

STEROIDAL ANALOGUES OF UNNATURAL CONFIGURATION—17¹

CONFORMATIONAL ANALYSIS OF 4,4,14 α -TRIMETHYL-19(10 \rightarrow 9 β) ABEO-5 α ,10 α -PREGNANE-6,11-DIONE

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Abstract—The *cis-transoid-cis* steroidal analogue **1** was predicted by force field calculations to have non-chair rings B and C. X-ray structure determination confirmed this result. The conformational effects of various salient features of **1** have been investigated by force field methods.

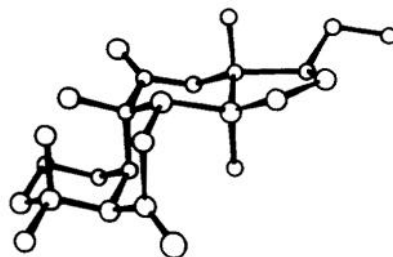
As part of a continuing investigation into the conformational properties of steroidal analogues disposed toward ring deformation,² 4,4,14 α -trimethyl-19(10 \rightarrow 9 β)*abeo*-5 α ,10 α -pregnane-6,11-dione (**1**) was examined. The compound **1**, obtained through acid-catalysed rearrangement of the related 5 β ,6 β -epoxide,³ has a *cis-transoid-cis* arrangement of rings A, B and C, and the all-chair conformation (**1a**) gives rise to severe steric interactions on both the α - and β -faces of the molecule. The most conspicuous contributors to these interactions are the 4 β - and 9 β -Me groups, whose relationship is akin to that of 1,3-diaxially disposed Me and *t*-Bu groups in cyclohexane, and the 14 α -Me group, whose contribution toward α -face congestion has been recognised² in related substances.

In keeping with the expectation, based upon the relative thermodynamic stabilities of the isomeric perhydrophenanthrenes,⁴ the compound **1** readily undergoes isomerisation into its 5-epimer **2**,³ in which β -face interactions of **1** are alleviated (see **2a**), whereas those upon the α -face are retained. Although *trans-transoid-cis* stereochemistry should be favoured even in the absence of the 4 β - and 9 β -Me groups, these features undoubtedly contribute toward the quantitative epimerization of **1** into **2** upon exposure to base.

The Dreiding model of **1a** reveals that a measure of relief from non-bonded interactions can be achieved through flattening of rings A, B and C, although only at the expense of severely increased Baeyer strain. Furthermore, it is unlikely that any advantage can be gained through selective deformation of rings B and C whilst ring A remains in the ⁴C₁ conformation,⁵ since the β -face interactions are thereby retained or exacerbated.

However, inversion of ring A to ¹C₄ results in elimination of the interaction involving the 4 β -Me group, but constrains rings B or C (or both) to adopt non-chair conformations.

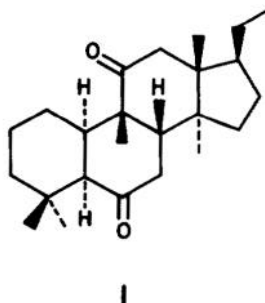
The conformational options for ring C are restricted, by the *trans* coupling with ring D, to two possibilities *viz.*, ⁸C₁₂, and that part of the pseudorotational cycle between ^{9,13}B and B_{11,14}. In the former case, ring B must perforce adopt the B_{5,8} conformation (**1b**) in which the stem-stern interaction between 5 α -H and the quasi *t*-Bu residue attached to C(8) is maximized. This interaction is not significantly diminished in the allowed pseudorotational cycle between ⁷T₅ and ⁹T₅. If ring C adopts the B_{11,14} conformation, the retention of ⁸C₅ in ring B is associated with acute Baeyer strain which may be relieved by ring C pseudorotation toward ^{9,13}B (**1c**). In this case, however, the interaction between the 9 β - and 13 β -Me groups is severe. An alternative non-chair con-



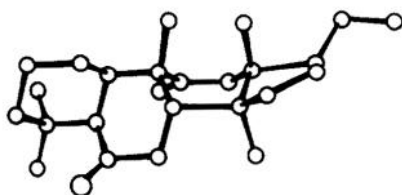
1a



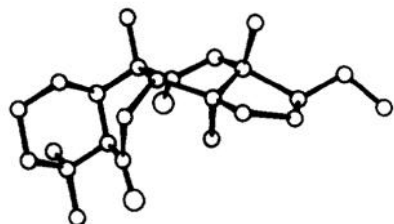
1b



1



1c



1d

formation of ring B, close to ${}^{7,10}B$, can accommodate $B_{11,14}$ in ring C; in this state (1d) the interaction between the 9β - and 13β -Me groups is largely alleviated, but the added Pitzer and Van der Waals strains associated with the presence of two non-chair rings must be accommodated.

A favoured conformation for 1 is not readily discernible from models since the energies associated with the various interactions described above cannot be intuitively quantified. However, on the basis of this analysis, it was possible to identify a limited number of feasible conformations of 1 which were used as points of departure for force field minimizations carried out with the MM-2 programme.⁶ The results are summarized in Table 1, and a comparison of the calculated steric energies

leads to the prediction that a CBB conformer ($\sim 1d$) should be thermodynamically favoured by a small margin compared with the CBC form ($\sim 1b$); both are substantially less energetic than the CCC form ($\sim 1a$). The results also show that the CTC and BBB conformers can be excluded from further consideration.

The puckering parameters show that it may best be described as ${}^1C_4({}^7T_5 + {}^{7,10}B)({}^9T_{14} + B_{11,14}){}^{13}T_{14}$, with rings B and C adopting positions of conformational compromise between the conflicting interactions.

An X-ray crystallographic investigation of 1 was carried out in order to compare the solid state conformation with that predicted by the MM-2 method for the isolated molecule. The refined coordinates are listed in Table 2, and the internal parameters derived from them in Fig. 1. A stereoscopic drawing of the X-ray structure is given in Fig. 2.

Comparison of the puckering parameters⁷ derived from X-ray data with those of the MM-2 method (Table 3) reveals close overall correspondence. The apparently large difference reflected by θ for ring A are inconsequential since θ is undefined at $\theta = 0$, but the differences between experimental and calculated θ and Q values for ring C indicate that it is slightly more flattened than predicted by MM-2 although its pseudorotational disposition is nearly identical. The overall accuracy of the conformational prediction of 1, where deformation of contiguous *cis*-coupled rings gives rise to a plethora of conformational possibilities, provides a further example of the reliability of the predictive method. The results also demonstrate the remarkable degree to which a polycyclic system can undergo conformational adaptation in response to steric interactions.

An interesting extension of the molecular mechanics approach to structure prediction, is the possibility of identifying those molecular features which are responsible for conformational aberrations. A series of calculations was carried out upon hypothetical compounds,

Table 1. Relative steric energies and approximate conformations of different conformers of 1 as derived from minimization with MM-2

INPUT	$\Delta E^a)$	FINAL CONFORMATION ^{b)}
4C_1 5C_8 ${}^8C_{12}$ ${}^{13}T_{14}$ (1a)	2.47	$({}^4C_1 + {}^2H_3)({}^5C_8 + {}^7H_8)({}^8C_{12} + {}^{13}E) {}^{13}T_{14}$
1C_4 9T_5 ${}^8C_{12}$ ${}^{13}T_{14}$ (1b)	0.60	1C_4 9T_5 $({}^8C_{12} + {}^{13}E) {}^{13}T_{14}$
1C_4 7T_5 ${}^8C_{12}$ ${}^{13}T_{14}$	4.01	1C_4 7T_5 ${}^{13}E$ ${}^{13}T_{14}$
1C_4 ${}^{7,10}B$ ${}^{9,13}B_{11,14}$ ${}^{13}T_{14}$ (1d)	0.00	${}^1C_4({}^7T_5 + {}^{7,10}B)({}^9T_{14} + B_{11,14}) {}^{13}T_{14}$
1C_4 8C_5 9,13B ${}^{13}T_{14}$ (1c)	0.00 ^{c)}	${}^1C_4({}^7T_5 + {}^{7,10}B)({}^9T_{14} + B_{11,14}) {}^{13}T_{14}$
${}^{2,5}B$ ${}^{7,10}B$ ${}^{9,13}B_{11,14}$ ${}^{13}T_{14}$	3.22	${}^2T_{10}({}^{7,10}B + {}^7T_5)({}^9T_{14} + B_{11,14}) {}^{13}T_{14}$

a) In kcal/mol with the lowest energy set to 0.

b) Two designations set in brackets indicate a conformer closer to the midpoint of the two than to either of the extremes.

c) MM-2 found no local minimum near conformation 1c. Ring B inverted to the non-chair form during minimization.

Table 2. Fractional coordinates ($\times 10^4$) with ESD's of the non-hydrogen atoms

ATOM	X/A	Y/B	Z/C
C(1)	5225(5)	5816(0)	8533(5)
C(2)	4332(5)	6346(14)	7272(5)
C(3)	4881(5)	6808(12)	6614(5)
C(4)	5773(5)	8545(11)	7139(5)
C(5)	6669(5)	7985(10)	8404(5)
C(6)	7423(5)	6148(12)	8609(5)
C(7)	7902(5)	4929(11)	9664(5)
C(8)	8046(4)	6061(10)	10731(5)
C(9)	6976(5)	7460(10)	10401(5)
C(10)	6086(5)	7620(11)	9063(5)
C(11)	7291(5)	9640(10)	10890(5)
C(12)	8368(5)	10035(11)	12067(5)
C(13)	9258(5)	8313(11)	12460(5)
C(14)	9173(5)	7261(11)	11430(5)
C(15)	10259(5)	5895(13)	12014(5)
C(16)	11146(5)	7262(13)	13044(6)
C(17)	10496(5)	9105(13)	13123(5)
C(18)	9123(6)	6714(14)	13223(6)
C(19)	6358(5)	6535(11)	10958(5)
C(20)	6293(6)	8810(17)	6407(6)
C(21)	5214(6)	10636(12)	7131(6)
C(22)	9311(5)	8884(11)	10655(5)
C(23)	10950(5)	9825(18)	14364(6)
C(24)	12074(5)	10988(19)	14864(7)
O(2)	6701(3)	11170(8)	10393(4)
O(1)	7655(5)	5536(14)	7924(4)

Table 3. Puckering parameters⁷ of 1 for the force field minimized and X-ray determined conformers

		<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
O	MM-2	4	98	80	-
	X-Ray	3	100	75	-
Ø	MM-2	113	221	285	344
	X-Ray	71	219	284	349
Q	MM-2	0.57	0.65	0.71	0.48
	X-Ray	0.59	0.67	0.64	0.48

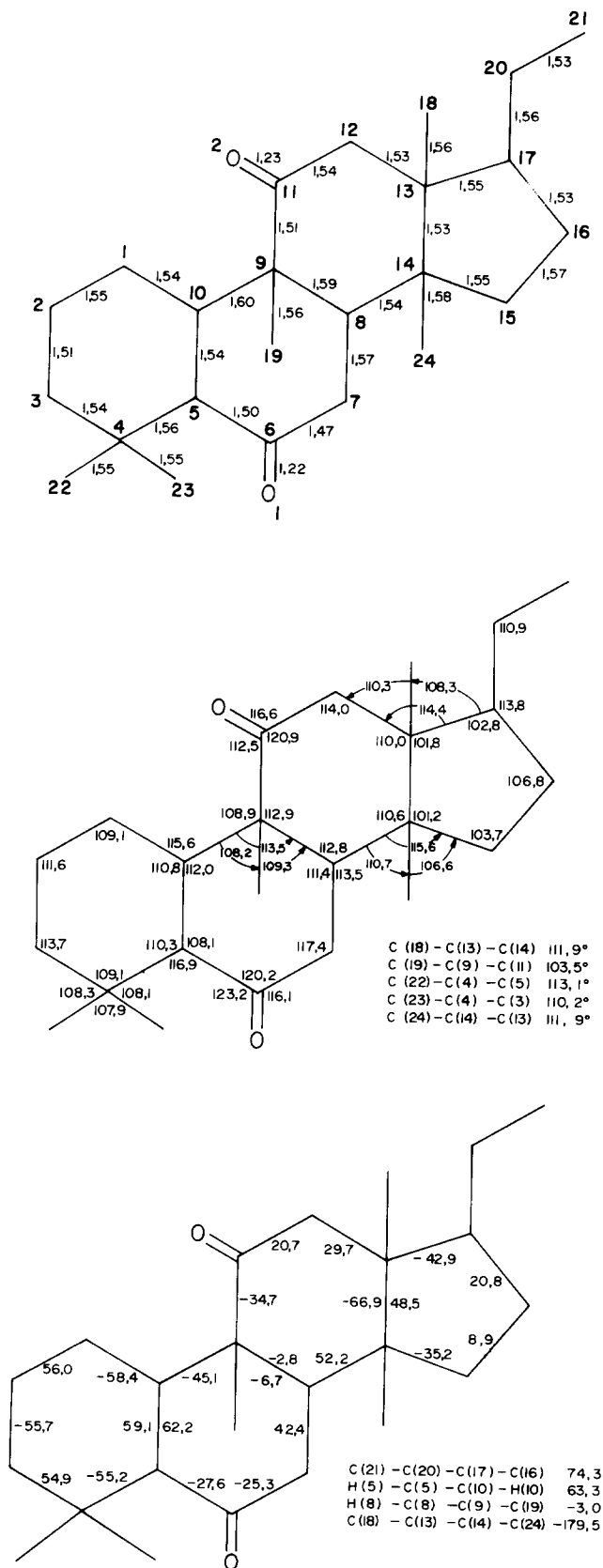


Fig. 1. Bond lengths (and atom numbering), bond angles, and torsion angles from the X-ray data of 1.

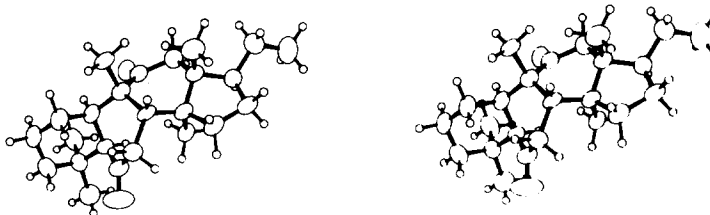


Fig. 2. The X-ray structure of 1.

Table 4. Steric energies and approximate conformations of analogues of 1 as calculated by MM-2

COMPOUND	STERIC ENERGY ^{a)} "CBB"	BEST CONFORMER ^{b)}
1	67.07	67.07 [¹ C ₄ (⁷ T ₅ + ^{7,10} B) (⁹ T ₁₄ + ^B _{11,14}) ¹³ T ₁₄]
19-nor-1	58.01	56.64 [⁴ C ₁ (B _{7,10} + ⁵ T ₇) ⁹ T ₁₄ ¹³ T ₁₄]
24-nor-1	56.77	54.73 [¹ C ₄ ⁹ T ₅ (⁸ C ₁₂ + ¹³ E) (¹³ T ₁₄ + ¹³ E)]
22,23-dinor-1	60.93	60.71 [⁴ C ₁ ⁵ C ₈ (⁸ C ₁₂ + ¹³ E) ¹³ T ₁₄]
11-desoxy-1	71.14	69.30 [¹ C ₄ ⁹ T ₅ (⁸ C ₁₂ + ¹³ E) ¹³ T ₁₄]
5-epi-1(=2)	63.51 ^{c)}	59.54 [¹ C ₄ ⁵ C ₈ (⁸ C ₁₂ + ¹³ E) ¹³ T ₁₄]

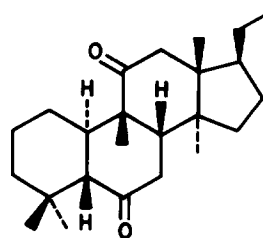
a) In kcal/mol, after minimization by MM-2.

b) Approximate descriptions of the ring conformations given in [].

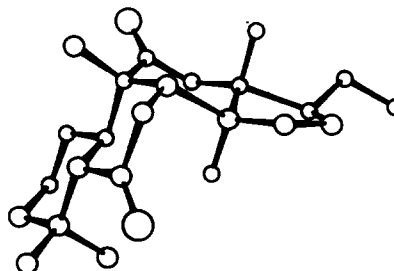
c) ¹C₄ ^{7,10}B ^B_{11,14} not possible for this compound. This energy is for ¹C₄(B_{7,10}+⁹T₇)(^B_{11,14}+⁹T₁₄)

in which features of 1, which had intuitively been implicated in the observed ring deformations, were removed individually. The results are summarized in Table 4. In each case, the steric energy of the CBB form is found to be higher than that of an alternative conformer. For example, the absence of the 14 α -Me or 11-oxo-groups allows ring C to revert to ⁸C₁₂ whilst ring B becomes ⁹T₅, and the absence of the 9 β -Me group allows ring A to revert to ⁴C₁, with a corresponding pseudorotation of the deformed ring B to (B_{7,10}+⁹T₇). Removal of the 4,4-dimethyl moiety results in a steric preference, albeit slight, for the all chair conformer. These results indicate that the CBB conformation of 1 is dependent on the presence of each of the structural features investigated.

It is also possible to quantify the isomerization of 1 to 2 with the aid of the force-field method. Calculations reveal (Table 4) that the steric energy of the all chair conformer (2a) is 7.53 kcal/mol lower than that of the favoured (CBB) conformer of 1. Furthermore, the CCC conformer of 2 is strongly preferred to that in which rings B and C are deformed; the most likely such conformer in the 5 β -series would be comparable to that of the related 6 α ,11 β -diol², i.e. ¹C₄(B_{7,10}+⁹T₇)(^B_{11,14}+⁹T₁₄)¹³T₁₄.



2



2a

EXPERIMENTAL

Crystal data. Crystals of **1** were obtained by recrystallization from CHCl₃-MeOH. The crystal data are: C₂₄H₃₆O₂, monoclinic, space group P2₁; *a* = 13.988 Å; *b* = 6.411 Å; *c* = 13.933 Å; β = 122.37°; *V* = 1055.3 Å³; *M* = 358.3 a.m.u.; *z* = 2; *d_c* = 1.13 g cm⁻³.

Intensity data were collected on a Hilger and Watts Y-290 diffractometer fitted with a graphite monochromator and using Cu-K_α radiation (*h* = 1.5418 Å). Accurate cell dimensions were determined from a least-squares fit of 20 reflections. 1614 reflections were measured, of which 3 were rejected as unobserved with *I* < 2σ(*I*). LP corrections were applied.

Structure determination and refinement. The structure was solved by direct methods using multiple tangent refinement (the MULTAN⁸ computer programme). The first Fourier map revealed the positions of all of the ring carbon atoms. Not all of the H atoms were revealed in the subsequent full-matrix least-squares refinement. All H atoms were therefore placed and refined in calculated positions. The C-H bond distances were constrained to 1.08 Å. An overall isotropic thermal parameter for the H atoms refined to *V* = 0.081 Å². The residual was 0.067. Initial computations were performed using the programme MULTAN.⁸ Subsequent refinement was carried out with the programme SHELX-78.⁹

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