Tetrahedron, 1967, Vol. 23, pp. 439 to 463. Pergamon Press Ltd. Printed in Northern Ireland

# CONFORMATION OF NON-AROMATIC RING COMPOUNDS—XXIV*

## ON THE GEOMETRY OF THE PERHYDROPHENANTHRENE SKELETON IN SOME STEROIDS

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(*Received* 22 *April* 1966)

Abstract—A quantitative description of the conformation of the A,B,C,-moiety of eight steroids in terms of valency and torsional angles is given. The geometrical details of the molecules from X-ray structure determinations are compared with those obtained from theoretical considerations on appropriately substituted cyclohexane and cyclohexene rings. It is shown that the use of such building material leads to a qualitative agreement. A number of interactions present in a steroid, but not in a cyclohexane unit, prevents a quantitative agreement. The steroid skeleton (all *trans*) has a somewhat bent overall shape. The occurrence of conformational transmission effects is discussed and a number of rules concerning the torsional angles around junctions given.

## INTRODUCTION

RECENTLY, the conformations of five- and six-membered ring systems have received considerable attention from a theoretical point of view.[1-3] The usual procedure in predicting conformations is to minimize the energy (enthalpy) content of the system. The part of the enthalpy varying with the conformation can be expressed as the sum of van der Waals energies and deformation energies. The former is due to interactions between non-bonded atoms, the latter to angle strain and torsional strain. According to Klyne and Prelog[4] the conformation of a six membered ring can be characterized by six valency angles and six torsional (Newman) angles.† Hendrickson[1] has given valuable information about the detailed geometry of common rings as a function of torsional and valency angles. Recently Bucourt and Hainaut[3] computed the minimum energies of several "basic" conformations of cyclohexane and cyclohexene as a function of the same quantities. The main difference of approach is the use of non-tetrahedral valency angles by the French authors for secondary and tertiary carbon atoms in $sp^3$-hybridization. Generally, the calculations have been made with invariant bond lengths.

One may hope that the obtained knowledge of possible conformations of six- and five-membered rings—the building materials of steroids—can be applied in analysing the shape of saturated polycyclic ring systems. Unfortunately, the experimental data on torsional angles are rather scarce. Limited information can be obtained

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* Part XXIII, H. T. Kalff and E. Havinga, *Rec. Trav. Chim.*, 25, 637 (1966).

† Mathematically, a smaller number of angles is sufficient to define a closed ring, but for convenience we report all angles.

[1] J. B. Hendrickson, *J. Amer. Chem. Soc.* 83, 4537 (1961); *Ibid.* 85, 4059 (1963); F. V. Brutcher Jr. and W. Bauer, *Ibid.* 84, 2233 (1962).

[2a] C. Altona, Thesis Leiden (1964); [b] H. J. Geise, Thesis Leiden (1964).

[3] R. Bucourt and D. Hainaut, *Bull. Soc. Chim.* 1366 (1965), R. Bucourt, *ibid.* 2080 (1964).

[4] W. Klyne and V. Prelog, *Experientia* 16, 521 (1960).

from IR studies,[5] while the interpretation of NMR spectra with the aid of the Karplus relation[6] is still intricate.

The purpose of this publication is to compare the conformations theoretically predicted, notably of the A,B,C,-moiety of some steroids, with the results of X-ray analyses. The conformation of ring D will be dealt with in a subsequent publication.[7] The valency angles ("observed values") were taken from the crystal structures of steroid molecules recently determined by X-ray analyses of high accuracy (angular standard deviation $< 2°$). Earlier structure determinations of some steroids such as cholesteryl iodide[8] and 4-iodo-5-nitrobenzoate of 9$\alpha$,10$\alpha$-ergosta-5,7,22-triene-3$\beta$-ol[9] (formerly called lumisterol) seemed less suited for our purpose.

The torsional angles ("observed values") were calculated from the atomic coordinates on an X1 computer with the aid of a program[10] developed by Geise and Rutten. The A,B,C,-moiety of the following steroids will be discussed:

| | |
|---|---|
| 2$\alpha$,3$\beta$-dichloro-5$\alpha$-cholestane[11] | (I) |
| 2$\alpha$,3$\beta$-dibromo-5$\alpha$-cholestane[11] | (II) |
| 3$\alpha$-hydroxy-5$\alpha$-androstan-17-one[12] | (III) |
| 2$\beta$,3$\alpha$-dichloro-5$\alpha$-cholestane[13] | (IV) |
| 4-bromo-estradiol[14] | (V) |
| 4-bromo-estrone[15] | (VI) |
| 4-bromo-9$\beta$,10$\alpha$-pregna-4,6-diene-3,20-dione[16] | (VII) |
| 2$\beta$,3$\beta$,14$\alpha$,22$\beta_P$,25-pentahydroxy-$\Delta^7$-5$\beta$-cholestenon-6[17] | (VIII) |

The structure formulae and numbering of atoms are given in Fig. 1. The observed values will be compared with the theoretical ones taken from Bucourt and Hainaut.[3]

The androstane skeleton (compounds I–IV) will be dealt with in section 2. Each ring will be considered as a separate unit, the basic conformations of which can be disturbed by external influences (e.g. different degree of substitution, other rings, etc.).

This study shows (section 3) that the overall geometrical features of steroid molecules cannot be fully understood by simple addition of the conformational properties of the separate A,B,C and D units. One observes the occurrence of conformational transmission effects. Since the transmission of a conformation

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[5] R. Granger, P. F. G. Nau, J. Nau and C. Francois, *Bull. Soc. Chim.* 496 (1962).

[6] D. Karplus, *J. Chem. Phys.* **30**, 11 (1959); K. B. Wiberg, B. R. Lowry and B. J. Nist, *J. Amer. Chem. Soc.* **84**, 1594 (1962); H. Conroy, *Advances in Organic Chemistry* Vol. II, p. 311. Interscience, New York (1960).

[7] C. Altona, H. J. Geise and C. Romers, to be published.

[8] C. H. Carlisle and D. Crowfoot, *Proc. Roy. Soc.* A**184**, 64 (1945).

[9] D. Crowfoot-Hodgkin and D. Sayre, *J. Chem. Soc.* 4561 (1952).

[10] H. J. Geise and W. Rutten, unpublished (see ref. 2b).

[11] H. J. Geise and C. Romers, *Acta Cryst.* **20**, 257 (1966).

[12] D. F. High, Thesis University of Washington; Univ. Microfilms Inc., Ann Arbor, Michigan, 1962.

[13] H. J. Geise, C. Romers and E. W. M. Rutten, *Acta Cryst.* **20**, 249 (1966).

[14] D. A. Norton, G. Kartha and Chia Tang Lu, *Acta Cryst.* **17**, 77 (1964).

[15] D. A. Norton, G. Kartha and Chia Tang Lu, *Acta Cryst.* **16**, 89 (1963).

[16] C. Romers, E. v. Heykoop, B. Hesper and H. J. Geise, *Acta Cryst.* **20**, 363 (1966); *Id.*, *Rec. Trav. Chim.* **84**, 885 (1965).

[17] R. Huber and W. Hoppe, *Chem. Ber.* **98**, 2403 (1965).

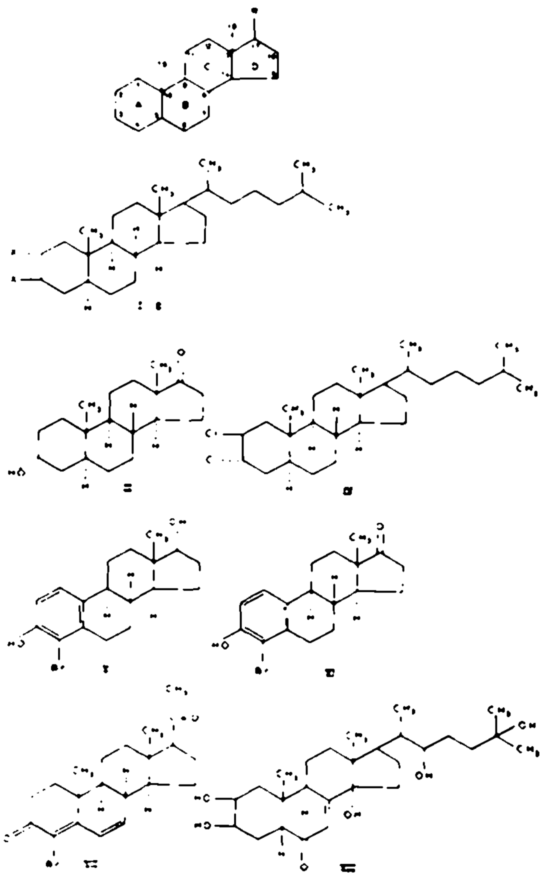

FIG. 1. Numbering of atoms in steroids and structure formulae of discussed compounds.

I: X = Cl; 2α,3β-dichloro-5α-cholestane
II: X = Br; 2α,3β-dibromo-5α-cholestane
III: 3α-hydroxy-5α-androstan-17-one
IV: 2β,3α-dichloro-5α-cholestane
V: 4-bromo-estradiol
VI: 4-bromo-estrone
VII: 4-bromo-9β,10α-pregna-4,6-diene-3,20-dione
VIII: 2β,3β,14α,22$\beta_F$,25-pentahydroxy-$\Delta^7$-5β-cholestenone-6.

perturbance propagates from one ring to the next via the junction, the rules governing the torsional angles around this bond are very important. Bucourt[8] deduced a number of relationships between torsional angles belonging to such a junction. These rules will be discussed in section 4.

## 2. *The androstane/cholestane skeleton*

The A,B,C,-moiety consists of three *trans*-connected cyclohexane units having a chair conformation.

(a) *Ring* A. No special distortions of ring A are expected in compounds I–III and, consequently, one is tempted to use *weighted averaged values** of torsional and

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* See Appendix I for the definition and notation of torsional angles (φ), projected angles (μ) and Appendix II for the calculation of weighted averages.

valency angles as *standard values*. Table 1 summarizes the observed, standard and theoretical[3] values of valency and torsional angles. The agreement between standard and theoretical values is reasonably good for the torsional angles ($\varphi$) but somewhat less for the valency angles ($\vartheta$). Two facts emerge from the tabulated data. Firstly, taking into account the standard errors, the mutual agreement between the various angles of the three compounds is excellent. This supports the hypothesis that the different packing of the molecules in their crystals is not an important factor in determining the ultimate geometry. Secondly, most valency angles are significantly larger than 109·5° and, hence, the torsional angles are significantly smaller than 60° (see Appendix III). In qualitative agreement with calculations of Bucourt and Hainaut[3] we observe increased valency angles (>109·5°) and decreased torsional angles (<60°) at sec. and tert. carbon atoms. The observed angles within a ring at the quart. carbon atom C(10) are significantly smaller than expected. This seems to be a general phenomenon in these compounds. Furthermore, ring A is slightly more flattened (2·5°) than the calculations would predict (see section 3).

TABLE 1. OBSERVED AND THEORETICAL VALUES OF TORSIONAL AND VALENCY ANGLES OF RING A AND STANDARD DEVIATIONS ($\sigma$) IN THE COMPOUNDS I, II AND III

| | col. 1 | col. 2 | col. 3 | col. 4 | col. 5 | col. 6 |
|---|---|---|---|---|---|---|
| | obs. I | obs. II | obs. III | standard values | theor. values[a] | Δ \|col. 4\| − \|col. 5\|. |
| Torsional angles | | | | | | |
| 1–2 | −55·8° | −56·4° | −55·7° | −55·8° | −57° | −1·2° |
| 2–3 | +55·4 | +55·0 | +51·9 | +52·3 | +55[b] | −2·7 |
| 3–4 | −58·3 | −54·3 | −52·3 | −52·6 | −56 | −3·4 |
| 4–5 | +61·5 | +56·4 | +56·3 | +56·5 | +58 | −1·5 |
| 10–5 | −56·4 | −52·6 | −55·3 | −55·1 | −58 | −2·9 |
| 10–1 | +55·2 | +51·0 | +55·3 | +54·9 | +58 | −3·1 |
| $\sigma$ | 4·7 | 2·6 | 0·8 | 0·8 | | ⟨Δ⟩ = −2·5 |
| Valency angles | | | | | | |
| 2–1–10 | 113·0° | 112·1° | 113·5° | 113·3° | 111° | +2·3° |
| 1–2–3 | 112·5 | 116·3 | 112·4 | 112·7 | 110·5[b] | +2·2 |
| 2–3–4 | 108·1 | 106·9 | 111·5 | 111·0 | 110 | +1·0 |
| 3–4–5 | 112·3 | 113·2 | 112·7 | 112·7 | 111 | +1·7 |
| 4–5–10 | 110·2 | 113·0 | 113·2 | 113·1 | 110·5 | +2·6 |
| 5–10–1 | 107·7 | 108·5 | 106·2 | 106·4 | 109·5 | −3·1 |
| $\sigma$ | 2·0 | 1·4 | 0·4 | 0·4 | | ⟨Δ⟩ = +1·1 |

[a] Model 1e of Ref. 3.

[b] Allowance for the effect of substituents at C(2) and C(3) increases the differences by 0·5° in $\vartheta$ and by 2° in $\varphi$.

In compound IV, containing two axial chlorine atoms, a strong repulsion exists between Cl(2) and C(19). This repulsion brings about an extra flattening of ring A. Table 2 shows that the observed values (col. 1) deviate strongly from the standard values (col. 3), found for the compounds I–III. The deviation is largest at the torsional angle $\varphi$(1–2–3–4). Model studies reveal that the distance between the sterically repulsive substituents can be enlarged by closing the torsional angle

$\varphi$(1-2-3-4) (observed value: 41°, standard value: 52°). All other valency and torsional angles have to be accommodated. In order to arrive at an adequate set of theoretical values the theoretical torsional angle $\varphi$(1-2-3-4) was made equal to the observed value of 41° and the other angles (Table 2, col. 2) were estimated from the curves given by Bucourt and Hainaut. These authors computed combinations of six valency and five torsional angles that give rise to minimum values of the energy content of the system as a function of the sixth torsional angle. These curves refer to the unsubstituted cyclohexane ring and we used them for a heavily substituted ring.

TABLE 2. TORSIONAL AND VALENCY ANGLES OF RING A AND STANDARD DEVIATION $\sigma$ IN THE COMPOUND IV.

| | col. 1 | | col. 2 | col. 3 |
|---|---|---|---|---|
| | obs. | | theor. values after deformation | standard values |
| Torsional angles | | | | |
| 1-2 | −42·9° | | − 48° | −55·8° |
| 2-3 | +40·9 | ⇔ | +41[*] | +52·3 |
| 3-4 | −49·7 | | −46 | −52·6 |
| 4-5 | +59·2 | | +57 | +56·5 |
| 10-5 | −56·7 | | −59 | −55·1 |
| 10-1 | +49·4 | | +55 | +54·9 |
| $\sigma$ | 1·7 | | | |
| Valency angles | | | | |
| 2-1-10 | 117·1° | | 115° | 113·3° |
| 1-2-3 | 114·8 | | 115 | 112·7 |
| 2-3-4 | 113·7 | | 113 | 111·0 |
| 3-4-5 | 112·5 | | 115 | 112·7 |
| 4-5-10 | 111·7 | | 111 | 113·1 |
| 5-10-1 | 107·3 | | 105 | 106·4 |
| $\sigma$ | 0·7 | | | |

[*] Theoretical value set equal to the observed value, denoted by ⇔.

On this ground a good comparison between "theoretical" and observed values cannot be obtained, but it is noteworthy that the observed values show shifts in the predicted direction.

It is also interesting that the valency angle C(2)-C(1)-C(10) is too large and the opposite angle C(3)-C(4)-C(5) too small, in accordance with the reflex-effect described by Ourisson and co-workers.[18]

Although ring A in compound IV is rather distorted, the deformation imposed on $\varphi$(1-2-3-4), however, does not seem to alter $\varphi$(1-10-5-4) to such an extent that it influences ring B seriously (see section 2b).

(b) *Ring* B. The arguments mentioned above led us to consider the *weighted averaged* values of torsional and valency angles of ring B in the compounds I-IV as *standard* values. The relevant numbers are summarized in Table 3. The differences found for the standard values do not allow to distinguish between sec. and tert.

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[18] B. Waegell, P. Pouzet and G. Ourisson, *Bull. Soc. Chim.* 1821 (1963), and other papers cited here. L. C. G. Goaman and D. F. Grant, *Tetrahedron* **19**, 1531 (1963).

carbon atoms, but again the valency angles are larger than the tetrahedral value and the dihedral angles smaller than 60°. The observation that the valency angle C(5)–C(10)–C(9), around the quart. carbon atom C(10) and the torsional angles around the bonds 6–7 and 7–8 are the smallest harmonizes qualitatively with the theory.

Table 3. Torsional and valency angles of ring B and standard deviation $\sigma$ in the compounds I, II, III and IV

| | col. 1 | col. 2 | col. 3 | col. 4 | col. 5 | col. 6 | col 7 |
|---|---|---|---|---|---|---|---|
| | obs. I | obs. II | obs. III | obs. IV | standard values | theor. values | Δ \|col. 5\| − \|col. 6\| |
| Torsional angles | | | | | | | |
| 9–10 | −60·9° | −57·7° | −56·7° | −56·9° | −56·9° | −59° | −2·1° |
| 10–5 | +62·5 | +59·1 | +57·7 | +58·0 | +58·0 | +58 | 0 |
| 5–6 | −59·3 | −54·3 | −57·3 | −57·8 | −57·2 | −57 | +0·2 |
| 6–7 | +54·2 | +50·1 | +53·5 | +54·3 | +53·4 | +56 | −2·6 |
| 7–8 | −54·0 | −50·6 | −51·7 | −53·1 | −51·9 | −56 | −4·1 |
| 8–9 | +59·2 | +54·8 | +54·2 | +55·7 | +54·6 | +58 | −3·4 |
| $\sigma$ | 4·7 | 2·6 | 0·8 | 1·7 | 0·7 | | ⟨Δ⟩ = −2·0 |
| Valency angles | | | | | | | |
| 10–9–8 | 109·7° | 110·7° | 112·7° | 112·6° | 112·5° | 111° | +1·5° |
| 9–10–5 | 105·2 | 108·1 | 107·4 | 106·9 | 107·2 | 109·5 | −2·3 |
| 10–5–6 | 111·6 | 113·0 | 112·1 | 112·6 | 112·2 | 110 | +2·2 |
| 5–6–7 | 110·7 | 110·7 | 111·5 | 111·0 | 111·3 | 111 | +0·3 |
| 6–7–8 | 112·1 | 114·8 | 113·2 | 112·5 | 113·1 | 111 | +2·1 |
| 7–8–9 | 111·0 | 111·9 | 110·8 | 110·5 | 110·8 | 110 | +0·8 |
| $\sigma$ | 2·0 | 1·4 | 0·4 | 0·7 | 0·3 | | ⟨Δ⟩ = +0·8 |

The observed flattening, as expressed by the torsional angles (Table 3, col. 5) is about 2° larger than predicted (see section 3).

The ring systems A/B and B/C are *trans* connected around the bonds 5–10 and 8–9, respectively. The sums (absolute values) of the torsional angles around these bonds are: $\varphi$(1–10–5–4) + $\varphi$(9–10–5–6) = 113° and $\varphi$(7–8–9–10) + $\varphi$(14–8–9–11) = 107°. The values are significantly smaller than the value (120°) assumed previously[8]; moreover, their mutual difference (7°) is also significant.

(c) *Ring* C. The *standard* values of angles in ring C, obtained by *averaging* the values of the compounds I–IV, are summarized in Table 4, column 5. Ring C resembles ring B with respect to the degree of substitution, but differs in that one neighbouring ring is a cyclopentane instead of a cyclohexane unit. Ignoring the latter fact we arrive at a set of theoretical values given in column 6. The influence of ring D, however, should be reflected in the torsional angles around 13–14. With the exception of Compound IV, ring D tends to a half-chair like conformation[7] in the androstane molecules under discussion. Consequently, the torsional angle $\varphi$(17–13–14–15) ranges from 46° to 50° (average value 48°). The opposite angle $\varphi$(12–13–14–8) ranges from 59° to 62° (average value 59·2°). Thus we arrive at a value slightly larger than the theoretical one (col. 6). Setting the theoretical value of $\varphi$(12–13–14–8) equal to the observed value of 59° we calculate, in the same way as described in section 2a, the set of theoretical values given in column 7. It can be seen that these

TABLE 4. TORSIONAL AND VALENCY ANGLES OF RING C AND STANDARD DEVIATION $\sigma$ IN THE COMPOUNDS I, II, III AND IV

| | col. 1 | col. 2 | col. 3 | col. 4 | col. 5 | col. 6 | col. 7 | col. 8 | col. 9 |
|---|---|---|---|---|---|---|---|---|---|
| | obs. I | obs. II | obs. III | obs. IV | standard value | theor. ignoring ring D | theor. deformed by ring D | $\Delta$ <br> $\lvert$col. 5$\rvert$ − $\lvert$col. 6$\rvert$ | $\Delta'$ <br> $\lvert$col. 5$\rvert$ − $\lvert$col. 7$\rvert$ |
| Torsional angles | | | | | | | | | |
| 11–12 | −57·8° | −56·3° | −54·8° | −55·0° | −55·0° | −56° | −56° | −1·0° | −1·0° |
| 11–9 | +55·3 | +52·8 | +53·8 | +53·1 | +53·7 | +57 | +56 | −3·3 | −2·3 |
| 9–8 | −53·5 | −50·3 | −52·9 | −53·4 | −52·8 | −58 | −58 | −5·2 | −5·2 |
| 8–14 | +59·6 | +54·8 | +56·3 | +58·9 | +56·7 | +58 | +58 | −1·3 | −1·3 |
| 14–13 | −61·8 | −58·7 | −59·0 | −60·0 | −59·2 | −58 | −59 | +1·2 | 0 |
| 13–12 | +57·3 | +56·1 | +55·4 | +55·8 | +55·6 | +58 | +58 | −2·4 | −2·4 |
| $\sigma$ | 4·7 | 2·6 | 0·8 | 1·7 | 0·7 | | | $\langle\Delta\rangle = -2·0$ | $\langle\Delta'\rangle = -2·0$ |
| Valency angles | | | | | | | | | |
| 11–12–13 | 111·0° | 111·0° | 109·7° | 111·3° | 110·2° | 111° | 110° | −0·8° | +0·2° |
| 9–11–12 | 110·8 | 112·0 | 110·5 | 112·8 | 111·1 | 111 | 112 | +0·1 | −0·9 |
| 8–9–11 | 112·8 | 113·2 | 111·5 | 111·3 | 111·6 | 110 | 111 | +1·6 | +0·6 |
| 9–8–14 | 106·7 | 108·5 | 109·0 | 108·9 | 108·9 | 110 | 109 | −1·1 | −0·1 |
| 8–14–13 | 116·8 | 116·4 | 113·4 | 114·0 | 113·8 | 110 | 109 | +3·8 | +4·8 |
| 12–13–14 | 104·6 | 107·5 | 110·5 | 107·6 | 109·5 | 109 | 108 | +0·5 | +1·5 |
| $\sigma$ | 2·0 | 1·4 | 0·4 | 0·7 | 0·3 | | | $\langle\Delta\rangle = +0·7$ | $\langle\Delta'\rangle = +1·0$ |

values agree slightly better with the observed ones (col. 5) than those of column 6, in which the cyclopentane character of ring D was ignored.

It should be emphasized that the sum of the torsional angles around the bond 13-14 is 107° and that $\varphi$(12-13-14-8) is increased by only 1°. *Trans*-fusion of the cyclopentane ring D to a cyclohexane ring C can thus be achieved without much perturbance of the latter ring. Nor are the valency and torsional angles of ring D affected[7] by the neighbouring ring C. The strain due to the misfit in *trans*-coupling a cyclopentane to a cyclohexane unit is especially reflected in a drastic increase of the *exterior angles* C(12)–C(13)–C(17) (116°) and C(8)–C(14)–C(15) (120°). The angles mentioned are significantly larger than the values (about 110°) expected for quart. and tert. carbon atoms. The concerning valency angles between bonds protruding from C(13) and C(14) are listed in Table 5.

### 3. *The overall shape of the 5α-androstane skeleton*

In the preceding section we have shown that a fair agreement between observed and theoretical values of angles is obtained, treating each ring as a separate unit. But there are systematic discrepancies, which can, at least partly, be explained by two hitherto neglected phenomena of the steroid skeleton.

Firstly treating ring A as a separate unit, the conformation of this ring is actually compared with the theoretical conformations of an isolated 1α,1β,2β-trimethylcyclohexane ring. The mutual influence of C(6), C(9) and C(19) on C(4), C(1) and C(2), respectively, is ignored. Similar arguments hold for e.g. ring B, where 1–3 and 1–4 interactions are omitted. It is possible that the result of calculations would be slightly different if these interactions had been taken into account.

Secondly, the skeleton of the three cholestane derivatives is not flat, but somewhat convex[11,18] towards the protruding methyl groups C(18) and C(19). The same effect was reported by High[18] for 3α-hydroxy-5α-androstan-17-one (compound III). In an undistorted model the vectors C(10)–C(19) and C(13)–C(18) are parallel. In the molecules I, II, III and IV they are at angles of 10°, 11°, 14° and 9° respectively. The bending of the molecule is also evident when one compares the distances of the atoms to two appropriately chosen least squares planes.[19] The first plane is defined by the atoms C(2), C(4), C(6), C(8), C(10), C(11) and C(13) (upper or β-atoms) the second one is defined by C(1), C(3), C(5), C(7), C(9), C(12) and C(14) (lower or α-atoms). In the four compounds investigated these planes are nearly parallel at a distance of about 0·45 Å. The distances of these atoms to their respective planes are given in Table 6. The atoms at both ends of the molecule are "below" (denoted by negative distances) and those in the middle region are mostly "above" (denoted by positive distances) the planes. This bending accounts qualitatively for a number of discrepancies observed in the valency angles. As a result of the displacements of the atoms, as indicated in Fig. 2, the valency angles will be either opened or closed (see Fig. 3a). The observed differences between the standard and the theoretical values are in good agreement herewith (Fig. 3b). The influence of these slight displacements on individual torsional angles is rather complicated, but, because on the average the valency angles are 0·9° larger, the torsional angles must be about 2·4° smaller than the theoretical ones (see also Appendix III). This is confirmed by the observed differences (Fig. 3c).

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[19] V. Schomaker, J. Waser, R. E. Marsh and G. Bergman, *Acta Cryst.* **12**, 600 (1959).

TABLE 5. VALENCY ANGLES AROUND THE ATOMS C(13) AND C(14) AND THEIR STANDARD DEVIATIONS $\sigma$.

| Valency angles | obs. I | obs. II | obs. III | obs. IV | obs. V | obs. VI | obs. VII | obs. VIII | standard value | theor. value |
|---|---|---|---|---|---|---|---|---|---|---|
| 12-13-14 | 104·6° | 107·5° | 110·5° | 107·6° | 113·8° | 108° | 106·4° | 108° | 109·8° | 109·5° |
| 12-13-18 | 110·8 | 110·3 | 112·5 | 110·2 | 109·9 | 113 | 111·9 | 111 | 111·5 | 109·5 |
| 17-13-18 | 112·8 | 109·3 | (105·5) | 109·7 | 110·4 | (101) | 110·3 | 113 | 110·8 | 109·5 |
| 14-13-18 | 113·2 | 112·4 | 111·9 | 112·5 | 116·6 | 116 | 112·4 | 110 | 112·7 | 109·5 |
| 14-13-17 | 99·1 | 100·6 | 99·2 | 99·8 | 98·5 | 103 | 98·3 | 99 | 99·3 | 100* |
| 12-13-17 | 115·6 | 116·6 | 116·4 | 116·7 | 113·7 | 114 | 116·8 | 115 | 115·8 | 115† |
| 8-14-13 | 116·8 | 116·4 | 113·4 | 114·0 | 111·1 | 112 | 113·9 | 113 | 113·2 | 110·5 |
| 13-14-15 | 102·7 | 104·9 | 104·3 | 104·2 | 104·2 | 106 | 104·1 | 104 | 104·3 | 100* |
| 8-14-15 | 116·4 | 117·9 | 120·8 | 118·6 | 117·9 | 118 | 118·5 | 120 | 119·6 | ~115 |
| $\sigma$ | 2·0 | 1·4 | 0·4 | 0·7 | 0·7 | 1·5 | 1·5 | 0·8 | 0·3 | |

The values given in brackets are affected by the ketogroup at C(17).

* Taken from Hendrickson.[1]

† Value geometrically determined by fixing the other five angles to the given values.

TABLE 6. DISTANCES (IN Å × $10^3$) OF $\beta$- AND $\alpha$-ATOMS TO THEIR RESPECTIVE BEST PLANES

| Compd | "$\beta$"-atoms | | | | | | |
|---|---|---|---|---|---|---|---|
| | C(2) | C(4) | C(6) | C(8) | C(10) | C(11) | C(13) |
| I | −4 | −8 | −1 | +4 | +18 | −2 | −7 |
| II | −3 | −10 | 0 | +7 | +18 | −1 | −10 |
| III | −9 | −8 | +1 | +3 | +19 | +6 | −13 |
| IV | −16 | −1 | −2 | 0 | +24 | +10 | −13 |
| | "$\alpha$"-atoms | | | | | | |
| | C(1) | C(3) | C(5) | C(7) | C(9) | C(12) | C(14) |
| I | +14 | −15 | +3 | −3 | +8 | −9 | −4 |
| II | +16 | −18 | +3 | −3 | +12 | −12 | −4 |
| III | +7 | −14 | +7 | +2 | +13 | −5 | −9 |
| IV | +7 | −15 | +9 | +2 | +12 | −5 | −10 |

The cause of the bending effect seems to be of steric origin. Both angular methyl groups hinder the axial hydrogens attached to C(8) and C(11) on the $\beta$-side of the molecule. Since these hydrogens cannot move out without disturbing ring C seriously, strain can be relieved by bending away the methyl groups. Convexing of the $\beta$-side of the molecule results in a compression of the $\alpha$-side. From this side only axial hydrogens protrude, which will not resist steric compression; their mutual distance (about 2·7 A) is even large enough to allow some attraction.

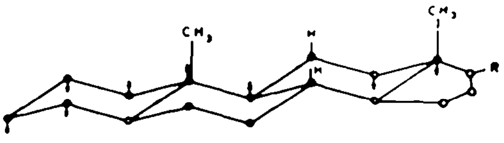

FIG. 2. Displacements of atoms from their least squares planes through either $\alpha$-atoms (open circles) or $\beta$-atoms (black circles).

It is of interest to note that it is not possible to pinpoint a spot in the molecule that suffers most from this strain; instead, small deviations in bond and torsional angles are distributed well over the skeleton.

### 4. *Junctions between rings*

Starting from the assumption that tert. carbon atoms have C–C–C valency angles of 110·5° one computes C–C–H valency angles of 108·2°. The (Newman) projection on a plane perpendicular to any of the C–C bonds of such a unit is given in Fig. 4a. For quart. carbon atoms all valency angles are assumed to be 109·5°. A similar Newman projection of the quart. carbon unit is given in Fig. 4b. In the latter case the three projected valency angles are 120°, whereas in the former case two angles are smaller and one is larger than 120°.

A *trans* fusion involving only tert. carbon atoms (e.g. B/C junction) requires coupling of two units of Fig. 4a. The junctions A/B and C/D require coupling of a unit of Fig. 4a to a unit of Fig. 4b. From this it follows that the sum of the torsional angles around a junction bond is a function of the degree of substitution of the

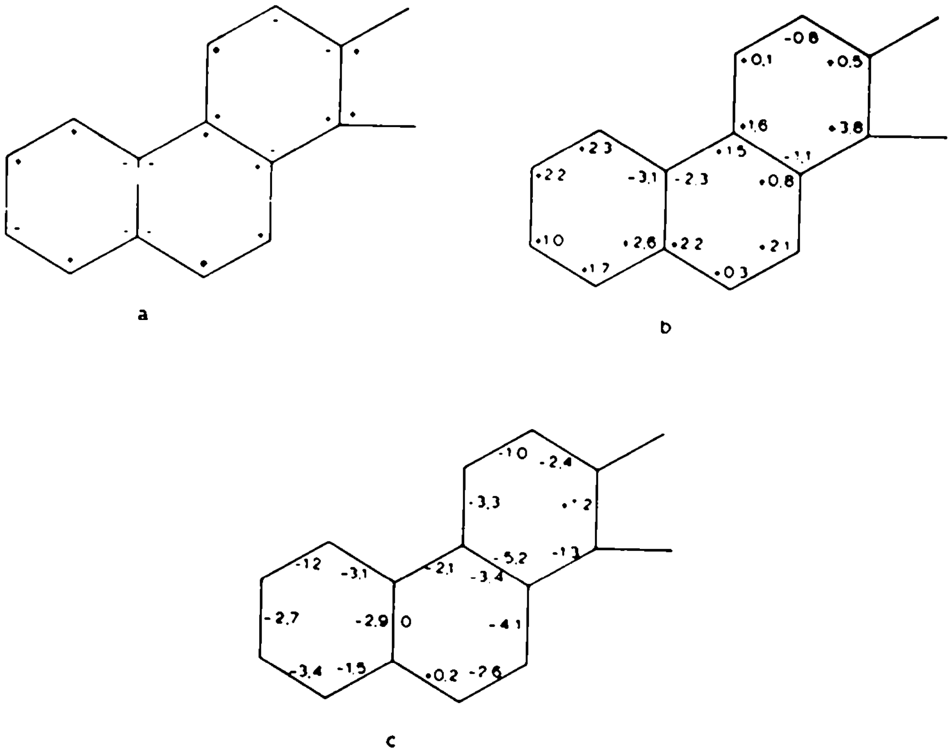

FIG. 3. Differences between standard and theoretical values as a result of the bending of the steroid skeleton

(a) expected differences in valency angles
(b) observed differences in valency angles
(c) observed differences in torsional angles
+ denotes |standard value| > |theoretical value|
○ denotes |standard value| = |theoretical value|
− denotes |standard value| < |theoretical value|

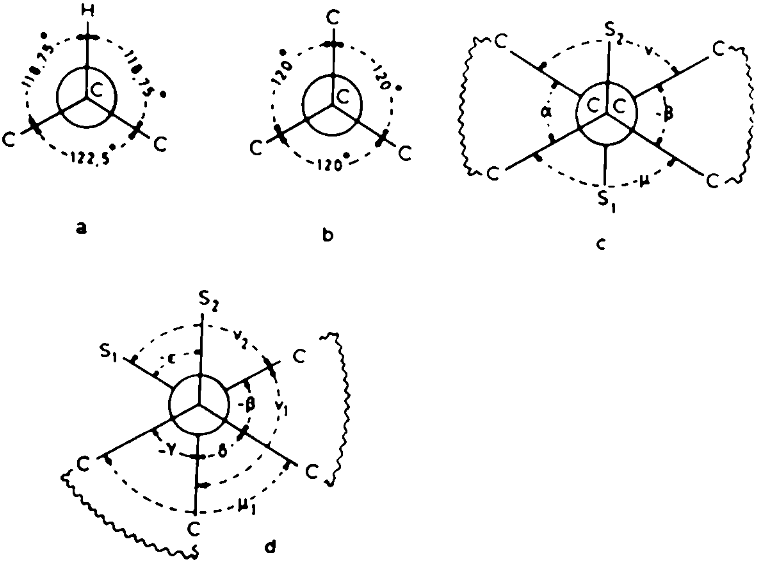

FIG. 4. Newman projections along a C–C bond: (a) of a tert. carbon atom, (b) of a quart. carbon atom, (c) of a *trans* junction, (d) of a *cis* junction.

bridge-head atoms. The following sum rules can be easily derived (see Fig. 4c and Fig. 5):

$$|\alpha| + |\beta| = 115^\circ, \quad \text{when } S_1 = S_2 = H \qquad (T_1);$$

$$|\alpha| + |\beta| = 117{\cdot}5^\circ, \quad \text{when } S_1 = H \text{ and } S_2 = CH_3 \text{ or vice versa} \qquad (T_2);$$

$$|\alpha| + |\beta| = 120^\circ, \quad \text{when } S_1 = S_2 = CH_3 \qquad (T_3);$$

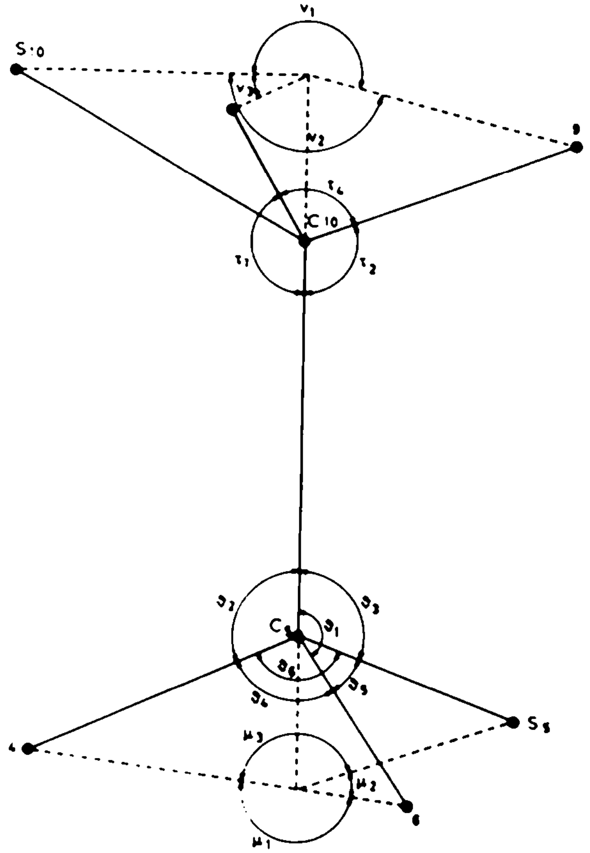

FIG. 5. Designation of valency angles ($\theta_i$, $\tau_i$) and projected valency angles ($\mu_i$, $\nu_i$).

For a *cis*-coupling (Fig 4d) holds $\beta = \nu_1 - \delta$ and $\gamma = \mu_1 - \delta$. Thus, strictly speaking, only if $\nu_1 = \mu_1$ is the "equality" rule $\beta = \gamma$ operative. This is the case when $S_1 = S_2$; i.e. when only tert. or quart. carbon atoms are involved in the junction.

In a A/B or B/C junction the theoretical torsional angles on both sides of the common bonds C(5)–C(10) and C(8)–C(9) are about 58°. Considered from a purely geometrical point of view cyclohexane rings in their usual chair conformation can be *cis*- or *trans*-connected without perturbance of conformation. However, the rules derived are no longer valid if increased v.d. Waals interactions or conflicting demands made e.g. by a cyclopentane ring or any other force deform the units of Fig. 4a and 4b.

Deviations in the order of magnitude of 10° can easily occur. The coupling rules will be violated in systems having bulky axial substituents and in systems in which a cyclopentane ring is coupled to a cyclohexane ring. The variation of projected angle ($\Delta\mu_i$) as a function of the variation of the valency angles ($\Delta\vartheta_i$) involved is given by the approximate expression (see Appendix IV):

$$\Delta\mu_1 \cong 0{\cdot}6(2\Delta\vartheta_4 + \Delta\vartheta_2 + \Delta\vartheta_1). \tag{i}$$

The designation of the angles can be seen from Fig. 5. Similar expressions hold for the other projected angles.

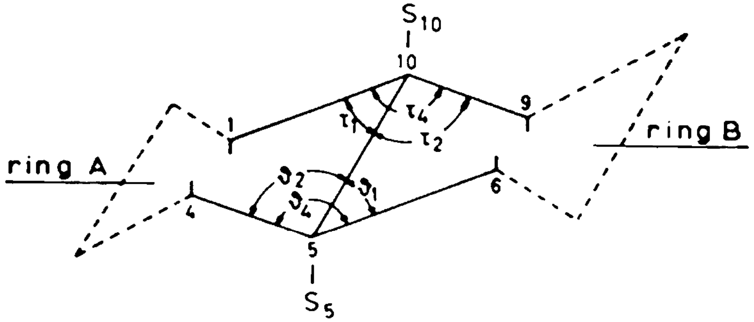

FIG. 6. Designation of some valency angles in a *trans* A/B junction.

(a) trans *Junction* A/B *and* B/C. It can be seen from Fig. 4c that the sum of the torsional angles

$$|\alpha| + |\beta| = 360 - (\mu_1 + \nu_1) \tag{ii}$$

In steroid molecules repulsions between the C(19) methyl group ($S_{10}$ in Fig. 6) and the axial hydrogens on C(4) and C(6) will result in an enlargement of the angle C(4)–C(5)–C(6) (i.e. the valency angle $\vartheta_4$). Probably the angles $\vartheta_1$ (i.e. C(10)–C(5)–C(6)) and $\vartheta_2$ (i.e. C(4)–C(5)–C(10)) will be increased too. Although the latter is offset by the decrease in $\tau_1$(C(5)–C(10)–C(1)) and $\tau_2$ (C(9)–C(10)–C(5)) the overall result is a decrease of the value of $|\alpha| + |\beta|$ from the theoretical value (rule $T_2$: 117·5°) to 113°, according to Eqs (i) and (ii). Following the same line of thought one can see that introduction of bulky axial groups on C(4) and C(6) will lower the sum $|\alpha| + |\beta|$ still more. In general the presence of pairs of axial groups in the neighbourhood of a junction always tends to reduce $|\alpha| + |\beta|$.

Our experimental results indicate that the axial methyl groups C(18) and C(19) cause such a decrease for the sum of the torsional angles notably around the B/C junction C(8)–C(9). In the compounds V and VI, lacking C(19), this sum is larger and approaches the expected value ($T_1$ = 115°). A review of the sum $|\alpha| + |\beta|$ for the A/B and B/C junction of the various compounds is given below:

| | I | II | III | IV | V | VI | standard value | expected value |
|---|---|---|---|---|---|---|---|---|
| A/B | 118·9 | 111·7 | 113·0 | 114·7 | — | — | 113·1 | 117·5° (rule $T_2$) |
| B/C | 112·7 | 105·1 | 107·1 | 109·1 | 114·0 | 119·1 | 107·4 | 115° (rule $T_1$) |

(b) *trans junction C/D.* In the case that ring D is in a half chair form[1,7] the angles C(17)–C(13)–C(14) and C(13)–C(14)–C(15) are about 100°; i.e. $\tau_2$ and $\vartheta_1$

(Fig. 7) are decreased with about 10°. On the other hand the angles C(12)–C(13)–C(17) ($\tau_4$) and C(8)–C(14)–C(15) ($\vartheta_4$) are increased (section 2c), thus counteracting the effect of the small interior angles of ring D on the sum $\varphi(12\text{–}13\text{–}14\text{–}8) + \varphi(17\text{–}13\text{–}14\text{–}15)$.

It can be shown with the aid of Eqs. (i) and (ii) that the sum rule is not affected by displacements of the atoms C(15) and C(17) parallel to the bond C(13)–C(14). Such displacements can only occur in highly symmetrical molecules (e.g. perhydrindane), but not in steroids (compare Table 5).

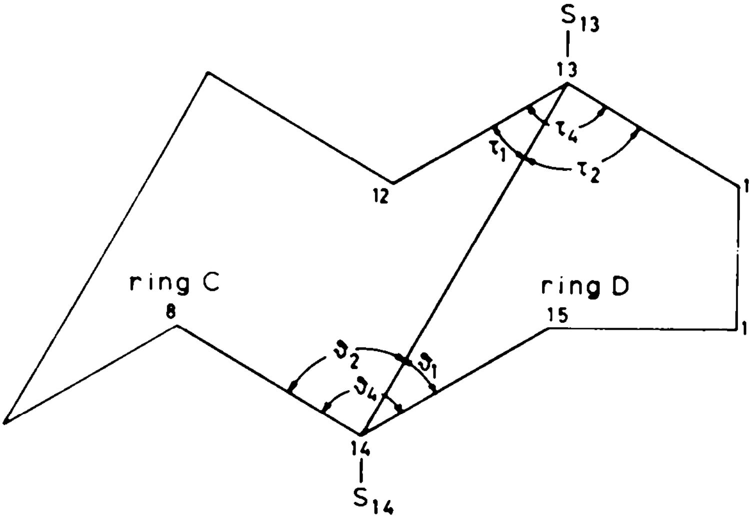

Fig. 7. Designation of some valency angles in a *trans* C/D junction.

The value of the sum $\varphi(12\text{–}13\text{–}14\text{–}8) + \varphi(17\text{–}13\text{–}14\text{–}15)$ will depend on the degree of substitution of the atoms C(13), C(14), C(15) and C(17). The empirical value is 109° ± 3° provided an axial methyl group is present at C(13) and C(17) bears a $\beta$-substituent (alkyl- or hydroxyl group), i.e. the compounds under discussion with the exception of III and VI.

(c) cis *Junctions*. Since there are as yet not many experimental data available we will discuss the *cis* junctions very briefly. The equality rule $\beta = \gamma$ (cf. Fig. 4d) holds only if $\nu_1 = \mu_1$. It is clear that any irregularity in the valency angles results in a breakdown of this rule. Model studies reveal that this will be the case when in a *cis* A/B junction (e.g. 5$\beta$-androstane derivatives) axial substituents are introduced on C(2), C(4), C(7) or C(9). In a *cis* B/C junction (e.g. 8$\beta$,9$\beta$-steroids) violation of the rule is to be expected when axial groups are present on C(5), C(7), C(11) or C(13). *Cis* B/C junctions will be discussed in sections 5b and 5c.

## 5. *More complicated systems*

(a) *4-Bromo derivatives of estradiol* (V) and *estrone* (VI). The ring A of these compounds is aromatic and essentially planar. The atoms C(9), C(10), C(5) and C(6) of the rings B are coplanar with the 'best' plane through the atoms of ring A in V and nearly so in VI, but the conformations of the resulting cyclohexene-like rings are not identical in these compounds. Figure 8 shows the projection of the B rings on the plane, going through C(6) and C(9) and perpendicular to the least squares plane through C(9), C(10), C(5) and C(6).

Focussing the attention first to the half chair form found in the diol (V), one can see that the observed torsional angles (Table 7, col. 1) differ from the theoretical values (col. 2) computed for an appropriately substituted cyclohexene ring of this conformation (model 6d in Ref. 3). The discrepancies—much more distinct than in the cholestane and androstane derivatives—can be understood in terms of a conformational transmission effect.

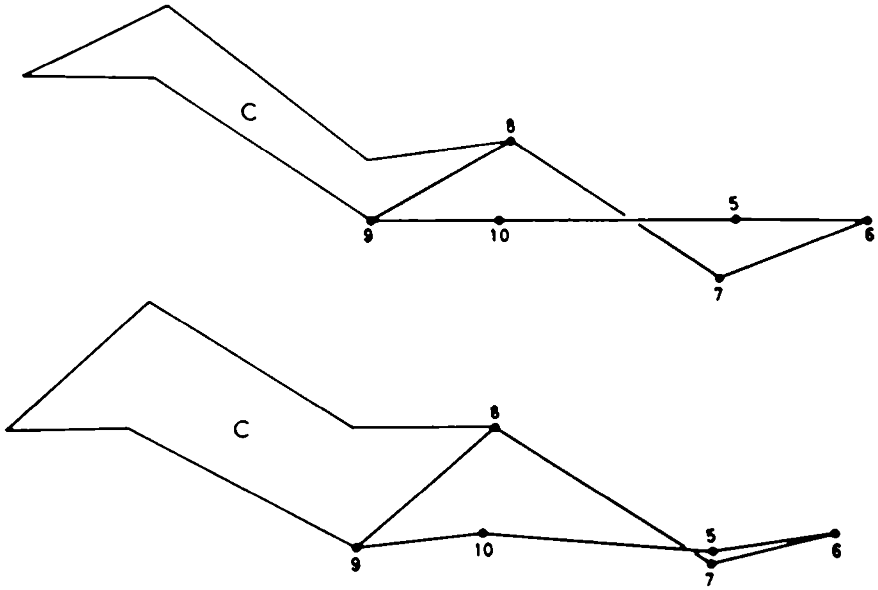

FIG. 8. Projection of the rings B and C of 4-bromo-estradiol, compound V (upper part) and of 4-bromo-estrone, compound VI (lower part).

If the torsional angle $\varphi(7–8–9–10)$ had the value of 47° demanded by an undistorted half chair then the opposite angle $\varphi(14–8–9–11)$ in ring C should be increased with an amount of 10° in order to reach the value of $58^\circ + 10^\circ = 68^\circ$, required by sum rule $T_1$ (Rule $T_1$ is to be applied because there are no distorting axial substituents). Such an increase would induce a strain in ring C, which would result in a decrease of $\varphi(12–13–14–8)$ with about 2° (calculated from the curves of Bucourt and Hainaut). The latter decrease, however, is incompatible with the increase of the same torsional angle (see section 2c) required by the neighbouring ring D (Table 7, col. 3 and 6). This dilemma can be solved in two ways: either by deforming both rings B and C or by passing over ring B into a sofa form,[8,20] which makes less conflicting demands upon ring C. Which alternative is accomplished depends on the relative energies involved. A deformation of the rings B and C, so that $\varphi(7–8–9–10)$ becomes 54°, raises the energy of ring B with about 0·4 kcal/mole.[8] The opposite torsional angle $\varphi(14–8–9–11)$ becomes $115^\circ - 54^\circ = 61^\circ$ and is increased with an amount of $61^\circ - 58^\circ = 3^\circ$ compared with the theoretical value. The observed value is 60° and the

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[20] E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc.* 167 (1958).

TABLE 7. TORSIONAL AND VALENCY ANGLES OF THE RINGS B AND C AND STANDARD DEVIATION $\sigma$ IN COMPOUND V

| | col. 1 | col. 2 | col. 3 | | col. 4 | col. 5 | col. 6 |
|---|---|---|---|---|---|---|---|
| | obs. | theor.[a] | theor.[b] | | obs. | theor.[c] | theor.[d] |
| Torsional angles ring B | | | | Torsional angles ring C | | | |
| 9–10 | −20·5° | −17° | −27° | 11–9 | +56·8° | +62° | +55° |
| 10–5 | 0·3 | 0 | 0 | 11–12 | −53·9 | −55 | −56 |
| 5–6 | −14·0 | −14 | − 8 | 13–12 | +55·3 | +53 | +58 |
| 6–7 | +48·4 | +44 | +39 | 14–13 | −64·3 | −57 | −60 |
| 7–8 | −69·7 | −63 | −68 | 8–14 | +65·8 | +64 | +58 |
| 8–9 | +53·7 | +47 | +58 | 8–9 | −60·3 | −68 | −57 |
| $\sigma$ | 1·7 | | | | 1·7 | | |
| Valency angles ring B | | | | Valency angles ring C | | | |
| 10–9–8 | 110·0° | 110·5° | | 11–12–13 | 109·2° | 112° | 110° |
| 9–10–5 | 120·5 | 124 | | 9–11–12 | 112·7 | 109 | 112 |
| 10–5–6 | 123·6 | 124 | | 8–9–11 | 109·6 | 108 | 111 |
| 5–6–7 | 110·1 | 111 | | 9–8–14 | 105·2 | 108 | 109 |
| 6–7–8 | 109·1 | 111 | | 8–14–13 | 111·1 | 108 | 109 |
| 7–8–9 | 107·6 | 110·5 | | 12–13–14 | 113·8 | 111 | 108 |
| $\sigma$ | 0·7 | | | | 0·7 | | |

[a] Col. 2. Theoretical values estimated for a simple 8,9 disubstituted half chair ring B.

[b] Col. 3. Theoretical values estimated for half chair ring B, allowing for a conformational transmission from ring D.

[c] Col. 5. Theoretical values estimated for chair form ring C, allowing for a conformational transmission from ring B.

[d] Col. 6. Theoretical values estimated for chair form ring C, allowing for a conformational transmission from ring D.

observed sum $\varphi(14\text{–}8\text{–}9\text{–}11) + \varphi(7\text{–}8\text{–}9\text{–}10) = 114°$. The energy of ring C has increased with ~0·3 kcal/mole. The total increase in energy, however, is not 0·7 kcal/mole, since a correction should be subtracted for the torsional energy around C(8)–C(9) that has been counted twice. Another correction should be added for the requirements of ring D. The total increase in energy of the whole system is estimated to be 0·7–0·9 kcal/mole.

Changing ring B into a sofa conformation would cost at least 1·1 kcal/mole. Thus in the diol it seems preferable to deform ring B as well as ring C, resulting in a deformed half chair ring B and a less symmetrical ring C (Table 7). The way in which the deformations influence the other valency and torsional angles cannot be predicted quantitatively by the theoretical curves.

The energy difference between the two alternatives, however, is small. Thus a change of ring B into a sofa conformation may be caused by a small alteration in the geometrical requirements of ring C. This conformation with C(8) outside the sofa plane is observed in 4-bromo-estrone (VI).* It has been demonstrated that the introduction of a 17-keto group induces a change in conformation of ring D into a

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* The possibility of a sofa conformation of ring B in estrane derivatives was anticipated by Bucourt.[8]

near envelope form (C(14) is flap of the envelope). In this case the torsional angle $\varphi(17\text{-}13\text{-}14\text{-}15)$ becomes 40°, and, applying the empirical sum rule of section 4b, the opposite angle $\varphi(12\text{-}13\text{-}14\text{-}8)$ becomes 70° (Table 8, column 1). This requires a closure of $\varphi(11\text{-}9\text{-}8\text{-}14)$ in ring C to about 55° and an opening of $\varphi(7\text{-}8\text{-}9\text{-}10)$ in ring B to about 60° (col. 4). On the other hand, a half chair form of ring B requires that these angles should be opened to 68° and closed to 47°, respectively (col. 7 and 3). The conflicting demands are still more pronounced than in the diol (V) and would require a greater deformation of both rings B and C. This compromise is no longer energetically preferable and ring B changes into a sofa conformation. The theoretical values for a sofa form of ring B and its requirements upon ring C are given in Table 8, col. 2 and 6. It can be seen that some deformations are still nesessary to give the best fit to the several geometrical requirements.

TABLE 8. TORSIONAL AND VALENCY ANGLES OF RINGS B AND C AND STANDARD DEVIATIONS $\sigma$ IN COMPOUND VI

| | col. 1 | col. 2 | col 3. | col. 4 | | col. 5 | col. 6 | col. 7 | col. 8 |
|---|---|---|---|---|---|---|---|---|---|
| | obs. | theor. | theor. | theor. | | obs. | theor. | theor. | theor. |
| Torsional angles ring B | | | | | Torsional angles ring C | | | | |
| 9–10 | −34·8° | −29° | −17° | −38° | 11–9 | +57·7° | +56° | +62° | +50° |
| 10–5 | +10·3 | 0 | 0 | 0 | 11–12 | −59·8 | −56 | −55 | −53 |
| 5–6 | +12·8 | 0 | −14 | +14 | 12–13 | +64·8 | +58 | +53 | +65 |
| 6–7 | +39·8 | +28 | +44 | +10 | 8–14 | +62·8 | +58 | +64 | +65 |
| 7–8 | −64·1 | −58 | −63 | −50 | 14–13 | −69·6 | −58 | −57 | −70 |
| 8–9 | +62·4 | +56 | +47 | +60 | 8–9 | −56·7 | −59 | −68 | −55 |
| $\sigma$ | 2·8 | | | | $\sigma$ | 2·8 | | | |
| Valency angles ring B | | | | | Valency angles ring C | | | | |
| 10–9–8 | 109° | 109° | 110·5° | | 11–12–13 | 106° | 111° | | 107° |
| 9–10–5 | 118 | 123 | 124 | | 9–11–12 | 106 | 111 | | 114 |
| 10–5–6 | 123 | 124 | 124 | | 8–9–11 | 111 | 110 | | 114 |
| 5-6–7 | 117 | 113 | 111 | | 9–8–14 | 106 | 111 | | 107 |
| 6–7–8 | 108 | 113 | 111 | | 8–14–13 | 112 | 110 | | 112 |
| 7–8–9 | 108 | 109·5 | 110.5 | | 12–13–14 | 108 | 109·5 | | 104 |
| $\sigma$ | 1·5 | | | | $\sigma$ | 1·5 | | | |

Theoretical values estimated for; col. 2, a sofa form ring B; col. 3, a half chair form ring B; col. 4, a sofa form ring B, allowing for a conformational transmission effect from ring D; col. 6, a chair form ring C, if ring B had a sofa form. col. 7, a chair form ring C, if ring B had a half chair form; col. 8 a chair form ring C, allowing for a conformational transmission effect from ring D.

(b) *4-Bromo-9β,10α-pregna-4,6-diene-3,20-dione* (VII). This compound is very interesting because of its *cis* B/C junction; moreover, five atoms should be coplanar in the rings A and B as a result of the 3-keto-4,6-diene system. The resulting conformations of rings A and B behave like cyclohexene sofa forms with C(1) and C(9) out of the respective sofa planes. Model studies reveal that a strong repulsion exists between the methyl group C(19) and the axial hydrogens on C(12) and C(14), when ring C is in the chair form. Relief of this steric hindrance might be achieved by passing over ring C into a flexible form at the cost of a sharp rise in torsional strain. In addition to the well-known increase in energy due to the chair-(twist) boat conversion the energy must be further increased by a distortion of ring B and/or ring A, in order to satisfy the demands of the conjugated 3-keto-4,6-diene system.

The way in which the methyl-hydrogen interactions are actually relieved is quite different. Ring C remains a chair, heavily distorted by opening the valency angle C(9)–C(11)–C(12) to 117°. The primary effect is to tilt the methyl group C(19) away from the $\alpha$-side of ring C, but it affects the further geometry in a rather complicated manner.

Firstly, a substantial opening of the torsional angles $\varphi$(9–8–14–13), $\varphi$(8–14–13–12) and $\varphi$(14–13–12–11) (see Table 9, col. 6) is required, which is strongly opposed by the demands of ring D (col. 7). The observed conformation of the part of ring C formed by the atoms C(12), C(13), C(14) and C(8) obeys neither requirements, but is rather normal (compare col. 4 and 5).

TABLE 9. TORSIONAL AND VALENCY ANGLES OF RINGS B AND C AND STANDARD DEVIATIONS $\sigma$ IN COMPOUND VII

| | col. 1 | col. 2 | col. 3 | | col. 4 | col. 5 | col. 6 | col. 7 |
|---|---|---|---|---|---|---|---|---|
| | obs. | theor. | theor. | | obs. | theor. | theor. | theor. |
| Torsional angles ring B | | | | Torsional angles ring C | | | | |
| 9–10 | +48·6° | +60° | 0° | 11–9 | +39·5° | +57° | +30° | +53° |
| 10–5 | −37·9 | −29 | −40 | 11–12 | −49·9 | −56 | −37 | −55 |
| 5–6 | +14·5 | 0 | +40 | 12–13 | +57·7 | +57 | +77 | +61 |
| 6–7 | −1·8 | 0 | 0 | 8–14 | +55·3 | +58 | +77 | +61 |
| 7–8 | +8·8 | +30 | +40 | 14–13 | −62·2 | −58 | −85 | −62 |
| 8–9 | −35·0 | −57 | −37 | 8–9 | −40·8 | −58 | −37 | −55 |
| $\sigma$ | 2·8° | | | | 2·8° | | | |
| Valency angles ring B | | | | Valency angles ring C | | | | |
| 10–9–8 | 116·0° | 113° | 115° | 11–12–13 | 112·1 | 111 | 101 | |
| 7–8–9 | 114·1 | 113 | 109 | 9–11–12 | 117·1 | 111 | ⇔117 | |
| 10–5–6 | 117·8 | 120 | 109 | 8–9–11 | 111·3 | 110 | 117 | |
| 5–6–7 | 124·0 | 122 | 120 | 9–8–14 | 113·4 | 110 | 100 | |
| 6–7–8 | 122·1 | 122 | 120 | 8–14–13 | 113·9 | 110 | 99 | |
| 9–10–5 | 108·3 | 109 | 115 | 12–13–14 | 106·4 | 109 | 98 | |
| $\sigma$ | 1·5° | | | $\sigma$ | 1·5° | | | |

Theoretical values estimated for: col. 2, a sofa form ring B; col. 3, a ring B, allowing for a conformational transmission from ring C; col. 5, a chair form ring C; col. 6, a chair form ring C, allowing for the deformation caused by opening C(9)–C(11)–C(12) to 117° (denoted by ⇔); col. 7, a chair form ring C, allowing for a conformational transmission from ring D.

Secondly, a closure of the torsional angles $\varphi$(13–12–11–9), $\varphi$(12–11–9–8) and $\varphi$(11–9–8–14) and an opening of the valency angle C(11)–C(9)–C(8) is also required. This is observed (qualitatively), indicating that the necessary deformation of ring B is relatively easy.

Due to the presence of strong v.d. Waals interactions the equality rule for *cis*-junctions should not hold strictly. It can be shown that the enlargement of the valency angles around C(9) (Table 9, col. 1) results in a decrease of $\varphi$(10–9–8–7) with respect to $\varphi$(11–9–8–14). The observed values are 35° and 41° respectively.

The value of 35° for $\varphi$(10–9–8–7) in ring B gives rise to conflicting demands for the other torsional angles of this ring (compare col. 2 and 3). On the one hand, the value of 35° requires a boat form ring B with C(5) as bowsprit. On the other

TABLE 10. TORSIONAL AND VALENCY ANGLES OF RING A AND STANDARD DEVIATIONS σ IN COMPOUND VII.

| | col. 1 | col. 2 | | col. 3 | col. 4 |
|---|---|---|---|---|---|
| | obs. | theor. values sofa-form | | obs. | theor. values sofa-form |
| Torsional angles | | | Valency angles | | |
| 1-2 | +52·6° | +57° | 2-1-10 | 112·4° | 113° |
| 2-3 | −23·9 | −29 | 1-2-3 | 113·0 | 113 |
| 3-4 | 0·8 | 0 | 2-3-4 | 118·9 | 120 |
| 4-5 | −3·2 | 0 | 3-4-5 | 121·6 | 122 |
| 5-10 | +30·4 | +30 | 4-5-10 | 121·2 | 122 |
| 10-1 | −54·3 | −60 | 1-10-5 | 108·5 | 109 |
| σ | 2·8 | | | 1·5 | |

hand, the planarity of the 3-keto-4,6-diene system requires a sofa form ring B with C(9) outside the plane.

The observed values (col. 1) are a compromise between these conflicting demands. It should be borne in mind that the theoretical values are taken from curves calculated for non-substituted rings and that, therefore, no quantitative conclusions are justified. But qualitatively the agreement is better than one might have expected.

The conformation of ring A, an almost ideal sofa form, is hardly affected by the strain found in the rings B and C. The actually observed conformation, however, is somewhat less puckered than the theoretical model (see Table 10).

TABLE 11. TORSIONAL AND VALENCY ANGLES OF RING A AND STANDARD DEVIATIONS σ IN COMPOUND VIII.

| | col. 1 | col. 2 | col. 3 | | col. 4 | col. 5 | col. 6 |
|---|---|---|---|---|---|---|---|
| | obs. | standard values | theor. values | | obs. | standard values | theor. values |
| Torsional angles | | | | Valency angles | | | |
| 1-2 | +57·8° | +55·8° | +57° | 2-1-10 | 114° | 113·3° | 111° |
| 2-3 | −55·0 | −52·3 | −57 | 1-2-3 | 111 | 112·7 | 110·5 |
| 3-4 | +54·6 | +52·6 | +56 | 2-3-4 | 110 | 111·0 | 110 |
| 4-5 | −56·6 | −56·5 | −58 | 3-4-5 | 112 | 112·7 | 111 |
| 5-10 | +53·9 | +55·1 | +58 | 4-5-10 | 113 | 113·1 | 110 |
| 10-1 | −55·4 | −54·9 | - 58 | 5-10-1 | 107 | 106·4 | 109·5 |
| σ | 1·8 | 0·8 | | σ | 0·8 | 0·4 | |

(c) *$2\beta,3\beta,14\alpha,22\beta,25$-Pentahydroxy-$\Delta^7$-$5\beta$-cholestenone-6* (*Ecdyson*). This molecule has a *cis* A/B junction. The values of torsional and valency angles of ring A (Table 11) show no serious deviations from the standard values for a substituted chair conformation. The *cis* fusion of two rings with one quart. and one tert. carbon atom in the junction invalidates the equality rule. It can be shown (see Fig. 4d, section 4c) that in such cases $|\beta| - |\gamma| = 2{\cdot}5°$. We observe here $|\varphi(9\text{-}10\text{-}5\text{-}6)| - |\varphi(1\text{-}10\text{-}5\text{-}6)| = 2{\cdot}4°$.

The planarity of the conjugated $\Delta^7$-enone-6-system requires a sofa form for ring B, having C(10) outside the sofa plane. Moreover, it requires $|\varphi(7\text{-}8\text{-}9\text{-}10)| + |\varphi(14\text{-}8\text{-}9\text{-}11)| = 180 - \delta$ (see Fig. 9). In case C(9) is a tert. carbon atom $\delta$ is about

122·5°. Thus an ideal sofa ring B (see Table 12, col. 2) would require a torsional angle $\varphi(14\text{-}8\text{-}9\text{-}11)$ in ring C of about 30·5° (col. 6). It follows, that unlike a sofa ring B with C(9) outside the sofa plane (as in compound VII, section 5b), the sofa form with C(10) outside its plane requires a considerable flattening of ring C. Although this could be achieved without opposing the demands of ring D, the energy contribution of ring C would be increased with at least 3·5 kcal/mole. Therefore it seems energetically preferable to drop the demand of strict planarity of the $\Delta^7$-enone-6 system, implying that, $|\varphi(7\text{-}8\text{-}9\text{-}10)| + |\varphi(14\text{-}8\text{-}9\text{-}11)| = 180 - \delta\,(=57{\cdot}5°)$ no longer holds. The sum becomes larger than $180 - \delta$ (observed 61·8°),

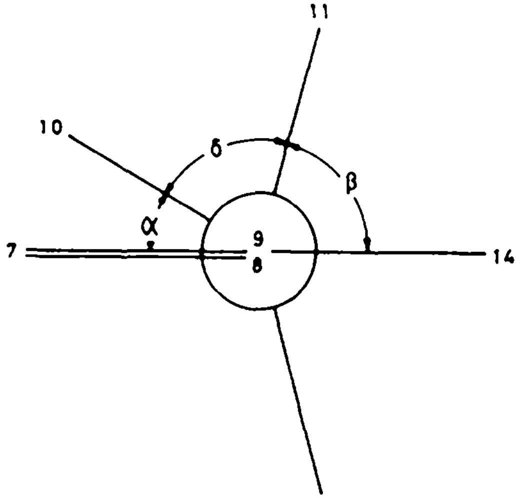

Fig. 9. Projection of a junction involving one trigonal carbon atom.

The puckering of the conjugated system will increase the energy contribution of this part of the molecule, but will allow a decrease of the contributions of both ring C and B; the latter can change into a (distorted) half-chair form. A projection of ring B onto a plane going through C(6) and C(9) and perpendicular to a plane defined by C(6), C(7), C(8) and C(9) shows (Fig. 10) marked deviations from planarity, especially for the bond C(8)–C(14).

Inspection of the data of Table 12 reveals that ring B forms an unsymmetrically distorted half-chair configuration (col. 1, 3 and 4). The chair configuration of ring C (col. 5) is much less flattened than would be required by either a sofa ring B (col. 6) or a half-chair ring B with planar double bond system (col. 7). The non-planarity of the $\Delta^7$-enone-6 system makes it impossible to derive a set of theoretical angles for ring C from the values found in ring B with the aid of transmission rules. A set of theoretical angles (col. 8), which are in good accordance with the observed values (col. 5) can be obtained by setting $\varphi(14\text{-}8\text{-}9\text{-}11)$ equal to 46° and applying the appropriate corrections[8] to the standard values of ring C (Table 4, col. 5).

### *Summary*

Although several details are not yet settled the following conclusions are justified:

Valency angles in cyclohexane rings around sec. and tert. carbon atoms are larger than those around quart. carbon atoms. The adoption of 111·5°, 110·5° and 109·5°

TABLE 12. TORSIONAL AND VALENCY ANGLES OF RINGS B AND C AND THEIR STANDARD DEVIATIONS σ IN COMPOUND VIII.

| | col. 1 | col. 2 | col. 3 | col. 4 | | col. 5 | col. 6 | col. 7 | col. 8 |
|---|---|---|---|---|---|---|---|---|---|
| | obs. | theor. | theor. | theor. | | obs. | theor. | theor. | theor. |
| Torsional angles ring B | | | | | Torsional angles ring C | | | | |
| 9–10 | −45·1° | −54° | −45° | −48° | 11–9 | +47·7° | +40° | +46° | +47° |
| 10–5 | +56·3 | +56 | +62 | +59 | 11–12 | −56·3 | −56 | −56 | −55 |
| 5–6 | −38·5 | −28 | −45 | −35 | 12–13 | +60·5 | +63 | +62 | +59 |
| 6–7 | +7·9 | 0 | +15 | ⇔ +8 | 8–14 | +52·1 | +40 | +48 | +50 |
| 7–8 | +3·6 | 0 | 0 | 0 | 14–13 | −60·0 | −59 | −59 | −59 |
| 8–9 | +16·0 | +27 | +15 | +21 | 8–9 | −45·8 | −30·5 | −42·5 | ⇔ −46 |
| σ | 1·8 | | | | σ | 1·8 | | | |
| Valency angles ring B | | | | | Valency angles ring C | | | | |
| 10–9–8 | 111° | 109·5° | 111° | | 11–12–13° | 109° | 108° | 109° | 109° |
| 7–8–9 | 124 | 123 | 124 | | 9–11–12 | 113 | 114 | 113 | 113 |
| 10–5–6 | 111 | 113·5 | 111 | | 8–9–11 | 114 | 116 | 114 | 114 |
| 5–6–7 | 118 | (113·5)* | (111)* | | 9–8–14 | 114 | 113 | 111 | 111 |
| 6–7–8 | 122 | 124 | 124 | | 8–14–13 | 113 | 117 | 116 | 116 |
| 9–10–5 | 110 | 110·5 | 111 | | 12–13–14 | 108 | 108 | 108 | 108 |
| σ | 0·8 | | | | σ | 0·8 | | | |

* Leaving the ketogroup at C(6) out of consideration. Theoretical values estimated for: col. 2, a sofa form ring B; col. 3, a half chair form ring B; col. 4, ring B, by setting $\varphi$(5–6–7–8) equal to 8° (denoted by ⇔); col. 6, ring C, if ring B had a sofa form; col. 7, ring C, if ring B had a half chair form; col. 8, ring C, by setting $\varphi$(14–8–9–11) equal to 46° (denoted by ⇔).

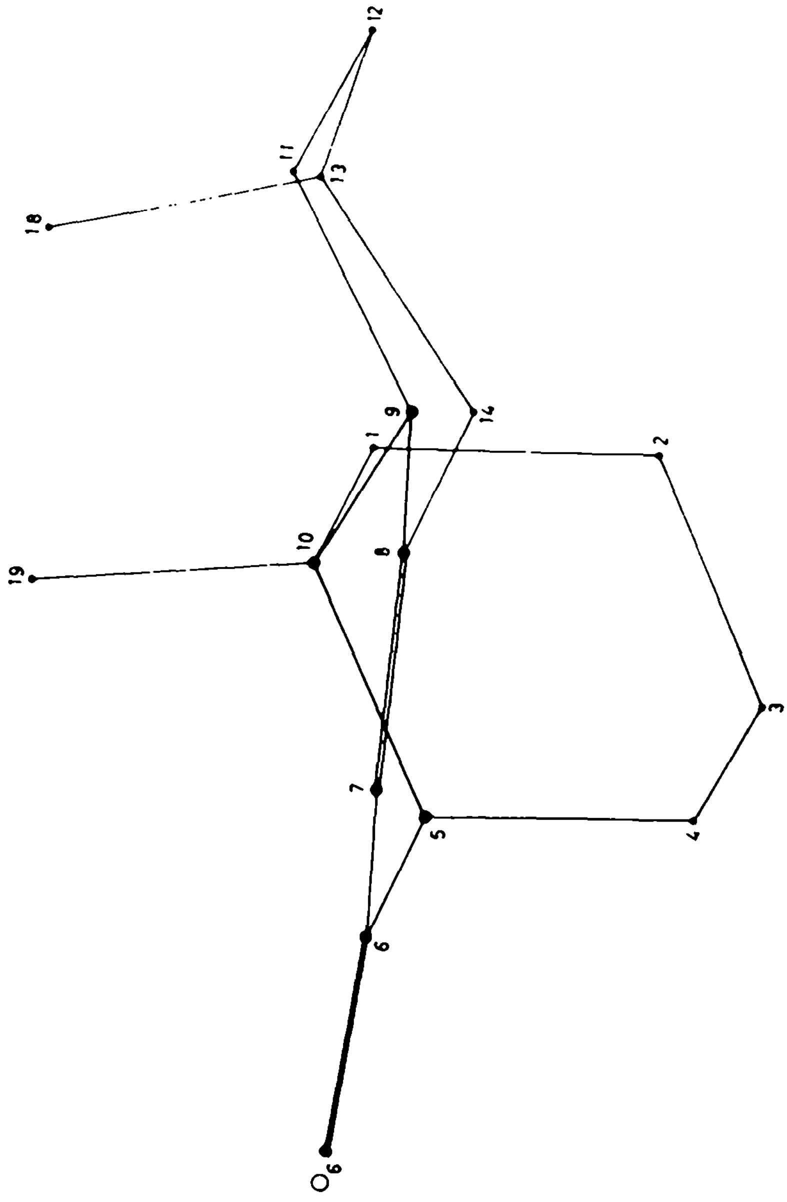

Fig. 10. Projection of $2\beta,3\beta,14\alpha,22\beta_F,25$-pentahydroxy-$\Delta^7$-$5\beta$-cholestenone-6 (compound VIII) showing the puckering of the $\Delta^7$-enone-6 system.

as standard values for sec., tert. and quart. carbon atoms has proved to be useful although some caution is called for. Torsional angles smaller than 60° are a consequence of valency angles larger than 109·5°. The decrease of torsional angles, down to about 55°, is greatest for those involving sec. carbon atoms.

In first approximation the curves of Bucourt and Hainaut, calculated for unsubstituted rings, can also be applied to more complicated systems in predicting qualitatively the alterations of valency and dihedral angles as a function of the variation of one dihedral angle.

The presence of two axial methyl groups—C(18) and C(19)—on the same side of the steroid skeleton influences the overall geometry of this skeleton. In conclusion it may be stated that in the simple addition of cyclohexane-like units to a steroid molecule many interaction terms that play a role in the energy balance are neglected, therefore, the actual geometry of steroids must be more complicated than the present models can predict. For *trans* junctions the rule $|\alpha| + |\beta| = K$ holds. $K$ has the following values:

$K = 120°$ for a quart.–quart. junction

$K = 117·5°$ for a quart.-tert. junction

$K = 115°$ for a tert.-tert. junction

$K = 109°$ for a C/D junction

For *cis* junctions the equality rule $\beta = \gamma$ holds only if the degree of substitution is the same for both atoms of the central bond. The presence of pairs of axial substituents suitably placed in the neighbourhood of a junction causes a breakdown of the rules. The influence on the sum rule is usually a decrease of $K$ with amounts of 5° to 10°.

The occurrence of conformational transmission effects has been shown, especially in the more complicated systems. The geometry of molecules in which the requirements of parts of the molecule are opposed can be understood qualitatively. Once the structure is known the observed valency and dihedral angles can be explained satisfactorily, but a quantitative treatment based upon energy calculations is not yet feasible.

*Acknowledgement*—We wish to express our gratitute to Prof. Dr. E. Havinga for his continuous and stimulating interest in this research.

## APPENDIX

I. *Notation of torsional and projected angles.* The torsional angle $\varphi$(1-2-3-4) denotes the angle between a plane defined by the atoms C(1), C(2) and C(3) and a plane defined by C(2), C(3) and C(4). (Fig. 11). In contrast to Hendricksons[1] notation the torsional angles is taken positive if the bond in front has to be turned clockwise in order to eclipse the rear bond. This choice of signs originates from Eyring[21] and has also been used by Klyne, Prelog[4] and Bucourt.[8] In the text, however, we refer to the absolute values only, because the sequence of signs and not the sign of the individual torsional angle is important information. This sequence is implicitly given by noting that the rings exhibit chair conformations, sofa conformations, etc. Individual signs depend on the adopted absolute configuration.

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[21] H. Eyring, *Phys. Rev.* **39**, [2] 746 (1932).

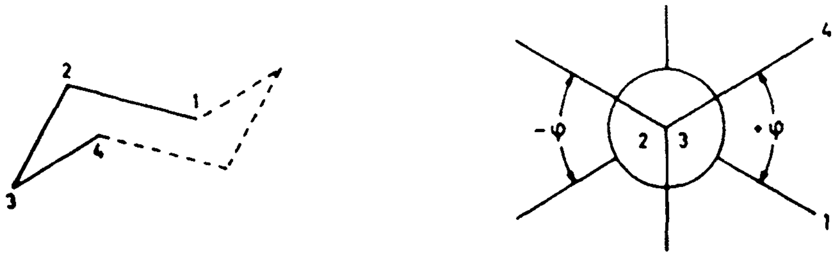

Fig. 11. Definition of torsional angle (see text).

Note, that we adopt the term projected angles for dihedral angles, which are projected valency angles of tetrahedral carbon atoms. They are *not* the usual torsional angles.

II. *Weighted averaged values* were calculated according to the formulae:

$$\mu_{av} = \sum_i \frac{\mu_i}{\sigma_i^2} \Big/ \sum_i \frac{1}{\sigma_i^2} \quad ; \quad \sigma_{av} = \left\{\frac{1}{\sum_i \sigma_i^{-2}}\right\}^{1/2}$$

where $\mu_i$ are the individual observations and $\sigma_i$ their standard deviations.

The standard deviations in the atomic coordinates—$\sigma(A)$—and those in the valency angles—$\sigma(\vartheta)$—were taken from the original publications. The standard deviations of the torsional angles—$\sigma(\varphi)$—were computed with an approximate formula given by Huber:[22]

$$\sigma(\varphi) = \frac{4\sigma^2(A)}{d^2 \sin^2 \vartheta}\{1 - (\cos\varphi + 1)\cos\vartheta(1 - \cos\vartheta)\}$$

in which $d$ is the C–C distance (taken as 1·54 Å) and $\vartheta$ is the valency angle (taken as 110°). The obtained numbers are summarized in Table 13. Although in most cases it is not justified to quote the angles in tenths of degrees, we have given this extra decimal in order to avoid round off errors.

The term "significant" has been used according to statistical criteria, generally accepted in X-ray work[23] e.g.: two quantities $q_i$ with standard deviations $\sigma_i$ are said to differ significantly if $(q_1 - q_2)/(\sigma_1^2 + \sigma_2^2) > 2{\cdot}2$.

III. *The relation between torsional angles* ($\varphi$) *and valency angles* ($\vartheta$) in a chair form cyclohexane ring is given by:

$$\cos\varphi = \frac{-\cos\vartheta}{1 + \cos\vartheta}$$

TABLE 13. STANDARD DEVIATIONS IN SOME PARAMETERS OF COMPOUNDS I, II, III AND IV.

| | I | II | III | IV | weighted average |
|---|---|---|---|---|---|
| $\sigma(A)$ | 0·025 Å | 0·014 Å | 0·004 Å | 0·009 Å | — |
| $\sigma(\vartheta)$ | 2·0° | 1·4° | 0·4° | 0·7° | 0·33° |
| $\sigma(\varphi)$ | 4·7° | 2·6° | 0·8° | 1·7° | 0·69 |

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[22] P. J. Huber, appendix in E. F. Huber-Buser and J. D. Dunitz, *Helv. Chim. Acta* **44**, 2027 (1961).

[23] D. W. J. Cruickshank and P. Robertson, *Acta Cryst.* **6**, 698 (1953). cf. W. L. Gore, *Statistical Methods for Chemical Experimentation.* Interscience, New York (1952).

This relation holds strict for a ring with symmetry $\bar{3}m$, but can be used also for deformed chair forms of lower symmetry, provided that the individual angles $\varphi$ and $\vartheta$ are replaced by the average of the six torsional angles and the six valency angles.[2] The variation of $\varphi$ as a function of the variation of $\vartheta$ is:

$$-\sin\varphi\,\mathrm{d}\varphi = \frac{\sin\vartheta\,\mathrm{d}\vartheta}{(1+\cos\vartheta)^2}$$

Thus with values of $\vartheta$ of about 110° and of $\varphi$ of about 58° an increase of $\vartheta$ with 1° causes a decrease of $\varphi$ with about 2·5°.

IV. *The relations of angles in a tetrahedron* (Fig. 5) are:

(a) $$\sum_i \mu_i = 2\pi.$$

(b) $$\cos\mu_i = \left.\frac{\cos\vartheta_{i+3} - \cos\vartheta_i\cos\vartheta_j}{\sin\vartheta_j\sin\vartheta_i}\right\} \begin{cases} i = 1,2,3 \\ j = 2,3,1 \end{cases}$$

The variation of e.g. $\mu_1$ as a function of variation of the corresponding $\vartheta$'s is given by:

$$\begin{aligned}\mathrm{d}\mu_1 = {} & \{\sin\vartheta_1\sin\vartheta_2\sin\vartheta_4\,\mathrm{d}\vartheta_4 - \sin\vartheta_2(\cos\vartheta_2 - \cos\vartheta_1 \\ & \times \cos\vartheta_4)\mathrm{d}\vartheta_1 - \sin\vartheta_1(\cos\vartheta_1 - \cos\vartheta_2\cos\vartheta_4)\,\mathrm{d}\vartheta_2\} \\ & \times \{-\sin\mu_1\sin^2\vartheta_1\sin^2\vartheta_2\}^{-1}.\end{aligned}$$

Assuming nearly tetrahedral valency angles with projected angles to match one obtains the useful approximate expression:

$$\Delta\mu_1 \cong 0{\cdot}6(2\Delta\vartheta_4 + \Delta\vartheta_2 + \Delta\vartheta_1).$$