# Conformations of Ten-membered-ring Sesquiterpenes. Crystal and Molecular Structures of Agerol Diepoxide and Ageratriol

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The crystal and molecular structures of agerol diepoxide (3) and ageratriol (2), which have been determined by direct methods and refined by least-squares to *R* 0.060 and 0.069 respectively, confirm the previously suggested biogenetic scheme from agerol (1). Theoretical calculations by a molecular mechanics method (GEMO program) show that the conformers observed in the crystals have the lowest strain-energy. N.m.r. measurements indicate that agerol diepoxide adopts this conformation also in solution.

AGEROL (1) and ageratriol (2) are the main sesquiterpene components of *Achillea ageratum*, and their absolute configurations have been determined by chemical methods.[1,2] Chemical transformation [3] of the diepoxide (3), isolated in very small amounts from the plant, into

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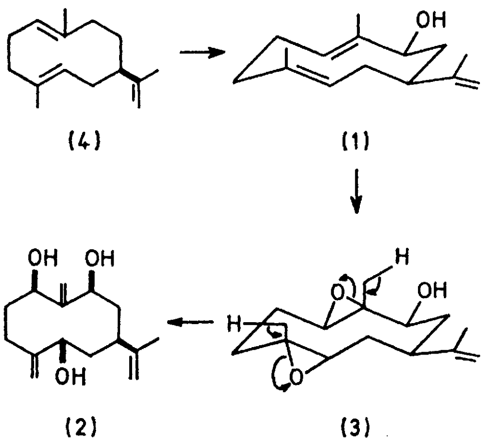
[1] R. Grandi, A. Marchesini, U. M. Pagnoni, and R. Trave, *Tetrahedron Letters*, 1973, 1765.

[2] R. Grandi, A. Marchesini, U. M. Pagnoni, R. Trave, and L. Garanti, *Tetrahedron*, 1974, **30**, 3821.

[3] F. Bellesia, U. M. Pagnoni, and R. Trave, *Tetrahedron Letters*, 1974, 1245.

(2) and biosynthetic studies[4] have suggested the following biogenetic scheme:



SCHEME

The stereostructures shown for agerol (1) and its diepoxide (3) have been inferred on the basis of the stereospecific reaction path[3] (1)→(3)→(2) and the stereochemistry of the product obtained by Cope rearrangement of (1).[1]

The understanding of the conformational details in medium rings started effectively from Dunitz's demonstration by *X*-ray diffraction of a unique conformation of the ten-membered ring skeleton in a number of cyclodecane derivatives.[5] As in the case of the chair form of cyclohexane, the carbon skeleton in medium-size rings tends to follow very closely the diamond lattice; however, since this causes an excessively close approach of some of the hydrogen atoms, a compromise is reached between angle opening, bond torsion, and hydrogen repulsion. The geometry of cyclic olefins may be derived from that of the saturated hydrocarbon by considering the double bonds as two bent bonds.[6] Further, a bivalent substituent can replace both hydrogen atoms of a $CH_2$ group to form a double bond, without greatly affecting the stereochemistry of the carbon framework.[7]

Conformational analyses of natural cyclodecane substances have shown expected deviations from the aforementioned generalizations; as the number of functional groups increases, the problem of stability of the medium-size ring becomes more complicated and the carbon framework takes advantage of its flexibility to reach a more stable conformation. Variable-temperature and n.o.e. n.m.r. studies have shown[8,9] that for many examples more than one conformer exists at equilibrium, and that the effect of temperature on the rate of ring inversion depends strongly on the type of substitution. However, in the case of *trans,trans*-1,5-dienes the conformation of the more stable isomer tends, whenever sterically possible, to follow the diamond lattice; the double bonds (or their equivalents, such as the epoxide groups) have a crossed orientation and the methyl groups a *syn* arrangement.[8] This geometry is also observed very frequently in the crystals,[10-13] as is well illustrated by an *X*-ray diffraction study[14] of a silver complex of germacrene B[15] [Figure (1a)]. The $sp^2$ hybridization at C(7) differentiates the ring system of

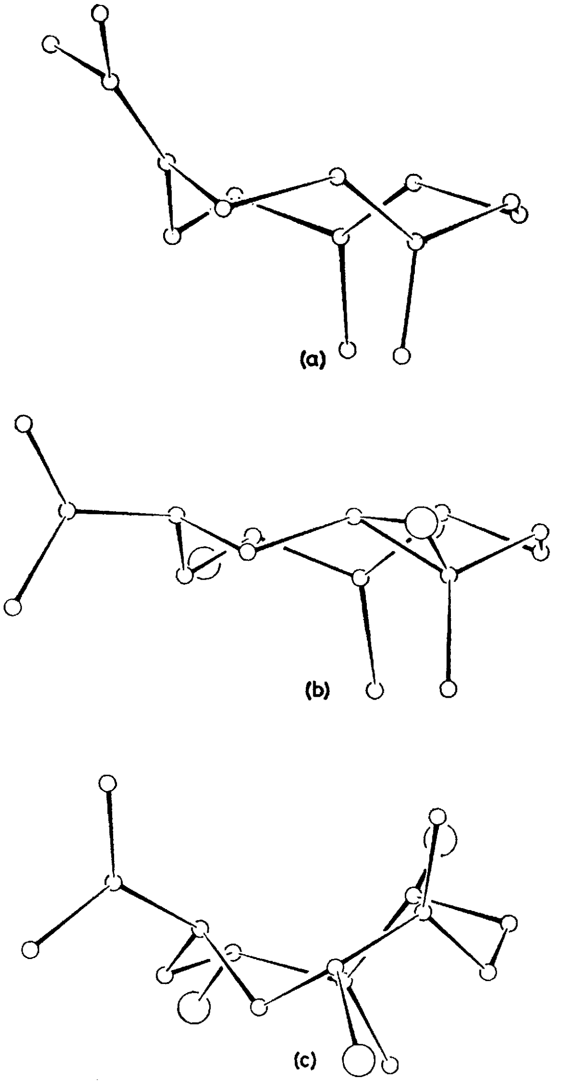


FIGURE 1 Projections of (a) germacrene B, (b) agerol diepoxide, and (c) ageratriol

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[4] F. Bellesia, R. Grandi, A. Marchesini, U. M. Pagnoni, and R. Trave, *Phytochemistry*, 1975, **14**, 1737.

[5] J. D. Dunitz and J. A. Ibers, *Perspectives in Structural Chem.*, 1968, **2**, 21.

[6] L. Pauling, *Proc. Nat. Acad. Sci. U.S.A.*, 1958, **44**, 211.

[7] J. Dale, *Angew. Chem. Internat. Edn.*, 1966, **5**, 1000.

[8] K. Takeda, *Tetrahedron*, 1974, **30**, 1525, and references therein.

[9] K. Tori, I. Horibe, Y. Tamura, K. Kuriyama, H. Tada, and K. Takeda, *Tetrahedron Letters*, 1976, 387.

[10] P. Coggon, A. T. McPhail, and G. A. Sim, *J.Chem. Soc.* (*B*), 1970, 1024.

[11] R. J. McClure, G. A. Sim, P. Coggon, and A. T. McPhail, *Chem. Comm.*, 1970, 128.

[12] S. M. Kupchan, Y. Aynehchi, J. M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *J. Amer. Chem. Soc.*, 1966, **88**, 3674.

[13] H. Hikino, K. Tori, I. Horibe, and K. Kuriyama, *J. Chem. Soc.* (*C*), 1971, 688.

[14] F. H. Allen and D. Rogers, *J. Chem. Soc.* (*B*), 1971, 257.

[15] For a nomenclature of germacratrienes see K. Morikawa and Y. Hirose, *Tetrahedron Letters*, 1969, 1799.

this compound from that of germacrene A (4) of which agerol (1) may be considered the structurally simplest oxygenated derivative so far isolated. Ageratriol (2) represents a derivative of a new type of germacratriene,[16] and its conformational characteristics could not be easily foreseen because suitable molecular models are lacking.

In view of both structural and biogenetic interests, we wished to confirm the conformational hypotheses[3] shown in the Scheme. We therefore carried out $X$-ray diffraction studies of the two chemical constituents of *A. ageratum* which we were able to obtain in crystalline forms suitable for diffractometric analyses, *e.g.*, agerol diepoxide (3) and ageratriol (2).

The geometries thus observed were successively compared with the calculated conformations of the molecules in the isolated state, by means of a molecular mechanics program. In the case of the diepoxide (3) it has also been possible to obtain information on the geometry of the molecule in solution, by n.m.r. studies.

## RESULTS AND DISCUSSION

(*a*) *Agerol Diepoxide.—Molecular geometry.* The arbitrary numbering scheme used throughout the $X$-ray analysis is shown in Figure 2, a diagrammatic view of the molecule.

TABLE 1

Agerol diepoxide (3)

(*a*) Intermolecular distances (Å)

| | | | |
|---|---|---|---|
| O(1)–C(4) | 1.482(5) | C(4)–C(11) | 1.513(9) |
| O(1)–C(5) | 1.463(6) | C(5)–C(6) | 1.503(8) |
| O(2)–C(1) | 1.444(7) | C(6)–C(7) | 1.570(7) |
| O(2)–C(10) | 1.467(8) | C(7)–C(8) | 1.516(7) |
| O(3)–C(9) | 1.457(7) | C(7)–C(13) | 1.527(6) |
| C(1)–C(2) | 1.509(7) | C(8)–C(9) | 1.528(8) |
| C(1)–C(10) | 1.479(9) | C(9)–C(10) | 1.507(6) |
| C(2)–C(3) | 1.536(8) | C(10)–C(12) | 1.504(8) |
| C(3)–C(4) | 1.512(9) | C(13)–C(14) | 1.323(6) |
| C(4)–C(5) | 1.485(5) | C(13)–C(15) | 1.477(9) |

C–H bond range 0.81(3)—1.16(4) Å; O(3)–H, 0.82(3)

(*b*) Bond angles (°)

| | | | |
|---|---|---|---|
| C(4)–O(1)–C(5) | 60.6(5) | C(6)–C(7)–C(8) | 116.0(6) |
| C(1)–O(2)–C(10) | 61.1(5) | C(6)–C(7)–C(13) | 108.5(6) |
| O(2)–C(1)–C(2) | 118.8(6) | C(8)–C(7)–C(13) | 111.7(6) |
| O(2)–C(1)–C(10) | 60.2(5) | C(7)–C(8)–C(9) | 117.5(6) |
| C(2)–C(1)–C(10) | 125.0(5) | O(3)–C(9)–C(8) | 105.7(5) |
| C(1)–C(2)–C(3) | 109.8(6) | O(3)–C(9)–C(10) | 108.7(5) |
| C(2)–C(3)–C(4) | 112.4(6) | C(8)–C(9)–C(10) | 115.5(6) |
| O(1)–C(4)–C(3) | 113.2(5) | O(2)–C(10)–C(1) | 58.7(5) |
| O(1)–C(4)–C(5) | 59.1(6) | O(2)–C(10)–C(9) | 113.1(5) |
| O(1)–C(4)–C(11) | 113.2(5) | O(2)–C(10)–C(12) | 111.9(5) |
| C(3)–C(4)–C(5) | 117.6(6) | C(1)–C(10)–C(9) | 118.1(6) |
| C(3)–C(4)–C(11) | 116.2(5) | C(1)–C(10)–C(12) | 121.8(6) |
| C(5)–C(4)–C(11) | 123.0(6) | C(9)–C(10)–C(12) | 117.4(6) |
| O(1)–C(5)–C(4) | 60.4(5) | C(7)–C(13)–C(14) | 121.3(5) |
| O(1)–C(5)–C(6) | 116.3(6) | C(7)–C(13)–C(15) | 117.6(6) |
| C(4)–C(5)–C(6) | 127.2(6) | C(14)–C(13)–C(15) | 121.2(6) |
| C(5)–C(6)–C(7) | 112.1(6) | | |

(*c*) Contacts <3.55 Å

| | | | |
|---|---|---|---|
| O(1) ··· O(2$^{\mathrm{I}}$) | 3.29(5) | O(1) ··· O(3$^{\mathrm{I}}$) | 2.83(6) |
| O(1) ··· H(19$^{\mathrm{I}}$) | 2.13(6) | | |

Superscript I denotes molecule at $x, y - 1, z$

All bond distances (Table 1) are as expected, although there is a significant shortening from the theoretical value for the C($sp^3$)–C($sp^3$) bond in both epoxide rings [C(5)–C(4) 1.485 (5), C(1)–C(10) 1.479 (9) Å]. However, there are significant distortions from the expected values for the C–C–C angles (Table 1). This fact is in agreement with the angular strains usually observed in medium-sized saturated carbocycles.[17] Excluding angles involving epoxide carbon atoms, the mean C–C–C bond angle is 113.9°, not far from 112.7° as suggested by Bixon and Lifson[18] for a zero-strain bond angle instead of the tetrahedral value.

As far as the endocyclic bond angles involving the epoxide carbon atoms are concerned, there is a remarkable deformation [C(4)–C(5)–C(6) 127.2 (6) and C(2)–C(1)–C(10) 125.0 (5)°]. The same distortions have been found in humulene diepoxide[19] with endocyclic bond angles of 124.6 and 123.5°. In both cases this distortion is connected with the strain caused by the epoxide ring which forces the endocyclic angles to be close to 60°. In the case of atoms C(4) and C(10) the strain is released on orientation of the methyl groups [C(5)–C(4)–C(11) 123.0 (6), C(1)–C(10)–C(12) 121.8 (6)°] which are *cis* with respect to C(6) and C(2) respectively.

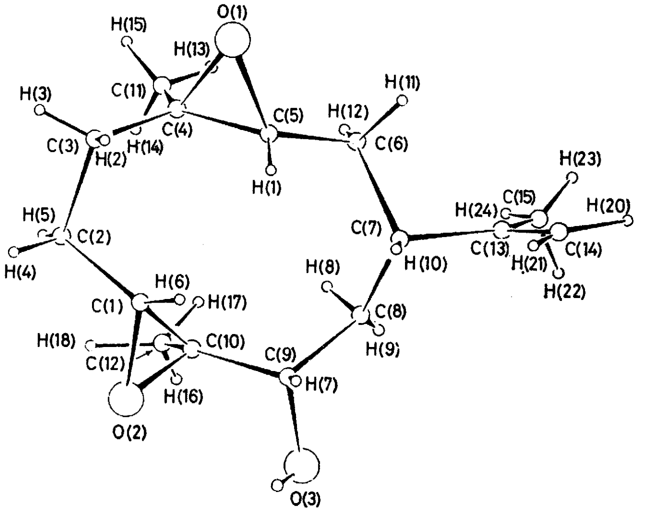

FIGURE 2 Agerol diepoxide (3)

The conformation of this highly substituted cyclodecane ring is described by the torsional angles reported in Figure 3. In Figure 1 are shown the projections of germacrene B along the *trans* double bonds and of agerol diepoxide and ageratriol along the corresponding bonds. The all-*trans* stereochemistry in germacrene B is also observed in the diepoxide, and Figure 3 enables comparison of endocyclic torsion angles. The conformation adopted by the ten-membered ring [idealized in Figure 4(a)] can be obtained from the energetically favoured conformation of cyclodecane [Figure 4(b)], reported by Dunitz and Ibers,[5] by inversion through the III–III

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[16] The recently isolated chrysandiol (T. Osawa, A. Suzuki, S. Tamura, Y. Ohashi, and Y. Sasada, *Tetrahedron Letters*, 1974, 1569) may be related to the same germacratriene type.

[17] F. H. Allen and D. Rogers, *J. Chem. Soc.* (*B*), 1968, 1047.

[18] M. Bixon and S. Lifson, *Tetrahedron*, 1967, **23**, 769.

[19] M. E. Cradwick, P. D. Cradwick, and G. A. Sim, *J.C.S. Perkin II*, 1973, 404.

(using Dunitz formalism) bonds. This is a consequence of the fact that a double bond (or the epoxide ring which has practically the same stereochemical effect) involves a couple of atoms of type III on one side, and one atom of type II and one of type III on the other, thus forcing the torsional angle around II–III to become closer to 180°. The torsion angles around the C–C bonds of the epoxide rings are: C(6)–C(5)–C(4)–C(3) 156.1 and C(2)–C(1)–C(10)–C(9) 152.6°, to be compared with 157 and 153° in humulene diepoxide,[19] and 156° in elephantol *p*-bromobenzoate.[20]

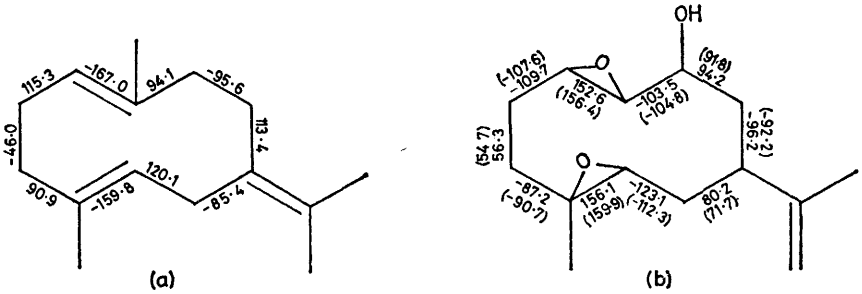

FIGURE 3 Experimental (*X*-ray) torsion angles in (a) germacrene B and (b) agerol diepoxide, with values calculated by the GEMO program in parentheses

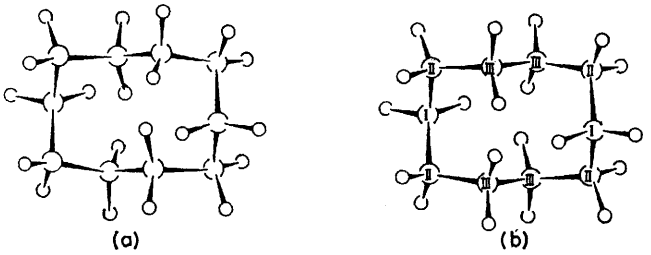

FIGURE 4 (a) Idealized conformation adopted by the ten-membered ring in agerol diepoxide. (b) Energetically favoured[5] conformation of cyclodecane

In this conformation the non-hydrogen substituents occupy the following positions: the epoxide rings, the hydroxy and prop-2-enyl group a semi-equatorial, and the two methyl groups an axial position.

*Discussion of Structure*.—The conformation of agerol diepoxide determined by *X*-ray investigation is characterized by the *syn*-arrangement of the methyl groups and by the crossed orientation of the C(1)–C(10) and C(4)–C(5) bonds; as already mentioned, these geometrical features have been discovered in a variety of germacrane sesquiterpenes, such as germacrene B,[14] elephantol,[20] shiromodiol,[11] and pregejerene.[10] This molecular arrangement agrees fairly well with the stereostructure previously suggested[3] on the basis of the stereospecific transformations (1)→(3)→(2).

The 100 MHz n.m.r. spectrum of agerol diepoxide in $CDCl_3$ shows that this type of conformation is very probably also the one most preferred in solution, at ambient probe temperature. In effect, the coupling constants of the hydrogens at C(1), C(5), and C(9) indicate dihedral angles in good agreement with those observed (Table 2).

This geometry agrees also with the paramagnetic shifts induced by tris(dipivalomethanato)europium(III), $Eu(dpm)_3$. If one supposes that the lanthanide metal ion is localized as shown in Figure 5, *e.g.* in a position intermediate between those of the hydroxy and epoxide oxygen atoms, the values indicated, as defined by Demarco[21] ($\Delta_{Eu} = \delta_{CDCl_3} - \delta^{n=1}_{Eu(dpm)_3}$), fall approximately on a straight line log Δ = *f*(log $r_i$) of slope −3.

TABLE 2

Experimental (*X*-ray) and calculated[a] n.m.r. H–C–C–H angles in agerol diepoxide (3)

| | *X*-Ray[b] | N.m.r. | $J$/Hz |
|---|---|---|---|
| H(6)–H(5) | 155 | 150–160 | 10 |
| H(6)–H(4) | 85 | 65–70 | 1.5 |
| H(1)–H(12) | 155 | 145—155 | 9 |
| H(1)–H(11) | 84 | 65–70 | 1.2 |
| H(7)–H(8) | 146 | 140–150 | 8 |
| H(7)–H(9) | 94 | 115—125 | 3.1 |

[a] Calculated from Newman projections of the Dreiding model. [b] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969.

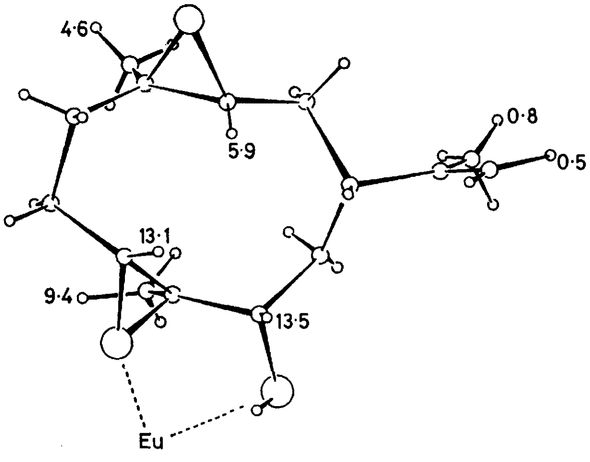

FIGURE 5 Paramagnetic induced shifts in agerol diepoxide

Variable-temperature $^1H$ n.m.r. studies indicate that the molecule exists in solution as one rigid conformer

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[20] A. T. McPhail and G. A. Sim, *J.C.S. Perkin II*, 1972, 1313.

[21] P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, 1970, **92**, 5734.

and inversion of the ten-membered-ring seems not to occur.

The stability of this type of conformation has been checked by a theoretical calculation with a program (GEMO)[22] which uses the Westheimer concepts to calculate the stable conformations of molecules, on the basis of a strain-energy minimization method. Use of this method, as in all search procedures of this type, does not avoid, however, the problem of false minima in multidimensional space; the certainty of having a true minimum depends on the number of initial conformations tried. It has further to be expected that in the case of medium ring systems this problem may be strongly enhanced by the great conformational flexibility. In effect, starting from several initial geometries suggested by examination of Dreiding models, different final conformations, with strain-energy in the range 61.79—81.20 kcal mol$^{-1}$, were obtained. The lower value corresponds to the conformation described by the torsion angles reported in Figure 3 and obtained starting from the geometry determined by *X*-ray. Comparison of the torsion angles in Figure 3 shows the results for the calculated and experimental geometry are very close.

TABLE 3

Strain-energy contributions

| | Germacrene A * | (3) | (2) |
|---|---|---|---|
| Bond str. | 0.475 | 0.851 | 0.492 |
| Angle bend. | 2.457 | 22.282 | 2.110 |
| Torsional strain | 12.200 | 30.941 | 8.252 |
| Non-bonded interaction: | | | |
| H · · · H | 4.317 | 4.408 | 4.949 |
| C · · · H | 2.711 | 2.337 | 4.353 |
| C · · · C | 3.465 | 0.681 | 1.352 |
| H · · · O | | 0.399 | 0.780 |
| O · · · C | | −0.099 | −0.109 |
| O · · · O | | −0.007 | 0.0 |
| Total | 25.625 | 61.793 | 22.180 |

* Calculation based on conformation similar to that found, by *X*-ray diffraction, for the silver complex of germacrene B.

Table 3 gives single contributions to the strain-energy of the molecule. The comparison with the data relative to germacrene A (4) shows that the diepoxide (3) is characterized by strong Bayer and Pitzer strain-energy contributions, which are localized in the epoxide rings.[23]

(*b*) *Ageratriol.—Molecular geometry.* A diagrammatic view of the molecule is shown in Figure 6, together with the numbering scheme used throughout the *X*-ray analysis.

Bond distances and angles are reported in Table 4. The exocyclic double bonds are highly localized [C(4)–C(11) 1.297 (6), C(10)–C(12) 1.312 (5) Å] and the deformations from the $sp^2$ geometry shown by C(4) and C(10) as far as the bond angles are concerned, are rather small [C(3)–C(4)–C(5) 117.2 (6), C(1)–C(10)–C(9) 115.2 (6)°]. Except for the angles involving the trigonal carbon atoms, the mean endocyclic C–C–C angle is 114.2°, slightly higher than the 112.7° predicted by Bixon and Lifson.[18] The conformation of the ring is described by the torsional angles reported in Figure 7.

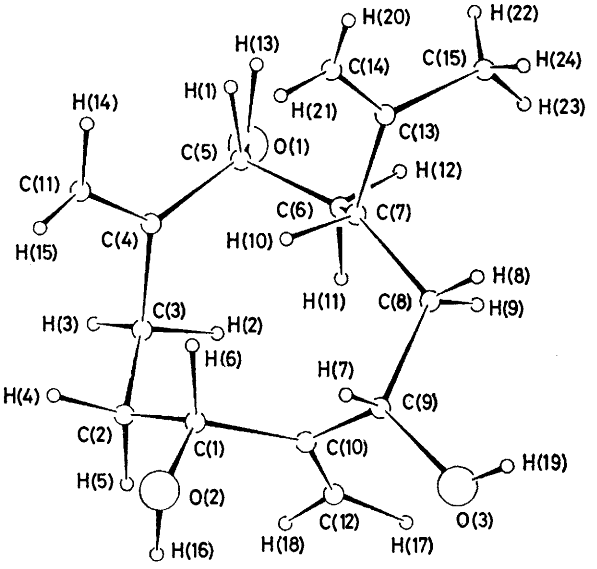

FIGURE 6 Ageratriol (2)

TABLE 4

Ageratriol (2)

| | | | |
|---|---|---|---|
| (*a*) Intermolecular distances (Å) | | | |
| O(1)–C(5) | 1.440(4) | C(5)–C(6) | 1.523(4) |
| O(2)–C(1) | 1.440(4) | C(6)–C(7) | 1.527(5) |
| O(3)–C(9) | 1.429(4) | C(7)–C(8) | 1.543(4) |
| C(1)–C(2) | 1.508(4) | C(7)–C(13) | 1.527(6) |
| C(1)–C(10) | 1.531(4) | C(8)–C(9) | 1.549(5) |
| C(2)–C(3) | 1.558(5) | C(9)–C(10) | 1.525(4) |
| C(3)–C(4) | 1.491(5) | C(10)–C(12) | 1.312(5) |
| C(4)–C(5) | 1.525(4) | C(13)–C(14) | 1.339(6) |
| C(4)–C(11) | 1.297(6) | C(13)–C(15) | 1.487(6) |
| C–H | 0.80(3)—1.17(3) | O–H | 0.97(4)—1.14(4) |
| (*b*) Bond angles (°) | | | |
| O(2)–C(1)–C(2) | 110.5(5) | C(6)–C(7)–C(13) | 112.0(7) |
| O(2)–C(1)–C(10) | 108.6(5) | C(8)–C(7)–C(13) | 112.5(7) |
| C(2)–C(1)–C(10) | 116.6(6) | C(7)–C(8)–C(9) | 115.5(6) |
| C(1)–C(2)–C(3) | 114.3(6) | O(3)–C(9)–C(8) | 108.6(5) |
| C(2)–C(3)–C(4) | 115.2(6) | O(3)–C(9)–C(10) | 109.1(5) |
| C(3)–C(4)–C(5) | 117.2(6) | C(8)–C(9)–C(10) | 113.8(6) |
| C(3)–C(4)–C(11) | 123.0(7) | C(1)–C(10)–C(9) | 115.2(6) |
| C(5)–C(4)–C(11) | 119.9(7) | C(1)–C(10)–C(12) | 122.9(7) |
| O(1)–C(5)–C(4) | 110.6(5) | C(9)–C(10)–C(12) | 121.8(7) |
| O(1)–C(5)–C(6) | 106.7(5) | C(7)–C(13)–C(14) | 121.8(7) |
| C(4)–C(5)–C(6) | 112.3(6) | C(7)–C(13)–C(15) | 118.2(7) |
| C(5)–C(6)–C(7) | 115.3(6) | C(14)–C(13)–C(15) | 119.9(7) |
| C(6)–C(7)–C(8) | 110.2(6) | | |
| (*c*) Contacts <3.55 Å | | | |
| O(1) · · · O($3^{\text{I}}$) | 2.78(1) | O(1) · · · C($1^{\text{III}}$) | 3.39(2) |
| O(1) · · · O($2^{\text{III}}$) | 2.73(1) | O(3) · · · O($2^{\text{II}}$) | 2.75(1) |
| O(1) . . . H($19^{\text{I}}$) | 2.15(4) | O(2) · · · C($12^{\text{IV}}$) | 3.26(2) |

Roman numeral superscripts denote the following equivalent positions:

| | | | |
|---|---|---|---|
| I | $x - \frac{1}{2}, \frac{1}{2} - y, -1 - z$ | III | $x - \frac{1}{2}, \frac{1}{2} - y, -z$ |
| II | $\frac{1}{2} - x, -y, z - \frac{1}{2}$ | IV | $\frac{1}{2} - x, y, \frac{1}{2} + z$ |

In the ten-membered-ring the reciprocal position of the trigonal carbon atoms is 1,5 and, according to

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[22] (*a*) N. C. Cohen, *Tetrahedron*, 1971, **27**, 789; (*b*) R. Bucourt, N. C. Cohen, and G. Lemoine, *Bull. Soc. Chim. France*, 1975, 903.

[23] The cyclopropane has a strain-energy, calculated from heats of combustion, of 27.6 kcal mol$^{-1}$ higher than that for a cyclohexane (N. L. Allinger, M. P. Cava, D. C. De Jongh, C. R. Johnson, N. A. Lebel, and C. L. Stevens, ' Organic Chemistry,' Worth Publishers, Inc., New York, 1971.

Dunitz,[5] the normal conformation should be distorted and an increase in the strain-energy of the system observed. The crystal structure has been already reported of a tetra-substituted 1,1,5,5-cyclodecane, *i.e.* 4,4,8,8-tetramethylcyclodecane-1-carboxylic acid,[24] in which two new conformations were obtained, both present to a different extent in a ' disordered ' structure (Figure 8). Both conformations minimize the calculated strain-energy with minima of 14.0 and 15.0 kcal mol$^{-1}$ respectively for conformations (*A*) and (*B*), compared with 11.9 kcal mol$^{-1}$ for the strain-energy of the stable conformation of cyclodecane. Figure 8 gives a comparison of torsional angles of the structure of ageratriol with those calculated for conformation (*B*). The good agreement is remarkable. The excess strain-energy of 3.1 kcal mol$^{-1}$ relative to the stable cyclodecane conformation can explain the significant increase in the mean C–C–C endocyclic angle. The thermal parameters observed in our structure are all quite normal, so, at least in the solid state, the favoured (*A*) conformation is not present. The non-hydrogen substituents occupy the following positions: the hydroxy groups and the prop-2-enyl group a semi-equatorial and the two methylene groups a quasi-axial position.

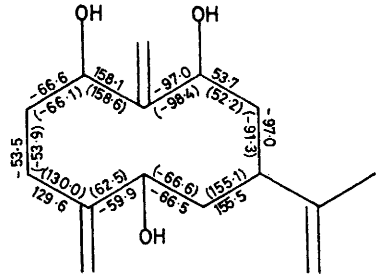
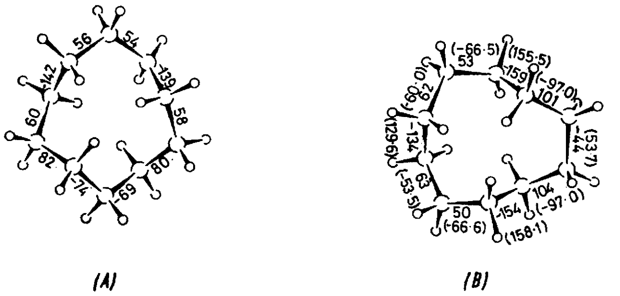


FIGURE 7 Experimental (*X*-ray) torsion angles in ageratriol, with values calculated by the GEMO program in parentheses



(*A*) (*B*)

FIGURE 8 Idealized (*A*) and (*B*) conformations of cyclodecane observed in 4,4,8,8-tetramethylcyclodecane-1-carboxylic acid.[24] Values in parentheses are those for ageratriol (3)

*Discussion of the structure.* The structure of ageratriol determined by *X*-ray diffraction may explain the reactivity of the molecule in solution. Thus the ease with which ageratriol produces a 1,3-acetonide [2] at C(1) and C(9) agrees very well with this crystal molecular structure. The preferred reduction [25] of the double bond at C(4) instead of that at C(10) is also in agreement with this geometry.

The conformational study of the molecule in solution by n.m.r. measurements (using n.o.e. and l.i.s. methods) was rendered problematic by the presence in the molecule of three structurally identical hydroxy groups and by the very small solubility of the compound in suitable solvents; unambiguous results have not been attained.

The stability of the conformation of ageratriol as determined by *X*-ray diffraction was checked, as for agerol diepoxide, by a theoretical calculation using the GEMO program. As no clearly preferred conformations are indicated by the Dreiding models for this molecule, several rather similar initial geometries were tried.

The conformation characterized by the lowest strain-energy (22.18 kcal mol$^{-1}$) was obtained starting from the parameters determined by *X*-ray; torsion angles of the stable form of the isolated molecule are not significantly different (Figure 7) from those determined in the crystal. Starting from different initial conformations, the energies of the final geometries are 3—14 kcal mol$^{-1}$ higher.

It can be seen that the strain-energy values indicated in Table 3 agree very well with the facile conversion of agerol diepoxide into ageratriol.

We consider, in conclusion, that also for many-function cyclodecane compounds, such as the germacrane sesquiterpenes, the experimental and calculated structures agree very well. However, comparisons between *X*-ray diffraction and theoretical methods must not be considered as rigorous. We wish only to indicate that the theoretical procedure may be useful in suggesting stable geometries for this type of molecule, and also in cases where insufficient experimental information is available.

## EXPERIMENTAL

X-*Ray Structure Analysis*.—(*a*) *Agerol diepoxide*. Crystals are colourless prisms, elongated along [0 1 0]. Preliminary cell dimensions and space-group data were obtained from oscillation and Weissenberg photographs. Lattice parameters were refined by least-squares using 14 $(\nu,\chi,\rho)_{hkl}$ measurements taken on a Siemens single-crystal diffractometer.

*Crystal data.* $C_{15}H_{24}O_3$, $M = 252.4$. Monoclinic, $a = 10.28(1)$, $b = 8.23(1)$, $c = 10.05(1)$ Å, $\beta = 123.4(2)°$, $Z = 2$, $D = 1.18$ g cm$^{-3}$, $U = 709.8$ Å$^3$. Cu-$K_\alpha$ radiation, $\lambda = 1.451\,8$ Å; $\mu(\text{Cu-}K_\alpha) = 6.5$ cm$^{-1}$. Space group $P2_1$ from systematic absences.

Intensity data were collected from a crystal 0.21 × 0.67 × 0.12 mm on a Siemens single-crystal diffractometer up to θ 70° by use of the ω—2θ scan method and the five-points technique [26] (nickel-filtered Cu-$K_\alpha$ radiation). Of 1 447 independent reflections measured, 1 349 were used in the crystal analysis, having intensity $>2[\sigma^2(I) + 10^{-4}I^2]^{\frac{1}{2}}$, where $I$ is the relative intensity and $\sigma^2(I)$ its variance. The effects of absorption were ignored.

*Structure analysis and refinement.* Data were put on an absolute scale by Wilson's method [27] and normalized

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[24] J. D. Dunitz and H. Eser, *Helv. Chim. Acta*, 1967, **50**, 1565.

[25] L. Garanti, A. Marchesini, U. M. Pagnoni, and R. Trave, *Tetrahedron Letters*, 1972, 1397.

[26] W. Hoppe, *Acta Cryst.* 1969, **A25**, 67.

[27] A. J. Wilson, *Nature*, 1942, **150**, 151.

structure-factor amplitudes $|E_{hkl}|$ were derived. The structure was solved from 178 reflections with $|E| \geqslant 1.49$. The basic set chosen using the program MULTAN[28] and the starting sets obtained by the phase-permutation technique were used as input to a weighted numerical addition routine.[29] An $E$ map computed by using the most consistent set of phases obtained with the reflections 2 1 − 8, 2 0 − 1, 3 0 − 1, assumed to have phase $\pi/4$ and the reflection 1 6 − 5 assumed to have phase $3\pi/4$, clearly revealed the position of all the atoms in the molecule except hydrogen. A structure-factor calculation carried out at this stage gave $R$ 0.28. The structure was refined by block-diagonal least-squares cycles, first with isotropic and then with anisotropic thermal parameters, reducing $R$ to 0.10. A difference-Fourier synthesis revealed significant residual peaks near the positions where the hydrogen atoms were expected. A few least-squares cycles were then computed, with hydrogen atoms included with isotropic thermal parameters, to give a final $R$ of 0.060.

TABLE 5

Agerol diepoxide (3)

(*a*) Fractional co-ordinates ($\times 10^4$), with standard deviations in parentheses, for non-hydrogen atoms

| | $x$ | $y$ | $z$ |
|---|---|---|---|
| O(1) | −1 690(4) | 1 521(4) | 4 275(4) |
| O(2) | −2 993(5) | 7 941(5) | 2 590(4) |
| O(3) | −2 407(5) | 9 058(5) | 5 735(4) |
| C(1) | −2 615(6) | 6 231(7) | 2 808(5) |
| C(2) | −3 553(6) | 5 095(7) | 1 415(5) |
| C(3) | −2 917(6) | 3 358(8) | 1 902(6) |
| C(4) | −2 897(5) | 2 770(6) | 3 339(6) |
| C(5) | −1 500(5) | 3 151(6) | 4 939(5) |
| C(6) | −1 407(6) | 3 262(7) | 6 482(5) |
| C(7) | −784(5) | 4 959(6) | 7 310(5) |
| C(8) | −1 964(6) | 6 329(7) | 6 666(5) |
| C(9) | −2 018(6) | 7 458(6) | 5 430(5) |
| C(10) | −3 191(6) | 7 014(7) | 3 714(5) |
| C(11) | −4 463(6) | 2 353(9) | 3 059(7) |
| C(12) | −4 873(6) | 6 914(9) | 3 179(7) |
| C(13) | −1(5) | 4 740(7) | 9 103(5) |
| C(14) | 1 534(6) | 4 736(9) | 10 086(6) |
| C(15) | −1 020(7) | 4 539(9) | 9 702(6) |

(*b*) Fractional co-ordinates ($\times 10^3$), with standard deviations in parentheses, for hydrogen atoms

| | $x$ | $y$ | $z$ |
|---|---|---|---|
| H(1) | −58(3) | 381(4) | 501(3) |
| H(2) | −179(3) | 334(4) | 208(3) |
| H(3) | −347(3) | 283(4) | 95(3) |
| H(4) | −343(3) | 540(4) | 53(3) |
| H(5) | −474(3) | 509(4) | 106(3) |
| H(6) | −140(3) | 617(4) | 350(3) |
| H(7) | −93(3) | 755(4) | 555(3) |
| H(8) | −260(3) | 649(4) | 712(3) |
| H(9) | −173(3) | 703(4) | 761(3) |
| H(10) | 21(3) | 517(4) | 727(3) |
| H(11) | −41(3) | 247(4) | 727(3) |
| H(12) | −247(3) | 307(4) | 631(3) |
| H(13) | −433(3) | 200(4) | 394(3) |
| H(14) | −516(3) | 315(4) | 268(3) |
| H(15) | −524(3) | 219(4) | 219(3) |
| H(16) | −516(3) | 768(4) | 349(3) |
| H(17) | −496(3) | 622(4) | 378(3) |
| H(18) | −555(3) | 742(4) | 207(3) |
| H(19) | −201(3) | 959(4) | 527(3) |
| H(20) | 217(3) | 502(4) | 958(3) |
| H(21) | 235(3) | 470(4) | 1 142(3) |
| H(22) | −189(4) | 349(5) | 900(4) |
| H(23) | −72(4) | 419(5) | 1 078(4) |
| H(24) | −203(4) | 475(5) | 901(4) |

Final positional parameters together with their standard deviations are given in Table 5.

(*b*) *Ageratriol.* Crystals are colourless plates with the least dimensions in the [1 0 0] direction. Cell parameters were derived as before and lattice parameters refined from a set of 15 $(\theta, \chi, \rho)_{hkl}$ measurements.

TABLE 6

Ageratriol (2)

(*a*) Fractional co-ordinates ($\times 10^4$), with standard deviations in parentheses, for non-hydrogen atoms

| | $x$ | $y$ | $z$ |
|---|---|---|---|
| O(1) | −959(2) | 3 568(1) | −1 984(3) |
| O(2) | 3 034(2) | 726(1) | −636(2) |
| O(3) | 2 928(2) | 850(1) | −5 289(3) |
| C(1) | 2 138(3) | 1 323(2) | −1 169(3) |
| C(2) | 1 058(3) | 1 361(2) | −52(4) |
| C(3) | 132(3) | 2 078(2) | −390(4) |
| C(4) | 692(3) | 2 921(2) | −469(3) |
| C(5) | 359(3) | 3 456(2) | −1 883(4) |
| C(6) | 766(3) | 3 066(2) | −3 426(3) |
| C(7) | 2 162(3) | 3 000(2) | −3 661(3) |
| C(8) | 2 465(3) | 1 296(2) | −4 825(4) |
| C(9) | 2 793(3) | 1 451(2) | −4 070(3) |
| C(10) | 1 836(3) | 1 144(2) | −2 891(3) |
| C(11) | 1 452(5) | 3 201(3) | 582(5) |
| C(12) | 873(3) | 708(2) | −3 329(4) |
| C(13) | 2 733(4) | 3 826(3) | −4 148(4) |
| C(14) | 3 619(4) | 4 191(3) | −3 297(5) |
| C(15) | 2 334(5) | 4 200(3) | −5 661(5) |

(*b*) Fractional co-ordinates ($\times 10^3$), with standard deviations in parentheses, for hydrogen atoms

| | | | |
|---|---|---|---|
| H(1) | 79(3) | 404(2) | −172(3) |
| H(2) | −31(3) | 201(2) | −148(3) |
| H(3) | −47(3) | 211(2) | 43(3) |
| H(4) | 138(3) | 150(2) | 105(3) |
| H(5) | 62(3) | 79(2) | −6(3) |
| H(6) | 250(3) | 192(2) | −114(3) |
| H(7) | 361(3) | 152(2) | −347(3) |
| H(8) | 322(3) | 247(2) | −556(3) |
| H(9) | 174(3) | 226(2) | −555(3) |
| H(10) | 257(3) | 280(2) | −258(3) |
| H(11) | 39(3) | 247(2) | −344(3) |
| H(12) | 47(3) | 337(2) | −436(3) |
| H(13) | −61(3) | 423(2) | −213(3) |
| H(14) | 135(3) | 354(2) | 126(3) |
| H(15) | 236(3) | 310(2) | 49(3) |
| H(16) | 258(3) | 21(2) | −55(3) |
| H(17) | 35(3) | 49(2) | −446(3) |
| H(18) | 30(3) | 46(2) | −252(3) |
| H(19) | 358(3) | 106(2) | −607(3) |
| H(20) | 349(3) | 458(2) | −233(3) |
| H(21) | 450(3) | 398(2) | −323(3) |
| H(22) | 279(3) | 467(2) | −504(3) |
| H(23) | 254(3) | 420(2) | −678(3) |
| H(24) | 140(3) | 439(2) | −555(3) |

*Crystal data.* $C_{15}H_{24}O_3$, $M = 252.4$. Orthorhombic, $a = 10.82(1)$, $b = 16.14(1)$, $c = 8.52(1)$ Å, $U = 1\,487.9$ Å$^3$, $Z = 4$, $D_m = 1.13$ g cm$^{-3}$. Cu-$K_\alpha$ radiation, $\lambda = 1.541\,8$ Å; $\mu(\text{Cu-}K_\alpha) = 6.2$ cm$^{-1}$. Space group $P2_12_12_1$ from systematic absences.

Intensity data were collected as before from a crystal 0.43 × 0.10 × 0.71 mm. Of 2 894 independent reflections measured, 54 were not used in the crystal analysis. Absorption effects were neglected.

*Structure analysis and refinement.* 204 reflections with $|E| \geqslant 1.47$ were used to solve the structure by direct methods. The most consistent set of phases derived from the basic set gave phase $\pi/2$ for the reflections 9 5 0 and 5 4 0, $\pi/4$ for the reflections 2 1 1 and 5 3 6, $3\pi/2$ for 5 10 0,

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[28] P. Main, M. M. Woofson, and G. Germain, MULTAN, 1971, University of York.

[29] G. D. Andreetti, VIth Meeting Italian Cryst. Assocn., 1973, Trieste, Italy.

π for 0 18 0, 5π/4 for 4 4 4. This set was used to compute an *E* map which revealed the whole structure. A structure-factor calculation based on the co-ordinates derived from the *E* map gave *R* 0.29. Refinement was carried out by means of cycles of block-diagonal least-squares first isotropically and then anisotropically until *R* was 0.098. A difference-Fourier synthesis was then computed and revealed significant residual peaks interpreted as hydrogen atoms position. All atom parameters were then refined (heavy atoms anisotropically and hydrogen atoms isotropically). The final value of *R* was 0.069. Final positional parameters together with their standard deviations are reported in Table 6.

The atomic scattering factors used for both crystal analyses were taken from ref. 30 for oxygen and carbon, and from ref. 31 for hydrogen.

For both compounds, observed and calculated structure factors and thermal parameters are listed in Supplementary Publication No. SUP 22119 (23 pp., 1 microfiche).*

*N.m.r. Analysis.*—The l.i.s. measurements on agerol diepoxide ($1.4 \times 10^{-4}$ mol in 0.4 ml of $CDCl_3$) were effected on a JEOL JNM C 60 HL spectrometer, with increasing concentration of $Eu(dpm)_3$ up to a molar ratio of metal complex–solute of 0.45. By extrapolating the straight lines to the point where the molar ratio is one ($n = 1$), the $\Delta_{Eu}$ values, as defined by Demarco,[21] were determined. The 100 MHz spectrum was recorded on a JEOL JNM PFT 100 instrument, using tetramethylsilane as internal standard.

*Strain-energy Minimization Procedure.*—The GEMO calculations were carried out on a CY 7600 computer (of CINECA, Centro Interuniversitario di Calcolo dell'Italia Nord-Orientale), using the program described by Cohen.[22] The molecules required (in media) 1—2 min of computer time. Force constant values were taken, unless indicated otherwise, from ref. 22*b* and from 'GEMO 802A' edited by the Centre de Recherches Roussel-Uclaf, Romainville, France.

TABLE 7

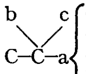
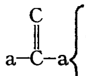
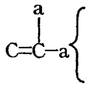
Energy functions and parameters used in the strain-energy program

(*a*) Bond stretching $E(l) = K_1(l-l_0)^2$

| | $l_0$/Å | $K_1$/kcal mol$^{-1}$ Å$^{-2}$ |
|---|---|---|
| $C(sp^3)-C(sp^3)$ | 1.533 | 300 |
| $C(sp^2)-C(sp^3)$ | 1.505 | 300 |
| $C(sp^2)=C(sp^2)$ | 1.331 | 640 |
| $C(sp^3)-H$ | 1.108 | 300 |
| $C(sp^2)-H$ [a] | 1.090 | 300 |
| $C(sp^3)-O$ [b] | 1.416 | 350 |
| O–H [b] | 0.952 | 500 |
| $C(sp^3)-C(sp^3)$(epoxide) [c] | 1.472 | 188 |
| $C(sp^3)$–O(epoxide) [c] | 1.436 | 265 |
| $C(sp^3)$–H(epoxide) [c] | 1.082 | 314 |

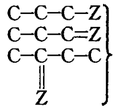
TABLE 7 (*Continued*)

(*b*) Angle bending $E(\theta) = K_\theta(\theta-\theta_0)^2$, for $\Delta\theta \leqslant 5.5°$

| | a | b | c | $\theta_0$/(°) | $K_\theta$/kcal mol$^{-1}$ deg$^{-2}$ |
|---|---|---|---|---|---|
|  | C | H | H | 112.4 | 0.025 00 * |
| | C | H | R | 111.0 | 0.017 51 |
| | C | R | R | 109.5 | 0.017 51 |
| | H | H | H | 110.1 | 0.057 18 * |
| | H | R | R | 107.9 | 0.012 06 |
|  | C | | | 112.0 | 0.018 87 |
| | H [d] | | | 122.4 | 0.012 05 |
|  | C | | | 124.0 | 0.028 30 |
| | H [d] | | | 118.8 | 0.014 45 |
| C–O–H [b] | | | | 95.2 | 0.016 64 |
| C–O–C (epoxide) [c] | | | | 63.3 | 0.582 00 |
| C–C–O (epoxide) [c] | | | | 59.2 | 0.681 00 |

(*c*) Torsion energy

(*i*) Around a single bond $E(\phi) = q\,[1 + \cos n\,(|\phi| + s\,†)]$



(Z = C or O)

| | $q$/kcal mol$^{-1}$ |
|---|---|
| C–C–C–Z | 1.70 |
| C–C–C=Z | 0.99 |
| C–C–C–C (=Z on second C) | 0.40 |

(*ii*) Around a double bond $E(\phi) = a\,[|\phi| - t]^2$

C–C=C–C $a = 26.2$ kcal mol$^{-1}$ rad$^{-2}$

(*d*) Non-bonded interactions $E(\text{nb}) = (A/d^9) - (B/d^6)$

| | $A$/kcal Å$^9$ | $B$/kcal Å$^6$ |
|---|---|---|
| H · · · H | 730.2 | 15.3 |
| C · · · H | 3 689.0 | 56.8 |
| C · · · C | 17 090.0 | 199.0 |
| O · · · H | 3 015.0 | 56.9 |
| O . · · C | 14 450.0 | 199.1 |
| O · · · O | 12 107.0 | 199.3 |

[a] N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, 1972, **94**, 5734. [b] N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, 1969, **91**, 337. [c] T. Hirokawa, *J. Sci. Hiroshima University*, 1975, **39**, 161. [d] N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, 1968, **90**, 5773.

* Global constant for the bending of all valency angles around the central atom.

† *s* is used for making $E(\phi) = 0$ for the $\phi_0$ value at equilibrium.

Energy functions and parameters used in the strain-energy computer program listed in Table 7.

[7/891 *Received*, 23*rd May*, 1977]

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* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1977, Index issue.

[30] D. T. Cromer and J. B. Mann, *Acta Cryst.*, 1968, **A24**, 321.

[31] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.