Rearrangements of Some Polycyclic Hydroxy Ketones in Strong Protic Acids

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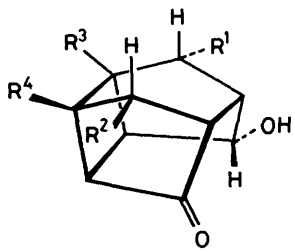
The polycyclic hydroxy ketones (**1**)–(**3**) are unaffected by treatment with 1 mol dm^{-3} aqueous hydrochloric acid. Hydroxy ketone (**5**) is also stable to fluorosulphonic acid–antimony pentafluoride in liquid sulphur dioxide at 0 °C. ^1H and ^{13}C NMR spectroscopy shows that (**5**) is protonated on both alcohol and carbonyl oxygens in this medium, and an activation energy, $\Delta G^{\ddagger}$, of 14.7 ± 0.8 kcal mol^{-1}, for geometric isomerism of the protonated carbonyl has been determined by dynamic NMR methods. The rate, k = 1.17 s^{-1} (23.3 °C) of degenerate rearrangement of (**5**) by 1,4-hydride shift from alcohol methine to carbonyl carbon in trifluoromethanesulphonic acid in liquid sulphur dioxide solution was determined by spin-saturation transfer experiments. The primary kinetic isotope effect was 2.30 ± 0.35. In trifluoromethanesulphonic acid, (**5**) also rearranges more slowly to (**7**) or (**8**). In strongly acidic media, hydroxy ketone (**6**) rearranges rapidly to a mixture of (**9**) and (**10**). The X-ray crystal structure of (**10**) has been determined.

In Meerwein–Ponndorf–Verley–Oppenauer (MPVO) redox reactions, hydrogen is transferred efficiently from primary or secondary alcohols to ketonic or aldehydic carbonyl.[1] The reaction is commonly catalysed by aluminium alkoxides, and the currently accepted transition structure is a six-centre array with the Al^{3+} binding oxygens at both receiving and donating groups, and formal transfer of hydride from alcohol methine or methylene to carbonyl carbon.[2] The catalyst thus exhibits a dual function, generating alkoxide from the donating alcohol and enhancing the electrophilicity of the receiving carbonyl. It has been suggested that the transfer of hydride and Al^{3+} from alcohol to carbonyl should be described as a pericyclic group-transfer process, and the degree and benefits of concert in this and related processes remain a matter of interest.[3]

Hydroxy ketones incorporating primary or secondary alcohol groups may rearrange under the influence of base in an intramolecular variant of the MPVO reaction.[4] It has been shown, however, that when simultaneous co-ordination of alcohol and carbonyl oxygen to metal cation is blocked by structural features, the rearrangement is inhibited, rather than promoted, by metal cation.[5,6] The catalysis then involves deprotonation of the alcoholic oxygen which enhances the hydridic character of the alcohol methine hydrogen.[7] Migration occurs in the anion, Scheme 1, and any co-ordination by cation, which occurs at alkoxide rather than carbonyl oxygen, lowers the hydridic character of the adjacent hydrogen. These anionic reactions have now been well studied[4] and data has accumulated which relates structure and reactivity[8] in rearrangements of polycyclic hydroxy ketones, as exemplified by the methylated 5-hydroxytetracyclo[4.4.$0^{3,9}$.$0^{4,8}$]decan-2-ones, (**1**)–(**6**). These have a wide range of reactivity[9] with rates of hydride shift within the alkoxides ranging from 2.5 s^{-1}, for (**4**) rearranging to (**3**) in water at 25 °C, to 2 000 s^{-1} for the corresponding rearrangement of (**1**) to (**2**).

Since the metal counter-ion is not involved in these rearrangements, measurements on the reactions may allow quantification of the benefits of catalysis in hydride transfer where simultaneous co-ordination is possible. However, data on acid catalysed rearrangements of the polycyclics would also be required, and although some related acid induced rearrangements of hydroxy ketones have been reported[10] these are much less well characterised than their base-induced counterparts. Although reasonably formulated as involving protonation on the carbonyl oxygen, interpretation of any kinetic measurements

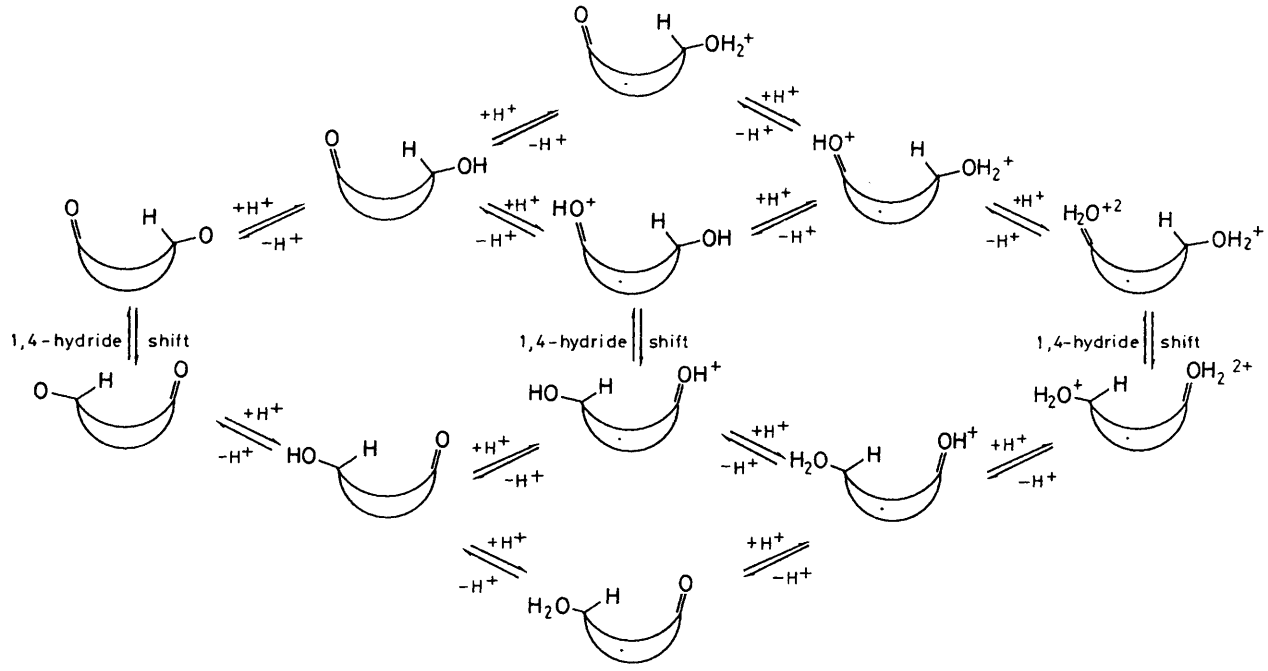


(**1**) R^1 = Me; R^2 = R^3 = R^4 = H
(**2**) R^2 = Me; R^1 = R^3 = R^4 = H
(**3**) R^3 = Me; R^1 = R^2 = R^4 = H
(**4**) R^4 = Me; R^1 = R^2 = R^3 = H
(**5**) R^1 = R^2 = Me; R^3 = R^4 = H
(**6**) R^3 = R^4 = Me; R^1 = R^2 = H

is complicated by competing protonation at the alcohol oxygen. Indeed, measurements on monofunctional compounds indicate that the alcohol or ethereal oxygen is 3–4 pK_a units more basic* suggesting preferential protonation at the 'wrong' oxygen for induction of hydride shift. Scheme 1 shows the likely acid–base behaviour of an hydroxy ketone, and its relationship to possible hydride shifts. Multiply protonated species are included since these have been implicated as intermediates in rearrangements in very strongly acidic media.[11]

We describe here an investigation of the effects of aqueous and non-aqueous acid on (**1**)–(**6**), undertaken in the hope of measuring rates of hydride shift in a carbonyl-protonated species. Crystal structure studies of (**1**)[9] and (**5**)[12] show close non-bonded approaches between the alcoholic oxygen and the pendant methyl on the same face of the molecule (2.944 and 2.915 Å between methyl-C···alcohol O, respectively). In contrast, the carbonyl oxygens occupy a relatively unhindered environment, and the difference is well seen (Figure 1) in a projection of the crystal structure of (**5**) on the plane containing the oxygens and their attached carbons. We speculated that steric hindrance[13] at alcohol oxygen might, particularly in the case of (**5**), be sufficient to modify the expected pattern of basicities, and allow a simple examination of the behaviour of a

* For a discussion of the basicity of carbonyl and alcoholic oxygen see 'The Proton; Applications to Organic Chemistry,' ed. R. Stewart, Academic Press, London, 1985, p. 113.



Scheme 1. Proton transfers and hydride shifts in hydroxy ketone rearrangements.

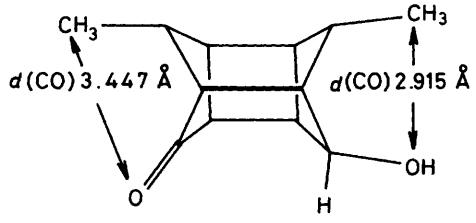


Figure 1. Stereochemical relationship of methyl groups and oxygens in (**5**).

Table 1. ^{13}C Chemical shifts for (**5**).

Signal assignment	δ_C		
	SO_2	SO_2–FSO_3H–SbF_5	SO_2–CF_3SO_3H
CH_3(10)	16.3	14.9	15.0
CH_3(7)	19.6	16.7	17.0
C(10)	31.9	35.0	35.0
C(7)	35.8	37.8	36.2
C(9)	39.4	42.2	41.2
C(3)	43.2	42.6	42.5
C(8)	43.7	46.0	45.3
C(4)	45.2	46.5	45.9
C(6)	49.4	51.5	50.8
C(1)	53.2	56.2	54.5
C(5)	79.2	91.6	85.6
C(2)	226.3	261.9	256.9

carbonyl oxygen protonated species in an appropriate acidic medium.

In our first experiments the effects of aqueous acid on (**1**) and (**3**) were examined. As noted above, these are equilibrated with their isomers, (**2**) and (**4**), in aqueous base at pH 13 with a half-life for isomerisation of (**1**) to (**2**) of 10 min. In contrast, no observable conversions of either hydroxy ketone occurred on treatment with 1 mol dm^{-3} HCl at 25 °C. Even after several weeks, they could be recovered unchanged so that the isomerisations are at least 10^3 times slower in acid reflecting either a much higher barrier to hydride transfer in the carbonyl protonated cation, or much more likely, an extremely low concentration of the appropriately protonated species. The effect of stronger protic acids in non-aqueous media on symmetrically methylated hydroxy ketones (**5**) and (**6**) was therefore examined. Since the intended hydride shift exchanges the pendant methyl group environments, dynamic NMR spectroscopic methods which were successfully applied in the anionic rearrangements[6] were used here, and it was hoped that chemical shift data would reveal the nature of the major protonated species.

Full ^1H and ^{13}C assignments in the spectra of (**5**) in chloroform have been obtained by a combination of 2-D $^{13}C/^1H$ correlation and INADEQUATE spectra.[14] Spectra in chloroform and liquid sulphur dioxide did not differ significantly, and it was possible to follow the shifts induced by addition of acid.

Table 1 lists ^{13}C chemical shifts in the absence and presence of excess fluorosulphonic acid–antimony pentafluoride in liquid sulphur dioxide. This acid is strong enough (H_0 *ca.* −17)[15] to protonate at both oxygens of simple aliphatic hydroxy ketones,[16] and the acid induced shift in the signal from the carbonyl carbon of (**5**) is comparable to those encountered in protonation of monofunctional cage ketones such as adamantanone,[17] suggesting that carbonyl protonation has occurred here. The signal due to the alcohol methine carbon is shifted in acid and comparison with observations on very simple alcohols[18] suggests that the shifts are consistent also with alcohol oxygen protonation. In fact, relevant data is rather scarce, with most protonated polycyclic alcohols dissociating to carbocation and water even at low temperatures. Remarkably, hydroxy ketone (**5**) is recovered in good yield from this acid mixture, even after extended periods at 0 °C, and we comment later on this stability.

The ^1H NMR spectra confirm that both oxygens are protonated. In these solutions, proton transfer is slow on the NMR timescale,[19] and, at −53 °C, the presence of both protonated carbonyl geometric isomers[20] is shown by signals at δ 14.84 and 14.81 (integrating to a total of one proton) from each isomer, and by a corresponding additional splitting of the

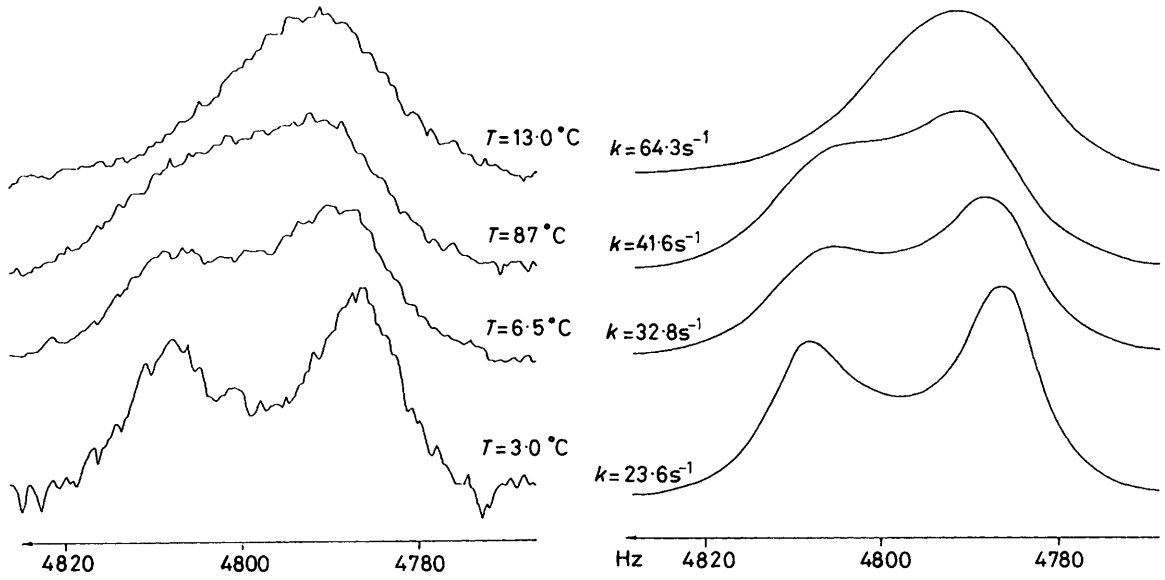


Figure 2. Temperature dependence of protonated carbonyl signals in the ^{1}H NMR spectrum of (**5**) in FSO_3H–SbF_5 solution.

doublet at δ 0.81 from the carbonyl side methyl. Any splitting of other signals was not resolved (at 300 MHz). The alcohol methine appears as a sharp singlet at δ 5.1 and a second singlet (two hydrogens) at δ 10.39 was assigned to the OH_2^+ of the protonated alcohol. Coupling between methine and OH_2^+ groups is observable (J 3.5 Hz) in the spectra of simple aliphatic protonated alcohols,[18] and we rationalise its absence in the spectrum of (**5**) as a conformational effect. Analogies with protonated water[21] suggest that the oxygen of protonated alcohol should be pyramidal. In (**5**), the close non-bonded approach of alcohol and methyl in the least hindered conformation of the C–O bond should place the OH bonds staggered about 60° on either side of the alcohol methine. If a rapid amine-like umbrella inversion at oxygen then occurs* the average H–C–O–H dihedral angle would be *ca.* 90° with corresponding loss of observable coupling.

The ^{1}H NMR spectra show temperature-dependent behaviour. The signals at δ 14.84 and 14.81 broaden, coalesce and resharpen to a singlet as the temperature is raised to 25 °C. These changes are accompanied by loss of the splitting in the carbonyl side methyl, and are most reasonably associated with interconversion of the isomers arising from carbonyl protonation by either rotation or inversion at carbonyl oxygen.[22] Rates obtained by lineshape analysis[23] of the carbonyl proton signals (Figure 2) at a range of temperatures gave $\Delta G^{\ddagger}$ 14.7 ± 0.8 kcal mol^{-1} for the process, comparable to barriers found in similar protonated ketone geometric isomerisations.[24]

Even at the highest temperature (+29 °C) the spectra gave no indication of any other rate process. The OH peaks remained sharp, establishing a lower limit of *ca.* 14 kcal mol^{-1} for activation energies of proton exchange between the acid and alcohol or carbonyl sites. Neither was there any detectable broadening of the methyl signals which might show the onset of the 1,4-hydride shift which exchanges the methyl group sites. Assuming that a broadening of 0.5 Hz would be detectable, an upper limit of 1 s^{-1} can be set for the rate of such a process.[25] As with the results in aqueous acid, the absence of such exchange is almost certainly associated with an extremely low concentration of the appropriate carbonyl-protonated hydroxy ketone.

We therefore also examined the effects of addition of the rather weaker trifluoromethanesulphonic acid (H_0 = −14.1),[26] in an attempt to favour formation of a singly protonated species. Table 1 includes the ^{13}C chemical shifts observed on addition of excess acid to a solution of (**5**) in liquid sulphur dioxide. Clearly there are strong resemblances to the spectrum in fluorosulphonic acid–antimony pentafluoride, but the acid-induced shifts in the carbonyl and alcohol carbons are both less by 5–6 ppm. Again, both oxygens seem involved in the acid–base equilibria, but with a lowered equilibrium concentration of doubly protonated species. The first five equivalents of acid induce relatively large shifts in the proton ^{1}H NMR spectrum. Most clearly, the alcohol methine hydrogen moves downfield by 0.56 ppm, a change comparable to that observed in with the stronger acid. However, proton exchange between the basic sites is now rapid on the NMR timescale so that separate signals from protonated carbonyl and alcohol oxygen are not observable.

The temperature dependence of the spectra was again examined for evidence of a rate process exchanging methyl sites. At the highest temperature (30 °C) the signals showed little broadening, but there were indications in the remainder of the spectrum (where exchanging signals were closer) of reversible changes. Unfortunately, the solutions were much less stable than those in the stronger acid medium and, at 30 °C, interpretation was complicated by a superimposed irreversible conversion ($t_{\frac{1}{2}}$ *ca.* 1 h at 25 °C) to a new material the characterisation and mode of formation of which are discussed later. The spin saturation transfer (Forsén–Hoffman)[27] method, which allows measurement of rates of exchange comparable to those of relaxation of nuclei in the separate exchanging sites, was applied to the methyl signals, at a temperature (23.3 °C) at which the solutions were sufficiently stable to allow completion of the experiment. Relaxation of the methyl hydrogens, measured by the usual inversion–recovery method,[28] was relatively rapid (T_1 1.0 ± 0.05 s in each case). At 300 MHz, the signals are separated by 90 Hz, and a DANTE sequence[29] allowed selective excitation of the lower-field signal. With the rapid relaxation of the methyl hydrogens total signal inversion was not achieved, but the behaviour of the signals following inversion (Figure 3), and the clear dip in the magnetisation of the uninverted signal provide evidence of spin transfer. Treatment of the data, with appropriate allowance for the incomplete inversion, gave k = 1.17 s^{-1} (95% confidence limit ±0.05) for the exchange.

* Calculations for H_3O^+ give a barrier 2.3 kcal mol^{-1}, W. R. Rodwell and L. Radom, *J. Am. Chem. Soc.*, 1981, **103**, 2865.

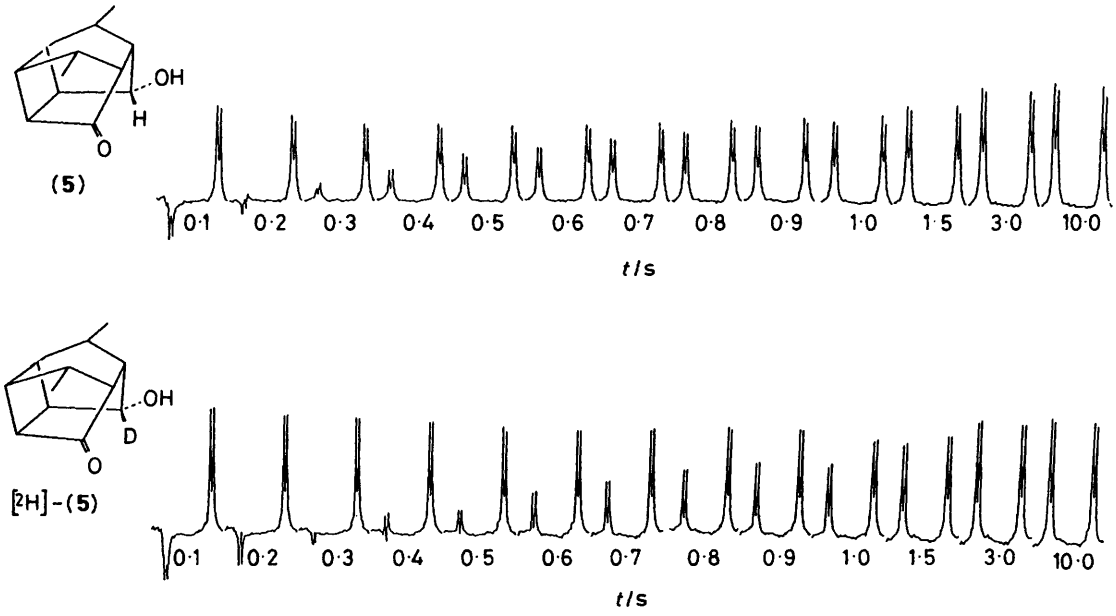


Figure 3. Spin saturation transfer between methyl groups in the ^1H NMR spectra of (5) and [^2H]-(5) in CF_3SO_3H–SO_2 solution.

These experiments measure rates of interconversion of the major component of the acid–base equilibria. To test the possibility that the rate determining step was a proton transfer to or from this major component, rather than the 1,4-hydride shift, a sample of (5) in which the migrating alcohol methine hydrogen had been replaced by deuterium was subjected to the same measurements. An exchange rate $k = 0.51$ s^{-1} (95% confidence limit ± 0.06) was determined. The primary kinetic hydrogen isotope effect, 2.30 ± 0.35 thus compares closely with that in the anionic rearrangement (2.11 at 35 °C)[9] of (5). Besides supporting rate limiting hydride shift in both cases, the similarity suggests that force constant changes in bonds to the migrating hydride are not strongly sensitive to charge on the delivering and accepting carbons.[30]

Clearly, the acid catalysed rearrangement involving the 1,4-hydride shift in these hydroxy ketones is observable, but it is equally clear that our optimistic speculation as to steric inhibition of the basicity of the alcoholic oxygen in (5) is unfulfilled, at least with protic acids. A simple carbonyl protonated species has not been observed and a rate for the 1,4-shift in this cation would only be obtained in conjunction with measurements of the acid–base equilibria which do not seem currently feasible. However, there are possibilities of selective co-ordination at carbonyl oxygen with more sterically demanding Lewis acids,[13] and these remain to be examined.

As noted above, the attempts to measure rates of degenerate hydride shifts in (5) were complicated by slower competing deep-seated rearrangements. Similar attempts to observe hydride shifts in (6) were completely unsuccessful with the competing rearrangements too fast at the necessary temperatures to allow observation of the methyl site exchange. These rearrangements have some interest in their own right, and the characterisation of their products are described here.

Monitoring of the ^1H NMR spectrum of a solution of (5) in trifluoromethanesulphonic acid at room temperature showed that all the hydroxy ketone had reacted in < 6 h. The conversion was apparently a clean one, with little colouring or other indication of general decomposition or polymerization. New signals were observed at δ 1.35 (d, *J* 7 Hz), 2.31 (br s), 3.46 (m), 4.29 (q, *J* 7 Hz), 6.95 (m), 7.96 (br s), and 8.15 (br d, *J* 5 Hz), and when the acid mixture was poured into aqueous methanolic sodium hydrogen carbonate, extraction yielded a single major component which was purified by preparative TLC.

The heaviest fragment observed by mass spectrometry was at *m/z* 174 corresponding to $C_{12}H_{14}O$, *i.e.* a dehydration product of (5). IR (ν_{max} 688 and 1 655 cm^{-1}) and UV spectroscopy (λ_{max} = 317 nm, ε_{max} = 7 800) both indicated the presence of an α,β-unsaturated ketone. The 400 MHz ^1H NMR spectrum is shown in Figure 4. The coupling pattern, established by decoupling difference spectroscopy, shows that the hydrogens occupy two separate spin systems, and partial structures which account for the oxygen and all hydrogens may be proposed. Two carbons only are lacking and these may form a tetrasubstituted ethylenic bond linking the two spin systems. The material was hydrogenated over platinum and when uptake was complete, GLC analysis indicated the presence of four major components of similar retention time in the product. GC–MS showed that all components had a molecular ion at *m/z* 180, corresponding to uptake of 3 H_2. Revealingly, the now UV-inactive material showed an IR absorption at 1 740 cm^{-1}, indicating a cyclopentanone.

The combined chemical and spectroscopic evidence is therefore satisfied by structure (7) or its geometric isomer (8). Alternatives with decalin frameworks are excluded.

Scheme 2 shows a possible mechanism for the formation of (7) or (8). In a dissociation of the alcohol-protonated hydroxy ketone (5), both the C1–C6 and C3–C4 bonds are suitably aligned[31] for participation, but C3–C4 involvement releases the cyclobutane ring strain, and either cleavage would yield an α-ketocarbocation. These have been generated in other arrays by solvolysis,[32] and their destablisation by inductive effects, is believed to be more than compensated by resonance stabilisation. The cyclopentylidenecyclopentane array with an allyl cation and α,β-unsaturated ketone is then formed by cleavage of the C8–C9 bond, and rapid hydride and methyl shifts yield a stable[33] protonated dienone the structure of which is consistent with the spectrum observed[34] before quenching and work-up. The degree of concert in the changes occurring remains a matter of speculation.

We have noted earlier that this rearrangement occurs less readily in the stronger FSO_3H–SbF_5 acid medium, in which protonation of (5) on both alcohol and ketone oxygens is effectively irreversible. Presumably, loss of water with participation of either aligned bond is rendered unfavourable since it leads to a protonated α-keto-carbocation, and no other bond (C–C or C–H) is aligned.

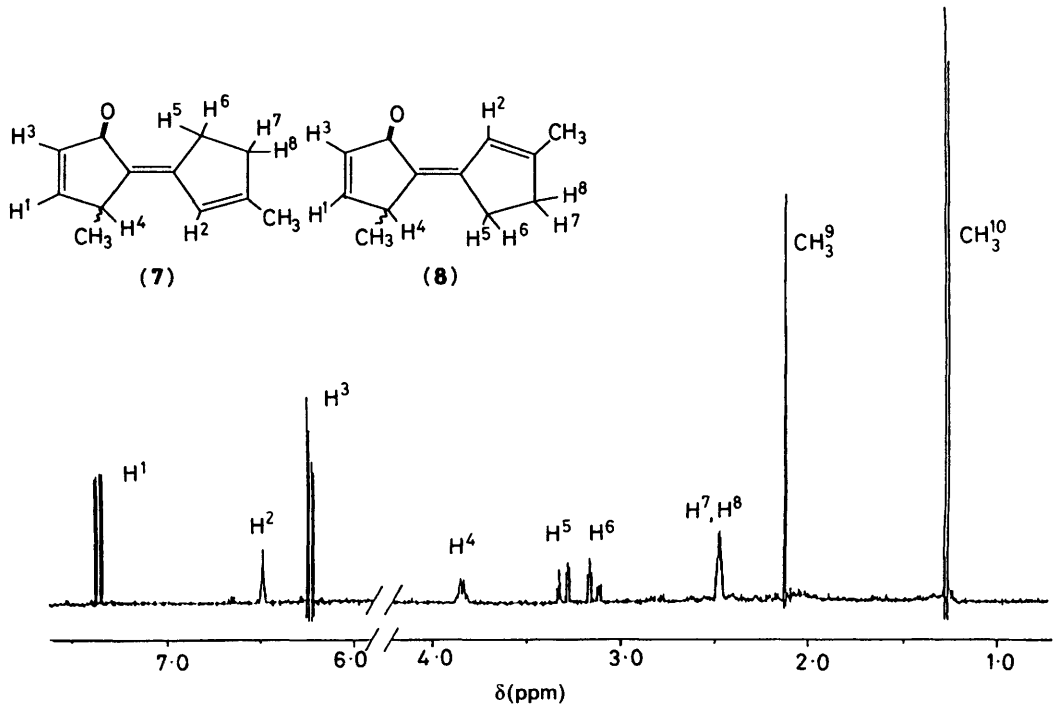
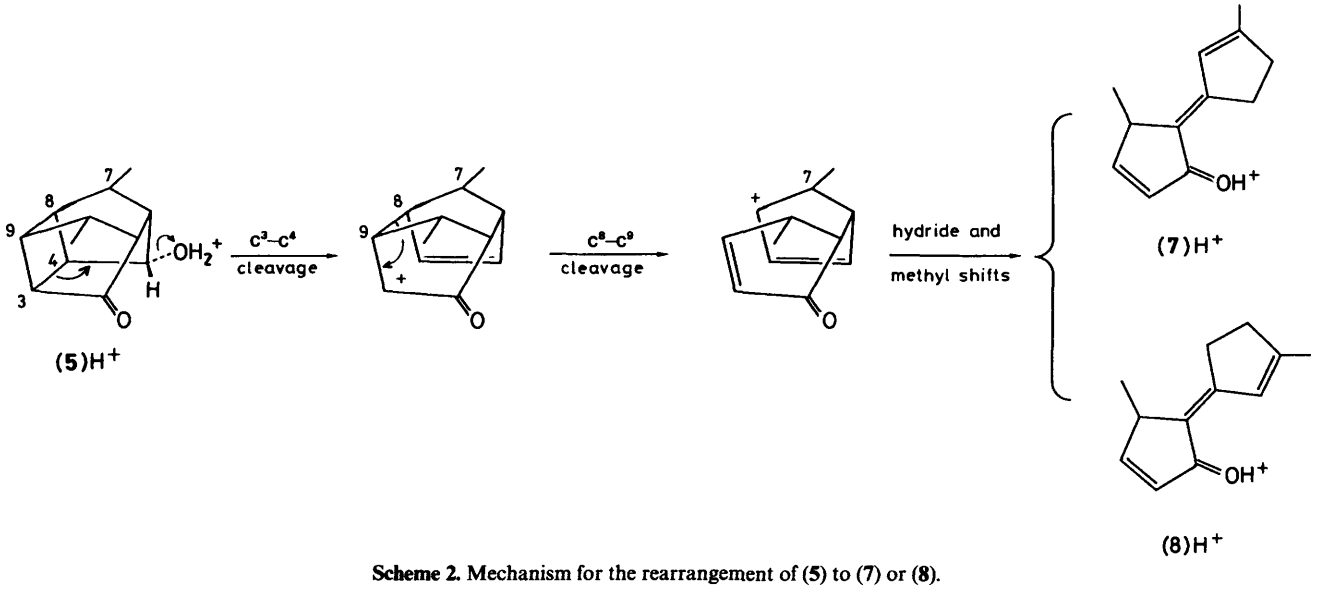


Figure 4. ^{1}H NMR spectrum of (**7**) or (**8**) in $CDCl_3$.



Scheme 2. Mechanism for the rearrangement of (**5**) to (**7**) or (**8**).

Similar acid treatments of the more labile isomeric hydroxy ketone (**6**) yielded not one but two rearrangement products, (**9**) and (**10**), which were isolated after quenching with aqueous hydrogencarbonate and extraction by preparative TLC on silica. The less polar component (**9**) was the minor product and was isolated only as a pale yellow oil. Mass spectrometry showed it to be an isomer of (**6**), and IR (ν_{max} 1 690 cm^{-1}) and UV spectroscopy (λ_{max} 219, ε_{max} 8 000) were again consistent with an α,β-unsaturated ketone functionality. Since no IR bands corresponding to an O–H stretch were found, a tricyclic array containing an ether link seemed most probable. The ^{1}H NMR spectrum (Figure 5) and coupling pattern revealed by decoupling experiments allows a complete tracing through the proton array, and indicated structure, containing the ether-bridged *cis*-decalin skeleton (**9**) satisfies the spectroscopic data.

The more polar second product from the acid treatment of (**6**) was a crystalline solid, and again, mass spectrometry showed it to be an isomer. The compound showed no strong UV absorption, and IR absorptions (1 710, 3 600, and 3 400 cm^{-1}) were indicative of saturated ketone and alcoholic OH groups. ^{13}C NMR spectroscopy showed, with the exception of the carbonyl carbon, no signal $<\delta$ 67, and its ^{1}H NMR spectrum (Figure 6) showed no signal associated with alkenic hydrogens. The couplings were identified by decoupling experiments, and as with (**9**) it was possible to trace the complete proton array.

Two quaternary carbons and methyl groups are not unambiguously placed by the data, but a small 2.5 Hz coupling between 4-H and 6-H is typical of a four-bond coupling between hydrogens in a W-configuration. If the carbons carrying these hydrogens are linked by one of the quaternary carbons, carrying a methyl, this arrangement is achieved. The unsatisfied valences might then be linked to the last C-Me group to yield

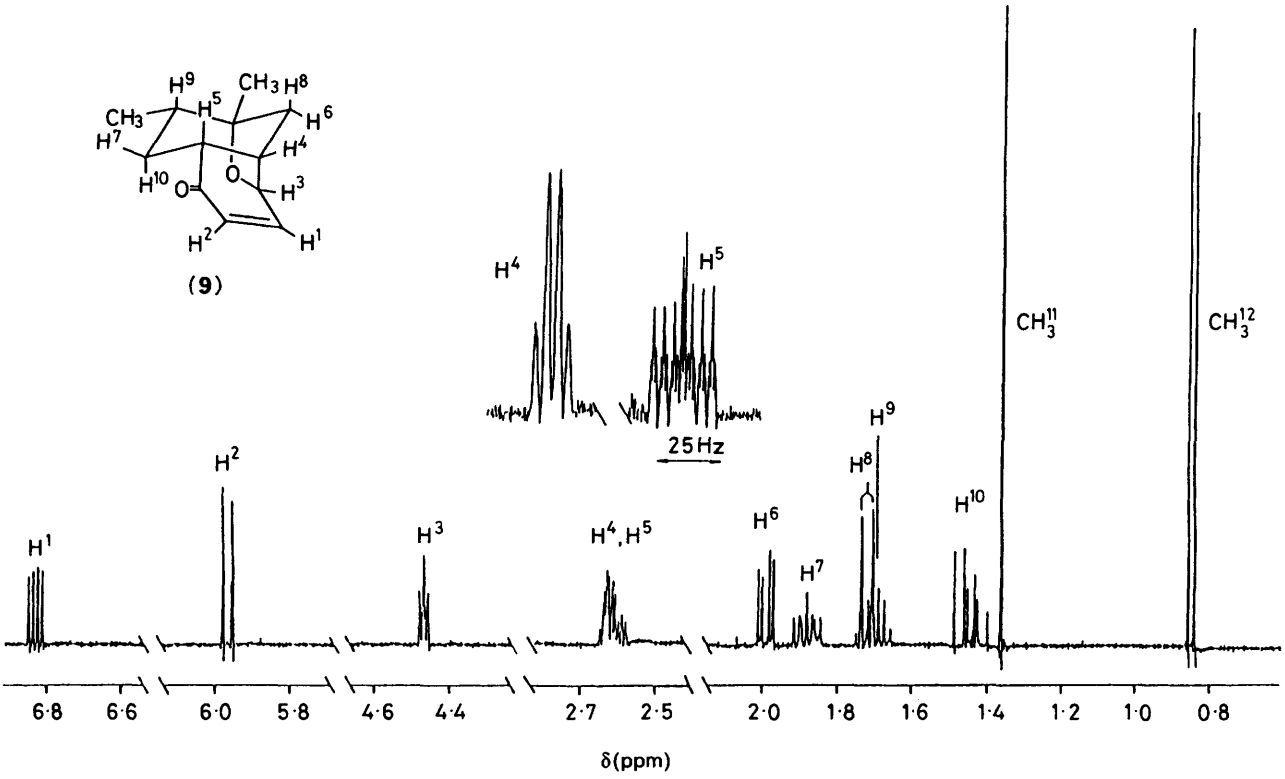


Figure 5. ^{1}H NMR spectrum of (**9**) in $CDCl_3$. *Inset:* expansion of H^4 and H^5 taken from 400 MHz NMR spectrum in C_6D_6.

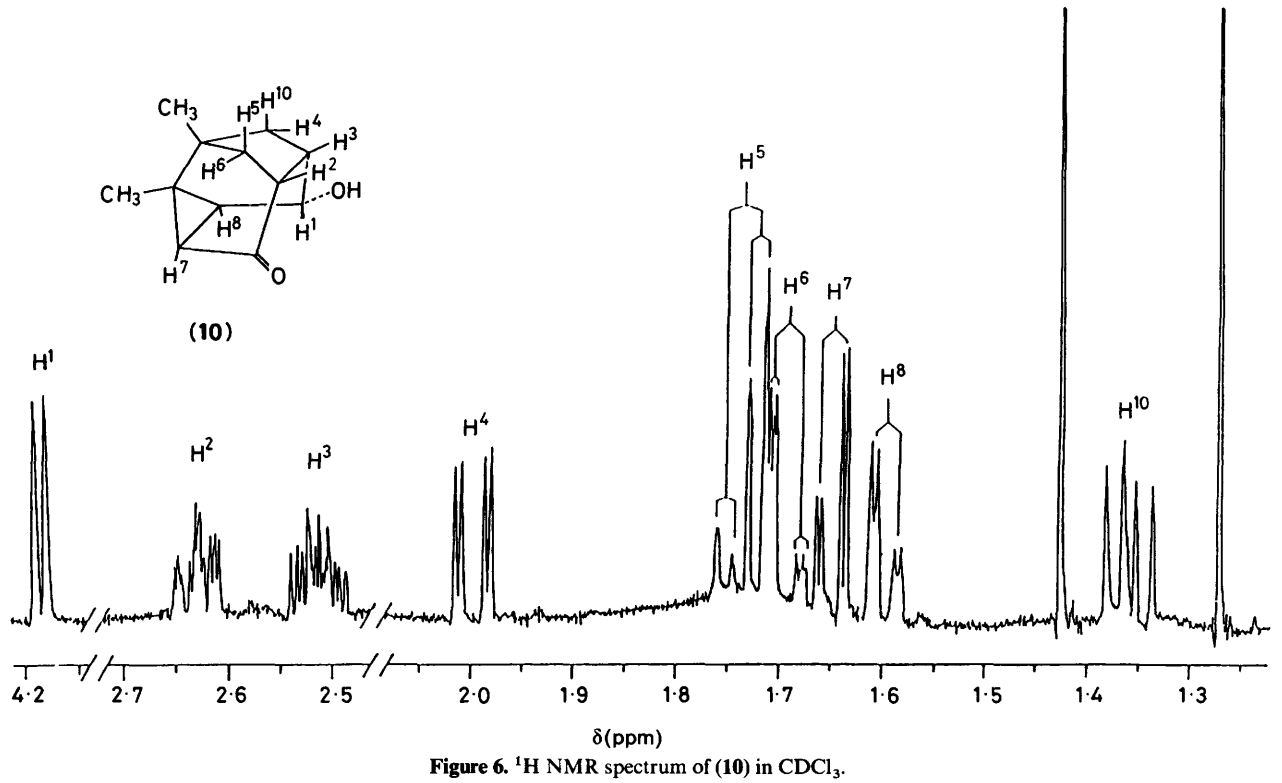
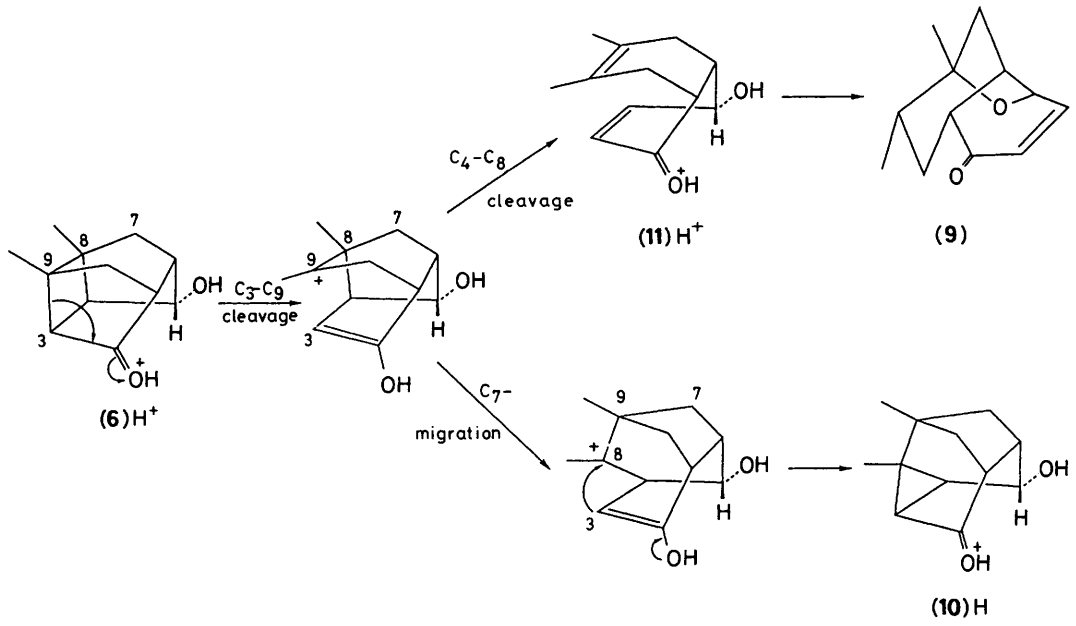


Figure 6. ^{1}H NMR spectrum of (**10**) in $CDCl_3$.

the cyclopropane-containing hydroxy ketone, (**10**). Alternative strained structures containing *gem*-dimethyl groups on a quaternary carbon and cyclobutane rings, however, are not excluded by the data and remaining uncertainties were resolved by an X-ray crystal structure determination which established the product as hydroxy ketone, (**10**). Details of its molecular geometry are presented and discussed below. Finally, Jones oxidation was shown to occur without any accompanying deep-seated reorganisation, yielding a product the ^{1}H NMR spectrum of which contained signals from two quaternary



Scheme 3. Mechanism for the rearrangement of (**6**) to (**9**) and (**10**).

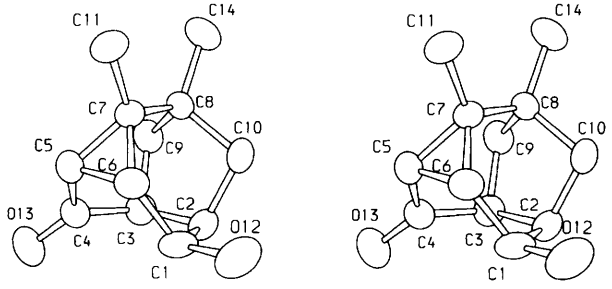


Figure 7. The X-ray crystal structure of (**10**).

methyl groups, and only four other two-hydrogen signals, two of which were clearly the components of methylene groups in the expected symmetrical 1,4-dione.

We rationalise the formation of (**9**) and (**10**) by the sequence shown in Scheme 3. The most economical mechanisms for the formation of both products are initiated by a cleavage in a carbonyl oxygen-protonated species, rather than dissociation of protonated alcohol. Related cleavages of protonated cyclobutyl ketone substructures are known,[35] the closest analogy being the fluorosulphonic acid induced conversion of *cis*-verbenone to 5-methyl-4-propylcyclohex-2-enones. Interestingly, the alignment of the cyclobutane C9–C3 bond with the π-array of the protonated in the parent ketone seems far from ideal with molecular modelling by empirical force-field calculation[36] giving φ (C9–C3–C1–O) = 148.2°. Presumably the cation-stabilising properties of a methyl group* at the C9 in the four-membered ring facilitate this process and relax the stereoelectronic requirements. Competing processes then lead reasonably to the two observed products. C4–C8 cleavage may then complete a net retro [2 + 2] process leading to (**11**) H^+. This 5-hydroxybicyclo[4.4.0]decadienone is in fact the synthetic precursor of (**6**) by photochemically induced [2 + 2] cyclobutane ring formation, and we were able to confirm that treatment of (**11**) with trifluoromethanesulphonic acid did indeed yield (**9**). Alternatively, a ring contraction by 1,2-shift of C7 yields a tertiary cation which after a small conformational change alkylates the enol to yield the cyclopropane ring in (**10**) H^+.

This rearrangement yielding (**10**) provides another structure containing a constrained boat conformation 4-hydroxycyclohexanone. As noted earlier, the reactivity in base induced 1,4-hydride shifts and the geometry in such molecules have been

* Estimated to be *ca.* 11 kcal mol^{-1}; J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1972, **94**, 4628.

Table 2. Atomic co-ordinates for structure (**10**).

Atom	*x/a*	*y/b*	*z/c*
C(1)	0.309 8(4)	0.195 9(3)	0.288 9(4)
C(2)	0.291 5(4)	0.151 8(3)	0.166 8(3)
C(3)	0.274 9(4)	0.013 5(3)	0.167 6(3)
C(4)	0.268 4(4)	−0.032 8(3)	0.286 1(3)
C(5)	0.129 0(4)	0.019 8(3)	0.356 7(3)
C(6)	0.151 4(4)	0.154 6(3)	0.356 1(3)
C(7)	−0.007 2(4)	0.101 1(3)	0.299 2(2)
C(8)	−0.014 4(4)	0.099 4(3)	0.165 9(2)
C(9)	0.085 1(5)	−0.007 9(3)	0.122 4(3)
C(10)	0.112 7(5)	0.193 7(3)	0.121 5(3)
C(11)	−0.182 9(5)	0.112 3(3)	0.363 1(3)
O(12)	0.315 7(4)	0.321 2(2)	0.294 5(3)
O(13)	0.365 6(4)	−0.112 1(2)	0.320 8(2)
C(14)	−0.202 2(5)	0.108 9(3)	0.116 8(3)
H(1)	0.419(4)	0.167(2)	0.317(3)
H(2)	0.394(4)	0.176(3)	0.120(3)
H(3)	0.364(4)	−0.037(2)	0.129(2)
H(5)	0.098(4)	−0.019(3)	0.427(3)
H(6)	0.125(5)	0.196(3)	0.419(3)
H(12)	0.375	0.346	0.231
H(91)	0.034(4)	−0.085(2)	0.154(2)
H(92)	0.082(4)	−0.013(2)	0.046(3)
H(101)	0.107(4)	0.199(3)	0.040(2)
H(102)	0.084(4)	0.270(3)	0.145(3)
H(111)	−0.264(5)	0.050(3)	0.343(3)
H(112)	−0.239(5)	0.182(3)	0.343(3)
H(113)	−0.166(6)	0.100(4)	0.444(3)
H(141)	−0.199(5)	0.112(3)	0.035(3)
H(142)	−0.260(5)	0.172(3)	0.137(3)
H(143)	−0.268(5)	0.045(3)	0.138(3)

Table 3. Bond lengths/Å, bond angles/°, and torsion angles/° for structure (**10**).

Atoms				Bond lengths			Bond angles		
A	B	C	D	AB	BC	CD	ABC	BCD	Torsion angle
C(1)	C(2)	C(3)	C(4)	1.523(5)	1.581(5)	1.488(5)	109.4(3)	111.4(3)	4.0(4)
C(1)	C(2)	C(3)	C(9)			1.534(5)		103.5(3)	114.5(3)
C(1)	C(2)	C(10)	C(8)		1.523(6)	1.531(5)	107.5(3)	101.6(3)	−84.4(3)
C(1)	C(6)	C(5)	C(4)	1.498(5)	1.547(5)	1.458(5)	113.6(3)	109.4(3)	−2.2(4)
C(1)	C(6)	C(5)	C(7)			1.532(5)		57.9(2)	−114.3(3)
C(1)	C(6)	C(7)	C(5)		1.491(5)		121.6(3)	61.5(2)	101.0(4)
C(1)	C(6)	C(7)	C(8)			1.562(4)		118.6(3)	−5.9(5)
C(1)	C(6)	C(7)	C(11)			1.514(6)		115.6(3)	−153.9(4)
C(2)	C(1)	C(6)	C(5)				108.6(3)		57.9(4)
C(2)	C(1)	C(6)	C(7)						−10.9(5)
C(2)	C(3)	C(4)	C(5)					113.8(3)	54.2(4)
C(2)	C(3)	C(4)	O(13)			1.224(5)		123.4(3)	−128.7(4)
C(2)	C(10)	C(8)	C(7)					108.1(3)	62.0(3)
C(2)	C(10)	C(8)	C(14)			1.518(6)		113.0(3)	−170.7(3)
C(3)	C(2)	C(1)	C(6)						−57.1(4)
C(3)	C(2)	C(1)	O(12)			1.430(5)		112.1(3)	−176.8(3)
C(3)	C(2)	C(10)	C(8)				104.3(3)		31.7(3)
C(3)	C(4)	C(5)	C(6)						−54.9(4)
C(3)	C(4)	C(5)	C(7)					118.5(3)	8.4(4)
C(4)	C(3)	C(2)	C(10)						−110.8(3)
C(4)	C(5)	C(6)	C(7)					60.5(2)	112.1(3)
C(4)	C(5)	C(7)	C(6)						−96.1(3)
C(4)	C(5)	C(7)	C(8)					116.9(3)	13.5(4)
C(4)	C(5)	C(7)	C(11)					114.4(3)	156.8(3)
C(5)	C(4)	C(3)	C(9)						−56.4(4)
C(5)	C(6)	C(1)	O(12)					108.4(3)	179.8(3)
C(5)	C(6)	C(7)	C(8)						−106.9(3)
C(5)	C(6)	C(7)	C(11)						105.1(3)
C(5)	C(7)	C(8)	C(10)						−91.7(3)
C(5)	C(7)	C(8)	C(14)					114.2(3)	141.6(3)
C(6)	C(1)	C(2)	C(10)						55.6(4)
C(6)	C(5)	C(4)	O(13)					122.7(3)	128.0(4)
C(6)	C(5)	C(7)	C(8)						109.6(3)
C(6)	C(5)	C(7)	C(11)						−107.1(3)
C(6)	C(7)	C(8)	C(10)						−21.1(4)
C(6)	C(7)	C(8)	C(14)						−147.8(3)
C(7)	C(5)	C(4)	O(13)						−168.7(3)
C(7)	C(6)	C(1)	O(12)						111.0(4)
C(9)	C(3)	C(2)	C(10)						−0.3(4)
C(9)	C(3)	C(4)	O(13)						120.7(4)
C(10)	C(2)	C(1)	O(12)						−64.0(4)
C(10)	C(8)	C(7)	C(11)						126.2(3)
C(11)	C(7)	C(8)	C(14)						−0.4(4)

examined[8] for indications of angular preferences in their transfer transition structures. We briefly draw attention to some of the structural parameters in the 4-hydroxycyclohexanone sub-unit in the X-ray crystal structure.

The crystal studied turned out to contain a single enantiomer. The hydroxy ketones formed hydrogen bonded-dimers with the components related by a twofold screw symmetry operation $-x, \frac{1}{2}+y, \frac{1}{2}-z$, and the closest intermolecular approach between O12 and O13. The structure of an individual molecule is shown in Figure 7. Table 2 lists atomic co-ordinates and Table 3 lists bond lengths and angles.

As is found in other compounds with the constrained boat 4-hydroxycyclohexanone, the potentially reacting atoms in the 1,4-hydride shift (O13, C4, H1, C1, and O12) are close to their mean plane (within 0.06 Å). The C1–C4 distance and H1–C4 distances (2.626 and 2.56 Å, respectively), although rather larger than those in (**5**) for example (2.265 and 2.524 Å), suggest steric compression between the oxygen functionalities. The ketone is oriented to allow near maximal overlap of its π-orbitals with those of the cyclopropane, and the expected shortening of the ring bond (C6–C7) distal from this electron withdrawing substituent is evident. Interestingly, the pyramidalisation at C1, as measured by its displacement from the plane of its heavy atom ligands (C6, C2, and O12) is the lowest (0.489 Å) we have found in any of the constrained 4-hydroxycyclohexanones we have examined; usually this parameter is > 0.54 Å. Possibly, the low value indicates interaction of the alcohol function with the carbonyl at C4 through the cyclopropane ring,* in which case the reactivity of (**10**) in 1,4-hydride shift should not fall simply into the pattern[8] of other constrained 4-hydroxycyclohexanones.

Experimental

GLC was carried out on a Carlo Erba 4130 chromatograph on a capillary column (5 m × 0.22 mm) with 0.25 μ OV-1 cross-

* Cyclopropane has 70% of the conjugative ability of vinyl; F. H. Allen, *Acta Crystallogr., Sect B*, 1981, **37**, 890.

bonded as the stationary phase. Carrier gas was hydrogen at 1 cm^3 min^{-1}. Merck precoated silica plates (0.25 mm of Kieselgel 60 F254) were used for analytical TLC and preparative TLC was carried out on plates (20 × 20 cm) prepared using Merck Kieselgel 60 PF254 (20 g per plate). Column chromatography used Kieselgel H and a range of solvents, all distilled before use. IR spectra were recorded on a Pye-Unicam SP3-200 spectrometer, on carbon tetrachloride solutions in 0.2 mm NaCl cells or using a Perkin-Elmer 1710 FT spectrometer on thin films on single NaCl plates. UV spectra were recorded on a Shimadzu UV-260 spectrometer on solutions in 95% EtOH. Routine ^1H NMR spectra were recorded on either a Varian SC 300 or Varian XL 300 spectrometers. Chemical shifts are in ppm (δ) relative to internal Me_4Si, and $CDCl_3$ was solvent unless otherwise stated. MS were determined on a KRATOS MS 25 instrument; EI spectra were routinely run at 70 ev, and ammonia was the ionising agent for CI measurements. M.p.s were determined on a Kofler hot-stage microscope and are uncorrected. Microanalyses were performed at the University of Manchester Microanalysis laboratory under the direction of Mr. M. Hart.

Antimony pentafluoride (Aldrich) was distilled (in flame dried glassware, under dry nitrogen) into a preweighed container, which could be closed with Teflon taps. The distilled antimony pentafluoride was stored under nitrogen, and its weight recorded. Fluorosulphonic acid (Aldrich, triply distilled) was obtained from the stabilising potassium fluoride present by distillation (twice), under nitrogen. The fluorosulphonic acid was also stored in a glass container fitted with Teflon taps. All subsequent manipulations were done by syringe, under positive nitrogen pressure. Fluorosulphonic acid (1 mol equiv.) was transferred to the antimony pentafluoride, and gentle shaking for 10 min gave a clear, homogeneous solution. Freshly prepared colourless solutions were used in the experiments described.

Trifluoromethanesulphonic acid was purified by distillation under nitrogen, and stored in similar apparatus. Subsequent manipulations were also carried out by syringe under a nitrogen atmosphere.

Sulphur dioxide was purified by passing, through neutral alumina (Woelm N, Act 1), freshly activated by heating to 300 °C at < 1 mm Hg for 2 h.

The hydroxy ketones samples were available from earlier published[6,30] work.

NMR Experiments.—All samples prepared contained an external capillary tube containing either $[^2H_2]$dichloromethane or $[^2H_6]$acetone to provide a lock signal. The residual undeuteriated signal was used as a reference peak, with chemical shifts of δ 3.91 and 1.71 for dichloromethane and acetone, respectively. The lock material used is indicated by either external CD_2Cl_2 or CD_3COCD_3, and the appropriate correction factor is used. ^{13}C chemical shifts for the acid solutions (Table 1) are quoted relative to external $[^2H_6]$acetone.

Probe temperatures were measured from chemical shifts in the spectra of a calibration sample containing a melting point capillary tube half filled with redistilled degassed methanol, placed coaxially in a sealed 5 mm NMR tube containing sulphur dioxide (0.5 cm^3) and $[^2H_2]$dichloromethane (0.1 cm^3). Frequency differences were converted to temperatures using the van Goet[37] equation. Preliminary work showed that a single pulse was as accurate as a multiple transient accumulation, and that the pulse sequence in data accumulation (no decoupling) did not detectably raise the temperature.

Variable Acid Protonation of (**5**).—To a clean, dry NMR tube, under a nitrogen atmosphere, was added (**5**) (10.2 mg). Sulphur dioxide (0.5 cm^3) was condensed into the NMR tube, and the spectrum recorded. Trifluoromethanesulphonic acid was added to the solution so that the total volume of acid was 2, 4, 6, 10, 25, 50, 100 mm^3, and NMR spectra were recorded (T − 33 °C) after each addition. The contents of the tube were quenched by pouring into aq. methanolic sodium hydrogencarbonate, and work-up gave starting material by GLC and IR spectroscopy.

Exchange Rates in (**5**).—Hydroxy ketone (**5**) (5.1 mg), was added to a clean, dry NMR tube, followed by an external lock, and the tube was then flushed with nitrogen for 5 min. Sulphur dioxide was then flushed through the tube and condensed up to a predetermined mark (0.50 cm^3). Trifluoromethanesulphonic acid (0.047 cm^3) was added in the usual way, and the tube then sealed. A second tube was also prepared under identical conditions, using 5-$[^2H_1]$-(**5**) (5.2 mg), in sulphur dioxide (0.50 cm^3) and trifluoromethanesulphonic acid (0.048 cm^3). These samples were then used to determine the rate of hydride transfer at 13.4 °C and 23.3 °C. The lower field methyl signal was inverted with a DANTE pulse sequence consisting of 50 pulses, each of duration 1.7 μs. The inverted signal was allowed to relax for a delay D and then a detection pulse of 37 μs was applied. The values of D used were 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 3.0, and 10.0 s.

Carbonyl Rotation or Inversion in (**5**).—An NMR sample containing (**5**) (5.8 mg), in sulphur dioxide, and a 1 : 1 mixture of fluorosulphonic acid and antimony pentafluoride (0.078 cm^3) was prepared by the method outlined previously. NMR spectroscopy showed that the diprotonated intermediate had been quantitatively formed. The temperature was increased to the range at which coalescence of the two protonated carbonyl signals occurred. The spectrum was recorded at 3.0, 6.5, 8.6, and 13.0 °C. A spectral width of 6 000 Hz and 32 768 data points gave a digital resolution of 0.37 Hz. Typically, 100 transients were needed to obtain an acceptable signal-to-noise ratio. Each low-field line shape was digitised and fitted to a computer generated lineshape. For the low temperature lineshape, the peak separation was optimised, giving a value of 25.0 Hz. This value was used as a fixed parameter fitting at higher temperatures. After the accumulation of the data, the contents of the tube were quenched by pouring into methanolic sodium hydrogencarbonate. Extraction and isolation in the usual way gave unchanged starting material (3.4 mg, 57%).

Non-degenerate Rearrangement of (**5**) *to* (**7**) *or* (**8**).—Hydroxy ketone (**5**) (70.3 mg), dissolved in $[^2H_2]$dichloromethane (0.200 cm^3), was added to a 5 mm NMR tube and the solvent was removed by gentle heating in a flow of nitrogen. Sulphur dioxide (2 cm^3) was condensed into the tube, and trifluoromethanesulphonic acid (0.100 cm^3) was added in the usual way to give a pale yellow solution. The tube was sealed, and left at room temperature. The decomposition was monitored by NMR spectroscopy and after 6 h the reaction mixture was quenched by rapidly pouring the contents of the tube into a cooled mixture of methanol (10 cm^3) and saturated aqueous sodium hydrogencarbonate (2 cm^3). The resultant solution was allowed to attain room temperature, and the sulphur dioxide was allowed to boil off over a period of 2 h. The methanol was removed under reduced pressure to give a brown precipitate. Dichloromethane and water were added and the organic material was extracted with dichloromethane (× 3). The combined extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a brown oil (38 mg, 54%). Purification by chromatography yielded a single compound, (**7**) or (**8**) (28.6 mg, 45%), as a pale yellow oil. $\nu_{max}(CCl_4)$ 3 055(w), 2 975(m), 2 938(m), 1 688(vs), 1 605(s), 1 240(m), 1 208(m), 1 037(m), and 915(w); λ_{max}(EtOH) 316.6 nm (ε_{max}

7 800), 234.2 (5 300); δ_H(400 MHz; $CDCl_3$) 1.27 (3 H, d, *J* 7.0 Hz), 2.13 (3 H, m), 2.48 (2 H, cm), 3.14 (1 H, br d, *J* 20.0 Hz), 3.30 (1 H, br d, *J* 20.0 Hz), 3.85 (1 H, cm), 6.23 (1 H, dd, *J* 5.8, 1.6 Hz), 6.50 (1 H, m), and 7.35 (1 H, dd, *J* 5.8, 2.8 Hz); *m/z* (EI) 174 (*M*, 100%), 173 (63), 131 (54), 91 (43), 115 (38), 113 (31), 77 (23), (CI) 191 (100), 190 (26), 143 (7), 126 (4), and 174 (2).

This unsaturated ketone was taken up in ethyl acetate (5 cm^3), and hydrogenated over a catalytic amount of platinum oxide (Type D, Johnson Matthey), until no further hydrogen was absorbed. The solution was then filtered through Celite, and the solvent was carefully removed under reduced pressure to yield a colourless oil that contained four major components by GLC. For the mixture: $\nu_{max}(CCl_4)$ 2 960(s), 2 875(m), 1 740(s), 1 460(m), 1 380(m), and 1 240(m), 1 155(w); *m/z* (EI) 83 (100%), 41 (45), 98 (43), 55 (38), 67 (36), 81 (34), 80 (31), 180 (*M*, 5), (CI) 181 (*M* + 1, 100), 198 (*M* + 18, 86), 163 (83), 81 (40), 165 (22), 182 (21), 164 (21), and 179 (21).

Non-degenerate Rearrangement of (**6**) *to* (**9**) *and* (**10**).—Hydroxy ketone (**6**) (48.5 mg), was added to a 5 mm NMR tube containing an external [$^2H_2$]dichloromethane lock, and the tube was flushed with nitrogen, then with sulphur dioxide which was condensed by means of an acetone–solid CO_2 slurry. A mixture of fluorosulphonic acid and antimony pentafluoride (0.100 cm^3, 1:1) was added slowly and solidified on the walls of the NMR tube. The acid was slowly dissolved by gentle shaking to give a dark red solution. The tube was warmed, and the reaction monitored by NMR spectroscopy. When the starting material had disappeared, the contents of the tube were quenched by being poured into methanolic sodium hydrogencarbonate, and the sulphur dioxide was allowed to boil off. The methanol was removed under reduced pressure, and the residue diluted with water. The organic material was extracted with ether (3 × 10 cm^3), the organic extracts combined, dried ($MgSO_4$) and the ether removed under reduced pressure to give a brown oil (34.4 mg, 71%) which was subjected to reparative TLC on silica, to give (**10**) (11.4 mg), which crystallised from ethyl acetate, and (**9**) (5.0 mg), a light yellow oil. These showed properties as follows: (**10**): m.p. 150–150.7 °C (Found, M^+ 192.1154. $C_{12}H_{16}O_2$ requires M^+ 192.1150); $\nu_{max}(CCl_4)$ 3 600(w), 3 400(w), 2 955(m), 1 710(s), 1 215(m), 1 058(m), and 905(m); δ_H(400 MHz; $CDCl_3$) 1.17 (3 H, s), 1.26 (1 H, dd, *J* 11.5, 7.5 Hz), 1.32 (3 H, s), 1.59 (1 H, dd, *J* 9.5, 2.5 Hz), 1.64 (1 H, dd, *J* 9.5, 2.0 Hz), 1.7–1.8 (1 H, br s), 1.70 (1 H, cd, *J* 12.0 Hz), 1.74 (1 H, dd, *J* 12.0, 6.0 Hz), 2.00 (1 H, dd, *J* 11.5, 2.5 Hz), 2.51 (1 H, cm), 2.63 (1 H, cm), and 4.18 (1 H, d, *J* 4.2 Hz); δ_C(20 MHz; $CDCl_3$) 209.7(s), 67.4(d), 51.1(t), 48.8(d), 41.9(d), 41.1(s), 40.0(s), 39.1(d), 37.9(t), 37.6(d), 22.2(q), and 20.2(q); *m/z* (EI) 192 (9) (*M*), 91 (100%), 131 (77), 39 (71), 107 (68), 41 (67), 55 (64), and 192 (*M*, 9), (CI) 193 (*M* + 1, 100), 175 (63), 191 (58), 208 (*M* + 18, 35), 147 (12), and 159 (10); (**9**) $\nu_{max}(CCl_4)$ 3 040(w), 2 970(m), 2 935(m), 1 690(s), 1 458(m), 1 380(m), 1 250(m), 1 120(m), 1 030(m), 970(m), 910(m), and 848(m); λ_{max}(EtOH) 218.6 nm (ε_{max} 8 000); δ_H(400 MHz; $CDCl_3$) 0.84 (3 H, d, *J* 6.4 Hz), 1.35 (3 H, s), 1.45 (1 H, ddd, *J* 14.0, 11.0, 10.5 Hz), 1.68 (1 H, cm), 1.71 (1 H, d, *J* 12.0 Hz), 1.87 (1 H, cm), 1.98 (1 H, dd, *J* 12.0, 4.5 Hz), 2.60–2.65 (2 H, cm), 4.47 (1 H, br t, *J* 4.5 Hz), 5.95 (1 H, d, *J* 10.0 Hz), and 6.83 (1 H, dd, *J* 10.0, 5.0 Hz); *m/z* (EI) 43 (100%), 163 (73), 192 (*M*, 53), 107 (52), 41 (37), 135 (29), 149 (22), (CI) 193 (*M* + 1, 100), 210 (*M* + 18, 30), 194 (30), 192 (23), 163 (13), 175 (12), and 177 (7).

Oxidation of (**10**).—To a solution of (**10**) (1.6 mg) in ether (1 cm^3) was added aqueous chromic acid (0.01 cm^3, 2 equiv.), and the solution was allowed to stand at room temperature for 30 min. The solution was diluted with ether, filtered through silica, and the solvent removed under reduced pressure to give a waxy solid that was a single component by GLC. (Found, M^+ 190.0996. $C_{12}H_{14}O_2$ requires M^+ 190.0994); $\nu_{max}(CCl_4)$ 2 970(w), 2 950(w), 1 730(s), 1 710(m), 1 465(w), 1 450(w), 1 280(m), and 1 080(m); δ_H(300 MHz; C_6D_6) 0.50 (3 H, s), 0.77 (3 H, s), 1.14 (2 H, br d, *J* 11 Hz), 1.34 (2 H, d, *J* 11 Hz), 1.77 (2 H, s), and 2.58 (2 H, br s); *m/z* (EI) 119 (100%), 190 (*M*, 77.5), 91 (68.8), 147 (51.0), 107 (49.5), 77 (40.0), 55 (38.6), (CI) 208 (*M* + 18, 100), 191 (*M* + 1, 51.6), 30 (23.9), 32 (23.1), 45 (17.4), and 44 (13.8).

Structure Determination of (**10**).—*Crystal data.* $C_{12}H_{14}O_2$, a = 7.468(2), b = 11.403(6), c = 11.697(3) Å; V = 996 $Å^3$, ρ_c = 1.28 g cm^{-3} for Z = 4. $F(000)$ = 416, absorption coefficient = 1.0 cm^{-1} (λ = 0.710 69 Å), space group $P2_12_12_1$ (No. 19).

A clear, colourless crystal, dimensions 0.18 × 0.17 × 0.17 mm, was mounted on the CAD4 diffractometer system and data collected to θ = 30° using Mo-K_α radiation. Standard reflection monitoring suggested no crystal deterioration, and since $\mu R < 0.02$, an absorption correction was not applied. Of the 1 728 reflections measured, 1 163 were unique and those with $F_{obs} > 3\sigma F_{obs}$) were subsequently used in structure refinement. The MULTAN direct methods program, using 204 *E* values >1.52, yielded a 16-atom trial solution. Initial least-squares refinement rejected three of these and a difference Fourier synthesis then revealed an additional atom to complete the structure. These techniques were repeated to find the hydrogen atoms, all of which were well resolved except for the hydroxy hydrogen. This was finally assigned and its position constrained while anisotropic thermal parameters for non-hydrogen atoms were included in the final refinement stages. Hydrogen atoms were refined to acceptable positions giving C–H distances of between 0.89 and 1.03 Å, and B values between 2.0 and 5.9 $Å^2$. During the final cycles a weighting scheme: $\omega^{-1} = (0.32 - 0.025F_{obs} + 0.000\,83F_{obs}^2)$ was applied. The final R factor was 5.19%.

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