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CONFORMATIONAL ANALYSIS—LXXVII*

THE RELATIVE STABILITIES OF THE ISOMERIC ANDROSTANE RING SYSTEMS†‡

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Abstract—The syntheses of four isomeric androstanes (5α14α, 5α14β, 5β14α, and 5β14β) are described. Equilibration over Pd at elevated temperatures gives the relative free energies of these isomers as 1·8, 0, 2·7 and 1·5 kcal/mole, respectively. Force field calculations give the structures of the compounds (bond lengths, bond angles and torsional angles), and these geometries are discussed. The heats of formation of the compounds were calculated, and the relative values agree with the equilibration results.

INTRODUCTION

CONFORMATIONAL analysis has been applied with a high degree of success to 6-membered rings as an aid to a correlation of their physical and chemical properties, and a prediction of such properties for previously unstudied systems.[1] Much of the success in this area has been due to the fact that 6-membered rings for the most part exist as a single chair conformation, and the rather high degree of symmetry and slight distortion in most compounds containing such rings leads to a simple additive analysis of their steric interactions. The situation is quite different with 5-membered rings. Cyclopentane itself exists in two extreme limiting conformations, and the molecule pseudorotates continuously between these extremes.[2] Any substitution into the molecule completely destroys the symmetry, so that there is a whole continuum of possible conformations in the general case. The simple additive type of calculation that has proven so successful with cyclohexane derivatives has been extended to cyclopentane derivatives, but the calculations are laborious and the results are of somewhat uncertain validity.[3]

The geometry of cyclopentane itself is now pretty well known,[2] and the force field which we described earlier[4] reproduces this geometry reasonably well, and gives approximately the same energy for the C_2 and the C_s forms, which is in agreement with experiment.[5] When applied to the hydrindane system, these calculations gave accurately the heats of formation known for these molecules, and structures which appear to be

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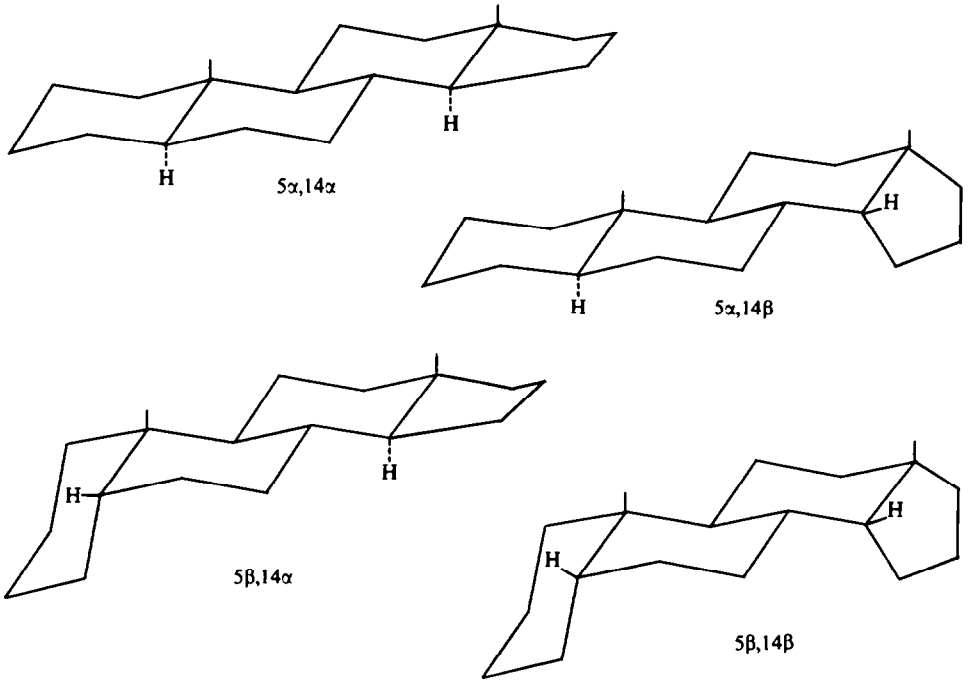
quite reasonable (the structures are not experimentally known). In addition, these calculations have been applied to decalin,[4] perhydroanthracene,[6] and perhydrophenanthrene[7] ring systems, and in all cases the structures and energies appear to be accurate in comparison with the available experimental data. In this paper we will discuss the next step in expanding these calculations, and consider the important androstane ring system (I), a basic ring system which occurs in a wide variety of natural products, particularly in steroidal compounds.[8]

The most commonly occurring androstane ring system which is found in nature is the one with the *trans-anti-trans-anti-trans* stereochemistry. This is the 5α,14α-androstane system, which appears to be generated in the squalene cyclization. It is not, however, the thermodynamically stable isomer.



The isomeric androstanes (I)

Another group of compounds of wide occurrence in nature are those related to coprostane, or the cholic acids, which have the 5β,14α-androstane ring system. These are generally thermodynamically less stable than the 5α,14α-isomers, but the energy difference is not very great.

The 5α,14β-androstane proved to be the thermodynamically stable isomer, and molecules with this stereochemistry are reasonably plentiful in natural products, though less so than the 14α isomers. The natural 14β compounds seem to usually be found with an OH at C-14. It seems likely that this OH is added in the biosynthesis via an oxidation at a later stage in most all cases, and the configuration at C-14 becomes β in the course of the transformation.

The other isomer of interest is the 5β,14β-androstane, which combines the relatively uncommon features of two of the above isomers. Compounds isomeric with the natural material at the B-C ring junctures are extremely scarce, and are generally expected to be quite unstable. We have not considered them in the present work.

We believe that calculations of the molecular mechanics type such as have been described previously by us and by several other research groups are now quite competitive with any available experimental methods for determining such items as the relative stabilities of isomers of the type discussed here. It is doubtful, for example, if heats of combustion could be measured to an accuracy of greater than about 2 kcal/mole for molecules as large as these. On the other hand, the epimerization–equilibration method which we have developed and applied extensively in simpler cases is often capable of giving very good results, but is dependent to some extent on the accuracy that happens to be available from the analytical technique used, usually vapor phase chromatography. The method typically gives free energy differences to an accuracy better than ±0·3 kcal/mole under favorable circumstances. Our calculational method, applied to a wide variety of molecules similar to those under discussion but of smaller molecular weight, has given heats of formation for the molecules in the gas phase to within about 0·4 kcal/mole of the experimental values, on the average. Since the calculation usually involves perhaps one or several orders of magnitude less effort on the part of the chemist, there is considerable reason to determine these structures by calculation, rather than by direct experimentation, if one is convinced that the results will be adequate. We have examined the present molecular system because it is fundamental in a wide variety of natural products, and the results are of practical interest. It is also the biggest system we have dealt with extensively to date, and we wish to try to establish the accuracy to which the calculation can be carried out in such a case.* We therefore wanted to equilibrate the androstanes, and determine experimental values for the free energy differences, and then see how closely the calculations could reproduce these numbers. All of these isomeric androstanes have been mentioned previously in the literature, but for two the syntheses have never been described.

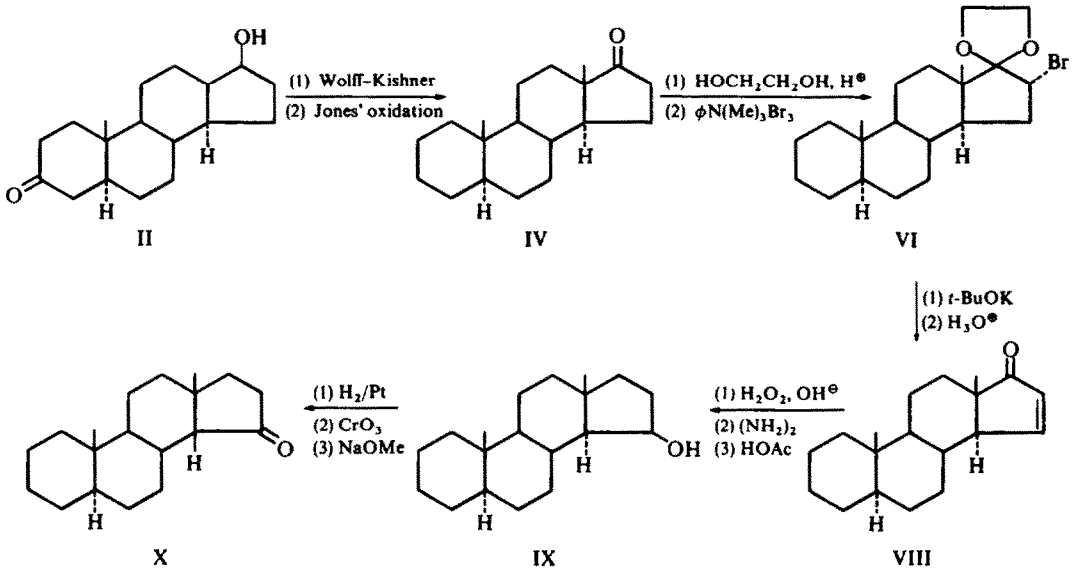
SYNTHETIC WORK

5α,14α-Androstane and 5β,14β-androstane are previously described compounds. They were obtained by standard methods, and their physical properties agree with those reported in the literature. 5α,14β- and 5β,14α-Androstane had not been previously described in the literature, and the syntheses devised for them were as follows.

The preparation of 5α,14β-androstane (Iαβ) was originally attempted by way of the reduction of 5α,14β-androstan-15-one, which is presumably available as outlined, as suggested by the work of Djerassi.[10]

5α,14α-Androstan-3-one-17β-ol (II), obtained from testosterone, was reduced to 5α,14α-androstan-17-ol (III) by a modified Wolff-Kishner reaction. The latter compound was oxidized to the ketone (IV), which was convereted to the ketal (V), which was in turn brominated[11] to the 16α-bromo ketal (VI). The latter was then dehydrobrominated to VII, which in turn was cleaved with acid to yield Δ^{15}-5α,14α-androsten-17-one (VIII). The preparation scheme was interrupted here because it was found that

* The only other attempt so far reported to study molecules of this size in this way used a rather similar force field to ours, and obtained results that appear to be quite good.[9]



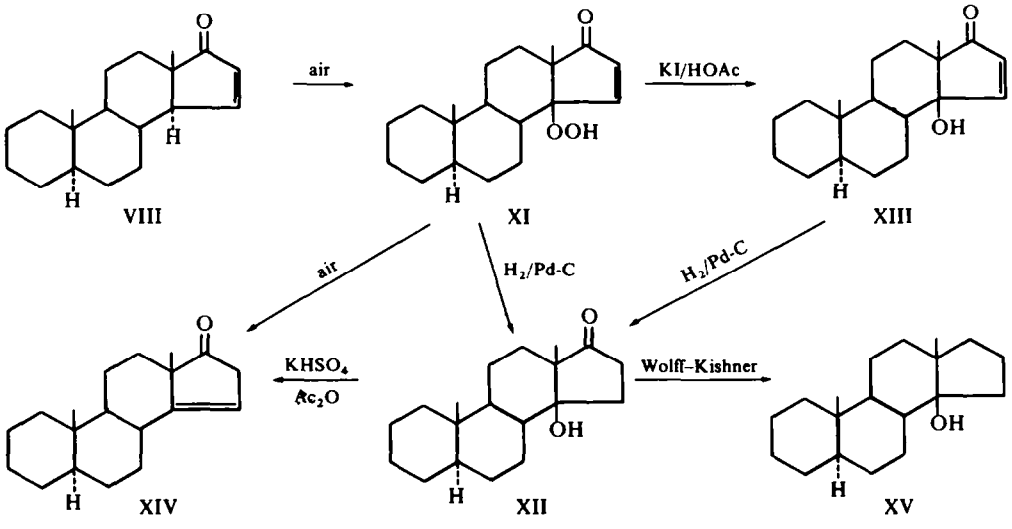
VIII was rapidly oxidized upon standing in air. This oxidation was also observed independently by Campbell *et al.*,[12] and was subsequently reported by them, along with characterization of the reaction product.

When Δ^{15}-5α,14α-androsten-17-one (VIII) was allowed to stand in the air for several days, a new compound (XI) was formed in high yield. Analytical data and mass spectrum indicated that this compound had the empirical formula $C_{19}H_{28}O_3$. The only large peak in the mass spectrum between 150 and 304 was at 288, which corresponds to the loss of an O atom. These data suggested that XI was Δ^{15}-14β-hydroperoxy-5-α-androsten-17-one. Compound XI showed an UV maximum at 214 nm. Although this appeared to be at rather short wavelength for a Δ^{15}-17-one chromophore (both the 14α- and 14β-isomers of the Δ^{15}-17-one absorb at 230 nm), substitution on the D ring may vary considerably the degree of planarity of the chromophore, and hence the absorption.[13] Assignment of the peaks in the NMR spectrum of XI was quite straightforward. A doublet at 5·78 δ was assigned to the vinyl proton at C-16 (coupled to vinyl proton at C-15; J = 6 Hz, area 1) and the other doublet at 6·92 δ was assigned to the vinyl proton at C-15 (coupled to the vinyl proton at C-16; J = 6 Hz, area 1). The IR spectrum of XI contained bands at 1680 (conjugated cyclopentenone) and 3230 cm^{-1} (OH).

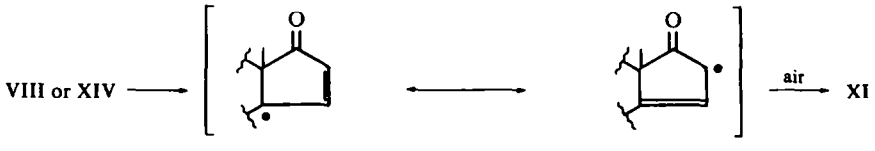
Hydrogenation of XI gave a saturated ketone (XII) (*m/e* 290, analytical data consistent with $C_{19}H_{30}O_2$, no vinyl protons in the NMR, no UV absorption 200–240 nm). The IR CO band appeared at 1730 cm^{-1}, indicating conjugation with the double bond in XI was removed. The OH group in compound XII was resistant to oxidation with Jones' reagent, indicating a tertiary OH group.

Based on the allylic oxidation of olefins, it was postulated that compound XI is a 14-hydroperoxy compound. For characterization, the hydroperoxide (XI) was treated with potassium iodide in acetic acid. It was converted quantitatively to Δ^{15}-5α-androsten-14β-ol-17-one (XIII). Elemental analysis and mass spectrum substantiated the molecular formula of $C_{19}H_{28}O_2$. Assignment of the peaks in the NMR of

XIII was again straightforward. A doublet at 6·25 δ was assigned to the vinyl proton at C-16 and the other doublet at 7·6 δ to the vinyl proton at C-15. Compound XIII was hydrogenated in the presence of Pd-C, furnishing 5α-androstan-14β-ol-17-one (XII). The low wavelength UV maximum of XIII at 210 nm is noted in several other 14β-hydroxy conjugated cyclopentenones.[13] The assignment of the 14β-configuration to the OH group in compound XIII was in keeping with its ORD, which showed a positive Cotton effect curve characteristic of 14β-substituted Δ^{15}-androsten-17-ones.[13]

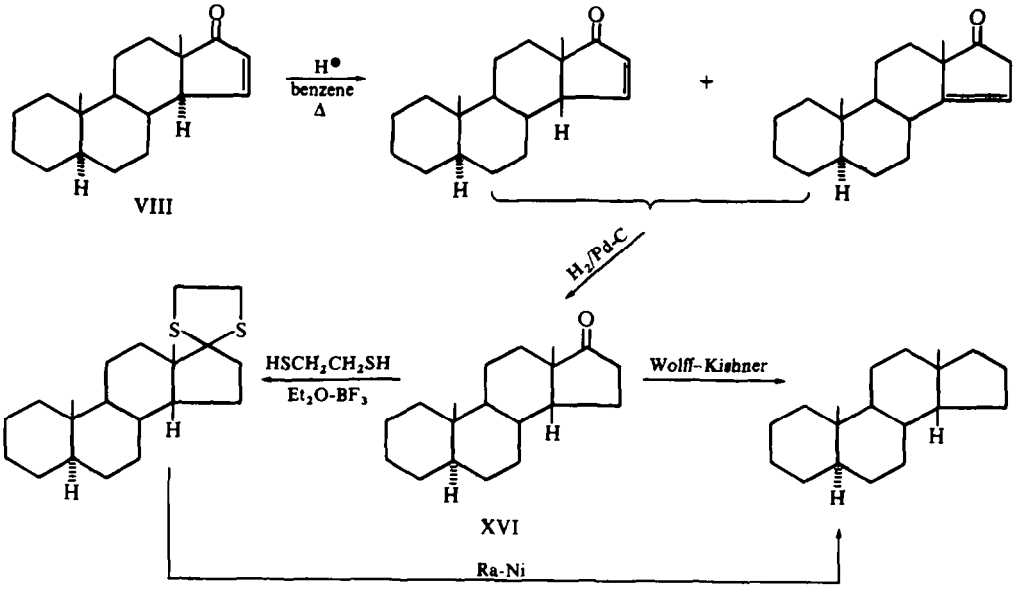


Dehydration of the 14β-hydroxy compound XII with potassium hydrogen sulfate in boiling acetic anhydride gave Δ^{14}-5α-androsten-17-one (XIV). Structural assignment of XIV was secured by its characteristic spectra. The mass spectrum gave a parent ion peak at 272 *m/e*. The IR spectrum contained bands at 1740 (non-conjugated cyclopentenone), 1670 (C=C stretching for a trisubstituted alkene), and 3050 cm^{-1} (C—H stretching for a trisubstituted alkene). The NMR spectrum showed a multiplet at 5·7 δ, which was assigned to the vinyl proton at C-15 (coupled to C-16 methylene protons, 1H) and the multiplet at 2·8 δ was assigned to the two methylene protons at C-16 (2H). Compound XIV also underwent oxidation upon standing in the air to 14β-hydroperoxy compound XI. The oxidation of compounds VIII and XIV presumably proceeds via the same radical intermediate.



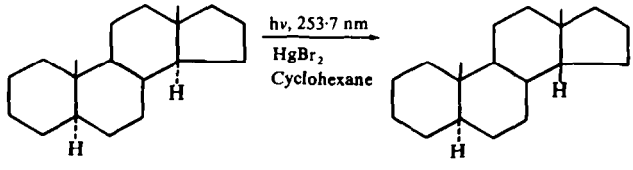
Various alternative methods to produce 5α,14β-androstane were also investigated. Unlike Δ^{14}-steroids containing a β-oriented side chain at C-17, which are hydrogenated from the α-side,[14] Δ^{14}-androsten-17-ones have been found to add hydrogen from the β-side to give 14β-androstane derivatives.[15] Hydrogenation of Δ^{14}-5α-

androsten-17-one was therefore expected to and did give 5α-14β-androstan-17-one (XVI).



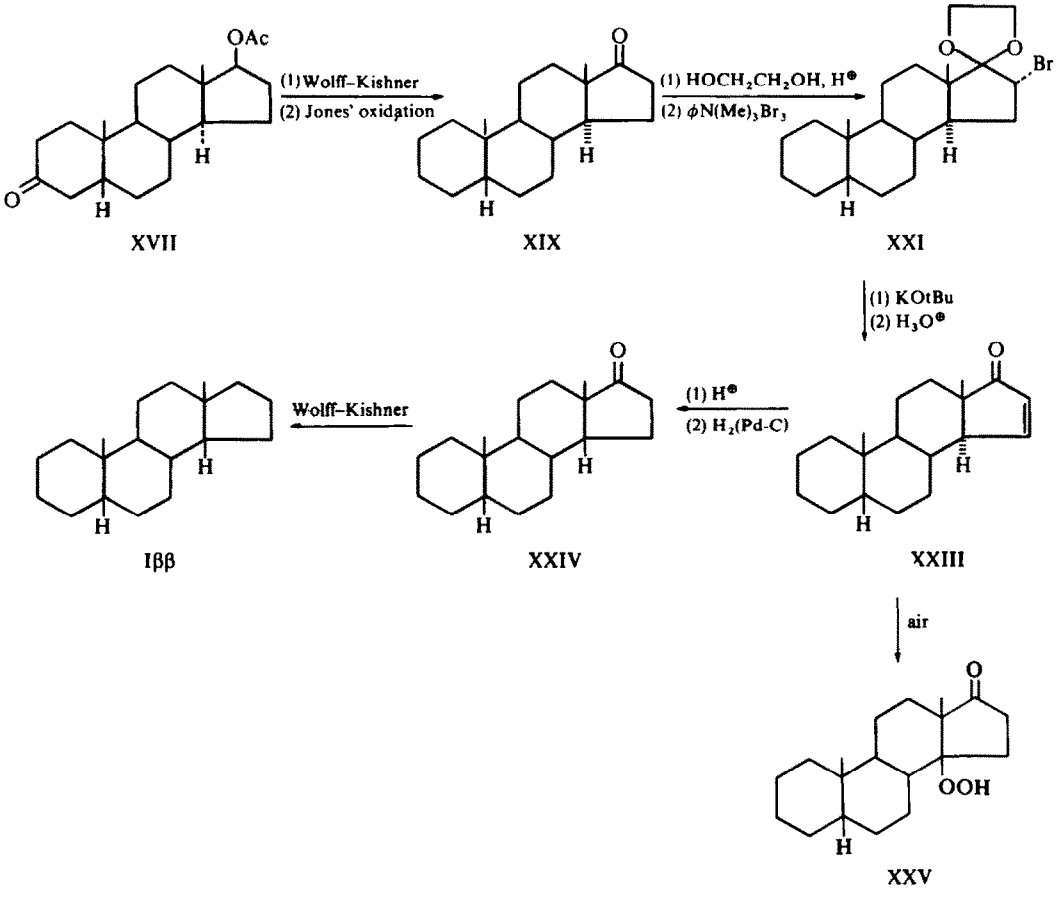
The 18 angular Me group of 5α,14β-androstan-17-one appeared at 1·07 δ while the 18 angular Me group of 5α,14α-androstan-17-one appeared at 0·867 δ. Compound XVI was subsequently reduced to 5α,14β-androstane (Iαβ) by a modified Wolff-Kishner reaction. The structure assigned to the 14β-androstane Iαβ is also borne out by the NMR data.[16] The removal of the CO group from compound XVI via the Raney-Ni desulfurization of its thioketal was also investigated. 5α,14β-Androstane (Iαβ) obtained from the Raney-Ni desulfurization of 17-thioketal has m.p. 47° and $[\alpha]_D^{23}$ +32°. The NMR spectrum of the compound Iαβ contained a singlet at 0·763 δ (19 angular Me) and a singlet at 0·988 δ (18 angular Me). The alternative way tried for preparing Iαβ was by epimerization[17a] of Δ^{15}-5α,14α-androsten-17-one (VIII) followed by hydrogenation to give 1α,14β-androstan-17-one (XVI).

The amount of compound Iαβ obtained by the methods mentioned was small, but just at this time a new method[17b] appeared in the literature for preparing 14β-steroids, which was tried here and proved to be successful. It is clearly a more practical method than the others under investigation. The yield of desired product is very high, and doubtlessly the reaction is thermodynamically controlled.



Iαα Iαβ

The synthetic scheme which was used for the preparation of 5β,14β-androstane (Iββ) is outlined.



5β-14α-Androstan-17β-ol-3-one acetate (XVII), prepared as described,[18] was reduced to 5β,14α-androstan-17β-ol (XVIII) by a modified Wolff-Kishner method. Oxidation of the latter, followed by ketalization and bromination gave the 5β,16α-bromoketal (XXI). Dehydrobromination of XXI to Δ^{15}-5β,14α-androsten-17-one ethylene ketal (XXII) was traced by TLC and IR and required a period of one week, whereas the 5α isomer VI required only 16 hr. This appears to be an interesting example of conformational transmission.[19] Cleavage of the ketal with acid led to Δ^{15}-5β,14α-androsten-17-one (XXIII), which showed the expected UV absorption maximum at 234 nm. Compound XXIII was found to be susceptible to oxidation in the air. Therefore, a freshly prepared sample was epimerized to the 14β derivative (some was converted to the Δ^{14} isomer simultaneously), which was directly hydrogenated to ketone XXIV. Wolff-Kishner reduction of the latter gave 5β,14β-androstane (Iββ), m.p. 58–59°, $[\alpha]_D^{23}$ +31·88°. Structural assignment of 5β,14β-androstane was secured by its physical properties being different from 5β,14α-androstane (mixed m.p., NMR and specific rotation) and the elemental analysis. The NMR spectrum of the compound

contained a singlet at 0·879 δ (19 angular Me) and a singlet at 0·983 δ (18 angular Me).

The physical properties of the four androstanes are summarized in Table 1.

TABLE 1. PHYSICAL PROPERTIES OF THE ANDROSTANES

Isomer	mp	Ret. time on vpc* (min)	$[\alpha]_D^{25}$	NMR 19-Me (δ)	NMR 18-Me (δ)
5α,14β-	50°	36·8	+33·82°	0·763	0·988
5β, 14β-	58–59	29·6	+31·88	0·897	0·983
5α,14α-	46–47	36·8	+1·32	0·793	0·700
5β,14α-	78–79	32·6	+2·03	0·933	0·700

* The VPC of the compounds were analyzed on Perkin–Elmer F-11 Gas Chromatograph with a 100 ft. SE-30 capillary column at 140° and a flow rate of 6 lbs.

EQUILIBRATION AND ANALYSIS

Having all four isomers available, they were examined with respect to their properties on VPC.

It was found with synthetic mixtures that the 5β,14β- and the 5β,14α-isomers could be cleanly separated, but the other two were obtained together as a single peak. Samples were then equilibrated at known temperatures in the presence of a Pd catalyst, and analyzed at appropriate time intervals, sufficiently spaced to establish that equilibrium had been reached. Some decomposition was noted in the analysis, which interfered somewhat.

What seemed like a possible alternative method for the analysis was to use the Me peaks in the NMR spectra of the mixtures. By adding authentic samples to the equilibrated mixture, it was possible to establish with certainty which peaks belonged to which isomers, and therefore to determine from the area under each peak the relative concentration of each isomer. There are two Me peaks visible for each isomer, and consequently the opportunity for two independent measurements on each isomer on each sample. Not all of the peaks for all of the isomers are completely separated, however.

From the VPC and NMR data together, it was possible to do two independent analyses. One set of data (A) was obtained from NMR peaks B, C, D, and E; the other set of data (B) was obtained from peaks *a* and *b* (the first two peaks eluted) of the VPC data, together with peaks A and F of the NMR. The two sets of data agreed within ±3% of known values on synthetic mixtures. This indicated that both methods were suitable for our purposes, and allowed two independent analyses for each sample so as to minimize the inaccuracies caused by impurities.

Equilibrations were carried out at five separate temperatures, each mixture was analyzed by both methods A and B, and two analyses were averaged, and the ΔG° values were tabulated for each temperature for each different isomerization. In Table 2 these numbers are listed for the 5α,14β-androstane ⇌ 5α,14α-androstane, which is typical.

TABLE 2. FREE ENERGY DATA FOR 5α,14β-ANDROSTANE ⇌ 5α,14β-ANDROSTANE

Temp °K	ΔG° kcal/mole
545	1·57 ± 0·18[a]
553	1·59 ± 0·03
573	2·04 ± 0·44
589	2·14 ± 0·65
602	1·77 ± 0·45

[a] These are average deviations.

These data are not of sufficient accuracy to permit the variation of the equilibrium constant with temperature to be determined, thus we cannot get entropies and enthalpies, but only free energies from the data. These were taken for the average temperature 573°K, and are summarized in Table 3.

TABLE 3. THE (EXPERIMENTAL) RELATIVE STABILITIES OF ANDROSTANES AT 573°K

Isomers	ΔG° (kcal/mole)
5α,14β-Androstane	0·00
5β,14β-Androstane	1·48 ± 0·35
5α,14α-Androstane	1·77 ± 0·45
5β,14α-Androstane	2·66 ± 0·22

CALCULATIONS

We have applied our molecular force field calculations to the androstane isomers. Previous work on the decalins, anthracenes, perhydrophenanthrenes, and hydrindanes has indicated that with such molecules we can usually calculate the energies with an accuracy competitive with the best that can be done experimentally. The error in equilibrium measurements is a function of unpredictable and uncontrollable things like the degree of separation that can be obtained on VPC, etc. Having run the calculations on molecules of this sort from various starting geometries a number of times, it would seem that in general the energy minimum is located to within about 0·3 kcal/mole. We believe that the force field gives results that are about this good in cases such as those described here, so the energy differences which we calculate between isomers are about as good as those obtained by actual measurement.

The heat of formation calculated for the most stable isomer, 5α,14β-androstane, is −67·18 kcal/mole (gas phase, 25°). The relative enthalpies of the other isomers are given in Table 4.

First, we note qualitatively that the 5α ring juncture is more stable than the 5β, and the 14β ring juncture is more stable than the 14α, in agreement with what one would guess from the model compounds decalin, 9-methyldecalin, and hydrindane,

TABLE 4. THE RELATIVE ENERGIES OF THE ISOMERIC ANDROSTANES

Compound	Energy[a] Calculated	Found
α,β	0·00	0·00
β,β	0·73	1·48 ± 0·35
α,α	1·18	1·77 ± 0·45
β,α	1·87	2·66 ± 0·22

[a] The calculated energy is an enthalpy while the experimental one is a free energy. Since the entropy differences are expected to be small, the comparison is made.

and in agreement with what was found by direct measurements reported in the previous section. The calculated and found differences in energy are qualitatively in agreement throughout. Thus the 5β ring juncture, while unfavorable, is not as unfavorable as the 14α ring juncture, both by experiment and by calculation.

We might ask whether or not the isomerization energies at the 5- and 14-positions are independent of one another, or is there a conformational transmission which leaves their energies to be non-additive. According to the calculations, they are additive, so that one might suppose the conformational distortion induced at one end of the molecule by the change at the other end is small. In terms of energy, this is certainly the case. To find whether or not this is true in terms of geometry, more intensive study is required.

DISCUSSION AND CONCLUSIONS

The androstane calculations which we have carried out give a great deal of information in terms of bond angles, dihedral angles, etc. Many of these data can be compared against known literature values, many cannot. We want to establish how good the correspondence is where the comparison is possible, which will give us an estimate of the reliability of the calculations where there is no direct experimental data.

If we consider cyclohexane first, there are two independent, reasonably accurate structure determinations, both by electron diffraction, for this compound.[20] In Table 5 are given the data reported by Davis and Hassel, the data reported by Buys

TABLE 5. THE STRUCTURE OF CYCLOHEXANE

	Calcd.	Found Davis–Hassel[20]	Buys–Geise[20]
C—C	1·530 Å	1·528 ± 0·005	1·520 ± 0·003
C—H	1·10 Å	1·104 ± 0·005	1·113 ± 0·003
C—C—C	111·1°	111·55 ± 0·15	111·05 ± 0·10–0·15
ω	55·8	54·5 ± 0·4	55·9 ± 0·3–0·4
H—C—H	107·0°		110 ± 4

and Geise, and the data which we have calculated. The agreement between our calculated values and the recent values reported by Buys and Geise (which were not available to us at the time of our calculations) is gratifying. It seems to be generally appreciated now that the C—C—C bond angle in cyclohexane is considerably larger than the tetrahedral value. It is less widely appreciated that this angle is also substantially smaller than the corresponding value found in open chain alkanes. If we accept a bond angle of 111·1° and a dihedral angle of 55·9° as typical values for the cyclohexane ring, then we are in a position to compare the values found by our calculations for the steroidal system with these typical values. In Table 6 are given the calculated torsional angles and bond angles in ring A in each of the isomeric androstanes, and also for comparison some X-ray data.

TABLE 6. CALCULATED TORSIONAL ANGLES (ω) AND BOND ANGLES (θ) OF RING A IN ANDROSTANES AND SOME X-RAY DATA FOR STEROIDS RING A

	5α-Steroids			5β-Steroids		
(ω)	Calcd.		Obs.	Calcd.		Obs.
10-1-2-3	−55·9°	−56·8°	−55·7°	+59·4°	+58·9°	+57·8°
1-2-3-4	+54·3	+54·5	+51·9	−57·1	−56·4	−55·0
2-3-4-5	−54·8	−54·0	−52·3	+55·2	+55·3	+54·6
3-4-5-10	+56·5	+55·7	+56·3	−52·9	−53·5	−56·6
4-5-10-1	−53·3	−53·1	−55·3	+48·9	+49·5	+53·9
5-10-1-2	+53·2	+53·6	+55·3	−53·4	−53·6	−55·4
(θ)	(1)	(2)	(3)	(5)	(6)	(4)
2-1-10	114·4	114·8	113·5	115·5	115·7	114·0
1-2-3	111·1	111·1	112·4	109·3	109·4	111
2-3-4	110·4	110·4	111·5	109·5	109·6	110
3-4-5	111·3	111·4	112·7	112·9	112·9	112
4-5-10	114·5	114·9	113·2	114·7	114·4	113
5-10-1	106·9	106·5	106·2	107·2	107·1	107

(1) 5α,14α-Androstane.
(2) 5α,14β-Androstane.
(3) 3α-Hydroxy-5α-Androstan-17-one.[21]
(4) 5β,14α-Androstane.
(5) 5β,14β-Androstane.
(6) Ecydson.[22]

In general, looking at the calculations for the 5α-androstanes, the dihedral angles are a little smaller on the average than they are in cyclohexane. Thus the ring is flattened slightly by the presence of the 19-Me and the fusion of the B ring. The differences are not very great, in all cases less than 3° in dihedral angle. If we look at the experimental values, we notice the differences of up to 3° between them for dihedral angles that should be equivalent. The calculated values in each case are within 2° of one or both of the observed values. Thus the calculations seem to accurately reproduce the experimental data, insofar as one can tell.

If we look at the bond angles in the same table, we see that there are three which are different from the values in cyclohexane by more than 3°; the C—C angles at C-1, at C-5, and at C-10. The latter two involve carbons which are not methylene groups as

in cyclohexane, but tertiary and quaternary carbons, respectively. The 19-Me, according to the calculations on methylcyclohexane, would be expected to expand the angles at C-1 and C-5 in an effort to relieve the repulsions between the Me and *syn-axial* hydrogens, and this is what is observed. The deformations are just what we expected from a consideration of model compounds. In addition, a comparison with the experimental values shows that the angles predicted to be large are in fact large, the one predicted to be small is in fact small, so quantitively the agreement is perfect. Quantitatively, the small angle at C-10 is well reproduced. The larger angles are calculated to be about 4° larger than in cyclohexane, and they are found to be about 3° larger. The agreement is certainly very good.

We were unable to locate any accurate data on the structure of a 5β-steroid where ring A was not substituted with complicating groups. The one selected for comparison is ecdyson, 2β, 3β, 14α, 22β, 25-pentahydroxy-Δ^7-5β-cholesten-6-one, and the agreement is perhaps as good as one might expect. The deviation of the dihedral angles from those in cyclohexane which is observed in the 5β-androstanes is somewhat larger than with the 5α-androstanes. On the whole, the diheral angles are smaller, by as much as 6 or 7° in one case, although one is conspicuously (3°) larger (10-1-2-3) than in cyclohexane. Going along with this, the bond angles at C-1 and C-5 are unusually large (3–4°), while those at C-2, C-3, and C-10 are unusually small. The angle at C-10 is small because the carbon is quaternary. The angles at C-2 and C-3 appear to be small in an effort to maintain the ring puckering and counterbalance the effect of the large angles at C-1 and C-5.

It might be remarked in passing that in trying to understand coupling constants in the nmr, the Karplus equation relating the constant to dihedral angle is a basic tool.[23] It should be noted that when bond angles change by several degrees relative to their nominal structure because of their particular environment, dihedral angles also change. In the cases discussed here so far, the dihedral angle change is comparable with the bond angle change. In other cases (for example, in cyclobutane), a change in bond angle of 1° may lead to a change in dihedral angle of the order of 20°. Clearly, any geometric conclusions reached from studying models, or from other similar first order approximations, may lead to dihedral angles which are very considerably in error. Naturally, the correlation between coupling constant and such approximate dihedral angles is going to be inaccurate.

Next we can turn our attention to ring B. We have done the calculations for two compounds with a 5α ring juncture, and these should be comparable to what is observed for 3α-hydroxy-5α-androstan-17-one. The data are summarized in Table 7. Looking first at the dihedral angles, not much trend is evident. The calculated and observed values are within about 4° of cyclohexane itself.

On the average, calculated and experimental values are both smaller than in cyclohexane, indicating a slightly flattened ring. Next, looking at the bond angles, the values calculated for our two examples are pretty similar, the largest difference being 1·6°. The experimental values are again pretty similar to the calculated ones, the largest angle by calculation is the second largest by experiment, and the smallest angle by both calculation and by experiment.

Good comparison data are not available for the 5β-steroids, but the calculated angles and dihedral angles are unexceptional, being within about 2° in each case of the 5α values.

TABLE 7. CALCULATED TORSIONAL ANGLES (ω) AND BOND ANGLES (θ) OF RING B IN ANDROSTANES AND SOME X-RAY DATA FOR STEROID RING B

	5α-Steroids			5β-Steroids	
(ω)	Calcd.		Obs.	Calcd.	
8-9-10-5	−55·7	−52·5	−56·7	−54·9	−53·5
9-10-5-6	+57·2	+56·8	+57·7	+54·6	+55·3
10-5-6-7	−57·9	−60·1	−57·3	−55·5	−57·0
5-6-7-8	+54·0	+55·5	+53·5	+53·5	+53·4
6-7-8-9	−52·7	−51·0	−51·7	−53·0	−50·4
7-8-9-10	+55·1	+51·1	+54·2	+55·2	+52·0
(θ)	(1)	(2)	(3)	(4)	(5)
10-9-8	113·0	114·6	112·7	113·1	114·3
9-10-5	107·3	107·6	107·4	108·7	108·5
10-5-6	112·7	112·4	112·1	112·5	112·2
5-6-7	111·1	110·6	111·5	112·4	112·1
6-7-8	111·3	111·6	113·2	111·2	112·0
7-8-9	111·7	112·2	110·8	111·7	112·0

(1) 5α,14α-Androstane.
(2) 5α,14β-Androstane.
(3) 3α-Hydroxy-5α-androstan-17-one.[21]
(4) 5β,14α-Androstane.
(5) 5β,14β-Androstane.

TABLE 8. CALCULATED TORSIONAL ANGLES (ω) AND BOND ANGLES (θ) OF RING C IN ANDROSTANES AND SOME X-RAY DATA FOR STEROID RING C

	14α-Steroids			14β-Steroids	
(ω)	Calcd.		Obs.	Calcd.	
9-11-12-13	−54·0	−53·3	−54·8	−57·4	−57·2
12-11-9-8	+46·0	+45·2	+53·7	+51·8	+50·7
14-8-9-11	−45·3	−44·6	−52·9	−48·9	−47·5
9-8-14-13	+55·4	+54·8	+56·3	+50·6	+49·8
8-14-13-12	−62·0	−61·7	−59·0	−50·6	−51·0
14-13-12-11	+59·6	+59·3	+55·4	+54·3	+55·0
(θ)	(1)	(2)	(3)	(4)	(5)
11-12-13	110·9	111·1	109·7	113·7	113·6
9-11-12	114·2	114·3	110·5	112·8	112·9
8-9-11	112·7	113·0	111·5	109·3	110·0
9-8-14	111·1	111·6	109·0	114·9	115·0
8-14-13	113·4	113·4	113·4	114·4	114·5
12-13-14	106·9	107·1	110·5	108·5	108·5

(1) 5α,14α-Androstane.
(2) 5β,14α-Androstane.
(3) 3α-Hydroxy-5α-androstan-17-one.[21]
(4) 5α,14β-Androstane.
(5) 5β,14β-Androstane.

The torsional angles in ring C (Table 8) show a little more deviation from the nominal value, especially by calculation, than those in rings A and B. The spread in dihedral angle is from 45·3° to 62°, which is appreciably greater than the observed spread of 52·9° to 59·0°. The experimental data are for a compound with a ketone group at C-17, however.

Two of the bond angles here (9-11-12 and 12-13-14) show deviations from the experimental ones which are more than 3°. For the remaining angles, the agreement is much better.

Ring D is more of a challenge from the calculational viewpoint, because it is not really clear *a priori* what basic structure (envelope or half-chair) is going to be found, or to be precise, it is not clear what dihedral angles are to be expected around the ring. In Table 9, the calculated dihedral angles show quite a spread, and the agreement with experiment is within 2° in each case. The experimental value is for a compound bearing a cholestane side chain, so the agreement is fortuitously good. The bond angles are also good to within 2°, and they show a substantial variation: about 6° difference between the smallest and largest values. The two 14β compounds studied have similar calculated values, and again they are thought to be comparable in accuracy to the 14α calculations, but experimental data are not available for comparison.

TABLE 9. CALCULATED TORSIONAL ANGLES (ω) AND BOND ANGLES (θ) OF RING D IN ANDROSTANES AND SOME X-RAY DATA FOR STEROID RING D

	(ω)	14α-Steroids Calcd.		Obs.	14β-Steroids Calcd.	
ω_0	17-13-14-15	+46·5	+45·8	+46·8	−38·2	−38·2
ω_4	13-14-15-16	−34·5	−33·7	−33·6	+27·4	+26·0
ω_3	14-15-16-17	+9·1	+8·3	+7·6	−5·5	−3·2
ω_2	15-16-17-13	+19·4	+20·0	+20·6	−18·5	−20·7
ω_1	16-17-13-14	−40·1	−40·1	−40·4	+34·9	+36·4
	(θ)	(1)	(2)	(3)	(4)	(5)
	17-13-14	100·5	100·6	100·6	102·1	102·0
	13-14-15	103·7	103·7	104·9	105·0	105·0
	14-15-16	103·6	104·0	102·9	105·9	106·1
	15-16-17	106·6	106·4	106·9	105·9	105·8
	16-17-13	104·1	104·2	103·2	106·3	106·0

(1) 5α,14α-Androstane.
(2) 5β,14α-Androstane.
(3) 2α,-3β-Dibromo-5α-cholestane.[24]
(4) 5α,14β-Androstane.
(5) 5β,14β-Androstane.

We believe (largely on the basis of studies other than those reported here) that our calculated geometries for molecules such as those discussed herein are of an accuracy competitive with those obtainable by X-ray diffraction, i.e. bond lengths almost always within 0·01 Å, and bond angles almost always within 2° (4° for angles involving hydrogens). The accuracies of the calculated energies have been commented on earlier.

In the long run, we must compare the expense of determining structures and energies by calculation with those from X-ray (or other) and heat of combustion (or other) measurements. The calculations required 20–40 minutes (IBM 360/65) for each molecule, starting from rough geometries based on models. Compared with experimental methods which require synthetic work of the sort of complexity met with herein, the computational approach is less expensive by a factor of 10–100 Exploratory calculations indicate that by using more sophisticated mathematical methods, it will be possible to reduce computing times by what we conservatively estimate will be at least a factor of 3. Thus we feel that there is no question but that the calculational method is by far the practical method for solving problems of the sort discussed here. The important qualification must be made, however, that the method is at present limited to molecules, not too highly strained, which fall within the boundary of limitations set by the approximations used in defining the force field. Some attention is now being given to the problem of relaxing some of these limitations.

EXPERIMENTAL

Testosterone was reduced to 5α,14α-androstan-17β-ol-3-one (II) with Li in ammonia, 57% m.p. 175–178° (lit.,[25] m.p. 181°). Modified Huang–Minlon reduction[27] gave the 17β-ol (III), purified by vacuum sublimation, m.p. 165–166° (lit.,[28] m.p. 165°), yield 94%. Jones oxidation[29] of III gave IV, 77% m.p. 117–119° (lit.,[30] m.p. 120°). The ketone IV was converted to the ketal (V) following the procedure of Djerassi,[10] yield 79%, m.p. 141–143°, reported[31] m.p. 145–146°. Bromination of the ketal[10] with phenyltrimethylammonium bromide perbromide[11] gave the 16α-bromo-5α,14α ethylene ketal, 71%, m.p. 148° (lit.,[11] m.p. 146–148°). Compound VII was obtained by dehydrobromination of the bromoketal,[10] 59%, m.p. 116–117·5°; reported[10] m.p. 120–121°. Hydrolysis of the ketal[10] gave VIII, 41%, m.p. 98–103° (lit.,[10] m.p. 98–101°). The NMR spectrum of this material showed a singlet at 0·857 δ (19 angular M peak: 3H), a singlet at 1·057 δ (18 angular Me peak; 3H), a doublet of doublets at 5·95 δ (the vinyl proton at C-16; $J_{15,16}$ = 6 c/s; 1H), and a doublet of doublets at 7·45 δ (the vinyl proton at C-15; $J_{15,16}$ = 6 c/s; 1H). The UV spectrum had an absorption at λ_{max}^{EtOH} 234 nm (ε 7,000).

Δ[15]-14β-*Hydroperoxy-5α-androsten-17-one* (*XI*).

This compound was obtained from VIII by air oxidation. The analytical sample was obtained by recrystallization from EtOAc, m.p. 182–4° (d) (Lit[12] m.p. 183–186°). The IR spectrum of this compound contained a band at 3230 cm^{-1} (OH) and a band at 1680 cm^{-1} (cyclopentenone). The UV spectrum had an absorption at λ_{max}^{EtOH} 214 nm (ε 4,900). The NMR spectrum of the compound contained a doublet at 5·78 δ (the vinyl proton at C-16: $J_{15,16}$ = 6 c/s: 1H) and a doublet at 6·92 δ (the vinyl proton at C-15: $J_{15,16}$ = 6 c/s: 1H). The mass spectrum of the compound gave a parent ion peak at 304 *m/e*. The ORD in methanol (*c*, 0·0052) showed: $[\alpha]_{590}^{25°}$ +63·1, $[\alpha]_{430}$ +252·4, $[\alpha]_{326.5}$ +1294 (peak), $[\alpha]_{295}$ −2196 (trough), $[\alpha]_{285}$ −2164 (peak), $[\alpha]_{260}$ −2555. (Found: C, 74·85; H, 9·56. Calcd. for $C_{19}H_{28}O_3$: C, 74·96; H, 9·27%).

5α-*Androstan*-14β-*ol*-17-*one* (XII).

(1) A soln of XI, (0·51 g) in 100 ml of abs EtOH was hydrogenated at atm pressure and room temp for 8 hr with 0·51 g 10% Pd–C. Removal of the catalyst and the solvent gave an oil residue which was tritutrated with ligroin to give 0·4 g (90%) of XII, m.p. 182–5°. Further recrystallization from ligroin yielded an analytical sample, m.p. 185–7°. The IR spectrum contained a band at 3500 cm^{-1} (OH peak) and a band at 1730 cm^{-1} (5-membered ring ketone). The mass spectrum of the compound gave a parent ion peak at 290 *m/e*. The ORD in MeOH (c, 0·0075) showed: $[\alpha]_{590}^{25°}$ +76, $[\alpha]_{430}$ +238, $[\alpha]_{358}$ +847 (peak), $[\alpha]_{312}$ −467 (trough), $[\alpha]_{303}$ −389 (peak), $[\alpha]_{259}$ −2128. The NMR spectrum of the compound contained a singlet at 0·817 δ (19 angular Me group, 3H), and a singlet at 0·987 δ (18 angular Me group, 3H).

Attempted Jones oxidation of XII furnished only recovered starting material (79%), m.p. 184–187°, as evidenced by the IR spectrum. (Found: C, 78·31; H, 10·32. Calcd. for $C_{19}H_{30}O_2$: C, 78·59; H, 10·41%).

(2) A soln of XIII (188 mg) in 15 ml EtOH was hydrogenated at atmos pressure and room temp with 30 mg 10% Pd–C. Removal of the catalyst and the solvent gave an oily residue which was triturated with ligroin to give 168 mg (89%) of crystalline needles, m.p. 185°. IR and NMR spectra were identical with the sample prepared in (1).

Δ^{15}-5α-*Androsten*-14β-*ol*-17-*one* (XIII)

Compound XI (0·22 g) was suspended in 10 ml of an AcOH-$CHCl_3$ soln (3:2 by volume), and to this 0·27 g KI in 15 ml AcOH soln (5 ml H_2O with 10 ml AcOH) was added. The mixture was heated until XI dissolved, and was then allowed to stand for 15 min. The I_2 liberated was destroyed by 15 ml 0·1 N $Na_2S_2O_3$, and the soln was then poured into water and extracted with ether. The extract was washed with $NaHCO_3$ aq, water, and dried over $MgSO_4$. Removal of the ether yielded 210 mg needles, m.p. 185–6°. Crystallization of the compound from acetone/hexane gave 188 mg (90%) of XIII, m.p. 188–9° (Lit[12] m.p. 190–1°). The IR spectrum of XIII contained bands at 3430 (OH) and 1680 cm^{-1} (cyclopentenone). The UV spectrum of the compound had an absorption at λ_{max}^{EtOH} 210 nm (ε 5,500). The NMR spectrum of the compound contained a doublet at 6·25 δ (the vinyl hydrogen at C-16; J_{15-16} = 6 c/s, 1H), and a doublet at 7·60 δ (the vinyl proton at C-15; J_{15-16} = 6 c/s, 1H). The mass spectrum of the compound gave a parent ion peak at 288 *m/e*. The ORD in MeOH (*c*, 0·0037) showed: $[\alpha]_{600}^{25°}$ +187, $[\alpha]_{360}$ +1928 (peak), $[\alpha]_{300}$ −2424 (trough), $[\alpha]_{290}$ −2424 (peak), $[\alpha]_{260}$ −4380 (trough), $[\alpha]_{250}$ −3177. (Found: C, 79·05; H, 9·87. Calcd. for $C_{19}H_{28}O_2$: C, 79·12; H, 9·79%).

Δ^{14}-5α-*Androsten*-17-*one* (XIV)

(1) *Dehydration of* 5α-*androstan*-14β-*ol*-17-*one* (XII). To a soln of XII, 399 mg, in 10 ml Ac_2O was added 229 mg fused potassium acid sulfate, and the mixture was refluxed for 1·5 hr. After the usual work up, the crude product showed two major spots on TLC. Neither of the spots corresponded to starting material. Chromatography on 25 g of Florex yielded a separation of the first spot (aoout 180 mg, 50%, of an oily material) which proved to be XIV by IR and NMR spectra. The IR spectrum of the compound contained bands at 1740 (non-conjugated cyclopentenone), 1670 (C=C stretching for a trisubstituted alkene), and 3050 cm^{-1} (C—H stretching for a trisubstituted alkene). The NMR spectrum of the compound contained a multiplet at 5·7 δ (the vinyl proton at C-15, coupled at C-16 methylene, 1H), and a multiplet at 2·8 δ (C-16 methylene group, 2H). The mass spectrum of the compound gave a parent ion peak at 272 *m/e*. Before a suitable solvent was found for crystallization, the compound had been air oxidized to XI as evidenced by m.p., IR and mass spectrum. As a result, no sample was available for elemental analysis (Lit[12] m.p. 56–57°).

(2) *Epimerization of* Δ^{15}-5α,14α-*androsten*-17-*one* (VIII). Δ^{15}-5α,14α-Androsten-17-one (1·27 g) in 10 ml benzene was heated under reflux with 31 mg *p*-toluenesulfonic acid monohydrate for 2 hr. After the usual work up, the crude product showed two major spots on TLC plus a third minor spot with a much lower R_f value. None of the spots corresponded to starting material. Chromatography on 35 g of Florex and using ligroin as the eluent yielded 400 mg of XIV. Structural assignment was secured by spectral comparison with the sample obtained from (1). Compound XIV was crystallized at low temp from hexane to give a m.p. of 48°. All attempts to separate the other two spots failed. The rest of the material on the column was eluted with 1% MeOH in ligroin and recrystallized from EtOAc to give 800 mg of XI as evidence by m.p. (m.p. 189°) and IR spectrum.

5α-*Androstan*-14β-*ol* (XV)

Compound XII (100 mg) was reduced by a modified Wolff-Kishner method. After the usual work up, the crude product was purified by column chromatography and gave 50 mg of an alcohol, m.p. 114·5–115·5°. The IR spectrum of the compound contained a band at 3500 cm^{-1} (OH peak), but no CO band. The NMR spectrum of the compound contained a singlet at 0·958 δ (18 angular Me group, 3H), and a singlet at 0·775 δ (19 angular Me group, 3H). The mass spectrum of the compound gave a parent ion peak at 276 *m/e*. (Found: C, 82·62; H, 11·44. Calcd. for $C_{19}H_{32}O$: C, 82·55; H, 11·66%).

5α,14β-*Androstan*-17-*one* (*XVI*)

(1) *Hydrogenation of* Δ^{14}-5α-*androsten*-17-*one obtained from dehydration of* 5α-*androstan*-14β-*ol*-17-*one* (XII). Compound XII (77·5 mg) was dehydrated with potassium acid sulfate in Ac_2O as described for the preparation of XIV. The mixture was worked up as usual and purified by preparative TLC. The Δ^{14}-5α-androsten-17-one obtained was dissolved in 15 ml abs EtOH and hydrogenated with 70 mg 10% Pd-C catalyst. After the usual work up, the crude product was recrystallized from hexane at low temp to give a

white solid (50 mg; 68%), m.p. 116–118°. The IR spectrum contained a band at 1730 cm^{-1} (5-membered ring ketone). The NMR of the compound contained a singlet at 0·759 δ (19 angular Me, 3H), and a singlet at 1·07 δ (18 angular Me, 3H). Although the synthesis of compound XVI has not been reported, the NMR data of the compound is known, and our NMR data agrees. The mass spectrum of the compound gave a parent ion peak at 274 *m/e*. (Found: C, 83·45; H, 9·19. Calcd. for $C_{19}H_{30}O$: C, 83·15; H, 11·02%).

(2) *Hydrogenation of* Δ^{14}-5α-*androsten*-17-*one obtained from epimerization of* Δ^{15}-5α,14α-*androsten*-17-*one* (VIII). Compound XIV (100 mg) obtained from the epimerization of Δ^{15}-5α,14α-androsten-17-one, was dissolved in 25 ml abs EtOH and hydrogenated with 100 mg 10% Pd-C. After the usual work up, the crude product was recrystallized from hexane at low temp to give a white solid (95 mg; 94%), m.p. 114–116°. The IR spectrum of the compound was identical with the spectrum of 5α,14β-androstan-17-one prepared in (1). A m.p. depression of over 20° was observed on admixture with a sample of 5α,14α-androstan-17-one, yet no m.p. depression was observed on admixture with the sample prepared in (1).

5α,14β-*Androstane* (Iαβ)

(1) *Photo-epimerization of* 5α,14α-*androstane* (Iα,α).[17b] 5α,14α-Androstane (642 mg) was dissolved in 85 ml reagent cyclohexane, and to this 636 mg mercuric bromide was added. N_2 was bubbled through the mixture for 3 hr to remove dissolved O_2. The rn mixture was then irradiated with 253·7 nm UV light for 53 hr. After the mercuric compound was removed by filtration, the solvent was removed, and the residue was chromatographed on 30 g Woelm alumina using hexane as the eluent to yield 640 mg (99%) crude 5α,14β-androstane (Iαβ), m.p. 35–38°. Crystallization from acetone for several times at low temp raised the m.p. to 50°, $[\alpha]_D^{3}$ +33·82°. The NMR of the compound contained a singlet at 0·763 δ (19 angular Me, 3H), and a singlet at 0·988 δ (18 angular Me, 3H). It was shown to be contaminated about 5% 5α,14α-androstane as calculated from NMR spectrum The VPC of the compound has a retention time of 25·7 min on a Perkin–Elmer F11 with 100 ft SE-30 capillary column at 160°, 6 lbs pressure. A m.p. depression was observed on admixture with a sample of 5α,14α-androstane. (Found: C, 87·69; H, 12·18. Calcd. for $C_{19}H_{32}$: C, 87·62; H, 12·38%).

(2) *Wolff-Kishner reduction of* 5α,14β-*androstan*-17-*one*. Compound XVI (37 mg) was reduced to 5α,14β-androstane (Iαβ) by a modified Wolff-Kishner reaction as described for the preparation of Iαα. The product (about 25 mg, 60%) was not purified, but gave an identical NMR spectrum to that from 5α,14β-androstane prepared in (1). A m.p. depression was observed on admixture with a sample of 5α,14α-androstane.

(3) *Raney-Nickel desulfurization of* 5α,14β-*androstan*-17-*one thioketal*. A mixture of XVI (25 mg) 0·1 ml ethanedithiol in a test tube was treated with 0·1 ml BF_3-etherate and the mixture was homogenized with a stirring rod. The mixture became warm and soon set to a stiff paste of white solid. After 5 min, one ml MeOH was added, the mixture was stirred well and cooled, and the solid was collected and washed with MeOH. The thioketal obtained was suspended in 5 ml MeOH which contained about 0·5 g wet Raney-Nickel catalyst. The mixture was shaken mechanically for 5 hr. After the catalyst was removed, the filtrate was evaporated to dryness and the residue was recrystallized from acetone at low temp to give a white solid compound, Iαβ (about 15 mg; 63%), m.p. 47°, $[\alpha]_D^{23}$ +32°. The NMR of the compound was identical with that from 5α,14β-androstane prepared by (1). A m.p. depression was observed on admixture with a sample of 5α,14α-androstane.

5β,14α-*Androstan*-17β-*ol* (XVIII)

Compound XVII (15·1 g) was reduced by a modified Wolff-Krishner method. The crude product was crystallized from ligroin to give 10 g of XVIII (80%), m.p. 128–129°. Further recrystallization from ligroin raised the m.p. to 130–131° (Lit[32] m.p. 133–134°).

5β,14α-*Androstan*-17-*one* (XIX)

A soln of XVIII (10 g) in 400 ml acetone was treated with Jones' reagent, and after the usual work up gave 9·5 g (96%) of XIX, m.p. 98°. Recrystallization from acetone-light petroleum yielded an analytical sample, m.p. 100–101° (Lit[33] m.p. 101–2°). The IR spectrum contained a CO band at 1740 cm^{-1}. (Found: C, 83·08; H, 11·28. Calcd. for $C_{19}H_{30}O$: C, 83·15; H, 11·02%).

5β,14α-*Androstan*-17-*one ethylene ketal* (XX)

A soln of XIX (7 g) 0·5 g of *p*-toluenesulfonic acid monohydrate and 80 ml ethylene glycol in 250 ml toluene was refluxed for 50 hr, using a Dean-Stark trap to remove the water generated. The soln was cooled, washed with $NaHCO_3$ aq and water. After drying and the removal of the solvent, oily material was obtained which was recrystallized from acetone (−80°) to give 6·86 (84%) of ketal, m.p. 61–62°. Further recrystalliza-

tion raised the m.p. to 62·5–64°. The IR spectrum showed no CO band in the 1665–1750 cm^{-1} region. (Found: C, 78·68; H, 10·55. Calcd. for $C_{21}H_{34}O_2$: C, 79·19; H, 10·76%).

16α-Bromo-5β,14α-androstan-17-one ethylene ketal (XXI).

Compound XX, (4·6 g) was dissolved in 55 ml anhyd THF and to this an equimolar amount of phenyltrimethylammonium bromide perbromide (5·4 g) was added. After the usual work up, there was obtained 4·55 g (79%) of XXI, m.p. 133–141°. The analytical sample was recrystallized from abs EtOH, m.p. 150–151° (Found: C, 63·34; H, 8·24; Br, 19·88. Calcd. for $C_{21}H_{33}O_2Br$: C, 63·47; H, 8·37; Br, 20·11%).

Δ^{15}-5β,14α-Androsten-17-one (XXIII)

A soln of K (10g) in 500 ml dry t-BuOH was distilled to dryness under reduced pressure. Xylene (100 ml) was added and removed by distillation 3 times to ensure complete removal of the alcohol. A soln of XXI (10 g), m.p. 150°, in 150 ml xylene was added to the t-BuOK and the mixture was heated under reflux under N_2 for 7 days. The soln was cooled, diluted with ice-water, and worked up. The ketal (XXII) obtained was oily, could not be induced to crystallize, and was employed in the next step. It gave a negative Beilstein test for halogen, and was dissolved in 600 ml 90% acetone with 400 mg *p*-toluenesulfonic acid monohydrate. The soln was allowed to stand at room-temp for 5 hr. Concentration of the soln, dilution with water, ether extraction of the mixture, and evaporation of the solvent yielded an oily residue which was dissolved in benzene and chromatographed on 250 g Woelm neutral alumina (activity III) with light petroleum. A solid material was obtained which was recrystallized from hexane at low temp to give 6 g (87%) of XXIII, m.p. 117°. The IR spectrum contained a band at 1720 cm^{-1} (cyclopentenone). An UV absorption of λ_{max}^{EtOH} 234 nm (ε 4,300) was observed. The NMR spectrum ($CDCl_3$) of this compound contained a singlet at 0·975 δ (19 angular Me peak, 3H), a singlet at 1·033 δ (18 angular Me peak, 3H), a doublet of doublets at 6·0 δ (the vinyl proton at C-16: $J_{15,16}$ = 6 c/s: 1H, and a doublet of doublets at 7·5178 (the vinyl proton at C-15, $J_{15,16}$ = 6 c/s: 1 H). The mass spectrum of the compound gave a parent ion peak at 272 *m/e*. When an attempt was made to raise the m.p. for analysis, it was found that the compound was air oxidized to XXV, m.p. 191–192.

5β,14β-Androstane (Iββ)

Compound XXIII (0·34 g) was dissolved in 6 ml benzene and to this 50 mg *p*-toluenesulfonic acid monohydrate was added. After heating the soln under reflux for 25 min, the starting material disappeared and a mixture of the two isomeric compounds (Δ^{15}-14β, and Δ^{14}-isomers) was obtained as evidenced by TLC. After the usual work up, the crude mixture in 15 ml abs EtOH was hydrogenated over 160 mg 10% Pd-C. When hydrogen had been absorbed and the uptake stopped, the catalyst and the solvent were removed. The crude material was crystallized from ligroin to give 0·3 g of XXIV (87%), m.p. 113°. A m.p. depression of over 20° was observed on admixture with a sample of 5β,14α-androstan-17-one. The crude product obtained from hydrogenation was not purified, but gave an IR spectrum containing a band at 1740 cm^{-1} (5-membered ring ketone). The crude 5β,14β-androstan-17-one was all converted to 5β,14β-androstane by a modified Wolff-Kishner method as described for the preparation of 5α,14α-androstane. No 5β,15β-androstan-17-one was available for analysis, because the precursor XXIII had been air oxidized to XXV. The 5β,14β-androstane obtained was purified by column chromatography and was recrystallized from acetone at dry ice-acetone bath temp to give 172 mg (53%) of Iββ, m.p. 54–56°. Further crystallization from acetone (low temp) gave an analytical sample, m.p. 58–59°, $[\alpha]_D^{23}$ +31·88°. The NMR spectrum of the compound contained a singlet at 0·898 δ (19 angular Me peak, 3H), and a singlet at 0·990 δ (18 angular Me peak, 3H). mixed m.p. depression was observed on admixture with a sample of 5β,14α-androstane. (Found: C, 87·77; H, 12·26. Calcd. for $C_{19}H_{32}$: C, 87·62; H, 12·38%).

TABLE 10.

Starting isomers*	Temp 329°	Composition of the equilibrated samples (4)	(3)	(1) + (2)	(5)	Length of runs (days)
(1) + (3)		15·63	14·83	61·78	7·76	3
(1) + (3)		16·05	17·63	57·09	9·23	4
(1)		16·04	16·69	58·52	8·75	5
(3)		16·22	15·62	59·53	8·63	5

* Iαα (1): Iαβ (2): Iβα (3): Iββ (4): Impurities (5)

TABLE 11. THE CHEMICAL SHIFT ASSIGNMENTS FOR THE ANGULAR METHYL GROUPS OF ANDROSTANES IN THE KNOWN SAMPLES

		Angular methyl groups of isomers
Peak A	0·694	18-Me for 5α,14α and 5β,14α
Peak B	0·763	19-Me for 5α,14β
Peak C	0·792	19-Me for 5α,14α
Peak D	0·898	19-Me for 5β,14β
Peak E	0·927	19-Me for 5β,14α
Peak F	0·990	18-Me for 5β,14β and 5α, 14β

Equilibration. The equilibrations were carried out using 5–25 mg of androstane at each temp. The samples of each pure isomer were placed in 4 mm Pyrex ampoules along with 5–25 mg 10% Pd-C, and the heating and work up procedures were those reported earlier.[34] The temp was mainted at the desired point for a time sufficiently long for equilibrium to be established.

TABLE 12. THE COMPOSITIONS OF THE EQUILIBRATED ANDROSTANES AT DIFFERENT TEMPERATURES

Composition	VPC %	Method A* %	Method B* %
Temp 545°K			
5α,14α	75·56	13·00	16·50
5α,14β	75·56	65·08	59·04
5β,14α	4·58	4·62	4·58
5β,14β	19·88	17·30	19·88
Temp 553°K			
5α,14α	76·29	14·47	14·70
5α,14β	76·29	63·29	61·59
5β,14α	4·26	4·52	4·26
5β,14β	19·45	17·71	19·45
Temp 573°K			
5α,14α	72·87	8·75	14·34
5α,14α	72·87	77·44	58·53
5β,14α	7·23	4·42	7·23
5β,14β	19·90	9·38	19·90
Temp 589°K			
5α,14α	71·55	7·08	15·66
5α,14β	71·55	76·78	55·89
5β,14α	6·94	5·46	6·94
5β,14β	21·51	10·68	21·51
Temp 602°K			
5α,14α	64·16	9·77	16·01
5α,14β	64·16	63·12	48·15
5β,14α	11·86	9·64	11·86
5β,14β	23·99	17·47	23·99

* Methods A and B—see text for definitions.

VPC studies for the equilibria of the isomeric androstanes. Samples of the isomeric androstanes equilibrated at the same temp were quenched at different time intervals and their compositions were analyzed by VPC. The results are shown in Table 10.

The time required for samples to reach the equilibrium at 272, 280, 300, 316, and 329° was about 17, 14, 8, 7, and 4 days, respectively. Three VPC analyses were carried out for each sample, and the relative ratios of the peaks were measured by the weight of the peaks.

NMR and VPC studies on the androstane system. It was established by suitable experiments that the assignments of the NMR peaks were valid, and not dependent on concentration or the presence of impurities. The NMR peaks used for the analyses are given in Table 11, and the details of the analyses of the equilibrium mixtures are in Table 12.

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