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OXIDATION OF RING-A AROMATIC STEROIDS

A Thesis
presented to the University of Auckland
for the Degree of
Doctor of Philosophy

by
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ABSTRACT

This thesis is concerned with a study of the oxidation of ring-A aromatic steroids using either chromium trioxide-aqueous sulphuric acid-acetone or chromium trioxide-aqueous acetic acid mixtures.

It was found that chromic acid oxidation of ring-A aromatic steroids substituted with a strong electron-donating group, gives rise to products with the site of oxidation being predominantly that para to the activating group. Thus C-3 methoxy ring-A aromatic steroids give the corresponding 9β-hydroxy-11-oxo and 9-oxo-9,11-seco-11-oic acid derivatives as the major products and the 6-oxo derivative as a minor oxidation product. However, a ketol was not formed if a C-3 methoxy ring-A aromatic steroid also contained a substituent at C-1. The C-1-methoxy-4-methyl ring-A aromatic steroids give the 4-carboxy derivative as the major product and again the 6-oxo compound as a minor neutral product. The acetoxy and methyl substituted ring-A aromatic steroids, however, all give rise to the 6-oxo derivatives as the major products. The usual oxidation product of a ring-A aromatic steroid is therefore the 6-oxo product unless it is substituted with a methoxy group in a position which will stabilise an electron deficiency at a site other than C-6. Oxidation will then occur
predominantly at the stabilised site unless it is sterically blocked.

A mechanism for the formation of ring-C oxygenated products obtained from oxidation of ring-A aromatic steroids is proposed. The initial product of chromic acid oxidation of a tertiary benzylic carbon atom is the corresponding tertiary alcohol and it seems probable therefore that the 9-hydroxy-11-oxo steroid derivatives are formed by initial hydroxylation at the C-9 position. Dehydration would then afford the Δ9,11-unsaturated steroid which could then be converted into the ketol by further direct oxidation. Alternatively the 9(11)-alkene could be oxidised to a 9(11)-epoxide and opened to a diol before further oxidation to the ketol.

In seeking support for the suggested pathway, the preparation and oxidation of a series of 3-methoxyestra-1,3,5(10),9(11)-tetraenes was investigated. The same major products were isolated from oxidation of these 3-methoxyestra-1,3,5(10),9(11)-tetraenes as from oxidation of the corresponding 3-methoxyestra-1,3,5(10)-triienes. These results provide evidence for intermediate 9,11-alkene formation when ring-C oxygenated products are obtained from oxidation of a ring-A aromatic steroid. The
oxidation of an estr-1,3,5(10),9(11)-tetraene with an acetate group para to the oxidation site gives the same major products as for a methoxy group in this position except that now the orientation of the C-9 hydroxyl group is different. This result indicates that once the 9(11)-double bond is formed in the oxidation of a ring-A aromatic steroid, it is rapidly oxidised further.

The 9-oxo-11-oic acid derivatives could arise as the expected C-9,11 cleavage products of the C-9,11 alkene or diol, or through further oxidation of the ketol itself. Evidence for this last possibility was obtained by oxidation of a ketol under the same conditions as for the other steroids studied, when 34% conversion to the 9-oxo-11-oic acid occurred.

During the preparation of one of the estratetraenes, an interesting aromatisation reaction was found. Both estrone(4h) and estrone-3-methyl ether(4c) on treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone give the corresponding 9(11)dehydroderivatives (29c) and (84a) in good yield. Other ring-A aromatic steroids have undergone ring-D-fission-C-aromatisation reactions with D.D.Q. (see p.73), even in systems capable of undergoing ring-C aromatisation without ring-D opening. In the present work,
D.D.Q. treatment of 3-methoxyestra-1,3,5(10)-triene(4e) gave, as well as a small amount of the expected 9(11)dehydro-compound, the steroidal dihydrophenanthrene 3-methoxy-12-methyl-18-norestra-1,3,5(10),8,11,13-hexaene(138), and the phenanthrene 3-methoxy-12-methyl-18-norestra-1,3,5,7,9,11,13-heptaene(139), where ring-C aromatisation had occurred by a shift of the C-18 methyl group without cleavage of ring-D.
During 1965-66 a study of the synthesis of 6-oxo ring-A aromatic steroids was undertaken by Cambie and Lequesne\(^1\) and by Cambie and Carlisle\(^2\) in view of current interest in the reported physiological activity of such compounds.\(^3\)\(^-\)\(^6\) This aromatic system was generally formed by first synthesising estrogenic-type steroids, i.e. with ring-A aromatic, starting from more readily available steroidal 4-en-3-ones, and oxidising them with chromium trioxide in aqueous acetic acid in order to introduce the 6-oxo group. Thus a series of similarly substituted ring-A aromatic steroids were treated with chromium trioxide in aqueous acetic acid at room temperature to form 4-methyl-6-oxoestra-1,3,5(10)-triene-1,17β-diol diacetate (2a, 30%), 4-methyl-6-oxo-19-norpregna-1,3,5(10)-triene-1,20β-diol diacetate (3b, 20%), 4-methyl-6-oxo-19-norcholesta-1,3,5(10)-trien-1-yl acetate (2b, 51%) and 4-methyl-6-oxo-19-norcholasta-1,3,5(10)-trien-1-yl benzoate (2c, 75%) from the corresponding ring-A aromatic steroids (1a, 3a, 1b, and 1c).

Prior to this work there had been only a few reported chromic acid oxidations of aromatic steroids, all of which have yielded compounds with a ketone function α to the aromatic ring as the only neutral products. Longwell and Wintersteiner\(^7\) reported that the oxidation of estradiol diacetate (4a) with chromic acid at room temperature gave 6-oxoestra-1,3,5(10)-triene-3,17β-diol diacetate (5a, 21%) and 3,17β-diacetoxy-8-oxo-5-nor-6,8-secoster-1,3,5(10)-trien-6-oic acid (6, 25%). It was postulated\(^7\) that the seco-acid (6) was obtained via formation of the 6,7-diketo compound (7),
Followed by oxidation of the latter's enol form to give the diketo-acid (8) which would readily decarboxylate. Caspi, Piatak, and Grover have found that oxidation of 4-methylestra-1,3,5(10)-tri-en-17β-yl acetate (1d) with chromium trioxide in aqueous acetic acid at 60°C gave 4-methyl-6-o xostra-1,3,5(10)-tri-en-17β-yl acetate (2d, 30%).

Oxidations of B- and C-ring aromatic steroids also yielded products with α-keto group α to the aryl ring. 19-Norergosta-5,7,9-trien-3β-yl acetate (9) with 8N-chromic acid gave 11-oxo-19-nor ergosta-5,7,9-trien-3β-yl acetate (10, 15%) as the main neutral product, while 22,23-dibromo-12-methyl-7-o xo-18-norergosta-8,11,13-trien-3β-yl acetate (12) and 22,23-dibromo-12-methyl-15-o xo-18-norergosta-8,11,13-trien-3β-yl acetate (13) were obtained as the neutral products from oxidations of 22,23-dibromo-12-methyl-18-norergosta-8,11,13-trien-3β-yl acetate (11).

Cambie et al. have reported that oxidation of 3-methoxyestra-1,3,5(10)-tri-en-17β-yl acetate (4b) with 8N-chromium trioxide-sulphuric acid gave the expected 3-methoxy-6-o xoestra-1,3,5(10)-tri-en-17β-yl acetate (5b, 43%). However, in a recent patent Suzuki claimed that oxidation of the same compound with chromium trioxide-acetic acid gave 9α-hydroxy-3-methoxy-11-o xoestra-1,3,5(10)-tri-en-17β-yl acetate (14, 35%) and the seco derivative, 17β-acet oxy-3-methoxy-9-o xo-9,11-secoestra-1,3,5(10)-tri-en-11-oic acid (15b, 45%). In view of this conflicting result Cambie and Manning re-examined the oxidation of this compound using both 8N-chromium trioxide-sulphuric acid and chromium trioxide-acetic acid according to the
conditions of their earlier report\textsuperscript{11} and those of Suzuki.\textsuperscript{13} The oxidation products from the use of 4N-chromium trioxide - 50\% aqueous sulphuric acid, a reagent used in a broader survey of the oxidation products of ring-A aromatic steroids\textsuperscript{15} were also examined. The composition of the neutral fraction from reaction with the three oxidants is shown in Table 1. The percentage given is the \textit{w/w} percentage of product from starting material, and, in order to compare relative yields of any one product, the \textit{w/w} percentage of product in the neutral (or acidic) fractions is given in parentheses.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Oxidation Products of 3-Methoxyestra-1,3,5(10)-trien-17\beta-yl Acetate (4b)} & \textbf{CrO}\textsubscript{3}-HOAc & \textbf{8N-CrO}\textsubscript{3}-H\textsubscript{2}SO\textsubscript{4} & \textbf{4N-CrO}\textsubscript{3}-H\textsubscript{2}SO\textsubscript{4} \\
\hline
\textbf{Starting material (4b)} & 5.0 (14.0) & 6.0 (18.0) & 3.5 (14.5) \\
\textbf{6-Oxo compound (5b)} & 7.0 (17.6) & 2.2 (6.5) & 0.9 (3.7) \\
\textbf{Ketol (16b)} & 24.0 (61.0) & 15.5 (46.0) & 7.4 (31.0) \\
\textbf{Diketo-ol (17b)} & 1.0 (3.0) & 8.2 (24.5) & 9.3 (41.0) \\
\textbf{Di and tri keto-ols} & & & \\
\textbf{(17b and 17a)} & 0.5 (1.3) & 1.6 (4.8) & 2.5 (10.0) \\
\textbf{Keto-acid (15b)} & 52 (100) & 8 (16) & 13 (24) \\
\textbf{Diketo-acid (15a)} & - & 22 (45) & 12 (20) \\
\hline
\end{tabular}
\caption{}
\end{table}
The major neutral product from each oxidation was indeed the 9-hydroxy-11-oxo derivative and evidence was presented to show that the 9-hydroxy group has a β configuration rather than the α-configuration assigned by Suzuki. The oxidation products from 3-methoxy-

estra-1,3,5(10)-trient-17β-y1 acetate which possessed a 17-keto group were thought to arise as a result of acid hydrolysis of the 17-acetoxy group during the reaction, followed by oxidation of the resulting secondary alcohol. The acidity of the oxidising agents increases from left to right in the Table and this is reflected in the increase in yields of the 17-keto products in the same direction, there appearing to be little hydrolysis of the acetoxy group in acetic acid.

Two acids were isolated from each oxidation, viz 17β-acetoxy-3-
methoxy-9-oxo-9,11-secoestra-1,3,5(10)-trient-11-oic acid (15b) and 9,17-dioxo-3-methoxy-9,11-secoestra-1,3,5(10)-trient-11-oic acid (15a). The former acid was the major product from the chromium trioxide-acetic acid oxidation, while the dioxo-acid (15a) was the major acid from the 4N- and 8N-chromium trioxide-sulphuric acid oxidations, but because of difficulty in their isolation no accurate assessment of their percentage yields could be made and hence no conclusions were drawn.

Since oxidation appeared to occur at either position 6 or 9, it was decided to examine the effect of varying the position and nature of aryl substituents on the oxidation of ring-A aromatic steroids and Chapter 2 of this thesis contributes to this study which was undertaken concurrently with another worker, Manning, of this
department. The present work is subsequent to preliminary studies reported by the author in her M.Sc. thesis.\textsuperscript{2} Chapter 1 is an account of the mechanism of chromic acid oxidation of hydrocarbons. In Chapter 3 a proposed mechanism for the formation of ring-C oxygenated products obtained from oxidation of ring-A aromatic steroids is discussed, and the results from experimental work carried out to test this mechanism are presented in Chapter 4.
CHAPTER ONE

Chromic Acid Oxidation of Hydrocarbons

Two reviews\textsuperscript{16,17a} dealing with oxidation by chromic acid and chromyl compounds have recently been published.

General Considerations

The mechanism of oxidation by chromium (VI) varies with the nature of the chromium (VI) species used, while the solvent has a marked effect on the rate and type of reaction which will occur. In aqueous solutions of chromium trioxide, and in the absence of other ions, the following equilibria exist:\textsuperscript{18-21}

\[
\begin{align*}
H_2CrO_4 & \rightleftharpoons H^+ + HCrO_4^- & K_1 = 1.21 \text{ moles/litre} \\
HCrO_4^- & \rightleftharpoons H^+ + CrO_4^- & K_2 = 3.0 \times 10^{-7} \text{ mole/litre} \\
2HCrO_4^- & \rightleftharpoons Cr_2O_7^{2-} + H_2O & K_d = 2.20 \text{ moles/litre} \\
HCr_2O_7^- & \rightleftharpoons H^+ + Cr_2O_7^{2-} & K_1 = 0.85 \text{ mole/litre} \\
H_2Cr_2O_7 & \rightleftharpoons H^+ + HCr_2O_7^- & K_1 = \text{large}
\end{align*}
\]

In water, at concentrations greater than 0.05M, dimeric chromium(VI) (Cr\textsubscript{2}O\textsubscript{7}\textsuperscript{2-}) and its protonated form are predominant while at lower concentrations monomeric chromium(VI) (HCrO\textsubscript{4}\textsuperscript{-}) predominates. The monomer-dimer equilibrium constant in 91%\textsuperscript{22} and 97%\textsuperscript{23} acetic acid has been determined, and it is known that monomeric chromium(VI) exists in these media predominantly as the acetochromate ion
(\text{CH}_3\text{COCr}_2\text{O}_4^-).^{23}

The most common lower oxidation state of chromium which is generally formed from oxidations is chromium(III). However, few if any reactions involve a 3-electron transfer in one step, and therefore most reactions lead either to chromium(V) or chromium(IV) species as intermediates. These intermediate species may effect further oxidations\textsuperscript{26,28} and may give rise to products different from those formed in the initial chromium(VI) oxidation.\textsuperscript{27} For example (Scheme I):

\[
\begin{align*}
\text{Cr(VI)} + \text{S} & \rightarrow \text{Cr(IV)} + \text{P}_6 \\
\text{Cr(IV)} + \text{S} & \rightarrow \text{R}^+ + \text{Cr(III)} \\
\text{Cr(VI)} + \text{R}^+ & \rightarrow \text{Cr(V)} + \text{P}_4 \\
\text{Cr(V)} + \text{S} & \rightarrow \text{Cr(III)} + \text{P}_5
\end{align*}
\]

Scheme I

where \(\text{R}^+\) is an intermediate free radical and \(\text{P}_6, \text{P}_5,\text{and P}_4\) are the products originating from reactions of the substrate \(\text{S}\) with a hexa-, penta-, and tetravalent chromium species, respectively. The best evidence for transient chromium intermediates comes from the phenomenon of induced oxidation\textsuperscript{29} in the reaction of the chromium(VI) species with other inorganic ions. For example, the reaction in dilute solution of iodide ion with chromic acid\textsuperscript{30} is very slow, but
in the presence of ferrous ions iodine is liberated rapidly. This indicates that the iodide ion is oxidised by some species other than chromium(VI) or iron(III), as the reaction of iodide ion with ferric ion is very slow under such conditions.\(^{30}\)

\[
\begin{align*}
\text{Cr(VI)} + I^- & \rightarrow \text{very slow reaction} \\
\text{Cr(VI)} + \text{Fe}^{2+} & \overset{\text{fast}}{\rightarrow} \text{Cr(V)} + \text{Fe}^{3+} \\
\text{Cr(V)} + I^- & \overset{\text{very fast}}{\rightarrow} \text{Cr(III)} + \text{IO}^- \\
\end{align*}
\]

**Scheme II**

Evidence exists for transient chromium(V) and chromium(IV) intermediates in the chromic acid oxidation of organic substrates. A polymer is precipitated during chromic acid oxidation of isopropyl alcohol and benzaldehyde in the presence of acrylonitrile.\(^{29}\) In the absence of isopropyl alcohol polymer precipitation is delayed and yields are low, while omission of the benzaldehyde leads to no polymer formation. It is thought that the intermediate chromium(IV) or chromium(V) species formed during oxidation of the alcohol is responsible for the radical products and that oxidation of benzaldehyde is involved in the initiation. The polymerisation reaction was completely eliminated by the addition of cerium(III) to the oxidation, the cerium(III) removing the lower oxidation states of chromium.\(^{27}\)

Rocek and Radkowsky\(^ {28}\) have presented evidence for a rapid reaction between chromium(IV) and cyclobutanol. Their approach was
based on the oxidation of vanadium(IV) by chromium(VI) for which a mechanism has been established$^{32}$ (Scheme III), wherein pentavalent chromium is formed in a rapid reversible reaction and chromium(IV) is produced in the rate-determining step.

$$\text{Cr(VI)} + \text{V(IV)} \rightleftharpoons \text{Cr(V)} + \text{V(V)}$$

rate-determining

$$\text{Cr(V)} + \text{V(IV)} \rightleftharpoons \text{Cr(IV)} + \text{V(V)}$$

$$\text{Cr(IV)} + \text{V(IV)} \rightarrow \text{Cr(III)} + \text{V(V)}$$

Scheme III

The chromic acid oxidation of vanadium(IV) proceeds under conditions which are mild enough to make any reaction of hexavalent chromium or pentavalent vanadium with organic compounds negligibly slow. It was shown that the chromic acid oxidation of cyclobutanol led to the formation of essentially two products, cyclobutanone and $\gamma$-hydroxybutyraldehyde. Cyclobutanone was the product of chromium(VI) oxidation whereas the hydroxyaldehyde was thought to originate from a reaction of cyclobutanol with either chromium(IV) or chromium(V). When cyclobutanol was introduced into the vanadium(IV)-chromium(VI) system, the yield of vanadium(V) was decreased, as part of the oxidant was used up in oxidising the alcohol to $\gamma$-hydroxybutyraldehyde, the sole organic oxidation product which was isolated. Despite extensive oxidation of the cyclobutanol, the overall rate of chromic acid reduction was
unaffected by introduction of the cyclobutanol. Since chromium(V) is formed in a rapid pre-equilibrium, the oxidation of cyclobutanol by chromium(V) would lead to a rate increase proportional to the concentration of the alcohol. As chromium(IV) is formed only in the rate determining step, a reaction of this species with the organic substrate can only affect the product composition but not the reaction rate, which is in agreement with the observed facts.

**Oxidation of Saturated Carbon-Hydrogen Bonds**

The oxidation of saturated carbon-hydrogen bonds may be conveniently divided into three main categories: (a) oxidation at a position \( \alpha \) to an aromatic ring, (b) oxidation at a position \( \alpha \) to a double bond, and (c) oxidation of purely aliphatic groupings.

There are five different reagents commonly used for the chromium(VI) oxidation of carbon-hydrogen bonds. They are chromic acid in water, acetic acid or aqueous acetic acid; dichromate ion in an aqueous solution at an elevated temperature; chromyl acetate in acetic anhydride; tert-butyl chromate in a variety of solvents; and chromyl chloride in an inert solvent. The nature of the chromium(VI) oxidation varies with the type of chromium(VI) species used while the solvent also has a marked effect on the rate and type of reaction which occurs. In the following discussion the oxidation of aryl alkanes will be considered first, followed by the
oxidation of alkanes. Allylic oxidation will be considered later along with the oxidation of alkenes.

Oxidation of Aryl Alkanes

Chromic Acid

Benzene is relatively resistant to oxidation by chromic acid in contrast to polycyclic aromatic hydrocarbons which are readily oxidised, e.g. naphthalene is readily oxidised to 1,4-naphthaquinone and phthalic acid,\(^ {33} \) and anthracene is oxidised to anthraquinone.\(^ {34} \)

With primary alkyl benzenes such as ethyl benzene, the position of initial attack appears to be at the α-position to the aromatic ring and the final major product is the aromatic carboxylic acid.\(^ {35-37} \)

The oxidation products of a compound with a secondary alkyl group, such as sec-butyl benzene,\(^ {38} \) are usually a ketone and a carboxylic acid and these can be considered to be formed (Scheme IV) by initial formation of a tertiary alcohol followed by dehydration

\[
\begin{align*}
R & \quad \text{Cr(VI)} \\
\text{C}_6\text{H}_5-\text{C-CH}_2\text{R}^1 & \quad \rightarrow & \quad \text{C}_6\text{H}_5-\text{C-CH}_2\text{R}^1 & \quad \rightarrow \\
& & \text{OH} & \quad -\text{H}_2\text{O} \\
\text{C}_6\text{H}_5-\text{C}=\text{CHR}^1 & \quad \text{Cr(VI)} & \quad \rightarrow & \quad \text{C}_6\text{H}_5-\text{C-} & \quad \text{Cr(VI)} \\
& & & \quad \text{R} & \quad \rightarrow & \quad \text{C}_6\text{H}_5\text{CO}_2\text{H}
\end{align*}
\]
and oxidation of an intermediate alkene.

**Aqueous Sodium Dichromate**

In the chromium(VI) oxidation of xylene and related compounds the amount of ring degradation increases with increasing acid concentration.\(^3\) However, use of essentially neutral solutions, such as aqueous sodium dichromate, suppresses attack at the aromatic ring. For synthetic purposes, aqueous sodium dichromate can be used for the oxidation of side chains on polynuclear aromatic systems where chromic acid would effect preferential ring oxidation. For example, methylnaphthalenes can be converted to the corresponding naphthoic acids in 95% yield whereas with chromic acid 2-methyl-naphthalène gives 2-methyl-1,4-naphthaquinone.\(^4\),\(^5\) Sodium dichromate oxidations of alkyl groups other than methyl were thought to proceed at the end of an aliphatic chain,\(^4\) but more recent and extensive studies of the oxidation of ethyl benzene showed that acetophenone and benzoic acid are obtained in varying ratios according to the reaction conditions.\(^6\) Earlier workers had claimed that phenyl acetic acid was the major product. It is now apparent that the applications of this reaction are not so general as was once supposed.

**Chromyl Acetate**

Oxidation of hydrocarbons with chromium trioxide-acetic anhydride\(^7\) in the presence of a strong mineral acid is useful for
the preparation of aromatic aldehydes as the aldehyde produced reacts with acetic anhydride to form an aldehyde diacetate which is resistant to oxidation. The rate of reaction of the aromatic aldehyde with acetic anhydride in the presence of a strong acid occurs much more rapidly than does oxidation of the aldehyde. In the absence of a strong acid, toluene is oxidised readily to benzoic acid and very little benzaldehyde is formed.

**Chromyl Chloride**

Etard\(^{44}\) found that the action of chromyl chloride on toluene in an inert solvent formed a complex with the composition \(\text{C}_6\text{H}_5\text{CH}_3\cdot2\text{CrO}_2\text{Cl}_2\), which on treatment with water gave benzaldehyde in 90% yield. In some cases\(^{45,46}\) a complex is formed between the aryl alkane and chromyl chloride without oxidation occurring. The Etard oxidation of alkyl benzenes takes place at the carbon atom β to the aromatic ring\(^{47,48}\) and thus contrasts with the action of chromic acid (oxidation at the position α to the aromatic ring).

**Mechanism of the Chromic Acid Oxidation of Aryl Alkanes**

The first detailed study of the oxidation of aryl alkanes with chromic acid was reported by Slack and Waters\(^{49}\) who studied the oxidations of diphenylmethane(18) and triphenylmethane(19) using glacial acetic acid as the solvent. They found that the rate of reaction decreased with increasing time and suggested that this
was due to the production of acetate ion during the oxidation. The addition of acetate ion retards the reaction whereas chromic ion has no effect. In the presence of a strong mineral acid the rate of reaction is essentially constant.

Ogata et al. studied the oxidation of toluene under similar conditions and found the kinetic behaviour was of the same type as that observed with diphenylmethane. They also found that electron-withdrawing groups retarded the reaction. However, the form of the rate expression differed with change of substituents, apparently as a result of a change in stoichiometry. Interpretation of the data from both of these investigations was difficult because the hydrogen ion concentration was not maintained constant and the form of chromium(VI) in acetic acid was not known. It may well be in the form of dimers, trimers, or larger units.

In order to reduce these difficulties Wiberg and Evans studied the oxidation of diphenylmethane and its substituted derivatives in 95% aqueous acetic acid with a high acid catalyst concentration compared with that of the chromium(VI) species. They found the reaction followed the rate law

\[ \text{rate} = k[\text{CrO}_3][\text{diphenylmethane}]h_0 \]

where \( h_0 \) is the Hammett acidity function. When the reacting hydrogen was replaced by deuterium, the rate of reaction was decreased by a factor of 6.4 at 30. The observation of a kinetic isotope effect
demonstrates that cleavage of the carbon-hydrogen bond occurred in the rate-determining step. The possible mechanisms for this step are shown in Scheme V.

(A) \[ R_3CH + \text{Cr(VI)} \rightarrow R_3C^+ + \text{Cr(IV)} + H^+ \]

(B) \[ R_3CH + \text{Cr(VI)} \rightarrow R_3C^- + \text{Cr(V)} + H^+ \]

(C) \[ R_3C\text{--H} \rightarrow R_3C\text{--O--Cr(IV)} \]

Scheme V

Any of these mechanisms will account for the preferential oxidation at the position α to the aromatic ring. The small difference in rate of reaction between toluene, diphenylmethane, and triphenylmethane, and the small value of the reaction constant \( \rho^+ = -1.40 \) observed in the oxidation demonstrate that process (A) cannot be correct. Considerably larger structural effects and effects of substituents would be expected for this mechanism.\(^{53,54}\)

It is not possible to distinguish between mechanisms (B) and (C) based on the data presently available but mechanism (B) is the most favoured since some evidence exists that it is operating in the oxidation of alkanes. In this mechanism the radical is probably oxidised by one of the other chromium species, possibly forming an ester similar to that formed in process (C).
The steps leading from the radical to the final product cannot be studied readily as they follow the rate-determining step.

Wiberg and Evans's work\textsuperscript{53} on the oxidation of diphenylmethane showed that the rate of reaction was proportional to the total chromium(VI) concentration. This is in contrast to the oxidation of alcohols and aldehydes\textsuperscript{55-59} where the rate constants were found to decrease with increasing chromium trioxide concentration. These workers also showed that the rate of reaction in aqueous acetic acid is increased by increasing the concentration of mineral acid or by decreasing the concentration of water.

In their investigation of the oxidation of substituted diphenylmethanes, Wiberg and Evans\textsuperscript{53} found that a plot of the logarithm of the relative rates of reaction against the Hammett $\sigma$ values\textsuperscript{60} gave a fair fit to a straight line with a slope of $-1.40$. Exceptions were the rates of oxidation of the $p$-methoxy substituted diphenylmethanes. These compounds react with chromic acid at a rate which is much greater than that for other substituted diphenylmethanes. This could be due to a change in mechanism, or to a change in the type of reaction. These possibilities were examined by Wiberg and Evans who demonstrated that the site of reaction was the same by showing that the ratio of $p$-methoxy-diphenylmethane consumed to $p$-methoxybenzophenone produced was the same as the ratio of diphenylmethane consumed to benzophenone
produced. The kinetic isotope effect was $K_R/K_D = 3.1$ and since in any series of related reactions the kinetic isotope effect decreases as the rate of reaction increases, the decrease in the isotope effect from the value observed for diphenylmethane itself (6.4) was as expected. It was clear that the rate-determining step was still the cleavage of the methylene carbon-hydrogen bond. The rate of the reaction was shown to be first order with respect to the concentration of $p$-methoxydiphenylmethane and also first order in oxidising agent. Wiberg and Evans found however, that the reaction proceeded more rapidly in 91% than in 95% acetic acid. This was the first example of a chromic acid oxidation proceeding more rapidly in a more aqueous solvent. To determine whether or not the reaction was a chain process, inhibition of the reaction by cerous or manganous ion was examined. It was clear from the data obtained that any chain process involving intermediate chromium species as chain carriers was ruled out. It was therefore concluded that the reaction which occurs in this case is probably one in which greater electron deficiency is found at the site of the reaction than with other diphenylmethane derivatives since the $p$-methoxy group is particularly well suited for stabilising an electron deficiency.

The effect of water concentration in the solvent, and the fact that the value of the entropy of activation was markedly different from that of diphenylmethane supported a change in mechanism for the oxidation of $p$-methoxydiphenylmethane. Wiberg and Evans stated
that one of the simplest rationalisations was that the process involved initial hydride abstraction leading to the benzhydryl cation. However it was difficult to present definite evidence for any particular mechanism based on the little data which was available.

Support for this theory comes from the fact that there are several examples of reactions in which the introduction of a \( p \)-methoxy group causes the mechanism to change from a free radical type to one involving a carbonium ion. For example, Criegee et al. \(^63\) examined the reaction of styrene and \( p \)-methoxystyrene with lead tetrabenoatoe in benzene solution. The former gave the normal product of a free radical type reaction, \textit{viz.} phenyl-1,2-ethanediol dibenzoate(\(20\)), whereas the latter gave a product, 2-\( p \)-methoxy-phenyl-1-ethanediol dibenzoate(\(21\)), which almost certainly arose from a cationic species.

\textbf{Oxidation of Alkanes}

The chromic acid oxidation of alkanes has not been widely used as a synthetic method because of the large variety of reactions which may follow the initial oxidation step. The relative rates of oxidation of primary, secondary, and tertiary carbon-hydrogen bonds are 1 : 110 : 7000.\(^{24,64,65}\) Thus, oxidation of a methyl group is rarely encountered since a primary carbon-hydrogen bond is unable to compete with the more reactive secondary or tertiary carbon-hydrogen bonds.
Oxidation of a secondary carbon-hydrogen bond gives a keto group. Ketones themselves are readily oxidised by chromic acid, apparently via the enol form,\textsuperscript{66-68} and thus the yield of the ketone obtained from this oxidation of a secondary carbon-hydrogen bond will depend on the relative rates of oxidation of the hydrocarbon and ketone, and on one's ability to stop the reaction at the point at which the yield of the ketone is maximal. Hence, in general, oxidation of secondary carbon-hydrogen bonds is not useful for synthetic purposes except in such cases as bornyl acetate\textsuperscript{(22)69} where the rate of enolisation of the ketone\textsuperscript{(23)} produced is reduced as a result of the ring strain involved in introducing a double bond into the system.

The major reaction in the oxidation of a tertiary carbon-hydrogen bond gives a tertiary alcohol. This could undergo dehydration to an alkene\textsuperscript{70,71} which might then be converted to the observed products via an epoxide or a related intermediate, which could then undergo a pinacol type rearrangement (c.f. oxidation of alkenes below). By careful control of the conditions the alcohol may be isolated as the major product.

**Mechanism of the Oxidation of Alkanes**

A considerable amount of data concerning the mechanism of oxidation of alkanes with chromium trioxide in aqueous acetic acid
has been accumulated and is summarised as follows:

1. The kinetic rate law is $v = k[\text{alkane}][\text{CrO}_3]\text{H}_2O^{24,65}$

2. The oxidations of triethylmethane$^{72}$ and of 3-methylheptane$^{73}$ show a kinetic hydrogen isotope effect. In the latter case $K_H/K_D = 2.5$.

3. The oxidation of 3-ethylpentane occurs 2.9 times as rapidly as that of isobutane and, in general, increasing bulk around the tertiary carbon increases the rate of oxidation.$^{65,66}$

4. No anchimeric assistance is found in the oxidations of camphane, isocamphane,$^{64}$ and cyclobutane.$^{74}$

5. The oxidation of a hydrocarbon with asymmetry at a tertiary position leads to a tertiary alcohol with retention of configuration. Cerous ion does not affect the degree of retention of configuration,$^{73}$ indicating that oxidation by chromium species of intermediate valence appears to proceed by a similar process to that of the chromium(VI) species.

6. In the oxidation of 3-ethylpentane in glacial acetic acid with added azide ion, 10% of 3-ethyl-3-pentyl azide is formed.$^{75}$

7. In the oxidation of neohexane(24), a major product is acetone which is produced via a rearrangement presumably involving 2,3-dimethyl-2-butene as an intermediate.$^{54,64}$

The kinetic isotope effect indicates that the rate-determining step is the cleavage of a carbon-hydrogen bond. Thus, as in the oxidation of aryl alkanes, there are the same three basic mechanisms
by which the reaction may occur (Scheme V).

(A) \[ R_3CH + Cr(VI) \rightarrow R_3C^+ + Cr(IV) + H^+ \]

(B) \[ R_3CH + Cr(VI) \rightarrow R_3C^+ + Cr(V) + H^+ \]

(C) \[ \begin{array}{c}
\text{HO} \\
\text{HO} \\
\text{HO}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{O} \\
\text{P} \\
\text{O}
\end{array} \quad \begin{array}{c}
\text{HO} \\
\text{HO} \\
\text{HO}
\end{array} \]

Scheme V

The small differences in rates of oxidation of primary, secondary, and tertiary hydrogens compared with the relative rates of solvolysis of primary, secondary, and tertiary halides \((\sim 1 : 10^5 : 10^7)\) makes oxidation by mechanism (A) unlikely. The relative rates of oxidation are similar to the relative rates of hydrogen abstraction by bromine atoms \((\sim 1 : 100 : 3000)\) and these data are permissive for mechanism (B). The lack of anchimeric assistance in the oxidation of cyclobutane, camphane, and isocamphane also makes mechanism (A) unlikely but is in accord with mechanism (B). If mechanism (C) was operative, then if the penta-coordinate carbon in the activated complex was to assume the trigonal bipyramid configuration, there would be increased crowding of the alkyl groups in the activated complex and one would expect a rate decrease in going from isobutane to 3-ethylpentane rather than the observed rate increase.

Thus it seems reasonable to assume that mechanism (B) correctly represents the course of the reaction. The following step
must be a combination of the carbon with one of the oxygens of the intermediate chromium species which is formed, in order to account for the retention of configuration. In structural terms this may be written as

\[
R_3CH + H_2CrO_4 \rightarrow [R_3C \cdot H_3CrO_4]
\]

\[
[R_3CH \cdot H_3CrO_4] \rightarrow R_3C-O-Cr(IV)
\]

\[
R_3C-O-Cr(IV) + H_2O \rightarrow R_3COH + Cr(IV).
\]

**Scheme VI.**

Here the first step is hydrogen atom abstraction which gives the carbon radical and the chromium(V) species in a solvent cage. The combination of these species within the solvent cage leads to the chromium(IV) ester of the alcohol as an intermediate. The hydrolysis of such an ester has been shown to proceed with Cr-O bond cleavage, and the overall process would give retention of configuration.

There remains the question of why rearrangement is observed in the oxidation of neohexane and some other compounds, and why azides are formed in the presence of azide ion. Rceck has tried to explain these by suggesting that the solvent cage trapped radical formed in the initial step should be written as a resonance hybrid of the structures

\[
[R_3C \cdot Cr(V)] \leftrightarrow [R_3C^+ Cr(IV)].
\]
This may be the proper formulation, but since this intermediate appears after the rate-determining step, it is not possible to obtain evidence either for or against the proposal. The kinetic data can only give information on the nature of the activated complex for the reaction. In terms similar to those used for explaining the "polar" effects found in free radical reactions the activated complex may be satisfactorily described by the structures

\[ [R_3\text{C-H} \text{OCrO}_3\text{H}_2] \leftrightarrow [R_3\text{C} \cdot \text{HOCrO}_3\text{H}_2] \leftrightarrow [R_3\text{C}^+\text{HOCrO}_3\text{H}_2] \]

where there is a small contribution from the third structure because of the electron-withdrawing character of the chromic acid and the possibility of stabilisation of the tertiary carbonium ion by the attached alkyl groups. The carbonium ion, which is certainly involved in some cases, may be formed by an electron transfer process, or by a reaction of the chromium(IV) ester with C-O bond cleavage. It is difficult to decide between these two possibilities and the formation of a small amount of azide and the rearrangement of neo-hexane may be explained in either way.
CHAPTER TWO

Oxidation of Ring-A Aromatic Steroids

During Cambie and Manning's re-examination\textsuperscript{14} of the chromic acid oxidation of 3-methoxyestra-1,3,5(10)-tien-17β-yl acetate(4b) the major neutral oxidation product was found to be the 9β-hydroxy-11-oxo derivative (16b) with the corresponding 6-oxo derivative (5b) as a minor product. Ring-C oxygenated products were also formed during oxidation of 3-methoxyestra-1,3,5(10)-tien-17-one(4c)\textsuperscript{14} and 3-ethoxyestra-1,3,5(10)-tien-17β-yl acetate(4d).\textsuperscript{13} However, 6-oxo derivatives are the only neutral products reported from the chromium trioxide oxidation of other ring-A aromatic Steroids.\textsuperscript{1,2,7,8,78} Table 2 shows the relative rates of oxidation of some primary, secondary, and tertiary benzylic hydrogen atoms and Table 3 shows the effect of substituents on the rate of chromic acid oxidation of diphenylmethane under the same reaction conditions as for the compounds oxidised in Table 2. From a comparison of the data in these Tables it appears that electronic rather than steric factors would determine the rate of oxidation of an aromatic hydrocarbon. Hence, where there are two or more positions α to the aromatic ring with oxidisable hydrogens, presumably electronic effects would predominate in selection of the site of oxidation. Therefore, in order to find out the factors which determine whether chromic acid oxidation would occur at positions C-6 or C-9 of a ring-A aromatic
### TABLE 2

**Relatives Rates of Chromium Trioxide Oxidation of Some Compounds in Acetic Acid**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative rate in 95% HOAc</th>
<th>Relative rate in 99% HOAc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ethylbenzene</td>
<td>3.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Diphenylmethane</td>
<td>6.3</td>
<td>71.1 (isopropylbenzene)</td>
</tr>
<tr>
<td>Triphenylmethane</td>
<td>8.1</td>
<td>1.3</td>
</tr>
<tr>
<td>t-Amylbenzene</td>
<td>0.34</td>
<td>0.054</td>
</tr>
<tr>
<td>Neopentylbenzene</td>
<td>0.19</td>
<td>0.03</td>
</tr>
</tbody>
</table>

### TABLE 3

**Effect of Substituents on the Chromic Acid Oxidation of Diphenylmethane (95% HOAc)**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$K/K^H$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$, $p^1$-dimethoxy</td>
<td>347</td>
</tr>
<tr>
<td>$p$-methoxy</td>
<td>91.3</td>
</tr>
<tr>
<td>$p$, $p^1$-dimethyl</td>
<td>6.42</td>
</tr>
<tr>
<td>$p$-methyl</td>
<td>2.28</td>
</tr>
<tr>
<td>hydrogen</td>
<td>1.00</td>
</tr>
<tr>
<td>$p$-chloro</td>
<td>0.76</td>
</tr>
<tr>
<td>$p$, $p^1$-dichloro</td>
<td>0.49</td>
</tr>
<tr>
<td>$m$-chloro</td>
<td>0.40</td>
</tr>
</tbody>
</table>
steroid, it was considered to be important to examine the effect of varying the position and nature of aryl substituents on the oxidation of ring-A aromatic steroids. There is some evidence for a change in oxidation site on changing the substituent in the aromatic ring in the chromic acid oxidation of ring-C aromatic diterpenoids. Zeiss and Tsutsui\textsuperscript{79} found that oxidation of methyl-14-nitrodehydroabietate(25a) under fairly vigorous conditions followed by treatment with heat, yielded the acid (26a). However, under the same oxidation conditions methyldehydroabietate(25b) gave the acid (26b) as well as a neutral compound (27, 17\%) where oxidation had occurred at the isopropyl residue. Using milder conditions Ritchie and Sanderson\textsuperscript{80} converted methyldehydroabietate to the 7-oxo derivative (28) in 52\% yield.

It is found that a substituent in an aromatic ring will be activated towards electrophiles if an electron-donating group is introduced at a position ortho or para to it. Reactions undergone by this substituent may be accelerated or in some cases the compound containing such a substituent may react by a different mechanism. For example, Tsuda \textit{et al.}\textsuperscript{81} found that bromination of 17-oxoestr-1,3,5(10),9(11)-tetraen-3-yl acetate(29a) gave a normal addition product, 9,11-dibromoestr-1,3,5(10)-trien-3-yl acetate(30). However, the methyl ether(29b) under the same conditions yielded equilenin methyl ether(31) because of activation of the C-9 position by the electron-donating group at C-3. As detailed earlier, Wiberg
and Evans\textsuperscript{53} concluded that the unusual increase in reactivity of the p-methoxy derivatives in the reaction of p-substituted diphenylmethanes with chromic acid was probably due to a change in mechanism. They suspected a change in mechanism from a free radical type to one involving a carbonium ion since the p-methoxy group would be particularly suited for stabilising an electron deficiency at the methylene group.

Since ring-C oxygenated products had arisen from estrogenc-type steroids containing a methoxy group \textit{para} to the predominant site of oxidation it was decided to test both the generality of the observation that ring-C products were produced in the oxidation of C-3-methoxy-substituted ring-A aromatic steroids, and the effect of placing this substituent elsewhere in the aromatic ring. Cambie and Manning\textsuperscript{14} had found that the greatest yield of ketol from 3-methoxyestra-1,3,5(10)-trien-17\beta-yl acetate(4b) was formed when the oxidant was 4N-chromium trioxide-50% aqueous sulphuric acid. This reagent was used therefore in subsequent oxidations since if a ketol was produced at all during the oxidation it should be so to the greatest extent under these conditions. Thus they found\textsuperscript{14,15} that ring-C-oxygenated derivatives were formed in each case when the methoxy group was substituted at C-3, the ketol being the major neutral product in each case (see Table 4). The only acidic products isolated were 9-oxo-11-oic acids, which also resulted from ring-C oxygenation. An exception was found in the oxidation of
TABLE 4

**Oxidation Products of C-3 Methoxy Substituted Ring-A Aromatic Steroids**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Starting Material returned</th>
<th>6-oxo derivative</th>
<th>9-hydroxy-11-oxo derivative</th>
<th>6,11-dioxo derivatives</th>
<th>9-oxo-11-oic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>4c</td>
<td>3.0 (7.9)</td>
<td>4.0 (10.5)</td>
<td>30.0 (79.0)</td>
<td>0.7 (2.0)</td>
<td>29(70)</td>
</tr>
<tr>
<td>4b</td>
<td>3.5(14.5)</td>
<td>0.9 (3.7)</td>
<td>17.2 (72.0)</td>
<td>2.5(10.0)</td>
<td>25(44)</td>
</tr>
<tr>
<td>4e</td>
<td>1.0 (3.5)</td>
<td>1.0 (3.5)</td>
<td>16.0 (55.0)</td>
<td>11.0(38.0)</td>
<td>23(100)</td>
</tr>
<tr>
<td>4f</td>
<td>8.6(16.0)</td>
<td>5 (9.5)</td>
<td>32.0 (60.0)</td>
<td>6.6(12.5)</td>
<td>-</td>
</tr>
</tbody>
</table>

Figures shown are the w/w percentage of product from starting material with the w/w percentage of product in the neutral (or acidic) fraction given in parentheses.

3-methoxyestra-1,3,5(10)-triene (4e) where the acidic fraction comprised only 14% of the product and from which no compounds were isolated. Because of difficulties in isolating the acidic products, the percentages of each acid present could not be accurately determined and any comparison of their yields is subject to this reservation.

Oxidation of 2-methoxy-4-methyl-19-norcholesta-1,3,5(10)-triene (32a) gave the 6-oxo derivative (32b) in high yield (80%) as a result of the activating effect of the C-2 para-methoxy group on the C-6 benzylic position. 2-Methoxy-7-oxa-19-norcholesta-1,3,5(10),8-tetraen-6-one (33, 9%) was also isolated from this
reaction and it is thought to arise from initial oxidation at C-6. According to Longwell and Wintersteiner\textsuperscript{7} chromic acid oxidation of ring-A aromatic steroids proceeds beyond the mono-ketone stage to a 6,7-diketone, which is oxidised further to the keto-acid that ultimately forms the unsaturated lactone of type (33).

Since a methoxy group in the C-1 position might be expected to activate the C-9 position in a manner similar to that of a C-3 methoxy group, the oxidation of 1-methoxy-4-methylestra-1,3,5(10)-trien-17β-yl acetate (1g) was examined during the present work.

4-Methylestra-1,3,5(10)-triene-1,17β-diol 17-acetate (1f) was first synthesised from 3-oxoandrosta-1,4-dien-17β-yl acetate (35d) by a dienone-phenol rearrangement\textsuperscript{82,83} using acetic anhydride and perchloric acid in ethyl acetate under the conditions developed by Edwards and Rao.\textsuperscript{84} The perchloric acid-catalysed reaction was complete in 45 min. compared with 24 hr. required by the Dreiding and Voltman\textsuperscript{85} procedure, to give an identical product in similar yield. The diacetate (1a) from the reaction was hydrolysed with methanolic potassium hydroxide (1.02 : 1 molar equivs) to give a solid which was shown by t.l.c. and its i.r. spectrum to be an approximately 1 : 2 mixture of the diol, 4-methylestra-1,3,5(10)-triene-1,17β-diol (1e) and the expected mono-acetate, 4-methylestra-1,3,5(10)-triene-1,17β-diol 17-acetate (1f), showing that hydrolysis of the phenolic acetate group was faster but not completely
selective. This material was then reacetylated and chromatographed on deactivated alumina and allowed to remain on the column overnight. Elution of the column then gave the selectively hydrolysed product (1f), which was treated with potassium and methyl iodide to give 1-methoxy-4-methylestra-1,3,5(10)-trien-17β-yl acetate (1g). Wenkert et al. have reported the removal of such a phenolic acetate group by chromatography on alumina in their work with ring-C aromatic diterpenoids.

Oxidation of 1-methoxy-4-methylestra-1,3,5(10)-trien-17β-yl acetate (1g) with 4N-chromium trioxide - 40% aqueous sulphuric acid, the reagent used for maximum 9,11-ketol formation, gave a neutral brown-red oil and a brown tarry acid fraction which were shown by t.l.c. to be composed of at least 10 and 6 compounds respectively. Preparative t.l.c. was attempted but no compounds could be isolated in sufficient quantity or purity to be identified. The large amount of intractable oil obtained from both the neutral and acid fractions of this oxidation was probably as a result of degradation of ring-A under the strongly acidic conditions, since the amount of ring degradation increases with increasing acid concentration. Therefore, the oxidation of 1-methoxy-4-methylestra-1,3,5(10)-trien-17β-yl benzoate (1j) was examined next in a less strongly acidic medium, viz. chromium trioxide in 95% acetic acid. Ogata et al. have shown from pH measurements that acetic acid solutions of
chromium trioxide have a larger acidity than pure acetic acid owing to the protolytic reaction

$$\text{CH}_3\text{COOH} + \text{CrO}_3 \rightleftharpoons \text{CH}_3\text{COOCrO}_3^- + \text{H}^+$$

although no accurate value of pH could be obtained. However, as the oxidation reaction with chromium trioxide proceeds, the concentration of chromic acetate increases and the acidity thus decreases until it finally drops below that of pure acetic acid. Presumably however, this oxidation medium would be less acidic then acetone-40% aqueous sulphuric acid.

The 1,4-dien-3-one system for subsequent aromatisation was introduced into 3-oxoandrost-4-en-17β-yl benzoate(34a) by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone(36) hereafter referred to as D.D.Q. This high potential quinone has found wide application in the steroid field for the selective dehydrogenation of ketones and its use has recently been comprehensively reviewed by Walker and Hiebert. Dieneone-phenol rearrangement of 3-oxoandrosta-1,4-dien-17β-yl benzoate(35a) followed by hydrolysis gave 4-methylestra-1,3,5(10)-triene-1-17β-diol 17-benzoate(1i). The C-17 benzoate was found to be less labile than the corresponding acetate above, and none of the diol(1e) was formed during this hydrolysis. Treatment of the monobenzoate(1i) with potassium and methyl iodide gave 1-methoxy-4-methylestra-1,3,5(10)-triene4,17β-diol 17-benzoate(1j). Oxidation of this with chromium
trioxide in 95% acetic acid gave neutral and acid fractions containing 6 and 7 compounds respectively, and again repeated preparative t.l.c. failed to yield any compounds that could be identified.

It was then decided to prepare 1-methoxy-4-methylestra-1,3,5(10)-trien-17-one(11) on a larger scale. The above oxidations had been carried out on 4g. and 1g. samples respectively. Androst-4-ene-3,17-dione(34b) was dehydrogenated and the resulting 1,4-dien-3-one(35b) was aromatised and the product hydrolysed to give 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one(1k). This was then methylated with methyl-p-toluene sulphonate according to the procedure of Cohen, Cook and Hewett to give the desired 1-methoxy-4-methylestra-1,3,5(10)-trien-17-one(11).

Repeated chromatography of the mother liquors from the dienone-phenol rearrangement product gave a second compound which had a similar i.r. spectrum to that of the major product, but which had stronger absorption in the u.v. indicating greater unsaturation [230 μ (ε 26,600) and 262.5 μ (ε 7270); c.f. 211 μ (ε 10,900) and 222 μ (ε 7300) for the major product]. The compound was too insoluble to give a clearly resolved n.m.r. spectrum and hence it was methylated to reduce its polarity. The CDCl₃ spectrum showed that the C-19 methyl resonance had disappeared and that there was an aromatic methyl resonance at δ2.47 and an aromatic methoxy proton resonance at δ3.68. There were four aromatic-vinylic type protons
whose splitting pattern justified the assignment of the compound as 3-methoxy-1-methylestra-1,3,5(10),6-tetraen-17-one(38b). A doublet at 65.85 with coupling constant 9.8 c./sec. was assigned to the C-7 proton and the corresponding doublet for the C-6 proton at 66.33 showed further splitting due to coupling with the C-4 aromatic proton (J = 2 c./sec.). These chemical shifts are in good agreement with the calculated values for olefinic protons using additive increments,\(^9^3\) which give estimated values of 65.89 and 6.57 for the C-7 and C-6 protons respectively. The only other peak in this region was a singlet at 6.32\(\delta\), which integration showed to be equivalent to two protons, and this was assigned to the C-2 and C-4 aromatic protons. The corresponding demethylated compound, 3-hydroxy-1-methylestra-1,3,5(10),6-tetraen-17-one(38a) had \([\alpha]_D^0\) and u.v. values in agreement with those recorded in the literature.\(^9^4\)

Further confirmation for the assignment of this compound comes from a mass spectral analysis which gave the molecular formula as C\(_{19}\)H\(_{22}\)O\(_2\). The major peaks of the mass spectrum correspond to those for 6-dehydroestrone,\(^9^5\) and presumably these compounds fragment in a similar manner. There are three peaks which arise from fragmentation initiated by benzylic cleavage of the C-9,11-linkage of the molecular ion to yield \((41)\) as the first step. The peak at \(m/e = 158\) arises from the fragment \((42)\) obtained from homolysis of the 8,14-bond of \((41)\), probably with concomitant elimination of ethylene from the neutral fragment. Migration of a hydrogen radical
from C-8 to C-11 of (41), gives a tertiary radical (43), which can undergo homolysis of the 13,14-linkage with double-bond formation to give (44). A second homolysis of the 15,16-bond then furnishes an ion radical (45) which gives rise to the peak at m/e = 184. A fragment with the same m/e value can also come from homolysis of the 8,14-bond of the initial molecular ion(40) to yield (46), followed by a concerted series of 1-electron shifts in a six-membered cyclic transition state (48) to give the fragment (49). Such a fragmentation pattern would explain the appearance of the ion (51) at m/e = 186 and m/e = 187 in equal parts in the mass spectrum of 15-d_{1}-estrone methyl ether(50). This result suggests that only 50% of the peak is due to (51). The other portion is presumably due to a fragment such as (52) which could arise via a mechanism similar to that of (46-49). Another fragment resulting from initial benzylid cleavage comes from further decomposition of (44) by migration of a hydrogen radical from C-15 to C-13 to give the conjugated radical (53). Homolysis of the 16,17-bond then yields ion (54) (m/e = 197). The other major fragment (55) at m/e = 171 comes from homolysis of the 11,12-bond of (47).

The above compound, 3-hydroxy-1-methylestra-1,3,5(10),6-tetraen-17-one(38a) is thought to have arisen from diene-one-phenol rearrangement of androsta-1,4,6-triene-3,17-dione(39). This triene(39) is a minor product of D.D.O. dehydrogenation of androst-4-ene-3,17-dione(34b), and was present as an impurity in the major
dehydrogenation product, androsta-1,4-diene-3,17-dione (35b).  

Steroidal 1,4-dien-3-ones (35) rearrange to phenols of type (59) or (63) according to the type of substituent on the substrate, the reaction conditions, and/or the acid catalysts present.  

Caspi, Grover, and Shimizu have degraded the products of dienone-phenol rearrangement of androsta-1,4-diene-3,17-dione 4-C$^{14}$ and androsta-1,4,6-triene-3,17-dione-4-C$^{14}$ and have thereby established the mechanisms for both rearrangements (56-59) and (60-63). In the rearrangement to a para-type phenol the reaction is initiated by attack on the carbonyl group. Rupture of the C-9 - C-10 bond then occurs, followed by formation of a spiro intermediate (58). Migration of the C-5 - C-9 bond to C-4 gives the p-type phenol (59). In the rearrangement to a meta-type phenol, it was concluded that protonation induced formation of the cation (61), and subsequent migration of the C-10 methyl group to C-1 (62) gave the m-phenol (63). Any functional group which tends to stabilise the positive charge at C-1 will result in formation of a meta-type phenol. Thus, with androsta-1,4,6-triene-3,17-dione (39), the complete conjugation of the three double bonds in the intermediate cation (61) is responsible for the location of the positive charge at C-1 resulting in formation of the meta-type phenol (38a).

The acidity of the oxidation medium was further reduced in the attempt to examine the effect of the C-1 methoxy substituent
on the oxidation of a ring-A aromatic steroid. 1-Methoxy-4-
methylestra-1,3,5(10)-trien-17-one(11) was therefore oxidised in
approximately 50% acetone-aqueous acetic acid (95%) as it has been
found that the pK values for acetic acid in acetone and acetone-
water are higher than in water (see Table 5).

**TABLE 5**

pK Values for Acetic acid in Different Media

<table>
<thead>
<tr>
<th>Medium</th>
<th>pK, electrometric method</th>
<th>pK, indicator method</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>4.75</td>
<td>12.55</td>
</tr>
<tr>
<td>50% aqueous acetone</td>
<td>6.26</td>
<td>5.86</td>
</tr>
<tr>
<td>acetone</td>
<td>12.55</td>
<td>10.6</td>
</tr>
</tbody>
</table>

The differentiating action of acetone is due to the formation of a
reaction product with a 1 : 1 composition of carboxylic acid :
ketone in contrast to the product with 1 : 2 composition obtained
in water. The different action is also related to a decrease in the
solvation energies of the anion of the carboxylic acid compared with
its solvation energy in water.

In this oxidation study, the aromatic steroids in solution
were usually treated dropwise at 0° with the chromic acid solution
and the reaction mixtures were then kept at room temperature for
18 hr, since if the reaction mixture was not cooled during the
addition of the chromic acid, or if the rate of addition was fast,
the product of oxidation was often a black intractable oil. Hence, in the oxidation of 1-methoxy-4-methylestra-1,3,5(10)-trien-17-one (1l, 8g), the chromic acid was added dropwise at -18° and the mixture was allowed to come to 15° over 24 hr. A large number of products were obtained, some of which were isolated by chromatography on silica gel and preparative t.l.c. The product composition is shown in Table 6. The oxidation was repeated, but this time the temperature was allowed to come to 0° over 10 hr. This resulted in a greater return of starting material and in formation of the same products in lower yields. 1-Methoxy-4-methylestra-1,3,5(10)-trien-17β-yl benzoate(1j) was oxidised under these conditions and the mixture allowed to come to 7° over 20 hr. The product compositions for this and for the oxidation of 1-methoxy-4-methyl-19-norcholesta-1,3,5(10)-triene(1m) carried out by Manning\textsuperscript{15} using the 4N-chromium trioxide - 50% aqueous sulphuric acid reagent are recorded in Table 6.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Starting mat. %</th>
<th>6-oxo product (64)</th>
<th>4-aldehyde (65)</th>
<th>4-acid (66)</th>
<th>Ring-A degraded product (67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1l</td>
<td>10 (13)</td>
<td>0.4 (0.5)</td>
<td>4 (5)</td>
<td>23</td>
<td>3.4 (4)</td>
</tr>
<tr>
<td>1l</td>
<td>40 (46)</td>
<td>0.2 (0.25)</td>
<td>3 (4)</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>1j</td>
<td>12 (17)</td>
<td>1.85 (2.7)</td>
<td>2.6 (3.8)</td>
<td>16</td>
<td>13 (17)</td>
</tr>
<tr>
<td>1m</td>
<td>1.9 (4.0)</td>
<td>4.5 (10.0)</td>
<td>-</td>
<td>19</td>
<td>-</td>
</tr>
</tbody>
</table>
No evidence for the formation of a C-9,11 ketol was obtained and examination of Table 6 shows that the yield of 6-oxo product (64) was very low in each case studied. Isolation of the 4-carboxy-1-methoxy ring-A aromatic steroid (66) as the major product indicates that the predominant site of oxidation appears to be the C-4 methyl group owing to activation by the electron-donating C-1 group. No C-4 methyl oxidised products were obtained from oxidation of 4-methyl-19-norcholesta-1,3,5(10)-triene (1n) (see later), in which the C-4 methyl group is not activated. Small amounts of 1-methoxy-estra-1,3,5(10)-tien-4-als (65) were obtained from these oxidations.

1-Methoxy-17-oxoestra-1,3,5(10)-tien-4-al (65a) was oxidised to the corresponding carboxylic acid (66a) with potassium permanganate, thus confirming the identification of both compounds. A Dreiding model of a 1-methoxy-4-methylestra-1,3,5(10)-triene shows that the methoxy group blocks the C-11 position and that introduction of a keto-group into this position would be subject to severe steric hindrance. Lack of ketols as products in the above oxidations is therefore not surprising.

A fourth neutral product was obtained from oxidation of both 1-methoxy-4-methylestra-1,3,5(10)-tien-17-one (11) and the corresponding 17β-benzoate (1j). The i.r. spectrum of the compound from oxidation of the 17-ketone (11) had hydroxyl bands at 3580 and 3340-3320 cm⁻¹, a broad peak in the carbonyl region (1765-1735 cm⁻¹), and a peak at 1665 cm⁻¹ assignable to a conjugated double bond. The
n.m.r. spectrum had no aromatic or vinylic proton signals however, but in addition to the C-18 methyl peak (δ 0.91) it did have a signal at δ1.63 equivalent to three protons on a tertiary carbon atom. The chemical shift of the δ1.63 resonance was consistent with a methyl group on a fully substituted carbon bearing two oxygen atoms. A mass spectral molecular weight analysis gave the formula C_{17}H_{22}O_{4} and the compound was assigned as 4-methyl-4,17-dioxo-1,4-seco-2,3-bisnorestra-5(10)-en-1-oic acid(67a). The compound (67a) might be expected to exist as a mixture of lactol(67) and open γ-keto acid(68) and hence the complexity of carbonyl bands in the infrared spectrum. This type of compound has been obtained in the oxidation of phenols of type(59) with alkaline hydrogen peroxide. Caspi et al. propose a possible mechanism for this oxidation by assuming the initial formation of a p-quinol (69) or an o-quinone(69a).

In the oxidation of alkyl substituted benzenes with chromic acid, it has been observed that the ratio of ring oxidation to side chain oxidation increases with increasing acid concentration and with increasing alkyl substitution on the ring. Electron-releasing groups such as a phenol group were found to increase this ratio and electron-withdrawing groups such as carboxyl to decrease the ratio. The reaction with the ring is therefore thought to occur via an electrophilic attack and the reagent involved is thought to be protonated chromic acid [see (73-75)]. It is possible that a
phenolic group could be introduced into the A-ring of 1-methoxy-4-methylestra-1,3,5(10)-tri-en-17-one(11) in a similar way, say at C-2, and the ortho-quinone(69a) could then be formed by oxidative demethylation (76-77-69a). This quinone could then be oxidised to the ring-degraded product(67) via the mechanism suggested by Caspi et al. 97 (69a-72).

Oxidation of 3-methoxy-1-methyl-19-norcholesta-1,3,5(10)-triene(78)15 yielded only the 6-oxo derivative in very small yield and showed no evidence of ketol formation. Dreiding models again indicate that a C-1 methyl group blocks the C-11 position, apparently to such an extent that oxidation at this position cannot occur.

There remains the C-4 position in the aromatic ring for which the effect of a methoxy substituent on the nature of the oxidation product has not been studied. There appears to be no suitable way of introducing a methoxy group into the C-4 position but ring-A aromatic steroids with the weaker electron-donating methyl group in this position have been prepared. Caspi et al. 8 found that oxidation of 4-methylestra-1,3,5(10)-tri-en-17β-yl acetate(1d) with chromium trioxide-acetic acid at 60° gave 4-methyl-6-oxoestra-1,3,5(10)-tri-en-17β-yl acetate(2d, 50%).

4-Methylestra-1,3,5(10)-triene are commonly prepared by the dienol-benzene rearrangement 38-104 of steroidal 1,4-dien-3-ones
with lithium aluminium hydride. However, steroidal 4-en-3-ones themselves have been successfully aromatised in ring-A to give the 4-methyl derivatives by heating with a mixture of acetyl bromide and α-bromo-propionic acid.¹⁰⁵,¹⁰⁶ The yields of the required aromatic steroid were variable, for generally the presence of a C-17 or C-20 oxygenated function induced simultaneous secondary reactions, e.g. creation of a C-16,17 double bond or reductive elimination of a C-21 hydroxyl group, giving rise to other aromatic products, viz. 1-methylestra-1,3,5(10)-triene derivatives, anthrasteroids, and naphthalenic hydrocarbons. However, it was decided to attempt to aromatise cholest-4-en-3-one(34c) by this method as this steroid did not have a C-17 oxygenated function to provide an entry point for side reactions. The reaction was found to proceed smoothly yielding 4-methyl-19-norcholesta-1,3,5(10)-triene(1n, 97%) in higher yield than the two-step process of the dienol-benzene rearrangement which would have resulted in a 48% overall yield at best. Oxidation of this steroid in acetone with chromium trioxide in 95% acetic acid gave a neutral fraction which contained ten compounds (t.l.c.) and a negligible acid fraction. Chromatography of the neutral fraction gave starting material (27%) and 4-methyl-19-norcholesta-1,3,5(10)-tri-en-6-one(2e, 11%) as the only products isolated. I.r. spectra of fractions with polarity expected for 9,11-ketols showed no bands for this type of compound.

The effects on the oxidation products of varying the position
of a methoxy group in the aromatic A-ring have been examined above. Oxidation was found to occur predominantly at the site para to the strongly electron-donating group. It was decided to investigate next the effect of an electron-withdrawing group such as the acetoxyl group, on the type of oxidation products obtained.

In previous work\(^7\), the 6-oxo derivative (5a) was the only neutral product isolated from the chromium trioxide-acetic acid oxidation of estra-1,3,5(10)-triene\(^3\),17\(\beta\)-diol diacetate (4a). Manning\(^{15}\) found on repeating this oxidation on estra-1,3,5(10)-tri-en-3-yl acetate (4g) with 4N-chromium trioxide-50% aqueous sulphuric acid, that during the actual oxidation, hydrolysis of the acetate group occurred. After reacetylation, 6-oxoestra-1,3,5(10)-tri-en-3-yl acetate (5d) was the only neutral product isolated, and no ketol formation was observed. The acid fraction from the oxidation, after treatment with acetic anhydride-sodium acetate gave 6-oxo-7-oxaestra-1,3,5(10), 8-tetraen-3-yl acetate (79a) analogous to the unsaturated lactone (79b) obtained from oxidation of estra-1,3,5(10)-triene\(^3\),17\(\beta\)-diol diacetate (4a).\(^7\) This lactone also arises from initial oxidation at C-6 (see p. 29).

Oxidation of 4-methylestra-1,3,5(10)-triene\(^4\),17\(\beta\)-diol
1-acetate 17-benzoate (1h) gave 4-methyl-6-oxoestra-1,3,5(10)-triene-
1,17\(\beta\)-diol 1-acetate 17-benzoate (2f, 30%). Thus it was found both in previous work\(^1,2\) and in the present more careful study, that
6-oxo derivatives were the only products isolated from oxidations of 1-acetoxy- and 1-benzoyloxy-4-methyl ring-A aromatic steroids. No evidence for oxidation of the C-4-methyl group was obtained.

The only other substituent effect investigated was that of a methyl group in the C-2 position. Estrone(80a) was first reduced to estra-1,3,5(10)-trien-3-ol(80b) by the Huang-Minlon modification of the Wolff-Kishner reaction to remove the C-17 keto group and thus reduce the number of products obtained in the oxidation. Estra-1,3,5(10)-trien-3-ol(80b) was then converted to the 2-methyl derivative(81b) by a Mannich reaction with formaldehyde and diethylamine followed by hydrogenolysis with Raney nickel. Treatment of 2-methylestra-1,3,5(10)-trien-3-ol(81b) with triethylamine and diethyl phosphite gave 2-methylestra-1,3,5(10)-trien-3-yl diethylphosphate(82). Kenner desoxygenation of this phosphate with lithium in liquid ammonia gave 2-methylestra-1,3,5(10)-triene(83a). Oxidation of this with chromium trioxide in 95% acetic acid gave mainly starting material(50%). 2-Methylestra-1,3,5(10)-trien-6-one(83b, 17%) was the only other product isolated from the neutral fraction, which contained at least nine products (t.l.c.). The acid fraction was negligible. The oxidation of both this hydrocarbon and of 4-methyl-19-norcholesta-1,3,5(10)-triene (1n) appeared to proceed at a much slower rate than the oxidation of any other steroids which were studied.
N.m.r. of 6-oxo ring-A Aromatic Steroids

Caspi et al. have found that the effect of introducing a C-11 keto group on the n.m.r. spectrum of a ring-A aromatic steroid is to shield a methyl group at C-1 and to deshield a methyl group at C-4. In each case examined during the present work, the C-4 methyl resonance underwent a large paramagnetic shift (average 0.39 p.p.m.) on introduction of a C-6 keto group. A Dreiding model of a ring-A aromatic 6-oxo steroid with ring-C in a chair conformation reveals an almost rigid structure with the plane of the trigonal carbon atom nearly coincident with the plane of the aromatic ring and hence with the C-4 methyl group. The large downfield shift of the C-4 methyl resonance is thus explicable since the diamagnetic anisotropic shielding effects of the aromatic ring and the C-6 keto group reinforce each other. The effect is not restricted to the C-4 methyl group since comparison of the corresponding ring-A aromatic steroids with and without C-6 keto groups (Table 7) shows that all substituents on the aromatic ring including protons are deshielded on the introduction of a C-6 keto group.

Conclusion

It has been shown in this study, that chromic acid oxidation of ring-A aromatic steroids substituted with a strong electron-donating group such as the methoxy group, gives rise to products
<table>
<thead>
<tr>
<th>Compounds</th>
<th>C-1 proton</th>
<th>C-2 proton</th>
<th>C-3 substituent</th>
<th>C-4 proton</th>
</tr>
</thead>
<tbody>
<tr>
<td>5b, 4b</td>
<td>0.33</td>
<td>0.55</td>
<td>0.17</td>
<td>1.16</td>
</tr>
<tr>
<td>5d, 4g</td>
<td>0.33</td>
<td>0.52</td>
<td>0.13</td>
<td>1.10</td>
</tr>
<tr>
<td>5g, 4f</td>
<td>0.34</td>
<td>0.57</td>
<td>0.17</td>
<td>1.14</td>
</tr>
<tr>
<td>5c, 4c</td>
<td>0.08</td>
<td>0.28</td>
<td>0.07</td>
<td>0.81</td>
</tr>
<tr>
<td>5e, 4e</td>
<td>0.08</td>
<td>0.31</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td>5f, 4i</td>
<td>0.17</td>
<td>0.48</td>
<td>-</td>
<td>1.18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compounds</th>
<th>C-1 proton</th>
<th>C-2 methyl</th>
<th>C-3 proton</th>
<th>C-4 proton</th>
</tr>
</thead>
<tbody>
<tr>
<td>83b, 83a</td>
<td>0.25</td>
<td>0.16</td>
<td>0.36</td>
<td>1.20</td>
</tr>
<tr>
<td>32b, 32a</td>
<td>0.07</td>
<td>0.11</td>
<td>0.10</td>
<td>0.44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compounds</th>
<th>C-1 substituent</th>
<th>C-2 proton</th>
<th>C-3 proton</th>
<th>C-4 methyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>64a, 1l</td>
<td>0.04</td>
<td>0.01</td>
<td>0.23</td>
<td>0.31</td>
</tr>
<tr>
<td>64b, 1j</td>
<td>0.09</td>
<td>0.26</td>
<td>0.48</td>
<td>0.44</td>
</tr>
<tr>
<td>64c, 1m</td>
<td>0.06</td>
<td>0.11</td>
<td>0.30</td>
<td>0.40</td>
</tr>
<tr>
<td>2g, 1i</td>
<td>-</td>
<td>0.21</td>
<td>0.51</td>
<td>0.44</td>
</tr>
<tr>
<td>2h, 1o</td>
<td>-</td>
<td>0.32</td>
<td>0.47</td>
<td>0.40</td>
</tr>
<tr>
<td>2f, 1h</td>
<td>0.06</td>
<td>0.02</td>
<td>0.25</td>
<td>0.24</td>
</tr>
<tr>
<td>3b, 3a</td>
<td>0.10</td>
<td>0.07</td>
<td>0.25</td>
<td>0.30</td>
</tr>
<tr>
<td>2a, 1a</td>
<td>0.14</td>
<td>0.22</td>
<td>0.42</td>
<td>0.45</td>
</tr>
<tr>
<td>2b, 1b</td>
<td>0.03</td>
<td>0.07</td>
<td>0.26</td>
<td>0.35</td>
</tr>
</tbody>
</table>
with the site of oxidation being predominantly that para to the methoxy group. Thus C-3-methoxy ring-A aromatic steroids give the corresponding 9β-hydroxy-11-oxo and 9-oxo-9,11-seco-11-oic acid derivatives as the major products and the 6-oxo derivative as a minor oxidation product. The C-1-methoxy-4-methyl ring-A aromatic steroids give the 4-carboxy derivative as the major product and again the 6-oxo compound as a minor neutral product. The C-2-methoxy-substituted ring-A aromatic steroid produces an almost quantitative yield of the 6-oxo product. A methyl substituent in the C-1 position of aromatic steroids substituted at C-3 with a methoxy group precludes ketol formation. The acetoxy and methyl substituted ring-A aromatic steroids however, all give rise to the 6-oxo derivatives as the major products.

It seems therefore that the usual major oxidation product of a ring-A aromatic steroid is the 6-oxo product unless it is substituted with a methoxy group in a position which will stabilise an electron deficiency at a site other than C-6. Oxidation will then occur predominantly at the stabilised site unless it is sterically blocked.
CHAPTER THREE

Mechanism of Formation of Ring-C Oxygenated Products
from Oxidation of Ring-A Aromatic Steroids

The second part of this thesis is concerned with an attempt to find some evidence for the mechanism of formation of 9β-hydroxy-11-oxo and 9-oxo-11-oic acid derivatives from chromic acid oxidation of 3-methoxy-ring-A aromatic steroids. A possible reaction path for the formation of the ketols is given in Scheme VII.

![Scheme VII]

I  ➡️  II  ➡️  III

↓

IV  ←  V  ←  VI
The initial product of chromic acid oxidation of a tertiary benzylic carbon atom is the corresponding tertiary alcohol and it seems probable that ring-C oxygenated derivatives are formed by initial hydroxylation at the C-9 position.

In general, tertiary alcohols are very unreactive towards direct oxidation. Except for the oxidation of 1-methylcyclobutane\textsuperscript{111} there is no clearly established example of a direct oxidation of a tertiary alcohol. The chromic acid oxidation of a number of tertiary alcohols has been studied\textsuperscript{112-116} and even though direct oxidation was originally postulated in some cases, kinetic studies later revealed\textsuperscript{117-119} that the oxidation is preceded by an olefin-forming elimination of a water molecule.

The tertiary alcohol first formed then, would dehydrate to give the $\Delta^9,11$-unsaturated steroid \textsuperscript{111}. This compound would be expected to be in equilibrium with the $\Delta^8,9$-isomer. However, Douglas \textit{et al.}\textsuperscript{119} found that 3-methoxyestra-1,3,5(10),9(11)-tetaen-17-one (84a) was more stable than 3-methoxyestra-1,3,5(10),8-tetaen-17-one (85). They converted (85) with boiling methanolic hydrochloric acid to (84) in quantitative yield, while under the same conditions it was found that the ketone (86a) gave an equimolar mixture of (86a and b) indicating comparable stabilities for this isomeric pair. These energy relations are at first sight, somewhat
surprising, since a C-8 double bond is hyperconjugated with five hydrogen atoms whereas a C-9,11 double bond is hyperconjugated with only three. However, the $\Delta 8$-isomers contain a homoannular diene-like system in ring-B whereas the $\Delta 9$-isomers contain a heteroannular diene-like system extending over rings B and C, and it is presumed that the first system is destabilised with respect to the second. The balance of controlling factors must be delicate because in related examples such as the ketone(87) the $\Delta 8$-14$\beta$-isomer was formed by acid treatment of the $\Delta 9,11$-8$\alpha,14\beta$-isomer.119

It is postulated (Scheme VII) that the $\Delta 9,11$-derivative is converted via the $\alpha$-epoxide IV to the diol V, or more probably, the chromium ester of this diol, which is then rapidly oxidised to the ketol VI. Evidence for epoxides as intermediates in the chromic acid oxidation of alkenes and a brief outlines of the products and mechanisms of oxidation of alkenes and diols is presented below before the mechanism proposed in Scheme VII is discussed further.

**Oxidation at Carbon-Carbon Double Bonds**

The chromic acid oxidation of alkenes may lead to a variety of products such as epoxides, ketols, acids, or ketones having the same number of carbon atoms as the alkene. Products of allylic oxidation may also be obtained, although allylic oxidation is a relatively minor reaction and is usually accompanied by oxidation of the double bond to an epoxide.
Although the initial reaction for oxidation of carbon-carbon double bonds may be the same in acetic or sulphuric acid, the ultimate products are sometimes different. When chromic acid oxidation is carried out in acetic acid, epoxides are often formed. For example, if there is a deficiency of chromium trioxide in the oxidation of \( P_1P_1^1 \)-dibromo-\( P_11 \), \( P_1^{11} \)-dichlorotetraphenylethylene(88), the product is primarily the corresponding epoxide(89). The use of a larger amount of oxidant leads to \( P_1 \)-bromo-\( P_1^1 \)-chlorobenzophenone.\(^{121}\)

Oxidation of ergost-\( \delta(14) \)-en-3\( \beta \)-yl acetate(90) leads to a mixture of ketones(91, 92) formed by allylic oxidation and to the epoxides(93, 94) derived from the ketones,\(^{122}\) while with ergosta-\( \delta \), 22-dien-3\( \beta \)-yl acetate(95),\(^{123}\) cholest-7-en-3\( \beta \)-yl acetate(96),\(^{124}\) and 1\( \alpha \)-methylcholest-7-en-3\( \beta \)-yl acetate(97)\(^{125}\) partial double bond migration occurs prior to epoxide formation.

The oxidation of other steroidal double bonds may lead to ketols. Mild chromic acid oxidation of cholesterol-\( \alpha \)-oxide(98) gave \( 5\alpha \)-hydroxycholestan-3,6-dione(99),\(^{126}\) which is also a major product of the oxidation of cholesterol.\(^{127,128}\) This could be rationalised in terms of initial formation of an epoxide followed by ring opening and further oxidation.

In the Barbier-Wieland degradation which involves reaction of an ester with a phenyl Grignard reagent followed by dehydration and chromic acid oxidation of a diaryl substituted alkene (Scheme VIII),
the oxidation step often proceeds quite well, with up to 70% of the chain-shortened acid being produced.\textsuperscript{128}

\[
\begin{align*}
RCH_2CO_2CH_3 + C_6H_5MgBr & \xrightarrow{\text{CrO}_3} RCH_2C - (C_6H_5)_2 \overset{\text{HAc}}{\longrightarrow} RCO_2H \\
RCH &= C(C_6H_5)_2
\end{align*}
\]

Scheme VIII

In contrast to the relative simplicity of reactions carried out in acetic acid, oxidation in aqueous acid media commonly leads to rearrangement. It has been suggested\textsuperscript{129} that an epoxide may be an intermediate in many of these reactions and indeed most of the rearrangement products which have been observed may be accounted for by assuming an acid-catalysed pinacol type rearrangement of an intermediate epoxide. For example, 4,4-dimethyl-2-neopentyl-1,2-epoxypentane\textsuperscript{(100)} on treatment with aqueous acid is readily converted to 4,4-dimethyl-2-neopentylbutyraldehyde\textsuperscript{(101)},\textsuperscript{130} and the acid\textsuperscript{(102)} corresponding to the latter is the principal product of the chromic acid oxidation of 4,4-dimethyl-2-neopentyl-1-pentene\textsuperscript{(103)}.\textsuperscript{130,131}

In the oxidation of 2,3-dimethylbut-2-ene\textsuperscript{(104)} the ratio of oxidation to acetone and oxidative rearrangement to pinacolone\textsuperscript{(105)} is acid dependent,\textsuperscript{132} the former being the major product when the sulphuric acid concentration is less than 50% and the latter predominating in more acidic solution.
Mechanism of Oxidation of Carbon-Carbon Double Bonds

No detailed mechanism for the chromium(VI) oxidation of alkenes is available because such oxidations usually yield complex mixtures of reaction products which are highly dependent on the reaction conditions used. Insufficient reaction product studies have been made as yet. Also, two-thirds of the products are formed in reactions involving intermediate chromium valence states [chromium(IV) and (V)] and, as these states react faster than chromium(VI), all information obtained from kinetic studies refers to chromium(VI) only.

The oxidation of alkenes by chromium(VI) is first order in alkene and chromium, and is acid-catalysed and solvent dependent. In an investigation of the effect of structure on oxidation rates using chromium trioxide in 95% acetic acid it was found that the number of allylic hydrogens seemed to have no effect on the overall rate of the oxidation reaction. Tertiary-butylethylene was oxidised faster than propene and 1-butene and it was assumed that little or no allylic oxidation takes place in the rate-determining step [i.e. by chromium(VI) oxidation]. It was found that, as in the chromium(VI) oxidation of alkanes, steric effects in the oxidation of alkenes are only of minor importance (Table 8). However steric effects seem to be dominant in the complex formation of alkenes with silver ions or in the oxidation of alkenes with palladium(II) chloride and this
sensitivity to steric effects is believed to be the result of the formation of direct metal to carbon bonds. Thus any formation of a direct chromium to carbon bond in the transition state of chromium(VI) seems unlikely.

### TABLE 8

Relative Reactivities of Substituted Ethylenes

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Ag complex formation</th>
<th>Epoxidation</th>
<th>Br₂ addn</th>
<th>Cl₂ addn</th>
<th>Cr(VI) oxdn</th>
<th>H⁺ catalysed hydration</th>
<th>Hydroxymercuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂=CH₂</td>
<td>2.4</td>
<td>0.045</td>
<td>0.016</td>
<td>-</td>
<td>v.slow</td>
<td>-</td>
<td>0.051</td>
</tr>
<tr>
<td>CH₃CH=CH₂</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.95</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>cis-CH₃CH=CHCH₃</td>
<td>0.59</td>
<td>-</td>
<td>43</td>
<td>63</td>
<td>8.42</td>
<td>1.68</td>
<td>0.058</td>
</tr>
<tr>
<td>trans-CH₃CH=CHCH₃</td>
<td>0.15</td>
<td>-</td>
<td>28</td>
<td>50</td>
<td>5.55</td>
<td>0.71</td>
<td>0.017</td>
</tr>
<tr>
<td>(CH₃)₂C=CH₂</td>
<td>0.43</td>
<td>22</td>
<td>89</td>
<td>58</td>
<td>7.28</td>
<td>10⁻³⁻¹⁰⁻⁴</td>
<td>v.fast</td>
</tr>
<tr>
<td>(CH₃)₂C=CHCH₃</td>
<td>0.088</td>
<td>230</td>
<td>1500</td>
<td>1.1⁻¹⁰⁻⁴</td>
<td>91.9</td>
<td>10⁻³⁻¹⁰⁻⁴</td>
<td>-</td>
</tr>
<tr>
<td>(CH₃)₂C=C(CH₃)₂</td>
<td>0.01</td>
<td>v.fast</td>
<td>-</td>
<td>4.3⁻¹⁰⁻⁵</td>
<td>469</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The rate of oxidation is determined primarily by the number of alkyl substituents rather than by their position on the double bond. Thus cis- and trans-2-butenes and isobutene react at about the same rate. In this respect the chromium(VI) oxidation resembles closely epoxidation and bromine and chlorine addition to alkenes (Table 8) i.e. reactions leading to a three-membered ring product or intermediate. Also the reaction differs greatly from acid-catalysed hydration and the hydroxy mercuration of alkenes. In these
reactions the electrophile attacks the double bond unsymmetrically leading to a transition state with a developing cationic centre. The rate of these reactions is then determined by the stability of the incipient carbonium ion and, hence, by the degree of substitution on the more highly substituted terminus of the double bond. These results suggest a symmetrical structure for the

Scheme IX

Scheme X
transition state of the rate-limiting step of the oxidation. Thus an acyclic mechanism of the type shown in Scheme IX as well as cyclic but nonsymmetrical mechanisms can therefore be excluded. Both the three-membered transition state leading to an epoxide and the five-membered transition state leading to a chromium(IV) ester of a vicinal diol are symmetrical. However, the relative reactivities of cyclopentene and norbornene with respect to cyclohexene are low and fall into the category characteristic for reactions with three-membered transition states. It is therefore concluded that an epoxide is the first oxidation product and that it is formed directly from the alkene and chromium(VI) (Scheme X). In acetic acid solutions chromic acid is known to exist predominantly in the form of its monoacetate\textsuperscript{134} and the reaction may proceed through transition state (2).

\begin{align*}
\text{(2)} & \quad \text{(3)} & \quad \text{(4)}
\end{align*}

Awasathy and Rocek\textsuperscript{133} suggested that as there appeared to be no basic difference in the way chromic acid oxidations proceed in acetic acid solutions and in aqueous solutions, it was possible
that epoxides could be formed in aqueous solutions by way of transition states (3) or (4).

These conclusions do not necessarily hold for the oxidation of aromatic systems. The almost 200-fold increase in reactivity in going from propene to styrene is unique for the chromium(VI) oxidation and is not found for either oxidation with peracids or for the bromination reaction (Table 9).

**TABLE 9**

Reactivities of Substituted Styrenes Relative to 1-Propene

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Cr(VI)</th>
<th>CH₃CO₂H</th>
<th>Br₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅-CH = CH₂</td>
<td>167</td>
<td>2.7</td>
<td>2.2</td>
</tr>
<tr>
<td>cis-C₆H₅-CH = CH-C₆H₅</td>
<td>56.4</td>
<td>2.6</td>
<td>0.024</td>
</tr>
<tr>
<td>trans-C₆H₅-CH = CH-C₆H₅</td>
<td>221</td>
<td>1.2</td>
<td>0.018</td>
</tr>
<tr>
<td>(C₆H₅)₂C = CH₂</td>
<td>363</td>
<td>11.4</td>
<td>55</td>
</tr>
</tbody>
</table>

It may well indicate a change in mechanism due perhaps to the high ability of the aromatic ring to stabilise a positive charge. This observation does not preclude the possibility of epoxide formation after the rate-limiting step as a secondary product, e.g. from an intermediate carbonium ion as in Scheme IX, path A. In view of the observation that chromium trioxide in acidic solution effects an electrophilic attack at an aromatic ring during oxidation of
alkyl substituted benzenes, and that oxidation of each of the 1,2-diphenyl-1,2-(p-chlorophenyl)ethylenes (106, 107) gave mixtures of the two stereoisomeric epoxides (108, 109), it seems possible that an electrophilic mechanism as in Scheme IX could be operative. With an electrophilic attack, rotation about the double bond of (106) and (107) could occur before ring closure to give a mixture of the two possible isomers.

Some arguments against the intermediacy of epoxides have been raised.\textsuperscript{135,136} The chromic acid oxidation of a group of 1,1-diaryl ethylenes gave only cleavage products such as benzophenones and acetone but no epoxides\textsuperscript{136} although the latter were the principal products using chromyl acetate as the oxidant. Most of the epoxides were found to be unreactive under the conditions used for the oxidation, and it was assumed that the epoxides were not intermediates in the chromic acid oxidation. It is likely that the initial attack is of the same type with both forms of chromium(VI), suggesting the formation of an intermediate which could lead either to the epoxide, or to the other products which were observed. It was thought possible that the lack of reactivity of the diaryl epoxides in aqueous sulphuric acid may result from low solubility in water. In this case, the epoxides could be intermediates in the oxidation in aqueous sulphuric acid since the epoxides would be formed in a highly dispersed state which would be much more reactive.
than in the bulk form.

The occurrence of rearrangement in the chromic acid oxidation of alkenes indicates that a carbonium ion may be formed at some point in the reaction. This may occur in the ring opening of the epoxide, or it may be formed from a chromium-containing intermediate which precedes epoxide formation. The available data does not permit a decision between the two possibilities.

**Mechanism of Allylic Oxidation by Chromium(VI)**

Two types of mechanism are possible for allylic oxidation. In the first (Scheme XI) a hydrogen atom (or hydride ion) is removed from the alkene giving an allylic free radical (or carbonium ion), which is ultimately converted to the unsaturated ketone.

\[
\begin{align*}
- \text{CH}_2 - \text{CH} = \text{CH} - \text{CH}_2 & \quad - \text{H}^+ \\
\rightarrow & \\
\begin{array}{c}
\text{CH} - \text{CH} = \text{CH} - \text{CH}_2 \\
\downarrow \\
\text{CH} = \text{CH} - \text{CH} - \text{CH}_2
\end{array}
\end{align*}
\]

**Scheme XI**

In the second mechanism (Scheme XII), oxidation at the double bond leads to a derivative of a ketol. Elimination of water then leads to the unsaturated ketone.
\[
- \text{CH}_2 - \text{CH} = \text{CH} - \text{CH}_2 - \quad \rightarrow \quad - \text{CH}_2 - \begin{array}{c}
\text{CH} \quad \text{O} \\
\text{Ox}
\end{array} - \text{CH}_2 -
\]

- \text{HOX}

\[
\rightarrow \quad - \text{CH} = \text{CH} - \begin{array}{c}
\text{C} \\
\text{O}
\end{array} - \text{CH}_2 -
\]

**Scheme XII**

Labelling experiments performed by Wiberg and Nielsen\(^{137}\) have shown that allylic oxidation of cyclohexene with chromic acid proceeds via Scheme XI. Awasthy and Rocc\(^{133}\) have suggested that allylic oxidation is due to the presence of intermediate valence states of chromium and does not represent a reaction of chromium(VI) itself. There is still much to be learned about the details of this mechanism.

**Oxidation of Diols**

Two reactions are possible in the chromic acid oxidation of glycols. In the first, normal oxidation occurs giving an \(\alpha\)-hydroxy carbonyl compound which may be oxidised further. In the case of ethylene glycol, both glyoxal and oxalic acid were isolated,\(^{138}\) and the kinetic rate law\(^{139}\) was found to be

\[
v = k_a [\text{dIol}] [\text{HCrO}_4^-][\text{H}^+] + k_b [\text{dIol}] [\text{HCrO}_4^-][\text{H}^+]^2
\]

This corresponds to the rate law for the oxidation of isopropyl alcohol, and presumably the first reaction occurs via the same mechanism which operates for oxidation of isopropyl alcohol:\(^{134}\)
\[
\text{HOCH}_2\text{CH}_2\text{OH} + \text{HCrO}_4^- + \text{H}^+ \rightleftharpoons \text{HOCH}_2\text{CH}_2\text{OCrO}_3\text{H} + \text{H}_2\text{O} \\
\text{HOCH}_2\text{CH}_2\text{OCrO}_3\text{H} \rightarrow \text{HOCH}_2\text{CH}=\text{O} + \text{Cr(IV)}.
\]

Scheme XIII

Further support for this suggestion comes from the fact that 2-methoxyethanol and ethylene glycol react at about the same rate, and that the rate of oxidation of ethylene glycol fits a Taft plot for the oxidation of primary alcohols.\(^{142}\)

In the second reaction, which is favoured by increasing methyl substitution, cleavage of the carbon–carbon bond occurs. The oxidation of a homologous series of glycols, ranging from ethylene glycol to pinacol gave 1.2% of formaldehyde and acetaldehyde from oxidation of ethylene glycol and 28.7% from 2,3-butylene glycol. A 67% yield of acetone was obtained from pinacol.\(^{139-141}\) The kinetic rate laws for the glycols giving cleavage products were

\[
\begin{align*}
\text{Propylene glycol} & \quad v = k[\text{dil}][\text{HCrO}_4^-][\text{H}^+]^2 \\
\text{Pinacol and} & \quad v = k[\text{dil}][\text{HCrO}_4^-] \\
\text{2,3-butylene glycol} & \\
\end{align*}
\]

In a more detailed study of the oxidation of pinacol\(^{143}\) a solvent isotope effect \(K_{\text{D}_2\text{O}}/K_{\text{H}_2\text{O}} = 2.7\) was found and the monomethyl ether of pinacol was oxidised with complex kinetics at a very low rate. The solvent isotope effect suggests that oxygen–hydrogen bond cleavage does not occur in the rate-determining step and since
the monomethyl ether was not readily oxidised, it appears that a cyclic chromate ester is probably the intermediate (Scheme XIV).

\[
\begin{align*}
R_2C\text{-OH} + HCrO_4^- + H^+ &\rightarrow R_2C\text{-O} - Cr\text{=O} \\
R_2C\text{-0} - Cr\text{=O} &\rightarrow R_2C = 0 \\
R_2C = 0 + Cr(IV)
\end{align*}
\]

**Scheme XIV**

Further evidence for cyclic chromate ester formation may be found in the observation that cis-1,2-dimethyl-1,2-cyclopentane diol is oxidised to 2,6-heptane dione at a rate 17,000 times faster than the trans-isomer. The large difference in rate cannot be accommodated if one assumes that the preferred reaction involves a noncyclic mechanism. The effect of methyl substitution on the rate of cleavage was studied, and for the series - ethylene glycol, propylene glycol, 2,3-butylen glycol, and pinacol - the relative rates were $10^{-5}$, $10^{-3}$, $10^{-2}$, and 1, respectively. It was assumed that alkyl substitution stabilised the activated complex for decomposition of the cyclic chromate ester.

Many examples of chromic acid oxidation of steroidal diols to the corresponding ketols have been reported. Oxidation of 3α-acetoxy-8α,9α-dihydroxy-5β-cholenic acid methyl ester(110) to the 8,9-seco diketone(111) provides a steroidal example of chromic acid oxidative cleavage of a diol.
From the evidence presented above it seems reasonable that Scheme VII could be operative in the formation of ring-C ketols from oxidation of aromatic ring-A steroids. There is good evidence for the formation of epoxides as transient intermediates in the oxidation of aliphatic alkenes, and although it has been suggested that oxidation of aromatic alkenes may proceed via a mechanism involving a carbonium ion in the transition state this does not preclude the possibility of epoxide formation occurring after the rate-determining step. The epoxide IV may undergo hydrolysis to the diol V (Scheme VII) or it may be directly oxidised to the ketol VI, which is a normal oxidation product of either epoxides or diols.

The 9-oxo-11-oic acid derivatives which with one exception appeared to be the major products of oxidation of 3-methoxy-ring-A aromatic steroids could arise as the expected C-9,11 cleavage products of alkene III\textsuperscript{113-117,121,129,132,133,135,136} or diol V\textsuperscript{132,138-141,143,144}, or through further oxidation of the ketol itself.\textsuperscript{150}

Attack of the \( \Delta^9,11 \)-steroid III would take place at the \( \alpha \)-face as a Dreiding model shows that the approach of the chromium species from the \( \beta \)-face is hindered by the C-18 methyl group. Tsuda et al.\textsuperscript{81} found that treatment of 17-oxoestra-1,3,5(10),9(11)-tetraen-3-yl acetate(112) with perbenzoic acid yielded the 9\( \alpha \),11\( \alpha \)-epoxide (113) as the major product (76%) and only a small amount of the \( \beta \)-
epoxide(114, 1.2%).

The opening of an epoxide ring in aqueous solution normally takes place by attack at the least substituted carbon, with inversion of configuration\textsuperscript{17b,151} (Scheme XV).

\[
\text{Scheme XV}
\]

If attack was at the least substituted carbon C-11 in the epoxide IV (Scheme VII), the diol VII (or chromium ester), would be obtained where the C-9 hydroxyl has an α-configuration. However in a recent review, Parker and Isaacs\textsuperscript{151} have given evidence for the fact that the direction of ring-opening is also determined by the ease of breaking of the carbon-oxygen bond. They state that the presence of electron-releasing groups will always facilitate the breaking of the bond between the oxygen and the carbon to which it
is attached. Therefore, in the epoxide IV the electron-releasing C-3 methoxy group would facilitate the breaking of the carbon-oxygen bond at C-9 in preference to that at C-11 and hence attack would occur at C-9 to give the 9β-hydroxy diol V or the corresponding chromium ester. This would then be oxidised to ketol VI with a 9β-hydroxy substituent in accord with the configuration of the ketol actually isolated from the oxidation.

In the following work, a series of estra-1,3,5(10),9(11)-tetraenes(84) were prepared, and their oxidation products investigated. These preparations and oxidations are discussed in Chapter 4, which is divided into two parts. Part A deals with the preparation of the steroids to be oxidised and Part B, with their oxidation.
CHAPTER FOUR

Part A

Hydrocortisone \([11\beta,17\alpha,21\text{-trihydroxypregn-4-ene-3,20-dione}]\) (115a) was used as starting material for the preparation of a series of \(\text{estra-1,3,5(10),9(11)-tetaenes}\), as the aromatic ring-A is easily introduced from its 4-en-3-one system, while the 9(11)-double bond can be prepared by dehydration of its C-11 hydroxyl group.

Preparation of 3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-one(84a)

A. From Hydrocortisone

The dihydroxyacetone side-chain of ring-D of hydrocortisone had to be modified as otherwise it would certainly be degraded in the final oxidation step. The bismethylenedioxy protecting group has been shown to be stable to a variety of reactions, e.g. alkylation, acylation, acid-catalysed rearrangements, and oxidations, \(^{152}\) and it seemed to be an attractive choice for protection of the C-17 side chain.

The rates of bismethylenedioxy formation and hydrolysis are significantly different for various substituents at C-11. \(^{153}\) For example, bismethylenedioxy cortisone (C-11 carbonyl group) is 10% hydrolysed after 2hr. whereas bismethylenedioxy hydrocortisone is 75% hydrolysed in the same time. There is no satisfactory
explanation for the influence of the C-11 substituent on the rate of acid hydrolysis, and it has been found that variation at even more remote positions of the steroid, e.g. in the A-ring, can have a marked effect on the rate of hydrolysis.\textsuperscript{154}

The methanol present in commercial formalin and another molecule of formaldehyde gives rise to an 11β-methoxy-methylenedioxy substituted bismethylenedioxy (B.M.D.) compound (116b) as well as the desired hydrocortisone-B.M.D. (116a), but formation of this 11-ketal can be mostly avoided by shortening the reaction time from the 44hr. for cortisone to 1hr or less.\textsuperscript{153}

In order to avoid this side product it was decided to first remove the 11β-hydroxy group of hydrocortisone by dehydration to form the 9,11-double bond which would be required later. Treatment of some dehydrated hydrocortisone(117a) supplied by another worker of this department with formalin and hydrochloric acid in chloroform for 72hr., [which is the reaction time used by Tsuda et al.\textsuperscript{155} on 17α,21-dihydroxy-pregna-1,4,9(11)-triene-3,20-dione(118a) as substrate], yielded a gummy product composed of two compounds. The i.r. spectrum of each showed the 4-en-3-one system (1665 and 1625 cm\textsuperscript{-1}) and the C-O-C str. bands characteristic of the B.M.D. entity. The less polar compound had additional bands at 1111 cm\textsuperscript{-1}. The n.m.r. spectrum of each showed a broad singlet at δ5.71 (C-4 olefinic proton) and a group of four singlets at δ5.23 - 5.04.\textsuperscript{156}
with the very small coupling constants (1.6 c./sec.) found for methylene protons of methylenedioxy entities, but no multiplet corresponding to the C-11 olefinic proton. The n.m.r. spectrum of the less polar compound had an extra AB quartet at δ4.73 and a singlet corresponding to three equivalent protons at δ3.43. The compounds were assigned as 17α,20,20,21-bismethylenedioxy-11β-hydroxyprogna-4-en-3-one(116a, 33%) and the corresponding 11β-methoxymethylenoxy ether(116b, 48%), and the starting material was therefore deduced to have been hydrocortisone. Both of the B.M.D. compounds were dehydrogenated with D.D.O., and since most of the material now had a protected C-11 hydroxyl group and this was required to be free for later dehydration to the Δ9(11)-alkene, the B.M.D. compounds were hydrolysed with formic acid and then acetylated to give 3,20-dioxopregna-1,4-diene-11β,17α,21-triol 21-acetate(120b). Treatment of the alcohol(120b) with methanesulphonyl chloride in conjunction with sulphur dioxide, (an efficient reagent for the dehydration of hindered alcohols such as the 11β-hydroxy group of a steroid), gave 3,20-dioxopregna-1,4,9(11)-triene-17α,21-diol 21-acetate(118b) in 90% yield. Aromatisation of this triene by heating under reflux with zinc in aqueous pyridine, according to the method of Tsuda et al., gave 20-oxoestra-1,3,5(10),9(11)-tetraene-3,17α,21-triol 21-acetate(121b).

This compound was prepared more directly by dehydration of hydrocortisone acetate and treatment of the product with D.D.O. to
give 3,20-dioxopregna-1,4,3(11)-triene-17α,21-diol 21-acetate (118b), followed by aromatisation to give the same estratetraene in 13% overall yield.

In order to simplify the system it was decided to remove the sensitive dihydroxyacetone side-chain altogether by oxidative cleavage of the C-17,20α-ketol system with sodium bismuthate thereby leaving a carbonyl group at C-17. The C-21 acetate group was removed from 20-oxoestra-1,3,5(10),9(11)-tetraene-3,17α,21-triol 21-acetate (121b) by hydrolysis and the product was oxidised with sodium bismuthate to yield 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (29c). Methylation with methyl-p-toluene sulphonate gave 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (84a).

B. From Androst-4-ene-3,17-dione (34b)

Introduction of the estra-1,3,5(10),3(11)-tetraene system into androst-4-ene-3,17-dione involved initial synthesis of the aromatic ring-A and dehydrogenation of this estratriene with D.D.O.

Androst-4-ene-3,17-dione (34b) was dehydrogenated with D.D.O. to give androsta-1,4-diene-3,17-dione (35b). Treatment of the 17-ethylene ketal (35e) with an excess of the radical anion derived from lithium metal and biphenyl in tetrahydrofuran effected aromatisation of the A-ring with expulsion of the angular methyl group as methyl lithuim. Acidification of the reaction mixture
hydrolysed the ketal function and gave estrone(4h) in 64% yield (122-124).

D.D.Q. has been found to be a powerful oxidising agent for phenols. In most of the recorded cases the products are dimers resulting from carbon-carbon or carbon-oxygen coupling. However, D.D.Q. treatment of some steroidal phenols has led to dehydrogenation. In some cases, ring-D cleavage products in which ring-C is fully aromatised are obtained, but these will be discussed more fully later.

Both estrone(4h) and estrone-3-methyl ether(4c) on treatment with D.D.Q. in methanol at room temperature for 15 min. gave the corresponding \( \Delta 3(11) \)-derivatives(29c) and (84a) in yields of 62% and 66%, respectively. However the product from dehydrogenation of estrone-3-methyl ether was shown by t.l.c. to contain some starting material. The triene showed up clearly when the chromic acid oxidation of the tetraene obtained by this method was followed by t.l.c. Therefore the best method for the last two steps was oxidation of estrone followed by methylation of the resulting tetraene. 3-Methoxyestra-1,3,5(10),9(11)-tetraene-17-one(84a) was thus prepared in 18% overall yield from androst-4-ene-3,17-dione (c.f. 9% overall yield from hydrocortisone and 45% from estrone as starting material).
Preparation of 3-Methoxyestra-1,3,5(10),9(11)-tetraen-17β-yl acetate(24b)

The C-17 side-chain of hydrocortisone was removed by oxidation with sodium bismuthate to give 11β-hydroxyandrost-4-ene-3,17-dione(125a, 67%). Some samples of sodium bismuthate oxidise the 11β-hydroxyl group\textsuperscript{170} and a small amount of androst-4-ene-3,11,17-trione(125b, 8%) was isolated in the present case.

It was intended to introduce the C-17β acetate group next by acetylation of a C-17β hydroxy group formed by selective reduction of 11β-hydroxyandrost-4-ene-3,17-dione(125a) with sodium borohydride in methanol, since C-17 steroidal ketones are more reactive to this reagent than C-4-ene-3-ketones.\textsuperscript{171} Norymberski and Woods\textsuperscript{171} found that both androst-4-ene-3,11,17-trione(125b) and androst-4-ene-3,17-dione (34b) were selectively reduced with this reagent to give the corresponding C-17β alcohols in 45 and 70% yields, respectively. In the present work, 11β-hydroxyandrost-4-ene-3,17-dione(125a) was subjected to identical reaction conditions but t.l.c. indicated that a substantial amount of the triol, androst-4-ene-3,11β,17β-triol (126) was being formed as well as the desired diol. Therefore, both the C-3 and C-17 carbonyl groups were reduced with the more reactive lithium aluminium hydride\textsuperscript{172} and the resulting triol was treated with activated manganese dioxide\textsuperscript{173} for selective oxidation of the C-3 allylic alcohol.
11β-Hydroxyandrost-4-ene-3,17-dione\(^{(125a)}\) on reduction with lithium aluminium hydride yielded a mixture of androst-4-ene-3β,11β, 17β-triol and -3α,11β,17β-triol\(^{(126, 7:2.5)}\).\(^{176}\) The stereospecificity observed in the lithium aluminium hydride reduction of steroidal ketones\(^{174-177}\) is thought to be due to the steric hindrance of the angular methyl groups and attack therefore proceeds from the α-face of the molecule.\(^{177}\) The mixture of triols was then oxidised with activated manganese dioxide,\(^{178}\) and 11β,17β-dihydroxyandrost-4-ene-3-one\(^{(127a)}\) was isolated in 65% yield (c.f. 62% by Nancera et al.\(^{172}\)) together with some of the higher oxidised products 11β-hydroxyandrost-4-ene-3,17-dione\(^{(125a, 12%)}\) and 17β-hydroxyandrost-4-ene-3,11-dione\(^{(128, 7%)}\) which were reduced again with lithium aluminium hydride and reoxidised with activated manganese dioxide. Other saturated steroidal alcohols have been oxidised with activated manganese dioxide,\(^{179, 180}\) but at a slower rate than for the allylic alcohols.

Acetylation of the major product led to 3-oxoandrost-4-ene-\(^{11β,17β}\)-diol 17-acetate\(^{(127b)}\) which was then dehydrogenated with D.D.O.\(^{89}\) to give 3-oxoandrosta-1,4-diene-\(^{11β,17β}\)-diol 17-acetate (127c). The 11β-hydroxyl group was removed by dehydration with p-toluenesulphonyl chloride in conjunction with sulphur dioxide,\(^{159}\) and the triene\(^{181}\) so obtained was aromatised with zinc in aqueous pyridine\(^{155}\) to give estra-1,3,5(10),9(11)-tetraene-3,17β-diol 17-acetate\(^{(130a)}\). This estratetraene was then methylated with
potassium and methyl iodide in dry benzene to give 3-methoxyestra-1,3,5(10),9(11)-tetraen-17β-yl acetate(130b) in 8% overall yield from hydrocortisone.

Alternatively, the required 3-methoxyestra-1,3,5(10),9(11)-tetraen-17β-yl acetate(130b) was prepared from 11β-hydroxyandrost-4-ene-3,17-diene(125a) obtained from sodium bismuthate oxidation of hydrocortisone, by first forming the desired estratetraene system and then reducing the C-17 ketone. Elimination of the 11β-hydroxy group to give the Δ9(11)-alkene, introduction of the C-1,2 double bond with D.D.Q., and aromatisation with zinc in aqueous pyridine, gave 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one(29c). Methylation, and reduction with lithium aluminium hydride in tetrahydrofuran gave a quantitative yield of the C-17 alcohol (c.f. 83% in diethyl ether) which was acetylated to give 3-methoxyestra-1,3,5(10),9(11)-tetraen-17β-yl acetate(130b) in 13% overall yield.

Preparation of 3-Methoxyestra-1,3,5(10),9(11)-tetraene(84c)

A. **From Estrone**

The first approach to the above compound was from estrone, by first removing the C-17 carbonyl group (Huang-Minlon) and methylating the product with a large excess of potassium and methyl iodide in benzene to give 3-methoxyestra-1,3,5(10)-triene(4e, 82%) together with some ring-methylated product 3-methoxy-4-methylestra-
1,3,5(10)-triene(131, 1.5%), which was identified by the presence of an extra aromatic methyl resonance and only two aromatic protons as an AB system in its n.m.r. spectrum.

It was proposed to introduce the C-9(11) double bond by treatment of 3-methoxyestra-1,3,5(10)-triene(4e) with D.D.Q. This method had been successful in the present work wherein D.D.Q. treatment of estrone-3-methyl ether in methanol or dioxane at room temperature had given the &ggr;9(11)-derivative(84a, 66%). Other ring-A aromatic steroids have undergone ring-D-fission-C-aromatisation reactions with D.D.Q. Treatment of the cycloethylene ketal(132) of estrone-3-methyl ether with excess D.D.Q. in benzene at room temperature for 5 min. gave a 77% yield of the substituted dihydrophenanthrene(133). The ring-opening reaction failed however with the ketal of dl-equilenin methyl ether(134) which underwent simple dehydrogenation to dl-14,15-dehydroequilenin methyl ether(135). The ring opening reaction also occurred in a system capable of undergoing aromatisation without ring opening; the ketal (136) of dl-9-iso-18-nor-D-homocestrone methyl ether gave more slowly (5hr) the dihydrophenanthrene derivative(137). It is thought that these reactions can be rationalised by mechanisms involving overall hydride abstraction from different positions of the steroid nucleus.

In the present work, 3-methoxyestra-1,3,5(10)-triene(4e) was
treated with D.D.Q. (1 : 1) in benzene at room temperature for 30 min. T.l.c. of the product showed that a large amount of starting material was still present and that two other more polar compounds had been formed. After reoxidation with further D.D.Q. for 24hr. at 20° and at reflux temperature for 24hr., t.l.c. indicated that the starting material-product ratios appeared unchanged. Chromatography of the product on alumina gave starting material(20%) and only a small amount of the expected 3-methoxyestra-1,3,5(10),9(11)-tetraene (84c). The tetraene(84c) was isolated in the form of a mixture with some starting material(19%).

The other two more polar products isolated were assigned as the steroidal dihydrophanthrene, 3-methoxy-12-methyl-18-norestra-1,3,5(10),8,11,13-hexaene(138, 12%) and phenanthrene, 3-methoxy-12-methyl-18-norestra-1,3,5,7,9,11,13-heptaene(139, 24%), respectively. The C-18 angular methyl group had migrated to the C-12 position to enable ring-C aromatisation without cleavage of ring-D as in the other literature examples cited above. Another example of methyl migration in the formation of a steroidal phenanthrene with D.D.Q. is the production of 1,17,17-trimethyl-18-norestra-1,3,5,7,9,11,13-heptaen-3-ol(141) from D.D.Q. treatment of 17β-hydroxy-17α-methylandrosta-1,4,9(11)-trien-3-one(140) with p-toluenesulphonic acid in refluxing dioxane.185

A mass spectrometric determination of the M.W. of the compound
assigned above as a steroidal dihydrophenanthrene gave the molecular formula as $C_{19}H_{20}$, indicating the loss of six hydrogen atoms from the starting material. The absence of asymmetric centres was revealed in the zero optical rotation. A striking feature of the n.m.r. spectrum was the complete absence of the broad "hump" of resonances normally observed for steroids and associated with aliphatic protons.\textsuperscript{186} The C-18 methyl resonance had moved downfield to 82.20, the region for aromatic methyl resonances, and there were four aromatic proton and eight benzylic proton resonances. Comparison of chemical shifts and splitting patterns with those of the substituted dihydrophenanthrenes(142) and phenanthrenes(143)\textsuperscript{187} provided good evidence for the assignments made for the dehydrogenation products above (see Table 10). Further confirmation of these assignments was provided by a comparison of their strong ultraviolet maxima with literature values for other dihydrophenanthrenes and phenanthrenes.\textsuperscript{168,187,188}

In the "dihydrophenanthrene" or "biphenyl" product(138) the additional resonance at 87.16 due to the aromatic proton at C-11 corresponds to the centre (87.18) of the AB quartet of the aromatic C-11, C-12 protons in the n.m.r. spectrum of 3-methoxy-13,17-secoestra-1,3,5(10),8,11,13-hexaen-17-ol(142b). The C-11 proton resonance shows a large frequency shift [1.03 p.p.m., 62c./sec. (c.f. 0.95 p.p.m. in the spectrum of (142b))] on further dehydrogenation of the steroid nucleus from a "biphenyl" to a "phenanthrene"(139).
TABLE 10

N.m.r. Data for estrane-3-methyl ether and related biphenyls and phenanthrenes

<table>
<thead>
<tr>
<th>Compound</th>
<th>aryl-Me</th>
<th>3-OMe</th>
<th>Benzylic Protons</th>
<th>C-16 Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>4c</td>
<td>0.89</td>
<td>3.76</td>
<td>2.77-3.07, C-6 protons</td>
<td>-</td>
</tr>
<tr>
<td>4e</td>
<td>0.75</td>
<td>3.77</td>
<td>2.74-3.02, C-6 protons</td>
<td>-</td>
</tr>
<tr>
<td>142b</td>
<td>2.31</td>
<td>3.74</td>
<td>2.76, C-6 and C-7 H's</td>
<td>1.52-1.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.53-2.90, C-15 protons</td>
<td></td>
</tr>
<tr>
<td>138</td>
<td>2.20</td>
<td>3.67</td>
<td>2.53-3.04</td>
<td>1.84-2.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C-6, C-7, C-15 and C-17 protons</td>
<td></td>
</tr>
<tr>
<td>143b</td>
<td>2.50</td>
<td>3.90</td>
<td>3.00-3.40, C-15 protons</td>
<td>1.52-2.25</td>
</tr>
<tr>
<td>139</td>
<td>2.46</td>
<td>3.93</td>
<td>2.87-3.48</td>
<td>1.85-2.67</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>C-15 and C-17 protons</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>C-1 proton</th>
<th>C-2 proton</th>
<th>C-4 proton</th>
<th>C-11 proton</th>
<th>C-12 proton</th>
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<tbody>
<tr>
<td>4c</td>
<td>7.18</td>
<td>6.70</td>
<td>6.63</td>
<td>-</td>
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<tr>
<td>4e</td>
<td>7.26</td>
<td>6.73</td>
<td>6.65</td>
<td>-</td>
</tr>
<tr>
<td>142b</td>
<td>7.54</td>
<td>6.74</td>
<td>6.68</td>
<td>7.38</td>
</tr>
<tr>
<td>138</td>
<td>7.48</td>
<td>6.67</td>
<td>6.57</td>
<td>7.16</td>
</tr>
<tr>
<td>143b</td>
<td>8.50</td>
<td>~7.22</td>
<td>7.17</td>
<td>8.33</td>
</tr>
<tr>
<td>139</td>
<td>8.54</td>
<td>7.23</td>
<td>7.23</td>
<td>8.19</td>
</tr>
</tbody>
</table>
This large shift is paralleled by the C-1 proton resonance which moves from 87.48 in the "biphenyl" to 88.54 in the "phenanthrene" [shift 1.06 p.p.m., 64 c./sec; c.f. 0.95 p.p.m. for the corresponding spectra of (142b → 143b)]. These proton resonance shifts may be rationalised in terms of the induced ring currents of the aromatic systems (4c, 4e), (138, 142) and (139, 143). In the simplest case (4e) with a single aromatic ring, the chemical shift between the C-1 and C-2 proton resonances has a value 0.53 p.p.m. (32 c./sec.) and the C-3 methoxy group is primarily responsible for this chemical shift. Aromatisation of ring-C as in the biphenyls(138, 142) leads to unequal extra deshielding of these protons, the downfield shift of the C-2 proton resonance being only 0.05 p.p.m. (3c./sec.) for (4c → 142b) and there being an upfield shift of 0.06 p.p.m. for (4e → 138) (which is within the range of error associated with the experimental determination of chemical shifts°3), as against 0.22 p.p.m. (13 c./sec.) for the C-1 proton, so that the latter resonance is now 0.81 p.p.m. (49 c./sec.) to lower field from the C-2 proton resonance. This extra deshielding of the C-1 proton is due to its close proximity to the aromatic ring-C and the magnitude of the shift indicates that the dihedral angle between rings A and C in the "biphenyls" must be small. In the phenanthrene analogues (139, 143) rings A and C are completely coplanar and the induced ring currents are more powerful. A comparison of the n.m.r. spectra of the ethers(138) and (139) revealed the presence in the latter of
a new singlet (δ 7.63) equivalent to two protons (small δ/J ratio) for the new aromatic protons at C-6 and C-7 and further approximate downfield shifts as follows: C-4 proton, 0.66 p.p.m. (39 c./sec.), C-2 proton, 0.56 p.p.m. (34 c./sec.), C-1 proton, 1.06 p.p.m. (64 c./sec.), C-11 proton, 1.03 p.p.m. (62 c./sec.). Bernstein, Schneider, and Pople 189 analysed the n.m.r. spectra of phenanthrenes and related systems and found the proton next to the greatest number of rings to have the lowest frequency, and the above data are thus in agreement with prediction. Increased aromaticity is also manifested in the downfield shifts of other proton resonances in the structural sequence (4 → 138 → 139) in which the number of aromatic rings rises from one to three (see Table 10).

The mass spectrum of 3-methoxy-12-methyl-18-norestra-1,3,5 (10),8,11,13-hexaene(138) has the parent peak at m/e = 264 and has peaks for metastables at m/e = 249 and 234 indicating the loss of two methyl radicals. This could occur via initial loss of the C-12 methyl group from the initial radical ion(144) to give fragment(145) (m/e = 249) after rearrangement of the double bonds to a conjugated hexaene system. Heterolytic cleavage of the C-14,15 bond of (145) would lead to fragment(146) which would readily lose a second methyl radical to form radical ion (147) (m/e = 234). Presumably the driving force for such a fragmentation pattern would be formation of the extended vinyl phenanthrene system.
The reaction of 3-methoxyestra-1,3,5(10)-triene(4c) with chloranil(37) in refluxing dioxane for 6 hr. gave starting material (17%), and again only a small amount of the required 3-methoxyestra-1,3,5(10),9(11)-tetraene(84c) was present, it occurring as mixtures with the starting material (19%). The major product was the steroidal dihydrophenanthrene(138, 28%), while some of the related phenanthrene(139, 4%) was also isolated. This result differs from that of Cross, Carpio and Crabbe187 who obtained a ring-D cleaved steroidal dihydrophenanthrene, 3-methoxy-13,17-secoestra-1,3,5(10), 8,11,13-hexaen-17-yl t-butyloate(142a) as the major product from chloranil treatment of 3-methoxyestra-1,3,5(10)-trien-17-one(4c) in a refluxing mixture of dioxane and t-butyyl alcohol for 40 hr.

Dehydrogenation of the steroidal dihydrophenanthrene(138) with D.D.Q. led to the phenanthrene(139), which further established the structural relationship between these two compounds.

From the above results it would appear that formation of ring-D cleaved products in chloranil and D.D.Q. dehydrogenation of 3-methoxyestra-1,3,5(10)-triene requires the presence of a functional group at C-17. In the case of 3-methoxyestra-1,3,5(10)-triene(4c) which has no functional group at C-17, migration of the C-18 methyl group to C-12 was necessary for ring-C aromatisation, without cleavage of ring-D.
B. From Hydrocortisone

The next approach tried for the preparation of 3-methoxyestra-1,3,5(10),9(11)-tetraene(84c) was from lithium aluminium hydride reduction of the C-17β tosylate. Accordingly, the p-toluene-sulphonate(84e) of 3-methoxyestra-1,3,5(10),9(11)-trien-17β-ol(84d) [which had been synthesised from hydrocortisone (see page 72)] was prepared, and then heated under reflux with lithium aluminium hydride in dioxane for 24 hr. to give 3-methoxyestra-1,3,5(10),9(11)-tetraene (84c) in 55% yield from the tosylate and in 8% overall yield from hydrocortisone. Reductive elimination with lithium aluminium hydride failed to go at lower reaction temperatures (e.g. refluxing ether or tetrahydrofuran). Johnson, Blizzard and Carhart\(^1\) found that lithium aluminium hydride reacts more sluggishly in reductive eliminations than in other reductions. They presented experimental evidence that all four hydrogen atoms of lithium aluminium hydride do not possess adequate reactivity toward alkyl halides, which are thought to resemble tosylates in this reduction. However, a steric factor may be involved here, as lithium aluminium hydride reduction of pregnane-20β-tosylates proceeds readily in refluxing ether.\(^2\)

Preparation of 17-Oxoestra-1,3,5(10),9(11)-tetraen-3-yl Acetate(112)

Dehydrogenation of estrone(80a) with D.D.Q. in benzene-methanol at room temperature for 20 min. gave 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one(29c, 62%). Acetylation gave 17-oxoestra-1,3,5(10),9(11)-
tetraen-3-yl acetate(112). An alternative preparation involving
dehydrogenation of estrone acetate required heating it with D.D.Q.
(1 : 1) under reflux in benzene for 2 hr (little visible reaction at
room temperature 166). However, t.l.c. of the product from this
reaction showed that only 50% conversion to the 9,11-dehydrogenated
product had occurred although all the D.D.Q. had undergone
conversion to the hydroquinone.

Attempted Preparation of an Estradi-1,3,5(10)-tien-9α,11α-epoxide

It was intended to form a series of 3-methoxyestra-1,3,5(10)-
trien-9α,11α-epoxides by epoxidation of each of the 3-methoxyestra-
1,3,5(10),9(11)-tetraenes prepared above. m-Chloroperbenzoic
acid192,193 appears to be the reagent of choice for epoxidations in
the recent literature 146,194-197 and hence reaction of this with
3-methoxyestra-1,3,5(10),9(11)-tetaen-17-one(84a) was tried first.
3-Methoxy-7α-methyl-9,11-epoxy-17,17-ethylenedioxyestra-1,3,5(10)-
triene(149) obtained from treatment of the corresponding 9(11)-alkene
(148) with m-chloroperbenzoic acid was reported in a recent patent.196

m-Chloroperbenzoic acid treatment of 3-methoxyestra-1,3,5(10),
9(11)-tetaen-17-one(84a) yielded a gum comprising nine products.
Chromatography gave starting material and, as the only other product,
a compound (25%) which had an i.r. spectrum almost identical with
that of 9β-hydroxy-3-methoxyestra-1,3,5(10)-trien-11,17-dione(16a)
obtained from oxidation of 3-methoxyestra-1,3,5(10)-trien-17-one(4c). However, it had a much higher m.p. 247-250° [c.f. 132-133° for the 9β-hydroxy dione(16a)] and thus was assigned as 9α-hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione(150a). Confirmation of this structural assignment was provided from an examination of the infrared spectra of the compound.

The OH (ν<sub>max</sub> 3480 cm<sup>-1</sup>) and carbonyl (ν<sub>max</sub> 1709 cm<sup>-1</sup>) bands in the i.r. spectrum of the methoxy-ketol(150a) varied slightly in position and in height relative to the other bands when dilution effects were studied, indicating that no intramolecular hydrogen bonding was occurring between the C-9 hydroxy and C-11 carbonyl groups. Inspection of a Dreiding model (Figure 1) shows that the 9β-hydroxy isomer (A) should exhibit strong intramolecular hydrogen bonding, while the 9α-hydroxy isomer (B) cannot.

(A)  
(B)  

Figure 1
The 9β-methoxyketol (16a) obtained from chromic acid oxidation\textsuperscript{14} was found to show intramolecular hydrogen bonding, and Hasegawa et al.\textsuperscript{198} found that 11,17-dioxo-9β-hydroxyestra-1,3,5(10)-trien-3-yl acetate (151b) showed intramolecular hydrogen bonding but the 9α-isomer did not. A similar effect has been observed for the meteogenone isomers (157a. and b.).\textsuperscript{199}

The assignment of a 9α-hydroxy configuration for the epoxidation ketol is also supported by n.m.r. evidence. An examination of a Dreiding model of 9α-hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione (150a) shows that the C-1 hydrogen lies just in the deshielding region of the C-11 carbonyl group and hence the absorption signal due to this proton would be expected to occur at a slightly lower field than for 3-methoxyestra-1,3,5(10)-trien-17-one (4c), and indeed a small downfield shift of 0.03 p.p.m. is observed. Moreover, the Dreiding model of 9β-hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione (16a) shows that here the C-1 hydrogen lies within the cone of shielding of the C-11 carbonyl group and inspection of the n.m.r. spectrum shows a marked upfield shift of 0.60 p.p.m. as expected for this isomer. Each of the other 9β-hydroxy-11-β-oxo derivatives (16a, c and d) isolated by Manning\textsuperscript{15} during his oxidation studies had only one signal due to the aromatic protons and this occurred at 0.32, 0.44, and 0.40 p.p.m. upfield from the corresponding proton signals of 3-methoxyestra-1,3,5(10)-
trienes. The three aromatic protons were magnetically equivalent in the 9β-hydroxy-3-methoxyestra-1,3,5(10)-trien-11-ones but not exactly equivalent in the 9α-isomer isolated from the above epoxidation. The n.m.r. spectra of the 9α- and 9β-isomers of 11,17-dioxo-9-hydroxyestra-1,3,5(10)-trien-3-yl acetate(150b and 151b) show an upfield shift of 0.40 p.p.m. for the C-1 proton of the 9β-hydroxy isomer and a downfield shift of 0.13 p.p.m. for the corresponding proton of the 9α-hydroxy isomer, relative to 3-methoxyestra-1,3,5(10)-trien-17-one(4c), which also supports the above assignments. Furthermore, optical rotation values support the 9α-hydroxy assignment (see Table 11).

**TABLE 11**

<table>
<thead>
<tr>
<th>Compound</th>
<th>M_D</th>
<th>Compound</th>
<th>M_D</th>
</tr>
</thead>
<tbody>
<tr>
<td>9β-hydroxyketol&lt;sup&gt;198&lt;/sup&gt;(151a)</td>
<td>+732</td>
<td>9β-methoxyketol(16a)</td>
<td>+643</td>
</tr>
<tr>
<td>9α-hydroxyketol&lt;sup&gt;198&lt;/sup&gt;(150c)</td>
<td>+1230</td>
<td>9α-methoxyketol(150a)</td>
<td>+1120</td>
</tr>
</tbody>
</table>

Thus it has been observed that epoxidation of 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one(84a) leads to the 9α-hydroxy-11-oxo compound whereas chromic acid oxidation of 3-methoxyestra-1,3,5(10)-trien-17-one(4c) leads to the 9β-hydroxy-11-oxo compound. Both reactions are thought to proceed via the 9α,11α-epoxide as a Dreiding model of the estratetraene shows that approach of the chromium species or m-chloroperbenzoic acid from the β-face of the steroid is
hindered by the C-18 methyl group. Opening of an epoxide ring in aqueous solution normally takes place by attack at the least substituted carbon with inversion of configuration. If attack is at the least substituted carbon, C-11 in the 9α,11α-epoxyestra-1,3,5(10)-triene, the diol would be obtained where the C-9 hydroxyl has an α-configuration. Hence the epoxidation ketol arises from normal epoxide opening and the chromic acid oxidation ketol arises from abnormal opening. The abnormal opening was rationalised (Chapter 3 p. 63) by saying that the electron-releasing C-3 methoxy group facilitated the breaking of the carbon-oxygen bond at C-9 in preference to that at C-11. However, some other factor must be operative to account for the product of normal epoxide opening in the epoxidation case. In a recent review, Parker and Isaacs have presented evidence that a greater proportion of abnormal opening products arise from media of increasing acidity and from aqueous rather than non-aqueous media since the transition state for abnormal attack is more polar than for normal attack. Either or both of these factors would explain the differently oriented products obtained from the two reactions above since m-chloro-perbenzoic acid is less acidic than the chromic acid solution and the epoxidation reaction is conducted in a non-aqueous medium. Hasegawa and Tsuda found that treatment of Δ9(11)-estrone(29c) with perbenzoic acid gave the epoxydienone(152, 40-50%) and 3,9α-dihydroxyestra-1,3,5(10)-triene-11,17-dione(150c, 3%). The ketol obtained under these
conditions is the oxidation product obtained after normal opening of an intermediate $9\alpha,11\alpha$-epoxide.

Tsuda et al. have reported the preparation of $9\alpha,11\alpha$-epoxy-17-oxoestra-1,3,5(10)-trien-3-yl acetate (113) from perbenzoic acid oxidation of 17-oxoestra-1,3,5(10),9(11)-tetraen-3-yl acetate (112), but when the present author repeated this work the product was an oil which was shown (t.l.c.) to contain thirteen products. $m$-Chloroperbenzoic acid oxidation of the same compound gave a gum containing eleven products. It would appear that the desired epoxides, once formed open readily and undergo further reaction. Other workers have found similar difficulty when attempting to epoxidise a double bond conjugated with an aromatic ring with an oxygenated function ortho or para to the oxidation site, in ring-C aromatic diterpenoids.

An alternative approach to the epoxide was attempted via hydroxybromination of the 9(11)-alkene (153b) with N-bromosuccinimide in acetone in the presence of perchloric acid to form the $9\alpha$-hydroxy-11-bromo derivative, and treatment of this with potassium acetate to give the $9\alpha,11\alpha$-epoxide. However, under these conditions, estra-1,3,5(10),9(11)-tetraene-3,17β-diol diacetate (153b) gave a yellow oil which comprised two compounds which appeared (t.l.c.) to be 11-bromoestra-1,3,5(10)-triene, $9\alpha,17\beta$-triol 17-acetate (154a) and the 3,17-diacetate (154b). The oil was treated with acetic
anhydride-pyridine in the usual manner, but when concentrated to dryness, the product turned black and decomposed.
**Part B**

**Oxidation of Some Estra-1,3,5(10),9(11)-tetraenes**

At the beginning of the study of the oxidation of 3-methoxy ring-A aromatic steroids, an investigation was made by Manning of the effect of varying the mole ratio of chromium trioxide to substrate in the oxidation mixture on the composition of the product obtained. A series of oxidations were carried out using 50 mg. samples of 3-methoxyestra-1,3,5(10)-trien-17β-y1 acetate(4b), and treating these at 0° with varying quantities of chromic acid. A 4N solution of chromium trioxide in 50% aqueous sulphuric acid was used and the mole ratio of chromium trioxide:substrate was varied from 1 to 10. The reaction mixture was kept at room temperature for 18 hr, an optimum reaction time which was estimated from further experiments. The neutral fraction obtained from each oxidation was analysed by comparison of the intensities of the corresponding spots for each fraction by t.l.c. It was found that the spot due to unreacted starting material left in the product after oxidation, had almost disappeared when the mole ratio of chromium trioxide:substrate was 8:1. Greater mole ratios caused an increase in the quantity of intractable material.

Of the three chromic acid reagents used in the oxidation study of 3-methoxyestra-1,3,5(10)-trien-17β-y1 acetate(4b), that producing the greatest yield of ketol was the 4N-chromium trioxide in 50%
aqueous sulphuric acid. As it was hoped that the ketol and the
9-oxo-11-oic acid would result from oxidation of the series of
estra-1,3,5(10),9(11)-tetraenes which had been prepared, the chromic
acid reagent for maximum ketol formation was the reagent of choice
here. However 40% sulphuric acid was used instead of 50%, and it
was found that if the reaction mixture was not cooled during the
addition of the chromic acid, or the rate of addition of the chromic
acid was fast, the product of oxidation was often a black
intractable oil.

Therefore, in this oxidation study, the aromatic steroids
were treated dropwise at -18°C in acetone solution with 4N-chromium
trioxide in 40% aqueous sulphuric acid using a mole ratio of
chromium trioxide to substrate of 8:1. The reaction mixtures
were allowed to rise to room temperature over 4 hr., except in the
case of 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one(84a) where
the temperature was allowed to rise more slowly over 11 hr. Excess
of reagent was then destroyed and the reaction mixture worked up.

The steroids, 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one
(84a), 3-methoxyestra-1,3,5(10),9(11)-tetraen-17β-y1 acetate(84b),
and 3-methoxyestra-1,3,5(10),9(11)-tetraene(84c) were oxidised with
4N-chromium trioxide in sulphuric acid. The composition of the
product from each oxidation is shown in Table 12a, where the
percentage shown is the w/w percentage of product from starting
material, with the w/w percentage of the product in the neutral or acid fraction given in brackets.

**TABLE 12a**

Oxidation Products of 3-Methoxyestra-1,3,5(10),9(11)-tetaenes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ketol(16)</th>
<th>Keto-acid(15)</th>
<th>6-oxo ketol(17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>84a</td>
<td>23(49)</td>
<td>31(57)</td>
<td>0.6(1.4)</td>
</tr>
<tr>
<td>b</td>
<td>37(67)</td>
<td>35(78)</td>
<td>-</td>
</tr>
<tr>
<td>c</td>
<td>35(70)</td>
<td>28(70)</td>
<td>-</td>
</tr>
</tbody>
</table>

**TABLE 12b**

Oxidation Products of 17-Oxoestra-1,3,5(10),9(11)-tetaen-3-yl Acetate

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ketol(150b)</th>
<th>Keto-acid(155)</th>
<th>Starting material</th>
</tr>
</thead>
<tbody>
<tr>
<td>112</td>
<td>28(64)</td>
<td>18(34)</td>
<td>2.7(5.7)</td>
</tr>
</tbody>
</table>

No starting material was isolated from these oxidations and the major products were the same ketols and acids as those obtained from oxidation of the corresponding 3-methoxyestra-1,3,5(10)-triene (Table 13).

The ketols were identified from their i.r. spectra which showed the presence of an α-hydroxy keto group (ν<sub>max</sub> 1709, 1708 and 1711 cm<sup>-1</sup>) and the presence of intramolecular hydrogen bonding. This
### TABLE 13

**Ring-C Oxygenated Products of 3-Methoxyestra-1,3,5(10)-triene**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ketol(16)</th>
<th>Keto-acid(15)</th>
<th>6-oxo ketol(17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4c</td>
<td>30.0(79.0)</td>
<td>23(70)</td>
<td>0.7(2.0)</td>
</tr>
<tr>
<td>4d</td>
<td>17.2(72.0)</td>
<td>25(44)</td>
<td>2.5(10.0)</td>
</tr>
<tr>
<td>4e</td>
<td>16.0(55.0)</td>
<td>23(100)</td>
<td>11.0(38.0)</td>
</tr>
</tbody>
</table>

was confirmed by dilution studies in carbon tetrachloride, which together with n.m.r. spectral evidence (C-1 proton upfield shifts) established the configuration of the 9-hydroxy groups as β. Melting points and all other spectra were identical with those of the same compounds isolated from oxidation of the corresponding trienes. There were seven products in each of the neutral fractions, four less polar than the ketol and two of greater polarity but these were in too low a yield to be isolated on the scale in which the oxidations were being carried out. In the oxidation of 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one(84a) which was allowed to react for a longer period, the ketol and acid were isolated in lower yields than in the other two examples studied. A small amount (0.6%) of the 6-oxo derivative(17a) of the ketol was also isolated.

The acidic fractions generally contained one or two more polar products than that isolated but again they were present in too low a yield to be isolated for identification. The isolated acids
were identified by their i.r. spectra which showed the characteristic broad OH stretching of a hydrogen bonded carboxylic group (3540-2560 cm⁻¹), and other peaks, 1710 (C = O str. of COOH) and 1685 cm⁻¹ (aryl ketone str.) consistent with their structure. Comparison of m.p.s. and all other spectral data with those of the same compounds isolated from oxidation of the corresponding trienes confirmed their identity.

It was then decided to oxidise 17-oxoestra-1,3,5(10),9(11)-tetraen-3-yl acetate(112) under the same conditions, to find out what effect the C-3 acetoxy group had on the oxidation of the double bond. This was the only oxidation in which a small amount of starting material (2.7%) was still present after 4 hr., which seems to indicate a slower rate of oxidation. The neutral fraction contained five other oxidation products but only the ketol, 11,17-diooxoestra-1,3,5(10)-triene-3,9α-diol 3-acetate(150b, 28%) was isolated after acetylation of the reaction product. Acetylation was carried out since some saponification of the acetate group had occurred during the oxidation. A 9α-configuration for the hydroxyl group was established by dilution studies of the i.r. spectrum and from shifts of the C-1 proton resonance [0.34 p.p.m. downfield from that of the C-1 proton in the n.m.r. spectrum of 3-methoxyestra-1,3,5(10)-trien-17-one(4c)].

The isolation of the 9α-hydroxy ketol from this oxidation
whereas all the above oxidations had led to the 9β-hydroxy ketol lends support to the rationalisation that the electron-releasing C-3 methoxy group facilitates the breaking of the carbon-oxygen bond of the 9α,11α-epoxide at C-9 in preference to that at C-11 and hence attack occurs at C-9 to give a 9β-hydroxy diol in the oxidation of 3-methoxyestra-1,3,5(10),9(11)-tetraenes(84). In the case of 17-oxoestra-1,3,5(10),9(11)-tetraen-3-yl acetate(112) where no such effect is operative, attack is at the least substituted carbon C-11 and the diol would be obtained where the C-9 hydroxyl has an α-configuration.

The acidic fraction contained three compounds of which only 3-acetoxy-9,17-dioxo-9,11-secoestra-1,3,5(10)-trien-11-oic acid(155) was isolated in 18% yield.

**Conclusion**

The above results provide evidence for intermediate 9,11-alkene formation when ring-C oxygenated products are obtained from oxidation of a ring-A aromatic steroid, since the same major oxidation products are isolated from oxidation of both 3-methoxyestra-1,3,5(10)-trienes and 3-methoxyestra-1,3,5(10),9(11)-tetraenes. The oxidation of an estra-1,3,5(10),9(11)-tetraene with an acetate group para to the oxidation site gives the same major products as for a methoxy group in this position except for the orientation of the C-9
hydroxyl group. This result indicates that once the 9(11)-double bond is formed in the oxidation of a ring-A aromatic steroid, it is rapidly oxidised further.

In a recent paper the chromic acid oxidation of 9α-hydroxyestrone-3-methyl ether (156) to 9(11)-dehydroestrone-3-methyl ether (84a) was reported. Thus, the dehydration step after initial formation of a tertiary alcohol at C-9 in the proposed mechanism for formation of ring-C oxygentated products (Scheme VII) is further supported.

The 9-oxo-11-oic acid derivatives could arise as cleavage products of olefin III or diol V (Scheme VII) or through oxidation of the ketol itself (see Chapter 3). Evidence for this last possibility was obtained by oxidation of 9β-hydroxy-3-methoxyestr-1,3,5(10)-trien-11,17-dione (16a) for 3 hr. under the same conditions as above, when 34% conversion to the 9-oxo-11-oic acid occurred.
EXPERIMENTAL

Microanalyses were carried out by Dr A. D. Campbell and his associates, University of Otago. Melting points were determined on a Kofler block and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 237 or 337 grating infrared spectrophotometer. Ultraviolet spectra were measured on a Jasco O.R.D./U.V.-5 spectrophotometer or a Unicam S.P.800 U.V. spectrophotometer, or if stated, on a Cary spectrophotometer. For the former two instruments maxima below 230 μ are unreliable. Optical Rotatory Dispersion (O.R.D.) measurements and optical rotations were determined with a Jasco O.R.D./U.V.-5 spectrophotometer. O.R.D. details are given as molecular rotation at a given wavelength (μ, subscript).

Nuclear magnetic resonance (n.m.r.) spectral measurements were carried out on a Varian A60 spectrometer, using tetramethylsilane as internal reference. N.m.r. details are given in the following order: position of peak (δ value), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J, c./sec.), proton integration, and assignment. \( \frac{W}{2} \) signifies peak width at half-height.

Column chromatography was carried out on P. Spence Type H alumina or on Riedel-De Haen Kieselgel. Deactivated alumina refers to P. Spence Type H alumina which had been deactivated by shaking with 5% v/v of 10% aqueous acetic acid. Kieselgel G was used for
thin-layer chromatography (t.l.c.), the compounds being detected by ceric sulphate - 70% sulphuric acid spray. Kieselgel PF_{254} + 366 was used for preparative t.l.c.

"Light petroleum" refers to the fraction b.p. 50-70\(^{\circ}\), and "ether" to diethyl ether. Anhydrous magnesium sulphate was used as a drying agent, except where otherwise stated.

Preparation of 1-Methoxy-4-methylestra-1,3,5(10)-trien-17\(\beta\)-yl acetate(1g)

4-Methylestra-1,3,5(10)-trien-1,17\(\beta\)-diol 17-acetate(1f)

A solution of acetic anhydride (45.4 ml.) and perchloric acid (72%, 0.47 ml.) in dry ethyl acetate (225 ml.) was added to a solution of 3-oxo-androsta-1,4-dien-17\(\beta\)-yl acetate(35d, 6.02 g.) in dry ethyl acetate (225 ml.) and the mixture was kept at 20\(^{\circ}\) for 45 min. Work-up in the usual manner and crystallisation of the product from light petroleum-ether gave 4-methylestra-1,3,5(10)-trien-1,17\(\beta\)-diol diacetate(1a, 5.71 g., 84%).

\[ \nu_{\text{max (CHCl}_3)} \] 1735 (C=17 OAc C = O str.), 1720 (C=1 OAc C = O str.), 1270-1200 (br. C-O-C asym. str.) and 1045-1020 cm\(^{-1}\) (C-O-C sym.str.).

4-Methylestra-1,3,5(10)-trien-1,17\(\beta\)-diol diacetate(1a, 5.71 g.) was hydrolysed with aqueous methanolic potassium hydroxide
(1.02 : 1 molar equivs). The solid product was collected and shown by t.l.c. and its i.r. spectrum to be an approximately 1 : 2 mixture of 4-methylestra-1,3,5(10)-trien-1,17β-diol(1e) and the corresponding 17-acetate(1f). This material was then reacetylated to form the diacetate and the product was chromatographed on deactivated alumina in benzene and allowed to remain on the column overnight. Elution with benzene-ether (8 : 2) gave 4-methylestra-1,3,5(10)-trien-1,17β-diол 17-acetate(1f, 4.46g., 88%) which crystallised from light petroleum-ether as needles, m.p. 193-195° (Lit. 86 m.p. 194-195°), [α]D²⁵ + 161° (c = 1.01 in CHCl₃) [Lit. 86 [α]D + 152° (c = 0.78 in CHCl₃)], \( \nu_{\text{max}}(\text{CHCl}_3) \) 3440-3340 (H-bonded OH str.), 1710 (C-17 OAc C=O str.), 1580 (phenyl nucleus), 1270-1210 (C-O-C asym. str.) and 1045-1030 cm⁻¹ (C-O-C sym. str.), \( \lambda_{\text{max}}(\text{EtOH}) \) 227 (ε 4750) and 286 μμ (ε 2140).

δ(CDCl₃) 0.85 (s, 3, C-18 Me), 2.04 (s, 3, C-17 OCCH₃), 2.13 (s, 3, C-4 aromatic Me), 4.72 (br.t., 1, C-17, dH), 5.69 (s, 1, C-1 OH) and 6.47 and 6.78 (2d, JAB 8 c./sec., 2, C-2 and C-3 aromatic protons).

1-Methoxy-4-methylestra-1,3,5(10)-trien-17β-yl acetate(1g)

4-Methylestra-1,3,5(10)-trien-1,17β-diol 17-acetate(1f, 4.35g.), potassium(3.11g.), and dry benzene (220ml.) was heated under reflux for 3hr. Methyl iodide(4.91ml.) was then added and the mixture was heated under reflux for a further 3hr. Filtration of the cooled reaction mixture, followed by concentration and chromatography on deactivated alumina in benzene gave 1-methoxy-4-methylestra-1,3,5(10)-
trien-17β-yl acetate (1g, 4.37g., 96%) which crystallised as needles from light petroleum-ether, m.p. 149-150°. A sample prepared for analysis had m.p. 172-176°, [α]_D^{25} + 141° (c = 1.18 in CHCl₃) (Found: C, 77.3; H, 8.9. C₂₂H₃₀O₃ requires C, 77.15; H, 8.8%).

ν_max (CHCl₃) 1720 (C-17 OAc C=O str.), 1580 (phenyl nucleus) and 1260-1210 cm⁻¹ (C-0-C str.).

λ_max (cyclohexane) 220 (ε 1130) and 284 mp (ε 940).

δ(CDCl₃) 0.85 (s, 3, C-18 Me), 2.02 (s, 3, C-17 OCOCH₃), 2.13 (s, 3, C-4 aromatic Me), 3.72 (s, 3, C-1 aromatic OMe), 4.54-4.86 (m, 1, C-17 cH) and 6.58 and 6.90 (2d, J_AB 8c./sec., 2, C-2 and C-3 aromatic protons).

Oxidation of 1-Methoxy-4-methylestra-1,3,5(10)-trien-17β-yl acetate(1g)

A solution of 1-methoxy-4-methylestra-1,3,5(10)-trien-17β-yl acetate(4.19g.) in acetone (240ml.) was treated dropwise at 0° with a 4N solution of chromium trioxide in 40% aqueous sulphuric acid (73.5 ml.) and the mixture was kept at 20° for 18hr. Methanol was added to destroy the excess of oxidising agent and the mixture was extracted with ether. The ether layer was washed with water and any remaining formic or sulphuric acids were removed by extraction with sodium bicarbonate solution. The point where the acidic reaction products began to react with the bicarbonate was recognised by colouration of the extract. The ether phase was then exhaustively
extracted with saturated sodium bicarbonate solution, washed with water, dried, and concentrated to yield a neutral brown-red oil (1.8g., 43%). The orange-red sodium bicarbonate extracts were acidified, ether extracted, and the ether removed to yield a brown tarry acid fraction (1.02g., 24%). Repeated preparative t.l.c. of both the neutral and acidic fractions failed to yield any compound in sufficient quantity for identification.

Preparation of 1-Methoxy-4-methylestra-1,3,5(10)-tien-17β-yl benzoate(1j)

3-Oxo-androsta-1,4-dien-17β-yl benzoate(35a)89

A solution of D.D.Q. (10.58g.) in dry benzene (250ml.) was added to a solution of 3-oxo-androst-4-en-17β-yl benzoate(34a, 10g.) in dry benzene (250ml.) and the mixture was heated under reflux for 24hr. The 2,3-dichloro-5,6-dicyanohydroquinone was filtered from the cooled reaction mixture and the solvent was removed in vacuo. Chromatography of the dark gummy product on deactivated alumina in benzene yielded 3-oxo-androsta-1,4-dien-17β-yl benzoate(35a, 7.98g., 80%), which crystallised from light petroleum-ether, m.p. 216-218° (Lit. 203 m.p. 206-215°), [α]D + 120° (c = 0.53 in CHCl₃).

υ_max (CS₂) 1720 (C=17 OBz C=O str.), 1670 (conj. C=O str.), 1630, 1605 (conj. C=C str.) and 1270 and 1112 cm⁻¹ (C-O-C asym. and sym. str.).
λ_max (EtOH) 235 μm (ε 23,700).
δ (CDCl₃) 1.01 (s, 3, C-18 Me), 1.23 (s, 3, C-19 Me), 2.22-2.53 (m, 2, C-6 vinylic protons), 4.67-5.05 (m, 1, C-17 αH), 6.12 (br.s., 1, C-4 olefinic H), 6.25 (2d, J₂₁ 10 c./sec., J₂₄ 2 c./sec., 1, C-2 olefinic H), 7.08 (d, J₁₂ 10 c./sec., 1, C-1 olefinic H) and 7.38-7.66 and 7.95-8.20 (2m, 5, OBF₃ protons).

4-Methylestra-1,3,5(10)-triene-1,17β-diol 1-acetate 17-benzoate (1h)₈₄

A solution of acetic anhydride (19ml.) and perchloric acid (72%, 0.15ml.) in dry ethyl acetate (75ml.) was added to a solution of 3-oxo-androst-1,4-dien-17β-yl benzoate (35a, 2.33g.) in ethyl acetate (75ml.), and the mixture was kept at 20° for 45 min. Work-up of the reaction mixture in the usual manner, and crystallisation of the product from acetone, gave 4-methylestra-1,3,5(10)-triene-1,17β-diol 1-acetate 17-benzoate (1h, 2.10g., 83%) as tablets, m.p. 187-189°, [α]D²⁵ + 157° (c = 0.77 in CHCl₃) (Found: C, 77.8; H, 7.5.

C₂₈H₃₂O₄ requires C, 77.75; H, 7.5%).

ν max (CS₂) 3100, 3080, 3040 (aromatic CH str.), 1755 (OAc C=O str.), 1720 (OBz C=O str.), 1605 (phenyl nucleus), 1220, 1205 (C-O-C asym. str.) 1120, 1075 (C-O-C sym. str.) and 900, 810, 760 cm⁻¹ (aromatic CH o.o.pl. def.).

λ_max (EtOH) 230 (ε 13,300) and 270 μm (ε 1090).
δ (CCl₄) 1.00 (s, 3, C-18 Me), 2.21 and 2.25 (2s, 6, C-4 aromatic Me and C-1 aromatic OCOCH₃), 2.50-2.82 (m, 2, C-6 benzylic protons),
4.85-5.16 (m, 1, C-17 αH), 6.78 (d, J_3,2 8 c./sec., 1, C-3 aromatic H), 7.03 (d, J_2,3 8 c./sec., 1, C-2 aromatic H), and 7.38-7.62 and 8.01-8.18 (2m, 5, C-17 OBz protons).

4-Methylestra-1,3,5(10)-triene-1,17β-diol 17-benzoate(1i)

Hydrolysis of 4-methylestra-1,3,5(10)-triene-1,17β-diol 1-acetate 17-benzoate (1h, 2.76g.) with 5% methanolic potassium hydroxide gave 4-methylestra-1,3,5(10)-triene-1,17β-diol 17-benzoate (1i, 2.43g., 97%), which crystallised as needles from light petroleum-ether, m.p. 214-216°, [α]_D^{25} + 155° (c = 0.31 in CHCl₃)

(Found: C, 80.2; H, 7.6; 0, 12.3. C_{26}H_{30}O_{3} requires C, 80.0; H, 7.7; 0, 12.3%).

ν₂₅_max (CHCl₃) 3420-3320 (OH str.), 1700 (OBz C=O str.), 1560 (phenyl nucleus), and 1275, 1290, and 1120 cm⁻¹ (OBz C=O-C str.).

λ_max (EtOH) 216 (ε 9,600), 231 (ε 11,400), and 286 μm (ε 1400).

δ (CDCl₃) 0.98 (s, 3, C-18 Me), 2.12 (s, 3, C-4 aromatic Me), 4.76-5.08 (t, 1, C-17 αH), 5.44 (s, 1, C-1 OH), 6.48 (d, J_3,2 8 c./sec., 1, C-3 aromatic H), 6.78 (d, J_2,3 8 c./sec., 1, C-2 aromatic H), and 7.31-7.47 and 7.91-8.09 (2m, 5, C-17 OBz protons).

1-Methoxy-4-methylestra-1,3,5(10)-triene-17β-yl benzoate(1j)

4-Methylestra-1,3,5(10)-triene-1,17β-diol 17-benzoate(1i, 2.4g.), potassium (1.5g.), and dry benzene (125ml.) were heated under reflux for 3hr. and then methyl iodide (3.8ml.) was added and the heating
under reflux continued for a further 3hr. Work-up in the usual manner and chromatography in light petroleum on deactivated alumina gave from light petroleum-benzene (7:3) eluates, 1-methoxy-4-methylestra-1,3,5(10)-trien-17β-yl benzoate (1j, 2.24g., 90%) which crystallised from aqueous acetone as needles, m.p. 100-100.5°C. A sample prepared for analysis had m.p. 123-125°C, [α]D^25 + 175° (C = 0.76 in CHCl₃) (Found: C, 80.0; H, 8.1; O, 11.7. C_{27}H_{32}O_{3} requires C, 80.2; H, 8.0; O, 11.9%).

V_{max}^\prime\prime (CCl₄) 3060, 3030 (aromatic CH str.), 1725 (C-17 OBz C=O str.), 1605, 1505 (phenyl nucleus), 1285, 1272 (C=O-C ester and ether str.) and 1115 and 1065 cm⁻¹ (C-O-C sym.str.).

λ_{max} (EtOH) 213 (ε 16,000), 230 (ε 23,000) and 284 μμ (ε 2700).

δ (CDCl₃) 0.97 (s, 3, C-18 Me), 2.10 (s, 3, C-4 aromatic Me), 3.68 (s, 3, C-1 aromatic OMe), 4.73-5.06 (br.t., 1, C-17 αH), 6.43 (d, J 3,2 8c./sec., 1, C-3 aromatic H), 6.77 (d, J 2,3 8c./sec., 1, C-2 aromatic H) and 7.28-7.47 and 7.88-8.04 (2m, 5, C-17 OBz protons).

**Oxidation of 1-Methoxy-4-methylestra-1,3,5(10)-trien-17β-yl benzoate(1j)**

A solution of 1-methoxy-4-methylestra-1,3,5(10)-trien-17β-yl benzoate (1.96g.) in acetic acid (60ml.) and acetone (50ml.) was treated dropwise at -18°C with a solution of chromium trioxide (1.57g.) in water (6ml.) and acetic acid (54ml.), and the mixture was allowed to come to 7°C over 20hr. Work-up in the usual manner (p.98-99)
afforded a neutral fraction (1.38g., 72%) and an acid fraction (225mg., 12%) which was discarded.

Repeated preparative t.l.c. of the neutral fraction gave starting material (1j, 239 mg., 12%) and 4 other products:

1-methoxy-4-methyl-6-oxo-estra-1,3,5(10)-tri-en-17β-yl benzoate (2i, 37 mg., 1.85%) as a yellow gum.

$\nu_{\text{max}}$ (CCl$_4$) 1720 (C-17 OBz C=O str.), 1690 (aromatic C=O str.), and 1605 and 1585 cm$^{-1}$ (phenyl nucleus).

$\lambda_{\text{max}}$ (EtOH) 203 ($\epsilon$ 19,000), 220 (sh., $\epsilon$ 19,000), 231 ($\epsilon$ 25,000), 258 ($\epsilon$ 6300) and 327 μ (ε 2600).

δ (CDCl$_3$) 0.98 (s, 3, C-18 Me), 2.54 (s, 3, C-4 aromatic Me), 3.77 (s, 3, C-1 aromatic OMe), 4.93 (br.t., 1, C-17 aH), 6.91 (d, J$_{3,2}$ 8c./sec., 1, C-2 aromatic H) and 7.03 (d, J$_{2,3}$ 8c./sec., 1, C-2 aromatic H) and 7.33-7.52 and 7.92-8.12 (2m, 5, C-17 OBz protons).

4-Formyl-1-methoxyestra-1,3,5(10)-tri-en-17β-yl benzoate (65b, 52 mg., 2.6%) was also obtained as a gum.

$\nu_{\text{max}}$ (CCl$_4$) 2720 (aldehydic CH str.), 1720 (OBz C=O str.), 1700 (aromatic aldehydic C=O str.) and 1580 cm$^{-1}$ (phenyl nucleus).

δ (CCl$_4$) 0.99 (s, 3, C-18 Me), 3.85 (s, 3, C-1 OMe), 4.76-5.06 (m, 1, C-17 aH), 6.73 (d, J$_{2,3}$ 8.4 c./sec., 1, C-2 aromatic H), 7.25-7.53 (m, 3, C-17 OBz protons), 7.55 (d, J$_{3,2}$ 8.4 c./sec., 1, C-3 aromatic H), 7.87-8.08 (m, 2, C-17 OBz protons) and 9.69 (s, 1, C-4 CHO).
The corresponding acid 17β-benzoyloxy-1-methoxyestra-1,3,5(10)-trien-4-oic acid (66b, 330 mg., 16%), which had escaped sodium bicarbonate extraction, was crystallised as leaflets from light petroleum-ether, m.p. 165-168.5°.

ν\textsubscript{max} (CHCl\textsubscript{3}) 3540-2540 (br. OH str. of H-bonded COOH), 1720 (OBz C=O str.), 1690 (carboxylic C=O str.), 1600, 1585, 1575 (phenyl nucleus), 1280-1200 (C-O str. of COOH coupled with OH i.pl.str., and asym. C-O-C OBz str.) and 1110 or 1070 cm\textsuperscript{-1} (sym. C-O-C OBz str.).

λ\textsubscript{max} (EtOH) 224 (ε 11,600) and 260 μμ (ε 7660).

δ (CCl\textsubscript{4}) 0.99 (s, 3, C-18 Me), 3.80 (s, 3, aromatic OMe), 4.75-5.07 (m, 1, C-17 αH), 6.64 (d, J\textsubscript{2,3} 9 c./sec., 1, C-2 aromatic H), 7.24-7.54 (m, 3, OBz protons), 7.76-8.04 (m, 3, C-17 OBz protons and C-3 aromatic H) and 9.74-10.04 (br.s., C-4 COOH).

R.D. (C = 0.17 in CHCl\textsubscript{3}); [\varnothing]\textsubscript{589} + 973°, [\varnothing]\textsubscript{500} + 1690°, [\varnothing]\textsubscript{400} + 3160°, [\varnothing]\textsubscript{300} + 11,700°, and [\varnothing]\textsubscript{240} + 19,200° (pk).

17β-Benzoxyloxy-4-methyl-4-oxo-1,4-seco-2,3-bisnorestra-5(10)-en-1-oic acid (67b, 240 mg., 13%) was crystallised from benzene as leaflets, m.p. 226-236° [Found: C, 72.9; H, 7.2; O, 20.35; M.W.
(mass spec.) 396.1930. C\textsubscript{24}H\textsubscript{28}O\textsubscript{5} requires C, 72.7; H, 7.1; O, 20.2%; M.W. 396.1937].

ν\textsubscript{max} 3580 (free OH str.), 3340-3320 (H-bonded OH str.), 1765-1740, 1725-1700, 1675 (OBz C=O str. and complex lactol C=O str.\textsuperscript{97}), 1600, 1580 (phenyl nucleus), 1290-1370 (asym. C-O-C str.) and 1115 cm\textsuperscript{-1} (sym. C-O-C str.).
λ_{max} (EtOH) 229 μm (ε 13,600).
δ (CDCl₃) 0.98 (s, 3, C-18 Me), 1.63 (s, 3, C-4 Me) and 7.37-7.61
and 7.85-8.16 (2m, 5, OBz protons).
R.D. (ε = 0.22 in CHCl₃); [α]_{589}^0 + 164°, [α]_{500}^0 + 236°, [α]_{400}^0
+ 436°, and [α]_{300}^0 + 1090°.

Preparation of 1-Methoxy-4-methylestra-1,3,5(10)- trien-17-one(11)

Androsta-1,4-diene-3,17-dione(35b)⁸⁸

A solution of D.D.O. (47.6 g.) in dry benzene (1250ml.) was
added to a solution of androst-4-ene-3,17-dione(50 g.) in dry
benzene (1250ml.) and the mixture was heated under reflux for 15hr.
Work-up in the usual manner and chromatography on deactivated
alumina gave androsta-1,4-diene-3,17-dione(35b, 35.5 g., 72%), which
crystallised from light petroleum-ether, m.p. 138-140° (Lit.⁹⁰ m.p.
140-141°), [α]_{D}^{25} + 117° (ε = 0.89 in CHCl₃) [Lit.⁹⁰ [α]_{D}^{25} + 118.8°
( in CHCl₃)].

1-Hydroxy-4-methylestra-1,3,5(10)- trien-17-one(1k)⁸⁴

A solution of acetic anhydride (180ml.) and perchloric acid
(72%, 1.86 ml.) in dry ethyl acetate (750 ml.) was added to a
solution of androsta-1,4-diene-3,17-dione (20.5g.) in dry ethyl
acetate (750 ml.) and the mixture was kept at 20° for 45 min. Work-
up of the reaction mixture in the usual manner and hydrolysis of the product with 10\% aqueous methanolic potassium hydroxide, gave after crystallisation from ethanol-chloroform, 1-hydroxy-4-
methylestra-1,3,5(10)-trien-17-one(1k, 16.40g., 80\%) as needles, m.p. 251-254\(^\circ\) (Lit.\(^{90}\) 249-251\(^\circ\)), [\(\alpha\)]\(_D\)\(^{25}\) + 279\(^\circ\) (\(c = 0.58\) in CHCl\(_3\)) [Lit.\(^{90}\) [\(\alpha\)]\(_D\)\(^{25}\) + 271.6\(^\circ\) (in CHCl\(_3\))],

\(\nu_{\text{max}}\) (CHCl\(_3\)) 3580 (free OH str.), 3360-3300 (intermol. H-bonded OH str.), 1735 (C-17 C=O str.), 1590 (phenyl nucleus) and 1300-1150 cm\(^{-1}\) (br. C-C str. of C-CO-C).

\(\lambda_{\text{max}}\) (EtOH) 211 (\(\varepsilon \) 10,900), 222 (\(\varepsilon \) 7300) and 285 my (\(\varepsilon \) 2200).

Repeated chromatography of the mother liquors on deactivated alumina in benzene and elution with benzene-ether (19 : 1), (9 : 1), (17 : 3), (8 : 2) gave a second compound, 3-hydroxy-1-methylestra-
1,3,5(10),6-tetraen-17-one(38a, 895 mg., 4\%) which crystallised from ethanol-chloroform, m.p. 271-276\(^\circ\) (Lit.\(^{94}\) m.p. 250-252\(^\circ\)), [\(\alpha\)]\(_D\)\(^{25}\) -75\(^\circ\) (\(c = 1.22\) in CHCl\(_3\)) [Lit.\(^{94}\) [\(\alpha\)]\(_D\)\(^{20}\) -87.7\(^\circ\) (in CHCl\(_3\))]

[Found: C, 80.6; H, 7.9; O, 11.4\%; M.W. (mass spec.) 282.1620. C\(_{19}\)H\(_{22}\)O\(_2\) requires C, 80.8; H, 7.85; O, 11.3\%; M.W. 282.1620].

\(\nu_{\text{max}}\) (CHCl\(_3\)) 3580 (free OH str.), 3340-3260 (intermol. H-bonded OH str.), 1735 (C-17 C=O str.), 1595, 1575 (phenyl nucleus) and 1300-1150 cm\(^{-1}\) (br. C-C str. of C-CO-C).

\(\lambda_{\text{max}}\) (EtOH) 230 (\(\varepsilon \) 26,600), 262.5 (\(\varepsilon \) 7270) and 304 my (\(\varepsilon \) 1480).

Methylation of this minor product with methyl-\(p\)-toluene
sulphonate in the usual manner\(^9\) gave 3-methoxy-1-methylestra-1,3,5(10),6-tetraen-17-one(38b) which crystallised as needles from ethyl acetate, m.p. 145-150\(^\circ\), \([\alpha]_{D}^{25}\) -170\(^\circ\) (c = 0.37 in CHCl\(_3\)) [Found: C, 80.2; H, 8.35; O, 11.75%; M.W. (mass spec.) 296.1769. C\(_{20}H_{24}O_2\) requires C, 81.0; H, 8.2; O, 10.8%; M.W. 296.1776].

\(\nu_{\text{max}}^\text{CHCl}_3\) 3040 (C-H str.), 1745 (C-17 C=O) and 1595 and 1570 cm\(^{-1}\) (phenyl nucleus).

\(\lambda_{\text{max}}^\text{EtOH}\) 228 (\(\epsilon\) 31,800), 267 (\(\epsilon\) 7990) and 302 \(\mu\mu\) (\(\epsilon\) 1480).

\(\delta^\text{(CDCl}_3\text{)}\) 0.86 (s, 3, C-18 Me), 2.47(s, 3, C-1 aromatic Me), 3.68 (s, 3, C-3 aromatic OMe), 5.85 (d, J\(_{7,6}\) 9.8 c./sec., 1, C-7 olefinic H), 6.32 (s, \(\mathbf{2}\) c./sec., 2, C-2 and C-4 aromatic protons) and 6.33 (2d, J\(_{6,7}\) 9.8 c./sec., J\(_{6,4}\) 2.0 c./sec., 1, C-6 olefinic H).

\(1\text{-Methoxy-4-methylestra-1,3,5(10)-tri-en-17-one}(11)\)

Methylation of 1-hydroxy-4-methylestra-1,3,5(10)-tri-en-17-one(1k, 8.21g.) with methyl-p-toluenesulphonate in the usual manner,\(^9\) followed by chromatography on deactivated alumina in benzene gave 1-methoxy-4-methylestra-1,3,5(10)-tri-en-17-one(11, 8.20g., 95%) which crystallised from ether as prisms, m.p. 116-118\(^\circ\) (Lit.\(^9\) m.p. 117-118\(^\circ\)), [\(\alpha\)]\(_D\)\(^{25}\) + 300\(^\circ\) (c = 0.32 in CHCl\(_3\)) [Lit.\(^9\) [\(\alpha\)]\(_D\)\(^{25}\) + 297\(^\circ\) (in CHCl\(_3\))].

\(\nu_{\text{max}}^\text{CCl}_4\) 1745 (C-17 C=O str.), 1595, 1585 (phenyl nucleus) and 1250 and 1180 cm\(^{-1}\) (asym. and sym. C=O-C str.)

\(\lambda_{\text{max}}\) 213 (\(\epsilon\) 8270), 222.5 (\(\epsilon\) 7860) and 282 \(\mu\mu\) (\(\epsilon\) 1870).
δ (CDCl₃) 0.91 (s, 3, C-18 Me), 2.16 (s, 3, C-4 aromatic Me), 2.53-
2.78 (m, 2, C-6 benzylic protons), 3.74 (s, 3, C-1 aromatic OMe),
6.59 (d, J₂,₃ 8.2 c./sec., 1, C-2 aromatic H) and 6.92 (d, J₃,₂ 8.2
 c./sec., 1, C-3 aromatic H).

Oxidation of 1-Methoxy-4-methylestra-1,3,5(10)-trien-17-one(11)

A solution of 1-methoxy-4-methylestra-1,3,5(10)-trien-17-one
(2.10g.) in acetic acid (243 ml.) and acetone (567 ml.) was treated
dropwise at -18⁰ with a solution of chromium trioxide (9.03g.) in
water (24.3 ml.) and acetic acid (218.7 ml.) and the mixture was
allowed to come to 15⁰ over 24 hr. Work-up in the usual manner
(p. 98-99) gave a neutral oil (6.35g., 78%) which was chromatographed
on silica gel in benzene. Benzene eluates gave starting material
(800 mg., 10%) and benzene-ether eluates gave fractions of mixtures
which were subjected to repeated preparative t.l.c.

1-Methoxy-4-methylestra-1,3,5(10)-triene-6,17-dione(64a, 34mg.,
0.4%) was obtained as a pale yellow gum.

υₘₐₓ (CCl₄) 1745 (C-17 C=O str.), 1690 (C-6 aromatic C=O str.) and
1580 cm⁻¹ (phenyl nucleus).

δ (CDCl₃) 0.94 (s, 3, C-18 Me), 2.47 (s, 3, aromatic Me), 3.78 (s, 3,
aromatic OMe), 6.82 (d, J₂,₃ 8.2 c./sec., 1, C-2 aromatic H) and 6.93
(d, J₃,₂ 8.2 c./sec., 1, C-3 aromatic H).
1-Methoxy-17-oxo-estra-1,3,5(10)-tren-4-al (65a, 343 mg., 4%) was also obtained as a colourless gum.

$\nu_{\text{max}}$ (CCl$_4$) 2720 (C-4 aldehyde CH str.), 1745 (C-17 C=O str.), 1700 (aryl aldehyde C=O str.) and 1580 cm$^{-1}$ (phenyl nucleus).

$\lambda_{\text{max}}$ (EtOH) 212 ($\epsilon$ 13,000), 233 ($\epsilon$ 12,000) and 276 μm ($\epsilon$ 8800).

δ (CCl$_4$) 0.83 (s, 3, C-18 Me), 3.87 (s, 3, aromatic OMe), 6.76 (d, $J_{2,3}$ 8 c./sec., 1, C-2 aromatic H), 7.50 (d, $J_{3,2}$ 8 c./sec., 1, C-3 aromatic H) and 9.60 (s, 1, C-4 CHO).

1-Methoxy-17-oxo-estra-1,3,5(10)-tren-4-oic acid (66a, 2.07g., 23%) was extracted from both acidic and neutral fractions and was crystallised from light petroleum-methylene chloride as leaflets, m.p. 184-186°. (Found: C, 73.2; H, 7.3; O, 19.4. C$_{20}$H$_{24}$O$_4$ requires C, 73.1; H, 7.4; O, 19.5%).

$\nu_{\text{max}}$ (CHCl$_3$) 3500-2620 (br. OH str. of H-bonded COOH), 1740 (C-17 C=O str.), 1690 (aryl carboxylic C=O str.), 1590, 1575 (phenyl nucleus), 1260-1200 (C-O-C asym. str. and C-C str. of C-CO-C) and 1075 cm$^{-1}$ (sym. C-O-C str.).

$\lambda_{\text{max}}$ (EtOH) 217 ($\epsilon$ 20,800) and 260 μm ($\epsilon$ 11,200).

δ (CDCl$_3$) 0.95 (s, 3, C-18 Me), 3.00-3.34 (m, 2, C-6 benzylic protons), 3.84 (s, 3, C-1 aromatic OMe), 6.78 (d, $J_{2,3}$ 7.8 c./sec., 1, C-2 aromatic H), 7.97 (d, $J_{3,2}$ 7.8 c./sec., 1, C-3 aromatic H) and 11.21 (br.s., 1, C-4 COOH).

R.D. ($\epsilon = 0.79$ in CHCl$_3$); $[\varphi]_{589} + 1250^0$, $[\varphi]_{500} + 2000^0$, $[\varphi]_{400} + 3660^0$, and $[\varphi]_{315} + 17,300^0$ (pK).
4,17-Dioxo-4-methyl-1,4-seco-2,3-bisnorestra-5(10)-ene-1-oic acid (67a, 268 mg., 3.4%) was crystallised from light petroleum-methylene chloride as needles, m.p. 240-243°, (Found: C, 70.05; H, 7.45; O, 22.2. \( \text{C}_{17}\text{H}_{22}\text{O}_{4} \) requires C, 70.3; H, 7.6; O, 22.0%).

\( \nu_{\text{max}}^{\text{CHCl}_3} \) 3400-3300 (H-bonded CH str.) and 1765-1735 cm\(^{-1} \) (complex lactol C=O str.\(^{97} \) and C-17 C=O str.).

\( \lambda_{\text{max}} \) (EtOH) 218 mp (\( \varepsilon \) 7600).

\( \delta \) (CDCl\(_3\)) 0.91 (s, 3, C-18 Me) and 1.63 (s, 3, C-4 Me).

R.D. (\( \varepsilon = 0.46 \) in CHCl\(_3\)): \( [\phi]^{589} + 543^\circ \), \( [\phi]^{500} + 828^\circ \), \( [\phi]^{400} + 1630^\circ \), \( [\phi]^{319} + 7210^\circ \) (pk), \( [\phi]^{299} 0^\circ \), and \( [\phi]^{282} - 4290^\circ \).

A second oxidation of 1-methoxy-4-methylestra-1,3,5(10)-triene-17-one (14.05 g.) using the same molar ratios of reagents was carried out, but the temperature of the reaction mixture was allowed to come to 0° over 10 hr. The yellow neutral oil (12.07 g., 85%) obtained after work-up in the usual manner gave starting material (5.59 g., 40%) and 2 of the above products in lower yields, viz. 1-methoxy-4-methylestra-1,3,5(10)-triene-6,17-dione (64a, 30 mg., 0.2%) and 1-methoxy-17-oxo-estra-1,3,5(10)-triene-4-al (65a, 480 mg., 3.3%).

1-Methoxy-17-oxo-estra-1,3,5(10)-triene-4-oic acid (66a, 2.12 g., 15%) was isolated from both neutral and acidic fractions.

Oxidation of 1-Methoxy-17-oxoestra-1,3,5(10)-triene-4-al (65a)

1-Methoxy-17-oxoestra-1,3,5(10)-triene-4-al (300 mg.) was dissolved in acetone (14 ml.), treated with potassium permanganate
(104 mg.) in acetone (35 ml.), and the mixture stirred at 20° for 4 hr. 10% Sodium bisulphite solution was added, and the mixture was extracted with aqueous sodium bicarbonate. The acidified bicarbonate extract was ether extracted and the organic phase was washed and dried to yield, after chromatography on silica gel, 1-methoxy-17-oxo-estra-1,3,5(10)-triene-4-oic acid (66a, 176 mg., 56%). Extraction of the neutral fraction yielded, after chromatography on silica gel, starting material (65a, 100 mg., 30%).

4-Methyl-19-norcholesta-1,3,5(10)-triene(1n)\textsuperscript{106}

A mixture of cholest-4-en-3-one(34c, 7.5g.), acetyl bromide (2.12 ml.), and 2-bromo-propionic acid (8.79 ml.) was heated under reflux for 7 hr. The cooled mixture was poured into ice-cold sodium carbonate solution, ether extracted, and the ether extract dried, and concentrated to yield a yellow gum which was chromatographed on alumina in light petroleum. Elution gave 4-methyl-19-norcholesta-1,3,5(10)-triene(1n, 6.14g., 97%), $\nu_{\text{max}}^{(\text{CS}_2)}$ 3060, 3030 (aromatic CH str.), 1580 (phenyl nucleus), and 775 and 735 cm\textsuperscript{-1} (acromatic o.o.pl. def.), as a colourless gum.

$\delta$(CCl\textsubscript{4}) 0.68 (s, 3, C-18 Me), 0.86 (d, J\textsubscript{26} and 27,25 6 c./sec., 6, C-25 \underline{gem} di-Me), 0.33 (d, J\textsubscript{21,20} 6 c./sec., 3, C-21 Me), 2.14 (s, 3, C-4 aromatic Me), 2.46-2.80 (m, 2, C-6 benzylic protons) and 6.79-7.09 (m, 3, A-ring aromatic protons).
4-Methyl-19-norcholesta-1,3,5(10)-trien-6-one(2e)

A solution of 4-methyl-19-norcholesta-1,3,5(10)-trien(e(1n, 2.50g,) in acetone (20 ml.) and acetic acid (20 ml.) was treated dropwise at 0° with a solution of chromium trioxide (2.27g.) in water (1.5 ml.) and acetic acid (28.5 ml.) and the mixture was kept at 20° for 20 hr. Work-up in the usual manner (p. 98-99) gave a neutral oil (2.19g., 88%) which was chromatographed on alumina in light petroleum and gave back starting material (1n, 0.68g., 27%). Elution with light petroleum-benzene(9 : 1) gave 4-methyl-19-norcholesta-1,3,5(10)-trien-6-one (2e, 289 mg., 11%) as a viscous oil which formed waxy crystals on storage, m.p. 68-70° (Found: C, 85.1; H, 10.6. C₂₇H₄₀O requires C, 85.2; H, 10.6%).

ν₅ max (CHCl₃) 3030 (aromatic CH str.), 1680 (aromatic C=O str.) and 1595 and 1575 cm⁻¹ (phenyl nucleus).

λ max (cyclohexane) 216 (ε 13,600), 250 (ε 9600) and 300 μμ (ε 1750).

δ (CDCl₃) 0.70 (s, 3, C-18 Me), 0.85-0.95 (m, 9, C-21 Me and C-25 gem di-Me), 2.65 (s, 3, C-4 aromatic Me) and 7.05-7.50 (m, 3, A-ring aromatic protons).

R.D. (ε = 0.39 in CHCl₃); [α]₅₈₉ + 21°, [α]₅₀₀ + 170°, [α]₄₀₀ + 1135°, [α]₃₆₄ + 3320° (pk) and [α]₃₂₁ 0°.

4-Methyl-6-oxo-estra-1,3,5(10)-trien-1,17β-diol 17-benzoate(2g)

A solution of 4-methylestra-1,3,5(10)-trien-1,17β-diol 1-acetate 17-benzoate(1h, 2.05g.) in acetic acid (30 ml.) was treated
dropwise at 0° with a solution of chromium trioxide (1.57 g.) in water (2.3 ml.) and acetic acid (13.7 ml.). The mixture was kept at 20° for 24 hr. and then worked up in the usual manner (p. 98-99).

The solid neutral residue was chromatographed on deactivated alumina to give starting material (1 h, 130 mg., 6.4%) from benzene eluates.

Benzene-ether (3:1) eluates yielded 4-methyl-6-oxo-estra-1,3,5(10)-triene-1,17β-diol 17-benzoate (2 g, 580 mg., 30%) which crystallised from ethanol-chloroform as tablets, m.p. 245-247° (Found: C, 77.5; H, 7.0; O, 15.8. C_{26}H_{28}O_{4} requires C, 77.2; H, 7.0; O, 15.8%).

ν max (CHCl₃) 3400-3300 (H-bonded OH str.), 3040, 3020 (aromatic CH str.), 1715 (C-17 OBz C=O str.), 1690 (aromatic C=O str.), 1605, 1580 (phenyl nucleus) and 1280 and 1120 cm⁻¹ (C=O-C asym. and sym. str.).

λ max (EtOH) 218 (ε 16,000), 232 (ε 24,000), 262 (ε 6400) and 332 μm (ε 2300).

δ (CDCl₃) 1.01 (s, 3, C-18 Me), 2.56 (s, 3, C-4 aromatic Me), 3.06-3.46 (m, 2, C-7 protons), 4.88-5.21 (m, 1, C-17 aH), 6.87 (s, 1, C-1 OH), 6.99 (s, 2, C-2 and C-3 aromatic protons) and 7.43-7.65 and 8.00-8.20 (2m, 5, C-17 OBz protons).

R.D. (ε = 0.44 in CHCl₃); [Φ]_{589} = +463°, [Φ]_{500} = +753°, [Φ]_{400} = +1400°, and [Φ]_{374} = +1770° (pk).

4-Methyl-6-oxo-estra-1,3,5(10)-triene-1,17β-diol 1-acetate 17-benzoate (2f)

Acetylation of 4-methyl-6-oxo-estra-1,3,5(10)-triene-1,17β-
diol 17-benzoate (2g, 210 mg.) with acetic anhydride-pyridine (20°, 24 hr.) followed by crystallisation of the product from light petroleum-ether gave 4-methyl-6-oxo-estro-1,3,5(10)-triene-1,17β-diol 1-acetate 17-benzoate (2f, 220 mg., 94%) as plates, m.p. 178-180°
(Found: C, 75.8; H, 6.8; O, 17.8. C₂₈H₃₀O₅ requires C, 75.3; H, 6.8; 0, 17.9%).

νₖₑₑₑ max (CHCl₃) 1765 (C-1 OAc C=O str.), 1720 (C-17 OBz C=O str.),
1690 (aromatic C=O str.), 1610, 1595, 1585 (phenyl nucleus), 1300-
1200 (C-C str. of C-CO-C and C-O-C asym.str.) and 1175 and 1075 cm⁻¹
(sym. C-O-C str.).

λₘₐₓ (EtOH) 221 (ε 10,800), 229 (ε 8900), 250 (ε 4300) and 304 μm
(ε 1100).

δ (CDCl₃) 0.97 (s, 3, C-18 Me), 2.27 (s, 3, aromatic OCOCH₃), 2.59
(s, 3, C-4 aromatic Me), 4.82-5.12 (br. t., 1, C-17 αH), 7.03 and 7.05
(2d, J₂,₃ 8 c./sec., C-2 and C-3 aromatic protons), and 7.25-7.55 and
7.86-8.13 (2m, 5, C-17 OBz protons).

R.D. (ε = 0.39 in CHCl₃); [Ω]₅₈₉ + 673°, [Ω]₅₀₀ + 1040°, [Ω]₃₉₀
+ 2120° (pk).

Preparation of 2-Methylenestra-1,3,5(10)-triene (83a)

Estra-1,3,5(10)-triien-3-ol (80b)¹⁰⁷

A mixture of estrone (9.08g.), diethylene glycol (90 ml.), and
100% hydrazine hydraté (9.8g.) was heated under reflux for 30 min.,
and was treated with 50% aqueous potassium hydroxide (9 ml.), and then heated to reflux for a further 20 min. The water was allowed to evaporate, the mixture heated at 200° for a further 2 hr., and then worked up in the usual manner. The crude product was crystallised from aqueous ethanol as needles of estra-1,3,5(10)-trien-3-ol(80b, 8.34g., 97%), m.p. 136-139° (Lit. [α]D + 102° (c = 0.56 in EtOH) [α]D + 89°).

ν max (Nujol) 3360-3150 (H-bonded OH str.), 3020 (aromatic CH str.), 1870, 1710 (overtone arom. C-H def.) and 1610 and 1580 cm⁻¹ (phenyl nucleus).

λ max (EtOH) 210 (ε 7000), 221 (ε 6650) and 283 μμ (ε 1810).

δ (CDCl₃) 0.73 (s, 3, C-18 Me), 2.63-2.92 (m, 2, C-6 benzylic protons), 3.48 (s, 1, C-3 OH), 6.57 (br.s., 1, C-4 aromatic H), 6.64 (2d, J₂,₁ 9 c./sec., J₂,₄ 2.8 c./sec., 1, C-2 aromatic H) and 7.16 (d, J₁,₂ 9 c./sec., 1, C-1 aromatic H).

2-Diethylaminomethylestra-1,3,5(10)-trien-3-ol(81a)

Formaldehyde (37%, 4.7 ml.) was added in two equal portions over 2 hr. to a solution of estra-1,3,5(10)-trien-3-ol(80b, 1.99g.) in benzene (24 ml.), ethanol (40 ml.), and diethylamine (7.8 ml.) After heating the mixture under reflux for 16 hr., chromatography of the product on deactivated alumina in benzene gave 2-diethylaminomethylestra-1,3,5(10)-trien-3-ol(81a, 1.20g., 44%) which crystallised from aqueous acetone as needles, m.p. 97-99° (Found: C, 81.0; H,
10.35; N, 4.1. \( \text{C}_{23}\text{H}_{35}\text{ON} \) requires C, 80.9; H, 10.3; N, 4.1%.

\( \lambda_{\text{max}} \) (EtOH) 229 (\( \epsilon \) 5100) and 288 \( \mu \) (\( \epsilon \) 3040).

\( \delta \) (CDCl\(_3\)) 0.73 (s, 3, C-18 Me), 1.07 (t, J = 7 c./sec., 6, Me of ethyl groups), 2.52 (q, J = 7 c./sec., 4, CH\(_2\) of ethyl groups), 3.71 (s, 2, C-2 CH\(_2\)N), 6.54 (s, 1, C-4 aromatic H) and 6.89 (s, 1, C-1 aromatic H).

R.D. (\( \epsilon = 0.29 \) in EtOH); \([\phi]_{589} + 596^0\), \([\phi]_{500} + 842^0\), \([\phi]_{400} + 1345^0\),

and \([\phi]_{292} + 3050^0\) (pk).

2-Methylestra-1,3,5(10)-trien-3-ol(81\text{b})\(^{108}\)

A suspension of Raney nickel catalyst (\( \text{W7,}^{204} \text{20g.} \)) in a solution of 2-diethylaminomethylestra-1,3,5(10)-trien-3-ol(81\text{a, 2.05g}) in ethanol (320 ml.) was heated under reflux for 22 hr. with continuous stirring. Work-up of the reaction mixture and chromatography of the product on silica gel in light petroleum gave 2-methylestra-1,3,5(10)-trien-3-ol(81\text{b, 1.20g.}, 74%) from light petroleum-benzene(4 : 6) eluates, which crystallised as needles from light petroleum, m.p. 105-108\(^0\) (Found: C, 84.65; H, 9.8; O, 5.8.

\( \text{C}_{19}\text{H}_{26}\text{O} \) requires C, 84.4; H, 9.7; O, 5.9%).

\( \lambda_{\text{max}} \) (EtOH) 204 (\( \epsilon \) 14,300) and 278 \( \mu \) (\( \epsilon \) 3090).

\( \delta \) (CDCl\(_3\)) 0.73 (s, 3, C-18 Me), 2.18 (s, 3, C-2 aromatic Me), 2.61-2.95 (m, 2, C-6 benzylic protons), 5.09 (s, 1, C-3 OH), 6.48 (s, 1, C-4 aromatic H), and 7.05 (s, 1, C-1 aromatic H).

R.D. (\( \epsilon = 0.47 \) in CHCl\(_3\)); \([\phi]_{589} + 211^0\), \([\phi]_{500} + 320^0\), \([\phi]_{400} + 548^0\),
$[\theta]_{300} + 1650^\circ$ (pk).

2-Methylestra-1,3,5(10)-trien-3-yl diethylphosphate(82)

Triethylamine (0.6 ml.) was added slowly with vigorous shaking to an ice-cooled solution of 2-methylestra-1,3,5(10)-trien-3-ol(81b, 1.17g.) in carbon tetrachloride (10 ml.) and diethyl phosphite (0.6 ml.) and the reaction mixture was kept overnight at 20°. Work-up, followed by chromatography of the product on silica gel in light petroleum gave, from light petroleum-ether (6:4) eluates, 2-methylestra-1,3,5(10)-trien-3-yl diethylphosphate(82, 1.47g, 92%), which crystallized from light petroleum as plates, m.p. 73-76° (Found: C, 68.1; H, 9.1. C$_{23}$H$_{35}$O$_4$P requires C, 68.0; H, 8.7%).

$\lambda_{\text{max}}$ (EtOH) 217 (ε 7980), 273 (ε 1270) and 281 mp (ε 1330).

$\delta$ (CDCl$_3$) 0.74 (s, 3, C-18 Me), 1.37 (t, J 7 c./scc., 6, CH$_3$ of ethyl protons), 2.28 (s, 3, C-2 aromatic Me), 2.70-3.03 (m, 2, C-6 benzylic protons), 4.18 and 4.32 (2q, 4, CH$_2$ of ethyl protons) and 7.06 and 7.17 (2s, 2, C-1 and C-4 aromatic protons).

R.D. ($\varepsilon = 0.35$ in CHCl$_3$); $[\theta]_{589} + 247^\circ$, $[\theta]_{500} + 288.5^\circ$, $[\theta]_{400} + 666^\circ$ and $[\theta]_{283} + 1780^\circ$ (pk).

2-Methylestra-1,3,5(10)-triene(83a)$^{109,110}$

2-Methylestra-1,3,5(10)-trien-3-yl diethylphosphate(82, 1.46g.) was stirred with liquid ammonia (10 ml.) while lithium (50 mg.) was added portionwise over 2 hr. Ether (5 ml.) was added,
and the mixture was stirred for another 1 hr before the ammonia was allowed to evaporate. Ether extraction followed by chromatography of the product on alumina gave 2-methylestra-1,3,5(10)-triene (83a, 480 mg., 50%) as needles (from ethyl acetate), m.p. 84-86° (Found: C, 89.5; H, 10.3. C_{13}H_{26} requires C, 89.7; H, 10.3%).

$\nu_{\text{max}}$ (CHCl$_3$) 3015-3000 (aromatic CH str.), 1610, 1585 (phenyl nucleus) and 850 and 810 cm$^{-1}$ (aromatic CH o.o.pl. def.).

$\lambda_{\text{max}}$ (cyclohexane) 213 ($\varepsilon$ 6540) and 272 mu ($\varepsilon$ 1010).

$\delta$ (CCl$_4$) 0.74 (s, 3, C-18 Me), 2.25 (s, 3, C-2 aromatic Me), 2.63-2.93 (m, 2, C-6 benzylic protons), 6.82 (s, 2, C-3 and C-4 aromatic protons), and 7.01 (s, 1, C-1 aromatic H).

R.D. ($\varepsilon$ = 0.86 in cyclohexane); $[\bar{\alpha}]_{589}^0 + 339^0$, $[\bar{\alpha}]_{500}^0 + 538^0$, $[\bar{\alpha}]_{400}^0 + 791^0$, and $[\bar{\alpha}]_{280}^0 + 3075^0$ (pk).

2-Methylestra-1,3,5(10)-triene-6-one (83b)

A solution of 2-methylestra-1,3,5(10)-triene (83a, 370 mg.) in acetic acid (2 ml.) and ether (5 ml.) was treated dropwise at 0° with a solution of chromium trioxide (480 mg.) in water (0.5 ml.) and acetic acid (4.5 ml.). The mixture was kept at 20° for 18 hr., and then worked up in the usual manner (p. 98-39). The yellow neutral gum (360 mg., 97%) was chromatographed on silica gel to give starting material (83a, 180 mg., 50%) from initial benzene eluates. Later benzene eluates yielded 2-methylestra-1,3,5(10)-triene-6-one (83b, 64 mg., 17%) which crystallised from light petroleum as needles,
m.p. 116-119°C (Found: C, 84.8; H, 8.95. C\textsubscript{19}H\textsubscript{24}O requires C, 85.0; H, 9.0%).

\( \nu \text{ max (CHCl}_3) 3080, 3040, 3010 \) (aromatic CH str.), 1675 (aromatic C=O str.), 1605 (phenyl nucleus) and 840 and 820 cm\(^{-1}\) (aromatic CH o.o.pl. def.).

\( \lambda \text{ max (EtOH)} 206 (\varepsilon 21,400), 255 (\varepsilon 16,100) \) and 292 \( \mu \) (\( \varepsilon 3830 \)).

\( \delta \) (CDCl\(_3\)) 0.74 (s, 3, C-18 Me), 2.41 (s, 3, C-2 aromatic Me), 7.18 (br. d, J\(_{3,4}\) 8 c./sec., 1, C-3 aromatic H), 7.26 (br. s., 1, C-1 aromatic H), and 8.02 (d, J\(_{4,3}\) 8 c./sec., 1, C-4 aromatic H).

R.D. (\( \varepsilon = 0.57 \) in CHCl\(_3\)); [\( \varphi \])\(_{589} + 432^\circ\), [\( \varphi \])\(_{500} + 583^\circ\), [\( \varphi \])\(_{400} + 807^\circ\), [\( \varphi \])\(_{358} + 1284^\circ\) (pk), [\( \varphi \])\(_{316} 0^\circ\), and [\( \varphi \])\(_{300} - 923^\circ\).

Preparation of 3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-one(84a)

17a,20; 20,21-Bismethylenedioxy-11\( \beta \)-methoxymethyleneoxypregna-1,4-dien-3-one(119b) and 17a,20; 20,21-Bismethylenedioxy-11\( \beta \)-hydroxypregna-1,4-dien-3-one(119a)

A mixture of hydrocortisone(11\( \beta \),17a,21-trihydroxypregn-4-ene-3,20-dione 115a, 13.29g.), chloroform (450 ml.), conc. hydrochloric acid (115 ml.), and formaldehyde (37%, 115 ml.) was shaken for 72 hr. at 20°. Work-up in the usual manner yielded a gum, which after chromatography on deactivated alumina gave 17a,20; 20,21-bismethylenedioxy-11\( \beta \)-methoxymethyleneoxypregn-4-en-3-one(116b,3.72g., 48%) as needles from ethanol-ether, m.p. 161-169° (Lit.\(^{153}\) m.p. 160-
$\delta$ (CDCl$_3$) 1.07 (s, 3, C-18 Me), 1.42 (s, 3, C-19 Me), 3.43 (s, 3, C-11 OMe), 4.00 (s, $\frac{W}{2}$ 1.6 c./sec., 2, C-21 methylene protons), 4.15-4.32 (m, 1, C-11 aH), 4.70, 4.77 (2d, $J_{AB}$ 3 c./sec., 2, C-11 methylenedioxy protons), 5.04, 5.04, 5.07, 5.23 (4s, $\frac{W}{2}$ 1.6 c./sec., 4, C-17, 20 bismethylenedioxy protons) and 5.71 (br.s., 1, C-4 olefinic H).

Later eluates yielded 17α,20; 20,21-bismethylenedioxy-11β-hydroxyprog-4-en-3-one (116a, 2.60 g., 33%), which crystallised from ethanol-chloroform as needles, m.p. 218-228° (Lit. 213 m.p. 220-223°), $[\alpha]_D^{25} + 31^0$ ($c = 0.29$ in CHCl$_3$) [Lit. 25 $[\alpha]_D + 26^0$ ($c \sim 1\%$ in CHCl$_3$)].

$\delta$ (CDCl$_3$) 1675 (C-3 conj. C=O str.), 1635 (conj. C=C str.), and 1111 and 945 cm$^{-1}$ (C=O-C asym. and sym. str.).

$\lambda_{max}$ 243 m\(\mu\) (e 13,200).

$\delta$ (CDCl$_3$) 1.13 (s, 3, C-18 Me), 1.47 (s, 3, C-19 Me), 4.02 (s, $\frac{W}{2}$ 1.6 c./sec., 2, C-21 methylene protons), 4.34-4.57 (m, 1, C-11 aH), 5.07, 5.07, 5.07, 5.24 (4s, $\frac{W}{2}$ 1.6 c./sec., 4, C-17, 20 bismethylenedioxy protons) and 5.71 (br.s., 1, C-4 olefinic H).

Treatment of each of the above bismethylenedioxy derivatives
with D.D.O. gave after chromatography on deactivated alumina, 17α, 20; 20, 21-bismethylenedioxy-11β-methoxymethylenoxypregna-1, 4-dien-3-one (119b, 2. 49g., 68%) as needles from ethanol-ether, m.p. 209-214° (Lit. 153 m.p. 217-220°, [α]D^25 -27° (ε = 0.34 in CHCl₃), and 17α, 20; 20, 21-bismethylenedioxy-11β-hydroxypregna-1, 4-dien-3-one(119a, 1. 72g., 68%), which crystallised from ethanol-chloroform to give needles, m.p. 310-320° (Lit. 153 m.p. 270-274°), [α]D^25 -36° (ε = 0.15 in CHCl₃) [Lit. 153 [α]D -20° (ε~1% in CHCl₃)].

3, 20-Dioxopregna-1, 4-diene-11β, 17α, 21-triol 21-acetate(120b) 158

A mixture of 17α, 20; 20, 21-bismethylenedioxy-11β-methoxymethylenoxypregna-1, 4-dien-3-one and 17α, 20; 20, 21-bismethylenedioxy-11β-hydroxypregna-1, 4-dien-3-one(119b and a, 4.16g.) and formic acid (60%, 140 ml.) was heated over a steam bath for 30 min. and gave after work-up 11β, 17α, 21-trihydroxypregna-1, 4-diene-3, 20-dione(120a, 2.35g.). Acetylation of the crude product gave 3, 20-dioxo-pregna-1, 4-diene-11β, 17α, 21-triol 21-acetate(120b, 2.51g., 96%), which crystallised from ethanol-ether, m.p. 241-242° (Lit. 206 m.p. 240-242°), [α]D^25 + 120° (ε = 0.36 in CHCl₃) [Lit. 206 [α]D^24 + 116° (in dioxane)].

3, 20-Dioxopregna-1, 4, 9(11)-triene-17α, 21-diol 21-acetate(118b) 159

3, 20-Dioxopregna-1, 4-diene-11β, 17α, 21-triol 21-acetate(120b,
2.47 g.) was slurried with collidine (5 ml.), and then dimethylformamide (15 ml.) was added. The mixture was cooled to 10° and methanesulphonyl chloride (1.51 ml.) containing sulphur dioxide (3.2%) was added over 2 min. The mixture was allowed to stir at 25-35° for 10 min. and then excess of reagent was destroyed by the gradual addition (1 min.) of water (2.5 ml.). The thin slurry was added gradually to hot water (150 ml.) and the mixture was stirred at 85-90° for 1 hr, cooled to room temperature and filtered. The product was washed, dried (2.15 g., 94%) and recrystallised from acetone to give needles of 3,20-dioxopregna-1,4,9(11)-triene-17α,21-diol 21-acetate (118 b, 1.97 g., 86%), m.p. 216-219° (Lit. 207 m.p. 223-226°), [α]D 25° + 48° (ε = 0.72 in CHCl₃) [Lit. 207 [α]D + 75° (in CHCl₃)].

υ max (CHCl₃) 3440-3360 (OH str.), 3030 (=C–H str.), 1745 (C=OAc C=O str.), 1725 (C–20 C=O str.), 1665 (C=C conj. C=O str.), 1620, and 1605 cm⁻¹ (conj. C=C str. and C-9,11 C=C str.).

λ max (EtOH) 240 μ (ε 12,100).

δ (CDCl₃) 0.66 (s, 3, C-18 Me), 1.42 (s, 3, C-19 Me), 2.18 (s, 3, C-21 OCOCH₃), 4.84, 5.16 (2d, J₂1,21 16 c./sec., 2, C-21 methylene protons), 5.52-5.80 (m, 1, C-11 olefinic H), 6.10 (br.s., 1, C-4 olefinic H), 6.32 (2d, J₂,4 1.5 c./sec., J₂,1 10 c./sec., 1, C-2 olefinic H) and 7.28 (d, J₁,2 10 c./sec., 1, C-1 olefinic H).
3,20-Dioxopregn-4-ene-11β,17α,21-triol 21-acetate(115b)

Acetylation of hydrocortisone(115a, 10 g.) with acetic anhydride-pyridine gave 3,20-dioxopregn-4-ene-11β,17α,21-triol 21-acetate(115b, 10.78 g., 97%) as prisms from aqueous acetic acid, m.p. 214-218° (Lit.\(^{208}\) m.p. 223-225°), \([\alpha]_D^{25} + 151° (\epsilon = 0.34 \text{ in CHCl}_3)\) [Lit.\(^{209}\) \([\alpha]_D^{24} + 158° (\epsilon = 0.6 \text{ in dioxane})\)].

3,20-Dioxopregna-4,9(11)-diene-17α,21-diol 21-acetate(117b)\(^{159}\)

3,20-Dioxopregn-4-ene-11β,17α,21-triol 21-acetate(115b, 10g.) was dehydrated by the procedure described above for 3,20-dioxopregna-1,4-diene-11β,17α,21-triol 21-acetate(120b). The crude product (9.16 g., 96%) was recrystallised from methanol to give needles of 3,20-dioxopregna-4,9(11)-diene-17α,21-diol 21-acetate(117b, 8.63 g., 90%), m.p. 230-232° (Lit.\(^{210}\) m.p. 236-237°), \([\alpha]_D^{25} + 125° (\epsilon = 0.48 \text{ in CHCl}_3)\) [Lit.\(^{210}\) \([\alpha]_D + 117° (\epsilon = 1 \text{ in CHCl}_3)\)].

\(\nu_{\text{max}}\) (Nujol) 3440-3380 (OH str.), 3050 (=C-H str.), 1740 (C-21 OAc C=O str.), 1720 (C-20 C=O str.), 1660-1630 (conj. C=O str. and conj. C=C str.) and 1610 cm\(^{-1}\) (C=C str.).

\(\lambda_{\text{max}}\) (EtOH) 240 mp (\(\epsilon 15,100\)).

\(\delta\) (CDCl\(_3\)) 0.64 (s, 3, C-18 Me), 1.35 (s, 3, C-19 Me), 2.18 (s, 3, C-21 OCOCH\(_3\)), 3.13-3.29 (m, 1, C-17 OH), 4.86, 5.09 (2d, J\(_{21,21}\) 18 c./sec., 2, C-21 methylene protons), 5.51-5.72 (m, 1, C-11 olefinic H) and 5.77 (br.s., 1, C-4 olefinic H).
3,20-Dioxopregna-1,4,9(11)-triene-17α,21-diol 21-acetate(118b)

A solution of D.D.Q. (10g.) in dry benzene (300 ml.) was added to a solution of 3,20-dioxopregna-4,9(11)-diene-17α,21-diol 21-acetate(117b, 10g.) in dry benzene (300 ml.), and the mixture was heated under reflux for 24 hr. Work-up in the usual manner followed by chromatography of the black gummy product on deactivated alumina in chloroform gave 3,20-dioxopregna-1,4,9(11)-triene-17α,21-diol 21-acetate(118b, 3.76g., 38%). Physical constants for this compound are recorded earlier.

20-Oxo-estra-1,3,5(10),9(11)-tetaene-3,17α,21-triol 21-acetate(121b)

A mixture of 3,20-dioxopregna-1,4,9(11)-triene-17α,21-diol 21-acetate(118b, 1.90g.) in pyridine (50 ml.) containing water (1 ml.) and freshly activated zinc dust (37.5g.) was heated under reflux for 25 min. After removal of the zinc dust from the reaction mixture, the filtrate was poured into water, and extracted with ethyl acetate. After washing and drying the extract, evaporation of the solvent left a solid residue which was chromatographed on silica gel in benzene and eluted with benzene-ether (9 : 1) to give 20-oxo-estra-1,3,5(10),9(11)-tetaene-3,17α,21-triol 21-acetate(121b, 1.05g., 57%), m.p. 218-219° (Lit. 155 m.p. 218-219°), [α]D25 + 174° (c = 0.14 in CHCl₃) [Lit. 155 [α]D + 174° (c = 1.21 in CHCl₃)].

υ max (Nujol) 3400-3340 (H-bonded OH str.), 3010 (aromatic CH str.)
1730 (C-21 OAc C=O str.), 1710 (C-20 C=O str.), 1630 (conj. C=C str.), 1615, 1575 (phenyl nucleus), 1290-1220 (C-O-C asym. str.), 1150, 1100, or 1050 (C-O-C sym. str.), 980, 870, 850 and 810 cm⁻¹ (aromatic CH o.o.p.l. def.).

λ_max (EtOH) 263 (ε 18,000) and 298 μ (ε 3000).

3-Hydroxyestra-1,3,5(10),9(11)-tetraen-17-one(29c)²¹¹

Hydrolysis of 20-oxo-estra-1,3,5(10),9(11)-tetraene-3,17α,21-triol 21-acetate(121b, 1g.) with 10% aqueous methanolic hydrochloric acid gave 3,17α,21-trihydroxyestra-1,3,5(10),9(11)-tetraen-20-one (121a), which was then dissolved in acetic acid (20 ml.) and water (20 ml.). Sodium bismuthate (4g.) was added, and the solution was stirred for 6 hr. at 55-60°. After cooling the reaction mixture, the surplus reagent was reduced with 10% sodium bisulphite solution (12 ml.) and after addition of 3N sodium hydroxide solution (40 ml.) the mixture was extracted with ether. The ethereal extract was washed, dried, and concentrated to yield 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one(29c, 465 mg., 64%) as leaflets from ether, m.p. 258-259° (Lit. ²¹² m.p. 257-259°), [α]_D²⁵ + 275° (c = 0.71 in CHCl₃) [Lit. ²¹² [α]_D²⁰ + 257.3°].

υ_max (Nujol) 3260-3280 (H-bonded OH str.), 3020 (aromatic CH str.), 1725 (C-17 C=O str.), 1616 (conj. C=C str.), and 1603, 1590 cm⁻¹ (phenyl nucleus).

λ_max (EtOH) 263 (ε 18,100) and 298 μ (ε 3160).
17-Ethylendioxyandrost-1,4-dien-3-one(35e)\(^{98}\)

A solution of androst-1,4-diene-3,17-dione(35b, 10g.), ethylene glycol (4.86 ml.), and \(p\)-toluenesulphonic acid (0.2g.) in dry benzene (500 ml.) was heated under reflux for 4 hr. with concomitant distillation of benzene (173 ml.). The cooled reaction mixture was made alkaline by the addition of 10% potassium hydroxide solution (3 ml.) and washed with water until neutral. After drying over anhydrous magnesium sulphate, a few drops of pyridine were added and the solvent removed in \(\text{vacuo}\). The product was crystallised from light-petroleum as needles of 17-ethylendioxyandrost-1,4-dien-3-one(35e, 10.20g., 88%), m.p. 172-173\(^{\circ}\) (Lit.\(^{98}\) m.p. 171-172\(^{\circ}\), \([\alpha]_D^{25}\) -11\(^{\circ}\) (\(\varepsilon = 0.71\) in CHCl\(_3\)) [Lit.\(^{98}\) \([\alpha]_D^{0}\) 0\(^{\circ}\) (in dioxane)].

\(\gamma^{\text{max}}\) (CHCl\(_3\)) 1665 (conj. C=O str.), 1620, 1600 (C=O conj. C=C str.), 1160, 1120, 1100, 1090, and 1050 cm\(^{-1}\) (ketal C-O str.).

\(\lambda^{\text{max}}\) (EtOH) 269 mp (15,200).

\(\delta\) (CDCl\(_3\)) 0.93 (s, 3, C-18 Me), 1.24 (s, 3, C-19 Me), 3.87 (s, 4, C-17 ethylendioxy protons), 6.07 (br.s., 1, C-4 olefinic H), 6.20 (2d, \(J_{2,1}\) 10 c./sec., \(J_{2,4}\) 2 c./sec., 1, C-2 olefinic H), 7.07 (d, \(J_{1,2}\) 10 c./sec., 1, C-1 olefinic H).

3-Hydroxyvestra-1,3,5(10)-trien-17-one(4h)\(^{164}\)

A solution of biphenyl (18.6g.) and lithium (953 mg.) in tetrahydrofuran (70 ml., freshly distilled from lithium aluminium
hydride) was stirred and heated under reflux in an atmosphere of nitrogen for 1 hr. The dark green solution was cooled to 35° and a solution of 17-ethylenedioxyandrosta-1,4-dien-3-one (35g, 10g.) and 2-methylnaphthalene (5.86g.) in tetrahydrofuran (70 ml.) was added. The reaction mixture was stirred and heated under reflux for 30 min. and then diluted carefully with 2N-hydrochloric acid. Ether extraction followed by washing, drying, and concentration left a crystalline gummy solid which was chromatographed on silica gel in benzene. Elution with benzene-ether (9 : 1) gave 3-hydroxyestra-1,3,5(10)-tren-17-one (4h, 5.28g., 64%), m.p. 258-260° (Lit.213 m.p. 260°).

3-Hydroxyestra-1,3,5(10),9(11)-treaen-17-one (29c)166

A solution of D.D.Q. (13.86g.) in dry benzene (750 ml.) was added to a solution of estrone (15g.) in dry benzene (750 ml.) and dry methanol (750 ml.) and the mixture was kept at 20° for 15 min., when the initial black solution paled to orange. 5% Sodium bisulphite solution was then added to the reaction mixture, which was diluted with ether, washed, dried and concentrated to yield a yellow solid (10.99g.) which contained some hydroquinone. The crude material was chromatographed in hot benzene on silica gel, and the product eluted with benzene-ether (9 : 1) and (8 : 2) as 3-hydroxyestra-1,3,5(10),9(11)-treaen-17-one (29c, 9.52g., 62%) which crystallised from ether as leaflets, m.p. 258-259° (Lit.182 m.p.
257-259°). Other physical constants for this compound are recorded earlier.

3-Methoxyestra-1,3,5(10),9(11)-tetaen-17-one (84a)

A solution of 3-hydroxyestra-1,3,5(10),9(11)-tetaen-17-one (29c, 8.20g), methanol (33 ml.), and 10% aqueous potassium hydroxide (33 ml.) at 100° was treated in portions with methyl-\textsubscript{p}-toluene sulphonate (10.80g.). After 1 hr further 10% aqueous potassium hydroxide (41 ml.) was added and the solution was kept under reflux for a further hour. The cooled mixture was acidified, ether extracted, and the ether extract was washed, dried, and concentrated to yield a solid which was chromatographed on deactivated alumina in benzene. The eluant, 3-methoxyestra-1,3,5(10),9(11)-tetaen-17-one (84a, 6.23g., 72%) was recrystallised from ethanol-ethyl acetate as needles, m.p. 145-147° (Lit.\textsuperscript{119} m.p. 146-147°), [\(\alpha\)]\textsubscript{D}\textsuperscript{25} + 276° (c = 0.51 in CHCl\textsubscript{3}) [Lit.\textsuperscript{213} [\(\alpha\)]\textsubscript{D} + 299° (in CHCl\textsubscript{3})].

\(\gamma\)\textsubscript{max} (CHCl\textsubscript{3}) 2650 (aromatic OMe str.), 1735 (C-17 C=O str.), 1625 (conj. C=C str.) and 1610, 1570 cm\textsuperscript{-1} (phenyl nucleus).

\(\lambda\)\textsubscript{max} (EtOH) 264 (\(\epsilon 19,900\)) and 298 m\textmu (\(\epsilon 3500\)).

\(\delta\) (CDCl\textsubscript{3}) 0.92 (s, 3, C-18 Me), 2.74-3.06 (m, 2, C-6 benzylic protons), 3.76 (s, 3, aromatic OMe), 6.00-6.24 (m, 1, C-11 olefinic H), 6.60 (br.s., 1, C-4 aromatic H), 6.70 (2d, \(J_{2,1} 8.5\) c./sec., \(J_{2,4} 2.5\) c./sec., 1, C-2 aromatic H) and 7.50 (d, \(J_{1,2} 8.5\) c./sec., 1, C-1 aromatic H).
3-Methoxyestra-1,3,5(10)-trien-17-one (4c)

Methylation of estrone (4h, 2.78 g.) according to the method of Cohen, Cook, and Hewett gave 3-methoxyestra-1,3,5(10)-trien-17-one (4c, 2.56 g., 92%) which crystallized from ethyl acetate as needles, m.p. 168-169° (Lit. 214 m.p. 168-169°, [α]D 25 + 164° (c = 0.44 in CHCl₃) [Lit. 215 [α]D + 160° (c = 1.227 in dioxane)].

υ max (CHCl₃) 3025 (aromatic CH str.), 2840 (CH str. of aromatic OMe), 1735 (C-17 C=O str.), 1610, 1575 (phenyl nucleus), 1250 (C-C str. of C-CO-C) and 1030 cm⁻¹ (=C-O-C sym. str.).

λ max (EtOH) 223 (ε 6530), 280 (ε 1770) and 288 mp (ε 1530).

δ (CDCl₃) 0.88 (s, 3, C-18 Me), 2.78-3.08 (m, 2, C-6 benzylic protons), 3.73 (s, 3, aromatic OMe), 6.70 (d, J 4,2 2.1 c./sec., 1, C-4 aromatic H), 6.75 (2d, J 2,1 8.5 c./sec., J 2,4 2.1 c./sec., 1, C-2 aromatic H) and 7.24 (d, J 1,2 8.5 c./sec., 1, C-1 aromatic H).

3-Methoxyestra-1,3,5(10),9(11)-tretaen-17-one (84a)

A solution of D.D.Q. (1.07 g.) in dry methanol (60 ml.) was added to a solution of 3-methoxyestra-1,3,5(10)-trien-17-one (4c, 2.41 g.) in dry methanol (60 ml.) and the solution was kept at 20° for 15 min. Most of the solvent was removed in vacuo until the product precipitated from the solution. The precipitated product was collected and chromatographed on deactivated alumina in benzene. The required product, with a small amount of highly coloured red
material, was eluted with benzene and crystallised from ethanol-ethyl acetate as leaflets of pink-coloured 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (84a, 1.57g., 66%), m.p. ranging from 142-161°. T.l.c. showed some starting material still present. Physical constants for this compound are recorded earlier.

Oxidation of 3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-one (84a)

A solution of 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (2.5g.) in acetone (625 ml.) was treated dropwise at -18° with 4N chromium trioxide in 40% aqueous sulphuric acid (53.1 ml.) and the mixture was allowed to come to room temperature over 11 hr. Work-up in the usual manner (p. 93-99) yielded a pale yellow neutral gum (1.32g., 53%) and a brown acidic gum (1.56g., 62%).

Chromatography of the neutral fraction in benzene on silica gel and elution with benzene-ether (19 : 1) followed by preparative t.l.c. gave 9β-hydroxy-3-methoxyestra-1,3,5(10)-trien-11,17-dione (16a, 649 mg., 23%) which crystallised from ether as needles, m.p. 132-133° (Lit.14 m.p. 132-133°), [α]D^25 + 205° (c = 0.76 in CHCl₃) [Lit.14 [α]D + 176° (c = 0.10 in CHCl₃)].

υ max (CHCl₃) 3490-3450 (intermol. H-bonded OH str.), 3030, 3010 (aromatic CH str.), 1745 (C-17 C=O str.), 1709 (C-11 C=O str.), 1610, 1575 (phenyl nucleus), 1255 (=C-O-C antisym. str.), 1235-1200 (br. C-C str. of C-CO-C) and 1035 cm⁻¹ (=C-O-C sym.str.).
\( \lambda_{\text{max}} \) (EtOH) 227 (\( \epsilon 10,000 \)), 277 (\( \epsilon 1470 \)) and 284 nm (\( \epsilon 1360 \)).
\( \delta \) (CCl\(_4\)) 0.85 (s, \( \frac{1}{2} \)), 2.8 c./sec., 3, C-18 Me), 2.22 (d, J = 12.8 c./sec., 1, C-12 \( \alpha \)H which shows further fine splitting due to coupling with C-19 Me), 2.57 (d, J = 12.8 c./sec., 1, C-12\( \beta \)H), 2.66–3.00 (m, 2, C-6 benzylic protons), 3.75 (s, 3, aromatic OMe), 4.05 (s, 1, C-11 OH) and 6.64 (s, 3, C-1, C-2 and C-4 aromatic protons).

Also isolated was a small amount of 9\( \beta \)-hydroxy-3-methoxy-estra-1,3,5(10)-triene-6,11,17-trione(17a, 18mg., 0.60%).

\( \psi_{\text{max}} \) 3490–3440 (intermol. H-bonded OH str.), 3020, 3010 (aromatic CH str.), 1745 (C-17 C=O str.), 1712 (C-11 C=O str.), 1690 (C-6 aromatic C=O str.), and 1605, 1580 cm\(^{-1}\) (phenyl nucleus).

\( \delta \) (CDCl\(_3\)) 0.96 (s, 3, C-18 Me), 4.00 (s, 3, aromatic OMe) and 6.94–8.04 (m, 3, C-1, C-2 and C-4 aromatic protons).

Chromatography of the acidic fraction yielded 9,17-dioxo-3-methoxy-9,11-secoestra-1,3,5(10)-trien-11-oic acid(15a, 893 mg., 31%) which crystallised from aqueous methanol as needles, m.p. 158–160\(^{\circ} \) (Lit.\(^{14}\) m.p. 158–160\(^{\circ} \)), [\( \alpha \)]\(_D\)\(^{25} \) - 89\(^{\circ} \) (\( C = 0.13 \) in CHCl\(_3\))

[Lit.\(^{14}\) [\( \alpha \)]\(_D\)\(^{25} \) - 82\(^{\circ} \) (\( C = 0.23 \) in CHCl\(_3\))].

\( \psi_{\text{max}} \) (CHCl\(_3\)) 3460–2500 (br. OH str. of H-bonded COOH), 1725 (C-17 C=O str.), 1703 (C=O str. of COOH), 1670 (C-9 C=O str.), 1600, 1575 (phenyl nucleus), 1260-1200 (=C-O-C asym. str. and C-C str. of C-CO-C) and 1020 cm\(^{-1}\) (=C-O-C sym. str.).
\( \lambda_{\text{max}} \) (EtOH) 212 (\( \varepsilon \) 11,600), 227 (\( \varepsilon \) 11,700) and 277 mp (\( \varepsilon \) 15,500).

\( \delta \) (CDCl\(_3\)) 0.99 (s, 3, C-18 Me), 2.82-3.00 (m, 2, C-12 protons or C-6 benzylic protons), 3.84 (s, 3, aromatic OMe), 6.65 (d, J\(_{4,2}\) 2 c./sec., 1, C-4 aromatic H), 6.78 (2d, J\(_{2,4}\) 8.5 c./sec., J\(_{1,2}\) 2 c./sec., 1, C-2 aromatic H) and 7.92 (d, J\(_{1,2}\) 8.5 c./sec., 1, C-1 aromatic H).

Preparation of 3-Methoxyestra-1,3,5(10),9(11)-tetraen-17β-yl Acetate\(^{84b}\)

11β-Hydroxyandrost-4-ene-3,17-dione(125a)

Hydrocortisone(115a, 10g.) was dissolved in acetic acid (200 ml.) and water (200 ml.). Sodium bismuthate (40g.) was added, and the solution was stirred for 6 hr. at 55-60°. After cooling, the surplus reagent was reduced with 10% sodium bisulphite solution (120 ml.), and after addition of 3N sodium hydroxide solution (400 ml.) the mixture was extracted with ether. The ether extract was washed, dried, and concentrated to yield a crystalline solid (6.57g., 79%) which was chromatographed on deactivated alumina in benzene and eluted with benzene-ether (9 : 1) and (8 : 2). Repeated chromatography gave androst-4-ene-3,11,17-trione(125b, 658 mg., 8%) which crystallised from ethanol as plates, m.p. 221-223° (Lit.\(^{217}\) m.p. 220-221°), [\( \alpha \)]\(_D\)\(^{25} + 288° \) (\( \varepsilon \) = 0.64 in CHCl\(_3\)) [Lit.\(^{217}\) [\( \alpha \)]\(_D\) + 271.3° (2.4% in acetone)].
Later benzene-ether eluates gave 11β-hydroxyandrost-4-ene-3,17-dione (125a, 5.57g., 67%) which crystallised from benzene, m.p. 201-202° (Lit. m.p. 195-197.5°), [α]D^25^25 + 204° (ε = 0.62 in CHCl₃) [Lit. m.p. 195-197.5°, [α]D + 219° (ε = 1.30 in CHCl₃)].

υₘₐₓ(CHCl₃) 3460-3420 (intermol. H-bonded OH str.), 1740 (C-17 C=O str.), 1665 (conjug. C=O str.) and 1620 cm⁻¹ (conjug. C=C str.).

λₘₐₓ(EtOH, Cary) 240 mp (ε 13,200).

δ(CDCl₃) 1.15 (s, 3, C-18 Me), 1.46 (s, 3, C-19 Me), 4.31-4.53 (m, 1, C-11 αH) and 5.65 (br.s., 1, C-4 olefinic H).

11β,17β-Dihydroxyandrost-4-en-3-one (127a)^172

A solution of 11β-hydroxyandrost-4-ene-3,17-dione (125a, 19.05g.) in dry tetrahydrofuran (1036 ml.) was added dropwise to a solution of lithium aluminium hydride (19.46g.) in dry tetrahydrofuran (1036 ml.), and the mixture was heated under reflux for 30 min. The cooled, stirred reaction mixture was then treated dropwise with water (20 ml.), 15% sodium hydroxide solution (20 ml.), and water (58 ml).^217^2 The precipitate was removed by filtration, washed with ethyl acetate and the filtrate was evaporated in vacuo. The solid material remaining (19.37g.) was composed mostly of androst-4-ene-3β,11β,17β-triol (126).

υₘₐₓ(Nujol) 3460-3120 cm⁻¹ (H-bonded OH str.) and lack of carbonyl peaks.
The crude reduction product (17.25g.) was stirred with activated manganese dioxide (172.5g.; prepared by the method of Attenburrow et al.⁷) in chloroform (1.725 l.) at 20° for 6 hr. The manganese dioxide was filtered, washed thoroughly with further chloroform, and the solvent was removed to yield a solid (16.42g.) which was crystallised from acetone to give 11β,17β-dihydroxyandrost-4-en-3-one(127a, 8.19g., 49%) as needles, m.p. 230-234° (Lit. 172 m.p. 232-234°), [α]D²⁵ + 143° (c = 0.21 in CHCl₃) [Lit. 172 [α]D²⁰ + 155°].

ν max (Nujol) 3500-3200 (intermol. H-bonded OH str.), 1660 (conj. C=O str.) and 1610 cm⁻¹ (conj. C=C str.).

λ max (EtOH) 244 μ (ε 15,100).

Repeated chromatography of the solid (8.23g.) obtained from the mother liquors on deactivated alumina in benzene, and elution with benzene, benzene-ether(9 : 1), (8 : 2), ... (2 : 8), gave further oxidised products:

11β-Hydroxyandrost-4-ene-3,17-dione(125a, 2.22g., 12%) was crystallised from benzene as needles, m.p. 196-198° (Lit. 161 m.p. 195-197.5°). Other physical constants for this compound are recorded earlier.

17β-Hydroxyandrost-4-ene-3,11-dione(128, 1.29g., 7%) crystallised from ethanol-light petroleum as needles, m.p. 184-189° (Lit. 172 m.p. 183-184°), [α]D²⁵ + 208° (c = 0.78 in CHCl₃) [Lit. 172
$[\alpha]_D^{20} + 210^\circ$ (in CHCl$_3$).  
$\nu_{\text{max}}$ (CHCl$_3$) 3470-3370 (intermol. H-bonded OH str.), 1710 (C-11 C=O str.), 1665 (C-3 conj. C=O str.) and 1615 cm$^{-1}$ (conj. C=C str.).

$\lambda_{\text{max}}$ (EtOH) 239 mp. ($\varepsilon$ 13,200).

$\delta$ (CDCl$_3$) 0.73 (s, 3, C-18 Me), 1.40 (s, 3, C-19 Me), 3.13 (br.s., 1, C-17 OH), 3.64-4.03 (m, 1, C-17 aH) and 5.68 (br.s., 1, C-4 olefinic H).

More of the required product (127a, 2.76g., 16%) was also obtained.

These higher oxidised products were treated with lithium aluminium hydride and reoxidised with activated manganese dioxide.

3-Oxo-androst-4-ene-11$\beta$,17$\beta$-diol 17-acetate (127b)

11$\beta$,17$\beta$-Dihydroxyandrost-4-en-3-one (127a, 14.77g.) was acetylated in the usual manner with acetic anhydride-pyridine ($20^\circ$, 72 hr.), and the resulting solid, which still contained some starting material, was chromatographed on deactivated alumina in benzene. The product was eluted with benzene-ether (19 : 1) and was crystallised from light petroleum-ether to give needles of 3-oxo-androst-4-ene-11$\beta$,17$\beta$-diol 17-acetate (127b, 11.68g., 71%), m.p. 166-169$^\circ$ (Lit. $^{172}$ m.p. 149-150$^\circ$), $[\alpha]_D^{25} + 115^\circ$ ($\varepsilon$ = 0.71 in CHCl$_3$) [Lit. $^{172}$ $[\alpha]_D^{20} + 123^\circ$ (in CHCl$_3$)].

$\nu_{\text{max}}$ (CHCl$_3$) 3520-3420 (intermol. H-bonded OH str.), 1725 (C-17
OAc C=O str.), 1665 (conj. C=O str.), 1630 (conj. C=C str.) and
1270-1210 cm⁻¹ (OAc C-O-C asym. str.).

λ_max (EtOH) 242 μ (ε 12,300).

δ (CCl₄) 1.02 (s, 3, C-18 Me), 1.43 (s, 3, C-19 Me), 1.97 (s, 3,
C-17 OCOCH₃), 2.58 (br.s., 1, C-11 OH), 4.22-4.64 (m, 2, C-11 αH
and C-17 αH) and 5.55 (br.s., 1, C-4 olefinic H).

3-Oxo-androsta-1,4-diene-11β,17β-diol 17-acetate(127c)²⁹

A solution of D.D.Q. (11.92g.) in dry dioxane (225 ml.) was
added to a solution of 3-oxo-androst-4-ene-11β,17β-diol 17-acetate
(127b, 11.52g.) in dry dioxane (225 ml.) and the mixture was
heated under reflux for 5.5 hr. Work-up in the usual manner and
chromatography on deactivated alumina in benzene gave 3-oxo-androsta-
1,4-diene-11β,17β-diol 17-acetate(127c, 7.93g., 69%) as slabs from
light petroleum-benzene, m.p. 167-169.5⁰, [α]D²⁵ +95⁰ (ε = 1.14 in
CHCl₃). A sample prepared for analysis had m.p. 190-192⁰ (Found:
C, 73.4; H, 8.1. C₂₁H₂₈O₄ requires C, 73.2; H, 8.2%).

ν_max (CHCl₃) 3500-3400 (intermol. H-bonded OH str.), 1725 (C-17
OAc C=O str.), 1670 (conj. C=O str.), 1625, 1620 (conj. C=C str.)
and 1270-1210 cm⁻¹ (OAc asym. C-O-C str.).

λ_max (EtOH) 245 μ (ε 13,800).

δ (CDCl₃) 1.10 (s, 3, C-18 Me), 1.48 (s, 3, C-19 Me), 2.03 (s, 3,
C-17 OCOCH₃), 2.63-2.87 (m, 1, C-11 OH), 4.30-4.69 (m, 1, C-17 αH),
6.02 (br.s., 1, C-4 olefinic H), 6.23 (2d, J₂,₁ 10 c./sec., J₂,₄
2 c./sec., 1, C-2 olefinic H) and 7.34 (d, J_{1,2} 10 c./sec., 1, C-1 olefinic H).

3-Oxo-androsta-1,4,9(11)-trien-17β-yl acetate(129a)

A solution of 3-oxo-androsta-1,4-diene-11β,17β-diol 17-acetate(127c, 7.82 g.), p-toluenesulphonyl chloride (18.84 g.), and dimethylformamide (57 ml.) was stirred and cooled to 10°, and collidine (19 ml.) was added. The solution was allowed to come to room temperature and was then treated with dimethylformamide (2.83 ml.) containing sulphur dioxide (4.7% by weight). The slurry went dark yellow-orange and the temperature rose quickly to 36°. 5 Min. after the temperature had reached 25° the excess of p-toluenesulphonyl chloride was decomposed by the slow addition of water (13.4 ml.). The clear red solution was added slowly to water (570 ml.) and the mixture was stirred at 25° for 1 hr, extracted with ether, and the ether extract was washed, dried, concentrated and chromatographed on a dry column of alumina (Grade III), which was developed with ether. Crystallisation of the appropriate fractions from light petroleum-ether gave 3-oxo-androsta-1,4,9(11)-trien-17β-yl acetate(129a, 5.39 g., 73%) as needles, m.p. 141-143° (Lit. m.p. 135°), [α]_D^{25} - 20° (c = 0.16 in CHCl₃) [Lit. [α]_D^{181} - 26° (in CHCl₃)].

υ max (CHCl₃) 1740 (C=O Ac C=O str.), 1655 (conj. C=O str.), 1630, 1610 (conj. C=C str.) and 1255-1235 cm⁻¹ (OAc asym. C-O-C str.).
$\lambda_{\text{max}}$ (EtOH) 238 mp ($\varepsilon$ 13,400).

$\delta$ (CDCl$_3$) 0.80 (s, 3, C-18 Me), 1.41 (s, 3, C-19 Me), 2.03 (s, 3, C-17 OCOCH$_3$), 4.50-4.80 (br.t., 1, C-17 aH), 5.42-5.63 (br.t., 1, C-11 olefinic H), 6.03 (br s., 1, C-4 olefinic H), 6.22 (2d, J$_{2,1}$ 10 c./sec., J$_{2,4}$ 2 c./sec., 1, C-2 olefinic H) and 7.17 (d, J$_{1,2}$ 10 c./sec., 1, C-1 olefinic H).

Estra-1,3,5(10),9(11)-tetraene-3,17β-diol 17-acetate(130a)$^{155}$

A mixture of 3-oxo-androsta-1,4,9(11)-trien-17β-yl acetate (123a, 5.15g.), pyridine (206 ml.), water (2 ml.), and freshly activated zinc dust (85.3g.) was heated under reflux for 25 min. The zinc dust was removed by filtration and the filtrate poured into water and extracted with ethyl acetate. After washing and drying the extract, evaporation of the solvent left a solid residue which was absorbed on alumina (Grade III) and was subjected to dry column chromatography with chloroform. Extraction of the appropriate fractions and crystallisation from methanol-ether gave estra-1,3,5(10),9(11)-tetraene-3,17β-diol 17-acetate(130a, 2.34g., 47%) as needles, m.p. 209-211°, $[\alpha]_D^{25} + 82^0$ (c = 0.64 in CHCl$_3$), (Found: C, 76.6; H, 7.3; O, 15.6. C$_{20}$H$_{24}$O$_3$ requires C, 76.9; H, 7.7; O, 15.4%).

$\gamma_{\text{max}}$ (CHCl$_3$) 3400-3200 (intermolecular H-bonded OH str.), 3040, 3020 (aromatic CH str.), 1725 (C-17 OAc C=O str.), 1630 (conj. C=C str.), 1605, 1580 (phenyl nucleus), 1270-1210 (OAc asym. C=O-C str.) and
885, 860 cm\(^{-1}\) (arom. C-H o.o.pl. def. pattern for 2 and 1 isolated Hg).

\(\lambda_{\text{max}}\) (EtOH, Cary) 263 (\(\varepsilon\) 19,600) and 300 mp (\(\varepsilon\) 3210).

\(\delta\) (CDCl\(_3\)) 0.82 (s, 3, C-18 Me), 2.08 (s, 3, C-17 OCOCH\(_3\)), 2.67-2.07 (m, 2, C-6 benzylic protons), 4.62-4.90 (m, 1, C-17 CH), 5.95-6.13 (m, 1, C-11 olefinic H), 6.54 (br.s., 1, C-4 aromatic H), 6.61 (2d, \(J_{2,1}\) 9 c./sec., \(J_{2,4}\) 2.5 c./sec., 1, C-2 aromatic H) and 7.43 (d, \(J_{1,2}\) 9 c./sec., 1, C-1 aromatic H).

3-Methoxyestra-1,3,5(10),9(11)-tetraen-17β-yl acetate

Estra-1,3,5(10),9(11)-tetraene-3,17β-diol 17-acetate(130a, 2g.) and potassium (1.4g.) in sodium-dried benzene (100 ml.) were heated under reflux for 3 hr. Methyl iodide (4.78 ml.) was added and heating under reflux was continued a further 3 hr. The solution was cooled, filtered, and the solvent was removed in vacuo to yield 3-methoxyestra-1,3,5(10),9(11)-tetraen-17β-yl acetate(84b, 1.99g., 95%) which crystallised from light petroleum-ether as needles, m.p. 116-118\(^{0}\), \([\alpha]_{D}^{25} + 46^{0}\) (\(\varepsilon\) = 0.27 in CHCl\(_3\)).

\(\gamma_{\text{max}}\) (CCl\(_4\)) 3040 (aromatic CH str.), 2850 (aromatic OMe sym. str.), 1735 (C-17 OAc C=O str.), 1625 (conj. C=C str.), 1605, 1570 (phenyl nucleus) and 1225 cm\(^{-1}\) (OAc asym. C-O=C str.).

\(\lambda_{\text{max}}\) (EtOH) 264 (\(\varepsilon\) 19,600) and 299 mp (sh., \(\varepsilon\) 3670).

\(\delta\) (CCl\(_4\)) 0.79 (s, 3, C-18 Me), 1.99 (s, 3, C-17 OCOCH\(_3\)), 2.64-2.93 (m, 2, C-6 benzylic protons), 3.69 (s, 3, C-3 aromatic OMe), 4.51-
4.83 (m, 1, C-17 oH), 5.85-6.07 (m, 1, C-11 olefinic H), 6.44 (br.s., 1, C-4 aromatic H), 7.03 (2d, J_{2,1} 9 c./sec., J_{2,4} 2.5 c./sec., 1, C-2 aromatic H) and 7.36 (d, J_{1,2} 9 c./sec., 1, C-1 aromatic H).

Oxidation of 3-Methoxyestra-1,3,5(10),9(11)-tetraen-17β-yl acetate(84b)

A solution of 3-methoxyestra-1,3,5(10),9(11)-tetraen-17β-yl acetate (2g.) in acetone (500 ml.) was treated dropwise at -18° with 4N chromium trioxide in 40% aqueous sulphuric acid (42.50 ml.), and the mixture was allowed to come to 20° over 4 hr. Work-up in the usual manner (p.98-99) gave a yellow neutral oil (1.2g., 63%) and an acidic solid (1.02g., 51%).

Chromatography of the neutral fraction on silica gel in benzene, and elution with benzene-ether (43 : 1) yielded 3-methoxy-11-oxo-estra-1,3,5(10)-triene-3β,17β-diol 17-acetate(16b, 800 mg., 37%) as a colourless oil, [α]_{D}^{25} + 75° (c = 0.64 in CHCl₃, [Lit. 14 [α]_{D}^{25} + 92° (c = 0.42 in CHCl₃)].

ν max (CHCl₃) 3460 (H-bonded OH str.), 3030 (aromatic CH str.), 1730 (OAc C=O str.), 1728 (C-11 C=O str.), 1610, 1575 (phenyl nucleus), 1240 (C-C str. of C-C=O-C) and 1035 cm⁻¹ (C-O-C sym. str.).

λ max (EtOH) 220 (ε 8300), 276 (ε 1800) and 203 με (ε 1660).

δ (CDCl₃) 0.83 (s, W₂ 2 c./sec., 3, C-18 Me), 2.04 (s, 3, C-17 OCOCH₃), 2.33 (d, J_{AB} 12.8 c./sec., 1, C-12 oH which shows further
splitting due to coupling with C-18 Me), 2.59 (d, J_{AB} 12.8 c./sec., 1, C-12 βH), 2.66-2.98 (m, 2, C-6 benzyllic protons), 3.80 (s, 3, aromatic OMe), 4.48 (s, 1, C-9 OH), 4.56-4.92 (m, 1, C-17 αH) and 6.76 (s, 3, C-1, C-2, and C-3 aromatic protons).

The acidic fraction was absorbed on silica gel in benzene and eluted with benzene-ether (9:1) to give 17β-acetoxy-3-methoxy-9-oxo-9,11-secoestra-1,3,5(10)-trien-11-oic acid (15b, 800 mg., 35%) which crystallised as needles from ether, m.p. 141-143° (Lit. 13 m.p. 145°), [α]_{D}^{25} = -20° (c = 0.50 in CHCl₃) [Lit. 14 [α]_{D} = -13° (c = 0.77 in EtOH)].

ν_{max} (CHCl₃) 3520-2560 (br. OH str. of H-bonded COOH), 1730 (C-17 OAc C=O str.), 1708 (carboxylic C=O str.), 1670 (conj. C=O str.), 1605, 1580 (phenyl nucleus), 1270-1200 (C-3 str. of COOH coupled with OH i. pl. str., and asym. C-O-C OAc str.).

λ_{max} (EtOH, Cary) 203 (ε 22,500), 224 (ε 14,100) and 247 μ (ε 18,600).

δ (CDCl₃) 1.10 (s, 3, C-18 Me), 1.99 (s, 3, C-17 OCOCH₃), 2.51-2.74 (m, 2, C-6 benzyllic protons), 2.83-3.14 (m, 2, C-12 protons), 3.88 (s, 3, aromatic OMe), 4.92-5.28 (m, 1, C-17 αH), 6.73 (d, J_{4,2} 2 c./sec., 1, C-4 aromatic H), 6.85 (2d, J_{2,1} 8.6 c./sec., J_{2,4} 2 c./sec., 1, C-2 aromatic H), 8.00 (d, J_{1,2} 8.6 c./sec., 1, C-1 aromatic H) and 8.89 (s, 1, COOH).
Preparation of 3-Methoxyestra-1,3,5(10),3(11)-tetraene (84c)

3-Methoxyestra-1,3,5(10)-triene (4e)

Estra-1,3,5(10)-trien-3-ol (4i, 6.24 g.), potassium (7.24 g.), and dry benzene (363 ml.) were heated under reflux for 3 hr. Methyl iodide (21.8 ml.) was added and the mixture heated under reflux for a further 3 hr. The solution was cooled, filtered and the solvent removed in vacuo to yield a solid which was dry column chromatographed on alumina. The column was developed with light petroleum and the product rechromatographed several times to yield 3-methoxyestra-1,3,5(10)-triene (4e, 5.37 g., 82%) which crystallised from ethanol-ether as prisms, m.p. 77-78°C (Lit. 184 m.p. 76.5°C), $[a]_{D}^{25} + 90°$ (c = 0.73 in CHCl₃) [Lit. 184 $[a]_{D}^{25} + 85°$].

υ max (CS₂) 3080, 3060, 3040, 3020 (aromatic CH str.), 1605, 1575 (phenyl nucleus), 1255 or 1235 (C-O-C asym. str.), 1035 (C-O-C sym. str.) and 870 cm⁻¹ (isolated aromatic H o. o. pl. def.).

λ max (cyclohexane) 225 (ε 7000), 275 (ε 3800) and 286 mp (ε 3550).

δ (CCl₄) 0.75 (s, 3, C-18 Me), 2.74-3.02 (m, 2, C-6 benzylic protons), 3.74 (s, 3, aromatic OMe), 6.65 (br.s., 1, C-4 aromatic H), 6.73 (2d, J₂, 1 8.6 c./sec., J₂, 4 2.6 c./sec., 1, C-2 aromatic H) and 7.26 (d, J₁, 2 8.8 c./sec., 1, C-1 aromatic H).

The minor product 3-methoxy-4-methyl estra-1,3,5(10)-triene (131, 105 mg., 1.5%) was crystallised from ethanol-acetone as needles,
m.p. 136-138°, $[\alpha]_D^{25} + 31^o$ (c = 0.14 in CHCl₃) (Found: C, 84.8; H, 10.2. C₂₀H₂₅O requires C, 84.45; H, 9.9%).

$\gamma$ max (CHCl₃) 3080, 3040, 3010 (aromatic CH str.), 1590, 1580 (phenyl nucleus), 1255 (C-O-C asym. str.) and 1090 cm⁻¹ (sym. C-O-C str.).

$\lambda$ max (EtOH) 208 (ε 14,100), 225 (ε 5160) and 282 μ (ε 930).

δ (CDCl₃) 0.72 (s, 3, C-18 Me), 2.09 (s, 3, C-4 aromatic Me), 2.61-2.87 (m, 2, C-6 benzylic protons), 3.77 (s, 3, aromatic OMe) and 6.68 and 7.01 (2d, J 8.5 c./sec., 2, C-1 and C-2 aromatic protons).

Dehydrogenation of 3-Methoxyestra-1,3,5(10)-triene(4e) with D.D.Q. 166,168

A solution of D.D.Q. (2.95g.) in dry benzene (80 ml.) was added to a solution of 3-methoxyestra-1,3,5(10)-triene(2.17g.) in dry benzene (80 ml.), and the mixture was kept at room temperature for 30 min. The solution was filtered and then poured through deactivated alumina (packed in light petroleum) and concentrated in vacuo to a yellow brown oil. T.l.c. showed that there was still starting material present besides two other more polar compounds. Chromatography on deactivated alumina yielded starting material (360 mg., 17%) and starting material-product mixtures (660 mg.). This material and further starting material (0.67g.) was treated again with D.D.Q. (0.84g.; 1 : 1 molar ratio). T.l.c. indicated that the starting material : product ratios appeared unchanged both
after 24 hr. at 20° and 24 hr. at 80°, and when a further equivalent
of D.D.O. was added. Chromatography on deactivated alumina in light
petroleum-benzene(9:1) gave starting material(4e, 196 mg., 20%)
and mixtures of starting material and 3-methoxyestra-1,3,5(10),9(11)-
tetraene(84c) (194 mg., 19%). Physical constants for 3-methoxyestra-
1,3,5(10),9(11)-tetraene(84c) are recorded later.

Later light petroleum-benzene eluates gave 3-methoxy-12-
methyl-18-norestra-1,3,5(10),8,11,13-hexaene(138, 50 mg., 5%) which
crystallised from ethanol-ether as plates, m.p. 94-96°, [α]_D^{25} 0° (c
= 0.94 in CHCl_3) [Found: C, 86.1; H, 7.9; O, 6.5%; M.W. (mass.
spec.), 264.1510. C_{19}H_{20}O requires C, 86.3; H, 7.6; O, 6.1%; M.W.
264.1514].

υ_{max} (CCl_4) 3030, 3010 (aromatic CH str.), 1605, 1570 (phenyl
nucleus) and 1240 and 1045 cm^{-1} (C=O asym. and sym. str.).

λ_{max} 283 μm (ε 20,900).

δ (CCl_4) 1.84-2.34 (m, 2, C-16 protons), 2.20 (s, 3, C-12 aromatic
Me), 2.53-3.04 (m, 8, C-6, C-7, C-15 and C-17 benzylic protons),
3.67 (s, 3, C-3 aromatic OMe), 6.57 (br.s., 1, C-4 aromatic H),
6.67 (2d, J_{2,1} 3 c./sec., J_{2,4} 2.5 c./sec., 1, C-2 aromatic H),
7.16 (s, 1, C-11 aromatic H), and 7.48 (d, J_{1,2} 9 c./sec., 1, C-1
aromatic H).

Later light petroleum-benzene eluates gave 3-methoxy-12-
methyl-18-norestra-1,3,5,7,9,11,13-heptaene(139, 162 mg., 17%),
which crystallised from light petroleum-ether as needles, m.p. 146-
148°, \([\alpha]_D^{25} + 5^\circ\ (c = 0.54\text{ in CHCl}_3)\).

\(\nu_{\text{max}}\text{ (CCl}_4\text{) 3050-3030 (aromatic CH str.)}, 1615, 1600 \text{ (phenyl}
\text{nucleus) 1250 or 1200 \text{ (C-O-C asym. str.) and 1035 cm}^{-1}\text{ (sym. C-O-C }
\text{str.)}.\)

\(\lambda_{\text{max}}\text{ (EtOH) 212 (log }\varepsilon\text{ 4.50), 228 (log }\varepsilon\text{ 4.42), 236.5 (log }\varepsilon\text{ 4.39),}
262 (log }\varepsilon\text{ 5.05), 282 (log }\varepsilon\text{ 4.32), 293 (log }\varepsilon\text{ 4.18), 306 (log }\varepsilon\text{ 4.03), 320 (log }\varepsilon\text{ 3.89), 341.5 (log }\varepsilon\text{ 3.86) and 355 m}\mu\text{ (log }\varepsilon\text{ 3.91).}
\delta\text{ (CDCl}_3\text{) 1.85-2.67 (m, 2, C-16 protons), 2.46 (s, 3, C-12 aromatic}
\text{Me), 2.87-3.48 (m, 4, C-15 and C-17 protons), 3.93 (s, 3, C-3}
\text{aromatic OMe), 7.23 (br.s., 1, C-4 aromatic H), 7.23 (2d, J}_{2,1}
10 \text{ c.}/\text{sec.}, J}_{2,4} 2.2 \text{ c.}/\text{sec.}, 1, \text{C-2 aromatic H), 7.63 (s, 2, C-6}
\text{and C-7 aromatic protons), 8.19 (s, 1, C-11 aromatic H), and 8.54}
(d, J_{1,2} 10 \text{ c.}/\text{sec.}, 1, C-1 aromatic H).\)

Mixtures of 3-methoxy-12-methyl-18-norestra-1,3,5(10),8,11,
13-hexaene(138) and 3-methoxy-12-methyl-18-norestra-1,3,5,7,9,11,
13-heptaene(139) accounted for 14%(138 mg.) of the product.

Dehydrogenation of 3-Methoxyestra-1,3,5(10)triene(4e) with
Chloranil\textsuperscript{187}

A solution of chloranil (6.44g.) in dry dioxane (84 ml.) was
added to a solution of 3-methoxyestra-1,3,5(10)-triene (2.7g.) in
dry dioxane (84 ml.) and the solution was heated under reflux for
6 hr. The hydroquinone was removed by filtration, the solvent removed in vacuo, and the black gum chromatographed on deactivated alumina in light petroleum-benzene. Elution of the column with light petroleum-benzene (9 : 1) gave starting material (4e, 468 mg., 17%) and a mixture of starting material and 3-methoxyestra-1,3,5(10), 9(11)-tetrane(84c) (500 mg., 19%). Preparative t.l.c. of later fractions gave 3-methoxy-12-methyl-18-norestra-1,3,5(10),8,11,13-hexaene(138, 500 mg., 19%) and a mixture of this compound and the related steroidal phenanthrene(139) \( \sim 2 : 1 \) (340 mg., 13%).

Dehydrogenation of 3-Methoxy-12-methyl-18-norestra-1,3,5(10),8, 11,13-hexaene(138) with D.D.O. 187

A solution of 3-methoxy-12-methyl-18-norestra-1,3,5(10),8,11, 13-hexaene (559 mg.) and D.D.O. (1.68 g.) in dioxane (14 ml.) was kept at 20° for 20 hr., and then diluted with ether, filtered, and chromatographed on alumina. Starting material (138) and 3-methoxy-12-methyl-18-norestra-1,3,5,7,9,11,13-heptaene(139) were obtained in a ratio \( \sim 1 : 2 \) (t.l.c.), (314 mg., 56%).

11β-Hydroxyandrosta-1,4-diene-3,17-dione(125c) 89

A solution of D.D.O. (39.4 g.) in dioxane (700 ml.) was added to a solution of 11β-hydroxyandrost-4-ene-3,17-dione(125a, 35 g.) in dioxane (700 ml.), and the mixture was heated under reflux for 6 hr.
Work-up of the product in the usual manner and chromatography on deactivated alumina in benzene gave from benzene-ether (9 : 1) eluates 11β-hydroxyandrosta-1,4-diene-3,17-dione(125c, 19.53g., 56%), which crystallised from light petroleum-ether as needles, m.p. 178-180° (Lit.219 m.p. 181-182°), [α]D25 + 130° (c = 1.17 in CHCl₃) [Lit.182 [α]D25 + 138° (in acetone)].

υmax (CHCl₃) 3480-3420 (H-bonded OH str.), 1735 (C=17 C=O str.), 1665 (conj. C=O str.) and 1620, 1600 cm⁻¹ (conj. C=C str.).

λmax (EtOH) 242 mp (ε 15,200).

δ (CDCl₃) 1.21 (s, 3, C-18 Me), 1.52 (s, 3, C-19 Me), 2.74-3.00 (m, 1, C-11 OH), 4.39-4.62 (m, 1, C-11 aH), 6.03 (br.s., 1, C-4 olefinic H), 6.26 (2d, J₂,1 10 c./sec., J₂,4 2 c./sec., 1, C-2 olefinic H) and 7.37 (d, J₁,2 10 c./sec., 1, C-1 olefinic H).

Androsta-1,4-diene-3,11,17-trione(125d, 814 mg.) was also eluted from the column and crystallised from diethyl ether as plates, m.p. 194-196° (Lit.219 m.p. 195-196°), [α]D25 + 244° (c = 0.41 in CHCl₃) [Lit.219 [α]D + 230° (in acetone)].

υmax (CHCl₃) 3020 (C=C C-H str.), 1745 (C-17 C=O str.), 1715 (C=11 C=O str.), 1660 (conj. C=O str.) and 1620, 1605 cm⁻¹ (conj. C=C str.).

λmax (EtOH) 243 (ε 15,100) and 295 mp (ε 1020).

This product arises from the use of the crude material from oxidation of hydrocortisone with sodium bismuthate, without prior chromatography.
Androsta-1,4,9(11)-triene-3,17-dione(129b)\textsuperscript{159}

11β-Hydroxyandrosta-1,4-diene-3,17-dione(125c, 7.55g.) was dehydrated with methanesulphonyl chloride in conjunction with sulphur dioxide\textsuperscript{159} as described above for 3,20-dioxopregna-1,4-diene-11β,17α,21-triol 21-acetate(120b). Crystallisation of the product from ether and chromatography of the mother liquors on deactivated alumina followed by elution with benzene-ether(19 : 1) gave androsta-1,4,9(11)-triene-3,17-dione(129b, 6.16g., 87%) which crystallised from ether as needles, m.p. 160-164° (Lit.\textsuperscript{182} m.p. 164-166°), [α]\textsubscript{D}\textsuperscript{25} + 100° (c = 0.55 in CHCl\textsubscript{3}) [Lit.\textsuperscript{182} [α]D + 102° (in CHCl\textsubscript{3})].

γ\textsubscript{max} (CHCl\textsubscript{3}) 1740 (C-17 C=O str.), 1665 (conj. C=O str.) and 1622, 1608 cm\textsuperscript{-1} (conj. C=C str.).

λ\textsubscript{max} (EtOH) 239 µm (ε 13,900).

δ (CDCl\textsubscript{3}) 0.93 (s, 3, C-18 Me), 1.45 (s, 3, C-19 Me), 5.50-5.68 (br.t., 1, C-11 olefinic H), 6.07 (br.s., 1, C-4 olefinic H), 6.26 (2d, J\textsubscript{2,1} 10 c./sec., J\textsubscript{2,4} 2 c./sec., 1, C-2 olefinic H) and 7.20 (d, J\textsubscript{1,2} 10 c./sec., 1, C-1 olefinic H).

3-Hydroxyestra-1,3,5(10),9(11)-tetraen-17-one(29c)\textsuperscript{155}

A mixture of androsta-1,4,9(11)-triene-3,17-dione(129b, 16.52g.), pyridine (577 ml.) containing water (5.77 ml.), and freshly activated zinc dust (292.5g.) was heated under reflux with stirring
for 20 min. Work-up in the usual manner gave a yellow solid which was crystallised from ethanol-chloroform to give 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (29c, 8.39g.), m.p. 256-258° (Lit. 182 m.p. 257-259°). Chromatography of the mother liquors on silica gel in benzene, and elution with benzene-ether (49 : 1) gave further product (1.58g.) to make a total yield of 64%. Other physical constants for this compound are recorded earlier.

3-Methoxyestra-1,3,5(10),9(11)-tetraen-17β-ol (84d)

3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-one (84a, 6.20g.) in dry tetrahydrofuran (150 ml.) was added dropwise to a solution of lithium aluminium hydride (1.59g.) in tetrahydrofuran (150 ml.) at 0°. The mixture was heated under reflux for 1 hr, cooled and the excess lithium aluminium hydride destroyed with water (1.6 ml.), 15% sodium hydroxide solution (1.6 ml.), and water (4.8 ml.). Filtration of the precipitate followed by ether extraction of the filtrate and washing, drying and concentrating of the ether extract yielded a pale oil which crystallised from methanol-ether as needles of 3-methoxyestra-1,3,5(10),9(11)-tetraen-17β-ol (84d, 5.93g., 95%), m.p. 71-72° (Lit. 220 m.p. 71-73°), [α]D25 + 87° (c = 0.58 in CHCl3) [Lit. 220 [α]D22 + 77.4° (c = 1.68 in CHCl3)].

υmax (CHCl3) 3500-3340 (H-bonded OH str.), 3030, 3000 (aromatic CH str.) and 1630, 1610 and 1580 cm⁻¹ (conj. C=C str. and phenyl nucleus).
\( \lambda_{\text{max}} \) (EtOH) 264 (\( \varepsilon \) 18,000), 300 (sh., \( \varepsilon \) 2790), and 310 \( \mu \) (sh., \( \varepsilon \) 1780).

\( \delta \) (CDCl\(_3\)) 0.82 (s, 1, C-18 Me), 2.76-3.12 (m, 2, C-6 benzylic protons), 3.89 (s, 3, aromatic OH), 3.77-4.07 (m, 1, C-17 aH), 6.26-6.47 (m, 1, C-11 olefinic H), 6.85 (br.s., 1, C-4 aromatic H), 6.94 (2d, J\(_{2,1}\) 9 c./sec., J\(_{2,4}\) 2.2 c./sec., 1, C-2 aromatic H) and 7.73 (d, J\(_{1,2}\) 9 c./sec., 1, C-1 aromatic H).

3-Methoxyestra-1,3,5(10),9(11)-tetraren-17\( \beta \)-yl tosylate (84e)

A solution of p-toluenesulphonyl chloride (6.77g., freshly purified by the method of Pelletier\(^{221}\)) in dry pyridine (25 ml.) was added to a solution of 3-methoxyestra-1,3,5(10),9(11)-tetraren-17\( \beta \)-ol (84d, 5.07g.) in dry pyridine (25 ml.) at 0\(^\circ\) and the solution, which quickly developed a crimson red colour, was kept at 20\(^\circ\) for 24 hr. The solution was poured into ice-cold 10% hydrochloric acid, ether extracted, and the ether extract was washed, dried and concentrated at room temperature to yield 3-methoxyestra-1,3,5(10),9(11)-tetraren-17\( \beta \)-yl p-toluenesulphonate (84e, 6.92g., 89%) which crystallised from ether as leaflets, m.p. 135-136\(^\circ\) (Found: C, 71.1; H, 6.7; 0, 14.6. \( \text{C}_{25}\text{H}_{30}\text{O}_{4}\text{S} \) requires C, 71.2; H, 6.9; 0, 14.7%).

\( \psi_{\text{max}} \) (CHCl\(_3\)) 3030, 3010 (aromatic CH str.), 2850 (aromatic OCH\(_3\) str.) 1630 (conj. C=O str.), 1610, 1570 (phenyl nucleus) and 1185 and 1175 cm\(^{-1}\) (OTs).
$\lambda_{\text{max}}$ (EtOH) 264 ($\varepsilon$ 19,500) and 299 $\mu$m (sh., $\varepsilon$ 2840).

$\delta$ (CDCl$_3$) 0.86 (s, 3, C-18 Me), 2.52 (s, 3, aromatic Me), 2.77-3.06 (m, 2, C-6 benzylic protons), 3.88 (s, 3, aromatic OMe), 4.35-5.27 (m, 1, C-17 $\alpha$H), 6.10-6.37 (m, 1, C-11 olefinic H), 6.84 (br.s., 1, C-4 aromatic H), 6.93 (2d, $J_{2,1}$ 9 c./sec., $J_{2,4}$ 2.5 c./sec., 1, C-2 aromatic H), 7.75 (d, $J_{1,2}$ $\sim$ 9 c./sec., 1, C-1 aromatic H) and 7.59 and 8.08 (2d, $J_{AB}$ 8.6 c./sec., 4, tosylate aromatic protons).

R.D. ($\varepsilon$ = 0.76 in CHCl$_3$); [\$\phi\$]$_{589}$ + 235°, [\$\phi\$]$_{500}$ + 396°, [\$\phi\$]$_{400}$ + 960°, and [\$\phi\$]$_{322}$ + 2990° (pk).

**3-Methoxyestra-1,3,5(10),9(11)-tetraene(84c)**

3-Methoxyestra-1,3,5(10),9(11)-tetraen-17β-y1 tosylate(84e, 6.41g.) in dry dioxane (640 ml.) was added dropwise to a solution of lithium aluminium hydride (4.43g.) in dry dioxane (640 ml.) and the mixture was heated under reflux for 24 hr. The cooled, stirred reaction mixture was treated dropwise with water (4.4 ml.), 15% sodium hydroxide solution (4.4 ml.), and water (13.3 ml.). The precipitate was filtered off, washed with ethyl acetate, and the filtrate was concentrated in vacuo to yield a gum which was chromatographed in benzene on alumina packed in light petroleum. The product was eluted with light petroleum-benzene(9 : 1) and crystallised from ether as prisms of 3-methoxyestra-1,3,5(10),9(11)-tetraene(84c, 2.24g., 55%), m.p. 85-87.5° (Found: C, 85.2; H, 9.0; O, 5.8. C$_{19}$H$_{24}$O requires C, 85.0; H, 9.0; O, 6.0%).
\[ \nu_{\text{max}} (\text{CS}_2) 3020, 3005 \text{ (aromatic CH str.)}, 2850 \text{ (aromatic OCH}_3 \text{ str.)}, 1625 \text{ (conj. C=C str.)}, 1600 \text{ (phenyl nucleus) and 880, 810, 800 and 760 cm}^{-1} \text{ (arom. o.o.pl.def.)}. \]

\[ \lambda_{\text{max}} \text{ (EtOH) 268 (e 18,000) and 281 mp (sh., e 6080)}. \]

\[ \delta \text{ (CDCl}_3) 0.78 \text{ (s, 3, C-18 Me)}, 2.78-3.10 \text{ (m, 2, C-6 benzylic protons)}, 3.87 \text{ (s, 3, C-3 OMe)}, 6.21-6.44 \text{ (br.t., C-11 olefinic H)}, \]

\[ \delta \text{ (br.s., 1, C-4 aromatic H)}, 6.93 \text{ (2d, J} _{2,1} 9.6 \text{ c./sec., J} _{2,4} 2.5 \text{ c./sec., 1, C-2 aromatic H) and 7.80 (d, J} _{1,2} 2.6 \text{ c./sec., 1, C-1 aromatic H)}. \]

R.D. \[ \text{ ([\alpha]}_25^0 + 268^\circ, [\alpha]_500 + 436^\circ, [\alpha]_400 + 895^\circ, \text{ and } [\alpha]_364 + 1313^\circ \text{ (pk)}. \]

**Oxidation of 3-Methoxyestra-1,3,5(10),9(11)-tetraene(84c)**

A solution of 3-methoxyestra-1,3,5(10),9(11)-tetraene(2g.) in acetone (500 ml.) was treated dropwise at \(-19^\circ\) with 4N chromium trioxide in 40% aqueous sulphuric acid (51.7 ml.) and the mixture was allowed to come to \(20^\circ\) over 4 hr. Work-up in the usual manner (p. 98-99) yielded a pale yellow neutral oil (1.13g., 57%) and an orange-yellow acidic gum (830 mg., 45%).

Preparative t.l.c. of the neutral oil gave 9\(\beta\)-hydroxy-3-methoxyestra-1,3,5(10)-trien-11-one(16c, 790 mg., 35%) which crystallised as plates from ether, m.p. 114-116\(^\circ\) (Lit. \(^\text{15}\) m.p. 114.7-116\(^\circ\), \([\alpha]_D^{25} + 174^\circ \text{ (e 0.57 in CHCl}_3) \text{ [Lit.} \(^\text{15}\) \([\alpha]_D^{25} + 170^\circ\)

\[ \text{Lit.} \(^\text{15}\) [\alpha]_D^{25} + 170^\circ\)
$\nu_{\text{max}}$ (CCl$_4$) 3463 (H-bonded OH str.), 3030 (aromatic CH str.), 1711 (C-11 C=O str.), 1610, 1575 (phenyl nucleus), 1255 (C-O-C asym. str.) and 1040 cm$^{-1}$ (C-O-C str.).

$\lambda_{\text{max}}$ (EtOH) 225 (ε 6800), 277 (ε 1460) and 284 με (ε 1330).

δ (CCl$_4$) 0.76 (s, $W_2$ 2 c./sec., 3, C-18 Me), 2.20 (d, J 12.8 c./sec., 1, C-12α H which shows further fine splitting due to coupling with C-18 Me), 2.51 (d, J 12.8 c./sec., 1, C-12 βH), 2.66-2.98 (m, 2, C-6 benzylic protons), 3.80 (s, 3, aromatic OMe), 4.24 (s, 1, C-9 OH) and 6.75 (s, 3, C-1, C-2, C-4 aromatic protons).

Chromatography of the acidic material on silica gel in benzene, and elution with benzene-ether (19 : 1) gave 3-methoxy-9-oxo-9,11-secoestra-1,3,5(10)-trien-11-oic acid (15c, 620 mg., 28%) as needles when crystallised from aqueous ethanol, m.p. 70-71° (Lit.$^{15}$ m.p. 70-71°), $[\alpha]_D^{25} - 28^\circ$ (ε = 0.10 in CHCl$_3$) [Lit.$^{15}$ $[\alpha]_D^{25} - 25^\circ$ (ε = 0.66 in EtOH)].

$\nu_{\text{max}}$ (CHCl$_3$) 3670 (free OH str.), 3460-2560 (H-bonded OH str. of COOH), 3030 (aromatic CH str.), 2850 (aromatic OCH$_3$ str.), 1710 (carboxylic C=O str.), 1675 (conj. C=O str.) and 1250-1210 cm$^{-1}$ (C-O str. of COOH coupled with OH in pl. str.).

$\lambda_{\text{max}}$ (EtOH, Cary) 203 (ε 27,000), 224 (ε 17,200) and 274 με (ε 22,600).

δ (CDCl$_3$) 1.08 (s, 3, C-18 Me), 2.41-2.67 (m, 2, C-6 benzylic protons), 2.84-3.12 (m, 2, C-12 protons), 3.86 (s, 3, aromatic OMe), 6.40 (s, 1, COOH), 6.81 (d, J$_{4,2}$ 2.2 c./sec., 1, C-4 aromatic H),
6.94 (2d, J₂,₁ 8.3 c./sec., J₂,₄ 2.2 c./sec., 1, C-2 aromatic H),
and 8.09 (d, J₁,₂ 8.3 c./sec., 1, C-1 aromatic H).

Attempted Isomerisation of 3-Methoxyestra-1,3,5(10),9(11)-
tetraene(84c)

A solution of 3-methoxyestra-1,3,5(10),9(11)-tetraene(2.24g.)
in methanol (175 ml.) and 10N hydrochloric acid (38 ml.) was heated
under reflux for 20 min. The cooled solution was diluted with
ether, and the ether solution was washed, dried, and concentrated
to give unchanged starting material. A longer reaction time (4 hr.)
failed to give any isomerised product.

Preparation of 17-Oxo-estra-1,3,5(10),9(11)-tetraen-3-yl Acetate(112)

17-Oxo-estra-1,3,5(10)-trien-3-yl acetate(4j)

Estrone (1g.) was acetylated with acetic anhydride-pyridine
in the usual manner to give 17-oxo-estra-1,3,5(10)-trien-3-yl
acetate(4j, 1.02g., 90%) which crystallised from ether as needles,
m.p. 125-127° (Lit.₂²²ᵃ m.p. 125°), [α]°²⁵ + 130° (ε = 1.39 in CHCl₃)
[Lit.₂²²ᵇ [α]° + 128° (in CHCl₃)].

Dehydrogenation of 17-Oxo-estra-1,3,5(10)-trien-3-yl acetate(4j)
with D.D.Q.₁⁶⁶

A solution of D.D.Q. (0.8g.) in dry benzene (100 ml.) was
added to a solution of 17-oxo-estra-1,3,5(10)-trien-3-yl acetate (1g.) and the mixture was heated under reflux for 2 hr, when all the D.D.Q. had been converted to hydroquinone. Work-up of the reaction mixture in the usual manner and t.l.c. showed that only half the material had been converted to 17-oxo-estra-1,3,5(10),9(11)-tetraen-3-yl acetate(112). The product was hydrolysed with 10% aqueous methanolic potassium hydroxide and retreated with D.D.Q. as 3-hydroxyestra-1,3,5(10)-trien-17-one(4h).

17-Oxo-estra-1,3,5(10),9(11)-tetraen-3-yl acetate(112)

3-Hydroxyestra-1,3,5(10),9(11)-tetraen-17-one(29c, 5.30g.) was acetylated with acetic anhydride-pyridine in the usual manner to yield 17-oxo-estra-1,3,5(10),9(11)-tetraen-3-yl acetate(112, 5.63g., 92%) which crystallised from ether as leaflets, m.p. 124-126° (Lit. 155 m.p. 125-126°), [α]D25 + 244° (ε = 1.13 in CHCl₃) [Lit. 223 [α]D + 234° (in CHCl₃)].

υₜₜ max (CHCl₃) 3040, 3020 (aromatic CH str.), 1755 (C-17 C=O str.), 1735 (C-3 OAc C=O str.), 1625, 1600, 1585 (conj. C=C str. and phenyl nucleus) and 1225 and 1040 cm⁻¹ (asym. and sym. OAc C-O-C str.).

λ max (EtOH) 259 (ε 18,000), 291 (sh., ε 4110), and 300 mμ (sh., ε 2870).

δ (CDCl₃) 0.94 (s, 3, C-18 Me), 2.28 (s, 3, C-3 aromatic OOCOCH₃), 2.79-3.07 (m, 2, C-6 benzylic protons), 6.11-6.32 (m, 1, C-11 olefinic H), 6.78 (br.s., 1, C-4 aromatic H), 6.82 (d, J₂,₁ 10 c./
sec., J_2,4 2 c./sec., 1, C-2 aromatic H) and 7.53 (d, J_1,2 10 c./
sec., 1, C-1 aromatic H).

Oxidation of 17-Oxo-estra-1,3,5(10),9(11)-tetraen-3-yl Acetate(112)

A solution of 17-oxo-estra-1,3,5(10),9(11)-tetraen-3-yl
acetate (2g.) in acetone (500 ml.) was treated dropwise at -18°
with 4N chromium trioxide in 40% aqueous sulphuric acid (42.5 ml.)
and the mixture was allowed to come to 20° over 4 hr. Work-up in
the usual manner (p. 98-99) yielded a pale yellow neutral oil
(950 mg., 48%) and a yellow acidic oil (1.2g., 60%).

Chromatography of the neutral fraction on silica gel in
benzene and elution with benzene-ether(19 : 1) gave starting
material (54 mg., 2.7%) and a mixture of 11,17-dioxo-estra-1,3,5(10)-
triene-3,9α-diol and the corresponding 3-acetate (600 mg.) which
was acetylated with acetic anhydride-pyridine in the usual manner
to yield 11,17-dioxo-estra-1,3,5(10)-triene-3,9α-diol 3-acetate
(150b, 610 mg., 28%), which crystallised from methylene chloride-
light petroleum as prisms, m.p. 250-252° (Lit. 198 m.p. 235-243°),
[α]_D^{25} + 347° (c = 1.32 in CHCl_3) [Lit. 198 [α]_D + 349° (c = 1.03 in
dioxane)].

ν_max (CHCl_3) 3520-3460 (br. OH str. of H-bonded OH), 3030, 3010
( aromatic CH str.), 1745 (C-17 C=O str.), 1725 (aromatic OAc C=O
str. and C-11 C=O str.), 1613, 1586 (phenyl nucleus), 1230-1200
(C=O-C asym. str.) and 1190, 1148 and 1010 cm\(^{-1}\) (C-O-C sym. str.).

\(\lambda_{\text{max}}\) (EtOH) 222 mp (\(\varepsilon 19,800\)).

\(\delta\) (CDCl\(_3\)) 0.84 (s, 3, C-18 Me), 2.32 (s, 3, C-3 COCH\(_3\)), 4.61-4.88
(m, 1, C-9 OH), 7.07 (br.s., 1, C-4 aromatic H), 7.13 (2d, \(J_{2,1}\) 10
c./sec., \(J_{2,4}\) \(\sim\) 2 c./sec., 1, C-2 aromatic H) and 7.58 (d, \(J_{1,2}\)
10 c./sec., 1, C-1 aromatic H).

Chromatography and preparative t.l.c. of the acidic fraction
yielded \(\text{3-acetoxo-9,17-dioxo-9,11-secoestra-1,3,5(10)-trien-11-oic acid}\) (155, 408 mg., 18%) which could not be crystallised but which
was concentrated from ether into feathery plates, m.p. 45-70º
(Found: C, 66.3; H, 6.55; O, 26.0. \(C_{20}H_{22}O_6\) requires C,
66.6; H, 6.9; O, 26.2%).

\(\nu_{\text{max}}\) (CHCl\(_3\)) 3540-2560 (br. OH str. of H-bonded COOH), 1740 (br.
C-17 C=O and aromatic OAc C=O str.), 1710 (C=O str. of COOH), 1685
(conj. C=O str.), 1605, 1585 (phenyl nucleus), 1230-1200 (asym.
C-O-C str.) and 1185 cm\(^{-1}\) (sym. C-O-C str.).

\(\lambda_{\text{max}}\) (EtOH) 210 (\(\varepsilon 15,200\)) and 250 mp (\(\varepsilon 10,100\)).

\(\delta\) (CDCl\(_3\)) 1.05 (s, 3, C-18 Me), 2.37 (s, 3, C-3 COCH\(_3\)), 7.28-7.45
(m, 3, C-1, C-2 aromatic protons and C-11 COOH), 7.20 (br.s., 1,
C-4 aromatic H), 7.22 (2d, \(J_{2,1}\) 10 c./sec., \(J_{2,4}\) 2.5 c./sec., 1,
C-2 aromatic H), and 8.17 (d, \(J_{1,2}\) 10 c./sec., 1, C-1 aromatic H).

R.D. (\(\varepsilon = 0.31\) in CHCl\(_3\)); \([\varphi]_{589} + 62^\circ\), \([\varphi]_{500} + 102^\circ\), \([\varphi]_{400} + 305^\circ\),
and \([\varphi]_{311} + 4950^\circ\) (pk).
Attempted Preparation of an Estra-1,3,5(10)-trien-9α,11α-epoxide

m-Chloroperbenzoic Acid Oxidation of 3-Methoxyestra-1,3,5(10),9(11)-
tetraen-17-one(84a)²⁰b,¹⁹³

A solution of m-chloroperbenzoic acid (85%, 2.71 g.) in
methylene chloride (75 ml.) was added dropwise over 10 min. to a
stirred solution of 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one
(3 g.) in methylene chloride (25 ml.). Iodimetric titration after
2 hr. showed that 88% of the peracid had been consumed and the
excess peracid was then destroyed by the dropwise addition of 10%
sodium sulphite solution which was added until a test with starch-
iodide paper was negative. The reaction mixture was diluted with
ether, washed with 5% sodium bicarbonate solution and water, and
the ether solution was dried and concentrated. Chromatography of
the resulting gum, which contained 9 products (t.l.c.), on
deactivated alumina in benzene gave, from benzene-ether (1:1)
eluates, 9α-hydroxy-3-methoxyestra-1,3,5(10)-trien-11,17-dione (150a,
785 mg., 25%) which crystallised from ethanol-ether as prisms, m.p.
247-250° (Found: C, 72.3; H, 6.9; O, 20.4. C₁₉H₂₂O₄ requires C,
72.6; H, 7.05; O, 20.4%).

υ^max (CHCl₃) 3500-3460 (H-bonded OH str.), 3040 (aromatic CH str.),
1740 (C-17 C=O str.), 1709 (C-11 C=O), 1610, 1570 (phenyl nucleus),
1250 (asym. C-O-C str.), 1230-1200 (br. C-C str. of C-CO-C) and
1030 cm⁻¹ (=C-O-C sym. str.).
$\lambda_{\text{max}}$ (EtOH) 224 ($\epsilon$ 10,500) 273 ($\epsilon$ 1420) and 281 $\mu$m ($\epsilon$ 1420).

$\delta$ (CDCl$_3$) 0.84 (s, 3, C-18 Me), 2.13 (s, 1, C-9 OH), 2.35 (d, J 12 c./sec., C-12$\beta$ H), 2.72-2.98 (m, 2, C-6 benzylic protons), 3.32 (d, J 12 c./sec., C-12$\alpha$ H showing further fine splitting due to coupling with C-18 Me), 3.77 (s, 3, aromatic OMe), 6.64 (m, 1, C-4 aromatic H), 6.77 (2d, J$_{2,1}$ 9 c./sec., J$_{2,4}$ 2.5 c./sec., 1, C-2 aromatic H) and 7.27 (d, J$_{1,2}$ 9 c./sec., 1, C-1 aromatic H).

R.D. (c = 0.51 in CHCl$_3$); [\(\phi\)]$_{589}$ + 1120$^\circ$, [\(\phi\)]$_{500}$ + 2020$^\circ$, [\(\phi\)]$_{400}$ + 3910$^\circ$, [\(\phi\)]$_{318}$ 19,600$^\circ$ (pk), and [\(\phi\)]$_{292}$ 0$^\circ$.

Perbenzoic Acid Oxidation of 17-Oxo-estra-1,3,5(10),9(11)-tetraen-3-yl Acetate(112)$^{81}$

A solution of 17-oxo-estra-1,3,5(10),9(11)-tetraen-3-yl acetate (500 mg.) in chloroform (2 ml.) was added dropwise to a solution of perbenzoic acid (245 mg.) in chloroform (6 ml.) at 0$^\circ$ and the mixture was kept at approximately 5$^\circ$ for 24 hr. The mixture was diluted with ether, washed with sodium bicarbonate solution and water, and the ether solution dried and concentrated to a yellow oil which was shown (t.l.c.) to contain 13 products.

m-Chloroperbenzoic Acid Oxidation of 17-Oxo-estra-1,3,5(10),9(11)-
tetraen-3-yl Acetate(112)$^{217b,193}$

A solution of m-chloroperbenzoic acid (85%, 334 mg.) in
methylene chloride (45 ml.) was added dropwise over 1 hr to a stirred solution of 17-oxo-estra-1,3,5(10),9(11)-tetraen-3-yl acetate (500 mg.) in methylene chloride (40 ml.) at 0°. Work-up in the usual manner after 6 hr., gave a pale yellow gum which was shown (t.l.c.) to contain 11 products.

Estra-1,3,5(10),9(11)-tetraene-3,17β-diol diacetate (153b)81

A solution of 17-oxo-estra-1,3,5(10),9(11)-tetraen-3-yl acetate (112, 2.5g) in dry tetrahydrofuran (58 ml.) was added dropwise to a stirred solution of lithium aluminium hydride (306 mg.) in dry tetrahydrofuran (58 ml.) at 0° and the mixture was allowed to stand overnight at 20°. Work-up in the usual manner and chromatography on silica gel in benzene-ether gave estra-1,3,5(10),9(11)-tetraene-3,17β-diol (153a, 1.74g, 80%) which crystallised from ether as needles, m.p. 182-184° (Lit. 81 m.p. 184-186°), [α]D 25 + 123° (c = 0.34 in CHCl₃) [Lit. 213 [α]D + 127°].

υ max (Nujol) 3380-3200 (H-bonded OH str.), 1630 (conj. C=O str.) and 1610 and 1575 cm⁻¹ (phenyl nucleus).

λ max (EtOH) 263 (ε 19,700), 292 (sh., ε 2350) and 302 μ (sh., ε 2040).

Acetylation with acetic anhydride-pyridine (3 hr. heated under reflux, when t.l.c. still showed some starting material was present), and chromatography on silica gel in benzene gave estra-
1\,3,5(10),9(11)-tetraene-3,17β-di\(\text{ol}\) diacetate (153b, 1.97 g., 88\%)
which crystallised from ether as plates, m.p. 150-152° (Lit. \(^{81}\) m.p. 148-149°), \([\alpha]_D^{25} + 91° (c = 0.65 \text{ in CHCl}_3) [\text{Lit.} \(^{81}\) [\alpha]_D + 94° (c = 0.85 \text{ in CHCl}_3)]\).

\(\lambda_{\text{max}}\) (CHCl\(_3\)) 3040, 3020 (aromatic CH str.), 1755, 1730 (C-3 and C-17 OAc C=O str.), 1630 (conj. C=C str.), 1603, 1575 (phenyl nucleus) 1260-1180 (br. asym. C-O-C str.) and 1145 cm\(^{-1}\) (sym. C-O-C str.).

\(\lambda_{\text{max}}\) (EtOH) 260 (\(\varepsilon\) 18,700), 292 (sh., \(\varepsilon\) 2950) and 302 mp (sh., \(\varepsilon\) 2040).

\(\delta\) (CDCl\(_3\)) 0.83 (s, 3, C-18 Me), 2.07 (s, 3, C-17 COOCH\(_3\)), 2.25 (s, 3, C-3 COOCH\(_3\)), 2.73-3.00 (m, 2, C-6 benzyllic protons), 4.63-4.92 (m, 1, C-17 αH), 6.09-6.27 (m, 1, C-11 olefinic H), 6.77 (br.s., 1, C-4 aromatic H), 6.83 (2d, \(J_{2,1}\) 9 c./sec., \(J_{2,4}\) 2 c./sec., 1, C-2 aromatic H) and 7.57 (d, \(J_{1,2}\) 9 c./sec., 1, C-1 aromatic H).

**Attempted Preparation of 11β-Bromoestra-1,3,5(10)-triene\(\text{-3,9a,17β-triol 3,17-diacetate}(154b)\)**

A solution of 0.2 N perchloric acid (3.48 ml.) was added to a solution of estra-1,3,5(10),9(11)-tetraene-3,17β-di\(\text{ol}\) diacetate (153b, 1.86 g.) and N-bromosuccinimide (932 mg.) in acetone (70 ml.) at 0 \(\sim\) 3° over a period of 23 min. and the solution was stirred for a further 35 min. at 0°. 5% Sodium bisulphite solution was added dropwise until starch-iodide paper was colourless. A large
amount of water was added slowly and the separated gummy product was ether extracted, and the ether extract was washed thoroughly with sodium carbonate solution, and concentrated to give a yellow oil which showed the presence of 2 compounds, neither of which was starting material. The oil was treated with acetic anhydride-pyridine in the usual manner, but when concentrated to dryness, the product turned black and decomposed.
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(C.A., 963, 59, 2906).
(1) $R = R' = \text{OAc}$

- $b$ $R = \text{OAc}$ $R' = \text{C}_8\text{H}_{17}$
- $c$ $R = \text{OBz}$ $R' = \text{C}_8\text{H}_{17}$
- $d$ $R = \text{H}$ $R' = \text{OAc}$
- $e$ $R = R' = \text{OH}$
- $f$ $R = \text{OH}$ $R' = \text{OAc}$
- $g$ $R = \text{OMe}$ $R' = \text{OAc}$
- $h$ $R = \text{OAc}$ $R' = \text{OBz}$
- $i$ $R = \text{OH}$ $R' = \text{OBz}$
- $j$ $R = \text{OMe}$ $R' = \text{OBz}$
- $k$ $R = \text{OH}$ $R' = \text{O}$
- $l$ $R = \text{OMe}$ $R' = \text{O}$
- $m$ $R = \text{OMe}$ $R' = \text{C}_8\text{H}_{17}$
- $n$ $R = \text{H}$ $R' = \text{C}_8\text{H}_{17}$
- $o$ $R = \text{OH}$ $R' = \text{C}_8\text{H}_{17}$

(2) $R = R' = \text{OAc}$

- $b$ $R = \text{OAc}$ $R' = \text{C}_8\text{H}_{17}$
- $c$ $R = \text{OBz}$ $R' = \text{C}_8\text{H}_{17}$
- $d$ $R = \text{H}$ $R' = \text{OAc}$
- $e$ $R = \text{H}$ $R' = \text{C}_8\text{H}_{17}$
- $f$ $R = \text{OAc}$ $R' = \text{OBz}$
- $g$ $R = \text{OH}$ $R' = \text{OBz}$
- $h$ $R = \text{OH}$ $R' = \text{C}_8\text{H}_{17}$
- $i$ $R = \text{OMe}$ $R' = \text{OBz}$

(3) $R = \text{H}_2$

- $b$ $R = \text{O}$

**Diagram:**

- (1) Molecular structure with $R = R' = \text{OAc}$
- (2) Molecular structure with $R = R' = \text{OAc}$
- (3) Molecular structure with $R = \text{H}_2$
(4a) $R = R' = OAc$

- b $R = OMe$  \hspace{1cm} R' = OAc
- c $R = OMe$  \hspace{1cm} R' = O
- d $R = OEt$  \hspace{1cm} R' = OAc
- e $R = OMe$  \hspace{1cm} R' = H_2
- f $R = OMe$  \hspace{1cm} R' = C_8H_{17}
- g $R = OAc$  \hspace{1cm} R' = H_2
- h $R = OH$  \hspace{1cm} R' = O
- i $R = OH$  \hspace{1cm} R' = H_2
- j $R = OAc$  \hspace{1cm} R' = O

(5a) $R = R' = OAc$

- b $R = OMe$  \hspace{1cm} R' = OAc
- c $R = OMe$  \hspace{1cm} R' = O
- d $R = OAc$  \hspace{1cm} R' = H_2
- e $R = OMe$  \hspace{1cm} R' = H_2
- f $R = OH$  \hspace{1cm} R' = H_2
- g $R = OMe$  \hspace{1cm} R' = C_8H_{17}

(7)

(8)

(9)

(10)

(11)

(12)
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