STUDIES IN THE TERPENOID AND STEROID SERIES.

A thesis submitted to the University of Glasgow
for the degree of Doctor of Philosophy
in the Faculty of Science.

by

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SUMMARY.

Forty-seven pure triterpenoidal ketones and ten steroidal ketones have been synthesized in which the structure of ring A and part of ring B has been kept constant throughout both series. Kinetic measurements have been made of their rates of condensation, at 25°C, with benzaldehyde in 0.1N-ethanolic potassium hydroxide.

Comparison of the condensation rates with lanost-8-en-3-one, which has been taken as the standard throughout, shows a variation in rate over a factor of 43.

It is shown that these rate differences cannot be explained by classical steric effects, by electrostatic effects through space or by bond induction.

The experimentally obtained results are discussed in the light of conformational effects and a new effect described as "conformational transmission" is postulated in order to explain the rate anomalies. It is suggested that the distortion of valence angles produced by the introduction of unsaturation into a molecule may be transmitted to the reaction site in ring A by two possible paths. Either by a flexing of valence angles resulting in a change of atomic coordinates of the whole carbocyclic system, or, by a series of 1:3-diaxial interactions of suitably disposed methyl groups. Arguments deduced show that whilst the former path is, unexpectedly, the more

probable, the axiality of the substituents does, in certain circumstances, play an important role.

With the exception of a few of the very slowly reacting ketones there is no correlation with molecular rotation differences for the change 3β-alcohol to 3-ketone.

16-Benzylidene androst-4-ene-3:17-dione has been shown to possess an anomalous ultra-violet absorption spectrum.

SECTION I

ELECTRONIC AND STERIC INTERACTIONS.

Electronic Interactions.

In the latter part of this work arguments will be developed regarding the relative unimportance of electronic interactions in explaining the experimentally obtained data. Prior to the presentation of these arguments, therefore, it is advisable to give a brief summary of these effects and the main mechanisms whereby they function.

During the past few decades electronic interactions have been extensively investigated with the result that today these comparitively short range effects are quite well understood. There are three mechanisms by which interactions between non-reacting molecules may occur.

1. Electrostatic Interactions.

Electrostatic interactions will be dependent upon the external electrostatic field created by polarization of atoms or groups in a molecule. The effect will obviously be the greatest and most far-reaching when the degree of polarization is at its maximum. This will occur when integral charges are present as, for example, in a carboxylate anion, and the electrostatic potential created by such a unit charge will be non-directional and will vary with distance as an inverse first-power. Polarization resulting from dipoles will result in fields

of lesser strength and these will diminish more rapidly with distance according to an inverse second-power. They will be directional. Even more local directional fields varying according to an inverse third-power will arise from quadrupole polarization.

2. Electro-kinetic Interactions (Dispersion Forces).

As an outcome of the Heisenberg Uncertainty Principle molecules, even in their lowest state, must possess a zero-point energy. Thus even in monatomic molecules the electrons and nuclei will be vibrating with respect to one another. As a result there will be created a series of fluctuating dipole-induced dipoles giving rise to short range attractive forces which will vary with distance as an inverse seventh-power. These forces, first recognized by London[1], are known as dispersion forces for they may be calculated from optical dispersion data. They are frequently the strongest attractive forces and are the cause of condensation. They are non-saturative.

3. Exchange Interactions.

These are very short range forces but at small distances they become all-important. Where possible they lead to covalent bond formation, but, when this is not possible strong repulsive forces come into play due to the interpenetration of electronic sheaths.

Calculation of the magnitude of these forces is difficult but several functions have been proposed. Hill[2] suggested that they should vary as an inverse twelfth-power of the distance whilst on the basis of quantal calculations Slater[3] indicates that the variation of energy, E, with distance, r, should be represented by an exponential law of the type $E \propto e^{r/a}$, where a is a constant. This exponential form was shown to be satisfactory by Born and Mayer[4] for a series of alkyl halides where the value of the constant a was found to be the same for all the alkyl halides studied. An exponential function was used in calculations relating to the theory of racemization of optically active biphenyls[5] and also by Ingold et al[6] in developing a semi-quantitative theory of steric hindrance in bimolecular nucleophilic substitution. Evans, however, used both an exponential[7] and power[7] function (of the type br^{-9}), whilst Aston et al[8] found that an inverse fifth-power law takes into account both the attractive forces (due to the dispersion energy) and the repulsive forces.

It is these forces which are the cause of most forms of steric strain and steric hindrance and give rise to the greater stability of the chair conformation of cyclo-hexane over the boat form.

The above interactions between non-reacting molecules are also applicable to suitably disposed parts of the same

molecule; but, in addition to these, there are other characteristically internal types of interaction which are dependant upon the mode of binding. If this were not so then it would be expected that a particular grouping would carry with it into a molecule its own specific physical and chemical properties, and that these would not be modified by the presence of other groups already present in that molecule. As evidence for this[9] we may quote the non-additivity of dipole moments and the failure of, for example, the sum of the ultra-violet absorption spectrum of a simple ketone and simple olefin to equal that of an $\alpha\beta$-unsaturated ketone.

Thus complementary to the above direct interactions there is also a series of transmitted interactions dependant upon electron displacements. A condition of any electron displacement theory of this type is that it shall preserve the stable duplet and octet groupings of the electrons. There are two ways of achieving this[10] :-

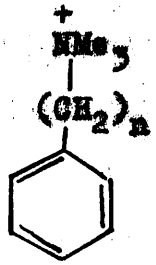
a) The bonding duplets may remain attached to their original atomic octets resulting in unequal sharing; the more electronegative atoms possessing a greater share of the electrons. This effect may be propagated along a chain of atoms by a series of dipole-induced dipoles (the force varying as an inverse fourth-power), and thus very rapidly diminishes. This is the inductive effect

and it is considered to be negligible after transmission through two or more saturatdd carbon atoms. The strength of the effect will be proportional to the initiating dipole and this will be greatest of all when the dipole is replaced by an integral charge. Thus the greatest magnitude of the inductive effect observable will be of the order shown in the example below - that is assuming that electron withdrawal from an aromatic ring favours meta-substitution. The percentage of meta-isomer formed in the nitration of compounds of type (I) is shown as a function of n, the number of saturated carbon atoms through which the inductive effect (originating from the positive charge on the nitrogen) passes.

n	% m-isomer
0	100[11]
1	88[12]
2	19[12]
3	5[13]

The inductive effect may be one of electron withdrawal (-I) or one of electron release (+I).

b) One duplet may be substituted for another in the same atomic octet. This effect is typical of conjugated



(I)

unsaturated systems and is known as the mesomeric (M) effect. Like the inductive effect a substituent may function by accepting (-M) or releasing (+M) electrons. When carried to an extreme form it results in the production of a dipolar molecule:-

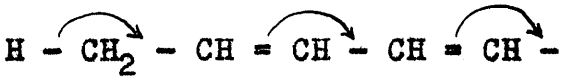
The actual state of the molecule is in between the polar and non-polar forms, the electrons being displaced to an extent which results in the molecule having a minimum of internal energy. The electron displacement will proceed until the resonance energy of the system is just balanced by the opposing electrostatic forces created by the electron displacement.

Both of the above effects exist in the normal state of the molecule and, as such, are to be regarded as permanent polarizations. Corresponding to these is the

polarizability of the system under the influence of an external reagent. The polarizability corresponding to the inductive polarization is known as the inductomeric effect and that corresponding to mesomerism is the electromeric effect. In as much as both these latter effects are ones of polarizability their direction is always such as to facilitate the reaction.

Hyperconjugation.

Carbon-hydrogen hyperconjugation was first observed by Baker and Nathan[14] who found that the electrons of a C-H bond in an alkyl group could conjugate with an unsaturated system in a manner similar to that of unshared electron pairs.



Hyperconjugation acts in the same direction as the inductive effect and, being dependant upon the number of suitably situated carbon-hydrogen bonds, decreases in the order methyl, ethyl, iso-propyl, tert-butyl.

In order to explain the difference in rates of bromination of tert-butyl benzene as compared to benzene a difference which could not be accounted for by an inductive mechanism alone, Berliner and Bondhus[15] invoked carbon-carbon hyperconjugation.

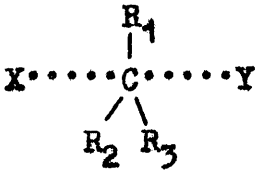
Hyperconjugation of carbon-halogen bonds has also been postulated.[16]

Steric Effects.

The first indication of the importance of steric effects upon the course of chemical reactions was observed during the classical work of Hofman[17], Claus[18], Kehrmann[19] and Meyer[20]. In subsequent years further information gradually accumulated[21]. However, a knowledge of steric effects depends upon a knowledge of steric orientation of reaction, and this, in turn, depends upon a knowledge of reaction mechanism, and thus no great understanding of steric effects was possible until the last one or two decades when the general mechanisms of organic reactions had been established.

These mechanisms fall into two general classes, unimolecular and bimolecular[22,23]. In a bimolecular nucleophilic substitution reaction (S_N2) the reagent, Y, attacks the molecule displacing a group X in a synchronous or concerted process in which the C-Y bond is being formed at the same time as the C-X bond is being broken. A nucleophilic unimolecular substitution reaction (S_N1) occurs in two steps, the first, which is rate determining, is a slow heterolytic fission of the C-X bond, and the second, rapid reaction of the resulting carbonium ion with the substituting anion.

Based upon experimental evidence of symmetrical exchange reactions[24] S_N2 reactions are considered to proceed with stereochemical inversion of configuration and thus the idealized transition state may be represented



where X·····C·····Y are linear and perpendicular to R_1, R_2 and R_3 which are coplanar. Thus, in the transition state five groups, or atoms, are to be found bonded or partially bonded to the carbon atom undergoing substitution. When the groups are large the compressional energy in the transition state will be greater than that in the initial state and steric retardation of reaction rate will be observed.

Conversely, in S_N1 reactions there is a decrease in the number of bonded groups attached to the relevent carbon atom and hence a decrease in the compressional energy[25] will occur in the initial rate controlling step resulting in a possible steric acceleration of reaction rate.

Dostrovsky, Hughes and Ingold[26] have thoroughly examined the S_N2 Finkelstein reaction for a series of

eight alkyl halides and have also provided a theoretical treatment of these systems[26]. The halides studied may be divided into two classes a) methyl, ethyl, iso-propyl and tert-butyl representing increasing α-branching, and b) ethyl, n-propyl, iso-butyl and neo-pentyl representing increasing β-branching with respect to the carbon atom undergoing substitution. Calculations showed that whereas there was a regular increase in the steric energies in the α-series, the β-series exhibited a greatly accelerated growth of steric energies. Whitmore et al[27] had previously drawn attention to the lack of reactivity of neo-pentyl halides, a fact which had remained unexplained under the classical views of steric hindrance. Thus knowledge of reaction mechanism and in particular an understanding of the transition state involved enabled this apparent anomaly to be correctly explained.

That relief of compression energy might accelerate reactions was first recognized by Brown in 1946[28,29] and, because it arises from the back of the molecule, has been termed B-strain.

Whilst other factors undoubtedly play a part, the rapid increase in solvolytic rate of alkyl halides accompanying increased β-branching must be due to a certain extent to relief of strain during the initial rate determining ionization, resulting in carbonium ion

formation. Thus if the rate of solvolysis of tert-butyl chloride be taken as unity the rates for tri-iso-propyl carbinyl chloride and di-tert-butyl iso-propyl carbinyl chloride are 230 and 40,000 respectively[30]. With less highly branched halides the rates are, of course, less; tert-butyl dimethyl carbinyl chloride solvolyses only 20 percent faster than tert-butyl chloride and the view that this small increase may well be due to polar causes has been proposed[31,32]. Electronic explanations appear to be eliminated, however, by the evidence[33] that (tert-butyl ethynyl) dimethyl carbinyl chloride and (tert-butyl vinyl) dimethyl carbinyl chloride solvolyse more slowly than the homologous methyl compounds $MeC{\equiv}C\text{-}CMe_2Cl$ and $MeCH{=}CH\text{-}CMe_2Cl$ where polar effects, unlike steric effects, may be transmitted across the unsaturated system.

In the case of the more highly branched alkyl halides an explanation based upon hyperconjugation has been proposed[32] and criticised[34]. The complexity of the situation is increased by virtue of the rearrangements which frequently occur during, or subsequent to, solvolysis and also, in some cases, the homogeneity of the starting materials has been doubtful.

Evidence has also been supplied[35] that tertiary alkyl iodides undergo S_N1 solvolysis more rapidly than

the bromides and the bromides more rapidly than the chlorides. Steric effects have been proposed as a contributing factor in this case[36].

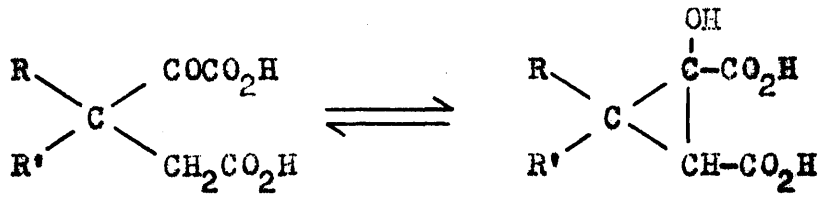
Steric effects may have their origin in either the compression of groups or atoms into spaces less than that dictated by their normal van der Waals radii, or the distortion of bond angles. Brown has classified the effects as F-strain, B-strain and I-strain according to their mode of operation.

The simplest of these is F-strain. It is, as envisaged by Kehrmann and Meyer, a simple bulk effect preventing free access of the attacking species to the reaction site. Thus, whilst it is possible to chlorinate $\alpha:\alpha:\alpha:\alpha':\alpha'$-pentafluoro-o-xylene by a free radical process to the hexahalogeno-derivative it is not possible to introduce a sixth chlorine atom into the equivalent pentachloro-o-xylene. The greater steric requirements of the large chlorine atoms already present are such that the sixth atom cannot approach sufficiently close to consumate the reaction.

Studies in the heats of dissociation of molecular addition compounds formed from amines and trimethyl boron[37] provides more information about F-strain and the difference in basicity between triethylamine and quinuclidine[37] also illustrates nicely this effect.

Examination of the ortho-meta and para-meta ratios of nitration products in mono-alkyl benzenes provides evidence of the importance of steric factors in ortho-substitution[38].

The position of equilibrium in compounds of the type



which show ring-chain tautomerism has been found to be dependant upon the size of the substituents R and R'[39]. Increasing the bulk of the substituents increases the amount of the cyclic tautomer. The reason may well be that the cyclic tautomer, with its ring angles of 60°, allows the R-C-R' angle to increase and hence relieves any steric compression resulting from the presence of large groups. This effect was predicted by Ingold[40] many years ago.

The mechanism of the Hofmann rule[41] relating to the decomposition of quaternary ammonium hydroxides has been subject to extensive investigation by Ingold and Hughes[42] who concluded that an electronic mechanism, largely inductive, was responsible for the direction of elimination. More recently Brown et al[34,43] have provided evidence which they interpret as pointing to steric control in

Hofmann eliminations.

Brown[44] has defined a further steric effect, I-strain, as "the change in internal strain which results from change in the coordination number of a ring atom involved in a chemical reaction". The normal bond angle for a tetrahedral carbon atom is 109° 28', whilst in the case of a trigonal carbon atom, carbonium ion or the three fixed groups in the transition state of an S_N2 reaction, the angle is 120°. In cyclopropane and cyclobutane ring systems the angles must be 60° and 90° i.e. the ring bond angle for a given carbon atom must be deformed approximately 50° and 20° when the ring atom is tetrahedral and 60° and 30° respectively when it is trigonal. There must thus be more strain in these ring systems when one, or more, atoms is in an sp^2 hybridized state. Hence carbonium ion formation and S_N2 reactions will be resisted, whilst addition to exocyclic double bonds will be favoured.

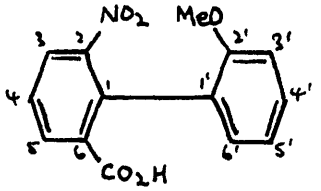
In five and seven to twelve membered rings angle strain is outweighed by conformational considerations and the change sp^3 to sp^2 hybridization is favoured. Similarly, conformational effects result in sp^3 states being more favoured than sp^2 in cyclohexane ring systems.

Buttressing Effects.

Calculations[45] based upon bond bending and stretching

force constants obtained from infra-red and raman spectra data show that whilst an energy of 2.9kcal/mole is required to alter the normal carbon-carbon single bond length by 0.1A only 0.7kcal/mole is necessary to change the normal tetrahedral valency angle by 10°. The importance of this resulting easy deformation of valence bond angles is particularly well illustrated in the racemization of optically active biphenyls[46] where substituents in the 2:2':6:6' positions can, by interference, restrict the rotation of the two nuclei around their common axis.

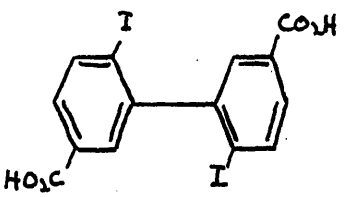
Adams et al measured the rates of racemization of biphenyls of type (II).



(II)

Whilst substitution with -OMe, -Me, -Cl, -Br, $-NO_2$ in the 5' position resulted in a slow decrease in racemization rate (over a factor of less than four) substitution at 3' caused a 200-fold decrease.

Even more striking are the results of Westheimer et al who measured racemization rates for the diiodo- and tetraiodo-biphenyls (III) and (IV). (III) racemizing



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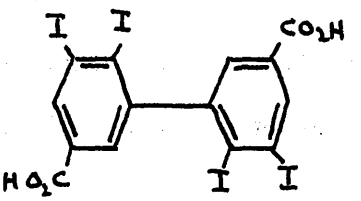

(IV)

30,000 times as fast as (IV).

For racemization to occur the 2 and 2' iodine atoms must be pushed out of the path of the 6' and 6 hydrogen atoms. In the case of the di-iodo- compound (III) this is relatively easy, whilst insertion of further iodine atoms at 3 and 3' provides a buttress for the iodine atoms already present, increasing thereby, the energy required to bend them out of the path of the passing hydrogen atoms.

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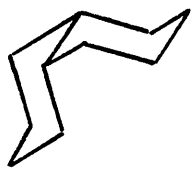
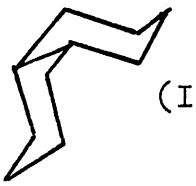
THE PRINCIPLES OF CONFORMATIONAL ANALYSIS.

The conformations of a molecule are defined as those non-superposable arrangements in space of the atoms of the molecule produced by the rotation or twisting of bonds. For most molecules this leads, theoretically, to an infinite number of conformations, but, in practice, energy considerations greatly restrict the number of preferred arrangements.

Discussion here will be limited to conformational effects in six-membered carbocyclic systems.

Cyclohexane, an energetically favoured structure as compared to other cyclic systems[1] can exist in only two conformations, the boat and the chair, which are free from angle strain[2]. Of these the chair is the more stable as shown by infra-red[3] and raman[4] spectroscopy, electron diffraction[5] thermodynamical[6] and theoretical[7] considerations. Consequently, on the assumption that the chair conformation is more stable than the boat there will be one unique conformation for trans-decalin (I) and two for cis-decalin (IIA and IIB), the two cis-forms being freely interconvertible[8].

(I)

(IIA)   (IIB)

As a modification of the semi-quantitative theoretical treatment of steric hindrance in bimolecular nucleophilic substitution developed by Ingold et al[9] Barton[7] was able to show that trans-decalin is more stable than cis-decalin and that the two-chair form of cis-decalin is more stable than the two-boat conformation. That this is so is borne out by electron diffraction studies[5,10] of cis-decalin in the vapour state and chemical evidence[11,12,13] of substituted cis-decalins.

The C-H bonds of the chair conformation of cyclohexane are of two distinct types. Six are arranged parallel to the three-fold axis of symmetry of the molecule, these are the axial (a) bonds, and six lie roughly in the plane of the molecule, these are the equatorial (e) bonds[14]. A given equatorial hydrogen atom is equidistant, approximately 2.5A, and skew to its four neighbouring hydrogen atoms (1:2-H:H-interactions); also, a given axial hydrogen atom is equidistant from, approx. 2.5A, and parallel to the other two axial hydrogen atoms on the same side of the molecule (1:3-H:H-interactions). With an axial substituent larger than

hydrogen the 1:3-diaxial distances become shorter than 1:2-diequatorial or equatorial-axial distances (owing to the parallel alignment of axial bonds) and thus the 1:3-repulsive interactions become all important. A given substituent will, therefore, if possible, adopt the more stable equatorial conformation. This is readily achieved in simple cyclohexane derivatives by passing the ring through a planar, or equivalent, conformation, a process restricted to the extent of a few k.cal/mole only. In condensed systems, however, this is generally not possible (cis-decalin is an exception), and epimerization must be carried out chemically. Thus equilibration of secondary alcohols with alkali[12] (involving an oxidation-reduction system[15]) results in an equatorial rich mixture the composition of which is roughly the same as that resulting from sodium-alcohol reductions of ketones[16].

Whilst the greater stability, on the basis of steric requirements, of the equatorial substituent cannot be overemphasized it is to be appreciated that electronic requirements can invert the normal stability order. This is the case with trans-cyclohexane-1:2-dicarboxylic acid which in solution adopts the diaxial configuration owing to the large electrostatic repulsion of the carboxylate anions[17]. That an integral charge is not

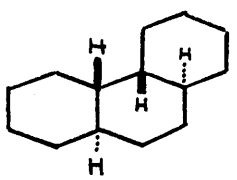
necessary to achieve this and that dipole interaction may be sufficient is exemplified by 2-bromo-cyclohexanone where the bromine atom prefers to be axial. Here the repulsion of the C=O and C-Br dipoles is reinforced by the non-bonded interaction arising from the eclipsed relationship of the groups (see below)[18].

Cis-cyclohexane-1:3-diol prefers to adopt an axial conformation[19] for, in this form, hydrogen bonding of the hydroxyls is possible.

It follows from the close proximity of the 1:3-axial substituents that these will be more hindered sterically than equatorial substituents; consequently, axial hydroxyl groups will be harder to esterify and hydrolyse[12,20,21] and will be more easily eluted from adsorbents[22] than will the epimeric equatorial alcohols. Conversely, an axial hydroxyl will be the more readily oxidized by chromic or hypobromous acids[23] (the rate determining step being the attack of nucleophilic reagent upon the equatorial hydrogen atom[24]. Chromic acid oxidations of axial hydroxyl groups have been shown to be susceptible to steric acceleration[25]. Also, as might be expected, axial esters solvolyse more rapidly than their equatorial isomers[26].

The most stable condensed cyclohexane systems will be those with the greatest number of rings in the chair

form, although under certain conditions a cyclohexane ring in a polycyclic system* may be forced to adopt a boat conformation. This is the case in trans-syn-trans-perhydrophenanthrene (III) which is less stable than the trans-syn-cis-isomer (IV)



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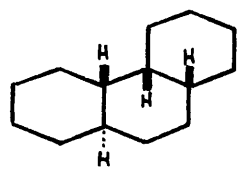

(IV)

The low stability of the boat conformation as compared to that of a chair is due a) to the eclipsed relation (resulting in non-bonded repulsive interactions) of the four pairs of hydrogen atoms on the 'sides' of the boat and the 1:4-carbon atoms and b) to the large non-bonded 1:4-H;H-interactions. The energy barrier between the chair and the boat conformations has been assessed at values varying from 5.6kcal/mole (a value which does not take into account the considerable 1:4-H:H-interactions) to 9-10kcal/mole[27].

The considerable compulsion for the boat conformation to revert to the chair conformation is well illustrated

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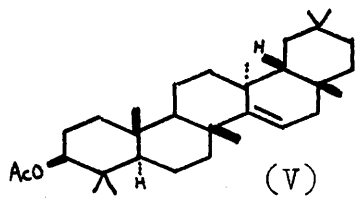
* 1:2:2- and 2:2:2-bicyclo-type systems where a boat is stucturally necessary will not be discussed here.

by the ease with which taraxerol acetate (V) rearranges under mildly acidic conditions to β-amyrin acetate[28].



(V)

$\xrightarrow{H^+}$ β-Amyrin acetate.

However, under favourable circumstances the reverse conformational change may be induced. This is so in the case of 3α:9α-epoxide formation in cis-A/B fused steroids[29].

Conformational effects are particularly apparent amongst spectroscopic properties. Infra-red spectroscopy shows that in general C-X stretching frequencies are higher for equatorial substituents than for axial ones. This has been found so for the C-O stretching frequencies of secondary alcohols[30] and acetoxy- and methoxy-groupings[31] in steroids and simpler compounds. Further, a carbonyl stretching frequency is increased by the presence of an α-equatorial halogen substituent but unaltered by α-axial substituents. These shifts have been explained[32] as the result of the stretching motion of the equatorial substituent inducing expansion and contraction of the ring system. The axially substituted isomer will not experience this effect to such a marked extent and thus the restoring force, and hence frequency, will be less.

However, a recent study[33] of 3α(a)- and 3β(e)-hydroxy-triterpenoids has shown that both the O-H and C-O stretching frequencies are higher for the axial than the equatorial hydroxyl. It is suggested[33] that this is due to the presence of the gem-dimethyl grouping at $C_{(4)}$.

The ultra-violet carbonyl absorption band of α-halogeno ketones is also susceptible to the conformation of the halogen substituent, equatorial halogen causing hypsochromic shifts and axial halogen bathochromic shifts[34]. α-Ketols and their acetates behave similarly[35].

It has been demonstrated[11,20,36] that ionic E2 reactions proceed most readily when all four centres are coplanar and anti-parallel; that is, 1:2-diaxial in rigid cyclohexane systems (Bordwell et al have provided an interesting exception[37]). This is to be compared to unimolecular pyrolytic eliminations of esters which require a cis-configuration for the eliminating groups[38] (see below).

As an extension of preferred diaxial elimination it has been established that addition to double bonds preferentially follows a trans-diaxial path[39], that electrophilic and nucleophilic opening of steroidal epoxides results in the formation of diaxial products[39] (see Cookson and Hudec[40]), and ring closure of halogeno-hydrins proceeds faster in the case of the trans-diaxial

isomer than with the trans-diequatorial[39,41].

The action of nitrous acid upon the epimeric 17a-α- and 17a-β-hydroxy-17β-amino-17a-methyl-D-homo-steroids[42] resulting in 17aα-17α-epoxide formation in the one case and methyl group migration to give 17a-ketone-17α-methyl compound in the other is an excellent example of conformational control of reaction path. The somewhat analagous reaction of dehydrating agents (in particular phosphorus pentachloride) upon the epimeric 3α- and 3β-hydroxy triterpenoids to give A-nor-hydrocarbons and Δ^2-unsaturated compounds is mentioned in the next section.

In connection with 1:2-pyrolytic eliminations it should be noted that although both the projected valency angles and distances between trans-1:2-diequatorial and cis-equatorial-axial substituents are identical it is easier to bring an axial and equatorial bond coplanar (this tends to flatten the ring and reduce the non-bonded interactions) than two equatorial bonds (which tends to increase the ring puckering, and hence non-bonded interactions). Thus 1:2-pyrolytic eliminations involve cis-substituents as does the formation of iso-propylidene derivatives of cyclohexane 1:2-diols[43].

Exchange of one sp^3 hybridized carbon atom for an sp^2 hybridized atom as in cyclohexanone does not involve distortion of the ring valency angles[44] but it does

result in the eclipsing of the carbonyl group and its two α-equatorial substituents. Introduction of two adjacent sp^2 hybridized atoms into a six-membered ring, as in cyclohexene, necessitates the coplanarity of four carbon atoms; the remaining two having the choice of being both on the same side of the plane produced by the coplanar atoms resulting in a half boat conformation, or, of being one on either side of the plane giving a half chair conformation. An energy difference of 2.7kcal/mole in favour of the half chair has been estimated[45].

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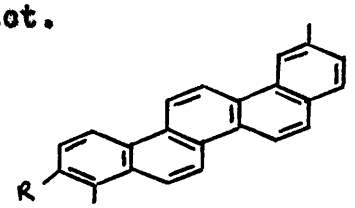
REVIEW OF THE CHEMISTRY OF THE TRITERPENOIDS.

The very nature of the work presented in this thesis dictated to a large extent the type of structure required by the compounds under investigation. It is obviously necessary to have a large molecule of rigid structure and known configuration and conformation in order to minimise, in so far as this is possible, the errors attending any attempt to fix the spatial position of the constituent atoms. The natural product field of tetra- and penta-cyclic triterpenoids and steroids presented such compounds and in the following section a brief review is presented of the triterpenoids and how the structures of the various parent compounds used in this investigation have been established.

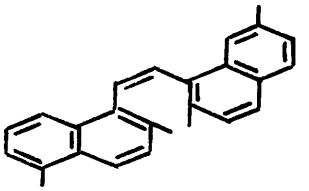
The triterpenoids which are found largely in the plant kingdom as esters, glycosides or in the free state are $C_{(30)}$ or $C_{(31)}$ compounds. They are either divisible into six isoprene units (empirical isoprene rule) or, more generally, may be regarded as being derived or built up from actual or hypothetical precursors, which obey the empirical isoprene rule, of the squalene, farnesol and geraniol type by accepted reaction paths (biogenetic isoprene rule). They are best classified according to

the number of carbocyclic ring systems present when they fall into three groups:- the tetra- and penta-cyclic groups and the squalene group which is based upon structure rather than the number of rings present.

Selenium or palladium-charcoal dehydrogenations have played a large part in the establishment of carbon skeletons, and, although the pentacyclic triterpenoids tend to rupture into two main naphthalenic fractions, larger pentacyclic hydrocarbons (I; R=H and R=OH) characteristic of the whole carbocyclic structure have been isolated. Particularly noteworthy is the hydrocarbon (II) which has been obtained from gypsogenin[1,2] and aescigenin[3], and was subsequently synthesized[4], in which all but four of the original carbon atoms remain intact.



(I)

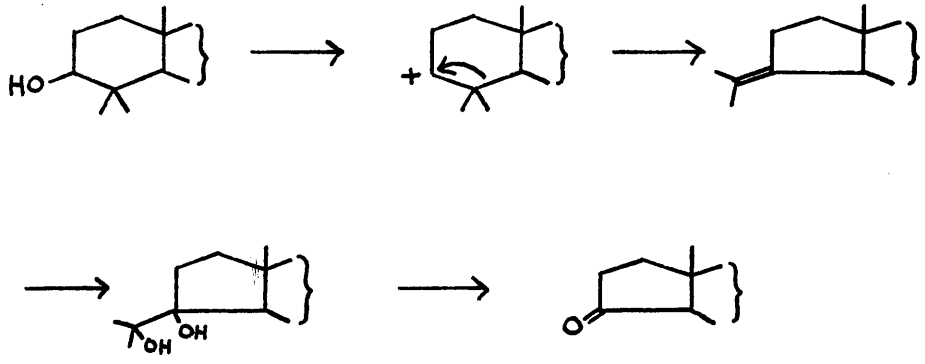


(II)

The main aromatic product from the dehydrogenation of tetracyclic triterpenoids e.g. lanosterol[5], dihydroeuphol[6] and elemadienolic acid[7] is 1:2:8-trimethylphenanthrene.

An important reaction sequence which shows the

presence of a gem-dimethyl group at $C_{(4)}$ adjacent to an equatorial (β) hydroxyl group situated in a six-membered ring is as follows. Treatment of the alcohol with phosphorus pentachloride gives a ring A-contracted product which with osmium tetroxide yields a dihydroxy compound; cleavage of this with periodic acid or lead tetra-acetate gives acetone and a five-membered ketone[8,9]. The rare 3α-(axial) hydroxy compounds undergo straightforward elimination to Δ^2-compounds in the initial step.



Many of the important inter-relationships of members within a group have been achieved by reaction sequences designed to convert carboxyl groups to primary alcohols or methyl groups[10,11].

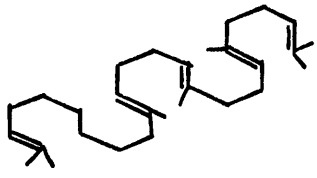
THE SQUALENE GROUP.

This group consists of only three members - each in its own way being unique.

Squalene itself (III) is acyclic. Its structure

deduced by Heilbron and his coworkers[12] was rapidly followed by a synthesis[13] from condensation of two moles of farnesyl bromide with potassium or magnesium. This synthesis, like most of the subsequent ones[14,15], resulted in the formation of an inseparable mixture of squalene and its many isomers. Recently however, the preparation of geometrically and stereochemically homogeneous squalene, identical with the naturally occuring compound, has been reported[16]. That the double bonds are arranged fully transoid throughout the molecule was shown by Nicolaides and Laves[17].

It is perhaps worthy of mention here that the tetracyclic triterpenoids recently isolated from dammar resin[18] have carbon skeletons which are squalenoid, e.g. dammarenediol (IV).



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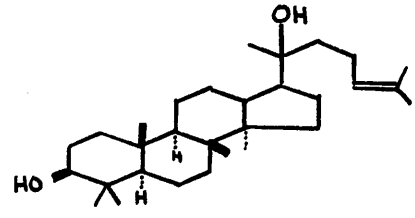

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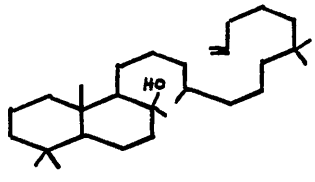

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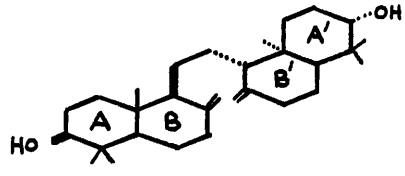


(VI)

The structure of the tricyclic ambrein (V) is due to Ruzicka and Lardon[19] and Lederer and his colleagues[20].

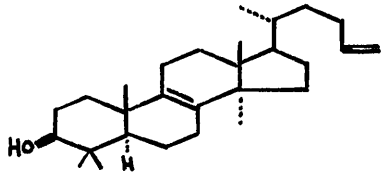
Barton and Overton[21] have shown that the structure of the only other member of this group, α-onocerin, is correctly represented by (VI). Proof of this structure is based upon a) dehydrogenation evidence, b) proof of the presence of two $-CH_2.CH_2.CH(OH).C.Me_2-$ groupings (rings A and A') and two $-CH_2.C(:CH_2).CH$ groupings (rings B and B'), c) proof of the equivalence of the two hydroxyl groups and the complete symmetry of the molecule. The stereochemistry was deduced from conformational and molecular rotation evidence and the absolute configuration at $C_{(5)}$, $C_{(5')}$, $C_{(10)}$ and $C_{(10')}$ has been established[22].

THE TETRACYCLIC TRITERPENOIDS.

The tetracyclic triterpenoids may be sub-divided into the lanosterol and euphol groups; the latter having the same carbon skeleton but being stereoisomeric at $C_{(13)}$, $C_{(14)}$ and $C_{(17)}$. Variations in these groups are apparent e.g. the fungal acids which are $C_{(31)}$ compounds where the extra carbon atom, in every case, is attached in the side chain at $C_{(24)}$, and compounds containing cyclopropane rings, (these strictly being pentacyclic).

The Lanosterol Group.

The lanosterol group proper consists of four naturally occuring members, lanosterol (VII), dihydro-lanosterol (VIII), agnosterol (IX) and dihydro-agnosterol (X) all of which are found in the non-saponifiable matter of woolfat[23] and have been inter-related.



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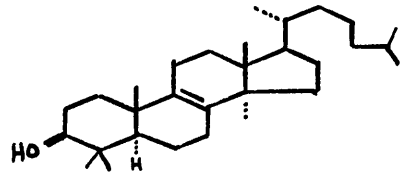

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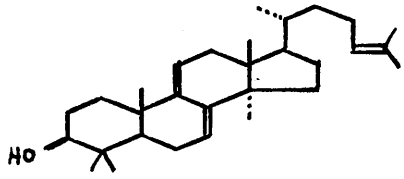

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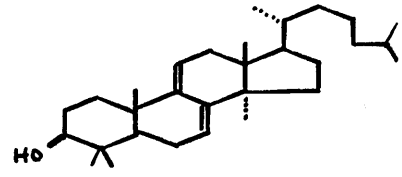


(X)

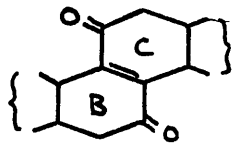
Like the other tetracyclic triterpenoids they do not obey the empirical isoprene rule although they do conform to the biogenetic isoprene rule[24].

Lanosterol.

Lanosterol posses two double bonds; one inert and tetra-substituted[25,26], the other as an easily hydrogenable isopropylidene group[5]. The phosphorus pentachloride

reaction sequence mentioned above established the nature of ring A[8,9]. Further confirmation of the six-membered nature of ring A and the presence of a free methylene group adjacent to the hydroxyl was provided by Ruzicka et al[5].

Chromic acid oxidation of lanostenyl acetate gives a fully transoid enedione (XI)[26,28,29] the double bond of which is easily reduced by zinc dust and acetic acid. Further oxidation with selenium dioxide affords a dienedione (XII) and a dienetrione (XIII) whose structures were assigned largely on spectroscopic evidence.



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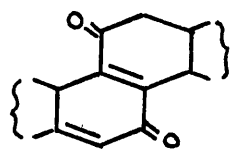

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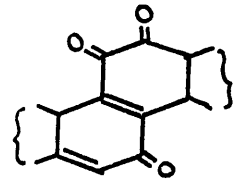


(XIII)

The presence of an α-diketone system in (XIII) was shown by oxidation to a dicarboxylic acid without loss of carbon[30,31].

Evidence for the $C_{(13)}$ and $C_{(14)}$ angular methyl groups has been provided by isomerization experiments[30] and by dehydrogenation[5,32,33].

Oxidation of a lanosterol derivative has given a ring D ketone which on infra-red spectroscopic evidence is shown to be five-membered[34,35]. Further, bromination

experiments revealed the presence of only one adjacent methylene group[34,35] indicating that the side chain must be attached at either $C_{(15)}$ or $C_{(17)}$. That $C_{(17)}$ is correct was shown by oxidative degradation[36] and by X-ray analysis of lanosteryl iodo-acetate[37] which confirmed independently in every detail the structure (and stereochemistry) of lanosterol.

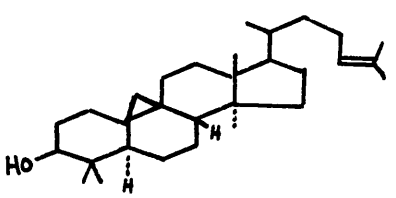
Molecular rotation data showed that the A/B ring junction is trans, that the $C_{(10)}$ methyl is β-oriented as in the steroids and penta-cyclic triterpenoids[38], that the $C_{(14)}$ methyl is α-oriented and that the configuration at $C_{(20)}$ is as shown in (VII). The $C_{(3)}$ hydroxyl is in the more stable (β) configuration on physical and chemical evidence. The high degree of steric hindrance observed with 11-oxo- and 11β-(axial) hydroxy compounds requires that the $C_{(13)}$ methyl group be on the same side of the molecule as the $C_{(10)}$ methyl, whilst conformational arguments based upon the method of preparation of the saturated parent compound, lanostanol, dictates that the B/C junction is trans and in the same sense as the cholestane derivatives. The side chain is attached in the more stable configuration.

Further confirmation of the stereochemistry comes from the high biological activity of 14-methyl 11-oxo-progesterone synthesized from lanosterol[39]. The

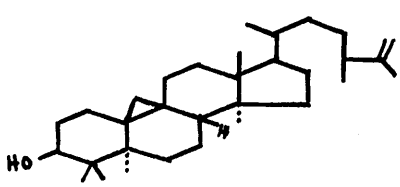
physiological activity of the progestational hormones being highly dependent upon both structure and configuration.

Finally, complete proof of structure and stereochemistry has been provided by the total synthesis of lanosterol, dihydro-lanosterol and agnosterol from cholesterol[40]. This, together with the already known conversion of lanosterol into dihydro-agnosterol represents the first total synthesis of all four wool-fat triterpenoids, and the first total synthesis of any cyclic triterpenoid.

The structure of two lanosterol type terpenoids containing cyclopropane rings have recently been established, cycloartenol (XIV)[41,42,43,44,45] and cyclolaudenol (XV)[46]. It should be noted that both these compounds have their B/C ring junction cis.



(XIV)



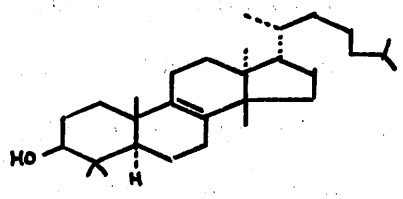
(XV)

Euphol.

The inert double bond, the isopropylidene group and the similarity of rings A, B and C to lanosterol have been

established by standard procedures and by experiments comparable to those carried out on lanosterol[25,47,48]. The nature of the side chain was also established by methods similar to those used for lanosterol[49]. The size of ring D was deduced by an ingenious indirect route dependant upon infra-red spectroscopic data[45,50,51].

Treatment of dihydro-euphol (euphenol) (XVI) with acid gives isoeuphenol (XVII)[52,53]. Oxidation of isoeuphenol gave a diketone (XVIII)[52] whose structure was assigned[50,51] on the basis of the hindered nature of both carbonyls, the consumption of five moles of bromine and spectroscopic evidence for the presence of two $-CH_2.CO-$ groups. From this the structure of isoeuphenol was deduced as (XVII). The rearrangement of (XVI) to (XVII) is explained[51] as a concerted double methyl group migration initiated by a conformational driving force provided by the greater degree of steric strain present in euphenol as compared to isoeuphenol. This also provides evidence for the stereochemistry of the C/D junction. The configuration of the side chain of euphenol was established by Ruzicka et al[54] and the isolation of D-(-)-2:6-dimethyl heptanoic acid[54] from degradational experiments established the configuration at $C_{(20)}$. Molecular rotation arguments have established the configuration at $C_{(3)}$, $C_{(5)}$ and $C_{(10)}$[51,52].



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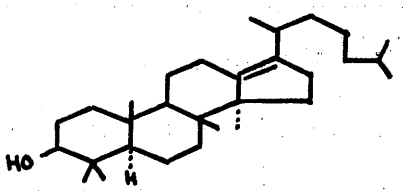
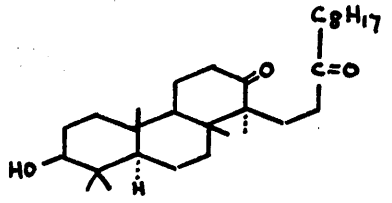


(XVII)

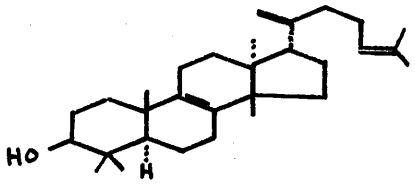


(XVIII)

Tirucallol.

The chemistry of tirucallol (XIX) and its dihydro-compound, tirucallenol, runs completely parallel to that of euphol and euphenol. The same degradational methods have been applied[55].

Oxidation of isotirucallenol gave an $\alpha\beta$-unsaturated ketone, which, on ozonolysis gave the keto-acid (XX) identical with the corresponding isoeuphenol oxidation product, and L-(+)-2:6-dimethyl heptanoic acid. Thus isotirucallenol differs only from isoeuphenol in being stereoisomeric at $C_{(20)}$.



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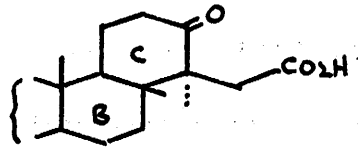


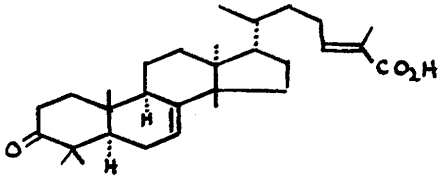
(XX)

Masticadienonic Acid.

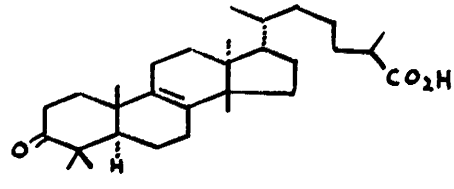
The structure of a new tirucallol type triterpenoid, masticadienonic acid (XXI), has recently been established by Barton and Seoane[56].

Masticadienonic acid differs from tirucallol only in possessing an $\alpha\beta$-unsaturated acid function instead of the terminal isopropylidene grouping and in the position of the nuclear double bond. Whilst catalytic hydrogenation over palladium-charcoal readily reduces the side-chain double bond, attempted hydrogenation of the nuclear double bond with platinum in acetic acid results only in the formation of dihydro-isomasticadienonic acid (XXII).

Lithium aluminium hydride reduction of dihydro-



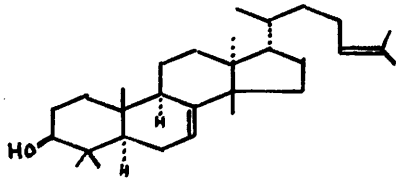
(XXI)



(XXII)

masticadienonic acid gave dihydro-masticadienediol; further reduction with lithium aluminium hydride of the ditoluene-p-sulphonate followed by acetylation and rearrangement of the acetate over platinum in acetic acid gave tirucallenol acetate.

The rearrangement of masticadienonic acid, its anomalous molecular rotation values and its negative reaction towards the Zimmermann reagent[57] (m-dinitrobenzene - usually indicative of a carbonyl group with a sterically unhindered α-methylene) are exactly paralleled in butyrospermol (XXIII), whose structure has also recently been established[58].



(XXIII)

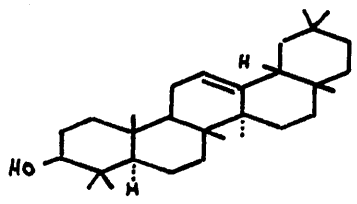
THE PENTACYCLIC TRITERPENOIDS.

The pentacyclic triterpenoids may be subdivided into three groups.

The β-Amyrin Group.

The pentacyclic alcohol β-amyrin (XXIV; R=H) has been subjected to the usual dehydrogenation procedures (indicating the nature of the carbocyclic system) and to

ring A-contracted experiments[59] indicating the general structure of that ring. The non-hydrogenable double bond at $C_{(12)}$-$C_{(13)}$ readily lactonizes when a carboxyl group is present at $C_{(17)}$ as in oleanolic acid (XXIV; R=CO_2H). Further information about rings A and B has been obtained by oxidative degradations after protection of the double bond by lactonization[59,60].



(XXIV)

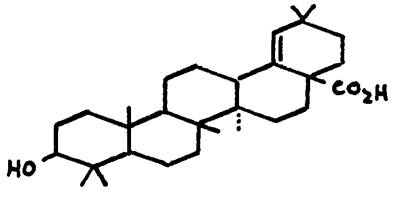
By oxidative and pyrolytic procedures oleanolic acid has been split into two identifiable bicyclic systems, and the relationship of the double bond to the carboxyl group has been established by pyrolytic experiments on the 9(11):13(18)-diene-12:19-dione obtained by selenium dioxide oxidation.

Conformational, mechanistic and molecular rotation arguments as well as physical and chemical properties have been used in establishing the complete stereochemistry of β-amyrin type triterpenoids[11,38,61,62].

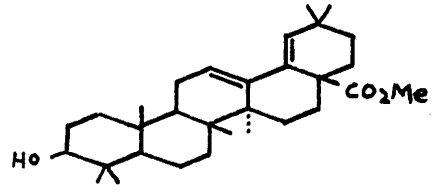
Complete confirmation of the assigned structure comes from the X-ray analysis of methyl oleanolate iodo-

acetate[63].

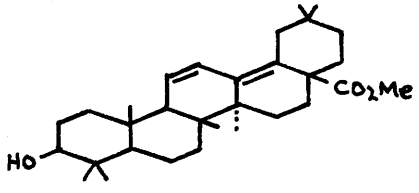
The structure of morolic acid (XXV) has been established by Barton and Brooks[11]. It was shown to be a double bond isomer of oleanolic acid by a) treatment of methyl morolate acetate oxide with mild acid, yielding methyl isodehydro-oleanolate (XXVI) isomerized by strong acid to the known methyl dehydro-oleanolate[64], which was recognized by Barton and Brooks as (XXVII) and b) the facility with which morolic acid could be decarboxylated.



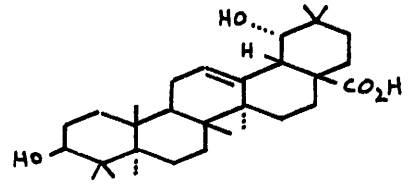
(XXV)



(XXVI)



(XXVII)



(XXVIII)

Starting from siaresinolic acid (XXVIII) Barton, Brooks and Holness[65] have synthesized morolic acid.

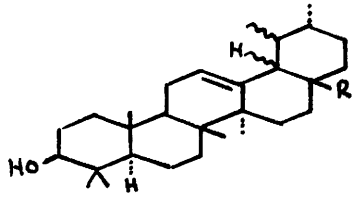
The structure of siaresinolic acid has been assigned largely on the work of Bilham, Kon and Ross[66] and Ruzicka and his colleagues[67]. Proof of the stereochemistry at

$C_{(18)}$ was provided by Barton and Holness[62].

The α-Amyrin Group.

Some of the finer details of the stereochemistry of α-amyrin have not yet been proven unambiguously but there is sufficient evidence to warrant the use of structure (XXIX; R=CH_3). Many of the reactions of α-amyrin parallel those of β-amyrin although the double bond is even more sterically hindered.

Molecular rotation differences suggest that rings A and B are similar to β-amyrin and this has been confirmed by Ruzicka et al[68] who have also provided evidence for rings D and E.



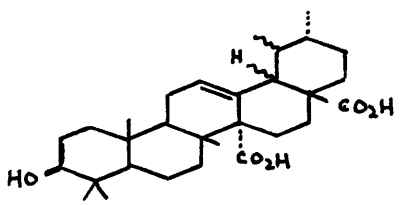
(XXIX)

By oxidative and pyrolytic proceedures similar to those employed on β-amyrin the whole molecule has been split into two identifiable bicyclic systems comprising rings A and B, and D and E.

In the light of the stereochemistry of oleanolic acid the configuration of all asymmetric centres, other than $C_{(17)}$, $C_{(18)}$ and $C_{(19)}$ can be regarded as having

been elucidated[68,69]. The conversion of an α-amyrin compound into a β-amyrin derivative[70] shows that the configuration at $C_{(17)}$ is the same in both series. Corey and Ursprung[71] have reviewed the α-amyrin stereochemistry.

Ursolic acid (XXIX; R=CO_2H) bears the same relationship to α-amyrin, into which it has been converted[72], as does oleanolic acid to β-amyrin. Its structure was largely elucidated by the Japanese workers Huzii and Osumi[73]. Related to ursolic acid is quinovic acid whose structure was first proposed by Ruzicka and his colleagues[74] and later confirmed by Barton and de Mayo[75] and the original workers, who converted it[76] by unambiguous methods into phyllanthol (XXXI).



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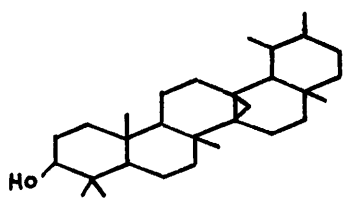


(XXXI)

The Lupeol - Betulin Group.

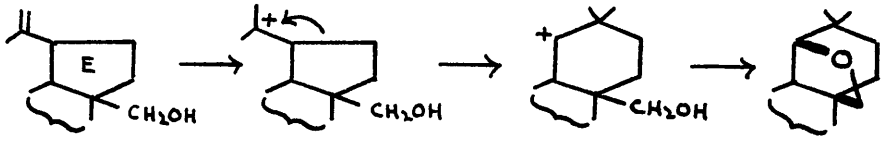
The ethylenic linkage of betulin (XXXII; X=H, (β)-OH; R=CH_2OH), betulinic acid (XXXII; X=H, (β)-OH; R=CO_2H) and lupeol (XXXII; X=H, (β)-OH; R=CH_3) is easily hydrogenated[77] and is present as an isopropenyl

group[78]. It is not attached to a quaternary carbon atom[79].

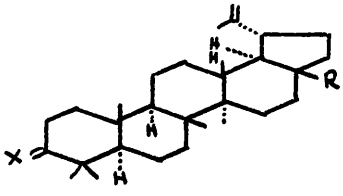
The constitution of lupeol (XXXII; X=H, (β)-OH; R=CH_3) was established by acid isomerization of ∝-lupene (XXXII; X=H_2; R=CH_3) and lupenone (XXXII; X=O; R=CH_3) to what was regarded as olean-13(18)-ene (XXXIII; X=H_2) and olean-13(18)-en-3-one (XXXIII; X=O) respectively[80], although these compounds have subsequently been shown[81] to be mixtures of the 13(18)-ene and 18-iso-12-ene. Betulin and betulinic acid have been similarly treated[82]. Betulonic acid (XXXII; X=O; R=CO_2H) has been directly related to morolic acid (XXV).

The stereochemistry of ring E has been established by Jones et al[83] and Barton and Holness[62].

Treatment of betulin with acid causes isomerization to allobetulin (XXXIV).



(XXXIV)



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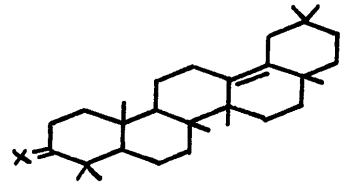

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SECTION III

REACTION SEQUENCES USED IN THE PREPARATION OF THE TRITERPENOID KETONES.

It is convenient, at this point, to summarize the various routes taken in obtaining the compounds used in this investigation.

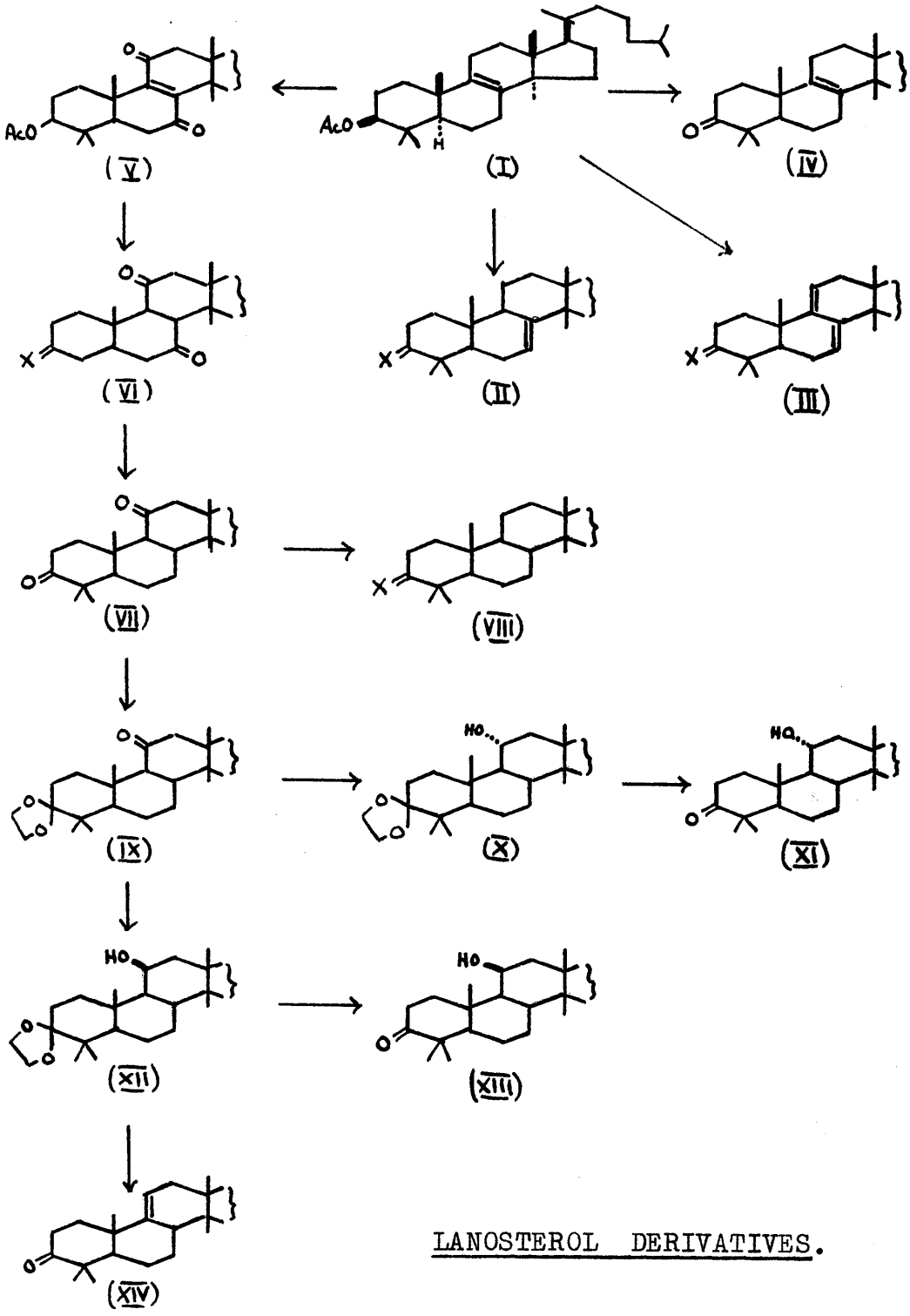
In the preparation of the ketone samples used for kinetic measurements special precautions were taken to ensure complete purity. All ketones were crystallized to constant melting point and rotation, and, where applicable, to constant ultra-violet absorption.

Lanosterol Derivatives.

Acetylation of 'technical' lanosterol and hydrogenation gave lanostenyl acetate (I), from which all the lanosterol type ketones were synthesized.

Isomerization of (I) with hydrogen chloride in chloroform gave an equilibrium mixture of the Δ^7- and Δ^8-acetates[1], separated by chromatography after brief but vigorous treatment with chromium trioxide in acetic acid. Hydrolysis and oxidation of the Δ^7-lanostenyl acetate (II; X=H, OAc) gave Δ^7-lanostenone (II; X=O).

Selenium dioxide oxidation of lanostenyl acetate (I) afforded dihydroagnostenyl acetate[2] (III; X=H, OAc); hydrolysis and oxidation provided dihydroagnostenone (III; X=O).



LANOSTEROL DERIVATIVES.

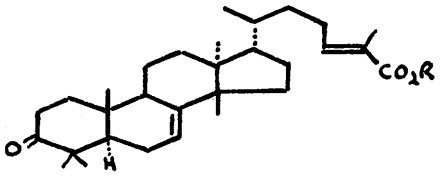
Δ^8-Lanostenone (IV) was obtained from lanostenyl acetate.

Chromic acid oxidation of (I) gave lanost-8-ene-7:11-dionyl acetate[3] (V) which was smoothly reduced by zinc and acetic acid to the saturated lanostanedionyl acetate (VI; X=H, OAc). Hydrolysis and oxidation yielded lanostane-3:7:11-trione (VI; X=O).

Wolff-Kishner reduction of lanostane-7:11-dionyl acetate (VI; X=H, OAc) provided, according to the conditions employed, lanostan-11-onyl acetate[4] (VII; X=H, OAc) or lanostanyl acetate[5,6] (VIII; X=H, OAc). Hydrolysis and oxidation gave lanostane-3:11-dione (VII; X=O) and lanostan-3-one (VIII; X=O) respectively.

Lanostane-3:11-dione (VII; X=O), using the conventional method, was converted into the 3-ethylenedioxy derivative (IX), reduction with sodium in n-propyl alcohol and with lithium aluminium hydride furnished the epimeric alcohols 3-ethylenedioxy-lanostan-11α-ol (X) and 3-ethylenedioxy-lanostan-11β-ol (XII) respectively. Removal of the ketal grouping with hot dilute acetic acid afforded 11α-hydroxy-lanostan-3-one (XI) and 11β-hydroxy-lanostan-3-one (XIII). Brief treatment of 3-ethylenedioxy-lanostan-11β-ol (XII) with perchloric - acetic acids gave, quantitatively, lanost-9(11)-en-3-one (XIV).

Masticadienonic acid (XV; R=H) and isomasticadienonic acid (XVI) were obtained from gum mastic[7]. Methylation of the former with ethereal diazomethane afforded methyl masticadienonate (XV; R=Me). Hydrogenation of isomasticadienonic acid with palladium-charcoal provided dihydro-isomasticadienonic acid (XVII).



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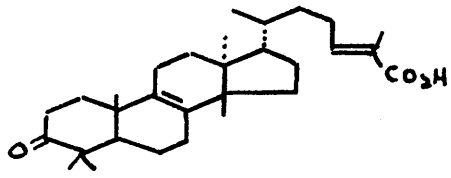

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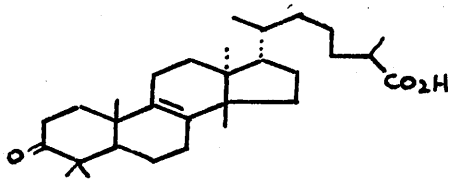
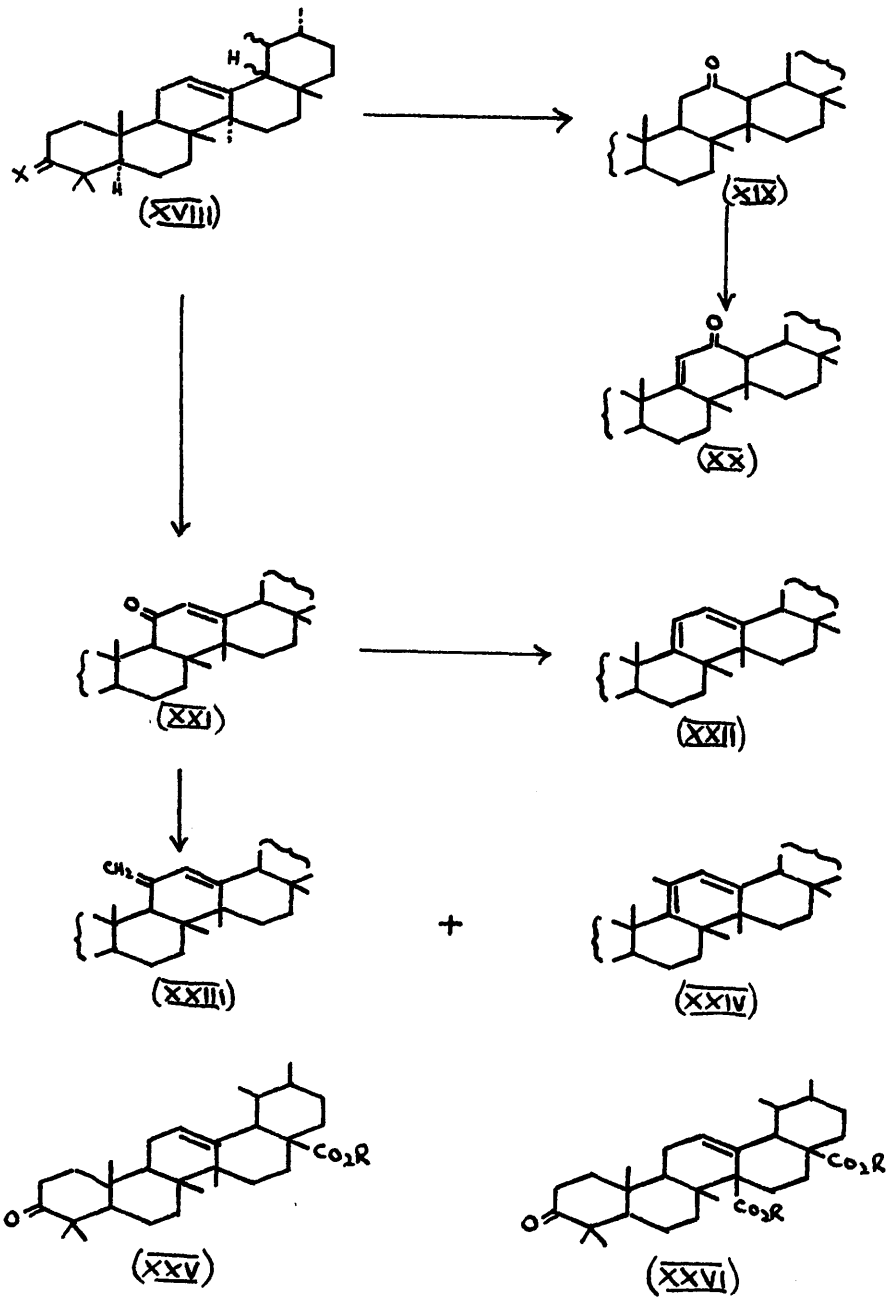


(XVII)

α-Amyrin Derivatives.

Ozonolysis of α-amyrin benzoate (XVIII; X=H, OBz) followed by treatment with acid[8] furnished α-amyran-12-onyl benzoate (XIX; X=H, OBz). Bromination[9] afforded 11-bromo-α-amyranonyl benzoate which on dehydrobromination in acetic acid[9] provided α-amyr-9(11)-en-12-onyl benzoate (XX; X=H, OBz). Hydrolysis and oxidation gave α-amyr-9(11)-ene-3:12-dione (XX; X=O).



α-AMYRIN DERIVATIVES.

α-Amyrone (XVIII; X=O) was obtained by oxidation of the corresponding alcohol (XVIII; X=H, OH).

Oxidation, with chromic - acetic acids, of α-amyrin benzoate[10] furnished the corresponding 11-oxo- compound. Oxidation of the derived alcohol yielded α-amyr-12-ene-3:11-dione (XXI; X=O).

Reduction of α-amyr-12-en-11-onyl acetate (XXI; X=H, OAc) with lithium aluminium hydride gave a mixture of epimeric $C_{(11)}$ alcohols which, without separation, were dehydrated with acetic anhydride and toluene-p-sulphonic acid in pyridine to afford α-amyra-9(11):12-dienyl acetate (XXII; X=H, OAc), hydrolysed and oxidized to α-amyra-9(11):12-dien-3-one (XXII; X=O).

Treatment of α-amyr-12-en-11-onyl acetate with methyl magnesium iodide[11] in boiling benzene gave, on working up the reaction mixture (without acidification), a mixture of two dienes, which, on careful extensive chromatography over alumina, were separated to give 11-methylene α-amyr-12-enyl acetate (XXIII; X=H, OAc) and 11-methyl α-amyra-9(11):12-dienyl acetate (XXIV; X=H, OAc). Oxidation of the derived alcohols afforded 11-methylene α-amyr-12-en-3-one (XXIII; X=O) and 11-methyl α-amyra-9(11):12-dien-3-one (XXIV; X=O) respectively. Structures were based upon method of formation, analysis and spectroscopic properties.

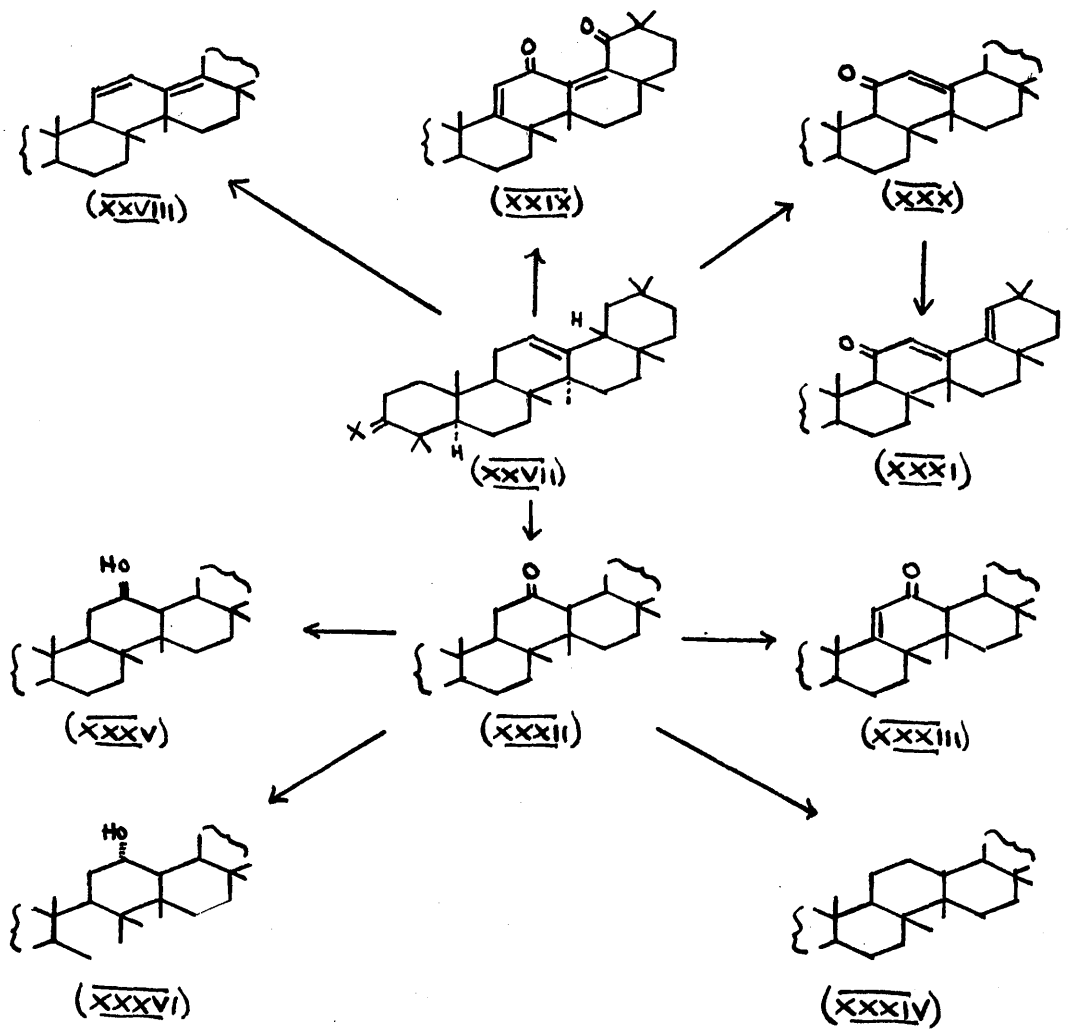
Extraction of finely powdered uva-ursi leaves with alcoholic potassium hydroxide[12] and acidification of the extract yielded, after purification, ursolic acid (XXV; X=H, OH; R=H). Methylation with ethereal diazomethane followed by oxidation gave methyl ursonate (XXV; X=O; R=Me), whilst oxidation of the acid gave ursonic acid (XXV; X=O; R=H).

Similarly, oxidation of quinovic acid afforded quinovenonedioic acid (XXVI; R=H), whilst methylation and oxidation gave quinovenonedioic acid dimethyl ester (XXVI; R=Me).

β-Amyrin Derivatives.

Oxidation of β-amyrin acetate (XXVII; X=H, OAc) with selenium dioxide in boiling acetic acid[11] gave dehydro-β-amyrin acetate (XXVIII; X=H, OAc). Hydrolysis and oxidation afforded dehydro-β-amyrone (XXVIII; X=O). More vigorous oxidation of β-amyrin acetate with selenium dioxide in a sealed tube furnished β-amyra-9(11):13(18)-diene-12:19-dionyl acetate (XXIX; X=H, OAc); oxidation of the alcohol gave β-amyra-9(11):13(18)-diene-3:12:19-trione (XXIX; X=O).

β-Amyrone (XXVII; X=O) was obtained by oxidation of β-amyrin with chromic acid at room temperature, whilst oxidation at 100°[11] of the acetate afforded β-amyr-12-en-11-onyl acetate (XXX; X=H, OAc) converted into



β-AMYRIN DERIVATIVES.

β-amyr-12-ene-3:11-dione (XXX; X=O). Bromination of the benzoate (XXX; X=H, OBz) with concurrent dehydrobromination[13] gave β-amyra-12:18-dien-11-onyl benzoate (XXXI; X=H, OBz). Oxidation of the derived alcohol yielded β-amyra-12:18-diene-3:11-dione (XXXI; X=O).

Oxidation of β-amyrin acetate with hydrogen peroxide in acetic acid[14] afforded the saturated β-amyran-12-onyl acetate (XXXII; X=H, OAc), which by hydrolysis and oxidation was converted to β-amyrane-3:12-dione (XXXII; X=O).

Selective ketalization[15] of the $C_{(3)}$ keto-group with ethylene glycol afforded 3-ethylenedioxy-β-amyran-12-one (XXXII; X=$OCH_2.CH_2.O$) which was reduced with sodium in n-propyl alcohol and lithium aluminium hydride to 12β-hydroxy- (XXXV;X=$O.CH_2.CH_2.O$) and 12α-hydroxy- (XXXVI; X=$O.CH_2.CH_2.O$) β-amyran-3-one 3-ethylene ketal. Removal of the ketal grouping by treatment with warm aqueous acetic acid furnished 12β-hydroxy-β-amyran-3-one (XXXV; X=O) and 12α-hydroxy-β-amyran-3-one (XXXVI; X=O) respectively.

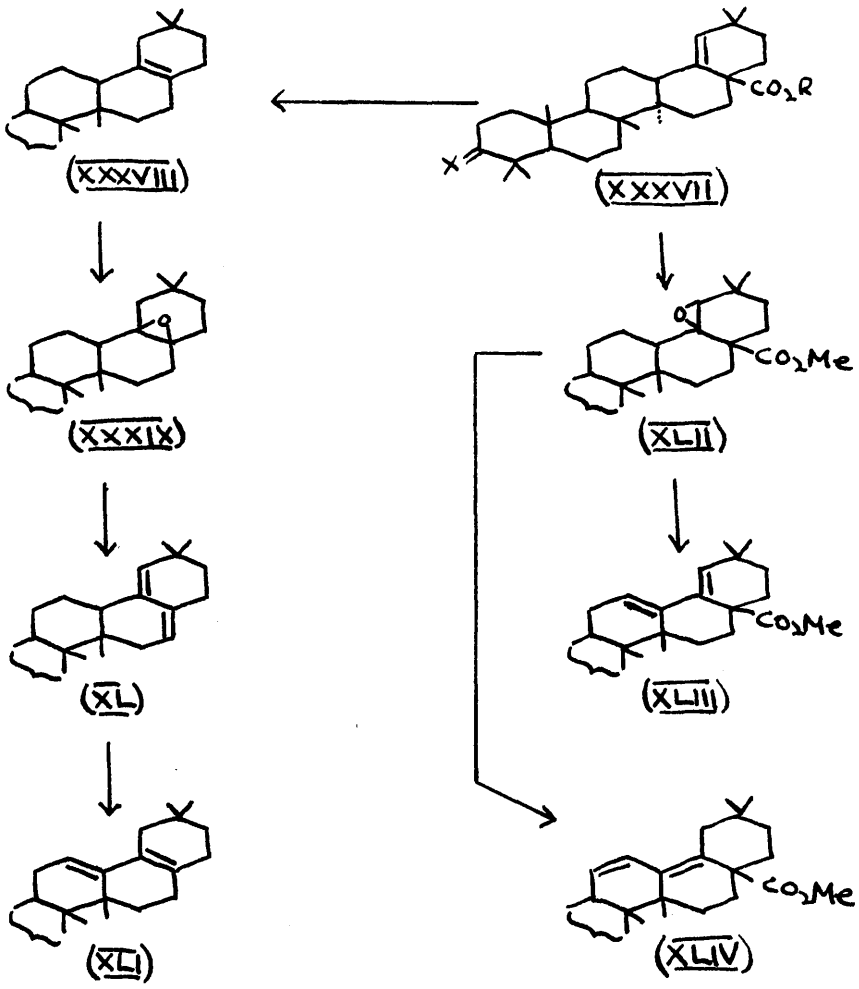
Bromination and dehydrobromination[9,16] of β-amyran-12-onyl acetate (XXXII; X=H, OAc) gave β-amyr-9(11)-en-12-onyl acetate (XXXIII; X=H, OAc) which afforded β-amyr-9(11)-ene-3:12-dione (XXXIII; X=O) on oxidation of the derived alcohol.

Wolff-Kishner reduction using the forcing conditions of Barton et al[6] of β-amyr-12-onyl acetate (XXXII; X=H, OAc) gave, on acetylation, β-amyranyl acetate (XXXIV; X=H, OAc). Hydrolysis and oxidation gave β-amyranone (XXXIV; X=O).

Morolic acid (XXXVII; X=H, OH; R=H) obtained from mora saponin[17] and methyl morolate (XXXVII; X=H, OH; R=Me) were oxidized to give moronic acid (XXXVII; X=O; R=H) and methyl moronate (XXXVII; X=O; R=Me).

Morolic acid was smoothly decarboxylated[17] at its melting point to afford oleanol (XXXVIII; X=H, OH) which with chromium trioxide and pyridine furnished oleanone (XXXVIII; X=O). Epoxidation with perphthalic acid gave the 18:19-epoxide (XXXIX; X=O) and treatment of this with dilute sulphuric acid - methanol provided norolean-16:18-dienone (XL; X=O) which was rearranged with hydrogen chloride in chloroform to the more stable norolean-12:17-dienone (XLI; X=O).

Methyl morolate acetate oxide (XLII; X=H, OAc) prepared by epoxidation of methyl morolate acetate with hydrogen peroxide[17] was treated with a) methanolic sulphuric acid to give methyl isodehydro-oleanolate (XLIII; X=H, OH) converted by oxidation to methyl isodehydro-oleanonate (XLIII; X=O) and b) hydrogen chloride in chloroform to give the rearranged methyl



DERIVATIVES PREPARED FROM MOROLIC ACID.

dehydro-oleanolate acetate (XLIV; X=H, OAc) which on subsequent hydrolysis and oxidation afforded methyl dehydro-oleanonate (XLIV; X=O).

Oxidation of methyl oleanolate (XLV; X=H, OH; R=Me) kindly supplied by Dr. K. H. Overton, afforded methyl oleanonate (XLV; X=O; R=Me).

Oleanonic acid was supplied by Dr. E. Seoane.

Extraction of Siamese gum benzoin[18] gave siaresinolic acid (XLVI; X=H, OH; R=H); oxidation of the methyl ester afforded the unstable methyl 3:19-diketo-olean-12-enoate (XLVII; X=O), rearranged by strong base to give, after remethylation, methyl 3:19-diketo-olean-13(18)-enoate (XLVIII; X=O).

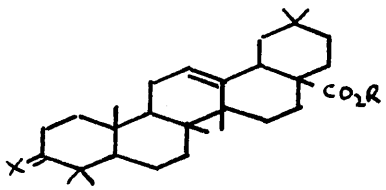
Lupeol, Betulin and Onocerin Derivatives.

By the action of formic acid, betulin (XLIX; X=H, OH; R=CH_2OH), obtained by chloroform extraction of birch bark, was converted to allobetulin formate (L; X=H, HCO_2). Hydrolysis and oxidation gave the desired allobetulone (L; X=O).

Oxidation of lupeol (XLIX; X=H, OH; R=Me) afforded lupenone (XLIX; X=O; R=Me) whilst lupanone (LI; X=O) was obtained by catalytic hydrogenation of lupenyl acetate (XLIX; X=H, OAc; R=Me) and subsequent oxidation of the derived alcohol.

α-Onoceradienedione (LII) was donated by Dr.K.Overton.

OLEANOLIC ACID AND SIARESINOLIC ACID DERIVATIVES.



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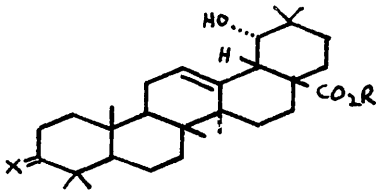

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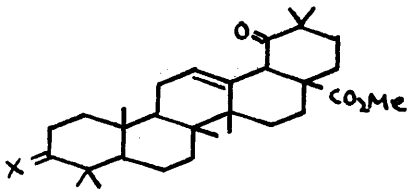

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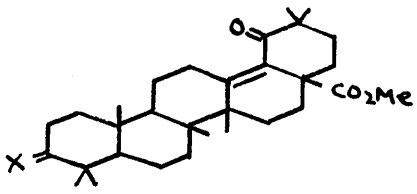

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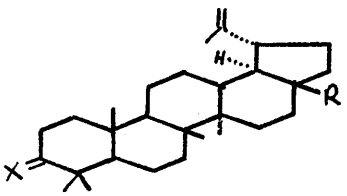
LUPEOL, BETULIN AND ONOCERIN DERIVATIVES.



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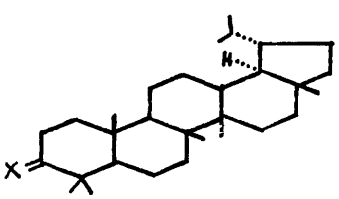

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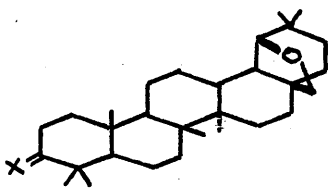

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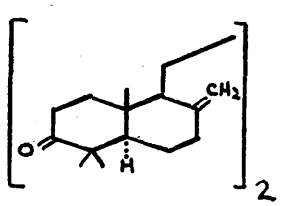

(LII)

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15. Allen, Bernstein and Littel, J.A.C.S., 1954, 76, 6116.
16. Pickard, Sharples and Spring, J.C.S., 1939, 1045.

17. Barton and Brooks, ibid., 1951, 257.

18. Winterstein and Egli, Z.physiol. Chem., 1931, 202, 207; Bilham, Kon and Ross, J.C.S., 1942, 540.

LONG-RANGE EFFECTS IN TRITERPENOIDS AND STEROIDS.

Introduction. As indicated in earlier sections, intra-molecular interactions over short distances have been subjected to thorough and intensive investigation, and, as a result are quite well understood. Longer range effects, however, have not been so treated. Indeed, little work has been done with the purpose of demonstrating their existence and none with the intent of elucidating the nature of their mechanism.

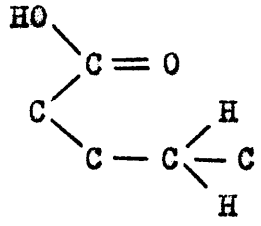
Bjerrum[1] predicted the effect of an electrostatic field acting upon an acid-base centre through space, as distinct from an inductive or conjugative mechanism. This was later shown to be so, in the case of aliphatic dicarboxylic acids involving unit charges, by Gane and Ingold[2].

Rothen[3,4] found evidence of a long-range effect in enzyme-substrate systems. Monolayers of bovine albumin were coated with monolayers of inert blanket material consisting of formvar, P.V.C., barium stearate or octadecylamine. In general, it was found that the number of layers of blanket material required to afford protection of the albumin substrate from trypsin deposited on top of the inert material was a function of the number of layers of underlying substrate. Thus the blanket thickness required to protect three double

layers of albumin was nearly three times that required for one double layer. With six monolayers of substrate (total thickness 48 A) a formvar blanket 600 A thick afforded no appreciable protection to trypsin.

Rothen's suggested explanation[4] of a long range effect involving a resonance phenomenon has been criticized by Trurnit[5] who suggests that the blankets are permeable to the enzyme although the original author[6] has presented evidence that simple diffusion cannot account for the known facts.

Newman[7] has shown that the rate of certain reactions involving addition to double bonds is greatly reduced as the size of substituents attached to the β-carbon atom is increased; an effect which he summarizes in his 'rule of six'. Atoms are numbered consecutively along the carbon chain, as shown, and the greater the size of the groups in the six-position the greater the degree of steric hindrance to be expected at the reaction centre.



This is particularly well illustrated by the acid catalysed esterification rates of aliphatic carboxylic

acids[8].

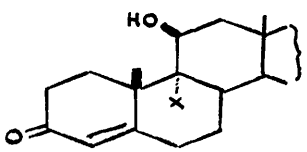
Anomalous rates of halogen exchange have been reported by Conant et al[9] during a kinetic investigation of the Finkelstein reaction. Unexpectedly fast rates were observed when n=3 in the series $Ph.(CH_2)_nCl$, $Ph.CO.(CH_2)_nCl$ and $CH_3.CO.(CH_2)_nCl$ and when n=4 in the series $CH_3.(CH_2)_nCl$ on displacement of chlorine with iodide ions.

Anomalous ultra-violet absorption spectra are typified by the following examples.

The ene-dione system of a Δ^4-3:6-diketo-steroid exhibits an absorption maximum at 250mμ. Introduction of a further (unconjugated) ketone at $C_{(11)}$ causes a hypsochromic shift of 5mμ of the band due to the ene-dione system[10].

A similar hypsochromic shift is observed in the introduction of the 11-keto group into 3-keto-$\Delta^{4:6}$-unsaturated steroids[11] (λ_{max}284mμ).

An interesting variation of these shifts has been observed by Fried et al[12] and Antonucci et al.[13] who measured the position of maximum absorption of the en-one system in steroids of the type (A)



(A)

when X is successively Br, Cl and F. The respective λ_{max} values are 243, 240 and 238mμ. Oxidation of the 11β-hydroxyl was also found to cause a hypsochromic shift of 4mμ. These systems have also been examined by the method of optical rotatory dispersion[14] when it was found that the principal maximum again underwent regular shifts.

By an examination of the optical rotatory dispersion data of epi-α-cyperone and 8-isotestosterone Djerassi et al[14] have concluded that steric interaction of the $C_{(4)}$ and $C_{(7)}$ -alkyl groups result in ring B of epi-α-cyperone assuming a boat conformation (either wholly or partially).

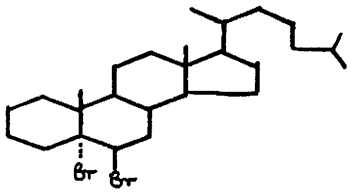
A recent paper by Barton, McGhie and Lewis[15] reports a conformational anomaly in lanosterol derivatives. Equilibration of either 2α- or 2β-bromo-lanostanone results in the quantitative formation of the 2α-bromo-isomer; but equilibration of 2α- or 2β-bromo-lanost-8-en-one affords a mixture of the two isomers in the ratio 2α:2β of 95:5. The difference in position of the equilibrium in the latter case must be a result of the presence of unsaturation at the B/C ring junction. Remarkable also, is the fact that ring A of both 2β-bromo-ketones exists in the boat conformation.

In order to investigate long-range effects better

and to overcome the conformational ambiguities inherent in acyclic systems Barton and Head[16] chose the steroid field where large numbers of compounds are readily available of rigid structure and known conformation.

Bromination of Δ^5-unsaturated steroids affords meta-stable 5α:6β-dibromides, which, in solution, undergo mutarotation to produce the stable 5β:6α-dibromides. The rates of mutarotation of four such systems (I-IV) were thoroughly studied by these authors and their results are given in the table below. (Rates are quoted as a percentage of the rate for 5α:6β-dibromo-cholestane.)

Compound	Rate
5α:6β-Dibromo-cholestane (I)	100
5α:6β-Dibromo-stigmastane (II)	100
5α:6β:22ξ:23ξ-tetrabromo-stigmastane (III)	75
5α:6β-Dibromo-deoxytigogenin (IV)	69



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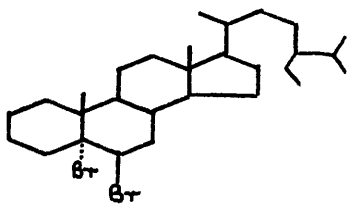

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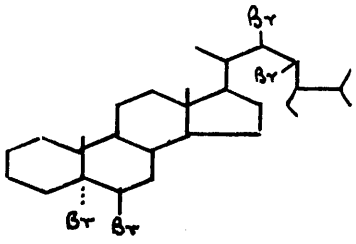

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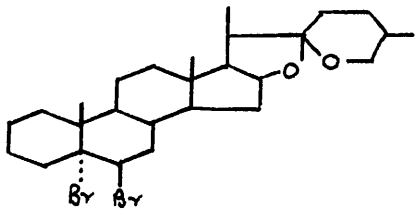
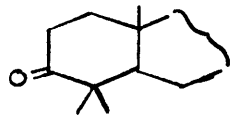


(IV)

It is shown that the anomalous results obtained with the tetrabromo-stigmastane (III) can only be due to the presence of the two side-chain bromine atoms and, likewise, the slow rate of mutarotation for the dibromo-deoxytigogenin (IV) is a result of the modified form of the side-chain.

The present work was undertaken in an attempt to investigate further the nature of long-range effects in conformationally unambiguous systems and in the hope that it would shed light upon the mechanism of such effects.

Results and discussion. All tetra- and penta-cyclic triterpenes of known constitution possess an oxygen function at $C_{(3)}$. This is usually an hydroxyl which can readily be oxidized to a ketone function. This achieved, the molecule can be made to undergo condensation reactions at the activated $C_{(2)}$ position. In particular, $C_{(3)}$ ketones (V) will condense, in a base catalysed reaction, with benzaldehyde to give benzylidene derivatives (VI).



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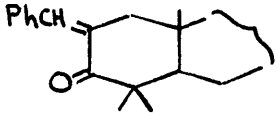


(VI)

The resulting benzal-ketone system shows a strong, broad absorption band in the ultra-violet region at 292mμ with ϵ 18,000 and thus the reaction can be conveniently followed spectrophotometrically.

The kinetics of such reactions have been investigated [17,18,19] and it is established that the rate is first-order with respect to ketone and aldehyde and almost certainly[17,18] with respect to base.

The rate law is thus[20]:-

$$\text{Rate} \propto [\text{Ketone}][\text{Aldehyde}][\text{Base}].$$

and the accepted mechanism[20] involves the following steps:-

$$-CH_2-CO- + OH^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} -CH=\overset{O^-}{C}- + H_2O$$

$$-\bar{C}H-CO- + PhCHO \xrightarrow[\text{slow}]{k_3} Ph-CH(OH)-CH-CO-$$

$$Ph-CH(OH)-CH-CO- \xrightarrow{\text{fast}} Ph-CH=CH-CO- + H_2O$$

Classical steric hindrance must be constant for all the terpenoid ketones and for all the steroid ketones (ring A and part of ring B is kept constant throughout both series) and thus k_3 must be substantially constant

in each series of ketones. If this is so then the rate differences must be due to a variation of the ratio of $k_1:k_2$. That is, the $k_1:k_2$ ratio must be greater for compounds with fast rates than those with slow rates. Thus the position of effective equilibrium of the ketone-enol system must differ and the observed rate must be dependent upon the enol concentration, for the concentration of base is constant and the concentration of aldehyde (in approximately ten molar excess) is corrected for. That k_3 should be different in both series of compounds by a constant ratio is expected and is found to be so.

The actual kinetic orders of the reactants are relatively unimportant here in as much as all kinetic runs were carried out under exactly the same conditions. A 0.1N-solution of ethanolic potassium hydroxide was employed throughout using 99% v/v aqueous ethanol in its preparation, and a known excess of benzaldehyde (about 10 moles). Thus the actual kinetics, with respect to the appearance of the 292mμ band were of the first order. A series of experiments in which the benzaldehyde concentration was varied over a factor of three showed the expected first-order relation in benzaldehyde.

All kinetic runs were carried out in pairs, a standard ketone (lanost-8-en-3-one) being run at the same time and under the same conditions as the test compound.

This ensured the cancellation of unforseen daily errors and that the rates were strictly comparable. An appropriate blank (without the ketone) was run with every experiment.

The results are summarized in the tables.

All compounds have a rigid, fully extended conformation and partial structure (V) is common to all triterpenoid ketones. Hence classical steric hindrance at $C_{(2)}$ must be constant throughout.

Rate differences which vary over a factor of 43-fold (i.e. masticadienonic acid (XXXIV; R=H) and β-amyra-9(11):13(18)-diene-3:12:19-trione (XXXIII) have rates of 8 and 344 respectively as compared to the standard lanost-8-enone (XLV), whose rate is taken to be 100) cannot therefore be due to straightforward steric effects.

Polar effects can be sub-divided into electrostatic effects through space and bond induction. That rate variations are not due to either is shown by the following arguments.

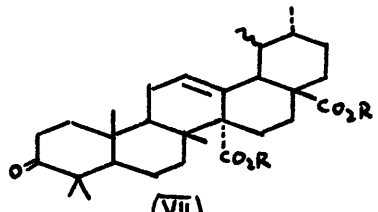
If electrostatic effects through space were the cause, then the greatest rate variations would be expected between molecules containing unit charges and those lacking them. In the penta-cyclic triterpenoids oleanonic acid (XVIII; R=H) with a rate of 97 is substantially the same as methyl oleanonate (XVIII; R=Me)

CONDENSATION RATES EXPRESSED AS % OF LANOST-8-ENONE

Penta-cyclic Triterpenoids.	No. of Runs	Rate	Limiting Values
Quinovenonedioic acid (VII; R=H)	2	33	31.8–33.2
12α-Hydroxy-β-amyranone (VIII) ..	2	53	51.7–53.6
11-Methylene α-amyrone (IX; R=CH_2)	2	66	44.8–67.0
α-Amyr-12-ene-3:11-dione (IX; R=O)	2	75	72.8–77.5
β-Amyr-12-ene-3:11-dione (X) ..	3	75	71.5–76.6
β-Amyra-12:18-diene-3:11-dione (XI)..	3	75	70.1–77.5
Moronic acid (XII)	2	78	77.2–78.5
Oleanone (XIII)	2	88	85.8–90.0
β-Amyranone (XIV)	2	88	88.2–88.5
12β-Hydroxy-β-amyranone (XV) ..	2	89	86.8–92.0
Norolean-16:18-dienone (XVI) ..	4	91	85.2–96.1
Ursonic acid (XVII; R=H)	2	91	90.4–91.2
Lupenone (XLIII; R=C(:CH_2)CH_3)..	2	95	94.3–95.0
Oleanonic acid (XVIII; R=H) ..	2	97	95.9–98.5
Lupanone (XLIII; R=$CHMe_2$)	2	98	97.6–98.1
11-Methyl α-Amyra-9(11):12-dienone(XIX).	2	100	99.2–100
α-Amyrone (XX)	3	100	98.2–103
alloBetulone (XXI)	2	100	99.3–101
β-Amyrone (XXII)..	4	108	103.3–111
Methyl moronate (XII; R=Me). ..	2	108	107–109
Methyl 3:19-diketo-olean-13(18)-enoate (XXIII)..	2	111	107–114

	No. of Runs	Rate	Limiting Values
Methyl ursonate (XVII; R=Me) ..	2	111	110-112
Methyl oleanonate (XVIII; R=Me)..	3	113	112-114
α-Amyra-9(11):12-dienone (XXIV)..	2	115	115-115
Noroleana-12:17-dienone (XXV) ..	2	116	115-118
α-Onoceradienedione (XXVI).. ..	2	117	117-118
β-Amyra-11:13(18)-dienone (XXVII)	3	124	117-132
Methyl isodehydro-oleanonate (XXVIII)..	5	128	125-132
Methyl dehydro-oleanonate (XXIX).	2	129	129-130
Quinovenonedioic acid dimethyl ester (VII; R=Me)..	2	154	152-155
β-Amyrane-3:12-dione (XXX).. ..	2	170	166-174
α-Amyra-9(11)-ene-3:12-dione (XXXI)..	3	266	263-269
β-Amyra-9(11)-ene-3:12-dione (XXXII)..	2	288	282-294
β-Amyra-9(11):13(18)-diene-3:12:19-trione (XXXIII)..	2	344	344-344
Tetra-cyclic Triterpenoids.			
Masticadienonic acid (XXXIV; R=H)	2	8	6.3-9.8
Methyl masticadienonate (XXXIV; R=Me)..	2	8	8.1-8.4
Δ^7-Lanostenone (XXXV)..	2	17	16.4-16.9
11β-Hydroxy-lanostanone (XXXVI)..	2	17	16.9-17.9
11α-Hydroxy-lanostanone (XXXVII).	2	35	34.7-35.0
Lanostane-3:11-dione (XXXVIII) ..	2	43	43.0-43.0

	No. of Runs	Rate	Limiting Values
Lanosta-7:9(11)-dienone (XXXIX)..	3	44	43.1-45.3
Lanostanone (XL)..	2	55	54.7-56.1
$\Delta^{9(11)}$-Lanostenone(XLI)	2	73	72.5-73.2
Lanostane-3:7:11-trione (XLII) ..	2	92	90.7-94.1
isoMasticadienonic acid (XLIV) ..	2	94	93.8-94.4
Δ^{8}-Lanostanone (XLV)	-	100	-
Dihydro-isomastica-dienonic acid (XLVI)..	2	108	107-108
Steroids.			
Cholestanone (XLVII)	2	182	181-183
Stigmastanone (XLVIII).	3	180	176-184
Ergost-22-ene-3:11-dione (XLIX)..	2	110	109-110
11α-Hydroxy-ergost-22-enone (L)..	2	125	123-126
11β-Hydroxy-ergost-22-enone (LI).	2	68	67.2-68.8
Ergost-22-ene-3:7:11-trione (LII)	2	360	348-371
Ergosta-7:22-dienone (LIII). ..	2	43	42.5-43.8
Ergost-8(14)-enone (LIV)	2	94	93.8-94.2
Tigogenone (LV)	2	175	173-176
3:11-Dioxo-bisnorallocholanic acid (LVI)..	2	103	102-103



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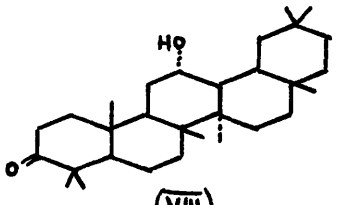

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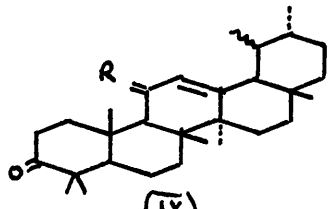

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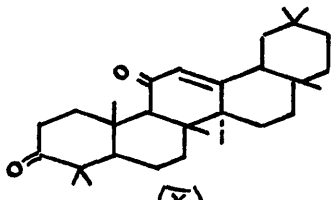

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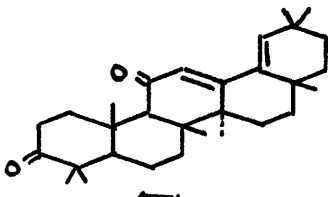

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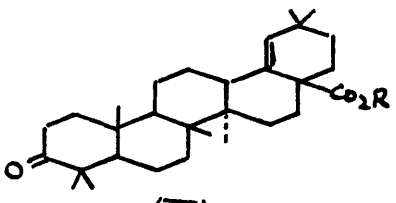

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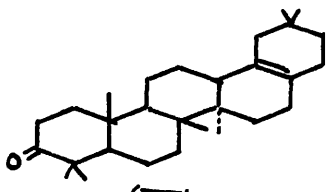

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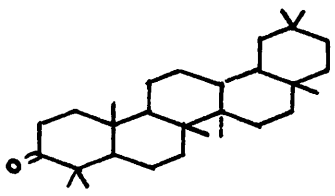

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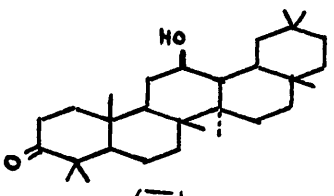

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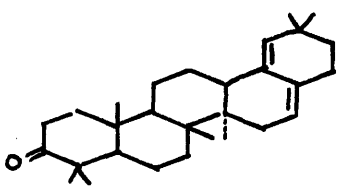

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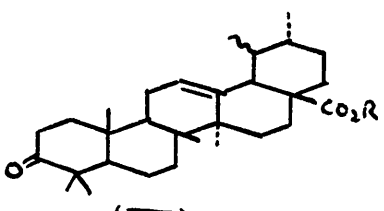

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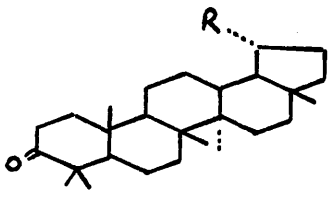

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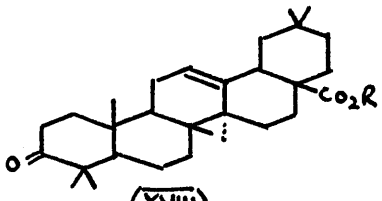

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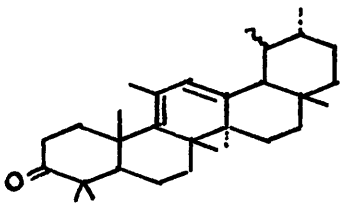

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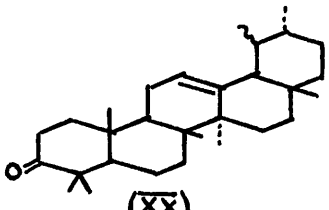

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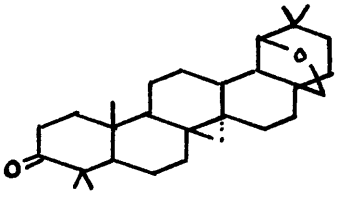

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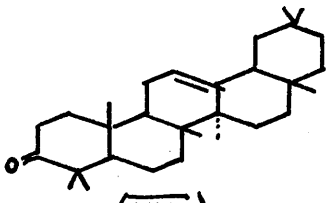

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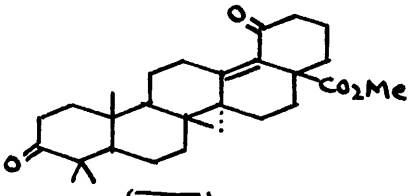

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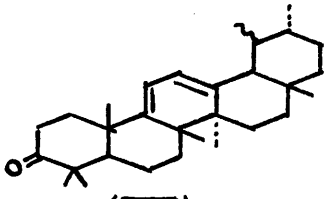

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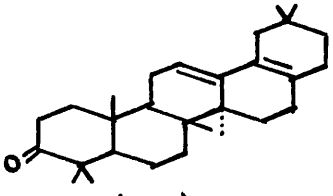

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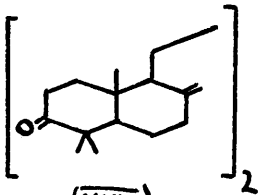

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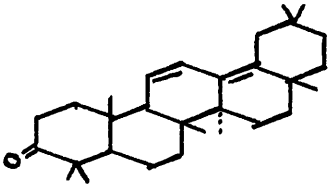

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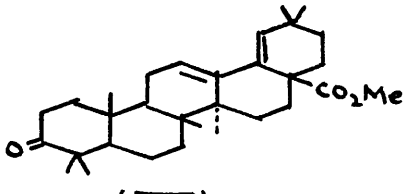

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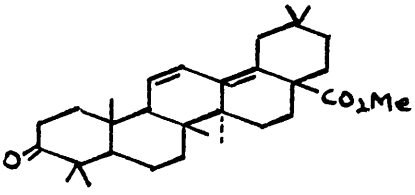

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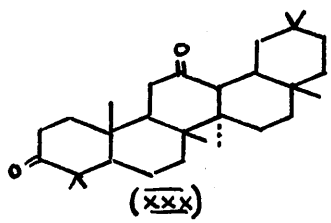

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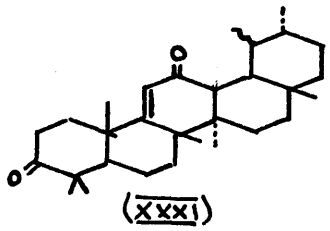

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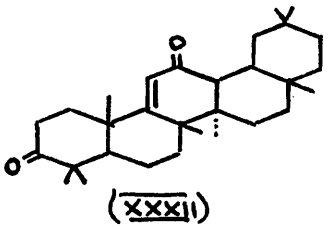

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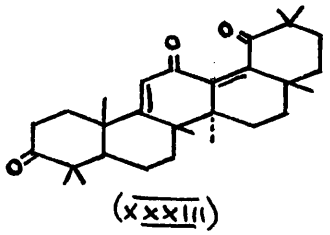

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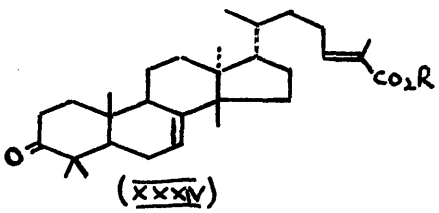

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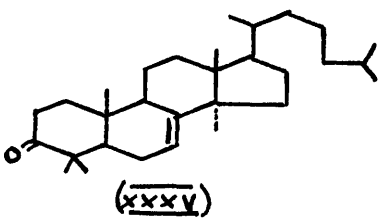

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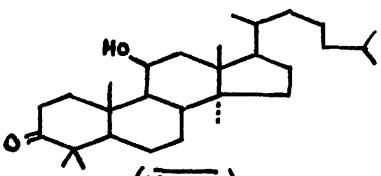

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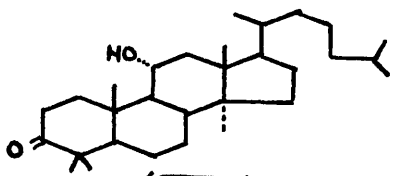

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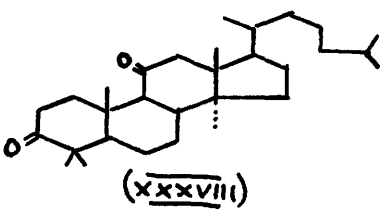

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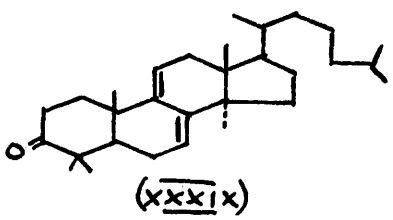

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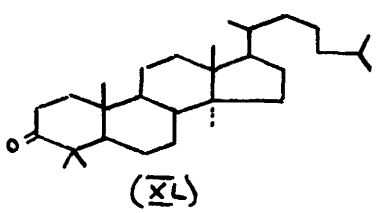

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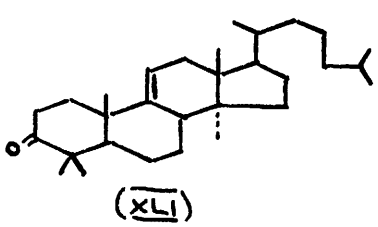

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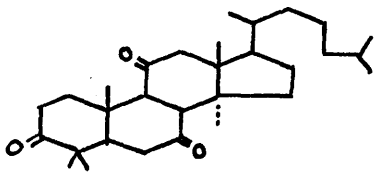

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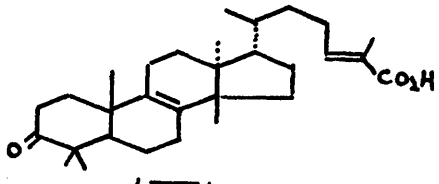

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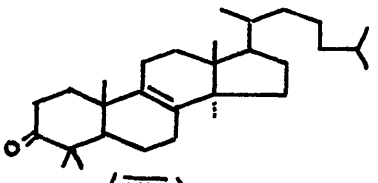

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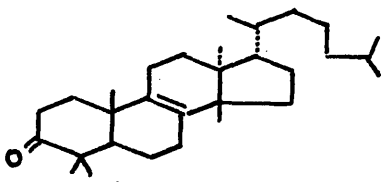

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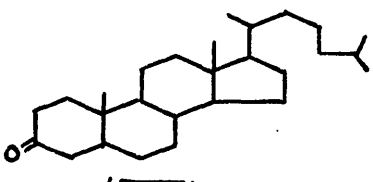

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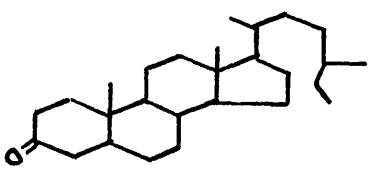

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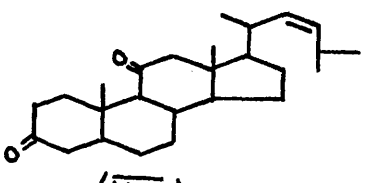

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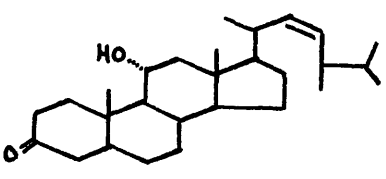

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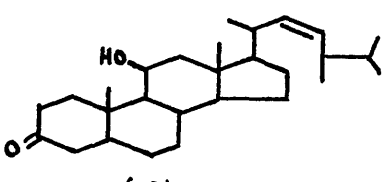
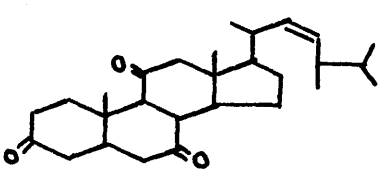


(LI)



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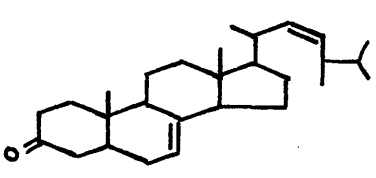

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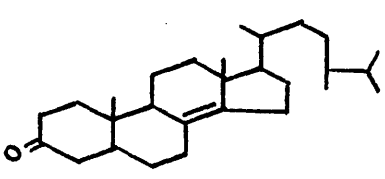

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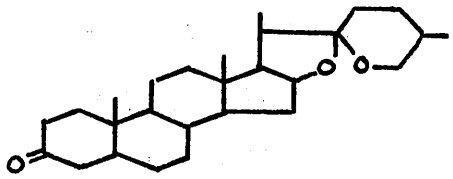

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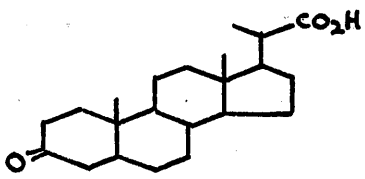

(LVI)

which has a rate of 113. Masticadienonic acid (XXXIV; R=H) and its methyl ester (XXXIV; R=Me), representitive of the tetra-cyclic triterpenoids, have identical rates and amongst the steroids ergost-22-ene-3:11-dione (XLIX) with a rate of 110 is virtually identical with 3:11-dioxo-bisnorallocholanic acid (LVI) whose rate is 103. In the case of quinovenonedioic acid (VII; R=H) and its dimethyl ester (VII; R=Me) the large rate difference may well be due to some extent to the presence of two integral charges on the dianion, but also, in view of arguments deduced below, must be due to a large degree to the increase in size accompanying the change $C_{(14)}$-methyl to $C_{(14)}$-CO_2^-.

The presence of an integral charge in the molecule has, therefore, no appreciable effect upon the rate. In the light of this it is unlikely that the electrostatic effect of a dipolar grouping should be the factor leading to rate variations. This is borne out by the results. Applying arguments similar to those above it would be expected that larger variations would occur between molecules containing dipoles and those which do not, on the one hand, and those having only ethylenic linkages, on the other. This is not so. Lanost-7-enone (XXXV), lanosta-7:9(11)-dienone (XXXIX), lanostanone (XL) and lanost-9(11)-enone (XLI) all react

much more slowly, oleanone (XIII) and norolean-16:18-dienone (XVI) react significantly more slowly, whilst α-amyra-9(11):12-dienone (XXIV), norolean-12:17-dienone (XXV), α-onoceradienedione (XXVI) and β-amyra-11:13(18)-dienone (XXVII) react significantly faster than lanost-8-enone. Apart from the $C_{(3)}$-keto group these compounds possess no polar linkages and the difference must be a result of the presence of unsaturation. α- (IX; R=O) and β-amyr-12-ene-3:11-dione (X) and β-amyra-12:18-diene-3:11-dione (XI) have slow rates whilst methyl 3:19-dioxo-olean-13(18)-enoate (XXIII) is fast and all $C_{(12)}$-ketones, β-amyrane-3:12-dione (XXX), α- (XXXI) and β-amyr-9(11)-ene-3:12-diones (XXXII) and β-amyra-9(11):13(18)-diene-3:12:19-trione (XXXIII) are very fast. Conclusive evidence comes from the similarity in rate for 11-oxo-α-amyrone (IX; R=O) and 11-methylene α-amyrone (IX; $R=CH_2$); both compounds have the same geometry and differ only in the polarity of their conjugated unsaturated functions. The slight difference in these two rates is readily attributable to the difference in size of the exocyclic methylene group and the doubly bonded oxygen at $C_{(11)}$. In confirmation of this it may be pointed out that exactly the same percentage difference exists between the rates for α-amyra-9(11):12-dienone (XXIV) and 11-methyl α-amyra-9(11):12-dienone

(XIX). More evidence comes from the rates for β-amyr-11:13(18)-dienone (XXVII) and methyl dehydro-oleanonate (XXIX) where the extra dipole in the latter ketone has no effect upon the rate. It follows from this and the fact that lupenone (XLIII; R=C(:CH_2)CH_3), lupanone (XLIII; R=$CHMe_2$), α-(XX) and β-amyrone (XXII), allobetulone (XXI) and methyl moronate (XII; R=Me) have substantially normal rate constants, that the diene system of methyl <u>iso</u>dehydro-oleanonate (XXVIII) also causes a change in rate. Thus in the absence of any disturbing unsaturation the partial system (V) must confer the same rate constant on a compound as does the system in lanost-8-enone (XLV).

That a bond inductive mechanism is responsible for the rate differences may be disposed of on the following grounds. In the α- (IX; R=O) and β-Δ^{12}-3:11-diketones (X) the slow rate would be due to the presence of a small positive charge on the $C_{(11)}$-carbon atom. Consequently, if bond induction were important then in compounds where the positive charge is greater and closer to $C_{(2)}$ the rate should be even slower. However, in (XXXI), (XXXII) and (XXXIII) where we have such a charge distribution the rate is in fact <u>faster</u> than the standard. Furthermore, the saturated β- amyrane-3:12-dione (XXX) where the positive charge is two saturated carbon atoms

further away from $C_{(2)}$ also has the same enhanced rate as the latter three compounds. This is not consistent with normal inductive effects where the extra carbon atoms should greatly reduce the effect. Placing the charge only one carbon atom further away as in methyl 3:19-diketo-olean-13(18)-enoate (XXIII) results in a rate only slightly greater than that of the standard.

Hyperconjugative effects are not operative for these, by definition, would produce alternating fast and slow rates. The three diene systems (XXIV), (XXVII) and (XXVIII) show no such alternation.

Masticadienonic acid (XXXIV; R=H) (and its methyl ester) have a structure similar to that of lanost-8-enone, the difference being in the position of the nuclear double-bond, the epimeric configuration at $C_{(13)}$, $C_{(14)}$ and $C_{(17)}$ and the presence of an $\alpha\beta$-unsaturated acid function in the side-chain. There is however a large difference in their reaction rates. That this rate difference is entirely due to the position of the nuclear double-bond is shown by consideration of the rates of <u>iso</u>masticadienonic acid (XLIV) and dihydro-<u>iso</u>masticadienonic acid (XLVI) which are quite normal. As further, and conclusive, evidence that the position of nuclear unsaturation is all important Δ^7-lanostenone (XXXV) was synthesized and found to condense at a slow

rate similar to that of masticadienonic acid.

Having then eliminated the known possible mechanisms which might have been responsible for the rate variations we must admit the existence of a new effect. The rate differences probably arise from conformational distortion produced by unsaturated substituents; these substituents must create a certain distortion which may well be transmitted through saturated carbon atoms over the whole structure. On this basis then, we may call the effect one of '<u>conformational transmission</u>'. The distortion may be regarded as being transmitted by either or both of the following paths. In the penta-cyclic triterpenoids angular methyl groups are present on the same side of the molecule at $C_{(4)}$, $C_{(10)}$ and $C_{(8)}$, i.e. 1:3 and diaxial with respect to each other. The distance between these 1:3- methyl groups in a completely strain-free system would be 2.54 A, but, as the van der Waals radius of a methyl group is 2.0 A, there must be a considerable amount of interaction. Thus at first sight this would present a plausible mechanism for strain, set up in one portion of the molecule, to be transmitted through the rigid carbocyclic system. The other method by which the strain could be transmitted - and this surely is the only path open to steroidal type molecules which do not bear angular methyl groups in the 1:3-

position - is through the carbocyclic system itself.

It would be reasonable to assume that if these two mechanisms are operable then variations in steroidal compounds would be less marked, for the strain, in being transmitted via the carbocyclic system itself, becomes distibuted over far more atoms than when it is simply transmitted across the rings by suitably disposed methyl groups. This is seen not to be the case in a comparison of the rates of condensation of the tetra-cyclic triterpenoids and steroids. In every case the rate for a specific steroid is approximately three times that for the corresponding lanosterol type ketone. The fact that the steroids are all faster than their analogous terpenes is in accordance with prediction (i.e. k_3 differs, in the two series, by a constant ratio). Thus cholestanone (XLVII), stigmastanone (XLVIII) and tigogenone (LV) all have identical rates which are three times that of lanostanone. Bearing in mind that compounds containing a carboxyl group are slightly slower than those with a methyl group, then 3:11-dioxo-bisnor<u>allo</u>cholanic acid (LVI) and ergost-22-ene-3:11-dione (XLIX) are, within experimental error, three times as fast as lanostane-3:11-dione (XXXVIII). Ergosta-7:22-dienone (LIII) is exactly three times as fast as lanost-7-enone (XXXV) and ergost-22-ene-3:7:11-trione (LII) is four times as fast

as lanostane-3:7:11-trione (XLII). Now, if 1:3-interactions are important, it is permissable to assume that where compounds have a slower rate than lanostanone (this being the parent saturated compound it is only proper to regard this as the standard) there is an increase in the non-bonded interactions of the methyl groups on going from the ketone to the enolic intermediate. Similarly, with compounds reacting faster than lanostanone one must assume a decrease in the interaction of the $C_{(4)}$ and $C_{(10)}$ diaxial methyl groups.

The steroids, however, have no angular methyl at $C_{(4)}$ and thus it is reasonable that there should be a fairly constant ratio for comparable derivatives in the steroid and tetra-cyclic triterpenoid series when the rates are faster than the parent saturated hydrocarbon and when they are slower. But it is not reasonable (if 1:3-interactions are important) for these two ratios to be the same - as in fact they are. Thus this argument, at least, shows the relative unimportance of the interactions between the non-bonded axial methyl groups.

There is however an equally valid argument based upon the experimental results which conclusively shows that in at least some circumstances the axiality of the substituents must be of considerable importance.

The hydroxyl group of 11α-hydroxy-lanostanone

(XXXVII) is equatorial and is not subject to great non-bonded interactions and consequently has a rate only slightly slower than lanostanone. The epimeric alcohol (XXXVI) bearing its hydroxyl in an axial conformation and thus suitably placed to interact strongly with the axial, and β, methyl groups at $C_{(10)}$ and $C_{(13)}$ condenses at exactly half the rate of its epimer. Similarly there is an identical ratio between the two other pairs of epimeric alcohols to be found amongst the experimental results. 11β-Hydroxy-ergost-22-enone (LI) with a rate of 66 is just half that of the epimeric 11α-hydroxy-compound (L) whose rate is 125, and the epimeric 12-hydroxy-β-amyranones (VIII) and (XV) have a similar rate ratio. Clearly then, these results, in which the structural changes do not of themselves involve distortion of the cyclic system, indicate that non-bonded interactions can play an important role. It must however be borne in mind that even in this case the effect may not be transmitted across the molecule entirely by 1:3-compressions. In view of the results it is most probable that the effective 1:3-interactions are those between the axial groups at $C_{(10)}$, $C_{(11)}$ and $C_{(13)}$ in the epimeric lanostanone and ergostenone alcohols. The two methyl groups causing distortion of the $O\text{-}C_{(11)}$ bond and the resulting deformation then being transmitted

through the carbocyclic system. In the case of the epimeric hydroxy-β-amyranones the reason probably lies in the fact that whilst the 12β(equatorial)-hydroxyl is not subject to any severe non-bonded interactions the 12α(axial)-hydroxyl is particularly close (owing to the D/E junction being cis) to both the $C_{(14)}$-axial methyl and to the $C_{(19)}$ methylene group.

Measurements made on accurate molecular models as described by Barton[21] show that the $C_{(14)}$ methyl is only about 1.2 A from the axial hydrogen attached to $C_{(19)}$ and that the oxygen of the 11α-hydroxyl is approximately 1.45 and 2.25 A from the equatorial hydrogen attached to $C_{(19)}$ and the $C_{(19)}$ carbon atom respectively. There must be considerable compulsion for the resulting overcrowding, and the consequent steric compression, to be reduced. This cannot be overcome by a twisting of the molecule about the D/E ring junction for twisting in order to relieve the hydroxyl - $C_{(19)}$ methylene interaction increases the compression between the $C_{(14)}$ methyl and the axial hydrogen at $C_{(19)}$, and vice versa. One possible way in which a large proportion of this strain could be relieved is for the molecule to flex upwards out of the plane of the rings A, B, C and D, and in particular for ring E (which owing to the cis fusion is bent beneath the plane of the rest

of the molecule) to flex upwards. This would result in an increase of the crowding of β-methyl groups at $C_{(4)}$, $C_{(10)}$ and $C_{(8)}$.

It is to be expected that more light would be shed upon the mechanism of long-range effects by measuring the rates of enolization by a bromometric method such as that developed by Schwartzenbach and Wittwer[22]. By this method enol contents as low as 10^{-5} percent. have been accurately determined.

In order that distances between angular methyl groups could be assessed with a fair degree of accuracy an attempt was made to improve upon the molecular models first made by Barton[21]. The main error attending the use of the Barton models was that the C-C bonds were not sufficiently strong to support the weight of a penta-cyclic model without distorting under their own weight. Also it was hoped to minimize errors introduced in these models by lateral movement of the bonds in their sockets. To this end more robust models were designed although the same scale was used i,e. 10cm equalled 1 A.(see Experimental). Increasing the size of the tetrahedral and trigonal type atoms ensured that the bonds could be inserted further and thus restrict to a minimum any adventitious sideways movement. This increase in the size of the atoms, and hence increase in weight,

necessitated an increase in the thickness of the stainless steel bonds.

Using these more rigid models, distances between the $C_{(4)}$ and $C_{(10)}$ axial methyl groups were measured for lanostanone, Δ^7- and Δ^8-lanostenones and β-amyr-9(11)-ene-3:12-dione in both the keto and enolic forms. The distances, however, were found to be 2.55 ± 0.05 A for all eight models.

Finally, it should be stated that there was no correlation between molecular rotation differences ($[M]_D^{C-OH} - [M]_D^{C=O}$) and rates of condensation, except that the ketones with very slow rates (masticadienonic acid, lanostanone, lanost-7-enone and dihydroagnostenone) were anomalous in that they had negative $\Delta[M]_D$ values. Also for these four compounds there is roughly a linear relationship between rate and $\Delta[M]_D$. The slower the rate the more negative (and anomalous) is the $\Delta[M]_D$ value.

Ketone	$[M]_D^{C-OH}$	$[M]_D^{C=O}$	$\Delta[M]_D$	Rate
Masticadienonic acid	-200	-350	-150	8
Lanost-7-enone	+64	-64	-128	17
Dihydro-agnostenone	+290	+204	-86	44
Lanostanone	+138	+99	-39	55

α-Onoceradienedione whose rate was slightly faster (117) than the standard also had a negative $\Delta[M]_D$ value (-88).

Attention has previously be drawn to anomalous molecular rotation differences[23] in the masticadienonic acid series and also in cycloartenol and butyrospermol.

The four ketones masticadienonic acid, lanost-7-enone, dihydro-agnostenone and lanostanone were also anomalous in that they give only very weakly positive colour reactions with ethanolic solutions of m-dinitro-benzene (the Zimmermann test[24]). The success of this test, which is usually positive for triterpenoid and steroid ketones which have a sterically unhindered methylene group adjacent to a keto-group, is presumably dependant upon reaction of the enolic intermediate with the m-dinitro-benzene. Hence it is not unexpected that only weak results are produced with the above ketones. All these weakly positive ketones are Δ^7-unsaturated. Butyrospermone whose double bond is similarly placed also gives only a weakly positive Zimmermann test[25].

Anomalous molecular rotation differences were observed during the preparation of the 3-ethylene dioxy-compounds. The results are summarized in the table below. No significance is attached to these anomalies

for such systems are known to give anomalous results[26].

Compound	$[M]_D$ Ketone	$[M]_D$ Ketal	$\Delta[M]_D$
β-Amyrane-3:12-dione	-53	-218	-165
12α-Hydroxy-β-amyran-3-one	+359	+78	-281
12β-Hydroxy-β-amyran-3-one	+173	-68	-241
Lanostane-3:11-dione	+293	+151	-142
11α-Hydroxy-lanostan-3-one	-27	±0	+27
11β-Hydroxy-lanostan-3-one	+125	+147	+22
Ergost-22-ene-3:11-dione	+248	+82	-166
11α-Hydroxy-ergost-22-en-3-one	-79	-106	-27
11β-Hydroxy-ergost-22-en-3-one	+50	±0	-50

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EXPERIMENTAL.

Melting points are uncorrected. Unless specified to the contrary, rotations were determined in chloroform solution at room temperature. Ultra-violet absorption spectra were determined with a Unicam S.P.500 spectrophotometer. Absolute ethanol was used except for kinetic runs (see below). Light petroleum refers to the fraction of boiling point 40-60°. Rate measurements were made at 25°C, in a thermostat (± 0.03°), flasks being tightly covered with tin-foil. All ketones were thoroughly dried *in vacuo* before being weighed for rate measurements. Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30-60 minutes in methanolic, ethanolic or dioxan - methanol solution depending on the solubility requirements of the ester. 'Working up in the usual way' signifies dilution of the reaction mixture with water, extraction with ether or suitable organic solvent, and washing with dilute sodium hydroxide (5%), 2N-hydrochloric acid (except where acid sensitive groups are present) and water and evaporation of the solvent in vacuo.

Final oxidation of the 3β-hydroxyl to ketone was achieved by the method of Sarett *et al*[1]. A 10% (w/v) suspension of AnalaR chromium trioxide in AnalaR

pyridine was prepared by cautious addition of the trioxide to the pyridine with cooling. To this was added a 10% (w/v) solution of the alcohol in AnalaR pyridine. About six times the theoretical amount of chromium trioxide was employed. For working up, the mixture was diluted with water, the excess of oxidant destroyed with sulphur dioxide, and the ketone extracted in the usual way.

Materials. 1) Ethanol. A large reservoir of ethanol was prepared by diluting absolute ethanol with water to 99% by volume. This solvent was used for all kinetic measurements. The addition of water minimises possible errors due to variable traces of water.

2) Benzaldehyde. The aldehyde was washed with 10% aqueous sodium carbonate solution, dried over calcium chloride and fractionated under reduced pressure in oxygen free nitrogen. The pure benzaldehyde was stored in sealed ampoules under oxygen free nitrogen. For each determination a fresh ampoule of benzaldehyde was employed.

3) Standard alkali. The following procedure was adopted for the storage of alcoholic potassium hydroxide. Approximately 0.15N-alcoholic potassium hydroxide was prepared by dissolving the requisite amount of the AnalaR reagent in freshly boiled-out 99% ethanol. The

solution was filtered through a sintered glass into a storage vessel in which the reagent could be kept under oxygen-free nitrogen, and from which it could be delivered by applying an external pressure of the same gas. In spite of these precautions to exclude carbon dioxide during the filling of the storage vessel, a little potassium carbonate was always deposited during the first two days storage; this did not, however, pass over with the alkali delivered from the storage vessel through the sintered glass disc. The alkali was stored in the dark. It was standardized against potassium hydrogen phtbalate in the usual way. For a rate determination exactly 0.1N-reagent was prepared by measuring the requisite amount of freshly boiled-out 99% ethanol into a volumetric flask and diluting it to the mark with standard alkali from the storage vessel. A fresh supply of standard alkali was prepared for every days kinetic measurements. From Caldin and Longs results[2] it would not be expected that the addition of 1-2% water to the 99% ethanolic solution would affect the concentration of ethoxide ion appreciably. This was confirmed by rate measurements, although any possible adventitious contamination with water is very much less than 1%.

4) Benzylidene derivatives. The following

procedure was employed. The ketone (1 mole) in 0.1N-potassium hydroxide in ethanol or dioxan - ethanol was treated with redistilled benzaldehyde (10 moles) in a stoppered flask overnight at room temperature. The mixture was worked up in the usual way, the ethereal extract being washed, first, with saturated sodium metabisulphite solution to remove the excess of benzaldehyde. Removal of the solvent and recrystallization of the residue, care being taken to avoid undue exposure to the light, gave the required benzylidene derivatives.

The light induced isomerization of the normal benzylidene derivatives in ethanol was achieved by irradiation with ultra-violet light in a quartz flask. At suitable intervals aliquots were withdrawn and the absorption at 276 and 292mμ measured. When neither band no longer changed in intensity the alcohol was removed in vacuo and the residue recrystallized from the appropriate solvent. The isobenzylidene compounds were, in general, more insoluble and more easily crystallized than the normal derivatives.

5) Ketones. The ketones were all carefully purified to constant melting point and rotation and, where applicable to constant ultra-violet absorption.

Absorption measurements. In order to correct

for any day-to-day variation in the behaviour of the Unicam S.P.500 spectrophotometer an absorption standard was prepared, consisting of pure naphthalene in ethanol (96%) measured against a blank of the same solvent. The intensities of the minimum at 284mμ and the maximum at 286mμ were determined with the same pair of stoppered 1cm cells on each occassion. No variation in the position of the maximum or minimum was ever observed (check on the wavelength scale). When variations in intensity were noted, both the maximum and the minimum changed simultaneously. Such changes were generally less than 1%, but occassionally larger discrepancies were noted which must be attributed to variation in the instrument. Measurements of the naphthalene solution on a particular day were taken as a standard value. The instrument was checked against this standard before each series of kinetic runs and, if instrument variation was detected, a proportional correction was applied to all measurements.

Technique. Kinetic runs were made as follows. 10-20mg of the ketone were weighed (semi-micro balance) into a 10ml graduated flask. About 4ml of freshly prepared exactly 0.1N-ethanolic potassium hydroxide (see above) were added and the ketone was dissolved (if necessary with gentle warming). An ampoule of benz-

aldehyde (see above) was opened and about 300mg (approx. 10 moles) weighed into a 25ml volumetric flask and made up to the mark with ethanolic 0.1N-potassium hydroxide. A portion (5ml) was pipetted into the ketone solution, and the mixture rapidly made up to the mark with ethanolic potassium hydroxide, the time being noted. All solutions were kept at thermostat temperature (25°) until thermally equilibrated before being mixed. An identical control was prepared (without the ketone).

At suitable intervals aliquot parts of both control and test solution were withdrawn and diluted at once to 10ml (volumetric flask) with 96% ethanol. The absorption of the test solution was measured at 292mμ against the blank solution, 1mm quartz cells being used. It was established by prior experiment that this dilution technique effectively quenched the reaction during the time required to make measurements. Measurements were made at the benzylidene maximum of 292mμ (for triterpenoids) and 294mμ (for steroids).

The stability of the control solution was examined and shown to vary only slightly with time (at 292mμ, at zero time, ϵ 945, after 3hours, ϵ 965 and after 70 hours ϵ 1134). The concentration of benzaldehyde diminishes by one molar proportion as the reaction proceeds and by measurement of the absorption spectrum

of benzaldehyde at 292mμ the observed intensities were corrected for this diminution.

The absorption of all compounds at 292mμ (or294mμ) was determined separately and, if significant, an appropriate correction to the observed extinction coefficient at this wavelength was made for each kinetic observation. Calculations were refered to a maximum absorption at 292mμ of ε 18,100 for triterpenoids, a value which was established by careful measurements on the benzylidene derivative of lanost-8-enone and shown to apply to several analogous benzylidene compounds (see above). Similarly a value of ε 17,000 at 294mμ was used in the case of steroidal benzylidene derivatives. The observations gave first-order plots from which the appropriate values of k were calculated and corrected for any slight variation in the 10:1 ratio of benzaldehyde to ketone. As emphasized in the text all experiments were run in pairs, one flask containing the standard lanost-8-enone and the other the ketone under examination. Expressing the results as the ratio of the two results cancelled any variation in unforseen factors. For ethanolic 0.1N-potassium hydroxide the mean rate constant for lanost-8-enone (106 runs) was 7.78 10^{-4} $mole^{-1}$ $l.sec.^{-1}$ at 25° with error limits (calculated from the formula

$$\sqrt{\frac{\Sigma \Delta^2}{n(n-1)}}$$

where the symbols have their usual significance) of ±0.05.

In preliminary experiments it was shown that three-fold variation in the benzaldehyde concentration had little effect (see table) on the rate constant calculated as above. Since the variation in the benzaldehyde:ketone ratio were, in fact, minor, the small correction applied (second order kinetics being assumed) are justified.

Lanost-8-en-one. (mole $l.^{-1}$)	Benzaldehyde (mole $l.^{-1}$)	$10^5 k$ ($sec.^{-1}$)	$10^4 k$/ PhCHO ($mole^{-1} l. sec.^{-1}$)
0.00258	0.0306	2.43	7.94
0.00248	0.0521	4.36	8.36
0.00237	0.0994	8.01	8.07

TRITERPENOID DERIVATIVES.

Lanost-8-en-3β-yl acetate. Technical lanosterol (75g.) was acetylated with acetic anhydride in pyridine overnight at room temperature. Working up in the usual manner afforded the acetate which, without purification, was hydrogenated in acetic acid - ether over Adams catalyst until there was no further uptake of hydrogen (approximately 0.5moles). Working up in the normal way gave lanost-8-enyl acetate (69g.) (from chloroform - methanol) m.p. 118.5 - 120.5. (Lit., m.p. 120-121[3]).

Lanost-8-en-3-one. Hydrolysis of lanostenyl acetate gave lanost-8-enol (from chloroform-methanol) m.p. 142-144. (Lit., m.p. 145-146[3]). Oxidation yielded, as plates from methanol, lanost-8-enone m.p. 118-119, $[\alpha]_D$ +77.6 (c 2.1); +75.5 (c2.34). At 292mμ ε 36. (Lit.[3], m.p. 119.5-120, $[\alpha]_D$ +77).

The derived benzylidene compound (needles from methanol) had m.p. 104-106, $[\alpha]_D$-22 (c 1.75), -19 (c 2.07), λ_{max} 292mμ ε 18120. (Found: C, 86.15; H, 10.55 $C_{37}H_{54}O$ requires C, 86.3; H, 10.55). Irradiation with light produced the isobenzylidene compound (from methanol) m.p. 110-111, $[\alpha]_D$ +42 (c 1.87), λ_{max} 276mμ ε 8900 (Found: C, 86.2; H, 10.4)

Lanost-7-en-3-one. Lanost-8-enyl acetate (5g.) was treated with dry hydrogen chloride in chloroform

(80ml) for two hours. Evaporation of the solvent gave an oil which was oxidized with chromium trioxide in acetic acid by the method of Marker et al[4]. The crude oxidation product on chromatography and crystallization from chloroform-methanol of the fractions eluted with light petroleum afforded lanost-7-enyl acetate (600mg.) as plates or needles, m.p. 141-144, $[\alpha]_D$ +32.2 (c 2.89) (Lit.[4] m.p. 149). Hydrolysis gave lanost-7-enol (from chloroform-methanol) m.p. 157-158, $[\alpha]_D$ +14.9 (c 2.08) (Lit.[4], m.p. 162). Oxidation gave, on chromatography, lanost-7-enone as colourless plates from chloroform-methanol) m.p. 144-146, $[\alpha]_D$ -15 (c 2.04) (Lit.[5], m.p. 146-147, $[\alpha]_D$ -20). The ketone gave a weakly positive Zimmermann reaction[6].

Lanosta-7:9(11)-dien-3-one. Lanost-8-enyl acetate (9g.) in acetic acid (500ml) and selenium dioxide (10g.) in water (20ml) were refluxed for 5 hours[7]. Filtration of the crude product, obtained by normal work-up proceedure, through alumina in benzene furnished lanosta-7:9(11)-dienyl acetate which from chloroform-methanol had m.p. 165-167, (lit.[8], m.p. 165-166). Hydrolysis gave lanosta-7:9(11)-dienol m.p. 155-157 (Lit.[9] m.p. 157-158). Oxidation and chromatography over alumina furnished lanosta-7:9(11)-dienone (thick colourless plates from methanol) m.p. 129-131,

$[\alpha]_D$ +48.4 (c 1.45), λ_{max} 236, 243.5 and 252mμ, ε 16250, 18700 and 12700 respectively. At 292mμ ε 18. (Lit.[8,10] m.p. 131-132, $[\alpha]_D$ +47.7 λ_{max} 234, 243 and 252mμ, ε 15000, 17500 and 11500 respectively).

The derived benzylidene compound (needles from methanol) had m.p. 107-109, $[\alpha]_D$ +9 (c 1.74), λ_{max} 236, 244 and 252mμ, $\lambda^{+291m\mu}$ ε 18500, 20800, 16100 and 16600 respectively (Found: C, 86.25; H, 9.85. $C_{37}H_{52}O$ requires C, 86.65; H, 10.2). Isomerization by light gave the isobenzylidene compound (fine needles from methanol) m.p. 120-121, $[\alpha]_D$ -71.5 (c 1.6), λ_{max} 236, 244, 252 and 271mμ, ε 24000, 24500, 18200 and 8900 respectively (Found: C, 86.85; H, 9.8).

Lanost-8-ene-7:11-dion-3β-yl acetate. Chromium trioxide (12g.) in water (12ml) and acetic acid (10ml) was added dropwise with good stirring to a solution of lanost-8-enyl acetate (10g.) in acetic acid (20ml), the temperature not being allowed to exceed 90°[11]. After the addition had been completed the temperature was maintained at 90° for 1.5 hours, by which time the reaction mixture was homogeneous. After cooling the solution was worked up in the normal way. Crystallization from methanol afforded yellow plates of lanost-8-ene-7:11-dionyl acetate (4.9g.) m.p. 154-157 (Lit.[12] m.p. 155-156).

Lanostane-7:11-dionyl acetate. Zinc dust (1g.) was added portionwise to a gently refuxing solution of lanost-8-ene-7:11-dionyl acetate (1g.) in acetic acid (35ml). After 15mins. reflux the mixture was cooled and freed from excess zinc and zinc acetate by filtration. Normal workup proceedure afforded lanostane-7:11-dionyl acetate as white lustrous plates from chloroform-methanol, m.p. 220-221, (lit.[13] m.p. 222-224).

Lanostane-3:7:11-trione. Alkaline hydrolysis of lanostane-7:11-dionyl acetate furnished lanostane-7:11-dionol (needles from methanol) m.p. 182-184 (Lit.[13] m.p. 183-184). Oxidation followed by chromotography over alumina afforded lanostane-3:7:11-trione as plates from methanol m.p. 164-166, $[\alpha]_D$ +46.3 (c 2.31), +47.2 (c 2.16). At 292mμ ε 100 (Lit.[14] m.p. 166-168, $[\alpha]_D$ +121).

Lanostan-3β-yl acetate. Lanostane-7:11-dionol (250mg) and anhydrous hydrazine (0.5ml) were heated under nitrogen at 200° for 1hr. in redistilled diethylene glycol (10ml). After cooling, sodium (300mg) in diethylene glycol (3ml) was added and the mixture refluxed, first at 220° for 2hrs. then at 230° for 4hrs. After normal work-up the crude product was acetylated with acetic anhydride in pyridine at room temperature overnight and chromatographed over alumina. The fractions

eluted by light petroleum afforded, on crystallization from chloroform-methanol, lanostanyl acetate m.p. 146 and remelts at 153-154, $[\alpha]_D$ +40.3 (c2.0) (Lit.[15] m.p. 150-151, $[\alpha]_D$ +41).

Lanostan-3-one. Hydrolysis of lanostanyl acetate gave lanostanol m.p. 176-177(e.c.), $[\alpha]_D$ +32.3 (c 2.05) (Lit.[15] m.p. 171-172(e.c.), $[\alpha]_D$ +35). Oxidation with chromium trioxide in pyridine at room temperature afforded lanostanone (plates from methylene chloride-methanol) m.p. 129-130, $[\alpha]_D$ +23.4 (c 2.27), +23.4 (c 1.8) (Lit.[15] m.p. 127-128, $[\alpha]_D$ +27).

Lanostane-3:11-dione. Lanostane-7:11-dionol (4g.) and hydrazine hydrate (100%, 2ml) in redistilled diethylene glycol (150ml) were refluxed for two hours. After cooling, sodium (4g.) in ethylene glycol (50ml), was added and the mixture refluxed at 220-230° for 6hrs. The semi-solid (4g.) obtained on working up was acetylated with acetic anhydride in pyridine on the steam-bath for 1.25hrs. Chromatography of the crude acetate afforded lanostan-11-onyl acetate (1.5g.) (from chloroform-methanol) m.p. 144-145, $[\alpha]_D$ +63.0 (c 1.7) (Lit.[15] m.p. 143-144, $[\alpha]_D$ +60). (Cf. McGhie et al[16]). Hydrolysis furnished lanostan-11-onol m.p. 161-162, $[\alpha]_D$ +59.8 (c 1.69) (Lit.[16] m.p. 161-162, $[\alpha]_D$ +60). Oxidation with Saretts reagent provided lanostane-3:11-dione as

plates from methanol, m.p. 118–120, $[\alpha]_D$ +60.9 (c 3.24) (Lit.[12] m.p. 120–123, $[\alpha]_D$ +69).

Lanostane-3:11-dione 3-ethylene ketal. Lanostane-3:11-dione (1.16g.), ethylene glycol (0.22ml), toluene-p-sulphonic acid (10mg) and dry benzene (50ml) were refluxed in a Dean and Stark apparatus for 18hrs. On cooling, the reaction mixture was poured into saturated sodium carbonate solution and the organic layer separated and washed with water. Evaporation of the solvent and recrystallization of the residue from benzene-methanol afforded lanostane-3:11-dione 3-ethylene ketal (1.13g.) m.p. 140–141, $[\alpha]_D$ +31.4, (c 1.37) (Found: C, 79.15; H, 11.2. $C_{32}H_{54}O_3$ requires C, 78.95; H, 11.2).

11α-Hydroxy-lanostan-3-one. To the ketal (150mg) in gently refluxing n-propyl alcohol (10ml) was added, over a period of 1hr., diced sodium (1g.), heating being adjusted to maintain gentle reflux. After the addition of the sodium was complete n-propyl alcohol (7ml) was added to destroy unreacted sodium, the mixture cooled and worked up in the usual fashion to give 11α-hydroxy-lanostan-3-one ethylene ketal (131mg) as large prisms from methanol, m.p. 165.5–166.5(K), $[\alpha]_D$ ±0.0 (c 1.88) (Found: C, 78.9; H, 11.75. $C_{32}H_{56}O_3$ requires C, 78.65; H, 11.55).

The hydroxy-ketal (180mg) in acetic acid (12ml)

and water (3.5ml) was heated for 10 min. on the steam-bath. Working up as usual provided 11α-hydroxy-lanostanone (150mg) as prisms from aqueous methanol, m.p. 151-151.5, $[\alpha]_D$ -6.0 (c 1.66) (Found: C, 81.1; H, 11.5 $C_{30}H_{52}O_2$ requires C, 81.0; H, 11.8).

11β-Hydroxy-lanostan-3-one. Lanostane-3:11-dione 3-ethylene ketal (200mg) and lithium aluminium hydride (220mg) were refluxed in dry ether (50ml) for 16hrs. Excess hydride was destroyed by addition of ethyl acetate-benzene and working-up in the usual way afforded 11β-hydroxy-lanostan-3-one 3-ethylene ketal (165mg) m.p.143-144, $[\alpha]_D$ +29.5 (c 2.0) (Found: C, 78.8; H, 11.4. $C_{32}H_{56}O_3$ requires C, 78.65; H, 11.55).

The hydroxy-ketal (270mg) in acetic acid (35ml) and water (5ml) were heated on the steam-bath for 10min. to give 11β-hydroxy-lanostanone (157mg) (plates from light petroleum) m.p. 188.5-189, $[\alpha]_D$ +28.2 (c 1.49) (Found: C, 81.05; H, 12.0. $C_{30}H_{52}O_2$ requires C, 81.0; H, 11.8).

Lanost-9(11)-en-3-one. Reduction of lanostane-3:11-dione 3-ethylene ketal (276mg) with lithium aluminium hydride as above gave crude 11β-hydroxy-compound (279mg) which was treated with perchloric acid (12 drops) in acetic acid (15ml) at room temperature for

15mins. Careful dilution of the reaction mixture with water gave lanost-9(11)-en-3-one (211mg) as plates from chloroform-methanol, m.p. 113-113.5(K), $[\alpha]_D$ +65.2 (c 2.67), +68.2 (c 1.7) (Found: C, 84.3; H, 11.6. $C_{30}H_{50}O$ requires C, 84.45; H, 11.8)

Methyl masticadienonate. Masticadienonic acid was methylated with ethereal diazomethane to give methyl masticadienonate (from aqueous methanol), m.p. 124, $[\alpha]_D$ -77.0 (c 2.24), -76.8 (c 1.38) (Lit.[17] m.p. 125, $[\alpha]_D$ -77).

α- and β-amyrin were extracted from manila elemi by the method of Vesterberg and Westerlind[18] and separated as their benzoates according to the method of Ruzicka et al[19].

α-Amyrone. Hydrolysis of α-amyrin benzoate yielded α-amyrin (from chloroform-methanol), m.p. 183, $[\alpha]_D$ +84.0 (c 1.87) (Lit.[20] m.p. 186, $[\alpha]_D$ +83). Oxidation gave α-amyrone m.p. 125-127, $[\alpha]_D$ +112.8 (c 2.51) [Lit.[21] m.p. 125-126, $[\alpha]_D$ +119 (Py)].

α-Amyr-9(11)-ene-3:12-dione. α-Amyrin benzoate (4g.) in dry chloroform (80ml) was treated with ozone at room temperature until the solution was negative to tetra-nitromethane. Partial evaporation of the solvent and addition of methanol gave needles (2.8g.). After filtration and drying these crystals were dissolved in

chloroform (15ml), acetic acid (60ml) and hydrochloric acid (3ml) and heated to 40° for 30min.[22] Working up as usual and many crystallizations from chloroform-methanol afforded α-amyran-12-onyl acetate (1.36g.) m.p. 225-229, $[\alpha]_D$ +22.9 (c 2.54) (Lit.[23] m.p. 227-229, $[\alpha]_D$ +24.7).

α-Amyranonyl acetate (250mg) in acetic acid (12ml) was treated dropwise with bromine in acetic acid (4ml; 4%), containing a trace of hydrogen bromide, at 60° with good stirring[24]. On cooling the mixture 11-bromo-α-amyran-12-onyl acetate separated (183mg) m.p. 178 decomp., $[\alpha]_D$ +25.1 (c 2.12) (Lit.[24] m.p. 177-178 decomp., $[\alpha]_D$ +22.5).

Treatment of the bromo-compound (887mg) with acetic acid (25ml) containing hydrogen bromide-acetic acid (1 drop; 50%) at 100 afforded α-amyr-9(11)-en-12-onyl acetate as octahedra from acetone-methanol, m.p. 206-208 (Lit.[24] m.p. 211-212). Hydrolysis furnished α-amyr-9(11)-en-12-onol (fine needles from light petroleum), m.p. 238-240, $[\alpha]_D$ +72.6 (c 1.46), λ_{max} 250mμ ε 11700 (Lit.[25] m.p. 236-238, $[\alpha]_D$ +72.1, λ_{max} 250mμ log ε 4.015). Oxidation afforded α-amyr-9(11)-ene-3:12-dione (from methanol) m.p. 192-194, $[\alpha]_D$ +91.1 (c 1.8), +91.7 (c 2.5), λ_{max} 248mμ ε 11000 (Found: C, 82.3; H, 10.25. $C_{30}H_{46}O_2$

requires C, 82.15; H, 10.55). At 292mμ ε 86.

α-Amyr-12-en-11-onyl benzoate. Chromium trioxide (5g.) in water (5ml) and acetic acid (300ml) was added dropwise (30min.) with good stiring to α-amyrin benzoate (10g.) in acetic acid (300ml) at 100°[26]. The solution was heated for a further 30min., carefully diluted with water, cooled and filtered. The crude product was filtered through alumina in benzene and recrystallized from chloroform-methanol to give α-amyr-12-en-11-onyl benzoate (6.9g.) m.p. 268-270 (Lit.[26] m.p. 266).

α-Amyr-12-ene-3:11-dione. Hydrolysis of α-amyren-onyl benzoate gave α-amyr-12-en-11-onol (from light petroleum) m.p. 202-206 (Lit.[26] m.p. 208). Oxidation afforded α-amyr-12-ene-3:11-dione (from methanol) m.p. 195-196, $[\alpha]_D$ +138.8 (c 2.6), λ_{max} 249-250mμ ε 12700. At 293mμ ε 50 (Lit.[26] m.p. 193, $[\alpha]_D$ +141).

The derived benzylidene compound (needles from methanol) had m.p. 212-215, $[\alpha]_D$ +51 (c 1.73), λ_{max} 232, 255 and 293mμ ε 12400, 17000 and 18300 respectively (Found: C, 84.35; H, 9.15. $C_{37}H_{50}O$ requires C, 84.35; H, 9.55). This compound was also obtained by acid catalysed condensation as follows. α-Amyrenedione (160mg) in ethanolic hydrogen chloride (40ml; 34%w/w) was treated with redistilled benzaldehyde (0.57ml) at room temperature overnight. Working up in the usual way

gave material identical with that described above.

α-Amyr-9(11):12-dien-3-one. α-Amyrenonyl benzoate (6.9g.) and lithium aluminium hydride (4.2g.) were refluxed in ether (300ml) for 5hr. The excess hydride was destroyed with ethyl acetate-benzene and working up in the usual manner gave the crude diol as a semi-solid. This was refluxed for 3hr. in acetic anhydride (30ml) with toluene p-sulphonic acid (20mg). Working up as usual folloed by filtration through alumina in benzene and crystallization from acetone-methanol afforded α-amyra-9(11):12-dienyl acetate (5.21g.) as needles, m.p. 168-169 (Lit.[27] m.p.166-167). Hydrolysis gave α-amyra-9(11):12-dienol m.p. 164-165 (Lit.[27] m.p.157-158). Oxidation of the alcohol (2g.) furnished, after chromatography, α-amyra-9(11):12-dienone (1.62g.) as needles from methanol, m.p. 145-148, $[\alpha]_D$ +411 (c 2.22 Py.), +414 (c 2.14 Py.), λ_{max} 281mμ ε 9600. At 292mμ ε 8000 (Lit.[28] m.p. 164-166, $[\alpha]_D$ +414, λ_{max} 282mμ ε 10200, but cf. Jacobs and Fleck[29] and Spring and Vickerstaff[26]).

α-Amyr-12-en-11-onyl acetate. Prepared exactly as for the benzoate (see above), had m.p. 208-210, λ_{max} 250mμ ε 11300.

11-Methylene α-amyr-12-en-3β-yl acetate and 11-methyl α-amyra-9(11):12-dien-3β-yl acetate. α-Amyr-12-en-11-

onol (1.5g.) in benzene was added dropwise with good stirring to an ethereal solution of methyl magnesium iodide (6.5g. magnesium and 8ml methyl iodide)[30]. After the addition was complete the ether was boiled off and the benzene solution refluxed for 55hr. Saturated ammonium chloride solution was added carefully and the organic layer separated, washed with water and evaporated. The crude reaction mixture was acetylated with acetic anhydride in pyridine at room temperature for 24hr. and the mixture of acetates obtained on working up extensively chromatographed over alumina (100 parts; activity 1). Elution with benzene:light petroleum (1:99) slowly removed all material. The latter fractions afforded 11-methylene α-amyr-12-enyl acetate (752mg) which on crystallization from chloroform-methanol had m.p. 229-232, $[\alpha]_D$ +142.5 (c 1.95), λ_{max} 246mμ ϵ 19700 (Lit.[30] m.p. 228-230, $[\alpha]_D$ +144). Treatment of this acetate, in chloroform, with dry hydrogen chloride for 30min. at room temperature afforded 11-methyl α-amyra-9(11):12-dienyl acetate (from chloroform-methanol) m.p. 164-166, $[\alpha]_D$ 328.4 (c 2.32) (Found: C, 82.7; H, 10.5. $C_{33}H_{52}O_2$ requires C, 82.8; H, 10.55). This material was identical with that obtained from the early chromatographic fractions.

11-Methylene α-amyr-12-en-3-one. Hydrolysis of the acetate gave 11-methylene α-amyr-12-enol as fine needles from methanol, m.p. 153-154, λ_{max} 246mμ ε 19300 (Lit.[30] m.p. 155-158, λ_{max} 245mμ log ε 4.3). Oxidation furnished 11-methylene α-amyr-12-enone as needles from aqueous methanol, m.p. 146-147, $[\alpha]_D$ +207.6 (c 1.2), λ_{max} 247mμ ε 19700 (Found: C,85.5; H, 11.3. $C_{31}H_{48}O$ requires C, 85.25; H, 11.1).

11-Methyl α-amyra-9(11):12-dien-3-one. Hydrolysis of the acetate gave 11-methyl α-amyradienol as an uncrystallizable gel. Oxidation of this and chromatography gave 11-methyl α-amyra-9(11):12-dienone (needles from methanol) m.p. 146-147, $[\alpha]_D$ +402.3 (c 1.34), +406.0 (c 1.0), λ_{max} 281mμ ε 9900 (Found: C, 85.05; H, 10.8. $C_{31}H_{48}O$ requires C, 85.25; H, 11.1).

Ursolic acid. Extraction of powdered uva-ursi leaves (700g.) with ethanolic potassium hydroxide solution according to the method of Bilham, Kon and Ross[31] afforded, on crystallization from ethanol, ursolic acid (5g.) m.p. 286-287 (e.c.) (Lit.[31] m.p. 291-292).

Ursonic acid. Oxidation of ursolic acid afforded ursonic acid (from aqueous methanol) m.p. 290-292 (e.c.), $[\alpha]_D$ +95.8 (c 1.7), +93.7 (c 1.7) (Found: C, 79.25; H, 10.6. $C_{30}H_{46}O_3$ requires C, 79.25; H, 10.2) (Lit.[32] m.p. 284-285).

Methyl ursonate. Methylation of ursolic acid with ethereal diazomethane gave methyl ursolate which was oxidized without purification to afford methyl ursonate as needles from methanol, m.p. 196–197, $[\alpha]_D$ +88.7 (c 1.95), +88.5 (c 2.0) [Lit.[33] m.p. 192–193, $[\alpha]_D$ +84 (Py.)].

Quinovenonedioic acid. Quinovic acid was oxidized in the usual fashion and purified via its sodium salt to afford quinovenonedioic acid (from methanol) m.p. 295 decomp., $[\alpha]_D$ +130.8 (c 1.3 Py.) (Found: C, 74.4; H, 9.8. $C_{30}H_{44}O_5$ requires C, 74.35; H, 9.15).

Quinovenonedioic acid dimethyl ester. Methylation of quinovic acid gave the dimethyl ester which was oxidized without purification to furnish quinovenonedioic acid dimethyl ester (plates from methanol) m.p. 152–154, $[\alpha]_D$ +149.0 (c 2.06), +149.1 (c 2.18) (Lit.[34] m.p. 149–150).

β-Amyrone. Hydrolysis of β-amyrin benzoate gave β-amyrin which was oxidized to β-amyrone m.p. 182–183, $[\alpha]_D$ +112.3 (c 2.08) (Lit.[35,36] m.p. 178–180, $[\alpha]_D$ +105.6).

β-Amyrin acetate. Obtained by acetylation of β-amyrin this had m.p. 240–242 (Lit.[20] m.p. 241).

β-Amyra-11:13(18)-dien-3-one. β-Amyrin acetate (1.5g.) and selenium dioxide (1g.) in water (1ml) and acetic acid (70ml) were refluxed for 2hr.[30] Working up in the usual

way yielded β-amyra-11:13(18)-dienyl acetate m.p. 227-229, $[\alpha]_D$ -61.8 (c 2.46) (Lit.[30] m.p. 228-229, $[\alpha]_D$ -62). Hydrolysis gave β-amyra-11:13(18)-dienol m.p. 229-230, $[\alpha]_D$ -73.3 (c 2.32) (Lit.[30] m.p. 228-229, $[\alpha]_D$ -72), oxidized to β-amyra-11:13(18)-dienone m.p. 241-242, $[\alpha]_D$ -54.3 (c 1.75), λ_{max} 242, 250 and 260mμ ε 26900, 30400 and 19600 respectively. At 292mμ ε 42. (Found: C, 84.85; H, 11.25. $C_{30}H_{46}O$ requires C, 85.25; H, 10.95) (Lit.[28] m.p. 236-240, $[\alpha]_D$ -49, λ_{max} 242, 250 and 260mμ ε 28200, 32400 and 21100 respectively).

β-Amyra-9(11);13(18)-diene-3:12:19-trione.

Oxidation of β-amyrin acetate (500mg) by the method of Ruzicka et al[37] with selenium dioxide (800mg) in redistilled dioxan (25ml) for 12hr. at 200-230° in a sealed tube afforded, after chromatography, β-amyra-9(11):13(18)-diene-12:19-dionyl acetate (263mg) (from aqueous methanol) m.p. 236-238, $[\alpha]_D$ -87.9 (c 1.9), λ_{max} 278mμ ε 12300 (Lit.[37] m.p. 239). Hydrolysis afforded β-amyra-9(11);13(18)-diene-12:19-dionol as needles from chloroform-light petroleum, m.p. 290-291, $[\alpha]_D$ -124.3 (c 1.3) (Lit.[38] m.p. 290-291). Oxidation of the alcohol afforded β-amyra-9(11):13(18)-diene-3:12:19-trione (needles from aqueous methanol) m.p. 289-291 decomp., $[\alpha]_D$ -95.9 (c 1.58), λ_{max} 277mμ ε 11600. At 292mμ ε 9900 (found: C, 80.35; H, 9.25. $C_{30}H_{42}O_3$ requires C, 79.95; H, 9.35).

β-Amyr-12-en-3:11-dione. Oxidation of β-amyrin acetate (7g.) with chromium trioxide (4g.) in acetic acid (300ml)[30], exactly as for the corresponding α-amyrin derivative, yielded β-amyr-12-en-11-onyl acetate (4.63g.) m.p. 259-261 (Lit.[30] m.p. 264-265). Hydrolysis afforded β-amyr-12-en-11-onol m.p. 231-235 (Lit.[30] m.p. 230-231). It has been shown[30] that epimerization to the 18-iso derivative requires more drastic conditions than those employed here.

Oxidation of the alcohol gave β-amyr-12-ene-3:11-dione (from chloroform-methanol) m.p. 240-242, $[\alpha]_D$ +145 (c 2.27), +142 (c 2.74), λ_{max} 251mμ ε 12750. At 292mμ ε 50. (Lit.[39] m.p. 237, $[\alpha]_D$ +143).

The derived benzylidene derivative (from methanol) had m.p. 152 decomp., $[\alpha]_D$ +59 (c 2.05), λ_{max} 231, 255 and 294mμ ε 11400, 16300 and 18100 respectively after drying (Found: C, 82.0; H, 9.55. $C_{37}H_{50}O_2 \cdot CH_3OH$ requires C, 81.65; H, 9.75).

β-Amyra-12:18-diene-3:11-dione. β-Amyr-12-en-11-onyl benzoate (m.p. 266-268), prepared as for the acetate above, was brominated and dehydrobrominated in acetic acid by the method of Pickard and Spring[40] to give β-amyra-12:18-dien-11-onyl benzoate (plates from chloroform-methanol) m.p. 251-252, $[\alpha]_D$ +322.6 (c 2.39),

λ_{max} 231 and 282mμ ε 18600 and 14200 respectively. (Lit.[40] m.p. 251-252, λ_{max} 283mμ log ε 4.08). Hydrolysis furnished β-amyra-12:18-dien-11-onol (plates from aqueous methanol) m.p. 237-238, $[\alpha]_D$ +363 (c 1.98) (Lit.[40] m.p. 239-240), which on oxidation afforded β-amyra-12:18-diene-3:11-dione m.p. 214-216, $[\alpha]_D$ +399.4 (c 1.71), +404.6 (c 1.12), λ_{max} 284mμ ε 12700. At 292mμ ε 11400 (Found: C, 82.4; H, 9.9. $C_{30}H_{44}O_2$ requires C, 82.5; H, 10.15).

β-Amyran-12-on-3β-yl acetate. Oxidation of β-amyrin acetate (15g.) in acetic acid (1250ml) with hydrogen peroxide (112ml; 100vol.) by the method of Spring et al[41] gave β-amyran-12-onyl acetate (8.1g.) (plates from chloroform-methanol) m.p. 298-299, $[\alpha]_D$ -15.1 (c 3.24) (Lit.[41] m.p. 299-300, $[\alpha]_D$ -15).

β-Amyrane-3:12-dione. Hydrolysis of β-amyr-12-onyl acetate provided β-amyran-12-onol m.p. 219-220, $[\alpha]_D$ -28.2 (c 2.98) (Lit.[41] m.p. 205-206, $[\alpha]_D$ -26). Oxidation furnished β-amyrane-3:12-dione (needles from aqueous methanol) m.p. 223-224, $[\alpha]_D$ -11.5 (c 2.1) (Lit.[42] m.p. 216-217).

β-Amyrane- 3:12-dione 3-ethylene ketal. A mixture of β-amyrane-3:12-dione (1.7g.) and toluene p-sulphonic acid (60mg) in redistilled ethylene glycol (160ml) was slowly distilled at 1.5mm pressure over a period of

2hr.[43] until only 15-20ml of glycol remained. Addition of dilute ethanolic potassium hydroxide solution and then water gave, on filtration, β-amyrane-3:12-dione 3-ethylene ketal (1.59g.) which from benzene-methanol had m.p. 279-281, $[\alpha]_D$ -44.5 (c 1.64) (Found: C, 79.55; H, 10.5. $C_{32}H_{52}O_3$ requires C, 79.3; H, 10.8).

12β-Hydroxy-β- amyran-3-one. The dione mono-ketal (150mg) in refluxing n-propyl alcohol (10ml) was treated over a period of one hour with diced sodium (1g.), the temperature being gradually increased to maintain gentle reflux (final temperature 170°)[44]. After addition of further n-propyl alcohol (5ml) to destroy excess sodium the mixture was cooled and worked up in the usual way to afford 12β-hydroxy-β-amyran-3-one 3-ethylene ketal (121mg) as plates from benzene-methanol, m.p. 272-274, $[\alpha]_D$ -12.3 (c 2.28), -13.8 (c 1.59) (Found: C, 78.7; H, 11.35. $C_{32}H_{54}O_3$ requires C, 78.95; H, 11.2). Brief treatment of the hydroxy-ketal (167mg) with aqueous acetic acid at 100° for 5min. followed by dilution with water and crystallization from aqueous methanol gave 12β-hydroxy-β-amyran-3-one (87mg) m.p. 210-213, $[\alpha]_D$ +39.0 (c 1.54) (Found: C, 81.45; H, 11.25. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.40).

12α-Hydroxy-β-amyran-3-one. Reduction of the dione mono-ketal (474mg) with lithium aluminium hydride (900mg)

in refluxing ether (150ml) gave, on normal work-up, crystalline material, (450mg). Chromatography over alumina afforde, on elution with benzene:light petroleum (1:1), and crystallization from benzene-methanol, 12α-hydroxy-β- amyran-3-one ethylene ketal (254mg) m.p. 261-263, $[\alpha]_D$ +16 (c 2.13) (Found: C, 78.7; H, 11.2. $C_{32}H_{54}O_3$ requires C, 78.95; H, 11.2), and on elution with benzene, 12β-hydroxy-β-amyranone ethylene ketal (123mg) m.p. 271-274. Treatment of the 12α-hydroxy-ketal with warm aqueous acetic acid yielded 12α-hydroxy-β-amyranone (from chloroform-methanol) m.p. 252-255, $[\alpha]_D$ +81.1 (c 1.11) (Found: C, 81.7; H, 11.15. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.4).

β-Amyr-9(11)-ene-3:12-dione. β-Amyran-12-onyl acetate (6g.) in acetic acid (550ml) at 40-50° was treated dropwise with bromine (2.2g; 1.1 mole) in acetic acid (20ml) containing a trace of hydrogen bromide. The crude product obtained from the usual work-up proceedure was refluxed for 1hr. in acetic acid containing a little hydrogen bromide. Crystallization from chloroform-methanol afforded colourless plates of β-amyr-9(11)-en-12-onyl acetate (4.95g.), m.p. 288-299, $[\alpha]_D$ +57.9 (c 2.23), λ_{max} 248mμ ε 10300(Lit.[41] m.p. 289-290, $[\alpha]_D$ +61). Hydrolysis provided β-amyr-9(11)-en-12-onol m.p. 244-247, $[\alpha]_D$ +46.4 (c 1.81) (Lit.[41] m.p.

249-250, $[\alpha]_D$ +57.5 cf. Pickard, Sharples and Spring[45]). Oxidation with chromium trioxide in pyridine gave β-amyr-9(11)-ene-3:12-dione (needles from methanol) m.p. 205-206, $[\alpha]_D$ +51.5 (c 1.34), λ_{max} 248mμ ε 9550 (Found: C, 82.2; H, 10.45. $C_{30}H_{46}O_2$ requires C, 82.15; H, 10.55).

β-Amyran-3-one. Wolff-Kishner reduction of β-amyran-12-onyl acetate (1.9g.) under the forcing conditions of Barton et al[46] gave, after acetylation and chromatography, β-amyranyl acetate (1.24g.) m.p. 275-277, $[\alpha]_D$ +21.5 (c 2.6) (Lit.[47] m.p. 285, $[\alpha]_D$ +21). Alkaline hydrolysis and chromatography afforded β-amyranol (fine needles from chloroform-methanol) m.p. 192-197, $[\alpha]_D$ +14.2 (c 1.76) (Lit.[47] m.p. 186-186.5, $[\alpha]_D$ +18.4). Oxidation yielded β-amyranone (from chloroform-methanol) m.p. 200-201, $[\alpha]_D$ +41.2 (c 0.97) (Found: C, 84.8; H, 11.9. $C_{30}H_{50}O$ requires C, 84.45; H, 11.8) (Lit.[47] m.p. 194-195).

Moronic acid. Saponification of mora saponin (20g.) with ethanol-concentrated hydrochloric acid according to the directions of Barton and Brooks[48] gave morolic acid (3.8g.) as fine cotton-woolly needles from dioxan-methanol, m.p. 265 decomp., $[\alpha]_D$ +33.3 (c 1.02) (Lit.[48] m.p. 273 decomp., $[\alpha]_D$ +33). Oxidation with chromium trioxide in pyridine afforded on purification via the sodium salt, moronic acid (needles from aqueous methanol),

loses solvent 156-160° and melts 218° with decomp., after drying at 130° in vacuo for 12hr. had m.p. 210° decomp., $[\alpha]_D$ +65.1 (c 2.09) (Found: C, 79.55; H, 10.6. $C_{30}H_{46}O_3$ requires C, 79.25; H, 10.2).

Methyl moronate. Methylation of morolic acid with ethereal diazomethane gave methyl morolate (from ethyl acetate-methanol) m.p. 228-230, $[\alpha]_D$ +28.7 (c 2.37) (Lit.[48] m.p. 228-229, $[\alpha]_D$ +26). Oxidation afforded methyl moronate (from methanol) m.p. 167-168, $[\alpha]_D$ +60.1 (c 2.4), +60.3 (c 1.91) (Lit.[48] m.p. 165, $[\alpha]_D$ +59).

Oleanone. Heating morolic acid in vacuo for 5min. at 280-300° gave, after crystallization from chloroform-methanol, oleanol m.p. 224-228, $[\alpha]_D$ +57.4 (c 2.2) (Lit.[48] m.p. 221-224, $[\alpha]_D$ +56). Oxidation afforded oleanone m.p. 178-181, $[\alpha]_D$ +96.3 (c 2.18), + 96.6 (c 2.37) (Lit.[49] m.p. 168-172, $[\alpha]_D$ +95.8).

Norolean-16:18-dien-3-one. Oleanone (630mg) in methylene chloride (10ml) was treated with 0.62N-monoperphthalic acid (20ml) in ether and the solution made up to 50ml with ether. After 17hr. (1.04 mols uptake of oxidant) the product was isolated, then taken up in methanol (100ml) and aqueous 2N-sulphuric acid (15ml) and refluxed for 30min. Filtration of the product through alumina in benzene-light petroleum gave norolean-16:18-dienone (from chloroform-methanol) m.p. 164-

166, $[\alpha]_D$ -14.1 (c 2.27), -15.3 (c 2.16), λ_{max} 240mμ ε 18100 (Found: C, 85.4; H, 10.55. $C_{29}H_{44}O$ requires C, 85.25; H, 10.85). This compound had ε 50 at 292mμ.

Norolean-12:17-dien-3-one. Isomerization of norolean-16:18-dienone (200mg) with hydrogen chloride in chloroform (20ml) at room temperature according to the general method of Barton and Brooks[48] yielded, after chromatography and crystallization from methanol, fine needles of norolean-12:17-dienone (112mg) m.p. 115-118, $[\alpha]_D$ +118.5 (c 1.33), λ_{max} 236 and 243mμ ε 19300 and 20900 respectively. At 292mμ ε 170 (Found: C, 84.85; H, 11.0. $C_{29}H_{44}O$ requires C, 85.25; H, 10.85). This ketone was found to become coloured on keeping and was prepared immediately before use.

Methyl morolate acetate oxide. Acetylation of methyl morolate with acetic anhydride in pyridine afforded methyl morolate acetate m.p. 263-265, $[\alpha]_D$ +38.3 (c 2.14) (Lit.[48] m.p. 263-264, $[\alpha]_D$ +38). Treatment of the methyl acetate (82mg) in acetic acid (100ml) with hydrogen peroxide (0.5ml) at 100° for 2hr. gave methyl morolate acetate oxide (50mg) m.p. 288-290, $[\alpha]_D$ +28.6 (c 1.85) (Lit.[48] m.p. 288, $[\alpha]_D$ +30).

Methyl isodehydro-oleanonate. Reflux (22hr.) of methyl morolate acetate oxide (500mg) in methanol (250ml) and 2N-sulphuric acid (25ml) afforded as fine

needles from aqueous acetone methyl isodehydro-oleanolate (294mg) m.p. 186–191, $[\alpha]_D$ +196.3 (c 2.17) (Lit.[48] m.p. 179–180, $[\alpha]_D$ +214). Oxidation of the alcohol and chromatography of the product yielded methyl isodehydro-oleanonate m.p. 153–154, $[\alpha]_D$ +236.7 (c 1.15), λ_{max} 232mμ ε 7500. At 292mμ ε 60 (Found: C, 79.9; H, 9.7. $C_{31}H_{46}O_3$ requires C, 79.8; H, 9.95).

Methyl dehydro-oleanonate. Treatment of methyl morolate acetate oxide (750mg) in chloroform (120ml) with hydrogen chloride for 30min at room temperature gave methyl dehydro-oleanolate acetate (435mg) (needles from chloroform-methanol) m.p. 225–227, $[\alpha]_D$ −130.6 (c 1.98) (Lit.[48] m.p. 220–221, $[\alpha]_D$ −127). Hydrolysis afforded methyl dehydro-oleanolate m.p. 170–172, $[\alpha]_D$ −139 (c 2.34) (Lit.[48] m.p. 168, $[\alpha]_D$ −139). Oxidation gave methyl dehydro-oleanonate m.p. 186–187, $[\alpha]_D$ −130 (c 1.44), λ_{max} 243, 251 and 260mμ ε 26100, 29,500 and 18500 respectively. At 292mμ ε 31 (Found: C, 79.95; H, 9.7. $C_{31}H_{46}O_3$ requires C, 79.8; H, 9.95).

Methyl oleanonate. Methyl oleanolate (m.p. 198–200) was oxidized to give methyl oleanonate (stout needles from methanol) m.p. 185–187, $[\alpha]_D$ +92.2 (c 2.18) (Lit.[50] m.p. 184–185).

Methyl 3:19-dioxo-olean-13(18)-enoate. Siamese gum benzoin was extracted[51,52] to give siaresinolic acid-

acetic acid complex m.p. 264-270 (Lit.[52] m.p. 268-270). Methylation afforded methyl siaresinolate m.p. 171-175, (Lit.[52] m.p. 176), which on oxidation provided methyl 3:19-dioxo-olean-12-enoate (needles from methanol) m.p. 210-213, $[\alpha]_D$ +141.9 (c 1.79) (Lit.[53] m.p. 212-213, $[\alpha]_D$ +142.6). Isomerization by refluxing for 1.25hr. in methanolic potassium hydroxide (25%) and remethylation afforded methyl 3:19-dioxo-olean-13(18)-enoate (from light petroleum) m.p. 194-195, $[\alpha]_D$ -194.9 (c 1.36), λ_{max} 251mμ ε 7400 (Lit.[53] m.p. 193-194, $[\alpha]_D$ -189, λ_{max} 253mμ log ε 3.85).

Lupenone. Oxidation of lupeol afforded lupenone m.p. 168-170, $[\alpha]_D$ +60.9 (c 1.56) (Lit.[54] m.p. 168-169, $[\alpha]_D$ +57.6).

Lupanone. Hydrogenation of lupenyl acetate (1g.) over Adams catalyst in acetic acid (30ml) and ether (30ml) yielded lupanyl acetate (873mg) as rectangular plates from chloroform-methanol, m.p. 244-246 (Lit.[55] m.p. 245-246). Hydrolysis gave lupanol (fine needles from chloroform-methanol) m.p. 187-189 (Lit.[56] m.p. 206). Oxidation furnished lupanone (from chloroform-methanol) m.p. 207-209, $[\alpha]_D$ +16.2 (c 1.73) (Lit.[57] m.p. 210).

Allobetulone. Powdered birch bark (750g.) was refluxed with chloroform (6 litres) for 2hr. Evaporation of the solution to convenient bulk (750ml), filtration

through alumina and further concentration of the eluate gave crude betulin on cooling. Recrystallized from ethanol to give betulin (15.6g.) as needles, m.p. 252-255, $[\alpha]_D$ +18.2 (c 2.53 Py.) [Lit.[58,59] m.p. 261, $[\alpha]_D$ +20 (Py)].

Treatment of betulin (5g.) with boiling formic acid (45ml) for 15min. gave allobetulin (2.6g.) as small plates from chloroform-methanol, m.p. 312-316 (e.c.), $[\alpha]_D$ +52.6 (c 2.11) (Lit.[58,59] m.p. 322 (e.c.), $[\alpha]_D$ +51). Hydrolysis gave allobetulin (triangular plates from chloroform-methanol) m.p. 266-270 (e.c.), $[\alpha]_D$ +47.3 (c 2.22) (Lit.[58,59] m.p. 279 (e.c.), $[\alpha]_D$ +48), which, on oxidation, yielded allobetulone (needles from absolute ethanol) m.p. 241-243 (e.c.), $[\alpha]_D$ +82.5 (c 2.0) (Lit.[59,60] m.p. 235-236, $[\alpha]_D$ +84.4).

α-Onoceradienedione. Kindly supplied by Dr.K.H. Overton this ketone had m.p. 184-187, $[\alpha]_D$ ±0.0 (c 3.47) (Lit.[61] m.p. 183-185, $[\alpha]_D$ -2).

The derived dibenzylidene compound (needles from methanol) had m.p. 213-216, $[\alpha]_D$ -37 (c 1.76 or 1.78), λ_{max} 225 and 292mμ ε 2×7600 and 2×17900 respectively (Found: C, 86.15; H, 8.6. $C_{44}H_{52}O_2$ requires C, 85.95; H, 8.85). Isomerization with light gave the iso-dibenzylidene compound (fine needles from chloroform-methanol) m.p. 223-224, $[\alpha]_D$ -225 (c 1.51), λ_{max} 221 and

274mμ 2x14100 and 2x8700 respectively (Found: C, 85.75; H, 8.85. $C_{44}H_{52}O_2$ requires C, 89.95; H, 8.85).

Oleanonic acid m.p. 165-167 slight decomp., $[\alpha]_D$ +94.4 (c 2.16) (Lit.[62] m.p. 166 decomp., $[\alpha]_D$ +102.6); masticadienonic acid m.p. 178-181, $[\alpha]_D$ -77.5 (c 2.0), λ_{max} 209mμ ε 11800 (Lit.[63] m.p. 178, $[\alpha]_D$-76); dihydro-masticadienonic acid m.p. 156, $[\alpha]_D$ -80 (c 1.13) (Lit.[63] m.p. 156, $[\alpha]_D$ -80); and dihydro-isomasticadienonic acid m.p. 155-157, $[\alpha]_D$ +27 (c 1.01) (Lit.[64] m.p. 155-157, $[\alpha]_D$ +27) were all kindly supplied by Dr.E.Seoane.

Stability of methyl esters to base. That the results of kinetic measurements on methyl esters were not invalidated by a reduction in base strength of the medium due to hydrolysis was established as follows. Methyl masticadienonate (18.7mg) in ethanolic 0.1N-potassium hydroxide (10ml) was kept at 25° for 7hr. The solution was just acidified and extracted with ether. The dried (Na_2SO_4) ethereal solution was evaporated to dryness and the residue analysed (Found: OMe, 5.5, calculated for $C_{30}H_{46}O_3$; 1 OMe, 6.6).

That the tertiary carboxyl esters are not hydrolysed easily, even by 190hr. refluxing in ethanolic potassium hydroxide has already been demonstrated[65].

STEROID DERIVATIVES.

Cholestanone, prepared by oxidation of cholestanol, had m.p. 129-130, $[\alpha]_D$ +42 (c 2.06) (Lit.[66] m.p. 128-129, $[\alpha]_D$ +43).

Stigmastanone, obtained by oxidation of the alcohol, had m.p. 157-158, $[\alpha]_D$ +42 (c 1.4) (Lit.[67] m.p. 157, $[\alpha]_D$ +40.5).

The derived benzylidene compound (from benzene-ethanol) had m.p. 151-152, $[\alpha]_D$ -108 (c 1.46), λ_{max} 294mμ ϵ 16500 (Found: C, 86.2; H, 10.5. $C_{36}H_{54}O$ requires C, 86.0; H, 10.85).

Tigogenone, from oxidation of the parent alcohol, had m.p. 204-206, $[\alpha]_D$ -53 (c 2.3) (Lit.[68] m.p. 201-203, $[\alpha]_D$ -55).

Ergost-8(14)-en-3-one (α-Ergostenone), had m.p. 129-131, $[\alpha]_D$ +28.5 (c 4.32) (Lit.[69] m.p. 129-130, $[\alpha]_D$ +30).

The derived benzylidene compound (needles from benzene-methanol) had m.p. 162-163, $[\alpha]_D$ -17.5 (c 2.4), λ_{max} 294mμ ϵ 17000 (Lit.[70] m.p. 161-162).

Ergosta-7:22-dien-3-one. Obtained by oxidation of the parent alcohol this ketone had m.p. 178-180, $[\alpha]_D$ +1 (c 2.14) (Lit.[71] m.p. 184, $[\alpha]_D$ +2).

Ergost-22-ene-3:11-dione (blades from methanol) had

m.p. 162-163, $[\alpha]_D$ +52.8 (Lit.[72] m.p. 162-163, $[\alpha]_D$ +51).

The derived benzylidene compound (needles from methanol) had m.p. 191-192, $[\alpha]_D$ -7.2 (c 1.5), λ_{max} 294mμ ε 17000 (Found: C, 83.7; H, 9.6. $C_{35}H_{48}O_2$ requires C, 83.95; H 9.65).

Ergost-22-ene-3:7:11-trione. Oxidation of ergost-22-ene-7:11-dione of m.p. 196-198, $[\alpha]_D$ -32 (c 2.32) (Lit.[73] m.p. 197-200, $[\alpha]_D$ -30) afforded as plates from methanol, ergost-22-ene-3:7:11-trione m.p. 194-195, $[\alpha]_D$ -8.8 (c 2.28) (Found: C, 78.75; H, 9.85. $C_{28}H_{42}O_3$ requires C, 78.8; H 9.9).

3:11-Dioxo-bisnorallocholanic acid. Oxidation of the parent alcohol gave 3:11-dioxo-bisnorallocholanic acid (plates from ethanol) m.p. 258-261, $[\alpha]_D$ +52 (c 2.54) (Found: C, 73.5; H, 9.05. $C_{22}H_{32}O_4$ requires C, 73.35; H, 8.95).

The derived benzylidene compound had m.p. 268-270, $[\alpha]_D$ -24 (c 2.28), λ_{max} 294mμ ε 16500 (Found : C, 77.6; H, 7.95. $C_{29}H_{36}O_4$ requires C, 77.65; H, 8.1).

Ergost-22-ene-3:11-dione 3-ethylene ketal. The 3:11-dione (1g.) was treated with ethylene glycol (300ml) and toluene-p-sulphonic acid (90mg) as described by Bernstein et al.[43] Crystallization from methanol yielded ergost-22-ene-3:11-dione 3-ethylene ketal as plates m.p. 153-154, $[\alpha]_D$ +18.8 (c 2.02) (Found: C, 78.9; H, 10.7.

$C_{30}H_{48}O_3$ requires C, 78.9; H, 10.6).

11β-Hydroxy-ergost-22-en-3-one. Reduction of the ketal (150mg) with lithium aluminium hydride (100mg) in refluxing ether (25ml) afforded, after chromatography and crystallization from methanol, 11β-hydroxy-ergost-22-enone ethylene ketal (100mg) m.p. 155-156, $[\alpha]_D \pm 0$ (c 1.6) (Found: C, 78.8; H, 10.6. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0). The ketal (100mg) in aqueous acetic acid (10ml) was heated to 100° for 15min. to afford 11β-hydroxy-ergost-22-en-3-one (from methanol) m.p. 170-172, $[\alpha]_D$ +11.5 (c 2.0) (Found: C, 81.15; H, 11.1. $C_{28}H_{46}O_2$ requires C, 81.1; H, 11.2).

11α-Hydroxy-ergost-22-en-3-one. Reduction of the ketal (200mg) with sodium (1.5g.) in refluxing n-propyl alcohol (15ml) by the method of Barton and Holness[44] afforded 11α-hydroxy-ergost-22-en-3-one ethylene ketal (150mg) as needles from methanol m.p. 186, $[\alpha]_D$ -22.6 (c 1.5) (Found: C, 78.55; H, 10.95. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0). Removal of the ethylene-dioxy grouping, as for the epimeric 11β-hydroxy-isomer above, furnished 11α-hydroxy-ergost-22-en-3-one (126mg) as needles from light petroleum, m.p. 142-144, $[\alpha]_D$ -19 (c 1.58) (Found: C, 81.25; H, 11.2. $C_{28}H_{46}O$ requires C, 81.1; H, 11.2).

The non-reactivity to benzaldehyde of the $C_{(4)}$ position of steroidal ketones. The $C_{(2)}$ benzylidene derivatives of 3:11-dioxo-bisnorallocholanic acid, ergost-22-ene-3:11-dione and stigmastan-3-one were treated with benzaldehyde in 0.1N-ethanolic potassium hydroxide under exactly the same conditions as employed in kinetic runs. No increase was observed in the value of the extinction coefficient at 294mμ over a period of three days.

Benzylidene compound	ε at 294mμ after 24hr	ε at 294mμ after 24hr
Ergost-22-ene-3:11-dione	15,800	15,370
Stigmastanone	15,300	15,000
3:11-Dioxo-bisnorallocholanic acid	15,900	15,600

The appropriate blank was used for all comparisons.

Construction of the new molecular models. The new models were identical in form and shape to the Barton models, the size only (but not scale) being increased. They were constructed as follows.

Solid duralumin was accurately machined to give a regular tetrahedron such that the vertical height was 3.5cm. and each side 4.25cm. Each apex was removed parallel to the corresponding base to give a truncated tetrahedron of vertical height 2.69cm. and side 2.25cm. Holes were drilled vertically from each truncated apex to a depth of 1.1cm. The diameter of the holes was such that it gave a good fit to the bonds and yet allowed completely free rotation. Holes were drilled, tapped and provided with screws in each face so that the screws engaged in the grooves in the bonds.

The trigonal carbon atoms were constructed of ½" brass sheeting, from which were cut equilateral triangles of side 4cm. The corners were truncated to 1.05cm. down each side and the truncated faces drilled to a depth of 1.2cm. i.e. 0.2cm. from the centre of the atom. Tapped holes with screws were made as for the Barton models.

Carbon-carbon single bonds were constructed from ⅛" stainless steel wire. The single bonds were 13.95cm. long, each one bearing two circular grooves 3mm. wide and approximately 1mm. deep situated with their centres

6mm. from either end of the bond.

Double bonds of length 12.9cm. were constructed from the same material. The ends of the bonds were ground flat and parallel to each other, by removing half the bond, for a distance of 1cm.

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NEW COMPOUNDS

Compound	m.p.	$[\alpha]_D$
2-Benzylidene lanost-8-en-3-one	104-106	-22
2-isoBenzylidene lanost-8-en-3-one	110-111	+42
2-Benzylidene lanosta-7:9(11)-dien-3-one	107-109	+9
2-isoBenzylidene lanosta-7:9(11)-dien-3-one	120-121	-71.5
Lanostane-3:11-dione 3-ethylene ketal	140-141	+31.4
11α-Hydroxy-lanostan-3-one 3-ethylene ketal	165.5-166.5	±0
11α-Hydroxy-lanostan-3-one ..	151-151.5	-6
11β-Hydroxy-lanostan-3-one 3-ethylene ketal..	143-144	+29.5
11β-Hydroxy-lanostan-3-one ..	188.5-189	+28.2
Lanost-9(11)-en-3-one	113-113.5	+65.2
α-Amyr-9(11)-ene-3:12-dione ..	192-194	+91.1
2-Benzylidene α-amyr-12-ene-3:11-dione ..	212-215	+51
11-Methyl α-amyra-9(11):12-dien-3β-yl acetate ..	164-165	+328.4
11-Methyl α-amyra-9(11):12-dien-3-one ..	146-147	+402.3
11-Methylene α-amyr-12-en-3-one	146-147	+207.6
Quinovenonedioic acid	295 decomp.	+130.8
β-Amyra-12:18-diene-3:11-dione	214-216	+399.4

β-Amyra-9(11):13(18)-diene-3:12:19-trione ..	289–291	−95.9
2-Benzylidene β-amyr-12-ene-3:11-dione ..	152 decomp.	+59
β-Amyrane-3:12-dione 3-ethylene ketal ..	279–281	−44.5
12β-Hydroxy-β-amyran-3-one 3-ethylene ketal ..	272–274	−12.3
12β-Hydroxy-β-amyran-3-one ..	210–213	+39
12α-Hydroxy-β-amyran-3-one 3-ethylene ketal ..	261–263	+16
12α-Hydroxy-β-amyran-3-one ..	253–255	+81.1
β-Amyr-9(11)-ene-3:12-dione ..	205–206	+51.5
Moronic acid	218–221 dec.	+65.1
Norolean-16:18-dien-3-one ..	164–166	−14.1
Norolean-12:17-dien-3-one ..	115–118	+118.5
Methyl isodehydro-olean-3-onate	153–154	+236.7
Methyl dehydro-olean-3-onate ..	186–187	−130
2:20-Dibenzylidene α-onocera-dienedione ..	213–216	−37
2:20-Di-isobenzylidene α-onocera dienedione ..	223–224	−225
2-Benzylidene stigmastan-3-one	151–152	−108
2-Benzylidene ergost-8(14)-en-3-one	162–163	−17.5
2-Benzylidene ergost-22-ene-3:11-dione ..	191–192	−7.2
Ergost-22-ene-3:7:11-trione ..	194–195	−8.8
3:11-Dioxo-bisnorallocholanic acid	258–261	+52
2-Benzylidene 3:11-dioxo-bisnor-allocholanic acid ..	268–270	−24

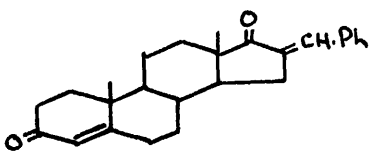
Ergost-22-ene-3:11-dione 3-ethylene ketal ..	153–154	+18.8
11β-Hydroxy-ergost-22-en-3-one 3-ethylene ketal ..	155–156	±0
11β-Hydroxy-ergost-22-en-3-one	170–172	+11.5
11α-Hydroxy-ergost-22-en-3-one 3-ethylene ketal ..	186	-22.6
11α-Hydroxy-ergost-22-en-3-one	142–144	-19

APPENDIX

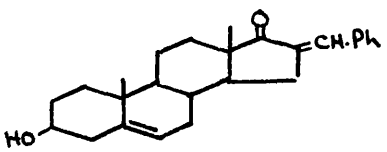
THE ANOMALOUS ULTRA-VIOLET ABSORPTION SPECTRUM OF 16-BENZYLIDENE ANDROST-4-ENE-3:17-DIONE.

Many anomalous ultra-violet absorption spectra have been reported (see previous section for examples and references). Another such anomaly in a steroidal compound has been found in the case of 16-benzylidene androst-4-ene-3:17-dione (I).

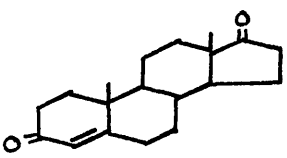
The absorption spectra of (I), 16-benzylidene Δ^5-dehydro-androsterone (II) and androst-4-ene-3:17-dione (III) have been measured at intervals of 1mμ from 220-310mμ. On the assumption that chromophores separated by a number of saturated carbon atoms do not interact, summation of the spectra of the two latter compounds should give a resultant spectrum identical with that obtained from (I).



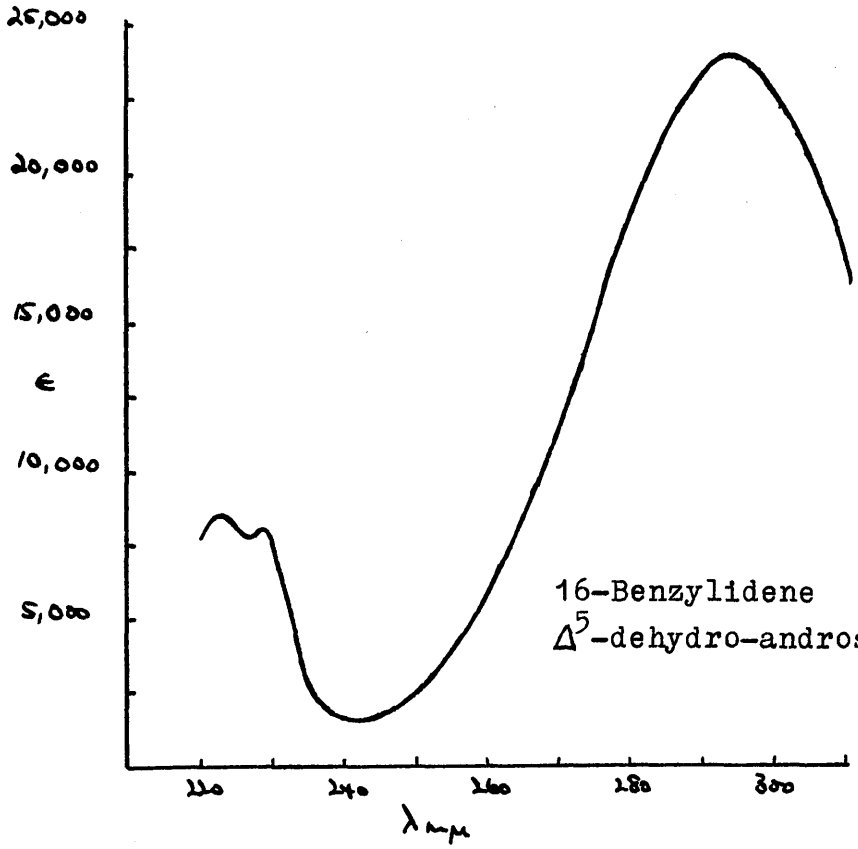
(I)



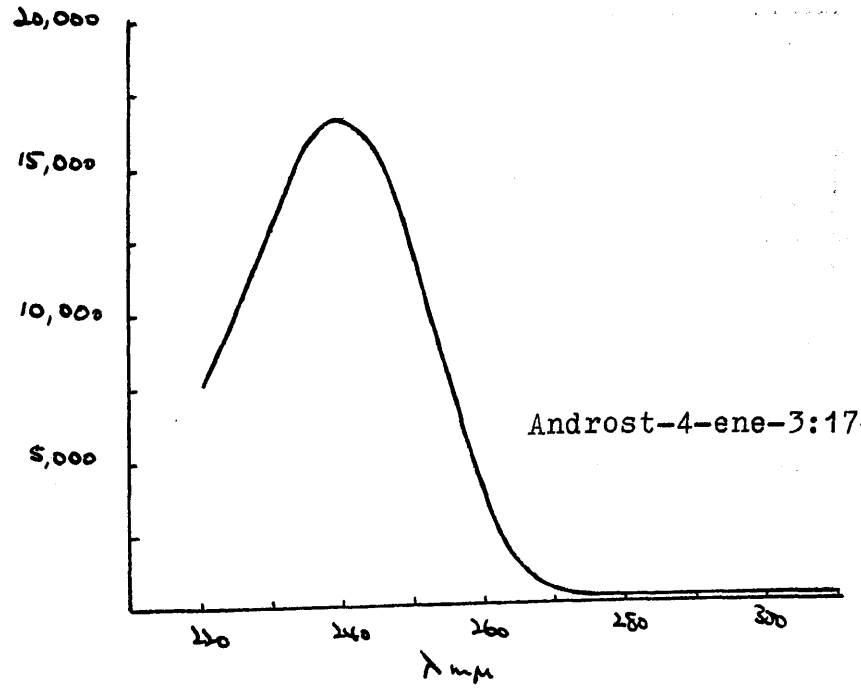
(II)



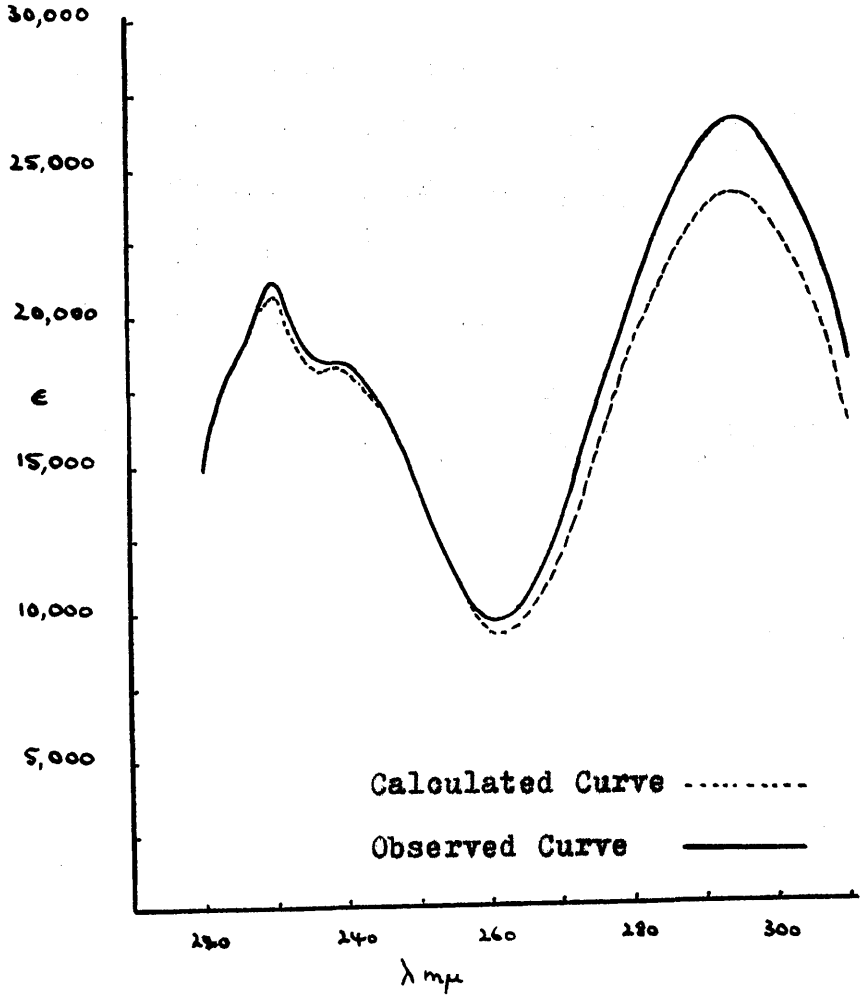
(III)



16-Benzylidene
Δ^5-dehydro-androsterone



Androst-4-ene-3:17-dione



(II)		(III)		(I) Obs.		(I) Calc.		Obs.-Calc.
λ_{max} mμ	ε	λ_{max} mμ	ε	λ_{max} mμ	ε	λ_{max} mμ	ε	ε
223	8570							
229	7970			230	21350	230	20900	+450
		239	16700	238	18600	238	18400	+200
294	24200			294	26800	294	24400	+2400

Inspection of the results, summarized above, shows that there is good agreement between the observed spectrum of 16-benzylidene Δ^4-androst-3:17-dione (I) and that calculated by summation of the spectra of 16-benzylidene Δ^5-dehydro-androsterone (II) and androst-4-ene-3:17-dione (III) in the region 220-260mμ. At the maximum of 230mμ (ϵ 21000) the discrepancy is only 2% based upon the calculated value of ϵ 20900. Above 260mμ the deviation between the calculated and observed curves gradually increases until at the maximum (294mμ) the difference amounts to an ϵ value of 2400, i.e. 10% of the calculated.

This discrepancy, which, in view of the precautions (see below) must surely be real, represents an interaction between two chromophores separated by five saturated carbon atoms in a rigid cyclic system.

The compounds were all dried for 24 hr. in vacuo at 90° prior to determination of spectra.

All spectra (determined on a Unicam S.P. 500 spectrophotometer) were measured at 1mμ intervals from 220-310mμ, cell corrections being applied to every reading. The same ethanol was used for each determination.

In order to show that Beer's Law was obeyed over the critical region the spectra of the two benzylidene compounds (I) and (II) were determined between 288 and 304mμ (at 1mμ intervals) at four different concentrations

varying over a factor of four. Within experimental error Beer's Law was found to be obeyed exactly (see Experimental). Cell corrections were, of course, applied to every reading.

As a further check that the anomaly was in fact real, the spectra were redetermined using samples which had been independantly prepared by Professor D.H.R. Barton, F.R.S., the physical constants of which were in good agreement with those of the original samples. Similar agreement between the calculated and observed curves was found between 220-260mμ, whilst a difference of 14% in the ε values was found at 294mμ.

Experimental.

16-Benzylidene Δ^5-dehydro-androsterone. Treatment of dehydro-androsterone (411mg) in ethanolic potassium hydroxide (0.1M, 50ml) with benzaldehyde (1.56g.) overnight at room temperature gave, on working up in the usual way, the crude benzylidene derivative. Acetylation with acetic anhydride in pyridine at room temperature overnight and filtration of the product through alumina in benzene, followed by crystallization from ethyl acetate and ethyl acetate-methanol, yielded pure 16-benzylidene Δ^5-dehydro-androsterone acetate (357mg) m.p. 251-252, $[\alpha]_D$-55.7 (c 1.62) (Lit.[1] m.p. 255-256).

Alkaline hydrolysis of the acetate, followed by crystallization from ethyl acetate, gave 16-benzylidene Δ^5-dehydro-androsterone m.p. 199-203, $[\alpha]_D$-26.3 (c 1.86), λ_{max} 223, 229 and 294mμ ϵ 8570, 7970 and 24200 respectively.

A sample of 16-benzylidene dehydro-androsterone acetate prepared independantly by Professor Barton had m.p. 256-257, $[\alpha]_D$-55. The derived alcohol had m.p. 199-204, $[\alpha]_D$-22.3 (c 2.02), λ_{max} 223, 229 and 293-294mμ ϵ 8160, 7550 and 22600 respectively. (Lit.[1] m.p. 209-210, $[\alpha]_D$-26.5).

16-Benzylidene androst-4-ene-3:17-dione. A mixture of 16-benzylidene Δ^5-dehydro-androsterone (426mg), dry

benzene (60ml, AnalaR), acetone (10ml, AnalaR) and aluminium tert-butoxide (430mg) were refluxed for 5hr. After cooling and washing the benzene solution with dilute sulphuric acid and water the solvent was evaporated in vacuo and the residue chromatographed over alumina. Recrystallization from n-hexane of the fractions eluted with ether-benzene (5%) gave 16-benzylidene androst-4-ene-3:17-dione m.p. 188-189, $[\alpha]_D$ -19.8 (c 1.52), λ_{max} 230, 238-9 (inflexion) and 294mμ ϵ 21350, 18600 and 26800 respectively.

A sample prepared by Professor Barton had m.p. 188-189, $[\alpha]_D$ -16.0 (c 1.19) λ_{max} 230, 237-8 (inflexion) and 294mμ ϵ 20400, 17850 and 26070 respectively. (Lit.[1] m.p. 188-189, $[\alpha]_D$ -20).

Androst-4-ene-3:17-dione. Prepared by oxidation of dehydro-androsterone with chromium trioxide in pyridine by the usual method, had, after chromatography and crystallization from n-hexane, m.p. 172-173, $[\alpha]_D$ +203.7 (c 1.35), +202.8 (c 1.52), λ_{max} 239mμ ϵ 16700.

A specimen prepared by Professor Barton had m.p. 172-173, $[\alpha]_D$ +203.5 (c 1.15), λ_{max} 239mμ ϵ 15210 (Lit.[2,3] m.p. 172, $[\alpha]_D$ +201; λ_{max} 239mμ ϵ 15100).

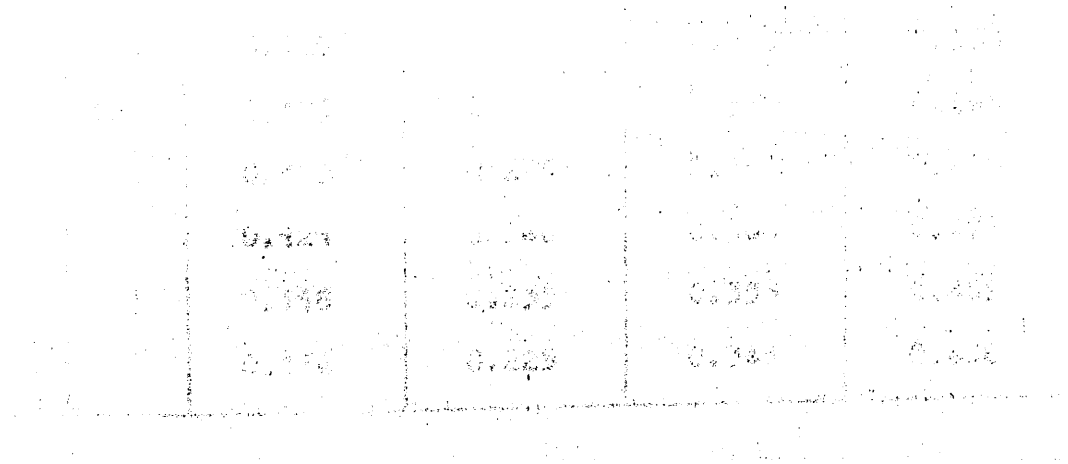
Determination of spectra. The spectra were all determined in absolute ethanol. Concentrations of 0.000835M were used for the two benzylidene compounds

and 0.00119M for the androstenedione.

Optical density readings were taken at 1mμ intervals over the whole range examined (220-310mμ) and cell corrections were applied to all values.

Verification of Beer's Law. Aliquots of 2, 4, 6 and 8ml of a solution (0.00137M) of the two benzylidene compounds were diluted to 10ml with absolute ethanol. Optical density readings were taken at 1mμ intervals, and cell corrections applied, between 288 and 304mμ.

Examination of the results given overleaf shows that, within experimental error, the law holds exactly over this four-fold range of concentration.



16-Benzylidene Δ^5-dehydro-androsterone.

λ mμ	0.000274M	0.000548M	0.000822M	0.001096M
288	0.126	0.250	0.376	0.499
9	0.128	0.254	0.381	0.506
290	0.129	0.257	0.386	0.513
1	0.131	0.259	0.390	0.518
2	0.131	0.260	0.391	0.520
3	0.132	0.261	0.393	0.522
4	0.131	0.261	0.394	0.522
5	0.131	0.260	0.393	0.520
6	0.131	0.260	0.391	0.519
7	0.130	0.259	0.388	0.515
8	0.129	0.255	0.383	0.511
9	0.128	0.252	0.379	0.505
300	0.125	0.248	0.373	0.495
1	0.123	0.245	0.367	0.488
2	0.121	0.240	0.360	0.478
3	0.118	0.235	0.353	0.469
4	0.116	0.229	0.345	0.458

16-Benzylidene androst-4-ene-3:17-dione.

λ mμ	0.000273M	0.000546M	0.000819M	0.001092M
288	0.132	0.266	0.398	0.524
9	0.136	0.270	0.404	0.532
290	0.137	0.274	0.409	0.539
1	0.138	0.276	0.413	0.544
2	0.139	0.276	0.416	0.547
3	0.139	0.279	0.417	0.549
4	0.140	0.280	0.418	0.552
5	0.139	0.279	0.417	0.550
6	0.139	0.279	0.416	0.548
7	0.138	0.277	0.413	0.545
8	0.137	0.273	0.409	0.540
9	0.135	0.270	0.403	0.531
300	0.133	0.265	0.398	0.525
1	0.130	0.262	0.391	0.518
2	0.128	0.258	0.386	0.510
3	0.125	0.252	0.378	0.500
4	0.123	0.248	0.370	0.488

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