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CONFORMATION OF NON-AROMATIC RING COMPOUNDS—XXV[1]

GEOMETRY AND CONFORMATION OF RING D IN SOME STEROIDS FROM X-RAY STRUCTURE DETERMINATIONS

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Abstract—A quantitative description of (solid state) steroid ring D puckering and conformation in terms of maximum angle of torsion φ_m and "phase angle" of pseudorotation Δ has considerably improved the approach to the problem of describing flexible 5-membered rings. The maximal torsional parameter (φ_m) of all steroid rings D is relatively constant (47°) although a slight tendency to increase with increasing phase angle is noted. The phase angles of 17-keto steroids are negative (= rotation toward C(14) envelope form), those of the otherwise substituted steroids are limited to a rather narrow range comprising about one quarter of the possible circuit. A C(13) envelope has not been found thus far.

Some empirical rules that may serve as a basis for the discussion of ring D conformation can now be recognized. In first approximation the nature of the C(17) or C(16) β substituent (except keto) has no discernible influence. Extreme deformations of rings A, B and/or C do affect ring D. The effect of the angular methyl groups C(18) and C(19) cannot yet be assessed for lack of information on nor-steroids. X-ray studies on a diversity of well chosen compounds will be necessary to elucidate the role of each conformation-determining factor. Solution data (NMR, infrared, ORD, CD, and dipole moments), interpreted in accordance with the now established "conformation laws" of ring D, may be of considerable help in this respect.

INTRODUCTION

IN a previous paper[1] a quantitative description of the conformation of the A,B,C moiety of some steroids was given in terms of valency and torsional angles. We wish now to discuss the geometrical details of ring D as found from X-ray analyses. The reason for treating ring D separately lies in the flexibility of the 5-membered ring (pseudorotation),[2-5] which necessitates a more refined approach to the description of its conformational and geometrical properties. The torsional angles are of special importance by virtue of their high sensitivity to slight changes in the pseudorotation parameter.

The compounds in question are given in section 1. Section 2 deals with the conformational problems inherent in the flexible cyclopentane ring and with the torsional angles about the *trans* C/D junction.

Finally (section 3), it will be shown that a "standard" ring D can be introduced. Invariably, each ring D has some "intermediate conformation", i.e. the exact form of each given 5-membered ring as it occurs in the crystal is unique.

A new method is developed which characterizes all these different conformations in terms of common properties. It describes more rigorously the conformation actually encountered than designations like "distorted envelope" or "approximately half-chair" because, in fact, the conformation is determined by two parameters: the maximum attainable torsional angle φ_m during pseudorotation and a specific phase angle Δ which locates the exact point on the pseudorotation pathway.

No direct experimental information seems to be available on the exact geometrical details of the unsubstituted cyclopentane ring. Consequently, attempts at conformational analyses of simple derivatives[3] have to be based on theoretical models. For *trans*-hydrindane systems calculations are lacking. One of the results of the present study is that the geometry of ring D largely agrees with the models calculated[3,6] for cyclopentane.

SECTION 1

The geometry and conformation of ring D in the following compounds will be discussed: (see also Fig. 1):

1. 4-bromo-estrone[7]
2. 3α-ol-5α-androstan-17-one[8]
3. 4-bromo-9β,10α-pregna-4,6-diene-3,20-dione (duphaston)[9]
4. calciferyl-4-iodo-3-nitrobenzoate[10]
5. 2β, 3α-dichloro-5α-cholestane[11]
6. 2β, 3β, 14α, $22\beta_F$, 25-pentahydroxy-Δ^7-5β-cholestenone-6 (ecdyson)[12]
7. 2α, 3β-dibromo-5α-cholestane[11a, 13]
8. 2α, 3β-dichloro-5α-cholestane[11a, 13]
9. samandarine hydrobromide[14]
10. suprasteryl II-4-iodo-5-nitrobenzoate[15]
11. 4-bromo-estradiol[16]

The compounds exhibit a progressive pseudorotation from the C(14)-envelope in the direction of the C(13)-envelope in the series **1**—**11**. The valency angles ϑ and their standard deviations were taken from the original literature[7–16] on the crystal and molecular structures as determined by X-ray analysis; the torsional angles φ were calculated from the atomic coordinates as usual.[1], * The structure formulae and the numbering of atoms are given in Fig. 1. Several earlier structure determinations of steroids were omitted because of the rather large standard errors.

The features common to the ring D and its structural environment in compounds **1**—**11** are:

(a) The *trans*-C/D junction.

(b) The angular methyl function on C(13).

(c) A β-substituent (= O, —O, —CRO, —CR_2H) on C(17) with the exception of **9**, which has a β hydroxyl group on C(16).

(d) The saturated ring C.

Fig. 1 shows that the remaining skeletal features vary widely, from the all-*trans* cholestane skeleton (**2**,**5**,**7** and **8**), or a *cis* B/C junction with a heavily distorted[1] ring C (**3**) to hydrindane-like systems with a double bond (**4**) or a 3-membered ring (**10**) attached to C(8). Notwithstanding this variety, the amplitude of puckering (as distinct from conformation)† shows surprising constancy in the series.

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* The convention defining the sign of a torsional angle and the calculation of their standard deviations and weighted averages are to be found in Ref. 1.

† The geometry embraces the entire pseudorotation circuit and describes the amplitude of puckering (φ_m, see section 3). The conformation of the 5-membered ring is given by its exact position on the pseudorotation itinerary relative to some chosen standard ("phase angle" Δ). In the solid state calculation of the torsional angles allows the unequivocal determination of φ_m and Δ; in solution pseudolibration may occur,[17] giving rise to a number of conformations belonging to one and the same conformer (roughly described as envelope or half-chair with substituents in either axial or equatorial position).

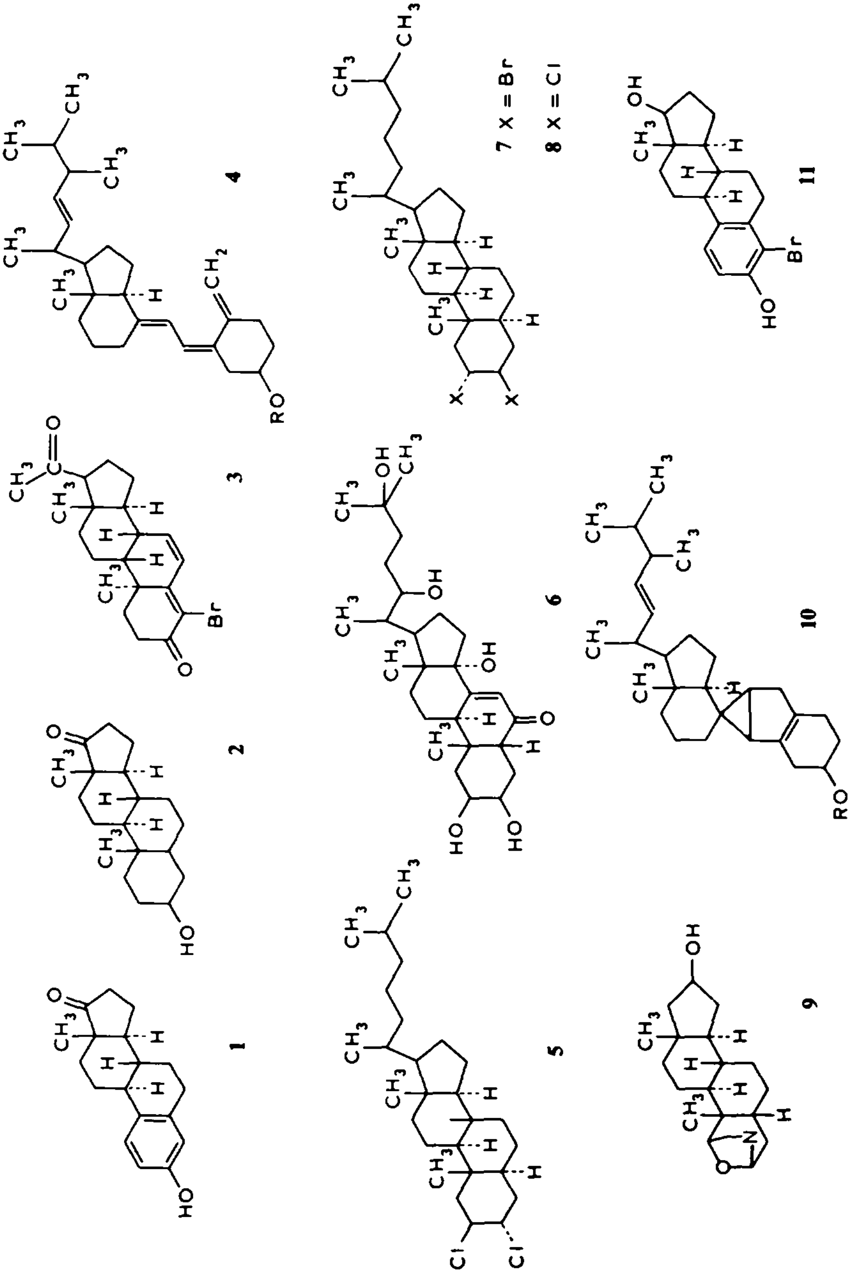

Fig. 1

It should be noted that, in the crystal, the conformation of ring D is "frozen". A flexing of the ring in the solid would be revealed by X-ray structure analysis in the form of disordering or abnormally high temperature factors of the atoms C(15), C(16) and C(17). No such effects have been observed.

SECTION 2

Conformation of cyclopentane, hydrindane and ring D

It is known from theory[2,3,6] as well as from experiment[4,17] that the cyclopentane ring is flexible. The puckering rotates around the ring without the interference of significant enthalpy barriers (pseudorotation). In unsubstituted cyclopentane a *continuum* of conformations of approximately equal energy but differing in torsional and bond angles is envisaged.

The presence of one or more substituents will, in general, change the delicate equilibrium between torsional and bond bending energies and introduces steric factors as well, thus giving rise to a potential energy barrier opposing pseudorotation.[3,17] Therefore, the importance of a substituent is its power to restrict the flexibility of the ring to a more or less narrow range depending on the shape and depth of the energy well.* Attention has often been focussed exclusively on two specific conformations, the C_s or envelope form with mirror symmetry and the C_2 or half-chair form with a two-fold rotation axis. There is not a priori reason, however, to assume that either of these forms or "basic models" actually represents the most stable conformation in any substituted cyclopentane. In cases where the intramolecular force field is unsymmetrical with respect to the C_s or C_2 conformation† an "intermediate conformer" will be the most stable one.

The total pseudorotation pathway of cyclopentane comprises 10 C_2 and 10 C_s forms. In ring D of steroids, as well as in the *trans*-hydrindane system, pseudorotation is limited to approximately $\frac{1}{10}$th of the 720° itinerary (Fig. 2), because ring C resists any tendency to close the torsional angle φ (17–13–14–15).

All forms in Fig. 2 have approximately equal energy. In the absence of substituents, including C(18), the ring D skeleton is not rigid but may be imagined to

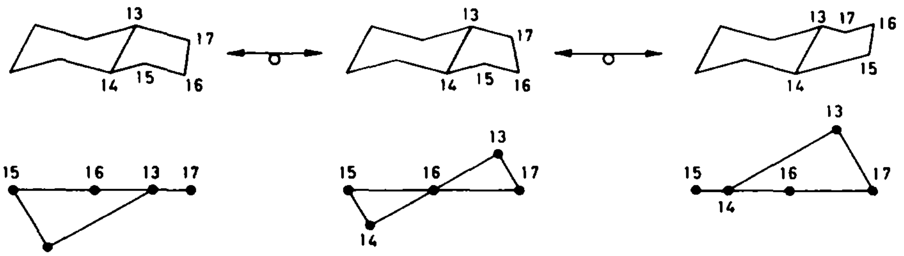

FIG. 2 Pseudorotation pathway for perhydrindane in perspective and in projection (steroid numbering).‡

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* See Ref. 17* for a more complete discussion.

† Possibly also in crystals, in cases where packing forces are markedly anisotropic with respect to the symmetrical forms.

‡ There seems to be no generally recognized symbol that represents the continuum of forms of a pseudorotation itinerary. We propose to use the notation ←o→

carry out a pseudolibration[17] movement about the C_2 form. In the compounds investigated (Fig. 1), the substituents (on C(13), C(17) or C(16)) introduce barriers unsymmetrical with respect to the forms a,b,c of Fig. 2. Hence, it can be concluded that:

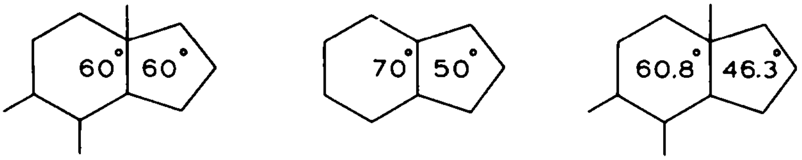
(i) The true energy minimum of ring D generally corresponds to an "intermediate" conformation.

(ii) The location of the energy minimum is determined by the position and nature of the substituents in conjunction with conformation-transmission effects.

The energy well is expected to be rather shallow in most cases (i.e. a few kcals/mole), hence anisotropic packing forces in the crystal may rotate ring D to some extent away from the minimum of the "free" molecule. It is difficult at present to evaluate the magnitude of this effect, but the consistency of the ring D data from widely different sources indicate that it cannot be an important factor.

C/D junction

Since ring D is *trans*-coupled to a 6-membered ring C, the valency and torsional angles about the ring junction are of primary interest. Some theoretical work on this subject has been published.[18, 19] It has been argued[22] that the angle of torsion between the vicinal ee valencies of a 6-membered ring cannot become greater than 60°; therefore, the torsional angle of ring D at the junction was set equal to 60°. ("maximally puckered" model).* More recently, Bucourt and Hainaut,[19] retaining the concept of trigonal symmetry about the junction, proposed a model for perhydrindane in which the 6-membered ring was puckered to 70°. The present results disagree with both theoretical predictions (Fig. 3).



(a) (b) (c)

FIG. 3 Torsional angles about C(13)—C(14); (a) model of Ref. 22; (b) model of Ref. 23; (c) weighted average of compounds **1**—**11**.

The discrepancy between theoretical predictions and experiment is brought about by the fact that the assumption of trigonal symmetry does not hold. The sum of the torsional angles on each side of a *trans*-junction $\alpha + \beta$ is found to be smaller than 120°. The sum is a function of the degree of substitution.

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* Energy calculations for the C_2 and C_s forms have been made by Brutcher and Bauer.[18] These authors used the "maximally puckered" model. Since the X-ray results demonstrate that the true geometry is rather less puckered, the Van der Waals interactions probably have been overestimated. The first experimental evidence that led to the conclusion that the maximally puckered model is incorrect came several years ago[11a] from an analysis of the torsional angles in compounds **5**, **7** and **8**. Recently, Brutcher and Leopold,[19c] using in part data from the same compounds, independently came to a similar conclusion.

This effect was shown[1] to originate from the bending of the valency angles about the bridge-head atoms. The standard values (= weighted averages) of the sum in steroid *trans*-junctions are presented below:

	Standard value	Theoretical (sum rules[1])	Theoretical (*trans*-decalin[19b])
A/B	113·1°	117·5°	
B/C	107·4°	115°	111·2°
C/D	107·1°	117·5°	

The standard values of the torsional and bond angles about the C/D junction are shown in Fig. 4 (compare Fig. 5 and Table 5 in Ref. 1). Numerical values for φ_C and φ_D are presented in Table 1.

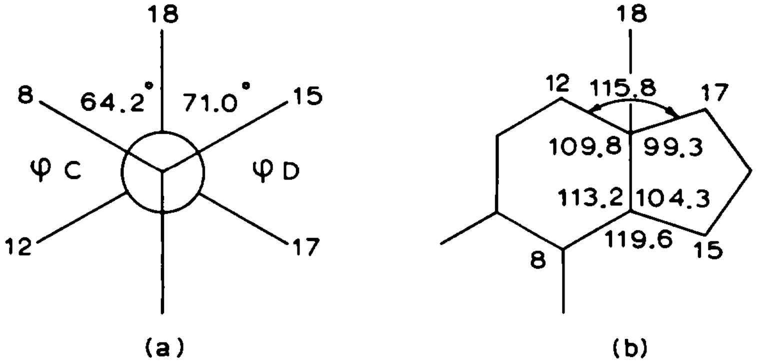

FIG. 4 (a) Newman projection along C(14)–C(13); (b) standard values of the bond angles about C(13) and C(14).

TABLE 1. TORSIONAL ANGLES φ ABOUT THE C/D JUNCTION AND THE STANDARD DEVIATIONS σ.

	1	2	3	5	6	7	8	11	Standard value	No-coupling value
φD	39·8°	44·9°	46·2°	47·0°	48·6°	46·8°	49·9°	49·5°	46·3°	44·0°
φC	69·6°	59·0°	62·2°	60·0°	60·0°	58·7°	61·8°	64·3°	60·8°	55·8°
sum	109·4°	103·9°	108·4°	107·0°	108·6°	105·5°	111·7°	113·8°	107·1°	99·8°
σ	2·8°	0·8°	2·8°	1·7°	1·8°	2·6°	4·7°	1·7°	0·7°	—

* The no-coupling values are the hypothetical torsional angles each ring would presumably have in the absence of ring fusion; the difference between these and the standard values is a measure of the adaptation of the rings. The no-coupling value of φ_C is the standard value along the bond C(1)—C(2) in the cholestanes; that of φ_D is the maximum torsional angle φ_m in strain-free cyclopentane, calculated from Hendrickson's data.[6] The compounds 4, 9 and 10 are omitted, because of their large standard deviations.

The standard value of φ_C (60·8°) is slightly greater than the standard torsional angles in the *trans* A/B junction of the cholestanes ($\varphi_A = 55{\cdot}1 \pm 0{\cdot}8°$, $\varphi_B = 58{\cdot}0 \pm 0{\cdot}7°$). Hence, the increase of φ_C due to the presence of ring D is in the order of 5° relative to the no-coupling value (Table 1) and 3° relative to φ_B.

The strain energy associated with each ring and with the junctions may throw some light on the problem of the geometry of the "free" cyclopentane molecule. It may be argued that ring D must be strained because ring C shows clear evidence of strain at the C/D junction. This means that cyclopentane is probably slightly "flatter" than ring D. A quantitative account will be given elsewhere.[5] Here the discussion is limited to the strain energy associated with the C/D junction.

The strain about the C(13)—C(14) bond is difficult to evaluate. First, the torsional barriers of such a highly substituted C–C fragment are not accurately known. Furthermore, the strict separation of torsional and bond angle deformation energy functions seems questionable in this case as marked deviations of trigonal symmetry occur. However, even with the necessary reservations, the calculations show clearly that the torsional energies involved are much smaller than the angle strain energies. Using a relatively high torsional barrier (6 kcal/mole) we find a torsional strain of only 0·2 kcal/mole, whereas the sum of the bond angle strain about C(13) and C/14) amounts to 5–6 kcal/mole. The latter value was calculated using the "normal" bond angles[19b] (111·0° for a tert. carbon and 109·5° for a quart. carbon).

Interestingly, a relatively large portion of the strain comes from the widening of the external valency angles ϑ (12–13–17) (115·8°, $E_\vartheta = 0{\cdot}84$ kcal/mole) and ϑ(8–14–15) (119·6°, $E_\vartheta = 1{\cdot}52$ kcal/mole). This effect has not been foreseen. The calculated strain energy about the A/B, B/C and C/D junctions (kcal/mole relative to 2,2,3-trimethyl-butane) are shown below:

	Bond angle strain	Torsional strain	Total
A/B	8·8 kcal/mole	~ 0 kcal/mole	0·8 kcal/mole
B/C	0·3	~ 0	0·3
C/D	5·9	0·2	6·1
C/D no coupling	3·3	1·1	4·4
Difference	2·6	−0·9	1·7

Ring D

The torsional and valency angles of ring D in compounds **1**—**11** are shown in Table 2. Since the conformation of the ring varies, the values cannot be simply averaged except perhaps $\varphi(17\text{–}13\text{–}14\text{–}15) = \varphi_D$ and the bond angles about C(13) and C(14). The standard deviations of the angles in compounds **4**, **9** and **10** are large, these compounds were therefore omitted from all averaging procedures.

The conformation of ring D and the progressive pseudorotation in the series **1**—**11** is easily visualized by projecting the ring onto the plane that is perpendicular to the plane C(15)—C(16)—C(17) and which goes through C(15) and C(17) (Fig. 5).

An interesting feature of these projections is the "wobbling" of the C(13)—C(18) bond vector with respect to the plane C(15)—C(16)—C(18). It seems that the position of the angular methyl group is not exactly predictable from molecular models. This makes the calculation of the important steric factors in ring D unreliable.

The distances of atoms C(13) and C(14) to the plane 15–16–17 are shown in Table 2. The sum of these distances, a measure of the amount of puckering, lies between 0·70 and 0·80 Å, weighted average: 0·73 Å.

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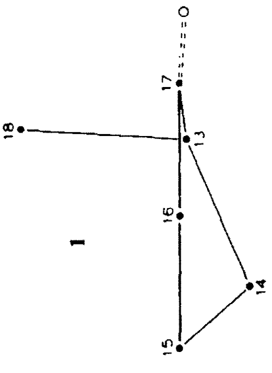
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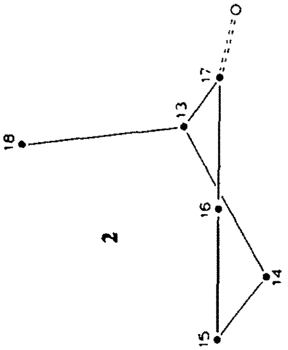
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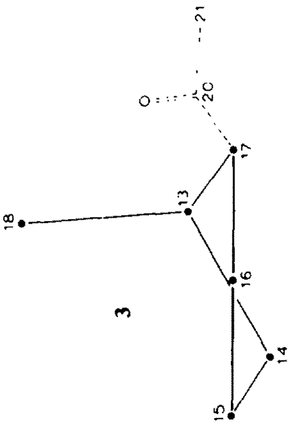
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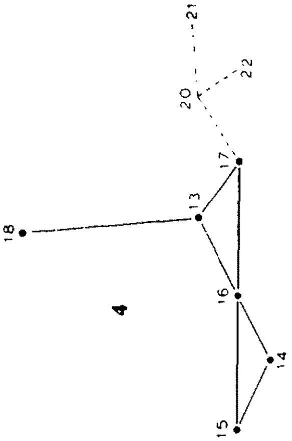
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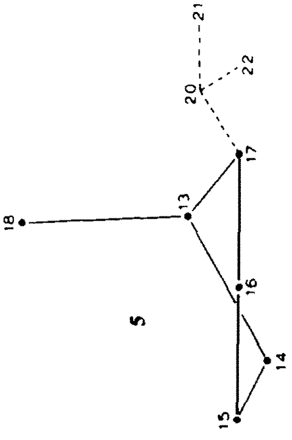
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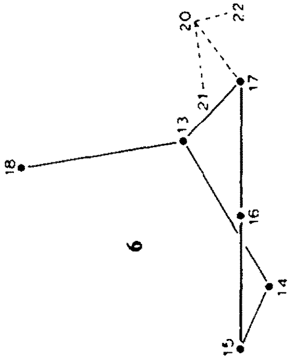
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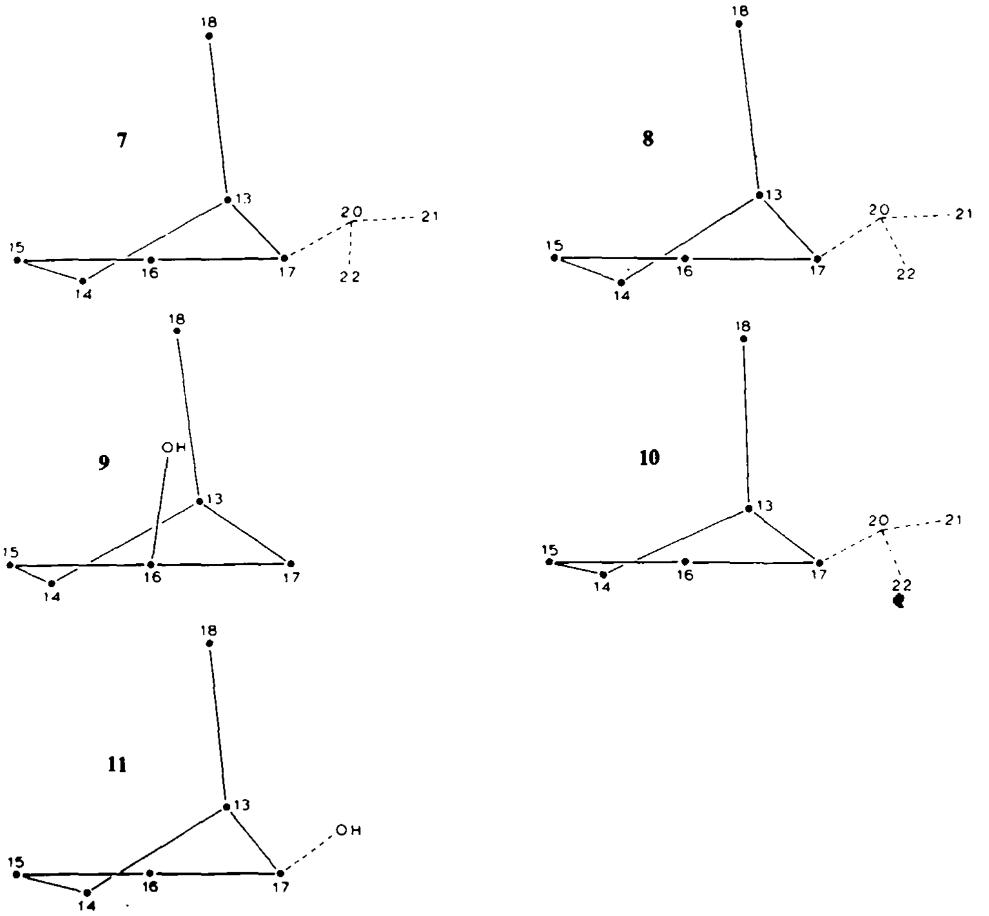

FIG. 5 Projection of ring D in compounds 1—11 (see text). The C(17) side chain has not been drawn to scale.

TABLE 2. TORSIONAL AND VALENCY ANGLES OF RING D AND STANDARD DEVIATION σ IN COMPOUNDS 1—11

Torsional angles	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
φ_0 13–14	+39·8°	+44·0°	+46·2°	+42·2°	+47·0°	+48·6°	+46·8°	+49·9°	+51·5°	+40·8°	+49·5°
φ_4 14–15	−41·1°	−38·6°	−38·4°	−33·5°	−36·1°	−36·3°	−33·6°	−36·0°	−33·9°	−28·2°	−34·6°
φ_3 15–16	+25·1°	+16·6°	+13·2°	+10·8°	+10·7°	+ 9·9°	+ 7·6°	+ 8·5°	+ 7·0°	+ 5·4°	+ 6·0°
φ_2 16–17	− 1·9°	+11·5°	+15·8°	+14·0°	+18·1°	+19·9°	+20·6°	+22·5°	+21·5°	+17·9°	+24·2°
φ_1 17–13	−23·6°	−34·3°	−37·7°	−35·3°	−39·1°	−40·8°	−40·4°	−43·9°	−42·3°	−[illegible]4·5°	−44·7°
σ	2·8°	0·8°	2·8°	—	1·7°	1·8°	2·6°	4·7°	—	—	1·7°
Valency angles											
ϑ_0 17–13–14	103°	99·2°	98·3°	102·4°	99·8°	99°	100·6°	99·1°		104·7°	98·5°
ϑ_4 13–14–15	106°	104·3°	104·1°	104·1°	104·2°	104°	104·9°	102·7°		106·4°	104·2°
ϑ_3 14–15–16	102°	102·6°	105·0°	101·5°	103·6°	103°	102·9°	103·4°		106·3°	101·1°
ϑ_2 16–17–13	102°	106·0°	105·5°	110·4°	106·8°	108°	106·9°	105·9°		107·7°	105·6°
ϑ_1 16–17–13	108°*	107·8°*	105·3°	103·9°	103·7°	103°	103·2°	103·7°		99·5°	104·5°
σ	1·5°	0·4°	1·5°	—	0·7°	0·8°	1·4°	2·0°	—	—	0·7°
Distance to plane through C(15) – C(16) – C(17)(Å)											
C(13)	−0·05°	+0·29°	+0·42°	+0·38°	+0·47°	+0·52°	+0·53°	+0·58°	+0·57°	+0·49°	+0·61°
C(14)	−0·65°	−0·43°	−0·34°	−0·30°	−0·27°	−0·26°	−0·20°	−0·22°	−0·18°	−0·13°	−0·16°
Abs. sum	0·70°	0·72°	0·76°	0·68°	0·74°	0·78°	0·73°	0·80°	0·75°	0·62°	0·77°

* Sp^2 hydridized

SECTION 3

Amplitude and phase angle of pseudorotation

Pitzer and Donath[3] characterized the geometry of a general cyclopentane (carbon skeleton only) by two variables, the parameter q (a measure of the amplitude of puckering) and the phase angle of pseudorotation. Their approach involved rather complicated computations and the authors limited their work to the symmetrical C_2 and C_s forms. Hendrickson[6] calculated bond and torsional angles by minimizing the total energy, ignoring symmetry restrictions. In his computer procedure it was prerequisite to define one torsional angle, three bond angles were independently

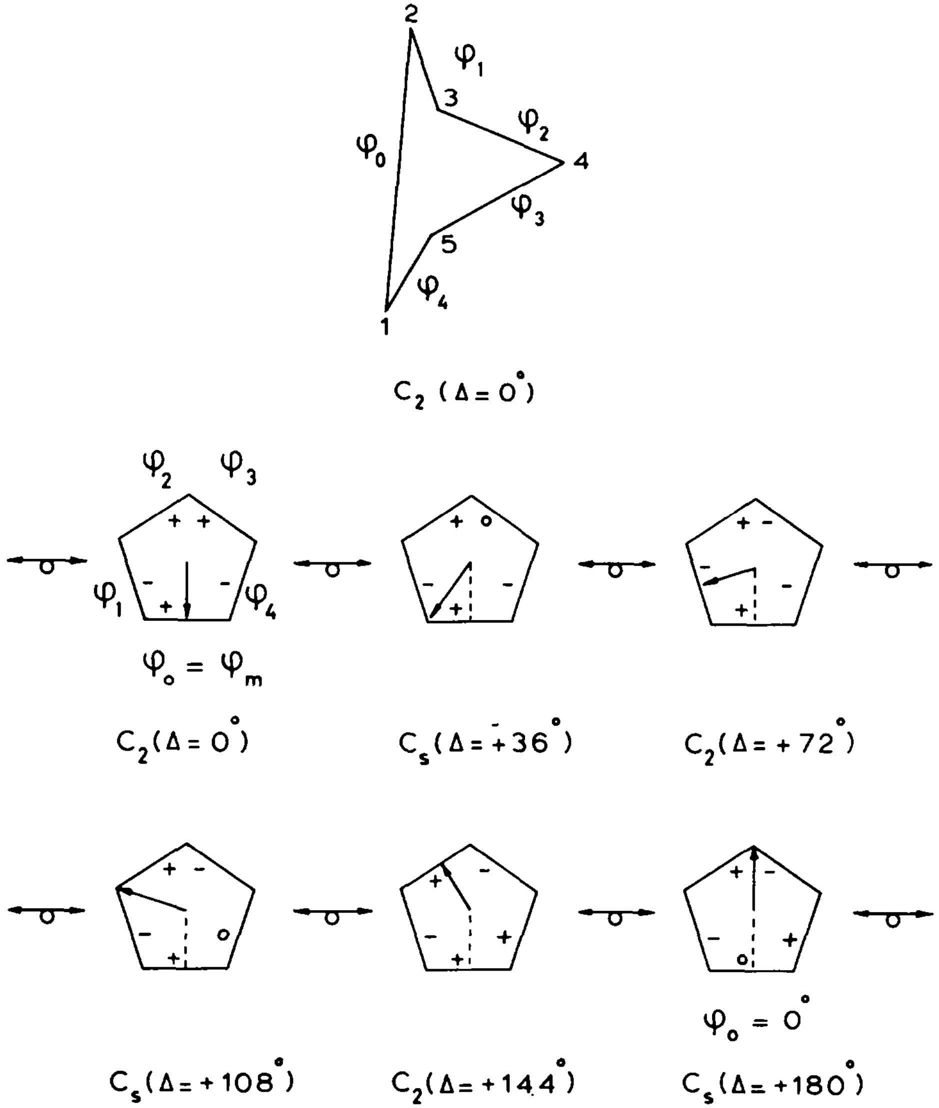

FIG. 6 Part of the pseudorotation circuit, from phase angle $\Delta = 0°$ to $\Delta = 180°$, showing the signs of the torsional angles.

varied and the remaining ones followed from a set of geometrical equations. Again bond lengths were assumed regular.

In this section we describe a new and simple method of calculating the torsional angles of any of the infinity of forms a regular cyclopentane ring can assume in the course of strain-free pseudorotation. The maximum possible torsional angle (φ_m) is used as a measure of the amplitude (geometrical parameter). Given in addition the conformational parameter, the "phase angle" Δ, all torsional and bond angles are defined. It will be shown that experimental determination of two or more torsional angles of a *general* cyclopentane ring is sufficient to calculate φ_m and Δ by hand. By substituting $\Delta = 0$ (half-chair) and $\Delta = \pm 36°$ (envelope) in Eq. (2) given below, the torsional angles characterizing the symmetrical forms that are *part of the same pseudorotation circuit* (= constant amplitude) are obtained.

Consider the half-chair form (Fig. 6) where the torsional angle about 1–2 bond $\varphi_0 = \varphi_m$ with positive sign; the phase angle Δ is set equal to zero. A pseudorotation over 360° yields the mirror image (φ_0 negative), a rotation over $\Delta = 720°$ restores the original molecule. Thus φ_0 (and each of the other φ's in turn) passes the values $+\varphi_m$, 0, $-\varphi_m$, 0, $+\varphi_m$, i.e. the magnitude of φ_0 oscillates between two extremes. Now any periodic motion can be described by sine and cosine functions (Fourier series) and it is logical to look for a function that fits the torsional angles. An analysis of the theoretical[3, 6] and experimental torsional angles suggests that a simple cosine function suffices. Hence, analogous to the equation proposed[3] for the amplitude of puckering, we write:*

$$\varphi_0 = \varphi_m \cos \frac{\Delta}{2} \tag{1}$$

$$(0 \leqslant |\Delta| \leqslant 720°)$$

Since the remaining angles may be generated by varying Δ from 0 to 720°, a single expression suffices to describe the torsional angles of all possible pseudorotation isomers:

$$\varphi_j = \varphi_m \cos\left(\frac{\Delta}{2} + j\delta\right) \tag{2}$$

$$\text{where } j = 0,1,2,3,4;\ \delta = 144°.$$

Numerical equations are given in the appendix. Note that only two values (unrelated by symmetry) are needed to obtain φ_m and $\tan \Delta/2$.

A more accurate formula utilizing all the available information is easily derived:

$$\tan \frac{\Delta}{2} = \frac{(\varphi_2 + \varphi_4) - (\varphi_1 + \varphi_3)}{3{\cdot}0777\, \varphi_0} \tag{3}$$

(φ_m follows from Eq. (1)).

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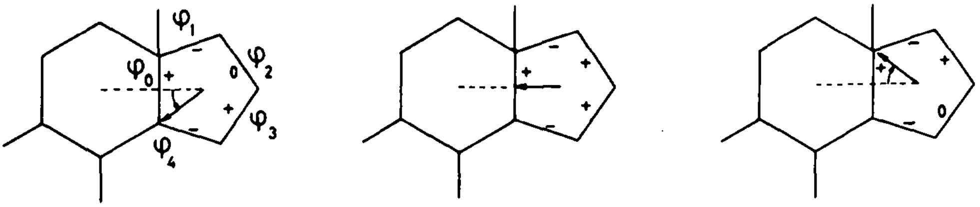
* Eq. (1), from which the remaining equations are derived, has not been proven mathematically. However, the excellent internal consistency of the results obtained from real molecules (ring D and furanoses[20]) as well as from literature models[3, 6] (see appendix) leaves little doubt as to its validity. The same reasoning can be applied to other flexible rings. For example, pseudorotation in the cycloheptane ring can be described by a slightly more complicated goniometric function: $\varphi_0 = A \sin(1/2\,\Delta) + B \sin(3/2\,\Delta)$ (C. Altona and H. J. Geise, unpublished results.)

TABLE 3. GEOMETRICAL PARAMETER (MAXIMUM TORSIONAL ANGLE) φ_m AND CONFORMATION PARAMETER (PHASE ANGLE OF PSEUDOROTATION) Δ OF COMPOUNDS **1**—**11***

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	Standard value
φ_m	42·3°	44·9°	46·2°	(42·2°)	46·7°	48·2°	46·6°	50·1°	(52·0°)	(41·4°)	49·9°	46·7°
Δ	—39·8°	—7·9°	+2·1°	(+4·4°)	+7·9°	+10·7°	+15·4°	+16·1°	(+16·1°)	(+18·8°)	+21·1°	

* The results from compounds **4**, **9** and **10** are considered to be less accurate and are given in parentheses.

Provided the numbering sequence is retained, another choice of φ_0 means a shift of the phase angle Δ by a multiple of 72°. Thus, the five dihedral angles can in turn be chosen to check the internal consistency of the data. With accurate X-ray determinations a consistency in φ_m and Δ of the order of 0·5 – 1° is found. The results of the calculations of ring D are shown in Table 3, the zero point on the Δ scale is defined in Fig. 7.



$\Delta = -36°$ (C(14) envelope) $\Delta = 0°$ (half-chair) $\Delta = +36°$ (C(13) envelope)

FIG. 7 Pseudorotation itinerary of ring D, from phase angle $\Delta = -36°$ to $\Delta = +36°$, showing the signs of the torsional angles.

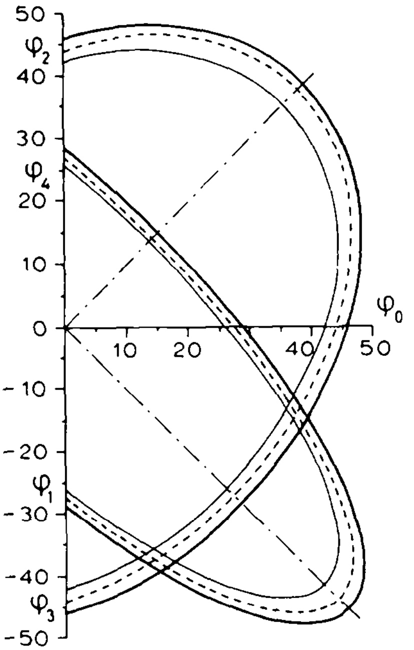


FIG. 8 Graphical representation of the course of the torsional angles during pseudorotation (see text). Thin line, theor. model of Ref. 6; dotted line, standard ring D; heavy line, theor. model of Ref. 3.

A convenient way to visualize the course of the torsional angles during pseudorotation is the φ_i–φ_j plot. It can be shown[5] from Eqs (1) and (2) that a graph of φ_0 on the ordinate axis vs. $\varphi_1 \ldots \varphi_4$ on the abcissa yields two ellipses with their main axes at an angle of 45° with the φ axes (Fig. 8). The "narrow" ellipse relates φ_0 to φ_1 (φ_4), the "broader" ellipse represents the relation between φ_0 and φ_2 (φ_3). The main axes are constant fractions of φ_m, hence the axial ratios are constants (appendix).

The application of eq. 2 to the problem of ring D conformation is illustrated in Fig. 8.

In the cholestane series (compounds **5**,**7**,**8**), Δ is between $+7°$ and $+17°$ (Table 3), Δ av $= 13°$. Excepting the 17-keto steroids, the Δ values for the entire series (**3**–**11**) range from $+2°$ to $+21°$, Δ av $= +14°$. No steroid has as yet been found in which ring D assumes an exact symmetry, although in **1** and **4** the ideal symmetry is closely approached (near-envelope and half-chair respectively).

The relatively narrow range for Δ in widely differing steroids (about 20° of the total possible range if **1** and **2** are omitted) leaves little doubt that the energy minimum for ring D does not correspond to C_2 or C_s symmetry, except when special features are present in the molecule (see below). The true energy minimum of ring D (androstane skeleton) seems to be near $\Delta = +15°$, the introduction of a 17-keto group (**2**) causes a pseudorotation by about $-20°$.

It is now possible to define a standard ring D by taking the weighted average of φ_m (46·7°). Using eqs. (1) and (a)—(d) in the appendix the standard torsional angles of the C_2, C_s and one intermediate form are calculated (Table 4).

TABLE 4. STANDARD TORSIONAL ANGLES OF THE SYMMETRICAL FORMS AND OF ONE INTERMEDIATE RING D CONFORMATION

	C_2 ($\Delta = 0°$)	($\Delta = 15°$)	C_s ($\Delta = 36°$)
φ_0	+ 46·7°	+ 46·3°	+ 44·4°
φ_1	− 37·8°	− 41·0°	− 44·4°
φ_2	+ 14·4	+ 20·1°	+ 27·4°
φ_3	+ 14·4°	+ 8·5°	0
φ_4	− 37·8°	− 33·9°	− 27·4°

Factors governing the geometry and conformation

A discussion of the factors responsible for the shape of ring D in each compound is at present necessarily qualitative and incomplete. Most compounds show many complicating features and a systematic study on the influence of the C(17) substituent, *cis* or *trans* B/C junction etc., is not yet feasible. A few outstanding features can be discussed, however:

(i) The effect of the torsional barriers about the bonds C(13)—C(17) and C(16)—C(17). When C(17) is sp^2 hybridized (keto-substituent), the torsional angles about 13–17 and 16–17 tend to be small due to lowering of the barrier and the conformation will rotate towards the C(14) envelope. This is indeed the case, only the rings D in oestrone (**1**) and in androsterone (**2**) have negative phase angles Δ. Although the conformations of **1** and **2** differ ($\Delta = -39{\cdot}8°$ and $-7{\cdot}9°$, respectively) their torsional parameters φ_m are the same within the error of measurement (Table 3). When C(17) is sp,^{3} the nature of its sidechain does not seem to influence the conformation of ring D when the atom attached to C(17) is carbon or hydrogen. When it is oxygen, as in oestradiol (11), the preference seems to be toward increasing positive Δ, thereby $\varphi(16\text{–}17\text{–}13\text{–}14) = \varphi_1$ is increased and so too the distance between C(18) and oxygen (see under ii, however, for an alternative explanation).

(ii) More important seem to be the steric requirements of ring C. It has been shown[1] that ring C is often strained because of conformational transmission of strain from rings A and/or B. This strain is partly taken up in ring C and probably also relayed to some extent to ring D. The magnitude and the directing effect of this relayed strain must be considered. A tendency to increase φ_C (Fig. 4a) causes a closure of φ_D. Ring D can accommodate this closure in two ways, either by changing its geometry (decreasing φ_m) and/or by pseudorotation toward one of the envelope forms (increasing Δ). Conversely, a tendency to decrease φ_C results in pseudorotation toward the half-chair form. The absolute values of the torsional angles are for the time being less important than predictions about the directing tendencies of the strain. Therefore, we will base the following discussion on calculations[19] of the effect of a change in a given torsional angle on the remaining angles in simple cyclohexanoid systems.

Fig. 9 illustrates the correlation between an increase or decrease of a torsional angle in the A, B or C ring, especially those at the (*trans*) junctions, on φ_C.

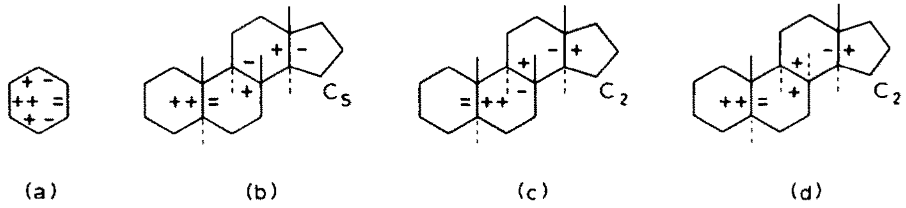


FIG. 9 The predicted effect of conformational transmission "through the junctions" on ring D (+ = opening of torsional angle, − = closure) provided the A, B and C rings have the chair form.

For example, the different conformations of ring D in estrone (**1**) and androstane (**2**) can be understood in this way. In **1** ring A is aromatic, as a consequence ring B is seriously deformed (sofa conformation[1]) which deformation has the effect of increasing the torsional angle $\varphi(7\text{–}8\text{–}9\text{–}10)$ to 62·4° (standard value in the cholestane skeleton: 54·6°), thus decreasing the opposite angle $\varphi(11\text{–}9\text{–}8\text{–}14)$ and increasing φ_C (= $\varphi(12\text{–}13\text{–}14\text{–}8)$). Ring D responds by pseudorotation to $\Delta = -40°$, possibly accompanied by a slight flattening ($\varphi_m = 42{\cdot}3°$, compare the standard value of $\varphi_m = 46{\cdot}7°$). The pseudorotation toward negative Δ and the flattening are, of course, aided by the requirements of the 17-keto group. On the other hand, the 17-hydroxy compound **11** is expected to rotate toward a more positive Δ value compared with the cholestanes and this is indeed the case. The effect is small, however, and the comparison between **1** and **11** calls for caution since ring B in **11** assumes a half-chair form[1] which requires less deformation of ring C.

Compound 3, duphaston, is a case that is more difficult to understand. The strong repulsions between the methyl group C(19) and the axial hydrogens on C(12) and C(14) cause a considerable deformation (flattening) of chair-ring C, the most prominent effect being an opening of the valency angle C(9)—C(11)—C(12) to 117°. Calculations[1] indicate a tendency to open φ_C (reflex effect[20]) and one expects a ring D conformation similar to that in **11**. Instead, a near half-chair form ($\Delta = +2{\cdot}1°$) is found. Clearly, one or more other factors must be at work. Perhaps the overriding factor is the strain induced by sofa-form ring B which is relayed by the *cis* B/C junction and results in a tendency to close φ_C (Fig. 9d); an effect exactly opposite to that seen in **1** which has a sofa ring B and a *trans* B/C junction.

It is not surprising that the few more or less clearcut examples of conformational transmission effects on the conformation of ring D concern steroids showing relatively large deformations of the A, B and/or C rings. We wish to point out that the meta position (1—3) of the ring junctions in the steroid skeleton has the consequence that a large change in φ at one junction induces minimal effect at the next junction, provided no double bonds are present.[21] For example, a decrease of φ by 20° at the A/B junction results in a calculated increase of only 3° at B/C. Hence, transmission effects "through the junctions" are damped over short distances.

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APPENDIX 1

Starting from Eq. (2), the expressions relating the torsional angles φ_j of a general cyclopentane ring to φ_m and Δ are (see Fig. 6):

$$\varphi_0 = \varphi_m \cos\frac{\Delta}{2}$$

$$\varphi_1 = \varphi_m\left(-0{\cdot}8090\cos\frac{\Delta}{2} - 0{\cdot}5878\sin\frac{\Delta}{2}\right) \tag{a}$$

$$\varphi_2 = \varphi_m\left(+0{\cdot}3090\cos\frac{\Delta}{2} + 0{\cdot}9511\sin\frac{\Delta}{2}\right) \tag{b}$$

$$\varphi_3 = \varphi_m\left(+0{\cdot}3090\cos\frac{\Delta}{2} - 0{\cdot}9511\sin\frac{\Delta}{2}\right) \tag{c}$$

$$\varphi_4 = \varphi_m\left(-0{\cdot}8090\cos\frac{\Delta}{2} + 0{\cdot}5878\sin\frac{\Delta}{2}\right) \tag{d}$$

It follows that:

$$\varphi_2 - \varphi_3 = 1{\cdot}9021\,\varphi_m \sin\frac{\Delta}{2} \tag{f}$$

$$\varphi_4 - \varphi_1 = 1{\cdot}1756\,\varphi_m \sin\frac{\Delta}{2} \tag{g}$$

$$(\varphi_2 - \varphi_3)/(\varphi_4 - \varphi_1) = 1{\cdot}618 \tag{h}$$

Eq. (h) provides a ready check upon the internal consistency of the torsional angles (with the condition *that* $\sin \Delta/2 \neq 0$.

The sum of (f) and (g) divided by φ_0 yields eq. (3). Because in principle each of the five torsional angles can be chosen as φ_0, the parameters φ_m and Δ can be fitted to the experimental data by means of a least squares procedure. The effect of small errors in the atomic parameters is thus smoothed out. Symmetry introduces inaccuracies (e.g. when $\varphi_2 \cong \varphi_3$ etc.) that are best avoided by excluding the greatest φ_j from the permutations.

The torsional angles of the symmetric conformations on the same pseudorotation pathway follow from:

$$\begin{array}{lcl} \varphi_0 = +\,1{\cdot}000\,\varphi_m & & \varphi_0 = +\,0{\cdot}9511\,\varphi_m \\ \varphi_1 = -\,0{\cdot}8090\,\varphi_m & & \varphi_1 = -\,0{\cdot}9511\,\varphi_m \\ \varphi_2 = +\,0{\cdot}3090\,\varphi_m & \text{(i)} & \varphi_2 = +\,0{\cdot}5878\,\varphi_m \qquad \text{(j)} \\ \varphi_3 = +\,0{\cdot}3090\,\varphi_m & & \varphi_3 = \quad 0 \\ \varphi_4 = -\,0{\cdot}8090\,\varphi_m & & \varphi_4 = -\,0{\cdot}5878\,\varphi_m \end{array}$$

The construction of the pseudorotation ellipses (Fig. 8) is facilitated by noting that:

(i) The main axes of the narrow ellipse that represents the relation between two torsional angles adjacent to each other e.g. φ_0 and φ_1 are given by:

$$l_1 = \varphi_m \sin\delta/(1+\cos\delta)^{\frac{1}{2}} = 1{\cdot}3450\,\varphi_m \tag{k}$$

$$l_2 = \varphi_m \sin\delta/(1-\cos\delta)^{\frac{1}{2}} = 0{\cdot}4370\,\varphi_m \tag{l}$$

(ii) The main axes of the broad ellipse (relation between φ_j's in 1,3 position) are given by:

$$s_1 = \varphi_m \sin 2\delta/(1+\cos 2\delta)^{\frac{1}{2}} = -\,1{\cdot}1441\,\varphi_m \tag{m}$$

$$s_2 = \varphi_m \sin 2\delta/(1-\cos 2\delta)^{\frac{1}{2}} = -\,0{\cdot}8313\,\varphi_m \tag{n}$$

An interesting conclusion is that the ratios l_2/l_1, s_2/s_1 etc. are independent of φ_m. The theoretical values are compared below with the ratios obtained from:

(i) Hendrickson's model (average)
(ii) Pitzer and Donath's model
(iii) Weighted average of ring D values

by means of ellipse equations without previous knowledge of δ (i.e. the axes were fitted to the data).

	H	P & D	ring D	theor.
l_2/l_1	0·328	0·330	0·326	0·325
s_2/s_1	0·733	0·736	0·729	0·727

The almost exact agreement with theory lends support to the approach outlined above.

It was found that compounds **9** and **10** yield grossly abnormal ratios (e.g. s_2/s_1, of 0·624 and 0·681, respectively). This may be an indication of large errors in the atomic parameters.

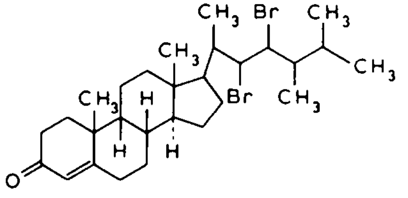
Equations similar to (1) and (2) describe the change in the valency angles during pseudorotation. It is also possible to construct a Lissajous figure giving the graphical relation between the φ_j 's and the ϑ_j 's. Knowing φ_m and Δ, the bond angles and thus the total strain energy (torsional and bond angle deformation) can be calculated. However, the mathematical relations are rather unwieldy and less suited for hand calculations. A computer program has been prepared.[5]

We wish to stress that the calculated parameters φ_m and Δ of any substituted cyclopentane have significance only at or near the observed conformation. The "pseudorotation" that yields values for C_2 and C_s forms is a purely mathematical operation. When important energy barriers (steric or otherwise) are encountered during "real" pseudorotation the molecule will tend to adapt its geometry so that the torsional parameter φ_m, may vary. Some indication of this effect may be seen in Table 3, which shows a slight increase of φ_m on going from negative to positive Δ values.

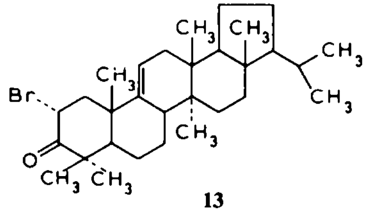
APPENDIX II

Recently, three more X-ray structure analyses of interesting compounds became available (Fig. 10):

12 22, 23-Dibromo-8β, 9β, 10β-ergost-4-ene-3-one[22]
13 2α-Bromoarborinone.[23]
14 17β-Bromoacetoxy-9β, 10α-androst-4-en-3-one.[24]



12

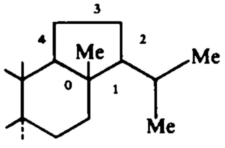


13

The torsional angles of the five-membered rings (D in **12** and **14**, E in **13**) are collected below:

	12	13	14
φ_0	(13–14) + 46·5°	(17–18) + 50·1°	(13–14) + 44·7°
φ_4	(14–15) − 34·2°	(18–19) − 36·2°	(14–15) − 29·1°
φ_3	(15–16) + 8·2°	(19–20) + 8·1°	(15–16) + 2·5°
φ_2	(16–17) + 19·3°	(20–21) + 23·8°	(16–17) + 26·8°
φ_1	(17–13) − 39·3°	(21–17) − 44·2°	(17–13) − 44·4°

The numbering sequence of ring E in **13** is as follows:



In order to compare the phase angle Δ in **13** with that in compounds **1–12**, the direction of positive Δ is here taken anti-clockwise. We calculate:

	φ_m	Δ
12	46·1°	+ 13·0°
13	50·5°	+ 17·3°
14	46·5°	+ 32·1°

These results agree well with those of Table 3. Ring E in **13** does not have the envelope form (as was concluded earlier from calculations of "best planes" through four atoms[21]) but, again, is halfway between the C_2 and C_s forms.