which causes more non-bonded interaction in the 13α-epimer. The o.r.d. curve of the 18-nor compound (93) is illustrated and this is a negative curve demonstrating that the compound here has the 13α-configuration.

The empirical assignment of the 13α-configuration is in agreement with the configuration which would be predicted from the application of the octant rule.[135] The projection of a Dreiding model illustrated shows that most of the steroid falls into the back top right octant which should confer a negative sign on the cotton effect curve.

EXPERIMENTAL SECTION

3β-Acetoxy-20β-hydroxypregn-5-ene (83).- This compound was prepared by following exactly the method of Heusler, Wieland and Meystre.[120] The 20β-hydroxy-compound (m.p. 161-164°) was obtained in an 80% yield.

3β-Acetoxy-18-hydroxypregn-5-en-20-one hemiacetal (85).- Lead

tetraacetate was freshly recrystallised and dried *in vacuo*, this material (15 g.) was rapidly transferred to a flask containing redistilled, sodium-dried cyclohexane (500 ml.) and dried calcium carbonate (10 g.) this mixture was refluxed for one hour. 3β-Acetoxy-20β-hydroxypregn-5-ene (5 g.) was then added followed by iodine (1.80 g.); the solution was irradiated from beneath with a 500 watt projector bulb, the light and heat from this bulb were concentrated on the flask by means of aluminium foil. The contents of the flask were stirred and the solution was boiled by the heat of the lamp; after twenty minutes the iodine colour had disappeared and the flask was cooled to room temperature. Filtering aid (Celite, 5 g.) was added and the solution was filtered, the filtrate was washed with aqueous sodium thiosulphate followed by water and dried with magnesium sulphate. Pyridine (5 ml.) was added to the solution and this was then evaporated to dryness *in vacuo* on a rotary evaporator at 30-35°. The residue was dissolved in acetone (100 ml.) and this solution was cooled to 2°; 8N chromic acid solution[121] (5.9 ml.) was added keeping the temperature below 5° and then the solution was stirred at 2-5° for 30 minutes. Sodium acetate (56 g.) in water (100 ml.) was added and the steroid was extracted into benzene (200 ml.); the benzene solution was washed with saturated sodium chloride solution, dried with magnesium sulphate and evaporated to dryness. The residue was dissolved in methanol (250 ml.) and freshly precipitated silver acetate (10 g.) was added, the resulting slurry was stirred and refluxed for two hours; the solution was cooled and filter aid (Celite) was added

The solution was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ether and this solution was placed on a column of Florisil (50 g.), elution with ether gave pregnenolone acetate (1.3 g.); further elution with chloroform gave 3β-acetoxy-18-hydroxypregn-5-en-20-one hemiacetal (85) (1.2 g.) m.p. 171-174°, (lit.[134] m.p. 158-161°) $[\alpha]_D$ +6° (c 0.1).

3β,18-Diacetoxy-17β-hydroxyandrost-5-ene (90).- 3β-Acetoxy-18-hydroxyandrost-5-en-20-one hemiacetal (4.6 g.) and p-toluenesulphonic acid (40 mg.) were dissolved in ether (10 ml.) and dioxan (20 ml.) and the solution was cooled to 2° in ice. 30% Hydrogen peroxide (4 ml.) was added over a period of 10 minutes keeping the temperature below 10°; the solution was then stirred for one hour at 2-5°. The solution was evaporated to 12 ml. in vacuo at 30° using a rotary evaporator, then benzene (50 ml.) was added. The benzene solution was washed with water followed by potassium bicarbonate solution and saturated salt solution, the benzene solution was dried with magnesium sulphate then evaporated to dryness at 40° in vacuo. The crystalline hydroperoxide (88) which remained was not purified further but was immediately acetylated. The crude hydroperoxide was dissolved in pyridine (4 ml.) and acetic anhydride (4 ml.) at 20°. After 4 hours more pyridine (4 ml.) was added and the solution was poured onto crushed ice. The mixture was stirred and crystallisation commenced, the crystals were filtered off, washed well with water and dried in vacuo (1.7 g.).

The hydroperoxide diacetate (89) was not purified further but was reacted directly with base. The crude hydroperoxide diacetate

(1.7 g.) was dissolved in dioxan (40 ml.), trimethylamine (4 ml.) and water (1.2 ml.). The solution was refluxed for one hour then evaporated to 10 ml. in vacuo. The solution was acidified with dilute hydrochloric acid then the steroid was extracted with ether. The ethereal solution was washed successively with water, sodium bicarbonate solution and saturated salt solution, dried with magnesium sulphate and evaporated to dryness. The residue was chromatographed on alumina (30 g.); elution with ether gave mixed fractions containing some saturated 20-ketone ($\nu_{max.}$ 1700 $cm.^{-1}$), further elution with ether-chloroform (4:1) gave crystalline 3β,18-diacetoxy-17-hydroxyandrost-5-ene (90). This material was recrystallised from methanol to give the pure diacetate (90) (580 mg.) m.p. 142-144°; $[\alpha]_D$ -40° (c 0.1); $\nu_{max.}$ 1740, 1240, 1034 and 819 $cm.^{-1}$; n.m.r. τ 8.96 (C-19 methyl), τ 7.97 (3-acetate methyl), τ 7.83 (18-acetate methyl), τ 5.75 (C-18 methylene) and τ 4.65 multiplet (6H). (Found: C, 70.4; H, 8.7. $C_{23}H_{34}O_5$ requires C, 70.7; H, 8.8%).

3β,18-Diacetoxyandrost-5-en-17-one (91).- 3β,18-Diacetoxy-17β-hydroxyandrost-5-ene (90) (540 mg.) in acetone (80 ml.) was cooled to 2° with ice. 8N. Chromic acid reagent[121] (4 ml.) was added slowly, keeping the temperature below 4°; stirring was continued for 20 minutes at 2-5°. Methanol (10 ml.) was then added and the steroid was extracted into ether. The ethereal solution was washed with sodium bicarbonate solution and saturated salt solution, dried with magnesium sulphate and evaporated to dryness. The residue was recrystallised from aqueous methanol to give 3β,18-

diacetoxyandrost-5-en-17-one (91) (450 mg.) m.p. 150-153°; $[\alpha]_D$ -15° (c, 0.1); $\nu_{max.}$ 1738, 1378, 1236, 1037 and 908 $cm.^{-1}$; n.m.r. τ 8.94 (C-19 methyl), τ 7.98 (3β-acetate and 18-acetate methyls), τ 5.74 doublet, J=3.5 c.p.s., (18-methylene), τ 4.62 multiplet (6H). (Found: C, 71.0; H, 8.5. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%).

3β,18-Dihydroxyandrost-5-en-17-one (92).- 3β,18-Diacetoxyandrost-5-en-17-one (91) (275 mg.) was dissolved in methanol (86 ml.) at 45°; water (10 ml.) and concentrated hydrochloric acid (4 ml.) were added and the solution was allowed to stand at 45° for 16 hours. Water (30 ml.) was added and the solution was evaporated to 40 ml. in vacuo at 45° on a rotary evaporator. The crystals which formed during this evaporation were filtered off, washed well with 50% aqueous methanol and dried in vacuo. The material was recrystallised from aqueous methanol to give 3β,18-dihydroxyandrost-5-en-17-one (92) (190 mg.) m.p. 208-213° (with slight decomposition); $[\alpha]_D$ +9° (c 0.4); $\nu_{max.}$ (nujol) 1739, 1054, 997 and 945 $cm.^{-1}$; n.m.r. τ 8.98 (C-19 methyl), τ 5.96 broad peak (C-18 methylene) τ 5.17 multiplet, 1 proton, (unassigned), τ 4.56 multiplet (6H). (Found: C, 74.8; H, 9.4. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.3%).

3β-Hydroxy-18-nor-13α-androst-5-en-17-one (93).- 3β,18-Dihydroxyandrost-5-en-17-one (92) was heated at 230° in a sublimation apparatus under a pressure of .01 mm. The product which sublimed was resublimed, then removed from the sublimation apparatus and weighed (80 mg.), the material was then recrystallised from

aqueous ethanol to give 3β-hydroxy-18-nor-13α-androst-5-en-17-one (22 mg.) m.p. 150-156°; $[\alpha]_D$ -179° (c 0.05) (methanol); $\nu_{max.}$ 1740 and 1063 $cm.^{-1}$; n.m.r. τ 9.15 (C-19 methyl), τ 6.5 broad multiplet (3α H), τ 4.61 multiplet (6H); o.r.d. (methanol, c 0.05) 20°C. $[\Phi]_{589}$ -450°, $[\Phi]_{313}$ -4360°, $[\Phi]_{280}$ +872° and $[\Phi]_{235}$ -2300°. An analytical sample was recrystallised from methanol m.p. 161-164°. (Found: C, 78.7; H, 9.4. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.55%).

The reaction of 3β,18-dihydroxyandrost-5-en-17-one with base.- 3β,18-Dihydroxyandrost-5-en-17-one (20 mg.) was dissolved in methanol (20 ml.) and powdered potassium hydroxide (10 mg.) was added. The mixture was stirred overnight. The steroid was recovered by an ether extraction and the ethereal solution was evaporated to dryness. The material did not crystallise well but a thin layer chromatogram showed one major spot. The retention time of the major component was identical to the retention time of 3β-hydroxy-18-nor-13α-androst-5-en-17-one prepared above (R_D = 0.94).

Bibliography

1. F. L. Mitchell, Vitamins and Hormones, 1967, 25, (in the press).
2. E. Block and K. Bernische, "The Human Adrenal Cortex" (Eds. A. R. Currie, T. Symington and J. K. Grant," 1962, p.589, Livingstone, Edinburgh.
3. H. F. Acevedo, L. R. Axelrod, E. Ishikava and F. Takaki, J. Clin. Endoc., 1963, 23, 885.
4. C. Cavallero and U. Magrini, Excerpta Medica International Series, 1966, 111, 63.
5. W. R. Eberlein, J. Clin. Endocrinol. Metab., 1965, 25, 1101.
6. N. Kretchmer, R. E. Greenberg and F. Sereni, Ann. Rev. Med., 1963, 14, 407.
7. J. W. Reynolds, J. Clin. Endocr., 1965, 25, 416; ibid., 1966, 26, 1251.
8. Private communication Drs. F. L. Mitchell and C.H. L. Shackleton.
9. C. H. L. Shackleton and F. L. Mitchell, Steroids, 1967, 10, (in the press).
10. K. H. Loke, G. F. Marrian and E. J. D. Watson, Biochem. J., 1959, 71, 43.
11. K. H. Loke, G. F. Marrian and E. J. D. Watson, Biochim. Biophys. Acta, 1957, 26, 230.
12. T. It-Koon and K. H. Loke, Steroids, 1966, 8, 385.
13. R. Knuppen, O. Haupt and H. Breuer, Steroids, 1966, 8, 403.
14. H. Hirschmann, J. Amer. Chem. Soc., 1952, 74, 5357.
15. R. N. Jones and F. Herling, J. Amer. Chem. Soc., 1956, 78, 1152.
16. P. Eneroth, K. Hellstrom and R. Ryhage, J. Lipid Res., 1964, 5, 245.

17. J. Diekman and C. Djerassi, J. Org. Chem., 1967, 32, 1005.

18. J. Sjovall and R. Vihko, Steroids, 1966, 7, 447.

19. B. P. Lisboa, J. Chromatog., 1965, 19, 333.

20. H. H. Wotiz and S. J. Clark, Gas Chromatography in the Analysis of Steroid Hormones, 1966, p.84.

21. F. A. Cutler, L. Mandell, D. Shew, J. F. Fisher and J. M. Chemerdã, J. Org. Chem., 1959, 24, 1626.

22. A. F. StAndre, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica and C. R. Scholz, J. Amer. Chem. Soc., 1952, 74, 5506.

23. O. Wintersteiner and S. Bergstrom, J. Biol. Chem., 1941, 137, 785; ibid., 1941, 141, 597; ibid., 1942, 143, 503.

24. T. Aoki, H. Yamamura, K. Takei and H. Mori, Chem. Pharm. Bull, 1964, 12, 808.

25. T. Yamada, H. Mori and T. Wada, Japan Patent 28,247 (1964) to Teikoku Hormone Mfg. Co.; Chem. Abs., 1965, 62, 11881.

26. L. F. Fieser and M. Fieser, Natural Products Related to Phenanthrene, 1949, p.263, Reinhold.

27. F. A. Cutler, L. Mandell, D. Shew, J. F. Fisher and J. M. Chermerda, J. Org. Chem., 1959, 24, 1621.

28. D. H. R. Barton and E. Millar, J. Amer. Chem. Soc., 1950, 72, 1066.

29. A. J. Solo and B. Singh, J. Org. Chem., 1955, 30, 1658.

30. E. S. Rothman and M. E. Wall, J. Amer. Chem. Soc., 1959, 81, 411.

31. O. Halpern and C. Djerassi, J. Amer. Chem. Soc., 1959, 81, 439.

32. K. I. H. Williams, M. Smulowitz and D. K. Fukushima, J. Org. Chem., 1963, 28, 2101.

33. G. Cooley, B. Ellis, F. Hartley and V. Petrow, J. Chem. Soc., 1955, 4373.

34. J. Fajkos and F. Sorm, Coll. Czech. Chem. Comm., 1959, 24, 766.

35. A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes and J. Jaques, Bull. Soc. Chim. France, 1961, 1822.

36. P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, J. Amer. Chem. Soc., 1950, 72, 5145.

37. W. F. Bruce and J. O. Ralls, Org. Synth., 1937, 17, 45.

38. E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle and L. Kuhlen, J. Amer. Chem. Soc., 1951, 73, 1144.

39. H. J. E. Loewenthal, Tetrahedron, 1959, 6, 269.

40. A. J. Birch and K. A. M. Walker, J. Chem. Soc. (C), 1966, 1894.

41. H. O. House, Modern Synthetic Reactions, 1965, p.37.

42. R. E. Marker and E. Rohrmann, J. Amer. Chem. Soc., 1939, 61, 3592; ibid., 1940, 62, 518.

43. S. Serota, H. A. Walens and M. E. Wall, J. Amer. Chem. Soc., 1955, 77, 5196.

44. F. H. Stodola, A. C. Kendall and B. F. McKenzie, J. Org. Chem., 1941, 6, 841.

45. J. W. Reynolds, Steroids, 1964, 3, 77.

46. A. Hassner and P. Catsoulacos, J. Org. Chem., 1966, 31, 3149.

47. H. Hirschmann, F. B. Hirschmann and J. W. Corcoran. J. Org. Chem., 1955, 20, 572.

48. B. Ellis, S. P. Hall, V. Petrow and S. Waddington-Feather, J. Chem. Soc., 1961, 4111.

49. A. A. Akhrem, A. V. Kamermitsky, V. A. Dubrowski and A. M. Moiseenkow, Proceedings of 2nd. International Congress on

Hormonal steroids, Milan, 1966.

50. E. S. Rothman and M. E. Wall, J. Org. Chem., 1960, 25, 1396.

51. M. Martin-Smith, J. Chem. Soc., 1958, 523.

52. E. S. Rothman and M. E. Wall, U.S. Patent 2,883,403; Chem. Abs., 1959, 53, 16216.

53. W. G. Dauben and J. F. Eastham, J. Amer. Chem. Soc., 1951, 73, 4463.

54. British Patent 868,374 (to Upjohn Co.); Chem. Abs., 1961, 55, 24839.

55. D. K. Fukushima and S. F. Teller, Steroids, 1963, 1, 121.

56. P. N. Rao and L. R. Axelrod, J. Org. Chem., 1961, 26, 1607.

57. L. F. Fieser, Org. Synth., 1955, 35, 43.

58. J. F. Klebe, H. Finkbeiner and D. M. White, J. Amer. Chem. Soc., 1966, 88, 3390.

59. A. J. Birch, J. Chem. Soc., 1950, 2325.

60. Advances in Heterocyclic Chemistry, 1966, volume 6, Academic Press.

61. H. J. Ringold and S. K. Malhotra, Tetrahedron Letters, 1962, 15, 669.

62. S. K. Malhotra and H. J. Ringold, J. Amer. Chem. Soc., 1962, 84, 3402; ibid., 1963, 85, 1538; ibid., 1964, 86, 1997; ibid., 1965, 87, 3228.

63. E. Shapiro, L. Weber, E. P. Oliveto, H. L.Herzog, R. Neri, S. Tolksdorf, M. Tanabe and D. F. Crowe, Steroids, 1966, 8, 461.

64. C. Djerassi and J. Gutzwiller, J. Amer. Chem. Soc., 1966, 88, 4537.

65. Private communication, Dr. I. McClenaghan.

66. C. E. Morreal, Steroids, 1966, 8, 671.

67. D. K. Fukushima, S. Dobriner and H. L. Bradlow, Biochemistry, 1966, 5, 1783.

68. H. L. Herzog, M. A. Jevnik, M. E. Tully and E. B. Hershberg, J. Amer. Chem. Soc., 1953, 75, 4425.

69. J. L. Johnson, M.E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl, J. Amer. Chem. Soc., 1956, 78, 430.

70. M. E. Herr and F. W. Heyl, J. Amer. Chem. Soc., 1953, 75, 5927.

71. J. A. Campbell, J. C. Babcock and J. A. Hogg, J. Amer. Chem. Soc., 1958, 80, 4717.

72. A. Wettstein and C. Meystre, German Patent 1,065,414; Chem. Abs., 1962, 56, 6037.

73. Private communication, Dr. R. Neher.

74. J. Fajkos, Coll. Czech. Chem. Commun., 1955, 20, 312.

75. E. R. Glazier, J. Org. Chem., 1962, 27, 2937.

76. J. Fajkos and F. Sorm, Coll. Czech. Chem. Commun., 1959, 24, 766.

77. J. H. Chapman, J. Elks, G. H. Phillipps and L. J. Wyman, J. Chem. Soc., 1956, 4344.

78. R. B. Moffat and D. I. Weisblat, J. Amer. Chem. Soc., 1952, 74, 2183.

79. C. Djerassi and C. T. Lenk, J. Amer. Chem. Soc., 1954, 76, 1722.

80. B. E. Edwards and P.N. Rao, J. Org. Chem., 1966, 31, 324.

81. W. R. Benson, E. T. McBee and L. Rand, Org. Synth., 1962, 42, 73.

82. R. F. Zurcher, Helv. Chim. Acta, 1963, 46, 2054.

83. P. Hofer, H. Linde and K. Meyer, Helv. Chim. Acta, 1962, 45, 1041.

84. A. Lardon and T. Reichstein, Helv. Chim. Acta, 1962, 45, 943.

85. H. Hasegawa, Y. Sato and K. Tsuda, Chem. Pharm. Bull. (Japan), 1961, 9, 409.

86. F. Sondheimer and S. Burstein, Proc. Chem. Soc., 1959, 228.

87. S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. L. Osborn, A. Weintraub, L. M. Reineke and R. C. Meeks, J. Amer. Chem. Soc., 1958, 80, 3382.

88. M. Nussim, Y. Mazur and F. Sondheimer, J. Org. Chem., 1964, 29, 1120.

89. J. Fajkos, Coll. Czech. Chem. Commun., 1958, 23, 1559.

90. W. S. Johnson and W. F. Johns, J. Amer. Chem. Soc., 1957, 79, 2005.

91. H. J. Dauben, V. R. Ben and J. H. K. Chiang, Abstracts of 123rd Meeting of Amer. Chem. Soc., Los Angeles, 1953, p.9.

92. C. Djerassi, G. Mutzenbecher, J. Fajkos, D. H. Williams and H. Budzikiewicz, J. Amer. Chem. Soc., 1965, 87, 817.

93. J. P. Turnbull and J. H. Fried, Tetrahedron Letters, 1966, 8, 801.

94. C. R. Engel and G. Bach, Steroids, 1964, 3, 593.

95. H. J. Ringold, F. Sondheimer and G. Rosenkranz, U. S. Patent 2,889,346; Chem. Abs., 1960, 54, 652.

96. C. Djerassi, L. B. High, J. Fried and E. F. Sabo, J. Amer. Chem. Soc., 1955, 77, 3673.

97. M. Delepine, Bull. Soc. Chim. France, 1901, 25, 580.

98. A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes and J. Jaques, Bull. Soc. Chim. France, 1961, 1822.

99. Private communication, Dr. D. N. Kirk.

100. E. W. Cantrall, R. Littel and S. Burstein, J. Org. Chem., 1964, 29, 64; ibid., 1964, 29, 214.

101. A. R. VanHorn and C. Djerassi, J. Amer. Chem. Soc., 1967, 89, 651.

102. S. Zeisel, Monatsh., 1885, 6, 989.

103. H. D. Youssefyeh and Y. Mazur, Tetrahedron Letters, 1962, 1287.

104. N. S. Bhacca and D. H. Williams, Applications of N.M.R. Spectroscopy in Organic Chemistry, 1964, Holden Day, San Francisco.

105. R. Pappo, U. S. Patent 3,087,926, (to G. D. Searle and Co.); Chem. Abs., 1963, 59, 10189.

106. C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, Helv. Chim. Acta, 1962, 45, 1317.

107. U. S. Patent 2,974,138, (to G. D. Searle and Co.); Chem. Abs., 1961, 55, 17693.

108. R. Pappo, U. S. Patent 3,080,360, (to G. D. Searle and Co.); Chem. Abs., 1963, 59, 8835.

109. R. D. Haworth and M. Michael, J. Chem. Soc., 1957, 4973.

110. R. Pappo, J. Amer. Chem. Soc., 1959, 81, 1010.

111. K. Heusler, P. Wieland and A. Wettstein, Helv. Chim. Acta, 1961, 44, 1374; K. Heusler, J. Kalvoda, C. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainelli, D. Arigoni and O. Jeger, Helv. Chim. Acta, 1961, 44, 502.

112. Advances in Photochemistry, Vol. 2, (Eds. W. A. Noyes, G. S. Hammond and J. N. Pitts), 1964, Interscience, New York.

113. R. Pappo, U. S. Patent 3,017,410, (to G. D. Searle and Co.); Chem. Abs., 1962, 56, 12987.

114. R. Pappo, U. S. Patent 3,001,987, (to G. D. Searle and Co.); Chem. Abs., 1962, 56, 2486.

115. C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, Experientia, 1961, 17, 475.

116. C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, Helv. Chim. Acta, 1962, 45, 1317.

117. G. Cainelli, M. Lj.Mihailovic, D. Arigoni and O. Jeger, Helv. Chim. Acta, 1959, 42, 1124.

118. P. Buchschacher, J. Kalvoda, D. Arigoni and O. Jeger, J. Amer. Chem. Soc., 1958, 80, 2905.

119. J. S. Mills and V. Petrow, Chem. and Ind., 1961, 946.

120. K. Heusler, P. Wieland and C. Meystre, Org. Synth., 1965, 45, 57.

121. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 1946, 39.

122. E. Iseli and D. K. Fukushima, Steroids, Supplement 1, 1964, p.11.

123. R. Anliker, M. Muller, M. Perelman, J. Wohlfart and H. Heusser, Helv. Chim. Acta, 1959, 42, 1071.

124. D. D. Cameron, W. S. Johnson, K. H. Loke, G. F. Marrian and W. L. Meyer, Biochim. Biophys. Acta, 1958, 28, 214.

125. W. S. Johnson and K. V. Yorka, Tetrahedron Letters, 1960, 8, 11.

126. L. Velluz, G. Amiand, R. Heymes and B. Goffinet, Compt. Rendus Paris, 1960, 250, 371.

127. E. Menini, J. C. Orr, R. C. Gibb and L. L. Engel, Proceedings of the Symposium on Gas Chromatography of Steroids, Ed., R. Scholler, Paris, 1967, in press.

128. A. J. Birch and J. A. K. Quarty, Chem. and Ind., 1953, 31, 489.

129. C. Djerassi, Optical Rotatory Dispersion, 1960, McGraw-Hill, New York.

130. N. Clauson-Kaas and F. Limborg, Acta Chem. Scand., 1947, 1, 884.

131. O. Mancera, G. Rosenkranz and F. Sondheimer, J. Chem. Soc., 1953, 2189.

132. P. Wieland and K. Miescher, Helv. Chim. Acta, 1949, 32, 1768.

133. L. F. Fieser, J. Amer. Chem. Soc., 1954, 76, 1945.

134. Belgian Patent 611,628, to CIBA Ltd.; Chem. Abs., 1962, 57, 16710.

135. W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, J. Amer. Chem. Soc., 1961, 83, 4013.

136. C.C. Sweeley, R. Bentley, M. Makita and W.W. Wells, J. Amer. Chem. Soc., 1963, 85, 2497.

Note on Publication

The following papers have been accepted for publication in the Journal of the Chemical Society and are in the press.

Synthetic Steroids Part I. The Preparation of 3β,16α-Dihydroxy-androst-5-ene-11,17-dione and 3β,11β,16α-Trihydroxyandrost-5-en-17-one. By R. W. Kelly and P. J. Sykes.

Synthetic Steroids Part II. The Deconjugation of Δ^4-3-Oxo-Steroids. An Improved Method for the Preparation of 3β-Hydroxy-androst-5-ene-11,17-dione.

By R. W. Kelly, I. McClenaghan and P. J. Sykes

Synthetic Steroids Part III. The Preparation of 3β,15β,17β-Trihydroxyandrost-5-ene and the Attempted Preparation of 3β,15α,17β-Trihydroxyandrost-5-ene.

By R. W. Kelly and P. J. Sykes