The Kinetics and Mechanisms of Additions to Olefinic Substances. Part 14.[1] Reactions of Cholest-5-en-3-one with Electrophilic Brominating Agents

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Electrophilic brominations of cholest-5-en-3-one with molecular bromine and with bromine chloride have been studied in several solvents. The major products are 5α,6β-adducts and the 6-bromocholest-4-en-3-ones; in some circumstances a small proportion of 5β,6α-adduct was recognised. Results obtained by using bromine chloride establish that the diaxial adducts arise by electrophilic attack on both the α- and the β-face of the steroid. 6α-Bromocholest-4-en-3-one is formed by proton loss from the ionic α-bromonium intermediate; study of 4β-H/D isotope effects on the rates and products of bromination establish that 6β-bromocholest-4-en-3-one is obtained not only by this route, in which the 4α-proton is preferentially released, but also by way of a concerted, stereoselectively *syn*, S_E2' mechanism. In the presence of excess of halide ion, substitution is reduced in proportion through catalysis of an Ad_E3 mechanism involving electrophilic attack on the α-face of the molecule to give the diaxial adduct. The pathways available for substitution and addition in cholest-5-en-3-one are compared with those found for the 3β-substituted cholest-5-enes (accompanying paper).

SOURCES of electrophilic chlorine or bromine, in reactions with cholest-5-ene or its 3β-substituted derivatives, normally give products of electrophilic attack on the α-face of the molecule. Although the corresponding reactions of cholest-5-en-3-one (1) have not been studied extensively, there have been a number of indications that different courses may be taken. Thus hypochlorous acid has been shown [2] to give the 'Markownikoff' adduct, 6β-chloro-5α-hydroxycholestan-3-one. Although bromination to give the known [3] 5α,6β-dibromoketone has been described,[4] we have found in a preliminary investigation [5] that other adducts are formed also, and that decomposition of the product mixture can give 6-bromo- and 2α,6-dibromo-cholest-4-en-3-ones by dehydrobromination and further bromination. The instability [5] of 5α,6β-dibromocholestan-3-one was reported by Barton and Miller; [6] our discovery [7] that this dehydrobromination is initiated homolytically and can be inhibited by scavengers of free radicals has enabled us now to investigate the bromination of cholest-5-en-3-one under conditions of kinetic control.

EXPERIMENTAL

Some of the materials and methods have been described in earlier papers.[1,5,8] The methods used to prepare and characterise other known compounds are given in Supplementary Publication No. SUP 22098 (see preceding paper); representative ^{1}H n.m.r. spectral details are given there also. The required 5α,6β- and 5β,6α-disubstituted cholestan-3-ones were prepared from the corresponding 5,6-disubstituted cholestan-3β-ols by oxidation with CrO_3 following Fieser's general directions,[3] and were characterised by ^{1}H n.m.r. spectroscopy. 5β,6α-Dibromocholestan-3-one prepared in this way contained 6α-bromocholest-4-en-3-one (20%); repeated attempts to obtain a purer sample failed, because in our hands the material decomposed in the solid phase with copious release of HBr.

Decomposition of 5-Bromo-6-substituted Cholestan-3-ones in $CDCl_3$.—When dissolved in $CDCl_3$ (reagent grade), 5β,6α-dibromo-, 5α,6β-dibromo-, 6β-acetoxy-5α-bromo-, and 5α-bromo-6β-chloro-cholestan-3-one each decomposed rapidly after an induction period (a few s for the 5β,6α-dibromide, and 10—40 min for the other compounds), with copious release of HBr and formation of an equilibrium mixture of the appropriate 6α- and 6β-substituted cholest-4-en-3-ones which were identified and estimated by using their ^{1}H n.m.r. spectra. When dissolved in $CDCl_3$ with added 0.02M-galvinoxyl (insufficient to interfere seriously with the determination of the ^{1}H n.m.r. spectrum), the induction periods for all compounds were extended to several hours. Details of the rates of decomposition with substrate initially 0.25M at 37 °C (the probe temperature of the spectrometer) have been given elsewhere.[7] The corresponding eliminations of HCl from 5α-chloro-6β-bromocholestan-3-one and from 5α,6β-dichlorocholestan-3-one, and of HOAc from 5α-acetoxy-6β-bromocholestan-3-one, were much slower. Under the same conditions, the dibromides derived from 3α- and 3β-substituted cholest-5-enes were stable for long periods.

Bromination of Cholest-5-en-3-one.—The products of bromination of cholest-5-en-3-one in acetic acid at 25 °C, no base having been added to the reaction mixture, varied with the conditions of the reaction and the length of time before work-up; but in general the results accorded with those reported earlier.[5] Reactions carried out in the presence of base, however, precautions having been taken to avoid homolytic decomposition of the 5-bromocholestanones, were now those formed under kinetic control. In a typical experiment, to cholest-5-en-3-one (1.54 g) and sodium acetate (0.33 g) in acetic acid (175 cm^3) under nitrogen at 25 °C was added a solution of bromine (0.64 g) in acetic acid (25 cm^3). Reaction was visibly complete in 2 min; work-up showed the presence of 6β-bromocholest-4-en-3-one (15%), 5α,6β-dibromocholestan-3-one (66%), and 5α-acetoxy-6β-bromocholestan-3-one (19%). The last compound had the expected ^{1}H n.m.r. spectrum, identical in

[1] Part 13, P. B. D. de la Mare and R. D. Wilson, preceding paper.
[2] S. Mori, K. Morita, and F. Mukawa, *Proc. Japan Acad.*, 1956, **32**, 585 (*Chem. Abs.*, 1957, **51**, 5103c).
[3] L. F. Fieser, *Org. Synth.*, 1963, **4**, 197.
[4] Schering-Kahlbaum A.G., G.P. 198,836 (*Chem. Zentr.*, 1939, **1**, 2642).
[5] P. B. D. de la Mare and B. N. B. Hannan, *J.C.S. Perkin II*, 1973, 1086, 1586.
[6] D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.
[7] P. B. D. de la Mare and R. D. Wilson, *Tetrahedron Letters*, 1974, 3777.
[8] P. B. D. de la Mare and R. D. Wilson, *J.C.S. Perkin II*, 1977, 157.

TABLE 1

Products (%) from the reaction of molecular bromine with cholest-5-en-3-one and some of its deuteriated derivatives in acetic acid containing sodium acetate at 25 °C under nitrogen in the dark

Substrate [a]	4-H	4β-D	4-H	4β-D	4-H	4β-D	4,4-D_2	4-H	4-H	4-H	4-H
Conc. (M)	0.008	0.008	0.005	0.005	0.02	0.02	0.02	0.04	0.04	0.02	0.02
[Br_2]/M	0.000 7 [b]	0.000 7 [b]	0.005	0.005	0.02	0.02	0.02	0.04	0.04	0.02	0.02
[NaOAc]/M	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.12	0.02	0.02
[LiBr]/M										0.04	
[LiCl]/M											0.04
Reaction time (min)	*b*	*b*	300	300	2	5	5	2	2	30	60
Product percentages:											
Δ^4-en-3-one	5	2									
6α-Br-Δ^4-en-3-one	5	3 [c]	Trace	Trace							
6β-Br-Δ^4-en-3-one	30	23 [d]	25	21 [d]	15	14 [d]	13	13	12	3	6
5α,6β-Br_2-3-one	47	50	49	52	66	67	69	73	76	94	62
5α-Br,6β-OAc-3-one	Trace	Trace									
5α-OAc,6β-Br-3-one	13	22	26	27	19	19	18	14	12	3	6
5α-Br,6β-Cl-3-one											26

[a] 4-H = Δ^5-enone; 4β-D = 4β-D-Δ^5-enone (83 ± 3% deuterium at 4β); 4,4-D_2 = 4,4-dideuterio-Δ^5-enone.[8] [b] Bromine equivalent in total to the substrate added in ten equal portions at intervals of *ca.* 15 min. [c] 4-H. [d] 33 ± 3% H at C-4.

form with spectra of the known 5α,6β-disubstituted cholestan-3-ones, but with additionally a sharp singlet at δ 1.97 (OAc). During several hours at 37 °C the mixture decomposed autocatalytically to give an equilibrium mixture of 6α- and 6β-bromocholest-4-en-3-one, accompanied by a small amount of acetic acid, identified by its n.m.r. signal at δ 2.08, which disappeared when the mixture was shaken with aq. $NaHCO_3$. The remainder of the product mixture was treated with pyridine (20 cm^3) at 100 °C for 5 min. Work-up and separation by t.l.c. on silica gel [n-hexane–ethyl acetate (9 : 1 v/v)] gave two fractions, from one of which was recovered 6β-bromocholest-4-en-3-one, identical with an authentic specimen (m.p., mixed m.p., and ^1H n.m.r. spectrum). The second fraction was mainly 5α-acetoxy-6β-bromocholestan-3-one, but tended to decompose during chromatography giving 6β-bromocholest-4-en-3-one, and had the same mobility as cholesta-4,6-dien-3-one. This had been formed from the 6β-bromo-enone compound during the treatment with pyridine at 100 °C, and was identified from its ^1H n.m.r. spectrum [signals at δ 5.67 (1 H, s, 4-H) and 6.12 (2 H, s, 6- and 7-H), identical with signals from authentic material prepared [9] from 6β-bromocholest-4-en-3-one and pyridine at 100 °C.

TABLE 2

Products (%) formed in the reaction of brominating agents with cholest-5-en-3-one and some of its deuterio-derivatives in chlorobenzene containing 1.0M-2-methyloxiran at 0 °C under nitrogen in the dark

Substrate [a]	4-H	4β-D	4,4-D_2	4-H	4-H
Concn. (M)	0.04	0.04	0.04	0.025	0.025
Reagent [b]	Br_2	Br_2	Br_2	BrCl	BrOAc
Product percentages (reaction time, 100—120 min):					
6α-Br-Δ^4-enone					4
6β-Br-Δ^4-enone	67	62 [c]	60	48 [d]	43
5α,6β-Br_2-3-one	33	38	40		
5α-Br,6β-Cl-3-one				23 [d]	
5α-Cl,6β-Br-3-one				Trace [d]	
5α-Br,6β-OAc-3-one					35
5α-OAc,6β-Br-3-one					18

[a] As Table 1. [b] Initial concentration slightly in excess of that of the substrate. [c] 45 ± 5% H at C-4. [d] Remainder of products through Cl_2 and Br_2.

Reactions aimed at the establishment of the proportions of products formed under conditions leading to kinetic control were carried out with reagents at other concentrations; and the corresponding reactions of 4β-deuterio- and 4,4-dideuteriocholest-5-en-3-one [8] were studied also. The most important of these results are given in Table 1; a complete tabulation of the results of all our product experiments is included in the Supplementary Publication.

TABLE 3

Products (%) from the reaction of brominating agents with cholest-5-en-3-one in acetic acid containing sodium acetate (0.02M) at 25 °C under nitrogen in the dark

Substrate [a]	4-H	4β-D	4,4-D_2	4-H	4-H	4-H	4-H	4-H	4-H
Reagent [b]	BrCl	BrCl	BrCl	BrCl	NBA	NBA	NBA	NBA	$BrOCMe_3$
[LiCl]/M				0.040	0.010	0.060	0.002	0.040	
[LiBr]/M							0.002	0.040	
Reaction time (min)	10	10	10	90	60	60	60	60	30
Product percentages:									
6α-Br-Δ^4-en-3-one	2	2 [c]		1	3	2	5 [d]		8
6β-Br-Δ^4-en-3-one	25	22 [e]	20	15	20	17	34	4	13
5α-Br,6β-Cl-3-one	35	36	40	61	32	52			
5α,6β-Br_2-3-one							11	93	
5α-Br,6β-OAc-3-one	19	20	20	12	30	17	23		61
5α-OAc,6β-Br-3-one	19	20	20	11	15	12	25	3	18

[a] As Table 1; initial concentration of reagents, 0.02M. [b] NBA = *N*-bromoacetamide; similar results were obtained with *N*-bromosuccinimide. [c] 4-H. [d] Also 2% of starting material. [e] 36 ± 3% of H at C-4.

In Table 2 we give a selection of the results obtained when chlorobenzene containing 2-methyloxiran was used as

[9] E. Dane, Y. Wang, and W. Schulte, *Z. physiol. Chem.*, 1936, **245**, 80; H. H. Inhoffen, G. Stoeck, and H. Martens. *Annalen*, 1949, **563**, 131.

solvent; in separate experiments it was shown that change in temperature over the range 0—25 °C, change in the concentration of 2-methyloxiran over the range 0.1—1.0M, and change in the concentration of the reagents over the range 0.0055—0.05M had no significant effect on the composition of the products. Results obtained by using bromine chloride or bromine acetate in this solvent are also included in this Table. In Table 3 are summarised the most significant results obtained from the reactions of bromine chloride and various other brominating agents with cholest-5-en-3-one in acetic acid containing sodium acetate.

The kinetics of bromination, molecular bromine being the reagent, were determined by the methods described in the preceding paper.[1] Deuterium-containing compounds were compared with their protio-analogues under conditions as nearly identical as possible. Results are given in Table 4.

TABLE 4

Rate coefficients and isotope-effect ratios for bromination of cholest-5-en-3-one at 25 °C under nitrogen in the dark

Solvent	HOAc	HOAc	PhCl	PhCl
[NaOAc]/M	0.020	0.020		
[2-methyloxiran]/M			0.10	1.0
[LiBr]/M		0.012 5		
k_2/l mol^{-1} s^{-1}	0.928 ±0.018	2.44 ±0.03		
k_3/l^2 mol^{-2} s^{-1}			46.6 ±0.8	188 ±8
$k^{4\beta\text{-H}}/k^{4\beta\text{-D}}$	1.63 ±0.20		1.36 ±0.16	
$k^{4,4\text{-H}_2}/k^{4,4\text{-D}_2}$	1.74 ±0.09	1.12 ±0.05	1.31 ±0.09	1.33 ±0.09

DISCUSSION

(a) *Kinetics of Bromination; Effect of the Carbonyl Group.*—The kinetics of bromination of cholest-5-en-3-one, as far as we were able to examine them, resembled those of the 3-substituted cholest-5-enes. In acetic acid containing sodium acetate (added to inhibit extraneous acid-catalysed processes) at concentrations below 0.001M, the second-order form [equation (i)] prevailed; it was superseded at higher concentrations by the reaction of order greater than one in bromine, probably of the form of equation (ii). The reaction was catalysed by added

$$-\mathrm{d}[\mathrm{Br_2}]/\mathrm{d}t = k_2[\mathrm{S}][\mathrm{Br_2}] \quad \text{(i)}$$

$$-\mathrm{d}[\mathrm{Br_2}]/\mathrm{d}t = k_3[\mathrm{S}][\mathrm{Br_2}]^2 \quad \text{(ii)}$$

bromide ion, through incursion of the kinetic form of equation (iii) (Nu = Br^-). Since in the reaction some

$$-\mathrm{d}[\mathrm{Br_2}]/\mathrm{d}t = k_3'[\mathrm{S}][\mathrm{Br_2}][\mathrm{Nu}] \quad \text{(iii)}$$

hydrogen bromide is liberated both by substitution and by addition, reaction through the last pathway must be significant even when no bromide is present initially, and must become progressively more important in the later stages of the reaction.

The third-order form of equation (ii) was dominant for the reactions examined in chlorobenzene as solvent. The influence of 2-methyloxiran, added in this solvent to remove hydrogen bromide as formed, was that of mild catalysis (see Table 4), almost certainly through the expected solvent effect; a tenfold change in its concentration had no effect on the composition of the products.

In its effect on the overall rate of bromination, the carbonyl group β to the 5,6-double bond was almost as effective as the 3β-chloro-substituent in reducing the rate of bromination; slightly less so in acetic acid, and slightly more so in chlorobenzene. On this basis a σ_1 value of *ca.* 0.47 could formally be attributed to the carbonyl group;[1] but our later arguments require that this estimate is a little low for general application, being in this system affected by the additional flexibility of ring A and by the incursion of a special mechanism of substitution.

To provide a suitable standard for comparison with the ketone, the isotope effect, $k^{4,4\text{-H}_2}/k^{4,4\text{-D}_2}$, for bromination of 3β-trifluoroacetoxycholest-5-ene had been determined[1] as 0.93 in acetic acid [kinetic form, equation (i)] and 0.97 in chlorobenzene [kinetic form, equation (ii)]. Values near to unity are expected, since here only a secondary isotope effect is possible. The values are, if anything, slightly less, rather than slightly greater, than unity; it appears that the slightly greater inductive effect of deuterium than of hydrogen[10] prevails in this system over any hyperconjugative influence, which could be effective especially from the 4β-position and would be in the reverse direction.[10,11] To return now to cholest-5-en-3-one (Table 4), a major new feature appears: the reaction is subject to a 4-H/D isotope effect substantially greater than unity, and almost entirely located at the 4β- rather than at the 4α-position. The values of $k^{4,4\text{-H}_2}/k^{4,4\text{-D}_2}$ (1.74 in acetic acid, 1.31 in chlorobenzene), though not large as primary isotope effects go, are too large to be attributed plausibly to secondary isotope effects.

It could be presumed solely from these results, therefore, that for the 5-en-3-one a second-order substitution with rearrangement mainly involving the 4β-hydrogen atom, with proton loss part of the rate-determining step, should make a substantial contribution to the products at high dilution in acetic acid. For analogous reactions,[12] isotope effects in the range 3—4 have been recorded; so perhaps *ca.* 50% of the product might be determined in this way. Added bromide ion would be expected to make the catalysed pathway [equation (iii)] dominant; and so, by diverting the reaction towards addition, to reduce the isotope effect. This is confirmed experimentally: $k^{4,4\text{-H}_2}/k^{4,4\text{-D}_2}$ is reduced to 1.12 in the presence of added 0.0125M-LiBr. The significance of the observation of a lower isotope effect for the third-order bromination in chlorobenzene remains obscure, because primary isotope effects relevant for comparison have not, as far as we know, been measured in this solvent.

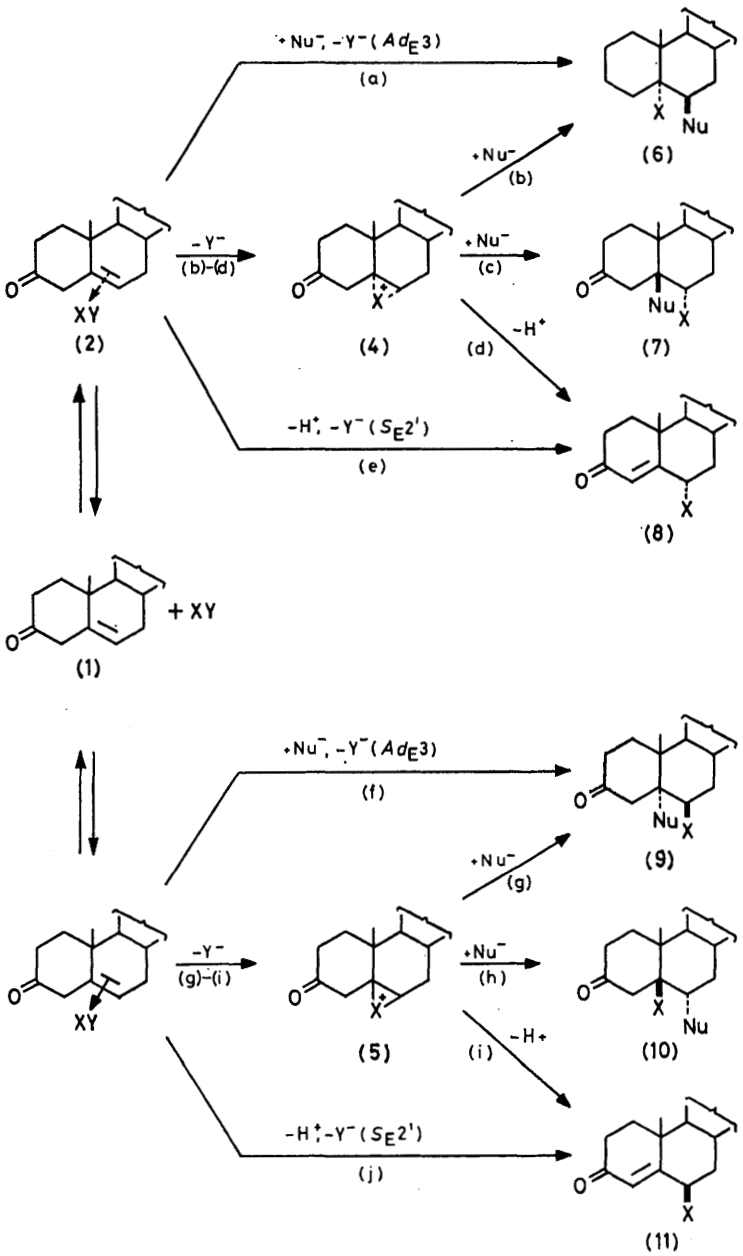
The conclusions derived above from the kinetics of

[10] E. A. Halevi, *Progr. Phys. Org. Chem.*, 1963, **1**, 109.
[11] E. A. Halevi, *Tetrahedron*, 1957, **1**, 174.
[12] P. B. D. de la Mare and A. Singh, *J. Chem. Soc.* (*B*), 1971, 1122.

bromination are confirmed and amplified through consideration of the product ratios discussed in the following sections.

(b) *Products of Halogenations; Pathways to Substitution.*—It is convenient for the purpose of this discussion to consider the reaction paths in terms of the Scheme, where (1) is the starting material; (2) and (3) are complexes of the stoicheiometry S,Hal-Nu but of unspecified detailed structure; (4) and (5) are halogenonium ions, not necessarily symmetrically bridged as indicated; and (6)—(11) are known products. This representation is highly simplified; ion-pair isomers of (2) and (3) may be involved also, and so may differently bridged or unbridged isomers of (4) and (5). The Scheme is sufficient, however, to enable description of many of the features of our reactions.

Our results exclude a number of possible paths, other than those labelled in the Scheme, by which substitution products, (8) and (11), might be formed. The 6β-halogeno-4-enones (11) do not arise by halogenation of cholesta-3,5-dien-3-ol, since it has been shown [8] that the enolisation of cholest-5-en-3-one is under the present experimental conditions slower by many powers of ten than the halogenations studied here. Conventional addition–elimination sequences leading to products of substitution can be excluded also; none of the adducts found to be products of our reactions underwent significant dehydrohalogenation under our experimental



SCHEME Possible and probable reaction pathways in the halogenation of cholest-5-en-3-one in the presence of base

conditions. There is no reason to believe that any of the unknown *syn*-adducts isomeric with their known *anti*-counterparts would behave differently, and *syn*-addition is very uncommon in reactions initiated by electrophilic bromine, so we regard it as highly unlikely that these compounds are involved in the formation of products of substitution under our conditions.

For the formation of each of these products (8) and (11) two main pathways are possible. In one [paths (e) and (j)] the proton loss is concerted with the establishment of electrophilic halogen at the 6-position, either following the formation of a complex [(2) or (3)] or directly from (1). This mode of reaction requires that a significant 4-H/D isotope effect be observed. In the second [paths (d) and (i)], a halogenonium ion is formed and then undergoes deprotonation. Such a reaction might well not be subject to a primary isotope effect, since the proton can be lost after the rate-determining stage. Either of these processes can be categorised as S_E2' reactions, by analogy with the S_E2 categorisation which includes concerted and non-concerted cases, some of the latter being subject to a primary isotope effect and others not.

In all of these S_E2' processes with which we are now concerned, the *p* orbital of C-4 associated with the breaking C–H bond becomes part of a conjugated O=C(3)–C(4)=C(5)– system in the product of substitution. Presumably this conjugation provides some of the driving force which makes substitution competitive with addition; in comparable brominations of the 3β-substituted cholest-5-ene system,[1] even when the 3β-substituent is more electron-withdrawing than the 3-oxo-group as shown by the rate of bromination, addition proceeds to the exclusion of substitution. To provide the necessary conjugation in the transition state for proton loss, the departing 4-proton should be disposed axially rather than equatorially. Both boat and chair conformations of ring A may be available for cholest-5-en-3-one (1), as well as for the derived intermediates (2)—(5), so either of the 4-protons might be able to be removed. We shall see that the present results establish marked differences in stereoselectivity between the concerted and non-concerted pathways, and marked differences also in the ratio of 4α- to 4β-displacement for attack at the 6-position on the two faces of the molecule.

(i) *Substitutions in acetic acid containing sodium acetate.* It was not possible to determine directly the product proportions for bromination at very low concentrations, but they can be estimated from the results of experiments in which bromine was supplied in small portions (Table 1). By the end of the first 50% of reaction the concentrations of bromide ion would have been at least 0.002M, sufficient to catalyse appreciably addition by the halide-catalysed mechanism [equation (iii; Nu = Br^-)], and to ensure that some of the dibromide is derived by pathways (a) and (f). We estimate from the isotope effects on rates and products that the limiting proportion of 6β-bromo-enone formed by the second-order bromination is in the range 40—60%, and that most but not all of this comes from the concerted pathway (j). The isotope effect for this pathway is in the range 3—4, as for the analogous bromodeprotonations with rearrangement already mentioned.[12] This pathway must be highly stereoselective, the entering bromine and the departing hydrogen being *syn*-related. Other concerted S_N2' reactions in this [8] and in related [13] systems also have *syn*-stereochemistry. Correction being made for the isotopic composition of the starting material, the 6β-bromo-4-enone derived from isotopically pure 4β-deuteriocholest-5-en-3-one contains *ca.* 20% of H and 80% of D at C-4. For reaction at low concentrations of bromine, this result accords with the concomitance of 6β-attack with displacement of the 4β-hydrogen or -deuterium. For reactions at high concentration of bromine, however, no product of 6α-attack was detected; but the proportion of 6β-substituted product was significantly reduced whilst the ratio of H to D at C-4 remained the same. There must, therefore, be a contribution to the formation of the 6β-bromo-4-enone from a pathway involving removal of the 4α-proton and subject only to a small isotope effect, *viz.* $k^{4\alpha\text{-H}}/k^{4\alpha\text{-D}}$ for 6β-bromination, *ca.* 1.4. This provides evidence for the contribution of pathway (i) to the formation of (11); only a small isotope effect might be expected for proton loss from such a highly energised intermediate. The conformation of ring A having the 4α-proton axial must, therefore, be accessible for the 5β,6β-halogenonium ion (5); elsewhere [14] we have argued similarly in relation to the stereochemical requirements for base-catalysed ring opening of the analogous 5β,6β-epoxide.

As far as substitution is concerned, the results for molecular bromination (Table 1) and those for bromochlorination (Table 3) are so generally similar that it is likely that the same types of reaction pathway are involved. It seems probable that the small amount of 6α-bromocholest-4-en-3-one formed by bromochlorination, or by bromination at low initial concentrations, comes by way of path (d) from the 5α,6α-bromonium ion by preferential removal of the 4β-hydrogen in a reaction subject to only a small 4-H/D isotope effect ($k^{4\beta\text{-H}}/k^{4\beta\text{-D}}$ for 6α-bromination, $\gtrsim$1.4). Our method of analysis would not have allowed us to detect the corresponding reaction leading to the loss of the 4α-hydrogen atom by the non-concerted pathway in the reaction of 4β-deuteriocholest-5-en-3-one; comparison with the reaction of the non-deuteriated compound (Table 1) puts its contribution at less than 2%.

(ii) *Substitution in chlorobenzene containing 2-methyloxiran.* The relative simplicity and stability of the product mixtures formed under these conditions (Table 2), and the lack of dependence of the product composition and of the isotope effect on the concentration of

[13] I. M. Cunningham and K. H. Overton, *J.C.S. Perkin I*, 1975, 2140.

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

2-methyloxiran, show that this solvent mixture is effective in avoiding extraneous acid-catalysed processes, and that 2-methyloxiran is not involved in the product-forming transition states for our halogenations. Bromination by molecular bromine, which was shown to take the third-order kinetic form of equation (ii), with two molecules of bromine involved in the rate-determining step, exhibited isotope effects on the total rate of reaction, $k_3^{4\beta\text{-H}}/k_3^{4\beta\text{-D}} = 1.36 \pm 0.16$ and $k_3^{4\text{-H}_2}/k_3^{4\text{-D}_2}$ 1.31 ± 0.12. The only detectable products were the 6β-bromo-4-enone and the 5α,6β-dibromide. Correspondingly, there was only a small change in the ratio of substitution to addition when protium was replaced by deuterium at the 4β-position. The substitution product from isotopically pure 4β-deuteriocholest-5-en-3-one can be calculated to have 40% of protium at C-4, a value intermediate between the results expected if either of the 4-substituents were exclusively subject to displacement. Bromochlorination in the same solvent gave only the 6β-bromo-4-enone and the 5α-bromo-6β-chloride. These results imply that three and only three pathways contribute to these brominations, *viz.* paths (b), (i), and (j). The 5α,6α-bromonium ion (4) gives only addition product. The 5β,6β-bromonium ion gives only substitution product by predominant removal of the 4α-proton. Path (j) contributes also, and involves predominant removal of the 4β-proton. The isotope abundances and isotope effects indicate that approximately half the 6β-bromocholest-4-en-3-one is formed by the concerted pathway (j), and half by the non-concerted pathway (i).

These conclusions are fully consistent with and confirm those derived from experiments in which acetic acid containing sodium acetate was the reaction medium (Tables 1 and 3). Comparing results in the two solvents under conditions conducive to reaction by the third-order mechanism with the kinetic form of equation (ii) shows that chlorobenzene (independently of the concentration of 2-methyloxiran) gives more concerted substitution [pathway (j)], more non-concerted substitution [pathway (i)], and less addition. Since the product composition varies little with the initial concentration of bromine, the three major reactions contributing to product formation in chlorobenzene must have rate-determining stages of the same stoicheiometry. We think that the results are best interpreted through the hypothesis that the function of the second molecule of bromine appearing in the kinetic form is to remove bromide ion from the complex S,Br_2 [*e.g.* (3)]; and that in chlorobenzene the resulting ion pair is 'tighter,' rearranging less readily to allow *anti*-addition. Proton loss may then supervene instead, to give substantial reaction by the non-concerted pathway as well as some concerted substitution. That the latter reaction, which has an isotope effect, has the same transition-state stoicheiometry, appears to us to support the view that this reaction involves the complex (3) (from which the removal of the anion Y^- can be catalysed by molecular halogen), and is not a fully concerted reaction between the steroid and the halogen.

Although we have not examined the kinetics of the bromochlorinations, we presume that the third-order kinetic form of equation (ii) is operative as in the kinetic investigations by White and Robertson,[15] so that the results for this reagent should be compared with those for the molecular brominations at relatively high concentrations.

(c) *Products of Bromination; Pathways to Addition.*—It is obvious from the Tables that the major pathways to addition found for cholest-5-ene and its 3-substituted derivatives [1] are available for cholest-5-en-3-one also. They lead to 5α,6β-dihalides in aprotic solvents, and in acetic acid to 5α-halogeno-6β-acetates also. Path (b), through the halogenonium intermediate (4), provides one route to these compounds. Halide ions added to or formed in the reaction medium bring in a new (Ad_E3) reaction of the kinetic form of equation (iii), and through pathway (a) provide a second route to these products. This reaction is competitive as far as both kinetics and products are concerned with the other pathways to halogenation, as can be seen for reactions in acetic acid containing sodium acetate in Tables 1 and 3.

The reactions without added halide ions in acetic acid show also a much more substantial incursion of the pathway which gives bromo-acetates of reversed orientation. Thus with molecular bromine, 13% of 5α-acetoxy-6β-bromocholestan-3-one is formed; the proportion of this adduct is increased, as would be expected, when the starting material carries deuterium in the 4-position. The 5β,6β-bromonium ion (5) must undergo ring opening in the 'Markownikoff' sense, in contrast with the ring-opening of the isomeric halogenonium ion (4), which gives the product of opposite orientation.

The above comments apply to reactions at low concentrations of bromine, when pathway (j) with its relatively large 4β-H/D isotope effect makes its maximum contribution. At higher initial concentrations, molecular bromine catalyses the reaction [kinetic form, equation (ii)], and substitution occurs mainly through pathway (i), having a much smaller isotope effect. Consequently the differences in composition of the products from the 4-protio-ketone and that of those from its 4-deuterio-analogues become much less marked, as is true also for the reaction of bromine chloride (Table 3). A noteworthy feature of these results is that both bromo-chloride and bromo-acetate are formed from attack on the 5α,6α-bromonium ion, but apparently only the bromo-acetate is formed from the 5β,6β-bromonium ion. No obvious reason can be seen for this difference; it may imply a greater ease of dissociation of the ion pair leading to (5) than of the ion pair leading to (4).

(d) *Bromination with Other Sources of Electrophilic Bromine.*—Tables 2 and 3 give some results also for bromination initiated by reagents other than molecular bromine or bromine chloride. The results obtained in acetic acid containing sodium acetate accord with

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

general expectations. t-Butyl hypobromite could act as an electrophile in its own right; but by analogy with what we know about the behaviour of t-butyl hypochlorite,[16] it might in this solvent be a good source of bromine acetate through rapid establishment of the equilibrium of equation (iv). Bromine acetate would

$$BrOCMe_3 + HOAc \rightleftharpoons BrOAc + HOCMe_3 \quad (iv)$$

be a very ready source of electrophilic bromine [17] and would be expected easily to give the bridged intermediates (4) and (5). These would be formed in kinetically controlled proportions, which the experimental results suggest is **69 : 31**. They would then react much as do the same intermediates derived in other ways; such differences as might be found could result from the different properties of ion pairs in which these intermediates were associated with different counter-ions. The 5α,6α-bromonium ion would then give some substitution and much addition (found ratio with $BrOCMe_3$, **8 : 61**). Its isomer would give substitution and addition products in more nearly similar proportions (found ratio for $BrOCMe_3$, **13 : 18**).

Reactions involving *N*-bromoacetamide or *N*-bromosuccinimide in the presence of halide ions, on the other hand, would be expected [18] to provide halogenating species through the equilibrium of equation (v).

$$BrNRR' + HHal \rightleftharpoons BrHal + HNRR' \quad (v)$$

Product proportions should then be as from molecular bromine or bromine chloride as appropriate, with external halide ion and the reagent present at the stationary concentration achieved during the reaction. Survey of the results obtained by using *N*-bromoacetamide or *N*-bromosuccinimide in the presence of lithium chloride in acetic acid containing sodium acetate show that the product mixtures are similar to those obtained with bromine chloride, the amount of bromo-chloride being dependent on the concentration of added chloride ions. The results obtained by using *N*-bromoacetamide with high concentrations of lithium bromide accord with those found for bromide-catalysed brominations in which the Ad_E3 pathway (a) is followed. When this reagent is supplied in the presence of low concentrations of bromide ion, the products resemble those obtained with low concentrations of bromine, with the exception that much more 5α-bromo-6β-acetate is obtained. This result suggests that *N*-bromoacetamide in acetic acid can itself act as supplier of electrophilic bromine, so that further reaction stages leading from the complex (2; Y = NHAc) are different because of the association of the intermediate (4) with a different counter-ion.

Reaction with bromine acetate in chlorobenzene containing 2-methyloxiran gives the same range of products as is found with t-butyl hypobromite in acetic acid; but there is relatively more attack on the β-face of the molecule, and the partition between addition and substitution for β-attack is different. Whether these differences are determined by differences in solvent or in the reagent is not known.

(e) *Electrophilic Attack on the β-Face of the Steroid.*—The present results confirm de la Mare and Hannan's speculation [5] that electrophilic brominating species give attack on the β-face of cholest-5-en-3-one with an ease which enables this pathway to compete with the corresponding α-attack to an extent which is much greater than found for cholest-5-ene and its 3-substituted derivatives. Discussion of possible reasons for this difference is deferred to the following paper, to enable comparison with results for chlorination, epoxidation, and other electrophilic reactions.

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[16] M. A. Rosser, personal communication; P. B. D. de la Mare, 'Electrophilic Halogenation,' Cambridge University Press, 1976, pp. 104—106.

[17] P. B. D de la Mare and J. L. Maxwell, *J. Chem. Soc.*, 1962, 4829.

[18] R. E. Buckles, *J. Amer. Chem. Soc.*, 1949, **71**, 1157; R. E. Buckles and J. W. Long, *ibid.*, 1951, **73**, 998.