D-Homo-steroids. Part 6.[1] 1-Acetyl-2,2-dimethylcyclopentanol: a Monocyclic Model for D-Homoannulation of 17-Hydroxypregnan-20-ones

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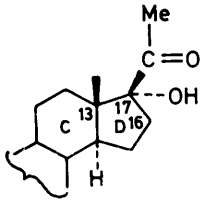
1-Acetyl-2,2-dimethylcyclopentanol, a monocyclic model for ring D of a 17-hydroxypregnan-20-one, rearranges in alkali under kinetic control to give 2-hydroxy-2,3,3-trimethylcyclohexanone, or in the presence of boron trifluoride to give the same compound accompanied by 2-hydroxy-2,6,6-trimethylcyclohexanone (4 : 1 ratio). Comparison with the results of rearrangements of 17α-hydroxypregnan-20-ones under similar conditions indicates that rearrangement of the steroidal compound by boron trifluoride is controlled by a combination of two factors: (i) the conformational rigidity imposed by the fusion of rings C and D and, (ii) electronic features of the transition state, as yet undetermined, which distinguish the Lewis acid-catalysed from the base-catalysed rearrangement.

THE major unsolved problem in the D-homoannulation of pregnane derivatives [2,3] is the preference for migration



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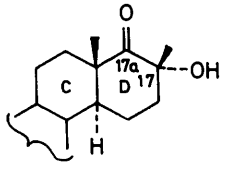

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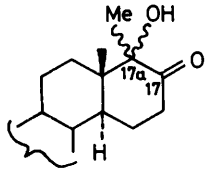
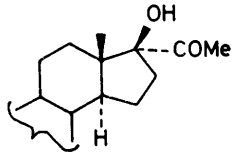


(3) 17aα-Me, β-OH
(4) 17aα-OH, β-Me

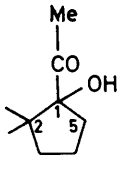


(5)

of C-16 when a 17α-hydropregnan-20-one (1) is treated with a Lewis acid (*e.g.* BF_3). The resulting acyloin rearrangement to give a 17α-hydroxy-17β-methyl-D-homoandrostan-17a-one (2) contrasts with the corresponding base-catalysed reaction, which affords exclusively 17a-hydroxy-17a-methyl-17-oxo-derivatives, (3) and (4), by migration of C-13. Irrespective of the nature of the catalyst, compounds of the 17β-hydroxy-17α-pregnan-20-one series (5) also react by migration of C-13 to give isomers (3) and (4).

The stereochemistry of these reactions is well understood,[4] but no satisfactory explanation has yet appeared for the single instance of migration of C-16. Discussions have included reference to the quaternary *vs.* secondary distinction between C-13 and C-16,[2,3] steric interactions between the 13β- and side-chain methyl groups,[5] effects of polar substituents,[1] and the incipient chair conformation of ring D in the transition state for migration of C-16, which contrasts with a developing boat conformation if C-13 is the migrating group.[6]

A reconsideration of the arguments suggested that the last of these factors is likely to be important, although its failure to control the base-catalysed rearrangement [2,3,7] shows that it is not in itself sufficient to explain all the reactions observed. Conformational restrictions which make for the chair *vs.* boat distinction are imposed upon ring D by its mode of fusion to ring C. We therefore decided to remove this cause of conformational control and determine the inherent migratory aptitudes of the competing quaternary and secondary carbon atoms, by studying the analogous rearrangement of the simplest monocyclic model compound which would imitate the



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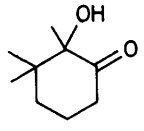

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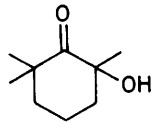


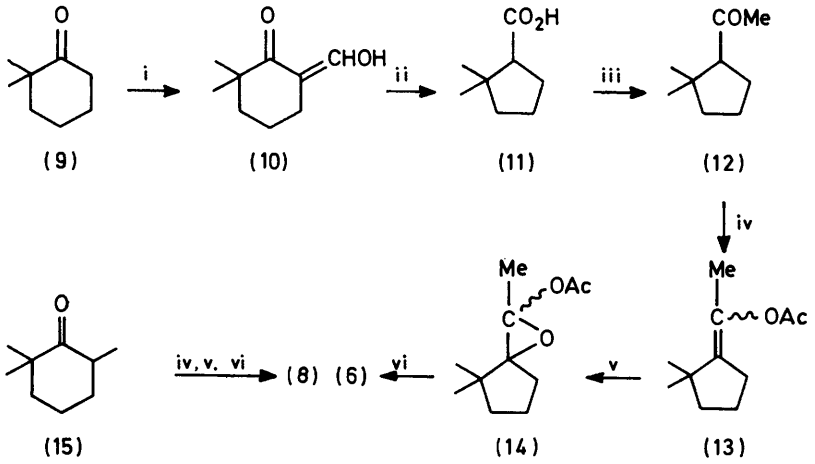
(8)

unsymmetrical environment of the steroidal α-ketol system. 1-Acetyl-2,2-dimethylcyclopentanol (6) does

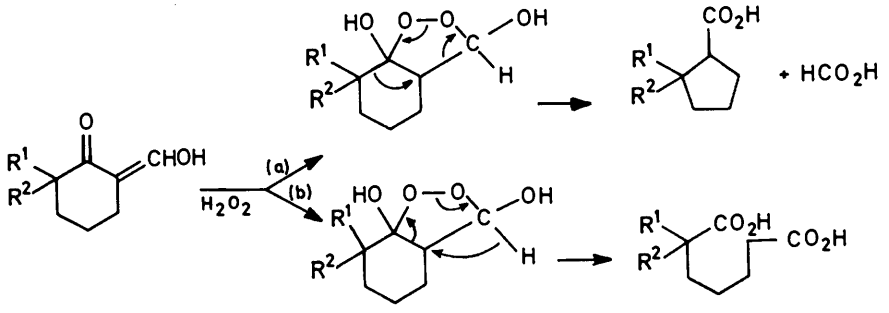
[1] Part 5, D. N. Kirk and A. Mudd, *J.C.S. Perkin I*, 1975, 1450.
[2] N. L. Wendler, in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1964, vol. 2, pp. 1099—1101 and 1114—1121, and references therein.
[3] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, pp. 294—301, and references therein.
[4] R. B. Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3484.
[5] D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling, and G. Roberts, *J. Amer. Chem. Soc.*, 1955, **77**, 6585.
[6] I. Elphimoff-Felkin and A. Skrobek, *Bull. Soc. chim. France*, 1959, 742; N. L. Wendler, D. Taub, and R. W. Walker, *Tetrahedron*, 1960, **11**, 163.
[7] D. N. Kirk and A. Mudd, *J. Chem. Soc.* (*C*), 1970, 2045.

this by presenting a choice between migration of C-2 or C-5, to give the cyclohexanone derivative (7) or (8), respectively.

Synthesis.—The route is outlined in Scheme 1. Base-catalysed methylation of 2-methylcyclohexanone gave a mixture containing 2,2-dimethylcyclohexanone (9), predominates in the non-methylated derivative but is the lesser reaction in the monomethyl compound. The *gem*-dimethyl derivative (10), in contrast, gave 2,2-dimethylcyclopentanecarboxylic acid (11) as the only product detected (Scheme 2), implying a strong preference for migration of quaternary carbon in this instance.



SCHEME 1 Reagents: i, HCO_2Et–MeONa; ii, H_2O_2; iii, MeLi; iv, Ac_2O–$HClO_4$; v, *m*-$ClC_6H_4{\cdot}CO_3H$; vi, NaOH



SCHEME 2 Alternative routes for the reaction of a 2-hydroxymethylenecyclohexanone with H_2O_2

$R^1 = R^2 = H$:	(a) 31%;	(b) 38%
$R^1 = H$, $R^2 = Me$:	(a) 50%;	(b) 14%
$R^1 = R^2 = Me$ (10):	(a) 54%;	(b) none found

which was conveniently separated from the 2,6-dimethyl isomer and other products by alkaline extraction of its 6-hydroxymethylene derivative (10).[8] Some 2,2,6-trimethylcyclohexanone (15), isolated by preparative g.l.c. from the residues, found use later (see below). Ring contraction of the hydroxymethylene ketone (10) to give 2,2-dimethylcyclopentanecarboxylic acid (11) was achieved by a little known reaction with hydrogen peroxide.[9] The proposed mechanism [9,10] (Scheme 2) is of special interest in the present context, because it provides an illustration of the normally greater migratory aptitude of a quaternary as compared with a tertiary or a secondary carbon atom.[11] The desired ring contraction generally competes with ring cleavage to give a heptanedioic acid. Published data [9] show that ring cleavage

[8] S. V. Kessar and K. P. Mahajan, *J. Indian Chem. Soc.*, 1962, **39**, 147.

[9] S. I. Zavialov, L. P. Vinogradova, and G. V. Kondratieva, *Tetrahedron*, 1964, **20**, 2745.

[10] G. B. Payne, *J. Org. Chem.*, 1961, **26**, 4793.

The acid (11) was converted into the methyl ketone (12) by an excess of methyl-lithium,[12] then the hydroxy-group was introduced to give 1-acetyl-2,2-dimethylcyclopentanol (6) by enol acetylation, epoxidation, and hydrolysis, a sequence well known in the steroid field.[13] The product (6) was characterised by its n.m.r. spectrum and by microanalysis of its semicarbazone.

2,2,6-Trimethylcyclohexanone (15) was used as indicated in Scheme 1 to synthesise an authentic sample of 2-hydroxy-2,6,6-trimethylcyclohexanone (8), one of the two expected products of acyloin rearrangement of compound (6). The final hydrolytic stages in the syntheses of the ketols (6) and (8) were carried out under the mildest possible alkaline conditions in order to avoid

[11] W. von E. Doering and L. Speers, *J. Amer. Chem. Soc.*, 1950, **72**, 5515; M. Stiles and R. P. Mayer, *ibid.*, 1959, **81**, 1497.

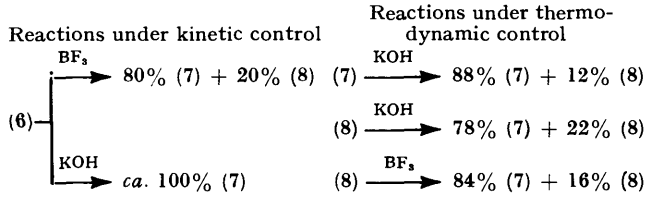
[12] T. M. Bare and H. O. House, *Org. Synth.*, 1969, **49**, 81.

[13] E. P. Oliveto, in ' Organic Reactions in Steroid Chemistry,' ed. J. Fried and J. A. Edwards, Van Nostrand–Reinhold. New York, 1972, vol. 2, p. 185.

the acyloin rearrangements which occurred readily when hydrolysis was more vigorous.

Acyloin Rearrangements.—Trial rearrangements of the ketol (6), either with boron trifluoride or with aqueous methanolic alkali, established that two isomeric ketols could be formed. One of them was identical with 2-hydroxy-2,6,6-trimethylcyclohexanone (8), and the other had the properties expected for 2-hydroxy-2,3,3-trimethylcyclohexanone (7). Mixtures of the three ketols could be analysed by g.l.c. analysis on two different columns: no single column was found capable of resolving all three isomers simultaneously. N.m.r. analysis of ketol mixtures provided confirmation of product compositions.

Alkaline rearrangement of the ketol (6) proceeded initially to give only 2-hydroxy-2,3,3-trimethylcyclohexanone (7), but when the reaction was prolonged the ketol (7) slowly underwent equilibration with the isomer (8) (Scheme 3). G.l.c. results indicated gradual



SCHEME 3 Rearrangement of ketols

destruction of ketols under forcing conditions, so that true equilibrium was probably not reached.

Rearrangement catalysed by boron trifluoride rapidly converted the ketol (6) into a mixture of the ring-enlarged isomers (7) and (8), in the ratio 80 : 20. Equilibration starting from the pure isomer (8) gave (7) and (8) in a similar ratio (84 : 16) (Scheme 3). An equilibrium ratio of *ca.* 4 : 1 in favour of isomer (7) was to be expected on the basis that the alternative ketol (8) cannot avoid an unfavourable ' 1,3-diaxial ' interaction of substituents without adopting a high energy twist-boat conformation; the D-homo-steroidal ketols (3) and (4) are similarly more stable than the isomer (2).[2,3] α-Ketols at the 11,12-[14] or 16,17-positions[15] in ordinary steroids, with secondary hydroxy-groups, also favour the isomer with the carbonyl group ' β ' to the ring junction (11-oxo- and 16-oxo-, respectively).

A study of the kinetics of the boron trifluoride-catalysed rearrangement of 1-acetyl-2,2-dimethylcyclopentanol (6) indicated that the reaction is first-order in ketol, but zero-order in boron trifluoride even at a BF_3 : ketol ratio as low as 1.25 : 1. Boron trifluoride therefore appears to act as a true catalyst, rather than as a reagent consumed in the reaction. Support for this interpretation was provided by the complete rearrangement of the ketol (6) even by only a 0.63 molar proportion of boron trifluoride, and by further work on the steroid ketol rearrangement, to be reported elsewhere.[16]

Discussion.—The rearrangements of 1-acetyl-2,2-dimethylcyclopentanol (6) show two important similarities to the D-homoannulation of 17α-hydroxypregnan-20-ones (1): (*a*) in the base-catalysed rearrangement, the product of kinetic control is that (7) resulting from migration of quaternary carbon; the ketol (7) is also the more stable isomer; (*b*) migration of secondary carbon occurs only in the boron trifluoride-catalysed rearrangement.

There is a significant difference from the steroid, however, in that the migration of quaternary carbon remains the principal reaction even when the model ketol is rearranged by boron trifluoride. This preference for quaternary carbon is normal.[11] It seems, therefore, that the *total specificity* of migration of the secondary C-16 when a 17α-hydroxypregnan-20-one reacts in the presence of boron trifluoride [1-3] does depend upon the particular conformational/steric factors which operate when the steroidal transition state is held rigid by the fusion of rings C and D. The postulated preference for a ' developing-chair ' conformation of ring D[6] is therefore seen as a major but not the only controlling factor in the selection of C-16 as the migrating group. Some additional factor, not associated with conformational rigidity in the expanding ring, must also act to permit some migration of secondary carbon in the boron trifluoride-catalysed reaction of the model ketol. The significant difference between Lewis acid-catalysed and base-catalysed rearrangements, even in the model compound, indicates that electronic factors also need to be explored in the search for a complete explanation of these reactions.

Reference will be made to the present results in a subsequent paper,[16] where we shall describe further studies on the nature of the transition state in the Lewis acid-catalysed rearrangement of 17α-hydroxypregnan-20-ones.

EXPERIMENTAL

Boron trifluoride–diethyl ether complex was purified by distillation under reduced pressure. 1,2-Dimethoxyethane was distilled from lithium aluminium hydride. N.m.r. spectra were obtained for solutions in $CDCl_3$ unless otherwise indicated.

2,2-Dimethylcyclopentanecarboxylic Acid (11).—6-Hydroxymethylene-2,2-dimethylcyclohexanone (10) [8] (5 g) in t-butyl alcohol (10 ml) was treated with 30% hydrogen peroxide (4 g). The reaction was exothermic, and the temperature was maintained between 30 and 40 °C by external cooling. After 1 h the solution was left at room temperature overnight, then heated for 4 h on a steam-bath, cooled, diluted with water (50 ml), and extracted with ether. The ethereal solution was extracted with saturated aqueous sodium hydrogen carbonate (100 ml; used in seven portions), then the combined extracts were washed with ether, acidified (4M-HCl), and again extracted, twice, with ether. This solution was dried ($MgSO_4$), and the solvent was removed to give crude 2,2-dimethylcyclopentanecarboxylic acid (3 g) as a liquid, τ 9.04 and 8.82 (s, s, Me_2) and 7.54 (t, *J* 8 Hz, H-1).

[14] E. Borgstrom and T. F. Gallagher, *J. Biol. Chem.*, 1949, **177**, 951.

[15] W. S. Johnson, B. Gastambide, and R. Pappo, *J. Amer. Chem. Soc.*, 1957, **79**, 1991; J. Fishman, *ibid.*, 1960, **82**, 6143.

[16] D. N. Kirk and C. R. McHugh, in preparation.

The crude acid was converted into its methyl ester (MeOH–HCl), which was distilled under reduced pressure; b.p. 78 °C at 25 mmHg, τ 9.13 and 8.88 (s, s, Me_2) and 6.35 (s, CO_2Me). The ester was hydrolysed (NaOH), and the partially purified acid was recovered by acidification and extraction with ether, as above. A portion of the acid was converted by the standard procedure into its *p-bromophenacyl ester*, needles, m.p. 55—57.7 °C (from EtOH), τ 9.05 and 8.81 (s, s, Me_2), 4.76 (s, $O{\cdot}CH_2{\cdot}CO$), and 2.29 (4 H, m, aromatic) (Found: C, 56.4; H, 5.6; Br, 23.4. $C_{16}H_{19}BrO_3$ requires C, 56.7; H, 5.6; Br, 23.6%).

1-*Acetyl*-2,2-*dimethylcyclopentane* (12).—This was prepared from the acid (11) by the method of Bare and House (MeLi) [12] (65% yield, based on acid consumed). The ketone was a liquid, b.p. 48—48.5 °C at 2 mmHg), τ 9.15 and 8.81 (s, s, Me_2), 7.89 (s, Ac), and 7.41 (t, *J* 8 Hz, H-1). The *semicarbazone* crystallised from aqueous ethanol as needles, m.p. 163—167 °C (Found: C, 61.0; H, 9.5; N, 21.5. $C_{10}H_{19}N_3O$ requires C, 60.9; H, 9.7; N, 21.3%).

1-*Acetyl*-2,2-*dimethylcyclopentanol* (6).—The ketone (12) (100 mg) in carbon tetrachloride (40 ml) containing acetic anhydride (5 ml) and perchloric acid (72%, 50 μl) was left at 20 °C for 1 h. The solution was then washed with aqueous 5% sodium hydroxide followed by saturated brine, and dried ($MgSO_4$). The solution contained the isomeric enol acetates (13) in a ratio *ca.* 5 : 1; τ(CCl_4) 8.93 (s, Me_2), 8.22 (t, apparent *J* 5 Hz, olefinic Me), 7.95 (s, OAc), and 7.63 (m, 5-H_2) for the major component; 8.80 (s, Me_2) and 7.99 (s) for the minor component. The olefinic Me triplet at τ 8.22 collapsed to a singlet on irradiation at the frequency of the 5-H_2 signal (τ 7.63).

The mixed enol acetates, in the CCl_4 solution obtained above, were treated with *m*-chloroperbenzoic acid (600 mg) and aqueous sodium hydroxide–potassium dihydrogen phosphate buffer (pH 7.6; 10 ml). The mixture was stirred for 1 h while being maintained at 14—18 °C by external cooling, then the organic layer was washed successively with aqueous sodium sulphite (20% $Na_2SO_3,7H_2O$; 2 × 25 ml), saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated under reduced pressure. The mixed epoxides (14) formed a liquid, τ 9.09 and 9.03 (s, s Me_2), 8.35 (s, side-chain Me), and 8.02 (s, OAc) for the major component; 8.88 (s, Me_2) for the minor component.

The mixed epoxides were dissolved in methanol (6 ml). (A trace of insoluble material, removed by filtration, was identified as bis-3-chlorobenzoyl peroxide, m.p. 123°, $\nu_{max.}$ 1 770 and 1 795 cm^{-1}, an impurity detectable in the sample of *m*-chloroperbenzoic acid.) The solution was treated with aqueous 2% sodium hydroxide (1.5 ml) for 1 h at 14—18 °C, then acidified with 4M-acetic acid (0.3 ml). Ether (20 ml) and aqueous sodium hydrogen carbonate were added, and the ethereal extract was washed and dried ($MgSO_4$). Evaporation left 1-acetyl-2,2-dimethylcyclopentanol (56 mg, 58%) as a pleasant smelling liquid, τ 9.07 and 8.98 (s, s, Me_2), 7.74 (s, Ac), and 7.2—6.2br (OH; removed by shaking with D_2O). The *semicarbazone* crystallised from ethanol as needles, m.p. 200—205 °C (Found: C, 56.6; H, 9.0; N, 19.9. $C_{10}H_{19}N_3O_2$ requires C, 56.3; H, 9.0; N, 19.7%).

2-*Hydroxy*-2,6,6-*trimethylcyclohexanone* (8).—2,2,6-Trimethylcyclohexanone (318 mg) was treated with the enol acetylating mixture as described above (25 ml) for 40 h to give 1-acetoxy-2,6,6-trimethylcyclohexene, τ(CCl_4) 9.03 (s, 6,6-Me_2), 8.60 (s, 2-Me), and 7.92 (s, AcO). Epoxidation with *m*-chloroperbenzoic acid (650 mg) in carbon tetrachloride for 1.5 h, and isolation as above, gave crude 1-acetoxy-1,2-epoxy-2,6,6-trimethylcyclohexane, τ(CCl_4) 9.01 and 8.98 (s, s, 6,6-Me_2), 8.80 (s, 2-Me), and 8.00 (s, AcO). Hydrolysis with aqueous methanolic alkali as above gave 2-hydroxy-2,6,6-trimethylcyclohexanone as a yellow oil (98.9 mg, 28%), τ 8.88 and 8.82 (s, s, 6,6-Me_2) and 8.63 (s, 2-Me). The semicarbazone formed prisms (from benzene), m.p. 178—180 °C (lit.,[17] 178—179°) (Found: C, 56.4; H, 9.0; N, 19.8. Calc. for $C_{10}H_{19}N_3O_2$: C, 56.3; H, 9.0; N, 19.7%).

2-*Hydroxy*-2,3,3-*trimethylcyclohexanone* (7).—1-Acetyl-2,-2-dimethylcyclopentanol (30 mg) in methanol (3.75 ml) and aqueous 10% potassium hydroxide (0.75 ml) was heated under reflux for 80 min. Water was then added, and the product was extracted with chloroform. Evaporation left 2-hydroxy-2,3,3-trimethylcyclohexanone as a liquid, τ 8.86, 8.79, and 8.60 (s, s, s, Me_3). The *semicarbazone* formed prisms (from ethanol), m.p. 202—204 °C (Found: C, 56.3; H, 9.0; N, 19.8. $C_{10}H_{19}N_3O_2$ requires C, 56.3; H, 9.0; N, 19.7%).

G.l.c. Analysis of Mixtures of Ketols (6)—(8).—Mixtures were analysed (*a*) at 70 °C on a 3 ft glass column of 4% Apiezon L on Anakrom ABS, 100—110 mesh, and (*b*) at 80 °C on a 6 ft glass column of 3% QFI on the same support. Retention times, relative to acetophenone (= 1.00) as internal standard, were: (6) (*a*) 1.61, (*b*) 1.53; (7) (*a*) 1.61, (*b*) 1.07; (8) (*a*) 1.33, (b) 1.07. Thus (8) was separated from (6) and (7) on column (*a*), and (6) from (7) and (8) on column (*b*), permitting complete analysis of ternary mixtures.

Rearrangements in Alkaline Solution.—(i) The rearrangement of 1-acetyl-2,2-dimethylcyclopentanol (20 mg) in methanol (2.5 ml) with aqueous 10% potassium hydroxide (0.5 ml), under reflux, was followed by g.l.c. of samples, with the results shown in Table 1. None of the isomeric ketol (8) was detected in the final sample.

TABLE 1

Time (min)	Ketol (7) (%)	Ketol (6) (%)
1	19.5	80.5
6.5	40.5	59.5
22	70.0	30.0
36	83.0	17.0

(ii) 2-*Hydroxy*-2,3,3-*trimethylcyclohexanone* (7). The solution from (i) was treated with solid potassium hydroxide (200 mg), and heating under reflux was continued for 5 days. G.l.c. showed that the ketols (7) and (8) were present in the ratio 88 : 12.

(iii) 2-*Hydroxy*-2,6,6-*trimethylcyclohexanone* (8). The ketol (20 mg) in methanol (2.5 ml) containing potassium hydroxide (200 mg) and water (0.5 ml) was heated under reflux, with g.l.c. examination of samples, as indicated in Table 2.

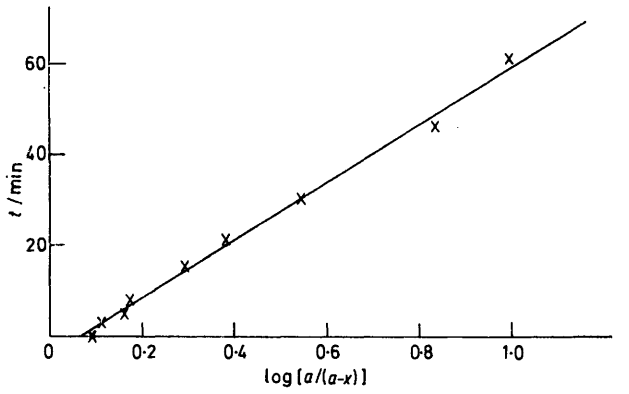
TABLE 2

Time (h)	Ketol (7) (%)	Ketol (8) (%)
0.75	25.5	74.5
24	49	51
80	71	29
200	78	22

Rearrangements with Boron Trifluoride.—(i) 1-*Acetyl*-2,2-*dimethylcyclopentanol* (6). (*a*) The ketol (10 mg,

[17] K. R. Bharucha, H. L. Cohen, and G. F. Wright, *J. Org. Chem.*, 1954, **19**, 1097; for i.r. data see W. C. Bailey, jun., A. K. Bose, R. M. Ikeda, R. H. Newman, H. V. Secor, and C. Varsel, *J. Org. Chem.*, 1968, **33**, 2819.

0.064 mmol) in 1,2-dimethoxyethane (2 ml) was treated with boron trifluoride–ether (10 μl, 0.080 mmol) and immediately distributed amongst eight stoppered tubes,



Kinetics of rearrangement of 1-acetyl-2,2-dimethylcyclopentanol with boron trifluoride: first-order plot, expt. (i) (*a*); a = initial concentration of 1-acetyl-2,2-dimethylcyclopentanol; x = amount reacted after t min

which were maintained at 18 °C. At suitable times the contents of a tube were quenched with saturated aqueous sodium hydrogen carbonate, and extracted with ether. The extract was examined by g.l.c. on column (*b*) in order to determine the proportion of unchanged ketol (6). The Figure presents the results as a linear first-order plot [log $a/(a - x)$ *vs.* time], with a first-order specific rate constant $k = 5.85 \times 10^{-4}$ s^{-1} (at 18 °C).

(*b*) A similar reaction at 19.5 °C also gave a satisfactory linear plot, with $k = 8.05 \times 10^{-4}$ s^{-1} (at 19.5 °C).

(*c*) A mixture of reactants like that in (*a*) was left at 18.5 °C for 25 min before extraction of products as described above. N.m.r. analysis indicated that the three ketols (6)—(8) were present in the ratios *ca.* 4 : 5 : 1, respectively. G.l.c. analysis on column (*b*) showed that 69% of the acetyl compound (6) had rearranged.

(*d*) A reaction similar to (*b*), but with the amount of boron trifluoride halved (5 μl, 0.040 mmol), was allowed to proceed for 18 h, giving only the rearranged ketols (7) and (8) in the ratio 80 : 20 (g.l.c.).

(ii) 2-*Hydroxy*-2,6,6-*trimethylcyclohexanone* (8). The ketol (10 mg) in 1,2-dimethoxyethane (2 ml) containing boron trifluoride–ether (40 μl) was divided amongst eight stoppered tubes and the reaction was allowed to proceed as above [expt. (i) (*a*)]. Analysis of batches indicated that equilibration [(7), 84%; (8), 16%] required about 2 days, with half-reaction at *ca.* 2.5 h. No other products were detected.

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