Kinetic Study of Elimination from 3α-Chloro-3β-methyl- and 3β-Chloro-3α-methyl-5α-cholestane promoted by Potassium t-Butoxide in t-Butyl Alcohol

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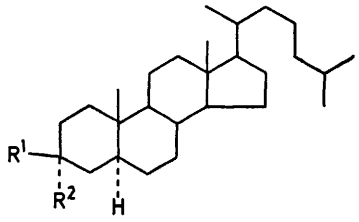
Elimination from 3α-chloro-3β-methyl- (1) and 3β-chloro-3α-methyl-5α-cholestane (2) to give 3-methylene-5α-cholestane (*exo*-olefin) and 3-methyl-5α-cholest-2-ene (*endo*-olefin) has been investigated in Bu^{t}OK–Bu^{t}OH solution. The *exo*:*endo* olefin ratio is affected by the Bu^{t}OK concentration but does not depend significantly upon the conformation of the chlorine substituent. This also holds for the reaction rates since the *endo*-olefin is formed at 100° only 1.7 fold faster from (1) (axial chlorine) than from (2) (equatorial chlorine). In contrast, elimination from 3α-chloro-5α-cholestane (3) is *ca.* 500 fold faster than from the equatorial isomer (4). The small difference between (1) and (2) in the rate of formation of the *endo*-olefin is due to compensation between enthalpy and entropy factors. A similar situation is also observed when the *exo*-olefin forming reactions from (1) and (2) are considered. The kinetic data and the activation parameters support the hypothesis that both olefins are formed from (2) in an anticoplanar process involving a skew-boat conformation.

It is recognized that elimination from cyclohexyl derivatives is strongly favoured when the proton and the leaving group can achieve an anticoplanar arrangement.[1] Thus, in the elimination reactions of conformationally restricted 1-X-1-methylcyclohexanes, formation of the endocyclic olefin should be much easier for the isomer having the X substituent in an axial conformation than for the equatorial isomer; in the latter case no ring proton is in an *anti*-diaxial relationship with the leaving group and the *exo*-olefin should be the main product of elimination. This conclusion has also found some use as a criterion to establish the configuration of carbon atoms bearing hydroxy and methyl groups in steroids.[2-5]

Recently, results at variance with the above predictions have been obtained from studies of the elimination reactions of *trans*- and *cis*-1-methyl-4-t-butylcyclohexanol [6] and of the corresponding chlorides.[7] For both the *trans*- and *cis*-isomer the *endo*-olefin was the main product and, more significantly, in the case of the chloro-derivative the isomer with the substituent in the equatorial conformation afforded a larger proportion of the *endo*-olefin than that with the axial substituent. To rationalize this result it was suggested [7] that the *trans*-isomer could react through a skew-boat conformation allowing an anticoplanar elimination.

This suggestion has certainly significant implications with respect to the important problem of the relationship between configuration at C–X and elimination products of steroids and raises some doubt about the actual degree of rigidity of systems which are frequently used to investigate the preferred stereochemical path of elimination reactions. With respect to the latter problem it is interesting to note that elimination from *trans*-4-t-butylcyclohexyl derivatives is usually discussed as occurring by an *anti*-diequatorial process involving a chair conformation.[8,9]

In considering of the latest results concerning the fundamental role of the nature of the base–solvent system with respect to the stereochemistry and mechanism of elimination reactions,[10] we felt that an additional and quantitative investigation of the above problem could be of interest. In particular, it appeared desirable



(1) $R^1 = CH_3, R^2 = Cl$
(2) $R^1 = Cl, R^2 = CH_3$
(3) $R^1 = H, R^2 = Cl$
(4) $R^1 = Cl, R^2 = H$

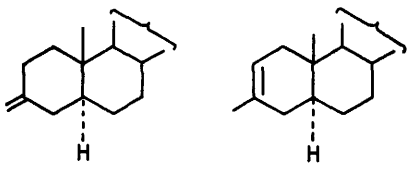
to acquire more information on the role played by chair ⇄ skew-boat conformational equilibria and by processes other than the anticoplanar one in elimination from conformationally restricted cyclohexyl derivatives. Thus, we have carried out a kinetic study of elimination from 3α-chloro-3β-methyl- (1) and 3β-chloro-3α-methyl-5α-cholestane (2) promoted by Bu^{t}OK in Bu^{t}OH. For comparison purposes some rate data have also been obtained for eliminations from 3α-chloro- (3) and 3β-chloro-5α-cholestane (4).

RESULTS AND DISCUSSION

The reactions of both (1) and (2) with Bu^{t}OK in Bu^{t}OH afforded a mixture of the *exo*-olefin, 3-methylene-5α-cholestane (5) and of the *endo*-olefin, 3-methyl-5α-cholest-2-ene (6). The proportions of (5) and (6) were determined by g.l.c. analysis and were found to be significantly affected by the Bu^{t}OK concentration as well as by the addition of 18-crown-6 ether. Blank experiments showed no significant isomerization of (5)

[1] W. H. Saunders, jun., and A. F. Cockerill, 'Mechanisms of Elimination Reactions,' Wiley, New York, 1973, pp. 116*ff*.
[2] D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 1956, 3500
[3] H. Heusser, N. Wahba, and F. Winternitz, *Helv. Chim. Acta*, 1954, **37**, 1052.
[4] E. J. Corey and R. R. Sauers, *J. Amer. Chem. Soc.*, 1959, **81**, 1739.
[5] J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Austral. J. Chem.*, 1965, **18**, 759.
[6] B. Cross and G. H. Whitham, *J. Chem. Soc.*, 1960, 3892.
[7] D. N. Kirk and P. M. Shaw, *J. Chem. Soc.* (*C*), 1970, 182.
[8] P. Beltrame, G. Biale, D. J. Lloyd, A. J. Parker, M. Ruane, and S. Winstein, *J. Amer. Chem. Soc.*, 1972, **94**, 2240.
[9] Ref. 1, p. 120.
[10] R. A. Bartsch, *Accounts Chem. Res.*, 1975, **8**, 239.

to (6) under the reaction conditions. The results are reported in Table 1.



(5) (6)

TABLE 1

Olefinic products of the reactions of 3α-chloro-3β-methyl-5α-cholestane (1) and 3β-chloro-3α-methyl-5α-cholestane (2) with Bu^{t}OK in Bu^{t}OH at 100 °C

Substrate	[Bu^{t}OK]/ M	*exo*-Olefin (%)	*endo*-Olefin (%)	*exo* : *endo* Ratio
(1)	0.190	47.6	52.4	0.91
	0.533	62.5	37.5	1.67
	0.983	72.9	27.1	2.69 [a]
	0.012 [b]	44.7	55.3	0.81
(2)	0.224	49.7	50.3	0.99
	0.460	56.6	43.4	1.30
	1.174	85.9	14.1	6.10
		32.6 [c]	67.4 [c]	0.48 [c]

[a] A value of *ca.* 1 is reported by Kirk and Shaw [7] for the reaction of (1) with Bu^{t}OK (1N) under reflux; we have no explanation for the difference between this value and ours. [b] In the presence of 18-crown-6 ether (0.024M) at 80 °C. [c] With MeONa (0.4M) in MeOH, at 100 °C.

The kinetic study of the elimination reactions was carried out by analysing, *via* potentiometric titration with $AgNO_3$, the chloride ion formed. The concentration of Bu^{t}OK, was at least 70 fold greater than that of the substrate. First-order plots were satisfactorily linear but the derived second-order rate constants (k_2) were found to decrease slightly as the concentration of the base increases. From the yields of *exo*- and *endo*-olefin obtained under the kinetic conditions the specific rate constants for the formation of the two olefins, k_{2exo} and k_{2endo}, were determined. Kinetic data obtained, for comparison purposes, at the same base concentration (*ca.* 0.5M) are reported in Table 2. The activation parameters are collected in Table 3.

The results in Table 1 show that both (1) and (2) give substantial amounts of the *endo*-olefin (6), which can become the predominant (even if to a small extent) reaction product when the Bu^{t}OK concentration is *ca.* 0.2M or in the presence of the crown ether. The relative proportions of *exo*- and *endo*-olefin are not significantly affected by the conformation of the chlorine substituent, the *exo* : *endo* olefin ratio being practically the same in the reactions of (1) (axial Cl) and (2) (equatorial Cl), when the comparison is made between ratios obtained at the same concentration of Bu^{t}OK. Thus, easy formation of the *endo*-olefin is also observed when the equatorial derivative is conformationally restricted by *trans*-fusion with another cyclohexane ring, which should make the system more rigid than in the case of monocyclic derivatives where the restriction is due to the presence of a t-butyl group.* More interestingly, the rate of formation of the *endo*-olefin is little influenced by the conformation of the leaving group, k_{2endo} of (2) being only 1.7 fold (at 100°) and 5.6 fold (at 25°) smaller than k_{2endo} of (1). In contrast, a very much different situation obtains in the eliminations from 3α- and 3β-chloro-5α-cholestane, where the isomer with axial chlorine reacts *ca.* 500 fold faster than the equatorial isomer.† Interestingly enough, it turns out that the introduction of a methyl group in the 3-position of 3-chloro-5α-cholestane exerts a very much different effect

TABLE 2

Kinetic data for the reactions of 3α-chloro-3β-methyl-5α-cholestane (1), 3β-chloro-3α-methyl-5α-cholestane (2), 3α-chloro-5α-cholestane (3), and 3β-chloro-5α-cholestane (4) with Bu^{t}OK in Bu^{t}OH

Substrate	*t*/°C	10^5k_2/ l mol^{-1} s^{-1} [a]	Olefin (%) [b] *exo*	Olefin (%) [b] *endo*	10^5k_{2exo}/ l mol^{-1} s^{-1}	10^5k_{2endo}/ l mol^{-1} s^{-1}
(1)	25.0				0.012 4 [c]	0.005 43 [c]
	78.6	3.95	64.7	35.3	2.55	1.39
	89.4	8.93	62.8	37.2	5.61	3.32
	100.5	22.81	62.5	37.5	14.26	8.55
(2)	25.0				0.001 33 [c]	0.000 97 [c]
	78.8	1.45	56.9	43.1	0.827	0.628
	89.0	4.27	56.3	43.7	2.41	1.87
	100.5	11.60	56.6	43.4	6.57	5.03
(3)	99.2	6.77				
(4)	99.2	0.0138				

[a] Average of at least two determinations. The concentration of Bu^{t}OK was *ca.* 0.5M in all experiments. The average error is ±2%. [b] Average of at least two determinations. The error is ±1%. [c] Values extrapolated from data for other temperatures.

TABLE 3

Activation parameters for the reactions of 3α-chloro-3β-methyl-5α-cholestane (1) and 3β-chloro-3α-methyl-5α-cholestane (2) with Bu^{t}OK in Bu^{t}OH [a]

Substrate	$\Delta H^{\ddagger}_{exo}$/ kcal mol^{-1}	$\Delta H^{\ddagger}_{endo}$/ kcal mol^{-1}	$\Delta S^{\ddagger}_{exo}$/ cal mol^{-1} K^{-1}	$\Delta S^{\ddagger}_{endo}$/ cal mol^{-1} K^{-1}
(1)	+19.8	+20.9	−23.7	−21.6
(2)	+24.2	+24.3	−13.4	−13.5

[a] The data were obtained by least-square analysis of the equation $\log k/T = 10.319 - \Delta H^{\ddagger}/4.575T + \Delta S^{\ddagger}/4.575$. The errors are ±1 kcal mol^{-1} for $\Delta H^{\ddagger}$ and ±2 cal mol^{-1} K^{-1} for $\Delta S^{\ddagger}$.

* In the elimination reactions of 3-hydroxy-3-methyl-5α-cholestanes with $POCl_3$, the *exo* : *endo* olefin ratio is, as expected, much smaller than 1 when the hydroxy-group is axial and slightly larger than 1 when it is equatorial. In contrast, with 1-hydroxy-1-methyl-4-t-butylcyclohexanes the *exo* : *endo* olefin ratio is independent of the conformation of the hydroxy-group.[7] This is in agreement with a greater degree of rigidity in the cholestane derivatives.

† In the reaction of 4-t-butylcyclohexyl bromide with Bu^{t}OK in Bu^{t}OH the *cis*-isomer (axial bromine) is *ca.* 500 fold more reactive (at 82°) than the *trans*-isomer (equatorial bromine).[11]

[11] J. Zavada, J. Krupicka, and J. Sicher, *Coll. Czech. Chem. Comm.*, 1968, **33**, 1393.

on the elimination rate of HCl, depending on whether it occupies the β- or α-position. In the first case the elimination rate remains practically unchanged; in the second case it rises by a factor of *ca.* 350.

These findings clearly show that the presence of a 3α-methyl group plays a very significant role in the elimination reactions of the cholestan-3-yl derivatives; they also exclude both an *anti*-diequatorial and a *syn*-process of elimination for the formation of the *endo*-olefin from (2). Accordingly, if such processes were of importance we should expect a large rate difference also between the reactions of (1) and (2) since there is no reason to believe that *anti*-diequatorial and *syn*-eliminations are much more favoured with (2) than with 3β-chloro-5α-cholestane or that *anti*-diaxial eliminations are much less favoured with (1) than with 3α-chloro-5α-cholestane. Furthermore, large *anti* : *syn* rate ratios are generally expected for eliminations from six-membered rings.[12]

Corresponding results are obtained when the *exo*-olefin forming reaction is considered; also in this case there is a small rate difference between the two substrates, k_{2-xo} of (2) being 9.3 fold at 25°, and 2.2 fold at 100°, smaller than k_{2exo} of (1).

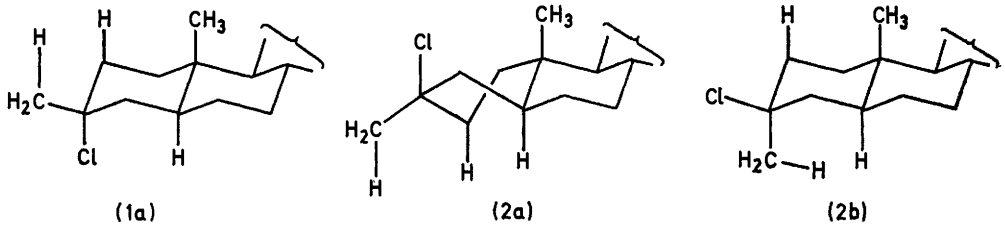
The two elimination reactions of (1) certainly occur by the same mechanism and they exhibit nearly identical values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. An analogous conclusion can be drawn, on the basis of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values, for the formation of the *exo*- and *endo*-olefin from (2). However, when the reactions of (1) and (2) are compared it turns out that the observed similarity in rate is due to compensation between enthalpy and entropy factors. Either elimination from (1) has an activation enthalpy substantially lower (*ca.* 4 kcal mol^{-1}) and an activation entropy much more positive (8—10 cal mol^{-1} K^{-1}) than the corresponding reaction from (2).

The very similar increase in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ observed for the reactions of formation of both olefins when the substrate is changed from (1) to (2) suggests a common origin for the phenomenon. In this respect the most reasonable hypothesis is that the *exo*- and *endo*-olefin are formed from (2) by an antiperiplanar process involving conformer (2a) in which ring A is in a skew-boat conformation. Accordingly, if the *anti*-elimination occurs at nearly the same rate from (2a) and the chair conformation (1a) of (1), the differences in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ between the elimination reactions of the two isomers should correspond to the enthalpy and entropy changes involved in the conversion of (2b), the more stable chair conformation, into (2a) and consequently should be practically the same for the two reactions.

Also the order of magnitude of the increase in $\Delta H^{\ddagger}$ appears to support the intervention of (2a) in the eliminations from (2). In the cyclohexane ring the difference in enthalpy between the chair and the skew-boat conformation is *ca.* 5.5 kcal mol^{-1}.[13,14] However, in the case of (2) this difference should be reduced as a consequence of the fact that in the chair conformation (2b) there are interactions due to the axial 3-methyl group, which are absent in (2a). Thus the observed difference in activation enthalpy between the reactions of (1) and (2) might be consistent with the presumed enthalpy difference between (2a) and (2b).

The more positive value of $\Delta S^{\ddagger}$ for the reactions of (2) is, likewise, in agreement with the hypothesis of the intervention of (2a) since skew-boat conformations have generally a higher entropy content than chair conformations. However it must be recognised that the increase in $\Delta S^{\ddagger}$ is larger than expected.*

The intervention of (2a) in the elimination leading to the *exo*-olefin from (2), in spite of the fact that this reaction might take place by an *anti*-process from the more stable (2b), is further supported by the following arguments. First, if (2b) were the reactive conformer it would be very difficult to rationalize the large differences in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ observed between the formation of the *exo*-olefin from (1) and (2), whereas the difference in rate is very small. Secondly, since *anti*-attack of the base at one proton of the axial methyl group of (2b) appears to be subject, as already suggested by Kirk,[7] to considerable steric hindrance, the use of a base with smaller steric requirements than Bu^{t}OK, such as MeONa in MeOH, should lead to an increase in the *exo* : *endo* olefin ratio, which is exactly the opposite of what is observed. This steric effect, which certainly must slow down the rate of the *anti*-elimination to the *exo*-olefin from (2b), and the small ground state free energy difference between (2a) and (2b), are probably the factors which make the reaction leading to the *exo*-olefin take place preferentially through conformer (2a).



Finally, we wish briefly to discuss the dependence of the *exo* : *endo* ratio upon Bu^{t}OK concentration (Table 1).

* In the case of the cyclohexane ring the entropies of the chair and skew-boat conformations differ by *ca.* 5 cal mol^{-1} K^{-1} [13,14] but it is doubtful that this value can be straightforwardly applied to the (2a) ⇌ (2b) equilibrium.

[12] 'Advances in Alicyclic Chemistry,' eds. N. A. LeBel, H. Hoat, and G. J. Karabatsos, Academic Press, New York, 1971, p. 218.

[13] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 206.

[14] E. L. Eliel, N. C. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Wiley, New York, pp. 38—40 and 470.

The phenomenon can be rationalized on the basis of the now well recognized difference in steric requirements between dissociated ions, ion pairs, and ionic aggregates.[10] With both (1a) and (2a) the approach of the base to 2-H (formation of the *endo*-olefin) is more difficult for steric reasons [interaction with the other ring protons and for (1a) also with 10-CH_3] than to the proton of the methyl group in the 3-position (formation of the *exo*-olefin). Thus the formation of the *exo*-olefin, which exhibits smaller steric effects, will be favoured as the concentration of Bu^tOK increases, *i.e.* as in the medium the concentration of the more bulky ionic aggregates increases. At lower Bu^tOK concentrations or in the presence of 18-crown-6 ether the active base should be the smaller dissociated t-butoxide ion;[10] accordingly, in these conditions a higher proportion of the *endo*-olefin is observed. Likewise, the high percentage of *endo*-olefin (*ca.* 67) found in the reaction of (2) with MeONa in MeOH is ascribed to the very small steric requirements of this base.

EXPERIMENTAL

Materials.—3-Chloro-3-methyl-5α-cholestanes were prepared by the reaction of corresponding tertiary alcohols with freshly sublimated PCl_5 in dry chloroform as described by Carman and Deeth.[15] 3α-Chloro-3β-methyl-5α-cholestane had m.p. 153—155° (lit.,[15] 154—156°), 3β-chloro-3α-methyl-5α-cholestane m.p. 134—136° (lit.,[15] 135—136°). 3-Chloro-5α-cholestanes were prepared from the corresponding secondary alcohols by the procedure used for the 3-chloro-3-methyl-5α-cholestanes. 3α-Chloro-5α-cholestane had m.p. 103—105° (lit.,[16] 103—104°), 3β-chloro-5α-cholestane m.p. 112—114° (lit.,[16] 113—114°).

[15] R. M. Carman and H. C. Deeth, *Austral. J. Chem.*, 1970, **23**, 1053.

3-Methylene-5α-cholestane (5) was obtained by the procedure described by Barton,[2] with the exception that n-butyl-lithium was used in the place of phenyl-lithium, m.p. 64—66° (lit.,[2] 65—66°). 3-Methyl-5α-cholest-2-ene (6) was prepared by reaction of a mixture of 3-methyl-5α-cholestan-3α- and -3β-ol with perchloric acid in glacial acetic acid, m.p. 81—83° (lit.,[2] 82—83°).

18-Crown-6 ether (Fluka) was purified by crystallization from n-hexane, m.p. 38.5—39.5° (lit.,[17] 39.5—40.5°).

Base–Solvent Solutions.—t-Butyl alcohol and methanol were distilled after treatment with potassium and sodium metal, respectively. Solutions of alkoxide were obtained by reaction, under nitrogen, of freshly cut potassium or sodium with the alcohol.

Kinetic Studies.—A known quantity of the desired compound was placed in a volumetric flask (50 ml) and a solution of alkoxide of appropriate concentration was added to the calibration mark. Portions (4 ml) of this solution were poured into Pyrex tubes (5 ml) which were then sealed and placed in a thermostatted bath. At recorded times the content of the sealed tubes was potentiometrically analysed for chloride ion with 0.01N-$AgNO_3$.

G.l.c. Analysis of Products.—These analyses were performed on a Carlo Erba model G1 gas chromatograph, equipped with a flame ionization detector and using nitrogen as carrier gas. The olefins were sufficiently separated on a 1.5 × 0.002 m column packed with 20% LAC 728 on 60—80 mesh Chromosorb W, at 175°. The molar response of the *exo*-olefin with respect to the *endo*-olefin was 1.071. No isomerization of the olefins occurred under the reaction conditions.

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[6/504 *Received*, 15*th March*, 1976]

[16] H. J. Geise, A. Tieleman, and E. Havinga, *Tetrahedron*, 1966, **22**(I), 183.

[17] R. N. Green, *Tetrahedron Letters*, 1972, 1793.