The Kinetics and Mechanisms of Additions to Olefinic Substances. Part 15.[1] Chlorination of Cholest-5-ene and its 3-Substituted Derivatives, including Cholest-5-en-3-one; Factors affecting the α : β Ratio for Electrophilic Attack, and for Product Formation, in Cholest-5-enes

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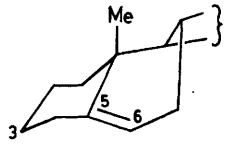
Reactions of cholest-5-ene or its 3β-substituted derivatives with chlorine in chloroform or chlorobenzene give as kinetically controlled products the expected 5α,5β-dichloride, accompanied by the isomeric 5β,6α-dichloride as a minor component. The proportion of the latter decreases with the electron-withdrawing power of the 3β-substituent. Neither added pyridine nor added chloride ion affects the product proportions significantly. Cholest-5-en-3-one, on the other hand, when treated with chlorine in chlorobenzene containing 2-methyloxiran gives not only the expected 5α,6β-dichloride but also much 6α- and 6β-chlorocholest-4-en-3-one. Comparison with the results for 4β-deuteriocholest-5-ene shows that the formation of 6α-chlorocholest-4-en-3-one involves mainly displacement of the 4β-hydrogen atom, and that the formation of its 6β-isomer involves mainly but not exclusively displacement of the 4β-hydrogen atom. Similar products are obtained in deuteriochloroform containing pyridine; in acetic acid, substitution is accompanied by little addition and much unidentified material The results are compared with the corresponding results for bromination, epoxidation, and iodination. It is argued that halogenation of cholest-5-en-3-one differs from that of cholest-5-ene and its 3-monosubstituted derivatives in the ratio of attack on the α- and β-faces of the molecule for two main reasons: because of the availability of a concerted pathway for substitution involving the chair conformation of ring A of the enone, and because in non-concerted pathways for addition and substitution, ring A of the intermediate halogenonium ion derived from the enone can reach a boat conformation. Two types of Ad_E3 additions having different stereochemical preferences can also be recognised.

THE double bond in the cholest-5-ene system (1) formally is modified by the attachment of three alkyl groups, the electronic effects of which would allow attack by electrophiles on either the α- or the β-face of the molecule, preferentially at the 6-position in either case. For reaction with a number of electrophiles, α-attack predominates; the reason most commonly given [2] is that the axial 19-methyl group on the β-face impedes attack on the 6-position sterically.

It is known [3] that chlorine in dimethylformamide reacts with cholest-5-ene and its 3β-substituted derivatives to give 5α-chloro-6β-formates, and that hypochlorous acid similarly gives 5α-chloro-6β-hydroxy-derivatives,[4,5] as does 3α-benzoyloxycholest-5-ene.[6] In all these reactions, the α-face of the steroid is attacked preferentially by the electrophile, and completion of addition gives the product of 'anti-Markownikoff-type' orientation, as for the related reactions involving electrophilic bromine. Cholest-5-en-3-one, on the other hand, has been reported to react with hypochlorous acid to give 6β-chloro-5α-hydroxycholestan-3-one,[5,7] apparently by electrophilic attack on the β-face of the steroid, with completion of the addition to give the product of 'Markownikoff-type' orientation.† Halogenation of this ketone can, however, be complicated by acid-catalysed reactions of the products first formed.[1] It was of interest, therefore, to obtain results for chlorination in the presence of base under conditions which would allow direct comparison with the related brominations, and would ensure the characterisation of products formed under kinetic control.



(1)

EXPERIMENTAL

Most of the materials and methods have been described in the accompanying or earlier papers; [1,8-10] some additional details are given in Supplementary Publication No. SUP 22098 (43 pp.) (see Part 13 [8]).

Products of Chlorination of Cholest-5-ene and its 3β-Substituted Derivatives.—(a) *With molecular chlorine.* To cholest-5-ene and to each of a series of its 3β-substituted derivatives (3β-HO, MeO, $MeCO_2$, $PhCO_2$, Cl, and $CF_3{\cdot}CO_2$) (2×10^{-4} mol) was added chlorine (2.5×10^{-4} mol) in $CDCl_3$ (0.5 ml) at room temperature, and after a few minutes the solutions were examined by ^1H n.m.r. spectroscopy. In each case the spectrum of the major product was clearly recognisable as that of the 5α,6β-dichloride.[11] That derived from chlorination of cholesterol was isolated

† The similar reaction of its ethylene acetal can be expected to have proceeded by hydrolysis to the ketone before chlorination.

[1] Part 14, P. B. D. de la Mare and R. D. Wilson, preceding paper.

[2] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, pp. 69—77.

[3] K. Morita, S. Noguchi, H. Kono, and T. Miki, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 90.

[4] S. Mori, *J. Chem. Soc. Japan*, 1953, **74**, 39, 42, 89 (*Chem. Abs.*, 1954, **48**, 10,758f).

[5] F. Mukawa, *J. Chem. Soc. Japan*, 1957, **78**, 452 (*Chem. Abs.*, 1959, **53**, 5338e).

[6] F. Mukawa, *J. Chem. Soc. Japan*, 1960, **81**, 1348 (*Chem. Abs.*, 1962, **56**, 7389b).

[7] S. Mori, K. Morita, and F. Mukawa, *Proc. Japan Acad.*, 1956, **32**, 585 (*Chem. Abs.*, 1957, **51**, 5103c).

[8] P. B. D. de la Mare and R. D. Wilson, accompanying paper (Part 13).

[9] P. B. D. de la Mare and R. D. Wilson, *J.C.S. Perkin II*, 1977, 157.

[10] P. B. D de la Mare and R. D. Wilson, *J.C.S. Perkin II*, 1977, 975.

[11] A. Zarecki, J. Wicha, and M. Kocór, *Tetrahedron*, 1976, **32**, 559.

by fractional crystallisation from ethyl acetate–methanol and was identical (m.p. and mixed m.p.) with authentic 5α,6β-dichlorocholestan-3β-ol. Attempts to isolate the minor product were unsuccessful.

The minor components formed in the reaction mixtures for all the substrates except the 3β-chloro-derivative had similar ^{1}H n.m.r. spectra. The minor product from chlorination of 3β-benzoyloxycholest-5-ene is illustrative; its spectrum included signals at δ 0.68 (s, 18-H_3), 1.19 (s, 19-H_3), 4.6 (1 H, 2d, J 12 and 5 Hz, 6-H), and 5.5 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 10 Hz, 3α-H). This spectrum is quite different from that of authentic 5α,6α-dichloro-3β-benzoyloxycholestane (see Supplementary Publication), and also different from that expected for the 5β,6β-dichloride, the 19-protons of which would have a chemical shift approximately the same as, or slightly greater than that of the 5α,6β-dichloride (δ 1.44) and the 6α-proton signal of which would be split by the two 7-protons into two doublets with $J_{6\alpha,7\alpha}$ *ca.* 2—5 and $J_{6\alpha,7\beta}$ 2—5 Hz. The spectrum is, however, fully consistent with that expected for the 5β,6α-dichloride; the characteristics of the absorbances and their positions relative to those of the corresponding 5α,6β-dichloride are the same as those for the 5β,6α- and 5α,6β-dibromides.

The relative proportions of 5α,6β- and 5β,6α-adducts in the product mixtures mentioned above and in those from the chlorination of cholest-5-ene in $CDCl_3$ with added pyridine and with added tetraphenylarsonium chloride, determined from the ^{1}H n.m.r. spectra, are given in Table 1.

Results identical within experimental error were obtained for the corresponding reactions of cholest-5-ene and of its 3β-benzoyloxy- and 3β-trifluoroacetoxy-derivatives in chlorobenzene at 0 °C (reagents 0.1M, reaction time, 30 min). The product mixtures formed by reaction in acetic acid, however, contained also so much unidentified material that they were not investigated further.

(b) *With chlorine acetate.* To cholest-5-ene (2.5×10^{-4} mol) or 3β-trifluoroacetoxycholest-5-ene (2.5×10^{-4} mol) was added chlorine acetate (5×10^{-4} mol) in chlorobenzene (5 ml) at 0 °C. The mixtures were set aside at 0 °C in the dark for 1 h and then the products were worked up and examined by ^{1}H n.m.r. spectroscopy. Both product mixtures contained much unidentified material giving rise to a variety of multiplets in the range δ 4—6 along with an approximately equal amount of the 5α-chloro-6β-acetoxy-adduct, clearly recognisable from its spectrum which was very similar to that of the corresponding 5α-bromo-6β-acetoxy-adduct. Only the one acetoxy-signal was visible (δ 1.8—2.2).

Reactions of Cholest-5-en-3-one with Molecular Chlorine in the Presence of Base.—The corresponding chlorinations of cholest-5-en-3-one were examined in several solvents, with bases added to minimise or prevent further acid-catalysed transformations of the products formed under kinetic control. 5β,6α-Dichlorocholestan-3-one was recognised as a minor product of chlorination in deuteriochloroform in the presence of pyridine by a ^{1}H n.m.r. signal at δ 2.99 (s, $W_{\frac{1}{2}}$ *ca.* 3 Hz, 4-H_2) and by its quantitative conversion into 6α-chlorocholest-4-en-3-one by prolonged treatment with pyridine. The products of chlorination in acetic acid containing sodium acetate were accompanied by much unidentified material giving rise in the ^{1}H n.m.r. spectrum of the mixture to sharp singlets (probably due to OAc) in the range δ 1.9—2.2, and to broad multiplets in the range δ 4—6. The chlorination of 4β-deuteriocholest-5-en-3-one [10] in chlorobenzene containing 2-methyloxiran was examined also. Results are summarised in Table 2.

TABLE 1

Dichloro-adducts (%) in the products from the reactions of 3β-substituted cholest-5-enes (0.4M) with chlorine (0.5M) in deuteriochloroform at *ca.* 20 °C in the dark (reaction time 5 min)

		Products (%)	
3β-Substituent	Added substances	5α,6β-Dichloride	5β,6α-Dichloride
H		80	20
H	Pyridine (0.4M)	80	20
H	Ph_4AsCl (0.4M)	80	20
HO		85	15
MeO		85	15
$MeCO_2$		90	10
$PhCO_2$		92	8
Cl		100	0
$F_3C{\cdot}CO_2$		97	3

TABLE 2

Products (%) from the chlorination of cholest-5-en-3-one and its 4β-deuterio-derivative in the presence of base

Substrate [a]	4-H	4-H	4-H	4β-D
Concn. (M)	0.020	0.4	0.010	0.010
$[Cl_2]$/M	0.020	0.5	0.011	0.011
[NaOAc]/M	0.020			
[2-methyloxiran]/M			0.10	0.10
[pyridine]/M		0.8		
Solvent	HOAc	$CDCl_3$	PhCl	PhCl
T/°C	25	*ca.* 20	25	25
Reaction time (min)	2	5	60	60
Product percentages:				
6α-Chlorocholest-4-en-3-one	*ca.* 27 [b]	26, 30 [c]	33	35 [d]
6β-Chlorocholest-4-en-3-one	*ca.* 25 [b]	19, 26 [c]	44	35 [e]
5α,6β-Dichlorocholestan-3-one	Trace	51,44 [c]	23	30
5β,6α-Dichlorocholestan-3-one		4, 0 [c]		

[a] 4-H = Δ^5-enone; 4β-D = 4β-deuterio-Δ^5-enone (83 ± 3% of deuterium at 4β; ref. 11). [b] Proportions 1.1 : 1; also much unidentified material. [c] After storage of the reaction mixture containing pyridine for 144 h at 37 °C. [d] 80 ± 10% H at C-4. [e] 35 ± 5% H at C-4.

DISCUSSION

Kinetic measurements have not been made for the chlorinations discussed in this paper; they would be too fast for satisfactory measurements by our techniques. We assume, however, that the well established [12] second-order form ($-d[Cl_2]/dt = k_2[S][Cl_2]$) is operative. Reactions of cholest-5-ene and its 3β-substituted derivatives in chlorobenzene or chloroform gave mainly the usual diaxial 5α,6β-adducts; but significant amounts of the diequatorial 5β,6α-isomers accompanied them. Since the inclusion of chloride ion in the reaction medium did not affect the product proportions significantly, the function of external chloride ion in contributing to the formation of the two types of adduct must be kinetically equivalent. At first sight it might seem natural to assume that the 5β,6α-dichlorides arise by electrophilic attack on the β-face of the molecule. As for the corresponding observations [10] relating to the formation of bromo-chlorides, however, this does not

[12] E. P. White and P. W. Robertson, *J. Chem. Soc.*, 1939, 1509.

account for the trend in product composition with the nature of the 3β-substituent. We believe, therefore, that these products, like their isomers, result from co-ordination of chloride ion to the intermediate formed by electrophilic attack on the α-face. The smaller size of chloride ion and the less powerful bridging by electrophilic chlorine probably contribute to the differences in the proportion of the diequatorial adduct in the products of chlorination, bromochlorination, and bromination.[10]

The corresponding chlorinations by molecular chlorine in acetic acid give mainly products having complex ^{1}H n.m.r. signals in the range δ 4—6; adducts were identified as present only in small proportion. Presumably this is another manifestation of the fact that bridging by chlorine to an adjacent carbocationic centre is relatively ineffective;[13] so proton loss from, and probably skeletal rearrangements of, non-bridged or weakly bridged cations are major product-forming processes. The same is true of chlorination by chlorine acetate in chlorobenzene. Here the 5α-chloro-6β-acetoxy-adduct can be recognised as a major product (*ca.* 50%). No 5β-acetoxy-6α-chloro-adduct was detected in the reaction mixture, even with cholest-5-ene which with chlorine under the same conditions was shown (Table 1) to give 20% of the diequatorial dichloride. This difference can be regarded as a further example of the necessity to elaborate the product-forming sequences to include the intervention of ion-pairs, the further reactions of which depend on the counter-ion.

Chlorination of cholest-5-en-3-one in acetic acid (Table 2), as for the 3β-substituted cholest-5-enes, gives very little product of addition; but here the products of substitution include major amounts of those formed with double-bond rearrangement facilitated by the presence of the carbonyl group. Both 6α- and 6β-chlorocholest-4-en-3-one are formed in approximately equal amounts. For reaction in deuteriochloroform in the presence of pyridine, no unknown products are obtained; the reaction mixture contains products of substitution accompanied by the expected 5α,6β-diaxial dichloride, along with a small proportions of its diequatorial 5β,6α-isomer. The corresponding results for chlorination in chlorobenzene containing 2-methyloxiran give information concerning the stereochemistry of proton loss; for reaction under these conditions we compared the composition of the product derived from the enone with that from its 4β-deuterio-derivative, and determined the isotopic composition at the 4-position in both the products of substitution of the latter compound. 6α-Chlorocholest-4-en-3-one is evidently formed by a non-concerted substitution not subject to a large primary 4-H/D isotope effect. It has predominantly protium rather than deuterium at C-4, so must require predominant displacement of the 4β-deuterium atom. The proportion of 6β-chlorocholest-4-en-3-one is less for the 4β-deuterio- than for the protio-enone. The amount of protium at C-4 in the product from the deuterio-compound shows that displacement both of the 4α- and of the 4β-hydrogen contributes to its formation. We presume, therefore, that 6β-attack with concerted displacement of the 4β-hydrogen and subject to a relatively large primary isotope effect ($k^{4\beta\text{-H}}/k^{4\beta\text{-D}}$ = *ca.* 4 for attack on the β-face) competes with non-concerted displacement of the 4α-hydrogen ($k^{4\beta\text{-H}}/k^{4\beta\text{-D}}$ = *ca.* 1 for attack on the α-face). These conclusions accord with and support those reached by consideration of the results for brominations and bromochlorinations.[1]

TABLE 3

Relative rates (k_α/k_β) of attack by electrophiles on 3-substituted cholest-5-enes as deduced from proportions of products [a]

Reagent	Reaction	Classification	Substrate (S) 3-substituents: H_2	H,3β-R	H,3α-R	=O	Ref.
$ArCO_3H$	S + O	Ad_E2	*ca.* 2.1	2—5	0.8—1.3	*ca.* 2.3	10
BrCl,Cl^-	S + Br^+ + Cl^-	Ad_E3	Not examined	>30	Not examined	>30	1, 10
BrOAc	S + Br^+ + OAc^-	Ad_E, *via* halogenonium ion	>30	>30	>30	2.0 [b]	1, 8
BrCl [c]	S + Br^+ + OAc^-	Ad_E, *via* halogenonium ion	Not examined	>30	Not examined	1.0 [d]	1, 8
BrY [e]	S + Br^+ − H^+	S_E2', concerted				≯0.1	1
Cl_2	S + Cl^+ − H^+	S_E2', concerted				≯0.1	This paper
Br_2 [f]	S + Br^+ − H^+	S_E2', not concerted				*ca.* 1.6	1
BrCl	S + Br^+ − H^+	S_E2', not concerted				*ca.* 1.0	1
Cl_2	S + Cl^+ − H^+	S_E2', not concerted				*ca.* 1.0	This paper

[a] For details of reaction conditions and evidence for mechanism see cited references. [b] 3.3, when reagent is supplied from $BrOCMe_3$ in HOAc. [c] Two molecules of BrCl in transition state. [d] 2.8, if bromochloride, probably formed by Ad_E3 addition, is included. [e] Y = Br; also Y = Cl. [f] One or two molecules of bromine in the transition state.

Ratio of α- to β-Attack by Electrophiles.—Quantitative comparisons of the ratios of attack by electrophiles are complicated in the cases of the simple halogens because dibromides or dichlorides usually comprise large fractions of the product, and could arise by attack on either face, or simultaneously on both faces, of the molecule. Argument by analogy from results obtained by using unsymmetrical reagents such as bromine chloride or bromine acetate, or by measuring the proportions of incorporations of solvent on the two faces, suffers from the difficulty that different nucleophiles, which can form different counter-ions for any carbocationic intermediate, co-ordinate to the two faces in different proportions. From the results in this and the accompanying papers,[1,8] however, certain clear-cut differences

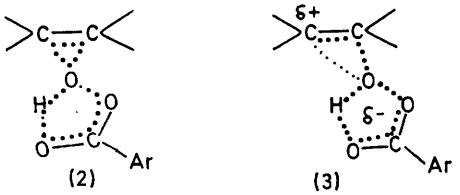
[13] S. Winstein, *Bull. Soc. chim. France*, 1951, C55.

between different reagents and mechanisms can be derived. It is useful to make comparison also with results obtained for epoxidation.[10] Table 3 provides a summary; it relates to reagents for which the product ratios are at least in part determined by the relative rates of electrophilic attack on the two faces of the steroid.

Several major points of comparison are shown by Table 3. The concerted Ad_E (epoxidation), Ad_E3 (halogenation), and S_E2' (halogenation) processes are markedly stereoselective, each in its own way; and for these processes no major differences are evident in comparison of the 3-monosubstituted cholestenes with cholest-5-en-3-one. The non-concerted substitutions differ considerably in their stereochemistry from the corresponding concerted reactions. Halogen additions differ considerably from epoxidation in giving much more α-attack on the 3-monosubstituted compounds; there is a major difference in stereochemistry between these reactions of 3-monosubstituted cholest-5-enes and those of cholest-5-en-3-one. Even for the same reagent, therefore, an overall estimate of the ratio of products obtained by attack on the two faces of the steroid can represent a complex blend of structural influences on reactions of a number of kinds; we now comment on the characteristics of the individual processes *seriatim*.

(a) *Concerted epoxidation.* In this reaction, both parts of the addendum are required to approach the olefinic centre simultaneously; the reagent which delivers electrophilic oxygen is rather bulky, and has generally been considered to be rather closely constrained in the transition state, which is usually depicted as in (2).[14,15] It might have been thought that these constraints would ensure that epoxidation was subject to large steric effects. The results show, however, that such effects, though they may be significant, are rather small in magnitude. Attack on the α-face of the steroid is favoured in cholest-5-ene by a factor of *ca.* 2 : 1, presumably because the 10-methyl group on the β-face slightly impedes attack on this side of the molecule. The effect of a 3β-substituent is to favour α-attack, and of a 3α-substituent to favour 3β-attack, again presumably for steric reasons. The result for cholest-5-en-3-one resembles that for cholest-5-ene, and indicates that approach by this reagent is affected similarly in the two systems.

Hanzlik and Shearer's recent study of secondary deuterium isotope effects in epoxidation[16] shows that the transition state for this reaction should be represented not in the rather symmetrical, highly constrained form (2) but instead in a much more unsymmetrical, virtually unbridged reactant-like form (3). Under these circumstances the reagent will be attached predominantly to the 6-position of the double bond in the steroid, directed there by the activating power of the additional substituent on C-5. The formation of the new bond to the reagent will not have progressed very far, as is consistent with the low Hammett ρ value found for epoxidations generally.[15,17] This formulation of the transition state for epoxidation is consistent with the smallness of the steric preference for the α-face of the molecule shown by electrophilic peroxy-acids.



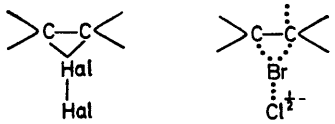
(b) *Concerted* (Ad_E3) *addition of halogen.* The Ad_E3 mechanism for halogen addition (kinetic form, $-d[\text{halogen}]/dt = k_3[S][\text{halogen}][\text{nucleophile}]$) has been recognised for many years;[18] its characteristics have been discussed recently by Fahey[19] and by Yates *et al.*[20] The mechanism is available most readily for reaction involving the bromine molecule and chloride or bromide ion; kinetic evidence for the involvement of the nucleophile allows its differentiation from reaction involving competitive capture of an intermediate carbocationic species after the rate-determining stage. In the present series of papers, this type of evidence has been provided only for the case of reaction through molecular bromine and bromide ion; here, catalysis by the nucleophile has been shown kinetically both for 3β-substituted cholest-5-enes [8] and for cholest-5-ene-3-one,[1] despite the opposing influence of the equilibrium between bromine and bromide ion ($Br_2 + Br^- \rightleftharpoons Br_3^-$, removing electrophilic bromine). For cholest-5-en-3-one, the intervention of this mechanism is accompanied by a change in the stereochemistry of addition; much more 5α,6β-dibromide is produced when bromide ion is added initially.

Although this kinetic evidence has not been provided for other reagents, we presume that a change in stereochemistry of this kind is diagnostic of the incursion of this mechanism, and we make this assumption in the ensuing discussion. For reaction of an unsymmetrically substituted olefinic compound by this mechanism, four different stereochemical descriptions are possible. The above result excludes the two which would lead to 5β,6α-derivatives; in a concerted reaction of this kind, the additional conformational changes in ring A required to give such products should be unfavourable according *inter alia* to the principle of least motion.[21] Reaction with bromine chloride in the presence of added chloride ions allows differentiation between electrophilic attack on the two faces of the molecule, and shows that α- is

[14] P. D. Bartlett, *Rec. Chem. Progr.*, 1950, **11**, 47.
[15] F. Freeman, *Chem. Rev.*, 1975, **75**, 439.
[16] R. P. Hanzlik and G. O. Shearer, *J. Amer. Chem. Soc.*, 1975, **97**, 5231.
[17] J. Nishimura, J. F. Furukawa, N. Kawabata, and M. Kitayama, *Tetrahedron*, 1971, **27**, 1799.
[18] P. B. D. de la Mare, *Quart. Rev.*, 1949, **3**, 126.
[19] R. C. Fahey, *Topics Stereochem.*, 1968, **3**, 237.
[20] K. Yates, R. S. McDonald, and S. A. Shapiro, *J. Org. Chem.*, 1973, **38**, 2460.
[21] J. Hine, *J. Org. Chem.*, 1966, **31**, 1236.

favoured over β-attack by a factor of *ca.* 30 for cholest-5-en-3-one. This difference, which is apparent also in the reactions of the 3-monosubstituted steroids, is probably of steric origin, and represents the effect of the 10-methyl group in inhibiting electrophilic attack on the β-face of the steroid. Dubois and Fresnet [22] have analysed the relative reactivities of a series of substituted cyclohexenes, and have evaluated the deactivating effect of a 4-axial methyl substituent in comparison with hydrogen as 7.5 kJ mol^{-1}, which would result in a relative rate ratio of *ca.* 20 : 1.

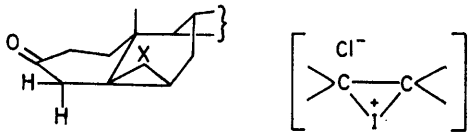
Such a difference could not have been predicted *a priori*. Indeed, the opposite result could easily have been rationalised, since it would have been possible to envisage a transition state for Ad_E3 addition rather like that for epoxidation, with little bond formation by the electrophile, a somewhat reduced response to the effects of substituents as compared with other modes of halogenation,[18] and *anti*-addition determined by the concerted nature of the reaction rather than by bridging of the electrophile to the adjacent carbocationic centre.[23] The result leads instead to the conclusion that this Ad_E3 addition involves a strongly bridged intermediate (4) formed prior to rate-determining attack by the halide ion. The equilibrium constant for its formation should be more favourable on the α- than on the β-face of the steroid, because bridging to the adjacent centre would bring the axial 10-methyl group too close to a β-bridging halogen. The detailed nature of the bonding need not be specified; and is open to argument particularly with regard to the number of electrons assumed to be associated with each bond. Different authors postulating such intermediates present different formulations; [15,19,22,23] structure (4) was first discussed by Williams.[24] The transition state for the rate-determining stage of chloride-catalysed bromochlorination is then to be depicted approximately as in (5). It is significant that cholest-5-en-3-one behaves as do the other 3-monosubstituted cholest-5-enes.



(4) (5)

(c) *Additions involving halogenonium intermediates.* For our systems, definite information concerning stereochemistry for reactions in which product formation is determined from intermediates more dissociated than (4) is available only where the anion from the solvent acetic acid becomes incorporated. For these reactions, the 3-bromocholest-5-enes give predominantly the product of attack by the electrophile on the α-face of the molecule. Cholest-5-en-3-one, however, gives instead the 6β-bromo-5α-acetate in substantial amount which differs according to the source of electrophilic bromine. Neither effects of direct steric hindrance nor polar influences satisfactorily explain this difference. For all these compounds, the intermediates are expected to be similar and strongly bridged, with the reagent well bonded to the substrate, as supported by evidence from stereochemistry,[25,26] from secondary H/D isotope effects,[27] and from structural effects on the rate of reaction.[8] The small differences in geometry around C-3 produce only small changes in the relationship of the 10-methyl group to the double bond, and should not make the β-face appreciably more accessible in the ketone. The polar effect of the oxo-group lies between those of the chloro- and trifluoroacetoxy-substituents,[1] so likewise cannot provide a plausible interpretation. Enhancement by the carbonyl group of hyperconjugation from the 4-hydrogen atoms would not be expected to enhance significantly the rate of attack on one face as compared with the other.

We suggest, therefore, that the main difference between cholest-5-en-3-one and the 3-monosubstituted cholest-5-enes lies in the ability of ring A of the former compound, but not of the latter, to adopt a boat conformation favoured by bridging on the β-face of the molecule; we have shown elsewhere [10] that the epoxide [(6; X = O)] analogous to the proposed halogenonium intermediate [(6; X = Br^+] undergoes ring opening with base to lose the 4α-hydrogen atom, which must therefore be able to become axially disposed, as shown. It seems that as long as the whole of the reacting halogen molecule is maintained on the β-face of the double bond, as in the intermediate (4), the system cannot gain any substantial



(6) (7)

advantage from moving towards the boat form, probably because of the steric requirements of the additional large halide ion. No special difference between the ketone and the other systems is seen, therefore, for Ad_E3 addition. Once halide ion is substantially lost, however, and the intermediate begins to resemble the halogenonium ion (6; X = Br^+), extra driving force derived from bridging between the two originally olefinic centres can be gained if the system can adopt this conformation. To cancel out the conflicting steric

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influence of the 10-methyl group, a facilitation by only *ca.* 8 kJ mol^{-1} is required. The torsional energy for chair–boat interconversion in the ketone is expected to be much less than in cholest-5-ene or its 3-substituted derivatives, since groups in the 3-position contribute to the activation energy for twisting of the ring.[28]

(d) *Substitution with rearrangement; the concerted* S_E2' *mechanism.* For the halogenations studied in this and the accompanying papers, substitution with rearrangement has been identified as a reaction pathway only for cholest-5-en-3-one, loss of the 4-hydrogen atom in competition with other pathways being significant only when activation is provided by the adjacent carbonyl substituent. When proton loss is part of the rate-determining stage, the stereochemical preference is quite different from those of the other processes described in Table 3; attack on the β-face predominates, and the 4β-proton is lost preferentially. The chair form of the ketone must, therefore, be under attack, to allow this proton to remain axially disposed. It is probable that the formation of the complex (4) precedes the concerted loss of bromide ion and proton, since this pathway is significant not only for second-order halogenations, but also for those involving more than one molecule of halogen in the rate-determining stage.[1]

(e) *Substitution with rearrangement; the non-concerted* S_E2' *mechanism.* The isotope effects on the rates and products of molecular bromination of cholest-5-en-3-one, and on the products of bromochlorination and of chlorination, establish that the stereochemical preference for this reaction of the proposed halogenonium intermediate resembles that for the capture of nucleophilic solvent. This would be expected, since the rate-determining processes should be the same, and both the α- and the β-halogenonium ion have a hydrogen atom axially disposed and available for release to the solvent as a proton. The values given in Table 3 are subject to considerable experimental error; but the qualitative comparison between the concerted and non-concerted pathways shows how important is this difference in stereochemical preference between the two types of process.

(f) *Additions involving electrophilic iodine.* Additions of iodine chloride [11,29] and of iodine fluoride [30] to cholest-5-ene and to cholesteryl derivatives apparently give product ratios quite different from those found with bromine chloride or bromine acetate. The main adduct is the 6β-iodo-5α-halide, obtained by electrophilic attack on the β-face of the molecule. Bowers *et al.*[30] attribute this difference to reversible formation of both α- and β-iodonium ions, with kinetically controlled attack by halide ion on the α-face of the β-ion rather than on the more congested β-face of the α-ion. They regard the resulting product as the thermodynamically more stable of the two possible diaxial dihalides, but we think that this is unlikely, because the larger halogen should be less comfortable adjacent to the bulky 10-methyl group. Reversible formation of the iodonium ions is, however, quite likely; if so, the rate-determining step is rather late on the reaction path, and a several-stage Ad_E3 reaction with the rate-determining transition state having stoicheiometry (7) must be under observation. In this, the additional steric hindrance to nucleophilic attack must more than outweigh the usual steric hindrance to electrophilic attack. The stereochemical preference for attack on the β-face of the steroid in this Ad_E3 process is in marked contrast with that found for reaction through the rate-determining transition state (5), which gives preferentially the product formed by electrophilic attack on the α-face of the molecule. Berliner and his co-workers [31] have discussed in analogous terms the possible transition states for iodinations; it should be remembered that a reaction following the sequence $S + ICl \rightleftharpoons SI^+ + Cl^- \longrightarrow$ products, with the product-forming stage rate-determining, should follow second, rather than third-order kinetics ($-d[ICl]/dt = k[S][ICl]$). No kinetic test of mechanism has been yet applied to a reaction giving the 6β-iodo-5α-halide.

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