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CONFORMATIONAL ANALYSIS—LXXX
THE HYDRINDANONE RING SYSTEM*[,1]

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Abstract—A previously described force-field method has been used to study the energies and structures of the *cis* and *trans* isomers of hydrindane, 8-methylhydrindane, the 1-, 2-, and 3-keto derivatives, and a series of more complicated molecules of the steroid and triterpene type which contain hydrindanone systems. The calculated energy differences are in good agreement with the experimentally known values, and it is now possible to understand the exact nature of the interactions which lead to the observed energy differences.

INTRODUCTION

WHEREAS THE CONFORMATIONAL ANALYSIS of six-membered rings has been extremely successful qualitatively, and to a large extent quantitatively, five-membered rings, with their ill-defined energy minima, have presented a much more difficult problem. In general they are much less well understood.[2] Specific problems involving cyclopentane rings have been attacked by calculational methods with much labor and some success,[3] but generally useful calculational methods have been lacking. We have recently described a force field which, when applied to a variety of hydrocarbons, has given excellent results with respect to molecular structures and energies.[4] Subsequently the calculations were extended to include carbonyl compounds.[1] In the present paper these methods have been applied to a study of simple hydrindane and hydrindanone ring systems, and also to such systems incorporated into large and complex natural products. In the past, *ad hoc* explanations have been given for the various observed stabilities of these ring systems, but no general understanding has been available. In the present paper it will be shown that straightforward application of the force field method to a wide variety of these compounds gives calculational results that are in good to excellent agreement with experiment, and by an analysis of the numerical results, it is possible to ascertain exactly what kinds of interactions are responsible for what is observed experimentally.

The hydrindanones

It is well established experimentally that *trans*-hydrindane has a more negative enthalpy than does the *cis* isomer, and the *cis* isomer has a higher entropy.[5] Depending on the temperature, ΔG° may take on either sign. An analysis of the strain in the hydrocarbons gives the following: the *trans* isomer has 0·6 kcal more bending energy than does the *cis*, and this is the result of trying to twist together two equatorial

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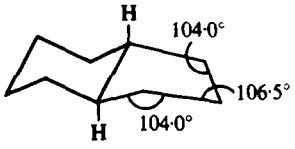
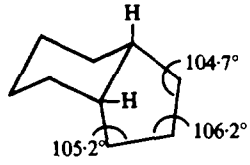
substituents on the cyclohexane ring, and join them with a five-membered bridge. The *cis* isomer, on the other hand, has more torsional (0·6 kcal) and van der Waals energy (1·1 kcal). This is in part because the five-membered ring is flatter, and hence more eclipsed, and partly because the five-membered ring acts as a substituent on the six-membered ring, one end of which is in an equatorial- and the other end in an axial-like position. We calculate, therefore, that *trans*-hydrindane has the lower enthalpy by 1·1 kcal/mole, in agreement with experiment.

Next, consider the substitution of a ketone into the 5-membered ring of the hydrindane system. Since the 5-membered ring in the hydrocarbon has C—C—C bond angles that average around 106°, there will obviously be considerable increase in strain attendant upon such substitution (I-strain[6]). There are two conformations for the *cis*-1-ketone. In one of these the carbonyl group is adjacent to an axial hydrogen, in which case the strain in the *trans* isomer is increased relative to that of the *cis*. As the figure below shows, the bond angle in the hydrocarbon is 104·7° for the *cis* isomer, and 104·0° for the *trans*.



trans-Hydrindane



cis-Hydrindane

Thus, in this conformation of 1-hydrindanone, the *trans* isomer has even more bending energy relative to the hydrocarbon than does this *cis* conformation (1·3 kcal/mole). The presence of the carbonyl group causes the five-membered ring to flatten out even more, however, so it is found now that the *cis* isomer has 1·1 kcal more van der Waals and 1·3 kcal more torsional energy than does the *trans*. Part of this difference in torsional energy results from the fact that the carbonyl group is nearly eclipsing an alkyl group in the *trans* isomer, while it is nearly eclipsing a hydrogen in the *cis* isomer. As is well known, 2-butanone,[7] propionaldehyde,[8] and related compounds prefer to have a methyl carbon rather than a hydrogen eclipsing the carbonyl group. The *trans*-1-ketone is therefore slightly destabilized over the *cis* relative to the hydrocarbons, the energy difference between them is 0·8 kcal.

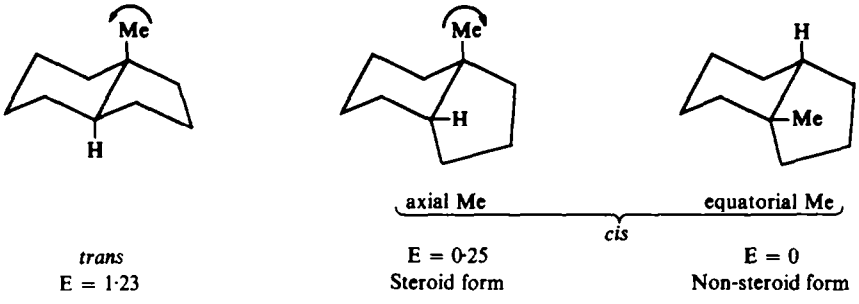
If the ketone is substituted into the 1-position of the *cis* isomer next to the equatorial bridgehead hydrogen, the bending energy is still less than that of the *trans* (by 1·0 kcal), and the van der Waals and torsional energies are less than in the other conformation. With this *cis* conformation the carbonyl group, rather than the methylene, is axial to the six-membered ring, thereby reducing the van der Waals repulsion between that group and the ring. The carbonyl here is almost eclipsed by the methylene of the six-membered ring, so the torsional energy is more favorable. This *cis* conformation thus has an energy of only 0·1 kcal less than that of the *trans*. Entropy again favors the *cis* isomer, so that in this case the *cis* isomer is calculated to be slightly more stable at low temperature, and becoming more so at higher temperature. The only experimental data[9] give *trans*/*cis* = 0·33 at 100° in Et_3N solvent.

If the carbonyl group is inserted in the hydrocarbon to give 2-hydrindanone, the calculated difference in energy between *cis* and *trans* isomers is 0·7 kcal, similar to that calculated for the hydrocarbon. The bond angles at C-2 in the hydrocarbon isomers are 106·2 and 106·5, respectively, so the bending-energy changes upon insertion of the 2-ketone are similar, and the energy differences between the isomers are essentially the same as with the hydrocarbon. Experimentally, the value of 0·4 kcal/mol has been measured.[10]

Thus we conclude from the above calculations, and the results are borne out by the available experimental data, that for the hydridanes the *trans* isomer is of lower enthalpy by about 1 kcal, and a 2-keto group does not alter this significantly. The 1-ketone isomers are of equal enthalpy. Entropies have to be examined individually.

The 8-methylhydrindanones

Next we may consider the 8-methylhydrindane system; that is, what does the presence of the angular Me group do to the *cis–trans* equilibrium?



As the figure indicates, when the Me group is placed at the bridgehead of the *trans* isomer, it is necessarily axial to the six-membered ring. The steric energy of the molecule therefore goes up, as one would anticipate. For the *cis* isomer, there are two possible conformations. If the Me is inserted at the equatorial bridgehead position in the *cis* isomer (the "non-steroid form"), the conformation obtained is 1·37 kcal/mole more stable than that of the *trans*. On the other hand, if the Me is inserted axial to the six-membered ring (in the "steroid form"), the energy goes up 0·25 kcal above that of the "non-steroid form." The *cis* fusion of the five-membered ring to the six- in the steroid form necessarily bends the axial and equatorial methylene carbons toward one another. This action tends to twist the Me away from the six-membered ring in the *cis*-axial methyl isomer, but pushes it back into this ring in the *trans* isomer, as shown by the curved arrows. As a result, the *cis* isomer with two substituents axial on the six-membered ring ends up being more stable than the *trans*; however, the "non-steroid form" of the *cis* isomer, with only one axial substituent, ends up being the most stable of all. The qualitative effect of adding the bridgehead methyl to hydrindane is similar to that of adding a methyl to decalin and for the same reason. In this case the stability order of the isomers is reversed, so that while *trans* hydrindane has a lower enthalpy than *cis*, for the 8-methylhydrindanes the reverse is *true*.

Next we wish to turn our attention to the 8-methylhydrindanone system. In general, the presence of the 8 Me group tended to stabilize the *cis* isomer relative to the *trans* in the hydrocarbons, and the same effect is noted with the ketones. Thus the 8-methylhydrindanones with the carbonyl group at C-1, C-2, or C-3 are all preferentially favored in the *cis* form, in contrast to the same compounds without the Me. In each case the *cis* isomer has two conformations, steriod (axial Me) and non-steroid (equatorial Me), and these are quite similar in energy for the 1- and 2-keto derivatives.

Table 1 gives the pertinent information on the 8-methylhydrindane system.

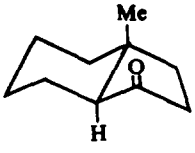
TABLE 1. STRAIN ENERGIES OF THE 8-METHYLHYDRINDANES[a]

	Hydrocarbon			1-keto			2-keto[b]			3-keto		
	trans	*cis*		*trans*	*cis*		*trans*	*cis*		*trans*	*cis*	
		ax	eq		eq	ax		eq	ax		eq	ax
Bend	1·8	0	0	2·4	0	−0·3	2·2	0·2	0	2·6	0·2	0
VDW	0·4	0·6	0	0·5	0	0·4	0·4	−0·2	0	0·4	−0·2	0
Torsion	0	0·5	0·7	−0·4	0	0·1	−0·5	0·2	0	−0·4	1·1	0·2
Total	1·5	0·4	0	2·5	0	0·2	2·1	0·2	0	2·6	1·1	0

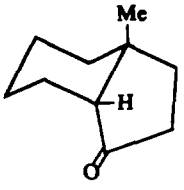
[a] The *cis* isomer has two conformations, which are designated as ax or eq, referring to the location of the Me group.

[b] Experimentally, the *trans* isomer has a more negative heat of formation by 2·8 kcal/mole.[10]

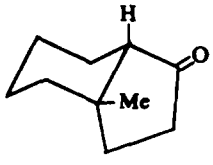
Attention is called to the 8-methyl-3-hydrindanones. The difference in energy between the *cis* steroid and non-steroid forms is considerable, with the steroid form being the more stable (by 1·1 kcal). This difference comes primarily from the torsional term. In the steroid form, the carbonyl is approximately eclipsing a methylene group, while in the non-steroid form it is approximately eclipsing a hydrogen.



E = 2·6



Steroid form
E = 0

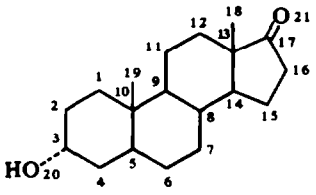


Non-steroid form
E = 1·1

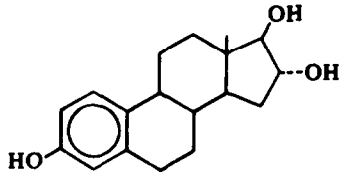
With each of these ketones (Table 1), the *trans* is a good deal higher in energy than the preferred *cis* conformation because of the angle strain effects discussed previously. The differences are sufficiently large that the *trans* ketone in the equilibrium mixture might be difficult to detect under ordinary circumstances.

More complex hydrindanone systems

In our study of the calculation of molecular structures of hydrocarbons and carbonyl compounds, we found that as long as the molecules are not too highly strained, we can in general reproduce bond lengths by calculation to approximately within the probable error of the experimental measurements. For bond angles, we do not do quite as well. One example of a complex hydrindanone system will be briefly discussed here. The compound androsterone has had its structure determined by X-ray crystallography, without any heavy atom being present, and is one of the most accurately known structures of a steroid available at the present time.[11]



Androsterone



Estriol

In Table 2 are listed the bond lengths and bond angles for the molecule (excluding those involving hydrogen) as determined by the X-ray method, together with the reported standard deviations. Also listed are our calculated values for these same quantities, and then the deviation between the experimental and calculated values. The overall root-mean-square discrepancy between the calculated and experimental bond lengths is 0·010 Å, which is 1·7 times the standard deviation in the X-ray values (0·006 Å), which constitutes agreement to within experimental error.* The RMS of the deviation of the X-ray C—C bond lengths from their average is 0·017 Å, which suggests that our values are meaningful. The corresponding RMS for our values for angles is 1·3°, compared with the experimental value of 0·3°. The factor of 4 here shows that our values are *not* completely in agreement with experiment. However, if these differences are regarded as significant, we believe that our values are probably *more* accurate than the experimental ones, as far as the isolated molecule is concerned. Crystal packing forces will distort the molecule in those degrees of freedom which have the lower force constants, and we believe that is what has happened here. For example, in the case of estriol,[12] there are two crystallographically different molecules within the same unit cell, which would of course be identical as isolated molecules. The RMS of the bond length and bond angle differences between the two structures are 0·017 Å and 1·43°, respectively. These values compare with the RMS estimated standard deviations in the same quantities of 0·007 Å and 0·35°, respectively. Thus the crystal forces appear to distort bond angles by more than what is usually considered to be experimental error in estriol, and probably in other molecules such as androsterone as well.

* The probable error is generally considered to be 2 or 3 times the standard deviation.

TABLE 2. A COMPARISON OF THE X-RAY AND CALCULATED STRUCTURES OF ANDROSTEROL

Bond	Exptl. length	Std. dev.	Calcd. length	Difference
C(1)—C(2)	1·532	0·005	1·532	0·000
C(1)—C(10)	1·544	0·005	1·539	0·005
C(2)—C(3)	1·512	0·007	1·523	−0·011*
C(3)—C(4)	1·491	0·006	1·529	−0·038*
C(3)—O(20)	1·444	0·006	1·475	−0·031*
C(5)—C(6)	1·529	0·005	1·528	0·001
C(5)—C(10)	1·550	0·006	1·541	0·009
C(6)—C(7)	1·500	0·006	1·527	−0·027
C(7)—C(8)	1·532	0·006	1·527	0·005
C(8)—C(9)	1·547	0·005	1·536	0·011
C(8)—C(14)	1·519	0·005	1·528	−0·009
C(9)—C(10)	1·551	0·005	1·548	0·003
C(9)—C(11)	1·534	0·006	1·539	0·005
C(10)—C(19)	1·541	0·005	1·538	0·003
C(11)—C(12)	1·546	0·005	1·534	0·012
C(12)—C(13)	1·507	0·006	1·525	−0·018
C(13)—C(14)	1·540	0·006	1·529	0·011
C(13)—C(17)	1·517	0·005	1·514	0·003
C(13)—C(18)	1·548	0·005	1·538	0·010
C(14)—C(15)	1·531	0·005	1·533	0·002
C(15)—C(16)	1·537	0·006	1·540	−0·003
C(16)—C(17)	1·520	0·008	1·512	0·008
C(17)—O(21)	1·189	0·006	1·222	−0·033*
		0·006		0·010
	RMS of individual C—C bond standard deviations		C—C RMS average difference	

Bond angle	Exptl. angle	Std. dev.	Calcd. angle	Difference
C(2)—C(1)—C(10)	113·5	0·3	114·6	−1·1
C(1)—C(2)—C(3)	112·4	0·3	111·3	1·1
C(2)—C(3)—C(4)	111·5	0·3	111·6	−0·1*
C(2)—C(3)—O(20)	107·1	0·4	104·7	2·4*
C(4)—C(3)—O(20)	111·0	0·3	107·9	3·1*
C(3)—C(4)—C(5)	112·7	0·3	112·4	0·3
C(4)—C(5)—C(6)	113·1	0·3	111·9	1·2
C(4)—C(5)—C(10)	113·2	0·3	114·7	−1·5
C(6)—C(5)—C(10)	112·1	0·3	112·4	−0·3
C(5)—C(6)—C(7)	111·5	0·3	111·1	0·4
C(6)—C(7)—C(8)	113·2	0·3	111·3	1·9
C(7)—C(8)—C(9)	110·8	0·3	112·1	−1·3
C(7)—C(8)—C(14)	112·0	0·3	111·4	0·6
C(9)—C(8)—C(14)	109·0	0·3	110·7	−1·7
C(8)—C(9)—C(10)	112·7	0·2	113·4	−0·7
C(8)—C(9)—C(11)	111·5	0·3	112·3	−0·8
C(10)—C(9)—C(11)	113·6	0·2	115·8	−2·2
C(1)—C(10)—C(5)	106·2	0·3	106·7	−0·5
C(1)—C(10)—C(9)	109·9	0·3	111·8	−1·9
C(1)—C(10)—C(19)	109·7	0·3	107·6	2·1
C(5)—C(10)—C(9)	107·4	0·2	107·6	−0·2
C(5)—C(10)—C(19)	112·4	0·3	112·5	−0·1

TABLE 2 (*Continued*)

Bond angle	Exptl. angle	Std. dev	Calcd. angle	Difference
C(9)—C(10)—C(19)	111·1	0·2	110·5	0·6
C(9)—C(11)—C(12)	113·4	0·3	114·4	−1·0
C(11)—C(12)—C(13)	109·7	0·3	109·9	−0·2
C(12)—C(13)—C(14)	110·5	0·3	108·7	1·8
C(12)—C(13)—C(17)	116·4	0·3	116·1	0·3
C(12)—C(13)—C(18)	112·5	0·3	111·2	1·3
C(14)—C(13)—C(17)	99·2	0·3	98·6	0·6
C(14)—C(13)—C(18)	111·9	0·3	115·8	−3·9
C(17)—C(13)—C(18)	105·5	0·2	106·1	−0·6
C(8)—C(14)—C(15)	120·8	0·3	120·8	0·0
C(13)—C(14)—C(15)	104·3	0·3	104·3	0·0
C(14)—C(15)—C(16)	102·6	0·4	103·2	−0·6
C(15)—C(16)—C(17)	106·0	0·3	104·5	1·5
C(13)—C(17)—C(16)	107·8	0·3	109·3	−1·5
C(13)—C(17)—O(21)	127·1	0·4	124·8	2·3*
C(16)—C(17)—O(21)	125·1	0·4	125·4	−0·3*
		0·29		1·31
	RMS of individual C—C—C ESD		C—C—C RMS average difference	

* Not used in statistical calculations.

We therefore conclude that the accuracy to which we can calculate a structure of this kind is competitive with what was determined by crystallography in this particular case.† It should be pointed out, however, that this case was an extremely favorable one for the X-ray method, and in general, we believe that within the area of applicability of the force field, our calculated structures are more accurate than those determined by crystallography.

There has been previously recorded in the chemical literature a considerable amount of data on the stabilities of more elaborate hydrindanone systems. These data have been of concern for some years, as the energy differences between isomers, often even the qualitative values, have not been easy to interpret.[13] In Table 3 are given those data with which the authors are familiar.

The *cis*-hydrindanone is usually seen to be more stable than its *trans* counterpart. The exceptional cases include hydrindane and 2-hydrindanone, which have already been discussed. In addition, compounds **1** and **5** are also more stable in the *trans* form. For compound **1** (15-oxoergost-22-ene-3β-yl acetate), the greater stability in the *trans* form[14] seemed peculiar for many years, but was finally shown by Djerassi and Horn[15] to result from the presence of the side chain. Compound **5** is similarly stable in the *trans* form, while compounds **2**, **3**, and **4** are stable in the *cis* form. If we begin with compound **2**, we might guess that the results would be similar to those

† C. Altona (personal communication) has carried out similar calculations with a force field he has developed. His RMS is similar to ours, 0·007 Å in bond length and 1·2° in bond angle, omitting parts of rings *A* and *D*, however.

TABLE 3. HYDRINDANE DERIVATIVES AND THEIR STABILITIES[a]

Compound	Experimental $-\Delta G°$ (kcal/mole)	Calculated $-\Delta G°$ (kcal/mole)[b]
	A. Those having stable *cis* isomers	
1-Hydrindanone	0·8 (100° C)	0·5 (100°C)
4-Hydrindanone[c]	stable *cis*	
8-Methylhydrindan-1-one[d]	stable *cis* (as oxime)	2·8
8-Methylhydrindan-2-one	2·8[10]	2·1
Equileinin[d]	1·8	
2	1·2	2·3
3	0·3	1·4
4	1·9	
6	0·2	0·6
7	>2·7	5·1
8	0·1	
9	1·1	
10	2·4	
	B. Those having stable *trans* isomers	
Hydrindane	0·4	0·7
2-Hydrindanone	0·4 (ΔH^{10})	0·7 (ΔH)
1	stable *trans*	
5	0·7	0·7

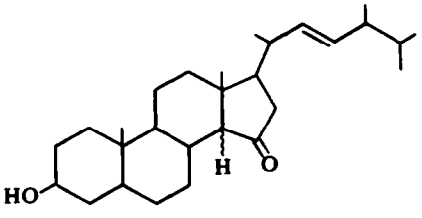
[a] The stable isomer is the one with the more negative free energy. In a few cases only the enthalpy difference is known, and these are indicated by (ΔH). All experimental data for about 25° in the liquid phase unless otherwise noted. Calculations are for 25° in the gas phase.

[b] Entropy from symmetry and mixing (only) allowed for.

[c] Linstead, *Ann. Rep. Chem. Soc.* (London), 305 (1935)

[d] Bachman and Dreiding, *J. Am. Chem. Soc.* 72, 1323 (1950) Related compounds behaved similarly.

found with the simple bicyclic analog. The C/D *cis* isomer is calculated to be stable in 5α,14α-androstan-15-one by 2·3 kcal/mole, which is in agreement with the value for 8-methyl-3-hydrindanone and in fair agreement with the experimental value of about 1·2 kcal/mole.*



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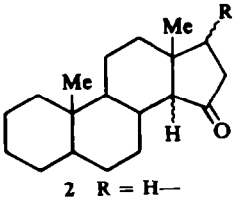


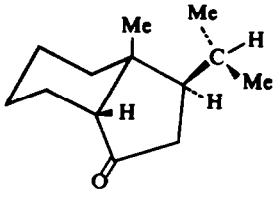
2 R = H—
3 R = β-Me—
4 R = α-Me—
5 R = β-iPr—

* There is some ambiguity in this number because the quenching of the reaction is not adequately described, and the temperature to which the equilibrium corresponds is uncertain. It appears that the *cis* isomer is more stable by 1·0–1·3 kcal/mole, which we have decided to call 1·2 kcal/mole.

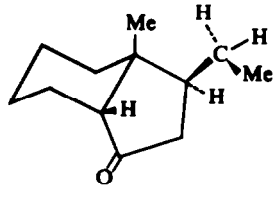
These values may be compared with those calculated for the hydrocarbons themselves: the *cis* isomer has a more negative enthalpy by 1·2 kcal (calculated) compared with 1·8 ± 0·5 kcal (experimental free energy, by equilibration over palladium at 300°).[16]

The presence of a β-alkyl group (C-20) attached to C-17 causes a quantitative change in the calculated relative stabilities of the C-14 epimeric 15-ketones.[15] The effect is small for Me, but sizeable for i-Pr. In this case the 14β Me isomer is still the more stable, but only by a calculated 1·4 kcal/mole. The experimental value is of the same sign, but is only 0·3 kcal/mole. The C-20 Me interacts unfavorably with the 14β hydrogen, but not the 14α. There are many other small interactions also.

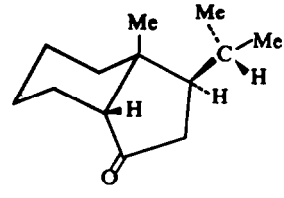
The presence of a β i-Pr group alters the stability of the C/D *cis*-15-ketone much more. There are three orientations the isopropyl can assume, and their energies (relative to the best conformation of the *trans* isomer) are shown:



E = 1·1



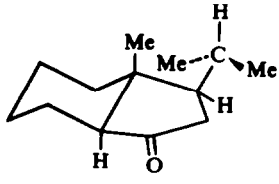
E = 0·7



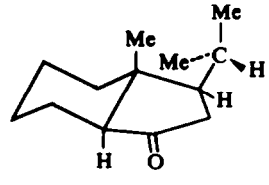
E = 3·4

The conformation with E = 0·7 kcal/mole is the best alternative open to this compound. In each of the other two conformations, an interaction between the 18-Me and a Me on the isopropyl is extremely unfavorable, similar to the *syn*-diaxial dimethyl interaction in a 1,3-dimethylcyclohexane.[17]

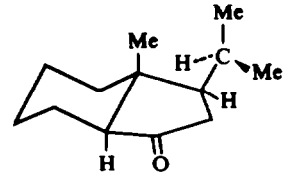
In the C/D-*trans*-15-ketone, again, two conformations are very unfavorable because of strong repulsions between the 18-Me and a Me of the isopropyl. The third conformation (E = 0) is reasonably comfortable, and better than the best *cis* conformation by 0·7 kcal/mole, in exact agreement with the experimental value.



E = 0



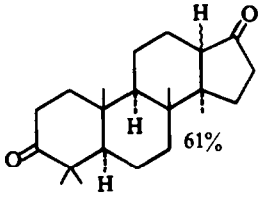
E = 3·7



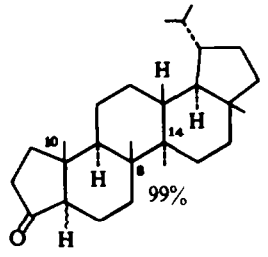
E = 3·1

From an examination of models it is clear that there are approaches between hydrogen atoms of the i-Pr group and other non-bonded atoms that are much less than the sum of the van der Waals radii in each conformation. The best conformation for each isomer can be correctly picked by examining models. The fact that the best conformation of the *trans* isomer is better than the best of the *cis* isomer is not apparent from models, however. The calculations show that one of the hydrogens on a Me of the isopropyl is only 2·35 Å from the 14β hydrogen in the *cis* isomer, and this interaction, together with the deformations which occur in trying to relieve it, appear to be the most serious problem in that compound, and the most important reason why the *cis* isomer is less stable than the *trans*. Note that only when the 17β side chain is branched (i-Pr or larger) will this interaction be present. With Me and Et it can be avoided. Thus 15-cholestanone derivatives with isopropyl-like side chains will have the 14α configuration the more stable, whereas for analogous compounds with small side chains (or none) the 14β configuration will be stable.

Horn and Djerassi,[15] from examination of Dreiding models, attributed the destabilization of the *cis* isomer by the β isopropyl side chain to the more nearly eclipsed conformation resulting between the side chain and the C-18 Me, and indicated their belief that the difference observed between the 17β-Me and 17β-i-Pr could not be due to the interaction of the side chain with the 14β-hydrogen in the case of the *cis* isomer. The present calculations show that Dreiding models give a wholly inadequate representation of the situation. The 17β-i-Pr is actually more nearly eclipsed in the *trans* isomer ($\omega = 36°$) than in the *cis* ($\omega = 46°$). The interaction



6



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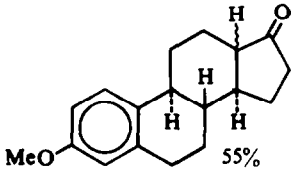

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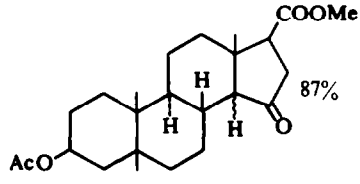
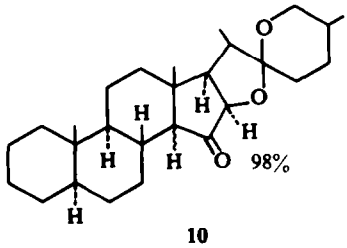


9



10

of this group with the 14β-hydrogen is very much more serious in the 17β-i-Pr derivative, in which there is interaction with the Me, than with the 17 β-Me where there is interaction with a hydrogen. In response to this repulsion, the molecule undergoes various deformations, but this type of interaction seems to be the most important.

Finally, we might consider the miscellaneous assortment of compounds **6**–**10**, all of which are more stable in the *cis* configuration, but by widely varying degrees.

Looking at compounds **6** and **7**, for example, it would seem that they are superficially quite similar. They are both hydrindanones, with a Me arranged so that they may be considered as 8-methyl-3-hydrindanone, and they are both stable in the *cis* configuration. However, with **6**, the equilibrium favors the *cis* isomer by 61%, whereas in **7** the number is 99%. The (*trans–cis*) energy differences which we calculate correspond respectively to 0·6 kcal/mole, and 5·2 kcal/mole. In other words, there is a 4·5 kcal difference, a very large difference, in the relative stabilities of the ring junctures in these two cases. An examination of models suggests why this is true, and the numerical data from the calculations bear out these suggestions.* The key to the interpretation involves the disposition of the angular Me groups. In **6**, the 8β Me is axial. The C/D *cis* isomer has C-17 *syn*-axial to it. The 8β Me therefore shifts the C/D equilibrium toward the *trans* isomer by destabilizing the *cis*. The calculation was repeated for the same molecule without the 8β Me, and indeed, it was found that here the *cis* was much more stable relative to the *trans* (3·6 kcal/mole), compared to the compound with the 8β Me (0·6 kcal/mole). The 8β Me thus destabilizes the *cis* isomer by 2·9 kcal/mole. This is not quite enough to make the *trans* isomer more stable than the *cis*, however. On the other hand, with compound **7** the Me at C-10 is β, as is the Me at C-8. The interaction of these two Me tends to push C-1 down. This deformation is easy if the A/B juncture is *cis*, but difficult if it is *trans*. The Me's on carbons 8 and 10 are thus much farther apart in the *cis* isomer (3·6 Å) compared with the *trans* (3·1 Å). Even so the repulsion between the nearer hydrogens on these Me's is substantial, even after the deformations have occurred to minimize their effect. The 8β Me therefore stabilizes the *cis* isomer relative to the *trans*. The *cis* is more stable by 5·1 kcal/mole in **7**, but in the compound without the 8β Me, the *cis* is more stable than the *trans* by only 0·6 kcal/mole. This is clearly a sizeable effect, which tends to make the *cis* isomer much more stable than it would otherwise have been. The *cis* isomer simply has the Me's bent away from one another. The deformation in the *trans* isomer is quite unusual and worth comment, however. The Me's do not bend away from one another nearly as much as in the *cis* isomer, since the tension in the ring system prevents that. A Drieding model shows that if the Me's had staggered conformations with respect to the carbons to which they are attached, the nearest hydrogens would be less than 1 Å apart. Each Me rotates, therefore, the torsional angles between the hydrogens on the 8-Me and the C-9 and C-14 carbons are only 24° and 20°, respectively. Interestingly, there is a very large repulsion (2·2 kcal/mole) between the Me hydrogen which is almost eclipsing C-14 and the axial hydrogen at C-15, which is only 2·1 Å away. That the deformation would occur in this way is not at all apparent from simple considerations.

* For computational simplicity, the calculations were carried out on structure **7** with the E-ring and the attached angular methyl and isopropyl removed.

Compound **8** is fairly unexceptional, being not a Me hydrindane, but just a simple 1-hydrindanone ring system restricted to the steroid conformation for the *cis* isomer. With the simple hydrindanone, the *cis* isomer was calculated to be 0·1 kcal more stable, which corresponds closely to what is observed with this molecule.

We are not prepared to deal with the ester groups in **9**, nor the ether oxygens in **10** at the present time. Since the carbomethoxyl is similar in size to Me, the observed equilibrium constant for **9** seems reasonable, being similar to that observed for **3**.

Predictions based on the examination of models have been tremendously useful in simple cases. In molecules such as **1–10**, however, such simple considerations are clearly a hazardous basis for prediction or interpretation, and in our opinion, such problems can be attacked in a realistic way only with the aid of calculations of the type described in this paper. The results of the calculations seem to be in general very good. In only two cases herein are discrepancies seen of as much as 1 kcal/mole between calculation and experiment.

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