STUDIES IN THE STEROID SERIES

A thesis submitted to the University of Glasgow

for the degree of

DOCTOR OF PHILOSOPHY

by

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SYNOPSIS

Part I

Two epimeric alcohols (3α-hydroxy-3β-methylcholestane and 3β-hydroxy-3α-methylcholestane) have been prepared from cholestanone and characterised as their p-nitrobenzoates. Their configurations have been assigned. The position of the ethylenic linkage in their anhydro-derivative has been shown to be at $C_2:C_3$. This compound was characterised by conversion to its epimeric dibromides. 3β-Methylenecholestane has been prepared and also characterised by transformation into its isomeric dibromides. All four compounds afford in high yield the same 3β-chloro-3α-methylcholestane on treatment with hydrogen chloride. The process is considered to be kinetically rather than thermodynamically controlled. Corresponding experiments with hydrogen bromide afford 3β-bromo-3α-methylcholestane. Reduction of these two halides with lithium and liquid ammonia affords, after protonation, 3β-methylcholestane. This compound has also been prepared in an unambiguous way.

Part II

3β-Acetoxyandrostane-11:17-dione, conveniently available by the degradation of hecogenin, has been converted, by fission and subsequent reclosure of the C_{13}-C_{17} bond and by other appropriate manipulations, into 3β-hydroxy-18-benzylidene-14 iso:17 iso-allopregnane-11:20-dione. Reduction of the 11-carbonyl group of the latter to 11β-hydroxyl followed by ozonolytic cleavage of the benzylidene group affords the masked aldehyde system characteristic of aldosterone. Under a different set of conditions fission and reclosure of this system led to the 13 iso:17 iso-allopregnane series. These experiments open up routes for the preparation of two of the possible three stable conformations of the C/D-steroid ring system in which C_{18} bears an oxygen atom. Attempts to synthesise the third (normal) isomer are described.

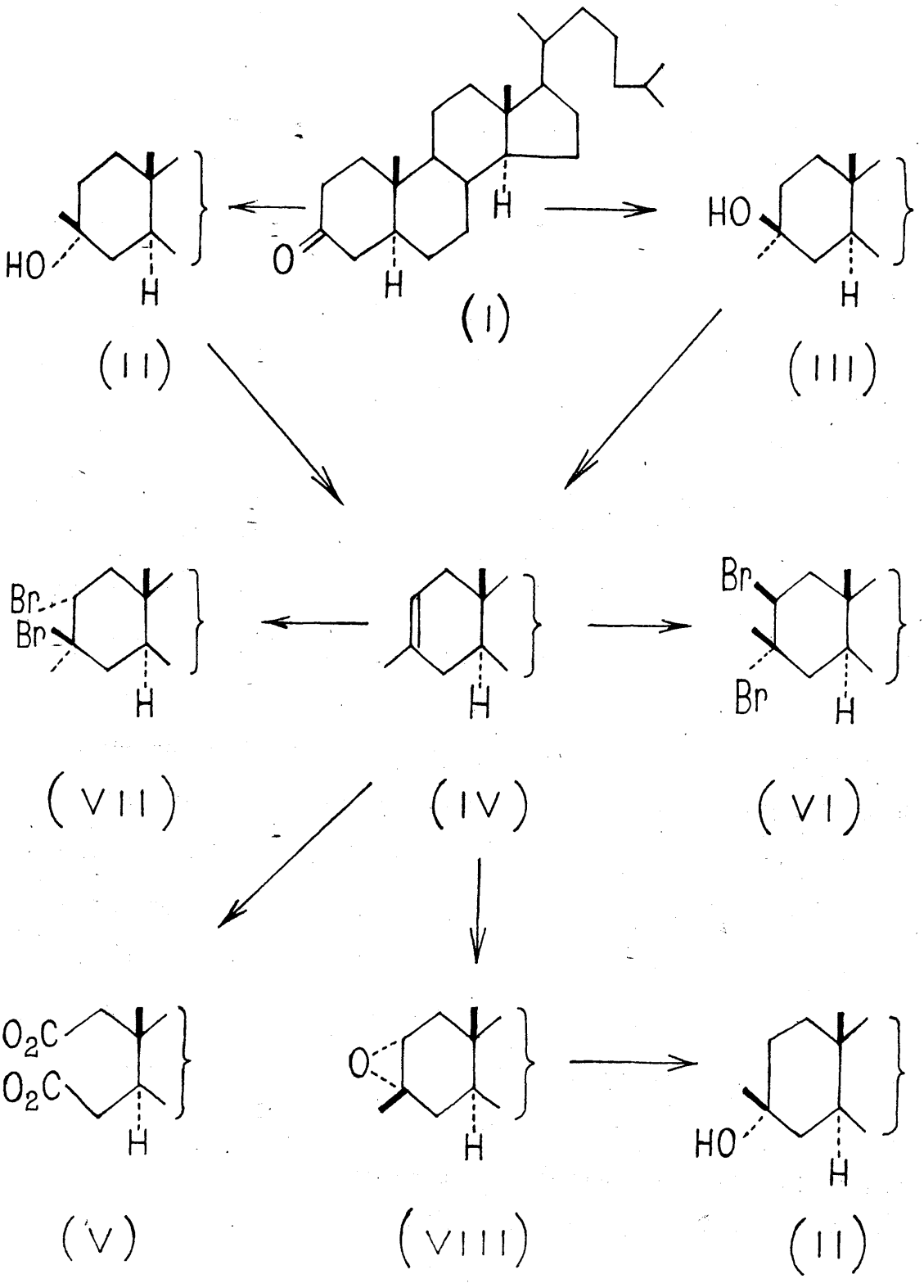
INDEX

PART I

The 3-Methylcholestanols and Derivatives

The S_N2 process of nucleophilic aliphatic substitution usually results in the inversion of configuration, for the transition state leading to inversion has less internal energy than that leading to retention of stereochemistry. However, in the case of an S_N1 process, in which a primary heterolysis leads to a carbonium ion, a racemic mixture will be obtained whenever the carbonium ion has a long-life, as in the case of its stabilization by mesomerism. In some cases, nevertheless, a slight excess of inversion over racemisation has been recorded[1,2]. The study of the S_N1 substitution in systems in which the energy content of the stereoisomers is different (as in alicyclic compounds) may have great interest, the subject having not been extensively investigated. The recognition of this was the main reason for the present investigation. For our work a tertiary carbonium ion was chosen, since tertiary carbonium ions are easily generated and are the best suited for such a study.

Cholestanone (I) (easily obtained from cholesterol by successive hydrogenation and chromic acid oxidation) on treatment with the methyl Grignard reagent yielded the epimeric alcohols[3,4,5] (II) and (III) which were


HO
H
O
H
HO
H
(II)
(I)
(III)
Br
Br
H
Br
Br
H
(VII)
(IV)
(VI)
HO2C
HO2C
H
O
H
HO
H
(V)
(VIII)
(II)

characterised as the respective p-nitrobenzoates. Both alcohols yielded the same, known, anhydro-derivative[3,4,5,6] (IV) on treatment with acetic acid-perchloric acid (trace). That the double bond of the latter compound was located at C_2 (a situation which was expected in view of the preferred enolisation of the 3-keto steroids towards C_2 rather than towards C_4) was rigorously proved by subjecting (IV) to successive oxidations with osmium tetroxide, lead tetra-acetate and sodium hypobromite. In fact, from such reactions, secocholestane-2:3-dioic acid[7] (V) was obtained.

For further characterisation 3-methylcholest-2-ene was treated with bromine. Chromatography over alumina of the mixture of the two epimeric dibromides thus obtained gave as the major product 2β:3α-dibromo-3β-methylcholestane (VI), together with a small amount of 2α:3β-dibromo-3α-methylcholestane (VII). The assigned configurations are based on the well established principle of the preferred diaxial addition and on the relative rotations [$[\alpha]_D$ +89° for (VI) and -15° for (VII)] as compared with those of the 2β:3α-dibromocholestane and its 2α:3β-epimer[8] ($[\alpha]_D$ +76° and -29° respectively). Moreover, in good agreement with the assigned configurations, the diaxial dibromide (VI) was less

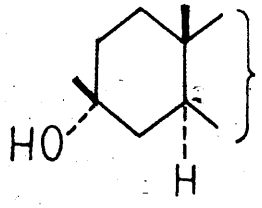
strongly adsorbed on alumina than its isomer (VII) and the first could be converted into the latter by prolonged heating in chloroform solution[8]. Furthermore, the diaxial epimer (VI) showed bands in the infra-red at 537 and 547 cm^{-1} and the diequatorial dibromide bands at 752 and 804 cm^{-1} in excellent agreement[9] (see table I) with the ascribed stereochemistry.

Configurations were given to the epimeric tertiary alcohols (II) and (III) from the following evidence. Treatment of 3-methylcholest-2-ene with perbenzoic acid afforded an epoxide (VIII) which gave the alcohol (II) on reduction with lithium aluminium hydride. The diaxial epoxide

TABLE I[10]

Characteristic Stretching Frequencies for C-X Bonds in cycloHexane Ring Systems

Bond	Frequency range (cm^{-1})	
	Equatorial	Axial
sec. C-D	2155-2162; 2171-2177	2114-2138; 2139-2164
sec. C-O of C-OH	1037-1044	996-1036
sec. C-O of C-OAc	1013-1022	1025-1031
sec. C-O of C-OMe	1100-1104	1086-1090
C-Cl	736-856	646-730
C-Br	682-833	542-692



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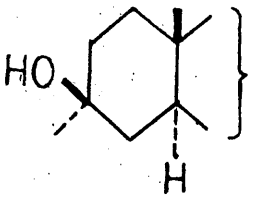

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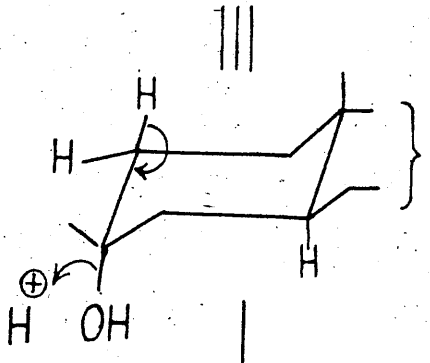

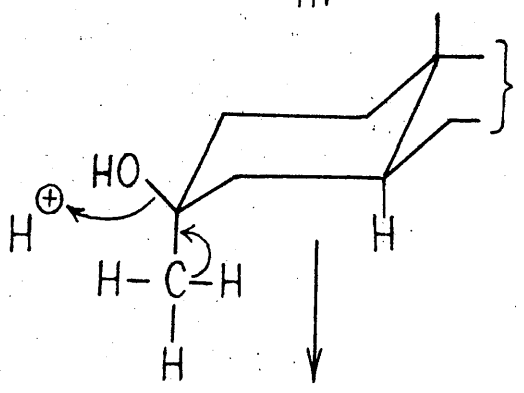

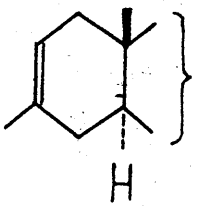

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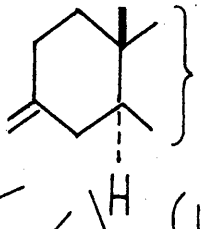

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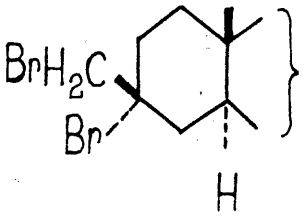
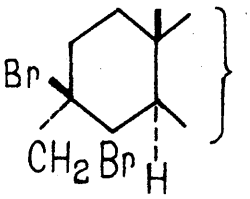
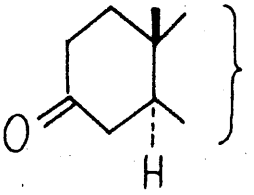


(X)

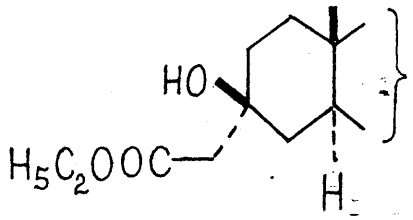


(XI)



(I)

opening rule requires that the hydroxyl group formed by reduction be axial, that is, α-oriented as in (II). It follows therefore that, as it would be expected, the epoxide has the α-configuration; the observed carbon-oxygen stretching frequencies at 940 and 893 cm^{-1} (in carbon disulphide solution) were in agreement[11] with the presence of equatorial and axial hydroxyl groups, respectively. In perfect agreement with the indicated stereochemistry is also the behaviour of the alcohols when submitted to dehydration with phosphorus oxychloride in pyridine solution. The axial alcohol (II) afforded in high yield 3-methylcholest-2-ene (IV) whereas the equatorial epimer (III) was converted into a mixture of isomeric olefins which was shown to be substantially (IX)[5c] by the infra-red spectrum [maxima at 883 (strong) and 1647 cm^{-1}; in Nujol], by its conversion into cholestanone (I) on successive oxidation with osmium tetroxide and lead tetra-acetate, and also by direct comparison with a pure sample of the olefin (IX) readily obtained by the Wittig reaction[12]. The exocyclic olefin was further characterised by its conversion into the epimeric dibromides (X) and (XI) which were different from those obtained from (IV). Configurations were



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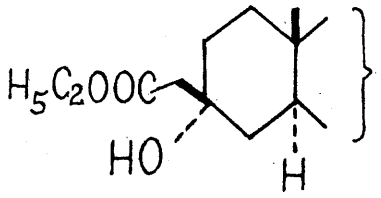

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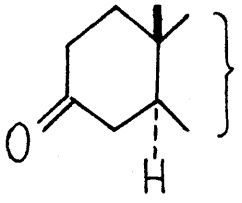
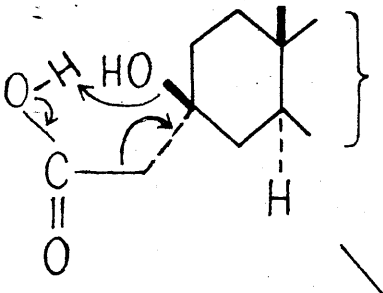


(I)



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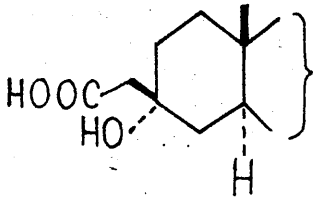
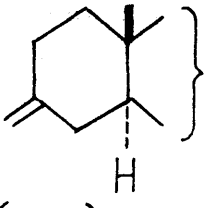


(XV)

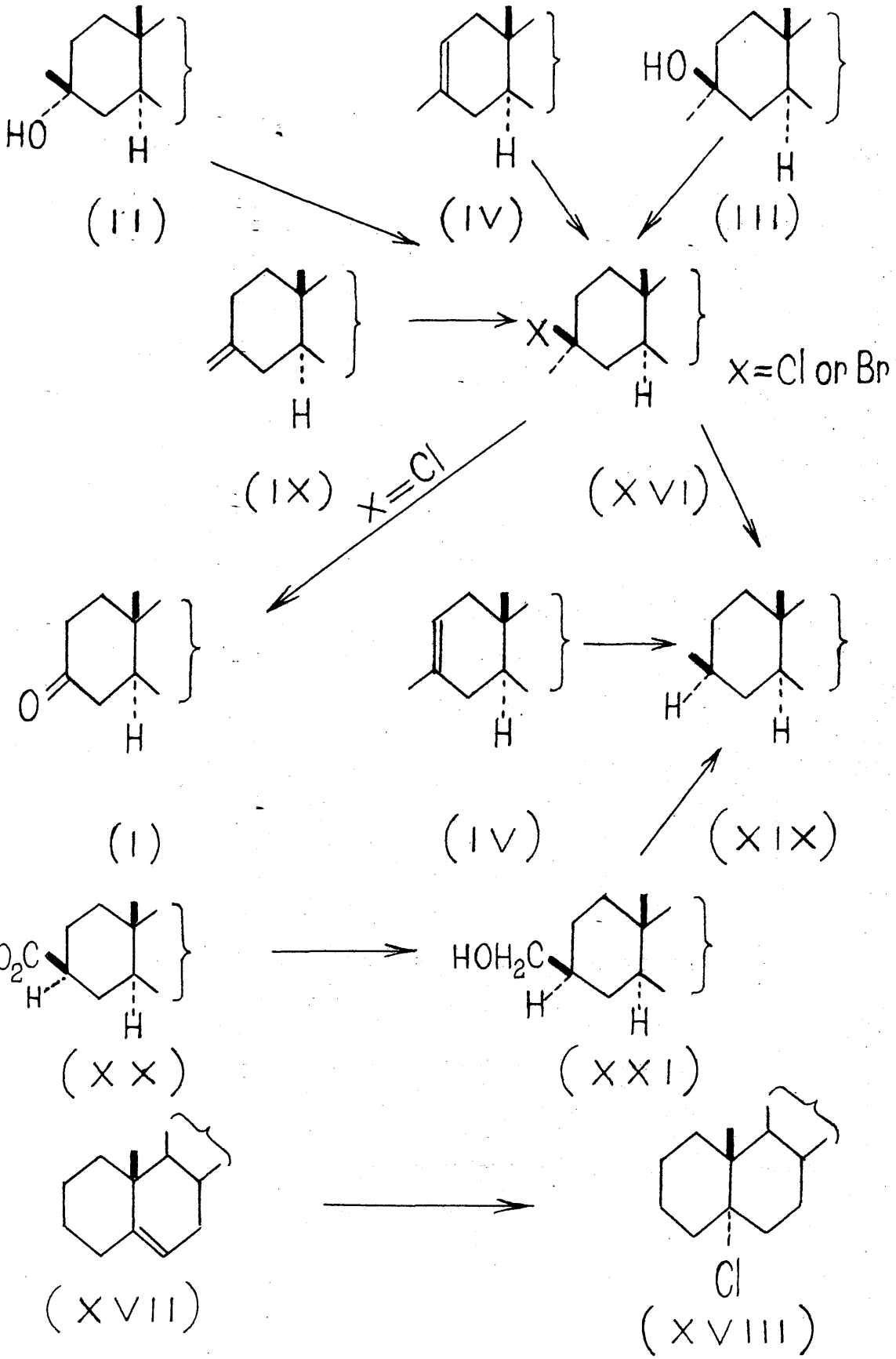


(IX)

tentatively assigned to the dibromides (X) and (XI) on the basis of the principle of preferred diaxial addition[8] and because the major dibromide [3α(axial)-bromide (X)] was thermally less stable than the 3β(equatorial)-epimer.

The α-alcohol (II), in which the hydroxyl group is axial, possesses four centres (2β-H, C_2, C_3, and 3α-OH) in the same plane, being therefore favourably disposed to eliminate water towards C_2. The same does not apply to the β-alcohol (III) with the hydroxyl group equatorially oriented, for it has no coplanar α-hydrogen atom. Coplanarity can, however, be achieved with the aid of a hydrogen from the 3-methyl group, thus giving the exocyclic olefin (IX).

Prior to the preparation of (IX) by the Wittig reaction an attempt was made to obtain it through a Reformatsky reaction with cholestanone. Two epimeric esters (XII) and (XIII) were thus obtained which on hydrolysis with ethanolic potassium hydroxide yielded the isomeric acids (XIV) and (XV), respectively. If the mechanism of pyrolysis is that shown on page 7 then either acid should have afforded the olefin (IX) when pyrolysed. However, pyrolysis of (XIV) and (XV) gave pure 3-methylcholest-2-ene in one case and a mixture, possibly of this with (IX), in the other.


HO
H
(II)
H
(IV)
HO
H
(III)
H
(IX)
X
H
X=Cl or Br
(IX) X=Cl
(XVI)
O
H
(I)
H
H
(IV)
H
H
(XIX)
HO2C
H
H
(XX)
HOH2C
H
H
(XXI)
(XVII)
Cl
(XVIII)

This unexpected result together with our interest in the determination of configurations for the products of the Reformatsky reaction is leading us to reinvestigate this problem in the near future.

Treatment of the alcohols (II) and (III), the 3-methylcholest-2-ene or the 3-methylenecholestane with a solution of hydrogen chloride in dioxan at room temperature gave the same chloride m.p. 154-6°, $[\alpha]_D$+33° in approximately 75% isolated yield. The total yield of the chloride was shown to be 82% by the isotopic dilution method. This chloride showed an infra-red frequency (in carbon disulphide solution) at 782 cm^{-1}, corresponding[9] to an equatorial chlorine (see Table I). The chloride on collidine dehydrochlorination afforded the olefin (IX) which was characterised by its conversion into the epimeric dibromides (X) and (XI) and by successive oxidation with osmium tetroxide and lead tetra-acetate to cholestanone. The direction of elimination of hydrogen chloride is consonant with the chlorine being equatorial (β), not axial (α). The sum of these facts led us to formulate the chloride as the 3β-chloro-3α-methylcholestane (XVI; X = Cl). This was regarded as the more stable epimer since 1-methylcyclohexyl chloride, where the molecule is free to

adopt either conformation for the C-Cl bond, showed only an infra-red frequency (in carbon disulphide solution) at 772 cm^{-1}, characteristic[9] of equatorial chlorine (see Table I).

In these four reactions, as well as in the hydrochlorination of cholest-5-ene (XVII) to give 5α-chlorocholestane[13] (XVIII), the major product was the more stable isomer. This conclusion would be self-evident if the reactions were reversible and therefore thermodynamically controlled. However, at least in the case of the chloride (XVI), this does not seem to be the case, for its extent of solvolysis in 90% aqueous dioxan at 20° was negligible even after seven days (complete recovery of starting material). In contrast, the approximate times of half-reaction for the formation of the chloride were as follows: from the olefin (IV), 13 minutes; from the α-alcohol (II), 30 minutes; from the β-alcohol (III), 4 hours. We regarded the formation of the more stable epimer as a rate-controlled and not a thermodynamically-controlled process in view of the fast rate of formation of the chloride as compared with that of its hydrolysis.

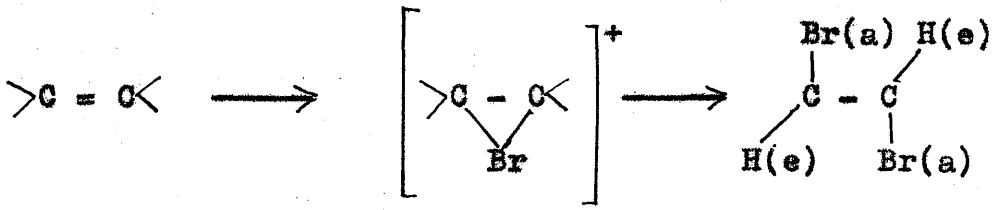
The formation of the 3β-chloro-3α-methylcholestane

may proceed directly through the carbonium ion or through the olefin (IV) since the rate of reaction of (IV) with hydrogen chloride is so fast. In order to bring some light to this problem all the experiments previously made with hydrogen chloride were repeated with deuterium chloride and the deuterium content of each specimen measured. Appropriate measurements showed that there was no exchange of deuterium either with the chloride once formed or with the solvent. The process used for the quantitative estimation of deuterium consisted in the study of the comparative areas of the C-D absorption bands in the infra-red at 2205 $\pm$15cm^{-1} of the deuterated chloride and of a standard substance with supposedly one $-CH_2D$ group. An assumption has to be made, of course, that the intensity of C-D bands will be independent of molecular environment. The standard compound used was the deuterated α-amyrin acetate (obtained by opening the cyclopropane ring of phyllanthyl acetate with deuterium chloride[14]). Prior to this work it would have been expected that all the specimens of the chloride would contain one atom of deuterium if the reaction proceeded exclusively through the olefin (IV). The quantitative determination

of deuterium furnished the following values: chloride obtained from the olefin (IV), 1 atom of deuterium; chloride from the α-alcohol (II), 0.87 atoms of deuterium; chloride from the β-alcohol (III), 0.64 atoms of deuterium. It was therefore concluded that the carbonium ion once formed is in part converted into olefin and in part directly into chloride, the latter process at least being irreversible and thus giving information about the stereochemistry involved. However, when the estimation of deuterium in the same samples was repeated using another technique the results indicated that the deuterium contents were appreciably greater than those described above. (See below).

Another problem of interest would be the comparison of the stereospecificity of addition of chlorine or bromine to the ethylenic linkage with that of hydrogen chloride, all additions being of the ionic type. It is in fact known that addition of chlorine or bromine to a cyclohexane system is of the trans-ionic type yielding mainly the diaxial isomer[8]. The first step in the addition is the formation of a three-membered intermediate. This then opens, by attack

of the nucleophile, to give a diaxial product - a course similar to that of the opening of an epoxide.



The addition of halogens to ethylenic linkages in cyclohexane systems does not always follow the same course. For instance, in the case of cholest-2-ene the addition product is diaxially substituted and the reaction follows the Markownikoff rule, whereas in the addition of halogen to the 5:6-double bond of cholesterol and its congeners, in which the halonium ion is formed on the less hindered α-side of the molecule to yield the 5α:6β-dihalide, the process is completed non-Markownikoff-wise[15]. In the same way, addition of hydrogen chloride to cholest-5-ene and 3-methylcholest-2-ene cannot be of analogous stereochemical form. The recent work of Corey[16] on the determination of the configuration of deuterium atoms in deuterated organic compounds by the infra-red method made possible the easy study of the mechanism

of addition of compounds of the DX type to cyclohexane systems for the configurations of both halves of the addendum can easily be determined. In order to examine the stereochemical course of such additions cholest-5-ene was treated with deuterium chloride in dioxan as had previously been done for the formation of 3β-chloro-3α-methyl-cholestane (see above). The measurements of the C-D frequencies were made with special accuracy by Dr. A.E. Martin of Messrs. Sir Howard Grubb, Parsons and Co., Newcastle, using the new Grubb Parsons Grating Spectrometer; for this we thank him very much. The deuterochloride prepared from the 3-methylcholest-2-ene showed C-D frequencies at 2158 and 2174 cm^{-1} characteristic[16] of equatorial deuterium. The addition product was therefore the 2α-deuterochloride being the addition <u>trans</u> and diequatorial; in contrast, addition of pure deuterium chloride to cholest-5-ene afforded a chloride (5α-chlorocholestane) which had C-D frequencies at 2158 and 2167 cm^{-1} also characteristic[16] of equatorial deuterium, the product being the 6α-deuterochloride and the addition <u>cis</u>-equatorial:axial. The easiest explanation of these results would be that the first

step of the addition was the formation of a π-complex with the proton on the less hindered α-side of the molecule which would then rearrange to give a classical carbonium ion and this add an anion to give the more stable of the two possible isomers. Unfortunately these results were later invalidated when another process of quantitative determination of deuterium was used. The latter showed that the chlorides prepared from the 3-methylcholest-2-ene and cholest-5-ene by reaction with deuterium chloride contained 1.46 and 1.49 atoms of deuterium, respectively. This process was as follows: The sample was combusted in a conventional combustion train, the water collected and stored in a sealed ampoule. The water sample was then compared with a known standard in a ratio recording infra-red spectrometer and the concentration of D_2O read from a calibration curve of the optical density at 2490 $cm.^{-1}$ against atom percent D_2O. Such a difference in the analyses can be explained if the α-amyrin acetate prepared from phyllanthyl acetate by treatment with deuterium chloride contained more than one atom of deuterium.* It might also be expected

* The opening of cyclopropane rings is at present being investigated (Barton, Eglinton and Rodger, private communication) and preliminary results indicate that more than one deuterium atom may be introduced.

that a C-D band, just as a C-H band, will vary in intensity and in frequency with environment, particularly when in the vicinity of polar groups (C=O, C-Br, C-Cl etc.) and when in some suitable conformation for maximum dipolar interaction.

When some of the above described experiments for hydrogen chloride were repeated using hydrogen bromide 3β-bromo-3α-methylcholestane (XVI; X=Br) was obtained in 75% (isolated) yield.* The configuration assigned is based on the infra-red frequency at 780 cm^{-1} (in carbon disulphide solution) characteristic[9] of equatorial bromine (see Table I).

It is generally accepted that reductions proceeding through carbanions usually afford the thermodynamically more stable product[17,18,19]. The explanation given for such stereochemical preferences is that a carbanion has a tetrahedral configuration in which the free electron pair has the required orientation to yield, on protonation, the more stable isomer. If this is so then the steric requirements of a C-C bond,

* The isotopic dilution method could not be applied in this case, as the bromide (XVI; X = Br) had been shown to exchange deuterium slowly under the conditions of its formation.

a carbanion and a C-H bond have to be in a diminishing order. That the bulk of the free electron pair of a carbanion is indeed greater than that of a C-H bond was shown by Roberts and Shoppee[22] who obtained cholestane-3β-carboxylic acid both from 3α-bromo- and 3β-bromocholestane on reaction with magnesium and further treatment with carbon dioxide. We can now give some evidence that the steric requirements of a C-C bond are greater than those of a carbanion. In fact, reduction of 3β-chloro- or 3β-bromo-3α-methylcholestane with lithium and liquid ammonia afforded the (expected)[17,22] more stable hydrocarbon - 3β-methylcholestane (XIX). This was also obtained by hydrogenation of 3-methylcholest-2-ene using platinum as catalyst. The 3β-methylcholestane obtained by both routes had, however, different physical properties from those recorded in the literature[5,23]. An authentic sample of the saturated hydrocarbon was therefore prepared in an unambiguous way. Thus, cholestane-3β-carboxylic acid (XX) was converted to the methyl ester[24,25] which was then submitted to a lithium aluminium hydride reduction to yield 3β-hydroxymethylcholestane (XXI). Conversion of this to the toluene-p-sulphonate and further reduction with the same reagent[26] afforded (XIX, identical in every respect with the product obtained above.

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NEW COMPOUNDS

Compound	m.p.	$[\alpha]_D$
3β-Methylcholestan-3α-yl p-nitrobenzoate	159-60°	+ 20°
3α-Methylcholestan-3β-yl p-nitrobenzoate	194°	+ 30°
2β-3α-Dibromo-3β-methylcholestane	106-8°	+ 89°
2α:3β-Dibromo-3α-methylcholestane	160-2°	- 15°
2α:3α-Epoxy-3β-methylcholestane	133-5°	+ 47°
3-Methylenecholestane	65-6°	+ 23°
3α-Bromo-3β-bromomethylcholestane	116-8°	+ 38°
3β-Bromo-3α-bromomethylcholestane	124-6°	+ 23°
3ξ-Hydroxy-3ξ-hydroxymethylcholestane	208-9°	+ 29°
3β-Hydroxymethylcholestane	151-2°	+ 28°
3β-Hydroxymethylcholestane toluene-p-sulphonate	113-4°	+ 22°
3β-Chloro-3α-methylcholestane	154-6°	+ 33°
3β-Bromo-3α-methylcholestane	138-9°	+ 35°
3ξ-Hydroxycholestanyl-3ξ-acetic acid ethyl ester	99°	+ 24°
3ξ-Hydroxycholestanyl-3ξ-acetic acid	195-7°	+ 21°
3ξ-Hydroxycholestanyl-3ξ-acetic acid methyl ester	107.5-8°	
3ξ-Hydroxycholestanyl-3ξacetic acid	220-1°	+ 24°
3ξ-Hydroxycholestanyl-3ξ-acetic acid methyl ester	92-3°	

EXPERIMENTAL

Rotations were taken in $CHCl_3$ solution. Infra-red spectra were kindly determined by Dr. J.E. Page of Messrs. Glaxo Laboratories Ltd., and by Dr. G. Eglinton using, unless stated to the contrary, carbon disulphide as solvent. The light petroleum used was of b.p. 40-60°.

3-Methylcholestan-3α-and-3β-ol

Cholestanone, m.p. 128-129° $[\alpha]_D$ + 39° (c, 1.21), (5.2 g.) in dry ether (50 ml.) was added to methyl-magnesium iodide [prepared from methyl iodide (4.8 g.) and magnesium (1.02 g.) in dry ether (18 ml.)] with good stirring during 30 minutes and the resulting solution refluxed for two hours. The product, in 3:2 - light petroleum: benzene (50 ml.) was chromato-graphed over neutralised alumina (75 g.) (27 fractions). Elution with the same solvent mixture, with benzene and with 9:1 - benzene:ether (19 fractions in all) gave 3β-methylcholestan-3α-ol (2.90 g.), m.p. (from ethyl acetate-methanol) 126-127°, $[\alpha]_D$ + 28° (c, 1.68). Elution with 1:1-benzene:ether and with ether alone (8 fractions in all) afforded 3α-methylcholestan-3β-ol (2.19 g.), m.p. (from acetic acid) 147-149°, $[\alpha]_D$ + 34° (c, 1.24). Kuwada and Miyasaka* reported m.p. 125° and 147-148° respectively.

* Kuwada and Miyasaka, J. Pharm. Soc., Japan, 1938, 58, 115; Chem. Abr., 1938, 7474.

The two alcohols were characterised as follows. The alcohol (1.0 g.) in dry ether (50 ml.) was stirred with a solution of phenyl lithium [prepared from bromobenzene (782 mg.) and excess of lithium wire in dry ether (150 ml.) with stirring for two hours] for one hour. p-Nitrobenzoyl chloride (2.0 g.) in dry ether (25 ml.) was added and the solution left overnight. Crystallisation of the product from ethyl acetate-methanol afforded 3β-methylcholestan-3α-ol p-nitrobenzoate, m.p. (needles) 159-160°, $[\alpha]_D$ + 20° (c, 1.03) (Found: C, 76.45; H, 9.45. $C_{35}H_{53}O_4N$ requires C, 76.2; H, 9.7%. The derivative from the β-alcohol was only obtained crystalline with difficulty (gel) by chromatography over neutralised alumina (45 g.) in benzene. Crystallisation from acetic acid gave 3α-methylcholestan-3β-ol p-nitrobenzoate, m.p. (needles) 194°, $[\alpha]_D$ + 30° (c, 1.75) (Found: C, 76.3; H, 9.7%).

3-Methylcholest-2-ene (IV)

The two stereoisomeric alcohols (see above) behaved in the same way on treatment with acetic acid-perchloric acid. The alcohol (40 mg.) in 'AnalaR' acetic acid (2 ml.) with addition of

perchloric acid (70%; two drops) was heated on the steam bath for 30 minutes. The product was filtered through alumina in light petroleum and crystallised from the same solvent, m.p. 82-83°, $[\alpha]_D$ + 74° (c, 1.32), + 74° (c, 1.39). The olefin can be conveniently prepared by the same treatment of the mixed alcohols from the Grignard reaction on cholestanone.

3-Methylcholest-2-ene (233 mg.) in dry dioxan (10 ml.) was treated with osmium tetroxide (210 mg.) in the same solvent (10 ml.) and left at room temperature in the dark for 3 days. The osmate was cleaved by saturation with hydrogen sulphide and, after filtration, the dioxan was removed in vacuo. The residue was taken up in 'AnalaR' acetic acid (30 ml.) with addition of lead tetra-acetate (740 mg.) in the same solvent (20 ml.) and left for one day (uptake 1.0 mole of lead tetra-acetate). The product in dry dioxan (20 ml.) was treated with sodium hypobromite solution (2.0 ml.) [prepared by adding bromine (2 ml.) to ice cold water (26.5 ml.) containing sodium hydroxide (6.3 g.)] and the solution stirred for five hours at room temperature.

The acidic fraction of the product was crystallised from ether: light petroleum to give seco-2:3-cholestanedicarboxylic acid (34 mg.), identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ + 35° (c, 0.85)]. The authentic specimen, prepared by chromic acid oxidation of cholestanol according to Windaus and Uibrig* had m.p. 196-198°, $[\alpha]_D$ + 35° (c, 0.95).

3-Methylcholest-2-ene (412 mg.) in carbon tetrachloride (20 ml.) was titrated with bromine (15% w/w; carbon tetrachloride). Removal of the solvent *in vacuo* at room temperature and chromatography over alumina in light petroleum developing with the same solvent gave two dibromides. Eluted more easily was 2β:3α-*dibromo*-3β-*methylcholestane* (440 mg.), m.p. (needles from ethyl acetate-methanol) 106-108° decomp., $[\alpha]_D$ + 89° (c, 1.23) (Found: C, 62.25; H, 8.65; Br, 29.15. $C_{28}H_{48}Br_2$ requires C, 61.75; H, 8.9; Br, 29.35%). Eluted with more difficulty was 2α:3β-*dibromo*-3α-*methylcholestane*, m.p. (from ethyl acetate-methanol) 160-162°, $[\alpha]_D$ - 15° (c, 0.82) (Found: C, 61.7; H, 9.05; Br, 29.4%). The 2β:3α-dibromide (220 mg.) in chloroform (35 ml.) was refluxed for 97 hours (no further change in

* Windaus and Uibrig, *Ber.*, 1914, *47*, 2384.

rotation). Removal of the chloroform *in vacuo* and crystallisation from ethyl acetate-methanol gave the 2α:3β-dibromide, identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ - 16° (c, 1.03)].

2α:3α-Epoxy-3β-methylcholestane (VIII)

3-Methylcholest-2-ene (500 mg.) was treated with three moles of perphthalic acid in ethereal solution overnight at room temperature (uptake of one mole). Filtration of the product in light petroleum over silica gel gave 2α:3α-epoxy-3β-methylcholestane, m.p. (from alcohol) 133-135°, $[\alpha]_D$ + 47° (c, 1.17) (Found: C, 83.85; H, 11.65. $C_{28}H_{48}O$ requires C, 83.95; H, 12.1%). This epoxide (1.4 g.) in ether (100 ml.) was reduced with an excess of lithium aluminium hydride (2.8 g.) in the same solvent (100 ml.) under reflux for 40 hours. Crystallisation from ethanol gave 3β-methylcholestan-3α-ol, identified by m.p. and mixed m.p.

3-Methylenecholestane (IX)

Triphenylmethylphosphonium bromide* (2.77 g.) was treated with lithium phenyl (651 mg.) in dry ether (46 ml.) with shaking for three hours. To this solution there was added cholestanone (3.0 g.) and

* Cf. Wittig and Schollkopf, Ber., 1954, 87, 1318.

the solution refluxed overnight. After washing with water the dried (sodium sulphate) ethereal solution was evaporated *in vacuo*. The residue was refluxed with excess of lithium aluminium hydride in ethereal solution. After working up in the usual way the product was filtered in light petroleum solution through alumina (50 g.). Elution with the same solvent (150 ml.) afforded 3-*methylenecholestane* (1.6 g.), m.p. (needles from ethyl acetate-methanol) 65-66°, $[\alpha]_D$ + 23° (c, 2.16 in CCl_4) (Found: C, 87.7; H, 12.45. $C_{28}H_{48}$ requires C, 87.4; H, 12.6%). This hydrocarbon (89.5 mg.) in carbon tetrachloride (10 ml.) containing one drop of 'AnalaR' pyridine was titrated with bromine (3.36% w/v) in the same solvent. After removal of the solvent *in vacuo* at room temperature the oily product was chromatographed over silica gel (2.0 g.) in light petroleum (5 ml.). Elution with the same solvent (30 ml.) gave 3α-*bromo*-3β-*bromomethylcholestane* (91.7 mg.), m.p. (flat needles from ethyl acetate) 116-118°, $[\alpha]_D$ + 38° (c, 1.65) (Found: C, 62.25; H, 8.8; Br, 29.45. $C_{28}H_{48}Br_2$ requires C, 61.75; H, 8.9; Br 29.35%). Further elution with the same

solvent (15 ml.) and (45 ml.) gave respectively a mixture (16.8 mg.) and then 3β-bromo-3α-bromomethylcholestane (16.6 mg.), m.p. (needles from ethyl acetate) 124-126°, $[\alpha]_D$ + 23° (c, 1.14) (Found: C, 61.35; H, 9.05; Br, 29.6%). The two dibromides gave a marked depression in m.p. on admixture.

Conversion of 3-Methylenecholestane to Cholestanone

3-Methylenecholestane (162 mg.) in dry dioxan (5 ml.) was treated with osmium tetroxide (139 mg.) in the same solvent (5 ml.) at room temperature for 48 hours. The osmium tetroxide complex was cleaved with hydrogen sulphide* and the product crystallised from ethanol to furnish the glycol, m.p. (blades) 208-209°, $[\alpha]_D$ + 29° (c, 0.71) (Found: C, 79.85; H, 12.45. $C_{28}H_{50}O_2$ requires C, 80.3; H, 12.1%). In an identical experiment the total glycol in ethanol (10 ml.) and dioxan (35 ml.) was treated with periodic acid (308 mg.) in water (5 ml.) for 16 hours (uptake of one mole of oxidant). After working up in the usual way the product was filtered in benzene solution through alumina (3 g.). Elution with the same solvent gave cholestanone (130 mg.; 80%) identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ + 39.5° (c, 1.53)].

* Cf. Barton and Elad, J. Chem. Soc., 1956, 2085.

The Reformatsky Reaction on Cholestanone

A solution of cholestanone (5.0 g.) and ethyl bromoacetate (1.6 c.c.) in dry benzene (25 c.c.) was added during 20 minutes to a flask containing zinc powder (0.875 g.), dry benzene (10 c.c.) and iodine (1 crystal). After 2 hours reflux, the reaction mixture was treated with dilute sulphuric acid and worked up in the usual way to yield an oil (6.1 g.) which in solution in benzene was chromatographed on silica gel (100 g.). Elution with the same solvent afforded an ester-alcohol (3.64 g.) which crystallised from ethanol in small needles m.p. 99°, $[\alpha]_D$ + 24° (c, 1.51). Found: C, 78.80; H, 11.35. $C_{31}H_{54}O_3$ requires: C, 78.40; H, 11.45%.

Further elution of the column with benzene-ether (9:1) furnished the epimeric ester-alcohol as an oil (2.56 g.) $[\alpha]_D$ + 26° (c, 1.2) which could not be crystallised.

Hydrolysis of the esters

The crystalline ester (1.0 g.) was dissolved in 5% methanolic potassium hydroxide (17.5 c.c.) and the solution refluxed for 30 minutes. After

addition of a large excess of water the acid was extracted in the usual way and crystallised from ethanol in clusters of needles (0.88 g.) m.p. 195-7° $[\alpha]_D$ + 20.6° (c, 1.53). Found: C, 78.15; H, 11.45. $C_{29}H_{50}O_3$ requires C, 77.95; H, 11.30%.

The methyl ester, prepared by reaction with diazomethane in ether, crystallised in needles (from ethanol) m.p. 107.5-8°. Found: C, 77.95; H, 10.95. $C_{30}H_{52}O_3$ requires: C, 78.20; H, 11.40%.

The second (oily) ester-alcohol of the above chromatogram (2.21 g.) was hydrolysed precisely as above to yield an acid (1.9 g.) which crystallised (from ethyl acetate) in microcrystalline aggregates m.p. 220-1°, $[\alpha]_D$ + 24.3° (c, 1.75). (M.m.p. with the first acid was 192-9°). Found: C, 77.60; H, 11.70%.

The methyl ester prepared as above crystallised from ethanol in needles m.p. 92-3°. (M.m.p. with the previous methyl ester was 75-94°). Found: C, 78.00; H, 11.00%.

Pyrolysis of the acids

The acid m.p. 195-7° (0.146 g.) was heated at 290-300° (bath temperature) under nitrogen for 1 minute. The resultant product was dissolved in

benzene and chromatographed on alumina (5 g.) to yield a mixture of olefins (0.055 g.) which crystallised from light petroleum in microcrystalline aggregates m.p. 67-81°, $[\alpha]_D$ + 34.5° (c, 1.44). The mixed melting point with 3-methylcholest-2-ene was 52-66°. That mixture could not be separated either by repeated crystallizations or by chromatography.

The second acid (0.130 g.) was subjected to the same treatment and the resultant product dissolved in benzene and filtered through alumina. The 3-Methylcholest-2-ene (0.057 g.) obtained was characterised by m.p., m.m.p. and rotation.

3β-Methylcholestane (XIX)

(a) From cholestane-3β-carboxylic acid.

Methyl cholestane-3β-carboxylate* (1.2 g.) in dry ether (50 ml.) was reduced with a large excess of lithium aluminium hydride in the same solvent under reflux for six hours. Crystallisation of the product from ethyl acetate-methanol gave 3β-hydroxymethylcholestane, m.p. (needles) 151-152°, $[\alpha]_D$ + 28° (c, 1.28) (Found: C, 83.65; H, 12.35. $C_{28}H_{50}O$ requires C, 83.5; H, 12.5%). This alcohol (1.1 g.) in dry pyridine (30 ml.) was treated with toluene-p-sulphonyl

* Cf. Corey and Sneen, J. Am. Chem. Soc., 1953, 75, 6234; Roberts, Schoppee and Stephenson, J. Chem. Soc., 1954, 2705.

chloride (3.0 g.) in the same solvent (20 ml.) overnight at room temperature to furnish the toluene-p-sulphonate, m.p. (from chloroform-methanol) 113-114°, $[\alpha]_D$ + 22° (c, 1.02) (Found: C, 74.65; H, 9.9. $C_{35}H_{56}O_3S.\frac{1}{2}CH_4O$ requires C, 74.45; H, 10.2%). This toluene-p-sulphonate (496 mg.) in ether (50 ml.) was reduced with a large excess of lithium aluminium hydride under reflux for 72 hours to give authentic 3β-methylcholestane (350 mg.) m.p. (from chloroform-methanol) 105-106°, $[\alpha]_D$ + 28° (c, 1.76). For this compound Baker, Minckler and Petersen* reported m.p. 97-98° $[\alpha]_D$ + 11°.

(b) From 3-methylcholest-2-ene.

The olefin (223 mg.) in 1:1-ethyl acetate: acetic acid (60 ml.) was hydrogenated over platinum to give 3β-methylcholestane (200 mg.), identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ + 27° (c, 1.23)].

(c) From 3β-chloro-3α-methylcholestane.

The chloro-compound (see below) (140 mg.) in dry ether (30 ml. was added during 10 minutes to a solution of lithium (150 mg.) in liquid ammonia at -60°C and the solution stirred for five hours. Excess of

* Baker, Minckler and Petersen, J. Am. Chem. Soc., 1955, 77, 3644.

ammonium chloride was added and ammonia left to evaporate. Crystallisation from chloroform-methanol gave 3β-methylcholestane (100 mg.), identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ + 28° (c, 0.84)]. In a second experiment 3β-chloro-3α-methylcholestane (102 mg.) in 1:1 - ether: acetic acid (60 ml.) was treated with excess of zinc dust during 18 hours at room temperature (good stirring). Chromatography of the product over silica gel (3.0 g.) in light petroleum solution gave 3β-methylcholestane (26 mg.), identified by m.p., mixed m.p., rotation [$[\alpha]_D$ + 28° (c, 0.89)] and negative Beilstein test as well as unchanged starting material (66 mg.), identified by m.p., mixed m.p. and positive Beilstein test.

(d) From 3β-bromo-3α-methylcholestane.

The bromo-compound (see below) (97.7 mg.) in dry ether (20 ml.) was slowly (10 mins.) dropped with stirring into a solution of lithium (101 mg.) in liquid ammonia (25 ml.) and left with stirring for 2 hours. Protonation with ammonium chloride and working working up in the usual way gave a crystalline residue (76.3 mg.). One crystallisation from ethyl

acetate-methanol gave 3β-methylcholestane (61 mg.), identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ + 27° (c, 1.12)].

Dehydration of the 3-Methylcholestanols

3β-Methylcholestan-3α-ol (see above) (240 mg.) in dry pyridine (25 ml.) and redistilled phosphorus oxychloride (290 ml.) was left for 24 hours at room temperature. Crystallisation of the product from chloroform-methanol afforded 3-methylcholest-2-ene (200 mg.), identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ + 70° (c, 1.29)].

Exactly the same dehydration procedure was applied to 3α-methylcholestan-3β-ol. The resulting olefin (194 mg.) was chromatographed over silica gel (50 g.) in light petroleum. All fractions melted indefinitely between 56 and 63° and had rotations close to 40°. A typical mixture had m.p. (from ethyl acetate-methanol) 57-59°, $[\alpha]_D$ + 44° (c, 0.85) (Found: C, 87.1; H, 12.25. Calc. for $C_{28}H_{48}$, C, 87.4; H, 12.6%). In order to characterise the olefin mixture the following experiments were performed. The mixture (1.4 g.) in carbon tetrachloride (25 ml.) was titrated with bromine (15% w/v) in the same solvent. The

resulting mixture of dibromides was chromatographed over silica gel in light petroleum eluting with the same solvent. The first eluted dibromide (1.2 g.) had m.p. (plates from ethyl acetate-methanol) 114° decomp., $[\alpha]_D$ + 44° (c, 1.12) and was identified (m.p. and mixed m.p.) as 3α-bromo-3β-bromomethylcholestane. The secondly eluted dibromide (260 mg.) had m.p. (needles from ethyl acetate-methanol) 124-126° decomp., $[\alpha]_D$ + 23° (c, 1.14) and was identified (m.p. and mixed m.p.) as 3β-bromo-3α-bromomethylcholestane.

The olefin mixture (400 mg.) in dry dioxan was treated with osmium tetroxide (400 mg.) in the same solvent (5 ml.) and left in the dark at room temperature for 2 days. After saturation with hydrogen sulphide and filtration, the dioxan was removed in vacuo and the residue in 'AnalaR' acetic acid (25 ml.) was oxidised with lead tetra-acetate (1.0 g.) in the same solvent (25 ml.) at room temperature for 4 hours (one mole uptake). The product (360 mg.) was chromatographed over neutralised alumina (8 g.) in light petroleum. Elution with 1:4-benzene:light petroleum gave cholestanone (192 mg. pure), identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ + 40° (c, 1.20)].

3β-Chloro-3α-methylcholestane (XVI; X = Cl)

3-Methylcholest-2-ene (265 mg.), 3-methylene-cholestane (250 mg.), 3β-methylcholestan-3α-ol (210 mg.) and 3α-methylcholestan-3β-ol (245 mg.) were treated separately with dry hydrogen chloride in dioxan (23% w/v; 25 ml.) for 8 days at room temperature and then for 3 days at 0°. All four solutions deposited pure 3β-chloro-3α-methylcholestane, m.p. 154-156°, unchanged on crystallisation from light petroleum, $[\alpha]_D$ + 32° (c, 0.92), + 33° (c, 1.02), + 33° (c, 0.93) and + 33° (c, 1.05) respectively (Found: C, 79.9; H, 11.6. $C_{28}H_{49}Cl$ requires C, 79.85; H, 11.7%). Concentration of the mother liquors in vacuo at room temperature gave further crops of the chloride, the total yields being 76, 70, 76 and 70% respectively. The experiments were repeated leaving for 24 hours only at room temperature with the same results.

In order to determine the total yield of chloride in the above experiments an isotope dilution method was employed. 3-Methylcholest-2-ene was converted to the chloride exactly as above but using deuterium chloride instead of hydrogen chloride.

The ordinary chloride has a strong infra-red band (carbon disulphide solution) at 783 cm.$^{-1}$ whereas the deuterated material shows no absorption at this frequency. It is a simple matter, therefore, to analyse mixtures of the two substances. 3-Methylcholest-2-ene (90.0 mg.) and the deuterated 3β-chloro-3α-methylcholestane (10.95 mg.) were treated with hydrogen chloride in dioxan exactly as above. The first crop of chloride, m.p. 154-156°, $[\alpha]_D$ + 33° (c, 1.05) was analysed for its content of labelled chloride and shown to contain 12.0%. The true yield of 3β-chloro derivative from the 3-methylcholest-2-ene is, therefore, 82%. The method of analysis is, of course, only valid provided that there is no exchange between ordinary chloride and deuterated chloride. This was checked in two ways: (a) the ordinary chloride was treated with deuterium chloride in dioxan, and (b) the deuterated chloride was treated with hydrogen chloride in the same solvent. Infra-red examination of the product (see above) showed that in each case there was no exchange.

In order to determine the approximate times of half-reaction the following experiments were

carried out. 3-Methylcholest-2-ene (92 mg.) in hydrogen chloride-dioxan (23% w/v; 25 ml.) was kept at room temperature (20°) and the reaction followed polarimetrically. The initial rotation was +75° (taken 8 minutes after dissolution) [cf. $[\alpha]_D$ for 3-methylcholest-2-ene: + 80° (c, 0.88 in dioxan)]. After 120 minutes the rotation was constant at 37°. The time of half-reaction was 13 minutes. 3β-Methylcholestan-3α-ol (108 mg.) was treated in the same way for 30 minutes. The product was chromatographed over silica gel (5 g.) in light petroleum. Elution with this solvent gave 3-methylcholest-2-ene (2.2 mg.), identified by m.p., mixed m.p. and negative Beilstein test. Further elution with the same solvent furnished the chloride (60 mg.; 53%), identified by m.p., mixed m.p. and positive Beilstein test. Elution with benzene afforded unchanged starting material (48 mg.). 3α-Methylcholestan-3β-ol (103 mg.), treated in exactly the same way for two hours, gave 3-methylcholest-2-ene (8 mg.), the chloride (29 mg.; 27%) and unchanged alcohol (68 mg.).

3β-Chloro-3α-methylcholestane (100 mg.) in dioxan (65 ml.) and water (5 ml.) was left for seven days at 20°. The solvent was removed in vacuo at room temperature to give back atarting material (100 mg.) unchanged (m.p., mixed m.p. and positive Beilstein test).

Treatment of 3β-Chloro-3α-methylcholestane with Collidine

The chloride (171 mg.) in dry redistilled collidine (5 ml.) was heated under reflux for three hours. The product was treated with osmium tetroxide and then with lead tetra-acetate exactly as described for the processing of the dehydration product of 3α-methylcholestan-3β-ol to give cholestanone (57 mg.), identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ + 40° (c, 1.23)]. In a second experiment the chloride (34 mg.), treated as above with collidine, furnished a product which on titration with bromine gave 3α-bromo-3β-bromomethylcholestane (30 mg.), identified by m.p., mixed m.p. and rotation [$[\alpha]_D$ + 44° (c, 0.75)]. This dibromide was worked up as before (see above).

3β-Bromo-3α-methylcholestane (XVI; X = Br)

3-Methylcholest-2-ene (203 mg.), 3β-methylcholestan-3α-ol (200 mg.) and 3α-methylcholestan-3β-ol (203 mg.)

were treated separately with dry hydrogen bromide in dioxan (25% w/v; 25 ml.) at room temperature (20°) for seven days. In each case 3β-bromo-3a-methylcholestane crystallised out in pure condition (76, 73 and 74% respectively). It had m.p. 138-139°, unchanged on recrystallisation from cold dry light petroleum, $[\alpha]_D$ + 35° (c, 1.09) (Found: C, 72.1; H, 10.35; Br, 16.8. $C_{28}H_{49}Br$ requires C, 72.25; H, 10.6; Br, 17.15%). The infra-red spectra of all three preparations were identical.

PART II

An Approach to the Partial Synthesis of Aldosterone from C_{18}-Methyl Steroids

Aldosterone, the adrenocortical hormone with a pronounced effect on the inorganic metabolism of the body, was first isolated in a crystalline state from cortical extracts in 1953 by Mattox[1] and was named electrocortin by this author. Later, in 1954, the joint efforts of three laboratories[2] were revealed in a series of papers which described the isolation, estimation, physiological properties and constitution of this potent mineralocorticoid hormone. It was renamed aldosterone, when it was realised that a masked aldehyde function was present in the molecule. During the preliminary isolation work, suprarenal extracts were assayed by paper chromatographic techniques. In a typical preparative isolation, 1000 Kg. of frozen ox adrenals were processed and finally submitted to a chromatogram lasting 70 days. The yield of crystalline aldosterone was 57 mg. The elegant work of the Swiss and English schools[2] on the constitution of the hormone is summarised in the following paragraphs.

Aldosterone has the molecular formula $C_{21}H_{28}O_5$ and is thus isomeric with cortisone. It crystallises from acetone-water as the monohydrate. On treatment with periodic acid formaldehyde is obtained, thus showing the presence of a $-CO-CH_2OH$ side chain.

The ultra-violet absorption spectrum (in ethanol) showed λ max. 240 mμ, log. ϵ 4.2 which is in excellent agreement with the value for a Δ^4-3-keto steroid. Antonucci[3,4] showed that a Δ^4-3-keto steroid with an 11-keto group had λmax. 238 mμ, and with an 11β-OH had λ max. 242 mμ. (See tables I and II).

Table I

Ultra-violet Absorption Maxima of 11-Ketosteroids

(Δ^4-3-keto)

Compound	λ max. mμ	Solvent
Dehydrocorticosterone acetate	237.5	Alcohol
12α-Bromodehydrocorticosterone acetate	238.5	Alcohol
Adrenosterone	237	Absolute alcohol
Cortisone	238	Alcohol
Cortisone acetate	238	Alcohol
Δ^4-Pregnene-17α:21-diol-3:11:20-trione-21-acetate-20-ethyleneketal	237	Absolute alcohol

Table II

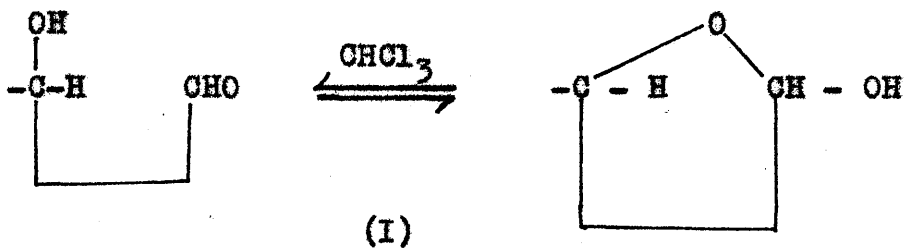
Ultra-violet Absorption Maxima of 11-Hydroxysteriods (Δ^4-3-keto)

Compound	λmax mμ	Solvent
11β-Hydroxyprogesterone	242	Alcohol
11α-Hydroxyprogesterone	242	Alcohol
Corticosterone	240	Alcohol
Hydrocortisone	242	Absolute alcohol
Hydrocortisone acetate	242	Absolute alcohol
11-Epi-hydrocortisone diacetate	240	Absolute alcohol

The infra-red spectrum showed the following peaks: 3610 cm^{-1} (free -OH); 3508-3278 $cm.^{-1}$ -broad absorption- (-OH + H bonding)* 1672 $cm.^{-1}$ (Δ^4-3-ketone); 1706 $cm.^{-1}$ (unconjugated 20 $>C = O$)

* This peak is missing in cortexone, corticosterone and 17-hydroxycorticosterone but is very marked in γ-hydroxyvaleraldehyde (I) in concentrated chloroform solution. At higher dilutions the band becomes weaker; at still greater dilutions it disappears altogether and only the free -OH band remains.

relatively weak as shown* by a comparison of the values in Table III. These show that the 20 >C = O absorption is weakened by intermolecular H-bonding. To summarise, in dilute chloroform aldosterone exists as a cyclohemiacetal with H-bonding, whilst at higher concentrations association by intermolecular H-bonding is evident.



(I)

* The determination of integrated intensities[5] of the 3- and 20-keto groups in aldosterone gives a value of A^*

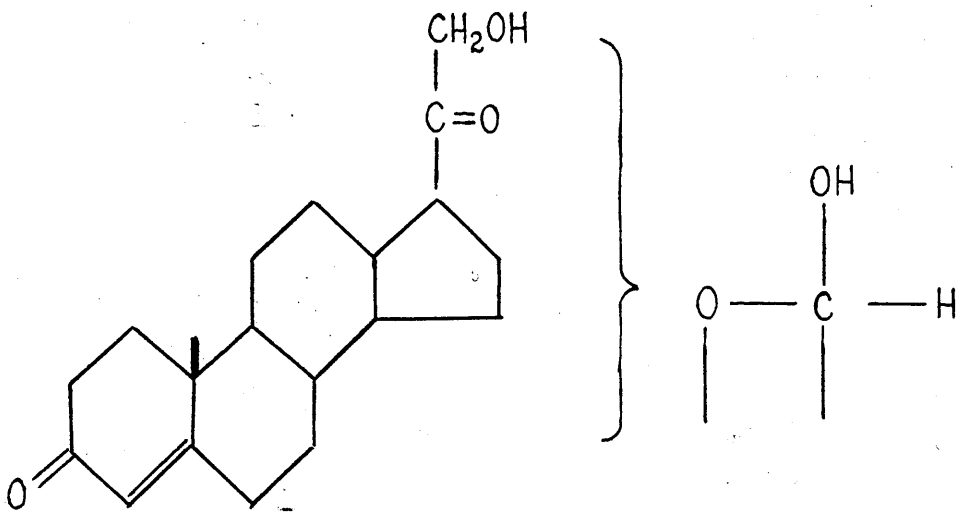
$$A^* = \frac{k}{CM.d}\int \log_{10}\left(\frac{Io}{I}\right) dv$$

$A^* = 1.97 \times 10^4$ l/g Mol. cm^2

Δ^4-3-keto= 1.6×10^4 " " "

20-keto= 0.8×10^4 " " "

That the practical value of A^* for aldosterone is less than the sum of the partial values must show that the total intensity ratio of 3.1 is due to a weakening of the 20-keto band.



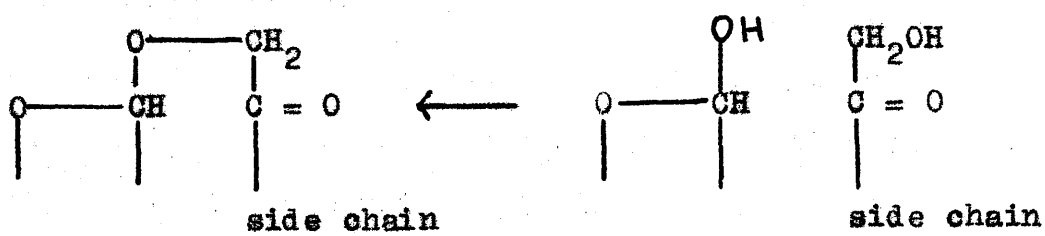
(11)

Table III

Substance	$\frac{\log. \frac{I_o}{I} \ (\Delta^4\text{-3-keto})}{\log. \frac{I_o}{I} \ (20\text{-keto})}$
Cortexone	1.9
Corticosterone	1.9
17-Hydroxycortexone	2.2
17-Hydroxycorticosterone	2.3
Aldosterone	3.1

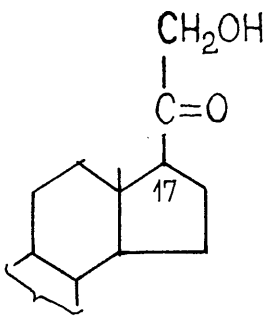
Moreover aldosterone (like γ-hydroxyvaleraldehyde) has reducing properties thus indicating a masked aldehyde group as depicted in partial structure II. On acetylation (with excess acetic anhydride-pyridine) aldosterone yields a diacetate which can be purified and characterised by paper chromatography. That this was in fact a diacetate was shown by measuring the activity of a sample acetylated with C^{14} acetic anhydride of known radioactivity, by Zaffaroni test[6], and by the disappearance of the -OH band in the infra-red spectrum. Partial acetylation

in dilute solution afforded the 21-monoacetate which gives no formaldehyde on treatment with sodium bismuthate[7]. Aldosterone was regenerated from both its mono- and di-acetylated derivatives by the action of potassium bicarbonate-aqueous methanol. This had hitherto only been possible by enzymatic means[8,9]. Aldosterone is relatively sensitive to acid and is in fact degraded faster in alcoholic than in aqueous solution. Partial structure (III) is suggested for the product of treatment with acid (no -OH in the infra-red spectrum).

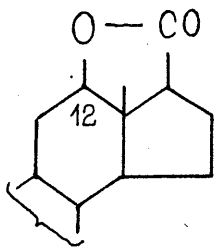


(III)

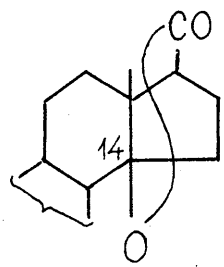
The degradative experiments to be described in the sequel are remarkable in that they were performed on quantities rarely exceeding 10 mg., and in many cases, several products were isolated by careful chromatography and characterised by analysis and light absorption measurements. The characterisation of aldosterone



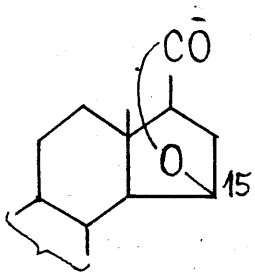
(IV)



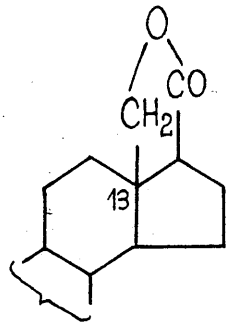
(V)



(VI)



(VII)

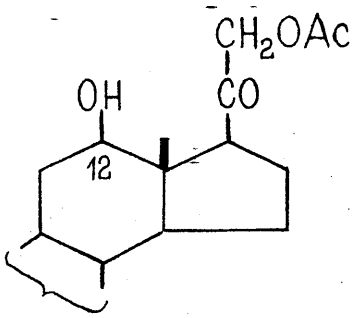


(VIII)

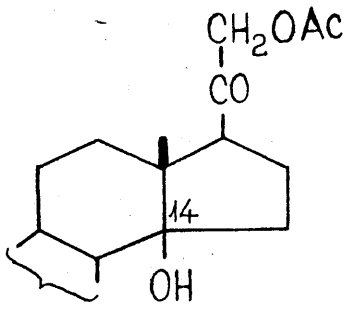
is indeed one of the finest examples of the masterly technique of the Swiss school of chemists.

Aldosterone, on treatment with sodium periodate in methanol solution yielded formaldehyde together with a neutral product which had excellent crystallising properties and could be sublimed in high vacuum. This compound, $C_{20}H_{24}O_4$, is a γ-lactone (IR. absorption at 1780 cm^{-1}); this accounts for the absence of free -OH. The γ-lactone has also no reducing properties.

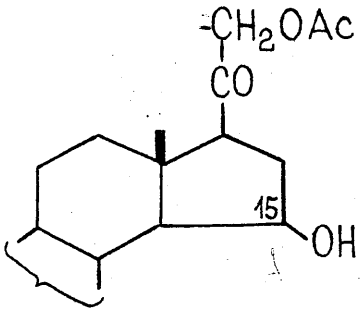
Assuming the partial formula (IV) for aldosterone the γ-lactone becomes (V), (VI), (VII) or (VIII). Since 12-hydroxyetianic acid does not easily lactonise[10] structure (V) is unlikely. A 17α-ketol group in aldosterone is most unlikely as steroids with a 17α side chain are biologically inactive. Also (VI) could be a possibility in the formation and properties of diacetylaldosterone. Likewise a formula with substituents at C_{12} and C_{17} β-oriented and having the C_{13} methyl group with α configuration seems improbable. Aldosterone must then have this -OH at C_{12}, C_{14}, C_{15} or C_{18}. In order to choose between these four formulae 21-monoacetylaldosterone [which does not yield formaldehyde on treatment with sodium bismuthate, thus


CH2OAc
CO
OH
12

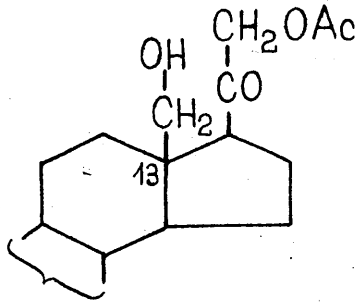
(IX)


CH2OAc
CO
14
OH

(X)

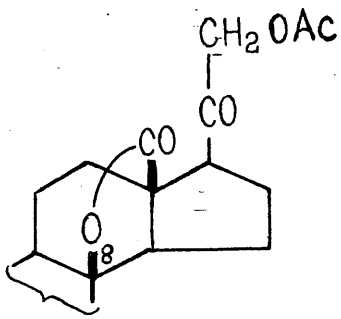

CH2OAc
CO
15
OH

(XI)

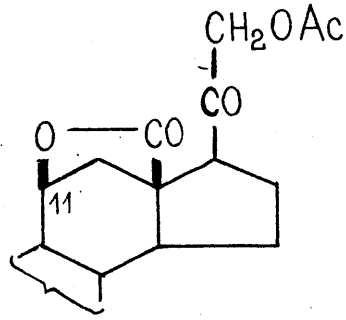

OH
CH2OAc
CO
CH2
13

(XII)

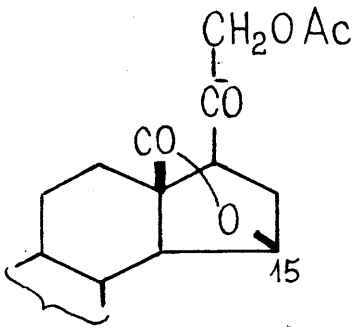
proving that the ketol group is acetylated and that the monoacetate is correctly represented by one of the partial formulae (IX), (X), (XI), or (XII)] was treated with chromic acid. This treatment should not attack the C_{14}-OH [partial formula (X)], but should give ketones either from (IX) or (XI) and an acid from (XII). In fact on such an oxidation a neutral product is obtained in good yield which still contains the 21-acetoxy group and retains the strong reducing properties. The infra-red spectrum of this compound shows, besides the expected bands (1677 and 1626 cm.$^{-1}$ - Δ^4-3-keto-; 1760 cm.$^{-1}$; 1739 cm.$^{-1}$ -21-acetoxy-20-keto), a strong band at 1782 cm.$^{-1}$ due to a γ-lactone. Since this group does not exist either in aldosterone or in its acetyl derivatives it should arise from the oxidation of the 21-acetylaldosterone without the participation of the 20-ketol atoms which were still present in the oxidation product. Now, the $>C = O$ group of the lactone is not situated at C_{19} for the -OH in aldosterone is at C_{12}, C_{14}, C_{15} or C_{18}, and the free 21-monoacetylaldosterone must be capable of lactone formation. If the reasonable assumption is made that the $>C = O$ is at C_{18}, then a γ-OH must be sought for lactone formation on reaction with chromic acid. This



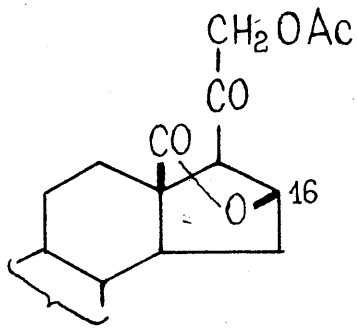
(XIII)



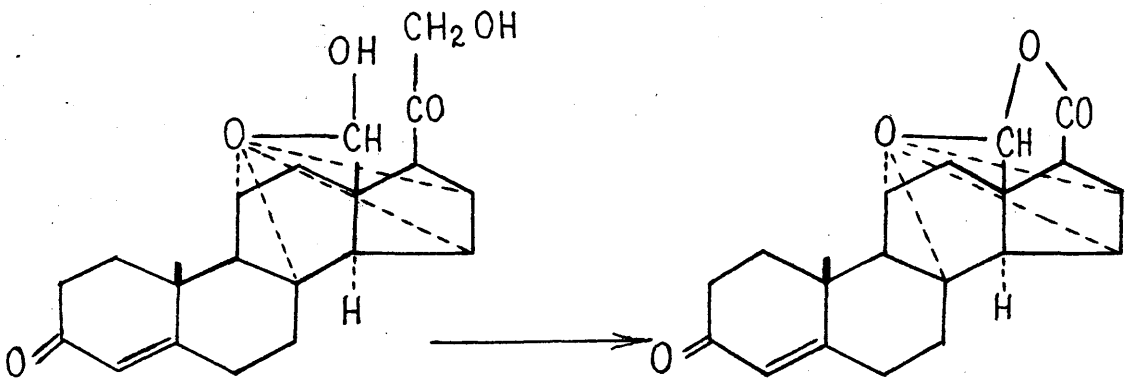
(XIV)



(XV)



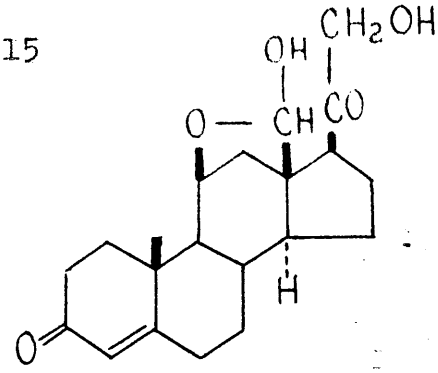
(XVI)



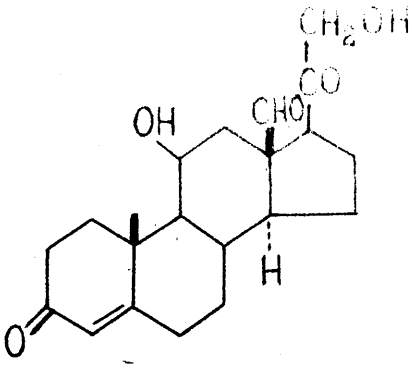
(XVII) (XVIII)

leads to the partial structures (XIII), (XIV), (XV) and (XVI), where the -OH group must have the β configuration. Since aldosterone contains not three but only two free hydroxyl groups it is likely that the compound exists as a cyclic hemiacetal form of an aldehyde group at C_{18}, and so partial structures (XVII) and (XVIII) can be written for aldosterone and its periodate oxidation product, respectively. The correct location of the terminus of the oxygen bridge was determined as follows. Ring A of the lactone (XVIII) was hydrogenated and acetylated (protection of the C_3-keto group) to the 3β-acetoxy-5α-compound, from which on Wolff-Kishner reduction followed by chromic acid oxidation, 3:11-dioxo-5α-etianic acid (characterised as the methyl ester) was obtained. It follows, therefore, that aldosterone has the normal steroid ring structure (XIX). The described degradative reactions are shown on page 15 .

The successful elucidation of the structure of aldosterone has prompted an intensive search for methods of introduction of an oxygen function to the C_{18} position of the steroid nucleus.

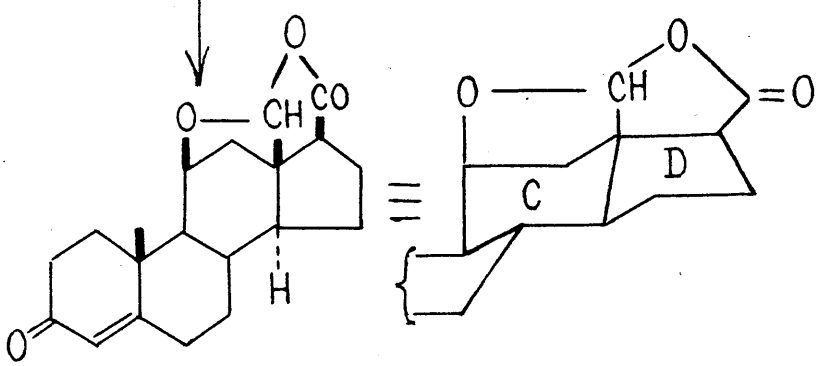


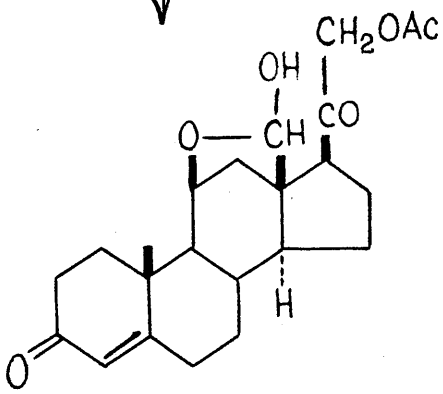
(XIX)



$NaIO_4$ or CrO_3

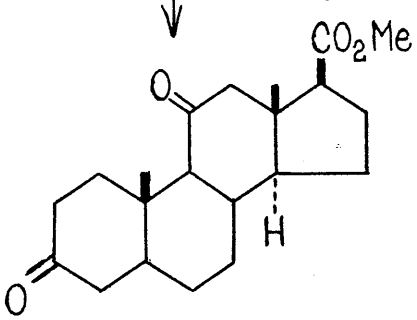
Ac_2O/C_5H_5N

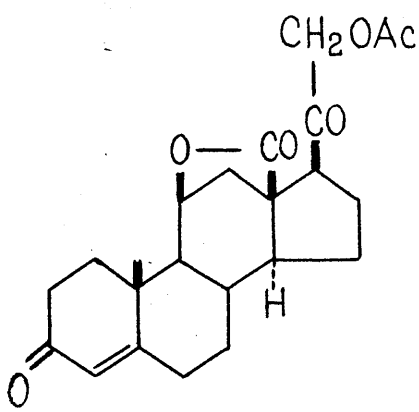


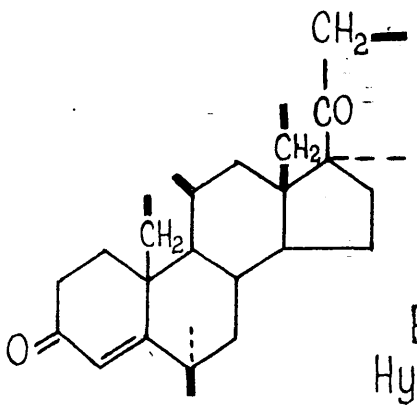


1 - H_2/Pt
2 - W/K
3 - CH_2N_2
4 - CrO_3

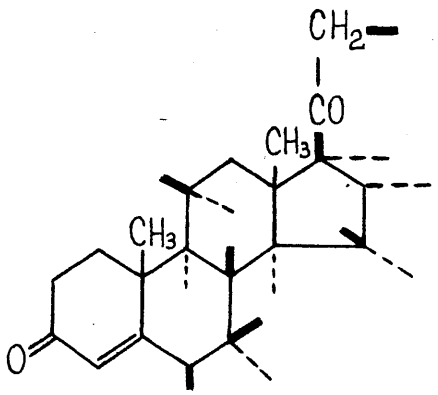
CrO_3







Biological Hydroxylation



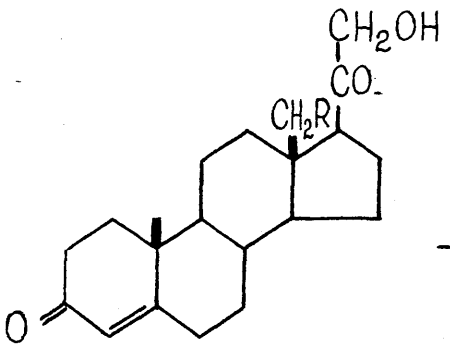
using adrenals

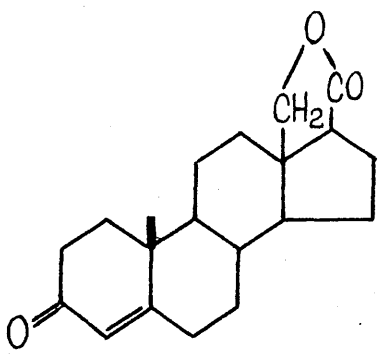
(6α, 6β, 11β, 17α, 18, 19, 21)

using microorganisms

(6β, 7α, 7β, 8β or 9α, 14α
15α, 15β, 16α, 11α, 11β, 17, 21)

×





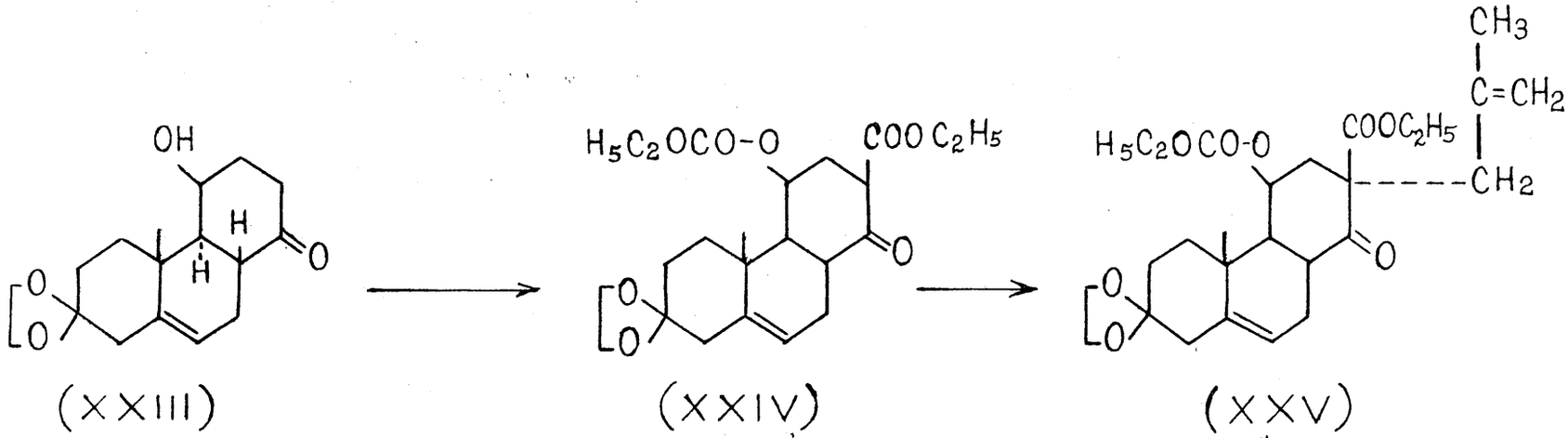
(XX) – R = H

(XXI) – R = OH

(XXII)

The introduction of functional groups into natural or synthetic starting materials using either the method of microbiological conversion or the conversion by animal tissue enzymes has been of great interest particularly in the field of the steroid hormones[11]. Thus, it has been possible to carry out hydrolysis, hydrogenation, dehydrogenation, oxidation-reduction, epoxydation, side chain degradation, ring cleavage to lactones and hydroxylation on steroid molecules, by biological means. In connection with the introduction of hydroxyl groups in such molecules it is interesting to compare the points of attack when adrenal preparations (6α, 6β, 11β, 17α, 18, 19, 21) or microorganisms (6β, 7α, 7β, 8β (or 9α), 14α, 15α, 15β, 16α, 11α, 11β, 17α, 21) are used. (See page 16).

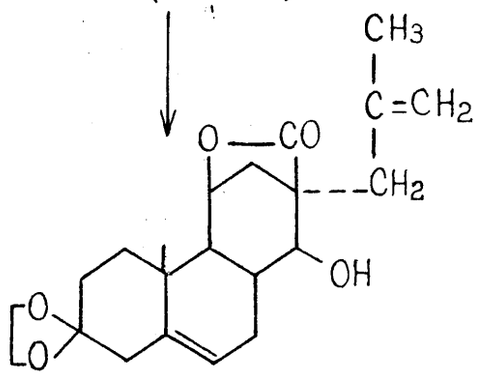
The introduction of a hydroxyl group at the inert C_{18} angular methyl group by adrenal perfusion experiments was described in 1955 by Kahnt, Neher and Wettstein[12] and is of great interest in connection with the biosynthesis of aldosterone. This important achievement was attained when a 10% ethanolic solution of cortexone (XX) was added to an ox adrenal preparation, the 18-hydroxycortexone (XXI) being obtained, which



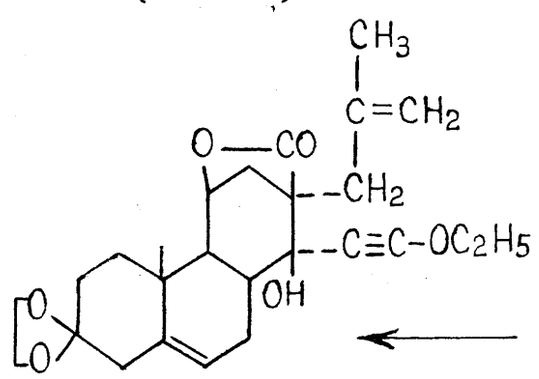
(XXIII)

(XXIV)

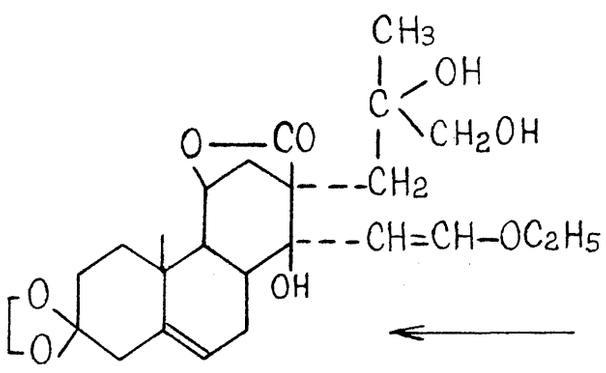
(XXV)



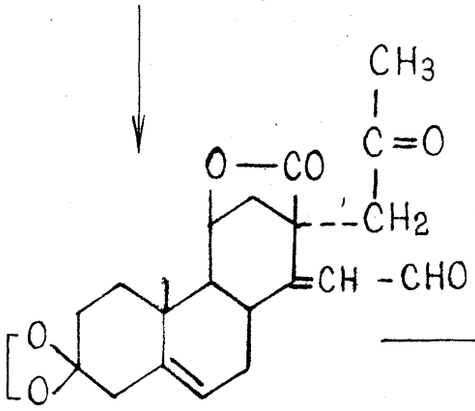
(XXVI)



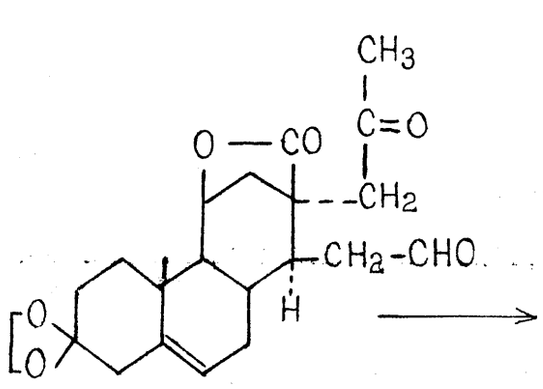
(XXVII)



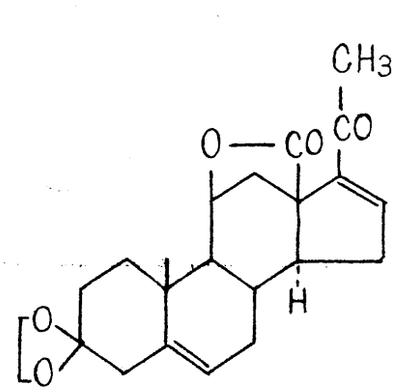
(XXVIII)



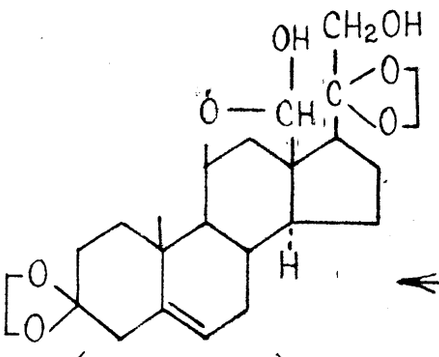
(XXIX)



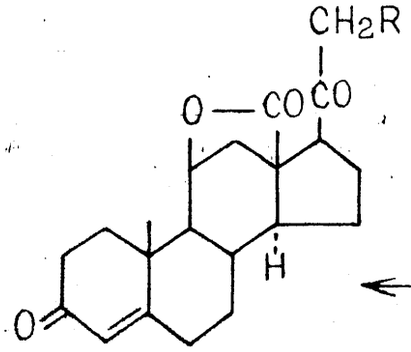
(XXX)



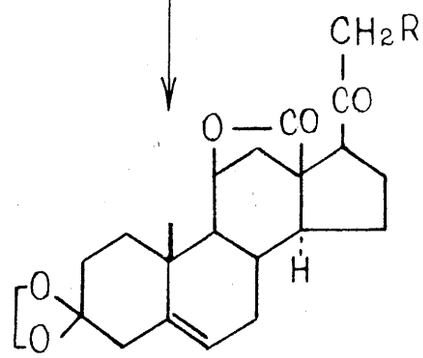
(XXXI)



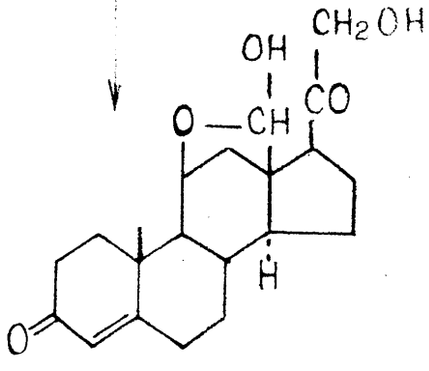
(XXXVII)



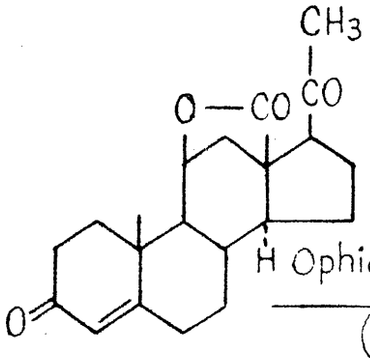
(XXXV)- R=H
(XXXVI)-R=OH



(XXXII)– R=H
(XXXIII)– R=CO-COOCH$_3$
(XXXIV)– R=OCOCH$_3$

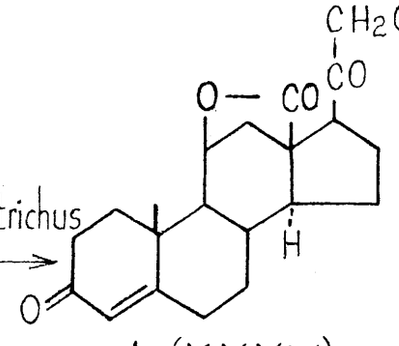


d,l-aldosterone



d,l-(XXXV)

Ophiobolus herpotrichus (Fr.) sacc.

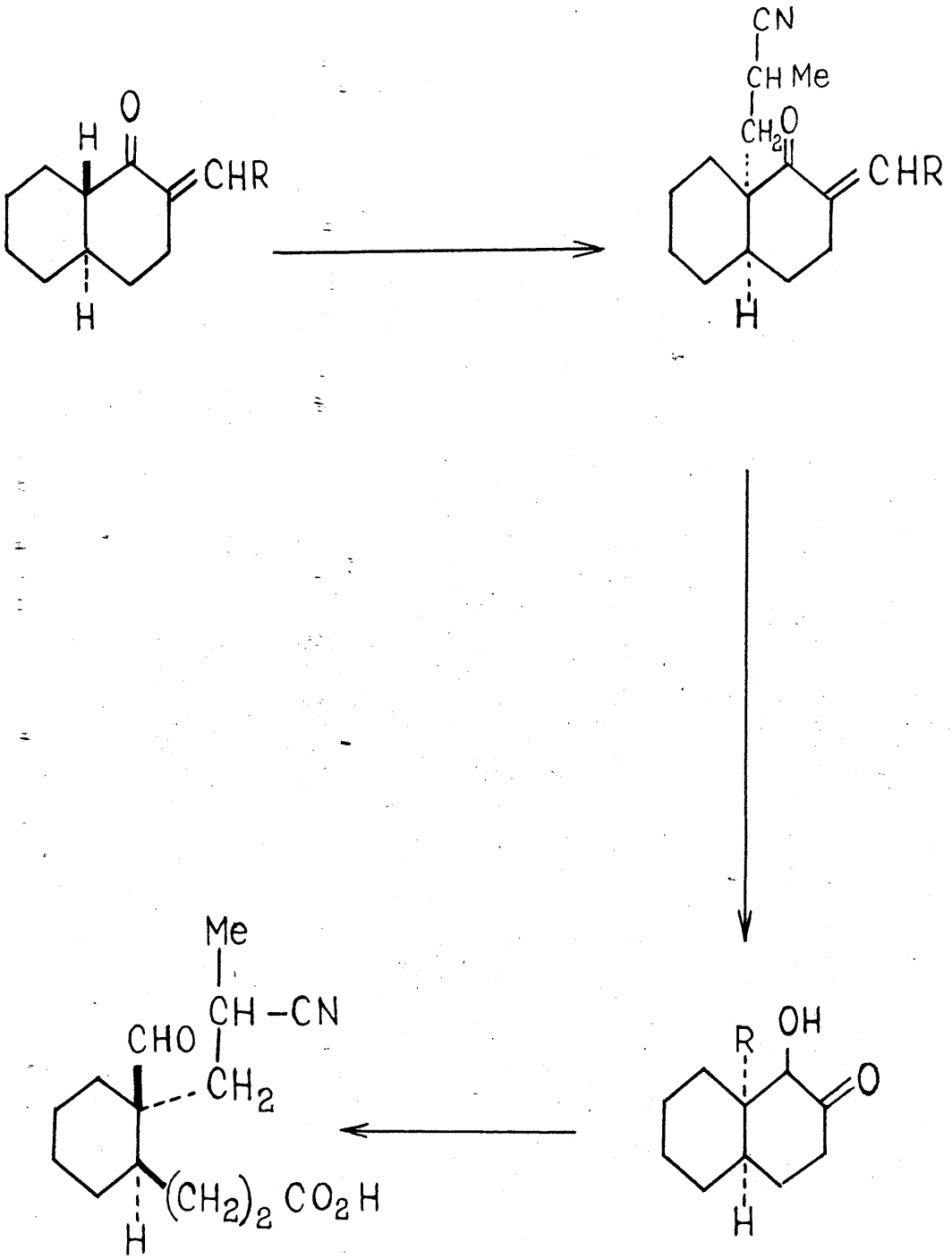


l-(XXXV) +
d-(XXXVI)

afforded the lactone (XXII) on periodic acid treatment. The proof of structure of this lactone showed unambiguously that the hydroxylation had occurred at the inert C_{18} methyl group.

In a second approach to the problem the organic chemist has again solved a major problem by total synthesis.

Using the Sarett ketone[13] as starting material, Wettstein[14] has achieved a remarkable total synthesis of d-aldosterone in the following way; - Saretts' ketone (XXIII) on reaction with diethyl carbonate was converted into the carbethoxy derivative (XXIV), which on treatment with methallyl iodide afforded the 2α-methallyl compound (XXV). This β-keto-ester on successive treatment with sodium borohydride, ethanolic potassium hydroxide and heating in benzene solution gave the hydroxylactone (XXVI). A suitable group for the formation of the 5-membered ring D was then added (after conversion of the free hydroxyl group into ketone) by reaction with ethoxy-ethinyl-magnesium bromide, leading to (XXVII), which on successive osmium tetroxide oxidation and hydrogenation (palladium carbonate-pyridine) yielded the vinylic


O
H
CHR
H
CN
CH Me
CH2
O
CHR
H
Me
CH–CN
CHO
CH2
(CH2)2 CO2H
H
R
OH
O
H

compound (XXVIII). The latter was converted into the aldehyde (XXX) [via the αβ-unsaturated aldehyde (XXIX)] which was cyclised to the pregnane derivative (XXXI), and this hydrogenated to (XXXII). The next step was the hydroxylation at C_{21}, easily obtained by condensation with oxalic acid dimethyl ester to give (XXXIII), and its conversion into the acetate (XXXIV), followed by hydrolysis to the 21-hydroxy-3:20-diketone (XXXVI). Then, protection of the keto group (condensation with ethylene glycol) was followed by lithium aluminium hydride reduction of the lactone to yield the cyclo-hemiacetal (XXXVII) readily converted into d,l-aldosterone on treatment with hydrochloric acid. Resolution of the d,l-lactone (XXXV) [easily obtained from (XXXII)] was achieved by selective microbiological hydroxylation [Ophiobolus herpotrichus (fr.) Sacc.] of the d-isomer to the α-ketol (XXXVI) which was then converted into d-aldosterone, identical in every respect with the natural product.

Johnson's method for introduction of the angular aldehyde into 1-decalone systems has recently been disclosed[15]. The sequence of his process is shown

on page 20 .

The obvious extension to 18-nor-17-keto-steroids is receiving further study.

It has been suggested that the bioassay methods used to measure the biological effects of adrenal cortical hormones can be divided in two groups[16,17]. In one, cortisone and hydrocortisone are the most potent steroids, and deoxycorticosterone has until recently been found to be the most potent member of the other. In the former group it is generally considered that effects on carbohydrate and protein metabolism are predominant whereas in the latter group the action on mineral metabolism is more important. On this basis all the adrenal hormones have some action on both mineral and carbohydrate metabolism. Bioassay methods, in which the effects of steroids on the radioactive or inert sodium/potassium urinary ratio of adrenalectomized rats is measured, have been used for the control of the isolation work because of the potent effect of aldosterone on mineral metabolism. The availability of crystalline material has made possible the assay of aldosterone in the "carbohydrate" group of tests, in which it has been shown to have appreciable activity[18,19].

Table IV shows the activity of aldosterone in certain bioassay methods. It can be seen from these results that although aldosterone is less active than cortisone or hydrocortisone in the "carbohydrate" group of tests, it must now be regarded as the most potent steroid so far tested in the "mineral" group.

Table IV[19]

Potency of crystalline aldosterone compared with deoxycorticosterone in the "mineral" group of assays.

Bioassay method	Potency (DOC or DOCA = 1)
$^{24}Na/^{42}K$ urinary ratio in adrenalectomized rats	120± 10
Na/K urinary ratio in adrenalectomized rats	100
Kagawa test-effect on sodium retention of adrenalect. rats	25
Kagawa test -effect on potassium excretion of adrenalect. rats	5
Maintenance of adrenalectomized dogs	25-30
Maintenance of sodium and potassium balances in Adison's disease	30

Potency of crystalline aldosterone compared with cortisone in the "carbohydrate" group of assays.

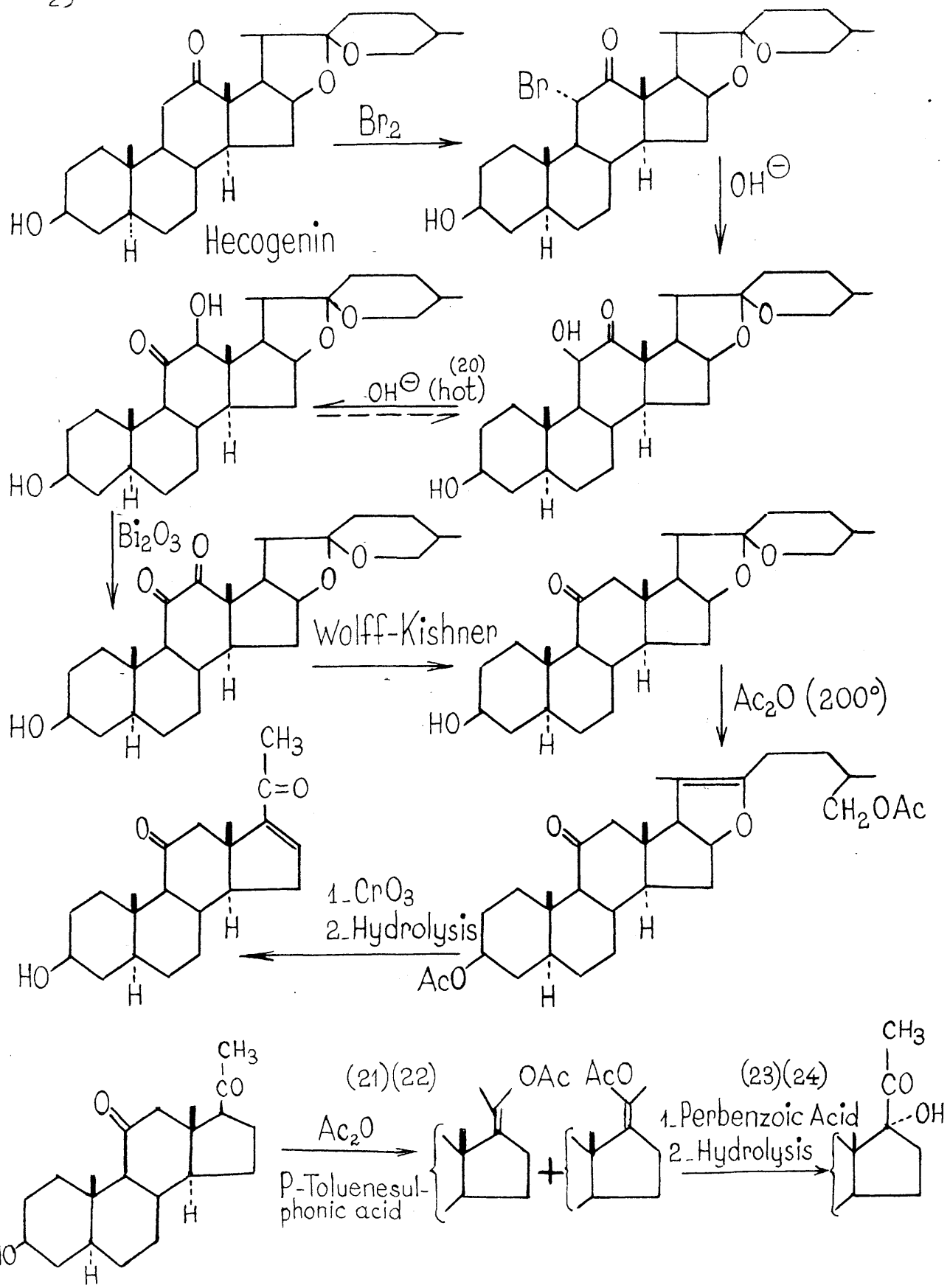
Bioassay method	Potency (cortisone or cortisone acetate = 1)
Eosinophil depletion test	0.25
Cold survival test	1
Liver glycogen deposition test	0.33
Water load test	< 1

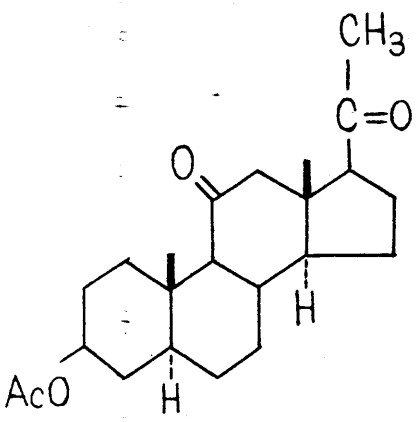
On the other hand the life supporting tolerance of aldosterone is 25 times that of DOCA.

The basic dosage in clinical experiments was 20-30 times smaller than that of acetyl-cortexone on two addisonian patients.* Aldosterone has a marked effect on carbohydrate exchange causes no abnormal water retention and does not raise the arterial blood pressure over the physiological level. Moreover, it is the only known substance having these properties, which also produces a marked decrease in the pigmentation associated with the disease.

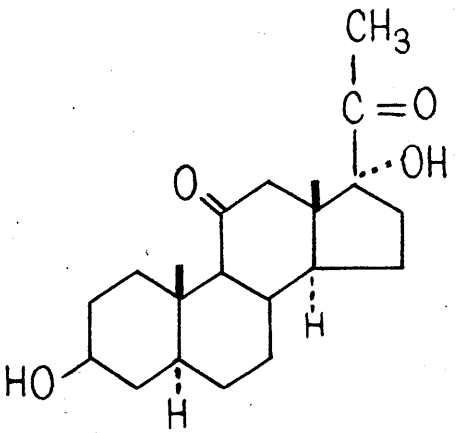
Aldosterone has a cortisone-like activity (see Table IV) of about 50%.

* Tubercular lesions of the suprarenal cortex leading to hypocortical adrenalism with a low Basal Metabolic Rate, fatal in 6 months without large dosage of DOCA and giving a mahogany pigmentation.


Hecogenin
Br2
OH⊖
OH⊖ (hot)
(20)
Bi2O3
Wolff-Kishner
Ac2O (200°)
1-CrO3
2-Hydrolysis
(21)(22)
Ac2O
P-Toluenesulphonic acid
(23)(24)
1-Perbenzoic Acid
2-Hydrolysis



(XXXVIII)



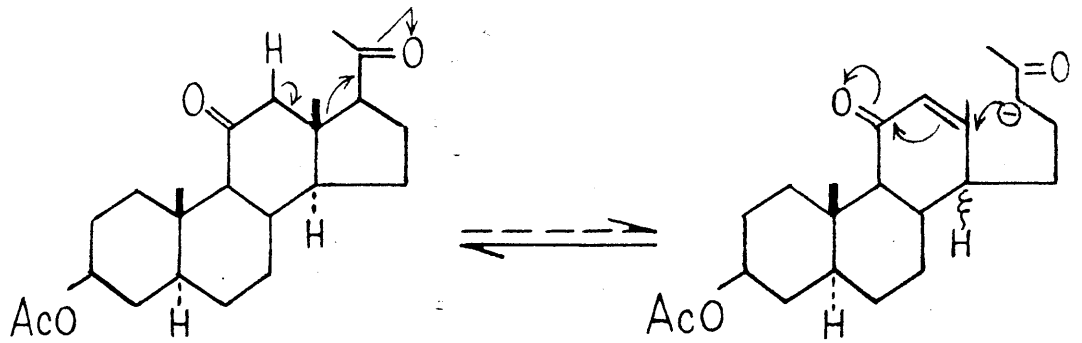
(XXXIX)

A partial synthesis of aldosterone from readily available steroid intermediates would be the preferred practical method for the production of the hormone in quantity as required in the medical field. Our efforts have been devoted to the study of such a partial synthesis from the readily accessible sapogenin hecogenin which is easily transformed into (XXXVIII) or (XXXIX) by standard methods as shown on page 25.

The essential feature of this problem and indeed the goal of our experiments was the introduction of an oxygen function, or a potential oxygen function, at the C_{18} methyl group, while preserving the required stereochemistry, that is, C/D-trans diequatorial ring junction and C_{17} β-side chain. This former requirement can only be achieved by some form of rupture of the ring system in order to activate the inert angular methyl group towards attack by suitable reagents. Having achieved this we must devise a stereospecific ring closure sequence.

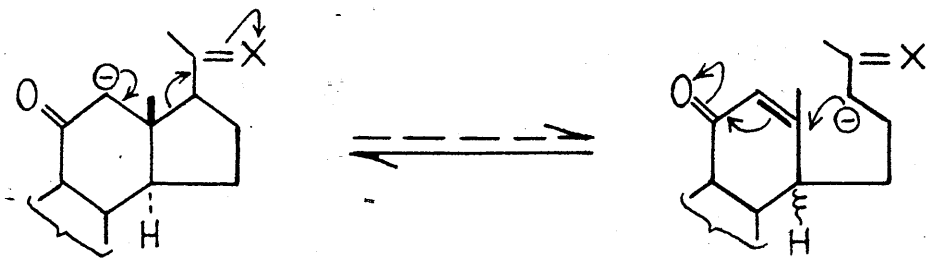
Our work can be divided into two distinct phases which we shall call: a) the 1:5-diketone approach and b) the β-elimination approach.

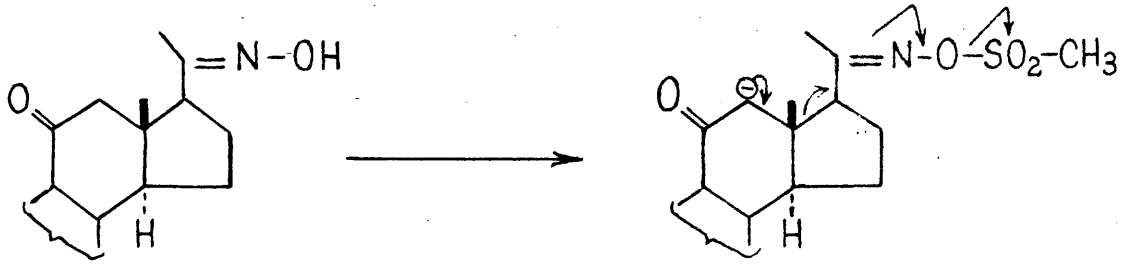
a)



(XXXVIII)

b)





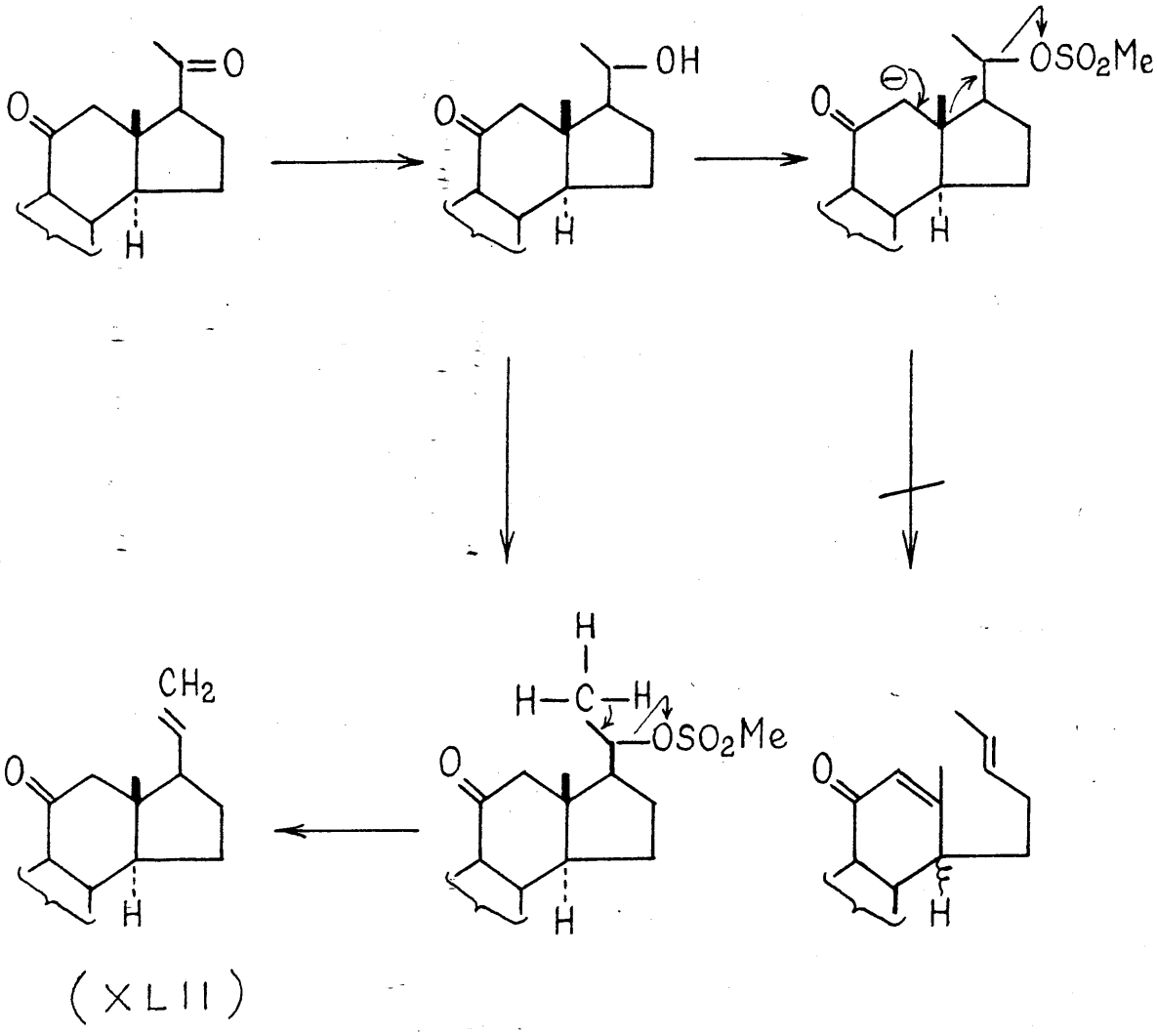
(XL)

(XLI)

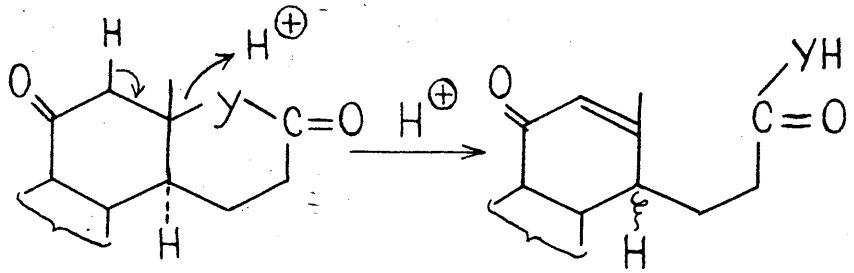
As will become apparent in the sequel, the former method failed completely, whilst the latter, although fulfilling the first part of our requirements showed that the second part, namely the preservation of the C/D-*trans* ring junction was fraught with stereochemical difficulties which, on gradual elucidation, allowed us to predict the course of the ring closure and to devise a synthesis which would lead unambiguously, albeit laboriously, to the desired result.

In the first of these approaches, we chose to open ring D rather than ring C as it was felt that more tractable products would be encountered in this system.

When the 11:20-dioxo-allopregnane derivative (XXXVIII) was treated with potassium *t*-butoxide no evidence of a reverse Michael reaction was forthcoming (examination of the ultraviolet spectrum; no maximum at 235-240 mμ). It was hoped that by introduction of an electron attracting moiety X at carbon atom C_{20} we might facilitate this reverse Michael reaction as shown in sequence (b) (page 28). To this end 3β-acetoxy-11:20-dioxoallopregnane-20-oxime (XL) was transformed to the oxime mesylate (XLI). This on treatment with potassium *t*-butoxide showed no trace

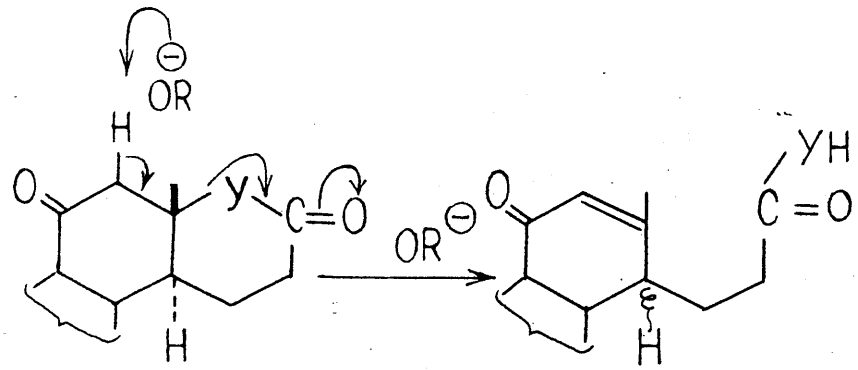


(XLII)



(y=-NH; -O-; etc.)

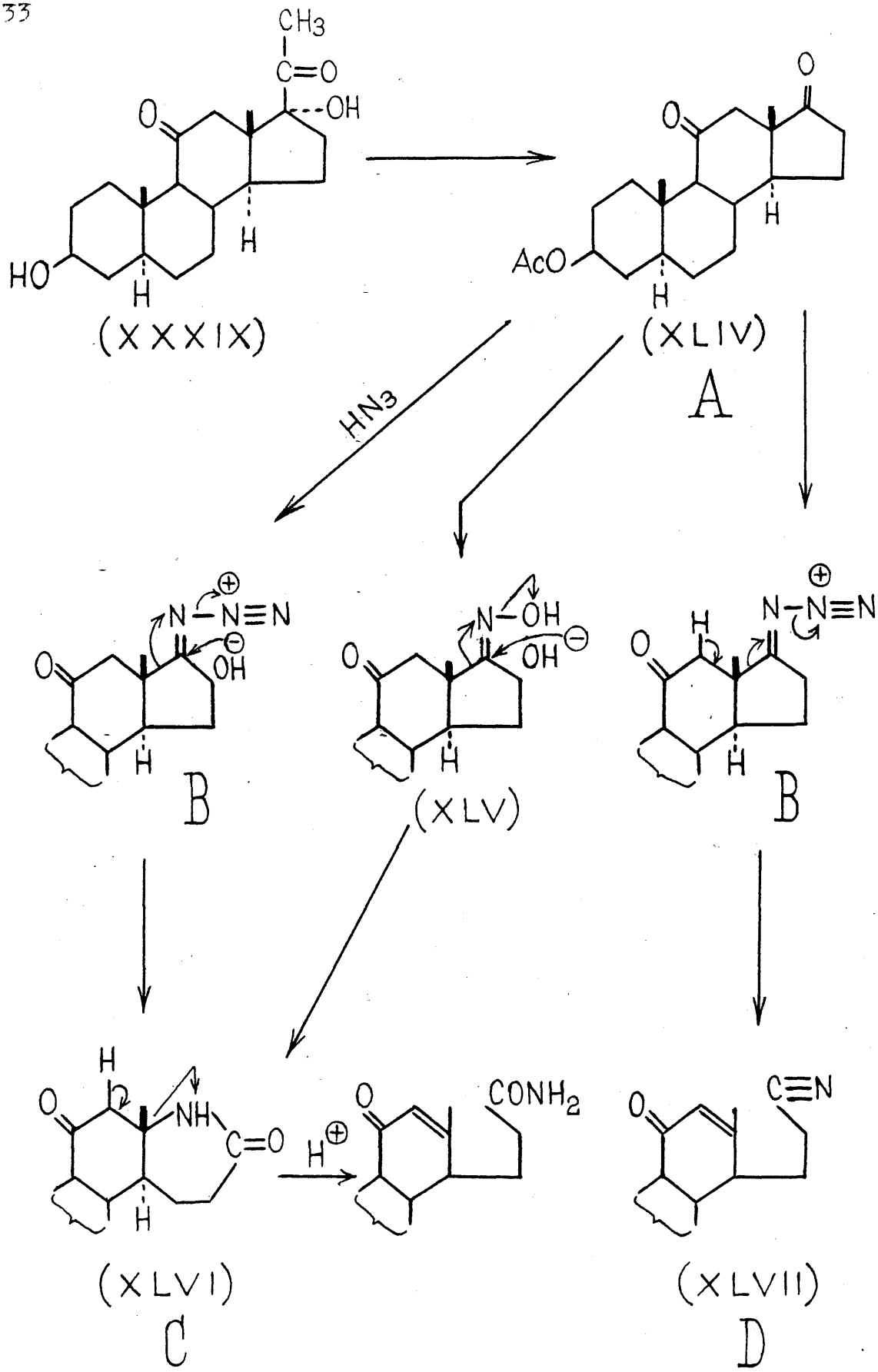
or:



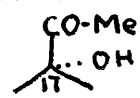
of αβ-unsaturated ketonic function. As a critical test of this ring opening procedure 3β-acetoxy-11:20-dioxoallopregnane was treated with sodium borohydride under conditions which lead to preferential reduction of the 20-carbonyl function[25]. Conversion to the methanesulphonate was followed by treatment with potassium t-butoxide. The sole isolable product (XLII) from the reaction mixture (which showed no selective absorption in the ultra-violet at 220-280 mμ) showed infra-red absorption at 3050, 1640, 992 and 910 cm^{-1} indicating a $>C=CH_2$ moiety, formed by E_2 elimination of sulphonate anion with the α-hydrogen atom on C_{21} (See page 30). The steric requirements for this E_2 elimination reaction must therefore be much less exacting than for the 1:5-elimination and it was reluctantly concluded that the fission of this 1:5-diketone system was foredoomed to failure.*

It was now felt that by introduction of a suitable heteroatom Y into ring D, ring opening could be achieved by a β-elimination (with respect to the 11-oxo group) by acidic or basic reagents (see page 31). Accordingly, 3β-acetoxy-11:17-dioxoandrostane (XLIV)

* Several other attempts for effecting 1:5-elimination were also unsuccessful (see Experimental).


CH3
C=O
OH
O
HO
H
H
(XXXIX)
O
O
H
AcO
H
(XLIV)
A
HN3
B
(XLV)
B
C
(XLVI)
CONH2
H⊕
C≡N
(XLVII)
D

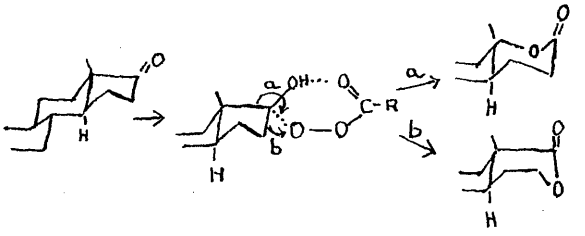
was prepared from 3β:17α-dihydroxy-11:20-dioxoallopregnane (XXXIX) by acetylation and chromic acid-acetic acid oxidation* in 55% yield. The 17-oxime (XLV) was formed in quantitative yield and rearranged (96% yield) to the corresponding 3β-acetoxy-11:17-dioxo-17α-aza-D-homoandrostane (XLVI). This lactam could also be prepared directly as the minor product of the Schmidt reaction on the 11:17-diketone (XLIV). The major product of this reaction was the Δ^{12}-seco-nitrile (XLVII) (λmax. 234 mμ.). A plausible mechanism for this transformation is outlined (A → B → C + D)[28]. That the lactam (XLVI) was not an intermediate in the Schmidt reaction was shown by stirring a solution of (XLVI) in chloroform with concentrated sulphuric acid (Schmidt conditions), starting material being obtained in quantitative yield. When the lactam (XLVI) was treated with a solution of concentrated hydrochloric acid (10%) in glacial acetic acid (100°), an absorption band appeared in the

* In order to obtain a carbonyl function at C_{17} one should (in theory) treat the α-ketol grouping with HIO_4 or lead tetraacetate. However, for reasons which are not obviously apparent, the system 

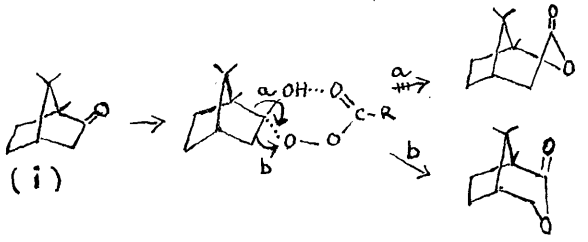
does not react with HIO_4 or lead tetra-acetate and is recovered unchanged[26].

ultra-violet at 234 mμ indicative of the required β-elimination. However, only a resinous product was obtained on working up the total reaction mixture[28]. It was now considered more advantageous to make use of the Baeyer-Villiger[29,30] lactone synthesis since the electronic factors were in favour of the formation of the 17a- (XLVIII) rather than 17-lactone (XLIX)* in

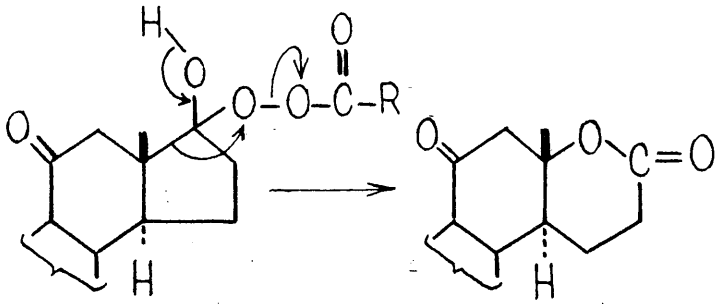
* The conformational factor of a "chair" transition state must also be considered in this connection[31]. Migration of the highly substituted C_{13} to the electron deficient 17a-substituent proceeds through a transition state in which the expanded ring D possesses a chair form, whereas migration of the less substituted C_{16} would pass through a transition state in which ring D would have the "boat" form.



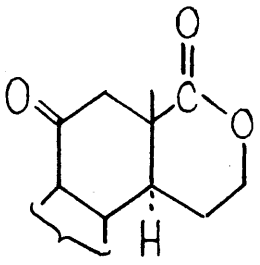
This situation is however reversed in the case of the camphor (i) where the C_3, and not the tertiary carbon C_1, moves thus involving a lower energy transition state of the chair form.



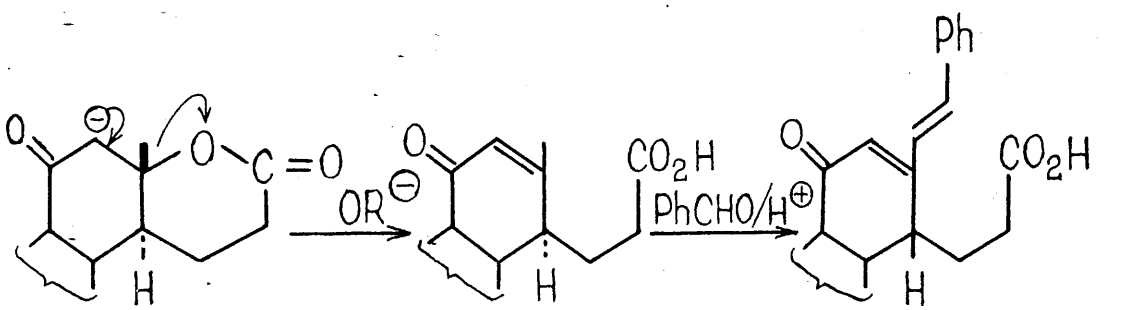
(i)



(XLVIII)



(XLIX)



(L)

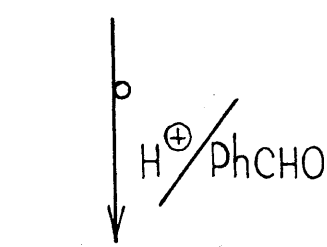
λmax. 239 mμ

$[\alpha]_D$ −4.0°

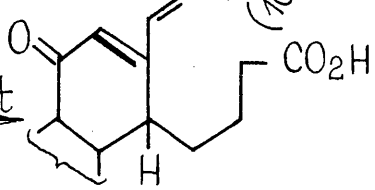
(LI)

λmax. 325 mμ

$[\alpha]_D$ +320°



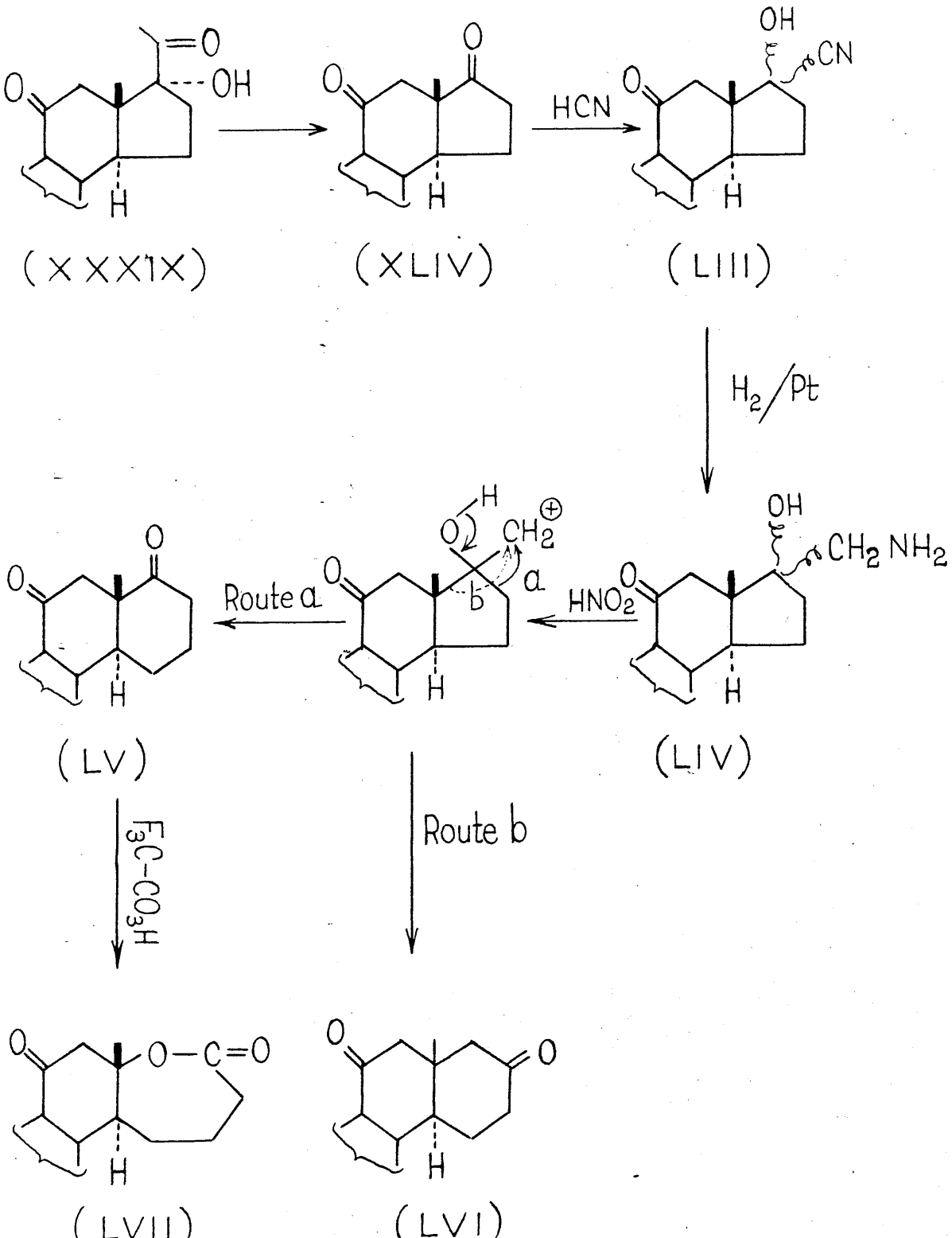
(LI)



(LII)

which the more highly substituted group moves. The lactone readily underwent base catalysed β-elimination on treatment with dilute solution of potassium hydroxide in ethanol at room-temperature, the derived 13(17)-seco-acid (L) (λmax. 239 mμ; ϵ 13,600) being obtained in excellent yield. A potential oxygen function was now introduced by forming the benzylidene derivative, most effectively by using saturated alcoholic hydrogen chloride solution. The resultant benzylidene acid (LI) had light absorption λmax. 325 mμ, ϵ 34,200 (cf. cinnamalacetone[32] λ max. 319 mμ, ϵ 36,300; piperitone benzal[33] λ max. 324 mμ, ϵ 31,000). The formation of the benzylidene derivative was most easily followed spectrophotometrically. For preparative purposes the lactone was treated directly with benzaldehyde - hydrochloric acid in ethanol solution and the acid (LI) isolated in 40% yield.*

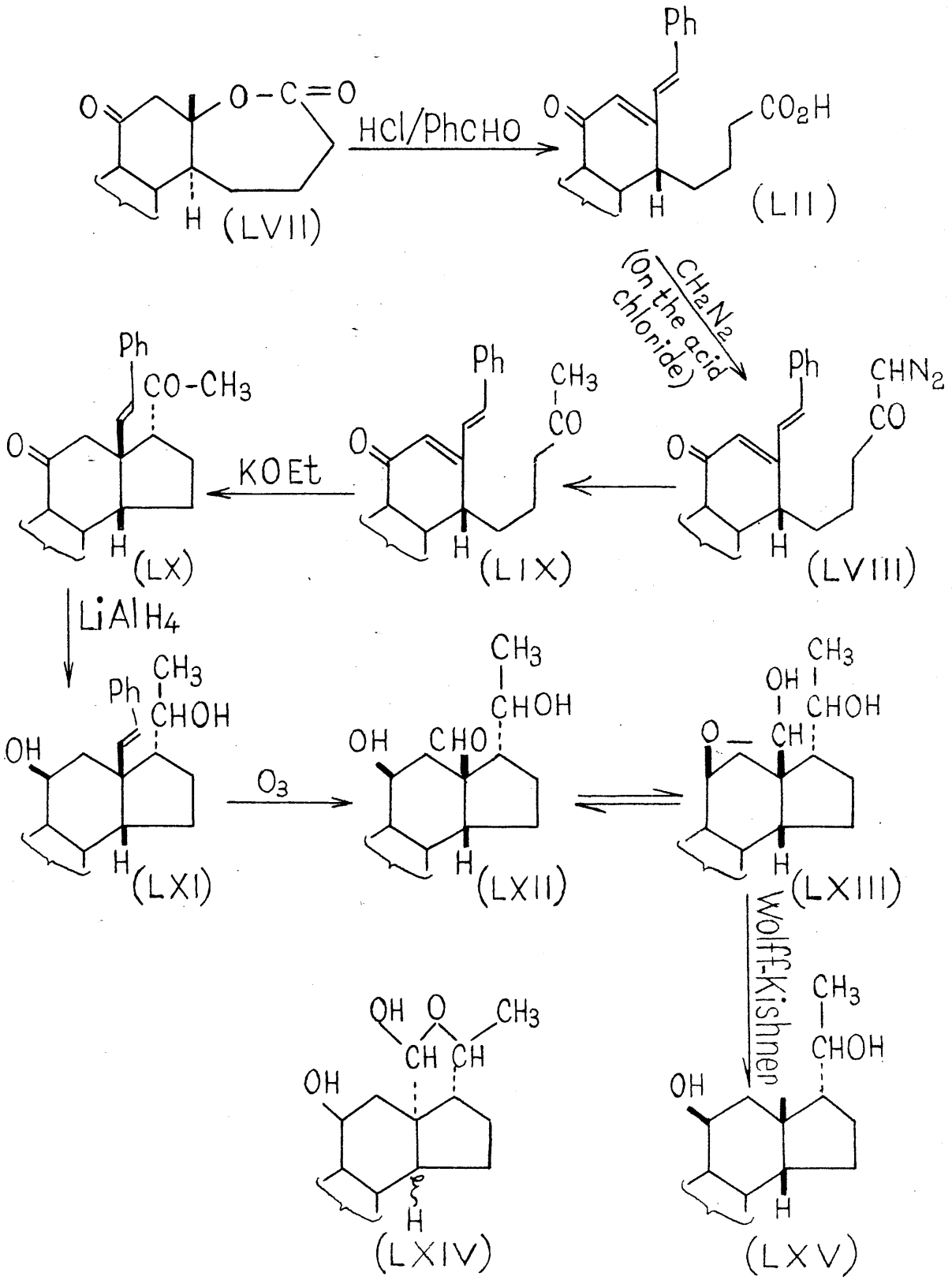
* For reasons which will be revealed in the sequel, not apparent at this stage of the description, we shall now assign the stereochemistry at C_{14} (as shown) to avoid confusion in the exposition of the theme.


(XXXIX)
(XLIV)
HCN
(LIII)
H2/Pt
(LIV)
HNO2
Route a
Route b
(LV)
F3C-CO3H
(LVII)
(LVI)

Conversion to the homologue (LII) was accomplished *via* an Arndt-Eistert synthesis, the Wolff rearrangement being effected in methanolic solution, using the silver benzoate/triethylamine catalyst[34]. Although the theoretical volume of nitrogen was usually collected during these rearrangements, the yields of pure acid (LII) obtained on ester hydrolysis (using either dilute sodium ethoxide or sodium bicarbonate solution) seldom exceeded 10-15%. This finding led us to devise a new route to the acid.

3β-Acetoxy-11:17-dioxoandrostane (XLIV) was now converted to a mixture of the epimeric cyanhydrins (LIII)[35,36]. These were not separated but reduced (hydrogen/platinum) directly to the corresponding primary amine epimers (LIV), diazotised and rearranged to yield 3β-acetoxy-11:17a-dioxo-D-homoandrostane (LV) [37% overall yield from starting 17α-hydroxy compound (XXXIX)].* The D-homoketone (LV) was recovered

* The presence of the isomeric 17-ketone (LVI) formed by route *b* is not excluded although a careful examination of the last chromatographic fractions of (LV) revealed only small quantities of oily side products. [37] On the A/B *cis* fused series Wendler, Slates and Taub[37] have recently shown that regardless of the configurations of the starting cyanhydrin the ratio of 17a/17-ketone (*a*/*b*) is 6/1.


HCl/PhCHO
(LVII)
(LII)
CH_2N_2
(On the acid chloride)
KOEt
(LX)
(LIX)
(LVIII)
$LiAlH_4$
O_3
(LXI)
(LXII)
(LXIII)
Wolff-Kishner
(LXIV)
(LXV)

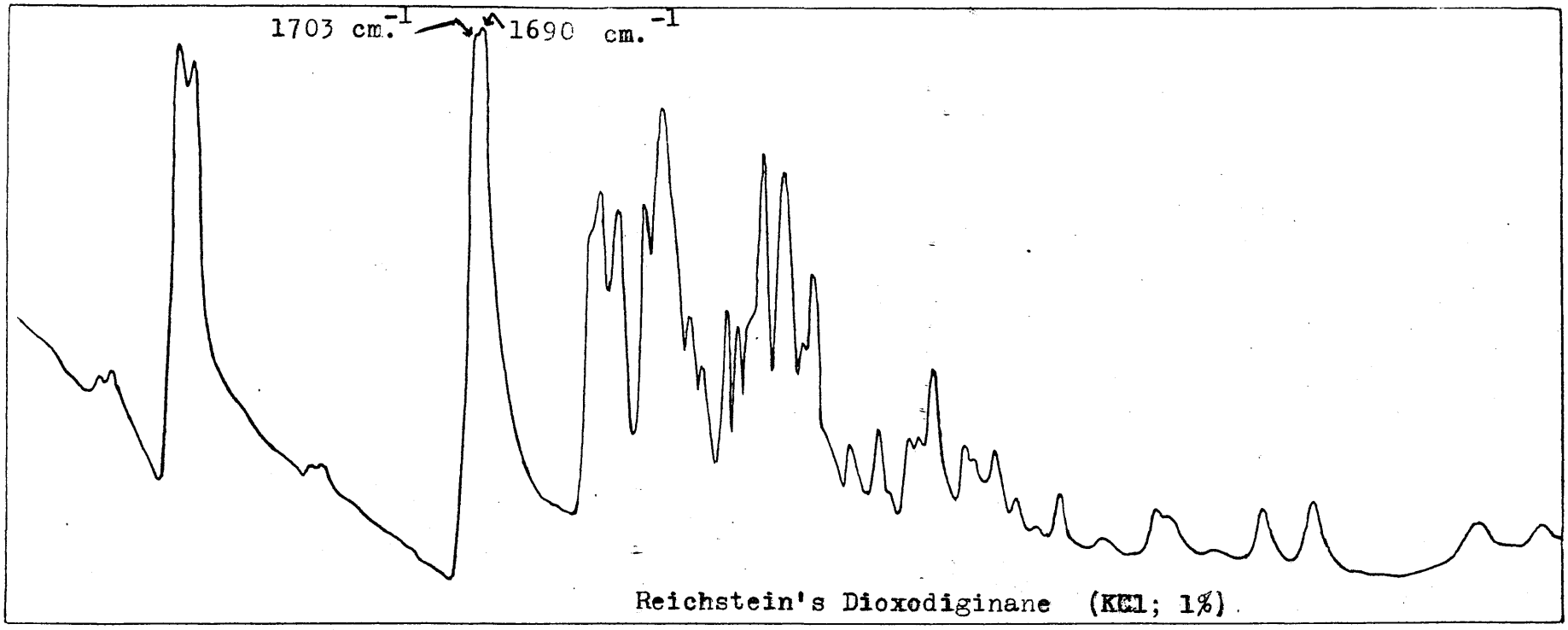
unchanged (after several days at 20°) from solutions of peracetic and perbenzoic acids. However, treatment with pertrifluoracetic acid [38,39] under rigorously controlled conditions afforded the desired seven membered ring D lactone (LVII) in 50-55% yield. Treatment with benzaldehyde-saturated hydrogen chloride furnished the benzylidene homoacid (LII) after repeated hydrolysis with 5% sodium bicarbonate in methanol solution (see Experimental) in 50% yield. This was now transformed to the methyl ketone (LIX) via the diazoketone[40,41,42,43] (LVIII). This ketone (obtained as an oil) was treated directly with potassium ethoxide (0.2 M). Michael addition was complete in 16 hours at room temperature (polarimetric and spectrophotometric control) and the derived cyclised ketone (LX) was isolated as a highly crystalline compound m.p. 193-4° $[\alpha]_D$ -26°. In the infra-red this compound showed bands at 1700 cm^{-1} (11- and 20-ketones) and 1630, 1600, 1585, 1494, 994, 747 and 694 cm^{-1} (trans-benzylidene)[44]. Reduction with lithium aluminium hydride gave (presumably)[45] the 3β:11β:20β-triol of (iso?)allopregnane (LXI). From controlled ozonolysis followed by reductive work-up

(zinc-acetic acid) were isolated benzaldehyde and the 18-aldehyde-triol (LXII) in equilibrium with the (11 → 18) hemiacetal-3:20-diol (LXIII). That the equilibrium favoured the hemiacetal form (LXIII) was demonstrated by the absence of carbonyl (-CHO) absorption in the infra-red spectrum. This leads to partial formulae (LXIII) and (LXIV) for the triol. Wolff-Kishner reduction gave (in 70% yield) an (iso)-allopregnane-3:11:20-triol (LXV) m.p. 202-3° $[\alpha]_D$ + 59° not identical with 3β:11β:20β-allopregnane triol m.p. 203-5° $[\alpha]_D$ + 60° (ethanol). From a consideration of optical rotation data (see Table V) it was concluded that the Michael ring closure had led to the 14-iso-17-iso series, a prediction which

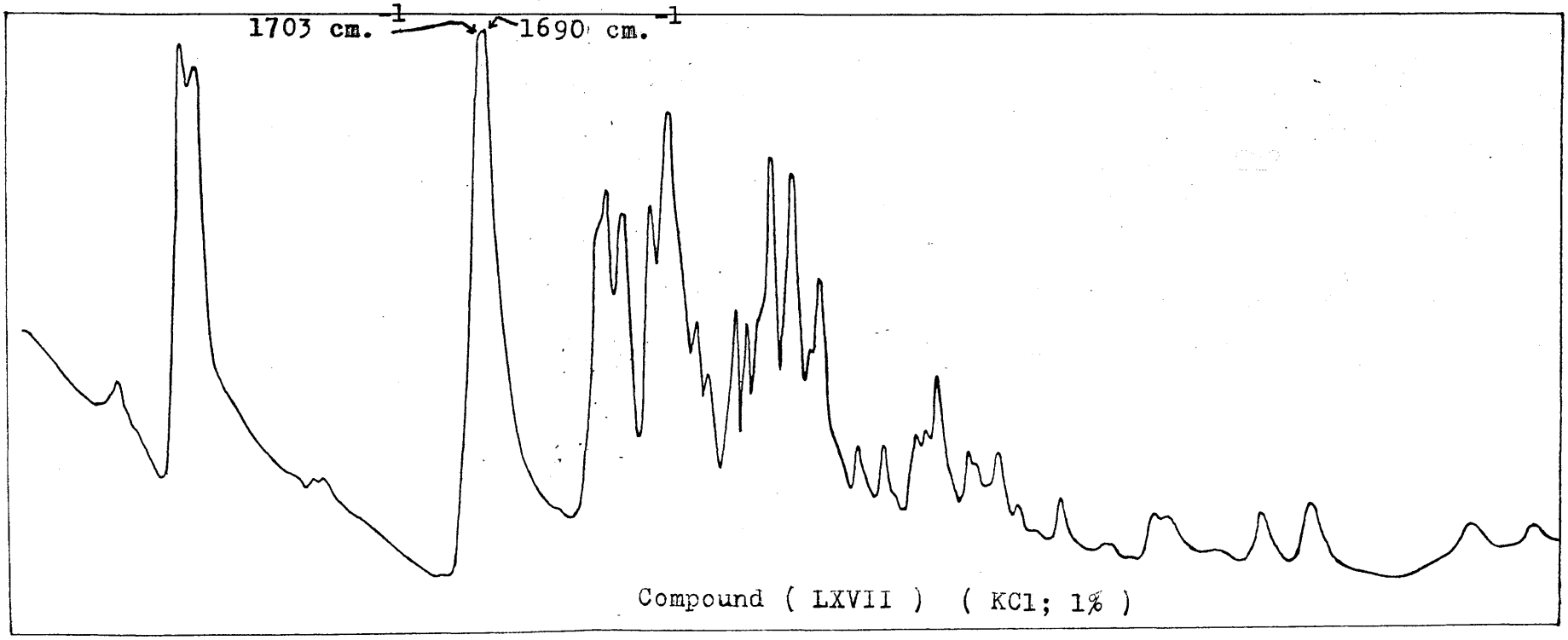
Table VI

Rotations of some stereoisomers in the allopregnane series.

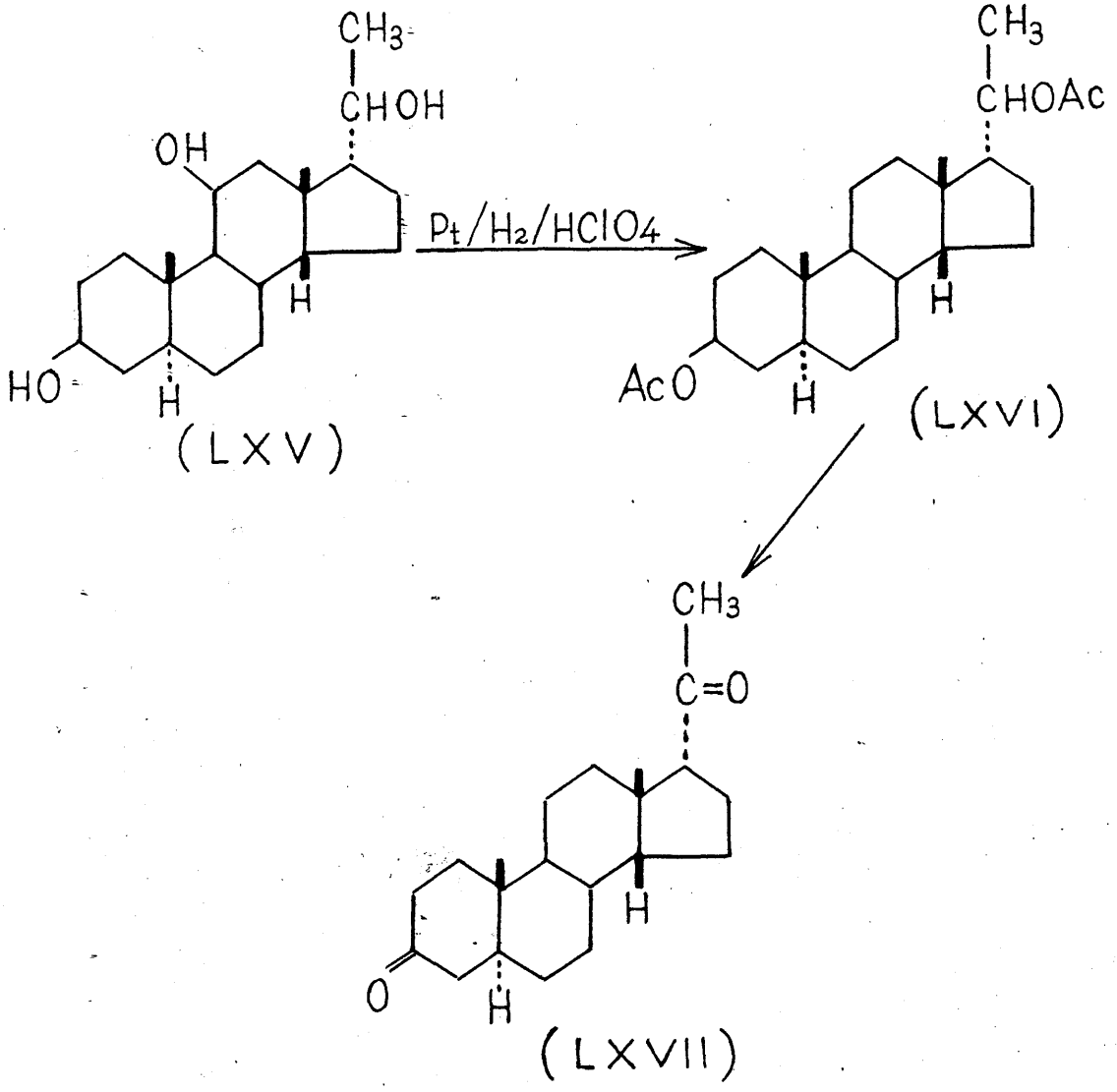
Compound	Series ($[\alpha]_D$°)		
	14n,17iso	14n,17n	14iso,17iso
Allopregnanolone	-78	+91	
Allopregnanolone Acetate	-75	+77	
Allopregnane-3:20-dione	-50	+121	+40
Allopregnane-3β:20β-diol diacetate		+22	
Allopregnane-3β:20α-diol diacetate		-0.3	



Reichstein's Dioxodiginane (KCl; 1%)

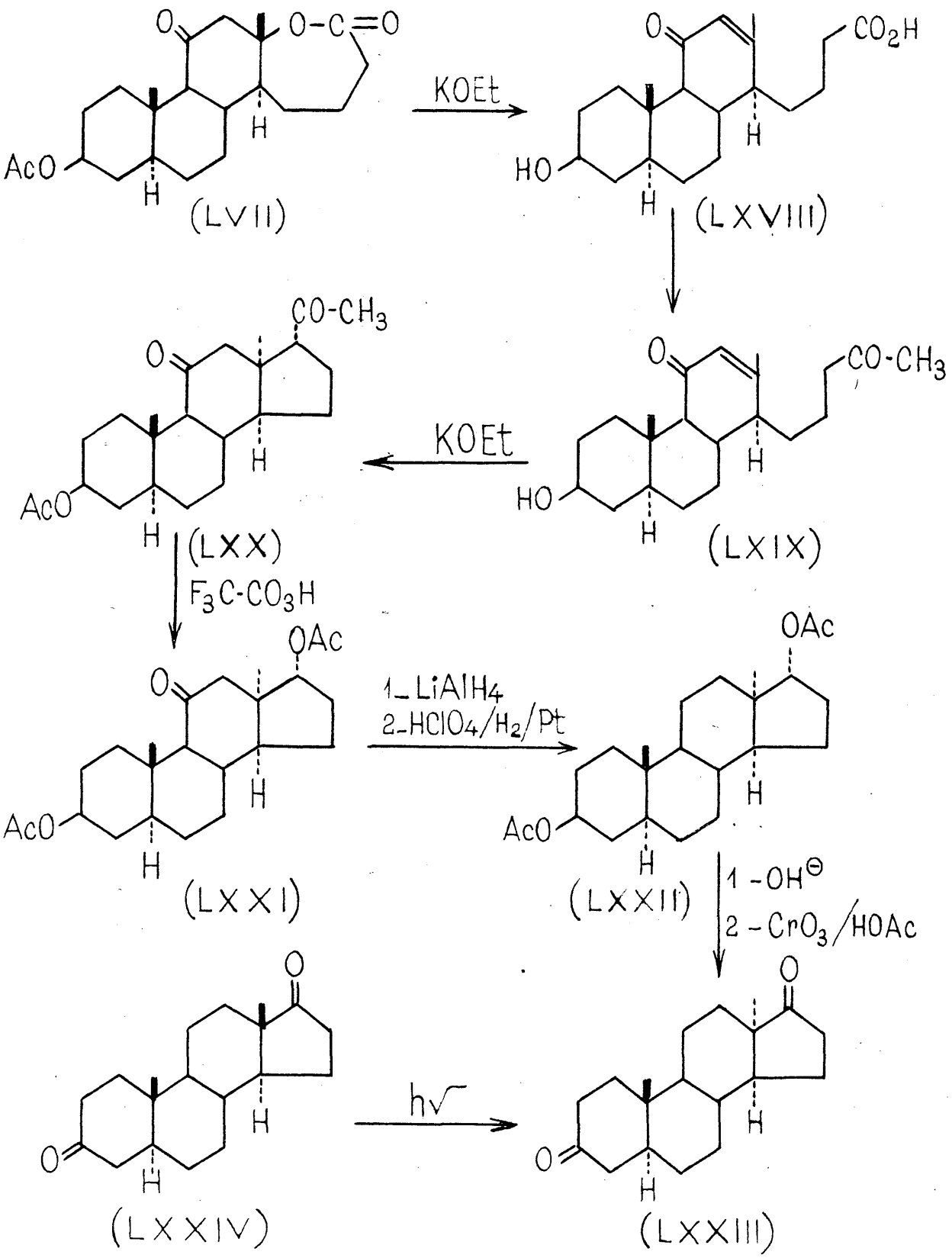


Compound (LXVII) (KCl; 1%)


CH3
CHOH
OH
HO
H
H
(LXV)
Pt/H2/HClO4
CH3
CHOAc
AcO
H
H
(LXVI)
CH3
C=O
O
H
H
(LXVII)

was confirmed by the following experiments. When the triol (LXV) was hydrogenated in solution in acetic acid containing perchloric acid in the presence of platinum facile trans-diaxial elimination of water (9: 11) was followed by hydrogenation of the 9:11 double bond. The resultant 3:20-diacetate (LXVI) was saponified and oxidised (chromic acid) to 3:20-dioxo-14-iso-17-iso-allopregnane (LXVII) identical in every respect with Reichstein's dioxodiginane[46] [m.p. mixed m.p., $[\alpha]_D$ + 39° and infra-red spectra (KCl disc)]. The infra-red spectra taken for the identification of those compounds are shown on page 43 .

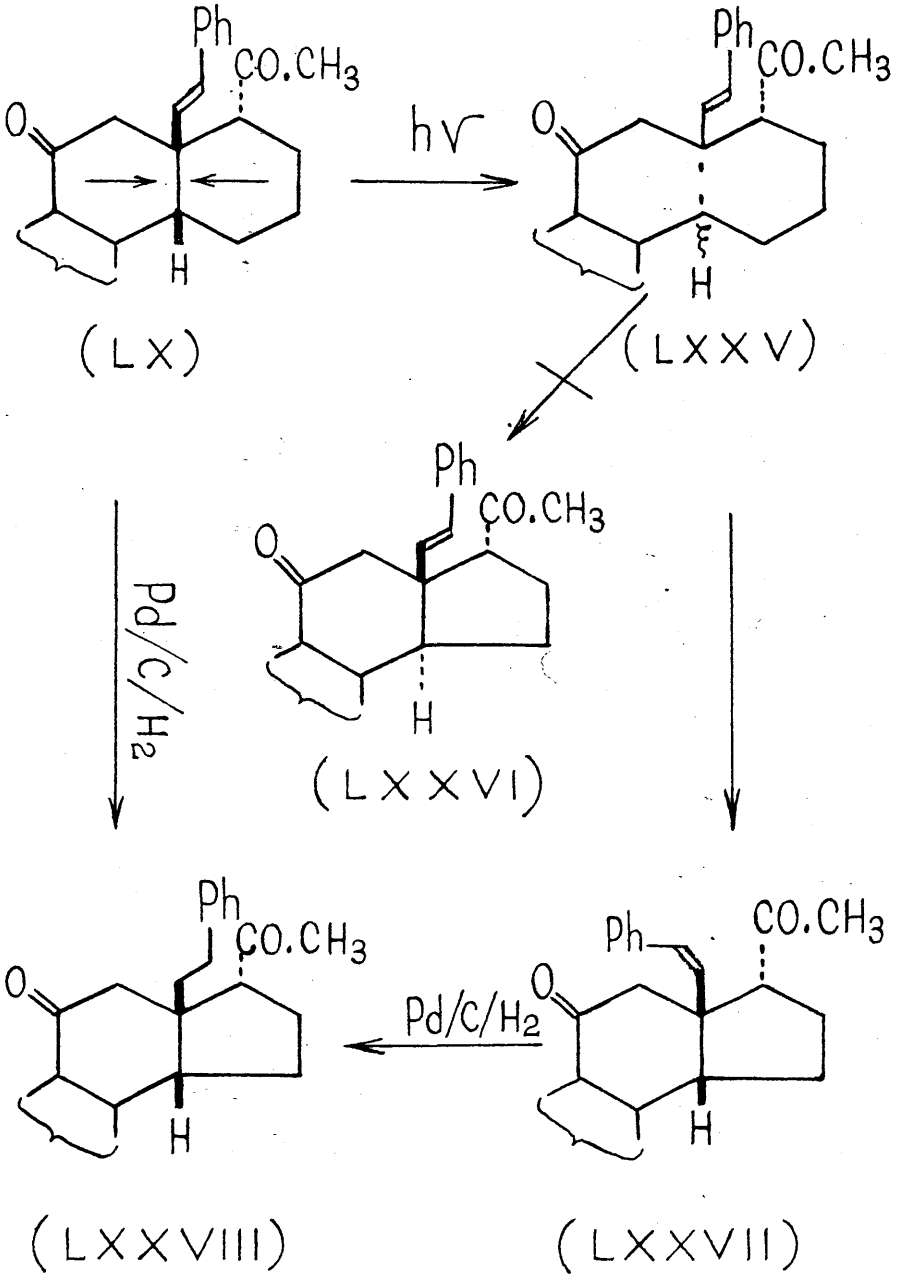
It now became important to determine if ring closure were directed by the configuration of the hydrogen atom at C_{14}. During the prolonged acid treatment necessary for 18-benzylidene formation this may have become inverted from its normal (14α) configuration. The other possibility was that equilibration may have taken place during the cyclisation. A choice between these alternatives was made as follows. Treatment of the 7-membered ring-D lactone (LVII) with potassium ethoxide (1 hour reflux under nitrogen) afforded the (oily) secoacid


KOEt
(LVII)
(LXVIII)
(LXIX)
(LXX)
KOEt
F3C-CO3H
1-LiAlH4
2-HClO4/H2/Pt
(LXXI)
(LXXII)
1-OH⊖
2-CrO3/HOAc
hν
(LXXIV)
(LXXIII)

(LXVIII) (λmax. 237 mμ). Direct conversion to the methyl ketone (LXIX) followed by ring closure (exactly as in the cognate preparation described above) afforded an isomer (LXX) of 3β-acetoxy-11:20-dioxoallopregnane, $[\alpha]_D$ -182°. From a consideration of rotation data combined with our first rationalisation of ring closure mechanism we now concluded that ring formation was indeed governed by the C_{14} configuration and that we had now entered the 13-iso-14-n-17-iso series. Demonstration of the truth of this assumption was forthcoming by comparison with a compound of the androstane series*. Peracid treatment of (LXX) afforded the 11-oxo-3:17-diacetate (LXXI). Reduction with lithium aluminium hydride was followed by removal of the 11β-hydroxyl group as before (dehydration-hydrogenation),** thus giving (LXXII). Saponification of the total mixture followed by chromic acid treatment afforded as main product 3:17-dioxo-13-iso-14-n-androstane (LXXIII) $[\alpha]_D$ - 74°. Correlation was made

* Correlation with other allopregnane series failed when the 11-oxygen was removed as above.

** This dehydration did not proceed so smoothly as in the 13-n series probably due to the rather different stereochemical environment. Indeed from the subsequent saponification and oxidation the 3:11:17-trione was obtained as a by product.

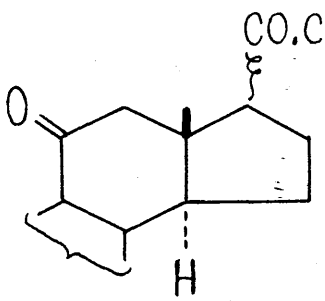

Ph
CO.CH3
O
H
hν
(LX)
(LXXV)
Pd/C/H2
(LXXVI)
Pd/C/H2
(LXXVIII)
(LXXVII)

by irradiating a benzene solution of 3:17-dioxo-androstane (LXXIV) to give the lumi-compound[47] (LXXIII) $[\alpha]_D$-76° identical in every respect with the synthetic 13-*iso*-3:17-diketone. To complete the study of the ring closure the 7-membered ring-D lactone was opened under *acid* conditions. The resultant mixture of acids was transformed *via* the methyl ketones to the cyclised product which, on conversion to the 3:20-diketone by the method described above, proved to be an inseparable mixture ($[\alpha]_D$ -22°) presumably containing the 13-*iso*-14-*n*- and 13-*n*-14-*iso*-stereoisomers.

As a final experiment in this phase of the investigation the 14-*iso*-benzylidene diketone (LX) ($[\alpha]_D$-26°; λmax. 235 mμ, ϵ 18,000) was subjected to ultra-violet irradiation (benzene solution). From this experiment an isomeric diketone was isolated ($[\alpha]_D$ + 10°; λmax. 252 mμ, ϵ 14,000).

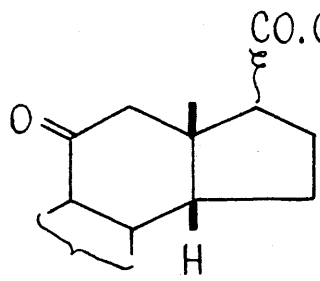
It was hoped that fission of the 13:14 bond (activated by the styrenoid grouping) might lead to a recombination of the fission product (LXXV) to the less stable isomer (LXXVI). However, the ketone with $[\alpha]_D$ + 10° proved to be the (expected) *cis* styrenoid

Trans 13(a), 14(a)



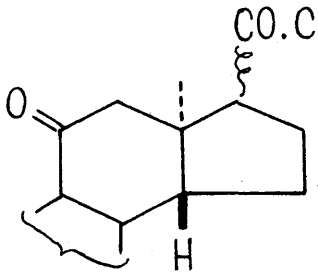
Series I

Cis 13(a), 14(e)



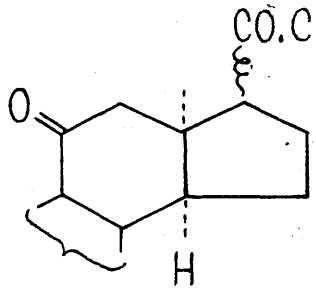
Series II

Trans 13(e), 14(e)



Series III

Cis 13(e), 14(a)



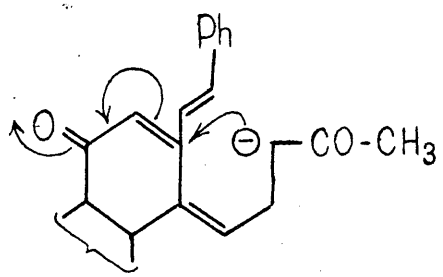
Series IV

isomer (LXXVII). This was shown by quantitative reduction (hydrogen-palladised charcoal) of (LX) and (LXXVII) to the same dihydro compound (LXXVIII). Although this experiment failed in its initial objective, it does however demonstrate the trans nature of the styrenoid moiety.

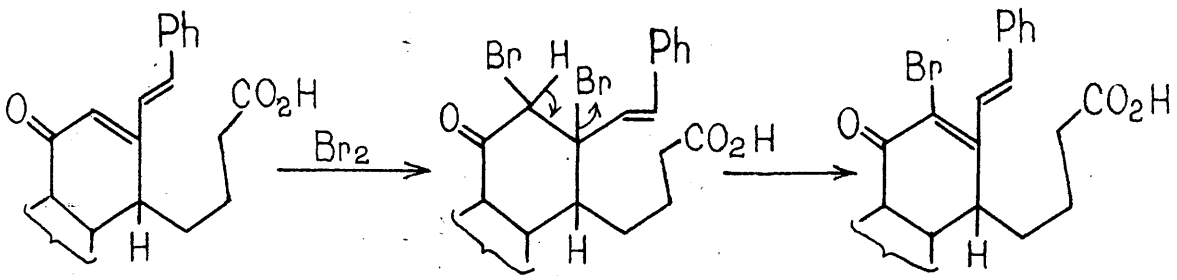
The experiments above confirm that for the system we have chosen a cis C/D ring fusion is more stable than a trans, since in effect we have been able to synthesise two out of the possible three stereochemical series.* Series III is excluded (trans-diaxial fusion of 5-membered ring D from which a boat ring C would be formed) leaving I (normal allopregnane series), II (13-n-14-iso series), and IV (13-iso-14-n series).

Now that series II and IV have come within our net it remains for us only to devise a synthesis that will lead stereospecifically to a trans hydrindane system. An approach which seemed (on consideration of molecular models) very attractive to us is now described. The goal of this partial synthesis is the $\Delta^{12:14}$ diene (LXXIX). This compound can only

* The centre at C_{17} will be disregarded in this discussion since the carbon atom subtended by it (C_{20}) carries a carbonyl group thereby affording the means of equilibration (at C_{17}).

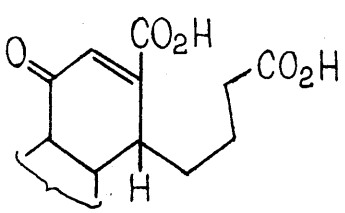


(LXXIX)

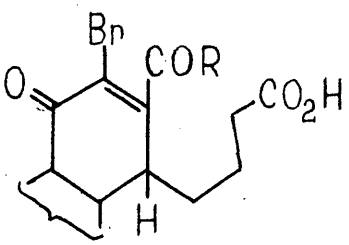


(LII)

(LXX)



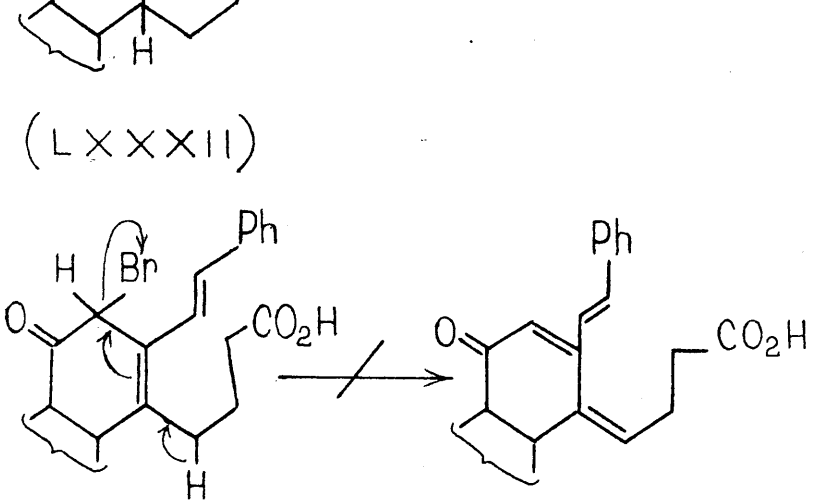
(LXXXII)



(LXXXI)

a - R = H

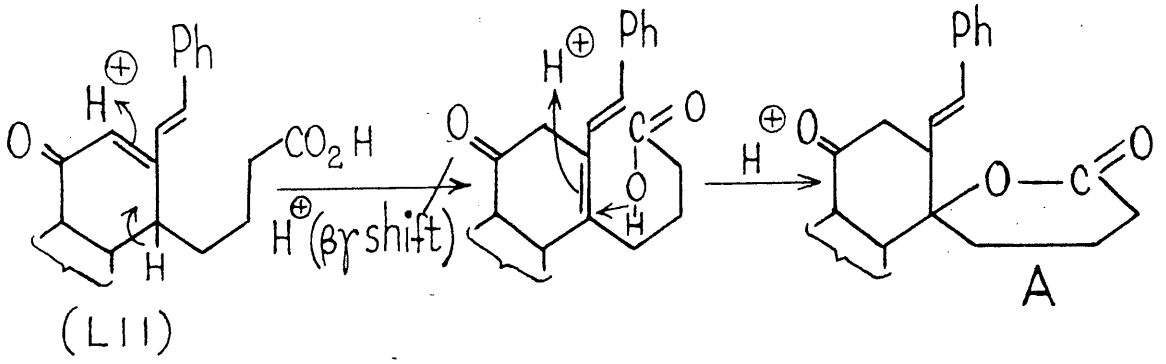
b - R = OH



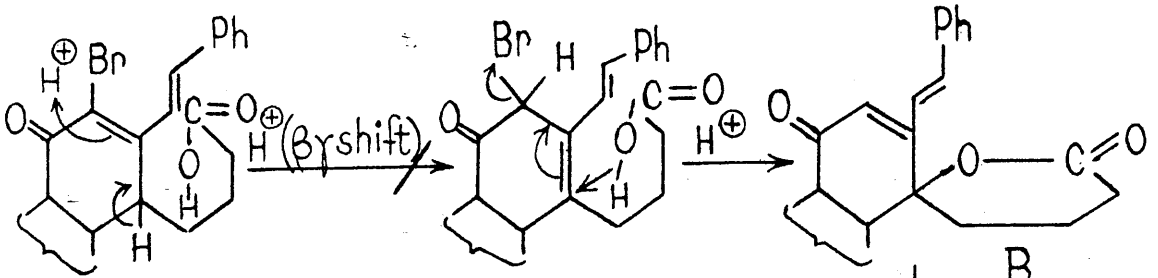
(LXXXIII)

cyclise in one mode in which the benzylidene methyl group finishes in the β-configuration, the side chain bearing the carbanion approaching from the α-face of the molecule. When a model was constructed it was found that a β approach in which the benzylidene methyl group went below the plane of the molecule to the α-configuration resulted in considerable strain in the transition state, the distortion in the nascent ring D only being relieved by the adoption of a boat form by ring C.

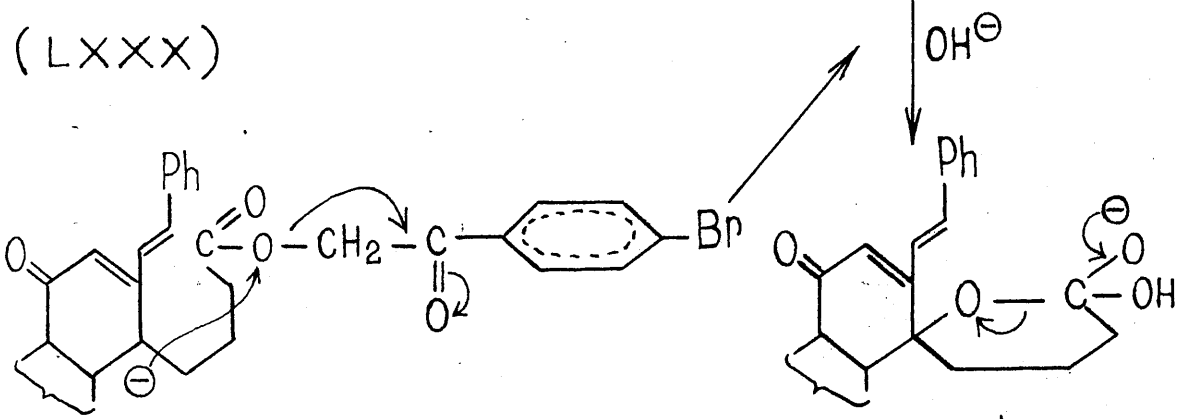
When the benzylidene acid (LII) was treated with bromine (IM) in presence of hydrobromic acid the 12-monobromo derivative (LXXX) was obtained (presumably by addition and dehydrobromination at C_{12}:C_{13})[48]. The substitution on the double bond was accompanied by the expected bathochromic shift of ca. 18 mμ in the ultra-violet absorption spectrum. Further proof of the position of the bromine atom at C_{12} was obtained by ozonolysis of the bromobenzylidene acid (LXXX) to an amorphous bromodicarboxylic acid (LXXXIb), λmax. 263 mμ, ε 5,500. This is in contrast with the chromophore produced by ozonolysis of the benzylidene acid, the diacid (LXXXII) in this case having λmax. 248 mμ, ε 11,000.

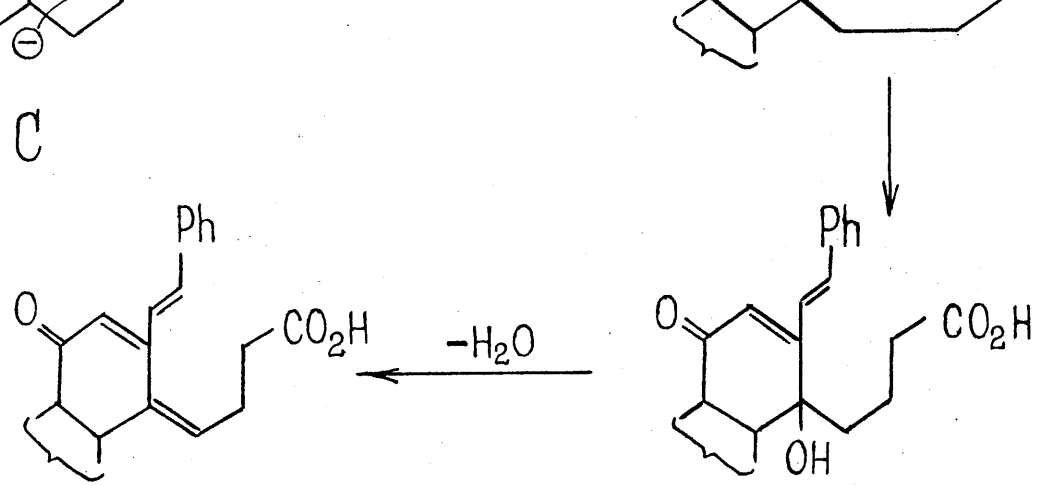

Ph
H
CO2H
H⊕(βγ shift)
H⊕
O
C=O
O—C=O
A

(LII)


Br
Ph
H
C=O
H⊕(βγ shift)
H⊕
O—C=O
B

(LXXX)

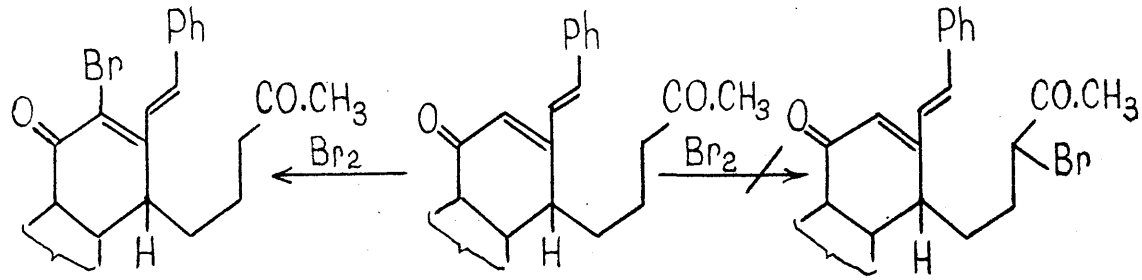

OH⊖
Ph
C—O—CH2—C
Br
O—C—OH
C


Ph
CO2H
-H2O
OH

An attack was now launched on the bromoacid in an attempt to effect 1:4 hydrogen bromide elimination [from the βγ form of the unsaturated ketone system (LXXXIII)]. However, the following sets of reagents and conditions left the starting acid substantially unchanged.

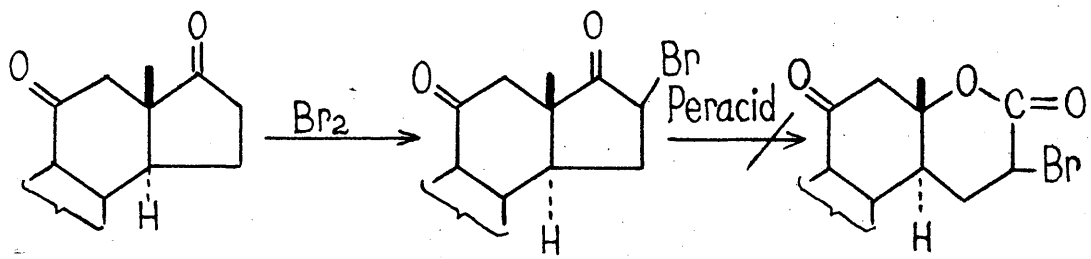
Reagent	Temperature	Time (hours
Collidine	170° (reflux)	1
Collidine	180° (sealed tube)	16
Lithium chloride-Dimethylformamide	reflux	18
Calcium carbonate-Dimethylacetamide	reflux	1
Sodamide-liquid Ammonia	20°	16
Sodiomethylaniline-Methylaniline	reflux	3
Potassium t-butoxide	reflux	0.5
Potassium t-butoxide	20°	24

Unsuccessful attempts were now made to convert the benzylidene acid (LII) or its 12-bromo derivative (LXXX) with perchloric acid to the corresponding spirolactones A and B further convertible to the Δ^{14}



(LXXXIV)
λmax.343mμ

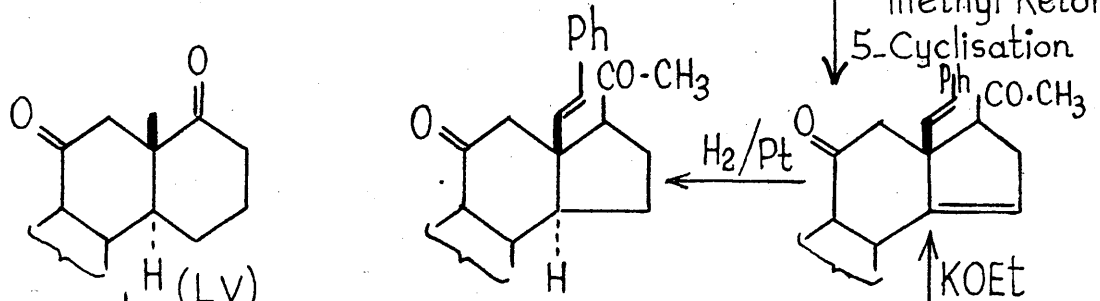
(LIX)
λmax.325mμ



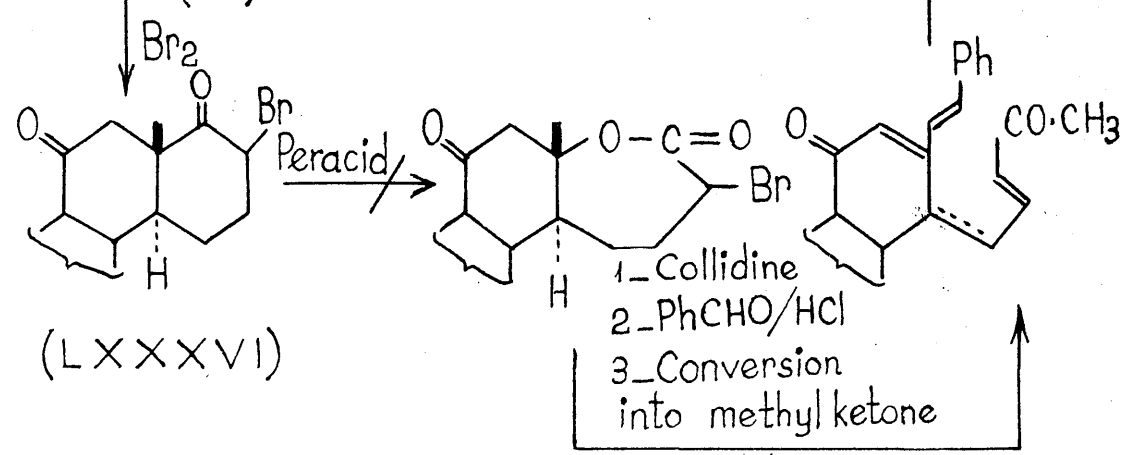
(XLIV)

(LXXXV)

1-Collidine
2-PhCHO/HCl
3_Arndt-Eistert
4_Conversion into methyl Ketone
5_Cyclisation



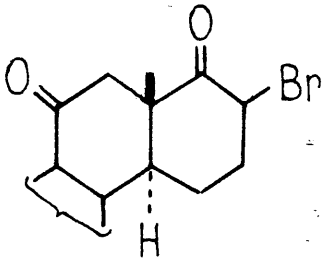
(LV)



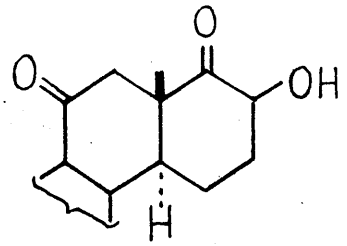
(LXXXVI)

series *via* the respective 14-hydroxy acids. During these investigations it was found that an ethanolic solution of the bromoacid (LXXX) rapidly lost its 343 mμ ($-C=\overset{Br}{\overset{|}{C}}-C=O$) absorption band, a band at 310 mμ taking its place. This change could be accelerated by exposing the solution to sunlight, and retarded by storing in the dark, and must be due to *trans* - *cis* isomerisation (or possible oxidative rupture) of the styrenoid chromophore.* One experiment devised to activate the carbanion elimination reaction (see page 54) by using the *p*-bromophenacyl ester C, led only to ester hydrolysis. As a further means of introducing a ring D unsaturation, a study of the bromination of the benzylidene *seco*-ketone (LIX) was undertaken. It was hoped that the methylene group (C_{17}) might brominate before the conjugated system, but addition of one mole of bromine under acid (hydrobromic acid) catalysis afforded only the 12-bromo compound (LXXXIV) (by addition-elimination; see page 52) as shown by the bathochromic shift in the ultra-violet absorption spectrum of 18 mμ. (See page 56).

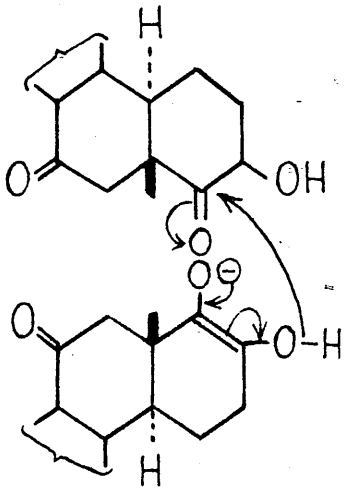
* This effect had not been observed in the debrominated series until the compounds were actually irradiated with ultra-violet light.

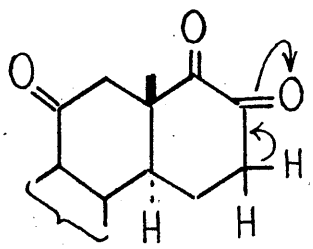


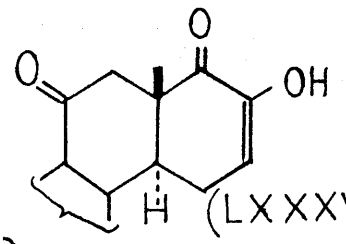
(LXXXVI)



(LXXXVII)







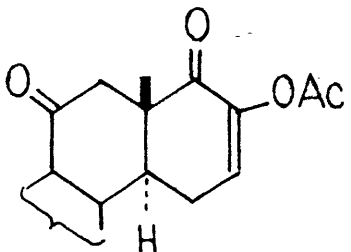
(LXXXVIII)

λmax. 270 mμ

ε 3,200

in base λmax. 310 mμ

ε 4,000



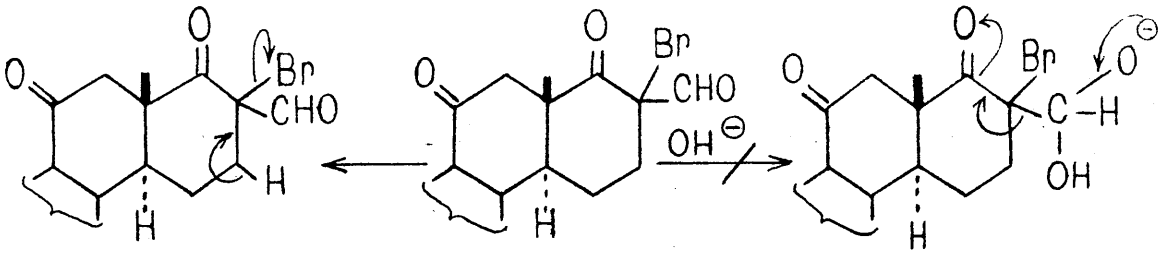
(LXXXIX)

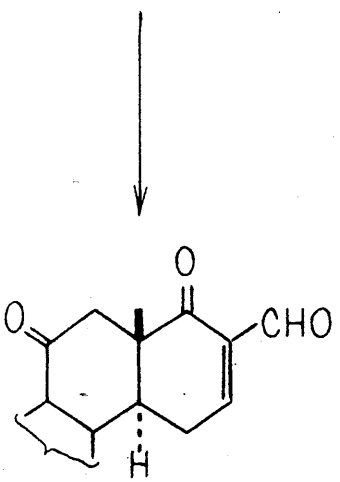
λmax. 235 mμ

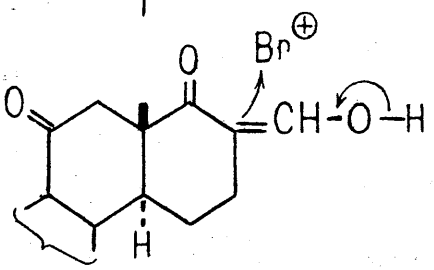
ε 7,200

Another attempted conversion to a Δ^{14} compound made use of the bromoketones in the androstane and D-homoandrostane series. Treatment of 3β-acetoxy-11:17-dioxoandrostane (XLIV) with one mole of bromine afforded the 16-bromo derivative (LXXXV) which, however, failed to react with pertrifluoracetic acid. In the same way, 3β-acetoxy-11:17α-dioxo-17-bromo-D-homoandrostane (LXXXVI)* [prepared by addition of one mole of bromine to the homoketone (LV)] was recovered unchanged after prolonged treatment with pertrifluoracetic acid. When a crude preparation from an attempted peracid oxidation of the 17-bromohomoketone (LXXXVI) was treated with mild base, there was formed a compound with light absorption corresponding to that of a diosphenol. This result can be rationalised by assuming an intermolecular disproportionation of the derived α-ketol (LXXXVII) leading to the ring D diosphenol (LXXXVIII), λmax. 270 mμ [λmax. 310 mμ in base; acetate (LXXXIX), λmax. 235 mμ]. During an attempt to locate the bromine atom of the bromohomoketone (LXXXVI) at C_{17} an effort was made to

* On the other hand, the use of 2.4 moles of bromine resulted in the uptake of 2.0 moles to afford a mixture of di- and tribromide (LXXXVI; LXXXVII?).

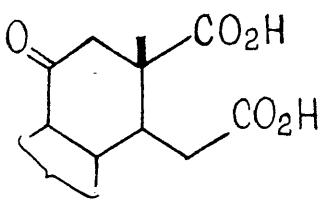




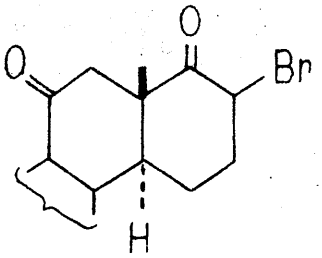


(XC)

CrO_3



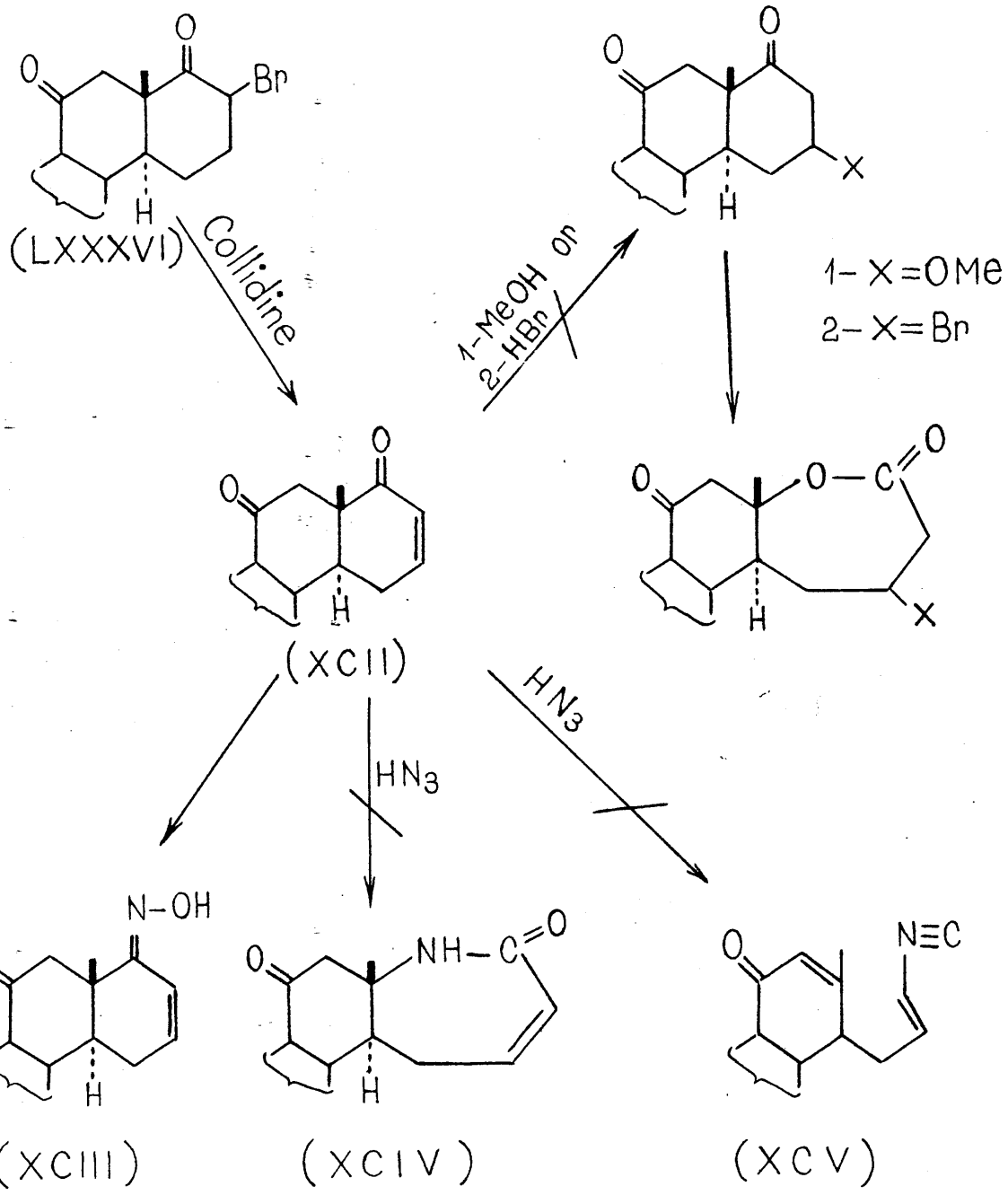
(XCI)

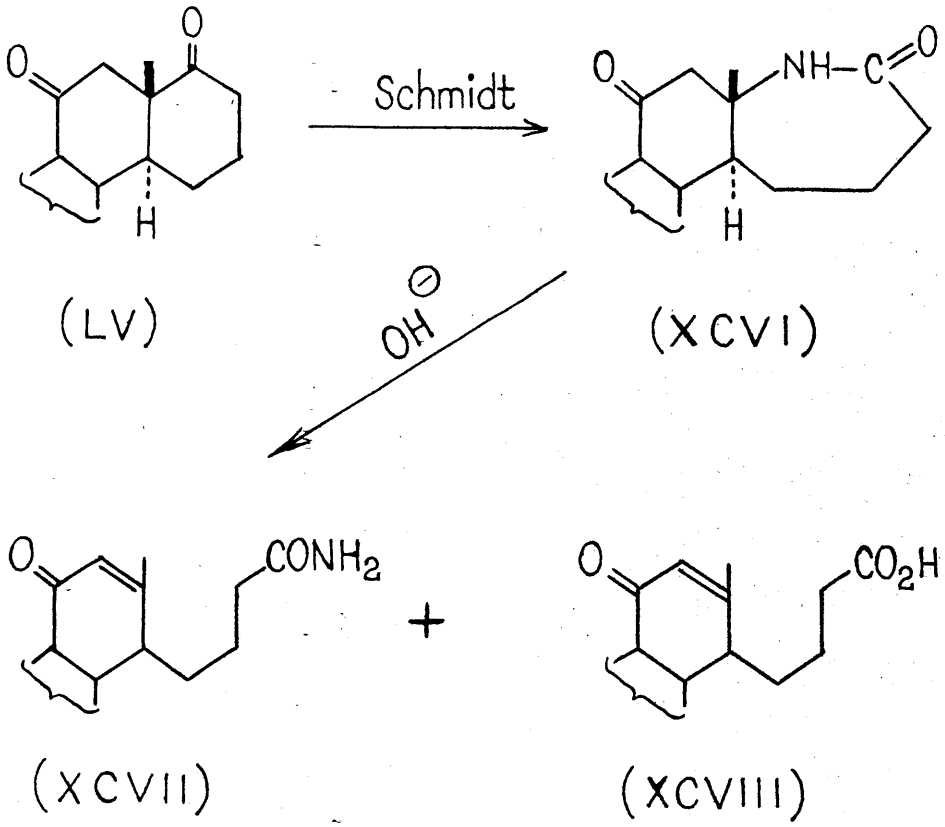


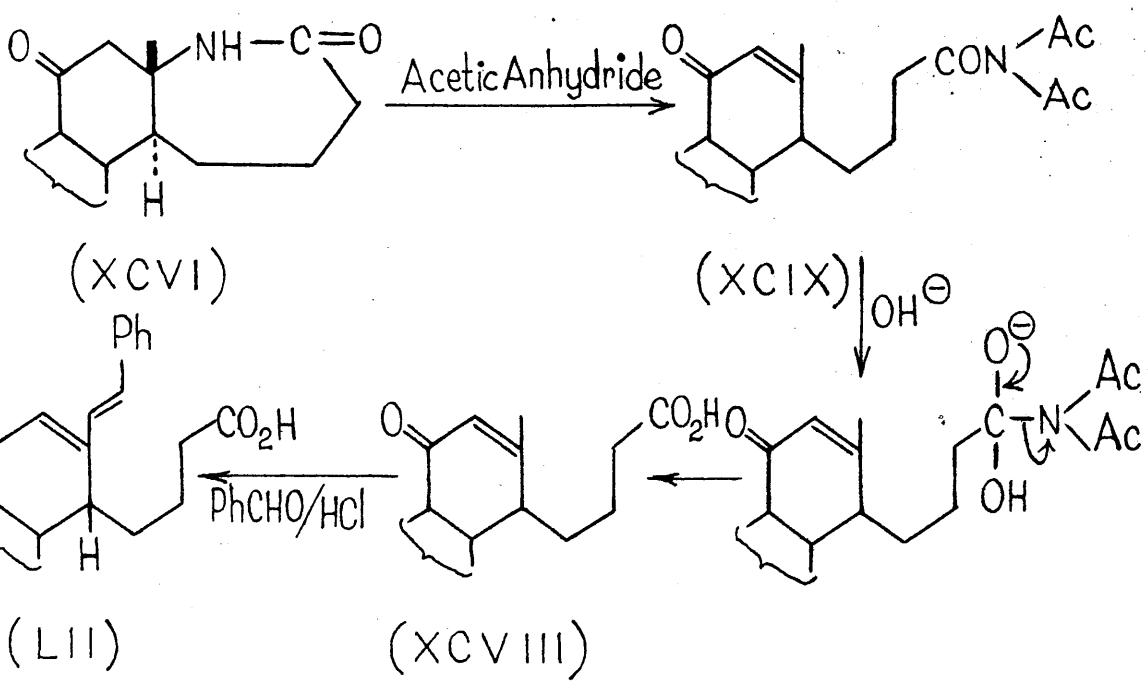
(LXXXVI)

synthesise the bromohomoketone via the 17-hydroxymethylene derivative (XC). This compound could be formed using either ethyl or amyl formate and had the expected light absorption (see Experimental). However, reaction with bromine did not follow the expected sequence (XC) → (LXXXVI) since the product (isolated as an oil) contained no bromine and its U.V. spectrum showed a maximum at 276 mμ. Oxidation with chromic acid led to a high melting acid, possibly the D-seco-acid (XCI) which was not investigated further.

We next devoted our attention to experiments with the Δ^{16}-17α-ketone (XCII), readily prepared from (LXXXVI) by treatment with refluxing collidine. Attempted addition of the elements of methanol or hydrogen bromide (to protect the double bond in the subsequent peracid treatment) met with no success. All attempts to introduce a lactonic function into ring D of the 17-bromo-D-homo-11:17α-diketone having failed, we returned to a consideration of the possibility of lactam formation. The site of bromination (C_{17}) was proved beyond doubt by subjecting

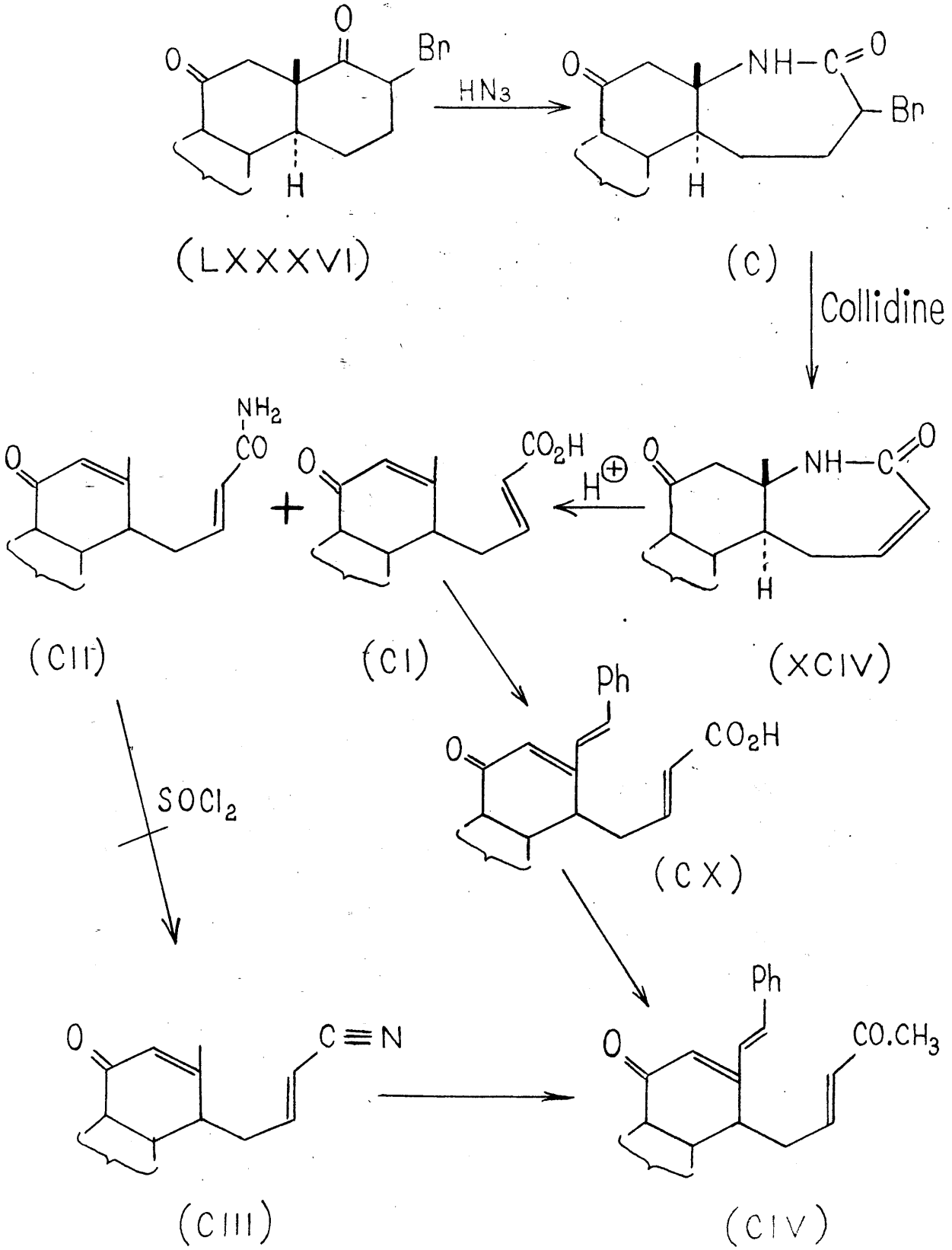

O
O
Br
H
(LXXXVI)
Collidine
1-MeOH or
2-HBr
O
O
X
H
1- X=OMe
2- X=Br
O
O
O—C=O
H
X
O
O
H
(XCII)
HN3
HN3
N-OH
O
H
NH—C=O
O
H
N≡C
O
(XCIII)
(XCIV)
(XCV)


Schmidt
NH—C=O
OH⊖
CONH2
CO2H
(LV)
(XCVI)
(XCVII)
(XCVIII)

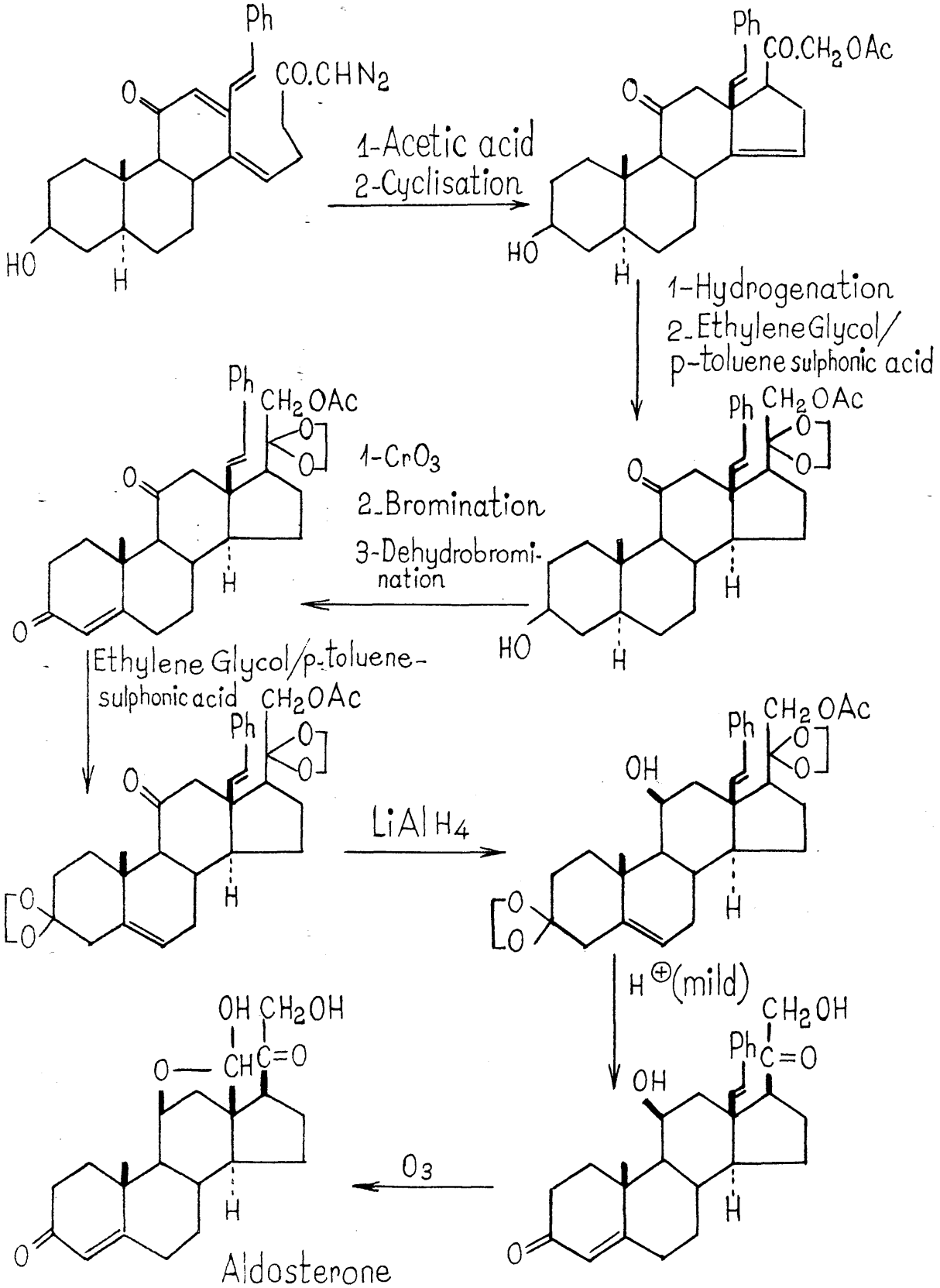

NH—C=O
Acetic Anhydride
CON
Ac
Ac
(XCVI)
(XCIX)
OH⊖
Ph
CO2H
PhCHO/HCl
C
N
Ac
Ac
OH
(LII)
(XCVIII)

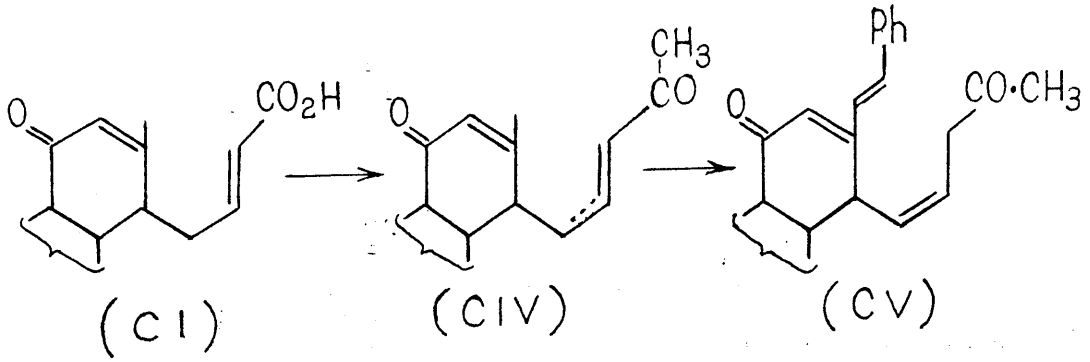
the bromoketone (LXXXVI) to dehydrobromination using refluxing collidine. The Δ^{16} ring D homoketone (XCII) was formed in moderate yield (λmax. 225 mμ). Unfortunately the derived oxime (XCIII) failed to undergo the Beckmann rearrangement to the required $\alpha\beta$-unsaturated lactam (XCIV) even under the most vigorous conditions (see Experimental). An abortive attempt to apply the Schmidt reaction to the Δ^{16}-homoketone (XCII) led only to the production of a bright yellow compound m.p. 320° which was not identical with the lactam (XCIV) and was not the nitrile (XCV) for it showed no -C≡N absorption (I.R. spectrum). The nature of this compound was not investigated further. When the D-homoketone (LV) was treated with hydrazoic acid under the Schmidt conditions a good yield of the bishomolactam (XCVI) was obtained. That the direction of the course of the reaction had taken the expected route was shown by β-elimination under acidic or basic conditions to afford a seco-amide (XCVII) together with a small yield of the seco-acid (XCVIII).*

* Several other attempts to obtain the seco-acid in good yield either by nitrosation of the lactam (XCVI) or of its seco-amide, were made under a wide range of conditions. (See Experimental).

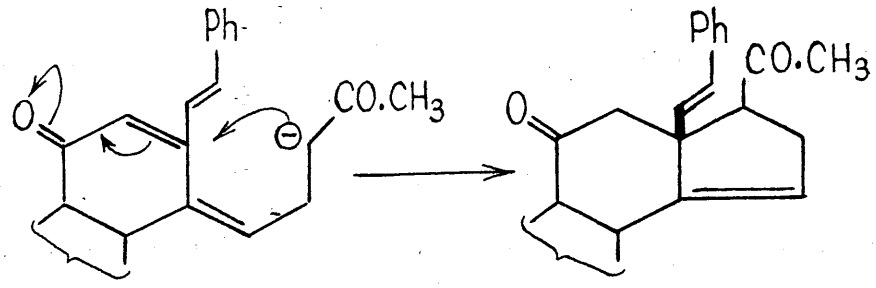

O
Br
HN3
NH—C=O
Br
H
(LXXXVI)
(C)
Collidine
NH2
CO
CO2H
H⊕
NH—C=O
(CII)
(CI)
(XCIV)
Ph
CO2H
SOCl2
(CX)
C≡N
Ph
CO.CH3
(CIII)
(CIV)

Hydrolysis of this amide proved to be most capricious, but of many procedures tried (see Experimental) the best results were obtained by effecting the β-elimination step with sodium acetate-acetic anhydride whereupon the resultant diacyl amide (XCIX) was readily converted to the seco-acid (XCVIII) under mild basic conditions. The proof of structure was completed by conversion to the benzylidene acid (LII) and comparison with a sample prepared via the lactone (LVII) (see page 40). Encouraged by this success we now applied the Schmidt reaction to the 17-bromide (LXXXVI). The bromolactam (C) was obtained in good yield and underwent dehydrobromination (refluxing collidine) to afford the αβ-unsaturated lactam (XCIV) which had the expected spectral properties[49]. β-Elimination of this compound (using sodium acetate) failed but prolonged heating with 10% hydrochloric acid - acetic acid afforded the acid (CI) as an oil (λ max. 236 mμ). The unsaturated amide (CII) was obtained during base catalysed β-elimination. An attempt to convert this to the nitrile (CIII) and thence to the methyl ketone (CIV) met with no success, for although the crude preparation from a dehydration of (CII) with thionyl chloride[50] appeared to contain the -C≡N grouping (IR. 2230 cm^{-1}) there was no selective


Ph
CO.CHN2
O
HO
H
1-Acetic acid
2-Cyclisation
Ph
CO.CH2OAc
1-Hydrogenation
2-Ethylene Glycol/
p-toluene sulphonic acid
Ph
CH2OAc
1-CrO3
2-Bromination
3-Dehydrobromi-
nation
Ethylene Glycol/p-toluene-
sulphonic acid
LiAlH4
OH
H⊕(mild)
CH2OH
Ph
C=O
O3
OH CH2OH
CH
Aldosterone

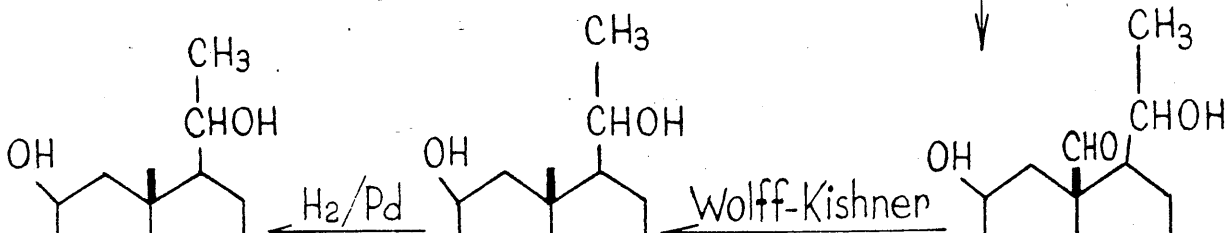


(CI) (CIV) (CV)



(CVI) (CVII)

1 - $LiAlH_4$
2 - O_3



(CIX) (CVIII)

absorption in the ultra-violet spectrum between 220 and 300 mμ. Perhaps addition of thionyl chloride to the 12:13 double bond had occurred.

The synthesis of the acid (CI) leaves the way clear for experiments on the cyclisation of ring D unsaturated compounds. For example, if we carry out the sequence (CI) → (CIV) → (CV) the βγ-unsaturated ketone [in equilibrium with (CIV)] is now capable of shifting into vinylogous conjugation (CVI) with the 11-ketone. Cyclisation will now afford the Δ^{14} compound (CVII) which on lithium aluminium hydride reduction and controlled ozonolysis should afford (CVIII). This on Wolff-Kishner reduction and hydrogenation of the 14:15 double bond should now give 3β:11β:20β-allopregnane triol (CIX). Having proved the stereospecificity of the cyclisation we could now easily extend the synthesis to elaborate the additional functional groups of aldosterone (21-hydroxyl; Δ^{4}-3-ketone) by standard methods. A proposed scheme is shown on page 67.

These steps lie in the future at the time of writing but the author feels that although he has

not succeeded in the partial synthesis of aldosterone itself he has exposed some of the pitfalls along a possible avenue and perhaps made the ground clear for a successful attack on what has been, for him, a most interesting chemical problem.

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NEW COMPOUNDS

	m.p.	$[\alpha]_D$
3β-Acetoxy-11-oxo-20-oximino-allopregnane	188-9°	+ 33°
3β-Acetoxy-11-oxo-20-methane-sulphonyloximinoallopregnane	124-5°	+ 25°
3β-Acetoxy-11-oxo-20-acetoxi-minoallopregnane	149-50°	+ 42°
3β-Acetoxy-11-oxoallopregn-20-ene ethylcyanoacetate	220°	-100°
3β-Acetoxy-11-oxoallopregnane-20-ol	192°	+ 13°
3β-Acetoxy-11-oxoallopregnane-20-methanesulphonate	170°	+ 26°
3β-Hydroxy-11-oxoallopregn-20-ene	147°	+ 13°
3β-Acetoxy-11-oxo-13(17)-secoan-drost-12-ene-17-nitrile	155-7°	- 55°
3β-Acetoxy-11-oxo-13(17)-seco-androstanolactone	218-9°	- 22°
3β-Hydroxy-11-oxo-13(17)-seco-androst-12-ene-17-carboxylic acid	155°	- 4.0°
3β-Hydroxy-11-oxo-18-benzylidene-13(17)-secoandrost-12-ene-17-car-boxylic acid	237-8°	+320°
3β-Hydroxy-11-oxo-18-benzylidene-13(17)-secoaetiochol-12-ene-20-carboxylic acid	233-4°	+301°
3β-Acetoxy-11-oxoandrostane-17-cyanhydrin	159-61°	- 12°
3β-Acetoxy-11:17a-dioxo-D-homo-androstane	185-6°	- 29°

	m.p.	$[\alpha]_D$
3β-Acetoxy-11:17a-dioxo-D-homo-androstanolactone	182-3°	- 66°
3β-Hydroxy-11:20-dioxo-18-benzylidene-14-iso-17-isoallopregnane	194-5°	- 26°
3β:11β:20ξ-14-iso-17-iso-18-benzylidenealloprégnane triol	237-8°	+ 59°
3β:11β:20ξ-Trihydroxy-14-iso-17-iso-allopregnane-18-al	210-2°	+106°(MeOH)
3β:11β:20ξ-14-iso-17-iso-allopregnane triol	202-3°	+ 59°
3β:11β:20ξ-14-iso-17-isoallopregnane-triol-3:20-diacetate	181-4°	+ 45°
3β-Acetoxy-11:20-dioxo-13-iso-17-iso-allopregnane	121-2°	-182°
3:11:20-Trioxo-13-iso-17-isoallo-pregnane	140°	-165°
3:20-Dioxo-13-iso-17-isoallopreg-nane	147-8°	- 61°
3β:17α-Diacetoxy-11-oxo-13-iso-androstane	123°	-125°
3:11:17-Trioxo-13-isoandrostane	174-5°	-160°
3β-Hydroxy-11-oxo-12-bromo-18-benzylidene-13(17)-secoaetiocholi-12-ene-20-carboxylic acid	248-9°	+241°
3β-Acetoxy-11:17α-dioxo-17-bromo-D-homoandrostane	225-7°	+ 24°
3β:17-Diacetoxy-11:17α-dioxo-D-homoandrost-16-ene	255-7°	
3β-Acetoxy-11:17α-dioxo-D-homoandrost-16-ene	170-2°	- 32°

	m.p.	$[\alpha]_D$
3β-Acetoxy-11-oxo-17a-oximino-D-homoandrost-16-ene	230-2°	-136°(Pyrid.)
3β-Acetoxy-11:17-dicxo-16-bromo-androstane	183-5°	+125°
3β-Hydroxy-11:20-dioxo-18-benzyl-idene-14-iso-17-isoallopregnane	193-4°	0±2°
3β-Acetoxy-11:17a-dioxo-17b-aza-D-bishomoandrostane	278-9°	-76.5°
3β-Hydroxy-11:17a-dioxo-17b-aza-D-bishomoandrostane	259-62°	-73°
3β-Acetoxy-17-bromo-11:17a-dioxo-17b-aza-D-bishomoandrostane	183-5°	-12°
3β-Acetoxy-11:17a-dioxo-17b-aza-D-bishomoandrost-16-ene	262°	-94.5°

EXPERIMENTAL

All rotations are in chloroform unless stated otherwise. All melting points are uncorrected. Ultra-violet absorption spectra were determined in ethanol. Infra-red spectra were kindly determined by Dr. G. Eglinton and his colleagues in Nujol unless specified to the contrary. The alumina for chromatography was Brockmann grade III. Light petroleum refers to the fraction b.p. 40-60° unless stated otherwise.

11:20 Dioxoallopregnane Series

3β-Acetoxy-11-oxo-20-oximinoallopregnane (XL)

3β-Acetoxy-11:20-dioxoallopregnane (2.0 g.) and hydroxylamine hydrochloride (2.0 g.) were dissolved in pyridine (25 c.c.), the solution heated for 30 minutes on the steam bath, then left overnight at room temperature. Removal of pyridine *in vacuo* followed by trituration with methanol afforded the crude oxime, m.p. 178-180° (1.90 g.). Crystallisation from methanol yielded clusters of colourless prisms, m.p. 188-189°, $[\alpha]_D$ + 33° (C, 1.38) (Found: C, 71.35; H, 9.20; N, 3.85. $C_{23}H_{35}O_4N$ requires C, 70.90; H, 9.05; N, 3.60%).

3β-Acetoxy-11-oxo-20-methanesulphonyloximinoallopregnane (XLI)

The foregoing oxime (320 mg.) was dissolved in

pyridine (1.5 c.c.), cooled to 0°C, and added to a solution of methane sulphonyl chloride (320 mg.) in pyridine (1.5 c.c.) at 0°. After 48 hours addition of crushed ice precipitated the crude oxime mesylate, m.p. 123-5° $[\alpha]_D$ + 23° (C, 1.12). After 4 recrystallisations from methanol the m.p. was 124-125° (colourless needles) $[\alpha]_D$ + 25° (C, 0.92). On final crystallisation for analysis needles began to form but rapidly changed to colourless prisms, m.p. 124-5° undepressed on admixture with the other crystalline form (Found: C, 61.40; H, 7.80; N, 2.95. $C_{24}H_{37}O_6NS$ requires C, 61.65; H, 8.00; N, 3.00%).

Solutions or precipitates of the pure mesylate in methanol slowly underwent transformation to a higher melting product (m.p. 247-8°). This same product was also formed when the crude precipitated mesylate was allowed to stand for a few days in presence of aqueous pyridine. When the mesylation was attempted at room temperature, the oxime (102 mg.) afforded this same compound, m.p. 242-5°, raised to 247-8° by crystallisation from benzene - petrol (b.p. 60-80°) and undepressed on admixture with the rearrangement

product above $[\alpha]_D$ - 33°, (C, 0.99). Further recrystallisation from methanol afforded the amide, m.p. 252° (needles) $[\alpha]_D$ - 35° (C, 1.06) (Found: C, 70.40; H, 9.00; N, 3.20. $C_{23}H_{35}O_4N$ requires C, 70.90; H, 9.05; N, 3.60%).

Attempted mesylation at -20° gave only unchanged oxime m.p. and mixed m.p. 188-9°.

The mesylate exhibited no selective absorption in the ultra violet between 220 and 270 mμ.

The Action of Potassium t-Butoxide on the oxime Mesylate

The above mesylate (280 mg.) dissolved in benzene (1 c.c.) was added to a solution of potassium (400 mg.; 14 M) in dry t-butanol (15 c.c.) under nitrogen. After 16 hours at room temperature a sample was withdrawn, acidified (HOAC), evaporated, diluted with water and extracted into ether. The UV spectrum of the resultant buff-coloured amorphous solid showed a maximum at 265 mμ ϵ ca. 2000. This maximum was still present after 8 hours reflux, after which time the solution was worked up in the same way as the aliquot. The solid isolated had m.p. 200-205° (sintering at 200°) (130 mg.) λ max 265 mμ ϵ ca. 1,600. Acetylation (pyridine-acetic anhydride) afforded a yellowish-brown amorphous solid m.p. 170-173° (97 mg.). Chromatography over silica gave

(in the benzene eluate) a red gum (25 mg.) together with a yellow solid (55 mg.) eluted with ether, m.p. 152-155° which has not yet been obtained crystalline.

3β-Acetoxy-11-oxo-20-acetoximinoallopregnane

The oxime (100 mg.) dissolved in acetic anhydride (1 c.c.) and pyridine (2 c.c.) gave, after two days at room temperature, the acetate (90 mg.) m.p. 137-145° ($[\alpha]_D$ + 40°, C, 1.01). Crystallisation from aqueous methanol afforded the oxime acetate as tiny needles m.p. 149-150° $[\alpha]_D$ + 42° (C, 0.96) (Found: C, 69.65; H, 8.65; N, 3.30. $C_{25}H_{37}O_5N$ requires C, 69.55; H, 8.65; N, 3.25%).

The acetate (64 mg.) in chloroform 2 c.c. was treated with perbenzoic acid (45 mg.; 2M) in chloroform (5 c.c.). After 168 hours at 0-5° titration revealed that no perbenzoic acid had been consumed.

Attempted Preparation of the C_{20}-Bromonitroso Compound*

The oxime (92 mg.) was suspended in water (2 c.c.) with zinc oxide (16 mg.). N-bromoacetamide (95%; 44.2 mg.) in water (1 c.c.) was added (temp., 5°C.) with stirring. After 30 minutes at 5° and 1 hour at 10-15° the filtered solution was titrated for Br^+ together with a filtered solution from zinc oxide (16 mg.), N-bromoacetamide (45.7 mg.) and water (3 c.c.).

The titration revealed that no uptake of Br^+ had occurred. The oxime was recovered from the filtered solid by solution in methanol, m.p. and mixed m.p. 188-189°. *(Cf. Iffland and Yen, J. Amer. Chem. Soc., 1954, 76, 4083).

3β-Acetoxy-11-oxo-allopregnane-20-hemithioketal

This was prepared by Djerassi's method* employing zinc chloride in dioxan solution and had m.p. 188-189° (lit. 191-193°) $[\alpha]_D$ + 32° (dioxan) lit. $[\alpha]_D$ + 35° dioxan. The hemithioketal could also be prepared in 80-90% yield by treating a solution of the 11:20-diketone (100 mg.) in β-mercaptoethanol (2 c.c.) with p-toluene-sulphonic acid (70 mg.; 1 M or with 7 mg.; 0.1 M). *(J. Amer. Chem. Soc., 1952, 74, 3634).

Reaction with Peracids*

(a) With perbenzoic acid. To a solution of the hemithioketal (77 mg.) in chloroform (2 c.c.) was added (at 0°C.) a solution of perbenzoic acid (72 mg.; 3M) in chloroform (8 c.c.). After 3 hours titration indicated that 2M of perbenzoic acid had been consumed. The chloroform solution was washed with sodium carbonate then water and the chloroform evaporated to yield material m.p. 125-127°. Crystallisation from acetone-

petroleum ether (b.p. 60-80°) gave plates m.p. 132-133° $[\alpha]_D$ + 80°.

(b) With peracetic acid. The hemithioketal (262 mg.) dissolved in glacial acetic acid (AR; 10 c.c.) was treated with a solution of peracetic acid (114 mg.; 2.3 M) in acetic acid (3 c.c.) at 5° C. After 2 hours the consumption of peracetic acid was 1.85 M. (iodometric titration) and remained at this value. After pouring the solution into water, the crystalline material was collected (160 mg.) m.p. 127-129°. 5 Crystallisations raised the m.p. to 142-143° undepressed on admixture with the ketone (142-143°), $[\alpha]_D$ + 84° (C, 1.87). The oxime, prepared in the usual way had m.p. and mixed m.p. 188-189° after one recrystallisation from methanol.

The product from this experiment did not depress the m.p. of the compound obtained from (a). *(Cf. Djerassi and Gorman, J. Amer. Chem. Soc., 1953, 75, 3704).

Reaction with Methyl Iodide

The hemiothioketal (97 mg.) was dissolved in methyl iodide (2 c.c.) and after 7 days the solvent was removed and the resultant reddish gum extracted with boiling petroleum ether (b.p. 60-80°) to furnish prisms m.p. 130-132° (60 mg.). Recrystallisation raised the m.p. to 134-5°, raised to 140-142° on admixture with

ketone (m.p. 142-143°).

Action of Oxalic Acid

A solution of equal weights of the hemithioketal and oxalic acid in acetic acid, after 24 hours at room temperature afforded only unchanged hemithioketal (m.p., mixed m.p. and rotation) on addition of water.

Condensation of 3β-Acetoxy-11:20-dioxoallopregnane with ethylcyanoacetate (Cf. Cope et al., J. Amer. Chem. Soc., 1941, 63, 3452, also Cragoe, J. Org. Chem., 1950, 15, 381).

A mixture of the diketone (0.94 g.) ethylcyanoacetate (280 mg.; 1 M) ammonium acetate (40 mg.) acetic acid (12 mg.) and benzene (4 c.c.) was heated in a Dean and Stark water separating apparatus at 130-160° for 6 hours. Water washing and removal of benzene left an oil which was filtered in benzene (700 c.c.) through neutral activated alumina (30 g.) to yield 0.69 g. of a viscous oil (light absorption $\lambda\lambda$max 245-6 mμ, 249 mμ; ϵ, 3,700, 4,000 respect.). Chromatography using a column of neutral activated alumina (21 g.) prepared in petrol gave a fraction eluted with benzene-petrol (1:1) m.p. 220° (needles) from methanol $[\alpha]_D$ - 100° (C, 1.00). Light absorption λmax. 248 mμ ϵ 10,800. I.R. acetate 1728, 1235 cm^{-1}; >C = O: 1712 cm^{-1}; -CN: 2200 cm^{-1}.

(Found: C, 71.45; H, 8.40; N, 3.45. $C_{28}H_{39}O_5N$ requires C, 71.60; H, 8.35; N, 3.00%). This pure cyanoester fraction (120 mg.) was accompanied by fractions eluted with benzene which consisted of a mixture m.p. 90-105° (30 mg.) and some oily fractions (150 mg.) both of which showed selective absorption at λmax. 248 mμ ϵ ca. 4000. Later benzene fractions deposited the starting ketone in small amount (ca. 20 mg.) m.p. and mixed m.p. 138-139°. No selective U.V. absorption.

Ozonolysis

The pure cyanester condensation product (m.p. 220°; 70 mg.) was ozonized in chloroform (5 c.c.) at 0°. After 1 hour the U.V. absorption was measured - the peak at 248 mμ had disappeared. Water (1 c.c.) was added and the mixture gently refluxed for 10 minutes. Removal of solvents afforded a colourless gum (60 mg.). This was introduced (in benzene -petrol/1:1) on to a column of neutral activated alumina (1.8 g.) prepared in petrol. Elution with petrol gave Fr. 1- oil (15 mg.); with benzene-petrol (1:1), Fr. II (15 mg.) which crystallised on trituration with petrol (60-80°) to give fine needles, m.p. 110-115°. 3 Recrystallisations

from acetone-petrol (60-80°) raised the m.p. to 133-4°. Mixed m.p. with diketone (m.p. 142-43°) was 139-140°.

The yield of pure cyanester, m.p. 220° could not be improved either by carrying out the reaction for 2 hours at 130-140°, or for 8 hours at 140-160°, or by gradual addition of the ammonium acetate catalyst. The starting ketone was recovered when the reaction was carried out in presence of base (8M $KOBu^t$ - 7 hours reflux).

Attempted Preparation of the Glycedic Ester

Condensation of 3β-acetoxy-11:20-dioxoallopregnane with bromocyanoacetic ester.

Bromocyanacetic ester was prepared by the method of Emira and Perciubesco (F. Saches, Ber., 1900, 33, 2976), b.p. 115-6°/ 18 mm n_D^{22}1.4719 (lit. b.p. 135°/40 mm.).

The diketone (0.94 g.) and bromc ester (0.55 g.) dissolved in benzene (5 c.c.) and t-butanol (5 c.c.) were added during 30 minutes to potassium (0.4 g.) in t-butanol (15 c.c.) at 10-15° with stirring under nitrogen. After 2 hours the product was isolated after acidification (HOAc) evaporation and benzene extraction as a reddish glass (0.637 g.) together with a black tar (0.25 g.) insoluble in benzene. Chromatography over neutral alumina (18 g.) gave frs. 8-11 (67 mg.) a crystalline

solid, m.p. 187-9° (needles) from benzene-petrol $[\alpha]_D$ + 98°. 2 Further recrystallisations gave the analytical sample, m.p. 187-9° $[\alpha]_D$ + 100° (Found: C, 76.00; H, 9.50. $C_{21}H_{32}O_3$ requires C, 75.85; H, 9.70%.

I.R. showed -OH, >CO, no-OAc. No selective U.V. Absorption. COMe; 1352 ; -OH-3450 ; >C = O; 1710 cm^{-1}.

Sodium Borohydride Reduction of 3β-Acetoxy-11:20-dioxo-allopregnane (Cf. Oliveto and Hershberg, J.A.C.S., 1953, 75, 488).

A: At Room Temperature -- A solution of sodium borohydride (1.0 g.) in water (2.5 c.c.) was added to the diketone (0.50 g.) in methanol (7.5 c.c.) at room temperature. After seven minutes crystallisation was induced by scratching and the precipitate collected after a further three minutes. The carbinol (264 mg.) had m.p. 186-7° and was recrystallised from aqueous methanol to furnish colourless needles of 3β-acetoxy-11-oxo-allopregnane-20-ol, m.p. 192° $[\alpha]_D$ + 13° (C, 1.85) Found: C, 73.70; H, 9.40. $C_{23}H_{36}O_4$ requires C, 73.35; H, 9.65%. Infra-red spectrum: Hydroxyl 3620 cm^{-1}; acetate 1720 cm^{-1}; ketone 1705 cm^{-1}.

The filtrate from the above preparation on dilution with water afforded an oil (200 mg.) which eventually

crystallised to give needles with a wide melting range (85-95°) which could not be improved by repeated recrystallisation.

When the diketone (400 mg.) was treated with sodium borohydride (800 mg.) in the same way as before but without isolation after 10 minutes, no precipitate appeared and on isolation after 10 hours at room temperature (addition of water and extraction into chloroform) a first crop of needles (260 mg.) was obtained from aqueous methanol m.p. 185-187°, depressed to 160-165° by the 20-carbinol above. Repeated crystallisation from aqueous methanol afforded tiny needles, m.p. 198-200° $[\alpha]_D$ + 17° (C, 1.91) identical with the compound (vide infra) obtained by using more vigorous conditions. The second crop (100 mg.) gave material m.p. 175-185° depressed to 160-4° on admixture with the 20-Carbinol (m.p. 192°).

B: At reflux temperature

When the diketone (100 mg.) in methanol (1.5 c.c.) was heated overnight on the steam bath with sodium borohydride (200 mg.) in water (0.5 c.c.) isolation by addition of water and chloroform extraction gave needles, m.p. 185-7° (92 mg.) undepressed on admixture

with the product obtained after 16 hours at room temperature, but depressed to 160-165° when mixed with the 20-carbinol. Four recrystallisations from aqueous methanol furnished 3β:11β:20ξ-Trihydroxyallopregnane as tiny needles, m.p. 198-200°, $[\alpha]_D$ + 17° (C, 1.09), identical with the specimen prepared later (see below).

3β-Acetoxy-11-oxoallopregnane-20-methanesulphonate

3β-Acetoxy-11-oxoallopregnane-20-ol (86 mg.) dissolved in pyridine (2 c.c.) was cooled to 0° and added to a solution of redistilled methane sulphonyl chloride (90 mg.) in pyridine (temp. 0-5°). After 16 hours at room temperature, addition of crushed ice precipitated the mesylate as glistening platelets, m.p. 170° (90 mg.). Recrystallisation from methanol furnished the analytical sample, m.p. 170° $[\alpha]_D$ + 26° (C, 1.06) as glistening prisms. Found: C, 64.05; H, 8.55. $C_{24}H_{38}O_6S$ requires C, 63.40; H, 8.45%.

3β-Hydroxy-11-oxoallopregnane-20-ene (XLII)

The foregoing mesylate (120 mg.) dissolved in benzene (1.0 c.c.) was heated under reflux with potassium (400 mg.) in t-butanol (16 c.c.) for 8 hours (under nitrogen). Acidification with acetic acid, evaporation and addition of water gave a product m.p. 125-30° (105 mg.).

Repeated crystallisation from aqueous methanol gave a main crop (a) m.p. 142-4° (45 mg.) $[\alpha]_D$ + 11° (C, 1.98) and further crops m.p. 135-9°. Recrystallisation of (a) gave needles m.p. 147° (aqueous methanol) $[\alpha]_D$ + 13° (C, 1.15). I.R. spectrum: Hydroxyl 3620, 1035 cm^{-1}; Carbonyl: 1708 cm^{-1}; C-Me: 1385 cm^{-1}; $-CH=CH_2$: 3050, 1640, 992, 910 cm^{-1}. Found: C, 77.90; H, 9.80. $C_{21}H_{32}O_2$, $\frac{1}{2}$ H_2O requires C, 77.50; H, 10.20.

3β-Acetoxy-17α-hydroxy-11:20-dioxoallopregnane

The 3β-hydroxy compound (10 g.) was dissolved in dry pyridine (200 c.c.) and treated with acetic anhydride (11.3 g.). After 18 hours at room temperature water (600 c.c.) was added and the crystalline precipitate washed with water and dried. Yield 96.3% (10.91 g.) needles (benzene-petroleum ether, or aq. methanol) m.p. 173-4°, $[\alpha]_D$ + 15° (c, 2.20).

3β-Acetoxy-11:17-dioxoandrostane (XLIV)

3β-Acetoxy-17α-hydroxy-11:20-dioxoallopregnane (10.91 g.) in acetic acid (AR; 250 c.c.) was treated with chromium trioxide (AR; 12.26 g.) in water (9 c.c.)-acetic acid (360 c.c.). After 20 hours at 22° excess chromic acid was destroyed by addition of methanol, solvents removed on the steam bath in vacuo and the residue treated with dilute hydrochloric acid.

Extraction into ether and isolation in the usual way afforded a colourless oil. Filtration through alumina (200 g.) in benzene gave, after removal of benzene, the crystalline dione (5.52 g.; 59.7%). Recrystallisation from petroleum-ether (b.p. 60-80°) gave 3β-acetoxy-11:17-dioxoandrostane as needles or prisms m.p. 162-3° $[\alpha]_D$ + 95° (c, 1.16; dioxan) [von Euw and Reichstein, Helv. Chim. Acta, 1942, 25, 998, give m.p. 162-3° $[\alpha]_D$ + 96.2° (dioxan)]. The IR. spectrum showed the expected carbonyl bands at 1740 cm^{-1} (acetate and 17-ketone), 1714 cm^{-1} (11-ketone) and 1240cm^{-1} (acetate). Elution with benzene-methanol (2:1) gave oily fractions (ca. 1.0 g.) which were not further investigated.

3β-Acetoxy-11-oxo-17-oximinoandrostane (XLV)

3β-Acetoxy-11:17-dioxoandrostane (200 mg.) was treated with hydroxylamine hydrochloride (200 mg.) in pyridine (5 c.c.). After 72 hours at room temperature addition of water gave the crystalline oxime (195 mg.) m.p. 205-210°. Recrystallisation from aqueous methanol afforded needles m.p. 216-218°, $[\alpha]_D$ + 15° (c, 1.19).

Beckmann Rearrangement

To the foregoing oxime (400 mg.) dissolved in pyridine (5 c.c.) was added a solution of p-acetylamino-

benzenesulphonyl chloride (400 mg.) in pyridine (2.5 c.c.). (cf. W. Kaufmann, J.A.C.S., 1951, 73, 1779). After 3 hours at room temperature, the solution was poured on to ice, neutralised with dilute hydrochloric acid and isolation effected by chloroform extraction. In this way the crystalline lactam (400 mg.) was obtained, m.p. 305-7° (subl.) as needles from methanol, undepressed on admixture with the secondary product of the Schmidt reaction (vide infra).

Treatment of the lactam (XLVI) with the following reagents showed (in all cases) no development of selective absorption in the ultra-violet region 215-290 mμ and, in appropriate cases (*) recovery of starting material was quantitative.

Reagent	Tempt. °C	Time (hrs.)	Recovery
H_2SO_4 - $CHCl_3$	0°	0.5	*
"	20	16	Gum
NaOEt (20M) (N_2)	20	16	(De)acetylated mixture
KOEt (1M) (N_2)	20	16	Mixture m.p. 270-80°

Action of Acid on the Lactam

When the lactam (1.0 g.) was treated with a solution of concentrated hydrochloric acid (2.0 c.c.) in glacial

acetic acid (18.0 c.c.) for 48 hours at 90-100° there was obtained an acid fraction (0.50 g.) as an orange coloured gum. Solution in benzene-ether (15 c.c.; 1:1) and chromatography over silica (15.0 g.) gave 7 fractions eluted with benzene-ether (1:1) of which the last 4 (145 mg.; oil) had light absorption λmax. 235 mμ ϵ 8,000. All attempts at crystallisation failed however.

Schmidt Reaction. 3β-Acetoxy-11-oxo-13(17)-secoandrost-12-ene-17-nitrile (XLVII)

To a solution of 3β-acetoxy-11:17-dioxoandrostane (344 mg.; 1 millimole) in chloroform (7.0 c.c.) was added concentrated sulphuric acid (A.R.; 2.0 c.c.). The mixture was cooled to 0° with stirring and then sodium azide (97 mg.; 1.5 millimoles) was added portionwise. Stirring was continued for 30 minutes whereupon the reaction mixture was poured on to ice, extracted with benzene-ether and worked up in the usual way to yield a colourless oil (300 mg.). Chromatography over alumina (6.0 g.) gave a fraction eluted with benzene which crystallised as tiny needles (105 mg.) from light petroleum, m.p. 155-7° $[\alpha]_D$ - 55° (c, 1.07). In a second experiment the 13(17)-seco-17-nitrile was obtained as stout needles m.p. 138°. An intimate mixture of the two samples had m.p. 136-7°. (Found:

C, 73.25; H, 8.10; N, 3.85. $C_{21}H_{29}O_3$ requires C, 73.45; H, 8.50; N, 4.10%). Light absorption: $\lambda\lambda$max 234, 311-315 mμ (plateau); ϵ 7,2000, 27 resp. The remaining fractions eluted with benzene showed $\lambda\lambda$max. 234 mμ, ϵ 5000-7000 but had inferior m.p.'s which could not be improved by crystallisation. From a fraction eluted with benzene-methanol (4:1) there crystallised the lactam m.p. 305-7° (subl.) (20 mg.) from aqueous methanol undepressed on admixture with the Beckmann rearrangement product.

3β-Acetoxy-11-oxo-13(17)-secoandrostanolactone (XLVIII) (cf. Jacobsen & Levy, J. Biol. Chem., 1947, 171, 71, 81).

3β-Acetoxy-11:17-dioxoandrostane (2.0 g.) in acetic acid (A.R.; 10 c.c.) was stored at 7-10° for 120 hours in a solution of peracetic acid (4.0 g.) in glacial acetic acid (20 c.c.) containing p-toluenesulphonic acid (20 mg.). At the end of this time the m.p. of the crystalline material obtained by discharging 1.0 c.c. aliquot samples into water (5.0 c.c.) had risen from 153-7° (16 hrs.) through 180-5° (60 hrs.) to a constant value (205-7°) and the precipitate with ethanolic 2:4-dinitrophenylhydrazine sulphate had become very slight. Careful addition of water to the acetic acid solution caused the lactone to crystallise in fine

needles m.p. 205.7-9° (1.10 g.) $[\alpha]_D$ - 20° (c, 1.51). Recrystallised from aqueous methanol, the compound formed needles m.p. 215-6° (1.07 g.) (soda glass capill). For analysis, two further crystallisations from aqueous methanol afforded stout needles m.p. 218-9° (pyrex capill). $[\alpha]_D$ - 22° (C, 1.81). (Found: C, 69.60; H, 8.30; $C_{21}H_{30}O_5$ requires C, 69.60; H, 8.35%). On dilution of the filtrate a further crop (0.42 g.) m.p. 195-8° $[\alpha]_D$ - 15° was obtained.

3β-Hydroxy-11-oxo-13(17)-secoandrost-12-ene-17-carboxylic acid (L)

To a solution of the foregoing lactone (1.068 g.) in ethanol (49 c.c.) was added a solution of potassium hydroxide (0.8 g.) in ethanol (200 c.c.) (final base strength, 0.05 M). The ring-opening reaction was followed by observation of the development of a maximum in the ultra-violet at 239 mμ. When $\epsilon^{239}_{max.}$ had become constant (10,300; 45 minutes) the solution was neutralised with acetic acid, solvents removed in vacuo and the acid fraction isolated in the usual way as a colourless oil (1.00 g.). Crystallisation from ether afforded the pure hydroxy acid as beautiful tiny needles m.p. 155° $[\alpha]_D$ - 4.0° (C, 1.76; 2.01) (Found: C, 71.05; H, 8.75. $C_{19}H_{28}O_4$ requires C, 71.20; H, 8.80%).

Light absorption: λ max. 239 mμ; ϵ 13,600.

3β-Hydroxy-11-oxo-18-benzyldene-13(17)-secoandrost-12-ene-17-carboxylic acid (LI) (cf. Wallach, Annalen, 1899, 305, 261)

The above acid (260 mg.) was dissolved in ethanolic hydrogen chloride (25 c.c.; 40% w/w) containing benzaldehyde (250 mg.). After 16 hours at 20° the solution had the following (constant) light absorption: λ max 230 mμ; ϵ 10,600; λ max. 320 mμ; ϵ 29,250. Water was added to the (cooled) solution and the resultant ethyl ester isolated in the usual way after removal of benzaldehyde with saturated sodium bisulphite solution. Chromatography over alumina gave the ester as an oil (190 mg.). Hydrolysis with potassium hydroxide (1.0 g.) in ethanol (50 c.c.) containing water (1.0 c.c.) at room temperature for 16 hours afforded an acid fraction, isolated in the usual way, as a yellow solid m.p. 210-5° (130 mg.) $[\alpha]_D$ + 278° (c, 1.25). (pyridine). Recrystallised from a small volume of methanol, the acid formed pale yellow needles m.p. 237-8° $[\alpha]_D$ + 320° (c, 1.25) (pyridine). (Found: C, 76.40; H, 8.30. $C_{26}H_{32}O_4$ requires C, 76.45; H, 7.9%). Light absorption: λ max. 240 mμ; ϵ 10,600; λ max. 325 mμ; ϵ 34,200.

The neutral fraction (40 mg.) was rehydrolysed to give a further quantity of acid (25 mg.) m.p. 205-9°. Filtration through silica in benzene-acetone (9:1) afforded needles m.p. 235-7° undepressed with the first hydrolysate.

3β-Hydroxy-11-oxo-18-benzylidene-13(17)-secoaetiochol-12-ene-20-carboxylic acid (LII)

To a suspension of the foregoing acid (1.64 g.) in dry benzene (7.0 c.c.) was added a solution of oxalyl chloride (3.0 g.) in benzene (3.0 c.c.). After 16 hours at room temperature solution was complete and no further evolution of gas was apparent. Solvents were removed at 50° in vacuo, the orange coloured oil dissolved in benzene (7.0 c.c.) and the solution added dropwise through a cotton wool filter to a cold (5°) solution of diazomethane (ca. 2.0 g.) in ether (200 c.c.). After 30 minutes at 5° and 15 minutes at 20° (no change in light absorption at 325 mμ) the ether and excess diazomethane were removed in vacuo (bath temp. $\not>$ 40°) to afford the diazoketone as a pale yellow oil which solidified under petroleum ether to give an amorphous (1.50 g.) mass m.p. 95-100° (dec.), used without further purification for the Wolff rearrangement.

To a solution of this diazoketone in methanol (50 c.c.), maintained at 46-48° was added, with stirring, the silver benzoate-triethylamine catalyst (Newman, and Beal, J.A.C.S., 1950, 72, 5163) in portions (0.5 c.c.) until nitrogen evolution was complete (5 additions; 15 mins.). The mixture was refluxed for 5 minutes, filtered, evaporated, extracted into benzene, washed with sodium bicarbonate solution, water and evaporated. The resultant dark oil was chromatographed over silica to give a fraction eluted with benzene-ether (1:1) (200 mg.) which on hydrolysis with ethanolic potassium hydroxide (50 c.c.; 2 %) at 20° for 16 hours and chromatography of the acidic fraction over silica, gave a fraction eluted with benzene-acetone (9:1), which crystallised from methanol in yellow prisms (175 mg.) m.p. 233-4° $[\alpha]_D$ + 301° (c, 0.82) (pyridine). On admixture with the nor-acid (m.p. 237-8°) the m.p. was 210-5°. Light absorption: λmax. 238 mμ; ϵ 14,000; λmax. 325 mμ; ϵ 35,200. A second crop m.p. 231-3° (40 mg.) was obtained from the crystallisation. Further elution with benzene-acetone (9:1) afforded fractions with inferior m.p. (500 mg.).

The neutral fraction, isolated by ether extraction as a yellow oil, weighed 190 mg.. Light absorption: λmax. 325 mμ ϵ 26,000.

In a second experiment 0.60 g. of pure homologous acid was obtained from 1.82 g. of nor-acid. 3β-Acetoxy-11-oxoandrostane-17-cyanhydrin.*(LIII).

To the foregoing dione (5.5 g.) in absolute ethanol (137.5 c.c.) was added potassium cyanide (AR; 33 g.) and the mixture kept at 0 - 5° whilst acetic acid (AR; 35.75 c.c.) was added with efficient stirring (ca. 1 hour). The resultant paste was stirred for a further 1½ hours at room temperature and then poured into water (1 l.). After 30 mins. the crystalline mass was filtered, washed well with water, and dried for 24 hours over P_2O_5 in vacuo to yield 5.80 g. of crude cyanhydrin (mixture of two epimers) used directly for the next step (m.p. 103-6° $[\alpha]_D$ - 6°; c, 2.30). The pure low-melting isomer could be readily obtained by crystallisation from ethyl acetate-petrol (b.p. 60-80°). It formed prisms m.p. 105-7° (with evolution of HCN) resolidifying at 115-120° and remelting at 159-61° (undepressed with starting ketone) $[\alpha]_D$ - 12° (c, 2.0) (Found: N, 3.75.

* Cf. Goldberg, et al., Helv. Chim. Acta, 1941, 24, 478, 295E, 1940, 23, 376, 840 and later papers.

$C_{22}H_{31}O_4N$ requires N, 3.75%). The high-melting epimer of the cyanhydrin could best be isolated by leaving the reaction mixture overnight at room temperature. It formed needles (ethyl acetate-petrol b.p. 60-80°) m.p. 178-80° but was not further characterised since better yields were obtained in experiments of short reaction times.

3β-Acetoxy-11:17a-dioxo-D-homoandrostane.* (LV)

(a) Hydrogenation. The crude, dried cyanhydrin (5.80 g.) in glacial acetic acid (AR; 160 c.c.) was shaken under hydrogen with Adam's catalyst (2.0 g.). Two moles of hydrogen were absorbed in 40 mins. Filtration (gravity) removed most of the catalyst and the (colloidal) solution was evaporated in vacuo to 25 c.c. and diluted to 250 c.c. with water.

(b) Deamination. The foregoing solution was cooled to 0- 5° and a chilled solution of sodium nitrite (10%; 36 c.c.) added (10 mins.). The mixture (pptn. occurs) was stored at 0-5° overnight, then at room temperature for 3 hours and the ketone removed in chloroform. The extract was washed with sodium carbonate solution, water, then concentrated on the steam bath at 18 mm. to give a semi-crystalline mass (4.88g.). Chromatography on alumina (100 g.) in benzene and elution with

* Cf. Goldberg, et al., Helv. Chim. Acta, 1941, 24, 478, 295E, 1940, 23, 376, 840 and later papers.

benzene gave the 11:17a-diketone as elongated prisms m.p. 185-6° (ethyl acetate-petrol 60-80°) (4.24 g.) $[\alpha]_D$ - 29° (c, 1.79) Found: C, 73.55; H, 8.75. $C_{22}H_{32}O_4$ requires C, 73.30; H, 8.95%. Elution with ethyl acetate afforded an amorphous solid (200 mg.), which may be the 11-17-homodiketone. The infra-red spectrum indicated carbonyl bands at 1735 and 1250 cm^{-1} (acetate) and 1716 cm^{-1} (6-membered ketones).

3β-Acetoxy-11:17a-dioxo-D-homoandrostanolactone (LVII)

To a solution of the foregoing homoketone (1.0 g.) in methylene chloride (10 c.c.) containing p-toluene-sulphonic acid (10 mg.) was added dropwise, with swirling, a solution of petrifluoroacetic acid* (715 mg. - 2M) in methylene chloride (5 c.c.) during 10 minutes so that the temperature of the reaction mixture did not exceed 5° (ice-cooling). The stoppered reaction flask was stored at 20° in the dark. Titration revealed that 1.0 M peracid was consumed in 70 minutes (from the first addition of reagent). The solution was then diluted with chloroform (25 c.c.) and very rapidly washed successively with water (50 c.c.), sodium bicarbonate solution (50 c.c.) and water (50 c.c.).

* Cf. Sager and Duckworth, J.A.C.S., 1955, 77, 189.

Evaporation in vacuo (steam bath) afforded an oil (1.0 g.) which on trituration with ether deposited fine needles (400 mg.) m.p. 178-80° $[\alpha]_D$ - 57° (c, 1.41), and a second crop (100 mg.) m.p. 171-3° $[\alpha]_D$ - 52° (c, 1.28). The mother liquors contained an appreciable amount of lactone determined by conversion to the seco benzylidene acid (vide infra). Recrystallised from ether the lactone formed needles m.p. 182-3° $[\alpha]_D$ - 66° (c, 1.05) Found: C, 70.80; H, 8.50. $C_{22}H_{32}O_5$ requires C, 70.20; H, 8.60%.

The homoketone (LV) was recovered unchanged from solutions of peracetic and perbenzoic acids after several days at room temperature.

For the next stage the total crude lactone was used directly.

(A) "Benzylidene" series

3β-Hydroxy-11-oxo-18-benzylidene-13(17)-secoaetiochol-12-ene-20-carboxylic acid. (LII).

To the foregoing lactone (1 g.) was added a solution of benzaldehyde (1 g.) in saturated alcoholic hydrogen chloride solution (20 c.c.). After 20 hours at room temperature the solution had $\epsilon^{320}_{max.}$ 25,000 (const.). Addition of water to the solution followed by ether extraction and removal of benzaldehyde with sodium

bisulphite afforded the crude ethyl ester together with some ethyl benzoate. Hydrolysis was effected in boiling methanolic sodium bicarbonate solution (5%; 100 c.c.) under nitrogen (4 hours). Addition of acetic acid followed by removal of solvents and extraction into sodium carbonate solution gave, after removal of the neutral fraction in ether (crude neutral fraction $[\alpha]_D$ - 20°) acidification and recovery in ether an acid fraction (0.8 - 0.9 g.) which after chromatography in benzene - acetone (9 : 1) over silica gel formed tiny glistening prisms from methanol m.p. 228-9°. Crystallisation from methanol gave the pure seco-acid as yellow prisms m.p. 233-4°, $[\alpha]_D$ + 301° (c, 0.82; pyridine) $\lambda\lambda_{max.}$ 238, 325 mμ (ϵ14,000; 35,200) Found: C, 76.95; H, 7.75. $C_{27}H_{34}O_4$ requires C, 76.75; H, 8.10%; overall yield from D-homodiketone (LV) was ca.20-25%. This acid was identical with the "homo" acid described above (m.p., mixed m.p., rotation, U.V. spectrum).

3β-Hydroxy-11:20-dioxo-18-benzylidene-13(17)-secoallopregn-12-ene (LIX)

The foregoing acid (1.0 g.) was ground to a very fine powder and suspended in dry benzene (5.0 c.c.).

Oxalyl chloride (1.0 g.) was added and when solution was complete (3-40 hours depending on the state of subdivision of the acid) solvents were removed at 60-70°/10 mm., then at 30-40°/0.5 mm.. The resultant deep yellow oil was dissolved in dry benzene (5 c.c.) and added dropwise with swirling to a solution of diazomethane (2 g.) in ether (150 c.c.) at 0 - 5°. After 30 minutes at 0 - 5° (orange-yellow) and 1 hour at room temperature, excess diazomethane and ether were removed *in vacuo* at ⊁40° and the (oily) diazoketone dissolved in chloroform (5 c.c.).

This solution was transferred to a separating funnel* and hydriodic acid solution (55% in water; 1.0 c.c.) added. Evolution of nitrogen was usually complete in 5 minutes, whereupon water (20 c.c.) was added together with a further amount (20 c.c.) of chloroform. After removal of iodine by shaking with sodium thiosulphate solution, the chloroform extract was washed with water and then evaporated to leave the methyl ketone as an oil(which gave an immediate yellow precipitate with ethanolic 2:4-dinitrophenyl-hydrazine sulphate), together with a trace of diacetyl which can be removed in a high vacuum.

* Cf. Wolfram *et. al.*, *J. Amer. Chem. Soc.*, (1942), *64*, 1701, 2329; *idem. ibid.*, (1943), *65*, 1021, 1516; *idem. ibid.*, (1944), *66*, 204.

Chromatography over silica did not afford crystalline material. The oil had light absorption $\lambda\lambda_{max.}$ 235, 325 mμ (ϵ10,000; 24,000 resp.).

3β-Hydroxy-11:20-dioxo-18-benzylidene-14-iso-17-isoallopregnane (LX)

The above crude seco-ketone (1.0 g.) dissolved in benzene (3 c.c.) was treated with methanolic solution of potassium ethoxide (0.2 M; 100 c.c.) for 16 hours at 20° under nitrogen. The specific rotation of the solution during this period changed from $[\alpha]_D$ + 200° (c, 1.00) (first measurable value) to $[\alpha]_D$ + 57° (c, 1.0) whilst the maxim in the U.V. spectrum ($\lambda\lambda_{max.}$ 235, 325 mμ) were replaced by a single absorption band at 255 mμ (ϵ12,000). The reaction solution was then acidified (HOAc), solvents removed *in vacuo* (steam bath), and the crude preparation obtained by chloroform extraction subjected to chromatography over silica gel to give a fraction eluted with benzene-ether (9:1) (330 mg.). Sublimation at 160/10^{-5}mm. gave the cyclised ketone as a white solid m.p. 191-3° (250 mg.). Recrystallised from ether it formed needles m.p. 194-5° $[\alpha]_D$ - 26° (c, 0.84) Found: C, 80.05; H, 8.40. $C_{28}H_{36}O_3$ requires C, 79.95; H, 8.65%. Light absorption $\lambda_{max.}$ 255 mμ

$\lambda\lambda$infl. 283.5, 293 mμ (ϵ 20,900; 2,600; 1,800 resp.).

3β:11β:20ξ-14-iso-17-iso-18-benzylideneallopregnane triol (LXI)

The above diketone (400 mg.) was placed in a Soxhlet extraction thimble over a refluxing solution of lithium aluminium hydride (400 mg.) in ether (150 c.c.). After 16 hours, decomposition with ethyl acetate and isolation in the usual way afforded the benzylidene triol (LXI) as tiny prisms (300 mg.) m.p. 237-8° (from ethyl acetate), $[\alpha]_D$ + 59° (c, 1.50) + 58° (c, 1.00) (Found: C, 79.05; H, 9.05. $C_{28}H_{40}O_3$ requires C, 79.20; H, 9.50%). Light absorption: $\lambda_{max.}$ 255 mμ, ϵ 20,800.

3β:11β:20ξ-trihydroxy-14-iso-17-isoallopregnan-18-al (LXII)

Ozonised oxygen (5%) was passed through a solution of the above triol (101 mg.) in methylene chloride (100 c.c.) at -60° until the styrene absorption band at 255 mμ disappeared, (determined by removing aliquots from the ozonising solution) - the band at 255 mμ (ϵ 20,800) was replaced by a lower intensity band at 245 mμ (ϵ 11,000). After 30 minutes ($\epsilon^{245}_{max.}$ constant) the ozonide was reductively decomposed by stirring with zinc dust* (0.5 g.)

(* HOAc/steam bath/2 hours followed by washing with water and drying at 100°).

and acetic acid (80%; 5 c.c.) whilst the temperature was allowed to rise from -60° to +20° (2 hours). The filtered solution was worked up in the usual way to leave an oil (100 mg.) with a strong smell of benzaldehyde. Addition of ethyl acetate induced the crystallisation of the aldehyde which formed tiny prisms (from ethyl acetate) or needles (from $CHCl_3$) m.p. 210-2° $[\alpha]_D$ + 106° (c, 1.30) (methanol). Found: C, 72.20; H, 9.65. $C_{21}H_{34}O_4$ requires C, 71.95; H, 9.80%. I.R. spectrum (nujol) showed hydroxyl (3350 cm^{-1}) but no appreciable carbonyl absorption (at least < 5%).

Wolff-Kishner Reduction

The foregoing aldehyde (150 mg.) was added to a mixture of sodium ethoxide (300 mg.) in ethanol (3 c.c.) and anhydrous hydrazine (15 c.c.). The sealed vessel was heated at 180° for 16 hours. Isolation in the usual way gave an oil (150 mg.) which on standing with ethyl acetate deposited prisms (140 mg.) m.p. 195-200°. Recrystallised from ethyl acetate 3β:11β:20β-14-iso-17-isoallopregnane triol (LXV) formed prisms m.p. 202-3° $[\alpha]_D$ + 59° (c, 0.73) [Found: C, 75.15; H, 10.80. $C_{21}H_{36}O_3$ requires

C, 74.95; H, 10.80%). On admixture with authentic 3β:11β:20β-allopregnane triol (vide infra) m.p. 203-5° the following mixed m.p.s were obtained successively: 200-203, 178-83, 194-8. Mixed m.p. with starting aldehyde (212°) was 182-193°.

3β:11β:20β-14-iso-17-isoallopregnane triol 3:20-diacetate

The above triol (56 mg.) in pyridine (1 c.c.) was treated with acetic anhydride (120 mg.). After 18 hours at room temperature, water was added and the diacetate recovered in ether - as needles (from methanol) m.p. 181-4° $[\alpha]_D$ + 45° (c, 0.70) depressed on admixture with authentic 3β:11β:20β-allopregnane triol 3:20-diacetate (m.p. 178-80°) to 157-60° $[\alpha]_D$ + 36 (c, 0.91) (Found: C, 71.75; H, 9.35. $C_{25}H_{40}O_5$ requires C, 71.40; H, 9.60%)

3:20-dioxo-14-iso-17-isoallopregnane (Dioxodiginane) (LXVII)

A solution of the triol (LXV) (140 mg.) in glacial acetic acid (20 c.c.) containing perchloric acid (72%; 0.2 c.c.) was shaken in an atmosphere of hydrogen over prereduced Adam's catalyst (70 mg.). After 24 hours (1 mole hydrogen absorbed) the filtered solution was diluted with water, extracted

with chloroform and the extract washed with sodium bicarbonate solution and then water and evaporated to leave the product (130 mg.) as stellate clusters m.p. 154-60°. This was directly transformed to the 3:20-diol by refluxing with methanolic potassium hydroxide solution (5%; 25 c.c.) and the diol, isolated in the usual way, obtained as needles (methanol) m.p. 163-4° (125 mg.) $[\alpha]_D$ + 43° (c, 2.30). This diol (125 mg.) in acetic acid (2 c.c.) was treated directly with a solution of chromium trioxide (99.0 mg.) in acetic acid (6 c.c.). After 16 hours at 20° excess chromic acid was destroyed by addition of methanol and then solvents were removed at 40°/0.5 mm. Isolation in the usual way afforded an oil (100 mg.) which deposited needles on standing under methanol. Chromatography of this preparation over alumina (grade 3; 3 g.; prepared in petrol) furnished on elution with petroleum ether (60-80°): benzene (9 : 1), fractions 2 - 6 (28 mg.) m.p. 137-9° $[\alpha]_D$ + 39° (c, 0.60) and with petroleum ether-benzene (1: 1) a fraction (20 mg.) m.p. 138-40° $[\alpha]_D$ + 39° (c, 1.10). Recrystallisation from petroleum ether gave needles m.p. 139-41° $[\alpha]_D$ + 39° (c, 0.91) (lit.* m.p. 138-41° $[\alpha]_D$ + 39.6 ± 2° (c, 1.36)), undepressed on

* Press and Reichstein, Helv. Chim. Acta, 1947, 30, 2127.

admixture with Reichstein's dioxodiginane. The I.R. spectra were also identical (see page 43).

(B) 13-iso Series

Base catalysed Lactone opening

3β-Acetoxy-11:17a-dioxo-D-homoandrostanolactone (LVII) (1.95 g.) was dissolved in ethanolic potassium ethoxide solution (5%; 100 c.c.) and heated on the steam bath for 1 hour under nitrogen. Neutralisation (HOAc) and working up in the usual way afforded an acid fraction (1.80 g.) (LXVIII) as an oil, $\epsilon^{max.}_{237}$ 12,600 , which could not be crystallised.

3β-Acetoxy-11:20-dioxo-13-iso-17-isoallopregnane (LXX)

The foregoing acid (1.8 g.) was transformed to the corresponding methyl ketone and cyclised as in the experiments described above for the benzylidene seco series, without isolation of intermediates, reactions being controlled spectrophotometrically. In this way the final (acetylated) cyclised diketone was obtained as a dark viscous oil (1.10 g.) which after chromatography over alumina in benzene gave a fraction recrystallised from petroleum ether (b.p. 60-80°) as needles (200 mg.) m.p. 121-2° $[\alpha]_D$ - 182° (c, 1.10). Found: C, 73.80; H, 8.80. $C_{23}H_{34}O_4$ requires C, 73.75; H, 9.15%.

3:11:20-Trioxo-13-iso-17-isoallopregnane

The 3β-acetoxy-11:20-dione above (300 mg.) was saponified (5% KOH-MeOH, steam bath, 3 hours) and the resultant 3β-hydroxy compound treated directly with chromic acid (200 mg.) in acetic acid (10 c.c.). Isolation in the usual way (after destruction of excess CrO_3 with MeOH) afforded the trione as needles (150 mg.) (ethyl acetate - petrol) m.p. 140°, $[\alpha]_D$ - 165° (c, 0.85). Found: C, 76.50; H, 9.25. $C_{21}H_{30}O_3$ requires C, 76.30; H, 9.15%.

3:20-Dioxo-13-iso-17-iso-allopregnane

To a solution of the acetoxydiketone (LXX) (300 mg.) in ether (20 c.c.) was added lithium aluminium hydride (300 mg.) in ether (180 c.c.) and reflux maintained overnight. Working up in the usual way afforded the triol as an oil (260 mg.). This triol was shaken in acetic acid (20 c.c.) with perchloric acid (0.2 c.c.) in an atmosphere of hydrogen over prereduced Adam's Catalyst (130 mg.). Hydrogen absorption was complete in 24 hours. The resultant product was hydrolysed to the 3:20-diol (oil; 230 mg.) and the latter product treated with chromium trioxide (200 mg.) in acetic acid (15 c.c.) for 16 hours at 20°. Working

up in the usual way gave the dione as an oil (100 mg.). Chromatography over alumina in carbon tetrachloride gave a fraction eluted with carbon tetrachloride which formed needles m.p. 147-8° (petroleum ether) $[\alpha]_D$ - 61° (c, 0.75). Found: C, 79.60; H, 10.20. $C_{21}H_{32}O_2$ requires C, 79.70; H, 10.20%.

3β:17α-Diacetoxy-11-oxo-13-isoandrostane (LXXI)

3β-Acetoxy-11:20-dioxo-13-iso-17-isoallopregnane (240 mg.) in methylene chloride (4 c.c.) was treated with a solution of peroxytrifluoracetic acid (150 mg.) in methylene chloride (1 c.c.). After one hour at room temperature (1.15 M peracid consumed) chloroform (10 c.c.) was added and the solution washed with sodium bicarbonate and water and then evaporated to leave the diacetate (200 mg.). Chromatography over alumina gave the pure diacetate as needles (130 mg.) (from petroleum ether) m.p. 123° $[\alpha]_D$ - 125° (c, 1.10). Found: C, 70.50; H, 8.95. $C_{23}H_{34}O_5$ requires C, 70.75; H, 8.80%.

3:17-Dioxo-13-isoandrostane (cf. Billeter and Miescher* Helv. Chim. Acta, 1951, 34, 2053) (LXXIII)

The foregoing diacetate (300 mg.) in ether

* Billeter and Miescher give m.p. 165-6° $[\alpha]_D$ -58° ± 3° (C, 0.6).

(100 c.c.) was treated with lithium aluminium hydride (300 mg.) and heated under reflux for 16 hours. Isolation in the usual way afforded the crude triol (300 mg.) which was directly dissolved in acetic acid (20 c.c.) containing perchloric acid (70%; 0.10 c.c.) and shaken for 24 hours under hydrogen with Adam's catalyst (150 mg.). The resultant 3:17-diacetate was saponified (5% KOH - methanol - 3 hours) and the resultant crude preparation of the 3:17-diol treated directly with chromium trioxide (AR: 160 mg.) in acetic acid (15 c.c.). After 16 hours excess chromic acid was destroyed by addition of methanol; solvents were removed in vacuo and the product recovered in ether. Chromatography in carbon tetrachloride over alumina (5 g.) gave a fraction (30 mg.) m.p. 165-7° $[\alpha]_D$ - 64° (c, 0.70). Recrystallisation from ether-petroleum ether afforded needles m.p. 165-7° $[\alpha]_D$ - 74° (c, 0.38)* I.R. absorption at 1716 cm^{-1} (6 m. >C = O) and 1730 cm^{-1} (5 m. >C = O) (Nujol), identical in every respect with the product of irradiation of 3:17-dioxo-androstane (m.p., mixed m.p., rotation, infra-red spectrum - vide infra). Development of the

* Billeter and Miescher give m.p. 165-6° $[\alpha]_D$ -58° ± 3° (C, 0.6).

chromatogram with benzene-petroleum ether (1:1) and with benzene gave a fraction (77 mg.) m.p. 174-5°. Crystallised from ether-petroleum ether 3:11:17-trioxo-13-isoandrostane formed stout needles or prisms m.p. 174-5° (both forms) $[\alpha]_D$ - 160° (c, 2.00). Found: C, 75.40; H, 8.70. $C_{19}H_{26}O_3$ requires C, 75.45; H, 8.65%.

Irradiation of 3:17-Dioxoandrostane

In the best of several experiments* the diketone (495 mg.) was dissolved in benzene (10 c.c.) in a silica tube and irradiated with U.V. light (from a source 4 mm. from the tube) under nitrogen. Dilution to 30 c.c. was necessary after 7 hours due to precipitation of insoluble matter on the walls of the tube. During the irradiation the specific rotation was measured as follows.

Time (hrs.)	$[\alpha]_D$	(c)
0	+ 104°	1.03
7	+ 71°	2.47
10.5	+ 60°	1.66
16.5	+ 31°	1.66
23	+ 16.3°	1.23

* Cf. Butenandt et. al., Ber., 1944, 77, 394 and previous papers.

The benzene was removed and the residue chromatographed in carbon tetrachloride over alumina (15 g.) to afford a fraction (200 mg.) eluted with carbon tetrachloride which formed needles from ether-petroleum ether m.p. 167-8° $[\alpha]_D$ - 76° (c, 0.63) identical in every respect with 3:17-dioxo-13-iso-androstane described above. Found: C, 79.30; H, 9.40. $C_{19}H_{28}O_2$ requires C, 79.10; H, 9.80%. Light absorption: >C = O, 1716, 1730 cm^{-1} (Nujol).

3β-Hydroxy-11-oxo-12-bromo-18-benzylidene-13(17)-seco-etiochol-12-ene-20-carboxylic acid (LXXX)

To the benzylidene acid (LII) (120 mg.) in glacial acetic acid (5 c.c.) containing hydrogen bromide (5% soln. in HOAc; 1 drop) was added a solution of bromine (48 mg. ; 1.0 M) in acetic acid (2.14 c.c.). After 10 minutes the reaction mixture was poured into water, extracted with chloroform, the extract washed with water, and evaporated to yield small prisms (from acetone/ether) (100 mg.) m.p. 235-7° (dec.) $[\alpha]_D$ + 241° (c, 0.30, pyridine). The analytical specimen (hemihydrate) had m.p. 248-9° (dec.) $[\alpha]_D$ + 241.3° (c, 0.29). Light absorption $\lambda\lambda_{max.}$ 238; 343 mμ. ϵ , 8,400; 22,800 respect. Found: C, 63.60; H, 6.90; Br, 15.70. $C_{27}H_{33}O_4Br, 0.5H_2O$

requires, C, 63.50; H, 6.70; Br, 15.65%. When a solution of the above acid in ethanol was stored in normal daylight for several hours, or exposed to sunlight for 10 minutes, the ultraviolet absorption maximum at 343 mμ (ε, 22,800) was replaced by a maximum at 310 mμ (ε, 11,000) [due to the isomerisation or other light induced change of the styryl chromophore].

Ozonolysis of the bromoacid

The above bromoacid (88 mg.) in methylene dichloride (100 c.c.) was ozonised for 5 mins. at -70°. The ultraviolet absorption of an aliquot revealed the presence of benzaldehyde (245 mμ) and a second chromophore (290 mμ) (aldehyde-acid [LXXXIa]). On working up the ozonide by decomposition with water, and chromatography of the chloroform extract on silica, from the fraction eluted with benzene was obtained benzaldehyde (5 mg.) with some benzoic acid (trace). The fraction eluted with benzene-acetone (9:1) furnished the bromodicarboxylic acid (LXXXIb) (20 mg.) as an amorphous pale yellow solid (EtOAc-light petroleum) m.p. 180-200°. Light absorption $\epsilon^{263}_{max.}$ 5,500. Found: Br. 17.90%. $C_{20}H_{27}O_6Br$ requires Br 18.00%.

Ozonolysis of the benzylidene acid (LII)

Ozonized oxygen was passed through a cooled (-60°) solution of benzylidene acid (LII) (12.0 mg.) in methylene chloride (100 c.c.), the ozonization being followed spectrophotometrically. Worked up as above afforded an oily dicarboxylic acid (LXXXII) which could not be crystallized and showed an ultra-violet maximum at 248 mμ ε 11,000.

Dehydrobromination Attempts

a) Using collidine

The foregoing bromoacid (LXXX) (250 mg.) was added to refluxing collidine (2.5 c.c.). Reflux was stopped when collidine hydrobromide precipitation seemed completed (10 minutes). The sole isolable product from this experiment crystallised from methanol as prisms m.p. 248-9° undepressed on admixture with starting material.

b) Collidine in a sealed tube (180°)

A solution of the brome-acid (100 mg.) in collidine (2 c.c.) was heated at 180° in a sealed tube, for 16 hours. Worked up in the usual way afforded starting material (m.p. 245-9°) undepressed m.m.p.; $\epsilon^{341}_{max.}$ 25,000).

c) Sodiomethylaniline in methylaniline

A solution of bromo-acid (100 mg.) in PhNHMe (1 c.c.) was added to a warm solution of sodiomethylanilin prepared under Fieser's instructions*. The reaction mixture was left refluxing with stirring for 16 hours. From this reaction only starting material (m.p., m.m.p., $[\alpha]_D$) was obtained on suitable working up.

d) Calcium Carbonate-Dimethylacetamide

The acid (43 mg.), as a fine microcrystalline powder, was added to refluxing (bath temperature 180°) dimethylacetamide (2 c.c.) in presence of calcium carbonate (AR.; 190 mg.). The bright yellow solution was refluxed for 50 minutes. On suitable working up only starting material (70 mg.) (identified by its m.p. and m.m.p.) was obtained.

e) Sodamide-Liquid NH_3

A solution of bromo-acid (200 mg.) in dry ether (25 c.c.) was added with stirring to a solution of sodamide (prepared from sodium - 2.2 g., and liquid NH_3-100 c.c.). Stirring was maintained for 8 hours, when ammonium chloride (2.5 g.) was added in small portions. Only starting material was obtained from this reaction.

* Edward and Fieser, J. Am. Chem. Soc., 1940, 62, 3789; Ziegler, Jakob, Wollthan and Wenz, Annalen, 1934, 511, 64.

f) Lithium Chloride-Dimethylformamide

A solution of bromo-acid (96.3 mg.) and LiCl (22 mg.) in NN-dimethylformamide (2 c.c.) was refluxed during 22 hours. The sole isolated product from this reaction was starting material (m.p., m.m.p., $\epsilon_{max.}^{340}$ 22,500).

g) Potassium t-butoxide

The bromo-acid (98 mg.) in solution in potassium t-butoxide (15 c.c.; prepared from potassium - 250 mg., and t-butanol -15c.c.) was heated (reflux) under nitrogen, during 8 hours. Worked up in the usual way this reaction gave starting material as the only isolated product.

Lactonisation Attempts

a) The bromo-acid (LXXX) and the acid (LII) were recovered unchanged from their solutions in perchloric acid/AR. acetic acid (10%).

b) The benzylidene acid (LII) was recovered from a solution of its p-bromophenacyl ester in potassium t-butoxide.

3β-Hydroxy-11:20-dioxo-12-bromo-18-benzylidene-13(17)-secoallopregn-12-ene (LXXXIV)

A solution of bromine in acetic acid (AR.; 0.5 c.c.; 1.5 M) was added to a solution of 3β-hydroxy-11:20-dioxo-18-benzylidene-13(17)-secoallopregn-12-ene (90 mg.) in acetic acid (AR.; 2 c.c.) containing 55% solution of hydrobromic acid in acetic acid (AR.; 1 drop). The resulting solution was shaken during 5 minutes, dropped into water and extracted in the usual way to afford a gum with the light absorption $\lambda_{max.}$ 343 mμ ε14,000. This compound which gave a positive Beilstein test failed to crystallise.

3β-Acetoxy-11:17a-dioxo-17-bromo-D-homoandrostane (LXXXV)

3β-Acetoxy-11:17a-dioxo-D-homoandrostane (LV) (1.0 g.) in acetic acid (AR.; 22 c.c.) containing hydrogen bromide (50% solution in HOAc; 5 drops) was treated with a solution of bromine (446 mg.; 1 mole) in acetic acid (AR.; 18.70 c.c.). The solution became colourless within 30 seconds of mixing. Addition of water (400 c.c.) followed by filtration, gave, after washing with water and drying, the monobromide (0.975 g.) as needles m.p. 225-7° (dec.) (from ethyl acetate-petrol) $[\alpha]_D$ + 24° (C, 2.0).

Found: C, 60.40; H, 7.30; Br, 18.20. $C_{22}H_{31}O_4Br$ requires C, 60.15; H, 7.10; Br, 18.15%.

When the 3β-acetoxy-11:17a-dioxo-D-homoandrostane was submitted to an identical bromination using 2.4 moles of bromine, titration after 30 minutes showed that 2 moles of bromine had been consumed and on the usual work up needles (from ether) were obtained (2.31 g.) m.p. 169-170° which on recrystallisation from $CHCl_3$-ether rose the m.p. to 185-6°, $[\alpha]_D$ + 138° (c, 1.32). The analysis corresponds to a mixture of di- and tribromides. Found C, 46.15; H, 4.95; Br, 36.90. $C_{22}H_{30}O_4Br_2$ requires C, 50.95; H, 5.85; Br, 30.85%.

Treatment of the above monobromoketone with petrifluoracetic acid (3 M) led to recovery of starting material (m.p., m.m.p., I.R.). The crude product (200 mg.) from such an attempted lactonisation was treated directly with ethanolic potassium hydroxide solution (5%) during one hour (steam bath). The sole isolable product from this reaction was the ring-D diosphenol (LXXXVIII) obtained as an oil (100 mg.) [$\epsilon^{270}_{max.}$ 3,200 ; $\epsilon^{310}_{max.}$ (base) 4,000] converted in the usual way to the acetate (LXXXIX) (60 mg.) m.p. 255-7°, needles (from methanol)

$\epsilon^{235}_{max.}$ 7,200, which retained methanol of solvation tenaciously. Found (in a sample dried at 120°/5 days/ 0.1 mm.) C, 68.05; H, 7.40. $C_{27}H_{32}O_6$,0.5MeOH requires C, 68.05; H, 7.85%.

3β-Acetoxy-11:17a-dioxo-17-hydroxymethylene-D-homoandrostane (XC)

The best conditions for the preparation of this compound were found to be the following: A solution of the D-homoketone (LV) (1.0 g.) in benzene (15 c.c.) containing ethyl formate (0.35 c.c.; 1.5 M) was added to a suspension of potassium t-butoxide (prepared from potassium-400 mg. and t-butanol) in dry benzene (15 c.c.) under nitrogen, with stirring. The mixture was left for 16 hours at room temperature after which amyl formate (18 c.c.) was added and the total mixture refluxed for 30 minutes. Worked up in the usual way gave an oily acidic fraction (990 mg.) which had the light absorption $\epsilon^{279}_{max.}$ 3,000 shifting to $\epsilon^{317}_{max.}$ 9,000 in alkaline solution.

Attempted bromination of the 17-hydroxymethylene compound (XC)

To the crude hydroxymethylene compound (430 mg.) in acetic acid (AR.; 10 c.c.) containing fused sodium

acetate (250 mg.) was added a solution of bromine in acetic acid (AR.; 8 c.c.; 2 M). After one hour, on suitable work up an oil was obtained which did not contain bromine and still showed the light absorption $\epsilon^{276}_{max.}$ 3,000. After acetylation, (pyridine-acetic anhydride) this oil was dissolved in acetic acid (AR.; 15 c.c.) and treated with a solution of chromic acid (3 M) in acetic acid (AR.; 15 c.c.). After 16 hours the reaction was worked up in the usual way to afford a semi-crystalline acid (soluble in dilute sodium bicarbonate) which did not melt up to 320°. Its dimethyl (?) ester (prepared by reaction with diazomethane) could not be crystallized.

3β-Acetoxy-11:17a-dioxo-D-homoandrost-16-ene (XCII)

When the above 17-bromoketone (800 mg.) was added to collidine (at reflux temperature) precipitation of collidine hydrobromide was judged to be complete in 15 minutes. Isolation in chloroform, after thorough washing with hydrochloric acid (3 N), afforded (after filtration in benzene solution through a short column of alumina) the αβ-unsaturated ketone (XCII) (300 mg.) as needles m.p. 170-2° (ether) $[\alpha]_D$ -32° (c, 2.30).

Found: C, 73.90; H, 8.15. $C_{22}H_{30}O_4$ requires C, 73.70; H, 8.45%. Light absorption $\lambda_{max.}$ 225 mμ; ϵ 8,200. The U.V. spectrum was substantially unchanged in presence of the following reagents (all conditions anhydrous): NaOEt; KOMe (20°C ——— 80°C); HBr (in acetic acid) (20°C.). When this αβ-unsaturated ketone (53 mg.) was dissolved in 3% solution of sodium in absolute ethanol (25 c.c.) its ultra-violet absorption did not change even after 16 hours. The same happened when that ketone (25 mg.) in solution in acetic acid (AR.; 1.0 c.c.) was treated with 55% solution of HBr in acetic acid (0.3 c.c.) and the resultant mixture left for 48 hours.

The derived oxime (XCIII) was prepared dissolving the Δ^{16} 17a-homoketone (190 mg.) and hydroxylamine hydrochloride (200 mg.) in pyridine (AR.; 5 c.c.), and leaving the reaction overnight. On suitable work up the oxime formed rectangular plates (from aqueous methanol) m.p. 230-2° (d.) $[\alpha]_D$ - 136° (C, 0.40; pyridine). Found: C, 70.90; H, 8.30; N, 3.95. $C_{22}H_{31}O_4N$ requires C, 70.75; H, 8.35; N, 3.75%. Light absorption: $\lambda_{max.}$ 236 mμ; ϵ 8,350.

Schmidt reaction on the 3β-Acetoxy-11:17a-dioxo-D-homo-androst-16-ene

To a solution of αβ-unsaturated ketone (1.0 g.) in chloroform (40 c.c.) containing sulphuric acid (AR.; 7 c.c.), at 0° and provided with vigorous stirring, NaN_3 (300 mg.; 1.5 M) was added in small portions. Stirring was maintained for 30 minutes. The solution was poured into ice-water and then worked up in the usual way to give, together with starting material, a yellow product not soluble in methanol (200 mg.) which crystallised in yellow prisms (from chloroform-methanol) m.p. 320-5° $[\alpha]_D$ - 52.7° (c, 0.74). Although its analysis fits for the αβ-unsaturated lactam (Found: C, 70.60; H, 8.45; N, 4.00; $C_{22}H_{31}O_4N$ requires C, 70.75; H, 8.40; N, 3.75%) it was a different compound as could be seen when the αβ-unsaturated lactam was prepared in a different way (see below). That yellow product had the light absorption $\epsilon^{228}_{max.}$ 3,400 and $\epsilon^{302}_{max.}$ 4,000. This compound was not investigated further.

Attempted Beckmann Rearrangement to 3β-Acetoxy-11:17a-dioxo-17b-aza-D-bishomoandrost-16-ene (XCIV)

To a solution of the foregoing oxime (200 mg.)

in pyridine (2.5 c.c.) was added a solution of p-acetaminobenzenesulphonyl chloride (200 mg.) in pyridine (1.25 c.c.). After 3 hours addition of water and chloroform isolation gave only unchanged oxime as did experiments using either benzene/PCl_5 (cf. Barnes, Barton, Fawcett and Thomas, J., 1952, 2339) or thionyl chloride (Regan and Hayes, J. Am. Chem. Soc., 1956, 78, 639).

3β-Acetoxy-11:17-dioxo-16-bromoandrostane (LXXXV)

To the diketone (XLIV) (1.00 g.) in acetic acid (AR.; 20 c.c.) containing hydrogen bromide (50% solution; 5 drops) was added a solution of bromine (463 mg. 1.0 M) in acetic acid (AR; 13.10 c.c.). After 3 hours ca. 3/4 of the colour had been discharged (rough visual estimation employing blank solutions). Further HBr solution (5 drops) was now added with vigorous shaking. The resultant pale yellow solution was now poured into water (200 c.c.) and extracted with chloroform to yield (after water and $NaHCO_3$ washing) as the main product a mixture of mono- and dibromides, m.p. 173-6° (softening 160°) $[\alpha]_D$ + 267.5° (c, 1.27). Repeated crystallisation from ethyl acetate afforded mixed crystals largely consisting of the dibromide m.p. 195-7° $[\alpha]_D$ + 230°

(c, 0.40). Found: C, 53.00; H, 5.85. $C_{21}H_{29}O_4Br$ requires C, 59.30; H, 6.85. $C_{21}H_{28}O_4Br_2$ requires C, 50.00; H, 5.60%. Further purification of material recovered from treatment of the total reaction mixture (above) with pertrifluoracetic acid afforded the monobromo ketone (LXXXV) as plates (ethyl acetate) m.p. 183-5° $[\alpha]_D$ + 125° (c, 1.06). Found: C, 58.90; H, 6.65%.

Attempted lactonisation of this bromoketone using pertrifluoracetic acid failed completely (as in the case of the homologous bromide).

Irradiation of 3β-Hydroxy-11:20-dioxo-18-benzylidene-14-iso-17-isoallopregnane (LX)

A solution of the diketone (270 mg.) in benzene (AR; 30 c.c.) contained in a silica test-tube was irradiated with U.V. light (source 10 mm. from tube base) at reflux temperature under nitrogen for 25 hours. During this time aliquot samples were withdrawn and rotations determined. The results are shown in Table I.

Table I

Time (hrs.)	$[\alpha]_D$ (c, 0.90, benzene)
0	- 48°
3	-43°
13.5	-22°
25	-14°

The solution was now evaporated and chromatographed in benzene over silica gel. From the early fractions eluted with benzene-ether (1 : 1) was obtained the starting material [m.p., mixed m.p., $[\alpha]_D$ - 26° (c, 1.0)] whilst fractions 7 - 9 (85 mg.) consisted of almost pure "lumi"-diketone (LXXVII) needles m.p.s 130° and 178-81° $[\alpha]_D$ + 10° (c, 1.80). The mixed m.p. determination of the isomeric ketones showed softening at 130° and later unsharp melting behaviour (180-5°). [A sample of the "lumi" diketone was melted (130°) and held on the Köfler block at 130-5° for 5 mins. On cooling to 60° a mass of prismatic needles grew from the melt. These now melted at 155-70° without softening at 130°].

Hydrogenation

(a) 3β-Hydroxy-11:20-dioxo-18-benzylidene-14-iso-17-isoallopregnane (62 mg.) was added to presaturated palladised charcoal (10%; 50 mg.) in ethyl acetate (5 c.c.). After shaking for 24 hours under hydrogen (0.96 M absorbed) catalyst was removed by filtration and the solvent evaporated. Recrystallised from ether, 3β-hydroxy-11:20-dioxo-18-benzyl-14-iso-17-isoallopregnane (LXXVIII) formed lustrous plates m.p. 193-4° $[\alpha]_D$ 0 ± 2° (c, 1.0) (no styryl absorption in the ultra-violet).

(b) When the "lumi" diketone (41 mg.) was hydrogenated under identical conditions, the same benzyl derivative was obtained as plates (40 mg.) m.p. and mixed m.p. 192-4° $[\alpha]_D$ - 1.0° (± 1°) (c, 3.0). Found: C, 79.60; H, 8.90. $C_{28}H_{38}O_3$ requires C, 79.60; H, 9.05%.

3β-Acetoxy-11:17a-dioxo-17b-aza-D-bishomoandrostane (XCVI)

To a mixture of 3β-acetoxy-11:17a-dioxy-D-homoandrostane (0.72 g.) in chloroform (14 c.c.) and sulphuric acid (AR; 4.0 c.c.) was added sodium azide (200 mg.) in small portions, the temperature being maintained at 0-5° with ice-cooling. After 30 minutes the reaction mixture was poured into crushed ice. After isolation

in chloroform, washing with sodium hydroxide solution and water, evaporation furnished the lactam (0.60 g.) as lustrous plates (methanol) m.p. 278-9° (after subliming into needles at 230-5°) $[\alpha]_D$ -76.5° (c, 1.01). Light absorption (nujol) 3175, 3057 cm^{-1} (-NH str.), 1727 cm^{-1} (OAc), 1706 cm^{-1} (>C = O), 1667 cm^{-1} (lactam >C = O), 1247 cm^{-1} (OAc). Found: C, 70.05; H, 8.50; N, 3.95. $C_{22}H_{33}O_4N$ requires C, 70.35; H, 8.85; N, 3.75%.

Attempted dehydration with Thionyl Chloride (Krinitsky and Carhart, Organic Synthesis, 32, 65.

The lactam (XCVI) (200 mg.) in dry benzene (10 c.c.) was treated with freshly redistilled thionyl chloride (0.5 c.c.) and the mixture heated at 80° for 4.5 hours. Ice-water decomposition of the excess of reagent and isolation in the usual way gave a brown gum (180 mg.) which showed no selective absorption in the ultra-violet between 220 and 300 mμ as well as in the infra-red between 2,240 and 2260 cm^{-1} (no - C ≡ N grouping).

3β-Hydroxy-11-oxo-18-benzylidene-13(17)-secoaetiochol-12-ene-20-carboxylic acid (LII)

As a result of many experiments, the following sequence was found most satisfactory. The foregoing

lactam (1.0 g.) was heated under reflux for 5 hours with acetic anhydride (50 c.c.) and sodium acetate (fused; 3 g.). Isolation into neutral and acidic fractions furnished the diacylamide (XCIX) (oil; 600 mg.; $\epsilon^{237}_{max.}$ 6,400) and the acid (XCVIII) (oil; 396 mg.; $\epsilon^{237}_{max.}$ 5,100) respectively. The crude acid (XCVIII) was now treated with benzaldehyde (0.5g.) in ethanol (50 c.c.) containing dry hydrogen chloride (40%). After 16 hours at room temperature the resultant recovered ester was hydrolysed with sodium bicarbonate-methanol (exactly as described in page E26). Isolation in the usual way afforded the benzylidene acid (LII) as yellow prisms m.p. 230-2° (methanol) $[\alpha]_D$ + 294° (c, 0.37; pyridine) identical in every respect with the acid prepared *via* the lactone (LVII) (see page E25). The yield of acid (XCVIII) could be improved by treatment of the diacylamide (XCIX) with a solution of sodium hydroxide (0.5 N; 25 c.c.) in ethanol (50 c.c.) for 16 hours at room temperature [cf. Battersby, *J. Chem. Soc.*, 1956, 2076]. In a typical experiment diacylamide (54.6 mg.) yielded the acid (XCVIII) as an oil (30.3 mg. $\epsilon^{237}_{max.}$ 4,800). Other experiments, including N-nitrosation either before or after

ring-opening and base-catalysed lactam hydrolysis under a wide variety of conditions led to inferior yields of the required seco-acid.

On attempted β-elimination using 0.2M KOH-EtOH only hydrolysis occurred, yielding the lactam -3β-ol. This was eluted from silica gel by ether-methanol (9:1) and crystallized in needles from methanol, m.p. 259-62° $[\alpha]_D$ - 73.2° (c, 0.66). Found: C, 72.30; H, 9.45; N, 4.50. $C_{20}H_{31}O_3N$ requires C, 72.05; H, 9.35; N, 4.20%. On acetylation this compound regenerated the lactam-3β-acetate.

3β-Acetoxy-17-bromo-11:17a-dioxo-17b-aza-D-bishomo-androstane (C)

3β-Acetoxy-11:17a-dioxo-17-bromo-D-homoandrostane (3.10 g.) in chloroform (60 c.c.) was treated with sulphuric acid (AR; 16.8 c.c.) and sodium azide (730 mg.) as in the cognate preparation described above. The resultant bromo-lactam (3.0 g.) recovered from the chloroform extract was crystallized from ethyl acetate as prisms m.p. 183-5° $[\alpha]_D$ - 12° (c, 1.09). Found: C, 58.15; H, 6.80; N, 3.45; Br, 17.9. $C_{22}H_{32}O_4NBr$ requires C, 58.10; H, 7.10; N, 3.10; Br, 17.60%.

3β-Acetoxy-11:17a-dioxo-17b-aza-D-bishomoandrost-16-ene (XCIV)

The above bromolactam (560 mg.) was added to refluxing collidine (bath temperature 190°). After fifteen minutes precipitation of collidine hydrobromide was judged to be complete and after a further 5 minutes the (cooled) mixture was dissolved in chloroform, the collidine removed in hydrochloric acid solution (6 N) and the extract washed with water and evaporated to leave the crude αβ-unsaturated lactam (XCIV). Chromatography over alumina afforded a fraction eluted with ether-methanol (9:1) which crystallised as prisms (ethyl acetate) m.p. 262° (subliming into plates, at 230°) $[\alpha]_D$ - 94.5° (c, 0.92). Light absorption: λλ shoulder 230-40 mμ; ε 3,000 * (Nujol) 3356, 3150 cm^{-1} (-NH str.), 1725 cm^{-1} (OAc), 1711 cm^{-1} (>C = O), 1675, 1648, 1620 cm^{-1} (αβ-unsaturated lactam*), 1255 cm^{-1} (OAc). Found: C, 70.70; H, 8.60; N, 4.10. $C_{22}H_{31}O_4N$ requires C, 70.75; H, 8.40; N, 3.75%.

* Cf. Edwards and Singh, Can. J. Chem., 1954, 32, 683.

Base-catalysed opening

A solution of the αβ-unsaturated lactam in 0,2 M solution of potassium hydroxide in ethanol (50 c.c.) was refluxed (steam bath) under nitrogen for 1 hour. Heating was maintained, after addition of water (10 c.c.) for a further 2 hours. Worked up in the usual way gave an acid fraction (oil; 50 mg.) having the light absorption $\epsilon^{239}_{max.}$ 7,000, and a neutral fraction (oil; 120 mg.) having the light absorption $\epsilon^{237}_{max.}$ 5,300. When the above lactam (50 mg.) and fused sodium acetate (150 mg.) were dissolved in acetic anhydride (20 c.c.) and the solution refluxed for a long time (30 minutes - 10 hours) the ultra-violet absorption spectrum showed that β-elimination had not taken place. 3β-Hydroxy-11-oxo-13(17)-secoaetiochol-12:16-diene-20-carboxylic acid (CI)

When the above lactam (300 mg.) was treated with a solution of conc. hydrochloric acid (2.5 c.c.) in glacial acetic acid (AR; 22.5 c.c.) on the steam bath, examination of the ultra-violet spectrum of aliquots removed at suitable intervals revealed that $\epsilon^{236}_{max.}$ 10,800 was achieved after 15 hours. The solution was poured into water extracted with ether and the

organic layer washed with water. The acidic fraction was isolated in sodium hydroxide solution. Acidification and working up in the usual way afforded the seco-acid as an oil (220 mg.) $\epsilon^{236}_{max.}$ 10,800 which was used directly for the next step. The neutral fraction (100 mg.) was dissolved in benzene (2.0 c.c.) and treated with redistilled thionyl chloride (0.2 c.c.). The mixture was heated at 80° for 3.5 hours. After suitable working up the gummy product thus obtained had no selective absorption in the ultra-violet between 220-300 mμ showing however a band in the infra-red at 2217 cm^{-1} ($-C \equiv N$).

3β-Hydroxy-11:20-dioxo-18-benzylidene-13(17)-secoallopregna-12:16-diene (CIV)

When the above crude acid (200 mg.) was dissolved in a stock solution of benzaldehyde-ethanol-hydrogen chloride aliquots revealed that $\epsilon^{325}_{max.}$ 22,600 was attained in 20 hours at room temperature. Ester hydrolysis and working up (see page E26) yielded the crude benzylidene acid (CX) as a pale yellow oil $\epsilon^{325}_{max.}$ 22,500. This was transformed to the oily methyl ketone (CIV) as described for the preparation of (LIX) ($R.COCl \longrightarrow R.CO.CHN_2 \longrightarrow R.CO.Me$; see page E26).

Attempted Cyclisation of (CIV)

The crude seco-ketone showed no change in the U.V. spectrum after prolonged refluxing with 0.2 M potassium ethoxide solution. When the seco-ketone (500 mg.) was dissolved in benzene (3 c.c.) and added to a solution of potassium (0.5 g.) in dry t-butanol (22 c.c.) and allowed to stand at room temperature for 16 hours an aliquot sample showed no selective U.V. absorption in the region 230-330 mμ.