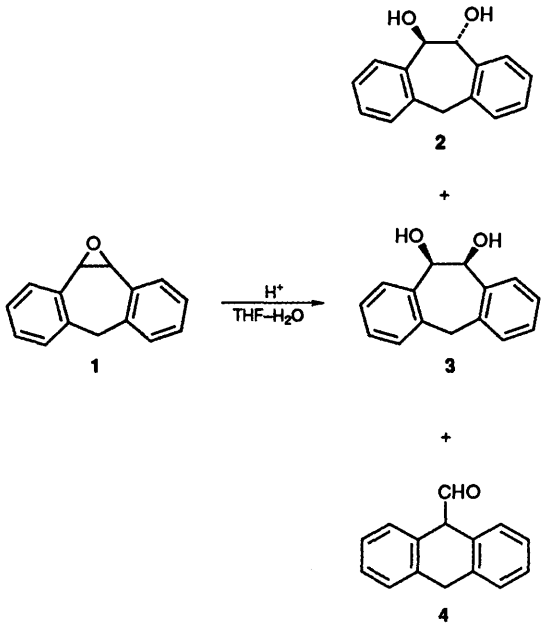
Reactivity and Crystal Structure of 10,11-Dihydro-10,11-epoxy-5*H*-dibenzo[*a*,*d*]cycloheptene. A Comparison with *cis*-Stilbene Oxide

Giuseppe Bellucci,*[a] Cinzia Chiappe,[a] F. Marioni[a] and Riccardo Spagna[b]
[a] *Dipartimento di Chimica Bioorganica, Università di Pisa, 56126 Pisa, Italy*
[b] *Istituto di Strutturistica Chimica 'Giordano Giacomello' del CNR, Monterotondo Stazione, Roma, Italy*

The kinetics and product distributions for the $HClO_4$ catalysed hydrolysis of 10,11-dihydro-10,11-epoxy-5*H*-dibenzo[*a*,*d*]cycloheptene **1** and of *cis*-stilbene oxide **6** in tetrahydrofuran–water (8:2), have been investigated by HPLC. The former epoxide gives 9,10-dihydroanthracene-9-carbaldehyde **4** and the *trans*- and *cis*-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-10,11-diols, **2** and **3**, in the ratio 6:6:1. *cis*-Stilbene oxide reacts with a rate constant *ca.* ten times lower, giving mostly (±)-1,2-diphenylethane-1,2-diol. These differences can be explained by the crystal structure of **1**, which shows considerable ring strain due to the enlargement of the bond angles at C(10) and C(11). This structure also suggests an explanation for the much lower rate of the microsomal epoxide hydrolase catalysed hydration of **1** relative to **6**.

In the course of investigations on the metabolic transformations of dibenzo-condensed seven-membered cyclic alkenes such as 5*H*-dibenz[*b*,*f*]azepine[1] and 5*H*-dibenzo[*a*,*d*]cycloheptene,[2,3] whose parent structures are present in several important central nervous system drugs,[4] we found that the epoxides formed by oxidation of the 10,11-double bond exhibit an unusual resistance to enzymatic hydrolysis to the corresponding 10,11-*trans*-dihydrodiols, in contrast with the behaviour of the structurally related *cis*-stilbene oxide. On the other hand, 5*H*-dibenz[*b*,*f*]azepine 10,11-oxide derivatives without strongly electron-withdrawing substituents at nitrogen are known[1,5–7] to undergo facile acid-catalysed oxirane ring opening, giving mainly acridane and acridine products resulting from a seven-membered ring contraction.

In the present paper we report on the similar behaviour of 10,11-dihydro-10,11-epoxy-5*H*-dibenzo[*a*,*d*]cycloheptene **1** under acidic conditions, *i.e.* behaviour at variance with that of *cis*-stilbene oxide **6**. Furthermore, a rationalization for the observed rates and product differences between the acid-catalysed ring opening of **1** and **6**, as well as for the differences in the acid catalysed and epoxide hydrolase catalysed hydrolysis of **1**,[3] based on an X-ray diffraction study of the latter epoxide, is proposed.



Results and Discussion

Freshly prepared,[2] colourless crystals of epoxide **1** exposed to air in daylight slowly turned yellow, and HPLC analysis revealed the formation of anthracene-9-carbaldehyde—responsible for the colour—and anthracene. This epoxide was stable in tetrahydrofuran (THF)–water at neutral pH and 25 °C for at least 10 h, but in the presence of $HClO_4$ comparable amounts of 9,10-dihydroanthracene-9-carbaldehyde **4** and *trans*-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-10,11-diol **2**,[8] in addition to a much smaller amount of the *cis*-10,11-dihydrodiol **3**,[8] were rapidly formed. It was shown that both these dihydrodiols were stable under the reaction conditions, so that aldehyde **4** was actually a primary reaction product. This was identified by comparison of the HPLC retention time and of the NMR signals with an authentic sample obtained by a BF_3-Et_2O induced rearrangement of **1**, occurring with seven-membered ring contraction. Although this sample appeared to be >95% pure by NMR spectroscopy, it showed several additional HPLC peaks, due to very small amounts of highly UV absorbing by-products, two of which were again identified as anthracene-9-carbaldehyde and anthracene. Attempts at purifying **4** both by column chromatography, TLC or by crystallization always resulted in the formation of anthracene, the loss of formaldehyde probably being favoured by formation of the aromatic system. A full purification and characterization was instead easily achieved by crystallization following reduction of the formyl group to the stable alcohol **5**.

The rates and the product distributions of the $HClO_4$-catalysed oxirane ring-opening of **1**, and, for comparison

Table 1. Product distribution for the $HClO_4$ catalysed oxirane ring opening of 0.1 mol dm^{-3} 10,11-dihydro-10,11-epoxy-5*H*-dibenzo-[*a*,*d*]cycloheptene **1** and 0.2 mol dm^{-3} *cis*-stilbene oxide **6** in THF–water (8:2) at pH 2.5 and 25 °C.

	Products (%)								
t/h	**1**[a]	**2**[a]	**3**[a]	**4**[a]	**6**[b]	**7**[b]	**8**[b]	**9**[b]	**10**[b]
2	71	12.5	2	14.5	97	2.5	0.3	0.2	0.05
3	58.5	18.5	3	20	95.5	3.5	0.6	0.3	0.1
4	49	23	4	24	94	4.7	0.7	0.35	0.12
5	41.5	27	4.5	27	93	5.5	0.8	0.4	0.14
6	33	30	5	32	92	6.5	1.0	0.5	0.17
7	28.5	32	5.5	34	91	7.3	1.2	0.55	0.18
8	26	33	6	35	89.5	8.3	1.3	0.65	0.2

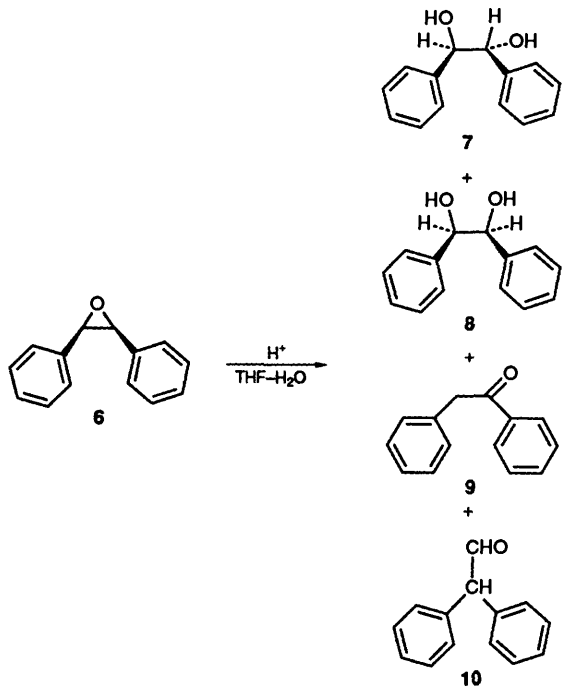
[a] Averages of triplicate runs with epoxide **1**. The estimated error is <2% of the quoted figures for **1**, <5% for **2** and **4**, and <10% for **3**. [b] Averages of triplicate runs with epoxide **6**. The estimated error is <2% of the quoted figures for **6**, <5% for **7**, and <10% for **8**–**10**.

purposes, of the acyclic analogue *cis*-stilbene oxide **6**, were investigated in THF–water (8:2) containing $HClO_4$ at pH 2.5 and 25 °C, using HPLC. Samples were withdrawn at intervals, neutralized by addition of solid calcium carbonate, and analysed after addition of *cis*-1-(*p*-methylphenyl)cyclohexane-1,2-diol[9] as a standard for the quantification of the unreacted epoxide and of the products. In the reaction of epoxide **1**, in addition to the main peaks corresponding to products **2**–**4**, several small peaks appeared with increasing reaction time, two of which corresponded to anthracene-9-carbaldehyde and anthracene. These products amounted to no more than 1% of the total products. At the end of the reaction the 300 MHz spectrum of the crude mixture showed only the signals of aldehyde **4** and of the *trans*- and *cis*-dihydrodiols **2** and **3** in the ratio *ca.* 6:6:1. This allowed us to exclude the formation of products other than **2**–**4** in detectable amounts, confirming that the additional HPLC peaks were actually due to trace amounts of by-products with high UV absorptions.

The average distributions of products **2**–**4**, determined at several times during the course of triplicate runs for the reactions of 0.1 mol dm^{-3} **1**, are given in Table 1. Direct HPLC determination of aldehyde **4** was difficult because of the difficulty of obtaining a sample sufficiently pure to allow a determination of its calibration curve relative to the added standard without interference from partially overlapping peaks due to impurities. The amounts of **4** reported in Table 1 were thus evaluated by measurement of the difference between the starting epoxide **1** and the sum of unreacted **1** and dihydrodiols **2** and **3** formed. The values obtained were found to be linearly related to the areas of the peak attributed to **4**. The validity of this evaluation was confirmed by the above-mentioned NMR spectroscopic analysis after complete reaction. The observed trace amounts of anthracene-9-carbaldehyde and anthracene are not quoted in Table 1.

Four products were detected, in addition to the unreacted epoxide **6**, in runs using *cis*-stilbene oxide (Table 1). The (±)-diol **7**, arising by *anti*-ring opening, was by far the main product, accompanied by a *ca.* ten times smaller quantity of the *meso*-diol **8** and by two rearranged carbonyl products, deoxybenzoin **9** and diphenylacetaldehyde **10**, in amounts that never exceeded 6 and 2% of the total ring opening products, respectively. Furthermore, under identical conditions, the reaction of *cis*-stilbene oxide was much slower than that of epoxide **1**, *ca.* 90% of unreacted **6** (as compared with only 26% of unreacted **1**) found after 8 h.

The data of Table 1 were used to evaluate the kinetic constants for the ring opening of epoxides **1** and **6**. In the case of **1** the disappearance of the epoxide cleanly obeyed the integrated



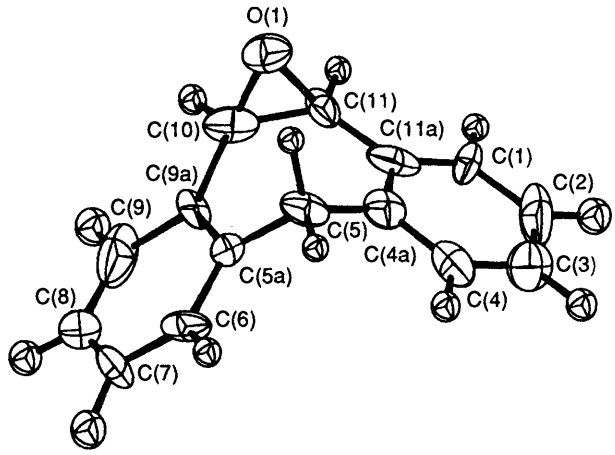


Fig. 1. The X-ray crystal structure of **1**.

first-order rate law of eqn. (1), with $k_1 = 2.9(0.1) \times 10^{-3}$ min^{-1}.

$$\ln[\text{epoxide}] = k_1 t + \ln[\text{epoxide}]_0 \qquad (1)$$

In the case of **6** the reaction was too slow to be followed for at least one half life without the interference of slow side reactions involving the primarily formed products. The value of k_1 was therefore evaluated, on the basis of the reasonable assumption of the same rate law found for the reaction of **1**, using the initial rate method. A value of k_1 $2.3(0.1) \times 10^{-4}$ min^{-1}, or a half life of 3.7×10^3 min, was thus obtained. The comparison of these two k_1 values shows that closure of the seven-membered ring by a methylene bridge to form the tricyclic compound **1** has the effect of increasing the ring-opening rate of *cis*-stilbene oxide by one order of magnitude. Furthermore, this rate increase is accompanied by a much more abundant formation of carbonylic rearrangement products, indicating an extensive incursion of carbonium ion intermediates in the opening of **1**.

A reason for the observed differences in rates and products of ring opening of epoxides **1** and **6** was sought in the molecular structure obtained by X-ray diffraction of **1**. A perspective drawing of compound **1** is shown in Fig. 1. Final atomic

Table 2. Atomic coordinates for structure **1** (esds in parentheses).

	x	*y*	*z*
O(1)	0.574 1(4)	0.616 2(6)	0.0000
C(1)	0.288(2)	0.676(2)	0.146 3(9)
C(2)	0.194(1)	0.584(3)	0.188 6(8)
C(3)	0.145(1)	0.388(3)	0.170 8(8)
C(4)	0.200(1)	0.283(2)	0.110 7(8)
C(4a)	0.294(1)	0.396(2)	0.065 0(7)
C(5)	0.346 7(6)	0.280 0(8)	0.000(1)
C(5a)	0.298(1)	0.387(1)	−0.063 8(8)
C(6)	0.192(1)	0.295(2)	−0.107 1(8)
C(7)	0.145(1)	0.375(2)	−0.167 5(9)
C(8)	0.198(2)	0.573(2)	−0.184 0(7)
C(9)	0.298(1)	0.687(2)	−0.140 4(8)
C(9a)	0.345(1)	0.607(1)	−0.081 9(8)
C(10)	0.447(1)	0.727(2)	−0.037 0(7)
C(11)	0.458(1)	0.712(1)	0.037 2(8)
C(11a)	0.347 9(9)	0.583(1)	0.081 7(7)

Table 3. Relevant bond lengths/Å and angles/° for structure **1** (esds in parentheses).

O(1)–C(10)	1.49(1)	C(5a)–C(9a)	1.50(1)
O(1)–C(11)	1.38(1)	C(9a)–C(10)	1.46(2)
C(4a)–C(5)	1.54(2)	C(10)–C(11)	1.46(2)
C(4a)–C(11a)	1.33(1)	C(11)–C(11a)	1.53(2)
C(5)–C(5a)	1.49(2)		
C(11)–O(1)–C(10)	61.0(8)	C(11)–C(10)–O(1)	55.9(6)
C(11a)–C(4a)–C(5)	122.5(10)	C(11)–C(10)–C(9a)	127.3(10)
C(5a)–C(5)–C(4a)	113.0(7)	C(10)–C(11)–O(1)	63.2(8)
C(9a)–C(5a)–C(5)	123.7(10)	C(11a)–C(11)–O(1)	120.5(7)
C(10)–C(9a)–C(5a)	120.6(10)	C(11a)–C(11)–C(10)	124.4(9)
C(9a)–C(10)–O(1)	119.0(8)	C(11)–C(11a)–C(4a)	124.3(10)

Table 4. Equations of least-squares best planes referred to the crystal axes and distances /Å of relevant atoms from the planes.[a]

Plane A $6.744\,33x - 2.463\,35y + 9.496\,67z = 1.665\,10$

C(1)*	=	0.001
C(2)*	=	−0.001
C(3)*	=	−0.018
C(4)*	=	0.038
C(4a)*	=	−0.040
C(11a)*	=	0.020
C(5)	=	−0.015
C(10)	=	−0.793
C(11)	=	0.019

Plane B $6.757\,09x - 2.530\,56y - 9.280\,80z = 1.579\,46$

C(5a)*	=	0.044
C(6)*	=	−0.036
C(7)*	=	0.006
C(8)*	=	0.013
C(9)*	=	−0.001
C(9a)*	=	−0.026
C(5)	=	0.052
C(10)	=	−0.057
C(11)	=	−0.635

Plane C $-7.329\,19x - 3.330\,07y + 0.010\,28z = -3.473\,31$
defined by C(4a), C(5) and C(5a)

Plane D $-4.578\,67x - 5.412\,46y - 0.380\,17z = -5.963\,75$
Defined by O(1), C(10) and C(11)

[a] An asterisk * refers to atoms which define the plane.

coordinates with standard deviations are listed in Table 2. Interatomic bond lengths and angles for the fused oxirane and seven-membered rings are reported in Table 3. The resulting oxirane ring was asymmetrical, the two O–C bonds being of significantly different lengths: 1.38(1) and 1.49(1) Å for O(1)–C(10) and O(1)–C(11), respectively, by comparison with a mean value for sp^3 C–O in oxirane systems of 1.44 Å.[10] The bond angles at the oxirane carbons, C(10)–C(11)–C(11a) and C(9a)–C(10)–C(11), had respective values of 124(1) and 127(1)°, considerably larger—especially the latter—than that found in *p*-nitrostyrene oxide (121.7°)[11] and in several epoxides having an oxirane ring fused to a benzo-substituted six-membered ring.[12–14] In particular, phenanthrene 9,10-oxide, which can be considered as an unstrained model for epoxide **1**, has internal angles at the oxirane carbons of 118.9 and 119°.[12] Furthermore, in **1** the C(9a)–C(10)–O(1) and O(1)–C(11)–C(11a) angles, having values of 119.0(8) and 120.5(7)°, respectively, were consistently larger than in other epoxides investigated,[13] including phenanthrene 9,10-oxide, where the pertinent angles are *ca.* 115.5°.[12]

In Table 4 are reported the equations of the best planes of relevant planar groups of the molecule. The angles of intersection of planes A and B, A and C, B and C were 122.8, 61.9 and 62.2°, respectively. Comparison of these data with the average parameters reported for related structures[15] shows a substantial agreement. The values of torsion angles C(9a)–C(10)–C(11)–C(11a), C(9)–C(9a)–C(10)–C(11) and C(10)–C(11)–C(11a)–C(1) were −7.4, 151.8 and −136.8°, respectively, confirming a quite unsymmetrical conformation of the molecule. The lines through atoms C(4a) and C(11a) and through atoms C(5a) and C(9a) formed an angle of 28.4° and the distance between the barycentres of the benzene rings was 4.93 Å. These values are very similar to those, 28.1° and 4.936 Å, reported for 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclopentene.[16] The seven-membered ring may be described as a boat, the C(5), C(10) and C(11) atoms being on the same side of the best plane through the atoms C(5a), C(9a), C(11a), C(4a), with distances of 0.64, 0.56 and 0.67 Å, respectively. Atoms C(9a), C(10), C(11) and C(11a) were coplanar within 0.030 Å and the dihedral angle between this plane and that of the oxirane ring, D, was 73°, while the angles between planes A and D, B and D, were 96 and 94°, respectively. The line through atoms O(1) and C(10) formed with the plane of the benzo ring C(9a),C(5a),C(6),-C(7),C(8),C(9) an angle of 32°; the line through O(1) and C(11) formed with the C(11a),C(4a),C(4),C(3),C(2),C(1) plane an angle of 29°.

The present data show unequivocally that of the two possible conformations of **1** with a quasi-axial or quasi-equatorial oxirane ring, which can be interconverted through ring inversion by torsion around the C(4a)–C(5)–C(5a) bonds, the former is adopted in the solid state.[17] The existence of a very low or a very higher barrier to inversion, or the presence of a highly dominant conformer in solution had been inferred[18] by a variable temperature NMR study of **1**, showing no spectral change between −90 and +140 °C. We have confirmed this observation for a $CDCl_3$ solution, in which the NMR spectrum, exhibiting a singlet at δ 4.25 for the oxirane protons and an AB quartet centred at δ 3.30 and 5.15 for the protons at C(5), remained unchanged between −50 and +30 °C. Mild support for a conformation with a quasi-equatorial epoxide ring was inferred[18] by NOE measurements for the 2-methoxy derivative of **1**. This was, however, in contrast with a previous report concerning the 5-hydroxy derivative,[19] for which a quasi-axial orientation of both the hydroxy group and the epoxide ring was suggested by the presence of an intramolecular hydrogen bond and by the high value of $J_{H\text{-}C\text{-}O\text{-}H}$.

The most relevant feature of the molecular structure of **1** is the enlargement of the bond angles at C(10) and C(11), producing a considerable ring strain at the bridgehead carbons. This strain, increasing the ground state energy of **1**, may be responsible for

an easier C–O bond breaking of the protonated epoxide, resulting in a faster reaction with respect to *cis*-stilbene oxide, and giving an α-hydroxy carbonium ion which is equally partitioned between attack by water to give the dihydrodiols **2** and **3** and ring restriction to give the six-membered ring formyl derivative **4**. The driving force for the latter process should again be the relief of the angle strain present in the seven-membered ring. This is consistent with the much lesser rearrangement to carbonyl products in the acid-catalysed ring opening of the unstrained *cis*-stilbene oxide.

Microsomal epoxide hydrolase is known[20] to promote oxirane ring opening by a general base-catalysed mechanism not involving oxirane oxygen protonation. Only *anti* addition of water, with the exclusion of any seven-membered ring contraction, must therefore be expected, and is actually found,[2,3] in the enzyme reaction. Its low rate relative to *cis*-stilbene oxide, in spite of the similarly low K_m values of these two substrates,[3] is thus probably due to a more difficult S_N2 type attack by water at the oxirane carbons of **1**. If **1** is accommodated in the enzyme-active site in the same conformation as that found in the solid state, this difficulty could be due (in addition to ring-strain effects possibly present in the diol product **3**),[3] to steric hindrance by the benzo groups, and in particular by the hydrogen atoms at C(1) and C(9), which opposes nucleophilic attack colinear to the breaking C–O bond.[21,22] This is supported by the low values of the angles formed by the orientation of the C–O bonds with respect to the planes of the adjacent benzo rings.

Experimental

^{1}NMR spectra were recorded on a Bruker AC-200 and a Varian XR 300 instrument using TMS as internal standard. IR spectra were determined with a Pye Unicam SP3-300 spectrophotometer. HPLC analyses were carried out with a Pye Unicam PU 4010 apparatus equipped with an UV PU 4020 detector.

Materials.—10,11-Dihydro-10,11-epoxy-5*H*-dibenzo[*a*,*d*]-cycloheptene **1**,[2,18] *trans*- and *cis*-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cycloheptene-10,11-diol **2** and **3**,[8] and the 1,2-diphenylethane-1,2-diols **7** and **8**[3] were prepared as reported. *cis*-Stilbene oxide (Aldrich), anthracene (Fluka), anthracene-9-carbaldehyde (Fluka) and deoxybenzoin (Aldrich) were commercial products. Diphenylacetaldehyde was obtained by BF_3·Et_2O promoted rearrangement of *trans*-stilbene oxide (Fluka) in anhydrous dichloromethane at room temperature, as described below for 9,10-dihydroanthracene-9-carbaldehyde, followed by distillation, b.p. 200 °C/2.5 mmHg. Anhydrous dichloromethane (Fluka) was used as such. THF (C Erba) was distilled before use.

9,10-*Dihydroanthracene*-9-*carbaldehyde* **4**.—BF_3·Et_2O (0.06 cm^3, 0.5 mmol) was added to a solution of **1** (0.04 g, 0.19 mmol) in anhydrous dichloromethane (4 cm^3) under an argon atmosphere. The mixture was allowed to stand at room temperature for 30 min before being washed with aqueous saturated $NaHCO_3$. Evaporation of the dried ($MgSO_4$) organic layer under reduced pressure yielded aldehyde **4** (0.35 g). δ_H($CDCl_3$): 3.95 (d, *J* 19 Hz, 1 H, CH_2), 4.10 (d, *J* 19 Hz, 1 H, CH_2), 4.85 (d, *J* 2.4 Hz, 1 H, C*H*CHO), 7.2–7.4 (m, 8 H, Ar) and 9.50 (d, *J* 2.4 Hz, 1 H, CHO); ν_{max}(Nujol): 1 720 cm^{-1}.

9-*Hydroxymethyl*-9,10-*dihydroanthracene* **5**. $LiAlH_4$ (0.04 g, 1.05 mmol) was added to a solution of **4** (0.2 g, 1 mmol) in anhydrous diethyl ether (20 cm^3). After being stirred at room temperature for 4 h, water was added and the organic layer was separated, dried ($MgSO_4$) and evaporated to give alcohol **5** (0.18 g) which was recrystallized from chloroform–hexane, m.p. 98–100 °C; δ_H($CDCl_3$, D_2O): 3.64 (d, *J* 7.2 Hz, 2 H, CH_2OH), 3.89 (d, *J* 19 Hz, 1 H, CH_2), 4.10 (t, *J* 7.2 Hz, 1 H CH), 4.13 (d, *J* 19 Hz, 1 H, CH_2) and 7.20–7.35 (m, 8 H, Ar) (Found: C, 85.7; H, 6.7. Calc. for $C_{15}H_{14}O$: C, 85.68; H, 6.71%).

Kinetics and Products of the Acid-catalysed Ring Opening of Epoxides **1** *and* **6**.—$HClO_4$ (0.1 mol dm^{-3}; 1.4 cm^3) was added to a solution of the epoxide (0.7 mmol of **1** or 1.4 mmol of **6**) in THF (5.6 cm^3) and the pH was adjusted to 2.5. The solutions were thermostatted at 25 ± 0.1 °C. Samples (0.5 cm^3) were withdrawn at the times reported in Table 1 and neutralized by addition of solid $CaCO_3$. The appropriate volume of a 9.7×10^{-3} mol dm^{-3} THF solution of *cis*-1-(*p*-methylphenyl)-cyclohexane-1,2-diol[9] as a standard was added, and the mixture subjected to HPLC analysis under the following conditions: reverse phase, 25 cm, 10 μm, C_{18} Techopack, MeOH–water (65:35) 1 cm^3 min^{-1}, 260 nm. Both reactions were repeated three times. The average product distributions are reported as percentages in Table 1. The products mixture obtained from **1** was also analysed at complete conversion by NMR spectroscopy (300 MHz). A 6:1:6 ratio of products **2**–**4** was calculated from the respective signals: **2**, δ 4.08 (s, CH_2) and 5.06 (s, C*H*OH);[8] **3**, δ 3.73 and 4.36 (AB quartet, CH_2), 5.29 (s, C*H*OH);[8] **4**, δ 3.95 and 4.10 (AB quartet, CH_2), 4.85 (d, CH) and 9.50 (d, CHO) ppm. No other relevant signals, except those of the hydroxylic and aromatic protons, were present.

The product *versus* time data reported in Table 1 for **1** were fitted to the integrated first-order rate eqn. (1) and the rate constant k_1 was obtained with the usual linear least-squares procedure. In the case of **6** the value of k_1 was obtained from the initial rate evaluated from the curve reporting the total products concentration *versus* time.

X-Ray Crystal Structure Determination of **1**.—*Crystal data.* $C_{15}H_{12}O$, *M* 208.23, orthorhombic, $a = 8.582(1)$, $b = 6.401(1)$, $c = 19.619(4)$ Å, *V* 1077.7 Å^3 (by least-squares refinement from the angular positions of 15 reflections in the range $23 < 2\theta < 39°$, $\lambda = 0.710\,69$), space group $Pna2_1$, $Z = 4$, $D_x = 1.284$ mg m^{-3}. Colourless, air-sensitive, crystal size, 0.48 × 0.25 × 0.125 mm; μ(Mo-Kα) = 0.85 cm^{-1}.

Data collection and processing. Nicolet R_3 diffractometer, ω/2θ mode with 2θ scan width 2.2°, 2θ scan speed 2.–20.3 deg min^{-1}, graphite-monochromated Mo-Kα radiation; 1924 reflections measured ($2° < 2\theta < 60°$, $+h,k,l$), 1624 unique, giving 831 with $I > 3\sigma(I)$.[23,24]

Structure analysis and refinement. (*Direct methods*). Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogen atoms in calculated positions (sp^3 C–H = 1.08 Å, and sp^2 C–H = 1.05 Å) with a *B* value of parent C atom allowed to ride on it. The weighting scheme $w = 1/(0.053\,15 + F_o + 0.028\,09F_o^2)$ gave a goodness of fit $s = 0.5$. Final *R* and R_w values are 6.98, 11.23. On the final difference-Fourier map of $\sigma(\rho) = 0.06$ e Å^{-3} and no regions were > 3 (esd). Atomic scattering factors were taken from ref. 25. The programs used were SIR88[26] and SIR CAOS[27] on the Data General MV8000/II of Istituto di Strutturistica Chimica CNR. Tables of thermal parameters and hydrogen atom coordinates together with tables of short intermolecular contacts < 3.6 Å have been deposited at the Cambridge Crystallographic Data Centre.*

Acknowledgements

This work was supported in part by grants from Consiglio

* See 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1990, Issue 1.

Nazionale delle Richerche and Ministero della Pubblica Istruzione. We thank Clara Marciante for technical assistance in the X-ray diffraction measurements.

References

1 G. Bellucci, G. Berti, C. Chiappe, A. Lippi and F. Marioni, *J. Med. Chem.*, 1987, **30**, 768.
2 G. Bellucci, G. Berti, C. Chiappe, F. Fabri and F. Marioni, *J. Org. Chem.*, 1989, **54**, 968.
3 G. Bellucci, C. Chiappe, F. Marioni and C. Simonelli, *Xenobiotica*, 1989, **19**, 279.
4 L. J. Kricka and A. Ledwith, *Chem. Rev.*, 1974, **74**, 101.
5 K. Kawashima and T. Ishiguro, *Chem. Pharm. Bull.*, 1978, **26**, 951.
6 T. Ohta, N. Miyata and M. Hirobe, *Chem. Pharm. Bull.*, 1981, **29**, 1221.
7 T. Ohta, N. Miyata and M. Hirobe, *Chem. Pharm. Bull.*, 1984, **32**, 3857.
8 G. Bellucci, R. Bianchini, C. Chiappe, F. Marioni and D. Catalano, *Tetrahedron*, 1988, **44**, 4863.
9 A. Balsamo, C. Battistini, P. Crotti, B. Macchia and F. Macchia, *Gazz. Chim. Ital.*, 1976, **106**, 77.
10 H. F. Allen, O. Kennard, D. G. Watson, L. Brammer and A. G. Orpen, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1.
11 D. J. Williams, P. Crotti, B. Macchia and F. Macchia, *Tetrahedron*, 1965, **31**, 993.
12 J. P. Glusker, H. L. Carrell, D. E. Zacharias and R. G. Harvey, *Cancer Biochem. Biophys.*, 1974, **1**, 43.
13 J. P. Glusker, D. E. Zacharias, H. L. Carrell, P. P. Fu and R. G. Harvey, *Cancer Res.*, 1976, **36**, 3951.
14 S. Neidle, A. Subbiah, C. S. Cooper and O. Riberio, *Cancerogenesis*, 1980, **1**, 249.
15 W. Weissensteiner, O. Hofer and G. Wagner, *J. Org. Chem.*, 1988, **53**, 3988.
16 J. P. Reboul, P. Cristau and G. Pepe, *Acta Crystallogr., Sect. B*, 1981, **37**, 394.
17 A similar conformation with quasi-axial oxirane ring was found by X-ray diffraction of the structurally analogous 10,11-dihydro-10, 11-epoxy-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide (G. Bellucci, C. Chiappe, F. Marchetti and F. Marioni, unpublished results).
18 R. R. Fraser and R. N. Renaud, *Can. J. Chem.*, 1971, **49**, 746.
19 N. L. Bauld and Y. S. Rim, *J. Org. Chem.*, 1968, **33**, 1303.
20 G. Bellucci, G. Berti, M. Ferretti, F. Marioni and F. Re, *Biochem. Biophys. Res. Commun.*, 1981, **102**, 838.
21 G. Bellucci, G. Berti, G. Ingrosso, A. Vatteroni, G. Conti and R. Ambrosetti, *J. Chem. Soc., Perkin Trans. 2*, 1978, 627.
22 E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 738.
23 F. Bachechi, L. Zambonelli, G. Marcotrigiano, *J. Cryst. Mol. Struct.*, 1977, **7**, 11.
24 L. E. McCandlish, G. H. Stout and L. C. Andrews, *Acta Crystallogr., Sect. A*, 1975, **31**, 245.
25 International Tables for X-Ray Crystallography; Kynoch, Birmingham, UK 1974; Vol. IV.
26 M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna and D. Viterbo, *J. Appl. Crystallogr.*, 1989, **22**, 389.
27 M. Camalli, D. Capitani D. G. Cascarano, S. Cerrini, C. Giacovazzo and R. Spagna, Ital. Pat. 34503c/86. SIR CAOS User Guide, Istituto di Strutturistica Chimica CNR, Rome, Italy.

Paper 0/02717K
Received 18*th June* 1990
Accepted 3*rd August* 1990