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THE SANTONINS

QUANTITATIVE CONFORMATIONAL ANALYSIS

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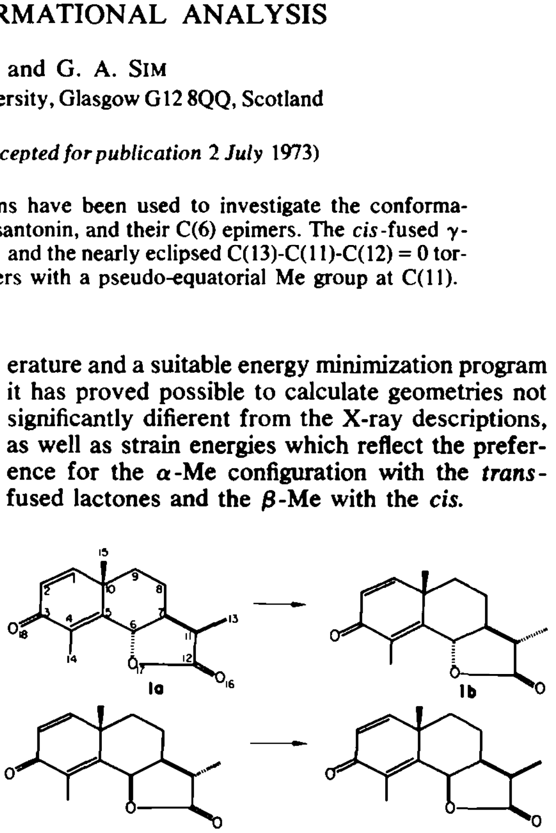
Abstract—Empirical valence force-field calculations have been used to investigate the conformations and relative strain energies of α-santonin, β-santonin, and their C(6) epimers. The *cis*-fused γ-lactone ring is energetically preferred over the *trans* and the nearly eclipsed C(13)-C(11)-C(12) = 0 torsion angle plays a key role in stabilising the isomers with a pseudo-equatorial Me group at C(11).

INTRODUCTION

Equilibration studies[1] have indicated the preferential isomerisation of β-santonin (**1a**) to α-santonin (**1b**) and conversely 6-epi-α-santonin (**1c**) to 6-epi-β-santonin (**1d**). Previous attempts[2] to justify the stability of the preferred isomers have been based upon an empirical consideration of intuitively selected intramolecular interactions. However, such arguments are somewhat lacking in authority because the interaction list is incomplete and also because the relative magnitudes of the various effects are not properly assessed. In particular, although the C(13) Me group is pseudo-equatorial in both α-santonin and 6-epi-β-santonin, where the CH_3—C—C=O torsion angles are syn-periplanar, no account was taken of the intrinsic stabilisation which is evident when these torsion angles are small.[3] The extent of this stabilisation ($\approx$ 1 kcal mole^{-1}) is of the same order of magnitude as the differences in strain energy between the preferred and less stable conformers, where the torsion angles in question are syn-clinal, and clearly cannot be neglected. The safest approach to rationalising conformational preferences, such as those discussed above, is undoubtedly a quantitative consideration of the complete set of intramolecular interactions insofar as this is feasible.

Quantitative conformational analysis has progressed considerably from the early work on small molecules involving relatively few adjustable parameters[4-6] to recent calculations concerning alkenes,[7] aldehydes and ketones,[8] lactams[9] and steroids[10] with up to forty or so atoms, in which full account is taken of the various contributions to the molecular strain energy. The application of an energy minimization procedure in order to generate geometric and strain energy descriptions for the C(11) epimers of santonin and 6-episantonin, for which X-ray[11-14] and thermochemical data[1] are available, appeared to be a feasible proposition.

Using force constants taken mainly from the literature and a suitable energy minimization program it has proved possible to calculate geometries not significantly different from the X-ray descriptions, as well as strain energies which reflect the preference for the α-Me configuration with the *trans*-fused lactones and the β-Me with the *cis*.



1a **1b** **1c** **1d**

METHODS

The equilibrium geometries and strain energies were computed by means of a program (PECALC) written by one of the authors (DNJW). The input is particularly simple and consists of the force field parameters and the cartesian coordinates of the atoms together with identifiers for atom type and degree of substitution. The relevant internal coordinates (bond lengths, angles and torsion angles) and non-bonded distances are generated automatically and matched to the appropriate force constants.

Strain energy minimization is accomplished by means of a Newton-Raphson iterative procedure in which the cartesian coordinates of the atoms are adjusted to converge upon the minimum energy position.

Let x_i^m ($i = 1,3$) represent the cartesian coordinates of a particular atom at the minimum energy position and x_i^t the trial position somewhere in the vicinity of the minimum. The partial derivatives of the strain energy, E, with respect to x_i^m may be expressed as the truncated Taylor series,

$$\frac{\partial E}{\partial x_i^m} = \frac{\partial E}{\partial x_i^t} + \sum_{j=1}^{3} \frac{\partial^2 E}{\partial x_i^t \partial x_j^t} \cdot \delta x_j \qquad (1)$$

where $\delta x_j = x_j^m - x_j^t$.

The minimum energy conformation of a molecule corresponds to a solution of the equations $\nabla E(x_i) = 0$ so that,

$$\frac{\partial E}{\partial x_i^t} = -\sum_{j=1}^{3} \frac{\partial^2 E}{\partial x_i^t \partial x_j^t} \cdot \delta x_j{}^* \qquad (2)$$

and the correction to the trial position is given by,

$$\delta x_j = -D_{x_i x_j}^{-1} \mathbf{D}_{x_j} \qquad (3)$$

where D is the three by three matrix of second derivatives and **D** the vector whose components are the first derivatives. These equations can be solved in δx_j for each of the atoms in turn, after introducing the appropriate constraints to define the position and orientation of the molecule, and the calculation iterated until the corrections become sufficiently small. However, for computational simplicity it is assumed that the shape of the potential energy surface in the vicinity of the minimum approximates to part of the surface of a sphere so that the off diagonal terms in $D_{x_i x_j}$ vanish† and

$$\delta x_j = -D_{x_j x_j}^{-1} \mathbf{D}_{x_j} \qquad (4)$$

The derivatives are evaluated numerically from the expression for E as a function of the internal coordinates and non-bonded distances,

$$E = \sum_l \tfrac{1}{2} k_l (l - l_0)^2 + \sum_\theta \tfrac{1}{2} k_\theta (\theta - \theta_0)^2 + \sum_\omega \tfrac{1}{2} k_\omega (1 \pm \cos n\,\omega) + \sum_\chi \tfrac{1}{2} k_\chi (\pi - \chi)^2 + \sum_r \epsilon\{-2{\cdot}25\alpha^{-6} + 8{\cdot}28 \times 10^5 \exp(-\alpha/0{\cdot}0736)\}$$

$$\alpha = r/(r_1^* + r_2^*)$$

via the appropriate transformations from cartesian to internal coordinates. The variables l, θ, r and ω are bond lengths, bond angles, 1,4 and higher interatomic distances, and torsion angles, respectively. Allowance is made for out-of-plane bending of the CO groups by means of the "improper" torsion angle χ, as defined by Lifson,[9] where $\frac{1}{2}k_\chi = 30{\cdot}0$ kcal mole^{-1} rad^{-2}.

In order to keep the size of the calculations within reasonable limits, (a) only those interatomic distances of 5 Å and less have been considered[10] and (b) coulombic interactions have been neglected. Whilst it is unlikely that these contribute significantly to the difference in strain energy between a given pair of α- and β-Me epimers, this is not necessarily the case for the difference between the *cis*- and *trans*-fused lactones which may be slightly underestimated.

The values for the various force constants k_l, k_θ, k_ω, and ϵ were taken mainly from refs. 7, 8 and refs. cited therein. The remainder are listed in Table I.

DISCUSSION

The root-mean-square discrepancies between the experimental (X-ray) and calculated bond lengths, angles and torsion angles are 0·011 Å, 1·3° and 1·6°, respectively, compared with r.m.s. estimated standard deviations of 0·009 Å, 0·5° and 1·0° derived from the least-squares refinement of the X-ray models. This comparison is not intended to be statistically rigorous but merely to illustrate that the calculated and experimental structures are very similar.

The components of the total strain energy of α- and β-santonin due to bond stretching (E_l), angle bending (E_θ), torsional strain (E_ω), out-of-plane bending (E_{opb}) and repulsion (or attraction) between non-bonded atoms (E_{vdw}) are shown in Table 2. The strain energies are in accord with the observed stability of α-santonin relative to its C(11)-β-epimer; the difference is essentially due to the torsional

Table 1. Force constants

Bond	l_0(Å)	$\frac{1}{2}k_l$(kcal mole^{-1} Å^{-2})
C_{sp2}—CO	1·480	316·65†
CO—O	1·334	474·97[16]
C_{sp3}—O	1·470	309·45[16]
Angle	θ_0	$\frac{1}{2}k_\theta$(kcal mole^{-1}rad^{-2})
C—C_{sp3}—O	110·6	36·12†
C—CO—O	115·6	40·38[17]
O═C—O	120·0	51·06[17]
H—C—O	108·4	31·74[17]
CO—O—C	114·8	72·56[16, 17]
Torsion angle	$\frac{1}{2}k_\omega$(kcal mole^{-1})	Fold (n)
A—C_{sp2}—CO—B	1·30	2†
A—CO—O—B	5·92	2†
A—C_{sp}3—O—B	0·20	3[18]
O—CO—C_{sp3}—C_{sp3}	0·05	3†
O—CO—C_{sp3}—H	−0·02	3†

†Estimated values, optimised empirically during the calculations.

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*Note that

$$\frac{\partial E}{\partial x_i^t} = -\sum_{j=1}^{3n} \frac{\partial^2 E}{\partial x_i^t \partial x_j^t} \cdot \delta x_j, \quad i = 1,3n$$

cannot be solved for cooperative movements of the atoms because $D_{x_i x_j}$ is singular in cartesian coordinates.[15]

†Current versions of the program use Eq (3).

Table 2

	α-Santonin	β-Santonin
E_t	0·5980	0·6648
E_{vdw}	− 3·5433	− 3·4930
E_θ	8·8036	8·4896
E_ω	2·6646	3·6925
E_{opb}	0·0519	0·0186
E_{TOTAL}	8·5749 mcal $mole^{-1}$	9·3724 kcal $mole^{-1}$

term, the almost eclipsed CH_3—C—C═O fragment of the γ-lactone in α-santonin imparting greater stability than the corresponding H—C—C═O fragment in β-santonin. The preferential eclipsing of a CO with a Me group, rather than an H atom, is an important consideration governing the minimum energy conformation of a variety of simple and biologically important molecules.[3,8,19] This preference may also be extended to include those cases where the Me group is substituted; as evidenced by the stereoselective formation of p-bromobenzenethiol adducts by α-methylene γ-lactones,[20] where the pseudo-equatorial $RSCH_2$ group lies on the α-face of the molecule in the *trans*-fused lactones and the β-face in the *cis*.

Further differences are, interestingly enough, intimately related to the primary torsional effect discussed previously. Newman projections down the C(11)—C(12) bond (Figs 1b and 2b) illustrate the differing torsional arrangements in α- and β-santonin. H(11), C(13) and C(7) are rotated anticlockwise by 4° in α-santonin relative to C(13), H(11) and C(7) in β-santonin, corresponding to the change in ω(C(7)—C(11)—C(12)—O) which is restricted by the inflexible γ-lactone ring, and additional bond angle deformation at C(11) in α-santonin accounts for the remaining difference of 7° in the other three torsion angles. Obviously, these deformations will also give rise to differences in the torsional situation around the C(7)—C(11) bond and the relevant Newman projections are shown in Figs 1c and 2c. The increased bond angle deformation at C(11) in α-santonin, which is largely responsible for 0·3 kcal $mole^{-1}$ increase in E_θ, relative to β-santonin, is more than compensated for by the decreased torsional strain around C(7)—C(11), where the angles are rather closer to the minimum energy values of 60°, and C(11)—C(12) where the C(13) Me comes closer to eclipsing the CO group than does H(11) in β-santonin. Strain energy reduction in β-santonin cannot be effected by this mechanism because any anticlockwise rotation about C(11)—C(12) and bond angle deformation at C(11) would result in unacceptable crowding of the C(13) methyl H atoms (Fig 2a) together with a much smaller decrease in torsional strain, relative to α-santonin, as H(11) rotates to eclipse the CO group. (*cf* the much less crowded environment of H(11) in α-santonin (Fig 1a) which does not significantly hinder small rotations about C(11)—C(12)).

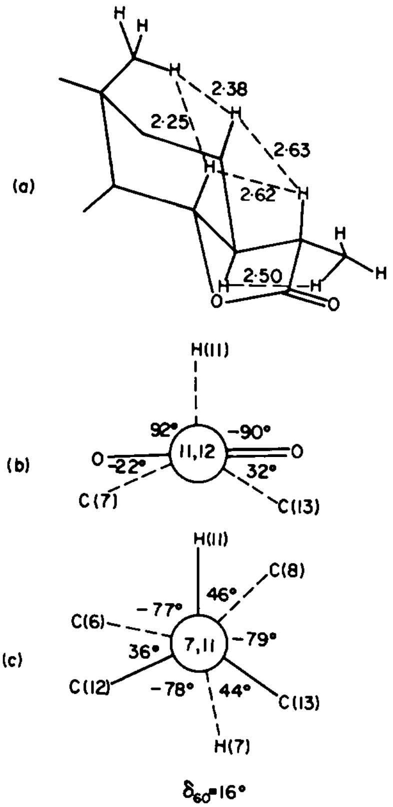

Fig 1. (a) α-santonin, non-bonded distances (Å); (b) and (c) Newman projections down C(11)–C(12) and C(7)–C(11). δ_{60} is the mean deviation of the torsion angles from the "strain free" values of ±60°.

A similar situation prevails in the 6-epi-santonins where the isomer with the pseudo equatorial β-Me group at C(11) has the lower strain energy (Table 3) and the difference in E_ω predominates. In this case, however, it is H(6) and H(7) which buttress the C(13) methyl H atoms, in 6-epi-α-santonin (Fig 3a), and prevent any further reduction in the H(11)—C(11)—C(12)═O torsion angle. The bond angles at C(11) in 6-epi-β-santonin are deformed to a much greater extent than the corresponding angles in α-santonin; C(7)—C(11)—C(13) and C(12)—C(11)—C(13) are 118° and 115° compared with 116° and 113° and this has the effect of moving the H atoms on C(13) away from those on C(8) (Fig

Table 3

	6-Epi-α-santonin	6-Epi-β-santonin
E_t	0·5733	0·5388
E_{vdw}	− 3·1006	− 3·1934
E_θ	6·0569	7·0581
E_ω	4·4846	3·1680
E_{opb}	0·0134	0·0303
E_{TOTAL}	8·0277 kcal $mole^{-1}$	7·6019 kcal $mole^{-1}$

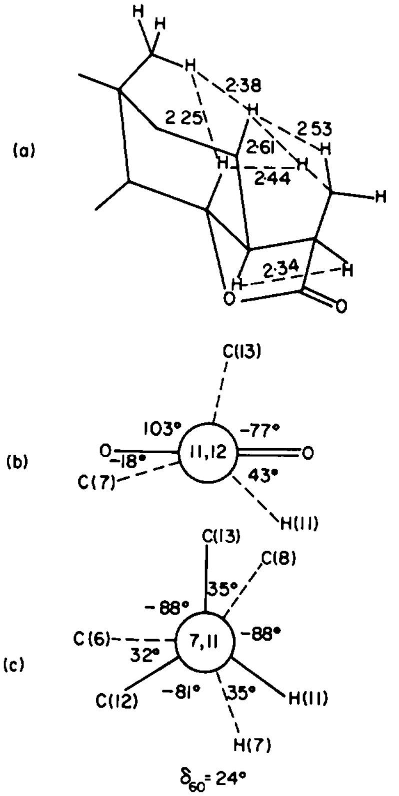

Fig 2. (a) β-santonin, non-bonded distances (Å); (b) and (c) Newman projections down C(11)–C(12) and C(7)–C(11).

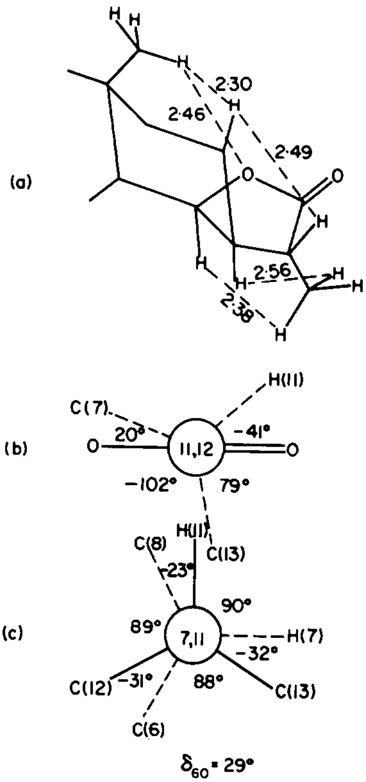

Fig 3. (a) 6-epi-α-santonin, non-bonded distances (Å); (b) and (c) Newman projections down C(11)–C(12) and C(7)–C(11).

4a) as well as reducing the C(13)—C(11)—C(12)═O torsion angle to an even more favourable value than in α-santonin.

These opposing effects do not balance however, and the dominant increase in E_θ leads to a diminished difference in the molecular strain energy between 6-epi-α and 6-epi-β-santonin compared to α- and β-santonin.

The differences between the santonins and 6-epi-santonins arising from the *trans* or *cis*-fused γ-lactone rings are of some interest and are in some respects similar to the differences between 2-hydrindanone with either a *cis* or *trans*-fused cyclopentan-2-one ring.[19] The santonins, with a *trans*-fused γ-lactone, have 1·6 kcal mole^{-1} more angle bending energy at C(6), C(7) than the *cis*-fused 6-epi-santonins. Conversely, the 6-epi-santonins have 0·65 kcal mole^{-1} more torsional strain around the C(6)—C(7) bond (Fig 5a–5d) and 0·2 kcal mole^{-1} more van der Waals strain energy. On balance therefore, the *cis*-fusion is energetically preferred to the extent of 0·75 kcal mole^{-1} and this is reflected in the generally lower molecular strain energy of the 6-epi-santonins. Although these effects operate in the same direction for the *trans* and *cis* 2-hydrindanones their magnitudes are different, 0·6, 0·6 and 1·1 kcal mole^{-1} respectively, and *trans*-fusion is favoured by 1·1 kcal mole^{-1}. The substantially lower van der Waals strain in *trans* 2-hydrindanone is associated with relief of the considerable steric repulsion between the syn axial cyclohexane hydrogens and one of the axial methylene hydrogen atoms in *cis* 2-hydrindanone. (Fig 6a and 6b) Returning now to the santonins and 6-epi-santonins, it is clear (Fig 7a and 7b) that there is little relief of van der Waals strain on going from *cis* to *trans*-fused γ-lactones as both the axial and equatorial substituents at C(6) are subject to steric repulsion by H atoms on C(14) and C(15). The excess angle bending energy of the santonins, over the 6-epi-santonins, would be comparable to that of the *trans* 2-hydrindanones if the strain at C(6) were equal to that at C(7). However, the bond angles at C(6) are deformed to an even greater extent than at C(7) in order to reduce the repulsion between O(17) and the C(14) methyl hydrogen atom which are then separated by 2·30 Å. These factors, therefore, are sufficient to tilt the equilibrium in favour of the *cis*-fused γ-lactone of the 6-epi-santonins in contrast to the preferred *trans* fusion of 2-cyclopentanone in the hydrindanones.

Finally, in Table 4 the available thermochemical

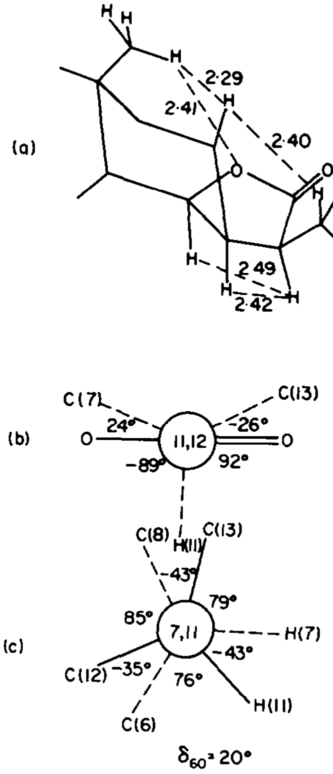

Fig 4. (a) 6-epi-β-santonin, non-bonded distances (Å); (b) and (c) Newman projections down C(11)–C(12) and C(7)–C(11).

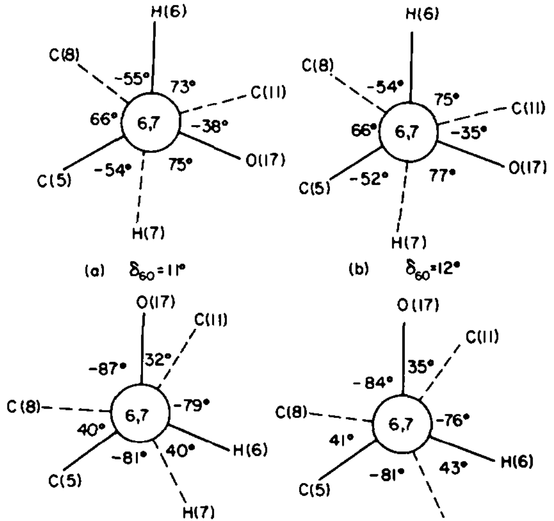

Fig 5. (a) and (b) Newman projections down C(6) and C(7) for α- and β-santonin; (c) and (d), the corresponding projections for the 6-epi-santonins.

Table 4

	$-H_c$	$-H_f(s)$	$-H_f(soln)$	S.E.
α-Santonin	1884·40	141·22	140·78	8·57
β-Santonin	1885·23	141·39	140·38	9·37
6-Epi-α-santonin	1885·80	139·82	140·91	8·03
6-Epi-β-santonin	1881·47	144·15	144·06	7·60

Enthalpies and strain energy in kcal mole^{-1}.

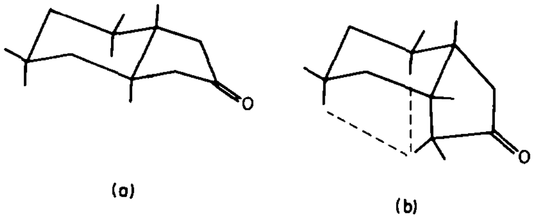

Fig 6. (a) *trans*-2-hydrindanone; (b) *cis*-2-hydrindanone.

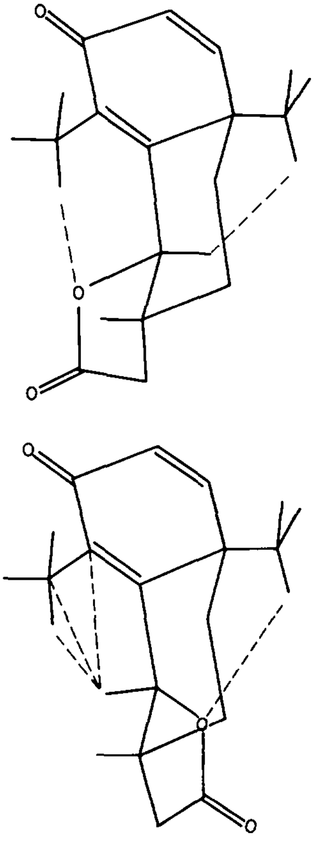

Fig 7. (a) *trans*-fused γ-lactone; (b) *cis*-fused γ-lactone.

data for the santonins and 6-epi-santonins are compared with the calculated molecular strain energies. Note that these are not strictly comparable, as the calculated strain energies are related to gas phase heats of formation, but serve as a useful guide to the validity of our conclusions.

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