D-Homo-steroids. Part 7.[1] Further Studies on the Mechanism of D-Homoannulation of 17α-Hydroxypregnan-20-ones with Lewis Acids

By **David N. Kirk** * and **Conor R. McHugh**, Medical Research Council Steroid Reference Collection, Chemistry Department, Westfield College, Hampstead, London NW3 7ST

The role of boron trifluoride in the D-homoannulation of a 17α-hydroxypregnan-20-one (1) is truly catalytic: kinetic and ^{19}F n.m.r. data for the rearrangements of suitable derivatives show that boron trifluoride is not consumed. Rates of reaction, however, approximate to a second-order dependence on the concentration of boron trifluoride. The thermal rearrangement of 3β,17α-dihydroxy-5α-pregnan-20-one (9) leads initially to a preponderance of the same D-homo-ketol as that which results from the Lewis-acid-catalysed reaction, although prolonged thermal rearrangement leads to an equilibrated mixture of isomeric ketols. Use of magnesium ethoxide as a catalyst with both Lewis-acidic and -basic characteristics, gives a mixture of D-homo-ketols even under conditions of kinetic control. A new structure (13) is proposed for the transition state in the Lewis-acid-catalysed rearrangement: the novel features are a *proton* as the species responsible for holding the two oxygen atoms of the ketol in a *syn*-orientation, and catalysis by co-ordination of each oxygen atom with a molecule of Lewis acid. Selection of C-16 as the migrating centre is attributed to steric effects associated with the conformational rigidity of the hydrogen-bridged transition state (13).

We have already reported [1-3] a series of investigations into the mechanisms of D-homoannulation of 17α-hydroxypregnan-20-ones [4,5] (1) under conditions of either basic or Lewis-acidic catalysis. The one major outstanding feature of these reactions, which has defied numerous attempts to find a wholly satisfactory explanation, is the anomalous formation of the ketol (2) by rearrangement of compounds (1) with Lewis-acid cata-

[1] Part 6, D. N. Kirk and C. R. McHugh, *J.C.S. Perkin I*, 1977, 893.

[2] D. N. Kirk and A. Mudd, *J. Chem. Soc. (C)*, 1970, 2045.

[3] D. N. Kirk and A. Mudd, *J.C.S. Perkin I*, 1975, 1450.

[4] 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.

[5] D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, pp. 294—301, and references therein.

lysts. Other related reactions [4,5] proceed through migration of the 13,17-bond to give isomeric ketols of types (3) and (4), but the conversion (1) —→ (2) involves an exceptional migration of the 16,17-bond.[3-5]

COMe
(1) (2) (3)

(4)
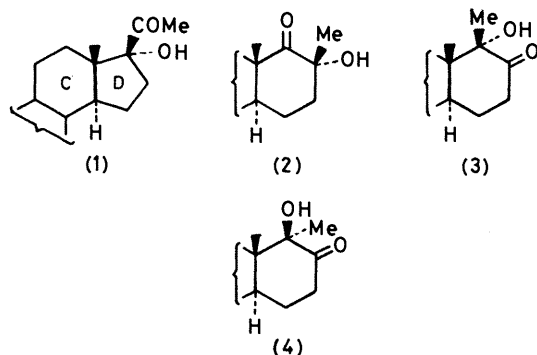
Our recent study [1] of the behaviour of a monocyclic model compound, 1-acetyl-2,2-dimethylcyclopentanol (5), supported the idea that the conformational restriction imposed upon ring D in a 17α-hydroxypregnan-20-one is a major factor controlling the steroid rearrangement, for the flexible model compound differed from the steroid in rearranging *mainly* by migration of quaternary rather than secondary carbon even under catalysis by boron trifluoride, giving the ketols (6) and (7) in the

COMe   OH Me   O Me
(5)   (6)   (7)
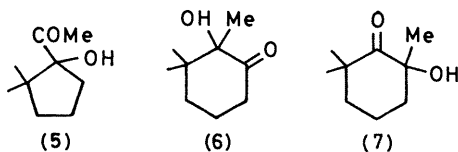
ratio *ca.* 4 : 1. The ketol (6) was the sole product of alkaline rearrangement. The occurrence of some ' abnormal ' migration of secondary carbon even in the model system, however, suggested that some factor other than the purely conformational one must be involved in the Lewis-acid-catalysed process.

The present paper describes further investigations aimed at understanding the special features of boron trifluoride catalysis. We report studies on: (i) the role of boron trifluoride in the reaction; (ii) the relevance of

Me 16 Me   COMe
20   --OH
17 13
F---B-O   RO   H
F
(8)   (9) R = H
           (10) R = CF₃CO
           (11) R = Ac
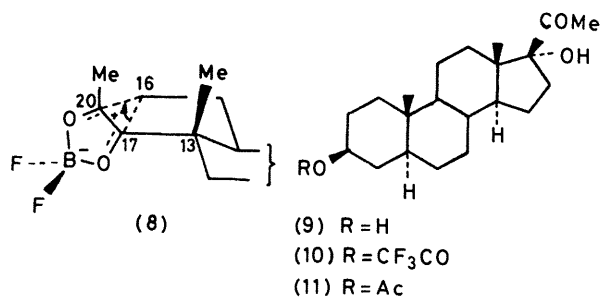
intramolecular hydrogen bonding in α-ketols; (iii) the thermal (uncatalysed) rearrangement of 3β,17α-dihydroxy-5α-pregnan-20-one (9); and (iv) the effects of other catalysts, of character intermediate between the

Lewis acids normally employed (boron trifluoride or aluminium alkoxides) and such strongly basic catalysts as potassium alkoxides. The results of these studies lead us to propose a new structure (13) for the transition state in the Lewis-acid-catalysed reaction.

(i) *The role of boron trifluoride.* Turner [6] suggested that boron trifluoride reacts with the ketol (1) to give a cyclic complex (transition state) of type (8). The structure (8) implies at least a temporary loss of fluoride ion from the boron trifluoride in order that the boron atom may co-ordinate simultaneously with two oxygen atoms. It is not clear from previous work, however, whether boron trifluoride is consumed in the reaction, or whether its role is truly catalytic. Furthermore, no attempt seems to have been made, prior to our own work, to determine the dependence of the rate of reaction on the concentration of boron trifluoride. We have recently reported [1] measurements of the kinetics of rearrangement of the model ketol (5), which showed the reaction to be of the first order with respect to ketol concentration, and of apparent zero order with respect to boron trifluoride when the latter was used at a single concentration. A kinetic study of the rearrangement of 3β,17α-dihydroxy-5α-pregnan-20-one (9) with boron trifluoride, in the molar ratio 3 : 4, respectively (see Experimental section), has now produced similar conclusions. The implication is either that boron trifluoride does not contribute to the rate-determining step, which would be nonsensical, or that the concentration of boron trifluoride remains effectively constant throughout the reaction.

To elucidate further the order of reaction with respect to boron trifluoride, the steroid ketol (9) was rearranged with three different concentrations of boron trifluoride, in the ratio $1 : \sqrt{2} : 2$. The respective measured first-order rate constants for the disappearance of the ketol (9) were in the ratios *ca.* 1 : 2.4 : 3.3. Although these limited data do not permit a precise analysis, they show clearly that the rate of reaction is not proportional simply to [BF₃], but approximates more nearly to being proportional to [BF₃]². We therefore considered possible transition states involving *two* molecules of boron trifluoride (below).

The implication from reaction kinetics that boron trifluoride is not consumed has been confirmed by a ¹⁹F n.m.r. study. To avoid any complicating interaction between boron trifluoride and the 3β-hydroxy-group, and to provide an internal reference signal, the steroid (9) was converted into its 3-trifluoroacetate (10). Separate solutions of the derivative (10) and of boron trifluoride–ether complex, each at 0.16M concentration in 1,2-dimethoxyethane (DME), gave signals 76.6 (sharp; OCOCF₃) and 155.8 p.p.m. (broad; BF₃) upfield from that of fluorotrichloromethane (see Experimental section). A single solution containing both solutes in the same concentrations showed only the same two signals. Heating this solution in a sealed tube for 20 min at 50 °C was sufficient to cause complete rearrangement of the

⁶ R. B. Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3484.

steroid (10) into the D-homo-ketol of type (2), but neither the area nor the chemical shift of either ^{19}F signal was affected by this change, and no new signal appeared. These observations indicate not only that boron trifluoride is not consumed, but also that the amount of any steroid–BF_3 complex present in solution in DME either before or after the rearrangement is very small. The expected sensitivity of the boron trifluoride signal to changes in its environment was established by successive dilution of boron trifluoride–diethyl ether complex with DME: the ^{19}F signal moved progressively upfield by a total of ca. 2.8 p.p.m. as the proportion of boron trifluoride–ether was reduced from 100 to 2%.

(ii) *Hydrogen bonding in α-ketols.* The i.r. spectra of 17α-hydroxypregnan-20-ones [7] in non-polar solvents show O–H stretching bands at 3 620 and ca. 3 500 cm^{-1} which are essentially invariant with the concentration of the solution, indicating an equilibrium between the non-associated and intramolecularly hydrogen-bonded forms, respectively. D-Homo-ketols of type (4) give evidence of strong intramolecular hydrogen bonding between the 17aβ-hydroxy- (equatorial) and 17-oxo-groups, exhibiting a broad band at ca. 3 485 cm^{-1}, but the 17aα-hydroxy-(axial) isomer (3) is only able to hydrogen bond intramolecularly in its unstable twist-boat conformation; the band at 3 620 cm^{-1} is therefore much more pronounced than that at ca. 3 500 cm^{-1} for this isomer.[8,9]

We have now examined the i.r. spectra of the ketol (10) and of the derived D-homo-ketols of types (2) and (3), each as its 3-trifluoroacetate to avoid complicating the O–H region. The important data are listed in Table 1 (an additional small sharp peak near 3 700 cm^{-1}

was ascribed to an overtone of the carbonyl stretching frequency). The shifts in O–H stretching frequencies due to H-bonding are in the range 90—112 cm^{-1}, indicative of the strong association normally found for the O–H $\cdots$ O=C bonding in α-ketols.[10] The relative intensities of the two bands, for ketol (10) and its rearrangement product (3), accord with the expectation that conformational equilibria are important in deciding the extent of hydrogen bonding in each compound, for

intramolecular hydrogen bonding is only possible in each case for a conformation of relatively high energy. The D-homo-ketol of type (2) appears to exist in solution substantially with the chair conformation of ring D, which permits hydrogen bonding, rather than in the twist-boat form which would relieve the strong 17β-Me,13β-Me interaction.[11] The strength of hydrogen bonding in both the ketol (10) and the product (2) of its kinetically favoured thermal rearrangement (see below) is compatible with our proposed transition state (13) for

(12)   (13)
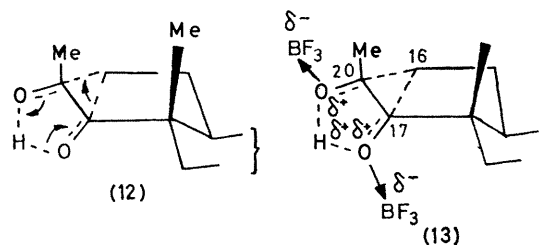
the Lewis-acid-catalysed rearrangement. We consider that the latter, like the thermal reaction (below), is conformationally constrained by the presence of a proton 'bridge' between the two oxygen atoms in the transition state (see Discussion section).

(iii) *Thermal rearrangement of the ketol* (9). 3β-Acetoxy-17α-hydroxy-5α-pregnan-20-one (11) has been reported [8] to rearrange on heating at 240 °C, to give a mixture containing unchanged ketol (11) (50%) and D-homo-ketols of types (2) and (3), each in 15% yield. The suggestion [8] that the stereospecificity of these rearrangements is a result of intramolecular hydrogen bonding, of the type discussed above, prompted us to investigate the thermal reaction in more detail. Table 2 records our results on heating the ketol (9) and the

TABLE 2

Thermal rearrangement of ketols

Reactant ketol	$t/°C$	Duration of heating (h)	Product ketols (%) [a]		
			(10)	(2)[b]	(3)[b]
(10)	244	1	50	35	15
(10)	244	3	0	0	100
(2) [b]	254	1	0	84	16

[a] By [1]H n.m.r.: see ref. 2 and Experimental section. [b] 3β-OH,5α-series.

derived D-homo-ketol of type (2) in evacuated sealed Pyrex tubes. Evidently the kinetically controlled D-homoannulation involves selective or specific migration of the 16,17-bond to give the ketol (2), which is converted more slowly into the stable isomer (3). The latter change may possibly occur by methyl migration (17β $\longrightarrow$ 17aβ), or more probably by reversion to the original ketol (9), the pathway already established [12]

[7] R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820.

[8] D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling, and G. Roberts, *J. Amer. Chem. Soc.*, 1955, **77**, 6585.

[9] C. W. Shoppee, N. W. Hughes, and B. C. Newman, *J. Chem. Soc. (C)*, 1970, 558.

[10] L. Joris and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 1968, **90**, 4599.

[11] R. S. Rosenfeld, *J. Amer. Chem. Soc.*, 1957, **79**, 5540; D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *ibid.*, 1960, **82**, 4012; N. L. Wendler, *Chem. and Ind.*, 1958, 1662; *Tetrahedron*, 1960, **11**, 213.

[12] R. B. Turner, M. Perelman, and K. T. Park, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 1108.

for the Lewis-acid-catalysed equilibration of D-homo-ketols. The initial stereospecific formation of the ketol (2) must occur through a cyclic hydrogen-bridged transition state (12),[8] which has a formal resemblance to that (8) postulated by Turner[6] for the boron-trifluoride-catalysed reaction.

(iv) *Rearrangements using magnesium or lithium alkoxides as catalysts.* Since the D-homoannulation path is critically dependent upon the nature of the catalyst (acidic[3-5] or basic[2,4,5]), it seemed possible that the electronic charge density and distribution in the organic part of the activated complex might be a factor contributing to the selection of either 13,17- or 16,17-bond migration. An anionic transition state, even if closely associated with a metal cation (K^+) in a cyclic complex, favours 13,17-bond migration,[2] whereas the thermal reaction (associated H^+) and the supposedly electron-deficient complex with a Lewis acid [BF_3 or $Al(OR)_3$] favour migration of the 16,17-bond. On the basis of different electronegativity values (K, 0.8; Li, 1.0; Mg, 1.2; Al, 1.5; B, 2.0)[13] we therefore examined lithium t-butoxide and magnesium ethoxide as alternative catalysts. Our expectation that one of these ' intermediate ' catalysts would afford a kinetically controlled *mixture* of rearranged ketols of types (2) and (3) was fulfilled by magnesium ethoxide. The more basic lithium reagent gave only the normal product (3) of a base-catalysed reaction with a *syn* orientation of ketol oxygen atoms.[2] Magnesium ethoxide in xylene–ethanol, in contrast, caused complete rearrangement of the ketol (11) to give the D-homo-ketols (2) and (3) in the ratio 30 : 70, most of the ethanol being removed by distillation during the reaction. A slower reaction in refluxing ethanol alone was sampled at intervals for analysis, giving the D-homo-ketols in the proportions indicated in Table 3. Although the rearrangement is predominantly

TABLE 3

Rearrangement of ketol (1) by magnesium ethoxide in refluxing ethanol

Time (min)	Ketols (%) [a]			
	(1)	(3)	(2)	(4)
0	100			
16	36	50	14	
50	24	56	11	9
110	21	50	14	14

[a] Ketols of 3β-OH,5α-series; analysis of mixtures by g.l.c. (see Experimental section).

of ' base-catalysed ' type, the simultaneous appearance of the ' acid-catalysed ' product (2) indicates that magnesium ethoxide is also able to function as a weak Lewis acid under the reaction conditions, although it is less effective in this respect than are aluminium alkoxides.

Discussion.—On the basis of the foregoing results we propose the ' hydrogen-bridged ' structure (13) for the
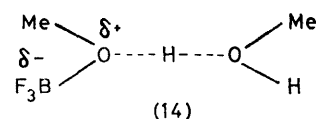
[13] See, for example, R. T. Sanderson, ' Chemical Periodicity,' Reinhold, New York, 1960, p. 34.
[14] P. Diehl, *Helv. Phys. Acta*, 1958, **31**, 685; see also N. N. Greenwood and R. L. Martin, *Quart. Rev.*, 1954, **8**, 1.
[15] A. Fratiello and C. S. Stover, *J. Org. Chem.*, 1975, **40**, 1244.

transition state in the Lewis-acid-catalysed reaction. The concept of a bridging hydrogen atom (or proton) rather than a $^-BF_2{}^-$ group is compatible with the need for *two* molecules of boron trifluoride (or presumably of any other Lewis acid), one being co-ordinated at each of the oxygen atoms. The boron-trifluoride-catalysed rearrangement is therefore visualized as being mechanistically similar to the thermal process, in which *only* hydrogen can be the bridging species.

A Lewis acid, by co-ordination with oxygen of the 17α-hydroxy-group, would increase the lability of the hydroxylic hydrogen atom. Boron trifluoride added to methanol is known[14] to promote hydrogen bonding between methanol molecules, forming complexes of the type (14) which can ionise to species such as $Me\overset{+}{O}H_2$-$MeOBF_3$, so that the solution is a moderately strong acid.

$$\begin{array}{c} \underset{F_3B}{\overset{Me}{\diagdown}}\underset{\delta-}{\overset{\delta+}{O}}\text{----}H\text{----}O\underset{H}{\overset{Me\cdot}{\diagup}} \\ (14) \end{array}$$

In an α-ketol (1), the Lewis acid presumably interacts initially with the more basic 17α-hydroxy-group rather than with the ketone,[15] thereby weakening the O–H bond, but hydrogen transfer between oxygen atoms during rearrangement of the ketol appears to be favoured
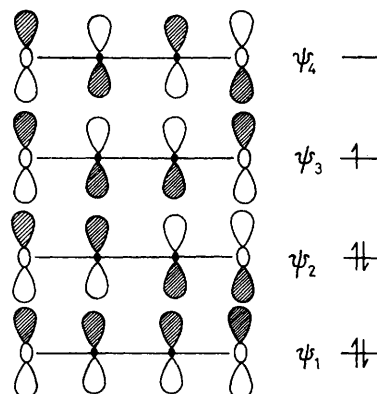
FIGURE 1   π Orbitals of semidione radical anion

by simultaneous association of *both* oxygen atoms with molecules of the Lewis acid. This is compatible with a substantial degree of ionisation of the O–H bond as the hydrogen atom (or proton) is transferred from one oxygen atom to the other.

A ' frontier molecular orbital '[16] analysis of the D-homoannulation sheds further light on its mechanism. Base-promoted α-ketol rearrangements are ' allowed ' in terms of orbital symmetry considerations, and have been described[17] in terms of a semidione radical anion interacting with the migrating group, which is looked

[16] I. Fleming, ' Frontier Orbitals and Organic Chemical Reactions,' Wiley–Interscience, London, 1976; G. B. Gill and M. R. Willis, ' Pericyclic Reactions,' Chapman and Hall, London, 1974.
[17] R. W. Alder, *Tetrahedron Letters*, 1971, 193.

on as an alkyl radical. The semidione radical anion (Figure 1) is considered to have five electrons in delocalised π-orbitals. The sixth electron is formally allotted to an orbital associated with the migrating group. The symmetry of the highest occupied molecular orbital (HOMO; ψ_3) of the notional semidione radical anion allows a concerted [1,2] sigmatropic migration of the alkyl radical (Figure 2), with retention of configuration in the migrating group.
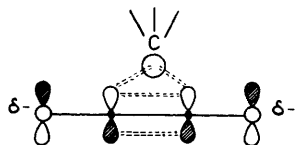

Figure 2   Symmetry-allowed [1,2]sigmatropic migration in α-ketol anion

This orbital model applies to the base-catalysed rearrangement; it is independent of the configuration (*cis* or *trans*) of the semidione component. A [1,2] sigmatropic shift of the type depicted in Figure 2 becomes ' forbidden,' however, if one of the five electrons is withdrawn from the semidione π-orbital system and allotted to the hydroxylic hydrogen atom, to permit it to retain covalent bonding to the π system in the *thermal* process. The HOMO of the semidione is then ψ_2, which possesses the wrong symmetry for a concerted [1,2] alkyl migration. A hydrogen transfer between termini of the π-system would, moreover, need to be of the improbable antarafacial [1,4] type. If, on the other

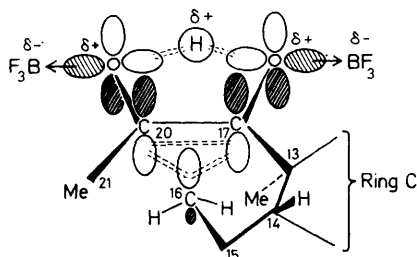Figure 3   Symmetry-allowed α-ketol rearrangement involving π orbital (' vertical' p lobes) and synchronous symmetry-allowed hydrogen migration between lone pairs (' horizontal' p lobes), with BF₃ catalysis

hand, the transition state for thermal rearrangement is visualised as comprising a six-electron combination of the π orbitals of a semidione with the migrating alkyl group, as in the base-catalysed process, while a hydrogen atom (proton) is transferred synchronously between ' lone pairs ' on the two oxygen atoms, in the plane of the σ framework, orbital symmetries ' allow ' both parts of the process.   Figure 3 depicts the π-orbital system as

* For simplicity in drawing, Figure 3 depicts BF₃ as being attached to the ' back lobe ' of an O — — — —H bonding p orbital, assuming sp-hybridised oxygen; an alternative but more crowded drawing, with sp^2 hybridisation at oxygen, would allow O — — — H and O — — — —BF₃ bonding via separate sp^2 hybrid orbitals; this does not conflict with the orbital symmetry requirements of the rearrangement.

orthogonal to the plane which contains both the σ-bond framework [O–C(20)–C(17)–O] and a coplanar ' lone pair ' orbital of p-type symmetry on each oxygen atom, with a proton in process of transfer between these ' lone pair ' orbitals. (To preserve overall electrical neutrality, the migrating hydrogen is formally regarded as a proton to counter-balance the extra electron allotted to the π-orbital system.)   Hoffmann and his co-workers [18] have applied a qualitative perturbation treatment to the through-bond coupling of lone pairs on atoms which are separated by three σ bonds, showing that the HOMO may be represented as a symmetric combination of atomic orbitals of the type illustrated in Figure 4.   A ' proton ' can therefore retain partial bonding to both oxygen atoms while passing from one lone pair to the other.   According to this model, the Lewis-acid-catalysed reaction is facilitated by the loosening of the proton
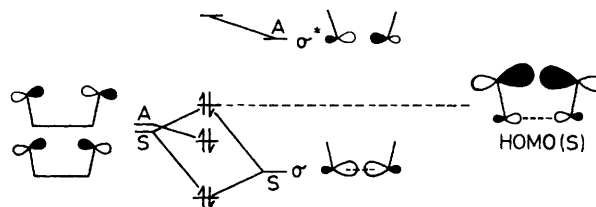

Figure 4   Through-bond interaction of lone-pairs: symmetry classification (S and A) with respect to the ' vertical' plane which bisects the four-atom system (*cf.* ref. 18)

(increased tendency to ionisation of the O ··· H bond), through association of the Lewis acid with oxygen.*   The orbital symmetry features of the reaction remain as in the thermal case.   This description represents both the thermal and the Lewis-acid-catalysed transition states as having some dipolar character, corresponding to the simultaneous existence of a migrating proton and a notional radical anion.   There is no qualitative difference, however, from the charge distribution formally associated with the framework of the molecule in describing the base-catalysed reaction.   This conclusion is consistent with our earlier Hammett-type treatment of the effects of the electron-withdrawing substituents,[3] which showed an unexpectedly small influence of substituent character on rates of reactions.

Base-catalysed rearrangements of ketols (1) in protic solvents proceed through a transition state in which the 17α- and 20-oxygen atoms are in an *anti*-conformation, from stereochemical evidence.[6]   The base-catalysed rearrangement in a dipolar aprotic solvent (KOBuᵗ–Me₂SO), however, like the thermal and Lewis-acid-catalysed processes, involves a *syn*-conformation in which a cation (K⁺) is assumed to be associated with *both* the oxygen atoms of the reacting ketol.[3]

In seeking to explain the differing selection of the migrating group under acidic and basic catalysis, we therefore considered the available information on the

[18]   R. Hoffmann, *Accounts Chem. Res.*, 1971, **4**, 1;   C. C. Levin, R. Hoffmann, W. J. Hehre, and J. Hudec, *J. C. S. Perkin II*, 1973, 210.

interactions between various cations and a semidione radical anion. Simple semidione radical anions exist in interconvertible *cis*- and *trans*-configurations.[19] A recent e.s.r. study has shown that lithium cations selectively stabilise the *cis*-isomer, presumably through simultaneous strong electrostatic interactions with both oxygen atoms. The larger cations Na^+ and K^+, however, associate less strongly with the oxygen atoms, and permit the anionic species to exist mainly in the *trans*-configuration under the experimental conditions. The ionic radius of Li^+ is only half that of K^+, whereas H^+ is effectively a point charge, and should interact most strongly of all with the two oxygen atoms of a semidione radical anion (or of an enediol dianion) in its *cis*-configuration. We therefore propose that the effect of a ' bridging ' proton in the transition state for rearrangement of a ketol is to impose maximum conformational rigidity upon transition states of types (12) and (13). Association of the anion with K^+, in contrast, would be relatively weak, and might therefore permit some flexibility of conformation in the transition state for rearrangement (*cf.* e.s.r. data for semidione radical anions,[19] where variations in measured parameters are thought to indicate departure from strict planarity in some cases). Dreiding models of ' bridged ' transition states for 16,17-bond migration (12) and (13) and the alternative migration of C-13 (15) show that steric strains, notably the compression between C-18 and C-21 methyl groups, would be increased as the complex attained the transition state (15) required for C-13

(15)
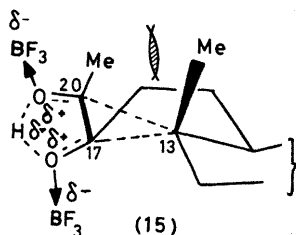
migration. Migration of C-16, in contrast avoids this increase in steric strain in the transition state; there may even be some relaxation of the compression between methyl groups as compared with that in the hydrogen-bonded ketol which precedes the transition state. Furthermore, as has been pointed out previously,[20] the transition state (12) or (13) is of ' developing-chair ' type, and is therefore conformationally favoured.

The question of relative migrating aptitudes of alkyl groups has often been discussed. It is generally found for cationic rearrangements that quaternary carbon migrates in preference to tertiary or secondary groups.[21] The ability of the migrating group to participate in delocalisation of the cationic charge is thought to be important. Reactions in anionic systems are less

common and are less well understood, but the evidence provided by our monocyclic model ketol (5) [1] indicates that there is an electronic preference for migration of the quaternary carbon atom, even despite the necessary ' boat ' conformation of the transition state for the D-homoannulation of the steroid ketol. Although carbanion stabilities in solution are generally considered to indicate that alkyl substituents have a destabilising effect, recent MO calculations and experiments in the gas phase suggest that negative charge can be stabilised by highly substituted alkyl groups,[22] through polarisability effects. Whatever the explanation, our model experiments [1] clearly demonstrate a general preference for the migration of quaternary rather than secondary carbon in an α-ketol which is free from strong conformational restraints.

We therefore propose that the special feature which, in the thermal and acid-catalysed reactions, tends to oppose the normal preference for migration of a tertiary rather than a primary alkyl group, is the exceptional conformational rigidity, and the resultant maximising of steric compression, imposed by the need for a ' bridging proton in the transition state. A ' bridging ' potassium cation in the aprotic basic system,[2] in contrast, exerts only weak control on the conformation of the *syn*-orientated ' semidione,' permitting relief of strains by conformational distortion away from strict coplanarity.

The observed dual behaviour of magnesium ethoxide may well result from competition between two mechanisms. As a base, the reagent may cause an anionic rearrangement, with Mg^{2+} as the species bridging the two oxygen atoms, while co-ordination of each oxygen atom with a molecule of magnesium ethoxide may permit a competing hydrogen-bridged reaction of Lewis acid type.

EXPERIMENTAL

For general notes on reagents, *etc.* see ref. 3.

Boron-trifluoride-catalysed Rearrangement of 3β,17α-Di-*hydroxy*-5α-*pregnan*-20-*one* (9).—(A) The ketol (9) (80 mg, 0.24 mmol) in 1,2-dimethoxyethane (40 ml) was treated with boron trifluoride–ether complex (40 μl, 0.32 mmol). The mixture was immediately distributed among eight stoppered tubes, which were incubated at 49.5 °C. Sampling was carried out after a suitable time interval by adding saturated aqueous sodium hydrogen carbonate (25 ml) to a tube, followed by water (20 ml). The precipitated organic material was collected and washed with water, then taken up in hot ethanol (4 ml). The solvent was removed under reduced pressure, and the residual dry solid was examined by [1]H n.m.r. in deuteriated dimethyl sulphoxide (see ref. 2). The extent of reaction was estimated by comparing the integral of the peak at τ 9.50 (18-H_3 in reactant) with that of the unchanging peak at τ 9.25 (19-H_3 in reactant and products).

Samples taken at intervals of 3 min (from 3 min to 21 min) gave extents of reaction ranging from 20.5 to 82.8%,

[19] G. A. Russell, D. F. Lawson, H. L. Malkus, R. D. Stephens, G. R. Underwood, T. Takano, and V. Malatesta, *J. Amer. Chem. Soc.*, 1974, **96**, 5830, and references therein.

[20] 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.

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

[22] T. P. Lewis, *Tetrahedron*, 1969, **25**, 4117; H. M. Niemeyer, *ibid.*, 1977, **33**, 775.

respectively; a linear first-order plot with respect to steroid reactant gave $k = 1.38 \times 10^{-3}$ s^{-1} (at 49.5 °C).

(B) A similar reaction using ketol (9) (80 mg, 0.24 mmol) and boron trifluoride–ether (56.5 μl, 0.45 mmol), sampled at 1.5 min intervals, gave a first-order plot with respect to steroid; $k = 3.27 \times 10^{-3}$ s^{-1} (at 49.5 °C).

(C) A reaction similar to (A) and (B) but with the boron trifluoride–etherate increased to 80 μl (0.64 mmol), and sampled at 1 min intervals, gave a linear first-order plot with respect to steroid; $k = 4.60 \times 10^{-3}$ s^{-1} (at 49.5 °C).

[19]F *N.m.r. Investigation into Boron Trifluoride Consumption.*—A Varian HA-100 spectrometer was used, with lock frequency 1 546 Hz. 1,1,2-Trichloro-3,3,3-trifluoropropene (TCFP) was used as external reference. The following systems were investigated at 30 °C.

(A) *Pure boron trifluoride–ether.* This showed a single peak 91.46 p.p.m. upfield from TCFP. Given [23] that the TCFP signal is 62 p.p.m. upfield from $CFCl_3$, the boron trifluoride resonance is 153.5 p.p.m. upfield from $CFCl_3$, identical with the value reported.[24]

(B) *Boron trifluoride–ether in dimethoxyethane.* Solutions were made up by adding boron trifluoride–ether to dimethoxyethane. The chemical shifts listed in Table 4

TABLE 4

[19]F N.m.r. spectra of $BF_3 \cdot Et_2O$ solutions in DME

Molar ratio of $BF_3 \cdot Et_2O$ to DME	Shift of ^{19}F signal (p.p.m. upfield from $CFCl_3$)
100% $BF_3 \cdot Et_2O$	153.5
1.65 : 1	154.5
0.825 : 1	155.1
0.413 : 1	155.6
0.165 : 1	156.1
0.041 : 1	156.2(6)
0.017 : 1	156.2(8)
0.008 : 1	156.3(3)

relative to $CFCl_3$ are calculated from those measured relative to TCFP $+62$ p.p.m. (see above). Peaks became broad at low concentrations of BF_3.

(C) 3β,17α-*Dihydroxy-5α-pregnan-20-one 3-trifluoroacetate* (10) (for preparation see below). Compound (10) (34.3 mg) in dimethoxyethane (500 μl) showed a sharp singlet 14.6 p.p.m. upfield from TCFP (76.6 p.p.m. upfield from $CFCl_3$).

(D) 3β,17α-*Dihydroxy-5α-pregnan-20-one 3-trifluoroacetate* (10) *and boron trifluoride–ether (mixture before reaction).* A cooled solution (0 °C) of the ketol 3-trifluoroacetate (10) (34.3 mg, 0.08 mmol) in dimethoxyethane (500 μl) in an n.m.r. sample tube was treated with boron trifluoride–ether (10 μl, 0.08 mmol). The tube was immediately sealed, and the contents were mixed and examined by n.m.r. (no rearrangement occurs under these conditions). A sharp singlet was observed at 76.6 p.p.m. and a broad line, of equal area, at 155.8 p.p.m. (relative to $CFCl_3$).

(E) *Mixture from* (D) *after reaction.* The sample tube from (D) was heated at 50 °C in a oil-bath for 20 min, and allowed to cool. N.m.r. examination again showed a sharp singlet at 76.6 p.p.m. and a broad line of the same area at 155.8 p.p.m. Immediately following n.m.r. examination the mixture was poured into saturated aqueous sodium hydrogen carbonate. The precipitated solid was collected, then taken up in methanol (20 ml) and stirred overnight with potassium carbonate (1 g) in water (2 ml) to remove the

trifluoroacetate group. The recovered steroid in deuteriated dimethyl sulphoxide exhibited an n.m.r. spectrum identical with that of pure 3β,17α-dihydroxy-17β-methyl-D-homo-5α-androstan-17a-one (2; 3β-OH, 5α).

Preparation of 3-Trifluoroacetates.—3β,17α-*Dihydroxy-5α-pregnan-20-one 3-trifluoroacetate* (10). 3β,17α-Dihydroxy-5α-pregnan-20-one (9) (448 mg) was stirred with anhydrous benzene (200 ml) while trifluoroacetic anhydride (5 ml) was added. A clear solution was obtained after 3 min, and was set aside for a further 25 min. Solvent and excess of reagent were then removed under reduced pressure and the residue was taken up in refluxing hexane (100 ml). Overnight, white crystals (218 mg) were deposited. Further crystals (208 mg) were obtained after concentration of the mother liquor (total yield 426 mg, 73%). Recrystallisation from hexane gave the *trifluoroacetate*, m.p. 178—184°; $\nu_{max.}$ 3 518, 1 778, and 1 695 cm^{-1}; $\tau(CCl_4)$ 9.34 (s, 18-H_3), 9.12 (s, 19-H_3), and 7.83 (s, 21-H_3) (Found: C, 64.1; H, 7.6; F, 13.4. $C_{23}H_{33}F_3O_4$ requires C, 64.1; H, 7.7; F, 13.25%).

3β,17α-*Dihydroxy-17β-methyl-D-homo-5α-androstan-17a-one 3-trifluoroacetate* (2; 3β-CF_3CO_2, 5α). (a) *By rearrangement of the ketol 3-trifluoroacetate* (10). Compound (10) (34 mg) in dimethoxyethane (500 μl) was treated with boron trifluoride–ether (10 μl) and heated at 50 °C for 25 min. The solution was then poured into water. The precipitated steroid crystallized from hexane to give the *trifluoroacetate* (2; 3β-CF_3CO_2, 5α) (21 mg, 62%), needles, m.p. 109—112°; $\nu_{max.}$ 3 560, 3 380, 1 772, and 1 705 cm^{-1}; $\tau(CCl_4)$ 9.14 (s, 19-H_3), 8.95 (s, 18-H_3), and 8.68 (s, 17β-CH_3) (Found: C, 64.0; H, 7.5; F, 13.5. $C_{23}H_{33}F_3O_4$ requires C, 64.1; H, 7.7; F, 13.25%).

(b) *By trifluoroacetylation of* 3β,17α-*dihydroxy-17β-methyl-*D-*homo-5α-androstan-17a-one.* The procedure (above) for trifluoroacetylation of 3β,17α-dihydroxy-5α-pregnan-20-one afforded the 3-trifluoroacetate of the D-homo-ketol, identical with the sample from (a).

3β,17aα-*Dihydroxy-17aβ-methyl-*D-*homo-5α-androstan-17-one 3-trifluoroacetate* (3; 3β-CF_3CO_2, 5α). This ester was prepared from the 3β-hydroxy-ketol as described for 3β,17α-dihydroxy-5α-pregnan-20-one. The 3-trifluoroacetate crystallised from hexane as needles, m.p. 225—231°; $\nu_{max.}$ 3 490, 1 778, and 1 709 cm^{-1}; $\tau(CCl_4)$ 9.34 (s, 18-H_3), 9.15 (s, 19-H_3), and 8.89 (s, 17a-CH_3).

Thermal rearrangement of Ketols (cf. *Table* 2).—Small quantities (10 mg) of the steroid ketols were sealed into evacuated Pyrex tubes and heated as indicated in Table 2. After cooling to room temperature the products were examined by [1]H n.m.r. in deuteriated dimethyl sulphoxide (cf. ref. 2).

Rearrangement of the ketol (9) *with lithium t-butoxide.* Lithium metal (160 mg) was dissolved in a mixture of t-butyl alcohol (25 ml) and heptane (75 ml). The ketol (9) (50 mg) in dimethoxyethane (10 ml) was added to 10 ml of this solution and the mixture was stirred for 30 min at 20 °C, then shaken with aqueous acetic acid (4M). The organic layer was separated, washed successively with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated; the residue was found (n.m.r.) to consist of reactant ketol (9) (80%) and the D-homo-ketol of type (3) (20%).

Rearrangements of ketols with magnesium ethoxide. (a) *In xylene–ethanol.* A solution of magnesium ethoxide [from

[23] J. Emsley, J. Feeney, and L. Sutcliffe, ' High Resolution Nuclear Magnetic Resonance Spectroscopy,' vol. 2, Pergamon, London, 1966, p. 962.

[24] R. A. Craig and R. E. Richards, *Trans. Faraday Soc.*, 1963, **59**, 1962.

magnesium] (15 mg) in ethanol (40 ml) was added to a solution of the ketol (1) (100 mg) in xylene (20 ml), and the ethanol was distilled off slowly over 40 min, the final solution temperature being 130 °C. The cooled mixture was diluted with benzene and washed with aqueous hydrochloric acid, water, aqueous sodium hydrogen carbonate, and water again (twice). The solvents were removed under reduced pressure; the residue was found (n.m.r.) to comprise ketols of types (2) and (3) in the ratio 3 : 7.

(b) *In ethanol*. Ethanolic magnesium ethoxide (0.003M; 20 ml) containing the ketol (9) (20.1 mg) was heated under reflux. Samples (4 ml) were removed at intervals, poured into water, and refrigerated (0 °C). The precipitated solids in each sample were collected, dried at 40 °C, and trimethylsilylated for g.l.c. analysis (see below).

G.l.c. analysis of ketol mixtures. Using a Hewlett–Packard 402 Gas Chromatograph and a 6 ft glass column packed with 3% QF1 on 80—100 mesh Chromosorb W it was possible to distinguish amongst the trimethylsilyl ethers of the five relevant ketols. Trimethylsilylations, which were slow, were carried out by treating the dried steroid (*ca.* 7 mg) with a freshly prepared mixture (500 μl) of *NO*-bistrimethylsilylacetamide (4 ml) and chlorotrimethylsilane (80 μl). The solution was covered and stored in a desiccator for 4 days. A 1 μl portion of this solution was then injected into the column. Retention times, relative to 5α-cholestane (= 1.00) were as follows (all ketol derivatives of the 3β-OH,5α-series): 3β,17α-dihydroxy-5α-pregnan-20-one (9) derivative, 2.10; D-homoandrostane derivatives: 17aβ-OH, 17aα-Me, 17-oxo (4), 2.25; 17aα-OH, 17aβ-Me, 17-oxo (3), 2.53; 17α-OH, 17β-Me, 17a-oxo (2), 2.08; 17β-OH, 17α-Me, 17a-oxo, 2.60.