STUDIES IN THE STEROID SERIES

A thesis presented by

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in partial fulfilment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

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Imperial College,

London, 1974

Abstract

The following original contributions to the chemistry of oestrone are described in this thesis:

(1) The elaboration of model compounds to test the amide photolysis method for functionalization at carbon-18 of oestrone and related compounds.

(2) The synthesis of a suitable ring A protected oestrone derivative, namely 17βcarbamoyl-oestra--3-mesylate and its conversion into 18-hydroxy oestrone.

(3) The discovery of a novel fragmentation of diphenyl carbinols by a photolytic method.

Acknowledgement

The author would like to thank Dr. J.E.Baldwin for his help and guidance during the course of this work and also Dr. I.Dainis for experimental assistance.

The author is especially grateful to Professor Sir Derek Barton, for his continuous guidance and encouragement and also for the privilege of working under his supervision on this research project.

Thanks are due to the microanalytical laboratories of Imperial College, to Mrs. A.Boston for the nmr spectra and to the technical staff.

The author wishes to acknowledge a fellowship from the Gulbenkian Foundation and another grant from Professor Sir Derek Barton.

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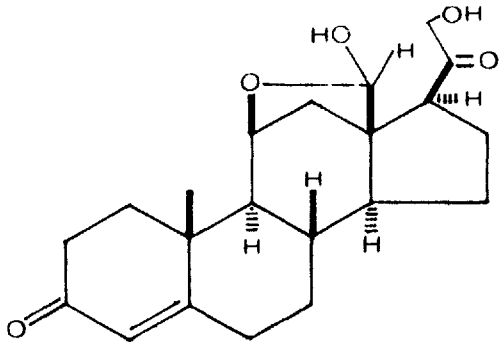
Introduction

The Functionalization of Non-Activated Carbon Atoms

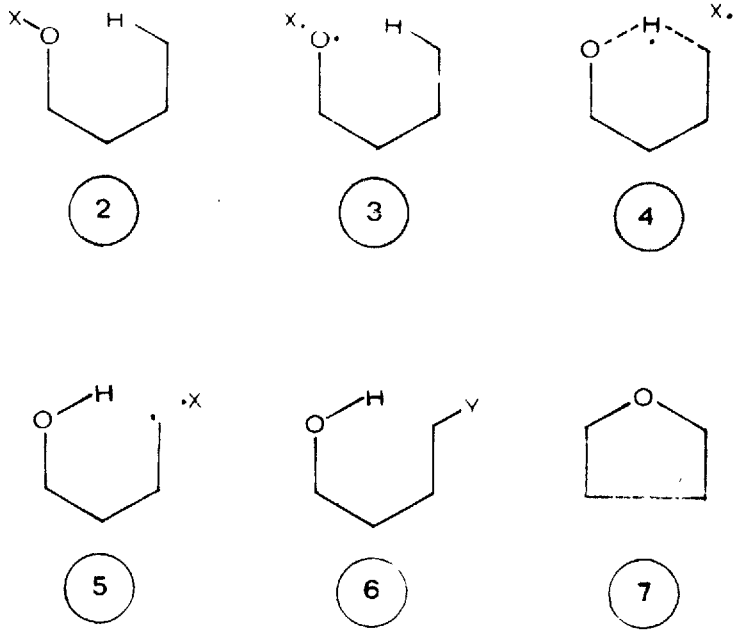
The need for methods of functionalizing the angular methyl groups of steroids was stimulated by the discovery of the structure of a salt retaining hormone, aldosterone (1) in 1954 [1].



(1)

Success was first reported [2] by use of the old Hofmann-Loffler-Freitag reaction [3] but the first convenient method was described by Barton [4] who also clearly stated the requirements for this type of reaction.

It was postulated that a radical species, for example an alkoxyl radical, (3) generated by bond homolysis of a suitable percursor, as (2) could abstract a suitably placed hydrogen atom through a six membered transition state, as (4), to yield a carbon radical (5) quenchable to some functionalized species (6).

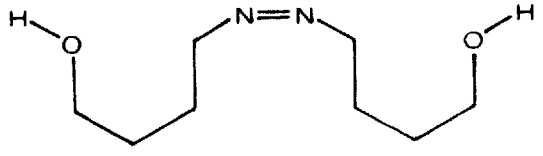


The importance of the six membered transition state was pointed out and suitable groups X were suggested [4].

In general these latter were those groups, for example NO, Cl, Br, I, which by some activation step, either thermal or photochemical, could yield the required alkoxyl radical.

This process, when X = NO, is known as the Barton reaction [5] and is achieved by photolysis of the nitrite ester (2, X = NO). The mechanistic data presently available is compatible with homolysis of the oxygen-nitrogen bond and intramolecular abstraction as represented by the pathway (2 to 5). Apparently the NO radical so released has sufficient freedom to pass away from the immediate neighbourhood of the reaction site, since experiments [6] with ^{14}N labelled nitrite esters have demonstrated the complete scrambling of nitrogen isotope in the products, and furthermore the carbon radical formed (5) may be preferentially quenched by some other external species present in excess, such as iodine [7].

The normal product from the Barton reaction is the nitroso-derivative (6, Y = NO) which easily dimerises to the nitroso-dimer (8), the latter being generally converted by mild acidic hydrolysis to the oxime (9) and when convenient to the hydroxy-aldehyde (10).



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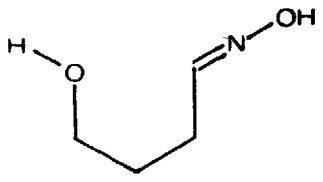

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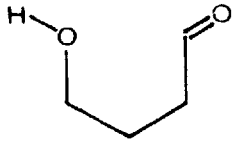

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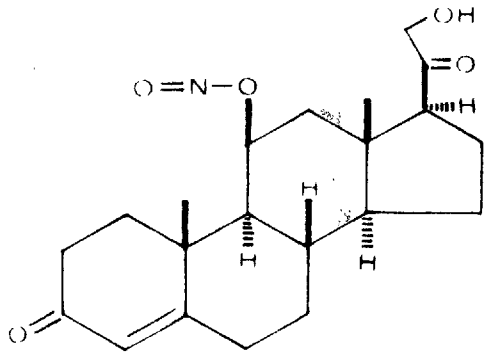
Accordingly, aldosterone (1) was elegantly synthesised [4] from the readily available corticosterone acetate by photolysis of the 11β-nitrite (11).

Examples of this general process when X = Cl and I, have been described by a number of workers and reviewed[5,9,10], the pathway being identical to that described for nitrite esters, although the last product (6) may not be isolable in some cases [11,12] due to facile displacement of X yielding the tetrahydrofuran ring (7).

Identical reactions occurred when the oxygen radical was formed by photolysis [13] or thermolysis [14] of an oxygen-

-lead bond [2, X = Pb $(OAc)_3$], or by thermolysis of nitrate esters in presence of one electron oxidants such as cupric or ferric salts[15], and it is presumed that all of these similarly proceed <u>via</u> the alkoxy radical (3).



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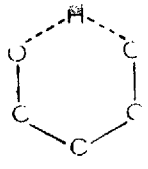
Stereochemistry of Abstractions

It appears from numerous examples in the literature that the dominant stereochemical requirements for this process is access to a relatively strain free six-membered transition state (12) such as is provided by the 1, 3 diaxial substituents in cyclohexanes[16] (13).



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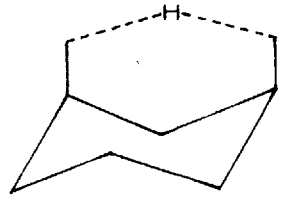

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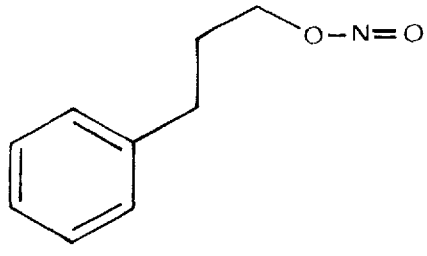
A study of the Barton reaction in phenyl aliphatic alcohols[17] is particularly revealing in this respect.

In this work it was demonstrated that the 3-phenyl--1-propylnitrite (14) does not give intramolecular attack even though the especially weak benzylic hydrogen was

abstractable through a five-membered transition state (15).



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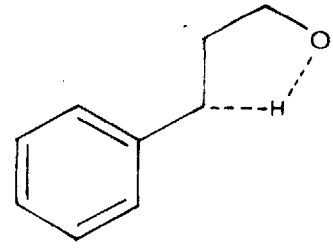

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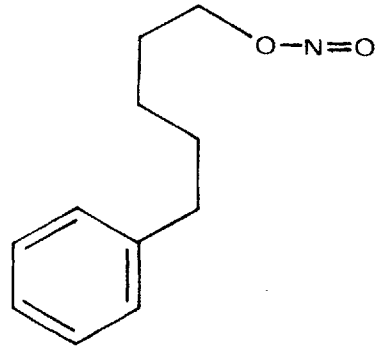
Similarly the higher homologue (16) only gave abstraction through the six-membered transition state (17).



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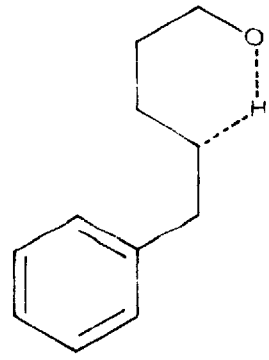


(17)

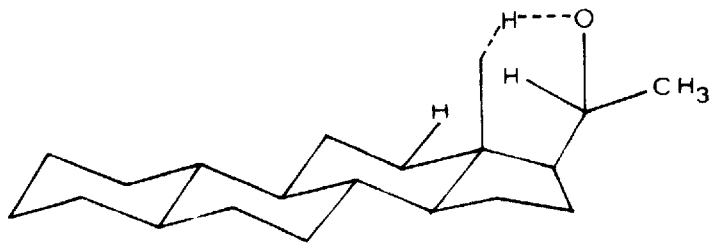
In both cases the bond energies[18] would have strongly favoured the abstraction of the benzylic hydrogen atoms by some 16 kcal/mol.

The dominant influence of stereochemistry is thereby clearly demonstrated.

Some cases of the same process within seven-membered transition states are known[19] to give low yields of abstraction. However this is only possible when configuration is such that the two atoms are in close proximity.

Reactions of epimeric 20-nitrites in the pregnanes also revealed the powerful influence of stereochemistry. It was found[20] that the 20 α-nitrite gives much higher yields of an 18-functionalized compound than the 20 β-epimer. The

results of the hypoiodite[21] reactions were also in agreement with these findings.



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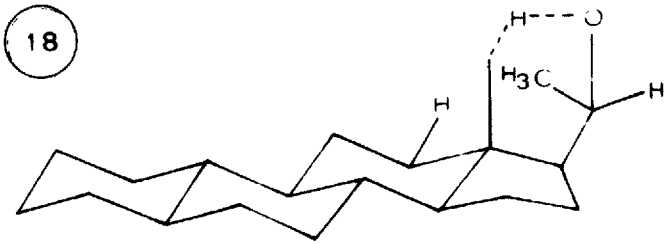


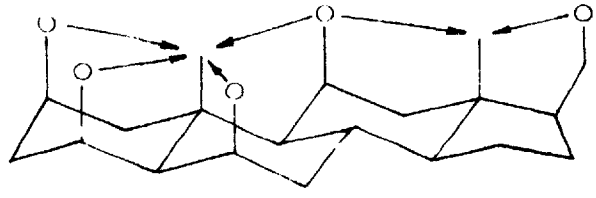
(19)

If the two transition states (18) and (19), 20 α and 20 β respectively, are considered, it is clear that the 20 β -epimer (19) involves a 1,3-diaxial like repulsion between the 21-methyl and the 12-methylene group[5]. Thus the relatively higher population of the less hindered 20 α --conformation is reflected in the relative yields of products.

Studies in straight chain aliphatic hydrocarbons also revealed that, whenever a six-membered strain free transition state was possible, the Barton reaction prevailed[9] over any

other rearrangements of the radical formed.

It was also found that secondary or tertiary nitrites possessing adequate side chains behave comparably to the primary nitrites and that the yield of abstraction is higher for a benzylic or tertiary hydrogen, lower for a secondary, and the n-butyl nitrite (primary hydrogen) gave only poor yield of abstraction product[17]. These results which are in accord with early findings for the photoinduced tert-alkoxy radical promoted chlorination of hydrocarbons[22] are reversed in the case of isolated methyls in the perhydrophenanthrene skeleton because of the rigidly defined stereochemistry of these compounds. In these cases high yields are obtained with primary hidrogens and, not surprisingly, the reaction has found most application in the steroid field for the functionalization of methyl carbons 18 and 19.of the steroid nucleous.



(20)

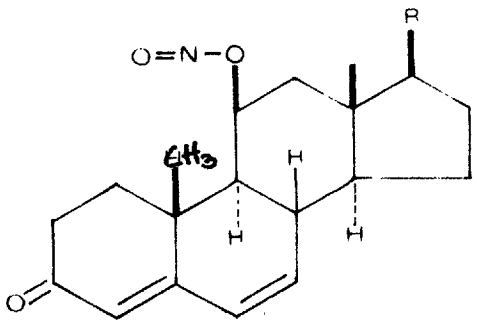
Abstraction has been observed at both these methyl groups according with the above geometrical relationship (20) from oxygen radicals in carbons 2, 4, 6, 11 and [20]9,10.

It was found in these rigid systems that the availability of a six-membered transition state is not always sufficient for an intramolecular abstraction. The distance between the oxygen radical and the carbon bearing the abstractable hydrogen also must be less than a certain critical limit.

The oxygen radical in the 11 β-position is equally distant from carbon 18 and 19 and, as expected abstraction in both methyl takes place, by photolysis of the corresponding

nitrite[23] .

However, when the 11 β-nitrite of compounds containing a doubly conjugated ketone in ring A, as (21) or (22), were photolysed only abstraction at carbon 18 was observed[24] .



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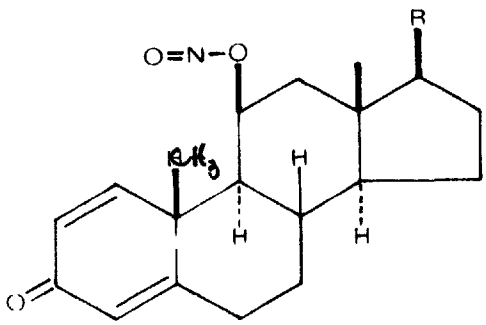

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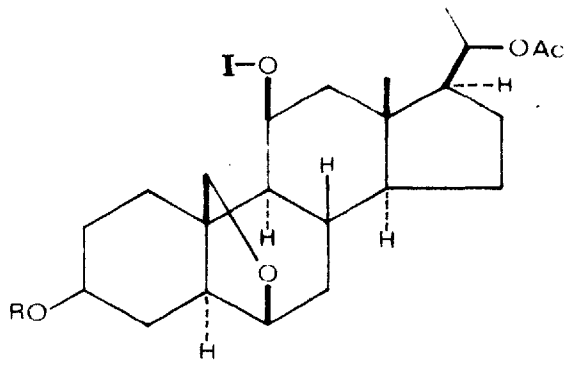
This may be due to distortion of rings A and B causing the methyl-19 to lie away from the 11 β-alcohol and suggests, that in rigid systems there is a critical distance between the oxygen radical and the hydrogen to be abstracted above which no reaction take place.

A more striking example is provided by the reaction of the cyclic ether (23) where by photolysis of the 11 β-hypoiodite only abstraction at the 18-methyl occurred[25]

although the 19-position would have been energetically favoured.



(23)

Since the distance between the oxygen and the carbon measured in models is in this case 2.9 Å for carbon-19 and 2.65 Å for carbon-18, it is acceptable to assume that the critical limit lies between these two values.

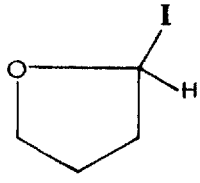
Photolysis of Hypohalites

The postulate put forward by Barton in the first paper on photolysis of nitrites[4], that a halogen-oxygen bond could be cleaved homolytically and so generate an oxygen radical with sufficient energy to abstract a proton from the δ-position, was later substantiated by the same author and others who observed that decomposition of aliphatic tert-hypochlorites gave rise to δ-chlorohydrins[26,27] and showed that functionalization of carbon-18[17,28] and carbon-19[29] of steroids could be achieved by photolysis of 20- and 6 β-hypochlorites respectively.

The success of this type of reaction was, however, related to the use of hypoiodites in presence of excess iodine. These can be easily prepared in situ by direct action of lead tetracetate[30], mercuric oxide, or tert-butyl hypochlorite[31], and iodine on the alcohols, the photolysis being generally carried out in presence of an excess of oxidant.

In these reactions, and especially when hypoiodites were used, the normal product was the tetrahydrofuran ring (7) obtained by internal displacement of the halogen by the regenerated alcohol as, for instance, when the carbon-19 of steroids is functionalized from a 6 β-hypohalite[29,32].

However, in some cases, particularly when the carbon-18 in steroids is functionalized from an hypoiodite at carbon-20[33] or at carbon-11[34] and also during functionalization of carbon-19 from the position 2 or 4[35], it was observed that further oxidation takes place and the reaction product is either a α-iodo-tetrahydrofuran (24) or a hemiacetal (25) resulting from hydrolysis of the former. The hemiacetals can be easily oxidized to the γ-lactones (26).



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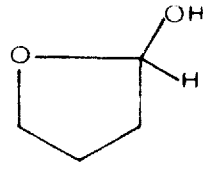

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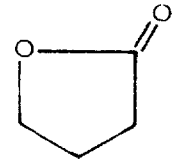

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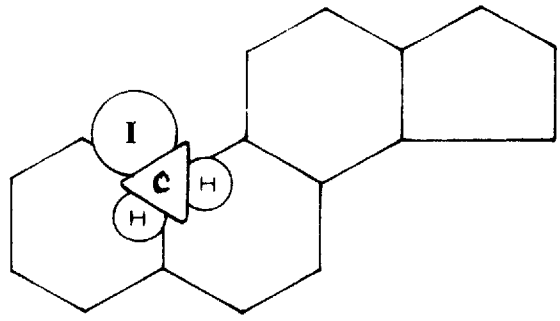

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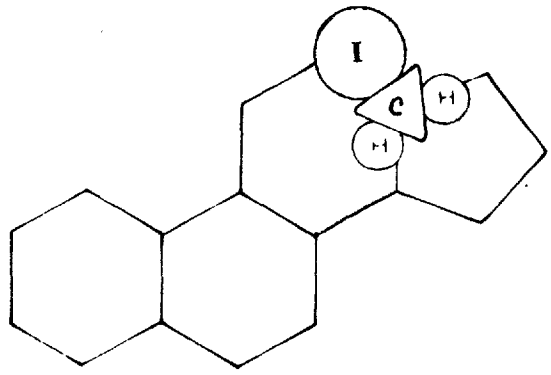
These results are a direct consequence of the use of excess oxidant and are rationalized by assuming that under these conditions the alcohol (6) regenerated after abstraction of the δ-hydrogen may be further converted to hypoiodite which then yields a new cleavage and another abstraction.

The lack of displacement to the tetrahydrofuran (7) in these systems was rationalized in the following way. It was assumed that in such rigid structures the iodo - -methyl group formed after the first abstraction is restricted to a fixed conformation, as represented in the following projections from the β-face (27 and 28), with the bulky iodine atom maintained in the least hindered space.



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Thus the relative position of the first iodine atom and the regenerated alcohol is the main factor determining the fate of the reaction.

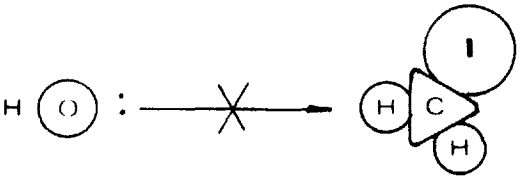
If the three atoms are in line (29) displacement takes place before the alcohol is further oxidized and a tetrahydrofuran ring is obtained.

This is the case for 6 β-alcohols as well as for all systems in which the iodo-methyl group is not restricted.

If however the three centres are such that the regenerated alcohol lies closer to an hydrogen atom (30) then, displacement being disfavoured, further oxidation takes place and with it a new abstraction of the closer

29

hydrogen atom generating a new carbon radical (31), which may be quenched or oxidized by another iodine atom to give a diiodo derivative (32) or a carbonium ion (33) both favouring formation of the α-iodo-tetrahydrofuran.



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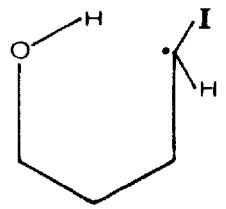

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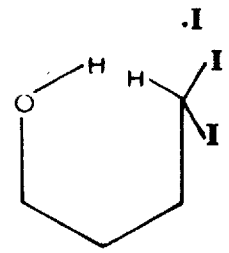

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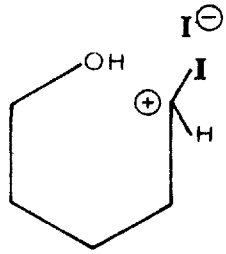
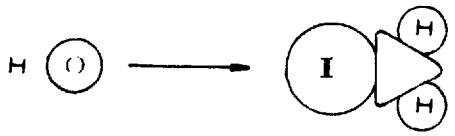


(33)

These pathways are observed during functionalization of 19-methyl from the 11-hydroxyl and also the 18-methyl from 20-hydroxyl.

Finally, if the relative position is such that the regenerated alcohol lies closer to the iodine as represented in (34), it is postulated[35] that the alcohol can be further oxidized and that an interaction between the iodine and the alkoxyl takes place in which the latter is oxidized by the former with assistance of iodine from the environment , yielding an iodotetrahydrofuran directly.



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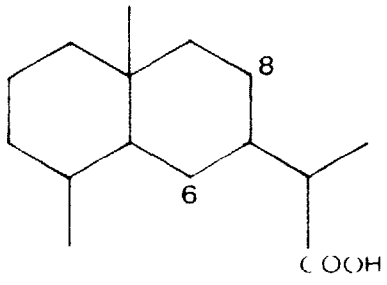
This is observed during functionalization of 19-methyl from 2-hydroxyl and 18-methyl from the 11-hydroxyl.

Sometimes mixtures of products resulting from single and double functionalization are obtained in yields that vary relative to each other for no obvious reason[36].

Photolysis of N-Iodoamides

The commonly observed natural occurrence of sesquiterpenoid lactones of the general types (35) and (36), in which hydroxylation is found only in position



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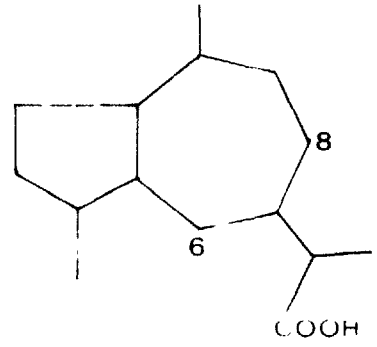

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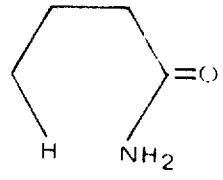
6 or 8 led Barton[37] to postulate that conceivably some biogenetic process of oxidation involving the carboxyl group and requiring a six-membered transition state as discussed above might be involved in their formation.

The generation of acyloxy-radicals by irradiation of the acyl hypoiodites was known to provoke a rapid decarboxylation [38]. Little or no indication was found for the formation of γ-iodo acids or γ-lactones.

However, the carbamoyl radicals formed by irradiation of the N-iodoamides showed a much greater stability towards decarboxylation and provided an excellent way to prepare γ-lactones[39].

It was postulated[40] that a N-iodoamide (38), formed by direct action of lead tetracetate and iodine on the amide (37) would suffer photolytical homolysis to give a radical (39) with enough energy to abstract a hydrogen from the γ-position giving a carbon radical (40), quenchable by the iodine to the γ-iodoamide (44) which would cyclize to the iminolactone (42) and subsequently hydrolized to a γ-hydroxyacid or γ-lactone (43).



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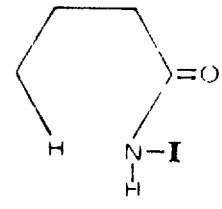

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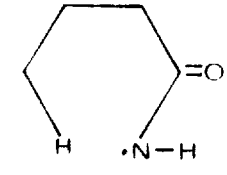

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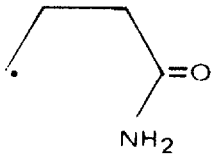

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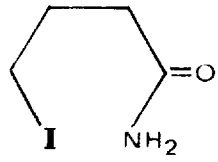

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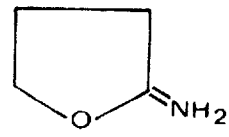

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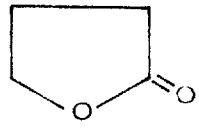
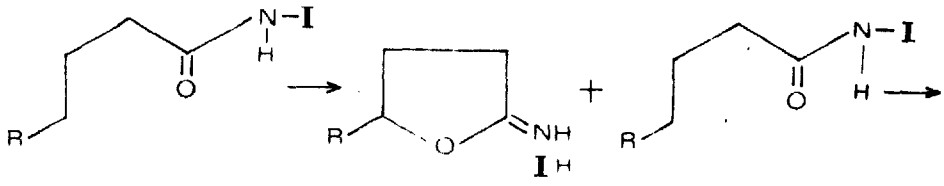
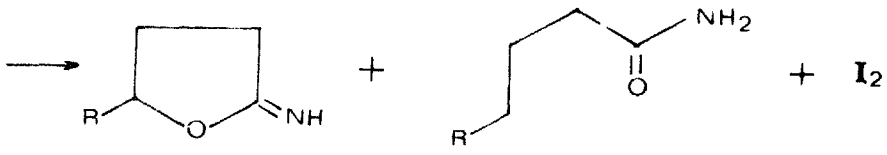


(43)

It was demonstrated that when N-iodoamides were photolyzed in the absence of excess oxidant the yields were less than 50% and all the iodine present appeared as molecular iodine (measured by U.V.); this was rationalized by proposing that the hydriodic acid so formed would reduce the still unchanged N-iodoamide , regenerating the starting amide and iodine according to the following scheme.



(44) (45) (46)

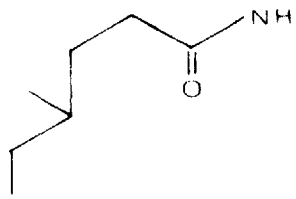


(47) (48)

An iodine monochloride complex of the postulated iminolactone was isolated in two cases and γ-iodoamides prepared by another route were seen to spontaneously cyclize and hydrolyze to lactones.

Further proof of the proposed mechanism and in particular the involvement of a free carbon radical was provided by the lactonization of an optical active amide (49) containing a chiral center in the γ-position which

on transformation gave racemized γ-lactone (50).



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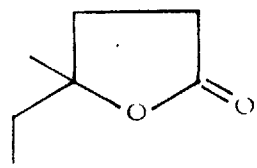

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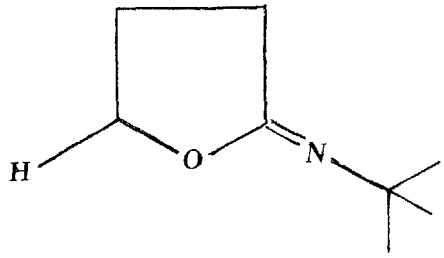
As expected the yields of lactonization in presence of an excess oxidant were higher than 50% and dependent on the strength of the carbon-hydrogen bond to be cleaved by abstraction in the same way as previously discussed, i.e. tert. > sec. > primary.

Substitution of the amide such as N-methyl , N-methoxyl, N-methylhydroxyl and N-phenyl amides showed that only the latter substituent gave lactonization in a moderate yield.

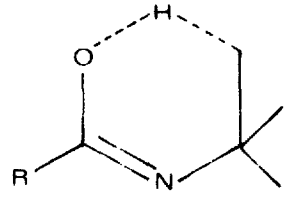
However, when N-bromo or N-chloro-tert-butyl amides were photolyzed, the yield of lactonization was increased

and N-substituted iminolactones (51) were easily isolated giving further proof of the proposed mechanism.



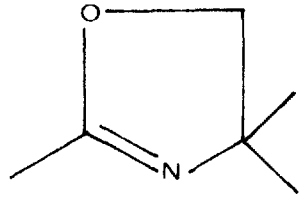
(51)

Surprisingly no abstraction in the tert-butyl group in accord with the transition state represented in (52) was observed when the alkyl chain had a γ-hydrogen but abstraction of this type was in evidence when N-chloro-N-tert-butyl-acetamide was irradiated.



(52)

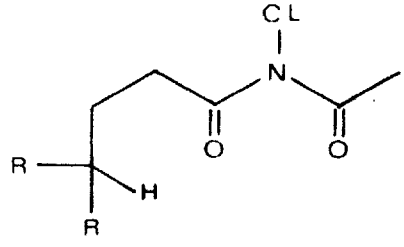
In this case the oxazoline (53) was identified (G.L.C.) in 37% yield together with N-tert-butylacetamide (48%).



(53)

N-chloroimides (54) have been shown[42] to produce upon irradiation the same type of reaction, giving after

hydrolysis the same γ-lactones.



(54)

During the course of our work a report appeared describing the application of these new reactions to steroids[43] .

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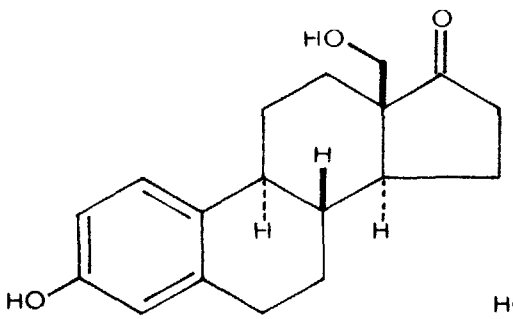
DISCUSSION

During their extensive investigations on the constituents of hydrolyzed human pregnancy urine, Marrian and his colleagues isolated [1-7] a number of hydroxylated oestrons derivatives. One of these was identified[6] as 18-hydroxyoestrone (55) by its ready conversion with alkali to formaldehyde and a noroestrone (56) shown to be identical with one of the 18-noroestrone isomers



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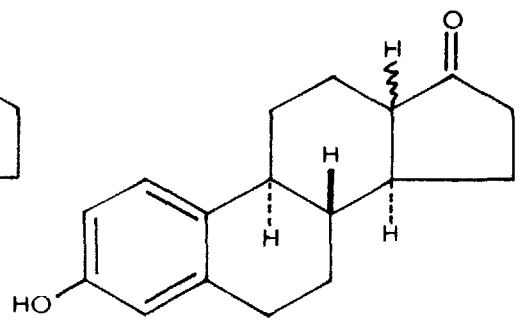

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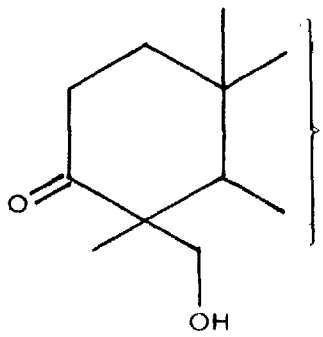
synthethised by W.S.Johnson and his colleagues[5]. The fact that Barton[8] had shown that primary β-ketols such as

methyl hederagonate and icterogenine (57) lose formaldehyde on treatment with alkali at room temperature to give the nor compound (58), through a retro-aldol condensation coupled with the findings that the same hydroxylated compound could be obtained by incubation of 18-hydroxy



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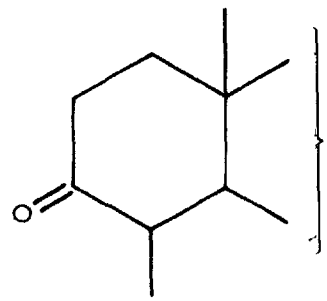

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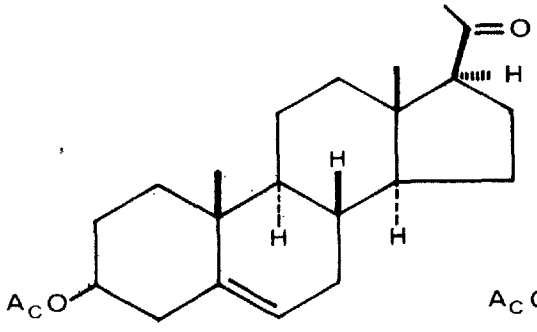
androsta-4-ene-3,17-dione with human placental tissue and by hydroxylation of oestrone with adrenal tissue preparations [4,7,10,11] supported the proposed structure.

The synthesis of such a compound (55) would present to the chemist a challenge similar to the one previously given by aldosterone and since it had been isolated in small amounts no biological properties were known. Moreover

the recently discovered functionalization of isolated carbon atoms in the steroid nucleous discussed in the previous chapter provided a possible route for synthesis.

Starting from pregnenolone acetate, for example, a serie of reactions (scheme I) already known[12] or with well founded precedents could be visualized in which a photochemical process would be advantageously used to aromatize ring A and functionalize the 18-carbon atom.



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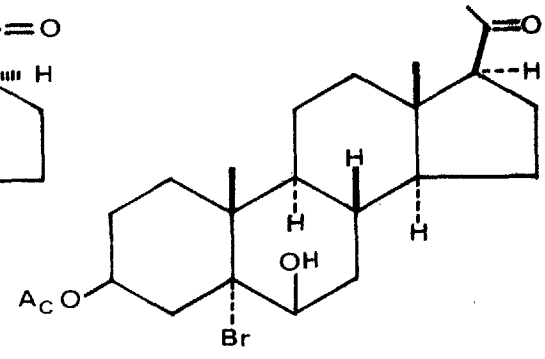

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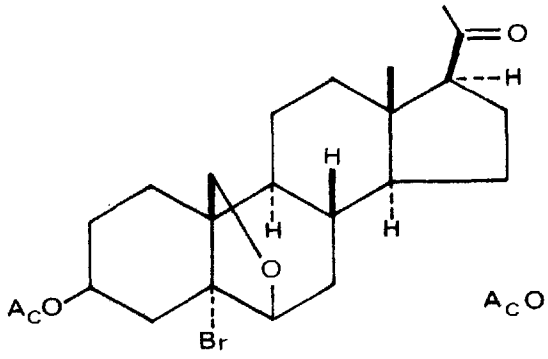

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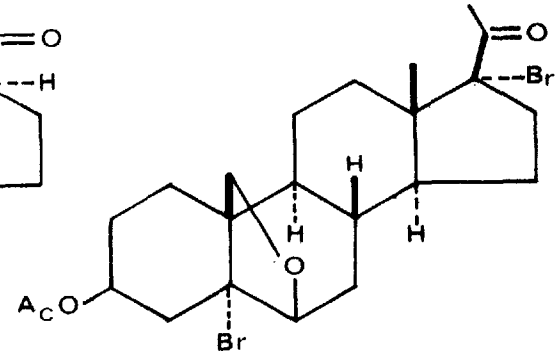

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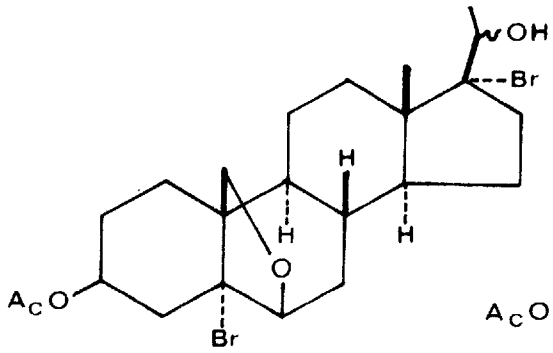

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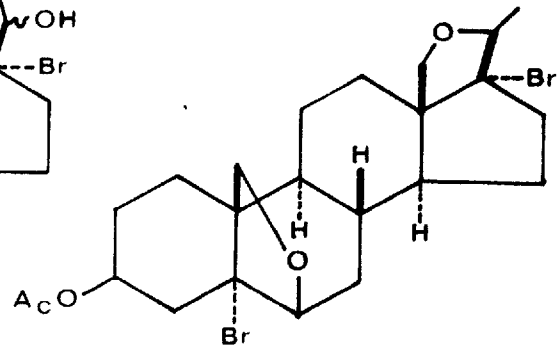

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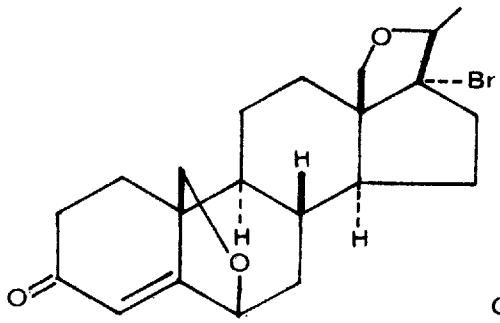

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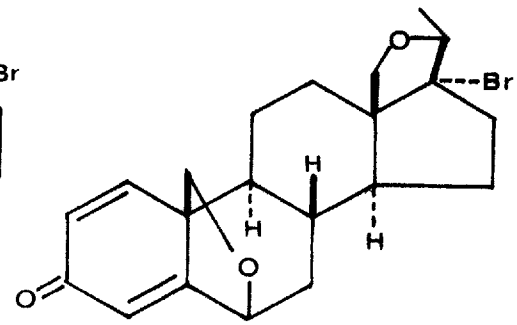

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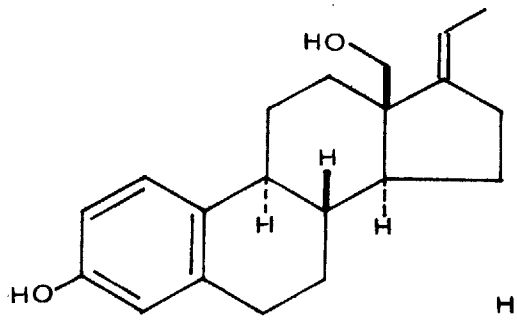

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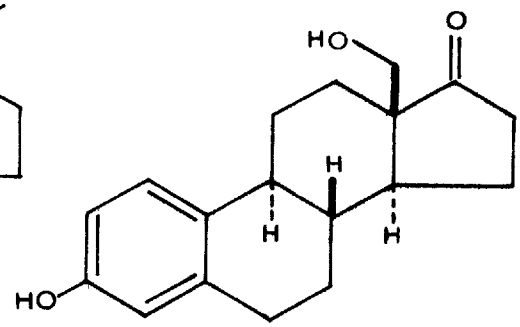

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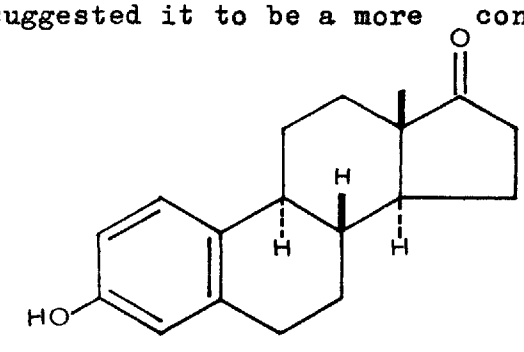
(SCHEME I)

The aromatization of ring A would probably be best achieved after introduction of the 1,2 double bond with selenium dioxide as indicated (65→66) as this would create a reasonable path for the elimination of carbon-19.

Such a scheme was considered at the beginning of our work when the functionalization of carbon-19 of cholesterol and pregnenolone acetates was carried out from the respective 5,6 bromohydrines (60) in presence of tert-butylhypochlorite-iodine and lead tetracetate--iodine in repetition of the work previously described 13, 33.

However the ready availability of oestrone (69) and its relationship to the discovered 18-hydroxylated compound suggested it to be a more convenient starting



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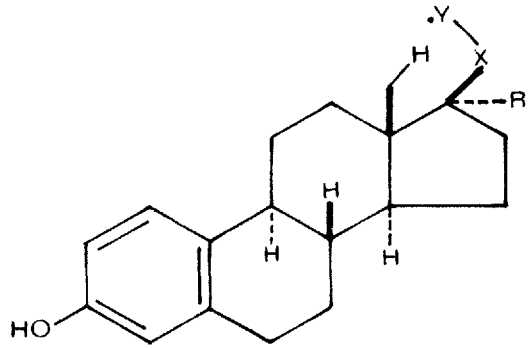
material and no further studies were carried out on cholesterol or pregnenolone precursors.

Elaboration of the C-17 side chain

The required six member transition state for the discussed functionalization reactions made it essential that a two atom fragment in the β position be attached at carbon-17 in order to achieve the configurational relationship between the carbon-18-methyl and the functionalizing radical, as in (70).

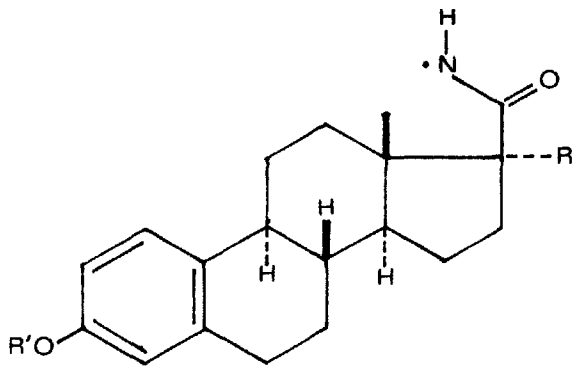


(70)

The selection of fragment X—Y was governed by two requirements: first that atom Y, as a radical, should abstract hydrogen in the manner described and secondly that X—Y be removable under mild conditions to regenerate the 17-ketone.

It was clear that the carbamoyl radical (71) was the method of choice since it was both easy to introduce (via the 17-cyanohydrin) and it had recently been amply demonstrated in our laboratory to be an active radical in the abstraction process[14, 15] .

Its introduction by hydrolysis of the appropriate cyanohydrin would further provide a 17 α-hydroxyl ,



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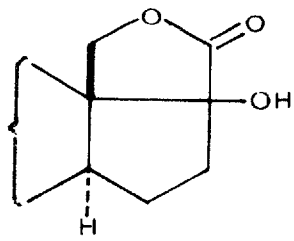
(71, R = OH), which after photolysis would give an α-hydroxy lactone (72) from which the regeneration of the 17-ketone could be achieved in one step under mild acidic[16] or neutral[17] conditions thus preventing the

elimination of the 18-carbon atom and yielding directly the 18-hydroxy compound (73).



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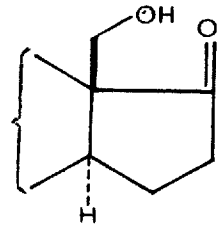

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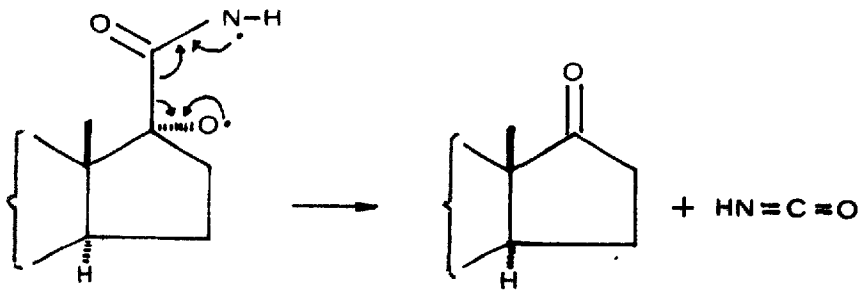
Under the photolytical conditions the 17α-hydroxyl group would be oxidized to an oxygen radical and although its configuration would prevent any intramolecular abstraction it could be foreseen that the carbamoyl group would probably collapse to regenerate the 17-ketone liberating cyanic acid (74 → 75) in preference to the desired abstraction of the 18-methyl proton.



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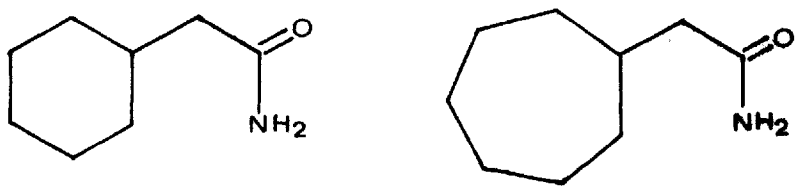
Therefore the 17 α-hydroxyl would require protection and to this end the tetrahydropyranyl group[18] was thought to be most appropriate.

At this stage some model studies were undertaken to find out separately whether all those considerations could have a practical confirmation.



76 77

The photolytic reaction was first studied in models

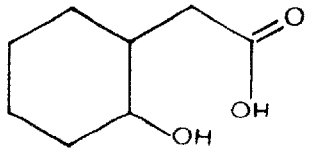
similar to the natural occurring sesquiterpenoid lactones[19], i.e., cyclohexyl and cycloheptyl acetamides (76 and 77, respectively) which were synthetised by known processes [20, 21, 22, 23] from the available cyclohexyl bromide and cycloheptanone.

The N-iodo amides were prepared *in situ* with excess *tert* butylhypochlorite-iodine[14,15] the photolysis being carried out in the same usual manner (see experimental). The crude products obtained were always treated with a base, either sodium bicarbonate or sodium hydroxide, and separated into two phases: acidic and neutral fractions. The former were essentially γ-lactones due to 1,4 abstraction and the neutrals contained in general a small percentage of the starting amide. The reactions were followed by the disappearance of the amide band in the infrared spectrum.

The yields obtained for the crude acidic fractions were 60% for the cyclohexylacetamide and 95% for the cycloheptylacetamide.

In systems such as this where the relevant groups are not forced to a fixed geometrical relationship and bearing in mind that these photolytic reactions were carried out in presence of excess oxidant several products different from the expected γ-lactones (78) could be

assumed to be formed. These could result from further oxidation at the α positions as in (79), (80) or (81) , including the cis and trans isomers of each hydroxyl function. However no evidence was obtained for any of



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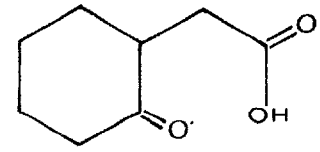

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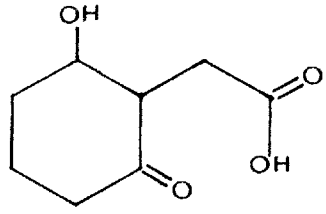

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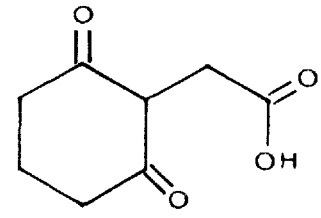


81

these secundary products. The infrared of the crude products did not reveal the presence of any ketone band and the only isolated substances were the starting amides in the neutrals and γ-lactones which were characterized through their benzylamides derivatives for the cyclohexane system and hydrazides for the cycloheptane system, both having been previously described[23, 24, 36].

The elaboration of the 17- β-carbamoyl fragment was studied with oestrone-3-methylether and the cyanohydrin

was first prepared by exchange with fresh prepared acetone cyanohydrin[25] in presence of a catalytic amount of triethylamine.

The product isolated had spectra and properties in accord with its formulation as the 17-cyanohydrin , analysed correctly and had a specific rotation of +72º with a wide melting zone 153 - 175º.

Molecular rotational differences calculated from the androstane analogues (Table I) suggested it to be a mixture of two isomers at the 17 position with a higher percentage of the 17- β -hydroxy-17 α -cyano-derivative.

This mixture could not be separated by selective crystallization or chromatography.

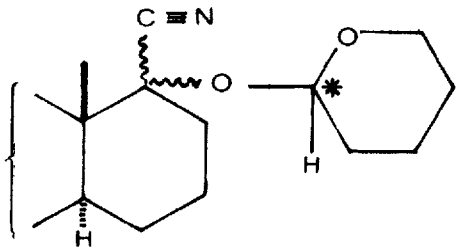
It was reported[26] that two similar isomers could be separated after selective acetylation with acetic anhydride in pyridine or by selective crystallization of the corresponding tetrahydropyranyl derivatives[18].

TABLE I

17 β Cyan α Hydroxyl	M_D = 301	$[\alpha]_D$=+ 106
17 α Cyan β Hydroxyl	M_D = 62	$[\alpha]_D$=+ 22

Calculated from values obtained[26] for 5 α androstanolone and Δ 5 androstenolone.

However our mixture did acetylate completely without any difference in rate (TLC) and although separation of the two isomers was accomplished by chromatography on alumina of the tetrahydropyranyl derivatives, the separate acidic hydrolysis of the tetrahydropyranyl group in the separate isomers gave back identical mixtures of the cyanohydrin isomers. The isomer isolated in higher yield (67%) had the higher rotation (see experimental) suggesting it to be the desired 17- β-cyano-17-α- tetrahydropyranyloxy compound albeit the protective group introduces as well a new asymmetric center (82).

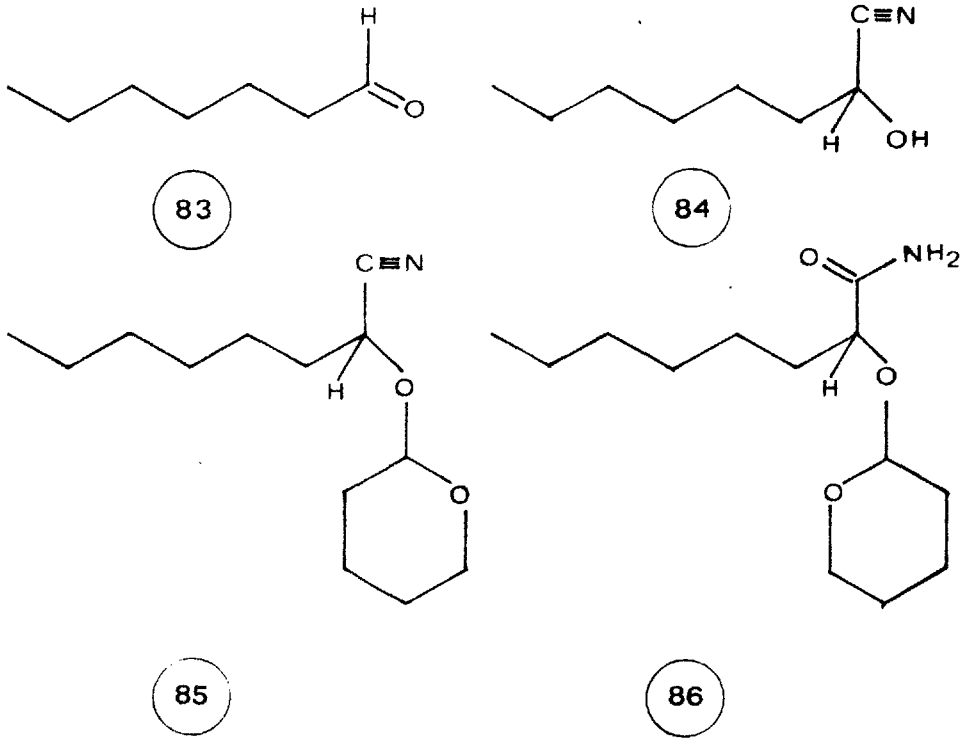


82

The preparation of the same cyanohydrin by direct action of cyanhydric acid prepared *in situ* by dropwise addition of acetic acid to an alcoholic suspension of potassium cyanide[27,28], gave in nearly quantitative yield a substance identical with the previous mixture and with a specific rotation, $[\alpha]_D$=+ 20º which by the Molecular Rotation Differences calculation would correspond to nearly 100% of the 17-α-cyano-17-β-hydroxy isomer.

Before going further in the characterization of these products their applicability for the photolytic process was ascertained. In particular it was necessary to find out how the protective group would stand up to the process and to this end model experiments were undertaken with 2-tetrahydropyranyloxy-*n*-octanamide (86).

This compound was prepared from heptaldehyde (83) in 30% overall yield through the cyanohydrin[28] (84), formation of the tetrahydropyraniloxy derivative (85) and hydrolysis of the cyano-group, as outlined in scheme III.



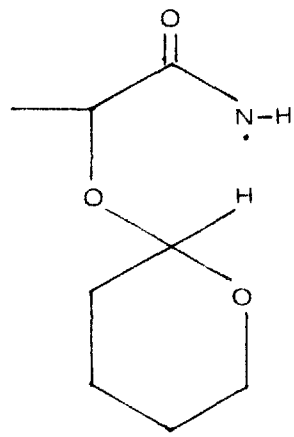
83 84 85 86

(Scheme III)

Photolysis of this compound (86) in presence of lead tetracetate-iodine failed to give abstraction in the carbon chain, the only product isolated after alkaline hydrolysis being the α-hydroxy-acid which was characterized after acetylation of the hydroxyl and methylation of the acid function by G.L.C. against an authentic separately synthetized from the correspondent amide. These results can be rationalized by assuming that the methine hydrogen in the tetrahydropyranyl group is in a stereochemically and energetically favourable position to be preferentially

abstracted by the carbamoyl radical (87).

The tetrahydropyranyl group being apparently unsuitable for the process and given the difficulties in obtainning the hydroxyamide with desired configuration at C-17, a more classical route (scheme IV) was considered in which the cyanohydrin (88) was dehydrated[29] to give the 16,17-double bond (89) and later hydrogenated in presence of an heterogeneous catalyst[30] to give the nitrile with the β-configuration (90) from which the amide (91) could be obtained by hydrolysis.



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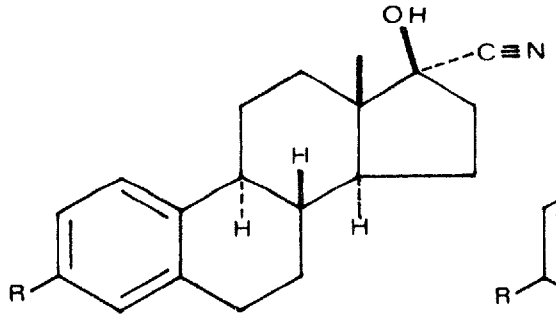

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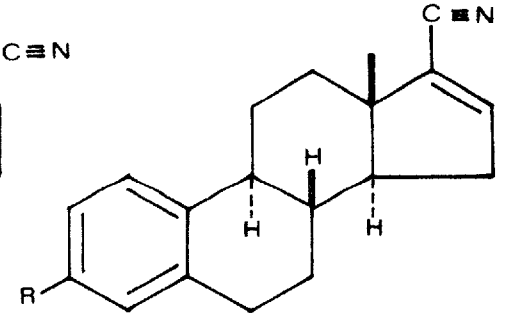

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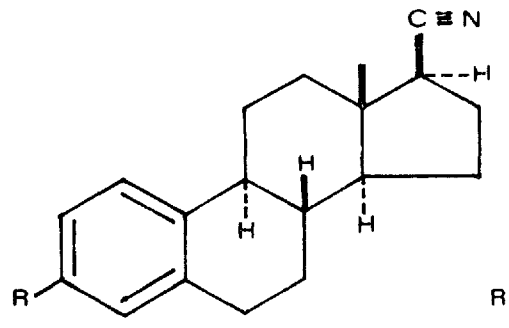

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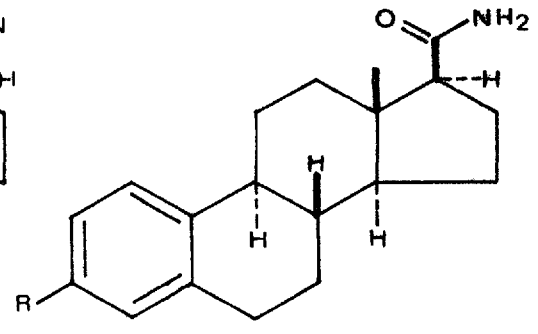

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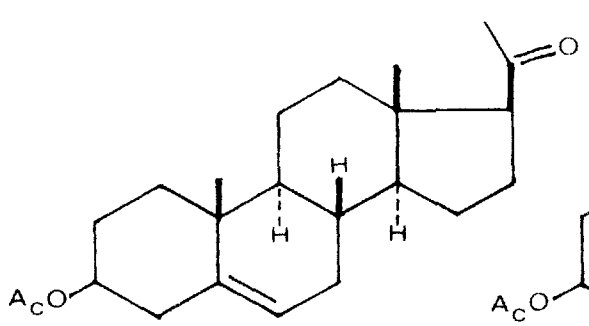
(Scheme 1V)



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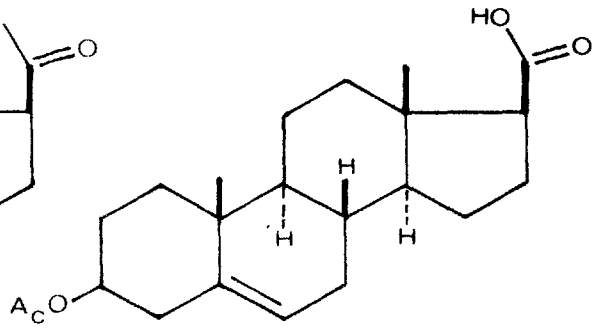
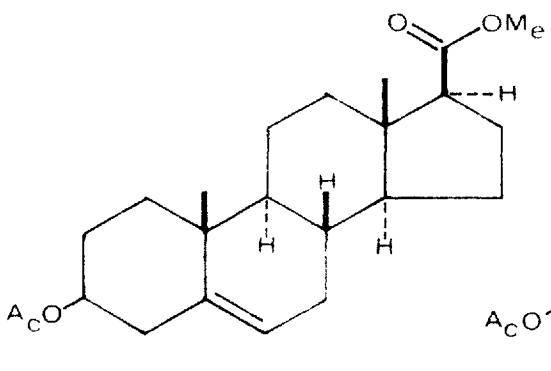


93

However before starting this preparation it was confirmed that the carbamoyl radical in the desired conformation would abstract a proton from the 18-methyl group. Thus 3 β -acetoxy aetianic acid amide (97) was chosen as model and prepared from 3- β -acetoxy pregnenolone (92) which was oxidized with sodium hypobromite[25] to aetienic acid (93), acetylated with

acetic anhydride-pyridine, and then methylated with excess diazomethane to give aetienic acid methyl ester 3 acetate (94). This compound was then hydrogenated at normal pressure in acetic acid with Adam's catalyst[31] to give the 5-α-3-β-acetoxy aetienic acid methyl ester(95), isolated in 76% yield after recrystallization from chloroform-diethyl ether. The hydrolysis of the methyl ester with dilute sodium hydroxide in dioxane gave after reacetylation the aetienic acid-3-acetate which was not epimerised at C-17. The final amide (97) was prepared through the acid chloride[32] (thionyl chloride) which was precipitated into ammonia hydroxide.



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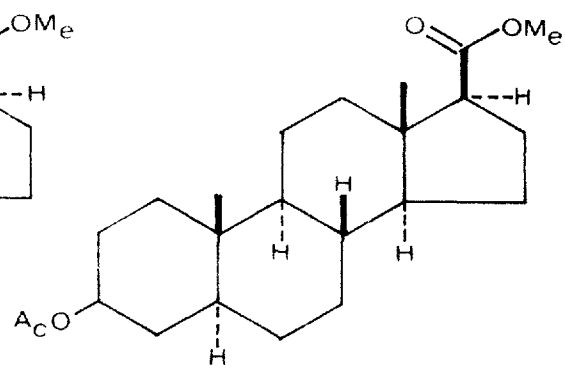

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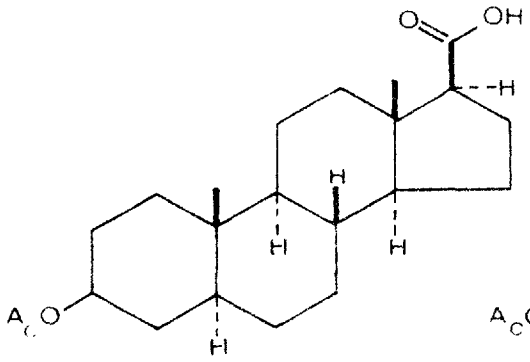
Photolysis of this amide in benzene in presence of excess lead tetracetate-iodine led to a crude acidic product which upon hydrolysis showed bands at 1840 and 1780 cm^{-1} in



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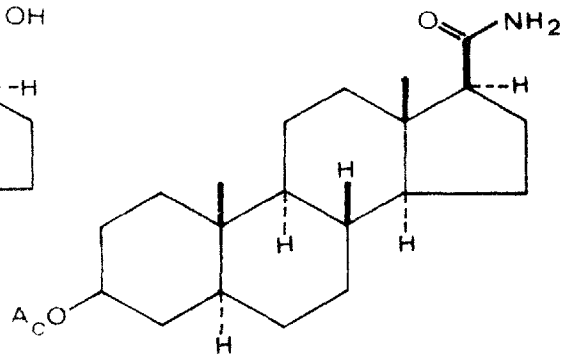
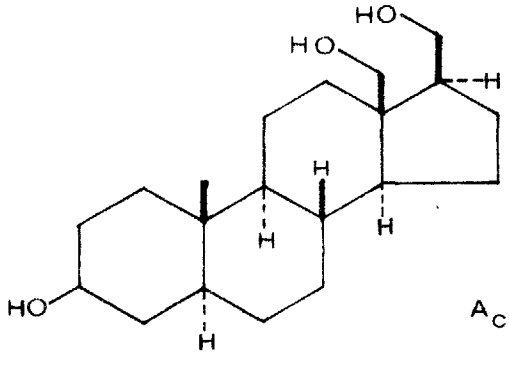


97

the infrared and no absorption for the 18-methyl group in nmr. After reduction of this product with excess lithium aluminium hydride in THF followed by chromatography on alumina the 3,18,20-trihydroxy oetiane (98) was isolated and characterized. When the crude product was shaken with zinc in acetic acid and lead salts cautiously removed

before evaporation, a yellowish oil was obtained which crystallized from diethyl ether as the 18,20-dicarboxylic acid anhydride (99) in 21% yield. The isolation of these compounds proved that the carbamoyl radical was able to



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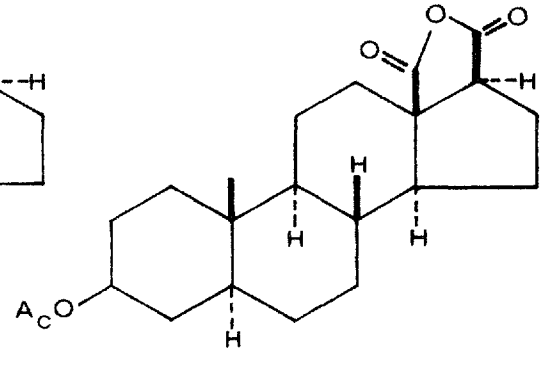


99

functionalize the 18-methyl group as desired. The fact that it went further to give more than one abstraction was not altogether unexpected due to stereochemical strain of the 18-iodomethyl intermediate, as discussed in the previous chapter. However only two electron oxidation products (aldehydes or hemiacetals) had been previously obtained. At this point without making further investigations to explain this result which due to absence of the

19-methyl group may not occur in the oestrone series, it only remained to elaborate in these compounds the carbamoyl group with the correct configuration. This was done by the pathway shown in scheme IV, from the 17-cyanohydrin previously prepared having the phenolic hydroxyl group protected with a methyl ether function. However when the corresponding amide was submitted to photolysis it became clear that the phenolic nucleus was sensitive to the reaction conditions and would require protection.

The protection of the phenolic residue

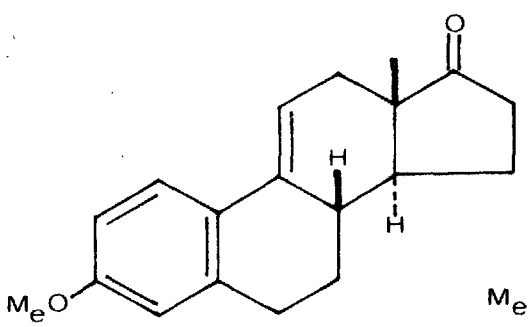
A scheme for evaluation of protecting groups was devised. Oestrone and its different 3-derivatives were submitted to exactly the same photolylic conditions for equal periods of time. After identical work up the mixtures obtained were compared by TLC with the starting materials and, whenever possible, these were isolated. The results are summarized on the following table:

3-derivatives	Product (TLC)
3-OH	No starting material (very complex mixture)
3-OMe	"

(Cont.)

3-derivatives	Product (TLC)
3-benzoyloxyl	No starting material
3-benzenosulphonyloxyl	"
3-tosyloxyl	40% starting material
3-mesyloxyl	60% starting material

It was evident that the more strongly electron--withdrawing groups were the more able to provide the desired protection. When the mixture obtained from the photolysis of oestrone methyl ether was dehalogenated by zinc in acetic acid before work up and then carefully chromatographed a crystalline mixture was obtained which showed U.V. λ max 268 mμ (9.000) and nmr τ 3.85 ($CDCl_3$) (multiplet) spectral properties compatible with a mixture of the 9,11 and 8,9 dehydroestrone 3 methyl ethers (100 and 101 respectively).



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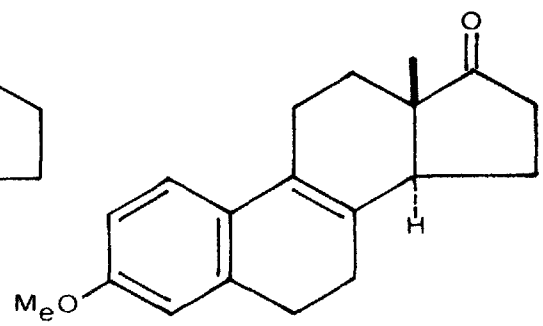
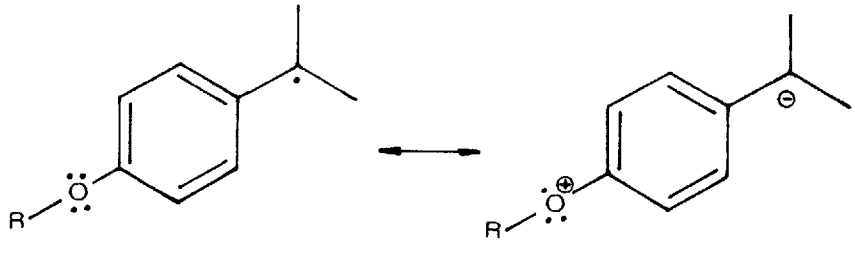


101

It therefore appeared that the carbon-9 methine hydrogen was sensitive to the reaction conditions. There is ample evidence in the literature that carbon radicals adjacent to oxygen are especially stabilized; for example the ready autoxidation of ethers is well known and this has been ascribed to a special stabilization of the carbon radical in the manner of (102) which could in our case be relayed through the aromatic ring to give a

(102)

stabilization in the manner of (103).

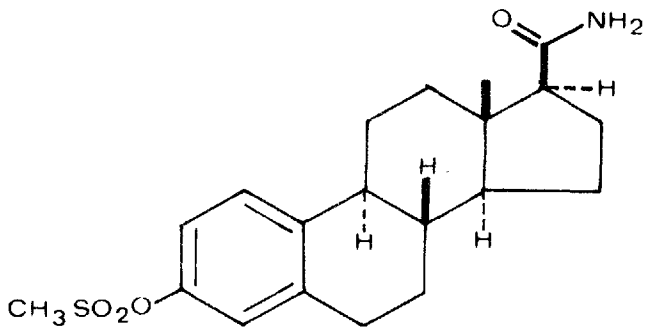


(103)

The presence of an electron withdrawing substituent in oxygen would therefore make the abstraction of the carbon-9-hydrogen less facile which was supported by the above results.

Photolysis of oestrone 17 carbamoyl

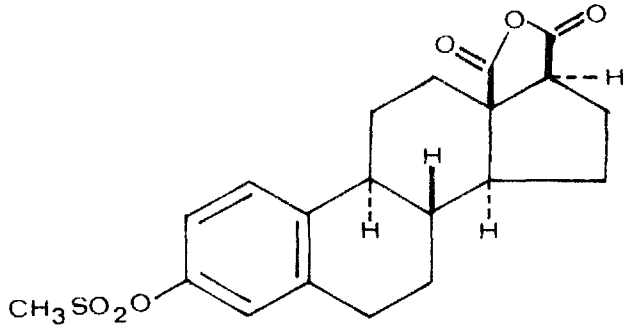
The same reactions as outlined in scheme 4 were carried out on oestrone-3-methanesulphonate and the amide (104) was obtained and submitted to the photolytic conditions, using lead tetracetate-iodine in benzene .



(104)

After the lead salts formed during the work up were removed and the neutrals separated in the usual way , an oil remained which could be crystallized from acetyl chloride and then from benzene to give the 18,20 -

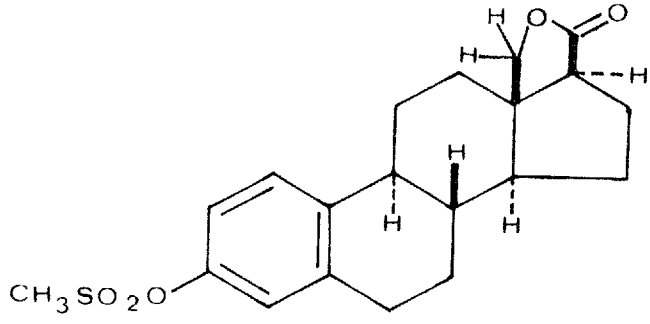
-dicarboxylic acid anhydride (105).



(105)

In the introduction a rationalization for further oxidation of carbon atoms was presented, based on the restricted rotation around the single bond between the carbon bearing iodine and the adjacent atom , this steric

impediment was attributed to the bulky iodine atom and to the C-19 methyl. From the results obtained in the cyclohexane and cycloheptane acetamides, (76) and (77) respectively, as well as from other known results and from the absence of C-19 methyl in our series, it was hopefully expected that no further oxidation would occur and the reaction product would be the 18-hydroxy--20-acid lactone (106). In this case the 18-alcohol could be easily protected by acetylation,the free acid

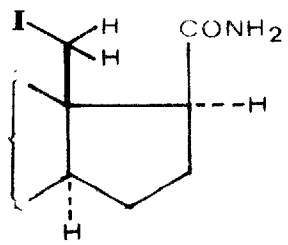


(106)

decarboxylated, and the ketone at C-17 easily regenerated to give the desired 18-acetoxyoestrone.

The discussion given in the introduction allows for the formation of a two electron oxidation by postulating that the iodomethyl compound (107) is forced into such a configuration that the functionalizing species being

regenerated by the excess oxidant would be in position to abstract a second hydrogen from the iodomethyl group as in projection (108).



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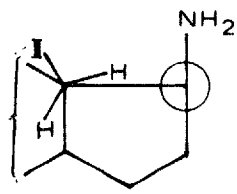
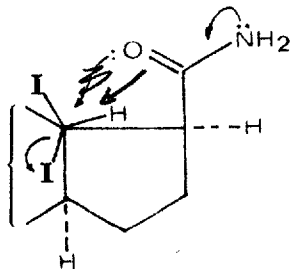


(108)

So the formation of an aldehyde function at C-18 would not be surprising. However it is difficult to understand how such a process could allow for further oxidation to the carbonic acid level.

A possible explanation for the formation of the diacid product (105) is as follows. If a second iodination of C-18 occurred, due to the steric factors mentioned above, this would lead to the formation of species (109), in which one iodine is sterically situated for an internal S_N2 displacement, see arrows,



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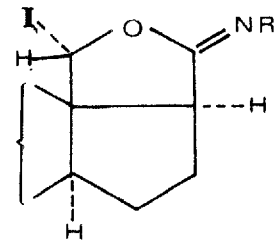

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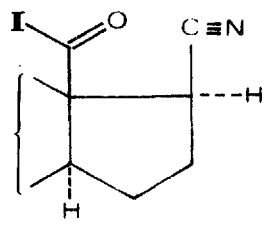
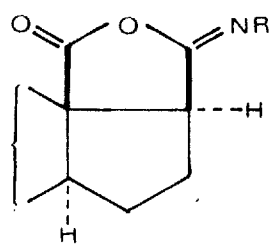
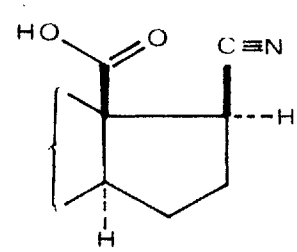


(111)

providing the imino-ether (110, R=H). Iodination at nitrogen of this intermediate to an N-iodo derivative (110, R=I) followed by elimination provides an intermediate acyl iodide (111). Exchange of the iodide in this species by acetate present in the reaction followed by ring closure



(112)

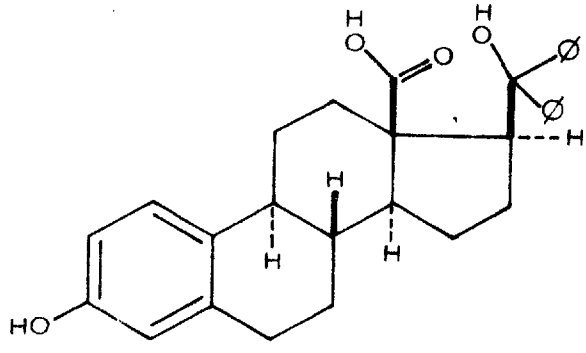


(113)

would yield the isomide (112, R=H). Exchange of iodide, without ring closure would provide the nitrile (113) . Evidence for the first of these intermediates (112) was obtained by carrying out a non-reductive work up which gave an oil, whose analytical composition and spectral properties were in accord with the formulation (112,R=I). Further, it was observed that by taking aliquots from the reaction it was possible to show by infrared the presence of a nitrile absorption, consistent with species such as (111) or (113).

Degradation of the side chain

We were confronted now with the problem of removing the side chain and reducing the carbonyl at C-18 in the product (105). The different steric environment of the carbonyls at C-20 and C-18 made it acceptable that the former could be preferentially attacked by Grignard reagents. In fact when the anhydride (105) was allowed to react with an excess of phenyl lithium or phenyl magnesium bromide in tetrahydrofuran the diphenylcarbinol (114) was formed and dehydrated with acetic anhydride to the lactone (115).



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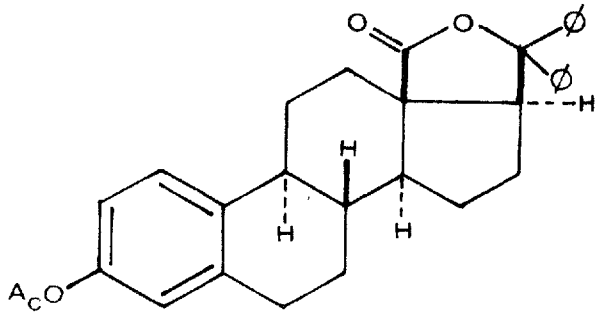
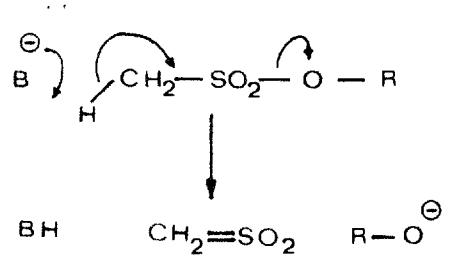


(115)

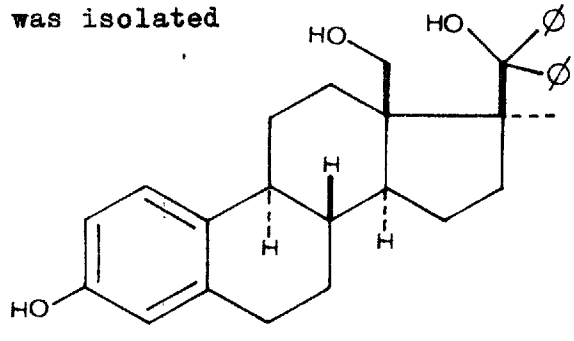
The loss of the 3-methylsulphonyl group during the reaction with phenyl lithium probably is the result of attack of the base on the methyl sulphonyl group, as

exemplified in the following scheme (116).



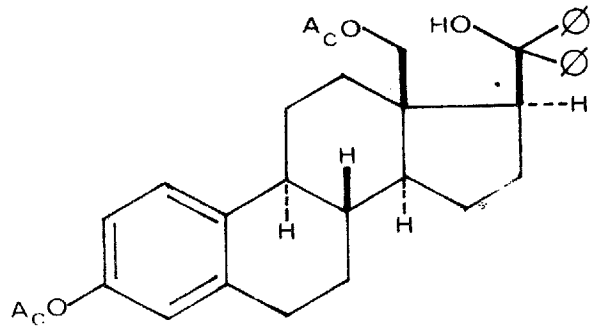
(116)

The lactone (115) was reduced with lithium aluminium hydride in tetrahydrofuran to the triol (117) which again was isolated as the



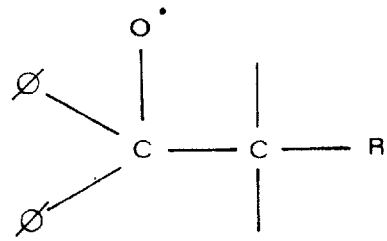
(117)

3,18-diacetate (118) after acetylation with acetic anhydride-pyridine.



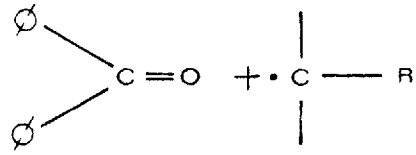
(118)

Having succeeded in differentiating between C-18 and C-20, and further having protected C-18 by acetylation it remained now to remove the diphenylcarbinol at C-17 in such a way that the C-17 ketone could be reformed. It was thought that if an oxygen radical, as (119), was formed at a carbon bearing two aromatic rings cleavage of the carbon-carbon bond to benzophenone and a



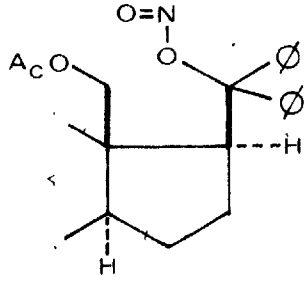
(119)

new carbon radical (120) might occur.

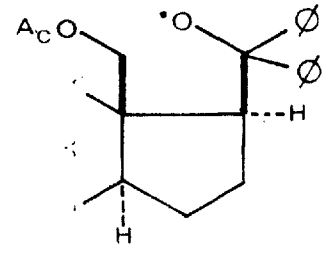


(120)

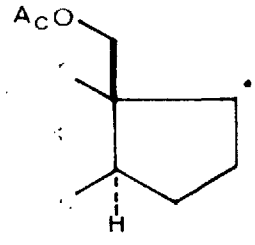
We proposed therefore to use the photolysis of the nitrite (121) to obtain the oxime (124), by way of the intermediate radicals (122) and (123).



(121)



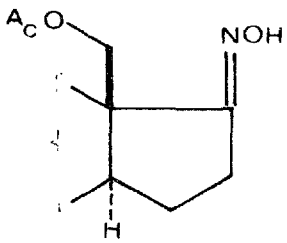
(122)



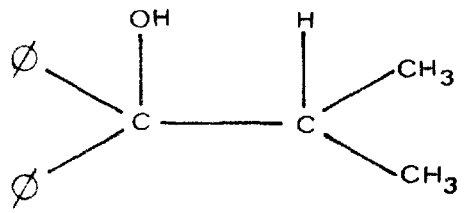
(123)

That the oxime could be easily removed was found when we showed that oestrone oxime upon treatment with nitrous acid gave oestrone in near quantitative yield.

This new carbon-carbon bond cleavage was therefore studied first in model compounds. Diphenylisopropyl carbinol (125) was prepared by action of an excess phenyl

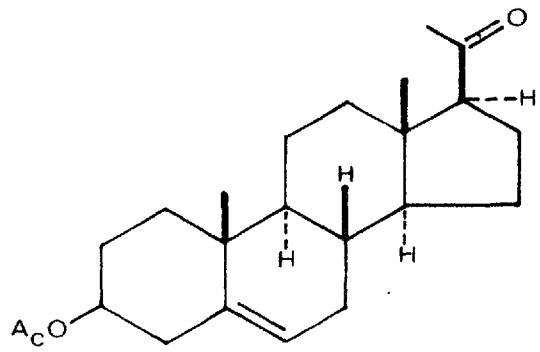


(124)



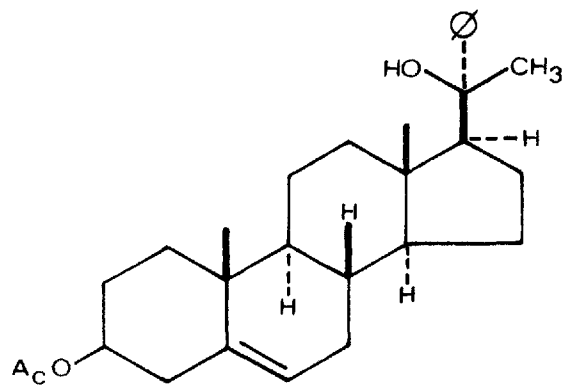
(125)

magnesium bromide on the methyl ester of isobutyric acid. The corresponding nitrite was prepared and photolysed in benzene where a very clean and nearly quantitative reaction was seen to occur in less than 15 minutes. Benzophenone and acetone isolated and characterized through the dinitro - phenylhydrazones, were formed, the later having been previously regenerated from the oxime with nitrous acid.

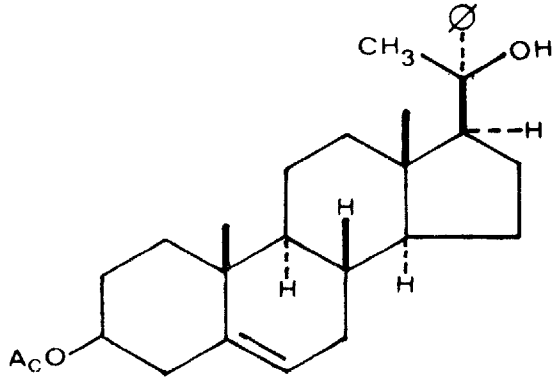


(126)

We next converted pregnenolone acetate (126) to the 20α and β isomeric carbinols, which were separated by crystallization of the 3-acetates (127) and (128).

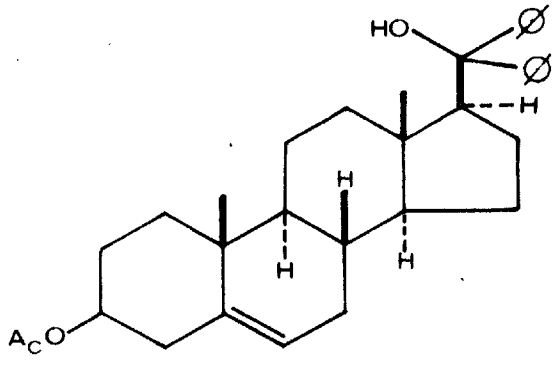


(127)



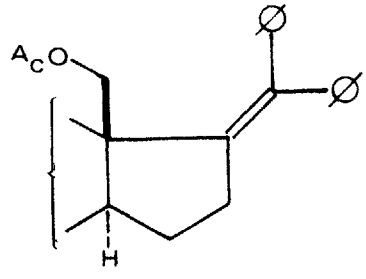
(128)

Photolysis of the mixture of isomeric nitrites carried out on a small scale did not show in TLC any spot corresponding to acetophenone and so a better model was prepared from aetienic acid methyl ester (94) which was reacted with an excess of phenyl magnesium bromide to yield, after acetylation, the diphenylcarbinol (129).

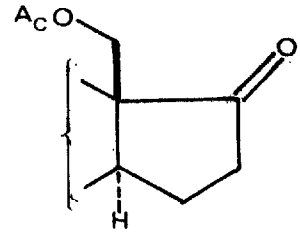


(129)

The crude product from photolysis of the corresponding nitrite did show on TLC six different spots all different from the expected benzophenone and the nmr carried out on a crude sample showed the absence of the 18-methyl signal. Clearly the abstraction of one or more hydrogens from the 18-methyl group was preferred to the expected cleavage , the steric configuration of the centers apparently was a major factor against the cleavage. This carbon-carbon cleavage thus proved to be useless in our problem and so another and more classical way was attempted, which involved the dehydration of the carbinol (119) to the ethylene (130). The latter would hopefully be ozonised to the 17-ketone (131).

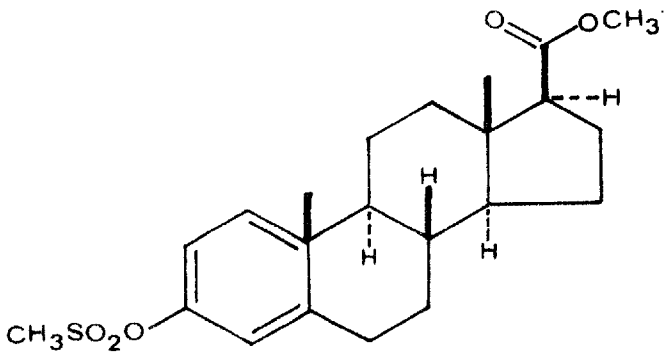


(130)



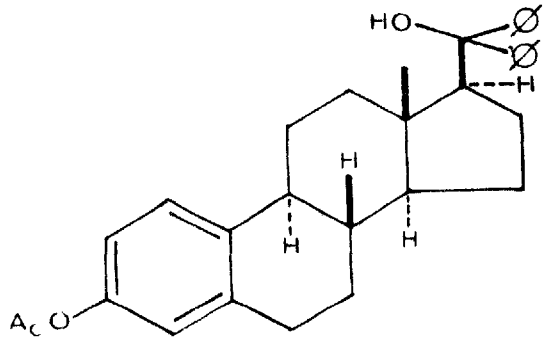
(131)

It was again convenient to study this reaction first on a model compound and in this case the nitrile (90) was hydrolysed to the corresponding acid and then treated with diazomethane to yield the methylester (132).



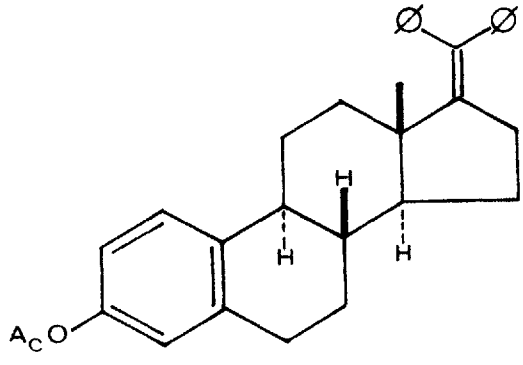
(132)

Treatment of this compound with excess of phenylmagnesium bromide proceeded to the 20-diphenylcarbinol (133) which was isolated after acctylation. This compound



(133)

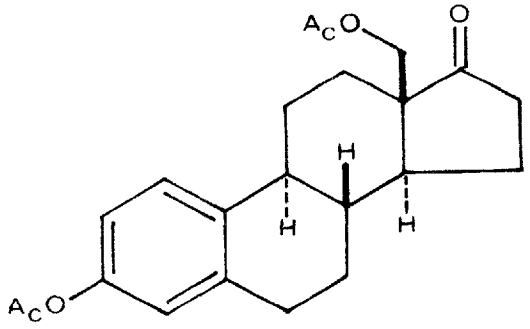
was dehydrated with thionyl chloride in pyridine to yield the olefine (134) and this could be ozonised to benzophenone and oestrone.



(134)

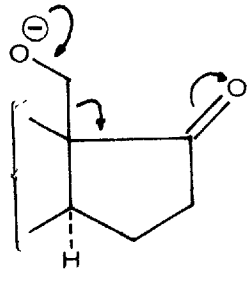
Repetition of this sequence on the carbinol (118) proceeded smoothly to the diacetate (135) of 18-hydroxyoestrone and we were left with the problem of hydrolysis of this

derivative. It had been previously noted by Marrian[3] that in alkaline media the C-18 carbon atom was lost by retroaldol reaction (136) to (137).

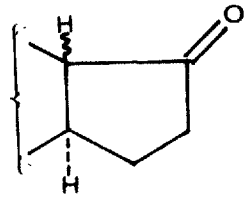


(135)

For this reason we first studied the hydrolysis of icterogenine acetate (138)[8].

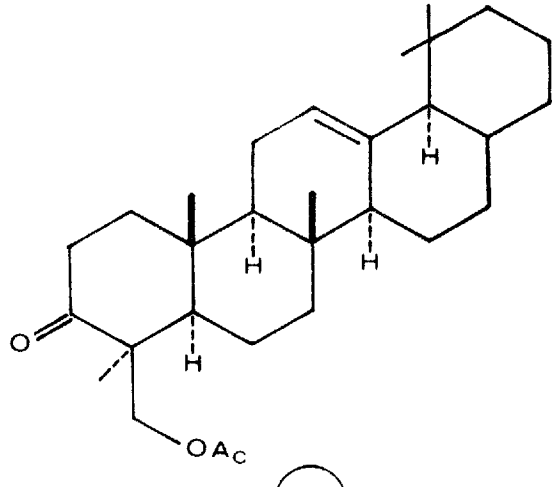


(136)



(137)

We found that by hydrolysis with dilute sodium hydroxide in methanol at room temperature it was possible to remove the acetyl residue without retroaldol reaction. However this hydrolysis was more easily carried out in acidic conditions, using hydrochloric acid in methanol. Application of this latter procedure to the ester (135) gave the desired 18-hydroxyoestrone (139), in good yield.



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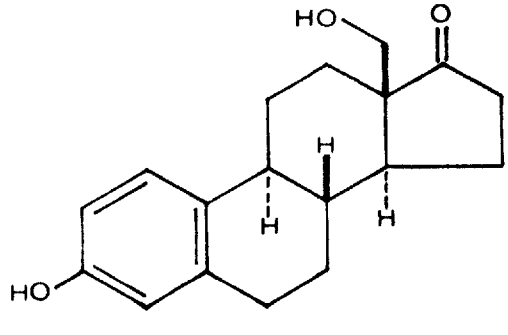

139

EXPERIMENTAL

Melting points are uncorrected and were determined on the Kofler hot stage unless otherwise specified. Infrared spectra were recorded on a Unicam SP200 in chloroform except where specified. NMR spectra were recorded on a Varian A 60 instrument in deuterochloroform or carbon tetrachloride as specified, using tetramethylsilane as internal reference . Rotations were measured in chloroform and U.V. spectra in ethanol. Light petroleum refers to the fraction boiling between 60 and 80º . Column chromatography was carried with acid washed alumina standardized to grade III or silica gel MFC grade (Hopkins and Williams). Lead tetracetate was dried under reduced pressure in presence of sodium hydroxide and phosphorus pentoxide.

Some special reagents were prepared as follows:

N-Bromoacetamide - E. P. Oliveto and C. Gerold, Organic Synthesis (1963) Coll. Vol. 4, 104. Yield 25%. This was stored at 0º C in the dark. When necessary it could be recrystallised from diethylether.

tert-Butylhypochlorite - H.M. Teeter and E.W.Bell Organic Synthesis (1952) 32 20; C.P.C.Bradshaw and A. Nechvatal Proc.Chem.Soc. (1963) 213. The solution was titrated by

iodometry and kept in a stoppered flask at 0º. No purification was necessary.

Cycloheptylbromide was prepared from cycloheptanone by reduction to cycloheptanol with lithium aluminium hydride in diethyl ether and conversion to the bromide by slow distillation from a mixture with hydrobromic acid according to O. Grummitt Org.Synt. (1939) 19 88; E.E.Reid, J.R. Ruhoff and R.E. Burnett Org.Synt. (1935) 15 24. B.p. 15 mHg, 80-83º

Acetone cyanohydrine was prepared by reaction of potassium cyanide with the sodium bisulphite adduct of acetone as described by R.F.B. Cox and R.T.Stormont Organic Synt.(1935) 15 1. It was not stored more than two days.

I) 5 α-Bromo-6 β-hydroxycholesteryl acetate

In a 250 ml three neck flask, protected from light, N-Bromoacetamide (1.6g, 2.3 mmol) was added in small portions to a stirred solution of cholesteryl acetate (2g) and perchloric acid (1 ml of 0.5 M aqueous sol.) in dioxane (30ml) and water (10 ml) at room temperature. The reaction was followed by TLC and, after completion, the excess of N-bromoacetamide was destroyed by a few drops of an aqueous solution of sodium thiosulphate. Water (100ml) was added and the product extracted with dichloromethane.

Evaporation under reduced pressure, followed by crystallization from chloroform-light petroleum, gave crystals (62% yield) m.p. 162-66º. Recrystallization from the same solvent pair gave a sample with m.p. 177-79º , $[\alpha]_D$= -37º (C, 0.1 $CHCl_3$) [33] .

II) 5 α-Bromo-3 β 6 β-dihydroxypregna-20-one-3-acetate

The procedure described in the previous example was repeated with pregnenolone acetate (2g) and crystallization from the same solvent pair gave 80% of TLC homogeneous crystals, m.p.166-67º C$[\alpha]_D$= + 7.7 º (C0.1 $CHCl_3$) values in agreement with the previous reports (m.p.165-67º,$[\alpha]_D$= + 6.5)[13].

III) 5 α-Bromo-6,19-oxidocholest-3yl-acetate

A) Lead tetracetate

A 250 ml three neck round bottom flask equipped with stirrer, reflux condenser, and a charging funnel with nitrogen inlet was immersed in water. Through a lead coil surrounding the flask running tap water was passed continuously during the reaction to prevent the temperature inside the flask rising above room temperature. The whole assembly was suspended over a 125 w high pressure mercury lamp and completely surrounded by thin aluminium foil.

To the flask a solution of the 5α-Bromo-6β-hydroxy cholesteryl-3β-acetate (2g) in benzene (250ml) was added, followed by dry lead tetracetate (10g). Iodine (6g) in benzene (100ml) was placed in the charging funnel and one third was added at once. The light was turned on and at one hour intervals the remaining iodine solution (3 additions) was added. The reaction was followed by the disappearance of the hydroxyl band in the infrared spectra carried out on small samples separately worked up and was seen to be complete after ten hours.

The precipitated lead salts formed were filtered through celite 500 and the solution shaken with aqueous sodium metabisulphite solution to remove excess iodine. Evaporation under reduced pressure gave a residue which, after chromatography on alumina, could be crystallised from methanol, (1.4g) (70%)crystals m.p.134-42°C$[\alpha]_D$=+ 7°. A recrystallized sample had m.p.151-53°,$[\alpha]_D$=+ 4.0 (CO.1) ν max 913 cm^{-1}, (Found C 66.7%, H 9.15%, Br 15.22%; $C_{29}H_{47}BrO_3$ requires C 66.53%, H 9.05%, Br 15.25%).

B) tert-Butylhypochlorite

Using the same assembly as above 1.6g of 5α-bromo-6β-hydroxycholesteryl acetate in benzene (100 ml)was photolysed in the presence of tert-butylhypochlorite (10 ml) which was added in three different potions (50%; 30%; 20%) over one

hour intervals. The residue obtained showed many different spots on TLC and after careful chromatography on alumina gave 44% yield of the 6,19-oxide, m.p.150-51º, $[\alpha]_D$ = 4º, infrared identical with the previous sample.

IV) 5α-Bromo-6,19-oxido-pregna-20-one-3yl-acetate

The same assembly as above used to photolyse the 5α-bromo-6β-hydroxypregna-20-one -3yl-acetate (1g) in benzene (100ml) and iodine (4g) to which tert butyl hypochlorite (10mls) were added in three different portions as described. The reaction proceeded for one hour after the last addition of tert-butylhypochlorite and was worked up by shaking the benzene solution with an aqueous solution of sodium metabisulphite, to eliminate excess iodine . Chromatography of the residue on neutral alumina gave , after crystallization from dichloromethane-light petroleum (0.250g) m.p. 145-48º, $[\alpha]_D$ = 57º (c 0.1), ν max 920 cm^{-1}., values in accordance with those previously reported[13].

V) Cyclohexylacetamide

Mettalic sodium (6g) was dissolved in freshly dried ethyl alcohol (100 ml). Diethyl malonate (30 g) and cyclohexylbromide (32 g) were added and the solution refluxed with stirring for 24 hours[20]. Water (300 ml) was added, the alcohol removed by evaporation and the oily

layer taken with diethyl ether and distilled to give 2-cyclohexylmalonic acid diethyl ester (25 g), b.p. (10 mmHg) 126-128º. This compound without further purification was hydrolized by refluxing in ethyl alcohol (50 ml) with 50% potassium hydroxide (40 ml) for one hour. Neutralization with hydrochloric acid followed by removal of the alcohol by evaporation precipitated the cyclohexylmalonic acid (17.6g) m.p.187-9º. Decarboxylation under nitrogen at 200º provided the cyclohexylacetic acid as an oil, which on distillation b.p. (10 mm/Hg)122-24º, solidified to m.p. 28º, (11.3 g).

The acid (11 g) was treated with neat thionyl chloride (10 ml) at reflux for one hour and then added dropwise to a cooled and well stirred concentrated ammonia solution. The precipitated solid was collected, washed with cold water and crystallized from water (11 g) , m.p.165-68º, yield 42%. A small sample was sublimed giving, m.p.169-70º [34], ν max 1585;1670;3400;3500 cm^{-1}, Found C 67. 78%, H 10.88%, N 10.04%, $C_8H_{15}NO$ requires C 68.04%, H 10.71%, N 9.92%.

VI) Cycloheptylacetamide

This compound was prepared from cycloheptylbromide *via* the malonic ester condensation as above, to give first

the cycloheptyl diethyl malonic ester, isolated by distillation (b.p.1 mm/Hg 130-2°,76% yield). This ester was hydrolysed and the diacid decarboxylated under nitrogen. The cycloheptylacetic acid thus obtained was transformed into the corresponding chloride by refluxing with excess thionyl chloride and then added dropwise to a stirred and cooled aqueous ammonia solution. The crystals formed were separated by filtration, dried and crystallised from ethyl acetate to give needles, m.p.147-50°, ν max. 1590,1675,3400,3500, $cm.^{-1}$ in agreement with values previously reported[22].

VII) Photolysis of cyclohexylacetamide

The same assembly as described above in III was used. Cyclohexylacetamide (1g) in benzene (135 ml) and chloroform (15 ml) was irradiated for 6 hours in presence of iodine (7.3 g) and tert-butylhypochlorite (1.7 ml) which was added in portions during the first three hours of the reaction as has been described[14;15].

The excess iodine was removed by shaking with excess sodium metabisulphite (30g) in water (150ml) and the organic layer separated and evaporated to dryness under reduced pressure. The residue was extracted with a 10% solution of

sodium bicarbonate (150 ml) and the neutrals extracted from this solution with dichlorometnane.

Evaporation of the dichlorometnane solution gave a residue, which, on crystallization from water, afforded the starting amide (200 mg), m.p.168-69º.

The sodium bicarbonate and sodium metabisulphite solutions were combined, acidified with hydrochloride acid, saturated with sodium chloride and continuously extracted with diethyl ether overnight. The ether was dried over sodium sulphate and evaporated to dryness do yield an oil (620 mg), ν max 1700; 1760 cm^{-1} which did not crystallize.

The oil (100 mg) was treated at reflux with benzyla mine (2 ml) in presence of ammonium chloride[36] during one hour, cooled, poured into water, acidified with hydrochloric acid, extracted with diethyl ether, evaporated to dryness and the residue chromatographied in alumina grade V to yield two different benzylamido-derivates. The first (15mg) had m.p. 132-34ºC and was identical with the benzylamino-derivative of cyclohexane acetic prepared separately by the same process. No depression on the mixed melting point and identical infrared ν max (Nujol) 1560; 1640; 3300 cm^{-1}.

The second (100 mg) was the benzylamido-derivative of the 2-hydroxycyclohexylacetic acid and was obtained in needles

from chloroform-light petroleum, m.p. 97-98.5º, ν max (Nujol) 1540,1640,2250cm^{-1}.,(Found C 72.52%, H 8.62% , N 5.72%, $C_{15}H_{21}NO_2$ requires C 72.71%, H 8.72%, N 5.65%).

The same m.p. was reported[36] for the cis-isomer whereas the trans-isomer had m.p. 141-2º.

VIII) Photolysis of cycloheptyl acetamide

The photolysis of this compound (500 mg) was carried out in the same manner as described in the previous example. After work up, the neutrals showed almost no starting amide and the acidic fraction accounted for 475 mg of an oil, showing acid and lactone bands in the infrared, ν max 1770 and 1700 cm^{-1}, respectively. This compound was characterized through the acid hydrazide derivative which was directly crystallized from chloroform-benzene to give m.p.123-8º, ν max 1630;1670;3380;3480 cm^{-1} (Found C 58.25% , H 9.58%, $C_9H_{18}N_2O_2$ requires C 58.0%, H 9.79%). The same compound was previously reported[23] to have m.p. 129-30º (cis) and 131-32º (trans).

IX) Oestrone-3-methylether

Oestrone (2 g) was dissolved by heating in 30% potassium hydroxide (400 ml). The solution was cooled and dimethyl sulphate (10 ml) added dropwise with stirring. After one hour, the precipitated solid filtered, washed with water

in the filter and dried under reduced pressure. Weight 1.98 g, m.p. 169-71°, $[\alpha]_D$=+ 167 (c 0.1); ν max (Nujol)1610, 1735 cm^{-1}, λ max 282 mu (ϵ=3,600 etnanol); nmr(C Cl_4) τ 9.12 (singlet 3H), 7.2 (multiplet 3H), 6.3 (singlet 3H), 3.51 (singlet 1H). Reported values[37] m.p. 169-70 $[\alpha]_D$ +169.

X) 3-Methoxyl-17-Cyano-17-Hydroxyoestra-1,3,5 (10)-triene

A) Acetone cyanohydrin exchange

Oestrone-3-methyl etner (1 g) was dissolved by warming in absolute ethanol (50 ml) triethylamine (2 drops) and recently prepared and dried acetone cyanohydrine (10 ml) was added. The solution was refluxed until the ketone band in infrared (1735 cm^{-1}.) was seen to remain constant. After evaporation of the alcohol under reduced pressure the residue was taken with dichloromethane and precipitated with light petroleum to yield 390 mg of a solid with m.p.153-75°, $[\alpha]_D$=+72° (c 1.5). The mother liquours treated again with acetone cyanohydrin afforded another crop (270 mg)m.p.145-80°, $[\alpha]_D$=+60. The combined crops were purified by crystallization from light petroleum to give m.p. 169-205°,$[\alpha]_D$=+75 (c 0.8); ν max 2250,3400,3600 cm^{-1}. (Found C 77.32%, H 8.11%,N 4.49%. $C_{20}H_{25}NO_2$ requires C 77.13%, H 8.09%, N 4.50%).

Acetylation with acetic anhydride in pyridine[26] was seen to proceed to completion without any discontinuity in

rate (TLC control).

The tetrahydropyranyl derivative was prepared by refluxing the cyanohydrin (1g) in dihydropyran (4ml) for 1.5 hours in presence of one drop of phosphorus oxychloride[18] and the crude product was chromatographed on alumina to yield two different compounds with infrared spectra consistent with formulation as tetrahydropyranyl derivatives having respectively m.p.117-24º,$[\alpha]_D$=+90º (c 0.7) and m.p.123-30º,$[\alpha]_D$= 0 (c 1.2). The separate hydrolysis in refluxing acetic acid of these two substances afforded cyanohydrins with identical infrared having respectively m.p.168-95º,$[\alpha]_D$=+73 (c 1.4) and m.p. 150-95º,$[\alpha]_D$=+ 56 (c 1.2).

A sample of the first tetrahydropyranyl derivative was purified by recrystallization from light petroleum to give m.p.123-25º,$[\alpha]_D$=+96 (c 1.4) νmax 990, 1610 , 2250 cm^{-1}., nmr τ 9.0 (singlet 1H), 8.3 (multiplet), 7.2 (multiplet 2H), 6.3 (singlet 3H), 5.04 (singlet 1H), (Found C 76.17%,H 8.31%, N 3.55%; $C_{25}H_{33}NO_3$ requires C 76.30%, H 7.94%, N 3.56%).

Hydrolysis in acetic acid gave again a cyanohydrin with $[\alpha]_D$=+72 (c 1.2).

B) Potassium cyanide

Oestrone 3-methyl ether (200 g) was dissolved in absolute ethanol (200 ml) and powdered potassium cyanide (6g) was added. With vigorous stirring acetic acid (7 ml) was added dropwise during half an hour and the suspension stirred for two hours. Addition to water (500 ml) precipitated a solid which, after filtration, was dried and crystallised from chloroform-light petroleum to afford 180 mg, m.p. 155-65°, $[\alpha]_D$=+20 (c 0.8), ν max (Nujol) 1570, 1610, 2250, 3400 cm^{-1}. The molecular rotation differences calculation (see Table I in discussion) suggested for the 17-α-cyano-17-β-hydroxy isomer a rotation in the vicinity of + 22°.

XI) 2-Tetrahydropyranyloxy-n-octanamide

A suspension of finely powdered potassium cyanide (12.7g) in a solution of heptanal (17 ml) in diethyl ether (70 ml) was vigorously stirred and cooled to 0°C (ice bath) while concentrated hydrochloric acid (13.5 ml) was added dropwise during 30 minutes. The resulting mixture was stirred for one hour at room temperature, the ether layer separated, washed with water and shaken for one hour with concentrated sodium metabisulphate solution[38], washed again with water, dried and evaporated to an oil (11g) ν max 2200; 3450 cm^{-1}.

The oil (11 g) was dissolved in dihydropyran (45 ml), conc. hydrochloric acid (0.2 ml) added and the solution

refluxed for 90 minutes. The resulting solution was taken into diethyl ether, washed with sodium bicarbonate and distilled to remove the excess dihydropyran. The remaining oil (16 g), showing no hydroxyl band in infrared spectrum, was taken into acetone (75 ml), 20% sodium hydroxide solution (75 ml) and 30% hydrogen peroxide (20 ml) added and the solution kept at 40ºC for two hours[39,40]. The acetone was evaporated under reduced pressure and the remaining aqueous solution neutralized with hydrochloric acid, extracted with dichloromethane, washed with sodium bicardonate, water , dried and evaporated. Chromatography on alumina to eliminate dihydropyran polymers afforded 10 g (30%) of crystals. A sample purified by recrystallization from light petroleum and sublimation showed m.p. 57-58º, ν max 995, 1570, 1680 , 3400, 3500 cm^{-1}. (Found C 63.9%, H 10.1%, N 6.1%, $C_{13}H_{25}NO_3$ requires C 64.2%, H 10.4%, N 5.8%).

Photolysis of 2-tetrahydropyranyloxy-n-octanamide

The above purified amide (100 mg) was submitted to photolysis in benzene (50 ml), iodine (0.34 g) and tert -butyl hypochlorite (1.08 ml) in the manner previously described. The reaction was complete after two hours (infrared control). The acidic fraction (53 mg) showed no lactone band in the infrared and after acetylation in acetic anhydride

pyridine, methylation with diazomethane, was shown to be identical and not separable from an authentic sample of 2-acetoxyl-n-octanoic acid methyl ester in mixed gas-liquid-chromatography.

XII) 3-β-Acetoxy-aetianic-acid-amide

Pregnenolone 3-acetate was converted to 3β-hydroxyaeti-5-enic-acid-3-acetate by sodium hypobromite in dioxane water as described[41]. After methylation with diazomethane and subsequent hydrogenation in acetic acid in presence of Adam's catalyst the predominant 5 α-isomer[31] was isolated, hydrolysed, reacetylated[32] and crystallized from methanol, m.p.245-49° [32].

This acid was dissolved in benzene, thionyl chloride (3 mols) added and refluxed on the steam bath for one hour. The excess thionyl chloride together with part of the benzene were removed under reduced pressure and the remainder was added to a cooled saturated solution of ammonia in diethyl ether. The ether solution was washed with water, dried and evaporated. The residue was crystallized from dichloromethane-light petroleum and afforded 3-β-acetoxyaetianicacidamide in 36% yield from pregnenolone acetate, m.p.222-3°, $[\alpha]_D$ +6(c 1.1), ν max 1590, 1675, 1715, 3420, 3520, 3520 cm^{-1}., nmr ($CDCl_3$) τ 9.28 (singlet 3H), 9.17 (singlet 3H) 7.98 (singlet 3H) 4-5.5 (broad absorption 2H) Found C 73.5%; H 9.4%, N 3.6% $C_{22}H_{35}NO_3$

Req. C73.1%;H9.8%;N3.9%).

XIII) 3 β-Acetoxyaetian-18,20-dicarboxylicacid anhydride

3 β-Acetoxyaetianicacid amide (500 mg) in benzene (200 ml) was irradiated for two hours in the presence of lead tetracetate (3.2 g) and iodine (800 mg) under the same conditions as described in III. Work up as described in VII gave in the acidic fraction an oil showing νmax 1780, 1840 cm^{-1}., and no 18-methyl signal in the nmr. This oil in dry tetrahydrofuran was reduced with lithium aluminium hydride. After work up the residue was chromatographied on alumina to afford 60 mg of 3β,18,20-triolaetiane which after crystallization from chloroform showed m.p.102-6º/172-6º , $[\alpha]_D$=+17 (c 0.5 methanol); ν max 3450 cm^{-1}, (Found C 74.42%, H 10.60%, $C_{20}H_{34}O_3$ requires C 74.49%, H 10.63%).

The photolysis was repeated and the crude product from the reaction was submitted to reduction with zinc in acetic acid to completely remove the iodo-compounds before proceeding to the normal work up. The acidic fraction (200 mg) afforded the title compound which on crystallization from diethyl ether had m.p. 209-11º,$[\alpha]_D$=+36 (c 0.9), ν max 1780, 1840 cm^{-1}(Found C 70.55%, H 7.95%, $C_{22}H_{39}O_5$ requires C 70.55%, H 8.1%).

XIV) 3-Methoxy-17-cyanoestra-1,3,5 (10)16-tetraene

3-Methoxyl-17-cyano-17hydroxyestra-1,3,5 (10) triene

(2.5 g) was dissolved in dry pyridine (15 ml) and phosphorus oxychloride[28] (6 ml) added and the solution was refluxed overnight and then added dropwise to a well stirred mixture of ice and dilute hydrochloric acid. The stirring was continued for one hour and the precipitate was removed by filtration, washed with water, boiled with charcoal in acetic acid and crystallized from this solvent to afford 1.8 g of the title compound having m.p.171-3 ,$[\alpha]_D$ +65 (c 1.2), ν max (Nujol) 1590,1610,2250 cm^{-1};nmr (C Cl_4) τ 9.04(singlet 3H) 7.2 (multiplet 3H) 6.3 (singlet 3H) 3.51 (singlet 2H) 3.2 (A/B System J=9 cps 2H);(Found C 81.70%,H 7.87%,N 4.76% , $C_{19}H_{23}NO$ requires C 81.87%, H 7.90%, N 4.77%).

XV) 3 Methoxy-17-Carbamoyloestra-1,3,5(10),16-tetraene

3 Methoxy-17-cyanoestra-1,3,5(10),16-tetraene(1 g) was dissolved in methanol (50 ml) and then 2N sodium hydroxide (5ml) and 30% hydrogen peroxide (3 ml) added. The solution was kept at room temperature overnight, poured into water, extracted with dichloromethane, washed with dilute hydrochloride acid , water, dried and evaporated to afford an oil (700 mg) which on crystallization from methanol-water yielded 520 mg of the title compound, m.p. 245-47°, ν max 1580, 1600, 1665, 3450, 3550 cm^{-1}; n.m.r. (C D Cl_3) τ 8.99 (singlet 3H) 7.15 (multiplet 3H) 6.21 (singlet 3H) 4.2-4.9 (broad absorption 2H) 3.52 (multiplet 1H) 3.37 (singlet 1H) 3.03 (A/B system J=9 cps 2H) (Found C 77.24%,

H 8.11%, N 4.78%, $C_{20}H_{25}NO_2$ requires C 77.13%, H 8.09% , N 4.50%).

XVI) 3-Methoxy-17 β-Cyanoestra-1,3,5(10)-triene

3-Methoxy-17-Cyanoestra-1,3,5(10),16-tetraene (1 g) was hydrogenated in acetic acid (150 ml) in presence of 10% Palladium-Charcoal catalyst at atmospheric pressure. The uptake of hydrogen stopped after 1 mol was consumed , the catalyst was filtered off and the product was directly crystallized by concentration under reduced pressure. Weight 700 mg, m.p. 182-3º, $[\alpha]_D$=+101º (c 0.8), ν max 1580, 1610 , 2260 cm^{-1} (Found C 81.7%, H 8.45%, N 4.64%; $C_{20}H_{25}NO$ requires C 81.31%, H 8.53%, N 4.74%).

XVII) 3-Methoxy-17-Carbamoyloestra-1,3,5(10)-triene

A) 3-Methoxy-17-Carbamoyloestra-1,3,5(10),16-tetraene (200 mg) was hydrogenated in acetic acid (30 ml) in presence of 10% Palladium on charcoal. After 1 mol the hydrogen uptake was stopped, the solution was filtered through celite, poured into water, extracted with dichloromethane, washed with sodium bicarbonate, water, dried and evaporated to dryness. The residue on crystallization from chloroform-light petroleum afforded 160 mg of crystals, m.p. 276-8º, ν max 1590, 1610 , 1675, 3420, 3520 cm^{-1} .

B) 3-Methoxy-17 β-Cyanoestra-1,3,5(10)-triene(500 mg) in methanol (30 ml) and 2 N sodium hydroxide (2 ml) was treated

with 30% hydrogen peroxide (5 ml) and kept at room temperature overnight. The solution was poured into water, the precipitate formed remmoved by filtration, washed with water, dried and crystallized from chloroform-light petroleum to afford 480 mg of crystals having identical infrared and showing no depression in the m.p. when mixed with the compound described in method (A), preceding.

Photolysis of 3-Methoxy-17 β-Carbamoylestra-1,3,5 (10)-triene. The title compound (200 mg) in chloroform (30 ml) and benzene (20 ml) was irradiated for 5 hours in presence of iodine (1.3 g) and tert-butyl hypochlorite (0.6 ml) added in small portions during the first 3 hours. After work up in the usual manner the acidic fraction (8 mg) showed no lactone or anhydride band and the neutrals showed on TLC more than five different compounds, all distinct from starting material.

XVIII) General procedure for the photolysis of Oestrone derivatives.

Some oestrone derivatives were submitted to irradiation under the following conditions:

A) With tert-butyl hypochlorite:

The substance (500 mg) and iodine (2.3 g) in dry benzene (50 ml) was stirred under nitrogen and cooled by running water in the assembly described in III above, and irradiated for 6 hours. tert-Butyl hypochlorite (1 ml) was added in four

portions during the first 4 hours. The reaction mixture was washed with sodium metabisulphite, the solution dried and evaporated under reduced pressure. The residue was finally reduced by stirring with zinc dust in acetic acid for twelve hours at room temperature and the product recovered by evaporation of the filtrate.The composition of the mixture was then evaluated by thin layer chromatography on Merck Silica Gel G, developed with sulphuric acid.

B) With lead tetracetate:

Exactly the same procedure was adopted as for tert-butyl hypochlorite except that iodine (1.0 g) and lead tetracetate (3.9 g) were added in one batch before starting the irradiation. The insoluble lead salts were removed by filtration after washing with sodium metabisulphite.

XIX) Test irradiation of Oestrone derivatives

i)Oestrone-methyl-ether

With tert-butyl hypochlorite there was recovered a mixture showing 16 components, different from starting material. Lead tetracetate provided a more tractable mixture having three main components which on chromatography on alumina afforded a crystalline mixture, m.p.210-46 º , ν max (Nujol) 1605; 1610; 1730 cm^{-1}; λ max 268 mμ(ϵ =9,000), 278 mμ (ϵ =9,000).

ii) Oestrone benzoate[42]

tert-Butyl hypochlorite afforded a mixture showing 10 components, different from starting material.

iii) Oestrone-p-toluenosulphonate

Prepared with p-toluenosulphonyl chloride in pyridine and crystallized from methanol to give m.p. 141-3º, $[\alpha]_D$=+101 (c 0.5), ν max (Nujol) 1170,1370,1600,1720 cm^{-1}. (Found C 71.10%, H 6.63%; S 7.67%; $C_{25}H_{28}O_4S$ requires C 70.74%, H 6.65%, S 7.67%). Photolysis in presence of tert-butyl hypochlorite afforded a mixture of nine different components, one of them having R_f identical to starting material. Chromatography on alumina gave a crystalline mixture (25 mg) containing three different components.

Irradiation of the title compound in presence of lead tetracetate afforded a more tractable mixture from which , after chromatography on alumina, 100 mg of starting material were isolated. Identical infrared and no depression in the mixed m.p. confirmed the assignment.

iv) Oestrone benzenesulphonate

Prepared from benzenesulphonyl chloride as described in the previous experiment recrystallized from methanol m.p.156-9º, $[\alpha]_D$=+100º (c 1.3); ν max 1095,1380,1585,1605 , 1730 cm^{-1}., λ max 269 mμ.(ϵ =5,700); (Found C 70.26%,H 6.62%,

S 8.0%; $C_{24}H_{26}O_4S$ requires C 70.22%, H 6.38%, S 7.79%).

This product when photolysed in the presence of tert-butyl hypochlorite gave three main components, one of which had the same R_f as starting material, together with nine minor ones.

v) Oestrone methylsulphonate

Prepared from methyl sulphonyl chloride in pyridine at 0º overnight. Crystallization from methanol afforded m.p. 152-55º; $[\alpha]_D$ = + 124º (c 1.2); ν max 1380, 1580, 1605, 1725 cm^{-1}; λ max 271 mμ (ϵ = 8,500), (Found C 65.51%, H 7.2%, S 9.29%, $C_{19}H_{24}O_4S$ requires C 65.49%, H 6.94%, S 9.20%).

This product when irradiated in the presence of tert-butyl hypochlorite afforded a cleaner mixture than the previous ones, being mainly three components, the major one corresponding to starting material.

Irradiation in presence of lead tetracetate afforded a clean mixture from which by direct crystallization from methanol yielded 200 mg of product showing identical infra-red and no depression in the m.p. of a mixture with starting material.

XX) 17-α-Cyano-17 β-hydroxyoestra-1,3,5(10)-triene 3yl-methanesulphonate

Oestrone methanesulphonate (2.6 g) in chloroform (20 ml) and absolute ethanol (50 ml) was stirred with finely powdered

potassium cyanide (13.5 g) at 0º and glacial acetic acid (12 ml) was added dropwise during 45 min. The crystalline slurry was diluted with ethanol (30 ml) and stirring was continued for a further 2 hours at room temperature. The mixture was diluted with water (200 ml) and the chloroform layer separated, washed with water, dried and evaporated under reduced pressure to give an oil (3.2 g). This product slowly crystallized from dichloromethane-carbon tetrachloride to give the title compound (2.0 g), m.p. 150-54º; $[\alpha]_D$=+ 20 (c 1.3). After purification by recrystallization the pure cyanohydrin had m.p. 151-54º, $[\alpha]_D$=+16 (c 1.94); ν max 1490, 1580,1605,2250,3400,3450 cm^{-1}; n.m.r.($CDCl_3$) τ 9.12(singlet,3H) 6.88(singlet,3H) 6.65(1H,removed by shaking with D_2O).(Found: C 63.7%,H6.7%,N 3.5%,S 8.5%; $C_{20}H_{25}NO_4S$ requires C 64.0% , H 6.7%, N 3.7%, S 8.5%).

XXI) 17-Cyanoestra-1,3,5(10)16-tetraene-3yl-methanesulphonate

The crude cyanohydrin from the previous reaction (4.6 g) in pyridine (15 ml) was treated with phosphorus oxychloride (3 ml) and the mixture refluxed overnight. The work up was made as described for the corresponding 3-methyl ether and the product obtained was twice crystallized from methanol to yield the title compound (3.5 g) m.p. 159-60º. A sample purified by recrystallization had m.p. 162-3º; $[\alpha]_D$=+52º(c 0.9); ν max 1150, 1380, 1590, 1605, 2250 cm^{-1}; n.m.r. ($CDCl_3$) τ 9.03

(singlet, 3H) 6.88(singlet, 3H) 3.30 (triplet,J=2 cps 1H). (Found: C 67.16%, H 6.54%, S 8.99%, N 3.98%; $C_{20}H_{23}NO_3S$ requires C 67.20%,H 6.48%, S 8.97%, N 3.92%).

XXII) 17β- Cyanoestra-1,3,5(10)-triene-3yl Methanesulphonate

The unsaturated nitrile mentioned above (1 g) was hydrogenated in acetic acid (20 ml) in presence of 10% Palladium-charcoal catalyst at normal pressure. After one mole uptake of hydrogen the reaction was stopped,the catalyst filtered off and the solution concentrated under reduced pressure. The crystalline residue was purified by crystallization from methanol affording 900 mg of the title compound, m.p. 178-80º. Recrystallization of a sample gave m.p. 182-3º,$[\alpha]_D$=+89º (c 1.1); ν max 1140,1380,1605,2250 cm^{-1}, n.m.r. ($CDCl_3$) τ 9.02 (singlet, 3H) 6.88 (singlet, 3H) 3.0 (singlet, 1H). (Found: C 66.74%, H 6.98%, N 3.90%, S 8.80%, $C_{20}H_{25}NO_3S$ requires C 66.82%, H 7.01%, N 3.90%, S 8.92%) .

XXIII) 17 β-Carbamoyloestra-1,3,5(10)-triene-3yl Methanesulphonate

The saturated nitrile obtained in the previous experiment (3.5 g) in acetic acid (50 ml) was stirred under nitrogen whilst concentrated sulphuric acid (10 ml) was added dropwise. The solution was warmed on the steam bath for 2 hours, the solution poured into a mixture of ice and water and the

product taken up in chloroform. This solution was washed with 0.1 N sodium hydroxide, water, and dried. Evaporation gave an oil which crystallized from methanolcarbon tetrachloride to yield the solvated title compound(4.6g) as needles m.p. 93-94°, $[\alpha]_D$=+41° (c 2.28); ν max 1585 , 1603, 1680, 3180, 3180, 3400, 3500 cm^{-1}., n.m.r.($CDCl_3$) 9.25 (singlet, 3H) 6.88 (singlet, 3H) 4.60-3.94 (broad absorptions 2H, exchangeable with D_2O). (Found C 47.7% , H 5.2%, Cl 26.3%, N 2.35%, S 6.0%; $C_{20}H_{27}NO_4SCCl_4$ requires C 47.6%, H 5.1%, Cl 26.8%, N 2.65%; S 6.05%. Recrystallization of the solvated amide from aqueous methanol gave needles m.p.173-4°;$[\alpha]_D$=+58° (c 0.92). (Found: C 63.4%, H 7.15% , N 3.6%, S 8.5%; $C_{20}H_{27}NO_4S$ requires C 63.6%, H 7.2%, N 3.7%, S 8.5%).

XXIV) Photolysis of 17-β-Carbamoyloestra-1,3,5(10) triene-3yl Methanesulphonate

The amide (0.5 g) in dichloromethane (10 ml) was added to an irradiated, stirred solution of lead tetracetate (4.0 g) and iodine (1.0 g) in benzene (50 ml) and the reaction continued under nitrogen for 3 hr. at room temperature. The mixture was then shaken with saturated aqueous sodium metabisulphite (10 ml) until precipitation of yellow lead iodide was complete. The solid remaining in the reaction flask was washed out with 6N hydrochloric acid into the yellow slurry, the benzene layer separated, and the aqueous phase

was extracted similarly with benzene (2 x 100 ml); with ethyl acetate (50 ml) and then filtered (Celite). The lead salts were washed with acetone (50 ml) and ethyl acetate (50 ml) and the yellow washings were diluted with water (200 ml) and then filtered (Celite). The combined organic phases were washed with aqueous metabisulphite, dried and then evaporated under reduced pressure to give a yellow gum (640 mg), ν max 1600, 1650, 1700-1720, 1770, 1800 , 1850, 2800, 3300 cm^{-1}., n.m.r. no absorption corresponding to the C-18-methyl group. The mixture (640 mg) was stirred with zinc dust (1 g) in acetic acid (5 ml) for 15 hr. at room temperature and the solution filtered and evaporated under reduced pressure to leave a pale yellow oil, ν max 1600, 1700-1720, 1760, 1850, 2800-3300 cm^{-1}., n.m.r. absorptions at 9.05 and 9.25 (singlets, C 13-methyl signals of the amide and nitrile). This oil in dioxan (5 ml) was shaken with 4N-sodium hydroxide (5 ml) for 5 min. at room temperature. Benzene (20 ml) was added, followed by water (20 ml) and the aqueous layer removed and washed again with benzene (20 ml). The combined benzene solutions , worked up in the usual manner, gave a pale yellow oil (120 mg), ν max 1500, 1580, 1602, 1605-1690, 1705-1740 , 2250, 3400, 3500 cm^{-1}., which contained the amide and foregoing saturated nitrile. Acidification of the aqueous solution and extraction into chloroform gave the acid

fraction (560 mg) as a yellow froth, ν max 1600,1700-1720, 1770, 1850, 2850-3500 cm^{-1}., which crystallized from benzene to give solvated 3-methanesulphonyloxyoestra-1,3,5 (10) triene-18,20-dicarboxylic acid (280 mg, 44%) as needles m.p.160-64º, $[\alpha]_D$=+69º (c 1.9), ν max 1140, 1380, 1580,1602, 1690, 1703, 2800-3200 cm^{-1}., nmr absorptions at τ 6.92 (s, 3H) 2.67 (singlet from benzene solvate) and - 1.75 (broad singlet 2H, exchangeable with D_2O).

When dichloromethane was used as solvent in the photolysis instead of benzene a similar yield of the diacid (isolated as the dimethyl ester) was obtained.

Recrystallization of the diacid from a mixture of benzene and chloroform gave needles, m.p. 170-2º,$[\alpha]_D$=+69 º (c 1.2) (Found: C 62.5%, H 5.95%, O 24.9%, S 6.85% . $C_{20}H_{24}O_7S,0.5C_6H_6$ requires C 61.8%, H 6.05%, O 25.0% , S 7.15%). Another recrystallization from ethyl acetate gave the diacid as large needles m.p. 193-7º,$[\alpha]_D$=+70º (c 1.05) (Found: C 57.3%, H 6.2%, O 25.9%, S 7.45%. $C_{20}H_{24}O_7S,H_2O$ requires C 57.6%, H 6.0%, O 28.8%, S 7.7%).

XXV) <u>3-Methanesulphonyloxyoestra-1,3,5 (10)-triene-17β-</u>
<u>-18-dicarboxylic acid anhydride</u>

The foregoing diacid (164 mg) was boiled with acetyl chloride (10 ml) for 30 min. and the excess of chloride was removed under reduced pressure. Recrystallization of the residue from benzene gave the title compound (62 mg, 47%)

as prisms m.p.187-90, $[\alpha]_D$=+69º (c 1.0), νmax 1582, 1602 , 1770, 1850 cm^{-1}., n.m.r. absorptions at τ 6.88 (singlet, 3H) (Found C 61.6%, H 5.7%, O 24.5%, S 8.2%. $C_{20}H_{22}O_6S$ requires C 61.5%, H 5.65%, O 24.5%, S 8.2%. The overall yield from the amide via the diacid was 21%. Distillation of the solvated diacid (148 mg) at 250º 5.10^{-4}mmHg also gave the anhydride (99 mg) which was recrystallized from benzene light petroleum as prisms (69 mg, 5 %), m.p. 185-92º , $[\alpha]_D$=+63º (c 0.9).

XXVI) 3-Acetoxy-17-hydroxy diphenylmethyloestra-1,3,5(10)--triene-18,20-carboxylic acid lactone

The anhydride (200 mg) was added to a stirred solution of phenyl-lithium (400 mg) in ether (10 ml) under nitrogen and the stirring was continued for 10 min. After the anhydride had disappeared (30 min. in all) saturated ammonium chloride (5 ml) was added, the mixture was diluted with water (20 ml) and the product extracted into ether. Removal of the solvent under reduced pressure and trituration of the residue with light petroleum left the impure lactone which , after acetylation overnight at room temperature with pyridine and acetic anhydride, gave the crude lactone acetate. This crystallized from acetone as prisms (123 mg) m.p. 264-95º , ν max 1702, 1750 cm^{-1}. . The contaminant of νmax 1702 cm^{-1} was removed by column chromatography of the product on silica gel and the chloroform eluted material was recrystallized

from acetone to give the title compound (94 mg, 38%) as small prisms m.p. 300-5º (decomp. after a phase change above 270º), $[\alpha]_D$=+70º(c 1.04), ν max 1375, 1455, 1500, 1582, 1604, 1750 cm^{-1}., n.m.r. τ 7.78 (singlet, 3H) 7.14 (multiplet, 2H) 6.66 (multiplet, 1H, bearing a superimposed quartet with J=5 cps) (Found: C 80.5%, H 6.5%, O 13.0%, $C_{32}H_{33}O_4$ requires C 80.4%, H 6.6%, O 13.0%).

The reaction between an excess of phenyl-magnesium bromide and the anhydride in tetrahydrofuran solution gave a larger yield (48%) of the lactone acetate.

XXVII) 3,18-Diacetoxyoestra-1,3,5(10)-triene-17β-diphenylmethanol

The mentioned lactone acetate (100 mg) in tetrahydrofuran (10 ml) was added to a stirred suspension of lithium aluminium hydride (200 mg) in the same solvent and stirring continued for 1 hr. After working up in the usual way, extraction of the product into ether gave crude 3,18-dihydroxyoestra-1,3,5(10)-triene-17β-diphenylmethanol (210 mg) as an oil, ν max 1500, 1580, 1605, 3380, 3600 cm^{-1}. This was directly acetylated with acetic anhydride (1 ml) and pyridine (2 ml) at room temperature for 54 hr. to give a pale yellow gum (178 mg). Purification of this gum by preparative thin layer chromatography, followed by crystallization from carbon tetrachloride-ethanol, gave the

solvated title compound (124 mg, 57%) as large needles m.p. 90-5º (deomp.). Dried in vacuo at 36º these had m.p. 105-51º, $[\alpha]_D$=+32 (c. 1.0), ν max (CCl_4) 1450,1500, 1600, 1750, 3007, 3505 cm^{-1}., n.m.r. τ 8.01, 7.77 (singlet, 1H, exchangeable with D_2O) and 5.64 (AB quartet, 2H , J_{AB}=12 cps). Recrystallization from ethanol gave needles m.p. 126-7º (after drying at 110º in vacuo ,$[\alpha]_D$=+36 º (c 1.0) ν max (CCl_4) 1600, 1750, 3505 cm^{-1}.. (Found C 77.9%, H 6.9%, $C_{35}H_{38}O_5$ requires C 78.0%, H 7.05%).

XXVIII) Diphenyl isopropyl carbinol

Freshly distilled isobutyric acid (5 g) was dissolved in thionyl chloride (10 ml) and refluxed for 20 min..The acid chloride formed was distilled and added dropwise to cold an stirred methanol (10 ml) containing some pyridine (0.5 ml). After dilution with water, extracted with benzene, washing with sodium bicarbonate solution, water, and then drying the benzene was evaporated. The residue in diethyl ether (30 ml) was added dropwise under nitrogen to a filtered solution of phenylmagnesium bromide (10 g) in diethyl ether (50 ml). The reaction was monitored by infra-red and seen to be complete after one hour. The work up was done as described for the phenyl lithium reaction above and the product distilled to yield the title compound[43] (3 g); ν max 1600, 3500, 3510 cm^{-1} . (Found: C 85.27%, H 7.81%, $C_{16}H_{18}O$ requires C 84.91% , H 8.02%).

XXIX) Photolysis of the Diphenyl-isopropyl carbinol nitrite

The alcohol (350 mg) in dry benzene (20 ml) and pyridine (5 ml) was saturated with nitrosyl chloride gas at -20º. The reaction solution was poured onto ice and the benzene layer separated, washed with water and dried (Na_2SO_4). One third of the solvent was removed under reduced pressure at room temperature and the residual solution was irradiated in a Pyrex flask using a high-pressure mercury arc lamp for 15 min. (thin-layer control). Removal of the solvent under reduced pressure and chromatography over silica gel gave benzophenone (210 mg) and then, on methanol elution, acetone oxime identified by conversion to the 2,4 -dinitrophenylhydrazone (80 mg).

XXX) 20-Hydroxy-20-phenylpregna-5en-3yl-acetate

Pregnenolone (1 g) in dry tetrahydrofuran (10 ml) was added dropwise to a freshly prepared solution of phenyl manesium bromide (2 g) in the same solvent (20 ml). The solution was refluxed for 30 min., cooled and saturated solution of ammonium chloride was added until a clear separation occurred (15 ml). The organic layer was taken in diethyl ether washed with dilute hydrochloric acid, water, dried and evaporated. The residue (1.2 g) was taken in pyridine (20 ml) and treated with acetic anhydride (3 ml) at room temperature per five hr. and then poured

into cold dilute hydrochloric acid. The solids were removed by filtration, washed with water, dried, taken in light petroleum and crystallized to give 600 mg of needles m.p. 188-204º, ν max 1720, 3550 cm^{-1}. showing two close spots in thin layer chromatography. Separation of the two isomers was achieved by chromatography in silica gel followed by crystallization to constant rotation from ethyl acetate and light petroleum respectively to give 160 mg of isomer A,m.p. 211-13º , $[\alpha]_D$=-56º(c o.6),n.m.r. τ 9.24 (singlet,3H) 9.08 (singlet, 3H) 8.5(singlet,3H) 8.0 (singlet,3H) 7.31 (multiplet, 1H, exc. with D_2O) 5.5, 4.65 (multiplet, 1H each) 2.7 (multiplet, 5H), (Found C 79.56%, H 9.18%, $C_{29}H_{40}O_3$ requires C 79.7% , H 9.23%). Isomer B (60 mg) m.p.247-8º,$[\alpha]_D$=-83º (c 1.2) , n.m.r. τ 9.08 (singlet, 3H) 8.97 (singlet, 3H) 8.32 (singlet, 3H) 7.97 (singlet, 3H) 7.37 (multiplet, 1H, exc. with D_2O) 5.5, 4.65 (multiplet, 1H each) 2.7 (multiplet, 5H) , (Found C 79.56%, H 9.18%, $C_{29}H_{40}O_3$ requires C 79.7%, H 9.23%.

Analogy with the isomers of 3,20-dihydroxy-20-methyl pregna-5-ene whose absolute configuration at C-20 are known [44, 45, 46, 47] suggests that isomers A and B have respectively the α and β configuration.

Photolysis - The 20-nitrite of the mixture of the two isomers (20 mg) was prepared as before and irradiated for

30 min. under the usual conditions. Thin layer chromatography showed the presence of several spots but none identical with the expected acetophenone.

XXXI) 17 β-Hydroxy diphenylmethyl-androsta-5-en-3 β-yl-acetate

3 β-acetoxyaetianic acid methyl ester (1.2 g) in dry tetrahydrofuran (50 ml) was treated with phenyl - magnesium bromide (from 5 g of bromobenzene) at reflux for 30 min. and worked up by addition of saturated ammonium chloride solution and extraction with diethyl ether as before. Acetylation with acetic anhydride in pyridine followed by crystallization from light petroleum afforded the title compound (2 g) m.p.245-46º, $[\alpha]_D$=-115º (c 1.5), ν max 1600, 1710, 3550 cm^{-1}., n.m.r. 9.15 (singlet, 3H) 9.06 (singlet, 3H) 8.02 (singlet, 3H) 7.71 (multiplet, 1H, exc.with D_2O) 5.50, 4.65 (multiplet, 1H each) 2.8-2.5(multiplet, 10 H). (Found C 81.96%, H 8.21%, $C_{34}H_{42}O_3$ requires C 81.89%, H 8.49%).

Photolysis - The 20-nitrite of this compound (500 mg) was prepared and irradiated in benzene for one hr. under the conditions described above. The crude product obtained after evaporation showed six different spots on TLC, none of them having R_f identical with benzophenone, the title compound or the respective nitrite. After chromatography

on alumina a fraction (80 mg) showing mainly one spot on TLC was isolated which had ν max 1600, 1640, 1655, 1720, 3450 cm^{-1}.. The n.m.r. of this substance showed the presence of the two aromatic rings but absence of the 3H singlet due to the 18-methyl group.

XXXII) 3-Methanesulphonyloxyoestra-1,3,5(10)-triene-17 β-carboxylic acid methyl ester

The 17 β-cyanoestra-1,3,5(10)-triene-3yl methanesulphonate (2 g) in acetic acid (50 ml) and water (20 ml) was treated with conc. sulphuric acid (25 ml) at reflux overnight. Addition to a stirred mixture of ice and water separated a solid which was collected by filtration, taken into dichloromethane, evaporated and treated with excess diazomethane in ether-tetrahydrofuran to yield , after crystallization, the title compound (1.5 g) m.p. 201-2°. $[\alpha]_D$=+ 86° (c 0.9), ν max 1380, 1432, 1502, 1595 , 1605, 1723 cm^{-1}., n.m.r. τ 9.30 (singlet, 3H) 6.90 (singlet, 3H) 6.31 (singlet, 3H). (Found C 64.0%, H 7.15%, S 8.2% ; $C_{21}H_{28}O_5S$ requires C 64.3%, H 7.2%, S 8.2%).

XXXIII) 3-Acetoxyl-20-diphenyloestra-1,3,5(10),17(20) tetraene

The ester prepared above (200 mg) in dry tetrahydrofuran (5 ml) was added dropwise to a freshly prepared and filtered solution of phenylmagnesium bromide (5 equivalents) in

tetrahydrofuran (20 ml) and left for one hr. at room temperature (thin-layer control). Saturated ammonium chloride solution (5 ml) was added, the organic layer separated, diluted with ether, and worked up in the usual way. The crude product (400 mg) was triturated with light petroleum to remove polyphenyls and then acetylated at room temperature with pyridine (5 ml) and acetic anhydride (1 ml) (thin-layer control). Crystallization of the product from light petroleum gave the diphenylalcohol (70 mg), m.p. 181-3°, $[\alpha]_D$=-53° (c 0.9), (Found C 82.0%, H 7.9%, $C_{33}H_{36}O_3$ requires C 82.5%, H 7.6%).

This alcohol (50 mg) in pyridine (5 ml) was treated by thionyl chloride (0.5 ml) during 40 hr. at room temperature, poured into water, acidified with hydrochloric acid, extracted with dichloromethane, dried and evaporated. The resultant title compound (48 mg), recrystallized from light petroleum, had m.p.150-3°, $[\alpha]_D$=-100° (c 1.0), νmax 1600, 1760 cm^{-1}, λmax 235 mμ (ϵ=12,100) (Found C 85.6%, H 7.3%, M.W. (mass.spec.) 462 $C_{33}H_{34}O_2$ requires C 85.7%, H 7.4%, M.W., 462).

XXXIV) Ozonolysis of 3-acetoxyl-20-diphenyloestra 1,3,5(10), 17(20)-tetraene

The tetraene previously obtained (20 mg) in ethanol free chloroform (3 ml) was ozonised at -20ºC for two hours. After flushing with nitrogen triphenylphosphine (10 mg) in chloroform (1 ml) was added at -20º C and the solution left for two hours before evaporation. Preparative TLC on alumina gave two substances. The first (3.4 mg) was identified as benzophenone by its spectra and 2,4-dinitrophenyl hydrazone. The second (4 mg) was shown to be identical by infra-red and mixed melting point with oestrone acetate m.p., 125-6º, $[\alpha]_D$=+138º (c 1.2) in accordance with reported values[48] .

XXXV) 3,18-Diacetoxy-20-diphenyloestra-1,3,5(10),17 (20)--tetraene

The diphenylmethanol (118) (61 mg) in pyridine (5 ml) was treated with thionyl chloride (0.5 ml) at 0º for 54 hr. Working up as above and crystallization from light petroleum (b.p. 40-60º) gave the title compound (37.8 mg) as plates, m.p. 160-2º, $[\alpha]_D$=+91º (c 1.1), ν max (CCl_4) 1370, 1443,1500,1600,1733,1758,3007 cm^{-1}., n.m.r. τ 7.91 (singlet, 3H) 7.80 (singlet, 3H) 7.20 (multiplet, 2H) 5.89 (A B quartet, 2H, J= 11 cps) (Found C 79. 8%, H 6.85%, O 13.1%, $C_{35}H_{36}O_4$;

1/2 H_2O requires C 79.5%, H 7.0%, O 13.6%).
A sample dried at 110ºC under reduced pressure had m.p. 160-2º, (Found C 80.6%, H 7.05%, O 12.5%; $C_{35}H_{36}O_4$ requires C 80.8%, H 6.9%, O 12.3%).

XXXVI) 3,18-Dicetoxyoestrone

The tetraene (30 mg) in dichloromethane (2 ml) was treated with an 0.03 M solution of ozone in the same solvent (13 ml) at -70ºC for 2 hr. After flushing for 20 min. with nitrogen, triphenylphosphine (15 mg) in dichloromethane (2 ml) was added at -70ºC and the solution was kept at room temperature for 15 hr. before evaporation under reduced pressure. Separation of the products by TLC gave two main fractions. The less polar one (13.8 mg) was identified as benzophenone. Recrystallization of the more polar fraction (9.3 mg) from light petroleum gave the title compound (5.7 mg) as needles m.p. 162-3º, $[\alpha]_D$=+99º (c 0.26), ν max 910, 1150, 1375, 1495, 1730 cm^{-1}., n.m.r. τ 7.97(singlet, 3H) 7.72 (singlet, 3H) 5.71 (A B quartet, 2H, J=12 cps) (Found C 71.3%, H 6.85%; $C_{22}H_{26}O_5$ requires C 71.3%, H 7.05%) . Recrystallization from methanol gave large prisms, m.p. 166-8º, $[\alpha]_D$=+86º (c 1.0) was kindly compared with the natural diacetate by Dr.G.F. Marrian F.R.S. and shown to be identical.

XXXVII) 18-Hydroxyoestrone

The diacetate (20 mg), m.p. 166-8º, in methanol (0.5 ml) was treated with a 3% solution of hydrogen chloride in methanol (0.5 ml) at room temperature for 12 hr. Evaporation of the solution under reduced pressure at room temperature and separation of the product from 18-noroestrone (less than 5% of the total) by TLC gave needles (12.5 mg). Recrystallization from ethanol gave title compound (9.7 mg), m.p. 215-23º (decomp.),265-70º (decomp. after sintering above 248ºC and darkening above 264ºC in a sealed evacuated capillary), $[\alpha]_D$=+134º (c 0.37, ethanol), ν max (Nujol) 1050,1600,1710,3400 cm^{-1}., (Found C 75.3%, H 7.66%, O 17.0%; $C_{18}H_{22}O_3$ requires C 75.5%, H 7.7%,O 16.8%). Lit[6] m.p. 255-7º C (sealed evacuated tube), $[\alpha]_D$=+146º (c 0.37, ethanol) νmax (KCl disc) 1408, 1725 cm^{-1}. for a sample of the natural product crystallized from ethanol.

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