Crystallographic and Spectroscopic Study of the Keto-acid–Hydroxy-lactone Isomerization Path

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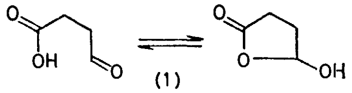
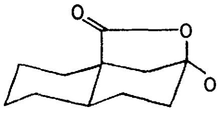
I.r. and n.m.r. spectroscopic evidence shows that 3-hydroxy-*trans*-bicyclo[4.4.0]decane-1,3-carbolactone (2a) and its keto-acid isomer coexist in solution as a rapidly interconverting equilibrium mixture. Results of crystal structure analyses of this carbolactone and of three related compounds, 3-methoxy-*trans*-bicyclo[4.4.0]decane-1,3-carbolactone (2b), methyl 3-oxo-*trans*-bicyclo[4.4.0]decane-1-carboxylate (3b), and 3-oxo-*cis*-bicyclo[4.4.0]decane-1-carboxylic acid (4), are described. The hydroxy- and methoxy-lactones display a pattern of bond-length and -angle deformations corresponding to an initial stage of the ring-opening reaction. On the ring-opened side, the keto-methyl ester and the keto-acid show structural features (short O · · · C=O distance, slight pyramidalization of the keto-group) corresponding to displacement along the reverse, ring-closure reaction pathway. The hydrogen-bonding patterns found in the hydroxy-lactone and the keto-acid correspond to incipient stages of the proton-transfer processes that accompany ring-opening and -closure.

THIS paper describes an attempt to use crystal structure analysis to obtain information about a chemical reaction path. The reaction chosen for study is the keto-acid–hydroxy-lactone isomerization (1). Ideally, we should like to be able to observe the structural parameters of the same molecule at different points along the isomerization path, but this is obviously out of the question since our observations are limited to systems at or near equilibrium.†

A more practicable possibility is to try to obtain structural information for a series of closely related compounds that undergo essentially the same isomerization but with different equilibrium or rate behaviour. The general idea would be to try to relate any observed differences in relevant interatomic distances from one molecule to another with the structural changes expected to occur in the course of the reaction. A previous study along these lines[1] has provided information about the coupling between out-of-plane twisting and bending co-ordinates in the *cis–trans* isomerization of amides.

In our study of the isomerization (1) we have carried out crystal-structure analyses of four compounds, two (2a, 2b) on the hydroxy-lactone side, two (3b, 4) on the keto-acid side of the transition state. From these results, together with i.r., and ^{1}H and ^{13}C n.m.r. evidence, some conclusions may be drawn about geometric and energetic features of the reaction path. At the same time, several questions are left open and some new ones are raised.





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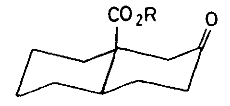
b; R = Me



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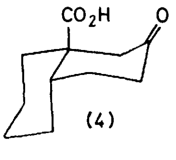

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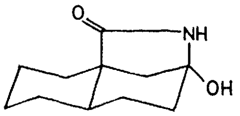

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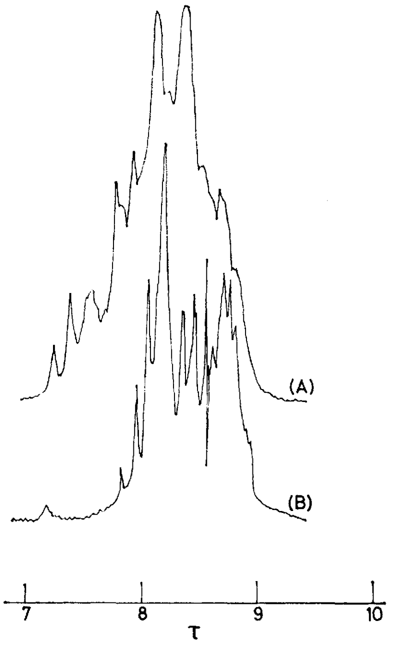

FIGURE 1 Highfield region of ^{1}H n.m.r. spectrum (100 MHz, room temperature) of (A) equilibrium mixture of keto-acid (3a) and hydroxy-lactone (2a) in CHCl$_3$, and (B) for hydroxy-lactam (5)

RESULTS AND DISCUSSION

Spectroscopic Evidence.—Our starting point was the observation that the keto-acid (3a) exists at room temperature in non-polar solvents (CHCl$_3$, CCl$_4$) as a mixture of open (3a) and closed (2a) isomers. The i.r. spectrum (CHCl$_3$ solution) displays carbonyl absorptions at 1 767 (γ-lactone), 1 754 (free acid?), and 1 708 cm^{-1} (ketone and H-bonded acid). A part of the ^{1}H n.m.r. spectrum of the mixture is shown in Figure 1(A) together with the corresponding spectrum (B) of the analogous

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† Structural parameters observed for a molecule in a crystal environment do not necessarily coincide with the equilibrium structure of the isolated molecule, but they are usually fairly close.

hydroxy-lactam (5), which exists exclusively in the closed form, both in solution and in the crystalline state.[2] It is evident that the signals in spectrum (A) are much broader than in (B), suggesting that the (2a)↔(3a) isomerization proceeds at a rate commensurate with the time-scale of the n.m.r. observation. Addition of D_2O broadens the signals of (A), H_2O has no effect, and a trace of HCl sharpens the signals. From these observations we conclude that the reaction rate is on the rapid-exchange side of the coalescence region, and that the rate-limiting step of the isomerization involves proton transfer.

Parts of the ^{13}C n.m.r. spectra at 303 and at 223 K are shown in Figure 2. Whereas at 303 K only five sharp signals are observed, the 22 signals expected for a mixture of (2a) and (3a) are present at the lower temperature: two sets of 11 in intensity ratio *ca.* 2 : 1 in favour of the hydroxy-lactone form (2a). At 153 K (4 : 1 mixture of carbon disulphide and deuteriated tetrahydrofuran as solvent), the signals of the keto-acid (3a) are no longer detectable. Activation parameters were estimated by full line-shape analysis of the temperature variation of the ^{13}C n.m.r. signals due to the carboxylic acid and lactone carbonyl carbons [$\delta(Me_4Si)$ 180.59 and 178.09 at 213 K in $CDCl_3$]. Three solutions of similar concentrations were examined, the results being summarized in Table 1. The spectra are extremely sensitive to minor differences in experimental conditions and are difficult to reproduce exactly from one experiment to another. For example, at the same temperature, the resonances under study appeared as one line in experiment (II) and as two lines in experiment (III) (see Table 1). This irreproducibility may be due to the presence

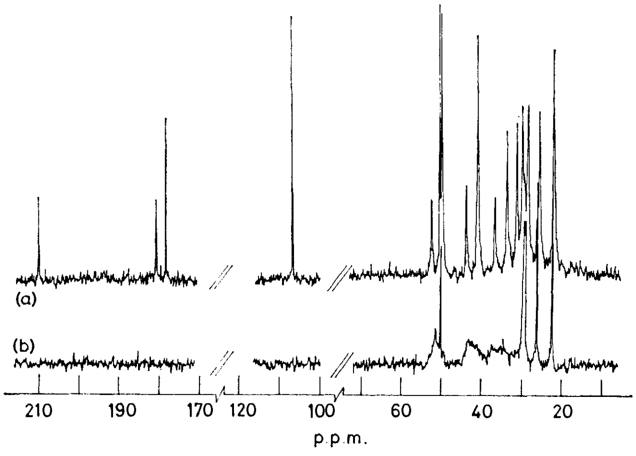


FIGURE 2 ^{13}C n.m.r. spectrum of equilibrium mixture of keto-acid (3a) and hydroxy-lactone (2a) in $CDCl_3$ at a, 223 and b, 303 K

TABLE 1

Activation parameters for the isomerization (3a)↔(2a) in $CDCl_3$ solution

Expt.	(I)	(II)	(III)
temperature range/K	295—313	263—305	253—293
E_a/kJ mol^{-1}	35.5	22.9	26.7
$\Delta H^‡$/kJ mol^{-1}	32.9	18.1	24.4
$\Delta S^‡$/J K^{-1} mol^{-1}	−81.6	−133.5	−134.9

In expts. (I) and (II) spectra displayed only one resonance for the carboxy and lactone carbonyl carbon atoms in the temp. range shown; in expt. (III) spectra displayed two resonances throughout temp. range. Activation parameters (from Arrhenius and Eyring linear least-squares plots, correlation coefficients generally >0.95) are for the isomerization (3a) →(2a). Internal precision for each experiment is within 5%.

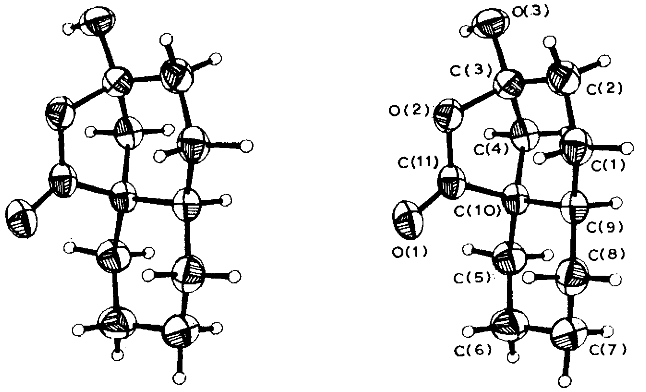


FIGURE 3 Stereoscopic view of a molecule of (2a) showing atom numbering system

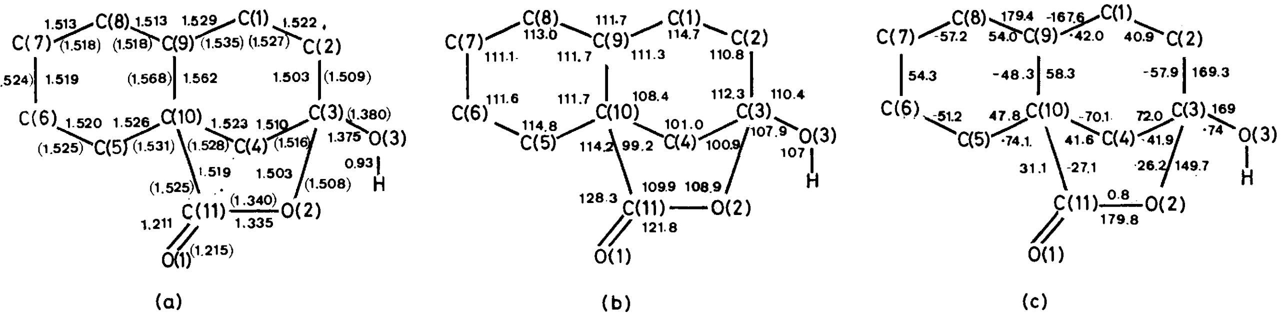


FIGURE 4 (a) Bond lengths (Å), (b) bond angles (°), and (c) torsion angles (°) in (2a) (values corrected for rigid-body libration are in parentheses). Estimated standard deviations are 0.004—0.006 Å for bond lengths and 0.3—0.4° for bond angles not involving H atoms. Some additional values are C–H 0.92—1.07; C(4)–C(10)–C(5) 115.1, C(11)–C(10)–C(9) 107.3, O(2)–C(3)–C(2) 107.3, O(3)–C(3)–C(4) 117.3, H–C–H 105—114; C(1)–C(2)–C(3)–O(2) 52.0, C(1)–C(9)–C(10)–C(5) −173.9, C(1)–C(9)–C(10)–C(11) −48.0, C(2)–C(3)–O(2)–C(11) −91.4, C(3)–C(4)–C(10)–C(5) 164.0, C(4)–C(10)–C(9)–C(8) −176.1, C(4)–C(10)–C(5)–C(6) 172.0, C(4)–C(10)–C(11)–O(1) 154.0, C(5)–C(10)–C(11)–O(2) −150.1, C(8)–C(9)–C(10)–C(11) 77.6, C(9)–C(10)–C(11)–O(1) −93.3, C(9)–C(10)–C(11)–O(2) 85.6, C(10)–C(4)–C(3)–O(3) −158.6, C(4)–C(3)–O(3)–H 39 of variable trace amounts of mineral acid; at least, this possibility would be in keeping with the involvement of proton transfer in the rate-limiting step.

Crystal Structure of the Hydroxy-lactone (2a).—Results of a crystal structure analysis (R 0.029) of the hydroxy-lactone (2a) are shown in Figure 3 (molecular structure), Figure 4 (interatomic distances and angles), and Figure 5 (crystal packing). The molecular geometry around the tetrahedral centre C(3) calls for special attention. In the first place, the endocyclic bond C(3)–O(2) [1.508(4) Å] is markedly longer than the corresponding bond (*ca.* 1.47 Å) in a typical γ-lactone, whereas the exocyclic bond C(3)–O(3) [1.380(4) Å] is markedly shorter than a typical alcoholic C–O bond (*ca.* 1.43 Å). These differences between the endo- and exo-cyclic bond lengths are matched by corresponding differences between the relevant bond angles, those involving O(3) being appreciably larger than those involving O(2) (110.4 *vs.* 107.3° and 117.3 *vs.* 100.9°). The angle differences mean that the shorter bond C(3)–O(3) has moved from the position it would have for a carbon with local C_{2v} symmetry towards the plane of C(2)C(3)C(4), *i.e.* towards the position expected for a carbonyl bond.

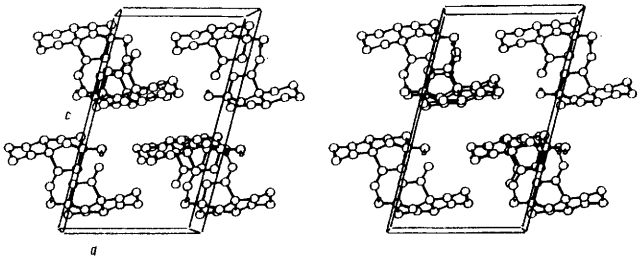


FIGURE 5 Stereoscopic view of crystal structure of (2a), showing hydrogen bonds (b into plane of paper)

An analysis [3] of *ca.* 25 molecules of the type $R^1R^2C(OR^3)(OR^4)$ has shown that as far as deformations from local C_{2v} symmetry of the central carbon atom are concerned, there is a good linear correlation between the quantities $\Delta d = d_2 - d_1$ (in Å) and $\Delta\beta = \beta_1 + \beta_{1'} - \beta_2 - \beta_{2'}$ (in °) involving C–O bond lengths and C–C–O bond angles, respectively (Figure 6): $\Delta\beta = 173\ \Delta d$ (correlation coefficient 0.84).

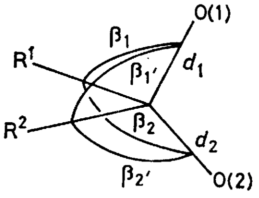


FIGURE 6 Definition of d and β (see text)

$$\text{With} \quad \Delta d = 1.508 - 1.380 = 0.128\ \text{Å},$$
$$\text{and} \quad \Delta\beta = (110.4 + 117.3) - (107.3 + 100.9) = 19.5°$$

the observed differences for (2a) lie close to the correlation line found in the earlier analysis and reveal (2a) to be among the most severely distorted examples of this structural type to date.

We interpret this distortion as an expression of a movement along the reaction co-ordinate for breakdown of the tetrahedral ring-closed addition product [hydroxy-lactone (2a)] to separated nucleophile and electrophile [keto-acid (3a)]. The hypothetical 'undistorted' addition product must have a higher potential energy than that observed for (2a), and its relaxation to the observed (2a) is presumably accompanied by a lowering of the strain energy of the tricyclic ring system. Since the strain-energy gain can only amount to a few kJ mol^{-1} we can infer that the energy profile along the reaction co-ordinate must be rather flat, and this would be consistent with the low energy barrier derived from the n.m.r. observations.

In contrast to the results for (2a) the C(3)–N and C(3)–O(2) bond lengths observed [2] in the corresponding ring-closed hydroxy-lactam (5) are close to typical values for such bonds. In particular the C(3)–O(2) bond [1.411(4) Å] is *ca.* 0.03 Å longer than the directly comparable bond of (2a) and, unlike the latter, shows very little if any 'carbonyl character.'

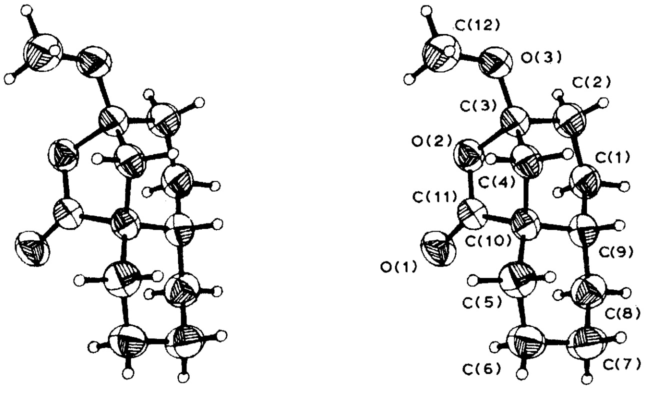
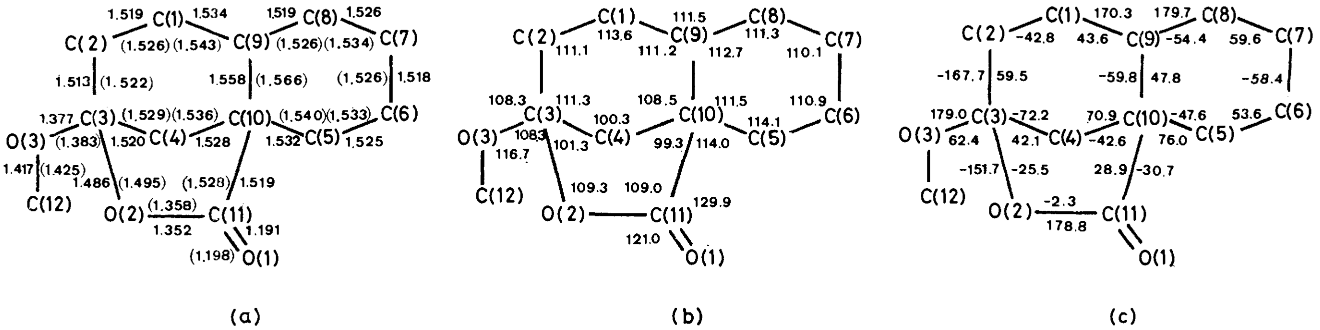


FIGURE 7 Stereoscopic view of a molecule of (2b), showing atom numbering system

The most interesting feature of the crystal packing of (2a) (Figure 5) is the hydrogen-bonding pattern. The hydroxy-group of each molecule makes a hydrogen bond (OH ··· O 2.767 Å, O–H ··· O 168°) to the carbonyl group of its neighbour to form infinite chains running parallel to the b axis of the crystal. This type of hydrogen bonding can be regarded as representing an incipient stage of the proton-transfer process involved in the rate-limiting step of the isomerization (1).

Another point to be noted here is the torsion angle O(2)–C(3)–O(3)–H of −74°. An obvious implication is that the lengthened and presumably weakened O(2)–C(3) bond is antiperiplanar to an sp^3 lone-pair orbital on O(3), in keeping with Deslongchamps' ideas [4] about the role of stereoelectronic factors in influencing the reactivity of such bonds. In the hydroxy-lactam (5), with 'normal' bond lengths and angles about the tetrahedral centre C(3), the relevant torsion angle N–C(3)–O(3)–H is 115°, *i.e.* there is no sp^3 lone-pair on O(3) which is antiperiplanar to the C(3)–N bond.

Crystal Structure of the Methoxy-lactone (2b).—Results



(a) (b) (c)

FIGURE 8 (a) Bond lengths (Å), (b) bond angles (°), and (c) torsion angles in (2b) (values corrected for rigid-body libration in parentheses). Estimated standard deviations are *ca.* 0.005 Å for bond lengths and 0.3° for bond angles not involving H atoms. Some additional values are: C–H 0.86—1.03; C(2)–C(3)–O(2) 107.8, C(4)–C(3)–O(3) 119.2, C(4)–C(10)–C(5) 114.1, C(9)–C(10)–C(11) 108.7, H–C–H 101—121; C(1)–C(2)–C(3)–O(2) −50.7, C(1)–C(9)–C(10)–C(5) 173.8, C(1)–C(9)–C(10)–C(11) 47.3, C(3)–C(4)–C(10)–C(5) −164.2, C(4)–C(3)–O(3)–C(12) −52.5, C(4)–C(10)–C(11)–O(1) −152.4, C(4)–C(10)–C(9)–C(8) 174.2, C(4)–C(10)–C(5)–C(6) −170.9, C(5)–C(10)–C(11)–O(2) 150.5, C(8)–C(9)–C(10)–C(11) −78.7, C(9)–C(10)–(C11)–O(2) −84.4, C(9)–C(10)–C(11)–O(1) 94.4, C(10)–C(4)–C(3)–O(3) 160.7, C(11)–O(2)–C(3)–C(2) 91.4

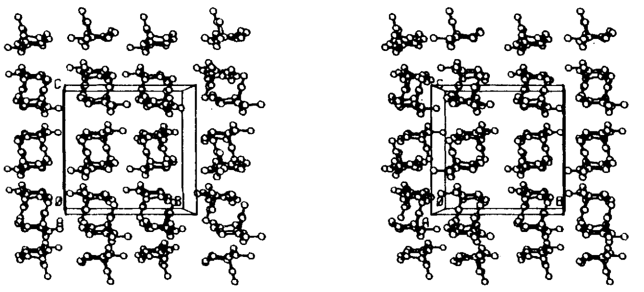


FIGURE 9 Stereoscopic view of crystal structure of (2b)

of the crystal structure analysis (*R* 0.034) of the closely related methoxy-lactone (2b) are shown in Figure 7 (molecular structure), Figure 8 (interatomic distances and angles), and Figure 9 (crystal packing). Comparison of Figure 7 with Figure 3 indicates that the conformations of (2b) and (2a) observed in their respective crystal structures are closely similar, and this is borne out by detailed comparison of corresponding torsion angles.[*] In particular, the O(2)–C(3)–O(3)–CH_3 torsion angle of 62° implies that the antiperiplanar relation between an O(3) lone-pair orbital and the C(3)–O(2) bond, found in (2a), is also present in (2b). Correspondingly, the two molecules show the same general pattern of bond-length and -angle distortions about the tetrahedral centre C(3) [Δd 0.112 Å, $\Delta\beta$ 18.4° in (2b) *cf.* 0.128 Å and 19.5° in (2a)]. If anything, the displacement from ' normal ' geometry is slightly less for the methoxy-lactone than for the hydroxy-lactone, *e.g.*

	C(11)–O(1)Å	C(11)–O(2)Å	O(2)–C(3)Å	C(3)–O(3)Å
(2a)	1.215	1.340	1.508	1.380
(2b)	1.198	1.358	1.495	1.383
' Normal '	1.20	1.38	1.46	1.43

where the ' normal ' values are based on observations for a range of typical esters, alcohols, and ethers. Replacement of hydrogen by methyl from (2a) to (2b) might in itself lead to a slight shortening of the C(3)–O(3) bond, since, according to Beagley[5] ' in molecules with C–O bonds, as in the amines, adding methyl groups to the heteroatom shortens the C–X bond.' Beagley's conclusion was based on data for molecules in the vapour phase but it is presumably valid for crystal data as well. On the whole, the results are consistent with a slightly greater displacement along the reaction co-ordinate in (2a) than in (2b), which seems reasonable since the intermolecular hydrogen bonding in (2a) should assist the displacement. At any rate, in spite of the much larger activation energy for the (2b)→(3b) isomerization compared with (2a)→(3a), the initial reaction paths for the ring-opening process appear to be remarkably similar for the two systems.

Crystal Structures of the Keto-methyl Ester (3b) *and the Keto-acid* (4).—We have also carried out crystal structure analyses for the methyl ester (3b) (*R* 0.045) and the *cis*-keto-acid (4) (*R* 0.032), on the other side of the transition state for the isomerization (1). Both substances, in solution and in the solid state, exist exclusively as the ' open ' structures. The results are shown in Figures 10—12 for (3b) and 13—15 for the keto-acid (4). For consistency, we shall continue to refer to the oxygen closer to the keto-group as O(2).

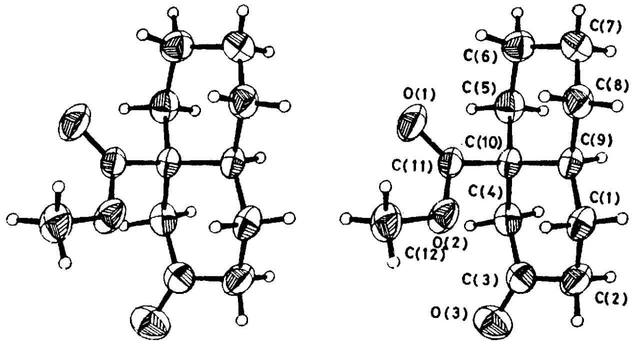


FIGURE 10 Stereoscopic view of a molecule of (3b) showing atom numbering system

In (3b) we are mainly interested in the orientation of the methoxycarbonyl group and the approach of O(2) to the electrophilic carbon C(3) of the keto-group (Figure

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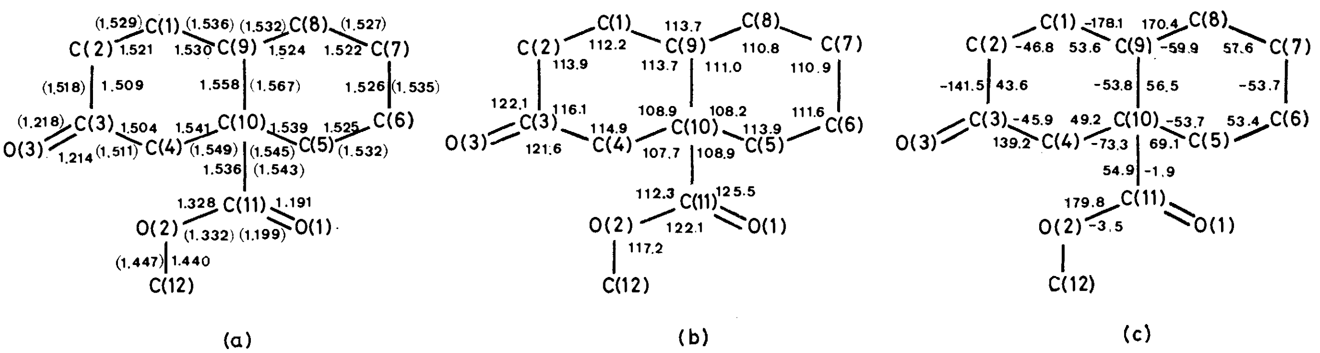
[*] Note that the conformation depicted in Figure 3 corresponds to the enantiomorph of that shown in Figure 7, and similarly for the torsion angles in Figures 4 and 8.

10). We draw particular attention to the following points.



(a) (b) (c)

FIGURE 11 (a) Bond lengths (Å), (b) bond angles (°), and (c) torsion angles (°) in (3b) (values corrected for rigid-body libration in parentheses). Estimated standard deviations are *ca.* 0.003 Å for bond lengths and 0.2° for bond angles not involving H atoms. Some additional values are: C–H 0.89—1.07; C(4)–C(10)–C(5) 110.4, C(9)–C(10)–C(11) 112.7, H–C–H 99—116; C(1)–C(9)–C(10)–C(5) −173.8, C(1)–C(9)–C(10)–C(11) 65.6, C(3)–C(4)–C(10)–C(5) 168.0, C(4)–C(10)–C(11)–O(1) −121.6, C(4)–C(10)–C(5)–C(6) −172.9, C(4)–C(10)–C(9)–C(8) 176.5, C(5)–C(10)–C(11)–O(2) 174.6, C(9)–C(10)–C(11)–O(1) 118.2, C(9)–C(10)–C(11)–O(2) −65.3, C(11)–C(10)–C(9)–C(8) −64.1

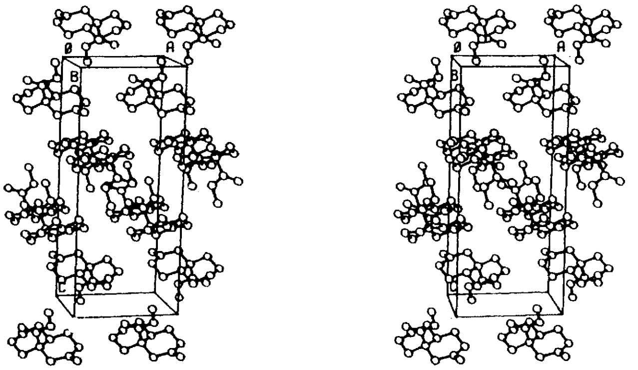


FIGURE 12 Stereoscopic view of crystal structure of (3b)

(*a*) The preferred conformation of carboxylic acids and esters has the C=O bond eclipsed with the C_α–C_β bond.[6] For a bridgehead-substituted decalin, there are three such conformations, and we have observed all of them in different derivatives. The conformation observed for (3b) is shown diagramatically in (6); it has the C=O bond eclipsed with C(10)–C(5) and is the only one of the three preferred conformations which puts the methoxy-oxygen in an almost optimal position for attack on the electrophilic carbon C(2).

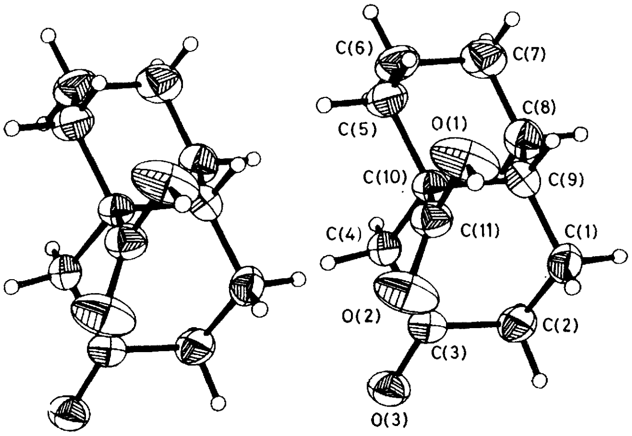
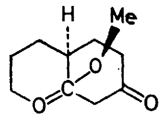


FIGURE 13 Stereoscopic view of a molecule of (4) showing atom numbering system

(*b*) The O · · · C=O angle is 104°, and the nucleophilic oxygen lies approximately in the local mirror plane bisecting the keto-group and its substituents C(2) and C(4). Structural data for several amino-ketones showing short N · · · C=O distances indicate[7,8] that this arrangement of atoms lies on or close to the preferred path for addition of nucleophilic N to a carbonyl group; SCF–LCGO–MO calculations[8,9] show that hydride-ion addition to formaldehyde also follows a very similar path. For O · · · C=O interactions,[3] the preferred angle of attack is not so clear, but the structural data show a definite tendency for angles in the range 100—110° and for the nucleophile to lie in the bisecting plane.



(3b) Showing conformation

(*c*) The O · · · C=O distance is 2.773 Å, close to the lower limit found for intermolecular approaches of this type (see examples in Table 1 of ref. 3). Appreciably shorter O · · · C–O distances have been observed only in molecules where they are imposed by geometric constraints, *e.g.* in *peri*-disubstituted naphthalenes such as 8-methoxynaphthalene-1-carboxylic acid, where the O · · · C=O distance is only 2.56 Å.[10]

(*d*) The electrophilic carbon C(3) is displaced (Δ) by 0.036(4) Å from the plane of its three substituents towards the approaching nucleophile O(2), indicative of an attractive interaction between these atoms. Similar displacements have been noted for many other molecules displaying short O · · · C=O distances.[3]

The *cis*-decalin keto-acid (4) shows an alternative orientation of the carboxy-group, which brings the carbonyl oxygen instead of the hydroxy-oxygen into the

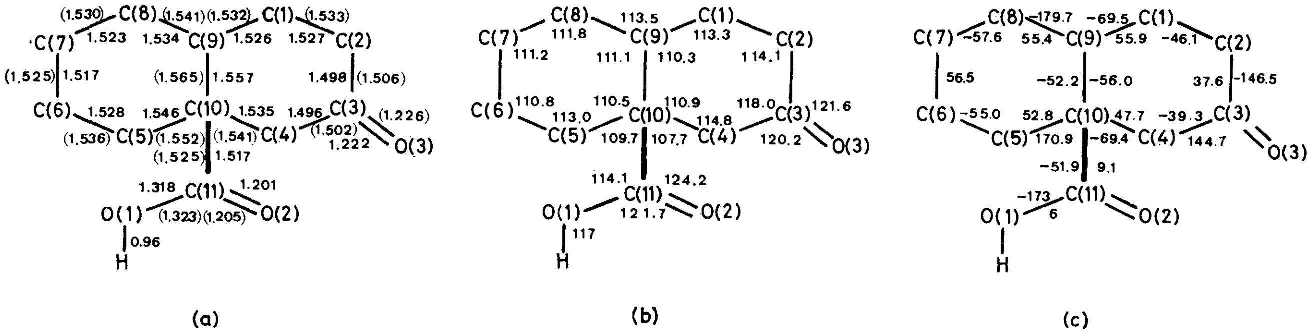
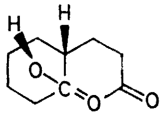


FIGURE 14 (a) Bond lengths (Å), (b) bond angles (°), and (c) torsion angles (°) in (4) (values corrected for rigid-body libration in parentheses). Estimated standard deviations are *ca.* 0.003 Å for bond lengths and 0.2° for bond angles not involving H atoms. Some additional values are: C–H 0.96—1.04; C(4)–C(10)–C(5) 110.6, C(9)–C(10)–C(11) 107.3, H–C–H 105—110; C(1)–C(9)–C(10)–C(5) −179.0, C(1)–C(9)–C(10)–C(11) 61.4, C(3)–C(4)–C(10)–C(5) 170.7, C(4)–C(10)–C(11)–O(1) −172.4, C(4)–C(10)–C(5)–C(6) −70.4, C(4)–C(10)–C(9)–C(8) 70.8, C(5)–C(10)–C(11)–O(2) 129.5, C(8)–C(9)–C(10)–C(11) −171.8, C(9)–C(10)–C(11)–O(1) 68.2, C(9)–C(10)–C(11)–O(2) −110.4

vicinity of the electrophilic carbon. For comparison with the previous structure we note: (*a*) the C=O bond of the carboxy-group approximately eclipses the C(10)–C(4) bond of the *cis*-decalin system, but the deviation from perfect eclipsing amounts to 9°, and is in such a sense as to bring the carbonyl oxygen O(2) closer to the keto-carbon C(3); (*b*) although the O · · · C=O angle is 102°, close to the value for (3b), the nucleophilic oxygen does not lie in the bisecting plane [C(2)–C(3)–O(2) 104, C(4)–C(2)–O(2) 67°]; (*c*) the O · · · C=O distance is 2.912 Å, longer than in (3b); and (*d*) Δ is 0.029(4) Å, only slightly, and barely significantly, less than for (3b).



(4) Showing conformation

The packing of the keto-acid (4) in the crystal deserves special comment. In crystals of most monocarboxylic acids the carboxy-groups form cyclic hydrogen-bonded dimers or else infinite hydrogen-bonded helices along a two-fold screw axis.[11] In the keto-acid structure (Figure 15), the hydrogen bond is formed between the carboxy-group O(1)H and the ketonic oxygen O(3) of a neighbouring molecule (at $\frac{1}{2} - x, -y, \frac{1}{2} + z$) (OH · · · O 2.654 Å, OH · · · O 173°). This type of hydrogen bonding is a perfect complement to the type that occurs in the structure of the hydroxy-lactone (2a) (Figure 5), between hydroxy OH and lactone C=O. In both cases, the hydrogen bonding represents incipient stages of the proton transfer process that has to occur in the course of the isomerization (1).

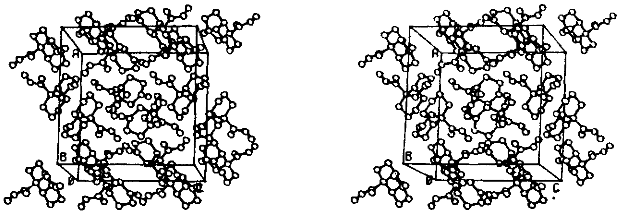
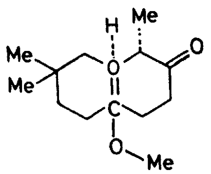


FIGURE 15 Stereoscopic view of crystal structure of (4). The only hydrogen atom shown is the carboxy O(1)H, which forms a hydrogen bond [*d*(OH · · · O) 2.65 Å] to the ketonic oxygen O(3) of an adjacent molecule

Unfortunately, since all attempts to isolate (3a) from solutions of the equilibrium mixture have failed, we do not know the orientation of the carboxy-group in the *trans*-decalin keto-acid. Very likely it resembles (3b) or (4) and can switch easily between these two structures, which appear to be rather finely balanced as far as their energies are concerned. Both structures can be regarded as possible starting points for the ring-closure reaction. Disregarding the distinction between hydroxy- and carbonyl-oxygen, which would anyway become more and more blurred as proton transfer proceeds, note that the torsion angle O(2)–C(11)–C(10)–C(4) is 55° in (3b), 9° in (4), and 26° in the two ring-closed molecules (2a) and (3a). Thus from either starting point, the plane of the carboxy-group has to rotate during the displacement along the reaction co-ordinate.



(6)

Before turning to the chemical aspects of this work, several minor structural regularities and differences emerge from the four crystal-structure analyses. In all four structures, the C(9)–C(10) bond is consistently long [(2a) 1.568, (2b) 1.566, (3b) 1.567, and (4) 1.565 Å]. In the *cis*-decalóne (4) the ring containing the keto-group is appreciably flattened compared with cyclohexane: the ring torsion angles around C(3)–C(2) and C(3)–C(4) are less than 40°. The flattening is less pronounced in the *trans*-decalóne (3b), where the relevant torsion angles are *ca.* 45°, and it appears to be absent in (6) (torsion angles *ca.* 54°),[12] where, incidentally, the C=O bond of the methoxycarbonyl group eclipses C(9)–C(10), an example of the third possible orientation for a carboxy-group on bridgehead carbon. The carboxy-groups of (3b) and (4) both show the typical bond-angle pattern [6] with C–C=O *ca.* 10° larger than C–C–OR. In the γ-lactone, the C–C–OR angle (now in a five-membered ring) decreases still further, but the C–C=O angle increases in a roughly equal amount so that the third angle, O=C–O, is practically constant at 121—122° throughout the series (see Figures 4, 8, 11, and 14).

For the two lactones, the vibrational ellipsoids * of the heavy atoms are accounted for fairly well in terms of rigid-body motions;[14] for the two open molecules the agreement is less good, *e.g.*:

	(2a)	(2b)	(3b)	(4)	
R *	0.066	0.064	0.151	0.131	
$\langle(\Delta U_{ij})^2\rangle^{1/2}$	24	27	65	48	$\times 10^{-4}$ Å^2

* Here R is an agreement factor defined as $\Sigma|\Delta U_{ij}|/\Sigma|U_{ij}|$ where $\Delta U_{ij} = U_{ij}(\text{obs.}) - U_{ij}(\text{calc.})$, analogous to the usual crystallographic R factor.

From Figures 10 and 13 one gets the impression that the methoxycarbonyl group of (3b) and the carboxy-group of (4) are carrying out torsional vibrations of considerable amplitude about the respective C(10)–C(11) bonds. Allowance for this non-rigid-body motion [15] in the least-squares fitting leads to a significantly improved agreement in both cases: R 0.106, $\langle(\Delta U_{ij})^2\rangle^{1/2} = 48 \times 10^{-4}$ Å^2 for (3b), and R 0.101, $\langle(\Delta U_{ij})^2\rangle^{1/2} = 34 \times 10^{-4}$ Å^2 for (4); root-mean-square libration amplitude 10.9(7)° for both.

Conclusions.—The n.m.r. results show that the keto-acid–hydroxy-lactone isomerization (3a)→(2a) has a low activation energy, so low indeed that proton transfer becomes involved in the rate-limiting step.† Moreover, both i.r. and n.m.r. evidence show that the equilibrium is finely balanced.

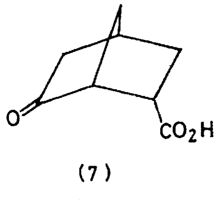
X-Ray crystallography has provided four ' snapshots ' along the interconversion pathway. On the ring-closed side, the hydroxy-lactone (2a) and the methoxy-lactone (2b) show very similar deviations from normal bond lengths and angles; in both molecules the pattern of deformations corresponds to that expected for the initial stage of the ring-opening reaction.

It is probably no accident that in both molecules the lengthened C–O bond happens to be antiperiplanar to a lone-pair orbital on the adjacent oxygen atom. The importance of interactions between lone-pair and σ^* orbitals in influencing the relative thermodynamic stabilities of certain molecular conformations and configurations (anomeric effect) has been recognized for some time,[18] and, more recently, it has become apparent [4,19] that such interactions largely determine the fate of the tetrahedral intermediates formed in the hydrolysis of esters and amides. According to Deslongchamps,[4] specific cleavage of a particular C–O or C–N in the tetrahedral intermediate is allowed only if the other two heteroatoms each have an orbital oriented antiperiplanar to the bond in question.[4,19] It thus seems quite reasonable to invoke n–σ^* mixing as being at least partially responsible for the lengthening and presumable weakening of the C(2)–O(3) bond in both (2a) and (3a).

On the ring-opened side, the keto-acid (3a) cannot be isolated, but its methyl ester (3b) displays structural features (short O · · · C=O distance, slight pyramidalization of the keto-group) that correspond to initial displacement along the reverse ring-closure reaction path. Very similar structural features are also shown by the *cis*-decalin keto-acid (4), which, however, has an orientation of the carboxy-group different from that of (3b). Crystals of (2a) and (4) show patterns of intermolecular hydrogen bonds corresponding to incipient stages of the proton transfers which accompany ring-opening and -closing. Although the rate studies carried out so far are not conclusive on this point, the large negative $\Delta S^{\ddagger}$ values are consistent with the idea that proton transfer in solution is an intermolecular process, in keeping with the indications from the crystal structures.

If the hydrogen-bonding patterns in the crystals truly mimic the situation in solution, then the preferred mode of hydroxy-lactone ring-opening involves protonation on the carbonyl oxygen rather than on the ring oxygen. The reverse ring-closure (3a)→(2a) would then have to involve nucleophilic attack by the carbonyl oxygen of the carboxy-group. Thus the *cis*-keto-acid (4) may be a better analogue of the non-isolable (3a) than is the keto-ester (3b).

However, the keto-acid–hydroxy-lactone equilibrium must be shifted appreciably to the keto-acid side in the *cis*-decalin series since the ring-closed form of (4) does not occur in solution in any detectable concentration. In solution, (4) has a flexibility not available to *trans*-decalins, and ring-closure to the hydroxy-lactone would be impossible in the alternative conformation, obtained by ring inversion, where the carboxy-group occupies an equatorial position on the ketonic ring. The entropy of mixing of the two alternative conformations would further disfavour the ring-closed form. Even if the observed conformation, with axial carboxy-group on the ketonic ring, were to predominate in solution, small differences in strain or in the disposition of the reacting



(7)

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* Thermal-vibration ellipsoids shown in Figures 3, 7, 10, and 13 are drawn by use of ORTEP (ref. 13) and are at the 50% probability level. Packing diagrams shown in Figures 5, 9, 12, and 15 are drawn by program PLUTO (available from the Crystallographic Data Centre, University Chemical Laboratory, Cambridge.

† Although hydrolysis of ortho esters is subject to general acid-catalysis, rate-limiting proton transfer to oxygen appears to be the exception rather than the rule. Acetal hydrolysis, which superficially resembles the isomerization (2a)→(3a), is only very occasionally subject to general-acid catalysis.[16,17]

groups between the *cis*- and *trans*-decalins could have a large effect on the kinetic and equilibrium behaviour.

TABLE 2

Atomic co-ordinates and isotropic U values ($\times 10^4$ for C and O, $\times 10^3$ for H atoms) for (2a)

	x/a	y/b	z/c	$\bar{U}$/Å^2
C(1)	1 741(4)	9 170(5)	812(2)	447
C(2)	393(4)	8 126(6)	692(2)	474
C(3)	116(4)	6 288(5)	1 225(2)	403
C(4)	1 391(4)	4 901(5)	998(2)	378
C(5)	3 752(4)	4 717(6)	1 501(2)	469
C(6)	4 940(4)	5 841(6)	1 775(2)	581
C(7)	5 448(4)	7 593(6)	1 192(2)	617
C(8)	4 180(4)	8 889(6)	1 150(2)	507
C(9)	3 014(4)	7 826(5)	837(2)	387
C(10)	2 480(3)	5 960(5)	1 390(2)	351
C(11)	1 459(4)	6 625(5)	2 239(2)	390
O(1)	1 745(3)	6 978(4)	2 923(1)	516
O(2)	113(2)	6 827(4)	2 141(1)	435
O(3)	−1 233(2)	5 542(4)	1 237(2)	597
H(1)C(1)	154(3)	987(5)	138(2)	50(9)
H(2)C(1)	214(4)	1 017(5)	29(2)	50(10)
H(1)C(2)	−49(4)	896(6)	88(3)	78(11)
H(2)C(2)	46(4)	781(5)	9(2)	51(10)
H(1)C(4)	111(3)	361(4)	134(2)	33(7)
H(2)C(4)	175(4)	473(5)	41(2)	61(10)
H(1)C(5)	327(4)	365(5)	194(2)	62(11)
H(2)C(5)	417(4)	409(5)	91(2)	55(10)
H(1)C(6)	458(3)	631(5)	237(2)	48(9)
H(2)C(6)	577(4)	485(6)	172(3)	76(11)
H(1)C(7)	619(4)	832(7)	144(3)	83(12)
H(2)C(7)	587(4)	712(6)	63(2)	59(10)
H(1)C(8)	370(3)	946(5)	176(2)	41(8)
H(2)C(8)	448(3)	1 010(5)	75(2)	52(9)
HC(9)	659(3)	271(4)	−21(2)	43(8)
HO(3)	−127(5)	430(7)	148(3)	80(12)

TABLE 3

Atomic co-ordinates and isotropic U values ($\times 10^4$ for C and O, $\times 10^3$ for H atoms) for (2b)

	x/a	y/b	z/c	$\bar{U}$/Å
C(1)	4 654(2)	6 234(2)	9 011(3)	601
C(2)	3 859(2)	6 755(2)	8 541(4)	642
C(3)	3 890(2)	8 018(2)	8 616(3)	519
C(4)	4 626(2)	8 427(2)	7 949(2)	522
C(5)	6 172(2)	8 744(3)	8 478(3)	613
C(6)	6 924(2)	8 270(3)	9 115(3)	724
C(7)	7 007(2)	7 021(3)	8 907(3)	762
C(8)	6 214(2)	6 418(3)	9 285(3)	658
C(9)	5 454(2)	6 842(2)	8 639(3)	516
C(10)	5 348(2)	8 135(2)	8 722(2)	453
C(11)	4 966(2)	8 419(2)	9 871(2)	478
C(12)	2 999(2)	9 605(3)	8 456(4)	875
O(1)	5 296(1)	8 676(2)	10 742(2)	689
O(2)	4 125(1)	8 321(2)	9 800(2)	543
O(3)	3 100(1)	8 427(2)	8 406(2)	684
H(1)C(1)	476(2)	543(3)	881(3)	88(10)
H(2)C(1)	464(1)	627(2)	984(3)	68(8)
H(1)C(2)	379(2)	658(2)	771(3)	70(8)
H(2)C(2)	335(2)	652(2)	902(3)	67(8)
H(1)C(4)	468(1)	813(2)	719(2)	52(7)
H(2)C(4)	462(1)	934(2)	789(2)	58(8)
H(1)C(5)	629(2)	866(2)	767(3)	82(9)
H(2)C(5)	614(1)	961(2)	865(2)	51(7)
H(1)C(6)	740(2)	873(2)	881(3)	84(9)
H(2)C(6)	686(2)	835(2)	995(3)	73(9)
H(1)C(7)	707(2)	689(2)	809(3)	79(9)
H(2)C(7)	744(2)	675(2)	938(3)	84(9)
H(1)C(8)	627(2)	559(2)	917(2)	63(8)
H(2)C(8)	612(2)	647(2)	1 012(2)	65(8)
HC(9)	554(1)	664(2)	664(2)	55(7)
H(1)C(12)	315(3)	992(3)	783(4)	151(15)
H(2)C(12)	237(3)	972(3)	856(4)	132(14)
H(3)C(12)	320(2)	988(3)	917(4)	129(14)

TABLE 4

Atomic co-ordinates and isotropic U values ($\times 10^4$ for C and O, $\times 10^3$ for H atoms) for (3b)

	x/a	y/b	z/c	$\bar{U}$/Å^2
C(1)	10 278(2)	5 565(3)	1 061(1)	492
C(2)	11 104(3)	7 027(3)	1 512(1)	559
C(3)	9 946(3)	8 542(3)	1 713(1)	471
C(4)	8 239(3)	7 990(3)	1 950(1)	454
C(5)	5 823(3)	5 801(3)	1 851(1)	492
C(6)	5 008(3)	4 212(4)	1 465(1)	570
C(7)	6 264(3)	2 717(3)	1 318(1)	591
C(8)	7 764(3)	3 458(3)	930(1)	505
C(9)	8 602(2)	4 968(3)	1 355(1)	391
C(10)	7 368(2)	6 558(3)	1 481(1)	361
C(11)	6 807(2)	7 490(3)	791(1)	406
C(12)	7 682(3)	9 229(4)	−183(1)	571
O(1)	5 410(2)	7 569(3)	568(1)	817
O(2)	8 060(2)	8 312(3)	472(1)	525
O(3)	10 399(3)	10 108(3)	1 733(1)	669
H(1)C(1)	1 088(5)	452(5)	107(2)	92(12)
H(2)C(1)	1 006(4)	609(4)	54(2)	49(8)
H(1)C(2)	1 139(4)	649(5)	199(2)	61(9)
H(2)C(2)	1 212(5)	755(5)	128(2)	88(11)
H(1)C(4)	833(4)	742(4)	241(1)	48(8)
H(2)C(4)	761(4)	914(5)	200(2)	71(10)
H(1)C(5)	618(4)	535(4)	234(2)	64(9)
H(2)C(5)	504(4)	688(4)	194(2)	69(10)
H(1)C(6)	401(4)	376(5)	171(2)	65(10)
H(2)C(6)	446(3)	461(4)	100(1)	46(8)
H(1)C(7)	661(4)	226(5)	180(2)	69(10)
H(2)C(7)	576(4)	188(5)	105(2)	70(11)
H(1)C(8)	863(5)	258(6)	83(2)	85(11)
H(2)C(8)	745(4)	384(4)	42(2)	55(9)
HC(9)	871(3)	444(4)	185(1)	41(8)
H(1)C(12)	683(5)	1 020(5)	−15(2)	79(10)
H(2)C(12)	723(4)	832(5)	−52(2)	73(10)
H(3)C(12)	873(6)	959(7)	−31(3)	135(16)

TABLE 5

Atomic co-ordinates and isotropic U values ($\times 10^4$ for C and O, $\times 10^3$ for H atoms) for (4)

	x/a	y/b	z/c	$\bar{U}$/Å^2
C(1)	2 314(2)	7 875(2)	5 792(2)	420
C(2)	2 630(2)	8 575(2)	4 861(2)	454
C(3)	3 395(2)	9 440(2)	5 117(2)	343
C(4)	4 203(2)	9 165(2)	5 890(2)	350
C(5)	4 764(2)	8 077(2)	7 470(2)	427
C(6)	5 394(2)	7 209(2)	6 908(2)	515
C(7)	4 739(2)	6 250(2)	6 578(2)	541
C(8)	3 863(2)	6 626(2)	5 895(2)	456
C(9)	3 204(2)	7 481(2)	6 449(2)	350
C(10)	3 849(2)	8 474(2)	6 821(2)	314
C(11)	3 173(2)	9 188(2)	7 491(2)	363
O(1)	2 910(2)	8 737(1)	8 385(1)	606
O(2)	2 875(2)	10 078(1)	7 239(2)	640
O(3)	3 401(1)	10 324(1)	4 672(1)	468
H(1)C(1)	195(2)	723(2)	553(2)	62(7)
H(2)C(1)	184(2)	834(2)	625(2)	53(6)
H(1)C(2)	295(2)	814(2)	431(2)	69(7)
H(2)C(2)	204(2)	893(2)	449(2)	55(7)
H(1)C(4)	475(2)	874(1)	549(2)	42(6)
H(2)C(4)	449(2)	988(2)	612(2)	56(7)
H(1)C(5)	520(2)	872(2)	765(2)	55(7)
H(2)C(5)	453(2)	779(2)	812(2)	49(6)
H(1)C(6)	572(2)	755(2)	626(2)	49(6)
H(2)C(6)	596(2)	697(2)	735(2)	63(7)
H(1)C(7)	514(2)	572(2)	620(2)	69(8)
H(2)C(7)	448(2)	588(2)	722(2)	62(7)
H(1)C(8)	411(2)	694(2)	518(2)	51(6)
H(2)C(8)	341(2)	598(2)	571(2)	64(7)
HC(9)	295(1)	714(2)	709(2)	42(6)
HO(1)	242(3)	913(3)	880(3)	115(10)

Thus, for example, *endo*-6-carboxybicyclo[2.2.1]heptan-2-one (7) cyclizes even more rapidly than the decalin analogue (3a), the thermodynamically more stable isomer in solution is the keto-acid rather than the hydroxy-lactone, and the keto-acid is also the exclusive isomer in the crystal.[20]

In conclusion, we believe that this exercise demonstrates the feasibility and usefulness of studying the mechanisms of chemical reactions by designing molecules expected to be ' some way along the reaction path ' and then solving their crystal structures. Data so obtained correlate well with results of kinetic studies in solution and reveal subtleties of atomic and electronic reorganization during reaction that are undetectable by other techniques.

EXPERIMENTAL

Syntheses.—Compounds (2a), (3b), and (4) were prepared by the method of Haworth,[21] compound (2b) by methylation of (2a) with methanol and toluene-*p*-sulphonic acid, followed by chromatography. Crystals were obtained by slow cooling (4) or evaporation (2b), (3b) of cyclohexane–ethyl acetate solutions or by slow evaporation of benzene solutions (2a).

Spectroscopic Data.—I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer. Proton n.m.r. spectra were measured on a Varian HA 100 spectrometer, carbon-13 spectra on a Bruker WH 90 spectrometer at 23.63 MHz. Solutions in $CDCl_3$ (dried over molecular sieves) were *ca.* 1 molar in substrate for the ^{13}C measurements.

Crystal Data.—(2a) 3-*Hydroxy*-trans-*bicyclo*[4.4.0]*decane*-1,3-*carbolactone*. $C_{11}H_{16}O_3$, $M = 196.12$, m.p. 113—114 °C. Monoclinic, $a = 9.505$, $b = 6.854$, $c = 15.912$ Å, $\beta = 75.20°$, $Z = 4$, $D_c = 1.30$ g cm^{-3}. Space group $P2_1/c$.

(*b*) (2b) 3-*Methoxy*-trans-*bicyclo*[4.4.0]*decane*-1,3-*carbolactone*. $C_{12}H_{18}O_3$, $M = 210.27$, m.p. 40—41 °C. Orthorhombic, $a = 15.989$, $b = 11.947$, $c = 11.744$ Å, $Z = 8$, $D_c = 1.25$ g cm^{-3}. Space group *Pbca*.

(*c*) (3b) *Methyl* 3-*oxo*-trans-*bicyclo*[4.4.0]*decane*-1-*carboxylate*. $C_{12}H_{18}O_3$, $M = 210.27$, m.p. 53—54 °C. Monoclinic, $a = 8.018$, $b = 7.398$, $c = 18.908$ Å, $\beta = 91.05°$, $Z = 4$, $D_c = 1.25$ g cm^{-3}. Space group $P2_1/c$.

(*d*) (4) 3-*Oxo*-cis-*bicyclo*[4.4.0]*decane*-1-*carboxylic acid*. $C_{11}H_{16}O_3$, $M = 196.12$. Orthorhombic, $a = 13.234$, $b = 12.209$, $c = 12.819$ Å, $Z = 8$, $D_c = 1.26$ g cm^{-3}. Space group *Pbca*.

Estimated standard deviations in cell dimensions are of the order of 0.02—0.04%. Intensity measurements (Enraf–Nonius CAD 4 diffractometer with graphite-monochromatized Mo-K_α radiation), structure analysis (MULTAN) [22] and structure refinement (*X*-Ray '72,[23] full- or block-matrix least-squares analysis) were carried out along much the same lines for all four crystals. The numbers of independent reflexions measured [those considered observed, having $I \geqslant 3\sigma(I)$, in parentheses] were (2a) 1 751 (734), (2b) 2 412 (880), (3b) 2 708 (1 405), and (4) 1 814 (1 060). For (2b), (3b), and (4) crystals were sealed in glass capillaries to prevent sublimation during the *X*-ray measurements. After preliminary least-squares refinement of non-hydrogen atom positions and isotropic vibration parameters, all hydrogen atoms could be located from difference-Fourier maps. Final refinement cycles with unit (2a) or experimental weights included anisotropic vibration parameters for non-hydrogen, isotropic for hydrogen atoms, and (for 2a) an extinction correction. Final *R* factors (based on significant reflexions only) were (2a) 0.029, (2b) 0.034, (3b) 0.045, and (4) 0.032.

Atom positions and mean vibration parameters are listed in Tables 2—5. Structure factors and components of vibration tensors are listed in Supplementary Publication No. SUP 22380 (35 pp., 1 microfiche).*

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REFERENCES

[1] J. D. Dunitz and F. K. Winkler, *Acta Cryst.*, 1975, **B31**, 251.

[2] D. J. Chadwick and J. D. Dunitz, *Acta Cryst.*, 1978, **B34**, 968.

[3] H. B. Bürgi, J. D. Dunitz, and E. Shefter, *Acta Cryst.*, 1974, **B30**, 1517.

[4] P. Deslongchamps, *Tetrahedron*, 1975, **31**, 2463.

[5] B. Beagley, in ' Molecular Structure by Diffraction Methods,' vol. 1, Chem. Soc. Specialist Periodical Reports, 1973, p. 88.

[6] J. D. Dunitz and P. Strickler, in ' Structural Chemistry and Molecular Biology,' ed. A. Rich and N. Davidson, Freeman, San Francisco, 1968, p. 443.

[7] H. B. Bürgi, J. D. Dunitz, and E. Shefter, *J. Amer. Chem. Soc.*, 1973, **95**, 5065.

[8] H. B. Bürgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, 1974, **30**, 1563.

[9] H. B. Bürgi, J. M. Lehn, and G. Wipff, *J. Amer. Chem. Soc.*, 1974, **96**, 1956.

[10] W. B. Schweizer, Doctoral Dissertation No. 5948, E.T.H., Zürich.

[11] L. Leiserowitz, *Acta Cryst.*, 1976, **B32**, 775.

[12] C. S. Huber and E. J. Gabe, *Acta Cryst.*, 1974, **B30**, 2519.

[13] C. K. Johnson, ORTEP: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, Oak Ridge National Laboratory Report ORNL 3794, 1965.

[14] D. W. J. Cruickshank, *Acta Cryst.*, 1956, **9**, 754, 757; V. Schomaker and K. N. Trueblood, *ibid.*, 1968, **B24**, 63.

[15] J. D. Dunitz and D. N. J. White, *Acta Cryst.*, 1973, **A29**, 93.

[16] E. H. Cordes and H. G. Bull, *Chem. Rev.*, 1974, **74**, 581.

[17] ' Comprehensive Chemical Kinetics,' vol. 8, ' Proton Transfer,' ed. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1977.

[18] C. Altona, ' Molecular Structure and Conformation of some Halogeno-1,4-dioxanes,' Doctoral Dissertation, Leiden, 1964; G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydrate Res.*, 1972, **25**, 117; S. David, O. Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, *J. Amer. Chem. Soc.*, 1973, **95**, 3806; J. M. Lehn, G. Wipff, and H. B. Bürgi, *Helv. Chim. Acta*, 1974, **57**, 493.

[19] P. Deslongchamps, P. Altani, D. Fréhel, and A. Maleval, *Canad. J. Chem.*, 1972, **50**, 3405; P. Deslongchamps, C. Lebreux, and R. J. Taillefer, *ibid.*, 1973, **51**, 1665; P. Deslongchamps, R. Chenevert, R. J. Taillefer, C. Moreau, and J. K. Saunders, *ibid.*, 1975, **53**, 1601.

[20] D. J. Chadwick and S. Whittleton, unpublished results.

[21] R. D. Haworth, B. G. Hutley, R. G. Leach, and G. Rodgers, *J. Chem. Soc.*, 1962, 2720.

[22] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1970, **B26**, 274.

[23] J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, and S. R. Hall, Technical Report TR 192, Computer Science Center, University of Maryland, 1972.